Animal: Neuroanatomy; Neurochemistry

THE EFFECTS OF ANTIPSYCHOTIC TREATMENT ON BRAIN VOLUME, INFLAMMATION AND GLUTAMATE SIGNALING GENES.

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Background: Brain volume loss and elevated microglial alongside other inflammatory markers are seen in schizophrenia. There are also known glutamatergic signal disruptions, evident from magnetic resonance spectroscopy in patients. However, the role of antipsychotic treatment in this is unknown.
Methods: We administered chronic haloperidol (0.05 mg/kg/day) or placebo drug pellets to either naïve (n= 8 and n=12 respectively) or lipopolysaccharide (LPS) systemically inflamed (n= 6 and n=6 respectively) rats (4 doses at 1mg/kg). Blood was taken for peripheral inflammatory marker analysis. Confocal images of cortical tissue stained for microglia (Iba-1) and nuclei (DAPI) were analysed, using custom Cell Profiler and Fiji programs. Microglial cell densities, cell body areas, process complexity and cell body stain intensity were the main outcome measures of analysis. We measured glutamatergic signalling associated gene expression to determine the effects of antipsychotic medication on these transcriptional events
Results: Whole brain volume was reduced in naïve rats treated with haloperidol (17% reduction $p<0.01$), however this was not present in the LPS and haloperidol dosed cohorts. We saw a striking difference in microglial responses between naïve and LPS treated animals. In naïve tissue, haloperidol resulted in a 40% reduction in cell density ($p<0.05$), LPS treatment resulted in a 50% increase in density ($p<0.01$). Haloperidol administration resulted in a normalisation of microglial density in the LPS model ($p>0.99$ versus control rats). Cell morphology increased in complexity with LPS (process lengths increased by 20% $p<0.01$). Haloperidol administration did not significantly alter cell morphology. Interestingly peripheral levels of CXCL1 and TNFα, which were elevated following LPS administration ($p<0.01$ and $p<0.001$ respectively), were not altered by haloperidol administration ($p>0.05$). We envisage the glutamatergic signalling associated gene results to be ready for presentation in ample time for the conference.
Conclusion: These findings suggest that chronic administration of haloperidol is able to reduce cortical volume and alter microglial cell dynamics in naïve and inflamed tissue. It will be important to translate these findings to a clinical setting as well as considering functional implications, as these changes may not have an impact on cognition.
ID: 2118643

ALTERATIONS OF CLOCK GENE EXPRESSION IN THE CHRONIC MILD STRESS MODEL: MODULATION BY CHRONIC LURASIDONE TREATMENT.

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Background: Genetic and epidemiological evidence suggests that disruption of circadian rhythms can contribute to the etiology of psychiatric disorders. The understanding of these alterations is of great importance to characterize systems and pathways whose dysfunctions are associated with mental illness as well as to identify new potential target for pharmacological intervention. Even if the master circadian clock of the organism is located in the suprachiasmatic nucleus, it has been demonstrated that other brain structures, such as hippocampus and prefrontal cortex, are profoundly affected by circadian misalignment. On these bases, the aim of our study was to investigate the expression of clock genes in an animal model of chronic mild stress (CMS), which recapitulates many features of psychiatric disorders, and to establish the impact of a pharmacological intervention on such alterations.
Methods: Male Wistar rats were exposed to CMS or sham manipulation for 2 weeks before being randomized to receive vehicle or the multi receptor drug lurasidone (3 mg/kg/day) for 5 more weeks, while continuing the stress procedure. Sucrose consumption was used to establish the anhedonic phenotype whereas the analyses of mRNA levels of Clock/Bmal1, Per1 and Per2, Cry1 and Cry 2 were carried out by Real-Time PCR in the hippocampus and in the prefrontal cortex. The effects of stress and of lurasidone treatment were analyzed with a two-way analysis of variance (ANOVA) followed by Fisher's LSD. Significance for the all tests was assumed for $p<0.05$.
Results: We found that the mRNA levels for Per2 and Cry2 were significantly down regulated in the prefrontal cortex of CMS rats, whereas Bmal1 expression was slightly up regulated. Interestingly, chronic treatment with lurasidone was able to normalize the anhedonic phenotype of CMS rats as well as the molecular changes induced by stress exposure. The modifications due to CMS exposure appear to be anatomically selective, since we did not observed any change in the hippocampus, although chronic treatment with lurasidone per se increased the expression of some clock genes within hippocampal sub-regions.
Conclusion: Our results suggest that changes in clock gene expression following CMS exposure may contribute to the dysfunctions associated with mood disorders. Moreover the ability of lurasidone to counteract the behavioral and molecular abnormalities in CMS rats may be important for ameliorating functions that are deteriorated in patients with stress-related disorders.
ID: 2114422

EFFECTS OF MATERNAL IMMUNE ACTIVATION ON OFFSPRING PREFRONTAL GABAERGIC CIRCUITRY AND ANXIETY

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Background: While altered GABAergic transmission in the prefrontal cortex has been implicated in the pathophysiology of several psychiatric disorders, the specific alterations in prefrontal GABA circuit function and their relationship to behavioral impairments have yet to be elucidated.
Methods: We used a murine model of prenatal maternal immune activation (MIA) - a risk factor for multiple forms of psychopathology, including schizophrenia - to identify alterations in functional GABAergic transmission from specific interneuron populations in the prefrontal cortex, as well as behavioral abnormalities, in adult MIA offspring. We then mimicked those cellular abnormalities using optogenetics to test a causal link with pathological behaviors.
Results: We uncovered profound reductions in GABAergic transmission onto prefrontal pyramidal neurons in adult MIA offspring that were specific to the parvalbumin-expressing (PV) class of interneurons. Surprisingly, despite this profound reduction in PV-mediated GABAergic transmission, working memory remained intact in adult MIA offspring, although these mice displayed pathologically enhanced levels of anxiety. Preliminary optogenetic data suggests that reducing PV GABAergic interneuron activity is sufficient to increase anxiety levels in adult mice.
Conclusion: These results demonstrate specific functional abnormalities in prefrontal PV interneurons in an environmental risk factor model for

schizophrenia, bipolar disorder and depression. A selective effect of MIA on PV interneurons may arise given that these cells' high metabolic demand makes them particularly susceptible to the effects of oxidative stress and because their prolonged period of maturation leaves them especially vulnerable to early developmental perturbations. Finally, they suggest that these abnormalities in prefrontal PV-mediated GABAergic transmission may be most relevant to anxiety, rather than working memory, symptoms associated with these disorders.
ID: 2117958

JUVENILE SOCIAL EXPERIENCE AND PREFRONTAL CORTEX MYELIN MATURATION

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Background: In humans, early social isolation or neglect results in adult behavioral and cognitive dysfunction that correlates with white matter alterations. However, how juvenile social deprivation influences myelination and the significance of these myelin defects in the adult remained undefined. To get insights into these processes, we used mice.
Methods: Wild type and mutant mice were exposed to different rearing environments, starting at their weaning age (P21). Conditions were regular housing (4 mice in a regular cage), enriched environment (8 mice in a large cage with numerous toys that were changed every two days), and social isolation (one single mouse in a regular cage). At different time points (up to P65), animals were analyzed for performance in behavioral assays that test prefrontal cortex function. Their prefrontal cortex was then subjected to morphological and molecular analysis of myelin.
Results: We found that mice isolated for 2 weeks immediately after weaning, have alterations in prefrontal cortex function and myelination upon reaching 65 days of age. Moreover, these changes do not recover with reintroduction into a social environment from P35 to P65. These alterations, which occur only during this critical period, are phenocopied by loss of oligodendrocyte ErbB3 receptors, and social isolation leads to reduced expression of the ErbB3 ligand neuregulin-1.
Conclusion: These findings indicate that social experience regulates prefrontal cortex myelination through Neuregulin-1/ErbB3 signaling and that this is essential for normal cognitive function, thus providing a cellular and molecular context to understand the consequences of social isolation.
ID: 2117997

TRANSDUCTION OF PERIPHERAL CYTOKINE SIGNALS TO THE BRAIN AND ITS RELEVANCE TO SCHIZOPHRENIA PHENOTYPES

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Background: Research over the last couple of decades has elucidated mechanisms underlying transduction of peripheral immune signals to the brain leading to changes in mood, cognition and behaviour. Inflammatory mediators that are released by activated innate immune cells at the periphery and in the central nervous system alter the metabolism and activity of neurotransmitters, generate neurotoxic compounds, decrease neurotrophic factors, and profoundly disturb the neuronal environment. These changes contribute to the pathogenesis of neuropsychiatric phenotypes, such as depression and fatigue. Inflammatory mechanisms are likely to be relevant for a number of aspects of schizophrenia: mood and cognitive dysfunction, negative symptoms, neurodegeneration are some of the most likely candidates. This presentation gives an overview of pre-clinical and clinical data illustrating, first, the mechanisms underlying transduction of peripheral immune signals to the brain, and secondly, the relevance of the immune-brain communication to schizophrenia phenotypes.
Methods: Experimental designs involving mouse and human samples.
Results: Peripheral inflammatory cytokines can communicate with the brain in a number of ways: retrograde axonal transport through the vagus nerve, by volume diffusion though circumventricular organs, soluble transport across the blood-brain barrier, by activating cytokine receptors of perivascular macrophages and endothelial cells of brain venules. Once within the CNS, the cytokine signal is amplified, which activates microglia, leading to the secretion of proinflammatory cytokines, chemokines, and proteases within the brain. These messengers breakdown tryptophan along the kynurenine pathway, leading to increased levels of kynurenic acid and its metabolite quinolonic acid, both involved in glutamatergic neurotransmission. Cytokines also increase oxidative stress, and activate the hypothalamic-pituitary-adrenal axis. These effects could contribute to the negative, cognitive and positive symptoms of schizophrenia, as well as to impaired mood, cognition, and perception that are important parts of other psychiatric disorders.
Conclusion: Inflammatory mechanisms are likely to be relevant for a number of aspects of schizophrenia such as mood and cognitive dysfunction, negative symptoms, neurodegeneration, and therefore, could provide important new targets for intervention and prevention.
ID: 2115690

RECEPTOR FOR ADVANCED GLYCATION END-PRODUCT (RAGE) AS LINKING MECHANISM BETWEEN NEUROINFLAMMATION AND OXIDATIVE STRESS

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Background: In schizophrenia pathophysiology, increasing evidence point to a critical role of redox dysregulation / oxidative stress leading to impairments of fast spiking parvalbumine interneurons (PVI) which are essential for gamma oscillations generation, thus contributing to cognitive deficit. Animal models of psychosis including the ketamine/PCP, NHVL, DISC1, GluN1-KO and gclm KO models converge in showing increase in oxidative stress markers and PVI impairment in prefrontal cortex. PVIs surrounded by perineuronal net (PNN), also express metalloproteases which are induced in inflammatory conditions. Evidence also indicates the implication of immune dysregulation in schizophrenia, highlighted by anomalies in peripheral immune cells and association with immune-related genes in genome-wide association studies. As oxidative stress is known to induce inflammation, we explored in a transgenic animal model with glutathione (GSH) synthesis deficit (gclm KO) if RAGE represents one potential link between oxidative stress and inflammation, as it is activated by ROS and induces inflammatory genes expression.
Methods: In gclm KO versus WT mice, we compared by immunohistochemistry the expression of oxidative stress markers (8-oxoDG), microglia markers (Iba1, CD11b and CD68), RAGE and the metalloprotease MMP9 in anterior cingulate cortex at peripuberty (P40) and adulthood (P90).
Results: At both time-points, the number of Iba1-immunoreactive (IR), CD11b-IR and CD68-IR cells were increased in gclm KO compared to WT mice. Microglia activation was found only in regions where oxidative stress was increased in gclm KO, suggesting a pro-inflammatory state

induced by oxidative stress. RAGE shedding was induced in neurons in both genotypes. At P40, RAGE shedding was increased in gclm KO compared with WT. However, at P90, RAGE shedding was decreased in gclm KO compared to WT. In addition, S100b, a ligand of RAGE, followed the same pattern as RAGE shedding at both time points, suggesting a feedback regulation of S100b. We found that MMP9 was increased in gclm KO at P40 and that in vivo inhibition of MMP9 with a siRNA prevented RAGE shedding, pointing to the involvement of MMP9 in this process.

Conclusion: RAGE shedding via MMP9 is a key regulatory mechanism by which oxidative stress interacts with neuroinflammatory condition. This pathological interaction, induced by RAGE, is a potential trigger of PVI and PNN impairments observed in schizophrenia.

ID: 2083361

CHRONIC EXPOSURE TO ANTIPSYCHOTIC MEDICATION CHANGES THE BRAIN STRUCTURE IN MONKEYS AND RATS

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Background: Many studies have found subtle structural brain changes in subjects with schizophrenia using postmortem or in vivo imaging techniques. However, most studied subjects have a history of antipsychotic medication. To robustly interpret such findings it is essential to determine if prolonged treatment with antipsychotic medications to some degree contributes to these brain changes. This is important both for elucidation of the disease process of schizophrenia and for gaining insight into the mechanisms underlying the effects of antipsychotic medications—these effects being both therapeutic and adverse.

Methods: To examine the effect of antipsychotic medication on brain structure several research groups have recently conducted experimental studies of non-human primates or rats. In one study, we exposed three groups each consisting of six experimentally-naïve, young adult, male macaque monkeys to twice-daily oral doses of haloperidol, olanzapine or placebo treatment, respectively, for approximately two years. After the period of medication exposure, the monkeys were euthanized and subsequently the total brain weight as well as weight and volume of the left hemisphere were obtained.

Results: Importantly, we observed significantly ~10% smaller total brain weights and volumes in both the haloperidol and olanzapine exposed groups. Subsequent histological studies of the cerebral cortex of the parietal lobe using stereological methods found a lower total glial cell number without a difference in total neuron number in the antipsychotic-exposed monkeys. In a subsequent immunocytochemical stereology study of the parietal lobe we found a significant 21% lower astrocyte number and a non-significant 13% lower oligodendrocyte number in the antipsychotic-exposed monkeys. Similar effects were observed in both the haloperidol and olanzapine groups.

More recently, several studies in antipsychotic-exposed rats, including longitudinal structural MRI imaging, have been published by other research groups. In general, the rat studies also report finding ~10% reduced brain or hippocampal volume, with a preserved total neuron number when examined. However, the glial cell reductions seen in the non-human primates have not been observed in the rat models.

Conclusion: In conclusion, the findings from the animal studies are consistent with the idea that chronic antipsychotic medications might cause some of the structural changes identified in schizophrenia.

ID: 2117887

A NEW RAT MODEL FOR SCHIZOPHRENIA SHOWS ALTERATIONS IN THE PLASTICITY, NEUROGENESIS AND NEUROCHEMISTRY OF THE MEDIAL PREFRONTAL CORTEX AND THE HIPPOCAMPUS

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Background: Alterations in neurodevelopment and aversive experiences are important risk factors for developing schizophrenia. To reproduce some of the observed alterations in patients, different developed animale models mimic some of the symptoms, constituting a valid approach to study the etiopathology of this disorder. The perinatal injection of N-methyl-d-aspartate receptor antagonists and the postweaning social isolation rearing are some of the most used models.

Methods: Combining these two animal models in a "double hit" model, it should be possible to produce a wider spectrum of alterations. Lister Hooded rats have been subjected to a single injection of MK-801 at postnatal day 7 and have been socially isolated from postweaning during 8 weeks.

Results: The new animal model, presented increased body weight gain and volume reductions in their medial prefrontal cortex (mPFC) and hippocampus. They also showed an increased number of activated pyramidal neurons and alterations in the numbers of parvalbumin and calbindin expressing interneurons in the mPFC. The expressions of the polysialylated form of the neural cell adhesion molecule (PSA-NCAM) and GAD67 are decreased in the deep layers of the mPFC. The mRNA level of calbindin was increased, while that of calretinin was decreased in the mPFC without changes in the hippocampus. Furthermore the model showed no apoptosis in the studied areas, but the number of immature neurons was altered in the dentate gyrus.

Conclusion: All these results point to the present "double hit" model may be a better tool to study the neurobiological basis of schizophrenia and to explore new therapeutic approaches. All these structural and neurochemical alterations, specially in cortical inhibitory circuits, are similar to those found in schizophrenic patients and are more numerous than in each of the single models.

ID: 2114296

TWO-PHOTON CALCIUM IMAGING OF VISUAL CORTICAL POPULATION DYNAMICS IN A CHRONIC KETAMINE MOUSE MODEL OF SCHIZOPHRENIA

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Background: Schizophrenia (SZ) may involve a fundamental disruption in the intrinsic dynamics at the cortical microcircuit level giving rise to global deficits in perceptual and cognitive processing, yet such dynamics have so far been accessed mostly with indirect electrophysiological (EEG, LFPs) or anatomical assays. Two-photon calcium imaging enables single-cell measurement of cortical populations (100+) and their patterned, synchronous activity dynamics in awake animals. We reasoned that examining cortical circuits at this level in a rodent model of SZ could yield key new insights on the neural substrate of psychotic states.

Methods: Given the ability of N-methyl D-aspartate glutamaterge receptor (NMDARs) antagonists to recreate key perceptual and cognitive symptomology of SZ in both healthy humans and rodents, we administered

subanesthetic levels of ketamine (KET; 30–60 mg/kg/day) or saline continuously with a subcutaneously implanted osmotic minipump in C57BL/6 mice. We expressed genetically encoded calcium indicators (Gcamp6s/f) in primary visual cortical neurons and, with 2-photon microscopy through a surgically thinned skull, measured the bursting activity of 70–200+ V1 neurons in awake mice before and 1 week after beginning treatment. We imaged at 4–8 Hz before and during the presentation of full-field moving squarewave gratings (6 orientations, 12 directions) of 100 % contrast and .08 cycles per degree. We estimated spike rates for single cells and quantified population-state similarity across time.

Results: At rest KET mice displayed i) a decrease in population activity-state dimensionality possibly reflecting highly stereotyped attractor states and impaired flexibility within the cortical network. While viewing moving gratings, KET mice displayed ii) stim-evoked activity comprised of population level patterns which were inconsistent across presentations of the same stimulus or hyperconsistent across all stimuli iii) in the context of reduced orientation selectivity at the single cell level.

Conclusion: The current study presents a novel depiction of disordered sensory cortical function in a mouse model of psychosis involving rigid default states and disordered externally driven states. These findings could provide a crucial foundation for understanding the biopathphysiological cascade from putative SZ risk genotypes and their molecular consequences to clinically measurable deviations in behavior and noninvasively acquired electrophysiology.

ID: 2093578

SYNAPTIC NMDA RECEPTOR ACTIVITY IS COUPLED TO THE TRANSCRIPTIONAL CONTROL OF THE GLUTATHIONE SYSTEM IN THE DEVELOPING FOREBRAIN

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Background: Deficits in the glutathione (GSH) antioxidant system have been implicated in the pathophysiology of several neuropsychiatric disorders, including schizophrenia. Moreover, It is thought that one of the harmful consequences of GSH system dysfunction in the brain is NMDA receptor (NMDAR) hypofunction. Synaptic NMDAR hypofunction is deleterious to developing forebrain neurons, and is associate with oxidative stress, but mechanisms are poorly understood

Methods: Primary mouse cortical neuronal culture models of synaptic NMDAR hypo/hyper function were employed as well as in vivo administration of NMDAR antagonist MK-801. Biochemical and live cell imaging measures of glutathione and glutathione pathway enzymes were performed, as were gene expression analyses of glutathione pathway genes and neuronal viability assays. Glutathione pathway enzyme activities were perturbed by siRNA and pharmacological inhibitors.

Results: We found that synaptic activity is coupled, via the NMDAR, to transcriptional control of the glutathione antioxidant system, tuning its capacity to reflect the elevated needs of an active neuron and maintaining the correct redox balance in the brain. This control is mediated via a coordinated program of gene expression changes that boosts the synthesis, recycling and utilization of glutathione, which together facilitate rapid ROS detoxification in neurons which otherwise triggers Puma-dependent apoptosis. Of particular importance to the developing brain is the direct NMDAR-dependent transcriptional control of glutathione biosynthesis. We find that the deleterious effects of NMDAR hypoactivity in vivo are due to this control being lost.

Conclusion: This study, coupled with previous published work shows that developmental NMDAR hypofunction and glutathione system deficits, separately implicated in several neurodevelopmental disorders, are mechanistically linked in a reciprocal manner. Moreover, it sheds light on how the developing brain's antioxidant defences adapt to the changing demands of enhanced electrical activity, as well as the mechanisms of synaptic NMDAR-mediated trophic signaling

ID: 2085491

ANGIOTENSIN SIGNALING IN THE DEVELOPMENT AND PATHOLOGY OF IMMUNE-ASSOCIATED PSYCHOSIS

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Background: Emerging evidence from human epidemiology, genetics, and biomarker studies implicate neuroinflammation in both the pathogenesis and pathophysiology of some neuropsychiatric disorders. However, the function of neuroinflammation in neuropsychiatric disorders is still debated because supporting evidence is indirect and no molecular mediators are identified.

Methods: We used a multiplex protein array to simultaneously measure several molecular markers in the cerebrospinal fluid from first episode anti-psychotic naïve schizophrenia patients and healthy controls. Next, we used the maternal immune activation (MIA) mouse model to investigate the inflammatory and pathway changes in a mouse model relevant to psychosis. We evaluated the rodent behavior, microglia inflammatory activation, microglia responsiveness to angiotensin treatment, and expression of angiotensin pathway components.

Results: We identified a molecular change in cytokines, cytokine receptors, and angiotensin-converting enzyme (ACE) in cerebrospinal fluid from first episode, anti-psychotic naïve schizophrenia patients and prodromal subjects suggesting a role for inflammation and the angiotensin pathway in disease, potentially through microglia (Hayes et al. 2014). To test these finding, we used the MIA mouse model. After MIA, the male mice exhibit hyperlocomotion to amphetamine challenge and deficits in social memory in the three-chamber social interaction paradigm. Next, we investigated the inflammatory potential of these mice. We isolated microglia from late embryonic (E18.5) mice after MIA and control treatment. We found MIA microglia were hypo-responsive to inflammatory stimulation and angiotensin treatment, further supporting a role for microglia dysfunction, inflammation, and the ACE pathway in pathology. Finally, we found microglia after MIA had decreased angiotensin receptor expression.

Conclusion: Altogether, the human and animal data suggest a common cellular deficit in psychosis and the MIA mouse model through the ACE pathway. Our future direction is to investigate the relationship between the ACE pathway and inflammation using human cells and the MIA mouse model. If the ACE pathway can modulate inflammatory alterations observed in pathology, it may provide a novel therapeutic target for neuropsychiatric disorders with inflammatory underpinnings.

ID: 2085564

THE PHOSPHODIESTERASE-4 INHIBITOR, ABI-4, ATTENUATES THE INCREASES IN BRAIN CYTOKINES AND TRANSLOCATOR PROTEIN BINDING CAUSED BY LIPOPOLYSACCHARIDE

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Background: Cyclic nucleotide phosphodiesterases-4 (PDE4) are a class of enzymes that regulate cellular signaling pathways involved in inflammation. The PDE4 inhibitors roflumilast and apremilast have been approved for the treatment of peripheral inflammatory disorders, however these drugs do not penetrate the brain. Neuroinflammation is also thought to contribute to the etiology of schizophrenia, with reports of elevated peripheral cytokines, and signs of central inflammation (e.g. CSF and brain cytokines and translocator protein (TSPO) binding). In light of these data, studies were run to test the ability of the novel brain penetrant PDE4 inhibitor, ABI-4, to modulate the effects of lipopolysaccharide (LPS) in the periphery and brain.
Methods: To assess in vitro anti-inflammatory effects, primary blood monocytes (PBMCs) were isolated from human blood. PBMCs were incubated with LPS (100 ng/ml) in the presence of rolipram, roflumilast or ABI-4 for 20h prior to measuring TNFα in the culture media. To assess anti-inflammatory effects in vivo, male CD-1 mice were dosed with LPS (1 or 10 mg/kg i.p.) plus vehicle or ABI-4 (0.1- 1 mg/kg s.c.) and euthanized 4h later to collect plasma and brain for cytokine analysis. Mice were co-dosed with LPS (0.32 mg/kg i.p.) and vehicle or ABI-4 (1 mg/kg s.c.) for 5 days. Brain and plasma samples were collected 4h after the final dose for measurement of cytokines and brain TSPO binding.
Results: All compounds were potent inhibitors of the TNFα response to LPS in human PBMCs (IC50: roflumilast 1.8 nM, rolipram 15.0 nM, ABI-4 14.4 nM) with potency in line with their binding affinity at PDE4B. LPS (1 mg/kg) also increased levels of IL-1β, TNFα and IL-6 in plasma. These increases were all significantly attenuated by co-administration of ABI-4 (≥0.1 mg/kg). LPS (10 mg/kg) induced increases in brain cytokines were also significantly attenuated by ABI-4 (≥0.32 mg/kg). Five day dosing with LPS caused significant upregulation of TSPO in mouse brain which was prevented by co-administration of ABI-4.
Conclusion: These data demonstrate that ABI-4 is a potent inhibitor of the in vitro effects of LPS in human monocytes and in vivo effects in mouse plasma and brain. ABI-4 also prevented LPS-induced upregulation of brain TSPO binding, indicating attenuation of microglial activation in the brain. These data suggest that the anti-inflammatory properties of ABI-4, together with the antipsychotic properties of this molecule make this an interesting potential treatment for schizophrenia.
ID: 2095497

DISC1 INDUCED EXPANSION OF THE HINDBRAIN OLIGODENDROCYTES PROGENITORS IN FOREBRAIN DURING DEVELOPMENT - RELEVANCE TO SCHIZOPHRENIA

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Background: Strong evidence corroborates involvement of oligodendrocyte (OLG) dysfunction in the pathophysiology of schizophrenia (SZ). DISC1 is a risk gene for several major mental illnesses including SZ. We previously showed that the forebrain-restricted expression of mutant human DISC1 (hDISC1) exerts a significant influence on oligodendrogenesis during early development and in adult hDISC1 mice, evidenced by premature OLG differentiation and increased proliferation of their progenitors in forebrain regions. Concurrent reduction of OLG progenitor markers in hindbrain regions during fetal stage suggested expansion of hindbrain glial progenitors into the forebrain of hDISC1 mice.
Methods: We tested this hypothesis by examining gene and protein expression of the molecular determinants of hindbrain OLG development (EGR2/Krox20 and Nkx2-2) in samples from forebrain and hindbrain regions at E15, P0, P14 and P21 days of hDISC1 mice. In postmortem study gene expression of hindbrain OLG markers were measured in the superior temporal cortex of persons with SZ (N=61) and cognitively normal controls (N=59).
Results: We found forebrain-restricted upregulation of gene and protein of the hindbrain markers of OLG progenitors (EGR2 and Nkx2-2) at E15, coinciding with the peaks of endogenous and human mutant DISC1 expression. Increased fetal expression of EGR2 was followed by its down-regulation in forebrain during CNS myelination from P14 to P21. Expression of early OLG progenitor markers (PDGFRA and NG2) and myelinating OLG markers (CNP and MAG) was also increased during prenatal but not postnatal periods. Similar to animal model, hindbrain OPC/OLG markers (PRX, LAMA1 and MPZ) were significantly upregulated in superior temporal cortex of persons with SZ.
Conclusion: Our findings show a significant effect of hDISC1 on hindbrain OLG development and suggest expansion of OLG progenitors responsible for developmental positioning of OLG identity cells along the rostrocaudal axis. Dislocation of OLG lineage cells as a result of their abnormal migration and premature differentiation may affect cortical organization of the brain.
Given the critical role of DISC1 in migration of neuronal and glial progenitors during brain development, our results provide new clues for the developmental mechanisms contributing to oligodendrocyte dysfunction in SZ.
ID: 2069180

DEVELOPMENTAL OXIDATIVE STRESS CAN PREDISPOSE SCHIZOPHRENIA-LIKE PHENOTYPE IN MICE

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Background: The prefrontal cortex GABAergic system does not reach functional maturity until adolescence and is thus susceptible to environmental insults/stressors during this developmental period. Parvalbumin (PV) positive GABA interneurons are particularly susceptible to adolescent exposure to drugs of abuse such as cocaine. These PV+ fast spiking inhibitory neurons profoundly affect the postnatal development of cortical circuitry and deficits in this inhibitory pathway may contribute to psychosis and cognitive impairments seen in schizophrenia and other related disorders. Here we examined the effect of adolescent exposure to the selective dopamine reuptake inhibitor GBR12909 on oxidative stress markers, PV-interneurons, and behavior relevant to schizophrenia. We also examined whether two oxidative stress events at two sensitive periods of cortical development would exacerbate the effects on cortical PV-expressing interneurons by combining perinatal ketamine and adolescent GBR12909 exposures.
Methods: C57BL/6 mice were injected with 30 mg/kg (s.c) ketamine or saline on postnatal day (PND) 7, 9 and 11. Half of the mice from each treatment group received daily injections of GBR12909 (5 mg/kg s.c) or saline from PND 35–44, during adolescence. Mice were then tested for locomotor and investigatory behavior and probabilistic reversal learning. PV+ neurons were labeled and counted in prefrontal cortex and hippocampus, as these circuits have a protracted, late adolescent maturation. 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-OxodG) is a biomarker of oxidative stress hence the levels were also measured in PV-neurons of mPFC to determine the degree of oxidative stress resulting from adolescent GBR12909.
Results: Adolescent administration of GBR increased locomotor activity ($p<0.05$) and investigatory behavior ($p<0.05$) in female but not in male mice measured in adulthood. In the probabilistic reversal learning task, GBR-treated male mice took longer to reach criterion ($p<0.05$) than saline-treated mice. Immunohistochemical analysis of PV-neurons in

medial prefrontal cortex but not in hippocampus also showed decrease in PV-expression in GBR treated mice. Combined treatment with GBR and ketamine increased premature responses in probablistic learning and levels of 8-OxodG in PV expressing neurons in mPFC ($p<0.01$).
Conclusion: Our data indicate that adolescent GBR perturbed PV-expressing GABAergic neurons, particularly in mPFC, through an oxidative stress mechanism. Behaviorally, adolescent GBR12909 increased exploratory and investigatory behavior and slowed learning in the between-session probabilistic learning task, indicating a potential learning deficit in this model. Hence GBR12909-induced oxidative stress in adolescence resulted in cognitive deficits and neurochemical changes particularly in PV-expressing neuron. Our results also indicate that adolescent exposure to GBR12909 in perinatal ketamine-exposed mice may exert long-lasting effects on impulsive behavior.
ID: 2119101

CLOZAPINE REDUCES TOLL-LIKE RECEPTOR 4/NF-KB-MEDIATED INFLAMMATORY RESPONSES THROUGH AKT INHIBITION IN MICROGLIA

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Background: Clozapine (CZP) is an atypical antipsychotic agent used in the treatment of psychotic disorders including schizophrenia and bipolar disorder. Accumulating evidence suggests that neuroinflammation is closely associated with the pathogenesis of schizophrenia as well as bipolar disorders.
Methods: In this study, we investigated the effect of CZP on anti-inflammatory activity in lipopolysaccharide (LPS)-stimulated microglia.
Results: CZP treatment suppressed LPS-induced phosphorylation of IκBα at Ser-32 and of p65/RelA at Ser-468, as well as NF-κB-dependent transcriptional activity, as revealed by a cis-acting reporter assay system and analysis of NF-κB target gene expression. CZP downregulated LPS-induced Akt phosphorylation at Ser-473. Pharmacological Akt inhibitors ameliorated LPS-induced NF-κB activation, whereas ectopic expression of the constitutively active form of Akt (gag-Akt) abrogated the inhibitory effect of CZP on LPS-induced NF-κB phosphorylation. Removal of extracellular Ca2+ by EGTA or sequestration of intracellular Ca2+ by BAPTA-AM attenuated LPS-induced Akt phosphorylation. Treatment with calmodulin (CaM) antagonists and the CaM kinase inhibitor, KN-93, also prevented LPS-induced Akt and NF-κB activation. Ca2+/CaM-mediated Akt activation is critical in LPS-induced NF-κB activation in microglia.
Conclusion: CaM antagonism by CZP plays an important role in anti-inflammatory activity through the inhibition of Akt-mediated NF-κB activation. The antipsychotic CZP could be a promising agent for prevention of TLR4-mediated neuroinflammation.
ID: 2086969

LONG-TERM EFFECTS OF NEONATAL MK-801 TREATMENT ON PROTEIN TRANSLATION SIGNAL PATHWAY IN THE RAT FRONTAL CORTEX

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Background: Systemic injections of MK-801, a selective NMDA receptor antagonist, into neonatal rats induce long-term neurochemical and behavioral changes. It has been suggested that these changes form the neurodevelopmental basis for schizophrenia-like behavior in rats.
Methods: In this study, postnatal 7-day (PN7) rats were treated with MK-801, and their frontal cortices at PN60 were examined to investigate the long-term effects on the molecules in signal pathway of protein translation.
Results: At PN60, the rats treated with MK-801 at PN7 showed increased locomotor activity and deficits in prepulse inhibition, as reported previously. Accompanied with the behavioral changes, the phosphorylation level of S6 at S240/244, which promotes protein translation initiation, was increased, and the phosphorylation of raptor at S792, which inhibits the activity of mTOR signal pathway, was reduced in the rat frontal cortex at PN60. Repeated treatments of electroconvulsive seizure (ECS) from PN51 to PN60 ameliorated the increased locomotor activity and prepulse inhibition deficits of PN7 MK-801-treated rats. In addition, ECS treatments recovered the PN7 MK-801-induced increase in the phosphorylation of S6 at S240/244 and decrease in the phosphorylation of raptor at S792. In summary, long-term behavioral changes induced by neonatal MK-801 treatment was accompanied with the increased phosphorylation of S6 in the brain, which were recovered by ECS treatments.
Conclusion: These findings may suggest an important role of aberrant long-term activation of protein translation machinery in the MK-801 neurodevelopmental animal model of schizophrenia.
ID: 2086942

CLOZAPINE RESPONSE TRAITS ON A NOVEL SUB-CHRONIC PCP ANIMAL MODEL OF TREATMENT-RESISTANT SCHIZOPHRENIA

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Background: The most severe form of schizophrenia is clozapine-resistant schizophrenia (CRS), however, there is no validated model of CRS which can allow investigation of drug resistance and development of novel treatments.
Methods: Mice (C57/bl males: n=9, females: n=9) were treated with sub-chronic PCP followed by clozapine. Each group went through Social Preference (SP) task at baseline, after PCP and after clozapine treatment. We used a selective breeding methodology in which we selected the most extreme non-responders and responders. Response was based on the elevation of the time spent with the novel mice following clozapine treatment. Males and females were mated to produce the trans-generational experiments. We replicated the selection process on each generation (G2-G4). We analyzed selected biochemical parameters of brain tissues from the hippocampus of mice from G3 and G4 of the responsive mice line.
Results: The average score of the male group of the resistant G2 represented resistance to clozapine while females of the same group and the whole responsive group showed response on average. This finding is in concordance with the clinical observation of a more severe form of the disorder in male patients, manifesting with earlier age of onset and poor prognosis. The apparent deficit in social abilities of resistant G2 male line has resulted in a very low fecundity that did not allow us to continue to G3 with the resistant colony. The responsive colony, however, was proliferative and allowed us to preform further behavioral and biochemical analysis to brain tissues. We observed an increase of the proportion of clozapine responders, on G2, G3 and G4, both on male and female groups of the responsive line.

Conclusion: In this pioneer study we aimed to establish a valid clozapine-resistant and clozapine responsive animal model through selective breeding of these traits in mice. Behavioral response to clozapine treatment in the SP task is augmented with generations, both in the resistant and the responsive mice lines. The clozapine responsive mice line showed increment of response rate through generation on both genders. Initial results indicate that there is a difference between generations on indices of GABA synthesis (GAD67) and neurotropic factors (BDNF and its receptor Trk B). There was also a gender difference in the trans-generational levels of neurotropic factors. In the future we wish to enhance these mice lines to gather a putative mechanism for response and resistance to clozapine.
ID: 2117909

REGION-SPECIFIC, DIFFERENTIAL DYSREGULATION OF NEUROTROPHIC SIGNALING AND NEUROINFLAMMATION IN RODENT MODELS OF PATHOLOGICAL NEURODEVELOPMENT

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Background: Several neurodevelopmental animal models address the impact of a genetic manipulation or an environmental insult on developmental brain trajectories. The Df1/+ mouse models a human 22q11 microdeletion that confers 20–30 fold increased risk of developing schizophrenia, and the gestational methylazoxymethanol (MAM) rats are exposed to a teratogen during a critical developmental period. As both models produce adult onset behavioral deficits related to schizophrenia, we examined transcriptional alterations in adult brain tissues from Df1/+ mice and MAM rats, focusing on genes and pathways previously shown to be dysregulated in human post-mortem schizophrenia brains, specifically GABAergic transcripts, BDNF-TrkB signaling and inflammation.
Methods: Brains were harvested from adult E17 MAM rats and Df1/+ mice. Frontal cortex, striatum and hippocampus were micro-dissected, flash frozen, and RNA was extracted. RNA was sequenced, and results for pathways of interest were followed up by RT-PCR.
Results: In frontal cortex, a number of transcripts involved in inflammation were upregulated in the MAM rat, including ADAMTS1, ITGAV, and PARP14. Also upregulated in MAM rat frontal cortex were truncated forms of the TrkB receptor and p75NTR. Several GABAergic transcripts showed a trend toward reduction in MAM frontal cortex, but only CALB1 was significantly reduced. In hippocampus, Df1/+ mice showed elevations in many inflammatory transcripts, including those elevated in MAM rat frontal cortex and multiple genes in the JAK-Stat signaling pathway. Both MAM rats and Df1/+ mice showed increased p75NTR and altered TrkB transcripts in hippocampus. The MAM rat showed also a reduction in CCK in hippocampus. In striatum, the Df1/+ mouse showed reductions in CCK, NPY and PV. Both models showed reductions in BDNF transcripts in striatum.
Conclusion: In summary, the MAM rat and Df1/+ mouse both show reductions in GABAergic markers and the BDNF-TrkB pathway, and regionally restricted increases in transcripts associated with inflammation. As schizophrenia is not a purely genetic or environmental disorder, these data suggest that models based on such singular events can replicate some of the molecular changes observed in schizophrenia, but a combination of multiple factors may be necessary to replicate the broad range of behavioral, cognitive, and neural alterations that comprise the disorder.
ID: 2087329

LONG TERM MODULATION OF THE ENDOCANNABINOID SYSTEM FOLLOWING ADOLESCENT CANNABINOID ADMINISTRATION

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Background: Schizophrenia is an illness of unknown pathophysiology. The adolescent use of cannabis is repeatedly implicated as a risk factor for this disease. In the mouse model, exposure to cannabinoids during adolescence has persistent behavioral consequences including schizophrenia-like behaviors.
Methods: We conducted a series of experiments to examine the long-term consequences of adolescent cannabinoid exposure on receptors involved in endocannabinoid signaling. Mice were administered with a cannabinoid receptor 1 (CB1) agonist, (WIN 55,212-2) or vehicle for 10 days by I.P. injection at different developmental ages. Behavioral tests and molecular studies were carried out.
Results: Mice administered WIN 55,212-2 (WIN) at 5 weeks of age display significant deficits in PPI and fear conditioning learning and memory paradigm. These behavioral deficits were not observed in mice treated with the CB1 agonist at later developmental time points. Group I metabotropic glutamate receptor (mGluR) activation drives endocannabinoid synthesis and release and we previously reported changes in CB1 and mGluR5 expression patterns in the hippocampus. Here, we extend those studies, examining endocannabinoid genes in the frontal cortex and striatum in mice and a human post mortem tissue cohort of control and schizophrenia cases divided into individuals with and without a significant adolescent cannabis use history. Mice treated with WIN 55,212-2 at 5 weeks of age show a distinct profile in CB1 and mGluR5 the frontal cortex and striatum. There is a significant upregulation of CB1 in both the frontal cortex and striatum while mGluR5 protein levels demonstrated a bidirectional expression pattern with significantly increases in the frontal cortex and strong trend to reduction in the striatum. Parallel human post mortem studies using prefrontal cortex (BA9) tissue from control and schizophrenia cases with prior adolescent cannabis use history are being analyzed. Immunohistoflourescence experiments to localize cell type distribution of CB1 and mGluR5 are ongoing.
Conclusion: These data suggest that adolescent cannabinoid administration leads to regionally specific persistent changes in receptors involved with endocannabinoid signaling. These data may be relevant to understanding the long term sequelae of significant adolescent cannabis use and may be of particular importance in understanding mechanisms by which adolescent cannabinoid exposure leads to molecular changes predisposing to schizophrenia.
ID: 2087658

CLOZAPINE MODULATES DOPAMINE RELEASE DOPAMINERGIC STATE DEPENDENTLY IMPLICATING ITS SPECIFIC ACTION IN CONTRAST TO HALOPERIDOL

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Background: Clozapine provides improved efficacy in treatment with schizophrenia, especially on the treatment-refractions and also their emotional symptoms. However the mechanism/s through which the therapeutic benefit arises from are not fully understood. The purpose of this study was

to demonstrate specific biochemical mechanism/s for clozapine related to its clinical benefits on emotional cognitive process. For the purpose, amygdala dopamine in response to an aversive conditioned cue was measured as a biochemical marker of the emotional cognitive processing. Previously we had developed a stress vulnerability model which was treated with chronic administration of methamphetamine followed conditioned to an auditory cue with aversive electrical stimulation. Using the model, we studied how clozapine influence basal dopamine release and phasic dopamine release in response to the aversive conditioned cue stimulation (CS).

Methods: Extracellular dopamine was taken from the amygdala of freely moving rats by in-vivo microdialysis and analyzed by high-performance liquid chromatography (HPLC). During the microdialysis, clozapine 1, 3 or 10 mg/kg, or haloperidol 1 mg/kg was injected intraperitoneally and fear conditioned cue was subjected. The changing ratio of dopamine from the basal level after drug treatment and CS was analyzed.

Results: Dopamine release in response to a CS was greater for methamphetamine-sensitized rats than non-sensitized rats. Haloperidol treatment increased basal level of dopamine both in non-sensitized and methamphetamine-sensitized rats. However, clozapine treatment did not elicit the increasing basal level in methamphetamine-sensitized rats at all while the drug increased basal level in non-sensitized rats, which was greater than haloperidol. Both clozapine and haloperidol attenuated the phasic dopamine release in response to a CS both in non-sensitized and methamphetamine-sensitized rats. The extent of the attenuation was greater for clozapine than for haloperidol both in non-sensitized and methamphetamine-sensitized rats.

Conclusion: The results suggest that a stabilization of dopamine release in the amygdala during emotional processing is a common therapeutic mechanism of antipsychotics. The dopaminergic-state dependent action of clozapine suggests that some receptors bound with clozapine may functionally regulate due to hyper-dopaminergic conditions and which may lead to superior effect of clozapine on broadly varied conditions of patients with schizophrenia

ID: 2117557

NEW DEVELOPMENTS IN BASIC RESEARCH OF GENE-ENVIRONMENT INTERACTION: ROLE FOR IMMUNITY AND INFECTION

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Background: Various immune and infectious factors contribute to the pathogenesis of schizophrenia via complex interactions with genetic risk factors in susceptible individuals. We have been modeling relevant gene-environment interaction (GEI) in mice that express a genetic risk factor, mutant Disrupted-In-Schizophrenia 1 (DISC1), and are exposed to maternal immune activation (MIA) or Toxoplasma gondii (T. gondii) infection to model GEI associated with psychotic disorders.

Methods: Separate cohorts of mutant DISC1 mice and their control littermates were 1) prenatally exposed to MIA using poly I:C at embryonic day 9; 2) exposed to vehicle or T. gondii infection at postnatal day 30 (juvenile) or 60 (adult). We evaluated the neurobehavioral, immune and molecular changes in control and mutant DISC1, exposed and unexposed mice at postnatal day 90.

Results: Only mutant DISC1 mice exposed to MIA demonstrated the brain and behavioral alterations consistent with aspects of affective disorders. These behaviors were associated with decreased volumes of the amygdala and periaqueductal gray matter and density of spines on dendrites of granule cells of the hippocampus. MIA in mutant DISC1 mice affected GSK-3β and NF-κB-dependent transcription activation.

The brain and behavior effects of chronic T. gondii infection are dependent on the time of exposure to the parasite, e.g., decreased (juvenile) vs. increased (adult) pre-pulse inhibition of the acoustic startle following administration of the psychostimulant, MK-801, and associated increased (juvenile) vs. decreased (adult) expression of the NR1 subunit of the NMDA receptor in the frontal cortex. Chronic T. gondii infection in juvenile mutant DISC1 mice produced hypoactivity in open field in a GEI manner. Importantly, some behavioral effects of T. gondii infection can be explained by the host's immune response as those phenotypes were still resent in mice exposed to immunogenic but replication-deficient parasites.

Conclusion: Our results suggest that mutant DISC1 and MIA interact to produce a range of behavioral, brain and molecular changes consistent with mood disorders in humans. Our studies with T. gondii infection demonstrate neurobehavioral effects of GEI in infected mutant DISC1 mice and indicate that the time of exposure and immune response to the pathogen play major roles in shaping the abnormalities resembling schizophrenia-like phenotypes.

ID: 2086218

THE SYSTEMICALLY ACTIVE KYNURENINE AMINOTRANSFERASE II INHIBITOR BFF816 ATTENUATES CONTEXTUAL MEMORY DEFICIT INDUCED BY PRENATAL KYNURENINE ELEVATION IN RATS

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Background: Schizophrenia (SZ), a catastrophic psychiatric disorder, results from a combination of genetic and environmental factors. The tryptophan metabolite kynurenic acid (KYNA) is an endogenous antagonist of α7 nicotinic acetylcholine and NMDA receptors, and increases in brain KYNA have been implicated in the pathology of SZ.

Methods: Based on the neurodevelopmental hypothesis of SZ, we evaluated the possible etiological role of KYNA in the disease by adding the KYNA precursor kynurenine (kyn) (100 mg/day) to the chow fed to pregnant dams from embryonic day (ED) 15 to ED 22 (control: ECon; kyn-treated: EKyn). Upon termination of the treatment, all rats were fed normal rodent chow until the animals were evaluated in adulthood [postnatal days 56–80]. This prenatal treatment causes increases in hippocampal KYNA and hippocampus-dependent cognitive dysfunctions in adulthood (Pocivavsek et al., Psychopharmacology, 2014). We now examined whether acute administration of BFF816, a systemically active inhibitor of kynurenine aminotransferase II (KAT II), a major KYNA-synthesizing enzyme in the brain (Wu et al., Schiz. Bull., 2014), normalizes neurochemistry and behavior in adult EKyn animals.

Results: Microdialysis in the hippocampus of unanesthetized adult rats revealed that basal extracellular KYNA levels were modestly but significantly elevated in EKyn rats (ECon: 2.3 ± 0.1 nM; EKyn: 2.8 ± 0.1 nM; n = 7–8/group; $P < 0.01$). In contrast, extracellular glutamate was decreased (ECon: 1.9 ± 0.03 μM; EKyn 1.6 ± 0.02 μM; n = 4–5/group; $P < 0.001$). BFF816 (30 mg/kg), administered orally after baseline collections, reduced KYNA levels in both ECon and EKyn adult rats, reverting KYNA in EKyn animals to baseline levels, and also raised glutamate levels in both ECon and EKyn adult rats (189% and 169%, respectively). In separate adult EKyn rats, we confirmed contextual memory deficits, evidenced as decreased avoidance latency during the retention trial of the passive avoidance paradigm (ECon: 118 ± 20 s; EKyn: 43 ± 13 s; $P < 0.05$). Pretreatment with BFF816 (30 mg/

kg, p.o.) 5 min prior to acquisition testing on day 1 attenuated this memory impairment (ECon: 100 ± 21 s; EKyn: 116 ± 23 s; n = 14–17/group).
Conclusion: Collectively, our results demonstrate that acute inhibition of KAT II in adulthood may be sufficient to overcome contextual memory deficits that arise as a consequence of elevated brain KYNA in early brain development.
ID: 2077115

THE ROLE OF NMDA RECEPTOR CO-AGONISTS IN CONDITIONED PLACE PREFERENCE AND LOCOMOTOR SENSITIZATION TO COCAINE: IMPLICATIONS FOR CO-MORBID SCHIZOPHRENIA AND SUBSTANCE ABUSE

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Background: Schizophrenia is associated with high susceptibility to substance abuse. Recent research suggests that dysregulation of NMDA receptor function via availability of receptor co-agonists, which bind at the allosteric glycine modulatory site (GMS), may play a role in the pathopyhsiology of both schizophrenia and drug addiction.
Methods: Our laboratory has developed two transgenic mouse lines to test the validity of this hypothesis. The first line is a constitutive knockout of the synthetic enzyme that produces D-serine, serine racemase (SR). Null mutants (SR-/-) exhibit NMDA receptor hypofunction, as D-serine serves as a NMDA receptor co-agonist. The second line is a constitutive knockdown of glycine transporter 1 (GlyT1), which regulates synaptic glycine, another NMDA receptor co-agonist. Heterozygous mutants (GlyT1+/-) exhibit NMDA receptor hyperfunction. We characterized the behavior of these lines in a cocaine-induced (20 mg/kg) conditioned place preference (CPP) and locomotor sensitization paradigm. Then, both GlyT1+/- and SR-/- mice were tested in the cocaine-induced CPP paradigm used previously, however, GlyT1+/- mice were treated chronically (17 days) with gavestinel (10 mg/kg on Day 1, 5 mg/kg on Days 2–17), a GMS antagonist, while SR-/- mice were treated chronically (17 days) with D-serine (300 mg/kg on Day 1, 150 mg/kg on Days 2–17).
Results: Briefly, compared to WT mice, GlyT1+/- mice displayed hastened extinction of cocaine-induced CPP, accompanied by robust cocaine-induced reinstatement, with no change in locomotor sensitization to cocaine. Interestingly, SR-/- mice appeared to immediately forget the learned preference, did not exhibit cocaine-induced reinstatement, and displayed attenuated locomotor sensitization to cocaine compared to WT and GlyT1+/- mice. Gavestinel caused GlyT1+/- mice to immediately forget the learned preference, had no effect on cocaine-induced reinstatement, and tended to attenuate locomotor sensitization to cocaine. In SR-/- mice, D-serine caused an aversion to the cocaine-paired side during extinction, had no effect on reinstatement of cocaine-induced CPP, and tended to reverse the deficit in locomotor sensitization to cocaine.
Conclusion: These results further elucidate the role of NMDA receptor co-agonists in cocaine-induced CPP and locomotor sensitization and may shed light on the neural mechanisms underlying co-morbid schizophrenia and substance abuse. Also, these findings may indicate that D-serine could be an effective treatment for cocaine abuse.
ID: 2092980

LACK OF CLINICAL ANTIPSYCHOTIC EFFICACY WITH PDE10A: SIFTING CLUES FROM THE ASHES

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Background: The past 25 years have seen well over a dozen circuit- or pathophysiology-based non-D2 mechanisms tested in schizophrenia yet no novel treatments have advanced into routine clinical use. Although patient selection, trial design and clinical endpoints are receiving increased attention as contributors to this disappointing record, it is also important to consider how these prior efforts can inform future drug development programs. PF-2545920, a selective inhibitor of phosphodiesterase-10A (PDE10A), was recently reported to be ineffective as a monotherapy in acute exacerbation of schizophrenia.
Methods: The rationale for the clinical testing of a PDE10A inhibitor was developed in preclinical studies comparing this mechanism and D2 receptor blockade.
Results: PDE10A is highly expressed in both types of striatal projection neurons where it regulates cAMP and cGMP signaling. Like D2 antagonists, PDE10A inhibition counters the reduction in indirect pathway activity produced by dopamine and enhances the sensitivity of D2 expressing striatopallidal neurons to cortical stimulation. Unlike D2 antagonists, PDE10A inhibition augments the effects of dopamine signaling on the D1 expressing direct pathway. PDE10A inhibitors are active in preclinical models of antipsychotic efficacy including amphetamine- or PCP-stimulated locomotion, CAR and amphetamine-disrupted auditory gating. The clinical failure of PF-2545920, despite its neurochemical, behavioral and electrophysiological similarities to D2 blockade, suggests gaps in our understanding of the clinical efficacy of D2 antagonist. Additional preclinical and clinical studies examining the differences between PDE10A inhibition and D2 blockade have initially focused on the consequences of direct pathway activation. In contrast to the effects of Haloperidol, both the disruption of CAR and the cataleptogenic activity of PF-2545920 are prevented by D1 agonist administration suggesting that the antipsychotic-like activity of PDE10A inhibition is uniquely sensitive to elevated drive on the direct pathway. Studies with selective cholinergic agents indicate that the disinhibition of striatal cholinergic interneurons during D2 blockade may be important in mitigating this complication for currently used antipsychotics.
Conclusion: The characterization of this and other distinct circuitry effects of D2 antagonism and PDE10A inhibition has the potential to identify critical features of antipsychotic efficacy that will direct future efforts in this field.
ID: 2097829

APPROACHES TO CREATING AN ANIMAL MODEL OF PSYCHOSIS: REVERSE TRANSLATION AND GENETIC RISK

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Background: Schizophrenia is a devastating mental illness affecting approximately 1% of the world's population. Schizophrenia is characterized by positive symptoms, also referred to as psychosis, as well as negative symptoms and cognitive symptoms. Analysis of post-mortem human tissue from schizophrenic patients revealed a specific pattern of hippocampal changes which we believe may underlie the symptoms of psychosis: reduced GluN1 in dentate gyrus, increased GluN2B-containing NMDA receptors and increased PSD95 in CA3, and increased spines on the CA3 pyramidal neurons. In these studies we compare two distinct methods at arriving at a model of psychosis in mice, and assess relevant behavioral and biochemical markers indicative of psychosis.
Methods: We use two strategies to arrive at an animal model of psychosis: the first in a reverse translational model, in which mice express a specific cellular phenotype consistent with data from human schizophrenics, a decrease in the GluN1 receptor subunit in the dentate gyrus. The second method combines a model of genetic risk, DISC1 deficiency, with environmental risk, either neonatal or adolescent stress. These mice were then tested in a battery of behavioral paradigms, and their brains were examined for biochemical markers similar to those seen in humans.

Results: Mice with decreased GluN1 expression in the dentate gyrus show a behavioral phenotype displaying aberrant declarative memory and deficits in prepulse inhibition. These mice, when treated with phencyclidine, also display the defining molecular characteristics. Likewise, the combination of genetic risk and environmental stress, especially when exposed to this stress neonatally, also reveal deficits in these behaviors, to an extent greater than either of these factors alone. Analysis of the molecular changes in these animals is currently underway.
Conclusion: Our results suggest the molecular signature of schizophrenia, as seen in the hippocampus of human post-mortem tissue, underlies the behaviors of psychosis, and this effect can be induced in experimental animals through the combination of risk-associated factors.
ID: 2118048

INTERPLAY OF OXIDATIVE STRESS PATHWAYS AND GLUTAMATE NEUROTRANSMISSION — GLUTATHIONE AS A NEURAL RESERVOIR OF GLUTAMATE

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Background: Glutamate is the principle excitatory neurotransmitter, present at the majority of cortical synapses, and aberrant glutamatergic signaling has been implicated in schizophrenia pathogenesis. Aberrant levels of the antioxidant, glutathione, are also increasingly recognized in schizophrenia, including in medication naive subjects. Glutathione, a tripeptide composed of the amino acids glutamate, glycine, and cysteine, serves important cofactor roles in antioxidant defense and drug detoxification. Because of the considerable quantity of brain glutathione and its rapid turnover, we hypothesized that glutathione is a physiologically significant glutamate reservoir, contributing to maintenance of glutamate levels, and possibly glutamate neurotransmission.
Methods: We quantified glutamate, glutathione, oxidative stress and cytotoxicity in primary cortical neurons, HT22 hippocampal neurons and PC12 after treatment with four distinct drugs that target three different enzymes of the glutathione cycle. Electrophysiological recordings of miniature excitatory postsynaptic currents (mEPSC) and depolarization induced calcium fluxes were assessed after treating with molecular inhibitors of enzymes of the glutathione cycle.
Results: Blocking enzymes that liberate glutamate from glutathione (OPLAH, GGT) leadd to decreases in neuronal glutamate, accompanied by decreases in mEPSC and depolarization induced calcium fluxes. However, inhibiting GCL, which uses glutamate to synthesize glutathione, results in glutamate accumulation, increased mEPSC frequency, and augmented depolarization associated calcium flux. Effects were not the result of cytotoxicity, as glutamate fluxes occur without accumulation of oxidative stress or decreased cell viability. Sulforaphane, a plant derived isothiocyanate, acutely increases glutathione and modulates glutamate, and may be a candidate treatment for neuropsychiatric disorders.
Conclusion: The glutathione cycle represents a significant reservoir of glutamate and suggests bridges between glutamatergic dysfunction and oxidative stress.
ID: 2122589

NMDA RECEPTOR-MEDIATED CHANGES IN PYRAMIDAL CELL INHERENT MEMBRANE EXCITABILITY

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Background: Neuronal activity at gamma frequency is impaired in schizophrenia (SZ) and is considered critical for cognitive performance. Such impairments are thought to be due to reduced N-Methyl-D-Aspartate Receptor (NMDAR)-mediated inhibition from parvalbumin (PV) interneurons, rather than a direct role of impaired NMDAR signaling on pyramidal neurons. However, recent studies suggest a direct role of pyramidal neurons in regulating gamma oscillations. In particular, a computational model has been proposed in which phasic currents from pyramidal cells could drive synchronized feedback inhibition from interneurons. As such, impairments in pyramidal neuron activity could lead to abnormal gamma oscillations. However, this computational model has not been tested experimentally and the molecular mechanisms underlying pyramidal neuron dysfunction in SZ remain unclear.
Methods: In the present study, we tested the hypothesis that SZ-related phenotypes could arise from reduced NMDAR signaling in pyramidal neurons using forebrain pyramidal neurons specific NMDA-R1 knocked-out mice.
Results: The mice displayed increased baseline gamma power as well as social and cognitive impairments. These phenotypes were associated with increased pyramidal cell excitability due to changes in inherent membrane properties. Interestingly, mutant mice showed decreased expression of GIRK2 channels, which has been linked to increase neuronal excitability.
Conclusion: Our data demonstrate for the first time that NMDAR hypofunction in pyramidal cells is sufficient to cause electrophysiological, molecular, neuropathological and behavioral changes related to SZ.
ID: 2118489

REVERSE TRANSLATION ANIMAL MODEL OF HIPPOCAMPAL DYSFUNCTION IN SCHIZOPHRENIA

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Background: Animal models for psychosis have been inadequate because the cellular and molecular characteristics of the condition itself have been obscure. As the disease neurobiology is advancing, it is becoming possible to develop animal models through reverse translation, mimicking the biology of the human condition. We have focused on modeling hippocampal pathology and its learning and memory component as it informs psychosis.
Methods: To explore a reverse translation animal model, we took two approaches. We crossed a POMC-Cre mouse line with a floxed P-GluN1 mouse to create a DG-specific knock down of GluN1 protein in the animal. Next we modified this mouse model using a 4-week phencyclidine (PCP) paradigm.
We tested hippocampus dependent behaviors (i.e. fear conditioning) as well as pre pulse inhibition. In order to evaluate our target proteins western blots were performed.
Results: The DG-specific GluN1 knock down animals have reduced levels of GluN1 restricted to DG (WT n=7; KO n=7). Behaviorally, these mice show decreased pre-pulse inhibition, reduced learning in the Morris Water Maze, increased freezing in a fear conditioning paradigm (Contextual FC p=0.04; Cued FC p=0.004) and an increased latency to respond in the passive avoidance paradigm (p=0.01). In tissue, we met the tissue phenotype of reduced GluN1 in DG but failed to generated the psychosis fingerprint of increased synaptic strengthen marker in CA3 at the NMDA receptor.
However, the 4-week PCP animal model showed both the behavioral phenotype of psychosis (noted above) and molecular evidence reflecting both the DG GluN1 reduction and the psychosis finger-print (increased GluN2B: WT n=7; KO n=7; p=0.035) in CA3.
Conclusion: Based on our human studies, we have developed the model that in schizophrenia psychosis CA3 is constitutively hyperactive as a risk factor for psychosis. When the hypersensitive molecular targets in

CA3 get sufficiently over-whelmed by the excitatory mossy fiber pathway and/or other afferents, then psychosis can result. We have suggested that psychosis can result from the hyperactivity-induced increased associations, with occasional mistaken associations, resulting in false memories, some with delusional content, which then get laid down in long-term memory—what we would then describe as delusions and hallucinations. Because this psychosis model includes behaviors and molecular changes which can both be recreated and modeled in an animal, we can test molecular correlates of these conditions using a mouse model.
ID: 2114625

Biomarkers: Electrophysiology; Eye Movement Physiology

TRANSDIAGNOSTIC PSYCHIATRIC SYMPTOMS RELATED TO VISUAL EVOKED POTENTIAL ABNORMALITIES

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Background: Early visual processing abnormalities have been reported across a range of psychotic and mood disorders, but are typically examined within a particular disorder. The current study used a novel transdiagnostic approach to examine broad diagnostic classes, clinician-rated current symptoms, and self-reported personality traits in relation to visual processing abnormalities.
Methods: We examined transient visual-evoked potentials (VEPs) using electroencephalography from 48 adults from the community (mean age = 35.88; 56% female), representing a wide range of psychotic, mood, and anxiety disorders, including a subset with no disorder. Stimuli were low contrast 8 x 8 check arrays presented on green and red backgrounds.
Results: Individuals with a schizophrenia-spectrum disorder had a reduced mean amplitude of the VEP P1 component in the red background condition, as compared to the rest of the sample. In contrast, there was no difference in P1 amplitude between either individuals with a history of psychosis or a history of a mood disorder without psychosis when compared to remainder of sample. Across entire sample, individuals with higher clinician-rated emotional withdrawal or higher self-reported eccentric/disorganized behavior had a reduced P1 amplitude with the green background. The N1 amplitude did not relate to any psychiatric variable.
Conclusion: While preliminary, it appears that a reduced P1 amplitude may be particularly prominent in schizophrenia-spectrum disorders and, regardless of diagnosis, individuals who have high levels of emotional withdrawal or eccentric/disorganized behavior. This study also provides an example of a novel methodological framework for examining a broader array of biomarkers using an RDoC approach.
This project was funded by an internal university "SEED" grant to author JSB from the University of Central Florida College of Sciences and Office of Research and Commercialization.
ID: 2088045

A SYSTEMATIC REVIEW OF STUDIES ON HEART RATE VARIABILITY IN SCHIZOPHRENIA

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Background: Increased cardiac mortality and morbidity is reported in patients with schizophrenia. Several factors such as physical inactivity, substance abuse and adverse effects of antipsychotics are hypothesized to have causative role in this phenomenon. Apart from the above factors dysregulated autonomic function might contribute to increased risk of cardiac death. Heart rate variability (HRV) is a non-invasive tool to characterize cardiac regulation. Several authors have reported aberration in the HRV parameters in schizophrenia patients as well as first degree relatives of patients. This systematic review aims at summarizing the evidences on various HRV measures in schizophrenia.
Methods: We conducted systematic review in the pubmed using key terms "schizophrenia", "Heart rate variability", "HRV". Total of 83 articles were retrieved. Abstracts were screened for the relevance. The studies which included at least one measure of HRV were included. Forty studies met the inclusion criteria.
Results: Majority of the studies reported decrease in the high frequency (HF) parameter of HRV suggesting loss of vagal tone. However, low frequency (LF) and LF/HF ratio findings were notably discordant, as studies reported either increased values or negative findings. Similarly, association between HRV measures and symptom severity was not consistent. Abnormalities in HRV were noted both in drug naïve patients and medicated patients. First degree relatives of schizophrenia patients demonstrated aberration in HRV measures.
Conclusion: Overall results indicate dysregulation of vagal function in schizophrenia. Evidences indicate that HRV abnormality particularly vagal tone disruption might be a trait marker. These results might have implication in understanding pathophysiology of schizophrenia as well as in developing therapeutics such as vagal nerve stimulation. HRV might be a good tool to study the cardiovascular adverse effect of antipsychotics.
ID: 2075656

ERRORS IN MEMORY GUIDED SACCADES COULD BE AN OCULOMOTOR ENDOPHÉNOTYPIC MARKER FOR SUBJECTS BELONGING TO THE SCHIZOPHRENIA SPECTRUM?

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Background: Landgraf et al. (2007) suggested that abnormalities in memory guided saccades in biological relatives of schizophrenic patients could be related for an endophenotypic marker.
Methods: Memory guided saccades were recorded in four groups of subjects: 30 patients with schizophrenia (PANNS mean = 61.4 ± 3.6; mean age 27.03 ± 0.8 years); 22 non psychotic healthy siblings (age: 27.18 ± 1.8 years); 15 subjects at high risk of developing schizophrenia (age: 21 ± 0.6 years) and 31 controls (age: 25.5 ± 0.7 years). Binocular eye movements were recorded using an infrared video-oculography system (MobilEBT®). The amplitude of memory saccades was randomly (6°, 12°, 18°) to the right and to the left side and the period of memorization was also randomly chosen (1, 2, 4 and 8 sec). We measured the percentage of errors, the peak velocity, the primary and the final gain of memory guided saccades.
Results: Patients, siblings and high risk groups showed significant higher error rates in performing memory guided saccades with respect to control group; the primary gain was significantly greater in high risk group compared to patients and siblings groups.
Conclusion: The alterations of the memory guided saccades in the high risk group supports the hypothesis of an oculomotor endophenotypic marker. The high errors reported in memory guided saccades performance could be related to a deficit in saccade planning and triggering and to a lack of control of inhibitory processes according to Clementz et al.

(1994), McDowell et al. (2001) and Landgraf et al. (2007). The gain difference found in patients and siblings compared to high risk group could be due to abnormalities in working memory. A larger sample of subjects at high risk of developing schizophrenia is needed to confirm these findings.
ID: 2083285

MOVEMENT ABNORMALITIES PREDICT TRANSITIONING TO PSYCHOSIS IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Improving upon the predictive validity of determining the transition from high risk to actual psychosis is a primary aim of early intervention research and previous work (e.g., Mittal & Walker, 2007) has suggested that premorbid spontaneous dyskinesias or movement abnormalities may be one possible predictor.
Methods: Dyskinetic movements were assessed with the Abnormal Involuntary Movement Scale (AIMS) at baseline of a multisite longitudinal study of 148 neuroleptic-naïve individuals at clinical high risk (CHR) of developing psychosis. All participants met Criteria of Prodromal States based on the Structured Interview for Psychosis-Risk Syndromes (SIPS; McGlashan, Walsh, & Woods, 2010); 145 (97.98%) met attenuated positive symptom syndrome (APSS) criteria, one (0.67%) met genetic risk and deterioration (GRD) criteria, and two (1.35%) met both APSS and GRD criteria. APSS includes the onset or worsening of subthreshold level disturbances in thought content, thought processes, and/or perceptual abnormalities over the past year whereas GRD requires either a first degree relative with a psychotic disorder diagnosis or the participant having schizotypal personality disorder in conjunction with at least a 30% drop in functioning on the General Assessment of Functioning scale over the past year. Mean age of the sample was 19.77 (4.60) years and the majority was Caucasian (77.00%).
Results: Twenty-eight (18.92%) individuals transitioned to a psychotic disorder over the course of the study. Mann-Whitney U group comparisons between transitioned and non-transitioned individuals indicated that, relative to those that were not observed to transition, participants that developed a psychotic disorder exhibited greater baseline spontaneous dyskinesias of the facial muscles, jaw, upper extremity, trunk, and, at a trend-level, tongue. Moreover, increased dyskinetic movements at baseline resulted in a more than two-fold increase in odds (OR = 2.22, 95% CI = 1.19–4.15) of developing a psychosis for each 1-point increase in AIMS scale score.
Conclusion: These findings suggest (a) that dyskinetic movements may constitute primary features of emerging psychosis rather than pure artifact of neuroleptic pharmacotherapy and (b) that individuals with greater premorbid dyskinetic movements may comprise a subset of CHR individuals at inordinate risk to decompensate into psychosis.
ID: 2084668

DEVELOPMENT OF A BLOOD-BASED MOLECULAR BIOMARKER TEST FOR IDENTIFICATION OF SCHIZOPHRENIA PRIOR TO DISEASE ONSET

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Background: No validated blood tests exist to identify individuals at risk of developing schizophrenia. The aim of our work was to identify, validate and evaluate the performance of a panel of serum biomarkers for prediction of schizophrenia.
Methods: The study consisted of three phases comprising 957 individuals. Phase I was a meta-analysis involving five independent cohorts of 127 first-onset antipsychotic-naive schizophrenia patients and 204 controls to identify a panel of diagnostic serum biomarkers. Phase II involved validation of the panel using two additional cohorts of 93 schizophrenia patients and 88 controls. Phase III was predictive testing of the panel in two independent retrospective cohorts: (1) USA military personnel who were diagnosed subsequently with schizophrenia (n=75), bipolar disorder (n=110), or remained healthy controls (n=184); (2) help-seeking individuals with prodromal symptoms who later developed (n=18) or did not develop (n=58) schizophrenia. Diagnostic/predictive performance of the serum biomarker panel was measured by the ROC-AUC (sensitivity and specificity).
Results: An optimal set of 26 serum biomarkers was selected by meta-analysis of the five patient cohorts. Testing this panel using the two validation cohorts gave an AUC of 0.97 [95% CI=0.95–1.00] for schizophrenia detection. Analysis of the military cohort yielded an AUC of 0.90 [0.86–0.95] for pre-schizophrenia and 0.53 [0.46–0.61] in pre-bipolar disorder personnel, indicating that this panel only showed high predictive performance for detection of schizophrenia. The AUC was 0.82 [0.71–0.93] for prediction of schizophrenia conversion in the psychiatric help-seeker cohort, and this increased to 0.90 [0.82–0.98] when CAARMS positive subscale symptom scores were incorporated into the model.
Conclusion: We report the development of a serum biomarker panel with excellent predictive performance to identify patients before disease onset. The current findings may represent the first successful steps towards meeting the critical need for early intervention in psychiatry. Further developments of a combined molecular/symptom-based test will aid clinicians in identification of vulnerable patients early in the disease process, allowing more effective therapeutic intervention. This research was supported by the Stanley Medical Research Institute and the EU-FP7 SchizDX research programme.
ID: 2085255

TEMPORAL AND FRONTAL AUDITORY ENCODING ABNORMALITIES AND ASSOCIATED GRAY-MATTER LOSS PREDICT ATTENTION DEFICITS IN SCHIZOPHRENIA

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Background: Superior temporal gyrus (STG) auditory encoding abnormalities, STG gray-matter loss, and cognitive deficits are all candidate schizophrenia (SZ) endophenotypes. Studies showing associations between STG function, STG gray matter, and cognition indicate that these endophenotypes are connected. As frontal regions are involved in auditory encoding, the present study evaluated associations between whole-brain auditory encoding network attributes (function and structure) and attention in healthy controls (HC) and SZ to understand how brain biomarkers contribute to cognitive endophenotypes.
Methods: Magnetoencephalography (MEG) recordings to click stimuli were obtained from 69 SZ and 70 HC. Vector-based Spatial-temporal Analysis using L1-minimum-norm provided whole-brain maps of activity from 80-130ms (M100). Gray-matter cortical thickness (CT) and a composite measure of attention (mean z-scores from Digit Span Forward, Spatial Span Forward, and CPT Clinical Index) were also obtained.
Results: SZ had weaker M100 responses than HC in bilateral STG and bilateral inferior frontal gyrus (IFG). In contrast, SZ had stronger M100 activity than HC in left superior frontal gyrus (SFG). In SZ, STG and SFG activity was related, with stronger left SFG M100 responses associated with weaker left STG M100 responses. Reduced CT in SZ versus HC was observed at all areas showing weaker M100 activity in SZ. Increased CT predicted stronger M100 activity in bilateral STG and right IFG, although this function-structure relationship was absent in SZ for the left STG. In regions where SZ showed weaker M100 activity than HC, stronger M100 activity and increased CT predicted better attention, with associations again absent in SZ for the left STG. Finally, stronger M100 activity in left SFG (area where SZ > HC) predicted poorer attention in both group.
Conclusion: Present findings suggest that abnormally increased left SFG M100 activity in SZ may disrupt early left STG encoding, with increased left SFG activity (and decreased left STG activity) associated with cognitive impairment. Although weak M100 responses in SZ were generally associated with CT pathology, a lack of left STG function-structure-cognition associations in SZ indicated greater disruption in left STG versus other auditory network nodes. Present findings suggest that treatments targeting gray-matter loss and/or normalizing auditory encoding network activity, with a focus on left STG, may improve cognitive ability in SZ.
ID: 2117984

ANTIBODIES AGAINST GLIADIN BUT NOT ANTIBODIES AGAINST DEAMINATED GLIADIN PEPTIDES ARE FREQUENT IN SCHIZOPHRENIA PATIENTS

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Background: An association between gluten sensitivity and schizophrenia has been reported, but it is unclear which serum biomarkers of gluten sensitivity are elevated. The presence of antibodies against either native gliadin protein (gliadin antibodies or AGA) or deaminated gliadin peptides (DGP antibody). The DGP antibody assay is a more specific and sensitive diagnostic test for celiac disease. Here we compare presence of gliadin and DGP antibodies in sera of schizophrenia patients.
Methods: Patients were referred by the Johns Hopkins Hospital Community Psychiatry Program or the Maryland Psychiatric Research Center for a double-blind randomized controlled trial of a gluten-free diet for treatment of gliadin-positive schizophrenia. All subjects had a diagnosis of schizophrenia or schizoaffective disorder and were between ages 18 and 64, both sexes were included. Sera were analyzed for antibodies against Gliadin IgA and IgG (INOVA 708650, 708655), DGP IgA and IgG (704520, 704525) and h-tTG IgA (708760). Results were interpreted according to the manufacturer guidelines (that is negative = less than 20U, weak positive = 20–30 U and moderate to strong positive = over 30U).
Results: Out of 40 schizophrenia patients only one (2.5%) was weakly positive for DGP IgA antibodies and none were positive for DGP IgG, which is not statistically different from the 2.1% and 0.6% positivity in non-celiac controls reported by the manufacturer. However, 5 out of 40 of schizophrenia patients (12.5%) were positive for gliadin IgA (2 strongly positive) and 18 out of 40 patients (45%) were positive for gliadin IgG (14 strongly positive). All 40 patients were negative for tTg IgA antibodies, excluding the possibility of undiagnosed Celiac Disease. According to the manufacturer only 3% or 5% of normal healthy controls are positive for gliadin IgA or IgG antibodies, respectively.
Conclusion: Forty-five percent of schizophrenia patients are positive for gliadin IgG antibodies and 12.5% are positive for gliadin IgA antibodies, a much higher proportion than expected based on normal healthy controls data. All patients except one weakly positive were negative for DGP IgG and IgA antibodies. The exclusive presence of anti-gliadin antibodies rather than DGP antibodies in the absence of tTg antibodies, underscores that the pathogenetic mechanism for gluten sensitivity associated with schizophrenia is different from that for Celiac disease. This work was supported by NIMH R34 MH100776-01.
ID: 2117841

PROBABILISTIC ASSESSMENTS OF TRANSITION RISK IN THE PSYCHOSIS PRODROME

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Background: The relatively poor predictive accuracy of clinical assessments used to predict the transition of individuals at clinical high risk (CHR) to a first episode of psychosis (FEP) limits clinical decision-making around the choice of appropriate interventions and is reflected in clinical guidelines promoting a 'watch and wait' approach.
Methods: Using data from published studies we developed a predictive model of transition to psychosis based on the odds ratio form of Bayes' rule. We simulated scenarios at low pretest probability (0.075) reflecting the general public and moderate pretest probability (0.5) reflecting a clinical sample, where clinical interview, neurocognitive testing, structural magnetic resonance imaging (MRI) and electrophysiology are part of the initial assessment process of a CHR individual.
Results: Simulation suggests that for members of the general population reporting occasional psychotic symptoms, at least 2 assessments (clinical

interview for UHR criteria + cognitive assessment) are necessary to confidently determine low risk for transition to psychosis (probability < 0.2). To confidently identify individuals at high risk of transition (probability > 0.8) at least 4 multimodal assessments are required. In a clinical sample with an increased base rate of transition at least three modalities of investigation are required to arrive at clinically meaningful conclusions. Adding an additional investigation appears particularly important for the group of patients whose first three assessments are inconsistent. Changing the sequence of assessments had little impact on overall findings in the simulation of general populations. However, at the higher base rate in clinical samples, performing MRI and electrophysiology before clinical and cognitive assessments produces strong predictive accuracy for some individuals. In those with inconsistent tests at least 4 assessments are still required to produce clinically meaningful prediction of psychosis risk.

Conclusion: Our findings indicate that for most at-risk patients, at least three types of assessment are necessary to arrive at a clinically meaningful differentiation into high, intermediate, and low-risk groups. In particular, patients with equivocal results in the initial assessments require additional diagnostic testing to produce an accurate risk profile. This suggests that multimodal assessment of patients at CHR of psychosis is required to accurately predict the risk of transition.

ID: 2118472

CONCEPTUAL APPROACHES TO THE IDENTIFICATION OF PSYCHOSIS TAXA, BIOTYPES AND OTHER CLASSIFIERS

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Background: Classification and treatment of brain diseases subsumed by psychiatry rely on clinical phenomenology. Available data indicate this scheme is untenable. Other branches of medicine have demonstrated that biological differentiation can result in classification of diseases with remarkably similar clinical presentations and pathology into distinct disorders. Clearly there is overlap in susceptibility across the psychoses, and considerable similarity between different psychotic disorders on symptoms, illness course, neurocognition, psychophysiology, and neurobiology. It is probable that clinical phenomenological diagnoses fail to capture neurobiologiocal distinctiveness, and that such distinctiveness is obscured by reliance on this diagnostic approach as gold standards for testing the utility of neurobiological variables.

Methods: B-SNIP consortium sites recruited, fully clinically characterized, and obtained multivariate biomarker panels on psychosis probands (n=711), their first-degree relatives (n=883) and demographically comparable healthy subjects (n=278). Six laboratory tasks that assess brain function at the neuro-cognitive/perceptual level were used for subsequent analyses: (i) BACS, (ii) Pro- and (iii) Anti-saccades, (iv) stop signal, and auditory ERP (v) paired-stimuli and (vi) oddball tasks. Individual and multivariate composite variable within-subject repeatability (e.g., intra-subject reliability estimates) and group membership classification accuracy (for DSM diagnoses and a novel psychosis subgroup scheme we call psychosis Biotypes) will be determined for these variable sets.

Results: Analyses address the following specific hypotheses:

1. Individual variable repeatability are moderate to high, too high to account for the large intra-DSM diagnostic group variance seen for these individual variables.
2. Composite variable repeatability is higher than for individual variables, but these composites do not help sufficiently to reduce DSM diagnostic group variance on these composites.
3. No individual variable is superior to composites for classifying individual cases into their respective diagnostic group. This is true for both DSM diagnoses and for the novel Biotype subgrouping scheme.

Conclusion: The within DSM diagnosis variance seen on reliable and neurobiologically meaningful psychosis biomarkers leads to the thesis that classification and conceptualization of the psychoses may require, at least partially, foregoing reliance on clinical phenomenology for their primary definition.

ID: 2118612

MODULATION OF VISUAL CORTEX ACTIVITY IN PSYCHOSIS AS A FUNCTION OF COGNITIVE CONTROL DURING SACCADIC TASKS

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Background: An highly studied behavior is the antisaccade response. Psychosis probands and their family members (notably in SZ families) make more errors than normal during such tasks, suggesting anti-performance may index constitutional liability for SZ. Antisaccade data are consistent with the thesis of a primary, perhaps genetically-mediated, deficit in prefrontal control of behavior among psychosis cases. Although deceptively simple, the task of looking away from novel targets depends on distinct component processes that are difficult to separate using behavioral data alone. Decomposing the elements of task performance, and their distinct neural substrates, is crucial for achieving the goal of using anti-performance as an optimally effective psychosis biomarker.

Methods: To decompose neural elements of performance, we used variations of pro- and anti-tasks while measuring the visual steady-state response (vSSR) with dense array EEG during response preparation. Subjects were 57 healthy, 43 SZ, and 43 bipolar disorder with psychosis (BDP) cases. Three checkerboards (one at central fixation and 2 at possible peripheral target locations) were presented. The central checkerboard was luminance modulated at 15 Hz for 5 sec prior to a saccadic response, with subjects knowing on every trial whether they were to perform a pro- or anti-response. Neural activity at the oscillation frequency during baseline (before trail onset) and steady state stimulation (but before peripheral cue onset) were quantified using frequency domain analyses.

Results: Psychosis subjects made more errors than normal on anti-saccade trials.

During baseline:

1. Some psychosis cases had lower activity than healthy subjects prior to eventual pro- trials at the steady-state frequency (before trial onset).
2. Prior to anti-saccade trials, however, the groups had more similar activity at the eventual steady-state oscillation frequency.

During stimulation:

1. Psychosis subjects had lower neural activations than healthy subjects (less increase above baseline across both pro- and anti-trials; main effect of group).
2. Both healthy and BDP subjects increased activity on anti- compared to pro-trials in relation to the central stimulus; SZ showed little evidence of such a neural modulation (group by task interaction).

Conclusion: Different neural features can account for similar manifestations of behavioral control failures across psychosis diagnoses. Comparing baseline and stimulus-evoked responses is critical for appreciating these differences.

ID: 2119130

MISSING STIMULUS MMN IN SCHIZOPHRENIA: FREQUENCY DECOMPOSITION REVEALS DEFICIENT AUDITORY GESTALT FORMATION

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Background: Formation of solitary percepts is necessary for interpretation of auditory patterns, for example, in speech and music perception. Deviance from expectations based on perceptual grouping is reflected in the auditory mismatch negativity (MMN). MMN can be generated even when the deviant stimulus is no stimulus at all (i.e. an expected tone is missing). The degree to which this response is truly related to violation of an auditory gestalt vs. an ongoing oscillation due to stimulus repetition is debated.
Methods: Oscillatory activity related to auditory patterns was examined in a missing stimulus MMN paradigm. Groups of six tones (50 ms. duration, 330 ms. stimulus onset asynchrony [SOA], 400 trials), were presented with an inter-trial interval (ITI) of 800 ms while schizophrenia patients (SP; n=13) and healthy controls (HC; n=15) watched a silent video. In 50 trials, the 6th tone was dropped resulting in a deviant 5-tone group. Our previous work showed that the missing 6th tone generated an apparent MMN in HC but not in SP. To determine whether this was a true MMN or whether the apparent MMN reflected a reverberant oscillation, we examined activity after both 5- and 6-tone trains. The evoked potential to each tone in the train was evident as an alpha burst of ~9 Hz, reflecting the P1, N1, and P2 (note this does not imply that the evoked potentials were bursts of alpha-band oscillations). We focused analysis on activity following the missing 6th stimulus (M6) and the homologous window following a 6-tone standard group (missing 7th, M7). If 5 tones caused the brain to oscillate, then, logically, so should 6 tones. If only the 5-tone sequence generated a response, the response must be MMN to a violation of expectation.
Results: Interactions were present between group (SP vs. HC) and time-window (M6 vs. M7) for both anterior (FCz) and posterior (PZ) alpha-band ERO's ($p<0.05$). Differences between M6 and M7 ERO's were significant only for HC ($p<0.01$), with greater activity for M6, indicating a true MMN response. During M6, this response was greater for HC than SP ($p<0.05$), while during M7, alpha power was greater for SP than HC ($p=0.06$, trend-level).
Conclusion: The results suggest that HC formed gestalt groups and that the missing 6th tone generated a MMN. By contrast, schizophrenia participants did not form gestalts. Rather, alpha-band activity was comparable for M6 and M7, suggesting that only oscillatory activity was present.
ID: 2118562

INCREASED NEURAL NOISE IS RELATED TO THE PSYCHOSIS-LIKE EFFECTS OF THC

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Background: Neural noise -the randomness of brain activity- is increased in schizophrenia. Increased neural noise may disrupt information processing thus contributing to psychosis. This raises the possibility that increased neural noise may underlie the psychosis-like effects of Δ9-tetrahydrocannabinol (THC).
Methods: The acute effects of THC on neural noise and power were studied in the baseline EEG of 24 healthy humans. Participants completed three test days during which they received intravenous THC (placebo, .015 and .03mg/kg) in a double-blind, randomized, cross-over, and counterbalanced design. Neural noise in the EEG was measured using Lempel-Ziv complexity (LZC), a non-linear measure of signal randomness. A 5-factor model of the positive and negative syndrome scale (PANSS) was used to measure psychosis-like effects. Relevant analyses included signal power as a covariate.
Results: THC increased LZC in a dose-dependent manner: the higher dose showed increased LZC compared to both the lower dose and placebo, and the lower dose showed increased LZC compared to placebo (all ps<.001). Analogous dose-related effects of THC were observed on PANSS factors (all ps<.03). The regressions of PANSS factors on LZC revealed a strong positive relationship between LZC and the positive ($\beta=.685, p<.001$) and disorganization ($\beta=.754, p<.001$) symptoms factors but not between LZC and the negative symptoms factor ($p>.1$). In addition, THC reduced signal power during both active drug conditions compared to placebo ($ps=.029$) but no relationship was observed between signal power and PANSS factors (all ps>.1).
Conclusion: At doses that induced psychosis-like effects, THC increased neural noise (LZC) in the EEG of healthy humans in a dose-dependent manner. Furthermore, neural noise showed a strong positive relationship with positive- and disorganization-like symptoms but not with negative-like symptoms. THC effects on noise and the relationship between noise and psychosis-like effects were independent of signal power. These findings suggest that increases in neural noise may contribute to the psychosis-like effects of THC and that LZC should be explored as a potential biomarker for psychosis. Given that information theory shows that random noise limits the amount of information transmitted within a network, it can be hypothesized that the results show a positive relationship between a deficit in the brain networks' capacity to transmit information and the emergence of psychosis-like effects.
ID: 2119314

MMN ELICITED BY MUSICAL SCALE DEVIANTS IN CHRONIC SCHIZOPHRENIA

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Background: Simple physical parameter deviations from repetitive auditory stimuli evoke MMN in healthy subjects but this response is reduced in chronic schizophrenia. Current research is studying complex stimulus paradigms to more clearly separate novelty-detection mechanisms from sensory adaptation, and to develop simple biomarkers of schizophrenia. Here we used a complex paradigm approximating a musical scale in healthy subjects and participants with chronic schizophrenia to measure MMN.
Methods: Twelve tones (SOA = 330ms) formed the scale, the first six ascending from 1.5 kHz to 4 kHz, the last six descending from 4 kHz to 1.5 kHz (500 Hz steps). For deviant patterns, the last six tones began the scale again instead of descending. Thus an "expected" 4 kHz tone was replaced by a 1.5 kHz tone. Twenty-three patients with chronic schizophrenia and 23 healthy controls, matched for age, gender, handedness, parental socioeconomic status, and premorbid intellect, heard tones while watching a silent video. MMN was measured from the difference waveform subtracting the deviant 1.5 kHz tone from the correct 4 kHz tone.
Results: Both groups generated a small MMN that was significantly different from zero (schizophrenia: -1.68 μV, control: -2.01 μV; both $p<.001$). MMN did not differ between groups ($t=.64$, $p>.5$). Peak MMN latency did not differ between groups (schizophrenia: 170.6 ms, control: 172.6 ms; $t=-.19$, $p>.8$). However, the latency of the MMN was highly variable (range from 100 - 250 ms).
Conclusion: Schizophrenia participants and matched controls did not differ in the complex pattern MMN to musical scale deviants. The amplitude of the MMN was 1 μV, consistent with other studies of pattern MMN. The pattern MMN was further affected by high latency variability, which suggests different innate ability in individuals to automatically detect pattern deviants. It remains unclear if true pre-attentive novelty detection is impaired in schizophrenia. Current work aims to reliably elicit pattern MMN with reduced variance in onset.
ID: 2119165

THE RELATIONSHIP BETWEEN GLUTEN SENSITIVITY AND PSYCHIATRIC SYMPTOMS IN PEOPLE WITH SCHIZOPHRENIA

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Background: The relationship between gluten sensitivity and schizophrenia has been of increasing interest and novel mechanisms explaining this relationship continue to be explored. Differences have been found between Gluten sensitivity and Celiac Disease in terms of immune response, biomarkers and symptom profile. Having antibodies to gliadin and associated gluten sensitivity (GS) may represent a subgroup of people with schizophrenia who have a different etiology or manifestation of schizophrenia related to this immune and inflammatory state.
Methods: Our single visit study was completed with 100 people with schizophrenia. Data on gliadin antibody levels (IgA and IgG), demographic information, and psychiatric symptoms were collected and compared to antibody and demographic information of 100 matched healthy controls. We also examined the relationship of symptoms to antibodies within the schizophrenia group using the Brief Psychiatric Rating Scale (BPRS) (total and domain scores) and the Calgary Depression Rating Scale.
Results: We found a higher prevalence of gluten sensitivity (9% vs. 1%, chi-square=6.74, df=1, p=0.0094) and higher mean antigliadin IgG antibody levels in those with schizophrenia when controlled for age (2.9 ± 7.7 vs. 1.3 ± 1.3, p=0.046, controlled for age). Positive symptom ratings from the BPRS were significantly lower in people who have elevated antigliadin antibodies (4.11 ± 1.36 vs. 6.39 ± 2.99, p=0.020). However, there were no other clinical symptom differences noted on other symptom domains when observed between the positive and negative antibody groups.
Conclusion: Our results suggest that a symptom profile will not distinguish people with schizophrenia and GS from people with schizophrenia who do not have GS. Therefore, laboratory measurement of gliadin antibodies is currently the only way to determine which people are GS. In light of the many associations between gluten and schizophrenia, future examination of other mechanisms including the role of the immune pathway might offer a better understanding of the relationship between antibodies and symptoms. Future studies are needed to examine the relationship of gliadin levels and immune function in schizophrenia and more attention is needed to the role of GS in psychiatric illness.
ID: 2092944

ANHEDONIA SEVERITY, CANNABIS USE HISTORY, AND EVOKED-RESPONSE POTENTIALS DURING REWARD PREDICTION IN A TRANSDIAGNOSTIC SAMPLE

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Background: It is unclear whether anhedonia primarily reflects reduced anticipation and reward seeking rather than reduced hedonic capacity. Environmental factors such as cannabis use have been linked to anhedonia and abnormalities in reward processing. This study examined the interaction of a chronic cannabis use history and subtypes of trait anhedonia on reward processing using a novel broad transdiagnostic approach.
Methods: A trandiagnostic sample of 48 adults (mean age: 35.52; 56% female) reporting a wide range of anhedonia completed a Pavlovian reward prediction task during EEG recording. We examined the medial frontal negativity (MFN) evoked-response potential component in response to unexpected reward and non-reward trials.
Results: We found an interaction between cannabis use history and social anhedonia measured by the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) in relation to the MFN amplitude during unexpected non-reward trials. Increased MFN amplitude during non-reward trials was significantly correlated with increased social anhedonia in individuals who reported a cannabis use history (N = 19). This relationship was not significant in individuals with no cannabis use history (N = 29).
Conclusion: This finding is consistent with the negative potentiation theory of anhedonia, and provides a new framework for examining moderating influences from environmental risk factors such as cannabis use.
ID: 2097620

VISUAL AND COGNITIVE PROCESSING OF FACE AND NON-FACE SIGNALS IN SCHIZOPHRENIA

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Background: Face perception is impaired in schizophrenia. The processing of face signals involves both specific and general visual and cognitive domains. Given the visual and cognitive problems implicated in this psychiatric disorder, it is critical to probe these information processing domains in order to understand the mechanisms underlying the face perception impairment.
Methods: In this study, we examined a series of visual and cognitive factors that contribute to face perception in schizophrenia patients (n=40) and healthy controls (n=39), based on their performances on relevant tasks. These tasks include 1) face detection (identifying the presence of a face), 2) tree detection (identifying the presence of a non-face visual object), 3) contour detection (identifying the presence of configural visual signals important for face perception), and 4) contrast detection (identifying the presence of basic visual signal).
Results: Performance accuracies of patients were significantly lower than those of controls for face detection (p=0.048) and contour detection (p=0.02) but not tree detection or contrast detection. In patients, averaged face detection was significantly correlated with averaged tree detection (r=.76), averaged contour detection (r=0.58) and average contrast detection (r=0.63). The poor face detection was moderately but not significantly correlated with PANSS negative subscale scores (r=-0.31).
Conclusion: This pattern of results highlights the contributions of basic visual signal and spatial integration to impaired face processing in schizophrenia. These results also suggest a potential association of face perception impairment with negative psychotic symptom status.
ID: 2115658

SERUM ANALYTES CORRELATE WITH CLINICAL SYMPTOMS IN SCHIZOPHRENIA, SCHIZOAFFECTIVE, AND BIPOLAR DISORDERS

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Background: There is increasing evidence that systemic changes in proteomic expression accompany severe psychiatric illness. The study of proteomics in schizophrenia has yielded promising preliminary results indicating that proteomic biomarkers may be used to increase accuracy in the diagnosis of schizophrenia (1) or help stratify patients with schizophrenia into diagnostic subgroups (2). However, it is unknown how proteomic measures may correlate with symptom severity, either within or across psychotic disorders.
Methods: Subjects included 86 individuals with diagnoses of schizophrenia (n = 31), schizoaffective disorder (n = 20), bipolar disorder (n = 13), and healthy controls (n = 22). Diagnosis was made through the Structured Clinical interview for DSM-IV. Positive and negative symptom subscales were assessed using the Positive and Negative Syndrome Scale (PANSS). Each subject was analyzed at one or more time points for a total of 144 observations, with corresponding proteomic analysis from blood serum. From each blood sample 243 analytes were measured and 205 analytes used in the analyses. Single and multiple regression analyses were conducted to explore potential relationships between proteomic analytes and PANSS component scores.
Results: Individual analytes were not correlated with PANSS scores, but groups of analytes strongly predicted PANSS component scores. Specifically, a regression model of 20 analytes predicted negative PANSS scores (R-squared = .67), a regression model of 16 analytes predicted positive PANSS scores (R-squared = .67), and a regression model of 18 analytes predicted general PANSS scores (R-squared = 0.61). A model of 20 analytes predicted total PANSS scores (R-squared = 0.72).
Conclusion: Groups of analytes together may be related to PANSS component scores, and this pattern is seen across diagnostic groups, including schizophrenia, schizoaffective, bipolar disorder, and controls. This finding corresponds to recent studies of biomarkers using other modalities (e.g., neuroimaging) to support a dimensional, rather than categorical, model of disease in psychotic disorders.
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ID: 2085083

STATISTICAL APPROACHES FOR DEALING WITH COMPLEX BIOMARKER DATA SETS

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Background: As new biomarkers are identified, the traditional approach of comparing groups based on traditional clinical diagnostic categories may limit our understanding of the complex interaction between biology and behavior. Characterization of new phenotypes based on homogeneous "biotypes" and unique clinical presentations may improve our understanding of mental illness.
Methods: We explore a variety of different approaches to the statistical development of numerical taxonomies based on homogeneous biologic presentation and their relationship with clinical symptomatology. We present methods based on nonparametric Bayesian clustering methods as well as methods drawn from multidimensional item response theory which can be used to synthesize biologic and clinical characteristics.
Results: We illustrate preliminary application of these methods using data from the NIMH funded BSNIP project.
Conclusion: New statistical approaches to the development of numerical taxonomies in neuroscience can segment heterogeneous patient populations into clinically and biologically meaningful homogenous biotypes.
ID: 2117941

IS THE COMPLEX PATTERN DEVIANT MMN HEALTHY IN SCHIZOPHRENIA?

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Background: The neural mechanisms that generate mismatch negativity (MMN) are fiercely debated. The main argument is whether MMN is generated by cortex specialized for novelty detection, or is a byproduct of sensory cells to deviant stimuli being non-adapted by repetition. Despite such uncertainty, MMN is being assessed as a biomarker for schizophrenia. In schizophrenia, MMN is smaller to stimulus deviants that differ in simple physical characteristics such as pitch or intensity. This suggests that primary auditory cortex is affected in schizophrenia, but it is unclear whether it reflects deficits in stimulus adaptation, novelty detection, or both. In addition to simple physical parameter deviants, MMN is elicited by rule-breaking deviants. MMN to a complex pattern deviant cannot be due to non-adapted cells. We measured MMN to complex pattern deviants to assess novelty-detection MMN in schizophrenia and healthy controls.
Methods: Eight tones differing in 500 Hz steps were used in a standard ascending pitch pattern of two-up one-down steps (i.e., the standard pattern was 1000, 2000, 1500, 2500, 2000, 3000, 2500, 3500 Hz). There were two final tone deviants: 2500 Hz (the repeat deviant), or 4000 Hz (the jump deviant). Subjects watched a silent video, and were presented with 5 minutes of the standard pattern with no deviants, then 80% standard patterns, 10% repeat deviant patterns, and 10% jump deviant patterns.
Results: Healthy controls (N=24) produced a significantly different from zero MMN (~1μv) to the repeat deviant (p=.011); however individuals with schizophrenia produced an MMN that was not significantly different from zero (~0.6μv, p=.139). One of the individuals with schizophrenia produced a large, positive potential that was greater than 2sd from the mean. When removed from the analysis, the MMN in the schizophrenia group was also significantly different from zero (p=.009). However, neither group produced MMN to the jump deviant. Overall, groups did not differ in repeat or jump MMN amplitudes.
Conclusion: MMN did not occur to jump deviants, suggesting that the jump may have been too small to detect. Repeat deviant MMN was smaller in amplitude (~1mv) than typically seen in simple MMN paradigms. This suggests that simple MMN may be partially generated by non-adapted sensory cells. Patients with schizophrenia may be showing deficits in adaptation without showing deficits in novelty detection. Current work continues to parse adaptation and novelty effects in MMN.
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ID: 2116840

P50 SENSORY GATING AND CLINICALLY RATED SYMPTOMS OF INATTENTION IN SCHIZOPHRENIA

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Background: Compromised sensory gating, referring to the ability to filter irrelevant sensory input, reflects a fundamental neural deficit in schizophrenia (Freedman et al. 1996). The P50 component of the event-related potential may provide an index of this phenomenon during a paired-click paradigm, in which the neural response to the initial stimulus (S1) activates an inhibitory mechanism that minimizes disruptive effects of the identical second stimulus (S2). Despite considerable evidence that schizophrenia patients exhibit impaired preattentive inhibitory processing, with poor suppression of the P50 S2 response (i.e., a higher S2/S1 ratio), findings regarding the clinical significance of this deficit have been mixed. The present study examined whether P50 gating abnormalities in a large sample of recent-onset and chronic schizophrenia patients are related to clinical ratings of attentional impairment.
Methods: 53 schizophrenia patients and 41 healthy control participants completed a standard paired-stimulus task. Patients' positive and negative symptoms were evaluated using the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms (SANS and SAPS; Andreasen 1984).
Results: As expected, schizophrenia patients exhibited poorer P50 suppression ratios (M = .59, SD = .41) than healthy control participants (M = .39, SD = .28), $t(92) = 2.73$, p = .008. In patients, high SANS global inattention score was associated with abnormally high P50 gating ratio (r = .39, p = .004). This effect was driven by the S2 P50 amplitude, which was associated with SANS inattention (r = .32, p = .021), whereas S1 P50 amplitude was not related to attentional difficulties. Additionally, the association between high SANS inattention scores and poor P50 suppression ratios was significant when added into the regression model after all other SANS and SAPS global subscale scores (i.e., affective flattening, alogia, apathy, anhedonia, hallucinations, delusions, bizarre behavior, positive formal thought disorder; β = .38, p = .026). Thus, inattention contributes unique variance to P50 gating. Furthermore, findings were specific to P50 and were not reflected in N100 measures of sensory gating.
Conclusion: These results from a large sample of patients document a relationship between P50 gating and a core phenomenological feature of schizophrenia and provide evidence for specificity of clinical inattention symptoms for predicting sensory gating impairments.
ID: 2084293

ASSOCIATION OF INFECTIOUS AGENTS WITH INFLAMMATION IN FIRST EPISODE PSYCHOSIS PATIENTS AND OXIDATIVE STRESS CHANGES IN CSF AND PLASMA

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Background: Increasing data from human biospecimens suggests inflammation and/or oxidative stress in the pathology of early stage psychosis patients. However, many questions remain in the field including the effect of antipsychotics, the role of infectious agents, the correlation between central and peripheral markers, and the relationship between oxidative stress and inflammation.
Methods: We used two cohorts (first, antipsychotic-naïve subjects with first episode of psychosis, recently diagnosed as schizophrenia in comparison with matched controls; and second, subjects with recent onset schizophrenia in comparison with matched controls) to address some of these outstanding questions. We used a wide array of techniques including: multiplex array of cerebrospinal fluid and plasma, biochemical measurement of superoxide dismutase-1, and enzyme linked immunosorbent assay (ELISA) for infectious agent antibodies. Using this combination of measurements, we gained a broader understanding of the role of inflammation and oxidative stress in early phase psychosis.
Results: We found an increase in multiple inflammatory markers in cerebrospinal fluid of antipsychotic-naïve schizophrenia and first episode of psychosis patients. Interestingly, several of these markers showed correlations with antibodies for the infectious agents Herpes Simplex Virus 1 (HSV1) and Toxoplasma gondii (TG). Furthermore, we observed a decrease in superoxide dismutase-1 among the first episode of psychosis population.
Conclusion: Altogether, these results suggest first episode schizophrenia is accompanied by changes in inflammation and oxidative stress. In addition, patients exposed to an infectious agent, such as HSV1 or TG, may result in an exacerbated inflammatory phenotype. Future studies will utilize preclinical models to investigate how oxidative stress and inflammation synergistically effect brain function.
ID: 2085560

PROGRESSIVE AUDITORY GAMMA OSCILLATION DEFICIT IN CLINICAL HIGH-RISK SUBJECTS AND FIRST-EPISODE SCHIZOPHRENIA

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Background: Deficits in the γ-band (30–100 Hz) auditory steady-state response (ASSR) and progressive volumetric decreases in primary auditory cortex have been detected shortly after the onset of schizophrenia, and may be associated with symptoms such as auditory hallucinations. Despite the importance of abnormal γ-band oscillations in schizophrenia, it remains unclear whether the γ-band ASSR deficit shows progressive change over time during the early stages of the disease including prodromal phase. Hence, a longitudinal electroencephalogram study of the ASSR is important to better understand the pathophysiology and trajectory of early-stage schizophrenia.
Methods: Subjects were 20 clinical high-risk individuals (CHR), 20 first-episode schizophrenia patients (FES) (12 treated and 8 untreated with antipsychotics), and 38 matched healthy control subjects (HC). The ASSR was evoked by binaural click trains (20/30/40-Hz rates), and indexed by phase locking factor (PLF) and evoked power. Test sessions (Time-1/Time-2) were 11.9 months apart.
Results: Both CHR and FES had deficits in 40-Hz ASSR PLF, and FES showed a deficit in 40-Hz ASSR evoked power as well. Both CHR and FES showed progressive reductions in 40-Hz ASSR PLF and evoked power, which were not related to antipsychotic medication in FES. At Time-2, the 40-Hz ASSR deficits were greater in FES than CHR. Progressive reduction of 40-Hz ASSR PLF and evoked power were correlated with increased perceptual abnormalities and hallucinations in CHR and auditory hallucinations in FES.
Conclusion: These findings demonstrate that γ oscillation dysfunction is present in CHR as well as FES, and worsens over time. The progressive

reduction of γ ASSR measures in FES is not related to antipsychotic medication. These deficits in CHR and FES are also related to changes in psychotic symptom presentation. Thus, γ-band oscillation deficits are not just present at the first episode but are also clinical markers of risk for developing schizophrenia.
ID: 2087079

ELECTRORETINOGRAM ANOMALIES CAN PROFILE PATIENTS AFFECTED BY SCHIZOPHRENIA

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Background: The schizophrenia pathophysiology remains elusive due in part to the paucity of instruments to non-invasively investigate the living brain. The retina has been tagged as an approachable part of the brain due to their common embryonic origin[1]. An efficient way to assess retinal function is the electroretinogram (ERG). In a sample of children/adolescents at high risk of major psychoses, we previously observed a rod b-wave amplitude reduction when compared to age and gender balanced controls along with a trend for a cone a-wave amplitude decrease suggesting a neurodevelopmental component in ERG[2]. The present ERG study is based on a large sample of patients with schizophrenia and healthy controls.
Methods: ERG cone and rod luminance response functions were recorded in non-dilated eyes on 150 unrelated schizophrenia patients and 150 healthy controls, with a mean age of 39.4 and 40.6 years old respectively.
Results: ERG clearly distinguished schizophrenia patients from controls with an accuracy of 90%, a specificity of 0.73 and sensitivity of 0.90. Values were improved when looking at patients in their first five years of illness (accuracy of 98%, specificity and sensitivity of 100 and 0.90). At the cone level, reduced a- and b-wave amplitudes were observed with prolonged b-wave implicit time. At the rods level, b-wave amplitude was reduced whereas a prolonged a-wave implicit time was present for the pure rod response. Quantity of antipsychotics was not correlated with ERG. Age, gender, tobacco use and pupil size were controlled for in the analyses. The subgroup of patients administered clozapine had differences in ERG which were accounted for.
Conclusion: Patients with schizophrenia showed cones and rods anomalies. Data suggest that ERG can provide insights on the pathophysiology and the neurodevelopmental roots of the disease. Based on the current study and previous work in children/adolescent at high genetic risk of psychosis[2, 3], ERG would be a valuable tool to investigate psychiatric disorder as the procedure is non-invasive, reproducible, very well tolerated by patients, healthy controls and children with no negative clinical reactions. The technique may also be valuable to investigate the underlying neurodevelopmental mechanisms of psychosis.
ID: 2118707

INTERHEMISPHERIC COHERENCE DURING OBJECT RECOGNITION IN SCHIZOPHRENIA

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Background: Schizophrenia has been conceptualized as a disorder of neural dysconnectivity. Deficits in interhemipsheric interaction, as assessed with electroencephalography (EEG), have been observed in a variety of tasks and may play a role in the visual processing abnormalities seen in schizophrenia. In this study, we examined interhemispheric interaction in the occipital region by measuring EEG coherence during a visual object recognition task.
Methods: Thirty-eight patients with schizophrenia and 30 healthy controls were administered an object recognition task. Object recognition was manipulated in the context of a backward masking paradigm. The target and masking stimuli were separated by 5 SOAs ranging from 13 to 80 ms. Interhemispheric synchronization was assessed for each level of visibility (i.e., SOA) by calculating EEG coherence between 2 electrode pairs in the occipital lobe (PO7-PO8; O1-O2) separately in 3 frequency bands: alpha (7.5–12.5), beta (12.5–30) and gamma (30–50).
Results: Behaviorally, both groups showed better object recognition as SOA increased, though patients were significantly worse across SOAs compared to controls. Examining coherence in the alpha band, there was a significant SOA main effect and SOA x group interaction. Controls had significantly decreased alpha coherence at the more difficult SOAs, whereas patients did not show a consistent differentiation according to difficulty, and actually increased at the easiest SOA. For beta, we found no significant main effects or interactions. For gamma, there was a significant group main effect in which patients had increased gamma-band synchronization across all SOAs compared to controls.
Conclusion: Results suggest that during an object recognition task, patients with schizophrenia have an abnormal pattern of interhemispheric alpha-band coherence and a higher degree of gamma-band coherence in the occipital region, relative to healthy controls. The alpha finding in controls could be due to lateralization of neural activity when objects are difficult to detect, reflecting hemispheric specialization for object perception. The lack of modulation of alpha coherence by object difficulty in patients may reflect dysfunction in lateralization of object perception. The gamma finding in patients is inconsistent with other studies showing task-related decreases in activity, though gamma has been shown to be increased in other procedures, such as during resting state.
ID: 2078747

ABNORMAL EVOKED RESPONSES TO TASK-IRRELEVANT STIMULI IN PSYCHOSIS PATIENTS CORRELATES WITH HALLUCINATION SEVERITY

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Background: Normally, there is robust top down attention-mediated modulation of sensory processing, filtering context-irrelevant stimuli as demand increases on an attended task. Whether this process is intact in schizophrenia and related psychotic disorders is not known. We sought to assess this as well as determine whether abnormalities may be linked to hallucinations using a detailed hallucination assessment, determining whether some aspects of hallucinations may be important correlates but not others.
Methods: Schizophrenia, schizoaffective, and psychotic bipolar patients (patients) and healthy controls (HC) performed an attention task during 128-channel EEG recordings. The task was to press a button when detecting an X in a briefly presented group of letters. The task had three difficulty levels. Increasing difficulty was expected to result in reduced processing of irrelevant sensory information, which was 40Hz white noise bursts played binaurally during the task, eliciting the N1 auditory evoked potential. Control sound-only trials were also administered. Patients were rated on the PANSS for general psychopathology, and the Chicago Hallucination Assessment Tool for quantification of different dimensions of hallucination severity (Physical, Cognitive, and Emotional; in the past, and currently).

Results: Performance was matched between groups, as was N1 during no task. HC displayed decreased N1 to irrelevant sounds on more difficult relative to easier tasks, the expected top down control effect. Patients showed the opposite: greater N1 response to irrelevant sounds when the task was more difficult relative to easy. Greater top down control abnormality correlated significantly with worse hallucination severity in the past. Among patients with ongoing auditory hallucinations, greater abnormality in top down control correlated with worse physical characteristics (frequency, duration, etc.) of current hallucinations, but not with general positive or negative symptoms.
Conclusion: Psychosis patients show abnormal top down control over responses to irrelevant sensory information, and these abnormalities appear to be related to hallucination severity in a manner not detectable without detailed symptom assessment. This study adds new insight into possible mechanisms of sensory system overdrive in psychosis, and suggests that pathophysiology of specific psychosis symptoms can be linked to biomarkers with sensitive symptom assessment approaches.
ID: 2085964

HOW ARE ENDOPHENOTYPE DATA BEST COMBINED WITH CLINICAL INFORMATION?

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Background: The accumulating research on biomarkers in psychotic disorders has increased hope that one day our diagnostic approaches, being biomarker-based, will be more aligned with etiology, prognosis and treatment response than the current symptom based approaches. However, doctors encounter patients who present to them with symptoms and signs, and not biomarker data, and one still needs symptomatic information as a starting point.
Methods. I will discuss in this presentation the need for a two-level diagnostic process: first to identify the broad diagnostic category (e.g. psychosis spectrum disorder) based on clinical data, and second, to classify such an entity using biomarker data. To this end, I will review data from the B-SNIP consortium that examine relationships between clinical and endophenotype data.
Results: Data in the B-SNIP consortium suggests that several structural and functional biomarkers relate better to continuous dimensions of psychopathology such as psychosis and cognitive impairment, than to traditional diagnostic continua (as measured by the schizobipolar scale).
Conclusion: Integrating clinical and neurobiology data might reveal subcategories that are not necessarily aligned to the current DSM typology, and may be of more practical value in outcome prediction, and treatment selection. If Kraepelin were to have knowledge of the current biomarker data, he would have sliced dementia praecox and manic depressive illnesss differently.
ID: 2115732

CORTICAL SUBSTRATES AND FUNCTIONAL CORRELATES OF AUDITORY DEVIANCE PROCESSING DEFICITS IN SCHIZOPHRENIA

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Background: Although sensory processing abnormalities contribute to widespread cognitive and psychosocial impairments in schizophrenia (SZ) patients, scalp-channel measures of averaged event-related potentials (ERPs) mix contributions from distinct cortical source-area generators, diluting the functional relevance of channel-based ERP measures.
Methods: SZ patients (n=42) and non-psychiatric comparison subjects (n=47) participated in a passive auditory duration oddball paradigm, eliciting a triphasic (Deviant−Standard) tone ERP difference complex, here termed the auditory deviance response (ADR), comprised of a mid-frontal Mismatch Negativity (MMN), P3a positivity, and Re-Orienting Negativity (RON) peak sequence. To identify its cortical sources and to assess possible relationships between their response contributions and clinical SZ measures, we applied independent component analysis to the continuous 68-channel EEG data and clustered the resulting independent components (ICs) across subjects on spectral, ERP, and topographic similarities.
Results: Six IC clusters centered in right superior temporal, right inferior frontal, ventral mid-cingulate, anterior cingulate, medial orbitofrontal, and dorsal mid-cingulate cortex each made triphasic response contributions. Although correlations between measures of SZ clinical, cognitive, and psychosocial functioning and standard (Fz) scalp-channel ADR peak measures were weak or absent, for at least four IC clusters one or more significant correlations emerged. In particular, differences in MMN peak amplitude in the right superior temporal IC cluster accounted for 48% of the variance in SZ-subject performance on tasks necessary for real-world functioning and medial orbitofrontal cluster P3a amplitude accounted for 40%/54% of SZ-subject variance in positive/negative symptoms.
Conclusion: Thus, source-resolved auditory deviance response measures including MMN may be highly sensitive to SZ clinical, cognitive, and functional characteristics.
ID: 2119184

VALIDATION OF MISMATCH NEGATIVITY AND P300 MEASURES FOR USE IN MULTI-SITE STUDIES OF SCHIZOPHRENIA: CHARACTERIZATION OF DEMOGRAPHIC, CLINICAL, COGNITIVE, AND FUNCTIONAL CORRELATES IN COGS-2

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Background: The Consortium on the Genetics of Schizophrenia (COGS-2) is a multi-site case-control study designed to examine the genetic basis of neurophysiological and neurocognitive endophenotypes of schizophrenia (SZ). In this presentation, Dr. Light will provide an overview of findings of neurophysiological endophenotypes including prepulse inhibition and oculomotor antisaccade with an emphasis on mismatch negativity and P300 auditory event-related potential measures that were added in years 2–4 of COGS-2 and not previously reported. The feasibility of adding these measures to an ongoing multi-site study of SZ and the extent to which demographic, clinical, cognitive, and functional contribute to response variability was examined.
Methods: Participants (SZ n=966; Healthy Comparison Subjects, HCS n=824) completed COGS-2 testing at 5 geographically distributed COGS

laboratories. Two auditory oddball paradigms were administered at the end of COGS-2 testing day under passive and active conditions to in order to assess mismatch negativity and P300 measures (P3a and P3b) via a custom 2-channel EEG recording system.
Results: Valid EEG recordings were obtained from over 90% of participants with nearly identical rates of usable data detected across groups. Highly significant MMN (d=0.96), P3a (d=0.93), and P3b (d=0.62) deficits were observed in SZ patients, comparable in magnitude to those observed in single-lab studies. Demographic characteristics accounted for substantial portions of variance in measures. Significant relationships were observed among demographically-adjusted measures with medication status as well as several clinical, cognitive, and functional characteristics of SZ patients. Feasibility of PPI and oculomotor antisaccade assessment, as well as their demographic, clinical, cognitive, and functional correlates, was confirmed in the COGS-2 sample consistent with previous COGS findings.
Conclusion: This study demonstrates that MMN and P300 measures can be feasibly used in multi-site clinical studies. As with many clinical tests of brain function, demographic factors contribute to ERP amplitudes and should be carefully considered in future biomarker-informed clinical studies.
ID: 2119413

MISSING STIMULUS MISMATCH NEGATIVITY IN CHRONIC SCHIZOPHRENIA

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Background: The mismatch negativity (MMN) is an event-related potential typically elicited by a deviant "oddball" tone occurring among repeated standard tones. The oddball tone deviates by some simple physical parameter, such as duration or pitch. MMN responses are reduced in schizophrenia. It has become unclear whether the reduced MMN seen on simple oddball tasks reflects a true novelty detection deficit or problems in stimulus-specific adaptation to the repeated standard tone. Apart from simple physical deviations, MMN responses are also elicited by deviations from abstract rules and complex patterns. We created a pattern MMN paradigm based on a single tone to examine complex MMN in schizophrenia.
Methods: Groups of 6 identical tones (330 ms apart) were separated by a 750 ms inter-trial interval (400 groups total). The Gestalt principle of perceptual grouping by proximity should cause participants to develop an expectation for groups of 6 tones. Deviants were created by deleting the 4th or 6th tone (50 groups each). Fourteen participants with schizophrenia and 16 healthy participants passively hear sounds while watching a silent nature video. To determine if any missing stimulus MMN impairment in schizophrenia was due to a failure to form Gestalt groups or to impairment in internal timing mechanisms needed for accurate prediction, subjects were presented the same auditory stimuli with visual cues for each actual or expected tone occurrence; i.e., the visual cue occurred for actual and omitted tones, reducing reliance on internal timing mechanisms.
Results: For missing tones alone, healthy subjects generated MMN to absent yet expected stimuli ($p=.009$), but schizophrenia participants did not ($p=.9$). For missing tones with a visual cue, both healthy subjects and schizophrenia participants showed significant MMN responses ($p<.001$).
Conclusion: Schizophrenia affects the ability of "primitive sensory intelligence" complex pre-attentive perceptual mechanisms to form implicit groupings based on expected stimulus timings. Importantly, this deficit must relate to abstract complex pattern analysis rather than stimulus sensory deficits in the disorder. However, that MMN appeared to be relatively normal in schizophrenia with visual cues suggests that MMN deficits in schizophrenia may be more related to internal timing impairments, as has been suggested for the duration deviant MMN, rather than inabilities to form abstract patterns.
ID: 2116913

THE ASCENDING PITCH PATTERN MMN IS UNIMPAIRED IN SCHIZOPHRENIA

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Background: Like deviants differing on some physical parameter from repetitive standard tones, rule-breaking deviants from an abstract stimulus pattern elicit MMN. Although simple stimulus parameter MMN is robustly reduced in long-term schizophrenia with a Cohen's d ~1, only one study examined MMN to pattern deviants in the disorder. This experiment measured MMN to violations of an increasing pitch pattern in controls and chronic schizophrenia patients.
Methods: Twenty-four participants with schizophrenia and 24 matched healthy control participants watched a silent film while a series of binaural tones were played over insert earphones. A standard pattern comprised 6 tones, beginning with a 1500 Hz tone and ascending by 500 Hz increments to the final 4000 Hz tone. For deviant patterns, the last tone descended by 500 Hz to 3000 Hz. Subjects were not informed about the pattern. Additionally, 11 control participants and 12 with schizophrenia received an initial 5 minute standard pattern block with no deviants, i.e. a passive training session to develop the pattern representation. MMN was measured from the peak negativity between 100 and 250 msec.
Results: Groups did not differ in MMN amplitude (Control FCz, -2.02 μV; Schizophrenia, -1.75 μV, $F1,46 = 0.18$, $p > .6$) or latency (Control FCz, 185.5 msec; Schizophrenia, 174.0 msec, $F1,46 = 1.44$, $p > .2$). Both groups MMN amplitudes were significantly different from zero (Control, $t = 4.7$, $p < .001$; Schizophrenia, $t = 3.9$, $p = .001$). There was no significant effect of training ($p > .29$). A trend for a group x training interaction ($p = .074$) indicated that participants with schizophrenia showed marginally greater benefit from training (0.9 μV) than controls (0.5 μV).
Conclusion: Unlike simple physical parameter deviants that generate large amplitude MMN which clearly distinguish psychiatrically-well versus schizophrenia participants (d ~1), pattern deviants evoke a small MMN that does not separate groups. Thus, the true novelty detection process reflected in pattern deviant MMNs may be intact in schizophrenia. Future work will examine the effect of explicit instruction on the size of the complex MMN to determine if group separation can be increased by controlled learning.
ID: 2116796

CUMULATIVE STRESS RESPONSE EFFECTS QUANTIFIED BY ALLOSTATIC LOAD IN RECENT ONSET AND LONG TERM SCHIZOPHRENIA

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Background: The stress response system is hypothesized to function abnormally in schizophrenia, with evidence that some abnormalities are present at prodromal, onset and chronic illness stages. Cross-sectional tests of stress response have limited utility as both blunted and increased cortisol responses have been reported. Allostatic load (AL), an index of cumulative stress load, is a relevant metric to examine the influence of stress responses, and may be particularly appropriate in diseases like schizophrenia (SZ) where stress pathology is present in different illness stages. We predict that AL may provide an intermediate marker explaining the increased comorbidity of physical health problems, and has yet to be examined in this population.
Methods: We assessed AL in 30 SZ patients and 20 healthy controls (HC) using 10 physiological and chemical biomarkers. Current perceived stress

was also measured. We assessed the influence of duration of psychosis by dividing the sample into those with disease duration of >2.5, 2.5 to 5, and >5 years since emergence of their first psychotic symptom. Functional capacity was assessed with the UPSA-2 and psychiatric symptoms with the BPRS.
Results: Controlling for age, SZ had significantly increased AL as compared to HC (SZ mean(SD)= 5.2(2.6) vs. HC mean(SD)= 3.8(2.4), p=0.007). After controlling for age, AL did not significantly differ by time since illness onset in SZ (p=0.075). Greater AL was significantly associated with reduced functional capacity (p=0.006) and greater psychotic symptoms (p=0.048) in SZ. AL was not significantly associated with perceived stress in either group.
Conclusion: In this first study of AL in SZ, greater AL was identified, likely reflecting increased bodily "wear and tear" accumulated from chronic high stress exposure or maladaptive stress responses over time. The find that greater AL in SZ corresponded to reduced functional capacity could be due to a lack of cognitive resources needed to both function successfully and respond adaptively to stress, or could reflect a greater chronic stress in persons with reduced functional ability. Increased AL is present in SZ beginning early in the course of the disorder, likely representing maladaptive stress physiology inherit to the disorder rather than medication or behavior effects. Our results suggest that interventions aimed at improving stress responses, perhaps early during the disease course, hold promise for improving functional capacity and reducing physical health comorbidity in SZ.
ID: 2095723

SENSORY ATTENUATION TO SELF-GENERATED SPEECH IN HIGHLY SCHIZOTYPAL INDIVIDUALS: PSYCHOPHYSIOLOGICAL EVIDENCE FOR A 'CONTINUUM OF PSYCHOSIS'

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Background: The concept of a 'continuum of psychosis' refers to the idea that psychotic-like experiences occur in the general population. If the 'continuum of psychosis' is valid, it might be expected that the psychophysiological abnormalities exhibited by patients with schizophrenia might also be present in non-clinical individuals who score highly on the personality dimension of schizotypy. N1-suppression abnormalities to self-generated speech have consistently been observed in patients with schizophrenia. The present study aimed to investigate whether N1-suppression abnormalities were also present in non-clinical individuals who scored high on schizotypy.
Methods: 37 non-clinical individuals who scored high on the Schizotypal Personality Questionnaire (SPQ) and 37 individuals who scored low on the SPQ underwent electroencephalographic (EEG) recording. The amplitude of the N1-component of the auditory-evoked potential was calculated while participants (a) vocalized simple syllables (Talk condition), (b) passively listened to a recording of these vocalizations (Listen condition) and (c) listened to a recording of these vocalizations, with each vocalization being preceded by a visual cue (Cued condition).
Results: The Low Schizotypy group exhibited N1-suppression during the Talk condition relative to both the Listen and Cued conditions. In contrast, the High Schizotypy group failed to exhibit N1-suppression in the Talk condition, relative to either the Listen or Cued conditions.
Conclusion: These findings suggest that non-clinical, highly schizotypal individuals exhibit subnormal levels of N1-suppression to self-generated speech. To the extent that these results resemble the N1-suppression abnormalities that have previously been observed in patients with schizophrenia, this study provides psychophysiological evidence in support of a 'continuum of psychosis'
ID: 2118197

THE EFFECTS OF CLONIDINE ON ELECTROPHYSIOLOGICAL PARAMETERS OF SELECTIVE ATTENTION OF PATIENTS WITH SCHIZOPHRENIA ON STABLE MEDICATION

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Background: Deficient selective attention has frequently been reported in patients with schizophrenia. Recently, we reported increased sensory as well as sensorimotor gating following administration of single dosages of clonidine to the treatment of stably medicated patients with schizophrenia. Now, we report on clonidine's effect on one of the electrophysiological representatives of selective attention, the P300 amplitude, in this same group of patients.
Methods: In a double blind, placebo controlled, randomized yet balanced cross-over design 20 male schizophrenia patients on stable medication were assessed in a selective attention task (auditory oddball paradigm) on 5 separate occasions: once after oral administration of placebo and following single doses of 25, 50, 75 and 150 µg of clonidine added to their medical treatment.
Results: Although on average clonidine appeared to decrease the P300 amplitude dose-dependently, none of these effects reached statistical significance.
Conclusion: This study indicates that those dosages of clonidine that effectively reduce sensory and sensorimotor gating deficits in patients with schizophrenia, do not affect electrophysiological parameters of selective attention. Since gating deficits are believed to be among the core deficits in schizophrenia, our results show promise for clonidine as an add-on therapy in the medical treatment of schizophrenia. However, additional research is warranted to investigate long term treatment effects of clonidine in schizophrenia.
ID: 2089790

REDUCED STEADY-STATE PHASE SYNCHRONIZATION DURING A COGNITIVE CONTROL TASK

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Background: Individuals with schizophrenia (SZ) have documented evidence of cognitive control abnormalities. This study investigated neural activity of those with SZ in comparison to healthy groups with high (HCC) and low cognitive control (LCC), the latter of which exhibit similar behavioral abnormalities on cognitive control tasks without exhibiting symptoms of schizophrenia. By using a flickering checkerboard, a steady-state (SS) neural response is induced and overall levels of neural entrainment can be measured and compared between groups. SZ have been shown to have marked impairments at different frequency bands. By using a steady-state response we investigated the overall neural entrainment using whole head EEG (64 sensor).
Methods: Participants completed a saccade task with increasing levels of difficulty in order to place sufficient demands on cognitive control. Trials consisted of flickering checkerboards in central (15 Hz) and both peripheral visual fields (12 Hz), followed by brightening of one peripheral

checkerboard (target) while all kept flickering. The three blocks were: (1) pro-saccade and NoGo randomly interleaved; (2) Anti-saccade and NoGo randomly interleaved; and (3) pro, anti, and NoGo randomly interleaved. Single trial power and inter-trial phase coherence (ITC) was and compared across groups and conditions.
Results: Group by Task ANOVA showed reduced ITC at 15 Hz for SZ ($p<.01$) during the Pro/Nogo and Pro/Anti/Nogo task that was significantly different from HCC and LCC ($p<.01$, $p<.01$). For Pro/Nogo block: the initial 15 Hz ITC response and 15 Hz ITC during the 1000ms leading up to the saccade cue correlated with likelihood of making a correct response. For Pro/Anti/Nogo: the first 1000ms 15 Hz ITC response correlated with the likelihood of making a correct response during the anti-saccade task. The 15 Hz ITC at 1000ms to 2500ms after onset of steady-state correlated with the likelihood of making a correct pro-saccade. SZ also showed reduced Theta ITC (4–7 Hz) that was significantly different from the HCC ($p<.01$) and LCC ($p<.01$ at first 500ms, and $p<.05$ at 1000ms to onset of cue). Behavioral results also indicated that LCC and SZ were not significantly different during the task with higher cognitive load (Anti/Nogo, Pro/Anti/Nogo blocks).
Conclusion: SZ shows reduced neural phase synchrony in response to a steady-state cue and reduced Theta ITC during a cognitive control task. Reduced phase synchronization could be indicative of underlying psychopathology of SZ.
ID: 2084740

HOW MULTIVARIATE APPROACHES CAN HELP INTERPRET GENETIC COMPONENTS ASSOCIATED WITH MULTIPLE PSYCHOSIS ENDOPHENOTYPES

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Background: Along with rare genetic alterations such as CNVs, common, complex diseases such as schizophrenia and bipolar illness are also likely underpinned by numerous genes of individually small effect interacting within networks. Univariate strategies such as GWAS fail to capture many such genetic variants or interactions. Multivariate analytic approaches such as parallel independent component analysis (Para-ICA) can address some of these problems due to their statistical efficiency. Typically for individual endophenotypes Para-ICA yields SNP components containing 10^2–10^3 members, that can be fed into functional annotation analyses to reveal information regarding underlying biological pathways. What remains unknown is the extent to which commonly used psychosis-associated endophenotypes are redundant, both as stand-alone measures and in terms of their underlying genetic structure and associated molecular biological pathways.
Methods: We examined 3 electrophysiological endophenotypes (the auditory oddball P 300, P 50, and resting state EEG measures) assessed in the multi-site BSNIP study, and their associated SNP components extracted via separate Para-ICA's, in probands with schizophrenia and psychotic bipolar disorder and healthy controls who were genotyped using a using a sub-set of SNPs from a 10^6 SNP Illumina chip. We then compared gene ontology processes and process networks (derived from GeneGo software) to examine those pathways and networks shared across all 3 endophenotypes using an FDR cutoff of 10^{-6}. We hypothesized that we would find processes concerned with CNS development, signal generation and transduction.
Results: All 13 processes meeting significance criteria fell within brain developmental categories, including neuronal differentiation, generation and projection, axon guidance, neurogenesis, neuron development, neuron projection morphogenesis, axonogenesis and cell morphogenesis involved in neuronal differentiation, etc.
Conclusion: Results suggest that 3 psychosis endophenotypes within a broad general category (electrophysiology) share meaningful genetic underpinnings at the level of gene process networks and ontologies, as derived from multivariate analytic procedures.
Despite the relatively immature state of gene process software suites, this approach is a rapidly developing one that is beginning to demonstrate that it can yield face-valid information to help interpret complex data derived from multivariate genotyping studies and to inform etiology.
ID: 2114899

DISCERNING RISK PATHWAYS FOR PSYCHOSIS IN THE NAPLS2 COHORT

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Background: The North American Prodrome Longitudinal Study (NAPLS) is a collaborative effort to illuminate mechanisms involved in the emergence of psychosis and identify psychosis vulnerability constructs. Our ongoing efforts involve prospective study of persons at clinical high risk (CHR) for psychosis based primarily on the presence of moderate to severe attenuated positive symptoms. This presentation focuses on psychosis risk prediction in the second NAPLS cohort (NAPLS2) using blood-based biomarkers. A particular emphasis is the value of blood-based biomarkers for psychosis risk, including that blood, as a highly regulated tissue contacting every cell the body, reflects a person's health state, as well as recent evidence that circulating immune cells and cytokines regulate brain function and may directly influence psychosis risk.
Methods: The NAPLS2 cohort incudes 765 CHR and 280 demographically similar unaffected subjects between the ages of 12 to 35. Included in this analysis are subjects, that donated blood samples and, as of March 2012, who converted to psychosis (n=32), who were non-converters followed at least two years (n=40), or were matched unaffected subjects (n=35). Plasma was analyzed using a Luminex multiplex platform, and leukocyte-derived RNA sequenced using an Illumina platform. RNA seq analysis focused on microRNAs that are small RNAs highly important in regulating gene

expression. A greedy algorithm validated by random relabeling was used to select markers best predicting psychosis risk.
Results: The area under the receiver operating curve predicting psychosis risk for progressed versus non-progressed subjects for the plasma analyte assay was .91, and for the microRNA assay was .86. Bioinformatic analysis of both assays suggested immune system activation. Examination of correlation networks of plasma analyte and leukocyte miRNA expression between groups revealed systematic changes; bioinformatic investigations suggested activation of innate and adaptive immune system.
Conclusion: Blood-based assays show promise in stratifying psychosis risk in persons with CHR symptoms. In addition examination of plasma analyte and leukocyte gene expression may help identify vulnerability constructs for psychosis.
ID: 2142211

SCHNEIDERIAN FIRST RANK SYMPTOMS & DIGIT RATIO IN SCHIZOPHRENIA

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Background: Recent studies indicate schizophrenia pathogenesis to involve fetal programming aberrations influenced by endocrine factors. The second to fourth-digit-ratio (2D:4D), an indicator of disrupted endocrine signaling during early development, can facilitate identification of fetal origins of adult diseases. Previous studies have shown inconsistent profile of 2D:4D in schizophrenia. This study evaluated status of 2D:4D in schizophrenia & its correlates with Schneiderian first rank symptoms.
Methods: We examined 155 DSM-IV schizophrenia patients (M:F=85:70) and 124 healthy controls (M:F=77:47). Digit lengths were measured using high-resolution images of hands by two raters blind to subject status with good inter-rater reliability (ICC>0.9). 2D:4D was computed by averaging ratio of second-to-fourth finger lengths of both hands.
Results: Two-way ANOVA revealed a significant effect of clinical status [F=6.9; p=0.009] as well as sex [F=10.9; p=0.001] on 2D:4D. Women had significantly greater 2D:4D than men. Patients with Schneiderian First Rank Symptoms had negative (trend level significance) digit ratio asymmetry than those without (p = 0.07).
Conclusion: 2D:4D observations in schizophrenia suggesting possible role of prenatal endocrine aberrations involving gonadal hormones in vulnerability towards schizophrenia. These aberrations might impact on brain asymmetry towards genesis of Schneiderian First Rank Symptoms.
ID: 2090103

PERINATAL CHOLINE: A POTENTIAL PREVENTION STRATEGY FOR IMPROVING EARLY BEHAVIOR AND DECREASING RISK FOR SCHIZOPHRENIA

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Background: The Neurodevelopmental Model postulates that risk for schizophrenia begins in the prenatal period. Even if the full conversion to schizophrenia never occurs, that early risk manifests as lifelong deficits in cognition and behavior. Decreasing risk will have lifelong benefits. Prenatal dietary choline, a natural alpha7 nicotinic agonist, may improve cerebral inhibition development and improve cognitive and behavioral outcomes. We assess the interaction between schizophrenia-associated genes (such and NRG1 and CHRNA7), environment (such as prenatal anxiety) and interventions (such as perinatal choline supplementation) on the development of cerebral inhibition (P50 sensory gating and mismatch negativity) and behavior.
Methods: Randomized controlled trial of perinatal choline supplementation in healthy mothers (phosphatidylcholine 6300 mg QD) and infants (phosphatidylcholine 700 mg QD). Outcomes of P50 sensory gating (1 and 3 months of age) and behavior (40 months of age). Infants were genotyped for CHRNA7 and NRG1.
Results: Homozygosity for a schizophrenia risk allele in either CHRNA7 or NRG1 is associated with delayed development of cerebral inhibition. The genetic effect is reversed by perinatal choline supplementation. Perinatal choline supplementation is also associated with less parent-reported attention and internalizing behavior symptoms at 40 months of age.
Conclusion: Prenatal choline supplementation compensates for genetic vulnerability's impact on the development of cerebral inhibition and is associated with lower symptomology at 3 years of age. Universal prevention strategies have a role in preventing major mental illnesses.
ID: 2077141

NOVELTY DETECTION AND COMPLEX MISMATCH NEGATIVITY TO A SINGLE REPETITIVE TONE IN SCHIZOPHRENIA

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Background: Background: Stimulus specific adaptation (SSA) models argue that repetitive tones cause dampening of sensory responses, and mismatch negativity (MMN) is an epiphenomenal effect of physically deviant tones activating non-adapted sensory cells, not elicited by stimulus deviation from a memory trace of past stimuli or a predictive model of stimulus patterns. The present experiment explored whether SSA was necessary to elicit MMN, and whether such true novelty MMN differed between well participants and schizophrenia.
Methods: A single tone paradigm used the Gestalt principle of proximity to form implicit groups of 5 stimuli (330 ms SOA, 750 ms ISI). Pattern models predict MMN will be elicited by an occasional 6th tone. By contrast, SSA models predict no MMN, as the same tone would necessarily activate adapted neurons. If MMN was elicited by extra tones, it must occur because of a mismatch with an expectation of 5 tones, not stimulation of non-adapted sensory neurons. Control and schizophrenic subjects performed a standard pitch-deviant and duration-deviant MMN task and the extra tone MMN task while watching a silent movie.
Results: Preliminary analysis of MMN at FCz revealed significant reductions of MMN in patients for pitch deviants (Con: -4.3μV, Sz: -1.5μV, t =-4.4, p<.05), and for duration deviants (Con: -2.4μV, Sz: -0.9μV, t =-2.7, p<.05), but not for extra tone MMN (Con: -1.0μV, Sz: 0.9μV, t =-0.5, p>.05).
Conclusion: Peak latency of the extra tone MMN was ~50 ms later than pitch deviant MMN. Assuming the pitch deviant MMN indicates the onset timing of non-adapted sensory cells, the much later extra tone MMN must necessarily arise from a different set of non-sensory neurons. However, the extra tone MMN was substantially smaller than pitch and duration deviant MMNs. These results demonstrate SSA is not necessary to generate MMN and that the auditory cortex performs pattern analysis sufficient to generate MMN, but that simple stimulus deviant MMNs likely do contain substantial contributions from non-adapted neurons. True novelty detection as reflected in

MMN may be intact in schizophrenia, at least for extra tones. The MMN deficit observed previously may reflect deficient SSA. However, how to optimize automatic pattern analysis is not fully understood, and the extra tone paradigm may need further development to maximize group differences.
ID: 2116738

EVOKED AND SPONTANEOUS GAMMA ABNORMALITIES IN SCHIZOPHRENIA

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Background: The electroencephalogram (EEG) is composed of a number of frequency bands, which are associated with activity in distinct neural circuits. Understanding how these circuits give rise to particular oscillations, and how dysfunctional elements in these circuits produce abnormal oscillatory activity in neuropsychiatric disorders, is a major challenge for translational neuroscience. Basic research with animal models of schizophrenia has focused on spontaneous oscillations, finding increased gamma (30–100 Hz) activity, while clinical research has focused on stimulus-evoked activity, finding decreased gamma responses in schizophrenia. We attempted to bridge these two areas of research by examining both stimulus-evoked and spontaneous oscillations in schizophrenia.
Methods: Auditory steady-state responses (ASSRs) to click trains presented at 20, 30, and 40 Hz were acquired from 24 chronic schizophrenia patients (SZ) and 24 matched healthy control subjects (HC). The EEG was recorded with a dense electrode array, and ocular, electromyographic, and cardiac artifacts were removed using independent component analysis. Dipole source localization of the ASSR was used as a spatial filter for measuring EEG activity in the auditory cortex.
Results: 40 Hz ASSR PLF but not evoked power was reduced in SZ compared to HC in the left hemisphere (LH). Spontaneous gamma power was increased in SZ compared to HC for each stimulation frequency, but only in the LH for 40 Hz stimulation. Thus, stimulus parameters influenced spontaneous activity. In SZ, spontaneous gamma power in the LH during 40 Hz stimulation was positively correlated with auditory hallucination symptoms and negatively correlated with ASSR PLF. Furthermore, normal patterns of evoked power/PLF correlations were absent in SZ in the LH during 40 Hz stimulation. Simulations of the ASSR and spontaneous activity suggest that increased spontaneous gamma power may result in the appearance of impaired ASSR phase locking.
Conclusion: Spontaneous oscillatory activity in the gamma band is increased in schizophrenia. This finding is consistent with recent findings of increased spontaneous brain activity in schizophrenia from functional neuroimaging. It is also consistent with the findings of increased spontaneous gamma power in NMDA receptor hypofunction animal models of schizophrenia. Psychosis may involve an increase in spontaneous brain activity in particular neural circuits that can be modeled in animals.
ID: 2118703

NICOTINIC CHOLINERGIC MECHANISMS IN FETAL BRAIN DEVELOPMENT

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Background: CHRNA7, the gene for the alpha7-nicotinic receptors subunit, is in the critical region of the chromosome 15q13 deletion, one of the Chromosomal Number Variations highly associated with schizophrenia. CHRNA7 is one of only a few genes associated with schizophrenia that is expressed more highly in fetal life than in adult life, and alpha7-nicotinic cholinergic receptors are expressed much more widely in the fetal brain than in adult life. CHRNA7 null mutant animals fail to develop cerebral inhibitory and excitatory circuits normally. Thus, alpha7-nicotinic receptor activation appears to be critical for the normal development of the circuits that are pathologically impaired in persons with schizophrenia. Alpha7-nicotinic receptors appear during initial neurogenesis and for most of fetal life are not innervated by cholinergic axons terminals, which do not reach the forebrain until slightly before birth. However, they are specifically activated by choline in millimolar concentrations, the level found in the amniotic fluid.
Methods: There are several rodent models of this pathogenic mechanism. DBA/2 mice have polymorphisms in the promoter of the CHRNA7 gene that are linked to its decreased expression in the hippocampus. DBA/2 mice also have decreased cerebral inhibition, as shown by their failure to inhibit the hippocampal response to paired auditory stimulus, a sensory gating measure analogous to human P50 sensory gating. Maternal diet was supplemented with choline.
Results: Supplementation of the maternal diet from conception through weaning with 5 times normal levels of dietary choline results in adult offspring with normal sensory gating, even after being fed normal choline diets after weaning. This dietary effect does not occur in CHRNA7 null mutants, which demonstrates the specificity of the effect to alpha7-nicotinic receptors.
Conclusion: Maternal dietary choline supplementation thus may potentially overcome the pathogenic effect of at least one putative genetic risk factor for schizophrenia.
ID: 2077001

EVALUATION OF SPONTANEOUS DENSE ARRAY GAMMA OSCILLATORY AND MINOR PHYSICAL ANOMALIES AS NEURODEVELOPMENTAL ENDOPHENOTYPE IN SCHIZOPHRENIA

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Background: Minor physical anomalies (MPAs) and gamma oscillatory activity have been proposed as associated endophenotypes in schizophrenia. Composite markers better predict disease risk.
Methods: Aim of this family study was to investigate MPAs and gamma oscillatory activity in schizophrenia patients, their unaffected first degree relatives and healthy controls and appreciate whether they can be used together as composite endophenotype. Thirty each of schizophrenia patients, their first degree relatives and controls were assessed for MPAs on the Extended Waldrop Scale. All participants underwent an awake, resting 192-channel EEG recording. Spectral power and coherence in 30–100 Hz gamma bands were estimated using Welch's averaged periodogram method. Statistics used were one-way ANOVA, Chi Square Test for comparing socio-demographic-clinical variables; MANOVA supplemented by one-way ANOVA (post-hoc Tukey HSD) for comparison of spectral measures; Pearson's correlation, step-by-step discriminant functional and intra-familial correlation analysis subsequently.
Results: An endophenotype pattern of finding was found for MPAs in the craniofacial region, the total number of MPAs, spectral power in right temporal region on all bands and in the right parietal region on 50-70Hz and 70-100Hz gamma bands. The three groups were most accurately classified when MPA total score, right temporal 30-50Hz gamma power and right occipital 'intra hemispheric' 50-70Hz gamma coherence were considered together than when considered independently. Significant intra familial correlation for MPA total score and right temporal gamma 30-50Hz power.
Conclusion: Composite evaluation of two developmentally linked markers i.e. MPAs and gamma spectral measures is useful in expanding the schizophrenia phenotype.
ID: 2086157

THE EFFECT OF AN INCREASING PROBABILITY OF MOTOR INHIBITION IN SCHIZOPHRENIA AND FIRST DEGREE RELATIVES: AN ERP STUDY

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Background: Schizophrenia is a polygenic, heritable mental disorder associated with motor inhibition deficits (Lichtenstein et al., 2009). An fMRI study by Vink, Ramsey, Raemakers, and Kahn (2006) has shown that there are functional abnormalities present in both schizophrenia patients and first degree relatives during a task designed to measure motor inhibition, although only the schizophrenia group showed behavioral abnormalities. In this study, we examined the effect of an increase in stop-signal probability on behavioral and event related potential (ERP) measures between patients with schizophrenia, their first degree relatives, and healthy controls.
Methods: The stop-signal task used in this study was a replica of that used by Vink et al. (2006). The task consisted of GO trials, where participants were prompted to respond to a GO stimulus, and STOP trials, where participants were presented with a GO stimulus followed by a STOP stimulus after a variable delay. The STOP stimulus signaled to the participants to withhold their response, which was essential in measuring stop-signal reaction time (SSRT), a measure of motor inhibition. With each subsequent GO trial the likelihood of a STOP trial increased.
Results: The schizophrenia group demonstrated a significantly longer SSRT than both the control and relatives groups, indicating deficits in motor inhibition ability. In general, the control and relatives groups demonstrated larger P300 amplitudes during trials of lower STOP probability and decreases in amplitude as STOP probability increased whereas the schizophrenia group demonstrated smaller P300 amplitudes that didn't significantly change between conditions. The relatives group also showed the largest change in P300 amplitude between the medium and high STOP probability GO trials. The control and relatives groups demonstrated changes in P300 peak latency that weren't observed in the schizophrenia group. The relatives group demonstrated a change in P300 peak latency at Cz that was not observed in the control group.
Conclusion: Similar to previous results, the schizophrenia group demonstrated impaired motor inhibition ability. Unlike previous results, the relatives group did not differ from controls in the same way as the schizophrenia group in neural responses to increasing STOP trial probability. However, unique P300 peak amplitude and latency effects were observed in the relatives group that were not demonstrated in either the schizophrenia or healthy control groups.
ID: 2081635

MIRNA BIOGENESIS IN SCHIZOPHRENIA, A CHINESE STUDY

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Background: Previous findings suggested associations between schizophrenia and the impairment of post-transcriptional regulation of brain development through miRNA systems.
Methods: Our study aims include 1) comparing the overall frequency of 121 rare variants in 59 genes associated with the miRNA-system in GWAS-derived data involving 768 schizophrenia cases and 1348 healthy controls, and validated in an independent GWAS data involving 1802 schizophrenia cases and 1447 controls; 2) profiling genome-wide miRNA expression in blood collected from 15 early-onset schizophrenia early onset cases and 15 healthy controls; and 3) constructing a miRNA-mRNA regulatory network using our previous genome-wide mRNA expression data generated from a separate sample of 18 early onset cases and 12 healthy controls collected in China.
Results: Our recent findings indicate that: 1) In genes associated with the miRNAs control, approximately 50% more RVs in schizophrenia cases than in controls were observed; 2) The observed lower miRNA activity in EOS patients compared to healthy controls suggests that miRNAs are abnormally downregulated; and 3) There is a predicted regulatory network among several downregulated and upregulated mRNAs. Rather than pinpointing specific deficiencies in gene products in the origin of schizophrenia, our results implicate an overall dysregulation of transcription. We would like to argue that schizophrenia is not the result of abnormalities in one or two pathways or biological systems, but arises rather from disruption throughout an entire cellular network.
Conclusion: To sum, our results indicate that the genetically based dysregulation of miRNA systems undermines the miRNAs' inhibitory effects, resulting in the abnormal upregulation of genome transcription in the development of schizophrenia. The encouraging message we would like to convey is that miRNA might serve as a pivotal regulator in the schizophrenia development process.
ID: 2093240

IMPAIRED EEG MU RHYTHM SUPPRESSION DURING MOTION IMAGERY TASK IN FIRST EPISODE OF PSYCHOSIS

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Background: EEG mu rhythm is detected in the 8–13 Hz frequency over sensorimotor cortex. Unlike alpha rhythm having the same frequency range and being suppressed with eyes opening, mu rhythm suppresses in response to self-initiated movements, observed movements and imagined movements and often refers to as a selective measure of the activity of the mirror neuron system. To date, impaired mu rhythm suppression in patients with schizophrenia was reported only in one study in which observed and actual hand movement's tasks were used. The aim of our study was to examine the properties of mu rhythm suppression in patients at the early stages of psychosis using motion imagery task.
Methods: We measured EEG spectral power (SP) of mu-rhythm in right-handed 223 subjects (patients with first episode of psychosis N=125 and healthy comparison subjects N=98 matched by age, gender) at rest and while performing the motion imagery task (with eyes closed). In order to disentangle mu-rhythm from alpha rhythm, the principal component analysis (PCA) was applied taking into the account the following specifications: mapping of mu-rhythm in sensorimotor cortex, the absence of the reaction on eyes opening, suppression of mu-rhythm during motion imagery task. Mean mu-rhythm spectral power (SP) in the 8–13 Hz range for the C3, Cz and C4 electrodes was calculated for the resting state and task condition at each electrode site separately. Mu-suppression was defined by the log-ratio of SP during task condition relative to the SP during the rest condition with eyes closed.
Results: Between group comparison of mu-rhythm SP at rest showed higher SP in patients with first episode of psychosis ($F(2, 356)=5.8623$; $p=.003$) as compared to controls. Post-hoc using Fisher LCD revealed elevated SP in C4

($p \leq 0.0001$) and Cz ($p \leq 0.01$). In task performance we observed less suppression of mu rhythm in patients in contrast to healthy controls ($F(1,179)=4.019$, $p=0.04$), post-hoc showed significant difference in C3 ($p \leq 0.05$) and C4 ($p \leq 0.01$). **Conclusion:** For the first time, we demonstrate the initial elevation of mu rhythm power in patients with first episode of psychosis. Likewise previous research showing the suppression of mu rhythm in schizophrenia patients during self-initiated or observed movements, we indicate impaired mu rhythm suppression while motor imagery task performance emphasizing the abnormal mirror neurons activity.
ID: 2117975

Clinical Neurochemistry; Therapeutics: Pharmacologic Probes

DISEASE BIOMARKERS FOR SCHIZOPHRENIA - FROM LABORATORY TO PATIENT BESIDE-

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Background: Schizophrenia is a multifaceted neuropsychiatric disorder which almost certainly presents a heterogeneous group of aetiologies. A better molecular understanding of the disease onset and progression is urgently needed. Multi-omics profiling approaches can be employed to investigate large numbers of patient and control samples in a single experiment. These large scale experiments are required to identify disease intrinsic molecular signatures as well as patient subgroups.

Methods: Multiple independent cohorts of first-onset, recent-onset, prodromal and pre-disease onset serum samples from patients with schizophrenia or prone to develop the disorder were investigated using a multiplexed ELISA approach to identify significantly changing proteins.

Results: We have identified a number of highly significant peptides and proteins in serum that distinguish first-onset paranoid schizophrenia patients from healthy controls. Our findings suggest alterations in glucoregulatory, inflammatory and hormonal processes in drug-naïve patients with first-onset schizophrenia. Interestingly, we also identified disease-relevant metabolic and inflammatory changes in affected and unaffected siblings of schizophrenia patients and have preliminary evidence for the existence of schizophrenia sub-groups, based on the expression of serum proteins.

Recently, we identified a biomarker panel for schizophrenia based upon a meta-analysis of five schizophrenia cohorts and tested their predictive performance in psychiatric at-risk individuals before the onset of schizophrenia or psychosis.

Validation testing of the panel on first-onset schizophrenia patients gave an AUC of 0.97 for disease detection and a true positive rate of 89%. Analysis of a cohort from the US military, where blood was collected prior to disease onset of either schizophrenia or bipolar disorder, yielded an AUC of 0.90 and 0.53 respectively. The AUC was 0.82 for prediction of schizophrenia conversion in a cohort of prodromal/UHR individuals, which increased to 0.92 when CAARMS positive subscale scores were incorporated into the model.

Conclusion: We have identified a robust biomarker panel for the diagnosis and prediction of schizophrenia. Future applications of this test could aid clinicians in identification of vulnerable patients early in the disease process, allowing more effective therapeutic intervention.

ID: 2114544

ODORANT INDUCED G PROTEIN MEDIATED INTRACELLULAR SIGNALING IS DIFFERENTIALLY REGULATED IN OLFACTORY NEUROEPITHELIAL CELLS FROM INDIVIDUALS AT CLINICAL RISK FOR SCHIZOPHRENIA AND PATIENTS WITH SCHIZOPHRENIA

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Background: Schizophrenia (SCZ) is associated with pervasive deficits in olfactory function. Nevertheless, little is known about the molecular underpinnings of olfactory dysfunction in SCZ or alterations during the prodromal period. We previously reported increased odorant induced electroolfactogram (EOG) measures in clinical high risk (CR) subjects as well as in SCZ patients. We hypothesized that odorant induced activation of G protein activation and/or its downstream signaling is increased in olfactory neuroepithelial (OE) cells of CR and SCZ subjects.

Methods: We examined mRNA and protein expression of key odorant signaling molecules in in vitro OE culture cells derived from 18 SCZ patients and 9 CR subjects and their age-sex matched controls using qPCR and Western blotting respectively. Ex vivo OE biopsy tissues from a subset of these subjects (10 matched pairs) were examined using LCM based qPCR. We tested odorant induced G protein activation in synaptosomal membranes from OE cells by incubating membranes with 35mM of odorants, and S35-GTPγS, followed by immunoprecipitation experiments with antibodies for Gαs/Golf, Gi, Go, Gq/11, G12 and G13.

Results: OE cells from SCZ patients showed a trend for decrease in Gαs/olf and a decrease in ACIII protein (student's t-test; two tailed, p=0.02). OE cells from CR subjects showed a significant decrease in Gαs/olf (p=0.02) and no change in ACIII, but an increase in PKA (p<0.0001). mRNA quantification of these molecules showed no differences either in LCM-qPCR of the OE sections or in OE culture cells. Activation of Gαs/olf and Go in response to odorant mixtures was decreased in the SCZ group (p=0.03, p=0.02, respectively), while it was unaltered in CR subjects. In contrast to the observed decreases in odorant induced G protein activation, dopamine induced activation of Gαs/olf and Gq/11 was increased in OE cells of SCZ patients but unaltered in CR subjects.

Conclusion: While increased EOG measures in SCZ or CR subjects predict increased odorant signaling, odorant induced G protein activation was decreased. This suggests that increases in EOG may be due to enhancement of molecular events downstream to G protein activation in both populations. While odorant induced signaling is altered in both SCZ and CR subjects, the pattern of dysregulation in G protein signaling differs between the groups. Future studies will test progression of odorant signaling dysregulations in CR subjects and their associations with neuropsychiatric symptoms.

ID: 2118656

MODELING PREDISPOSITION TO SCHIZOPHRENIA USING HIPSCS

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Background: Schizophrenia (SZ) is a debilitating neurological disorder. Though postmortem studies have revealed reduced neuron size and spine density in SZ brain tissue, the molecular mechanisms underlying the disease state remain unclear.

Methods: To address this, we directly reprogrammed fibroblasts from SZ patients into human induced pluripotent stem cells (hiPSCs) and subsequently differentiated these disorder-specific hiPSCs into neural progenitor cells (NPCs) and neurons.

Results: Gene expression comparisons of our hiPSC-derived neural progenitor cells (NPCs) and 6-week-old neurons to the Allen BrainSpan Atlas indicate that our hiPSC neural cells, from controls and patients with SZ, most resemble fetal rather than adult brain tissue, indicating that hiPSC-based models may not yet be suited for the study of the late features of this disorder. Our analysis confirms that a significant fraction of the gene signature of SZ hiPSC-derived neurons is conserved in SZ hiPSC neural progenitor cells (NPCs), suggesting that at least some of the molecular events contributing to SZ are established prior to neuronal maturation. We observed aberrant migration and increased oxidative stress in SZ hiPSC NPCs, and diminished neuronal connectivity in conjunction with decreased neurite number, PSD95-protein levels and glutamate receptor expression in SZ hiPSC neurons. Key cellular and molecular elements of the SZ phenotype were ameliorated following treatment of SZ hiPSC neurons with the antipsychotic loxapine.

Conclusion: To confirm these findings across a larger cohort of patients, we have now generated hiPSCs from thirteen patients with childhood-onset

SZ (COS) and twelve additional controls. COS is a rare and particularly severe form of the disorder, with an onset of psychosis prior to age twelve. We anticipate that neural cells derived from patients with COS will have accelerated and/or more severe cellular phenotypes relative to those we have already reported for adult-onset SZ, and so might be better suited for stem-cell based models of SZ predisposition.
ID: 2086064

CHARACTERIZATION OF THE PERIPHERAL CANNABINOID SYSTEM IN SCHIZOPHRENIA: CORRELATES WITH CLINICAL MEASURES

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Background: Cannabis use during development could potentially be a risk factor for later development of psychosis. Cannabinoid signaling is extensive, with receptors exerting multiple regulatory functions in both immune and central nervous systems. In the brain, cannabinoid receptors (CNR) directly modulate dopaminergic and serotoninergic systems. Additionally, in the peripheral lymphocyte, CNRs are primarily responsible for mediating cytokine release, a dysregulated mechanism in schizophrenia. The literature has indicated the cannabinoid system is strongly involved in neuropsychiatric disorders, including schizophrenia. Thus, further characterization of this signaling system and its correlations with behavioral outcomes is needed.
Methods: mRNA levels of CNRs and their interacting proteins were measured in human lymphocytes obtained from 70 participants (35 normal controls, 35 patients with schizophrenia). Changes in mRNA expression were measured using qRT-PCR with β-Actin and GAPDH for normalization. Clinical measurements were also collected and included the MATRICS cognitive battery, the Hamilton Depression Scale (HAM-D), and the Heinrichs-Carpenter Quality of Life Scale (QLS).
Results: There were significant diagnostic increases in the expression of the CNR mRNA panel in peripheral lymphocytes. Additionally, significant correlations existed between the CNR panel mRNA and the clinical measurements collected. Specifically, as mRNA levels increased, cognitive processing was significantly impaired, while depressive symptoms were increased. Self-reported quality of life scores were also significantly decreased with elevated mRNA levels.
Conclusion: These results suggest that further exploration of the cannabinoid system in psychotic illness could lead to a better understanding of cognition, affect regulation and underlying systemic physiology.
ID: 2103004

GLUCOCORTICOID-IMMUNE DYSREGULATION IN RESPONSE TO PSYCHOLOGICAL STRESS IN SCHIZOPHRENIA

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Background: Abnormalities in glucocorticoid and inflammatory pathways have been identified as possible mechanisms in the pathophysiology of schizophrenia. These systems are activated by stress, and typically interact dynamically to optimize adaptation to challenging environmental conditions. We hypothesized that patients with schizophrenia would exhibit dysregulation of glucorticoid-mediated suppression of immune responses to stress.
Methods: 40 healthy controls and 37 individuals with schizophrenia underwent a computerized psychological challenge involving two tasks (mirror tracing and mental arithmetic) designed to be frustrating and obnoxious. In this paradigm, participants who forego a monetary award and quit both tasks early are classified as distress intolerant (DI). Saliva samples were collected prior to and at 3 time points following completion of the stress challenge and salivary cortisol and IL-6 responses were assayed by ELISA.
Results: A repeated measures ANOVA of salivary IL-6 using diagnosis and distress intolerance as group factors revealed a significant effect of time ($F=4.65$, $p=.024$), a trend for interaction of time and diagnosis ($F=3.49$, $p=.053$), and an interaction of time, diagnosis, and DI ($F=4.44$, $p=.027$). Patients who were DI exhibited greater levels of IL-6 at baseline and a greater rise in IL-6 following stress compared to non-DI patients. In controls, greater acute rise in cortisol (change from baseline to immediately following task) was associated with a greater decrease in IL-6 following stress (change from immediately following stress to last time point following stress; $r=-.456$, $p=.007$). In contrast, this relationship was positive in schizophrenia patients ($r=.434$, $p=.013$).
Conclusion: Levels of IL-6 in the saliva rose significantly following exposure to this stress paradigm in both patients and controls. In healthy controls, a more robust acute cortisol response suppressed IL-6 levels following stress, corresponding to the usual anti-inflammatory effects of cortisol. However, this relationship in patients was in a statistically significant, opposite direction. These results implicate inability to down-regulate inflammatory responses to stress in schizophrenia.
ID: 2087547

CHASING THE REPRODUCIBLE BIOMARKER …

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Background: Background: The burden of psychiatric disorders on society is immense. Biomarkers have the potential to reduce this burden by transforming both the diagnosis and treatment of these disorders. However, the poor reproducibility of CNS biomarker studies is driving skepticism about whether the periphery can be informative about these disorders.
Methods: Methods: We considered the impact of study design (i.e. power and recruitment), quality control (i.e. plate effects and identification of outliers), handling of missing data and statistical analysis (i.e. variable selection and resampling methods) on the reproducibility of proteomic studies. We evaluated these factors using data from the Netherlands Study of Depression and Anxiety (NESDA) - an ongoing eight-year longitudinal, multi-site naturalistic cohort study with 3,000 participants recruited from the general population, general practices, and mental health organizations in the Netherlands.
Results: Results: Unsurprisingly, the design of proteomic studies was essential. For example, we demonstrated that females on birth control can have a devastating impact on biomarker studies. For molecular analytes that passed quality control, missing data can dramatically reduced the sample-size when we modeled the joint effects of putative biomarkers. Although multiple imputation allows for the uncertainty in the imputed data, we found estimates obtained across the imputed data sets tended to be consistent. We avoided overfitting the original data by using different variable selection approaches in conjunction with resampling methods such as cross-validation. As expected, resampling improved the accuracy of response estimates on new observations for all of the variable selection approaches evaluated. However, variable selection approaches that efficiently search the model space, like lasso and Bayesian regression, tended to perform more consistently when applied to new data. In addition, the model posterior probabilities provided by Bayesian approaches, allowed competing models to be considered. Finally, we found that undetected sex-specific effects also impacted on reproducibility.
Conclusion: Conclusion: We evaluated a number of solutions for commonly encountered obstacles to biomarker studies being more reproducible. Although based on patients with depression and anxiety, the findings are also applicable to patients with schizophrenia.
ID: 2115293

BI 409306, A NOVEL PHOSPHODIESTERASE 9A INHIBITOR, PART I: POTENCY, SELECTIVITY AND IN-VITRO FUNCTIONAL CHARACTERIZATION ON SYNAPTIC PLASTICITY

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Background: Inhibition of specific phosphodiesterases (PDEs) in the brain has gained attention as a potential new approach for memory enhancement. Among those PDEs is PDE9A which is specific for cyclic guanosine monophosphate (cGMP) and expressed in cognition relevant regions of the brain. cGMP is an important second messenger in neurons related to NMDA receptor signalling, and thereby, involved in synaptic plasticity and memory formation. Thus, PDE9A inhibitors are hypothesized to improve cognitive function via increasing NMDA receptor related cGMP signalling pathway to strengthen synaptic plasticity. This study characterizes the potency and selectivity of the novel PDE9A inhibitor BI 409306. In addition, the effect of this drug was tested on long-term potentiation (LTP) in rat hippocampal slices, a widely accepted cellular experimental model of synaptic plasticity and memory formation.
Methods: The molecular potency and selectivity of BI 409306 for PDE9A and other PDE enzymes were determined using cytosolic extracts of SF9 insect cells over-expressing full-length human enzyme, employing SPA or radiometric technology for measuring cGMP or cAMP. Selectivity against other non-PDE targets was evaluated using receptor binding assays. Functional effects of BI 409306 regarding synaptic plasticity were tested on LTP in rat hippocampal slices using weak or strong high-frequency stimulation paradigms for LTP induction in CA1 region of the hippocampus.
Results: The IC50 value of BI 409306 on PDE9A was determined to be 52 nM. The selectivity of BI 409306 for other PDEs was assessed against PDE1A (IC50 = 1.4 μM), PDE1C (IC50 = 1.0 μM), PDE2A, PDE3A, PDE4B, PDE5A, PDE6AB, PDE7A, and PDE10A (IC50 all > 10 μM). BI 409306 demonstrated no significant activity against further 95 non-PDE targets at 10 μM. Regarding hippocampal LTP, BI 409306 application to rat hippocampal slices led to a significant enhancement of LTP in both study paradigms.
Conclusion: Enzymatic and receptor binding assays demonstrate that BI 400396 is a potent and selective PDE9A inhibitor which increases LTP in rat hippocampal slices. Corroborating previous reports on functional effects of other PDE9A inhibitors, these data demonstrate that inhibition of PDE9A may be an effective way of increasing glutamatergic signalling and strengthening synaptic plasticity which could be a potential approach for memory enhancement in CNS disorders.
ID: 2085494

PHARMACOKINETIC AND SAFETY EVALUATION OF LURASIDONE IN PEDIATRIC PATIENTS WITH PSYCHIATRIC DISORDERS

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Background: The aims of this open-label, multicenter, single and multiple ascending dose study of lurasidone were to characterize the pharmacokinetic (PK), safety, and tolerability profiles of lurasidone in a pediatric/adolescent population (6–17 years old) and to identify a tolerated dose range for subsequent pediatric clinical studies.
Methods: Patients from four age groups (6–9, 10–12, 13–15, and 16–17 years) diagnosed with ADHD with aggressive behavior (ie, comorbid conduct disorder or other disruptive behavior disorder), bipolar disorder, schizophrenia, Tourette syndrome, or autism spectrum disorder were assigned to one of five lurasidone dosing cohorts (20, 40, 80, 120 or 160 mg/d). Dose cohorts entered the study sequentially, beginning with the 20 mg/d cohort; if a dose level was tolerated, the next dose cohort was initiated. In the single-dose phase, patients received one dose of lurasidone; blood samples for PK analysis were collected predose and over a 48-hour period postdose. After a 2-day washout period, patients entered the multiple-dose phase and received once-daily lurasidone for 7–9 days; PK samples were collected before and over a 24-hour period after the final dose. Maximum serum concentration (Cmax) and area under the concentration-time curve (AUC) for lurasidone were calculated. PK parameters in adults were derived from a 3-compartment population PK model.
Results: A total of 105 patients were enrolled in the study. The observed lurasidone pediatric PK exposures (Cmax and AUC0-24 hours) following multiple-dose administration across the dose range studied were generally similar to the PK model of adult exposure at steady state. The most common adverse events (AEs) were somnolence (42%), sedation (18%), and nausea (17%); incidence of AEs was dose-dependent across the 20–160 mg/d dose range. All 6- to 9-year olds experienced somnolence at 120 mg/d; therefore, lurasidone 160 mg/d was not evaluated in this age group. Two serious AEs (parkinsonism, dystonia) were reported, both at 80 mg/d.
Conclusion: The results of this study indicate that lurasidone exposure in this heterogeneous pediatric population was similar to that observed in adults following single and multiple doses of lurasidone 20–160 mg/d. The AE profile of lurasidone in this pediatric patient population was generally consistent with that observed in adult patients. Based on this study, doses of lurasidone 20–80 mg/d are being evaluated in clinical trials with pediatric patients.
Funding: Sunovion Pharmaceuticals Inc.
ID: 2087789

L-ARGININE METABOLISM BEFORE AND AFTER 10 WEEKS OF ANTIPSYCHOTIC TREATMENT IN FIRST-EPISODE PSYCHOSIS

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Background: Alteration of L-arginine metabolism has been reported in schizophrenia patients. The aim of this study was to explore the changes in the plasma levels of L-arginine and its metabolites such as agmatine, L-citrulline and ornithine before and after 10 weeks of antipsychotic treatments in the first-episode psychosis patients.
Methods: The patients with first-episode psychosis (n=41) were recruited to study and followed up for 10 weeks. The blood samples were obtained before initiating the antipsychotic treatment and at the follow up after ten weeks. LC/MS/MS method was used to measure L-arginine, L-citrulline, ornithine and agmatine levels. To evaluate the psychotic symptoms the inventories, SANS, SAPS and BPRS were applied before and after treatment period. A decrease in BPRS score more than 40% was used to indicate treatment respond. Healthy volunteers (n=30) matched for age, sex and education levels were used as the control group.
Results: The plasma L-arginine, L-citrulline and agmatine but not ornithine levels were significantly higher compared to healthy controls in the first-episode psychotic patients ($p<0.0001$). After the treatment, plasma L-arginine and L-citrulline levels were significantly increased ($p<0.05$) while ornitine level remained similar ($p>0.05$). On the other hand after the treatment, plasma agmatine level was significantly decreased but it was still higher than the control subjects ($p<0.05$). The initial plasma agmatine level was negatively correlated with SANS and SAPS scores which were evaluated at the end of 10 weeks ($r=-0.43$ and $r=-0.34$, respectively; $p<0.05$). The initial L-arginine levels was positively correlated with the SANS score ($r=0.40$, $p<0.01$) and negatively correlated with SAPS

score (r=-0.36, p<0.05). The initial L-citrulline levels were negatively correlated with SANS, SAPS and BPRS scores not only before the treatment but also at the end of the 10 weeks treatment. Moreover the plasma L-arginine level in the treatment-responder group was significantly higher compared with the non-responder group (248.9 ± 18.5 vs. 191.4 ± 18.4, respectively; p<0.05).
Conclusion: L-arginine and its metabolites L-citrulline and agmatine have an important role in the pathology of first-episode psychosis. Their plasma levels significantly correlated with the symptom scales and they differentially changed with the treatment. Importantly initial agmatine and L-citrulline levels may predict the treatment response after 10 weeks.
ID: 2117702

GLUCOCORTICOID AND INFLAMMATORY RESPONSE TO A PSYCHOSOCIAL STRESSOR IN PEOPLE WITH SCHIZOPHRENIA

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Background: Psychological stress and stress hormones can modulate immune function in schizophrenia (SZ) and accumulating evidence suggests that immune dysregulation may be present in people with the illness. In this study we compare the response of patients with SZ and healthy controls (HC) to a psychosocial stressor.
Methods: Sixteen participants (8 SZ and 8 HC) were exposed to the Trier Social Stress Test. Levels of serum free cortisol, adrenocorticotropic hormone (ACTH), interleukin (IL)-6, and tumor necrosis factor (TNF)-alpha were assessed at baseline and repeatedly at 15-, 30-, 45- 75- and 105- minutes following the stressor. IL-6 and TNF alpha levels were log transformed and between group differences were analyzed.
Results: Both groups were matched on sex, race and age. At baseline serum IL-6 and cortisol did not significantly differ between SZ and HC. Serum cortisol decreased at 45 minutes and returned to near baseline in the SZ group while there was a steady increase in the HC group (F=4.35, df=53.4,4, p=0.004). TNF-alpha levels were significantly lower in the SZ (log transformed 2.23 ± 2.27 pg/mL) group compared to HC group (log transformed 3.81 ± 3.96 pg/mL) (t=11.29, df=23.1, p=0.00078). TNF-alpha was unchanged following stress in participants with SZ but decreased in HC (group x time effect: F=4.38, df=4, 16.5, p=0.013). IL-6 increased similarly in both HC and SZ during the 105 minutes. We plan to investigate the relationship of cortisol and immune markers to kynurenine pathway metabolites.
Conclusion: SZ patients are known to have a blunted cortisol stress response to a psychological stressor compared to HC. These data indicate that after a psychological stressor, cortisol response was indeed blunted. TNF-alpha changes seen in HC were also blunted in SZ patients. More work is needed to understand the role of stress and inflammation to the pathophysiology of schizophrenia.
ID: 2092798

PERIPHERAL BIOMARKERS FOR SCHIZOPHRENIA: DIAGNOSIS, PROGNOSIS AND FOLLOW-UP OF TREATMENT

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Background: Biomarkers have been intensely searched to help diagnosis, prognosis and follow-up of treatment of psychiatric diseases. Our group has focused on two peripheral biochemical markers, putatively related to schizophrenia (SCZ), S100B and BDNF. S100B is a calcium-binding protein secreted by astrocytes and other glia cells. Higher levels of peripheral S100B (serum or CSF) have been reported in schizophrenic than healthy individuals.BDNF is a neurotrophin produced by neurons, and its reduction has been associated to schizophrenia.
Methods: We have investigated peripheral levels of these proteins measured by ELISA as well as S100B secretion in cell cultures.
Results: We have observed in astroglial cultures that S100B secretion induced by interleukins is attenuated by antipsychotics, in agreement with some findings observed in schizophrenics. A recent meta-analysis shows that peripheral BDNF levels (in serum and plasma) were moderately reduced in SCZ compared to controls (Fernandes et al, 2014, Molecular Psychiatry, in press). Moreover, in plasma, but not serum, peripheral BDNF levels are consistently increased after antipsychotic treatment irrespective of the patient's response to the medication.
Conclusion: It has been assumed that peripheral levels of these brain-derived proteins reflect the brain activities where they are involved. However, it is need caution to interpret peripheral levels of these proteins to assure its appropriate use as biomarkers in the schizophrenia and other psychiatric diseases.
ID: 2097080

PERIPUBERTAL STRESS REDUCTION AND THE AMYGDALA-HIPPOCAMPAL PATHWAY IN MAM RATS: PATHWAYS TO PREVENTION OF TRANSITION TO PSYCHOSIS

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Background: Although antipsychotic drugs are of use in the treatment of schizophrenia, perhaps a more effective approach would be to identify individuals at risk for schizophrenia, and administer treatments that may prevent the emergence of this disorder.
Methods: We tested rats administered the mitotoxin methylazoxymethanol acetate (MAM) during gestational day 17; a procedure shown to consistently result in adult animals showing anatomical, behavioral, and pharmacological alterations consistent with an animal model of schizophrenia. MAM or saline rats were administered either saline, diazepam, or the cannabinoid agonist WIN55-212-2 during pre-post puberty periods. Rats were then tested as adults.
Results: Consistent with studies of schizophrenia patients, we found that MAM rats tested prepubertally showed evidence of increased stress responses (as evidenced from increased footshock-induced vocalizations) and increased anxiety (as measured in the elevated plus maze) as well as disruptions in corticosterone response. These rats also showed abnormally high activity of the basolateral amygdala, consistent with increased stress. Furthermore, at this stage MAM rats exhibited loss of parvalbumin staining without cell loss. This contrasts with the adult rat in which the parvalbumin neurons are lost (as evidence by decreased constitutive staining for substance P receptors). In order to prevent this pathological process, we examined whether peripubertal intervention could circumvent the transition to psychosis. MAM and saline rats were treated with diazepam at PD 31–40 and tested as adults. In contrast to the MAM-saline rats, the MAM-diazepam rats did not develop dopamine hyper-responsivity as measured electrophysiologically and behaviorally. Furthermore, MAM-diazepam rats did not show elevated anxiety in the adult stage compared to MAM-saline rats. Interestingly, although treating normal rats with the cannabinoid agonist WIN55,212-2 administered during PD40-65 induced alterations similar to those seen in MAM rats, administering this compound to MAM-treated rats actually attenuated the increase in dopamine neuron firing observed in MAM-saline rats.

Conclusion: These data suggest that individuals at genetic risk for schizophrenia may be identified by examining their response to stressors, and that intervention during the peripubertal stage to limit the effects of stress exposure may be preventative toward transition to psychosis later in life.
ID: 2087613

HAIR CORTISOL IS ASSOCIATED WITH SELF-REPORT OF CHILDHOOD ABUSE AMONG INDIVIDUALS WITH A PSYCHOTIC DISORDER

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Background: In recent years, cortisol has become a hormone of increasing interest for researchers of serious mental illness (SMI). Both schizophrenia-spectrum and bipolar disorders appear to be associated with a dysregulated hypothalamic-adrenal-pituitary axis (HPA). Additionally, childhood abuse, which is common among individuals with SMI, has been found to permanently alter HPA-axis functioning for some individuals who later develop mental illness. The purpose of this study is to determine the feasibility of using hair cortisol analysis for evaluating HPA axis functioning in psychotic disorders. The assessment of cortisol concentrations in hair is unique in providing a long-term average of cortisol production and is not subject to diurnal fluctuations.
Methods: Hair samples were collected from a community sample of 57 individuals with SMI (44 schizophrenia-spectrum, 13 bipolar I). Cortisol concentrations were determined using an enzyme-linked immunosorbent assay (ELISA) procedure. All participants completed surveys that included questions about physical, sexual, and emotional childhood abuse, as well as neglect.
Results: Partial correlations controlling for age and sex indicated significant associations between self-reported childhood sexual abuse ($r=0.38$, $p=0.005$; physical abuse ($r=0.335$, $p=0.013$; and emotional abuse ($r=0.27$, $p=0.049$). No significant association was found between cortisol levels and childhood neglect ($r=0.17$, $p=.2$).
Conclusion: Within an SMI population, self-reported childhood abuse appears to be positively associated with hair cortisol levels in adulthood. These results contrast with recent studies that found people with a history of trauma had lower cortisol levels than controls. While antipsychotic medication is known to suppress cortisol, medication effects do not appear to account for the findings in this preliminary analysis. Findings suggest that the interaction between childhood abuse and adult production of cortisol may have a unique relationship among people who later develop an SMI.
ID: 2118005

A COMPARISON OF B CELL REPERTOIRE IN CEREBROSPINAL FLUID OF PATIENTS WITH SCHIZOPHRENIA AND HEALTHY INDIVIDUALS

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Background: The biological basis of schizophrenia is complex and reflects dysfunction in various systems that are closely interlinked such as gene expression, cellular pathways, neurotransmitter system, and immune regulation. The involvement of some facets of the immune system in the mechanisms that underlie this disorder is inevitable as the immune system is an integral part of the biological network. B and T cells are key players of the adaptive immune system. In the peripheral blood of healthy human subjects, the B cell repertoire is distinct and diverse. B cells have receptors that can bind and effectively react to a multitude of antigens. However, very little is known of the B cell repertoire in the cerebrospinal fluid (CSF) of healthy individuals as well as patients with schizophrenia. The primary objective of this project was to sequence and compare B cells in CSF of patients with schizophrenia and compare with B cells in CSF of healthy volunteers.
Methods: Samples of CSF from healthy volunteers and patients were obtained, and the B cells were isolated via single cell sort using Fluorescent-Activated Cell Sorting (FACS). After reverse transcription to produce cDNA, a two-step PCR was performed to amplify the IgG and IgM heavy chains. The resulting product was sent out to Genewiz for sequencing. Analysis of the data looking into B cell repertoire involved; VH, DH, and JH family and subfamily usage (recombination of VDJ regions allow for unique antibodies), N region addition (adding nucleotides to become more specific to target new antigens), and mutations.
Results: After analyzing multiple sequences from 2 individuals, initial results indicate that,
VH family usage is different in CSF of patients versus healthy individuals while the average N region length is similar in B cells from both populations. Mutation analysis is underway.
Conclusion: Our initial results suggest a difference in the B cell repertoire in the CSF of patients with schizophrenia compared to healthy controls. This novel finding opens new questions and possibilities on the preference of a selective B cell repertoire in the CSF of patients. While this knowledge will expand our understanding of a typical B cell repertoire, it may ultimately aid in evaluating the relationship between clinical symptoms and immune dysfunction through study of B cell antibodies and analysis of immune cell cytokines in patients with schizophrenia.
ID: 2132462

TRUTH OR FICTION: EVALUATING THE MERITS OF A CLASSIFIER

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Background: Background: Why are so many biomarker studies reported by top scientists published in major journals not replicated?
Methods: The problem of replicating studies has three main facets: pre-analytic variability in sample collection, methodological variability in conducting the assay, and variability in the analysis procedures used to interpret the data. Regarding the latter, the sine qua non of verification is "random labeling," widely applied in drug development, cancer biomarkers, and other lines of research that propose classifiers. The problems is that Nature hides many interdependencies among biomarkers and that from such interdependencies modern classification algorithms enabled on computers can generate seemingly convincing patterns from nonsense (randomly scrambled case/control data). The solution is testing by random relabeling, meaning development of a classifier by any preferred means and then scrupulously reenacting that development with randomly relabeled cases and controls.
Results: Analyses of biomarker data from studies of schizophrenia show that it is too easy to find patterns from nonsense data but that stringent random labeling tests imply good performance by surviving classifiers in unlikely by chance.
Conclusion: Only when multiple reenactments of the entire development process by exactly the same protocol repeatedly fails to yield a classifier with performance as good as the true classifier, does the entire exercise deserve credibility. Beware that numerous shortcuts appear in the literature; they are not acceptable. In this presentation data from the North American Longitudinal Study project will be used to illustrate the value of random relabeling.
ID: 2115469

GLYCINE MAGNETIC RESONANCE SPECTROSCOPY IN CARRIERS OF A MUTATION AT 9P24.1

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Background: We carried out proton magnetic resonance spectroscopy (MRS) in 2 carriers of a triplication of the gene encoding glycine decarboxylase (GLDC), the enzyme that catabolizes glycine, to assess effects of acute glycine administration on brain glycine levels. GLDC triplication would be expected to accelerate degradation of glycine, resulting in low levels of brain glycine, in low occupancy of the NMDA receptor glycine modulatory site, and in NMDA receptor hypofunction, which has been strongly implicated in the pathophysiology of psychotic disorders. The triplication carriers were a woman with a diagnosis of bipolar disorder with psychotic features and her son, who had a diagnosis of schizo-affective disorder. Comparison subjects were 9 healthy controls, including 2 relatives of the triplication carriers.
Methods: Subjects underwent MRS scans in a 4 Tesla scanner (Agilent Inc.). After acquisition of anatomical images, a 2x2x2cm MRS voxel was positioned medially in the grey matter of the parieto-occipital cortex (POC). MRS data were acquired using a glycine-optimized MRS protocol (1). Following a baseline scan, participants were removed from the scanner and consumed glycine (0.4g/kg, up to 30 g) in a lemon-flavored drink over a 10-minute interval. The subjects were repositioned for post-glycine MRS scans using anatomical landmarks, thereby maximizing MRS voxel co-registration with their baseline position. MRS scans were collected over the next 1.5 hours. Glycine/creatine ratios were derived using LCModel fitting software (2) and in-house processing software. Peak brain glycine increases (%baseline) were determined and were corrected for the actual glycine dose administered to each subject (g/kg).
Results: A larger increase in dose-normalized peak brain glycine levels was observed in the two subjects with GLDC triplication (677 ± 166%/g/kg) compared to all other subjects (393 ± 149%/g/kg) (two-sided unpaired t=2.4, df=9, P<0.04).
Conclusion: These results indicate that GLDC triplication carriers may experience greater brain glycine increases after acute glycine administration than controls, supporting the hypothesis that glycine augmentation therapy may be efficacious in select populations of individuals with genetic abnormalities that affect NMDA receptor glycine modulatory site occupancy.
ID: 2085837

NESTIN EXPRESSION BEFORE AND AFTER 10 WEEKS OF ANTIPSYCHOTIC TREATMENT IN FIRST-EPISODE PSYCHOSIS

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Background: Nestin, an intermediate filament protein, was originally described as a neuronal stem cell marker during central nervous system development (1). Its expression was shown to be upregulated in progenitor cells and then it decreased when the cells reach their differentiated state (2). Schizophrenia is a neurodevelopmental disorder largely become chronic after a psychotic episode. Here we investigated nestin expression in the peripheral plasma of the patients with first-episode psychosis and after a 10-week treatment.
Methods: Nestin messenger RNA (mRNA) levels were measured in the plasma samples of 41 first episode psychosis patients, diagnosed according to DSM-IV criteria. The blood sample was obtained from antecubital vein before initiating any treatment. The psychotic symptoms were evaluated by using SANS, SAPS and BPRS inventories. After a 10-week treatment the same inventories were repeated and the blood samples were collected. RNA was isolated from the plasma samples and cDNA was synthesized. RT-PCR method was applied to all samples. β-actin housekeeping gene was used as internal standard.
Results: Nestin is highly expressed in peripheral plasma samples of 38 patients and its mean expression level was not change with the 10 weeks of treatment (96.70 ± 26.33 and 71.06 ± 13.30, p>0.05). However its expression level was positively correlated with SAPS score on 10th week (r=0.38, p<0.05), and negatively correlated with the percent change in SAPS and BPRS scores (r=-0.62, p<0.001 and r=-0.46, p<0.01, respectively).
Conclusion: This is the first study to show nestin mRNA can be isolated and measured in the peripheral blood samples of a patient group. Nestin is highly expressed in the first episode psychosis patients. Although its expression did not change with the treatment, difference in individual expression levels gave significant information about the clinical outcome by means of inventory scores. Specifically decreased nestin expression can be related with good clinical outcome in the first episode psychosis patients.
References:
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ID: 2084124

DIFFERENTIAL PRO- AND ANTI-INFLAMMATORY DYSREGULATION IN FIRST-EPISODE PSYCHOSIS DEPENDING ON AGE OF ONSET

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Background: Contribution of inflammatory/anti-inflammatory mediators to first-episode psychosis (FEP) has already been established (1), but differential role of particular components based on age of onset remains understudied. We aimed to compare the pro/anti-inflammatory balance in blood between FEP with onset ≤18 (early-onset) and ≥25 years (late-onset).
Methods: Differences in demographic and clinical characteristics between early- and late-onset patients were assessed using Chi-square, t-test, or Mann-Whitney as appropriate. As normality of continuous variables was not met for most biological markers assessed, we used a 2-tailed non-parametric Mann-Whitney U test to compare levels of pro/anti-inflammatory markers between early- and late-onset FEP both at baseline and

at 6-months follow-up. Wilcoxon signed ranks test was used to test for baseline-6month differences in the same biomarkers. Trajectories of change of pro- and anti-inflammatory parameters between the 2 time points were compared by means of non-parametric general linear model.
Results: 27 patients with early-onset and 43 with late-onset FEP were included. Clinical variables (diagnosis, DUP, PANSS, YOUNG, MONTAS, GAF, cannabis dose, lifetime cannabis use, antipsychotic dose, BMI) were not significantly different between both FEP groups (except lower age of onset of cannabis use in early-onset). Pairwise comparisons showed significantly higher levels of NFkB and PGE2 at baseline, and higher levels of PGE2 and iNOS at 6-months follow up in early-onset FEP. During the 6-month follow-up, both patient groups showed significant increase in PGE2 and TBARS and decrease in 15dPGJ2, whereas late-onset patients showed also increase in COX2 and NO-2, and decrease in NFkB, iNOS and PPARy. Direct comparisons of trajectories of change for each parameter showed significant time-group interaction for iNOS.
Conclusion: We found higher activation of the oxidative/nitrosative parameters in patients with early-onset psychosis at baseline and at 6-moths follow-up. Inflammation and its consequences in patients with early-onset FEP are more focused on inflammatory prostaglandins than on the rest of parameters evaluated. Implication of these results for medication development depending on age of onset seems warranted.
ID: 2095852

GLIAL AND WHITE MATTER ABNORMALITIES IN SCHIZOPHRENIA: SYSTEMATIC REVIEW

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Background: We previously reported the results of a systematic review of human data from neuropathological and neuroimaging studies on the relationship between neuroinflammation and white matter pathology in schizophrenia [*PMID: 24948485*]. Here, we aimed to extend these findings by performing a systematic review focusing of the related evidence from human genetic and biochemical studies.
Methods: We searched PubMed from inception to 19 September 2014 for peer-reviewed, English language, journal articles that met the following eligibility criteria: (*i*) study design: case-control or prospective/retrospective cohort; (*ii*) cases: participants with schizophrenia, determined by standard diagnostic criteria; (*iii*) controls: healthy or no controls; (*iv*) outcomes: genetic mutations or cerebrospinal fluid (CSF) or blood concentrations of myelin and/or oligodendroglia-related genes or proteins and neuroinflammation-related genes or proteins.
Results: Five studies (n=54 559) met eligibility criteria [*PMIDs: 25191916, 24586781, 23956119, 17043297, 15660663*]. A biochemical study (278 schizophrenia, 260 controls) found an association between schizophrenia and lower blood levels of myelin basic protein (F=207.21, p<0.001), glial fibrillary acid protein ([GFAP] F=33.67, p<0.001), and brain-derived neurotrophic factor (F=16.50, p<0.001), and higher blood levels of S-100B (F=12.75, p<0.001) and interleukin-6 (F=15.25, p<0.001). A second biochemical study (17 schizophrenia, 12 controls) found no association between schizophrenia and CSF levels of myelin basic protein (p=0.94), CSF or blood levels of either GFAP (p=0.94; p=0.79) or NSE (p=0.88; p=0.39), but did find an association with higher age-adjusted S-100B levels in CSF (F=5.25, p=0.004) and blood (F=6.42, p=0.032). A genetic study (9394 schizophrenia, 12 462 controls) found an association between schizophrenia and SNPs in astroglia- and oligodendroglia-related gene sets (p=0.0005); microglia-related gene sets were not assessed. A genome-wide association study (13 689 schizophrenia, 18 226 controls) found an association between schizophrenia and astroglia- and oligodendroglia-related, but not microglia-related, gene sets. A third genetic study (111 schizophrenia probands) found no association with 2 SNPs affecting myelin oligodendrocyte glycoprotein.
Conclusion: Genetic, and to a lesser extent biochemical findings, are consistent with neuroimaging and neuropathological evidence linking glia-related white matter inflammation to the pathophysiology of schizophrenia.
ID: 2086487

PRESYMPTOMATIC ANTIOXIDANTS PREVENT ADULT DEFICITS IN A DEVELOPMENTAL RODENT MODEL OF SCHIZOPHRENIA

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Background: A large body of data suggests oxidative stress and inflammatory processes may play a role in schizophrenia, particularly in early stages. As developmental rodent models provide an opportunity to study neurobiological changes in a brain bound to show behavioral deficits during adolescence, we explored whether rats with a neonatal ventral hippocampal lesion (NVHL) exhibited oxidative stress and whether presymptomatic antioxidant treatment prevented the emergence of a diverse set of behavioral, neurochemical, and electrophysiological deficits in this model.
Methods: NVHL or sham rats received the antioxidant N-acetyl cysteine (NAC) or vehicle from postnatal day (P) 5 to 55 in some and from P 35 to 50 in other rats. Rats were tested at two age groups: P21, when no behavioral anomalies are yet detected, and P61, when rats are adults and behavioral deficits are evident. We assessed the presence of oxidative stress, parvalbumin leves, and set of interneuron-dependent physiological and behavioral parameters.
Results: Juvenile and adolescent treatment with the NAC prevented the reduction of prefrontal parvalbumin interneurons observed in the NVHL model, as well as behavioral (prepulse inhibition deficits) and electrophysiological deficits (loss of dopamine modulation of interneuron physiology) present in adult rats with a neonatal hippocampal lesion. Furthermore, NVHL rats exhibited reduced mismatch negativity in auditory evoked potentials, and this deficit was prevented by NAC treatment.
Conclusion: The data suggest that inflammatory responses and oxidative stress could be linked to loss of interneuron function and that targeting inflammatory processes and oxidative stress balance may be a beneficial approach for early intervention and preventive strategies in schizophrenia.
ID: 2090613

PROGRESSION OF BRAIN BIOENERGETICS ABNORMALITIES FROM FIRST EPISODE TO CHRONIC SCHIZOPHRENIA

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Background: Several lines of evidence suggest that brain bioenergetics is abnormal in schizophrenia. Specifically, abnormalities have been reported in mitochondrial function suggesting that the process of generation and utilization of ATP may be compromised. Since energy production is essential for supporting glutamatergic neurotransmission, these abnormalities may manifest themselves in abnormal brain activation and information processing. In a series of studies, we are using 31P MRS to observe levels of high energy phosphate metabolites and reactions rates of enzymes involved in brain energy metabolism in the prefrontal cortex in schizophrenia.
Methods: 31P MRS data are collected using custom-built coils at 4 Tesla. The volume of interest is in the prefrontal cortex. Data acquisition includes a magnetization-transfer approach which allows quantification of forward reaction rates (Kf) of the creatine kinase (CK) enzyme. Patients are recruited from the clinical services at McLean Hospital, including McLean On Track, a program specializing in the care of patients experiencing a first episode of psychosis. Age and sex matched healthy controls are recruited from the community.

Results: Chronic schizophrenia patients showed normal concentrations of ATP and its storage form Phosphocreatine (PCr) in the prefrontal cortex. However, Kf of the CK enzyme was about 22% reduced in patients compared to controls. In addition, brain pH was reduced by about 7% in patients, consistent with a failure in oxidative phophorylation and a shift towards glycolysis. First episode schizophrenia patients show a similar normal pattern of ATP and PCr concentrations, and an equally abnormal CK Kf as the chronic patients. Brain pH is normal in first episode patients, however.
Conclusion: These findings suggest a "partially compensated" bioenergetics system in first episode and chronic patients with schizophrenia. Brain concentrations of important high energy phosphate metabolites are normal, but the CK enzyme that shuttles energy between them is substantially impaired. The CK enzyme is needed for replenishing ATP from PCr during times of high energy demand such as brain activation. Therefore, brain bioenergetics likely becomes abnormal during such times. Importantly, first episode patients do not yet show an acidic brain pH, suggesting that the long term consequences of energy metabolism failure have not yet set in at that stage, and that acidic brain pH is a marker of chronic schizophrenia.
ID: 2084821

PREDICTING PSYCHOSIS IN PERSONS AT CLINICAL HIGH RISK

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Background: Clinical criteria reliably identify persons with an approximate 15-30-fold elevated risk of developing psychosis over the general population. Still, about two-thirds of those meeting clinical high risk criteria will not progress to psychosis, limiting the development and use of preventative interventions. In the North American Longitudinal Study (NAPLS) we have evaluated various biomarkers with an aim of improving risk prediction and understanding mechanisms. This presentation focuses on the use of plasma assays for psychosis risk prediction.
Methods: Using a multiplex platform we evaluated 117 plasma analytes involving immunity and hormones, and oxidative stress in 72 clinical high risk (35 who subsequently developed psychosis) and 35 unaffected subjects.
Results: A combination of 15 analytes increased psychosis risk prediction with an area under the receiver operating curve of 0.88, ($p<.0001$). The use of the risk prediction analytes to understand molecular pathways leading to psychosis will be further explored.
Conclusion: This study of subjects with Clinical High Risk adds significant potential for planning for these young people and potentially for treatment.
ID: 2115435

DO ANTIPSYCHOTICS AFFECT INSIGHT IN PSYCHOSIS DIFFERENTIALLY? DATA FROM THE EUFEST TRIAL

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Background: Although antipsychotics are widely prescribed, their effect of on improving poor illness insight in schizophrenia has seldom been investigated and therefore remains uncertain. This paper examines the effects of low dose haloperidol, amisulpride, olanzapine, quetiapine, and ziprasidone on insight in first-episode schizophrenia, schizoaffective disorder, or schizophreniform disorder.
Methods: The effects of five antipsychotic drugs in first episode psychosis on insight were compared in a large scale open randomized controlled trial conducted in fourteen European countries: the European First-Episode Schizophrenia Trial (EUFEST). Patients with at least minimal impairments in insight were included in the present study (n=455). Insight was assessed with item G12 of the Positive and Negative Syndrome Scale (PANSS), administered at baseline and at 1, 3, 6, 9, and 12 months after randomization.
Results: The use of antipsychotics was associated with clear improvements in insight over and above improvements in other symptoms. This effect was most pronounced in the first three months of treatment, with quetiapine being significantly less effective than other drugs.
Conclusion: Use of antipsychotics was associated with an improvement in insight, over and above their effects on other symptoms of schizophrenia. Effects of spontaneous improvement cannot be ruled out due to the lack of a placebo control group, although such a large spontaneous improvement of insight would seem unlikely. Notably, the improvement of insight was less pronounced for quetiapine compared to haloperidol, amisulpride, olanzapine, quetiapine, and ziprasidone.
ID: 2090067

BI 409306, A NOVEL PHOSPHODIESTERASE 9A INHIBITOR, PART II: IN-VIVO CHARACTERIZATION REGARDING TARGET ENGAGEMENT AND COGNITION TASKS IN RODENTS

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Background: Inhibition of specific phosphodiesterases (PDEs) in the brain has gained attention as a potential new approach for memory enhancement. Among those PDEs is PDE9A which is specific for cyclic guanosine monophosphate (cGMP) and expressed in cognition-relevant regions of the brain. CGMP is an important second messenger in neurons involved in synaptic plasticity and memory formation. Thus, PDE9A inhibitors are hypothesized to improve cognitive function via increasing cGMP signalling pathway to strengthen synaptic plasticity. This study characterizes the effects of the novel PDE9A inhibitor BI 409306 on cGMP increase in rat brain and cerebrospinal fluid (CSF). In addition, the drug was evaluated in two rodent cognition tasks addressing working or episodic memory domains.
Methods: Effects on cGMP levels in rat prefrontal cortex were determined by using microdialysis technique following intraperitoneal administration of BI 409306. Concentrations of cGMP in microdialysis probes were measured using a cGMP-specific radio-immunoassay. Concentrations of cGMP in rat CSF samples collected from cisterna magna following oral administration of BI 409306 were determined by HPLC-MS/MS technique. Regarding cognition, BI 409306 was tested for reversal of MK-801 induced memory impairment in the mouse T-maze spontaneous alternation task as well as in the novel object recognition task in naïve mice after oral and intraperitoneal administration, respectively.

Results: BI 409306 induced a dose-dependent increase of cGMP in rat CSF and prefrontal cortex at the highest dose tested. Regarding cognition, BI 409306 could reverse MK-801 induced memory deficits in the mouse T-maze task and improved memory performance in the mouse object recognition task addressing working and episodic memory domains, respectively.
Conclusion: Systemic administration of BI 409306 led to an increase in cGMP levels in the rat prefrontal cortex and CSF demonstrating functional target engagement, i.e. PDE9A inhibition in the brain. This shows that cGMP levels in CSF can be used to assess PDE9A inhibition centrally which might also be used to evaluate central target engagement in clinical trials. Corroborating previous reports on memory enhancing efficacy of other PDE9A inhibitors in rodents, this data further demonstrates that PDE9A inhibition may be a potential approach to pharmacologically improve cognition in CNS disorders.
ID: 2084652

ASSESSMENT OF PROTEOMIC MEASURES ACROSS SERIOUS PSYCHIATRIC ILLNESS SUBJECTS AND CONTROLS

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Background: The research in proteomic measures has demonstrated the differences between subjects with schizophrenia and controls. To extend the understanding and issues related to proteomic research, this study assessed patients across the domain of serious psychiatric illness - schizophrenia, schizoaffective disorder, and bipolar disorder versus a control group. Also, the stability of the measure was assessed by a six-month follow-up.
Methods: Following review by the University of Minnesota IRB, ads to participate in research were placed and volunteers (patients and controls) had a preliminary assessment of the study. When found to be eligible, subjects received a SCID interview and the interview was reviewed in a group setting of staff and faculty. Patients also received PANSS and MATRICS assessments. At six months, the subjects were re-assessed and had a sample for proteomics attained.
Results: The subjects included in the analysis were 26 subjects diagnosed with schizophrenia, 20 with schizoaffective disorder, 16 with bipolar disorder and 23 controls. Gender was noted as 35.3% females and 64.7% males and mean age was 37.7 years old. Analysis of the proteomic measures demonstrated the 3 psychiatric conditions were not different from one another, but were statistically different from the control group (LDA.) Higher order modeling may be able to discriminate between some psychiatric conditions. A further step using a three-dimensional LDA showed a difference between schizophrenia, schizoaffective disorder and bipolar disorder. Further analysis demonstrated a substantial correlation of PANSS Positive (R2=0.68), Negative (R2=0.67), General (R2=0.60), and Total (R2=0.72) symptoms to proteomic measures. From the MATRICS assessment there were substantial correlations of measures such as continuous performance test (R2=0.67), speed processing (R2=0.75) and visual learning score (R2=0.69).
Conclusion: In this study of proteomics in the significantly psychiatric ill subjects versus controls, there were significant differences between patient groups and controls, but not between patient groups. Further, there were significant correlations between the proteomic measures and severity of illness and cognitive measures. These assessments have significant potential to address DSM diagnoses and measures of symptom severity and cognition.
ID: 2115397

ANTIPSYCHOTIC TREATMENT AND RESILIENCE: A REVIEW AND CLINICAL IMPLICATIONS

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Background: While antipsychotic drugs have been thought to exert their effects by diminishing abnormally enhanced dopaminergic neural transmission, the dopaminergic system can also be regarded as a key moderator for the sake of recovery when resilience is taken into account, which is addressed in this review.
Methods: Data for this review were identified by searches of PubMed (1950–2014) and references from relevant articles and books. Search terms included antipsychotic, neuroleptic, dopamine, recovery, relapse, and resilience, and only articles written in English or Japanese were consulted. Studies, reviews, and books pertaining to antipsychotic effects and/or dopamine in association with resilience were appraised.
Results: Although the pathophysiology of schizophrenia still remains elusive, the evidence for the involvement of the dopaminergic system is unequivocal and the locus of the most pronounced abnormality is presynaptic. The data in 1980's showed high pre-treatment homovanilic acid levels followed by their reduction with antipsychotic treatment in responders, but not in non-responders, which suggests the dopaminergic system has to be, at least in part, intact for the down-regulation for successful antipsychotic treatment. Those findings are compatible with brain imaging data that reveal the presence of non-responders despite sufficient blockade of dopamine D2 receptors with antipsychotic drugs. Moreover, a low chance to respond to a second antipsychotic drug among non-responders to an initial choice also seems to support this notion. Thus, it appears natural to assume the involvement of the dopaminergic system not only in the pathoetiology but also in the recovery process. In light of favorable outcomes of cognitive remediation, social skills training and family therapy in conjunction with pharmacotherapy, they are expected to share the same goal to enhance patients' resilience to the illness.
Conclusion: While the quest for pathoetiology of schizophrenia has been ongoing, it is also critically important to focus on the process of recovery to seek new treatment approaches. Psychopharmacology can be regarded as one of the treatments that contribute to enhance patients' resilience to the illness; this "rational therapeutic constellation" may be interpreted in the context of Neo-Hippocratism.
ID: 2081222

Clinical Neuropsychology

BARRIERS AND SOLUTIONS TO SUCCESSFUL REAL WORLD CR IMPLEMENTATION IN THE FRENCH SINGLE PAYER SYSTEM OF CARE.

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Background: In France, Psychiatric care is dispended by private and public structures. The latter relying on sectors" links one citizen to a geographical ambulatory center and to a hospital's department. This dispensation of care is free. Since 1970, mental health emergency and day care units, work and rehabilitation, as well as supports in social life structures exist everywhere, sort of assertive community treatment, providing a soil for psychosocial therapy. Recently the need of the National Health Agency to reduce hospitalization and to mutualize health system resources obliged some units to promote innovative rehabilitation structures.
Methods: In Lyon, a pioneer cognitive remediation (CR) and rehabilitation center emerged in 2010, immediately followed by another one in Paris. These reference centers deliver care, teach neurocognitive remediation, translate and promote new programs for social cognition. Furthermore, their mission accorded the National Health Agency demand is also to encourage the installation of centers. Subsequently CR centers have been disseminated, with treatments for patients with schizophrenia, bipolar disorders and recently for genetic or neurodevelopmental psychosis, anorexia nervosa, or in child psychiatry. The "sectorisation" background facilitates vocational programs, and personalized pathways for CR and rehabilitation. Psychologists and occupational therapists who are present in every unit encourages neuropsychological evaluation to shape tailored CR. A dissemination group of CR (AFRC) was founded in 2009 to promote techniques, national and international events, and homogenize neuropsychological evaluations. In this stream, since 2010, a network for CR enhances multicentric studies, implement and validate new CR techniques.
Results: Nowadays, in France small or larger centers are created under the impulse of these conjugated regional agencies and AFRC efforts, unifying a homogenous implementation and dissemination of CR. Units benefit from the expertise of the pioneer centers to utilize their care resources, with advice to expand their structures according to their local specificities.
Conclusion: Despite the local disparities still existing, the paucity of programs not disseminated everywhere, cognitive remediation and rehabilitation in France will undoubtedly exponentially grow up under this strong conjugated will from the National agency and the organization of the psychiatric experts in Cognitive Remediation. .
ID: 2087156

IMPLICIT EMOTIONAL REGULATION IN PATIENTS WITH SCHIZOPHRENIA: AN INVESTIGATION USING THE EMOTIONAL GO/NO-GO TASK

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Background: The performance on emotional Go/No-go tasks has been used to measure not only behavioral inhibition but also implicit emotional regulation. Especially, performance differences in response to happy and sad facial expressions presented in the task have been used to estimate the effect of emotional information in biasing behavioral inhibition in healthy adults as well as patients with anxiety and depression. In schizophrenia, there is no study to date examining implicit emotional regulation using the emotional Go/No-go task.
Methods: A total of 29 patients with schizophrenia and 33 control controls completed the emotional Go/No-go task as well as self-report measures of social anxiety and emotion regulation. Commission errors, omission errors, reaction times, the perceptual sensitivity(d') and response bias(β) were calculated from the emotional Go/No-go task, which consists of happy and sad facial stimuli. Correlational analysis was conducted to investigate the relationships between performance on emotional Go/No-go tasks, self-report measures and psychiatric symptoms.
Results: Participants with schizophrenia showed significantly lower perceptual sensitivity to happy faces than healthy controls (t=2.470, p=.017). Repeated measures ANOVA indicate that there were no interactions between emotion types (happy vs. sad) and groups (patients vs. controls). Both groups showed greater perceptual sensitivity to happy faces (t=5.467, p<.000 for patients; t=5.336, p<.000 for controls) than sad faces, and showed fewer omission errors but more commission errors in happy faces (t=-2.888, p<.000 for patients, omission errors; t=-3.627, p=.001 for controls, omission errors; t=2.107, p=.046 for patients, commission errors; t=4.229, p<.000 for patients, commission errors). Biases to happy and sad faces were negatively correlated with social anxiety (r=-.451, p=.027; r=-.437, p=.033, respectively). There were no correlations between performance on the emotional Go/No-go task and symptom severities.
Conclusion: The results demonstrate that individuals with schizophrenia had difficulty in implicit emotion regulation (i.e., discriminating happy faces from sad faces) than healthy controls, which was also related to greater social anxiety. However, both patients with schizophrenia and healthy controls showed similar patterns in responding to happy and sad facial expressions. The patterns found in individuals with schizophrenia exist even after controlling for their symptom severities.
ID: 2087188

EMPATHY IN THE CONTEXT OF MORAL REASONING IN SCHIZOPHRENIA

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Background: Research on the emotions in schizophrenia has revealed emotion recognition and expression deficits, as well as differences in the experience of emotion. The effect of these emotion deficits on moral reasoning has not yet been explored. Identification of others' emotion and a congruent emotional response, known as empathy, underpins healthy moral engagement. Thus far, the measurement of empathy in schizophrenia has relied heavily on self-report. The purpose of the current study was to compare a new behavioral measure of empathy in the context of moral reasoning to a self-report measure of empathy in schizophrenia.
Methods: We administered Kohlberg's Moral Judgment Interview (MJI) to 24 participants with schizophrenia and 20 healthy controls. "Moral maturity" scores based on Kohlberg's cognitive-developmental stage theory were calculated. Measures included the Repeatable Battery for Assessment of Neuropsychological Status, and the National Adult Reading Test to estimate IQ. Social cognitive abilities were assessed using the ToM Picture Sequencing Task and Faux Pas Task. Self-report empathy was measured using the Interpersonal Reactivity Index (IRI). To provide a behavioral measure of the cognitive and affective dimensions of empathy, MJI responses were recoded for presence or absence of IRI-derived dimensions of Personal Distress, Empathic Concern, Fantasy and Perspective Taking. General psychopathology and functioning were assessed using the Depression, Anxiety and Stress Scale and the Social and Role Functioning Scales.
Results: Cases had significantly lower MJI moral maturity scores than controls (Mann-Whitney: U=113.50, p = .003), however these impaired performances were explained by neuro- and social-cognitive deficits and negative

symptoms in patients. Cases had significantly lower MJI Empathic Concern scores in the context of moral reasoning compared to controls (U = 130.50, p = .01) and expressed significantly less MJI Emotional Perspective Taking (U = 130.00, p = .009). Similar differences were seen in the self-report IRI measures, however between-group differences were not significant.
Conclusion: This study represents a first examination of empathy as expressed in the context of moral reasoning in schizophrenia. It is also unique in developing a new behavioral measure of empathy. In conclusion, findings suggest that self-report measures of empathy may underestimate deficits in affective responsiveness and perspective taking in relation to moral reasoning in schizophrenia.
ID: 2118858

STRENGTHENING REHABILITATION: NEW DIRECTIONS IN LEARNING POTENTIAL RESEARCH

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Background: Learning potential has been explored as a possible mechanism to predict positive rehabilitation outcomes in people with SMI (e.g., Green et al. 2000). More recent research has identified a strong relationship between attention and working memory tasks and improvement after training on dynamic assessments (i.e. learning potential), which may indicate a dependence on these key neurocognitive constructs. The primary aim of the current study, to measure the influence of working memory and attention skills within the learning process, is an important next step in current research investigating learning potential in people with SMI.
Methods: A total of 192 participants with an SMI diagnosis (schizophrenia spectrum, bipolar disorder and major depressive disorder) completed a battery of neurocognitive and psychiatric measures. Participants also completed a test-train-test intervention using the Wisconsin Card Sorting test. Participants were categorized as high performers, learners or non-learner based on their intervention performance.
Results: Correlational analyses revealed that large and moderate effect sizes were seen in relationships between learning potential and variables conceptualized to capture working memory and attention. Further, comparison of the strength of correlations between neurocognitive variables and learning potential showed a stronger relationship with tasks associated with working memory. Specifically, complex tasks of working memory that not only require immediate recall of information, but also require a manipulation of that information (such as Letter Number Sequencing, Months Ordering or Digits Backward), demonstrated the strongest relationships with learning potential performance.
Conclusion: It has been demonstrated that cognitive performance can serve as an indicator of how well a person will do in response to interventions designed to improve functional outcomes. By measuring learning potential performance, intervention response can be further enhanced by identifying target areas for remediation, such as working memory. Rehabilitation efforts and functional outcomes can be strengthened by a greater understanding of the learning process and knowledge of how people with SMI learn, therefore maximizing the utility of current intervention and community services.
ID: 2084750

IS THE CLINICAL PROFILE OF PSYCHOSIS FOLLOWING TRAUMATIC BRAIN INJURY (PFTBI) DIAGNOSTICALLY DISTINCT FROM SCHIZOPHRENIA/SCHIZOAFFECTIVE DISORDER?

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Background: Persons who suffer with symptoms of psychosis following a brain injury live with a complex dual diagnosis that is often accompanied by substantial distress and disability due to their psychotic symptoms. However, a comprehensive examination of the clinical presentation of PFTBI using standardised clinical measures has not been reported in the literature. This information is vital for the accurate diagnosis and efficacious treatment of these patients.
Methods: Patients with PFTBI (n =10) and schizophrenia (n =23) participated in a comprehensive clinical assessment that included the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I/P), the Positive and Negative Syndrome Scale (PANSS), the Scale for the Assessment of Positive Symptoms (SAPS), and the Thought Language and Communication Index (TLC).
Results: PFTBI participants met the symptom and course criteria for schizophrenia (n = 6), schizoaffective disorder (n = 2), schizophreniform disorder (n = 1), and paranoid psychosis (n = 1). No significant differences between schizophrenia and PFTBI clinical profiles were found, with the exception of i) the PANSS negative total score, and ii) SAPS lifetime grandiose delusions. On both of these indices schizophrenia patients scored significantly higher than the PFTBI cohort.
Conclusion: The clinical profile of PFTBI appears to be comparable to schizophrenia/ schizoaffective disorder, perhaps with the exception of negative symptoms and lifetime (but not current) grandiose delusions. Reduced negative symptoms in PFTBI have previously been reported in a small number of case studies, and may represent an aspect of the PFTBI clinical profile that distinguishes itself from schizophrenia.
This research was supported by the Austin Hospital Research Foundation (M.H., grant number 2-1372), and an Australian Postgraduate Award.
ID: 2073394

COGNITIVE DEFICITS CHARACTERIZATION USING THE COGSTATE RESEARCH BATTERY IN FIRST-EPISODE PSYCHOSIS PATIENTS

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Background: Several computerized cognitive batteries have been developed and are currently being used in schizophrenia research since they improve testing and scoring conditions for patients and researchers. The computer-based CogState Research Battery (CSRB) has been designed to follow the MATRICS recommended cognitive domains structure and was previously validated with enduring schizophrenia samples. The aim of this study was to compare cognitive performance on the CSRB and on a traditional pen and paper battery in a historical cohort of first-episode psychosis patients.
Methods: Among patients entering an early intervention program between 2004 and 2014, 182 patients competed a traditional pen and paper cognitive battery while 97 patients completed the CSRB. Composite z-scores were derived using normative data of 64 (pen and paper) and 69 (CSRB) matched controls and were compared between the two testing modalities for the 7 cognitive domains.

Results: The interaction between cognitive domains and type of cognitive battery used was statistically significant (F(6,1662)=18.634, p<0.001) and therefore post-hoc comparisons were performed on each domain corrected for multiple comparisons. The cohort tested using the CSRB performed better on the domains of speed of processing, attention, visual memory, and verbal memory than the cohort tested using the pen and paper battery (all p<0.001). Performance did not differ between the cohorts tested using the two types of batteries in the working memory (p=0.160), executive functions (p=0.255), and social cognition domains (p=0.139). Analyses also showed a significant main effect of type of neurocognitive battery used (F(1,277)=36.877, p<0.001) where patients who did the CSRB performed better overall than those who did the pen and paper battery. There was also a main effect of cognitive domain (F(6,1662)=24.838, p<0.001) indicating that level of impairment was not similar on all cognitive domains when results on both batteries were combined.
Conclusion: Better performances on the CSRB may be primarily due to the minimal demand of the computerized tests on graphomotor abilities and reading speed compared to the pen and paper tests. The CSRB is well suited for longitudinal testing of first-episode psychosis patients throughout treatment and our investigation offers a better understanding on how the results obtained may compare to earlier work done with traditional batteries.
ID: 2113443

NEUROPSYCHOLOGICAL CORRELATES OF AUDITORY VERBAL HALLUCINATIONS

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Background: "Inner speech" models of auditory verbal hallucinations (AVH) suggest that the core cognitive functions underlying AVH reside in language functioning. A neuropsychological test battery was administered to test the extent to which the dimensions of AVH may relate to linguistic ability.
Methods: Thirty patients with schizophrenia (mean age = 40.26, standard deviation (sd) = 11.8) and frequent AVH (mean PANSS Hallucinatory Behavior score = 4.53) were administered a comprehensive battery of standardized neuropsychological tests and the Psychotic Symptoms Rating Scales (PSYRATS).
Results: Mean estimated full scale IQ was in the average range (mean FSIQ = 102.22, sd = 11.03). Mean neuropsychological test performance ranged from one to two standard deviations below published test norms. PSYRATS total score was significantly and negatively correlated with measures of verbal fluency, phonological awareness, phonological working memory, and verbal learning. Relationships between PSYRATS total score and tests of memory, attention, executive functioning, and visuospatial ability did not approach significance.
Conclusion: Language problems in schizophrenia have been likened to those seen in acquired aphasia, and the present results suggest that deficits in linguistic functioning are closely related to the overall severity (assessed as PSYRATS total score) of AVH. Detailed analysis of the PSYRATS dimensions revealed that AVH negativity, disruption, and frequency are all significantly negatively correlated with language functioning scores.
ID: 2119496

THE EFFECT OF SMOKING STATUS ON WORKING MEMORY PERFORMANCE AND GAMMA OSCILLATORY ACTIVITY IN PATIENTS WITH SCHIZOPHRENIA COMPARED TO HEALTHY SUBJECTS

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Background: Cigarette smoking prevalence remains among the highest in patients with schizophrenia (SZ) compared to other mental illnesses. Nicotine is suggested to mediate cognitive processes such as working memory in this population, and could account for these high smoking rates. This study assessed working memory performance and gamma oscillatory activity, which is known to be aberrant in patients with SZ, in both smoker and non-smoker patients with SZ compared to smoker and non-smoker healthy subjects.
Methods: Working memory was assessed using the N-back task (1- and 3-back conditions) while electroencephalography was recorded. To date, we have tested sixteen SZ smokers (M=39.6 years old, SD=10.4), eighteen SZ non-smokers (M=39.8 years old, SD=6.1), twenty healthy smokers (M=38.4 years old, SD=11.3), and sixteen healthy non-smokers (M=33.2 years old, SD=10.7).
Results: A repeated measures ANOVA with diagnosis and smoking status as the between-subjects factors revealed a main effect of accuracy (F(68)=207.346, p<0.001) and a significant accuracy x diagnosis interaction (F68)=4.609, p=0.03). Between-subjects effect of diagnosis was significant (F(66)=4.390, p=0.04) for accuracy, and smoking status was trending toward significance (F(66)=3.472, p=0.06). Post-hoc tests revealed significant differences on the 3-back condition between SZ and healthy subjects regardless of smoking status, in which patients with SZ performed significantly worse (M=40.9, SD=20.9) compared to healthy subjects (M=53.8, SD=26.2); p=0.02. A repeated measures ANOVA with diagnosis and smoking status as the between-subjects factors found a trending effect of smoking status for gamma (F(51)=3.339, p=0.07). Across all groups, there was a significant negative correlation between accuracy and gamma power on the 3-back condition, r(55)=-0.28, p=0.03.
Conclusion: Our ongoing findings suggest that smoking status may alter gamma oscillatory activity and working memory performance in both patients with SCZ and in healthy subjects. Modulation of nicotinic acetylcholine receptors by nicotine may therefore play a role in working memory in these populations.
ID: 2117760

EFFECTS OF COGNITIVE REMEDIATION ON NEGATIVE SYMPTOMS DIMENSIONS: EXPLORING THE ROLE OF WORKING MEMORY

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Background: Recent theories suggested that memory problems may be the cognitive underpinning of negative symptoms in people with schizophrenia. In particular working memory problems are thought to deregulate hedonic experience, negatively influence motivation and goal directed behaviour by corrupting storage, retrieval and utilization of past experience. In this study we first explore the effect of cognitive remediation (CR) on two clusters of negative symptoms (i.e. Expressive and Social Amotivation) and then assess the relevance of working memory gains as a possible mediator of symptom improvement.

Methods: Data were accessed for 336 people with schizophrenia from the NIMH Database of Cognitive Training and Remediation Studies (DoCTRS) database. Approximately half of the participants received CRand the rest were allocated to a control condition. All participants were assessed before and after therapy. Expressive and Social Amotivation symptoms scores were calculated from the Positive and Negative Syndrome Scale (PANSS). Working Memory was assessed with the digit span and the letter and number sequencing test.
Results: No significant association was found between working memory and either Expressive or Social Amotivation symptoms at baseline. Participants who received CR had a significant improvement in (standardised) working memory scores (0.63; 95%. C.I.: -0.55 to 0.72, p<0.001) and a significant reduction in Social Amotivation levels compared to those in the control condition (b= -1.1; 95%. C.I.: -1.6 to -0.60, p<0.001). Working memory change did not mediate the effect of CR on Social Amotivation (indirect effect: -0.04; 95% C.I.: -0.11 to 0.04, p=0.34, standardised b=-0.006).
Conclusion: The results suggest that a course of CR may have positive effect on negative symptoms; particularly on behavioral symptoms. Despite hypotheses linking memory problems with negative symptoms the current findings do not support the role of this cognitive domain as a significant contributor to this symptom cluster. The results indicate that working memory improves independently from negative symptoms reduction. The effects of CR on negative symptoms may be relevant to support recovery and functional improvement.
ID: 2114279

PROCESSING SPEED TRAINING AND SOCIAL FUNCTIONING IN TEENAGERS AND YOUNG ADULTS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Deficits in processing speed (PS) have found to be correlated with social aptitude in CHR cohorts and variably identified as risk markers for psychosis. Among those with attenuated positive symptoms, processing speed has been related to social and role functioning regardless of conversion to Sz. These information processing dysfunctions seem to be upstream to broader, top-down cognitive and social skills. When subprocesses are degraded, the brain must adjust by lengthening space and time integration constants in effort to detect relevant signals. This adaptation comes at a cost since the brain cannot accurately represent details of spatiotemporally complex signals. This results in slowed speed of information processing in a social situation. We examined the feasibility of improving information processing relevant to social situations in CHR, including its sustainability at 2 months, and its association with concurrent social function.
Methods: This was a double-blind RCT where 39 CHR participants were randomized to Processing Speed Training (PST) or an active control matched for training format and the same dose and duration of treatment. PST is a tablet-based program that uses pupillometry to continually adjust training parameters for an optimal cognitive load and improve visual scanning efficiency by inhibiting selection of non-essential targets and discriminating figure-ground details.
Results: The PST group showed faster motorical and non-motorical PS at post (F [2,35]=5.09, p=.00) and 2 months (F [4,31]=4.49, p=.01). Subsequent results in social functioning at 2 month follow-up showed the PST group reporting better overall social adjustment (F [4,31]=3.72, p=.02) and less anxiety about engaging in new social situations (F [4,31]=3.15, p=.02). Of note, changes in PS from baseline to 2 months were correlated with overall social adjustment (r=.28-.39, p=.00-.02) and social avoidance (r=.29, p=.01) regardless of group assignment. Furthermore, processing speed at baseline predicted social adjustment outcome at 2 mo, even after accounting for variance attributable to group assignment and symptoms (R2=.49, F [4,31]=4.60; p=.01).
Conclusion: To our knowledge, this is the first study to test focal cognitive training for PS deficits in a putatively prodromal phase of Sz to address social morbidity. Targeting PS appears to be a promising pathway to improving co-morbidity and mitigating a risk factor for psychosis.
ID: 2117341

COMPUTERIZED VOCAL AND FACIAL ANALYSIS IN SCHIZOPHRENIA DURING SOCIAL INTERACTIONS: DATA FROM THE BASELINE PHASE OF THE CIDAR STUDY

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Background: Expressive deficits are hallmark symptoms of schizophrenia-spectrum disorders, and seem to demarcate a particularly pernicious illness course. Their nature is poorly understood. In large part, this reflects the fact that their measurement is dependent on symptom ratings made by trained clinicians during relatively artificial social interactions (i.e., clinical interviews). To better understand how expressive deficits manifest in schizophrenia, the present study employed highly-sophisticated computerized vocal and facial analysis of people with schizophrenia while engaging in social interactions with trained confederates. To our knowledge, this study is the first time these technologies have been paired together; and the first time they have been applied to a role-play task.
Methods: Data for 42 outpatients with schizophrenia were examined as part of the baseline phase of the Centers for Intervention Development and Applied Research (CIDAR) study. Participants were required to meet a priori criteria for persistent negative symptoms. Our analyses focused on a wide range of expressive variables (i.e., vocal production, variability in vocal signal, tongue articulatory movement, positive and negative facial emotions, and head movements) and their relations to clinically-rated negative symptom and neurocognitive and social functioning data.
Results: Measures of vocal and facial expression were highly stable across two independently administered role play tasks. Interestingly, the measures of vocal and facial expression were not highly inter-correlated; suggesting that expression was relatively independent across distinct channels of communication. Moreover, vocal and facial expression variables were significantly correlated with clinical measures of blunted affect/alogia, but not with measures of avolition, anhedonia/asociality. This supports the relative independence of expressive and experiential/motivational negative symptoms. Expressive variables were significantly associated with a range of neurocognitive and social cognitive variables in the hypothesized direction.
Conclusion: Expressive deficits in schizophrenia are more complicated than previously assumed. They are not consistent across channels of communication, at least, when observed during laboratory-based social interactions. Implications of this, and potential links to neurocognitive and social functioning are discussed.
ID: 2095211

THE RELATIVE VALUE OF INTERVIEW-BASED AND OBJECTIVE COGNITIVE ASSESSMENTS FOR PREDICTING GLOBAL FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA

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Background: NIMH has recommended that functional gains be prioritized when developing cognitive enhancements for patients with schizophrenia. This initiative highlighted critical gaps in the measurement of cognition and in our understanding of the pathways from cognition to global functioning. Evidence indicates that both objectively measured cognitive performance (MCCB) and intermediate measures of cognitive functioning, such as the interview-based Cognitive Assessment Interview (CAI), are valid predictors of global functioning. However, patients with schizophrenia have demonstrated poor insight into their cognitive deficits. This leaves open the question of whether cognitive functioning can be validly assessed by patient interview alone vs informants.
Methods: Cross-sectional data were obtained from 137 schizophrenia patients (ages 18 to 64, 80% male) recruited from Los Angeles are psychiatric clinics. Trained raters verified diagnoses using the SCID and assessed objective cognitive performance (MCCB), interview-based cognitive functioning (CAI), insight into cognition (MIC-SR, MIC-CR), and global functioning (SCLOFS).
Results: CAI patient interview-based ratings of cognitive deficits were significantly correlated with CAI informant ratings (r= .71), and also with objective cognitive performance (MCCB) (r=-.38). Objective cognitive performance did not significantly predict global functioning beyond patient interview-based ratings of cognitive functioning. Furthermore, patient interview-based cognitive functioning mediated the relationship between objective cognitive performance and global functioning (Pm=.57). Interestingly, insight into cognition moderated the relationship between patient interview-based cognitive functioning and global functioning (t(132)=-3.45, p<.001). Among patients with greater insight, cognitive performance (MCCB) and cognitive functioning (CAI) were both less predictive of global functioning.
Conclusion: Evidence is mounting that patient interview-based assessments of cognitive deficits (CAI) are valid intermediate measurement tools that help predict global functioning. Furthermore, cognitive functioning, as assessed by patient interview (CAI), helps to explain the relationship between objective cognitive performance (MCCB) and global functioning. This relationship appears to be true even for patients with lower levels of insight into their cognitive deficits.
ID: 2119594

COGNITIVE SUBGROUPING IN PEOPLE WITH SCHIZOPHRENIA AND THEIR SIBLINGS: A FOCUS ON COGNITIVELY "PRESERVED" SCHIZOPHRENIA

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Background: Heterogeneity in schizophrenia has led to a search for ways to divide the diagnostic category into subgroups relevant to etiology, course, and/or treatment response. Current analyses examined a subgrouping scheme advanced by Weickert et al. (2001), based on indicators of current and pre-morbid cognitive performance, which yielded cognitively "compromised," "deteriorated," and "preserved" subgroups in earlier work.
Methods: Comprehensive assessment data for 558 people with schizophrenia (Sz), 366 unaffected siblings (Sib), and 1090 community controls (Ctrl), were available from the NIMH/CBDB Study of Genetic Risk for Schizophrenia. In the Sz sample, latent class analysis, with estimated premorbid IQ (WRAT reading) and current full scale IQ (WAIS) indicators, was used to derive subgroups. Error bar graphs and GLM analyses compared Ctrl with Sz and Sib cognitive subgroups on selected variables, controlling for age, sex and race. GLM repeated measures analyses were used in analyses of affected/unaffected sibling pairs.
Results: Latent class analysis yielded three balanced Sz subgroups showing premorbid/current IQ patterns similar to the earlier findings - SzLowLow (N=151, WRAT M=87.2 (7.3), IQ M=83.8 (8.2)), SzHighLow (N=211, WRAT M=104.8 (5.8), IQ M=86.9 (6.5)), and SzHighHigh (N=196, WRAT M=110.0 (6.4), IQ M=104.0 (6.6)). As expected, the Sz subgroups differed markedly in terms of general cognitive performance (e.g., main effect of group for global cognitive composite - p<1.0E-10). They also differed in regard to symptoms and functioning. Especially for cognitive variables, SzHighHigh individuals performed similarly to Sib and Ctrl, while SzHighLow and SzLowLow performance was more similar and dramatically worse than SzHighHigh, Sib and Ctrl. Nevertheless, all Sz subgroups, including SzHighHigh, were symptomatic and functionally impaired. Moreover, when SzHighHigh were compared with their own siblings, rather than Sib generally, quite significant cognitive impairment was revealed (e.g., affected/unaffected sibling pair main effect for cognitive composite - p<1.0E-10)
Conclusion: Cognitive performance can be used to divide Sz into subgroups that show dramatic differences in symptoms and functioning, as well as cognition. Across variables, SzHighHigh appear most distinct from others with schizophrenia. Notwithstanding above average cognitive performance, SzHighHigh are symptomatic and functionally impaired, with significantly worse cognitive performance than their own siblings.
ID: 2083622

THE CENTRAL NATURE OF 'LOWER-ORDER' COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

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Background: Clinical manifestations of schizophrenia often include behavior, speech and thinking that are disorganized in ways suggestive of reduced or ineffective executive control. The 'dominant paradigm' in cognitive research in schizophrenia has emphasized executive and WM dysfunction (and PFC abnormalities). The relevant literature is extensive. Current analyses reconsidered this conceptualization, meta-analytically and in family data.
Methods: A large database of study-by-study cognitive data was available from two earlier meta-analyses performed in our group. Across-studies effect sizes were calculated using standard random effects models. Additionally, comprehensive cognitive data for 558 people with schizophrenia (Sz), 366 unaffected siblings (Sib), and 1090 community controls (Ctrl), were available from the NIMH/CBDB Study of Genetic Risk for Schizophrenia. Error bar graphs and GLM analyses compared groups on selected variables, controlling for age and sex.
Results: The combined meta-analysis included approximately 11,000 people with schizophrenia and 9,500 controls, from more than 130 international datasets. Comparison of cases and controls yielded a grand mean cognitive impairment effect of d=-1.11. The largest impairment effects were seen in domains of processing speed (d=-1.27) and episodic memory (d=-1.31). Effects for WM and executive function were notably less severe (respectively, d=-0.88 and d=-0.96). This pattern held true in NIMH/CBDB schizophrenia data, and extended, in attenuated form, to unaffected siblings (eg, sibling digit symbol d=-0.35, vs sibling card sorting effect d=-0.21 and n-back effect d=-0.28). Recent findings in other very large datasets are consistent.
Conclusion: While executive and WM impairment continue to be emphasized in schizophrenia research, the broad literature demonstrates that cognitive impairment is generalized and more prominent on simple cognitive tasks than on so-called 'higher-order' tasks - both in schizophrenia and in unaffected family members. Leading pathophysiological hypotheses invoke general biological systems and mechanisms, and genetic and developmental effects on cognition seem more likely to be diffuse than specific. Altogether, evidence suggests that cognitive impairment in schizophrenia reflects problems with the basic foundation for cognitive processing - ie, with engagement, organization of simple behaviors, fluency, quickness - which are shared across simple and complex cognitive measures.
ID: 2119235

CORTICAL THICKNESS AND LOW INSIGHT INTO SYMPTOMS IN ENDURING SCHIZOPHRENIA

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Background: Studies on insight recognize the existence of multiple dimensions including awareness of illness and symptom-specific insight. Poor insight into symptoms is common in patients with schizophrenia and is associated with poorer outcomes and treatment non-adherence. To date, however, the association between cortical thickness and insight into symptoms has received scant attention. We conducted an exploratory whole-brain cortical thickness (CT) analysis to identify potential neural correlates of symptom-related insight in patients with enduring schizophrenia. Based on the extant literature, we expected to see reduced CT measures in the dorsolateral prefrontal cortex, cingulate cortex, temporal lobe, and insula among patients with poor insight.
Methods: Fifty-nine patients with schizophrenia (duration >4 years) and 25 healthy controls completed MRI scanning and IQ, depression, and anxiety assessments. Researchers evaluated psychotic symptoms in patients and used the Scale to Assess Insight-Expanded (SAI-E) to measure insight into symptoms. Scores on SAI-E Item 7 divided patients into 2 groups: low insight (0–2; n=29), and high insight (2.01–4; n=30). An automated whole-brain CT analysis procedure compared group differences in brain morphology with sub-voxel resolution, covaried for age and sex.
Results: Groups were matched on age, sex, handedness, IQ, anxiety, and symptom severity. Thinner cortex was observed in low insight patients compared to controls in the right temporal and insular cortex, posterior cingulate cortex, inferior parietal lobe and fusiform gyrus ($p<0.05$, corrected). Comparisons between patient groups also revealed thinner cortex for those with low insight in the right temporal and insular cortex ($p<0.01$, uncorrected). No significant CT differences were found between controls and high insight patients.
Conclusion: Patients with low insight into symptoms displayed thinner cortex in areas thought to subserve self-monitoring, error awareness, and correct symptom attribution. Patients with high insight into symptoms displayed a trend toward thicker cortex in these areas, with cortical morphology more similar to controls. Our results are consistent with studies using other neuroimaging methods and suggest a prominent association between low insight and cortical thinning in the right hemisphere. This finding mirrors anosognosia, a clinical deficit of self-awareness caused by right fronto-temporal-parietal lesions, and supports a contribution of biological factors to insight.
ID: 2118856

ABNORMAL SUPPRESSION OF ALPHA AND BETA SUPPRESSION DURING CONSOLIDATION IMPLICATES QUALITATIVELY DISTINCT NEURAL SUBSTRATES OF WORKING MEMORY STORAGE IN SCHIZOPHRENIA

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Background: Though schizophrenia has long been characterized in part by impairments in working memory (WM), a mechanistic account for these deficits has yet to be identified. Among healthy control subjects (HCS), mechanisms that appear to underlie normal WM storage include posterior suppression of alpha and beta frequency bands (Fukuda & Vogel, 2012). The present study was conducted to test the hypothesis that one of these mechanisms—suppression of alpha and beta during the delay period of a visual WM task—accounts for reduced storage capacity observed in people with schizophrenia (PSZ).
Methods: 17 HCS and 17 PSZ participated in the present study. EEG was recorded while participants completed a change detection paradigm in which colored squares were presented for 200 ms, followed by a delay period of 1800 ms, and then by a test array in which one of the squares changed colors on 50% of the trials. The number of items maintained in WM (K) was then estimated from task accuracy.
Results: Time frequency analysis revealed a large suppression in alpha and beta frequency bands that peaked approximately 200 ms after the offset of the sample array. After this suppression peak, sustained suppression in both frequency bands was observed over the remainder of the delay period. PSZ exhibited a significantly attenuated delay suppression peak compared to HCS in alpha & beta (p's<0.01). A mixed linear model revealed that the magnitude of suppression during the delay period was significantly associated with K for alpha ($F=7.83$; $p<0.05$) and beta ($F=5.23$; $p<0.05$). Spearman correlations indicated that K was significantly associated with alpha suppression ($r=-0.59$; $p<0.05$), and associated with beta at the trend-level ($r=-0.47$; $p=0.06$) among HCS. By contrast, PSZ exhibited a significant association between K and beta suppression ($r=-0.49$; $p<0.05$), and no relationship between K and alpha suppression ($r=-0.02$; $p=0.95$).
Conclusion: Taken together, these observations suggest that (1) group differences in activation of neural substrates of WM storage emerge early in the sequence of cognitive events, with no evidence of accelerated decay in PSZ; and (2) the neural mechanisms that maintain items in WM storage may be qualitatively different between the two groups, as evidenced by the moderator effect of group on the relationship between K and alpha suppression during the delay period.
ID: 2118951

THE IMPACT OF AGE OF ONSET AND IQ ON COGNITIVE DEFICITS IN ANTIPSYCHOTIC-NAÏVE ADOLESCENTS AND ADULTS WITH SCHIZOPHRENIA

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Background: There is compelling evidence that schizophrenia is a neurodevelopmental disorder in which combined genetic and environmental factors impact critical neural circuitry leading to the onset of symptoms once a critical threshold has been reached. The timing of illness onset appears to be influenced both by the severity of aberrant neurodevelopment but also by individual differences in resilience to neuropathology. A proxy measure

of this type of resilience is intelligence (IQ), which has been demonstrated to be a risk factor for schizophrenia.
Early onset schizophrenia (EOS) is phenotypically and neurobiologically continuous with adult onset schizophrenia (AOS), but characterised by more premorbid risk factors and a more severe course of illness. The aim of this study was to examine the impact of age of onset and IQ on psychopathology and cognitive deficits in first-episode EOS and AOS.
Methods: Two samples of antipsychotic-naïve, first-episode patients with schizophrenia or schizoaffective disorder were recruited: 1. Adolescent patients (N=53; mean age 15.5, SD 1.4; range 12–17), and matched, healthy controls (HC) (N=44); and 2. Adult patients (N=59; mean age 24.9, SD 6.3; range 18–44) and matched, HC (N=60). Diagnoses were made according to ICD-10 criteria. Psychopathology was rated using the Positive and Negative Syndrome Scale (PANSS). IQ was estimated using 4 subtests from WISC or WAIS versions III or IV. Cognition was assessed with the Brief Assessment of Cognition in Schizophrenia (BACS).
Results: Positive and negative symptoms did not differ between patient groups, but AOS patients had significantly more general (p=0.00007) and total (p= 0.03) PANSS scores than EOS patients. EOS and AOS patients differed significantly from their respective HC groups on almost all cognitive measures (ES=0.3–1.0). The severity of specific cognitive deficits was similar between patient groups. Both patient groups had significantly lower IQ scores than their HC groups (p<0.0001), but EOS patients also had significantly lower IQ (mean 89.2, SD 18.3) than AOS patients (mean 98.4, SD 19.1; p=0.03). IQ did not have a significant effect on psychopathology scores, but was strongly correlated with several cognitive scores, particularly in the patient groups.
Conclusion: The results indicate that EOS may not be characterised by more severe psychopathology or cognitive deficits than AOS, but suggest that lower IQ may be a proxy indicator of reduced resilience affecting the timing of illness onset.
ID: 2083780

THE DETECTION OF INTENTIONAL CONTINGENCY IN EARLY PSYCHOSIS

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Background: Paranoid delusions have been hypothesized to arise from an overattribution of meaning or malevolent intentions to others' actions. Evidence for this mechanism has been found in samples with chronic schizophrenia, but its role in the aetiology of symptoms in the early stages of the illness is unclear. This study investigated whether patients with early psychosis overattribute contingency to agents' actions and whether this mechanism is associated with paranoid delusions.
Methods: 38 adolescents with early psychosis and 93 controls (age 13 to 19) watched four types of films showing two moving shapes. In the: 1) animate contingent condition one shape moved when it 'saw' the other; 2) animate non-contingent condition one shape moved independently of the other; 3) mechanistic contingent condition one shape's movement was launched by the other's; and 4) mechanistic non-contingent condition one shape passed by the other without touching. Participants saw five films of each category and rated the strength of the relationship between the shapes' movements. Paranoid delusions were assessed with the PANSS. Group differences in ratings of relationship strength and associations with paranoid symptoms were analysed with multilevel random regression analyses to account for repeated measures.
Results: Participants rated the relationship between the shapes' movements significantly stronger in the mechanistic contingent than the non-contingent condition, but perceived little difference between animate contingent and non-contingent movements. In the animate condition there was a non-significant trend effect for patients to perceive the relationship between the shapes' movements weaker than controls (p = 0.08). A similar trend was present in the mechanistic contingent condition (p = 0.09), but there were no group differences in the mechanistic non-contingent condition. Patients' levels of paranoia were unrelated to their ratings of relationship strength.
Conclusion: The results show an intact perception of intentional contingency in early psychosis and demonstrate that contingency perception in the early stages of the illness is unrelated to paranoia levels. These findings contradict research in chronic schizophrenia samples that associated the presence of paranoid delusions with an overattribution of contingency to unrelated actions of agents. This suggests that the early illness stages might present a window of opportunity for interventions that aim to prevent the biased attribution of intent.
ID: 2089905

COGNITIVE SUBGROUPS IN SCHIZOPHRENIA: CONTRASTING HIGH COGNITIVE PERFORMANCE CASES WITH THEIR OWN UNAFFECTED SIBLINGS ON COGNITIVE, CLINICAL, AND FUNCTIONAL VARIABLES

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Background: To better understand illness heterogeneity, schizophrenia researchers have searched for robust subgrouping schemes. One approach has used indicators of pre-morbid and current IQ to divide people with schizophrenia (Sz) into cognitive subgroups.
Methods: Cognitive, clinical, and other data for 558 Sz, 366 unaffected siblings (Sib), and 1090 community controls (Ct) were available from the NIMH/Clinical Brain Disorders Branch Study of Genetic Risk for Schizophrenia. In the Sz sample, unsupervised cluster analysis, with estimated pre-morbid IQ (WRAT reading) and current full scale IQ (WAIS) indicators, was used to derive subgroups. Error bar graphs and GLM analyses compared Ct with Sz and Sib cognitive subgroups on selected variables, controlling for age, sex, and race. GLM repeated measures analyses were used in analyses of affected/unaffected sibling pairs.
Results: Cluster analysis yielded three cognitive subgroups for Sz: high WRAT-high WAIS (HH; n=196, mean WRAT=110 (6.41), mean IQ=104 (6.58)), high WRAT-low WAIS (HL; n=211, WRAT=105 (5.82), IQ=87 (6.51)), and low WRAT-low WAIS (LL; n=151, WRAT=87 (7.31), IQ=84 (8.21)). The designation for each Sz was carried over to his or her Sib. Within the Sz sample, people in the HH subgroup consistently performed better on average than those in the Sz HL and Sz LL groups across a wide range of cognitive variables (e.g., p<1.0E-5 for the general cognitive ability composite for both HH v HL and HH v LL), and showed reduced symptoms and better role functioning. This pattern of differentiation was seen to a lesser degree in the corresponding Sib subgroups. When compared to their own unaffected siblings, the Sz HH group showed marked cognitive impairment (e.g., p<1.0E-5 for the general cognitive composite in repeated measures analysis).
Conclusion: Collectively, these results add support for the validity of IQ-based subgrouping in people with schizophrenia. In our sample, this method yielded a high-functioning schizophrenia subgroup that differed dramatically from the Sz HL and Sz LL groups in terms of cognition, functional ability, and symptoms. In contrast to what some have argued, however, the Sz HH group should not be considered "neuropsychologically normal." Although people in the Sz HH group were better off on average than the Sz HL and Sz LL groups, they nevertheless were impaired cognitively relative to their own siblings, and showed prominent symptomatology and impaired daily functioning.
ID: 2087468

IMPROVEMENTS IN AEROBIC FITNESS AND BRAIN HEALTH ARE ASSOCIATED WITH BETTER MEMORY IN CHRONIC SCHIZOPHRENIA PATIENTS

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Background: The beneficial effects of aerobic exercise on cognition and brain health have been well established (Hillman et al., 2008). However, much less is known about these relationships in the context of severe mental illness. We examined the effects of aerobic exercise in a sample of chronic, refractory schizophrenia patients to determine whether improved aerobic fitness, increased regional cortical thicknesses, and hippocampal volumes were associated with enhanced verbal memory.
Methods: Sixteen (10 M, 6 F) chronic schizophrenia patients completed a 12-week exercise program consisting of thrice weekly 30-minute sessions at moderate intensity followed by 15 minutes of stretching.
The Hopkins Verbal Learning Test - Revised was used to index verbal memory. Physical measures included V02 Max, body mass index, resting heart rate, and blood pressure. A 3T MRI scanner was used to ascertain structural brain images and Freesurfer software was used to compute regional cortical thicknesses and hippocampal volumes. Assessments conducted at baseline and 12-week follow-up were used to compute change scores for cognitive, physical, and structural brain variables over the 12 weeks of exercise. Candidate independent variables (e.g., changes in physical and structural variables) and demographic variables were screened for use in a subsequent regression analysis based upon their association with a verbal memory change outcome score.
Results: Change in V02 Max and change in entorhinal thickness (left) were retained for the final analysis (cut-off = $p < .10$). No associations with hippocampal volumes were observed. The regression model accounted for 65.3% of the variance in verbal memory change ($F = 11.27$, $p = .002$). Improvement in V02 Max was associated with better verbal memory ($t = 3.19$; $\beta = .55$; $p = .008$). Further, increased left entorhinal cortical thickness was associated with greater improvement in verbal memory ($t = 3.06$; $\beta = .53$; $p = .010$), after accounting for change in V02 Max.
Conclusion: Following a 12-week exercise program, we observed that gains in aerobic fitness and increased entorhinal cortical thickness were related to better verbal memory performance in chronic, refractory schizophrenia patients. These results are in line with findings from Pajonk et al. (2010), though we did not observe an association between memory and hippocampal volume. Future studies should examine potential moderators of these effects, including intensity of exercise and the influence of anti-psychotic medication.
ID: 2107955

COGNITIVE DEFICIT IN SCHIZOPHRENIA SPECIFIC OR GENERAL: A NEUROPSYCHOLOGICAL STUDY

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Background: Although cognitive impairment is not a diagnostic criterion for schizophrenia, schizophrenia patients often present impairments in specific cognitive domains together with a general cognitive impairment, as reflected by mean IQ scores of 1–2 standard deviations below norms. Most of the previous studies in this field did not match schizophrenia patients to controls on IQ, therefore it is conceivable that some of the abnormalities reported in the literature might be related to general cognitive impairment. The purpose of this study is to understand which neuropsychological deficit in schizophrenia is related to the generalized cognitive deficit and not to schizophrenia per se.
Methods: Based on their WAIS-III full scale IQ score, 28 patients with schizophrenia and 28 controls were matched for IQ, age and gender. 28 additional controls were matched for age and gender only. Subjects were assessed using the MATRICS, and social cognition was assessed using the University of Pennsylvania Computerized Neuropsychological Test Battery (PENN-CNP).
Results: The mean MATRICS domains scores of the age and gender matched controls were significantly higher than those of the IQ matched controls and schizophrenia patients on all domains.
Significant differences between schizophrenia patients and IQ matched controls were found only in speed of processing (SOP): the scores of schizophrenia patients ($M=38.22$, $SD=6.67$), were lower than that of the IQ matched controls ($M=43.97$, $SD=10.48$) and of the age and gender matched controls ($M=51.24$, $SD=9.92$).
The PENN-CNP emotion battery analyses revealed statistically significant differences in the emotion recognition task ($(F(2,52)=3.6$, $p=0.03)$. Post hoc comparisons revealed that age and gender matched controls had more correct responses as compared to schizophrenia patients and IQ matched controls.
In the Emotion differentiation task statistically significant differences were found ($F(2,52)=4.31$, $p=0.01$). Post hoc comparisons revealed that schizophrenia patients had fewer correct responses compared to controls.
No significant difference was found for the emotion acuity test.
Conclusion: When matched for IQ, many of the differences usually observed between schizophrenia patients and controls are attenuated or even disappear. However, compared to IQ matched controls, patients with schizophrenia had slower processing speed and impaired ability to judge differences in intensity of emotions. These may be considered the core cognitive deficits in schizophrenia.
ID: 2118959

HIGH SCHIZOTYPES SHOW SELECTIVELY REDUCED TRUST OF MALEVOLENT BUT NOT BENEVOLENT OPPONENTS DURING SOCIAL INTERACTION COMPARED TO LOW SCHIZOTYPES

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Background: Paranoia in non-clinical schizotypy shares common components of clinical paranoid delusions, however various methodological shortfalls have limited our understanding of trust and paranoia, such as a lack of an ecologically-valid socially-interactive framework to understand these processes. To overcome previous methodological limitations, the present study utilised a redesigned version of the Prisoner's Dilemma Game (PDG) to explicitly measure levels of trust within social interactions. It was primarily hypothesised that high schizotypy (HSCZ) would be related to greater competition in a social interaction task, and this would be related to paranoia. HSCZ participants would produce significantly lower ratings of trust and would 'jump' to absolute trustworthiness decisions quicker than low schizotypy participants (LSCZ).
Methods: Forty-eight healthy participants categorised into high and low schizotypy groups completed a social interaction task, paranoia measures, data gathering, jumping to conclusions (JTC) and neuropsychological tests.

Anxiety, mood, attributional bias and theory of mind deficits were also measured. ANOVA were used to investigate between group differences on the measures used.
Results: High schizotypes had significantly higher levels of state and trait paranoia. Competitive interaction in the first round of the PDG was positively associated with state paranoia. High schizotypes were selectively less trusting than low schizotypes when interacting with a malevolent but not a benevolent opponent and this was accompanied by a hastier decision-making style not apparent in the benevolent or non-social data-gathering tests indicating a specific JTC to negative social information. Only trait not state paranoia nor mood, anxiety, theory of mind, nor attribution biases predicted trust ratings to negative social interaction.
Conclusion: People with high schizotypy show significantly lower trust and hastier decision-making about trustworthiness when interacting socially with someone acting negatively but not positively toward them - and so demonstrate a selective not global bias to trust others less. This bias is specifically related to elevated trait paranoia, not mood, anxiety, theory of mind, attribution or neuropsychological deficits. The study supports the utility of the amended PDG in studying paranoia and also suggests that the identification of specificity of paranoia and trust and data gathering can provide new avenues to understand paranoia in patient populations.
ID: 2119547

COGNITIVE CHANGES OVER TIME: INSIGHTS FROM THE NEW YORK HIGH-RISK PROJECT

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Background: Several researchers, including our investigative group, have reported an association between low IQ and risk for schizophrenia. Recently, there have been a number of reports suggesting that declines in cognitive performance during adolescence are associated with increased risk for schizophrenia. It is less clear, however, whether a decline in IQ is associated specifically with schizophrenia risk, or risk for psychosis in general.
Methods: In the New York High-Risk Study (NYHRP), children at risk for schizophrenia or affective disorder and a normal control group were studied longitudinally from mid-childhood to mid-adulthood. As part of the project, the children were administered cognitive assessments during childhood (mean age = 9 years), adolescence (mean age =15 years) and early adulthood (mean age = 25 years). Depending upon the assessment wave, cognitive performance was assessed using the WISC, WISC-R, WAIS, or WAIS-R. We compared the change in cognitive performance within individuals over time and between risk groups.
Results: Although there were significant effects of Risk Group, and Time effects, we observed no significant Time x Group effect. Similarly, we observed no significant interaction between Time and Diagnostic Outcome, though the individuals who developed psychosis during adulthood had significantly lower IQs overall.
Conclusion: Cognitive decline over time does not appear to be unique to individuals at risk for, or later diagnosed with, schizophrenia. Rather, IQ decline is seen in individuals who are later diagnosed with a psychotic illness in adulthood. Other promising indicators, in addition to a genetic diathesis, are more likely to enhance prediction efforts than consideration of IQ decline.
ID: 2095522

MEASURING INTRACORTICAL FACILITATION IN CANNABIS DEPENDENT PATIENTS COMPARED TO NON-USING PATIENTS WITH SCHIZOPHRENIA: A TMS STUDY

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Background: High rates of substance use disorders in patients with schizophrenia are well established and cannabis remains to be the most commonly used illicit drug within this population. Research has reliably shown that cannabis use in schizophrenia results in symptom exacerbation, frequent relapses, and poorer prognosis. Intracortical facilitation (ICF) is a transcranial magnetic stimulation (TMS) protocol used to index N-methyl-D-aspartate (NMDA) function. ICF has been shown to be elevated in recreational cannabis using first-episode patients with schizophrenia; however, ICF has not been evaluated in cannabis dependent patients with schizophrenia. The objective of this study is to evaluate ICF in cannabis dependent patients compared to non-using patients with schizophrenia.
Methods: ICF is a paired pulse TMS protocol used to index cortical excitability that is mediated, in part, by NMDA. At the beginning of each testing session, the resting motor threshold (RMT) was determined, defined as the lowest intensity needed to evoke a motor evoked potential (MEP) of at least 50 μV in 50% of the trials. We then identified the intensity needed to produce an average MEP amplitude of 1 mV peak-to-peak and used this value as the test stimulus intensity. Using the ICF protocol, TMS was delivered to the left motor cortex with interstimulus intervals of 10, 15 and 20 ms separating the subthreshold (80% of the RTM) conditioning stimulus from the proceeding test stimulus (1 mV).
Results: To date, we have tested 7 cannabis dependent patients with schizophrenia (mean age 26.7 ± 6.2 years) and 7 patients with no drug use (mean age 40.7 ± 7.9 years). ICF was reduced in cannabis dependent patients compared to non-using patients with schizophrenia at each interstimulus intervals, however, this was not statistically significant (10 ms: Cohen's d=0.685, p=.267; 15 ms Cohen's d=0.771, p=.220; 20 ms Cohen's d=0.619, p=.343).
Conclusion: Though preliminary, these results suggest that cannabis use among patients with schizophrenia may reduce NMDA function. Additional subjects may help to better understand the effects of chronic cannabis use on brain function and guide the development of future treatments targeting this common co-morbidity. Supported in part by NARSAD Young Investigator Grant (Barr), Canadian Institute of Health Research (CIHR) operating grant MOP#115145 (George).
ID: 2112237

IMPROVEMENT OF SELF-INITIATION OF SEMANTIC ENCODING STRATEGIES IN INDIVIDUALS WITH SCHIZOPHRENIA FOLLOWING SPECIFIC EPISODIC MEMORY TRAINING

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Background: Episodic memory (EM) is a core cognitive function impaired in schizophrenia, however, there is currently no medication with clear positive impact on EM performance. Available cognitive remediation interventions

have significant but relatively small to moderate impact. Thus, there is a need to develop more efficient complementary treatments to improve EM in schizophrenia focusing exclusively on some deficient memory processes as opposed to a more global approach where multiple cognitive domains are explored. Hence, the present study aimed to develop an EM training in which self-initiation of semantic encoding strategies were specifically targeted.

Methods: Twenty-two participants with enduring schizophrenia performed our Semantic Encoding Memory Task (SEMT), a novel EM task. To select patients with deficits, one condition isolated self-initiation of semantic encoding strategies. This condition identified deficits in 10 of the 22 participants, which were consequently included in our training group. The training consisted of two 60-minute sessions (one per week) including a short meta-memory presentation, categorisation and semantic encoding strategies memory exercises, and a brief bridging period. After completion of training, patients memorized new items in a different version of the SEMT task. Alternating versions of the CVLT (a standardized measure of the use of semantic encoding strategy) and the BVMT (a control spatial memory task) were used to quantify memory before and after training.

Results: Memory training in self-initiation of semantic encoding strategies led to a significant improvement only in tasks where such a process was expected to improve performance. Indeed, we observed a clear increase in the condition in the SEMT where participants needed to self-initiate semantic encoding strategies ($p < 0.02$) following the training. Participants also increased the number of words recalled in the first 5-trials of the CVLT ($p < 0.001$), and more importantly, the number of semantic clustering ($p < 0.01$). No significant differences were found in the BVMT, which was used as a control task.

Conclusion: The current study demonstrates that training patients in developing memory strategies can help them improve a faulty memory process in schizophrenia and have a significant impact on memory performance. It will be necessary for future randomized studies to test our novel memory-training module appropriately and to explore the neural correlates of such an improvement in memory performance.

ID: 2115673

ADOLESCENT CANNABIS USE AND COGNITION IN INDIVIDUALS WITH PSYCHOSIS

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Background: Cognitive deficits are considered to be core symptoms of schizophrenia. Several studies suggest that heavy cannabis use during adolescence is associated with less cognitive impairment in schizophrenia. In this study, we examined the relationship between adolescent cannabis use and cognition in individuals with psychosis, including with schizophrenia, schizoaffective disorder and bipolar disorder with psychosis.

Methods: Participants with a DSMIV diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features and healthy controls were recruited at the University of Texas Southwestern Medical Center site of the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. Subjects were characterized by their history of cannabis use into adolescent users (onset before age 18), late cannabis users (onset after age 18) and non-users.

The psychosis (N=97) and control (N=64) groups were divided into six groups: control with no cannabis use (CCB-; N=38), control with adolescent cannabis use (CCB+; N=16), control with late cannabis use (N=10), psychosis with no cannabis use (PCB-; N=48), psychosis with adolescent cannabis use (PCB+; N=33), and psychosis with late cannabis use (N=16). All participants completed the Brief Assessment of Cognition in Schizophrenia (BACS) neuropsychological battery. Demographic variables including age, education, and WRAT-4 reading test score, gender, race, alcohol use disorder, and drug use other than cannabis were collected and assessed for inclusion as potential covariates. Analysis of Covariance (ANCOVA) was used to analyze data with significance level set at $p<0.05$.

Results: Education and WRAT-4 reading scores differed between groups and were included as covariates. BACS composite scores between the adolescent cannabis use diagnostic groups, CCB+ and PCB+, were not significantly different ($F=0.72$; $p=0.4$) whereas PCB+ group performed significantly better than PCB- ($F=7.87$; $p<0.01$).

Conclusion: Prior studies suggest that a history of adolescent cannabis use is associated with less cognitive impairment in schizophrenia. In this study, we extend those findings to psychosis as a spectrum, finding that individuals with psychosis and adolescent cannabis use have less impaired overall cognition compared to those with psychosis and no cannabis use history as measured by the BACS. These findings may have important clinical implications and may be a factor to consider in design of clinical trials with potential cognitive enhancers.

ID: 2085572

COMPUTERISED WORKING-MEMORY FOCUSED COGNITIVE REMEDIATION THERAPY FOR PSYCHOSIS - A PILOT STUDY

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Background: Cognitive deficits are prevalent in people with psychosis and are associated with decreased levels of functioning. Of these cognitive deficits, deficits in working memory have been shown to have a marked impact on cognition and on the ability to function in daily life. This study aims to examine the effects of a working memory focused cognitive remediation therapy (CRT) on cognitive difficulties experienced by patients with psychosis.

Methods: Participants with a diagnosis of psychosis, (n=62) underwent either 8 weeks of CRT (approximately 24 hours) or 8 weeks of treatment as usual. IQ, working memory and episodic memory were measured both pre and post intervention at weeks 0 and 8 for all participants.

Results: While participation in CRT led to improvements on the trained working memory tasks, this did not generalize to non-trained working memory tasks. By comparison, CRT participation was associated with significant improvements in two tests of episodic memory. No association between CRT and general cognitive ability (IQ) was found.

Conclusion: Working-memory specific CRT is associated with improvements in episodic memory in people with psychosis. This is important, as episodic memory is cognitively the area of greatest impairment in these patients.

ID: 2118399

IDENTIFYING PSYCHOLOGICAL FACTORS ASSOCIATED WITH VIOLENCE IN PATIENTS WITH SCHIZOPHRENIA

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Background: The risk of violence in schizophrenia is increased. However the factors that underpin that risk, particularly those that are specific to schizophrenia rather than linked to co-morbidities such as drug use remain unclear. This is important because their identification would represent risk management targets.
While there is robust evidence of a range of cognitive deficits in schizophrenia, their links with the risk of violence remain poorly understood. Emerging evidence suggests that neurocognitive and emotion processing deficits may be associated with violence both in patients with schizophrenia, and more widely.
Methods: Fifty male patients with DSM-IV schizophrenia and thirty-nine healthy controls were assessed across domains of general intellectual ability, executive functioning, emotion processing and social processing. Substance misuse, childhood conduct disorder, psychotic symptoms and psychopathy were determined. Lifetime propensity to violence was quantified using the Gunn Robertson Scale, which incorporates multiple facets of violence including frequency, severity and outcome.
Results: Patients with schizophrenia were significantly compromised across the majority of tasks compared to healthy controls. Overall, general intellectual ability and memory processes were not significantly associated with violence propensity. Violent patients however showed significantly poorer response inhibition, after accounting for relevant clinical variables. A greater lifetime propensity to violence was associated with an attentional bias towards anger, a heightened sensitivity to the recognition of fear and with poorer complex Theory of Mind performance.
Conclusion: Our results have allowed us to develop a hypothetical model of the risk of violence in schizophrenia. We propose that heightened sensitivity to environmental negative emotional cues and poorer understanding of complex social situations, combined with a poorer ability both to quickly process but also inhibit pre-potent responses results in a greater propensity to violence in patients with schizophrenia. We propose that this model sits alongside the risk associated with other factors such as illicit drug use. These findings need to be tested further but could have implications for the treatment and management of violence risk in patients with schizophrenia.
ID: 2077351

CORTISOL AND COGNITION IN POSTPARTUM PSYCHOSIS

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Background: Psychosis unrelated to gestation is characterized by a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, in particular a blunted cortisol awakening response and increased cortisol during the day (Mondelli et al., 2010). Furthermore, this blunted cortisol awakening response, found in patients with psychosis unrelated to gestation, has been found to be associated with poorer verbal memory (Aas et al., 2011). Our research group has also reported increased cortisol awakening response and higher daily cortisol levels in women with and at risk of postpartum psychosis (PP) compared to controls. The aim of this study was to replicate our previous findings and to investigate cortisol awakening response and cortisol levels during the day in relation to verbal memory in a sample of women with and at risk of PP.
Methods: 29 women were assessed on average 14 weeks following delivery (range 3 - 43). 7 women had PP, 12 were at risk of PP and 10 were controls. Participants completed assessment of HPA axis (cortisol awakening response and cortisol levels during the day). Verbal memory was assessed using the WMS-III logical memory task (Wechsler, 1997).
Results: There was no significant difference between the 3 groups in cortisol awakening response, as indicated by delta cortisol at 15 and 30 minutes. However, there was a significant difference between the 3 groups in daily cortisol levels, as indicated by AUC, with women with PP and at risk of PP having higher daily cortisol levels than healthy controls (M = 52.9, SD = 30.4; M = 76.5, SD = 97.9; M = 32.9, SD = 9.6, respectively; K-W(2) = 8.1, p = 0.017). There was no significant difference between the 3 groups in immediate or delayed logical memory performance. Furthermore, there were no significant correlations between the cortisol awakening response or the daily cortisol levels and immediate or delayed logical memory.
Conclusion: Unlike individuals with psychosis unrelated to gestation, we did not find a difference in cortisol awakening response in women with and at risk of PP compared to healthy controls. Furthermore, neither cortisol awaking response nor daily cortisol levels were associated with poorer verbal memory in PP groups. However, in line with previous findings, we did show that women with and at risk of PP had higher daily cortisol levels compared to healthy controls.
ID: 2093780

HOW NORMAL IS COGNITIVELY "NORMAL" SCHIZOPHRENIA ANYWAY?

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Background: The validity, nature and significance of normal-range neurocognition in schizophrenia remain unclear and controversial. Questions motivating our research were whether normal-range patients and controls demonstrate equivalent profiles across measures, including those hypothesized to mediate psychotic psychopathology (e.g. probabilistic reasoning, Theory of Mind). In addition, we were interested in comparing below normal-range control subjects with cognitively impaired patients. It is known that a portion of the general population scores below the average range on ability measures, but this subpopulation is seldom accessed in schizophrenia research. Finally, we were interested in assessing whether these cognitively-based subgroups map onto differential connectivity in the left and right cerebral hemispheres.
Methods: Performance normality was defined as a MATRICS Consensus Cognitive Battery (MCCB) composite T score between 40 and 60. Patients meeting the criterion (n=16) were matched individually to 16 non-psychiatric participants. The same procedure was applied to 13 controls scoring below 40 who were matched individually to patients. Additional measures included WRAT-4 Reading, Reading the Mind in the Eyes and Faux Pas Theory of Mind tasks and the Beads task (probabilistic reasoning). Each participant underwent MRI brain imaging with a 3T scanner to generate fractional anistrophy (FA) values for 5 major fiber tracts in each hemisphere. Tract FA data were averaged to produce left and right hemisphere values.
Results: Cognitively normal range patients were marginally superior to cognitively normal range controls on the Working Memory and marginally inferior on the Processing Speed and Reasoning and Problem Solving MCCB domains. Performance was equivalent across other domains and across all measures of Theory of Mind and probabilistic reasoning and structural connectivity. Cognitively below normal range patients and controls performed equivalently on all comparisons except left hemisphere connectivity, with higher FA values in the patient group.

Conclusion: Cognitively normal-range schizophrenia patients are largely indistinguishable from cognitively normal range controls, with possible subtle differences in working memory, processing speed and problem solving, but no differences in theory of mind or probabilistic reasoning. More typically impaired patients are cognitively indistinguishable from low-performing controls, but show anomalies in left hemisphere connectivity.
ID: 2067980

THEORY OF MIND PERFORMANCE IN FIRST-EPISODE SCHIZOPHRENIA PATIENTS AND THEIR UNAFFECTED SIBLINGS

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Background: "Theory of mind" (ToM) impairment has been consistently demonstrated in patients with schizophrenia, but most prior studies has focused on patients with chronic illness. It is also unclear as to whether ToM impairment exists in the unaffected relatives of patients with schizophrenia. There were also limited studies conducted to examine the affective and the cognitive components of ToM in schizophrenia patients and their unaffected relatives.
Methods: In this family-based case-control study, we have recruited 41 clinically stable outpatients with first-episode schizophrenia (mean age=27.66 years, SD=6.45 years; mean duration of illness=20.01 months, SD=13.04 months), 43 unaffected first-degree siblings of schizophrenia patients, and 42 healthy controls. The participants were matched in age, gender and years of education. Their performance in affective and cognitive ToM was measured by two paradigms: (1) a computerised "Yoni Task" which measured participants' ability to understand first- and second-order affective versus cognitive ToM; and (2) the *Faux Pas* Task which tapped into the integration of the affective and cognitive components of ToM. A battery of neurocognitive tests on IQ, memory and executive functions was also administered.
Results: Compared to controls, schizophrenia patients and their unaffected siblings performed poorer on second-order affective condition of the Yoni Task ($F[2,123]=6.620$, $p=0.002$, $\eta p2=0.097$) and the *Faux Pas* Task ($F[2,118]=10.573$, $p<0.001$, $\eta p2=0.152$), with siblings having intermediate performance between patients and controls. Schizophrenia patients performed significantly worse than controls in the second-order cognitive condition of the Yoni Task ($p=0.002$), but their unaffected siblings did not ($p=0.524$). We did not find any significant Group-by-Condition interaction effect in the Yoni Task (Hotelling's Trace; $F[4,242]=1.099$, $p=0.358$, $\eta p2=0.018$), suggesting the affective and cognitive components of ToM were comparably impaired in patients and their siblings.
Conclusion: Patients with first-episode schizophrenia and their unaffected siblings, albeit to a lesser extent, exhibited ToM impairments. The attenuated ToM deficits in unaffected siblings could possibly be interpreted as a trait marker reflecting their genetic liability to develop schizophrenia. Our findings support the notion that ToM deficit may be a trait marker of schizophrenia.
ID: 2117468

EMOTION-BASED DECISION-MAKING IN THOSE AT HIGH RISK FOR SCHIZOPHRENIA

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Background: Deficits in emotion processing and experience are a key component of schizophrenia. This study aims to examine emotion-based decision-making in children and adolescents (ages 5 to 19) at high risk (HR) for schizophrenia as compared to healthy control (HC) subjects. We used an Iowa Gambling Task (IGT) in which subjects make serial selections from four decks of cards yielding monetary gains and losses, as a clinical measure of emotion-based decision-making. Lesion and imaging studies implicate ventromedial cortex, orbitofrontal cortex and amygdala involvement on this task. It was hypothesized that, contrasted with the HC group: 1) the HR group will show impaired overall performance on the IGT (lesser selection from the advantageous decks and greater selection from the disadvantageous decks) and 2) the HR group will show impaired learning over time.
Methods: IGT performance of a sample of high-risk children and adolescents (n=17), i.e., having at least one first-degree relative (parent or sibling) with schizophrenia, was compared to an age- and sex- matched sample of healthy controls (n=27).
Results: Significant differences were found between the groups on task performance, with the high-risk group showing impaired learning and decision-making.
Conclusion: Emotion-based information processing deficits may be characteristic of children at risk for schizophrenia.
ID: 2081626

SCHIZOTYPY TRAITS OR FEATURES IN NONPSYCHOTIC FIRST-DEGREE RELATIVES OF PATIENTS WITH SCHIZOPHRENIA

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Background: Schizotypy, or schizotypal personality disorder has been proposed to represent a milder expression of the schizophrenia genotype, manifesting milder forms of neurocognitive and social behavioural deficits that resemble schizophrenia. Schizotypy appears to be a multidimensional construct, with positive schizotypy (PS) and negative schizotypy (NS) shown to have differential profiles of neurocognitive performance, and NS suggested to represent more closely the genetic liability to schizophrenia. This study aimed to explore, in a population of first-degree relatives of schizophrenia patients, whether cluster analysis could generate similar clusters of schizotypy as previous studies in non-clinical populations. The study also aimed to examine the neurocognitive and social behavioural performance of relatives with NS.
Methods: In the first phase of this study, cluster analysis was performed on 194 first-degree relatives of patients with schizophrenia using the Chapman Psychosis Proneness Scales. Twenty-eight of the relatives belonging to the NS group from this phase were then recruited into the second phase of the study, along with 29 patients with schizophrenia and 33 healthy controls. Neurocognitive measures, including verbal, visual and working memory, sustained attention and executive functions were assessed and compared among the three groups. Theory of mind (ToM) performance and social and occupational functioning were also examined.
Results: Cluster analysis yielded four schizotypy cluster groups, namely negative schizotypy (NS), mixed schizotypy (MS), positive schizotypy (PS) and low schizotypy (LS). It was found that the NS relatives were significantly impaired in visual memory, working memory and affective ToM compared to healthy controls, and their performance did not differ significantly from schizophrenia patients. The NS relatives were also found to have impaired social and occupational functioning.
Conclusion: These findings support the idea that NS in first-degree relatives of schizophrenia patients manifest some neurocognitive deficits that resemble patients with schizophrenia, and may represent an underlying heightened genetic liability to schizophrenia.
ID: 2118206

BIASED ATTENTION IN SCHIZOPHRENIA: RELATIONSHIP TO NEGATIVE SYMPTOMS

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Background: Previous studies indicate that abnormal interaction of attention and emotion is implicated in the negative symptoms of schizophrenia (Strauss et al. 2011). However, temporal courses and components of such attentional abnormalities involved in negative symptoms, i.e., difficulty in disengagement from negative stimuli and/or avoidance of positive stimuli, have not been fully investigated. In the current study, we aimed to investigate attention biases to positive and negative emotions in people with schizophrenia and their relationship to the negative symptoms.
Methods: A dot-probe task designed to measure attention biases to emotions was administered to inpatients diagnosed with schizophrenia (n=26) and matched healthy controls (n=36). A cue composed of a pair of facial stimuli, one with neutral expression and another with emotional expression (happy, sad, or angry) was presented randomly for 50, 500, or 1,000ms before the probe appeared.Negative symptoms were assessed by Positive and Negative Syndrome Scale (PANSS) and the Motivation and Pleasure Scale-Self Report (MAP-SR).
Results: Repeated measures ANOVAs indicated that individuals with schizophrenia tended to respond more slowly to the probes which appeared after happy faces than neutral faces at 500ms time point suggesting attentional avoidance to the happy faces, compared to no bias in healthy controls, $F(2,122)=4.145$, $p=.018$. The extent of avoidance of the happy face presented at the 500ms time point was correlated with lower motivation in close relationship and total scores of the MAP-SR ($r=.554$, $p=.004$ and $r=.353$, $p=.077$, respectively). In addition, individuals with schizophrenia tend to avoid angry faces across time points as compared to healthy controls although it was a trend level significance, $F(1,61)=3.280$, $p=.075$. As with happy faces, the avoidance of the angry face presented at the 500ms time point was correlated with lower motivation in close relationship and total scores of the MAP-SR, and higher scores of PANSS negative symptom ($r=.421$, $p=.032$, $r=.390$, $p=.049$ and $r=-.350$, $p<.086$, respectively).
Conclusion: The results suggest that the avoidance of both happy and angry faces presented at 500 ms time point appears to be associated with deficits in social motivation in schizophrenia. It is speculated that abnormalities in attention to emotions may indicate underlying pathology responsible for negative symptoms in schizophrenia.
ID: 2087214

NEUROCOGNITIVE PROFILES, PSYCHOPATHOLOGY AND BRAIN VOLUME IN FIRST-EPISODE ANTIPSYCHOTIC-NAIVE SCHIZOPHRENIA PATIENTS WITH STABLE OR DETERIORATING IQ

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Background: Approximately 50% of patients with schizophrenia experience a deterioration in IQ before or around illness onset. The aim was to examine the association of current IQ in combination with estimated IQ trajectory from premorbid levels with psychopathology, neurocognitive profiles and brain volume in relation to age in a cohort of antipsychotic-naïve first-episode schizophrenia patients.
Methods: This is a cross-sectional study of 51 first-episode antipsychotic-naïve schizophrenia patients and 57 matched healthy controls. Patients were divided into 4 subgroups based on estimated IQ trajectory from premorbid levels (stable vs. deteriorating) and current IQ at illness onset (high vs. low) using the Danish version of the National Adult Reading Test and 4 subtests from Wechsler Adult Intelligence Scale, 3rd ed. These groups were compared using the Positive and Negative Syndrome Scale, selected tests from the Brief Assessment of Cognition in Schizophrenia and Cambridge Neuropsychological Test Automated Battery and a combined 3T MRI generated measure of grey and white matter volume corrected for skull size.
Results: Eleven patients (21.5%) were defined as deteriorated low, 10 patients (20%) as deteriorated high, 11 patients (21.5%) as stable low and 19 patients (37%) as stable high. Patients with stable low IQ had significantly more negative symptoms compared to the patients in the high IQ groups ($p<0.01$). The neurocognitive deficit pattern ranged from subtle deficits in the stable high (overall effect size (ES) using the healthy controls as reference -0.20) and deteriorated high (ES -0.45) patients to more pronounced and severe deficits in the stable low (ES -1.28) and deteriorated low (-1.44) patients, respectively. The effect of age on brain volume was significant in the stable low (-8.4 ml/year, $p=0.001$) and the deteriorated low patients (-9.0 ml/year, $p=0.004$), while the stable high (-1.1 ml/year) and deteriorated high (-1.9 ml/year) patients were comparable to the healthy controls (-0.8 ml/year). This indicates a more substantial impact of age on brain volume in patients with lower intelligence than in patients with high intelligence.
Conclusion: Patients with deteriorated low IQ have the most severe cognitive deficits and a more pronounced impact of age on brain volume. These findings offer new perspectives on the pathophysiological heterogeneity of schizophrenia, supporting the presence of differential neurodevelopmental and neurodegenerative processes.
ID: 2090587

OVERLAPPING AND DISEASE SPECIFIC ASPECTS OF IMPULSIVITY IN CHILDREN AND ADOLESCENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS OR ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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Background: Attention-Deficit/Hyperactivity Disorder (ADHD) and schizophrenia show several associations. For example, an increased rate of ADHD diagnoses is observed in the offspring and siblings of patients with schizophrenia (1). Additionally, ADHD is associated with an increased risk for schizophrenia (2). Given such cross-diagnostic associations, the purpose is to identify disease specific and overlapping aspects of impulsivity in children and adolescents with early-onset schizophrenia spectrum disorders or ADHD.
Methods: Indices of motor impulsivity (Stop Signal Task), reflection impulsivity (Information Sampling Task), and trait impulsivity (Barratt Impulsiveness Scale -11) are compared between three groups of children and adolescents between 12 and 17 years of age: patients with early-onset schizophrenia spectrum disorders (EOS) (N=29), patients with ADHD (N=29), and healthy controls (N=45).
Results: In terms of reflection impulsivity, the probability of making a correct response at the point of decision making is significantly decreased in patients with ADHD, whereas the patients with EOS perform non-significantly different from the healthy controls. Neither the ADHD nor the EOS group show significant response inhibition deficits. Both clinical groups show significantly increased trait impulsivity as compared to the healthy controls.
Conclusion: Increased reflection impulsivity appears specific to ADHD and may reflect an inability to delay their decision making to gather more

information. Both disorders appear to share increased trait impulsivity. The lack of significant response inhibition deficits in the young patients with EOS appears in line with an earlier result (3).

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ID: 2085299

LINK BETWEEN AUTOBIOGRAPHICAL MEMORY AND THEORY OF MIND IN SCHIZOPHRENIA: A PILOT STUDY

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Background: Autobiographical memory (ABM) helps to remember past social interactions, comprises memories of one's own past that are characterized by a sense of subjective time and autonoetic awareness. Capacities of ABM are linked with neurocognitive abilities and probably domains of social cognition.Theory of Mind (ToM) is the ability to attribute mental states (beliefs, desires) to other people in order to understand and predict their behavior. In patients with schizophrenia, these ABM and ToM are impaired. However, even these domains may be probably linked, there are very few studies focusing on the interaction between ABM and ToM. The aim of this study is to explore correlations between MA and cognitive functions in patients with schizophrenia: ToM, executive functions (verbal fluency, planification, flexibility, speed of processing) and memory functions (encoding, stocking, recall).
Methods: In 2014, we recruited in several psychiatric departments from Psychiatric Clermont de L'Oise Hospital (Picardie area, France) a sample of 20 stabilized patients with schizophrenia according to DSM-IV-TR criteria and a sample of 20 healthy controls. We used clinical assessments (clinical and demographical data) and neuropsychological tools: for ToM we used V-Lis (Bazin and al.,2009), for ABM we used TEMPau tool (assessment of 2 sub-types: episodic ABM and global ABM at 5 period of life, since childhood to age being) (Piolino and al., 2008) and Grober et Buschke, D2 tests, WAIS IV, MEM III for memory, speed of processing and executive functions. We used Pearson's correlations and Wilcoxon's tests ($p < 0,05$).
Results: First results confirm significantly the global cognitive deficits in patients with schizophrenia in comparison with healthy controls. Then results show a significant deficit in ABM in patients with schizophrenia ($p < 0,8$. 10–3) and significant correlations between ABM and ToM ($p < 0,02$) at each period of time, between ABM and executive functions ($p < 0$, 3. 10–3) depending on the sub-type of ABM and the period of time and between ABM and memory ($p < 0,1.10$-2), depending of the sub-type of ABM and the period of time
Conclusion: These results suggest that ABM could represent a function which could mediate social cognition abilities. ABM could be used in rehabilitation and in cognitive remediation, especially in the initial assessment of the patient and in the development of a cognitive remediation program based on a narrative therapy. Further studies must be conducted in this way.
ID: 2115169

HIGH SENSITIVITY C-REACTIVE PROTEIN (HSCRP) LEVELS ARE A SIGNIFICANT PREDICTOR OF FUNCTIONAL CAPACITY ABILITIES IN SCHIZOPHRENIA

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Background: Schizophrenia is a heterogeneous disorder characterized by impaired cognition and poor functional outcomes. C reactive protein (CRP), a serum marker associated with inflammatory states, has been shown to be elevated in schizophrenia. The aim of this study was to determine whether inflammation associated with high sensitivity CRP (hsCRP) levels was related to executive functioning or functional capacity deficits in schizophrenia using a well characterized sample.
Methods: We assessed high sensitivity CRP (hsCRP) levels, executive functioning (Delis Kaplan Executive Functioning System - DKEFS) ability, and functional capacity (UCSD Performance Based Skills Assessment-Brief - UPSA-B) in 114 clinically stable adults with schizophrenia or schizoaffective disorder and 99 age-matched healthy comparison subjects (HCs).
Results: People with schizophrenia had elevated hsCRP levels ($t = -3.9$, $p = <.001$, $d = .625$), poorer executive functioning performance ($t = 11.1$, $p = <.001$, $d = -1.5$), and functional capacity deficits ($t = 8.6$, $p = <.001$, $d = -1.2$) compared to HCs. Higher hsCRP levels were significantly correlated with poorer executive functioning in HCs ($r(71) = -.246$, $p = .039$) but not in people with schizophrenia ($r(88) = -.030$, $p = .778$). Lower total UPSA-B scores were correlated with higher hsCRP levels in schizophrenia ($r(86) = -.255$, $p = .018$) but not in HCs ($r(71) = -.154$, $p = .200$). Hierarchical linear regressions were performed to model the relationships between hsCRP and executive functioning or functional capacity. After accounting for significant demographic (race, education level) and lifestyle factor (BMI, HDL level, current smoking status) correlates; hsCRP levels were a significant predictor of total UPSA-B scores independent of diagnosis ($\Delta R2 = .024$, $\Delta F = 4.1$, $p = .046$). HsCRP levels did not predict executive functioning composite scores in people with schizophrenia or HCs over and above lifestyle factors ($\Delta R2 = .009$, $\Delta F = 1.5$, $p = .231$).
Conclusion: These data suggest that demographic and lifestyle independent factors may contribute to the relationship between hsCRP levels and functional capacity. The relationship between hsCRP and executive functioning deficits is largely moderated by lifestyle factors in this study. Future studies may help elucidate the potential neurotoxic effects of hsCRP and metabolic dysfunction on cognitive or functional decline in schizophrenia.
ID: 2098158

THE SCHIZOPHRENIA COGNITION RATING SCALE: RELIABILITY, VALIDITY AND SENSITIVITY

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Background: Interview- and performance-based cognitive assessments represent two methods for the quantification of clinically meaningful change

in cognition. However, the reliability, validity and sensitivity of interview-based measures is largely unknown. The present research examines these features for one such interview-based measure, the Schizophrenia Cognition Rating Scale (SCoRS).
Methods: To investigate the reliability, validity and treatment sensitivity of the SCoRS, we examined data from two investigations. One was a validation study involving 79 patients with schizophrenia assessed at 3 academic research centers in the US. The other was a 32- site clinical trial conducted in the US and Europe comparing the effects of encenicline, an alpha-7 nicotine agonist, to placebo in 319 patients with schizophrenia. Analyses examined test-retest reliability in both treatment and non-treatment based settings, correlations with performance-based measures of cognition (MCCB), and sensitivity to treatment effects.
Results: SCoRS interviewer ratings demonstrated high test-retest reliability in both non-treatment (ICC=.90) and treatment-based studies (ICC=.80), suggesting the measure is appropriate for use in both settings. Ratings were also correlated with cognitive performance assessed with the MCCB (r=.35). The SCoRS was responsive to treatment, demonstrating significant sensitivity to differences between encenicline and placebo-treated groups (p<.001).
Conclusion: Results highlight the potential utility of the SCoRS as a reliable interview-based measure for the assessment of change in cognition. High reliability coupled with treatment sensitivity suggest the SCoRS is appropriate for use in clinical trials and clinical practice alike.
ID: 2095066

MULTITASKING ABILITIES IN PERSONS DIAGNOSED WITH SCHIZOPHRENIA: A NEW TOOL AND COGNITIVE MODEL.

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Background: Difficulties in everyday life activities are core features of persons diagnosed with schizophrenia, and in particular during multitasking activities (Semkovska et al., 2010). Multitasking refers to activities (e.g. preparing a meal) where the person has to: (a) carry out and alternate between different tasks that vary in terms of priority, difficulty and duration; (b) define the tasks' targets; (c) and where the person is faced with unexpected problems during the realization of these tasks (Burgess, 2000). However, the cognitive underpinnings of multitasking abilities have never been adequately explored in schizophrenia. Further, only two cognitive models exist in the literature, which are based on student (Logie et al., 2011) and neurological (Burgess et al., 2000) samples. Both of these models suggest three primary constructs: Memory, Planning and Intent. There are, however, several limitations related to the way multitasking abilities were evaluated in these studies. We thus developed a computerized real-life activity task - the Computerized Meeting Preparation Task (CPMT), which was specifically designed to take into account the multitasking nature of certain everyday life activities. Using this task, and based on previous studies (Burgess et al., 2000; Logie et al., 2011), the aim of the present study was to evaluate multitasking abilities in schizophrenia and to do so in a new cognitive model of multitasking that takes into account certain cognitive functions that are not integrated in existing models.
Methods: Fifty-seven individuals with schizophrenia and 41 matched healthy controls completed the CMPT. Participants were also evaluated with a battery of cognitive tests.
Results: The results suggest that the CMPT possesses good sensitivity and confirmed the three underlying constructs of multitasking (Memory, Planning and Intent), which were found to be underpinned by several cognitive functions and multitasking aspects.
Conclusion: Taken together, this new cognitive model and the CMPT could be a good basis for cognitive interventions of multitasking abilities in schizophrenia.
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ID: 2085325

COGNITION AND PSYCHOMETRIC SUPPRESSOR EFFECTS OF SCN2A IN SCHIZOPHRENIA

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Background: A recent Genome Wide Association Study has revealed that the Single Nucleotide Polymorphism (SNP) rs11074400 exerted a significant effect on cognition in schizophrenia individuals (Dickinson et al., 2014, Differential Effects of Common Variants in SCN2A on General Cognitive Ability, Brain Physiology, and messenger RNA Expression in Schizophrenia Cases and Control Individuals). In silico replication of the results were conducted in a sample of community recruited participants.
Methods: Schizophrenia cases (n = 314) and healthy controls (n = 394) that were matched on a General Cognition Factor cognitive g distributions derived from the original discovery sample. Subjects with history of neurological disorder, substance abuse, substance dependence or abuse, and color blindness were excluded. Additionally, healthy subjects with family history of psychosis were excluded. Factor Analysis and Principal Components Analysis were used to extract the General Cognition factor, consistent with the earlier study and negative syndromes. .
Results: The SCN2A SNP was significantly associated with cognitionthe General Cognition Factor, however, the effect sizes werewas in the opposite from previously reportedted direction. Linear regression revealed that negative syndrome and chlorpromazine equivalents were significant moderators of the association. Binary Logistic regression revealed that SNP rs11074400 was a significant predictor of case control status in the presence of cognition suggesting the presence of psychometric suppressor effects.
Conclusion: Results suggest that beyond the endophenotype and epiphenomenal models for cognitive and genetic factors, the suppressor model, might yet be another alternative framework that illuminates the complex interplay between cognition, genes, and disease. Furthermore, SCN2A is a known drug target for antiepileptic and mood stabilizing agents. Evidence implicating SCN2A in schizophrenia cognition continues to hold promise for future pharmacological investigation in this area.
ID: 2087155

DOES WORKING MEMORY TRAINING IMPROVE HEDONIC CAPACITY? PILOT DATA FROM INDIVIDUALS WITH SOCIAL ANHEDONIA

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Background: Individuals with social anhedonia have been found to show decreased hedonic experiential pleasure in the social interaction. However, very little is known about whether this diminished hedonic capacity observed in individuals with social anhedonia can be improved or remediated by cognitive training. The purpose of the present study was to explore whether such a diminished hedonic capacity could be altered through extensive working memory (WM) intervention.
Methods: Individuals with social anhedonia were screened with the Revised Chapman Social Anhedonia Scale (RSAS) from a large sample of college students, with a score above 1.96SDs of the normative data of our laboratory. A total of 17 participants with social anhedonia (6 men; an averaged RSAS score of 24.47 (SD = 2.95) were identified and invited to participate the WM training programme. All participants had to take the dual n-back training for 20 sessions. Each session lasted for 20 to 30 minutes. They had to complete the training 5 days per week up to 4 weeks. An Affective Incentive Delay (AID) task capturing hedonic capacity was administered to all participants at pre- and post-training. Moreover the Temporal Experience of Pleasure Scale (TEPS) was administered to assess the state anhedonia experience. Performances before and after the training were compared with the norms of our laboratory.
Results: Our findings showed that there was a significant main effect of condition in the AID task performances after the WM training [$F(2, 52) = 15.488$, $p < 0.001$]. The reaction time in the neutral condition ($M = 239.32$, $SD = 25.61$) was longer than the punishment condition ($M = 234.62$, $SD = 25.22$) ($p = 0.03$), whereas the reaction time in the punishment condition was longer than the reward condition ($M = 227.44$, $SD = 26.15$) ($p < 0.001$). However, the originally significant interaction between group and condition before training [$F(2, 52) = 4.094$, $p = 0.019$] turned to be not significant after training ($F(2, 52) = 0.158$, $p = 0.85$). Moreover, the RSAS score in the individuals with social anhedonia was significantly decreased after training [$t(16) = 2.37$, $p = 0.024$] although the self-report trait and state anticipatory hedonic experience was still worse than the healthy norms.
Conclusion: These preliminary findings suggest WM training could ameliorate the impaired hedonic processing ability in individuals with social anhedonia.
ID: 2082737

AUDITORY PROCESSING SPEED AS A MARKER FOR GENERALIZED COGNITIVE FUNCTION IN SCHIZOPHRENIA

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Background: Previous research indicates that impairments in elementary levels of sensory processing are prominent in schizophrenia. However, the relationship of such impairments to higher-order neuropsychological deficits is unclear.
Methods: In order to determine whether deficits in low-level auditory processing show a relationship to neuropsychological test performance, 93 adult participants with schizophrenia (Age: 34.4 SD: 13.9) completed an auditory processing speed (APS) task, the MATRICS Consensus Cognitive Battery (MCCB), and PANSS and GAF ratings before (Time 1) and after (Time 2) participating in a cognitive training trial.
In the APS task, which requires 10 minutes, participants judged the direction of tonal change in a sequence of two frequency modulated tones. Equivalent stimulus durations and inter-stimulus intervals (ISI) were incrementally shortened based on the patients' performance using a progressive difficulty algorithm. The resulting threshold score used for the analysis was the number of milliseconds of ISI at which the participant correctly performed 66% of trials, allowing for a precise measure of auditory psychophysical threshold under moderate perceptual challenge. Non-parametric Spearman correlations were used to test whether performance on the APS task was associated with MCCB scores, PANSS ratings, or GAF ratings.
Results: At both time points, APS performance was significantly negatively correlated with MCCB speed of processing, verbal working memory, verbal learning, executive functioning, and global cognition. At Time 1, APS performance showed a trend-level association with PANSS negative symptoms subscores and GAF ratings.
Conclusion: These findings suggest that impairments in basic auditory processing are a key cognitive feature of schizophrenia, and that the APS tasks may serve as an efficient and reliable measure of general neuropsychological cognitive functioning, which has implications for the assessment, research, and treatment of patients with schizophrenia.
ID: 2085029

EMOTION RECOGNITION, THEORY OF MIND, PERCEPTIONS OF HOSTILITY AND ATTRIBUTIONAL STYLE IN FIRST EPISODE PSYCHOSIS: RELATIONSHIP WITH SYMPTOMATOLOGY

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Background: Substantial evidences of social cognition impairments in schizophrenia have been gathered in the past 2 decades. 4 domains of social cognition for schizophrenia studies were identified including emotion processing, social perception, theory of mind (ToM) and attribution bias. It has been suggested that social cognition can be used to study the development of clinical symptoms of schizophrenia, however, the role of social cognition in relation to psychotic symptoms revealed inconsistent results. This study aims to explore the symptoms in first episode psychosis and their relations to social cognitions of different levels.
Methods: 40 first episode psychosis patients (FEP) diagnosed with schizophrenia (18 men and 22 women) recruited from Shanghai Mental Health Center and 34 healthy controls (17 men and 17 women) underwent social cognition tasks including emotion recognition (ER40), ToM (Brüne cartoon sequencing), attribution bias (speech samples obtained from the participants were analyzed with Leeds Attributional Coding System) and ambiguous intentions hostility questionnaire (AIHQ). Patients were rated on clinical symptoms on PANSS and a five-factor model was used to subdivide the items.
Results: FEP performed worse on recognition of fear, sad and neutral expressions than control, of which neutral recognition had the biggest effect size. Patients were significantly impaired on ToM tasks including false belief, mutuality and deception. FEP displayed greater use of external-personal and internal-personal attributions for negative events than the control group. In a sub group analysis, patients with paranoid delusions showed greater scores of hostility for ambiguous situations compared to patients without paranoid delusions. ToM deficits were significantly related to disorganized symptoms while external-personal, internal-personal attributions for negative events and hostility under ambiguous situations are significantly correlated with positive symptoms.

None of the social cognition tasks showed correlations with negative symptoms.
Conclusion: External-personal attribution style and hostile attribution under ambiguous situations contribute to paranoid delusions, worse performance on recognition of neutral faces is related to paranoid delusions but to a lesser degree, while ToM deficit is more related to disorganized symptoms.
ID: 2087039

ARE PATIENTS WITH SCHIZOPHRENIA HAVING A DEFECTIVE TRANSLATION OF BOTH EMOTIONAL VALENCE AND AROUSAL INTO MOTIVATED BEHAVIOUR: A CROSS-CONTROL LABORATORY STUDY

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Background: Consistent evidence suggested that patients with schizophrenia experience the same degree of "in-the-moment" pleasure as healthy controls in laboratory "emotion-induction" paradigms. A few studies suggested that such intact emotion experiences are not translated into motivational salience in patients with schizophrenia. Previous studies examined the translation of emotion valence into motivated behaviour; yet the role emotion arousal in motivation has not been well studied empirically in patients with schizophrenia.
Methods: Participants were 25 patients with schizophrenia (mean duration of illness=14.64 years, SD=8.77 years) and 22 healthy controls. We employed an "emotion-induction" paradigm (Heerey & Gold, 2007) which consisted of IAPS pictures of positive, neutral and negative valence, and measured participants' button-pressing behaviour for seeking pleasurable slides or avoiding undesirable slides. We analysed and compared the group differences in subjective emotion experiences to the slides, as well as the group difference in button pressing behaviour across slides of different valence and arousal.
Results: The schizophrenia and healthy groups did not differ in emotion experiences in terms of their pleasantness rating and arousal rating to IAPS slides. Though the two group did not differ in the total effort of button pressing during the entire laboratory paradigm, the group with schizophrenia pressed buttons at speeds that were more similar across slides of different valences than did healthy participants. In other words, schizophrenia groups' affective experiences appeared less predictive of their behaviour as compared to controls. This kind of defective translation of emotional salience into motivated behaviour involved both emotion valence and arousal.
Conclusion: Our work suggested an emotion-volition decoupling in the aspect of valence and arousal, which may constitute one of the biological underpinnings of avolition in schizophrenia. Though emotional arousal is thought to be having higher behavioural activations than emotional valence, both constructs failed to efficiently translate emotional salience into motivated behaviour in patients with schizophrenia.
ID: 2118136

NEUROCOGNITION AND OCCUPATIONAL FUNCTIONING IN SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Functional loss is prominent in schizophrenia and impaired neurocognition has been proposed as a "rate-limiting" factor in vocational rehabilitation. Neurocognitive measures may not be optimal proxies for occupational functioning. As supported employment programs have gained momentum, there is a need for assessment tools measuring functioning on-the-job to help clients enhance occupational skills and employability. The Vocational Cognitive Rating Scale (VCRS) and Work Behavior Inventory (WBI) provide comprehensive functional assessments of persons with schizophrenia in an occupational setting. The purpose of the current study was to explore the relationships between neurocognition and these measures of occupational functioning in a sample of patients with psychoses entering vocational rehabilitation.
Methods: 131 participants were examined using the MCCB, the WBI and VCRS at the beginning of vocational rehabilitation.
Results: Analyses revealed significant correlations between the VCRS total score and all MCCB domains, except verbal learning. Hierarchical multiple regression analysis of selected MCCB domains yielded a significant model ($F9, 99 = 5.82$; $p < .001$), explaining 35 % variance in overall vocational cognitive functioning, with gender, previous employment and education as significant predictors in addition to attention, working memory and visual learning. Processing speed and attention were the neurocognitive domains yielding most significant correlations with the WBI subscales, whereas work quality was the WBI subscale most frequently associated with neurocognitive performance. There were also robust relationships between the WBI global score and the MCCB domains, except for verbal learning. Hierarchical multiple regression analysis revealed processing speed as a significant predictor of social skills, cooperativeness, work habits and personal presentation (β's ranging from .20-.28, p's <.05), whereas attention was a significant predictor of work quality (β.19, p <.05).
Conclusion: We found several significant associations between neurocognition and occupational functioning, supporting the functional validity of the MCCB. Given that neurocognitive impairments may be a rate-limiting factor in rehabilitation, the WBI and VCRS bridge an important gap between structured test settings and occupational settings and thus provide valuable and more specific information about impairments related to occupational functioning.
ID: 2118449

THE SCHIZOTYPY PARADOX: DEFICITS IN PERCEIVED ACCURACY OF EMOTION RECOGNITION

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Background: The ability to correctly recognize emotions has been found to be impaired in schizophrenia patients. However, research examining this domain has been sparse in individuals with psychometrically-defined schizotypy, a group experiencing schizophrenia-like traits that is theorized to be at putative high risk for developing psychotic and other psychiatric disorders. Prior research has demonstrated that people with schizotypy experience similar deficits, albeit at an attenuated level, to those with schizophrenia on a variety of social cognitive domains.Based on this pattern, we hypothesized that people with schizotypy would perform worse on an emotion recognition task compared to healthy controls. We also predicted the schizotypy group would report lower subjective accuracy scores based on prior findings that those with schizotypy tend to rate themselves lower on subjective measures than non-schizotypy groups regardless of objective performance.
Methods: Emotion recognition was measured in schizotypy (n=31) and non-schizotypy (n=34) samples using the Bell-Lysaker Emotion Recognition Task (BLERT).

Table 1. Disorganized symptoms moderate links between neurocognition and other cognitive processes (n = 67).

Moderator	Social Cognition				Metacognition			
	R2	B	SE B	β	R2	B	SE B	β
Model 1	0.27				0.15			
Neurocognition		0.20	0.06	0.38**		0.26	0.11	0.28*
Conceptual Disorganization		-0.59	0.20	-0.33**		-0.41	0.36	-0.14
Neurocognition X Conceptural Disorganization		-0.06	0.04	-0.15+		-0.19	0.08	-0.29*
Model 2	0.27				0.26			
Neurocognition		0.16	0.06	0.30*		0.11	0.11	0.12
Lack of Insight		-0.51	0.23	-0.25*		-1.50	0.41	-0.43**
Neurocognition X Lack of Insight		-0.10	0.06	-0.20*		-0.10	0.10	-0.11

Notes: **p < .01; *p < .05; +p < .10.

Results: Contrary to our hypothesis, no significant differences were found in emotion recognition between the two groups (t[1,63] = .865, p =.390). However, we did find differences in perceived accuracy (t[1,63]= -1.877, p =.032), with the schizotypy group reporting significantly lower scores than the non-schizotypy group. In conclusion, the schizotypy group thought that they performed worse than they actually did; this was not the case for the non-schizotypy group.
Conclusion: Although our hypothesis regarding between-group performance was not supported, this secondary finding is in line with an emerging trend in schizotypy research known as the schizotypy paradox. Regarding this paradox, people with schizotypy subjectively report more severe impairment than their actual performance suggests. These findings highlight the need for future research examining the mechanism driving the discrepancies between perceived and actual impairment in this population.
ID: 2115359

COGNITIVE REMEDIATION THERAPY FOCUSING ON STRATEGY COACHING FOR PATIENTS WITH SCHIZOPHRENIA

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Background: Cognitive impairment is broadly considered as one of the core components of schizophrenia, which affects social and everyday functioning. Cognitive remediation therapy (CRT) for schizophrenia has been developed as a psychosocial approach to address cognitive impairments, but few studies on the subject have focused on Japanese patients. The aim of the present study was thus to examine the effectiveness and applicability of CRT, focusing on strategy coaching for Japanese patients with schizophrenia.
Methods: Twenty-six participants diagnosed with schizophrenia were assigned to either the CRT plus treatment as usual group or to the treatment as usual alone group. The type of CRT used in our study, administered over 12 weeks in weekly group sessions, was the compensatory cognitive training intervention, focusing on four cognitive domains (prospective memory, attention, verbal memory, and executive functions). Cognitive, functional, and clinical symptom measures were implemented at pre-intervention (baseline), following the completion of CRT (post-intervention), and three months after CRT (follow-up).
Results: Mixed design analyses of variance for group and time for each measure demonstrated that effects of CRT on verbal memory, processing speed, and social functioning at post-intervention were significant. Results also revealed that the effects on processing speed were maintained at follow-up. The effect sizes (Cohen's d) of CRT on cognitive measures at post-intervention were medium-to-large on verbal memory, large on processing speed, and small-to-medium on executive functions, and these effect sizes remained at follow-up.
Conclusion: Our study suggests that CRT focusing on strategy coaching have beneficial effects on cognitive functions, improving functional outcomes in Japanese patients with schizophrenia. Additionally, the high degrees of attendance rate and level of satisfaction rated by the CRT participants ensure the applicability of this methodology to this population.
ID: 2083172

SOCIAL COGNITION ACROSS PHASE OF ILLNESS IN SCHIZOPHRENIA: AN EXAMINATION OF LOW-LEVEL AND HIGH-LEVEL PROCESSES

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Background: Individuals with schizophrenia exhibit impairment on a variety of social cognitive tasks, including tasks assessing low-level (e.g., perception of biological motion) and high-level processes (e.g., mental state attributions). However, the evidence is mixed regarding the pattern and magnitude of these impairments over the course of illness. We present preliminary data from an ongoing study of social cognition in recent-onset (ROSz) and chronic schizophrenia (CSz).
Methods: Twenty-one ROSz, 10 demographically similar healthy controls (RO-Ctrl), 24 CSz, and 20 demographically similar healthy controls (C-Ctrl) completed two social cognitive tasks: 1) a low-level task of emotion perception from biological motion (Emo Bio), and 2) a high-level task of mental state attributions involving detection of lies and sarcasm (TASIT). Group differences were analyzed using ANOVA.
Results: Overall, RO-Ctrl exhibited the best performance across tasks, CSz the poorest performance, and ROSz and C-Ctrl were intermediate. For Emo Bio, there was a significant effect of group (p<0.01); ROSz significantly outperformed CSz (p=0.01), but did not differ from the two control groups. On the TASIT, there was a main effect of condition (Sarcasm < Lie, p<0.01), a main effect of group (p<0.01), but no condition x group interaction. ROSz were less accurate than RO-Ctrl (p=0.01), but did not significantly differ from CSz or C-Ctrl. CSz were less accurate than both control groups (p<0.01). For each patient group, effect sizes were computed

comparing performance to the respective control sample. The effect sizes were large across all tasks: dROSz=-0.98 and dCSz=-0.75 for Emo Bio, dROSz=-1.16 and dCSz=-1.04 for TASIT Sarcasm, and dROSz=-1.15 and dCSz=-0.91 for TASIT Lie.
Conclusion: Based on the raw scores, ROSz did not differ significantly from controls on a low-level social cognitive task and but did on a high-level task, while CSz differed from controls on both tasks. However, examination of the effect sizes suggests that both patient groups performed below expectations on all tasks compared to their respective control groups. The effect sizes were of similar magnitude for the low- and high-level tasks in both patient groups. These analyses are limited by the small sample sizes; data collection is ongoing. These preliminary data underscore the importance of employing demographically-similar control samples when investigating performance across phase of illness in schizophrenia. NIMH MH095878, MH066286, MH102529; CIHR120919.
ID: 2091671

COGNITIVE EMPATHY CONTRIBUTES TO POOR SOCIAL FUNCTIONING IN SCHIZOPHRENIA: EVIDENCE FROM A NEW SELF-REPORT MEASURE OF COGNITIVE AND AFFECTIVE EMPATHY

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Background: Cognitive empathy impairments have been linked to poor social functioning in schizophrenia. However, prior studies primarily used self-reported empathy measures developed decades ago that are not well-aligned with contemporary models of empathy.
Methods: We evaluated empathy and its relationship to social functioning in schizophrenia using the recently developed Questionnaire of Cognitive and Affective Empathy (QCAE). Schizophrenia (n=52) and healthy comparison (n=37) subjects completed the QCAE, Interpersonal Reactivity Index (IRI), and measures of neurocognition, symptoms, and social functioning. Between-group differences on the QCAE, and relationships between QCAE subscales and IRI, neurocognition, symptoms, and social functioning were examined.
Results: The schizophrenia group reported significantly lower cognitive empathy than comparison subjects ($p<0.01$), which was driven by low online simulation scores ($p<0.001$). Cognitive empathy explained significant variance in social functioning after accounting for neurocognition and symptoms ($\Delta R2 = 0.11$, $p<0.01$). Group differences for affective empathy were variable; the schizophrenia group reported similar proximal responsivity, but elevated emotion contagion relative to comparison subjects.
Conclusion: These findings bolster support for the presence and functional significance of impaired cognitive empathy in schizophrenia using a contemporary measure of empathy. Emerging evidence that some aspects of affective empathy may be unimpaired or hyper-responsive in schizophrenia and implications for the assessment and treatment of empathy in schizophrenia are discussed.
ID: 2082055

DISORGANIZED SYMPTOMS WEAKEN LINKS BETWEEN COGNITIVE PROCESSES: THE ROLE OF SPECIFIC MODERATORS

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Background: Although disorganized symptoms appear to moderate links between neurocognition and other cognitive processes in schizophrenia (Minor & Lysaker, In Press), two essential questions remain: 1) at what level of symptom severity do links between cognitive processes breakdown?; and 2) do specific disorganized symptoms drive these effects?
Methods: In this study, these questions were examined using validated instruments to assess symptoms, neurocognition, social cognition, and metacognition in a schizophrenia sample (n = 67). Regressions were analyzed to investigate potential moderators. The Johnson-Neyman technique was used to identify levels of disorganized symptom severity where links between cognitive processes were no longer significant.
Results: For both social cognition and metacognition, we observed that neurocognition held a significant effect until participants reached mild levels of disorganization. Regarding specific symptoms, lack of insight moderated the neurocognition-social cognition relationship and conceptual disorganization moderated neurocognition-metacognition links (Table 1). Relationships between cognitive processes broke down once moderate levels of lack of insight and minimal levels of conceptual disorganization were reached.
Conclusion: Our results illustrate that disorganized symptoms are an integral component of cognitive pathways, with even mild levels of disorganization weakening links between cognitive processes. These findings highlight the need to develop and test strategies that target disorganized symptoms so individuals with schizophrenia can foster greater social cognitive and metacognitive abilities.
Reference
Minor KS, Lysaker PH (In Press). Necessary, but not sufficient: Links between neurocognition, social cognition, and metacognition in schizophrenia are moderated by disorganized symptoms. Schizophrenia Research.
ID: 2082219

A SYSTEMATIC REVIEW OF EVIDENCE ON RESILIENCE RESEARCH IN SCHIZOPHRENIA AND FUTURE DIRECTIONS

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Background: Resilience can be defined as "the capacity of a dynamic system to withstand or recover from significant challenges that threaten its stability, viability, or development" (Masten 2011). The concept of resilience is considered relevant in understanding the counterparts of vulnerability and heterogeneous outcomes of patients with schizophrenia. We systematically reviewed the literature with the following goals: 1) to elucidate how resilience has been discussed in patients with schizophrenia, 2) to clarify the methods used to assess resilience, 3) and to review candidate biological mechanisms of resilience in schizophrenia.

Methods: Published articles until September 2014 were searched using EMBASE, MEDLINE, PsycINFO, PubMed, and the Cochrane Library. We used the following search terms: (schizophreni* or schizoaffective or psychosis or psychoses or "severe mental illness") and (resilien*). Peer-reviewed, original articles that assessed resilience (as defined in individual studies) in patients with schizophrenia or related psychoses were included. We also included animal studies that investigated the neurobiological bases of resilience in preclinical models of schizophrenia. References of relevant articles were hand-searched for additional articles.
Results: From the initial list of 834 records, 38 published articles were included; of these, 34 reported results of clinical studies, 2 were published protocols of clinical studies, and 2 focused on animal models of schizophrenia. 72% (26/36) of the clinical studies were cross-sectional. Methods used to assess resilience in the clinical studies were highly heterogeneous; 12 studies used psychological scales (e.g. the Connor-Davidson Resilience Scale) to quantify resilience while others used methods including qualitative assessment of patient interviews, assessment of recovery, and assessment of other psychological measures (e.g. quality of life). Reports regarding biological data were scarce; clinical studies (N=6) included a report on correlations between genetic polymorphisms of the glycogen synthase kinase 3 and grey matter volume, and animal studies (N=2) included a report on Abelson helper integration site 1 knockout mice and stress resilience.
Conclusion: In light of the heterogeneity in resilience scales and other parameters used to assess resilience, future studies should seek common grounds on valid, clinically meaningful assessments of resilience in this population. Furthermore, more longitudinal and biological studies are warranted.
ID: 2084976

CONSTRUCT VALIDATION OF THE MOVIE CLIPS TASK: A NOVEL PROCEDURE FOR ASSESSMENT OF SOCIAL COGNITION IN SCHIZOPHRENIA

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Background: The primary objectives of the study were to: 1) assess construct validity (sensitivity to clinical versus non-clinical group differences) of a novel laboratory measure of social reasoning, the Movie Clips Task (MCT); and 2) evaluate the internal consistency of the MCT procedure, including subscale scores for behavioral responses to movie and cartoon scenes.
Methods: The MCT is an interactive task in which the subject views and responds to questions about scenes from the movie *Ordinary People*, and the cartoon *Toy Story*. Questions about characters in these scenes call for inferential reasoning across five social reasoning domains: emotions (Empathic Cognition), change in mood (Affective Change), insight into the subject's reaction to the emotions of others (Personal Empathic Cognition), thoughts (Cognitive Inference), and motives for the actions of a character (Motive). After viewing a scene, the participant is asked to summarize the scene and answer a standard set of questions that tap these domains. The coding system was designed to reflect levels of cognitive complexity based on the cognitive developmental model of Case (1987). Participants were 34 healthy controls (65% males; *M* [SD] age = 43.9 [11.3] years) and 34 individuals with DSM-IV/SCID schizophrenia (80% males; *M* [SD] age = 50.1 [6.9] years).
Results: Results supported the hypothesized difference between the schizophrenia (SZ) and healthy control (HC) samples, based on one-way MANOVA, Wilks' $\lambda = .77$, $F(2, 65) = 9.48$, $p < .001$, partial eta-squared = .23. Univariate *F* tests showed that HC subjects performed better on both *Ordinary People*, $F(1, 66) = 19.25$, $p < .001$, and *Toy Story*, $F(1, 66) = 7.26$, $p = .009$, as compared with SZ subjects. Among SZ subjects, those employed had higher scores than those unemployed, $F(1, 32) = 4.14$, $p = .05$. For SZ subjects, MC scores were positively correlated with years of education achieved ($r = .38$, $p < .03$; and $r = .35$, $p < .05$) for the two tasks, respectively. Internal consistency was good for the overall MC measure, based on subscale scores (Cronbach's *alpha* = 0.76).
Conclusion: Results provide preliminary evidence for the construct validity of the MCT and its sensitivity to impaired social reasoning in schizophrenia. Contents do not represent views of the Department of Veterans Affairs or the US Government. This research was supported, in part, by a NARSAD Independent Investigator Award (PI: G. Haas) and VA VISN4 MIRECC funds (Site PI: G. Haas).
ID: 2117937

COGNITIVE PREDICTORS OF FUNCTIONAL OUTCOME AND CLINICAL COURSE AFTER A FIRST SCHIZOPHRENIA EPISODE: THE IMPACT OF PSYCHOSOCIAL INTERVENTIONS

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Background: Although cognitive deficits are well-established as key predictors of functional outcome in later years of schizophrenia, a recent comprehensive review concluded that results were mixed for the initial period of the illness (Allott, Liu, Profitt, & Killackey, 2011). Furthermore, the impact of psychosocial treatments that focus on functional outcome on the cognition-functioning predictive relationship is unknown.
Methods: We examined the relationship between baseline outpatient cognitive performance and functional outcome 9–12 months later in four separate samples of patients who had experienced a first schizophrenia episode within the last two years. The total sample was greater than 250 recent-onset schizophrenia patients. The first two samples were drawn from longitudinal studies that did not provide interventions focused on functional outcome. The third sample was from a randomized controlled trial of supported employment and supported education. The fourth sample was provided supported employment/education and additional cognitive remediation or healthy behavior training.
Results: The severity of cognitive deficit at outpatient baseline predicted work/school functioning 9–12 months later in each sample, with magnitudes ranging from moderate to strong. In samples that were not provided supported employment/education, baseline cognitive performance predicted likelihood of return to work or school. When supported employment/education was provided to compensate for deficits, cognitive deficit no longer predicted return to work or school but did predict the quality of performance at work or school.
Conclusion: Severity of cognitive deficit in the initial period after a first schizophrenia episode is a consistent predictor of work/school functioning in the following year. A compensatory psychosocial intervention, supported employment/education, can override the ability of cognitive deficit to predict who returns to work or school. However, then initial cognitive deficit level predicts the level of performance at work or school. Continued efforts to develop interventions to reverse cognitive deficits early in the course of schizophrenia are critical to functional recovery and prevention of chronic disability.
ID: 2117290

SYMPTOM REMISSION AND NEUROCOGNITIVE FUNCTIONING

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Background: The prevalence of symptom remission and its relation to neurocognitive functioning in patients with schizophrenia/schizoaffective disorder remain unclear. There are discrepancies in the current literature, with some studies reporting that remitted patients outperform non-remitted patients on cognitive measures, while other studies have found no differences. The conjecture that symptom remission is prevalent, but varies independently with cognitive impairment has seldom been tested in a Canadian outpatient context and with measures selected for their sensitivity to schizophrenia. The current study examines neurocognitive performance in patients meeting criteria for full symptomatic remission as well as non-remitted and partially remitted patients. Also of interest is whether symptom remission is related to functional competence.
Methods: Patients' remission status was determined according to Andreasen et al.'s (2005) 6- month criteria applied to n=53 participants with schizophrenia or schizoaffective disorder. This yielded 11 patients meeting criteria for full remission, 10 with selectively remitted positive and 13 with remitted negative symptoms along with 19 patients who were persistently symptomatic across assessment points. Neurocognition was measured with the MATRICS Consensus Cognitive Battery (MCCB). Functional competence was measured with the Canadian Objective Assessment of Life Skills (COALS).
Results: There was a significant difference on the MCCB composite score, with remitted patients outperforming the non-remitted group. Significant differences were found on the Speed of Processing index, where both remitted and negative remission groups outperformed the non-remitted patients. There was also a significant difference on the Verbal Memory index, where remitted patients were superior to both non-remitted and positive remission groups.
Conclusion: Patients meeting criteria for symptom remission outperform unremitted or partially remitted patients in processing speed and verbal memory, two aspects of neurocognition most frequently and severely affected by psychotic illness. However, full remission appears to be relatively low in terms of prevalence (21%) in a Canadian outpatient setting.
ID: 2090106

WHY DON'T YOU GIVE ME A CALL? —THE IMPACT OF MEMORY DEFICITS ON EVERYDAY ACTIVITIES

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Background: Patients with schizophrenia have impaired functional and cognitive abilities. Memory dysfunction is one of their most consistently reported cognitive deficits. In everyday activities, the ability to remember things is often needed—even when performing a simple task such as dialing a telephone number. The ability to recall and dial a telephone number can be measured with the Brief UCSD Performance-based Skills Assessment (UPSA-B). The purpose of this study was to examine if there were any differences in cognitive profile among those patients with schizophrenia who managed to perform the UPSA-B telephone subtask and those who did not.
Methods: Data collection took place within the ongoing project Clinical Long-term Investigation of Psychosis in Sweden (CLIPS), which examines psychiatric outpatients. In this study, 172 patients with schizophrenia participated. They were divided into two groups based on their results on the UPSA-B subtask of dialing a telephone number. The groups were compared regarding results from neurocognitive instruments measuring immediate memory, long-term memory, and auditory working memory. Non-parametric statistics were used to analyze differences in their neurocognitive abilities.
Results: There were 30 participants who managed to dial the phone number read out by the test administrator, and 142 participants who failed. Differences between these groups could be seen in the cognitive tests measuring long-term memory and auditory working memory. However, there was no significant difference between the two groups in the cognitive test measuring immediate memory.
Conclusion: Patients are often expected to remember verbal information such as treatment ordinations, medical changes, and new appointments. Hence, knowledge about the patient's verbal memory is important in many treatment situations. Our findings show that relevant information about a patient's verbal memory function could easily be obtained by asking him or her to dial a telephone number.
ID: 2087375

WHY WE SHOULD BE MEASURING SMOKING STATUS IN RESEARCH ON COGNITION IN SCHIZOPHRENIA

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Background: Research continues to study relationships between cognition and cognitive impairments and key aspects of etiology, pathophysiology, treatment and outcome in schizophrenia and related psychoses. Nicotine plays a potential role in cognitive performance given the high prevalence of smoking among patients relative to nonpsychiatric controls and evidence suggesting beneficial effects of acute nicotine consumption on cognition. However, other studies have reported that smokers in general are disadvantaged on cognitive measures. Despite the possible importance of smoking status in interpreting cognitive data, researchers seldom control or even report smoking status in their study samples.
Methods: Accordingly, we examined the relationship between smoking status, cognition and regional cortical thickness in 71 patients and 63 nonpsychiatric control participants. Cognitive measures included the MATRICS Consensus Cognitive Battery (MCCB) as well as the Faux Pas and Reading the Mind in the Eye social cognition tasks. General intelligence (IQ) and premorbid functioning were both assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) and Wide Range Achievement Test (WRAT-4). Neuroanatomical data were collected using a high-resolution 3-Tesla MR scanner to measure cortical thickness.
Results: Cognitive test results indicated main effects of both psychiatric status (schizophrenia vs. controls) and smoking status (smokers vs. nonsmokers) on all MCCB domains (e.g., attention, processing speed, etc.). A single interaction was significant whereby control nonsmokers outperformed control smokers, patient smokers and patient nonsmokers on the Reasoning and Problem-Solving summary score. The results of the neuroimaging revealed widespread cortical thinning among patients relative to controls. Cortical thinning was also found among all smokers compared to all nonsmokers in the inferior and middle temporal gyri and banks of the superior temporal sulcus of the right hemisphere. Interestingly, patient smokers and control nonsmokers had similar cortical thickness patterns in the left parahippocampal gyrus and bilateral medial orbitofrontal gyri.
Conclusion: The data suggest that smoking status is an important variable to report and investigate in cognitive research on schizophrenia and may interact with the disease process in selective and complex ways. Failure to control for smoking status in cognitive studies may confound results and contribute to the variability found in schizophrenia research.
ID: 2094300

THE GENETIC STRUCTURE OF COGNITIVE ENDOPHENOTYPES FOR SCHIZOPHRENIA: A MULTIPLEX, MULTIGENERATIONAL FAMILY STUDY OF SCHIZOPHRENIA

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Background: Although studies have identified many putative cognitive endophenotypes that are abnormal among schizophrenia probands' relatives, little is known regarding their interrelation. Do different schizophrenia genetic effects affect cognitive endophenotypes differently? Are some cognitive functions more affected by schizophrenia genetic effects than are others? Here we apply for the first time a technique, targeted factor analysis, which can powerfully address these important questions.
Methods: A total of 771 participants, including 636 relatives from 43 multigenerational families with at least two schizophrenia relatives (multiplex) and 135 unrelated controls underwent diagnostic interview and the Penn Computerized Neurocognitive Battery. Genetic covariances of the 20 cognitive test accuracy and speed scores were factor analyzed using targeted rotation to maximize factor loadings with schizophrenia.
Results: Only one schizophrenia genetic factor was identified, which had a genetic correlation of .57 with the diagnosis of schizophrenia. Individual test loadings on the schizophrenia genetic factor ranged between .70 - .35 (M = .48) for accuracy scores and .44 - .04 (M = .30) for reaction times. The WRAT Reading Test had the highest loading (.70).
Conclusion: 1) Much of the genetic effects on schizophrenia also affect cognition (R=.57). 2) The presence of only a single genetic factor implies that schizophrenia genetic effects have interchangeable effects on cognition. Thus, different schizophrenia genetic effects affected cognitive tests similarly. 3) Although cognitive test accuracy measures were somewhat more sensitive to schizophrenia genetic effects (Mean R=.48) than reaction times (Mean R=.30), there were relatively few differences in loadings for accuracy among different tests, suggesting that cognitive functions are largely affected by schizophrenia liability in a general deficit fashion across multiple tests. Interestingly, the highest loading on the schizophrenia genetic factor was a test of reading performance, which may reflect cognitive deficits that were manifest at least during childhood. Although these different tests may be less useful in identifying different specific genetic effects, the ability to aggregate across multiple genetically correlated tests using this technique should increase their sensitivity to detect schizophrenia genetic effects.
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ID: 2084078

SOCIAL PERCEPTION AND THEORY OF MIND SKILLS IN PATIENTS AT ULTRA-HIGH RISK FOR PSYCHOSIS: A CASE-CONTROL STUDY

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Background: Only relatively few studies have examined social cognition in patients at ultra-high risk (UHR) of developing psychosis. Even though findings are not consistent, most studies have documented impairment in various social cognitive domains, including emotion perception and theory of mind. However, the profile of social cognitive deficits in UHR patients remains largely unknown. The social cognitive deficits may constitute part of the predisposition to psychosis and be targets for early intervention. The purpose of this study was to examine social perception and theory of mind skills in a UHR cohort.
Methods: We examined cross-sectionally 36 patients meeting criteria for being at UHR for onset of first psychotic disorder and 50 matched healthy control (HC) subjects with social cognitive tests focusing on social perception and theory of mind skills. These included the videotape-based Awareness of Social Inference Test (TASIT) (only Part 2) and the Benton Facial Recognition Test (BFRT).
Results: The UHR patients were significantly impaired on the test measuring social perception and theory of mind skills, displaying deficits in terms of appreciating sincere (p = .26, two-tailed) and sarcastic conversational (p= <.001, two-tailed) interactions. The UHR patients did not have impaired face recognition.
Conclusion: The study indicates that the UHR patients have impaired social perception and theory of mind skills compared to the matched HC subjects. This may reflect difficulties in understanding conversational inferential hints and judging intentions, beliefs and feelings of others. These social cognitive impairments may contribute to the well-documented deficits in social functioning in UHR patients. The results point towards social cognitive deficits as important treatment targets that may be addressed in social cognitive training.
ID: 2118698

THE EFFECT OF BILATERAL TRANSCRANIAL DIRECT CURRENT STIMULATION ON COGNITION IN SCHIZOPHRENIA

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Background: Individuals with schizophrenia experience very high levels of disability and poor community outcome, resulting in a major public health concern. Over the last decades, the treatment of schizophrenia has shifted fundamentally from a focus on symptom reduction to a focus on recovery and improving aspects of functioning. Needed improvements in community outcome for patients with these disorders will not occur simply through better control of clinical symptoms. Instead, new treatments are needed that address the key determinants of poor functional outcome.
Methods: In this preliminary study, we examined the effect of transcranial direct current stimulation (tDCS) on neurocognitive and social cognitive functions. This procedure is non-invasive and painless and results in increase or decrease of spontaneous neuronal firing in the brain. Unlike other non-invasive brain stimulation techniques, such as transcranial electrical stimulation or transcranial magnetic stimulation, tDCS does not induce neuronal firing

by suprathreshold neuronal membrane depolarization, but rather modulates spontaneous neuronal network activity. tDCS was administered bilaterally over the dorsolateral prefrontal cortex (DLPFC). The current intensity was set at 2 mA (1 mA on each side) and was maintained for two 20-minute sessions, with a one hour break between the sessions. Assessments were conducted immediately following each session, in a counterbalanced order of administration. Preliminary data were analyzed on 30 individuals with schizophrenia in an ongoing study: 10 participants received anodal tDCS (enhancing cortical excitability), 10 received cathodal tDCS (decreasing cortical excitability), and 10 received a sham tDCS (stimulation with no current).
Results: No systematic effects were detected across the neurocognitive and social cognitive domains. Findings demonstrate the safety and ease of administration of this procedure in schizophrenia, but raise dose and laterality related issues.
Conclusion: In accordance with accumulating evidence from studies in healthy volunteers, a unilateral stimulation with at least a 2 mA over DLPFC may be necessary to attain a therapeutic effect on cognition in schizophrenia.
ID: 2082562

TRAJECTORY OF NEUROCOGNITIVE FUNCTIONING IN PSYCHOTIC DISORDERS

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Background: Although cognitive deficits are recognized as a core feature of schizophrenia, and are evident in non-schizophrenic psychotic disorders as well, their trajectory over the course of illness remains debated. First, in the context of four distinct diagnostic groups, we compared neuropsychological performance among patients experiencing their first psychotic episode. Next, we examined if cognitive abilities decline, remain static or modestly improve through the first 10 years of illness.
Methods: The first (baseline) analyses form part of the AESOP (Aetiology and Ethnicity in Schizophrenia and Other Psychoses) study, a population-based, case-control study of patients with first-episode psychosis. A neuropsychological test battery was administered to 187 patients with a diagnosis of schizophrenia (N=65), bipolar disorder or mania (N=37), depressive psychosis (N=39), or other psychotic disorders (N=46) following index presentation, as well as to healthy comparison subjects (N=177). The presence of specific and generalized cognitive deficits was examined. In the second (follow-up) analyses we included 108 patients followed up-to 10 years from index admission. 103 healthy controls were also followed up.
Results: Early in the course of psychotic illness cognitive deficits are present in all psychotic disorders, but are most severe and pervasive in schizophrenia and least pervasive in bipolar or mania. In schizophrenia and bipolar disorder deficits in verbal abilities become more severe over the course of illness. In contrast, deficits in memory and processing speed, evident early in schizophrenia, remain static.
Conclusion: Both schizophrenia and bipolar/mania patients show dynamic changes in general and specific cognitive functions. Some of the deficits start early and are severe already at first hospitalization while others continue to worsen across life span.
ID: 2119230

A LONGITUDINAL STUDY OF WISCONSIN CARD SORTING TEST PERFORMANCE AND LEARNING POTENTIAL IN PEOPLE WITH SCHIZOPHRENIA

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Background: Learning potential (LP), or the ability to improve cognitive performance following instruction, has been of interest to schizophrenia researchers because it may be a predictor of rehabilitation response. LP is generally measured via dynamic assessment, which combines instruction with test administration in a pre-test, training, post-test design. Validity evidence for LP has included findings that groups who differ in learning ability can be distinguished in terms of cognitive functioning, and that dynamic LP methods appear to assess different cognitive abilities than traditional testing formats. To our knowledge, only two studies have addressed the longitudinal stability of LP. Fiszdon and Johannesen (2010) found acceptable 2-month test-retest stability of an LP list-learning task and Weingartz et al. (2008) examined LP stability across a 12- month period. The present study extends these findings by examining the stability of LP across a longer time period.
Methods: Twenty-eight individuals with schizophrenia completed baseline LP assessment and follow-up testing an average of 31 months later. LP was evaluated with the Wisconsin Card Sorting Test (WCST), using methods outlined by Wiedl (1999) and others. Specifically, participants completed a standard WCST (Trial 1), followed immediately by training involving enhanced instructions and feedback (Trial 2). Following training, the participants completed a third WCST administration with standard instructions (Trial 3).
Results: Analyses revealed strong relationships between performance at Baseline and Follow up for all of the respective WCST trials. In other words, trial 1 performance at baseline was significantly correlated with trial one performance at follow up (r=0.52). Trial three performance at baseline was significantly correlated with trial three performance at follow up (r=0.69). Interestingly, trial three performance at baseline was not significantly correlated with trial 1 performance at follow up.
Conclusion: These findings indicate that LP performance is highly stable, even at a follow up period of approximately 2.5 years. These data also indicate that despite training on the task at baseline, there was no generalized practice effect: i.e., post-training performance on the WCST was not associated with trial 1 WCST performance at the follow up period. These results provide additional support for the usefulness of LP methods, and will be discussed in terms of rehabilitation implications.
ID: 2089221

PROCESSING OF SPATIAL-FREQUENCY ALTERED FACES IN SCHIZOPHRENIA: EFFECTS OF ILLNESS

Phase and Duration

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Background: Low spatial frequency (SF) processing has been shown to be impaired in people with schizophrenia, but it is not clear how this varies with clinical state or illness chronicity.
Methods: We compared schizophrenia patients (SCZ, n=34), first episode psychosis patients (FEP, n=22), and healthy controls (CON, n=35) on a gender/facial discrimination task. Images were either unaltered (broadband spatial frequency, BSF), or had high or low SF information removed (LSF and HSF conditions, respectively). The task was performed at hospital admission and discharge for patients, and at corresponding time points for controls. Groups were matched on visual acuity.

Results: At admission, compared to their BSF performance, each group was significantly worse with low SF stimuli, and most impaired with high SF stimuli. The level of impairment at each SF did not depend on group. At discharge, the SCZ group performed more poorly in the LSF condition than the other groups, and showed the greatest degree of performance decline collapsed over HSF and LSF conditions, although the latter finding was not significant when controlling for visual acuity. Performance did not change significantly over time for any group. HSF processing was strongly related to visual acuity at both time points for all groups.
Conclusion: We conclude that: 1) SF processing abilities in schizophrenia are relatively stable across clinical state; 2) face processing abnormalities in SCZ are not secondary to problems processing specific SFs, but are due to other known difficulties constructing visual representations from degraded information; and 3) the relationship between HSF processing and visual acuity, along with known SCZ- and medication-related acuity reductions, and the elimination of a SCZ-related impairment after controlling for visual acuity in this study, all raise the possibility that some prior findings of impaired perception in SCZ may be secondary to acuity reductions.
ID: 2093453

SCHIZOPHRENIA AND CREATIVITY

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Background: Schizophrenia is highly stigmatized and the strengths that psychosis can generate, such as creativity, are rarely considered.
Methods: Research suggests, however, that creativity may be enhanced in those with schizophrenia (Keefe & Magaro, 1980; Prentky, 1979). Some have suggested that creativity in individuals with schizophrenia may be seen as a survival strategy (Zaidel, 2014).
Results: The understanding of both creativity and schizophrenia remain limited, but new research suggests that an increase in dopaminergic activity is associated with both increased creativity and an increased feeling of reward (Acosta, 2014). Other research suggest that increased ventricle size and decreased activation in the prefrontal cortex in those with schizophrenia may increase creative ability through a decrease in gatekeeping and latent inhibition (Mayseless, et al., 2014; Carson, Peterson, & Higgins, 2003).
Conclusion: This study will review the literature linking schizophrenia and creativity and discuss how current treatments for schizophrenia may be enhanced by helping individuals with schizophrenia focus on their creativity.
ID: 2119360

THE RELATIONSHIP OF NEUROCOGNITION AND NEGATIVE SYMPTOMS TO SOCIAL AND ROLE FUNCTIONING OVER TIME IN INDIVIDUALS AT CLINICAL HIGH RISK

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Background: Impaired social, role, and neurocognitive functioning are pre-illness characteristics of people who later develop psychosis. In people with schizophrenia, neurocognition and negative symptoms are associated with functional impairment. We examined the relative contributions of neurocognition and symptoms to social and role functioning over time in clinically high-risk (CHR) individuals and determined if negative symptoms mediated the influence of cognition on functioning.
Methods: Social, role and neurocognitive functioning, and positive, negative and disorganized symptoms were assessed in 167 individuals at CHR for psychosis in the North American Prodromal Longitudinal Study (NAPLS-1), of whom 96 were re-assessed at 12 months.
Results: Regression analyses indicated that negative symptoms accounted for unique variance in social and role functioning at baseline and follow-up. Composite neurocognition accounted for unique, but modest, variance in social and role functioning at baseline and in role functioning at follow-up. Negative symptoms mediated the relationship between composite neurocognition and social and role functioning across time-points. In exploratory analyses, individual tests (IQ estimate, Digit Symbol/Coding, verbal memory) selectively accounted for social and role functioning at baseline and follow-up after accounting for symptoms. When negative symptom items with content overlapping with social and role functioning measures were removed, the relationship between neurocognition and social and role functioning was strengthened.
Conclusion: The modest overlap among neurocognition, negative symptoms and social and role functioning indicates that these domains make substantially separate contributions to CHR individuals.
ID: 2112786

NEUROCOGNITIVE ENDOPHENOTYPES IN THE COGS-2 STUDY

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Background: The use of heritable, quantitative neurocognitive endophenotypes to dissect the genomic basis of schizophrenia has been one of the most robust approaches to understanding the nature of schizophrenia. In

both COGS-1 and COGS-2, two of the largest endophenotype studies ever conducted, detailed information was collected using the same neurocognitive endophenotypes allowing direct comparison across studies, as well as offering an opportunity to evaluate moderating factors such as smoking.
Methods: COGS-1 examined 300 schizophrenia families and > 500 controls. COGS-2 examined 2,500 schizophrenia cases and controls, although subject totals differ slightly across the endophenotypes. The neurocognitive endophenotypic domains and measures included: verbal memory (California Verbal Learning Test-II/CVLT), vigilance (Degraded Stimulus Continuous Performance Test/ DSCPT) and the CPT-Identical Pairs (CPT-IP), working memory (Letter Number Sequencing/LNS), and a range of neurocognitive measures using the Penn computerized neurocognitive battery (CNB).
Results: Deficits on all measures and intermediate deficits in family members in the endophenotypes were found in a range similar to the heritability of schizophrenia itself in COGS-1. The severity of impairments when taking into account control performance, was largely the same in the two COGS studies, although absolute performance was lower in COGS-2 than COGS-1 (CVLT-II & CNB). Schizophrenia patients who smoked showed a larger impairment than nonsmoking patients (LNS, CVLT). Tests involving working or long-term memory had the largest effect sizes, especially involving mental manipulation.
Conclusion: The pattern of results across COGS-1 and 2 reinforces the robustness and utility of these measures in understanding the neurobiology of schizophrenia. The two different genetic designs (family study vs. case-control), and to some extent the worse overall performance in the case-control study highlights the effects and importance of differing cohorts. The significance of smoking needs to be investigated further to determine its cause or effect relationship to neurocognive deficit. Future studies with these samples will involve identifying the relationships between the neurocognitive endophenotypes and genetic substrates of schizophrenia.
ID: 2116879

NEUROCOGNITIVE FUNCTIONING IN CLINICAL HIGH RISK STUDIES AND IMPLICATIONS FOR COGNITIVE ENHANCEMENT IN THE PSYCHOSIS PRODROME

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Background: Intervention strategies for reducing disability and preventing psychotic disorders have evolved from the first episode of psychosis to the Clinical High Risk (CHR) "prodromal" phase and may eventually evolve to earlier phases of pre-psychotic illness that are examined by family high-risk studies. In this talk, we will review the literature on neuropsychological studies of CHR samples with some emphasis on recent findings from the second phase of the North American Prodrome Longitudinal Studies (NAPLS-2). We will also discuss potential applications of cognitive remediation in the CHR period.
Methods: Results from our recent meta-analysis on neuropsychological studies of youth at risk for psychosis will be summarized as well as recent results from the NAPLS-2 study including CHR individuals who transitioned to psychosis (CHR-T, n=41) vs. those who didn't (CHR-NT, n=286) based on the first half of the NAPLS-2 study. We will also discuss preliminary findings from the few studies of cognitive enhancement in the CHR period.
Results: Neurocognitive impairment is common in youth at CHR for psychosis, and the impairments (which are maximal in working and declarative memory) are significantly worse in those who convert to psychosis (large effect sizes). Moreover, the effects were as large in unmedicated as medicated participants, and there were no significant age by group interactions. Preliminary data from a pilot, intensive, internet-based Targeted Cognitive Training (TCT) intervention suggests it is feasible to use and has potential cognitive benefits for CHR. Symptoms improved during the treatment period as well.
Conclusion: There is now strong evidence indicating that cognition in adolescent/ young adult CHR participants is significantly impaired, especially in those who convert to psychosis. A promising but uncontrolled pilot study showed improvements in cognition and symptoms, but no conclusions can yet be drawn about specific benefits of TCT over other interventions or natural fluctuations in cognition and function. The findings demonstrate the importance of early intervention and simultaneously highlight the challenge to the field to develop strategies that could arrest or even reverse these cognitive impairments, and whether TCT interventions can extend to symptomatic improvement as well.
ID: 2116568

HEALTHY NORTH AMERICAN ADOLESCENT PERFORMANCE ON THE MATRICS COGNITIVE CONSENSUS BATTERY (MCCB): DEVELOPMENTAL AND NORMATIVE DATA FROM THE NAPLS AND CIDAR STUDIES

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Background: The MCCB fills a significant need for a standardized battery of cognitive tests to use in clinical trials of therapeutic interventions for schizophrenia. The success of initial validation studies in adults aged 20–59 now underscores a need to validate its utility at younger ages in which the risk of schizophrenia is also elevated. Toward this end, we assessed developmental patterns and performance in healthy adolescents aged 12–19.
Methods: Baseline MCCB, reading and IQ data were obtained from healthy controls in the NIMH-funded NAPLS-2 (n=126) and CIDAR (n=13) studies. All MCCB tests were administered except the MSCEIT. NAPLS-2 data were collected from 4 geographical regions across North America; CIDAR data was collected in Boston. Developmental MCCB scores were presented in four

2-year age cohorts as T-scores for each test and cognitive domain, based on the overall sample of 139 participants, and analyzed for effects of age and, gender.
Results: Due to IQ differences between age groups, IQ served as a covariate in subsequent analyses. Overall and gender-based raw scores for individual MCCB tests were presented for each age-based cohort. Standardized performance by age generally showed differential improvement in most MCCB cognitive domains. Most domains showed greater relative improvement at younger ages, but most also showed continued improvement in the oldest age band.
Conclusion: These normative data show that healthy adolescence is a dynamic period that is marked by substantial improvement in MCCB performance throughout the 8-year age range assessed in this study. These findings emphasize the importance of normative comparison data at different ages within adolescence to facilitate research and clinical evaluations of adolescents at risk for schizophrenia.
ID: 2118708

EMOTION PERCEPTION IN SCHIZOPHRENIA AND ANTISOCIAL PERSONALITY DISORDER

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Background: Schizophrenia is known to associate with deficits in facial emotion perception (FEP), which the later was postulated to contribute to aggression. This study aimed to examine if schizophrenia patients with antisocial personality disorder (ASPD), a subgroup with higher violence propensity, are more impaired in FEP than patients with schizophrenia and healthy individuals. The relationships between FEP and clinical variables, neurocognitive functions and aggression, in this subgroup of schizophrenia patients with ASPD were also examined.
Methods: Three groups each consisting of 30 individuals, including subjects with DSM-IV diagnosis of schizophrenia comorbid with ASPD, schizophrenia patients, and healthy controls were recruited. All participants completed FEP tasks for six universal emotion types, a battery of neurocognitive assessments and a scale measuring aggression history. Multivariate and univariate analyses of variances, and correlational analyses were performed.
Results: Schizophrenia patients with ASPD had the most severe FEP impairment, in particular in identifying emotions with negative valence; whereas patients with schizophrenia had worse FEP performance than the healthy controls. Schizophrenia patients with ASPD were also found to have more severe impairments in other neurocognitive functions. In addition, history of aggression had a significant negative correlation of moderate strength with identification of negative facial emotions in schizophrenia patients with ASPD.
Conclusion: While impairment of FEP was found in schizophrenia patients, the deficit was more severe in the group of schizophrenia patients comorbid with ASPD who had significantly more aggression history. Given our findings of significant correlation between history of aggression and FEP impairment, clinicians should be aware of the possibility of FEP impairment contributing to aggression in this group of patients. Our findings lend support to the need of social cognitive training targeted to FEP deficit in this particular subgroup of patients.
ID: 2118298

SELF-AGENCY IMPAIRMENTS IN SCHIZOPHRENIA AND THEIR RELEVANCE FOR SYMPTOMS AND SOCIAL FUNCTIONING

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Background: When I shout my friend's name, he looks over his shoulder and laughs. It is clear my actions caused him to do so. Such so-called self-agency experiences are fundamental for social communication and interaction, are usually automatic and need no attention. Schizophrenia patients typically experience no agency over their actions and consequences of those actions and exhibit difficulties in distinguishing their own actions from those of others. There is some evidence suggesting that abnormal self-agency processing might underlie symptoms related to self and other, such as delusions of alien control and hallucinations. Previously, we showed that when an action outcome matches a primed outcome, patients do not show increased self-agency over these outcomes, while healthy controls do. In the current study we investigated whether these abnormalities are related to the severity of symptoms and to level of social functioning.
Methods: A total of 31 schizophrenia patients and 31 controls performed the "Wheel of Fortune" task. They were instructed to perform actions (button presses) and subsequently indicated whether or not they were the agent of the consequence of this action (the outcome, i.e., the location of a rotating square) on a 9-point scale. Briefly priming a matching or mismatching outcome before action performance was used to manipulate feelings of agency. Furthermore, the Positive and Negative Symptoms Scale (PANSS) and the Social Functioning Scale (SFS) were administered.
Results: Controls showed a significant increase in experienced self-agency when the outcome matched v mismatched the prime ($p=0.02$), while patients showed no such effect ($p=0.35$), replicating previous findings. Patients showed no significant correlation between the matching effect (agency experienced during matches - agency experienced during mismatches) and severity of positive, negative or general symptoms of the PANSS or total or subscale scores of the SFS, after correction for multiple comparisons ($p<0.01$).
Conclusion: These findings suggest that the abnormalities in implicit processes leading to a failure to experience self-agency over an action in schizophrenia cannot explain severity of symptoms or level of social functioning.
ID: 2092637

THEORY OF MIND PERFORMANCE IN FEMALES WITH SCHIZOPHRENIA COMPARED TO FEMALES WITH BORDERLINE PERSONALITY DISORDER

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Background: Impairments in social cognition, including theory of mind (ToM), are present in both schizophrenia (SZ) and borderline personality disorder (BPD), but whether the deficits are comparable in the two disorders is unclear.
Methods: The ToM performance of 23 females with SZ was compared to that of 25 females with BPD using independent samples t-tests. Scores were standardized based on the performance of 24 healthy females. ToM was assessed with the ecologically valid measure Movie for the

Assessment of Social Cognition (MASC), a short movie showing 4 people meeting for dinner. Respondents are asked questions about the thoughts, intentions and emotions of the characters. Scores used were overall number of correct responses as well as types of ToM errors: overmentalizing and 2 types of undermentalizing: 'reduced ToM' and 'no ToM'.

Results: Females with SZ had large deficits in overall ToM ability, performing more than 2 standard deviations below healthy females. Compared to healthy females, they committed a substantial number of undermentalizing errors, especially 'no ToM', but also overmentalizing errors. Females with BPD had a slightly reduced overall ToM, about half a standard deviation below healthy females. They committed fewer 'reduced ToM' errors than healthy females and had hardly any 'no ToM' errors, but had elevated levels of overmentalizing errors. Females with SZ performed significantly worse than females with BPD for all ToM measures, except for overmentalizing where the performance of the 2 groups was indistinguishable.

Conclusion: Females with SZ had large deficits in ToM due to problems with both overmentalizing and undermentalizing. Females with BPD had a slight reduction in ToM ability that can be attributed to overmentalizing. Our study confirms that social cognitive impairments are present in both disorders to a differing degree, but additionally implies a more global deficit in SZ, whereas BPD appears to be characterized by a tendency to overattribute mental states to other people.

ID: 2111638

STABILITY AND PREDICTION OF FUNCTIONING FOR COGNITION AND NEGATIVE SYMPTOMS DURING ONE-YEAR FOLLOW-UP AND EIGHT YEARS LATER IN RECENT-ONSET SCHIZOPHRENIA

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Background: Cognitive deficits and negative symptoms are stable and associated with poor functional outcome in schizophrenia, suggesting they both are important targets for intervention. However, few studies of early course patients have examined the long-term stability and predictive power of these two aspects of psychopathology in the same sample.

Methods: This eight-year longitudinal study involved recent-onset schizophrenia outpatients (n=77) recruited from Los Angeles area hospitals who were on average 21.7 (SD =3.3) years old, had 12.5 (SD =1.8) years of education, and were 5.9 (SD =6.3) months from psychosis onset. Patients were assessed at baseline, one year, and eight years later (n=53) for negative symptoms (BPRS, SANS), cognitive functioning (early perceptual processing, sustained attention, working memory load, verbal ability, Shipley-Hartford IQ), and functional outcome (social, school, and work functioning).

Results: Cognitive functioning in the domains of early perceptual processing, sustained attention, and working memory were highly stable during the initial year of treatment (r =.67 to 79). Both baseline (r =.43 to .49) and one year levels (r =.46 to .68) significantly predicted performance within these same cognitive domains eight years later. However, only general WAIS measures of verbal ability and IQ assessed at one-year predicted work functioning eight years later (r =.58 to .74). Similarly, negative symptoms were moderately stable from baseline to one-year (BPRS, ICC =.64, and SANS, ICC =.66) and significantly predictive of negative symptom severity eight-years later (r =.30). Baseline level of negative symptoms were significantly associated with social functioning (r =-.34) and work functioning (r =-.25) at one year, but did not significantly predict functioning at the eight-year follow-up.

Conclusion: During the first outpatient year in recent-onset schizophrenia patients cognitive functioning and negative symptoms were highly stable. Initial levels of cognitive functioning were highly predictive, while negative symptoms were moderately predictive, of severity levels on the same measures eight years later. Only WAIS measures of general verbal ability and IQ, in contrast to negative symptoms or cognitive functioning in particular domains, significantly predicted work functioning eight years later.

ID: 2119045

DIFFERENTIAL PROFILES OF PROSPECTIVE MEMORY IN PATIENTS WITH SCHIZOPHRENIA, BIPOLAR DISORDER AND OBSESSIVE-COMPULSIVE DISORDER

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Background: Remembering to implementing future intentions namely, prospective memory (PM) is important in daily life. PM was severely impaired in schizophrenia and other various psychiatric disorders. However, it is still not clear whether there are differential PM impairments observed across these neuropsychiatric disorders.

Methods: The current study attempted to address this issue by comparing PM and other cognitive functions in patients with schizophrenia, obsessive-compulsive disorder, and bipolar disorder. Twenty-six patients with schizophrenia, 30 patients with bipolar disorders, 58 patients with obsessive-compulsive disorders, and 58 healthy controls were recruited. All participants were administered with two computerized PM tests and a set of neurocognitive functions tests. Patients also reported the subjective appraisal of their PM functions in daily life.

Results: The findings showed that patients with schizophrenia were most severely impaired in both event- and time-based PM, whereas patients with bipolar disorder and obsessive-compulsive disorder were only impaired in time-based PM. All three groups reported similar frequency of PM failures in daily life as healthy controls, but objective and subjective PM were only correlated in patients with obsessive-compulsive disorder. In patients with schizophrenia, superior time-based PM performance correlated with better working memory and controlling for it in multivariate analysis led to significant reduction of PM deficits. In patients with obsessive-compulsive disorder, switching difficulty was uniquely impaired and correlated with both objective and subjective PM. In patients with bipolar disorder, higher anxiety correlated with subjectively-rated PM.

Conclusion: In summary, the three clinical groups were impaired in PM but the extent and nature of PM deficits varied, which is informative clinically in identifying the key cognitive functions to target for in developing interventions to improve PM in different clinical groups.

ID: 2117672

ABNORMAL EYE-CONTACT PERCEPTION: A PHENOMENON SPECIFIC TO SCHIZOPHRENIA OR A TRANS-DIAGNOSTIC DEFICIT?

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Background: Our previous study found that individuals with Schizophrenia (SCZ) over-perceived eye contact when gaze direction was ambiguous and showed less dichotomous perception than healthy controls (HC). These abnormalities explained socio-emotional deficits beyond neurocognition in SCZ. This study investigated if abnormalities in eye-contact perception are also present in other severe mental illnesses.
Methods: Thirty-five participants with Schizophrenia or Schizoaffective Disorder (SCZ), 30 participants with Bipolar Disorder (BP), and 23 HC completed the eye-contact judgment task. They viewed faces with varying gaze directions (from averted to direct with ten 10% increments), head orientations (forward, 30° averted), and emotion (neutral, fearful) and responded whether the person was looking at them. Participants' eye-contact endorsement rates were first analyzed with mixed-model ANOVA. Then each individual's responses to forward faces were analyzed in a psychophysical approach to estimate thresholds and the slope of the eye-contact perception curve. These measures were then correlated with socio-emotional functioning measures.
Results: Overall, SCZ endorsed more eye contact than HC, with BP's endorsement rate in the middle, $F(2, 85) = 4.52$, $p < .001$. This group difference varied with head orientation and gaze direction, $F(9.2, 389.4) = 2.72$, $p = .004$. With forward heads, both SCZ and BP over-perceived eye contact the most with ambiguous gaze. With averted heads, SCZ over-perceived eye contact the most with more direct gaze, while BP over-perceived about the same across all gaze directions.
As for psychophysics measures for forward faces, SCZ had lower thresholds than HC when using a response cutoff of 60% or lower, with BP's thresholds falling in between SCZ and HC, $F(2.0, 87.0) = 3.19$, $p = .045$. The three groups also differed in slope of the eye-contact perception curve, $F(2, 85) = 4.10$, $p = .020$, such that HC had the steepest slope, followed by BP, and then SCZ. Steeper slope predicted better emotional intelligence (MSCEIT) in SCZ and HC, but not in BP.
Conclusion: This study revealed that previously observed abnormalities in eye-contact perception in SCZ were also present but to a lesser degree in BP, which had a different relationship with social-emotional functioning from SCZ, suggesting differential psychopathologic mechanisms between SCZ and BP.
ID: 2096288

NEUROCOGNITIVE AND CLINICAL PREDICTORS OF LONG-TERM OUTCOME IN ADOLESCENTS AT ULTRA-HIGH RISK FOR PSYCHOSIS: A 6-YEAR FOLLOW-UP

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Background: Most studies aiming to predict transition to psychosis for individuals at ultra-high risk (UHR) have focused on either neurocognitive or clinical variables and have made little effort to combine the two. Furthermore, most have focused on a dichotomous measure of transition to psychosis rather than a continuous measure of functional outcome. We aimed to investigate the relative value of neurocognitive and clinical variables for predicting both transition to psychosis and functional outcome.
Methods: Forty-three UHR individuals and 47 controls completed an extensive clinical and neurocognitive assessment at baseline and participated in long-term follow-up approximately six years later. UHR adolescents who had converted to psychosis (UHR-P; n = 10) were compared to individuals who had not (UHR-NP; n = 33) and controls on clinical and neurocognitive variables. Regression analyses were performed to determine which baseline measures best predicted transition to psychosis and long-term functional outcome for UHR individuals.
Results: Low IQ was the single neurocognitive parameter that discriminated UHR-P individuals from UHR-NP individuals and controls. The severity of attenuated positive symptoms was the only significant predictor of a transition to psychosis and disorganized symptoms were highly predictive of functional outcome.
Conclusion: Clinical measures are currently the most important vulnerability markers for long-term outcome in adolescents at imminent risk of psychosis.
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ID: 2087170

Cognitive Neuroscience

RESTING CONNECTIVITY PREDICTS COGNITIVE EMPATHY ABILITIES IN SCHIZOPHRENIA AND HEALTHY CONTROLS

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Background: Cognitive empathy (CE) involves taking the emotional perspective of others and typically recruits neural regions such as the inferior frontal gyrus, insula, anterior cingulate, supplemental motor area, temporo-parietal junction, and precuneus. We evaluated whether functional connectivity within networks containing these a priori CE regions predicted performance on a CE task.
Methods: Schizophrenia (n=30) and healthy control (n=32) subjects completed a 5-minute resting state scan and a CE task. Resting state data was decomposed into a set of neural networks using Independent Component Analysis to produce 60 intrinsic connectivity networks (ICNs). Within-network functional connectivity metrics were computed for each subject per network. We selected 3 networks for confirmatory analysis that contained: i) posterior cingulate cortex and precuneus (ICN24), ii) supplementary motor area, anterior cingulate cortex, and temporal parietal junction (ICN29), and iii) inferior frontal gyrus and insula (ICN45). Connectivity values were entered in a regression model with group status included as a covariate. Exploratory whole-brain analyses were conducted using ridge regression and non-parametric bootstrapping.
Results: The confirmatory results indicated that ICNs 29 and 45 significantly predicted CE performance ($F_{4,55}=9.813$, $p<0.001$). We calculated partial correlations to determine whether each of these networks predicted CE above and beyond the contribution of group status and the other two networks included in the model. The results revealed significant relationships for both ICN29 ($r=-0.28$, $p=0.03$) and ICN45 ($r=0.42$, $p<0.01$) when controlling for the three other variables in the model. The exploratory results similarly identified ICN45 as significant, as well as a network containing the primary and supplementary motor regions.
Conclusion: The findings suggest that ICNs 29 and 45 contribute to CE performance for both study groups. These findings are consistent with prior studies indicating that the insula is critical to integrating cognitive and emotional information. Coherence between the insula and inferior frontal gyrus may therefore be critical to CE processes. Also, coherence in the primary motor network may be important in motor empathy or the interpretation of bodily postures and cues. To summarize, the results suggest that within-network functional connectivity for networks containing a priori regions predict CE abilities in both individuals with schizophrenia and healthy controls.
ID: 2079333

PAVLOVIAN BIASES IN SCHIZOPHRENIA

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Background: There has been increasing interest in identifying distinct components of reinforcement learning (RL) deficits seen in patients with schizophrenia. RL tasks used to date have generally required active responses for both the acquisition rewards and the avoidance of punishments, or they have required Pavlovian contingent responses (i.e., reward trials require a "Go" response while punished trials require a "NoGo" response). In tasks that orthogonalise action requirements and outcome valence, healthy participants perform best during Pavlovian-congruent conditions and poorest during Pavlovian-conflict conditions, with inhibiting responses to obtain gains particularly difficult due to basal-ganglia associated reward induced invigoration. We investigated whether Pavlovian biases exist to a similar extent in patients with schizophrenia during a RL task that orthogonalises action and valence.
Methods: Forty-five clinically stable patients with schizophrenia or schizoaffective disorder and 25 controls participated in the study. The RL task crossed action requirements ("Go"/"NoGo") with outcome valence ("Win"/"Loss") to create 4 conditions: Go-to-Win, Go-to-Avoid-Loss, NoGo-to-Win, and NoGo-to-Avoid-Loss. Win/Stay or Avoid/Lose probability was set at 0.75 for each condition. In addition to performance accuracy, an overall Pavlovian Performance Bias score was calculated by averaging reward-based invigoration and punishment-based suppression.
Results: While there was no overall accuracy difference between groups pooled across all four conditions, patients were more accurate during NoGo-to-Win and less accurate during NoGo-to-Avoid-Loss. Analysis of the Pavlovian Performance bias indicated less bias in patients compared to controls. This finding appears to be driven by paradoxically better performance by patients in the NoGo-to-Win condition and equivalent performance within patients across the NoGo-to-Avoid-Loss and Go-to-Avoid-Loss conditions. In controls the NoGo-to-Avoid-Loss and Go-to-Avoid-Loss was differentially affected in controls consistent with a Pavlovian bias enhancement during NoGo-to-Avoid-Loss.
Conclusion: An orthogonalised approach to RL indicated a reduction in the normative "Go" and Pavlovian biases in patients, highlighting possible disruptions in RL circuitry. Reductions in Pavlovian biases may alter how patients process feedback, leading to both performance impairments as well as paradoxical performance advantages relative to controls depending on specific task contingencies.
ID: 2084048

ASSOCIATIVE INFERENCE IMPAIRMENT IN NON-AFFECTIVE EARLY PSYCHOSIS

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Background: Relational memory, which requires the binding together of distinct memory elements, is impaired in patients with established schizophrenia. However, it is unknown whether prominent relational memory deficits are present at the onset of psychosis, or develop throughout the course of illness. We used the well-established associative inference paradigm to investigate if relational memory impairments are present during the early stage of psychosis and whether clinical symptoms may predict impairment.
Methods: We studied 42 healthy control subjects and 45 matched early psychosis patients (mean duration of psychosis: 15 weeks), comprised of a non-affective psychosis group, meeting criteria for schizophreniform disorder (n=24), and an affective psychosis group, meeting criteria for bipolar disorder I with psychotic features (n=21). Subjects were trained on three sets of paired associates: 30 House-Face pairs (H-F1), 30 House-Face pairs (H-F2, same house and new face), and 30 Face-Face pairs (F3-F4). After training, participants were tested on the previously learned pairs and on 30 new Face-Face pairs (F1-F2), whose relationship could only be inferred through overlapping associations with the same house.

Results: Relational memory ability differed between the three groups (pair type by group interaction: $F = 3.74$, $p < 0.05$), with healthy controls ($p < 0.001$) and affective psychosis patients ($p < 0.001$) showing significantly greater accuracy for relational (F1-F2) than non-relational (F3-F4) pairs. This effect was not seen in the non-affective psychosis group ($p > 0.05$). Healthy controls ($p < 0.001$) and affective psychosis patients ($p < 0.05$) showed greater relational memory accuracy than the non-affective psychosis group. In patients, relational memory accuracy was negatively correlated with illness duration ($p < 0.01$), HAM-D ($p < 0.05$), PANSS negative ($p < 0.01$), PANSS general ($p < 0.05$), PANSS total scores ($p < 0.01$).
Conclusion: We found evidence for impaired relational memory ability in the early stage of a non-affective psychosis. This pattern is consistent with previous findings of relational memory impairments in patients with chronic schizophrenia. We found that greater severity of psychopathology correlates with relational memory impairment in early psychosis. The greater impairment in the non-affective subgroup suggests that relational memory ability may discriminate between these two psychosis groups early in the course of the illness.
ID: 2113423

EFFICACY AND SAFETY OF ABT-126, AN A7 NICOTINIC CHOLINERGIC AGONIST, IN TREATMENT OF COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA: RESULTS FROM A PHASE 2B STUDY IN NONSMOKERS

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Background: A previous study in stable subjects with schizophrenia demonstrated procognitive effects of ABT-126, an α7 nicotinic receptor agonist, in the nonsmoking subset of subjects. This study evaluated the dose-response of ABT-126 in the same population.
Methods: Design was double-blind, placebo-controlled, parallel-group, multicenter. Clinically stable subjects receiving antipsychotics were eligible. The first ~280 subjects were randomized to placebo or ABT-126 25 mg, 50 mg or 75 mg QD (Stage 1). The next ~150 subjects were randomized to either placebo or a selected dose of ABT-126 (Stage 2) as determined by an unblinded interim analysis. Treatment was 24 weeks; however, primary analysis was comparison of change from baseline to Week 12 on the MCCB neurocognitive composite score for the selected ABT-126 dose vs. placebo using a mixed-model for repeated-measures. Other efficacy measures included the UPSA-2ER and NSA-16.
Results: 432 subjects were randomized; 80% completed the study. Mean baseline MCCB score was 28.6. The 50 mg dose was selected for Stage 2. No statistically significant difference was observed on the change from baseline on the primary analysis (LS mean [SE] 2.66 [0.54] for ABT-126 50 mg and 2.46 [0.56] for PBO; 1-sided $p = 0.398$). Results for the UPSA-2ER (cognitive functional battery) were similarly negative. There was a trend for improvement at Week 24 on the NSA-16 total score for ABT-126 50 mg (-4.27 [0.58] v. -3.00 [0.60] for PBO; $p = 0.059$).
Regional differences were observed; US subjects (49% of subjects) showed greater improvement vs. placebo on efficacy measures than Russian subjects (48% of subjects), who showed larger practice effects and placebo responses. There was a statistically significant improvement in US subjects for ABT-126 50 mg at Weeks 12 and 24 on the NSA-16.
Adverse event rates were similar for ABT-126 and PBO. Most frequent (>5%) AEs for subjects taking ABT-126 were headache and nasopharyngitis.
Conclusion: This study did not demonstrate a procognitive effect for ABT-126 in nonsmokers. Very large placebo effects in Russia may have affected the ability to detect a signal. The improvement in negative symptoms seen in US subjects may warrant further study.
ID: 2091780

NEUROPHYSIOLOGICAL EVIDENCE FOR COGNITIVE CONTROL AND STRIATAL DYSFUNCTION DURING REINFORCEMENT LEARNING IN SCHIZOPHRENIA

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Background: Recent theories suggests that abnormalities of motivation and goal-oriented decision-making in schizophrenia may arise due to maladaptive reward learning. One potential explanation for such deficits are blunted striatal responses to the anticipation and receipt of rewards. However, cognitive control network (CCN) regions such as the dorsolateral prefrontal cortex have been implicated in the maintenance, and implementation of value and goal representations. In addition, the anterior cingulate cortex has been implicated in evaluating conflict monitoring and error detection. The goal of the current study was to examine the relative involvement of deficits in the activation of striatal versus CCN regions in reinforcement learning in schizophrenia.
Methods: Individuals with schizophrenia (SCZ: N=58) and healthy controls (CON: N=36) completed a probabilistic reversal-learning paradigm during fMRI scanning. During the task, participants choose between two stimuli. At the start of each run, one stimulus was correct and rewarded 80% of the time, the other was incorrect and rewarded 20% of the time. The reward contingencies reversed periodically as the participant learned the more rewarded stimulus. We used a General Linear Model analysis to code trials for WinStay-LoseShift decision making behavior. We also coded the final error that preceded a reversal.
Results: SCZ achieved fewer reversals than CON, and demonstrated decreased winstay-loseshift behavior. On LoseShift compared to WinStay trials, SCZ showed reduced activation compared to CON in a network of brain regions associated with cognitive control and the maintenance and updating of value representations for goal-oriented decision-making, as well as in regions associated with basic reward processing (e.g., striatum). Importantly, activity in the cognitive control, but not striatal, regions, was strongly associated with task performance. Further, the relationships between diagnosis and task behavior were mediated by alterations in cognitive control network activity, but not by striatal activity.
Conclusion: These findings confirm an important role for frontal-parietal cognitive control networks in mediating reinforcement learning impairments in SCZ, and are consistent with the idea that these cognitive control deficits may contribute to a wide range of cognitive and affective dysfunctions. Such results provide biological targets for further inquiry as researchers attempt to discover new pathways for negative treatment interventions.
ID: 2096252

DISRUPTING GLUTAMATERGIC TRANSMISSION DURING NEURODEVELOPMENT RESULTS IN DEFICITS IN PROBABILISTIC REVERSAL LEARNING: LINKS TO IMPAIRED VALUE REPRESENTATION AND NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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Background: Schizophrenia is a neurodevelopmental disorder characterized by a wide spectrum of symptoms. The negative symptoms of schizophrenia, including deficits in reward-related processing, predict the functional outcome of patients and are currently unresponsive to available medications. The ability to regularly update current representations of reward value, and adjust behavior in response to alterations in reward, is required to maintain goal-directed behavior. This process can be assessed in the probabilistic reversal learning procedure and schizophrenia patients exhibit deficits in this task that result from diminished reward sensitivity. Our aim was to determine whether neonatal phencyclidine (PCP; NMDA receptor antagonist) treatment produced deficits in value representation in the probabilistic reversal learning task in rats.
Methods: Rats were administered PCP (10 mg/kg, s.c., n=14) or saline (0.9% s.c., n=14) on postnatal day (PND) 7, 9, and 11 and behavioral testing began on PND 60. Rats were tested in the probabilistic reversal learning procedure once daily for 20 days. Each session consisted of 300 trials. During each trial two apertures were illuminated and the rat had to identify the target location. Target responses were rewarded on 80% of trials and non-target responses were rewarded on 20% of trials. After 8 consecutive target responses the reward contingencies switched and the previous non-target location became the target location. Switching continued throughout the session once the target location was correctly identified.
Results: Overall performance was impaired in PCP- vs. saline-treated rats; fewer successful reversals ($p<0.05$) and a reduction in Win-Stay behavior ($p<0.05$) was observed. No difference was observed in Lose-Stay behavior between saline- and PCP-treated rats. Inspection of performance for the last 10 days of training indicated that PCP treatment increased the number of trials required to make the initial discrimination and first reversal ($p<0.05$), suggesting that overall learning was impaired. Moreover, Win-Stay behavior was also diminished during these initial stages of the session ($p<0.05$).
Conclusion: Disrupting NMDA receptor transmission during neurodevelopment led to a selective deficit in positive reward sensitivity when animals reached adulthood. These findings implicate disrupted NMDA receptor activity during neurodevelopment as a potential mechanism for the emergence of diminished reward sensitivity observed in schizophrenia.
ID: 2117838

DOES 28-DAY ABSTINENCE INCREASE WORKING MEMORY EVOKED GAMMA OSCILLATIONS IN CANNABIS DEPENDENT PATIENTS WITH AND WITHOUT SCHIZOPHRENIA?

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Background: Cannabis dependence among patients with schizophrenia represents a significant co-morbidity resulting in the worsening of positive and negative symptoms, however, the effects on cognition are unclear. Working memory represents a core deficit in patients with schizophrenia that is associated with excessive gamma (30–50 Hz) oscillations in the dorsolateral prefrontal cortex (DLPFC). Given that gamma oscillations are mediated by GABAergic inhibitory activity and that cannabis modulates GABA, it is possible that cannabis may alter working memory evoked gamma oscillations in cannabis dependent patients with schizophrenia. The aim of this study was to evaluate working memory evoked gamma oscillations prior to and following a 28-day abstinence period in cannabis dependent patients and non-psychiatric controls.
Methods: In an on-going study, we have tested 4 (mean age 25.5 ± 3.9 years) medicated patients with schizophrenia and 5 (mean age 27.8 ± 4.3 years) non-psychiatric controls prior to and following a 28-day abstinence period. All subjects were male. The verbal N-back task administered at the 1- and 3-back working memory load while EEG was recorded. Gamma oscillatory power was measured from the frontal electrodes encompassing the DLPFC for correct responses to targets and averaged across the entire epoch from -1000 to 2000 ms relative to stimulus onset.
Results: Reduced gamma oscillatory activity was observed among patients with schizophrenia compared to non-psychiatric controls at baseline (1-Back: Cohen's d=0.686; 3-Back: Cohen's d=0.839). Following 28-day abstinence, gamma oscillatory activity was enhanced among patients with schizophrenia (1-Back: Cohen's d=0.665; 3-Back: Cohen's d=0.903) and controls (1-Back: Cohen's d=0.511; 3-Back: Cohen's d=0.682) compared to baseline.
Conclusion: Though preliminary, these findings suggest that cannabis use reduces gamma oscillations in patients with schizophrenia possibly through the modulation of GABAergic inhibitory activity. Furthermore, the increase in gamma oscillations with abstinence suggests that methods in which modulate gamma oscillations such as repetitive transcranial magnetic stimulation may be a potential treatment for this common and significant co-morbidity. Supported in part by NARSAD Young Investigator Grant (Barr), Canadian Institute of Health Research (CIHR) operating grant MOP#115145 (George).
ID: 2085663

EEG ALPHA SUPPRESSION AND THETA BAND SYNCHRONIZATION AFTER SHORT-TERM, INTENSIVE WORKING MEMORY TRAINING IN SEVERE MENTAL ILLNESS

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Background: Neurocognitive training programs find evidence for working memory improvement using computerized training. Suppression of the alpha frequency of frontal EEG and increased theta band activity during cognitive tasks is associated with better task performance, however, individuals with severe mental illness show reductions in these biomarkers compared to healthy controls.
Methods: 18 individuals with severe mental illness were randomized to two weeks of either active or placebo working memory training. Active training consisted of computerized exercises directly targeting working memory that increased in difficulty throughout training. Placebo training consisted of computerized exercises targeting visual and auditory attention that did not increase in difficulty. All participants completed three 1-hour training sessions per week with a facilitator, and were encouraged to complete 40 minutes of at-home practice on days without facilitated training. Participants were assessed one week prior to training and one week after training with the Trail Making Task Parts A and B, Letter Number Sequencing, Spatial Span Task, and the Tower of London Task. Participants also had continuous EEG recorded from 64 channels during resting state and computerized working memory tasks.
Results: Compared to individuals in the placebo condition, individuals in the active training condition had a greater increase on the Trail Making Task B, d = .45, Letter Number Sequencing, d = .76, Spatial Span Backwards,

d = 1.0, and Tower of London, d = .81, after training. Participants in the active training condition also had a greater increase in alpha suppression, d's = .24 - .89, and a greater increase in theta band power, d's = .24 - .90, over midline frontal electrode sites during computerized working memory exercises compared to the placebo condition.
Conclusion: Two weeks of computerized working memory training with exercises that increase in difficulty and specifically target working memory have a greater effect on working memory ability than visual and auditory attention training with exercises that remain at the same difficulty. This increase in working memory ability is also observable in the synchronization of frontal theta activity and the desynchronization of frontal alpha activity during task engagement. This suggests that active neurocognitive exercises may result in working memory improvements through the facilitation of neural synchronization.
ID: 2117914

ADJUNCTIVE YOGA OR PHYSICAL EXERCISE CAN ENHANCE COGNITIVE FUNCTIONS AMONG PERSONS WITH SCHIZOPHRENIA

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Background: Cognitive dysfunction is a core feature of schizophrenia (SZ) that is relatively intractable to pharmacotherapy. In uncontrolled trials, yoga was reported to improve cognitive function among SZ patients, but randomized controlled trials(RCT) have not been conducted.
Methods: Consenting, clinically stable outpatients with SZ (DSM IV criteria) were recruited to a single blind RCT. In addition to routine antipsychotic treatment, participants were randomized to receive adjunctive yoga training (YT), adjunctive physical exercise (PE) or continued treatment as usual (TAU). YT consisted of supervised one hour sessions (physical postures + breathing exercises) using a manualized protocol, 6 days / week for 21 days. PE consisted of supervised manualized aerobic exercises with the same frequency and duration. Cognitive functions were measured blind to treatment arms using the Penn computerized neuropsychological battery (eight domains of cognition, speed/accuracy). Participants were evaluated at baseline, at the end of 3 weeks and were followed up over six months.
Results: We randomized 340 participants to YT(n=119), PE (n=106) and TAU (n=115) of whom 238 (70%) completed the study (YT=86, PE=75, TAU=77). The groups were comparable for age, gender and key physical and clinical variables. Cognitive enhancement was observed in YT and PE groups (significant effect sizes ranged from 0.261 to 0.522). Cognitive changes were compared using MANOVA. After 21 days, participants in both interventions showed significant improvement compared with TAU but the patterns of changes differed.YT improvement was greater than TAU on speed indices of spatial memory (p=0.023) and emotion (0.024). PE was significantly better than TAU for working memory(accuracy (p-0.005); speed indices of face memory (p=0.004), working memory (p=0.041), emotion (p=0.022). PE showed greater improvement than YT for accuracy of face memory (p=0.038).
Conclusion: Adjunctive YT, as well as PE can enhance cognition in patients with SZ, with differing patterns of improvement. Non-pharmacological treatment can benefit key aspects of SZ disability.
ID: 2114076

BIG SCIENCE: HARMONIZING NEUROPSYCHOLOGICAL MEASURES FROM MULTIPLE SAMPLES FOR GENETIC ASSOCIATION ANALYSIS IN THE GENUS CONSORTIUM

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Background: The Genetics of Endophenotypes of Neurofunction to Understand Schizophrenia (GENUS) consortium aims to clarify the neurobiological role of schizophrenia (SCZ) risk genes by testing independent and polygenic risk variants identified in recent GWAS for association with cognitive and neuroimaging measures. Here we describe the data harmonization process for multi-site neuropsychological data and evaluation of case-control differences, in preparation for the genetic analyses.
Methods: Fifteen research groups contributed 20 samples with cognitive and genetic data, totaling ~4,575 SCZ cases, ~4640 controls, and ~875 genetic risk individuals. A subset of these samples also has structural neuroimaging data. Literature review and meta-analysis identified cognitive traits with relatively high heritability (h2>0.5) and robust case-control differences. Based on this, cognitive tests from the MATRICS battery (or equivalent tests) have been selected as the primary cognitive phenotypes for genetic analysis, in addition to general cognitive ability "g". They cover the cognitive domains of processing speed, attention/vigilance, verbal and visual learning, working memory, and reasoning/problem solving. To harmonize multi-site cognitive data, controls for each test version were pooled after regressing out site, age, and sex effects; and standardized residuals were calculated for both cases and controls: [(x - predicted x) / residuals SD controls]. Z-score data distributions were compared across sites and disease status.
Results: Phenotypic analyses confirmed the presence of case-control differences on the MATRICS tests and domains in this sample collection, with genetic risk individuals performing at a level in between that of cases and controls. The data distributions showed a slight shift in SCZ means across sites. For some of the measures this coincides with a difference in average illness duration. There were significant differences in illness duration between several sites, so further analyses will include this variable as a covariate.
Conclusion: Confirming the presence of case-control differences for these cognitive phenotypes is an essential first step in preparation of the planned genetic association analyses. Association analyses of known SCZ risk variants and polygene sets with cognitive (and neuroimaging) traits in one of the largest sample collections of its kind may contribute towards understanding the function of existing SCZ risk variants in neural processes underlying SCZ pathophysiology.
ID: 2118755

ABERRANT SALIENCE AND ITS RELATIONSHIP TO CANNABIS-INDUCED PSYCHOTIC SYMPTOMS

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Background: Cannabis is a widely used recreational drug which increases the risk of psychosis. We have recently found that regular cannabis use is associated with reduced striatal dopamine synthesis capacity (DSC), contrary to a leading interpretation of the dopamine hypothesis which postulates that elevated striatal DSC causes psychosis by creating "Aberrant Salience" (AS). We sought to test the hypothesis that cannabis users exhibit AS and explore the relationship between AS and striatal DSC.
Methods: We tested 17 cannabis users (CU) and 17 age and sex-matched non-user control via the Salience Attribution Test (SAT), a reaction-time probabilistic reward learning task using cue stimuli that vary along task-relevant and task-irrelevant dimensions. Measures of adaptive and aberrant salience were calculated from latency and subjective reinforcement probability rating differences across dimensions. Within CU, cannabis-induced psychotic-like symptoms were measured with the Psychotomimetic States Inventory (PSI). DSC, indexed as the influx rate constant Kicer, was measured in 10 users and 6 controls with [18F]-DOPA positron emission tomography (PET).
Results: There was no significant difference in AS between the groups ($F[1,32] = 1.12$, $p=0.30$ [implicit]; $F[1,32]=1.09$, $p=0.30$ [adaptive]). Within CU, there was a significant relationship between cannabis-induced psychotic-like symptom severity and explicit AS ($r=0.61$, $p=0.04$) and users who met DSM-IV-TR dependency/abuse status criteria had elevated implicit AS compared to users who did not meet criteria ($F[1,15]= 5.8$, $p=0.03$). Within controls, implicit AS was inversely correlated with whole striatal dopamine synthesis capacity ($r=-.91$, $p=.01$). Within CU, there were no significant relationships between AS and DSC. Cannabis use was associated with the loss of an inverse relationship between implicit AS and DSC ($z=-2.05$, $p=.04$).
Conclusion: These results suggest that regular long-term cannabis use is not associated with differences in behavioural measurements of salience processing. However, these results indicate a relationship between explicit AS and cannabis-induced psychotic-like symptom severity, and also show preliminary evidence for a difference in implicit AS between cannabis who do and do not meet DSM-IV criteria for cannabis abuse/dependence. The results also indicate a loss of relationship between implicit AS and DSC in the whole striatum associated with long-term cannabis use.
ID: 2119227

THE RDOC DOMAIN OF PERCEPTION: HOW IT INFORMS HETEROGENEITY AND FUNDAMENTAL SYMPTOMS OF SCHIZOPHRENIA AND OTHER DISORDERS

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Background: RDoC includes Perception as a construct in the domain of Cognitive Systems. An RDoC approach to perception involves extending research beyond associations with DSM diagnoses, to determine if altered perceptual functioning represents a dimension that contributes to symptoms and functioning in a cross-diagnostic fashion.
Methods: This presentation reports data from two studies of this issue, covering two perceptual functions: 1) Gain Control, which refers refers to the rate at which a neuron's output increases with the strength of the driving input and is a function of surrounding context, was assessed with a steady-state visual evoked potential (ssVEP) contrast gain paradigm and via contrast sensitivity; and 2) Visual Integration, which refers to the ability to represent spatially separated features as belonging to the same edge, surface, or object, was assessed with contour integration and Ebbinghaus illusion paradigms.
Results: Across developmental disorders, people with schizophrenia (n=111) showed impaired ssVEP contrast gain and contrast sensitivity ($p<0.001$) compared to controls (n=105), as did people with autism spectrum disorders (n=24; $p<0.001$). However, in a study to determine if the apparently similar visual integration impairments in schizophrenia and body dysmorphic disorder are both examples of perceptual organization failure, people with schizophrenia (n=24; $p<0.001$), but not with body dysmorphic disorder (n=20) or obsessive-compulsive disorder (n=20), showed impaired contour integration compared to controls (n=20) on both tasks, with findings being stronger for the lower level contour integration task. In addition, unlike in past studies of schizophrenia, performance in the body dysmorphic disorder group was unrelated to level of psychotic symptoms.
Conclusion: This supports past data suggesting that impaired perceptual organization may be specific to schizophrenia, in that it is not found in other psychotic disorders, and that it is related to forms of (fragmented) thought disorder that are more characteristic of schizophrenia than other disorders such as bipolar disorder. By learning from data such as those presented here, when disordered perceptual functions map onto symptoms or classes of disorders, but also when they do not map onto them, we can refine our understanding of psychopathology in a manner consistent with RDoC.
ID: 2118784

ATTENTION LAPSES, PERCEPTION AND COGNITIVE CONTROL IN SCHIZOPHRENIA

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Background: Attention lapses are considered an aspect of the "generalized deficit" in cognition in schizophrenia and recently have been show to have an impact on and confound the interpretation of performance on perceptual as well as other types of tasks by individuals with the illness. Attention lapsing and the related phenomenon of "mind wandering" have received increasing attention in cognitive neuroscience and we sought to adopt this approach to understanding the cognitive and neural basis of attention lapsing in people with schizophrenia.
Methods: We used event-related fMRI to better understand the cognitive and neural mechanisms underlying attention lapsing in healthy young control subjects and individuals with first episode schizophrenia. Partial lapses during Stroop task performance were examined using RT distribution analysis and brain activity during partial lapsing was compared to that associated with non-lapse trials. In a second study we used fMRI to examine brain activity during "total lapses" during AX CPT performance in schizophrenia patients and controls.
Results: Both healthy controls and patients showed engagement of cognitive control networks that was greatest during slow versus fast responses, consistent with previous studies. Schizophrenia patients showed increased RT variability and a higher rate of very long response times, along with decreased activation in frontal cortex and other elements of the cognitive control network, suggesting both increased rates of proactive control lapses and impaired reactive control. In healthy subjects, increased activity was seen in the default mode network during lapse trials, consistent with other studies of "mind wandering". In contrast, schizophrenia patients showed increased rates of lapsing along with reductions in activation in cognitive control networks during these trials, without evidence of the DMN intrusions seen in control.
Conclusion: Together these data suggest that attention lapses are an important aspect of cognitive impairment in the illness that are qualitatively different from the usual "mind wandering" seen in healthy subjects and

appear to be related to the cognitive control deficits that have been previously described in the illness.
ID: 2091950

THE FACE PROCESSING SYSTEM IN SCHIZOPHRENIA DOES NOT POSSESS A CORE FUNCTIONAL PROPERTY: FACE-SELECTIVITY

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Background: Face perception impairments in schizophrenia have long been recognized. Yet, the brain mechanisms underlying this socially important behavioral problem are elusive. Previous studies found altered structures of the brain regions subserving face perception in this mental disorder, but the functional integrity of the face processing system (fusiform face area (FFA), occipital face area (OFA) and superior temporal sulcus (STS)) has remained an outstanding question.
Methods: In this study, we examined functional activation of the face processing system during face detection, a basic aspect of face perception, in schizophrenia patients (n=23) and healthy controls (n=22). To disassociate face-specific processing with general perceptual processing, we measured fMRI responses during the performance of face detection and a non-face comparison task - tree detection. To take into account the variability of individual visual capacities, we equated the salience of face and tree stimuli across participants according to their perceptual thresholds which were pre-determined psychophysically. Three levels of visual salience (contrast) were used for fMRI - perceptual threshold, two times perceptual threshold and 100%.
Results: During face detection, both FFA and OFA regions were similarly active in both subject groups. However, the differences in response to face vs. tree, an index of face-selectivity, were significantly reduced in FFA of patients, especially in the presence of non-salient visual stimuli. STS was virtually inactive during both face and tree detection tasks. These data indicate that while generally responsive during face detection, FFA of patients does not differentiate face from non-face stimuli.
Conclusion: This result identifies a lack of core functional property of the face processing system - face-selectivity - as a brain mechanism linked to face perception impairment in schizophrenia, resolving the mystery of patients' seemingly intact functional brain activation in contrast to impaired performance during face perception. This result also points to training focused on face stimuli and boosting visual saliency as a potential therapeutic venue for improving face perception and social functioning.
ID: 2083578

EMPATHY IN SCHIZOPHRENIA: EVIDENCE FROM EVENT-RELATED POTENTIALS (ERPS) AND BEHAVIORAL MEASURES

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Background: Empathy is a multidimensional construct critical for successful social interactions. Electrophysiological responses to empathy are comprised of two interacting components: an early-affective component (EA) and a late-cognitive one (LC). The EA takes place within the first 300 ms of the empathic response, and the LC takes place after that. Despite recent efforts, these components are not well understood in schizophrenia (SZ).
Methods: In a previous study, our group examined the empathic components in SZ using Evoked Related Potentials (ERPs) in a task with pictures of physical pain. We found that SZ showed a decreased EA response and deficits modulating the LC one. In this symposium, I will present data from a new sample of patients with SZ (n=26) and matched healthy controls (HC; n=33) in a novel naturalistic context: observing somebody in emotional pain (e.g., in a midst of a natural disaster) or in neutral situations (e.g., walking on the street) with two Conditions: Pain Condition (PC) - decided whether the individual was in emotional pain; or Gender Condition (GC) - decided the gender of the individual.
Results: Preliminary data suggest an enhanced EA response in P180 in SZ as well as deficits in increasing the pain response in the PC by means of a decreased P3 and Late Positive Potential. Behavioral evidence revealed that both groups performed better when observing a neutral stimuli regardless of condition ($p<0.001$) and were significantly distracted by the painful stimuli in the GC ($p<0.001$) although just the SZ showed this distraction in the PC ($p=0.02$) as well. Groups also significantly differed in empathic ratings of the pictures ($p=0.01$), various empathic questionnaires, social cognition (e.g., alexithymia, ToM, facial affect recognition) and functioning (e.g., quality of life, functional capacity). Only alexithymia and quality of life correlated with the empathic self-ratings of the stimuli ($r = -0.33$; $p= 0.04$; $r = 0.32$; $p= 0.05$) and IRI-Personal distress correlated with unpleasantness when watching the pictures ($r = 0.33$; $p= 0.04$).
Conclusion: Overall, SZ exhibited both behavioral and electrophysiological deficits in recognizing when a person is in emotional pain. In this symposium, I will discuss the potential factors underlying these deficits, and I will also compare our results to studies using empathy for physical pain. Lastly, I will relate our results to other social cognitive constructs and will discuss potential implications for treatment.
ID: 2084940

COGNITIVE DEFICITS IN ADOLESCENT SUBJECTS WITH PSYCHOSIS RISK SYNDROME

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Background: Cognitive deficits are central manifestations of psychosis risk syndrome (PRS). Few studies have directly reported the pattern of cognitive deficits among adolescents with PRS. The goal of this study was to investigate the cognitive deficits among adolescent PRS as well as among adult PRS.
Methods: PRS subjects were recruited using 2 step methods, screened using Prodromal Questionnaire-Brief version (PQ-B) and interviewed with Structured Interview for Prodromal symptoms (SIPS). Twenty-three adolescent PRS subjects (mean age, 15.8 ys, age range 14–17 ys) and 29 adult PRS subjects (mean age, 24.6 ys, age range 18–37 ys) were included. 25 healthy adolescents (mean age, 16.2 ys, age range, 14–17 ys) and 35 healthy adults (mean age 25.4 ys, age range 18–41 ys) were recruited as the healthy controls (HC). Cognitive functioning was assessed using Chinese version of MATRICS Consensus Cognition Battery (MCCB).

Results: Both PRS groups performed significantly worse than their age-matched control groups in speed of processing and visual learning. Moreover, the adolescent PRS group performed significantly worse than the adolescent control group in verbal learning (PRS, 24.1±6.2; HC, 29.1±3.3; F=12.526, P=0.001), working memory (PRS, 15.1±4.1; HC, 18.3±3.0; F=9.533, P=0.003), reasoning (PRS, 16.4±6.6; HC, 21.6±4.8; F=9.537, P=0.003) and attention/vigilance (PRS, 2.1±0.8; HC, 3.0±0.5; F=21.333, P<0.001). Among the adolescent PRS subjects, the performance on verbal learning task was also correlated with negative symptom score of SOPS (scale of prodromal symptoms) (r=-0.618, P<0.01).
Conclusion: Adolescent PRS subjects have more severe cognitive deficits as compared to adult PRS. The correlation of their verbal learning task with negative symptoms supported the neural developmental hypothesis of schizophrenia.
ID: 2086229

COGNITIVE EFFORT IN SCHIZOPHRENIA: A BEHAVIORAL ECONOMIC APPROACH

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Background: Recent theories have postulated that the motivational deficits associated with schizophrenia may, in part, be due to abnormal effort-cost computations. Several studies have provided evidence for this hypothesis, finding that individuals with schizophrenia are less likely than controls to exert physical effort to obtain monetary rewards. However, this finding has not been replicated in the cognitive domain. The current study aimed to extend these findings by directly quantifying the subjective cost of cognitive effort among individuals with schizophrenia, relative to healthy controls.
Methods: To test the hypothesis about abnormal effort-cost computations, we utilized a novel behavioral economics paradigm (Westbrook et al., 2013). First, participants practiced increasingly demanding levels of a working memory task (N-Back: levels N = 1–4) where they were instructed to identify letters, presented one at a time on a computer screen, as targets or non-targets. Next, participants completed a series of 2-alternative forced choices during which they choose between repeating a more difficult version of the N-Back (2–4 Back) for more money or an easy version (1-Back) for less money. The value offered for completing the easy version was stepwise titrated, until participants were indifferent between two offers. The indifference point, then, reflects the relative cost of the more demanding option for that participant, or, alternatively, the subjective cost of effort.
Results: Preliminary results support that cognitive effort is more subjectively costly for individuals with schizophrenia relative to healthy controls. Participants in both groups showed systematic influences of reward and task demands on choice patterns. Critically, however, participants with schizophrenia discounted rewards more steeply, indicating that effort was more costly for this group. Moreover, effort was more costly, even controlling for key differences in objective demand. These results support both that behavioral economic methods can be used to investigate diminished cognitive motivation in schizophrenia, and that effort costs are higher among those with the disorder.
Conclusion: Conclusions: These preliminary results extend recent findings of motoric effort abnormalities in schizophrenia by providing evidence in the cognitive domain. Such findings have important implications to the etiology of abnormalities in goal-oriented behavior in schizophrenia.
ID: 2114315

DISSECTING THE BRAIN'S MECHANISMS FOR REINFORCEMENT LEARNING IN HEALTH AND DISEASE

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Background: Recent research combining computational modeling and experiments have characterized the brain's mechanisms for reward learning in detail. I review the approach and a series of studies from our laboratory and our collaborators' dissecting learning in healthy undergraduates, and suggest that these same processes may be disrupted in psychiatric disorders. For instance, a prominent hypothesis is that schizophrenia is characterized by aberrant associative learning, but research has now distinguished multiple distinct systems for associative learning, and it is not yet clear how these are differentially impacted in the disorder.
Methods: Healthy human subjects performed trial-and-error decision tasks for monetary gain and loss, while being scanned using functional MRI. We examine trial-by-trial adjustments in choice behavior and choice-related BOLD signals as a function of the feedback (reward or punishment)

Table 1. Differences between diagnostic groups

Outcome variables	Group		Group differences			Controlled analyses*		
	BIP (n = 36) Mean (SD)	SQZ (n = 83) Mean (SD)	Statistic U/ X2	Sig.	Effect Size (Z/√n)	Statistic F	Sig.	Effect Size (Z/√n)
Age	49.52 (7.54)	41.9 (11.57)	638	< 0.001	0.3	-	-	
Sex. Men/Women	13 / 23	57 / 26	X2 =6.74	0.009	OR = 1.35	-	-	
TMT - Cognitive flexibility	2.32 (1.13)	1.72 (1.88)	575.5	0.003	0.29	11.08	0.001	0.12
TMT - Processing speed	45.39 (18.29)	90.55 (63.89)	421	<0.001	0.44	-	-	
Premorbid IQ	112.88 (10.01)	89.93 (12.32)	154.5	< 0.001	0.57	-	-	
TAVEC: Learning capacity	38.22 (8.7)	33.61 (9.4)	842.5	0.06	-	0.194	0.66	
Reinforcement Learning parameters:								
Reward sensitivity (R)	0.73 (0.23)	0.44 (0.4)	978	< 0.001	0.27	1.363	0.246	
Punishment sensitivity (P)	0.54 (0.4)	0.14 (0.25)	422	< 0.001	0.59	6.145	0.015	0.06

BIP = Bipolar; SQZ= Schizophrenia group. X2 =Chi-Square Test. U = U Mann-Whitney Test. Sig= P-values of significance level. OR = Odds ratio.
TMT = Trail Making Test. WAIS = Wechsler Adult Intelligence Scale. TAVEC = Spanish Complutense Verbal Learning Test.
*Processing speed, premorbid Intelligence Quotient, sex and age used as covariates.

received. By fitting computational learning models to these timeseries, we can dissociate distinct strategies for learning and investigate their neural substrates. In recent work using psychiatric populations or trait questionnaires, we have begun to examine how these processes may be disrupted in psychiatric disorders, including OCD and depression.
Results: In normal circumstances, subjects' decisions reflect both a simple reinforcement rule (repeating previously rewarded actions, known as model-free learning) and also a more prospective strategy (consistent with learning the structure of the task and evaluating options by mental simulation, known as model-based learning). Behaviorally, these strategies are dissociably affected by dual-task interference, variations in reward statistics, and covary with individual differences in several other cognitive tasks; neurally they are associated with activity (and cortical thickness) in distinct cortical areas, but their influences apparently merge at the level of striatum. Disorders of compulsion, including OCD and substance abuse, are associated with a selective impairment in model-based learning, suggesting a computational counterpart to the hypothesis that compulsion involves the compromise of habitual reinforcement mechanisms.
Conclusion: These core mechanisms for learning and decision are likely to be a substrate for compromise in psychiatric disorders; the time is particularly ripe to investigate how processes of this sort are affected in schizophrenia.
ID: 2119110

PRESYNAPTIC DOPAMINE: IMPLICATIONS FOR GOAL-DIRECTED BEHAVIOR AND INTERACTIONS WITH GLUTAMATE

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Background: Schizophrenia patients suffer from cognitive deficits which have been linked to impaired goal-directed behavior. Striatal presynaptic dopamine is elevated in schizophrenia while the same measure promotes cognitive functions in healthy individuals. So far, the impact of striatal presynaptic dopamine on goal-directed behavior and its neural learning signals remains unknown. Biological theories of schizophrenia postulate aberrant dopaminergic modulation of glumatergic plasticity as a key mechanism. Here, we aim to elucidate these processes by means of computational modelling of goal-directed behavior in combination with multimodal functional neuroimaging.
Methods: We use a two-step decision task to examine goal-directed behavior in terms of model-free and model-based choices. Computational modeling was applied to analyze the observed choices. 29 healthy participants performed the task during fMRI and also underwent FDOPA PET to assess striatal presynaptic dopamine synthesis capacity. Glutamate MRS (lateral prefrontal cortex and ventral striatum) was acquired in partially overlapping healthy volunteers. Additionally, 20 patients diagnosed with schizophrenia underwent the task behaviorally.
Results: First, we show that higher ventral striatal presynaptic dopamine levels promote model-based, goal-directed choices in healthy participants and this was accompanied by enhanced model-based, goal-directed signatures in lateral prefrontal cortex. Second, we provide evidence that ventral striatal presynaptic dopamine correlates negatively with lateral prefrontal glutamate levels but positively with ventral striatal glutamate levels. Third, schizophrenia patients displayed severely impaired model-based, goal-directed behavior.
Conclusion: Here, we show that higher ventral striatal presynaptic dopamine levels bias towards more goal-directed choices in healthy individuals while schizophrenia patients did not show hallmarks of goal-directed behavior. In healthy participants, higher ventral striatal presynaptic dopamine levels also promote goal-directed signatures in lateral prefrontal cortex. Further, ventral striatal presynaptic dopamine interacts differently with striatal and prefrontal glutamate as surrogate markers of synaptic plasticity. These findings point towards a fine-tuned regulation of presynaptic dopamine acting in a narrow, optimal window. A disruption of this balance may result in reduced capacities for goal-directed behavior as observed in schizophrenia patients.
ID: 2084049

SKILLS OF DAILY LIVING IN SCHIZOPHRENIA AND EXPOSURE TO HERPES SIMPLEX VIRUS 1

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Background: Herpes Simplex virus, type 1 (HSV-1) causes lifelong latent infection in sensory ganglia (~60% of adults), with periodic lytic recurrences in mucosal membranes. Post-mortem studies suggest that latent infection also occurs in the brain, with severe encephalitis in immune-compromised individuals. Exposure to HSV-1 is not a proven risk factor for schizophrenia (SZ), but it has been replicably associated with cognitive dysfunction among SZ patients. As cognitive impairment adversely affects daily living skills, we explored HSV-1 exposure in relation to daily living skills.
Methods: Indian patients with schizophrenia (DSM IV criteria) were assessed using the Diagnostic Interview for Genetic Studies (DIGS) and the Independent Living Skills Scale (ILSS); HSV-1 exposure was assessed with serological IgG antibody assays. Linear regression was used to examine the association of HSV-1 exposure status with ILSS total scores; covariates included age, gender and socioeconomic status.
Results: Among 254 participants, more women were exposed to HSV-1 (Men 43%, women 56.5%). There was significant association between HSV-1 exposure and total ILSS score (self rated) ($F(2, 251)=8.164$, $p=0.005$) after covarying for age and gender. In informant rated version of ILSS, HSV-1 is associated with domains of money management ($F(2,171)=5.18$, $p=0.007$) and job seeking ($F(2,139)=3.28$, $p=0.041$). After considering cognitive and clinical variables in linear regressions money management remains significant in both versions.
Conclusion: HSV-1 exposure is associated with impairment in daily living skills in SZ. As exposure is common, the associations have substantial public health significance.
ID: 2114132

WORKING MEMORY SUBPROCESSES AND CATECHOL-O-METHYLTRANSFERASE VAL158MET POLYMORPHISM IN SCHIZOPHRENIA PATIENTS, BIPOLAR DISORDER PATIENTS, AND THEIR RELATIVES

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Background: Schizophrenia is known to be characterized by working memory deficits. However, it is unknown whether theses deficits are specific to subprocesses of maintenance, monitoring, and manipulation. Additional research

is needed to investigate whether these deficits are specific to schizophrenia or are also present in bipolar disorder. Given research supporting a genetic liability for both disorders, subprocess deficits were also assessed in first-degree relatives of schizophrenia and bipolar disorder. Finally, COMT Val158Met polymorphism has previously been associated with working memory function. This polymorphism was associated with performance on the subprocesses of working memory to investigate whether subprocess deficits are more common among particular COMT genotypes of this polymorphism.
Methods: Patients with schizophrenia, their first-degree biological relatives, patients with bipolar disorder, their first-degree biological relatives, and nonpsychiatric controls were genotyped for the COMT Val158Met. Additionally, performance scores from all participants were calculated for the Spatial Delayed Response Task (maintenance), Self Ordered Pointing (monitoring), Digit Span Backwards (low-demand manipulation) and Letter Number Sequencing (high-demand manipulation).
Results: Results showed that schizophrenia patients and their relatives performed worse on maintenance, low-demand manipulation and high-demand manipulation tasks compared to controls and patients with bipolar disorder. No genotype group differences were found across diagnostic groups. Examinations of genotype differences within diagnostic groups revealed for the low-demand manipulation task, schizophrenia patients with the Val homozygote trended towards performing worse than heterozygote patients. For the high-demand manipulation task, Met homozygous schizophrenia patients performed worse than heterozygous patients.
Conclusion: Results indicate that schizophrenia patients have impairments in maintenance and manipulation subprocesses of working memory. These deficits are shared with their relatives, suggesting a genetic component to this deficit. No deficits were found in either bipolar patients or bipolar relatives, indicating that working memory deficits are not associated with this disorder and that the pathophysiology of bipolar disorder is distinct from schizophrenia. Finally, there may be Val158Met genotype group differences in working memory within schizophrenia patients and this genotype merits further exploration.
ID: 2087671

COMPUTATIONAL PARAMETERS OF REINFORCEMENT LEARNING IN SCHIZOPHRENIA: A COMPARISON WITH BIPOLAR DISORDER

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Background: Schizophrenia involves marked motivational and learning deficits that may reflect impairment in reward processing. We aimed to explore reward (R) and punishment (P) sensitivity parameters based on the Wisconsin Card Sorting Test (WCST), study their association with cognitive variables and compare them between schizophrenia and bipolar disorders. If reinforcement parameters are dependent on the pathophysiology of negative symptoms, these abnormalities may not be presented in bipolar.
Methods: A sample of 83 individuals with schizophrenia and 36 with bipolar disorder were assessed with the WCST. Cognitive outcomes were premorbid Intelligent Quotient, The Trail Making Test and The Spanish Complutense Verbal Learning Test. Computational modeling was performed using the R syntax developed by Bishara et al. (2010) to calculate R (reward sensitivity) and P (punishment sensitivity). Schizophrenia and bipolar group differences were studied using nonparametrics; and with MANCOVA using processing speed, premorbid IQ, age and sex as covariates.
Results: Cognitive outcomes, R and P parameters were significantly superior in bipolar individuals. When comparing schizophrenia and bipolar groups through controlling for covariables, the abnormalities in P parameter and cognitive flexibility were the outcomes that remained significant for schizophrenia.
Conclusion: Decreased punishment sensitivity and cognitive flexibility appeared to be more idiosyncratic of schizophrenia. Both diagnostic groups showed inferior levels of reward sensitivity than those previously reported in healthy controls (Cella et al., 2013). Cognitive deficits may carry some confusion regarding the magnitude of reward processing abnormalities.
ID: 2088830

REINFORCEMENT LEARNING DEFICITS IN SCHIZOPHRENIA

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Background: Several studies have demonstrated that patients with schizophrenia demonstrate impairments in reinforcement learning, including learning from positive and negative feedback. The present study examined whether patients with schizophrenia, who are relatively early in the disease course, are differentially impaired in learning from rewards versus punishment, while controlling for general learning ability.
Methods: Thirty-six patients with schizophrenia and twenty-four healthy control subjects, aged 18–35 years, completed the probabilistic selection task. For this task participants are initially trained to choose the correct stimulus in high-, medium-, and low-probability stimulus pairs, corresponding to 80%, 70% and 60% correct feedback, respectively. After adequate training, which entailed developing a preference for the more rewarded stimuli in each probability condition during the same block or training for 6 blocks, participants were tested on novel combinations of stimuli.
Results: Twenty-two patients with schizophrenia (61%) and twenty-two healthy control subjects (92%) adequately learned to choose the most rewarding stimulus over the least rewarding stimulus during the testing phase; patients were significantly less likely to demonstrate adequate learning performance ($p<.05$). Only patients who demonstrated adequate learning were included in the subsequent analyses; these patients did not demonstrate significant impairments in their learning of any of the stimulus pairs during the first block of training trials (all p's>.05). For the novel test pairs patients showed a decreased preference for avoiding the least rewarded stimulus ($p<.05$), but did not differ from healthy control subjects in their preference for selecting the most rewarding stimulus ($p>.05$).
Conclusion: Many patients with schizophrenia show impairments in reinforcement learning; patients simply do not learn reward contingencies, even gradually after several hundreds of trials. Even the patients who demonstrate adequate learning of reward contingencies evidence deficits in their use of reward information to guide decision making. As previous work has demonstrated relatively unimpaired punishment-driven learning in chronic patients with schizophrenia, a larger sample size is required to confirm the observed impairments in learning from negative outcomes in early-course patients.
ID: 2079527

FINDING THE MISSING STIMULUS MISMATCH NEGATIVITY (MMN) IN EARLY PSYCHOSIS: ALTERED MMN TO VIOLATIONS OF AN AUDITORY GESTALT

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Background: The mismatch negativity (MMN) is an EEG-derived event-related potential (ERP) elicited by any violation of a predicted auditory 'rule', regardless of whether one is attending to the stimuli, and is thought to reflect updating of the stimulus context. Chronic schizophrenia patients exhibit robust MMN deficits, while MMN reduction in first-episode and early phase psychosis is significantly less consistent. Traditional two-tone MMN measures of sensory information processing may be considered too simple for use in early phase psychosis in which pathology has not progressed fully, and a paradigm that probes higher order processes may be more appropriate for elucidating auditory change detection deficits. This study investigated whether MMN deficits could be detected in early phase psychosis (EP) patients using an abstract 'missing stimulus' pattern paradigm (Salisbury, 2012).
Methods: The stimuli were 400 groups of six tones (1000 Hz, 50 ms duration, 330 ms stimulus onset asynchrony), which was presented with an inter-trial interval of 750 ms. Occasionally a group contained a deviant, meaning it was missing either the 4th or 6th tone (50 trials each); the paradigm is unique because its mismatch is the absence of a sound rather than the presentation of a new one. EEG recordings of 13 EP patients and 15 healthy controls (HC) were collected. HCs were matched as closely as possible to the clinical group with respect to age and gender. Patients and controls did not significantly differ on age or years of education.
Results: Analyses of MMN amplitudes elicited by missing stimuli revealed amplitude reductions in EP patients, suggesting that these deficits are present very early in the progression of the illness. While there were no correlations between MMN measures and measures such as duration of illness, medication dosage or age, MMN amplitude reductions were correlated with positive symptomatology (i.e. auditory hallucinations).
Conclusion: These findings suggest that MMNs elicited by the 'missing stimulus' paradigm are impaired in psychosis patients early in the progression of illness and that previously reported MMN-indexed deficits related to auditory hallucinations in chronic patients may also be present in EP patients. As such, this paradigm may have promise in identifying early processing deficits in this population.
ID: 2084469

THE EFFECT OF ENCENICLINE, AN A7 POTENTIATOR, ON MEMORY AND NEUROTRANSMITTER RELEASE IN RATS

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Background: Numerous neuropsychiatric conditions are characterized by impaired cognition, which reduces quality of life and limits function. Previous clinical and preclinical studies have validated the rationale for α7 receptor (α7R) agonists as a procognitive treatment strategy across CNS disorders. Encenicline, an α7R partial agonist in clinical development for cognitive dysfunction in schizophrenia and Alzheimer's disease, primes the α7R at low concentrations to potentiate the effects of acetylcholine (ACh). In this study, the effects of encenicline on neurotransmitter systems and cognition in rats were examined.
Methods: Encenicline α7R binding and function were characterized in vitro by measuring (1) the displacement of methyllycaconitine (MLA) and α-bungarotoxin by encenicline; (2) the binding selectivity against >60 molecular targets; and (3) ion currents in Xenopus oocytes transfected with human α7Rs. In animal studies, rodents were administered an oral, intraperitoneal, subcutaneous, or continuous minipump dose of encenicline. Then neurotransmitter release in the rat brain and memory in an object recognition task were evaluated.
Results: Encenicline bound to α7Rs, significantly increased currents through α7Rs, and improved memory of rats. Moreover, encenicline significantly enhanced the release of ACh, glutamate (Glu), and dopamine (DA) in prefrontal cortical areas of the rat brain at low concentrations. MLA blocked neurotransmitter release and procognitive effects. In electrophysiology experiments of encenicline with ACh in Xenopus oocytes, desensitization occurred at free drug concentrations of encenicline >3 nM, while lower concentrations (~0.3 nM) increased the ACh-evoked response.
Conclusion: The concentrations of encenicline that potentiated ACh-evoked currents and neurotransmitter release in oocytes were consistent with projected brain free drug concentrations that enhanced procognitive effects in preclinical animal studies and in completed clinical trials. The data in the current study indicate that at subnanomolar free brain levels, encenicline acts as an α7R partial agonist by potentiating ACh-induced currents in vitro, and enhancing neurotransmitter release and memory in rats. Further, encenicline may potentiate α7R-mediated release of ACh, Glu, and DA in brain regions that govern cognition. Thus, low doses may sufficiently stimulate procognitive effects while maintaining a favorable tolerability profile.
ID: 2124067

PATIENTS WITH SCHIZOPHRENIA HAVE DIFFICULTIES WITH TIME ORDER AT THE SUB-SECOND LEVEL: AN ELEMENTARY DISTURBANCE?

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Background: We repeatedly showed that patients have difficulties following events over very short intervals at an implicit level (<20ms, Lalanne et al, 2012, Schizophr Bull). We suggested this might reflect a disruption of time continuity, and sub-tend a range of disorders ranging from language to self disorder (Capa et al, 2014, Schizophr Res; Brice et al, 2014, Frontiers in Psychol).
Methods: To explore the impact of elementary time disorders, we checked to which extent patients with schizophrenia have a difficulty at larger delays, and especially when required to give an explicit judgment of time order. In Experiment 1 (Capa et al, 2014, Schizophr Res), we compared temporal order judgment and simultaneity/asynchrony discrimination in 20 patients with schizophrenia and 20 matched controls. In both tasks, two stimuli were displayed on each side of a screen, with a stimulus onset asynchrony of 0 to 92 ms. In one task subjects had to press to the side of the 2d stimulus (temporal order judgment). In the other task they pressed to the left side for simultaneous stimuli, and to the right side for asynchronous ones. In Experiment 2, we explored implicit and explicit timing in the same task. We tested new groups of patients and controls, and added a group of patients with bipolar disorder. Two prime frames were first displayed on the screen, either simultaneously or with an asynchrony of 17 ms (it was systematically checked that this asynchrony was undetectable). These two frames were then filled in, with a delay of 100 ms between the two fillings. Subjects had to press to the side of the second filled-in frame (temporal order judgment). A control task consisted in checking the influence of subliminal asynchronous frames when only one frame was filled in and subjects had to detect it.
Results: The results showed in all tasks that patients with schizophrenia had a difficulty with temporal order judgment. This was true even at delays of 92 ms, i.e. in the most easy conditions. Patients detected these asynchronies, but were impaired at judging order. Moreover implicit mechanisms

explored in Experiment 2 were also impaired when time order was involved, but only in patients with schizophrenia. Results were preserved in patients with bipolar disorders and were similar in all groups in the detection task.
Conclusion: The results suggest that elementary time disorders have an impact on the ability to order events, consistent with the proposal that it impacts the temporal structure of consciousness.
ID: 2117936

ELECTROPHYSIOLOGICAL EVIDENCE FOR IMPAIRED DISTRACTOR SUPPRESSION IN SCHIZOPHRENIA

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Background: Recently, we reported eye movement and ERP evidence that people with schizophrenia (PSZ) focus their processing resources in an overly narrow and intense fashion impacting WM and attentional control. Here we examine this issue with a simple target detection task using a paradigm where controls demonstrate active suppression of distractors that match the color of search targets following initial capture by the distractor. If feature search templates are abnormally intense in PSZ, they should show enhanced capture by distractors that match the target feature appearing at irrelevant locations.
Methods: Twenty PSZ and 20 healthy controls (HC) participated. Subjects were instructed to attend to a central colored circle (red, green, or blue were targets on different blocks) flanked by a lateral filled colored circle on each side. Subjects made a target color present/absent judgment on each trial. Target colors appeared on 10% of trials: 90% of trials had a grey central circle. One flanking nontarget circle sometimes matched the target color. A 60-trial visual change localization task was used to assess working memory capacity.
Results: In HC, arrays containing a target-color distractor elicited a brief N2pc component (reflecting a capture of attention) followed by a large Pd component (reflecting a suppression of the attention shift). In PSZ, a large and long-lasting N2pc was observed, with no Pd, indicating an overcommitment of attention to the target-color distractor. Pd amplitude was significantly greater in HC than SZ whereas N2pc amplitude was significantly greater in SZ than HC. In addition, PSZ showed significantly elevated theta power relative to HC. Despite being abnormally elevated, higher theta power was correlated with better task performance, with greater Pd amplitude on color matching distractor trials, and with increased working memory capacity, exclusively in PSZ. These correlations were absent or reversed in HC.
Conclusion: In HC, irrelevant distractors briefly capture attention, but this is then actively suppressed, evidenced in the Pd. PSZ were unable to suppress processing of features that match a stored search template, resulting in greater allocation of attention to an irrelevant location. These results demonstrate that the focusing of spatial attention can be disrupted by the influence of task representations stored in memory.
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ID: 2079187

WORKING MEMORY CAPACITY LIMITATIONS IN SCHIZOPHRENIA

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Background: Background: Impairments in working memory(WM) have been a central focus of cognitive neuroscience research in schizophrenia for over 20 years with robust evidence of impaired behavioral performance coupled with aberrant neurophysiology during the performance of working memory tasks. However the precise mechanisms implicated in WM capacity reduction have remained obscure as has the clinical significance of WM impairment.
Methods: Methods: A series of case-control experiments will be reviewed where we have used variants of simple visual change detection and change localization tasks to estimate WM capacity and the role of selective attention in WM encoding. Correlational analyses include over 100 people with schizophrenia (PSZ) and 100 healthy controls (HC).
Results: Results: PSZ show robust reductions in WM capacity (Cohen's D > 1.0). These capacity reductions do not appear to be related to failures in filtering distractors at the encoding stage, a critical mechanism implicated in normal individual differences in WM. In contrast, multiple lines of behavioral and electrophysiological evidence suggest that PSZ may focus attention in an overly narrow and intense fashion resulting in capacity reduction. WM capacity is robustly correlated with general cognitive ability in both PSZ and HC, and WM accounts for approximately 40% of the between-group differences in IQ and general neuropsychological performance. However, WM capacity shows minimal relationship with measures of symptom severity or employment status.
Conclusion: Conclusions: WM impairment is a key feature of the broad impairment of higher-order cognitive functions observed in PSZ. Somewhat surprisingly, it appears that symptomatic and functional outcome signals may be diminished, as cognitive measures become more process specific. Importantly, it appears that the determinants of WM performance in PSZ may be different than in HC. This is a challenge to the RDoC approach that presupposes continuity of function in critical neural systems from health to disease. Research on normal individual differences needs to be supplemented by research on illness-emergent alterations in neural systems.
ID: 2117867

MULTIMODAL EXERCISE IMPROVES SYMPTOMS, COGNITION AND NEUROMUSCULAR PERFORMANCE IN PERSISTENT MENTAL ILLNESS

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Background: In addition to psychotic and mood symptoms, cognitive deficits are major determinants of disability in the persistent mental illnesses (PMI) schizophrenia and bipolar disorder. There are also high rates of physical health limitations that amplify these pre-existing symptomatic and cognitive deficits through additive or even interactive effects on disability. We developed a novel multimodal physical exercise training program aimed at improving physical limitations in obese persons with PMI.
Methods: Eight week, high-speed circuit training twice a week, using 11 computerized Keiser pneumatic exercise machines targeting different muscle groups. Participants performed 3 circuits of 10–12 repetitions with computer-adjusted load on the eleven machines moving from machine to machine with minimal recovery, performing the concentric phases of each exercise as fast as possible and the eccentric phase for two seconds. Increases in loading across the training period were based on plateaus in power production for individual exercises as defined by failure to increase power by at least 5% across two training days.
Results: We recruited a sample of 12 (9M, 3F), community-dwelling obese patients with schizophrenia (n=9) and bipolar disorder (n=3). Mean age was 44.0 ± 12 years. Mean BMI was 33.3 ± 5.7. Participants showed significant increases in strength and power in all major muscle groups. There were significant positive cognitive changes measured with BACS by a trained rater: BACS summary scores improved significantly (t=-3.3;

p=0.008), as did Digit Sequencing and Symbol Coding T-scores (t=-3.07; p=0.01) and t=-4.5; p=0.001, respectively). In contrast, Verbal Memory and Verbal Fluency T-scores did not improve (t=-1.8; p=0.096 and t=-0.82; p=0.43, respectively). CDSS scores improved significantly (t=5.2; p=0.002). PANSS scores all showed significant improvements including PANSS Positive (t=3.4; p=0.003), PANSS Negative (t=3.3; p=0.004), PANSS General (t=3.8; p=0.001) and PANSS Total Symptoms Scores (t=3.9; p=0.001).

Conclusion: In addition to significant improvements in neuromuscular performance, predictive of everyday functioning, there were unexpectedly large positive changes in cognition and mood. The cognitive domains that showed the greatest improvements (memory and processing speed) are the most highly predictive measures of disability in schizophrenia. Moreover, the improvements seen in depression suggest this type of exercise intervention may be a valuable add-on therapy for bipolar depression.

ID: 2118145

BRAIN-BEHAVIOR PHENOTYPING OF YOUTHS AT RISK FOR PSYCHOSIS IN A POPULATION-BASED SAMPLE

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Background: Early identification is prerequisite for effective prevention and intervention. A growing literature has examined the clinical course of help-seeking individuals with prodromal presentation. The inclusion of brain-behavior measures has added to the prediction of clinical course. A challenge for early detection is finding youths on a trajectory to psychosis before they become help seeking. Such efforts require population-based samples. The goal of the present study was to examine prospectively youths who have endorsed psychotic symptoms and evaluate neurocognitive functioning and brain structure and function cross-sectionally and longitudinally.

Methods: The Philadelphia Neurodevelopmental Cohort includes about 9,500 genotyped youths (age 8–21) who presented to pediatric clinics at Children's Hospital of Philadelphia. They had a structured clinical interview including measures of psychosis spectrum symptoms. A computerized neurocognitive battery (CNB) evaluated performance (accuracy, speed) of executive function, episodic memory, complex cognition, emotion processing, sensorimotor speed. A subsample (1,500) underwent neuroimaging including sMRI, DTI, fMRI and perfusion. Follow-up of psychosis spectrum (PS, n=300) and typically developing (TD, n=200) individuals at ~2 years interval included comprehensive clinical assessment and repeated CNB and neuroimaging.

Results: The psychosis spectrum group (PS) showed deficits in neurocognitive performance across several domains that were more pronounced for accuracy than for speed. The deficits implicate executive-control, episodic memory and social cognition systems. MRI volumetric analysis indicated overall lower intracranial volume in the PS group and reduced volume specific to gray matter in several cortical and subcortical regions. Functional MRI showed reduced resting connectivity and impaired activation for a working memory and emotion identification tasks. PS at intake who remained PS at follow-up performed worse on social cognition and face memory as well as verbal reasoning speed, compared to those who were asymptomatic at follow-up. These trajectories are correlated with multimodal neuroimaging parameters.

Conclusion: We found that the pattern of neurocognitive impairment and neuroimaging abnormalities in PS ascertained in a population-based sample is similar to that observed in help-seeking youths at clinical risk. Deficits in social cognition portend persistence of psychotic features and therefore a target for intervention.

ID: 2115921

DOES GENDER EXERT A MODERATING INFLUENCE ON SOCIAL PERSPECTIVE-TAKING IN SCHIZOPHRENIA?

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Background: Since Kraepelin, longitudinal studies of individuals with schizophrenia have generated interest in evidence that females have better premorbid adjustment, earlier onset and a milder course of illness (i.e., fewer relapses and hospitalizations) as compared to males. Whether origins of gender-related variance in the course of illness stem from the neurobiology, clinical symptomatology and/or neurocognitive manifestations of the disorder has been inconclusive. Using a conventional Theory of Mind (False Belief) task and a laboratory-based interactive measure of social reasoning or mentalizing ability, we investigated whether gender exerts a moderating influence on social perspective-taking in schizophrenia.

Methods: Participants (ages 28 to 62 years) were 48 (32% female) clinically stable outpatients with DSM-IV (SCID) schizophrenia psychoses (SZ) and 37 healthy control (HC) individuals (30% female) free from Axis I disorders. Subjects were evaluated on measures of inferential reasoning in regard to the mental state of another person: a conventional False Belief Task (FBT) and a laboratory measure of social reasoning, the Movie Clips Task (MCT). A subset of subjects (32 HC and 27 SZ individuals) were also administered the Hinting Task (HT).

Results: Results supported the hypothesized difference between the schizophrenia (SZ) and healthy control (HC) samples, based on a one-way MANOVA, Wilks' $\lambda = .84$, $F(2, 79) = 7.67$, $p = .001$. HC subjects performed better than SZ subjects on both the FBT, $F(1,80) = 7.57$, $p = .009$, and the MCT, $F(1,80) = 14.36$, $p<.0001$. In association with an overall gender effect favoring females, Wilks' $\lambda = .93$, $F(2, 79) = 3.12$, $p = .050$, gender differences were found, favoring females, on the FBT ($p=.048$) and the MCT ($p =.025$). Gender differences were also observed, favoring females, on the HT ($p=.004$). No diagnosis-by-gender effects were observed, although females consistently scored higher than males on average, across all measures for both groups. Gender effects were driven largely by specific effects for HC subjects.

Conclusion: Whereas among healthy (non-psychiatric) adults, females performed better than their male counterparts on social cognitive (perspective-taking) tasks, this female advantage was not sustained among individuals with schizophrenia.

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ID: 2117931

EFFICACY AND SAFETY OF ABT-126, AN A7 NICOTINIC CHOLINERGIC AGONIST, IN TREATMENT OF COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA: RESULTS FROM A PHASE 2B STUDY IN SMOKERS

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Background: A previous study in stable subjects with schizophrenia demonstrated procognitive effects of ABT-126, an α7 nicotinic receptor agonist, only in the nonsmoking subset of subjects. This study evaluated ABT-126 for cognitive impairment in subjects who were current smokers.

Methods: Design was double-blind, placebo-controlled, parallel-group, multicenter. Eligible subjects receiving stable doses of antipsychotics were randomized to ABT-126 25 mg, ABT-126 75 mg, or placebo QD for 12 weeks. Smoking restrictions in proximity to cognition testing were not applied. Post randomization clinic visits were scheduled every 2 weeks. The primary analysis was comparison of change from baseline to Week-12 on the MCCB neurocognitive composite score vs. placebo using a mixed-model for repeated-measures. Other efficacy endpoints included the UPSA-2ER and NSA-16 total scores.
Results: 157 subjects were randomized and 82% completed the study. Mean baseline MCCB total score in this study was 29.0. No statistical differences between ABT-126 dose groups and PBO were observed on change (LS mean [SE]) from baseline to Week 12 on MCCB neurocognitive composite score (1.42 [0.88], 0.28 [0.81] and 0.41 [0.85], respectively, for PBO, 25 mg and 75 mg ABT-126). No significant differences were detected for the UPSA-2ER cognitive functional battery (3.99 [1.61] PBO, 3.39 [1.49] 25 mg and 1.93 [1.61] 75 mg). The NSA-16 (negative symptom assessment) showed a trend for improvement at the 75 mg dose (-0.86 [0.87] PBO, -0.87 [0.81] 25 mg, -2.80 [0.86] 75mg (1-sided p = 0.053)). Rates of overall adverse events, serious adverse events, and adverse events leading to study drug discontinuation for ABT-126 were similar to those of placebo. Adverse events reported for 2 or more subjects in either ABT-126 dose group were headache, hypertension, insomnia, laceration, muscle tightness and sedation; none were statistically different from placebo. There was no evidence of worsening underlying psychosis in subjects treated with ABT-126 compared to placebo.
Conclusion: Failure of ABT-126 to demonstrate a procognitive effect at 25 or 75 mg QD was consistent with the earlier Phase 2a study findings, in which no cognitive effect was observed in the smoker subgroup despite statistically significant cognitive improvements noted in the nonsmokers in the 10 - 25 mg QD dose range. The trend for improvement in negative symptoms at the 75 mg dose may warrant further study.
ID: 2115828

RESILIENCE AND INTERNALIZED STIGMA

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Background: Internalized stigma, the inner subjective experience of stigma and its psychological effects resulting from applying negative stereotypes and stigmatising attitudes to oneself, is a barrier to recovery in patients suffering from schizophrenia. We present preliminary data of a cross-sectional study investigating the associations between resilience and internalized stigma across patients from Austria and Japan.
Methods: Clinically stable outpatients with DSM-IV schizophrenia between the ages of 19 and 60 were included. Diagnoses were confirmed with the Mini International Neuropsychiatric Interview (M.I.N.I.). Next to the assessment of psychopathology by means of the Positive and Negative Syndrome Scale (PANSS) the Resilience Scale (RS-25) as well as the Internalized Stigma of Mental Illness Scale (ISMI) were used.
Results: So far, 100 patients were included into the study (Japan: N=60, Austria: N=40). The two groups were comparable with regard to sociodemographic data, PANSS scores and ISMI scores. However, RS-25 scores were significantly lower in Japanese as compared to Austrian patients (109.6 ± 25.2 vs. 130.8 ± 21.7, p<0.001; higher scores indicate higher resilience). In both samples, higher PANSS scores and lower RS-25 scores were associated with a higher level of internalized stigma. The correlation between the severity of symptoms and resilience was significant in the Austrian sample, but not in the Japanese sample.
Conclusion: Whereas both the severity of symptoms as well as a lower degree of resilience appear to be associated with an increased inner subjective experience of stigma in patients with schizophrenia, resilience itself might depend on religious and cultural backgrounds. Further studies are needed in order to investigate whether therapeutic interventions could increase resilience in patients suffering from schizophrenia and whether this might have a positive effect on patients' outcomes.
ID: 2081287

A SENSORY-MOTOR SYSTEM MEDIATING LOWER AND HIGHER-LEVEL SOCIAL DISTANCE

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Background: Social spacing, or "personal space", is a poorly understood, non-verbal process that is disrupted in schizophrenia. Like eye gaze and facial expressions, personal space, defined as the distance that one individual maintains from another nearby person, plays an important role in communication with others. Although the neural mechanisms mediating social spacing-related behaviors are not well understood, studies in non-human primates have found that the space near the body is monitored by a network of parietal and frontal regions. Some neurons in these areas respond best to a stimulus moving, or "looming", towards the head or body, entering personal space.
Methods: To localize responses to "looming" stimuli in the human brain in healthy subjects and patients with psychotic disorders, we collected fMRI data in participants while they viewed social (faces) and non-social (cars, spheres) stimuli that appeared to move towards and away from the viewer.
Results: We found that in healthy individuals, the dorsal intraparietal sulcus (DIPS) and the ventral premotor cortex (PMv) showed selective responses to looming social stimuli and were functionally coupled. In addition, DIPS-PMv functional connectivity was negatively correlated with the size of personal space. In patients with psychotic disorders, personal space size was significantly elevated (compared to healthy subjects) and correlated with negative symptom levels. Moreover, the patients showed significantly greater DIPS responses to looming social stimuli than controls, which also correlated positively with personal space size. Since personal space size was positively correlated with social anhedonia across several samples, social spacing-related behaviors (and activity within the associated parietofrontal network) appear to reflect aspects of social motivation and habitual social behavior.
Conclusion: Taken together, these findings suggest that comfort with the physical proximity of others and day-to-day social motivation require efficient functioning of a parietofrontal network involved in monitoring the space near the body. In individuals with psychotic disorders, this network may be disrupted, potentially contributing to social anhedonia and withdrawal. Quantitative measurements of the functioning of this system may prove useful in future studies as markers of changes in social functioning in people at different stages of psychotic illness.
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ID: 2117720

INFLUENCE OF THE LATERAL PREFRONTAL CORTEX ON EMOTION REGULATION AND DAILY FUNCTIONING IN SCHIZOPHRENIA

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Background: Lateral prefrontal cortex (LPFC) dysfunction is a well-established characteristic of schizophrenia-spectrum pathology related to illness-chronicity and functional disability. However, the mechanisms by which LPFC dysfunction influences symptom expression and functional outcome is unclear. Normally, LPFC deploys cognitive skills, such as attention and inhibition, to manage emotional response to affective stimuli. Interpersonal conflicts are emotionally challenging events which require the regulation of emotion and behavior for successful resolution.
Methods: We used a combination of fMRI and experience-sampling methods to examine whether LPFC deficits associated with schizophrenia-spectrum pathology create a vulnerability for symptom exacerbation after interpersonal conflict. Three schizophrenia-spectrum groups were tested: adults with high social anhedonia (a negative schizotypal trait), adults with schizophrenia disorder; and adolescents/young adults with a first-degree relative with schizophrenia. During fMRI, participants completed an implicit emotion regulation task in which they viewed emotionally provocative interpersonal social cues. Afterwards, they completed an online daily-diary questionnaire for 21 days. Each evening, participants reported occurrence of interpersonal conflict and rated their mood, symptoms, and behavior.
Results: Results showed that all schizophrenia-spectrum groups had reduced LPFC activity in response to emotional stimuli. Analysis of daily-diary data revealed that the interaction of LPFC activity and interpersonal conflict predicts daily mood and behavior. Specifically, among people with high social anhedonia, lower LPFC activity to positive social signals (e.g. accepting>neutral faces) was related to lower positive mood and worse productivity. Schizophrenia and familial high risk participants showed more pronounced LPFC deficits in response to negative social signals, and, among those with low LPFC activity, interpersonal conflict was related to the exacerbation of negative mood and psychotic symptoms the following day.
Conclusion: These results suggest that social anhedonia is associated with reduced LPFC activity when processing social cues, and that reduced LPFC control-related mechanisms associated with schizophrenia may be a biologically-based vulnerability for symptom exacerbation in response to social stress.
ID: 2119048

PREDICTIVE CODING ABNORMALITIES IN SCHIZOPHRENIA: RELATIONSHIP TO PSYCHOTIC SYMPTOMS

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Background: Converging evidence in schizophrenia indicates that excess D2 stimulation in the associative striatum relates to the severity of psychotic symptoms, although the pathway involved in the expression of these symptoms remains unclear. A prominent theory suggests that the cognitive mechanism ultimately responsible for psychotic symptoms is a disruption in predictive learning about sensory information. However, empirical evidence for this theory is scarce and its relationship to the dopaminergic dysfunction in the associative striatum remains an open question.
Methods: We present fMRI and behavioral experiments in patients with schizophrenia and healthy controls using sensory learning tasks (an interval reproduction task and a speech discrimination task, respectively) and computational models of learning to examine trial-to-trial adjustments in subjective perception and in BOLD signals in sensory regions, in particular sensory prediction-error (PE) signals. We also examine regional patterns of striatal connectivity during resting-state fMRI scans.
Results: Our fMRI data is compatible with a deficit in sensory prediction errors in patients, the magnitude of which relates to severity of auditory hallucinations and to increased activity of auditory cortex during silence, a well-established neural phenotype of hallucinations (Horga et al., J Neurosci 2014). Behavioral data during the interval reproduction task in healthy individuals similarly suggests that abnormalities in sensory learning relate to propensity to psychosis-like phenomena in non-clinical populations. Finally, our resting-state connectivity data indicates that regions of the auditory cortex involved in auditory hallucinations are strongly connected to the associative striatum and that patients have an overall disruption in striatal connections.
Conclusion: Our recent studies suggest dysfunction in striatal dopamine and sensory learning as likely mechanisms underlying psychotic symptoms. Although the role of dopamine in sensory learning is still unclear, our findings suggest a possible pathway through which abnormal functioning of the associative striatum (due to excess dopamine transmission) could impact sensory functioning of auditory cortex, leading to hallucinations and perhaps other psychotic symptoms.
ID: 2119044

MEG ANALYSIS OF NETWORK OSCILLATORY ACTIVITY DURING THE TRANSITION INTO AUDITORY VERBAL HALLUCINATIONS (AVH-ON) AND OUT OF (AVH-OFF) TRANSITIONAL PERIODS

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Background: Magnetoencephalography (MEG) was used to identify the brain state occurring during the transition into auditory verbal hallucinations (AVH), and during the transitional period as AVHs end. It was hypothesized that knowledge of brain state during AVH transitional phases may help to understand the baseline neural network configuration in which AVH are created and to understand the network configuration to turn AVHs off.
Methods: Twenty adult patients with schizophrenia and frequent auditory verbal hallucinations underwent MEG scanning, using a button-press paradigm to signal AVH-onset and AVH-off during scanning.
Results: After offline preprocessing, epochs for AVH onset and offset were constructed using 1.5 seconds after the respective motor responses. Using MNE-python, phase slope index (PSI) was computed relative to superior temporal gyrus (STG) for AVH onset and offset in the theta and alpha bands. Individual PSI estimates were registered to the MNI template brain using a spherical morphing procedure and compared using paired t-tests. The largest changes between AVH-onset and AVH-off occurred in the theta band. Significant differences in PSI were detected for left

middle frontal gyrus (offset>onset), superior frontal gyrus (onset>offset), inferior temporal gyrus (offset>onset), and right orbitofrontal cortex (onset>offset). In the alpha band, significant differences in PSI were detected for left middle frontal gyrus (onset>offset), inferior temporal gyrus (onset>offset), and right middle frontal gyrus (onset>offset).
Conclusion: Changes in auditory cortex functioning have been documented as being associated with the acute experience of AVH. The present MEG analyses show that a unique theta- and alpha-band signature is associated with the transition into an AVH. This process appeared to reverse itself during transition out of AVH.
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ID: 2119673

ATTACHMENT STYLE AS A PREDICTOR FOR THE EFFECTS OF OXYTOCIN ON SOCIAL COGNITION

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Background: Individuals with schizophrenia have significant deficits in social cognition that are strongly associated with functional outcomes, yet there are no pharmacologic treatments available to reduce these deficits. The neuropeptide oxytocin has been shown to have prosocial effects when administered intranasally in humans, suggesting therapeutic potential. However, these prosocial effects are not universal. Recent research has suggested that individual attachment style might modulate the prosocial effects of oxytocin.
Methods: We administered 40 IU of oxytocin and saline placebo intranasally to 38 subjects with schizophrenia and 31 age-matched, healthy controls in two randomized, double-blind, placebo-controlled, cross-over studies. Attachment style and social cognition were assessed with the Experience in Close Relationships Questionnaire (ECR) and The Awareness of Social Inference Test (TASIT), respectively. We examined how attachment style modulates the effect of oxytocin administration on controlled social cognition (the ability to comprehend indirectly expressed emotions, thoughts, and intentions through complex deliberations) in individuals with and without schizophrenia using univariate linear regression and Pearson correlation analyses.
Results: Attachment avoidance predicted the effects of oxytocin on TASIT performance ($R=0.21$, $p<0.05$); high attachment avoidance predicted greater oxytocin-induced gains and low attachment avoidance predicted less gains or even losses. Attachment avoidance had similar moderating effects among males in subjects with schizophrenia ($R=0.24$, $p=0.11$) and healthy controls ($R=0.21$, $p=0.12$). Attachment anxiety did not correlate with the effects of oxytocin on TASIT performance.
Conclusion: Intact social cognitive abilities are associated with better functional outcomes in individuals with schizophrenia. Our data suggest that individuals with high attachment avoidance may experience greater gains in social cognition from intranasal oxytocin, compared to individuals with low attachment avoidance or high attachment anxiety. They support the further exploration of the moderating factors for oxytocin, and how oxytocin can serve as a potential adjunct treatment to improve controlled social cognition in schizophrenia.
ID: 2083424

ALPHA SYNCHRONY DURING COGNITIVE CONTROL ACROSS THE SCHIZOPHRENIA-BIPOLAR SPECTRUM: FINDINGS FROM THE BIPOLAR-SCHIZOPHRENIA NETWORK ON INTERMEDIATE PHENOTYPES

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Background: Individuals with schizophrenia (SZ) and psychotic bipolar disorder (BDP) show poor performance on executive and cognitive control tasks and may have distinct and shared neurophysiological indicators of disease risk. The current study examined synchronization of neural responses in the alpha range in healthy individuals and individuals with SZ and BDP.
Methods: 59 healthy persons (H), 41 SZ, and 55 BDP completed blocked pro- and anti-saccade tasks while electroencephalography (EEG) data was gathered on a 64 channel NeuroScan system. Trials consisted of checkerboards in central and both peripheral visual fields, followed by brightening of one peripheral checkerboard (cue) after 5sec. The central checkerboard flickered at 15Hz. The degree of 10Hz (middle of alpha range) synchronization between the 2016 sensor pairs was assessed and compared using intersensor phase coherence (ISC).
To use ISC data from every sensor pair and thus to most accurately and comprehensively capture the shared variance in the spatial topographies of distributed synchronization of neural responses across time, data reduction using spatial principle components analysis (PCA) was performed. Further analyses included only sensor pairs with ISC values in the 99th percentile (20 pairs each).
Results: There were two significant components: (1) trans-medial occipital to parietal and (2) trans-medial occipital connections (limited to extended visual cortex). Virtual sensors for each PCA component indicate a transient boost in ISC for H following presentation of the checkerboards. This is in contrast to both proband groups, who show a decrease from baseline before plateauing after 1sec for occipital to parietal connections and, for occipital to occipital connections, never change from baseline. For occipital to parietal connections, all groups show increased ISC for Anti than for Pro, with proband groups showing greater task differences than H. Healthies also show the lowest ISC levels though out the tasks, with BDP having the greatest. For occipital to occipital connections, H again exhibit lowest ISC levels than probands, but SZ and BDP do not differ.
Conclusion: These results suggest that absolute levels of alpha synchrony, as well as cognitive control related modulation, between parietal and occipital regions may differ slightly between SZ and BDP. They also suggest that alpha synchrony within extended visual processing regions is equivalent across the schizophrenia-bipolar spectrum.
ID: 2119438

ASSOCIATIONS BETWEEN COGNITION AND STRUCTURAL AND FUNCTIONAL CONNECTIVITY IN ANTIPSYCHOTIC-NAÏVE FIRST-EPISODE SCHIZOPHRENIA: A STUDY DESCRIPTION

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Background: Cognitive deficits are core features of schizophrenia. The impairments are present throughout the course of illness and have major impact on the clinical outcome of patients. Thus it is of great importance to understand the pathophysiology underlying cognitive deficits. Schizophrenia patients have been shown to have impaired structural and functional connectivity in brain regions which are heavily involved in cognitive processing. Specifically, positive correlations between cognitive functions such as executive functions and working memory and the structural connectivity (measured with diffusion-weighted MRI) in frontotemporal areas have been demonstrated. Similar associations between cognitive impairment and functional frontotemporal connectivity (measured with resting state fMRI) have been reported.
Across different studies reduced frontotemporal connectivity appears relatively stable at various stages of the illness. However, direct longitudinal evidence of the stability of the cognitive ability and the frontotemporal connectivity is warranted. The aim of the study is to examine the relation between cognitive deficits and structural and functional connectivity in a cohort of antipsychotic-naïve, first-episode schizophrenia patients before and after 6 weeks of antipsychotic treatment.
Methods: This is a prospective longitudinal study of 60 initially antipsychotic-naïve first-episode schizophrenia patients and 60 matched healthy controls. Cognition is assessed with Cambridge Neuropsychological Test Automated Battery (CANTAB), Brief Assessment of Cognition in Schizophrenia (BACS), WAIS-III (Weschler's Adult Intelligence Scale, 3rd ed.), Danish Adult Reading Test (DART) as well as tests of social cognition. Structural connectivity is measured with diffusion weighted imaging (in combination with fiber tracking) and functional connectivity with resting state fMRI on 3 Tesla MR scanner.
Results: In the antipsychotic-naïve state we expect positive correlations between cognitive ability and structural and functional connectivity, particularly between frontal and temporal regions. We expect this correlation to persist after antipsychotic treatment.
Conclusion: The study will yield a greater understanding of the interrelations between cognitive deficits and structural and functional connectivity in schizophrenia.
ID: 2102411

SELF-REFERENTIAL MEMORY IN SCHIZOPHRENIA: AN FMRI STUDY

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Background: Social information, especially information related to the self, enjoys a special processing status relative to non-social information. One advantage of this privileged status is enhanced memory for information about oneself, or self-reference memory (SRM). Self-processing is reliably associated with activation in ventrolateral and medial prefrontal cortex (PFC) and posterior cingulate/precuneus (PCC/PC). Studies of the SRM effect during encoding show selective engagement of mPFC during "self" relative to other semantic processing conditions. Previous behavioral work in our lab indicated that patients with schizophrenia fail to benefit from this memory boost. However, the neural correlates of this deficit are not known.
Methods: In an ongoing study, we have completed a preliminary sample of 5 schizophrenia outpatients and 2 healthy controls on a self-referential recognition memory paradigm during event-related fMRI. During encoding, trait adjectives were judged in terms of their structural features ("case" condition), social desirability ("other" condition), or as self-referential ("self" condition). Following a 12-minute delay, memory for trait adjectives was tested during an unexpected yes-no recognition test.
Results: There were no performance differences between groups at encoding in terms of desirability judgments for the trait adjectives. During retrieval, both groups demonstrated better recognition (d-prime) for adjectives from the "self" and "other" conditions compared to the "case" condition; there was no notable difference between the "self" and "other" conditions. fMRI obtained during encoding indicated that both patients and controls had greater activation during the "self" condition relative to the "case" condition in lateral PFC and orbital frontal cortex (OFC). Patients also showed increased activation for this contrast in left frontal pole, mPFC, PCC/PC, and left posterior parietal lobe. Furthermore, patients showed greater activation during the "self" condition relative to the "other" condition in lateral PFC, OFC, right posterior temporal lobe, and amygdala.
Conclusion: Despite comparable behavioral performance between groups during encoding and retrieval phases, preliminary analyses suggest that patients show greater BOLD activation than controls while processing self-oriented information. When data collection is complete, we can refine the regions that distinguish the groups in terms of self-relevant memory processing.
ID: 2115433

COGNITIVE DECLINE IN FIRST EPISODE SCHIZOPHRENIA. HOW CAN IT ILLUMINATE FUTURE TREATMENTS.

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Background: There is growing evidence for progressive brain alterations in schizophrenia. In addition, schizophrenia is characterized by global cognitive impairments as well as by deficits in specific cognitive domains such as verbal memory and executive functioning. Positive correlations between IQ and volume of total brain and GM have been foundin patients, but so far relationships between change in IQ and change in brain structure over time have not been reported. The latter seems particularly relevant in view of the above-mentioned changes in brain volume over time in schizophrenia.
Methods: This study investigated the association between IQ and brain measures in schizophrenia over time in a longitudinal study comparing patients with schizophrenia and healthy controls. MRI of the brain and IQ scores were obtained at baseline and at three-year follow-up including 84 patients (mean illness duration of 4.35 years) with schizophrenia and 116 age-matched healthy controls.
Results: Over time, cerebral gray matter volume and volume and thickness of the cortex decreased more in patients as compared to controls. Patients showed additional loss in cortical volume and thickness of the right supramarginal, posterior superior temporal, left supramarginal and postcentral, and occipital regions. Although IQ increased to a similar extent in patients and controls, only in the patients change in IQ was significantly correlated to change in lateral ventricular volume and cortical volume and thickness the latter both globally and in widespread regions across frontal, temporal, parietal, and cingulate cortices. These findings were independent of symptom severity, cannabis use, and cumulative antipsychotic medication over the interval.
Conclusion: In conclusion, results suggest that in patients who show a relative decrease in IQ - or a failure to benefit from practice - over time, brain

loss is more prominent than in those patients who do not display cognitive decline during the first years of their illness. This subgroup of patients, characterized as it is by both brain loss and cognitive underperformance, may be both clinically and genetically distinct with implications for diagnosis, treatment and drug development in schizophrenia.
ID: 2117744

DIFFUSION TENSOR IMAGING OF THE EXECUTIVE AND REWARD NETWORKS: RELATIONSHIP TO RISK TAKING BEHAVIOR

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Background: Although their brains are still developing, during adolescence individuals begin to be held responsible for larger social, health, and academic decisions, and to enter situations in which disadvantageous decision making may lead to substantial risk and permanent consequences. However, decision making in adolescents may be limited by factors such as susceptibility to social influences, poor self-regulation, impulsivity, and risk-taking. In patient populations, adults with both schizophrenia and bipolar disorder have been shown to have decision making deficits. While decision making almost certainly relies on a series of wide-spread brain networks, little is known about the contributions of white matter integrity to decision making and risk taking either in healthy development or in those with psychosis.
Methods: We assessed an adolescent (age 12–21) sample of healthy controls and individuals with psychosis using both laboratory based and real-life decision making measures, as well as neuroimaging assessments that included diffusion tensor imaging (DTI). Real life decision making was measured based on self-reported life events through the CDC's Youth Risk Behavior Surveillance System (YRBSS). Laboratory based decision making was measured using a version of the Balloon Analogue Risk Task (BART).
Results: In an age-matched sub-sample, we found higher real-life risk taking in the psychosis group relative to healthy controls, particularly the Suicidality, Tobacco Use, Health Behavior and Cannabis Use scales. In an initial analysis in 33 control subjects, we found that fractional anisotropy (FA), an index of white matter integrity, in both the executive network (superior longitudinal fasciculus, SLF) and reward network (accumbofrontal tract) were associated with differences in real life risk taking behavior. Analyses in an age-matched subsample of older adolescents (16 patients, 21 controls) revealed significantly lower FA in the SLF in adolescent psychosis patients relative to controls.
Conclusion: These findings support the hypothesis that decision making deficits in adolescents may be related to changes in white matter integrity across development. Further analysis will inform the question of the degree to which observed white matter differences contribute to behavioral differences in risk taking between diagnostic groups.
ID: 2118721

ALTERATIONS IN ADAPTIVE AND ABERRANT SALIENCE ATTRIBUTION IN PSYCHOSIS

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Background: Schizophrenia patients have been hypothesized to attribute aberrant salience to irrelevant events which might contribute to the formation of psychosis (Heinz, 2002; Kapur, 2003). The Salience Attribution Test (SAT; Roiser et al., 2009), assesses adaptive and aberrant salience on a behavioural level. Here, we tested if schizophrenia patients and healthy delusion-prone individuals displayed higher aberrant salience compared to healthy controls.
Methods: 28 schizophrenia patients, 24 delusion-prone participants and 51 healthy controls completed the SAT. Subjects were instructed to increase their wins by rapid responses to a cue that was preceded by conditioned stimuli. The latter varied on two dimensions: a relevant dimension with one reinforced and one non-reinforced manifestation and an irrelevant dimension with two equally reinforced manifestations. Salience attribution was measured implicitly via reaction time differences. Whereas aberrant salience was calculated using the absolute differences between equally reinforced conditioned stimuli, adaptive salience was calculated for reinforced compared to non-reinforced conditioned stimuli. Analyses of variance were performed for adaptive and salience attribution including age as covariate.
Results: Implicit aberrant salience showed significant group differences ($F = 3.379$, $p = 0.038$) due to higher values in schizophrenia patients compared to healthy controls ($p = 0.011$) while delusion-prone individuals displayed an intermediate value. Concerning adaptive salience, delusion-prone subjects and schizophrenia patients both displayed reduced values ($F = 5.089$, $p = 0.008$).
Conclusion: In line with the aberrant salience hypothesis, we found that schizophrenia patients showed higher implicit measures of aberrant salience. Aberrant salience attribution was less marked in the delusion-prone group than in schizophrenia patients compatible with a dimensional approach. Measures of adaptive salience, which is relevant for dissociating reinforced from non-reinforced conditioned stimuli, were reduced in both schizophrenia patients and delusion-prone individuals similar to previously described learning deficits in psychotic patients (Murray et al., 2008; Schlagenhauf et al., 2013). In a next step, the neural correlates of salience attribution will be investigated within a novel classical conditioning paradigm during fMRI. This task will assess adaptive and aberrant prediction error signals during dynamic learning of reversing reinforcement contingencies.
ID: 2085368

REWARD LEARNING NETWORKS AND THE SYMPTOMS OF SCHIZOPHRENIA AND PSYCHOSIS

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Background: Striatum reward learning mechanisms are associated with a range of psychopathology, including psychosis and mania.
Methods: The striatum is functionally heterogeneous (e.g., ventral striatum/learning which rewards to motivationally want; dorsomedial striatum/learning which stimuli predict getting rewards we want). Across a set of studies, we have found consistent evidence that psychosis risk (i.e., delusions & hallucinations) is associated with behavioral and neural evidence of impairment in dorsomedial striatum reward learning.
Results: For instance, in one EEG study, consistent with increased striatal dopamine, psychosis risk was associated with (a) behaviorally increased sensitivity to reward feedback relative to punishment feedback; and (b) decreased feedback-related negativity (FRN) to punishment. As another example, in a behavioral study, psychosis risk participants were especially impaired on the probabilistic reinforcement learning Weather Prediction Task that is especially associated with the dorsomedial striatum and involves correctly learning which stimuli predict reward. Hence, consistent with other research (e.g., Dandash et al., 2014; Howes al., 2009), psychosis risk appears to be especially associated with dorsomedial striatum dysfunction. Our research also suggests that increased dorsomedial striatal

dopamine could help produce anomalous experiences of aberrant salience that could contribute to psychotic symptom development. In contrast, we have found that mania risk is more associated with behavioral performance on tasks associated with the ventral than dorsomedial striatum (e.g., Learned Irrelevance). However, measures of psychosis and mania risk can be strongly correlated, making it important to concurrently study relationships between striatal reward learning mechanisms with psychosis and mania across diagnostic categories. Conversely, we have not found any evidence that anhedonia in people at risk is associated with any striatal-related neural or behavioral measure.

Conclusion: Overall, this research suggests that these different Positive Valence domain constructs may account for different manifestations of psychotic and manic symptoms.

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ID: 2118130

A SINGLE-BLIND RANDOMIZED CLINICAL TRIAL OF AEROBIC EXERCISE IN INDIVIDUALS WITH SCHIZOPHRENIA: IMPACT ON BRAIN-DERIVED NEUROTROPHIC FACTOR AND NEUROCOGNITION

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Background: Individuals with schizophrenia display substantial neurocognitive deficits for which available treatments offer only minimal to limited benefits. Yet, findings from animal and human studies converge in linking improvements in neurocognitive functioning to increases in aerobic fitness (AF) via aerobic exercise training (AE). Such improvements have been speculated to relate to increases in Brain-Derived Neurotrophic Factor (BDNF), which have been found to support neuroplasticity and is susceptible to up-regulation by physical activity. However, the impact of AE on neurocognition, and the putative role of BDNF, has not been investigated systematically in individuals with schizophrenia.

Methods: Employing a single-blind randomized clinical trial design, 33 individuals with schizophrenia were randomized to receive standard psychiatric treatment ("treatment as usual"; TAU; n=17) or attend a 12-week, 3x/week, 1-hour AE training program using Xbox 360 Kinect active-play video game systems along with traditional AE equipment (n=16). Participants completed research assessments of AF, neurocognition, and BDNF before and after and 12-week period. The main outcomes measures were changes in AF (VO2max mL/kg/min), neurocognition (MATRICS Consensus Cognitive Battery composite score), and serum BDNF.

Results: The AE participants attended 79% of the scheduled AE sessions and at follow-up improved their AF by 18.0% vs. a -0.5% decline in the TAU group (p=.002). Changes in AF were significantly correlated with the mean in-session AE training intensity (r=.71, p<.001), as indexed by heart rate monitors over the 12-week training program. At follow-up, the AE participants improved their neurocognitive functioning by 15.1% vs. a -2.0% decline in the TAU group (p=.025; Cohen's d=.93) and had larger increases in serum BDNF (12.0% vs. 1.9% in the TAU group; not significant). Separate regression analyses indicated that changes in AF and BDNF predicted 16.9% and 14.6% of the variance in neurocognitive improvement (respectively), controlling for demographic and clinical variables.

Conclusion: AE is effective in improving neurocognition in individuals with schizophrenia. Such improvements are attributed, in part, to AE-related up-regulation of BDNF. Low AF may represent a modifiable risk factor for neurocognitive dysfunction in schizophrenia for which AE training offer a novel, non-stigmatizing, side-effect-free intervention to ameliorate such deficits. Active-play video game systems can enhance such training programs.

ID: 2087861

COURSE OF ILLNESS IN SCHIZOPHRENIA: A LONGITUDINAL INVESTIGATION OF BIOMARKERS AND SIGNIFICANCE FOR OUTCOME

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Background: In a longitudinal study of initially antipsychotic naïve patients we will investigate the course of illness with the aim of identifying biomarkers and their significance for pragmatic outcome. Longitudinal studies of schizophrenia patients are important because they offer knowledge that is lost in cross-sectional studies due to sampling errors. The current project focuses on the longitudinal course of cognitive deficits, and their relation to outcome.

Methods: The study involves a reexamination of initially antipsychotic-naïve patients and healthy controls matched on gender and age included in two studies from 1998–2001: (patients N=27 and controls N=26) and 2004–2008: (patients N=48 and controls N=54). With a follow up period of up to 16 years, we will study the complex interaction of psychopathology, cognition, structural brain changes and psychophysiology and their significance for societal outcome in terms of e.g. number of inpatient days since illness onset, working ability, educational level and use of primary health care services. The neurocognitive test battery will consist of subtests from Weschler's Adult Intelligence Scale 3rd ed., subtests from Cambridge Neuropsychological Test Automated Battery, the Danish Adult Reading Test (similar to NART), Wisconsin Card Sorting Test, emotion hexagon and selected paper-pencil tests. Psychopathology will be measured with Positive and Negative Syndrome Rating Scale and Mini International Neuropsychiatric Interview. Global Assessment of Functioning, Personal and Social Performance Scale and WHO-Five Well-being Index will be used for assessment of functional level and life quality.

Results: Our hypotheses are:
1. Deficits of cognitive functioning will be associated with long-term poor occupational functioning and high cumulated use of mental health services.
2. Intact cognitive functioning at baseline will be associated with long term recovery in terms of sociatal and functional outcome.
3. Cognitive deficits will be largely stable in a longitudinal perspective with the exception of a decline in verbal memory.

Conclusion: Increased knowledge of the long term outcome in schizophrenia in relation to biomarkers both at baseline and follow up will contribute to a better understanding of the illness and thus may be important for a more individualized treatment of schizophrenia in the future.

ID: 2084427

CREATIVE ACHIEVEMENT AND SCHIZOTYPAL TRAITS

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Background: The idea that there is a link between creativity and mental illness has long generated both interest and controversy. Most evidence comes from large-scale epidemiological studies where creativity is indexed by employment categories, or smaller studies of groups pursuing creative professions. While examples of exceptional creativity exist in individuals with schizophrenia, most aggregated results show no increase and often a decrease in creative achievement. Higher creativity has been reported in people with schizotypal traits and healthy relatives of people with schizophrenia.
Methods: By studying healthy individuals unselected with respect to profession, we aimed to examine the association of creative achievement with schizotypal features and other personality characteristics derived from five-factor theory. We assessed 298 healthy young individuals (aged 21–50 years old) with at least an 8th grade education and without neuropsychological illnesses or a history of drug and alcohol abuse. We measured schizotypal traits with Chapman scales of Magical Ideation (Mag) and Perceptual Aberration (Per) and lifetime creative achievement with the Creative Achievement Questionnaire (CAQ).
Results: We found higher levels of creative achievement in those with 'high' levels of Mag (scores > 15), relative to those 'low' on Mag. Further analysis with the NEO Personality Inventory (NEO PI-R) revealed correlations (R^2 from 0.04 to 0.10) between higher scores on Mag and Per with higher neuroticism and openness to new experience, and with lower scores on agreeableness and conscientiousness. These results complement our findings of an association of creative achievement with higher openness and lower agreeableness.
Conclusion: These findings support the hypothesis that "subclinical" levels of schizotypal traits are associated with higher levels of creative achievement, and suggest that this effect may be mediated by personality characteristics involving high openness and low agreeableness (non-conformism). The findings are compatible with the inverted-U model associating creativity with psychopathology traits and genetic vulnerability for psychosis. Further development of this work includes efforts to examine this association in individuals of exceptional creativity.
This work was supported by research grants from The Michael E. Tennenbaum Family Center for the Biology of Creativity and the John Templeton Foundation.
ID: 2118155

α 7 RECEPTOR PRIMING MODULATES NEURONAL FIRING AND THETA RHYTHMS: A PUTATIVE MECHANISM FOR ENHANCED COGNITION IN CLINICAL AND PRECLINICAL MODELS

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Background: Schizophrenia patients have cognitive deficits and associated functional impairments. Previous clinical and preclinical studies have validated the rationale for α7 nicotinic acetylcholine receptor (α7R) agonists as a procognitive treatment strategy across CNS disorders. We recently reported that encenicline—an α7R partial agonist—elicits physiologic activity at α7Rs at concentrations below the binding constant, consistent with the range of unbound plasma concentrations that resulted in significant procognitive effects in clinical studies and preclinical animal models. The mechanism is thought to require the natural ligand acetylcholine (ACh), suggesting that encenicline "primes" the α7R and thereby potentiates its physiologic response to ACh. Here we present data addressing how α7 agonists affect the neuronal networks involved in cognition.
Methods: GABAergic inhibitory post-synaptic currents, glutamatergic excitatory post-synaptic currents, and long-term potentiation (LTP) were measured in rat brain slices. Hippocampal theta rhythms generated by stimulation of the nucleus pontis oralis (nPO) were recorded in mice and rats. Pharmacokinetic (PK) studies were also performed in both species for PK/pharmacodynamic (PD) modeling.
Results: An encenicline analog increased GABAergic and reduced glutamatergic neuronal firing at priming concentrations; the GABAA receptor antagonist bicuculline blocked these effects, suggesting involvement of GABAergic interneurons. In electrophysiologic studies of rat hippocampal slices, priming concentrations of α7 agonists enhanced LTP, while similar concentrations in intact animals enhanced theta rhythms generated by nPO stimulation. These data support a PK/PD model describing an inverted U-shaped dose-response curve. Importantly, plasma concentrations capable of eliciting theta rhythms in vivo corresponded to priming concentrations in vitro and to efficacious concentrations in preclinical models of cognition.
Conclusion: The priming activity at α7Rs exerts distinct effects on cellular models of memory and on higher-order neuronal systems, eliciting theta oscillations that are thought to play a role in cognition. At priming concentrations, encenicline increased synaptic strength in a well-validated model of LTP in a bicuculline-sensitive manner. The data suggest an important role for increased GABAergic tone, mediated by interneurons, in the generation of theta rhythms and their concomitant enhancement of memory.
ID: 2123671

IMPAIRED AUDITORY PERCEPTION AND EMOTION IDENTIFICATION IN SCHIZOPHRENIA

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Background: Basic perceptual processes, such as auditory pitch processing, are impaired in schizophrenia and may explain key social deficits such as the ability to identify emotions in other people. These auditory deficits may be closely linked to the neural circuits relevant for the development of psychotic symptoms and thus may be useful predictors of psychosis onset and promising therapeutic targets. However, progress in these areas is impeded by the incomplete assessment of auditory deficits in schizophrenia and a lack of information regarding the relationship between basic auditory processing deficits and impairments in emotional processing, cognition and functional capacity.
Methods: We have assessed 27 patients with schizophrenia and 31 healthy controls between the ages of 18 and 55 on a comprehensive battery of tasks spanning the five empirically derived domains of auditory function. We explored group differences across the battery of basic auditory tasks using between groups t-tests. We also explored the relationship between basic auditory processing and auditory emotion identification within the patient group using correlational analysis and multiple regression.

Results: We observed significant group differences in the ability to identify emotion in vocal samples and in several basic auditory skills, including intensity discrimination t(56)=-2.35, p<.05, detection of frequency modulation at 2Hz t(56) = 3.22, p<.05, at 10 Hz t(56) = 2.39, p<.05 and vowel formant discrimination t(56) = -2.31, p<.05. Of the basic auditory skills impaired in the patient group, intensity discrimination (r=.54, p<.01) and formant discrimination (r=.56, p<.01) correlated significantly with auditory emotion identification. Multiple regression analysis revealed that formant discrimination accounted for an additional 20% of variance in emotion identification beyond that accounted for by intensity discrimination (F1,24.= 6.82, P<.01).
Conclusion: These results suggest that individuals with schizophrenia are impaired in several basic auditory skills and that deficits in formant discrimination may be key contributors to difficulty understanding emotion from the auditory qualities of speech. As such, exercises designed to improve formant discrimination may hold promise in ameliorating emotional processing deficits in patients with schizophrenia and individuals at-risk of developing the disorder.
ID: 2119060

VIDEO-BASED QUANTIFICATION OF BODY MOVEMENT IN PSYCHOPATHOLOGY INTERVIEWS INDICATES NEGATIVE SYMPTOMS - A REPLICATION

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Background: In schizophrenia, abnormalities in nonverbal behaviors have always been considered as highly relevant. However, due to methodological limitations, nonverbal behavior was rarely quantified objectively. Recent methodological advances now allow a quantification of body movement from ordinary video recordings. We showed that patients' objectively measured amount of movement in social role-play interactions was closely associated with their symptom profiles (Kupper, Ramseyer, Hoffmann, & Tschacher, Schizophrenia Research, 2010). In the present study, a replication of these results in the context of semi-standardized PANSS (Positive and Negative Syndrome Scale) interviews was intended.
Methods: 17 patients with schizophrenia were analyzed during the initial 15-minute sequence of a videotaped PANSS interview using Motion Energy Analysis (MEA). The amount of patients' movement was then correlated with their PANSS symptom scores.
Results: Sizeable and significant correlations between negative symptoms and reduced movements (r=-.68, p<0.01) and reduced movement speed (r=-.80, p<0.001) were found. Moreover, cognitive symptoms were related to reduced movement speed (r=-.70, p<.01).
Conclusion: Negative symptoms were reliably indicated by patients' nonverbal behavior in psychopathology interviews. Hence, the main result of our earlier study, examining patients' nonverbal behavior in role play tests, was replicated for the less structured interactions in psychopathological interviews. Results could encourage the use of MEA in a wide range of videotaped social interactions of patients with schizophrenia.
ID: 2093175

INVESTIGATING THE STRUCTURE OF SEMANTIC ORGANIZATION IN SCHIZOPHRENIA

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Background: Semantic fluency is widely used and has shown to be useful in detecting cognitive deficits across a wide range of disorders as multiple cognitive processes are implicated in fluency performance. Patients with schizophrenia have also consistently shown impairments in such tasks. The semantic fluency task provides an efficient way to investigate semantic memory organisation as it has been observed that words tend to be generated in semantically grouped clusters, yet, scarce network research has been conducted. In particular the animal category has shown to be universal across languages and cultures, with only minor differences across countries, educational systems and age groups.
Methods: Data were collected from 1004 healthy controls and 656 patients with schizophrenia. A previously published statistical framework for determining the association between co-occurring concepts and how they are represented as a network was used to analyse the data (Goñi et al., 2011). The evaluation of different neighbourhoods using the generalised topological overlap measure (GTOM) allows for the identification of modules within a network.
Results: The mean number of words produced differed significantly between patients (M= 15.87, SD= 5.02) and controls (M=20.28, SD= 5.17). The links between the concepts were compared and only those above chance (p < .05) were retained. The patient data separated into 18 modules as compared to 7 for the control data. Qualitatively, the patient data appears to be more fragmented but upon inspection, can be combined to form larger modules. In terms of modularity, the control data had a higher degree of overlap between modules as evidenced by the GTOM output as compared to the patient data.
Conclusion: The current results offer an insight into semantic organization and retrieval and the degree of fragmentation could imply a possible degradation of semantic stores and impaired retrieval abilities. This could also be due, in part, to the loosening of associations commonly found in patients with schizophrenia. The inclusion of such higher level network analyses could significantly change the way such cognitive processes are understood and may enable the clarification of mechanisms that underlie poorer neuropsychological performance of patients with schizophrenia, which in turn, would impact upon treatment and remediation efforts.
ID: 2083684

MCCB AND COGSTATE CROSS-VALIDATION IN SCHIZOPHRENIA

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Background: Cognitive impairment associated with schizophrenia (CIAS) is a strong predictor of the functional outcome (Green et al. 2000). The MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein et al. 2008, Kern et al. 2008) is held as the gold standard in assessing cognitive

impairment in schizophrenia but there are concerns about its ease of administration, reliance on language and possible practice effects. The CogState Schizophrenia Battery (SB; Cairney & Maruff 2007) is increasingly used as a non-language-based alternative, but there is no independent comparison of the two batteries.
Methods: The reliability and validity of the MCCB and SB was compared in 143 participants with DSM-IV schizophrenia and schizoaffective disorder in 3 studies - a longitudinal observational study and two randomised controlled trials. Each of the studies administered the MCCB and SB at baseline on consecutive days and again 3–4 weeks later.
Results: The two batteries' test-retest reliability were similar between baselines (SB composites r0.66-0.82, MCCB domains r0.69-0.90), and between baseline 2 and follow-up (SB composites r0.65-0.80, MCCB domains r0.62-0.87). The MCCB tasks' practice effects (d0.0.04–0.40) exceeded SB's (d0.07-0.22). While the batteries' total scores correlated strongly (r0.79-0.82), cognition domains across batteries correlated between 0.22 and 0.69. Non-smokers showed lower correlations in both the SB domains (r0.66-0.75 smokers, r0.68-0.91 non-smokers) and MCCB domains (r0.61-0.89 smokers, r0.82-0.92 non-smokers).
Conclusion: Initial practice sessions of either battery would help reduce practice effects in clinical trials, but the SB would be better suited to measuring change without the benefit of practice sessions. The low correlations between equivalent domains indicate substantial differences between some supposed counterparts, casting doubt on the validity of the domains and suggesting the batteries' tasks do not measure cognition in the same way but the overall method of measuring cognition is similar.
ID: 2096684

MINDING OTHER PEOPLE'S INTEREST: NEURAL CORRELATES OF SOCIAL MINDFULNESS IN ADOLESCENTS WITH PSYCHOSIS.

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Background: Many studies have shown that the understanding of other people's perspective ('mentalising') is impaired in patients with schizophrenia. Less is known about the implications of impaired mentalising on social decision making. We investigated Social Mindfulness, 'minding other people's interest, leaving them a choice by suspending your own needs for the sake of others'.
Methods: The new Social Mindfulness paradigm was used, featuring choices of one item out of two similar categories (red and green apples) presented in a ratio 2-2 (control) and 3-1. In the 3-1 ratio, the choice has implications for the second player: When choosing the single item (the 'unmindful choice'), there will be no choice left. First, spontaneous choices were made, then instructions were provided to keep in mind the interests of a second person choosing after them. 24 patients (16-21yrs) and 25 healthy controls performed this task in the fMRI scanner.
Results: Spontaneously, patients made more unmindful choices, choosing the single item (t=2.109, p=.041). Following instruction this difference was no longer significant (p=.098). After instruction, controls were faster in making mindful choices (t=4.9, p=.000). In the spontaneous mindful choices, controls showed more right precuneus and left mid cingulum activation. In the instructed mindful choices patients showed greater left insula recruitment. In the spontaneous unmindful choices, patients activated more right caudate and thalamus. In patients unmindfulness (spont unmind - spont mind) elicited more activation in the right caudate, and instruction (instr mind - spont mind) more in the right mPFC, ACC, hippocampus, putamen and left insula.
Conclusion: Both groups reacted similarly to instruction, controls' performance on mindful choices becoming faster. Patients' caudate activation in unmindful choices illustrates more goal-directed behavior in order to obtain reward, choosing for themselves. The reaction to instruction suggests that patients have to exert more cognitive control and perceive more conflict when choosing mindfully.
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ID: 2092552

COMPARING THE EFFICACY OF TWO TYPES OF COMPUTERIZED COGNITIVE REMEDIATION THERAPY IN SCHIZOPHRENIA: COGPACK VS. BRAIN FITNESS

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Background: Cognitive deficits are a major determinant of social and occupational dysfunction in schizophrenia. Cognitive remediation strategies designed to improve cognitive functioning have been found to be effective in imrproving these deficits. Most training interventions target higher-order cognitive processes, but more recent interventions have targeted basic perceptual processes and shown that auditory and visual perceptual abilities can be improved. This study compares a bottom-up intervention targeting basic auditory processes (PositScience, Brain Fitness) to our standard cognitive training program (COGPACK; Marker Software), a top-down intervention, in patients with schizophrenia.
Methods: In and outpatients were evaluated on a standardized battery of neuropsychological (MCCB), functional skills and clinical symptoms at baseline and at endpoint. Patients were randomized to four groups (COGPACK Alone; Brain Fitness Alone; COGPACK + Mind Reading (Social Cognition software); Brain Fitness + Mind Reading) for 3 hours a week for 12 weeks. Here we present interim data on the two groups (COGPACK and Brain Fitness with and without MRIGE program).
Results: 75 patients have been enrolled to date; 13 are active patients, 49 were randomized and 13 were terminated early. There were no significant differences at baseline between the two groups. The mean level of education was 10.75 (1.65) years for the COGPACK group and 12.07 (2.14) years for the Brain Fitness group. Mean PANSS score at baseline was 74.10 (11.14) and 74.28 (8.69) for the COGPACK and Brain Fitness group, respectively. Results showed a significant improvement for the global cognitive index for both groups combined (Mean baseline = 15.77 (10.54), Endpoint = 18.64 (10.47); F (1,21) = 3.025, p = 0.047), and for Working Memory (Mean baseline = 21.35 (12.38), Endpoint = 25.26 (10.95); F (1,22) = 6.31, p = 0.02. There was a significant increase in scores on the MSCEIT for the Brain Fitness group (T-Score = 26.08 (6.45) to 33.67 (9.59)) compared to the COGPACK group (T-Score = 38.55 (11.91) to 35.64 (12.04)).
Conclusion: Both therapy methods tend to be efficacious, with working memory benefitting in both programs. Brain Fitness showied unexpectedly greater improvements in social cognition. This may relate to the program's focus on remediation of perceptual deficits. Further analysis will attempt to establish which subjects are more likely to benefit from one method or the other.
ID: 2118880

PREDICTORS OF TARGETED OUTCOMES IN COGNITIVE REMEDIATION THERAPY IN SCHIZOPHRENIA

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Background: Cognitive remediation (CRT) has shown promising results for ameliorating cognitive impairment in schizophrenia. Given the time- and cost-intensiveness of CRT, it is important to examine both biological and clinical variables that predict response to CRT. Our primary objective was to identify predictors of treatment response in patients who showed a clinically significant and quantifiable change in domains of cognitive impairment during a clinical trial of CRT.
Methods: 178 patients (mean age = 42.35, 4.87) completed a 12-week course of computerized CRT using COGPACK. It contains 64 programs with training levels and variants for cognitive domains. Baseline and endpoint blinded evaluations included PANSS, MCCB, PSP, ER-40 and Dynamic Social Cognition Battery (DSCB). All raw scores for the MCCB domains at endpoint were converted to comparable units by expressing them in z-score units relative to the baseline domain. Estimates of change in each domain were derived by subtracting the baseline from the endpoint composite. Estimates of the means at each domain, and of the changes from one domain to the next, were obtained from structural equation models for each domain. Predictors included: age, chronicity, length of last/current hospitalization, education, length of time on antipsychotics, PANSS Marder factor and baseline emotional recognition.
Results: Of the 178 subjects, 56.74% (n=101) were classified as improvers in Working Memory, 57.87% (n=103) in processing speed, 55.62% (n = 99) in Verbal Learning and Reasoning & Problem Solving, and 51.12% (n = 91) in Visual Learning. Regression analyses resulted in an overall significant model for CRT ($\chi 2 = 15.867$, $P < .01$). Patients participating in CRT who were younger and had less illness chronicity were significantly more likely to achieve a treatment response in domains of Reasoning & Problem Solving and Processing Speed (OR = 1.114, $P < .01$, OR = 1.101, $P < .01$). Those with higher scores on emotion recognition at baseline were 1.48 times more likely to achieve a improvement in Working Memory and Verbal Learning.
Conclusion: Patients showed improvements in specific and different cognitive domains. Performing the same CRT treatment on all patients may not benefit those with specific domain deficits. Attention to pre-treatment predictors could allow for targeted selection and training in cognitive deficits and thus tailoring CRT to individual cognitive domain deficits could improve response.
ID: 2100516

IMPROVED COGNITION AND POSITIVE SYMPTOMS WITH TARGETED AUDITORY PROCESSING TRAINING IN RECENT-ONSET SCHIZOPHRENIA: 6-MONTH FOLLOW-UP

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Background: Cognitive deficits are already present in first-episode schizophrenia, may worsen with illness progression, and predict later functional outcome. Therefore, they should be targeted for aggressive early intervention.
Methods: This two-site double-blind randomized controlled trial investigated targeted cognitive training of auditory/verbal processing in young individuals with recent-onset schizophrenia. Subjects performed 40 hours of auditory training (AT) or commercial computer games (CG) over an 8 week period via laptop computer. Subjects were assessed on symptoms, functioning and an abbreviated MATRICS-recommended neurocognitive battery at baseline, post-training and 6 months later.
Results: Results: 103 participants completed baseline and post assessments, and 74 completed the 6 month follow-up assessment. In an Intent To Treat analysis, AT participants (N=55) showed significantly more improvement from baseline to post training, compared to CG subjects (N=48) in global cognition (p=.002), speed of processing (p=.04), and verbal learning and memory (p=.01), with a trend towards significance in problem solving (p=.09). From baseline to 6 month follow-up, AT participants showed a trend towards significant ($.05<p<.10$) improvement in global cognition, speed of processing, and verbal learning and memory relative to CG participants. There was a main effect of Time from baseline to 6 months for PANSS Positive (p=.01) and General symptoms (p=.01), such that both groups improved slightly, likely due to many participants receiving concurrent treatment at an early psychosis clinic. There was a significant Group X Time interaction for PANSS Positive symptoms (p=.04) and Role Functioning at trend level significance (p=.09), with AT subjects improving more than CGs from baseline to 6 months post-training.
Conclusion: Neuroscience-informed cognitive training via laptop computer represents a promising treatment approach for cognitive dysfunction in young adults with recent-onset schizophrenia. We demonstrate cognitive gains immediately after testing, with some signal of maintenance up to 6 months after training and a reduction in positive symptoms at 6-month follow-up. Future studies should investigate methods for improving treatment adherence to training, whether booster session can increase maintenance of cognitive gains, and whether combination with evidence-based psychosocial interventions more strongly improves real-world functioning and long-term outcomes.
ID: 2119875

COGNITIVE FUNCTION AND BDNF POLYMORPHISMS IN PATIENTS WITH SCHIZOPHRENIA AND NORMAL CONTROLS IN A CHINESE POPULATION

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Background: Accumulating evidence has shown that BDNF may be involved in the pathogenesis of schizophrenia. Moreover, the BDNF genetic variant, especially the Val66Met polymorphism may influence specific aspects of human cognition. This study aimed to investigate the potential association of BDNF gene polymorphisms with susceptibility to schizophrenia, the psychopathological symptoms and cognitive impairments in patients with schizophrenia in a Han Chinese population
Methods: Four polymorphisms (rs6265, rs12273539, rs10835210 and rs2030324) of the BDNF gene were analyzed in a case-control study of 1892 Han Chinese individuals (849 patients and 1043 controls). Cognitive function was measured using the repeatable battery for the assessment of neuropsychological status (RBANS) in 598 patients and 434 controls. We assessed 825 patients for psychopathology using the Positive and Negative Syndrome Scale.
Results: In single marker analyses the rs10835210 mutant A allele was significantly associated with schizophrenia. Haplotype analyses revealed higher frequencies of haplotypes containing the mutant A allele of the

rs10835210 in schizophrenia than controls. We also found that this polymorphism rs10835210 was associated with positive symptoms, and the patients carrying the mutational allele A showed more positive symptoms. Further, we found that the BDNF rs12273539 played a stronger role in cognitive performance among both schizophrenics and healthy controls, especially on attention and language; however, the BDNF rs10835210 had a weak effect on language performance in schizophrenia.
Conclusion: These findings suggest the role of these BDNF gene variants in susceptibility to schizophrenia, in clinical symptom severity and in some aspects of cognitive function.
ID: 2086713

VISUAL WORKING MEMORY IN PEOPLE WITH SCHIZOPHRENIA AND THEIR RELATIVES: ELECTROPHYSIOLOGICAL AND BEHAVIORAL CORRELATES

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Background: Though working memory (WM) deficits have been well documented in people with schizophrenia (PSZ), the underlying mechanisms are not well understood. Recent work has focused on the role of stimuli that are highly salient [1] and/or task irrelevant [2]. We examined electrophysiological correlates of performance on a WM task in PSZ and REL, with a special focus on salient distractor stimuli.
Methods: A spatial delayed response task was given to PSZ, REL, and healthy controls (HCs). In this task, participants were presented a series of stimuli in various onscreen locations; these stimuli were either targets (circles) or distractors (squares). Afterwards, a probe stimulus was presented, and participants were asked to respond whether or not the probe appeared in the position of a previous target stimulus. EEG was recorded during the task and used to compute ERPs to various task stimuli.
Results: PSZ showed a performance deficit on trials where the probe appeared in the position of a previous target or a previous distractor, whereas REL showed a relative impairment only on trials where the probe appeared in the position of a previous distractor. Electrophysiological results indicate group differences in brain responses over occipital and frontal brain regions (i.e., N1) about 200 ms after probe onset. REL and HCs N1 responses differentiated between probes at previous stimulus locations versus elsewhere while PSZ failed to show such differences.
Conclusion: Behavioral and electrophysiological results suggest a failure to recognize the significance of probes in task-relevant locations in PSZ; though REL show differential electrophysiological responses to these probes, they fail to gain the same performance advantage as HCs when probes appear at a previous distractor location, suggesting a sensitivity in REL to these salient distractor stimuli. Further analyses will be performed on our complete sample to clarify these group differences and their implications for WM performance.
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ID: 2117662

METACOGNITION AS A PREDICTOR OF PROSPECTIVE LEVELS OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA CONTROLLING FOR NEUROCOGNITION AND SOCIAL COGNITOIN

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Background: Negative symptoms are a treatment resistant feature of schizophrenia. Little is known about what sustains negative symptoms, however. To explore this issue this study examined one factor which may influence the expression of negative symptoms: metacognitive mastery. Metacognition refers to a spectrum of psychological activities in which persons form ideas about themselves and others. Mastery refers to the ability to use this metacognitive knowledge to respond to psychological and social challenges. Deficits in metacognitive mastery have been suggested to degrade the ability to experience and to express internal states such as thoughts, affects and desires which may be manifested as continuous negative symptoms.
Methods: Participants were 53 adults with a SCID confirmed diagnosis of a schizophrenia spectrum disorder enrolled in vocational rehabilitation. Negative symptoms were assessed with the Positive and Negative Syndrome Scale at four points in time: baseline and 1, 9 and 17 weeks later. Metacognitive mastery was assessed with the Mastery subscale of Metacognitive Assessment Scale-Abbreviated at baseline. Neurocognition and social cognition were assessing using the MATRICS battery at baseline.
Results: Participants were divided in two groups based on their metacognitive mastery scores: High (n=27) and Low (n=26). A repeated measures ANCOVA was then conducted comparing assessments of negative symptoms over four time points between the groups, with age, education, MATRICS social cognition and overall score as covariates. Analysis revealed that the low mastery group had significantly higher levels of negative symptoms at all four time points than the high mastery group. There were no time or interactions effects. Partial correlations revealed baseline levels of mastery were significantly related to assessment of negative symptoms at weeks 9 and 17 even after controlling for the previous assessment of negative symptoms.
Conclusion: Metacognitive mastery may be related to concurrent and prospective assessments of negative symptoms independent of general levels of neurocognition or social cognition. Levels of baseline mastery were related to prospective assessments of negative symptoms independent of earlier levels of negative symptoms. Results point to the need to develop metacognitive oriented interventions. Promising treatment avenues include newly emerging forms of integrative individual psychotherapy such as Metacognitive Reflection and Insight Therapy (MERIT).
ID: 2090062

EDGE OF THE MATRIX: ADDITIONAL CONSTRUCTS AND CONNECTIONS TO CAPTURE PSYCHOTIC SYMPTOMOLOGY

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Background: The current version of the RDoC matrix suggests that the symptoms of major mental disorders can be accounted for by impairments across

a number of normative constructs from cognitive neuroscience. Without suggesting a return to diagnostic categorization, this talk will first test the explanatory power of this presumption for psychosis in general and in the case of persecutory ideation in particular. Second, patients diagnosed with schizophrenia show correlated abnormalities across a wide variety of constructs, a phenomenon of interdependence that is not easily accounted for by the current scheme.
Methods: For the first question, patients with schizophrenia, healthy monozygotic twins preselected for their level of discordance in persecution, and a large general population sample were tested using a variant of the trust game in which a first-mover decided whether to trust (for a risky but potentially greater gain) or distrust (for a smaller gain) an anonymous partner. For the second question, schizophrenia patients and demographically similar controls were tested across a number of cognitive control, visual integration and memory domains and the relationships of these domains.
Results: Patients performance on the Trust Game, as well as persecuted MZ twins, showed an adequate capacity in the domain of Understanding Mental States, in so far as they were able to model their partners' motivations during low risk trials. However more persecuted individuals showed a specific abnormality in decision making as risk increased, but only in trials when a human partner, not a coin flip, decided the outcome. The findings also reflect a broad generalized impairment even when examining specific deficits.
Conclusion: The patterns of behavior associated with persecutory ideation do not appear to map clearly on to constructs in either the Systems of Social Processing nor the Negative Valence domains. This suggests that top-down mapping from phenomenology to constructs could provide an important supplement to be able to account for important symptoms. In addition, an observation of a general negative manifold associated with psychotic illnesses suggests that recognizing the links between various constructs will be an important future direction for bridging from constructs to symptoms. One approach to this challenge, *reliability engineering*, which is the applied mathematical study of how things fall apart, suggests how to capture these disparate phenomena.
ID: 2117737

PHARMACOLOGICAL AND PSYCHOSOCIAL STRATEGIES FOR IMPROVING SOCIAL COGNITION

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Background: Individuals with schizophrenia commonly have impairments in social cognition. Because these impairments are related to functional outcome, recent attention has focused on treatment strategies for improving social cognition. Studies of training interventions found that different approaches are effective for improving social cue detection particularly emotion recognition. However, these approaches were less effective for processes that require mentalizing. In a previously presented study at ICOSR we found that intranasal oxytocin (OT) facilitated the learning of empathic accuracy. More recent work which will be presented in this symposium focused on the development of paradigms to indicate targt engagment by OT.
Methods: 27 males with schizophrenia participated in a 6-week (12-session) course of Social Cognitive Skills Training (SCST) that focused on 3 areas: 1. Facial Affect Recognition; 2. Recognizing non-verbal gestures and vocal cues; 3. Empathy. Subjects were randomly assigned to receive either intranasal OT (40 IU) or placebo 30 minutes prior to each session. Subjects were assessed at baseline, one week following the final training session and one month later.). In a subsequent study, we explored two putative measures of target engagement by OT: pupil dilation during an emotion recognition task and EEG mu suppression while observing biological motion. For this study, 13 subjects received a single dose of 40 IU of OT or placebo separated by one week in randomized order.
Results: On social cognitive tests, subjects receiving OT demonstrated significantly greater improvements on the Empathic Accuracy Test than those receiving placebo (p=.03, d=.92 post-treatment and p=.03, d=.98 at 1 month follow-up). We also found that OT administration in a single dose affected our proposed paradigms for target engagment: pupil dilation and mu suppression.
Conclusion: OT may be an effective medication for facilitating the learning of higher level inferential social cognition processes such as empathy. Promising indicators of target engagment by OT may advance our understanding of its mechanism of action.
ID: 2089530

EFFECTS OF ADULT AND NEONATAL PHENCYCLIDINE TREATMENT ON REWARD PROCESSES IN RATS

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Background: The negative symptoms of schizophrenia reflect reward and motivational deficits that can be quantified in non-human subjects using established procedures. The induction of these deficits involves manipulations that, by definition, involve a hypothesis about the neuropathology that leads to negative symptoms. N-methyl-D-aspartate (NMDA) receptor dysfunction is such a neuropathology. Consistent with this notion, administration of the NMDA receptor antagonist phencyclidine (PCP) induced schizophrenia-like symptoms in healthy human and exacerbated symptoms in schizophrenia patients. We explored whether acute, subchronic or chronic PCP administration in adulthood would induce reward and motivational deficits in rats. Further, based on the hypothesis that schizophrenia is a neurodevelopmental disorder, we explored whether neonatal PCPwould result in deficits in the ability to update reward value representations. The ability to update representations of reward value and accordingly adjust behavior is required to maintain goal-directed behavior.
Methods: To assess brain reward function the intracranial self-stimulation (ICSS) procedure was used that provides reward thresholds a reward in rats. Reward value representation was assessed in the probabilistic reversal learning procedure in rats.
Results: Chronic or subchronic PCP in adulthood did not induce reward deficits in rats, as assessed by ICSS thresholds. Nevertheless, these treatments disrupted performance in the ICSS procedure and the 5-choice serial reaction time task in a manner that suggests attentional deficits, slowing in cognitive processing and inability to inhibit inappropriate responding. PCP treatment in adulthood induced reward deficits only during withdrawal from chronic PCP, suggesting that chronic dysfunction of glutamate transmission is required to induce reward deficits in adulthood. Neonatal PCP impaired performance in the probabilistic reversal learning task in adulthood reflected in fewer completed changes in behavior to earn rewards and a reduction in Win-Stay behavior.
Conclusion: Disrupting NMDA receptor transmission in adulthood inrats disrupts cognitive and attentional performance and disinhibits inappropriate responding. Disruption of NMDA transmission in neonatal rats induced deficits in reward value representation. These findings implicate disrupted NMDA receptor function during neurodevelopment as a mechanism for the emergence of negative symptoms of schizophrenia in adulthood.
ID: 2117990

THE EFFECTS OF THE DOPAMINE D_2-FAMILY RECEPTOR PARTIAL AGONISTS, CARIPRAZINE AND ARIPIPRAZOLE, ON PCP-INDUCED DEFICITS ON ATTENTION ASSESSED IN THE 5-CHOICE SERIAL REACTION TIME TASK

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Background: Attention deficits are a hallmark of schizophrenia. The 5-choice serial reaction time task (5-CSRTT) has high construct validity for assessing attentional processing in animals. NMDA receptor hypofunction may play a central role in the pathophysiology of schizophrenia. NMDA receptor antagonists (eg, phencyclidine [PCP]) can disrupt 5-CSRTT performance enabling the investigation of attentional deficits. These deficits are reversible by clozapine suggesting that this model can assess novel treatments that may attenuate schizophrenia-associated attentional deficits. This study evaluated cariprazine, a D_3-preferring D_3/D_2 partial agonist antipsychotic in the 5-CSRTT.
Methods: Wistar rats were trained to detect a 1 s stimulus in the 5-CSRTT. Animals were administered PCP (2 mg/kg, SC) and 5-CSRTT performance was assessed. For the next 3 days animals were then administered either vehicle (2% Tween80), cariprazine (0.03, 0.1, or 0.3 mg/kg, PO) or aripiprazole (1, 3, or 10 mg/kg, PO) 60 min before 5-CSRTT testing. After 30 min, all rats were administered PCP (2 mg/kg, SC) and 5-CSRTT testing was initiated 30 min later. Baseline was calculated by averaging the 4 days preceding PCP treatment; treatment effects were calculated by averaging the last 3 days of performance.
Results: PCP increased incorrect ($P<.01$), premature ($P<.05$) and timeout responses ($P<.01$). Low-dose cariprazine (0.03 mg/kg) selectively attenuated PCP-induced 5-CSRTT impairments. Higher doses of cariprazine (0.1, 0.3 mg/kg) induced nonspecific response suppression (eg, reduced correct responding, trials completed, and increased omissions; $P<.01$). PCP-induced 5-CSRTT disruptions were attenuated by aripiprazole (1, 10 mg/kg) but not 3 mg/kg aripiprazole. Response suppression similar to high-dose cariprazine was associated with all aripiprazole doses tested (1–10 mg/kg).
Conclusion: These results indicate that cariprazine and aripiprazole show dose-sensitive effects in attenuating PCP-induced impairment in the 5-CSRTT. Both compounds likely induced nonspecific effects at the highest doses tested. However, at the lower doses tested, there were clear indications that cariprazine reversed inappropriate responses induced by PCP more selectively than aripiprazole. Aripiprazole, at all doses tested, may impair selective attention resulting in reduced stimulus detection. Cariprazine may attenuate selective aspects of attentional and perhaps other cognitive deficits characteristic of schizophrenia.
ID: 2085784

CHARACTERIZING LARGE, RARE COPY NUMBER DELETIONS IN SCHIZOPHRENIA: A CLINICAL, COGNITIVE, AND NEUROIMAGING STUDY

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Background: Large, rare copy number deletions are associated with risk for schizophrenia. However, little is known about the phenotypic differences associated. Schizophrenia is a heterogenous disorder and subtyping at the clinical, cognitive, and neuroimaging level may assist with both understanding the aetiology of disease and aid treatment efforts.
Methods: Data was collected across a wide range of variables. Clinical data from 629 SZ patients, including 60 with large, rare deletions; A broad neuropsychological battery on 81 SZ patients including 17 with large, rare deletions and 50 age and sex matched healthy controls (HCs); Neuroimaging data including voxel-based morphometry, diffusion-tensor imaging on 29 SZ patients including 9 with large, rare deletions and 17 age and sex matched HCs; functional MRI data whilst completing a theory of mind (ToM) task was collected for 29 SZ patients including 9 with large, rare deletions.
Results: Compared with patients not carrying large, rare deletions, patients with large, rare deletions had less comorbid cannabis abuse and a later age at onset.They had reduced general cognitive ability and further deficits on measures of word fluency, language, and decision-making. ToM performance was comparable but network differences were identified in the perigenual anterior cingulate cortex, ventromedial prefrontal cortex, and lingual gyrus. Grey matter volumes were larger in clusters with peaks in the cerebellum bilaterally, left hippocampus, and right rectal gyrus. Increased white-matter integrity was located in the body and genu of the corpus callosum. Grey and white matter profiles were intermediate to those found in healthy controls and patients without large, rare deletions.
Conclusion: Large, rare deletions are associated with clinical, cognitive, and brain structural and functional differences. Future research should aim to increase sample sizes in the cogntive and neuroimaging doamins, but evidence from the current study suggest that clinical, cognitive, and structural neuroimaging variables may prove fruitful in understanding the subtype of schizophrenia patients who carry large, rare copy number deletions.
ID: 2115023

EFFECTS OF COGNITIVE REHABILITATION USING ORIGINAL COMPUTER SOFTWARE IN SCHIZOPHRENIA: A RANDOMIZED CONTROLLED TRIAL

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Background: Neurocognitive deficits in schizophrenia are among the strongest predictors of social outcomes. Therefore, methods to improve neurocognitive impairments through cognitive rehabilitation are of important research interest. So we have developed the original computer software which were added the auditory tasks to visual tasks, referring to COGPACK which provided practice across a broad range of cognitive functioning, including psychomotor speed, attention, memory, executive functions, and fluency. This study examined whether cognitive rehabilitation using original computer software is more effective than the standard treatment in both cognitive and social functioning.
Methods: Twenty-four outpatients with schizophrenia in 4 sites were randomized to either a cognitive rehabilitation group (CRG) or wait-list control group (CG). Subjects were engaged in 2 sessions of the cognitive

training per week for 12 weeks and took part in 1 session of bridging group per week for 12 weeks. Psychiatric symptoms, cognitive functioning and social functioning assessments were evaluated at baseline and at 12 weeks.
Results: After 12 weeks intervention, cognitive functioning and social functioning were improved, but not significantly in the CRG as compared with the CG.
Conclusion: The number of participants might not be enough to reach significance level. We are scheduled to examine the effect of the software, examining a greater number of subjects which is assumed to be a total of at least 32 participants calculated statistically using our previous efficacy study of CogPack at announcement date.
ID: 2087154

EVALUATING ENDOPHENOTYPES ACROSS AND WITHIN THE SCHIZOPHRENIA-SPECTRUM

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Background: There has been considerable research on endophenotypes within the context of the schizophrenia spectrum, notably in terms of patients, relatives of patients and also schizotypy - defined as the personality organization underlying risk for schizophrenia. While a variety of endophenotypes are gaining empirical support, the specificity of these endophenotypes to the schizophrenia spectrum is not fully clear.
Methods: In this presentation, I will present a systematic research program on visual backward masking that shows a high specificity to the schizophrenia spectrum.
Results: Deficits on visual backward masking are observed across the schizophrenia-spectrum, notably in patients, their relatives, off-spring of patients and also in individuals high in schizotypy. Moreover, the deficits are absent in patients with major depression as well as in patients with previous drug dependence. Additional data will be presented suggesting that visual backward masking deficits are associated with a specific facet of schizophrenia - notably involving cognitive disorganization, and are relatively unrelated to positive or negative schizophrenia-spectrum symptoms and traits.
Conclusion: The present findings highlight the importance of examining the specificity of endophenotypes both across and within traditionally-defined disorders
ID: 2117359

LONGITUDINAL DECLINE IN COGNITION IN HSV-1 EXPOSED SCHIZOPHRENIA PATIENTS AND CONTROLS

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Background: Herpes Simplex virus, type 1 (HSV-1) produces lytic mucosal lesions, and rarely, encephalitis. It invariably initiates latent infection in sensory ganglia thus enabling persistent, lifelong infection. Though definitive evidence of latent infection in the brain is lacking, exposure untraceable to encephalitis has been repeatedly associated with impaired working memory and executive functions, particularly among schizophrenia patients, in cross-sectional studies. Longitudinal studies would enable more definitive conclusions of causality - one US study indicates temporal cognitive decline in HSV-1 exposed SZ cases.
Methods: Indian participants with or without schizophrenia (SZ, DSM IV criteria) were assessed for HSV-1 exposure using serological assays for HSV-1 IgG antibodies. Cognitive performance was assessed using the Penn computerized neurocognitive battery (CNB, 8 cognitive domains, assessed for accuracy/ speed). All participants were re-assessed after 1–2 years.
Results: The overall exposure rate was 61.5%, with non-significant HSV-1 exposure differences between persons with/without SZ (total N=226, SZ, N = 138, non-SZ, N= 88). Following imputations for missing data using multiple iterations, we used the imputed datasets for generalized linear model. At baseline, three cognitive domains showed nominally significant impairment in HSV-1 exposed individuals co-varying with SZ diagnostic status, sex and age: spatial memory (B= -0.26, p=0.029), spatial ability (B= -0.20, p=0.046) and emotion (B= -0.26, p=0.025). Next, with change in performance between baseline and follow-up on domain scores as the outcome measure, we evaluated HSV-1 exposure, co-varying with SZ diagnosis, sex, age, time interval between tests and the baseline score. Two cognitive domains showed significant impairment in HSV-1 exposed persons: abstraction and mental flexibility (B= -0.24, p=0.011) and emotion (B= -0.24, p=0.014).
Conclusion: Certain cognitive domains decline over time in HSV-1 exposed adults irrespective of SZ diagnosis.
ID: 2110566

EMOTION REGULATION AND DELUSIONS: HOW EMOTION REGULATION AND NEGATIVE AFFECT INFLUENCE THE OCCURRENCE AND INTENSITY OF DELUSIONS.

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Background: In accordance with the vulnerability-stress model, risk factors for the occurrence of psychopathological symptoms have been investigated: Negative affect and the use of maladaptive emotion regulation strategies increased the risk for subsequent delusional moments whereas stable self-esteem reduces the occurrence of delusional moments. Hence the present study explores whether negative affect, self-esteem and the use of emotion regulation strategies influence the occurrence of delusions in healthy people (n = 40) and patients with delusional thoughts (n = 2, planned 40).
Methods: Data was collected with the Experience Sampling Method (ESM), a structured diary technique which has allows the assessment of experiences in daily life and is proved to be highly ecologically valid. For six days participants answered questions on an IPod about psychopathological symptoms, mood-states, use of emotion regulation strategies and self-evaluation (self-esteem, self-acceptance and self-stigmatisation) ten times a day within a random interval of 80 minutes. Inclusion criterion for the patients is the occurrence of delusional thoughts during the last two weeks.
Results: Multi-level linear regression models were estimated to examine the associations between negative affect, emotion regulation strategies and delusional thoughts. In general, persons reported more severe delusions symptoms if they experienced negative emotions. On the contrary, when people reported positive emotions and a high self-esteem they experienced less delusional symptoms. Moreover, delusions were more severe the more maladaptive emotion regulation strategies were reported.
Conclusion: In order to reduce delusional symptoms in patients with psychosis it might be useful to focus more closely on the promotion of positive affect in daily life, the stabilisation of self-esteem and the improvement of their emotion regulation strategies to reduce negative emotions.
ID: 2095134

THE RELATIONSHIP BETWEEN SOCIAL SKILLS AND EPISODIC MEMORY IN PATIENTS WITH SCHIZOPHRENIA

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Background: Schizophrenia patients performed significantly worse than controls on measures to assess social skills and episodic memory.The aim of this study was to evaluate the association between social abilities and episodic memory in patients with schizophrenia.
Methods: A group of 17 outpatients with schizophrenia according to the DSM-IV TR and evaluated by the PANSS were compared with 31 healthy volunteers, with no personal or family history of psychiatric disorders All participants had IQ > = 80 (WASI). All subjects were evaluated using a self-report questionnaire, the Brazilian Social Skills Inventory (SSI-Del-Prette) and The Logical Memory (WMS-III).
Results: As compared with controls, patients with schizophrenia had lower IQ (p=0.002), lower IHS scores in the following domains: self-affirmation and expression of positive affect, (p=0.046), conversational skills/social self-confidence (p< 0.001) and social openness to new people/situations (p<0.001). No difference were found in terms of ability to control aggressiveness, anger or anxiety in the case of aversive stimulus (p=0.579). We found no correlation between IQ and measures of social skills, but there were negative correlations between conversational and social self-confidence skills and the following subscales of the PANSS: Negative (- 0.530, p= 0.029), General (- 0.637, p=0.006) and Total (- 0.127, p=0.002).
Patients also showed significant impairments relative to controls in short and long episodic memory (p< 0.001; p= 0.003 respectively) as measured by Logical Memory subtest (WMS-III). There was a positive correlation between negative PANSS and immediate logical memory (- 0.503, p=0.04).
Both groups showed significant and positive correlation between IQ and logical memory, immediate recall (0.554, p=0.03) and delayed recall (0.643, p=0.007). Finally, there were significant positive correlations between logical memory, immediate recall (0.547, p=0.001) and delayed recall (0.397, p=0.005) with conversational and social self-confidence skills.
Conclusion: Poor social skills and deficit in verbal memory are core characteristics of schizophrenia and they can be considered as one of the key feature. The present data strongly support the critical role of neurocognitive factors, such as episodic memory, in recovery of work functioning in schizophrenia.
ID: 2086460

COGNITIVE PERFORMANCE DURING THE FIRST YEAR OF TREATMENT IN FIRST-EPISODE SCHIZOPHRENIA: A CASE-CONTROL STUDY

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Background: Several questions remain unanswered regarding the magnitude and time course of cognitive improvement in response to antipsychotic treatment. The purpose of this study was to assess changes in cognitive performance in antipsychotic naïve or minimally medicated patients with first-episode schizophrenia during the first 12 months of treatment, in a case-control design. Patients were treated according to a fixed protocol with flupenthixol decanoate depot injection, according to a standard algorithm. The primary outcome measure was change in MCCB composite score over 12 months.
Methods: The sample comprised 92 patients and 100 healthy controls matched for age, sex, ethnicity and educational status. Cognitive function was assessed by means of the MATRICS Cognitive Consensus Battery (MCCB). Clinical outcomes were measured with the Positive and Negative Syndrome Scale (PANSS), the Social and Occupational Functioning Assessment Scale (SOFAS), the Calgary Depression rating Scale for Schizophrenia (CDSS), the Birchwood Insight Scale (BIS), the World Health Organization Quality of Life Questionnaire-Brief Version (WHOQOL-BREF) and the Premorbid Adjustment Scale (PAS). We conducted Pearson correlational coefficient analyses to investigate relations between changes in MCCB scores and changes in psychopathology and clinical outcomes. To determine whether cognitive improvements were secondary to improvement in symptoms we did an analysis of covariance with MCCB Composite as dependent variable and PANSS Total as covariate.
Results: A mixed effects model identified a significant between group difference over time (p=<0.0001) for the MCCB composite score, with patients showing clear improvements from baseline to month 6 but not from month 6 to month 12, but remaining significantly lower than control scores. For the other MCCB domains there were group differences at adjusted significance level for attention and vigilance (p=<0.0001), visual learning (p=<0.0001), verbal learning (p=0.005), and working memory (p=<0.0001), but not for reasoning and problem solving (p=0.04), speed of processing (p=0.03), and social cognition (p=0.06). There were moderate correlations between change in MCCB composite score and change in symptomatology as assessed by PANSS factor-analysis derived domains.
Conclusion: Substantial improvements in cognitive function were observed over and above a practice effect, and were significantly correlated with improvements in psychopathology and functionality.
ID: 2092615

HOW DO TEMPORAL BASED HAPTIC DISTORTIONS IMPACT THE FEELING OF CONTROL IN PATIENTS WITH SCHIZOPHRENIA AND IN PATIENTS WITH BIPOLAR DISORDER?

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Background: Time disorders have been described in patients with schizophrenia at a clinical level. More recent studies show that patients are impaired in temporal processing (Lalanne et al, 2012, Schizophr Bull), especially when processing short asynchronies. We explore the hypothesis this makes patients vulnerable during motor action and impact their ability to feel in control. We focus on this question due to a possible impact on delusions of control, i.e. the attribution of one's own action to an external agent. A decreased feeling in control might weaken the sense of agency and pave the way for delusions.
Methods: We designed a new original paradigm based on pointing tasks using a robotic device that can record movement trajectory and create virtual surfaces by generating haptic feedbacks. Participants had to perform vertical pointings on a virtual surface without any visual feedback. In the first session, subjects realized a sequence of 15 pointing actions. During the sequence (6th to 9th action at random), the haptic feedback was slightly postponed in time by 15 ms subliminal distortions or 65 ms supraliminal distortions. The following pointings were realized by keeping the surface at the distorted level. This allowed us to evaluate the adaptation of the trajectory to the distortion, by measuring parameters reflecting the anticipation of the contact with the surface, i.e. the duration of the deceleration phase. In the second session, subjects executed sequences of

5 pointings where we introduced varying numbers of supraliminal or subliminal distortions. Subjects were asked to rate their subjective feeling of control after the sequence. In the last session we checked the ability to detect a distortion.
Results: The results indicate that with the exception of patients with bipolar disorder, patients with schizophrenia and controls adapt their movement efficiently following a supraliminal distortion. The feeling of control is altered in all groups following supraliminal temporal distortions. However, for subliminal distortions, the feeling in control is altered only in patients with schizophrenia.
Conclusion: These results are consistent with the hypothesis that abnormal sensitivity to short asynchronies in patients with schizophrenia could represent a vulnerability factor for the development of delusions of control.
ID: 2118406

IMPLICIT SELF-AGENCY PROCESSING IN SCHIZOPHRENIA PATIENTS AND UNAFFECTED SIBLINGS

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Background: Self-agency, i.e., the feeling that one causes their own actions and consequences of those actions, is disturbed in schizophrenia patients. They experience difficulties in distinguishing between own and other's actions, which is reflected in a variety of symptoms. Previously we showed that patients experience impairments in the implicit processes involved in self-agency experiences, indicating that when information about an outcome is implicitly (or outside awareness) available, the sense of agency is not enhanced, while in controls it is. Research suggests that individuals at genetic risk for psychosis also show disturbances in self-processes. Therefore, the current study investigates implicit self-agency processing in schizophrenia patients, unaffected siblings of patients and healthy controls.
Methods: A total of 54 patients, 19 unaffected (unrelated) siblings and 54 controls performed the 'Wheel of fortune task'. Participants believed that their action resulted in a specific outcome, while in reality the outcome was pre-programmed. Participants performed an action (button press) and indicated whether they thought they were the agent of the consequence (the location of a rotating square) of this action, rated on a 9-point scale. Outcomes were implicitly primed and these primes could either match or mismatch the actual outcome.
Results: A (trendlevel) significant matching effect was found in healthy controls and siblings ($p<0.01$, $\eta p\ 2=0.24$; $p=0.07$, $\eta p\ 2=0.17$, respectively), but not in patients ($p=0.32$, $\eta p\ 2=0.02$). Furthermore, we found a significant groupXmatching effect ($F(1,124)=3.30$, $p=0.04$). Follow-up analyses showed that healthy controls experienced more agency in the presence of a match as compared to a mismatch between prime and outcome, which was not the case in patients ($p=0.01$). This has been shown before in a smaller sample, which is included in the current sample. Interestingly, siblings scored in between patients and healthy controls but neither contrast reached significance ($p=0.28$ and $p=0.42$ respectively).
Conclusion: This study showed that healthy controls and siblings are able to use implicitly available information in the environment to establish a sense of agency, whereas schizophrenia patients do not. We provide suggestive evidence that people at increased risk for psychosis do not show disturbances in the implicit route to self-agency.
ID: 2090034

USE OF SIMULTANEOUS EYE-MOVEMENTS AND FMRI TO REVEAL SPECIFIC RELATIONAL MEMORY DEFICITS IN SCHIZOPHRENIA

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Background: Eye-movements can index memory, as participants increase viewing of changed portions of a remembered scene. We previously demonstrated that individuals with schizophrenia (SZ) increased viewing when individual items in the scenes changed (item-specific memory), but not when there were relational changes. Here, we adapted this paradigm for fMRI to test whether or not these specific relational memory deficits in SZ are related to reduced fronto-temporal activation.
Methods: 26 HC and 24 SZ participants studied from the UC Davis Early Psychosis Programs. fMRI was acquired on a 3 Tesla Siemens scanner, and eye movements were recorded during scanning using an ASL remote eye-tracker. Participants first studied a series of complex scenes and at test, they were shown unchanged versions of studied scenes, changed scenes with either item or relational changes, and novel scenes. Memory was assessed by comparing the proportion of time spent viewing the critical region of changed scenes, relative to time spent viewing comparable regions of unchanged scenes. fMRI preprocessing and statistical analyses were performed in FSL, contrasting changed scenes with unchanged scenes, and relational with item changes. A priori regions of interest included dorsolateral (DLPFC) and ventrolateral (VLPFC) prefrontal cortex, hippocampus (HI), perirhinal cortex (PRc), and parahippocampal cortex (PHc). Statistical analyses were performed with one- and two-sample t-tests, thresholded at $z=2.3$ ($p<.01$), cluster-corrected at $p<.05$.
Results: As previously, both groups showed eye-movement-based memory effects for item-specific changes, but only HC participants showed memory effects for relational changes. HCs also showed greater HI, PHC DLPFC, and VLPFC activation compared to people with SZ when correctly identifying relational changes. There were no fMRI group differences following an item-specific change.
Conclusion: Eye-movement and fMRI results support the conclusion that individuals with SZ have disproportionate memory impairments when they must recruit MTL and PFC memory networks in order to represent items in a spatial and relational context. In contrast, memory for specific item features appears to be a relative strength in people with SZ and may serve as a compensatory strategy that can be used to reduce the overall severity of memory dysfunction in the disorder.
ID: 2090442

CONVERGENT EVIDENCE FROM DEVELOPMENTAL NEUROPSYCHOLOGY AND NEUROIMAGING FOR THE ORIGINS OF THE WORKING MEMORY IMPAIRMENT IN SCHIZOPHRENIA

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Background: There is substantial neuropsychological decline in schizophrenia from the premorbid to the postonset period. While working memory is thought to represent a core cognitive deficit in schizophrenia, little is known about the extent and developmental progression of decline. Further,

the pathophysiological mechanisms that underlie early deficits in working memory remain unknown.
Methods: Participants were members of a representative birth cohort: Avon Longitudinal Study of Parents and Children (ALSPAC). Neuropsychological assessment of working memory was conducted at ages 4,5,8, and 20, when participants also took part in functional magnetic resonance imaging (fMRI) study using the N-BACK task, and psychotic experiences where assessed using a semi-structured interview.
Results: Children who developed psychotic experiences in adulthood showed no impairment in working memory at age 4. Decline in working memory began soon after (effect size of change at age 5= -0.14), and the impairment continued to increase up to age 20 (effect size of change at age 20= -0.33, $p<0.05$). Participants with psychotic experiences performed worse on the 2 and 3-back conditions, and this was also reflected in differences in the BOLD response in brain regions associated with phonological storage ($p<0.0001$).
Conclusion: These findings suggest that the origins of the working memory impairment in schizophrenia can potentially be traced back to early childhood (age 5). Neural circuitry involved in phonological storage provides an underlying physiological abnormality.
ID: 2118190

GENERALIZED AND SPECIFIC COGNITIVE DEFICITS ACROSS THE PSYCHOSIS SPECTRUM

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Background: A generalized cognitive impairment is understood to be a core feature of schizophrenia; whether this is apparent in related disorders, such as psychotic bipolar disorder, is of increased interest. Identifying specific deficits in discrete cognitive processes in the context of this broad impairment remains a major challenge. We summarize the cognitive findings from the Bipolar Schizophrenia Network on Intermediate Phenotypes (BSNIP) consortium, with emphasis on identifying proband and relative group deficits on specific tasks that persist after accounting for generalized impairment.
Methods: Probands with schizophrenia (Scz), schizoaffective disorder (SczA) and psychotic bipolar disorder (BP), their 1st-degree relatives, and controls completed the Brief Assessment of Cognition in Schizophrenia (BACS) battery as a measure of generalized neuropsychological functioning. Subjects also underwent testing with several tasks putatively assessing specific cognitive processes including: Antisaccade, Spatial Span, Penn Conditional Exclusion Test, Dot Pattern Expectancy, Stop Signal, and Penn Emotion Recognition.
Results: Among probands, effect size of deficits on specific tasks ranged from small (0.24) to large (.93). However, only Antisaccade error rate (Scz .72; SczA .51; BP .40) and regressive errors on the Conditional Exclusion Test (Scz .21; Scz-A .37; BP .27) remained impaired after accounting for BACS scores. Effects sizes of deficits were more modest among relatives (.25 to .52), with only Antisaccade error rate remaining impaired after accounting for BACS performance (Scz .27; SczA .40; BP .29).
Conclusion: Performance impairment on many cognitive tasks appears to result from the association with generalized deficit rather a cognitive process tapped by a particular paradigm. Assessing generalized impairment and putative specific cognitive processes concurrently is important to determine whether specific tasks uniquely measure disease or familial-risk effects rather than merely tracking the generalized deficit.
ID: 2109780

MULTIMODAL NEUROIMAGING ASSESSMENT OF MEMORY FUNCTION IN SCHIZOPHRENIA: AGE MATTERS

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Background: Memory impairments are associated with poorer functional outcomes and lower quality of life in schizophrenia. Some evidence suggests that these memory impairments are worse later in the illness, in older persons with schizophrenia, but little is known about the underlying neurobiology. The purpose of this project was to assess glutamate (Glu) with magnetic resonance spectroscopy (MRS), cerebral blood flow (rCBF) with arterial spin labeling (ASL), and functional connectivity with resting state fMRI and the relation to memory function in younger and older participants with schizophrenia. Regions involved in memory function, the medial temporal lobe (MTL) and the anterior cingulate (AC), were examined.
Methods: Seventy participants completed this study. MR scanning was conducted on a 3T Siemens Tim Trio equipped with a 32-channel head coil. Spectra were acquired from MTL and AC using a PRESS sequence (TR=2s,TE=30ms, NEX=256 (MTL) and 128 (AC)). rCBF data were acquired using a pCASL sequence (TR/TE=4000/16ms, # of slices=23, slice thickness=5mm, labeling offset=90mm, labeling duration 1.85s, post labeling delay=0.93s). Functional connectivity data were acquired using resting state fMRI for 8 minutes. Patients were evaluated for psychopathology and all participants completed tests of memory function.
Results: MTL glutamate was lower in older ($p = 0.02$) but not younger ($p=0.8$) participants with schizophrenia. rCBF was lower in older participants irrespective of diagnosis ($p < 0.05$) in the AC and MTL, and older participants with schizophrenia had the lowest rCBF. MTL functional connectivity was altered in schizophrenia irrespective of age. Importantly, poorer memory function was related to higher MTL glutamate ($p< 0.05$) and rCBF ($p<0.05$) in older participants with schizophrenia only. MTL functional connectivity was not related to memory function. These relationships were not observed in younger schizophrenia or healthy participants.
Conclusion: This is the first study to use multimodal neuroimaging study to study memory function in older and younger persons with schizophrenia. Older participants with schizophrenia were distinguished by lower MTL glutamate and rCBF, and poorer memory function. Compromised MTL glutamatergic and blood flow contributes to memory impairments later in the illness, in older persons with schizophrenia. Interventions to improve memory function should consider the differential underlying neurobiology accompanying aging/illness phases in schizophrenia.
ID: 2092858

HOW ARE NEUROCOGNITIVE DEFICITS ASSOCIATED WITH CLINICAL AND FUNCTIONAL OUTCOME IN EARLY ONSET SCHIZOPHRENIA PATIENTS?

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Background: A substantial proportion of patients suffering from schizophrenia exhibit a general cognitive impairment at illness onset. Neurocognitive impairment has been found to be more severe in early onset schizophrenia (EOS) patients than in adult onset patients (AOS). Approximately 5% of the schizophrenia population has an early onset (before 18). Adolescence is a period of multiple changes in the brain structures and brain connectivity, where undifferentiated systems develop into more specialized neural networks, and the efficiency of neurocognitive functions increases. However, the development of neurocognitive functions in EOS patients is understudied. To our knowledge only five longitudinal studies have been carried out. They have all used different test batteries. Further, how neurocognition is related to clinical variables like duration of untreated psychosis (DUP), symptoms, and relapses has barely been investigated in any of the five studies. The aim of the current study is to examine neurocognitive functions longitudinally in EOS patients and to investigate how neurocognition at baseline is related to clinical variables like DUP, relapses and symptoms.
Methods: Twenty patients with EOS and 41 healthy controls (HC) were tested with the MATRICS Cognitive Consensus Battery (MCCB) at baseline, after 1 year and 2 years. Mean age of the EOS group was 15.6 years. Mean duration of illness was 1.7 years at baseline.
Results: EOS had significantly lower scores than HC on all neurocognitive domains. A relative stable course of neurocognition was found, with a certain improvement in both EOS and HC on all measures, except for verbal learning. No relationship between DUP and any of the neurocognitive measures was found. Results showed a strong relationship between neurocognitive course and negative symptoms.
Conclusion: The present study confirms previous research on both first-episode and EOS samples: There is a great stability in neurocognitive functioning after illness onset. The lack of an association between DUP and the course of neurocognitive impairment weaken the neurotoxicity hypothesis. Further, a significant association between neurocognition and negative symptoms also confirms what has been found earlier in first-episode schizophrenia samples. To summarize, EOS seems to follow much of the same neurocognitive course and be related to the same clinical factors as schizophrenia patients with a later onset and thus confirm continuity between early onset and adult onset schizophrenia.
ID: 2088703

REWARD-GUIDED LEARNING AND DOPAMINE IN SCHIZOPHRENIA

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Background: Reward-guided learning is impaired in schizophrenia patients. Brain regions that receive input from dopamine neurons, e.g. the ventral striatum, code the expected value of rewards and also compute learning signals that compare delivered rewards with expected values, so-called reward prediction errors. Thus, elevated dopamine levels observed in schizophrenia may crucially contribute to a disruption of reward-guided learning.
Methods: During the anticipation and the delivery of rewards, schizophrenia patients show remarkable reductions of brain activation, in particular in ventral striatum (Juckel et al., 2006; Schlagenhauf et al., 2009; Heinz & Schlagenhauf, 2010). These activation patterns also show relationships with variability of symptom levels across nosological boundaries (Hagele et al., 2014). When studying the dynamic process of reward-guided learning in unmedicated schizophrenia patients, computational modeling enabled the identification of patients who were not able to adapt their behavior according to an accurate internal model of the learning task (Schlagenhauf et al., 2014).
Results: Patients who could adapt their behavior showed stronger prefrontal activation compared to patients who could not adapt their behavior but showed no difference compared to healthy controls. Most strikingly, all unmedicated patients were characterized by reduced ventral striatal reward prediction errors (Schlagenhauf et al., 2014). When using the same learning task during fMRI in combination with FDOPA PET, healthy controls showed an inverse correlation between ventral striatal presynaptic dopamine and ventral striatal reward prediction errors (Schlagenhauf et al., 2013); we have recently replicated this result (Deserno et al., under review).
Conclusion: These findings point towards neural correlates of impaired reward-guided learning in schizophrenia patients, in particular reward prediction errors in ventral striatum, that may result from elevated presynaptic dopamine levels. Computational modeling techniques appear a promising tool to dissect the heterogeneous entity schizophrenia into behaviorally and biologically characterized subgroups (Deserno et al., 2013).
ID: 2119129

DIFFERENTIAL RELATIONSHIP BETWEEN AGE AND FUNCTIONAL NETWORK INTEGRATION IN THE PREDICTION OF COGNITIVE ABILITY IN SCHIZOPHRENIA

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Background: Healthy aging is associated with a loss of functional integration between brain regions that support higher-order cognition, and these age-related alterations are associated with worse cognitive performance. Patients with schizophrenia reliably exhibit impairments in higher-order cognition which, in addition to shorter lifespan and other age-related conditions, have led some to hypothesize that schizophrenia is a disorder of "accelerated aging". In the current study, we aimed to test the hypothesis that schizophrenia is associated with a differential relationship between age and reductions in functional integration, which in turn are related to cognitive impairments.
Methods: 47 schizophrenia patients and 53 healthy controls completed ~60 minutes of functional neuroimaging, as well as five neuropsychological tasks measuring different cognitive domains. Graph theory was used to analyze the global and local efficiency of the whole brain, fronto-parietal network (FPN), cingulo-opercular network (CON), and default mode network (DMN) -- networks hypothesized to support higher-order cognition.
Results: Across all subjects, age significantly negatively predicted global and local efficiency of the whole brain, FPN, CON, and DMN (all p's<.001). However, a significant main effect of diagnosis and a significant diagnosis x age interaction was observed only for the CON (p's<.01), driven by a much stronger negative relationship between age and CON efficiency in schizophrenia than in healthy controls. Additionally, we found that the observed association between CON global efficiency and cognitive ability was significantly mediated by age for the schizophrenia group, but not for the healthy controls. Finally, we observed a significant reduction in local efficiency in older patients compared to older controls only within the CON, a relationship that trended for CON global efficiency.
Conclusion: Together, these findings provide evidence for a differential relationship between age and functional integration of a brain network that supports higher-order cognition in individuals with schizophrenia. Importantly, these findings suggest that the relationship between higher-order cognitive ability and functional integration of the CON is more strongly influenced by age in patients with schizophrenia, suggesting that normal aging processes that underlie cognitive decline in healthy individuals may be occurring earlier or more rapidly in schizophrenia.
ID: 2101291

COGNITIVE DEFICITS IN SCHIZOPHRENIA, BIPOLAR DISORDER AND THEIR FIRST-DEGREE RELATIVES

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Background: Cognitive deficits are a core feature of schizophrenia and bipolar disorder. There is significant phenomenological overlap between the two mental disorders, as well as evidence of shared genetic liability. This study explored the nature of impaired cognition across groups of illnesses and included first-degree biological relatives in order to determine whether cognitive deficits were shared in groups with heightened genetic liability for the two disorders. Findings have implications for understanding the shared and disorder-specific aspects of cognitive dysfunction in schizophrenia and bipolar disorder.
Methods: We recruited 564 subjects with schizophrenia (n=134), their relatives (n=113), bipolar disorder (n=74), their relatives (n=59), and community controls (n=184) from the Minneapolis Veterans Affairs Health Care System (VAHCS) and surrounding community. In the context of a larger family study, subjects completed a battery of clinical assessment and neuropsychological assessment using standard measures of intelligence, verbal memory, learning potential, verbal fluency, visual attention, task switching, executive function, and academic achievement.
Results: Preliminary group comparisons yielded evidence of the largest and most generalized cognitive deficits in schizophrenia probands, with relatives of schizophrenia patients and bipolar affective disorder probands exhibiting intermediate deficits on select cognitive measures. Additional contrasts will be carried out to fully delineate shared and disorder-specific aspects of cognitive deficits in schizophrenia and bipolar affective disorder.
Conclusion: Measures of cognitive function hold promise for examining the landscape of brain dysfunction in severe psychopathology because they can be experimentally assessed, are relatively stable, and are more proximal to neural functions than clinical symptoms. Preliminary findings are consistent with cognitive indices capturing not only variations in brain dysfunction related to severe psychopathology but also genetic risk for these conditions.
ID: 2119644

A REPORT ON MCCB: UPSA DOMAIN SCORE CORRELATIONS FROM CLINICAL TRIALS FOR COGNITIVE IMPAIRMENT ASSOCIATED WITH SCHIZOPHRENIA

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Background: Two tests commonly used in clinical trials to assess changes in cognition and cognitive functioning, respectively, in patients with schizophrenia are the MATRICS Consensus Cognitive Battery (MCCB) and University of California Performance-Based Skills Assessment-2 (UPSA-2). The MCCB contains ten tests covering seven cognitive domains while the UPSA-2 uses six role-play tests to evaluate cognitive functional capacity. Baseline correlations between the MCCB and UPSA are consistently reported to be ~0.60; however, correlations between specific MCCB domain scores and UPSA total scores have not been reported. This analysis evaluated baseline and change score correlations between the MCCB and UPSA-2 total and domain scores in two 12-week, Phase 2 clinical trials.
Methods: Two multicenter trials at 45 U.S. sites in stable subjects with schizophrenia receiving antipsychotics were conducted to investigate procognitive effects: Trial A (N=207) with the histamine-3 antagonist ABT-288, and Trial B (N=214) with the selective alpha-7 nicotinic acetylcholine agonist ABT-126. Each trial employed a placebo and two active dose groups. Eligibility criteria were consistent with MATRICS guidelines. The MCCB, the primary endpoint, was administered at screening, baseline, Week 6, and Week 12; while the UPSA-2, a secondary endpoint, was administered at baseline and Week 12. Data from the two studies were combined for these analyses.
Results: The overall correlation (r) between the MCCB and UPSA-2 total scores at baseline was 0.621 (n=411). The correlations between the MCCB domains and UPSA-2 total score were 0.465, 0459, 0.570, 0.265, 0.389, 0.404, and 0.426 for Speed of Processing, Verbal Learning, Working Memory, Reasoning and Problem Solving, Visual Learning, Attention/Vigilance, and Social Cognition, respectively. Change score correlation between MCCB composite and UPSA-2 total scores (baseline to Week 12) was 0.156 (N=325), while change score correlations between MCCB domains and UPSA-2 total scores ranged from -0.011 (Speed of Processing) to 0.139 (Attention/Vigilance). Correlations between MCCB domain and UPSA-2 domain scores ranged from 0.088 (MCCB Reasoning and Problem Solving with UPSA-2 Household Skills) to 0.503 (MCCB Working Memory with UPSA-2 Financial Skills).
Conclusion: While the overall correlation between MCCB and UPSA-2 total scores was strong, the individual MCCB domain scores correlated more weakly to the UPSA-2 total scores. The highest correlation was detected with Working Memory.
ID: 2076317

SINGLE-DOSE OXYTOCIN CHALLENGE TO PROBE THE REACTIVITY OF THE MIRROR NEURON SYSTEM

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Background: The socially relevant neural circuit, Mirror Neuron System (MNS) appears to be dysregulated in disorders with social deficits. We designed a study to investigate MNS' responsiveness in schizophrenia (SCZ) patients and Healthy Controls (HC) in response to the pharmacologic probe, oxytocin (OT). "Mu suppression" or desynchronization of 8-13Hz EEG oscillations to biological motion is an easily administered test of MNS engagement that has been used in both typical and clinical populations. OT was chosen due to its important effects on social behavior in mammals and previous reports of engaging the MNS.
Methods: The socially relevant neural circuit, Mirror Neuron System (MNS) appears to be dysregulated in disorders with social deficits. We designed a study to investigate MNS' responsiveness in schizophrenia (SCZ) patients and Healthy Controls (HC) in response to the pharmacologic probe, oxytocin (OT). "Mu suppression" or desynchronization of 8-13Hz EEG oscillations to biological motion is an easily administered test of MNS engagement that has been used in both typical and clinical populations. OT was chosen due to its important effects on social behavior in mammals and previous reports of engaging the MNS.
Results: RM-ANOVA revealed that HC had significantly greater MSSI than SCZ subjects (significant main effect of diagnostic group [$F(1, 28) = 4.3$, $p<0.05$]), irrespective of treatment or electrode site. There was also a non-significant trend of drug treatment [$F(2, 56) = 2.5$, $p=0.09$] revealed by a dose-dependent OT-induced increase in MSSI compared to placebo irrespective of diagnostic group or electrode site. Individual subject data showed a majority of subjects in both groups (HC: 92%; SCZ: 54%) responded to single dose OT in expected manner; Within the SCZ group 23% subjects showed no response.
Conclusion: The study is a first step in building a systematic paradigm to determine the utility of single-dose OT challenge to probe the reactivity of the MNS in SCZ patients. Just as blood culture sensitivity assays are conducted prior to starting antibiotic treatment, we sought to explore whether

MNS reactivity to OT may provide a measure of the remediation potential of this circuit prior to instituting treatment. The results suggest that single-dose OT increases information processing in the MNS in a majority of SCZ patients, but not all and that OT induced changes in MSSI can serve as a useful index to isolate the neural processing of social information.
ID: 2117901

A COMPUTATIONAL MODEL OF LOW AND HIGH LEVEL INFLUENCES ON VISUAL PERCEPTUAL ABNORMALITIES IN SCHIZOPHRENIA

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Background: Clarity regarding how low- and high-level modulatory influences contribute to the errant neural function in schizophrenia is critically important to designing and targeting interventions that effectively improve the lives of people with schizophrenia. Here we propose a quantitative model as a means of integrating findings across experiments in order to precisely describe low and high-level influences on perception.
Methods: Because schizophrenia is associated with visual misperceptions and hallucinations, and accurate grouping of visual elements is central to being able to perceive objects, we carried out a set of experiments that assessed the strength with which elements of a visual display would be grouped together. The experiments manipulated the probability of visual elements being grouped by adjusting the similarity (e.g., relative orientation and contrast) of stimuli. To additionally examine whether the quantitative model generalized to other disorders with psychotic symptoms and individuals who carry genetic liability for schizophrenia, we also studied bipolar affective disorder patients and first-degree biological relatives of individuals with schizophrenia. Participants completed several visual perceptual tasks (i.e., Tilt Illusion, Orientation Dependent Surround Suppression, Degraded-Stimulus CPT). A computational model derived from work by Schwartz and colleagues that included terms for divisive normalization and scene segmentation was used to predict performance from each group.
Results: Using this model to predict our pilot data we find that the parameters for control (CTRL) data could be manipulated ways to predict performance in people with schizophrenia (SZ). Estimates of the selectivity for grouping (likelihood of long-range modulations) were weaker and the strength of surround effect was higher for SZ patients. Additional model development will be presented considering data from individuals with bipolar affective disorder and first-degree biological relatives of people with schizophrenia.
Conclusion: A leading interpretation of the role of divisive normalization in visual information encoding is related to efficiency of neural processes: inhibition of similar signals results in a spatially decorrelated neural code that efficiently encodes information. Weak high-level grouping signals may fail to regulate low-level gain control mechanisms, creating inefficient or aberrant neural coding.
ID: 2119580

CONNECTIVITY PATTERNS DURING WORKING MEMORY DEFINE CLINICALLY DISTINCT SUBGROUPS OF SCHIZOPHRENIA

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Background: Contemporary pathophysiological theories of schizophrenia emphasise the role of abnormal long-range connectivity, which in turn may result from aberrant neuromodulatory control of synaptic plasticity. This presentation outlines a translational neuromodeling framework which aims at establishing "computational assays" for inferring subject-specific indices of connectivity, synaptic plasticity and neuromodulation.
Methods: We present an initial case study where we combined a variational Gaussian mixture model (GMM) with a simple three-region dynamic causal model (DCM), consisting of visual, parietal and prefrontal regions (Brodersen et al. 2014). The DCM was applied to working memory data from an fMRI task in 41 medicated patients with schizophrenia and 42 controls (data from Deserno et al. 2012), and the resulting maximum a posteriori estimates of connection strengths entered the variational GMM.
Results: Our procedure identified three subgroups of patients as the most plausible clustering solution (i.e., highest log evidence). These subgroups were distinguished by different visual-parietal-prefrontal connectivity patterns and specifically different modulation of prefrontal connections by working memory load. Notably, these three connectivity-defined subgroups show significant differences in negative symptoms, indicating that the model-based physiological partitioning relates to clinical symptomatology.
Conclusion: Clinically plausible subgroups of patients can be detected using a simple model of inter-regional connectivity. This motivates future studies in which we strive to overcome the present methodological limitations (coarse physiological interpretability of the model, cross-sectional investigation) by using a prospective design and more refined generative models of neuroimaging data.
ID: 2119173

UNSUPERVISED CLUSTERING ALGORITHM SHOWS 3 COGNITIVE CLUSTERS IN SCHIZOPHRENIA AND EGF SYSTEM SINGLE NUCLEOTIDE POLYMORPHISMS ASSOCIATE WITH MEMBERSHIP OF THESE CLUSTERS

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Background: Disaggregating clinical clusters such as cognitive performance within schizophrenia (SCZ) will assist in identifying pathological mechanisms and possible biomarkers and help devise appropriate treatments. Extensive data implicates the epidermal growth factor (EGF) system in SCZ and from our data we have proposed deficient EGF signalling is ameliorated by clozapine through EGF receptor transactivation in treatment resistance (TRS). We have previously shown that candidate SNPs within the EGF system associate with SCZ.
Methods: Clinical and cognitive data and DNA from participants with a diagnosis of DSM-IV SCZ (n=449) & healthy controls (HC) (n=637) were accessed from the Australian Schizophrenia Research Bank. Using an unsupervised clustering algorithm, Kohonen's Self Organising Map (SOM), cognitive performance was analysed based on WTAR, WASI, 5 RBANS domains, COWAT and LNS scores. Genotyping for 31 SNPs in the EGF system was performed using Multiplex and Taqman assays.

Results: The Kohonen's algorithm provided a 3 cluster solution. A MANCOVA was performed with 'age at onset of illness', 'age at assessment' and 'number of years of education (YoE)' as covariates. Cluster 1 was significantly different to HC only on the RBANS Immediate Memory domain; clusters 2 & 3 differed highly significantly ($p<0.001$) from HC on all scales. Multinomial regression indicated that EGFR SNPs rs845551, rs7787739, rs2072454, rs884225; NRG1 SNPs rs35753505, rs6994992 (HapICE SNPs), rs3924999; ERBB4 SNPs rs707284, rs839523 and BDNF SNP rs6265 (Val66Met) and YoE significantly associated with membership of different clusters. Interaction analysis showed the strongest association for alleles GG of rs845551 (EGFR A/G) and TT of rs35753505 (NRG C/T) (cluster 2>cluster 1>cluster 3; OR=1.58–4.35, $p<0.001$), and for alleles GG of rs845551 and CC of rs35753505 (cluster 1>cluster 2>cluster 3; OR=1.63–1.93, $p<0.001$).
Conclusion: These data demonstrate that cognitive performance appears to separate out SCZ patients into 3 clusters. Candidate SNPs in EGF system associate with SCZ and membership of cognitive clusters suggesting a functional involvement of the EGF in SCZ consistent with our hypothesis that deficient EGF signalling may underpin a more severe form of illness. This provides possible biomarkers that may predict which persons with SCZ are likely to be better functioning cognitively and which ones will not, enabling identification of discrete pathologic mechanisms and better treatments.
ID: 2118143

ALTERED ATTENTIONAL AND PERCEPTUAL PROCESSES AS INDEXED BY N170 DURING GAZE PERCEPTION IN SCHIZOPHRENIA: RELATIONSHIP WITH PERCEIVED THREAT AND PARANOID DELUSIONS

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Background: Using gaze information to orient attention and guide behavior is critical to social adaptation. Previous studies suggest that abnormal gaze perception in schizophrenia (SCZ) may lie in abnormal early attentional and perceptual processes, and may be related to paranoid symptoms. Using event-related brain potentials (ERP), this study investigated altered early attentional and perceptual processes during gaze perception and their relationship to paranoid delusions in SCZ.
Methods: Twenty-eight individuals with schizophrenia or schizoaffective disorder and 32 demographically matched healthy controls (HC) completed a gaze discrimination task with face stimuli varying in gaze direction (direct, averted), head orientation (forward, deviated) and emotion (neutral, fearful). ERPs were recorded during the task. Participants rated perceived threat for each face after the task.
Results: SCZ participants were as accurate as, though slower than, HC participants on the task. SCZ participants displayed enlarged N170 responses over the left hemisphere to averted gaze presented in fearful relative to neutral faces, indicating a heightened encoding sensitivity to faces signaling external threat. This abnormality was correlated with increased perceived threat and paranoid delusions. SCZ participants also showed a bilateral reduction of N170 modulation by head orientation (normally increased amplitude to deviated faces relative to forward faces), suggesting less integration of contextual cues of head orientation in gaze perception.
Conclusion: The psychophysiological deviations observed during gaze discrimination in SCZ underscore the role of early attentional and perceptual abnormalities in social information processing and paranoid symptoms in schizophrenia.
ID: 2079081

HISTORY OF CHILDHOOD PHYSICAL TRAUMA HAS A NEGATIVE IMPACT ON COGNITIVE FUNCTIONING IN INDIVIDUALS AT ULTRA HIGH RISK FOR PSYCHOSIS

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Background: In our previous studies we reported that there were more childhood trauma (CT, 1) and cognitive deficits (2) in UHR group. The aim of this study is to measure the relationship between CT and cognitive functioning in UHR group.
Methods: Sixty-four individuals at UHR for psychosis were applied a neurocgnitive battery assessing attention, processing speed, verbal learning and memory, working memory, interference inhibition and sustained attention. CT was assessed by short version of Childhood Trauma Questionnary (CTQ).
Results: We dychotomized the sample by using cut off scores for the existence of emotional, physical and sexual trauma, physical and emotional neglect. Those with history of physical trauma had worse performance on Digit Span-forward, Trail making B (time), Stroop test-difference between colour and word reading times, WCST-completed categories. Physical trauma scores were negatively correlated with WCST-completed categories, and physical neglect scores were negatively correlated with Digit span test-forward.
Conclusion: Our findings suggest that history of physical trauma has a negative impact on cognitive functioning in individuals at UHR for psychosis.
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ID: 2116229

MAGNETOENCEPHALOGRAPHY AS A TOOL IN COGNITIVE NEUROSCIENCE: A TRANSLATIONAL PERSPECTIVE

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Background: I will summarize our recent work with Magnetoencephalography (MEG) which has examined the role of neural oscillations during normal brain functioning as well as in the pathophysiology of schizophrenia.
Methods: Our studies in normal participants suggest that single-trial fluctuations of neural oscillations can be used to predict working memory capacity, highlighting the mechanistic contribution of rhythmic activity towards higher cognitive processes. Moreover, we have successfully applied MEG source-reconstruction techniques to assess phase-coupling between cortical gamma-band activity and thalamic alpha oscillations, highlight the suitability of MEG to examine cortical-subcortical interactions. In addition, we have carried out several studies which have examined the role of gamma-band oscillations and event-related fields (ERFs) in sensory processing in schizophrenia.
Results: These results highlight a pronounced impairment in high-frequency activity in both chronic and unmedicated patients as well as the potential contribution of impaired prediction processes as revealed by the analysis of the magnetic mismatch negativity field (MMF) towards perceptual impairments in the disorder. The pattern of dysfunctional gamma-band activity and aberrant ERF-responses in schizophrenia are consistent with the effects of ketamine in healthy volunteers, highlighting the central role of aberrant NMDA-receptor functioning for the understanding of abnormal circuit functioning in schizophrenia.

Conclusion: Our work highlights the importance of MEG as a tool to examine neural oscillations and ERF responses in schizophrenia and during normal brain functioning.
ID: 2117994

ABNORMALITIES IN THE ESTABLISHMENT OF FEELING OF SELF-AGENCY IN SCHIZOPHRENIA

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Background: People usually feel they cause their own actions and the consequences of those actions, also referred to as the experience of self-agency. Schizophrenia patients typically fail to experience agency over their own actions and exhibit difficulties in distinguishing their own actions from those of others (e.g., as in delusions of control). Normally, the experience of agency arises when the outcome of an action matches the outcome one had in mind before performing the action (Wegner, 2002). Hence, briefly presenting (i.e., priming) an outcome before it occurs enhances experienced self-agency (van der Weiden et al., 2013). Previously, we showed that such outcome-priming mainly enhances experienced self-agency when behavior is represented in terms of action-outcomes (rather than in terms of action-performance; van der Weiden et al., 2010). Also, we showed that patients are unaffected by outcome-primes (Renes et al., 2013). In the present study we tested whether patients' abnormalities in experiencing self-agency result from a failure to represent behavior in terms of action-outcomes.
Methods: 31 schizophrenia patients and 31 controls repeatedly performed an action (button press) and observed the resulting outcome (stop location of a moving square). After observing the outcome, they indicated to what extent they felt they (instead of the computer) caused the outcome on a 9-point scale. To manipulate experienced agency, a matching or mismatching outcome was primed before action performance. Behavior representation level was manipulated by instructing participants to focus on the outcome, or not.
Results: Controls experienced more agency over outcomes that matched versus mismatched the primed outcome, $F(1,30) = 6.57$, $p = 0.02$, $\eta p2 = 0.18$, while patients showed no such effect, $F < 1$. Outcome focus did not affect patients' experiences of agency, $F < 1$. Surprisingly, for controls the matching effect on self-agency disappeared when focusing on outcomes, $F(1,30) = 1.34$, $p = 0.26$, $\eta p2 = 0.04$.
Conclusion: These findings suggest that patients' abnormalities in experiencing self-agency cannot be explained by the level at which they represent their behavior. Perhaps it is not the focus on outcomes, but rather a more general failure to perceive causal relations between actions and outcomes that impedes normal agency processing (van der Weiden et al., 2011). Future research will further explore abnormalities in agency processing and address the potential consequences for social functioning in schizophrenia.
ID: 2085218

PATTERN SEPARATION DEFICIT IN SCHIZOPHRENIA

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Background: Subjects with schizophrenia show robust episodic memory deficits but their nature and neural underpinnings remain to be determined. Tamminga et al.'s (2010) hippocampus-based model of psychosis posits that schizophrenia patients show a deficit in dentate gyrus-dependent pattern separation, required for the formation of non-overlapping memory representations, and an increase in CA3/CA1-dependent pattern completion, required for associate retrieval based on partial information. Based on this model, we hypothesized that subjects with schizophrenia show pattern separation deficits compared with healthy controls.
Methods: Twenty-nine subjects with schizophrenia and 26 healthy volunteers performed the Mnemonic Similarity Task (MST; Stark and colleagues, 2007) during high-resolution imaging of the hippocampus. The MST is a continuous recognition task during which participants are shown novel, repeated, or similar (lure) objects and are asked to indicate whether the current object shown is "new", "old", or "similar" to any of the objects shown during the task. Pattern separation bias is computed as [p("Similar"[Lure] - p("Similar"[Foil]), which quantifies the extent to which items are successfully separated while correcting for response bias between groups. A group comparison of pattern separation bias was performed using a t-test.
Results: The subjects with schizophrenia did not differ in mean age ($p=0.45$) and sex distribution ($p=0.59$) compared with the healthy volunteers. Subjects with schizophrenia (mean=0.18, SD=0.20) had a significantly lower separation bias than healthy volunteers (mean=0.39, SD=0.19; $p<0.0004$).
Conclusion: Subjects with schizophrenia show a deficit in separation bias compared with healthy volunteers. This deficit may be at the core of their episodic memory deficits and provides cognitive neuroscience-based behavioral support for dentate gyrus dysfunction in schizophrenia.
ID: 2118977

MOTIVATIONAL DEFICITS IN SCHIZOPHRENIA AND THE REPRESENTATION OF VALUE: IMPLICATIONS FOR FUNCTIONAL OUTCOME

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Background: Evidence indicates that social cognitive processes may be less related to measures of cold cognition and more related to processes such as reward sensitivity and reinforcement learning (RL). Neural responses to rewards have been shown to relate to negative symptoms in schizophrenia (SZ), which correlate strongly with measures of functional outcome. Based on the established contribution of motivational deficits to functional outcome, we hypothesized that behavioral and neural measures of reward sensitivity and motivation might drive the relationship between social cognitive skill and functional outcome in SZ.
Methods: We administered multiple tasks of reward processing and RL to individuals with SZ or schizoaffective disorder, including a Sensory-specific Satiety (SSS) paradigm designed to assess the tendency to devalue food stimuli, on which subjects were fed to satiety. This involved feeding subjects 0.7-mm squirts of liquid foods (V8 juice and chocolate hazelnut drink), as well as a control solution, using syringes. In each of 2 sessions, subjects received 16 squirts of each rewarding food and 32 squirts of the control solution. In between the 2 sessions, each subject was instructed to drink one of the foods (determined through counterbalancing) until he/she felt "full, but not uncomfortable". Subjects rated each liquid 10 times (across the 2 sessions, at regular intervals),

from 0 to 100, on a Likert-type scale. The difference in across-session ratings changes between sated and unsated foods served as a measure of SSS.
Results: Mann-Whitney U-tests revealed group differences in SSS effects. Within-group tests revealed that controls showed an effect of satiety that was sensory-specific, whereas patients showed an effect of satiety that was not sensory-specific. Furthermore, magnitudes of SSS effects in patients correlated with SANS avolition scores and MATRICS Social Cognition domain scores, and were a strong predictor of employment status.
Conclusion: We observed systematic relationships between an experimental measure of the ability to flexibly and rapidly update representations of the value of food stimuli, in SZ, and standard measures of social cognitive skill and functional outcome. We argue that the ability to flexibly and rapidly update representations of the value of stimuli and actions figures critically in the adaptive motivation of goal-directed behavior, and functional outcome in patients, as a consequence.
Support: NIMH Grants R21 MH086739, R01 MH080066, K12 RR023250
ID: 2084092

STRATEGY TRAINING - ITS EFFECTS ON COGNITIVE AND FUNCTIONING OUTCOMES

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Background: Strategic remediation approaches highlight instruction and provide experience of evaluation of strategy efficiency during therapy which builds metacognitive knowledge and metacognitive regulation. Both aspects of metacognition are thought to be important to the transfer of skills to situations outside the remediation context. A recently developed computer approach - CIRCuiTS allows these strategies to be recorded as part of the training programme and we interrogate these data to answer questions relating to strategy use and perceived usefulness in relation to the outcomes in an RCT.
Methods: Strategy use data were extracted for 45 people with schizophrenia taking part in cognitive remediation trial using CIRCuiTS. Each task first prompted participants to consider a range of strategies and after completion prompted participants to rate their usefulness. All participants were assessed before and after the therapy with verbal and non-verbal measures of cognition and executive functions. Functional outcomes were also assessed. Using a median split participants were divided into improvers and "non-improvers" for each domain assessed.
Results: Overall participants attended an average of 28.8 (SD 6.9) sessions of CRT and completed 137.5 (SD 58.3) tasks. The average number of strategy used was 195.4 (SD184). Strategy use was, as expected, correlated with the number of sessions ($r=.53$, $p<.0001$) and tasks ($r=.41$, $p<.0001$). A comparison of strategy use between improvers and non-improvers revealed that people who improved on non-verbal executive function (i.e. WCST) had used more strategies during therapy ($F(1,39)=4.1$, $p<.05$; Improvers strategy average 238(SD120), non-improvers strategy average 164(112). There were no significant differences in strategy use for the other cognitive domains or for functional outcome.
Conclusion: This is the first report to systematically consider strategy use in the context of a cognitive remediation program. Strategy may be important to improve performance on certain cognitive tasks but strategic approach may also result in poorer performance on tasks where there is a strict time demand. In these tasks people may not have enough time to plan and use strategy effectively within constraints of the task. Strategy use does not seem to have an immediate effect on functional outcome but it is possible that functional improvement may require a longer time period to become evident.
ID: 2118270

THE VIROME OF INDIVIDUALS WITH SCHIZOPHRENIA

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Background: Mucosal sites such as the oropharynx contain a wide range of microorganisms, collectively designated as the microbiome. The microbiome can affect behavior through a number of neurobiological and immunological mechanisms relevant to the pathogenesis of schizophrenia. Most previous studies have focused on the bacterial components of the microbiome. However, the microbiome also includes viruses such as bacteriophages, which are viruses which infect bacteria and alter their metabolism and replication.
Methods: We employed metagenomic analysis to characterize bacteriophage genomes in the oral pharynx of 41 individuals with schizophrenia and 33 control individuals. This analysis was performed by the generation of more than 100,000,000 sequence reads from each sample and the mapping of these reads to databases.
Results: We identified 79 distinct bacteriophage sequences in the oropharyngeal samples. Of these, one bacteriophage genome, Lactobacillus phage phiadh, was found to be significantly different in individuals with schizophrenia ($p<0.00037$, $q<0.03$ adjusted for multiple comparisons). The differential levels of Lactobacillus phage phiadh remained significant when controlling for age, gender, race, socioeconomic status, or cigarette smoking (coefficient=2.0, $p<0.006$) and were correlated with the level of host bacterial DNA. Within the group of individuals with schizophrenia, the level of Lactobacillus phage phiadh was correlated with the prevalence of immunological disorders as well as with the administration of valproate, which has been shown in animal models to alter the microbiome
Conclusion: The bacteriophage composition of the oropharynx in individuals with schizophrenia differs from that of controls and may be related to co-morbid immunological abnormalities.
ID: 2114479

OLIGOPEPTIDASE ACTIVITY IN AN ANIMAL MODEL OF SCHIZOPHRENIA AND INSIGHTS INTO ITS CORRELATION WITH THE CLINICS

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Background: Schizophrenia (SCZ) is a severe chronic mental disease. Deficits in an operational measure of sensorimotor gating - the prepulse inhibition of startle (PPI) - are presented in psychiatric disorders such as SCZ and other mental disorders. Spontaneously hypertensive rats (SHRs) was characterized as an animal model to study some aspects of SCZ, including the sensorimotor gating abnormalities. SHRs present deficits in PPI specifically reverted by clozapine. However, classically the SHRs are used as an animal model for hypertension, with suggestive involvement of the renin-angiotensin system and its key enzyme, the angiotensin I-converting enzyme (ACE), for this phenotype. The main role of ACE is the conversion of the Ang I into Ang II, which has hypertensive activity. However, ACE also catalyzes the degradation of other oligopeptides, as neurotensin (NT), which was implicated in the pathophysiology of SCZ due to the potential antipsychotic activity. In a previous work, we showed a significant higher ACE activity in the plasma of SCZ patients compared to health control (HCs). We also

demonstrated that the ACE might be associated to cognitive deficits in SCZ using ACE transgenic mice. In this work, we investigated the ACE activity in plasma and several regions of SHRs brain, which were compared to control Wistar rats (WRs), aiming to evaluate the potential similarities between this animal model for SCZ and the human patients, and to explore the potential correlations between the brain and plasma activity levels.
Methods: ACE activity in the plasma and brain regions (cortex, hippocampus, striatum and nucleus accumbens) of males WRs and SHRs was measured using specific FRET substrate.
Results: In the same way as observed for the plasma of SCZ patients compared to HCs, a higher ACE activity in plasma and also in the cortex and hippocampus was observed in SHRs compared to WRs.
Conclusion: Higher ACE activity was observed in the plasma of both human SCZ patients and SHRs compared to their respective controls, suggesting a strong correspondence between humans and this specific SCZ animal model. Patients with hypertension were excluded in this analysis. SCZ patients and animal models under the treatment with the same antipsychotics are currently ongoing in our laboratory and they might bring some important information regarding the potential of this specific enzyme activity measurements as a biomarker of pharmacological interventions and treatment follow-up.Acknowledgement: FAPESP, CNPq and CAPES.
ID: 2107753

TARGETING DOPAMINE D1-RECEPTORS TO IMPROVE REWARD-ASSOCIATIVE LEARNING; IMPLICATIONS FOR TREATING NEGATIVE SYMPTOMS

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Background: Negative symptoms experienced by patients with schizophrenia are recognized as core to the disorder, predicting functional outcome. The variety of negative symptoms and their being measured using self-report and observer ratings have limited opportunities to identify their underlying mechanisms and develop targeted therapies. Recent evidence linking blunted responses after rewards to negative symptoms, however, has provided an opportunity to study mechanisms and treatment options. Using a probabilistic learning paradigm we can investigate learning in response to reward as well as to punishment. There are opportunities therefore, to examine mechanisms underlying this blunted reward-associative learning, and develop putative treatments. Striatal dopamine D1 receptors (DRD1) have been implicated in learning from positive rewards and it was hypothesized that targeting these receptors would enhance reward-associative learning.
Methods: We trained two groups of male C57BL/6JN mice (n=15 and 24) in a probabilistic reward learning task requiring responses to target vs. non-target stimuli rewarded and punished at an 80/20 and 20/80 ratio, respectively. Group 1 was treated with vehicle or one of three doses of amphetamine (AMP; 0.1, 0.3, or 1.0 mg/kg, ip) in a within-subjects design before testing. Group 2 was counter-balanced into two groups and treated with vehicle or the full dopamine D1 receptor agonist (+)-doxanthrine (DOX).
Results: AMP treatment improved probabilistic learning as measured by trials to criterion ($F(1,14) = 3.4$, $p<0.05$). AMP-induced improvement was based on enhancement of staying after being rewarded at the target stimulus (target win-stay; $F1,14) = 4.3$, $p<0.01$) without affecting non-target win-stay, nor target, non-target lose-shift, premature responses, or mean reward latency ($F<1$, ns). DOX improved probabilistic learning as measured by the total trials to criterion ($t(23)=2.3$, $p<0.05$). DOX did not significantly affect any other measure, however ($t<1$, ns), except lowering non-target win-stay ($t(23)=2.8$, $p<0.05$).
Conclusion: Thus, both direct (DOX) and indirect stimulation (AMP) of DRD1 improve probabilistic learning. Secondary analyses are consistent with this improvement being a result of altering post-rewarded decision-making behavior. It remains possible therefore, that a DRD1 agonist may improve reward-associative learning in patients with schizophrenia. Such enhancement could assist cognitive rehabilitation, and potentially reduce negative symptom severity.
ID: 2096147

SCHIZOPHRENIA PATIENTS EXHIBIT REVERSED TOPOGRAPHIC DISTRIBUTION PATTERNS OF MIDDLE-LATENCY SENSORY PROCESSING TO TARGET AND NON-TARGET TRIALS IN THE 5-CHOICE CONTINUOUS PERFORMANCE TEST

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Background: There is growing recognition that sensory processing abnormalities contribute to the widespread impairments in cognitive and psychosocial functioning in schizophrenia patients. Core aspects of early perceptual and attentional dysfunction are promising new treatment targets. The development of pro-cognitive therapeutics has been disappointing to date however, in part due to cognitive paradigms with limited cross-species translational validity. The 5-choice continuous performance test (5C-CPT) task was developed to address this limitation. Here, we determined whether patients with schizophrenia exhibit abnormalities in early visual sensory processing in the 5C-CPT.
Methods: Continuous EEG was recorded during 5C-CPT performance in 30 schizophrenia outpatients and 28 non-psychiatric comparison subjects. Consistent with previous ERP studies, centroids representing the amplitude weighted center of gravity of the positive area of the electrical field were calculated for each participant when responding to target and inhibiting responding to non-target stimuli. The centroid locations were quantified by a coordinate system resulting from the planar projection of the electrode array numbering from 1 to 10 in the anterior/posterior direction. Analyses were performed for only correct responses.
Results: Three ERP peaks were identified for each condition representing early, middle, and later stages of sensory and cognitive information processing. Across both trial types, no group or group x centroid interactions were seen in the early or late windows of visual processing. In contrast, group by centroid interactions were detected for middle-latency peaks in target ($p<0.05$) and non-target ($p<0.05$) 150–250 ms trials. Post hoc analyses revealed that schizophrenia patients had significant amplitude reductions over frontal regions, plus significantly larger amplitude responses over parietal and occipital regions.
Conclusion: In behaviorally-matched trials, a significant double-dissociation was observed in the topographic distribution of middle-latency visual processing in patients with schizophrenia. Future planned analyses will examine the extent to which sensory processing abnormalities contribute to impaired attentional functioning concurrently assessed during the 5C-CPT. Well-validated, cross-species cognitive tests such as the 5C-CPT will allow for a better understanding of impaired cognition in schizophrenia and the development of ERP biomarkers for assessing pro-cognitive therapeutics.
ID: 2119253

ADULT-ONSET MICRORNA DEPLETION DISRUPTS THALAMIC INPUTS TO THE AUDITORY CORTEX IN SCHIZOPHRENIA MODELS

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Background: Schizophrenia (SCZ) is one of the most debilitating and severe forms of mental illness. The positive symptoms of SCZ, namely auditory hallucinations, are among the most enigmatic. Antipsychotic agents acting via D2 dopamine receptors (DRD2s) alleviate auditory hallucinations in most patients, but they are almost ineffective at treating other symptoms (e.g., cognitive deficits, dampened emotions, and social withdrawal). Although the beneficial effect of antipsychotics on positive symptoms is obvious, the deficient neural circuits underlying these symptoms and the mechanisms of selective sensitivity of these faulty circuits to antipsychotics are unknown.
Methods: We used single-cell electrophysiological recordings, 2-photon imaging, and optogenetics to screen several neuronal projections in the auditory cortex (ACx) of murine models of 22q11 deletion syndrome (22q11DS), a genetic disorder associated with SCZ, and identified a specific and age-dependent disruption of synaptic transmission at thalamocortical (TC) projections.
Results: The TC deficit was caused by deficient glutamate release because of the aberrant elevation of Drd2s in thalamic relay neurons. The increased expression of Drd2s rendered mutant TC projections abnormally sensitive to antipsychotics, which rescued the TC deficit in 22q11DS mice. Also, DRD2s were upregulated in postmortem samples of the thalamus of SCZ patients, suggesting a common pathogenic mechanism in 22q11DS and SCZ. A functional screen of individual genes from the 22q11-deletion region revealed that haploinsufficiency of the microRNA (miRNA)-processing gene Dgcr8 underlies Drd2 elevation and causes TC disruption and aberrant sensitivity of TC projections to antipsychotics.
Conclusion: Our findings support that Dgcr8-miRNA-DRD2-dependent disruption of TC synaptic transmission is the pathogenic event underlying the positive symptoms of SCZ.
ID: 2115533

THEORY OF MIND DEFICITS IN YOUTH AT CLINICAL HIGH RISK OF PSYCHOSIS

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Background: The frequency of putatively prodromal psychosis in Chinese clinical populations peaks in adolescence and early adulthood (16–21 years old). These youths often express contradictions between their inferences about others' intentions (ToM, the cognitive ability to understand the mental state of others) and realistic expectations based on current and past experience. The goal of this study was to investigate the characteristics of ToM performance in youths at clinical high-risk (CHR) of psychosis.
Methods: To assess prodromal psychosis, we used the Structured Interview for Prodromal Syndromes (SIPS) that aims to identify subjects who are at high clinical risk of psychosis. The Presence of Psychosis Scale (POPS) of the SIPS/SOPS was used to determine conversion into psychosis. The Reading Mind in Eyes Task (RMET), including own-race and other-race eyes, was administered to 40 CHR youths; 42 age-, gender-, and education-matched healthy controls (HC); and 62 adult patients with schizophrenia (SZ). Nine-month follow-up data were collected from 31 CHR subjects, of whom 7 (22.6%) had made the transition to psychosis.
Results: CHR youths showed significant impairment in RMET performance compared to HC youths, but performed better than SZ patients. Moreover, they were significantly slower than HC youths in responding to the eye-task, with a response time similar to that of SZ patients. In particular, they had significantly poorer accuracy in interpreting positive and neutral eye expressions compared to the HC group, but not in interpreting negative eye expressions. The results from the own-race eyes in the Chinese sample are comparable to those of the other-race eyes. Preliminarily follow-up data showed a trend toward significance ($p=0.079$) for eye-task performance between those who converted to psychosis and those who did not.
Conclusion: Our data contribute to the evidence that being able to correctly interpret the mental state of others from their eyes is impaired in youths with prodromal psychotic syndromes. This study provides the first data showing that CHR youths have more difficulty in decoding the positive and neutral mental states of others, compared to negative states. According to these findings, ToM enhancement would be expected to help youths who are suffering from social interaction impairments, and even prevent the further progress toward psychosis and the serious negative outcomes that arise during the prodromal phase.
ID: 2086210

Diagnosis; Phenomenology

COMPARISON OF THE POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS) FACTOR STRUCTURE IN PATIENTS WITH REFRACTORY VERSUS NON REFRACTORY SCHIZOPHRENIA

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Background: The Positive and Negative Syndrome Scale (PANSS) is the most widely used scale for the evaluation of symptom severity in schizophrenia. Several reviews of PANSS Factor Analyses (FA) showed that the best solution is the five factor model (positive, negative, cognitive, anxiety-depression and excitement) but it is unclear whether the severity of the disorder has an influence in such factor structure. In patients with Refractory Schizophrenia (RS), which are considered to be the most severe cases, there is only one study of PANSS factors in this population. The aim of the present study is to investigate by FA whether the PANSS factor structure differs in patients with RS as compared with non-refractory schizophrenia (NRS).

Psychopathological Dimensions of Schizophrenia in Refractory (RS) and Non Refractory patients (NRS)

Dimension	RS	NRS
Positive	Present	Present
Negative	Present	Present
Cognitive	Present	Absent
Depression	Absent	Present
Anxiety	Present	Present
Motor	Absent	Present

RS= Patients with Refractory Schizophrenia
NRS= Patients with Non Refractory Schizophrenia

Methods: We conducted an exploratory FA of 291 patients with schizophrenia (150 RS and 141 NRS). Two principal component of FA with Varimax rotation were applied to the complete items set of the PANSS.
Results: The sample was composed of 66% males, mean age of 35.54 (sd: 9.14), 10.10 (3.34) years of schooling, age of onset of 18.96 years old(6.54) and duration of illness of 16.46 (8.58). RS patients had a total PANSS of 73.8 (20.82) with subscales: Positive of 18.64 (6.89), Negative 21.21 (7.54), General Psychopathology of 33.23 (9.38). NRS patients had a total PANSS of 70.33 (25.54) with subscales: Positive 17.63 (7.63), Negative 20.09 (8.49), General Psychopathology 33.11 (11.71). FA of patients with NRS yielded a model which accounted for 66.64% of the total variance with 6 factors: Negative, Positive, Excitement, Depression, Anxiety and Motor Component. In RS a five factor solution was found (57.16% of the total variance): Negative, Positive, Excitement, Cognitive/ Disorganization and Anxiety.
Conclusion: Differences between the factorial structures of PANSS in patients with RS (5 dimensions) as compared with NRS (6 dimensions) were found, with both groups sharing four common factors: Positive, Negative, Excitment and Anxiety.
ID: 2109884

THE VALIDITY RESULTS OF THE STANDARD FOR CLINICIANS' INTERVIEW IN PSYCHIATRY (SCIP)

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Background: Existing standardized diagnostic interviews are not used by psychiatrists in clinical settings (1–5). There is an urgent need for a practical clinician-administered tool for assessment of adult psychopathology that produces dimensional measures, in addition to categorical diagnoses.
Methods: The Standard for Clinicians' Interview in Psychiatry (SCIP) is a new diagnostic interview designed to be used in clinical settings. The reliability and validity of the SCIP were tested in clinical populations (1,004 inpatient and outpatient subjects) at six sites (one hospital and two clinics in USA, two hospitals in Egypt and one clinic in Canada) between 2000 and 2012.
Results: The SCIP items and dimensions were shown to be reliable and published in a 2014 manuscript (6). The validity of the SCIP diagnoses was measured against gold standard diagnoses: diagnoses generated by an expert and a clinician using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN). Kappa was fair to good (greater than 0.5) for generalized anxiety, posttraumatic

Table 1. Base Rate, Number of Positive Diagnoses, Kappa, Kappa Standard Error (SE), Sensitivity and Specificity of SCIP Diagnoses against the Gold Standard Diagnoses (Diagnoses Generated by the SCAN Interview and the Expert Clinician) in Patients at William R. Sharpe Jr. Hospital.

	Diagnosis	Base Rate (%)	Number of Positive Diagnoses	Kappa	SE	Sensitivity (%)	Specificity (%)
1	Generalized anxiety disorder	4.5	11	0.6	0.09	100	94.3
2	Panic disorder	7.2	15	0.45	0.09	62.5	93.2
3	Posttraumatic stress disorder	8.1	11	0.68	0.09	66.7	98
4	Major depression	11	21	0.54	0.09	75	90.9
5	Bipolar I	9	18	0.51	0.09	70	92.1
6	Bipolar I, mixed features	5.4	10	0.3	0.09	33.3	96.2
7	Schizoaffective disorder	16	20	0.46	0.09	38.9	97.8
8	Schizophrenia	18	30	0.68	0.09	90	89
9	Alcohol use disorder	27	38	0.69	0.09	80	90.1
10	Cannabis use disorder	14	20	0.61	0.09	62.5	95.8
11	Cocaine use disorder	4.5	13	0.52	0.08	100	92.5
12	Opioid use disorder	7.2	13	0.74	0.09	100	95.1
13	Sedative use disorder	6.3	10	0.54	0.09	57.1	97.1

stress, major depression, bipolar I, schizophrenia and substance use disorders. Kappa was poor (less than 0.5) for panic, bipolar I, mixed and schizoaffective disorders. Sensitivities and specificities of SCIP diagnoses against the gold standard diagnoses were good (greater than 70%) for 73% of diagnoses
Conclusion: In addition to being a reliable diagnostic interview, the SCIP is a valid instrument for assessing the main psychiatric diagnoses against the gold standard diagnoses.
ID: 2085805

SUBSTANCE USE IN INDIVIDUALS AT CLINICAL HIGH RISK OF PSYCHOSIS

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Background: A series of research reports has indicated that the use of substances such as cannabis, alcohol and tobacco are higher in youth at clinical high risk (CHR) of developing psychosis than in controls. However, little is known about severity, frequency, the longitudinal trajectory, or the relation with later transition to psychosis with respect to substance use in this CHR population.
Methods: At baseline and 6- and 12-month follow ups, 735 CHR and 278 control participants completed the Alcohol and Drug Use Scale and a cannabis use questionnaire. The longitudinal trajectory of substance use was evaluated with linear mixed models.
Results: CHR participants endorsed significantly higher cannabis and tobacco use severity, and lower alcohol use severity, at baseline and over a one year period compared to controls. CHR youth had higher lifetime prevalence and frequency of cannabis, and were significantly younger upon first use, and were more likely to use alone and during the day. Baseline substance use did not differentiate participants who later transitioned to psychosis (n=69) from those who did not transition (n=231). CHR participants with a poorer clinical outcome at the 2-year assessment had endorsed higher cannabis use at baseline compared to controls.
Conclusion: Cannabis and tobacco use is higher than controls and this pattern persists across the first year after contact with research related mental health services. Evaluation of clinical outcome may provide additional information on the longitudinal impact of substance use that cannot be detected through evaluation of transition/non-transition to psychosis alone.
ID: 2084311

DETERMINING THE PREVALENCE OF PERSISTENT NEGATIVE SYMPTOMS IN AFFECTIVE AND NON-AFFECTIVE PSYCHOSIS DURING THE FIRST 12 MONTHS FOLLOWING A FIRST EPISODE OF PSYCHOSIS

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Background: Negative symptoms can be categorized based on their longitudinal intractability. In fact, research has recently focused on the study of persistent negative symptoms (PNS), a subset of negative symptoms that are prolonged and intractable in schizophrenia and contribute to poor functional outcome. A study by Hovington and al. (Hovington et al., (2012) BMC Psychiatry 12(1): 224) defines persistent negative symptoms as having at least one negative symptom rated at moderate or greater severity sustained for at least 6 consecutive months. These symptoms are not secondary to positive, depressive or extrapyramidal symptoms. Based on this definition, the objective of the present study is to determine the prevalence of persistent negative symptoms across twelve months in a heterogeneous sample of first-episode psychosis patients with a diagnosis of affective or non-affective psychotic disorder.
Methods: Four hundred and one first episode psychosis patients were part of a longitudinal outcome study on first-episode psychosis and were recruited though the Prevention and Early Intervention Program for Psychosis at the Douglas Mental Health Institute in Montreal, Canada. We examined persistent negative symptoms from 6 to12 months following admission to the clinic using the Scale for the Assessment of Negative Symptoms (SANS). In addition, positive, depressive and extrapyramidal symptoms were observed at initial assessment and at 6 and 12 months using the Scale for the Assessment of Positive Symptoms (SAPS), the Calgary Depression Scale (CDS) and the Extrapyramidal Symptom Rating Scale (ESRS), respectively.
Results: When looking at the entire cohort of first episode psychosis patients, 29% (N=102) of patients present persistent negative symptoms during the first 12 months. We observed a substantial prevalence of persistent negative symptoms in both affective (about 31%, N=22) and non-affective (about 35%, N=80) psychosis.
Conclusion: These initial results suggest that core symptoms of schizophrenia are present in both affective and non-affective psychosis and confirm the importance of providing early interventions for these symptoms.
ID: 2119748

SHARED SERUM BIOMARKER CHANGES IN SCHIZOPHRENIA AND BIPOLAR DISORDER PATIENTS. EVIDENCE FOR A COMMON DISEASE PROCESS?

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Background: Bipolar disorder (BD) is often misdiagnosed as major depressive disorder (MDD) or schizophrenia (SCZ) due to the overlap of symptoms and disease presentation. An inaccurate diagnosis is a frequent occurrence and results in suboptimal treatment with deleterious consequences for patients. Biomarker tests could provide an objective tool to increase diagnostic confidence for a given disorder.
Methods: Eight independent BD patient cohorts from five clinical centres were analysed using a multiplexed ELISA platform. Control and BD samples from a total of 332 individuals were analysed as discovery cohorts. A fixed effects linear regression model was applied to identify significant differences between groups. The results were validated in two additional cohorts comprised of a total of 401 patients (BD, pre-onset BD, and MDD) and control samples. The panel was also tested in 5 cohorts of SCZ patient samples.
Results: We were able to identify a mood state independent diagnostic biomarker panel for BD, consistent of 20 blood protein analytes, which can separate bipolar patients and controls with an AUC=0.90. The signature is also capable to distinguish between pre-onset BD and recent onset MDD

patients (AUC=0.90) and to a lesser extent between bipolar disorder and schizophrenia. Over half of the proteins identified as changing in BD versus controls are involved in inflammation and acute phase response. A second prominent category of changing proteins is involved in lipid metabolism. Several of the protein changes identified in BD patients are also changed in MDD. Serum biomarker changes in BD and SCZ overlapped substantially and could imply similar disease processes for these disorders.
Conclusion: A proteomic biomarker panel for BD of 20 analytes could be identified. The panel has a predictive power of 90% for the separation between BD patients and healthy controls and recent onset MDD, but is less good in distinguishing schizophrenia from bipolar disorder patients. The overlap in molecular serum changes in SCZ and BD could imply that underlying disease processes are similar and that the disorders are not distinct at the pathophysiological level.
ID: 2084723

TRANSDIFFERENTIATED BLOOD CIRCULATING MONOCYTES INTO NEURONAL-LIKE CELLS REPLICATE DOPAMINE 1 RECEPTOR DEFICITS FROM BRAINS OF PATIENTS WITH SCHIZOPHRENIA

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Background: Mounting evidence indicates that schizophrenia is a developmental illness (1) with associated abnormalities in the dopaminergic system including decrease in dopamine 1 receptors (DR1) in brains of patients with schizophrenia naïve to antipsychotics (2). However, the exact role of dopamine in schizophrenia is still a matter of debate. The limited understanding of schizophrenia stems from a lack of models able to provide a window into de neurodevelopment of patients with this illness.
Methods: We transdifferentiated blood circulating monocytes into neuronal-like cells by combining growth factors and conditioned media. Unlike other models such as induced pluripotent stem cells, the genome is not altered with viral insertions (3) which can become a confounder in an illness with a strong but still misunderstood genetic component.
Results: We initially transdifferentiated monocytes into neuronal-like cells from 40 individuals and established that transdifferentiated neuronal-like cells resemble human neurons early in development, express neuronal markers such as Nestin, Neurofilament and MAP2 and they present spontaneous action potentials as well as postsynaptic inhibitory and excitatory currents. During differentiation these cells undergo similar structural stages to those present in neurons while developing from rounded neuroblasts into neurons with complex shapes (4). We have also determined that when these neuronal-like cells are exposed to either dopamine or colchicine, they respond similarly to neurons by retracting their neuronal arborizations (5,6). In neurons, this structural response is mostly mediated by the DR1 (7). Monocytes lack DR1 but transdifferentiation into neuronal-like cells elicits the expression of this receptor. In comparing transdifferentiated cells from 7 patients and 8 control subjects, no differences were evident at day 4, 7 and 10 during the differentiation process. Both groups had differentiation rates of 15%, but cells from patients with schizophrenia, compared to controls, had a statistically significant decrease in DR1 expression.
Conclusion: Monocytes can be consistently transdifferentiated into neuronal-like cells that resemble human neurons during development and express early neuronal markers. These cells replicate structural responses found in neurons and also replicate findings from brains of patients with schizophrenia. Consequently, transdifferentiated neuronal-like cells may provide a window into the neurodevelopment of patients with schizophrenia.
ID: 2085887

ANOMALOUS SENSE OF SELF, SYNESTHESIA AND SCHIZOTYPY

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Background: Synesthesia is a neurological condition in which stimulation of one sense involuntarily yields a simultaneous perception in a separate sensory modality. Synesthesia is hypothesized to arise from abnormal connectivity among sensory cortical areas. Supporting evidence for a link between synesthesia and the schizophrenia-spectrum comes from research indicating that synesthetes score higher on psychometric measures of schizotypy compared to controls. Moreover, the defining features of 'mirror-touch' synesthesia are increased self-other mapping and blurred sense of self; both are implicated in schizophrenia (SZ). Indeed, anomalous or weakened sense of self was central to early theories of SZ and recent empirical studies have documented disturbances in body ownership and increased susceptibility for dissociative experiences such as the out of body experience (OBE) in the SZ-spectrum.
Methods: The major aim of the current study was to test the hypotheses that synesthesia predisposes individuals to psychosis-proneness via increased propensity for multisensory, dissociative experiences. We administered a series of questionnaires to SZ patients and healthy controls to assess synesthesia, schizotypy and dissociative experiences. Specifically, we used an adaptation of the Eagleman Synesthesia Battery, the synesthetic absorption subscale of The Absorption Scale, the Schizotypal Personality Questionnaire, the Dissociative Experiences Scale II, and a questionnaire assessing OBE history and frequency.
Results: We found that SZ patients reported greater levels of synesthesia and dissociative experiences compared to healthy controls. Synesthetes reported greater levels of positive schizotypal traits than those without synesthesia. Further, synesthetes were more likely to report OBE history and more dissociative experiences than those without synesthesia. Similarly, individuals with OBE history reported greater levels of synesthetic absorption than those without OBE history. Finally, as hypothesized, levels of dissociative experiences were found to mediate the relationship between synesthesia and schizotypal personality in healthy participants.
Conclusion: Future research should utilize this fascinating sample of individuals (i.e., synesthetes) to elucidate further how multisensory mechanisms contribute to sense of self and how these processes may become unraveled in individuals at risk for psychosis.
ID: 2107896

A QUANTITATIVE MEASURE OF HANDWRITING DYSFLUENCY FOR ASSESSING TARDIVE DYSKINESIA

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Background: Tardive dyskinesia (TD) is a persistent disfiguring and socially disabling movement disorder commonly associated with chronic exposure to antidopaminergic medications. The consensus from a growing body of

research indicates that this disorder has not disappeared and continues to challenge the effective management of psychotic symptoms in patients with schizophrenia. A fundamental component in an effective strategy for managing TD is its reliable and accurate assessment.
Methods: We examined the clinical utility of a brief handwriting dysfluency measure for quantifying TD. Digitized samples of handwritten circles and loops were obtained from 62 psychosis patients with or without TD and from 50 healthy subjects. Two measures of dysfluent pen movements were extracted from each vertical pen stroke, including average normalized jerk (ANJ) and the number of acceleration peaks (APK). Nine healthy subjects and 15 psychosis patients on stable medications were tested twice over a one month period. Cronbach's α coefficients for ANJ were above 0.80 for both groups indicating good test-retest reliability for this measure.
Results: TD patients (n=32) exhibited significantly greater ANJ ($p<0.0001$) and APK ($p<0.0001$) scores than non-TD patients (n=30) or controls (n=50) across handwriting tasks. Severity of handwriting movement dysfluency was significantly correlated with AIMS severity ratings for circles ($r=0.41$; $p=0.001$ for ANJ and $r=0.37$; $p=0.003$ for APK) and loops ($r=0.37$; $p=0.004$ for ANJ).
Conclusion: These findings offer empirical support that TD can be detected and objectively quantified with a very brief and easily administered battery of handwriting tasks. Handwriting movement analyses are naturalistic, require minimal training, involve a lost-cost commercially available digitizing tablet, notebook computer, and software, require no analytic decisions such as trial segmentation, and can be performed in any clinical setting in less than ten minutes. The procedure can be standardized for use across multiple sites with no known site-related variation. These results suggest that measures of handwriting movement dysfluency may be particularly useful for objectively evaluating the efficacy of pharmacotherapeutic strategies for treating TD.
ID: 2074382

PHENOMENOLOGICAL ASPECTS OF SUB-CLINICAL PSYCHOTIC SYMPTOMS AMONG ADOLESCENTS: MECHANISMS, MEANINGS AND THERAPEUTIC IMPLICATIONS

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Background: Sub-clinical psychotic-like experiences (PLEs) are not uncommon among adolescents and have been found to be associated with adverse life experiences, co-morbid psychopathology and later mental disorder. The phenomenology of PLEs in youth populations has received little attention and may provide important insights into the mechanisms through which PLEs emerge.
Methods: Qualitative data from 53 Irish adolescents who reported PLEs were analysed. The sample came from a larger sample of 212 Irish adolescents aged 11–13 years who took part in the Adolescent Brain Development Study, a population-based study on psychotic symptoms during adolescence. The study sample was clinically assessed for the presence of adverse life events, PLEs and psychopathology using the Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime Versions. All young people who were rated as having definite PLEs were included in the current analysis. Specific psychotic symptom subtypes of reported PLEs were initially quantified using SPSS V22. Using NVivo 10, a content analysis of available qualitative data was then undertaken to explore themes within the data and to determine whether there were any relationships between the content of reported PLEs and adverse life events within the sample.
Results: Considerable phenomenological heterogeneity was evident in the type and content of PLEs reported and there was evidence that, for some of the sample, a process of aberrant cognitive misattribution preceded the development of delusional beliefs. A key trend that emerged from this study was that, for many adolescents the content of their PLEs was related to their life experiences, particularly the experience of adverse life events. Adverse life events were found to pre-date the onset of PLEs for at least one-third of the sample. Fear emerged as a dominant emotional theme within the content of PLEs and, for a number of adolescents, their reported PLEs reflected potentially unconscious struggles regarding control.
Conclusion: These findings provide new phenomenological evidence on the mechanisms and meanings of PLEs in adolescent populations and on the relationship between PLEs and adverse life events. They support other empirical evidence that has demonstrated a relationship between emotion and psychosis and point to a need to develop more refined, personalised and effective psychotherapeutic and other interventions for young people who experience PLEs.
ID: 2086645

MARKERS OF INFLAMMATION IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Abnormalities in markers of inflammation and other blood analytes have been found in schizophrenia and in bipolar disorder but few studies have examined both populations in the same study using the same clinical and laboratory measures
Methods: The sample consisted of 143 persons with schizophrenia and 79 with bipolar disorder drawn from the same treatment settings and 111 non-psychiatric controls from the same geographic area. Each participant had a blood sample drawn from which were measured 193 multi-analyte markers involved in hormonal responses, inflammation, growth, oxidative stress, and metabolism. The markers were developed by Myriad Rules Based Medicine and analyzed with their bead-based multiplex immunoassay system. Linear regression models were used to compare the level of each marker in both psychiatric groups to that of the control group adjusting for age, gender, race, maternal education, and cigarette smoking.
Results: Of the 193 markers, 21 were significantly different in the schizophrenia group alone; 25 in the bipolar disorder group alone; 22 in both psychiatric groups in the same direction and none in opposite directions; and 115 in neither psychiatric group. Many of the markers that distinguished the psychiatric groups from the controls are molecules involved in inflammation and the immune response to infection. Markers which were uniquely different in schizophrenia included the complement c3 protein, C reactive protein, and IgA and IgE class immunoglobulins. Markers which were uniquely different in bipolar disorder included t-cell ligands cd5 and cd40; the inflammatory modulators trefoil factor 2 and matrix metalloproteinases 1 and 9; macrophage defined chemokine (MDC); and TRAIL, a tumor necrosis factor-related apoptosis-inducing ligand. Markers that were different in both psychiatric groups from the controls included alpha1 and beta2 microglobulins and matrix metalloproteinase 7.
Conclusion: Our results indicate that while there is some overlap between schizophrenia and bipolar disorder, markers of inflammation may distinguish these disorders. Several of these markers modulate the function of T-lymphocytes and other immune-based cells. Further research is needed to confirm these findings and to rule out confounding factors. A multiplex blood assay would be of potential benefit in the diagnostic assessment of patients with schizophrenia to distinguish them from controls and also from those with bipolar disorder.
ID: 2083653

MULTIRESOLUTION ANALYSIS OF BRAIN IMAGES FOR SCHIZOPHRENIA RECOGNITION

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Background: Machine learning methods are increasingly utilized for automated classification and diagnosis in various areas of medicine. In schizophrenia, however, the straightforward approaches fail to achieve accuracy and robustness sufficient for clinical application. A promising tool to deal with problems specific for medical image-based classification (high feature space dimensionality, redundancy of features and their complex spatial relations) is discrete wavelet transform (DWT). This method enables extracting key features on multiple scales and spatial locations. High potential of this approach has been demonstrated in several studies, however, the exact influence of various parameters of DWT and following classification on final accuracy is unclear and has not yet been examined. The aim of the presented study was to perform a systematic analysis of influence of parameters of wavelet transform on classification of patients with first episode of schizophrenia (FES) and healthy controls (HC).
Methods: Whole-brain T1 images of 52 FES and 52 HC were obtained by 1.5T MR device. DWT was applied to the normalized grey and white matter images and to Jacobians of deformations used for spatial normalization. DWT coefficients were thresholded and those with the most discriminative power were selected and used as an input for a linear support vector machines (SVM) classifier. The classification accuracy was estimated by leave-one-out cross-validation. The whole procedure was performed multiple times with all combinations of following parameters: data modality, wavelet family, level of DWT decomposition, percentage of DWT coefficients retained, number of coefficients selected and SVM regularization parameter C.
Results: Analysis of classification accuracy of all combinations of the six examined parameters revealed complex nonlinear relations among them. The best combination of parameters achieved accuracy over 92% (with balanced values of sensitivity and specificity). These values were robustly estimated by 100 repetitions of stratified 52-fold cross-validation runs.
Conclusion: The achieved accuracy is superior to the recent studies aimed at automated classification of FES patients. Moreover, the strengths of our approach include robust sensitivity and specificity, correct cross-validation and large dataset. Wavelet transform provides a useful tool for extracting important information from medical images.
ID: 2116193

MODELLING MEDICATION ATTITUDES, INSIGHT AND SELF ESTEEM IN EARLY NON-AFFECTIVE PSYCHOSIS

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Background: We modelled predictors of poor adherence in a cohort of early schizophrenia sufferers to discover what variables predicted outcome, when, and how they affected one another longitudinally.
Methods: 309 first and second episode DSM IV non-affective psychosis sufferers (83% first episodes) were recruited from consecutive presentations to defined catchments in England. Within 3 weeks of presentation the completed the Positive and Negative Symptom Scale (including the g12, insight, item), the Birchwood Insight Scale (with subscales Re-Labelling Symptoms, RLS; Awareness of Illness, AWI; recognising Need for Treatment, NFT) & Rosenberg Self Esteem scale (RSE). These were repeated at 6 weeks and 3 & 18 months. At these 3 visits the Drug Attitudes Inventory (DAI) and a visual analogue scale for satisfaction with treatment were also completed.
Scales' relapse prediction was analysed with ROC curves. Relations between scales were analysed with structural equation models (SEMs).
Results: ROC curves showed that initial but not later insight scale score <7 predicted relapse, while 6 week DAI<2 best predicted relapse.
SEMs of each stage: NFT, DAI and Satisfaction always loaded onto one latent variable (Medication Attitudes), RLS, AWI and g12 another (Insight) and RSE a third (Self Esteem). AWI specifically predicted RLS. Self esteem predicted AWI but nothing else.
Longitudinally: Growth Curve Models of Attitudes, Insight and Self Esteem fitted best, with intercept factors all correlating but change score factors not.
Conclusion: Self reported insight during acute illness best predicted relapse, better than objective insight. Medication attitudes were predictive. Recognising illness preceded need for treatment, but was affected by self esteem. NFT related better to Medication Attitudes than Insight. Each individual's insight, attitudes and self esteem scores are characteristic and intercorrelate, but are modified by change independently of each other.
ID: 2119568

ANTICIPATING THE HIGHS AND LOWS OF EVERYDAY LIFE IN SCHIZOPHRENIA: AN EXPERIENCE SAMPLING STUDY

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Background: It has been hypothesised that there is a specific deficit in anticipatory pleasure in schizophrenia in the context of intact consummatory or "in the moment" pleasure. Findings to date are mixed with reduced, heightened and similar anticipatory pleasure found in individuals with schizophrenia compared to controls. Our study assesses anticipatory and consummatory pleasure using two new measures. The experimental task included in this study identified a difficulty distinguishing highly pleasurable stimuli from low pleasure stimuli in people with schizophrenia. The same participants also completed an experience sampling week with the aim of replicating this lab finding in real-time emotional responses during everyday life.
Methods: A healthy control group (n=44) and a group of individuals with schizophrenia (n=36) completed an experience sampling study using portable devices. They rated their motivation, mood, functional and leisure activity levels; anticipatory and consummatory pleasure seven times a day for six days. Multi-level regression models were constructed to address the research questions.
Results: In line with our previous research there was no difference in consummatory ratings between the groups (p>.05). Anticipatory pleasure was higher for functional activities in the schizophrenia group; there was no difference for leisure activities (p<.05). A within-group analysis found anticipatory pleasure for functional activities was lower than for leisure activities in the control group as expected. However, there was no difference in the anticipatory pleasure for the two types of activity in the schizophrenia group. Individuals with schizophrenia completed fewer functional activities than controls, but leisure activities occurred at a similar frequency in both groups.
Conclusion: The results support our previous finding of a reduced ability to identify less pleasurable activities in schizophrenia. This over-estimation of pleasure from less pleasant activities may lead to frequent disappointment and a reduced sense of satisfaction when chores or work are completed. Indeed, individuals with schizophrenia complete fewer functional activities than controls despite this heightened anticipation. Future research and interventions should focus on the process of anticipatory pleasure and its links with activity, particularly helping individuals to anticipate different activities more accurately.
ID: 2077429

COMPUTATIONAL LINGUISTICS REVEALS MARKERS OF DISTRESS AND SOCIAL ISOLATION IN SCHIZOPHRENIA

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Background: Clinicians often remark on the jumbled form and odd ideas in schizophrenic speech. Despite careful listening, they are left uncertain about meaning, risk, prognosis, and importantly, treatment. Here we aim to augment the clinician's ear with an unbiased, computational approach to language analysis. Previous work in the area has identified specific linguistic markers of depression and impending suicide. We analyzed word-use patterns in blogs written by schizophrenic groups and control groups with strong beliefs, odd beliefs, medical illnesses, or psychiatric illnesses.
Methods: We applied Linguistic Inquiry and Word Count (LIWC) software to blog entries to reveal frequencies of words in 68 pre-defined grammar and thematic categories. Using the R mclust package, we clustered blog entries by word-use patterns. Group differences in single-word categories were identified by one-way ANOVA with false discovery rate correction for multiple comparisons followed by Tukey post-hoc tests. We used qualitative methods based in grounded theory to further investigate the context of specific word categories.
Results: I. Clustering analysis shows that schizophrenia blogs are more similar to other illness blogs than to strong- or odd-belief blogs. Sixty-four percent of schizophrenia blogs fell in Cluster 2, together with 63–86% of the other illness groups. Cluster 3 contained 56–71% of the non-illness blogs.
II. The word categories Body, Health, First-Person, Past Tense Verbs, and Time were used more frequently in the ill than non-ill groups (ANOVA and Tukey's post-hoc $p<0.05$.)
III. Social word use, however, places schizophrenia blogs together with other socially isolated groups, not ill groups. Qualitative analysis of social word use in these groups reveals more speculation about others' intentions, decreased talk of self, and little talk of paranoid ideas.
Conclusion: Language in schizophrenia contains markers of distress and social isolation that are not specific to mental illness or odd belief frameworks. Though clinicians may know of their patients' difficulties, computational linguistics more precisely identifies these symptoms. Future studies will allow us to test how these markers change during clinical improvements and relapses.
ID: 2119536

FACTOR STRUCTURE AND TEMPORAL STABILITY OF THE PANSS IN MARGINALLY HOUSED PERSONS WITH PSYCHIATRIC ILLNESS

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Background: Most factor analytic PANSS studies have identified a 5-factor model, yet limited consensus exists among these solutions (Schizophrenia Research, 85, 273–279). This psychometric inconsistency is notable given the relative homogeneity of the samples examined to date, most of which consist solely of persons with schizophrenia. The aim of this study was twofold; 1) identify the PANSS factor structure in a heterogeneous sample consisting of marginally housed persons with psychiatric illnesses, including high rates of psychosis, and 2) determine the temporal stability of the factor solution.
Methods: Participants were recruited from Single-Room Occupancy Hotels in the Downtown Eastside of Vancouver. They were administered clinical assessments including the PANSS. These clinical composites were randomly assigned to either exploratory (EFA, n = 100) or confirmatory factor analytic subsamples (CFA, n = 200); allowing identification then replication of initial findings. PANSS data (n = 201) collected at one-year follow-up was then used to 1) replicate the baseline CFA model, and 2) compute invariance analyses to assess for temporal stability of the latent structure of the CFA model.
Results: EFA suggested a unique 3-factor solution was most viable for the baseline PANSS data. This model was supported by CFA, and replicated with follow-up data. All items loaded significantly upon hypothesized factors and model goodness of fit analyses were in the acceptable to good range. An invariance analysis comparing Time 1 and Time 2 CFA models indicated remarkable consistency between points of measurement.
Conclusion: In summary, we were able to identify and confirm a novel 3-factor model, as well as determine the stability of these unique symptom dimensions across time, providing confidence that the PANSS is an appropriate measure for more heterogeneous marginalized samples. Yet the current model differs from those previously published in samples limited to schizophrenia participants, which may reflect the heterogeneity of the current sample.
ID: 2105677

A MULTI-LEVEL APPROACH TO DELINEATING PERCEPTUAL SOURCES OF ERROR IN AUDITORY HALLUCINATIONS

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Background: Several contending views seek to explain the mechanisms through which individuals perceive meaningful auditory information in the absence of external stimuli (i.e., auditory hallucinations). To date, studies have demonstrated that individuals with schizophrenia who experience auditory hallucinations demonstrate difficulties processing auditory information. However, none have evaluated whether the articulation process is a contributing factor in the production of auditory hallucinations.
Methods: This study evaluated the relation between differing sources of auditory error and auditory hallucinations in a sample of individuals with schizophrenia with (n = 11) and without (n = 11) auditory hallucinations, and healthy controls (n = 16). Four auditory processing and speech production tests were completed evaluating the following: (i) externalizing errors in a source monitoring task, (ii) perceived auditory errors in a signal-detection task, (iii) boundary perception in a phonemic boundary synthetic speech task, and (iv) changes in articulation during a formant perturbation task.
Results: Among individuals with schizophrenia, those with auditory hallucinations demonstrated significantly more externalizing errors than those without hallucinations ($p = .02$); a similar pattern emerged relative to controls at the trend level ($p = .06$). None of the other group comparisons reached a level of statistical significance ($p > .05$). Additional data from continuing data collection will also be presented.
Conclusion: These findings suggest that among individuals with schizophrenia, those who experience auditory hallucinations are more prone to ascribe the source of auditory information as being generated from an external source when the true source was internal. Further studies, particularly those with a larger sample size, are needed to more clearly delineate the mechanistic underpinnings of auditory hallucinations.
ID: 2084370

FURTHER VALIDATION OF A "SECOND GENERATION" CLINICAL ASSESSMENT MEASURE OF NEGATIVE SYMPTOMS

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Background: The number one recommendation from a NIMH consensus meeting on advancing novel treatment development for negative symptoms was to create and validate new clinical assessment tools grounded in contemporary research findings. Following this recommendation, the Clinical Assessment Interview for Negative Symptoms (CAINS) was recently created through an iterative, multisite scale development process. A key advancement of the CAINS is its incorporation of separate subscales that assess two primary negative symptom subdomains: (1) Motivation and pleasure (MAP): subjective experience from and engagement in goal-directed and pleasurable activities and (2) Expression (EXP): non-verbal and verbal communication.
Methods: This presentation describes recent advances in the validation of the CAINS, focusing on two new studies.
Results: In study 1, higher scores on both CAINS subscales were found in outpatients with schizophrenia (n = 35) compared to outpatients with bipolar disorder I (n = 38) and healthy controls (n = 35), though the bipolar group also showed higher MAP scores than controls. In addition, higher MAP scores significantly correlated with lower community functioning within the schizophrenia (r = -.50) and bipolar (r = -.55) groups. In study 2, schizophrenia outpatients (n = 98) and healthy controls (n = 48) completed the CAINS, a self-report measure of approach motivation, and a probabilistic reversal learning task. Patients showed significantly impaired learning, which correlated with higher MAP scores and lower approach motivation.
Conclusion: These findings provide further evidence for the validity of the CAINS. They also demonstrate the utility of considering distinct negative symptom subdomains by finding support for hypothesized links between impaired reinforcement learning processes and MAP-related negative symptoms.
ID: 2096158

PHOSPHORYLATION OF DISC1-DEPENDENT DELAYED NEURAL DIFFERENTIATION, DISTURBED NEURAL CIRCUITRY FORMATION, AND COGNITIVE IMPAIRMENT IN PSYCHOTIC DISORDERS

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Background: One major limitation that has blocked mechanistic understanding of major mental illnesses is the difficulty in accessing neuronal cells from patients. To overcome this issue, our program has established an infrastructure of translational research in which we conduct multiple tissue biopsies to establish neuronal cell lines, brain imaging, and clinical/neuropsychological assessment simultaneously from each study participant. This infrastructure allows us to perform experiments in which molecular, cellular, anatomical, and behavioral data are obtained from the same individuals. Meanwhile, we reported that a specific phosphorylation of the DISC1 protein, a major susceptibility factor for major mental illnesses, determines neural fate during development in animals. The aim of this study is to validate this molecular signature (phosphorylation of DISC1 at Serine713) as a biological marker for brain anatomy and function relevant to psychotic disorders, such as schizophrenia (SZ).
Methods: We established olfactory cells and iPS cells via nasal biopsy and skin biopsy, respectively. Olfactory cells were positive for b-tubulin III (a marker for immature neurons) to near homogeneity and their molecular profiles were similar to those of developing neurons. iPS cells were differentiated into neurons. The phosphorylation levels of DISC1 at Serine713 in olfactory neurons as well as iPS cell-derived neurons were compared between controls and patients. In addition, the effect of this phosphorylation on neural maturation was studied in vitro and in vivo. Finally, the associations between the phosphoarylation levels and clinical phenotypes were analysed.
Results: We observed that the level of phosphorylation of DISC1 at Serine713 was decreased in neurons obtained from patients with SZ compared to those from controls. This decrease led to delayed neural differentiation in SZ. Furthermore, the decreased DISC1 phosphorylation was associated with smaller middle frontal gyrus volume and impaired cognitive function in SZ.
Conclusion: This study may clarify how behavior and neuroanatomical abnormalities relevant to SZ are quantitatively (or at least semi-quantitatively) associated with a specific molecular signature (phosphorylation of DISC1 in this study).
ID: 2092122

RETHINKING THE AUDITORY IN AUDITORY VERBAL HALLUCINATIONS: FINDINGS FROM A TRANS-DIAGNOSTIC STUDY OF THE PHENOMENOLOGY OF VOICES

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Background: Auditory Verbal Hallucinations (AVHs) are important trans-diagnostic symptoms. To date, only two large-sample (n >100) studies have investigated the phenomenology of AVHs in detail (McCarthy-Jones et al., 2014; Nayani & David, 1996); both utilized semi-structured interviews. A concern is that such interviews may over-determine participant responses; large-sample unstructured interviews remain critical.
Methods: A mixed methods survey was developed to explore the phenomenological characteristics of AVHs and administered online (n = 158). Qualitative data was coded using NVivo 10 by two independent coders (k = .85) using both inductive and theoretical approaches. The analyses presented here focus on subjects' descriptions of the acoustic and non-acoustic qualities of AVHs.
Results: 82% of subjects reported a psychiatric diagnosis; the largest categories were 38% schizophrenia spectrum (SZ), 34% affective psychosis, 11% DID, and 11% PTSD. Only 46% of this sample reported literally auditory AVHs (laAVH). 36.6% reported exclusively thought-like voices (tlAVH) and the remainder mixed or in-between AVHs (mAVH). The percentage of laAVHs by diagnosis ranged from 9.1% in DID to 47.3% SZ. Further analyses grouped tlAVH and mAVH into four sub-categories: (1) entitative phenomena with access to information the subject claimed not to have; (2) entitative phenomena endowed with personality characteristics experienced as foreign; (3) phenomena physically originating outside the self; and (4) phenomena described as similar to (normal) memories of an external interlocutor and/or imagined conversation.
Conclusion: Data emerging from this project suggest that a large percentage of self-reported AVHs may not in fact be experienced as literally auditory, with significant differences reported across diagnostic groups. While our study is limited by diagnostic self-report, our findings nevertheless underscore the importance of further research on the acoustic qualities of AVHs across diagnoses. Our data also suggests a need to better deconstruct possible overlap between abnormal perceptions and abnormal thoughts or cognitions.
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ID: 2086415

EXCHANGE THE MAGNIFYING GLASS FOR A MICROSCOPE: THE CHICAGO HALLUCINATION ASSESSMENT TOOL (CHAT)

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Background: Hallucination pathology remains poorly understood. Typically studies attempt to link greater abnormality on a given biomarker (brain regional connectivity, evoked potentials, etc.) to greater hallucination severity using hallucination measures that collapse features of hallucinations into a single score or only assess a single feature such as frequency, rendering such severity measures possibly insensitive. We developed the Chicago Hallucination Assessment Tool (CHAT) to quantify hallucination severity along a number of dimensions. The CHAT is an expansion of the Psychotic Symptom Rating Scale for auditory hallucinations (Haddock et al., 1999), assessing hallucinations in multiple sensory modalities and at different time points (present and worst time in the past). For each sensory modality, the CHAT yields an overall severity score and subscales severity scores for Physical, Cognitive, and Emotional severity. Here we report psychometric properties of the CHAT.
Methods: We administered the CHAT and other standard diagnostic and symptom assessment instruments to 68 psychotic disorder patients endorsing at least one hallucination in their history. 23 were re-assessed at least one month later. Test-retest indicators were calculated for ratings of "past, worst time."
Results: Prior work established high inter-rater reliability. Test-retest reliability was also high, with 83% perfect agreement for types of chronic hallucinations reported as ever experienced. For those 83%, test and retest total severity scores correlated r = 0.9. For the whole sample, test-retest total severity scores correlated r = 0.8. Auditory and visual hallucination subscale scores had test-retest correlations each of 0.7. Neither interval length between test and retest nor general illness severity predicted differences between test and retest scores. The Physical, Cognitive, and Emotional severity subscale scores correlated with one another moderately (r's range 0.3–0.6). Current and past/worst severity ratings correlated 0.4. Current, but not past, CHAT severity ratings correlated with the PANSS Positive scale (r=0.4), but not PANSS Negative or General scales.
Conclusion: The CHAT appears to be psychometrically sound and meets the goal of quantifying related but not largely overlapping dimensions of hallucinations. This may be useful for understanding the symptom in its own right as well as determining if only certain aspects of hallucinations are related to biomarkers or may be useful outcome measures.
ID: 2119471

THE BRIEF NEGATIVE SYMPTOM SCALE: INTERNATIONAL ADAPTATION, VALIDITY AND DISSEMINATION VIA AN ONLINE TRAINING PLATFORM

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Background: To provide a synthesis and update of the rapidly-expanding international adaptation and validation of the Brief Negative Symptom Scale (BNSS), a next-generation negative symptom rating instrument developed in response to the NIMH-sponsored Consensus Development Conference on Negative Symptoms. Dissemination via an online training platform is detailed.
Methods: Using published reports and supplementary unpublished data obtained by scale authors, we provide a synthesis of the development, translation, and psychometric properties of the English, Spanish, and Italian versions of the BNSS. We also describe a new online training program to disseminate BNSS training internationally, which provides gold standard training videos and consensus ratings. Three training videos, each showcasing different symptom profiles, were highlighted in our training program.
Results: The BNSS has shown excellent cross-cultural validity, indicating it is appropriate for use in international settings. Excellent reliability was demonstrated in a large Italian sample (n= 921 patients) and a smaller Spanish sample (ICC's for total score were 0.97 Spanish, 0.99 Italian), estimates that are comparable to the U.S. validation sample (0.93). Good convergent validity was demonstrated in the Spanish sample, with positive correlations with the SANS (r=0.68; p=0.001) and the PANSS negative subscale (r=0.74; p<0.001), values comparable to the U.S. sample (SANS r=.80, p<.001, BPRS Negative Subscale r=.68, p<.001). The BNSS has shown a similar factor structure in the Italian sample and the U.S. sample, with one factor reflecting internal experience (avolition/asociality/anhedonia) and the other diminished expressivity (blunted affect and alogia). The developers of the German translation provide data on their results at the current meeting.
Raters from three centers in the United States as well as the Italian center have used the online training program, which is being improved in response to feedback.
Conclusion: The BNSS translations have shown excellent reliability and cross-cultural validity, and are appropriate for dissemination via online training platforms. There are now 7 translations with back translations: Mandarin (Simplified Chinese), Korean, Turkish, Dutch, German, Spanish and Italian. The results show that the concepts of the English version of the BNSS lend themselves well to translation and cross-cultural use.
ID: 2119311

DIMENSIONS OF INSIGHT IN SCHIZOPHRENIA: EXPLORATORY FACTOR ANALYSIS OF MULTIPLE SELF- AND INTERVIEWER-RATED MEASURES OF INSIGHT

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Background: In schizophrenia, insight is regarded as a multidimensional construct that comprises aspects such as awareness of the disorder and recognition of the need for treatment. The proposed number of underlying dimensions of insight is variable in the literature. While independent dimensions have been identified in the factor structures of various measures of insight, to date, no study has simultaneously evaluated the factor structure of items from multiple insight measures. In an effort to identify a range of existing dimensions of insight, we conducted a factor analysis on combined items from multiple measures of insight.
Methods: We recruited 99 participants with enduring schizophrenia (treated for > 4 years) from various outpatient and inpatient units of the Douglas Institute and affiliated external resources in Montreal. Exploratory factor analysis was conducted on itemized scores from four measures of insight, including two interviewer-rated measures: the Schedule for the Assessment of Insight-Expanded and the Scale to assess Unawareness of Mental Disorder; and two self-report measures: the Birchwood Insight Scale and the Beck Cognitive Insight Scale.
Results: A five-factor solution was identified as the best-fitting model. The factors appeared to suggest the following dimensions of insight: 1) awareness of illness and the need for treatment; 2) awareness and attribution of symptoms and consequences of disorder; 3) self-reflection related to thoughts, attitudes, and understanding of experiences; 4) self-reflection related to beliefs and reasoning; and 5) self-certainty.

Conclusion: These results are novel as they suggest merging awareness of illness and the need for treatment into a single dimension, and separating the self-reflectiveness dimension of cognitive insight into two independent dimensions. Subsequent steps will examine the identified dimensions of insight in relation to various psychological and biological factors, including symptoms, neuropsychological functioning, and brain imaging data. This information can be used to develop clinically useful models of insight, including its contributing factors, with the goal of designing effective interventions to improve insight and outcome in affected patients.
ID: 2086361

VIOLENCE IN PATIENTS WITH SCHIZOPHRENIA: PREDISPOSING FACTORS AND SYMPTOMS.

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Background: Emotional dysregulation, excitation, psychopathy and executive dysfunction have been shown to predispose to violence in schizophrenia, while negative symptoms have a protective effect. We compared violent and non-violent patients with schizophrenia on these variables; we also examined the extent of the relationship between these variables and violence in the violent group.
Methods: Violent patients with schizophrenia (VS; N=40) were compared to non-violent patients with schizophrenia (NV; N=33) and to healthy controls (HC; N=32). The Life History of Aggression (LHA) Questionnaire was completed on the basis of patient and staff interviews and review of all records. VS were required to have an episode of physical assault within the past year, and a total LHA score of ≥20. NV were required to have a LHA score below 16, and could not present with physical aggression over the past year. Psychiatric symptoms were assessed through the Positive and Negative Syndrome Scale (PANSS) and its 5 factors: Positive and Negative Symptoms, Excitation, Cognitive Impairment and Depression/Anxiety. Psychopathy was measured through the Psychopathy Checklist (PCL-SV) which includes a personality factor (factor 1) and an antisocial history factor (factor 2). Wisconsin Card Sorting Test (WCST) Perseverative errors provided a measure of executive function.
Results: VS had higher scores than NV on PANSS Excitation (ANCOVA; F= 4.15, df=71, p<.05) and Depression/Anxiety (F=6.31, df=71, p=.01). NV had more severe negative symptoms (F= 4.88, df=71, p=.03). The groups differed on PCL-SV Total score (F=43.0, df=2,93, p<.0001), and on the first (F=34.7, df=2,93, p<.0001) and second (F=35.3, df=2,93, p<.0001) factors. VS had higher scores than HC and NV on these variables; HC and NV did not differ. WCST Perseverative errors did not differ in VS and NV. Within the violent group there was a positive relationship between the extent of violence (as measured by the LHA score), and PCL-SV factor 2 (r=.48, N=37, p<.01), PANSS Depression/Anxiety (r=.41, N=40, p<.01), and WCST Perseverative errors (r=.41, N=39, p<.01).
Conclusion: There are symptoms and traits that underlie a basic predisposition to violence in schizophrenia. Once this predisposition is present, however, the severity/extent of violence is affected only by some of these factors, i.e., affective symptoms, antisocial history, and executive dysfunction.
ID: 2118844

AUTOANTIBODIES IN FIRST EPISODE PSYCHOSIS: A MATCHED CASE-CONTROL STUDY

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Background: Autoimmune pathology has been suggested as aetiology for some cases of first episode psychosis (FEP) and schizophrenia, with recently discovered brain-reactive antibodies being identified in the sera of patients with psychosis. Previous studies have not looked at the prevalence of autoantibodies to N-Methyl-D-Aspartate receptor (NMDA-R), Voltage Gated Potassium Channel (VGKC) and Glutamate Decarboxylase (GAD) in the initial acute phase of FEP compared to healthy comparison subjects.
Methods: A case control study to examine autoantibody levels and rates of antibody seropositivity in ninety six patients presenting with FEP and ninety six controls matched for age and sex. We measured NMDA-R, VGKC and GAD autoantibodies using live cell based assays and visual neuronal screening.
Results: VGKC antibodies were the most prevalent antibody finding in both cases (n=18) and controls (n=19), without being significantly different between the groups. There were no cases and one control (402pM) with high positive VGKC-complex antibodies. (>400pM). GAD antibody positivity was found in 3% (n=3) of controls and in none of the patients. NMDAR seropositivity was found in 5% (n=5) of cases and 3% (n=3) of the controls (x2= 0.565, p=0.349). Neuronal staining was positive on a visual screen in 3 of the patients and in 6 controls.
Conclusion: This is the largest matched case control study looking at the prevalence of autoantibodies in FEP. These findings fail to support the hypothesis that FEP may be an autoimmune mediated process for a subgroup of patients and provide a cautionary note on routine mechanised antibody screening of patients with FEP. The likelihood is that a more case specific approach to screening for antibodies in FEP is called for, with phenotypic characteristics of a patient's presentation indicating who should be tested. Visual examination for neuronal staining may be informative.
ID: 2116523

	TOTAL	WHITE	BLACK	OTHER	MALE	FEMALE
	N=					
NMDA	8					
CASES + (%+)	5	2	1	2	3	2
CONTROL + (%+)	3	3	0	0	3	0
GAD	5					
CASES + (%+)	0	0	0	0	0	0
CONTROL + (%+)	3	2	1	0	1	2
VGKC (including CASPR and LGI1)	37					
CASES + (%+)	18	5	9	4	5	13
CONTROL + (%+)	19	9	7	3	10	9

RISK FACTORS FOR SCHIZOPHRENIA AND THE CONTINUUM OF PSYCHOSIS: ADVANCED PATERNAL AGE (APA) IS ALSO ASSOCIATED WITH PSYCHOSIS IN BIPOLAR DISORDER

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Background: APA is a risk factor for schizophrenia (Sz) and bipolar disorder (BP). Putative mechanisms include heritable genetic factors, de novo mutations in the aging male germ line, and epigenetic mechanisms. Few studies have explored phenotypic features, namely psychosis, associated with APA.
Methods: The Genomic Psychiatry Cohort (GPC) is a multi-institutional collaboration that has established a clinically well-characterized repository of genomic samples from subjects with a Sz-BP diagnosis or unaffected controls. All subjects gave blood and completed a health history questionnaire; ill subjects were interviewed using a structured instrument, the Diagnostic Interview for Psychosis & Affective Disorders (DI-PAD). Inclusion criteria for this analysis were paternal age ≥ 13 and participant age ≥ 18 years. Parental age information exists for ~13,000 subjects, including 3,942 with Sz (all types including schizoaffective disorder), 1,375 with BP (941 with history of psychotic features [PF], 434 without), and 7,658 unaffected controls. Paternal age was categorized as <20, 20–24, 25–29, 30–34, 35–39, 40–44, & 45+ years. Multinomial logistic regression estimated relative risk ratio (RRR) for each disorder type (Sz; BP w/PF; BP w/o PF) relative to the control group, comparing each paternal age group to the reference group 20–24 years. RRR>1 for a given age group and disorder indicates greater risk of having that disorder relative to reference age group. Analyses were adjusted for sex, race, age, and paternal minus maternal ages. We used PROC LOGISTIC in SAS 9.3; all tests were two-sided at 0.05 level of significance. The Holm-Bonferroni adjustment for multiple comparisons was used to adjust for multiplicity of testing between paternal age groups.
Results: Age, sex & race were significantly associated with risk of disorder. After adjusting for these covariates and correcting for multiple comparisons, subjects with fathers age 45+ had significantly higher risk than those with fathers age 20–24 for BP w/PF (RRR=1.939) and Sz (RRR=1.442), but not BP w/o PF (RRR=0.934).
Conclusion: This report replicates APA as a risk factor for Sz. Moreover, it represents the first examination of APA effect in a BP sample stratified by psychosis history, extending this positive association in BP with but not without psychosis history. These results suggest that phenotypic expression of APA effect in Sz-BP spectrum is psychosis, per se, rather than other aspects of these complex disorders.
ID: 2091820

MALADAPTIVE DSM-5 PERSONALITY TRAITS IN PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDERS AND THEIR FIRST-DEGREE BIOLOGICAL RELATIVES

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Background: The DSM-5 contains a new model of maladaptive personality traits that may be relevant in understanding not just personality disorders, but also risk for other serious mental illnesses, such as schizophrenia spectrum and bipolar disorders.
Methods: To explore how familial risk for schizophrenia spectrum and bipolar disorders is expressed in personality, the five DSM-5 trait domains were examined in patients with schizophrenia spectrum or bipolar disorders, relatives of patients, and healthy controls.
Results: When categorized by the discrete DSM diagnoses or familial relation to a patient with a DSM diagnosis, the five groups differed significantly from healthy controls across all DSM-5 domains, indicating that personality reflects risk for severe mental illness. Domain scores were similar between patients with bipolar disorder and their relatives, while patients with schizophrenia differed from their relatives in multiple domains.
Conclusion: The findings demonstrate that the Personality Inventory for DSM-5 (PID-5) captures a broad range of maladaptive personality traits in schizophrenia spectrum and bipolar disorders, that may represent shared features of genetic liability and expression of clinical disorders.
ID: 2091855

SELF-REPORTED AFFECTIVE TRAITS AND CURRENT AFFECTIVE EXPERIENCES OF BIOLOGICAL RELATIVES OF PEOPLE WITH SCHIZOPHRENIA

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Background: Schizophrenia is characterized by self-reported trait anhedonia but intact hedonic responses during laboratory experiments. Affective traits of first-degree biological relatives may be similar to those of people with schizophrenia, and measures of hedonic response in relatives may be free of antipsychotic medication or cognitive confounds. Relatives also self-report increased anhedonia, yet it is unclear whether, like in patients, this anhedonia is paired with largely intact hedonic self-report.
Methods: In this study, first-degree relatives of people with schizophrenia (n=33) and nonpsychiatric controls (n=25) completed a wide range of questionnaires and tasks assessing social and physical anhedonia, positive and negative affective experience, and anticipatory and consummatory pleasure. Valence, intensity, frequency, and the arousal of current emotion were assessed. Extraversion and current positive and negative affective state were also examined in relation to self-reported social anhedonia.
Results: Relatives evidenced the same disjunction of increased self-reported anhedonia and intact affective response observed in people with schizophrenia. Group differences in anhedonia were not better accounted for by decreased current positive affect, increased current negative affect, or decreased extraversion in relatives.
Conclusion: Results suggest that, like people with schizophrenia, first-degree relatives report intact hedonic response on both questionnaire and laboratory measures despite significant elevations in self-reported social anhedonia.
ID: 2074356

PSYCHOTIC EXPERIENCE SUBTYPES IN A COMMUNITY SAMPLE OF CHINESE ADOLESCENTS AND YOUNG ADULTS

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Background: Previous factor analytic studies of the Community Assessment of Psychic Experiences (CAPE) have resulted in three-, four- and five- factor structures for the positive dimension (CAPE-pos) and a tripartite structure for the negative dimension (CAPE-neg). However, such studies were typically conducted in Caucasian populations. It was unclear whether similar factor structures would emerge in a population of non-Western sample. This study seeks to explore the factor structure of CAPE-pos and CAPE-neg using an Exploratory Factor Analysis (EFA) in a sample of Chinese young adults.
Methods: 324 participants (138 male, 186 female) with a mean age of 19.73 years were recruited. All participants filled in the Chinese-translated CAPE, a 42-item questionnaire tapping positive, negative and depressive psychotic-like experiences. Participants reported frequency and distress associated with each item on a four-point Likert scale. The positive and negative subscales showed excellent internal consistency (Cronbach's alpha = .85 and .86 respectively). Separate EFA with Principal Axis Factor extraction and Varimax rotation were performed for the CAPE-pos and CAPE-neg frequency items.
Results: The number of factors was determined by eigenvalue <1, inspection of scree plot and factor loadings on extracted factors. EFA of the positive dimension revealed five factors, with only one item loaded onto the fifth factor. Hence, a four-factor model was retained. The model consisted of 'Persecutory ideation', 'Grandiosity', 'Bizarre experiences and magical thinking' and 'Perceptual abnormalities', explaining 54.89% of the variance. Internal consistency of the identified subdimensions ranged from .63 to .83. EFA of the negative dimension revealed three factors: 'Social withdrawal', 'Affective flattening' and 'Avolition'. These subscales explained 52.56% of the variance. Internal consistency of the identified dimensions ranged from .68 to .80.
Conclusion: This study explored positive and negative psychotic experience dimensions in a general population of Chinese young adults. Results from the EFA and internal consistency of identified subscales corroborated the majority of previous findings that CAPE-pos possessed a four-factor structure. Our finding that CAPE-neg consisted of three factors was also in line with all previous factor analytic studies of CAPE-neg. Taken together, there is preliminary evidence that the Chinese-translated CAPE is appropriate for use in a Chinese young adult population.
ID: 2096670

PERCEPTION, MEMORY, CONTEXT: HOW DELUSIONS FORM AND PERSIST

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Background: Phenomenologically-oriented psychiatrists describe a loss of context as fundamental to delusional-formation both in the original perceptual experience and its memory. Binswanger and Conrad, key figures in phenomenological psychiatry, observed that it is not only the perception which, due to its abnormal salience, is loosened from its background-context in the original delusional experience but how it is remembered. Low-level perceptual abnormalities are accompanied by compensatory schemas, which become overgeneralized apart from their original context. The delusion becomes independent from its original source memory and "monotonously" spreads to more and more situations in the patient's life.
Methods: Phenomenological data from these earlier reports as well as from our own delusions-scale were extracted to examine what extent patients were able to remember the origins of their delusions and to what extent perceptual abnormalities played a role in developing the delusions.
Results: The hypothesis that low-level perceptual abnormalities are accompanied by subsequent fixed delusional schemas was supported.
Conclusion: Perceptual anomalies (Mishara and Uhlhaas, 2007) may be accompanied by the formation of compensatory delusional schemas, which are maintained and overgeneralized apart from their original context. The hippocampus and associated structures are involved in the rapid, automatic aspects of context-specific event encoding and retrieval, whereby the creation of lasting event-context memories involves the integration of new information with existing mental frameworks or schemas (Tse et al., 2007). We provide a predictie coding account of how such schemas may be disrupted during acute phases of psychosis in schizophrenia and thus contribute to the selective "salience" of details and in memories related to acute illness which are then generalized to more and more aspects of the patient's experience.

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ID: 2126476

POSTURAL MARKERS OF CEREBELLAR DYSFUNCTION PREDICT COURSE OF NEGATIVE SYMPTOMATOLOGY IN YOUTH AT HIGH-RISK FOR PSYCHOSIS

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Background: Negative symptomatology in psychosis has been shown to significantly precede the onset of positive symptoms and be closely tied to core underlying pathogenic features.1 However, to date attention in biomarker research in the psychosis prodrome has focused almost exclusively on predicting the onset of formal positive symptoms. The cerebellum, one region that has been closely tied to negative symptomatology in prominent theoretical conceptions, 2 is an ideal target for predicting the course of negative symptomatology in youth at ultra high-risk (UHR) for psychosis.
Methods: In this study, we utilized a sophisticated balance apparatus to examine postural sway, a sensitive marker of abnormal cerebellar-specific function,3 to assess 45 UHR and 43 healthy matched controls (mean age=18.28; SD=2.26). Clinical symptoms were assessed at baseline and then again one year later.
Results: We observed that the total sway area was significantly larger in the UHR (mean=40.47, SD=49.23) group when compared with the healthy controls (mean=27.34, SD=23.03), $t(86)=1.65$, $p \leq .05$, and closely tide to negative ($r=.40, p \leq .01$) but not positive symptomatology in UHR youth. Furthermore, when holding baseline negative symptomatology constant, total sway area significantly predicted the course of negative symptomatology, explaining an additional 9% of the variance in this domain one year later, ($\beta=.35$, $p \leq .05$). Results for positive symptoms were not significant.
Conclusion: Findings implicate cerebellar abnormalities prior to the onset of psychosis, and suggest that utilizing novel balance methodologies hold significant promise for biomarker research. The ability to predict negative symptomatology is particularly critical as this domain substantially contributes to disability4 and may shed light on the etiology of psychosis.
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ID: 2074077

CLINICAL VARIABLES ASSOCIATED WITH DEPRESSION IN THE CLINICAL COURSE OF SCHIZOPHRENIA SPECTRUM DISORDERS: A LONGITUDINAL ASSESSMENT

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Background: When diagnosing schizophrenia and related disorders (Schizophrenia Spectrum Disorders, SSDs) physicians may pay greater attention to psychotic symptoms relative to depression. It has been widely established that depression may impact clinical course and prognosis of SSDs. Therefore assessing these depression may be of paramount import. To support clinicians in the comprehensive assessment of depression, clinical variables associated with depression in SSDs were examined.
Methods: The sample for this study constituted of patients with SSDs followed in a modified assertive community treatment program, the Community Support Network of Springfield, Illinois. The study design was prospective with repeated assessments over four time points. Clinical variables associated with depression at initial evaluation and following assessment times were examined longitudinally by calculating relative risks (RR) using (GENMOD) generalized estimating equations in SAS.
Results: Rate of depression was high in the study sample. Depression was associated with greater number of hospital visits. Clinical variables associated with depression in SSDs were auditory hallucinations, delusions, poor insight and poor judgment. Schizophrenia and schizoaffective disorder did not significantly vary in symptomatology. However, the use of mood stabilizers and antidepressants had negative association with schizoaffective disorder compared to schizophrenia.
Conclusion: These results support the notion that depression may be an integral part of psychotic episodes in SSDs and so should be dutifully assessed. These findings are preliminary given the relatively small the sample size. Also, the sample of severe and chronically ill mental health patients may limit the generalizability of the findings.
ID: 2084982

MOLECULAR PROFILES IMPLICATED IN MCCB COGNITIVE DOMAINS

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Background: Challenges in the objective diagnosis and effectiveness of treatments in psychiatric medicine propel endophenotype identification. As schizophrenia is marked by disturbances in cognition, proteins operating on the neural regulation of cognitive processes are viable treatment targets. Merging data from diseased and control groups, we use multiplexed immunoassay to identify molecular panels capable of predicting performance on each of the fundamentally impaired cognitive domains represented in the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB).
Methods: One-hundred fourteen (disease (80) and control (34)) subjects who had completed a diagnostic battery, consisting of an interview using the Structured Clinical Interview for the DSM-IV (SCID) or the Structured Interview for Prodromal Syndromes (SIPS), MCCB, physical assessment and blood draw, were included in the sample. The disease group was constructed of 6 clinical groups of competing diagnoses: Schizophrenia (25), Bipolar Disorder (13), Schizoaffective Disorder (17), First-Episode Schizophrenia (6), Drug Induced Psychosis (2), and Prodrome (17). Post data pre-processing, 205 proteomic analytes were used in the final analysis. To achieve our aim of identifying analyte predictors for each standardized MCCB domain t-score, we employed a series of multiple regression analyses.
Results: Proteomic models of 16 to 27 analytes, predicting MCCB component scores with coefficients of determination ranging from 0.49 to 0.75 were derived: Speed of Processing (27 analytes, R-squared = 0.75), Attention/Vigilance (16 analytes, R-squared = 0.49), Working Memory (24 analytes, R-squared = 0.65), Verbal Learning (17 analytes, R-squared = 0.57), Visual Learning (23 analytes, R-squared = 0.69), Reasoning and Problem Solving (16 analytes, R-squared = 0.59), and Social Cognition (21 analytes, R-squared = 0.63). A model of 19 analytes (R-squared = 0.70) predicted Overall Composite Score, the MCCB t-score for the combination of cognitive components.
Conclusion: These results suggest a foundational molecular profile for the distinct cognitive deficit components considered to be most crucial in schizophrenia. Understanding the mechanism of expression and production of these proteins may be central to new diagnostic and therapeutic strategy development.
ID: 2086241

CLINICAL CHARACTERISTICS OF CHILDREN AND ADOLESCENTS WITH FIRST-EPISODE SCHIZOPHRENIA IN THE TOLERABILITY AND EFFICACY OF ANTIPSYCHOTICS (TEA) TRIAL

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Background: We aimed to expand the evidence on clinical characteristics of first-episode (FE) early-onset schizophrenia (EOS) comparing males and females at entry into treatment.
Methods: Analysis of baseline data from EOS patients (12–17 years) recruited into the TEA[1] trial from 7 Danish child and adolescent mental health centers.
Results: Altogether 113 patients with schizophrenia (SZ) spectrum/affective psychosis were enrolled (30% boys; no age/sex difference from 113 screening failures). In the SZ sample (n=70) (table) males (37%) and females (63%) did not differ on age, age at onset, Duration of Untreated Psychosis (DUP), Global Assessment of Psychosocial Disability (GAPD), Clinical Global Impressions-Severity (CGI-S) scale and Positive and Negative Syndrome Scale (PANSS) scores. In females, there were trends toward higher PANSS depression factor scores and higher rates of recurrent thoughts of death, while acts of self-harm were significantly more prevalent than in males (p=0.013).
Conclusion: In this FE EOS sample DUP was longer and females more prevalent than in other adolescent and, even adult samples. The female preponderance is in line with Danish register findings of a recent change in EOS sex distribution from male to female excess[2]. The clinical profile was similar in males and females, but females seemed to require special attention for self-harm. Examination of outcome patterns related to longer DUP is relevant in this sample.
[1]Pagsberg et al. BMC Psychiatry. 2014.
[2]Okkels et al. Acta Psychiatr Scand. 2013
ID: 2117691

THE RELATIONSHIP BETWEEN SOCIAL/ INTERPERSONAL PLEASURE AND PERSONALITY DISORDER SYMPTOMS IN PSYCHOMETRICALLY AT-RISK INDIVIDUALS

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Background: Previously, the Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS) has been shown to be associated with the Revised Social Anhedonia Scale (rSAS) as well as the No Close Friends Scale on the Schizotypal Personality Questionnaire (SPQ). Further, previous research (Camisa et al., 2005) has found that individuals with schizophrenia-spectrum personality disorders (specifically Cluster A PDs) were more socially withdrawn than controls.
Methods: The goal of the current study was to investigate the relationship between social anhedonia and personality traits in a cross sectional sample as well as to examine the relationship between levels of interpersonal pleasure, as measured by ACIPS and personality disorder symptoms. Personality disorder symptoms were assessed using the SCID-II. We identified psychometric schizotypes using the Chapman psychosis-proneness scales specifically because individuals who score high on the rSAS are at heightened risk for the later development of a schizophrenia spectrum disorder including schizoid, schizotypal, paranoid, and avoidant personality disorders (Gooding et. 2005, 2007).
Results: Consistent with prior findings, individuals who scored high on the rSAS had lower ACIPS scores than the other two comparison groups. Upon interview, participants in the negative schizotypy group revealed a greater number of Cluster A personality disorder symptoms compared to the positive schizotypy and no schizotypy groups. We also observed that across the entire sample, total ACIPS scores were significantly and negatively associated with Cluster A personality disorder symptoms, i.e. lower ACIPS scores were associated with a higher number of Cluster A personality disorder symptoms.
Conclusion: Social/interpersonal pleasure deficits appear to be an important target for intervention in individuals with Cluster A personality disorders.
ID: 2096328

SUBGROUPING SCHIZOPHRENIA BASED ON SYMPTOM DIMENSIONS: THE DEFICIT SYNDROME AND MORE?

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Background: Severe, enduring negative symptoms-which are not secondary to anxiety, depression, medicine or other factors-are thought to identify a 'deficit syndrome' subtype of schizophrenia (Kirkpatrick et al., 2001).

*DUP (weeks) median/IQR for males vs. females: 96.5/225 vs. 90.5/168; nonparametric median test: n.s. (p=0.803). **Data missing on n=2. *** Sum of 3 items (anxiety, guilt feelings, depression)

	All, N=70	Males, N=26 (37.1%)	Females, N=44 (62.9%)	Males vs. Females
	Mean (SD)	Mean (SD)	Mean (SD)	Mann Whitney U test, p
Age, years	15.2 (1.4)	15.2 (1.6)	15.2 (1.3)	0.670
Age at onset, years	12.2 (3.5)	12.1 (3.9)	12.3 (3.2)	0.845
DUP, weeks*	157.1 (173.3)	164.5 (182.8)	152.5 (169.3)**	0.801
GAPD score	4.4 (1.1)	4.3 (1.0)	4.5 (1.2)	0.477
PANSS Total score	78.5 (13.2)	80.0 (15.3)	77.5 (12.0)	0.706
PANSS Positive score	20.2 (3.7)	21.2 (4.5)	19.7 (3.1)	0.287
PANSS Negative score	18.1 (4.8)	18.9 (5.4)	17.7 (4.4)	0.373
PANSS General score	37.1 (6.8)	36.7 (7.4)	37.4 (6.5)	0.404
PANSS Depression factor score***	10.4 (2.5)	9.7 (2.9)	10.9 (2.3)	0.057
CGI-severity score	4.8 (0.7)	4.7 (0.7)	4.8 (0.7)	0.723
Kiddie-SADS-Present and Lifetime Version, items	**N (%)**	**N (%)**	**N (%)**	**Chi-square test, p**
Recurrent Thoughts of Death (score=3)	31 (44.3)	8 (30.8)	23 (52.3)	0.080
Suicidal Ideation (score= 3)	19 (27.1)	5 (19.2)	14 (31.8)	0.253
Suicidal Acts - Seriousness (score= 3)	2 (2.9)	0	2 (4.5)	0.270
Suicidal Acts - Medical Lethality (score= 3)	2 (2.9)	0	2 (4.5)	0.270
Non-Suicidal Physical Self-Damaging Acts (score= 3)	17 (24.3)	2 (7.7)	15 (34.1)	0.013

We hypothesized that a deficit syndrome subgroup would emerge through unsupervised cluster analysis of selected symptom dimensions from a large sample of people with schizophrenia (PSz), and that the deficit subgroup would differ from other PSz in analyses of cognitive, clinical, and functional data.
Methods: Data were available for 549 PSz from the NIMH/ Clinical Brain Disorders Branch Study of Genetic Risk for Schizophrenia. We performed 2-step clustering with PANSS negative and distress symptom factors as indicators. Error bar graphs and GLM analyses compared symptom subgroups on selected variables, controlling for age and sex.
Results: The cluster analysis yielded a 5-subgroup scheme for the PSz. In addition to a deficit syndrome group with very high negative symptoms and low distress (n=108), we found an overall low symptom group (n=156), a medium negative and low distress group (N=118), a medium negative and medium distress group (N=118), and a high overall symptom group (N=49). The deficit syndrome group showed poor cognition (e.g., p=4.2E-05 for contrast of deficit subgroup with all other PSz on a general cognitive ability composite), more limited education than other PSz, and poorer overall functioning. Two of the other subgroups identified in this analysis showed cognitive/clinical/functional profiles that may merit further investigation. The largest subgroup (n=156) showed very low symptoms on average, cognitive performance within normal limits, and a 50% current employment rate (p<1E-05 for contrast of low symptom subgroup with all other PSz). The smallest group (n=49), with high negative and high distress symptoms, showed cognition and education similar to the low symptom group (p's>.52), yet had the highest overall symptom ratings (e.g., p=2.5E-04 for comparison with deficit group) and poor overall functioning.
Conclusion: A latent class analysis of PANSS symptom data yielded a deficit syndrome group with characteristics similar to those previously described in the literature. Additionally, separate very low and very high symptom subgroups showed profiles of cognitive, clinical and functional characteristics that were distinct from other groups and also may be worth examining further for relevance to etiology, course of illness and/or treatment response.
ID: 2089358

REPROGRAMMING HUMAN CELLS TO STUDY MENTAL DISORDERS

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Background: Schizophrenia is a neurodevelopmental disorder that affects 1% of the worldwide population. Symptoms can either be classified as cognitive (attention, memory or planning deficit), positive (hallucinations and delirium) or negative (speech or emotional disabilities), and may arise individually or in combination. Schizophrenia is one of the ten most incapacitating diseases in the world. In Brazil, around R$ 200 million are spent each year in public health care for this disorder and its indirect costs are incalculable since schizophrenia affects individuals and their relatives at the peak of their productive lives. At present, there is no disease-modifying treatment for schizophrenia.
Methods: Human induced pluripotent stem (iPS) cells represent a novel model to study neurodevelopmental disorders, including schizophrenia. Our laboratory has successfully generated iPS cells from controls and patients with schizophrenia. Briefly, cells were plated and viral infection was performed by the addition of four Sendai viruses. Neural cells were characterized by a series of neuronal development assays and also mitochondrial morphology, physiology and unbalance of trace-elements.
Results: We described that neural cells, derived from 2 clones of iPS cells generated from skin fibroblasts of a clozapine-resistant schizophrenic patient, presented a twofold increase in extramitochondrial oxygen consumption as well as elevated levels of reactive oxygen species (ROS), when compared to controls. We also used synchrotron radiation X-ray microfluorescence spectroscopy to analyze trace element levels in those neural progenitor cells. Our data reveal the presence of elevated levels of potassium and zinc in schizophrenic NPCs. Neural cells treated with valproate, an adjunctive medication for schizophrenia, reduced ROS levels and brought potassium and zinc content back to control levels.
Conclusion: Our model shows evidence that metabolic and trace-elements changes occurring during neurogenesis are associated with schizophrenia, highlighting potential targets for drug screening.
ID: 2083281

A NETWORK ANALYSIS ON TRAUMA, DISSOCIATION AND SCHIZOPHRENIC SYMPTOMS IN SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Schizophrenia spectrum disorders and dissociative disorders are described in the DSM-5 and ICD-10 as two categorically distinct diagnostic groups. However, several studies have shown high comorbidity between these diagnoses. In addition, symptoms typically associated with one of the two diagnostic groups have been found in the other diagnostic group (e.g. dissociation and hallucinations). It has been suggested that the overlap in dissociative symptoms might be caused by a shared causal factor, specifically trauma. The aim of the current study was to examine the relationship between trauma, dissociation and schizophrenic symptoms. The study builds on previous research by examining the data through the network model of psychopathology.
Methods: The sample consisted of 300 patients diagnosed with a schizophrenia spectrum disorder. Participants were interviewed with the Positive and Negative Syndrome Scale (PANSS). Participants also filled in the Dissociative Experiences Scale and Trauma History Questionnaire. Correlations were computed between trauma, dissociation, and schizophrenia symptoms. This was followed by a regression analysis predicting dissociation from trauma and schizophrenic symptoms. Lastly the data were analyzed through network analysis using R with the package Qgraph.
Results: Sexual and physical trauma correlated significantly with dissociation. Sexual trauma also correlated with the PANSS general symptoms scale. Crime related trauma correlated significantly with positive symptoms but trauma did not correlate with negative symptoms. Dissociative symptoms and positive symptoms correlated significantly with each other. The regression analysis showed that sexual trauma and positive symptoms explained 15% of the variance in dissociative symptoms. The network analysis showed that dissociative symptoms formed a unique symptom cluster. Individual dissociative symptoms were strongly related to each other but loosely with schizophrenic symptoms and trauma.
Conclusion: The results are in line with previous research showing relations between trauma dissociation and positive symptoms. However, this study also shows these relations explain only a small part of the dissociation in this patient group. In addition, the results indicate that, although dissociation is related to positive symptoms, it should be treated as a separate symptom of interest.
ID: 2086539

RELATIONAL DIMENSIONS BETWEEN VOICE-HEARER AND VOICES: A PHENOMENOLOGICAL ANALYSIS

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Background: Auditory Verbal Hallucinations (AVHs) exist along a continuum in psychiatric and non-psychiatric populations. Complex AVHs are frequently experienced as interpersonal characteristics with attributes of actual individuals. Patients often interact with their AVHs and have described their relationships as similar to relationships with other people (Hayward et al. 2011). Strikingly, systematic investigations of the first person descriptions of the phenomenology of the relationship between the hearer and voices is virtually absent from the literature (Waters et al. 2014).
Methods: Subjects between the ages of 21 and 65 with AVHs were recruited from the University of Illinois Medical Center. A mixed methods triangulation design involving qualitative (Atlas/ti) and quantitative components were used. A priority-sequence model of complementarity was applied by which the quantitative data examined furthered the principal qualitative analyses in order to test elements of emergent themes. The primary measure used was the Maastricht Interview for Voice Hearers (Romme & Escher, 2000).
Results: Of the total sample (n=20), 85% were diagnosed with schizophrenia and 15% with bipolar disorder with psychosis. The qualitative analysis identified three overarching constructs pertaining to the relationship between self and voices: 'voices and interpretation of origin', 'voices as distinct interpersonal identities', and 'voices and locus of control'. When subjects actively engaged and conversed with the voices, they reported increased ability to influence, change, control and refuse orders ($X2=6.29, df=1, p<0.01$). Subjects who experienced more than one voice frequently reported unique and distinct relationships between themselves and their AVHs as well as 'voice to voice' relationships with dialogue between different voices ($X2=4.67, df=1, p<0.03$).
Conclusion: Data emerging from this study suggests that the dimensions of the relational phenomena between hearer and voice(s) are dynamic, can be influenced, and changed by the hearers' engaging, conversing, and negotiating with their voices. These findings strongly affirm the value of future work on the relational phenomenology of voices.
ID: 2083386

PREVENTING PSYCHOSIS: A EUROPEAN PERSPECTIVE ON GUIDELINES, MODELS AND NEXT TASKS

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Background: As prevention of psychosis becomes more widely accepted, it seems necessary to provide guidance for prediction as well as prevention, reflecting their current capabilities, but also their requirements and limitations. And, to further improve risk estimation and thereby optimize the cost-benefit ratio of preventive measures, additional variables have to be considered.
Methods: Two sets of meta-analyses were performed to inform the guidance project of the European Psychiatric Association. Methodological approaches like risk stratification and pattern recognition as well as neurocognitive/-biological methods related to information processing or brain morphology were investigated to improve prediction.
Results: 42 samples, mainly defined by ultra-high risk criteria and/or the basic symptom criterion 'COGDIS', were included into the prediction related meta-analyses. Pooled conversion rate at >4-year follow-up was 37.0% in UHR samples and 61.3% in COGDIS samples. 15 studies were included into the meta-analyses on prevention. The 12-month pooled risk ratio was 0.44, the NNT was 10. Psychosocial functioning seemed not to improve, however results were inconclusive due to methodological issues of the trials. Both meta-analyses indicated age related differences.
Recent studies on new markers identified neurocognitive and ERP/EEG measures as well as structural MRI as most promising candidates to support an individualized risk estimation based on risk stratification.
Conclusion: Several recommendations were developed to guide prediction and prevention, emphasizing the need for age-adapted strategies.
Regarding information processing, MMN seems to be the most promising candidate for a multi-step algorithm for risk estimation, followed by P300 and processing speed; regarding imaging based approaches, support vector machine based analysis of structural MRI produced first impressive results.
However, all current criteria and prediction models rely on baseline measures, treating them as stable over time and thus linearly related to a future mental state. Yet, with regard to current developmental models of psychotic disorders, risk should be conceptualized as dynamically modulated over time and thus presumably non-linearly related to future outcome. Therefore, studies need to consider the fluid interplay of risk and resilience factors to advance prediction significantly, as does the EU funded PRONIA project, which started this year (FP7/2007–2013; Grant Agreement N° 602152; www.pronia.eu).
ID: 2087552

NOVEL OBJECTIVE ASSESSMENT OF EXPLORATORY BEHAVIOUR AND ACTIVITY PREFERENCE IN SCHIZOPHRENIA USING MOTION CAPTURE

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Background: Motivational deficits are a key feature of schizophrenia that confers substantial functional consequences. Deficits have been observed in exploratory behaviour and non-passive activity engagement, both important components of motivated behaviour. However, previous findings have relied heavily on subjective assessment. Our aim was to objectively evaluate novelty exploration and activity engagement in schizophrenia.
Methods: Stable adult outpatients with schizophrenia (SZ) and matched healthy controls (HC) were assessed using our Novelty Exploration Task (participants spent time in a novel environment with familiar and uncommon objects) and Activity Preference Task (participants were offered the choice between two activities, one of which required active

engagement). Participants were alone in a room for three blocks of five minutes for each task while behavioural data were collected by wireless motion capture. Clinical assessments of positive and negative symptoms, apathy, depression, cognition, and community functioning were also administered.
Results: Preliminary results from 16 SZ and 13 HC subjects were analyzed non-parametrically due to the substantial variance in motion data for this small sample. There were trends towards significant differences between how SZ and HC engaged in the exploration task, namely in the complexity of movement during the initial block and in the tendency to sustain movement throughout the task (for both Mann-Whitney U(27)=60.000, Z=-1.930, p=0.054). Further, clinical measures of apathy correlated with tendency to interact with objects in this task, both in the SZ group (Spearman ρ=-0.566, p=0.022) and in the overall sample (ρ=-0.371, p=0.048). Although there were no group differences in the latter task, engagement in non-passive activity in the SZ group was also strongly correlated with apathy (ρ=-0.806, p<0.001), as well as with negative symptoms (ρ=-0.682, p=0.004) and functioning (ρ=0.506, p=0.045), and to a lesser extent in the overall sample with apathy (ρ=-0.499, p=0.006) and functioning (ρ=0.357, p=0.057).
Conclusion: Initial findings from this pilot study suggest that this novel approach may be a valuable means of quantifying exploratory behaviour and activity engagement in schizophrenia. A larger sample size is needed to further establish the validity and utility of this methodology. Ultimately, this approach may offer advantages over current subjective assessments of important deficits in schizophrenia.
ID: 2086659

DECLINING TRANSITION RATES TO PSYCHOSIS: THE ROLE OF DIAGNOSTIC SPECTRA AND SYMPTOM OVERLAPS IN INDIVIDUALS WITH ATTENUATED PSYCHOSIS SYNDROME

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Background: Transition to psychosis in at-risk individuals has markedly declined in recent years. So far it has never been discussed in detail that with the growing awareness increasing availability of early psychosis services, a much broader diagnostic spectrum is now being seen in these services. Subsequently, subjects present with symptoms that meet psychosis risk on a purely psychometric basis but may be the phenotypical expression of another underlying mental disorder.
Methods: A critical review is provided four groups of symptoms and clinical features that are frequently reported by individuals with suspected psychosis risk states, yet share strong commonalities with other mental disorders and conditions: isolated hallucinations; unusual bodily perceptions, hypochondriatic fears and cenesthetic psychotic symptoms; depersonalization; obsessive-compulsive, overvalued and delusional ideas.
Results: Of the 616 individuals so far assessed in the Bruderholz Early Psychosis Outpatient Service for Adolescents and Young Adults, 218 (30.5%) met ultra-high risk (UHR) criteria, 188 (86.2%) of which suffered from one of the four above mentioned symptom groups.
Conclusion: The appraisal of the diagnostic spectra and their overlapping symptoms constitute a tremendous challenge in the clinical assessment of each referred individual. The final conclusion of a clinical assessment should not end with the mere assignment - or non-assignment - to a presumed psychosis risk group, but needs to take into account the 'Gestalt' of these particular symptoms and clinical features and thus be based on many more facets than solely a psychometric or nosological approach. Such an approach may break down the heterogeneous psychosis risk group and enable appropriate treatment regimes.
ID: 2141987

FORMAL THOUGHT DISORDER IN NON-CLINICAL INDIVIDUALS WITH AUDITORY VERBAL HALLUCINATIONS.

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Background: Auditory verbal hallucinations (AVH) and formal thought disorder (FTD) may originate from the same aberration in the language system. The hypothesis of a shared neurobiological basis would be strengthened by the presence of FTD in individuals who frequently experience AVH, but do not meet DSM-IV criteria for a psychotic disorder.
Methods: In this study, FTD was quantified in 40 non-clinical subjects with AVH, in 50 healthy subjects without AVH and in 40 schizophrenia patients with AVH. Recorded speech samples were analysed by one rater who was blind to the presence/absence of AVH and to diagnosis, using the Thought and Language Index.
Results: Negative FTD was barely present in non-clinical subjects with AVH and in healthy controls without AVH. Positive FTD, however, was significantly higher in both groups experiencing AVH than in controls without AVH. Severity of positive FTD did not differ significantly between non-clinical subjects with AVH and schizophrenia patients with AVH.
Conclusion: Negative FTD (alogia) appears not to be associated with AVH. However, the fact that positive FTD (disorganised speech) in schizophrenia patients with AVH is equally high in non-clinical subjects with AVH indicates that these two symptoms tend to co-occur, which may be suggestive of a shared neurobiological substrate.
ID: 2149415

COMPARISON OF LANGUAGE, AFFECTIVITY AND MOTOR BEHAVIOR DOMAIN USING THE BERN PSYCHOPATHOLOGY SCALE (BPS) IN PATIENTS WITH SCHIZOPHRENIA AND MAJOR DEPRESSION

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Background: The study aimed to test whether patients with affective and non-affective endogenous psychoses would differ in three domains of psychopathology (language, affectivity and motor behavior) as assessed by the Bern Psychopathology Scale (BPS) in a cohort of patients with major depressive disorder (MDD) and schizophrenia spectrum disorders.
Methods: The study was conducted at the University Hospital of Psychiatry Bern, Switzerland and included 146 patients with schizophrenia spectrum disorders (77 men, 69 women) and 58 patients with MDD (31 men, 27 women). Inclusion criteria were MDD or psychotic episode due to schizophrenia, schizoaffective disorder or schizophreniform disorder. The global assessment of the severity of disturbance of the domains language (GSL), affectivity (GSA) and motor behavior (GSM) was rated on a seven-point scale (-3 = severely inhibited, -2 = moderately inhibited, -1 = mildly inhibited, 0 = normal, +1 = mildly disinhibited, +2 = moderately disinhibited, +3 = severely disinhibited). Patients were additionally interviewed using the Positive and Negative Syndrome Scale (PANSS) and the Hamilton Rating Scale for Depression (HAMD).

Results: In each domain the majority of patients endorsed normal or slightly abnormal ratings (0, -1 or +1), irrespective of the diagnostic entity. At group level more pronounced negative ratings of affect were seen in MDD. In contrast, group comparisons of the severity ratings on language or motor behavior yielded no differences between schizophrenia spectrum disorders and MDD. In terms of endorsement of severity ratings, schizophrenia spectrum disorders demonstrated increased variance in the language and affect domains, but not in the motor domain. At the individuals' levels, extreme ratings in the language and motor domain were more frequent in schizophrenia and in the affect domain more frequent in MDD.
Conclusion: Schizophrenia spectrum disorder patients and patients with acute major depressive episodes share many psychopathological features as assessed by the BPS. There are no unique symptom profiles. However, the groups differ in the severity of affect ratings as well as in the distribution of language and affect ratings with more variance among the group of non-affective psychoses. Thus, psychopathological heterogeneity among schizophrenia spectrum disorders is more common than among depressed patients.
ID: 2070326

CONFIRMATORY AND EXPLORATORY FACTOR ANALYSIS OF THE SOPS

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Background: The Scale of Psychosis-Risk Symptoms (SOPS), the rating part of the Structured Interview for Psychosis-risk Syndromes (SIPS, Miller et al. 2003), has been widely employed to assess putative prodromal symptoms of psychosis. As there are 19 subscales, studies assessing symptom intensity typically use the sum scores of the a priori defined Positive, Negative, Disorganized, and General Symptoms scales. This approach is simplistic in assuming the validity of the original categorization, and equal linear weight as evidence of all the subscales forming a sum score.
Methods: To extract the underlying latent dimensions, several studies have examined the factorial structure of the SOPS (Hawkins et al. 2004; Comparelli et al. 2011; Jung et al. 2010; Klaassen et al. 2011). We tested these models in confirmatory factor analyses (CFA) of SOPS ratings of the adolescents in the combined baseline samples of the JERI and Helsinki Prodromal studies (N=211), and followed up with an explorative factor analysis of our data. All these models all showed fairly poor fit, with CFI <.88, and RMSEA >.1. The only exception was the Klaassen (2011) model, which had a CFI of .92, but used only 13 of 19 variables. A likely explanation for the poor fit was that the samples in the previous studies were small, and that inappropriate linear factoring models were employed.
Results: In exploratory one- to five-dimensional factor analyses of all 19 items, using the five-dimensional model showed the best fit (RMSEA 0.05, CFI 0.98, WRMR 0.45). The five dimensions were easily interpretable as Positive, Grandiosity, Negative, Disorganization, and General symptoms. However, significant cross-loadings were present for six items. The found structure had several differences from the a priori model as, for instance, the Disorganized Communication item primarily loaded on Disorganization rather than positive symptoms.
Conclusion: The Klaassen 2011 and the present latent trait models offer significant improvements over using default sum scores, and are recommended for all future research using SOPS factors.
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Miller TJ, et al., 2003. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophr Bull 29(4) 703–15.
ID: 2118294

RESILIENCE AND RECOVERY: SHORT AND LONG-TERM OUTCOMES

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Background: In two longitudinal studies we examine the relationship between resilience and recovery from schizophrenia, and aim to explore resilience as a possible predictor for better short- and long-term functioning.
Methods: The long-term study included 17 persons, who at baseline were considered to be fully recovered from schizophrenia. They were assessed at 15-year follow-up with measures of psychosocial functioning (Global Assessment of Functioning) and resilience (Connor Davidson Resilience Scale). Evaluations of outcomes were based on operational criteria of remission and full recovery. In the study of short- term outcome (3 year follow-up), results were derived from the ongoing prospective Oslo Multi-follow-up Study. Twenty eight first-episode schizophrenia patients are assessed at multiple follow-up points with a clinical interview, an inventory of social and role functioning (Global Functioning: Social; Global Functioning: Role) and a measure of resilience (Connor Davidson Resilience Scale). Operational criteria of remission and full recovery are applied as well. The participants are divided into three separate groups according to their scores on the social and role functioning inventory: non-remitted, remitted, and fully recovered. Further analyses are performed with these groups.
Results: In the long-term study (15-year follow-up), a significant correlation between resilience and present psychosocial functioning was shown. There was also a significant difference between fully recovered participants and those in remission regarding their resilience scores. The majority of participants had maintained their recovery, had not used medication for seventeen years, and was more resilient. In the short-term study, statistical analyses with mixed models showed that resilience was related to role functioning. Resilience did not vary significantly over time, but there was a significant difference between remitted and fully recovered participants in role functioning at the time of follow-up.
Conclusion: Thus, a sustained full recovery without medication seems possible for a subgroup of schizophrenia patients characterized by high resilience. In the early course of the disorder resilience appears to be negatively affected by the illness, but contributes to better role functioning when symptom intensity decreases.
ID: 2085405

NOVEL INSTRUMENTAL DEVICES MEASURING MOVEMENT DISORDERS IN PSYCHIATRY: A PARADIGM SHIFT

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Background: For the purpose of diagnosis, prognosis, treatment, and prevention of mental disorders, motor disorders (MD) are less used, than mental and cognitive symptoms and signs. However, the accuracy of both mental and cognitive symptoms and signs are limited in this respect, whereas motor dysfunctions may be more accurate predictors, possibly

as they are phenotypes of neurodevelopmental vulnerability and may be highly informative in terms of treatment and prognosis. Indeed, several studies showed that subtle MD predict conversion to psychosis in Ultra High Risk individuals1.
Therefore, a case can be made for standard measurement of MD in psychiatric research and clinical practice. This requires valid, reliable, sensitive and practicable devices for measuring MD. Previously, we showed that a mechanical device for measuring lingual dyskinesia, tremor, and bradykinesia, was reliable and valid and was significantly more sensitive in detecting MD than traditional clinical MD-rating scales 2,3.
However, electronic devices are more feasible and therefore we studied recently, two electronic devices.
Methods: The validity, reliability and feasibility of an electronic device measuring bradykinesia was studied, and also the practical use of an actimeter in a lifestyle program.
Results: The wearable motion-capture device (XSENS technology®) had a high reliability (ICC=0.79, p<0.01, N=25) and high validity for measuring bradykinesia. These results are based on the correlation between the Unified Parkinson Disease Rating Scale (UPDRS; bradykinesia subscale) and the XSENS data (r2 = 0.55, p < 0.01, N=64).
In a lifestyle program, an actimeter (ActiGraph GT3X+) revealed lower activity during a lifestyle program in long-stay patients with a mental disorder (N=184), than in healthy controls (N=54).
Also, we will present the novel potential use of Kinect technology for measuring dyskinesia.
Conclusion: Several available devices for measuring MD are promising, as they have good diagnostic and treatment and possible also prognostic and preventive value in psychiatry.
Literature
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ID: 2074112

VIRTUAL REALITY EXPERIMENTS LINKING SOCIAL ENVIRONMENT, STRESS SENSITIZATION AND PSYCHOSIS

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Background: Environmental factors such as childhood trauma and ethnic minority status may be related to risk for psychotic disorders by the mechanism of sensitization to social stress. Virtual Reality (VR) provides the opportunity to test this mechanism by controlled experimental exposure to different social environments.
Methods: Patients with different psychosis liability (first-episode psychosis (FEP; N=56), siblings (N=45), ultra high risk individuals (UHR; N=19) and healthy controls (N=54)) were repeatedly exposed to a virtual environment. In five experiments in random order, degree of virtual environmental social stress was varied, by manipulation of population density, ethnic density and hostility of virtual characters. State paranoia (SSPS) and subjective distress (SUD) were measured at baseline and after each experiment. Repeated measures ANOVA was used to test differences between groups and experiments.
Results: State paranoia increased with degree of virtual social stress, F=62.01 (df=4), p<0.001, and differed across groups (interaction experiment and liability group, F=2.32 (df=12), p=0.007). FEP and UHR responded with higher levels of paranoia and distress to social stress exposure than siblings and controls in all experiments. Participants with a history of childhood trauma reported more paranoia and distress. There was a significant interaction between liability to psychosis, childhood trauma and degree of virtual social stress, both for paranoia (F=1.569, df=23.27 [with Huynh-Felt correction], p=0.045) and distress (F=1.811, df=28 [sphericity assumed], p=0.007). Ethnic minorities had lower state paranoia than Dutch across conditions.
Conclusion: This large experimental study shows that exposure to virtual social stress environments is related to increased state paranoia and subjective distress, in particular in individuals with high liability to psychosis and a history of childhood trauma, but not in those with ethnic minority status.
ID: 2117512

SPONTANEOUS GROSS MOTOR ACTIVITY - LESSONS LEARNED FROM ACTIGRAPHY

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Background: Abnormal motor behavior is found throughout the course of treated and untreated schizophrenia spectrum disorders. The complexity of clinical presentations and the scarcity of assessment methods however have hampered investigations of the schizophrenia motor dimension. Our group used objective means of assessing spontaneous motor behavior in real life situations to study the association of motor behavior with clinical course and neurobiology in schizophrenia.
Methods: In a series of studies, we assessed motor activity in patients with schizophrenia spectrum disorders with 24 h of continuous wrist actigraphy (Actiwatch) at the nondominant arm. The marker activity level (AL) was derived as mean sum of movements per hour during the individual wake periods of the 24 h recording time. We explored associations with psychopathological rating scales and MR-imaging of grey matter density.
Results: 1. Course- Comparing AL between admission and discharge from inpatient treatment of an acute psychotic episode in 34 patients failed to detect differences (T = 0.03, p = 0.779). This is despite pronounced changes in PANSS scores. However, AL at admission predicted the outcome of negative symptoms: patients with low AL at baseline experience a decline in negative syndrome scores during treatment. Likewise, AL remains stable between psychotic episodes (n = 18) with high correlation between time points (r = 0.81, p < 0.001). 2. Early psychosis- We detected higher AL in subjects with the first episode of psychosis (n = 33) compared to subjects with multiple episodes (n = 115), correcting for age, negative syndrome scores and chlorpromazine equivalents (F = 6.2, df = 4, p < 0.001). Interestingly, higher antipsychotic doses were associated with reduced AL in first episode patients (r = -0.46, p = 0.008), but CPZ were not correlated to AL in multiple episode patients. 3. Neuroimaging correlates- In a recent study in 32 schizophrenia patients, AL correlated with grey matter density in the left lateral premotor cortex (T = 6.07, p = 0.044 with family wise error correction).
Conclusion: Wrist actigraphy allows for convenient, objective assessment of spontaneous motor activity in schizophrenia spectrum disorders. It is informative on a number of clinical issues and aids investigating the cerebral motor system in schizophrenia. In the future, actigraphy should be implemented in clinical trials in order to objectively monitor spontaneous motor behavior.
ID: 2074312

PLURIPOTENTIALITY AND INCIDENT DIAGNOSTIC OUTCOMES IN PATIENTS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: It is generally accepted that the clinical high-risk syndrome (CHR) for psychosis is pluripotential with respect to conversion to psychosis vs syndrome persistence vs remission. Whether the CHR syndrome is also pluripotential with respect to diagnostic specificity of incident outcomes, however, is controversial.
Methods: We collected two samples (NAPLS-1, PREDICT) of CHR patients that were affiliated with control groups drawn from patients who responded to CHR recruitment efforts but did not meet CHR criteria on interview (help-seeking controls, HSC). Incident diagnostic outcomes were defined as the first occurrence of either a SIPS-defined psychosis or a structured interview diagnosis from one of three non-psychotic DSM-IV groups (bipolar, non-bipolar depression, anxiety), when no diagnosis in that group was present at baseline.
Results: Logistic regression analyses revealed no significant study x baseline status interaction for any incident diagnostic outcome; data from the two studies were therefore combined. CHR (n=271) vs HSC (n=171) incident outcomes were: psychosis 18.5% vs 1.2%, bipolar disorders 1.1% vs 1.2%, non-bipolar depression 4.8% vs 5.3%, and anxiety disorders 5.9% vs 5.8%. The main effect of CHR vs HSC was statistically significant (OR=19.5, 95% CI 4.7 to 81.6, df=1, p<0.001) for incident psychosis but not for any incident nonpsychotic disorder. Within the CHR group psychosis was significantly more likely than nonpsychotic disorder (bipolar, non-bipolar depression, and anxiety combined, Q=4.5, df=1, p=0.035).
Conclusion: Incident nonpsychotic disorders emerged during follow-up of CHR patients no more frequently than in non-CHR patients. Psychosis was relatively specific as an incident diagnostic outcome in CHR patients.
ID: 2118857

THE SUICIDE IDEATION AND BEHAVIOR ASSESSMENT TOOL (SIBAT): DEVELOPMENT OF A NOVEL MEASURE OF SUICIDAL IDEATION AND PERCEIVED RISK

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Background: Suicide is one of the leading causes of preventable death. Clinicians wanting to monitor suicide ideation, behavior, and risk require a tool that includes all of these components. Ideally, it should allow assessment of change as the result of intervention. We describe the development of such an instrument, the Suicide Ideation and Behavior Assessment Tool (SIBAT), and present preliminary information on item content.
The SIBAT is based on an established measure of suicide ideation and behavior, the ISST-Plus. Items from the ISST-Plus have been reorganized into 10 modules that allow for efficient, comprehensive data collection. It is divided into patient-self-report and clinician-rated sections. Its modular structure allows for customization, and the administration of specific modules can be adjusted to meet clinicians' needs. Thus, responses less susceptible to change (eg, demographics, medical history) are segregated into modules distinct from those responses more likely to fluctuate (eg, current suicidal ideation).
Methods: The SIBAT Consortium, a group of clinical trial and academic experts in scale development, suicidology, and clinical management of suicidal patients, met regularly over 18 months and developed a modular instrument based on consensus, review of suicide literature, and the ISST-Plus. During revisions of the provisional version of the SIBAT scale, modules were added and item wordings refined. A draft version agreed upon by the SIBAT Consortium was reviewed by 14 patients from a psychiatric clinical research setting and by 686 members of Patients Like Me, an online patient community. All subjects, who had a history of suicide ideation/behavior, evaluated SIBAT items in patient-reported modules in terms of semantic clarity, relevance, and adequacy of response. This feedback was incorporated and approved by the SIBAT Consortium. A validation trial is planned to examine reliability, and will include exploratory factor and item response theory analyses.
Results: Modifications of selected SIBAT items based on these cognitive interviews will be presented.
Conclusion: The SIBAT facilitates comprehensive assessment of suicide ideation, behavior, and risk by combining a flexible modular structure and comprehensive patient-reported assessments that can be systematically reviewed by clinicians for assessing suicide risk. The extensive cognitive reviews allowed incorporation of input from diverse sources to support broad application.
ID: 2091364

STIGMA OF THE HIGH RISK STATE FOR PSYCHOSIS AND ITS RELATIONSHIP WITH ANXIETY AND DEPRESSION

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Background: Despite the great benefits offered by the 'high-risk' for psychosis (HRP) identification in the early detection of psychosis, concerns have been expressed about the HRP designation as a stigmatizing status for young adults, because >60% of those identified as HRP will not progress to psychosis. We hypothesize, in one of the first studies of stigma in this group, that stigma will be associated with difficulties in socioaffective constructs, including anxiety and depression.
Methods: Thirty-eight (n=38) HRP subjects were recruited from 2010–2014 from Columbia University's Center of Prevention and Evaluation. Stigma and socioaffective constructs were assessed cross-sectionally. Cases were identified using the Structured Interview for Prodromal Syndromes (Kappa >.7). Internalized stigma measures included "Stereotype Awareness", "Stereotype Agreement", 'Shame-related emotions' and "Stigma engulfment" (when stigma becomes fully internalized). The intercorrelations between stigma variables were tested. Socioaffective constructs distinct from HRP symptomatology were measured by: 1) Social Anhedonia; 2) Social Anxiety; 3) General Anxiety; 4) Beck Depression Inventory. Multivariate regressions were conducted with each socioaffective construct and stigma variables entered as independent variables, with positive symptoms, negative symptoms, and disorganized symptoms associated with the HRP syndrome controlled for.
Results: Patients were ethnically diverse, 62.5% were male, with mean 21.8 (3.3) years. Stigma variables were significantly associated in the hypothesized manner; 'stereotype awareness' was associated with 'stereotype agreement' (r(38)= .36, p<.05), 'stereotype agreement' was associated with 'shame-related emotions' (r(38)= .37, p<.05), and 'shame-related emotions'

was associated with 'identity engulfment' ($r(38)= .39$, $p<.05$). When examining stigma's association with socioaffective constructs via regression, none of the HRP symptomatology variables were significantly associated with socioaffective constructs. However, the stigma variable of 'identity engulfment' remained significantly associated with social anxiety ($p=.011$), general anxiety ($p=.003$), and depressive symptoms ($p=.014$), and evidenced a trend association for social anhedonia ($p=.058$) even after accounting for HRP symptomatology.

Conclusion: Internalized stigma was associated with socioaffective constructs among HRP individuals, and reducing stigma might ameliorate anxiety and depression.

ID: 2116759

Drug Side Effects & Physical Illness; Health Economics & Services

COMPARISON OF FOUR FIRST EPISODE PSYCHOSIS FIDELITY SCALES

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Background: Program fidelity has been defined as the extent to which delivery of an intervention adheres to the protocol of an evidence-based program model. Fidelity scales provide a list of objective criteria by which a program is judged to adhere to a reference standard for the intervention. Fidelity Scales can be developed using different strategies and can use different measurement strategies. We describe the development of The Calgary First Episode Psychosis Team Scale (CFEPS) and compare the components and measurement scales with three other scales, two used in North America and one in the United Kingdom.
Methods: The components for CFEPS were identified from, a systematic review of the peer reviewed literature of FEPS published between Jan 1980 to April 2010, an International expert Delphi consensus process and a systematic review of fidelity measures for team based mental health services. The level of supporting evidence was the primary criterion for selecting components. An iterative process between the investigators was used refine the descriptors and the anchor points. We compared the content of the scale with the content of 3 other fidelity measures.
Results: Seventy five components were identified from the systematic review. The expert Delphi consensus process reduced the number to 32. The final scale includes 32 items including service components identified in the second systematic review. 29 items assess the services delivered and 11 describe team functioning. In comparison to other scales, The CFEPS had the fewest items 32, the UK scale the largest at 64. Most of the CFEPS components are common to the other 3 measures but there are components in the other scales that differ. Scales also differ in how they report the results with some using a threshold for acceptability, others a five point rating scale.
Conclusion: CFEPS offers a parsimonious scale that uses a five point rating scale for each measure. It has been developed using formal knowledge synthesis strategies and is designed to assess any program rather than a particular program model. Its components are common to other measures which include quality measures that are not specific to early intervention services.
ID: 2117568

CALGARY FIRST EPISODE PSYCHOSIS FIDELITY SCALE

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Background: Program fidelity has been defined as the extent to which delivery of an intervention adheres to the protocol of an evidence-based program model. Fidelity scales provide a list of objective criteria by which a program is judged to adhere to a reference standard for the intervention. There is no generally accepted fidelity scale to measure how the services conform to evidence-based practices. The Calgary First Episode Psychosis Team Scale has been developed to fill this need.
Methods: The components in this scale were identified from three sources, a systematic review of the peer reviewed literature of FEPS efficacy covering the period Jan 1980 to April 2010, an expert Delphi consensus building process and a systematic review of fidelity measures for team based mental health services. The level of supporting evidence was the primary criterion for selecting components. An iterative process between the investigators was used refine the descriptors and the anchor points. The scale was piloted in a single centre and a semi structured interview guide was developed to aid raters. We developed two versions of the scale, a team version designed to assess the services delivered by a team and a patient version designed to assess the services delivered to an individual patient.
Results: Seventy five components were identified from the systematic review. The expert Delphi consensus process reduced the number to 32. The final scale includes 32 items including service components identified in the second systematic review. 29 items assess the services delivered and 11 describe team functioning. Each item is composed of a stem, which describes a service component. Priority was given to items that are specific to FEPS. Each component is rated on a scale of 1 to 5.Descriptors provide anchor points for each rating. In a pilot study items were rated based on information from health system databases, health records, interviews with staff, patients and families. All items could be assessed during the study. The content was compared with audit tools developed for use in the United States and United Kingdom.
Conclusion: We have developed a fidelity scale that can be used for both research and for accreditation or quality control. It has face validity in that the items are based on a literature review and review by experts. The item content is similar to that being used in a number of FEPS program audit tools developed in the United States and United Kingdom. Inter rater reliability testing is underway.
ID: 2093118

DRUG INDUCED MOVEMENT DISORDERS ARE AS FREQUENT IN THOSE ON SECOND GENERATION ANTIPSYCHOTICS AS THOSE ON FIRST GENERATION IN SEVERELY MENTALLY ILL HOSPITALIZED PATIENTS

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Background: In the controlled trials of second generation antipsychotics (SGA) compared with first generation antipsychotics (FGA) the rates of movement disorders were much lower in SGA. The impression of those working in long term hospitals is that there is much less movement disorder than 30 years ago. But there are a number of surveys and community studies showing rates are similar in FGA and SGA.
Methods: 169 of 246 patients in a State Psychiatric Hospital were examined for the following movement disorders: Tardive Dyskinesia (TD) with the Abnormal Involuntary Movement Scale (AIMS); Parkinsonism with the Simpson Angus Neurological Rating Scale (SANRS); Akathisia with the Barnes Akathisia Scale (BAS); Dystonia with this item from the Chouinard Extra-Pyramidal Rating Scale; and Intention Tremor.
Results: The overall rate of TD was 32%. 36% of the 22 on FGA, 28% of the 108 on SGA and 3% of the 38 on both FGA and SGA had TD.
The overall rate of Parkinsonism was 34%: 42% in the 21 on FGA, 33% in the 107 on SGA and 35% in the 37 on both.
Only five of the 156 fully examined for Akathisia had it, all on SGA: 4 of 104 only on SGA, one of 33 on both FGA and SGA. 11 had Pseudo-Akathisia: 2 of 19 (10%) on FGA only, 6 of 107 (6%) on SGA and 3 of 36 (8%) on both.
1 of 16 (6%) on FGA, 12 of 103 (12%) on SGA and 2 of 36 (6%) on both had dystonia.

1 of 12 (8%) on FGA, 15 of 80 (19%) on SGA and 4 of 28 (14%) on both had intention tremor.
Mean age of those on SGA was 52, on FGA 45 and on both 46.
52% of those on FGA, 21% on SGA and 68% on both were taking anticholinergics.
The mean Chlorpromazine equivalent daily dose of those on FGA was 1333mg but with Parkinsonism or TD it was around 2300mg and without these it was around 1100mg; for those on SGA the mean was 652mg and the same with or without Parkinsonism or TD; for those on both SGA and FGA the mean was 2217mg and about the same with and without Parkinsonism or TD.
Conclusion: In this population movement disorders occurred at about the same rate in those on SGA as FGA but TD is much lower in those on both. Perhaps SGA somehow protect from FGA induced TD. Akathisia rates were surprisingly low, perhaps because thes patients had been taking antipsychotics for so long.
Possible reasons for the broadly similar rates were the older age of those on SGA (7 years) and higher rates of anticholinergic use in FGA, but not the dosage which was much lower in SGA.
The overall rate of TD (32%) was half that in a similar State Hospital in 1978 (62%), using the same criteria.
ID: 2090501

METABOLIC PARAMETERS PRIOR TO THE ONSET OF PSYCHOSIS IN THE NORTH AMERICAN PRODROME LONGITUDINAL STUDIES (NAPLS) CONSORTIUM

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Background: Patients with schizophrenia have a high prevalence of metabolic disorders and cardiovascular mortality. Few studies have examined metabolic risk factors in drug-naive psychotic patients, but higher than expected rates of insulin resistance, elevated plasma glucose, and cortisol have been reported and may be present prior to the onset of psychosis. In this study we investigate metabolic and cardiovascular indices in a cohort at Clinical High Risk (CHR) for psychosis from the NAPLS Omega 3 Fatty Acid Clinical Trial.
Methods: Subjects met CHR criteria per the Structured Interview of Prodromal Syndromes, received physical exams and metabolic monitoring prior to randomization into the Omega 3 trial. Antipsychotic medication or history of diabetes were exclusions. Anthropometrical measures, vital signs, glucose and lipids were assessed.
Results: The sample included 109 CHR subjects (46% Female) ages 12–29 (Mean/SD = 18.3/4.4). The mean calculated BMI was 24.2 (range 16–52.8) with 31% of the sample either Overweight (13.2%) or Obese (17.9%). 24.4% met criteria for abdominal obesity and 39.3% met criteria for prehypertension (>120–139/80-89mm Hg) or hypertension (>140/90mm Hg). Mean total cholesterol (Mean/SD: 157.3/30.3), LDL (88.6/23.1), HDL (51.7/12.2), and Triglycerides (82.9/41.2) were all within the normal range but 43.3% of the sample showed evidence of dyslipidemia. The mean fasting glucose was 84.2 (range 54–226) with 4.2% meeting criteria for prediabetes or diabetes. Using a proxy measure of insulin resistance (Triglycerides/HDL), 9% of the sample were in the insulin resistance range (>3.5). Metabolic parameters (BMI, Abdominal Circumference, glucose) were significantly associated with prodromal symptoms and worse role functioning (r's 0.22–0.30, p's <0.05-0.002). Greater levels of negative symptoms was associated with a diet consisting of few Omega 3 fatty acid rich foods (r -.20, p<0.05).
Conclusion: Teenagers and young adults at CHR for psychosis have rates of metabolic abnormalities including obesity, dyslipidemia and hypertension that approach those observed in an older first episode psychosis sample. Additionally, metabolic abnormalities are associated with greater symptoms and worse functioning at initial assessment suggesting that these parameters may be predictive of future outcome. Prevention and early detection of metabolic disturbances is crucial since most of these are modifiable with the potential for significant gains in terms of quality of life and physical health.
ID: 2117971

A POTENTIAL MECHANISM UNDERLYING ATYPICAL ANTIPSYCHOTIC INDUCED LIPID DISTURBANCES

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Background: Disturbances in lipid metabolism are frequently present in schizophrenia patients following treatment with atypical antipsychotic drugs (AAPDs). Previous findings suggested that a four-protein complex including sterol regulatory element binding protein (SREBP), a progesterone receptor membrane component 1 (PGRMC1), insulin induced genes (INSIGs) and SREBP-cleavage activating protein (SCAP), within the endoplasmic reticulum appears to be an important regulator responsible for AAPD-induced dyslipidemia.
Methods: Effects of typical and atypical antipsychotic drugs, as well as treatment outcome of steroid antagonist mifepristone on PGRMC1/INSIG/SCAP/SREBP pathways were investigated in rat liver by Western Blotting. Lipid metabolism were further evaluated by systematic analyses of serum triacylglycerols, total cholesterol, free fatty acids, and various hormones including progesterone, corticosterone and insulin.
Results: Following treatment with clozapine and risperidone, both lipogenesis and cholesterogenesis were enhanced by stimulating SCAP/SREBP expression via inhibition of PGRMC1/INSIG-2. Such effects, however, were not demonstrated in rats treated with aripiprazole, haloperidol and sertraline. Moreover, the add-on treatment of mifepristone is effective in reversing AAPD-induced dyslipidemia by upregulating the expression of PGRMC1/INSIG-2 and subsequent down-regulation of SCAP/SREBP.
Conclusion: Taken together, our findings suggest that disturbances in lipid metabolism occur at early stage of treatment prior to the presence of AAPDs-induced weight gain. Such metabolic defects can be corrected by an add-on treatment of steroid antagonist mifepristone mediated through an up regulation of PGRMC1 pathway.
ID: 2095377

Metabolic indices.

Experiment	Index	Control	Sertraline	Haloperidol	Aripiprazole	Risperidone (a)	Clozapine (a)
I	Lipids: Triglyceride (mmol/L)	0.79 ± 0.38	0.69 ± 0.20	0.61 ± 0.14	0.78 ± 0.19	1.22 ± 0.18*	1.21 ± 0.30*
	Total cholesterol (mmol/L)	1.50 ± 0.32	1.57 ± 0.30	1.53 ± 0.36	1.82 ± 0.33	2.07 ± 0.52*	2.55 ± 0.84**
	Free fatty acid (mmol/L)	0.74 ± 0.14	0.73 ± 0.12	0.88 ± 0.20	1.01 ± 0.28	2.41 ± 0.55***	2.94 ± 0.85***
	Hormones: Progesterone (nmol/L)	44.0 ± 28.9	124.6 ± 11.0	80.1 ± 48.8	65.4 ± 26.0	222.0 ± 81.5**	312.6 ± 16.9***
	Corticosterone (μmol/L)	0.54 ± 0.26	0.12 ± 0.11	0.82 ± 0.40	0.88 ± 0.29	3.14 ± 1.15***	1.76 ± 0.49**
	Insulin (mIU/L)	36.7 ± 12.1	39.2 ± 11.9	38.2 ± 11.8	32.0 ± 11.2	41.0 ± 8.5	43.0 ± 12.1
		Control	Clozapine	Risperidone	Clozapine+Mifepristone (b)	Risperidone+Mifepristone (b)	Mifepristone
II	Lipids: Triglyceride (mmol/L)	0.55 ± 0.33	1.86 ± 0.56	1.46 ± 0.35	0.29 ± 0.10***	0.29 ± 0.07***	0.41 ± 0.15
	Total cholesterol (mmol/L)	1.60 ± 0.33	2.67 ± 0.70	2.12 ± 0.57	1.34 ± 0.26**	1.03 ± 0.25***	1.27 ± 0.26
	Free fatty acid (mmol/L)	1.68 ± 0.55	3.09 ± 0.87	2.62 ± 0.54	1.31 ± 0.48***	1.33 ± 0.39**	1.33 ± 0.15
	Hormones: Progesterone (nmol/L)	49.8 ± 15.4	283.1 ± 20.6	139.6 ± 74.0	234.2 ± 84.2	139.6 ± 67.8	69.8 ± 18.1
	Corticosterone (μmol/L)	0.48 ± 0.23	2.67 ± 0.22	1.82 ± 0.47	2.13 ± 1.21	1.63 ± 0.97	0.52 ± 0.17
	Insulin (mIU/L)	28.7 ± 4.4	28.4 ± 5.9	30.5 ± 8.4	22.9 ± 7.1	23.3 ± 6.7	22.9 ± 4.2

a: vs control;
b: vs AAPD monotherapy;
*p<0.05, **p<0.01 and ***p<0.0001.

ENVIRONMENTAL CHARACTERISTICS THAT FACILITATE SUCCESSFUL COGNITIVE REMEDIATION IMPLEMENTATION IN AUSTRALIA

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Background: Treatment outcomes for people diagnosed with psychosis remain suboptimal due in part to the limited implementation of evidenced based practice (Proctor, 2009). In January 2012 a large metropolitan Mental Health service committed to a fundamental structural change to enhance evidenced based practice, moving from the traditional model of generic services being provided for a geographical area to a model of specialisation and triage based on diagnosis. A research study examined potentially modifiable organisational baseline factors that may influence the implementation of evidenced based cognitive interventions for psychosis.
Methods: One hundred-and-six mental health staff from Australia were surveyed to ascertain their attitudes, competencies and interest in Cognitive Behavioural Therapy for psychosis (CBTp) and Cognitive Remediation Therapy (CRT). In addition, a validated instrument the Organisational Culture Profile (OCP) was used to explore perceptions of organisational values..
Results: 82.1% of surveys were completed. Over 50% of staff were interested in CBTp and CRT approaches to psychosis. Staff were aware of existing local CBTp and CRT programs but these were not uniformly available throughout the service. Thirty one percent of staff identified as CBT therapist and 19 % were trained CRT facilitators. Only 19% of staff were receiving therapy specific supervision. The Organisational Culture Profile (OCP) at baseline revealed mixed results with innovation and communication receiving the lowest ratings.
Conclusion: The survey data and the CBTp and CRT programs in existence at baseline attest to a pre existing recognition of the benefit of these therapies in psychosis care in the service studied. Organisational issues identified included a need to develop training and supervision structures to up skill staff and sustain the programs. The current organisational culture is not characterised as innovative. These baseline organisational factors need to be accounted for to facilitate the dissemination of CBTp and CRT within the service. Understanding the baseline environmental characteristics of an organisation or population is necessary to plan for the successful implementation of new programs such as cognitive therapies for psychosis.
ID: 2086829

SINGLE VS. MULTIPLE ANTIPSYCHOTIC USE IN SCHIZOPHRENIA: COMPARISON OF DEMOGRAPHIC AND CLINICAL CHARACTERISTICS IN AN ACUTE INPATIENT SETTING

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Background: The prescription of antipsychotic polypharmacy continues to be an increasing practice in psychiatry despite the lack of sufficient

evidence to support its use. Antipsychotic polypharmacy is associated with increased hospitalization length of stay, treatment cost, total antipsychotic doses, side effects, and poor medication compliance. In this study, we aimed to investigate the use of single versus multiple antipsychotics in hospitalized patients with schizophrenia and compare the demographic, social and clinical characteristic between these groups.
Methods: Charts of 193 adult patients diagnosed with schizophrenia were examined retrospectively. Demographic and clinical data including past psychiatric history, length of stay, and antipsychotic prescription pattern was obtained. A questionnaire was created to register the information.
Results: From our study population, 146(76%) patients were on antipsychotic monotherapy (AM), 33(17%) on antipsychotic long-acting monotherapy (AMLA) and 14 (7%) on antipsychotic polytherapy (AP). Thirteen (93%) out of 14 patients on antipsychotic polytherapy, were admitted involuntarily. This finding was statistically significant (p=0.023) in comparison with patients in antipsychotic monotherapy. The antipsychotic long acting monotherapy group had vastly longer lengths of hospitalization (mean 11.58 ± 2.8 days; p=0.009). Interestingly, this group had less number of readmissions during the study period. This result was statistically significant (p=0.015). Most of the patients (98%) admitted on AM were discharged on one antipsychotic. Conversely, from 14 patients discharged on AP 6 were admitted on this regimen.
Conclusion: In this study, patients on AP were most likely admitted under involuntary status, suggesting that this population is sicker than the ones on AM. Patients on AMLA had longer stay in the hospital and less number of readmissions, suggesting that clinicians observe for response and side effects of the oral treatment before administering the long-acting medication and medication adherence improves after long-acting antipsychotic use, respectively.
ID: 2087357

CHANGES IN BODY MASS, METABOLIC PROFILE AND BRAIN MORPHOLOGY ASSOCIATED WITH ANTIPSYCHOTIC TREATMENT IN FIRST-EPISODE SCHIZOPHRENIA

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Background: We assessed relationships between changes in body mass index (BMI) and metabolic indices in antipsychotic-naïve or minimally treated patients during their first year of treatment, and in a subset of patients we investigated acute brain morphological changes in regions representing the homeostatic and hedonic food intake regulatory systems
Methods: 107 first-episode patients with schizophrenia or schizophreniform disorder were treated according to a standard algorithm with long-acting injectable flupenthixol decanoate over 12 months. BMI, fasting glucose and lipid profiles were assessed at baseline, 6 and 12 months. A subset 22 antipsychotic-naive patients and 23 matched healthy volunteers underwent structural MR imaging at weeks 0, 4 and 13 to assess acute effects of treatment on brain morphology. Images were reconstructed using freesurfer whole brain segmentation including a longitudinal processing stream. The ventral diencephalon and prefrontal cortex were selected to represent the homeostatic and hedonic food intake regulatory systems respectively.
Results: Eighty-three (78%) participants completed the 12 months of treatment. There were significant increases in BMI (p< .0001), waist circumference (p=0.0006) and triglycerides (p=0.03) and decrease in HDL (p=0.005), while systolic (p=0.7) and diastolic blood pressure (p=0.8), LDL (p=0.1), cholesterol (p=0.3), and glucose (p=0.9) values did not change over time. The triglyceride:HDL ratio increased by 91%. Change in BMI was significantly correlated with change in triglycerides (p=.008). For the subgroup undergoing MRI imaging, linear mixed effect models indicated significant group*time interactions for ventral diencephalic volume bilaterally. Ventral diencephalic volume reduction was significantly correlated bilaterally with body mass increase and HDL-cholesterol reductions, and unilaterally with blood glucose elevation. There were no significant changes in prefrontal cortical thickness.
Conclusion: The risks of weight gain and metabolic syndrome associated with antipsychotic treatment in first-episode schizophrenia are not restricted to second generation antipsychotics. This is a global problem, and developing communities may be particularly susceptible. The MRI findings implicate the ventral diencephalon, of which the hypothalamus is the main component, in the acute adipogenic and dyslipidaemic effects of antipsychotic medication.
ID: 2092245

VITAMIN D AND ITS CLINICAL CORRELATES IN EARLY AND ESTABLISHED PSYCHOSIS

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Background: Evidence from epidemiology, basic neuroscience and clinical studies connects low vitamin D to psychosis. Importantly, given the high rates of early death in psychosis, low vitamin D is also a cardiovascular risk factor.
Methods: We examined vitamin D levels at first onset of psychosis and in the same people 12 months later.
We also measured Vitamin D in a separate sample of 324 community patients with established psychosis.
All comparisons were adjusted for age, sex, ethnicity and season of sampling
Results: At first onset (n=166, 64% male), 18.7% had "sufficient" vitamin D (>20ng/ml), 39.2% "insufficient" (10–20 ng/ml) and 42.2% were deficient (<10ng/ml). Mean vitamin D was 13.64 (SD9.27). Low vitamin D at presentation correlated with Global Assessment of Function (GAF) scores at the time (r=.29, p=0.02) and with poorer function (GAF) (r=.33, p=0.05) and higher Calgary Depression scores (r=-.43, p=0.01) 12 months later. 12 month Vitamin D correlated with 12 month PANSS positive scores (r = -.34, p =.03) and quality of life (EQ5D)(r = .33, p =0.02)
In established psychosis (n= 324, 59.6% male), 13.9% had sufficient vitamin D while 48.8% were deficient. Mean vitamin D was 12.38 (SD 7.3) ng/ml. There was no effect of duration of illness. There were no correlations between vitamin D levels and GAF, PANSS or MADRS, but Quality of life (EQ-5D visual analogue) was lower in those deficient than in those not so, and MADRS scores were higher (p=0.02).
In established psychosis, vitamin D levels were negatively correlated with BMI (r=-0.133, p=0.03), triglycerides (r=-0.203, p=0.001), total cholesterol (r=-0.140, p=0.03), obesity (r=-0.136, p=0.03) and hypertension (r=-0.135, p=0.03). Vitamin D levels were similar in smokers to non-smokers, but those engaging in low intensity exercise had lower vitamin D than those engaging in moderate/ high activity (p=0.002). Those vitamin D deficient spent less time outdoors than those not deficient(p=0.04).
Conclusion: Vitamin D levels are extremely low at all stages of psychosis. Low vitamin D is linked to quality of life, mood and cardiometabolic risk in established psychosis and highlights the need for holistic management of psychosis. Low D at first presentation predicts function and mood 12 months later. While a more chronic premorbid course may result in lower vitamin D at presentation and poorer outcomes perpetuate the problem, the idea of Vitamin D as potentially neuroprotective in psychosis deserves exploration.
ID: 2118519

METFORMIN PARTIALLY REVERSES OLANZAPINE-INDUCED GLUCOSE DYSREGULATION

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Background: Atypical antipsychotics (AAP) are linked to type 2 diabetes (DM2), even in absence of weight gain. In this regard, evidence from rodent models consistently supports pronounced direct effects on insulin sensitivity (peripheral and hepatic), following acute dosing of specific AAP agents. Metformin, a first line treatment in the general population for prediabetes and DM2, has been studied as an adjunctive intervention for AAP-related weight gain. The majority of these studies also show improvements in indirect measures of insulin sensitivity. To our knowledge there are no studies which specifically examined metformin in patients on AAPs with DM2. In this regard, the question remains whether antidiabetic drugs are efficacious to reverse direct molecular effects of AAPs on glucose pathways, a distinguishing factor for schizophrenia populations.
Methods: Here, we tested 2 metformin doses to prevent impairments seen following a single dose of olanzapine (3mg/kg) in glucokinetics measured through gold-standard hyperinsulinemic euglycemic clamps (HIECs). Metformin (Met) (150mg/kg; n=13, or 400mg/kg; n=11) or Vehicle (Veh) (n=11) was administered through gavage preceding overnight fast, followed by a second dose the morning prior to the HIEC.
Results: Basal glucose was similar across groups. The Met400 group had a significantly increased rate of hepatic glucose production (HGP) in the basal period compared to Veh and Met150. During the hyperinsulinemic phase, glucose infusion rate to maintain euglycemia (reflective of whole body insulin sensitivity), was higher in the Met150 animals compared to Veh and Met400. High dose Met-treated rats had a significantly lower increase in rate of glucose utilization in response to hyperinsulinemia vs. Veh, with no differences between Veh and Met150. Suppression of HGP during hyperinsulinemia was significantly higher in the Met150 group relative to Veh and Met400. Given the unexpected increase in basal HGP seen with Met400, we measured serum lactate (a substrate for HGP), finding significantly increased lactate in Met400.
Conclusion: Metformin attenuates hepatic insulin resistance observed with acute olanzapine administration, but fails to affect peripheral insulin resistance. Use of supratherapeutic doses of metformin may mask metabolic benefits by increasing lactate. Our findings could suggest that patients who develop DM2 on AAPs require combination therapy; for example, employing a peripheral insulin sensitizer in addition to metformin for optimal management.
ID: 2081814

TREATMENT OF ANTIPSYCHOTIC-ASSOCIATED OBESITY WITH A GLP-1 RECEPTOR AGONIST: PROTOCOL FOR AN INVESTIGATOR-INITIATED PROSPECTIVE, RANDOMISED, PLACEBO-CONTROLLED, DOUBLE-BLINDED INTERVENTION TRIAL - THE TAO STUDY

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Background: Antipsychotic medication is widely associated with dysmetabolism including obesity, type 2 diabetes, cardiovascular-related diseases, and early death. Obesity is considered the single most important risk factor for cardiovascular morbidity and mortality. Interventions against antipsychotic-associated weight gain are limited and insufficient. Glucagon-like peptide-1 (GLP-1) receptor agonists are approved for the treatment of type 2 diabetes, but their bodyweight lowering effect is also recognized in non-diabetic patients. The purpose of this trial is to examine if treatment with a GLP-1 receptor agonist (exenatide once-weekly) facilitates weight loss in non-diabetic schizophrenia patients with antipsychotic-associated obesity.
Methods: Forty obese patients with schizophrenia or schizoaffective disorder treated with antipsychotic drugs will be randomised to subcutaneous injection of exenatide once-weekly (2 mg) or placebo for 3 months, adjunctive to their antipsychotic treatment. The primary endpoint is weight loss after 3 months of treatment. Secondary endpoints include several metabolic measurements, various psychopathological and cognitive measures, and structural and functional brain magnetic resonance imaging.
Results: The TAO-study is ongoing. Currently we have enrolled 33 patients. Twenty-four patients have completed the study, 4 patients have dropped out and 5 patients are active.
Conclusion: This is the first randomised, placebo-controlled, double-blinded trial investigating effects of a GLP-1 receptor agonist in patients with schizophrenia and antipsychotic-associated obesity. The TAO study may provide evidence of the potential weight reducing properties of GLP-1 receptor agonism in patients with antipsychotic-associated obesity. In addition, potential neuroprotective and procognitive effects of GLP-1 agonism may be unraveled. Thus, the outcome may well have direct clinical implications for the future management of antipsychotic-associated obesity.
Results are expected to be submitted in peer-reviewed international journals in 2015/16.
ID: 2083280

SUCCESSFUL TREATMENT OF TARDIVE DYSKINESIA WITH A NEW VMAT2 INHIBITOR: A CASE STUDY

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Background: Tardive dyskinesia (TD) is a neurological condition characterized by involuntary movements of the orofacial region, limbs and trunk for which no definitive treatments have been established. KINECT 2 is a Phase II study of the efficacy and safety of a vesicular monoamine transporter 2 (VMAT2) as a treatment for TD. Preliminary results showed a significant reduction in TD severity. Group mean scores from the Abnormal Involuntary Movement Scale (AIMS) showed a significant decline at Week 6 compared to baseline in TD symptoms ($p < 0.001$) for the group receiving study drug. We present an in-depth case study of a subject with severe TD who participated in KINECT 2 and received active study medication. History, laboratory values, and AIMS ratings

will be presented (a video of pre- and post- AIMS ratings is available, with subject permission).
Methods: The subject is a 62-year old, white male with a 40-year history of paranoid schizophrenia. From 1982–96 he was treated primarily with stelazine (high doses). At age 45 TD symptoms appeared, consisting of facial grimacing. The TD significantly worsened to include abnormal movements in limbs and trunk.
In 2013 he enrolled in the KINECT 2 study, participating in a 6-week treatment period with a 2-week follow-up. There were 6 study visits, which included AIMS ratings, laboratory assessments, psychiatric rating scales, and PK testing which documented medication compliance.
Results: Subject completed the study with no adverse events or study deviations. On breaking the study blind it was revealed that the subject had received the active study drug which had been titrated from 25 to 75 mg/daily, the maximum dose. AIMS ratings at Week 6 were reduced by 50% as compared to baseline. Subjectively, he experienced a meaningful clinical improvement for which he even received unsolicited positive comments from friends which were as important to him as the actual amelioration TD symptoms.
Conclusion: While the exact mechanism of TD is unknown, the most compelling evidence suggests TD results from neuroleptic-induced dopamine super-sensitivity in the nigrostriatal pathway. The transporter protein VMAT2 plays an important role in regulating monoamine uptake to the synaptic vesicle for storage and release. Thus, an agent that selectively inhibits VMAT2 in the human brain might be useful for the treatment of TD. The KINECT 2 findings await replication in larger Phase III studies.
ID: 2112084

DECREASED NEED FOR MEDICATIONS FOR EXTRAPYRAMIDAL SIDE EFFECTS OF LONG-ACTING INJECTABLE RISPERIDONE AFTER AN INITIAL EPISODE OF SCHIZOPHRENIA

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Background: Long-acting injectable antipsychotic medication is associated with better medication adherence. However, does this better adherence lead to greater levels of side effects?
Methods: At the UCLA Aftercare Research Program, we compared the clinical efficacy of the long-acting injectable formulation of risperidone (RLAI, N=40) to the oral form (RisO, N=43) in a 12-month RCT in patients with a recent first episode of schizophrenia. Each patient's adherence was rated on a 1–5 scale based on timeliness of injections for RLAI, and on pill counts, which were verified with plasma levels (QHS dosing, morning draws), MEMS®, patient reports, and psychiatrist judgments for oral medication. Signs of metabolic syndrome, rates of extrapyramidal symptoms (EPS), and use of medications to control EPS are the secondary outcome variables reported here.
Results: Adherence with RisO did not differ between the two groups prior to randomization, but adherence was better for RLAI compared to RisO during the randomized treatment ($p < .001$). Average plasma levels did not appear to differ between the RLAI and RisO groups ($p=.26$) despite lower adherence among RisO patients. The rate of early treatment discontinuation due to intolerable side effects did not appear to differ between the RLAI and RisO groups (10.0% vs. 21.4%, respectively, $p=.14$). Treatment with RLAI compared to RisO was not differentially associated with increased Body Mass Index ($p=.53$), body weight ($p=.35$), total cholesterol ($p=.24$), hemoglobin A1c ($p=.31$), prolactin ($p=.97$), or with systolic ($p=.69$) or diastolic blood pressure ($p=.59$). RLAI was not associated with significantly increased involuntary movements ($p=.29$), or increased akathisia ($p=.31$), which were rare in both groups. However, adjunctive medications to treat EPS-related side effects were used more frequently in the RisO group (akathesia medication, $p=.02$; EPS medication, $p=.02$).
Conclusion: Contrary to the expectation that treatment with RLAI would result in more frequent occurrences of side effects because of the more consistent medication exposure, the occurrence of side effects did not appear to differ. It is possible that the more constant plasma levels for RLAI without the daily peaks associated with oral administration lead to lower need for EPS side-effect medication, and that the use of these medications obscured a higher EPS burden in the RisO group. Alternatively, side-effect medication initiated early in treatment might have unnecessarily been continued in the RisO group.
ID: 2083161

GENDER AND ANTIPSYCHOTIC DIFFERENCES IN METABOLIC FUNCTIONING IN SCHIZOPHRENIA

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Background: Extant research supports increased metabolic risk in schizophrenia, which is related to medication use. However, little is known regarding gender differences in metabolic functioning related to different

Gender and antipsychotic differences in metabolic variables

Metabolic Variable/ Mean ± SD	Clozapine or Olanzapine		Quetiapine, Risperidone, Iloperidone, or Paliperidone		All other antipsychotics	
	Men	Women	Men	Women	Men	Women
Total Cholesterol	163.3 ± 38.1	188.7 ± 42.7**	168.7 ± 36.4	177.5 ± 36.6	172.2 ± 43.5	182.6 ± 43.9
LDL	103.60 ± 35.4	119.9 ± 40.9*	101.9 ± 29.4	110.0 ± 36.5	106.5 ± 41.2	115.9 ± 33.6
HDL	47.1 ± 15.0	65.0 ± 17.0***	50.7 ± 13.6	59.3 ± 16.5***	51.6 ± 15.8	56.3 ± 18.8
Leptin	11.0 ± 9.6	46.1 ± 41.6***	14.6 ± 13.5	40.7 ± 25.5***	17.6 ± 21.1	35.7 ± 19.1
Hip-to-Waist Ratio	1.05 ± 0.10	1.06 ± 0.09	1.05 ± 0.09	1.06 ± 0.12	1.01 ± 0.08	1.10 ± 0.08***
BMI	29.7 ± 6.7	35.8 ± 11.3**	30.4 ± 6.4	35.0 ± 8.7***	32.2 ± 7.1	34.8 ± 8.0*
Systolic BP	123.3 ± 15.4	122.2 ± 18.5	122.2 ± 16.6	119.3 ± 22.3	128.1 ± 15.0	120.5 ± 16.0**

*p<0.1, **p<0.05, ***p<.01

antipsychotics. This study examined metabolic profiles in regards to gender and different antipsychotics in individuals with a schizophrenia-spectrum diagnosis.
Methods: Analyses were conducted using cross sectional data from schizophrenia participants screened for metabolic syndrome (NCEP-ATP-III Criteria) after fasting. Antipsychotic medications were grouped as follows: 1) clozapine and olanzapine, 2) quetiapine, risperidone, iloperidone, and paliperidone, and 3) all other antipsychotics. Differences between genders and medication category were examined using t-tests.
Results: A total of 271 subjects were included, with an average age of 45.15 ± 11.40 years, 38.4% were female, and 55.7% were Caucasian. There were no differences in age or race between men and women in the three medication groups. Significant gender differences in metabolic functioning were seen for each medication group. For women on clozapine or olanzapine, total cholesterol, HDL, and BMI were higher; leptin, HDL, and BMI were higher in women than in men in women in the 2nd medication group; leptin and hip-to-waist circumference ratio were higher in women than in men in the third group whereas higher systolic BP was found in men than in women in this group (Table 1).
Conclusion: Findings indicate a differential impact of antipsychotics and gender on metabolic functioning in schizophrenia. Therefore, gender may be an important variable to consider when choosing antipsychotic therapy and determining initial metabolic risks seen with these medications.
ID: 2079499

THE CHALLENGES OF TRAINING CLINICIANS AND READYING CLINICS TO PROVIDE CR IN JAPAN

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Background: In 2006, Tottori University Psychiatry Department commenced an initiative to disseminate cognitive remediation (CR) at mental health facilities across Japan,, This initiative included a quasi experimental research component. Two Japanese CR clinicians, trained to teach cognitive remediation techniques, have to date held 8 training workshops and 186 therapists from 78 institutes including 44 non-academic sites have been approved as cognitive remediation specialists (CRS) by passing the qualification examination following the workshop. The trained CRS were 35% clinical psychologists, 34% occupational therapists, 20% psychiatrists and 11% others.The trainers acted as a supervisor after the workshops to maintain fidelity and quality of treatment programs.
Methods: In 2010 a pilot questionnaire survey was sent to assess dissemination progress.
Results: Answers were received from 16 institutes- 10 of which were nonacademic. Within the 16 institutes, CR was actually implemented in 12. 312 clients finished the program with 42 dropouts and 60 currently enrolled clients. The most frequent reason for cessation was, from the therapists' viewpoint, "exacerbation of the illness" and "lack of motivation". 73% of the clients were diagnosed with schizophrenia and 18% mood disorders. For the assessment, 11 institutes were using BACS (Brief Assessment of Cognition in Schizophrenia) for evaluating the effect on cognitive function. In addition, SFS (Social Functioning Scale) was used in 5 institutes, indicating strong interest of the therapists in cognitive and social functioning.
Conclusion: The CR program has achieved large interest from therapists, clients and their families in a wide range of clinical populations.
ID: 2079607

COMPARATIVE OUTCOMES OF PATIENTS SWITCHING TO LURASIDONE OR QUETIAPINE: A REAL WORLD ANALYSIS OF MEDICAID-INSURED SCHIZOPHRENIA PATIENTS

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Background: Direct healthcare costs for schizophrenia-related hospitalizations account for a large component of economic burden. Previous research from a 12-month clinical trial demonstrated a reduced risk of hospitalization for patients with schizophrenia who were taking lurasidone compared with quetiapine XR. This study examines hospitalizations (all-cause and schizophrenia-related) and associated expenditures among patients with schizophrenia who newly initiate lurasidone or quetiapine after discontinuation of another atypical antipsychotic.
Methods: A retrospective analysis using the MarketScan Multi-State Medicaid Database was conducted in adult patients with schizophrenia initiating lurasidone or quetiapine (10/1/2010 - 12/31/2012) after switching from another atypical antipsychotic. Patients had ≥6 months continuous enrollment before and after treatment initiation. Treatment episodes were required to have ≥2 lurasidone or quetiapine claims and ended upon treatment discontinuation, switch to another antipsychotic or end of study follow-up. Outcomes included time to treatment discontinuation, all-cause or schizophrenia-related hospitalizations (ICD9-CM diagnosis any position), length of stay (LOS) and direct costs.
Results: Overall 252 lurasidone and 397 quetiapine patients with schizophrenia had 125 and 226 monotherapy treatment episodes, respectively. Mean (SD) time to treatment discontinuation was longer for lurasidone, 85 days (41), compared to quetiapine, 62 days (35) ($p<0.05$). Lurasidone patients had fewer treatment episodes resulting in all-cause (15% vs 23%) or schizophrenia-related (13% vs 16%) hospitalizations compared to quetiapine patients. Mean LOS was shorter for lurasidone compared to quetiapine for all-cause (5.4 vs 6.7 days) and schizophrenia-related (5.6 vs 7.6 days) hospitalizations, respectively ($p<0.05$). Mean (SD) costs of all-cause hospitalizations were lower for lurasidone $15,488 ($13,741), than for quetiapine $22,012 ($23,581) ($p<0.05$). Similarly, mean (SD) costs for schizophrenia-related hospitalization were lower for lurasidone $14,193 ($12,876), than for quetiapine $21,579 ($24,034) ($p<0.05$).
Conclusion: This Multi-State Medicaid analysis suggests that patients with schizophrenia who switched to lurasidone had longer treatment persistence and lower hospitalization costs than those who switched to quetiapine. These lower costs with lurasidone were driven by fewer episodes with admissions and shorter hospital stays.
ID: 2118905

I'VE GOT MORE CONFIDENCE: THE EXPERIENCE OF PARTICIPATING IN A HEALTHY LIFESTYLE GROUP

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Background: The issue of weight gain is an increasing global problem for the general population, for people with a mental illness, it has also become

an increasing problem due to the side effects of common psycho-pharmacological treatments and links to physiological processes related to mental illness. This paper brings to light the experience of a group of people with schizophrenia who participated in a healthy lifestyle program - Passport 4 Life. The participants' were asked about their experience of attending the weekly healthy lifestyle group sessions.
Methods: An exploratory qualitative study was undertaken with volunteers from a larger randomized control trial (RCT) conducted to determine the effect of a healthy lifestyle program on weight, for people with serious mental illness who were taking Second Generation Anti-psychotics. The results of the RCT have been reported previously. This exploratory qualitative study was undertaken to explore the experience of people with schizophrenia who were participating in a healthy lifestyle program. Semi-structured interviews were audio taped (n=10) and transcribed. The interview transcripts were subjected to content thematic analysis. The transcripts were read and re-read to identify common themes.
Results: Four common themes emerged from the interviews that give an insight into the experience of participating in a healthy lifestyle program. The themes were: Learning how to make healthy choices; Recognizing the importance of exercise to weight management; Support from a health professional, and Being part of a group.
Conclusion: This study found like other studies that the benefits of participating in a healthy lifestyle program are more than just physical health improvements. The experience of feeling part of a group cannot be underestimated, as so often people with schizophrenia report feelings of isolation and disconnection.
ID: 2116849

LIAISON WITH PRIMARY CARE TO DETECT INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS: THE LEGS CRCT

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Background: The early detection and referral to specialised services of young people at high risk (HR) of developing psychosis may improve prognosis. General practitioners (GPs) usually are the professionals contacted first on the help-seeking pathway of these individuals. Previous research has attempted to increase GPs' awareness and knowledge of early psychosis in order to generate more accurate or increased referrals to Early Intervention Services (EIS). However, the lack of an explicit theoretical framework in these designs precluded appreciation of the causal mechanisms responsible for any observed improvement and valid conclusions concerning the efficacy of the interventions.
Methods: In this cluster randomised controlled trial, primary care (PC) practices in Cambridgeshire and Peterborough, UK, were randomly allocated into two groups to establish which is the most effective and cost-effective way to identify people at HR. One group (low intensity) received postal information about the local early intervention in psychosis service, including how to identify young individuals who may be in the early stages of a psychotic illness. The second group (high intensity) received the same information plus an additional, ongoing theory-based educational intervention with dedicated liaison practitioners to train clinical staff at each site. The primary outcome of this trial was count data over a two year period: the yield - number of HR referrals to a specialist EI in psychosis service - per PC practice.
Results: The low intensity postal campaign was no more effective than practice as usual. The high intensity intervention significantly raised awareness of potential psychotic symptoms and increased sensitivity in GPs' referral behaviour but lacked some specificity. However, sixty eight percent of the individuals that were identified as false referrals had significant impairment in their mental health. The high intensity intervention was more cost-effective than the low intensity postal campaign.
Conclusion: Our theory-based educational intervention provides strong foundation for the detection of HR for psychosis in PC. Early identification of these individuals in PC is a significant cost-effective contribution to reducing the duration of untreated illness.
ID: 2115771

EFFECTS OF INTRANASAL OXYTOCIN ON SATIETY SIGNALING IN PEOPLE WITH SCHIZOPHRENIA

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Background: Approximately 40–60% of people with schizophrenia are overweight or obese as compared with 30% of the general population. Intranasal oxytocin has shown to play a role in appetite control in humans. Hence, intranasal oxytocin may be an effective treatment or preventative agent for obesity and weight gain in the schizophrenia population.
Methods: The purpose of this study was to test a single dose of intranasal oxytocin (24 IU), compared to placebo, in a within-subjects, crossover design, to see if oxytocin would improve satiety signaling (behaviorally and/or by self report) compared to placebo in people with schizophrenia.
Results: Eight males and eight females (N=16; 7 White, 7 Black, 2 other) between the ages of 22 and 56 (32 ± 10.2) with a DSM-5 diagnosis of schizophrenia were included in the preload-test meal study. All 16 participants completed both conditions. Participants rated themselves (millimeters on a visual analogue scale (VAS)) as significantly less hungry when administered intranasal oxytocin (36.37 ± 21.0) than placebo (44.81 ± 28.6) 60 minutes following the consumption of the standardized preload (20 oz. vanilla Ensure®) (F=8.05, df=15.5, p=0.012). The total test meal intake did not differ between the conditions (t=0.12, p=0.908).
Conclusion: Intranasal oxytocin may be a promising agent in curbing appetite in people with schizophrenia. Further study is needed to test whether it may curb food consumption and help in weight loss.
ID: 2086346

PSYCHOSIS AND SLEEP DEPRIVATION: PROS AND CONS OF EXISTING AND NEW TREATMENTS

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Background: Regular timing and good efficiency of sleep are needed for the mind and body to rest and repair, and to aid in the consolidation of information.

In contrast, chronic sleep deprivation causes misperceptions, temporary delusions and distress which are followed by an acute psychosis state unless the need for sleep is relieved. In this talk, three questions will be explored: What are the mechanisms linking chronic sleep deprivation and psychosis (including hallucinations)? Which types of interventions are suitable to address sleep disturbances in psychotic populations? What are the attitudes and views of people living with psychosis towards different types of sleep interventions?
Methods: Systematic literature reviews and data collected from focus groups (n = 14). Focus group informants discussed their sleep problems, the impact of sleep dysfunction on personal and daytime functioning, and relationship with clinical symptoms. Informants also discussed the pros and cons of different treatments for sleep problems.
Results: Chronic sleep loss is associated with increased paranoia and distressing voices as well as considerable daytime dysfunctions. The qualitative data provided rich and thoughtful perspectives regarding the pro and cons of different existing and new intervention approaches.
Conclusion: There is strong evidence derived from both the clinical literature and personal narratives of a relationship between sleep loss and intensity of psychopathology. Focus group interviews also revealed novel salient themes, which provide strong avenue for future research. Finally, people with psychosis have strong preferences about treatment options, which are derived from their own efforts in controlling poor sleep.
ID: 2119940

MINOCYCLINE AND TOBACCO CRAVING IN SCHIZOPHRENIA

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Background: Minocycline (MIN) is a tetracycline antibiotic that may have effects on the reward pathway or craving. MIN inhibits formation of nitric oxide (NO), which acts as second messenger for glutamate and dopamine receptors as well as facilitates the effects of nicotine in the reward circuit. NO has been demonstrated to eliminate nicotine abstinence symptoms in rats. Since tobacco dependence is high in schizophrenia and of high concern due to its profound impact on health, it is important to study MIN as a possible new anti-craving intervention in this population.
Methods: Participants diagnosed with schizophrenia were included in a clinical trial of MIN adjunct to clozapine. Cigarette smokers with schizophrenia (SWS) who were enrolled in this study and smoked at least five cigarettes per day were also invited to participate in this pilot study of minocycline's effects on craving. Participants (n=13) were diagnosed with schizophrenia and remained symptomatic despite treatment with clozapine. MIN (200 mg daily) or placebo (PLB) were administered in a randomized, double-blind fashion for 10 weeks. Measures of tobacco dependence and craving were administered at baseline and endpoint, including a cue-reactivity virtual reality (VR) craving platform.
Results: Eight participants were randomized to MIN and five to PLB. Participants did not differ on baseline BPRS score, age, education, age of onset, FTND score, average years smoked, cigarettes smoked daily, number of cravings daily, or length of schizophrenia diagnosis. A VR cue-reactivity platform was used at baseline and endpoint to measure tobacco craving. At endpoint, no significant craving changes were found in TCQ-SF scores between MIN and PLB groups ($t=0.536$, $df=1$, $p=0.46$).
Conclusion: In this small pilot of participants in a larger clinical trial, craving scores and nicotine dependence did not differ between SWS treated with MIN or PLB over a 10 week period adjunctively to clozapine. Factors that limit the generalizability of these findings include that all participants were taking clozapine, participants were not selected for intensity of nicotine dependence, and inadequate power due to pilot nature of this study. Further research is needed to determine if MIN may have a role in tobacco craving in SWS.
ID: 2116716

Epidemiology

POLYGENIC RISK SCORES, PSYCHIATRIC FAMILY HISTORY AND THE RISK OF SCHIZOPHRENIA: A DANISH POPULATION-BASED CASE-CONTROL STUDY

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Background: Polygenic risk scores (PRS) and family history of psychiatric disorders (FH) are associated with the risk of schizophrenia. Few studies have evaluated the simultaneous impacts of PRS and FH on the risk of schizophrenia.We aim to 1) assess the impacts of PRS and FH on the schizophrenia risk, 2) quantify the fraction of subjects with schizophrenia that would have been prevented if the effects associated with the PRS and FH were absent, 3) determine the proportion of the risk associated with FH that is mediated through the PRS.
Methods: We used a population-based sample with 866 cases with schizophrenia, 871 controls and their first-degree relatives. FH was extracted from the National Health Registers. The genomic data was obtained from the Psychiatric Genomics Consortium (PGC) after samples had been processed from the Danish Neonatal Screening Biobank. PRS based on the Danish case-control sample were calculated using discovery effect size estimates weights from the latest PGC-GWAS mega-analysis (excluding the Danish sample). FH was categorized to indicate whether the subject's relatives had been diagnosed with: schizophrenia or related psychosis, bipolar affective disorder or any other psychiatric disorder.
Results: The risk of schizophrenia was elevated in individuals with relatives with schizophrenia-like psychoses (OR:4.2 [2.6–6.8]), bipolar affective disorders (2.8 [1.9–4.3]) or other psychiatric disorders (2.6 [2.0–3.4]). Based on 24755 SNPs (p-value threshold of 0.05) in the PGC sample, there was a dose-response relationship with the risk score and the risk of schizophrenia with an OR of 8.0 (4.5–14.1) in the upper decile vs the lowest decile. The attributable risks associated with FH and the PRS were 26% (23%-28%) and 52% (50%-53%). The interaction p-value was 0.03. To assess the part of FH that was mediated through the PRS, we calculated the mediating proportion under interaction, which suggested that 64% (26%-103%) of the effect of a FH of psychosis among subjects with a FH of psychosis was mediated through the risk score while 24% (14%-34%) was mediated in subjects without a FH of psychosis.
Conclusion: PRS and FH are strong and dependent indicators of schizophrenia and a sizeable proportion of cases can be attributed to these two factors. A particularly large proportion of the effect associated with an FH of psychosis is mediated through the PRS for subjects with an FH of psychoses, with room left open for non-genetic factors.
ID: 2142490

MATERNAL CYTOKINE LEVELS AT BIRTH, FETAL HYPOXIA, AND THE DEVELOPMENT OF SCHIZOPHRENIA IN ADULT OFFSPRING

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Background: Pregnancy and birth complications, particularly those associated with fetal hypoxia, are associated with increased risk for schizophrenia later in life. Such factors are also related to increased severity of certain neuropathological features of schizophrenia, including hippocampal and cortical gray matter reduction and ventricular enlargement, among individuals with a genetic susceptibility to the disorder. However, the molecular mechanisms underlying these associations are unknown.
Methods: Here we sought to determine whether inflammatory factors are differentially expressed in maternal serum samples at the time of birth following particular obstetric stressors among offspring who were subsequently diagnosed with schizophrenia as adults, as compared with demographically matched controls.
Results: Among cases, fetal hypoxia was associated with an increase in proinflammatory cytokines in maternal serum samples, while among control subjects, hypoxia was associated with a reduction in proinflammatory cytokines. This differential response to fetal hypoxia among cases was not explained by other maternal conditions or complications of pregnancy.
Conclusion: These findings provide serologically based prospective evidence of disrupted immunologic signaling in response to specific biological stressors in the molecular pathogenesis of schizophrenia.
ID: 2116522

DURATION OF UNTREATED PSYCHOSIS AND ITS CLINICAL CONSEQUENCES IN THE LONGER TERM

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Background: There is firm evidence for an association between a longer duration of untreated psychosis (DUP) and a broad range of untoward short-term outcomes. Data on the association between DUP and longer term outcomes are relatively scarce, and sample sizes are often small. Considering the continuous nature of outcomes, not much is known about the extent in which outcome in the short-term intervenes with outcome in the longer term. Our aim is to examine whether we can replicate and extend earlier found associations between DUP and outcome in the longer term in a large study, while accounting for a possible mediating effect of outcome in the short-term.
Methods: Patients with a non-affective psychotic disorder were recruited from mental health care institutes from 2004 to 2008. Of the 1120 patients enrolled, 852 are included in the present analysis. The outcome measures we are examining are total duration of psychosis, severity of negative symptoms, general functioning, neurocognitive functioning and number of unmet needs. For the analysis DUP is divided into five ordinal categories, according to other publications: less than one month, one month to three months, three months to six months, six months to twelve months

and twelve months and over. Regression analyses are used to examine the association between DUP and longer term outcome, while controlling for possible confounding factors.
Results: Median DUP is less than one month (range < 1 - 226; interquartile range 2). DUP has a heavily skewed distribution, with a majority of patients (63.1%) having a DUP of less than one month. Mean illness duration at last follow-up is 6.2 years. Preliminary analyses show no significant association between DUP and the severity of negative symptoms, general functioning, neurocognitive functioning nor the number of unmet needs in this longer term.
Conclusion: No association is found between DUP and outcome in the longer term. Sensitivity analyses will be performed to further investigate this lack of association.
ID: 2094814

SCHIZOPHRENIA; FROM EPIDEMIOLOGY TO MOLECULAR EPIDEMIOLOGY

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Background: Our work aims at studying the cascade of different factors which are responsible for schizophrenia in Pakistani population from environmental factors to genetic changes i.e. epidemiology to molecular epidemiology.
Methods: We have developed the questionnaire according to global diagnostic and statistical manual (DSM-V) and verification was done by psychologists of concerned hospitals. In case of molecular epidemiological risk factors study; the research is segmented into four parts: Genotyping of CNR1 gene variants in controls and cannabis non user- schizophrenic patients; study of schizophrenia in cannabis users; comparison of studies and organizing a molecular pathway for further studies. Genomic DNA has been extracted and used in genotyping by PCR-RFLP. Statistical analysis was done by SPSS v 16 using Chi-Square and the SNPs frequencies were estimated by Fisher`s exact test.
Results: Schizophrenia is as prevalent in Pakistan as in other countries of world but many variations are found in finding the epidemiological risk factors. Catatonic subtype of schizophrenia was observed more prominent in cannabis non users- schizophrenics and was found statistically associated with low marital outcome. In case of cannabis addicted schizophrenics, residual type was observed significantly important. Genetic variants on codon 453 of the CNR1 gene are not found significantly associated with schizophrenia, so risk allele A may not be consider susceptible to schizophrenia in Pakistani population. However, regarding to CNR1 gene variations, our gene pool has found sharing with Eastern countries as compared to Western gene pool.
Conclusion: In non addicted patients, catatonic subtype of schizophrenia was observed more prominent and was found statistically associated with low marital outcome. In case of cannabis addicted schizophrenics' residual type was observed significantly important. Genetic variants on codon 453 of the CNR1 gene are not found significantly associated with schizophrenia, so risk allele A may not be consider susceptible to schizophrenia in Pakistani population.
ID: 2088828

LIFE EVENTS AND PSYCHOSIS: CONTEXTS AND MECHANISMS

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Background: Since the seminal work of Brown and Birley, the potential link between life events and psychosis has been the focus of research and speculation. However, the role of life events prior to the initial onset of psychosis is still speculative due to a lack of robust research studies and a limited consideration of contextual influences, such as type and severity. It has been suggested that intrusive experiences may show specificity for psychosis, but this has not been thoroughly explored. The aims of this study were to investigate the impact of recent experiences on psychosis onset by considering the wider context in which they occurred, and explore potential synergistic effects and mediating factors.
Methods: Data on 253 first-presentation psychosis cases and 301 unaffected population-based controls were drawn from an epidemiologically derived case-control study in London, UK. Life events and difficulties experienced one year prior to onset (cases) or interview (controls) were assessed with the Life Events and Difficulties Schedule. Potential causal partners included negative schematic beliefs (assessed using the Brief Core Schema Scales) and potential mediators included symptoms of anxiety and depression (assessed using the Hamilton Anxiety and Depression Questionnaires).
Results: There was strong evidence that exposure to severe and intrusive experiences were particularly associated with psychosis, showing a three- to twelve-fold increase in odds. The impact of severe experiences was found to be cumulative. These findings were reasonably robust to the potentially confounding effects of age, gender, ethnicity, social class, cannabis use, and family history of psychosis. There was also tentative evidence that low social class and negative self-schemas combined synergistically with these experiences to increase the odds of psychosis. However, there was no evidence of mediation via affective symptoms.
Conclusion: This study has shown that the one year period before the initial onset of psychosis is likely to be a time of serious psychosocial stress, potentially characterised by threatening and intrusive experiences. Individuals with psychosis were found to report more severe, chronic and intrusive events and difficulties in the year prior to onset compared with controls. Research must continue to examine potentially modifiable mechanisms that may link such stressors and psychosis in order to improve understanding and treatment of these disorders.
ID: 2087189

RATES OF NON-PUBLICATION OF TRIALS FUNDED BY THE STANLEY MEDICAL RESEARCH INSTITUTE

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Background: Progress in developing drugs in medicine in general and in psychiatry in particular is plagued by non-publication of studies. We examined rates of publication of 253 studies funded by the Stanley Medical Research Institute (SMRI) since the year 2000.
Methods: We reviewed all studies funded by SMRI from 2000 to 2009 (N=253).
Results: Of the 253 studies funded, 12.3% were not completed. Of the studies completed, rates of publication ranged from 73% of those funded in

2000 to 26% of those funded in 2006. Mean rates of publication from 2000 to 2009 was 46.3%. Mean time to publication ranged from 2 to 4 years. Further analyses will be done in order to compare the primary outcome measures which are indicated in these studies' protocols and the outcomes presented in the publications.
Conclusion: Rates of publication in SMRI are similar to those of studies in non-psychiatric fields funded by the NIH. Lack of communication of results is damaging for the field, as compounds which have already been tested but have not been published might be tested again, leading to unnecessary exposure of patients to study procedure/placebo and to a waste of funds that might be used for innovative compounds instead. Thus, funding agencies might consider withholding part of the grant's payment until the study's results are published.
ID: 2118892

EPIDEMIOLOGICAL EVIDENCE FOR INFLAMMATION AND NICOTINE EXPOSURE AS PRENATAL RISK FACTORS FOR SCHIZOPHRENIA

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Background: We investigated two prenatal factors implicated in schizophrenia, maternal immune activation (MIA) and nicotine exposure, in a large national birth cohort. Mounting evidence supports prenatal infection in schizophrenia, most likely due to MIA. Cigarette smoking during pregnancy is one of the most common toxic exposures during fetal life. Prenatal nicotine inactivates fetal nicotinic receptors, alters neurotransmission, and impairs cerebral inhibition. We examined whether elevated pregnancy levels of maternal C-reactive protein (CRP), a well-established biomarker of inflammation, and cotinine, a nicotine metabolite, are associated with schizophrenia in offspring from a large national birth cohort.
Methods: The study is based on the Finnish Prenatal Study of Schizophrenia (FiPS-S), consisting of virtually all pregnancies (over 1 million) in Finland since 1983 with archived maternal prenatal serum specimens prospectively drawn during the first and early second trimesters. Cases were identified from a national psychiatric registry. Maternal CRP and cotinine were quantified during pregnancies of schizophrenia cases (N=784 for CRP, 977 for cotinine) and controls matched 1:1 on birthdate, sex, and residence in Finland.
Results: Maternal CRP levels were significantly increased in pregnancies of case compared to control offspring [OR=1.28, 95% CI=1.07–1.54, p=.007), adjusting for maternal age, previous births, maternal education, maternal psychiatric disorders, and other covariates, indicating a 28% increase in risk of schizophrenia for every unit increase in maternal CRP. The prevalences of high levels of maternal cotinine (defined as >50 ng/ml) were significantly greater in cases (20.2%) than controls (14.7%) (OR=1.38, 95% CI=1.05–1.82, p=0.02), adjusting for maternal age, parental psychiatric disorder, and birth province.
Conclusion: First, these findings provide the most robust evidence that maternal inflammation plays a role in schizophrenia. Second, we have reported the first evidence to date that maternal smoking is related to adult schizophrenia. Although replication is required, these findings suggest that interventions including prevention of immune activation during pregnancy, and reducing smoking during gestation may lead to a decreased risk of schizophrenia. These results may also provide new insights into the pathogenic mechanisms that underlie the disorder.
ID: 2076752

CANNABIS USE IN PSYCHOSIS: THE EFFECTS ON METABOLIC HEALTH

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Background: Studies in the general population show cannabis use has a beneficial effect on metabolic disorders. Given the increased cardiometabolic risk in patients with psychotic disorders, as well as their prevalent use of cannabis, we aim to investigate whether such effects are also evident in these patients.
Methods: 3176 patients with chronic psychotic disorders from four mental health institutions in the Northern Netherlands were included in the study. The mean age was 47 years, the mean illness duration was 19.4 years and 62% was male. With a multivariate regression analysis we examined the effects of cannabis use on metabolic risk factors; BMI, waist circumference, blood pressure, cholesterol, HDL-C, LDL-C, triglycerides, glucose and HbA1c. Age, sex, smoking, alcohol use and antipsychotic drugs were included as confounders. Next, we examined change in metabolic risk factors after one-year follow up for cannabis users, non-users, discontinuers and starters. Last, a linear regression analysis was performed to examine the effects of cannabis use on the PANSS-remission scores.
Results: We found a significant negative association between cannabis use and BMI (p=0.003), waist circumference (p<0.001), diastolic blood pressure (p=0.015) and HbA1c (0.004). One year later, the patients who had discontinued their cannabis use had a greater increase of BMI (p=0.002) and waist circumference (p=0.011) than other patients. They also had a greater increase of diastolic blood pressure than non-users (p=0.036) or starters (p=0.004).
Psychotic symptoms were more severe in cannabis users compared to non-users (p=0.016). After one year, the psychotic symptoms of discontinuers were more decreased than the psychotic symptoms of users (p=0.002) and non-users (p=0.004).
Conclusion: Patients with a psychotic disorder using cannabis had a lower BMI, diastolic blood pressure, HbA1c and a smaller waist circumference than non-users. Discontinuation of cannabis use increased metabolic risk. Cannabis use appeared to be a protective factor for metabolic disturbances. To stop cannabis use is often an important treatment goal, because it will reduce psychotic symptoms. However, physicians should be aware of the increased metabolic risk in patients who discontinue the use of cannabis. Extra attention should be paid to the monitoring and treatment of metabolic parameters in these patients, in order to prevent cardiovascular diseases and premature cardiovascular mortality.
ID: 2116353

SUICIDE REVISITED: SIGNIFICANT REDUCTION OF SUICIDE RATE OVER THE LAST TWO DECADES - A REPLICATION STUDY OF A DUTCH INCIDENCE COHORT WITH RECENT ONSET PSYCHOSIS.

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Background: Suicide is still the leading cause of premature death in patients with psychotic disorders with incidences many times higher than for the general population. In early studies, the lifetime suicide risk in schizophrenia was established at around 10%. More recent reviews suggest that this risk has decreased to 5%. The primary aim of this study is to compare the current suicide risk after recent onset psychosis to the situation two decades ago in the same catchment area by using data of the Psychosis Recent Onset Groningen - Survey (PROGR-S). Secondly, we aim to investigate the possible predictors of suicide risk.
Methods: The diagnostic protocol of the Psychosis Recent Onset Groningen - Survey (PROGR-S) started in 1997 for those living in of the province of Groningen (north of the Netherlands with 550.000 inhabitants) in the Netherlands, who were referred to a psychiatric institute with a (suspected) first psychotic episode (< 2 years) or evaluated for a recurrent psychotic episode not diagnosed as such before. There were no exclusion criteria with regard to age, diagnoses, substance abuse, or ethnicity. Medical file search was used to determine the current status of all patients admitted between 2000 and 2009. The suicide rate was compared to a study executed in 1973–1988 in the same catchment area. Predictors of suicide were investigated using Cox regression.
Results: The status of 424 out of 614 individuals in the PROGR-S database was known at July 1st 2011. In this group, suicide occurred in 2.4% of the psychotic patients (n=10; mean follow-up 5.6 years); 6 out of 10 suicides took place within 2 years. Within two decades the suicide rate has dropped from 11% (follow-up 15 years, 8.5% after 5 years) to 2.4%. The Standardized Mortality Rate (SMR) of suicides compared to the general population was 41.6. A higher age was the only significant predictor for suicide. Neuroticism, living situation, disorganized and negative symptoms, and passive coping all contributed to the risk, but were trending significant.
Conclusion: A significant reduction of suicide rate was found in psychosis. Given the high SMR, suicide research should have highest priority. Unraveling the predictors may contribute to a further reduction of suicide in patients with psychosis.
ID: 2092530

PREVALENCE, PSYCHOSOCIAL AND PHYSICAL HEALTH CORRELATES OF PSYCHOTIC DISORDERS IN HONG KONG: THE HONG KONG MENTAL HEALTH MORBIDITY SURVEY

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Background: Psychotic disorders are severe mental illnesses that constitute one of the highest disease burdens globally. It is known that rate and psychosocial correlates of psychosis vary across different populations. The Hong Kong Mental Morbidity Survey (HKMMS) is the first territory-wide, population-based study in Hong Kong (HK) to examine prevalence of psychotic disorders, their associated factors and impacts on psychosocial disability.
Methods: A two-phase design was adopted. In Phase I, 5719 randomly selected and demographically representative Chinese participants aged 16–75 years were assessed on functioning, quality of life (QoL), alcohol and substance use, physical health status, and a comprehensive array of socio-demographic variables between November 2010 and May 2013. Psychosis Screening Questionnaire (PSQ) was administered. Participants who were screened positive with PSQ (n=238) or had self-reported history of psychosis / antipsychotic treatment (n=74) were recruited to Phase II for diagnostic confirmation (n=232) of psychotic disorders using Structured Clinical Interview for DSM-IV and / or medical record review.
Results: The weighted prevalence of psychotic disorders was 2.5% (95%CI: 2.1–2.9). Participants with psychotic disorders were significantly more likely to be single and unemployed, to have lower educational attainment, lower household income, family history of psychosis, less perceived social support, history of physical or sexual trauma, and poorer psychosocial functioning and QoL than those without psychotic disorders. Participants with psychosis exhibited higher degree of physical disease burden, higher body mass index (BMI), and were more likely to be a smoker and to have substance dependence.
Conclusion: Our findings indicate that, in HK, 1 in 40 people in the community suffer from psychotic disorders. Psychosis is associated with more adverse socio-economic situations, worse functioning, and poorer physical health. Prevalence estimate highlights substantial unmet treatment needs for people who have psychosis but have not yet received psychiatric care (approximately 1.5% of the population with psychosis). These data helps guide future development of psychiatric service for psychosis in HK.
ID: 2086091

GENE-ENVIRONMENT INTERACTIONS IN SCHIZOPHRENIA - THE EPIDEMIOLOGICAL EVIDENCE

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Background: Data from our several large Finnish population-based cohort studies will be reviewed to support the role of environmental and developmental stressors in the etiology of schizophrenia and the possibility that these risk factors interact with underlying genetic vulnerability.
Methods: The data, from a number of different cohorts, are prospectively collected and include data on schizophrenia patients, their parents, siblings and healthy controls.
Results: There is strong evidence that early adverse environmental factors increase risk for schizophrenia and that they are interacting with underlying genetic risk. The evidence also suggests that immune alterations may act

as a common mediator of the impact of these diverse environmental risk factors. Our data show that a range of neurodevelopmental disorders such as schizophrenia, autism, intellectual disability and epilepsy seem to be on a continuum of neurodevelopmental impairment which clusters within families. Individuals with schizophrenia had a 6-fold increase in the odds of having a first-degree relative with intellectual disability (OR 5.9, 95%CI: 2.1–16.8); a 4-fold increase in the odds of having a first-degree relative with an autism spectrum disorder (OR 3.8, 95%CI: 1.4–10.2); and an almost 2-fold increase in the odds of having a first-degree relative with an affective disorder (OR 1.8, 95%CI 1.1–2.7). Our data also show some common risk factors across disorders such as older paternal age at conception and some differentiating risk factors such as prenatal stress - women who prospectively reported significant mental stress during pregnancy had twice the odds of having a child who would later develop schizophrenia compared to unstressed women (OR 1.9, 95% CI:1.1–3.6) and 4 times the odds of having a child who would later develop bipolar disorder (OR 4.7, 95%CI: 1.0–21.7).

Conclusion: The familial clustering of neurodevelopmental disorders is most likely underpinned by multiple genetic and environmental factors interacting in complex ways to produce disorders that appear phenotypically distinct but may in fact be different end products of many shared aberrant pathophysiological processes.

References

[1] Cannon M, Clarke M.C., Cotter D.R. Priming the brain for psychosis: maternal inflammation during fetal development and the risk of later psychiatric disorder. American Journal of Psychiatry. Advance online publication September 2014.

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ID: 2087205

EPIDEMIOLOGICAL EVIDENCE FOR THE ROLE OF PRENATAL STRESS IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: There is convincing evidence from animal studies of the adverse effects of prenatal stress on behavioural and emotional outcomes in offspring. There is some evidence in human studies but we are still lacking strong evidence as to whether the effects persist into adulthood and if they are mediated or moderated by other subsequent adverse events during fetal/early childhood development. We examined whether maternal emotional and physical distress during pregnancy increases the risk of schizophrenia and other neurodevelopmental disorders in the offspring in adulthood.

Methods: All pregnant women in Helsinki in 1975/1976 were asked to complete a questionnaire at antenatal clinic visits which assessed feelings of stress, anxiety and depression as well as any physical problems experienced over the previous month. 3,500 women completed at least one questionnaire during pregnancy. We linked this pregnancy and childhood information with hospital-based register information on adult outcomes.

Results: Women who reported significant mental stress during their antenatal visits, compared to those who did not, had twice the odds of having a child who would later develop schizophrenia (OR1.9, 95%CI:1.1–3.6) and 4-times the odds of having a child who would later develop bipolar disorder (OR4.7, 95%CI:1.0–21.7). There was no such association with mood disorder or other neurodevelopmental disorders such as intellectual disability or epilepsy in the offspring. Women who reported a 'notable' adverse change in their mood during pregnancy compared to pre-pregnancy had an almost 4-fold increase in the odds of having a child who would later develop schizophrenia (OR3.7, 95%CI: 1.2–11.4). There was no such association seen with other disorders.

Conclusion: We need to pay closer attention to the mental health and well-being of expectant mothers, for their own health and for the future mental health of their children. A significant strength of this investigation is the use of a subjective measure of maternal stress. Previously used objective measures may be a less accurate quantification of the effect on the mother.

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Cannon M, Clarke M.C., Cotter D.R. Priming the brain for psychosis: maternal inflammation during fetal development and the risk of later psychiatric disorder. American Journal of Psychiatry. Advance online publication September 2014.

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ID: 2091362

A LONGITUDINAL GENERAL POPULATION BIRTH COHORT STUDY OF PSYCHOTIC EXPERIENCES, HYPER-THEORY OF MIND, AND PUTATIVE ANTECEDENTS AND CORRELATES IN PREADOLESCENCE

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Background: Knowledge on the risk mechanisms of psychotic experiences (PE) is still limited. We have previously found a stronger association between PE and the exaggerated, hyper-mentalizing type of Theory-of-Mind (HyperToM) than between PE and an overall low level of ToM functioning in the Copenhagen Child Cohort 2000 (CCC2000). The aim of the current study was to explore the cross-sectional and longitudinal associates of PE with a particular focus on the role of HyperToM as a potentially specific marker of PE. The specificity of HyperToM as correlate of PE as opposed to correlate of any mental disorder was studied. Finally, we examined if PE and Hyper-ToM shared some of the well-established antecedents of psychosis and Schizophrenia.

Methods: We investigated 1,630 children from CCC2000 with psychopathological interviews and assessments of PE and of Hyper-ToM at the age of 11–12 years. Simple and multinomial logistic regression analyses were performed to test the correlates of PE and of Hyper-ToM, and the specificity of correlates of PE versus correlates of any DAWBA-based DSM-IV mental disorder.

Results: Univariate analyses showed familial psychiatric liability; parental mental illness during early child development; change in family

composition; low family income; regulatory problems in infancy; onset of puberty; being involved in bullying; having a concurrent DSM-IV mental disorder, and HyperToM to be associated with PE. However, when examining these predictors and correlates in a single multivariate regression analysis to estimate their adjusted effects, only low family income, having a concurrent DSM-IV mental disorder, being involved in bullying, and HyperToM remained significantly associated with PE. Further analyses of the specificity of these correlates with regard to outcome revealed that bullying was associated with any mental disorder, PE, and the combination, and low family income was associated with any mental disorder, whereas HyperToM was the only variable specifically associated with PE without concurrent mental disorder. Finally, HyperToM did not share any of the investigated precursors with PE.
Conclusion: The findings suggest that many family and child variables are predictive of psychopathology in general, including PE, whereas HyperToM is specifically associated to PE. These findings indicate that the construct of HyperToM may be useful in delineating differential pathways to psychopathological outcomes.
ID: 2092571

ELEVATED INFLAMMATORY MARKERS IN INDIVIDUALS WHO TRANSITION TO PSYCHOSIS FROM THE AT- RISK-MENTAL-STATE.

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Background: The involvement of inflammation in psychotic disorder is increasingly accepted. Epidemiological, cellular and molecular evidence shows that disruptions in inflammatory proteins and pathways predispose to and are associated with psychosis. As the early treatment of psychosis is associated with improved outcome, detection of markers of the inflammatory process may allow early identification and treatment of these disorders. We questioned whether raised levels of plasma inflammatory markers could predict transition from the at risk mental state to psychotic disorder.
Methods: We investigate 39 individuals at ultra-high risk of psychotic disorder. After one year, 11 of these individuals transitioned to psychotic disorder, and 28 individuals remained at risk. 40 neuroinflammation biomarkers were quantitatively measured by commercially available electrochemiluminescence immunoassays in blood plasma samples. An association with transition to psychotic disorder was tested by ANOVA including age, BMI and gender as covariates.
Results: Of the markers that passed quality control (CRP, Eotaxin, Eotaxin 3, ICAM-1, IFN-g, IL-12, IL-16, IL-7, IL-8, IP-10, MCP-1, MCP-4, MDC, MIP-1a, MIP-1b, PIGF, SAA, sFLT-1, TARC, Tie-2, TNF-a, VCAM-1, VEGF, VEGF-A, VEGF-D), 3 markers were significantly increased in subjects who transitioned to psychotic disorder individuals ($p<0.05$), and of these one marker, Interleukin 12 (IL12/23p40), was significantly elevated (1.5 fold increase) following FDR (0.0013).
Conclusion: The association of the inflammation biomarkers with transition to psychotic disorder from at risk mental state is supported by current models on the immunopathogenesis of schizophrenia through the Th17 pathway. Validation, replication and mechanistic insight are required to further support a role for neuroinflammation biomarkers in psychosis. The findings have implications to the early identification and of subjects in the at-risk-mental state who are at greatest risk on converting to psychosis and may represent an opportunity for early targeted treatment. In addition, modulation of inflammatory proteins and processes may represent a novel treatment strategy for schizophrenia.
ID: 2088792

PSYCHOTIC EXPERIENCES & SUICIDE ATTEMPTS: TESTING FOR ENVIRONMENTAL CONFOUNDING

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Background: Recent epidemiological studies have demonstrated strong associations between sub-threshold psychotic experiences and risk for suicide attempts. It is unclear whether this reflects a causal relationship or is due to confounding. The primary aim of this study was to test whether the association between psychotic experiences and suicide attempts was attenuated or eliminated when controlling for a comprehensive set of shared risk factors.
Methods: A non-clinical sample of young adults (n=321) completed surveys assessing psychotic experiences (Prodromal Questionnaire-Brief), suicidal behavior (Columbia-Suicide Severity Rating Scale), and all known mutual risk factors based on prior research, including self-esteem, depressive and anxiety symptoms, immigration, urban upbringing, childhood school and residential mobility, substance use, bullying and victimization, trauma exposure, relationship status, employment status, socioeconomic status, sexual orientation, age, and sex. Logistic regression analyses were used to test the hypotheses that psychotic experiences would be related to suicidal behavior, and that this relationship would persist following adjustment for socioenvironmental risk factors.
Results: Psychotic experience scores were associated with greater risk for all measures of suicidal behavior, including attempts, aborted attempts, interrupted attempts, and preparatory behaviors. A dichotomous variable was created indicating the presence of any attempt or preparatory behavior. Scores on the prodromal questionnaire-brief were strongly associated with this indicator of suicidal behavior in logistic regression, Wald $X2=20.59$, $p<0.001$, OR(95% CI)=1.07(1.04–1.11). This significance and effect size of this association was not changed when controlling for shared socioenvironmental risk factors, Wald $X2=7.69$, $p=0.006$, OR(95% CI)=1.07(1.02–1.12). Results were similar when excluding individuals reporting preparatory behaviors but no history of attempts.
Conclusion: The now well-established relationship between psychotic experiences and suicidal behavior appears to be robust to extensive adjustments for socioenvironmental risk factors. This lends support to causal explanations, or alternatively, shared genetic factors, which could not be tested in these data. Understanding the nature of this relationship has implications for suicide prevention efforts.
ID: 2116725

CLINICAL AND SEROLOGICAL PREDICTORS OF MORTALITY IN AN EXPANDED COHORT OF INDIVIDUALS WITH SCHIZOPHRENIA

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Background: The reduced life expectancy of persons with schizophrenia has been established in multiple studies from around the world and is due largely to death from natural causes. Cigarette smoking, antipsychotic medications, and co-occurring diabetes have been associated with this premature mortality. However, few studies have examined the association between infectious and immune markers and subsequent mortality.

Methods: We prospectively assessed a cohort of persons with schizophrenia with a clinical evaluation including an assessment of cognitive functioning, psychiatric symptom severity, and co-occurring medical illnesses. Each participant had a blood sample drawn from which antibodies to human herpes viruses and Toxoplasma gondii were measured along with C=reactive protein. Mortality and cause of death was determined with data from the National Death Index. We used regression models to examine the role of demographic, serological, and clinical factors on mortality.
Results: A total of 25 of 517 (5%) persons died of natural causes in a follow-up period of up to 11 years. The standardized mortality ratio was 2.80 (95 % CI 0.89, 6.38). After adjusting for age and gender, mortality from natural causes was predicted in separate models by cigarette smoking (RR=4.66, p=0.0029); lower cognitive score (RR=0.96, p=0.013); level of antibodies to Epstein Barr Virus (RR=1.22, p=0.0041), level of antibodies to Herpes Simplex Virus type 1 (RR=1.19, p=.030); co-occurring immunologic disease (RR=3.14, p=0.044) and genitourinary disease (RR=2.70; p=.035). We will update these results with data from the National Death Index covering the period through December 2012, a period up to 14 years, in a cohort of 690 patients with schizophrenia and 5618 person years of follow-up.
Conclusion: Exposure to infectious agents, cigarette smoking and comorbid illnesses are associated with increased mortality in individuals with schizophrenia. The identification of risk factors for mortality will lead to improved methods for the prevention of pre-mature death in these individuals.
ID: 2082602

THE COST OF SCHIZOPHRENIA IN NORWAY

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Background: Schizophrenia can generate substantial financial and social burdens for patients, their families and the wider society. Despite the wide-ranging cost implications associated with the illness, the only attempt to study these costs in Norway dates back to 1995. The purpose of this study was to provide an up-to-date prevalence based estimate of direct costs of schizophrenia in Norway.
Methods: We used a prevalence based design obtaining data through national registers for the period 1st January through to 31st December 2012.
Schizophrenia was defined by ICD-10 codes F20 - schizophrenia and F25 - schizoaffective disorder.
The estimates are based on comprehensive registry data from The Norwegian Patient Register (NPR), The Health Economics Administration, The Prescription Database and the Norwegian Labour and Welfare Administration (NAV). We used a representative cohort of 744 patients and data from Statistics Norway and NAV to extrapolate costs for supported housing and welfare benefits.Data on correctional services were estimated from previously published statistics.
Two-way between-groups multivariate analyses of variance were used to explore the impact of sex and age on number of days in treatment, and disability payments.
Results: There were 9 748 persons registered in the NPR with schizophrenia, giving a 12-month prevalence of 0.19 %.
The total direct cost of services for people with schizophrenia in Norway was USD 1,241,083,961.00. Medical costs accounted for 64 % of the total, with hospitalizations being the most significant. 14 % was spent on housing and correctional services, and 22 % on social security benefits.
The interaction between sex and age was statistically significant for all specialized mental health treatment modes (F (5, 11879) = 4.04, p = .001; F (5, 7633) = 3.34, p = .005; F (5, 223273) = 2.4, p = .034). However, the effect sizes were small (partial eta squared = .002, .002 and > .001). For disability payments the interaction between sex and age was not statistically significant, F (5, 108) = .27, p= .93.
Conclusion: Schizophrenia is a costly illness accounting for 20 % of costs in specialized mental health services. One third of the treatment costs go to the age group 20–29, primarily due to higher hospital costs and longer durations of hospitalization for this group. Compared to the costs found by Rund (1995) and adjusted for the consumer price index the total cost of schizophrenia in Norway has increased by approximately USD 135 million.
ID: 2116344

PREVALENCE OF NEW-ONSET PSYCHOSIS IN U.S. SERVICE MEMBERS DEPLOYED TO KANDAHAR, AFGHANISTAN: IMPLICATIONS FOR TRAINING PSYCHIATRIC TECHNICIANS

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Background: Psychotic disorders usually present in late adolescence-early adulthood; often in response to stressful situations. Many U.S. Military Service Members (SM) deployed in support of Operation Enduring Freedom are in this age range and are exposed to significant stressors including separation from friends and family, demanding schedules, and threat of physical danger. Military psychiatric technicians are first-line treatment providers for SM with mental health problems. In this performance improvement project, we sought to establish the prevalence of new-onset psychosis in a deployed setting in order to determine the level of training on psychotic disorders appropriate for military psychiatric technicians.
Methods: The population of interest was defined as the number of individuals presenting for mental health care/evaluation at the NATO Role 3 Hospital in Kandahar, Afghanistan, over the period 01 JAN 2012 - 31 DEC 2013. Cases of psychosis were determined by examination of the medical record in Armed Forces Health Longitudinal Technology Application-Theater version (AHLTA-Theater). Any symptoms of psychosis led to inclusion even if the ultimate diagnosis was not of a psychotic disorder.
Results: Medical records from 2290 individuals were examined and 21 cases with psychotic symptoms were identified. Three were non-U.S. SM (one Albanian Army, one contractor, one DoD civilian employee). The prevalence rate of psychosis among mental health evaluations was 0.9%. The average age of those with psychosis was 30 ± 9.5; (range 20–53). Diagnoses were 24% psychotic disorder (delusional, schizophrenia/schizophreniform), 43% psychosis nos, 19% mood disorder (bipolar, major depression with psychotic features), and 14% other (including PTSD).
Conclusion: Given the prevalence rate of nearly 1%, and the number of SM seen by mental health annually at the Kandahar Role 3, psychiatric technicians can expect to see about 7 new cases of psychosis during a typical 9-month deployment. Therefore, training on recognition and management of psychotic symptoms in an acute setting would be extremely useful for deployed psychiatric technicians.
ID: 2081972

PREDICTORS OF TREATMENT RESISTANCE IN SCHIZOPHRENIA

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Background: The ability to predict treatment-resistant schizophrenia (TRS) at the time of first diagnosis of schizophrenia would be of great clinical benefit, allowing prompt treatment with clozapine in patients unlikely to respond to non-clozapine antipsychotics. Knowledge about TRS risk factors at illness onset is limited. We aimed to identify baseline predictors of TRS and to investigate whether known risk factors of schizophrenia could help to elucidate the underlying nature of TRS.
Methods: Using Danish National registry data we conducted a population-based cohort study on all patients with incident schizophrenia between 1995 and 2007 followed until 2011. Patients initiating clozapine treatment or meeting eligibility criteria for clozapine were defined as TRS. We performed multivariable Cox proportional hazards regression analysis.
Results: Of 8,632 patients with schizophrenia, 34.2% met criteria for TRS during follow-up (median 9.1 years, IQR: 6.3–11.9), and 13.2% initiated clozapine. Age, female sex, living in less urban areas, early retirement pension, psychiatric hospitalization, paranoid subtype, comorbid psychiatric disorders, psychotropic drug use, suicide attempt, and substance abuse were significantly associated with an increased rate of TRS. Female sex and non-urban residence were notable, since the associations were in the opposite direction as for schizophrenia in general.
Conclusion: The identified factors could potentially be used in the development of a prediction model for identifying patients with TRS early after schizophrenia diagnosis. Sex and urbanicity were associated with TRS incidence in opposite direction as for schizophrenia incidence suggesting that TRS may have a different set of etiological factors than treatment-responsive schizophrenia.
ID: 2119467

CAN SOCIAL SUPPORT PROVIDE RESILIENCE AGAINST PSYCHOSIS IN THOSE EXPOSED TO SEVERE CHILDHOOD ADVERSITY?

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Background: Studies have reported an association between various adversities in childhood and psychosis, yet the majority of exposed individuals do not develop psychosis. As support from caregivers and peers following early trauma has been found to be one of the strongest protective factors associated with resilience to other mental health outcomes, this study explored whether social support modifies the association between childhood trauma and psychosis. Moreover, as psychosis patients are found to have impaired activity of the hypothalamic-pituitary-adrenal (HPA) axis, it was explored whether levels of support ameliorate the deleterious effects of early trauma on regulation of the HPA axis in individuals with psychosis.
Methods: Data on 277 first-presentation psychosis cases and 297 unaffected population controls were drawn from the Childhood Adversity and Psychosis Study. Reports of adversity before 17 years (physical or sexual abuse, bullying victimisation) and perceived childhood support (from adults, peers, and perceived loneliness) were obtained from the Childhood Experience of Care and Abuse Interview. Saliva samples were collected to measure diurnal cortisol levels and the cortisol awakening response. Data was analysed using logistic regression (and tested for interaction on an additive scale).
Results: Compared with controls, cases more commonly reported exposure to severe bullying victimisation (adjusted odds ratio [aOR] 2.31, 95% Confidence Interval [CI] 1.23–4.34), and severe sexual (aOR 2.34, 95% CI 1.22–4.48) and physical abuse (aOR 1.81, 95% CI 1.16–2.84). Whilst perceived support did not modify the relationship between physical abuse and psychosis, the effect of severe sexual abuse on case-control status appeared to be modified by levels of peer support (adjusted Interaction Contrast Ratios [aICR] 3.63, 95% CI -1.21–8.46), whilst the impact of severe bullying victimisation on psychosis was mitigated by high support from adults (aICR 4.99, 95% CI -2.44–12.42). Analyses in a sample of 67 cases revealed that support normalised HPA activity in those who reported severe childhood adversity.
Conclusion: High levels of social support from adults and from peers appear to provide resilience in those who had experienced severe bullying victimisation and severe sexual abuse in childhood, respectively. Moreover, this study hints at a potential neurobiological mechanism for the protective effects of social support. These findings have significant implications for the intervention of psychosis.
ID: 2094181

DEVELOPMENTAL STRESS AND LONG-TERM PSYCHIATRIC OUTCOMES: SHAPING PATHOLOGY BY GENE-ENVIRONMENT AND ENVIRONMENT-ENVIRONMENT INTERACTIONS

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Background: Epidemiological research and translational work in animal models suggest that exposure to traumatizing experiences during sensitive periods of postnatal brain maturation can increase the risk of long-term psychiatric disorders. The nature and strength of this association is likely influenced by the genetic background of the affected individuals and/or by interactions with other environmental adversities.
Methods: To explore the specificity of brain pathology following developmental stress exposure, our research team compares the effects of peripubertal or adolescent stress in multifactorial mouse models that encompass epidemiologically relevant environmental risk factors and specific susceptibility genes implicated in schizophrenia and related disorders.
Results: We have recently demonstrated that peripubertal stress exposure induces more severe neuropathological long-term effects in offspring with a history of prenatal immune activation as compared to offspring without such a history. Hence, prenatal immune adversities can function as a "disease primer" that increases the offspring's vulnerability to the detrimental neuronal effects of subsequent stress exposure during peripubertal life. Our ongoing research now reveals that peripubertal stress exposure can similarly interact with rare copy number variation (CNV) in the form of a 15q13.3 microdeletion syndrome. In both cases, we further found that a later application of stress in adolescence did not elicit the interaction with the environmental (prenatal immune activation) or genetic (15q13.3 microdeletion) predisposing factor, suggesting that the precise timing of postnatal stress is a critical determinant of long-term brain pathology in multifactorial disease models.
Conclusion: Our findings provide experimental support for the hypothesis that the impact of developmental stress on adult brain functions is strongly

influenced by the genetic and environmental contexts in which it occurs. Exposure to peripubertal stress may thus be an important etiological risk factor for long-term psychiatric illness especially in individuals with genetically and/or environmentally driven disease predisposition.
ID: 2086765

META-ANALYSIS OF CYTOKINE ALTERATIONS IN ACUTELY ILL PSYCHIATRIC PATIENTS: COMPARISONS BETWEEN SCHIZOPHRENIA, BIPOLAR DISORDER, AND DEPRESSION

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Background: Schizophrenia, bipolar disorder, and major depressive disorder (MDD) have all been associated with aberrant blood cytokine levels. However, the pattern of cytokine alterations across disorders has not been compared. We performed a meta-analysis comparing and contrasting blood cytokine levels in schizophrenia, bipolar disorder and MDD, during acute illness episodes (pre- and post-treatment) and in chronic illness.
Methods: We identified articles by searching Pub Med, PsychInfo, and ISI, and the reference lists of identified studies. 107 studies met the inclusion criteria, including 23 studies of bipolar disorder, 32 studies of major depressive disorder, and 52 studies of schizophrenia.
Results: Levels of four cytokines-IL-6, TNF-α, sIL-2R, and IL-1RA-were significantly increased (pre-treatment) in acutely ill patients with schizophrenia, bipolar mania, and MDD compared to controls ($p<0.01$ for each). IL-6 levels significantly decreased following treatment for acute depression. IL-6 decreased at the trend level ($p=0.07$) and sIL-2R significantly increased following treatment for acute psychosis ($p=0.04$). Levels of IL-1RA significantly decreased ($p=0.02$) and sIL-2R levels decreased at the trend level ($p=0.08$) following treatment for acute mania. Euthymic patients with bipolar disorder had significantly increased sIL-2R levels ($p=0.01$). IL-6 and TNF-α levels were significantly elevated in patients with chronic schizophrenia and MDD ($p<0.01$ for each). Sensitivity analyses did not change the pattern of the results.
Conclusion: Overall, there were many similarities in the pattern of cytokine alterations in schizophrenia, bipolar disorder, and MDD during acute illness episodes and in chronic illness. Cytokine alterations were less pronounced following treatment for acute illness episodes. These findings raise the possibility of common underlying pathways for immune dysfunction, including the stress response to acute illness, and have important implications for our understanding of the pathophysiology and treatment of major psychiatric disorders.
ID: 2085065

THE EFFECT OF MATERNAL ANTIPATHY ON COGNITIVE-PERCEPTUAL AND INTERPERSONAL SCHIZOTYPY IS MEDIATED BY SENSITIVITY TO STRESS.

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Background: Schizophrenia and those at risk for schizophrenia share many risk exposures, including maternal antipathy. It is unclear whether maternal antipathy directly contributes to schizophrenia liability, or whether the association reflects the influence of another mechanism. Sensitization to stress is evident in those at risk for schizophrenia. Also, offspring of mothers who show antipathy tend to be more sensitive to stress. We hypothesise that stress sensitivity mediates the relationship between maternal antipathy and schizophrenia risk.
Methods: Undergraduates ($n = 211$, age $M = 20.9$, 75% female) completed the Schizotypal Personality Questionnaire (to measure schizophrenia risk), the Acute Hassles Scale (to measure stress sensivitiy), the Childhood Experience of Care and Abuse Questionnaire (to measure maternal antipathy), and provided demographic details. The hypothesis was examined separately for cognitive-perceptual (positive), interpersonal (negative), and disorganised features of risk using bivariate correlations and multiple regression controlling for age, sex, and depression.
Results: Higher reported maternal antipathy predicted higher sensitivity to stress, (beta = .17, $p = .013$, more cognitive-perceptual features (beta =.15, $p = .032$), and more interpersonal features (beta = .15, $p = .020$). When sensitivity to stress was added to the models, the direct contributions of antipathy to cognitive-perceptual and interpersonal features were reduced (beta = .09, $p = .191$, and beta = .12, $p = .065$, respectively), and greater stress sensitivity predicted higher cognitive-perceptual and interpersonal features (beta = .37, $p < .001$, and beta = .18, $p = .005$, respectively). For disorganised features, greater antipathy remained a strong direct predictor before (beta = .31, $p < .001$) and after (beta = .27, $p < .001$) stress sensitivity (beta = .20, $p = .003$) was added to the model.
Conclusion: Stress sensitivity mediated and partially mediated the associations of antipathy with cognitive-perceptual and interpersonal features, respectively. However, antipathy had a robust direct relationship with disorganisation features. The findings suggest that environmental risk, such as maternal antipathy, may impact positive features of schizophrenia liability by increasing sensitivity to stress. Interestingly, stress sensitivity appears to be less involved in the relationship between maternal antipathy and negative features, suggesting possible distinction in symptom development.
ID: 2092361

AVERAGE LIFESPAN AMONG SCHIZOPHRENIA PATIENTS IS MORE CLOSELY LINKED TO COGNITIVE ABILITY THAN TO SYMPTOM ACTIVITY

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Background: Patients with schizophrenia have a shorter life expectancy than the normal population; numerous of studies support this finding. In Sweden, the average lifespan is approximately 18 years shorter for this patient group. This study explored if there were any specific common characteristics among deceased patients with schizophrenia.
Methods: The analyzed data were obtained from a twelve year longitudinal study where 64 patients out of 502 had died during the time they were followed. Differences in baseline assessments of symptoms and cognitive ability were analyzed between patients who had died during the time of the study and those who were still alive. Symptoms were measured with the PANSS, and symptom remission was assessed according to the Andreasen criteria. Cognitive remission was assessed with a battery of instruments measuring vigilance, working memory, learning, short-term memory, and executive function.
Results: The average age of the 64 patients who had died was 61.1 years, which could be compared with the average age of mortality for the general Swedish population, which is about 80 years. Two patients committed suicide and together they lowered the average lifespan of the study sample

with 0.25 years. The baseline assessments showed no difference regarding symptoms or remission status between those patients who had died and those who were still alive. Instead, the cognitive baseline assessments highlighted that those who had died had performed at a lower level in many areas.
Conclusion: Our study shows that although suicide is uncommon, the average age of death is still low for this patient group and cannot be explained by differences in illness activity. However, our findings indicate that patients' cognitive abilities might be of special interest for promoting patients with schizophrenia to live longer.
ID: 2083957

CANNABIS USE IS ASSOCIATED WITH 3 YEARS EARLIER ONSET OF NON-AFFECTIVE PSYCHOSIS IN A LARGE, NATURALISTIC, MULTI-SITE SAMPLE

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Background: Patients with non-affective psychosis and substance use may have an earlier onset of illness compared to those without substance use. It is unclear whether this association is related to a specific type of substance or influenced by familial vulnerability to psychosis. The present study aimed to examine the relationship between type and age at onset of non-affective psychosis in a large, naturalistic, multi-site sample, controlling for family history of psychosis.
Methods: Patients with non-affective psychosis (N = 1119) were recruited consecutively from catchment areas in Oslo, Stavanger and Bergen, Norway, and thoroughly screened for substance use history. Linear regression analysis was used to examine the relationship between substance use and age at onset of illness.
Results: Patients with substance use (n = 627) had about 3 years earlier age at onset (23.0 years) than the abstinent group (n = 492; 26.0 years). Only cannabis was significantly related to earlier age at onset. Family history did not influence the results.
Conclusion: Cannabis use is associated with 3 years earlier onset of psychosis.
ID: 2112533

INVESTIGATING ETHNICITY AND MIGRATION AS PREDICTORS FOR SUICIDE IN SCHIZOPHRENIA

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Background: Our current study proposes that an individual's ethnicity, defined as their geographical ancestry, and whether or not they have migrated during their lifetime, may have predictive value for those who suffer from schizophrenia and may be susceptible to suicide.
Methods: From our sample of 360 schizophrenia patients, we conducted cross-sectional assessments to collect information regarding their self-identified ethnicity, migration history, and suicide history. Ethnicity was defined according to self-report and STRUCTURE analysis of 359 SNPs using a Customized Illumina Chip to employ population stratification. Using the available data, we tested for associations between suicide history and migration and/or ethnicity.
Results: Our preliminary analysis failed to demonstrate an association between ethnicity (p=0.135) and migration (p=0.827) with suicide history. However, we found that ethnicity has a strong relationship with a patient's frequency of hospitalizations (p=0.009).
Conclusion: While ethnicity and migration status are not predictive of suicidal behaviour, these dimensions may hold predictive value for other aspects of treatment for patients of different backgrounds with schizophrenia.
ID: 2119307

EFFECTS OF AGE AT ONSET TO SCHIZOPHRENIA LIABILITY, DATA FROM A NATIONWIDE TWIN SAMPLE

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Background: Robust data from studies of incidence rates in schizophrenia have yielded evidence for a peak in onset at age 22 years in both males and females. An early age of illness onset has been discussed as a more severe

	SCZ (N=449)				SCZ+ (N=787)			
	HR	Std error	p-value	96%CI	HR	Std error	p-value	96%CI
Age at onset								
>=22	Reference	-	-	-	Reference	-	-	-
≤22	4.50	1.85	<0.001	2.01–10.07	4.39	1.21	<0.001	2.56–7.52
Zygosity								
DZ	Reference	-	-	-	Reference	-	-	-
MZ	5.41	2.24	<0.001	2.40–12.16	4.19	1.21	<0.001	2.38–7.38

subtype of schizophrenia, characterized by a worse illness course. These observations indicate that age at onset might be a distinct liability marker of schizophrenia possibly linked to the genetic underpinnings of the illness. Studying twin data, we wanted to see whether if an early onset of schizophrenia spectrum disorder in the first diagnosed twin (<22 years) would increase the risk of disorder in the second twin.
Methods: By linking 2 national registers in Denmark, The Danish Twin Register and The Danish Psychiatric Central Research Register we identify a nationwide twin sample, containing MZ and DZ twin pairs born in Denmark from 1951–2000, concordant or discordant for a schizophrenia diagnosis. To see if an early age at onset of the first diagnosed twin was associated with an increased risk of disorder in the second twin, we followed the second twin from birth until either diagnosis, censoring (June 1st 2011) or death occurred. An early illness onset was defined as having a diagnosis before age 22. The analysis used was cox regression.
Results: N=31524 pairs, were included in the analysis. Of these N=474 (450 pairs) were affected with schizophrenia and N=842 (788 pairs) were affected with schizophrenia spectrum disorder. When adjusting for zygosity the risk of the second twin having schizophrenia (SCZ) was 4.5 times higher if the first twin has an onset of schizophrenia before age 22, compared to an onset after age 22 (Hazard ratio (HR)=4.50, 95% CI=(2.01–10.09)). See table.
Conclusion: Our results of an increased risk in twin two if twin one has an illness onset before age 22 indicates that an early onset may reflect an increased genetic vulnerability, thus supporting that an early illness onset can be viewed as a specific liability marker of schizophrenia. The risk is significantly higher when being MZ compared to DZ, most pronounced in the narrow disease definition.
ID: 2084485

THE CONTRIBUTION OF SUBSTANCE USE DISORDERS TO MORTALITY IN SCHIZOPHRENIA

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Background: Psychotic disorders have been repeatedly linked to excess mortality from somatic illnesses. Lifetime comorbid alcohol or substance use disorders may have occurred in as many or even more than one third of patients diagnosed with schizophrenia or other psychotic disorders. We aimed to investigate the influence of cannabis use disorder, alcohol use disorder, and substance use disorder of other illicit substances, in patients with schizophrenia.
Methods: Nationwide registers were used to identify people with schizophrenia born in Denmark in 1955 or later. We calculated hazard ratios for all-cause and cause-specific mortality. Standardized mortality ratios (SMR) were calculated to compare the mortality to that of the general population. As a further point of interest, the mortality of people with schizophrenia and comorbid substance use disorders was compared to people with psychoses induced by the different substances (in particular alcohol, cannabis, and amphetamines).
Results: In schizophrenia, the SMR in those with lifetime substance use disorder was 8.46 (95% confidence interval (C.I.) 8.14–8.79), compared to 3.63 (95% C.I. 3.42–3.83) in those without lifetime substance use disorders. All substances were independently statistically significantly associated with increased risk of all-cause mortality. No substance use disorders were consistently associated with an increased risk of dying from suicide in the three study populations, but substances significantly predicted suicide attempts.
In people with alcohol-induced psychosis, neither comorbid misuse of cannabis nor hard drugs was significantly associated with increased all-cause mortality. Similarly, in people with psychosis induced by cocaine or other psychostimulants, neither alcohol nor cannabis misuse further increased mortality. In people with cannabis-induced psychosis, alcohol misuse did not further increase mortality, but hard drugs did, with a hazard ratio of 1.37 (95% C.I. 1.07–1.76), p=0.01.
Conclusion: Much of the excess mortality observed in people with severe mental illness was associated with substance abuse disorders, particularly misuse of alcohol and hard drugs. Awareness of the markedly increased mortality associated with substance abuse in people with mental illness could potentially help in efforts to reduce the excess mortality. Mortality associated with substance uuse disorders appears to be different in populations with schizophrenia and populations with alcohol- or substance induced psychosis.
ID: 2081389

VALIDITY AND BIAS IN ASSESSMENTS OF ABUSE AMONG CASES WITH PSYCHOSIS

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Background: There has been a renewed interest in the role of childhood adversity in the aetiology and course of psychosis, leading some researchers to conclude that childhood trauma causes psychosis in later adulthood. However, findings have been criticised on the grounds that reports of early adversity may be unreliable in those experiencing an episode of psychosis. We therefore sought to investigate levels of agreement of abuse ratings between self reported and interview based measures of childhood adversity.
Methods: Data were drawn from an incidence and case-control study of first presentation psychosis conducted in south London. A sample of 225 cases and 292 population based controls were assessed, all of whom were aged 18–64 and living within either the London boroughs of Lambeth or Southwark.
Childhood adversity was assessed using both the Childhood trauma questionnaire (CTQ) and the Childhood Experience of Care and Abuse interview (CECA). The CTQ is a 25 item retrospective, self-completed questionnaire which asks the participants to record the frequency of maltreatment experiences. The CECA is conducted by a trained researcher and designed to collect more detailed information on a range of adversities based on concrete aspects of events rather than respondents' subjective impressions. Interviews are then scored on a range of 1=marked, 2=moderate, 3=mild or 4=little/none. Only physical abuse (PA) and sexual abuse (SA) were included in analysis as they were comparable from both measures.
Results: We found a strong association between CTQ and CECA ratings of PA in cases (rtetrachoric=0.69, s.e.=0.07, P<0.001) and controls (rtetrachoric=0.70, s.e.=0.06, P<0.001), suggesting good convergent validity in both groups. Levels of agreement of CTQ and CECA PA ratings were similar in cases (κ=0.48, s.e.=0.07, P<0.001) and controls (κ=0.49, s.e.=0.06, P<0.001). Further, in both cases and controls, sensitivity and specificity were high: cases (sensitivity=77%, 95% CI 69.1% to 83.7%; specificity=72.1%, 95% CI 61.4.0% to 81.2%), and controls (sensitivity=77.3%, 95% CI 68.7% to 84.5%; specificity=72.3%, 95% CI 64.9% to 78.8%). Findings for SA were similar.
Conclusion: We found good levels of agreement in reports of physical and sexual abuse between self-report and interview based assessments. Further, levels of agreement were similar between cases and controls, suggesting the method of assessing abuse does not result in biased estimates of the prevalence of these exposures.
ID: 2091356

THE CCC2000 STUDY OF REGISTER-BASED FAMILY HISTORY OF MENTAL DISORDERS AS PREDICTOR OF PSYCHOTIC EXPERIENCES IN OFFSPRING

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Background: A history of psychotic disorders in first-degree relatives has been established as the strongest single indicator of risk of psychotic disorder in offspring. Psychotic experiences (PE) in individuals of the general population are hypothesized to mark the early expression of the pathology underlying psychosis. If PE mark psychosis vulnerability, PE are expected to share genetic liability with psychotic disorders. While twin studies have suggested heritability of PE, general population-based studies of PE and self-reported family psychiatric histories have showed mixed results, and two recent studies of genetic variants, weakly associated with Schizophrenia, failed to show significant associations with PE. The purpose of the present study was to examine whether PE in childhood was associated with a family history of psychotic disorder rather than a family history of non-psychotic mental disorder; and whether this association differed by the severity of PE.
Methods: The study examined data on 1,632 children from a general population birth cohort assessed at age 11–12 years by use of a semi-structured interview (K-SADS-items) covering 22 psychotic symptoms. The Danish national registers were linked to describe the complete family history in all first- and second degree relatives of hospital-based psychiatric diagnoses coded according to the ICD-10. Uni- and multivariable logistic regressions were used to test whether a family history of psychotic disorder, and of non-psychotic mental disorder, versus no diagnosis, was associated with increased risk of PE in offspring (three-level hierarchical exposure variable).
Results: The occurrence of PE in offspring was significantly associated with a history of psychosis among the first-degree relatives (adjusted RR=3.17, 95% CI 1.75–5.74, P=0.0001) as compared with no diagnosis of mental disorder. The risk was increased for increased severity of PE in offspring as indicated by the combination of hallucinations and delusions (adjusted RR=5.64, 95% CI 2.49–12.80, P=0.000001). A history of non-psychotic mental disorders in first-degree relatives did not contribute to the risk of PE in offspring, nor did any mental disorder among second-degree relatives.
Conclusion: The higher familial load of psychosis in children with PE supports the notion of PE as a vulnerability marker of psychosis. The effect of psychosis in first-degree relatives may operate through shared genetic as well as environmental factors.
ID: 2096884

CHILDHOOD TRAUMA AND PSYCHOSIS IN A PROSPECTIVE COHORT STUDY: CAUSE, EFFECT AND DIRECTIONALITY

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Background: Using longitudinal and prospective measures, the authors assessed the relationship between childhood trauma and psychotic experiences, addressing the following questions: 1) Does exposure to trauma predict incident psychotic experiences? 2) Does cessation of trauma predict cessation of psychotic experiences? 3) What is the direction of the relationship between childhood trauma and psychotic experiences?
Methods: This was a nationally representative prospective cohort study of 1,112 school-based adolescents 13 - 16 years of age, assessed at baseline and at 3 month and 12 month follow-ups for childhood trauma (physical assault and bullying) and psychotic experiences.
Results: A bidirectional relationship was observed between childhood trauma and psychosis, with trauma predicting psychotic experiences over time and vice versa. However, even after accounting for this bidirectional relationship with a number of strict adjustments (only newly incident psychotic experiences occurring over the course of the study following exposure to traumatic experiences were examined), trauma was strongly predictive of psychotic experiences. A dose-response relationship was observed between severity of bullying and risk for psychotic experiences. Moreover, cessation of trauma predicted cessation of psychotic experiences, with the incidence of psychotic experiences decreasing significantly in individuals whose exposure to trauma ceased over the course of the study.
Conclusion: After a series of conservative adjustments, the authors found that exposure to childhood trauma predicted newly incident psychotic experiences. The study also provides the first direct evidence that cessation of traumatic experiences leads to a reduced incidence of psychotic experiences.
ID: 2109514

EARLY-LIFE EPSTEIN BARR VIRUS INFECTION, CHILDHOOD IQ AND PSYCHOTIC EXPERIENCES IN ADOLESCENCE: A PROSPECTIVE SEROLOGICAL STUDY

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Background: Early-life infection is associated with risk of adult psychotic illness. Cross-sectional studies have reported increased prevalence of Epstein Barr virus (EBV), a member of the Herpesviridae family in schizophrenia; also, a possible role of herpes virus in cognitive dysfunction in schizophrenia and healthy controls. Using data from the general population-based Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, we report a longitudinal study of the association between early-life EBV infection, childhood IQ and subsequent risk of psychotic experiences (PE) in early adolescence.

Methods: Antibodies to EBV (anti-VCA IgG) in serum were measured at age 4 years in a representative subsample of the cohort (N=530). The assessments for IQ at age 9 years and PE at age 13 years were attended by 392 and 366 of these individuals, respectively. Logistic regression calculated odds ratios (OR) for PE in the EBV-exposed compared with the unexposed individuals. Mean IQ scores were compared between these exposure groups; mediating effects of IQ on the EBV-PE association was examined. Potential confounders included age, gender, ethnicity, social class, household crowding, and depression at the time of assessment of PE.
Results: About 25% of the sample was exposed to EBV at age 4 years. EBV exposure was associated with a five-fold risk of PE; OR for definite PE 5.37 (95% CI 1.71–16.87), which remained significant after adjusting for potential confounders. EBV-exposed individuals performed worse on all measures of IQ; mean difference in full-scale IQ between EBV-exposed and unexposed groups was 4.55 (95% CI 0.88–8.23); however, this was explained by socio-demographic differences.
Conclusion: Early-childhood EBV infection is associated with the increased risk of PE in early adolescence; an association not mediated by IQ. CNS alterations arising from early-life infections that lead to an increased risk of psychotic outcomes may be independent of childhood cognitive deficit as captured by IQ test. Scientific endeavour to unravel the mechanisms underlying the link between psychosis and early-life infection should, therefore, consider alternative pathways, possibly immune and genetic.
ID: 2091385

CHILDHOOD CNS INFECTION AND NON-SPECIFIC LOW-GRADE SYSTEMIC INFLAMMATION AS RISK FACTORS FOR ADULT PSYCHOSIS

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Background: While interference with brain development from childhood CNS infections is consistent with a neurodevelopmental view of schizophrenia, any links between non-specific, low-grade, systemic inflammation in childhood and risk of adult psychosis is less intuitive. Using general population-based longitudinal data, this presentation includes a meta-analysis of childhood CNS infections and a primary analysis of childhood serum inflammatory markers in healthy individuals, in order to examine whether the risk of adult psychotic illness depends on the type of early-life immune activation, CNS or systemic.
Methods: The meta-analysis included three population-based longitudinal datasets of childhood CNS infection and adult psychosis identified from systematic search of PubMed. The analysis of low-grade systemic inflammation included data from 4500 subjects from the ALSPAC cohort, where serum interleukin 6 (IL-6) and C-reactive protein (CRP) were measured at age 9 years and assessments for psychosis and depression were carried out at age 18 years. Psychotic experiences (PE) and psychotic disorder were measured by a standard, face-to-face, semi-structured interview, and depression was measured by a clinical interview (CIS-R) and a questionnaire (MFQ).
Results: Meta-analysis of up to 2424 cases and over 1.2 million controls showed childhood CNS infection was associated with increased risk of adult non-affective psychosis; risk ratio 1.59 (95% CI, 1.10–2.29). Similar findings were seen for schizophrenia; risk ratio 1.80 (95% CI, 1.04–3.11). Childhood low grade systemic inflammation was also associated with subsequent psychotic outcomes. In the ALSPAC cohort, after adjusting for a number of potential confounders, participants in the top third of IL-6 values compared with the bottom third at age 9 were more likely to develop psychotic experiences and psychotic disorder at age 18: adjusted OR 1.81 (95% CI, 1.01–3.28) and 2.40 (95% CI, 0.87–6.62), respectively. The risk of depression at age 18 was also increased with higher IL-6 at baseline; adjusted OR 1.55 (95% CI, 1.13–2.14).
Conclusion: Childhood CNS infection and non-specific low grade systemic inflammation, both are associated with higher risk of psychotic outcomes in adulthood. These findings indicate complex immune-brain interactions contribute to the pathogenesis of schizophrenia, rather than an immune component to its aetiology being restricted to frank developmental insults such as a CNS infection.
ID: 2102547

DETERMINANTS OF HELP SEEKING IN FIRST EPISODE PSYCHOSIS IN THE ALSPAC BIRTH COHORT

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Background: It has been hoped that early detection and intervention for people with psychotic experiences (PE) would prevent transition to psychosis. However, it is likely that similar to people with clinical disorders help seeking behaviour vary between people with sub-clinical symptoms, and is related to various clinical and non-clinical factors. We examined determinants of seeking help from a professional source for PE in 18 year old young adults from the population-based ALSPAC birth cohort.
Methods: At age 18 years, PE occurring at any time since age 12 years were measured by the psychosis like symptoms interview (PLIKSi), which is a standard, face-to-face, semi-structured interview to elicit twelve psychotic symptoms across three domains of 'positive' symptoms, hallucinations, delusions and thought interference. Data on social and occupational functioning, help seeking from a professional source (family physician, mental health service, counsellor, etc.), comorbidities, childhood IQ, and socio-demographic parameters were gathered using questionnaires and interviews. An operational diagnosis of psychotic disorder at 18 years was created based on the frequency and effects of PE over the preceding six months. Individuals with PE who were help-seeking were compared with those who were not seeking any help.
Results: At age 18 years, 4720 participants were interviewed, of which 432 reported PE, 79 met the criteria for a psychotic disorder. Only 50 individuals reported seeking help from a professional source for PE. Help seeking was associated with the number and frequency of auditory hallucinations, perceived distress, effects on social and occupational functioning, comorbid depression and anxiety, but were unrelated to IQ, sex, social class, ethnicity or maternal education.
Conclusion: In British young adult individuals, help seeking for PE depends on symptom severity, perceived distress, functional impairment, and comorbid non-psychotic mood and anxiety symptoms.
ID: 2109024

SERUM INTERLEUKIN-6 AND C-REACTIVE PROTEIN IN CHILDHOOD AS PREDICTORS OF DEPRESSION AND PSYCHOSIS IN YOUNG ADULT LIFE: A POPULATION-BASED LONGITUDINAL STUDY

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Background: Mechanisms involving monoamines underpin contemporary pathophysiologic explanations and drug therapy for psychosis and depression. However, heterogeneity in presentation, course and treatment responses suggest additional mechanisms. Supported by a number of observations, cytokine mediated communication between the immune system and the brain has been recently implicated in the aetiology of schizophrenia and depression. Animal model studies have demonstrated how higher levels of circulating inflammatory cytokines, such as interleukin (IL) 6, influence the brain leading to changes in mood, cognition and behaviour. Meta-analyses of human population-based cross-sectional studies also confirm increased serum IL-6 and C-reactive protein (CRP) in first episode psychosis, acute psychotic relapse and depression. However, longitudinal studies are needed to establish the direction of this association.
Methods: We used data from approximately 4500 individuals from the general population-representative ALSPAC birth cohort. Serum IL-6 and CRP were measured in non-fasting blood samples obtained at age 9 years. At age 18 years, psychotic experiences and psychotic disorder were measured by a standard, face-to-face, semi-structured interview. Depression was measured in two ways: Clinical Interview Schedule-Revised, and Mood and Feelings Questionnaire, thus allowing internal replication.
Results: After adjusting for gender, age, BMI, ethnicity, social class, past psychological problems, and maternal depression, participants in the top third of IL-6 values, compared with the bottom third, at age 9 were more likely to develop psychotic experiences and psychotic disorder at age 18: adjusted OR 1.81 (95% CI, 1.01–3.28) and 2.40 (95% CI, 0.87–6.62), respectively. The risk of depression at age 18 was also increased with higher IL-6 at baseline; adjusted OR 1.55 (95% CI, 1.13–2.14). Besides, IL-6 was associated with risks of subsequent psychotic experiences and depression in a linear, dose-response fashion.
Conclusion: Higher levels of IL-6 in childhood are associated with risks of psychosis and depression in young adulthood. Processes in the inflammatory pathway may be targets for therapeutic intervention and prevention for these disorders. Low grade systemic inflammation might explain the high co-morbidity between schizophrenia, depression, cardiovascular disease, and diabetes mellitus.
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ID: 2085310

MAKING THE CASE FOR EI: MATCHING WHAT WE KNOW TO WHAT PAYERS BELIEVE

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Background: Early intervention (EI) for people with psychosis has been the policy in a number of countries for a decade or more. In England the original policy was prescriptive: based on a standardised incidence rate of 15 new cases per 100k people per year, fifty new EI teams were expected to benefit 7000 young people each year. Services were mandated throughout the country and implementation of a detailed service specification represented a step-change for the better in commissioning and mental health service provision. Nevertheless, in some parts of the country, particularly in rural areas, commitment to the model was patchy with some detractors; this was in contrast to urban areas where caseloads were high and the new EI teams popular with service users, families and staff. Opinion is now split and EI teams are being disbanded in some areas. We consider program fidelity in terms of the actual demand on services compared with the demand predicted in the policy and original commissioning guidelines.
Methods: Following meta-analysis of existing studies we used epidemiological data on the neighbourhood and social determinants of psychosis incidence to develop general linear models predicting the numbers of new cases of psychosis arising each year within small areas (counties and, more fine grained, local authority districts). These have been made freely available through a readily accessible web-based tool www.psymaptic.org
Results: The Psympatic model shows wide - more than fifty-fold - geographical variation in psychosis incidence rates across the UK, suggesting the original blanket rate was not accurate. While there are four (95% prediction interval 1, 8) new cases each year in the county of Rutland, there are 269 (231, 306) new cases per year in Birmingham. The incidence rate is much lower in the former area, accounting for population size and sociodemographic confounders. Thus, the rates in the inner-cities can be many times higher than in rural areas where first episode psychosis may be seen only occasionally by mental health teams. The model now provides precise information for commissioners and service providers, taking into account population size.
Conclusion: A single EI service model may not fit all areas. Specialist teams may not be the most effective use of limited resources where rates are low, whereas in inner-cities the contrary is true. Evidence-based commissioning should allow flexibility in determining best-value, particularly as finances become constrained.
ID: 2117977

META-ANALYSIS OF THE ASSOCIATION BETWEEN SUICIDAL IDEATION AND LATER SUICIDE AMONG PATIENTS WITH EITHER A SCHIZOPHRENIA SPECTRUM PSYCHOSIS OR A MOOD DISORDER

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Background: Suicide remains a major cause of premature mortality in schizophrenia and it is generally accepted that the assessment of suicidal ideation is central to suicide risk assessment and prevention. Recent studies of patients with a mix of psychiatric diagnoses have suggested a modest or weak association between suicidal ideation and later suicide. The aim of this study was to examine the extent to which the association between expressed suicidal ideation and later suicide varies according to psychiatric diagnosis.
Methods: A systematic meta-analysis of studies that report the association between suicidal ideation and later suicide in patients with 'Mood Disorders', defined to include major depression, dysthymia, and bipolar disorder, or 'Schizophrenia Spectrum Psychosis', defined to include schizophrenia, schizophreniform disorder and delusional disorder.
Results: Suicidal ideation was strongly associated with suicide among patients with Schizophrenia Spectrum Psychosis (14 studies reporting on 567 suicides, OR = 6.49, 95% confidence interval (CI) 3.82 to 11.02). The association between suicidal ideation and suicide among patients with Mood Disorders (11 studies reporting on 853 suicides, OR = 1.49, 95% CI 0.92 to 2.42) was not significant. Diagnostic group made a significant contribution to between study heterogeneity (Q-value = 16.16, df = 1, $p<0.001$) indicating a significant difference in the strength of the associations between suicidal ideation and suicide between the two diagnostic groups. Meta-regression and multiple meta-regression suggested that methodological issues in the primary research did not explain the findings. Suicidal ideation was weakly but significantly associated with suicide among studies of patients with Mood Disorders over periods of follow-up of less than 10 years.
Conclusion: Although our findings suggest that the association between suicidal ideation and later suicide is stronger in Schizophrenia Spectrum Psychosis than in Mood Disorders this result should be interpreted cautiously because of the high degree of between study heterogeneity and because studies that used stronger methods of reporting had a weaker association between suicidal ideation and suicide.
ID: 2115190

INCIDENCE OF INFECTIONS IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Severe mental illness (SMI), comprising schizophrenia or bipolar affective disorder, is associated with an excess mortality resulting in a 15–20 year shorter life expectancy. High rates of suicide are an important factor of the excess mortality, however, most of the excess mortality stems from excess mortality from natural causes. Much higher frequencies of non-communicable diseases (i.e. diabetes, heart diseases, or cancers) are found among people with schizophrenia or bipolar disorder, but, these high frequencies only partly explain the excess mortality.
Infections are the leading communicable cause of death, and the aim of this study was to examine whether persons with SMI are at higher risk of acquiring an infection, and thus, introducing a possible explanation of some of the excess mortality.
Methods: We used the Danish Civil Registration System to establish a population-based cohort. Data were analysed in a survival analysis setup using the log-linear Poisson regression, with the logarithm to the person years as an offset variable (SAS GENMOD version 9.2 procedures). Outcome was incidence rate ratios of a first hospital contacts with a diagnosis of infections among people with SMI compared to the general population.
Results: In total, the study population comprised 5,055,242 persons over 15 years of age at risk for admission with a diagnosis of infection during the study period 1995–2011. Approximately 16% of the cohortees had been admitted with an infection. A total of 56,248 cohortees had been in contact with a psychiatric hospital with SMI.
Overall the incidence rate ratio of infections was twice (2.00 (95% CI 1.97 - 2.04)) as high among people with SMI, compared to the general population. The highest incidence rate ratio was found for HIV/hepatitis with an incidence rate ratio of 4.18 (3.76–4.66). The comorbid presence of non-communicable diseases or substance abuse was associated with an even higher incidence of infections in this patient group with an incidence rate ratio up to 8.51 (8.09–8.92).
Conclusion: This study shows that infections are much more common in people with SMI, compared to the general population. One out of five persons with SMI has an infection that needs treatment at a hospital. Infections are a known risk factor for excess mortality and thus the high rates of infections in people with SMIs are important to examine further, in the elucidation of the unacceptably high mortality among people with SMI.
ID: 2118554

STUDYING A CREATIVE SUBJECT AT UNIVERSITY IS ASSOCIATED WITH INCREASED RISK FOR PSYCHOSIS: A CASE CONTROL STUDY AND DISCORDANT SIB-PAIR ANALYSIS OF 4,454,763 INDIVIDUALS USING SWEDISH POPULATION DATA

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Background: The belief in an association between creativity and mental disorder has a long history. However, most attempts to study the association have suffered from selection bias, observer bias, reporting bias, low power or a combination of the above. To study this association objectively, large unbiased population samples are required. In this study we used data from national registries on higher education to test for an association between studying a creative subject and subsequent hospital admission for schizophrenia or bipolar disorder.
Methods: Using linked population based registries, we conducted a case control design, N=4,454,763. Cases were defined as individuals admitted with a primary diagnosis of schizophrenia (N=20,333) and bipolar disorder (N=28,293) under ICD 9 or 10 criteria. The exposure was tertiary education in an artistic field (visual arts, dance, music, drama,media production and design). In sensitivity analyses, we examined alternative exposures that were not judged creative (social sciences, law and jurisprudence) and alternative outcomes (migraine and diabetes). We adjusted for educational level and conducted a sib pair analysis comparing sib pairs discordant for the exposure, to adjust for unmeasured familial confounders.
Results: Compared to the general population, individuals with an artistic education had approximately double the odds of developing schizophrenia (OR=1.90, 95% CI= [1.69; 2.12]) and also an increased odds of bipolar disorder (OR= 1.62 [1.50; 1.75]). These results remained in the sib pair analysis. In sensitivity analyses, the odds of migraine (0.88 [0.83; 0.93]) and diabetes (OR = 0.99 [0.92; 1.06]) were not increased in students of artistic subjects, and students social sciences law and jurisprudence had no increased odds of schizophrenia (0.93 [0.76; 1.14]) or bipolar disorder (0.92 [0.81; 1.04]).
Conclusion: Compared to the general population, students of artistic subjects at university have approximately double the odds of developing schizophrenia and 1.6 times the odds of developing bipolar disorder. Sensitivity analyses, using different exposures and outcomes, found no associations, indicating that these results are unlikely to have arisen through biases in the study design.
ID: 2119078

DECLINING INTELLECTUAL TRAJECTORY IN CHILDHOOD/ADOLESCENCE IN OFFSPRING AT RISK OF MAJOR PSYCHOSES: CONVERGENCE WITH RESULTS IN POPULATION-BASED SAMPLES AND IMPLICATIONS FOR PRE-CLINICAL STAGING.

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Background: Children born to a parent affected by psychoses carry in childhood/adolescence cognitive dysfunctions that adult patients display[1]. Recent findings suggest that the form of the cognitive trajectory may also matter. A relative cognitive decline was found in children from the general population who later developed schizophrenia[2, 3]. However, little is known about the clinical features of children with such declining trajectory. Relying on a 25-year longitudinal follow-up of large kindreds densely affected by psychoses, we observed a significant IQ decline by age 18 in high risk children/adolescents (HRs), suggesting early brain dysfunctions beginning many years before disease onset. To inform clinical practice, we measured clinical features in the youths who incurred a IQ falloff.
Methods: Starting with 1500 clinically characterized adult members from 48 densely affected multigenerational kindreds, we identified 400 patient with major psychoses[1, 4]. Focusing on children born to these patients, we can report on 40 HRs who were administered, between ages 6 and 26 at an interval of 5.7 years, two successive Wechsler IQ, clinical assessments and lifetime diagnoses.
Results: By means of a paired t test, we found in whole HR sample a significant average full-scale IQ decline of -2.7 IQ points (SD 8.3) between baseline and follow-up (t(29)=-1.75, one-sided p=.045). Compatibly, one third of the offspring experienced an 8 to 20 point IQ decline over a few years, mainly before age 18. No baseline IQ levels were spared. Surprisingly, declining and non-declining offspring were not different in terms of social functioning (GAF), rates of non-psychotic DSM diagnoses at baseline and follow-up.

Conclusion: The present declining trajectory patterns from a high-risk cohort mirror results from population-representative cohorts 2, 3, strengthening evidence of a relative decline in cognitive performance before age 18. This cognitive decline might be clinically silent which would make it difficult to detect by the clinical practitioner or educator. These findings combined with risk endophenotypes in other modalities[1, 5] may provide basis for models of pre-clinical staging of the risk trajectory in childhood/adolescence.

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ID: 2118678

RECURRENT URINARY TRACT INFECTIONS IN ACUTE PSYCHOSIS

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Background: Schizophrenia is associated with increased infections, and infections are associated with acute psychosis. We have replicated an association between urinary tract infection (UTI) and acute psychosis in schizophrenia. The aims of this study were to evaluate the prevalence of recurrent UTIs and acute psychosis in schizophrenia, and to compare demographic, clinical, and laboratory features between subjects with acute psychosis with and without recurrent UTIs.
Methods: All subjects age 18–64 who were admitted two or more times to our adult inpatient psychiatry unit between January 2008 and December 2013 for an acute episode of DSM-IV schizophrenia or schizoaffective disorder were included (n=152). UTI was defined as positive leukocyte esterase and/or positive nitrites on urinalysis and ≥5–10 leukocytes/high-powered field on urine microscopy.
Results: 36% of subjects (n=55) had at least one UTI, and 16% (n=25) had two or more UTIs. Compared to subjects with no UTI, subjects with two or more UTIs were more likely to be female, had a higher BMI, and a greater number of hospitalizations, but otherwise did not differ based on demographic or clinical features. A UTI was found during 59% of all admissions (64 of 109) among the subjects with two or more UTIs. Subjects with two or more UTIs had significantly higher absolute monocyte (p=0.02) and eosinophil (p=0.04) counts, and significantly lower differential lymphocytes (p=0.04) in the peripheral blood during admissions with versus without UTI.
Conclusion: We found that a significant proportion of patients with schizophrenia have recurrent UTIs at the time of hospitalization for acute psychosis. Although the mechanism of this association remains unclear, findings provide additional evidence that infections may be relevant to the etiopathophysiology of relapse in some patients with schizophrenia. The results also highlight the importance of monitoring for co-morbid UTI in this patient population.

ID: 2093166

LONGITUDINAL STUDY OF BLOOD CYTOKINE LEVELS AND RELAPSE IN SCHIZOPHRENIA

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Background: Clinical course in schizophrenia is often characterized by recurrent relapses, which are associated with adverse outcomes. In a meta-analysis, we found that the cytokine interleukin-6 (IL-6) may be a state maker for relapse in schizophrenia: blood IL-6 levels are increased in episodes of acute psychosis, and decreased following antipsychotic treatment for relapse. However, few previous studies have assessed longitudinal, intra-individual changes in blood cytokine levels in patients with schizophrenia as a predictor of relapse, and none have measured IL-6. In the PROACTIVE study, we tested the hypothesis that an increase in blood IL-6 level precedes and predicts relapse in schizophrenia, after controlling for potential confounding factors.
Methods: A multiplex panel of cytokines, including IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, and TNF-α in all available blood samples from the PROACTIVE study (n=2273) was measured. A Relapse Monitoring Board independently determined illness relapse.
Results: Blood samples in the PROACTIVE study were collected every 6–12 weeks for up to 30 months. The mean±SD number of blood samples available per subject was 8.1 ± 6.8. 37% (n=109) of subjects experienced at least one illness relapse. Blood samples were available for 46% (n=50) of subjects at the time of relapse. A mean±SD of 4.0 ± 3.8 blood samples were available prior to illness relapse.
Conclusion: The PROACTIVE study has a substantial number of cases with longitudinal data, including serial blood samples prior to well-defined illness relapse. Blood cytokine levels may have utility as a potential clinical state and relapse predictive marker in schizophrenia that could be used to assess treatment effectiveness, advance relapse prevention efforts, and inform on immune-based therapeutic interventions, thereby reducing the burden of relapse and improving clinical care of patients with schizophrenia.

ID: 2093145

PRESCRIPTION STIMULANT USE FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER IS ASSOCIATED WITH EARLIER ONSET OF PSYCHOSIS

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Background: Amphetamine sensitization is characterized by long-term increases in dopamine release after exposure to amphetamine. Since increased presynaptic dopamine release is a highly replicated finding in psychosis, we hypothesized that individuals with psychotic disorders exposed to stimulants during childhood/adolescence will have an earlier age of onset of psychosis (AOP).
Methods: Patients with psychotic disorders (n=239) were recruited from McLean Hospital. AOP was compared in individuals with and without prior exposure to stimulants controlling for gender, IQ, education and exposure to nicotine, cannabis or other drugs of abuse. This analysis was repeated in those who were prescribed stimulants for a diagnosis of attention deficit hyperactivity disorder (ADHD).
Results: Forty eight percent (n=115) of patients reported a history of stimulant use. AOP was significantly earlier in those exposed to stimulants (20.5 vs. 24.5 years stimulants vs. no stimulants, p<0.001). After controlling for gender, IQ, education, smoking, and lifetime history of cannabis or other drugs of abuse, the association between stimulant exposure and earlier AOP remained significant (p=0.007). The subset of patients who were prescribed stimulants specifically for a diagnosis of ADHD (n=86) also showed an earlier AOP (20.2 vs. 24.5 years, p<0.001). All were exposed to amphetamine or both amphetamine and methylphenidate. Significantly more individuals were exposed to cannabis in those who were prescribed stimulants (55.4% vs. 32.5%, p=0.001). However, after controlling for cannabis use, the relationship between earlier age

of onset and prescribed stimulants remained significant (p=0.003). The association of prescribed stimulant use and earlier AOP was present in the subset of individuals exposed to cannabis (18.7 vs. 22.3 years prescribed vs. not prescribed stimulants, p=0.001) and a trend was observed in those not exposed to cannabis (21.9 vs. 25.4 years, p=0.07). There were no significant differences in education, IQ, gender, smoking status, and exposure to other drugs of abuse in the prescribed vs. not prescribed stimulant groups, and the relationship between prescription stimulants and earlier AOP remained significant after controlling for these variables (p=0.03).

Conclusion: Individuals with psychotic disorders with a history of being prescribed stimulants for a diagnosis of ADHD have an earlier onset of psychosis, and this relationship does not appear to be mediated by cannabis use.

ID: 2086477

TIMING AND IMPACT OF SOCIAL STRESSORS IN A COHORT OF CHILDREN AT FAMILIAL HIGH RISK FOR PSYCHOTIC ILLNESS

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Background: In the mid-1950s, Barbara Fish published her first paper on abnormal development in infants of mothers with schizophrenia. Since then, there has been half a century of research into developmental antecedents of schizophrenia in children at high familial risk, including the formulation of the neurodevelopmental hypothesis of schizophrenia in the late 1980s. In a modern version of the familial high-risk paradigm, utilising longitudinal data collected via record-linkage methodology, our aim was to examine whether exposure to social stressors in childhood, including timing of exposure, is a risk factor for psychotic illness, independent of familial liability.

Methods: We used record-linkage across statewide administrative registers (midwives, psychiatric, child protective services and mortality, among others) to identify 15,486 offspring born in Western Australia between 1980 to 2001 to mothers with a lifetime history of psychotic illness (case children) and compared them with 452,459 offspring born in the same period to mothers with no known psychiatric history (comparison children).

Results: 4.1% of case children had developed a psychotic illness compared to 1.1% of comparison children. Odds of psychotic illness increased significantly following exposure to discontinuity in parenting, including death and hospitalisation. Length of discontinuity (for hospitalisation), and age at time of discontinuity (for both hospitalisation and death) impacted on risk. For example, odds of a psychotic illness increased from 1.4 (CI 1.3–1.5) for maternal hospitalisation occurring before the age of one, to 1.9 (CI 1.8–2.1) for maternal hospitalisation between ages 5 to 9 years. Children exposed to childhood abuse also had significantly increased odds of psychotic illness (OR 4.4, CI 3.9–4.9). However, at the same time, case children were also significantly more likely than comparison children to experience discontinuity in parenting and childhood abuse.

Conclusion: Exposure to social stressors is associated with psychotic illness, and timing of exposure is important. However, children already at increased familial risk for psychotic illness are also at increased risk of experiencing these social stressors. In work in progress, we are using multivariate models to disentangle the impact of these social stressors from other competing risks for psychotic illness including familial liability.

ID: 2113960

SOCIODEMOGRAPHIC, CLINICAL AND CHILDHOOD DETERMINANTS OF VICTIMISATION IN A LARGE, NATIONAL SURVEY SAMPLE OF ADULTS WITH SEVERE MENTAL ILLNESS

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Background: High rates of adult victimisation have been reported for people with severe mental illness. This study examined the additional contribution of clinical profile to established risk factors for assault victimisation in people with a psychotic disorder.

Methods: The Australian national psychosis survey used a two-phase design to draw a representative sample of adults aged 18–64 years with psychotic disorders in contact with public treatment services from a population of 1,464,923 adults. Interview questions covered psychopathology, cognition, sociodemographics, substance use, criminality, and childhood and adult victimisation, among others. Multivariable logistic regression models were used to explore the independent contribution of (i) general population risk factors, (ii) clinical profile, and (iii) childhood abuse on risk of assault. Differences between men and women were examined.

Results: Over a 12 month period, 38.6% of adults with a psychotic disorder reported being victimised; 16.4% reported actual assault (15.2% of males and 18.3% of females). The strongest predictors of assault in this sample were established risk factors including: age, living in the most disadvantaged neighbourhood, being homelessness, lifetime alcohol abuse/dependence and criminal offending in the past year. Few clinical variables remained significant in the multivariable model other than having an episode of mania and committing deliberate self-harm in the past year. Neither global functioning nor cognition were significant. Childhood abuse was independently associated with assault victimisation (odds ratio 1.7, CI 1.2–2.3).

Conclusion: Victimisation is common among people with psychosis. As in the general population, various forms of disadvantage are important risk factors for victimisation. However, people with psychosis are much more likely to experience socioeconomic disadvantage than the general population. Victimisation may impact on recovery, and needs to be taken into consideration in clinical practice.

ID: 2069469

SCHIZOPHRENIA VS. BIPOLAR DISORDER: EPIDEMIOLOGICAL AND BIOMARKER FINDINGS FROM DENMARK.

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Background: Schizophrenia and Bipolar Disorder together consttitute a classical dichotomy in psychiatric nosology. However, molecular genetic studies, genetic epidemiology and epidemiological studies of environmental risk factors have documented both overlaps and discrepancies.

Methods: In my presentation I will review some key findings from this large literature and exemplify with recent results from population based analyses of Danish registers and biobanks.

Results: Schizophrenia and Bipolar disorder differ with respect to occurrence and other aspects of descriptive epidemiology, with respect to risk factors, and genetic liability. at the same time there is considerable individual and familial co-occurrence.

Conclusion: Studies of bipolar disorder and schizophrenia, directly comparing their genetic and environmental risk factors, and integrating with the study of other mental illnesses continue to be important in the search for schizophrenia etiology
ID: 2131515

TEN-YEAR FOLLOW-UP OF THE OPUS SPECIALIZED EARLY INTERVENTION TRIAL FOR PATIENTS WITH A FIRST EPISODE OF PSYCHOSIS

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Background: Specialized early intervention programs such as the Danish OPUS treatment are efficient in treating patients with a first episode of psychosis (FEP) at least after two and five years. Few studies have examined long-term outcomes of these interventions. Our aim was to examine the effect of two years of OPUS vs. treatment as usual (TAU) within an FEP cohort, 10 years after inclusion into the OPUS trial.
Methods: From 1998 to 2000, participants were randomized to OPUS or TAU. Ten years later, we conducted comprehensive interviews and performed register-based follow-up on all participants in national Danish registers. We analyzed participants according to the intention to treat principle.
Results: Of the 547 participants included in the study, 347 (63.4 %) took part in this follow-up. While there was evidence of a differential ten-year course in the development of negative symptoms, psychiatric bed-days, and possibly psychotic symptoms in favor of OPUS treatment, differences were driven by effects at earlier follow-ups and had diminished over time. Statistically significant differences in the course of use of supported housing were present even after eight to ten years. There were no differences between OPUS and TAU regarding income, work-related outcomes, or marital status.
Conclusion: Most of the positive short-term effects of the OPUS intervention had diminished or vanished at this long-term follow-up. We observed a clear tendency that OPUS treatment leads to fewer days in supported housing. There is a need for further studies investigating if extending the intervention will improve outcomes more markedly at long-term follow-ups.
ID: 2109326

SIMILAR PATTERNS OF COMBINATIONS OF COGNITIVE AND PHYSIOLOGICAL ENDOPHENOTYPES IN CHILDREN AT RISK AND IN ADULT PATIENTS: A DEVELOPMENTAL MODEL FOR CHILDREN BORN TO AN AFFECTED PARENT.

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Background: Background: Risk endophenotypes in childhood (cognitive[1] or electrophysiological[2]) are found in children born to a parent affected by affective and non-affective psychoses. However, even if endophenotypes found in adult patients can be detected in children/adolescents at risk, their performance as predictive markers of later illness needs investigation since they are also present in non-affected adult relatives of patients[3]. The present results suggest that cognitive and electrophysiological endophenotypes in children/adolescents at risk and in patients may have similar patterns of differences with healthy controls, when the risk of carrying a single endophenotype or of carrying several endophenotypes is considered in an individual.
Methods: We used i) a High-Risk sample of 85 offspring (HR, aged 6 to 26 yo) descending from 48 densely affected multigenerational kindreds from Eastern Quebec and 189 controls balanced for age and gender, and ii) a sample of patients affected by schizophrenia (n=132) or bipolar disorder (n=128) and 135 adult controls. All participants were administered a neuropsychological battery (processing speed, visual and verbal episodic memory, working memory, executive functions) and electroretinographic (ERG) measures[2].
Results: The presence of 1 cognitive or 1 ERG endophenotype in an individual was significantly more frequent in adult patients and in HR than in controls, but was nevertheless found in 10–15% of healthy controls. In contrast, the presence of combinations or clusterings of endophenotypes in an individual were found more specific in adult patients and youths at risk than in controls: 20% in HRs, around 50% in patients and only 4% in controls.
Conclusion: Data suggest that single endophenotypes are relatively frequent in the general population, hence diminishing power to detect the children at risk of future disease. The difference between patients or subjects at risk and healthy controls was greater when combinations of endophenotypes in an individual were considered. These trends were similar for cognitive and ERG anomalies. Our results may have relevance for models of pre-clinical staging of youths at risk and for the surveillance of the developmental risk trajectory. Our findings are also compatible with the multi-trait polygenic theory of psychosis.
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ID: 2118097

RACIAL-ETHNIC DISPARITIES IN SPECIFICITY AND OVERLAP OF SUBCLINICAL PSYCHOSIS AND MANIA SYMPTOMS IN A U.S. SAMPLE OF YOUTH

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Background: A number of studies document racial/ethnic disparities in the frequency of psychosis at both the disorder and symptom level. However, few studies have been conducted in the U.S. and almost none have focused on community samples of children and youth.
Methods: We investigated associations of race/ethnicity with specificity and overlap of subclinical psychosis and mania symptoms among 8,647 8-21 year-olds in the Philadelphia Neurodevelopmental Cohort. Participants were recruited from the community healthcare network and pediatric clinics of the Children's Hospital of Philadelphia. Symptoms included 12 sub-psychosis items and 7 mania items without duration criteria. Correlates were race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and "other"), sex, age, maternal education, and physical health. Latent class analysis was used to assign participants to one of four pre-hypothesized symptom groups, sub-psychosis only, mania only, both, and neither, with good classification quality (entropy=.904).

Results: In general, minority youths were more likely to belong to one of the symptom classes than to the "neither" class. This was also observed after restricting to those without significant physical health conditions, although Hispanic and "other" youths were not more likely than non-Hispanic whites to belong to the "mania only" class. After further adjustment for age, sex, and maternal education, non-Hispanic blacks were the only group to have higher odds of belonging to all three symptom classes compared to the "neither" class. Hispanic ethnicity was associated with being in the "both" class only, while "other" race was associated with being in the "sub-psychosis only" and "both" classes. Non-Hispanic blacks were more likely than the other groups to belong to the "sub-psychosis only" class. They were also more likely to belong to the "sub-psychosis only" class (OR=2.08, 95%CI=1.71–2.52) or the "both" class (OR=2.39, 95%CI=1.87–3.04) than to the "mania only" class (OR=1.41, 95%CI=1.17–1.69).
Conclusion: We found evidence for racial/ethnic disparities in subclinical psychosis and mania symptom patterns among U.S. youths. Disparities were greatest for non-Hispanic blacks. Considering minority status as a risk factor, our results indicate the presence of both generality and specificity of association with psychosis and mania at the subclinical symptom level. Findings have implications for continuum models of psychosis and the etiology of non-affective and affective psychotic disorders.
ID: 2105686

PREVALENCE OF METABOLIC SYNDROME IN TREATMENT RESISTANT SCHIZOPHRENIA

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Background: Individuals with schizophrenia have higher rates of metabolic syndrome (MetS) when compared to general population. This increases the incidence of diabetes, coronary heart disease and mortality from cardiovascular disease. We aimed to clarify the prevalence of MetS in adults with treatment resistant schizophrenia (TRS).
Methods: A retrospective chart review of 30 inpatients with TRS was conducted to examine the rates of MetS. TRS was defined on the basis of two failed adequate antipsychotic trials. MetS was defined based on the NCEP IIIa criteria.
Results: The overall rate of MetS was 50%. Rates of MetS were the highest in patients older than 38 years (86%), prescribed clozapine or olanzapine (73%) and in those treated with two or more antipsychotic medications (67%). Waist circumference was most useful in predicting higher rates of MetS with a sensitivity of 77% and specificity of 91%. There were no differences in rates of MetS between gender or different ethnic populations.
Conclusion: Our findings suggest that patients with TRS should be classified into a separate high risk group for developing MetS as they tend to be older, more likely to be treated with clozapine or olanzapine and often prescribed two or more antipsychotic medications. People with TRS should be routinely screened for metabolic abnormalities using sensitive measures like waist circumference. Cardio-metabolic risk factors particularly weight gain must be aggressively treated with diet, increase in physical activity and pharmacological interventions such as metformin and topiramate to lower rates of morbidity and mortality.
ID: 2080855

THE PREVALENCE OF ANTIBODIES AGAINST NEURONAL CELL SURFACE TARGETS IN ACUTE FIRST EPISODE PSYCHOSIS

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Background: The pathogenesis of schizophrenia is unknown, but NMDA receptor hypofunction provides a good model. Anti-NMDA receptor antibodies (Vincent, 2011) have been identified in patients with encephalitis characterised by prodromal psychosis in 2/3 of patients, as well as seizures and movement disorders. A pilot study found 6.5% of patients with first episode of psychosis (FEP) screened for neuronal membrane antibodies were positive for either antibodies to the NMDA receptors or voltage-gated potassium channel complex (VGKC; Zandi et al., 2011). The estimated prevalence of these antibodies in FEP has varied from 0–11%. We undertook a large scale screening study of FEP to estimate the prevalence of the antibodies more accurately.
Methods: Patients were recruited from Early Intervention services in England (37 sites). Inclusion criteria: between 14–35 years of age, primary diagnosis of a first psychotic illness, <6 weeks antipsychotic medication. Exclusion criteria: other neurological disorders inc. limbic encephalitis or primary drug induced psychosis.
Patients were assessed across a number of domains using the Positive and Negative Syndrome Scale (PANSS; Kay et al, 1987), Catatonia Rating Scale (CAS; Fink 1996), Global Assessment of Function (GAF) & Addenbrooke's Cognitive Examination-Revised (ACE-R). Antibody testing was conducted using RAI (VGKC) and cell based assay (NMDAR & VGKC; Zandi et al, 2011).
Results: Of the 180 patients recruited, 17 (9.44%) screened positive for NMDA (7) or VGKC (10) antibodies, with a mean age of 18.5 years (±9.91). Positive patients scored a mean PANSS total of 68.2 (±23.6), with a mean positive score of 19.3 (±4.49), negative score of 15.4 (±9.92) and general score of 33.5 (±10.8). Positive patients' mean ACE-R total score was 76.8 (±16.9). Verbal fluency was the most impaired area of cognition (mean score 9.77/14), followed by memory (mean score 19.8/26), language (mean score 21.2/26), attention (mean score 15.8/18) and visuospatial abilities (mean score 14.45/16).
Conclusion: This study indicates that there is a clinically significant proportion of the acute FEP population who are positive for either NMDA-r or VGKC antibodies. This sub-set of patients have high PANSS scores and cognitive deficits most evident in the verbal fluency domain. Further clinical exploration is required to identify whether this group present as a distinct cognitive and clinical phenotype compared to antibody-negative patients.
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ID: 2118491

PRODROMAL SERVICES IMPROVE CLINICAL OUTCOMES IN PEOPLE WHO PRESENT WITH AN ESTABLISHED FIRST EPISODE OF PSYCHOSIS

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Background: Over the last two decades, specialised prodromal clinical services have been developed for people at high risk for psychosis. Around one third of people referred to these services are found to already be in the first episode of psychosis (FEP) when they are assessed. They are usually referred on directly to a specialised first episode clinical service. The impact of this 'fast-tracking' to specialised treatment is unknown. We investigated clinical outcomes among this group compared to those presenting to standard mental health services.
Methods: Retrospective study comparing outcomes of people with FEP who presented to the OASIS prodromal service (n=164) to those who presented to conventional mental health services (n=2779) in the South London and Maudsley NHS Trust (UK). The primary outcome measure was duration of hospital admission; secondary outcome measures were time to diagnosis, need for compulsory hospital admission and frequency of admissions. Regression models were performed to analyse the effect of presentation to the prodromal clinic on clinical outcomes. Age, gender, ethnicity, marital and employment status, borough of residence, diagnosis, and exposure to antipsychotics were included as covariates.
Results: People with FEP presenting to the prodromal service were more likely to be male (68.3%), younger (mean age 23.6 years) and from a Black and Minority Ethnic (BME) group (68.9%) compared to those presenting to conventional mental health services (59.8% male; mean age 25.1 years; 55.5% BME). People with FEP who had initially presented to a high risk service spent 17 fewer days in hospital (95% CI -33.7,-0.3), had a shorter time to diagnosis (B coefficient -74.5 days, 95% CI -101.9, -47.1), a lower frequency of hospital admission (IRR: 0.49 [95% CI 0.39, 0.61]), and a lower likelihood of compulsory admission (OR: 0.52 [95% CI 0.34, 0.81]) in the 24 months following referral, as compared to first episode psychosis patients who were first diagnosed at conventional services.
Conclusion: Prodromal services for people at high risk for psychosis may improve clinical outcomes in patients who are already psychotic. These findings suggest a potential role for prodromal clinics to facilitate access to healthcare for people with FEP who may otherwise face difficulties in engaging with traditional mental health services.
ID: 2098271

WHAT ARE THE IMPACTS OF FAMILY ECONOMIC LEVELS ON THE 14-YEAR OUTCOMES OF PATIENTS WITH SCHIZOPHRENIA DURING RAPID SOCIAL DEVELOPMENT IN CHINA?

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Background: It is not clear whether family economic levels will influence the long-term (e.g., over 10 years) outcome of patients with schizophrenia in community. This study was to explore the impacts of family economic levels on the 14-year outcome of patients with schizophrenia during the period of rapid economic growth in China.
Methods: A 14-year follow-up study among a 1994 cohort (n=510) of patients with schizophrenia was conducted in Xinjin, Chengdu, China. All patients and their informants were followed up in 2008 using Patients Follow-up Scale. This study analyzed the data for the period of 1994–2008.
Results: Compared with patients in 1994, more patients' family economic level had declined to lower level (<mean) in 2008. Patients in lower family economic level (<mean) in 1994 had significantly higher rate of homelessness (11.5%) in 2008 than those in higher family economic level (≧mean) (4.1%). Among patients who were alive (n=328 cases) in 2008, compared with patients in higher family economic level, patients in lower family economic level in 1994 had significantly lower rate of marriage, higher mean scores on PANSS negative score, general mental score and total score, higher rate of never-treated, lower rate of traditional Chinese medicine, poor relatives' attitudes toward the patients, and lower mean score on GAF.
Conclusion: Family economic level is a predicting factor of long-term outcome of patients with schizophrenia in rural community. Patients in lower family economic level will have a significant poor long-term prognosis than those in higher family economic level. How to improve patients' family economic status is a crucial issue for development of mental health services. Patients' family economic status should be considered in making mental health policy and providing social welfare and mental health services.
ID: 2082575

SHIZOPHRENIA AND DISRUPTED CAREGIVING FOR CHILDREN - A NATIONWIDE, REGISTER-BASED COHORT STUDY

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Background: Multiple studies have established that schizophrenia and other serious mental illness are often associated with impaired parenting skills, deficits in child-rearing environments and adverse childhood experiences for the children. Psychiatric symptoms sometimes prevent parents from providing proper care for children to such a degree that out-of-home care becomes a necessity. The extent of such more extreme cases of disrupted care giving has not yet been investigated.
Methods: We conducted a prospective, register-based cohort study covering all first-born singletons in the entire Danish population born after 1982 (n=782,092) and their parents. Rates of out-of-home placement of children with parents diagnosed with schizophrenia, bipolar disorder or depression were analysed. The rates were compared with those of children with parents from the general population.
Results: A parental diagnosis of schizophrenia was the most prominent risk factor for children placed outside the home, with an accumulated risk for being placed in care at some point during childhood of 40% for children with mothers with schizophrenia and 20% for children with fathers with schizophrenia Children of mothers (IRR= 23.75; 95% CI (20.94, 26.93)) and fathers (IRR= 7.85; 95% CI (6.67, 9.25) with a diagnosis of schizophrenia had the overall highest incidence rate ratios (IRR) of placement in care. Having a mother with bi-polar disorder was the second most prominent risk factor (IRR=5.76; 95% CI (4.50, 7.36)), followed by a maternal diagnosis of unipolar depression (IRR=4.28; 95% CI (3.73, 4.90)). Risks were especially high during the child's first year of life, indicating a critical period, especially for children with mothers with schizophrenia (IRR= 80.10; 95% CI (68.02, 94.33)). Risks varied greatly with parents' socio-economic factors in all diagnostic groups.
Conclusion: Parental mental illness, especially schizophrenia, is a strong risk factor for placement of children in out-of-home care. For all diagnostic groups the risk of placement in care was much higher if the mother rather than the father had a mental illness.
ID: 2114189

NEUROPSYCHOLOGICAL FUNCTIONING AND PSYCHOTIC EXPERIENCES IN A DIVERSE LONDON POPULATION SAMPLE

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Background: Psychotic disorders are associated with moderate to severe neuropsychological impairment, and understanding the causes of neuropsychological dysfunction may have important implications for understanding the etiology of the disorders. However, several important factors, including medication, substance use and illness chronicity, shown to effect neuropsychological functioning, may bias such associations. The goal of the study was to characterize the psychosis-associated neuropsychological deficit without the confounding effects of medication and illness chronicity, and controlling for important soci-demographic characteristics.
Methods: A random sample of households within the London boroughs of Lambeth and Southwark resulted in a sample of 1,677 participants (43.7% males). Psychotic experiences were assessed using the Psychosis Screening Questionnaire (PSQ). Neuropsychological functioning was assessed using tasks selected based for their known association with schizophrenia: General intellectual ability (IQ), Declarative memory, Working memory, and Processing speed.
Results: 171 participants (10.2%) reported experiencing psychotic symptoms. Overall, participants with psychotic experiences showed the greatest impairment on general intellectual ability (Effect size: 0.58, p<0.001). Impairments in memory and working memory were less severe (Effect sizes: 0.31 to 0.45, p-values <0.001). Processing speed was not significantly impaired (Effect size: 0.12, p=0.11). However, further analyses demonstrated that the association between psychosis and neuropsychological functioning was moderated by age, and there was evidence for substantial confounding effects. The association between psychotic experiences and neuropsychological functioning was attenuated in participants younger than 55. Only participants 55 years or older with psychotic symptoms showed statistically significant impairments after controlling for the effects of socioeconomic status, cannabis and alcohol use, life events and common mental disorders (all Effect sizes >1.0 p<0.03).
Conclusion: In this population sample the pattern of association between neuropsychological functioning and psychotic experiences is not the same as the one in schizophrenia. These findings may support a need for a shift from the traditional view of psychotic experiences as specifically predictive of later psychotic illness to indicative of more general psychopathology.
ID: 2119250

STRESS SENSITIVITY AS A PSYCHOLOGICAL MECHANISM IN THE ONSET OF PSYCHOSIS: AN EXPERIENCE SAMPLING STUDY

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Background: Consistent evidence has accrued that suggests elevated stress sensitivity, characterized by intense emotional reactions in response to daily hassles, may have a role in the onset of psychosis. However, to date, there is no evidence whether daily hassles increase intensity of psychotic experiences via more intense emotional reactions, such that stress sensitivity is a first step on a causal path to psychosis. We sought to investigate: 1) whether daily hassles increase intensity of psychotic experiences via (i.e. is mediated through) more intense emotional reactions; and 2) whether, compared with controls, the indirect effects of daily hassles on psychotic experiences via emotional reactivity are stronger in cases with first episode psychosis and subjects with an at-risk mental state (ARMS).
Methods: The Experience Sampling Method (ESM) was used to assess daily hassles (defined as distinctive unpleasant events in daily life), emotional reactivity, and psychotic experiences in three groups: cases with first episode psychosis, ARMS subjects, and population-based controls. Multilevel moderated mediation models were used to examine indirect effects of daily hassles on psychotic experiences via emotional reactivity by group.
Results: The ESM was completed by 51 cases, 46 ARMS, and 53 controls. There was evidence that, within each group, daily hassles were associated with negative affect (cases, B=0.08, p<0.027; ARMS, B=0.16, p<0.001; controls, B=0.10, p<0.001), which, in turn, was associated with psychotic experiences (cases, B=0.36, p<0.001; ARMS, B=0.29, p<0.001; controls, B=0.26, p<0.001). While, within each group, indirect effects of daily hassles on psychotic experiences via more intense emotional reactions were significant at conventional levels (cases, p=0.041; ARMS, p<0.001; controls, p<0.001), no significant direct effects of daily hassles on psychotic experiences were observed (cases, p=0.825; ARMS, p=0.114; controls, p=0.918), indicating evidence for full mediation via emotional reactivity. What is more, indirect effects of daily hassles via emotional reactivity were stronger in ARMS (B=0.048, p<0.001) than in cases (B=0.030, p=0.041) and controls (B=0.026, p<0.001).
Conclusion: Our findings provide evidence that daily hassles increase intensity of psychotic experiences via more intense emotional reactions. This suggests that stress sensitivity is an important, tractable psychological mechanism, in particular in the prodrome, that may be targeted to prevent transition to psychosis.
ID: 2088968

MORTALITY IN SCHIZOPHRENIA AND OTHER PSYCHOSES: 10-YEAR FOLLOW-UP OF THE AESOP FIRST EPISODE COHORT

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Background: The excess mortality in people with psychotic disorders is a major public health concern, but little is known about the clinical and social risk factors which may predict this health inequality and help inform

preventative strategies. We aimed to investigate mortality in a large epidemiologically characterised cohort of individuals with first episode psychosis compared with the general population and to determine clinical and social risk factors for premature death.
Methods: AESOP-10 is a 10-year follow-up study of a cohort of 557 individuals with a first episode of psychosis initially identified in the two centres (i.e. Southeast London, Nottingham, UK) of the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study. All patients with a first episode of psychosis who presented to mental health services within defined catchment areas were screened for inclusion at baseline. We identified all occurrences of death and emigration in the cohort at 10-year follow-up via a person-tracing procedure. Standardized mortality ratios (SMRs) for all, natural, and unnatural causes of death were calculated. Poisson regression modelling was conducted to quantify the effect of clinical and social factors on risk of all-, natural-, and unnatural-cause mortality, while controlling for potential confounders.
Results: All-cause mortality in the cohort was raised almost 4-fold (SMR 3.6, 95% CI 2.6–4.9). When broken down further, an approximately 2-fold increase in natural-cause mortality was observed (SMR 1.7, 95% CI 1.0–2.7), compared with a 13-fold increase in unnatural-cause mortality (SMR 13.3, 95% CI 8.7–20.4). The longer the time to first remission, the higher the risk of natural-cause mortality (adj. RR 6.61, 95% CI 1.33–32.77); illicit drug use increased all-cause mortality risk (adj. RR 2.31, 95% CI 1.06–5.03); and full family involvement at first contact reduced risk of unnatural-cause mortality (adj. RR 0.09, 95% CI 0.01–0.69).
Conclusion: Our findings suggest that the mortality gap in people with psychotic disorders remains huge and may be wider for unnatural-cause mortality than previously reported. Efforts should now focus on further understanding and targeting these tractable clinical and social risk factors of excess mortality. Early intervention and dual diagnosis services may play a key role in achieving more rapid remission and carer involvement and addressing substance use problems to reduce excess mortality in psychosis.
ID: 2083536

INCREASED MATERNAL PRE-PREGNANCY BMI IS ASSOCIATED WITH OFFSPRING PSYCHOSIS-RELATED OUTCOMES: A BIRTH COHORT STUDY

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Background: Maternal obesity has been identified as a risk factor for neurodevelopmental disorders in offspring. Previous studies that have shown an association between pre-pregnancy obesity and risk of psychosis-related outcomes have been limited by an inability to adjust for a broad range of potential confounders.
Methods: Using a large population-based birth cohort (the Mater University Study of Pregnancy), maternal Body Mass Index (BMI) reported prior to pregnancy was recorded at the First Confinement Visit (FCV). At age 21, the cohort offspring (n=2303) were assessed for three psychosis-related outcomes (the presence of any delusion; the presence of any hallucination; and total count of delusional-like experiences) measured with the Composite International Diagnostic Instrument Interview and the Peters Delusional Inventory (PDI). Associations between maternal pre-pregnancy BMI and psychosis-related outcomes were examined using logistic regression adjusted for maternal age, education and income at FCV, child sex, age and birth complications.
Results: Pre-pregnancy BMI was significantly higher in the mothers of offspring who experienced any hallucination or any delusion at 21 years. After adjusting for confounding variables, there was a significant association between mothers being overweight or obese prior to pregnancy and offspring at 21 years reporting any delusion (adjusted OR and 95% CI 1.54; 1.09- 2.17), highest quartile PDI compared to lowest quartile PDI (adjusted OR and 95% CI 1.40; 1.00–1.97) and a trend for offspring to report any hallucination (adjusted OR and 95% CI 1.42; 0.98–2.07).
Conclusion: There is an association between maternal obesity and psychosis-related outcomes even after adjusting for potential confounders. The increased risk of psychosis-related outcomes in offspring of overweight or obese mothers may be explained by non-exclusive biological mechanisms including maternal oxidative stress, dys-regulation of maternal immune or endocrine systems and changes in foetal micronutrient status. Given the global increase in prevalence of obesity, it is increasingly important to identify mechanisms explaining this association.
ID: 2106829

RELIGIOSITY IN YOUNG ADOLESCENTS WITH AUDITORY VOCAL HALLUCINATIONS

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Background: Auditory vocal hallucinations (AVH), occur relatively frequent in the general population in both children and adults, yet commonly disappear over time. However, sometimes these experiences become more persistent. The course of psychotic experiences over time depends on various individual and environmental factors. One of these factors could be religiosity, since several studies have demonstrated that religiosity is associated with a higher prevalence of psychotic experiences. The aim of this study was to examine the associations between religiosity and auditory vocal hallucinations (AVH) and delusions in a general population sample of young adolescents.
Methods: A sample of 337 now 12- and 13-year-old youth, stemming from a case-control sample from the general population with and without AVH, were re-assessed after five years on the presence of AVH, delusions and religiosity. Persistence, remittance, and onset of AVH were examined in relation to religiosity.
Results: A significant association between AVH and religiosity was found ($X2 (2) = 8.55$, $p<0.05$). Moderately religious children were 2.6 times more likely to report AVH than non-religious children, but there were no differences between strongly religious children and moderately or non-religious children. Moderately religious children were 7.8 times more likely to have recently developed AVH as compared to strongly religious children, again there were no differences between strongly or moderately religious children and non-religious children. Moderately or strongly religious children did not label AVH as more positive or less severe than their non-religious counterparts, and the religiosity groups showed no differences in reporting delusions.
Conclusion: The present findings suggest that there may be a non-linear association between religiosity and hearing voices in children. Specifically only moderately religious children were more likely to report and develop AVH. We speculate that the beliefs of these children are in conflict with the convictions of their family or community, providing long-term stressors and increasing the likelihood of developing anomalous experiences. This study is - to the best of our knowledge - the first study on religiosity and AVH in children, and may generate ideas for further prospective research in this area.
ID: 2094784

HOW CONNECTED ARE PEOPLE WITH SCHIZOPHRENIA? CELL PHONE, COMPUTER, EMAIL, AND SOCIAL MEDIA USE

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Background: Technologies such as Internet based social media network (SMN) websites are becoming an important part of many adult lives; however, less is known about their use in patients with schizophrenia. We need to determine 1) how "connected" are patients with schizophrenia?, 2) do these technologies interfere with the patient's illness?, and 3) do patients envision these technologies being involved in their treatment?
Methods: We recruited 80 inpatients and outpatients age 18–70 with schizophrenia to complete a brief survey on the prevalence and frequency of cell phone, text messaging, computer, email, and SMN use, and associated attitudes.
Results: 56% of subjects use text messaging, 48% have an email account, and 27% of subjects use SMN sites daily, with Facebook being the most popular. Many current users agreed that these technologies help them interact/socialize more, expressed interest in receiving text messages from their doctors, and disagreed that these technologies make symptoms worse.
Conclusion: These preliminary findings should be investigated in larger samples, but suggest that these technologies afford a unique opportunity to engage and improve treatment for some patients with schizophrenia.
ID: 2093196

ADDITIVE INTERACTION BETWEEN CANNABIS USE AND SOCIAL ADVERSITY ON PREDICTING PSYCHOSIS: BEYOND THE MAIN EFFECTS

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Background: A number of studies have suggested that age of cannabis use (Arseneault 2002), type of cannabis used (high potency cannabis preparations such as skunk) and frequency (Di Forti 2009) might be more important than the use of cannabis per se in increasing risk of psychosis.
We hypothesized that the combined effect of skunk/every day use of cannabis and the experience of social adversity in adulthood would increase the likelihood of a diagnosis of psychosis over and beyond the main effects of cannabis use and social adversity alone.
Methods: Detailed data on patterns of cannabis use and socio-demographic information have been collected as part of the GAP study and the on-going EU-GEI study of first episode psychosis being conducted in London, UK. A sample of 406 cases and 407 controls was recruited. To assess interaction on an additive scale, Interaction Contrast Ratios [ICR] were calculated.
Results: The regression model indicated that, compared with controls, cases were around 16 times (OR 16.2, 95% CI 7.4–35.1) more likely to report both social adversity and skunk and/or everyday use of cannabis. A significant interaction was found between pattern of cannabis use and social adversity (ICR 9.82, 95% CI 0.80–18.83, p=0.03).
Conclusion: There was evidence of additive interaction between pattern of cannabis use and social adversity. In essence, this suggests there were some people who developed psychosis who would not have developed it if either social adversity or heavy pattern of cannabis use had been absent.
ID: 2117919

DETERMINANTS OF MORTALITY IN PSYCHOTIC DISORDERS

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Background: We investigated mortality and its determinants in people with psychotic disorder and in people using antipsychotics in a general population survey.
Methods: A nationally representative two-stage cluster sample of 8028 persons aged 30 or over from Finland was selected for a comprehensive health survey conducted in years 2000–2001. Participants were screened for psychotic disorder, and all screen positives were invited to a SCID interview. DSM-IV psychotic disorders were diagnosed based on SCID interview and / or medical records from all mental health treatments. Mortality was followed up until December 2011. Among people with psychotic disorders (n=202), we investigated which factors were significantly associated with mortality risk, using the following baseline explanatory variables: age, sex, smoking, daily use of vegetables, antipsychotic medication use, alcohol use disorder, course of psychotic disorder, marital status, education, type 2 diabetes, coronary heart disease, metabolic syndrome and high-sensitivity C-reactive protein (CRP) level.
Results: During the follow-up, 29.9% of people with schizophrenia, 34.5% of people with other nonaffective psychoses (ONAP), and 18.4% of people with affective psychoses had died, compared to 19.5% of people without these diagnoses. Adjusting for age and sex, people with schizophrenia (HR 2.80, 95% CI 1.82–4.30) and other nonaffective psychoses (HR 1.68, 95% CI 1.13–2.50) but not people with affective psychoses (HR 0.70, 95% CI 0.34–1.42) had elevated mortality risk compared with the general population. In persons with psychotic disorder, mortality risk was predicted by smoking (HR 6.66, 95%CI 1.66–26.68, P=0.007), age (HR 1.10, 95%CI 1.05–1.15, P<.0001) and CRP level (HR for each unit increase in CRP level 1.18, 95%CI 1.06–1.31, P=0.002). Marital status (HR 0.31, 95%CI 0.09–1.05, P=0.06 for married and cohabiting) and type 2 diabetes (HR 2.75, 95%CI 0.84–9.01, P=0.09) were almost significant predictors.
Conclusion: We have previously reported mortality data from the same population until September 2009 (Suvisaari et al. 2013). In this study, we had a longer follow-up, and we also had data on hs-CRP level. As previously, smoking was a significant predictor of elevated mortality risk, but now hs-CRP level was a significant predictor whereas type 2 diabetes was not. Our results suggest that chronic low-grade inflammation in people with psychotic disorders is an important predictor of elevated mortality risk.
ID: 2085164

RISK OF SCHIZOPHRENIA AND MINORITY STATUS: A COMPARISON OF THE SWEDISH-SPEAKING MINORITY AND THE FINNISH-SPEAKING MAJORITY IN FINLAND

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Background: Approximately five percent of the Finnish population are Swedish-speaking, and they have higher socioeconomic position and longer life expectancy than the Finnish-speaking majority. Previous studies have not investigated whether Swedish-speaking Finns have lower risk of schizophrenia spectrum disorders (SSD) than Finnish-speaking Finns.
Methods: We compared the risk of SSD in Swedish-speaking and Finnish-speaking Finns in a representative sample of 47 445 Finns born in 1972–1984. Hazard ratios of SSD between language groups were assessed with conditional proportional hazards regression. Sex, parental ages at birth, paternal employment around conception, parental psychosis and place and residence in the capital area were used as other explanatory variables.
Results: The prevalence of SSD was 0.7% in the Swedish-speaking minority and 1.5% in the Finnish-speaking majority. In the adjusted regression model, belonging to the Swedish-speaking minority was associated with lower risk of SSD (hazard ratio (HR) 0.41, 95% confidence interval (CI) 0.24–0.69). When males and females were analyzed separately, the protective effect was evident among Swedish-speaking males (HR 0.32, 95% CI 0.15–0.68) but marginal in females (HR 0.75, 95% CI 0.41–1.37). Parental psychosis and place of birth in the capital area were associated with higher risk of SSD, whereas paternal employment at the time of conception was associated with lower risk of SSD.
Conclusion: Our results support the role of social factors in the etiology of schizophrenia. Belonging to a minority with high socioeconomic status and social capital may be protective against schizophrenia, especially for males. It is also possible that genetic factors may explain some of the observed differences.
ID: 2095490

FAMILIALITY OF PREMORBID SOCIAL FUNCTIONING IN PSYCHOSIS-RISK SYNDROME: A CLINICAL HIGH RISK FAMILY STUDY

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Background: In clinical high risk (CHR) youth, poor "premorbid" social adjustment predicts greater severity of psychosis-risk symptoms, worse global functioning, and higher risk of frank psychosis. Prediction of psychosis-risk symptom severity and future psychosis could be enhanced by examining the extent to which within-family effects, including shared genetic factors, and non-familial effects contribute to this association.
Methods: Utilizing a discordant sibling-pair design, this in-progress pilot study aims to determine if there is 1) a significant familial component to premorbid social adjustment in childhood, early adolescence, late adolescence, or adulthood and 2) a significant familial component to the association between premorbid social adjustment and subsequent psychosis-risk symptoms. Subjects are CHR-discordant sibling-pairs (CHR probands and non-CHR siblings) and control sibling-pairs, age 12–30 years. Premorbid social adjustment is rated on the Cannon-Spoor Premorbid Adjustment Scale and psychosis-risk symptoms are rated on the Scale of Prodromal Symptoms.
Results: Preliminary group analysis of social adjustment ratings in the 12 CHR probands and 20 non-CHR siblings enrolled to date suggests that CHR probands and non-CHR siblings do not differ in social adjustment in childhood or early adolescence. Differences in social adjustment between CHR and non-CHR siblings may emerge towards late adolescence (p=.069) into adulthood (p=.025), with non-CHR siblings showing better social adjustment over time. Results are independent of age, sex, education, or age of first positive symptom in CHR probands.
Conclusion: These early results suggest an important familial component to social functioning in childhood and early adolescence. In contrast, social functioning in late adolescence and adulthood may be particularly influenced by non-shared factors (e.g., peers) relevant to functional improvement. This study provides initial evidence that application of family study methods in CHR samples is feasible and offers unique, valuable data relevant to both etiology and symptom management. Given the small sample size and limited power, these results are preliminary and may misestimate familial and non-familial effects on social adjustment. To our knowledge, this is the first study to apply behavior-genetics methodology in a sample of clinical high-risk probands and their siblings. This research is supported by a NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation to S. Tarbox.
ID: 2091680

IQ, THE URBAN ENVIRONMENT AND SCHIZOPHRENIA RISK

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Background: Urban environmental exposure during critical periods of early brain development and low IQ are two established risk factors for schizophrenia. It is not known however how these factors relate to one another.
Methods: In order to explore this relationship data were pooled from the North Jutland regional draft board IQ examinations and the Danish National Board of Health. Data was initially available for 168,929 men born between 1955 and 93. We excluded all subjects who developed schizophrenia within one year of the cognitive assessment leaving to a final cohort of 153,170 men of whom 580 were diagnosed with a schizophrenia spectrum disorder.
Results: We found significant effects of urbanicity (IRR=1.69, 1.20 to 2.38), and increase in urbanicity before the age of 10 years (1.45, 1.05 to 2.01) on schizophrenia risk. IQ had a protective effect (0.68, 0.63 to 0.73), that was significant for those with IQ below the median and whose urbanicity increased before 10 (0.59, 0.39 to 0.88), but not for those whose IQ was above the median (1.51, 0.81 to 2.82).
Conclusion: Here we show for the first time that moving to an urban environment before the age of 10 conveys advantage for some individuals. Given the prediction that by 2050 over eighty percent of the developed world's population will live in an urban environment (UN 2012) this link may become a public health issue.
ID: 2117387

FAMILIAL RISK AND CHILDHOOD ADVERSITY INTERPLAY IN THE ONSET OF PSYCHOSIS

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Background: The association between childhood adversity and psychosis in adulthood is well established. However, genetic factors might confound or moderate this association.
We explored the main effects of, and synergy between, childhood adversity and family psychiatric history on the onset of psychosis.
Methods: Childhood adversity (separation from parents, parental loss, physical and sexual abuse) was assessed retrospectively for 224 first-presentation psychosis cases and 256 community controls from South London, UK, using the Childhood Experience of Care and Abuse Questionnaire (CECA.Q). Occurrence of psychotic and affective disorders in first-degree relatives was ascertained with the Family Interview for Genetic Studies FIGS.
Results: Parental history of psychosis did not confound the association between childhood adversity and psychotic disorder. There was no evidence that childhood adversity and family liability combined synergistically to increase odds of psychotic disorders beyond the effect of each individually.
Conclusion: Our results do not support the hypothesis that family psychiatric history amplifies the effect of childhood adversity on odds of psychosis.
ID: 2094822

PSYCHIATRIC MORBIDITY AMONG CAREGIVERS OF SCHIZOPHRENIA PATIENTS - A STUDY IN TERTIARY CARE PSYCHIATRIC HOSPITAL IN DHAKA

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Background: Severe mental illness like schizophrenia has far-reaching consequence for both patients and caregivers and their relatives and they also experience feeling of loss and grief. They are confronted with uncertainty and emotion of shame, guilt and anger like the patients they feel stigmatized and socially isolated. Caring for a family member with schizophrenia is an enduring stressor and causes considerable amount of burden. so the present study was done to assess mental health status of the caregivers of schizophrenia patients.
Methods: This descriptive cross sectional study was done among the caregivers of schizophrenia patients in outpatient and inpatient department of National Institute of Mental Health (NIMH), Dhaka, Bangladesh from September 2010 to February 2011. A semi-structured Questionnaire and General Health Questionnaire-28 (GHQ-28) were applied to the caregivers of schizophrenia patients who fulfilled the inclusion criteria. Among the respondents whose GHO-28 score were 4 or above Structured Clinical Interview for DSM-IV Axis I Non Patient (SCID-I/NP) version was applied to identify psychiatric disorders among the caregivers of schizophrenia.
Results: Out of 272 respondents most of them were female (88.97%), housewife (72.42%) of 21 to 50 yrs age (80.51%). In this study 22.43% of respondents were suffering from different types of mental disorders. Among them major depressive disorder were most prevalent (11.8%). Other psychiatric disorders were found generalized anxiety disorder (4.8%), pain disorder (2.9%). Less common were panic disorder, social phobia, adjustment disorder and undifferentiated somatoform disorder (0.7% in each type).
Conclusion: Significant proportions of the caregiver of schizophrenic patients were suffering from psychiatric disorders that did not get any psychiatric treatment. So the service providers, policy makers and planers should address the issue carefully. Further broad based study is recommended in this regard.
ID: 2085794

THE RELATIONSHIP BETWEEN CHILDHOOD TRAUMA AND SCHIZOTYPY AND PATHWAYS UNDERLYING THIS ASSOCIATION: PRELIMINARY FINDINGS FROM THE EU-GEI FIRST-EPISODE PSYCHOSIS CASE-CONTROL STUDY

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	Association with psychotic disorder					
Combination of risk factors	Unadjusted OR	95% CI	P value	Adjusted* OR	95% CI	P value
Parental loss (PL)						
PL only (FMI absent)	1.53	0.71–3.27	0.276	0.92	0.31–2.80	0.896
FMI only (PL absent)	1.20	0.81–1.78	0.354	1.12	0.67–1.89	0.664
Both PL and FMI present	3.82	1.24–11.73	0.019	2.57	0.070–9.36	0.153
	ICR: 2.09, 95% CI -2.29 to 6.47, p=0.350			ICR: 1.52, 95% CI -1.90 to 4.93, p=0.384		
Parental Separation (PS)						
PS only (FMI absent)	3.09	2.02–4.72	<0.001	4.14	2.19–7.81	<0.001
FMI only (PS absent)	1.90	1.13–3.20	0.015	2.25	1.11–4.54	0.024
Both PS and FMI present	2.33	1.38–3.93	0.002	2.20	1.09–4.44	0.028
	ICR: -1.66, 95% CI -3.48 to 0.15, p=0.072			ICR: -3.18, 95% CI -6.33 to 0.04, p=0.047		
Physical abuse (PA)						
PA only (FMI absent)	2.53	1.43–4.48	0.001	1.69	0.74–3.88	0.212
FMI only (PA absent)	1.63	1.07–2.48	0.023	1.59	0.90–2.82	0.113
Both PA and FMI present	1.18	0.61–2.30	0.622	0.80	0.34–1.91	0.617
	ICR: -1.97, 95% CI -3.74 to 0.21, p=0.028			ICR: -1.48, 95% CI -3.29 to 0.33, p=0.109		
Sexual abuse (SA)						
SA only (FMI absent)	1.73	0.90–3.33	0.101	2.32	0.87–6.20	0.092
FMI only (SA absent)	1.41	0.95–2.11	0.091	1.33	0.78–2.28	0.298
Both SA and FMI present	1.19	0.54–2.66	0.663	1.33	0.46–3.81	0.596
	ICR: -0.95, 95% CI -2.49 to 0.60, p=0.231			ICR: -1.64, 95% CI -4.09 to 0.80, p=0.188		

*Adjusted for gender, age at interview, ethnicity and level of education. CI, confidence interval. ICR, interaction contrast ratio. OR, odds ratio.

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Background: There is a growing body of literature demonstrating an association between childhood trauma and increased schizotypy. However more research is required to go beyond the methodological limitations of previous studies, explore the relationship between a range of childhood traumatic experiences and schizotypy and look at the possible pathways underlying this association.
Methods: The data for analyses was drawn from a case-control study of first episode psychosis conducted in London, UK. An initial sample of 212 controls, age 18–64, living within a defined catchment area, with no evidence of current or past psychosis was assessed using a modified version of the Childhood Experience of Care and Abuse (CECA) interview, an adapted version of the Bullying Questionnaire, the Structured Interview for Schizotypy-revised, the Brief Score Schema Scale, the Hamilton Rating Scale for Depression, the Life Events and Difficulties Schedule and the Cannabis Experience Questionnaire.
Results: 59.2% of participants reported at least one childhood traumatic event. Looking at specific types of trauma, psychological (β=3.68, p=0.001), physical (β=3.29, p<0.001) and sexual abuse (β=2.49, p=0.003) as well as bullying (β=1.90, p=0.005) predicted schizotypy load in a linear fashion. Even more robust support was observed between childhood trauma and the top 10% of schizotypy total scores, with the strongest support observed for psychological (OR=6.59, p=0.001) and physical abuse (OR=6.18, p<0.001) that especially predicted positive schizotypy (OR=3.78, p=0.008 and OR=3.38, p=0.001 respectively). Psychological abuse and schizotypy association was partially explained by negative beliefs about the self (OR=1.48, p=0.037, explained 26%) and depression score (OR=1.65, p=0.015, explained 32%); physical abuse was mediated by negative beliefs about others (OR=1.51, p=0.008, explained 23%), negative beliefs about self (OR=1.35 p=0.029, explained 16%) and depression score (OR=1.39, p=0.018, explained 19%).
Conclusion: Consistent with previous research, individuals with a history of any type of childhood trauma showed elevated levels of schizotypy in a dose-response manner. Psychological and physical abuse were especially strongly associated with schizotypal symptoms. Negative beliefs about self and depression score were the main mediators of these associations. The study has an important value for clinical practice but needs to be considered in the light of its limitations.
ID: 2087235

THE ORIGIN OF SOCIAL IMPAIRMENTS IN SCHIZOPHRENIA; DEVELOPMENTAL TRAJECTORIES AND FAMILIAL INFLUENCES

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Background: Impaired social functioning is a core feature of schizophrenia. However, little is known about the developmental origin and etiological factors of these impairments. We examined three key components of social functioning: Social Engagement, Individual Autonomy and Functioning in Structured Environments before and after hospitalization for schizophrenia and determined whether they are familial.
Methods: Data from the Israeli Draft Board Registry on 700,000 Israeli males aged 16–17 was linked with data from the Israeli National Psychiatric Hospitalization Case Registry. The linkage identified 5,000 individuals who were hospitalized for schizophrenia. Data for 350,000 sibling pairs, of whom 1,600 hospitalized for schizophrenia, was similarly ascertained. Schizophrenia cases, their unaffected siblings and controls were compared by time between Draft Board assessment and time to hospitalization.
Results: Overall schizophrenia cases had premorbid impairments only in two components of social functioning: Social Engagement (Effect size: 0.55) and Functioning in Structured Environments (Effect size: 0.37). For Social Engagement differences between cases and controls were progressively greater for cases admitted closer to the time of testing (p value for time trend < 0.001). The impairment in Social Engagement first increased approximately 12 years before first hospitalization, and then further increased 5 years before hospitalization, continuing to increase thereafter. Impairment in Individual Autonomy also started increasing 5 years before hospitalization. In contrast, no change in the magnitude of impairment in Functioning in Structured Environments was evident. Impairments in Social Engagement and Functioning in Structured Environments were familial. Siblings of cases also showed small impairments compared to controls (Effect size: 0.2). Impairments in siblings showed no progressive increase.
Conclusion: Different components of the social impairment in schizophrenia follow different developmental trajectories. Impairments in Social Engagement are present early and increase progressively already more than a decade before first hospitalization. Our findings provide clues about appropriate timing of interventions and suggest that deficits in individual autonomy may be most amenable in treatment.
ID: 2115718

A POPULATION BASED LONGITUDINAL STUDY OF SUICIDE RISK IN MALE SCHIZOPHRENIA: PROXIMITY TO FIRST ADMISSION AND THE MODERATING EFFECT OF PREMORBID IQ

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Background: Suicide is a major cause of death in schizophrenia. Identifying people with schizophrenia who have increased risk of suicide, and the time periods in which their risk is most elevated, might assist in suicide prevention. This study examined risk of suicide in male schizophrenia patients using population-based data, examining the timing of suicide in relation to illness onset and hospital treatment, and the effect of premorbid IQ (Intelligence Quotient) on risk of suicide.
Methods: Data on 930,000 male adolescents from the Israeli military draft board were linked with data from the Israeli Psychiatric Hospitalization Case Registry and death records from the Israeli Ministry of Health. The relationship between premorbid IQ and risk for suicide was examined among 3,813 males with schizophrenia and compared to a control group of 847,448 males from the same cohort who were not hospitalized for schizophrenia, using survival analysis methods.
Results: Over a mean follow-up period of 9.9 years (standard deviation=5.8, range: 0–22 years), 91 males with schizophrenia died by suicide (76.0 per 100,000 per year). A third (33.0%) of the suicides occurred within a year of discharge from the first hospital admission for schizophrenia. Risk of suicide was higher in male schizophrenia patients with high premorbid IQ (HR= 3.24, 95% CI 1.45–7.25) compared to those with normal premorbid IQ. This was not the case in the control group, in which low

premorbid IQ (HR=1.24, 95% CI=1.05–1.46), rather than high premorbid IQ, was associated with increased risk of suicide, in comparison with normal premorbid IQ.
Conclusion: These findings show that the rate of suicide is highest during the first year after the first hospitalization, and that male schizophrenia patients with high premorbid IQ are at particularly high risk of suicide. Male patients with high premorbid IQ should be considered at higher risk for suicide, especially over the months following their first hospitalization, and carefully monitored.
ID: 2118343

RESILIENCE IN PATIENTS WITH SCHIZOPHRENIA: A COMPARATIVE STUDY BETWEEN A DISTANT ISLAND AND AN URBAN AREA

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Background: Resilience is described as phenomena whereby some individuals remain healthy or easily recover from adverse events whereas others are vulnerable to disorders. The degree of resilience is expected to be influenced by various factors, including location of living, illness severity, and life-style as well as social welfare system. The aim of this study was to compare the resilience level among those patients with schizophrenia living in an island and an urban area that belong to the same administrative district (i.e. Tokyo prefecture). We also examined characteristics in association with the degree of resilience.
Methods: This cross-sectional study was conducted for patients with schizophrenia or schizoaffective disorder who visited Ohshima Medical Center in Ohshima Island and Ohizumi Hospital in Nerima ward (an urban area), Tokyo between June 2013 and September 2014. Ohshima Island is located 120 km away from the center of Tokyo, and the population is approximately 8,000 with relatively few inflow and outflow. Ohshima Medical Center is the only hospital that provides psychiatric care in the island. Patients who visited Ohshima Medical Center were first enrolled, and sex- and age- matched patients in Ohizumi Hospital were then recruited. Values of interest were compared, using independent t-test or chi-squared test. Linear regression analysis was performed to identify factors that were associated with the degree of resilience. Clinical assessments included the Resilience Scale (RS), the EuroQol and the Positive and Negative Syndrome Scale.
Results: Sixty-four subjects have been included so far (39 in Ohshima Island and 25 in the urban area). No significant difference was found in the RS score between those two groups (104.2 ± 26.3 in Ohshima Island and 107.2 ± 19.4 in the urban area, p=0.63). The linear regression analysis revealed that the longer duration of illness and higher visual analogue scale score in the EuroQol were significantly associated with greater RS score (p=0.04 and p=0.02, respectively) whereas the illness severity and use of any social resources failed to show any association with the resilience level.
Conclusion: Patients with schizophrenia living in the island and urban area show comparable degrees of resilience despite markedly different lifestyles. In addition, greater resilience level in those with longer duration of illness may represent their psychological strength obtained through their illness experiences.
ID: 2081321

Functional and Psychosocial Outcome

NEUROCOGNITION, PREMORBID ADJUSTMENT, AND PSYCHOPATHOLOGY AS PREDICTORS OF FUNCTIONAL STATUS AND QUALITY OF LIFE IN SCHIZOPHRENIA

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Background: Neurocognitive deficits and psychopathology have been observed to contribute to disability in schizophrenia. Studies have also linked deficits in premorbid adjustments to neurocognition and functional outcomes in schizophrenia. Using canonical correlational analyses (CCA) and structural equation models (SEM), we addressed: 1) whether specific profiles of premorbid adjustment predict neuropsychological functioning in adulthood; 2) whether domain-specific neurocognitive deficits predict functional status over and above general intellectual ability; 3) the degree to which neurocognitive effects on functioning is transmitted through changes in positive and negative symptoms.
Methods: In 292 people with schizophrenia, current neuropsychological functioning and intelligence were indexed via the RBANS and WAIS-III respectively. The reading subtest of the Wide-Range Achievement Test assessed premorbid intelligence. Participants completed the Premorbid Adjustment Scale, the Schedule for the Deficit Syndrome and the Scale for the Assessment of Positive Symptoms as measures of premorbid adjustment, negative, and positive symptoms respectively. Psychosocial functioning was measured with the Level of Functioning (LOF) scale.
Results: The CCA linked poor scholastic performance in childhood and early and late adolescence and poor school adaptation in childhood and late adolescence to deficits in working memory, delayed memory, attention, global neurocognition, premorbid IQ and adult estimated IQ. CCA also linked deficits in all neurocognitive variables except visual search to hospitalization, employment, independent living skills, and overall level of function. There was mixed evidence that neurocognitive domains predict LOF independently of IQ. For overall level of function, working memory remained a significant predictor; whereas delayed memory remained significant for employment, independent living skills (along with attention), and duration of hospitalization. An SEM model that included neurocognition and negative symptoms as mediators on the path to disability and positive symptoms as a direct predictor of disability best fit the data.
Conclusion: Early premorbid adjustment profiles contribute to adult neurocognitive impairments in schizophrenia. Working and delayed memory deficits may independently contribute to some aspects of psychosocial disability over deficits in general intellectual ability. Unlike negative symptoms, positive symptoms contribute to disability independent of neurocognition.
ID: 2093971

ETHNIC VARIATIONS IN OUTCOME DURING THE 5-YEARS FOLLOWING A FIRST EPISODE OF PSYCHOSIS

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Background: Admission to hospital remains the most expensive form of psychiatric treatment; however, little is known about predictors of illness course and hospitalization over the first few years after a first episode of psychosis (FEP). In this study we identified the pattern and predictors of hospitalization of patients with FEP for those of white, black and other (i.e. Asian and mixed ethnicity) ethnicity
Methods: 353 patients (41% black, 35% white and 24% other ethnicities), aged 20–64 who met ICD-10 criteria for non-organic psychosis (F20-F29 and F30-F33) (SCAN WHO, 1992), were followed up after a FEP in London between 2002 and 2011. Data on outcomes were collated via an electronic patient journey system (e-PJS) (UK NHS)
Results: During the course of the illness, the ethnic groups didn't differ in age (p=0.82), gender (p=0.70), DUP (p=0.61), duration of follow up (p=0.30), employment (p=0.61) and presence of anti-social behavior (p=0.36). A higher proportion of patients of black ethnicity lived alone (x2(4)=14.8 p=0.005) or were either separated or divorced (x2(4)=28.3 p<0.001). Ethnic groups didn't differ in symptom severity during psychotic episodes (x2(4)=4.6 p=0.32), negative symptoms (x2(4)=4.5 p=0.34) nor likelihood of having had a remission (x2(2)=1.9 p=0.40). Including the index episode, patients of black ethnicity had more hospital admissions (CI=0.87–0.98 p=0.02) with an average inpatient stay of 156.7 days. Ethnic groups were equally likely to require compulsory treatments (OR=0.45 CI=0.18–1.13 p=0.09); however, the likelihood of police involvement during admissions was higher for patients of back ethnicity (OR=1.74 95%CI=1.11–2.73 p=0.02). A number of different antipsychotics prescribed over 5 years was higher for patients of black ethnicity (IQR=1–5)(CI=0.84–0.99 p=0.03); though rates of treatments with Clozapine was similar across all ethnic groups (x2(4)=1.02 p=0.91). Ethnic groups did not differ in rates of transition of baseline diagnosis of schizophrenia (CI=0.70–1.13 p=0.32), bipolar affective disorder (CI=0.82–1.67 p=0.40), schizoaffective disorder (CI=0.57–2.17 p=0.75) and other psychosis (CI=0.78–1.29 p=0.98)
Conclusion: In a 5-year course of psychosis patients of black ethnicity had more frequent and prolonged hospitalizations compared to other ethnicities. This difference isn't explained by clinical presentation at baseline, but may be contributed to by a lack of social support and struggle of London psychiatric services to provide optimum care for their black patients
ID: 2114230

NEUROPSYCHOLOGICAL PERFORMANCE IN SCHIZOPHRENIA SUBJECTS WITH HIGH AND LOW SOCIAL FUNCTIONING

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Background: Schizophrenia is characterized by poor social functioning (e.g., social relationships, occupational outcomes). This impairment is the ultimate treatment target to facilitate recovery. The literature suggests that targeting cognitive functions for treatment will contribute to improved social functioning, yet there is limited evidence-based specificity regarding the most appropriate targets for intervention. Thus, we attempt to identify a specific cognitive treatment target by comparing six domains of cognitive functioning between individuals with schizophrenia (SCZ) who were identified as having high social functioning (HF) and low social functioning (LF). This approach may provide a new ecologically valid method to understand the specific cognitive functions that are related to functional recovery.
Methods: A sample of 60 SCZ and 45 controls (CON) completed three independent measures of social functioning, including interview-based social attainment, a social competence role-play, and lab-based functional capacity task. Subjects also underwent neuropsychological evaluation that generated scores in the following domains: processing speed, attention,

verbal working memory, nonverbal working memory, verbal learning, and problem solving and reasoning. Cluster analysis techniques using the social functioning measures generated clusters representing HF and LF in SCZ. We used MANOVA to identify an overall group effect and between-group differences in cognition.
Results: The cluster analysis revealed two distinct groups, consisting of 29 HF-SCZ and 31 LF-SCZ. We found neuropsychological performance differences across the three groups (F=13.5, p<.001) with CON generally outperforming both SCZ groups. Post-hoc tests revealed that SCZ-HF had elevated verbal working memory compared to SCZ-LF (p≤.05, d=.78), but did not differ on other domains. CON had higher verbal working memory performances than both HF-SCZ (p≤.05, d= -.76) and LF-SCZ (p<.001, d= -1.30).
Conclusion: This study demonstrated that a sample of SCZ could be characterized as high or low functioning based on several measures of social functioning using cluster analysis. Findings show that the high and low functioning groups only differed on verbal working memory, even when controlling for verbal intellect. Our results suggest individuals with schizophrenia are able to function well in the community despite cognitive deficits and that verbal working memory may be a critical treatment target for the functional recovery from schizophrenia.
ID: 2084102

HELICOPTER PARENTING AND SELF-STIGMA TOWARD SEEKING HELP FOR SERIOUS MENTAL ILLNESS

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Background: Despite the availability of effective means for dealing with serious mental health issues, the majority of adolescents fail to seek needed treatment. Research has shown that one reason relates to the fear of shame and self-loathing that can be associated with seeking help. The phenomenon of internalization of negative attitudes toward mental illness has been termed self-stigma, and has been found to be an important barrier to seeking help (Vogel, Wade & Haake, 2006). Research has not yet explored how different styles of parenting may contribute to the development of adolescents' self-stigmatization and attitudes towards seeking treatment. One form of parenting style that may be relevant has been termed helicopter parenting (Schiffrin et al., 2013), which has identified parents who tend to be overbearing in contrast to parental autonomy support styles which encourage children to develop a sense of independence. Empirical studies to date have determined that helicopter parenting has been associated with lower levels of well-being and increased susceptibility toward mental health problems (Le Moyne & Buchanan, 2011). Our research extends this initial work by exploring whether adolescents who report being raised with helicopter parenting style are more likely to experience reluctance to seek treatment.
Methods: Students from a metropolitan secondary school (N = 87) completed a series of questionnaires related to stigma of mental illness, attitudes toward seeking help and perceived parenting styles. Participants answered questions about how they perceived their parents' style of parenting on two scales, helicopter parenting and parental autonomy support.
Results: There was a significant negative correlation between self-stigma of seeking help and the autonomy support scale (p < .05). Multiple regression analysis revealed that both reduced autonomy support (Beta = -.32, p < .05) and heightened helicopter parenting (Beta = .23, p < .05) were significant predictors of self-stigma of seeking help.
Conclusion: These findings are the first to explore the relationship between parenting styles and hesitancy to seek help amongst adolescents. The results indicate that parents may play a vital role in the development of adolescents' feelings toward mental illness and their willingness to seek help. Parenting that is not overbearing, but rather encouraging of independence allows adolescents to experience less shame and be more comfortable with seeking help for mental health issues.
ID: 2086727

DECLINE IN SOCIAL AND ROLE FUNCTIONING PRIOR TO BASELINE IN THE NAPLS 2 HIGH-RISK SAMPLE

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Background: High-risk syndromes typically require the presence of attenuated positive symptoms that have onset or worsened in the year prior to study entry. Although positive symptoms meeting this criterion are strong predictors of psychosis, functional deficits are also often present at baseline and can enhance the prediction of those at greatest risk (Cannon et al, 2008). However, it is unclear whether these functional deficits are stable prior to baseline or if they show declines similar to positive symptoms in the year prior to entry. This poster will examine this issue in a large high-risk sample using two functioning measures specifically developed for this population: the Global Functioning:Social (GF:S) and Global Functioning:Role (GF:R) scales (Cornblatt et al, 2007).
Methods: The sample includes 1045 subjects (765 high-risk patients, 280 controls) enrolled in the 8-site North American Prodrome Longitudinal Study (NAPLS) Phase 2 sample. The GF:S and GF:R scales are rater administered measures with scores ranging from 1 (extreme problems) to 10 (superior functioning). The GF:S emphasizes peer relationships and GF:R assesses achievement in role setting (school vs work). High-risk symptoms were assessed with the Structured Interview of Prodromal Syndromes (SIPS).
Results: The GF scales significantly correlated with SIPS total negative symptoms(r=-.53 social, r=-.47 role), but not with total positive symptoms. Baseline GF:S and GF:R mean scores were significantly lower in patients vs controls (GF:S-6.19 vs 8.85; GF:R-5.96 vs 8.56; both p<.001), as were the highest and lowest GF scores in the year prior to baseline (p values<.001). A significant 3-way interaction (group x domain x functional change over the past year) was observed. Patients showed a significant decline from highest to current and from current to lowest functioning in both social and role domains (p values<.01), compared to controls. There was also a significant change from highest to current social and role functioning in the year prior to study entry for converters relative to non-converters (p≤.05).
Conclusion: In summary, social and role functioning were found to be independent of positive symptoms. However, similar to positive symptoms, social and role functioning showed a distinct pattern of decline in the year

prior to baseline. Importantly, this decline was significantly greater in converters versus non-converters, highlighting that functional decline prior to baseline has the potential to enhance psychosis prediction.
ID: 2118791

ASSOCIATION BETWEEN LONG-TERM HEALTH-RELATED QUALITY OF LIFE AND EMPLOYMENT STATUS AMONG PATIENTS SWITCHING TO LURASIDONE: ANALYSIS OF THE 6-MONTH OPEN-LABEL EXTENSION OF A SCHIZOPHRENIA SWITCH TRIAL

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Background: Previous results from a 6-week open-label switch trial (core study NCT01143077) demonstrated that antipsychotic treated with schizophrenia who switched to lurasidone reported significant improvements in health-related quality of life (HRQoL). Given the importance of employment in functional recovery among those with schizophrenia, this analysis evaluated the effect of lurasidone on HRQoL from the 6-month extension trial of NCT01143077and also assessed HRQoL differences, if any, between the employed and unemployed.
Methods: Lurasidone (40 mg/day-120 mg/day) data from the 6-month extension trial of stable but symptomatic outpatients with schizophrenia or schizoaffective disorder who previously completed the core study was analyzed. Personal Evaluation of Transition in Treatment (PETiT) scale, a 30-item measure of 2 domains (psychosocial and adherence) with higher scores denoting better HRQoL, was used to collect data at the core study baseline (week 0) and the extension study endpoint (week 30). All patients with full or part-time work were categorized as employed while all others were categorized as unemployed. PETiT score changes between employed and unemployed were compared using ANCOVA adjusting for age, gender, study treatment, and baseline PETiT score.
Results: Of the 95 patients who completed the extension trial and PETiT scale, 15% (N=14) were employed and 85% (N=81) were unemployed at baseline. For employed and unemployed patients, the mean (SD) core study baseline PETiT total score was 38.3 (9.0) and 33.2 (8.7) and week 30 scores were 46.1 (7.4) and 37.7 (8.8), respectively. Adjusted least-square (LS) mean (95% CI) PETiT total score change was 9.6 (6.0 - 13.1) for employed patients compared to unemployed patients 4.2 (2.7 - 5.7), p=0.008. LS Mean change in PETiT psychosocial domain score was 7.3 (4.3–10.3) for employed vs. 3.1 (1.9–4.4) for unemployed patients ($p<0.05$). Similarly, mean change in PETiT adherence domain score was 2.2 (1.2–3.2) for employed vs 1.1 (0.7–1.4) for unemployed patients, respectively ($p<0.05$).
Conclusion: This analysis demonstrates that both employed and unemployed patients with schizophrenia that are switching to lurasidone was associated with long-term improvement in HRQoL. While the unemployed group had a smaller magnitude of HRQoL improvements, future observational research of lurasidone effects on recovery may shed light on HRQoL impact and consequent employment status.
ID: 2119377

NEUROLOGICAL SOFT SIGNS (NSS) IN THE CLINICAL COURSE OF SCHIZOPHRENIA: RESULTS OF A META-ANALYSIS

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Background: Neurological soft signs (NSS) comprise subtle deficits in sensory integration, motor coordination, and sequencing of complex motor acts which can be established in the majority of schizophrenia patients including first-episode cases and neuroleptic-naïve first-episode patients prior to medication exposure. However, recent studies clearly demonstrate that NSS are not a static feature of the disease but vary in the clinical course of the disorder.
Methods: This effect was further investigated in a meta-analysis which involved 17 longitudinal studies published between 1992 and 2012. Studies included between 10 and 93 patients with schizophrenia spectrum disorders (total number 858) with follow-up periods between 2 and 208 weeks. Beside the Neurological Examination Scale, the Cambridge Neurological Inventory and the Heidelberg NSS Scale were used to investigate NSS.
Results: All but three studies found NSS to decrease with remission of psychopathological symptoms. This effect was more pronounced in patients with a remitting than a chronic course (Cohens d 0.81 vs. 0.28) and was significantly correlated with length of the follow-up period (r=-0.64) but not with age (r=0.28). NSS scores did not decrease to the level typically observed in healthy controls.
Conclusion: From a clinical perspective, NSS may therefore be used to identify subjects at risk to develop schizophrenia and to monitor the disease process.
ID: 2119475

A PROSPECTIVE STUDY OF ATTITUDES TOWARDS INVOLUNTARY ADMISSION AND THEIR CLINICAL DETERMINANTS IN PATIENTS FROM ACUTE ILLNESS THROUGH TO RECOVERY

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Background: The aim of this study was to assess attitudes towards coercive treatment and their clinical determinants in individuals detained involuntarily shortly after their admission and three months after revocation of their involuntary admission order, when they had returned to their baseline clinical condition
Methods: Three hundred and thirteen consecutive involuntarily admitted patients over a 30 month period in a regional catchment areas service were invited to participate and 205 were recruited. Clinical data collected included Client Assessment of Treatment (CAT), Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-1), Brief Psychiatric Rating Scale (BPRS), Scale for Assessment of Insight in Psychosis (SAI-E), Global Assessment of Functioning (GAF), Hogan Drug Attitude Inventory (HDAI), MacArthur Admission Interview at admission and three months post revocation. Multivariate analyses were employed to assess the optimal determinants of variation of attitudes towards their care
Results: Of the two hundred and five individuals who participated at baseline, one-hundred and twenty seven (61%) completed follow-up. The most common Axis I diagnoses was schizophrenia (n=43, 33.9%) and bipolar affective disorder (n=39, 30.7%). Significant improvements in BPRS ($p<0.001$), SAI-E ($p<0.001$), GAF ($p<0.001$), CAT (p=0.027), HDAI ($p<0.001$), procedural justice (p=0.001), and attitudes to the process of admission (p=0.001) were detected at follow-up.

A multiple linear main effects regression model demonstrated that greater insight at baseline (p=0.002) was associated with higher CAT scores, while psycho-active substance misuse (p=0.005) and higher BPRS scores (p=0.02) were associated with lower baseline CAT scores (p=0.01) after adjusting for baseline values of several different clinical variables including gender, diagnosis, psycho-active substance use, seclusion and restraint. In addition, age (p<0.01) and baseline BPRS scores (p<0.01) had a significant positive effect on attitude change over time (CAT score) adjusting for several other clinical variables

Conclusion: This study highlights that the best predictors of positive attitudes towards involuntary admission and treatment were likely illness related factors such as symptomatic improvement, good insight and less substance misuse. Coercive experiences such as seclusion and restraint, were not associated with negative attitudes towards care when other clinical factors were accounted for

ID: 2094193

THE MODERATING ROLE OF MOTIVATIONAL DEFICITS ON NEUROCOGNITIVE FUNCTIONING ACROSS THE COURSE OF SCHIZOPHRENIA

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Background: Neurocognitive impairment in schizophrenia undermines patients' ability to adhere and benefit from evidence-based interventions, impacts everyday functioning and subsequent perpetuation of disability. Evidence suggests that cognitive test performance is not purely a measure of ability and can be influenced by several psychological variables, including motivation. Although poor effort and decreased motivation are known to affect performance on cognitive testing little work has examined the relationship between motivation, neurocognition and functional outcome in individuals with schizophrenia.

Methods: In this cross-sectional design, a total of 198 participants completed study measures, including 60 participants at clinical high risk for schizophrenia, 60 recent-onset schizophrenia participants and 78 chronic schizophrenia participants. We examined cognitive measures recommended by the Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative (MATRICS). To index motivational system functioning, we assessed anticipatory versus consummatory pleasure (using the Temporal Experience of Pleasure Scale (TEPS)), and behavioral drive, behavioral inhibition, and reward responsivity (using the Behavioral Inhibition Scale/Behavioral Activation Scale (BIS/BAS)). Symptom severity using the PANSS and functional status using the Global Assessment of Functioning were also assessed.

Results: Level of anticipatory pleasure, behavioral drive and reward responsivity were significantly and positively correlated with MATRICS global cognitive test performance, a relationship that held after statistically controlling for symptom severity and overall functioning.

Conclusion: Motivational and cognitive deficits are core features of schizophrenia, present prior to the onset of psychosis and both closely linked with functional outcomes. Findings in the present study provide strong support for a robust and reliable relationship between motivation and cognitive performance. The assessment and interpretation of cognitive impairment in schizophrenia should consider potential moderating variables such as effort and motivation. Treatment approaches that target synergistically multiple key determinants of long term outcome, including deficits in neurocognition and motivation, are likely to yield significant improvements in real-world functioning for individuals with schizophrenia.

ID: 2119626

FAILING TO BENEFIT: SYSTEMATIC REVIEW AND META-ANALYSIS OF 'LEARNING POTENTIAL' IDENTIFIES SUBGROUP THAT IS AT HIGHEST RISK FOR NON-RESPONSE TO PSYCHOSOCIAL INTERVENTION

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Background: Psychosocial interventions can reduce the cognitive and functional deficits prevalent in schizophrenia. However, effects are typically modest and outcomes heterogeneous. A better understanding of individual response to intervention could aid clinical decision making and improve treatment outcomes. The dynamic Wisconsin Card Sorting Test (D-WCST) is a test-train-retest administration of the standard WCST used to identify individual 'learning potential.' Subjects are categorized according to three groups: High Scorers (HSs), Learners (Ls), and Non-Retainers (NRs). We conducted a systematic review and meta-analysis of the D-WCST literature to examine the relative frequency of each group, neurocognitive differences, and response to intervention.

Methods: We identified 11 studies reporting data on relative frequency (N=628), 6 studies on neurocognitive performance (N=442), and 3 studies on response to intervention (N=87). We calculated mean relative frequencies with confidence intervals, and effect sizes for the neurocognitive differences between the groups. For response to intervention, we ran Chi-squared tests and calculated odds ratios (OR).

Results: Across 9 different sites from 3 different counties, the mean relative frequencies for each group were HSs: 45.7% [39.05%, 52.43%], Ls: 36.1% [31.87%, 40.33%], and NRs: 18.2% [13.63%, 22.77%]. There was complete separation in the neurocognitive proflies of the three groups, with HSs > Ls (d = .377*), HSs > NRs (d = .994***), and Ls > NRs (d = .623***). For response to psychosocial intervention, 70% of HSs were classified as 'Responders', and 53% of Ls, but only 6% of NRs. The effect of group on outcome was highly significant (X2=19.46, p <0.0001). We then chose to examine the predictive value of NR status versus the other two groups (HSs and Ls). NR status was highly predictive of poor response to psychosocial intervention (OR=26.44, p=0.002).

Conclusion: Results of the meta-analysis strongly suggest that the D-WCST is a useful diagnostic tool, revealing 3 distinct neurocognitive subgroups, which would be missed using the standard WCST. The severe non-responsiveness of the NRs (94%) suggests a significantly large (18%) subgroup of patients at high risk for treatment failure. Clinically, these patients may need an alternative approach (e.g., errorless learning). Moreover, when unaccounted for, this subgroup represents a potential research confound, diluting effect sizes and obscuring the benefits of an otherwise efficacious intervention.

ID: 2116939

PRIMARY NEGATIVE SYMPTOMS AND REMISSION IN FIRST-EPISODE PSYCHOSIS: A LONGITUDINAL APPROACH

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Background: Negative symptoms are consistently related to a worse functional outcome and represent an unmet therapeutic need in people with psychosis. The importance of negative symptoms was highlighted in 2005 when both positive and negative symptoms were included in the consensus definition of remission in schizophrenia. However, no study to date has investigated the direct relationship between primary negative symptoms and remission.

Methods: Using a large, well defined sample, we set out to explore primary negative symptoms in relation to remission in people with a first-episode of psychosis (FEP). This study included 350 FEP patients who were treated over a 2 year period in a specialized early intervention program. Remission was defined following the 2005 consensus definition (Andreasen et al, Am J Psychiatry, 162:441–449). Primary negative symptoms were identified using a persistent negative symptoms (PNS) definition, i.e., having at least one negative symptom rated at moderate or greater severity sustained for at least 6 consecutive months not secondary to positive, depressive, and extrapyramidal symptoms.
Results: After one year of treatment (n=350), 276 (79%) of the FEP patients were not considered to be fully remitted with 158 (57%) not achieving remission due to negative symptoms alone. Notably, 102 (37%) patients presented with primary negative symptoms with avolition and anhedonia being the most prominent (n=71, 25.7%); 70 (25%) had secondary negative symptoms. Importantly, 69% were remitted on positive symptoms at month 12. After two years of treatment (n=232), 174 (75%) of the FEP patients were not considered to be fully remitted with 100 (57%) not achieving remission due to negative symptoms alone. Notably, 61 (35%) patients presented with primary negative symptoms with avolition and anhedonia being the most prominent (n=48, 27.6%); 34 (20%) had secondary negative symptoms. Importantly, 69% were remitted on positive symptoms at month 24.
Conclusion: Negative symptoms alone account for over half of the FEP patients not achieving full remission after two years of treatment in a specialized early intervention treatment program with amotivation (avolition and anhedonia) as the overwhelming negative symptom. Considering amotivation may be amenable to behavioral interventions, targeting this early on in treatment could lead to a better outcome for more people with psychosis.
ID: 2119449

FACTOR STRUCTURE OF THE AUTONOMY PREFERENCE INDEX IN PEOPLE WITH SEVERE MENTAL ILLNESS

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Background: People vary in the amount of control they would like to have in making healthcare decisions. Given the emphasis on patient-centered care and shared decision-making, effectively measuring these autonomy preferences is critical. The Autonomy Preference Index (API) is a widely used measure in the general health domain, but less is known about the performance of the scale for measuring preferences of those with severe mental illness. The aim of this study was to assess the factor structure and performance of the API in individuals with severe mental illness.
Methods: Data for this analysis came from three separate studies investigating autonomy preferences of people with severe mental illness (predominantly schizophrenia spectrum disorders; N = 234) who were currently receiving outpatient mental health and/or primary care/integrated care services. Performance of the API was assessed both with regard to preferences in psychiatric services and in primary care services. Confirmatory factor analysis was used to assess the fit of the hypothesized two-factor structure of the API (decision-making autonomy and information-seeking autonomy); fit was evaluated using three common fit indices: the comparative fit index (CFI), the root mean square error of approximation (RMSEA), and the standardized root mean square residual (SRMR).
Results: Results indicated that in both conditions, the API did not exhibit adequate fit to the two-factor model. Three problematic items were identified, all of which were reverse-coded in comparison to other items on their respective subscales, indicating poor fit may be due to methodological factors. These items were dropped, resulting in adequate to good fit for all indices with regard to both psychiatric care (X^2 = 104.82; df = 43; CFI = .94; SRMR=.076; RMSEA=.079) and primary care (X^2 = 57.50; df = 43; CFI = .97; SRMR=.054; RMSEA=.053).
Conclusion: Overall, results suggest that the API can be used successfully in this population with the omission of some items, and that the API functions similarly when respondents are asked about psychiatric services and primary care services. The modified API may have clinical and research utility for those with severe mental illness in the burgeoning field of autonomy in patient-centered healthcare.
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ID: 2088199

AFFECTIVE LEARNING DEFICITS IN SCHIZOPHRENIA

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Background: To date, there has been an abundance of research on emotional memory in schizophrenia, which has shown that individuals with the disorder often exhibit a decrement in the recall of positive stimuli. Few studies have looked at the relation of this impairment to negative symptoms, and none have used socially affiliative stimuli. With regard to social stimuli, recent research has shown that healthy individuals utilize even minimal exposure to affective behavioral cues when learning about the positive and negative value of others (Bliss-Moreau, Barrett, & Wright, 2008). The current study will assess whether individuals with schizophrenia exhibit affective learning deficits related to social stimuli. Specifically, we hypothesize that individuals with schizophrenia, in comparison to healthy controls, will show impairments in learning positive affective associations with neutral faces, and that this deficit will be associated with negative symptoms.
Methods: This is an ongoing study; eight stabilized outpatients with schizophrenia or schizoaffective disorder and seventeen demographically matched healthy controls have been recruited to date. Participants completed an Affective Learning Task in which they were instructed to memorize neutral faces paired with sentences describing positive, negative, or neutral social behaviors by imagining the person completing the behavior. Afterwards, participants viewed the faces without the sentences and made snap judgments about the valence of the faces.
Results: Preliminary analyses indicate that controls were able to learn the correct affective valence of the faces more likely than chance for faces paired with positive and negative behavioral acts, while individuals with schizophrenia were able to learn the correct affective valence of faces paired with positive, but not negative, behavioral acts. Independent t-tests revealed that individuals with schizophrenia were less adept than controls at learning positive associations; t(23) = 2.653, p = .014. Further analyses will be conducted on an enlarged sample and examine the contribution of negative symptoms to affective learning deficits.
Conclusion: The findings suggest that while individuals with schizophrenia show largely intact affective learning overall, they are impaired in the ability to learn positive affective associations in comparison to healthy controls. This impediment may play a role in the diminution of goal-related behavior and symptoms of social anhedonia and amotivation.
ID: 2096133

Preliminary Group Attendance and Stepcount Readings (n=9) (40% Completion of Project)

Average Attendance (%)	Average Daily Steps at Program Start	Average Daily Steps at Current Time
76%	5576	6994

WALKING AROUND CHAPEL HILL (WACH): A PILOT EXERCISE PROGRAM FOR INDIVIDUALS WITH SCHIZOPHRENIA

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Background: The purpose of the current study was to develop and evaluate the impact of a group, pedometer-based walking program on the health of individuals with schizophrenia.
Methods: Subjects (n=20) with a diagnosis of schizophrenia completed the Short Form-36 (SF-36), International Physical Activity Questionnaire (IPAQ), Multidimensional Scale of Perceived Social Support (MSPSS), 6-Minute-Walking-Test (6MWT), Positive and Negative Syndrome Scale (PANSS), World Health Organization Quality of Life Scale (WHOQOL), and were weighed at baseline, post-test and 1-month follow up. We also collected daily pedometer step count readings and within group mood ratings (taken before and after each group) using the Positive and Negative Affect Scale, Positive Mood (PANAS) from all subjects. We developed a walking program that included 30-minute walking groups twice per week for 10 weeks for 2 cohorts of subjects. Additionally, all subjects received a Yamax DW pedometer to wear during all waking hours and were asked to report daily steps and provide weekly step count goals.
Results: Results from the first cohort of subjects (n=9) will be presented in this poster. The current walking program is currently at 40% completion; but will have all data collected and analyzed by January 2015. Within group effect sizes will be calculated for primary domains of interest (physical health, mental health, physical activity, and social support). Total attendance rate of 76% with 100% attendance rate of 6 out of 9 subjects indicate that the walking group is initially viewed as acceptable by subjects. Average daily steps obtained from pedometer readings indicate that subjects have steadily increased physical activity outside of group (5576 steps/day to 6994 steps/day).
Conclusion: Preliminary data on attendance and pedometer readings suggest initial acceptability and success of the walking program (See Table).
ID: 2117523

THE DEVELOPMENTAL COURSE OF SOCIAL AND ROLE FUNCTIONING IN THE PRODROMAL STAGES OF PSYCHOSIS

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Background: Recent work has shown that impaired social and role functioning in schizophrenia are vulnerability traits that can improve the prediction of impending illness. However, the impact of emerging psychotic symptoms on age-related changes in functioning that occur early in development are unclear. This study examined the trajectories of social and role functioning from adolescence to young adulthood and evaluated age-related changes in functioning in clinical high risk (CHR) subjects that developed psychosis over the course of a 2-year prospective longitudinal study.
Methods: 765 CHR subjects and 280 healthy controls (HCs) were enrolled and prospectively followed in Phase 2 of the 8-site North American Prodrome Longitudinal Study (NAPLS). Attenuated positive symptoms and conversion to full psychosis were measured with the SIPS. Social and role functioning was assessed using the GF:Social and GF:Role scales at baseline and every 6 months for up to 2 years. Linear mixed-effects models estimated the 2-year course of functioning in HCs vs. CHR subjects. In addition, an accelerated longitudinal cohort approach analyzed the trajectories of GF scores over a broad age span (ages 12–30) in order to determine the relationship between functioning, age and psychosis conversion status.
Results: Over the course of 2-years, HCs showed stable and significantly higher social and role functioning scores when compared to CHR subjects (group effect, $p<.001$). The overall CHR group displayed stable moderate impairments in both social and role functioning, with improvements over time that did not reach, however, normal healthy control levels (time effect, $p<.001$). Age-related changes in social functioning varied as a function of true-prodromal patients (i.e., CHR converters to psychosis) and false-positives (i.e., subjects that did not develop psychosis during the study). A significant age by conversion interaction ($p=.0045$) indicated that starting in early adolescence CHR converters show a reduction in social, not role, functioning with advancing age, with the largest impairments seen in mid-adolescence (ages 16–18).
Conclusion: These findings suggest that early social functioning in true-positive prodromal patients shows a deteriorating course that bottoms out in mid-adolescence. This critical period of vulnerability coincides with the maximum risk period of developing schizophrenia, suggesting that social functioning is linked with the neurodevelopmental changes that occur during the progression of the illness.
ID: 2118187

REDUCED SENSITIVITY TO SOCIAL REWARDS IN SCHIZOPHRENIA

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Background: Facial affect perception has been identified as a deficient social cognitive skill that impacts social functioning in schizophrenia (SZ). These tasks traditionally assess negative affective states (sad, fear, disgust, anger,

etc.), and do not evaluate nuanced positive expressions. Further, these tasks do not evaluate the positive, rewarding value of expressions that typically guide the motivation and desire to engage in social interactions.
Methods: The current study adapted a matching pennies game (Shore & Heerey, 2011) to assess the subjective value of social feedback (genuine and polite smiles) in terms of a more common currency: money. Patients with SZ (n = 41) and controls (CN) (n = 19) were instructed to choose the same side of a coin as six computerized opponents, each of whom provided different rates of monetary feedback and types of social feedback. In a later test phase, participants chose which opponent to play from amongst pairs of opponents. A smile discrimination task was conducted to evaluate facial affect perception ability. Additional recruitment is currently underway.
Results: Preliminary analyses indicate that both groups adequately learned reward contingencies. A logistic model estimated preferences for social and monetary rewards. CN valued genuine smiles significantly more than SZ, $t(58) = -2.21$, $p = .03$, and valued money more than SZ at trend level, $t(58) = -1.86$, $p = .07$. There were no group differences in the valuation of polite smiles, $t(58) = -.61$, $p = .54$. Facial affect perception abilities did not differ between groups. Moreover, the undervaluation of genuine smiles in SZ was not related to smile discrimination ability (d'), $r(40) = .06$, $p = .70$, or categorization bias (C), $r(40) = -.04$, $p = .83$. After eliminating questionable learners from the analysis, money was no longer differentially valued between groups, $t(42) = -1.16$, $p = .25$, yet SZ still undervalued genuine smiles compared to CN, $t(42) = -2.78$, $p = .01$. Further analyses will examine the contribution of negative symptoms and trait social anhedonia on preferences for social rewards.
Conclusion: SZ failed to use genuine smiles to motivate choices on the matching pennies game to the same extent as CN; however, money was equally valued. These findings suggest that there is reduced sensitivity to social rewards in SZ. The undervaluation of social rewards in SZ was not related to the ability to distinguish between facial expressions, nor was it related to a decreased ability to learn reward contingencies.
ID: 2090382

EARLY INTERVENTION FOR PSYCHOSIS INTERVENTION: A REAL-LIFE SYSTEM IN HONG KONG.

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Background: In Hong Kong, Early Intervention for Psychosis developed in the background of a low-resource, high-stigma setting similar to many Asian locations. Prior to Early Intervention Initiatives, there were high reliance on inpatient services, crowded outpatient services, and high levels of stigma. Public awareness efforts were aligned with improved access to specialised services.
Methods: This is a review of several large scale longitudinal studies carried out in first episode psychosis in Hong Kong over a decade, using largely comparable outcome measures. The review aims to characterise the effect of intervention in people with different age of onset, as well as with different durations of untreated psychosis.
Results: Cohort comparisons suggested that intervention may have improved aspects of outcome such as suicide, hospitalisation and functioning. Controlled study demonstrates that benefits can be obtained by intervention extending from the second into the third year after psychosis onset. Long-term follow-up studies suggest that some of these benefits may still be discernible many years later. Innovative approaches to improving functional and cognitive outcome are being evaluated.
Conclusion: Using real-life data from Hong Kong, it is demonstrated how early intervention principles interacted with real-life factors to shape service developments and outcomes for psychotic disorders in Hong Kong.
ID: 2118146

PSYCHOLOGICAL PREDICTORS OF MOTIVATION AND TREATMENT ATTENDANCE IN ADOLESCENTS AT CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Decreased motivation for goal-directed behavior, such as engaging in treatment, is a feature of schizophrenia and may also be the case for those at clinical high risk (CHR) for psychosis (Schlosser et al., 2014). Research suggests that self-esteem and treatment motivation may be related to constructs that influence treatment adherence. Self Determination Theory (SDT) distinguishes between internal (autonomous) motivations for goal-directed behaviors that meet intrinsic needs, while external (controlled) motivations are driven by outside reinforcement. Greater internal regulation has been associated with self-esteem and better treatment engagement, yet external reinforcers may also improve treatment engagement by shaping more autonomous regulation over time (Silverstein, 2010). This study explored how motivation relates to treatment attendance in CHR. Based on SDT, we hypothesized that better treatment attendance would be related to greater baseline controlled regulation and more externalized reasons for entering treatment in those with low baseline self-esteem, whereas better treatment attendance would be related to greater autonomous regulation and more internalized reasons for entering treatment in the high baseline self-esteem group. Further, we hypothesized that baseline treatment motivation would be a better predictor of treatment attendance than baseline prodromal symptoms.
Methods: As part of a larger study, 37 adolescents at CHR had 30 hours of cognitive remediation over 2 months. Outcome measures were motivation, perceived competency, self-esteem, and symptom severity.
Results: Contrary to hypotheses, in those with low baseline self-esteem, better treatment attendance corresponded to baseline autonomous regulation ($\rho = 0.27$, $p < .05$) and more internalized baseline reasons for entering treatment ($\rho = 0.29$, $p < .05$). Treatment attendance was inversely related to negative symptoms in this group. For the high self-esteem group, better treatment attendance was related to confidence in treatment efficacy. In the overall sample, baseline perceptions of competency were related to treatment attendance in both self-esteem groups (low, $\rho = 0.30$, $p < .05$; high, $\rho = 0.40$, $p < .01$) and were a better predictor of treatment attendance above self-esteem, prodromal symptoms, or treatment motivation at baseline ($\beta = 0.29$, $p = .01$).
Conclusion: These results suggest perceived competency and autonomous motivation as targets for those with low self-esteem at CHR, who are low in treatment attendance.
ID: 2118070

TRAUMATIC BRAIN INJURY AND PSYCHOSIS IN GPC MEMBERS

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Background: Approximately three million individuals in the United States sustain traumatic brain injury (TBI) every year, with documented impact

on a broad range of neurological and psychiatric disturbances. Mania, depression, and psychosis have all been found to succeed TBI, however current studies suffer from a lack of standardized classification for both psychiatric symptomatology and extent of injury. Additionally, identification of subsets of individuals that may demonstrate increased propensity for posttraumatic symptoms, and who may share genetic vulnerabilities for gene-environment interactions is necessary to better understand, predict, and ultimately prevent this phenomenon.
Methods: A sample of 11,489 cases from the Genomic Psychiatry Cohort (GPC), a National Institute of Mental Health-managed data repository for the investigation of schizophrenia and bipolar disorder, was used for this study. Participants carried diagnosis on the schizophrenia and bipolar spectrums. Cases were excluded if TBI was deemed causal to the development of mental illness; all TBI occurred after a diagnoses of bipolar or schizophrenia spectrum disorder had been determined. A k-means clustering algorithm was used to probe differences between schizophrenia and bipolar disorder associated with variables including onset age, hallucinations, delusions, head injury, and TBI.
Results: Cases were separated into an optimum number of seven clusters, with two of the clusters (1 and 4) including all cases with brain injury. The correlation between the occurrence of bipolar disorder with psychosis and brain injury was not significant for the whole sample, however was significantly correlated in cluster 4. 72% of cases in cluster 4 were male, and 99.2% of the subjects sustained head injury, with the longest average period of unconsciousness among the clusters.
Conclusion: This study demonstrates that TBI is associated with psychosis in bipolar cases, and thus may increase the risk of psychosis in such individuals, lending further weight to the increasing contribution of environmental factors to the development of psychosis and mental illness. The presence of TBI in this subset of individuals demonstrates that traumatic stressors have the ability to impact gene expression in a vulnerable population.
ID: 2115194

THE ROOTS OF PSYCHOMETRIC SCHIZOTYPY: A DISRUPTION IN BASIC REASONING

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Background: An important paradox has emerged from the literature regarding schizotypy - defined as the personality organization reflecting a putative liability for schizophrenia-spectrum disorders. Across certain cognitive, emotional, social, communicative, quality of life and other functional variables, individuals with schizotypy report experiencing extreme levels of psychopathology. These levels have been documented in several recent meta-analyses. These impairments are paradoxical in that individuals with schizotypy, typically recruited from undergraduate college populations, should be healthier in virtually every respect than chronic, older outpatients with schizophrenia. Importantly, on objective evaluations in these same domains, individuals with schizotypy fail to show abnormalities to any commensurate degree. The present talk will evaluate this issue.
Methods: We will first present data from our lab documenting the stability and magnitude of this "objective-subjective dyjunction" in schizotypy; using both normative and patient data to anchor the performance of individuals with schizotypy. Secondly, experimental data from three laboratory studies will be presented exploring the roots of this dysjunction. As part of these studies, individuals with schizotypy were administered tests of cognitive and emotional ability and asked to evaluate their own performance in context of their peers.
Results: Collectively, the performance of individuals with schizotypy was grossly normal, but they showed a fundamental abnormality in their ability to accurately estimate their own behavior. Interestingly, in some cases, they were unusually accurate in their ability to predict the behavior of others.
Conclusion: Our data suggests that schizotypy is characterized by a demonstrative and predictable reasoning and self-estimation bias. This abnormality will be discussed in terms of its continuity with schizophrenia-spectrum disorders and in terms of potential neural compensation in individuals with schizotypy. Collectively, these results can inform the development of new and sophisticated endophenotypes of the schizophrenia-spectrum; ones that can be efficiently evaluated in large groups of people and capitalize on the use of multimodal data.
ID: 2106188

FUNCTIONAL OUTCOME IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS: MODELING THE IMPACT OF NEUROCOGNITION, FUNCTIONING, NEGATIVE SYMPTOMS, AND CONVERSION TO PSYCHOSIS

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Background: Recent research has found that the persistent functional difficulties associated with psychosis risk states are determined by multiple factors, including neurocognition, functioning, and negative symptoms. However, the interrelationships and impact of these variables along with the transition to full-blown psychosis on long-term social (i.e., interpersonal relationships) and role (i.e., school/work) difficulties is unclear. The present study used a structural equation modeling (SEM) approach to integrate these factors to determine the specific determinants and pathways that lead to poor long-term functioning in a large sample of treatment-seeking adolescents and young adults at clinical high-risk (CHR) for psychosis.
Methods: 192 CHR subjects aged 12–22 (M=15.96, S.D.=2.18) were assessed and prospectively followed at the Recognition and Prevention (RAP) Program (M=3.0 years, S.D.=1.9). Neurocognitive performance and negative symptom levels were assessed at baseline. Social and role functioning was assessed at baseline and study end with the GF:Social and GF:Role scales. Prodromal symptoms were assessed using the Scale of Prodromal Symptoms (SIPS/SOPS). Model estimation was performed using AMOS v16. Two SEM models were built, one for each domain of functioning (i.e., social and role).
Results: The final trimmed models for social (RMSEA=0.05, CFI=0.952) and role (RMSEA=0.069, CFI=0.902,) outcomes had good fit indices. In both models, neurocognition and negative symptoms were directly related to baseline, but not outcome, social and role functioning. Conversion to psychosis was directly related to functional outcomes, however, it was not the only determinant of long-term functioning. A comparison of both models demonstrated a stable course of functioning from baseline to outcome. Moreover, these pathways were domain specific, that is, baseline role functioning was only related to role functioning at study outcome, while baseline social functioning was only related to social outcome.
Conclusion: Our findings reveal a complex relationship between baseline neurocognition, functional impairments, and negative symptoms and long-term functional outcomes in individuals at CHR for psychosis. Long-term social and role functioning was not entirely dependent on the emergence of psychosis, suggesting that early intervention prior to the onset of psychosis may have an impact on the early course of social and role functioning and possibly limit future disability.
ID: 2119442

ANTICIPATORY PLEASURE AND ITS IMPLICATIONS ON LEARNING IN SCHIZOPHRENIA

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Background: Anhedonia is a hallmark negative symptom of schizophrenia, which can be a serious barrier for learning. Many patients with schizophrenia are less willing to complete treatment tasks that they do not find enjoyable. Previous studies have demonstrated that patients with schizophrenia have impaired reward processing, yet seem to have preserved hedonic experience. Distinctions between anticipatory pleasure (AP), thinking a task will be enjoyable, and consummatory pleasure (CP), enjoying a task that is presently occurring, have also been identified (Gard et al., 2007), yet research has not explored their relationships to math learning. The present study sought to establish if AP or CP was related to learning performance in patients with schizophrenia. Understanding this relationship may facilitate development of intervention programs that target hedonic and cognitive deficits.
Methods: Participants included 50 outpatients diagnosed with schizophrenia. The intervention consisted of a 4-week computer-based adaptive-difficulty arithmetic training program. Assessments at baseline and post-treatment included the SANS (Anhedonia subscale) as a measure of state anhedonia, TEPS Anticipatory and Consummatory subscales as a measure of task-related anhedonia, and learning (pre-to-post change in arithmetic performance scores).
Results: As expected, AP at baseline was negatively correlated with state anhedonia ($r=-.283$, $p<0.05$). Higher baseline AP was related to greater improvement in math performance ($r=.297$, $p<0.05$). CP was unrelated to learning over the course of the intervention. A scatter plot of a median split (high/low) revealed that those with low and high levels of state anhedonia had a similar distribution of scores for task-related anhedonia, suggesting that task and state anhedonia may not be necessarily tied together in this population.
Conclusion: Our results indicate that AP is related to learning performance. This is the first study examining anhedonia and anticipatory and consummatory pleasure in relation to cognitive performance in patients with schizophrenia. Of interest, the amount that patients enjoyed the task while they were doing it was not as important as how much they thought they would enjoy doing it again. The findings suggest that AP plays an important role in predicting performance and may be more important than CP as a treatment target for improving motivation for goal-directed learning.
ID: 2118001

THE DEVELOPMENT AND VALIDATION OF A COMPUTER-BASED SKILLS TRAINING (CAST) PACKAGE

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Background: People with severe mental illness (SMI) such as schizophrenia or those with cognitive impairments often experience difficulty performing routine everyday tasks such as money or medication management that are critical to independent living. Thus, there is increasing interest in developing treatment approaches to remediate cognitive and functional problems. Most functional skills training programs require multiple sessions of in-person training by skilled interventionists in clinical settings, which incur a high intervention cost. This presentation will discuss an ecologically valid technology-based adaptive training functional skills training package.
Methods: The package was developed using an adaptive training approach. Adaptive training involves varying the difficulty levels of the to-be-learned material based on an individual's level of ability and current performance. Specifically, each training module: 1) Identifies the current levels of an individual's ability on the functional task of interest with Item response theory (IRT) strategies; 2) Uses dynamic-titration feedback from immediate task performance to adjust the difficulty of task performance; and 3) Provides immediate trial by trial feedback and, most critically, instructional responses following errors, followed by repetition of the previously failed item. The package includes training modules for a variety of everyday functional tasks including money and medication management, shopping, travel, and way finding. The package is build so that it can be deployed on a variety of technology platforms such as tablets or PCs in a variety of settings (e.g., clinical settings, home environments) and in multiple languages. The package is being evaluated with a sample of adult schizophrenic patients and non-impaired older adults.
Results: Preliminary data indicate that use of a computer-based approach is feasible with our participant populations. The participants are able to complete the program. Further, the package is sensitive to individual differences and training performance is related to cognitive abilities such that people with higher abilities demonstrate better performance.
Conclusion: The use of a computer-based functional skills training program, based on an adaptive training approach, is feasible for older adults and patient populations. This type of approach will help to overcome many of the logistic problems associated with current functional skills training strategies.
ID: 2082628

INVESTIGATING THE ROLE OF METACOGNITION IN NEUROCOGNITIVE IMPAIRMENT AND FUNCTIONAL OUTCOME IN SCHIZOPHRENIA: A META-ANALYTIC STUDY

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Background: Previous research has identified the significant role of neurocognition in predicting functional outcome in schizophrenia. Recent estimates, however, suggest that neurocognition explains only about 40% of the total variance in functional outcome, and the contribution of psychopathology to this outcome is limited. This has led to the search for alternative constructs which account for additional variance in functional outcome, and which may prove valuable targets for therapeutic intervention. Metacognition, or the ability to reflect on one's cognitive skills, may be one such candidate. Metacognition has been demonstrated to correlate with neurocognition. There is nascent evidence to suggest that it may predicate functional outcome in schizophrenia, and it has been proposed as a potential target of cognitive remediation therapy.
Methods: Two random-effect model meta-analytic procedures were run to explore this relationship further firstly investigating the relationship across studies of (I) neurocognition and metacognition and secondly investigating the relationship across studies between (ii) metacognition and functional outcome.
Results: For the relationship between neurocognition and metacognition, the pooled studies sample size comprised 1038 participants across 20 studies, and a significant mean effect size of 0.28 was found. The relationship between individual neurocognitive domains (memory, executive function, IQ) and metacognition was also explored.
Fewer studies have investigated the relationship between metacognition and functional outcome. The pooled studies sample size here comprised 285 participants across 5 studies, with a significant mean effect size of 0.33. Both measures of functional capacity and outcome were included
Conclusion: These findings indicate that metacognition may relate differently to different cognitive domains and support evidence that there may be multiple levels of metacognitive processing available to the individual. This study also offers evidence that metacognitive ability may predict additional variance in functional outcome on top of that already predicted by cognition alone and offers prima facie evidence that metacognition may mediate

the known relationship between neurocognition and function. Specific metacognitive processes may thus represent valuable targets of cognitive remediation and cognitive behavioural interventions.
ID: 2119373

ADHERENCE TO A NEW WORKING MEMORY FOCUSED COGNITIVE REMEDIATION THERAPY FOR PSYCHOSIS

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Background: Cognitive deficits are recognized as a core symptom of psychosis and are a strong predictor of social and occupational functioning. Cognitive remediation therapy (CRT) has emerged as a research focus in recent years demonstrating medium effects sizes across CRT programmes (Wkyes et al., 2011) but adherence to such programmes is yet to be investigated. The purpose of this pilot study is two-fold - 1) to investigate the rates of adherence to a new working memory focused computerised CRT programme in a pilot study sample and 2) identify what type of participant is likely to drop out of the programme
Methods: Participants included 59 outpatients enrolled in a pilot study for an 8 week long CRT programme. Participants completed a neuropsychological battery at baseline and follow-up and a structured Clinical Interview for DSM-IV Axis 1 Diagnosis (SCID) (First et al., 2002) at baseline.
Results: Results showed large non-adherence rates (55.9%) but no significant difference between completers of the CRT programme and dropouts in terms of age, gender, education, diagnosis or IQ. Similarly, both groups did not differ on any neuropsychological measures for episodic or working memory at baseline. The two groups did differ significantly however in their measure of positive symptoms at baseline for global ratings of hallucinations, severity of delusions and severity of bizarre behavior - as measured by the Scale for the assessment of negative symptoms (SAPS), (Andreasen, 1984) - where positive symptoms were associated with poor adherence to the CRT programme
Conclusion: The results from this CRT pilot study suggest that increased positive symptoms may impact adherence to CRT and warrant further investigation in a larger scale study. Further investigation into components of adherence including benefits and barriers to treatment, social support and insight is necessary in order to better understand who is most likely to adhere to CRT and ultimately optimize treatment to counter non-adherence rates
ID: 2118365

CHARACTERIZING AFFECTIVE RESPONSES TO AN ACUTE BOUT OF MODERATE-INTENSITY EXERCISE IN PEOPLE WITH SCHIZOPHRENIA

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Background: Several randomized control trials have observed mental health enhancing effects of exercise among people with schizophrenia. Despite this, no studies have characterized the effects of a single bout of moderate-intensity exercise on basic affect (feelings of pleasure and arousal), a key component of subjective wellbeing, among people with schizophrenia. Furthermore, anhedonia (an inability to derive pleasure from normally pleasurable stimuli) has long been considered a core symptom of schizophrenia, thus it is unclear if individuals with schizophrenia will demonstrate the pattern of increased pleasure post-exercise observed in the general population.
Methods: A randomized crossover design compared affect experienced before, during, and after a 14 min bout of moderate-intensity exercise on a treadmill to passive sitting. Feelings of pleasure and arousal were measured at baseline, 6 min into the task, immediately post-task, and 10 min post-task using the Feeling Scale and Felt Arousal Scale respectively. Thirty participants enrolled in the study; 28 participants completed the study. Separate mixed model analyses of variance (ANOVA) were conducted for pleasure and arousal, with test order as the between-subject factor, and time and task as within-subject factors.
Results: For pleasure, a significant main effect for time, $F(2.2, 57.4)=4.76$, $p=.01$, $\varepsilon=.74$, and an interaction effect between time and task $F(2.1, 53.6)=4.86$, $p=.011$, $\varepsilon=.69$, emerged after Greenhouse-Geisser corrections; there was no main effect for task. No main or interaction effects were observed for arousal. Test order had no main or interaction effects on either pleasure or arousal. Post-hoc Bonferroni corrected t-tests ($\alpha=.007$) revealed significant differences between pleasure at baseline and both post task, $t(27)=2.98$, $p=.006$, and 10 min post-task, $t(27)=2.98$, $p<.001$.
Conclusion: This study provides initial support that individuals with schizophrenia can derive pleasure from exercise, similar to the general population. Thus exercise may provide a method of regulating affect to improve mental health. Furthermore, this study provides further evidence that anhedonia, as it is currently defined, requires reassessment as a symptom of schizophrenia. Finally, the lack of differences between tasks may, in part, explain why people with schizophrenia tend to be inactive. Future studies should examine the links between affective responses to health behaviours such as exercise, with adherence to those behaviours.
ID: 2113851

MACROPHAGE-DERIVED CHEMOKINE (MDC, CCL22) IS ASSOCIATED WITH MEASURES OF SOCIAL COGNITION CAPACITY IN SCHIZOPHRENIA

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Background: Social cognition is impaired in schizophrenia, is relatively independent of purely neurocognitive domains such as attention or executive functioning, and may be the strongest predictor of functional outcome in this disease. There is growing evidence that the cognitive symptoms of schizophrenia are a consequence of an imbalance in the inflammatory response to psychosocial stresses that lead to loss of grey and white matter in the CNS by chronically-activated microglia.
Methods: To test for social cognitive capacity among patients (n=60) and healthy controls (n=20), we administered a new social cognition test, the Waiting Room Task (WRT).
Results: Using bead-based flow immunoassay, we found that macrophage-derived chemokine (MDC, CCL22) plasma levels showed statistically significant Spearman's rho scores for correlation with WRT subscales for social cognitive capacity and self-referential bias.
Conclusion: MDC is a central activator in the amplification circuit of polarized T helper 2 responses that have been shown to be upregulated in schizophrenia.
ID: 2116383

BASELINE ANTIOXIDANT STATUS IS ASSOCIATED WITH 1- AND 2-YEAR FUNCTIONAL OUTCOME IN EARLY-ONSET SCHIZOPHRENIA

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Background: Previous studies from our group have found an association of baseline antioxidant levels with gray matter loss and cognitive functioning in early-onset psychosis (Fraguas et al., 2012; Martinez-Cengotitabengoa et al., 2012). To date, no previous study has assessed the association between antioxidant markers and functional outcome in this population.
Methods: 2-year prospective, naturalistic study assessing adolescents with a first episode of early-onset schizophrenia (EOS; including schizophrenia or schizoaffective disorders) or affective psychosis (EO-AFP; bipolar disorder or psychotic depression). Functioning was assessed at baseline and 1-year 2-year follow-up using the Child Global Assessment Scale (CGAS). Total antioxidant status (TAS) at baseline was determined by standardized spectrophotometric assays. Duration of untreated psychosis (DUP) was calculated as the time elapsed since the emergence of the first psychotic symptom and baseline visit. Premorbid adjustment was assessed at baseline using the Cannon-Spoor Premorbid Adjustment Scale (PAS). Bivariate correlations and stepwise linear regression models (using baseline CGAS, PAS and DUP as covariates) were used to assess the relationship between baseline TAS and CGAS at 1-year and 2-year follow-up. All statistical analyses were performed using SPSS 18.
Results: Twenty-eight patients with EOS (age 15.8 ± 2 years, 72.3% male) and 22 patients with EO-AFP (16.7 ± 1 years, 68.2% male) comprised the study sample. In patients with EOS, baseline TAS was significantly correlated with 1-year ($r=0.621$, $p<0.001$) and 2-year ($r=0.480$, $p=0.01$) CGAS. No significant correlations were found between TAS and CGAS at any timepoint in patients with EO-AFP. In patients with EOS, higher CGAS scores at 1-year follow-up were significantly predicted by higher baseline TAS ($r2=0.362$) and better premorbid adjustment ($r2=0.109$), $p<0.001$; whereas higher CGAS scores at 2-year follow-up were significantly predicted by higher baseline TAS ($r2=0.201$) and shorter DUP ($r2=0.101$), $p=0.004$.
Conclusion: Higher baseline antioxidant capacity is associated with better functional outcome in early-onset schizophrenia. Treatment with antioxidants could improve functional outcome in this population.
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ID: 2118284

CROSS-SECTIONAL FINDINGS FROM THE PATTERN STUDY IN STABLE PATIENTS WITH SCHIZOPHRENIA

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Background: Persistent symptoms of schizophrenia are related to functional impairment. Pattern is a non-interventional, prospective, cohort study designed to evaluate persistent symptoms, burden of illness, caregiver burden and pharmacoeconomic outcomes, in outpatients with schizophrenia. The Pattern study included both a cross-sectional and longitudinal phase. Here the results of the cross-sectional phase are reported.
Methods: Pattern is a 12- to 24-month, prospective, observational study of stabilized outpatients with schizophrenia. Inclusion criteria: adult patients with schizophrenia (DSM IV-TR/ICD-10), as assessed by Mini International Neuropsychiatric Inventory (MINI), with no psychotic exacerbation in the previous 3 months. Patients were evaluated by the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Schizophrenia (CGI-SCH) Scale, Personal and Social Performance (PSP) Scale, Short Form-36 (SF-36), EuroQoL-5 Dimensions and Client Socioeconomic and Services Receipt Inventory (CSSRI). Patients were classified as: predominantly negative symptoms, sub-optimally controlled positive symptoms, symptomatic remission with poor level of functioning, and recovery.
Results: The primary analysis population comprised 1379 patients: Argentina (n=110), Brazil (n=100), Canada (n=117), France (n=237), Germany (n=250), Italy (n=219), Spain (n=207) and the UK (n=139). Patients were predominantly male (71%), with a mean age of 44 (standard deviation [SD], 11) years. The main co-morbidities were current or past substance abuse (35%), another mental disorder (14%), vascular disease (7.8%), gastrointestinal disorders (7.5%) and metabolic disorders (7.5%). The mean duration of persistent positive and negative symptoms was 9.6 (SD, 8.8) and 8.9 (SD, 9.6) years, respectively. Treatment resistance was observed in 21% of patients. Clozapine use varied between countries, ranging from 16% in France to 72% in Brazil (overall 29%). Symptom subgroups were predominantly negative persistent symptoms (39%); sub-optimally controlled positive persistent symptoms (20%); symptomatic remission with poor level of functioning (34%); and recovery (3.0%). More than 86% of patients experienced a degree of disability classified as greater than mild on the PSP scale.
Conclusion: Persistent symptoms are prevalent in patients with schizophrenia. Patients with persistent symptoms experience substantial social impairment and differ in terms of their pharmacological treatments cross-nationally.
ID: 2096320

SUBJECTIVE COGNITIVE COMPLAINTS AND FEAR OF DIAGNOSTIC DISCLOSURE INFLUENCE RECOVERY

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Background: Recovery from serious mental illness (SMI) is a multifaceted concept. Insight, a construct defined by awareness of one's illness, may be a precursor to recovery (Frese et al., 2009). However, insight could promote negative consequences, such as awareness of stigma (Lysaker et al., 2007). Stigma also constitutes a barrier to recovery due to avoiding SMI disclosure for fear of social reprisal (Corrigan, 2004). Awareness of cognitive symptoms is important in understanding SMI because cognitive impairment can impede insight and recovery goals, such as employment (Giusti et al., 2014). The purpose of this study was to examine relationships among awareness of cognitive symptoms, fear of diagnostic disclosure, and recovery.
Methods: Individuals with SMI (N=49) were recruited from a community mental health center. The Structured Clinical Interview for the DSM-IV (First et al., 2002) was utilized for diagnostic confirmation. The Stages of Recovery Instrument (Andresen et al., 2006), Stigma Scale (King et al., 2007), Subjective Scale to Investigate Cognition in Schizophrenia (Stip et al., 2003), and a cognitive battery were utilized to measure recovery, fear of diagnostic disclosure, subjective executive functioning (EF), and objective EF, respectively.
Results: Three regression analyses were performed to estimate mediation (Baron & Kenny, 1986). Recovery was the DV with subjective and objective EF as IV's, and fear of disclosure as the mediator. Bootstrapping was used to determine significance of the mediated effect (Bollen & Stine, 1990). Analysis 1 revealed that subjective EF predicted lower recovery scores (B=-.762, p<.05) but objective EF did not (B=.428, ns). Analysis 2 found that subjective EF predicted greater fear of disclosure (B=.113, p<.001) but objective EF did not (B=.072, ns). Analysis 3 revealed that the relationship between subject EF and recovery was non-significant (B=-.228, ns) after accounting for the impact of fear of disclosure on recovery (B=-4.992, p<.01).
Conclusion: These results indicate that fear of diagnostic disclosure mediated the relationship between EF complaints and recovery. Specifically, EF complaints predicted greater fear of disclosure, predicting lower recovery. Objective EF did not predict either factor. This suggests that when stigma factors are associated with cognitive awareness, it may negatively impact recovery, independent of actual cognitive functioning. Areas for future research and interventions for SMI populations will be discussed.
ID: 2089470

TRUST VS. PARANOIA: THE DYNAMICS OF SOCIAL INTERACTION IN EARLY AND CHRONIC PSYCHOSIS

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Background: Psychosis is associated with severe social dysfunction. Impaired trust and an insensitivity to positive social cues of others have been shown to impact negatively upon social interactions of adults with chronic psychosis. However, the tendency to trust and to cooperate changes from adolescence to adulthood. As such, the early stages of psychosis might present a window of opportunity to foster trust and social sensitivity. To elucidate this we investigated interpersonal trust and its impact on social interactions in early and chronic psychosis.
Methods: Two multi-round trust games with a pre-programmed cooperative and unfair game partner were used to assess changes in trust in response to positive and negative social partner behaviour. The sample consisted of 79 patients with psychosis (39 early and 40 chronic cases) and 140 controls. Associations between group status and trust (amount invested) were analyzed by means of multilevel random regression analyses. In addition, we investigated the associations between trusting behaviour and psychotic symptoms in the patient groups.
Results: Patients with early and chronic psychosis did not differ in their basic trust (initial investments) towards others but both groups had significantly lower basic trust than controls ($p < 0.01$). Patients with early psychosis increased their trust towards similar levels as controls ($p = 0.37$) during cooperative interactions. Patients with chronic psychosis, in contrast, had lower levels of trust than patients with early psychosis and controls (both $p < 0.01$). The three groups did not differ in levels of trust towards the unfair game partner. There were no significant associations between (basic) trust and symptom levels in early or chronic psychosis patients.
Conclusion: Psychosis is associated with compromised (basic) trust towards others, regardless of illness phase and symptom levels. Suggestive of a higher sensitivity to positive social signals, early psychosis patients increased their levels of trust towards the levels of controls in response to a cooperative interaction partner. In line with earlier research, chronic psychosis was specifically associated with an insensitivity to cooperative others. The loss of basic trust paired with an insensitivity to positive social signals may aggravate social dysfunction in chronic illness stages. The findings suggest that the early illness stages present a window of opportunity for interventions that aim to keep the behavioural flexibility towards others intact.
ID: 2084511

RESPONDING TO STIGMA WITH FEAR OF NEGATIVE EVALUATION IS ASSOCIATED WITH HIGHER SYMPTOMS AND LOWER GOAL AND SUCCESS ORIENTATION

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Background: While research on self-stigma has focused largely on the consequences of applying negative beliefs regarding mental illness toward oneself (Livingston & Boyd, 2010), an area that has the potential to compound these detrimental effects but has received less empirical attention in the context of stigma is the cognitive process of fear of negative evaluation; therefore, the purpose of this study was to explore fear of negative evaluation in the context of responding to encounters with stigma and to examine whether this process is associated with symptoms and goal and success orientation.
Methods: Forty-one participants with schizophrenia-spectrum disorders completed a mixed-methods study involving a semi-structured interview (Lysaker et al., 2002) were descriptions of encounters with stigma were coded using content analysis (Hsieh & Shannon, 2005) to better understand fear of negative evaluation in the context of responding to stigma; then, participants who discussed fear of negative evaluation regarding stigma were compared to those who did not using independent samples t-tests to examine differences regarding symptoms and goal and success orientation.
Results: Qualitative descriptions of fear of negative evaluation involved cognitive and emotional processing of stigma that were associated with negative beliefs about personal success and patterns of withdrawal or isolating. Notably, 15 of the 41 participants (36.6%) described fear of negative evaluation as part of their response to encounters with stigma. Those who expressed fear of negative evaluation had significantly higher overall symptoms (t=-2.60, p<.01), positive symptoms (t=-2.28, p<.05), negative symptoms (t=-2.16, p<.05), and emotional discomfort symptoms (t=-2.29, p<.05) as well as lower goal and success orientation (t=2.28, p<.05) than those who did not describe fear of negative evaluation.
Conclusion: Fear of negative evaluation may be a response to stigma that leads to heightened symptoms and lower beliefs about success and targeting beliefs surrounding the cognitive process fear of negative evaluation using psychosocial treatments may lead to lower symptoms and increased goal and success orientation.
ID: 2118859

INVESTIGATING THE BENEFITS OF EXERCISE IN FIRST EPISODE PSYCHOSIS

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Background: Physical exercise has been shown to be an effective adjunctive treatment in schizophrenia, for positive symptoms, negative symptoms, cognitive deficits and cardio-metabolic dysfunction. However, this has yet to be explored in first-episode psychosis (FEP). Poor adherence and high attrition have been a problem in previous exercise trials in schizophrenia, so any trial in the FEP group needs to evaluate interventions which are accessible and engaging.
Methods: This study was a within-subjects feasibility trial of individualised exercise interventions in FEP. Thirty participants were recruited from Early Intervention Services. Each met with a research assistant to formulate a 10-week exercise plan, based on their personal incentives, preferences and required levels of support. Participants were also provided with a 'training partner' (research assistant) for two 1 hour sessions per week to facilitate their engagement in chosen activities. Adherence and attrition were recorded to determine the feasibility of implementing individualised exercise in FEP. Participants also completed a broad range of physical, psychiatric and neurocognitive assessments pre-and-post intervention to determine suitable outcome measures for future trials.
Results: Participants had good adherence to exercise, achieving 107 mins of moderate/vigorous exercise per-week. Furthermore, only 2 participants dropped out during the intervention. Measures of cardio-metabolic health, positive and negative symptoms, psychosocial functioning and cognitive performance showed significant improvement after 10 weeks of exercise. Blood tests and brain scans were not widely consented to by participants.
Conclusion: We present a standardised method of formulating and delivering individualised exercise interventions in FEP. We found that exercise interventions which are tailored to individual preferences / needs are engaging and accessible for FEP patients, widely enabling them to achieve sufficient levels of moderate-to-vigorous exercise per week. Furthermore, such interventions may significantly improve various physical and mental health outcomes in FEP, although randomised trials are required to establish the magnitude of effect.
ID: 2083868

DEFAULT MODE NETWORK CONNECTIVITY PREDICTS SOCIAL FUNCTIONING IN SCHIZOPHRENIA

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Background: Social functioning is theorized to recruit brain regions from the default mode network (DMN), which include the medial prefrontal cortex, the posterior cingulate cortex, and the precuneus. In the present study, we evaluated whether functional connectivity for DMN networks was related to self-reported real-world social functioning.
Methods: Schizophrenia (n=30) and healthy control (n=32) subjects completed a 5-minute resting state scan in addition to the Specific Level of Functioning (SLOF) questionnaire. Resting state data was processed using Independent Component Analysis to generate 60 intrinsic connectivity networks (ICNs). Within-network connectivity metrics were computed for each subject for all 60 networks. We also calculated interconnectivity metrics, which reflected the synchrony between the timecourses of all ICN pairs. We identified two DMN networks for our analyses: i) frontal pole and anterior cingulate cortex (ICN8) and ii) posterior cingulate cortex and precuneus (ICN24). We setup a linear regression model to predict social functioning. The model included the within-network connectivity values for ICNs 8 and 24, as well as the interconnectivity metric between these two networks. We determined the presence of any group by network interactions.
Results: Significant interactions were found for within network connectivity of ICN8 and the interconnectivity between ICNs 8 and 24 when predicting the social functioning scores ($F_{7,52}=5.055$, $p<0.001$). Thus, we produced two follow-up models to assess these relationships for schizophrenia and control subjects, separately, which contained metrics for variables with significant interactions only. Follow-up results indicated the interconnectivity between 8 and 24 predicted social functioning among schizophrenia ($\beta=0.42$, $p=0.03$), but not control subjects ($\beta=-0.15$, $p=0.38$). However, within network connectivity in the ICN8 predicted social functioning in control ($\beta=-0.39$, $p=0.03$), but not schizophrenia subjects ($\beta=0.01$, $p=0.94$).
Conclusion: The results suggest that the synchrony between the networks containing anterior and posterior portions of the DMN was a stronger predictor of social functioning than within-network connectivity for either ICN alone. These findings are consistent with prior studies indicating that the DMN is critical to social functioning. Coherence between subsystems of the DMN may therefore be critical to social functioning processes.
ID: 2079372

CUT-OFF POINT FOR DURATION OF UNTREATED PSYCHOSIS IN FIRST EPISODE EARLY ONSET PSYCHOSIS: THE DECISIVE 60 DAYS

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Background: Shorter duration of untreated psychosis (DUP) in patients with early onset psychosis (EOP) has been associated with better clinical, functional and cognitive outcome (Fraguas, 2014a, 2014b). We aimed to estimate a cut-off point for DUP, below which the likelihood of better outcome would be increased.
Methods: A total of 80 subjects (31.3% females, mean age 16.0 ± 1.8 years) with first episode EOP were enrolled in the study. The best DUP cut-off point was determined by the highest likelihood ratio for better outcome (considered as c-GAF score at 2-year follow-up assessment higher than 70) by receiver operating characteristic (ROC) curve. The level of significance was set at $p<0.05$. All statistical tests were two-tailed using SPSS software for Windows version 18.0.

Results: Mean and median DUP were 65.3 ± 54.7 and 49.5 days, respectively. A DUP of 57.5 days provided the best trade-off between sensitivity (0.587) and specificity (0.765), with an area under curve of 0.703 (95% interval confidence 0.587–0.819). DUP shorter than 60 days was related to better outcome at 2-year follow-up (c-GAF score above 70) (Chi-2: 7.662, p=0.006).
Conclusion: A DUP shorter than 60 days was related to better outcome in first episode EOP. These findings support the importance of early detection programs, which help shorten DUP.
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ID: 2118812

PSYCHOSOCIAL FUNCTIONING AND QUALITY OF LIFE IN SCHIZOPHRENIA AND BIPOLAR-I-DISORDER

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Background: Schizophrenia and bipolar disorder rank among the leading causes of disability worldwide. This study aims to highlight potential differences in psychosocial functioning and quality of life between these two patient-groups.
Methods: We present preliminary data of an ongoing cross-sectional study on social functioning and quality of life in outpatients suffering from schizophrenia or bipolar-I-disorder. Psychosocial functioning was assessed by means of the German version of the Global Assessment of Functioning Scale (GAF) and the Personal and Social Performance Scale (PSP). Quality of life was assessed using the German version of the Lancashire Quality of Life Profile, the Berliner Lebensqualitätsprofil (BELP).
Results: So far, 46 schizophrenia patients (26 males, mean age 45.9 ± 10.3 years, mean PANSS score 53.4 ± 12.9) and 54 bipolar patients (31 males, mean age 46.6 ± 11.7 years, mean MADRS score 6.7 ± 6.4, mean YMRS score 3.4 ± 4.4) have been included. Schizophrenia patients showed significant lower psychosocial functioning scores than bipolar patients (GAF: 59.7 ± 12.6 vs. 67.0 ± 14.0, p=.004; PSP: 60.6 ± 13.7 vs 68.9 ± 13.2, p=.008), whereas the two groups did not differ in any of the quality of life subscales.
Conclusion: Personal and social functioning is an important treatment target in patients suffering from schizophrenia and bipolar-I-disorder. Our results highlight the need of disease-specific interventions for the improvement of the psychosocial functioning level. Further investigations are needed to explore the relationship between quality of life and psychosocial functioning in both of our patient samples.
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ID: 2085285

TRANSITIONAL CARE: THINKING OUTSIDE THE BOX

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Background: The time of transition from hospital to community services is particularly critical for individuals with severe mental illness. As many as 40% of patients do not attend any outpatient visits in the 30 days following discharge. The Association of Community Psychiatry developed guidelines for transitions in behavioral health care. We describe concrete ways in which a transitional care clinic (TCC) designed to take care of individuals with SMI in the immediate post-discharge period (up to 90 days) has addressed these guidelines to improve transitions.
Methods: 1) Active outreach to inpatient units. TCC staff meet with patients, families and inpatient staff prior to the individual's discharge. Hospital staff use a web-based system available 24-hours/day to make intake appointments at the TCC that are convenient for the patient and upload documentation to ensure continuity of care. TCC staff call all patients prior to the initial appointment to identify any barriers to attendance, and contact all who miss their initial appointment. 2) Rapid access to services via a group intake procedure. Rather than provide individual intake appointments, patients are seen in small groups run by a multidisciplinary team. Each person briefly describes reasons for admission to the hospital and immediate needs, such as lack of medication, substance use treatment, housing, insurance). Group process is followed by a staff huddle to assign individuals to appointments based on the immediacy of their needs. Individuals are given a person directed plan containing all initial appointments (psychiatric, counseling, and care coordination), care coordination goals and a preliminary transition plan to the next level of care. 3) Cognitive Adaptation Training (CAT), the use of in home environmental supports, established on weekly to twice weekly visits to help individuals follow through with treatments, cope and obtain services.
Results: The TCC has been in operation for 2 1/2 years seeing over 2000 individuals in transition. Initial data support a significant decrease in preventable hospital readmissions, and a 85% follow through with first prescriber appointments after the intake process. Despite all of the efforts to get individuals to initial intake, show rates for the access group remain at approximately 50%.
Conclusion: Successful transition requires novel approaches to meet individual needs. Future goals include providing transportation
ID: 2085902

SUBJECTIVE RESPONSES TO AFFILIATIVE INTERACTIONS IN SCHIZOPHRENIA: EXAMINING THE CONTRIBUTIONS OF NEGATIVE SYMPTOMS AND PLASMA OXYTOCIN

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Background: Negative symptoms in schizophrenia are related to substantial deficits in social functioning. Although laboratory studies indicate that negative symptoms are not associated with impaired hedonic responding to laboratory stimuli, few studies have examined responding to affiliative social interactions. In this study, we sought to examine if higher negative symptoms are related to diminished pleasure and interest in response to a standardized affiliation interaction. Further, given findings that oxytocin (OXT) may be associated with individual differences in affiliation, we sought to determine if lower plasma levels of OXT contribute to negative symptom severity and less positive subjective responding within an affiliative interaction.
Methods: Negative symptoms and plasma OXT were measured in 56 individuals with schizophrenia prior to completing a role-play task intended to elicit affiliation and positive affect. Following the role-play task,

participants completed self-report measures of positive and negative mood and subjective reactions to the partner.
Results: Negative symptom severity was not related to post-interaction self-reported mood, reactions to the partner, or willingness to interact with the partner in the future. Plasma levels of OXT were not related to negative symptoms severity nor was OXT related to mood or to subjective reactions to the partner after the role-play.
Conclusion: These results indicate that clinical ratings of anhedonia and asociality are not related to subjective responding to affiliative interactions. OXT does not appear to be informative in understanding negative symptoms or subjective responding to social interactions within schizophrenia. Behavioral ratings of social skill and their relation with symptoms and plasma OXT will be examined. This research was funded by an NIMH grant to W. Carpenter.
ID: 2117888

THE ROLE OF FAMILY INTERVENTION IN COORDINATED SPECIALTY CARE FOR FIRST EPISODE PSYCHOSIS

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Background: There is growing interest in the US in providing coordinated, specialized care tailored to meet the needs of individuals experiencing a first episode of psychosis. This speciality care often has several components, one of them being famiy work to enhance the recovery environment..
Methods: The Recovery After an Initial Schizophrenia Episode (RAISE) project is an NIMH-funded 34 site randomized controlled trial evaluating the benefits of participation in a multicomponent pharmacological and psychosocial intervention, NAVIGATE, on clinical and functional outcomes after a first psychotic episode. One key NAVIGATE psychosocial component is a comprehensive individual family program including engagement, assessment, illness education, follow-up, and skills-training customized to participant need. The intervention is grounded in a resilience framework and much of the content reinforces the individual resiliency training offered to individuals in NAVIGATE.
Results: This presentation will provide an overview and rationale for this family intervention, as well as a description of key components. Data on uptake and participant characteristics will also be presented.
Conclusion: While the family program in NAVIGATE could be successfully implemented with many study participants, there were also challenges. Particular attention will be paid to highlighting clinical issues which emerged in conducting the NAVIGATE family intervention and require attention when working with early psychosis in families. These topics include the impact of divorce and blended families of origin on engagement, family members who use illicit substances with the consumer, relatives who are highly ambivalent or hostile towards use of the consumer's antipsychotic medication, and role strain and distress in conjugal partners of individuals experiencing an initial psychotic episode.
ID: 2141449

PSYCHOLOGICAL TREATMENTS FOR EARLY PSYCHOSIS CAN BE BENEFICIAL OR HARMFUL, DEPENDING ON THE THERAPEUTIC ALLIANCE: AN INSTRUMENTAL VARIABLES ANALYSIS

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Background: The quality of the therapeutic alliance (TA) has been invoked to explain the equal effectiveness of different psychotherapies, but prior research is correlational, and does not address the possibility that individuals who form good alliances may have good outcomes without therapy. Before the 1990's, psychological therapies for people with psychosis and schizophrenia were widely held to be ineffective and potentially harmful. Since then, meta-analyses of the many randomized controlled trials have indicated that CBT delivered in addition to routine care is more effective in improving symptoms than routine care alone. However, these trials often report positive results for non-specific psychological therapies (counselling, befriending) used as controls, which also turn out to be better than routine care alone.
Methods: We evaluated the causal effect of TA using instrumental variable (structural equation) modelling on data from a three-arm, randomized controlled trial of 308 people in an acute first (80%) or second (20%) episode of a non-affective psychosis. Patients aged 21–35 were recruited (67% male). The trial compared CBT over 6 weeks plus routine care (RC) versus supportive counseling plus RC versus RC alone. Subjects met DSM 4 criteria for schizophrenia or schizophreniform disorder. Follow-up rates were high (73%). We examined the effect of TA, as measured by the client-rated CALPAS, on the primary trial 18 month outcome of symptom severity (PANSS), which was assessed blind to treatment allocation.
Results: Both adjunctive CBT and SC improved 18 month outcomes, compared to RC. We showed that, for both psychological treatments, improving TA improves symptomatic outcome. With a good TA, attending more sessions causes a significantly better outcome on the PANSS total (effect size -2.91, 95% confidence interval -0.90 to -4.91), With a poor TA, attending more sessions is detrimental (effect size +7.74, 95% confidence interval +1.03 to +14.45).
Conclusion: This is the first ever demonstration that therapeutic alliance has a causal effect on symptomatic outcome of a psychological treatment, and that poor TA is actively detrimental. This has implications for training and quality assurance, at least with respect to psychosis. These effects may extend to other therapeutic modalities and disorders.
ID: 2117800

EXPOSURE TO TOBACCO-RELATED CUES DOES NOT ENHANCE CRAVINGS IN PATIENTS WITH PSYCHOTIC DISORDERS RELATIVE TO CONTROL SMOKERS

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Background: Rates of tobacco smoking in patients with psychotic disorders are strikingly high (70–90%). Moreover, successful cessation rates continue to be poor (9%). It is known that exposure to smoking-related cues (e.g., seeing a lit cigarette) enhance cravings in dependent smokers. It is unclear whether these same cues affect psychosis smokers in the same way or as intensely as in non-psychosis smokers. Since successful smoking cessation is predicted by control over smoking cue reactivity, a greater understanding of cue reactivity and ways of controlling these responses may lead to more specific treatment strategies and enhanced treatment outcomes.

The aim of this study was to examine cue reactivity to smoking-related cues in dependent smokers, comparing psychosis patients and non-psychosis (healthy control) subjects. We hypothesized that psychosis smokers would have an enhanced reactivity to the smoking video cues relative to the control smokers.
Methods: Dependent smokers were presented with short video clips of people smoking (smoking cue condition) and people getting hair cuts (neutral cue condition). The neutral cues always preceded the smoking cues. The degree of craving and withdrawal symptoms were compared at baseline, after the neutral cue video and then post smoking cue video using the Questionnaire for Smoking Urges Brief (QSUB) and a visual analogue scale (VAS) to quantify craving.
Results: Twenty (16 male) psychosis patient smokers (mean age 26.5 sd 5.7) and 30 (20 male) healthy control smokers (mean age 27.5 sd 6.8) took part in the study. For VAS ratings of 'like cigarette', and QSUB factor 1 (intention to smoke), significant increases in ratings were noted in controls (but not in patients) after viewing the smoking video compared to the neutral video. For VAS ratings of 'crave cigarette' the cue main effect was significant, with both groups showing greater cravings after the smoking cues relative to neutral cues. No significant main effects nor interactions were noted on QSUB factor 2 (withdrawal relief). In all cases, patients' ratings were lower than control subjects'.
Conclusion: In contrast to our hypotheses, smoking cues enhanced craving ratings that were greater in controls than in patients. This pattern suggests that patients may not be affected by tobacco cues as are healthy control subjects. These results have implications for treatment planning.
This work was funded by Canadian Institutes of Health Research and the Nova Scotia Health Research Foundation.
ID: 2117616

FACILITATING ENGAGEMENT AND HOPE TO PROTECT AGAINST SOCIAL DISABILITY: THE EARLY YOUTH ENGAGEMENT (EYE) PROJECT AND BEYOND

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Background: This study aimed to determine the factors influencing engagement of young people in early intervention in psychosis (EIP) services, and specifically, the role of hope in promoting engagement and social inclusion.
Methods: First, a cross-sectional qualitative study investigated facilitators and barriers to engagement from the perspective of EIP service users, their relatives and healthy young people. Forty focus groups/individual interviews were conducted, and thematic analysis was applied to the transcribed data. A delphi consultation with 27 clinicians, managers and experts, enabled the development of a new Early Youth Engagement service model. Second, a cross sectional study investigated the role of positive (social and occupational hope) and negative (defeatist social and performance) self-beliefs on social inclusion in 387 healthy young people. These relationships were explored in youth (aged 14–18: n= 152) and older people (aged 19–36: n = 235). Finally, a longitudinal study of 51 service users and their lead clinician explored the role of the therapeutic relationship in promoting hope and social inclusion.
Results: Thematic analysis revealed that facilitators to engagement include (i) transparent, hopeful communication; (ii) socially inclusive practice; (iii) open, accessible services (iv) positive goal-directed, hope inspiring relationships with staff, and (v) engagement-oriented personal characteristics. Structural modelling confirmed that social inclusion was influenced by both positive and negative self-beliefs, but whilst negative self-beliefs were higher in younger people, only positive hopeful beliefs influenced social inclusion in this young age group (14–18 years). Social inclusion for older people (19–36 years) was impacted also by negative beliefs. Path analyses in psychosis demonstrated that hope-inspiring therapeutic relationships facilitated social inclusion (and occupational) outcomes, whilst negative beliefs and self-stigma reduced social inclusion.
Conclusion: Strategies to promote engagement and enhance hopefulness may protect against social disability in young people with psychosis.
ID: 2117487

SMOKING STATUS AND ITS RELATIONSHIP TO CLINICAL AND DEMOGRAPHIC CHARACTERISTICS IN FIRST EPISODE PSYCHOSIS

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Background: Elevated rates of cigarette smoking are observed prior to the onset of psychosis and remain stable in the early stages of illness. Cannabis use frequently co-occurs with cigarette smoking and is associated with deleterious outcomes. Nevertheless, past research has failed to control for cannabis use in cigarette smokers with first episode psychosis, making it difficult to draw meaningful conclusions on the unique contribution of cigarette smoking to the clinical profiles of these patients.
Methods: One hundred and sixty-three patients consecutively admitted to a specialized treatment program for first episode psychosis were divided into three groups according to their current smoking status: non-smokers (0 cigarettes/day; n=73), light/moderate smokers (1−19 cigarettes/day; n=62), and heavy smokers (≥ 20 cigarettes/day; n=28). Smoking status, demographic characteristics, psychiatric symptoms, and global functioning were assessed at program entry.
Results: The prevalence of cigarette smoking in the present study was 55% at baseline. Cigarette smoking was highly associated with frequency of cannabis use. After controlling for frequency of cannabis use, significant between-group differences emerged with respect to clinical and demographic factors. Heavy cigarette smokers were older than light/moderate and non-smokers at program entry, $F(2, 156)=3.48$, $p=.03$, and had a later age of onset of psychotic symptoms than light/moderate and non-smokers, $F(2, 135)=3.98$, $p=.02$. In addition, heavy smokers had a longer duration of untreated illness than light/moderate smokers, $F(1, 122)=9.47$, $p=.003$. With respect to premorbid adjustment, light/moderate smokers exhibited lower functioning in early adolescence compared to non-smokers, $F(1, 75)=6.38$, $p=.01$. Depressive symptoms were higher for heavy smokers compared to non-smokers, $F(1, 155)=7.87$, $p=.006$. Positive, negative, and anxiety symptoms did not differ between groups. Non-smokers had better global functioning than light/moderate and heavy smokers, $F(2,138)=6.55$, $p=.002$.
Conclusion: The present study supports and extends past research by demonstrating that tobacco and cannabis use is prevalent in first episode psychosis, and that cigarette smoking status is associated with differential clinical and demographic characteristics. Prospective, longitudinal studies are needed to better understand the clinical implications of tobacco use and factors that contribute to the initiation and continuation of smoking in the early stages of illness.
ID: 2118894

UNDERSTANDING COMPLEX FAMILY INTERACTIONS IN EARLY EPISODE PSYCHOSIS

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Background: Family support is a pillar of early intervention services in psychosis; however, little is known about the factors that initiate and maintain adaptive family functioning in this population. Family functioning is conceptualized as a combination of family cohesion and flexibility in response to stress.
Methods: This study employed two methodologies to examine family functioning: (1) a survey that asked caregivers about their experiences, coping strategies, family satisfaction, as well as use and perceived helpfulness of community resources; and (2) an experimental study of the affective states and dynamic flexibility of family interactions in real time.
Results: Findings of the survey revealed that caregivers of a family member with early episode psychosis report more rigid and chaotic ($\chi2=10.11$, p=.017) and less cohesive ($\chi2=11.45$, p=.003) family structures compared to healthy control families. Furthermore, in families with an individual with psychosis, negative appraisals about one's caregiving role was correlated with more frequent use of maladaptive coping strategies (r=.43, p=.002), whereas positive appraisals about one's caregiving role was associated with greater perceived helpfulness of community resources (r=0.39, p=.006). A stepwise regression revealed that greater perceived helpfulness of resources and the use of positive coping strategies were predictive of adaptive family functioning in families with an individual with early episode psychosis.
The experimental component of this study is the first to employ state space grid (SSG) analysis to families with an individual with psychosis. A SSG is a visual model of the complex behavioural patterns that the family system has developed over time, such as the real time pattern of affective states (e.g., affection, interest, tension, hostility). Participants were video recorded, and the authors will present a visual graphic SSG analysis of the family interaction patterns that emerged during family discussions.
Conclusion: The results of this study have potential implications for the field of early intervention in psychosis, and could inform relevant treatment targets for family-based intervention.
ID: 2086350

INVESTIGATING THE UTILITY OF A BRIEF MEASURE OF FUNCTIONAL CAPACITY IN SCHIZOPHRENIA

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Background: Despite advances in treatment, persons with schizophrenia continue to experience poor functioning. Research shows that cognitive deficits are related to functional impairments in schizophrenia. As such, researchers have developed tests of functional capacity that more closely resemble tasks of daily life versus the abstract constructs used in cognitive tests. To date, findings are mixed regarding the efficacy of such measures. Our ongoing research explored the utility of a brief performance-based test of functional capacity in assessing functionality in schizophrenia.
Methods: 25 outpatients with schizophrenia or schizoaffective disorder were assessed for real-world functioning with the Multidimensional Scale of Independent Functioning (Jaeger et al., 2003), which yields global ratings for role position (level of responsibilities for a given role),
Results: Having fewer role responsibilities was significantly correlated with greater deficits in both procedural (r=.42, p=.036) and executive knowledge (r=.51, p=.009). Global support was positively correlated with symptom severity in general (r=.50, p=.013), and depressive symptoms in particular (r=.61, p=.002). No significant correlations were found for global performance. Last, greater disability in overall real-world functioning was significantly related to greater deficits in executive knowledge (r=.40 p=.048). No other significant correlations were found.
Conclusion: The COALS-B outperformed other measures related to functionality as it was the only test significantly related to various aspects of real-world functioning among schizophrenia patients. These preliminary results lend support to the utility of a brief measure of functional capacity as a practical and informative tool for capturing functional ability in schizophrenia.
ID: 2080347

PREDICTORS OF SOCIAL OUTCOMES IN PEOPLE WITH SCHIZOPHRENIA: SOCIAL COGNITION, SOCIAL COMPETENCE, AND NEGATIVE SYMPTOMS

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Background: Social deficits are common in people with schizophrenia and the treatment of social skills deficits has been a long-time strategy. There has been an increase in interest in social cognition as both a determinant of social deficits and as a treatment target. However, negative (i.e., deficit) symptoms also contribute substantially to social dysfunction. Our previous research suggested that negative symptoms account for more variance in social outcomes than social competence, raising the question as to whether assessment of social cognition would improve the prediction of social outcomes.
Methods: In this study, we examined the prediction of social outcomes by negative symptoms, social competence, measured with a performance based assessment, and 6 different social cognition measures in 198 patients with schizophrenia. These measures were selected as the best outcomes measures to date in with a RAND panel procedure. Social outcomes were rated by a high contact clinician who was unaware of the rest of the data collected. We examined the influences of social cognition on social competence as well as as the prediction of social outcomes with social cognition, social competence, and negative symptoms.
Results: The combination of social cognition, social competence, and negative symptoms accounted for 30% of the variance in social outcomes. Social cognition accounted for 20% of the variance in social competence. When we used a step-wise model to identify the individual negative symptoms and social competence domains that predicted social outcomes, we found that active social avoidance was the best predictor of social deficits (12% variance), followed by social competence (8%), emotion recognition(Bell-Lysaker emotion Recognition test: 5%), and blunted affect (5%). When we examined social cognition variables alone, the overall variance accounted for was unchanged, suggesting that social cognition did not overlap with negative symptoms.
Conclusion: These data suggest that negative symptoms exert a substantial influence on social outcomes and that social competence and social cognition also exert independent influences. As would be expected, deficits in social cognition, particularly emotion recognition, are associated with impairments in social skills. Treating negative symptoms appears to be a possible path for improving social outcomes and one that may have a larger impact than interventions aimed at either social cognition or social competence alone.
ID: 2079310

SOCIAL COGNITION AND INTERACTION TRAINING (SCIT) FOR DEAF PEOPLE WITH SCHIZOPHRENIA: PRELIMINARY FINDINGS

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Background: SCIT is a manual-based group intervention designed to improve social cognition (SC) in schizophrenia (SCZ). Previous research has revealed that SCIT improves emotion perception and theory of mind (ToM), two SC domains consistently related to functional outcomes. Ongoing work by this researcher and others aims to evaluate SCIT's effectiveness in reducing SC deficits. This pilot study was novel; its purpose was to examine the intervention's feasibility and effectiveness with deaf subjects. It was hypothesized that SCIT would be well tolerated due to its emphasis on social interaction and role-play.
Methods: Subjects were recruited from a psychiatric center in NY. A total of 6 people completed the training (3 with SCZ and 3 with other psychotic disorders). Two fluent signers facilitated the intervention. An uncontrolled, pre-post design was employed and outcomes were evaluated by symptom and client satisfaction ratings; cognitive and SC outcome measures assessed emotion perception, ToM, visual-spatial and word memory. Dependent sample t-tests were analyzed for each variable (pre-/post-test scores, one-tailed, $p<.10$); intra-individual effect sizes were estimated using Cohen's d.
Results: Client satisfaction ratings revealed a high level of acceptability for SCIT. There was a significant reduction in affective and thought disorder symptoms for all subjects from pre- to post testing (change in mean [ΔM])=.42, $p<.10$, d= -1.09; ΔM=.17, $p<.10$, d=-1.09, respectively). Word memory ability improved significantly for all participants (ΔM=10.67, $p<.10$, d=.82), while a trend level reduction was apparent in levels of visual-spatial memory (ΔM=4.5, $p<.12$, d=.67). Among SCZ patients, large effect sizes and significant (positive) intra-individual differences in pre- and post-test scores were found for emotion perception (ΔM=5.34, $P<.05$ d=4.62) and ToM (ΔM=3.34, $p<.05$, d=1.44).
Conclusion: Subjects who received an adaptation of SCIT showed a significant reduction in affect and thought disorder symptoms. SC improved only in patients with SCZ, suggesting that SCIT is particularly effective with this population. This study provides preliminary evidence that a modified version of SCIT can be used effectively with deaf people. Practice implications relate to expanding opportunities for deaf individuals to participate in meaningful treatment experiences, like SCIT, that broaden social interactions and create opportunities to engage with high-level signers.
ID: 2117981

EXPERIENTIAL RECOVERY, CLINICAL, AND PSYCHOSOCIAL FUNCTIONING IN PEER SPECIALISTS WITH SERIOUS MENTAL ILLNESS

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Background: Qualitative studies suggest that peer specialist training, while primarily geared towards preparing peer specialists to provide services to others, may be secondarily beneficial to peer specialists themselves by enhancing their own recovery, coping, and community functioning. The current study quantitatively examined the benefits of being active as peer specialist on recovery, psychopathology, and community outcomes and the possibility that enhanced recovery attenuates the impact of stressors and psychopathology on community functioning.
Methods: Participants were 84 peer specialists with schizophrenia, schizoaffective disorder, bipolar disorder, or major depressive disorder. Participants completed the Maryland Assessment of Recovery in Serious Mental Illness, the Social Functioning Scale, and the Social Support Questionnaire, the Brief Symptom Inventory, Brief COPE, the Internalized Stigma of Mental, and an episodic stressors index. We classified and compared active (n=49) versus inactive (n=35) peer specialists on the outcome measures using a MANOVA. We examined the putative mediating role of recovery on the impact of stress on psychopathology and community functioning using Mediated Multiple Regressions.
Results: There was a significant main effect of activity status on overall community functioning; recovery; and internalized stigma. Active peer specialists were more likely to interact with others and engage in activities that require competence such as searching for a job. Active peer specialists endorsed greater hope and empowerment than peer specialists who were inactive and were less likely to endorse common stereotypes about people with mental illness and more likely to resist stigmatizing attitudes. There were no significant differences in psychopathology or coping; however, effect size differences tended to fall in the small to moderate range for most outcomes in favor of active peer specialists. In the mediation models, recovery fully mediated the association between life stressors and psychopathology and the association between psychopathology and community functioning.
Conclusion: Results preliminarily support the assertion that explicit training in recovery philosophy and opportunities to serve in a professional role enhances recovery, community living, and clinical outcomes for people with schizophrenia and other serious mental illnesses. Future randomized control trials of peer-led interventions should seek evidence of their benefits in care recipients and peer providers.
ID: 2094010

FUNCTIONAL LEVEL, QUALITY OF LIFE AND COGNITIVE DEFICITS IN OUTPATIENTS WITH SCHIZOPHRENIA

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Background: We tried to find the relationships between a few indicators of actual psychopathology, quality of life, functional capacity and cognitive performance in patients with schizophrenia.
Methods: We conducted a non-interventional, cross-sectional study of patients with schizophrenia in outpatient care unit. 27 patients were included. The patients were examined with the battery of cognitive tests: RAVLT, Stroop Task, London Tower, NART and TMT. The functional capacity was measured by PSP scale, quality of life by WHO QOL - BREF and SOS-10. We followed actual psychopathology by PANSS. Relationship between variables was due to small sample calculated as nonparametric Spearman's correlation coeficient.
Results: We found significant correlations ($p < 0,05$) in a few of observed parameters. There was a correlation between total PSP score and some cognitive functions: immediate recall ($\rho = 0,692$), retention and delayed recall ($\rho = 0,494$). Quality of life was correlated with premorbid intelligence (NART). The correlation was significant in domains 1 ($\rho = 0,489$) and 3 ($p = 0,413$). The PSP-A, B and C and PSP total score are all correlated with PANSS N1-7, G1-16 and PANSS total except of relationship between domain C and PANSS G1-16 that is non-significant. There is also a close relationship between PANSS and QOL or SOS. SOS score was correlated with PANSS N1-7 ($\rho = 0,436$) and PANSS P1-7 ($\rho = 0,434$). QOL domain 1 was correlated with PANSS N1-7 ($\rho = 0,479$), G1-16 ($\rho = 0,559$) and PANSS total score ($\rho = 0,517$). QOL domain 3 was correlated with PANSS P1-7 ($\rho = 0,467$). QOL domain 4 was correlated with PANSS G1-16 ($\rho = 0,552$) and PANSS total score ($\rho = 0,437$). Finally, we found significant correlation between QOL and PSP scale. Specifically there was a relationship between QOL domain 1 and 4 and PSP-B subscale ($\rho = 0,549$; $\rho = 0,454$).
Conclusion: We proved significant correlation between functional capacity and cognitive deficit in items of attention and memory. There is a lower quality of life in patients with higher premorbid IQ. As the WHO QOL - BREF is self-assessing questionaire, we suppose that these patients are more critical to their current quality of life. Actual psychopathology, except of positive symptomatology, is correlated with functional level. The actual

psychotic symptoms have also an influence on the quality of life and specifically, the positive symptoms have impact on social relationships. The level of interpersonal relationships is important for patients quality of life.
ID: 2117853

SYMPTOM REMISSION AND QUALITY OF LIFE DOMAINS AMONG PERSONS WITH FIRST-EPISODE PSYCHOSIS IN CHENNAI, INDIA

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Background: We investigated Quality of Life (QOL) in a sample of individuals experiencing first-episode psychosis (FEP) in India and examined how personal and illness characteristics and antecedents to psychosis are related to QOL. There is a growing body of literature examining the predictive validity of the consensus criteria for symptomatic remission with respect to functional outcomes in FEP. Few studies have studied the validity of these criteria for subjective QOL. This study also addresses this gap, investigating the impact of treatment on self-reported QOL in a FEP sample from India
Methods: Patients presenting to a FEP clinic in Chennai, India were included. The Wisconsin QOL Scale, providing self-assessment of 9 domains, was administered at entry and one year after treatment. Data were collected on duration of untreated psychosis, symptoms, anxiety, depression, and global functioning at baseline and Months 3, 6 and 12. Regression analyses and t-test analyses were conducted to: a) determine the contribution of personal, illness and antecedent factors to overall QOL and QOL domains at baseline; and b) test the contribution of symptom remission (consensus criteria) to QOL one year post-treatment, controlling for established predictors of QOL; and changes in QOL, respectively.
Results: Participants rated moderate dissatisfaction with occupation, psychological well-being and physical health; in other domains, they were undecided or mildly satisfied. Multivariate regression yielded a significant model for overall weighted QOL with global functioning and anxiety as the most significant predictors. At 12 months, patients were mildly or moderately satisfied in most QOL domains, with higher ratings in social relations and symptoms. Except physical health, remitted compared to non-remitted patients reported higher scores on all QOL domains. In regression analyses, remission status was the largest significant predictor of overall QOL and all QOL domains, except physical health and money. At one year post-treatment, there were significant improvements in all QOL domains and overall QOL.
Conclusion: Participants reported greatest satisfaction with social relations, and were dissatisfied with their occupation, which may be partially due to culturally-driven family and societal structures. Given the positive impact of remission on patients' subjective QOL, achieving and maintaining it must be critical targets in the treatment of FEP.
ID: 2090047

AN EXAMINATION OF SUICIDE RISK FACTORS IN PSYCHIATRIC INPATIENTS WITH PSYCHOTIC DISORDERS

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Risk Factor	t	df	p
Perceived burdensomeness*	-2.691	102	.008
Thwarted belongingness	-0.522	101	.603
Suicide ideation*	-2.751	100	.007
Previous suicide attempts	-1.214	78	.229
Problem-solving*	2.610	104	.010
Executive functioning	-4.711	106	<.001

Background: Suicide is the tenth leading cause of death in the U.S. (CDC, 2014), and those with serious mental illness (e.g., schizophrenia) are at greater risk for suicide than the general population (Conwell et al., 1998). Risk factors for suicide in psychiatric inpatients include suicide ideation (SI) and cognitive difficulties (Huber et al., 2012; Kaviani et al., 2005; Wenzel et al., 2011). Perceived burdensomeness (PB; i.e., believing that one is a significant liability to others; Joiner, 2005) and thwarted belongingness (TB; i.e., a lack of reciprocal caring social relationships; Joiner, 2005) have been linked to elevated SI in psychiatric inpatients (Monteith et al., 2013). However, no research has explored PB and TB in a sample with serious mental illness, and relatively little has examined other risk factors in this population. Social and cognitive disruptions are often associated with both psychotic disorders and suicide (Conwell et al., 1998); therefore, we hypothesized that psychiatric inpatients with psychotic disorders would have elevated previous suicide attempts, SI, PB, TB, executive functioning, and problem-solving compared to those without such disorders.
Methods: Psychiatric inpatients admitted for elevated suicide risk (N = 109; n = 10 with psychotic disorders) were recruited. Participants completed self-report questionnaires and interviews to assess the variables of interest. T-tests were used to compare levels of each risk factor across two groups (those with psychotic disorders versus those without).
Results: Those with psychotic disorders evidenced poorer executive functioning and problem-solving, and elevated PB and SI. See table for details.
Conclusion: Psychiatric inpatients with psychotic disorders may be at even greater risk for suicide than psychiatric inpatients without psychotic disorders; therefore, it is critical to screen for current psychotic symptoms when assessing suicide risk. In addition, a newly examined risk factor, PB, may be important in this population, and interventions aimed at reducing PB, SI, and cognitive deficits may help reduce suicide risk.
ID: 2085023

VALIDATION OF A COMPUTERIZED ASSESSMENT OF FUNCTIONAL CAPACITY

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Background: Regulatory guidance for schizophrenia cognition clinical trials recommends that the assessment of cognitive change is accompanied by an assessment of a functionally meaningful endpoint. We have developed a computerized virtual reality assessment that contains the components of a shopping trip, including searching the pantry, making a list, taking the correct bus, shopping, paying for purchases, and getting home. Previous work has indicated that the assessment of functional capacity with virtual reality methodology is feasible and meets criteria for use as a co-primary measure in cognitive clinical trials. The primary aims of the current study were to: 1) assess the validity, sensitivity, and reliability of the Virtual Reality

Functional Capacity Assessment Tool (VRFCAT) as a primary measure of functional capacity in schizophrenia; 2) examine the VRFCAT's ability to quantify changes in functional capacity by comparing it to the UCSD Performance-based Skills Assessment (UPSA-2-VIM); and 3) determine the association between performance on the VRFCAT and performance on the MATRICS Consensus Cognitive Battery (MCCB).
Methods: Participants included 160 patients with schizophrenia (91 male, 69 female) and 158 healthy controls (80 Male, 78 Female). All subjects completed the VRFCAT, UPSA-2-VIM, and the MCCB at Visit 1. The VRFCAT and UPSA-2-VIM were completed again at Visit 2. Key outcome measures for the VRFCAT included total time to complete all objectives as well as errors. Analyses examined test-retest reliability as well as performance differences and correlations between measures.
Results: High test-retest reliability was demonstrated for VRFCAT Total Completion Time in both Patient and Control groups (ICCs= 0.80 and 0.78 respectively). Test-retest reliability for the UPSA-2-VIM was also high for both groups (ICCs= 0.77 and 0.78 for Patients and Controls, respectively). VRFCAT Total Completion time was negatively correlated with both UPSA-2-VIM ($r=-0.55$, $p<0.0001$ for patients and -0.65, $p<0.0001$ for controls) and MCCB Composite ($r=-0.50$, $p<0.0001$ for patients and -0.64, $p<0.0001$ for controls). A composite score will be developed once data collection has been finalized.
Conclusion: These findings extend previous results and indicate the VRFCAT is a highly reliable and sensitive measure of functional capacity with associations to the UPSA-2-VIM and MCCB. These results provide encouraging support for a computerized functional capacity assessment for use in schizophrenia.
ID: 2081367

THE EFFECTS OF ERRORLESS LEARNING ON WORK OUTCOME IN SCHIZOPHRENIA

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Background: Of the functional impairments common to schizophrenia, those affecting the ability to attain and maintain employment are perhaps the most challenging to overcome. It is widely substantiated that cognition is related to work outcome in schizophrenia; and a number of rehabilitation interventions currently target cognitive impairments with the aim of improving work outcome. Errorless learning (EL) is a behavioral training intervention designed to compensate for impairments in cognition by recruiting relatively intact cognitive processes to compensate for impaired ones.
Methods: The present findings were drawn from subsamples (schizophrenia or schizoaffective disorder outpatients) of two studies of EL and supported employment; one was conducted at a VA hospital (n=64) and the other was conducted at a community mental health center (n=40). At both sites, participants were recently registered in a supported employment program. Participants who got jobs were randomized (1:1) to receive EL or enhanced supported employment services to address difficulties in a work-related skill area identified after beginning the job. Participants were then followed for 12 months from the initial job start date. At the VA, training was conducted by VA employment specialists; at the community mental health center, training was conducted by research staff. Dependent measures of interest were work performance measured by the Work Behavior Inventory, and traditional work outcome measures of job tenure and wages earned.
Results: Group comparisons on work performance were analyzed using repeated measures ANOVA; group comparisons on wages earned were analyzed using independent t-tests; group comparisons on job tenure were assessed using survival analyses. The ANOVA results revealed a significant 3-way interaction (group x time x site) with differences in work performance favoring EL subsequent to training primarily due to differences at the VA site. There were no significant group differences in wages earned. However, results of the survival analysis revealed a significant effect favoring EL. Approximately 64% of EL participants stayed on their competitive community-based jobs the full 12-month period of follow-up compared to 36% of participants in the comparison group.
Conclusion: These results provide cautious optimism that the disabling effects of cognitive impairment on work outcome can be alleviated by behavioral training interventions such as EL.
ID: 2083573

FAIR DINKUM: FIDELITY TO A MODEL OF EARLY INTERVENTION IN PSYCHOSIS IN AUSTRALIA

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Background: Early Intervention for psychosis services were first developed in Australia in the early 1990s. Despite being adapted and adopted in many places internationally since then, the wide scale systematic implementation of early psychosis services in Australia has only been conducted in the last two years. The national roll out of a model of early psychosis intervention has been funded by the Commonwealth Government. As a condition of their funding this AUD$250 million reform, the Commonwealth have required the development of a fidelity measure.
Methods: The model of intervention services to be implemented was fully described in a manual developed as part of an earlier phase of work on this reform initiative. This model describes 16 core elements of early intervention for psychosis services. The fidelity scale in development will have capability to examine fidelity to these 16 elements in detail. An initial brief version will provide high-level estimates of fidelity.
Results: The focus of this presentation is on the development of the scale. It will highlight challenges in the development of a scale to measure fidelity of an intervention that is being nationally disseminated, in varying environments in the Australian context.
Conclusion: There has not been a national implementation of a single model of first episode psychosis intervention on such a geographical scale previously. While the model is based on 25 years of research, translation to sites in diverse regions requires the construction of a flexible yet accurate fidelity tool. Fidelity is an important construct both for ensuring that young people with first episode psychosis receive the highest level of care, and to ensure that funders get what they have paid for.
ID: 2117621

THE ETIOLOGY AND SPECIFICITY OF THE ASSOCIATION BETWEEN COGNITION AND COMMUNITY FUNCTIONING IN SCHIZOPHRENIA

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Background: Although cognition is one of the most important predictors of community functioning in schizophrenia, little is known about the causes of this association. This study is the first to our knowledge to examine the extent to which this correlation is genetically and/or environmentally mediated and its degree of specificity to schizophrenia.
Methods: 636 relatives from 43 multigenerational families with at least two schizophrenia relatives and 135 unrelated controls underwent diagnostic interview and community functioning assessment along with the Penn Computerized Neurocognitive Battery, Trail Making Test and California Verbal Learning Test. Factor analyses yielded one general cognition factor and one community functioning factor while a social cognition factor was calculated as an average of two tasks. SOLAR (Sequential Oligogenic Linkage Analysis Routines; Almasy & Blangero, 1998) was used to conduct family-based analyses quantifying genetic and environmental effects on the cognition/functioning association.
Results: As expected, among the 103 relatives with schizophrenia, there were both considerable deficits and variation in community functioning and cognitive performance and a significant correlation between the two ($Rp=0.335$, $p=0.005$). Shared genetic effects were significant contributors to this relationship ($Rg=0.956$, $p<0.001$) whereas idiosyncratic environmental experiences were not. In contrast, among the 258 relatives with no diagnosis, the cognition/functioning correlation ($Rp=0.333$, $p<0.001$) was significantly mediated by idiosyncratic environmental experiences ($Re=0.269$, $p=0.005$) but not by shared genetic effects. Furthermore, community functioning in schizophrenia was not significantly predicted by cognition among relatives with other diagnoses. Across all analyses, the contributions of social cognition to functioning were similar to and fully accounted for by general cognition.
Conclusion: The association between general cognition and community functioning in schizophrenia is largely attributable to genetic factors specific to the disorder that also account for the association between social cognition and community functioning. These findings provide a foundation from which heritable factors contributing to community functioning in schizophrenia can be differentiated from those contributing to functioning in psychiatric disorders in general, which may inform the development of environmental interventions. Funding: NIMH MH63480, MH42191, MH61622
ID: 2084140

COMPARING TWO STRATEGIES FOR IMPROVING VERBAL EPISODIC MEMORY IN SCHIZOPHRENIA: THE ROLE OF NARRATIVE AND IMAGERY

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Background: Cognitive remediation (CR) is increasingly recognized as an effective means for producing small to moderate-sized improvements in cognitive skills in schizophrenia. However, existing treatments are complex and usually consist of practice on multiple exercises and application of many different strategies and thus the active ingredients of these interventions remain unknown. The current study was designed to investigate two brief, specific and alternative compensatory strategies for improving verbal episodic memory in schizophrenia (adapted from the head injury literature). The goal was to provide a rationale for inclusion in broader CR training batteries.
Methods: Forty participants with schizophrenia or schizoaffective disorder were randomly assigned to one of three groups: group one "the story method" consisted of presenting participants with to-be-learned words in the context of a detailed narrative. In condition two, participants were presented with pairs of words and asked to imagine these pairs of words interacting with one another, with no further narrative structure. In group three participants were exposed to the to-be-learned words an equivalent number of times, but without provision of a strategy. Outcomes were assessed with learning measures from the trained word-lists, as well as measures of generalization to both a word list task consisting of different words from those selected as part of the training, and a prose recall task. Assessments were conducted by blinded administrators both before and immediately after the intervention and at a one-week follow-up.
Results: Results revealed that the story method produced learning on the trained words that generalized to a prose recall task (but not a list learning task). This evidence of generalization, however, was only evident at the one-week follow-up. The imagery training, as well as repeated passive exposure to a word list in the non-trained condition, did not produce improvement on the list learning or prose recall outcome tasks.
Conclusion: These results support the potential role of narrative strategies for improving verbal episodic memory in programs of CR for schizophrenia. These findings also suggest that the effects of these strategies may require consolidation over time.
ID: 2118194

EXPERIENCING PERSECUTION AS A CONSEQUENCE OF FEELING LONELY? AN EXPERIMENTAL DESIGN TO INVESTIGATE THE RELATIONSHIP BETWEEN INDUCED FEELINGS OF LONELINESS, NEGATIVE AFFECT AND PARANOIA

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Background: In concordance with the vulnerability-stress model social environmental risk factors such as lack of social support have been investigated in the pathogenesis of psychosis. Epidemiological studies show evidence for a relation between loneliness and psychosis. The role of loneliness as an etiopathological factor of psychosis is largely unexplored with hardly scientific proof for loneliness as a causal factor of paranoia so far. Research shows that social exclusion triggers paranoid ideation in subclinical individuals. The present study assessed the direct impact of loneliness on paranoid beliefs using an experimental design. Moreover, it was investigated whether negative affect mediates and proneness to psychosis moderates the association between loneliness and paranoid beliefs.
Methods: A nonclinical population sample (n=60) was randomly assigned to two experimental groups (EG1, EG2) and one control group condition (CG). In EG1, we induced a high level of loneliness by reporting a false feedback on a questionnaire that supposedly measured person's high level of loneliness. EG2 received the opposite feedback reporting a low level of loneliness. CG received a neutral feedback. Trait-psychosis was measured at baseline. State-adapted negative affect and paranoia beliefs were measured before and after the experimental conditions.
Results: Pre-post changes in self reported loneliness correlated moderately positive to pre-post changes in paranoia beliefs. After feedback of a low level of loneliness, there was a significant decrease of paranoia beliefs in EG2. Concordant with the hypothesis there was a trend indicating an increase of paranoia beliefs in EG1 (non significant). Proneness to psychosis proved to be a significant moderator on the relation between loneliness and paranoia beliefs. The postulated mediator effect showed not to be statistically significant, but by testing for interaction effects a moderator effect revealed: An increase in negative emotions led to higher relation between loneliness and paranoia beliefs.
Conclusion: In summary the experimental design showed a good feasibility in a subclinical sample. Paranoia depends subsequently on loneliness and proneness to psychosis and negative affect as moderators could be

proven. As a consequence of small effects sample size should be increased. Results need to be confirmed in a clinical sample to draw conclusions about the patient related processes between loneliness and paranoia in order to improve therapeutic interventions.
ID: 2092709

A GROUP COGNITIVE BEHAVIORAL INTERVENTION FOR PEOPLE REGISTERED IN SUPPORTED EMPLOYMENT PROGRAMS: CBT-SE

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Background: Supported employment (SE) programs are highly effective in helping people with severe mental illness obtain competitive jobs. However, job tenure is often brief. Among obstacles, dysfunctional beliefs regarding the workplace and one's own abilities have been identified. Objectives: The purpose is twofold: 1) to present the feasibility and acceptability of the intervention; 2) to investigate preliminary work outcomes.
Methods: A group CBT intervention of 8 sessions (one month) was tailored to facilitate the learning of CBT skills specific to the workplace. 160 participants registered in SE programs participated in a RCT (80 receiving the CBT-SE). Measures pertaining to work outcomes (hours and weeks worked) as well as pertaining to work-related constructs (motivation, self-esteem as a worker) were measured.
Results: Results: Preliminary results reveal that therapists and participants all mentioned finding the group useful and helpful. The only negative feedback was related to the frequency of the meetings (many would prefer one two hour session per week instead of two one-hour sessions). Participants attended on average 6/8 sessions. 50% of participants in both conditions obtained competitive work. The number of participants working more than 24 hours per week at the 12 month follow-up was higher in the CBT-SE group (75% vs 50%) and higher for those with early psychosis. There was also a trend towards a larger number of consecutive weeks worked for those having received CBT-SE (22.5 vs 18.3 weeks). More analyses are underway and will be presented.
Conclusion: Preliminary data suggest that the CBT-SE intervention might help participants use skills and gain the needed confidence enabling them to sustain their employment.
ID: 2084035

INSIGHT IN FIRST EPISODE PSYCHOSIS: THE RELATIONSHIP BETWEEN COGNITIVE AND CLINICAL INSIGHT AND SYMPTOMS

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Background: Insight is considered an important element of schizophrenia spectrum disorders and has been shown to be associated with recovery. The current study sought to examine the relationship between symptoms and two complementary, but not synonymous types of insight: clinical and cognitive in individuals with First Episode Psychosis (FEP). We hypothesized that clinical insight (awareness of illness, need for treatment, consequences of illness) would better predict positive symptoms than cognitive insight (ability to evaluate one's judgments and perceptions), because positive symptoms have been shown to be correlated with increased distress and may thus lead individuals with such symptoms to be more aware that they are experiencing difficulties and are in need of help. This has been found to be true in studies of chronically ill patients with schizophrenia.
Methods: The sample included 40 individuals diagnosed with schizophrenia, schizoaffective disorder, or psychosis NOS with their first psychotic break occurring within 5 years prior to data collection. Initially, clinical insight was assessed with the Scale to Assess Unawareness of Mental Disorder, cognitive insight was assessed with the Beck Cognitive Insight Scale, and symptoms were assessed with the Positive and Negative Symptom Scale.
Results: Factor analysis was employed to clarify insight constructs. Correlations were then run between all demographic factors (age, race, gender, and education) and insight factors. The only demographic factor that was significantly correlated with insight factor was age: r= -0.33, p=0.04, indicating that younger participants had less clinical insight. Results from the regression analysis showed that, when controlling for age, clinical insight significantly predicted positive symptoms, β= .41 t(2.55), p=.02, with overall model fit R^2= .10, F(2, 39)= 3.48, p=.04; as well as negative symptoms, β.65, t(5.08), p<.001, with overall model fit R^2= .46, F(2, 39)= 15.75, p< .001. Cognitive insight did not significantly predict symptoms.
Conclusion: Clinical and cognitive insight appear to have different relationships with symptoms for individuals with FEP. Clinical insight significantly predicted both positive and negative symptoms, after controlling for age, demonstrating that individuals with more clinical insight experienced less positive and negative symptoms. This relationship with symptoms and insight has implications that merit further exploration, including adapting treatment to reflect this relationship.
ID: 2084607

DEVELOPMENT OF COORDINATED SPECIALTY CARE TEAMS FOR EARLY PSYCHOSIS AT PARC

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Background: The impact of schizophrenia is substantial, as the disease is associated with poor psychosocial functioning, increased health service utilization, and high direct costs of care. Early intervention (EI) may improve all of these domains. An unprecedented opportunity to increase EI services was presented in January 2014 with the passage of the Consolidated Appropriations Act (P.L. 113–76), which provides funding to the Substance Abuse and Mental Health Services Administration (SAMHSA) to expand new initiatives for the treatment of early psychosis (EP). SAMHSA, in collaboration with the National Institute of Mental Health, has published evidence-based guidelines for the implementation of these programs through Coordinated Specialty Care (CSC) teams.
Methods: The Prevention and Recovery Center for Early Psychosis (PARC) is an EI program which has served over 500 individuals in the early stages of non-affective psychotic disorders since 2009. Utilizing the funding and implementation resources above, PARC has initiated three CSC teams composed of a physician, team leader, registered nurse, therapist, case manager, and a supported employment and education specialist. In addition, an education and outreach coordinator provides clinical outreach and education to community stakeholders about EP to enhance early detection and prompt referrals. Identified goals of the CSC teams are to a) provide comprehensive psychosocial and psychopharmacologic treatment to restore adaptive functioning, decrease relapse rates, and prevent suicide, b) provide primary care referrals, metabolic monitoring, and nicotine cessation

treatment to address morbidity and early mortality associated with psychotic disorders, c) enhance early detection, prompt initiation of treatment, and engagement for individuals in their first episode of psychosis via outreach and education.
Results: Baseline demographic variables (n=77 enrolled to date, mean age 21.7 yrs, 65 M/12 F), illness severity, psychosocial functioning, suicide attempts and completions, and health service utilization will be reported. Quarterly data will be presented, providing longitudinal information on functional and service utilization outcomes of interest.
Conclusion: As a result of expanded SAMHSA funding for EP, evidence based EI services can be implemented without marked administrative or economic burden and provides an opportunity to improve outcomes for patients in the early stages of psychosis.
ID: 2116550

PSYCHOTIC-LIKE SYMPTOMS AND PSYCHOSIS PREDICTION IN A GENERAL ADOLESCENT PSYCHIATRIC SAMPLE

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Background: We identified adolescents with Clinical high-risk (CHR) state from all adolescents who sought help from public psychiatric services in the capital of Finland, Helsinki, and investigated whether CHR status is as predictive of psychosis in these services as it is in services specialized for the treatment of psychosis prodrome. We wanted to gain information on psychotic-like symptoms and to investigate which symptoms predict psychosis and hospitalizations among adolescents in general psychiatric care.
Methods: The Helsinki Prodromal Study is a prospective study of psychosis risk among adolescent psychiatric patients. 731 adolescents aged 15–18 years were screened with the Prodromal Questionnaire (PQ) and 174 adolescents interviewed with the Structured Interview for Prodromal Syndromes (SIPS) and the SCID. Information on cognitive performance, functioning, depression, anxiety, and hopelessness were collected. The participants were followed via patient files and the national hospital discharge register for 3–9 years. Outcomes were hospital care for psychosis and any psychiatric disorder, and intentional self-harm or suicide.
Results: Of all who had filled in the PQ, 4.8% had been hospitalized for psychosis after three years. Of the interviewed sample, 35.6% met criteria for CHR and 4.7% converted to psychosis (8.5% of the CHR and 2.9% of the non-CHR group). Hospital admissions for psychotic disorder were predicted by SIPS Positive symptoms and PQ Depersonalization factor, but not CHR status. Any psychiatric hospitalization was predicted by CHR status, SIPS Positive and General symptoms, and PQ Role functioning factor. SIPS N3 Decreased expression of emotions predicted self-harm during follow-up.
Conclusion: Patients in a non-selected public health care sample report a lot of psychotic-like symptoms, but the CHR status is not specifically predictive of psychosis. Identifying and treating psychotic-like symptoms is important, as they can predict hospitalization and indicate a more serious disorder.
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ID: 2079002

THE DAILY ACTIVITY REPORT: A NOVEL MEASURE OF FUNCTIONAL OUTCOME FOR SERIOUS MENTAL ILLNESS

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Background: The assessment of treatment impact on real-world functional outcomes in clinical trials for medications targeting negative symptoms and cognitive impairment is extremely important. This study tested the psychometric properties of the Daily Activity Report (DAR), a novel assessment of productive daily activity.
Methods: We developed the DAR based upon a comprehensive review of available instruments assessing daily activity and functional outcome in schizophrenia and input from multiple stakeholders. We administered the DAR and additional assessments of functional outcome, functional capacity, cognition and symptomatology to 50 individuals with schizophrenia/schizoaffective disorder and 25 healthy controls at two time points, one month apart. The DAR records a person's daily activity for seven consecutive days based upon phone calls made three times a day. A total score and scores for complexity in three domains; instrumental domestic activities, social activities, and nondomestic work or school related activities are generated.
Results: Test retest reliability based on the Pearson correlation was .67 for the DAR Total and .45 for Instrumental Activity, .75 for Social Involvement and .48 for Non-domestic work (all p's <.0001). The ICC for the DAR total across one month was .80. For individual DAR scores the ICC were .62 for instrumental, .86 for social and .63 for non domestic work. Reliabilities are higher with shorter time intervals. The total DAR score as well as scores for social activity and non-domestic work/school differed significantly between control and patient participants (Z=6.45 P<.0001, Z=4.27 p<.0001; Z=6.84 p<.0001; respectively). Instrumental activity significantly differed by group only on weekends (when control participants were not at work). Total DAR score was significantly correlated with negative symptoms and community functioning. Functional capacity was correlated significantly with both Instrumental Activities and non-domestic work on the DAR. With respect to discriminant validity, total DAR scores were only weakly related to positive symptoms.
Conclusion: The study provides some support for the preliminary reliability and validity of the DAR. The development of the DAR for a patient reported instrument using smart phone technology is the next step.
ID: 2119240

VIOLENT CONTENT IN ATTENUATED PSYCHOTIC SYMPTOMS IN THOSE AT CLINICAL HIGH-RISK FOR PSYCHOSIS

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Background: The relationship between psychosis and violence has typically focused on what factors are likely to predict who will commit violent acts. A number of factors have been found to increase the likelihood of violent acts being committed by those experiencing psychosis including demographic variables, the experience of negative emotions, substance abuse, trauma and the duration of untreated psychosis. One unexplored area is an examination of violence in the content of positive symptoms. The aim of the current study was to examine violent content in the attenuated psychotic symptoms of individuals who are at clinical high risk (CHR).
Methods: The sample consisted of 442 CHR individuals who had attenuated psychotic symptoms (APS). CHR status was determined with the Structured Interview for Prodromal Syndromes (SIPS). The description of the APS symptoms was taken from comprehensive vignettes based on the SIPS and the Scale of Prodromal Symptoms. The content of these APS symptoms were coded as being present or absent using the Content of Attenuated Positive Symptoms (CAPS) Codebook. Measures included the Calgary Depression Scale for Schizophrenia, the Social Interaction Anxiety Scale, the Self-Rating Anxiety Scale, Global Functioning: Social & Role Scale, Alcohol/Drug Use Scale, Brief Core Schema Scale, trauma and, perceived discrimination.
Results: The sample was divided into those who presented with violent content in their APS (n=106) and those without (n=336). The groups did not differ on any of the measures nor in demographics. The only exception was that those who endorsed violent content were significantly younger than those who did not ($Z= -2.12$, $p < 0.05$). There were no differences in rates of conversion to psychosis between the groups.
Conclusion: There is no evidence of clinical or functional differences or differences in early experiences between CHR individuals who have violent content in their APS and those who do not. Further work in this area needs to explore violent content with actual behavior.
ID: 2091428

COMPARISON OF STIGMA ON MENTAL ILLNESS AND HIV/AIDS AMONG PEOPLE

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Background: As it is certain that Stigma plays an important role in ineffective treatment and early detection of HIV/AIDS and Mental illness, my study aimed in assessing the levels of stigma prevailing and comparing the duo for a better planning and outcome.
Methods: A descriptive survey approach, non-experimental comparative descriptive survey design was selected for conducting the study with non-probability convenient sampling technique. Total 100 samples were assessed using self structured stigma assessment scale.
Results: The comparison of levels of stigma between HIV/AIDS and Mental Illness revealed that majority of the selected participants fall under the category of Moderate stigma. The values projected were, out of total 100 samples 51% had moderate stigma and 49% high stigma towards mental illness where as in case of HIV/AIDS 54% has moderate stigma and 46% has high stigma. There is no significant difference between the two with 't" value 1.711, df (98) 1.982 at table value $P<0.05$. On assessing the correlation between stigma levels of mental illness and age, obtained $r =0.754$ was statistically significant at the level of $P<0.05$ showing strong positive correlation where as the tabulated value for Stigma levels of HIV/AIDS and age, $r=0.234$ at $p< 0.05$ showed weak correlation.
Conclusion: I conclude that since there is no much difference between the stigma levels of HIV/AIDS and Mental illness it is necessary to plan and implement health educations and interventional programs appropriate to the disease condition and evaluations has to be followed up.
ID: 2085085

SOCIAL FUNCTIONING IN INDIVIDUALS AT CLINICAL HIGH RISK OF PSYCHOSIS

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Background: There is accumulating evidence that individuals at clinical high risk (CHR) of developing psychosis typically have poor functioning and that poor functioning may be a predictor of later conversion to psychosis. Furthermore, even for those who do not go on to develop psychosis more that 50% continue to function poorly. The purpose of this study was to examine social functioning in a large sample of individuals at CHR of psychosis and to determine its role in conversion.
Methods: The sample consisted of 153 young people (64 females, 89 males) at CHR of psychosis, 27 of whom later developed psychosis. The sample was part of the PREDICT study which was a multisite project conducted at the Universities of Toronto, North Carolina and Yale. The Structured Interview for Prodromal Syndromes (SIPS) was used to determine criteria and the Scale of Prodromal Symptoms (SOPS) for determining severity of symptoms. Social functioning was assessed with Birchwood's Social Functioning Scale (SFS) which assesses seven domains of social functioning that include social engagement, interpersonal communication, performance, competence, recreation, prosocial behavior and occupation, as well as an overall score. Role functioning was assessed with the role functioning subscale and role satisfaction subscale from Heinrich and Carpenter's Quality of Life Scale (QLS).
Results: On average this sample demonstrated poor social functioning. Those who converted demonstrated significantly poorer functioning with respect to the overall score ($p<0.001$) and for 5 of the 7 sub scores namely interpersonal communication, performance, recreation, prosocial behavior and occupation (p values ranged from $p<0.01$ to $p<0.001$) on the SFS. Those who converted to psychosis also performed more poorly on the role function subscale of the QLS compared to those who did not convert. However, there was no difference between those who converted and those who did not on role satisfaction. Poor functioning was unrelated to attenuated psychotic symptoms but significantly related to negative symptoms ($p<0.01$).
Conclusion: This data supports earlier studies that demonstrated poor functioning in those who are at risk for psychosis. Those who make the transition to a full blown psychotic illness at initial assessment have poorer social and role functioning than those who do not; however this is more pronounced for social rather than role functioning.
ID: 2091901

ACUTE AND LONG-TERM EFFECTS OF PHYSICAL EXERCISE ON AFFECT IN FIRST-EPISODE SCHIZOPHRENIA PATIENTS

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Background: Depressive symptoms are a common feature in schizophrenia and are associated with increased rates of suicide and relapse, poorer social functioning, low motivation, and poor adherence to psychosocial interventions. Recently, there has been a growing interest in the impact of physical exercise on mental health. Studies suggest exercise may be an effective adjunctive treatment to combat depression during the early phase of schizophrenia. Additionally, exercise has few side effects and is an intervention method that is low cost, simple to implement, and less demanding of staff training compared to many other psychosocial interventions.
Methods: Sixteen patients with a recent first episode of schizophrenia from the UCLA Aftercare Research Program were randomly assigned to cognitive training (CT, N=8) or to cognitive training plus exercise (CT&E, N=8). Both groups completed computer-based neurocognitive and social cognitive training 4 hours/week. The CT&E group completed 2 hours/week of exercise in the clinic and two 30-min exercise sessions per week at home. To examine acute changes in mood we used the self-report Positive and Negative Affect Scale (PANAS, Likert Scale: 1–5) before and after a single exercise session (CT&E group) or before and after a cognitive training session (CT group) in the clinic. To examine the long-term outcome effects of exercise on mood, the Brief Psychiatric Rating Scale (BPRS, Scale: 1–7) was completed by a clinician at study baseline and at 8-week follow-up.
Results: Patients in the CT&E group experienced increased positive affect after their exercise session (M=+3.9, SD=7.0), whereas the CT group experienced decreased positive affect after a cognitive training session (M=-2.1, SD=5.6) (Cohen's d effect size=.94). Patients in the CT&E group also experienced a greater decrease in negative affect (M=-2.8, SD=5.3) than the CT group (M=0.0, SD=2.4) (Cohen's d=-.74). Regarding tonic mood states, the CT&E group had a greater reduction in depressive symptoms (M=-1.38, SD=1.69) than the CT group (M=-.13, SD=.99) (Cohen's d=-.90) at 2-month follow-up.
Conclusion: These results indicate that regular physical exercise leads to acute increases in positive affect and reductions in negative affect. These preliminary data suggest that exercise is a low risk, non-pharmacological means of producing clinical improvements in mood in first-episode schizophrenia patients. This study is ongoing at the UCLA Aftercare Research Program.
ID: 2083143

COGNITIVE ENHANCEMENT AND ILLNESS SELF MANAGEMENT IN VOCATIONAL REHABILITATION

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Background: The Thinking Skills for Work program (TSW) is a combined cognitive remediation and vocational rehabilitation (VR) program that incorporates restorative task practice and compensatory strategies to improve cognitive functioning and optimize work functioning. Five randomized controlled trials comparing TSW + VR vs. VR alone have shown that clients in TSW improved more in cognition than clients who received VR alone and had better work outcomes over a 18–36 months follow up. However, some participants, particularly those earlier in the course of their illness, have difficulty managing their illness, leading to relapses, hospitalizations, and disengagement from rehabilitation. The current study sought to explore the impact of integrating the Illness Management and Recovery Program (IMR), an evidence based practice for teaching clients how to manage and cope with their illness, with TSW for VR participants.
Methods: Sixty-one ethnically diverse clients (73% were ethnic minorities) with schizophrenia (75%) and other severe mental illnesses were randomized to receive TSW+IMR+VR (N=32) or VR alone (N=29), with comprehensive cognitive (MATRICS), symptom (PANSS), quality of life (QLS), and IMR Clinician and Client Scales of illness self-management skills administered at baseline, 9- and 18-month post-randomization, with 36 months of weekly tracking of work activity.
Results: High treatment exposure rates demonstrated the feasibility of integrating IMR with TSW and VR (88% received 6 or more cognitive sessions, and 78% attended 10 or more IMR groups), and were associated with significant improvements on MATRICS measures of working memory (F(1,42)=4.52; p=0.39), cognitive flexibility (F(1,42)=10.01; p=0.002), social cognition (F(1,42)=5.48; p=0.02), Client and Clinician IMR scales (F (1,39) =4.61;p=0.038; F (1,38) =2.87; p=0.09), respectively, PANSS Total (F(1,43) =8.31;p=0.006), and competitive work outcomes F(1,54)=6.52; p=0.01.
Conclusion: This study established the feasibility of integrating illness self management skills into the Thinking Skills for Work program in vocational rehabilitation participants, and demonstrated superior outcomes in targeted domains of cognition, illness self management, and employment.
ID: 2118963

"THE ROLE OF COACHING STRATEGIES IN MAXIMIZING BENEFIT FROM COGNITIVE REMEDIATION WHEN COMBINED WITH SUPPORTED EMPLOYMENT"

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Background: Practice of cognitive exercises is a core component of many cognitive remediation programs for persons with severe mental illness (SMI). Increasingly, task practice is supplemented with individually tailored suggestions, or strategy coaching, to aid performance improvements. Because of the individualized nature of teaching such strategies, a trained facilitator is needed to monitor cognitive exercise practice, which adds significantly to the costs of running cognitive remediation programs. However, the benefits of providing strategy coaching in addition to cognitive practice on cognitive performance or functional outcomes is not known.
Methods: The current analyses address this question by comparing performance on a standardized cognitive exercise curriculum drawn from training using Cogpack cognitive software in two groups of people with SMI who were receiving vocational rehabilitation services: 30 participants in a cognitive remediation program that included a trained facilitator who provided instructions on use of the software and strategy coaching, vs. 48 participants in another cognitive remediation program that included a trained facilitator who provided similar instructions on use of the program but no strategy coaching. Change in performance on a verbal learning task (a 6 item "shopping list" visually presented with 30 seconds of encoding time and immediate free recall, with different words used in the second presentation) initially presented in the first session of the cognitive program, and again in the 6th session of the program, was compared in the two groups of participants.
Results: Results were that the group receiving strategy coaching demonstrated significantly greater learning (M = 1.15 words improvement, SD = 1.9) than the group that did not receive strategy coaching (M = 0.46 words improvement; SD = 2.1).
Conclusion: These findings suggest that learning ability is enhanced by individualized teaching of strategies to facilitate learning above and beyond the effects of practice alone. To evaluate the generalizability of strategy coaching on Cogpack exercise tasks to independent measures of neuropsychological functioning, the two groups of study participants will also be compared on changes in standardized verbal learning and memory tests given at baseline and post cognitive training, and employment outcomes.
ID: 2119440

FACTOR STRUCTURE OF THE SCALE OF PRODROMAL SYMPTOMS AND EMPIRICAL DEVELOPMENT OF A BRIEF VERSION IN YOUTH AT HIGH RISK FOR SCHIZOPHRENIA

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Background: Limited research has been performed to track prodromal symptoms in individuals with familial high risk youth, a population which is at an increased possibility of developing psychosis. We examined the Scale of Prodromal Symptoms (SOPS) and developed a two-factor solution to adequately characterize prodromal symptomatology in youth at high familial risk for schizophrenia. A new four item assessment, the Brief Scale of Prodromal Symptoms, was developed and has been shown to correlate highly with the larger original scale.
Methods: One hundred and one high risk (HR) individuals with a first or second degree family member living with either schizophrenia or schizoaffective disorder were included in this study. Prodromal symptoms were assessed by trained interviewers through the Structured Interview for Prodromal Syndromes (SIPS) using the Scale of Prodromal Symptoms (SOPS). These individuals were assessed at study entry and then yearly for up to 3 years (averaging 1.37 years). A series of exploratory factor analyses were used to examine the relationship between items.
Results: Results of a two-factor solution separated items between Positive Symptoms/Functional Impairment and Disorganization/Thought Disturbance. We proceeded to examine the possibility of constructing a brief version of the SOPS based on the items with the highest factor loadings. The relationship between the B-SOPS and the total scale was evaluated to examine the convergent of the B-SOPS, and was found to be correlated highly at r = .92. The B-SOPS was shown to be significant in predicting the development of psychosis; for every 1 point elevation on the B-SOPS, individuals were 1.69 times more likely to develop psychosis at follow up. Convergent validity was evaluated by examining the relationship of the B-SOPS to the GAS at baseline ($r = -.65$, $p < .001$, $N = 92$) and then again at follow up ($r = -.50$, $p < .001$, $N = 61$).
Conclusion: Our findings showed that a two factor solution separated items on the SOPS between Positive Symptoms/Functional Impairment and Disorganization/Thought Disturbance and that the B-SOPS is a significant tool in predicting the development of psychosis among youth at familial high-risk for psychosis.
ID: 2069588

INTERNALIZED STIGMA, SYMPTOMS, AND METACOGNITION IN FIRST EPISODE PSYCHOSIS

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Background: Stigmatizing beliefs about psychotic disorders affect treatment engagement and long term outcomes in those suffering from such illnesses. Little is known about the inner subjective experience of stigma and its psychological impact on young people experiencing first episode psychosis (FEP). This study aimed to replicate and extend upon previous findings related to internalized stigma in persons with chronic schizophrenia (Nabors et al., 2014).
Methods: Participants (N=40; mean age 24 yrs) were diagnosed with a psychotic disorder and recruited through the Prevention and Recovery Center for Early Psychosis. Participants were assessed for stigma using the Internalized Stigma of Mental Illness Inventory (ISMI), symptoms using the Positive and Negative Syndrome Scale, and metacognition using the Indiana Psychiatric Illness Interview. Mean ISMI subscale scores (Alienation, Stereotype Endorsement, Discrimination Experience, Social Withdrawal, and Stigma Resistance) were correlated with symptoms (positive, negative, disorganization, and depression) and metacognition.
Results: All reported correlations were statistically significant at $p < .05$ or less and positive, unless otherwise specified. Stereotyped endorsement was linked to all four symptom measures, discrimination experience was linked to positive, negative, and disorganized symptoms, and alienation was linked to negative and disorganized symptoms. Social withdrawal was not related to symptoms. Interestingly, stigma resistance was negatively correlated to positive symptoms and stereotype endorsement was the only subscale related to depression. Stigma was not associated with metacognition.
Conclusion: Internalized stigma seems to have unique relationships with symptoms and metacognition in young people with FEP. Unlike findings in persons with chronic illness, stereotype endorsement and discrimination experience were strongly correlated with negative and disorganized symptoms and metacognition was not linked to stigma resistance. Further, in FEP we found that depression was only linked to stereotype endorsement. Understanding the factors related to internalized stigma in FEP will aid increasing treatment engagement and improving long term outcomes.
ID: 2119493

DEVELOPMENT OF THE DANISH FIDELITY-SCALE FOR SPECIALIZED EARLY INTERVENTION TEAMS.

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Background: The efficacy of the Danish Specialized Early Interventions (SEI) treatment, OPUS, has in a randomized clinical trial proved to be very strong compared to treatment as usual. Proliferation of SEI-teams is increasing in Denmark. However, a prerequisite for upholding positive effects along with the creation of new teams is to preserve the critical components from the concept that was tested in the randomized trial. However, there is a lack of validated fidelity-scales for SEI services, and thus currently it is not possible to measure presence or absence of the critical components in current and future SEI-teams in Denmark.
Methods: In order to establish an Danish SEI-fidelity-scale, and based on international essential evidence-based components of SEI services we interviewed experts from five Danish EIS-teams, using an adapted version of the Delphi Consensus method.
Results: A 15-point scale was conducted. The scale was divided into two dimensions: one concerning the structure of the SEI-team and the other concerning the character and content of the treatment. Each component can be rated either 1 or 0 (1 point=fulfilling the requirements for the components; and 0 point=the requirements was not met). The maximum score was a total of 15 points, and in order to "pass" the SEI-fidelity scale, the total score must be between 13 to15 points of which 5 of the components are mandatory.
Conclusion: Development of a fidelity scale can be an important tool for securing the quality of SEI treatment in Denmark and can be a part of an internationally accepted and common fidelity scale.
ID: 2117837

PERSISTENCE ISN'T FUTILE: PSYCHOLOGICAL PREDICTORS OF IMPROVEMENT ON A MATH LEARNING PROGRAM IN SCHIZOPHRENIA

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Background: Learning in schizophrenia is integral to psychiatric rehabilitation, but may depend on non-cognitive factors like negative symptoms or learning-related constructs. This is the first study to explore if learning persistence (LP) predicts math learning outcome for people with schizophrenia. LP is defined as the perseverance of effort on a task, and interest for long-term goals. The Intrinsic Motivation Inventory's (IMI) Effort and Interest subscales served as post-hoc proxy measures for LP. Study questions were: Do people with schizophrenia show individual differences in LP, can they be categorized by baseline LP, and do these differences at baseline predict performance gains? Also, is LP related to greater goal-directed behavior for learning and does it predict learning above baseline performance and negative symptoms?
Methods: 89 patients were enrolled in a 4-week, computer-based math learning program, using addition, subtraction, division, multiplication and parenthetic operations to solve adaptive-difficulty math problems. Outcome measures were attention; motivation; self-competency; symptom severity; learning improvement (program progression and change in scores); goal directed behavior (program completion).
Results: IMI Effort and Interest scores were submitted to cluster analysis, which identified 3 distinct clusters characterized by high, moderate, and low LP (HLP, MLP, and LLP respectively). One-way ANOVA revealed that the 3 clusters significantly differed on pre-post change in math scores, with HLP and MLP showing greater improvement relative to LLP, but with significant differences between HLP and MLP ($F[4, 79]=11.09$, $p=.001$). Pair-wise comparisons (Tukeywi HSD test) showed HLP had more improvement in math relative to MLP ($p=.037$). Also, more participants in HLP completed the entire training program compared to MLP or LLP ($p=.010$). Baseline avolition/apathy on the SANS and HLP accounted for most of the variance in math improvement at post, even when accounting for baseline math ability ($R2=.43$, $df=5, 73$, $F=5.10$, $p=.00$).
Conclusion: Patients with HLP and MLP improved much more than LLP, with HLP doing the best and completing the program at a higher rate than MLP. Learning programs in psychiatric rehabilitation may benefit from catering to individual levels of LP, a potentially distinct psychological phenomenon, to maximize learning. Further research on LP and its relationship with negative symptoms and potential use for targeting negative symptoms will be discussed.
ID: 2094607

PREDICTORS OF CHANGE IN FUNCTIONAL CAPACITY AND REAL-WORLD BEHAVIOR FOLLOWING COGNITIVE REMEDIATION FOR SCHIZOPHRENIA

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Background: Cognitive remediation is efficacious (improves neurocognitive abilities), but not all participants demonstrate its effectiveness on proximal measures (e.g., performance-based assessments of functional ability gain) and fewer manifest effective real-world behavior change. The current investigation was undertaken to explore the association between the changes in these three outcome variables and examine the role that residual symptoms play in mediating treatment outcomes.
Methods: 73 outpatients with schizophrenia were assessed prior to and following participation in a 12-week cognitive remediation program. Efficacy was defined as change in the neurocognitive composite score. Proximal effectiveness was examined as change in functional ability (as assessed using the UC-San Diego Performance-Based Skills Assessment), while distal effectiveness was rated as the change in real-world behavior (measured using the Specific Levels of Functioning Scale). Clinical symptoms were examined with the standard rating scales.
Results: Change in neurocognitive functioning was significantly correlated with change in functional ability ($r = .43$) as well as with real-world functional behavior ($r = .39$). However, the magnitude of the relationship between functional ability change and real-world behavior change ($r = .62$) was significantly larger ($z = 1.83$, $p = .03$). When forcing functional ability change into the first block of a hierarchical regression, the variance in real-world functioning accounted for by cognitive change was no longer significant. Negative symptoms contributed an additional 10% of variance in predicting real-world behavior change after accounting for cognitive change, and 5% after accounting for functional ability change. Depression was associated with cognitive and functional change, but did not significantly contribute additional variance in predicting real-world outcomes.
Conclusion: Improvements in cognition following cognitive remediation are associated with gains in functional life skills as well as the deployment of those skills in everyday life. However, the degree to which people with schizophrenia translate cognitive gains to enhanced everyday functioning appears to hinge on also acquiring living skills and a lower level of negative symptoms. Additional efforts to reduce negative symptoms and ensure an opportunity to learn functioning skills might be necessary for truly effective results following cognitive remediation.
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ID: 2115338

A MODEL FOR NEUROCOGNITION, FUNCTIONAL CAPACITY AND OUTCOME IN SCHIZOPHRENIA

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Background: Outcome in schizophrenia is being regarded increasingly in functional rather than symptomatic terms. A number of factors have been implicated in key aspects of real world functionality, including community independence. Nevertheless, neurocognition is still regarded as the best predictor of outcome (Green et al., 2004). This relationship, however, is believed to be mediated by functional capacity, an aspect of cognition grounded in real world pragmatics. At the same time, the measurement of functional capacity or practical cognition continues to evolve with introduction of new instruments. The present study aimed to evaluate the relationship amongst these variables using new and less standard measures of capacity and outcome.
Methods: Data were collected from 100 patients with a diagnosis of schizophrenia or schizoaffective disorder. Functional capacity measures included the Canadian Objective Assessment of Life Skills (McDermid Vaz et al., 2013), which assesses procedural knowledge routines and executive operations aspects of functional capacity, and the UPSA (Patterson et al., 2001). Outcome was assessed through the Multidimensional Scale of Independent Functioning (Jaeger et al., 2003) which evaluates functional role responsibilities, supports received, and performance across work, education, and residential settings. Clinical (PANSS) and neurocognitive (WASI-II, WRAT-4 Reading, MCCB) measures were also included.
Several competing models of pathways to outcome were established a-priori. Structural equation modeling (SEM) was used to evaluate competing models.
Results: Although all SEMs had excellent fit statistics, a two-factor model in which functional capacity mediates the relationship between cognition and outcome was the most parsimonious and thus chosen as the model that best fit to the data.

Conclusion: The results of this analysis suggest that a simple model in which functional capacity mediates the relationship between cognition and outcome may best explain the pathway to outcome. This data replicates previous findings suggesting that the model and findings are not artifacts of popular instruments, but rather reflect the nature of the underlying constructs they are said to measure. Understanding of the contributors to outcome should be used for the identification of appropriate treatment targets and the development of refined interventions.
ID: 2117801

EXPLORING SOCIAL COGNITION IN COMORBID SCHIZOPHRENIA

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Background: Individuals with schizophrenia(SZ) suffer from various sociocognitive deficits namely in emotion recognition(ER),Theory of Mind(ToM) and attributional style(AS) and it hinders their social functioning(SF)(1).Further complicating this issue,is the fact that the various comorbidities found in SZ,namely social anxiety(2)(30% of SZ) and substance abuse(3)(50% of SZ), are rarely considered in research though they could create different sociocognitive patterns.Our objective is to identify sociocognitive profiles for comorbid schizophrenia in order to put in place appropriate trainings/therapies.We posit that deficits in ER and ToM will predict social anxiety and paranoia(SZ),with an interaction for AS that will differentiate both: externalizing for paranoia and internalizing for social anxiety.Also,SZ alone will show greater deficits in ER than SZ with substance use thus showing better social functioning.
Methods: 29 participants, with either SZ alone or SZ and substance abuse. ER was assessed with virtual reality avatars displaying 7 emotions(sadness, anger, disgust, happiness, fear, surprise, neutrality),SF,ToM and AS measured via questionnaire.
Results: Our first hypothesis was not supported.But,those with comorbid substance abuse were significantly better at recognizing negative emo tions($F(1,27)=4.2$,$p=0.05$,$\eta2=0.1$) with a main effect of gender,with men being better at recognition(Men:$\mu=0.7$,SD=0.08;Women:$\mu=0.6$, SD=0.1). Within that same group,those who took stimulants versus cannabis were better at identifying negative emotions,specifically for the emotion of fear($F(1,15)=5.9$,$p=0.03$, $\eta2=0.3$). For AS,those with externalizing biases were better at overall ER($F(1,27)=4.48$, $p=0.04$, $\eta2=0.1$),specifically positive emotions ($F(1,27)=15.54$, $p=0.001$, $\eta2=0.4$).Paranoia was also associated with both worst SF($r=-0,48$,$p=0.009$) and social anxiety ($r=0.48$, $p=0.008$).
Conclusion: Consistent with previous studies were those with SZ and substance abuse showed a different pattern of affective memory than those with SZ alone(4),there seems to be a distinct sociocognitive profiles for individuals with SZ and substance use. Further assessment of those measures should be conducted on a greater sample size in order to ascertain these differences.(1)Morrison&Heimberg(2013),An Rev Clin Psych,9,249–274.(2) Kingsep et al.(2003).Schi Res,63,121–129.(3)Regier et al.(1990).J Am Med As,264,2511-2518.(4)Bourque et al. (2012).Biol Psyc,71(267S).
ID: 2102945

EXPLORING PSYCHOTIC EXPERIENCES IN NON-NEED FOR CARE POPULATIONS: FINDINGS FROM THE UNIQUE STUDY (UNUSUAL EXPERIENCES ENQUIRY STUDY)

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Background: People displaying persistent, full-blown psychotic experiences without a need-for-care in the general population are an ideal group to investigate to differentiate those factors that are linked to distress and dysfunction from those that are merely associated with benign anomalous experiences. The UNIQUE study investigated the cognitive and social processes predicted by cognitive models of psychosis to differentiate between benign and pathological outcomes of psychotic experiences.
Methods: 259 individuals were recruited (84 'need-for-care'; 92 non need-for-care; 83 controls) from urban (South-East London) and rural (North Wales) UK sites. The three groups were compared on clinical and psychological measures, and on their appraisals of experimental tasks inducing anomalous experiences (of thought interference symptoms and auditory hallucinations).
Results: As predicted, the clinical group endorsed more maladaptive appraisals ratings of the experimentally-induced anomalous experiences than the non-need for care group, who did not differ from the controls. A similar pattern was found for salience, distress and threat, and likelihood to incorporate the experimental set-up into their ongoing experiences. The clinical picture demonstrated a mixture of overlap and distinctive pattern of psychotic experiences, while the demographic and psychological profiles of the two groups were markedly different.
Conclusion: The results of this study identified a number of specific factors that are protective against transition to psychosis in individuals with persistent psychotic experiences. They also provide robust experimental evidence for the key role of appraisals in determining outcome, as postulated by cognitive models of psychosis.
Funding: Medical research Council, UK
ID: 2091348

THE SOCIAL COGNITION PSYCHOMETRIC EVALUATION (SCOPE) STUDY: RELIABILITY AND VALIDITY

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Background: In schizophrenia, social cognition is strongly linked to functional outcome and is increasingly seen as a viable treatment target. The goal of the Social Cognition Psychometric Evaluation (SCOPE) study is to identify and improve the best existing measures of social cognition so they can be suitably applied in large-scale treatment studies. Initial phases of this project developed consensus on critical domains of social cognition and identified the best existing measures of social cognition for use in treatment studies. An initial psychometric study was then conducted to evaluate the reliability and validity of the identified measures.
Methods: Individuals with schizophrenia or schizoaffective disorder (N=179) and healthy controls (N=99) completed eight measures of social cognition: Ambiguous Intentions Hostility Questionnaire (AIHQ), Bell Lysaker Emotion Recognition Task (BLERT), Penn Emotion Recognition

Test, Relationships Across Domains (RAD), Reading the Mind in the Eyes Test, The Awareness of Social Inferences Test, Hinting Task, and Trustworthiness Task. Analyses were conducted to examine the internal consistency and test-retest reliability of these measures as well as criterion-related validity. Utility as a repeated measure was also assessed by evaluating practice effects and floor and/or ceiling effects.
Results: All measures showed adequate test-retest reliability and good internal consistency with the exception of the AIHQ. While generally low, correlations of task performance and functional outcomes indicated that functional capacity and social competence were most highly related to Hinting performance and that real-world outcomes were most highly related to BLERT performance. Practice effects on all tasks were relatively small, and there was limited evidence of floor or ceiling effects except for the RAD, which showed floor effects. Finally, all measures were sensitive to group differences and demonstrated higher performance in healthy controls.
Conclusion: With the exception of the AIHQ and RAD, the current tasks show favorable psychometric characteristics. The majority demonstrated adequate reliability and utility as a repeated measure, but they also showed relatively weaker criterion validity. Future SCOPE efforts will be aimed at modifying the existing measures to increase their utility for predicting functional outcome.
ID: 2084071

CORRELATES OF PARENTAL BONDING IN FIRST EPISODE PSYCHOSIS AND CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Adverse early life experiences can be detrimental to mental health in adolescence and adulthood. Psychological factors such as high self-esteem, coping skills and social support might increase resilience towards negative mental health outcomes. The present study investigated the associations of parental bonding with functional and symptomatic outcomes at different stages on the psychosis continuum. In subgroup analyses, we explored the association of parental bonding with hypothalamus-pituitary-adrenal (HPA) axis function and the potential mediating role of several resilience factors on the observed associations.
Methods: Participants were 102 patients diagnosed with a first episode of psychosis (FEP), 30 individuals at clinical high risk for psychosis (CHR), and 32 healthy community controls. Parental bonding was assessed with the Parental Bonding Instrument (PBI), and functional and symptomatic outcomes were measured repeatedly over 24 months with the Brief Psychiatric Rating Scale (BPRS) and the Global Assessment of Functioning (GAF) scale. HPA axis function was determined with the Cortisol Awakening Response (CAR), and putative resilience factors were assessed with the Self-esteem Rating Scale (SERS), the Brief COPE and the Multidimensional Scale for Perceived Social Support (MSPSS).
Results: Both FEP and CHR patients reported deficits in parental bonding compared to healthy controls. Higher perceived levels of care during childhood in particular by the father were related to less severe symptoms of psychosis (positive, negative and depression) and better global functioning at different time points of follow up (3, 6, 12, and 24 months). Subgroup analyses showed that better parental bonding was positively correlated with higher cortisol awakening response (in FEP) and with higher self-esteem, active coping and perceived social support (in FEP and CHR). Linear regression analyses revealed a mediating role of self-esteem on the relationship of paternal care with symptoms and HPA axis function.
Conclusion: Our results point to an important role of the father-offspring relationship during childhood for mental health outcomes in adolescence and adulthood. This relationship appears to be mediated by self-esteem. The implementation of psychosocial interventions targeted at improving children's relationship with their fathers and measures for the enhancement of self-esteem might have the potential to boost resilience and to prevent the development or worsening of psychotic illness.
ID: 2083007

PREDICTORS OF EMPLOYMENT IN ADULTS WITH SCHIZOPHRENIA: THE IMPORTANCE OF BOTH INTRINSIC AND EXTRINSIC MOTIVATION

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Background: Motivational deficits are a key predictor of employment outcomes for people with schizophrenia. Intrinsic motivation is often associated with the initiation and maintenance of goal-oriented behaviors; increasingly, extrinsic motivators are also being included in models of motivation in schizophrenia. Extrinsic motivators include environmental context and opportunities for rewards. Motivational drive is likely determined by the degree of synchrony between intrinsic motivation and extrinsic motivators.
Methods: For the current study, we examined employment outcomes over a two-year period in relation to intrinsic and extrinsic motivation. Participants were 157 individuals diagnosed with serious mental illness, assessed with the Intrinsic Motivation Inventory for Schizophrenia Research (IMI-SR) and the Motivators and Barriers to Employment Questionnaire (MBEQ).
Results: When we compared those who worked at least once (part-time job of any duration) (n=44) and those who did not work at all (n=113), we found significant differences in both extrinsic and intrinsic motivation. When we compared those who worked the entire two years (n=27) with those who worked part or none of the study period (n=122), the extrinsic motivators and barriers remained significant but intrinsic motivation no longer differentiated the groups. Logistic regression indicated a significant interaction between intrinsic and extrinsic motivation and worker outcome such that both groups were equivalent in intrinsic motivation but those with lower extrinsic motivation were significantly more likely not to work (odds ratio = 7.2). Extrinsic but not intrinsic motivation also predicted hours worked and wages earned and these findings remained significant when we controlled for cognition and psychiatric symptoms.
Conclusion: Overall, our results highlight the importance of extrinsic motivation (perceived barriers and rewards) for work success among adults with schizophrenia. Environmental barriers (i.e., losing disability income, experiencing stress-induced symptoms, or lacking anticipatory pleasure for monetary gains) may be more predictive of work outcomes for adults with schizophrenia than intrinsic motivation (i.e., valuing the task, gaining a sense of purpose from holding a job). Interventions that address perceived barriers and extrinsic motivators may positively impact work outcomes for people with schizophrenia.
ID: 2119199

INTERPERSONAL CONSEQUENCES OF BLUNTED FACIAL EXPRESSIVENESS IN SCHIZOPHRENIA

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Background: Blunted facial expressiveness is a common observation in people with schizophrenia, known as a part of the negative symptoms of the

disorder. Findings from social psychology suggest that people who smile less in first encounters are liked less by their respective interaction partners. However, whether the lack of emotional facial expressions affects interpersonal relationships of people with schizophrenia is largely unknown. Thus, this study tests whether healthy people will like people with schizophrenia less than people without a psychiatric diagnosis after a first encounter with them and how the liking of a person relates to the facial behavior shown by that person.
Methods: We recruited three groups of participants: Group 1 were participants with a diagnosis of schizophrenia. Group 2 were matched healthy controls. Group 3 were healthy controls who served as an interaction partner for each of two matched participants from Groups 1 and 2. All healthy participants were unaware that people with schizophrenia were participating in the study. Group 3 interaction partners met their assigned participants separately in a dyadic setting and discussed positive and negative life events with them. After the encounters, we asked all participants to indicate how much they liked their counterpart. We measured smiling and frowning in all participants during the conversations via electromyography. We obtained negative symptoms ratings for all participants with the Clinical Assessment Interview for Negative Symptoms (CAINS).
Results: Our preliminary data on 9 participants per group show that the interaction partners liked participants with schizophrenia significantly less than their matched controls. Participants with schizophrenia tended to show fewer smiles than their matched controls during the discussion of positive life events. More impairment on the CAINS expression scale correlated highly but non-significantly with less smiling during positive events and less liking of that participant (r = -.42 and r = -.37). The correlation of liking and smiling during positive events (r = .41) was also high in magnitude but non-significant.
Conclusion: Our data indicate that the restricted use of smiling during positive verbal reports might be partly responsible for the fact that people with schizophrenia are more readily rejected by interaction partners. We hope to have tripled the sample size of this study by the time of the congress to enhance the power of our analyses and generalizability of our results.
ID: 2119346

THE ROLE OF SOCIAL MEDIA AND THE INTERNET IN PATHWAYS TO CARE FOR YOUTH WITH PSYCHOSIS

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Background: The evolution of internet and social media represents a profound shift in communication and access to information, particularly for youth. While the onset of psychotic symptoms for many individuals occurs during adolescence, there has been little research on how these platforms impact pathways to care. We set out to explore how youth with psychotic disorders are using online resources in the early stages of illness.
Methods: Pathways to care data were collected on 69 youth (mean age: 18 years) with first-episode psychosis (n= 41) and recent onset mood disorders (n=28), emphasizing internet and social media utilization in response to the evolution of symptoms.
Results: 98% of participants regularly use social media, spending approximately 2.5 ± 2.1 hours per day online. 29.8% of our sample attributed early symptoms to stress (29.3% psychosis, 32.1% mood). 18.5% (19.4% psychosis, 17.2% mood, p=0.82) reported waiting to reach out for help as they thought symptoms would go away. Both groups reported waiting 15.4 ± 33.0 weeks before reaching out for help. 79.7% of subjects (68.3% psychosis, 93.1% mood, p=0.017) noticed changes in their social media habits during symptom emergence. 30.0% of participants reported discussing their symptoms on social media (22.0% psychosis, 41.4% mood, p=0.081). Participants with non-psychotic mood disorders were primarily interested in obtaining information on how to stop symptoms (48.3% vs 13.2%, p=0.0016) while youth with psychosis were most commonly interested in what caused their symptoms (23.7% vs 17.2%, p=0.52). Significantly more patients with psychosis (46.7% vs 18.5%, p=0.024) would prefer to receive mental health information via the internet. 62.7% of participants (63.2% psychosis, 62.1% mood, p=0.93) were amenable to a mental health clinician reaching out to them via social media during symptom emergence prior to initiating psychiatric care. 74.6% of participants (76.3% psychosis, 72.4% mood, p=0.72) liked the idea of obtaining help/advise from a professional via social media.
Conclusion: Given the severity and potentially long lasting negative impact of untreated psychosis, mental health clinicians must explore innovative and novel strategies of early identification, engagement and care. The internet and social media provide an unprecedented opportunity to supplement and potentially transform early intervention services.
ID: 2082071

COGNITIVE REMEDIATION THERAPY: DOES IT GENERALIZE TO SIGNIFICANT OUTCOME AREAS?

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Background: Cognitive Remediation Therapy (CRT) approaches have demonstrated to be effective in improving cognitive functions in schizophrenia. However, there is a lack of integrated CRT approaches that target multiple neuro- and social-cognitive functions with a special focus on generalization of therapy effects to functional outcome and negative symptoms.
Methods: This 8-site randomized controlled trial evaluated the efficacy of a novel cognitive-behavioral group therapy approach called Integrated Neurocognitive Therapy (INT). INT includes manual-based exercises to improve all neuro- and social-cognitive domains as defined by the Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative by compensation and restitution. One hundred and fifty-six outpatients with schizophrenia or a schizoaffective disorder according to DSM-IV-TR were randomly assigned to receive 15 weeks of INT or Treatment As Usual (TAU). INT patients received 30 bi-weekly therapy sessions. Each session lasted 90 minutes. Mixed models were applied to assess changes in neurocognition, social cognition, negative symptoms, and functional outcome at post-treatment and at 9-month follow-up.
Results: Compared to TAU, INT patients showed significant improvements on multiple neuro- and social-cognitive domains, negative symptoms, and functional outcome after therapy and at 9-month follow-up. Number-needed-to-treat analyses indicated that only five INT-patients are necessary to produce durable and meaningful improvements in functional outcome.
Conclusion: Integrated interventions on neuro- and social cognition have the potential to improve not only cognitive performance but also functional outcome and negative symptoms. These findings are important as treatment guidelines for schizophrenia have criticized CRT approaches for their poor generalization effects.
ID: 2118534

MODEN: A FRENCH INTEGRATIVE PROGRAM INCLUDING COGNITIVE REMEDIATION THERAPY, EDUCATIONAL SESSIONS AND SOCIAL SKILLS IN SCHIZOPHRENIA BASED ON BALANCE AND NUTRITION: PRELIMINARY RESULTS

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Background: Schizophrenia cause psychological difficulties and also cognitive disabilities. Moreover, concerning patients, 40 to 60% suffer from an excess of weight or obesity. In our center of rehabilitation, we have created a structured integrative French-speaking program, called MODen based on the specific cognitive deficits in schizophrenia. Thus, MODen is a therapeutic educational tool aiming at improving cognitive functions and the symptoms, by using "nutritional balance" as an aid and taking account individualized ecological context..The objective of this study is to assess clinical and cognitive improvement among a group of patients with schizophrenia in comparison with a control group.
Methods: In 2014 we recruited 13 stabilized patients with schizophrenia in the Clermont de l'Oise's psychiatric departments (area Picardie, France) according to DSM-IV-TR criteria. Seven patients participated to MODen's program and 6 patients participated to an usual cooking activity in a psychiatric day center. Socio-demographical and clinical data were collected. At the beginning of the program (T0), all the patients were assessed with clinical tools and with neurocognitive tests. At mid-program all the patients were assessed a second time (T1). To compare the 2 groups and each group at the 2 times (T1-T0) we used wilcoxon tests.
Results: We found significant improvement on several PANSS sub-dimensions, positive (p < 0,02), general (p < 0,02), disorganization (p < 0,03), anxio-depression (p < 0,03) and on the total score (p< 0,02). Regarding cognitive tests, we found only a significant improvement on the short term memory (p<0,03). No improvement was found in the control group. These first results were confirmed with other statistical analysis comparing mean changes (T1-T0) between the 2 groups regarding PANSS sub-dimensions, general (p< 0,005), disorganization (p< 0,02), anxio-depression (p< 0,03) and total PANSS score (p< 0,004) but not regarding cognitive tests. No significant change were found regarding antipsychotic treatment between the 2 times of assessment.
Conclusion: These preliminary results with a control group are encouraging. We will continue the validation of this program using randomized larger samples (MOden versus usual psychoeducational programs) with other clinical and cognitive assessments.
ID: 2117758

EFFECTS OF COGNITIVE REMEDIATION AND SUPPORTED EMPLOYMENT FOR PEOPLE WITH SEVERE MENTAL ILLNESS IN JAPAN_A RANDOMISED CONTROLLED TRIAL

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Background: Despite of a large number of those who wish to work among people with severe mental illness (SMI) in Japan, employment services for people with SMI have not been well-managed. The employment rate of people with SMI was lower than those with mental retardation or physical impairment (SMI 28.5%, mental retardation 51.9%, physical impairment 45.5%). On the other hand, a combination program of cognitive training and supported employment has demonstrated notable evidence for work-related outcomes in the past studies, in terms of the effective employment services for individuals with SMI. However little is known about the effects of this combination approach in a Japanese setting. Therefore, the objective of this study was to examine effectiveness of the combination approach of cognitive remediation (CR) using the "Cogpack" and supported employment (SE), compared to the traditional vocational services based on brokering approach (TVS) in Japan.
Methods: We set the following eligible criteria of the study participants; 1) outpatients, 2) having severe mental illness, 3) 20–45 years old, 4) personal need to work, and 5) having cognitive impairment. Participants (n = 94) were randomly assigned to the CR+SE group or the TVS group. The outcomes included psychiatric symptoms, social functions, neurocognitive functions, performance of tasks, variables related working. The outcome assessments were conducted at baseline (T0), 4 months (T1) and 12 months (T2) after baseline. A chi-test and a repeated ANCOVA controlling for the total score of GAF as covariates were conducted to compare the study outcomes between the two groups.
Results: We found significant improvements in time by group interaction on total score of GAF (F=6.488, p<.01), verbal memory (F=4.610, p<.05), digit sequencing (F=4.137, p<.05), letter fluency (F=7.553, p<.01), symbol coding (F=8.170, p<.01), composite scores of BACS-J (F=6.746, p<.01) and score of Napkin-Folding task (F=5.643, p<.01) in the CR+SE group, compared to the TVS group at T1. In addition, these trends about variables that were showed significant improvements were maintained even at T2. The CR+SE group had a greater number of individuals who were employed in 12 months than those in the TVS group ($\chi 2$=15.797, p<0.01).
Conclusion: An employment program including cognitive remediation and supported employment appears to be effective not only for cognitive functioning but also for working outcomes in Japan.
ID: 2085120

IMPLICIT PROCESSING OF SOCIAL THREAT CUES AND PARANOIA IN SCHIZOPHRENIA

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Background: Those with schizophrenia show more deficits on explicit, relative to implicit, emotion perception tasks. We sought to determine whether implicit processing of overt and subtle social threat cues would be intact in patients and whether that ability may be related to paranoid ideation.
Methods: 58 controls (HC) and 112 patients with schizophrenia (SZ) completed two versions of the Affect Misattribution Procedure (AMP), an implicit measure of affective reactions through which perceptions of primes are projected onto neutral targets (Payne et al., 2005). In the emotional version, angry, happy, and neutral faces were overt threat primes; in the structural version, emotionless faces perceived as threatening, approachable, or neutral via structural manipulation (e.g., of eye size; Oosterhof & Todorov, 2008) were subtle threat primes. Whether the groups differed in percent of targets perceived as threatening following each prime (see table) was assessed by a 2 (group: HC vs. SZ) x 2 (version: emotional vs. structural) x 3 (threat: threatening vs. nonthreatening vs. neutral) ANOVA. The self-report Paranoia Scale (Fenigstein & Vanable, 1992) was also administered. To assess whether paranoid ideation related to processing of emotionless social threat cues in patients, a correlation between paranoia scores and threat ratings following structural primes was computed.
Results: A main effect of threat emerged, $F(1.3,195.8)=84.21$, $p<.001$, $\eta p^2=.351$, revealing that ratings of targets were affected by whether the primes were threatening, nonthreatening, or neutral. The interaction between threat and version, $F(1.4, 218.5)=57.28$, $p<.001$, $\eta p^2=.269$, was also significant: Emotional and structural primes influenced threat ratings differently. No other main effects or interactions emerged (all $p \geq .270$ and

Threat Ratings (%) Following Face Primes

	HC (Mean, SD)		SZ (Mean, SD)	
Threat Level of Prime	Structural	Emotional	Structural	Emotional
Threatening	45.9, 19.7	60.9, 27.0	43.4, 21.1	62.5, 28.6
Nonthreatening	33.8, 19.4	26.8, 20.6	37.6, 23.5	28.9, 22.2
Neutral	34.7, 17.1	27.2, 19.8	39.7, 21.9	32.8, 21.8

$\eta p^2 \leq .008$). Percent of targets perceived as threatening following structural primes was associated with self-reported paranoia in patients ($r(110)=.212$, $p=.030$).

Conclusion: Despite explicit emotion perception difficulties, those with schizophrenia appear able to implicitly process overt and subtle social threat cues. Further, patients' sensitivity to emotionless facial marks of threat seems related to enhanced paranoid ideation.

ID: 2086278

SOCIAL COGNITION IN THE SCHIZOPHRENIA SPECTRUM

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Background: Abnormalities in social cognition represent a core feature of the schizophrenic disorders. Schizotypal personality disorder (SPD) is the prototypic spectrum disorder, characterized by social cognitive impairments including decreased understanding of others' mental states, altered salience of social information and attention to social cues which contribute to their impaired social skills. We evaluated social cognition tasks and interventions to improve social cognition in SPD patients.

Methods: Social cognition and emotion processing abnormalities in SPD and other personality disorder patients were evaluated using social cognition paradigms, genetic strategies, structural neuroimaging and pharmacologic/behavioral treatment strategies. A cognitive remediation intervention with the randomized double-blind co-administration of the alpha2- adrenergic agonist guanfacine or placebo was tested.

Results: SPD patients demonstrated lower empathic accuracy during a negative valence video correlated with having lower social support ($p < 0.05$). On a test of social cognition, the Movie for the Assessment of Social Cognition (MASC), SPD patients demonstrated more hypomentalizing errors (concrete, deficient responses) than controls ($p < 0.05$). Genetic variation in SNPs in the opioid, oxytocin, and vasopressin systems were significantly associated with altered social behaviors and attachment patterns ($p < 0.05$). SPD patients had lower fractional anisotropy (FA) in a critical node for social cognition, the genu of the corpus callosum, compared to healthy controls and was significantly associated with symptomatology of greater interpersonal impairment ($p < 0.05$). A cognitive remediation intervention in conjunction with guanfacine compared to placebo showed significant improvement in social cognition (MASC) and executive functioning (problem solving) and category fluency in patients with SPD ($p < 0.05$).

Conclusion: Baseline social cognition is impaired in SPD and genetic variation in peptide neuromodulators are related to defects in attachment and empathy. These alterations are associated with altered brain structure and a combined intervention with the cognitive enhancing alpha-2 adrenergic agonist guanfacine and cognitive remediation is associated with improvements in social cognition, suggesting that a pharmacologic enhancement of working memory enables a remediation intervention that improves social cognition.

ID: 2112833

SHOW ME THE MONEY REVISITED: MONETARY REINFORCEMENT VERSUS INTRINSIC REWARD FOR LEARNING IN SCHIZOPHRENIA

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Background: Recent studies show that diminished hedonic experience may affect the representation of information about reward, and the subsequent motivation for goal-directed behavior. We sought to (a) examine how experimental provision of intrinsic and extrinsic rewards would impact learning performance and subjective evaluations of learning, and (b) identify patient characteristics related to better learning outcome in the context of internal or external rewards.

Methods: Eighty-two adults with Sz were enrolled in a computer-based arithmetic learning study that consisted of ten 30-minute sessions over the course of 6 weeks. Participants were randomized into learning conditions with 4 cells that manipulated (a) intrinsically rewarding (IR) learning cues, and (b) cash payment as an external reward (ER) for performance. In the two IR conditions, the arithmetic learning program was made into an intrinsically-rewarding and enjoyable game, with and without cash payment for performance. In the two ER conditions, the same arithmetic learning program was void of all intrinsically-rewarding game elements to create an austere learning experience, with and without cash payment.

Results: Overall, ER was related to greater learning compared to IR ($F[2,80]=5.19$, $p=.014$) and this improvement in arithmetic was associated with greater hedonia and perceived therapeutic value. There was a decline in experienced pleasure and intrinsic motivation--irrespective of IR--when ER was removed but no associated decline in self-efficacy or learning. Furthermore, for those with low baseline motivation, ER was related to greater learning, greater hedonia, and greater perceived therapeutic value. IR was modestly associated with greater learning only in patients with high baseline motivation. Baseline symptom of amotivation predicted learning outcome by accounting for a total of 53% of the variance in the entire sample ($R2=.53$, $F[3,78]=5.95$; $p=.008$).

Conclusion: In contrast to the non-psychiatric literature, IR had no impact on learning outcome when a highly desirable ER was available for reinforcing performance. The extent of learning taking place, irrespective of IR, was associated with greater hedonic experience and perceived therapeutic value. IR had minimal impact on those with a low degree of motivation to learn, especially when ER was available. IR offered some benefit but only to those who were already highly motivated. Amotivation was found to predict learning outcome more than other patient factors.

ID: 2118186

VIRTUAL REALITY JOB INTERVIEW TRAINING AND 6-MONTH EMPLOYMENT OUTCOMES FOR INDIVIDUALS WITH SCHIZOPHRENIA

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Background: Schizophrenia is a debilitating chronic illness that is associated with low employment rates and the job interview presents a critical

barrier for individuals with this disorder to obtain competitive employment. Virtual reality training has recently demonstrated efficacy at improving job interview skills and employment outcomes among individuals with autism, bipolar disorder, depression, or PTSD, however, the effects of this training on individuals with schizophrenia is currently unknown. Our objective is to evaluate the efficacy of virtual reality job interview training (VR-JIT) at improving job interviewing skills and employment outcomes among individuals with schizophrenia.

Methods: We evaluated VR_JIT efficacy in a small randomized controlled trial (n=20 VR-JIT trainees, n=10 waitlist treatment-as-usual (TAU) controls). Trainees completed up to 10 hours of simulated job interviews using the innovative VR-JIT software and reviewed information and tips about job interviewing, while controls received services as usual. Primary outcome measures included two pre-test and two post-test video-recorded role-play interviews scored by blinded human resource experts and self-reported interviewing self-confidence. Six-month follow-up data on employment outcomes was collected via telephone survey.

Results: Trainees attended 89% of lab-based VR-JIT sessions and found the intervention easy-to-use, helpful, and prepared them for future interviews. VR-JIT trainees demonstrated significantly greater improvement on role-play interview performance ($p=0.002$) and demonstrated a larger effect for within-subject change (Cohen's $d=0.92$ vs. $d= -0.27$) compared to TAU controls. VR-JIT performance scores increased significantly over time (R-Squared=0.85). VR-JIT trainees demonstrated greater improvement in self-confidence compared with TAU controls ($p=0.04$) and demonstrated a larger effect for within-subject change (Cohen's $d=0.67$ vs. $d=0.12$). After accounting for neurocognitive function and the number of months since prior employment, theVR-JIT group was more likely to receive a job offer after completing an interview by 6 month follow-up (OR: 9.0, $p<0.05$).

Conclusion: Results provide preliminary support that VR-JIT is acceptable to trainees and may be efficacious for improving job interview skills and self-confidence in individuals with schizophrenia. Moreover, participating in the VR-JIT intervention was associated with a greater likelihood of receiving a competitive job offer by the 6 month follow-up.

ID: 2081660

TACKLING STIGMA: DO CLIENTS AND RESIDENTS EXPERIENCE STIGMA IN THEIR NEIGHBOURHOOD?

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Background: Stigmatisation is a serious problem for people with psychiatric problems. Experiencing stigma can take place in multiple areas of life, for example at work, with family or friends, or in neighbourhoods. Key elements of stigma are limited knowledge, prejudice, and discrimination. Increasing knowledge in the general public about psychiatric problems and personal contact between those stigmatising and the stigmatised group are effective in changing stigma.

In the Netherlands more and more mental health clients live in residential areas, this may bring along the risk of an increase in stigmatisation. Therefore it is essential to tackle stigma concerning mental health right now. In order to come up with a concrete plan how to tackle stigma locally, an important first step is gaining insight in the actual local stigma problems.

Methods: Using separate structured discussion groups with mental health care clients (Serious Mental Illness; SMI) and neighbourhood residents, stigma in two neighbourhoods in Assen, the Netherlands will be investigated. Each group will consist of 8–10 participants and two moderators, namely the researcher and an expert by experience. The main topics that will be discussed among SMI clients as well as other residents are: 1. experiences with stigma in the neighbourhood, 2. how to improve the neighbourhood by decreasing stigma. Various subtopics will be discussed as well.

Participating neighbourhoods have been selected based on: 1. number of mental health service clients, 2. comparable demographic characteristics, 3. overall satisfaction of residents regarding their living environment. Clients will be approached by mail if they live in the participating neighbourhoods and are still in active care, other residents will be invited using flyers, a website, and local papers.

The results of the discussion groups will be used to develop interventions with main aim the reduction of stigma in the participating neighbourhoods.

Results: Results of the structured discussion will be presented on the poster. Outcomes will be presented for both the SMI client groups and the residents groups. Based on previous research we expect reported problems with e.g. isolation, avoidance, and access to social roles.

Conclusion: Conclusions will be presented on the poster. This will include recommendations with regard to interventions on a local level.

ID: 2087294

TWO SUBDOMAINS OF NEGATIVE SYMPTOMS AND THEIR CLINICAL CORRELATES IN CHRONICALLY ILL PATIENTS WITH A PSYCHOTIC DISORDER

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Background: Research suggests a two factor structure for negative symptoms: social amotivation and expressive deficits (Messinger, 2011). This subdivision may be valuable for predicting outcomes and targeting treatments. However, few studies investigated the relation of these domains to psychosocial functioning. We aimed to investigate 1) whether the factor structure of negative symptoms is also supported in chronically ill patients with a psychotic disorder and 2) the relationship between these factors and psychosocial functioning.

Methods: 1405 patients with a psychotic disorder and duration of illness > 5 years were included in the study (data selected from the Pharmacotherapy Monitoring Outcome Survey (PHAMOUS)). A confirmatory factor analysis was performed using items of the Positive and Negative Syndrome Scale (PANSS) previously identified to reflect negative symptoms (N1-4, N6, G5, G7, G13 and G16) (Liemburg et al., 2013). The factors defined by this analysis were used as predictor variables in a hierarchical regression analysis with quality of life (Manchester Short Assessment of Quality of Life, MANSA), functional outcome (Health of the Nation Outcome Scales, HoNOS) and depression (Calgary Depression Scale for Schizophrenia, CDSS) as dependent variables. In addition, we investigated the mediating

role of antipsychotic dosage (chlorpromazine equivalents, CE) and anticholinergic drug burden (Anticholinergic Cognitive Burden Scale, ACB).
Results: Results confirmed that the factors social amotivation and expressive deficits can be distinguished in chronically ill patients. Both factors predicted worse quality of life and functional outcome and more depression. Amotivation was the strongest predictor for quality of life and depression, while expressive deficits more strongly predicted functioning. When CE and ACB were added as predictors, the predictive value of both factors remained significant. ACB additionally predicted depression scores, while CE additionally predicted functional outcome.
Conclusion: Both factors are confirmed in chronically ill patients. Moreover, each factor predicted clinical outcomes above and beyond CE and ACB. Previous studies suggested amotivation as a critical predictor for functional outcome (Foussias & Remmington, 2010). The finding that expressive deficits predicted HoNOS scores may be explained by the nature of the HoNOS (the HoNOS is clinician-rated). In conclusion, the two factor structure may be informative and valuable for diagnosis, treatment and research.
ID: 2093875

THE PHYSICAL ACTIVITY PREFERENCES OF INDIVIDUALS WITH SCHIZOPHRENIA

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Background: Physical inactivity and obesity are prevalent co-morbid conditions affecting individuals with schizophrenia. The purpose of this research project was to understand the physical activity (PA) preferences of individuals with schizophrenia in order to inform future PA programs that will be tailored specifically to this population.
Methods: Fifty-four outpatients with schizophrenia (34 males, 20 females; mean age 42.3 ± 12.1) from the Centre for Mental Health and Addiction (CAMH) in Toronto completed a survey assessing their views on their health, weight and perceived interest in PA.
Results: Sixty-five percent of participants indicated that they were "slightly overweight" or "very overweight" and were dissatisfied with their weight. Approximately 60% of participants reported not being active on a regular basis and the majority of these individuals considered it important to be more physically active. Seventy percent of the sample indicated interest in a PA program designed specifically for people with schizophrenia. Participants preferred a program that consisted of moderate intensity walking and they would be interested in wearing a pedometer to track their daily steps. Participants want a program that would give them the independence to carry out their own PA routine but also the professional guidance from a fitness specialist to get started and then regular contact to help them reach their fitness goals. Participants also indicated that they would be interested in starting a PA program immediately but there was greater variability in some parameters of a potential PA program (e.g. when, where, with whom).
Conclusion: This study suggests that individuals with schizophrenia are interested in receiving support to be more physically active. There also appears to be some consistent preferences for the type of physical activity program that would be most attractive. These findings will be used in the development and evaluation of a physical activity intervention for this population.
ID: 2117979

FUNCTIONAL RECOVERY IN PATIENTS WITH SCHIZOPHRENIA: PREDICTING FACTORS FOR WORK OUTCOME

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Background: Returning to work is one of the most important and satisfying attainments for individuals with schizophrenia. The purpose of this study was to investigate predictors for work outcome and the relationships among the predictors.
Methods: Sixty-four Japanese patients meeting DSM-IV-TR criteria for schizophrenia (mean age=35.2 (11.2)) and 111 normal controls (mean age=30.9 (10.2)) entered the study. The study was approved by the ethical committees at the respective study sites.
Neurocognition, daily-living skills, and social functioning were assessed by the MATRICS Cognitive Consensus Battery (MCCB) Japanese version, the UCSD Performance-based Skills Assessment-Brief (UPSA-B) Japanese version (Sumiyoshi et al., 2011), and the Social Functioning Scale Individuals' version Modified for MATRICS-PASS (Modified SFS for PASS), respectively. Work outcome was evaluated by Modified Social Adjustment Scale Work Outcome (Subotnik. et al., 2008).
Results: Principal component analyses were carried out to reduce the domains of the MCCB and the SFS. In the patient group, extracted factors were interpreted as MCCB-EM (MSCEIT Emotional Management), MCCB-General for the MCCB, and SFS-General for the SFS. For normal controls, two factors were extracted both for the MCCB and the SFS.
Multiple logistic regression analysis for current work status was computed using the principal component scores of these factors and the UPSA subscales (Finance, Communication) scores as predictive factors. Work status was dichotomized into the better or poor category by means of a median sprit of working hours in the recent 3 months. SFS-General (β=0.94, p =0.01) and MCCB-EM (β=0.70, p =0.07) remained in the final model for the patient group (χ2=11.85, $p < 0.01$), yielding a 66.7% predictive accuracy.
Confirmatory path analysis was conducted assuming that social functioning would be determined by neurocogniton mediated by the UPSA-B subscale scores. In the patient group, paths were significant between MCCB General and the UPSA-B Finance score (β=0.47, $p < 0.01$), and between the UPSA-B Communication and SFS General (β=0.29, $p < 0.05$). For normal controls, only MCCB-EM/Memory was associated with the UPSA-B Communication score (β=0.30, $p < 0.01$).
Conclusion: Our findings support a previous finding that neurocognition is a key factor for work-outcome in patients with schizophrenia (Nuechterlein, 2011), revealing that skills needed to manage in everyday life and social functioning/involvement mediate the route to the recovery.
ID: 2086529

MINDFULNESS, EMOTION REGULATION, AND NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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Background: Mindfulness is emerging as an important topic for clinical researchers. Defined in various ways, mindfulness involves sustaining attention on the present moment with curiosity and acceptance. Mindfulness can be measured at both the state and trait level. Trait mindfulness is positively associated with physical and mental health constructs, including adaptive emotion regulation. In schizophrenia (SCZ) research, recent evidence indicates that emotion regulation is impaired and provides a reasonable target for intervention. Mindfulness-based interventions have been adapted for psychosis and early studies show promising results, especially for improving negative symptoms. However, no study has examined the relationship between mindfulness, emotion regulation, and negative symptoms in SCZ.
Methods: This study had three objectives: (1) to examine group differences in trait mindfulness (Mindful Attention Awareness Scale; MAAS) between healthy controls and SCZ patients, (2) to examine the relationship between trait mindfulness and emotion regulation (MSCEIT Managing Emotions) in patients, and (3) to examine the relationship between trait mindfulness and negative symptoms (Clinician Administered Interview for Negative Symptoms; CAINS) in patients. Participants included community-dwelling outpatients with SCZ (n=23) and matched healthy controls (n=25).
Results: Results indicated that patients (MAAS mean=4.09, SD=1.03) had lower trait mindfulness than controls (MAAS mean=4.59, SD=1.08). Though not statistically significant (p=0.11), the effect size was medium-large (Cohen's d=0.48). As expected, trait mindfulness was positively correlated with MSCEIT Managing Emotions (r=0.43, p<.05). Finally, correlations between trait mindfulness and negative symptoms were not significant, but trended in the expected direction (CAINS experiential: r= -0.29, p=0.19; CAINS expressive: r= -0.35, p=0.11).
Conclusion: This was the first study to examine relationships among mindfulness, emotion regulation, and negative symptoms in SCZ. Results provide initial support for a positive association between trait mindfulness and emotion regulation. In addition, patients tended to report lower trait mindfulness than controls, and trait mindfulness was non-significantly associated with lower negative symptoms. These preliminary results suggest that mindfulness-based interventions may hold promise for improving emotion regulation and negative symptoms in patients with SCZ.
ID: 2081514

SYMPTOM IMPROVEMENTS AND MAINTENANCE OF PSYCHIATRIC STABILITY IN A RESIDENTIAL PSYCHIATRIC REHABILITATION SETTING

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Background: Medication management during acute stays is the recommended method to stabilize symptoms among people with schizophrenia spectrum disorders (Lehman et al., 1998), but psychiatric rehabilitation post-discharge also benefits functioning and symptom management (Farkas & Anthony, 2010; Liberman, 2008). We hypothesized that participation in residential psychiatric rehabilitation would maintain stabilization and improve remaining symptoms via service involvement and increased community functioning.
Methods: We used data from 76 people with schizophrenia spectrum disorders participating in a residential psychiatric rehabilitation program. The average score of the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) and individual symptom scores were used as outcome variables to track changes in symptoms. Predictors included measures of service involvement, community functioning, legal involvement, and dual diagnosis.
Results: Fixed and random effects of time were added to each model first, and then the predictors were tested and retained in each model if significant. The final model for average BPRS score was a random linear time model. The effect of time was significant (contextual effect = -0.048, SE = 0.022, p = 0.035). There was also a significant effect of service engagement (contextual effect = 0.590, SE = 0.189, p = 0.002), a nonsignificant effect of community ability (contextual effect = -0.124, SE = 0.106, p = 0.245), and a significant interaction between time and community ability (contextual effect = -0.031, SE = 0.015, p = 0.037). There was also a significant random effect of time, (contextual effect = 0.895, SE = 0.069, p < .0001). The specific symptom models found similar effects, although many did not have a significant effect for time. Some models found significant effects for engagement in therapy, day rehabilitation, adult day care, and being declared not responsible by reason of insanity.
Conclusion: Residential psychiatric rehabilitation participants' continued psychiatric stabilization and improvement of remaining symptoms was attributed to increased community functioning and engagement in specific treatment modalities for particular symptoms. Participants had their own trajectories of change, indicating that the heterogeneity of this population impacted outcomes. Therefore benefits of psychiatric rehabilitation appear to include increasing and maintaining progress made in acute settings, and individualizing treatment is likely to maximize these benefits.
ID: 2091562

EFFECT OF PALIPERIDONE PALMITATE ONCE-MONTHLY IN IMPROVING AND MAINTAINING FUNCTIONING IN SUBJECTS WITH SCHIZOAFFECTIVE DISORDER USING THE DOMAINS OF THE PERSONAL AND SOCIAL PERFORMANCE SCALE

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Background: Improvement in social functioning is an important long-term treatment goal in patients with schizophrenia and schizoaffective disorder (SCA). This analysis evaluated the role of paliperidone palmitate once-monthly (PP1M) in improving and maintaining the 4 specific functioning domains of the Personal and Social Performance (PSP) scale in patients with SCA.
Methods: This randomized, double-blind (DB), placebo-controlled, international study (NCT01193153) included subjects meeting the DSM-IV diagnosis of SCA who experienced an acute exacerbation of psychotic and mood symptoms. Subject functioning was evaluated for those subjects stabilized on PP1M during the 25-week open-label (OL) phase who then entered the 15-month DB relapse-prevention phase. Functioning was evaluated using the PSP, scored from 1 to 100; higher scores indicated better functioning based on evaluation of 4 domains: socially useful activities, personal/social relationships, self-care, and disturbing/aggressive behaviors. Each PSP domain was assessed on a 6-point severity scale (absent to very severe impairment). Treatment response comparisons of PSP domain scores at DB endpoint were conducted using a Cochran-Mantel-Haenszel test. No adjustments were made for multiplicity.
Results: Of 667 subjects enrolled in the 25-week open-label phase, 334 subjects were stabilized on PP1M, entered the DB phase, and included in the analysis. After OL treatment with PP1M (OL endpoint = DB baseline), the percentage of subjects with good functioning (absent through mild impairment) for the 4 PSP domains increased (Table). A significant difference at DB endpoint favoring PP1M over placebo was observed for all 4 PSP domains in the proportion of subjects maintaining good functioning (P≤0.008 for all 4 PSP domains).

	SCA Subjects With Good Functioning							
Subjects, %	Socially useful activities		Personal and social relationships		Self-care		Disturbing and aggressive behavior	
OL Baseline	7.5		10.2		67.7		58.4	
OL Endpoint	63.5		76.3		97.6		99.4	
	Placebo	PP1M	Placebo	PP1M	Placebo	PP1M	Placebo	PP1M
DB Baseline	60.6	66.5	76.5	76.2	98.2	97.0	99.4	99.4
DB Endpoint	48.2	64.0	56.5	70.8	83.9	95.0	88.1	98.1

Conclusion: Among subjects with an acute exacerbation of SCA who completed 25 weeks of OL treatment with PP1M and then entered the DB phase, the 4 specific functioning domains of the PSP improved. These improvements were maintained with PP1M compared to placebo during the DB relapse-prevention phase for all 4 domains.
ID: 2087290

CLAYMATION ART THERAPY AS ADJUNCTIVE TREATMENT TO PROMOTE RECOVERY IN EARLY PSYCHOSIS: A PILOT STUDY

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Background: The Nova Scotia Early Psychosis Program (NSEPP) is interested in psychosocial interventions that can complement pharmacological treatments to promote clinical and personal recovery.
Preliminary research suggests that art therapy can improve mood symptoms, self-esteem and social skills in people with mental illness as well as strengthen identity and decrease negative symptoms in people with chronic psychosis.
Methods: We conducted a pilot study of 13-week Claymation art therapy group (n=9) in young adults with early phase psychosis to determine if this intervention could improve global and social functioning, as well as psychological domains of recovery such as hope, self-stigma, self-efficacy and scope of identity. Paired t-tests were used to examine pre to post and 3 month follow-up changes on these outcome measures. We also did a thematic qualitative analysis of individual exit interviews to deepen our understanding of how the program impacted the participants.
Results: Our pilot study demonstrated that this intervention was feasible for our program to deliver and had high patient adherence (31% attrition rate and 81% attendance rate). There were statistically significant improvements post-intervention in the clinician-rated global assessment of functioning scale (p=.006) and the personal and social performance scale (p=.04) that were maintained at the 3 month follow-up. There were trends towards significance post-intervention in the self-reported Miller Hope Scale (p=.063) and the Modified Engulfment Scale (scope of identity) (p=.072) which achieved significance at the 3-month follow-up (p=0.001 for both). We identified four dimensions from the qualitative analysis of participants' individual exit interviews: Participant Identity, Program Structure, Program Impact, and Recovery Perspectives. Program Impact was the most frequently occurring domain in the qualitative analysis. The themes in this domain identified positive program effects important to recovery: fostered emotional well-being, fostered skill development, enabled personal empowerment and fostered connection with others.
Conclusion: The results of our pilot study suggest Claymation art therapy is an engaging intervention to promote recovery for young adults with early phase psychosis that should be studied more rigorously in a randomized controlled trial.
ID: 2118441

COGNITIVE ADAPTATION TRAINING (CAT) AS A NURSING INTERVENTION IN LONG-TERM RESIDENTIAL PATIENTS WITH SEVERE MENTAL ILLNESS: A MULTICENTER CLUSTER RANDOMIZED CONTROLLED TRIAL

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Background: Despite the well-known impact of cognitive deficits in everyday functioning in patients with Severe Mental Illness (SMI), evidence-based interventions directed at these problems are scarce especially for SMI patients in long-term clinical facilities. Cognitive Adaptation Training (CAT) is a compensatory approach that aims at creating new routines in the patients' living environment through the use of environmental supports. Previous studies showed that CAT improves functioning in outpatients with schizophrenia when CAT is given by psychologists. The aim of this study is to evaluate the effect of CAT as a nursing intervention in SMI inpatients, predominantly with psychotic disorders who reside in long-term clinical facilities.
Methods: This is a multicenter cluster randomized controlled trial comparing CAT (intervention group) to Treatment As Usual (TAU, control group). The primary goal is to evaluate the effectiveness of CAT on everyday functioning.

The study has a duration of one year, with four follow-up measurements will be conducted at 15, 18, 21 and 24 months for the intervention group. Primary outcome measures are the Multnomah Community Ability Scale (MCAS) and the Social and Occupational Functioning Scale (SOFAS).
Results: Preliminary analyses (data available for 12 patients in each group on baseline, T3 & T6) showed no differences between the intervention and the control group on functional outcome.
Conclusion: The lack of a significant difference is not surprising given the small sample size and the fact that improvements in this chronic population is slow (Onken et al., 2002). However, based upon pilot results (Quee et al., 2014) we expect that functional outcome will be improved at 12 months and that these improvements will be sustained or further improved after that. If CAT is effective as a nursing intervention, it may be recommended to include CAT in the guidelines for SMI care and to implement the method in standardized care.
ID: 2095793

THE EFFICACY OF OCCUPATIONAL GOAL INTERVENTION FOR REHABILITATION OF EXECUTIVE FUCTIONS IN PATIENTS WITH TREATMENT-RESISTANT SCHIZOPHRENIA: RANDOMIZED CONTROLLED TRIAL

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Background: The executive deficits in schizophrenia are related with functional impairments that impede that the patients have an independent life. The aim of this study is to test the efficacy of Occupational Therapy (OT) based on the Occupational Goal Intervention (OGI) for the improvement of executive functions (EF) in patients with Treatment-Resistant Schizophrenia (TRS) as compared with a Control Group (CG).
Methods: Single blinded controlled trial (RTC), with 29 participants ages 18–55, who were randomized to the OGI group or the CG (craft activities). The patients were evaluated before (T0) and after treatment (T1) and after 6 month follow-up without intervention (T2). EF outcomes: The Behavioral Assessment of Dysexecutive Syndrome (BADS), the Direct Assessment of Functional Status (DAFS), which measures functional aspects and the Independent Living Skills Survey (ILSS) which assesses the occupational performance of patients in basic and instrumental activities of daily living. Cognition was measured by a standard neuropsychological battery. Both groups realized 30 sessions over a period 14–15 weeks and follow-up. Mixed Model Analysis was used.
Results: Both groups showed no differences in terms of demographic variables and disease severity at the baseline. The OGI was significantly more effective than the CG in terms of improvement EF, and the effect remained after 6 months. The BADS total showed a group effect (p=0.04). The DAFS showed a group effect (p=0.04) and time effect (p=0.03) on the temporal orientation subscale, showing that the OGI was superior to the CG in this subitem throughout the whole the study. The ILSS showed a group effect (p=0.00) in OGI when compared to the CG, even with the slight decrease in the follow-up. We found no statistically significant differences between groups in terms of cognitive functions, except a group and time effects on the Stroup 1 (p=0.04), Stroop 2 (p=0.03), Stroop 3 (p=0.03) as well the Wisconsin test (p=0.01).

The table shows Group Effect, Time Effect and Group versus Time Effect

Effects	BADS	DAFS	ILSS	Stroop 1	Stroop 2	Stroop 3	WISC
Group	p=0.04*	p=0.04*	p=0.00*	p=0.85	p=0.58	p=0.39	p=0.47
Time	p=0.21	p=0.03*	p=0.20	p=0.08	p=0.03*	p=0.03*	p=0.01*
Group*Time	p=0.75	p=0.06	p=0.06	p=0.04*	p=0.53	p=0.27	p=0.69

Conclusion: The OGI method showed efficacy in terms of global improvement and in some measures of EF, which were maintained after 6 months follow up, without intervention.
ID: 2082247

THE IMPACT OF RESILIENCE ON QUALITY OF LIFE IN PATIENTS WITH SCHIZOPHRENIA

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Background: Resilience can be defined as the successful adaptation despite risk and adversity and is becoming an important topic in patients with schizophrenia since there is evidence that it increases the probability for long-term recovery in those patients. The aim of this study was to investigate to what extent quality of life correlates with resilience and severity of illness.
Methods: We recruited patients with schizophrenia on an out-patient basis. Diagnoses were confirmed with the Mini International Neuropsychiatric Interview (M.I.N.I.). Resilience was assessed by the Resilience-Scale (RS-25) and psychopathology was assessed by the Positive and Negative Syndrome Scale (PANSS). In addition, the German version of the Lancashire Quality of Life Profile, the Berliner Lebensqualitätsprofil (BELP) was used.
Results: So far, a total number of 40 patients (19 males, 21 females) with a mean age of 45.3 ± 10.2 years took part in this study. The mean duration of illness was 15.8 ± 2.9 years. The mean PANSS total score was 58.2 ± 18.6, the mean RS-25 score was 130.8 ± 21.7, and the BELP subscales showed a mean score of 4.65 (range 1–7). Statistical analysis showed a stronger correlation between quality of life (QOL) and resilience (r=0.56, correlation with general life satisfaction) than between QOL and psychopathology (r= -0.39). The majority of the correlations between QOL (BELP subscales) and resilience remained significant after adjustment for psychopathology by partial correlation analysis. This applied in particular to the BELP subscales of work, social life (friends) and mental health.
Conclusion: Preliminary results show that schizophrenia patients' quality of life correlates stronger with resilience than with the severity of illness. Accordingly, resilience might have an important impact on long-term recovery of patients with schizophrenia.
ID: 2105277

THE IMPACT OF PSYCHOSIS RISK SYMPTOM CHANGE ON SOCIAL AND ROLE FUNCTIONING

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Background: Previous findings suggest lower levels of functioning associated with psychosis risk symptoms. Although social and role functioning

generally improve among those at risk for psychosis who do not transition to psychosis, researchers advocate monitoring individuals for signs of early symptom remission or deterioration. The current study seeks to examine the relation between psychosis-risk symptom change and social and role functioning over a six-month period. We hypothesize that psychosis-risk symptom change from baseline to six month follow-up will predict social and role functioning at six months.

Methods: Sixty-four adolescents (age 12–22) currently receiving mental health services were interviewed at baseline and 6-month follow up regarding symptoms of psychosis-risk and current functioning. Difference scores were calculated for baseline and 6-month psychosis-risk symptom domains, such that negative difference scores indicated worsening symptoms, positive difference scores indicated improving symptoms and no change in symptoms was regarded as stable. Separate linear regressions were run for social and role functioning as dependent variables, with baseline social or role functioning scores; and positive, negative, general, and disorganized difference scores entered into the regression model.

Results: Results of the linear regression models indicate that changes in positive and negative symptoms significantly contribute to six-month assessment of social and role functioning.

Conclusion: At six months, symptom severity across psychosis-risk domains largely appears to improve. Change in risk symptoms over six months predicts functioning at six months, with positive and negative symptom change being significant contributors to prediction. Among those demonstrating worsening symptom severity over time, this decline seemed particularly related to role functioning. Early positive and negative symptom deterioration may indicate a subgroup of individuals who warrant closer monitoring to ensure that symptom severity does not further decline over time.

ID: 2119444

LONG-TERM OUTCOME FOLLOWING EARLY DOSE-REDUCTION OF ANTIPSYCHOTICS IN REMITTED FIRST EPISODE PSYCHOSIS

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Background: Long-term functional outcome of dose-reduction strategies in first episode psychosis (FEP) has not been studied before. The present study compared 7-year outcome of an early antipsychotic dose-reduction/discontinuation (DR) strategy with maintenance treatment (MT). Primary outcome was (symptomatic and functional) recovery; relapse rates, functional and symptomatic remission were secondary outcomes.

Methods: FEP patients (N=128) symptomatically remitted for 6m during their first treatment year who completed an 18 months trial comparing MT and DR were followed-up at 7 years. Symptomatic remission criteria were adopted from Andreasen et al., functional remission criteria were based on a functioning scale. Recovery was defined as meeting both criteria sets. MT or DR strategy, and baseline parameters were entered in a logistic regression analysis with symptom and functional remission and recovery at 7-years follow-up as dependent variables.

Results: 103 patients consented to participate. DR-patients showed twice the recovery-rate of MT-patients (40% against 18%), odds ratio 3.5 (P=.014). Symptomatic remission-rates were equal (69% and 67%). Better DR recovery-rates were attributable to higher functional remission-rates (46% vs. 20%) in DR. Predictors of recovery were DR, baseline living together and less severe negative symptoms. During the last 2 years of follow-up the mean daily dose in haloperidol equivalents was 2.20mg in DR vs. 3.60mg in MT (P=.031).

Relapse-rates were initially higher in DR but leveled at 3 years; 61.5% relapsed in DR and 68.6% in MT in 7 years.

Conclusion: DR of antipsychotics during early stages of remitted FEP significantly improved 7-years outcome in terms of recovery and functional remission compared to maintenance treatment. Though initially relapse-rates in GD were higher, these equaled those in MT from 3 years to the end of the study. While the necessity of immediate antipsychotic treatment in FEP and positive symptoms relapse is robustly demonstrated in a great number of studies, this study suggests that we are faced with a dilemma concerning the drawbacks of long-term maintenance antipsychotic treatment on functional capacity. Though antipsychotic discontinuation appears only feasible without relapse in a substantial minority of patients, guided dose-reduction as far as positive symptoms remain subsided and allow it, appears a feasible strategy in view of functional recovery, doing justice to both sides of the dilemma.

ID: 2117435

A CHILDHOOD WITHOUT MALTREATMENT PROTECTS AGAINST POOR LONG TERM FUNCTIONING IN THE ULTRA HIGH RISK GROUP

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Background: The rate of development of schizophrenia and other psychotic disorders has traditionally been the main outcome of interest in the Ultra High Risk (UHR) ("prodromal") group. However, the majority of UHR patients do not develop psychotic disorder even up to 10 years post identification yet many remain symptomatic and disabled. It is important therefore to study psychosocial functioning as an outcome. To date, studies that have examined functional outcome in the UHR population have tended to have small sample sizes and either cross-sectional or only medium-term follow up data Long-term follow up studies are needed. Additionally, although bullying in childhood has been associated with poor functioning cross sectionally and sexual abuse in childhood has been associated with risk for transition, the role of childhood trauma in relation to functioning over the long term has not yet been examined.

We therefore aimed to determine which clinical factors, including history of childhood maltreatment, predict poor functional outcome in UHR individuals

Methods: Participants were from the PACE (Personal Assessment and Clinical Evaluation) clinic in Melbourne, Australia. The current data are part of a longitudinal study aimed at reassessing all participants who were in research studies at PACE between 1993 and 2006 (N=416). The current sample consists of the 268 UHR participants (152 females; 116 males) who completed assessment of functioning at follow-up interview between 2.39 and 14.87 years post-identification.

Results: Positive and negative symptoms, impaired emotional functioning prolonged duration of untreated illness, baseline low functioning and history of childhood maltreatment all predicted poor functioning at follow up in a univariate analysis. In the multivariate regression, only childhood maltreatment was associated with poor functioning. The association remained significant even after adjusting for transition status.

Conclusion: Childhood maltreatment not only predicts development of psychosis but also poor long term functioning in the UHR group. This underlines the importance of recognising childhood trauma and managing it in treatment. We also speculate about the mechanisms, both biological and psychological, of the association and the interaction between these mechanisms.

ID: 2107734

Genetics: Basic; Clinical

CHARACTERIZATION OF A DELETION AT THE SLC1A1 GLUTAMATE TRANSPORTER GENE THAT COSEGREGATES WITH SCHIZOPHRENIA IN A 5-GENERATION FAMILY

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Background: Glutamatergic systems have been strongly implicated in the pathophysiology of psychosis. Our newly discovered deletion at the SLC1A1 gene carried by members of a 5-generation family in the Pacific island of Palau co-segregates with schizophrenia. SLC1A1 gene encodes EAAT3, a neuronal glutamate transporter. The deletion eliminates the entire promoter, start codon and the first transmembrane domain of the protein. The present study sought to determine if the sequence replacing the native promoter in deleted SLC1A1 allele can promote transcription and if the 5'-truncated EAAT3 is functional in transporting glutamate.
Methods: 1 Kb of the native exon 1 promoter and putative exon 2 promoter sequence were cloned into firefly luciferase vector. A dual luciferase assay was performed to compare the promoter activity of cloned regions transfected into HEK293 cells (n=20).
Xenopus oocytes were injected with either truncated or non-truncated SLC1A1 mRNA and incubated for 3–5 days (n=15). Oocytes were clamped to a holding potential of -60 mV and 2mM glutamate was bath applied. Glutamate-induced inward currents were recorded by two electrode voltage clamp.
Results: The promoter activity of the exon 2 upstream sequence was more than 7-fold higher than the native promoter (p<5.7E-8).
Electrogenic glutamate transport was apparent in the oocytes expressing WT EAAT3. However, the current was negligible in oocytes expressing the truncated EAAT3, and resembled the results seen following water injection.
Conclusion: The intron 1 sequence replacing the native promoter in partially deleted SLC1A1 allele promote expression but the truncated expressed protein cannot function as a glutamate transporter.
ID: 2119516

NOVEL STATISTICAL APPROACHES TO WHOLE EXOME AND GENE EXPRESSION DATA IN LARGE PEDIGREES

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Background: High-throughput genome-wide genomic and transcriptomic approaches are revolutionizing genetic studies of complex phenotypes, making it feasible to comprehensively assess protein coding variants and to screen thousand of potential biomarkers or endophenotypes. MicroRNAs represent one such intermediate phenotype that may be useful for gene identification or for understanding mechanisms that connect genotype to illness. As we turn from screening common genetic variants through genome-wide association studies to identification and characterization of rare, perhaps even private, functional mutations through genome sequencing, the study of carefully selected extended pedigrees presents both analytical challenges and opportunities. In particular, large pedigrees offer the chance to sample multiple copies of rare alleles through relatives who inherited them from a common ancestor. We will discuss the study design advantages of large pedigrees, present new statistical genetic approaches we are developing to study rare variants, and show results from exome and gene expression screens in multiplex schizophrenia (SCZ) pedigrees from the Multiplex-Multigenerational Genetic Investigation (MGI) study.
Methods: Exome sequencing using the Illumina TruSeq platform has been completed in 134 individuals from 8 families, including 25 individuals with SCZ or schizoaffective disorder, depressed type. In total, 11,878 missense variants were identified that passed standard quality control filters. MicroRNAs were extracted from lymphoblastoid cell lines of 574 MGI participants and sequenced on the Illumina GAIIx utilizing TruSeq small RNA technology.
Results: We identified 1279 variably expressed microRNAs of which 928 are heritable. Has-miR-937 is associated with performance on a test of verbal memory (p = 5.4x10-5) and levels of this microRNA are lower in individuals with SCZ (p = 9.8x10-3). In analyses of exome sequence, we identified two variants significantly associated with SCZ after correcting for multiple testing, in AMACR and TMEM176A. In a region of chromosome 5 previously linked to abstraction and mental flexibility (ABF), we identified two additional missense mutations associated with ABF and SCZ, in SYNPO and WWC1. Both of these genes are linked to AMPA receptor trafficking.
Conclusion: Large pedigrees offer unique advantages for identifying and characterizing genetic influences on complex phenotypes, particularly within the context of analysis of exome sequence data to identify rare risk alleles.
ID: 2088171

MICRORNA MECHANISMS IMPLICATED BY RARE COPY NUMBER VARIANTS AND SCHIZOPHRENIA CAUSATION

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Background: Rare copy number variants (CNVs) such as 22q11.2 deletions are now known to be major contributors to causation of schizophrenia. These deletions and duplications not only overlap protein-coding genes but also microRNAs (miRNAs), thus potentially implicating target genes genome-wide.
Methods: We identified 1) miRNAs overlapped by the 22q11.2 microdeletion and 2) in well characterized cohorts of schizophrenia cases and controls, miRNAs overlapped by other rare CNVs. Two standard miRNA prediction tools were used to generate predicted target genes. We then performed functional gene-set enrichment analyses using these genes.
Results: We found that 22q11.2 deletions and other rare CNVs are enriched for miRNAs. The genes predicted to be targeted by these miRNAs are significantly enriched for neurodevelopmental functions. These include genes such as NTRK2, PAK2 and SYNGAP1, and others that implicate glutamatergic and dopaminergic networks.
Conclusion: The miRNA mechanisms implicated by rare CNVs associated with schizophrenia support an expanded multihit model of causation have potential implications for miRNA-based therapeutics.
ID: 2093148

DOSAGE EFFECTS OF 22Q11.2 GENES ON BRAIN STRUCTURE AND FUNCTION.

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Background: Recent findings show that duplications at 22q11.2 are substantially less common in schizophrenia cases than in the general population, indicating that duplications at this locus may represent a putative protective mutation for schizophrenia. However, duplications at the 22q11.2 locus are increasingly associated with autism risk. Investigating the effects of these

reciprocal imbalances on underlying neural processes may offer a potential window into how these CNV's disrupt the brain and ultimately, contribute to disease pathogenesis.
Methods: Here we used high-resolution structural magnetic resonance imaging (MRI) and network
analyses of blood-based gene expression data to investigate whether specific dosage effects of genes within the 22q11.2 locus regulate neuroanatomic traits in a reciprocal manner. We investigated neuroanatomic variation in sixty children and adolescents with 22q11.2 deletions or duplications, relative to typically developing, age-matched controls. Next, we conducted whole-genome transcriptional profiling and used systems biology methods (Weighted Gene Coexpression Network Analysis; WGCNA) to identify networks of co-expressed genes associated with symptoms and neuroanatomic traits.
Results: Similar to children with idiopathic autism, patients with 22q11.2 duplications showed volumetric increases in the medial orbitofrontal cortex (mOFC), cingulate
gyrus, precuneus, insula and the fusiform gyri, brain regions critically implicated in social cognition and affective processing. In contrast, 22q11.2 deletion patients showed significant decreases in these same regions relative to controls. WGCNA identified 3 gene expression modules that were enriched for brain-expressed genes, which were significantly associated with reciprocal variation in these brain regions. Moreover, genes co-expressed in these modules were down-regulated in 22q11.2 deletion patients with psychotic symptoms.
Conclusion: This "genetics first" approach reveals that dosage-sensitive genes in the 22q11.2
locus give rise to mirrored phenotypes in brain regions critical for social processes. Further, gene co-expression modules were significantly related to psychotic symptoms and brain structure. This approach may accelerate the shift towards personalized therapeutic approaches, and contribute new insights into the pathogenesis of neuropsychiatric disorders associated with these CNV's, particularly schizophrenia and autism.
ID: 2117961

CNVS AND POLYGENIC SCORES INTERACT TO CONTRIBUTE TO SCHIZOPHRENIA RISK

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Background: Both rare copy number variants (CNVs) and common single nucleotide polymorphisms (SNPs) contribute to the genetic risk for schizophrenia. Several specific CNV regions and an increased burden of large deletion CNVs have demonstrated associations with schizophrenia. A significantly higher polygenic risk score in subjects with schizophrenia has also been established, confirming that many common SNPs confer risk for this disorder as well. The relationships between these rare and common genetic risk factors have not been thoroughly investigated, and we sought to address the following questions: 1) Do cases with CNVs have lower polygenic risk scores compared to cases without CNVs? 2) Do cases with CNVs have higher polygenic risk scores compared to controls with CNVs? 3) Do controls with CNVs have lower polygenic risk scores than controls without CNVs?
Methods: CNV and GWAS data from 22,065 schizophrenia cases and 21,700 controls the Psychiatric Genomics Consortium were used. CNV carriers were defined by the classes of CNVs conferring the greatest disease risks: 1) having one of 14 specific CNVs previously associated with schizophrenia, or 2) carrying any large CNV deletion greater than 500kb.
Results: SNPs and CNVs both contribute to risk for schizophrenia and the results imply interactions between these risk factors. Complex relationships between the different definitions of CNV carrier status and polygenic risk were revealed.
Conclusion: These results offer insight into the genetic architecture of schizophrenia by illuminating the ways in which different types of established genetic risk loci interact to confer disease risk.
ID: 2118820

INTEGRATING GENOMIC NETWORKS AND NEURAL CIRCUITS IN SCHIZOPHRENIA

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Background: The COGS-1 family study and COGS-2 case control study have now deeply (endo)phenotyped and are genotyping over 4000 individuals. This includes over 1500 subjects from the 296 COGS-1 family study and 2500 subjects from the COGS-2 case control study. To account for heterogeneity and to facilitate accurate genotypic analyses, the subjects were carefully examined over 1–2 days of diagnostic, clinical, neurocognitive and neurophysiological endophenotyping.
Methods: COGS-I ascertained and deeply endophenotyped 296 families (over 1,500 subjects). FIGS-based diagnostic information was obtained on an additional 2,000 family members. COGS-2 used a well standardized approach for endophenotypic analyses of 2500 subjects in a "case-control" follow up study. In all, 20 schizophrenia-related endophenotypes were assessed, in addition to detailed demographic, clinical and functional outcome data and genotyping.
Results: An overview of results to date will be presented, including behavioral, genomic, and an integrated view of how all these data can be parsimoniously organized in order to illuminate the march to precision-personalized medicine. The results replicate a 42 gene network centered around ERBB4-NRG1, a reflection of glutamate-related deficits.
Conclusion: Research into organ based disorders are made more challenging when the organ in question, the brain, is encased as it is in a cranial vault. Adding to this challenge, common heritable psychiatric disorders also reflect dysfunction of complex neural circuits rather than discrete, cellular-specific mitotic events. This presentation will thus be both empirical and conceptual, discussing emerging new strategies and new approaches to deconstructing and overcoming the functional disabilities associated with schizophrenia. The discussion will center on integrating what COGS has discovered behaviorally in the largest deeply endophenotyped study in schizophrenia. The discussion will also center on how emerging related genomic information is being translated from lab to clinic.
ID: 2119517

MOSAICISM MAY UNDERLIE PLEIOTROPIC PSYCHIATRIC PHENOTYPES

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Background: Copy number variants (CNVs) involving the 9p region have been observed in patients with SZ, ASD, BPD, and ID. Using a

genome-wide copy-number scan (Nimblegen HD2 2.1 M), we identified a ~1.8 Mb duplication-triplication on 9p.24.1 in a proband with a diagnosis of schizo-affective disorder and in his mother, who has a diagnosis of bipolar disorder with psychotic features. Remarkably, the triplicated region includes GLDC and KDM4C; deletions and duplications involving those genes have been observed in ASD cohorts as well as in patients with SZ, BPD or ID. GLDC is the enzyme that catabolizes glycine, a co-agonist of the NMDA receptor (NMDAR). Triplication of GLDC would be expected to accelerate degradation of glycine, resulting in low levels of brain glycine and NMDAR-mediated hypofunction, which has been strongly implicated in the pathophysiology of psychotic disorders.
Methods: We designed a custom high density array CGH and further sequenced breakpoint junctions to gain insights into the novel 9p molecular structure. Study of the mRNA from lymphoblastoid cell lines was also performed to check for fusion gene formation. In addition, fibroblasts from proband and mother were obtained and are currently being reprogrammed into human induced pluripotent stem cells (hIPSCs).
Results: This rare CNV was confirmed as a de novo event in the mother using a customized high-density Agilent array CGH platform. Sequencing of the CNV breakpoint junctions revealed that this CNV was more complex than originally thought due to the presence of insertions of variable sizes into the junction, including a 65.2 kb segment that was copied from the intron of the nearby gene PTPRD. This rearrangement caused the formation of a fusion gene (UHRF2-KDM4C) as revealed by mRNA expression in the proband. We also found evidence that the mother was mosaic for this de novo rearrangement as the CNV was present in genomic DNA extracted from blood and from her fibroblasts but not in the derived lymphoblastoid cell line or in the derived iPSCs.
Conclusion: Breakpoint junction sequencing studies provides valuable information that complements the results of copy-number scans and helps to further characterize structural variants. The mosaicism in the mother may be related to her less severe clinical phenotype. Mosaicism may be a factor in pleiotropic phenotypes as well as variable penetrance.
ID: 2089468

METHYLOMIC ANALYSIS OF THE PSYCHOTIC TRANSITION

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Background: Schizophrenia is a complex disorder involving both genetic and environmental factors. Epigenetic is a growing theory to explain these interactions at a molecular level. It is well-known that schizophrenia begins with prodromal symptoms and patients undergoing sub-threshold symptoms are named ultra-high risk (UHR) subjects. Therapeutic and prognostic attitude remain challenging for this population. According to the model of the gene-environment interactions, the psychotic transition in adolescence could be related to epigenetic changes during the psychotic transition.
Methods: We designed and performed the first longitudinal study about whole-genome DNA methylation changes. 39 UHR patients were recruited in specialized center C'JAAD - Centre Hospitalier Ste Anne - Paris (France). During follow-up, 14 of them became psychotic (converters) according to the validated scale CAARMS. Initial and final methylation were investigated by Infinium Human Methylation450 BeadChip for 450 000 CpG after bisulfite conversion.
Results: The psychotic transition was not associated with global methylation changes. Linear models failed to identify CpG and genes significantly associated with psychotic transition after Bonferroni correction. Analyses of the top results provided a cluster which could classify perfectly converters and non-converters. These genes of interest are over-represented in biological pathways with relevance for psychotic physiopathology. Individual analyses highlighted the biological heterogeneity of the psychotic transition.
Conclusion: Improving physiopathological understanding of psychotic transition is a current challenge to identify biomarkers and to develop targeted preventive interventions available in clinical practice for UHR subjects. The epigenetic processes and in particular DNA methylation could be interesting factors.
ID: 2118593

LEVERAGING MOLECULAR PATHWAY DATA FROM SCHIZOPHRENIA GENOMIC STUDIES

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Background: Background: Schizophrenia is a complex genetic syndrome likely involving a contribution from a number of molecular etiologies spread across a spectrum of risk alleles. Most progress has been made in studies of common variants of small effect (genome-wide association studies (GWAS)). We know that these account for 25–35% of genetic variance, representing a contribution from thousands of individual loci of which ~108 have been confirmed. Genomic sequencing approaches make it possible to assay rare coding point mutations and small insertions and deletions (indels): these represent a class of mutation likely to be enriched for genetic variants of larger effect and may be easier to interpret in animal and cellular models.
Methods: Methods: Identifying convergent molecular etiology across genetic models of schizophrenia is a potentially approach to understanding schizophrenia biology. Defining which models to test represents a significant challenge.
Results: Results: Results from the GWAS studies provide limited power for hypothesis-free pathway analysis. Approaches to candidate gene selection will be discussed and applied in a meta-analysis of currently available sequence data. This will facilitate direct testing of metabolic pathways for functional mutations.
Conclusion: Conclusions: Schizophrenia is a heterogeneous, etiologically complex syndrome. Modern advances in genomics, transcriptomics and proteomics offer unprecedented potential to identify the molecular etiology involved.
ID: 2118375

NMDA RECEPTOR DYSFUNCTION IN SCHIZOPHRENIA: THE ROLE OF THE RISK GENE, SERINE RACEMASE

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Background: Considerable evidence supports the hypothesis that NMDA receptor (R) hypofunction contributes to the cognitive deficits and negative symptoms in schizophrenia. Serine racemase (SR), which catalyzes the synthesis of D-serine, the NMDAR co-agonist in forebrain, has been shown to be a risk gene for schizophrenia in a recent large genome wide association study (GWAS). As there has been controversy over the cellular localization of SR and D-serine in brain, we have coupled immunocytochemistry with cell selective conditional suppression of SR expression to determine their localization and the effects of cellular loss of SR.

Methods: Mice with exon 1 of SR flanked with loxP sites were crossed with mice constitutively expressing Cre (SR-/-) or mice with Cre driven by a CamKinase IIα promoter (glutamatergic neurons), glial fibrillary acidic protein (GFAP) promoter (astrocytes) or a glutamate decarboxylase (GAD65) promoter (GABAergic neurons). Immunocytochemistry for SR and D-serine used SR-/- as controls to ensure specificity of immunostaining. Reactive astrocytes were induced in vivo in adult mouse hippocampus and cortex.
Results: Previous studies indicate that SR-/- male mice exhibit structural deficits (reduced dendritic complexity, reduced spines, cortical atrophy and ventricular enlargement), neurochemical stigmata, and cognitive impairments similar to schizophrenia that can be reversed by treating sub-chronically with D-serine. Cell selective suppression of SR expression indicates that ~75% of hippocampal SR is expressed in neurons with <25% localized to astrocytes whereas in the striatum ~ 50% of SR protein is expressed in glutamatergic terminals and the rest in GABAergic inter-neurons with no detectable astrocytic expression. However, GFAP-positive reactive astrocytes do express SR.
Conclusion: These findings indicate that constitutive inactivation of the SR gene, a risk gene for schizophrenia, results in a robust replication of many of the phenotypic features of schizophrenia due to reduced activation of synaptic NMDARs by D-serine synthesized in forebrain neurons. However, inflammatory activation of astrocytes results in their SR expression, thereby facilitating the stimulation of extra-synaptic NMDARs and further compromising neuronal function in schizophrenia. Thus, schizophrenia may involve both hypo- and hyper-functional NMDARs.
ID: 2085528

DENDRITIC SPINE MORPHOLOGY IS ALTERED IN HUMAN INDUCED PLURIPOTENT STEM CELL (IPSC) DERIVED NEURONS WITH CHROMOSOME 15Q11.2 DELETIONS

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Background: A copy number variant (CNV) on chromosome 15q11.2 causes deletion of four genes and elevates risk for several neurodevelopmental disorders. Altered expression of CYFIP1, one of the deleted genes causes profound changes in dendritic spine morphology and function in rodent neurons. Human induced pluripotent stem cells (iPSCs) bearing the CNV show altered differentiation patterns in neuronal and glial lineages also attributable to hemizygous expression of CYFIP1, but it is not known whether iPSC derived neurons (i-neurons) bearing the CNV also have altered dendritic spine morphology
Methods: iPSCs were generated from fibroblasts provided by a mother and her offspring (both carrying the 15q11.2 CNV), and an individual without the CNV. The iPSCs were differentiated into i-neurons and quantitative real time PCR performed for the genes from the CNV region. Morphological features of dendritic spines were quantified in pEGFP transfected i-neurons. Using confocal microscopy, dendrites and dendritic spines were manually reconstructed and subjected to automated Sholl analysis using Imaris software
Results: The i-neurons expressed vGLUT1 and functional ligand-gated channels. Reduced expression of four CNV-related genes was present in iPSCs, neurons and NPCs derived from the mother and the offspring. CNV bearing i-neurons also had reduced levels of CYFIP1 protein, reduced dendritic spine density and increased proportions of immature-to-mature spines
Conclusion: The observations are consistent with published rodent CYFIP1 knockout studies. The altered dendritic morphology observed in the i-neurons could serve as an additional feature in iPSC-based models of 15q11.2 CNVs; they may reflect developmental abnormalities noted earlier.
ID: 2095720

CPG SNPS AND DIFFERENTIAL ALLELIC EXPRESSION IN SUICIDAL BEHAVIOR AND SCHIZOPHRENIA

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Background: Several studies have suggested that suicidal behavior is partially determined by genetic factors, supporting a search for candidate genes involved in the neurobiology of suicidal behavior. HTR1B has been highlighted in the literature as being involved in suicidal behavior. We analyzed the parent-of-origin effect (POE) in suicide attempters and the differential expression of HTR1B rs6296 C/G alleles in suicide victims.
Methods: Methods: We performed a family-based association study of rs6296 polymorphism in 273 nuclear families with at least one subject affected by affective and non-affective psychosis with suicidal behavior, and compared C861G (rs6296) allele-specific mRNA levels in post-mortem brain samples from suicide and non-suicide victims in 165 frontal cortices from the Stanley Medical Research.
Results: We did not find preferential transmission of C861G in suicide attempters when we considered paternal or maternal meiosis and we did not find any altered allelic expression ratio in suicide victims compared to controls.
Conclusion:: These data do not support a role for allelic imbalance or POE of HTR1B for suicidal behaviour in major psychoses.
ID: 2119378

GENOME-WIDE GENE-BASED ANALYSIS OF PSYCHOTIC ILLNESS SYMPTOM DIMENSIONS BASED ON A NEW SCHIZOPHRENIA-SPECIFIC MODEL OF THE OPCRIT

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Background: Enhancing phenotype measurement could more effectively identify genes that modify schizophrenia symptoms. Previous research has used quantitative phenotypes based on factor analyses that included both affective and non-affective psychosis cases. It is possible that deriving "schizophrenia-specific" factor loadings from analysis of pure cases would yield more sensitive factor scores for gene pathway and gene ontology analyses. Using an Irish case sample, this study sought to 1) factor analyze cases with schizophrenia only, 2) score the full psychosis sample based on these factor loadings, and 3) implement genome-wide association (GWAS) and gene-based analysis of these schizophrenia-based symptom factors.
Methods: Clinical interview, medical records, and established consensus methods had been used to determine psychiatric diagnosis. We conducted a factor analysis of 60 clinician-rated OPCRIT items in the schizophrenia cases using R, and scores were empirically derived for the entire Irish family case sample and merged with available DNA data (final N = 507). The sample had been genotyped on the Illumina 610-Quad platform and was imputed to the 1000 Genomes reference panel. We conducted GWAS on each of the three symptom factors using MERLIN-Offline to determine whether factor scores would more sensitively detect association.

Results: Three factors emerged from the analysis of symptom ratings of the schizophrenia cases: an Affective/Negative symptom factor, a Depressive symptom factor, and a Schneiderian symptom factor. In gene-based analyses, multiple genes had q<0.01. PTPRG and WBP1L, top genes associated with the first two symptom factors, have previously been implicated in schizophrenia case-control status in PGC samples. Gene pathway analyses of the first, primary factor indicated over-representation of glutamatergic transmission, vascular health, GABA A receptors, and cyclic GMP pathways.
Conclusion: When factor-analyzing symptom ratings in the schizophrenia-only case sample, factors emerged that were more sensitive than previously derived factors to gene pathway and gene ontology associations. This is consistent with genetic overlap between affective and negative symptoms of schizophrenia. Results suggest that pathways affecting glutamate, GABA, and vasodilation have influence on core schizophrenia symptom presentation.
ID: 2076705

SEXUAL DIMORPHISM OF THE CATECHOL-O-METHYLTRANSFERASE GENE AND SOCIAL FUNCTIONING

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Background: For patients with schizophrenia, impaired social functioning has been documented and associated with dopamine metabolism. The catechol-o-methyltransferase (COMT) 158 Val/Met variant has been examined in relation to cognition, due to its role in dopamine metabolism and reported sex related differences in activity. Our study sought to extend this research and examine the relationship between the COMT 158Val/Met variant and sex on social functioning.
Methods: Participants with schizophrenia receiving antipsychotics consented to DNA testing, and completed demographic questions, the Social Adjustment Scale-Self-Report (SAS-SR), and the Brief Assessment of Cognition in Schizophrenia (BACS) as a cross-sectional assessment. Reverse-mean scores were calculated from the SAS-SR. A factorial analysis examined the main effects and interactions of Val-carrying status (Val and non-Val carriers) and sex (male and female) with BACS scores as a covariate on SAS-SR scores.
Results: A total of 121 participants with schizophrenia were included (56.9% males). The mean age was 45.1 ± 11.4 and 43.1% were Caucasian. A main effect of sex was significant (p=0.01) indicating that males had higher social functioning. An interaction of COMT and sex was also significant (p=0.009), where male non-Val carriers had the highest levels of social functioning (M=4.07) while female non-Val carriers had the lowest (M=3.18). Male and female Val-carriers (M=3.27 and W=3.78) did not significantly differ.
Conclusion: These results suggest that in regards to social functioning, the Val-variant allele is detrimental for males, but beneficial for females. Future research should establish the sexual dimorphic influence of the Val-allele on dopamine metabolism and specify its impact on different domains of social functioning.
ID: 2091866

QUALITY CONTROL AND QUANTITATIVE ANALYSIS OF RNA SEQUENCING DATA IN POST-MORTEM CLINICAL SAMPLES

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Background: Schizophrenia is a complex psychiatric disorder whose disease course is proposed to initiate prenatally, followed by an acute break of the disease in the late teens through third decade of life, after which subjects may persist with the disease late into geriatric stages of life. The syndromic nature of the disease, coupled with the prolonged disease duration, concomitant polypharmaceutic treatments and drug of abuse confounds (ie tobacco usage) and frequent long postmortem intervals preceding tissue collection contribute to create a challenging dataset for transcriptome analysis.
Methods: We have developed a comprehensive quality control and statistical analysis process for qualification of RNAseq data and subsequent quantitative analysis of resulting data. The quality control process incorporates standard RNAseq measures (base quality/composition, template length and duplicate frequency) coupled to novel heterologous organism and 3' bias detection methods, sample identity and mixing analysis to identify and quantify potential confounds in RNAseq data. Incorporation of this information into statistical models allows more discrete resolution of technical versus biological variables in subsequent analyses.
Results: We identified a small subset of samples (among 746 total) which had aberrant read quality/base composition/duplicate content profiles, which will be evaluated to determine the impact on overall data quality. Additionally, heterologous organism analysis identified minor rodent contamination in 2 samples but no overt viral content or fusion events. 3' bias analysis identified a continuum of quality which we have currently classified in 4 categorical groups. Sample identity analysis, leveraging RNAseq as well as DNA SNP information, identified a small group of samples with suggested discordance which are being further investigated. Ethnicity analysis identified a small group of samples with informatically-predicted ethnicity different than human-reported ethnicity.
Conclusion: RNAseq analysis of the transcriptome integrates many sources of technical and biological variation. The single molecule-level resolution of this data allows the deconvolution of these variables in far greater detail than have been previously available with other methodologies (eg microarray). Our QC analysis provides the information necessary to incorporate these variables into subsequent quantitative analyses of gene expression, which will lead to a more robust and accurate result.
ID: 2118525

REDUCED PROTEIN SYNTHESIS IN OLFACTORY NEUROSPHERE-DERIVED STEM CELLS FROM SCHIZOPHRENIA PATIENTS

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Background: Schizophrenia-derived neural stem cells are accessible disease models that have the potential to provide novel insight into the broad molecular mechanisms that are dysregulated in the disease. We aimed to identify functional dysregulation in schizophrenia-derived olfactory neurosphere-derived stem cells through discovery-based proteomic expression profiling followed by targeted functional analyses. Olfactory mucosa

biopsies obtained from 9 patients with schizophrenia and 9 controls were grown as neurospheres, and then in adherent cultures.
Methods: Protein expression was assessed using quantitative mass spectrometry. Differentially expressed proteins were validated by western blotting and targeted mass spectrometry. Pathway analysis of protein and gene expression changes identified dysregulated cellular signalling pathways. Protein synthesis was assessed in vitro using a fluorescent reporter and image-based quantification. Finally, gene-based testing and gene-set enrichment analyses of dysfunctional protein pathways were used to identify significant associations with the schizophrenia phenotype in GWAS data from >13,000 schizophrenia patients, available through the Psychiatric Genetic Consortium.
Results: 102 proteins were differentially expressed in schizophrenia-derived ONS cells, including significant reductions in 17 ribosomal proteins. Pathway analysis of proteomic and mRNA expression data from the same cells identified significant deficits in eIF2α, eIF4, and mTOR signalling pathways concerned with regulation of protein synthesis. The phosphorylation state of eIF2α, which regulates the initiation of protein synthesis, was significantly decreased in schizophrenia-derived cells. Quantification of protein synthesis demonstrated a significant deficit in the rate of protein synthesis in schizophrenia-derived ONS cells but not in (non-neural) fibroblasts from the same patients. Finally, a genetic link with the eIF2α signalling pathways emerged from reanalysis of published GWAS data which identified an association with the regulatory kinase EIF2AK2.
Conclusion: Our findings indicate that there is a reduction in eIF2 regulated protein synthesis in schizophrenia. As deficits in eIF2 mediated protein synthesis disrupt synaptic plasticity and long-term memory in mouse models, our findings provide a mechanism through which synaptic function could be altered in schizophrenia and offer candidate targets for therapeutic intervention.
ID: 2082770

USING POLYGENIC SCORES TO DELINEATE RELATIONSHIPS AMONG IMPULSIVITY ENDOPHENOTYPES, SCHIZOPHRENIA, AND BIPOLAR DISORDER

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Background: Schizophrenia (SZ) and bipolar disorder (BD) are highly heritable individually and share substantial heritability. Despite this, few genetic loci have been identified to confer individual or shared risk, and the variance they account for is far below that attributable broadly to genetic factors. Two approaches used to address this issue —endophenotype and polygenic scores — may be possible to fruitfully combine using polygenic scores trained to endophenotypes. These may be useful to ascertain endophenotypic overlap between disorders. Impulsivity is a multidimensional and heritable trait associated with both SZ and BD.
Methods: Here, we tested whether four components of impulsivity are endophenotypes for SZ and BD in a sample of 123 twin pairs with and without psychopathology, recruited from the Swedish Twin Registry. We used heritability modeling in Mx to test whether there is evidence for common pathways among impulsivity phenotypes and with SZ. We found that factors of the Barratt Impulsiveness Scale (BIS) patterned as endophenotypes for SZ and BD, and Stop Signal Task (SST) Stop Signal Reaction Time (SSRT) did not. We found evidence of shared heritability among phenotypes using a common pathways model. Using methods outlined by Purcell et al. (2009), we then generated polygenic scores trained to these impulsivity variables and tested for relationships among the scores. We also directly tested whether these scores correlated with previously derived polygenic scores for SZ risk.
Results: We found that impulsivity polygenic scores were significantly higher in cases than controls, with effect sizes greater than the group differences observed using behavioral measures. Although twin pair was entered as a random variable in all linear mixed models tested, we also observed higher scores in co-twins than controls across all BIS phenotypes for both SZ and BP, suggesting that some genetic relationships among phenotypes may be obscured when looking only at self-report measures. Finally, we observed strong correlations between impulsivity phenotype polygenic scores and schizophrenia risk scores calculated using variants identified by the Psychiatric Genomics Consortium in a large case-control sample (SWG, 2014).
Conclusion: This suggests that common genetic variation influences impulsivity phenotypes in schizophrenia and bipolar disorder, and that a common set of genes may impact these phenotypes in both disorders. We plan next to test the scores in a replication sample.
ID: 2119414

IDENTIFYING POTENTIAL BLOOD GENE EXPRESSION MARKERS FOR POSTPARTUM PSYCHOSIS

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Background: Postpartum psychosis (PP) is the most severe psychiatric disorder associated with childbirth, with an onset typically occurring in the first 6 weeks after delivery. Previous evidence has shown gene expression alterations in immune and endocrine profile in women with PP. The main aim of this study was to conduct an exploratory analysis of a gene expression profile that could distinguish women with PP from women at risk who do not develop PP after delivery.
Methods: We obtained preliminary data from a transcriptomic study performed in the blood of 24 women at risk of PP (N=12 who developed a PP episode and N=12 who did not develop PP) and 21 healthy controls, matched by age, ethnicity and weeks after delivery. Women were considered at risk if they had a diagnosis of bipolar disorder, schizoaffective disorder or family history of PP. Using microarray analysis, we compared the 3 groups gene expression signature using ANOVA.
Results: We identified a total of 719 genes (threshold of mRNA fold change=1,23 and p values=0.05) differently expressed amongst women at risk who developed PP and those at risk who did not develop an episode. The women that developed PP presented upregulation of several genes involved in the inflammatory pathway such as CXCL5, HLA-DQB1, GZMK, PTGER2, BCL2, ATF3 and IL6. Moreover, they presented increased gene expression levels of SLC22A6, GRIA4, EPHA6, AKT3, SP4 and NRG1 genes, which have been previously described in psychotic disorders and within this genes group, KCNC2 was upregulated in women at risk compared to the ones that developed a PP and Healthy controls too. In contrast, compared to women at risk, those with a PP episode showed downregulation of ENTPD4, CREB1, QKI genes and MAOB that presented decreased gene expression levels related to Healthy controls. These genes are relevant to neurodevelopment and schizophrenia. Importantly, women that developed PP episode also showed downregulated endocrine genes compared to the at risk group and Healthy controls, such as the receptor of the thyroid hormone THRA, involved in inflammatory and postpartum diseases
Conclusion: These preliminary results reveal an immuno-neuro-endocrine dysregulation in PP, with an upregulation of the immune system in women that developed PP, but a downregulation of structural proteins involved in psychotic disorders
ID: 2084461

CORRELATION BETWEEN MIR-132 AND IL-1B IN CEREBROSPINAL FLUID OF PATIENTS WITH SCHIZOPHRENIA

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Background: Prior studies have consistently reported elevations in pro-inflammatory cytokines, such as IL-6 and IL-1B, in peripheral blood and cerebrospinal fluid of patients with schizophrenia. Recently, microRNAs (miRNAs) have been implicated as molecules capable of modulating the immune system by post-transcriptional regulation of transcripts at various levels of the inflammatory signaling pathway, such as miR-132, which has been shown to downregulate interlekin-1 receptor-associated kinase 4 after induction of an inflammatory state induced by lipopolysaccharide. However, there are no reports in the literature that have examined the relationship between miRNAs and cytokine levels in cerebrospinal fluid samples of patients with schizophrenia.
Methods: Ten patients with schizophrenia-spectrum disorders and ten healthy volunteers matched to patients in age, sex, and race underwent a lumbar puncture and a blood draw. 15–25 cc of CSF were obtained from each subject. Four selected miRNAs were measured using standard qPCR (miR-132, miR-532-3p, miR-532-5p, miR-660). Levels of 16 Cytokines were quantified by multiplex ELISA cytokine array using Q-Plex™ technology (Quansys Biosciences).
Results: Both groups were equally distributed in sex, age and race. Mean cycle threshold (CT) values for each miRNA were normalized using Mammu6 levels for each subject for each sample. As seen in prior studies, IL-1B was significantly increased in schizophrenia patients compared to controls (15.3 pg/ml, SD=1.9 vs. 13.1 pg/ml SD=2.1; p=0.02). The same was observed with IL-8 (31.0 pg/ml, SD=2.3 vs. 18.8 pg/ml, SD=1.3; p=0.0002). Even though IL-6 was also elevated in patients compared to controls (1.0 pg/ml, SD=1.3 vs. 1.7 pg/ml, SD=0.4), it did not reach statistical significance (p=0.08). Correlation analysis showed a significant positive correlation between IL-1B and miR-132 (r=0.73, p=0.02). There were no statistically significant correlations between miRNAs and cytokines in the healthy volunteer sample.
Conclusion: As previous studies have shown, we found elevations of IL-1B and IL-8 in schizophrenia patients, but for the first time we showed a significant correlation between levels of miR-132 and IL-1B in cerebrospinal fluid, which suggests that CSF could be a good biofluid to capture the dynamic interaction between miRNAs and cytokines in our search for clinically relevant biomarkers in schizophrenia.
ID: 2087788

GENETIC ASSESSMENT OF CANDIDATE ENDOPHENOTYPES FROM THE CONSORTIUM ON THE GENETICS OF SCHIZOPHRENIA FAMILY STUDY

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Background: We have previously reported the results of our efforts to characterize the genetic architecture of 12 primary endophenotypes for schizophrenia. Here we describe the characterization and genetic analyses of nine secondary measures that may serve as additional endophenotypes for schizophrenia.
Methods: Each of the 296 families from the Consortium on the Genetics of Schizophrenia phase 1 (COGS-1) consists of a proband with schizophrenia, both parents, and at least one unaffected sibling for a total of 1,004 subjects characterized for a variety of secondary measures derived from the primary endophenotype test paradigms. These measures were evaluated for their ability to significantly discriminate between schizophrenia patients and controls and heritability in the family sample. Candidate gene association and genome-wide linkage were also performed using variance component and regression-based methods.
Results: Of the secondary measures investigated, nine were found to discriminate between schizophrenia patients and controls and were also at least moderately heritable (31 to 62%). Candidate gene analyses performed using the COGS SNP Chip identified associations to several prominent schizophrenia candidate genes, including CTNNA2, ERBB4, GRID1, GRID2, GRIK3, GRIK4, GRIN2B, NOS1AP, NRG1, and RELN, across multiple endophenotypes. Linkage analyses performed using a genome-wide SNP array identified significant or suggestive linkage peaks for six of the secondary endophenotypes, and known candidate genes for schizophrenia were identified beneath the linkage peaks (e.g., CSMD1, DISC1, DLGAP2, GRIK2, GRIN3A, and SLC6A3) in addition to several other genes of potential interest.
Conclusion: While the partial, but incomplete, convergence between genes implicated by linkage and association likely reflects differences in the density of gene coverage provided by the two platforms, it may also be an indication of the differential contribution of rare and common variants for some genes in different portions of this sample. Collectively, these results suggest additional endophenotypes for schizophrenia and provide evidence for a functional network of genes involved in glutamate regulation and neuregulin-ErbB4 signaling in schizophrenia pathogenesis.
ID: 2117107

ABERRANT BRAIN DEVELOPMENT AND PSYCHOSIS IN 22Q11.2 DELETION SYNDROME

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Background: The 22q11DS is characterized by heterogeneous neuropsychiatric presentation most notable for the emergence of psychosis in adolescence and early adulthood in about 25% of individuals. Efforts at early identification of individuals at risk for psychosis in the general, non-deleted, population have prompted a parallel effort in youths with the deletion. Clinical characterization with established assessment tools has been enhanced by neurocognitive and neuroimaging measures that can contribute to the understanding of pathological processes.
Methods: We evaluated large samples of 22q11DS and non-deleted participants over 200 per group. Both groups included individuals with and without psychotic features. All participants underwent phenotypic clinical assessment including characterization of subthreshold psychotic symptoms. A computerized neurocognitive battery evaluated performance accuracy and speed in several domains: executive, episodic memory, complex cognition, social cognition and sensorimortor speed. Multimodal neuroimaging, in a subsample, included structural MRI and DTI.
Results: 22q11DS was associated with increased presence of psychotic symptoms and impaired performance in accuracy across domains. Patients with 22q11DS demonstrated increased gray matter cortical thickness associated with reductions in surface area, reduced local gyrification, and lower cerebral volumes. Findings were principally in the frontal lobe, superior parietal lobes, and in the paramedian cerebral cortex. White matter volumes were smaller in several brain regions and WM microstructural organization, as measured by fractional anisotropy, was reduced in multiple tracts.
Conclusion: The overlapping patterns of generally thicker cortex, smaller surface area, and reduced gyral complexity and WM abnormalities are suggestive of aberrant neural organization and migration, most pronounced in the frontal and parietal lobes and midline occipital lobe.
ID: 2117554

LONGITUDINAL PATTERNS OF NEUROCOGNITIVE MEASURES

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Background: Schizophrenia is a heritable, complex brain disorder, and progress in understanding its pathophysiology requires integration of genetic and neurobiological methods. Quantitative measures of brain structure and function have fuelled the field of imaging genomics. The MGI initiative provides a unique opportunity to investigate the impact of shared genetic ancestry on structural and functional brain abnormalities. Here we: 1) estimate the heritability of subcortical brain volumes and shape and, 2) associate functional MRI activation patterns and performance on a computerized neurocognitive battery in MGI families.
Methods: 190 members from 32 Multiplex-Multigenerational families with schizophrenia and 249 healthy individuals underwent structural and functional MRI. Heritability was estimated for volume and shape of subcortical brain structures. In addition, cross-validated sparse regression of regional brain activation was used to predict concurrent performance on six computerized neurocognitive tasks.
Results: Subcortical volume and shape were heritable in MGI families. Estimates of heritability ranged from 0.45 in the right hippocampus to 0.84 in the left putamen. Heritability estimates of subcortical shape exceeded estimates of volume alone. Functional brain activation patterns were domain-specific; prediction of performance was robust across neurocognitive tasks, particularly for abstraction/mental flexibility and visuo-spatial memory.
Conclusion: Our work identifies specific neuroimaging phenotypes in large Multiplex-Multigenerational families with schizophrenia. The specificity obtained using advanced neuroimaging methods in large extended pedigrees may improve the selection of imaging phenotypes that better reflect the underlying neurobiology of schizophrenia. Such localized features may be related to distinct dimensions of psychopathology or may be determined by specific genetic risk factors unique to patients with schizophrenia, or to particular families.
ID: 2091238

MYELIN NEUROBIOLOGY IN SCHIZOPHRENIA

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Background: Multiple genetic, neuroimaging, protein and gene expression studies have identified oligodendrocyte and myelin related (OMR) abnormalities in schizophrenia (SZ). Here we tested the hypothesis that the disconnectivity syndrome in SZ could arise from failures of saltatory conduction and abnormalities at the nodes of Ranvier (NOR) interface where oligodendrocytes, astrocytes and axons interact.
Methods: Microarray analyses were performed on multiple (17) postmortem brain regions representing the frontal, temporal, parietal and occipital lobes, hippocampus and basal ganglia from 16–45 persons with SZ and 19–34 comparison controls. qPCR and Western blot analyses in an independent postmortem cohort (N=46) were used to assess the expression of tight junction adhesion genes and proteins associated with NOR, including Ankyrin3, Neurofascin, NrCAM, TJP1 & 2 and Contactin. The distribution of ANK3 polymorphisms were then tested in a case/control postmortem brain study (N=272).
Results: mRNA expression of multiple NOR genes was decreased in SZ. The ANK3 gene and its rs9804190 C allele was associated with lower ANK3 mRNA expression levels in SZ, higher risk for SZ in the postmortem case/control cohort, and poorer working memory/executive function performance and increased prefrontal activation during a working memory task in healthy living individuals. Weighted gene coexpression network analysis (WGCNA) identified myelin associated modules to be among the pathways most closely associated with SZ. Mice with conditional knockout of forebrain ANK3 have been prepared and are being tested for possible gene expression, behavioral and electrophysiological abnormalities.
Conclusion: These findings show that persons with schizophrenia evidence reduced expression of genes and proteins essential for the maintenance of intact nodes of Ranvier. Abnormalities in the expression of genes and protein associated with the integrity of the NOR suggest that they represent some of the substrates for the disconnectivity syndrome in SZ. The association of ANK3 with lower brain expression levels implicates a molecular and potentially functional mechanism for its genetic, clinical and cognitive associations with SZ.
ID: 2112516

DOPAMINE D1, D2 RECEPTOR GENE INTERACTION IN RELATION TO SCHIZOPHRENIA AGE AT ONSET AND CLOZAPINE RESPONSE

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Background: We are investigating the interaction of the dopamine D1 receptor (DRD1) and D2 receptor (DRD2) genes in schizophrenia (SCZ) based

on the fact that the D1 and D2 receptor proteins form heterodimers in vivo. The D1-D2 heterodimer has different pharmacologic signaling properties than either receptor alone. Differences in quantity or quality of either or both receptors in the dimer could significantly influence SCZ risk or illness characteristics. Our initial investigation of DRD1-DRD2 gene interaction is in relation to age at onset (AAO) and clozapine (CLZ) response.
Methods: Based on published reports or functional annotation databases, three DRD1 SNPs and seven DRD2 SNPs were selected then analyzed for AAO and CLZ response. Measured as the age of first hospitalization for psychotic symptoms, AAO was examined in 240 Caucasian SCZ patients with DSM-IV SCZ or schizoaffective disorder diagnosis. The CLZ response group included 335 SCZ patients (283 Caucasian, 52 African-American) with DSM-III-R or DSM-IV SCZ-diagnoses obtained from research sites in the USA (n=232) and Germany (n=103). Genotyping, LD analysis, and HWE were performed using standard procedures and HaploView4.2.
Results: One-way ANOVA tests between AAO and each SNP revealed significant associations for two DRD2 SNPs, rs2005313 (p=0.014) and rs4586205 (p=0.017). For rs2005313, posthoc testing revealed a significant difference in AAO between the AG and AA genotypes, a finding that withstood both Tukey (p=0.038) and Bonferroni (p=0.043) multiple testing corrections. For rs4586205, posthoc testing revealed a significant difference in AAO for TG and GG, which withstood Tukey testing correction (p=0.047), but not Bonferroni (p=0.054). No DRD1 SNP associations reached significance. No association with CLZ response has been observed as of yet, but further analyses are in progress. Two-way ANOVAs were used to test for DRD1-DRD2 SNP interaction effects, but none achieved significance.
Conclusion: The results so far suggest there are no significant DRD1-DRD2 gene interaction effects in relation to SCZ-AAO for the SNPs examined in our relatively small sample. That said, the results do provide preliminary evidence for DRD2 SNPs rs2005313 and rs4586205 predicting AAO. We intend to expand our range of SNPs analyzed by including the DRD2 rs2514218 SNP that Ripke et al. (2014) found to be strongly associated with SCZ risk. Overall, the D1-D2 heterodimer biology remains an intriguing hypothesis to test in SCZ, in this case using genetic tools.
ID: 2117874

FUNCTIONALLY MAPPING CLINICAL RISK SNPS FOR SCHIZOPHRENIA TO LOCAL EXPRESSION LEVELS IN HUMAN FRONTAL CORTEX

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Background: 108 genetic loci have now reached "genome-wide" significance for clinical association with schizophrenia, utilizing 37k cases and 113k controls [O'Donovan et at, Nature 2014]. However, these loci span ~21Mb and contain 331 RefSeq genes across 1154 transcripts (574 genes across 1884 transcripts within +/- 100kb). How do we functionally determine the potential mechanisms of these risk variants?
Methods: We performed genotyping and RNA sequencing in dorsolateral prefrontal cortex (DLPFC) tissue from 238 adult non-psychiatric controls (age > 13) and 51 fetal subjects. We evaluated the association of clinical risk SNPs in the 108 loci on nearby gene expression levels using an expression quantitative trait loci (eQTL) framework, where gene expression levels were represented separately by gene, exon, and junction read counts. Analyses controlled for ancestry via multidimensional scaling components based on genotype data and principal components estimated from the expression data.
Results: We identified significant genetic control of nearby expression for 64 of the GWAS-positive loci at any gene expression summarization level (gene, exon or junction) in the adult subjects - only 26 of these loci are associated with expression across all three summarization levels. Junction-level analyses identified a subset of loci where the risk variant only associates with a single transcript within 1 megabase of the risk variant, including potentially novel transcripts not present in the current Ensembl annotations. Furthermore, 520 of the 2107 loci (~25%) reaching at least marginal significant in the GWAS (at $p < 10–5$) are associated with nearby expression levels in the frontal cortex, expanding up recent reports of enrichment for eQTLs within GWAS-positive loci [Nicolae et al, PLoS Genetics 2010]. Lastly, many of these eQTL associations are present in both Caucasians and African Americans, as well as in the fetal samples.
Conclusion: We have identified the likely candidate gene for a subset of schizophrenia-associated genetic risk loci based on associations with nearby gene expression levels in the transcriptomes of non-psychiatric controls.
ID: 2117921

GENE CO-EXPRESSION NETWORK ANALYSIS IDENTIFIES GENE MODULES ASSOCIATED WITH NEUROANATOMIC MEASURES AND PSYCHOTIC SYMPTOMS IN 22Q11.2 MICRODELETION SYNDROME

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Background: 22q11.2 deletion syndrome (22q11DS) is a neurogenetic syndrome associated with elevated rates of psychosis (≈30%). We examined how variability in gene expression profiles was related to neuroanatomic measures and psychotic symptomatology in 22q11DS (N=78).
Methods: RNA was extracted from whole blood using the PAXgene extraction kit (QIagen) and whole-genome transcriptional profiling was performed using Illumina Human HT-12 microarrays. We acquired high-resolution T1-weighted structural scans from 22q11DS participants. All scans were processed through a Freesurfer pipeline. Clinical symptomatology was assessed with the Structured Interview for Prodromal Symptoms. We conducted Weighted Gene Co-expression Network Analysis (WGCNA), a systems biology approach used to identify networks of co-expressed genes in relation to phenotypic data. To test for significance of over-representation of brain-expressed genes within identified modules, we ran hypergeometric probability tests. Gene ontology (GO) annotation was performed using DAVID (http://david.abcc.ncifcrf.gov/).
Results: WGCNA identified 2 gene expression modules (Salmon, Orange) related to cortical thickness and surface area measures and psychotic symptomatology in 22q11DS patients. Hypergeometric tests revealed significant enrichment of brain-expressed genes in both modules. Neither module was associated with age, gender, antipsychotic use, scanner location, or batch number. Genes co-expressed in the Salmon module were down-regulated in 22q11DS participants with more severe psychotic symptoms (p=.009); this module was also associated with increased cortical thickness in the right caudal anterior cingulate (p=.02). GO categories associated with the Salmon module were related to RNA processing and cellular transport. In the Orange module, up-regulation of gene expression was associated with increased psychotic symptoms (p=.009) and reduced surface area in the left temporal pole (p=.04) in 22q11DS. GO analyses revealed that genes in the Orange module were primarily related to immunological processes.
Conclusion: In 22q11DS, peripheral changes in gene expression are significantly related to underlying brain structure and psychotic symptomatology. Brain structures associated with these gene expression profiles have been previously associated with idiopathic schizophrenia, providing further support for the use of peripheral tissue in the study of major mutational models of schizophrenia.
ID: 2118051

A MULTI-MODAL APPROACH TO UNDERSTANDING ASSOCIATIONS BETWEEN GENETIC VARIANTS AND FUNCTIONAL BRAIN CONNECTIVITY IN 22Q11.2 DELETION SYNDROME

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Background: Intrinsic functional brain networks derived from resting state functional MRI studies are viewed as promising constructs in studies of genetic underpinnings of schizophrenia (Meda et al., 2014). Atypical functional connectivity has been reported in the default mode network (DMN) (Debanne et al., 2012) of individuals with 22q11.2 deletion syndrome (22q11DS), which poses a 25-fold increase in risk for schizophrenia. Accordingly, we examined the associations between DMN connectivity and single nucleotide polymorphisms (SNPs) of genes on the healthy (non-deleted) chromosome of 22q11.2 in a sample of individuals with this genetic syndrome.
Methods: A group-level spatial Independent Components Analysis(GIFT toolbox using the Infomax algorithm, http://mialab.mrn.org/software/gift/) of resting state fMRI data was conducted on a sample of 44 individuals with 22q11DS and 26 unaffected comparison subjects. Based on published Brainmap templates (Laird et al., 2011) we identified five default mode networks that significantly differentiated neural activation between our study groups.
Affymetrix 5.0 / 6.0 SNP data were available on 30 of the 44 individuals with 22q11DS in our study. SNPs that were not in linkage disequilibrium, and for which data on all participants were available,were chosen for subsequent analysis. Thus, we performed a follow-up multivariate analysis (Parallel-ICA, FIT toolbox, http://mialab.mrn.org/software/fit/, Meda et. al. 2014) of the associations between the five DMN components and genetic variants of 69 SNPs on 30 individuals with 22q11DS.
Results: Lower neural connectivity of several DMN subnetworks was associated (Z>2.5) with genetic variation in seven genes. Four of the seven genes are expressed in brain and associated with increased psychiatric risk in non-syndromal populations, including PIK4CA (involved in synaptic transmission and, putatively, myelin development), SNAP29 (involved in membrane trafficking and synaptic transmission), MED15 (an RNA polymerase transcriptional cofactor), and DGCR8 (involved in microRNA processing). The remaining genes are involved in protein binding (KLHL22), cell adhesion (SCARF2) and immune function (SERPIND1).
Conclusion: Several schizophrenia-susceptibility genes, for which individuals with 22q11DS are hemizygous, may mediate functional brain disconnectivity in individuals with this syndrome, potentially contributing to their increased risk for psychosis.
ID: 2115687

EVIDENCE OF DYSKINESIA AS PREDICTIVE OF SCHIZOPHRENIA RATHER THAN UNEXPRESSED GENETIC LIABILITY: A FAMILY STUDY OF MOTOR CONTROL THROUGH DIGITIZED HANDWRITING ASSESSMENT

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Background: Motor abnormalities have been increasingly reported in individuals with schizophrenia and those with high behavioral and genetic liability for the disorder. Dyskinetic movements, thought to reflect regulatory disinhibition within the basal ganglia, have been identified in and used to predict outcome for prodromal individuals. The aim of the current study was to examine whether similar dyskinetic movement is present in first-degree relatives, or individuals who carry unexpressed genetic liability for the development of schizophrenia.
Methods: To assess dyskinesia, handwriting samples were obtained from individuals with schizophrenia (n=51), first-degree relatives (n=32), and controls (n=62). Specifically, participants wrote "lleellee" under a variety of size conditions (i.e. 1, 2, and 4 cm in height). The average normalized jerk (ANJ), which examines changes in handwriting acceleration within a stroke and is believed to assay dyskinesia, was calculated for each handwriting sample across each size.
Results: Repeated measures ANOVA revealed a significant main effect of group, ($F(2,142)=3.641$, $p=0.029$), with individuals with schizophrenia demonstrating significantly more ANJ than controls ($p = 0.018$) or relatives ($p = 0.026$), while there was no significant difference between controls and relatives. Chlorpromazine equivalent dosage data were available for approximately half of the individuals with schizophrenia (n=25), and preliminary analyses indicate no significant correlations between antipsychotic medication dosage and ANJ for any handwriting size.
Conclusion: It is of note that increased handwriting dyskinesia has previously been reported in prodromal individuals, which may be a manifestation of increased dopamine tone in the basal ganglia. The absence of handwriting dyskinesia in first-degree relatives in the current study is consistent with previous retrospective studies indicating that abnormal movements differentiate individuals who eventually develop schizophrenia from their non-affected siblings. Taken together, these results provide evidence that dyskinetic movements (possibly involving a hyperdopaminergic mechanism) may be a specific risk marker for actual risk of conversion to psychosis, rather than a marker of genetic liability.
ID: 2119351

DECONSTRUCTING SCHIZOPHRENIA AND BIPOLAR DISORDER: A CROSS-DIAGNOSTIC CLUSTER ANALYSIS OF ENDOPHENOTYPE ASSESSMENTS

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Background: Schizophrenia (SZ) and bipolar disorder (BD) have a large overlap in terms of genetic risk, but the extent of shared risk remains elusive. Further, high heterogeneity within each disorder, and overlapping clinical features between two disorders, suggest that identifying subgroups with shared endophenotypes (including early auditory and visual perception, non-social cognition, social cognition), could be valuable for determining genetic risk that is common to both disorders. This study employed a data-mining approach to identify subgroups of patients across the two disorders that share endophoentypic profiles.
Methods: A battery of EEG and behavioral assessments for endophenotypes were administered on 48 BD patients, 28 SZ patients and 27 healthy controls who had complete data across measures. A K-means cluster analysis was conducted on endophenotype assessments of all participants. Assessments for clinical symptoms, functional capacity, and functional outcome were also administered to patients.

Results: A two-cluster solution across 3 groups was the most stable. Cluster A included 23 BD patients (BD-A), 25 SZ (SZ-A) patients and 3 controls and Cluster B included 25 BD patients (BD-B), 3 SZ patients and 24 controls. For Cluster A, BD-A and SZ-A subgroups showed similar endophenotype patterns across measures with the SZ-A subgroup showing poorer performance than BD-A subgroup. The SZ-A had poorer community functioning and lower levels of substance use than BD-A. When comparing BD-A and BD-B subgroups, we observed both qualitatively and quantitatively different profiles of endophenotypes across two subgroups. There was no significant difference for clinical symptoms, but BD-A subgroup showed higher levels of alcohol use than BD-B subgroup.
Conclusion: A data-mining cluster analysis of endophenotype assessment across diagnoses revealed a similar endophenotype profile for a majority of SZ patients and one BD subgroup. The two BD subgroups showed different endophenotype profiles and comparable clinical features with one exception: the levels of alcohol use. A Similar endophentopye profile between SZ and one BD subgroup suggests the high likelihood of shared genetic architecture. These findings also suggest that a categorical approach based on clinical features is not well suited for identifying shared genetic risk between SZ and BD.
ID: 2119163

DRUGGING THE SCHIZOPHRENIA GENOME: A FAST TRACK STRATEGY FROM GWAS TO CLINIC

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Background: The Psychiatric Genomics Consortium has recently published a genomewide association study (GWAS) identifying >100 replicable genetic loci, encompassing a total of 341 protein-coding genes, which convey risk for schizophrenia (PGC-SCZ, 2014). Rapid utility from GWAS results may be obtained by the identification of drug/target combinations which have already been validated and have progressed to human clinical trials and/or FDA approval. In the present study, we examined all genes implicated by PGC-SCZ GWAS hits against databases of drug targets.
Methods: The primary source of confirmed druggable targets was the curated list of 1030 genes recently published by Rask-Anderson et al. (2014). We supplemented this with 3 additional databases: CiteLine, DrugBank, and the Drug-Gene Interaction database. Genes were only considered to be true drug targets if direct pharmacologic binding had been demonstrated; indirect effects of up- or down-regulation were not included.
Results: Of the 341 genes on the PGC list, 27 (7.92%) are drug targets (approved or in trial) on the Rask-Anderson list, a 56% enrichment compared to the whole genome (binomial test, p=.03). Using the supplemented list of drug targets, we identified 20 genes that are the targets of approved drugs. We prioritized genes that produce neurotransmitter receptors, ion channels, or ion transporters, and those which aresole members of the linkage disequilibrium (LD) block surrounding a PGC-SCZ GWAS hit, given that many of the LD blocks in the PGC-SCZ paper contain multiple genes (up to 26 genes at a single locus). In addition to DRD2, 5 genes meet these criteria: CACNA1C, CACNB2, CACNA1l, GRIN2A, and HCN1. An additional 20 genes without approved indications, but which are the target of drugs in registered clinical trials, were also identified.
Conclusion: Despite the unparalleled success of GWAS as a method for rapidly advancing knowledge, questions remain about the potential clinical utility of GWAS findings. Our results demonstrate: 1) that these results are enriched for validated targets of both approved and registered pharmaceutical compounds; and 2) that, amongst these targets, there are several examples of "low-hanging fruit" - genes that are plausibly connected to schizophrenia pathophysiology, and are relatively likely to be influenced by the SNPs identified by the PGC-SCZ GWAS. Of course, one of the genes meeting criteria for "low-hanging fruit" is DRD2, which is already well-known in the context of schizophrenia treatment.
ID: 2118709

SUCCESSFUL TARGETED TREATMENT OF A MEDICALLY ACTIONABLE MUTATION IN PSYCHOTIC DISORDERS

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Background: The identification of mutations in specific genes could enable personalized, "medically actionable" treatment interventions. We identified a potentially informative mutation, a rare structural rearrangement that includes a triplication of the glycine decarboxylase gene (GLDC). GLDC is the enzyme that catabolizes glycine, a co-agonist of the NMDA receptor (NMDAR). Four copies of GLDC would be expected to accelerate the degradation of glycine, resulting in low levels of brain glycine and NMDAR-mediated hypofunction, which has been strongly implicated in the pathophysiology of psychotic disorders. Carriers of this mutation may especially benefit from augmentation of psychotropic drug treatment with glycine or other NMDAR co-agonist site modulators.
Methods: We carried out a double-blind placebo-controlled clinical trial (six weeks per arm), followed by six weeks of open-label glycine, in two related individuals who are carriers of the GLDC mutation, one with a diagnosis of bipolar disorder with psychotic features and the other with a diagnosis of schizo-affective disorder. Clinical assessments were carried out every two weeks using the PANSS, BPRS, YMRS, HAM-D, and CGI.
Results: Here, we report that the subjects showed dramatic clinical improvements while on glycine both during blinded and open label glycine treatment. Both subjects relapsed when glycine augmentation was discontinued. Subsequent resumption of glycine augmentation restored the symptom remission observed previously.
Conclusion: Other carriers of duplications or triplications of GLDC, or carriers of other genetic variants resulting in NMDAR hypofunction, also may benefit from augmentation with glycine or other NMDAR positive modulators, regardless of clinical phenotype.
ID: 2083012

THE RELATION BETWEEN AKT1, CANNABIS USE AND METABOLIC RISK FACTORS IN PSYCHOSIS

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Background: Cardiovascular and metabolic problems combined with a bad lifestyle are a major cause of a shortened life expectancy in chronic psychotic disorders. While the incidence of cannabis use is twice as high in psychosis compared to the general population, use of cannabis has been associated with better outcomes on cardiometabolic risk factors. This study investigates whether this effect is mediated by the AKT1 gene, as activation of the related enzyme by cannabis may cause changes in metabolism.
Methods: Patients with a recent onset psychosis (n = 623) were included from a cohort study (GROUP). Cannabis use, based on self-report and urine screening, was related to Body Mass index (BMI). Next the mediating effects of six AKT1 polymorphisms (rs1130214, rs1130233, rs2494732, rs2498784, rs3730358 and rs3803300) were investigated.
Results: There was a strong, negative association between BMI and cannabis use. Moreover, two SNP's (rs1130233 and rs2494732) showed an association with cannabis use, but did not mediate the effect of cannabis on BMI.
Conclusion: In conclusion, cannabis use results in a lower body weight in patients with a psychosis. While AKT1 is related to cannabis use, it does not affect body mass via AKT1. Instead, AKT1 risk alleles may increase the incidence of cannabis use. Future studies may investigate whether other genes mediate the effect between cannabis and metabolic risk factors.
ID: 2116166

LEVERAGING DE NOVO MUTATIONS FOR SPORADIC PSYCHOSIS TO FIND HIGH IMPACT GENES FOR SCHIZOPHRENIA

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Background: Schizophrenia is a debilitating syndrome with high heritability. While more than a hundred genetic variants are linked to the disease based on single nucleotide polymorphisms from genomic studies, these are of small effect size and are not specific to psychosis. This presentation describes a novel framework to find high impact genes for the disease.
Methods: Whole exome sequencing comparing sporadic cases to both parents in 14 complete trios yielded a handful of disruptive de novo gene mutations. Next, the association of these alleles with schizophrenia was tested through targeted exome sequencing in 48 well-characterized, unrelated, ethnically diverse schizophrenia cases, recruited and characterized by the same research team in New York.
Results: In 5/14 sporadic cases we identified 5 different damaging de novo gene mutations (PTPRG, TGM5, SLC39A13, BTK, CDKN3). These cases had older mean paternal age than trips without de novo mutations. The replication study demonstrated extremely rare and potentially damaging variants in 3 of these genes (MAF < 0.01) in a quarter of the cases from NY (12/48 cases) for PTPRG (5 cases), SCL39A13 (4 cases) and TGM5 (4 cases). Cases differed in cognition and illness features based on which mutation-enriched gene they carried.
Conclusions: Genes with functional de novo mutations identified from sporadic schizophrenia cases can illuminate high impact genes for disease risk across ethnicities and family history. This is a novel strategy to identify high impact genes for psychosis.
ID: 2209649

GENETIC DIVERSITY AND DLPFC EXPRESSION OF THE HSPA1L IN SCHIZOPHRENIA

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Background: The Hsp70-hom encoded by the HSPA1L gene preserves cell viability by chaperoning proteins and exerting an anti-apoptotic function, and is found in a highly significant risk associated MHC locus in the latest PGC2 GWAS of schizophrenia (SZ). Recent report indicated a significant association of the HSPA1L rs2075799*A allele and rs2227956-rs2075799 haplotype with SZ in Korean population [Kim JJ et al, Eur Arch Psychiatry Clin Neurosci. 2008; 258(4):239–44]. Thus, we performed an eQTL study of HSPA1L in post-mortem brain prefrontal cortex (DLPFC) and association with SZ of rs2227956 T/C(M493T) and rs2075799 G/A(T407T) polymorphisms in European-American population.
Methods: 296 European-American families and 383 unrelated healthy controls were investigated. Genotyping was performed with TaqMan® SNP Assay chemistry and analyzed using FBAT with 10000 permutations. RNA sequencing data derived from DLPFC samples of 89 cases vs. 92 controls were compared by t-test after log transformation and QC covariates. RNA SNPs were decoded by using Galaxy platform. Genotype effects on cognitive phenotypes were tested in ~370 healthy unrelated Caucasians using linear regression based on the 7 factor scores.
Results: SNPs were in HWE (P>0.05) and linked weakly (R2<0.1). In contradiction to previous study, in the European-American sample, FBAT revealed transmission distortion of rs2075799*G alleles to SZ offspring (p<0.048). A case-control comparison of rs2075799 genotypes in the post-mortem sample validated the family based association (allelic: p<0.009). SZ was associated with increased (>12.5%) expression of the HSPA1L in DLPFC (t=2.39, p<0.017). Rs2227956*C was associated with high gene expression in DLPFC (p<0.0002). Interestingly, in non-independent case-control analysis, the rs2227956*T/C genotype was associated with SZ (OR=1.46, p<0.03), as well as with 20% increase of HSPA1L expression in DLPFC (T/T vs. T/C: p<0.0001) and with low processing speed and IQ (coef=-0.13, p<0.016).
Conclusion: We report evidence of eQTLs related to brain expression of schizophrenia risk associated alleles in HSPA1L. Adolescent brain specimens were obtained from the NICHD Brain and Tissue Bank for Developmental Disorders at the Maryland University. KRM, AAH & AGKh acknowledge the grant #13-1F291 of the SCS, MES, RA and KRM - the Fulbright scholarship #68130188.
ID: 2094278

PHARMACOGENETICS OF RELAPSE IN SCHIZOPHRENIA IN THE PROACTIVE TRIAL

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Background: In the PROACTIVE study the rates of relapse or hospitalization between long-acting injectable risperidone (LAI-RIS) (42%) and oral second generation antipsychotics (SGA) (32%) were not significantly different. These findings similar to other studies, confirm a substantial rate of relapse even with continuous antipsychotic treatment. Previous studies have shown an association between genetic variation and more rapid relapse in schizophrenia and outcome with antipsychotic treatment. To date, very few studies have assessed the role of genetic variation in relapse

in individuals with schizophrenia. We tested the hypothesis that genetic variations of genes that code for the serotonin transporter, dopamine receptors and/or P-glycoprotein transporter are associated with the likelihood of relapse during long-term antipsychotic therapy, after controlling for potential confounding factors.
Methods: We utilized a focused candidate gene approach to study the role of genetic variation in relapse in the PROACTIVE sample of 305 individuals with schizophrenia or schizoaffective who were randomly assigned to LAI-RIS or oral SGA, and evaluated for up to 30 months. Relapse and/or hospitalization for symptom exacerbation was determined by a masked Relapse Monitoring Board. We genotyped DNA from participants for the 5HTTLPR, DRD2 (A-241G and -141C Ins/Del), and PGP transporter (C3435T, C1236T, and G2677TA) SNPs.
Results: We obtained DNA for 207 of the 305 subjects who participated in the study; this included 106 of 153 subjects (69%) who were randomized to LAI-RIS and in 101 of 152 subjects (66%) who were randomized to oral SGA (NS). DNA was available in 72/109 (66%) of subjects who experienced a relapse (40/59 in the LAI-RIS group & 32/49 in the oral SGA group; NS) and in 135/197 (68%) (NS) who did not experience a relapse (66/94 in the LAI-R group & 69/103 in the oral SGA group; NS).
Conclusion: Based on a growing literature, genetic variability may be a potential predictor for relapse in schizophrenia. An understanding of the genetic factors involved in relapse would provide clinicians a method to identify patients who are at the highest risk for relapse and allow them to modify their treatment plan accordingly.
ID: 2090347

IS POOR ANTISACCADE PERFORMANCE IN HEALTHY FIRST-DEGREE RELATIVES OF SCHIZOPHRENICS AN ARTIFACT OF STUDY DESIGN?

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Background: A number of traits associated with schizophrenia aggregate in relatives of schizophrenia patients at rates much higher than that of the clinical disorder. These traits, considered candidate endophenotypes, may be alternative, more penetrant manifestations of schizophrenia risk genes than schizophrenia itself. Performance on the antisaccade task, a measure of ability to inhibit prepotent responses, is one of the most widely studied candidate endophenotypes. However, there is little consensus on whether poor antisaccade performance is a true endophenotype for schizophrenia. Some studies comparing the performance of healthy relatives of schizophrenia patients (RelSZ) to that of normal controls (NC) report that RelSZ show significantly more errors, while others find no statistically significant differences between the two groups. A recent meta-analysis of these studies noted that some studies used stricter exclusion criteria for NC than RelSZ and found these studies were more likely to find significant effect sizes (Levy et al. 2004). Specifically, NC in these studies with a personal or family history of psychopathology were excluded whereas all RelSZ, including those with psychotic conditions, were included.
Methods: In order to determine whether a difference in antisaccade performance between NC and RelSZ remains after controlling for differences in psychopathology, we fit a binomial regression model to data from an antisaccade task. We estimated both "symmetric" (RelSZ compared to NC with similar personal histories of psychopathology) and "asymmetric" (RelSZ compared to NC with no personal history of psychopathology) linear contrasts.
Results: Only asymmetric comparisons yielded statistically significant differences in antisaccade error rates.
Conclusion: We demonstrate that both personal psychopathology and familial history affect antisaccade performance.
ID: 2086038

EXPLAINING VARIATION IN SCHIZOPHRENIA ENDOPHENOTYPES VIA EPISTASIS

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Background: Many studies have successfully shown a polygenic component explains a small but significant amount of variation in endophenotypes for schizophrenia. Epistasis is frequently overlooked, but may also play an important role in the underlying genomic architecture. My recent work has examined variation in cognitive endophenotypes for schizophrenia explained by (1) epistasis in the ZNF804A pathway (defined as differentially expressed genes after ZNF804A knockdown) in working memory above the contribution of the polygenic score and (2) epistasis between genes annotated by the Mouse Genome Informatics abnormal behaviour phenotype using machine learning algorithms.
Methods: Psychosis patients from the WTCCC2 were assessed in cognitive function impaired in schizophrenia (e.g., IQ, memory). For the ZNF804A (1) study, the polygenic score was created using the PGC1 schizophrenia case-control study results. In the abnormal behaviour (2) study, the median variable importance measure across 500 runs of the Random Forest algorithm was used to rank SNPs. The top 30 SNPs were tested for interactions using linear regression.
Results: In the ZNF804A study (1) increased polygenic scores were associated with poorer performance in psychosis patients on endophenotypes. The variation explained (R2) by the polygenic score ranged between 1–3%, which is similar to that observed in other studies. Using a newly-developed statistical model that simultaneously models both polygenic and epistatic components, epistasis in the ZNF804A pathway was found to explain 2–3 times more variability in working memory than the polygenic score. This increase was replicated in two independent samples, including a "narrow psychosis" ($p = 0.016$) and "broad psychosis" set ($p = 0.036$) as well as combined psychosis ($p = 0.0012$). In the abnormal behaviour (2) study, a significant interaction was observed between DISC1 and FOXP2 ($R2 = 1.8$, $p = 0.0083$) and a 3-way interaction with the addition of TUBA1A increased the R2 to 3.6 ($p = 0.0062$). These findings were replicated in the NIMH/Lieber Sibling Study, with the DISC1-FOXP2 interaction explaining (R2) 1.9% of variation ($p = 0.037$), and the 3-way interaction explaining 4.7% ($p = 0.024$).
Conclusion: We show replicated epistasis between 2–3 SNPs can explain a significant amount of variation in schizophrenia intermediate phenotypes, and provide both a standard generalised linear model approach (1) and a machine learning method to apply to high-dimensional data (2) to reliably detect epistasis.
ID: 2085301

GENE ENVIRONMENT INTERACTIONS IN HUMAN IPSC DERIVED NEURONS FOLLOWING NEUROTROPIC INFECTION

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Background: Gene-environmental interaction analyses (GEI) are often hampered by inaccurately estimated environmental variables. As exposure to many infectious agents can be measured accurately, we have modeled GEI using exposure to Herpes Simplex virus, type 1 (HSV-1) and cytomegalovirus (CMV). Both agents have been repeatedly associated with human cognitive impairments untraceable to acute encephalitis. We have also repeatedly found MRI evidence for structural brain damage in apparently healthy HSV-1 exposed persons, suggesting persistent infection in the brain with attendant dysfunction. Further, antiviral medication mitigates a portion of the cognitive impairment. Hence we modeled infections in human induced pluripotent stem cell (iPSC) derived cells to investigate GEI.
Methods: Human iPSC-derived neuroprogenitor cells (NPCs) and mature, functional neurons (i-neurons) were incubated with a genetically engineered HSV-1 virus that expresses green fluorescent protein and red fluorescent protein at a multiplicity of infection (MOI) of 0.3 in the presence or absence of inhibitors of viral replication. Unfixed cells were tested for expression of GFP and RFP and using immunohistochemistry. Establishment of HSV-1 latency was analyzed by RT-PCR using latency-associated transcript-specific primers. Similar experiments were conducted using CMV strain Ad169. Global gene expression was analyzed using the Illumina HumanHT-12 v4 array. Genome-wide association data related to cognitive variation were mined from the NCBI database using the HuGE Navigator (v.2.0).
Results: Gene expression patterns were analyzed and significant changes identified using preset criteria. There were distinctive host responses in NPCs and neurons; with no significant correlations for HSV-1 vs CMV infections. Among gene pathways differentially activated by HSV-1 in NPCs (fold change > 1.5, N=193) and CMV (fold change greater >1.25, N=58 genes) the EGF pathway was shared (NIH DAVID software). These patterns were evaluated in relation to genes / loci with SNPs that are significantly associated with human cognitive variation in mapping studies (N=166 'cognitive' genes; N =155 with probes on the Illumina array). In NPCs, few 'cognitive genes' were differentially activated (HSV-1, N=4; CMV, N=1).
Conclusion: HSV-1 and CMV induce different pattern of gene expression in human neuronal cells; GWAS associated 'cognitive genes' are not preferentially affected in the host cellular responses.
ID: 2092775

NOVEL (AND NOT SO NOVEL) PHARMACOLOGICAL APPROACHES TARGETING THE NMDA-OXIDATIVE STRESS PATHWAY

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Background: The mounting evidence on inflammation and oxidative stress playing a role in schizophrenia pathophysiology and their link to the NMDA receptor hypofunction hypothesis, suggests a number of possible novel therapeutic avenues. Animal models that test the impact of altered developmental trajectories, such as rats with a neonatal ventral hippocampal lesion (NVHL), rats with a gestational exposure to methylazoxymethanol (MAM), and the Df1/+ mouse, which models a human 22q11 microdeletion conferring increased risk of schizophrenia, are useful tools to test for inflammatory responses and the impact of their treatment on deficits.
Methods: We examined transcriptional alterations in adult brain tissue from these neurodevelopmental animal models, with an emphasis on genes and pathways previously shown to be dysregulated in human post-mortem schizophrenia brains. We used RNA Sequencing assessing expression in hippocampus, prefrontal cortex, and striatum. In NVHL rats, we also introduced antioxidant treatment (with N-acetyl cysteine) to assess whether oxidative stress had a causal role on their adult-onset deficits.
Results: The global transcriptional profiles of MAM rats and Df1/+ were enriched for a minority of the genes and pathways differentially expressed in schizophrenia. However, certain key pathways proposed to be dysfunctional in schizophrenia were impacted in both rodent models. A number of inflammation-related transcripts were upregulated in the PFC of MAM rats and in the hippocampus of Df1/+ mice, including multiple genes in the JAK-Stat signaling pathway. NAC treatment prevented PPI deficits in NVHL rats, along with a normalization in mismatch negativity in EEG recordings, and a prevention in the loss of PV interneurons in the anterior cingulate cortex.
Conclusion: Overall, the data suggest that inflammatory responses and oxidative stress could be linked to an NMDA hypofunction-dependent loss of interneuron function and that targeting inflammatory processes and oxidative stress balance may be a beneficial approach for early intervention in schizophrenia.
ID: 2083591

GENES, INFLAMMATION, IMMUNITY AND SCHIZOPHRENIA.

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Background: Supportive evidence that altered function of the immune system contributes to the pathogenesis of schizophrenia comes from a range of observations including associations between schizophrenia and a winter season of birth, altered antibody status to certain pathogens such as toxoplasmosis, altered immune biomarkers, and a complex relationship between the schizophrenia and the prevalence of autoimmune disorders. However, it is unclear if any of these observations reflect causal mechanisms rather reverse causation.
Methods: Using new genetic datasets generated in house in combination with the recently published data set from the Psychiatric Genomics Consortium (combined N cases =42,000) we have been conducting a series of analyses using multiple pathways analyses approaches (e.g. ALIGATOR, FORGE, MAGENTA) targeting immune and inflammation focused pathways as defined by public databases (e.g. Gene Ontology, REACTOME, KEGG) and as defined by expression in immune cell lines.
Results: Genetic association was found between schizophrenia and the extended Major Histocompatibility Complex (P<10–6). In addition evidence suggests associations are highly significantly enriched at loci that are preferentially transcriptionally active in immune tissues (P<10–7), particularly for B-lymphocyte lineages involved in acquired immunity, including CD20 (P<10–8), and CD19 (P<10–5) cells, and also in glutamatergic genes, including NMDA 2A receptors, metabotropic type 3 glutamate receptors and serine racemase (all P<10–4).
Conclusion: The results provide some support for a causal relationship between genes regulating immune and inflammatory functions, glutamatergic function and schizophrenia. However, given that genetic association implicate genomic regions rather than specific genes, and moreover that gene products are multi-purpose, is premature to conclude this is a proven case. Additional analyses aiming to clarify this link by evaluating the functions of subsidiary gene sets within the broader set of those that are transcriptionally active in immune tissues are underway
ID: 2118828

GENETIC PATHWAYS ASSOCIATED WITH SOURCE-BASED MORPHOMETRY MEASURES IN SCHIZOPHRENIA

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Background: Schizophrenia is associated with grey matter concentration (GMC) deficit throughout the cortex, as recently validated through the largest Source-Based Morphometry (SBM) analysis of the illness to date (Cota et al., under review). These patterns of deficit comprise regions in the the anterior temporal and medial frontal lobes, remaining robust even in a heterogeneous aggregated dataset. SBM measures are thus an ideal phenotype for a targeted understanding of genetic contribution to grey matter abnormalities in schizophrenia.
Methods: We performed independent SBM decompositions on GMC images from five datasets (total 486 patients, 411 healthy controls) with corresponding genome-wide scan data. Imaging data consisted of T1-weighted images processed in a standard voxel-based morphometry pipeline (Turner et al., 2012). The voxel-wise images were analyzed using independent component analysis to identify gray matter patterns. For each dataset, the SBM component indicating the greatest difference between diagnostic groups was selected as a phenotype for GWAS association with 1 million variants. P-values from linear regression of genotype and diagnosis on coefficients were collected from each dataset and meta-analyzed using METAL (Willer et al., 2010). The SNPs which presented in over 90% of participants and retrieved meta-analysis p-values of less than 1x10-2 were matched to host genes. Those genes were then processed using Ingenuity Pathway Analysis (IPA, QIAGEN) to determine the extent of their involvement in biological processes.
Results: The linear regression of genotype on SBM coefficients yielded approximately 1500 SNPs and 400 corresponding genes that were significantly related to SBM coefficients. The top enriched pathways for these genes included synaptic long-term depression (p=7.4E-06) and dopamine feedback in cAMP signaling (p=5.3E-04), as well as a strong general association of these genes to nervous system development (p=3.9E-07—p=1.7E-2).
Conclusion: SBM components are endophenotypes for the genetic study of schizophrenia, as they do not impose a priori regional restrictions but yet confirm previous reports of GMC deficit patterns in the illness. Our study reports a significant relationship between nervous system genes implicated in abnormal neurodevelopment and SBM coefficients predicting GMC differences between diagnostic groups. Thus, our work may provide a refined direction for future work investigating genetic abnormalities and morphological disturbances in schizophrenia.
ID: 2119055

WHOLE-TRANSCRIPTOME ANALYSIS OF HIPPOCAMPAL CA3 AND GENE VERIFICATION IN SCHIZOPHRENIA

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Background: Schizophrenia (SZ) is one of the thirty most incapacitating conditions and affects over 67 million people worldwide; suicide occurs in 10% of those diagnosed with schizophrenia. Symptoms are persistent and often severe. They include hallucinations, delusions, thought disorder, and deficits in executive function and memory. Treatments available are not always efficacious. 20–40% of people with schizophrenia are resistant to treatment and less than 20% completely recover after one episode of psychosis. Due to a lack of understanding of the molecular pathophysiology of schizophrenia, its diagnosis is based on behavioral symptomatology. Unfortunately, due to only phenomenological diagnoses, these categories are inadequate. Therefore, we are examining human tissue for molecular causes and correlates of the illness. Our lab has proposed a model of psychosis as a disorder of learning and memory that critically involves dentate gyrus (DG) and CA3. We suggest that reduced glutamatergic neurotransmission from DG to hippocampal CA3 serves to generate an increase in CA3 basal activity and function through homeostatic plasticity changes within CA3. This increase in function may lead to the generation of inappropriate or illogical memories with psychotic content. Our lab has shown an increase in perfusion in CA3 in schizophrenia, a correlate of neuronal activity level, as well as an increase in spine density and dendritic complexity and increased protein levels of synaptic plasticity markers like GluN2B and PSD-95 in CA3 of schizophrenia postmortem tissue.
Methods: Using a hypothesis generating approach, we have analyzed the CA3 transcriptome from control and off-drug schizophrenia cases, in a global and unbiased manner, using whole transcriptome (WT) sequencing to identify additional molecular changes, which have not been hypothesized.
Results: These analyses have focused our interest on genes like GRPIN1, AGAP1, and BCR among others. We have conducted differential expression analysis, gene coexpression network analysis, and variant mining analysis for this data set and are currently verifying the RNA-seq results through qRT-PCR and Sanger sequencing.
Conclusion: We expect to show a network of abnormalities in CA3, which support the increases in activity we have shown with our in vivo imaging analyses.
ID: 2119418

ENVIRONMENTAL AND SHARED GENETIC FACTORS WITHIN MULTIPLEX MULTIGENERATIONAL FAMILY CONTEXT UNDERLYING RISK FOR SCHIZOPHRENIA

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Background: Gene-environment interactions influencing cognitive performance are of particular interest to elucidate pathophysiology of schizophrenia (SZ) and the familial risk. The association of exposure to neurotropic DNA virus, herpes simplex virus type 1 (HSV1) with cognitive deficits and brain structural changes in SZ is widely replicated. However, the association of HSV-1 exposure with brain morphology and cognitive performance is not investigated as widely among unaffected relatives of SZ and healthy controls (HC).
Methods: Within the Multiplex Genetic Investigation (MGI) sample, we examined the association of HSV-1 exposure among 122 relatives (HSV1+/- 55/67) and 187 healthy subjects (HSV1+/- 115/72) with brain morphological changes and cognitive performance. Structural MRI data from two sites (Pittsburgh and Philadelphia) were examined using voxel-based morphometric approach in relation to HSV-1 exposure, controlling for site, age, sex and socioeconomic status, and corrected for multiple testing. Morphometric changes were examined within variance components analysis for the association with proximity to probands. Cognitive test scores were similarly examined for their correlation with morphometric changes.
Results: We observed a main effect of HSV-1 exposure on gray matter volume at the prefrontal cortex (PFC), posterior cingulate gyrus and the orbitofrontal cortex in the pooled sample of relatives and controls. HSV-1 exposed relatives showed significant reduction in the left PFC whereas controls showed more widespread reductions in bilateral PFC and superior temporal gyrus. Prefrontal volumes correlated with sustained attention and visual object memory in the entire sample controlling for case status, age and sex, and among healthy subjects controlling for age and sex. Morphometric changes showed greater variations as the proximity to proband increased.
Conclusion: This is the first study to report volumetric reductions and their correlation with cognitive impairments among non-psychotic individuals exposed to HSV-1, similar to those noted in schizophrenia patients.

Morphometric changes associated with exposure to HSV1 interacted with shared genetic factors within the multiplex families.
ID: 2088266

SEX-SPECIFIC ASSOCIATIONS BETWEEN DNA METHYLATION OF THE OXYTOCIN RECEPTOR GENE AND EMOTION RECOGNITION IN PSYCHOSIS

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Background: Emotion processing is impaired in psychotic disorders. Data suggests that this deficit is influenced by sex and oxytocin. Emerging evidence suggests that changes in oxytocin receptor epigenetics may be implicated in emotion processing deficits in autism, but whether that is true in psychotic disorders is unknown. In this study we test the hypothesis that modulation of DNA methylation of the oxytocin receptor gene (OXTR) will be associated with impaired social cognition in individuals with a history of psychosis. The assumption is that increased methylation of the OXTR promoter may have reduced functioning by silencing the OXTR receptor gene.
Methods: Participants included 167 individuals with psychosis (92 women, 75 men) and 75 healthy controls (38 women, 37 men) who completed the Penn Emotion Recognition Test (ER-40), a facial emotion recognition task. DNA methylation of OXTR was detected using bisulfite pyrosequencing of peripheral blood mononuclear cells. We measured the amount of cytosine methylation at site -934 upstream of the OXTR start codon.
Results: Individuals with and without psychosis did not show differences in DNA methylation of OXTR site -934 ($p=0.55$). However, increased methylation was observed in women compared to men ($B=-3.99$, $SE=0.82$, $p<0.001$). Increased methylation was associated with poorer recognition of emotional expressions in females with psychosis ($\beta=-0.22$, $p<0.03$) and female controls ($\beta=-0.34$, $p=0.02$) but not in men. Specifically, increased methylation was associated with greater difficulties identifying angry ($\beta=-0.31$, $p<0.01$) and sad faces ($\beta=-0.24$, $p<0.05$) in females with psychosis. Increased methylation was also associated with greater difficulties identifying low-intensity facial expressions in both females with psychosis ($\beta=-0.31$, $p<0.01$) and controls ($\beta=-0.35$, $p<0.05$).
Conclusion: Increased methylation of the OXTR receptor gene is more common in women and is associated with emotion processing difficulties in females. In women with psychotic disorders, this may be clinically relevant as the presence of methylation may further impair social cognition that is already impaired in the disorder. Results help to define an epigenetically tractable model for one factor contributing to social cognition deficits in psychotic disorders and may suggest novel treatment strategies involving manipulation of the epigenome.
****Rubin, L.H. and Connelly, J.J. were equally contributing first authors
ID: 2082838

RNASEQ TRANSCRIPTOME STUDY IMPLICATES IMMUNE-RELATED GENES IN SCHIZOPHRENIA

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Background: GWAS have implicated over 100 loci as being associated at genome-wide significant levels with risk for schizophrenia (SZ). Regulation of mRNA expression may be involved in the etiology for some of these loci. In a previous transcriptomic profiling study (Sanders et al., 2013), using arrays on samples from 268 SZ cases and 446 controls of European ancestry (EA), we found 89 genes to be differentially expressed by affection status (FDR<0.05) and enriched for immune-related genes, consistent with hypothesized immune contributions to SZ risk.
Methods: For the current study, we assayed expression by RNAseq on another EA set of 490 SZ cases and 662 controls from the Molecular Genetics of SZ (MGS) dataset. After normalization of expression data, we used regression analysis to identify genes differentially expressed, while simultaneously controlling for confounding effects, focusing here on the 8,466 genes detected well with both array and RNAseq.
Results: We found 807 genes to be differentially expressed (Bonferroni $p<0.05$). These differentially expressed genes were somewhat enriched for genes involved in autoimmunity (Fisher $p=0.01$), and their pathway analyses showed gene ontology term enrichment (FDR<0.05) for several categories including immune response. Of the 89 genes differentially expressed in our previous array study, 80 had appreciable expression in the RNAseq data, and 18 of those were differentially expressed (Bonferroni $p<0.05$, all with the same direction of effect). Notable examples thereof included DBNDD2 (which mediates neural differentiation and apoptosis), B3GNT2 (GWS association with rheumatoid arthritis), and SYT11 (GWS association with Parkinson's Disease).
Conclusion: Our RNAseq differential expression study provided evidence for replication of many of the genes found in our earlier array-based expression study, as well as providing additional support for immune-gene enrichment through pathway analyses. We are currently analyzing a further enlarged RNAseq-assayed EA dataset from MGS (~550 SZ cases and ~750 controls), and an AA MGS dataset of ~400 SZ cases and ~400 controls. In other future work, we will identify the expression quantitative trait nucleotides (eQTNs) for the detected differentially expressed genes and examine the relationship of these eQTNs to GWAS findings. This work was supported NIH grants RC2MH090030, R01MH094091, and R01MH094116.
ID: 2119422

CHARACTERIZATION OF RNA-EDITING SITES IN LIFESPAN-SPECTRUM OF NORMAL AND SCHIZOPHRENIA

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Background: RNA editing, mainly A-to-I, is the co/post-transcriptional modification of single nucleotides in RNA which causes variety of gene products. Although the identification of some RNA editing sites (e.g, 5-HT2CR) has been known in Schizophrenia, systematic genomewide

profiling of potential RNA editing sites in Schizophrenia comparing to normal human brain development has not been preceded. In order to understand the function of RNA editing in Schizophrenia, a concrete characterization of potential RNA editing profiling on brain samples is necessary.
Methods: We analyzed the polyA-selected unstranded RNA sequencing data from post-mortem dorsolateral prefrontal cortex (DLPFC) of 438 brain samples (254 Control and 184 Schizophrenia) for potential RNA editing sites. RNA-seq reads are achieved by Poly-A selection without strand specific protocols followed by high-throughput sequencing.The sequencing depth is 100bp paired-end 80–100 mappable sequencing reads which are aligned back to the human transcriptome by BWA v0.7.3a, with default parameters. The resulting alignment files were processed by samtools (v0.1.18) and picard (v1.88) to sort and mark duplicated reads, respectively. The variant calling was performed by GATK (v2.4.9) after base recalibration with dbsnp_137.
Results: Our data extend previous findings for RNA editing in human brain. We have further characterized potential RNA editing sites in protein-coding sequences between Normal and Schizophrenic brains during the lifespan development with varying editing ratios. With the current median depth, we identified 1,462,215 editing sites in protein-coding sequences. About 90% of these sites are recognized as A to G editing. We found out that the schizophrenic samples are enriched in the subgroup of the population. Interestingly this subgroup is characterized by the decrease in editing efficiency in several genes including GRIA2 which, for example shows 20% decrease of editing rate on average. Interestingly, there are several trends of editing ratio between Normal and Schizophrenic brains which can be explained developmentally.
Conclusion: We describe the characterization of potential RNA editing sites in Normal and Schizophrenia brains. Since a significant portion of genes that experience RNA-editing perturbation pre- and post-natally are involved in neural development, we may expect that these same genes may be differentially edited between schizophrenics and controls although the editing ratio is low.
ID: 2116343

CLINICAL CORRELATES OF SUICIDE IN HIGH RISK SUICIDAL PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS AND AFFECTIVE DISORDERS

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Background: This study examines the clinical correlates of suicide in high risk suicidal patients with schizophrenia spectrum disorders (SSD) and affective disorders (AD).
Methods: The study, which was conducted at the Emergency Psychiatry and Acute Care (EPAC) Services at the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, India, during June 2011and May 2012, included 120 psychiatric patients (aged 17–60 years) with high suicidal risk. The patients were evaluated using Beck Depression Inventory (BDI), Beck Hopelessness Scale (BHS), Beck Suicide Intent Scale (SIS), and Suicide Behavior Questionnaire (Linehan, 1981). Assessments were done within 48 hours of inpatient care. Pearson's Chi-square test, independent samples t-test, and one-bivariate correlations analysis were used for data analysis.
Results: The diagnostic breakup was: SSD, 35 (29 %); AD, 78 (65%); and, other disorders 7 (5.8%). Ninety-three percent (111) of the sample had made a suicide attempt. SSD patients did not differ significantly from AD patients in respect of socio-demographic variables. Suicide attempters were more in SSD (97%) patients as compared to AD (89.5%) patients. Life time history of suicide attempts and non-suicidal self-injury (NSSI) was higher in SSD patients (100% and 42.85%) as compared with AD patients (94.9% and 34.61%). Frequency of NSSI was positively correlated with the number of suicide attempts ($r = 0.317$, $p<0.01$). The mean BDI scores ($p = <0.001$), BHS scores ($p = 0.013$), and SIS scores ($p = 0.034$), were significantly lower in SSD patients as compared to AD patients.
Conclusion: To conclude, patients with SSD had a higher life time history of attempted suicide and more attempts in the previous months as compared to those with AD. Although no significant difference was found between the SSD and AD patients with regards to frequency of NSSI behavior, the frequency of NSSI appears to be an independent factor for increased suicide risk as it has a strong association with the number of suicidal attempts. Hence, early detection and intervention in case of psychiatric patients with past suicide attempts and NSSI behavior would be relevant in preventing suicide at a later date.
ID: 2118837

GENOME-WIDE ASSOCIATION STUDY OF ANTIPSYCHOTIC RESPONSE IN FIRST EPISODE PSYCHOSIS

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Background: The degree of clinical symptom response to antipsychotics is variable. We conducted an exploratory genome-wide association study to identify potential genetic predictors in first episode psychosis patients.
Methods: Eighty-eight patients experiencing their first psychotic episode (schizophrenia n=69, bipolar disorder with psychotic features n=11, major depressive disorder with psychotic features n=8) and who were currently untreated with no or minimal prior antipsychotic exposure were enrolled into a pharmacogenomic study of antipsychotic treatment response. Symptoms were evaluated using the Brief Psychiatric Rating Scale (BPRS) before and after 6 weeks of treatment. Risperidone was the preferred antipsychotic (n=70) with others chosen as secondary options when clinically indicated. Genotyping was performed using the Affymetrix SNP 6.0 Array. A linear regression model was used for genome-wide analyses where BPRS change (pre-minus post treatment) score was the quantitative trait dependent variable with clinical covariates (ancestry, diagnosis, baseline symptoms, and chlorpromazine equivalent dose) also included in the model. The genome-wide significance threshold was defined as 5x10-8. Permutation analysis (n=10,000) was used to generate point-wise significance values to analyze the robustness of individual SNP associations.
Results: Two SNPs in complete linkage disequilibrium located in the human glutamate receptor delta (GRID2) gene (rs9307122 and rs1875705) reached genome-wide significance (p=1.56x10-8). Adjusted mean BPRS change scores were 14.3, 8.9, and 3.4 for the rs9307122 CC, CA, and AA genotypes, respectively. These associations retained significance in the subpopulation of schizophrenia patients (p=3.93x10-8). An additional SNP (rs687279) in a poorly characterized region of chromosome 8 was also associated with response in those with schizophrenia (p=1.30x10-8).

Conclusion: These findings suggest a genetic influence on antipsychotic response in first-episode psychosis. The top associations were located in GRID2, which encodes the human glutamate receptor delta-2 (GluD2). This receptor does not bind glutamate directly, however recent evidence indicates that glutamate can trigger GluD2 gating through an interaction with the metabotropic glutamate receptor 1. These findings should be replicated in an independent sample, but they build upon mounting literature that suggests a role for the glutamate system in schizophrenia risk and treatment response.
ID: 2085522

MRNA-MIRNA ASSAYS INDICATE CANDIDATE ASSOCIATIONS IN POSTMORTEM DLPFC FROM PERSONS WITH SCHIZOPHRENIA

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Background: MicroRNAs (miRNAs) are small non-coding RNAs that act as potent regulators of gene expression. Several GWASs have associated the rs1625579 SNP with schizophrenia, the SNP is in linkage disequilibrium with miR-137. We investigated the potential roles of miRNAs, including miR-137, in the pathophysiology of schizophrenia.
Methods: The overall miRNA profile of the dorsolateral prefrontal cortex (DLPFC), a region involved in schizophrenia, was assayed for known miRNAs with Nanostring, and mRNA using RNA-Seq, in a pilot sample (n = 10 controls, and n = 10 persons with schizophrenia). Significant correlations between miRNA-mRNA pairs were calculated for those pairs that are predicted to interact by TargetScan.
Results: We found an overall increase in significant miRNA- mRNA target correlations in pathways related to neural development. We found a global reduction in mRNA in the cortical region and an increased expression of the number of miRNA in schizophrenia compared to controls. The expression levels of miR-137 in the DLPFC of postmortem brain did not differ between diagnoses. We examined the relationship between rs1625579 genotypes and miR-137 expression in 125 subjects. Significantly lower miR-137 expression levels were observed in the homozygous TT subjects (risk allele for schizophrenia) compared to TG and GG subjects in the control group (30% decrease, p-value=0.03).
Conclusion: Globally decreased mRNA expression was associated with increased miRNA expression. This seems to be a strong effect, and worthwhile to replicate further to advance the idea that alterations in miRNA profiles can be relevant to the pathophysiology of schizophrenia. However, the decreased miR-137 expression is associated with the risk allele for schizophrenia of rs1625579. Thus, the general increase in miRNA expression seen in DLPFC was met with an opposite finding for mir-137 decreased expression by risk allele variant. Decreased miR-137 expression is proposed to have significant effects on downstream targets involved in neurotransmission. The approach of studying both miRNA-mRNA pairs in the same samples offers additional support for involvement of miRNA and downstream targets as mechanisms of risk for schizophrenia and other psychiatric disorders.
ID: 2116718

MITOCHONDRIAL ALTERATIONS IN SCHIZOPHRENIA

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Background: Mitochondrial DNA (mtDNA) mutations are known to alter brain energy metabolism, neurotransmission, and cause neurodegenerative disorders. A considerable body of evidence supports the role of mitochondrial dysfunction in psychiatric disorders. The purpose of this study was to investigate the involvement of mtDNA variation in schizophrenia, using next generation sequencing, qPCR assays, and GWAS and exome-sequencing analysis.
Methods: We sequenced the entire mtDNA genome with an average coverage of >4000X, confirmed novel and rare variants by traditional sequencing and genotyping methods, and identified sequencing error hotspots. MtDNA sequences were compared to MitoMap, containing over 28,500 human mtDNA genomes. The accumulation of the mtDNA common deletion was measured using a quantitative assay across 10 brain regions to determine if disease specific brain differences of the somatic mtDNA common deletion (4,977 bp) could be observed in major depressive disorder, bipolar disorder, and schizophrenia compared to a control group. We analyzed mutations and large deletions in mtDNA, and common SNPs in nuclear DNA utilizing pathway analysis to annotate GWAS results published by the PGC.
Results: We observed an excess of non-synonymous mutations in individuals with schizophrenia compared to controls. Novel and rare non-synonymous mutations in mtDNA genes were found in psychiatric cases and not controls. We validated mtDNA heteroplasmy in brain, at a locus previously associated with schizophrenia (T16519C) and replicated association of mtDNA T16519C with schizophrenia in meta-analysis. A significant decrease in the global accumulation of mtDNA common deletion in subjects with schizophrenia was observed compared to major depression, bipolar disorder, and controls. The decreases in mtDNA common deletion in schizophrenia were largest in dopaminergic regions. Pathway analysis of significantly associated exome sequencing variants supports alterations of mitochondria functions.
Conclusion: This data is consistent with our prior findings of excess substitution and excess transversions in schizophrenia. Although, schizophrenia does not have symptoms associated with classic mitochondrial diseases, the mtDNA signature in schizophrenia may interact with nuclear factors to predispose to energy dysfunction in brain, and perhaps in regional specific manner as shown by our survey of 10 brain regions.
ID: 2119257

TRANSLATIONAL STUDIES OF EPISTASIS: PHENOTYPIC COMPARISONS BETWEEN MICE MUTANT FOR EITHER OR BOTH OF TWO SCHIZOPHRENIA RISK GENES

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Background: While a heritable basis to schizophrenia is established, the underlying genetic abnormality is poorly understood. The most recent genome-wide association study identified 108 loci. However, these can account only for less than one-third of the heritability estimate. One explanation for this 'missing heritability' is that individual genes interact with each other (epistasis). This phenomenon has now been studied in mice mutant for schizophrenia risk genes.
Methods: We generated mutants with disruption of either or both of the schizophrenia risk genes Disrupted-in-Schizophrenia 1 (DISC1) and neuregulin 1 (NRG1) by intercrossing mice with heterozygous (HET) deletion of NRG1 [homozygous (HOM) deletion of NRG1 being lethal] and HET or HOM mutation of DISC1. This was followed by phenotypic evaluation of all resultant genotype-wildtype (WT) combinations: (a) NRG1WT/DISC1WT; (b) NRG1WT/DISC1HET; (c) NRG1WT/DISC1HOM; (d) NRG1HET/DISC1WT; (e) NRG1HET/DISC1HET; (f) NRG1HET/DISC1HOM. This allowed us to resolve those phenotypes subject to epistatic regulation from those for which DISC1 and NRG1 exert independent, additive, or no effects.
Results: We reveal epistasis via three exemplar behavioural phenotypes related to positive, negative and cognitive features of psychotic illness.

NRG1 mutants exhibited hyperactivity, in a manner unrelated to DISC1 genotype, while DISC1 mutants did not; thus, NRG1 phenotype was unaltered by co-disruption of DISC1. In contrast, while disruption of either NRG1 or DISC1 alone was without effect on sociability, co-disruption of DISC1 and NRG1 abolished sociability, indicating epistasis. Neither disruption of DISC1 or NRG1 alone nor or co-disruption of both genes resulted in impairment in spatial working memory, indicating no individual mutant phenotypes or epistasis.
Conclusion: While hyperactivity, an index of positive symptoms, showed a NRG1 phenotype that was independent of DISC1 genotype, sociability, an index of negative symptoms, was impaired only on co-disruption of both DISC1 and NRG1, indicating robust epistasis; spatial working memory, an index of cognitive dysfunction, was unrelated to DISC1 or NRG1 genotype. These findings demonstrate epistasis between the schizophrenia risk genes DISC1 and NRG1 that is specific for a distinct domain of psychopathology, with other domains being subject to alternative genetic regulation.
ID: 2076912

TREATMENT RESISTANT SCHIZOPHRENIA: PRECISION GENETICS OR MORE OF THE SAME?

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Background: It is not known whether treatment-resistant schizophrenia (TRS) represents a distinct biological sub-type or simply a more severe form of the same condition. Furthermore little is known about the genetic architecture of treatment resistant schizophrenia (TRS). In this study we use large-scale genetic data to answer 3 questions: 1. Are polygenic and CNV burdens higher in TRS than generic schizophrenia (Sz) samples i.e. those not selected for treatment response -suggesting a more severe form of the condition? 2. Do GWAS and CNV analyses identify genetic risk factors specific to TRS? 3. Do genes identified by GWAS and CNV analyses in TRS hit glutamate and dopamine pathways at different rates than in generic Sz?
Methods: 9000 samples of those taking clozapine constituted the TRS sample-cases with a clinical diagnosis of TRS, together with 10 000 healthy controls. The TRS GWAS and CNV analysis followed established procedures for calling, QC and analysis. Polygenic overlap, training on PGC2 schizophrenia, was compared between TRS and generic Sz samples as were rates of CNVs. To identify genetic variants specific to TRS we sought to replicate SNPs from the GWAS in a sample of TRS (n=3000) versus non-TRS cases (n=3000). The pathway analyses focused on dopamine and glutamate/NMDA receptor gene sets.
Results: There was evidence that TRS is associated with a minimally stronger polygenic signal than generic Sz samples (r2 (TRS)=0.17, r2 (generic Sz)=0.14). After combining all TRS samples we identified eleven genome-wide significant SNPs in GWAS, 4 of which appear were specific to TRS. The genes associated with these SNPs are involved in neural cell adhesion and neurogenesis. Rates of CNVs were broadly equivalent between samples. There were differences in CNVs hitting genes in dopamine and glutamate pathways. CNVs in TRS cases were associated more strongly with glutamate pathways than in generic Sz. In contrast there was evidence for weaker association for CNVs hitting dopamine pathways in TRS compared with generic Sz.
Conclusion: Our results highlight specific polymorphisms associated with TRS and thus point toward the involvement of distinct molecular pathways. There is evidence for a somewhat stronger polygenic signal in TRS compared to generic schizophrenia but no evidence that large CNVs occur at a higher rate in TRS. We present genetic data indicating novel gene set findings that implicate weaker dopamine and stronger glutamate signals for CNVs in TRS compared with generic Sz.
ID: 2092626

EPISTASIS IN SCHIZOPHRENIA GENETICS: WHAT'S MISSING IS NOT HERITABILITY

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Background: GWAS for common genetic disorders typically examine association between individual SNPs and case status. In the latest GWAS of schizophrenia, adding all SNPs showing even nominal statistical association ($p < 0.05$), accounts for only 7% of trait liability. This approach fails to account for the genomic and functional pathways in which genes are embedded and the integrative effects of their combinations. Numerous studies of genotype-phenotype relationships in yeast, flies and mice show that individual gene effects are critically modulated by other genes in epistatic networks.
Methods: We explored a strategy for identification and validation of epistasis involving first hypothesis testing in iPS cell models of structural genomic variants that are biologically and clinically highly penetrant but that do not show clinical association with common variants in the same loci, and then testing common variant interactions that model the molecular biology, followed by confirmation in risk associated intermediate phenotypes derived from fMRI during memory in normal subjects.. .
Results: In one examle, we found that the abnormal dendritic architecture of DISC1 knockdown in new neurons of adult hippocampus was dependent on coexpression of the sodium- chloride co-transporter (NKCC1) encoded by SLC12A27. Epistatic models built on interactions of alleles in these two genes associated with decreased expression of the respective mRNAs in human brain were significant in association with schizophrenia in two independent case control samples and in a combined analysis of three samples. No individual SNP showed significant association in any sample. The same interaction model showed significant epistasis in prefrontal cortical engagement during working memory measured with fMR,which was confirmed in a second sample. We took a similar approach to identify genetic interactions involving genes in the 15q11 CNV. We identified CYFIP1 and interactors in the WAVE complex that is involved in actin polymerization and stabilization. We identified variants in these interacting genes that are associated with expression in human brain and showed that while no single SNP was associated with schizophrenia by itself, combinations were significantly associated in epistatic models of clinical risk. These results also have been confirmed in fMRI studies of prefrontal function during WM
Conclusion: As in other biological systems, epistasis is likely to be a ubiquitous characteristic of genetic risk for common medical disorders.
ID: 2083457

TRANSLATING SUSCEPTIBILITY GENES FOR SCHIZOPHRENIA INTO THERAPEUTIC HYPOTHESES: AN INDUSTRY PERSPECTIVE

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Background: Robust susceptibility loci identified through unbiased human genetics studies are rational starting points for evidence-based drug discovery. In light of the recent identification of dozens of novel such loci for schizophrenia, we face unprecedented opportunities to derive new drug targets. We summarize here our perspective on challenges and opportunities of such data, and provide an industry perspective on the path from susceptibility locus to testable therapeutic hypotheses for schizophrenia.
Methods: We begin by outlining how the genome-wide significant loci identified by the schizophrenia working group of the Psychiatric Genomics Consortium (PGC) can best be mapped to the likely 'causal' genes by linkage disequilibrium and/or physical distance. A key next step then is to

contextualize these 'causal' genes with annotations on function and pathways, tissue expression and subphenotypes in addition to systematically mining the literature. These analyses are aimed at (a) assessing the potential causal relationship to schizophrenia, directionality of effect, cellular context, and potential safety liability, and (b) identifying a putative hypothesis for therapeutic intervention. These nascent hypotheses are then further prioritized based on confidence in disease mechanisms, chemical do-ability, and availability of reagents and tools.
Results: From a starting list of 125 susceptibility loci, we mapped 107 putatively causal genes (85%). After gene triaging and prioritization as described above, we selected 10–12 high priority genes within well-defined biological pathways potentially relevant to schizophrenia, including calcium homeostasis, synaptic transmission, solute carrier transporters and inflammatory processes. The identified high priority targets are currently being followed up in exploratory studies as potential novel drug targets for schizophrenia.
Conclusion: While recent advances in human genetics hold great promise for defining the pathogenesis of brain disorders such as schizophrenia, the path from genetics to new medicines is long and currently not well defined. We note that large population-based datasets with genome-wide genotyping and RNA-seq data in the relevant tissue (such as the LIBD-pharma precompetitive consortium) are essential in this path to better interpret the susceptibility loci. Our strategy to generate testable hypotheses to facilitate the translation from human genetics into new therapeutics is readily generalizable beyond schizophrenia.
ID: 2118825

NICOTINIC CHOLINERGIC MODULATION OF THE FETAL BRAIN RESPONSE TO MATERNAL IMMUNE ACTIVATION

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Background: Mutation of human chromosome 15q13.3 increases the risk for autism and schizophrenia. One of the noteworthy genes in 15q13.3 is CHRNA7, which encodes the nicotinic acetylcholine receptor alpha 7 subunit (α7nAChR) associated with schizophrenia in clinical studies and rodent models. This study investigated the role of α7nAChR in maternal immune activation (MIA) mice model, a murine model of environmental risk factor for autism and schizophrenia.
Methods: We provided choline, a selective α7nAChR agonist, in the diet of C57BL/6 wild-type dams throughout gestation and the lactation period and induced MIA at mid-gestation. The adult offspring behavior and gene expression profile in the maternal splenic-placenta-fetal brain axis at mid-gestation were investigated.
Results: We found that the choline supplementation prevented several MIA behavioral abnormalities in the wild-type offspring. Pro-inflammatory cytokine IL-6 and Chrna7 gene expression in the wild-type fetal brain were elevated by poly(I:C) injection and were suppressed by gestational choline supplementation. We further investigated the gene expression level of IL-6 in Chrna7 mutant mice. We found the basal level of IL-6 gene expression was higher in Chrna7 mutant fetal brain, which suggests that α7nAChR may serve an anti-inflammatory role in the fetal brain during development. Lastly, we induced MIA in Chrna7+/- offspring and tested for their behavior. The Chrna7+/- offspring were more vulnerable to MIA, showing several behavioral abnormalities.
Conclusion: Our study shows that the α7nAChR modulates the inflammatory response in the fetal brain and offspring behavior development after maternal infection.
ID: 2077235

MATERNAL IMMUNE ACTIVATION PERTURBS FETAL BRAIN DEVELOPMENT AND ADULT BEHAVIORS THROUGH PLACENTAL TROPHOBLAST IL-6 ACTIVATION

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Background: Epidemiologic studies indicate maternal infection as a risk factor for autism and schizophrenia in the offspring. Maternal immune activation (MIA) in the dam, an animal model for maternal infection, leads the offspring exhibiting autistic- and schizophrenia-like behaviors. However, the mechanism of how MIA perturbs fetal brain development and precipitates the offspring behavior deficits and brain neuropathologies remains elusive. Prior works demonstrate maternal interleukin-6 (IL-6) is a key cytokine that mediates the effect of MIA on the offspring. Placenta as an interface between dam and fetus presumably plays a role in mediating the acute response to MIA in maternal-placental-fetal axis. Here, we are investigating the role of placental IL-6 activation in the etiology of MIA caused autistic and schizophrenia-like phenotypes.
Methods: Induction of MIA is done by injecting viral mimic poly(I:C) into the dam at mid-gestation. The inflammatory responses in the fetal brain after poly(I:C) injection is examined to understand the impact of MIA to the brain development. To further investigate the role of placental IL-6 activation in MIA model, we specifically delete the receptor for IL-6, IL-6Ra, in the placenta of mice. By using placenta-specific IL-6Ra knockout mice, we are allowed to ask whether blocking placental IL-6 activation can prevent the acute inflammation in the placental-fetal axis and offspring behavioral abnormalities and neuropathologies.
Results: We demonstrate MIA causes acute inflammatory responses in the fetal brain, including increased IL-6 expression and activated IL-6 downstream signaling in fetal prepontine and pontine hindbrain. The acute inflammatory response in the fetal brain following by MIA is found to depend on IL-6 level in the dam. Knockout of IL-6Ra in the placental trophoblast effectively blocks the inflammation in the placenta and ceases the inflammatory signaling in the fetal brain. Furthermore, the behavioral abnormalities and loss of cerebellar Purkinje cells seen in MIA offspring were successfully prevented by knockout IL-6Ra in the placental trophoblast.
Conclusion: IL-6 activation in the placenta during maternal infection is indispensible for relaying the inflammatory signal from mother to fetal brain and impacting brain development and adult behaviors. Intervention of IL-6 activation in the placenta after infection could be a potential precaution for offspring developing autism and schizophrenia.
ID: 2077457

COMMON VARIANTS FOR SCHIZOPHRENIA ASCERTAINED THROUGH GENOME-WIDE ASSOCIATION WITH A COGNITIVE ENDOPHENOTYPE

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Background: Schizophrenia is genetically complex, likely involving 1000s of common variants. To overcome small individual effect sizes, one approach is to create a polygenic risk score combining risk across SNPs (including those below the significance threshold) and weighted individually by their effect sizes. Here, we directly tested whether polygenic variants associated with an endophenotype for schizophrenia - verbal memory performance - in healthy controls (HC) predicted memory performance in independent HC and schizophrenia patient (SZ) samples. We also explicitly tested the implications of the common variant, common disease model by examining the relationship between endophenotype-generated polygenic scores and schizophrenia-related polygenic risk scores in patients with schizophrenia.
Methods: Caucasian healthy controls (N = 649) and schizophrenia patients (N = 58) recruited for the Consortium for Neuropsychiatric Phenomics, as well as SZ (N = 61) and HC (N = 63) subjects recruited from the Swedish Twin Registry, completed the California Verbal Learning Task, a list-learning measure of verbal memory. A bootstrapping analysis of associations between CVLT performance and common variants was run (1000 iterations) in the CNP control sample and multiple cut-points (SNPs present in 700, 800, and 900 of 1000 associations) were used to calculate CVLT polygenic scores. Schizophrenia risk scores were calculated using variants identified by the Psychiatric Genomics Consortium in a large case-control sample.
Results: Polygenic memory scores derived from weights based on the CNP control sample revealed significant associations with CVLT performance in the Swedish HC sample, as well as the CNP SZ sample. Higher schizophrenia risk scores were associated with lower CVLT polygenic scores (CVLT scores and performance are positively correlated) in both patient samples.
Conclusion: Polygenic memory scores reflecting variation in CVLT performance in healthy controls significantly predicted CVLT performance in independent HC and SZ samples. This is the first demonstration, to our knowledge, of polygenic scores derived from an endophenotype-based, genome-wide association study in schizophrenia successfully predicting the same phenotype (i.e., memory performance) in an independent sample. Furthermore, the relationship between schizophrenia risk scores and CVLT-derived scores provides the first genome-wide, molecular genetic evidence of the shared etiology between episodic memory performance and schizophrenia.
ID: 2091524

Neuroimaging, Functional

ALTERATIONS IN INTRINSIC CONNECTIVITY NETWORKS AND CORRELATIONS WITH PSYCHOPATHOLOGY IN ANTIPSYCHOTIC-NAÏVE FIRST-EPISODE SCHIZOPHRENIA PATIENTS

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Background: The BOLD-signal with fMRI during rest is not a random signal but is highly organized in several functional networks. These Intrinsic Connectivity Networks (ICN's) are believed to be a fundamental function of the brain although their origins are unclear at this point. In this study we wanted to investigate the relation between network connectivity and psychopathology in a cohort of Antipsychotic-Naïve First-Episode patients which has only been done in very few studies [1, 2]. Especially, we wanted to test for correlations between psychopathology and the connectivity in the Directed Effort Network (DEN) and the Representational Network (RN); networks suggested to play a key role in the development of schizophrenia [3].
Methods: To study this we used a case control design. All subjects were scanned with 10 min resting state fMRI (3T). The analysis contains 50 patients and 50 controls. After standard fMRI preprocessing steps Independent Component Analysis (ICA) was applied firstly as a means to reduce the effect of noise. Subsequently, ICA was applied to define prominent networks, and supplemented with frequency analysis as well as a seed-based approach.
Results: Using ICA to define networks of interest the connectivity within areas mapping out DEN and the RN correlated significantly with PANSS negative symptoms but not with positive and general symptoms. Within the same areas patients showed a higher connectivity than controls e.g. in frontal pole (corr. p= 0.0046) and in anterior cingulate gyrus (corr. p= 0.011). This is work in progress and it will be supplemented by the results of the frequency analysis and the seed-based approach.
Conclusion: The significant correlation with PANSS negative symptoms and the connectivity in areas within the DEN and the RN, networks also showing significant group differences, further support the hypothesis of these networks playing a key role in the development of schizophrenia. At the same time it is important to be cautious when interpreting group differences in connectivity as they can be confounded by even small group differences in noise.
Literature: [1] Lui et al., Arch Gen Psychiatry. 2010, 67(8), 783–792. [2] Wenting et al., Am J Psychiatry 2013; 170:1308–1316. [3] Williamson et Allman, Front Hum Neurosci. 2012, vol. 6, 184.
ID: 2116293

NEURAL CORRELATES OF A FIVE-FACTOR MODEL OF PSYCHOSIS

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Background: Psychiatric nosology currently relies solely on clinical symptoms and course for defining diagnostic categories. Yet symptoms must arise from altered activity of neural circuits, knowledge of which could reveal underlying disease mechanisms, disorder subtypes, and treatment targets. Resting state functional connectivity MRI (rs-fcMRI) shows network integrity across diverse brain systems and could aid data-driven discovery of the neural correlates of psychotic symptomatology.
Methods: To determine whether core clinical features depend on unique or shared brain systems, we performed a factor analysis based on clinical questionnaire responses in a large sample (n=1147) of patients with a history of psychosis and diverse DSM-IV diagnoses (schizophrenia, schizoaffective disorder, psychotic bipolar disorder, MDD with psychotic features). In a subset of >140 participants in whom rs-fcMRI and symptom measures were obtained, we examined the relationship between factor scores and functional connectivity across 122 brain regions. Analyses were designed to discover relationships between symptoms and variation in functional connectivity.
Results: Consistent with prior reports, we identified five clinical factors in our sample: (in descending order of variance explained) mania, depression, negative symptoms, positive symptoms, and substance abuse. Structured functional connectivity differences were observed for mania, negative symptoms and positive symptoms. Higher mania scores associated with higher correlation between the dorsal attention network (DAN) and the default network (DN) and frontoparietal control network (FCN), which both typically anti-correlate with the DAN. Higher negative symptom scores associated with higher correlations in the Ventral Attention Network (VAN) and Salience Network (SN). Higher positive symptom scores associated with FCN changes.
Conclusion: Clinical dimensions of psychosis may have specific neural signatures, and distinct patterns of altered functional network interactions may explain individual psychosis presentations. For example, reduced anti-correlations between systems occurred in acute mania and also to a lesser degree non-manic patients with history of mania. These reduced anti-correlations may be biological determinants of the mood and cognitive dysregulations of bipolar disorder and may inform illness definition, exploration of the mechanisms underlying mania, and treatment testing and design.
ID: 2083893

ABNORMALITIES IN THE SIGNALING OF EXPECTED VALUE, BUT NOT REWARD PREDICTION ERROR, IN SCHIZOPHRENIA, IN THE CONTEXT OF A PROBABILISTIC LEARNING TASK

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Background: In a previous study (Gold et al., 2012) we observed that aberrant performance by avolitional schizophrenia (SZ) patients could be accounted for by maladaptive representations of expected value (EV), in the presence of intact signaling of reward prediction errors (RPEs). This finding suggested that operant learning impairments in SZ might originate from aberrant prefrontal cortical (PFC) signals related to EV, rather than aberrant striatal RPE signals. We tested this hypothesis with functional MRI.
Methods: 19 SZ patients and 23 controls performed a variant of a probabilistic reinforcement learning paradigm (Pessiglione et al. 2004), in which participants learned 3 discriminations where a choice of the better stimulus was reinforced 80%, and punished 20% of the time, and a choice of the worse stimulus was reinforced 20% and punished 80% of the time. In a "Gain-Miss" (GM) pair, possible outcomes were a gain of 25 cents, or a neutral outcome. In a "Loss-Avoid"

(LA) pair, outcomes were either neutral or a loss of 25 cents. In a "Correct-Incorrect" (CI) pair, subjects received only "Correct" and "Incorrect" as verbal feedback. For group analyses, we performed whole-brain analyses with factors of diagnostic group, stimulus pair (GM, LA, or CI), and RPE valence.
Results: Significant GROUP x PAIR interactions were observed in both dorsal and ventral medial PFC, as well as posterior temporal cortex, bilaterally. Relative to SZs, controls showed greater activations in both dorsal and ventral medial PFC, in anticipation of potential gains (vs. potential losses). Although main effects of PAIR valence and OUTCOME valence were observed in ventral striatum for the entire sample, those main effects were not modulated by GROUP. A significant GROUP x PAIR x OUTCOME interaction was observed in the left insula, with controls showing greater activations than patients for surprising reward omissions ("misses"). The GROUP x PAIR interaction also correlated with symptoms, where patients with more severe symptoms exhibited a weaker EV signal.
Conclusion: These results suggest that PRL deficits in SZ patients are more likely to be the product of disrupted frontal EV signals than aberrant striatal RPE signals. The finding of disrupted frontal EV signals fits with evidence that motivational deficits in SZ result from faulty representations of the costs and benefits of prospective actions, rather than an impaired ability to signal the goodness or badness of outcomes.
ID: 2089423

EFFECT OF ANTIPSYCHOTIC MEDICATION ON ANTERIOR CINGULATE CORTEX FUNCTION IN FMRI IN SCHIZOPHRENIA

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Background: Conflict monitoring and response inhibition are fundamental cognitive operations that allow adaptive behavior to emerge based on contextual information. Their functions have been ascribed to the dorsal anterior cingulate cortex (dACC). Previous research in schizophrenia (SZ) has found neuroimaging evidence of impaired functioning of the dACC during performance of these cognitive operations; however these studies were performed while patients were medicated, and some drugs that modulate dopamine are known to interfere with these cognitive processes. In this study, we evaluated unmedicated SZ, before and after a 6 week course of an antipsychotic drug, during performance of a task tapping into those operations.
Methods: fMRI data were acquired during performance of the Stroop color naming task (TR/TE) 2100/30msec, Flip angle= 70 degrees, slice thickness=4mm, 1mm gap, FOV=240mm). SZ were scanned while unmedicated (n=20) and after 1 (n=20) and 6 (n=20) weeks of treatment. Matched healthy controls (HC) were scanned twice, 6 weeks apart. Data were analyzed using SPM8. Preprocessing included coregistration to a high resolution structural scan (MPRAGE), slice timing correction, realignment, normalization to MNI space and smoothing (4mm FWHM) using DARTEL At the single subject level five conditions were included as regressors in the context of the general linear model: incongruent trials, congruent trials, error trials, no response trials, and stimulus repetitions. At the group level, contrast images representing the Stroop effect (incongruent-congruent trials) were entered into statistical analyses. Between group analyses were conducted using independent t-tests ($p<.01$, false discovery rate (FDR) corrected). Within group repeated measures analyses were conducted using paired-samples t-tests with small volume correction ($p<.05$). Small volume correction was conducted using a mask generated from the between group image differences.
Results: Compared to HC, unmedicated SZ had significantly less activation in the ACC, caudate, putamen, thalamus, insula, inferior-superior frontal gyri, posterior cingulate, precuneus, and parietal cortices. After 6 weeks of treatment, there was a significant increase in the blood oxygenated level dependent (BOLD) signal in the dACC, caudate, thalamus, precuneus, inferior and middle frontal cortices.
Conclusion: Impaired dACC function is seen in unmedicated SZ and partially restored by antipsychotic medication. This could be a necessary step to symptom improvement.
ID: 2118816

INTERNETWORK CONNECTIVITY DURING WORKING MEMORY: RELATIONSHIPS TO TASK PERFORMANCE AND CORTICAL DOPAMINE RELEASE CAPACITY IN HEALTHY CONTROLS AND SCHIZOPHRENIA PATIENTS

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Background: Efficient coupling between task-positive brain networks and the default-mode network promotes performance in working memory and other aspects of cognition. Cortical dopamine is also important for working memory but the effect of cortical dopamine release capacity on internetwork coupling is not known.
Methods: A sample of 17 healthy controls and 9 schizophrenia patients underwent fMRI and PET scans. BOLD fMRI signal was measured while subjects performed a shape variant of the n-back working memory task. PET imaging was performed with [11C]FLB457 before and following 0.5mg/kg P.O. amphetamine. Spatial maps and time courses for brain networks were determined using independent components analysis. The number of networks was estimated to be 29, of which 4 networks were selected for further analysis, a higher-order visual processing network (VN), a working memory network (WMN) and anterior (DMNa) and posterior (DMNb) components of the default mode network. The coupling between pairs of networks was calculated from the Pearson correlation between network time series.
Results: In the healthy control group, coupling between the working memory network (WMN) and all three other networks was correlated to working memory performance: WMN-VN, $R = -.70$, $p < .01$; WMN-DMNa, $R = .51$, $p < .05$; WMN-DMNb, $R = -.61$, $p < .01$. Dopamine release capacity in the dorsolateral prefrontal cortex (DLPFC) was correlated to coupling between WMN and VN, $R = -.49$, $p < .05$ suggesting that greater dopamine release capacity is associated with reduced anticorrelation between these networks. In the patient group the coupling between the working memory network and all three other networks was not significantly correlated to task performance (absolute value of all R values < .11). Similar to controls, there was a negative correlation between DLPFC dopamine release and WMN-VN coupling ($R = -.35$, $p > .3$).
Conclusion: These results suggest that efficient coupling of working memory networks is important for working memory performance and that cortical dopamine may play a role in functional coupling in activity across networks. Preliminary results from a small patient sample suggest this may be less apparent for schizophrenia patients.
ID: 2119576

THE WEAKEST LINK: NEGATIVE SCHIZOTYPY SHOWS ABNORMALITIES IN STRUCTURAL AND RESTING-STATE NETWORKS

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Background: The current study sought to examine the underlying brain structural and connection abnormalities in individuals with schizotypy.

Methods: We administered a set of questionnaires to specifically capture the schizotypy traits from college students. Thirty-five individuals with schizotypy and 34 healthy controls were identified and invited to take part in brain scans for structural and resting-state.
Results: Voxel-based morphology analysis showed that individuals with schizotypy showed reduced grey matter (GM) density in the insula and the dorsolateral prefrontal gyrus as compared to controls. The graph theoretical analysis revealed that individuals with schizotypy show both similar and distinct hubs of the functional network with healthy controls. For example, both individuals with schizotypy and controls show hubs of networks in the insula, the lingual gyrus, the postcentral gyrus and the rolandic operculum. However, individuals with schizotypy were found to show fewer hubs in the occipital lobe. The schizotypy individuals were also found to show weaker functional connectivity between the left insula and the putamen, but stronger connectivity between the cerebellum and the medial frontal gyrus.
Conclusion: These findings suggest that individuals with schizotypy present changes in terms of grey matter and resting state functional connectivity, especially in the frontal lobe.
ID: 2106736

AN FMRI INVESTIGATION OF TDCS-INDUCED CHANGES IN CORTICAL FUNCTION DURING AUDITORY VERBAL HALLUCINATIONS

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Background: Brunelin et al (2012) reported significant reduction in the severity of auditory verbal hallucinations (AVH) in a transcranial direct current stimulation (tDCS) treatment trial; the present study uses fMRI to link changes in AVH severity with changes in neural activations.
Methods: Two female volunteers with schizophrenia and AVH despite treatment (ages 39 and 55) were administered the 5-day tDCS treatment program first described by Brunelin et al. Pre and post treatment fMRI scans; pre, mid, and post psychotic symptoms rating scales (PSYRATS); and pre, mid, and post positive and negative syndrome scales (PANSS) data were collected. AVH-on and AVH-off were tracked during scanning using a button-press paradigm, and participants also completed a listening task during scans.
Results: Decrease in the severity of PSYRATS score with tDCS treatment was associated with significantly increased activation in auditory cortex, both during AVH and during a listening task.
Conclusion: These findings are consistent with AVH models suggesting that atypical function of auditory cortex is associated with the presence and severity of AVH. These results also serve as a preliminary indication of the mechanism by which tDCS neuromodulation may be used to affect schizophrenia AVH.
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ID: 2119147

GABA INTERNEURON FUNCTION AND WORKING MEMORY INTERFERENCE AS A PREFRONTAL MECHANISM IN SCHIZOPHRENIA

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Background: Results of working memory (WM) fMRI studies comparing healthy controls and people diagnosed with schizophrenia (SZ) have shown discrepancies in prefrontal signal (hypofrontality, hyperfrontality, both, or none). Can this be explained by the differential WM interference caused by the interaction of GABA pathology with different inter-stimulus interval (ISI) timings?
Methods: We combined experimental fMRI and theoretical computational techniques. Experimentally we compared 14 healthy and 13 schizophrenia participants in an fMRI study using a novel parametric manipulation of phonological and orthographic interference during a one-back task at two different ISI (1000 and 1600 milliseconds). Theoretically, we used a biologically-based laminar WM model with two types of GABA interneurons linked to the pathophysiology of schizophrenia: the fast-spiking cholecystokinin-positive basket cell (CCK+bc), and the low-threshold spiking somatostatin-positive cell (SST+lts). Using this WM circuit, we simulated parametric perturbations to different prefrontal GABA interneurons in order to evaluate the resulting synthetic fMRI/PET signal at different ISI. Simulations for the perturbations of the CCK+ bc and the SST+lts interneurons were evaluated separately.
Results: Experimentally, we demonstrated that the interaction of group x interference x ISI was significant and that the parametric interference effect shows different net outcomes of the prefrontal fMRI/PET signal (hypofrontality, hyperfrontality, both, or none). Theoretically, the CCK+bc perturbation allowed the presence of representations of the unwanted stimuli in the delay units from the WM circuits (Interference). The perturbation of the SST+lts interneuron population, did not enable unwanted representations, but rather generated interference between sequential stimuli. In both cases the fMRI/PET signal varied depending on the ISI by having an inverted "U" behavior.
Conclusion: By experimentally showing that interference type and timing generate different outcomes in the two groups AND theoretically linking perturbations of different interneurons at different ISI with interference and different fMRI/PET outcomes, we are able to suggest a link between functional neuroimaging results and underlying pathophysiology in schizophrenia
ID: 2086243

DYSCONNECTIVITY, BRAIN HUBS, AND THE RISK OF PSYCHOSIS.

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Background: The understanding of the underlying neural mechanisms in psychosis would facilitate identification of clinically relevant neuroimaging markers in the prodrome. However, both task-based functional neuroimaging studies and structural VBM studies in schizophrenia have identified abnormalities that are widely distributed across the brain, and that are difficult to integrate into a system-level pathophysiology. We here revisited the functional and structural neuroimaging literature on schizophrenia from a network perspective, analysing the network position where abnormal activations or structural atrophy emerged, particularly focusing on the hubs of the brain.
Methods: We included 314 published functional neuroimaging studies, including a wide range of tasks, and 51 VBM studies comparing schizophrenia patients and controls (with a total of >5000 and >4000 participants respectively). After mapping the coordinates of differential activations between groups onto a normative network template, we examined the network-level similarities of the brain regions involved.
Results: Meta-analysis of structural VBM studies found an anatomically distributed network of abnormalities in schizophrenia. The probability of a region being abnormal was correlated with its level of connectivity (degree). Similarly, functional studies reported underactivations in patients compared to controls in widespread areas of the brain, with anatomical locations varying according to the task used. From a network perspective, the probability of an underactivation was also correlated with the degree of the regions, irrespective of the task.
Conclusion: These data suggest that schizophrenia involves dysfunction in anatomically distributed regions of the brain that normally operate as hubs. Early functional or structural abnormalities in hub regions in the prodrome could potentially inform future outcome in the at risk mental state.
ID: 2094173

PATTERN SEPARATION DEFICIT IN SCHIZOPHRENIA: BEHAVIOUR AND IMAGING FINDINGS

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Background: Human studies have consistently supported involvement of hippocampal dysfunction in schizophrenia. The hippocampus has long been implicated in forming new memories, storing them independently, retrieving memories from partial cues and flexibly applying stored memories to partial cues. Hippocampal-mediated memory allows the discrimination of similar events as distinct and orthogonal, called pattern separation (PS). Motivated by evidence that the dentate gyrus differentially mediates the PS component of declarative memory function and that it harbors molecular and cellular pathology in schizophrenia, we examined PS performance in schizophrenia (SZV) vs healthy volunteers (HV) using the Behavioral Pattern Separation (BPS) task (Stark et al., Neuropsychologia, 2013).
Methods: In well-characterized SZV and HV, we contrasted behavioral performance and fMRI BOLD activation during the BPS task, fMRI scans being acquired whilst the volunteers performed the task. Behaviorally, we calculated two outcome measures, PS and Recognition Memory (RM). The BPS task included an incidental 'encoding' phase (runs 1–2) (with 128 pictures of everyday objects) where volunteers identified each object as "indoor" or "outdoor". A subsequent 'test' phase (runs 3–4) exposed volunteers to 192 pictures/run, with 64 repetitions (old), 64 new objects (foils) and 64 similar objects (lures) to pictures shown in runs 1–2, and volunteers were instructed to identify objects as repeated, new, or similar.
Results: The SZVs showed a significant decrement in PS performance relative to HV (mean±SEM, SZV: 3.1 ± 2.7%; HV: 17.1 ± 5.8%; *p=0.039); whereas SZV and HV did not significantly differ in RM performance (SZV: 50.1 ± 8.1%; HV: 59.3 ± 5.5%; p=0.350) (Das et al., in press in Schizophrenia Research). We have acquired high resolution fMRI BOLD task-associated scans on 3T Philips Achieva. Hippocampal images are being analysed using 3D Slicer, MATLAB and SPM5.
Conclusion: We hypothesize that SZV will activate the DG/CA3 hippocampal subfield to a significantly lower degree than HV for correct lure identification and that the magnitude of activation will correlate with PS performance. fMRI BOLD data will be presented by group and by subfield. Hence our behavioral finding of lack of pattern separation in schizophrenia leads us to expect a dysfunctional dentate gyrus in the illness, a feature that could contribute to declarative memory impairment in the disorder and possibly, schizophrenia psychosis.
ID: 2087901

THE RELATIONSHIP BETWEEN AFFECTIVE MENTALIZING AND IMPAIRED INSIGHT IN PATIENTS WITH SCHIZOPHRENIA: AN FMRI STUDY

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Background: Impaired insight appears in 50 to 80% of patients suffering from schizophrenia. It has been associated with negative outcomes, indicating the importance of studying underlying factors. In this study we focus on the relationship between impaired insight and affective mentalizing using neuroimaging. Affective mentalizing (or: affective theory of mind) is defined as the ability to understand mental and emotional states of others and to predict someone's behavior based on that belief state. Affective mentalizing is often impaired in patients with schizophrenia, several studies found less brain activation during an affective mentalizing-task. In this study, an affective mentalizing-task in an fMRI scanner was used to examine the relationship between brain activity and impaired insight in patients with schizophrenia.
Methods: Thirty five participants with a diagnosis of schizophrenia and with varying levels of insight viewed static social scenes in an fMRI-scanner. Each social scene comprised a False Belief character or a True Belief character. Patients had to identify or infer an emotion of the character. The Schedule of Assessment of Insight - Expanded (SAI-E) was used to asses clinical insight and the Beck Cognitive Insight Scale (BCIS) to assess cognitive insight.
Results: Results showed that stronger activation in brain regions (right temporal pole, left precuneus and right insula) involved in emotion inference during affective mentalizing was related with better cognitive, but not clinical insight.
Conclusion: The results of the present study suggest a positive association between activity in brain areas involved in affective mentalizing and cognitive insight. This relationship may reflect an inability to predict and infer other people's emotions using perspective taking and using that information to correct faulty self-evaluations. This effect was not found for clinical insight, implying that this effect might be specific for cognitive insight.
ID: 2089910

LANGUAGE PATHWAYS IN THE BRAIN AND THEIR BASIS FOR THE SYMPTOMS OF SCHIZOPHRENIA

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Background: The underlying basis for schizophrenia is unknown, but it seems clear that regardless of whether or which genes and/or environment contribute to risk, the brain pathways relevant to language and thought have developed in a deviant manner. Those specifically involved in language production have been studied extensively in schizophrenia with various tasks that evoke response in functional imaging.
Methods: A series of research studies focused on language were performed over the years from the late 1990's through the present using fMRI, structural MRI, and cognitive measures in people at high genetic risk for schizophrenia (GHR).
Results: While GHR individuals consistently have findings that are more deviant than low genetic risk controls (GLR), they are not as deviant as patients with chronic schizophrenia. These studies will be reviewed in detail.
Conclusion: A variety of measures of language abilities may potentially be useful as screening measures for whether someone at GHR for schizophrenia is likely to develop illness and thus together with other measures of overall functioning may have implications for treatment strategies aimed toward prevention. More research, however, will need to be performed to refine the measures so that they will be useful clinically.
ID: 2147964

EVIDENCE FROM DIFFUSION TENSOR IMAGING FOR FRONTOTEMPORAL DEFICITS IN SUBCLINICAL PSYCHOSIS

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Background: In recent years, schizophrenia (SZ) has increasingly been viewed as a disorder of dysconnectivity in which decreased connections between brain areas is associated with frank psychosis. This view is consistent with findings of reductions in white matter (WM) integrity, particularly in frontotemporal regions, in patients with SZ. Recent examination of patients with schizotypal personality disorder (SPD), however, have revealed a similar pattern of WM abnormalities suggesting that frontotemporal lobe dysfunction may represent a core component of a more general psychosis phenotype. To date, few studies have examined whether WM integrity is associated with subclinical psychotic symptoms in adults who do not meet criteria for a psychiatric illness and even fewer studies have examined this relationship in typically developing adolescents.
Methods: We administered diffusion tensor imaging (DTI) exams to healthy adolescents (N=57) and healthy adults (N=138) who were characterized for subclinical psychosis. Fractional anisotropy (FA) in 5 association tracts traversing the frontal and temporal lobes including the inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), cingulum bundle, superior longitudinal fasciculus (SLF) and uncinate fasciculus (UF) were examined in relation to severity of subclinical psychotic symptoms.
Results: In the adult sample, we found an association between subclinical psychotic symptoms and FA in the IFOF ($F(1,133) = 4.90$, $p = .029$) such that individuals characterized as high in subclinical symptoms had lower FA than those characterized as low in subclinical symptoms. In the adolescent sample, examination of tract-based spatial statistics revealed a significant association (pFWE<.05) between overall levels of subclinical psychotic symptoms and FA within a cluster comprising the SLF and IFOF.
Conclusion: These findings are broadly consistent with data derived from the study of patients with SZ and SPD and suggest that frontotemporal lobe dysfunction may represent a core component of the psychosis phenotype. These data add to the growing evidence that psychosis should not be viewed as a dichotomous category but rather, a dimensional construct.
ID: 2070441

NOVELTY, EMOTIONAL PROCESSING AND OTHER FORMS OF SALIENCE ABNORMALITIES IN PEOPLE WITH EARLY PSYCHOSIS

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Background: Salience is the property of the stimuli to attract attention and drive behaviour. Abnormal salience processing has been proposed to underpin the formation of psychotic symptoms in schizophrenia and related conditions. Previous research demonstrated abnormalities in the incentive or motivational salience in people with psychosis. However, little is known about the other forms of salience in these patient groups.
Methods: FMRI was used to compare neural activity in response to stimulus novelty and other forms of salience, namely rareness, negative emotional valence and targetness (task-driven salience). A total of 16 subjects with a first episode of psychosis (FEP), 31 people at high clinical risk of developing psychosis (ARMS), and 39 healthy volunteers took part in our study. Participants performed a visual oddball task, adapted from that of Bunzeck and Duzel (2006). The results are family wise error cluster corrected across the whole brain.
Results: Healthy volunteers showed a greater haemodynamic response to all forms of salience except for rareness. For the emotional stimuli, controls showed more activity in the amygdala, especially the right amygdala, than patients with FEP. Both emotional and novel stimuli elicited activation in the thalamus of healthy volunteers, in contrast to people with FEP. For novel stimuli, we observed control versus FEP differences in the striatum, medial prefrontal cortex, left hippocampus and visual cortex. The anterior cingulate and paracingulate were more active in healthy volunteers compared with patients with ARMS in response to target, emotional and novel stimuli. Rareness evoked strong responses in the anterior cingulate cortex of the ARMS patients, but not in the other groups. In contrast with the previous literature, where the hippocampus and dorsal striatum responded to rareness, we did not find any statistically significant activity in these brain regions in healthy volunteers.
Conclusion: Our study thus demonstrates abnormal function of the neural substrates of various forms of salience in patients with first-episode psychosis.
ID: 2142926

IMPROVEMENT IN ANTI-CORRELATION BETWEEN REGIONS OF THE 'TASK POSITIVE' AND DEFAULT MODE AND NETWORKS INDUCED BY CANNABIS AND THC IN PATIENTS WITH SCHIZOPHRENIA: IMPLICATIONS FOR WORKING MEMORY?

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Background: Almost half of patients with schizophrenia (SCZ) have a co-occurring cannabis use disorder (CUD), which has been associated with poorer long-term outcomes. Despite this, patients with SCZ who use cannabis have shown improved cognitive functioning relative to non-using patients. Default mode network (DMN) hyperconnectivity and reduced anticorrelation with the task positive network (TPN) have been implicated in symptom severity and cognitive impairment in SCZ, respectively. We examined resting state functional connectivity (rs-fc) within the DMN and correlations between the medial prefrontal cortex (MPFC) component of the DMN and the dorsolateral prefrontal cortex (DLPFC), a component of the TPN that supports executive functions, in association with working memory performance.
Methods: Twelve patients with SCZ and CUD and 12 healthy controls completed two fMRI resting scans. Prior to the second scan, patients either smoked a 3.6% THC cannabis cigarette or ingested a 15mg THC pill. We examined the positive correlations within the DMN and the strength of the anticorrelation between the MPFC and the DLPFC. We then explored the effects of cannabis and delta-9-tetrahydrocannabinol (THC) on functional connectivity of the DMN in association with working memory performance.
Results: Our findings revealed DMN hyperconnectivity, as well as reduced DMN/TPN anti-correlation in patients relative to controls. Cannabis and THC exerted opposing effects, with cannabis lowering and THC increasing, DMN hyperconnectivity in the patient group. Both agents, however, significantly increased the MPFC-to-DLPFC anticorrelation ($p<0.05$, FDR corrected), which was significantly associated with working memory performance ($p<0.05$).
Conclusion: Functional pathology of DMN connectivity in SCZ may contribute to the inability to appropriately distinguish and shift attention between internally generated thoughts and external goal-oriented tasks. Cannabinoid induced enhancement in the DMN/TPN anticorrelation and its association with working memory performance may explain why cannabis-using patients with SCZ have improved cognition when compared to non-users; by improving the functional coupling between these networks, low dose cannabis may enhance the ability to distinguish between internal and external modes of processing. These preliminary findings suggest that cannabinoid agonists alter functional connectivity of the DMN and may have potential as an adjunctive pharmacotherapy in patients with SCZ and CUD.
ID: 2093927

THE NEURAL CORRELATES OF EFFORT VALUATION IN A VIRTUAL ENVIRONMENT IN SCHIZOPHRENIA

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Background: Motivational deficits figure prominently in the negative symptoms of schizophrenia, and confer significant functional consequences in both first-episode and chronic populations. Recent work has served to highlight the multifaceted nature of motivation, whereby hedonic experience and reward prediction serve to inform both the reward and effort/cost valuation associated with achieving a rewarding outcome, followed by goal-directed action to achieve the desired outcome. Within this framework, recent behavioral studies have highlighted impairments in effort valuation in schizophrenia. Using a novel virtual reality-based strategy, this study sought to delineate the neurobiology of such effort valuation impairments in schizophrenia in the context of simulated everyday tasks.
Methods: Stable adult outpatients with schizophrenia (SZ) and matched healthy controls (HC) were recruited for this study. All participants underwent clinical assessments followed by functional MRI while performing our novel Virtual Reality Progressive Ratio (ViPR) task, where participants worked for reward in the face of increasing effort requirements. Our main analyses examined group differences in brain activity associated with increasing effort demands, and with reward attainment after increasing effort requirements.
Results: To date, 20 participants (10 SZ and 10 HC) have completed this study. Preliminary analyses have revealed reduced ventromedial prefrontal cortex (vmPFC) activation in SZ participants in response to increasing effort requirements compared to HC participants. Further, during reward attainment following progressively increasing effort demands, SZ participants exhibited reduced anterior cingulate (ACC) and medial prefrontal cortex (mPFC) activation.
Conclusion: Using a virtual reality-based progressive ratio task coupled with fMRI, this study investigated the neural correlates of effort valuation impairments in schizophrenia. Preliminary findings revealed reduced engagement of vmPFC during effort expenditure, and ACC/mPFC during eventual reward attainment in individuals with schizophrenia. These findings provide some early insights into the neurobiology of effort valuation and more broadly cost-benefit decision impairments in schizophrenia. In light of the functional consequences of such motivational deficits, understanding their neural underpinnings is critical as we strive to develop effective treatments to improve outcomes in schizophrenia.
ID: 2118950

RESTING STATE FUNCTIONAL CONNECTIVITY IN EARLY PHASE PSYCHOSIS

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Background: The purpose of this study is to elucidate functional connectivity at rest in individuals with early phase psychosis (EPP).
Methods: EPP subjects (N= 46) were recruited through the Prevention and Recovery Center for Early Psychosis. The control group (N = 17) was comprised of healthy subjects who were free of major psychiatric disorders and matched for age race, and gender. Subjects underwent functional magnetic resonance imaging (fMRI) with a Siemens 3T Tim Trio scanner during a 6-minute resting-state scan. After standard preprocessing, each participant's fMRI time-series was bandpass-filtered (0.01–0.1 hz), and physiological noise effects were reduced by regressing out mean signals from white matter and CSF. In contrast to most previous work, controlling for the global mean signal, which may introduce spurious

anticorrelations, was not performed. To characterize default mode network connectivity, the correlation of the average time series from the posterior cingulate with each voxel's time series was calculated. Default mode network (DMN) connectivity was then characterized as the correlation of each voxel's time series with mean time series in the posterior cingulate cortex (PCC). DMN connectivity was contrasted between EPP and control groups (EPP vs. control) on a voxel-by-voxel basis throughout the entire brain, using $p < .05$, corrected for multiple comparisons. Subjects were administered the Brief Assessment of Cognition in Schizophrenia (BACS), used to examine the relationship between cognition and activation pattern.

Results: In both groups, PCC connectivity was strongest with the bilateral medial prefrontal cortex, precuneus, inferior parietal cortex, and middle temporal cortex, reflecting characteristic DMN connectivity. Controls, compared to those with EPP, had significantly greater connectivity within DMN structures (PCC, precuneus, medial prefrontal cortex) as well as between the PCC and other regions throughout the brain, including the visual cortex bilaterally, bilateral postcentral gyrus, and cerebellum. There was no association between BACS performance and PCC connectivity in either group.

Conclusion: Results suggest altered functional connectivity of resting state circuitry in first-episode psychosis. These findings add to a growing body of research implicating disrupted integration of resting state circuits in the pathophysiology of schizophrenia.

ID: 2092169

THE ROLE OF NEUROIMAGING IN UNDERSTANDING COGNITIVE PREDICTORS OF FUNCTIONAL AND CLINICAL OUTCOME IN THE EARLY PHASES OF PSYCHOSIS

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Background: The early years of psychosis represent a critical period that likely sets the stage for the substantial clinical and social deterioration experienced by many patients. Associations between cognition and outcome in schizophrenia are very robust particularly in the case of working memory (WM). Neuroimaging techniques have allowed us to delineate the neural circuitry that underpins this association.

Methods: Two methodological approaches were used. First we conducted a meta-analysis of functional magnetic resonance imaging (fMRI) studies focusing on patterns of activation and functional interaction within the WM network that may be associated with transition to overt psychosis. Second, we conducted a longitudinal fMRI examination of the neural circuity underpinning performance of the 2-back WM task in 40 patients with early onset schizophrenia. Patients were first scanned within at onset and then after a mean interval of 4 years. Functional interactions among brain regions involved in WM, in particular between dorsolateral prefrontal (DLPFC), dorsal anterior cingulate (dACC) and parietal cortical regions were examined in relation to psychosocial and clinical outcome.

Results: Progressive reduction in the functional connectivity of the DLPFC with the ACC and parietal regions emerged as a consistent meta-analytical finding associated with transition to overt psychosis. Further support was provided by the longitudinal study that found that deterioration in prefrontal dysconnectivity over time was predictive of greater impairment in social function at 4 years post-onset.

Conclusion: Our findings suggest that the functional integrity of dorsal fronto-cingulate-parietal networks contributes both the cognitive dysfunction and clinical expression and outcome in schizophrenia.

ID: 2118724

ALTERED AMYGDALA FUNCTIONAL CONNECTIVITY IN NEONATES AT RISK FOR SCHIZOPHRENIA

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Background: Amygdala-prefrontal cortex functional connectivity is abnormal in adults with schizophrenia, as well as in adolescents at clinical risk for psychosis. Given evidence that altered brain circuitry associated with schizophrenia may arise very early in brain development, we sought to determine if abnormalities of amygdala functional connectivity were present in neonates at genetic high risk for schizophrenia.

Methods: Mothers with schizophrenia (SCZ), bipolar illness (BP), and no major psychiatric illness were recruited during pregnancy. After birth, offspring underwent resting state functional MRI on a 3T scanner during natural sleep. The bilateral amygdala were defined using a probabilistic subcortical atlas and seed-based whole brain functional connectivity analyses were carried out. Quality scans were obtained on 15 neonates of mothers with schizophrenia, 20 with BP, 20 with Mood DO NOS, and 20 control mothers.

Results: In neonates, connections exist between the amygdala and medial temporal cortex, pre-/post-central gyrus, medial visual cortex, anterior/middle cingulate cortex, lateral temporal cortex, lateral prefrontal cortex and insula. Compared to controls, all three at-risk groups demonstrate common hyper-connectivity with bilateral thalamus and hypo-connectivity with bilateral medial visual cortices for the right amygdala, without significant between-risk-group differences. The left medial prefrontal cortex (mPFC) shows common hyper-connectivity with the left amygdala for SCZ and BD but not for MD-NOS; left dorsal lateral prefrontal cortex (dlPFC) demonstrates hyper-connectivity with the left amygdala for both SCZ and MD-NOS but it is most severe in SCZ.

Conclusion: We found that abnormalities of amygdala functional connectivity are already present in neonates at genetic risk for schizophrenia, as well as in neonates at risk for bipolar illness and mood disorder NOS. Both common and disorder-specific abnormality profiles were detected which could discriminate between at-risk and control neonates. These findings indicate that functional connectivity abnormalities associated with genetic risk likely arise during prenatal and early neonatal brain development. This study also suggests that it may be possible to develop imaging-based early identification of risk for later psychiatric illness at the earliest stages of postnatal life.

ID: 2088024

HIGH-SENSITIVITY C-REACTIVE PROTEIN, VASCULAR ENDOTHELIAL GROWTH FACTOR AND CEREBRAL BLOOD FLOW IN FIRST EPISODE PSYCHOSIS

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Background: Both high-sensitivity C-Reactive Protein (hs-CRP) and Vascular Endothelial Growth Factor (VEGF) are involved in the regulation of blood flow. However, it remains unclear whether they are associated with the alterations in regional Cerebral Blood Flow (rCBF) observed in patients with psychosis. We investigated, for the first time, whether hs-CRP and VEGF serum levels are associated with rCBF in patients with first episode psychosis and healthy individuals.
Methods: Thirteen first episode psychosis patients (27.1 ± 5.6 years; 8 males) and 14 healthy controls matched for age and gender were included in this study. Regional CBF was assessed using a pseudo-continuous arterial spin labelling (pCASL) sequence acquired in a 3T GE scanner, whilst at rest with eyes open. We measured serum levels of hs-CRP and VEGF and explored the relationship between rCBF and peripheral markers. Significant clusters were identified using a threshold $p<0.05$, not controlled for global perfusion changes.
Results: Compared to controls, patients had higher hs-CRP (1.8 ± 2.3 vs. 0.5 ± 0.1 respectively, $p=0.07$) and higher VEGF levels (66.7 ± 18.5 vs. 58.7 ± 36.9 respectively, $p=0.04$). Patients showed lower rCBF than controls in the subcallosal gyrus and the uncus ($p<0.05$, FWE corrected). In patients, higher levels of hs-CRP were correlated with lower rCBF in the hypothalamus and caudate ($p<0.05$, FWE corrected). Also, lower levels of VEGF correlated with higher rCBF in the superior temporal and inferior frontal gyrus (Figure 3) ($p<0.05$, FWE corrected). In controls, we did not find any correlation between the rCBF and peripheral levels of hs-CRP and VEGF.
Conclusion: These findings go beyond previous evidence that peripheral inflammatory markers are raised in psychosis, revealing increased VEGF peripheral levels in patients with psychosis. Furthermore, we show that the higher CRP and VEGF may be associated with lower perfusion in brain areas implicated in the pathophysiology of schizophrenia. Further work will clarify the role of CRP and VEGF in modifying rCBF and their relationship with antipsychotic treatment and symptom severity.
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ID: 2094942

FUNCTIONAL NEUROIMAGING FAMILY STUDY OF EMOTION RECOGNITION DEFICITS IN SCHIZOPHRENIA

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Background: Emotion recognition performance is related to community functioning in individuals with schizophrenia making it an important area of inquiry. One controversy in the facial emotion recognition literature is whether deficits in this domain reflect a specific deficit or can be accounted for by a deficit in facial processing or general cognitive dysfunction. Given the inconsistency in findings, there has been a call for more paradigms and research that can differentiate a specific deficit in emotion recognition from generalized dysfunction. In addition to deficits in affected individuals, a number of studies have found behavioural deficits in the nonpsychotic relatives further supporting the idea that the abnormality may mark genetic liability for the disorder; however, this is not a wholly consistent finding. Therefore, in this study we use a facial emotion recognition task that has been previously demonstrated to tap a specific deficit to investigate brain activity in individuals with schizophrenia, relatives, and controls.
Methods: We investigated approximately 25 participants per group: schizophrenia patients, relatives, and controls. During the facial emotion recognition condition, participants responded target or non-target to the emotion that each 'block' requires be discriminated (e.g., within the SAD block, participants will view a face and determine whether the emotion depicted is sad or not and respond with a button press accordingly). Participants' responses to four facial emotions was investigated, anger, fear, happy, and sad. The age recognition condition required participants to respond whether or not the face presented is above or below the age of 30 and was used to control for general impairment.
Results: Individuals with schizophrenia had reduced behavioural performance for specific emotions compared to controls and relatives. Preliminary analysis of the fMRI data suggested less activity for specific emotions in schizophrenia patients compared to controls in frontal regions and that relatives also demonstrated less activity in frontal regions compared to controls.
Conclusion: By using a family study design we are better able to determine whether these abnormalities are related to the genetic vulnerability for the disorder. Learning more about the neural correlates of emotion recognition may be an initial step in developing strategies to improve community functioning in schizophrenia.
ID: 2093635

HYPERDEACTIVATION OF THE DEFAULT NETWORK IN PEOPLE WITH SCHIZOPHRENIA WHEN ENGAGING IN COGNITIVE FUNCTIONS IMPAIRED IN SCHIZOPHRENIA

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Background: The default mode network (DMN) is a set of brain regions that deactivate during external processing tasks relative to passive rest, thought to reflect suppression of stimulus-independent thought. Reduced task-induced deactivation of the DMN has been reported in people with schizophrenia (PSZ), interpreted as inability to suppress intruding internal thought. However, reduced DMN deactivation may also reflect reduced task engagement as a result of failing to recruit processes and networks necessary to perform the cognitive operations.
Methods: 20 PSZ and 20 healthy control subjects (HCS) performed a visuospatial stimulus detection task (SDT) and a color change detection working memory task (CDT) while undergoing functional MRI. Practicing a full-length version of the tasks on a separate day preceding the scan ensured complete familiarity with all task operations.
Results: In both tasks, PSZ had more no-response trials than HCS in the training but not in the subsequent MRI test session, suggesting that the training minimized group differences in task engagement. In the SDT, PSZ displayed greater performance benefits than HCS of spatially predictive relative to non-predictive cues, replicating previous findings. In the CDT, PSZ displayed subtly impaired working memory performance at the largest set size of 4 items. In HCS, a frontoparietal attentional control network was active in response to spatially predictive relative to non-predictive cues (SDT), and displayed increased activation with larger set size (CDT). In PSZ, recruitment of these regions was reduced in both tasks. Typical DMN regions were identified as task-negative regions. Opposite to previous reports, PSZ displayed greater DMN deactivation than HCS in the SDT in response to predictive cues and to target stimuli following non-predictive cues, i.e., in conditions that elicit spatial shifts of attention. In the CDT, PSZ but not HCS displayed step-wise greater DMN deactivation with increasing set size, with significant hyperdeactivation at set size 4.
Conclusion: When PSZ engaged in performance similarly to HCS, increased, not reduced, DMN deactivation was seen in PSZ under task conditions particularly challenging for PSZ. This may be a compensatory mechanism

for a failure to engage brain systems mediating the cognitive functions currently challenged, perhaps reflecting non-specific effort.
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ID: 2118081

A MULTI-SITE VOXELWISE ANALYSIS OF THE AMPLITUDE OF LOW-FREQUENCY FLUCTUATIONS IN SCHIZOPHRENICS: EXPLORING THE EFFECTS OF HALLUCINATION TYPE

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Background: Individuals with schizophrenia (SZ) show resting-state (rs) abnormalities compared to controls in their blood oxygenation level dependent (BOLD) signals, including overall lower amplitudes of low frequency fluctuations (ALFF) (1). In addition, patients with predominantly visual hallucinations show greater resting connectivity between the visual cortex and the amygdala, than those with predominantly auditory hallucinations (2). We compared rsALFF between subgroups of patients with SZ who express different hallucination profiles.
Methods: Eyes-closed rsfMRI scans were collected from seven sites (5:24 min; n = 334, 159 SZ). Data were preprocessed (slice-timing, realignment, normalization) using SPM. Six rigid-body motion parameters, mean white matter and cerebral spinal fluid signals were regressed out. Power in the slow-5 frequency band (0.01–0.027 Hz), slow-4 frequency band (0.027–0.08 Hz) and the typical low frequency band (0.01 to 0.08 Hz) were calculated following linear detrending and spatial smoothing (8 mm full width at half-max). One-way ANOVAs in SPM were performed to explore the effect of hallucinatory subgroup (auditory, visual, non-hallucinators and controls) on frequency-specific alternations in ALFF.
Results: Results were thresholded at $p < .05$ FWE corrected. Across the lowest frequency slow-5 passband, SZ subjects with visual hallucinations (VIS, n=43) had greater ALFF in the bilateral hippocampus compared to those with auditory hallucinations (AUD, n=49), while non-hallucinating SZ subjects (NONH, n=67) had greater ALFF in the medial frontal orbital region compared to AUD. An analysis of ALFF across the higher frequency slow-4 passband revealed a unique set of functional differences between SZ subgroups. Across both slow-4 and typical bands, VIS had greater ALFF in the precuneus compared to AUD, while NONH showed greater ALFF in the insula compared to AUD.
Conclusion: The underlying neural activity coherence in different regions as captured by spectral frequencies of the rsfMRI signal is associated with unique hallucination profiles, suggesting that SZ with auditory hallucinations have a separate pattern of dysfunction from SZ with visual hallucinations, with the latter showing increased low frequency power in the hippocampus and precuneus.
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ID: 2083994

NEUROBEHAVIORAL CORRELATES OF SOCIAL EMOTION AND COGNITION IN CRIMINAL OFFENDERS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Impaired socio-emotional (SE) functioning is a prominent feature of psychotic disorders including schizophrenia (SZ) and bipolar disorder (BP). Prior SZ and BP studies have reported neurobehavioral deficits related to component SE processes (e.g., facial expression recognition). Fewer studies have examined higher-order SE function in the context of realistic social interactions. Even fewer studies have examined criminal offenders with SZ or BP, due to the challenges of conducting neuroimaging studies in prison settings. We deployed a mobile MRI scanner to two state prisons and scanned criminal offenders with and without SZ or BP while they performed an emotional perspective taking task.
Methods: The mobile MRI system was used to scan male SZ and BP criminal offenders (N = 21) and offenders with no history of a psychotic disorder (N = 24). During functional MRI scanning, participants made two types of decisions: 1) Which of two facial expressions best matched the "blanked out" face of one individual depicted in a two-person social interaction, 2) Which of two shapes best matched the shape superimposed on the face of one individual depicted in a social interaction. Psychotic symptoms were assessed using the Positive and Negative Symptom Scale (PANSS). Self-reported tendencies towards aggressive behavior were also evaluated using the Buss-Perry Aggression Questionnaire (BPAQ).
Results: SZ/BP offenders, relative to non-SZ/BP offenders, showed no significant differences in emotion or shape decision accuracy. PANSS positive symptom scores among SZ/BP participants were negatively correlated with emotion (but not shape) decision accuracy. During emotion decisions, hemodynamic responses among SZ/BP offenders relative to non SZ/BP offenders were characterized by reduced activation in the medial prefrontal cortex (mPFC) and temporo-parietal junction (TPJ). TPJ responses were negatively correlated with PANSS positive symptoms. mPFC responses were negatively correlated with total BPAQ scores.
Conclusion: SZ/BP offenders showed reduced engagement of brain regions within socio-emotional networks, coupled with poorer task performance in SZ/BP offenders with high levels of positive psychotic symptoms. The results indicate that SZ/BP criminal offenders show neurobehavioral deficits in social emotion and cognition.
ID: 2116724

INTACT PAIN EMPATHY IN SCHIZOPHRENIA: AN FMRI STUDY

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Background: Although it has been proposed that schizophrenia is associated with impaired empathy, several recent studies have found that people with this disorder actually show intact neural responses on some fMRI and electrophysiological empathy tasks. The current fMRI study used a validated pain empathy paradigm from the social neuroscience literature that has been found to activate a largely overlapping network of brain regions while one is directly experiencing pain versus observing others experiencing pain. A few prior studies have reported impaired electrophysiological

responses during pain empathy tasks in schizophrenia, though we are unaware of any fMRI studies of pain empathy in this population
Methods: 21 schizophrenia outpatients and 21 healthy controls completed an fMRI task that involved (a) observing videos of the faces of medical patients while they received a painful sound stimulation treatment (observation of pain) or (b) listening to the painful tones used in the treatment (1st hand experience of pain).
Results: Within each group, the observation and 1st hand experience of pain activated of a common set of regions found in prior studies, including anterior cingulate cortex, anterior insula, and inferior frontal cortex. There were no significant between-group activation differences.
Conclusion: Individuals with schizophrenia showed generally normal patterns of neural activation while observing others in physical pain. These results converge with findings from our lab and other research groups that people with schizophrenia show intact empathic responses during at least some fMRI and electrophysiological task conditions.
ID: 2084222

DOPAMINE AND GLUTAMATE: MULTI-MODAL IMAGING FINDINGS FROM THE PRODROME, FIRST EPISODE AND CHRONIC, REFRACTORY SCHIZOPHRENIA

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Background: The neurobiological basis for treatment resistant schizophrenia is not known. We sought to investigate whether there were differences in glutamate (GLU) and dopamine (DA) function in patients during the course of schizophrenia.
Methods: We conducted four studies. [18F]-DOPA PET was used to index dopamine synthesis capacity in the striatum and [1H]-MRS was used to index glutamate levels in the anterior cingulate cortex. Two cohorts of patients meeting modified Kane criteria for treatment resistance (n=12 discovery cohort and n=20 replication cohort) were recruited and compared to matched patients (n=12, and n=20) who met standardized criteria for good treatment response (Andreassen remission criteria) and matched controls (n=12). In separate longitudinal studies we studied cohorts of people at risk of psychosis (n=16) and first episode psychosis (n=21; who then received standard antipsychotic treatment and assessment of clinical response at 8 weeks).
Results: Patients with treatment resistant schizophrenia showed significantly lower DA than treatment responders (mean (sd) Ki/min= 0.013 (0.0013) versus 0.014 (0.0014) respectively; effect size (ES)=1.11, $p<0.001$), but significantly elevated GLU (water scaled, corrected for CSF) compared to healthy volunteers (mean (sd) glutamate levels=10.32 (1.41) versus 8.62 (1.02) respectively; $p<0.05$, ES=1.7). In the second cohort directly comparing treatment resistant patients with treatment responders, GLU were significantly elevated in the treatment resistant patients (Glu/Cr ratio (mean (sd) treatment resistant=1.57 (0.23) versus treatment responders=1.38 (0.24), $p<0.05$, ES=0.76).
The prodromal sample showed an inverse relationship between GLU and DA function ($r=-0.54$, $p<0.05$) that was not seen in controls, and that was strongest in the subjects that developed psychosis ($p<0.05$). In the longitudinal first episode cohort treatment non-responders showed significantly lower DA compared to treatment responders from illness onset (mean (sd) treatment non-responders= 0.0125 (0.001); treatment responders=0.0138 (0.001), ES=1.3; $p<0.05$).
Conclusion: These findings provide evidence for a double dissociation in glutamatergic and dopaminergic alterations suggesting there are neurobiologically distinct sub-types of schizophrenia, and provide evidence that this is present from the prodrome.
ID: 2117700

ALTERED INTER-NETWORK CONNECTIVITY BETWEEN DEFAULT MODE NETWORK AND SALIENCE NETWORK IN PEOPLE WITH SCHIZOPHRENIA

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Background: Two task positive networks, the salience network (SN) and the central executive network (CEN), are important for appropriate task performance, and on the other hand the default mode network (DMN) is deactivated during performance of tasks. As the relationship among these 3 networks, the right anterior insula, the main component of SN, is thought to influence the switching between the CEN and the DMN (Sridharan, 2008), and the anticoorelation between these 2 networks can be affected in people with schizophrenia (Whitfield-Gabrieli, 2012). We used neuroimaging to identify the characteristics of functional connectivity within and among the 3 networks in people with schizophrenia.
Methods: Resting state functional MRI (rsfMRI) data were performed to 55 schizophrenia patients (Sc) and 46 age and gender matched healthy controls (Hc), using T2*-weighted echo-planar sequences (TR=2s, TE=30ms), on a 3T scanner. The rsfMRI data were analyzed by independent component analysis (ICA). Five networks of interest were identified: 2 for DMN (anterior DMN and posterior DMN), 1 for SN, and 2 for CEN (right CEN and left CEN). Group differences of intra-network connectivity within each network were tested for both contrasts (Hc-Sc, Sc-Hc), using a clusterwise family wise error (FWE) correction, and group differences in inter-network connectivity were calculated by partial correlation between the time series of each network.
Results: In the intra-network connectivity analysis, Sc showed significantly decreased connectivity within both DMNs. In the inter-network connectivity analysis, Sc showed a significantly increased partial correlation between the anterior DMN and the SN ($p<0.05$, FWE corrected).
Conclusion: Intra-network connectivity of the DMN was altered in people of schizophrenia, and an attenuated coupling between the DMN and the SN was also detected in patients. Our findings suggest that the disintegration of switching between task positive and negative network can be one of the key deficits as pathophysiology of schizophrenia.
ID: 2119234

NEURAL MECHANISMS OF LOCAL AND DISTANT VISUAL CONTEXT MODULATION IN SCHIZOPHRENIA

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Background: Abnormal visual perception is common in schizophrenia (SZ). The success of perceptual functions is in part determined by how context modulates the relative activity of neurons to elements of a visual scene (i.e., gain control). High-level functions of attention have been found to regulate the size of the gain control pool (i.e., the degree to which context modulates responses to a stimulus). Evidence suggests that in SZ the gain control pool is poorly regulated, but it is unclear whether this purely derives from low-level abnormalities in visual perception or from more generalized high-level functions such as attention.

Methods: We gathered functional magnetic resonance imaging (MRI) data during a visual contour task completed by people with SZ (PSZ) and healthy controls. A functional localization method using structural and functional MRI with projection of magnetoencephalography data to cortical vertices yielded cortical electromagnetic source signals for activity in visual cortex (V1, V2, V3, V4, and LO) representing the visual contour. Cortical source signals were subjected to time-frequency analyses to determine which visual cortical regions, frequencies, and time periods were most sensitive to local contextual effects of neighboring visual elements as well as the presence of the contour. We then examined the synchronization of frequencies between visual ROIs and areas of activity beyond the visual cortex to determine if functional disconnection might account for deviant visual phenomena in SZ.
Results: Cortical responses in areas V1 and V2 tended to be lateralized to the hemisphere contralateral to the visual contour. PSZ generally failed to lateralize early responses in the presence of the collinear contour while controls had robust lateralization effects. The local context modulated activity in the visual regions contralateral to the contour later than the contour sensitive response. Such contextual modulation was absent in the PSZ. Phase synchrony analyses for frequency bands composing cortical source activity will be carried out further to describe neurophysiological activity possibly associated with local and long-range modulation of visual perception.
Conclusion: Findings suggest that context effects on early visual (V1, V2) responses are absent in SZ, and that abnormalities in coordinated activity between brain regions may reflect the failure of context to influence perception in PSZ.
ID: 2118049

FUNCTIONAL IMAGING OF AVERSIVE FACE CONDITIONING IN SCHIZOPHRENIA AND CLINICAL RISK

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Background: The amygdala and its circuitry are critical for social-emotional processing, particularly in the context of aversive learning. We hypothesize that in schizophrenia and those at clinical risk, amygdala dysfunction drives aberrant aversive social conditioning, contributing to negative symptoms and social deficits. Here we report the design and preliminary results of an ongoing 3T fMRI study testing this hypothesis using passive aversive conditioning. The study is part of an integrated translational Conte program that also includes a parallel human EEG study, human postmortem brain tissue and genetics, and rodent models.
Methods: fMRI participants (n=31 analyzed to date) are youth or young adults in three groups: schizophrenia (SC), clinical risk (CR) and healthy control (HC). During fMRI subjects performed a resting state scan and aversive conditioning and reversal paradigms. Male faces with neutral expressions served as conditioned stimuli (CS), and an aversive sound (mixture of male and female screams) was the aversive unconditioned stimulus (aUS), coterminating with 50% contingency. Pupil dilation and changes in subjective ratings of CS also indexed conditioning. Clinical evaluation focused on negative symptoms using the CAINS, and also measured positive symptoms and anxiety. Preliminary fMRI analysis focused on amygdala activation and functional connectivity, and included a Rescorla-Wagner model (RW) to quantify conditioning parameters and relate activation to CS value and US-related prediction errors.
Results: Task-activation was robust in amygdala and auditory cortex. Amygdala responses to CSs increased over time but with wide variation across subjects. HC exhibited task-modulation of amygdala-vmPFC connectivity, which was not seen in SC and CR. Amygdala activity correlated significantly with trial-by-trial variation in RW prediction errors. SC showed a higher RW learning rate (2.4) than CR (0.7) or HC (0.3) suggesting greater reactivity and/or less prolonged temporal integration of outcomes in amygdala. Pupil dilation and subjective face ratings showed discriminative conditioning effects, with trend diminution in SC and CR.
Conclusion: These preliminary results provide initial support for aversive conditioning abnormalities in early and established psychosis. As the sample increases we will have power to characterize group differences and dimensional symptom correlations, and will integrate fMRI analysis with pupillometry and EEG.
ID: 2118135

THOUGHT AND LANGUAGE DISORDERS AND THEIR NEURAL PATHOPHYSIOLOGY

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Background: Speech and language disorders, such as concretism and formal thought disorder (FTD) are core symptoms of Schizophrenia, but do occur to a similar extent in other diagnoses such as bipolar disorder and major depression.
Methods: We will review clinical rating scales of FTD and introduce a new, validated scale, the TALD. Further, structural and functional brain imaging data will be reviewed and own novel findings presented, relating speech and language dysfunctions to neural networks, within schizophrenia and across the "functional psychoses".
Results: The impact of genetic variance and NMDA receptor blockage on brain function will be addressed with a particular focus on speech and language (dys-)function.
Conclusion: We demonstrate, from the genetic to the brain structural and functional level, that particular aspects of the neural language system is disrupted in patients with FTD across traditional diagnoses.
ID: 2142876

NEURAL CORRELATES OF PLANNING PERFORMANCE IN PATIENTS WITH SCHIZOPHRENIA - RELATIONSHIP WITH APATHY

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Background: Patients with schizophrenia often suffer from apathy: a quantitative reduction of voluntary, goal-directed behaviors that impairs daily functioning. We hypothesized that schizophrenia patients with high levels of apathy would show decreased activation in brain regions involved in planning and goal-directed behavior.
Methods: Patients with schizophrenia or psychotic spectrum disorder (n = 47) and healthy controls (n = 20) performed the Tower of London (ToL) task during fMRI scanning using arterial spin labeling (ASL). To investigate the relationship between apathy and planning in patients, a proxy

measure of apathy (items N2, N4 and G16 of the Positive and Negative syndrome scale) were regressed against the task-related brain activation. Brain activation was also compared between patients and healthy controls.
Results: Higher levels of apathy were associated with less task-related activation within the inferior parietal lobule, precuneus and thalamus. Compared to controls, patients showed lower activation in lateral prefrontal regions, parietal and motor areas, and a higher activation of medial frontal areas.
Conclusion: Apathy was related to abnormal activation in parietal regions during the ToL task. This supports the hypothesis that impaired function of brain regions involved in planning and goal-directed behavior may underlie apathy in schizophrenia. Moreover, impaired lateral prefrontal activation in schizophrenia patients compared to controls is consistent with the hypofrontality model of schizophrenia. In contrast, stronger medial frontal activation in patients may be related to increased effort to perform a task with conflicting task solutions.
ID: 2116248

NEURAL CORRELATES OF REWARD PROCESSING IN HEALTHY SIBLINGS OF PATIENTS WITH SCHIZOPHRENIA

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Background: Reward processing (RP) underlies human motivation and the ability to adjust behavior. Deficits in motivational behavior often observed in schizophrenia (SZ) may be driven by deficient RP. Using fMRI, studies in patients with SZ have found less activation in the ventral striatum (VS), anterior cingulate cortex (ACC) and dopaminergic midbrain regions during anticipation of reward compared to healthy controls. During reward consumption, the prefrontal cortex (PFC) shows less activation in patients than in controls. Yet, the interpretation of findings in patients is complicated by the differential effects of antipsychotics on the neural correlates of RP. Therefore, the current study investigated RP in nonpsychotic first-degree relatives of SZ patients, who have an increased genetic risk for the illness but do not use antipsychotic medication.
Methods: The sample consisted of 94 non-psychotic siblings of SZ patients and 57 healthy controls. Participants completed a classic RP task, the Monetary Incentive Delay task, during fMRI. Group differences in hemodynamic responses during reward anticipation and consumption were assessed at the whole-brain level.
Results: Behaviorally, there were no significant performance and reaction time differences between siblings and controls. During reward anticipation, siblings showed less deactivation in the insula, the posterior cingulate cortex (PCC), medial frontal gyrus (MFG) and more activation in the paracentral lobule compared to deactivation in the control group. During reward consumption, siblings showed less deactivation in the PCC and the right MFG compared to controls and activation in contrast to deactivation in controls in the precuneus and the left MFG.
Conclusion: The results do not point to altered brain activity in classical RP brain areas, such as the VS and PFC. Nonetheless, in the absence of behavioral differences between the groups, neural differences in other brain regions may indicate differential RP mechanisms in siblings. Moreover, weaker deactivation was seen in brain areas typically associated with the default mode network (DMN) and could therefore indicate reduced task-related suppression (i.e. hyperactivation) of the DMN. DMN hyperactivation in SZ and their relatives has been suggested in previous research. Our finding of less deactivation in siblings in the PCC and MFG may suggest stronger internally-focused processing during RP. The implications for motivational behavior should be addressed in future research.
ID: 2089893

FUNCTIONAL NETWORK ARCHITECTURE IN UNMEDICATED PATIENTS WITH SCHIZOPHRENIA AND CHANGES WITH ANTIPSYCHOTIC MEDICATION

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Background: Few attempts have been made to effects of antipsychotic medication on functional network architecture, despite evidence suggesting that networks are sensitive to dopaminergic neuromodulation.
Methods: 34 subjects with schizophrenia (off antipsychotic medications for at least 2 weeks) and 34 matched controls entered the study. Imaging was done on a 3T scanner. Resting state scans were obtained at baseline and after six weeks of treatment with risperidone. The scan was acquired during a five-minute gradient recalled EPI sequence. Preprocessing included slice time correction and realignment, normalization, and smoothing using DARTEL. Following preprocessing and motion scrubbing1, statistical parametric maps of four functional networks were created. Spherical seeds with 6mm radius were placed at the following MNI coordinates: (1) 1/-55/17; default mode network, (2) -42/34/20 and 44/36/20; executive control network, (3) -32/26/-14 and 38/22/-10; salience network, and (4) +/-25/-53/52 and 25/-57/52; dorsal attention network. The first eigenvariate of the BOLD time series from each region was extracted and correlated to the time series of all other voxels to create functional connectivity maps. Maps were converted to normally distributed values using Fisher's r-to-Z transform. Group-level connectivity maps were obtained with one-sample t-tests on each group's participant-level connectivity maps. Group differences were assessed with two-sample t-tests on the groups' participant-level connectivity maps, change over time was assessed with paired sample t-tests on the groups' participant-level connectivity maps.
Results: In unmedicated patients compared to controls we found increased resting state functional connectivity in the executive control network, salience network, and dorsal attention network, but not in the default mode network. Over the course of treatment, connectivity attenuated only in the dorsal attention network. Baseline connectivity in the dorsal attention network was predictive of response to antipsychotic medication after six weeks of treatment.
Conclusion: Our findings are consistent with the concept of schizophrenia as a disorder of brain network organization and indicate that effects of antipsychotic medications on connectivity vary across networks.
ID: 2118826

HIPPOCAMPAL GLUTAMATE AND DISTURBANCE OF HIPPOCAMPAL-PREFRONTAL EFFECTIVE CONNECTIVITY IN SCHIZOPHRENIA: EFFECT OF ANTIPSYCHOTIC MEDICATION

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Background: Using MRS we previously reported an increase in hippocampal glutamate + glutamine (Glx) in unmediated patients with schizophrenia (SZ). To further characterize glutamatergic (Glu) abnormalities in SZ, we measured Glx in the dorsal anterior cingulate (dACC) and hippocampus before and after antipsychotic drug (APD) treatment. In addition, given our previous findings of hippocampal rCBF elevation in unmedicated SZ and reduction with APD that was associated with good treatment outcome, we hypothesized that known fronto-temporal functional connectivity disruption in SZ measured with fMRI might originate from abnormal hippocampal function and could partially be restored by APD.
Methods: Using MRS and voxels in the dACC and hippocampus, we compared SZ (n=20) scanned unmedicated, and after 6 weeks of APD treatment. Spectra were acquired (PRESS; TR/TE=2000/80 ms) and analyzed using jMRUI. In addition, we measured effective connectivity (EC) accessed with multivariate autoregressive Granger causality and obtained from latent neural signals estimated from blind deconvolution of fMRI during episodic memory retrieval. We evaluated EC between frontal (3) and temporal (2, including hippocampus) nodes when patients were unmediated (n=21) and after one-week of treatment (n=16). Matched healthy controls (HC) were scanned as well.
Results: After 6 weeks of treatment, there was a significant reduction in the ratio of Glx/N-acetylaspartate in the hippocampus (p=.03), but not in the dACC. In HC, the right hippocampus was identified as a major node of a fronto-temporal network with connections from the hippocampus to all bilateral frontal nodes. Compared to HC, unmedicated SZ had significant EC reduction from the right hippocampus to the right medial frontal node. After 1-week of treatment SZ showed significant EC increase from the right hippocampus to all bilateral frontal nodes.
Conclusion: Our data indicate that APD modulate Glu function in a manner that is regionally specific. In addition, in unmedicated SZ, we observe a reduced hippocampal to frontal EC that is partially reestablished with treatment. Because elevated Glu levels might result from GABA interneuron hypofunction and hippocampal interneurons generate oscillations in the gamma frequency ranges that are thought to synchronize brain activation, their dysfunction could affect fronto-temporal connectivity. Changes in functional connectivity with treatment could be a necessary intermediary step to symptomatic improvement.
ID: 2115843

THE NEUROBIOLOGY OF TREATMENT RESISTANCE: WINDOW INTO THE HETEROGENEITY OF SCHIZOPHRENIA

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Background: Approximately 30% of patients with schizophrenia (SZ) will not improve with antipsychotic drug (APD) treatment. Importantly, the neurobiology of treatment resistance might index an aspect of the illness heterogeneity. In our previous imaging study (Lahti et al., 2009), lack of modulation of neural response in limbic regions after 1 week of treatment predicted subsequent poor treatment response. In this study, we hypothesized that pretreatment brain functional connectivity (FC) and neurochemistry would also be predictive of treatment response. We measured the FC of the ventral tegmental area (VTA), the source of mesocorticolimbic dopaminergic projections thought to be critical for APD action, prior to treatment, when patients were not medicated. In addition, since recent studies suggest APD may modulate glutamate, we measured glutamate + glutamine (Glx) levels in the dorsal anterior cingulate cortex (dACC).
Methods: Using a 3T head-only MR scanner, we scanned unmedicated SZ (n=21) prior to APD treatment. Patients were then entered into a 6-week trial with risperidone. Treatment response was quantified as the percent change in Brief Psychiatric Rating Scale scores from baseline to week 6. Resting state functional MRI scans were acquired during a 5-min gradient recalled EPI sequence. Using a seed-based approach and SPM 8, we examined the FC of the VTA. Using MR Spectroscopy (MRS) (PRESS; TR/TE = 2000/80 msec), we collected MRS data from a voxel in the dACC (2.7 x 2 x 1 cm3). We quantified the spectra in the time domain using the AMARES algorithm in jMRUI
Results: Pre-treatment VTA connectivity strength to the dACC was positively correlated with good response to a 6-week course of APD, whereas connectivity to the default mode network (ventromedial prefrontal, posterior cingulate, precuneus, and lateral parietal cortices) was negatively correlated (analyses of covariance corrected with FDR at <0.05). Pre-treatment dACC Glx levels were positively correlated (r (18) = .48, p = .03) with subsequent good response.
Conclusion: VTA FC in unmedicated patients predicted patients' subsequent response to treatment, suggesting that the brain is wired in a way that does or does not favor treatment response. In addition, pretreatment ACC Glx might index the potential for brain's plasticity in response to treatment. These and the results from our previous study suggest that patients who do not respond to medication have an underlying neurobiology that is different than those who do.
ID: 2091683

EFFECTS OF PAST MILD CANNABIS USE ON COGNITION IN FIRST EPISODE SCHIZOPHRENIA: A MULTIMODAL ANALYSIS OF BRAIN STRUCTURE AND FUNCTION

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Background: Cannabis (CN) use has been repeatedly linked to psychosis onset, however, the relationship of CN use to brain structure and function abnormalities in first episode schizophrenia (SZ) patients is less well understood. While CN use in healthy subjects is linked to detrimental effects on cognition, there is some evidence for higher performance in CN users with SZ on executive functioning measures. Further, the relationship between brain structure and CN use in this population is quite mixed. Therefore, we used multi-modal analyses to investigate the relationship between past CN use and measures of brain function, structure, and behavioral performance.
Methods: First episode SZ patients with a history of mild CN use (n=33) and patients with no history of use (n=24) were identified from referrals to the UC Davis EDAPT clinic using the SCID-I. All patients urine-screened negative for CN on the date of scan and did not meet criteria for CN abuse or dependence. Images were obtained on a 1.5-T GE scanner and processed using Freesurfer 4.3 and SPM8. Cortical thickness and fMRI analyses were thresholded at p<.01 and FWE cluster corrected (p<.05). The expectancy AX Continuous Performance Test (AX-CPT) was used as a measure of cognitive control and all volumetric structural analyses included intracranial volume, age, and gender as covariates.
Results: Analyses of behavioral data revealed higher performance on the AX-CPT in past CN users (d'-context and BX accuracy, p<.05). However, there were no significant differences in cortical thickness or fMRI activity between groups, although past users showed a trend for greater

fronto-parietal activity. In terms of total cerebral cortex volume, past CN users showed significantly greater gray matter volume in both hemispheres with no significant differences in white matter volume. Finally, of the a priori subcortical regions examined, only the left accumbens was significantly larger in patients with past CN use.
Conclusion: These findings highlight the complex relationship between CN use and the structural, functional, and behavioral deficits repeatedly identified in SZ. While subjects with a history of mild CN use showed better cognitive control performance, larger whole-brain gray matter volume, and larger nucleus accumbens, CN use may not be the primary causal factor. Alternatively, as other groups have proposed, patients with premorbid CN use may represent a subgroup with better premorbid adjustment and potentially greater cognitive reserve.
ID: 2089540

ASSESSMENT OF DYNAMIC FUNCTIONAL CONNECTIVITY IN PATIENTS WITH SCHIZOPHRENIA

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Background: Examination of functional connectivity (FC), the measure of correlations between spatially separate regions of the brain, is a common practice used to analyze resting-state functional magnetic resonance imaging (rsfMRI). However, these methods are based on the assumption that functional connections within the brain remain constant over a time course. As an alternative, dynamic functional connectivity (dFNC) takes into account the fluctuations in connections over time by calculating transient patterns of functional connectivity via sliding windows.
Methods: In this study, we assess the dynamic changes in FC in patients with schizophrenia (nSZ=33) and matched (age, gender, smoking status, and socio-economic status) healthy controls (nHC=35) utilizing the Group ICA of fMRI Toolbox (GIFT; http://mialab.mrn.org/software/gift). Patients with schizophrenia completed a 5-minute (150 volume) rsfMRI scan while acutely psychotic, before beginning antipsychotic medication, after one week of treatment, and again after six weeks of treatment. Preprocessed data were decomposed into 100 independent components via group independent component analysis and 42 were labeled as components of interest - as opposed to artifact. dFNC analysis was then performed on identified component time courses to generate windowed connectivity matrices using a sliding window analysis. Subsequent k-means clustering of windowed matrices resulted in 5 connectivity states.
Results: Traditional FC results indicated significantly different overall FC between healthy controls and baseline patients, as well as after 1 week of medication. However, we found no significant difference in overall FC between healthy controls and patients after 6 weeks of medication ($p=0.1277$). dFNC results illustrated the dynamic nature of FC given that cluster centroids significantly differed from each group's respective traditional FC matrix. Additionally, connectivity strengths and dwell times (i.e., percentage of occurrence) within respective dynamic connectivity states varied between the two groups, which may be attributable to the connectivity abnormalities often characterized in schizophrenia. Specifically, patient dwell time in the hyperconnected state 4 significantly decreased between each scan (12.48% to 6.81% to 2.29%).
Conclusion: Based on these results, we anticipate that the additional information presented by dFNC analysis will provide greater insight into the role of network connectivity in the disorder of schizophrenia.
ID: 2118843

ENDOGENOUS-CUE PROSPECTIVE MEMORY TASK PERFORMANCE IN SCHIZOPHRENIA: AN FMRI STUDY

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Background: Examination of the brain regions that show aberrant activations and/or deactivations during endogenous-cue prospective memory could pave the way for a better understanding of the fronto-parietal network mediated cognitive dysfunction in schizophrenia. We aimed to examine the pattern of functional magnetic resonance imaging blood oxygen level dependent activations and deactivations during a prospective memory paradigm.
Methods: Functional magnetic resonance imaging was performed on 15 participants with schizophrenia and 24 matched healthy controls during the performance of a prospective memory task (Halahalli et al 2014) where the delayed intention was triggered by an endogenous cue generated by incremental updating of working memory.
Results: The performance of patients with schizophrenia was significantly inferior to that of healthy control subjects in the Prospective memory (PM) condition. Group comparison between patients with schizophrenia and matched healthy samples controlling for confounding variables namely age, gender, WAIS-III Matrix reasoning score, accuracy difference between PM and Ongoing condition (OT) conditions, reaction time difference between PM and OT conditions, and neuroleptic dosage revealed more extensive activations in schizophrenia subjects for the PM vs OT condition contrast.
Conclusion: More extensive brain activations despite inferior performance, reflects an inefficient task performance in schizophrenia subjects by the recruitment of greater number of brain regions. These findings are in agreement with previously published work from our laboratory (John et al 2011). This inefficient cognitive performance in schizophrenia patients may be secondary to two important network dysfunction that mediate various cognitive processes, rostral pre- frontal cortex (rPFC/ BA 10) mediated switching between stimulus-dependent cognition and stimulus-independent cognition and insula mediated 'salience network' involved attentional controlling.
ID: 2084438

LACK OF FACE SELECTIVITY FOR PUTATIVE NEURAL MARKERS OF FACE PROCESSING IN SCHIZOPHRENIA: CONVERGING EVIDENCE FROM ERP AND FMRI RESPONSES DURING FACE DETECTION

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Background: Faces are a sui generis stimulus class that conveys key information for social interaction. Face detection, an ability to identify a visual stimulus as a face, is impaired in patients with schizophrenia. While this perceptual deficit may contribute to patients' poor social functioning, its underlying brain mechanisms are not well understood. Previous MRI studies have shown that patients have altered structure of brain regions subserving face perception such as fusiform gyrus, but functional responses of these regions to face images appeared to be normal. Previous event-related potential (ERP) studies showed lower amplitudes of face-evoked responses such as N170 in patients. The face processing system possesses a key functional property - face selectivity - that has seldom been examined in schizophrenia.
Methods: In this study, we examined temporal dynamics (using ERP) and spatial locus (using fMRI) of face selectivity in medicated schizophrenia patients (n=19) and healthy controls (n=18). Specifically, we measured and compared N170 responses, a putative temporal neural marker of face processing, with BOLD responses in fusiform face area (FFA), a putative spatial neural marker of face processing, during face detection and tree detection.
Results: For controls, N170 amplitudes were significantly greater for faces than trees across all three visual salience levels tested (manipulated using contrast at perceptual threshold, two times perceptual threshold and 100%). For patients, however, N170 amplitudes did not differ between faces and trees. This pattern of result indicates reduced face selectivity (indexed by the difference in response to face vs. non-face stimuli) on the N170, mirroring a finding of our recent fMRI study (to be also presented in this conference). In controls, significant correlations between N170 and BOLD signal in FFA were found for faces, but not for trees. In patients, no significant correlations between N170 and FFA activation were found for either faces or trees.
Conclusion: These ERP and fMRI results provide converging evidence for a lack of face-selectivity in spatial and temporal responses of putative brain machinery for face processing in patients with schizophrenia. This neuroimaging finding suggests that face processing should be specifically targeted during the remediation of social functioning in schizophrenia.
ID: 2119237

FUNCTIONAL NEURAL CORRELATES OF SOCIAL APPROVAL IN SCHIZOPHRENIA

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Background: Social approval is a type of reward that uses specific abstract social reinforcers to help guide interpersonal interactions. While reward processing is clearly altered in schizophrenia, few studies have specifically explored social reward processing and its related neural substrates in this population. The presented analysis reports findings of a functional magnetic resonance imaging study that explores social approval in schizophrenia.
Methods: 13 patients with schizophrenia and 12 healthy controls participated in a two-part study, consisting of a self-introduction phase conducted in the laboratory and a social approval task administered in the scanner. Participants were led to believe they were participating in a personality study, where their results from various questionnaires and a short interview would be assessed by a panel of clinicians. Participants were then presented with the results of their supposed evaluation in the scanner. In reality, the presented personality traits were chosen from a predefined list. The social approval task involved obtaining subjective reports of pleasure associated with receiving positive or slightly negative feedback about the self, compared to viewing the evaluation of a stranger.
Results: Results within the control group revealed significant activation of basal ganglia structures (e.g. caudate and putamen) and limbic structures such as the parahippocampal gyrus and amygdala; by contrast, patients did not show activation of such regions when receiving both positive and slightly negative feedback directed towards the self. Overlapping brain activation was found, where patients recruited medial prefrontal cortical regions, but in a differential manner compared to controls. Both groups rated traits from the high social reward condition as significantly more pleasurable than the low social reward condition; however, patients' subjective ratings of slightly negative/neutral feedback was significantly higher than controls.
Conclusion: These findings reveal that patients exhibit differential patterns of brain activation compared to controls when interpreting the reward value of presented traits in the scanner, especially when examining activation in brain structures believed to underlie reward and affect-related processing. Evidence suggests a potential deficit in cognitive processing underlying the representation of social reputation in schizophrenia.
*This work was supported by the Quebec Bio-Imaging Network (QBIN).
ID: 2115582

ANTIPSYCHOTIC TREATMENT AND FUNCTIONAL CONNECTIVITY OF THE STRIATUM: A PROSPECTIVE CONTROLLED STUDY IN FIRST-EPISODE SCHIZOPHRENIA

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Background: Previous evidence has implicated corticostriatal abnormalities in the pathophysiology of psychosis. Although the striatum is the primary target of all efficacious antipsychotics, the relationship between its functional connectivity and symptomatic reduction remains unknown.
Methods: We examined the longitudinal effects of treatment with second-generation antipsychotics on functional connectivity of the striatum during resting state MRI in twenty-four patients with first-episode psychosis, in addition to twenty-four healthy participants, matched for age, sex, education, and handedness. Patients were scanned at baseline and after 12 weeks of treatment with either risperidone or aripiprazole, as part of a prospective controlled study, with medications administered in a double-blind, randomized manner. Psychotic symptoms were evaluated with the Brief Psychiatric Rating Scale at baseline and follow-up. Healthy participants were scanned twice with a twelve week interval to account for the effects of time and/or habituation to the scanning environment. Functional connectivity of striatal regions was examined using a seed-based approach with a GE 3T magnet. Changes in functional connectivity of these seeds were compared with changes in ratings of psychotic symptoms.
Results: As psychosis improved, we observed an increase in functional connectivity between striatal seed regions and the anterior cingulate, dorsolateral prefrontal cortex, and limbic regions such as the hippocampus and anterior insula. Conversely, a negative relationship was observed between reductions in psychosis and functional connectivity of striatal regions with structures within the parietal lobe.
Conclusion: Our results indicate that corticostriatal functional dysconnectivity in psychosis is a state-dependent phenomenon. Increased functional connectivity of the striatum with prefrontal and limbic regions may be a biomarker for improvement in symptoms associated with antipsychotic treatment.
ID: 2090314

BUILDING SOCIAL AFFILIATION IN SCHIZOPHRENIA

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Background: Humans are inherently social beings who experience physiological and emotional benefits from social affiliation. However, given the presence of negative symptoms, such as social anhedonia, it is unclear whether individuals with schizophrenia may experience similar benefits from social affiliation. Using a novel fMRI Hand Holding Task (Coan et al., 2006), we are interested in whether social support in the form of holding the hand of an affiliative partner may attenuate neural reactivity to threat in individuals with schizophrenia. We further sought to develop a novel experimental task to create an affiliative relationship within the laboratory that could then be examined in the fMRI paradigm. The present pilot study examined whether (1) interactions with a researcher could build social affiliation through a series of social affiliation enhancement tasks, (2) increases in social affiliation would be related to negative symptoms, (3) completing the fMRI hand holding task is feasible.
Methods: Participants (healthy controls; individuals with schizophrenia) will complete a series of social affiliation enhancement tasks (involving conversation, synchrony, team building) with a research partner, pre/post measures of social affiliation, the fMRI Hand Holding Task, and assessments of negative and positive symptoms and depression.
Results: Data collection and analysis are ongoing, but paired t-tests with preliminary data (N=15) indicate increases in social affiliation after interacting with a research partner ($p < .05$). Additionally, correlations suggest that increases in social affiliation analyses are uniquely associated with lower levels of negative symptoms ($p < .05$), but not positive symptoms or depression. Lastly, the majority of participants successfully completed all study procedures.
Conclusion: The current study demonstrates the ability to build social affiliation in the laboratory, the feasibility of task procedures, and the negative relationship between negative symptom severity and increases in affiliation. Ongoing data collection will provide data from controls and individuals with schizophrenia that will allow us to examine the extent to which social affiliation attenuates neural threat responding in these two groups and whether such reactions are related to negative symptoms. Funding support: University of Maryland Dean's MRI Research Initiative Award.
ID: 2083033

TRANSLATING IMAGING FINDINGS IN SUBJECTS AT UHR FOR PSYCHOSIS INTO CLINICAL PRACTICE.

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Background: Over the last ten years, the application of neuroimaging research has provided a great deal of new information about how the structure, physiology, neurochemistry and connectivity of the brain are altered in people who are at ultra high risk (UHR) for psychosis. Furthermore, when UHR samples are subdivided according to subsequent clinical outcomes, there are cross-sectional and longitudinal neuroimaging differences between subjects who go on to develop psychosis and subjects who do not. These findings suggest that neuroimaging measures could help to predict which UHR subjects are most likely to develop psychosis.
Methods: Two main approaches have been use to examine the relationship between neuroimaging measures in UHR subjects and clinical outcomes. First, neuroimaging data collected at presentation have been compared in subjects who do or do not develop psychosis in the period subsequent to scanning. This cross-sectional approach has been complemented by longitudinal studies, which study UHR subjects at baseline and again at the end of a follow up period, during which time a proportion will have developed psychosis. These approaches have been applied to volumetric MRI data, functional MRI data, resting blood volume data, and F-Dopa PET data.
Results: At presentation, UHR subjects who go on to develop psychosis differ from those who do not in having smaller medial temporal volumes, greater physiological activity in the medial temporal and prefrontal cortex and in the midbrain, and greater dopamine function in the striatum and midbrain. In UHR subjects who then make the transition to psychosis, there is a progressive increase in medial temporal activity, a progressive reduction in medial temporal volume and a progressive increase in subcortical dopamine function.
Conclusion: There are significant neuroimaging differences between UHR subjects who are have similar clinical features at presentation, but have distinct clinical outcomes. Statistical approaches such as machine learning provide a means of translating research findings at a group level into predictive tests that can be made on the basis of neuroimaging data from a single subject. A key challenge for neuroimaging research in psychiatry is to develop tools that can be used in a clinical setting to improve clinical care. A number of multi-centre studies in large samples of UHR subjects are currently seeking to develop such tools.
ID: 2091574

CLASSIFICATION OF PEOPLE WITH TREATMENT-RESISTANT AND ULTRA-TREATMENT-RESISTANT SCHIZOPHRENIA USING RESTING-STATE EEG AND THE NEUCUBE

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Background: Clozapine (CLZ) is uniquely effective for treatment-resistant schizophrenia (TRS) but may cause serious adverse effects and is not equally successful for all patients. Electroencephalography (EEG) abnormalities in people with schizophrenia have been reported to both precede and result from treatment with antipsychotic medicines. In a previous analysis, we demonstrated that multilayer perceptron could be used to accurately classify 87% and 100% of participants with ultra-treatment-resistant schizophrenia (UTRS) and TRS, respectively, using event-related potential data from auditory oddball, selective attention and Go/No-Go tasks. The current analysis explored the use of spiking neural networks to classify participants with schizophrenia using resting-state EEG data collected with the eyes open and eyes closed.
Methods: We utilised EEG recordings from people with TRS who responded well to CLZ (TRS) or were receiving a combination of two antipsychotics after failing treatment with CLZ monotherapy (UTRS). The analysis was conducted as part of a larger cross-sectional study investigating biomarkers of TRS; only participants with TRS (n=20) or UTRS (n=16) were included in this analysis. Resting-state EEG with the eyes open and eyes closed was collected over two minutes at 500 Hz using a 26-channel EEG system (Neuroscan). Data were analysed using random sub-sampling cross validation in the recently proposed NeuCube framework, a three-dimensional evolving spiking neural network system. Data were too large to incorporate into the NeuCube in their raw state and so

every second time point was removed and a sample of 5000 data points was selected for each participant.
Results: We achieved 80% classification accuracy with the NeuCube using eyes-closed EEG data, with 82% of participants with TRS and 78% of participants with UTRS being correctly classified. Eyes-open data gave 75% classification accuracy, with 82% and 67% of TRS and UTRS groups correctly classified.
Conclusion: Results demonstrated that the NeuCube was able to successfully differentiate people with TRS and UTRS using resting-state EEG data. Future investigations will attempt to predict whether a person with treatment-resistant schizophrenia is likely to become ultra-treatment-resistant based on EEG data collected before initiation with clozapine.
ID: 2118179

HIGHER-DIMENSIONAL META-STATE DYNAMIC ANALYSIS REVEALS SUPPRESSIVE EFFECTS OF HALLUCINATIONS AND NEGATIVE SYMPTOMS ON CONNECTIVITY DYNAMISM IN RESTING FMRI

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Background: Network connectivity remains a central focus of much resting-state fMRI research. Until very recently, most studies have assumed functional network connectivity (FNC) to be effectively stationary in the resting brain. Interest is growing however in the dynamical properties of network connectivity. Our approach models FNC matrices computed on successive windowed segments of network timecourses (wFNCs) as weighted sums of maximally temporally independent basis connectivity patterns (BCPs). This approach is motivated by a desire to understand network connectivity dynamics in terms of (not necessarily observable) correlation patterns that "pipe in" and fade out of observed time-varying FNCs in a relatively independent manner.
Methods: This study was conducted on a large fMRI dataset (N=314; 163 healthy (HC), 151 schizophrenia patients (SZ)). Data was preprocessed and decomposed into functional networks using group ICA. wFNCs were computed from subject-specific network timecourses. Five maximally mutually independent timecourses (TCs) with associated BCPs were then estimated from the wFNCs using group temporal ICA (tICA). Estimated TCs were discretized into signed quartiles (reassigned values in {±1,±2,±3,±4} designating quartile position among same-sign TC values)
Results: We focus here on the general dynamic behavior of so-called meta-states. These are the length-five vectors of discretized weights characterizing each subject's wFNC at each time window. There are 8^5 possible such meta-states and we investigate four inter-related measures of dynamism in this state space. Schizophrenia was significantly negatively correlated with all four measures of connectivity dynamism (CD). In this work we explore the ways specific symptoms affect CD. In addition to the expected CD-suppressing role of many negative symptoms, we also find that hallucinatory behavior correlates strongly with reduced CD.
Conclusion: Using a higher-dimensional model of time-varying connectivity that has recently yielded strong and consistent evidence of reduced connectivity dynamism in SZ patients, we now present a more detailed picture of symptom effects. Most negative symptoms are CD-suppressing as one might expect. However hallucinatory behavior, a central positive symptom of the disease, also exhibits strong, pervasive suppressive effects on connectivity dynamism.
ID: 2117384

ALTERED CONNECTIVITY WITHIN AND BETWEEN TWO DIFFERENT SALIENCE RELATED NETWORKS IN PEOPLE WITH SCHIZOPHRENIA

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Background: Dopamine dysfunction may lead to psychotic symptoms through an effect on salience processing (Kapur, 2003). It has been suggested that this dopamine dysfunction is driven by hippocampal overactivity, which influences midbrain dopamine neurons via inputs through the basal ganglia (Lisman and Grace, 2005). On the other hand, independent research suggests that there is a "salience network (SN)", which comprises the insula and anterior cingulate cortex (ACC). We used neuroimaging to investigate functional connectivity within and across these two different salience related networks in people with schizophrenia.
Methods: Resting state functional MRI (rsfMRI) data were acquired from 55 schizophrenia patients (Sc) and 46 age and gender matched healthy controls (Hc), using T2*-weighted echo-planar sequences (TR=2s, TE=30ms), on a 3T scanner. The rsfMRI data were analyzed by independent component analysis (ICA). Three networks of interest were identified: hippocampal network (HN) (Holmes et al, 2014), basal ganglia network (BGN) (Robinson S et al, 2009), and SN. Group differences of intra-network connectivity within each network were tested for both the Hc>Sc and Sc<Hc contrasts, using a clusterwise family wise error (FWE) correction across all 6 tests, yielding a threshold of $p<0.0083$ for each contrast. Group differences in inter-network connectivity were calculated by partial correlation between the time series of each network.
Results: In the intra-network connectivity analysis, Sc showed both increased and decreased connectivity within the HN and BGN. In the inter-network connectivity analysis, Sc showed a significantly increased partial correlation between the BGN and SN ($p<0.05$, FWE corrected).
Conclusion: Schizophrenia was associated with intra-network abnormalities in both the HN and BGN, and with heightened coupling between the BGN and SN. These data provides further support for the role of altered medial temporal connectivity in the pathophysiology of schizophrenia, and also unites two different salience related networks.
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ID: 2091197

SHARED NEURAL BASIS OF SCHIZOPHRENIA AND SMOKING DURING VIEWING OF SMOKING CUES

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Background: This study aims to investigate the neural basis of the high rate of smoking among schizophrenic patients through the use of smoking-related images in a visual discrimination paradigm during functional magnetic resonance imaging.
Methods: Thirty-one normal controls (22 nonsmokers and 9 smokers) and thirty schizophrenic patients (18 nonsmokers and 12 smokers) participated in this study. During the task participants were asked to match one of the two pictures to a single target picture. There were three groups of pictures. One group consisted of smoking related scenes (like a hand holding a cigarette ready to be lit). Another group consisted of closely matching scenes (like a hand holding a pencil). The third group consisted of shapes. Event types were organized into blocks. Each block has 5 consecutive displays of a particular type of matching event. Each event was displayed for 4 seconds with a jittered ISI. Data were analyzed by comparing four groups: normal control smokers (NC-SK), normal control nonsmokers (NC-NSK), schizophrenia smokers (SZ-SK) and schizophrenia nonsmokers (SZ-NSK).
Results: NC and SZ had no statistical difference in performance. There were no significant group differences in activations during the shape discrimination for any group comparisons. However, during discrimination of smoking-related scene pictures, SZ patients showed significantly higher activation in the ventralmedial prefrontal cortex, left cingulate and left superior frontal gyrus. When comparing NC smokers and NC non-smokers during discrimination of smoking-related scene pictures, smokers showed a significantly higher activation in the left superior frontal gyrus. When comparing SZ smokers and SZ non-smokers during discrimination of smoking-related scene pictures, smokers showed a significantly higher activation in the left inferior frontal gyrus and significantly lower activation in the left postcentral gyrus.
Conclusion: Both schizophrenia and smoking are marked by abnormal activation in the frontal regions. Schizophrenic specific abnormalities are located in the ventralmedial prefrontal cortex and left insula. Smoking abnormalities are located in the cingulate and frontal regions. High risk of smoking in schizophrenia may be associated with a shared abnormal network involving prefrontal, cingulate, and insula areas.
ID: 2103195

THE OPTIMAL DOPAMINE D2/3 RECEPTOR OCCUPANCY BY ANTIPSYCHOTICS IN PATIENTS WITH LATE-LIFE SCHIZOPHRENIA: A [11C]-RACLOPRIDE PET STUDY

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Background: A safe therapeutic window of striatal dopamine D2/3 receptors (D2/3R) by antipsychotics is between 65% and 80% in younger patients with schizophrenia. In contrast, the minimal therapeutic dose for late-life schizophrenia (LLS) remains unknown. This study was aimed to find the optimal range of D2/3R occupancies by antipsychotics in LLS.
Methods: This open-label prospective study included outpatients with stable schizophrenia (Positive and Negative Syndrome Scale [PANSS] scores ≤ 3 for positive symptoms), ≧50 years, treated with the same dose of olanzapine/risperidone for ≧6 months. [11C]-raclopride positron emission tomography (PET) scans were performed before and after dose reduction. Antipsychotic dose was gradually reduced to 60% of the baseline dose with a target dose not lower than the recommended dose. Subjects were clinically followed-up for three-six months using PANSS, Barnes Akathisia Scale (BAS), Simpson-Angus Scale (SAS), and Udvalg for Kliniske Undersøgelser Side Effect Rating Scale (UKU). Relationships between clinical outcomes and striatal D2/3R occupancies were assessed.
Results: 35 subjects (age=60 ± 7 years, PANSS=61.3 ± 14.4, olanzapine/risperidone =20.8 ± 6.6/4.7 ± 2.9 mg/day) were included. 29 subjects remained stable after the dose reduction. PANSS total score decreased (p=.02), and total scores in SAA, BAS, and UKU and serum prolactin levels decreased (p<.001, p=.03, p<.001, and p<.001, respectively). D2/3R occupancies decreased from 67.6 ± 11.4% to 61.1 ± 11.0%. The baseline D2/3R occupancies were lower in those with clinical deterioration than those remained stable (55.4 ± 13.1 (38.3–56.1)% vs. 69.7 ± 9.9 (45.9–88.0)%, p=.03). The lowest D2/3R occupancy associated with clinical stability was 45%. Extrapyramidal symptoms (EPS) were more likely shown with D2/3R occupancies higher than 60%. The D2/3R occupancies after dose reduction were not different between both groups (51.1 ± 18.6 (37.4–72.3) % vs. 63.1 ± 9.2 (48.3–76.6) %). There was a trend toward correlation between the changes in the putaminal D2/3R occupancy and SAS (r = 0.39, p = .09) among the subjects with baeline EPS.
Conclusion: Antipsychotic dose reduction is feasible in stable patients with LLS, improving side effects associated with decreases in D2/3R occupancies. The results suggest that D2/3R occupancies by antipsychotics associated with a therapeutic window are lower in patients with LLS (45%-60%) than previously reported in younger patients. Further research is required to validate this finding.
ID: 2068195

ABNORMAL STRIATAL REWARD RESPONSE IS ASSOCIATED WITH TREATMENT RESISTANCE OF NEGATIVE SYMPTOMS IN ANTIPSYCHOTIC NAÏVE SCHIZOPHRENIA PATIENTS

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Background: Disturbances of the brain reward system are suggested to be central in the pathogenesis of negative symptoms. Negative symptoms are often treatment resistant, but amisulpride has been found to improve negative symptoms, at least in a subgroup of patients. In this study we compare reward related brain activity in patients improving and not improving in negative symptoms after treatment with amisulpride.
Methods: Fifty-nine antipsychotic naïve patients and 60 healthy controls were included. At baseline functional magnetic resonance imaging with a monetary rewarding game (a modified MID-task) was performed, and psychopathology of the patients was characterised. Patients were treated with individual doses of amisulpride (mean dose 269 mg) for six weeks, and the examinations were repeated. Follow up data were complete in 41 patients and 49 healthy controls.
Results: Patients had a mean baseline PANSS total score of 80, and the positive, general and total PANSS score improved after treatment (p<0.001). A subgroup of 14 patients had an improvement of negative symptoms of 20% or more. These patients were older and had a higher baseline PANSS negative score (p<0.05). Further, they improved more on general and total PANSS score (p<0.05). One way ANOVA of reward anticipation activity showed a significant group difference in nucleus accumbens and caudatus

bilaterally (all p< 0.02), with the non-improving patients having a decreased reward response compared to healthy controls and the improving patients. Repeated measure ANOVA showed a significant group*time interaction, most pronounced in left caudate (p=0.001), with the healthy controls and the improvers decreasing and the non-improvers increasing in reward anticipation activity after treatment.
Conclusion: The identified subgroup of patients improving in negative symptoms can be characterized by older age, more severe negative symptoms and a more pronounced improvement on total and general PANSS score. Further, they had a normal function of the reward system at baseline, while non-improving patients initially showed decreased striatal reward-activity. This finding together with the normalization of striatal reward disturbance following treatment in non-improving patients suggests that striatal reward disturbance might not be related to the negative symptom domain. The results are preliminary and analyses of specific negative symptom items and possible reward disturbances in prefrontal regions are planned.
ID: 2084439

A POLYGENIC SCORE OF DRD2 CO-EXPRESSION PREDICTS BOLD ACTIVITY DURING WORKING MEMORY PERFORMANCE

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Background: Co-expressed genes are likely to be co-regulated and to cluster together in contributing to explain phenotypic variance. Genetic variants in the D2 dopamine receptor pathway are associated with schizophrenia and its intermediate phenotypes, like working memory (WM) cortical activity. However, it is not known whether DRD2 genetic variation is part of a common pathway characterizing risk for schizophrenia phenotypes. We hypothesized that novel genetic variants associated with transcription levels of genes in the D2 interactome would be associated with dorsolateral prefrontal (DLPFC) activity during WM performance.
Methods: Weighted gene co-expression network analysis identifies clusters of co-expressed genes (modules) based on transcriptome microarray data (Braincloud [1]). The sample included 199 subjects with postnatal age and RNA integrity estimate >7.0. We selected the module including the probe for the mRNA of the D2L isoform of the D2 dopamine receptor and computed its first principal component (module eigengene, ME). D2L receptors are mainly post-synaptic and are known to modulate WM physiology. We used ANOVA to investigate associations between SNPs within the module genes and the ME. We collapsed the effects of these SNPs into a polygenic score (PS) negatively correlated with the ME (R squared=0.4). A sample of 125 participants performed the 2-back WM task during fMRI and we associated the PS of each participant with DLPFC activity during 2-back.
Results: The module included 85 genes and was enriched for genes involved in DNA packaging (DAVID, corrected p=.009). The ME explained 33% of the module variance and was associated with eight SNPs surviving FDR correction for multiple comparisons at a threshold suitable for polygenic traits (corrected p<.25 [2]). DLPFC activity during WM negatively correlated with the PS (whole-brain cluster level Bonferroni corrected p<.05; PS explained 23% of the variance).
Conclusion: Shared variance among co-expressed genes was associated with genetic variants which also modulate a well-known intermediate phenotype of schizophrenia. Results are consistent with the established role of D2L in the DLPFC further suggesting that DRD2 is part of a common pathway. The robust fMRI statistics suggest that investigating ensembles of genes is relevant to understand the relationship between specific molecular pathways and specific brain/behavioral traits.
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ID: 2090280

COMPARATIVE HERITABILITY OF BRAIN STRUCTURE AND FUNCTION IN SCHIZOPHRENIA

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Background: The heritability of the brain's structure and function in schizophrenia remains elusive.
Methods: Total brain, grey and white matter and hippocampal volumes were established from structural MR images from twin pairs varying in their zygosity and concordance for schizophrenia. Brain function was indexed using a verbal fluency functional probe.
Results: Whole brain, grey and white matter volumes were significantly heritable, while the hippocampus was more environmentally sensitive. There was a significant phenotypic correlation between schizophrenia and reductions in all the brain volumes except for left hippocampus. For whole brain and grey matter and the right hippocampal volumes the aetiological links with schizophrenia were principally due to shared family environment. Patients and their unaffected relatives developed greater activation in the left inferior frontal gyrus, and greater deactivation in the left hippocampal and middle temporal gyri bilaterally. When the analysis was restricted to the unaffected relatives and healthy controls, a similar pattern was evident, with the unaffected relatives showing greater inferior frontal and left superior temporal activation, and greater right medial and lateral temporal deactivation. Genetic modelling indicated a phenotypic correlation between schizophrenia and increased activity in the inferior frontal gyrus and reduced activity in the left middle temporal gyrus and left hippocampus.
Conclusion: Whole brain, grey and right hippocampal volume reductions and altered frontal, medial and lateral temporal activation are linked to schizophrenia. The volume changes principally through correlated familial risk, which is probably linked to the shared familial environment, Altered medial and lateral temporal activity may be more intimately linked to the genetic risk for schizophrenia. The degree of influence of aetiological factors varies between brain structures and their function, leading to the possibility of a neuroanatomically specific aetiological imprint.
ID: 2118393

NEURAL CORRELATES OF EXPERIMENTALLY INDUCED SPEECH-ILLUSIONS IN NON-CLINICAL SUBJECTS: AN FMRI STUDY USING THE WHITE NOISE PARADIGM

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Background: Research on the functional neuroanatomy of auditory verbal hallucinations so far focussed utmost on detection of spontaneous hallucinations. However, at least in subjects with elevated hallucination proneness, experimental speech illusion paradigms may induce phenomena similar to hallucinations. A classical paradigm is the white noise paradigm (e.g. Merckelbach and van de Ven, J behav ther exp psychiat 32, 2001) which induced the illusion of hearing music in a remarkable proportion of healthy individuals in previous studies.
Methods: In this event-related functional magnetic resonance imaging (fMRI) study, we investigated the neuroanatomy of speech and music illusions using two adopted fMRI versions of the white noise paradigm.
15 healthy subjects (10 female, all German native speakers) with no history of psychiatric treatment or disease were included and particpated in two fMRI experiment and completed several personality questionaires including the German versions of the SPQ (schizotypal personality questionaire), PDI (peters delusion inventory) and LSHS (Launay-Slade hallucination scale). Subjects were selected out of a population of 132 university students that responded to advertisement for an fMRI study on the basis of their SPQ score and availability.
In fMRI experiment 1, subjects were instructed to detect an earworm (wind of change from the German rockband the Scorpions, a very popular piece of music) within white noise. Experiment 2 was a word detection paradigm with white noise.
Results: The mean SPQ total score in the sample was 30.6. In experiment 1, subjects had 1–28 false positive alarms. During false positive music detection, a predomantly left-lateralised network including inferior frontal and temporal brain regions was activated.
The rate of false positives was lower in the second paradigm. Nevertheless, during speech illusion subjects showed robust activation of a predominantly left-lateralised language comprehension network.
Conclusion: This pilot study suggests the white noise paradigm reflects a promising approach to investigate neural correlates of experimentally induced auditory verbal hallucinations. Results are discussed in the context oft the only previous fMRI study using a similar paradigm. Nevertheless, differences between speech illusions and hallucinations represent one of several important limitations.
ID: 2119524

CLASSIFICATION OF SCHIZOPHRENIA AND BIPOLAR PATIENTS USING STATIC AND DYNAMIC RESTING FMRI CONNECTIVITY

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Background: Diagnosis of severe mental disorders such as schizophrenia and bipolar disorder has been a very challenging issue, as clinically the basis for diagnosis is comprised of the patient's self-reported experiences and observed behavior over the longitudinal course of the illness. In this work, we propose a framework for automatic classification of schizophrenia, bipolar and healthy control subjects based on static and dynamic functional network connectivity (FNC) features. Our results show that disrupted functional integration in schizophrenia and bipolar patients as captured by FNC analysis reveal powerful information for automatic discriminative analysis.
Methods: After standard preprocessing, group independent component analysis (ICA) was applied to resting state fMRI data. Static FNC (sFNC) was estimated from subject-specific component time-courses (TC), as measured by the sample covariance matrix. Dynamic FNC (dFNC) was computed as the covariance between ICN time-courses using a sliding window approach. The classifiers were trained using support vector machine with the features from sFNC, dFNC and combined features from both FNCs. Also the generalization error of the proposed classifiers was estimated using a 10-fold cross-validation scheme.
Results: The static FNC approach showed an overall classification accuracy of 59.12%, whereas the dynamic FNC approach showed an overall classification accuracy of 84.28%. The combined static and dynamic FNC approach showed an overall accuracy of 88.68%. The confusion matrices are given in Table 1.
Conclusion: Classification based on dFNC features provides more accurate classification result compared to the sFNC based approach. The combined approach with features from sFNC and dFNC provides the highest overall classification accuracy, as these FNCs are complementary (sFNC provides the average connectivity and dFNC provides the local connectivity at different time points). The promising results of the proposed approaches may help in differential diagnosis of mental disorders. Further study with more robust features from dFNC (e.g., transitions from one state to another) will provide an important tool to better classify different mental illness.
ID: 2094437

SCHIZOPHRENIA-SPECIFIC DISRUPTIONS IN COGNITVE CONTROL NETWORK CONNECTIVITY DURING RESTING STATE FMRI

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Background: Schizophrenia (SZ) is a disorder characterized by problems in cognitive control (CC). These problems have been documented using imaging measures like resting state fMRI (rsfMRI), which show disrupted connectivity of networks that subserve CC. SZ comparison groups are typically composed of healthy people with high CC, which may skew results toward differences in general cognitive abilities rather than those specific to SZ. An alternative is to recruit comparison groups who are similar in CC to those with SZ so as to identify connectivity disruptions unique to SZ as opposed to those due to poor CC.
Methods: Two comparison groups were used: one more typical group (those with high CC; HCC) and one more appropriately matched to the SZ group (those with low CC; LCC). Participants completed a 9-minute rsfMRI scan. Data were motion corrected, smoothed (4mm), and aligned (MNI template): melodic ICA was used to remove noise components. "Denoised" data were entered into a group ICA to identify the cognitive control network (CCN). Results of the group ICA were put into FSL's dual regression, which results in a map identifying voxels that are significantly correlated or anti-correlated with the CCN. Pair-wise comparisons (2 sample t-tests) were performed on the correlations arising from the dual regression. Two main patterns were of interest: a) SZ-specific regions, or clusters of voxels that differentiated both healthy groups from the SZ group and b) CC-specific regions, or clusters of voxels that differentiated LCC and SZ groups from the HCC group.

Table 1. Confusion matrices for all classification approaches

		Static FNC Approach (Predicted Class)			Dynamic FNC Approach (Predicted Class)			Combined Static and Dynamic FNC Approach (Predicted Class)		
True Class		Healthy	Schizophrenia	Bipolar	Healthy	Schizophrenia	Bipolar	Healthy	Schizophrenia	Bipolar
	Healthy	40	18	3	55	3	3	54	5	2
	Schizophrenia	9	39	12	5	50	5	5	51	4
	Bipolar	7	16	15	4	5	29	1	1	36

Results: SZ-specific regions included the left inferior parietal lobule (anterior) and medial prefrontal cortex. Those with SZ had lower connectivity in both areas with the CCN than the LCC and HCC groups. CC-specific regions included the right and left inferior parietal lobule (posterior) and left middle temporal gyrus. The HCC group had higher connectivity with the CCN in both parietal lobules than the LCC and SZ groups. Also in those with HCC, temporal cortex was anti-correlated with the CCN, but was involved to a limited extent in those with LCC and SZ.
Conclusion: Using HCC and LCC groups when quantifying CC disruptions in SZ may help identify circuitry disruptions that are specific to SZ rather than general CC ability. Identification of SZ-specific disruptions may identify targets for treatment of CC problems which is important given that they are related to functional outcomes in the disorder.
ID: 2107264

TIME-SPECIFIC ALTERATIONS IN WORKING MEMORY-RELATED BETA BAND ACTIVITY IN PATIENTS WITH SCHIZOPHRENIA STUDIED WITH MEG WHILE ON AND OFF ANTIPSYCHOTIC MEDICATION

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Background: While working memory (WM) impairment and corresponding prefrontal dysregulation are well established in schizophrenia, a detailed understanding of temporal (millisecond) characteristics of these abnormalities is needed to clarify the pathophysiology and refine the treatment of this devastating disorder; therefore, we used magnetoencephalography (MEG) to detect beta band activity during WM and evaluated its modulation by antipsychotic medication in patients with schizophrenia.
Methods: Eighteen psychiatric inpatients with schizophrenia and 50 healthy individuals group-matched for age, sex, ethnicity, handedness, and WM performance, completed 20-second trials of a 2-back WM and 0-back control task (six trials per task condition) during neuromagnetic recording with a 275-channel whole head MEG system. Controls completed the task once, and the patients twice: after at least 2 weeks of atypical antipsychotic medication treatment, and after at least 2 weeks of placebo treatment in a counterbalanced and double-blinded fashion. Synthetic aperture magnetometry, an adaptive beamforming technique, was used to localize beta band (14-30Hz) activity in 200ms windows time-locked to responses, in the 2-back relative to the 0-back condition. Voxelwise t-tests for group and medication comparisons were performed using AFNI.
Results: WM-related activation, measured by differences in beta band desynchronization between 2-back and 0-back during the pre-response period (peaking at 300 to 100ms before responses), was reduced in unmedicated patients compared to controls in bilateral prefrontal cortex (PFC) and increased in visual cortex ($p<0.05$, FDR corrected). Medication treatment attenuated these differences with trend level significance ($p<0.005$, uncorrected).
Conclusion: These results extend prior accounts of PFC dysfunction in schizophrenia by demonstrating that even when achieving similar WM accuracy as controls, during a specific epoch of task performance patients show attenuated PFC beta band activation that may be ameliorated by antipsychotic treatment. The temporal specificity of this finding suggests that only select cognitive processes during WM task engagement may be particularly relevant to PFC dysfunction in schizophrenia, though better dissection of such cognitive components and delineation of how neuroleptic therapy might improve (or obscure) this particular abnormality await future translational work.
ID: 2115291

ALTERATIONS IN BRAIN ACTIVATION DURING COGNITIVE EMPATHY ARE RELATED TO SOCIAL FUNCTIONING IN SCHIZOPHRENIA

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Background: Impaired cognitive empathy (i.e. understanding the emotional experiences of others) is associated with poor social functioning in schizophrenia. However, it is unclear whether the neural activity underlying cognitive empathy relates to social functioning. This study examined the neural activation supporting cognitive empathy performance and whether empathy-related activation during correctly performed trials was associated with self-reported cognitive empathy and measures of social functioning. Investigating this relationship can elucidate potential biological markers to guide intervention development.
Methods: Individuals with DSM-IV diagnosed schizophrenia (n=30) and healthy controls (n=24) completed a cognitive empathy paradigm during a 3T functional magnetic resonance imaging scan. The paradigm assessed the ability to take the perspective of others who experienced anger, fear, disgust, sadness, happiness, and neutrality. Neural activity corresponding to correct judgments about the expected emotional expression in a social interaction was compared in schizophrenia subjects relative to control subjects. Data was processed using AFNI to examine the percent change in the blood oxygenation level-dependent and a whole-brain analysis generated between-group differences clusters corrected for multiple comparisons. Participants also completed a self-report measure of empathy and two social functioning measures (social competence and social attainment).

Results: Schizophrenia subjects demonstrated significantly lower accuracy in task performance and were characterized by hypoactivation in empathy-related frontal, temporal, and parietal regions as well as hyperactivation in occipital regions compared to control subjects during accurate cognitive empathy trials. A cluster with peak activation in the supplementary motor area (SMA) extending to the anterior midcingulate cortex (aMCC) correlated with task accuracy, social competence, and social attainment in schizophrenia subjects but not controls.
Conclusion: These results suggest that neural correlates of cognitive empathy may be promising targets for interventions aiming to improve social functioning. Specifically, brain activation in the SMA/aMCC region could be used as a biomarker for monitoring treatment response and help guide future research to improve recovery-oriented treatment and community-based outcomes.
ID: 2084184

CEREBRAL BLOOD FLOW REVEALS RELATIONSHIPS OF THREE SCHIZOPHRENIA SYMPTOM DIMENSIONS WITH AMYGDALA, HESCHL'S GYRUS, AND ANTERIOR CINGULATE CORTEX

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Background: In order to match behavioural dimensions to specific brain circuitries, we developed the Bern Psychopathology scale (BPS) grouping psychotic symptoms into three biologically relevant dimensions, related to language, motor and emotional dysregulation. The aim of the present study was to investigate whether these dimensions could be linked to abnormalities in resting state cerebral blood flow (CBF) in the respective brain systems.
Methods: 44 patients with schizophrenia (DSM-5 criteria; 59% men, mean age 38) underwent structural 3T-MR imaging. All patients but four were treated with typical or atypical antipsychotics. Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS) and the BPS. Based on the severity of BPS ratings, patients were grouped into three groups in each dimension (severe, mild, no dysregulation). CBF was measured by arterial spin labeling and was analyzed with own MATLAB programs. The primary focus of the analyses was the effect of the symptom dimensions on CBF. CBF differences were explored among subgroups using whole brain ANOVAs to CBF data.
Results: Subgroups did not differ in duration of illness, number of episodes, Chlorpromazine equivalent dosage, PANSS scores, duration of education, age, gender or global cerebral blood flow. Whole brain analysis revealed different CBF patterns for each dimension. Language dysregulation was associated with increased CBF in right Heschl's gyrus (p(FEW-corr)=0.039), while motor dysregulation was associated with increased CBF in the left ACC (p(FEW-corr)=0.024). Emotional dysregulation showed no effect applying family wise error correction for multiple comparision. However, exploratory analysis revealed a main effect of emotional dysregulation in the left amygdala (p<0.001-uncorr).
Conclusion: Using the BPS dimensions, we identified subgroups of patients based on the severity of psychotic symptoms referring to language, motor and emotional dysregulation. The associations of these symptom dimensions with regional CBF patterns were meaningful and specific for the respective brain circuitries: Heschl's gyrus as part of the language system, amygdala as crucial for emotional regulation, and the ACC for higher order motor control. The results indicate a central role of different specialized brain systems in generating the different symptom patterns of schizophrenia, and provide further evidence that biological and clinical heterogeneity of schizophrenia can be disentangled.
ID: 2094721

RESTING STATE NETWORK DISRUPTIONS IN THE LANGUAGE CIRCUITRY RELATED TO FORMAL THOUGHT DISORDERS

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Background: Language related symptoms in schizophrenia include auditory verbal hallucinations and formal thought disorders like incoherence or mutism. In a functional imaging study abnormal network dynamics was found in the language system during formal thought disorders (FTD) in schizophrenia. In particular, severe formal thought disorders were specifically related to functional MRI findings indicating neural hyperexcitation in language related sensory and motor areas; further gray matter volume was reduced in Wernicke's region (Horn et al. 2009). In a recent resting state study on the semantic network, Broca's region was discoupled from the language network during formal thought disorders (Horn et al. 2012).
Methods: 17 schizophrenic patients performed a semantic task and were measured with BOLD fMRI. 6 patients had severe FTD, 9 patients had no FTD, and two patients had mild FTD assessed with a clinical rating scale. Four regions of the semantic network previously determined as independent components were applied as seed regions for Granger causality mapping (GCM). Positive and negative values were compared with unpaired t tests.
Results: In two cortical regions, GCM was decreased in thought disordered patients. Further, an abnormal modulatory impact of cortical and subcortical regions on the left inferior frontal gyrus was found.
Conclusion: The study confirmed abnormal semantic network dynamics in FTD. In addition to previous findings of a general hyperactivity of the language system and a discoupling of relevant functional components, the present study indicates that the possible causal direction of the disconnection involves the modulation of the motor components of the language system by executive regions, rather than a functional discoupling of the language system's downstream functions.
ID: 2140655

MENTALIZING IMPAIRMENT IN SCHIZOPHRENIA: AN FMRI STUDY OF SOCIAL AND CONTEXTUAL INTEGRATION

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Background: Mentalizing deficits are a well-documented feature of schizophrenia. Importantly, mentalizing involves not only integrating social cues, but also contextual information, to build and adapt mental state inferences. To further explore the cognitive processes and associated neural networks of mentalizing in schizophrenia, this study examines whether these deficits are strictly related to the social nature of an inference, or also to the level of contextual integration.
Methods: We employed a novel fMRI paradigm in which participants had to infer and select the cause of written scenarios between two choices. These scenarios fit a 2 (social vs. nonsocial) x2 (congruent vs. incongruent context) design. Social or nonsocial events were presented, followed by the addition of context: congruent context was designed to confirm

a spontaneous inference (about the cause of the event), and incongruent context was to provoke an adaptation of the inference. 15 patients with a schizophrenia spectrum disorder and 19 age- and gender-matched controls underwent scanning.
Results: Results showed only a main effect of group (F=42.37, p<.001) and context (F=7.79, p=.006) on response accuracy, and no interactions were found. For social vs. nonsocial events, patients and controls both recruited the mentalizing network, including the medial prefrontal cortex, precuneus, temporoparietal junction (TPJ), and temporal poles. Patients exhibited heightened neural activation compared to controls in the anterior cingulate cortex (ACC), superior parietal lobe, insula, and striatum. For the incongruent vs. congruent context, both groups showed activation in the inferior frontal gyrus, TPJ, caudate, and thalamus. Patients differed from controls, displaying more activation in the cingulate cortex, supplementary motor area, insula, and fusiform gyrus.
Conclusion: These results suggest that patients with schizophrenia recruit a similar network as controls for attributing mental states. However, patients seem to recruit additional resources for both social and contextual conditions. Although the task presented neutral social events, regions typically associated with emotional processing, including the ventral ACC, insula, and striatum were also activated in patients. This may suggest aberrant emotional attributions, particularly in social conditions. Overall, while typical mentalizing network appears to be recruited in patients, hyperactivation outside this network may be linked with mentalizing impairment in schizophrenia.
ID: 2117905

SELF-OTHER BOUNDARY IN SCHIZOPHRENIA: TOWARD A BODY-CENTERED FRAMEWORK OF SOCIAL IMPAIRMENTS

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Background: It is commonly accepted that empathy, and social functioning in general, requires, at some level, an integration of self and other. Individuals with schizophrenia have profound social functioning abnormalities, and altered self-other boundaries have long been associated with illness. In a collection of studies, we examine basic mechanisms of self-other integration difficulties in schizophrenia and speculate on how these low-level impairments might cascade into their real-world social difficulties.
Methods: In one study, we examined brain activation in the so-called mirror neuron system during action imitation. Successful action imitation requires a shared representation of self and other. The mirror neuron system, a network of brain regions that respond during action observation and action execution, provides a mechanism that allows for such resonance between self and other. In a second study, we investigate body ownership in patients with schizophrenia by using a well-known body illusion in which synchronous tactile stimulation applied to one's own unseen hand and a visible rubber hand often provides the sensation of ownership over the rubber hand.
Results: Individuals with schizophrenia show less finely-tuned activation for relevant social information in posterior aspects of the mirror neuron system. They underactivate this system during action imitation and overactivate this system during non-imitative action execution. We also present evidence for an altered sense of body ownership in schizophrenia. Patients more readily adopt a rubber hand into the representation of their own body, suggesting that patients have a more flexible sense of their body in space.
Conclusion: We argue that on a basic bodily level, self-other distinctions are already blurred in schizophrenia and might result in disorganized self-other integration with regard to mental states. This could manifest in the clinical presentation of schizophrenia, which is marked both by heightened self-other integration (e.g. paranoia) and weakened self-other integration (e.g. social withdrawal and poor theory of mind).
ID: 2093532

LATERAL PREFRONTAL ACTIVATION DURING COGNITIVE CONTROL OF TASK-RELEVANT EMOTIONAL INFORMATION PREDICTS SOCIAL FUNCTIONING IN EARLY PSYCHOSIS

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Background: Cognitive control of emotion, reliant on fronto-limbic cognitive control mechanisms, particularly the lateral prefrontal cortex (LPFC), is fundamental for successful navigation of the social world. LPFC dysfunction is well established in psychosis, but how it contributes to core symptoms and social impairments remains unclear. Consistent with the diathesis-stress model, LPFC dysfunction may be a biological vulnerability that in the presence of social stressors contributes to symptoms and social impairments via impaired cognitive control of emotion. We investigated whether Early Psychosis (EP) participants show LPFC deficits during cognitive control of emotion, and whether these LPFC deficits prospectively predict symptoms and real-world social behavior measured using a smartphone application.
Methods: EP participants aged 14-30 were recruited from the UC Davis Early Psychosis Programs. Demographically matched healthy controls (HC) were recruited from the Sacramento community. During fMRI, EP and HC participants completed the Emotion Stroop, which dissociates cognitive control of task-relevant emotional information (emotion conditions) and task-irrelevant emotional information (gender conditions). Following the fMRI scan, EP participants used a smartphone application for a 4-week period to complete daily surveys assessing quantity and quality of social contact, and weekly surveys assessing symptoms.
Results: Preliminary results indicate that, compared to HCs, EP participants have reduced LPFC activation during cognitive control of task-relevant versus task-irrelevant emotional information (whole-brain p<0.01 uncorrected). Moreover, among EPs, higher LPFC activation during cognitive control of task-relevant emotional information related to higher self-reported social enjoyment and daily mood. Enrollment is ongoing. Additional relationships between LPFC activation and the quantity and quality of social contact will be examined.
Conclusion: Results are consistent with previous findings of reduced LPFC activation during cognitive control of emotion in psychosis. Moreover, intact LPFC functioning in EP may contribute to important social factors and better social functioning.
ID: 2119518

NEURAL CORRELATES OF EMPATHY FOR PAIN IN SCHIZOPHRENIA: PRELIMINARY RESULTS USING FMRI.

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Background: Behavioral evidences of empathy impairments (i.e, impairments in sharing and understanding the emotional states of others) have been increasingly reported in the literature on schizophrenia over the past

years. However, the neural bases of these deficits are largely understudied and remain unclear.
This study aimed to investigate the neural correlates of empathic disorders in schizophrenia using the classic and well-validated task consisting in observing and evaluating painful vs. neutral scenarios (1).
Methods: Fifteen schizophrenia patients and 21 healthy controls, matched for gender and age, participated in this study. During fMRI, participants were presented with sequences of pictures (pseudo-dynamic presentation) of hands engaged in everyday life actions (e.g., cutting a slice of vegetable). Picture sequences were manipulated such that they ended either with a painful or a neutral event. These two types of stimuli defined our two main conditions: Pain and NoPain. Participants' task was to evaluate how painful each situation would be by moving a cursor on a visual analogue scale (transformed thereafter into a rating score).
Results: Both groups rated the painful pictures higher than the neutral ones. No difference between groups was found. At the neural level, contrasting Pain and NoPain conditions in healthy controls showed the expected pattern of activation in the pain matrix regions, i.e, the anterior midcingulate cortex (aMCC), extending to the supplementary motor area (SMA) and the anterior cingulate cortex (ACC), as well as the bilateral anterior insula (AI). In patients, these regions were also activated but at a lesser extent. The between-group comparison showed a significant difference in activation in the ACC only.
Conclusion: Although no group difference was found at the behavioral level, these preliminary findings show abnormal activation of the ACC in patients during empathy for pain. A recent metaanalysis shows that this region is associated with the automatic and affective (as opposed to cognitive and evaluative) aspect of empathy (2). Our results then suggest that this particular aspect of empathy is impaired in schizophrenia. The present study contributes to refine our comprehension of the empathic impairments in schizophrenia.
Ref.: (1) Jackson P.L et al. (2005). NeuroImage24(3), 771-9; (2) Fan Y. et al. (2011) Neurosci. and Biobehav. Rev.35, 903-11.
ID: 2118008

METACOGNITION AND PREFRONTAL FUNCTIONAL CONNECTIVITY IN FIRST EPISODE PSYCHOSIS

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Background: Metacognition involves recognition of cognitive processes, including thoughts, feelings, and an array of complex contextual information about the self and others. Patients with first episode psychosis (FEP) have altered metacognitive capacity, which has been linked to a number of behavioral correlates and poor outcomes. Less is known however about the neural systems associated with metacognition in this population. The purpose of this study was to elucidate the possible link between metacognition and prefrontal cortex (PFC; associated with self reflectivity and higher order cognitive processes) functional connectivity at rest in persons with FEP.
Methods: Participants (N=19; 13 male; mean age 23.2 yrs) were recruited through the Prevention and Recovery Center for Early Psychosis, diagnosed with a psychotic illness, and had initiated treatment within the last 5 years. Participants were assessed for metacognitive capacity using the Indiana Psychiatric Illness Interview. Each participant also underwent fMRI with a Siemens 3T Trio scanner during a 6-minute resting-state scan. After standard preprocessing, each participant's fMRI time-series was bandpass-filtered (0.01-0.8 hz), and physiological noise effects were reduced by regressing out mean white matter and CSF signals. To characterize PFC functional connectivity, the correlation of the average time series from the middle frontal gyrus (MFG; separately on each side) with each voxel's time series was then calculated.
Results: On each side, patients' total metacognition score was negatively correlated with lateral PFC functional connectivity with a large cluster in medial PFC ($p < .05$, corrected for multiple comparisons). In other words, functional connectivity with seed regions in lateral PFC (MFG) was higher in medial PFC in persons with lower metacognition. Results suggest that the metacognitive deficits observed in FEP may be in part due to altered functional connectivity of resting state circuitry in middle frontal gyrus.
Conclusion: These findings support the hypothesis that network connections relevant to metacognition may be affected by cortical hyperexcitability and reduced cortical efficiency, a finding consistent with previous studies demonstrating frontal hyperactivation in schizophrenia. This link represents an important step in understanding the path through which the biological roots of psychotic illness may culminate into a disrupted life.
ID: 2109696

ALTERED CORTICO-STRIATAL FUNCTIONAL CONNECTIVITY IN INDIVIDUALS WITH SOCIAL ANHEDONIA

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Background: Social anhedonia has been considered to be an important indicator for the development of schizophrenia spectrum disorders. The purpose of the present study was to explore whether abnormalities of cortico-striatal functional connectivity has been demonstrated in individuals with high social anhedonia.
Methods: Fifteen participants who scored high (mean score = 16.67, SD=2.66) and 15 participants who scored low (mean score = 2.00,SD=1.31) on the Chapman Social Anhedonia scale were recruited to undertake the resting state functional MRI scanning. The two groups did not differ in terms of age and gender proportion. According to previous study (Martino et al., 2008), we used the 6 subdivisions of striatum on each hemisphere as seeds, including nucleus accumbens (NAcc), ventral caudate, dorsal caudate, dorsal caudal putamen, dorsal rostral putamen and ventral rostral putamen. The voxel-wise functional connectivity analyses were conducted between the mean time series of each seed and the whole brain. After transferring the r to z, the GLM analyses were conducted to compare the group differences with age and gender as covariates.
Results: Hyper-connectivity was demonstrated in individuals with social anhedonia be-tween cortex and striatum: 1) NAcc and superior temporal gyrus (BA41), 2) ventral caudate and superior temporal gyrus (BA22), 3) dorsal caudate and medial frontal gyrus (BA6), 4) dorsal rostral putamen and medial frontal gyrus (BA8), and 5) dorsal rostral putamen and caudate. On the other hand, hypo-connectivity was observed in individuals with social anhedonia in the following regions: 1) ventral caudate and superior frontal gyrus (BA10); 2) dorsal caudate and middle temporal gyrus (BA21); and 3) dorsal caudate and superior temporal gyrus (BA38). The correlation analyses in individuals with high social anhedonia further showed that, the

functional connectivity between dorsal caudate and superior temporal gyrus (BA38) was inversely associated with the social anhedonia scores (r = -0.57).
Conclusion: Altered cortico-striatal functional connectivity was found to be associated with social anhedonia, especially the connectivity between the striatum and the temporal/frontal lobe. These empirical findings support the dysconnectivity hypothesis in patients with schizophrenia and shed light on the early changes of brain functions in these at-risk individuals for psychosis.
ID: 2087089

NEURAL CORRELATES OF PROSPECTIVE MEMORY IMPAIRMENTS IN SCHIZOPHRENIA

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Background: Prospective memory (PM) refers to remember to do something at a future time. Schizophrenia is characterized by PM impairments which are thought to be correlated with their prefrontal cortex deficits but have never been examined directly. The present study aimed to examine brain activation abnormalities during PM task in schizophrenia patients.
Methods: Twenty two schizophrenia patients and 25 matched healthy controls were scanned in a 3-T MRI machine while performing a PM task.
Results: The results showed that schizophrenia patients demonstrated a decreased brain activations in bilateral middle frontal gyri [Brodmann area 10 (BA 10)], the left inferior frontal gyrus, the left cingulate gyrus, the right superior temporal gyrus, the right parahippocampal gyrus, the left precuneus and the left putamen compared with healthy participants. Moreover, weakening of functional connectivity between bilateral middle frontal gyri, medial frontal gyrus, cingulated gryus, precuneus, and putamen were also observed in schizophrenia patients.
Conclusion: Our findings confirmed the importance of prefrontal cortex in PM performance, and indciated hypofrontality in schizophrenia patients while performing a PM task. The inefficient brain functional connectivity may also be associated with PM deficits in schizophrenia.
ID: 2082739

CONTRIBUTION OF SUBSTANTIA NIGRA GLUTAMATE TO PREDICTION ERROR SIGNALS IN SCHIZOPHRENIA: A COMBINED MAGNETIC RESONANCE SPECTROSCOPY/FUNCTIONAL IMAGING STUDY

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Background: Hypofunction of N-methyl-D-aspartate receptors on γ-aminobutyric acid neurons could lead to excess glutamate (Glu) release in schizophrenia. Because the substantia nigra (SN) receives Glu projections from cortical areas, increased cortical Glu transmission could affect SN dopamine (DA) transmission. Reward learning tasks are known to modulate the DA system. Prediction errors (PE) occur when reward outcomes differ from predictions and this in turn alters DA firing rates. Magnetic resonance spectroscopy (MRS) of the SN and fMRI during PE were used to compare patients with schizophrenia (SZ) and healthy controls (HC). We hypothesized that in SZ (1) glutamate+glutamine (Glx) in SN is elevated, (2) the relationship between blood-oxygen-level dependent (BOLD) signal and PE in the midbrain and striatum is aberrant, and (3) elevated Glx is related to abnormal PE signaling.
Methods: 22 stable, medicated SZ and 19 matched HC completed a probabilistic monetary reward decision task. Imaging was done on a 3T scanner. fMRI was acquired using the gradient recalled EPI sequence (TR/TE = 2000/25ms, FOV = 192mm, 6mm slices). fMRI data were preprocessed and analyzed in SPM8. At the 1st level decisions and reward presentations were included as regressors in a General Linear Model. Reward presentations were parametrically modulated by their respective PE. Contrasts for the linear effect of PE in the midbrain and striatum were entered into 2nd level analyses using two sample t-tests with small volume correction ($p<.05$). Images were acquired using a turbo spin echo sequence with magnetization transfer contrast to visualize the left SN and aid in placement of the MRS voxel (13mm3). MRS was collected with the PRESS sequence and analyzed in jMRUI. Glx was quantified with respect to creatine (Glx/Cr). An ANCOVA, controlled for age and smoking, was conducted to compare Glx levels between groups. Statistical parametric maps for the linear effect of PE were correlated with Glx in HC and SZ.
Results: SZ had elevated SN Glx, and demonstrated a significantly greater relationship between BOLD and PE in the midbrain and striatum compared to HC. A correlation between Glx and midbrain PE BOLD signal was present in HC but not in SZ.
Conclusion: We found elevated SN Glx related to PE abnormalities in SZ, supporting that NMDA hypofunction may be underlying observed deficits, suggesting a possible pathophysiological mechanism that could be utilized as biomarker for targeted interventions.
ID: 2119229

IMAGING OXYTOCIN IN SCHIZOPHRENIA: OXYTOCIN ATTENUATES NEURAL ACTIVITY IN THE AMYGDALA AND TEMPOROPARIETAL JUNCTION DURING A DECISION-MAKING TASK INCORPORATING IMPLICIT FACIAL PROCESSING

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Background: Schizophrenia is very often a severe chronic and debilitating mental illness, frequently accompanied by social deficits that hinder individuals' abilities to interact with, and integrate in, society. Such social problems are not effectively treated by anti-psychotic medication and psychosocial interventions show limited gains. Oxytocin has emerged as a putative therapeutic agent for treating social deficits in schizophrenia.
Methods: We scanned 20 patients with schizophrenia after taking either an oxytocin (40IU) or matching placebo nasal spray. During each scan, participants performed a decision-making task incorporating faces of varying social valence which were stochastically rewarded. Participants were presented with two faces, either a happy and an angry face or two neutral faces of different identities and were asked to identify which face they thought was more likely to be rewarded.
Results: It was found that oxytocin administration exerted a positive prosocial effects in the patients with schizophrenia by attenuating the normal bias toward choosing a happy face - or attenuation of the aversion toward an angry face - which was accompanied by the attenuation of neural activity in social regions including the amygdala and temporoparietal junction (TPJ).
Conclusion: These findings demonstrate that oxytocin administration is capable of inducing a robust effect on neural activity in patients with schizophrenia in similar regions as healthy controls with potentially beneficial prosocial effects.
ID: 2114194

INTRINSIC CONNECTIVITY DURING A TRUST GAME IN PERSECUTED SCHIZOPHRENIA PATIENTS AND MONOZYGOTIC TWINS

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Background: Persecutory ideation is a symptom that can have devastating consequences, and has low heritability. Using a socio-economic decision-making task during fMRI we parametrically evaluated persecutory ideation through trusting behaviors, and characterized the connectivity associated with this symptom.
Methods: Thirty-eight individuals with schizophrenia and 21 pairs of discordant monozygotic twins were scanned while completing the task which differentiated forms of distrust to measure rational mistrust (chance of a loss decided by a partner who has incentive to betray) and suspiciousness (chance of a loss decided by a partner who has no incentive to betray) across conditions varying in financial risk. Persecutory ideation was additionally assessed using levels of suspiciousness from the BPRS (patients) and traits of alienation from the MPQ (twins). Twins were discordant for high/low alienation. Connectivity networks from fMRI data were tested in multivariate regression models for prediction of persecutory ideation. Two alternative hypotheses were tested: persecutory ideation was associated with dysfunction of 1) a frontal-striatal-amygdala circuit, or 2) a temporal-parietal-hippocampal circuit.
Results: In patients with schizophrenia the temporal-parietal-hippocampal circuit significantly predicted persecutory ideation ($F = 2.94$, $p = 0.039$, $R2 = 0.322$, R2 adj. = 0.213), and the frontal-striatal-amygdala circuit did not ($F = 0.789$, $p = 0.543$, $R2 = 0.112$, R2 adj. = -0.030). Follow-up univariate analyses revealed that reduced connectivity in a network composed mainly of temporal-parietal junction (TPJ) and inferior parietal (IP) areas was the only significant predictor of persecutory ideation ($r(28) = -0.49$, $p = 0.0056$). The extent to which discordance of this connectivity metric predicts discordance in persecutory ideation in monozygotic twins will test for convergent evidence about the networks involvement in this symptom, and the influence of non-genetic factors on the expression of this dimension.
Conclusion: Findings provide preliminary evidence that reduced connectivity between the TPJ and IP regions may be important for understanding mechanisms involved in persecutory ideation in patients with schizophrenia. Given prior literature, it is possible that dysfunctions in social cognition or the integration of internal and external information may play a role in this relationship.
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ID: 2096339

FRONTO-LIMBIC NEUROPLASTICITY EFFECTS OF COGNITIVE ENHANCEMENT THERAPY DURING EMOTION REGULATION IN SCHIZOPHRENIA PATIENTS WHO ABUSE CANNABIS

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Background: Individuals with schizophrenia and comorbid cannabis abuse diagnoses are burdened with significant impairments in emotion regulation. While studies have shown that there is a neural basis underlying emotion dysregulation in schizophrenia patients that abuse substances, no study has ever investigated the neuroplasticity effects of cognitive enhancement treatment on emotion regulation in these patients who abuse substances. This study examined brain activation in schizophrenia patients with comorbid cannabis use during an emotion regulation task post-cognitive remediation treatment compared to schizophrenia patients with comorbid cannabis use in usual treatment.
Methods: Schizophrenia outpatients with comorbid cannabis abuse were randomized to either cognitive enhancement therapy (CET: n = 10) or treatment as usual (TAU: n = 4). An emotion regulation version of a 2-back n-back task was performed by patients during functional magnetic resonance imaging (fMRI) after completing 18 months of either CET or TAU. A 2 (CET vs. TAU) x 3 (happy, fearful, neutral) general linear model was used to investigate group differences in regional brain activation during emotion regulation following CET. Regions of interests (ROIs) included fronto-limbic areas, which were the bilateral amygdala, insula, dorsolateral prefrontal cortex (DLPFC), ventromedial prefrontal cortex, orbitofrontal cortex, striatum, and cingulate cortex.
Results: Compared to the TAU group, CET patients showed increased activation during the emotion regulation task in the bilateral DLPFC, bilateral inferior orbital frontal cortex, right middle and superior orbital frontal cortex, right anterior cingulate, left middle cingulate, right putamen, left caudate, and the right insula.
Conclusion: CET contributes to neuroplasticity in fronto-limbic brain regions that are important for emotion regulation in schizophrenia patients that abuse cannabis. These results support the use of cognitive enhancement interventions in patients with schizophrenia who have substance abuse problems.
ID: 2119495

AMOTIVATION IN SCHIZOPHRENIA AND FIRST-DEGREE RELATIVES: FUNCTIONAL NEUROIMAGING AND ASSOCIATION WITH SOCIAL VS. NONSOCIAL IMPAIRMENT

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Background: Amotivation plays a central role in disability caused by schizophrenia, but its pathophysiology remains poorly understood. Here we characterize the neurobehavioral correlates of amotivation, and explore their specificity for social vs. non-social impairment.
Methods: 41 individuals with schizophrenia (SCH), 40 first-degree relatives (FAM), and 36 controls (CTR) performed a progressive ratio task (PRT) quantifying effort exerted in pursuit of monetary reward, and a 3T fMRI paradigm probing ventral striatum (VS) responses to monetary feedback (win > loss) or facial affective feedback (happy>angry). A separate ongoing study applies an effort discounting fMRI paradigm to examine effort-reward tradeoff decisions, with a parametric design independently manipulating effort and reward magnitude.
Results: Both SCH ($p=0.03$) and FAM ($p=0.03$) showed reduced PRT motivation relative to CTR and did not differ from each other ($p=0.7$). Across SCH and FAM covarying for diagnosis, lower PRT motivation related to more severe recreational-vocational amotivation measured with the Clinical Assessment Interview for Negative Symptoms (CAINS; $p=.01$), and less strongly to social amotivation ($p=.04$). Higher PRT motivation also related to better occupational function on the Quality of Life Scale ($p=.02$), with a trend relationship to social function ($p=.09$). In SCH, lower PRT motivation related to greater premorbid social impairment on the Premorbid Adjustment Scale ($r=-.36$, $p=.02$), but not to premorbid

academic impairment (r=-.08, p=0.6). Across SCH and FAM, lower PRT motivation was associated with reduced VS activation to monetary feedback (p=.049) but not facial affective feedback (p=0.54). Preliminary data from the effort-discounting fMRI paradigm additionally implicate anterior cingulate (AC) dysfunction, as low motivation correlated with effort-related hypofunction in this region.
Conclusion: Our results support the hypothesis that hypofunction in a VS-AC circuit contributes to amotivation in schizophrenia, and may reflect a heritable vulnerability. Our monetary PRT related to both social and non-social indices of clinical impairment, suggesting it captures a core deficit across domains. However, the mixed pattern of social vs. non-social specificity points to a need for further efforts to clarify common versus domain-specific mechanisms of amotivation. This will require addressing substantial challenges in imaging studies of social motivation.
ID: 2118101

ABNORMAL MOVEMENT SEQUENCING IN SCHIZOPHRENIA AND RELATED CORTICAL ACTIVATION PATTERNS

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Background: Minor motor and sensory impairments, including movement sequencing, are frequent symptoms in schizophrenia. In a previous study we showed abnormal cortico-cerebellar functional connectivity during execution of motor task only in schizophrenia patients (SZP) with sequencing deficit. This suggests that the abnormal connectivity reflects rather symptoms that are domain-specific, than the diagnoses of schizophrenia per se. In order to parse out the differences in brain activity during motor learning that are disease-specific (i.e. common to all SZP relative to healthy controls) versus domain-specific (i.e. specific only to SZP with sequencing deficit), we conducted a new and more detailed analysis of the data from the previous study.
Methods: We used functional magnetic resonance imaging to examine brain activity during finger-tapping task in 24 SZP and 24 healthy control participants. The task had two experimental conditions, in which participants had to execute blocks of sequenced finger movements (SQ condition) and non-sequenced movements (ALL condition). Prior to the imaging session, outside the scanner the movement sequencing skills were assessed through Neurological Evaluation Scale (NES). Based on the NES scores the patients were subdivided into two groups, those with sequencing abnormalities (SQ+), and those without movement sequencing deficit (SQ-). We performed whole brain analysis to identify regions with higher activation during SQ as compared to ALL blocks and we analyze these results as a function of movement sequencing skill.
Results: In the left motor and parietal cortices all patients had higher activation than healthy subjects in both ALL and SQ conditions. However, our analysis revealed that this effect was driven mainly by the SQ- subgroup in motor cortex, and by SQ+ group in parietal cortex. No such differences were seen in the contra-lateral cortices.
Conclusion: Executing a non-sequenced motor task is more demanding for SZP than controls (disease-specific), since they show constantly higher activation in left motor and parietal cortex. Notably, although the overactivation of motor cortex seems to be a good compensating strategy to achieve adequate motor performance, the hyperactivation of parietal cortex seems to be linked to motor deficit symptoms (domain-specific).
ID: 2118542

Neuroimaging: Neurochemical; Structural

IMPACT OF ANTIPSYCHOTIC MEDICATION ON FRACTIONAL ANISOTROPY IN SCHIZOPHRENIA

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Background: In this prospective study, we examined antipsychotic-naïve/antipsychotic-free DSM-IV schizophrenia (SCZ) patients for white matter abnormalities at baseline in comparison with healthy controls (HC) and the effect of 3-6 months of treatment with antipsychotic (AP) medications on white matter micro-structure.
Methods: Diffusion tensor imaging (DTI; 64-directions) was performed on right handed SCZ patients [N=28; 22 drug-naïve; age=31.7±6.0 years, 19 male, years of education (YoE)=10.2±5.5, duration of illness 3.8±4.3 years] at baseline and after 4.4±0.6 months of AP therapy [all patients were on oral atypical agents, additionally two patients were on fluphenazine depot injections], and age, sex and handedness matched HC [N=28, Age=31.8±6.7 years, 20 male, YoE=13.5±3.0] in a 3-Tesla MRI. Psychopathology was assessed using the Scale for Assessment of Positive Symptoms (SAPS) and the Scale for Assessment of Negative Symptoms (SANS). DTI images were processed using Tract Based Spatial Statistics implemented in FSL to analyze fractional anisotropy (FA) with multiple comparison correction using threshold-free cluster enhancement [5000 permutations, $p<0.05$].
Results: SCZ patients had significantly greater FA at baseline compared to HC in bilateral white matter tracts including superior and inferior longitudinal fasciculi, corticospinal tract, corpus callosum, thalamic radiation, and internal and external capsule. Patients at baseline had significantly greater FA compared to that at follow-up in multiple bilateral white matter tracts.There was no significant difference in FA between patients at follow-up and HC. Change in FA (pre minus post) correlated positively with AP dose in bilateral superior longitudinal fasciculus, corticospinal tract, corpus callosum, left anterior thalamic radiation, and left internal and external capsule. SAPS total score reduced significantly from 26.6±12.1 to 6.6±8.4 ($t=8.5$, $p<0.001$). Change in SANS score was not statistically significant. Change in FA did not correlate with change in psychopathology when controlled for AP dose or with age of onset of illness, duration of illness, duration of untreated psychosis or duration between scans.
Conclusion: Study findings suggest that SCZ patients at baseline have greater FA compared to HC indicating possible aberrant hyperconnectivity. AP might "normalize" this aberration through glia-mediated mechanisms.
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ID: 2085457

VOXEL-BASED MORPHOMETRY SHOWS GREY MATTER VOLUME DIFFERENCES IN TREATMENT-RESISTANT AND NON-TREATMENT RESISTANT SCHIZOPHRENIA

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Background: Approximately one third of people with schizophrenia are treatment-resistant and some do not achieve remission with clozapine, the gold-standard antipsychotic medication for treatment-resistant schizophrenia. This study aimed to compare global and regional brain volumes between treatment-responders and treatment-resistant patients with schizophrenia, including a group of patients who were clozapine-resistant.
Methods: T1-weighted structural brain MRI were acquired on a 3T scanner in 20 controls and 52 people with schizophrenia who were selected based on their symptomatic response to antipsychotic medication: 18 responding well to first-line atypical antipsychotics (FLR), 19 who were treatment-resistant but responsive to clozapine monotherapy (TR), and 15 who were ultra-treatment-resistant and did not respond to clozapine (UTR). Treatment groups were matched for disease duration and current psychopathology. We used SIENAX and FSL-VBM to investigate differences between groups in global brain, grey matter (GM), white matter (WM), ventricular CSF volumes, and regional GM volumes.
Results: Whole GM volume was significantly reduced in TR and UTR groups compared with controls and the FLR group ($p<0.05$). Voxel-based morphometry showed significant regional GM volume loss in TR patients compared with FLRs in the superior, middle and inferior temporal gyri, pre/post-central gyri, middle and superior frontal gyri, supramarginal gyrus and lateral occipital cortex. Reduced GM was observed in patients with UTR schizophrenia compared with FLRs in the right parietal operculum and left cerebellum. There were no significant differences between TR and UTR groups.
Conclusion: GM volume loss is more pronounced in people with treatment-resistant schizophrenia compared with non-treatment-resistant schizophrenia. This may represent an accelerated disease course or a different underlying pathology in treatment-resistant schizophrenia.
ID: 2118025

PREFRONTAL CORTICAL THINNING IN FIRST-EPISODE SCHIZOPHRENIA AND ITS CLINICAL CORRELATES

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Background: Prefrontal grey matter deficits in schizophrenia are frequently, but not consistently found on MRI scanning. The functional diversity of the prefrontal cortex suggests that abnormalities in the region may in part explain the difficulties in cognitive and emotional integration that characterize the clinical manifestation of schizophrenia. Here, we compare prefrontal cortical thickness between 93 patients with minimally treated first-episode schizophrenia (FES) and 92 matched healthy controls (HC). We then examine correlations between prefrontal cortical thickness and clinical symptoms scores.

Methods: T1 weighted scans were processed and analyzed using Freesurfer stable release version 5.1. We conducted t-tests corrected for multiple comparisons to compare cortical thickness differences between patients and controls. Pairwise correlations and multiple regression analysis were performed examining left and right hemisphere prefrontal composite measures and clinical measures.
Results: We found a reduction in prefrontal composite thickness bilaterally as well as in the left medial orbitofrontal cortex, left frontal pole, left superior frontal gyrus, the right dorsolateral prefrontal cortex, right lateral orbitofrontal cortex and right superior frontal gyrus. We found a positive correlation between PANSS positive factor domain scores and RH prefrontal composite thickness, higher PANSS G12 Insight item score and a reduction in bilateral prefrontal composite thickness, and a negative correlation between the BIS total score and bilateral prefrontal composite thickness. The G12 insight score remained significant on multiple regression analysis.
Conclusion: In this, the largest known study to specifically examine prefrontal cortical thickness and its clinical correlates in schizophrenia, we found evidence of reduced bilateral prefrontal cortical thickness as well as reduced thickness in several prefrontal cortical regions. Key prefrontal cortical deficits may be crucial to the pathogenesis of positive symptoms and insight early in schizophrenia. Longitudinal studies are needed to identify the effect of disease progression on cortical thickness and its relationship with clinical symptoms.
ID: 2094796

ABNORMAL HIPPOCAMPAL-THALAMIC WHITE MATTER TRACT DEVELOPMENT AND DISEASE COURSE IN ADOLESCENTS AT ULTRA HIGH-RISK FOR PSYCHOSIS

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Background: Abnormal development of the hippocampus and thalamus has been reported in adolescents at ultra high-risk (UHR) for psychosis. However, the white matter connections between these critical structures have yet to be studied. As both structures are believed to significantly contribute to symptoms and characteristics seen in patients with psychotic disorders, understanding these connections in the UHR period is of key importance to improving pathophysiological conceptions.
Methods: 26 UHR individuals (18.73+1.77 years old) and 21 healthy matched controls (17.71 +2.65 years old) were assessed at baseline and 12-months later. Symptoms were assessed using the Structured Interview for Prodromal Symptoms (SIPS), and all participants underwent diffusion tensor imaging scans. Using a probabilistic tractography approach, we traced connections between the thalamus and hippocampus and extracted fractional anisotropy (FA). This method allowed us to look at specific white matter connections of interest, rather than pulling FA from all white matter in the brain.
Results: Controlling for baseline age and antipsychotic medications (n=3 UHR) we found significant group by time point interactions in both hemispheres. There was little change in FA in the UHR group, while FA in the controls increased (interaction, right: $F(1,43)=10.80$, $p<.005$, $\eta 2p=.20$; left: $F(1,43)=9.60$, $p<.005$, $\eta 2p=.18$). Furthermore, we investigated relationships between baseline FA in the thalamic-hippocampal tract and symptoms 12-months later. Across both groups, controlling for baseline positive symptoms, age, and antipsychotic medications, baseline right hemisphere FA significantly predicted positive symptoms. Abnormal higher FA in the right hemisphere at baseline was associated with worsening positive symptoms 12-months later (beta=.16, $p<.05$), and there was a trend in the left hemisphere (beta=.14, $p=.07$). When we look only at the UHR group, the same patterns hold (in both cases, beta>.27, $p<.04$ one-tailed).
Conclusion: These findings provide important evidence indicating abnormal white matter development in thalamic-hippocampal white matter in a UHR population, which is associated with disease progression. Given the purported role of both the hippocampus and thalamus in the etiology of psychosis, particularly related to positive symptoms, this is an especially important area of further investigation.
ID: 2087759

ELEVATED HIPPOCAMPAL GLUTAMATE LEVELS PREDICT THE LATER ONSET OF PSYCHOSIS

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Background: Animal models suggest that hippocampal glutamate function plays a key role in the pathophysiology of psychosis, and recent neuroimaging studies have reported increased hippocampal glutamate levels in unmedicated patients with schizophrenia. However, it is unclear if hippocampal glutamate function is altered before the onset of the disorder. We addressed this issue by examining hippocampal glutamate levels in subjects at Ultra High Risk (UHR) for psychosis.
Methods: Levels of glutamate in the left hippocampus were assessed using proton magnetic resonance spectroscopy at 3 Tesla (PRESS: Point-RESolved Spectroscopy; TE=30ms; TR=3000ms; 96 averages; voxel size 20x20x15) in 68 UHR subjects and 30 healthy controls. Spectra were analysed using LCModel version 6.3-0A, and water-scaled glutamate levels were corrected for voxel CSF content. The UHR subjects were scanned at first clinical presentation, and then followed up for a mean duration of 19 months. Subsequent to scanning, 9 UHR subjects made a transition to psychosis, as defined using the criteria in the Comprehensive Assessment of At-Risk Mental State (CAARMS).
Results: There were no significant group differences in hippocampal glutamate levels between controls and UHR subjects (6.94 ± 0.92 and 7.14 ± 1.16). The UHR sample was subdivided according to clinical outcome into transition and non-transition subgroups. There was a trend towards differences in hippocampal glutamate levels across these two subgroups and the control group ($p=0.069$). Post-hoc tests revealed that UHR subjects who subsequently developed psychosis had higher glutamate levels than both UHR subjects who did not become psychotic (7.87 ± 0.87 vs 7.03 ± 1.17, $p=0.042$) and controls (7.87 ± 0.87 vs 6.94 ± 0.92, $p=0.011$). There were no differences between controls and UHR subjects who did not develop psychosis.
Conclusion: These data indicate that hippocampal glutamate levels were selectively elevated in the subgroup of UHR subjects who subsequently made a transition to psychosis. This is consistent with animal models that propose that elevated glutamatergic function in the hippocampus is fundamental to the onset of psychosis. Our findings also suggest that neuroimaging measures of hippocampal glutamate function could be used to help predict outcomes in people at high risk of psychosis in a clinical setting.
ID: 2090102

ELEVATED HIPPOCAMPAL GLUTAMATE LEVELS PREDICT THE LATER ONSET OF PSYCHOSIS

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Methods: Levels of glutamate in the left hippocampus were assessed using proton magnetic resonance spectroscopy at 3 Tesla (PRESS: Point-RESolved Spectroscopy; TE=30ms; TR=3000ms; 96 averages; voxel size 20x20x15) in 68 UHR subjects and 30 healthy controls. Spectra were analysed using LCModel version 6.3-0A, and water-scaled glutamate levels were corrected for voxel CSF content. The UHR subjects were scanned at first clinical presentation, and then followed up for a mean duration of 19 months. Subsequent to scanning, 9 UHR subjects made a transition to psychosis, as defined using the criteria in the Comprehensive Assessment of At-Risk Mental State (CAARMS).
Results: There were no significant group differences in hippocampal glutamate levels between controls and UHR subjects (6.94 ± 0.92 and 7.14 ± 1.16). The UHR sample was subdivided according to clinical outcome into transition and non-transition subgroups. There was a trend towards differences in hippocampal glutamate levels across these two subgroups and the control group ($p=0.069$). Post-hoc tests revealed that UHR subjects who subsequently developed psychosis had higher glutamate levels than both UHR subjects who did not become psychotic (7.87 ± 0.87 vs 7.03 ± 1.17, $p=0.042$) and controls (7.87 ± 0.87 vs 6.94 ± 0.92, $p=0.011$). There were no differences between controls and UHR subjects who did not develop psychosis.
Conclusion: These data indicate that hippocampal glutamate levels were selectively elevated in the subgroup of UHR subjects who subsequently made a transition to psychosis. This is consistent with animal models that propose that elevated glutamatergic function in the hippocampus is fundamental to the onset of psychosis. Our findings also suggest that neuroimaging measures of hippocampal glutamate function could be used to help predict outcomes in people at high risk of psychosis in a clinical setting.
ID: 2082952

MODELING THE NEUROCOGNITIVE AND NEUROANATOMICAL MECHANISMS OF COGNITIVE INSIGHT IN NON-CLINICAL SUBJECTS

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Background: Previous research in psychosis has suggested that cognitive insight (i.e., Self-Reflectiveness and Self-Certainty) may be in part dependent on verbal memory and neuroanatomy in the hippocampus and ventrolateral prefrontal cortex (VLPFC). In the current study we explored whether similar relations exist in non-clinical participants by examining relationships between cognitive insight, hippocampal volumes, VLPFC cortical thickness, and neurocognition.
Methods: Fifty-one non-clinical subjects completed the Beck Cognitive Insight Scale. Hippocampal volumes and VLPFC cortical thickness, as well as cortical thickness in three VLPFC subdivisions (pars orbitalis, pars triangularis and pars opercularis) were examined using FreeSurfer. In a subset of the sample (n=27), neurocognition was examined with global measures of seven domains.
Results: Significant associations were observed for Self-Certainty and cortical thickness in total left VLPFC. No significant effects emerged between Self-Reflectiveness and VLPFC in either hemisphere. No associations emerged between either measures of cognitive insight and hippocampal volumes. A significant positive correlation was seen for Self-Reflectiveness and performance on a global measure of speed of processing, and inverse correlations were seen between Self-Certainty and working memory and attention.
Conclusion: The results suggest the left VLPFC may be a viable brain area that underlies Self-Certainty in non-clinical subjects. Research to date suggests that the brain areas underlying cognitive insight may be different in non-clinical samples and in psychosis. The results provide a framework of mechanisms underlying cognitive insight in non-clinical participants, and allow evaluation of how these process may become dysfunctional in psychosis through cognitive neuropsychiatric modeling.
ID: 2082993

FIVE-YEAR INVESTIGATION OF PROGRESSIVE STRUCTURAL BRAIN ABNORMALITIES IN ASSOCIATION WITH FIRST-EPISODE PSYCHOSIS IN SAO PAULO, BRAZIL

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Background: São Paulo, Brazil, is one of the regions with fastest-growing level of urbanization in the world. We conducted the first large-scale MRI investigation of first-episode psychosis (FEP) in such large urban center using a longitudinal design. We sought to determine: patterns of structural brain abnormalities associated with FEP in our environment; whether FEP subjects show progressive regional grey matter changes compared with healhty individuals recruited from the same neighborhood; and whether those changes are associated with diagnosis, illness course or antipsychotic use.
Methods: Using a population-based, case-control study design, 122 subjects with FEP (including both schizophrenia-spectrum disorders and affective psychoses) and 94 healhty controls were investigated using structural MRI at study entry in Sao Paulo city. Subgroups from these samples were re-assessed clinically and with MRI at 18 months and again after 4 to 5 years. FEP patients were treated at community settings, and about half of them remained mainly untreated. Voxel-based volumetric measurements and several other morphometric indices were obtained at the three time points.
Results: Main findings included: volumetric reductions in fronto-temporal cortices and insula in FEP patients relative to controls at study entry; no significant progressive changes in gray matter regional volumes either in the overall subgroup with schizophreniform psychosis or in the affective psychoses subgroup; brain volume decrements circumscribed to FEP patients with a non-remitting course, both in the schizophrenia and affective psychoses subgroups, differentially affecting the frontal and temporal neocortices; and a significant association between antipsychotic use and regional gray matter decrements in the insula.
Conclusion: In a large middle-income urban centre, FEP-related neuroanatomical abnormalities are similar to those documented by MRI previous studies carried out in other environment across the globe. The long-term progression of brain abnormalities in FEP subjects is restricted to those

with a poor outcome. Antipsychotic intake is associated with a different pattern of gray mattter reduction over time.
ID: 2077800

GABA AND GAMMA OSCILLATIONS IN SCHIZOPHRENIA: EFFECT OF ADOLESCENT CANNABIS EXPOSURE

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Background: Adolescent cannabis abuse is a risk factor for schizophrenia. Cannabis may affect GABAergic interneuron function and evoked or induced brain oscillatory function in the gamma range. In healthy individuals, occipital GABA levels are directly correlated with occipital transitory gamma oscillations. We examined the impact of history of cannabis abuse in occipital GABA and corresponding gamma oscillations in schizophrenia and healthy comparison subjects.
Methods: Firstly, in a sample of 3 healthy control (HC) and 5 subjects with schizophrenia (SP) we used MEGA-PRESS at 3T to examine reproducibility of measurement of GABA in a medial occipital 27 cc voxel. GABA, fitted with LCModel (with CRLB≤20), separate from macromolecules (MM) and partial volume corrected, had a coefficient of variation of 9%. Subsequently, we used this approach to study a separate group of 19 subjects with schizophrenia (10 with and 9 without history of adolescent cannabis abuse) and 13 HCs. None of the subjects were current cannabis users. Magneto-encephalography was used to measure gamma oscillations in the occipital cortex during passive viewing of visual grating stimuli.
Results: GABA was highest among the schizophrenia group with cannabis history relative to the schizophrenia group without cannabis use and the healthy control group (p=0.005). GABA was negatively correlated with premorbid intelligence among the whole sample (p=0.05). Within schizophrenia, the group with cannabis history had reduced peak gamma frequency in the left occipital cortex (p=0.02) relative to the group without cannabis history. For the whole sample, there was a positive correlation between GABA and right hemisphere transitory gamma frequency when controlling for age (p=0.034).
Conclusion: Cannabis exposure during adolescence may down-regulate post-synaptic GABA receptors, with a compensatory long-term up-regulation of GABA levels in a subgroup of subjects who eventually develop schizophrenia. This may in part underlie dysfunction in gamma oscillations, as well as some of the cognitive deficits seen in the illness.
ID: 2089146

PRELIMINARY ESTIMATION OF ENDOGENOUS DOPAMINE AT D2/3 RECEPTORS IN MEDICATED PATIENTS WITH SCHIZOPHRENIA USING THE AGONIST RADIOTRACER [11C]-(+)-PHNO

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Background: Using positron emission tomography (PET) it is possible to estimate endogenous dopamine (DA) occupying D2/3 receptors (D2/3R) in the living human brain. It has been shown that persons with schizophrenia (SZ) (both previously medicated and antipsychotic naïve) have increased endogenous DA occupying D2/3R in the dorsal striatum, in particular the caudate. It is unknown whether patients currently taking antipsychotics still demonstrate increased DA levels at D2/3R. Moreover, DA levels have not been estimated in SZ using agonist radiotracers, which may offer a more sensitive quantification than antagonists.
Methods: Using the agonist radiotracer [11C]-(+)-PHNO and an acute DA depletion challenge (AMPT 64 mg/kg p.o.), DA levels were estimated at D2/3R (ΔBPND) in three patients with SZ (Male, Mage=30 ± 16). Patients were currently being treated long-term with Olanzapine (147 ± 88 nmol/L). Results were compared 10 previously collected healthy controls (HC's).
Results: Compared to HC's, medicated persons with SZ had greater ΔBPND in the left caudate (U=2, Z=-2.20, p=.03) and right putamen (U=2, Z=-2.20, p=.03). There was a trend increase in the left ventral striatum (U=4, Z=-1.86, p=.06). No differences were observed in the globus pallidus.
Conclusions: We show that it is possible to estimate endogenous DA at D2/3R in patients with SZ currently taking antipsychotics. Despite being medicated, patients continue to have increased endogenous DA at D2/3R. This is consistent with observed increases in striatal DA synthesis capacity, and lends more biological support to the clinical observation that relapses in symptoms can occur in the face of complete antipsychotic discontinuation. A larger sample size is warranted to further clarify these findings.
ID: 2211263

ABNORMAL SHIFT IN ERBB4 SPLICING IS ASSOCIATED WITH LOWER EXCITATORY INPUTS ONTO PARVALBUMIN-POSITIVE INTERNEURONS IN SUBJECTS WITH SCHIZOPHRENIA

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Background: Dysfunction of the dorsolateral prefrontal cortex (DLPFC) in schizophrenia (SZ) is associated with markers of lower activity in parvalbumin (PV)-positive interneurons which might reflect lower excitatory inputs onto these cells. ErbB4, a receptor tyrosine kinase primarily localized in the dendrites and cell body of PV and calretinin (CR)-positive interneurons, plays an essential role in excitatory input formation. Total ErbB4 mRNA levels are unaltered, but levels of ErbB4 splicing variants, JM-a and CYT-1, are higher in DLPFC of SZ, suggesting that dysregulated splicing of ErbB4 may be associated with lower excitatory inputs onto PV cells in SZ. In this study, we investigated the association between the levels of ErbB4 splicing variants and the density of excitatory inputs onto PV cells in the DLPFC of subjects with SZ.
Methods: DLPFC layers 2 or 4 were selectively laser microdissected from matched pairs (N=39) of SZ and control subjects. RNA was isolated and qPCR was performed using primers for three house-keeping genes (beta-actin, GAPDH, cyclophilin A), two layer enriched markers (CR and PV), four ErbB4 splicing variants (JM-a, JM-b, CYT-1, CYT-2) and Pan-ErbB4. In a subset (N=20) of subject pairs, tissue sections containing DLPFC area 9 were processed for fluorescent immunohistochemistry using antibodies for PV, PSD-95 and Vglut-1. Vglut-1 and PSD-95 were used to identify pre- and postsynaptic excitatory terminals, respectively. The density of appositions of Vglut-1 and PSD-95 puncta on PV cell body was quantified.
Results: In layer 2, CR mRNA levels were ~10X fold higher than PV mRNA, whereas in layer 4 PV mRNA levels were ~10X fold greater than CR mRNA, indicating that the samples of layers 2 and 4 were enriched for CR and PV cells, respectively. In layer 4 of SZ subjects, JM-a levels were 22% higher and JM-b levels were 17% lower, suggesting that the splicing at JM locus is abnormally shifted in PV cells. Finally, the JM-a:JM-b ratio was inversely correlated with PV mRNA levels in layer 4 of SZ. Results of the immunohistochemistry study are in progress.

Conclusion: As PV levels depend on excitatory inputs onto PV cells, our qPCR data support the interpretation that the higher JM-a:JM-b ratio is associated with fewer excitatory inputs onto PV cells in SZ. We predict that the density of excitatory inputs onto PV cells is lower in SZ and is inversely correlated with the JM-a:JM-b ratio in layer 4 of SZ.
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ID: 2116666

PRODROMAL SYMPTOM SEVERITY PREDICTS ACCELERATED GRAY MATTER REDUCTION AND THIRD VENTRICLE EXPANSION AMONG CLINICALLY HIGH RISK YOUTH DEVELOPING PSYCHOTIC DISORDERS

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Background: A recent prospective longitudinal neuroimaging study of 274 prodromal risk syndrome subjects revealed that those who later developed full-blown psychotic symptoms exhibited accelerated gray matter loss and third ventricle expansion around the time of onset of psychosis. Previous studies also indicate that higher levels of unusual thought content during prodromal states are a significant predictor of psychosis in clinically high-risk youth (CHR). However, the relationship between clinical symptoms and changes in neuroanatomical structure has not been previously examined in the North American Prodrome Longitudinal Study (NAPLS) sample at the atlas level.
Methods: In this report, we investigated whether symptom severity as measured by the Scale of Prodromal Symptoms (SOPS) predicted the accelerated gray matter decline in 274 CHR cases, including 35 who converted to psychosis.The reconstructed baseline and follow-up scans were processed using Freesurfer longitudinal stream to extract change in thickness and volume estimates.
Results: Higher levels of unusual thought content (pre-delusional) symptoms at baseline were associated with a steeper rate of gray matter loss in the prefrontal cortex bilaterally and third ventricle expansion among converters. In contrast, there was no association found among non-converters.
Conclusion: Steeper gray matter loss seems to be unique to those (CHR) individuals with higher levels of persisting and intensifying sub-psychotic pre-delusional symptoms and may reflect pathophysiological processing driving emergence of psychosis. This is consistent with the theoretical view that increasing clinical symptom severity during the prodromal state is a consequence of increasing disruption in synaptic activity and functional connectivity in the brain, of which accelerated gray matter loss may be an indicator.
ID: 2083072

POSTERIOR ASSOCIATION CORTEX IS RELATED TO WORKING MEMORY AND NEGATIVE SYMPTOM DEFICITS IN SCHIZOPHRENIA

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Background: Schizophrenia is a neurobiologic disorder affecting the development and formation of brain structures, which consequently disrupts cognition and elicits various clinical symptomatology. Most studies focus attribution of these disruptions to changes in prefrontal cortices, while relatively fewer works have studied the impact of posterior cortical abnormalities. The aim of this study was to characterize thinning patterns of posterior association cortex in schizophrenia and their contribution to working memory (WM) deficits and negative symptomatology (NS).
Methods: Schizophrenia (SCZ) = 100 and healthy control volunteers (CON) =73 matched for age, gender and handedness. WM was calculated as a domain score based on selected neuropsychological measures. NS were assessed using global scales of anhedonia, affective flattening, avolition and alogia from the SANS. T1-weighted MPRAGE images were processed with FreeSurfer v5.3.0. Cortical thickness was estimated from the following regions of interest and averaged across hemispheres: Superior (SPL) and Inferior (IPL) Parietal Lobules, Precuneus (PRE), and Lateral Occipital Cortex (LOC). Statistical analyses included vertex-wise GLMs between SCZ and CON across the entire brain surface, with follow-up GLMs for specified ROIs. Pearson correlations were also conducted between ROIs and WM/NS scales in SCZ. Follow-up stepwise regression models with cortical ROIs as independent variables were used to explain variance in WM and NS.
Results: Whole-brain comparisons revealed posterior cortical thinning in SCZ, which also held true for ROI-based GLMs (all $p<.03$). The SPL ($r=.22$, $p=.03$), PRE ($r=.23$, $p=.02$) and LOC ($r=.23$, $p=.02$) were significantly positively correlated with WM. Affect flattening was correlated with the SPL ($r=.23$, $p=.02$), IPL ($r=.27$, $p=.01$), PRE ($r=.28$, $p=.01$), and LOC ($r=.21$, $p=.03$). Avolition correlated with IPL ($r=.28$, $p=.01$) and PRE ($r=.26$, $p=.01$). Alogia correlated with LOC ($r=-.20$, $p=.04$). LOC alone was found to explain significant variance in both WM and alogia (both $p<.04$). PRE significantly explained variance in affect flattening ($p=.006$), and IPL for avolition ($p=.004$).
Conclusion: Select aspects of posterior association cortex were strongly related to WM, as well as NS expression. These areas are known to integrate various mental functions prior to higher-level processing. Findings represent a bottom-up disruption pathway for deficit functioning, and suggest selective network-level involvement specific to individual aspects of NS.
ID: 2117046

IMPACT OF CONNECTOME ORGANIZATION ON LONGITUDINAL CHANGES IN GENERAL FUNCTIONING, SYMPTOMS AND IQ IN CHRONIC SCHIZOPHRENIA

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Background: Emerging evidence suggests that schizophrenia involves widespread alterations in the wiring architecture of the brain network (van den Heuvel & Fornito, 2014), including reduced white matter connectivity of central brain hubs (van den Heuvel et al., 2013). Whether, and if so how, connectome (Sporns, 2005) alterations relate to the progression of illness after first onset remains to be determined.
Methods: In this study, connectome reconstructions derived from diffusion-weighted MRI scans were obtained from 40 chronically ill schizophrenia patients and examined in context of longitudinal changes in general functioning, clinical symptoms and IQ, during 3-years follow-up. Effects in patients were compared to correlations between connectome organisation and changes in IQ and subclinical symptoms in 51 healthy controls and 54 unaffected siblings of schizophrenia patients.
Results: Investigating the patient sample revealed a significant relationship between brain network organisation - particularly the level of structural connectivity among key brain hubs - and progressive changes in general functioning ($p=0.007$), suggesting that more prominent impairments of hub connectivity may herald future functional decline. In addition, our study indicates that more affected local connectome organisation relates to longitudinal increases in total PANSS symptoms ($p=0.013$) and decreases in total IQ ($p=0.003$). No significant associations were observed in controls and siblings, suggesting that the findings in patients represent effects of ongoing illness, as opposed to e.g. normal time-related changes.
Conclusion: Our findings are indicative of an influential role of connectome structure on the longitudinal course of illness in chronic schizophrenia, highlighting the potential of advanced brain network measures in informing prognosis in schizophrenia.
ID: 2118273

THE ROLE OF SUBSTANCE ABUSE IN WHITE MATTER INTEGRITY IN FIRST EPISODE PSYCHOSIS

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Background: Disruption in brain connectivity has been hypothesized to play a key role in the pathophysiology of schizophrenia. Evidence suggests that disrupted limbic system network integrity may underlie cognitive (attention, memory) and emotional disturbances in schizophrenia. Diffusion Tensor Imaging (DTI), an MRI modality, can help measure and quantify tissue orientation and structure, making it an ideal tool for measuring cerebral white matter and neural fiber tracts. While more and more DTI studies have revealed white matter abnormalities in chronic schizophrenia, the evidence of how these abnormalities develop is conflicting. We do not have clear evidence to show if these abnormalities exist at illness onset. We postulated that part of the conflicting evidence of white matter damage found in the literature is due to the heterogeneity of the patient populations examined.
Methods: We recruited 32 unmedicated patients with first episode psychosis (FEP) and 18 healthy volunteers (HC) to participate in this study. Subjects underwent DTI of the fornices and bilateral cingulum bundle, acquired using a Siemens Sonata 1.5T MRI scanner. Post-processing analysis of the images was done using MRISTUDIO software.
Results: There was a significant decrease in the FA values in the patient group in the fornices ($p<0.05$) when compared to healthy controls. However, when the patient group was subdivided into FEP-schizophrenia (n=12), FEP-drug induced psychosis (n=10) or FEP-other (n=10), the effects on FA were due to the contribution of the FEP-drug induced psychosis group. This subgroup analysis showed a significant decrease in FA value in the fornices of both hemispheres of the FEP- drug induced psychosis compared to HC ($p<0.05$) but no significant differences for the other two groups. Interestingly, the axial diffusivity value, which is related to axonal integrity, was reduced in the FEP group in the right hemisphere for the fornix ($p<0.01$). When the patient group was subdivided, the significance for the fornix was in the FEP-schizophrenia group ($p<0.05$).
Conclusion: These data provide preliminary evidence for disrupted white matter tract integrity, which may be related to disease-related attention and working memory abnormalities seen early in Schizophrenia. Our findings also point to the importance of considering the underlying etiology of the psychosis and in particular the role of a collecting and accounting for drug use histories in DTI analysis.
ID: 2095387

PRE- AND POSTSYNAPTIC MOLECULAR MARKERS OF DENDRITIC SPINES IN DEEP LAYER 3 OF THE DORSOLATERAL PREFRONTAL CORTEX IN SCHIZOPHRENIA

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Background: Morphological alterations of pyramidal (PYR) cells in the dorsolateral prefrontal cortex (DLPFC) may contribute to cognitive deficits in schizophrenia (SZ). For example, the density of dendritic spines, the principal site of excitatory inputs to PYR cells, is significantly lower by ~25% on DLPFC deep layer 3 PYR cells in SZ subjects. In contrast, these changes are layer-specific as spine density in layers 5 and 6 PYR cells was unchanged. The layer-specificity of these morphological alterations is intriguing since alterations in markers of GABA neurotransmission are particularly pronounced in DLPFC layer 3, and recent findings indicate that GABA inputs may regulate spine stability. Although many spines receive their excitatory synaptic inputs from corticocortical glutamate boutons, 15-30% of spines also receive synaptic input from GABA boutons. However, whether dendritic spine pathology in SZ reflects 1) fewer spines receiving only excitatory synapses, 2) a subpopulation of these spines receiving corticocortical input and/or 3) dendritic spines receiving both excitatory and inhibitory synapses is unknown
Methods: To distinguish among these possibilities, we used the following pre- and postsynaptic markers of dendritic spines: Vglut1, specific to excitatory terminals of cortical origin; spinophilin, protein phosphatase 1 binding protein that is highly concentrated in spines; PSD95 and gephyrin, scaffolding proteins for excitatory and inhibitory synapses, respectively. Using quadruple-label fluorescence immunohistochemistry and spinning disk confocal microscopy we quantified the relative density of the following subpopulations of spines: 1) spines solely receiving excitatory synapses (spinophilin+/PSD95+/gephyrin-); 2) spines receiving excitatory corticocortical input (Vglut1+/spinophilin+/PSD95+/gephyrin-); and 3) spines receiving both excitatory and inhibitory synapses (spinophilin+/ PSD95+/ gephyrin+). These analyses were conducted in deep layer 3 of the DLPFC from 20 matched pairs of SZ and healthy comparison subjects
Results: Our preliminary results indicate that all 3 subpopulations of spines are quantifiable in human DLPFC. We predict that mean density of spinophilin+/PSD95+ spines is lower in layer 3 in subjects with SZ and that the proportion of spines receiving GABA input is lower
Conclusion: These findings would support a preferential decrement in spines receiving GABA input, suggesting the idea that GABA dysfunction contributes to dendritic spine pathology in SZ
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ID: 2116655

IDENTIFYING IMAGING SIGNATURES OF NEUROPSYCHIATRIC AND NEURODEGENERATIVE DISORDERS VIA IMAGING PATTERN ANALYSIS AND MACHINE LEARNING

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Background: Neuropsychiatric and neurodegenerative disorders have been associated with anatomical changes in several brain regions. Computational anatomy and machine learning methods have enabled integration of complex imaging measurements into indices with high individualized sensitivity/specificity. They have also begun to elucidate heterogeneity of these anatomical phenotypes. This talk discusses the general principles of these methods, and presents examples of their diagnostic and predictive value
Methods: General principles of machine learning as a tool to integrate spatial imaging patterns into individualized indices of disease are presented, starting with the popular support vector machines. Examples from identification of structural imaging patterns for classification of schizophrenia (SCZ) and Alzheimer's Disease (AD) are presented. The use of AD-specific anatomical patterns is examined in separate populations, including mild cognitive impariment (MCI) patients, cognitive normal (CN) older adults, and Parkinson's Disease (PD) patients, revealing high predictive value of these patterns in terms of cognitive decline and clinical progression. Moreover, SCZ-like structural patterns are detected in unaffected family members of SCZ patients, pointing to endophenotypes of the disease. Finally, clustering methods are discussed in the context of characterizing the heterogeneity of these disorders, by investigating whether there is a single or multiple imaging signatures associated with disease, i.e. whether patient sub-populations display different neuroanatomical alterations
Results: Classification rates of ~80% for SCZ and ~90% for AD are achieved, thereby allowing us to build SCZ/AD-specific indices, which we call SPARE-SCZ and SPARE-AD scores. We evaluate the predictive value of SPARE-AD in MCI and PD patients, as well as in CN, and we find it to be highly predictive of future cognitive decline. We evaluate the SPARE-SCZ index in unaffected family members, who were found to have SPARE-SCZ scores in-between patients and controls, suggesting that SPARE-SCZ is capturing endophenotypic signatures of SCZ. Finally, using clustering and heterogeneity analysis, we identify 3 subtypes of brain atrophy in AD patients
Conclusion: Complex imaging patterns, revealed by machine learning, constitute neuroanatomical signatures of schizophrenia and AD, and can serve as important individualized biomarkers of the diseases. Moreover, these methods can reveal neuroanatomic heterogeneity in patient populations
ID: 2203513

PSYCHOTIC EXPERIENCES IN A POPULATION-BASED COHORT: CORRELATES WITH BRAIN STRUCTURE, FUNCTION AND CONNECTIVITY

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Background: The significance of psychotic symptoms experienced by young people in non-clinical populations is much debated. It is not known whether such experiences are related to underlying neurobiological processes similar to those in psychosis. We used MRI to study structural differences in the grey (GM) and white matter (WM), network connectivity and functional activation, in individuals with verified psychotic experiences (PE) and matched controls.
Methods: 252 subjects were selected from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, on the basis of the presence or absence of PE from interviews conducted at 17 years of age. At the time of scanning subjects were 20 years old.
A 3T GE HDx MRI system was used. Structural data were acquired with a high-resolution 3D-FSPGR sequence. HARDI data were acquired with a cardiac-gated EPI sequence with 60 gradient orientations. General linear model (GLM) analysis compared the PE and control groups while covarying for total brain volume. Fractional anisotropy (FA), axial diffusivity (AD) and radial diffusivity (RD) was derived from a corrected diffusion tensor imaging (DTI) model. FA, AD and RD were analysed using tensor based spatial statistics (TBSS). Additional tractography was carried out using the damped Lucy-Richardson algorithm.
Results: Voxel based morphometry (VBM) analyses revealed just one significant cluster of voxels with lower GM volumes in the left temporo-parietal junction in the PE group compared to controls. TBSS showed significant decreases in FA, AD and increases in RD in a white matter junction in the left medial frontal lobe when PEs were analysed along a continuum from none to those meeting clinical criteria for psychotic disorder. Seeding tracts from this region implicated the left cingulum and anterior thalamic radiation. fMRI during an n-back working memory task did not reveal differences between those with and without PEs. Connectivity analysis showed reduced efficiency and density globally as well as locally in the default mode network.
Conclusion: The results suggest that PEs unconfounded by medication and illness are associated with structural brain changes particularly in white matter and connectivity in areas relevant to higher cognitive functioning and self-processing. It appears that at this stage there is a degree of functional/physiological compensation although the longitudinal trajectory of such changes (and symptoms) is yet to be determined.
ID: 2100549

STRUCTURAL MRI STUDIES OF TREATMENT RESPONSE AND DISEASE PROGRESSION AFTER THE FIRST EPISODE OF PSYCHOSIS

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Background: Response to treatment and long-term outcome following the first-episode of psychosis are very heterogeneous, with only about 50% of patients responding to antipsychotics within 3-months, and approximately 30% developing an incapacitating illness course. Therefore, the early identification of individuals destined to have a worse illness course is of crucial importance, since it can reduce disability, healthcare costs, and eventually improve long-term outcome.
Methods: We used Magnetic Resonance Imaging in multiple datasets of patients scanned at their first psychotic episode (n=260) and followed up clinically for periods rangingfrom 3 months to 6 years. We estimated cortical morphology, grey matter volumes, and white matter integrity using volumetric, Support Vector Machine (SVM), Freesurfer and TBSS approaches in both single and combined datasets of brain maps obtained with SPM8.
Results: At onset, brain alterations of likely neurodevelopmental origin (reduced frontal and temporal gyrification and altered white matter microstructure of interconnecting tracts) were associated with poorer early outcome (all $p<0.05$ corrected); furthermore, smaller volumes were predictive of subsequent illness episodes with significant accuracy (70% correctly classified; $p=0.005$). However, brain changes were also observed after illness onset.

Among these, hippocampal volume increase (present in 29% of patients) was predictive of better clinical, functional and cognitive outcomes at 6 years (all p<0.03).
Conclusion: Distributed brain alterations are present already at illness onset and may be used to identify those individuals destined to a poorer outcome. However, other factors, such as medications, exposure to stress or to a different environment may contribute to brain changes that are in turn associated with better outcomes. It is crucial that we study what factors may affect brain plasticity and hence contribute to modifying illness trajectories.
ID: 2082759

1H MRS MEASUREMENT OF BRAIN GABA IN ANTIPSYCHOTIC-NAIVE FIRST-EPISODE PSYCHOSIS PATIENTS BEFORE AND AFTER 4 WEEKS OF ANTIPSYCHOTIC TREATMENT

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Background: Increased γ-Aminobutyric Acid (GABA) levels have been described in the medial prefrontal cortex (MPFC) of unmedicated patients with schizophrenia. Our current study sought to determine whether similar GABAergic abnormalities are also present in the precomissural dorsal-caudate of medication-naive first-episode psychosis (FEP) patients and the effect of antipsychotic treatment on GABA levels in the caudate and MPFC.
Methods: Twenty-seven antipsychotic-naive FEP patients and 20 age- and gender-matched controls were studied. Patients were treated with risperidone for 4 weeks with doses adjusted based on clinical judgment. Concomitant medications were not allowed and response to treatment was defined as a reduction of at least 25% on the total PANSS score after 4 weeks of treatment. GABA levels were obtained using the standard J-editing technique and expressed as peak area ratios relative to the unsuppressed voxel tissue water in the bilateral caudate and MPFC.
Results: Antipsychotic-naive patients showed higher levels of GABA in comparison with controls in the caudate (p=0.04) and in the MPFC (p=0.04). After antipsychotic treatment GABA levels decreased in both regions to similar levels than controls (caudate, p=0.35 and MPFC, p=0.94). Twenty-two patients responded to treatment and 5 did not respond. Responders and not responders showed similar GABA levels in the caudate (p=0.70) and MPFC (p=0.21).
Conclusion: Our results suggest that GABA elevations seen in FEP before treatment normalize after 4 weeks of antipsychotic treatment. While the comparison between responders and non-responders suggests that GABA is normalized regardless of the clinical response, a larger sample of not responders is required to confirm the results.
ID: 2118960

IS INCREASED GLUTAMATE IN THE ASSOCIATIVE STRIATUM A RELIABLE BIOMARKER IN ANTIPSYCHOTIC-NAÏVE FIRST-EPISODE PSYCHOSIS PATIENTS?

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Background: Increased glutamate levels have been described in the associative striatum (precommissural dorsal caudate) of antipsychotic-naïve first-episode psychosis (FEP) patients. This increase has been reported by our group in two previous independent cohorts, and longitudinally, we have also reported that glutamate normalized after clinically effective antipsychotic treatment with risperidone. The biomarkers in psychiatry have been challenging. Therefore, the current study was aimed to replicate, in a new cohort of antipsychotic-naïve FEP individuals, the increased striatal glutamate levels in comparison to age- and sex-matched healthy controls.
Methods: Twenty-nine antipsychotic-naïve FEP patients and 28 age- and sex-matched controls were included. All participants underwent a proton magnetic resonance spectroscopy scan performed in a 3T scanner using point-resolved spectroscopy (TE=35ms) centered on the right precommissural dorsal caudate. Water-suppressed spectra were analyzed using LCModel (version 6.3e) and glutamate levels were corrected for the proportion of cerebrospinal fluid in the voxel.
Results: FEP patients showed higher levels of glutamate compared to the control group (t= 3.7, p<0.001; Cohen's d effect size=1.05).
Conclusion: The present study replicates the results of two previous cohorts including antipsychotic-naïve FEP patients, supporting the notion that increased glutamate in the associative striatum is a reliable biomarker. Our results still require replication by other groups and may provide a framework to discuss the potential mechanism and clinical implication of striatal glutamate normalization after antipsychotic treatment.
ID: 2118968

MULTI-ATLAS BRAIN MASKING FOR MRI ANALYSIS IN CONTROLS AND SCHIZOPHRENIA: COMPARISON WITH OTHER MASKING TECHNIQUES AND MANUAL MASKING

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Background: Brain Masking separates brain from surrounding tissue and its accuracy is important to further imaging analyses. Many automated masking techniques are inaccurate and manual masking (MM) is extremely time consuming. We implemented a new brain masking technique based on multi-atlas brain segmentation (MABS). We compared MABS to masks generated using FreeSurfer (FS; version 5.3), Brain Extraction tool (BET), and Brainwash, with MM as the gold standard. MRIs of healthy (HC) and schizophrenia (SZ) subjects were assessed using different brain masking techniques. Further, volumes of 10 cortical and 4 subcortical regions, and total gray matter volume, were compared, after using the different masking techniques.
Methods: Images were acquired on a 3-Tesla MR Echospeed system General Electric scanner on age-, sex-, IQ- matched HC (5) and SZ (5) subjects. Automated masks were generated from MABS, FS, BET, and Brainwash, and compared to MM. Four metrics were used to compare the accuracy of the masking tools: a) volume difference from manual masks; b) number of masks where volume differed more than 3% from MM; c) Dice coefficient (an overlap measure) to MM; and d) Intra-class correlation coefficients.
Results: Mean volume difference between MABS and MM masks was significantly lower than the difference between FS masks or BET masks and MM masks ($p<0.01$ for both comparisons). A 3 % volume difference cut-off from MM showed that 10/10 FS masks, 9/10 BET masks and none of MABS masks, differed by >3% from MM's volumes [Fisher test; $p<0.001$ for both comparisons]. Dice coefficient of MABS-MM (0.997 ± 0.002) was significantly higher than that of FS-MM (0.93 ± 0.02; $p=0.001$), BET-MM (0.97 ± 0.006; $p=0.04$), or Brainwash-MM (0.85 ± 0.13; $p=0.04$). For subcortical and left cortical regions, MABS was closer to MM than BET or FS. In the right, MABS was closer to MM than BET.
Conclusion: Brain masking is an essential preprocessing step to many further image analyses and it is important that they be accurate. The gold standard of MM is time and labor intensive (as long as 8 hours). Improvement in accuracy and time to create masks is thus critically important, particularly in large-scale studies. Our findings show that FS, BET, and Brainwash masks are rapidly obtained and inexpensive, but are less accurate than MM. MABS masks, in contrast, resemble more closely the gold standard of the MM, offering a viable alternative, and, if needed, can be edited to MM in under 30 minutes.
ID: 2117752

EVIDENCE FROM IMAGING STUDIES FOR OXIDATIVE STRESS MECHANISMS IN FIRST EPISODE SCHIZOPHRENIA

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Background: During brain development of mice with genetically impaired glutathione (GSH) synthesis (gclm ko), redox dysregulation leading to oxidative stress, induces alterations of prefrontal cortex interneurons and myelin formation. In patients such mechanisms play an important role in the emergence of schizophrenia. We have reported that a GAG trinucleotide repeat polymorphism in the key GSH synthesizing gene gclc is associated with the disease and with a decreased GSH synthesis in patients fibroblasts.
Methods: Magnetic resonance spectroscopy (MRS) and diffusion spectrum imaging (DSI) in first episode patients and diffusion tension imaging (DTI) in gclm ko mice.
Results: We now show by MRS that this "high-risk gclc" genotype predicts a decreased GSH levels in medial prefrontal cortex (mPFC). Furthermore, in healthy controls, multimodal brain imaging (MRS & DSI) revealed a positive association between mPFC GSH levels and both white matter integrity (as estimated by gFA) and resting-state functional connectivity along the cingulum bundle. In early psychosis patients, only white matter integrity was correlated with GSH levels. gFA was also decreased in fornix/fimbria of both gclc ko mice and early psychosis patients, where it correlated positively with hippocampal volume. Interestingly, the oxidation status in blood cells (ratio of enzymatic activity of GSH peroxidase to reductase) was associated with smaller hippocampal volume in early psychosis patients. On the other side, in the prefrontal cortex of peripubertal gclm ko mice, mature oligodendrocyte numbers, as well as myelin markers, were decreased. At the molecular levels, under GSH-deficit conditions induced by shRNA targeting gclc, oligodendrocyte progenitors showed a decreased proliferation mediated by an upregulation of Fyn kinase activity, reversed by either the antioxidant N-acetylcysteine or Fyn kinase inhibitors. In addition, oligodendrocyte maturation was impaired. Interestingly, the regulation of Fyn mRNA and protein expression was also impaired in fibroblasts of patients deficient in GSH synthesis.
Conclusion: GSH and redox regulation have a critical role in myelination processes and white matter maturation in the prefrontal cortex of rodent and human, a mechanism potentially disrupted in schizophrenia.
ID: 2083319

FRONTAL FASCICULI AND PSYCHOTIC SYMPTOMS IN ANTIPSYCHOTIC-NAÏVE SCHIZOPHRENIA BEFORE AND AFTER SELECTIVE DOPAMINE D2/3 RECEPTOR BLOCKADE

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Background: Positive psychotic symptoms are core clinical features of schizophrenia. A recent hypothesis proposes that psychotic symptoms stem from irregularities in myelination of white matter (WM) tracts projecting into the frontal cortex. We investigated WM integrity in first-episode antipsychotic-naïve schizophrenia patients and healthy controls before and after selective dopamine D2/3 receptor blockade.
Methods: Thirty-eight patients (25.9 ± 6.5 years) and 38 matched controls (25.8 ± 6.4 years) underwent baseline examination with 3T MRI diffusion

tensor imaging and clinical assessments. Voxelwise group differences of fractional anisotropy (FA) were assessed using tract-based spatial statistics (TBSS). Subsequently, patients underwent 6 weeks of antipsychotic monotherapy with amisulpride (mean dose: 262 ± 177 mg). Twenty-eight patients and 28 healthy controls were re-examined.
Results: At baseline, whole brain TBSS analyses revealed lower FA in patients in right anterior thalamic radiation (ATR), right cingulum, right inferior longitudinal fasciculus and right corticospinal tract (CT). Region of interest analyses showed that positive symptoms were significantly associated with FA of frontal fasciculi, specifically right arcuate fasciculus and right superior longitudinal fasciculus.
At re-examination, all correlations between positive symptoms and frontal fasciculi had resolved. FA in ATR increased significantly more in patients than in controls. Amisulpride dose correlated positively with FA changes in right CT.
Conclusion: Antipsychotic-naïve schizophrenia patients displayed subtle deficits in WM integrity. As predicted, psychotic symptoms appeared specifically associated with the integrity of frontal fasciculi. Six weeks of selective dopamine D2/3 receptor antagonism normalized WM integrity possibly by remyelination. Further research on frontal fasciculi and psychosis is encouraged.
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ID: 2083029

MEASURING GABA WITH MRS: METHODOLOGY AND PITFALLS

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Background: The inhibitory neurotransmitter GABA is increasingly being targeted for MRS studies of inhibitory function in schizophrenia; this symposium will introduce the methods used for measuring GABA, and some pitfalls and limitations.
Methods: The MR spectrum of GABA is heavily overlapped by resonances from other metabolites. Acquisition strategies center around separating these signals by either: acquisition optimization to minimize overlap; removing overlying signals by spectral editing; reducing overlap by adding a second dimension. Each approach has drawbacks, including limited separation of GABA signals from other signals at the same frequency and robustness to movement, and different artifacts that can occur. As the most widely used experiment, discussion will focus on the strengths and limitations of MEGA-PRESS, including limited sensitivity (requiring large voxel acquisitions), co-editing of macromolecules (MM), and sensitivity to movement and scanner instability. MM contamination can be addressed experimentally, but at the expense of increased sensitivity to instability. Various post-processing and quantification tools are available (including LCModel and Gannet). The concentration of GABA differs between gray and white matter and CSF. Both CSF correction and GM correction have been proposed to account for differing voxel compositions; we will introduce a new GM/WM correction. MEGA-PRESS is implemented as a modification of vendor-delivered PRESS sequences, which impacts the editing efficiency and expected lineshape of edited signals. We discuss the extent to which it is possible to compare GABA measurements between scanners, vendors, studies and brain regions.
Results: Frequency-and-phase correction of edited data substantially improves the robustness of MEGA-PRESS editing to frequency drift and subject movement. Different implementations of the MEGA-PRESS sequence give different edited lineshapes in phantom and in vivo. Measurements can be compared between scanners and implementations by accounting for differences in editing efficiency of GABA and co-editing contamination of MM. GM/WM correction outperforms either CSF correction or GM correction in accounting for voxel segmentation differences.
Conclusion: MRS provides a robust measurement of GABA that is physiologically interesting, especially in the pathological trajectory of schizophrenia. Interpretation of studies is dependent on a working knowledge of the strengths and limitations of the methodology
ID: 2090364

GENETIC VARIATION IN THE TRANSLOCATOR PROTEIN NEUROINFLAMMATION MARKER AND EFFECTS ON BRAIN STRUCTURE

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Background: The translocator protein (TSPO) is up-regulated in activated microglia and may be a marker for neuroinflammation. Recent studies have found that TSPO and its ligands affect processes related to inflammation that are implicated in the etiopathology of neuropsychiatric disorders. The TSPO rs6971 polymorphism results in a change in protein structure that determines TSPO ligand binding in the brain; however, no study has examined the consequence of this variation on MRI-based neuroimaging phenotypes.
Methods: 134 healthy individuals (age range 18-86) underwent MRI-based neuroimaging and genetics protocols. T1-weighted images were processed using the CIVET pipeline for vertex-wise thickness analyses. To quantify white matter microstructure using DTI, whole brain tractography was performed. Ten fronto-temporal tracts were manually extracted and mean FA values along the fiber were calculated. All subjects were genotyped directly for TSPO rs6971, and two SNPs in APOE (rs7412 and rs429358). Linear regression was used to evaluate the effect of TSPO genotype on average regional cortical thickness and average tract FA, co-varying for age, sex, APOE ε4 status, ethnicity, and handedness. Age by genotype interaction terms were also tested.
Results: Cortical thickness analysis found no significant association of TSPO genotype with any region when controlling for age. However, age by genotype interactions significantly predicted bilateral parietal (left, pcor=0.003; right, pcor=0.024) and left frontal (pcor=0.028) cortical thickness, whereby High Affinity Binders had thinner cortex at younger ages, but thicker cortex at older ages, when compared to Low Affinity Binders and Medium Affinity Binders. No significant main effects or interactions were observed for TSPO genotype and white matter tract FA (all pcor>0.1).
Conclusion: We found age-dependent effects of the functional TSPO variant on cortical brain structure. Previous studies in PET imaging show up to 30 percent differences in TSPO ligand binding based on this marker. Our findings provide important complementary evidence by demonstrating the effects of this functional variant on frontal and parietal cortical structure and thus providing a potential risk mechanism for schizophrenia and other severe mental illnesses. Neuroinflammatory effects indexed by this variant, as well as neurotherapeutic effects of TSPO itself may be age-dependent, which is consistent with some animal studies, and requires further investigation.
ID: 2086277

PSYCHOTIC EXPERIENCES ARE ASSOCIATED WITH REDUCED CORTICAL THICKNESS IN A LARGE COMMUNITY SAMPLE OF CHILDREN AND ADOLESCENTS

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Background: Psychotic experiences (PE) have been associated with a higher severity of general psychopathology measures, comorbid psychiatric diagnoses and suicide in adolescents. It has not been investigated if PE are associated with brain structures changes during neurodevelopment. Herein we investigate if PE are associated with cortical thickness among children and adolescents in a large community sample.
Methods: 720 subjects aged 6-14 year-old were recruited from a large community school based study, none presented a psychotic diagnosis. Parents were assessed with the Well-Being Assessment (DAWBA) and the Child Behavior Checklist (CBCL) to evaluate the diagnosis and measure general psychopathology, to measure PE we have developed a CBCL-psychosis subscale from the 112 questions, which included 7 psychotic experiences such as hearing voices, feeling observed and disorganized behavior. We evaluated the association of PE (measured by the CBCL-psychosis subscale) with the presence of any psychiatric diagnoses using a logistic regression model. High-resolution T1 images were acquired in 1.5T scanners. Images were processed using freesurfer software. The CBCL-psychosis total score was correlated with measures of cortical thickness. Random field theory was used to correct for multiple testing in vertex-wise analyses (height and extent threshold: $p < 0.05$).
Results: The mean age of the sample was 10.6 years (sd=1.9), 53,9% were male, 56.5% did not report any PE. There were no age or gender differences between the groups presenting PE or not. The group that reported one or more PE presented 5.2 times higher chance of having any psychiatric diagnosis ($p<0.001$; ExpB=5.2 95% CI 3.6-7.5). Clusters of cortical thickness measures localized in the right prefrontal and temporal cortices showed a significant negative correlation with CBCL-psychosis. Conversely, we found a positive correlation between PE and the occipital cortices bilaterally.
Conclusion: We found that higher CBCL psychosis scores were associated with cortical thickness reduction; more pronounced in frontal and temporal cortices, regions traditionally related to psychotic diagnosis in adults. Interestingly, the correlations with the occipital cortices worked in an opposite direction. Our findings of PE associated with brain changes may indicate subtle deviant brain maturation processes that may represent risk for several disorders. This hypothesis will be addressed in a follow-up study that we are conducting with this sample.
ID: 2118038

EOTAXIN SERUM LEVELS IS INCREASED IN PATIENTS WITH SCHIZOPHRENIA AND CORRELATED WITH LENGTH OF DISEASE, VERBAL MEMORY PERFORMANCE, AND HIPPOCAMPUS AND FRONTAL CORTEX SIZES.

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Background: A particular chemokine, called eotaxin, increases with age in both humans and rodents. Clinical studies have shown increased eotaxin in individuals with chronic SZ; and that eotaxin serum levels were inversely correlated to the performance in a working memory test. Besides that, our group has found differences in eotaxin serum levels compared to controls in chronic patients with SZ but not in individuals with SZ at recent onset. The objective of this study was to investigate the possible differences in eotaxin serum levels between patients with SZ and controls; and its possible correlation with hippocampus and frontal cortex volumes, length of disease and verbal episodic memory performance.
Methods: Sixty-two subjects were enrolled; thirty-five patients with SZ and 27 controls matched for age, gender and level of education. All subjects had 10mL of peripheral blood collected for eotaxin measument by sandwich-ELISA. They were assessed with the Hopkins Verbal Learning Test - Revised (HVLT-R) for verbal learning measures. Images were acquired at Philips Achieva 1.5T MRI scanner. Images were processed using the automated pipeline of FreeSurfer v5.1. Intracranial volume was regressed out from hippocampus and frontal cortex volumes.
Results: Eotaxin serum levels were increased in patients ($p=0.001$); total hippocampus ($p<0.0001$), total frontal cortex size ($p<0.0001$) and HVLT-R immediate free recall scores ($p<0.0001$) were decreased in patients. There were negative correlations in a linear regression model between total hippocampus size ($p=0.002$, $r=-354$), total frontal cortex size ($p=0.018$, $p=-268$), HVLT-R scores ($p=0.004$, $r=-333$) and eotaxin levels. There was a positive correlation between length of disease and eotaxin serum levels ($p=0.004$, $r=0.446$).
Conclusion: Supporting the hypothesis that SZ is associated with a pro-inflammatory activation, this study importantly suggests that higher levels of serum peripheral eotaxin are increased in patients and is correlated to hippocampus and frontal cortex sizes, verbal memory performance and length of disease. This is probably related to a greater inflammatory activation, impaired functionality, increased mortality, and to other clinical diseases that overlap in patients with SZ. It also would suggest that the broad impairment seen in individuals with SZ would be associated with an accelerated aging process.
ID: 2119455

ARE THERE CUMULATIVE OR INTERACTIVE EFFECTS OF NEURODEVELOPMENTAL DEVIATIONS ON COGNITIVE CONTROL DEFICIT IN FIRST EPISODE SCHIZOPHRENIA?

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Background: Neurological soft signs (NSS) (Bombin Schizo Bull 2005; Gay Schizo Bull 2013), mixed-handedness (Deep-Soboslay Brain 2010; Katsanis Am J Psych 1989), ventricle/sulcal enlargement (Gilmore Am J Psych 2010; Rais Psychol Med 2012) and symmetrical sulcation of the anterior cingulate cortex (ACC) (Cachia Dev Cog Neurosc 2014; Clark Schizo Res 2010) are clinical and radiological markers of early neurodevelopmental deviations that have been independently associated with cognitive impairment in schizophrenia: the aim of this study was to test the cumulative or interactive effects of these factors on cognitive control (CC) in schizophrenia.
Methods: 41 first-episode schizophrenia-spectrum patients were recruited and underwent a structural Magnetic Resonance Imaging (MRI). CC efficiency was evaluated from TMT A and TMT B tasks and derived scores (Perianez Arch Clin Neuropsych 2007). NSS were assessed using Krebs' standardized 23-item scale (Krebs Schizo Res 2000). Handedness was assessed using the Edinburgh Handedness Inventory. The ACC sulcal pattern was manually classified using Yucel's 3-level nomenclature: no paracingulate sulcus (PCS), present PCS and prominent PCS (Yucel Biol Psych 2002). Ventricle/sulcal enlargement was assessed from the ratio between ventricle and sulcal CSF volume and total intracranial volume. Linear models were used to test the effects of NSS, mixed-handedness, ACC sulcal pattern and ventricle/sulcal enlargement on TMT scores, adding age and educational level as confounding covariates.
Results: There was a significant main effect of ACC sulcal pattern asymmetry on TMT B - TMT A ($p = 0.04$) along with significant interactions

between ACC sulcal pattern and NSS and between ACC sulcal pattern and ventricle size ($p < 0.006$).
Conclusion: Our study provides the first evidence of interactive effects of different neurodevelopmental markers on CC efficiency in schizophrenia. Effects of treatment and illness duration were limited by the study design involving only first-episode patients. Such findings is in line with the neurodevelopmental model of schizophrenia and support the notion that CC impairments in this disorder may be the final common pathway of complex early neurodevelopmental mechanisms.
ID: 2090052

HIPPOCAMPAL SUBFIELD VOLUMES IN PATIENTS WITH SCHIZOPHRENIA AND THEIR UNAFFECTED FIRST-DEGREE RELATIVES

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Background: Hippocampal volume reductions are commonly found in schizophrenia. This study attempted to determine whether hippocampal subfield abnormalities were associated with age and cognitive function in patients with schizophrenia and their unaffected first-degree relatives.
Methods: High resolution T1-weighted MRI scans were acquired using a 3 T Siemens scanner from 106 patients with schizophrenia (mean age, 45.78 ± 10.95 years; range, 22-72), 50 unaffected first-degree relatives (mean age, 58.30 ± 12.34; range, 24-80), and 86 healthy controls (mean age, 46.68 ± 15.44 years; range,22-77). Imagines were processed by Freesurfer 5.3.0. A set of cognitive tests were administrated to all the subjects, including short-form of IQ, visual reproduction, logical memory, spatial working memory, and verbal fluency
Results: Age-associated hippocampus subfield volume reductions were found among patients with schizophrenia, unaffected first-degree relatives, and healthy controls. However there was no significant interaction between aging and group on any subfield volumes. Further ANCOVA analyses controlling for intracranial volume, age, and gender showed that patients with schizophrenia demonstrated significantly smaller bilateral presubiculum (left, $p=2.32 \times 10^{-7}$; right, $p=7.90 \times 10^{-4}$) and subiculum (left, $p=2.20 \times 10^{-6}$; right, $p=3.02 \times 10^{-6}$) than healthy controls. No significant differences were observed between unaffected first-degree relatives and healthy controls. Linear regression results also indicated that smaller left presubiculum significantly predicted delay visual reproduction ($\beta=0.195$, $p<0.05$), whereas smaller right subiculum significantly predicted spatial working memory search errors ($\beta=-0.196$, $p<0.05$) in patients with schizophrenia.
Conclusion: The current findings suggested that hippocampal abnormalities were only demonstrated in patients with schizophrenia but not their unaffected first-degree relatives. These abnormalities were indispensible of age.
ID: 2118725

EFFECTS OF DOPAMINE D2 RECEPTOR BLOCKADE ON MULTIMODAL DISTURBANCES IN ANTIPSYCHOTIC-NAÏVE FIRST-EPISODE SCHIZOPHRENIA PATIENTS

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Background: The influence of antipsychotics on brain abnormalities and the characterization of predictive markers for treatment outcome are key questions in schizophrenia research. We have studied the effects of striatal and extrastriatal dopamine D2-receptor blockade on multimodal disturbances in never previously medicated schizophrenia patients - and further related outcome to baseline D2 receptor binding potentials (BPND).
Methods: Two comparable cohorts of antipsychotic-naïve first-episode schizophrenia patients went through psychopathological, cognitive, MRI, and SPECT examinations. Patients in cohort A (N=25) were scanned with SPECT using the D2/3-receptor ligand [123I]epidepride for assessment of extrastriatal receptors before and after 3 months of treatment with risperidone or zuclopenthixol. Striatal D2/3-receptors were assessed with 123labeled iodbenzamid (cohort B; N=66) before and after 6 weeks of treatment with amisulpride. The examination program also included a variant of the monetary incentive delay task (fMRI). Not all patients went through all examinations.
Results: The data suggest that high frontal and low baseline striatal BPnd are associated with the effect of D2 blockade on positive symptoms. Normalization of reward abnormalities was linked to D2 blockade in the responders. Cohort A data further suggest a possible protective effect of D2 blockade on cortical gray matter volumes whereas cohort C data suggest a normalization of subtle deficits in white matter integrity after treatment. In contrast, all associations between extrastriatal occupancy and cognition as well as function were negative. The data represent work in progress.
Conclusion: The data do not support a detrimental effect of D2 blockade on cortical volumes, but point to an increase in white matter integrity. Taken together with our previous data showing an association between high doses and increased hippocampal volume loss, this would imply that the effects of D2 blockade depend on the dose and the region. Confirmation of a connection between normalization of salience abnormalities and D2 blockade validate preclinical findings of a connection between dopamine activity and reward. In contrast to the beneficial effects of blockade on reward abnormalities and differentiated effects on bran volumes, we observed detrimental effects on cognition and function. Compared to the potential predictive value of baseline D2 receptor BPnd, this stress the importance of an individualized response to D2 blockade.
ID: 2117498

STRUCTURAL MRI IN FIRST EPISODE PSYCHOSIS: AN INTERNATIONAL COLLABORATIVE MEGA-ANALYSIS OF INDIVIDUAL ADULT PATIENT DATA

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Background: The aim of this study was to examine regional brain structures in individuals with First Episode Psychosis (FEP) compared to healthy subjects by conducting an international collaborative mega-analysis. Thus, we were able to adjust for between-study differences, enabling us to compare regional brain measurements of individuals with FEP to those of healthy

controls, whilst co-varying for relevant confounds, not possible in conventional meta-analysis.
Methods: Published brain volumetric studies were identified through systematic database searches for articles published between 1980 and 2013. Consequently 43 international research groups who had employed robust methodology in MRI data acquisition in relation to individuals with FEP or healthy subjects were invited to participate in this study. MRI and clinical data (e.g. age, gender, duration of untreated psychosis, psycho-active substance use, age of onset of illness, diagnosis, medication usage) was provided by 24 international research groups on 1095 individuals with FEP and 1024 healthy subjects. Statistical analysis was undertaken utilising linear mixed effects regression models, with study centre, gender, age and additional factors including intracranial volume included n the model.
Results: Brain regions with reduced volume in individuals with FEP compared to healthy subjects included the cerebrum, total brain grey matter, total brain white matter, hippocampus, thalamus and orbitofrontal cortex (all $p < 0.01$) with increased volume of the lateral ($F = 4.725$, $p = 0.03$) and third ventricles demonstrated ($F = 22.868$, $p < 0.001$). These results remained when controlling for cerebral hemisphere or intracranial volume and were of the same or greater magnitude when we compared individuals with schizophrenia alone to healthy subjects. Cannabis use was associated with reduced hippocampal volume in individuals with FEP. No association was found between any regional brain volumes and duration of psychosis or duration of untreated psychosis.
Conclusion: Similar to meta-analyses of aggregate data, we demonstrated that individuals at their first episode of psychosis have several brain abnormalities compared to healthy controls, including reduced volume of the hippocampus and total brain grey matter and increased ventricular volume. Cannabis use was associated with more significant reductions of the hippocampus in individuals with FEP and its use may be associated with additional deleterious structural brain abnormalities.
ID: 2095241

REDUCED WHITE MATTER INTEGRITY IN A MULTISITE LONGITUDINAL STUDY OF YOUTH AT RISK FOR PSYCHOSIS

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Background: Individuals with schizophrenia show alterations in white matter microstructure suggestive of disrupted structural connectivity. Whether this plays a role in psychosis onset is not yet clear. Diffusion tensor imaging (DTI) studies have tentatively revealed alterations in white matter microstructure in individuals at clinical high risk (CHR) for psychosis. However, these studies have generally included small sample sizes and produced inconsistent results. In the present study, we tested white matter integrity across the primary tracts using subjects from the North American Prodrome Longitudinal Study (NAPLS), a large multisite study designed to identify factors associated with risk for and onset of psychosis.
Methods: 468 individuals meeting CHR criteria and 207 healthy controls (HC) underwent a DTI scanning protocol. Of the CHR subjects, 55 subsequently converted (CONV) to a full psychotic disorder within a 24-month follow-up period. Whole brain voxel-based analysis using Tract Based Spatial Statistics (TBSS) was performed on fractional anisotrophy (FA). In addition, white matter tract regions of interest were extracted from the TBSS skeleton for tract-specific comparisons. Group differences in these measures were tested. 123 HC, 212 CHR and 31 CONV individuals also underwent follow-up DTI acquisition.
Results: Group differences in FA between CHR and HC were found in both the body ($F(1,661)=9.195$, $p=.002$) and the genu ($F(1,661)=7.542$, $p=.006$) of the corpus callosum as well as in the fornix ($F(1,661)=5.515$, $p=.02$). Across all individuals, there was a significant correlation between age and increasing FA values ($r(666)=.1317$, $p=.0006$). Moreover, there were significant group by time interactions for change from baseline to follow-up in regions including the corpus callosum ($F(2,322)=5.293$, $p=.004$) and superior corona radiata ($F(2,322)=5.509$, $p=.004$), such that CONV showed a smaller magnitude of increase in FA over time compared with the other groups.
Conclusion: Individuals at risk for psychosis demonstrate reduced white matter integrity in multiple regions of the brain that have previously been implicated in schizophrenia, including the corpus callosum and the fornix. More importantly, the rate of increase in FA over time is reduced in CHR cases who convert to psychosis, suggesting that the factors involved in onset of psychosis are associated with a disruption in the normal developmental increases in myelination in the peri-adolescent period.
ID: 2083088

LONGITUDINAL STUDY OF HIPPOCAMPAL SUBFIELD VOLUMES IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Volume deficits of the hippocampus and its subfields have been found in schizophrenia and bipolar disorder, which share phenomenological and familial overlap. However, the comparative trajectories of hippocampal subfield volumes in schizophrenia and bipolar disorder are unknown. Here we sought to determine whether there are differential progressive subfield volume deficits in schizophrenia and bipolar disorder over time.
Methods: A longitudinal magnetic resonance imaging study of three demographically matched cohorts that included 34 patients with schizophrenia, 14 patients with bipolar disorder and 41 healthy controls (mean age of 30.9 ± 9.1, 32.3 ± 7.6, 31.6 ± 9.3 years and mean follow-up of 4.5, 3.8 and 5.3 years respectively) was performed. A new and automated algorithm

(based on a computational atlas constructed from ultra-high resolution images from 15 autopsied hippocampal tissue) was used to label the subfields. Linear mixed effects modeling—with diagnosis, time, diagnosis and time interaction, intracranial volume, age, years of education, duration of psychosis and medication as fixed effects, and individual variability in baseline volumes and atrophy rate as random effects—was used to test for diagnostic differences in subfield volume change over time.
Results: In the right hemisphere, the volumes of the granule cell layer (GCL), CA4, CA3, CA1, molecular layer (ML) and subiculum—but not the tail—decreased at a greater rate in schizophrenia and bipolar patients, when compared to healthy controls ($p<.01$). In the left hemisphere, the volumes of GCL, CA3, CA1 and ML decreased at a greater rate in schizophrenia patients when compared to healthy controls ($p<.01$). Further, schizophrenia patients compared to bipolar patients showed greater atrophy in left CA3 ($p<.05$). Post-hoc, atrophy of subfields in the right hemisphere of both schizophrenia and bipolar groups broadly correlated with illness severity: significant correlations included GCL, CA1, CA3 and ML with negative symptom severity, and subiculum with declining psychosocial functioning.
Conclusion: Progressive volume deficits in subfields of the right, anterior/mid-body hippocampus were found in both schizophrenia and bipolar disorder, which broadly correlated with measures of illness severity. Atrophy of the left hippocampal subfields was found only in schizophrenia. These findings add to data that potentially clarify specific versus cross diagnostic neurobiological changes underlying psychotic spectrum disorders over time.
ID: 2084385

BIOTYPES VS. DSM DIAGNOSES: DO GRAY MATTER VOLUME BIOMARKERS SUPPORT NOVEL BIOLOGICALLY-DRIVEN DISEASE DEFINITIONS?

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Background: Current definitions of psychotic illness lack neurobiological mechanisms and don't map onto emerging biomarkers. An alternative strategy aiming to capture more homogeneous biologically-driven groups of cases is multivariate biomarker analysis carried out on the entire psychosis dimension independent of categorical diagnoses. Based on this approach, we examine gray matter volume (GMV) characteristics across two constructs: biotypes, the psychosis groups derived from cognitive and neurophysiologic biomarkers vs. DSM diagnoses.
Methods: The biotypes were developed based on stepwise multivariate analyses (PCA, unsupervised clustering, canonical discriminant analysis) of cognitive and neurophysiologic measures in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) sample. GMV measures from 3T T1-w images were extracted in SPM8/VBM8/DARTEL and contrasted by biotype vs. DSM diagnosis.
Results: Biotypes (n=1,409): Compared to healthy controls (HC), biotype1 (B1) probands had diffuse cortical/subcortical GMV reductions as well as most impaired cognitive and sensorimotor function; B2 probands showed lesser and more localized GMV reductions, impaired cognitive function and exaggerated sensorimotor reactivity; B3 probands had near normal GMV consistent with normal cognitive and sensorimotor characteristics. B1 relatives showed GMV reductions similar to their probands but less extensive; B2 relatives had posteriorly distributed GMV loss (cerebellum, occipital lobe); whereas B3 relatives had normal GMV. DSM diagnoses (n=1,681): Compared to HC, schizophrenia (SZ) and schizoaffective (SAD) probands had extensive and overlapping GMV loss in numerous cortical/subcortical regions, whereas psychotic bipolar-I (BDP) probands showed small clusters of GMV reduction in fronto-temporal, cingulate, and insular cortices. Similar but less extensive GMV changes were seen in SZ and SAD relatives; in contrast, BDP relatives had normal GMV. The distribution of DSM diagnoses poorly mapped onto biotypes.
Conclusion: Our findings support partially divergent brain structure biomarkers for SZ/SAD (diffuse cortical/subcortical GMV loss) vs. BDP (small localized GMV reductions in fronto-temporal limbic regions). Re-slicing this psychosis sample into biomarker-driven groups-biotypes-captures more homogenous clusters of proband/relative cases characterized by consistent cognitive, sensorimotor, and GMV characteristics, largely independent of DSM diagnoses.
ID: 2082342

A LONGITUDINAL STUDY OF CORTICAL THICKNESS AND SURFACE IN ANTIPSYCHOTIC-NAÏVE FIRST-EPISODE SCHIZOPHRENIA PATIENTS: THE IMPACT OF NEUROCHEMICAL DISTURBANCES AND COGNITIVE DEFICITS.

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Background: It is presumed that a subgroup of patients who suffer from progressive brain tissue loss, may be linked to glutamatergic and dopaminergic disturbances and cognitive deficits, and is characterized by poor treatment response and functional outcome. In the present multimodal study, we will investigate cortical thinning and reduced surface area in two large longitudinal cohorts of initially antipsychotic-naïve first-episode schizophrenia patients and matched healthy controls.
Methods: Using high-resolution 3D T1 weighted structural images, acquired from a 3 Tesla MR scanner, measurements of the cortical thickness and surface area will be conducted using an automated surface-based analysis (FreeSurfer). In an already finished cohort, patients have undergone SPECT using the ligand [123benzoamid] for estimation of D2/3 receptors in the striatum and in an ongoing cohort; the patients undergo 1H-MRS (PRESS and MEGA-PRESS) for two voxels positioned in the dorsal anterior cingulate cortex (dACC) and the left thalamus. Current and premorbid IQ will be obtained from a neurocognitive battery including WAIS-III and DART. All examinations are performed before and after 6 weeks (and again after 6 months) of treatment with aripiprazole, a partial D2 agonist.
Results: Ten patients and 4 controls have been included since January 2014, and 8 patients and 4 controls have gone through 6 weeks follow-up, and 5 patients and 1 control have gone through 6 months follow-up (by August 2014). We expect to include 40 patients and 40 controls by the end of 2016.
Conclusion: It is expected that a reduced cortical thickness and surface area at baseline is related to glutamatergic disturbances and low premorbid and current IQ. Progressive cortical thickness reductions and poor treatment response are expected to be correlated to glutamatergic disturbances in the dACC and left thalamus and a high D2/3 receptor binding potential (believed to reflect decreased endogenous levels of dopamine) in the

striatum. Cortical surface is expected to be relatively stable over time and correlated to premorbid IQ measured at baseline.
ID: 2076938

INFLAMMATION IN THE BRAIN OF EARLY ONSET SCHIZOPHRENIA: AN IN-VIVO STUDY

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Background: There is increasing evidence that neuroinflammation is associated with schizophrenia. Increased expression of the translocator protein 18 kDa (TSPO) occurs in glial cells in response to neuroinflammation or brain injury and can be measured in vivo using the PET ligand (R)-[11C] PK11195. The aim of this study was to examine regional (R)-[11C]PK11195 binding potential (BPND) in the early stage of schizophrenia.
Methods: The subjects included in this study were 29 patients with schizophrenia and 27 age- and sex-matched healthy controls. Dynamic 60 minutes (R)-[11C]PK11195 scans were acquired using a Philips Gemini TF PET/CT scanner and Siemens ECAT EXACT HR+ scanner. BPND images were obtained using receptor parametric mapping and supervised cluster analysis to derive the reference tissue input function (1,2). Subsequently, gray matter regions of interest were delineated on a T1-weighted structural MRI scan using an automatic probabilistic procedure, resulting in the following regions: frontal, temporal, and parietal cortex, striatum, thalamus, and total gray matter. Multivariate analysis of variance (MANOVA) was used to test for differences in BPND between patients and healthy controls with group as between-subjects factor and region of interest as within-subjects factor.
Results: Patients had been ill for a mean (SD) duration of 1.7 (1.5) years. In general, the binding potentials were mildly increased in all regions of interest. Significantly higher (R)-[11C]PK11195 BPND was seen in the total gray matter, which was most prominent in the temporal cortex and thalamus. There were no significant differences in mean (R)-[11C]PK11195 BPND in the other areas tested.
Conclusion: Our findings of increased regional binding potential imply that the increased TSPO binding in the total gray matter primarily is due to increased TSPO binding in the temporal cortex and thalamus. These results support and extend previous PET studies using plasma input analysis showing activated microglial cells in total gray matter and hippocampus in schizophrenia (3,4). This suggest neuroinflammation or brain injury in the temporal cortex and thalamus in the early stage of the disease. Further investigation is warranted to assess the efficacy of anti-inflammatory treatment in schizophrenia.
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ID: 2085476

PROSPECTIVE STUDY OF THE EFFECT OF HIPPOCAMPAL MORPHOLOGY AT FIRST-EPISODE SCHIZOPHRENIA ON ILLNESS COURSE DURING 4-YEAR FOLLOW-UP

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Background: Several lines of evidence suggest adverse effect of psychotic episodes on brain morphology. In our recent cross-sectional study we found a negative correlation between the number of previous psychotic episodes and hippocampal gray matter volume (Hyza et al., 2014). It is not clear, however, if this correlation reflects a cumulative effect of psychotic outbursts with gradual progressive reduction of hippocampal tissue, or, rather, an increased tendency for psychotic episodes in patients with smaller hippocampus at the beginning of illness.
Methods: A longitudinal 4-year prospective study of patients with first episode schizophrenia (FES, N=58). Baseline brain anatomical scans (at FES) were analyzed using voxel-based morphometry and atlas-based volumetry of hippocampal subfields. The effect of duration of the first episode, illness course with relapses, number of psychotic episodes, and residual symptoms during 4-year follow-up were analyzed.
Results: A significant negative correlation between duration of illness and hippocampal morphology was detected. On the other hand, there was no effect of relaps, number of psychotic episodes, or residual symptoms on baseline hippocampal volume.
Conclusion: We have replicated the effect of fist-episode schizophrenia duration on the hippocampal morphology, which supports the concept of toxicity of psychosis. Moreover, the indices of later unfavorable course of schizophrenia had no effect on baseline brain morphology, suggesting that there is no baseline morphological abnormality that predispose for frequent psychotic outbursts. The findings of correlations between psychotic episodes and brain morphology therefore reflect an additive adverse effect.
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ID: 2117907

GABA AND GLUTAMATE DYSFUNCTION IN SCHIZOPHRENIA: DISTINGUISHING MEDICATION EFFECTS FROM NEUROBIOLOGY

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Background: The GABA and glutamate (Glu) systems have been implicated in the pathophysiology of schizophrenia (Scz). Postmortem studies suggest deficient GABA function in fast-spiking, parvalbumin-positive interneurons. NMDA receptor hypofunction (NRH) has been hypothesized in the illness and has been shown in preclinical studies to stimulate Glu release when induced acutely. The GABA and Glu systems have become amenable to in vivo study using proton magnetic resonance spectroscopy (1H MRS). We focus on studies suggesting that abnormalities in these systems in Scz may be related to NRH and are markedly changed by antipsychotic medication.
Methods: 1H MRS at 3T was used to acquire GABA and Glu in patients with Scz. Comparisons were made between medicated and unmedicated patients and healthy controls. The same MRS methods were used to assess the time course of GABA and Glu response to acute administration of ketamine in healthy volunteers. In addition, longitudinal MRS data for patients off and later on medication are presented.

Results: A study comparing unmedicated patients, medicated patients, and healthy controls found elevations in GABA and Glu in the medial prefrontal cortex in the unmedicated but not in the medicated patients. Both GABA and Glu were related to the PANSS positive symptom subscale across the patient groups. A longitudinal study of Glu in first-episode patients found elevated Glu in the associative striatum that decreased to normal levels following 4 weeks of antipsychotic medication treatment. The time course of GABA and Glu levels following acute ketamine administration in healthy subjects showed acute ketamine-induced increases in both, with a course similar to that of extracellular Glu surges reported in rodents with acute ketamine challenge.
Conclusion: These data suggest that GABA and Glu levels are abnormally elevated in first-episode as well as unmedicated patients with Scz, and that second-generation antipsychotic medication treatment lowers these levels to the normal range. The similarity to the changes induced in healthy subjects by ketamine is consistent with a role for NRH in Scz. The relationship of positive symptoms to GABA and Glu levels, which persist in medicated patients, suggests that patients whose positive symptoms are the least treatment-responsive may be those whose GABA and Glu levels respond the least. Future study is needed to investigate whether these nonresponders may be the best candidates for potential glutamatergic or GABAergic pharmacotherapy.
ID: 2119167

FINDING THE SITES OF GLUTAMATE CIRCUITRY ABNORMALITY IN SCHIZOPHRENIA WITH PROTON MRS

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Background: Support for the glutamate (Glu) hypothesis of schizophrenia (Scz) has grown from symptom induction by NMDA receptor antagonists to observations of abnormal Glu levels in the illness. Proton MR spectroscopy (1H MRS) has revealed a consistent circuitry pattern of Glu levels in unmedicated patients. Nodes in the Glu circuitry that have been studied include hippocampus (HIP), striatum, medial prefrontal cortex (mPFC), dorsal anterior cingulate cortex (dACC), and dorsolateral prefrontal cortex (dlPFC). These studies are summarized and compared to Glu measurements in healthy subjects given ketamine.
Methods: 1H MRS at 3T with PRESS J-editing was used to compare Glx (the combination of Glu and glutamine) levels in two prefrontal brain regions in patients on antipsychotic medication, unmedicated patients, and healthy controls. The same MRS technique was used to follow the time course of response of Glx in mPFC to acute i.v. administration of ketamine (0.5 mg/kg over 40 min) in a group of healthy volunteers (n=12). Findings of 1H MRS studies of additional brain regions were compared. GABA and Glu levels were compared in studies that acquired both.
Results: In unmedicated patients, 30% elevations were found in mPFC in both GABA (P = .02) and Glx (P = .03) levels compared with controls, but not in the dlPFC or in medicated patients. GABA and Glx levels were highly correlated in patients and controls in both regions. Comparison with other studies showed a replicated regional pattern of elevations (HIP, dorsal caudate, mPFC) or normal levels of Glu (dlPFC, dACC). In healthy volunteers given ketamine, Glx in the mPFC increased by 17% (P = .02) and GABA by 11% (P = .04, repeated measures ANOVA). Despite high Glu levels, studies that also acquired GABA found preservation of excitation-inhibition balance both in Scz and in ketamine administration.
Conclusion: The similarity of Glx and GABA changes in Scz to changes in response to ketamine in healthy subjects is consistent with NMDA receptor hypofunction in the illness. Alterations of GABA in the same direction as Glx suggest a nonlocal or circuitry-based component to these changes that maintain excitation-inhibition balance despite abnormally high levels. Further investigation is needed to clarify the contrast between sites found to exhibit normal Glu levels and those found to be hyperglutamatergic in schizophrenia.
ID: 2118126

ANTERIOR COMMISSURAL WHITE MATTER FIBER ABNORMALITIES IN FIRST-EPISODE PSYCHOSIS: A TRACTOGRAPHY STUDY

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Background: The Anterior Commissure is an important interhemispheric pathway that connects contralateral temporal lobes and orbitofrontal areas[1]. The role of the anterior commissure is not yet well understood, although abnormalities in this white matter tract have been reported in patients diagnosed with chronic schizophrenia[2]. However, it is not known whether changes in the anterior commissure are present at earlier stages of the disease.
Methods: Diffusion Magnetic Resonance Images (dMRI) were acquired from 17 First Episode Schizophrenia Patients (FESZ) and 20 healthy controls. The anterior commissure was reconstructed using a streamline tractography approach[3]. DMRI measures, including Fractional Anisotropy (FA), Trace, Axial Diffusivity (AD) and Radial Diffusivity (RD) were computed in order to assess microstructural changes in the anterior commissure.
Results: The analysis of the dMRI measures extracted from the anterior commissure revealed that FA was reduced, while trace and RD increased in FESZ. AD did not show differences between the FESZ and control group.
Conclusion: We conclude that the observed changes in the dMRI measures, namely reductions in FA and increases in trace and RD, without changes in AD, likely point to myelin abnormalities of the anterior commissure [4], and provide evidence of white matter pathology present in the early phases of schizophrenia.
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ID: 2118903

STRUCTURAL MRI DIFFERENCES IN PATIENTS WITH FIRST RANK SYMPTOMS

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Background: Early in the 20th century Kurt Schneider introduced the concept of first rank symptoms (FRS). FRS have been explained as a disconnection between frontal and parietal areas. Indeed, MRI studies have shown associations between FRS and reduced volumes of the inferior parietal lobe, parahippocampal gyrus, frontal cortex, cingulate gyrus, basal ganglia and thalamus. On the other hand, earlier MRI studies found no specific associations between FRS and brain volume, leaving doubt whether FRS are related to abnormal structural brain measures. Here we aim to investigate whether the presence of FRS is associated with specific neuroanatomical abnormalities.
Methods: We included three independent samples of patients; a sample of first onset schizophrenia (SZ) patients (N=151; 69.5% with FRS; mean illness duration=2.3 (SD=2.4) years), a sample with recent onset SZ patients (N=146; 88.1% with FRS; mean illness duration=3.8 (SD=3.4) years) and a chronically ill sample (N=104; 92.5% with FRS; mean illness duration=14.7 (SD=10.6) years). In each sample, patients were divided in two groups based on the presence of FRS. T1-weighted MRI images of the brain were acquired. (Sub)cortical reconstruction and volumetric segmentation of the brain was performed with Freesurfer 5.1.0. The analyses were corrected for multiple comparisons using FDR.
Results: Patients with or without FRS did not differ on relevant demographic and clinical characteristics in each of the samples, except for illness duration, which was significantly longer in patients with FRS relative to those without in the first onset sample. No significant differences were found in cortical and subcortical volumes between patients with and without FRS after multiple comparison correction (all p's>0.01), except for a smaller bilateral nucleus accumbens in first onset patients with FRS.
Conclusion: In three independent samples, at different stages of the illness, we were not able to replicate any of the previously reported associations between FRS and brain abnormalities. We only found reduced volume of the nucleus accumbens in first onset patients with FRS as compared to those without. Interestingly, there is convincing evidence for specific abnormalities in cognition and brain activation in patients with FRS. This suggests that there are brain abnormalities underlying these functional and cognitive deficits, but the current study suggests that these abnormalities are too subtle to pick up using structural brain imaging.
ID: 2094905

ASSOCIATION OF CORTICAL THICKNESS AND NEUROLOGICAL SOFT SIGNS IN PATIENTS WITH CHRONIC SCHIZOPHRENIA AND HEALTHY CONTROLS

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Background: Neurological soft signs (NSS), i.e., subtle neurological abnormalities, have been frequently found in schizophrenia. Neuroimaging studies in schizophrenia have shown abnormal cortical thickness changes across the cortical mantle. However, few studies have examined relationships between NSS and cortical thickness abnormalities in schizophrenia.
Methods: Twenty patients with chronic schizophrenia and 20 age- and gender-matched healthy controls were included. Cortical thickness was assessed on high-resolution 3T MRI by using Freesurfer and NSS were rated on the Heidelberg Scale.
Results: Significant negative correlations between NSS and cortical thickness were found in prefrontal, superior and inferior temporal, superior and inferior parietal cortices, precuneus and posterior cingulate in the schizophrenia patients. In the controls, however, this negative correlation was largely found in anterior and posterior cingulate regions.
Conclusion: Our results not only confirmed the association between NSS and cortical thickness in chronic schizophrenia, but also indicated that patients and controls have different anatomical-substrates of NSS.
ID: 2090126

EXPLICIT MEMORY FUNCTION IN SCHIZOPHRENIA IS RELATED TO HIPPOCAMPAL GLUTATHIONE

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Background: Impairments in learning and memory performance in schizophrenia are related to poorer functional outcomes. Hippocampal dysfunction, a consistent finding in schizophrenia, is thought to underlie learning and memory impairments. This study tested the hypothesis that increased oxidative stress in the hippocampus, as reflected by glutathione measures with magnetic resonance spectroscopy (MRS), would specifically contribute to learning and memory performance in patients with schizophrenia. We predicted that better memory performance would be related to higher glutathione levels.
Methods: Thirty-four controls and 28 schizophrenia patients were enrolled in this study. MR scanning was conducted on a 3T Siemens Tim Trio with a 32-channel head coil. Spectra were acquired from a 4.5 cm3 voxel in the left hippocampus (LH) and a 6 cm3 voxel from the bilateral anterior cingulate (AC) using a PRESS sequence (TR/TE=2000/30-ms, 2500 Hz spectral width, 2048 complex points, 16-step phase cycle, NEX=256 (HP) and 128 (AC). Quantification was conducted with LCmodel. Patients were evaluated for psychopathology, and all participants completed neuropsychological tests of explicit verbal and spatial memory, working memory, attention, reasoning, social cognition, and experimental tests of relational memory.
Results: Hippocampal glutathione levels were not significantly different between control and schizophrenia groups (p = 0.14). However, hippocampal glutathione levels were significantly related to all tests of explicit and relational memory function (r's ranged from -0.37 to -0.53) but not tests of attention, working memory, social cognition, or reasoning in the schizophrenia group. These relationships were neither observed in the control group nor with anterior cingulate glutathione.
Conclusion: To our knowledge, this is the first study to investigate the relationship between hippocampal glutathione, a marker of oxidative stress, and memory measures in schizophrenia. Contrary to our hypothesis,

greater hippocampal glutathione was related specifically to poorer memory performance. This could reflect a compensatory mechanism as suggested by Woods et al (2009) who reported higher hippocampal glutathione in first episode patients with schizophrenia.
ID: 2118157

EXERCISE-ASSOCIATED HIPPOCAMPAL PLASTICITY AND HIPPOCAMPAL MICROVASCULAR PLASTICITY IN CHRONIC REFRACTORY SCHIZOPHRENIA PATIENTS.

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Background: Hippocampal deficits are a commonly reported finding in chronic schizophrenia patients, and may contribute to severity of illness. Regular exercise is thought to remediate both hippocampal volume reductions and neurovascular flow to this region.
Methods: Seventeen chronic refractory schizophrenia patients were enrolled in a 12-week exercise intervention trial. Clinical assessments (PANSS, SOFAS, Hamilton Anxiety Scale (HAMAS), Calgary Depression Scale, Extrapyramidal Symptom Severity Scale), physical assessments (BMI, resting heart rate (RHR), blood pressure (BP), VO2 Max) and 3T MRI data (3D structural MRI, susceptibility weighted imaging) were ascertained at baseline and 12 weeks. Repeated measures ANOVAs with total (L+R) hippocampal and total hippocampal venule volumes expressed as ratios to total brain volume and total hippocampal volume respectively. Additional correlational models were applied.
Results: Patients had a significant increase in total hippocampal volume after 12 weeks of exercise ($F(1, 33) = 6.8$, $p. = 0.019$. Total hippocampal venule volume was not significantly increased after exercise ($F(1, 33) = 0.17$), although the overall increase in venule volume was 7-7.5%. A significant positive relationship between absolute change in total hippocampal volume and absolute change in hippocampal venule volume was observed ($r = .52$, $p. = 0.04$). Patients exhibited reduced symptom severity ($p. = 0.0005$), improved social and occupational functioning ($p. = 0.0004$), and a strong trend for reduced depression severity ($p. = 0.06$) at the end of the 12-week exercise intervention. Measures of BMI, RHR, BP and VO2 Max were not statistically different at 12 weeks, however exploratory investigations revealed a potential, but statistically nonsignificant relationship between improved VO2 Max capacity and reduced HAMAS score ($r = -.44$, $p. = .067$).
Conclusion: We observed exercise-associated hippocampal volume increases after 12 weeks of regular exercise in chronic refractory schizophrenia patients, as was previously reported by Pajonk et al, 2010. Moreover, these changes in hippocampal volume were correlated to changes in hippocampal venule volumes. These data support the hypothesis that regular exercise offers remediation in both hippocampal tissue volume and hippocampal microvascular volume in chronically treated refractory patients. Relationships to other clinical measures still remain to be clearly established.
ID: 2093853

CEREBRAL BLOOD FLOW IN THE THALAMUS AS A POTENTIAL BIOLOGICAL MARKER FOR SCHIZOPHRENIA

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Background: In patients with schizophrenia elevated glutamate availability may lead to increased metabolism causing increases in cerebral blood flow resulting in cortical atrophy (1,2).
Recently we started a study to determine if glutamate concentration, blood flow or cortical thickness - or a combination of these three - can serve as endophenotypes (i.e. biological markers having a hereditary basis) for schizophrenia using a twin study design. Using information from the Danish national twin registry we aim to include all MZ twins in Denmark suitable for the study and diagnosed within the schizophrenia spectrum.
Here we report on our initial findings with respect to regional cerebral blood flow (rCBF) as a potential biological marker. Establishing heritability of rCBF is part of future work.
Methods: At present, 25 monozygotic (MZ) and 15 dizygotic (DZ) twin pairs con- or discordant for schizophrenia (ICD-10, F. 20-29) have been examined along with 14 MZ healthy control (HC) pairs and 8 DZ HC pairs. All patients were diagnosed using SCAN interviews. rCBF was measured using a pseudo continuous arterial spin labeling (pCASL) sequence on a 3 tesla Philips MR system, while phase-contrast mapping was used to measure global flow for normalization purposes. Three bilateral regions of interest (ROIs) were defined: the thalami, the caudate nuclei and the anterior cingulate cortices.
Results: Preliminary analyses of rCBF data using two-sided Student's t-test showed increased flow in the thalami in patients compared with healthy controls ($t=2.7$, $df=57$, $p < 0.01$) and patients compared to their healthy co-twins ($t=2.3$, $df=56$, $p < 0.025$). No differences were found in rCBF for the other two ROIs.
Conclusion: This preliminary analysis indicates that the level of perfusion in thalamus is indeed increased in patients with schizophrenia and is therefore a potential biological marker for the disease. Further analysis will address the heritability of rCBF data in combination with glutamatergic availability and cortical thickness in a larger sample, to determine if they can be used as an endophenotype for schizophrenia - separately or as part of a composite endophenotype.
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ID: 2083824

DIFFUSION MEASURES OF FREE WATER AND 1H-MRS MEASURES OF GLUTATHIONE IN FIRST EPISODE PATIENTS WITH SCHIZOPHRENIA - A MULTI-MODAL INVESTIGATION OF AN INFLAMMATORY MODEL FOR PSYCHOSIS

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Background: Evidence has been accumulating for an immune-based component to schizophrenia (SZ) etiology. Advancements in diffusion magnetic

resonance imaging (MRI) has enabled estimation of extracellular free water (FW), a putative biomarker of neuroinflammation. Furthermore, there is evidence that neuroimmune activation may alter brain levels of metabolites (e.g., glutathione [GSH]) that can be measured non-invasively with proton magnetic resonance spectroscopy (1H-MRS). Consequently, we sought to test the hypothesis that first episode patients with SZ have increased extracellular FW and decreased GSH levels when compared to healthy controls (HC).
Methods: First-episode SZ (n=14) and HC (n=9) participants were identified using the SCID-I. Participants underwent a diffusion MRI scan on a Siemens TIM Trio 3T scanner in which multiple b-value shells were acquired to improve estimation of extracellular FW. 1H-MRS was performed during the same scan and GSH/creatine ratios were calculated for voxels located in dorsolateral prefrontal cortex (DLPFC) and visual cortex. Poverty, Disorganization, and Reality Distortion syndrome scores were calculated.
Results: First-episode SZ patients demonstrated significantly elevated extracellular FW in whole-brain gray matter (p=0.02) but not white matter (p=0.21). At the time of writing, only a subsample of 7 SZ and 6 HC was available to evaluate GSH levels and there was no significant difference between groups (p>0.3). Notably, even in these small subsamples, both groups showed strong inverse relationships between DLPFC GSH and gray matter FW, and patients showed a trend for a steeper slope compared to controls (p=0.09). A significant positive relationship was also identified between symptoms of Reality Distortion and gray matter FW (p=0.03) in SZ.
Conclusion: These data provide compelling convergent evidence for the presence of neuroinflammatory processes in first episode SZ patients. The identified inverse relationship between GSH in DLPFC and gray matter FW implies a common linkage to neuroinflammatory processes that may be more pronounced in patients with SZ, who show increased gray matter FW. Furthermore, our identification of a positive relationship between psychotic symptomatology and gray matter FW suggests that increased FW levels may signal greater disease severity. Ultimately, these data suggest that FW and GSH show promise as early stage neuroinflammatory biomarkers and provide a tractable treatment target for pharmacological intervention.
ID: 2089543

FRONTOSTRIATAL DYSCONNECTIVITY IN SCHIZOPHRENIA

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Background: Frontostriatal white matter connectivity may be disrupted in schizophrenia. The striatum and frontal cortex can be divided into limbic (L), associative (DLPFC (A1); VLPFC (A2)) and sensorimotor (SM) functional subregions, which are connected via corticostriatal white matter tracts. We hypothesized abnormal frontostriatal white matter pathway connections in schizophrenia, as reflected by group differences in the number of connectivity-based labeled surface voxels on the striatum, in particular, in limbic and associative frontostriatal pathways.
Methods: We used MR diffusion weighted imaging (DWI) 2-tensor tractography to calculate frontostriatal pathway fiber counts between the cortex and striatum in 27 medicated, chronic SZs and 26 matched healthy controls (HCs). We employed a connectivity-based parcellation strategy to label surface voxels on the striatum based upon the relative proportion of inputs from the functional cortical ROIs described above. The dominant input voxels (L, A1, A2, SM) were required to receive 0.7 of their fiber counts from a single functional cortical zone; voxels receiving inputs under this threshold from a single functional cortical zone were labeled mixed (MX). We tested for group differences in number of surface voxels labeled as above.
Results: A repeated measures ANOVA of number of surface voxels with group as 'between-subjects' factor and hemisphere (left hemisphere (LH), right hemisphere (RH)) and region (L, A1, A2, SM, MX) as 'within-subjects' factors showed a main effect for group ($F(1,51)=4.24$; $p=0.045$), but no significant interactions. Follow-up t-tests revealed fewer LH mixed voxels in SZ subjects compared with NCs (256.9+109.0 vs 336.7+98.6 voxels; $t(51)=2.79$; $p=0.007$), but not RH mixed voxels (403.7+162.0 vs 473.5+225.0 voxels; $t(51)=1.30$; $p=0.2$). Results were similar when we used 0.5 and 0.9 as threshold cut-offs.
Conclusion: These results show that striatal 'surface volumes' when defined by a connectivity-based parcellation approach using DWI tractography, in contrast to being defined on the basis of anatomic landmarks, are smaller in medicated, chronic SZ subjects compared with HCs. The mixed voxel group difference is of particular interest as such striatal surface voxels may serve integrative functions.
ID: 2086698

PERIPHERAL IMMUNE MARKERS, GROWTH FACTORS AND THEIR ASSOCIATION WITH COGNITIVE AND STRUCTURAL NEUROIMAGING FINDINGS IN FIRST-EPISODE PSYCHOSIS AND FAMILIAL HIGH-RISK PATIENTS

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Background: Current research implicating inflammation as the underlying etiopathology for a subset of schizophrenia continues to grow, but studies are limited in evaluating whether inflammatory indices are altered in those at familial risk or early schizophrenia. Thus, I hypothesized that inflammatory cytokines and growth factors are elevated in familial high risk and first episode psychosis subjects, which correlates with changes in cognition and medial temporal lobe structures.
Methods: Human growth factor panel (bFGF, VEGF, sFlt-1, BDNF, PlGF) and human proinflammatory cytokine 9-plex (GM-CSF, IFNγ, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12, TNFα) were measured in plasma from individuals with familial high risk for schizophrenia (HR, age, 18±4 yrs, n=36), medication naïve first-episode psychosis (FEP, age, 25±9 yrs, n=51), and demographically balanced healthy controls (HC, age, 25±6 yrs, n=43) using a Meso Scale Discovery's multiplex immunoassay system. A battery of cognitive tests and voxel based morphometry from baseline 3-T T1-weighted MRI images was applied to the three groups. These measures were then submitted to group comparisons and Pearson correlations to determine significance.
Results: HR adolescents had significantly increased levels of VEGF, and sFlt-1 compared with HC. FEP patients had significantly increased levels of IL-1β. In the HR group, Pearson correlations performed between these immune markers and medial temporal lobe structures demonstrate that increased levels of VEGF and sFlt-1 are significantly correlated with a reduction in the left parahippocampus and left entorhinal cortical volume. Also, increased VEGF is inversely correlated with right hippocampal volume in the HR group. In the FEP group, increased VEGF was inversely correlated with the right entorhinal cortical volume. No significant correlations were observed between cytokines and cognition in the three groups.
Conclusion: Increased levels of pro-inflammatory cytokines and vaso-endothelial growth factors are consistent with the hypothesis of inflammation and altered microvascular circulation in schizophrenia and those at risk. The findings in our HR group suggest that genetic and environmental risk

may mediate these alterations, thus tipping the balance towards inflammation resulting in cortical volume loss in the medial temporal lobe structures. Future studies will examine the value of inflammatory markers in predicting the development of psychosis, severity of illness, and likelihood of relapse.
ID: 2116606

EXPLORING THE RELATIONSHIP OF GRAY AND WHITE MATTER STRUCTURAL PATHOLOGY IN FIRST-EPISODE SCHIZOPHRENIA THROUGH MUTUAL INFORMATION

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Background: Schizophrenia (SZ) has been characterized as a neurodevelopmental disorder for over 20 years (1). Structural brain abnormalities are consistently reported at all stages of SZ for both gray (GM) and white matter (WM). GM structural pathology in SZ commonly manifests as a wave of cortical thinning initiating in the parietal lobe and progressing to the temporal and frontal lobes (2). Studies of WM in schizophrenia report reductions in WM volume and global reductions in fractional anisotropy (FA)(3). However, despite the fact that SZ is posited to be a "disconnection disorder" (4), very few studies have attempted to understand the connection between GM and WM structural pathologies in schizophrenia.
Methods: In this study, we present findings from a novel integrative analysis that explores the relationships between GM and WM structural pathology in 20 first-episode SZ subjects (FES). FES subjects provide an optimal population because there are no confounds related to medication, chronicity, or aging. To quantify relationships between GM and WM pathology we utilize mutual information (MI), a measure gauging how much information two variables share (5).
Results: We use MI to analyze relationships between multiple GM measures (e.g., surface area, cortical thickness) and WM tract-based measures (e.g., FA, fiber dispersion) in FES subjects and matched controls.
Conclusion: This study is one of the first to explore the connection between GM and WM abnormalities that have been previously reported in SZ and will provide a more complete picture of the morphological alterations occurring within the brains of individuals at initial onset of psychotic symptoms.
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ID: 2116580

SCHIZOPHRENIA-RELATED THINNING OF THE OUTER CORTICAL LAMINAE IN BRODMANN AREAS 44, 45 REVEALED USING MRI AT 3T

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Background: Various MRI studies on schizophrenia consistently reported widespread reductions in cortical thickness but did not provide any information on which of the cortical laminae may be implicated. This information is crucial for a better understanding of the mechanism(s) underlying the cortical thinning. We developed a method that automatically reconstructs detailed mean cortical profiles per brain region with the same myelo-/cytoarchitecture (e.g. Brodmann areas) using T1-weighted MRI scans acquired at conventional field strength (e.g. 3T). Here we applied this new method to determine if schizophrenia-related reductions in cortical thickness are evenly distributed over the different laminae or that only a subset of the laminae is affected.
Methods: High-resolution 3D FFE T1-weighted images were used from 49 schizophrenia patients and 48 healthy controls who participated in a previous study[1]. Using Freesurfer (surfer.nmr.mgh.harvard.edu) to determine the cortical boundaries and a combination of 3D-deconvolution and resampling (full method will be described elsewhere) normalized mean cortical profiles were computed for Brodmann areas (BA) 44, 45, as well as for BA 4a, 4p, and 17 in both hemispheres. The BAs were identified using the Jülich histological atlas[2]. Initial standard Freesurfer analysis revealed significant differences in cortical thickness for BA44 and B45 in both hemispheres but not for BA 4a, 4p and 17. For the comparison between groups the positions of 3 characteristic points (2 local maxima and 1 local minimum in between) where computed for each mean cortical profile per BA per subject. GLM analysis was used to test for group differences in these positions using age and sex as covariates.
Results: For patients with schizophrenia the position of the local minimum was found to be significantly closer to the cortical surface than for healthy controls for BA44 ($t=3.54$, $p < 0.00062$) in the right hemisphere and BA45 ($t=3.49$, $p < 0.00075$) in the left hemisphere.
Conclusion: The significant shift of the local minimum for schizophrenia patients towards the cortex surface found for BA44 in the right hemisphere and BA45 in the left hemisphere points to a reduced thickness of the outer laminae (i.e. lower layer numbers 1-4), which is consistent with previous post-mortem findings[3].
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ID: 2116177

NEUROIMAGING FINDINGS IN YOUNG PEOPLE AT ULTRA HIGH RISK FOR PSYCHOSIS.

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Background: A series of studies using MR-based techniques and PET have shown that young people who are at ultra high risk (UHR) for psychosis differ from controls in terms of the structure, physiology, neurochemistry and connectivity of the brain. Further work suggests that within high risk samples, there are neuroimaging differences that correspond to different clinical outcomes. To date, most of this research has focused on identifying neuroimaging findings that are associated with the later onset of psychosis.
Methods: MRI, functional MRI, resting cerebral blood flow/volume, MR spectroscopy and PET techniques have been used to compare high risk subjects who have similar clinical features at presentation but go on to have divergent clinical outcomes in the following 2-3 years. Most of these studies have been single-centre studies with modest samples, although there are increasing numbers of multi-centre studies that provide a means of recruiting larger samples. This is a relatively new field: most of the studies have been conducted in the last 15 years.
Results: Cross-sectional comparisons within high risk samples at baseline have revealed differences at baseline in resting activity, task-related activation, grey matter volume and glutamate levels in the medial temporal region, as well as differences in striatal and midbrain dopamine function. Longitudinal studies suggest that transition to psychosis is also associated with progressive within-subject changes in many of these measures.
Conclusion: These human data are consistent with animal models that propose that the onset of frank psychosis involves interactions between medial temporal, striatal, thalamic and midbrain areas, and alterations in glutamate and dopamine function. The findings suggest that neuroimaging measures might in future be used to stratify young people at high risk according to later clinical outcomes. This could allow clinicians to tailor the nature of the intervention to the level of clinical need. However, the research findings in these studies are at a group level: translation into clinical practice requires the ability to make predictions on the basis of neuroimaging data from an individual subject. Addressing this issue is a key goal for ongoing research in this area.
ID: 2109042

MORPHOMETRY OF THE MIRROR NEURON SYSTEM AND SOCIAL COGNITION PERFORMANCE IN SCHIZOPHRENIA

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Background: Emerging evidence from neurophysiological studies suggests that a dysfunctional mirror neuron system (MNS) - comprised of the inferior frontal gyrus (IFG), ventral premotor cortex (vPMC), inferior parietal lobule (IPL) and superior temporal sulcus (STS), underlies social cognition (SC) deficits in schizophrenia. However, it is not known how morphometry of these brain regions relate to SC performance.
Methods: Data obtained from the Brain Imaging, Cognitive Enhancement and Early Phase of Schizophrenia Study on 56-schizophrenia/schizoaffective disorder patients (DSM IV, mean±SD age = 24.13±4.61 years & duration of illness = 4.04±3.39 years, 43 males) were analyzed. SC-composite score was calculated as an average of the z-scores derived from the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT)-Managing Emotions branch, the Awareness of Social Inference Test, the Hinting Task and the Penn Emotion Recognition Test. Neurocognition (NC)-composite score was similarly derived from the MATRICS Consensus Cognitive Battery, sans the MSCEIT. Cortical thickness measures of the abovementioned MNS regions were extracted from T1-weighted structural MRIs using FreeSurfer v5.3. Partial correlations were used to examine the associations between the SC-composite and cortical thickness of individual MNS regions, with NC and other confounders as covariates.
Results: SC-composite had trend-level correlations with the left IFG (mean thickness of pars opercularis & triangularis, weighted for local surface area) and left vPMC (caudal middle frontal gyrus) thickness ($r=0.22$, $p<0.1$). Male patients had greater impairments on the SC-composite, when compared to females ($t=1.67$, $p<0.1$). Separate gender-based analyses revealed that the SC-composite had significant correlations with left IFG ($r=0.36$, $p=0.03$) & left vPMC ($r=0.34$, $p=0.04$) thickness after covarying for age, duration of illness, site, intracranial volume and NC performance, only in males. NC composite score did not correlate with cortical thickness in any of the MNS regions. There were no correlations between SC-composite and cortical thickness in regions outside the MNS (e.g., medial prefrontal cortex, temporal pole & occipital cortex).
Conclusion: Reduced cortical thickness of the left anterior MNS (IFG and vPMC) had a fairly specific association with poorer SC composite scores in male schizophrenia patients. Thus, structural integrity of the MNS may be critical for accurate social information processing, especially in males with schizophrenia.
ID: 2116966

PREDICTING RESPONSE TO ANTIPSYCHOTICS WITH GLUTAMATE PROTON MAGNETIC RESONANCE SPECTROSCOPY (MRS)

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Background: Little is understood about how to predict patient response to antipsychotic treatment. It has been found previously that non-responding patients tend to have higher levels of glutamatergic metabolites (Glx: glutamate+glutamine) compared to responders (Szulc et al. 2013). Here we acquired 1H-MRS on inpatients with psychosis using a sequence that allowed for the separation of glutamate alone. We predicted that glutamate levels would be associated with percentage improvement in symptoms, especially positive symptoms.
Methods: 13 patients with psychosis participated in double blind cross-over design where all medications were suspended for 4-6 weeks (placebo phase) or a single antipsychotic was administered at a stable dose (active phase). The positive and negative symptoms scale (PANSS) was collected, blind to the medication status of the patients. We acquired MRS during the placebo phase using TE-averaged PRESS at 3T, with a single voxel placed in the ACC. The metabolite values, N-acetyl-aspartate (NAA), Glutamate (Glu), and Choline (Cho), all referenced to creatine (Cr), were used as independent variables in multiple regression models predicting change in PANSS score between the placebo and active phases while controlling for age and sex. Change in PANSS score was measured as 1) the average score across all 30 and as 2) the average of positive symptoms only.
Results: Glu/Cre was not predictive of antipsychotic response for either overall symptoms or positive symptoms. Cho/Cre in the ACC was significantly

negatively associated with change in positive symptoms (p = 0.0171, the higher the Cho/Cre the lower the difference in PANSS between placebo and active phases). In the Cho/Water model, the metabolite (p = 0.0334) and sex (p = 0.0434) had a significant relationship with response; females had a larger response than males. No other metabolites were found to be significant with symptoms.
Conclusion: In a largely overlapping group of patients, we had found that Glx during the placebo phase was associated with treatment response in the same direction as Szulc et al. The current data may indicate that glutamine, rather than glutamate may be the main predictor of response in this sample. The choline finding was unexpected and was not present in data acquired with a different sequence aiming to detect primarily GABA in the same patients. A larger sample size is required to confirm the validity of these results.
ID: 2094478

GLOBAL MICRO-STRUCTURAL WHITE MATTER ALTERATIONS IN THE FIRST-EPISODE ANTIPSYCHOTIC-NAIVE SCHIZOPHRENIA PATIENTS.

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Background: An important question when studying the white matter fiber connections in schizophrenia is whether any reductions in fiber integrity are directly related to the disease itself or whether they are merely a consequence of the use of antipsychotic medication. One way to exclude antipsychotic medication use as a confounding factor is to compare antipsychotic-naive schizophrenia patients with healthy volunteers. In this study we combined diffusion tensor imaging (DTI) with magnetization transfer imaging (MTI) to detect aberrations in the white matter microstructure in antipsychotic-naive patients with schizophrenia.Aberrations that therefore can only be attributed to the disease itself.
Methods: Fifty-seven first-episode, antipsychotic-naive schizophrenia patients and 57 matched healthy controls were scanned on a Philips 3T MR scanner for DTI and 52 pairs for MTI. Whole brain DTI (2 sets with opposite phase-encoding directions; 5 diffusion unweighted (b=0) and 30 diffusion weighted (b=1000) non-collinear directions) and MTI (2 volumes) were de-noised to remove Rician noise. DWI images were corrected for head motion, eddy current distortion and susceptibility artifacts.
DTI and MTI images were co-registered and voxel-wise analyses were performed using TBSS (Tract-Based Spatial Statistics) on various skeletonized DTI derived parameter maps: fractional anisotropy (FA); parallel diffusivity (L1); radial diffusivity (L2L3); mode (MO) as well as magnetization transfer ratio (MTR).
Results: Voxel-wise statistics using skeletonized FA and MO maps of the whole brain identified deficiencies in patients, revealing reduced FA in the right cingulum (cluster size=244 voxels;p-values<0.05) and reduced MO in the corpus callosum (cluster size=2852 voxels;p-values<0.05). Unpaired t-test reveals that the reduced FA within the right cingulum cluster is associated with reduced L1 (p=0.0006) and reduced MO (p=0.004). No significant group differences in L2L3 or MTR were found.
Conclusion: These preliminary results indicate that there are WM deficiencies present in never-medicated schizophrenia patients, especially in the right cingulum and corpus callosum. Lower FA in combination with lower L1 and MO in the right cingulum cluster might indicate alterations in axonal microstructure. Lower MO in the corpus callosum cluster (without differences in MTR, FA, L1 or L2L3) indicates that patients have less crossing fibers compared to healthy controls. Further analyses of follow-up data and clinical implications are ongoing.
ID: 2118308

DOPAMINE DYSFUNCTION IN PEOPLE AT ULTRA HIGH RISK FOR PSYCHOSIS- THE CRITICAL ROLE OF STRESS AND CANNABIS

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Background: Research on the environmental risk factors for schizophrenia has focused on either psychosocial stress or drug exposure, with limited investigation of their interaction. A heightened dopaminergic stress response in individuals at Ultra High Risk (UHR) for psychosis supports the dopaminergic sensitization hypothesis. Cannabis is believed to contribute, possibly through a cross-sensitization with stress.
Methods: Twelve healthy volunteers (HV), 12 UHR and 12 cannabis-using UHR (UHR-CU, 11 dependent) subjects underwent [11C]-(+)-PHNO positron emission tomography scans while performing a sensorimotor control task (SMCT) and a stress condition (Montreal Imaging Stress task; MIST). The simplified reference tissue model was used to obtain binding potential relative to non-displaceable binding (BPND) in the whole striatum, its functional subdivisions (limbic striatum (LST), associative striatum (AST) and sensorimotor striatum (SMST)), globus pallidus (GP) and substantia nigra (SN).
Results: First, we found a significant difference between groups (HV, UHR) in the AST (F = 8.13, df = 2,31, p = .001), and at the SMST (F = 3,64, df = 2,31, p = .03) but not in the LST (F = .43, df = 2,31, p = .40) with UHR having larger [(11)C]-(+)-PHNOdisplacement in response to stress. Bonferroni-corrected comparisons confirmed that HV displacement (-2.86%) in the AST was significantly different than in UHR (6.97%). Furthermore, while stress elicited a significant reduction in BPND in the UHR group, UHR-CU group exhibited an increase in BPND. Stress-induced changes in regional BPND between UHR-CU and UHR were significantly different in AST (p<0.001), LST (p=0.007), SMST (p=0.002), SN (p=0.021) and whole striatum (p=0.001), with trend level in the GP (p=0.099). All UHR subjects (including UHR-CU) experienced an increase in positive (attenuated) psychotic symptoms (p=0.001) following the stress task.
Conclusion: Our results suggest altered DA stress reactivity in UHR and UHR-CU. First, this study reveals a sensitized dopaminergic response to stress in UHR as compared to HV. Second, our finding does not support the cross-sensitization hypothesis, which posits greater dopaminergic reactivity to stress in UHR-CU. These findings may have important theoretical and clinical implications regarding efforts to abort or delay relapse and/or conversion to psychosis in UHR.
ID: 2093043

DOPAMINE D2 AND D3 RECEPTOR AVAILABILITY IN ANTIPSYCHOTIC-FREE PATIENTS WITH LATE-LIFE SCHIZOPHRENIA: A CROSS-SECTIONAL [11C]-(+)-PHNO AND [11C]-RACLOPRIDE PET STUDY

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Background: Schizophrenia is a lifelong illness requiring maintenance antipsychotic treatment across the life span. Age-related changes in dopamine D2/3 receptor (D2/3R) are expected to result in enhanced antipsychotic

sensitivity as patients grow older. However, no study has examined the D2R and D3R availability in antipsychotic-free patients with late-life schizophrenia.
Methods: Our study included patients with schizophrenia, ≧50 years, and having been antipsychotic-free for at least 2 weeks. We compared the non-displaceable binding potential (BPND) of [11C]-raclopride and [11C]-(+)-PHNO between patients and sex- and age-matched controls (n=11). ROIs included the caudate, putamen, and ventral striatum for [11C]-raclopride and [11C]-(+)-PHNO, and the globus pallidus, substantia nigra, hypothalamus, and ventral pallidum for [11C]-(+)-PHNO.
Results: In total, 11 patients participated: 5 females, 4 antipsychotic-naïve and 7 antipsychotic-free, age=66.0 ± 11.0 years, duration of illness=37.0 ± 20.0 years, duration of untreated illness=2.2 ± 4.0 years, PANSS score=82.6 ± 27.5. 10 participants were scanned with [11C]-raclopride, and 7 with [11C]-(+)-PHNO [6 with both radiotracers]). No differences were found between antipsychotic-free patients and healthy controls in the BPND in any of the ROIs ($F(1,72)=.00$, $p=.96$ for [11C]-raclopride; $F(1,80)=.79$, $p=.38$ for [11C]-(+)-PHNO, respectively).
Conclusions: Our study is the first to explore the availability of D2R using antagonist ([11C]-raclopride) and agonist ([11C]-(+)-PHNO) PET radiotracers, and D3R using [11C]-(+)-PHNO in patients with late-life schizophrenia. The preliminary results suggest no differences in D2R and D3R availability in patients with late-life schizophrenia in comparison with healthy controls.
ID: 2193224

INCREASE IN STRIATAL VOLUME IS ASSOCIATED TO POSITIVE SYMPTOMS BUT NOT DOPAMINE D2 RECEPTOR BLOCKADE IN ANTIPSYCHOTIC NAÏVE SCHIZOPHRENIA PATIENTS

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Background: Schizophrenia is associated with structural brain changes as well a dysfunctional dopamine system. Antipsychotic medication remains the cornerstone in the treatment of schizophrenia, though to what extend antipsychotic medication affect grey matter volume remains elusive. Here we investigate volumetric striatal (caudate nucleus and putamen) alterations after dopamine D2/3 receptor blockade. Moreover associations with psychopathology are investigated.
Methods: Twenty antipsychotic naïve first episode schizophrenia patients matched with 21 healthy controls were scanned with structural magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) using the ligand IBZM at baseline. After baseline examinations patients were treated with amisulpride for 6 weeks. At follow-up patients were MRI and SPECT scanned whereas controls were only MRI scanned. Patients were assessed with positive and negative syndrome scale (PANSS) at both time points. MRI data was processed using FSL and SPECT data was co-registered to MRI images. Four regions of interest (left and right caudate and left and right putamen) were segmented and quantified. Occupancy was calculated from BPp values.
Results: Repeated measure ANOVA on striatal volume (caudate plus putamen) showed significant [group x time] interaction ($p = 0.009$) with patients having an increase in volume ($p = 0.048$), whereas controls did not (paired samples T-test). Dividing striatum into sub-regions [group x time] interaction remained significant in the left ($p =0.001$) and right ($p = 0.01$) caudate, with significant volume increase in left ($p = 0.005$) and right ($p = 0.02$) caudate nucleus and numerical increase in putamen. No significant associations was found between dopamine D2/3 receptor blockade and volume change in striatum or any sub-region ($p<.2$). Volume change in striatum showed a significant positive correlation with improvement in positive symptoms ($p = 0.03$). This correlation was mainly driven by positive correlations between change in the left caudate ($p = 0.01$), right putamen ($p = 0.006$) and improvement in positive symptoms.
Conclusion: Our preliminary data of initially antipsychotic-naive first episode schizophrenia patients indicate that striatal volumes increase after six weeks of amisulpride treatment. However, dopamine D2/3 receptor occupancy does not explain the observed volume increase. Rather, our data indicate that the volume increase in striatum is related to improvement in positive symptoms.
ID: 2092531

ADVANCED DIFFUSION IMAGING REVEALS EARLY WHITE MATTER BRAIN CHANGES IN ADOLESCENTS EXPERIENCING PSYCHOTIC SYMPTOMS.

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Background: White matter (WM) changes are frequently described in individuals who fulfil the criteria for At Risk Mental States (ARMS) and DSM IV for schizophrenia and have proved invaluable in our understanding of how the clinical symptomology of the disease relates to associated neuroanatomical alterations. These changes have identified key affected brain structures, such as targeted frontal abnormalities driven by the disease onset, and more recently, in individuals categorized as ultra-high risk (UHR) (Carletti et al, 2012, Peters et al., 2009). Yet, the genesis of these morphologies, prior to transition to schizophrenia and psychosis remains elusive. Are similar patterns of WM change evident in adolescents experiencing psychotic symptoms? Advancing imaging techniques such as High Angular Resolution Diffusion Imaging, may provide a mechanism to capture these changes during their formative phases and thus provide clinicians with a possible means to identify those individuals with increased vulnerability to the disease and influence early interventional strategies for a better prognosis.
Methods: 28 young people aged 13-16 years who reported psychotic experiences and 28 young people who did not, matched for age, gender and handedness, featured in the study. Data was preprocessed using ExploreDTI. Whole-brain WM analysis using Tract Based Spatial Statistics (TBSS) followed by Constrained Spherical Deconvolution (CSD) based deterministic tractography and a tract resampling technique was performed. Diffusion metrics were extracted per tract, to investigate if WM differences are present in adolescents with psychotic symptoms.
Results: Results: Whole brain WM analyses identified differences between young people with psychotic symptoms and those without, localised

bilaterally in striatal regions in proximity to the putamen (p=0.01 FDR corrected). CSD tractography in proximity to these regions identified WM tract anomalies in the frontal projections of the right inferior fronto-occipital fasciculus (IFO) and bilaterally in the uncinate fasciculus (UNC) (p≤0.05 corrected).
Conclusion: These findings provide the first evidence of WM anomalies in both frontal and fronto-temporal regions in young adolescents experiencing psychotic symptoms in the pre prodromal phase, prior to the transition to psychosis These regions may be targeted during adolescent developmental surges thus rendering these individuals with increased risk of psychosis.
ID: 2097206

BIOTYPE CLASSIFICATION DISTINGUISHES SUBGROUPS OF PSYCHOSIS WITH DISTINCTIVE POLYGENE-CORTICAL THICKNESS PROFILES

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Background: Psychosis is likely comprised of subgroups with distinct etiologies. We compared cortical thickness and gene-structure relationships among subgroups of psychosis using a biotype classification and polygenic risk scores (PGRS).
Methods: In prior work by the BSNIP Consortium (Clementz et al, under review), subjects with schizophrenia, schizoaffective or bipolar I with psychosis were clustered into 3 'biotypes' via k-means clustering of phenotypic data (EEG, cognitive testing, saccadic eye movements). Biotype 1 (BT1) demonstrated greater abnormalities than biotypes 2 (BT2) and 3 (BT3).
In this analysis, subjects included 93 BT1, 105 BT2, 148 BT3 individuals, and 119 healthy controls (HC). Freesurfer v5.1 was used to process T1-weighted structural MRIs and Matlab and SurfStat were used for whole brain, vertex-based analysis (http://www.math.mcgill.ca/keith/surfstat/). Group comparisons of cortical thickness were performed between each BT and HC, with random field theory for multiple comparison thresholding. Covariates included age, sex, study site and race.
Next, PGRS were generated for each subject. Genotypes were collected using the Illumina Human Omni-1 Quad Chip and underwent quality control. Odds ratios for each SNP (from the PGC2 Consortium) were used to compute PGRS in PLINK 1.07 using a standard formula.
Last, significant clusters of vertices were then used as regions of interest and were regressed on PGRS, with covariates of age, sex, site, and two components representing population stratification, with Hochberg correction.
Results: 28 regions of cortical thickness significantly differed between BT1 and HC, of which 3 were inversely correlated with PGRS. 22 regions differed between BT2 and HC, and 14 regions differed between BT3 and HC, of which none were correlated with PGRS. Effect sizes for significant differences were largest in BT1.
Conclusion: Biotype classification distinguishes a subgroup of psychosis, BT1, with greater cortical thinning than other biotypes and some relationships between this thinning and PGRS. Our results support the view that classification of psychotic disorders based on neurobiology and genetics may be superior to symptom-based classifications.
Reference: Clementz BA, Sweeney JA, Hamm JP, et al. "Identification of Distinct Psychosis Biotypes Using Brain-Based Biomarkers". Under review.
ID: 2084262

THE MELBOURNE CLINICAL HIGH-RISK AND EARLY PSYCHOSIS STUDIES: UNDERSTANDING PROGRESSIVE BRAIN CHANGES USING MRI AND PET IMAGING AND IMPLICATIONS FOR TREATMENT

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Background: Over the last decade we have characterized the nature of progressive brain changes in psychosis and schizophrenia. These changes are most evident at the earliest stages of psychosis, including those at clinical high-risk (CHR) and first episode psychosis (FEP). Such changes are consistent with the clinical picture of psychosis, which is characterized by episodes of relapse and remission associated with progressive functional deterioration. However, there is limited understanding of the mechanisms underlying such brain changes. Further, while recent work with neuroprotective agents (fish oil, lithium) may be relevant to improving outcome for CHR/FEP, there are limited data on their neurobiological effects.
Methods: I will review the findings from a series of magnetic resonance imaging (MRI) and neurocognitive studies mapping trajectories of the disorder from clinical high-risk to 10 years followup. More recently, we have undertaken positron emission tomography (PET) studies investigating microglial activity at different illness stages, as an index of neuroinflammation. Studies investigating the role of eicosapentaenoic acid (EPA; fish oil) as a neuroprotective agent were examined using MR Spectroscopy (MRS). The effect of low dose lithium was examined using T2-relaxometry.
Results: Progressive changes in frontal and temporal regions, insula and anterior cingulate are most apparent over the transition to psychosis and over the first 4-5 years following onset. Microglial activation with PET identified differences in microglial activity in frontal, cerebellar (increased), and temporal/insula (decreased) regions. Using MRS, we identified increase in glutathione and glutamate/glutamine peaks in response to EPA; lithium decreased T2 signal in the hippocampus.
Conclusion: Long-term followup studies in the Melbourne cohorts (CHR and FE) identify the greatest progressive brain changes at the earliest stages of psychosis. Neuroinflammation, indexed using PET imaging may be relevant to such changes. Interventions using neuroprotective agents may prevent such changes and help to improve outcome.
ID: 2121745

DIFFUSION MRI FOR THE IDENTIFICATION OF NEUROINFLAMMATION IN SCHIZOPHRENIA: FINDINGS AND CHALLENGES

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Background: Despite accumulating evidence for the involvement of neuroinflammation in schizophrenia, the exact role of neuroinflammation in the etiology of the disorder is not understood. Neuroimaging methods that are

able to identify neuroinflammation in-vivo and to follow its progression are a potential key for understanding this role.
Methods: Diffusion MRI (dMRI) is a clinically available technique sensitive to microscopic structural changes. The acquisition is non-invasive and safe, unlike imaging methods such as PET, which involve exposure to ionizing radiation. Recent advances in dMRI provide models that account for free-water found in the extracellular space[1]. Changes in free-water may, in-turn, represent extracellular changes that are observed in the different stages of neuroinflammation.
Results: dMRI experiments conducted on first episode patients demonstrate widespread excessive extracellular free-water compared with normal controls[2]. These experiments also show potential axonal damage that is limited to focal areas in the frontal lobes. In contrast, experiments with chronic patients demonstrate an opposite pattern with widespread signs of axonal damage, and a smaller extent of excessive free-water[3]. Preliminary results from prodromal patients reveal trends of increased extracellular space. Taken together, these results suggest that neuroinflammation may play a more prominent role in the early stages of the disorder, whereas degeneration may be the primary pathology in the progressive stages. A pattern shared by many neurodegenerative disorders, in which prolonged inflammation leads to degeneration.
Conclusion: dMRI and the quantification of free-water show promise as a novel method for identifying neuroinflammation in schizophrenia. However, excessive extracellular space may be caused by additional factors, such as atrophy and various imaging artifacts, challenging the specificity of free-water to neurionflammation. Studies combining advanced dMRI with PET and MR spectroscopy, as well as studies of animal models are needed to define better the sensitivity and specificity of dMRI to neuroinflammation. An additional challenge is our ability to identify early and likely subtle signs of neuroinflammation. If indeed neuroinflammation is related to the onset of schizophrenia, early identification and treatment may prevent the neurodegenerative cascade, potentially minimizing the associated symptoms.
[1]MRM, 2009; 62:717-30
[2]J Neuroscience, 2012; 32:17365-72
[3]Schizophr Res, 2014; Epub ahead of print
ID: 2083850

POSITIVE SYMPTOMS IN FIRST EPISODE SCHIZOPHRENIA PATIENTS CORRELATE WITH EXCESSIVE EXTRACELLULAR SPACE

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Background: Free-water imaging uses conventional diffusion MRI (dMRI) data to identify water that is free to diffuse in the extracellular space[1]. Our previous work identified widespread excessive extracellular space, likely corresponding to neuroinflammation, in patients following their first psychotic episode (FE)[2]. Here we aim to identify clinical correlates of free-water measures.
Methods: dMRI from 29 FE patients and 28 matched healthy controls (see[2]) were analyzed using free-water imaging[1], providing free-water maps (FW) and diffusion tensors corrected for free water, from which corrected fractional anisotropy maps (FAt) were calculated. In addition, conventional FA maps were calculated. We used streamline tractography (3D-Slicer) to delineate the Cingulum bundle (CB), inferior and superior longitudinal fasciculi (ILF, SLF), Arcuate and Uncinate fasciculi (AF & UF). The different maps were averaged over each fiber, and then compared between groups and correlated with clinical symptoms. The symptoms were evaluated using the Scale for the Assessment of Negative Symptoms (SANS) and the Scale for the Assessments of Positive Symptoms (SAPS). Significance level for all tests was set at $p<0.05$.
Results: Compared to healthy controls, FE patients exhibited higher FW in the right SLF and bilaterally in the CB, and ILF, and no FAt differences. Additionally, compared to non-hallucinating patients, hallucinating patients evinced higher FW in bilateral AF, left SLF and right CB. Conventional FA correlated with individual SANS and SAPS symptoms in many of the tested fibers. Applying free-water revealed that FW correlated only with SAPS scores, with the exception of the right ILF.
Conclusion: Our findings establish a relation between excessive free-water and positive symptoms in the early stages of schizophrenia. In our previous work we suggested that free-water is increased due to excessive extracellular space, which may indicate neuroinflammation[2]. We also previously found that in chronic patients, negative symptoms are related to decreased FAt, which may indicate neurodegeneration[3]. Taken together it is likely that neuroinflammation as measured with FW is more prominent in the early stages of the disorder, manifested mainly in positive symptoms, whereas neurodegeneration, as measured with FAt, is more prominent in the chronic stages, manifested in negative symptoms.
[1]MRM, 2009; 62:717-30
[2]J Neuroscience, 2012; 32:17365-72
[3]Schizophr Res, 2014; Epub ahead of print
ID: 2085277

INCREASED MYO-INOSITOL AND CHOLINE LEVELS WITHIN THE ASSOCIATIVE STRIATUM OF ANTIPSYCHOTIC-NAÏVE PATIENTS WITH FIRST-EPISODE PSYCHOSIS

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Background: Though the dopaminergic and glutamatergic systems have been largely implicated in the pathology of schizophrenia, abnormalities in myo-inositol (mI) and choline compounds (Cho) appear to also exist. mI has been reported to be a marker of glial activity and an intermediate in the metabolism of membrane and myelin phospholipids, whereas Cho is believed to be related to membrane turnover. The purpose of the present

study was to investigate mI and Cho levels in a sample of antipsychotic-naïve patients with first-episode psychosis (FEP).
Methods: 58 patients experiencing their first non-affective psychosis episode and 58 age- and sex-matched healthy controls were recruited into this study. Proton magnetic resonance spectroscopy (1H-MRS) was obtained in a 3T GE scanner using point-resolved spectroscopy, with the voxel centered on the right dorsal-caudate nucleus. In addition, each participant was assessed with the Positive and Negative Syndrome Scale (PANSS). 1H-MRS acquisitions were analyzed using LCModel and corrected for CSF composition within the voxel. mI and Cho levels were compared between groups using a general linear model. Pearson correlations were carried out to investigate the relationship between metabolite levels and PANSS total scores.
Results: mI in the associative striatum was higher in patients with FEP compared to healthy controls ($p<0.05$). Cho in the associative striatum was also higher in patients with FEP in comparison to healthy controls ($p<0.01$). A trend level positive correlation existed between mI levels and PANSS total positive scores ($r=0.250$, $p=0.059$). Exploratory investigations controlling for multiple comparisons identified a significant correlation between mI levels and P5 (Grandiosity) ($r=0.401$, p-corrected<0.05). The relationship between mI levels and P3 (Hallucinatory Behavior) approached significance ($r=0.319$, p-corrected>0.05).
Conclusion: mI and Cho appear to be concomitantly elevated in the associative striatum of antipsychotic-naïve patients with FEP. This parallel increase may be an attempt to compensate for neuronal damage by improving glial proliferation to modulate vascular and metabolic activities, and may also provide evidence for early neuroinflammation in schizophrenia. The relationship between mI levels and positive symptoms warrants further investigation.
ID: 2091319

BRAIN TEMPERATURE AND GLUTAMATE IN 7T MRS: DECOUPLING OF METABOLIC CASCADES AND GLUTAMATE NEUROTRANSMISSION IN FIRST EPISODE SCHIZOPHRENIA

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Background: Glutamate is the primary excitatory neurotransmitter in the mammalian central nervous system. Aberrant glutamatergic neurotransmission has been suggested in the pathology of schizophrenia. Meanwhile, recent evidence has suggested the pathological role of oxidative stress, inflammation, and dysfunctional metabolic signalling. However, the link between glutamatergic neurotransmission and homeostatic metabolic signalling remains elusive.
Temperature is an important physiological parameter, reflecting the amount of heat produced and sustained by biological processes. An index of brain metabolism, as well as a factor directly affecting cellular activity and function, brain temperature may be used as a good indicator of cerebral energetics. Nonetheless, in vivo BT measurement has been limited, due to the invasive nature of conventional measurement methods.
Magnetic resonance spectroscopy (MRS) can measure BT in a non-invasive manner,
relying on the chemical shift difference between the resonance peaks of water and N-acetyl aspartate (NAA).
Methods: Fifteen patients diagnosed with recent onset schizophrenia and fifteen healthy volunteers have been studied using 7 Tesla proton magnetic resonance spectroscopy. A combination of semi-LASER and STEAM sequences was utilized to measure absolute brain temperature, glutamate and NAA levels in the anterior cingulate cortex (ACC). All participants completed a broad neuropsychological battery, assessing a wide variety of cognitive domains.
Results: We identified a significant inverse correlation between glutamate and brain temperature in the control group. In contrast, such inverse correlation was lost in patients with schizophrenia. Similarly, the positive correlation between NAA and glutamate in healthy controls was disrupted in people with schizophrenia.
Conclusion: First, this study showcases the decoupling of NAA and glutamate in the ACC of people with schizophrenia. NAA, a reservoir of glutamate, is primarily synthesized in the mitochondria of neurons and in part reflects mitochondrial function. Thus, the first result may suggest decoupling of metabolic cascades to glutamate neurotransmission. Second, the data of brain temperature and glutamate highlights a disrupted relationship between brain metabolism and glutamate in the schizophrenia population. We now explore if these indices may reflect and indicate the pathology of schizophrenia in which oxidative stress and inflammatory pathways cross-talk with altered glutamate neurotransmission.
ID: 2118729

NAD$^+$/NADH DYSFUNCTION UNDERLYING FAMILIAL RISK FOR SCHIZOPHRENIA

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Background: Nicotinamide adenine dinucleotide (NAD), in oxidized (NAD^+) or reduced (NADH) form, plays an important role as co-enzymes regulating critical neuronal functions such as redox reactions, energy metabolism, cell signaling, DNA repair and telomere maintenance. Abnormalities in these functions in schizophrenia (SZ) are well documented. Altered NAD levels are especially important in the glutamtaregic, GABAergic and kyneurenine pathways implicated in SZ. Direct examination of NAD (i.e., NAD^++NADH) using phosphorus magnetic resonance spectroscopy (^{31}P MRS) may further support significance of alterations in these pathways among SZ and familial at risk (HR) subjects.
Methods: We acquired 3D whole-brain, multi-voxel ^{31}P MRS data at 3 Tesla on 92 subjects (SZ=36, HR=22, HC=34). Mean age of SZ did not differ from HR subjects. HR subjects were younger than HC. We examined 21 right and left cortical/subcortical ^{31}P MRS voxels (e.g. the prefrontal cortex (PFC), hippocampus). Post-processing was done by shifting the 3D MRS voxel grid relative to the anatomical images prior to the Fourier Transform to extract and quantitate the ^{31}P signal within the voxels for the metabolites (PE, PC, GPC, GPE, PCr, ATP, NAD) which was 100% automated. Metabolite levels were expressed as mole % of the total signal. We used generalized estimating equation based-regression models to examine group differences using age, sex and grey matter proportion within the voxel as covariates (SAS PROC GENMOD).
Results: We noted diagnosis main effect on NAD levels in the inferior parietal lobule (IPL), postcentral gyrus and cerebellar vermis (all $p<0.05$) with a trend at the inferior frontal gyrus (IFG), dorsal hippocampus, orbitofrontal cortex (OFC) and superior parietal lobule (SPL). Posthoc tests showed a significantly increased NAD in the IPL, SPL and postcentral gyrus and decreased NAD in the dorsal hippocampus, OFC, anterior cingulate cortex and vermis of HR compared to HC and SZ (all $p<0.009$ except vermis $p=0.046$). SZ subjects showed trend for an increase in NAD in the PFC, SPL and postcentral gyrus compared to HC.
Conclusion: NAD levels suggest altered reaction rate, depletion or impaired replenishment in each region. Increased NAD results in increased reactive oxygen affecting GABA/glutamate/kyneurenine signaling. Reduced NAD in some regions in HR subjects suggest depletion due to increased redox reaction rate. Our results support NAD as a novel molecular target for drug discovery.
ID: 2088194

REDUCED CB1R AVAILABILITY IN SCHIZOPHRENIA

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Background: Converging lines of evidence suggest several relationships between cannabinoids and psychosis. According to the exogenous hypothesis, exposure to cannabinoids is associated with psychosis outcomes. Further, there is evidence of endocannabinoid (EC) dysfunction in schizophrenia (SCZ). Emerging evidence suggests abnormalities in the EC system in SCZ. SCZ patients show elevations in levels of ECs in CSF or blood that correlated with psychotic symptoms. Postmortem data in SCZ patients found alterations in regional distribution of CB1R or mRNA, but the data have been mixed.
Methods: 25 male SCZ patients with no recent cannabis use or a cannabis use disorder were compared to 21 age (± 3 years) and gender matched healthy controls (HC); 7 of the patients were antipsychotic free (SCZ-UNMED) and eighteen antipsychotic treated (SCZ-MED). CB1R availability was measured using the 11C-OMAR tracer and High Resolution Research Tomography. Primary regions-of-interest included amygdala, globus pallidus, caudate, putamen, hippocampus, thalamus, and cerebral cortices. Group differences in mean composite as well as regional [11C]OMAR VT values were compared between SCZ and HC. Effects of symptoms (scores on the positive and negative syndrome scale (PANSS)), antipsychotic medication and smoking status were examined. All analyses were co-varied for age and body mass index.
Results: There were statistically significant [11C]OMAR VT differences between SCZ and HC (p=.007) with SCZ-UNMED < SCZ-MED < HC. Group X Region analyses revealed significant effect of group (p=.018), region (p<.0001) and group X region interaction (p<.0001) between SCZ and HC. Reduced [11C]OMAR VT in SCZ was observed even after controlling for cigarette smoking. There were no group differences in PANSS scores between SCZ-UNMED and SCZ-MED or SCZ Smokers and SCZ Non-smokers. There were no significant correlations between PANSS scores and CB1R availability in SCZ patients.
Conclusion: CB1R availability was lower in SCZ patients compared to matched healthy controls and provide support for altered EC function in SCZ. These results are in contrast with other PET studies that found increased CB1R availability in schizophrenia patients. Whether the reductions in CB1R availability are primary or secondary to the course of the illness is not clear. Furthermore, the observation that [11C]OMAR VT in SCZ-MED was in-between SCZ-UNMED and HC, suggests a "normalizing" effect of antipsychotic treatment on the EC system.
ID: 2119473

THE KETAMINE MODEL OF SCHIZOPHRENIA - RELATION BETWEEN GLUTAMATE LEVEL AND CEREBRAL BLOOD FLOW

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Background: The pathophysiology of schizophrenia is complex and only partly understood. Abnormalities in glutamatergic neurotransmission may be involved, particularly in patients not responding to antipsychotic treatment,. As the N-Methyl-D-Aspartate receptor (NMDAR) is central in glutamatergic neurotransmission, we use administration of the NMDAR antagonist S-ketamine (KET) in a sub-anesthetic dose to study the neurochemistry and neurophysiology in a model of schizophrenia. We investigate the temporal relation between glutamate level and cerebral blood flow (CBF) in anterior cingulate cortex (ACC).
Methods: Twenty-five healthy volunteers are included after exclusion of somatic and psychiatric diseases and abuse. Subjects are continuously MRI scanned for 90 min with dual echo Pseudo-Continuous Arterial Spin Labeling (pCASL). In the present abstract we focus on perfusion, but this sequence enables both perfusion and resting state connectivity. Glutamate levels in anterior cingulate cortex (ACC) are assessed by MR Spectroscopy (MRS). MRI assessments are done before, during, and after infusion of KET (total dose 0.375 mg/kg). The Positive And Negative Assessment Schedule (PANAS) and the Positive And Negative Syndrome Scale (PANSS) are used to assess psychopathology before and after scanning.
Results: Preliminary results (n=25) show significant increment in the PANSS total score after KET infusion (paired t-test, p = 0.001). The CBF (n=16) increase following infusion of KET, particularly in the ACC and medial frontal cortex (corrected level), reaching peak values at 20-30 min. Preliminary our analysis of the MRS data does not suggest glutamate levels in the ACC to be significantly affected by KET administration.
Conclusion: This work-in-progress validates previous findings showing that KET administration induces psychosis-like symptoms and increase CBF in frontal areas of the brain in healthy subjects. Surprisingly KET administration does not seem to increase ACC glutamate levels. Further analyses are required to validate these findings.
ID: 2116256

WHITE MATTER INTEGRITY AND CORTISOL LEVELS IN RELATION TO TREATMENT RESPONSE IN FIRST-EPISODE PSYCHOSIS PATIENTS

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Background: Previous studies have showed that first-episode psychotic (FEP) patients who show poor response to antipsychotic medication have significantly impaired white matter (WM) microstructure when compared to Responders. More recently, it has also been showed that baseline cortisol levels could also predict clinical outcome in FEP. It is therefore interesting to speculate whether stress and the activation of the HPA axis could mediate the clinical outcome through an impact on WM

microstructure. In this study, we explore for the first time the relationship between HPA axis activity, WM microstructure and clinical outcome in FEP patients.
Methods: MRI DTI data were acquired in 63 FEP patients and in 52 healthy control (HC) subjects. Positive and Negative Syndrome Scale (PANSS) was also used to evaluate treatment response after 12-weeks of treatment, and patients were classified as Responders or Non-Responders according to treatment outcome. To assess HPA axis activity we collected salivary cortisol during different periods of the day, and two measures of HPA axis activity were then calculated: Area Under the Curve (AUC) of cortisol levels during the day and the cortisol awakening response (CAR). Tract-based spatial statistics (TBSS) was used to assess the relationship between cortisol levels and WM microstructure.
Results: TBSS analysis examining the relationship between cortisol levels and WM structure showed a positive correlation between the CAR and Fractional Anisotropy (FA). In fact, the lower - more blunted - the CAR the lower the FA values in a number of WM regions, including the fornix and corpus callosum. We also observed a significant negative correlation between the CAR and Mean Diffusivity (MD), with the WM generally overlapping the ones observed in the FA analysis. There was no such relationship in the HC group for any of the different diffusivity measures analyzed. FA and MD values were examined in relation to cortisol levels and treatment outcome via a logistic regression analyses, showing a significant interaction between cortisol levels and FA in predicting treatment outcome.
Conclusion: To our knowledge, this is the first study to analyse the association between cortisol levels and WM microstructure in relation to treatment response in FEP. These findings suggest that the blunted cortisol response could mediate response to treatment through its effect in the microstructure of WM.
ID: 2119710

HERITABILITY OF MULTIMODAL BRAIN IMAGING MEASURES IN MULTIPLEX FAMILIES WITH SCHIZOPHRENIA

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Background: Schizophrenia is a heritable, complex brain disorder, and progress in understanding its pathophysiology requires integration of genetic and neurobiological methods. Quantitative measures of brain structure and function have fuelled the field of imaging genomics. The MGI initiative provides a unique opportunity to investigate shared genetic ancestry on structural and functional brain abnormalities. Here we: 1) estimate the heritability of subcortical brain volumes and shape and, 2) associate functional MRI activation patterns and performance on a computerized neurocognitive battery in MGI families.
Methods: 439 participants from two sites completed 3-Tesla structural magnetic resonance imaging.190 members from 32 Multiplex-Multigenerational families with schizophrenia and 249 healthy individuals underwent structural and functional MRI. Heritability was estimated for volume and shape of subcortical brain structures. In addition, sparse regression of regional brain activation was used to predict concurrent performance on six computerized neurocognitive tasks.
Results: Subcortical volume and shape are heritable in MGI families. Estimates of heritability ranged from 0.45 in the right hippocampus to 0.84 in the left putamen. Heritability estimates of subcortical shape exceeded estimates of volume alone. Functional brain activation patterns were domain-specific; prediction of performance was robust across neurocognitive tasks, particularly for abstraction/mental flexibility and visuo-spatial memory.
Conclusion: Our work identifies specific neuroimaging phenotypes in large Multiplex-Multigenerational families with schizophrenia. The specificity obtained using advanced neuroimaging methods in large extended pedigrees may improve the selection of imaging phenotypes that better reflect the underlying neurobiology of schizophrenia. Such localized features may be related to distinct dimensions of psychopathology or may be determined by specific genetic risk factors unique to patients with schizophrenia, or to particular families.
ID: 2088375

CANNABIS-RELATED EPISODIC MEMORY DEFICITS AND HIPPOCAMPAL MORPHOLOGICAL DIFFERENCES IN HEALTHY INDIVIDUALS AND SCHIZOPHRENIA SUBJECTS

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Background: Cannabis use has been associated with episodic memory (EM) impairments and abnormal hippocampus morphology among both healthy individuals and those with schizophrenia. Considering the role of the hippocampus for EM, research is needed to evaluate the relationship between cannabis-related hippocampal morphology and EM among healthy and clinical groups. We examined differences in hippocampus morphology between control and schizophrenia subjects with and without a past (but not current) cannabis use disorder (CUD).
Methods: Subjects group-matched on demographics included 44 healthy controls, 10 subjects with a CUD history, 28 schizophrenia subjects with no history of substance use disorders, and 15 schizophrenia subjects with a CUD history. Large-deformation, high-dimensional brain mapping with MRI was used to obtain surface-based representations of the hippocampus, compared across all four groups, and correlated with EM and CUD history. Surface maps of the hippocampus were generated to visualize morphological differences.
Results: There were parametric decreases in EM between subjects with and without a past CUD. Controls with CUD displayed both inward and outward shape differences compared to controls with no CUD ($F=7.4$, $p=0.01$). Schizophrenia subjects with CUD were characterized by exacerbated inward shape differences compared to schizophrenia subjects with no CUD ($F=5.6$, $p=0.02$). Cannabis-related shape was associated with poorer verbal EM among controls with CUD ($r=-0.25$, $p=0.04$). A longer duration of CUD abuse ($r=0.50$, $p=0.04$) and shorter duration of CUD abstinence ($r=-0.57$, $p=0.03$) were associated with cannabis-related shape differences among schizophrenia subjects with CUD.
Conclusion: These cross-sectional findings suggest both CUD groups were characterized by EM deficits and hippocampal morphology differences. The observed pattern of cannabis-related shape differed between controls and schizophrenia subjects. Hence, cannabis may interact with schizophrenia in a way that differs from otherwise healthy controls. Longitudinal research can help clarify whether cannabis use contributes to the observed shape differences or whether they are biomarkers of a susceptibility to the effects of cannabis.
ID: 2082937

FRONTAL GABA ACROSS AGE-SPAN IN SCHIZOPHRENIA: RELATION TO WORKING MEMORY

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Background: GABA dysfunction has been implicated in the pathophysiology of schizophrenia. Reduced expression of GAD67, a GABA synthesis enzyme, is a well-replicated molecular finding in schizophrenia. GABAergic interneurons are thought to facilitate the rhythmic entrainment of pyramidal cell discharge and their abnormalities may lead to cognitive dysfunctions in schizophrenia. Prior MRS studies of schizophrenia report abnormal GABA plus macromolecules (GABA+) levels, that varying depending upon medication status, illness duration/age, and brain region. This study tested the hypothesis that older participants with schizophrenia would have lower medial frontal GABA levels (not contaminated with macromolecules) and this would be related to working memory impairment.
Methods: A total of 145 participants completed this study. MR scanning was conducted on a 3T Siemens Tim Trio equipped with a 32-channel head coil. For detection of GABA, spectra were acquired from a medial frontal/anterior cingulate using a macromolecule-suppressed MEGA-Point REsolved Spectroscopy Sequence (MEGA-PRESS) sequence: TR/TE=2000/68 ms, 14 ms editing pulses applied at 1.9 (ON) and 1.5 (OFF) ppm, and 256 averages; water unsuppressed 16 averages. Quantification was conducted with GANNET 2.0 toolkit, a Matlab program specifically developed for analysis of GABA MEGA-PRESS spectra Patients were evaluated for psychopathology and all participants completed neuropsychological tests of working memory, processing speed, and functional capacity.
Results: GABA levels were significantly lower in the older participants with schizophrenia compared to older controls (p=0.003) but not between the younger control and schizophrenia groups (p=0.994). Age strongly predicted GABA levels in the schizophrenia group accounting for 42% of variance, but the effect of age was less in the control group accounting for 5.7% of the variance. GABA levels were specifically related to working memory but not processing speed performance, functional capacity, or positive or negative symptom severity.
Conclusion: This is by far the largest MRS study of GABA in schizophrenia and the first to examine GABA without macromolecule contamination, a potential confound in all previous studies. GABA levels more rapidly declined with advancing age in the schizophrenia compared to the control group. Interventions targeted at halting the decline or increasing GABA levels may improve functional outcomes and quality of life as patients with schizophrenia age.
ID: 2092825

FUNCTIONAL AND STRUCTURAL MRI STUDIES IN INDIVIDUALS WITH GENETIC OR CLINICAL HIGH RISK FOR SCHIZOPHRENIA

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Background: Intervention strategies for reducing disability and preventing psychotic disorders have evolved from First Episode to Clinical High Risk (CHR) "prodromal" phases and may evolve to earlier phases of pre-psychotic illness that are highlighted by family high-risk (FHR) studies. In this talk, we will review the literature on functional and structural MRI studies of FHR and CHR samples with some emphasis on recent findings from the second phase of the North American Prodrome Longitudinal Studies (NAPLS-2).
Methods: Results from our 2 recent reviews on structural and functional MRI studies of youth at risk for psychosis will be summarized as well as recent results from the NAPLS-2 study.
Results: In FHR studies, brain structural alterations are observed as young as 7 years of age, and are most robust in prefrontal cortex (PFC) and hippocampus. Such structural alterations are related to various functional alterations, including default mode functioning, cognitive impairments and schizotypal symptoms. Functional MRI studies reliably implicate PFC and temporal cortical dysfunctions. The Edinburgh HR study demonstrated PFC decline from adolescent FHR status to first episode of psychosis. Likewise, new results from NAPLS-2 demonstrate reduction of cortical volume over time. In NAPLS-2, controlling for multiple comparisons throughout the brain, CHR converters showed a steeper rate of gray matter loss in right superior frontal, middle frontal, and medial orbitofrontal cortical regions, as well as a greater rate of expansion of the third ventricle, compared with CHR non-converters and healthy controls. Differential tissue loss was present among cases who had not received antipsychotic medications during the inter-scan interval and was predicted by baseline levels of an aggregate measure of pro-inflammatory cytokines in plasma.
Conclusion: There is now strong evidence indicating that the adolescent/ young adult development of individuals at genetic and clinical high risk for schizophrenia is associated with smaller brain volumes, particularly in frontotemporal cortical areas, and that the further reduction in brain volumes is not explained by exposure to antipsychotic drugs. The findings demonstrate the importance of early intervention and simultaneously highlight the challenge to the field to develop strategies that could arrest or even reverse these brain changes.
ID: 2115562

BRAIN GLUTAMATE AND ELEVATED TRANSLOCATOR PROTEIN (TSPO) IN THE DEVELOPMENT OF PSYCHOTIC ILLNESS: A MULTIMODAL BRAIN IMAGING STUDY

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Background: Microglia perform immune surveillance roles and mount inflammatory response to injury. When microglia are activated in response to inflammatory stimuli they release glutamate that may cause neurotoxicity. Abnormal brain immune-response has been proposed as a mechanism associated with the brain volume decreases seen in schizophrenia. Microglia activation can be measured in vivo with positron emission tomography (PET) using radioligands specific for the 18KD translocator protein (TSPO), a marker expressed on microglia associated with inflammation. Recent PET in-vivo brain imaging studies show elevated TSPO binding in patients with schizophrenia. However it remains unclear how this relates to the onset of psychotic illness. To determine whether total grey matter TSPO is altered in individuals with ultra high-risk (UHR) symptoms for psychosis, prior to the onset of first psychotic episode. We also seek to determine how the TSPO correlates with cortical glutamate.
Methods: We quantified brain TSPO binding using PET and [11C]PBR28, a TSPO ligand in fourteen subjects with UHR symptoms and 14 patients with schizophrenia. All the subjects were age and TSPO genotype matched with control subjects. UHR subjects and controls also underwent [1H]-magnetic resonance spectroscopy (MRS) to index cortical glutamate levels. The main outcome measure was total grey matter [11C]PBR28 distribution volume ratios (DVRs). We also studied the interaction between total grey matter [11C]PBR28 and cortical glutamate in UHR subjects.

Results: Multiple analysis of variance analysis demonstrated an elevation in total grey matter [11C] PBR28 DVRs in both UHR subjects (controls 2.03 (0.02), UHR 2.09 (0.02); F=10.33; p=0.004) and patients with schizophrenia (p<0.001) when compared with respective controls. UHR symptoms, as measured with the Comprehensive assessment of the at risk mental state (CAARMS) were positively correlated with total grey matter [11C] PBR28 DVR (r=0.73; p<0.01) in UHR subjects. Altered glutamate-PBR28 DVRs relationships were examined. There was a significant negative correlation between whole brain grey matter [11C] PBR28 signal and the grey matter volume of patients with schizophrenia (p<0.01), which was not present in UHR subjects.
Conclusion: Increases in [11C] PBR28 in UHR subjects and patients with schizophrenia suggest that neuroinflammatory changes are associated with the development of psychosis, and may contribute to glutamatergic neurotoxicity.
ID: 2117795

IMPROVING TREATMENT OF PATIENTS WITH SCHIZOPHRENIA - DOPAMINE SYNTHESIS CAPACITY MEASURED WITH [18F]-DOPA PET-CT

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Background: Insufficient response to antipsychotics constitutes a challenge in the treatment of patients with schizophrenia. The aim is to stratify antipsychotic-naïve first-episode patients with schizophrenia based on striatal dopamine synthesis capacity (DSC) - and evaluate the prognostic value of stratification in terms of treatment response. The study is the first to combine examination of DSC (PET) with examinations of glutamate and GABA levels (MR-spectroscopy) and brain structure (structural and functional MRI). Psychophysiological- and cognitive examinations are performed. We hypothesize that responders are characterized by disturbances in DSC measurable prior to pharmacological treatment, while non-responders are characterized by no or minor disturbances in DSC but increased glutamate availability.
Methods: A prospective follow up study of 40 antipsychotic-naïve first-episode schizophrenia patients and 40 matched healthy controls. Projected start in autumn, 2014. Subjects are examined at baseline and after 6 weeks of treatment with flexible doses of aripiprazole (patients only). DSC will be related to psychopathology and level of functioning before and after 6 weeks of treatment, and to disturbances in the above-mentioned modalities. Dynamic scans will be performed in an integrated PET-CT scanner using fluorodopa (3,4-dihydroxy-6-[18F]fluoro-L-phenylalanine). Premedication is given to minimize pheripheral enzymatic degradation of fluorodopa. Arterial samples are used for analyzing kineticts for fluorodopa clearance especially the relationship between DSC and the loss of dopamine metabolites.
Results: Findings will add pathophysiological insights into the implications of DSC for treatment response. Previous studies have only included few antipsychotic-naïve first-episode patients and no previous studies have examined this patient group before and after first antipsychotic treatment. The data will provide insights into the interaction between dopaminergic and glutamatergic disturbances, clinical symptoms and level of functioning. Subgrouping patients with schizophrenia based on distinct pathophysiological disturbances is crucial, since DSC and glutamate levels may serve as markers for best choice of treatment.
Conclusion: It is hypothesized that a subgroup of patients with no or minor abnormalities in DSC and high levels of glutamate, will have poor treatment response and declining social functioning; while the inverse relationship will be found in a subgroup of responders.
ID: 2083873

DECREASED GLUTAMATE CONCENTRATIONS IN ANTERIOR CINGULATE IN SCHIZOPHRENIA

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Background: Convergent lines of evidence indicate that schizophrenia involves alterations in glutamate neurotransmission. While human postmortem and animal-model studies have been critical in achieving this understanding, any definitive testing of existing models requires in vivo demonstration in humans of neurotransmitter system pathology. In this study we aimed to measure glutamate-related neurochemical profiles in schizophrenia using proton magnetic resonance spectroscopy (MRS) at 7 T, taking advantage of the high field benefits of signal gain and spectral resolution enhancement. The concentrations of glutamate were measured in the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC), two regions critically involved in the pathophysiology of the disease, both in medicated volunteers with schizophrenia (SZ) and normal controls (NC).
Methods: Scanning included a scout scan and several spectral acquisitions with a region of interest focused on the anterior cingulate and dorsolateral prefrontal cortex. For each region, an optimized PRESS scan was conducted at 7T: PRESS (TE1, TE2) = (31, 61) ms for measurement of glutamate, glutamine, NAAG, NAA, creatine, and choline. MRS data acquisition parameters included TR = 2.5 s, Nave = 256, sweep width = 5 kHz, and number of sampling points = 4096 (scan time ≈ 10 min).
Results: Preliminary results from a sample of N = 14 normal volunteers and N= 25 volunteers with schizophrenia indicated lower glutamate in the anterior cingulate cortex of volunteers with schizophrenia (NC: 1.1 ± 0.06; SZ: 1.056 ± 0.1; p = 0.01) and no significant difference between the groups in the levels of DLPFC glutamate.
Conclusion: These preliminary results are consistent with previous reports of the levels of neurometabolites in schizophrenia. We intend to expand the sample by scanning additional participants, as well as unmedicated schizophrenia volunteers.
ID: 2090736

POSTURAL KNOWLEDGE OF GESTURES IN SCHIZOPHRENIA IS LINKED TO STRUCTURAL ALTERATIONS IN KEY REGIONS OF GESTURE PROCESSING AND CONNECTING LONG ASSOCIATION FIBERS

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Background: Higher order processes such as recognition of gestures rely on a network of distinct and distant brain areas. Particularly the role of key regions such as the left inferior frontal gyrus (IFG) and the inferior parietal lobe is subject to ongoing debate. Schizophrenia patients suffer from impaired gesture performance and recognition. However, neural correlates of impaired gesture recognition have not yet been investigated. We therefore aim to test associations between structural brain imaging and postural knowledge in schizophrenia using voxel based morphometry (VBM) and tract based spatial statistics (TBSS).
Methods: In total, 44 patients with schizophrenia (DSM-5 criteria; 59% men, mean age 38) underwent structural MR imaging and performed the comprehensive postural knowledge task (PKT) for hand gestures. All patients except four were treated with antipsychotics. T1-weighted images were processed using SPM8 and DTI-data using FSL TBSS routines. We explored correlations of PKT scores and gray matter (GM) volume in VBM data and correlations of PKT scores and white matter (WM) integrity in TBSS data. Results were corrected for multiple comparisons using family wise error correction.
Results: Impaired postural knowledge was related to reduced GM volume and WM integrity. Whole brain analyses revealed effects of postural knowledge on gray matter volume within right IFG extending to the insula, the superior parietal lobe and left hippocampus. Furthermore, significant correlations within fiber tracts connecting these regions - particularly alterations within the bilateral cingulum bundle and cingulum, the right superior longitudinal fasciculus, the right anterior limb of internal capsule, and the left fasciculus uncinatus - were associated with PKT performance.
Conclusion: Postural knowledge performance in schizophrenia patients was associated with GM volume of meaningful brain regions. Our results are in line with the literature as particularly lesions in the left IFG were found to predict poor gesture recognition in brain damaged patients. In addition an effect of postural knowledge on WM integrity was shown within fiber tracts connecting key regions of gesture processing. Furthermore, hippocampus is part of a brain system responsible for spatial memory and navigation and volume reduction is a consistent structural finding in schizophrenia. The results suggest that structural brain alterations in the common gesture network contribute to impaired postural knowledge in schizophrenia.
ID: 2084600

DIFFERENCES IN CORRELATIONS BETWEEN CORTICAL THICKNESS AND EMPATHIC FUNCTIONING IN SCHIZOPHRENIA

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Background: Schizophrenia (SCZ) is a debilitating disease that decreases social functioning. Although several studies evaluated SCZ-related structural brain abnormalities and their association with neurocognition, few studies have evaluated the relationship between brain structure and social cognition (e.g., cognitive empathy) in this population. Cognitive empathy has been defined as taking the emotional perspective of others. In this study, we examined the relationship between cortical thickness and cognitive empathy in SCZ and control (CON) subjects.
Methods: CON (n=40) and SCZ (n=42) subjects completed a cognitive empathy task and a 3T MRI scan. Cortical thickness was measured bilaterally in the inferior frontal gyrus (IFG), insula, anterior midcingulate cortex (aMCC), supplementary motor area (SMA), temporoparietal junction (TPJ), and precuneus. T-tests were used to evaluate between-group differences with respect to the cognitive empathy measures and a priori neural regions. We used Pearson correlations to evaluate the relationship between cortical thickness and cognitive empathy within each group.
Results: Between-group differences were observed for cognitive empathy performance (CON>SCZ, $p<.001$). Compared to CON, SCZ subjects were characterized by cortical thinning in the IFG, insula, SMA, aMCC, TPJ, and precuneus ($p < .05$). Among CON, we observed that higher performance-based cognitive empathy was related to greater thickness in the IFG (RH r=.45), insula (LH r=.57, RH r=.56), aMCC (LH r=.45, RH r=.43), SMA (LH r=.40, RH r=.32), TPJ (LH r=.58, RH r=.47), and precuneus (LH r=.45, RH r=.52) (all $p < .05$). We did not observe any significant correlations between cortical thickness and cognitive empathy in SCZ subjects.
Conclusion: The observed patterns of cortical thinning in the empathy-related neural regions of SCZ subjects are consistent with prior research. The correlation analyses suggest that there is an important, widespread relationship between cortical thickness in empathy-related neural regions and cognitive empathy performance in CON that diverges among SCZ subjects. The findings suggests that impaired cognitive empathy in schizophrenia may not be related exclusively - or even primarily - to a decrease in thickness in empathy-related brain regions. Thus, there may be other neurobiological etiologies of empathic dysfunction in schizophrenia, such as local neuronal hypo- or hyperactivity, irregular connectivity between brain regions, or dysregulation by higher order brain regions.
ID: 2119057

WHITE MATTER MICROSTRUCTURAL ALTERATIONS IN FIRST-EPISODE AND CHRONIC PSYCHOSIS

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Background: There is considerable controversy in the literature regarding progression of white matter abnormalities over the course of psychosis. In this cross-sectional study we used diffusion tensor imaging to characterize putative white matter integrity in a cohort of 113 patients at different stages of psychosis and 111 healthy volunteers over the age range of 14 to 64.
Methods: All individuals participating in the study received diffusion tensor imaging exams and were categorized into 1 of 4 groups based on having a history of psychosis or being a healthy volunteer (no history of psychosis or major mood disorder) and being younger (age < 30) or older (age ≥ 30). The 4 groups thus included: (1) younger psychosis patients (N=65; 47M/18F - mean age = 20.7; SD = 3.5); (2) younger healthy volunteers (N=63; 40M/23F - mean age = 20.3, SD = 3.6); (3) older psychosis patients (N=48; 30M/18F - mean age = 45.5, SD = 9.0); and (4) older healthy volunteers (N=48; 29M/19F - mean age = 44.4; SD = 8.9). The trajectories of two inter-hemispheric tracts, two projection tracts, and five bilateral association tracts were traced and quantified using probabilistic tractography.
Results: The main finding that distinguished patients with psychosis from healthy volunteers was a significant ($p < .05$) group x region interaction for fractional anisotropy. Post-hoc analyses indicated that fractional anisotropy was significantly ($p < .05$) lower in patients compared to healthy volunteers (across age groups) both in the inferior longitudinal fasciculus and superior longitudinal fasciculus. Subsequent analyses revealed that patient-control differences were significant ($p < .05$) and effect sizes comparable for the inferior longitudinal fasciculus and superior longitudinal fasciculus in

both the younger (effect sizes i.e., eta-squared = .047 and .058, respectively) and older (effect sizes = .071 and .043, respectively) age groups.
Conclusion: To our knowledge, this is the largest study to examine the relationship between age and microstructural integrity of the major white matter tracts in the first-episode of psychosis and chronic illness. Taken together, these findings argue against progression of white matter abnormalities over the course of psychosis. Moreover, these findings implicate comparable white matter alterations in two independent samples of patients with psychosis compared respectively to age- and sex-matched healthy volunteers.
ID: 2083279

ALTERATIONS OF WHITE MATTER AMONG CHINESE DRUG-NAIVE SUBJECTS AT ULTRA HIGH RISK OF PSYCHOSIS

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Background: Impaired integrity of white matter (WM) has been demonstrated in schizophrenia patients. By examining white matter alterations among subjects at ultra high risk of psychosis, we attempt to determine whether these abnormalities are present before illness onset.
Methods: We recruited 17 drug-naive subjects at ultra high risk of psychosis (UHR, 26.23 ± 8.30 yrs, 11 male / 6 female), 18 first-episode schizophrenia patients (FSZ, 25.11 ± 9.01 yrs, 14 male / 4 female) and 23 age/sex-matched healthy controls (HCs, 26.43 ± 7.46 yrs, 15 male / 8 female) from Shanghai Mental Health Center in China. Diffusion weighted images were collected from each individual using Siemens' 3T Trio MR system. By using tract-based spatial statistics (TBSS), one-way ANOVA was performed to access group differences in fractional anisotropy (FA) among UHR, FSZ and HCs.
Results: The UHR group showed reduced FA values ($P<0.05$) over the bilateral cingulum, left inferior fronto-occipital fasciculus, left inferior longitudinal fasciculus, left superior longitudinal fasciculus and left uncinate fasciculus as compared with HCs. The FSZ group showed more extensive reductions of FA values ($P<0.05$) over the anterior thalamic radiation, bilateral cingulum, bilateral inferior fronto-occipital fasciculus, bilateral inferior longitudinal fasciculus, bilateral superior longitudinal fasciculus, bilateral uncinate fasciculus and bilateral superior longitudinal fasciculus.
Conclusion: These findings reflected white matter abnormalities among UHR subjects as well as among FSZ patients. However, the distribution of WM alterations among UHR subjects was mainly localized over the left hemisphere, which was different from that among FSZ patients. The left-hemisphere WM alterations might play an important role in illness onset.
ID: 2090234

GLUTAMINE, GLUTAMATE, AND GABA CONCENTRATIONS IN THE STRIATUM AND VISUAL CORTEX OF SCHIZOPHRENIA PATIENTS AND HEALTHY FIRST-DEGREE RELATIVES: A ^{1}H-MRS STUDY AT 7T

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Background: In recent years, the NMDA-receptor hypofunction model of schizophrenia has gained increasing support. This model predicts a somewhat paradoxical increase in glutamate transmission, resulting in cortical overexcitation. One hypothesized route to this increased excitation is via a reduction in GABAergic interneuron activity. In the current study we aimed to address this hypothesis by measuring γ-aminobutyric acid (GABA), glutamate (Glu), and glutamine (Gln) concentrations in patients with schizophrenia using proton magnetic spectroscopy (^{1}H-MRS) at an ultra-high field strength, which allows separation of these metabolites that would otherwise overlap at lower field strengths. In addition, we investigated the degree to which putatively altered levels of GABA, Glu, and Gln reflect genetic vulnerability towards schizophrenia by including healthy first-degree relatives.
Methods: 21 chronic, medicated schizophrenia patients, 21 healthy first-degree relatives of schizophrenia patients, and 17 healthy non-relatives underwent ^{1}H-MRS at 7T. Glu, Gln, and GABA were measured in both the right striatum, given its postulated role in disease symptomatology, and the occipital cortex. Glu and Gln were measured with a semi-LASER sequence and GABA was measured with a MEGA-sLASER sequence. Metabolites were quantified using an automated fitting procedure, which relies on a priori knowledge of the spectral components. Quantities were expressed as ratios relative to water.
Results: Preliminary results indicate altered levels of GABA and Gln, but not Glu, in the visual cortex of patients with schizophrenia. Patients had less GABA than healthy controls and, at a trend level, healthy relatives. However, patients with schizophrenia had significantly more Gln than controls. These differences remain even after accounting for differences in tissue composition of the voxel across individuals. Group differences in metabolite/water ratios in the striatum did not meet significance.
Conclusion: This is the first study to measure GABA, Glu, and Gln in patients with schizophrenia and their healthy relatives at 7T. Greater cortical Gln accompanied by reduced GABA in patients with schizophrenia provides evidence supporting a mechanism by which NMDA receptor hypofunction leads to an imbalance between cortical excitation and inhibition, potentially via dysfunction of GABAergic interneurons.
ID: 2087161

NEUROCHEMICAL PROFILE OF FRONTAL WHITE MATTER IN EARLY PHASE SCHIZOPHRENIA: A 1H-MRS STUDY AT 4 TESLA

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Background: The neurochemical profile of schizophrenia, as measured by brain in vivo magnetic resonance spectroscopy (1H-MRS), still remains to be fully characterized. While advances have been made in our understanding of the potential directions of changes at various phases of illness, a reduction of clarity of findings has resulted from studies examining voxels of mixed brain tissue types (white matter (WM) and grey matter (GM)). Additionally, while the past focus has been on GM, current theoretical work implicates the need to further assess WM's role in schizophrenia.
Methods: Proton spectroscopy was acquired at 4 Tesla, from a large frontal brain region encompassing an average of 95% of white matter (the superior longitudinal fasciculus). We used 384 sampling acquisitions for each of the neurochemical and macromolecules spectra, a LASER sequence and a short time of echo (TE = 46 ms). Eleven neurochemical signals were reliably resolved, using internal water as a reference: N-acetyl aspartate plus N-Acetyl-aspartyl-glutamate (NAA+NAAG), Phospho-creatine plus creatine (PCR+CR), glycerophosphocholine plus Phosphocholine (GPC+PC), Glutamate plus Glutamine, Myo-Inositol (mI), Syllo-Inositol, Alanine, Lactate, Gluthathione, NAA alone, and NAAG alone.

Results: We present preliminary data from 30 outpatients in their early phase of schizophrenia (less than 5 years of illness), compared to 49 matched healthy controls. Patients displayed significant reductions in levels of Myo-Inositol (effect size Cohen's d = 0.7), of PCR+CR (d = 0.6) and of GPC+PC (d = 0.5).
Conclusion: Myo-inositol and GPC+PC have important roles in myelination processes, thus pointing to irregularities in myelination and/or in glial cell densities occurring in early phase schizophrenia. We are currently running sensitivity analyses to uncover the footprint of white matter neurochemical abnormalities in early phase schizophrenia.
ID: 2116705

STRESS-INDUCED DOPAMINE RELEASE IN SUBJECTS AT CLINICAL HIGH RISK FOR PSYCHOSIS: PRELIMINARY RESULTS FOR A [11C]-FLB457 PET STUDY

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Background: The etiology of schizophrenia (SCZ) is complex and multifactorial. The underlying neurobiological condition that leads to increased vulnerability of developing psychotic episodes in patients with SCZ and those at clinical high risk for the disease (CHR) remains unclear, while stress may play a key modulatory role. The pre-clinical findings supports that repeated stress, despite an increase in striatal dopamine levels, decreases dopamine levels in prefrontal cortex (PFC). However, stress-induced cortical dopamine release in SCZ and CHR has never been tested. The current study aims to examine the effects of stress in the dorsolateral and medial PFC to elucidate prefrontal abnormalities in dopamine release. A blunting of cortical stress-induced dopamine release in CHR and drug-naïve SCZ is hypothesized, compared to age-matched healthy volunteers (HV).
Methods: To examine changes in dopamine release outside the striatal regions, we took advantage of very high-affinity dopamine D2/3 PET tracer: [11C]-FLB 457. We aim to compare the displacement of [11C]-FLB457 by the endogenous DA levels under social stress in CHR and drug-naïve SCZ to age-matched healthy volunteers. All subjects will undergo two PET scans on separate days: one while undergoing the stress-inducing Montreal Imaging Stress Task (MIST) and one while undergoing an arithmetic Sensory-Motor Control Task (SMCT). The MIST is a validated social-stress challenge paradigm, known to elicit a safe and reproducible behavioral and neuroendocrine response together with dopamine release in humans.
Results: 6 HV, 8 CHR and 9 SCZ subjects have been examined so far. Compared to HV, we found a trend towards increased displacement of [11C]-FLB457 by endogenous DA during MIST in CHR and SCZ in anterior cingulate and medial PFC regions. In contrast, during SMCT a trend toward decreased binding potential for [11C]-FLB457 in dorsolateral and medial PFC regions in SCZ was observed.
Conclusion: Against our hypothesis, trends of higher DA release regarding stress in CHR and drug-naïve SCZ, and lower DA release during non-stress cognitive task in SCZ were both observed. While the group sizes are still too small to draw a conclusion, these preliminary findings speculate that the cognitive demands would induce less prefrontal DA release in drug-naive SCZ, while the cortical DA response to social stress in CHR and drug-naive SCZ might have been progressively sensitized. Larger sample sizes is warranted to confirm the results.
ID: 2087424

STRUCTURAL ANOMALIES OF THE PERIPHERAL OLFACTORY SYSTEM IN INDIVIDUALS AT CLINICAL RISK FOR SCHIZOPHRENIA

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Background: Schizophrenia patients have prominent olfactory deficits, which reflect structural and functional impairments of the underlying peripheral olfactory sensory apparatus. These olfactory deficits precede the onset of illness and are also seen in clinical high-risk (prodromal) adolescents (CR), where they may predict future conversion to illness. We therefore hypothesized that CR subjects would also exhibit structural abnormalities of the peripheral olfactory system, consistent with and reflecting the system's development during a critical embryonic risk period for psychosis.
Methods: 22 CR and 21 low-risk (LR) subjects of comparable age and sex distribution were assessed with multiple probes of olfactory system integrity. These included behavioral tests of olfactory ability, acoustic rhinometry to assess nasal cavity volume, high-resolution T2-weighted and DWI diffusion-weighted MRI scans to assess volume and microstructure of the olfactory bulbs, and T1-weighted MRI to assess primary olfactory cortex gray matter volume.
Results: Consistent with previous findings, CR subjects were significantly impaired in their ability to detect, discriminate and identify odors. Mirroring what we have observed for schizophrenia patients, CR subjects also had significantly smaller volumes of both the posterior nasal cavities and the olfactory bulbs. In addition, they had reduced diffusivity (ADC) in the olfactory bulbs, implying reduced extracellular bulb parenchyma. Finally, they had selective reductions in gray matter volume in the olfactory (perirhinal) paleocortex, but not in the immediately adjacent temporal pole neocortex.
Conclusion: Adolescents at clinical risk for developing schizophrenia exhibit structural anomalies at all three levels of the peripheral olfactory system - the nasal cavities, the olfactory bulbs, and the primary sensory cortex. The selectivity of these deficits, as distinct from the adjacent neocortex, implies a specific embryonic etiology, rather than a global or degenerative process. The olfactory system develops in the late first trimester, in close conjunction with the overlying forebrain. This is a critical period during which environmental stressors can increase the risk for psychosis. These findings suggest that structural anomalies of the olfactory system are sensitive indicators of an intrauterine disturbance during this embryonic period and robust neurodevelopmental biomarkers of future risk status.
ID: 2118976

MEDICATION-NAÏVE, FIRST-EPISODE SCHIZOPHRENIA PATIENTS SHOW INCREASED EXCITABILITY OF NEURAL CIRCUITS: INSIGHTS FROM MAGNETOENCEPHALOGRAPHY (MEG)

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Background: We assessed Magnetoencephalographic responses in 1) a group of n =17 medication-naive first-episode (FE) schizophrenia (ScZ) patients 2) a sample of chronically medicated ScZ patients (n = 18) and 3) a group of healthy volunteers (n = 15) who were administered a subanesthetic dose

of Ketamine. The latter group was included to examine the potential compatability of findings in FE-ScZ patients with NMDA-R hypofunctioning of ScZ.
Methods: ScZ-studies: MEG signals were analyzed in the 5-140 Hz range and a dynamical imaging of coherent sources (DICS) beamformer and transfer-entropy was computed between sources as an index of effective connectivity during resting-state and during two perceptual tasks: 1) a face processing task requiring perceptual organisation of visual elements 2) a moving sinusoidal grating.
MEG-data during Ketamine: Neural oscillations were recorded in a group of 15 healthy volunteers during the administration of a sub-anesthetic dose of ketamine (0.006 mg/Kg) and a placebo saline solution in a within-subject design. MEG-data were recorded during the presentation of a sinusoidal grating at rest.
Results: Resting-State Data: FE-ScZ patients revealed an increase in resting-state neural oscillations and connectivity in the gamma-frequency range in a network including hippocampus, temporal gyrus and cerebellum. This upregulation was not present in chronic ScZ-patients.
Task-Related MEG-Responses: Similar to chronic ScZ-patients, the amplitude of 60-120 Hz power was significantly reduced at illness-onset although the impairment was less pronounced. In addition, the analysis of M100, M170 and M250 components revealed increased responses in FE-ScZ patients while in chronic patients reductions in all components were observed. Ketamine lead to an upregulated gamma-band activity both at rest and during visual processing in health controls.
Conclusion: The analysis of MEG-data reveals distinct pattern of neural responses in FE-ScZ patients which is supported by elevated, spontaneous gamma-band activity as well as increased amplitude of ERF-responses which were not observed in chronically medicated ScZ-samples. This pattern of MEG-activity at illness onset is consistent with the effects of the NMDA-R antagonist Ketamine on MEG-parameters in healthy volunteers, suggesting that aberrant glutamatergic neurotransmission may underlie the increased excitability of neural circuits.
ID: 2117956

STRUCTURAL IMAGING CORRELATES OF IMPAIRED GESTURE PERFORMANCE IN SCHIZOPHRENIA

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Background: Schizophrenia is associated with poor nonverbal communication. Impairments in the performance of hand gestures have been shown in 67 % of patients with schizophrenia. These deficits are similar to those seen in Apraxia, which is often due to lesions in the inferior parietal (IPL) lobe, insula and inferior frontal gyrus (IFG). In Schizophrenia however, the neural correlates are unknown. Therefore, we investigated structural correlates of impaired gesture performance in schizophrenia.
Methods: In 43 patients with schizophrenia spectrum disorders, gesture performance was assessed by the comprehensive Test of Upper Limb Apraxia (TULIA). Performance was video recorded and blindly rated for accuracy. Structural brain imaging was measured in all patients using a 3-T MR Scanner. Grey matter density was correlated with TULIA scores using Whole-Brain Voxel-Based Morphometry (VBM) and intracranial volume as covariate. White matter integrity was correlated with TULIA scores using Tract-Based Spatial Statistics (TBSS) and age as covariate.
Results: The TULIA total score correlated with grey matter density in three clusters at $p < 0.05$ FWE-corrected: right insula, posterior cingulate cortex and anterior cingulate cortex. Poor gesture performance was associated with reduced grey matter density in these clusters. In addition white matter integrity correlated significant at $p < 0.05$ (corrected) with the TULIA total score in clusters of the frontal white matter in the anterior cingulum and corona radiate bilaterally as well as left uncinate fasciculus. These clusters were located close to the anterior cingulate cortex cluster of the grey matter results.
Conclusion: Aberrant brain structure is associated with poor gesture performance in schizophrenia. Particularly in key regions of the praxis network, i.e. insula, parietal cortex, we detected correlations of gesture performance and grey and white matter markers. In addition, the anterior cingulate cortex grey matter was correlated to gesture performance, a region implicated in action planning and control. Therefore, specific brain structural alterations may contribute to deficits in nonverbal communication in schizophrenia.
ID: 2080633

INFLAMMATION IN THE ANTERIOR CINGULATE CORTEX (ACC) AND ASSOCIATIONS WITH OLFACTORY HEDONICS AND ANHEDONIA IN SCHIZOPHRENIA

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Background: Abnormalities in the anterior cingulate cortex (ACC), a paralimbic structure implicated in the processing of emotional stimuli, have been identified in schizophrenia. Neuroinflammation has been noted in schizophrenia, but has yet to be studied specifically in the ACC. Additionally, the affective and perceptual correlates of ACC pathology have not been well-studied in the context of schizophrenia. Thus, the present study examined the presence of inflammation in the rostral (r) and caudal (c) ACC in schizophrenia, and the relationship between inflammation in these regions, hedonic judgment of odorants, and self-reported anhedonia.
Methods: The sample included 20 cases with schizophrenia-spectrum disorders and 11 healthy comparison subjects. Magnetic resonance (MR) imaging and three-dimensional 3-T voxel proton MR spectroscopy were used to measure absolute rostral and caudal ACC myo-inositol (mI) and creatine (Cr). Participants ranked the pleasantness of three similar pleasant (acetate) and unpleasant (acid) odorants of differing concentrations. Patterns for odorant ranking were observed in healthy controls (n=20), and patient response patterns were correlated with the control rankings. Anhedonia was measured with the Chapman Anhedonia Scales.
Results: Highly significant strong positive correlations between ACC mI and Cr concentrations suggest neuroinflammatory processes in cases (r=.736;

p<.001), but not in controls (r=.573, p=.065). In cases, ACC inflammation was negatively associated with judgment of unpleasant odors (r=-.452, p=.045); similar results were observed specifically for the cACC (r=-.476, p=.034). The ratio of r:cACC inflammation was positively associated judgment of unpleasant odors (r=.738, p<.001). cACC inflammation was also positively correlated with judgment of pleasant odors (r=.508, p=.023). rACC inflammation presented no significant relationships with judgment of odors. Social anhedonia was positively correlated with judgment of unpleasant odors (r=.396, p=.006) and negatively correlated to judgment of pleasant odors (r=-.336, p=.022).

Conclusion: These results support a relationship between inflammation in the ACC and perceptual and affective abnormalities in schizophrenia. Specifically, inflammation in the cACC was related to impaired hedonic judgment of unpleasant odors, consistent with a recent ACC model (Etkin et al., 2011) in which affective processing is not restricted to the rACC. This has implications for future research on emotion processing in schizophrenia.

ID: 2083528

STRUCTURAL IMAGING CORRELATES OF IMPAIRED NONVERBAL SOCIAL PERCEPTION IN SCHIZOPHRENIA

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Background: Nonverbal social perception is impaired in schizophrenia. Poor nonverbal social perception has been linked to poor functional outcome. However, the neural correlates of this deficit are unknown. In this study, we aim to investigate whether performance in a nonverbal social perception test was correlated with parameters of structural brain imaging.

Methods: In 43 patients with schizophrenia spectrum disorders, we applied the Mini-Profile of Nonverbal Sensitivity (Mini-PONS). On the same day, we acquired structural brain imaging at 3T including T1 weighted images and diffusion tensor imaging (DTI). Patients' mean age was 43 years. Average PANSS total scores were 72. Grey matter density was correlated with PONS scores using voxel based morphometry and the intracranial volume as covariate. White matter integrity was correlated with PONS using tract based spatial statistics using age as covariate. VBM results were corrected using family-wise error correction (FWE), DTI results were corrected using Monte-Carlo-Simulations with 5000 iterations.

Results: The PONS total score correlated with grey matter density in three clusters at $p < 0.05$ FWE-corrected: left insula, right superior parietal lobe and right precuneus. The subscore for combined face and voice stimuli correlated with grey matter in the left insula (FWE-corrected).

White matter integrity was not correlated with the PONS total score at $p < 0.05$ (corrected). However, white matter integrity was correlated with PONS subscore face and voice stimuli in clusters of the left external capsule close to insula, left superior longitudinal fasciculus close to the superior parietal lobe and in bilateral posterior corona radiata extending in the occipital cortex.

Conclusion: Poor nonverbal social perception in schizophrenia is linked to aberrant brain structure. Particularly the left insula and its adjoining white matter were correlated to PONS performance. The left insula area is critical for correct decoding of gestures, prosody and emotions in healthy subjects. Furthermore, grey matter density of the parietal cortex and white matter integrity of the adjoining superior longitudinal fasciculus were correlated to nonverbal sensitivity. These parietal areas are part of a gesture network. Structural alterations in critical brain areas in schizophrenia contribute to poor understanding of nonverbal communication.

ID: 2080469

SCHIZCONNECT: A ONE-STOP WEB-BASED RESOURCE FOR LARGE-SCALE SCHIZOPHRENIA NEUROIMAGING DATA INTEGRATION

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Background: Increasingly, sharing of large-sample data is needed in schizophrenia research to address the heterogeneity and complexity of the disorder. However, despite developments of recent consortia such as the Functional Biomedical Informatics Research Network (FBIRN), the MIND Clinical Imaging Consortium (MCIC) and others, existing technical barriers limit combination of data from these databases. We present SchizConnect, a resource for seamless integration of schizophrenia neuroimaging databases.

Methods: SchizConnect has 3 components: 1) The data sources - individual databases with idiosyncratic platforms, interfaces, but similar variables. Currently these are NUSDAST (http://www.nitrc.org/projects/nusdast/), FBIRN HID (http://fbirnbdr.nbirn.net:8080/BDR/), and COINS (http://coins.mrn.org/dx). 2) The Mediator - the data integration engine, containing common data models that mediate across the different data sources. 3) The web portal for data query and download. The data remain at the sources, but are accessible through SchizConnect in one interface.

At http://SchizConnect.org, the user builds a query using a graphical user interface (GUI), which constructs an SQL query over the common schema. The Mediator translates the user query into a query over the sources schemas, and then queries each data source directly using source-specific protocols. The returns are collated and presented to the user as a unified table that includes mediated common data model terms and associated provenance. The user then interacts with SchizConnect.org to complete the data use agreements (DUAs) and download.

Results: Currently, neuroimaging and non-imaging metadata from 1,120 subjects are accessible through SchizConnect. Queryable (i.e., mediated) variables are grouped into data models for subject (e.g., age, gender, diagnosis), scanner (e.g., scanner manufacturer, model, field strength), and protocol (e.g., structural, resting state, task paradigm functional).

SchizConnect returns summary counts and detailed subject-level information/data to the unregistered and registered user, respectively. For downloading, images are transferred out of the data sources and made available at SchizConnect.org host along with the queried data.

Conclusion: SchizConnect overcomes current data sharing barriers, and allows for querying and combing of neuroimaging data from different databases within a single interface.

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ID: 2084766

HIGH BLOOD CYTOKINE LEVELS ARE LINKED TO DECREASED VERBAL FLUENCY AND BROCA'S AREA VOLUME REDUCTION IN SCHIZOPHRENIA

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Background: There is increasing evidence for the role of the immune system in the pathogenesis of schizophrenia. We predicted a subset of people with schizophrenia would display increased immune activity which would be related to more severe cognitive and structural brain abnormalities.
Methods: In 42 patients with schizophrenia and 42 age and sex matched controls we assayed cytokine mRNA (IL1β, IL8, IL6, IL18 and IL2) from white blood cells, cognition and structural MRI.
Results: Applying a two-step clustering algorithm, we identified two subgroups characterized by either high (n=35) or low (n=49) cytokine levels. The high inflammatory group contained significantly more people with schizophrenia (n=22/35) than controls (n=13/35, $\chi 2=3.97$, $p<0.05$). There was no IQ difference between high and low inflammatory groups; however, verbal fluency was significantly lower in the high inflammation group, $t(40)=-2.32$, $p<0.05$. A forward stepwise linear regression showed that IL1β mRNA had a significant inverse relationship with verbal fluency in schizophrenia, $\beta= -.35$, $F(1,40)=5.51$, $p=0.02$. The schizophrenia high/low inflammatory groups (n=36) differed significantly across language region volumes in the left hemisphere, $F(4,26)=3.38$, $p=0.02$. Post-hoc analysis showed only the left pars opercularis volume was significantly (15%) smaller in the high inflammatory group, $F(1,29)=5.31$, $p<0.03$.
Conclusion: These results show that increased levels of peripheral immune mRNAs are significantly related to both poorer verbal fluency and reduced Broca's area brain volume in schizophrenia. These results raise the possibility of administering anti-inflammatory treatments that may reverse language deficits and associated brain abnormalities in subgroups of people with schizophrenia identified by immune related biomarkers.
ID: 2089392

INTELLECTUALLY CATEGORIZED SUBGROUPS IN SCHIZOPHRENIA: INDEPENDENT REPLICATION AND HIPPOCAMPAL VOLUMETRIC REDUCTION IN THE DETERIORATED GROUP

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Background: Schizophrenia is a heterogeneous illness characterized in part by cognitive impairment. Current and premorbid IQ differences have been useful for classifying schizophrenia. Here we aim to replicate and extend previous classification work in an independent sample first by using similar criteria to define these groups and then by determining the extent to which regionally distinct volumetric brain abnormalities are present in these subgroups.
Methods: Ninety-six chronically ill out-patients (age: 18-55 years old, mean age 36 SD 8.4, 59 males) with schizophrenia or schizoaffective disorder were recruited in Sydney and in Adelaide, Australia. All patients were administered a four subtest version of the Wechsler Adult Intelligence Scale 3rd edition to assess current IQ, the Wechsler Test of Adult Reading to assess premorbid IQ, the Positive And Negative Syndrome Scale (PANSS) to assess symptom severity, and 60 patients received a structural MRI brain scan. All patients were classified on the basis of current and premorbid IQ differences. Regional MRI brain volumetric differences among the cognitive groups were tested with Univariate ANOVAs using sex and age as covariates.
Results: Clinical based grouping produced 33% preserved (no decline from normal premorbid IQ), 62% deteriorated (~10 point decline from premorbid IQ with disease onset), and 5% compromised (low IQ before and after illness onset). Empirical based grouping using k-mean clustering produced 26% preserved, 63% deteriorated, and 11% compromised. All PANSS scores were significantly worse in the clinically deteriorated relative to preserved group (p's < 0.03). The empirically defined deteriorated group (n = 34) showed significantly reduced left hippocampal grey matter volume relative to the preserved group (n = 21), p = 0.002.
Conclusion: Using an independent sample we obtained intellectually derived subgroups in proportions that approximate previous work. Hippocampal volumetric reduction is characteristic of apparent cognitive deterioration in schizophrenia.
ID: 2080260

USING NETWORK-BASED NEUROIMAGING ANALYSES TO DISSECT THE HETEROGENEITY OF SCHIZOPHRENIA IN MULTIPLE SAMPLES

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Background: The clinical heterogeneity of schizophrenia has hindered neurobiological investigations aimed at identifying neural correlates of the disorder. The main objective of this study was to identify network-based biomarkers across the spectrum of impairment present in this disorder by evaluating subjects with 'deficit' and 'nondeficit' subtypes of schizophrenia separately
Methods: This neuroimaging study included patients with the deficit subtype and nondeficit subtype of schizophrenia, as well as people with bipolar disorder and healthy controls. Patients with schizophrenia (N=128) and matched healthy controls (N=130) from two academic centers and patients with bipolar disorder (N=39) and matched healthy controls (N=43) from a third site were included. Schizophrenia patients at each site in the top quartile on the proxy scale for the deficit syndrome were classified as having deficit schizophrenia and in the bottom quartile as nondeficit schizophrenia. All subjects underwent a MRI scan. Network-level properties of cortical thickness were assessed in each group. Inter-regional cortex-wide coupling was compared among the groups and graph theoretical approaches were used to assess network density and node degree, betweenness, closeness and eigenvector centrality.
Results: Stronger fronto-parietal and fronto-temporal coupling was found in patients with deficit schizophrenia compared to those with nondeficit schizophrenia. Nondeficit schizophrenia and bipolar

disorder patients did not show differences in coupling relative to controls. The networks formed from patients with deficit schizophrenia demonstrated increased density of connections and high node centrality in supramarginal, middle and superior temporal and inferior frontal regions. Network properties were similar in deficit patients from both sites.
Conclusion: Schizophrenia patients at one end of a spectrum show characteristic signatures of altered intra-cortical relationships compared to schizophrenia patients at the other end of that spectrum, bipolar patients and controls. Cortical connectomic approaches can be used to reliably identify neural signatures in clinically heterogeneous groups of patients.
ID: 2086264

ALTERED GLUTAMATE AND REGIONAL CEREBRAL BLOOD FLOW LEVELS IN OLDER ADULT SCHIZOPHRENIA: A 1H-MRS AND PCASL STUDY

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Background: The neurobiology of schizophrenia (SZ) may be distinctly different in older SZ compared to younger SZ such that lower doses of antipsychotic medication are needed and less severe general psychopathology is observed. To gain a better understanding of the brain pathophysiology late in life, measurements of glutamate (Glu) using a novel magnetic resonance spectroscopy (MRS) technique and regional cerebral blood flow (rCBF) using arterial spin labeling (ASL) were acquired in a large sample of older and younger adults with SZ and age-matched healthy controls (HC).
Methods: The data were collected on a Siemens TIM TRIO 3-T MRI system from 27 younger SZ, 29 older SZ, 36 younger HC, and 34 older HC. The MRS voxel was localized in the medial prefrontal region using phase rotation STEAM sequence with a TE=6.5ms. Data were quantified in LCModel, and only metabolites with CRLBs ≤ 20% were used. A pCASL sequence was utilized for quantification of rCBF in units of mL per 100 g per minute. Two-way ANOVAs with diagnosis and age as main effects were performed, and Pearson product moment correlations were performed to examine the relationship between Glu and rCBF.
Results: Two-way ANOVAs with diagnosis and age as main effects revealed significant effects of age ($p<0.001$), diagnosis ($p<0.001$), and age-by-diagnosis interaction for Glu levels ($p = 0.014$). Younger SZ had lower Glu levels than younger HC, and these differences were more pronounced in the older cohorts such that older SZ had the lowest Glu levels. There was an age effect ($p = 0.016$) effect for rCBF such that rCBF was lower in older versus younger groups. A significant correlation was found between Glu and rCBF across groups ($r=0.247, p=0.012$) with the strongest correlations in OSZ ($r=0.236, p=0.245$) and YSZ($r=0.301, p=0.163$). Additional analyses showed a significant diagnosis effect for GSH levels and age effect for tCho, mI, and Gln levels.
Conclusion: This is the first study to combine two MRI techniques to study older SZ and HC. This study provides new insight into the illness later in life since it shows an altered glutamatergic system as evidenced by lower tissue Glu levels from MRS and via Glu and rCBF correlation since rCBF is affected by local Glu neurotransmission. Thus, this study suggests that the pathophysiology of SZ may be altered late in life.
ID: 2118978

ENLARGED PUTAMEN IN DUAL-DIAGNOSIS PATIENTS WITH SCHIZOPHRENIA AND ADDICTION DISORDER

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Background: Structural brain MRI studies in schizophrenia research consistently report volumetric increases in the basal ganglia volumes (1,2). Psychotic symptoms of schizophrenia (SCHZ) and substance-induced psychosis (SIP) can be indistinguishable (3), yet common basal ganglia enlargements in these two populations have not been fully explored. Our goal was to determine if striatal enlargements are similar in both SCHZ and SIP.
Methods: Brain magnetic resonance images were acquired in 44 SCHZ, 39 SIP, and 83 Non-psychotic substance users (NPS) matched for age, socioeconomic status and patterns of substance use. Volumes were obtained for structures of interest using automatic segmentation in FSL v4.1.9. Left and right subcortical volumes were summed and group differences in volume of caudate, putamen, and pallidum were investigated via an omnibus one-way ANCOVA co-varying for age and total brain volume.
Results: The volume of the putamen significantly differed between groups ($(F(2,94) = 3.76, p=0.03.)$ Tukey's LSD post-hoc analysis revealed larger putamen volumes in SCHZ subjects compared to NPS ($p=0.004$) and SIP ($p=0.03$), but no differences between SIP and NPS ($p=0.67$). Caudate and pallidum volumes did not differ between groups (all p-values > 0.05).
Conclusion: Our finding of an enlarged putamen in the SCHZ subjects is congruent with prior reports. That enlargement is significant in the SCHZ group only suggests that basal ganglia volumetric changes are not a phenomenon of psychosis in general, but are more closely related to schizophrenia.
ID: 2100922

BRAIN STRUCTURE IN NEUROPSYCHOLOGICALLY DEFINED SUB-GROUPS OF SCHIZOPHRENIA AND PSYCHOTIC BIPOLAR DISORDER

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Background: Neuropsychological impairment is heterogeneous in psychosis. The association of intracranial volume (ICV) and total brain volume (TBV) with cognition suggests brain structure abnormalities in psychotic disorders will co-vary with the presence and pattern of cognitive impairment. We tested the following hypotheses: 1) brain structure abnormalities will be more extensive in neuropsychologically impaired psychosis patients; 2) psychosis patients with evidence of cognitive decline will demonstrate a loss of brain tissue (i.e. smaller TBV with normal ICV); and 3) psychosis patients with pre-morbid cognitive limitations will show evidence of hypoplasia (i.e. smaller ICV, but relatively normal TBV).
Methods: 131 individuals with a psychotic illness and 97 healthy subjects underwent structural MRI and neuropsychological testing. Patients were divided into neuropsychologically normal and impaired groups. Neuropsychologically impaired patients were further sub-divided into deteriorated and compromised groups if estimated pre-morbid intellect was

average or below average, respectively. ICV and TBV were compared across groups. Localized brain volumes were qualitatively examined using voxel-based morphometry (VBM).
Results: TBV was reduced in neuropsychologically impaired patients. Cognitively deteriorated patients exhibited smaller TBV, widespread white matter volume loss, but relatively normal ICV. Conversely, neuropsychologically compromised patients had smaller ICV, but relatively normal TBV. Unexpectedly, TBV was also reduced in neuropsychologically normal patients.
Conclusion: Classifying psychosis patients on the basis of neuropsychological functioning reveals evidence of different disease processes. Neuropsychologically normal and deteriorated patients show evidence of brain tissue loss consistent with progression or later cerebral dysmaturation. Patients with long-standing cognitive limitations exhibit a pattern consistent with early cerebral hypoplasia.
ID: 2080757

STRIATAL $D_{2/3}$ RECEPTOR BLOCKADE, PSYCHOPATHOLOGY AND REWARD PROCESSING - A LONGITUDINAL STUDY ON INITIALLY ANTIPSYCHOTIC-NAÏVE FIRST-EPISODE SCHIZOPHRENIA PATIENTS

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Background: The association between positive psychotic symptoms and abnormalities in striatal dopamine activity is one of the best validated findings in schizophrenia. Furthermore, in un-medicated patients, an attenuated striatal blood oxygen level dependent (BOLD) response during reward anticipation is a consistent finding. We have previously demonstrated a partial normalisation of these disturbances following treatment with the selective $D_{2/3}$ receptor antagonist, amisulpride.(1) However, a direct link between striatal $D_{2/3}$ blockade and reward processing abnormalities is still missing.
In the present study, we examined the association between striatal $D_{2/3}$ receptor blockade, alterations in reward processing and psychopathology in a longitudinal study on antipsychotic-naïve first-episode patients with schizophrenia.
Methods: Twenty-one antipsychotic-naïve first-episode schizophrenia patients and 26 matched healthy controls were examined with Single Photon Emission Computed Tomography using [^{123}I]-iodobenzamide. Reward disturbances were measured with functional Magnetic Resonance Imaging using a variant of the monetary-incentive-delay task. Patients were assessed before and after six weeks of treatment with flexible doses of amisulpride. There was an overlap of 9 patients and 6 controls between the present study and our previous study on reward processing.(1)
Results: The final data confirmed an attenuated striatal BOLD response in the patients at baseline, which was no longer significant at follow-up. This increase in the BOLD response correlated positively with the improvement of positive symptoms.
$D_{2/3}$ receptor occupancy was significantly correlated with the BOLD response at follow up (p=0.026). Furthermore, in patients who responded to treatment, there was a positive correlation between the occupancy and the change in the BOLD response (p=0.035).
Conclusion: Our final data demonstrate a direct influence of striatal $_{2/3}$ receptor blockade on striatal brain activity during reward anticipation in a longitudinal study on initially antipsychotic-naïve first-episode schizophrenia patients. The data further confirm a relation between normalisation of the BOLD response and improvement in positive symptoms.
1) Ref: Nielsen MO, Rostrup E, Wulff S, Bak N et al (2012): Improvement of Brain Reward Abnormalities by Antipsychotic Monotherapy in Schizophrenia. Arch Gen Psychiatry:1-10
ID: 2087261

GABA AND GLUTAMATE ASSESSED BY MAGNETIC RESONANCE SPECTROSCOPY IN VISUAL CORTEX IN SCHIZOPHRENIA

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Background: Deficits in visual processing in lateral occipital visual cortex (area LO) are known to correlate with poor functional outcome in schizophrenia, but the underlying physiology of this deficit is unknown (1).
Methods: We used magnetic resonance spectroscopy (MRS) to measure concentrations of GABA and glutamate in bilateral LO as well as primary visual cortex (V1) in subjects with schizophrenia (SZ), and healthy controls (HC). We used the MEGA-PRESS method to analyze GABA concentration, a protocol designed to better separate GABA signal from neighboring peaks (2). We hypothesized GABA and glutamate levels would be decreased in both LO and V1 in SZ compared to HC.
Results: Preliminary results (SZ: n = 7, HC: n = 6) demonstrate feasibility of data collection, with Cramer-Rao Lower Bound (CRLB) errors of under 20% in 35 out of 39 voxels analyzed for GABA and 38 out of 39 voxels analyzed for glutamate. Preliminary GABA concentration analysis shows data is in the direction of lower GABA in area LO, but not in area V1, in SZ compared to HC. Preliminary glutamate concentration analysis is in the direction of higher glutamate in SZ than HC, in both LO and V1.
Conclusion: We demonstrate consistent, high-quality measurement of absolute concentrations of both GABA and glutamate in visual cortex of subjects with schizophrenia and in healthy controls. Our preliminary dataset is too small to perform rigorous statistics and therefore to make strong conclusions, however, we see data in the direction of higher levels of GABA and glutamate in SZ than in HC with the exception of area LO, where there may be a trend toward lower GABA levels in SZ than HC. Were this finding to hold true upon further data collection and statistical analysis, it would be consistent with our hypothesis that visual processing deficits in schizophrenia may be in part due to deficient GABA signaling in area LO of the visual cortex.
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ID: 2084125

OLFACTORY FUNCTION AND HEDONIC CAPACITY IN INDIVIDUALS WITH SCHIZOTYPY: A STRUCTURAL MAGNETIC RESONANCE IMAGING STUDY

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Background: Anhedonia, a diminished ability to experience pleasure emotion, has been considered a core negative symptom in schizophrenia spectrum disorders. However, little is known about hedonic capacity and its related neural basis for the individuals with schizotypy. Processing of emotion and olfactory stimuli is governed by similar neural substrates. Thus, the purpose of the current study was to examine the relationship between olfactory function and hedonic capacity in schizotypy.

Methods: Eighteen individuals with schizotypy and 18 age- and sex-matched controls participated in this study. Hedonic capacity was assessed with the Chapman Scales for Physical and Social Anhedonia (CSAS and CPAS). Olfactory function was assessed with the Sniffin' Stick Test (odor threshold, odor discrimination and odor identification). All of them also undertook a structural imaging scan in a 3.0 T scanner for later volumetric measurements.

Results: The findings showed that individuals with schizotypy demonstrated significantly higher CSAS and CPAS scores than the healthy controls but with normal olfactory performance. Moreover, odor identification ability was inversely correlated with physical and social anhedonia in the schizotypy group. The right amygdala, right piriform cortex and entorhinal cortex were positively correlated with odor identification score, and negatively correlated with CSAS and CPAS scores. However, no such relationships were found in controls.

Conclusion: These findings suggest there is a subtle relationship between olfactory function and hedonic capacity observed in individuals with schizotypy.

ID: 2083218

Neuropathology: Histology; Biochemistry

ALTERED EXPRESSION OF INNATE IMMUNE SYSTEM COMPONENTS IN PREFRONTAL CORTEX IN SCHIZOPHRENIA

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Background: Multiple lines of evidence have implicated immune system dysregulation in schizophrenia. Several potential schizophrenia susceptibility genes are associated with immune function. In addition, altered levels of immune-related molecules have been reported in the periphery in this disorder. However, it is not yet clear whether similar changes are present in brain tissue. The aim of this study was to compare protein and/or mRNA expression of components of the innate immune system, including cytokines and members of the complement system, in prefrontal cortex in schizophrenia and controls.
Methods: Expression of cytokines and complement was quantified in 35 individuals with schizophrenia and 35 controls. Samples were obtained from the orbitalfrontal and dorsolateral prefrontal regions courtesy of the Stanley Medical Research Institute. mRNA expression was measured in orbitalfrontal cortex using quantitative PCR, while proteins were quantified in dorsolateral prefrontal cortex by immunoblotting. Data were compared between groups using ANOVA or Mann-Whitney U tests.
Results: Factor B, a component of the alternative complement pathway, and C5b-9 protein levels were significantly increased in schizophrenia. Cytokine expression did not differ significantly between groups. Lifetime antipsychotic dose correlated with expression of cytokines IL-6, TNFα and IL-1β, with a similar trend for C1q.
Conclusion: These results suggest that complement activation is altered in schizophrenia, and appear consistent with a previous report describing upregulation of alternative complement pathway activity in serum in this disorder. Increased complement expression may be indicative of an inflammatory response, although the complement system has also been implicated in other CNS functions including neurogenesis and synaptic plasticity.
This work was supported by the Canadian Institutes of Health Research.
ID: 2115564

GLIA/EXTRACELLULAR MATRIX INTERACTIONS IN THE PATHOPHYSIOLOGY OF SCHIZOPHRENIA

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Background: Growing evidence shows that interactions between glial cells and the brain extracellular matrix (ECM) are required for neurodevelopment and key adult neural functions. Chondroitin sulfate proteoglycans (CSPGs), main ECM components, are secreted by glia into the ECM, where they mediate emerging glial functions. CSPGs secreted by astrocytes are critical to the formation and maintenance of specialized ECM structures, e.g. perineuronal nets, which in turn interact with glia to control synaptic plasticity and glutamatergic transmission. Distinct glia/CSPG clusters we recently described in human subjects, are hypothesized to function as specialized macrodomains affecting neuronal activity. Oligodendrocyte precursor cells (OPCs) strongly express CSPGs, including brevican and OPC-selective NG2, which potently regulate oligodendrocyte maturation, nodes of Ranvier and myelination. Converging evidence points to CSPG/ECM abnormalities in schizophrenia (SZ). We tested the hypothesis that CSPG expression in glial cells may be altered in subjects with SZ.
Methods: Quantitative light and confocal microscopy were combined to measure astrocytes and OPCs expressing CSPGs in the amygdala of healthy control and SZ subjects. Corresponding mRNA was measured by qRT-PCR.
Results: Our results show markedly altered numbers of astrocytes and OPCs expressing CSPGs in SZ. Astrocytes labeled with the lectin wisteria floribunda agglutinin (putatively detecting the chondroitin sulfation (CS) pattern CS-4) show striking increases in SZ, ranging from 400 to 1100% with respect to control subjects. In contrast, glial cells expressing the CSPG aggrecan and glial/CSPG clusters expressing the CS-6 pattern were significantly reduced in SZ. Astrocytes expressing CD44, a hyaluronan receptor that potently affects OPC migration and maturation, were also robustly decreased. Consistent with this latter finding, numbers of NG2-positive OPCs were substantially lower in SZ
Conclusion: Together, these results point to encompassing abnormalities affecting glia/ECM interactions in SZ. Speculatively, as suggested by GWAS findings, these abnormalities may result from genetic vulnerabilities related to ECM remodeling enzymes, which may represent a common denominator, impacting a broad range of ECM molecules and thus glia/ECM interactions. As a result, seemingly unrelated functions, such as synaptic plasticity, volume transmission and myelination, may be disrupted, contributing to key aspects of the pathophysiology of SZ.
ID: 2116769

GENETIC AND ENVIRONMENTAL DETERMINANTS OF MIRNA DYSREGULATION IN SCHIZOPHRENIA

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Background: Analyses of miRNA expression in several studies suggest these molecules are dysregulated in schizophrenia. These small non-coding RNA play a significant role in brain development and activity by regulating ribonucleoprotein complexes controlling the fate of mRNA. MiRNA achieve this by acting as adapter sequences for homology based target recognition. These molecules and their effector complexes form regulatory modules on genes and are influential nodes in the network architecture supporting complex neural structure and function. The pattern of miRNA expression in the brain is highly regulated in space and time, so their dysregulation in schizophrenia is probably the result of many influences, both heritable and environmental. Understanding these influences will be important for developing interventions for schizophrenia that can modify miRNA and the physiologically significant pathways they regulate.
Methods: Postmortem tissue from subjects with schizophrenia and non-psychiatric controls was dissected from the dorsolateral prefrontal cortex (DLPFC). Gene and miRNA expression was then analysed using microarray and their interactions analyzed to investigate how genes responded to the disease-associated change in miRNA expression, as well as identify changes in genes associated with the miRNA biogenesis pathway and its regulatory network. We further explore to influence of microprocessor gene DGCR8 overexpression on miRNA and gene expression in transfected human neuroblasts.
Results: Schizophrenia-associated gene and miRNA interactions in the DLPFC were investigated and suggest that miRNA regulated pathways are critical in the pathophysiology of the disorder. We also confirm the

involvement of genes in the miRNA biogenesis pathway including DGCR8. We then show that overexpression of DGCR8 induces a change in miRNA expression, which is consistent with many of the schizophrenia-associated changes observed in the DLPFC. Moreover, we demonstrate that changes in miRNA biogenesis can also influence schizophrenia candidate gene expression. This was highlighted by RELN, which is regulated by multiple miRNA altered in schizophrenia and by overexpression of DGCR8 in cultured neuroblasts.
Conclusion: This study suggests that dysregulation of cortical miRNA expression is associated with changes in gene expression in schizophrenia, and that genetic and epigenetic factors affecting miRNA genes and the molecules regulating their biogenesis play a significant role in the neuropathology of the disorder.
ID: 2115216

PROTEOMIC STUDIES OF SCHIZOPHRENIA BRAIN, PRENATAL AND STEM CELL MODELS: IS THERE A CONVERGENCE?

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Background: Proteomic analysis of schizophrenia brain and patient derived stem cells provides the opportunity for unique insights into schizophrenia. While postmortem brain perhaps most closely reflect the disease process, patients derived stem cells such as those from olfactory neurosphere-derived (ONS) cell lines from the human olfactory musosa regenerate throughout life from neural stem cells and offer complementary insights. Similarly, animal models of schizophrenia such as those involving prenatal inflammation and prenatal iron deficiency offer insights in schizophrenia pathophysiology. Considered together these studies may provide convergent information re core pathways and processes involved in schizophrenia.
Methods: We assessed; 1., olfactory mucosa biopsies were obtained from patients with schizophrenia (N = 9) and healthy controls (N = 9), and grown as neurospheres in defined medium; 2., postmortem corpus callosum tissue and postsynaptic density enriched anterior cingulate cortex tissue from 20 schizophrenia, and 20 controls from the Stanley Medical Research Institute Array Collection; 3., frontal cortex of adult rat offspring following a)., prenatal polyinosinic:polycytidylic acid and, separately, b)., following prenatal iron deficiency model.
Results: LC-MS/MS analysis identified; 1. 103 were significantly differentially expressed ($p < 0.05$) between between schizophrenia and patient derived ONS cell lines groups. Ingenuity pathway analysis (IPA) indicated that protein synthesis via altered EIF2 signaling and ribosomal function (18 molecules) was the major category disturbed; 2. 143 differentially expressed in the specific postsynaptic density fraction involving prominent changes in NMDA interacting proteins and with IPA implicating endocytosis, long-term potentiation and calcium sigmalling; 113 differentially expressed in the corpus callosum with IPA particularly implicating glycolysis and gluconeogenesis. The prenatal animal models converged in implicating the core metabolic pathways of glycolysis and oxidative phosphorylation.
Conclusion: Our studies converge in implicating mitochondrial functions in both prenatal animal models of schizophrenia and the corpus callosum in schizophrenia. The stem cell model did not show mitochondrial related function to among the top implicated pathways although robust changes in these proteins were identified. We discuss the convergence of these findings.
ID: 2118839

PYRAMIDAL CELL HETEROGENEITY IN PREFRONTAL CORTICAL DENDRITIC SPINE LOSS

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Background: A number of postmortem studies of schizophrenia have documented a decrease in the density of dendritic spines on pyramidal cells (PCs) in the prefrontal cortex (PFC). A number of mechanisms contribute to spine remodeling. We previously reported that dopamine (DA) denervation of the PFC, or genetic ablation of certain DA receptors, results in loss of dendritic spines on layer V (L5), but not L2/3, PCs in the PFC. However, some PFC L5 PCs are vulnerable to DA denervation while others do not respond.
Methods: PFC PCs innervating different targets, including the mediodorsal thalamic nuc (MD), nuc accumbens (NAS), basolateral amygdala (AMG), ventral tegmental area (VTA), and contralateral PFC (cPFC), were retrogradely-labeled with fluorescent latex microspheres (FLMs), and the DA innervation of the PFC lesioned by 6-OHDA injections of the VTA of the rat. Retrogradely-labled cells were either intracellular filled with a dye for dendritic spine measurements or acquired by laser capture microdissection for qPCR and RNAseq analyses
Results: L5 PFC PCs that innervate the MD and NAS showed a loss of dendritic spines; L6 cells labeled from the MD did not lose spines, nor did L2/3 PCs innervating the NAS. L5 PCs projecting to the AMG, VTA, or cPFC did not suffer spine loss. In the DA-denervated PFC, the distribution of spine head diameter: spine length ratios differed significantly from control animals only for L5 PCs innervating the MD and NAS, with the thin spines preferentially involved. qPCR analyses did not reveal a simple difference in expression of D1 or D2 receptor mRNAs. We were unable to detect D4 mRNA in the PFC despite significant positive results in other areas (olfactory bulb, cardiac atrium), and both D3 and D5 mRNAs were present in vanishing low abundance. However, preliminary data suggest that the type of dopamine receptor and presence or absence of alpha2c receptor mRNA may differentiate vulnerable from resilient PCs.
Conclusion: Loss of dendritic spines on PFC PCs in response to DA denervation depends on the projection target of the PC, but not to the dopamine receptor expressed by the cell. Thus, there are presumably other molecules that confer vulnerability of PFC PCs to DA loss. The heterogeneity of cortical PCs has long been overlooked. Attention to differences across PCs may reveal specific distributed corticofugal circuits emanating from within and across different cortical lamina of the same cortex that are differentially related to different symptoms in schizophrenia.
ID: 2119525

OXIDATIVE STRESS: BIOMARKERS GUIDED TREATMENT AND PREVENTION IN PSYCHOSIS

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Background: Developmental manipulations yielding adult deficits in rodents provide an opportunity to explore mechanisms involved in a delayed emergence of anomalies driven by developmental alterations and to test hypotheses about pathophysiological scenarios, such as redox dysregulation. Oxidative stress markers, related to genetic risk factors, were observed in brain and periphery of SZ patients. In a mouse model with impaired glutathione (GSH) synthesis (gclm ko), additional stress (excess dopamine) leads to impairments of parvalbumine interneurons (PVI) with their perineuronal net (PNN) in anterior cingulate cortex. These effects

were only present and persistent when the additional stress was applied during youth but not in adulthood. Application of the antioxidant N-acetylcysteine (NAC) prevented these deficits. In ventral hippocampus, gclm ko mice present a parallel decrease of β/γ oscillations and relevant cognitive functions. We now present evidence that similar oxidative stress is instrumental in another developmental model of SZ, in which the redox/GSH system is not primarily affected.
Methods: A neonatal ventral hippocampal lesion (NVHL, PND 7) in rats yields adult animals with electrophysiological, neurochemical, and behavioral anomalies related to SZ, all of which emerge during adolescence. With and without various antioxidants NAC, Ebselen or apocynin, PVI/PNN were characterized by immunochemistry and electrophysiological recording, and the mismatch negativity (MMN) and prepulse (PPI) inhibition were tested.
Results: We observed increased level of oxidative stress immunolabeling in the PFC of juvenile NVHL rats, along with a decrease in PV cell counts, PPI deficit, altered dopamine modulation of local PFC circuits, and deficits in MMN in adulthood. All these deficits were prevented with NAC treatment from P5 to P50. PPI deficits were also prevented if NAC treatment was initiated during adolescence (P35) and by the other antioxidants.
Conclusion: Our data suggest that oxidative stress in PFC is a core feature mediating alterations induced by the NVHL, and antioxidant treatment prevents these alterations. These results open the possibility that antioxidants applied during development could prevent the emergence of SZ. Together with the improvement of negative symptoms and MNN in clinical trial with NAC in chronic patients, these data suggest that MNN could be considered as a potential marker for assessing treatment success.
ID: 2092540

HIPPOCAMPUS IN SCHIZOPHRENIA, DEPRESSION, AND SUICIDE: A POSTMORTEM STEREOLOGICAL STUDY OF HIPPOCAMPAL VOLUME AND CELL NUMBER

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Background: Numerous in vivo imaging studies have reported hippocampal changes including volume reduction in subjects with schizophrenia. Also, in vivo imaging studies indicate that the volume of hippocampus may be reduced in depression. Furthermore, substantial evidence suggests that structural plasticity in the hippocampus may play an important role in the pathophysiology of depression and its treatment. Thus, in the present study we search for cellular correlates to these findings.
Methods: The study is based upon postmortem brain samples from 10 subjects with schizophrenia, 8 subjects with major depression, 11 suicide victims with a history of depressive disorder, and 10 control subjects with no history of psychiatric or neurological diseases. The schizophrenia and major depression subjects were carefully selected, excluding psychiatric comorbidities and suicide, from the large old Brain Collection at Aarhus University Hospital, Risskov which contains approximately 9500 brains from psychiatric patients. The control and suicide subjects were selected from brains collected for previous studies at the Stereology and Electron Microscopy Laboratory.
We use stereological techniques to analyze if schizophrenia, severe depression, or suicide is associated with reduced volume of the hippocampal formation and/or changes in the numbers of neurons and/or glial cells in the different subregions of the hippocampus. The microscopic analysis is based on state of the art design-unbiased stereological techniques: The Cavalieri estimator is used to estimate the volume of hippocampus and its subregions, and the optical fractionator method is used to estimate the total number of neurons and glial cells in the individual cell layers in four main regions of hippocampus: the granular cell layer, hilus, CA2/3, and CA1.
Results: The final results will be reported at the meeting.
Conclusion: We hope our results can provide a better understanding of the pathophysiology of schizophrenia and depression and help developing new strategies for treatment.
ID: 2117902

AUTOPSY STUDIES OF FRONTAL WHITE MATTER IN SCHIZOPHRENIA

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Background: Diffusion tensor imaging of cerebral white matter shows lower anisotropy in white matter of individuals with schizophrenia than in those without psychiatric disease. Although demyelinating lesions are associated with decreased diffusion anisotropy, there is little other evidence for demyelination in schizophrenia, while there are other possible causes of low anisotropy. We therefore undertook histological and biochemical analyses of white matter in autopsy brains of over 200 individuals with schizophrenia, with major depressive disorder, or without evidence of psychiatric disease.
Methods: Psychiatric diagnoses or their absence were determined by psychological autopsy interview and standardized reviews of medical records, applying DSM-IV-R criteria. Systematically randomly selected fields in Verhoeff-stained paraffin sections of left prefrontal white matter were rated on a semiquantitative scale by a neuropathologist. Immunohistochemical staining for degenerating myelin basic protein (MBP) was segmented with Visiomorph software, and fractional areas of staining were determined. In frozen samples of dorsal prefrontal, ventral prefrontal, and cingulate white matter, mRNA for MBP, myelin-associated glycoprotein (MAG), proteolipid protein 1 (PLP1) and and 2', 3'-cyclic nucleotide 3'-phosphodiesterase (CNP) were measured by a commercial system based on immobilized and branched DNA probes and normalized to a set of "housekeeping" genes. Spatial densities of resting, activated, and perivascular microglia were determined in paraffin sections double-labeled for ionized calcium-binding adapter molecule 1 (IBA1) and cluster of differentiation 68 (CD68).
Results: We found no evidence for demyelinating lesions in schizophrenia. Ratings of Verhoeff stains showed a small, statistically significant decrease with age, but there was no effect of diagnosis. Microglial densities were statistically affected by age and suicide, but not by diagnosis. However, there were significant effects of both age and diagnosis on mRNA. Levels of mRNA for CNP and PLP1 were both significantly lower in schizophrenia than in major depression or in cases without psychiatric illness.
Conclusion: We conclude that schizophrenia is not associated with histological evidence of demyelination. Differences in levels of mRNA may reflect altered turnover of myelin-related proteins.
ID: 2088310

ALTERATIONS OF BOUTONS ARISING FROM CALBINDIN AND CALRETININ GABAERGIC NEURONS IN THE PREFRONTAL CORTEX OF SUBJECTS WITH SCHIZOPHRENIA

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Background: Convergent findings indicate that GABA circuitry is altered in the prefrontal cortex (PFC) of subjects with schizophrenia, with calbindin-expressing (CB+) GABAergic neurons being one of the affected subtypes. GAD65 and GAD67 catalyze the synthesis of GABA within synaptic boutons. We recently showed that CB+ neurons give rise to boutons containing detectable levels of only GAD65 (GAD65+), only GAD67 (GAD67+), or both GADs (GAD65/67+). In addition, we show here that protein levels of GAD65 and GAD67 are ~20% lower in PFC boutons from schizophrenia subjects. Thus, the goal of the present study was to determine if GAD65 and/or GAD67 is reduced in boutons arising from CB+ neurons, and whether the density of these boutons is altered.
Methods: PFC tissue sections from 20 matched pairs of schizophrenia and comparison subjects were quadruple-labeled for GAD65, GAD67, vesicular GABA transporter (vGAT), and CB immunoreactivity. Because neurons that express calretinin (CR+), which have been reported to be unaffected in schizophrenia, also give rise to GAD65+, GAD67+, and GAD65/67+ boutons, a parallel assay that assessed GAD levels in CR boutons was performed for comparison purposes.
Results: Within CB/GAD65+ and CB/GAD65/67+ boutons, mean GAD65 levels were significantly 18% lower in schizophrenia. In addition, mean GAD67 levels in CB/GAD67+and CB/GAD65/67+boutons were also significantly 18% lower in schizophrenia. Surprisingly, similar significant reductions in GAD65 and GAD67 levels were present in CR/GAD+ boutons. An assessment of bouton density found a significant 29% increase in CB/GAD65+ and a modest nonsignificant decrease in CB/GAD67+ and CB/GAD65/GAD67+ bouton densities. In contrast, CR/GAD65+ bouton density did not differ between subject groups whereas the densities of CR/GAD67+ and CR/GAD65/GAD67+ boutons were significantly lower by 22% and 17%, respectively.
Conclusion: Because pyramidal neuron dendrites are a main target of CB-expressing neurons, the apparent lower capacity of CB boutons to synthesize GABA would presumably lead to decreased inhibition of pyramidal neurons in schizophrenia. However, the effect of an increase in CB/GAD65+ bouton density is unknown. CR neurons mostly synapse onto other inhibitory neurons. Thus, reduced inhibitory output from CR+ neurons in schizophrenia might reflect a primary GABA deficit in non-CR+ GABAergic neurons (e.g., CB+) such that the changes detected here are compensatory. Alternatively, they might reflect a primary deficit in CR+ neurons.
ID: 2081788

PROTEOMIC PROFILING OF THE ADULT RAT PREFRONTAL CORTEX FOLLOWING EXPOSURE TO PRENATAL IRON DEFICIENCY AND RISPERIDONE IN ADOLESCENCE

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Background: Prenatal exposure to maternal iron deficiency (ID) significantly increases the risk of schizophrenia in the offspring, as adequate prenatal nutrition/ iron is fundamental to the development of the fetal brain including normal myelination and gliogenesis. Alterations in these processes may predate the neurodevelopmental and behavioral abnormalities that occur from ID in early life. Myelin and glial abnormalities are amongst the most robust neuropathological changes observed in schizophrenia and it has been proposed that atypical antipsychotics act to normalize myelination changes in schizophrenia. We hypothesized that prenatal ID will cause myelin changes that can be prevented by antipsychotic treatment in adolescence.
Methods: Pregnant dams were fed an iron deficient or control diets from gestational day 5 to postnatal day 21. All offspring were then maintained on an iron sufficient diet and treated with the atypical antipsychotic drug Risperidone or saline in adolescence (PND21-35). We performed mass spectrometry on the prefrontal cortex of offspring prenatally exposed to ID with or without Risperidone in adolescence.
Results: Over 800 proteins were identified and statistical analysis carried out with ANOVA. Pathway analyses implicated changes in core metabolic pathways, including glycolysis, oxidative phosphorylation and the tricyclic acid cycle following prenatal exposure to ID compared to controls. The majority of proteins were classed as belonging to mitochondria, further implicating an impact on cellular metabolism. Some, but not all of these protein changes were absent in the prefrontal cortex of ID exposed offspring that received Risperidone. Interestingly, significant reductions were observed in myelin proteins following the main effect of ID which were non-significant with the main effect of Risperidone. Validation with western blotting revealed a significant decrease in MBP1 expression in ID offspring, which was increased in ID offspring treated with Risperidone. The same pattern was seen for phosphorylated MAPK1 which was increased in ID offspring but decreased with the addition of Risperidone. A significant increase was also evident for pMAPKAPK2 which was prevented with the addition of Risperidone treatment.
Conclusion: Overall, our data suggests that prenatal ID may contribute to an increased risk for schizophrenia through mechanisms involving metabolic function and myelin formation and that Risperidone in adolescence may in part prevent or reverse such changes.
ID: 2084445

GABAA AND GABAB RECEPTOR SUBUNITS ARE ALTERED IN FRONTAL CORTEX OF SUBJECTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: There is evidence that GABAergic signaling system is impaired in subjects with schizophrenia and mood disorders based on postmortem studies that have shown altered expression of GABAergic proteins.
Methods: In the current study we seek to examine whether there are changes in protein levels of selected GABAA and GABAB receptor subunits in frontal cortex (BA9) of subjects with schizophrenia and bipolar disorder vs. matched controls via SDS-PAGE and western blotting. Postmortem samples were derived from BA9 from subjects with schizophrenia (N=19), bipolar disorder (N=19), and controls (N=28) from the Harvard Brain and Tissue Bank McLean 74 Cohort. All results will be normalized against two housekeeping proteins - beta actin and neuronal specific enolase (NSE) - and will be expressed as ratios to beta actin and NSE.

Results: Experiments are currently underway and we hypothesize that we will identify altered expression of some of the GABAA and GABAB receptor subunits in BA9 of subjects with schizophrenia and bipolar disorder.
Conclusion: We have previously observed altered expression of GABAA and GABAB receptor subunits in the lateral cerebella of subjects with schizophrenia, bipolar disorder, and major depression. The results of the current studies have the potential to provide further evidence of GABAergic dysfunction in brains of subjects with schizophrenia and bipolar disorder. The generous support by the National Institute of Mental Health (5R01MH086000-05), the Bernstein Endowed Chair in Adult Psychiatry, and the Ewald Bipolar Disease Research Fund to S.H.F. is greatly appreciated.
ID: 2083552

LOWER REGULATOR OF G PROTEIN SIGNALING 4 MRNA AND PROTEIN LEVELS IN THE PREFRONTAL CORTEX IN SCHIZOPHRENIA

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Background: Altered signaling of G protein coupled receptors (GPCRs) in the prefrontal cortex (PFC) has been implicated in the pathophysiology of impaired cortical and cognitive functioning in subjects with schizophrenia. Signaling via Gi- and Gq-coupled GPCRs can be attenuated by the GTPase activating protein, regulator of G protein signaling 4 (RGS4). RGS4 is robustly expressed in PFC, and can act to inhibit the activity of a number of GPCRs implicated in schizophrenia, including group I metabotropic glutamate receptors, D2 family dopamine receptors, and mu and delta opioid receptors. Previous studies of RGS4 mRNA and/or protein expression in PFC of schizophrenia subjects have produced inconsistent results, with three showing no change and three showing lower expression.
Methods: Here, we quantified both mRNA and protein levels of RGS4 within the same subjects. RGS4 mRNA levels were assessed by quantitative PCR in right PFC area 9 gray matter from 62 matched pairs of schizophrenia and healthy comparison subjects. RGS4 protein levels were quantified in left PFC area 9 in a subset of 23 subject pairs using confocal immunofluorescence microscopy. Fluorescence intensity, which reflects relative protein levels, was measured across all cortical layers.
Results: Mean RGS4 mRNA levels were 13% lower in the schizophrenia subjects relative to comparison subjects ($p<0.001$, paired ANCOVA; $p<0.001$, unpaired ANCOVA). In the subset of 23 pairs, RGS4 relative protein levels were 11% lower ($p=0.02$, paired; $p=0.03$, unpaired), and RGS4 mRNA and protein levels were modestly correlated ($r=0.28$, $p=0.03$). Lower RGS4 mRNA and protein measures within schizophrenia subjects were not attributable to factors commonly comorbid with the diagnosis.
Conclusion: These findings suggest that, on average, schizophrenia is associated with lower levels of RGS4 mRNA and protein in the PFC. Determining the underlying causes of lower RGS4 mRNA and protein expression has important implications for understanding the pathophysiology of PFC dysfunction in schizophrenia. For example, the modest correlation between RGS4 mRNA and protein levels suggests that other regulatory mechanisms may affect RGS4 translation, including microRNAs. Finally, because RGS4 can affect several different GPCR and neurotransmitter systems across pyramidal cells and interneurons, further investigation determining which receptor systems and neuronal populations are affected will provide valuable insight into the schizophrenia disease process. MH043784 & MH096985.
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USING POST-MORTEM BRAINS TO INVESTIGATE THE MECHANISMS AND THERAPEUTIC POTENTIAL OF SCHIZOPHRENIA RISK GENES

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Background: Many approaches are needed to investigate the function of schizophrenia risk genes, and to reveal their pathogenic role and therapeutic potential. Studies using post mortem human brain tissue are an essential component of this work, since key aspects may not be recapitulated in other tissues or species.
Methods: Two studies will be described. (1) D-amino acid oxidase (DAO) degrades the NMDA receptor co-agonist D-serine, and is a therapeutic target as well as a potential contributor to NMDA receptor dysfunction in schizophrenia. DAO mRNA, immunoreactivity, and enzyme activity were measured in human brain from schizophrenia, bipolar disorder, and healthy comparison subjects. In parallel, DAO expression, and the effects of DAO inhibition or DAO gene deletion on dopaminergic function, were measured in rodent brain. (2) Zinc finger protein 804A (ZNF804A) is a GWAS-positive schizophrenia gene of unknown function. Its protein expression was examined in human brain, and ZNF804A-immunoreactive neurons were analysed in schizophrenia and healthy comparison subjects genotyped for the risk polymorphism rs1344706.
Results: (1) DAO is expressed widely in human brain, and is present in neurons as well as glia. Its expression and activity are increased in the cerebellum in schizophrenia but not bipolar disorder. DAO is expressed in dopaminergic nuclei, and influences dopamine neuron firing and cortical dopamine release. (2) ZNF804A immunoreactivity is present in human cerebral cortex throughout life, and is concentrated in pyramidal neurons, with no differences in distribution or abundance identified in schizophrenia nor related to genotype.
Conclusion: These data illustrate the value of post mortem human brain studies as part of the efforts to understand the biological, pathological, and therapeutic significance of schizophrenia risk genes. The DAO data are relevant to the therapeutic candidacy of DAO inhibitors, as well as clarifying the roles which DAO, and thence D-serine, may play in NMDA receptor (dys)function. The ZNF804A data strengthen the case for a lifelong functional role of this gene in brain, particularly in pyramidal neurons.
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ID: 2089909

DRUG DISCOVERY NEEDS HUMAN POST-MORTEM STUDIES IN SCHIZOPHRENIA

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Background: When handled carefully after death, certain human brain proteins retain a surprising amount of functional activity. As an example, the postsynaptic neuregulin-erbB4 signaling interaction is intact in post-mortem tissue and can be evoked to investigate NMDA receptor hypofunction using an in vitro system (1). A different presynaptic protein-protein interaction complex also demonstrates functional integrity, and may be a useful target for linking postmortem research to drug discovery.
Methods: Three proteins, syntaxin, VAMP and SNAP-25 (SNARE proteins) must interact together in order for vesicular neurotransmission to occur. The catastrophic effects of botulinum toxin on the ability of these

proteins to interact demonstrates the critical importance of this protein-protein interaction to normal brain function. Work from studies of post-mortem schizophrenia tissue shows increased SNARE protein-protein interactions in schizophrenia (2), supporting findings from the blind-drunk mouse, a mutant with increased syntaxin-SNAP-25 interaction and phenotypic features of schizophrenia (3).
Results: Using a novel strategy for human brain, "blue native" non-denaturing electrophoresis, we demonstrated increased (40-45%) SNARE protein-protein interactions in orbitofrontal and cingulate cortices in two independent schizophrenia cohorts. Multiple mechanisms may contribute to the altered SNARE protein-protein interaction in schizophrenia. Exploring the factors contributing to these interactions, we demonstrated increasing nitration or nitrosylation of SNARE proteins increases interactions (JF Wang, personal communication), dephosphorylation of SNARE proteins shifts the molecular composition of complexes, and the small molecule bioflavonoid, myricetin inhibits SNARE complex formation in human brain in a dose-dependent fashion. The myricetin finding encouraged development of a screening strategy for small molecules that could decrease SNARE interactions, and this was implemented in a series of libraries including three from NIH. Encouraging "hits" were obtained, and are being characterized in greater detail.
Conclusion: These studies demonstrate "proof of principle" for using post-mortem tissue to aid drug discovery.
(1) Hahn et al., Nat Med 2006;12:824
(2) Barakauskas et al., Neuropsychopharmacol 2010;35:1226
(3) Jeans et al, Proc Nat Acad Sci 2007;104:2431
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ID: 2092337

ABNORMAL PRENYL-ASSOCIATED GTPASE EXPRESSION IN SCHIZOPHRENIA

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Background: Recently, abnormalities in post translational modifications (PTMs) such as glycosylation, ubiquitination, myristoylation, and phosphorylation have become targets of schizophrenia (Scz) research and are implicated in the neuropathophysiology of this illness. Prenylation is a lipid modification that regulates protein synthesis, function, and localization of many proteins, including small GTPases. The mTOR and MAPK/ERK signaling pathways are activated by prenyl-modified GTPase proteins and are known to be dysregulated in Scz. Preliminary data from our lab has shown the key enzymes responsible for prenylating GTPases are decreased in Scz, making these proteins a compelling target for further investigation.
Methods: In this study we measured the expression of a subset of prenyl-associated GTPases to identify alterations consistent with reduced prenylation in dorsolateral prefrontal cortex (DLPFC) between 13 paired Scz and comparison (Comp) subjects. To identify changes in protein expression we used SDS-PAGE and western blot analysis to probe for twelve candidate GTPases associated with the mTOR pathway, MAPK/ERK pathway, or general protein trafficking.
Results: We found two of the GTPases have increased total expression in Scz, HRas ($t(12) = 2.20$, $p = 0.047$) and Rab2 ($t(12) = 2.35$, $p = 0.039$), while there was no difference between groups for NRas, KRas, RhoA, Cdc42, Rac1, Rac2, Rab1A, Rab1A, or Rab7. We also assessed both the prenylated (Rap1A) and unprenylated (UP-Rap1A) forms of the small GTPase Rap1A. While UP-Rap1A expression was not significantly different between diagnostic groups, we found prenylated Rap1A expression decreased by 34% in Scz ($t(12) = 2.55$, $p=0.025$).
Conclusion: These data demonstrate an altered ratio of prenylated to unprenylated Rap1A and provide evidence that there is a reduced prenylation of some proteins in Scz. We have also demonstrated increased expression of two small GTPases, HRas and Rab2, that are known to be targets of prenylation in Scz. This study can conclude that GTPase expression abnormalities and disrupted prenylation of GTPases may be a potential mechanism contributing to abnormalities in downstream signaling processes which have been implicated in the neuropathophysiology of Scz.
ID: 2087763

GENETIC NEUROPATHOLOGY IN HUMAN BRAIN DEVELOPMENT AND SCHIZOPHRENIA

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Background: Recent advances in combining genome-wide association studies have led to the identification of over 100 genetic variations, single nucleotide polymorphisms (SNPs), associated with increased risk for schizophrenia($p<10-8$)(Psychiatruc Genomics Consortium (PGC), Nature, 2014). Although these genetic variations each increase risk to a relatively small degree, understanding their mechanisms has the potential to have a large impact with regard to diagnosis and treatment. However, translating the discovery of these risk-associated genetic variations into improved understanding and/or treatment of schizophrenia requires elucidating the molecular biological mechanisms which are largely unknown. The molecular biology mechanisms by which genetic variation increases risk for schizophrenia involve expression of specific alternative transcripts thought to be critical for early brain development. Many of these transcripts may be brain and/or primate specific.
Methods: We have used postmortem human tissue from over 800 brains focusing on dorsolateral prefrontal cortex (PFC)and hippocampus in patients with schizophrenia, affective disorders and normal controls from age 14 weeks prenatal to 80 years postnatal. All brains were genotyped for over 650,000 SNPs and expression studies were done with either microarrays, qRT-PCR or RNA sequencing. PGC genes studied thus far include ZNF804A, DRD2, GRM3 and CACA1C.
Results: The SNP rs 1344706 which is associated with increased risk for schizophrenia and bipolar illness is associated with expression of a truncated alternate transcript in fetal PFC.($p< .02$)This same transcript is preferentially expressed in fetal PFC. Moreover, this transcript had decreased expression in PFC from patients with schizophrenia ($p<.006$), but increased expression in patients with major depression ($p<.001$). (Tao R et al, JAMA Psychiatry 71, 2014. Similar results will be presented for other PGC positive genes including GRM3, CACNA1C and DRD2.
Conclusion: Genetic variation in a number of PGC loci are associated with specific transcripts in human brain that are critical for brain development and risk for schizophrenia.Some of these transctipts are abnomally expressed in postmortem brain tissue from patients with schizophrenia as well.
ID: 2124909

DISTINCTIVE TRANSCRIPTOME ALTERATIONS OF PREFRONTAL PYRAMIDAL NEURONS IN SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

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Background: Schizophrenia is associated with alterations in working memory that reflect dysfunction of dorsolateral prefrontal cortex (DLPFC) circuitry. Working memory depends on the activity of excitatory pyramidal cells in DLPFC layer 3, and to a lesser extent in layer 5. Although many studies have profiled gene expression in DLPFC gray matter in schizophrenia, little is known about cell type-specific transcript expression in these two populations of pyramidal cells.
Methods: Individual pyramidal cells in DLPFC layers 3 or 5 were captured by laser microdissection from 36 subjects with schizophrenia or schizoaffective disorder and matched normal comparison subjects. The mRNA from cell collections was subjected to transcriptome profiling by microarray followed by qPCR validation.
Results: Expression of genes involved in mitochondrial (MT) or ubiquitin-proteasome system (UPS) functions were markedly down-regulated in the patient group (p values for MT-related and UPS-related pathways were $<10^{-7}$ and $<10^{-5}$ respectively). MT-related gene alterations were more prominent in layer 3 pyramidal cells, whereas UPS-related gene alterations were more prominent in layer 5 pyramidal cells. Many of these alterations were not present, or found to a lesser degree, in samples of DLPFC gray matter from the same subjects, suggesting that they are pyramidal cell-specific. For example, the mRNA expression level of UQCRQ (ubiquinol-cytochrome c reductase, complex III subunit VII) was significantly decreased by 26% ($q<10^{-4}$) in layer 3 pyramidal cells schizophrenia but was not altered (-2.3%) in grey matter. Furthermore, these findings principally reflected alterations in the schizophrenia subjects, were not present or present to a lesser degree in the schizoaffective disorder subjects (diagnosis of schizoaffective disorder was the most significant covariate, $p<10^{-6}$), and were not attributable to factors frequently comorbid with schizophrenia.
Conclusion: These findings suggest that the disease process of schizophrenia involves pyramidal cell-specific alterations in gene expression regulating MT and UPS functions that are both common to and distinctive between pyramidal cells in DLPFC layers 3 and 5, and not shared by subjects with schizoaffective disorder. Importantly, these findings suggest that layer 3 pyramidal cells are hypometabolic, and by inference hypoactive, in individuals with schizophrenia.
This work was supported by Bristol-Myers Squibb and NIH Grants MH043784, MH084053, and MH103204.
ID: 2093203

MOLECULAR CHARACTERISTICS OF CEREBRAL NETWORKS FOR PSYCHOSIS

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Background: Hippocampal hyperactivity has been demonstrated in schizophrenia, potentially generating false memories with psychotic content within relevant brain networks.
Methods: To identify the cerebral networks associated with this hippocampal pathology, we performed regional seed connectivity analyses on N=87 resting state fMRI acquisitions from psychosis probands and found alterations in connectivity between anterior hippocampus and medial, dorsolateral and cingulate prefrontal cortex as well as with superior temporal gyrus and cerebellum. Guided by these outcomes, we are carrying out a molecular analysis of hypothesized protein alterations in the regions of these circuits.
Results: We started to analyze molecular markers of synaptic strength in ACC, cerebellum and DLPFC in a single postmortem tissue cohort (N=21 SZ; N=21 HC). In layers 1-3 of ACC, we found trend increases of Glu2B in all schizophrenia cases (p=0.099) and in off medication schizophrenia cases (p=0.10). We did not observe any change in GluN1 (p=0.82), Glun2A (P=0.49), GAD67 (p=0.39), ERK1 (P=0.67) or ERK2 (p=0.93) in schizophrenia cases. In layers 5a-6 of ACC, we found a significant increase in GluN2B (p= 0.034) in off medication cases, though the increase was not significant in all schizophrenia cases (p= 0.15). There was a trend increase in GluN2A (p=0.10) in off medication schizophrenia cases though the increase was not observed in all schizophrenia cases (p= 0.76). There was no significant change observed in GluN1 (p=0.19), GAD67 (p=0.57), PSD95 (p=0.48), GluA1 (p=0.79), ERK1 (p= 0.73), or ERK2 (p=0.78) in schizophrenia cases. In cerebellum, we found a significant increase of Glu2B in all schizophrenia cases (p=0.03), but this increase was not significant in off medication schizophrenia cases (p=0.29). We did not observe any change in GluN1 (p=0.59), GAD67 (p=0.39), GluA1 (p=0.48), PSD95 (p=0.32) or GluN2A (p=0.68) in schizophrenia cases. In DLPFC, we found insignificant increases of Glu2B in all schizophrenia cases (p=0.29; Effect size=0.73) and in off medication schizophrenia cases. We did not observe any change in GluN1 (p=0.62; Effect size=0.23) or GAD67 (p=0.89; Effect size =0.13) in schizophrenia cases. Data from other regions in this circuit will be reported and correlations between regional molecular markers and hippocampus will be developed.
Conclusion: Ultimately, regional transcriptome analyses might be the strongest way to identify the molecular signaling systems which mediate this functional connectivity.
ID: 2119589

ALTERED GLUTAMATE SIGNALING PROTEIN CO-EXPRESSION NETWORK TOPOLOGY CORRELATES WITH SPINE LOSS IN THE AUDITORY CORTEX OF SCHIZOPHRENIA

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Background: The goal of this study is to observe synaptic glutamate signaling protein network features linked to spine loss in the auditory cortex of schizophrenia subjects.
Methods: Whole tissue homogenates were prepared from auditory cortex grey matter of 22 SZ and matched control subjects. 155 selected synaptic proteins were quantified therein by a targeted proteomics approach. Co-expression networks were evaluated by Weighted Gene Co-expression Network Analysis. Spine density measurements were determined in a subset of this cohort by immunohistochemistry and quantitative fluorescence confocal microscopy.
Results: Comparison of average protein amounts and functional pathway analysis revealed significant differences in the expression of Glutamate Signaling Pathway proteins (p = 2.5E-6, q = 1.5E-3), such as decreased expression of the neuronal Na+/K+ channel subunit ATP1A3. Protein co-expression was significantly reduced in schizophrenia (p-permuted = 0.015). Four postsynaptic density proteins were the exception to this effect, comprising a unique module present only in the SZ network. Interestingly, the average expression of these inversely correlated with spine density in SZ (r = -0.72, p = 0.0018), but not control.
Conclusion: The SZ specific co-expression module that inversely correlates with spine density could represent a pathological process linked to spine pathology or conversely, a coordinated response to spine loss. ATP1A3 mutations contribute to polygenic burden for SZ and have been linked to cognitive impairments and psychosis with auditory hallucinations in a separate neurological illness, rapid onset dystonia parkinsonism. Thus decreased ATP1A3 may contribute to schizophrenia symptoms. This work was funded by National Institutes of Health grants MH 071533, T32 MH 16804, and P30CA047904.
ID: 2118920

DECREASED EXPRESSION OF HYALURONAN RECEPTOR CD44 IN THE AMYGDALA OF SUBJECTS WITH SCHIZOPHRENIA

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Background: Hyaluronan and chondroitin sulfate proteoglycans (CSPGs) are two major components of the extracellular matrix (ECM) in the brain. We recently found pronounced abnormalities affecting CSPGs in the amygdala, entorhinal cortex, prefrontal cortex, and hippocampus of subjects with schizophrenia (SZ). CD44 is the main hyaluronan receptor and is responsible for the organization of the ECM. It is predominantly expressed by glial cells, and has an important role in their development. The main goal of this study was to test the hypothesis that CD44 expression is decreased in subjects with SZ.
Methods: Amygdala tissue blocks from 12 control, 12 SZ and 8 bipolar disorder (BD) subjects were obtained from Harvard Brain Tissue Resource Center. Stereology-based cell counts of CD44-immunoreactive (IR) glia in distinct amygdala nuclei was performed blindly to diagnostic group, using computer assisted quantitative light microscopy. ANCOVA was used to test for statistical significance of changes relative to the main outcome values, accounting for potential confound variables, including gender, age, hemisphere, exposure to therapeutic drugs, and cause of death particularly as it relates to inflammation/immune responses. To investigate the phenotype of CD44-IR cells we used CD44 and glial fibrillary acidic protein (GFAP) dual immunofluorescence labeling and confocal microscopy analysis.
Results: Our results show that the numerical density of CD44-IR glia is significantly decreased in the lateral ($p=0.0003$), basal ($p<0.0001$), accessory basal ($p= 0.0001$), cortical ($p=0.007$), medial ($p<0.0001$), and central ($p=0.0005$) nuclei of the amygdala. Numerical density of CD44-IR cells in subjects with BD was unaltered. Presence of peripheral inflammation at time of death (e.g. pneumonia) had a significant effect on CD44 expression. Over 80 % of CD44-IR cells in healthy controls are GFAP-IR.
Conclusion: To our knowledge, this is the first study to investigate CD44 abnormalities in SZ. Together with our previous findings, showing normal number of GFAP-IR cells in the amygdala of SZ subjects, our results point to decreased expression of CD44 by glial cells. These findings support the hypothesis that a dysregulation of CD44 expression in SZ may contribute to ECM abnormalities in this disorder. Our results also add to emerging evidence for anomalous glia maturation in SZ. Importantly, CD44 decrease may be specific to SZ, as we found no changes in BD.
ID: 2084160

EMPLOYING PROTEOMICS TO EXPLORE THE ENERGETIC COMPONENT OF SCHIZOPHRENIA

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Background: In 1919, the Dutch researcher F.H. Kooy published data on one of the most consistent findings in schizophrenia research, which is the dysfunction of the energy metabolism. Since then, several fields of study such as in vivo imaging, neurochemistry, neuropathology, genetics and transcriptomics confirmed these findings. Likewise, the proteomic investigations we performed on 5 post-mortem brain regions and the cerebrospinal fluid from schizophrenia patients and controls also associated energy metabolism to schizophrenia's pathobiology.
Methods: Aiming to follow up our results on the involvement of the energy metabolism in schizophrenia, we investigated postmortem human brain tissue as well as in vivo and in vitro schizophrenia pre-clinical models. We compared in a non-hypothesis driven manner the proteomes of the dorsolateral prefrontal cortex proteomes from schizophrenia and depression patients to controls using state-of-the-art shotgun mass spectrometry. Results led us to investigate in a targeted manner the proteome of the prefrontal cortex of PCP-treated rats using selective reaction monitoring (SRM). In parallel, we evaluated the proteomes of cell lines treated with MK-801 to investigate more specifically its effect over the energy metabolism.
Results: The investigation on post-mortem brains suggested that, at cellular level, schizophrenia is associated to glycolysis, while depression to oxidative phosphorylation. The quantitation of metabolites such as pyruvate, NADPH and ATP confirmed these results. Following up, the multivariate analyses of SRM data obtained in PCP-treated rats based on glycolytic enzymes generated a bi-dimensional chart that can distinguish the models from the controls. Finally, MK-801-treated cells suggest that oligodendrocytes might be the origin of such metabolic dysfunction, going along with recent data on the importance of glia in schizophrenia's pathobiology.
Conclusion: Proteomic findings support the dysfunction in energy metabolism, more specifically on glycolysis. Our results provide new insights about the cellular biochemistry of schizophrenia, warranting further investigations in how this pathway may be useful as target for alternative and innovative therapies.
ID: 2119249

IS THE ENERGY DYSFUNCTION OBSERVED IN SCHIZOPHRENIA BRAINS BEING ORIGINATED IN OLIGODENDROCYTES?

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Background: While comparing the proteomes of 5 post-mortem brain regions and cerebrospinal fluid from schizophrenia patients to controls, we consistently observed alterations in energy metabolism, cell growth and maintenance, synaptic function, and myelinization processes. Considering the nature of these analyses, it was not possible to reveal which particular cell types display such alterations. This is essential information given increasing evidence of glia cells as pivotal players in schizophrenia. With this in mind, we analyzed the proteomes of cultured astrocytes, oligodendrocytes and neurons treated with MK-801, a NMDA-receptor antagonist which impairs glutamatergic transmission as postulated in schizophrenia. The central aim of this study is to observe which cell types present proteome changes similarly to those we found in our earlier analysis of human brain tissue, in order to understand the role of each cell type in schizophrenia. MK-801-treated cells were also treated with clozapine for observing antipsychotic effects over the proteome.
Methods: Cell cultures were acutely (8 hours) and chronically (72 hours) treated with MK-801 and further submitted to state-of-the art proteomic analyses. Additionally, glycolysis enzymes were analyzed by western blot considering the differential status of this metabolic pathway in schizophrenia.
Results: MK-801-treated astrocytes, and especially MK-801-treated oligodendrocytes displayed several proteins differentially expressed which overlapped exactly with previous findings of schizophrenia human brains. On the other hand, MK801-treated neurons displayed very few differences in their proteome, an overlap with previous findings in human brain tissue below 10%. More interestingly, the dysregulation of glycolytic enzymes in MK801-treated oligodendrocytes are very similar to our observations in schizophrenia brain tissue, corroborating with recent findings about of the importance of oligodendrocytes in the energy status of the brain.
Conclusion: Proteomic data have provided integrated pictures of the biochemical systems involved in schizophrenia. The treatment of cell cultures with neural transmission agonists and antagonists and antipsychotic medication may provide insights about the molecular interaction of schizophrenia as well as useful leads about the molecular role and involved pathways

of each cell type in the disorder. Our data suggest glycolytic enzymes as targets to alternative therapies for treating schizophrenia.
ID: 2084225

THE PROTEOME OF SCHIZOPHRENIA POSTMORTEM BRAINS: DECIPHERING THE INFLUENCE OF DISTURBED ENERGY METABOLISM IN OLIGODENDROCYTES

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Background: In the post-genomic era, proteomics has emerged as a powerful tool to unravel biomarker candidates and to understand human diseases from the molecular point of view. Within a decade, our group mapped the proteome of 5 post-mortem brain regions and the cerebrospinal fluid from schizophrenia patients and controls to help deciphering schizophrenia's pathobiology. These results led us to following up leads on energy metabolism and oligodendrocytes dysfunction.
Methods: Following the obtained results in schizophrenia post-mortem brains, we investigated in vivo (PCP-treated) and in vitro (MK801-treated) pre-clinical models to schizophrenia and post-mortem brains from 24 patients suffering from depression plus 12 mentally healthy controls using state-of-the-art mass spectrometry-based proteomics.
Results: In schizophrenia brains, we have found recurrently the differential expression of glycolytic enzymes, while in depression we found proteins associated to the respiratory chain and oxidative phosphorylation. Both pre-clinical models - PCP and MK801-treated samples - also supported glycolysis involvement in schizophrenia.
We also found in schizophrenia brains consistent differences regarding oligodendrocyte- and myelin-associated proteins. Interestingly, MBP and MOG found differently in brain tissue and in the cerebrospinal fluid from a separate sample cohort of first-onset patients.
Considering the findings above and on the basis of impaired glutamatergic transmission, we treated cultured oligodendrocytes, astrocytes and neurons with MK-801. We observed that the most similar proteome differences to schizophrenia human brains were observed in MK801-treated oligodendrocytes, specially those regarding glycolysis.
Conclusion: Proteomics findings may provide an integrated picture of schizophrenia's pathobiology and the identification of energy metabolism dysfunction in oligodendrocytes reinforces their involvement in schizophrenia's origin. These data are useful to the development of innovative therapeutic strategies.
ID: 2119315

UNRAVELING PROTEOMIC BIOMARKER CANDIDATES FOR A SUCCESSFUL ANTIPSYCHOTIC RESPONSE IN THE PLASMA OF SCHIZOPHRENIA PATIENTS

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Background: Schizophrenia is an incurable disorder, demanding continuous healthcare, which generates substantial expenses. Additionally, as a multivariate disorder presenting a wide range of symptoms, schizophrenia treatment success varies significantly among patients, including no response and undesirable side effects. Hence, it is mandatory to identify biomarkers that may indicate the likelihood of a successful treatment for their implementation in the clinic. And this task may be achieved by proteomics.
Methods: Plasma proteomes collected from living patients prior to antipsychotic treatment (T0) and after 6 weeks of medication (T6) were assessed by state-of-the-art quantitative mass spectrometry-based proteomics. A cohort of 56 drug-free patients submitted to different atypical antipsychotic drugs - olanzapine, quetiapine, and risperidone - was analyzed. These patients were divided in responders and non-responders according to their PANSS observed clinically. We focused the proteomc analysis in discovering biomarkers candidates with predictive power to a successful medication response.
Results: Our results shown 44 differentially expressed proteins at T0. These are involved in 7 different biological processes and showed potential to compose a panel of biomarkers to distinguish responders from non-responders before the initiation of the medication. Moreover, 69 proteins were found differentially expressed at T6, which might serve as sensors of an effective response.
Conclusion: This project goes towards the development of a personalized medicine strategy to schizophrenia by understanding the molecular bases of antipsychotic medication and by identifying predictive biomarkers for clinical implementation.
ID: 2084195

ELEVATED EXCITATORY INPUT TO THE NUCLEUS ACCUMBENS IN SCHIZOPHRENIA: FINDINGS FROM A POSTMORTEM ELECTRON MICROSCOPIC STUDY

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Background: The etiological origin of schizophrenia (SZ) is unknown and no single region of the brain can be pinpointed as an area of primary pathology. Rather, SZ is a disorder resulting from dysfunction of multiple neurotransmitter systems and likely miswiring between brain regions. In order to advance our understanding of SZ pathology, it is necessary to elucidate how communication between brain regions in SZ is disrupted. The nucleus accumbens (NAcc) has long been thought to be a prime region of interest in SZ; it serves as a region of integration for inputs from numerous brain areas altered in SZ, and plays a role in motivation, reward, and salience processing. It has been suggested that aberrant signaling in the NAcc could lead to symptoms in SZ, but it is unknown if these abnormalities are actually present. Electron microscopy (EM) allows for directly studying the morphology of synaptic connections, the structural manifestation of connectivity between neurons.
Methods: EM was used in this study to analyze synapses in the NAcc of subjects with SZ to determine if miswiring is present in this region. In the NAcc of 6 SZ subjects and 8 controls matched for demographics and tissue quality (obtained from the Maryland and Alabama Brain Collections), we compared the density and proportion of synapse types, as well as other synaptic features.
Results: SZ subjects had an elevated density of asymmetric axospinous synapses (characteristic of excitatory input) in the NAcc core (19% increase, $p=0.04$), but not the shell. In both regions there were similar densities of symmetric synapses (characteristic of inhibitory input) between groups. The postsynaptic densities of asymmetric synapses had a smaller average area (22% reduction, $p=0.002$) in the core, and were similar in the shell. Postsynaptic densities of symmetric synapses were similar between groups in both regions. Mitochondria were similar in number, size, and appearance between groups.
Conclusion: These results suggest that the NAcc core receives increased excitatory input in SZ, which could lead to dysfunction of dopamine neurotransmission and processing of cortico-striato-thalamic stimuli. The reductions in average postsynaptic density size of asymmetric synapses suggests that signaling at these synapses could be impaired. These findings enhance our understanding of how this critical region of the brain might play a role in SZ and how glutamatergic and dopaminergic abnormalities may interact in SZ.
ID: 2082999

ALTERED LOCALIZATION OF ASTROGLIAL GLUTAMATE TRANSPORTER AND ASSOCIATED PROTEINS IN SCHIZOPHRENIA

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Background: Converging evidence suggests that changes in astroglial glutamate transporter expression may underlie a disease mechanism in which reduced glutamate reuptake capacity leads to increased glutamate spillover. Increased extrasynaptic glutamate levels may activate extrasynaptic glutamate receptors, potently modulating synaptic plasticity. Excitatory amino acid transporters bind and transport glutamate, limiting spillover from synapses due to their dense perisynaptic expression primarily on astroglia. Thus, the spatial arrangement of glutamate synapses, their glutamate transporter buffering zones, and extrasynaptic glutamate receptors will determine the extent and effects of glutamate spillover. Excitatory amino acid transporter 2 (EAAT2) activity depends on Na+ and K+ gradients generated by Na+/K+ ATPase and ATP. Hexokinase 1 (HK1), an initial enzyme of glycolysis, binds to mitochondrial outer membrane where it couples cytosolic glycolysis to mitochondrial oxidative phosphorylation, producing ATP utilized by the EAAT2/ Na+/K+ ATPase protein complex to facilitate glutamate reuptake.
Methods: We hypothesized that the protein complex formed by EAAT2, Na+/K+ ATPase and mitochondrial proteins in human postmortem prefrontal cortex is disrupted in schizophrenia. Using immunoisolation and mass spectrometry, we found that EAAT2, Na+/K+ ATPase, HK1 and aconitase form a protein complex in human brain.
Results: We next measured levels of glutamate transport complex proteins in subcellular fractions and found increases in the EAAT2B isoform of EAAT2 in a fraction containing extrasynaptic membranes, and increased aconitase1 in a mitochondrial fraction in schizophrenia. An increased ratio of HK1 protein in the extrasynaptic membrane/mitochondrial fraction was found in subjects with schizophrenia, suggesting that HK1 protein is abnormally partitioned in this illness. We also found a change in the spatial distribution of EAAT2 protein in the frontal cortex using immunohistochemistry and electron microscopy.
Conclusion: Our findings indicate that the integrity of the glutamate transport protein complex may be disrupted, leading to decreased perisynaptic buffering and reuptake of glutamate, as well as impaired energy metabolism in schizophrenia. We postulate that diminished perisynaptic glutamate buffering and reuptake may be a common pathophysiological mechanism in schizophrenia, making it a high yield target that may be exploited for the development of new treatments for this often devastating illness.
ID: 2113987

ABNORMAL GLUTAMATE RECEPTOR TRAFFICKING IN CORTICAL AREAS IN SCHIZOPHRENIA

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Background: Accumulating evidence suggests abnormalities of glutamate transmission in schizophrenia. While many findings of abnormal glutamate receptor expression in schizophrenia have been published, findings are subtle or even contradictory. These conflicting studies on the expression of these receptors leads to a reconsideration of the "glutamate hypothesis of schizophrenia" as not "too many" or "too few" receptors, but rather one of alterations in the cell biological processes that manage the total pool of receptors. We have recently published data pointing to abnormalities of glutamate receptor trafficking, delivery, dendritic localization, recycling, and degradation in the brain in schizophrenia.
Methods: Using postmortem brain samples for persons that had suffered from schizophrenia and comparison subjects, we have made a series of observations consistent with abnormal intracellular localization and trafficking of glutamate receptors in this illness.
Results: We have found altered expression of proteins of the NMDA receptor-associated motor complex; changed levels of AMPA and NMDA associated trafficking and chaperone proteins; decreased molecular mass of N-linked glycosylation localized to the endoplasmic reticulum (ER) and Golgi of AMPA and kainate receptor subunits]; abnormal expression of posttranslational modifications of glutamate receptors known to be ER retention signals;
and changes in glutamate receptor expression and associated binding partners within specific subcellular compartments including the ER/Golgi, synapse and endosomes.
Conclusion: Taken together, these studies reflect the complexity of molecular and intracellular abnormalities of glutamate signaling-associated molecules in schizophrenia. Our work to date supports a model of subcellular abnormalities of glutamate receptor and transporter expression and handling. We have interpreted these data as reflecting accelerated ER/Golgi exit and forward trafficking of glutamate receptor complexes, and abnormalities in the dynamics of these receptors at the postsynaptic density (PSD); these data are consistent with abnormalities of insertion, expression, and regulation of these receptor complexes at the synapse.
ID: 2129159

DIRECT EVIDENCE OF VIRAL INFECTION AND MITOCHONDRIAL ALTERATIONS IN THE BRAIN OF FETUSES AT HIGH RISK FOR SCHIZOPHRENIA

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Background: There are increasing evidences that favor the prenatal beginning of schizophrenia. These evidences point toward intra-uterine environmental factors that act specifically during the second pregnancy trimester producing a direct damage of the brain of the fetus. The current available technology doesn't allow observing what is happening at cellular level since the human brain is not exposed to a direct analysis in that stage of the life in subjects at high risk of developing schizophrenia.
Methods: In 1977 we began a direct electron microscopic research of the brain of fetuses at high risk from schizophrenic mothers in order to finding differences at cellular level in relation to controls.
Results: In these studies we have observed within the nuclei of neurons the presence of complete and incomplete viral particles that reacted in positive form with antibodies to herpes simplex hominis type I [HSV1] virus, and mitochondria alterations.
Conclusion: The importance of these findings can have practical applications in the prevention of the illness keeping in mind its direct relation to the aetiology and physiopathology of schizophrenia. A study of amniotic fluid cells in women at risk of having a schizophrenic offspring is considered. Of being observed the same alterations that those observed previously in the cells of the brain of the studied foetuses, it would intend to these women in risk of having a schizophrenia descendant, previous information of the results, the voluntary medical interruption of the pregnancy or an early anti HSV1 viral treatment as preventive measure of the later development of the illness.
ID: 2085760

SYNAPTIC DYSREGULATION IN A HUMAN IPS CELL MODEL OF MENTAL DISORDERS

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Background: Dysregulated neurodevelopment with altered structural and functional connectivity is believed to underlie many neuropsychiatric disorders, and 'a disease of synapses' is the major hypothesis for the biological basis of schizophrenia. Although this hypothesis has gained indirect support from human post-mortem brain analyses and genetic studies, little is known about the pathophysiology of synapses in patient neurons and how susceptibility genes for mental disorders could lead to synaptic deficits inhumans
Methods: We generated induced pluripotent stem cells (iPSCs) from four members of a family in which a frame-shift mutation of Disrupted-in-schizophrenia-1 (DISC1) co-segregated with major psychiatric disorders and we further produced different isogenic iPSC lines via gene editing
Results: We found that mutant DISC1 causes synaptic vesicle release deficits in iPSC-derived forebrain neurons. Mutant DISC1 depletes wild-type DISC1 and, furthermore, dysregulates expression of many genes related to synapses and psychiatric disorders in human forebrain neurons.
Conclusion: Our study reveals that a psychiatric disorder-relevant mutation causes synapse deficits and transcriptional dysregulation in human neurons and our findings provide novel insight into the molecular and synaptic etiopathology of psychiatric disorders.
ID: 2086307

ABNORMAL EXPRESSION OF ADAPTOR PROTEIN COMPLEX SUBUNITS IN THE SUPERIOR TEMPORAL CORTEX IN SCHIZOPHRENIA

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Background: Schizophrenia is a devastating psychiatric illness thought to involve the dysfunction of several neurotransmitter systems, including glutamatergic and GABAergic transmission, which have been hypothesized to contribute to the pathophysiology of schizophrenia. Recent work from our lab has shown that glycosylation provides a common mechanism thought to contribute to the observed synaptic dysfunction in these various neurotransmitter systems. In schizophrenia, glutamatergic and GABAergic molecules associated with neurotransmission may exhibit altered intracellular trafficking that we hypothesize is vital to the underlying mechanisms of the illness. Adaptor protein (AP) complexes are involved in the transport of vesicular glutamate transporters (VGLUTs) and the GluR2 subunit of the AMPA receptor, components previously shown to be altered in schizophrenia.
Methods: Considering that the AP complexes may have a regulatory role in AMPA receptor and VGLUT cellular localization, we measured transcript and protein expression of AP1/2 complex subunits, VGLUTs, and AMPA receptor subunits in the superior temporal gyrus (STG) of patients with schizophrenia (N=16) and matched comparison subjects (N=16).
Results: We found significant increases in transcript expression of select AP complex subunits, including AP1B1 and AP2A1, and GluR2. In addition, AP subunits and VGLUT1/2 or GluA2 transcript and protein levels were analyzed for significant correlations in comparison and schizophrenia samples. AP complex genes AP1S1 and AP2S1 had significantly altered associations with GluR2 in schizophrenia.
Conclusion: Given the significant alterations in gene expression and correlation of these AP subunits with GluR2, the APs may be an underlying mechanism contributing to the altered intracellular trafficking and subsequent synaptic dysfunction observed in schizophrenia. These data support a model of accelerated forward trafficking and altered receptor maintenance at the synapse.
ID: 2087620

A ERYTHROCYTE MEMBRANE PHOSPHOLIPID CLUSTER IDENTIFIES A GROUP OF SCHIZOPHRENIA PATIENTS WITH SIGNIFICANTLY WORSE COGNITIVE SCORES

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Background: Membrane phospholipids (PL) and their fatty acids (FAs) play a critical role in the structure and function of the developing nervous system. Lipid membrane abnormalities are associated with several neuropsychiatric disorder, in particular schizophrenia (SCZ) and autism. Several membrane PL abnormalities have been identified in ultra- high risk individuals and associated with cognitive impairment. The present study aimed at identifying whether a subgroup of schizophrenia patients with a cluster of PL abnormalities exhibits worse cognitive score in comparison with patients with other cluster.
Methods: Cognitive characteristics and membrane lipid composition of chronic medicated SCZ patients (n=75) have been examined and compared to a healthy control (HC) population (n=40). WCST and PANSS cognitive component were measured in the SCZ population. Red blood cell (RBC) membrane phospholipid (PL) and fatty-acid (FA) composition was identified and measured by using LC-MS/MS method. Univariate analysis of the PL nature and species allowed identifying significant differences between SCZ and HC. ROC curves could also identify 2 classes (abnormal vs normal) of lipid composition in the SCZ population.
Results: Seven independent lipid variables could be determined (phosphatidylserine (PS), sphingomyelin (SM), phosphatidylcholine, phosphatidylethanolamine (PE), external PE, external lysoPE, and plasmalogen). A cluster analysis identified 3 independent cluster of patients. Cluster 1 (n=43) corresponds to SCZ individuals with abnormal SM and a variety of other abnormalities, Cluster 2 (n=17) identified patients without abnormal membrane lipids, and Cluster 3 (n=14) with only both abnormal PS and external PE, but no SM abnormality.
Cognitive scores from cluster 1 patients significantly differ from those of Clusters 2 and 3 for WCST for trials (p=0.0092), errors (p=0.0032), perseverative responses (p=0.0022), perseverative errors (p=0.0018), as well as non-preservative errors (p=0.0082). The cognitive/excited component of the PANSS was also significantly worse (p= 0.0211) in the patients from the Cluster 1 compared to both cluster 2 and 3.
Conclusion: A cluster of RBC membrane PL was able to identify a group of stabilised medicated SCZ patients with significantly worse cognitive scores in the WCST and PANSS cognitive component.
ID: 2118430

PHOSPHOSERINE PHOSPHATASE ACTIVITY IS ELEVATED AND NEGATIVELY CORRELATED WITH SERUM D-SERINE CONCENTRATION IN SCHIZOPHRENIA PATIENTS

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Background: Several studies have supported the N-methyl-D-aspartate receptor (NMDAR) hypofunction hypothesis as the pathophysiology of schizophrenia. D-Serine and glycine are endogenous NMDAR co-agonists that are important factors for NMDAR excitement. Both of these endogenous amino acids are synthesized from L-serine. Therefore we hypothesized that the L-serine synthesis pathway could be a possible pathophysiological pathway in schizophrenia.
Methods: In peripheral blood mononuclear cells (PBMCs), the activity of phosphoserine phosphatase (PSP), which is a rate-limiting enzyme for L-serine synthesis, was measured in 59 schizophrenia patients (SCZs) and 49 normal control subjects (NCSs). Serum amino acids (L-serine, D-serine, glycine, glutamine and glutamate) were measured by high performance liquid chromatography (SCZs: n=56, NCSs: n=45). mRNA expression levels of 3-phosphohydroxypyruvate dehydrogenase (PHGDH), phosphoserine aminotransferase 1 (PSAT1) and PSP in the peripheral blood were compared between SCZs and NCSs by quantitative real-time PCR methods (SCZs: n=75, NCSs: n=61). Data are presented as the expression levels relative to beta-actin and GAPDH expression. L-Serine biosynthesis requires three enzymatic steps catalyzed by PHGDH, PSAT1 and PSP.
Results: Activity of the PSP enzyme was significantly higher in SCZs than in NCSs, as determined by a logistic regression analysis ($p<0.01$). The mean value was 36.9±22.0 μU in SCZs and 25.3±21.1 μU in NCSs. In male SCZs, the serum L-serine concentration was higher than that in NCSs (87.7±19.1 μM vs 78.3±16.2 μM). In SCZs, serum D-serine concentration ($\beta = -0.61$, $p <0.01$), serum L-serine concentration ($\beta =0.37$, $p= 0.049$), glycine concentration ($\beta= -0.36$, $p=0.030$) and age ($\beta=0.36$, $p =0.046$) were correlated with PSP activity by multiple linear regression analysis with the backward elimination model. However, in the entire group and in NCSs, no correlation was found between PSP activity and any amino acids. mRNA expression levels of PSP, PSAT1 and PHGDH were lower in the SCZs than in the NCSs by the Mann-Whitney U test ($p<0.01$), except when the PHGDH expression level was compared with the beta actin expression level ($p=0.34$).
Conclusion: The L-serine synthesis pathway could be a possible pathophysiological pathway in schizophrenia. PSP activity could be a biological trait marker of schizophrenia. A strategy that modifies the L-serine synthesis pathway may lead to a novel treatment for schizophrenia.
ID: 2079800

ALTERATIONS IN THE PRENYLATION ENZYMES IN PREFRONTAL CORTEX IN SCHIZOPHRENIA

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Background: Abnormal protein trafficking has been previously implicated in multiple neurotransmitter pathways known to be altered in schizophrenia. Recently, our lab has found evidence that post translational modifications, including glycosylation, myristoylation, phosphorylation and S-palmitoylation, may be contributing to abnormal subcellular localization of membrane proteins. Cytosolic prenylation is another post translational lipid modification that targets proteins to membranes, facilitating their forward trafficking to the plasma membrane. Based on these findings, we hypothesized that this lipidation is abnormal in schizophrenia. We measured the expression of enzymes necessary for prenylation homeostasis to ascertain if disruptions of prenylation may be contributing to altered neurotransmission in schizophrenia.
Methods: We measured protein expression of regulatory prenylation enzymes by western blot analysis on 1D-SDS-PAGE in postmortem cortex from 13 matched pairs of schizophrenia and comparison subjects. Intensity values, as a measure of protein expression, were normalized to an intra-lane loading control.
Results: The three prenylation enzymes are each comprised of two subunits; decreased protein expression was found in one or both subunits for each enzyme. FNTA ($t (12) =3.74$, $p=0.003$), PGGT1B ($t (12) =2.90$, $p=0.013$) and RABGGTB ($t (12) =2.287$, $p=0.041$) were all decreased in schizophrenia subjects. Expression did not change between groups for FNTB or RABGGTA, nor was any change found in the Rab escort protein (REP). We also assayed farnesyl pyrophosphate synthase (FDPS), geranylgeranyl pyrophosphate synthase (GGPS1), Ras-converting enzyme (RCE) and isoprenyl cysteine carboxyl methyltransferase (CMT) but did not find a difference in expression between groups.
Conclusion: We have demonstrated decreased protein expression of subunits of the necessary prenylation enzymes, FNTA, PGGT1B, and RABGGTB in schizophrenia. We also examined upstream synthases, FDPS and GGPS1, and enzymes downstream of prenylation, RCE and CME, finding no differences between groups.
Taken together, these data suggest the alterations found in the subunits of prenylation enzymes may lead to abnormal prenylation ratios of membrane proteins, which suggests this pathway may be a common mechanism contributing to the abnormal protein trafficking in a myriad of neurotransmitter systems in schizophrenia.
ID: 2087872

GENE EXPRESSION LEVELS OF DOPAMINE PATHWAY-RELATED MOLECULES IN THE SUBSTANTIA NIGRA IN SCHIZOPHRENIA

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Background: Schizophrenia involves a presynaptic dopamine dysfunction in the associative striatum, which receives dopamine projections from the substantia nigra. It is unknown how gene expression of dopamine-pathway related molecules are changed in the substantia nigra in schizophrenia. We investigated how gene expression levels of dopamine-related molecules are changed in the human substantia nigra from schizophrenia and control brains.
Methods: We examined mRNA expression by quantitative PCR of the dopamine synthesis molecule, tyrosine hydroxylase (TH), dopamine reuptake molecules, dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT2), dopamine receptor D2 isoforms (DRD2 pan, short, long and longer) as well as dopamine breakdown enzymes, catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) A and B in the substantia nigra of control (n=29) and schizophrenia post mortem brains (n=29) provided by the New South Wales Brain Bank, Sydney Australia.
Results: We found no change in TH mRNA ($p=0.67$) levels but a 36% ($p=0.014$) and a 43% ($p=0.0002$) decrease in VMAT2 and DAT mRNA, respectively, in substantia nigra from schizophrenia brains compared to

control brains. We also found a 30% (p=0.04), 37% (p=0.02) 36% (p=0.007) and 25% (p=0.04) decrease in DRD2pan, DRD2short, DRD2long and DRD2longer mRNA, respectively, in SN from schizophrenia brains compared to control brains. Expression of MAOA mRNA was increased by 38% (p=0.02) in SN from schizophrenia brains compared to control whereas MAOB (p=0.4) and COMT (p=0.6) expression were unchanged.
Conclusion: These data provide evidence of changes in dopamine pathway-related molecules in the region of dopamine cell bodies. Possible effects of antipsychotic medication on these dopamine-related molecules will be assessed. This data begins to elucidate proximal changes to the presynaptic dopamine dysfunction reported in the striatum of schizophrenia patients.
ID: 2116061

PROTEOMIC PATHWAY ANALYSIS OF THE HIPPOCAMPUS IN SCHIZOPHRENIA AND BIPOLAR AFFECTIVE DISORDER IMPLICATES 14-3-3 SIGNALING, ARYL HYDROCARBON RECEPTOR SIGNALING, AND GLUCOSE METABOLISM.

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Background: The Molecular mechanisms underlying structural and cellular changes in the hippocampus of people with schizophrenia or bipolar disorder remain poorly understood.
Methods: We used data from two comprehensive difference-in-gel electrophoresis (2-D DIGE) investigations of postmortem human hippocampus of people with schizophrenia and bipolar disorder, covering the acidic (isoelectric point (pI) between pH 4-7) and, separately, the basic (pI between pH 6-11) sub-proteome, for Ingenuity Pathway Analysis (IPA) of implicated protein networks and pathways.
Results: Comparing disease and control cases, we identified 58 unique differentially expressed proteins in schizophrenia, and 70 differentially expressed proteins in bipolar disorder, using mass spectrometry. IPA implicated, most prominently, 14-3-3 and aryl hydrocarbon receptor signaling in schizophrenia, and gluconeogenesis/glycolysis in bipolar disorder. Disease-associated protein networks implicated free radical scavenging, cellular assembly and organization, and cellular protein endocytosis, -transport, and -ubiquitination.
Conclusion: These findings converge on hippocampal GABAergic interneuron pathology in psychotic disorders, and may help generate novel hypotheses for diagnostics and drug development.
ID: 2118412

DOPAMINE AND SEROTONIN RECEPTOR SUBTYPE EXPRESSION IN LASER CAPTURE MICRODISSECTION ISOLATED CELLULAR SUBPOPULATIONS OF POSTMORTEM DORSOLATERAL PREFRONTAL CORTEX

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Background: Altered dopamine and serotonin signaling is known to contribute to the pathophysiology of schizophrenia. Both dopaminergic and serotonergic neurons innervate the dorsolateral prefrontal cortex (DLPFC), a region in which abnormalities have been observed in schizophrenia and are associated with cognitive dysfunction in patients. Dysregulation of these two neurotransmitter systems may contribute to pathophysiology in the DLPFC in schizophrenia. This study aims to characterize the mRNA expression of dopamine and serotonin receptor subtypes within defined cellular subpopulations in human postmortem DLPFC and identify potential differences of expression in schizophrenia.
Methods: Two cellular subpopulations were isolated from postmortem DLPFC using laser capture microdissection (LCM). The "large cell" population is enriched for glutamatergic neurons, and the "small cell" population is enriched for GABAergic interneurons. Relative mRNA expression of dopamine receptor subtypes D1, D2, and D5 and serotonin receptor subtypes 5HT2a, 5HT2c, and 5HT6 in the DLPFC was measured in each subpopulation in paired schizophrenia and comparison subjects (N = 12) using RT-PCR.
Results: This study found D1 and D2 equally expressed in large and small cells, expression of D5 ($z=-4.01$, $p < 0.01$), 5HT2a ($z=3.94$, $p < 0.01$), and 5HT2c ($z=-3.70$, $p < 0.01$), higher in large cells, and expression of 5HT6 ($z= -3.05$, $p=0.01$), higher in small cells. No differences were observed in dopamine and serotonin receptor expression in either cellular subpopulation between comparison and schizophrenia subjects.
Conclusion: This study gives evidence for a distinct pattern of expression of dopamine and serotonin receptor subtypes in defined cellular subpopulations. While no difference in receptor mRNA expression was found between diagnostic groups, future studies investigating dopamine and/or serotonin dysfunction should consider the cell-type specific expression of different receptor subtypes to fully understand how abnormalities may affect excitatory/inhibitory neural networks. Together these data suggest that further studies of dopamine and/or serotonin dysfunction in schizophrenia should prioritize identifying abnormalities of receptor processing downstream of mRNA transcription.
ID: 2087810

CLOZAPINE PROMOTES GLYCOLYSIS AND MYELIN LIPID SYNTHESIS IN OLIGODENDROCYTES

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Background: Clozapine has stronger systemic metabolic side effects than haloperidol and it was hypothesized that the therapeutic antipsychotic and adverse metabolic effects might be related. Considering that cerebral disconnectivity through oligodendrocyte dysfunction has been implicated in schizophrenia, it is important to determine the effect of these drugs on oligodendrocyte energy metabolism and myelin lipid production.
Methods: We, therefore, compared the effects of clozapine and haloperidol on glucose and myelin lipid metabolism in cultured OLN-93 oligodendrocytes. Glycolytic activity was assessed by measurement of extra- and intracellular glucose and lactate levels. The expression of glucose (GLUT) and monocarboxylate (MCT) transporters were determined after 6h and 24h. Mitochondrial respiration, acetyl-CoA carboxylase, free fatty acids, and expression of the myelin lipid galactocerebroside were measured to study oligodendrocyte lipid metabolism and maturation.
Results: Both drugs altered oligodendrocyte glucose metabolism, but in opposite directions. Clozapine improved the glucose uptake and production and release of lactate, without altering GLUT and MCT. In contrast, haloperidol led to higher extracellular levels of glucose and lower levels of lactate, indicating reduced glycolysis. The number of functionally intact mitochondria was not significantly altered by these drugs, but clozapine enhanced the efficacy of oxidative phosphorylation and expression of galactocerebroside.

Conclusion: Confirming clozapine's well documented superior impact on white matter integrity in schizophrenia, these findings suggest that clozapine improves the energy supply and maturation of oligodendrocytes. Thus, clozapine may act as a modulator of energy metabolism and myelin lipid synthesis in oligodendrocytes. Characterizing the underlying signal transduction pathways may pave the way for novel oligodendrocyte-directed schizophrenia therapies.
ID: 2068553

SPHINGOMYELIN DECREASE IN RBC MEMBRANE OF SCHIZOPHRENIA PATIENTS IS ASSOCIATED WITH A PATTERN OF OTHER MEMBRANE LIPID ABNORMALITIES AND DISEASE SEVERITY

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Background: Sphingomyelin (SM) decreased content in serum is associated with increased risk of neuropsychiatric disorders. It was recently shown to predict phenoconversion to Alzheimer's disease within 2 years with over 90% accuracy in an elderly population of individuals with currently no signs of cognitive impairment (Mapstone M, Nat Med. 2014). An abnormal content and distribution of membrane phospholipids (PL) is also described in schizophrenia patients where SM decreased percentage in RBC and neuron membranes is a common finding. The purpose of the present study was to identify if a significant SM membrane decrease is associated with a pattern of other membrane PL abnormalities as well as disease severity.
Methods: Major membrane PL ratios were measured in the RBC membrane of chronic medicated SCZ patients (n=75) and compared to those of matched healthy control (HC) (n=40) by using LC-MS/MS method. Univariate analysis followed by ROC curves for significant PL ratios between schizophrenia and healthy individuals allowed identify cut-off for each populations. In the present poster, only SM cut-off was used as specifier distinguishing patients with an under threshold value (SM- or abnormal) and those with an above threshold value (SM+ or HC-like). SM- and SM+ were then compared for other variables themselves separated when possible between abnormal/normal (in comparison with HC) or severe vs mild (for the patient population)
Results: A significant decrease in SM was fond in 36.0% of the schizophrenia population (vs only 7.95% for HC) ($p<0.0001$). Compared to SM+, schizophrenia SM- individuals also exhibited decreased external LysoPE ($p=0.0002$), decreased phosphatidylcholine ($p<0.001$), increased phosphatidylserine ($p=0.0001$), and decreased plasmalogen ($p<0.0001$). The clinical and cognitive characteristics also significantly differed between the SM- and SM+ schizophrenia groups with a lower education level ($p=0.0461$), higher PANSS values in the SM- population for the PANSS total ($p=0.0100$) and positive ($p=0.0142$). WCST values also differed in SM- on the number of trials ($p=0.0052$), errors ($p=0.0013$), perseverative responses ($p=0.0015$), perseverative errors ($p=0.0015$), and non-perseverative errors ($p=0.0025$) when compared to SM+.
Conclusion: Stabilised and medicated chronic schizophrenia patients with a lower SM percentage in their RBC membrane exhibited both a specific pattern of membrane lipid abnormalities and characteristics of clinical severity.
ID: 2118473

MARKERS OF INFLAMMATION AND STRESS DISTINGUISH SUBSETS OF INDIVIDUALS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER

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Background: Schizophrenia and bipolar disorder share a number of common features, both symptomatically and biologically. Abnormalities in markers of the neuroimmune and the stress-signalling pathways have been previously identified in brains of individuals with both diseases. However, the possible relationship between abnormalities in stress and neuroimmune signalling within the cortex of people with psychotic illness has not been defined. We tested the hypothesis that combined alterations in brain stress responsiveness and neuroimmune/inflammatory status are characteristic of some individuals suffering from major mental illness
Methods: We examined gene expression in the Stanley Array Cohort of 35 controls, 35 individuals with schizophrenia and 34 individuals with bipolar disorder. We measured levels of 8 inflammatory-related transcripts and 12 glucocorticoid receptor signalling (stress) pathway transcripts via qPCR. Using biologically defined subgroups, we tested which microarray-assessed transcriptional changes may be associated with high inflammatory/stress groups using ingenuity analysis
Results: We found that an immuno-regulator, SERPINA3 mRNA, was significantly elevated in individuals with schizophrenia ($F(2,88)=4.137$, $P<0.05$) and that a stress receptor co-factor, FKBP5 mRNA, was altered according to diagnosis ($F(2, 87)56.00$, $=0.005$), with a 68% increase in schizophrenia cases relative to controls ($p= 0.001$; and a 48% in bipolar disorder cases relative to controls ($p<0.05$). Based on gene expression levels of multiple markers in these pathways, we distinguished two clusters of individuals: a high inflammation/stress group (n=32) and a low (n=68) inflammation/stress group. The high inflammation/stress group has a significantly greater number of individuals with schizophrenia (n=15, 42%), and a trend toward having more bipolar disorder individuals (n=11, 32%), when compared with controls (n=6, 17%). We found that an extended network of gene expression changes involving growth factors, inhibitory neurons and cell death also distinguished these subgroups.
Conclusion: Our work demonstrates that some of the heterogeneity in schizophrenia and bipolar disorder may be partially explained by biological changes in cortical inflammation/stress markers and that these likely interact. Further, this high inflammation/stress biological subtype cuts across Diagnostic and Statistical Manual of Mental Disorders (DSM)-defined categories of bipolar and schizophrenia.
ID: 2092329

HOMEOSTATIC IMBALANCE OF PURINE CATABOLISM IN SCHIZOPHRENIA POSTMORTEM BRAIN

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Background: Previous studies in schizophrenia (SZ) indicated that purine catabolism may contribute to mitochondrial antioxidant defense by producing uric acid (UA). Failure to maintain elevated xanthine and UA occurred contemporaneous to progressive mitochondrial dysfunction. Thus, purine catabolism appears to be a homeostatic response of mitochondria to oxidant stress and may act against progressive mitochondrial dysfunction in

SZ. In the present study, we specifically examined whether oxidative stress is linked to altered purine catabolism in schizophrenia postmortem brain.
Methods: Using high-pressure liquid chromatography coupled with a coulometric multi-electrode array system, we compared 6 purine breakdown metabolites simultaneously in the anterior cingulate cortex (ACC) of postmortem brain among SZ (60 ± 11 years, n = 7), and control subjects with (49 ± 17 years, n = 7) and without (55 ± 21 years, n = 7) psychiatric disorders.
Results: Compared to the normal and psychiatric control groups, the SZ group showed significantly higher levels of xanthine (ANOVA, p = 0.0006, df = 2,18, F = 11.64) and lower levels of hypoxanthine (ANOVA, p = 0.0166, df = 2,18, F = 5.19) in the ACC region. Moreover, the ratio of UA to xanthine was significantly lower (p = 0.0336) in SZ than in control group without psychiatric disorders. However, levels of xanthosine, guanine, and guanosine were not significantly different among three groups.
Conclusion: The steady-state formation of antioxidant UA from purine catabolism is altered not only in SZ patients early in illness, as previously demonstrated in plasma of high-risk or first-episode psychosis patients, but also in the present study of postmortem ACC from patients with chronic SZ. Our data further support the existence of ACC pathology in SZ, and specifically homeostatic imbalance of purine signaling in SZ pathology.
(Supported by Department of Veterans Affairs)
ID: 2118353

Therapeutics, Treatment Trials

ANTIPSYCHOTIC RE-CHALLENGE IN PREVIOUS FIRST EPISODE SCHIZOPHRENIA RESPONDERS

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Background: Whether schizophrenia represents a neuroprogressive or neurodevelopmental disorder continues to be debated. In terms of the latter, it has been proposed that psychosis may be 'neurotoxic', with response attenuated in the face of repeated relapses. However, to date there has been a very limited body of evidence to support this position.
The present study represents data extracted from a clinical database where individuals with first-episode schizophrenia are systematically treated with two trials of Second Generation antipsychotics before being considered for a trial of clozapine. In each case, relapse was attributed to non-adherence and patients were reinitiated on the same antipsychotic at the same dose as what had been employed to achieve remission during the first treatment trial.
Methods: Antipsychotic-naïve individuals diagnosed with first-episode schizophrenia were treated following an algorithm. In the case of relapse due to non-adherence, the same medication/dose that achieved response previously was offered again for the second episode. Repeated measures was used to compare the time course of symptom reduction between first-episode and second-episode.
Results: 132 patients (79% male; average age=22) relapsed due to non-adherence after meeting criteria for response to first antipsychotic trial during their first psychotic episode. Over a period of 2 years all relapsed due to non-adherence were treated once again with the same antipsychotic and dose.
BPRS improvement was significantly greater for the first compared to second episode at every time point over a 6-month interval in each case.
Conclusion: Reinitiating antipsychotic treatment for a second episode of psychosis was associated with an attenuated response to antipsychotic medication. More recently, attention has turned to the notion that schizophrenia is best characterized as a neurodevelopmental disorder and there is compelling evidence for this position. However, it may be the case that there is as well a neuroprogressive component, at least for a subgroup of individuals, which may be linked to relapse. In summary, there is clear evidence that outcome varies considerably in schizophrenia and the role of relapse and possible biological underpinnings remains to be clarified.
ID: 2119830

TREATMENT EFFECT WITH PALIPERIDONE PALMITATE COMPARED TO ORAL ANTIPSYCHOTICS IN PATIENTS WITH EARLY AND MORE CHRONIC SCHIZOPHRENIA

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Background: Long-acting injectable (LAI) antipsychotics are typically reserved for patients with schizophrenia who have a long history of illness. LAI antipsychotic therapy has not been well studied in early-illness patients. We present an exploratory analysis of relative outcomes in patients with early and more chronic illness after treatment with either once-monthly paliperidone palmitate (PP) or daily oral antipsychotics (OAs) from a study designed to reflect real-world schizophrenia, as defined by patients, interventions, and outcomes.
Methods: A randomized, open-label, event monitoring board-blinded study assessed treatment failures in 444 subjects with schizophrenia randomly assigned to PP or OA for 15 months (NCT01157351). Event-free probabilities were estimated using the Kaplan-Meier method; hazard ratios (HRs) were estimated using Cox proportional hazards models. Assessments included time to first treatment failure, time to first psychiatric hospitalization or arrest/incarceration, and adverse events (AEs). Data were analyzed by disease duration (≤5 years [early illness] or >5 years [chronic illness] since psychiatric diagnosis).
Results: 77 subjects met the criteria for early illness (42 PP, 35 OA) and 365 for chronic illness (183 PP, 182 OA). HRs (95% confidence intervals [CIs]) for treatment failure risk with OAs vs PP were 1.73 (0.87-3.45) for early illness and 1.37 (1.02-1.85) for chronic illness. HRs (95% CIs) for first psychiatric hospitalization or arrest/incarceration were 1.79 (0.88-3.62) for early illness and 1.38 (0.99-1.92) for chronic illness. The most common AEs in early-illness PP vs OA groups, respectively, were injection-site pain (26% vs 0%), increased weight (14% vs 6%), akathisia (14% vs 9%), insomnia (12% vs 17%), and anxiety (12% vs 6%). The most common AEs in chronic-illness PP vs OA groups, respectively, were injection-site pain (17% vs 0%), increased weight (12% vs 6%), akathisia (10% vs 7%), insomnia (19% vs 10%), and anxiety (10% vs 8%).
Conclusion: This exploratory analysis suggests that PP might have a more robust effect in reducing the risk of treatment failure than OAs in patients with schizophrenia who are early in their illness compared to those with more chronic illness. The subgroup comparisons were not powered to draw definitive conclusions, but they may guide future research.
ID: 2085600

OLANZAPINE "LONG-ACTING" IN MAINTENANCE THERAPY OF SCHIZOPHRENIA: A STUDY WITH PLASMA LEVELS

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Background: This prospective observational study was performed to evaluate clinical efficacy and tolerability of Olanzapine long-acting (OLZ-LAI) and the relationship between OLZ plasma concentration (PL) and the clinical outcome in maintenance therapy of Schizophrenia.
Methods: This 9-month study involved 25 outpatients, affected by schizophrenia (DSM VI-TR criteria), after clinical stabilization. The patients were prescribed OLZ-LAI at doses of 210-300-405 mg/ 4 weeks on the basis of clinical judgment and of their previous oral Olanzapine doses. Oral supplementation of Olanzapine was not required.
At baseline and every 4 weeks, patients were clinically tested by BPRS (Brief Psychiatric Rating Scale) and PANSS (Positive and Negative Syndrome Scale); plasma concentration of OLZ, and metabolic profile (AST, ALT, HDL, LDL, Total CHO, Glucose) were also determined.
Results: BPRS and PANSS showed a statistically significant decrease at the end of the study: BPRS (mean 26,00 ± 3,08 vs. 45,42 ± 12,74 SD; p<0,001) with an amelioration of 38,44 %. Total PANSS (mean 48.4 ± 7.23 SD vs. 79.23 ± 24.16 SD; p<0,001) with an amelioration of 32,33%; positive, negative and psychopathological scores significantly improved (mean 11.4 ± 3.04 SD vs. 20.94 ± 8.00 p<0,001; mean 13.0 ± 3.80 SD vs. 19.47 ± 7.81 p = 0.02; mean 24.0 ± 2.73 SD vs. 38.82 ± 12.87 p<0,001 respectively).
Olanzapine plasma level (PL) ranged from 4,0 ng/ml to 78,9 ng/ml, showing an high inter-individual variability. There was not a statistically positive significant correlation between OLZ dose and PL at any times, except at t0, where PL referred to the previous oral administration (r=0,74 and p<0,05).
Weight gain >7% has been observed in 7 patients (28%).
Two patients showed an increase of total CHO and LDL-CHO >7%.. No PDSS (Post Injection Delirium Sedation Syndrome) has been observed.

Conclusion: Our data support the efficacy and good tolerability of OLZ-LAI in the long term treatment of Schizophrenia. OLZ-LAI seems to be useful to control non-adherence and to guarantee constant plasma concentration of the drug. Moreover a reasonable stability in plasma concentrations was a predictive factor associated with an enduring clinical benefit in our patients sample.
ID: 2083307

DESIGN OF TRIALS TO REDUCE SUICIDALITY:THE INTERSEPT EXPERIENCE

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Background: Schizophrenia is associated with a high prevalence of l suicidality (33-50%). Knowledge gained with the InterSept trial may provide valuable insights for future endeavors.
Methods: The International Suicide Prevention Trial (InterSePT) was a prospective randomized controlled trial that encountered substantial challenges that requiring the Sponsor, FDA and Academia to work closely.
The challenges included defining; "suicidality", diagnoses (schizophrenia, schizo-affective, or both), population (currently suicidal or those with a suicidal trait),outcome measure (attempts, suicides, or scales, etc), ensuring statistical power (requiring a certain number of events) versus the ethical obligation to prevent suicidal attempts (resulting in reduced power). Measuring change in suicide risk posed an enormous enormous challenge. significant hurdle as all had to be on "Standard of care" concomitant therapy was provided suicidal patients for all patients, however, this could mask lack of efficacy. The choice of comparator was difficult as placebo or neuroleptics (worsen suicidality) would be unethical. Blinding was also a problem, as investigators insisted on knowing the treatment a suicidal patient was receiving
Results: Extensive discussions with FDA led to pragmatic decisions on design, use of blinded raters, Primary outcome variable,,severity/ history of suicidality, concomitant.medications The primary outcome variable was defined as time to a significant suicide attempt or to a hospitalization for imminent risk of suicide An Independent Suicide Monitoring Board received reports on every case prepared by the Principal Investigator that allowed the Board to determine cases of gestures, or event that did not meet the definition of an " attempt".Based on the complexity of the data that comprised the outcome variable, there was close interaction with the FDA and statistical experts on developing new statistical methods for analyzing the data.
Conclusion: The InterSept trial dispelled some common prejudices relating to interaction with Health Authorities, designing trials together with FDA, Sponsor and Academia, evaluating indications that were not included in DSM IV, use of outcome variables that had never been used, or validated, the acceptability of data from an open-label study albeit with blinded raters, and performing a trial in high-risk patients with high morbidity. Understanding how these difficult issues were handled may help in the design of new trials to reduce suicidality.
ID: 2119150

PSYCHOSOCIAL INTERVENTIONS IN FIRST EPISODE PSYCHOSIS

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Background: The natural course of psychosis is characterized by repeated relapses. Psychosocial interventions may reduce chances of a relapse after a first psychotic episode.
Methods: We performed a 9-month, randomized, rater-blinded clinical trial involving 55 adolescent patients with early-onset psychosis and either or both of their parents. A psychoeducational problem-solving group intervention (n = 27) was compared with a nonstructured group intervention (n = 28). The primary outcomes were number of hospitalizations, days of hospitalization, and visits to the emergency department. The secondary outcome measures were clinical variables and family environment.
Results: Assessments were performed before and after the intervention. At the end of the group intervention, 15% of patients in the psychoeducational group and 39% patients in the nonstructured group had visited the emergency department ($\chi 2 = 3.62$, df = 1, p = .039). The improvement in negative symptoms was more pronounced in the psychoeducational group (12.84 [7.87]) than in the nonstructured group (15.81 [6.37]) (p = .039).
Conclusion: A parallel psychoeducational group intervention providing written instructions in a structured manner could help patients with a first psychotic episode and their relatives to manage crises by implementing problem-solving strategies within the family, thus reducing the number of visits to the emergency department. Negative symptoms seem amenable to improve with psychosocial interventions. Evidence on other psychosocial interventions in the treatment of first episode psychosis will be reviewed.
ID: 2115833

EFFICACY OF ADD-ON PROLONGED-RELEASE MELATONIN VERSUS PLACEBO FOR BENZODIAZEPINE DISCONTINUATION IN PATIENTS WITH SEVERE MENTAL ILLNESS: A RANDOMIZED CLINICAL TRIAL

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Background: Benzodiazepines are frequently prescribed in patients with mental illness due to high rates of comorbid anxiety and insomnia. Discontinuation of benzodiazepines after few weeks of treatment is often difficult because of development of dependence and addiction. We aimed to assess if prolonged-release melatonin can facilitate the withdrawal of long-term benzodiazepine administration in patients with severe mental illness.
Methods: Randomized, blinded, single-center, parallel superiority trial. Eligible patients were adults with a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder and treated with antipsychotic drug(s) and at least one benzodiazepine derivative for a minimum of three months. Participants were randomized to prolonged-release melatonin 2 mg daily versus matching placebo and were continuously instructed and guided to gradually reduce their usual benzodiazepine treatment. We examined the participants at baseline and after 8, 16, and 24 weeks of treatment and contacted them weekly by telephone. The primary outcome was mean benzodiazepine dose at 24 weeks follow-up and secondary outcomes included benzodiazepine cessation rate, pattern of benzodiazepine dose over time and benzodiazepine withdrawal symptoms.
Results: In total, 86 patients (21-74 years) were enrolled. Analysis was intention to treat. Median benzodiazepine dose at baseline was 20.0 mg diazepam equivalents in both intervention groups. For the primary outcome there was no difference between groups; median dose in melatonin

group was 5.0 mg diazepam equivalents and median dose in placebo group was 1.9 mg diazepam equivalents (P=0.19), both at 24 weeks. Likewise, there was no difference between treatment groups when assessing benzodiazepine cessation rate; 38.1% in the melatonin group and 47.7% in the placebo group (OR 1.57; 95% CI 0.64 to 3.84; P=0.32). Dosages steadily declined with time in both groups (main effect of time, P<0.0001) with a borderline significant interaction between intervention and time (P=0.05). Benzodiazepine withdrawal symptoms did not change with benzodiazepine dose reduction in neither intervention group. Groups were similar regarding frequency of serious and non-serious adverse events.

Conclusion: Benzodiazepine dose was comparably low between groups after 24 weeks of guided gradual dose reduction. In this context, prolonged-release melatonin did not seem to further facilitate benzodiazepine discontinuation.

ID: 2085409

THE LONGITUDINAL IMPACT OF SUBSTANCE USE SEVERITY AMONG INDIVIDUALS WITH SCHIZOPHRENIA

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Background: Comorbid substance use disorders (SUDs) are common in schizophrenia, affecting nearly 50%, and complicating its consequences, leading to homelessness, re-hospitalizations, and infectious diseases. Such consequences often stem from the severity of substance use, and this population remains difficult to engage in treatment and tends to make slow progress. Deficits in intrinsic motivation may contribute to these challenges such that low levels diminish the capacity of such adults to perceive that reducing their substance use will positively impact their recovery. This study sought to examine longitudinal relationships between intrinsic motivation and substance use severity in a sample of patients with comorbid SUD and schizophrenia.

Methods: Researchers using the Alcohol/Drug Use Scales assessed substance use severity for 536 patients with schizophrenia and comorbid SUD at baseline, 6-, and 12-months for the Clinical Antipsychotic Trials of Intervention Effectiveness. Intrinsic motivation was determined by a measure derived from three Quality of Life Scale items (purpose, motivation, and curiosity).

Results: At baseline, patients with low intrinsic motivation had greater alcohol use severity than those with high intrinsic motivation ($p = .005$), but those with high/low intrinsic motivation had comparative drug use severity ($p = .240$). Growth curve models then examined whether patients' baseline intrinsic motivation had an impact on reducing their alcohol/drug use severity over 12-months. Patients exhibited, on average, reductions in both alcohol and drug use severity over 12-months (all $p < .001$). Patients with high intrinsic motivation showed faster reductions in alcohol and drug use severity than those with low intrinsic motivation over 12-months (all $p < .036$).

Conclusion: Pervasive patterns of alcohol and drug use severity attenuated considerably among adult patients with schizophrenia and SUD over the 12-month study, but those who enrolled with low intrinsic motivation exhibited significantly slower longitudinal rates of recovery. Results underscore the importance of future research development efforts that not only seek to address the motivational deficits of schizophrenia, but that also pay particular attention to substance use severity and its impact on recovery among those with schizophrenia and comorbid SUD.

Declaration of Interest: The results of this research are based on NIMH grant NO1 MH90001.

ID: 2094555

THE LONG TERM EFFECTIVENESS OF TELEPHONE INTERVENTION PROBLEM SOLVING (TIPS) FOR SCHIZOPHRENIA SPECTRUM DISORDERS (SSDS)

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Background: As many as 74% of persons with schizoaffective disorder, schizophreniform disorder and schizophrenia (schizophrenia spectrum disorders-SSDs) do not fully adhere (take 80% of doses) to prescribed antipsychotic medications. Problem solving has long been among the most effective treatments to improve psychiatric medication adherence; the research evidence supporting this approach spans nearly 30 years. In spite of their documented effectiveness and recommendation by experts, problem-solving interventions are not routinely offered to community-dwelling persons with SSDs. Telephone Intervention Problem Solving (TIPS) incorporates several features shown to be successful and recommended by experts such as individualized treatment, frequent contact, and concrete problem-solving strategies. IN four prior studies of up to 5 months in length, we have demonstrated TIPS feasibility, refined TIPS intervention and training procedures, and documented that TIPS improved psychiatric medication adherence (measured by monthly pill count) by an average of 20% over treatment as usual.

Methods: This project is a 9-month, randomized controlled trial comparing medication adherence, medication self-efficacy and psychiatric symptoms in community dwelling persons with SSDs. One hundred twenty eight participants will be provided a cellular telephone with unlimited local calling for 9 months and assigned to receive treatment as usual plus weekly TIPS via cellular telephone or treatment as usual only (TAU). All subjects will receive assessments of medication adherence (pill count and serum medication level), medication attitudes (Medication Adherence Rating Scale and Medication Adherence Self-Efficacy Scale) and symptoms (Positive and Negative Syndrome Scale) at baseline, 3- 6- and 9- months.

Results: We have recruited 105 participants (toward our goal of 128) as of this writing. This partial sample consists of 55 males (52%) and 50 females ranging in age from 19-75 years (mean 46.0, SD 13). Sixty eight participants are diagnosed with schizoaffective disorder (65%) and the rest with schizophrenia. A majority are Caucasian (n = 65, 62%) and the remainder African American. Most live with family members (n = 50, 48%) or alone (n = 44, 42%) and the rest live with a paid caregiver. Most report completing high school (n = 54, 51%). At this writing, 48 participants have completed their three month follow up and 11 have completed their 6 month follow up. These partial data indicate experimentals (n = 24) had lower PANSS scores and higher medication adherence self-efficacy scores than controls (n = 24) at month 3 and experimentals (n = 5) had lower PANSS scores than controls (n = 6) at 6 months. By March 2015, recruitment will be concluded, and we will have a complete 9- month data set on 75 participants.

Conclusion: TIPS is flexible enough to be useful for a variety of difficulties that impact psychiatric medication adherence, provides weekly monitoring to identify problems early, and guides the participant through a step by step process to solve adherence-related problems. TIPS requires less time than face-to-face intervention, (reducing treatment costs), and uses a protocol manual for standardization. Finally, providing TIPS via cellular telephone increases access. This study incorporates the longest follow up period of any TIPS study to date.

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ID: 2068230

COGNITIVE TRAINING TO ENHANCE WORK PROGRAM OUTCOMES: PRELIMINARY FINDINGS

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Background: Our previous RR&D funded study demonstrated significantly better vocational outcomes for people with schizophrenia when cognitive training augmented their participation in Incentive Therapy. We have found in a subsequent NIMH funded study involving cognitive training and supported employment that competitive employment outcomes were better for those who received cognitive training. Moreover, we found that patients with the poorest community function at intake were very unlikely to obtain competitive employment unless they received the cognitive training. The current study tests the effectiveness of cognitive training by extending it to a broader range of participants with psychotic disorders participating in all types of work programs including Incentive Therapy, Compensated Work Therapy, and Supported Employment. We also compare two types of cognitive training to determine whether cognitive game software (Nintendo BrainAge) works as well as narrowly focused cognitive exercises (PositScience BrainFitness and Insight).
Methods: 78 participants from VA CT and CMHC were randomized to one of two types of cognitive training—PositScience or Nintendo BrainAge. Intake included psychosocial, neuropsychological, and psychiatric assessments. Assessments were repeated at 6-months and 12 month follow-up. Cognitive training consisted of computer-based cognitive exercises and a weekly group that focused on improving work behaviors. BrainAge employed engaging cognitve game software and PositScience used specially designed exercises that narrowly focus on discrete cognitive processes. Work services were provided as usual to both conditions.
Results: Adherence was significantly better for PositScience than Nintendo. Comparsions of neurocognitive, vocational and quality of life outcomes will be presented for the first time at this symposium.
Conclusion: This is the first study to compare two active cognitive training programs as augmenting procedures for work rehabilitation programs. Findings will be presented in light of the growing interest in cognitive interventions in recovery.
ID: 2119634

EFFICACY AND SAFETY OF PALIPERIDONE PALMITATE 3 MONTH FORMULATION: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Background: The long-acting 3-month (3M) formulation of paliperidone palmitate (PP) may offer a valuable treatment option for patients with schizophrenia, due to a less-frequent dosing schedule in comparison with available alternate treatment options.
Methods: This phase-3, randomized, double-blind, placebo-controlled relapse prevention study enrolled patients (aged 18 to 70 years) with DSM-IV-TR diagnosis of schizophrenia. Patients received flexible, once-monthly (1M) PP doses (50, 75, 100, or 150 mg eq.) during a 17-week open-label (OL) transition phase, followed by a single injection of PP3M (3.5 times the PP1M stabilized dose) during a 12-week OL maintenance phase, and were randomized (1:1) to either PP3M fixed doses (175, 263, 350 or 525 mg eq.) or placebo (double-blind [DB] phase; variable duration).
Results: Of 506 patients enrolled and dosed (OL phase), 305 patients were randomized to receive PP3M (n=160) or placebo (n=145) in DB phase. The majority of patients enrolled were men (75%), white (59%), with mean (SD) age of 38.4 (11.15) years. An Independent Data Monitoring Committee recommended early study termination based on prespecified interim analysis results: primary efficacy measure (time to relapse) favored PP3M vs. placebo (p = 0.0002, two-sided log rank test). Hazard ratio for relapse (placebo/PP3M) was 3.45 (95% CI: 1.73; 6.88); median time to relapse was 274 days in placebo group and not estimable for PP3M group. Final results were consistent with interim analysis. Secondary endpoints: mean (SD) change from DB baseline to endpoint LOCF showed a maintenance effect in PP3M-treated patients for both PANSS total score (−0.5 [8.36]) vs. worsening in placebo (6.7 [14.40]; p<0.001); and in CGI-S score; (0.1 [0.60]) vs. placebo (0.4 [0.87]; p<0.001). Total 330 of 506 (65.2%) patients in OL phase and 183 of 305 (60.0%) patients in DB phase (PP3M group: 99 [61.9%]) had ≥1 treatment-emergent adverse event (TEAE). Serious TEAEs occurred in 33 (6.5%) patients in OL phase and in 4 (2.5%) DB phase PP3M-treated patients. The TEAEs noted more frequently in PP3M group vs. placebo (DB phase) were nasopharyngitis (5.6% vs. 1.4%), weight increased (8.8% vs. 3.4%), headache (8.8% vs.4.1%) and akathisia (4.4% vs. 0.7%).
Conclusion: Compared to placebo, PP3M significantly delayed time to first relapse in patients with schizophrenia, previously treated for 4 months with PP1M. PP3M was generally tolerable with a safety profile consistent with other marketed formulations of paliperidone.
ID: 2087240

THE MRC COMMAND TRIAL: RESULTS OF A MULTI-CENTRE, RANDOMISED CONTROLLED TRIAL OF COGNITIVE THERAPY TO PREVENT HARMFUL COMPLIANCE WITH COMMAND HALLUCINATIONS

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Background: Acting on command hallucinations in psychosis can have serious consequences for self and others and is a major source of clinical and public concern. There are no evidence-based treatment options to reduce this risk behaviour. Our new treatment uses cognitive therapy to challenge the perceived power of voices to inflict harm on the voice hearer if commands are not followed, thereby motivating compliance.
Methods: COMMAND is a pragmatic, single blind, intention-to-treat, randomized controlled trial comparing Cognitive Therapy for Command Hallucinations (CTCH) + Treatment as Usual (TAU) with TAU alone. Eligible participants were from UK mental health services reporting

command hallucinations for at least 6 months leading to major episodes of harm to self or others. The primary outcome was harmful compliance and secondary outcomes: beliefs about voices' power and related distress; psychotic and depression symptoms. Outcome was assessed at 9 and 18 months. The trial was registered under controlled-trials.com (ISRCTN62304114).

Results: 197 participants were randomly assigned (98 to CTCH+TAU and 99 to TAU), representing 81.4% of eligible individuals. At 18 months, 46% of the TAU participants fully complied compared to 28% of those receiving CTCH+TAU (odds ratio= 0.45, 95% confidence interval 0.23 to 0.88, p=0.021). The estimate of the treatment effect common to both follow-up points was 0.57 (95% confidence interval 0.33 to 0.98, p=0.042). The total estimated treatment effect for voice power common to both time points was -1.819 (95% confidence interval, -3.457 to -0.181, p=0.03). Treatment effects for secondary outcomes were not significant.

Conclusion: The trial demonstrated a large and significant reduction in harmful compliance, in parallel with the singular target of treatment, the perceived power of the voice. We believe this marks a significant breakthrough in this high risk group which consumes much clinical and public concern.

Funding: Medical Research Council UK and the National Institute for Health Research.

ID: 2091222

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP PROOF OF MECHANISM STUDY TO ASSESS THE PHARMACOKINETICS AND PHARMACODYNAMIC EFFECT OF DIFFERENT SINGLE ORAL DOSES OF BI 409306 IN HEALTHY MALE VOLUNTEERS

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Background: Cognitive impairment in schizophrenia is hypothesized in part to involve impaired functioning of glutamatergic pathways in (pre-) frontal cortical and limbic areas of the brain. By increasing cyclic guanosine monophosphate (cGMP) levels, glutamatergic signaling may be enhanced, strengthening synaptic plasticity. The objectives of this trial were to assess the exposure of BI 409306, an inhibitor of PDE-9, in cerebrospinal fluid (CSF) relative to plasma as well as to evaluate the effect of different doses of BI 409306 on the cGMP levels in CSF.

Methods: This was a randomized, parallel-group, double-blind, double-dummy, single dose, placebo-controlled trial in healthy male volunteers. Four dose levels of BI 409306 (25, 50, 100 and 200 mg/d) and placebo were assessed with 4 healthy volunteers per group.

Results: All subjects (n=20) completed the trial according to the clinical trial protocol. Mean age was 37.9 years; mean BMI was 25.9 kg/m2. Following administration, plasma concentrations of BI 409306 increased rapidly, with a median tmax of 0.75 h to 1.25 h across dose groups. Delay in maximum CSF concentration of BI 409306 was shown (median tmax in CSF of 1.5 h to 2.0 h across the dose groups). The maximum concentration in CSF was 28.3% of the maximum plasma concentration. CSF cGMP concentrations increased with increasing doses of BI 409306. The maximum level was achieved within the first 2 h to 5 h and then declined to approximately baseline levels at 10 h to 14 h after drug administration. Overall, good safety and tolerability was observed in this trial. There were no clustering of specific adverse events (AEs) and no apparent dose-dependent increases in the number or intensity of the reported AEs in any treatment group. The majority of AEs were of mild intensity and related to the study procedures. No deaths or serious AEs were reported, and there were no clinically relevant findings reported for laboratory parameters, ECG recordings, vital sign measurements, or visual tests.

Conclusion: Following single oral administration of BI 409306 at the 25 mg to 200 mg dose levels, BI 409306 crosses the blood-brain barrier and subsequently triggers a dose- and concentration-dependent increase in cGMP in CSF.

ID: 2096748

MONOTHERAPY WITH ONCE MONTHLY PALIPERIDONE PALMITATE FOR PSYCHOTIC, DEPRESSIVE, AND MANIC SYMPTOMS IN SCHIZOAFFECTIVE DISORDER

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Background: Schizoaffective disorder (SCA) is associated with the presence of psychotic, depressive, and manic symptoms, leading to complex pharmacologic management with combinations of antipsychotics, antidepressants, and mood stabilizers. Daily oral paliperidone has been shown to be efficacious for acute treatment of these symptoms in SCA, as monotherapy or as adjunctive to mood stabilizers/antidepressants. Injectable paliperidone palmitate once-monthly (PP1M) has been shown to be effective for SCA maintenance treatment. This analysis focuses on the effects of PP1M as monotherapy for relapse prevention in SCA.

Methods: Subjects experiencing an acute exacerbation of psychotic, depressive, and/or manic symptoms were enrolled in this multiphase study (NCT01193153). This analysis included subjects who were not receiving adjunctive treatment with antidepressants or mood stabilizers during the study (PP1M monotherapy group). After symptom stabilization with PP1M during a 25-week open-label (OL) phase, stable subjects were randomized to PP1M or placebo in a 15-month, double-blind (DB), relapse-prevention phase. Relapse was defined as psychiatric hospitalization, interventions to avoid relapse, self-injury/homicidal or suicidal ideation/behavior, or worsening of clinical scores (protocol defined). Time to relapse estimated by the Kaplan-Meier method and treatment differences were evaluated using log-rank test. Risk of relapse was examined using the Cox proportional hazards model.

Results: Of 667 enrolled subjects, 320 (48%) received PP1M monotherapy. Of these, 148 (46%) were stabilized on PP1M monotherapy during the 25-week OL phase and randomized in the DB phase. PP1M monotherapy significantly delayed relapse of depressive, manic, and psychotic symptoms (log-rank P<0.001). Observed overall relapse rates were 32.9% (24/73) with placebo and 11.5% (9/78) with PP1M monotherapy; relapse risk was 3.38-times greater with placebo (hazard ratio [95% confidence interval] 3.38 [1.57-7.28]; P=0.002, Cox proportional hazards model). Most common (≥5% in PP1M group) adverse events (PP1M vs placebo, respectively): nasopharyngitis (6.4%, 5.5%), upper respiratory tract infection (6.4%, 2.7%), weight increased (10.3%, 2.7%), headache (10.3%, 6.8%), insomnia (6.4%, 6.8%), and SCA (5.1%, 8.2%).

Conclusion: PP1M demonstrated maintenance efficacy as monotherapy in patients with SCA by significantly delaying and reducing relapse of psychotic, depressive or manic symptoms.

ID: 2088108

SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF BI 409306 FILM-COATED TABLETS GIVEN ORALLY QD FOR 14 DAYS IN PATIENTS WITH SCHIZOPHRENIA

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Background: The primary objective of this trial was to investigate the safety and tolerability of BI 409306 in patients with schizophrenia following oral administration of 25, 50, or 100 mg/d doses over 14 days. A secondary objective was to explore the pharmacokinetics (PK) and pharmacodynamics (PD) of BI 409306.
Methods: This randomized, double-blind, parallel-group, placebo-controlled trial evaluated patients with mild-to-moderate schizophrenia. Three dose levels of BI 409306 (25 mg, 50 mg, 100 mg) and placebo, in a 1:1:1:1 ratio, were assessed. All treatments were administered once daily (QD) for 14 days.
Results: Of 40 patients randomized, 38 (95%) patients completed the trial. Subjects were predominantly male (87.5%), and African American (52.5%) or white (47.5%), with a mean age of 40.2 years. After single-dose administration, BI 409306 Cmax was reached within 30 to 45 minutes. Geometric mean (gMean) Cmax ranged from 138 to 998 nmol/L across the dose groups, and gMean AUC0-∞ ranged from 217 to 2020 nmol*h/L. After absorption, BI 409306 was rapidly eliminated with a gMean terminal half-life (t1/2) ranging from 1.10 h to 1.85 h. After multiple-dose administration, BI 409306 was rapidly absorbed, with Cmax,ss reached within the first hour after dosing, and the elimination phase was similar to that observed after a single dose. Total exposure at steady state was similar to total exposure after a single dose, with an accumulation ratio close to 1 (range: 0.758 to 1.13 for AUC and 0.768 to 1.40 for Cmax), indicating minor to no accumulation with multiple dosing. There were no deaths, serious adverse events (SAEs), or adverse events (AEs) leading to discontinuation. Treatment-emergent AEs were all mild in intensity and there were no apparent dose-related trends for any AE. No clinically relevant trends were identified on visual tests, laboratory tests, vital signs, or ECGs. There was no deterioration in schizophrenia disease symptoms, as assessed by PANSS, suicidal ideation or behavior, or overall clinical status in this trial population. PD parameters of cognition were evaluated using HVLT-R and BVMT-R.
Conclusion: Satisfactory safety and tolerability were observed following administration of BI 409306 25 mg, 50 mg, or 100 mg QD for 14 days in patients with mild-to-moderate schizophrenia. BI 409306 PK was characterized by rapid absorption, rapid monophasic to biphasic elimination, and minor accumulation with multiple dosing.
ID: 2096821

FACILITATORS AND BARRIERS TO IMPLEMENTATION OF COORDINATED SPECIALTY CARE IN U.S. COMMUNITY MENTAL HEALTH CLINIC

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Background: Coordinated specialty care such as NAVIGATE for young people with first episode psychosis (FEP) includes medication management, individual recovery counseling, family intervention and supported employment/education (SEE). In this model, a team provides the services and coordinates care via team meetings and supervision.
Methods: In the RAISE-ETP study, 17 community clinics across the U.S. were randomly assigned to implement NAVIGATE. We conducted qualitative analyses of baseline clinic characteristics, identifying four dimensions relevant to implementation and demonstrated variation within them: communications, organization, staffing, and service array. We further evaluated facilitators and barriers to implementation within these domains.
Results: Overall, the clinics were adequately staffed and organized to provide NAVIGATE. Two key areas of variation in capacity posed potential implementation challenges. In organization, some clinics relied solely on Medicaid rehabilitation funding and were not prepared to obtain reimbursement from private insurances or to find sources of support for care for uninsured patients with FEP. In service array, some clinics had limited ability to provide SEE. This key service facilitates rapid job searches or school enrollment to help people find competitive employment or to enter school. SEE workers then provide practical support for managing illness symptoms during work or school. Not all state Medicaid programs include this effective intervention and private insurances do not cover it, limiting access.
Conclusion: Organizations wishing to implement coordinated specialty care for first episode psychosis can leverage facilitators and plan to overcome barriers in order to deliver this model of care.
ID: 2139216

OXYTOCIN AND GALANTAMINE FOR THE TREATMENT OF NEGATIVE SYMPTOMS AND COGNITIVE IMPAIRMENTS IN SCHIZOPHRENIA

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Background: Negative symptoms and cognitive impairment are unmet therapeutic needs in schizophrenia. In the context of a NIMH Center for Intervention Development and Applied Research, the hypothesis that these two pathology domains are separate therapeutic targets was tested in a rat model, a biological relative model, and a clinical trials model. Here we report results from an efficacy evaluation of intranasal oxytocin versus placebo for social affiliation/negative symptoms and galantamine versus placebo for cognitive impairment in a schizophrenia cohort.
Methods: Participants (N = 56) with a diagnosis of DSM-IV-TR schizophrenia who met clinical stability criteria, and met criteria for persistent negative symptoms were randomly assigned to intranasal oxytocin, galantamine or placebo in a 6-week, double dummy design, randomized clinical trial. Primary outcome measures were the modified Scale for the Assessment of Negative Symptoms (SANS) total score for negative symptoms and the MATRICS Consensus Cognitive Battery (MCCB) composite score for cognitive impairment. Other clinical assessment included the Brief Psychiatric Rating Scale (BPRS) positive symptom item score and Calgary Depression Rating Scale (CDRS). Other cognitive assessments included social cognitive tests, including the Trust Game and Hinting Task.
Results: Therapeutic hypotheses were not supported. Neither oxytocin nor galantamine was superior to placebo on the primary or secondary outcome measures. Estimated effect sizes on primary and secondary outcome measures were all small to moderate (Cohen's d versus placebo at Week 6: d=-0.15 for galantamine, d=-0.10 for oxytocin on SANS total score; d=0.09 for galantamine, d= 0.15 for oxytocin on MCCB composite score).
Conclusion: The number of participants in each group resulted in inadequate power. Nonetheless, the absence of trends favoring experimental

treatments argues against the therapeutic hypotheses. In the absence of efficacy, the question of whether negative symptoms and cognition represent distinct therapeutic targets with separate pathophysiologies could not be addressed.
ID: 2097655

SECOND AND THIRD RELAPSES IN A RELAPSE PREVENTION TRIAL OF LONG-ACTING INJECTABLE VERSUS ORAL ANTIPSYCHOTICS: A COMPARATIVE ANALYSIS OF SUCCESSIVE RELAPSES OVER 30 MONTHS

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Background: Earlier relapse prevention studies involving long-acting injectable (LAI) formulations of first generation antipsychotics (FGA) showed continued risk of relapse beyond the initial first relapse. PROACTIVE (Preventing Relapse Oral Antipsychotics Compared to Injectables Evaluating Efficacy) is a modern day relapse prevention study of second generation antipsychotic (SGAs) medications (Buckley et al, 2014), wherein 305 patients with schizophrenia or schizoaffective disorder were randomly assigned to LAI risperidone (LAI-R) or physician's choice oral second generation antipsychotics (SGAs).
Methods: Patients were evaluated during the 30-month study by masked, centralized assessors using two-way video, and monitored bi-weekly by on-site clinicians and assessors who knew treatment assignment. Relapse was evaluated by a masked Relapse Monitoring Board. First and successive relapses were determined.
Results: There were no significant differences between LAI_R and oral SGA treatment in time to first relapse and hospitalization. Across treatment groups 37% experienced a relapse with a rate of 42% in the LAI-R and 32% in the oral SGA groups that were not significantly different. In contrast, psychotic symptoms and BPRS total score improved significantly more in the LAI-R group. Whether this relative advantage for psychotic symptoms confers any propensity for fewer subsequent relapses or rehospitalizations on LAI-R versus over oral SGAs will be examined in the study sample who experienced successive relapses.
Conclusion: While the close monitoring overall and greater flexibility in changing medication in the oral treatment arm may contribute to the inability to detect differences between LAI and oral SGA treatment in the first relapse, it is plausible that these effects may be less in play among patients with multiple relapses.
ID: 2088861

A META-ANALYSIS OF PLACEBO-CONTROLLED TRIALS OF OMEGA-3 FATTY ACID AUGMENTATION IN SCHIZOPHRENIA: POSSIBLE STAGE-SPECIFIC EFFECTS

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Background: Omega-3 supplements have shown promise in clinical trials as an adjunctive treatment for schizophrenia. However, clinical efficacy across studies has been inconsistent. We conducted a meta-analytic assessment of the data and hypothesized that omega-3 fatty acid augmentation may have differential efficacy at various stages of schizophrenia.
Methods: An online search was conducted using PubMed for placebo-controlled, randomized, double-blind, clinical trials (RCTs) using the terms "omega-3," "EPA," "eicosapentaenoic acid," "PUFA," "polyunsaturated fatty acid," "schizophrenia," "prodrome", "schizophreniform," and "schizoaffective". A meta-analysis was conducted on applicable trials.
Results: 11 trials met criteria for inclusion. Of these, six included the Positive and Negative Syndrome Scale (PANSS) as an outcome measure for patients in the chronic stage of schizophrenia (N=319). A meta-analysis of these six studies indicated non-significant effects for Omega-3 on Total PANSS scores, where weighted d=.18, and weighted d=.11 when corrected for unreliability and range restriction. In the remaining studies, Omega-3 had an adverse effect regarding prevention of recurrence of symptoms after discontinuation of antipsychotic therapy (d=-0.58, N=33) and prevention of symptom worsening in acute exacerbation (d=-0.29, N=57). However, Omega-3 decreased non-psychotic symptoms, decreased required antipsychotic medication dosage (d=.40), and improved early (6 week), but not late (12 week), treatment response rates in first episode schizophrenia (N=69). It was also significant in reducing both the conversion rate and psychotic symptom severity in prodromal patients at very high risk for psychosis (d=0.7, N=81).
Conclusion: The data in this study suggests a differential benefit of omega-3 at various stages of schizophrenia, with higher efficacy in prodromal and first-episode patients as adjunct therapy to antipsychotic medications, while its efficacy for chronic schizophrenia appears tenuous. In fact, it may worsen acute exacerbations of schizophrenia. The neurobiological and therapeutic implications of these findings are discussed.
ID: 2169387

EFFECTIVENESS OF A LONG-ACTING INJECTABLE ANTIPSYCHOTIC IN FIRST-EPISODE SCHIZOPHRENIA: THE EONKCS STUDY

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Background: Depot antipsychotics were developed in the 1960s to address the adherence problem in schizophrenia. It can be argued that the greatest benefits of depot antipsychotics would be observed in the earlier phase of illness, in line with public health principles of early intervention and prevention of accruing morbidity. Our aim was to assess the feasibility and effectiveness of depot antipsychotic (flupenthixol decanoate) combined with an assertive monitoring program (AMP) in first-episode schizophrenia
Methods: This was a prospective, non-comparative, longitudinal study conducted over 12 months assessing patient acceptance, adherence, outcome in domains of psychopathology, functionality and quality of life, and tolerability.
Results: Of 207 participants, 149 (72%) completed 12 months of treatment. Acceptance of, and adherence to depot was good. Treatment response was

achieved by 170 (82%) participants and remission by 124 (60%). Thirty-three (19%) responders relapsed and 10 (5%) participants met a priori criteria for treatment resistance. Treatment was generally well tolerated.
Conclusion: Combination of depot antipsychotic with an AMP may be an effective and safe intervention in early phases of schizophrenia, and may be particularly suitable for resource-constrained settings.
ID: 2114151

FEASIBILITY STUDY OF THE ACTIVATION OF BEHAVIOR AND MOTIVATION FOR NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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Background: Negative symptoms, a core feature of schizophrenia, limit the impact of treatment on therapeutic outcomes. There is an unmet need to reach out to individuals who are not engaging in daily routines, activities, and/or treatment, and to address ambivalence and lack of motivation (Campbell et al., 2011; Drake & Bond, 2011). With advancements in the biopsychosocial aspects of the negative symptoms of schizophrenia, we have developed a novel psychosocial treatment, based mainly on learning principles and motivational theories.
Methods: To examine the feasibility and preliminary efficacy of the Activation of Behavior and Motivation for Negative Symptoms (ABM-NS), twenty-two outpatients with negative symptoms were assigned to one of the two conditions (11 each): (1) ABM-NS + TAU, (2) TAU.
Results: There were two dropouts from the ABM-NS group (one for employment, one for relocation) as compared to four from the TAU group. The rates for task completion were over 90% for all participants. Despite the increased number of tasks assigned for each session, levels of task-specific motivation and perceived self-competency were significantly increased in the treatment group. The results indicated a trend toward improvement in negative symptoms, as measured by the Positive and Negative Syndrome Scale (PANSS) and the Motivation and Pleasure Scale-Self-Report (MAP-SR), as compared to the TAU only group.
Conclusion: The results of the current study demonstrate the feasibility of a novel psychosocial approach (i.e., ABM-NS) to reduce the negative symptoms of schizophrenia. The ABM-NS approach was related to high levels of acceptability and motivation enhancement. Even though the improvements approached a level of significance, given the small samples in the current analyses, this trend should be further examined with a larger sample to determine whether task-specific motivation and negative symptoms would be significantly enhanced, and whether changes in motivation indices would be related to changes in negative symptoms. We are presently in the process of data collection. The current findings will be updated with a larger sample.
ID: 2084436

EFFECTS OF LURASIDONE ON HOSTILITY IN PATIENTS WITH AN ACUTE EXACERBATION OF SCHIZOPHRENIA: A POOLED POST HOC ANALYSIS OF FIVE SHORT-TERM STUDIES

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Background: This post hoc analysis evaluated the efficacy of lurasidone for reducing hostility in patients hospitalized with an acute exacerbation of schizophrenia.
Methods: Individual patient data were pooled from 5 double-blind, placebo-controlled, 6-week studies of fixed-dose, once-daily lurasidone (40-160 mg/d). The primary outcome measure was the overall change from baseline to week 6 on the hostility item (P7) of the Positive and Negative Syndrome Scale (PANSS) in patients with evidence of hostility at baseline (as defined by a score of ≥2 on the PANSS hostility item). Treatment group differences were analyzed using a mixed-model repeated-measures (MMRM) analysis, with and without adjustment for the presence of positive symptoms of schizophrenia and somnolence as covariates.
Results: A total of 1148 patients met the criteria for hostility at baseline: 775 lurasidone-treated and 373 placebo-treated patients. Lurasidone was significantly superior to placebo in reducing the PANSS hostility item throughout the 6-week study period starting at Week 1 (P=0.002) and at all subsequent study visits (P<0.001). To examine whether antihostility effects were independent of improvement in positive symptoms, the MMRM model was adjusted for PANSS positive symptoms as a time-varying covariate. After controlling for changes in positive symptoms, lurasidone was found to be significantly better than placebo in decreasing the PANSS hostility item starting at Week 2 (P=0.014) and at every time point measured throughout the 6-week study period (P<0.05). The presence of somnolence was also added as a covariate to the model to control for its effect on hostility. In this analysis, lurasidone significantly reduced the PANSS hostility item relative to placebo beginning at Week 2 and at every time point measured thereafter (P<0.05), except for Week 6. The proportion of patients who demonstrated any improvement (≥1 point change) on the PANSS hostility item score from baseline to endpoint was 63.1% (489/775) for patients randomized to lurasidone and 55.0% (205/373) for patients randomized to placebo (number needed to treat=13; 95% confidence interval, 8-49).
Conclusion: The results of this post hoc analysis showed that lurasidone significantly improved symptoms of hostility compared with placebo. This was a specific antihostility effect; improvement in hostility was found to be independent of change in other positive symptoms, as well as somnolence.
Funding: Sunovion Pharmaceuticals Inc.
ID: 2087816

HOW SHOULD WE DEVELOP NEW ANTIPSYCHOTICS? CURRENT CLINICAL PATHS FORWARD

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Background: There have been a large number of failed efforts to develop truly novel therapies for schizophrenia, and many pharmaceutical companies are considering whether this area should remain a priority for novel drug development.
Methods: This talk will briefly review the current results of trials of novel therapies for schizophrenia, using publically available data. Discussion of possible paths forward which could lead to the actual development of clinically relevant novel therapies for schizophrenia will be discussed from the author's perspective as a development leader within the pharmaceutical industry.
Results: While it remains possible to develop new antipsychotics based on dopamine-D2 antagonism or partial agonism, major efforts involving novel pharmacology have failed to produce new clinical treatments. This includes efforts to develop novel therapies for acute psychosis, cognitive deficits, and negative symptoms associated with schizophrenia. Current preclinical efforts suggest that exposure to D2 antagonists may irreversibly alter neuronal physiology in a manner that decreases the likelihood of response to other therapies. However, clinical trials suggest this effect may not be categorical, with relatively brief exposures to D2 antagonists possibly not leading to treatment resistance to other therapies. Major efforts by large pharmaceutical companies have led to late phase III

efficacy failures to the degree that our ability to develop new treatments for schizophrenia is being effected.
Conclusion: A major change in the development of new treatments for schizophrenia is warranted. Current animal models do not reliably translate into the clinic. Human research must separate between observational and treatment relevant therapy. Both are needed, but government funding of research should be more balanced. Preclinical studies of treatment response dependent on no exposure to dopamine antagonists are not clinically relevant now or in the foreseeable future. Genetic modeling of response, methods of maintaining reemission, modeling relevant functional outcomes, and treating prodromal relapse conditions, such as sleep disturbance, may all lead to useful new therapies. We need to decide, as a field, if treatment research itself is relevant in our area, and act if we decide it is important.
ID: 2114466

CARDIOMETABOLIC RISK IN FIRST-EPISODE SCHIZOPHRENIA-SPECTRUM DISORDERS

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Background: Individuals with schizophrenia have high cardiovascular morbidity and premature mortality. However, risk status and moderators/mediators in the earliest illness stages are less clear.
Methods: We assessed cardiometabolic risk in first-episode schizophrenia-spectrum disorders (FES) and its relationship to illness duration, and antipsychotic treatment duration and type, using baseline results of the NIMH-funded Recovery After an Initial Schizophrenia Episode (RAISE) study. Patients aged 15-40 years FES and <6 months lifetime antipsychotic treatment were assessed at 34 community mental health facilities. Pre-baseline antipsychotic treatment was based on community clinician's/patient's decision.
Results: In 394/404 subjects with cardiometabolic data (age=23.6 ± 5.0 years) with 47.3 ± 46.1 days of antipsychotic treatment, 49.3% were obese/overweight (23.1%/26.2%), 50.8% smoked, 46.3% had dyslipidemia, 39.9% had pre-hypertension, 10.0% had hypertension, and 13.2% had metabolic syndrome. Prediabetes (glucose-based=4.0%, HbA1C-based=15.4%) and diabetes (glucose-based=3.0%, HbA1C-based=2.9%) were less frequent. Total psychiatric illness duration correlated significantly with higher body composition markers, whereas antipsychotic treatment duration correlated significantly with higher metabolic variables. Olanzapine was associated with higher triglycerides, insulin and insulin resistance, whereas quetiapine was associated with higher triglyceride/HDL-cholesterol levels.
Conclusion: These data underscore that prevention of/early interventions for psychiatric illness and treatment with lower-risk agents, routine antipsychotic adverse effect monitoring and smoking cessation interventions are essential from the earliest illness phases.
ID: 2140780

LONG-TERM SAFETY OF BREXPIPRAZOLE (OPC-34712) IN SCHIZOPHRENIA: RESULTS FROM TWO 52-WEEK OPEN-LABEL STUDIES

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Background: The long-term safety and tolerability of brexpiprazole were evaluated in patients with schizophrenia, based on pooled data from two large open-label extension studies.
Methods: These two studies were open-label, 52-weeks, flexible-dose (study 1 [NCT01649557]: 1 to 6mg/day and study 2 [NCT01397786]: 1 to 4mg/day) studies with brexpiprazole. Study 1 enrolled patients who had completed a phase II study (NCT00905307) while study 2 enrolled de novo patients as well as patients who had completed one of the two pivotal phase III studies in acute schizophrenia (NCT01396421 or NCT01393613). As study 2 is still ongoing, the data presented are based on a data-cut from 31 Jan 2014.
Results: A total of 813 patients entered the studies [28 from study 1 and 785 from study 2 of which 223 were de novo patients]. Of these, 26.3% (214/813) completed 52 weeks of treatment. Adverse events reported by ≥5% of the patients in the extension studies were schizophrenia (12.2%), insomnia (9.1%), weight increased (7.4%), headache (5.8%), agitation (5.3%), and akathisia (5.0%); the adverse event profile was similar to what was observed in the short-term lead-in studies. The mean weight gain was 1.3kg at week 26 (N=406) and 2.0kg at week 52 (N=213) for the observed cases, and 0.6% (5/813) of patients discontinued due to treatment-emergent adverse events associated with weight increase. The increases in body weight were not accompanied by meaningful changes in lipid profiles or glycemic parameters.
Conclusion: Long-term treatment with brexpiprazole (1 to 6mg daily) was safe and well tolerated in patients with schizophrenia, as evaluated in two open-label extension studies.
ID: 2089877

UPDATE ON THE PHARMACOLOGICAL TREATMENT AND CLINICAL PREDICTORS OF THERAPEUTIC RESPONSE TO ANTIPSYCHOTICS IN FIRST-EPISODE SCHIZOPHRENIA

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Background: The successful management of first episode of schizophrenia cannot be overestimated, as achieving response and remission early on set the stage for the remaining illness trajectory and chances for recovery. Conversely, prolonged psychosis and relapse have been shown to negatively impact the biopsychosocial aspects of patients' lives.
Methods: Literature review of predictors of therapeutic response to antipsychotics and remission in first episode schizophrenia with a focus on synthesizing the literature from the last decade.
Results: Most identified clinical outcome predictors were non-specific and/or non-modifiable. Non-modifiable predictors for poor odds of response or remission include male sex, younger age at disease onset, poor premorbid adjustment and severe baseline psychopathology. Modifiable risk factors that clinicians can act upon include longer duration of untreated illness, non-adherence to antipsychotics, comorbidities (especially substance misuse), lack of early antipsychotic response and lack of improvement with non-clozapine antipsychotics, predicting clozapine response.
Conclusion: Few reproducible predictors of early therapeutic outcome have been identified, but some modifiable variables should inform treatment strategies and service development. It is hoped that this limited number of reliable outcome predictors in first episode schizophrenia will increase as pathophysiological understanding broadens, meaningful patient subgroups can be delineated, and/or additional treatments with novel mechanisms of action for specific aspects of schizophrenia become available.
ID: 2115700

INCORPORATING NEW TECHNOLOGIES IN CLINICAL TRIALS: A SPONSOR PERSPECTIVE

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Background: New technologies are changing the way sponsors view clinical trials and the data generated by them.
Trial sponsors are assessing a range of new technologies to optimize trial management for success. For example, as remote access to real-time data becomes more easily and reliably generated, we are able to monitor trial progress, data quality and patient compliance from the time of first patient randomized. Patient recruitment, selection and evaluation are all evolving based on new approaches.
This talk will discuss how one sponsoring company is assessing these new technologies and trends,and integrating them specifically in neuroscience clinical programs.
Methods: A review of company initiatives regarding integrating new technologies
Results: N/A
Conclusion: Our future trials will incorporate several new technologies to support 'smart' trials in the future, to improve success rates and increase efficiency. As an example these will enable investigators to identify appropriate patients, support their patient recruitment efforts, provide electronic source data entry, monitor patient compliance on a daily, real-time basis, track site enrollment trends and allow sponsor to remotely monitor data for quality. These technologies will allow sponsors to collect more accurate data, in a more timely manner,for more rapid drug development.
The implications of this for investigators will be discuss.
ID: 2121129

TRAJECTORY OF CARIPRAZINE TREATMENT EFFECTS ACROSS SCHIZOPHRENIA SYMPTOMS: POST HOC ANALYSIS OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND ACTIVE-CONTROLLED TRIAL

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Background: Clinical trials with cariprazine (CAR) have shown efficacy in adults with acute exacerbation of schizophrenia. A post hoc analysis of a Phase 3 study (NCT01104766) evaluated the trajectory of CAR effects across a range of schizophrenia symptoms.
Methods: Patients received CAR 3 mg/d (n=155), CAR 6 mg/d (n=157), aripiprazole 10 mg/d (ARI) (n=152), or placebo (n=153) for 6 weeks of double-blind treatment. The primary efficacy outcome was change from baseline to Week 6 in PANSS total score (adjusted for multiplicity). Additional efficacy analyses included change in PANSS positive and negative subscale scores. Post hoc analysis included changes in PANSS general psychopathology and cognitive (items P2, N5, N7, G10, and G11) subscale scores.
Results: Least squares mean differences (LSMDs) from placebo in PANSS total score were: CAR 3 mg/d, -6.0, *P*=.0044; CAR 6 mg/d, -8.8, *P*<.0001; ARI, -7.0, *P*=.0008. Significant advantage over placebo was observed at Week 1 with CAR 6 mg/d, Week 3 with CAR 3 mg/d, and Week 1 with ARI. Both doses of CAR and ARI showed significantly greater improvements on all 4 PANSS subscales at Week 6 (Table). CAR 6 mg/d was associated with early improvement on each PANSS subscale (at Week 2 for positive, general psychopathology, and cognitive scores; at Week 1 for negative scores). CAR 3 mg/d showed significant improvement vs placebo by Week 3 for all 4 subscales. ARI showed early improvement on positive (Week 1), general psychopathology (Week 1), and negative (Week 2) subscales; for cognitive symptoms, significant advantage vs placebo was seen at Week 3. LSMDs vs placebo at Week 6 were numerically higher in the CAR 6 mg/d relative to CAR 3 mg/d and ARI for all 4 PANSS subscale scores.
Conclusion: In patients with schizophrenia, treatment with CAR 6 mg/d resulted in significant and sustained improvement vs placebo within 2 weeks across all PANSS symptoms domains. CAR 3 mg/d also demonstrated efficacy on all PANSS outcomes, with significant advantage over placebo within 3 weeks of treatment initiation.
ID: 2086005

Change in PANSS subscale scores (LSMD vs Placebo)

	Positive Symptoms			Negative Symptoms			Psychopathology			Cognitive		
LSMD by visit	CAR 3 mg	CAR 6 mg	ARI 10 mg	CAR 3 mg	CAR 6 mg	ARI 10 mg	CAR 3 mg	CAR 6 mg	ARI 10 mg	CAR 3 mg	CAR 6 mg	ARI 10 mg
Week 1	-0.0	-0.6	-0.7*	-0.5*	-0.7*	-0.5	-0.3	-0.8	-1.2*	-0.1	-0.3	-0.3
Week 2	-0.4	-1.5*	-1.3*	-0.4	-0.9*	-0.9*	-0.4	-2.1*	-2.2*	-0.0	-0.5*	-0.4
Week 3	-1.3*	-1.8*	-1.9*	-1.1*	-1.4*	-1.5*	-2.1*	-3.3*	-3.4*	-1.0*	-1.1*	-1.0*
Week 4	-2.3*	-2.7*	-2.9*	-1.2*	-1.4*	-1.2*	-3.7*	-4.8*	-4.9*	-1.2*	-1.2*	-1.0*
Week 5	-2.1*	-2.7*	-2.7*	-1.4*	-1.8*	-1.1*	-3.3*	-4.4*	-4.8*	-1.4*	-1.4*	-1.2*
Week 6	-1.5*	-2.2*	-1.9*	-1.4*	-1.7*	-1.2*	-2.9*	-4.7*	-3.8*	-1.2*	-1.2*	-1.0*

*P<.05 vs placebo

RANDOMIZED CONTROLLED TRIAL OF N-ACETYLCYSTEINE FOR COGNITION AND EEG CORRELATES IN SCHIZOPHRENIA

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Background: Schizophrenia is associated with significant neurocognitive deficits which predict poor functioning. Electrophysiological (EEG) biomarkers related to cognitive dysfunction in schizophrenia have been linked to abnormal NMDA glutamatergic neurotransmission. N-acetylcysteine

(NAC) is an amino acid that modulates NMDA receptor function and has been previously shown to improve clinical symptoms of schizophrenia. The current pilot study evaluated whether NAC could improve cognitive function and related EEG biomarkers.
Methods: 26 adult outpatients with schizophrenia were randomized (double-blind) to receive 1200mg NAC or placebo twice daily for 8 weeks as an adjunct to antipsychotic treatment. Patients were assessed at baseline, 4 weeks, and 8 weeks on measures of clinical psychopathology (Positive and Negative Syndrome Scale (PANSS); Clinical Assessment Interview for Negative Symptoms (CAINS); Clinical Global Impression (CGI)), cognition (MATRICS Consensus Cognitive Battery (MCCB)), and side effects. Participants also underwent an EEG assessment battery examining mismatch negativity, gamma oscillation power and synchrony, and visual cortical neuroplasticity. Generalized linear mixed models for repeated measures were used to compare effects of NAC vs. placebo across the 8 weeks.
Results: 17 participants completed all study visits (8 who received NAC and 9 who received placebo). There were no significant effects of NAC vs. placebo on the PANSS total score (p=.494) or subscales; the CAINS (p=.211 on motivation/pleasure and p=.751 on expression scales); the CGI (p=.595); or the MCCB composite score (p=.830) or subdomain scores. EEG data on mismatch negativity, gamma oscillations, and the visual cortical plasticity paradigm are undergoing analysis and will be presented. The treatment was generally well-tolerated, with gastrointestinal complaints representing the most commonly reported side effect.
Conclusion: This study demonstrates the feasibility of assessing clinical symptoms and EEG biomarkers in a longitudinal clinical trial evaluating a potential treatment for schizophrenia. In our limited sample size, we found no evidence supporting NAC for improving clinical symptoms or cognitive deficits of schizophrenia. Analysis of EEG data will determine whether NAC had measurable effects on electrophysiological biomarkers related to cognition and NMDA glutamatergic function.
ID: 2086799

ANALYSIS OF EFFICACY AND METABOLIC TOLERABILITY PROFILE FROM TWO PHASE 3 STUDIES OF BREXPIPRAZOLE IN PATIENTS WITH ACUTE SCHIZOPHRENIA

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Background: In two phase 3 clinical studies (230 and 231; NCT01393613 and NCT01396421), brexpiprazole (a rationally designed serotonin-dopamine activity modulator) demonstrated statistically significant efficacy compared with placebo and favorable tolerability for patients with acute schizophrenia. This analysis examined the secondary endpoints and metabolic parameters from these trials for additional information on the profile for brexpiprazole 2mg and 4mg.
Methods: Secondary endpoints assessed in the clinical studies as change from baseline to week 6 included: Clinical Global Impression Severity of Illness (CGI-S) and Improvement (CGI-I); Personal and Social Performance scale (PSP); subscales of the PANSS, including positive and negative symptoms, Excited Component (PEC), and Marder factor scores; discontinuation due to lack of efficacy; and response rate (improvement of ≥30% from baseline in PANSS Total Score or CGI-I score of 1 or 2). Metabolic parameters were assessed through body weight and cardiometabolism-related laboratory measurements.
Results: In both studies, brexpiprazole 4mg showed improvements in CGI-I and CGI-S compared with placebo (p=0.0002-0.0422). The PANSS subscales for positive and negative symptoms, PEC excitability component, Marder factors for negative symptoms, disorganized thought and uncontrolled hostility, and response rates also supported efficacy of the 4mg dose compared with placebo in both studies. A moderate increase in body weight was observed (1.23-1.89kg vs 0.35-0.42kg for placebo) but with little evidence of clinically relevant adverse effects on metabolic parameters compared to placebo (Table).
Conclusion: Brexpiprazole demonstrates clinical efficacy in patients with acute schizophrenia in both primary and most secondary endpoints. Consistent effects were seen across studies at the 4mg dose, with one study demonstrating efficacy at the lower dose of 2mg.The clinical profile of brexpiprazole appears to be consistent with its pharmacological profile.
ID: 2092605

THE EFFECT OF BILATERAL TRANSCRANIAL DIRECT CURRENT STIMULATION ON MISMATCH NEGATIVITY AND P300 IN SCHIZOPHRENIA

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	Mean Change from Baseline to Last Visit					
	Study 230			Study 231		
Parameter (Units)	Brexpiprazole 2mg Mean (SD) [N]	Brexpiprazole 4mg Mean (SD) [N]	Placebo Mean (SD) [N]	Brexpiprazole 2mg Mean (SD) [N]	Brexpiprazole 4mg Mean (SD) [N]	Placebo Mean (SD) [N]
HDL-C, fasting (mg/dL)	3.73 (28.20) [172]	1.79 (27.10) [171]	-3.35 (28.84) [162]	1.33 (9.91) [163]	0.48 (7.26) [159]	-1.21 (8.91) [163]
LDL Direct, fasting (mg/dL)	1.36 (22.76) [170]	2.15 (22.25) [170]	-1.51 (26.63) [162]	-0.70 (28.00) [162]	2.57 (26.79) [157]	-2.12 (24.70) [163]
Triglycerides, fasting (mg/dL)	-1.32 (85.46) [172]	-4.85 (81.31) [171]	1.54 (46.94) [162]	-1.45 (66.35) [163]	6.76 (69.54) [159]	-0.79 (72.54) [163]
Glucose, fasting (mg/dL)	-1.12 (15.31) [171]	2.12 (14.38) [171]	0.71 (14.53) [162]	0.70 (17.84) [162]	1.13 (14.72) [158]	0.13 (15.40) [163]
Body Weight (kg)	1.31 (3.45) [180]	1.26 (3.28) [184]	0.24 (2.78) [181]	1.07 (3.41) [183]	1.12 (3.35) [178]	0.09 (2.72) [181]

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Background: Schizophrenia (SZ) is an illness characterized by deficits in neurocognition and early sensory processing. Current treatments focus on management of positive symptoms, but have little impact on neurocognition and sensory processing, both of which are significant predictors of long term functional outcome. Transcranial direct current stimulation (tDCS) is a novel non-invasive neuromodulatory technique that has been shown to reduce hallucinations and improve working memory in SZ. In the current study we examined the effects of tDCS on neural measures of basic auditory processing (mismatch negativity, MMN) and cognitive processing, the P300 oddball response.
Methods: 30 outpatients with SZ were randomized into a single-blinded between subjects study with 10 subjects each receiving bilateral anodal, cathodal, or sham tDCS (active tDCS- 30 min, 2mA). Active stimulation was delivered through two 5X7 cm electrodes (0.02mA/cm2) placed bi-frontally at Fp1 and Fp2 positions (same polarity), with a reference electrode placed on the upper arm. Subjects underwent the ERP protocol at baseline and one week later approximately 1 hr after receiving a single tDCS stimulation. MMN and P300 amplitudes were measured as the mean of activity in the 135-205ms and 250-350ms latency range, respectively.
Results: Anodal stimulation yielded a significant decrease ($p<0.02$) in the MMN amplitude (post-stimulation verses baseline). No statistically significant changes in MMN amplitude were observed for cathodal or sham conditions. The P300 measure did not demonstrate significant changes for any of the three stimulation conditions. All subjects tolerated the stimulation procedure with no reports of adverse events or dropouts.
Conclusion: The change in MMN amplitude after bifrontal anodal stimulation is the first demonstration that a single bilateral session is sufficient to affect change in an auditory ERP signal in SZ. These findings support the model-adjustment hypothesis where MMN is generated through a comparison of current auditory input verses preceding auditory context via top-down modulation of the auditory cortex by the prefrontal cortex. The coordinated connectivity of these two cortices may explain why modulation of one region without concurrent stimulation of the other disrupts a homeostatic balance in the network resulting in a diminished MMN response. That treatment of impaired networks in schizophrenia may require simultaneously targeting multiple nodes of a given network in order to improve functioning.
ID: 2075093

COGNITIVE ENHANCEMENT THERAPY IN SUBSTANCE MISUSING SCHIZOPHRENIA: RESULTS OF AN 18-MONTH FEASIBILITY TRIAL

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Background: Substance use is a frequent problem in schizophrenia, and although many substance misusing patients with the disorder also experience considerable cognitive impairments, such individuals have been routinely excluded from clinical trials of cognitive remediation that could support their functional and addiction recovery. This study conducted a small-scale feasibility trial of Cognitive Enhancement Therapy (CET) in substance misusing schizophrenia patients to assess the feasibility and efficacy of implementing comprehensive neurocognitive and social-cognitive remediation in this population.
Methods: A total of 31 schizophrenia outpatients meeting addiction severity criteria for alcohol and/or cannabis use were randomized to 18 months of CET or usual care. Comprehensive measures of cognition, functional outcome, and substance use were assessed prior to treatment and every 6 months for 18 months. General linear mixed-effects models were used to examine differential changes in cognition and behavior over the course of the study between patients treated with CET versus usual care.
Results: Feasibility findings indicated high degrees of satisfaction with CET, but also presented significant challenges in the recruitment and retention of substance misusing patients, with high levels of attrition over the study period, primarily due to symptom instability. Intent-to-treat efficacy analyses showed large and significant differential improvements in neurocognition (d = .86), social cognition (d = 1.13), and social adjustment (d = .92) favoring CET. Further, individuals treated with CET demonstrated significant reductions in alcohol use over the course of treatment.
Conclusion: Once engaged and stabilized, CET is a feasible and potentially effective treatment for cognitive impairments in patients with schizophrenia who misuse alcohol and/or cannabis. Substance misusing patients who are able to engage in treatment may be able to benefit from cognitive remediation, and the treatment of cognitive impairments may help improve substance use outcomes among this underserved population.
ID: 2097040

INVESTIGATING THE RATES AND CONSEQUENCES OF RELAPSE AFTER TREATMENT DISCONTINUATION IN SCHIZOPHRENIA

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Background: Antipsychotic maintenance clinical trials consistently report benefits for patients treated with antipsychotics versus those receiving placebo. However, in real world settings multiple relapses characterise the course of illness for most patients with schizophrenia. Despite this, the nature and consequences of these relapse episodes has not been extensively researched.
Methods: We conducted a systematic review investigating relapse rates after treatment discontinuation and a further review to investigate the consequences of relapse. We also report on two studies investigating the pre-and post-relapse treatment response, one in a first-episode sample and the other in a multi-episode sample. We sought evidence for "supersensitivity psychosis" by comparing the phenomenology of the relapse events, and assessed whether relapse events played a role in treatment non-response.
Results: Relapse rates are very high when treatment is discontinued, even after a single psychotic episode, and rates are not influenced by duration of treatment. Many patients relapse soon after treatment discontinuation and transition from remission to relapse is often abrupt. However, the nature of the relapse events was not consistent with "supersensitivity psychosis", but rather suggested re-emergence of the original illness. While most patients responded promptly to re-introduction of antipsychotic treatment after relapse, the response time was variable and notably, treatment failure emerged in about 1 in 6 patients. We did not find evidence of tolerance or breakthrough symptoms developing in patients receiving assured antipsychotic treatment.
Conclusion: In the shorter term, continuous antipsychotic treatment is associated with favourable outcomes. Relapse may be a critical factor in the emergence of treatment failure.
ID: 2114859

VOCATIONAL REHABILITATION FOR PERSONS WITH PSYCHOTIC DISORDERS - THE JUMP STUDY

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Background: Although most people with schizophrenia want to work, unemployment rates remain high. Employment holds several economic, social and psychological benefits for people with psychotic disorders. Possible barriers to employment are related to both internal factors such as cognitive impairment and psychotic symptoms, and external factors such as stigma, service availability and benefits.
The purpose of the JUMP (Job Management Program) study is to explore the feasibility of vocational rehabilitation for people with psychotic disorders in a Scandinavian welfare society, and to examine the association between employment and psychotic symptoms.
Methods: Participants (n=148) were enrolled in a 10 months vocational rehabilitation program offering close collaboration between health- and vocational services, competitive or sheltered work and either cognitive remediation therapy (CR) or cognitive behavioral therapy (CBT) focusing on work related issues. Participants were assessed with several clinical, neurocognitive, and functional measures - in the present presentation we examine employment status, income status and SCI-PANSS.
Results: At baseline (T1), 13 % of the participants were employed but none had paid work as their main income. At 10 months (T2), the employment rate had increased to 77 % and 5 % had paid work as their main income. In a matched comparison group receiving treatment as usual the corresponding employment rates were 16% at T1 and 18% at T2. The symptom levels improved slightly, but significantly in both groups. The JUMP participants worked on average 10.5 hours (sd = 7.3) per week during the last four weeks of the intervention. Logistic regression analyses showed that for the average level of the different PANSS dimensions, a positive change in employment status was at least 33 times more likely in the JUMP group compared to the comparison group. The group difference increased with the level of PANSS for all dimensions, which is interpreted as effect modification by PANSS. In other words, the benefit of the JUMP intervention increased by increasing symptom levels.
Conclusion: The analyses suggest that people with psychotic disorders in a Scandinavian welfare society are able to work, at least part time, both in competitive and sheltered settings, when given access to vocational rehabilitation and adequate support.
ID: 2118613

UNDERSTANDING SOCIAL SITUATIONS (USS): A NEW SOCIAL COGNITIVE INTERVENTION TARGETING THEORY OF MIND AND ATTRIBUTIONAL BIAS IN PSYCHOSIS

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Background: Social cognition has been identified as a potential treatment target for interventions aimed at improving social functioning in schizophrenia. While there are many efficacious interventions for affect recognition, there have been far fewer studies of, and more mixed results for, interventions targeting higher-order social cognitive domains like Theory of Mind (ToM) and Attributional Bias (AB). We speculated that the limited efficacy of interventions targeting ToM and AB may be due to their task demands, i.e. cognitively taxing psychoeducation and discussion.
Methods: We developed a social cognitive intervention that limits cognitive load by relying on methods that have previously been successfully used in neurocognitive remediation: errorless learning, hierarchical training, massed drill and practice, and verbal mediation, to name a few. Module content was largely adapted from successful lab-based manipulations of ToM and AB. The new intervention, called Understanding Social Situations (USS), is administered over the course of 7-10 sessions, and consists of four successive modules: (1) Separating social facts from guesses; (2) Making probability judgments and not jumping to conclusions about social situations; (3) Determining others' mental states; and (4) Inducing a positive interpretive bias in ambiguous social situations.
Results: We have completed initial development and refinement, and are currently conducting a proof-of-concept, double-baseline pilot. Participants who completed the pilot to date (n=18) report the training is easy and useful. There is evidence that participants significantly increase their knowledge of content presented during the training, and a moderate effect for improvements on a primary measure of AB, but not ToM. Data from the completed pilot will be presented. We will also discuss the potential impacts of baseline social cognitive impairment and the psychometric properties of outcome measures on final study findings.
Conclusion: Preliminary data suggest that higher-order social cognitive content can be successfully taught using neurocognitive remediation methods that lessen cognitive load. Additional work will focus on further refining the intervention and examining its' effects when embedded within more comprehensive rehabilitation programs that offer bridging opportunities.
ID: 2092976

RELAPSE PREVENTION IN SCHIZOPHRENIA: DO CHOICE OF DRUG AND ROUTE OF ADMINISTRATION MATTER?

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Background: The efficacy of maintenance treatment with antipsychotics is one of the best documented findings in clinical psychopharmacology. There is not a single prospective clinical trial in which antipsychotics where not shown to be superior to placebo and many studies using active comparators or case control designs support these findings. Nevertheless, despite impressive NNTs of single digits, many psychiatrists still feel ambivalent to suggest long-term antipsychotic prophylaxis to patients and, many patients are reluctant to accept it. Choice of drug, mainly with respect to safety / tolerability and acceptance is felt to play a relevant role in this context. The field struggles with the difficulties of translating results from clinical trials, which are based on average evaluations of side effects, to the individual patient.
Secondly, ever since the introduction of long-acting i.m. depot antipsychotics their role in the long-term management of schizophrenia has been controversial. While some clinicians argue for their superior efficacy compared to oral antipsychotics based on enhanced compliance management, others hold reduced patient autonomy and limitations in the possibilities for dose adjustment against them.
Methods: Comparative clinical trials have been performed to inform practicing clinicians with respect to relapse prevention using oral antipsychotics. Prominent examples include CATIE and EUFEST. Similarly, depot antipsychotics have been compared to oral medications.
Results: Findings have been controversial with respect to choice of antipsychotic and route of administration. Studies have made clear that a simplistic differentiation into "typical" and "atypical" medications is not clinically meaningful. Drugs in the respective groups differ significantly from each other. Stage of illness also appears to play a role. Similarly, trials comparing depots to oral antipsychotics have not provided unequivocal results.

Conclusion: Often, controversial findings can be explained by methodological differences between studies. This also has a considerable impact on meta-analyses.
I will review the relevant literature and provide a critical appraisal of available findings. Next to that, suggestions for trial designs relevant to every day clinical decision making will be presented.
ID: 2118493

LONG-ACTING INJECTABLE ANTIPSYCHOTICS IN FIRST EPISODE SCHIZOPHRENIA

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Background: Depot antipsychotics were introduced in the 1960s, haloperidol decanoate being the first approved compound. Since then a number of antipsychotics, including new generation drugs, have been made available as i.m. depots. Despite sound efficacy regarding their efficacy / tolerability profiles in relapse prevention studies their use is often restricted to chronically ill schizophrenia patients with long disease histories and erratic compliance behavior.
Methods: The relevant literature was surveyed using a pubmed search.
Results: Despite increasing evidence that early episode schizophrenia patients show much better treatment response than those with chronic illness, and that these patients present a significant challenge with respect to adherence, the use of depots in this group of patients has hardly been contemplated and, consequently hardly studied. Only a few small scale clinical trials have evaluated the effectiveness of depots in first episode patients. These studies provide strong preliminary support for an earlier use of these compounds.
Conclusion: The evidence will be reviewed and critically discussed. Advantages of the early use of depot antipsychotics will be balanced against potential risks. Clinicians and patients attitudes need to be weighed into this decision process.
ID: 2116188

PALIPERIDONE PALMITATE TREATMENT RESPONSE IN EARLY AND CHRONIC ILLNESS SCHIZOAFFECTIVE DISORDER PATIENTS

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Background: Schizoaffective disorder (SCA) presents with mixed symptoms of psychosis, depression, and mania, and is associated with significant functional impairment. Once-monthly paliperidone palmitate (PP), as monotherapy or adjunctive treatment, significantly reduced relapse risk in the first placebo (PBO)-controlled, relapse-prevention SCA study (NCT01193153). Exploratory analyses examined PP treatment response in patients with SCA early in their illness and those with a longer duration of illness.
Methods: Subjects stabilized (psychotic and mood symptom scores) in a 25-week open-label (OL)-phase could enter the 15-month double-blind (DB) relapse-prevention phase. OL phase: Early- (diagnosis <5 years) and chronic-illness (≥5 years) subpopulations were evaluated for changes at endpoint in PANSS, HAMD, YMRS, and PSP (between group: t-test; within group: paired t-test); OL adverse events (AEs) were summarized. Percentages of early- and chronic-illness subjects meeting OL-stabilization criteria and entering DB-phase were compared (Chi-square test). DB phase: time-to-relapse Kaplan-Meier estimates were determined for PP vs PBO in each subpopulation; risk of relapse was assessed (Hazard Ratios, 95%CI; Cox proportional hazards models); and AEs summarized.
Results: 667 (206 early; 461 chronic) subjects enrolled in the OL PP treatment phase. OL phase: Significant within treatment group improvements were observed in symptom and functioning scores (PANSS, HAMD, YMRS, and PSP, all $p<0.001$), with greater improvements in the early- versus chronic illness subpopulations (all $p<0.05$). In the early- and chronic-illness subpopulations, respectively, the most common adverse events were akathisia (5.8%; 13.4%), injection site pain (7.3%; 12.1%), and insomnia (7.8%; 11.1%). A higher percentage of early- than chronic-illness patients met OL-stabilization criteria (70.4% [143/203] and 60.0% [270/450], respectively; $p=0.01$) and entered DB randomization (57.8% [119/206] and 46.6% [215/461]; $p=0.008$). DB phase: Significantly fewer early illness subjects treated with PP than PBO relapsed (10.2% vs 30.0%, $p=0.014$; HR 2.8 [95% CI 1.11, 7.12; $p=0.029$]). Significantly fewer chronic illness subjects treated with PP than PBO relapsed (18.1% vs 35.5%, $p=0.001$; HR 2.38 [95% CI 1.37, 4.12; $p=0.002$]).
Conclusion: Exploratory analyses suggest that early versus later treatment with PP in SCA results in greater symptom improvement and numerically lower relapse rates.
Supported by Janssen Scientific Affairs, LLC.
ID: 2081116

A QUANTITATIVE SYSTEMS PHARMACOLOGY STUDY OF THE COMBINATION OF GALANTAMINE AND MEMANTINE FOR COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

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Background: Galantamine is an acetylcholinesterase inhibitor with allosteric potentiating effects on nicotinic receptors (nAChR) and memantine is a weak NMDA-antagonist with preferential affinity against the excitatory-inhibitory synapses in cortical networks. Both compounds are approved for Alzheimer's disease, but their individual effect in cognitive impairment in schizophrenia (CIAS) has yielded equivocal results. A recent position paper suggests that their combination, although untested might be more effective.
Methods: We use an advanced version of a computer-based Quantitative Systems Pharmacology (QSP) platform, a mechanism-based computer model of the relevant humanized cortical networks that has been developed for clinical readouts in psychiatry and neurology, has been calibrated with group average clinical data and has been able to blindly and correctly predict an unexpected clinical outcome in schizophrenia and Alzheimer's disease (AD). The model has been calibrated for clinical cognitive outcomes in conditions of chronic schizophrenia.
Results: Galantamine has a modest effect on cognition in CIAS as a stand-alone in the computer model, while memantine has a much smaller impact. However the combination shows a clear synergistic effect. The effect of increased nAChR desensitization induced by smoking affects the degree of synergism. Donepezil's effect is only additive to memantine, suggesting an important contribution of nicotinic receptor allosteric potentiation. We also tested the effect of the combination on a pathology that is more representative of early psychosis. Finally the impact of the common genotypes COMTVal136Met and 5-HTTLPR and the heterozygous microdeletion on 15q13.3, leading to lower expression of a7 nAChR was simulated.
Conclusion: Galantamine interacts in a complex way with memantine due to the effect of nAChR-mediated effects on glutamate and GABA. The combination of memantine and galantamine has potential in reversing cognitive impairment in schizophrenia in conditions of chronic schizophrenia; however clinical trials need to proceed cautiously as smoking conditions and genotypes might affect the outcome. QSP is a platform that possibly can generate useful insights on the optimal conditions for such clinical trials.
ID: 2118555

DOPAMINE-1 RECEPTOR STIMULATION IN SCHIZOPHRENIA: A RANDOMIZED, CLINICAL TRIAL

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Background: Cognitive deficits are a core feature of schizophrenia. Evidence from preclinical and human studies suggest that cortical hypodopaminergia may contribute to cognitive deficits in schizophrenia. The purpose of this trial was to test whether stimulation of dopamine-1 receptors via a full, selective agonist of the dopamine-1 receptor (DAR-0100A) would improve cognitive deficits in schizophrenia.
Methods: We first performed a phase I, single, ascending dose trial of DAR-0100A in order to identify a maximal tolerated dose of DAR-0100A and to characterize the safety of DAR-0100A. We then randomized 49 clinically stable individuals with schizophrenia to 3 weeks of intermittent treatment with high dose (15mg), low dose DAR-0100A (0.5mg) or placebo (normal saline). fMRI BOLD imaging was used to evaluate the effects of drug administration on patterns of brain activity during performance of a working memory task. Effects on cognition were also assessed using the N-Back, MATRICS, and CogState batteries. Secondary objectives were to investigate the effects of DAR-0100A on negative symptoms.
Results: There were no observed treatment effects on either the BOLD fMRI signal during working memory tasks, on working memory domains of the MATRICS battery, nor on other clinical measures. However, there were large effect size improvements in cognition as measured by the CogState Schizophrenia Battery in only the high dose group, as well as improvements in attention on the MATRICS battery in both treatment groups.
Conclusion: These results are mixed but do suggest a possible pro-cognitive effect of a full, D1 receptor agonist in schizophrenia. DAR-0100A is limited by its pharmacokinetic profile. Therefore, other D1 agonists are needed to more fully test the efficacy of this mechanism for cognitive enhancement in schizophrenia and reconcile the findings from this trial.
ID: 2118665

PUBLICATION IMPACT FROM NIMH FUNDED CLINICAL TRIALS

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Background: Most major mental illnesses lack effective treatments, partially due to limited understanding of underlying disease mechanisms. Recently, NIMH has developed a focus on experimental therapeutics, where interventions will also required to be used as scientific probes to understand disease mechanisms as well as tests of efficacy. Simultaneously, NIMH has also decided to improve the efficiency of clinical trials it funds.
Methods: In this presentation data will be presented on publication records of NIMH funded clinical trials. We will identify how many trials were funded by the NIMH during a specific period, and how many of those resulted in publications. We will present average time of publication from the origination of the trial and whether the data were made available for the use by other investigators after the trial completion. We will analyze correlation between primary outcome proposed in the grant application and that presented in the publication.
Results: A recent report suggested that many of the NIH funded clinical trials do not culminate in publication of their findings, and take a much longer time to completion than originally proposed. NIMH trials are likely to follow a similar pattern of publication.
Conclusion: These analyses will provide a clearer understanding of the current state of affairs of NIMH funded clinical trials and data to make necessary changes to improve the efficiency of NIMH funded clinical trials.
ID: 2119056

PRIOR TREATMENT WITH HALOPERIDOL PREVENTS ANTIPSYCHOTIC-LIKE ACTIONS OF A NOVEL COMPOUND IN MAM SCHIZOPHRENIA MODEL

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Background: There is increased focus on GABA-glutamate balance in the limbic hippocampus as the pathological site that overdrives the DA system in schizophrenia. However, drugs developed to target this state and that have shown promise preclinically have failed in clinical trials. However, one issue is that clinical trials are performed on patients that have received D2 blocking drugs for years before one week withdrawal and novel drug testing. Since administration of D2 blockers will strongly impact the brain, we examined whether 3 weeks of haloperidol treatment and 1 week withdrawal would impact the ability of a novel GABA A alpha 5 positive allosteric modulator (alpha5PAM) to restore DA neuron activity and behavioral response to amphetamine in MAM schizophrenia model rats.
Methods: Pregnant dams were treated with MAM at gestational day 17, and the offspring tested as adults (>PD65). Haloperidol (0.6mg/kg, PO) was administered for 21 days, followed by 7 days withdrawal before the rats were given the alpha5 PAM SH-053-2'F-R-CH3 (10 mg/kg IP) 20 min prior to recording or behavioral testing. The ventral hippocampus was inactivated using TTX infusion, and DA neurons were recorded using the cells/track protocol.
Results: Following 3 weeks of saline treatment, MAM rats exhibited elevated numbers of DA neurons firing and elevated locomotor response to amphetamine. Apha5PAM administration or ventral hippocampal inactivation both restored DA neuron firing and amphetamine locomotion to control levels. In contrast, following 3 weeks of haloperidol and 1 week withdrawal, both MAM rats and saline rats exhibited heightened locomotor response to amphetamine. Furthermore, MAM rats withdrawn from haloperidol failed to show altered DA neuron firing or reversal of amphetamine hyper-responsivity as observed in the rats withdrawn from saline.
Conclusion: Haloperidol treatment was found to induce DA supersensitivity in both control and MAM rats. As a result, manipulations that normally restore DA neuron activity and behavioral response to amphetamine in MAM rats were no longer effective at reversing this pathological state. Prior antipsychotic drug treatment is therefore proposed to change the DA system from a hippocampal-overdriven state to a postsynaptic supersensitivity hyperDArgic state. As a consequence, drugs that target the site of proposed pathology in the schizophrenia brain would not be effective following short periods of withdrawal from D2 blocking antipsychotic drugs.
ID: 2087723

NUPLAZID™ - A NOVEL CONCEPT FOR PSYCHOSIS THERAPY

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Background: The existing antipsychotic drugs (APDs) are not optimal. Lack of efficacy and side effects with APDs lead to poor compliance in schizophrenia therapy. In elderly demented patients with psychosis, the

frequent off-label use of APDs worsens cognition and increases mortality. The APDs interact with a large number of targets and a safer and more tolerated therapy may be achievable with selectively acting drugs.
Methods: We have discovered and are developing a selective 5-HT2A inverse agonist, NUPLAZID™ (pimavanserin), as the first example of a new generation of psychosis therapy with an attractive clinical safety and tolerability profile1.
Results: In a recent Phase III trial, NUPLAZID demonstrated an impressive combination of antipsychotic efficacy, tolerability and safety in the treatment of patients suffering from Parkinson's disease psychosis (PDP)2. NUPLAZID also improved quality of sleep without inducing sedation2. This characteristic may further enhance the attractiveness of NUPLAZID therapy in PDP patients where sleep problems are common. An ongoing open-label extension study has further demonstrated that NUPLAZID is safe and well-tolerated with long-term use.
Conclusion: ACADIA has announced plans to submit an NDA for NUPLAZID in PDP in Q1-2015.
1 Hacksell U. et al. Neurochem Res. (2014) 39:2008-2017
2 Cummings J. et al. The Lancet (2014) 383:533-40
ID: 2190090

HOW CAN TECHNOLOGY IMPACT MEDICATION ADHERENCE IN CLINICAL TRIALS?

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Background: Clinical trials collect a mix of self-reported medication adherence data - often unreliable - and periodic bioassays that only provide a snapshot of the participant's adherence and response to the drug. These monitoring methods present significant limitations and introduce noise and risk to the research process. This is particularly true within Schizophrenia research. Accurately tracking patient medication adherence and behavior through technology eliminates the need for self-reporting and allows for targeted intervention.
Methods: A number of medication adherence monitoring technologies will be reviewed and data from a Phase II Schizophrenia study utilizing a novel adherence monitoring platform will be presented.
Results: Each adherence technology has its own merits and should be selected according to the risk profile of the trial. A monitoring platform using artificial intelligence in a Phase II trial was found to be feasible for use in Schizophrenia research. Early behavior was predictive of future behavior while overall medication adherence rates were better than expected.
Conclusion: Adherence technologies can improve data integrity within Schizophrenia trials and offer a new standardized approach to patient monitoring and intervention.
ID: 2125379

INTERNET BASED COGNITIVE REMEDIATION CAN ASSIST PEOPLE WITH SEVERE MENTAL ILLNESS TO GAIN AND RETAIN EMPLOYMENT - THE COGREM STUDY

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Background: One of the most significant problems for people with a severe mental illness is their difficulty in finding and retaining paid employment. This is despite work being one of their top priorities. One of the predictors of poor outcome in severe mental illness is poor cognition. Cognitive remediation programs have demonstrated an ability to significantly improve cognition, and when combined with a supported employment program to significantly increase the likelihood of individuals obtaining and staying in work. However individual cognitive remediation treatment is difficult to provide in stretched mental health systems. The CogRem study examined the capacity of internet-based cognitive remediation combined with a supported employment program to return people with severe mental illness to work.
Methods: Eighty six people with severe mental illness (mean age 39.6 yrs; male: n= 55) who were unemployed and who had joined a supported employment program were randomised between an internet-based cognitive remediation program (CogRem) and an internet based information control (WebInfo). Subjects were followed up at 6 months and 12 months for employment outcomes. Non-parametric statistics were used to explore the data.
Results: At 6 months those participants randomised to CogRem had worked significantly more hours (p=0.11), more of which were paid (p=0.47) and had earned significantly more money (p=0.32) than those participants randomised to the WebInfo control condition. These results were continued at 12 months though participant drop-out eroded the strength of the results.
Conclusion: In this study internet-based cognitive remediation when combined with a supported employment program significantly improved the likelihood of people with a severe mental illness in finding and retaining work. This result supports the use of cognitive remediation programs and suggests that the combination of such programs with other psychosocial interventions may provide synergistic value.
ID: 2118189

THE LONG-TERM EFFICACY OF ANTIPSYCHOTICS FOR SCHIZOPHRENIA: A 20-YEAR MULTI-FOLLOWUP STUDY

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Background: Little is known about the efficacy of antipsychotic medications for schizophrenia (SZ) over long time periods (more than 10 years). Even less is known about the long-term outcome of schizophrenia patients not prescribed antipsychotics.
Methods: From the Chicago Followup Study, 139 young psychotic patients, including 70 schizophrenia patients (SZ), were studied at 6 followups over a 20 year period. Using standardized research instruments, patients were evaluated at each followup for positive symptoms, negative symptoms, mood disorders, cognitive impairments, work disability, recovery, relapse, and antipsychotic treatment.
Results: A. Longitudinally, SZ continuously prescribed antipsychotics after the acute phase had psychotic activity significantly more frequently than SZ not prescribed antipsychotics for prolonged periods.
B. Starting at the 4.5 year followups and continuing until the 20-year assessments, over 60% of the SZ who were continuously not on antipsychotics were working, half time or more.
C. Longitudinally, after the first few years, antipsychotics do not eliminate the frequency of psychotic activity.
D. Periods of recovery are more frequent in SZ who are not in pharmacological treatment.
Conclusion: Recent analysis by our own research team, and other major investigators, such as Leucht, Wunderink, and others, have raised questions about the efficacy of long-term antipsychotic treatment. Our data indicate that, contrary to current thinking about the unconditional need for antipsychotic treatment, a surprising number of SZ show good post-hospital outcome without medications. These data provide a major and unexpected

surprise and pose challenges to our views about the course of SZ who leave treatment after an initial hospitalization.
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ID: 2114543

THE CONTINUOUS ADMINISTRATION OF ANTIPSYCHOTIC MEDICATIONS OVER 20-YEARS FOR SCHIZOPHRENIA: RELAPSE AND RECOVERY

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Background: The PORT (Schizophrenia Patient Outcomes Research Team) (2010) reports, based on over 350 treatment studies, affirm that continuous use of antipsychotic medications is the standard of care for schizophrenia (SZ). However, despite positive assumptions about long-term reductions of psychosis and other major symptoms, there has not been a test of the long-term use of antipsychotics, comparing outcome and potential recovery in SZ prescribed antipsychotics with those not prescribed antipsychotics for a prolonged period (over 15 years).
Methods: 139 early young psychotic patients (mean age=23 years) from the Chicago Followup Study, including 70 schizophrenia patients (SZ) and 69 initially psychotic patients with mood disorders were studied longitudinally with 6 followups over a 20-year period. This included 24 SZ continuously prescribed antipsychotics and 15 SZ not on medications over the last 18 years. Using standardized research instruments patients were assessed at each followup for positive symptoms, negative symptoms, cognitive impairments, depressive symptoms, work disability, rehospitalizations, recovery, and use of antipsychotic medications.
Results: A) The data indicate that when SZ are initially hospitalized at the acute phase, antipsychotics reduce or eliminate flagrant psychosis. B) 4-5 years later those SZ not on antipsychotics for a prolonged period were significantly more likely to experience periods of recovery. C) Long-term use of antipsychotics was significantly associated with poor work functioning (usually unemployment). However, multiple other factors (positive symptoms, negative symptoms, poor premorbid work functioning and cognitive impairment) also were involved in poor work functioning in SZ.
Conclusion: 1) The 20-year longitudinal data raise questions about the assumption that all SZ need to be treated with antipsychotic medications throughout their lifetime and suggest the role of non-treatment factors which may influence both psychosis and periods of recovery.
2) Work disability in SZ may be increased by antipsychotics, which block dopamine receptors and reduce motivational salience.
3) Views about the long-term efficacy of antipsychotics are often based on the results from short-term (0-3 years) evaluations. More long-term studies are needed.
Supported by USPHS Grants MH-26341 and MH-068688 from NIMH and the Foundation for Excellence in Mental Health Care (Dr. Harrow).
ID: 2082938

EVIDENCE OF LEARNING-INDUCED NEUROPLASTICITY IN THE NEURAL SYSTEMS SUPPORTING SOCIAL COGNITION

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Background: People with schizophrenia-spectrum disorders have deficits in social cognition, particularly emotion recognition and theory of mind. These deficits contribute to functional disability and mediate the impact of cognitive problems on functional outcome. Individuals at clinical high risk (CHR) for psychosis also have social cognition deficits which are associated with outcome. Thus, social cognition deficits may be an important target for treatment and prevention. However, intervention development is hampered by limited knowledge about the neural systems that support social cognition and the factors that promote improvement.
Methods: Here, we use intensive, computer-based social cognition training to investigate learning-induced neuroplasticity in brain systems supporting emotion recognition and theory mind. Schizophrenia and CHR participants completed 40-50 hours of a combined cognitive plus social cognitive (Cog+SocCog) training program; each hour of training included 10-15 minutes of emotion recognition and theory of mind exercises. Assessments included a functional MRI scan of facial emotion recognition and behavioral measures of social cognition.
Results: Results show training-induced neural changes in regions involved in emotion recognition, including the amygdala, superior temporal sulcus, and somatosensory-related cortices. Specifically, for schizophrenia participants, amygdala and somatosensory-related cortex activity increased after Cog+SocCog training (versus placebo computer-games activity), and, across participants, greater increase in neural activity was related to greater behavioral improvement in emotion recognition skills. CHR participants, compared to healthy controls before training, had higher activity and lower functional connectivity in the emotion recognition network. After Cog+SocCog training (in a single-arm design), CHR participants showed reduced activity and increased connectivity in the emotion recognition network. Greater training-related neural change was associated with greater gains in social cognition and daily functioning.
Conclusion: The findings suggest that the neural system for emotion recognition, which becomes increasingly compromised in schizophrenia-spectrum pathology, shows learning-induced neuroplasticity after intense, progressively difficult behavioral training in emotion recognition skills. With additional research, social cognition training may provide a low-cost, non-pharmacological intervention that improves functional outcome.
ID: 2118715

EFFECTS OF WEEKLY ONE-HOUR HATHA YOGA THERAPY ON RESILIENCE AND STRESS LEVELS IN SCHIZOPHRENIA: A RANDOMIZED CONTROLLED EIGHT-WEEK TRIAL

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Background: Resilience is a positive adaptation and maintenance of competent function even in the presence of prolonged stress. The purpose of this trial was to examine the effects of Hatha yoga therapy on resilience, brain-derived neurotrophic factor (BDNF) levels, and salivary alpha amylase (SAA) activity in patients with schizophrenia-spectrum disorders.
Methods: In this eight-week single-blind, randomized controlled study, outpatients with schizophrenia or related psychotic disorders (ICD-10) were randomly assigned to either the yoga group or control group. In the yoga group,

subjects received weekly Hatha yoga sessions in addition to regular treatment for eight weeks while those in the control group underwent their regular treatment that included a day-care rehabilitation program. The assessments included the 25-item Resilience Scale (RS), Positive and Negative Syndrome Scale (PANSS), plasma and salivary BDNF level, and SAA activity. The data were collected between November 2012 and April 2013, in Yamanashi Prefectural Kita Hospital, Japan. Analysis of covariance (ANCOVA) with baseline values as covariates was used to compare changes at week eight in the variables of interest between the yoga and control groups. Pearson's test was utilized to examine correlations in the changes of the variables. Main analyses were performed, using a last-observation-carried-forward (LOCF) method.

Results: Fifty subjects (25 each) (mean±SD age, 50.9±11.3 year-old; mean±SD duration of illness, 25.0±10.3 years; mean±SD total PANSS score, 78.2±17.3) participated in this study. Seven participants (28.0%) each in the yoga and control groups prematurely withdrew from the study, respectively. No significant differences in changes in any of the variables from baseline to week eight were found between the two groups (RS score, -1.6±19.9 vs. 0.3±17.2; PANSS total score, 0.5±12.0 vs. 5.0±15.6; plasma BDNF, 41.6±377.0 pg/dl vs. 73.4±346.0 pg/dl, SAA, -26.2±72.6 kU/l vs. -13.8±68.0 kU/l, respectively).

Conclusion: Adjunct yoga therapy failed to show any positive changes in resilience level and stress markers in the present study. Duration and intensity of Hatha yoga sessions and our focus on chronic patients may be potential reasons for our negative observations in light of past positive evidence regarding Hatha yoga therapy. These negative findings provide insights into the better format and design of future yoga therapy, including its frequency and duration.

ID: 2085175

EFFECTS OF GLUTAMATE MODULATORS ON COGNITIVE IMPAIRMENTS IN SCHIZOPHRENIA: A META-ANALYSIS OF DOUBLE-BLIND CONTROLLED TRIALS

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Background: The hypofunction of N-methyl-D-aspartate receptor has been proposed to play an important role in cognitive impairments in schizophrenia, which in turn suggests that glutamate modulators may be effective to reverse such difficult-to-treat conditions. However, the results of the individual studies thus far have been inconsistent. We therefore conducted a meta-analysis to examine whether glutamate modulators as an adjunctive therapy have beneficial effects on cognitive functions in schizophrenia.

Methods: A literature search was conducted to search for double-blind randomized placebo-controlled trials using PubMed, Medline, Embase and PsychInfo. Effects of glutamate positive modulators for cognitive deficits were evaluated on the total cognitive function and 8 cognitive domains: (1) attention/vigilance, (2) cognitive control, (3) reasoning/problem solving, (4) social cognition, (5) speed of processing, (6) verbal learning, (7) visual learning and (8) working memory by calculating the standardized mean differences (SMDs) between active drugs and placebo.

Results: 17 studies (N=1378) were included in this meta-analysis. As a whole, glutamate positive modulators were not superior to placebo in terms of the total cognitive function (SMD=0.08, CI=-0.06 to 0.22) (11 studies, N=858) and each of 8 cognitive domains (SMDs=-0.03 to 0.11) (N=367 to 938). Regarding individual compounds, minocycline had beneficial effects on attention/vigilance (SMD=0.42, CIs=0.03 to 0.82) (2 studies, N=100) while D-cycloserine (DCS) had negative effects on visual learning (SMD=-0.48, CIs=-0.86 to -0.09) (2 studies, N=108). In a subgroup analysis, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor modulators, including CX516 and minocycline, showed beneficial effects on attention/vigilance (SMD=0.33, CIs=0.01 to 0.64) (4 studies, N=205).

Conclusion: On the whole, glutamate agonistic modulators may not be effective to counteract cognitive impairments in schizophrenia as an adjunctive therapy. Minocycline and AMPA receptor positive modulators may be effective to improve attention/vigilance whereas DCS may further worsen visual learning deficits.

ID: 2114646

HIGH READINESS TO PARTICIPATE AND LOW DROPOUT RATE AMONG PEOPLE WITH SCHIZOPHRENIA IN A RANDOMIZED CONTROLLED TRIAL

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Background: Recruitment is one of the most serious challenges in performing randomized controlled trials. Often clinical trials with participants diagnosed with schizophrenia are terminated prematurely because of recruitment challenges resulting in a considerable waste of resources in the form of time, funding, and the participants' efforts. Dropout rates in schizophrenia trials are also high.

This study reports how overcoming recruitment challenges not related to patients revealed high readiness to take part and low dropout rates in a one year long randomized controlled trial testing Guided Self-Determination (GSD) among outpatients with schizophrenia receiving treatment in Assertive Outreach Teams in the northern part of Denmark.

Methods: Descriptive data on strategies to overcome recruitment challenges were derived from notes and observations made during the randomized controlled trial testing of GSD in six outpatient teams

Results: Three types of recruitment challenges not related to patients were identified and met during the trial: 1) organizational challenges, 2) challenges with finding eligible participants and 3) challenges with having professionals invite patients to participate. These challenges were overcome through: 1) extension of time, 2) expansion of the clinical recruitment area and 3) encouragement of professionals to invite patients to the study. Through overcoming these challenges, we identified a remarkably high patient-readiness to take part (101 of 120 asked accepted) and a low dropout rate (8%).

Conclusion: Distinction between recruitment challenges was important in discovering the readiness among patients with schizophrenia to take part in and complete a trial with the GSD-intervention.

ID: 2085202

WHAT MIGHT THE FUTURE LOOK LIKE? TECHNOLOGY AND SOCIAL TRENDS THAT WILL CHANGE HOW WE CONDUCT SCHIZOPHRENIA CLINICAL RESEARCH

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Background: The conduct of clinical research in schizophrenia has remained relatively unchanged in the past few decades.
However we are now in an era of rapid social and technological changes that are impacting society in general.
These trends will also be impacting science including clinical research.
This symposium will review new technologies and social trends that may have an impact on the conduct of clinical trials in schizophrenia. These range from synthetic biology, genomics, specialized software, artificial intelligence, sensors, and digital health to social media, citizen scientists, and crowdsourcing.
The areas that may be impacted by new technology include research subject recruitment, selection, and diagnosis; adherence to medication, study design, and new sources of data such as patient activity and function.
This talk will give an overview of these developments and their possible impact on the future of schizophrenia clinical research.
Methods: A review of new technologies and societal trends was undertaken to assess their possible impact on clinical research in patients with Schizophrenia
Results: The results of this review will be presented, and the impact on schizophrenia clinical research will be discussed.
Conclusion: We are in a period of profound changes affecting science, medicine, and clinical research, driven by new technologies and social trends.
As scientists we need to be aware of these factors and assess how they will impact our work, and how we can leverage these to improve our work developing new treatments for patients with Schizophrenia.
ID: 2120400

EFFICACY OF LOW DOSE LURASIDONE IN PATIENTS WITH SCHIZOPHRENIA: RESULTS OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Background: Lurasidone, in the dose range of 40-160 mg/d, has demonstrated efficacy in the treatment of patients with acute schizophrenia, in 5 previous placebo-controlled studies. This abstract summarizes the results of a new, 6-week study that was designed to evaluate the efficacy of lurasidone 20 mg/d in patients with schizophrenia.
Methods: Hospitalized patients with an acute exacerbation of schizophrenia who had a Positive and Negative Syndrome Scale (PANSS) total score ≥80, a PANSS subscale score ≥4 (moderate) on ≥2 PANSS items (delusions, conceptual disorganization, hallucinations, unusual thought content), and a CGI-S score ≥4 were enrolled. Eligible patients were randomized to double-blind treatment with a fixed dose of lurasidone 20 mg/d (6 weeks), or lurasidone 80 mg/d (2 weeks), or placebo (6 weeks), in a 1:2:1 ratio. After two weeks of treatment, patients demonstrating early improvement (≥20% reduction in PANSS by Week 2) in the lurasidone 80 mg group were continued on the same dose for the remaining 4 weeks of the study. Patients with <20% PANSS improvement were re-randomized, in a 1:1 ratio, to lurasidone 80 mg/d, or lurasidone 160 mg/d for the remainder of the double-blind phase. The primary efficacy variable (change from double-blind baseline in PANSS total score) was assessed using a mixed model for repeated measures (MMRM) analysis. Change from baseline in the Clinical Global Impression, Severity (CGI-S) scale was the key secondary variable.
Results: The intent-to-treat population consisted of 101 patients randomized to lurasidone 20 mg/d (male, 64.4%; mean age, 41.5 years; mean baseline PANSS total score, 96.7) and 112 patients to placebo (male, 69.6%; mean age, 40.7 years; mean baseline PANSS total score, 97.8). Lurasidone 20 mg/d did not demonstrate significant improvement in PANSS total score vs. placebo at Week 6 (-17.6 vs -14.5; P=0.25; primary efficacy endpoint). Change in the CGI-S score was also not significant for lurasidone 20 mg/d vs placebo at week 6 (-0.93 vs -0.73; P=0.17). The proportion of patients who discontinued due to an adverse event was 2% on lurasidone 20 mg, and 7% on placebo.
Conclusion: In this double-blind, 6-week trial in patients with an acute exacerbation of schizophrenia, treatment with lurasidone 20 mg/d was well-tolerated, but did not result in significant improvement in PANSS total score compared with placebo. These results support the current lurasidone starting dose recommendation of 40 mg/d.
Sponsored by Sunovion Pharmaceuticals Inc.
ID: 2115396

RAISE-ETP: NAVIGATE VS USUAL CARE- TWO YEAR OUTCOMES

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Background: Background: The RAISE-ETP program was designed to develop and evaluate an integrated treatment for first episode psychosis (NAVIGATE) in "real world," non-academic, community treatment sites in the USA
Methods: Methods: We selected 34 clinics, located in 21 states, and randomized the sites (clusters), rather than individuals, to either implement NAVIGATE or to provide customary Community Care for subjects in the study. Cluster randomization insured that clinicians at Community Care sites were not exposed to NAVIGATE in order to avoid spillover/contamination effects. Diagnostic interviews and major assessments were conducted by trained remote, centralized personnel utilizing live, two-way video. This allowed them to remind blind to study design and treatment assignment. Study enrollment was completed in July 2012 with 223 subjects receiving NAVIGATE and 181 Community Care.
Results: Results: The final RAISE ETP study sample consisted of 404 subjects. Mean age is 23, 73 % are male, 54% Caucasian, 37% African American. Eighty-eight (17%) were recruited from community outreach activities for the study and the remaining 335 (83%) of subjects came from the usual referral sources for the sites (e.g. a local inpatient unit). Approximately half of subjects met DSM-IV criteria for schizophrenia at study entry with the next most common diagnoses being schizophreniform disorder and schizoaffective disorder and 83% had had severe enough symptoms to warrant psychiatric inpatient hospitalization. Data from two years of treatment and follow up are currently being analyzed.
Conclusion: Conclusion: We believe that we have succeeded in both designing a multimodal treatment intervention that can be delivered in real world clinical settings and implementing a controlled clinical trial which can provide the necessary outcome data to determine its impact on the trajectory of early phase schizophrenia.
ID: 2089440

THE EFFECT OF PROMOTING FUNCTIONING COMBINED WITH THERAPEUTIC RELATIONSHIP ON HEALTH STATE OF PEOPLE WITH SCHIZOPHRENIA

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Background: This study focused on comparison the health state of people with schizophrenia before and after received the promoting functioning combined with therapeutic relationship program, and comparison the health state of people with schizophrenia who received the promoting functioning combined with therapeutic relationship program and those who received regular caring activities.
Methods: The sample of 40 people with schizophrenia under responsibility of Somdet Jaophraya Psychiatric Institute who met inclusion criteria was purposively recruited. They were matched-pair according to age and incomes and then randomly assigned to experimental group and control group, 20 subjects in each group. The experimental group received the promoting functioning combined with therapeutic relationship program, whereas the control group received regular caring activates. Research instruments were: 1) the promoting patient functioning combined with therapeutic relationship program 2) health status measurement, and 3) Social skill life profile. The all instruments were validated for content and reliability by 4 experts. Cronbach's Alpha Coefficient reliability of instruments number 2 and 3 were .92 and .87 respectively. Descriptive statistic, t-test, Analysis of Co-Variance, and Effect size were used in data analysis.
Results: The health state of people with schizophrenia and effect size who received promoting functioning combined with therapeutic relationship program was significantly higher than that before at the .05 level. After the experiment, the health state of people with schizophrenia and effect size who received promoting functioning combined with therapeutic relationship program was significantly higher than those who received regular caring activities at the .05 level.
Conclusion: The promoting functioning program is an effective nursing program that can contribute to schizophrenic patients to be healthy in order to living with their family and community.
ID: 2118137

ONCE-MONTHLY PALIPERIDONE PALMITATE COMPARED WITH ORAL ATYPICAL ANTIPSYCHOTIC TREATMENT IN PATIENTS WITH SCHIZOPHRENIA

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Background: Relative benefits of long-acting injectable atypical antipsychotic compared with oral antipsychotics (OAs) remain a subject of debate. This exploratory analysis of the Paliperidone palmitate Research In Demonstrating Effectiveness (PRIDE; NCT01157351) study compared treatment outcomes following once-monthly paliperidone palmitate (PP) or 1 of 5 atypical OAs (of 7 OAs allowed).
Methods: PRIDE was a 15-month prospective, randomized, open-label, event-monitoring board-blinded study. 444 subjects with schizophrenia were randomly assigned to PP or to 1 of 7 commonly prescribed OAs. Primary endpoint was time to first treatment failure (TF), defined as arrest/incarceration, psychiatric hospitalization, suicide, discontinuation due to inadequate efficacy or safety/tolerability, treatment supplementation due to inadequate efficacy, or increase in psychiatric services to prevent psychiatric hospitalization. Kaplan-Meier analysis estimated event-free probabilities. This exploratory analysis reported randomization-based individual comparisons of PP vs olanzapine (n=143, n=36), aripiprazole (n=157, n=33), and quetiapine (n=146, n=29) as well as PP vs oral risperidone (n=168, n=37), and paliperidone (n=200, n=48) (different delivery of same or similar molecule).
Results: Incidences of extrapyramidal symptom-related adverse events (AEs) were 8.3%, 33.3%, 6.9%, 5.4%, 14.6%, and 23.9% for olanzapine, aripiprazole, quetiapine, risperidone, paliperidone, and PP, respectively. Incidences of prolactin-related AEs were 5.6%, 3.0%, 3.4%, 5.4%, 2.1%, and 23.5%, respectively. Incidences of ≥7% weight increase were 20.0%, 6.7%, 14.3%, 25.0%, 8.9%, and 32.4%, respectively. Compared with PP, risk for first TF was 41% higher with atypical OAs (HR:1.41;95%CI:1.06-1.88). Compared with PP, risk for first TF was 22%, 26%, and 57% higher with olanzapine, aripiprazole, and quetiapine, respectively, and 40% and 43% higher with risperidone and paliperidone (Table). Mean (SD) daily dose of prescribed atypical OAs and monthly PP dose are shown in the Table.
Conclusion: These exploratory analyses suggest a lower risk of TF following treatment with PP compared to treatment with atypical OAs. Additional studies are needed to confirm the findings.
ID: 2085788

INSIGHT AS A PREDICTOR OF RELAPSE IN SCHIZOPHRENIA: SECONDARY ANALYSES OF THE PROACTIVE STUDY

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Background: The PROACTIVE (Preventing Relapse Oral Antipsychotics Compared to Injectables Evaluating Effectiveness) randomized controlled trial (RCT) compared long-acting injectable risperidone (LAI-R) to oral atypical antipsychotics in schizophrenia. Relapse and hospitalization rates, time to first relapse and hospitalization were not related to treatment. This analysis tested the hypothesis that poor insight at study entry would lead to increased relapse.
Methods: At eight sites, 261 subjects with DSM-IV diagnosis of schizophrenia or schizoaffective disorder were included in the study. Subjects were between 18-65 years old, had symptom exacerbation within the last 12 months, were moderately ill (Clinical Global Impression scale) and were treated for up to 2.5 years. Insight was assessed with Modified Scale to Assess Unawareness of Mental Illness. Relapse was defined by psychiatric hospitalization, psychiatric emergency room visit, crisis intervention, deliberate self-injury, clinically significant suicidal or homicidal ideation or violent behavior.
Results: Good insight was seen in 175 (67%), fair in 51 (20%) and poor in 35 (13%). Those with fair insight were excluded from further analysis. Mean age (SD) was 39.8 (11.1) and 33.5 (12.2), 67% and 94% males, 69% and 80% Caucasians in the good and poor insight groups, respectively. Good insight was a predictor of more relapses compared to poor insight ($p<0.02$). Similarly, good insight was a predictor of more hospitalizations compared to poor insight ($p<0.03$). There was no significant association between insight and the time to first relapse and time to first hospitalization.

	Olanzapine	Aripiprazole	Quetiapine	Risperidone	Paliperidone
Hazard Ratio (Atypical OA vs PP) (95% CI)	1.22 (0.72, 2.07)	1.26 (0.72, 2.21)	1.57 (0.94, 2.65)	1.40 (0.86, 2.29)	1.43 (0.92, 2.24)
Mean (SD) daily atypical OA dose	13.3 (6.44)	15.3 (5.89)	339.9 (180.35)	3.6 (1.61)	6.6 (2.44)
Mean (SD) monthly PP dose	184.2 (33.47)	178.9 (34.21)	181.9 (31.34)	179.0 (34.52)	180.6 (34.98)

Conclusion: A higher percentage of PROACTIVE subjects had good insight compared to prior reports; medication nonadherence was low and did not differ between insight groups. Counter to our hypothesis, good insight predicted relapse and rehospitalization. The study sample represented subjects who agreed to participate in an RCT of LAI medication. Perhaps, recruitment of a relatively adherent population and the biweekly monitoring provided in the trial resulted in greater willingness to receive higher levels of care by subjects with good insight. This may have contributed to the higher rates of relapse and hospitalizations in good insight group compared to the poor insight group.
ID: 2076780

KV3 MODULATORS FOR THE TREATMENT OF SCHIZOPHRENIA

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Background: Kv3 (KCNC) voltage-gated potassium channels are expressed by fast-spiking, parvalbumin-positive (PV+) interneurons in corticolimbic circuits. The channels permit accurate, high frequency firing of PV+ interneurons to coordinate the generation of gamma frequency oscillations that underlie attention, sensory processing, and cognition. Deficits in cortical gamma frequency oscillations are consistently observed in patients with schizophrenia, and post-mortem studies have identified deficiencies in cortical GABA, reductions in PV (Lewis 2012, TiNS 35, 57), and reduced expression of Kv3.1 (Yanagi 2014, Mol Psych 19, 573). We propose that positive modulation of Kv3 channels could restore network function and ameliorate cognitive deficits and negative symptoms of schizophrenia. Furthermore, since Kv3.1 channels are also expressed by GABAergic neurons in the basal ganglia, including medium spiny neurons of the striatum and inhibitory neurons in dopamine cell body nuclei, modulation of the channels might also reduce symptoms of psychosis associated with altered dopamine transmission.
Methods: The efficacy of a novel and selective modulator of Kv3.1 and Kv3.2 channels, AUT6 (10-60mg/kg), has been investigated in a series of behavioural and electrophysiological models relevant to the pathophysiology of schizophrenia.
Results: AUT6 prevented acute amphetamine-induced hyperactivity in mice, in the absence of sedation, and modulated ketamine-induced brain activation as measured by phMRI in rats, effects predictive of antipsychotic activity in patients. In a rodent model of deficit symptoms of schizophrenia induced by sub-chronic PCP (Neill 2014, Eur Neuropsychopharm. 24, 822), rats showed reduced corticolimbic PV expression, and deficits in short term memory, executive function, and social interaction. AUT6 ameliorated each of these symptoms, predictive of efficacy to improve the range of deficits shown by patients with schizophrenia. When dosed daily for 21 days, AUT6 also reversed the reduction in cortical PV expression. Finally, AUT6 enhanced gamma oscillations in prefrontal cortical brain slices from sub-chronic PCP-treated rats, whereas the compound had no effect on slices from normal rats.
Conclusion: These data provide strong support for the clinical evaluation of AUT6 in patients with schizophrenia. Given the spectrum of efficacy indicated by the animal data, these results suggest that treatment with the drug early in the course of the illness might be particularly beneficial.
ID: 2184292

INITIAL SEVERITY AND EFFICACY OF ANTIPSYCHOTICS FOR SCHIZOPHRENIA: INDIVIDUAL LEVEL ANALYSES OF SIX PLACEBO-CONTROLLED STUDIES

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Background: Antipsychotic drugs constitute the mainstay in the treatment of schizophrenia and their efficacy has been shown in many randomized controlled trials. However, it is unknown if and how effective they are across the wide range of baseline symptom severity. This study aims to examine the influence of baseline severity on the efficacy of antipsychotic psychopharmacological treatments.
Methods: Meta-analyses were computed with individual-level participant data from three pivotal randomized trials of acute schizophrenia comparing olanzapine or risperidone versus placebo (N=611) and three pivotal trials in patients with predominant negative symptoms of schizophrenia (N=475) comparing amisulpride versus placebo. The primary outcomes were change scores up to six weeks on the Positive and Negative Syndrome Scale (PANSS), and the Scale for Assessment of Negative Symptoms (SANS). The relationship between baseline and change scores for the drug and placebo groups was examined with eight competing three-level mixed-effects models for repeated measures.
Results: The best fitting models showed that, for both types of patients, the interactions between baseline symptom severity and treatment were statistically significant ($p<0.01$). The severer the baseline severity, the greater the magnitude of the differences between the active treatment and placebo. In acute treatment, the differences in PANSS change scores were 9.5 points for patients mildly ill at baseline, 13.7 for moderately ill, and 18.8 for markedly ill. In treatment of predominant negative symptoms, the differences in SANS change scores were 1.7 for moderately ill and 5.7 for markedly ill patients.
Conclusion: Benefits are expected of antipsychotic drugs for the full spectrum of patients that are likely to be treated for acute schizophrenia and for highly symptomatic patients with predominant negative symptoms. Toward the mildest end of the spectrum, clinicians need to be aware that patients benefit less from symptom improvement but may experience full side-effects of antipsychotics.
ID: 2072239

AEROBIC EXERCISE AND YOGA HOLD PROMISES FOR IMPROVING NEURO-COGNITION AND SYMPTOM IN EARLY PSYCHOSIS

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Background: The current study aims to explore the effects of aerobic exercise and mind-body exercise (yoga) on cognitive function and clinical symptom in female patients with early psychosis. The potential neuromechanism underlying the clinical consequences was also investigated.
Methods: Female patients (n=120) diagnosed with schizophrenia spectrum disorders and psychotic disorder were recruited from outpatient clinic. They were randomized into integrated yoga therapy group, aerobic exercise programme group, and waiting list as the control group. Both interventions were held three times weekly for 12 weeks. Neuro-cognition and clinical symptom were compared between baseline and 12 weeks among the three groups using repeated measures ANOVA. Structural MRI data was collected in 60 patients and analysed using FreeSurfer V5.1 and Qdec V1.4.
Results: Both yoga and aerobic exercise improved verbal memory ($p<0.01$) and working memory ($p<0.01$) with moderate to large effect sizes compared to control group. Additionally, yoga group showed enhanced attention and visual-motor coordination ($p<0.05$). Both yoga and aerobic exercise reduced overall symptom ($p<0.05$) and depressive symptom ($p<0.05$) after 12 weeks. Furthermore, yoga increased cortical thickness in post-central gyrus ($p<0.001$) and aerobic exercise increased cortical thickness in superior frontal gyrus ($p<0.001$).
Conclusion: Both types of exercise improved cognition in early psychosis patients, with yoga having a superior effect on attention and visual-motor coordination. Observed increments in the cortical thicknesses may indicate improved neurogenesis. The present study indicates possible interventions for cognitive impairments in the patients with early psychosis, which are non-invasive and mostly safe.
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ID: 2087194

TREATMENT RESPONSE AND DIMENSIONS OF PSYCHOSIS SYMPTOM SEVERITY IN PATIENTS WITH SCHIZOPHRENIA

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Background: The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) provides a "Clinician-Rated Dimensions of Psychosis Symptom Severity" assessment (Section III: Emerging Measures and Models). The objective of this analysis was to evaluate lurasidone treatment response using this dimensional assessment.
Methods: Data were derived from a 6-week, placebo and active-controlled trial of lurasidone in hospitalized patients with an acute exacerbation of schizophrenia using Mixed Effects Model. The standard 7 point scale for each PANSS item (1=Absent to 7=Extreme) was mapped on to the 5 point scale for each domain of the DSM-5 dimensional assessment (0=Not present, 1=Equivocal, 2 = Mild, 3=Moderate, 4=Severe).
Results: Of the 482 patients including in this analysis, most had moderate severity symptoms at study baseline including hallucinations (70%), delusions (86%), disorganized speech (67%), and negative symptoms (75%); mild (41%) to moderate (35%) abnormal psychomotor behavior, and mild (36%) to moderate (38%) depression. Both lurasidone (160 mg/d or 80 mg/d) and quetiapine XR (600 mg/d) showed significantly greater improvement (vs. placebo) at study endpoint on the 6 domains of psychosis symptoms that were assessed.
In patients with at least moderate severity negative symptoms at study baseline (n=360), the higher lurasidone 160 mg/d dose group had significantly greater effect size (1.09) compared to the lower lurasidone 80 mg/d dose group (0.63) and the quetiapine XR 600 mg/d group (0.83) ($p<0.05$). In patients with at least moderate severity depression symptoms at study baseline (n=181), the higher lurasidone dose group (1.26) and the quetiapine XR 600 mg/d group (1.0) had significantly greater effect size than the lower lurasidone dose group (0.57) ($p<0.05$).
For the other 4 psychosis domains, effect size was numerically greater in the higher lurasidone dose group compared to the lower dose group in patients with moderate to severe symptoms. Severity of negative or depressive symptoms at study baseline was a significant predictor of treatment response at week-6.
Conclusion: Larger treatment effects were consistently observed at the higher lurasidone dose (160 mg/d) in the treatment of moderate to severe psychosis symptoms. The lower lurasidone dose (80 mg/d) was comparably effective to the higher dose for less severe symptoms. Dimensional assessment of symptom severity (per DSM-5) can aid understanding of treatment response across the various domains of psychotic illness.
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LURASIDONE FOR MAJOR DEPRESSIVE DISORDER WITH MIXED FEATURES: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED 6 WEEK TRIAL

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Background: DSM-5 introduced a "with mixed features" specifier for major depressive disorder (MDD) when subthreshold manic or hypomanic features are present. Mixed features have been estimated to occur in 20-40% of patients with MDD. The aim of this study was to evaluate the efficacy and safety of lurasidone in patients with major depressive disorder (MDD) presenting with mixed (subthreshold hypomanic) features.
Methods: In this multi-regional study, conducted in the US and Europe, patients were required to meet DSM-IV-TR criteria for MDD, with a Montgomery-Asberg Depression Rating Scale (MADRS) score ≥26, and to be experiencing 2 or 3 DSM-5 mixed features criteria manic symptoms on most days over at least the 2 weeks prior to screening. Patients with any lifetime history of bipolar I manic episodes, or any mixed manic episodes, were excluded. Eligible patients were randomized to 6 weeks of double-blind treatment with either lurasidone 20-60 mg/d or placebo. Changes from baseline in MADRS total score (primary assessment) and Clinical Global Impression, Severity (CGI-S) scales were analyzed using a mixed model for repeated measures (MMRM) analysis. Responder rates (≥50% reduction from baseline in MADRS total score) were analyzed using logistic regression.

Results: Patients were randomized to lurasidone (N=109; baseline MADRS, 33.2), or placebo (N=100; MADRS, 33.3). Treatment with lurasidone was associated with significantly greater improvement compared with placebo from Weeks 2 through 6 on both the MADRS and CGI-S. At Week 6, LS mean change for lurasidone vs placebo on the MADRS total score was (-20.5 vs -13.0; P<.001; effect size, 0.80), and on the CGI-S score was (-1.83 vs -1.18; P<.001; effect size, 0.60). Week 6 responder rates, for lurasidone vs placebo, were 67.6% vs 33.0%; P<.001; NNT=3. The incidence of adverse events resulting in discontinuation was 2.8% and 5.0%, respectively on lurasidone and placebo. Nausea was the only adverse event that occurred with an incidence ≥5% (and greater than placebo) on lurasidone (6.4% vs 2.0%). Minimal changes in weight, lipids and measures of glycemic control were observed on lurasidone.
Conclusion: In this study, the first ever placebo-controlled trial we are aware of in an MDD with mixed features population, lurasidone demonstrated significant efficacy on multiple primary and secondary endpoints. Lurasidone was well-tolerated, with an overall discontinuation rate that was comparable to placebo.
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OPTIMIZING TREATMENT WITH LURASIDONE IN PATIENTS WITH SCHIZOPHRENIA: RESULTS OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Background: Lurasidone, in the dose range of 40-160 mg/d, has demonstrated efficacy in patients with schizophrenia, based on results from 5 previous studies. The current abstract summarizes the results of the first antipsychotic study we are aware of that uses a randomized, double-blind, placebo-controlled design to determine optimal dosing strategy for patients not achieving a clinically meaningful reduction in the Positive and Negative Syndrome Scale (PANSS) total score by Week 2 of standard dose lurasidone treatment.
Methods: Hospitalized patients with an acute exacerbation of schizophrenia who had a PANSS total score ≥80, a PANSS subscale score ≥4 (moderate) on ≥2 PANSS items (delusions, conceptual disorganization, hallucinations, unusual thought content), and a CGI-S score ≥4 were enrolled. Patients were randomized to double-blind treatment with a fixed dose of lurasidone 20 mg/d (6 weeks), or lurasidone 80 mg/d (2 weeks), or placebo (6 weeks), in a 1:2:1 ratio. After two weeks of treatment, patients demonstrating early improvement (≥20% reduction in PANSS by Week 2) in the lurasidone 80 mg group were continued on the same dose for the remaining 4 weeks of the study. Patients with <20% PANSS improvement were re-randomized, in a 1:1 ratio, to receive either lurasidone 80 mg/d, or lurasidone 160 mg/day for the remainder of the double-blind phase. The primary efficacy variable (change from baseline in PANSS total score) was assessed using a mixed model for repeated measures (MMRM) analysis. Change from baseline in the Clinical Global Impression, Severity (CGI-S) scale was the key secondary variable.
Results: The ITT population consisted of 112 patients on placebo and 198 patients on lurasidone 80 mg/d. Patients with early non-response who were re-randomized to lurasidone 160 mg/d (n=43) achieved significantly greater improvement in PANSS total score, from Week 2 to Week 6, compared with non-responding patients (n=52) who continued on the 80 mg/d dose (-16.6 vs. -8.9; p=0.023). Improvement in the CGI-S score, from Week 2 to Week 6, was -1.0 for the lurasidone 160 mg/d group and -0.6 for the 80 mg/d group (P=0.052). The proportion of patients discontinuing due to an adverse event was 2% in the lurasidone 160 mg/d group and 4% in the lurasidone 80 mg/d group.
Conclusion: In patients with early non-response (at Week 2), dose escalation was a well-tolerated and effective strategy for optimizing treatment response to lurasidone.
ID: 2114720

A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 12-WEEK STUDY OF ENCENICLINE, AN A7 NICOTINIC ACETYLCHOLINE RECEPTOR PARTIAL AGONIST, FOR COGNITIVE IMPAIRMENT IN PATIENTS WITH SCHIZOPHRENIA

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Background: Cognitive impairment in patients with schizophrenia significantly impairs quality of life and limits functioning in interpersonal relationships, workplace and community. Antipsychotics are the mainstay of pharmacologic treatment for the positive symptoms of schizophrenia; however, they offer minimal, if any cognitive benefit. Encenicline, an α7 nicotinic acetylcholine receptor partial agonist is in clinical development for the treatment of cognitive impairment in schizophrenia and Alzheimer's disease. This study assessed the efficacy and safety of encenicline for cognitive impairment in patients with schizophrenia on stable atypical antipsychotic therapy.
Methods: 319 subjects with schizophrenia were treated with placebo or encenicline (0.27 mg or 0.9 mg once daily) for 84 days. The primary efficacy endpoint was the Overall Cognitive Index (OCI) score from the CogState battery and Trails 2 and 4 tasks from the Neuropsychological Test Battery (NTB). Secondary endpoints included the MATRICS Consensus Cognitive Battery (MCCB), the Schizophrenia Cognition Rating Scale (SCoRS) and the Positive and Negative Syndrome Scale (PANSS) total and subscale scores.
Results: Treatment with encenicline was associated with broad cognitive improvements. The OCI plus Trails 2 and 4 showed a statistically significant improvement for the 0.27 mg dose of encenicline compared to placebo (P=0.034). A positive trend for improved cognition was also noted on the MCCB at both doses. The change from baseline was greater for the 0.9 mg (P=0.069 vs. placebo) than for the 0.27 mg. Subanalyses were also performed that supported the primary outcomes in this study.
Significant effects in clinical function were seen with encenicline treatment as measured by the SCoRS. The mean change from baseline in the SCoRS total score between the 0.9 mg group and the placebo group was significant (P=0.011). Statistically significant improvement on the PANSS Cognition Impairment domain was noted in encenicline 0.9 mg vs. placebo (p=0.029) and for PANSS negative subscale scores in encenicline 0.9 mg group vs. placebo (p=0.028). No individual serious treatment-emergent adverse event was experienced by more than one subject per treatment group and all events were judged as not related to study drug.
Conclusion: Significant procognitive effects and functional improvements were observed with encenicline. Phase 3 trials have been initiated based on these and other data.
ID: 2207646

A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 12-WEEK STUDY OF ENCENICLINE OR PLACEBO IN SCHIZOPHRENIA SUBJECTS ON CHRONIC STABLE ATYPICAL ANTIPSYCHOTIC THERAPY

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Background: Cognitive deficits in patients with schizophrenia persist despite treatment with antipsychotics, adversely affecting everyday functioning and quality of

life. Studies link impaired α7 receptor (α7R) signaling to cognitive dysfunction in schizophrenia. Encenicline is in clinical development for the treatment of cognitive dysfunction in schizophrenia and Alzheimer's disease. Studies suggest that encenicline potentiates α7-mediated release of multiple neurotransmitters and thereby modulates the neural networks that govern cognition. This study assessed the efficacy and safety of encenicline in stable patients with schizophrenia.
Methods: 319 subjects with schizophrenia were treated with placebo or encenicline (0.3 mg or 1 mg once daily) for 84 days. Efficacy was evaluated using the Overall Cognition Index (OCI) from the CogState testing battery plus Trails 2 and 4, the MATRICS Consensus Cognitive Battery (MCCB), the Schizophrenia Cognition Rating Scale (SCoRS), and the Positive and Negative Syndrome Scale (PANSS).
Results: Encenicline was associated with procognitive effects. The OCI plus Trails 2 and 4 suggested that 0.3 mg of encenicline was associated with improvement in general cognitive function (P=0.034), compared with placebo. This positive effect on the OCI was supported by a positive trend for improved cognition on the MCCB (evaluated in US patients only, n=166). The mean change from baseline at day 84 in the overall Composite T-score (3.6) was higher for the 1 mg dose group than for the 0.3 mg dose group (3.0) and placebo group (1.8). Significant effects in clinical function were seen with encenicline treatment as measured by the SCoRS Interviewer Rating. The mean change from baseline in the SCoRS Interviewer Rating over all visits between the 1 mg group and the placebo group was significant (P=0.011). No individual serious treatment-emergent adverse events (TEAEs) were experienced by more than one subject and all events were judged as not related to study drug. A greater percentage of subjects in the placebo group (8.6%) than the 0.3 mg group (1.9%) or the 1 mg group (4.8%) discontinued study drug because of a TEAE.
Conclusion: Significant procognitive effects and functional improvements were observed with encenicline. Further studies evaluating the safety and efficacy of encenicline in subjects with schizophrenia are underway. Phase 3 trials (NCT01716975; NCT01714661; NCT01714713) have been initiated based on these and other data.
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INTER-RATER RELIABILITY ASSESSMENT OF ASPECT-R (A STUDY PRAGMATIC-EXPLANATORY CHARACTERIZATION TOOL-RATING)

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Background: The increasing importance of real world data for clinical and policy decision making is driving a need for close attention to the pragmatic vs. explanatory features of trial designs. ASPECT-R (A Study Pragmatic-Explanatory Characterization Tool-Rating) is an instrument derived from a previously described tool (PRECIS) developed to assist researchers designing trials that are more pragmatic or explanatory (Thorpe, 2009; Tosh, 2011). ASPECT-R refined the PRECIS trial design domains and includes a detailed anchored rating system. This analysis established the Inter-Rater Reliability (IRR) of ASPECT-R.
Methods: 9 raters (identified from a convenience sample of persons knowledgeable about psychiatry clinical research / study design) received ASPECT-R training materials and 12 study publications. Selected studies assessed antipsychotic treatment in schizophrenia, were in peer-reviewed journals, and represented a range of studies across a pragmatic:explanatory continuum as determined by authors (CB/LA). Raters had 12 weeks to review the materials and rate the study domains using ASPECT-R. Intra-Class Correlations (ICC) were determined for the total and domain scores. Qualitative ratings then were assigned to describe the IRRs (per Cicchetti, 1994).
Results: ASPECT-R scores were available for the 12 studies by 7 raters. ASPECT-R total score ICC was 0.87, corresponding to an excellent IRR. Domain ICCs were 0.85-0.31; ranging from excellent-poor IRRs (Table).
Conclusion: ASPECT-R's total score IRR was excellent, with excellent-good IRRs for most domains. The fair-poor IRR for 2 domains may reflect a need for improved domain definition, anchoring, or training materials. ASPECT-R can be used to help understand the pragmatic:explanatory nature of completed or planned trials.
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MEDICATION NONADHERENCE IN SCHIZOPHRENIA: PRELIMINARY OBSERVATIONS FROM A NOVEL APPROACH FOR DETECTING ANTIPSYCHOTIC DRUG LEVELS

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Background: Medication nonadherence and detection thereupon are substantial challenges in the treatment of schizophrenia. This study sought to assess urine levels of aripiprazole and metabolites among patients receiving steady state dosing of aripiprazole.
Methods: 150 adults, judged compliant with a stable aripiprazole regimen, had observed dosing for five consecutive days. Urine specimens, obtained on days 1, 4 and 5, were analyzed for pH, creatinine, specific gravity, and for aripiprazole, OPC3373 and dehydroaripiprazole. Linear regression was used to assess the association between unadjusted urine levels of each drug/metabolite and dose taken, and linear stepwise multiple regression was performed to identify variables that added to the explanation of the variance.
Results: OPC3373 was found in 97% of urine samples, whereas, unchanged aripiprazole and dehydroaripiprazole were found in only 58% and 39% of samples, respectively. Variance in urine metabolite levels accounted for by medication dose was relatively low for each individual drug/metabolite, r2 only 0.13 to 0.23. However, when OPC3373 was adjusted for age, weight, sex and urine creatinine values the r2 improved to 0.63, and further improved to 0.70, when height, urine specific gravity and the presence of dehydroaripiprazole were added in a stepwise multiple regression model.
Conclusion: Unadjusted urine levels of aripiprazole and metabolites are not strongly related to aripiprazole dosing, however, accounting for key variables yields a strong relationship between measurable urine parameters and dose taken. By defining the expected range of adjusted urine levels for each dose, the potential exists for a clinical test to identify partially non-adherent individuals who would not have been identified by conventional 'present vs. absent' urine drug testing.
ID: 2090373

THE NEURAPRO-E STUDY: A MULTICENTER RCT OF OMEGA-3 FATTY ACIDS AND COGNITIVE-BEHAVIOURAL CASE MANAGEMENT FOR PATIENTS AT ULTRA HIGH RISK OF SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS

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ASPECT-R: ICCs and IRRs

Parameter	ICC	IRR Rating[1]
Total Score	0.87	Excellent
Participant Eligibility domain	0.55	Fair
Intervention Flexibility—Experimental/ Comparison (mean) domain	0.85	Excellent
Medical Practice Setting—Experimental/ Comparison (mean) domain	0.64	Good
Follow-up Intensity domain	0.76	Excellent
Primary Trial Outcome domain	0.31	Poor
Participant Compliance domain	0.76	Excellent

1. ICC cut-offs: <0.40=poor; ≥0.40 and ≤0.59=fair; >0.59 and ≤0.74=good; >0.75=excellent (Cicchetti, 1994).

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Background: Recent meta-analyses have indicated that preventive intervention is likely to benefit patients 'at-risk' for psychosis, in terms of symptom reduction, improved functioning, and delay or even prevention of onset of threshold psychotic disorder. The strong preliminary results from a single-site RCT of the effectiveness of omega-3 polyunsaturated fatty acids (PUFA), coupled with the reduced transition rate in ultra high-risk (UHR) samples, mean that further study of such benign, potentially neuroprotective, interventions is clinically and ethically required. We designed and conducted an international multi-centre RCT with a large sample size to seek to replicate the results of the initial RCT of omega-3 PUFAs in the UHR stage of illness.
Methods: The trial was a 6-month, double-blind, randomized, placebo controlled trial of 1.4 grams/day omega-3 PUFAs in UHR patients aged between 13 and 40 years. The primary hypothesis was that UHR patients receiving omega-3 PUFAs plus cognitive behavioural case management (CBCM) will be less likely to transition to psychosis over a 6-month period compared to treatment with placebo plus CBCM. Secondary outcomes will examine 12-month transition rates and symptomatic and functional outcomes, as well as examining if candidate risk factors and biomarkers predict response to omega-3 PUFAs treatment in the UHR group.
Results: 977 subjects were screened at 10 centres internationally. 304 were randomized. 78% were retained at 6 months. The mean age was 19.1 years and 50% were at least moderately ill on CGI. Survival analysis, in particular the logrank test and Cox regression, will be used to compare differences in transition rates between the treatment groups. The primary analysis will be based on the intention-to-treat approach. For secondary outcome measures, general linear model analysis will be used for level of symptomatology and level of functioning.
Conclusion: Utilizing a large sample, results from this study form an important step in testing the evidence base for indicated prevention of schizophrenia and other psychotic disorders, which may be the strongest avenue for reducing the burden, stigmatization, disability, and economic consequences of these disorders.
ID: 2113630

FACTORS IMPACTING SUCCESSFUL CR IMPLEMENTATION IN NEW YORK OUTPATIENT MENTAL HEALTH CLINICS

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Background: Cognitive Remediation (CR) is a recovery-oriented, neuroplasticity based intervention that targets cognition in order to enhance functional outcome. The demand for CR from families and patients outpaces availability of programs, leading to questions about how best to promote implementation of CR. According to the Promoting Action on Research Implementation in Health Services (PARIHS) framework, successful implementation of CR is a function of the interplay between three major components: (1) the nature of the evidence for CR as perceived by multiple stakeholders, (2) the context or the quality of the environment where the CR is implemented, and (3) the type of facilitation needed to support implementation and maintenance of CR.
Methods: A recent initiative by New York State Office of Mental Health to implement CR in 8 mental health clinics across the state has provided an opportunity to study the challenges to implementation as a function of these three components: perception of evidence, environmental context and facilitation.
Results: Perception of evidence, which initially differed among the stakeholders, became more congruent as the emphasis shifted to enhancing recovery, and not just cognitive outcomes. Environmental context proved challenging as mental health clinics often experienced difficulty in providing some of the essential conditions required for successful delivery of CR. For example, the frequency of CR sessions and requirement for consistent attendance created challenges for programs which average biweekly attendance and for clients who have irregular attendance. Lack of staff knowledge about cognitive deficits needed to be addressed to facilitate the referral and assessment process; lack of access to computer based CR programs had the potential to erode fidelity to delivery of restorative models of CR. Further, fiscal instability and staff turnover in the larger delivery system impacted implementation, requiring dynamic approaches to assure sustainability. Facilitation of the implementation efforts at both the system and agency levels was used to support the initiation and expansion of the CR programs.
Conclusion: The programmatic context and conditions affecting CR implementation and the steps that were taken by the larger and individual service organizations in order to move toward a state of "readiness", provided greater understanding of the factors contributing to a gap between the real world and necessary conditions for CR implementation.
ID: 2080351

PILOT DOUBLE BLIND, PLACEBO CONTROLLED AND RANDOMIZED STUDY TO ASSESS ELECTROCONVULSIVE THERAPY EFFICACY AS AUGMENTING STRATEGY TO CLOZAPINE IN SUPER-REFRACTORY SCHIZOPHRENIA

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Background: Clozapine to be the first line treatment of resistant schizophrenia (TRS) such condition however about 30% of patients with TRS do not respond satisfactorily to clozapine and remain predominantly psychotic. These patients are termed incomplete responders, partial responders or super-refractory patients (SRS). For these patients, many attempts have been made to augment clozapine effect which showed a modest effect, there is no evidence that any pharmacological intervention is efficacious as add-on therapy.Electroconvulsive Therapy (ECT) is less appreciated in this cases.There are no placebo controlled studies examining the efficacy of ECT in patients with partial response to clozapine or so called STRS.
Methods: Inclusion criteria were DRM-IV-TR criteria for schizophrenia, age between 18 and 55 years old, men and women. All patients were on clozapine treatment for at least six months, with or without add-on therapy, with unsatisfactory response, defined as CGI ≥ 4, and PANSS total ≥ 60 at baseline. Patients were randomized to two experimental groups (ECT or Sham ECT) and were assessed in the baseline and after 12 sessions by raters who were completely blind throughout the study. The serum blood levels of clozapine were measured before the initiation of the trial.The outcome variables were the PANSS (and its subscales - positive, negative and general psychopatology) and CGI.
Results: 20 patients participated in the study. ECT group (11 patients) or the Sham- Group (9 patients). In the ECT group the PANSS positive subscale was reduced from 18.40 to 14.90 (-19.0 % - p = 0.009), the total PANSS was reduced from 79.70 to 72.70 (-8.78% - p = 0.026) whereas the CGI scores had a reduction from 5,20 to 4,0 (-23.0% - p = 0.000).In the SHAM group improvements also occurred with PANSS positive subscale which showed a reduction from 25,17 to 18,17 (-27.81 % - p = 0.023), the Total PANSS score was reduced from 102.50 to 86.83 (-15.27% - p = 0.032), and the CGI was reduced, from 6,17 to 4,67 (-24.31% - p = 0.045).However the ANCOVA analysis of endpoint outcome variables showed no differences in both groups.
Conclusion: We found no evidence that active ECT is superior to SHAM-ECT for the improvement of psychopathology as measured by the PANSS. However there are several limitations that must be considered. One possible explanation could be the cumulative factors that can increase placebo effect, also described and found in other clinical trials.
ID: 2097239

THE EFFECTS OF A SINGLE DOSE OF MODAFINIL ON MATRICS CONSENSUS COGNITIVE BATTERY PERFORMANCE IN CHRONIC SCHIZOPHRENIA

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Background: Cognitive impairment associated with schizophrenia is a strong predictor of the functional outcome of the illness and no effective treatments are currently available. MATRICS Consensus Cognitive Battery (MCCB) was designed as an outcome measure for trials of cognitive-enhancing drugs in schizophrenia. Findings from a small number of studies suggest that modafinil, a wakefulness-promoting agent, may have cognitive-enhancing effects in schizophrenia (Turner et al., 2004; Scoriels et al., 2012). Our goal was to test the effects of a single dose of modafinil on MCCB in patients with chronic schizophrenia.
Methods: 49 clinically stable outpatients with schizophrenia were enrolled in a randomised, double-blind, placebo-controlled study across two sites (Institute of Psychiatry, King's College London and University of Manchester) and received 200mg of modafinil or placebo 2 hours prior to MCCB administration. This study is a part of a larger trial that tested the feasibility and cognitive effects of the combination of cognitive training exercises with repeated doses of modafinil in chronic schizophrenia [ISRCTN60687844 (www.isrctn.org)].
Results: 42 participants provided outcome data and were included in the final analysis. A single dose of modafinil did not induce any significant changes on the MCCB composite score (99.38% CI -6.567, 1.749), while it significantly worsened performance on the visual learning (99.38% CI -14.922, -3.160) and executive function (99.38% CI -12.741, -0.667) domains compared to placebo.
Conclusion: To our knowledge, this is the first study that used MCCB, the current gold standard neuropsychological battery for cognition in schizophrenia, to test the cognitive effects of a single dose of modafinil in schizophrenia. In our population of chronic patients, modafinil showed adverse effects on cognitive function. Our results are at odds with those of previous single-dose studies in schizophrenia and suggest that the role of modafinil as a potential cognitive-enhancing drug for chronic schizophrenia needs further investigation for definite conclusions to be drawn.
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ID: 2093974

EXERCISE-BASED COGNITIVE REMEDIATION FOR YOUTH AT ULTRA HIGH-RISK FOR PSYCHOSIS

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Background: Accumulating evidence suggests that cardiovascular activity can affect cognition and brain structure in schizophrenia. Given the literature suggesting that the medial temporal structures play a critical pathogenic role, understanding activity levels in the high-risk period may inform targeted early interventions. Recently, exercise has been studied during the prodrome, and our group has reported links with the integrity of medial temporal structures in ultra high-risk (UHR) youth. However, the potential for exercise-based cognitive remediation has not been evaluated, and to date, there has not been a controlled trial with an exercise treatment in this group.
Methods: This investigation examined 29 UHR and 27 matched controls to determine relationships between activity level and cognitive function. Participants were assessed with actigraphy for a 5-day period, a short cognitive battery and magnetic resonance imaging (MRI).
Results: When compared with controls, the UHR group exhibited less moderate to vigorous activity, smaller medial temporal volumes, and poorer performance in verbal fluency, trail making, and verbal learning. Higher levels of physical activity in the UHR group were moderately correlated with larger parahippocampal gyri bilaterally (right: r=.44, p≤.01; left: r=.55, p≤.01) with a similar trend in the left hippocampus (r = 23, p=.09). Furthermore, elevated activity in the UHR group was associated with improved performance in verbal fluency (r=.35, p≤.01), trail making (r=.28, p≤.05), and verbal learning (r=.25, p≤.05).
Conclusion: These data were employed for the basis for an ongoing rater-blind randomized trial that assigns 3 month's of aerobic exercise (supervised sessions at 65-85% intensity) or a waitlist condition to UHR youth

and tracks changes in cardiac output, medial temporal structure and cognition post intervention. The results of the actigraphy study, and early data from the 5-year exercise trial are discussed in this presentation.
ID: 2072153

INTERNALIZED STIGMA REDUCTION FOLLOWING GROUP COGNITIVE-BEHAVIORAL THERAPY FOR SOCIAL ANXIETY IN AT-RISK MENTAL STATE AND FIRST-EPISODE PSYCHOSIS

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Background: Schizophrenia has a population incidence of 1% yet it is a leading cause of disability worldwide (Lopez et al, 2006). Beyond the attainment of symptomatic remission, the chronic difficulties surrounding psychosocial functioning in schizophrenia remain unaddressed despite current findings. Stigma has become an area of interest when it comes to promoting recovery in severe mental illness. The importance of targeting stigma as part of better understanding and seeking improved psychosocial functioning related to recovery in mental illness is clear, mainly based on the fact that stigma is believed to have potential limiting effects on recovery. There has been a consensus that stigma should be further investigated (Knight, Wykes, & Hayward, 2006; Lysaker et al., 2007) and become a prominent and essential component of treatment and rehabilitation programs alike (Byrne, 2000). Despite advances in pharmacological treatments over the past two decades,many patients with schizophrenia continue to experience chronic difficulties with psychosocial and vocational functioning. Similarly, social anxiety, although it represents an important barrier to quality of life and social functioning, often goes unnoticed in schizophrenia (Lysaker et al., 2010). A recent study revealed that internalized stigma was related to social anxiety (Lysaker et al., 2011). Objective: This study was to investigate whether a group-based cognitive-behavioral therapy (CBT) for social anxiety in a first-episode of psychosis and at-risk for developing psychosis resulted in a reduction of internalized stigma.
Methods: Thirteen patients with social anxiety attended a group-based cognitive behavior (CBGT) intervention. The CGBT was provided weekly for 14 weeks in 1.5-hour sessions. Baseline and post-treatment ratings of social anxiety were measured using the Social Interaction Anxiety Scale, the Social Phobia Inventory and the Brief Social Phobia Scale. Internalized stigma was assessed using the Internalized Stigma in Mental Illness scale.
Results: Using paired-samples t-test analyses, following participation in the intervention, participants displayed significantly less symptoms of internalized stigma (ISMI) [$t(12) = 2.36$, $p = .03$].
Conclusion: Interventions targeting social anxiety as part of at-risk and first-episode psychosis appear to be associated with improvements in symptom-severity of internalized stigma. Interventions should incorporate comorbid conditions as part of treatment of at-risk and psychotic symptoms.
ID: 2118465

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE I STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF SINGLE RISING DOSES 0.5MG TO 500MG OF BI 409306 ADMINISTERED ORALLY IN HEALTHY MALE VOLUNTEERS.

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Background: BI 409306, a phosphodiesterase 9 inhibitor, is being developed for symptomatic treatment of cognitive impairment associated with schizophrenia. The primary objective of this first-in-human study was to investigate the safety and tolerability of BI 409306 in healthy male volunteers. Secondary objectives included exploring dose proportionality and comparing the safety and pharmacokinetics of 2 different groups of CYP2C19 genotyped subjects (extensive metabolizers [EM] and poor metabolizers [PM]).
Methods: Single rising doses of BI 409306 were evaluated in healthy male volunteers in this randomized, double-blind, placebo-controlled within dose group, single-center trial.
Results: A total of 79 Caucasian, healthy male subjects (mean age 36.7 years) were treated in 10 sequential dose groups. Eight PM subjects were treated with 10mg/d and 100mg/d doses of BI 409306. Within each dose group, 6 subjects received active treatment and 2 received placebo. In total, 17 of 71 EM subjects (23.9%) reported 28 AEs; 6 of 8 PM subjects (75.0%) reported 8 AEs; 20 subjects (25.8%, 14 EM, 6 PM) reported AEs that were considered related to BI 409306 by the investigator. All AEs were of mild to moderate intensity, limited duration, and resolved without sequelae. The most commonly reported AEs in the higher dose groups starting at 100mg/d were visual symptoms. These AEs showed a trend that correlates with dose, with the maximum tolerated dose in EM subjects set at 350mg/d. No deaths, SAEs, or other significant AEs were reported. Overall, there were no observed relevant changes with BI 409306 compared to placebo for laboratory, ECG recordings, vital signs, and cardiac monitoring. Absorption was rapid, reaching maximum plasma concentrations at <1h after drug administration. The highest systemic exposure was achieved in the 350mg/d EM group. CYP2C19 PM subjects showed about 2.2 to 2.3-fold higher maximum plasma concentrations and 4.1 to 5.0-fold higher total plasma exposure compared to EM subjects. Terminal half-life ranged from 0.995h to 2.71h across dose groups and was similar in PM subjects when compared to EM subjects receiving higher doses.
Conclusion: There were no notable safety findings and no indication of a safety risk for the subjects who participated in this trial. BI 409306 was rapidly absorbed and eliminated, with systemic exposure being higher in PM compared to EM subjects at the same dose level. Overall, good to satisfactory safety and tolerability was observed in EM and PM healthy male subjects.
ID: 2096699

DESCRIPTION AND IMPLEMENTATION OF THE RAISE-ETP STUDY PSYCHOSOCIAL TREATMENT MODEL: THE NAVIGATE PROGRAM

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Background: The NAVIGATE program was developed in response to an NIMH mandate to evaluate a program for first episode psychosis that could be delivered in non-academic community treatment systems in the U.S. and paid for by existing reimbursement mechanisms.
Methods: NAVIGATE was developed following a review of other comprehensive first episode treatment program, and is a multidisciplinary program typically staffed by five members who work collaboratively with each other,

the client, and family. Four core services are provided in NAVIGATE, including: the Family Program (aimed at developing a collaborative relationship with family members, providing information about psychosis and treatment, and harnessing support for the client), Individual Resiliency Training (an individual psychotherapeutic approach aimed at enhancing clients' wellness and personal resiliency, providing information about psychosis and its treatment, improving illness self-management, and facilitating progress towards social and health goals), Supported Employment and Education (aimed at helping clients identify or develop personally meaningful goals related to education or competitive employment, and pursuing those goals), and individualized pharmacological treatment. Standardized training, consultation, and fidelity assessment methods were developed and implemented for the three psychosocial components of the program and the overall program at the 17 sites randomized to NAVIGATE.
Results: Fidelity assessments indicated that the core psychosocial components of the NAVIGATE program could be successfully implemented at the 17 participating sites. Information about the implementation and fidelity to the specific psychosocial treatment components will be presented.
Conclusion: The newly developed comprehensive treatment program for first episode psychosis, the NAVIGATE program, was feasible to implement in non-academic community mental health care settings that provide routine services to a range of persons with serious mental illness. The results suggest that the NAVIGATE program has potential for wider dissemination in similar community-based treatment settings in the U.S.
ID: 2092176

STIMULATING LEARNING: A PILOT STUDY OF TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) AND COGNITION IN SCHIZOPHRENIA

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Background: Cognitive dysfunction (CD) in schizophrenia is largely unresponsive to conventional antipsychotic treatment and is responsible for a large part of the functional problems that patients experience in daily life. CDs are recognised to be primarily associated with the frontal cortex of the human brain, and modulating activity in this brain region forms the basis of different interventional approaches. transcranial direct current stimulation (tDCS) has consistently shown to improve performance on a range of cognitive tasks in both healthy, and in preliminary studies in clinical populations. The aim of the study is investigate the acute and medium-term effects of tDCS on a working memory task performance in schizophrenia.
Methods: Following baseline assessment, 47 right-handed schizophrenia patients (SZP) on stable doses of anti-psychotic medication, were randomized into sham or real tDCS stimulation group. The study comprised 4 days of cognitive testing (Day 1, 2, 14 and 56). At each testing day, two training sessions were conducted, which included the n-back working memory task. tDCS was applied to the dorsolateral prefrontal cortex for 30 minutes at 2mA at session 2- day 1 and session 2 day 14.
N-back task performance was calculated as d'= Z (hit rate) - Z (false alarm rate) for the 2 and 3-back only. Multilevel regressions (MLR) were applied to analyse the data. The MLR included the d' measures from five assessments, the baseline, acute stimulation (day 1-session 1 and day-14 session 6) and follow-ups, day- 2 (session 2) and day-56 (session 7).
Results: There were no significant difference between groups at baseline (b=-.31; p=0.27) or during acute tDCS administration (b= .26; p= .33 day-1 session 1; b=.46 p=0.10 day-14 session 6). However a significantly better performance on the n-back was observed in real stimulation as compared to the sham stimulation at day- 2 session 2 (b=.67; p=0.014) and day-56 session 7(b=.71; p=0.011).
Conclusion: This is the first study to show beneficial effects of tDCS in schizophrenia. Contrary to our hypothesis we did not find significantly higher performance during acute stimulation. However, we found strong consolidations effects on performance, with schizophrenia individuals in real tDCS group showing significantly better performance the following day (session 2) and at the day 56 follow-up visit (session 7).
These preliminary findings provide a promising avenue for improving cognitive function in schizophrenia.
ID: 2091494

TRANSCRANIAL CURRENT STIMULATION FOR THE TREATMENT OF MEDICATION REFRACTORY AUDITORY HALLUCINATIONS

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Background: Auditory hallucinations (AH) are a hallmark of schizophrenia; with 30% of patients refractory to medications. Transcranial current stimulation (tCS) has shown promise for AH, and includes both transcranial direct current (tDCS) and transcranial random noise (tRNS) stimulation. Both involve applying weak electrical current (2mA or less) to the scalp resulting in cortical excitability. Brunelin et al (2012) utilized tDCS to reduce medication refractory AH while Vanneste et al (2013) applied tRNS to reduce the loudness and distress associated with tinnitus. Given the neurophysiological similarity of tinnitus and AH (Johns et al., 2002), our study examines the efficacy of tRNS in the treatment of medication refractory AH as compared to tDCS and sham.
Methods: This study is double-blind and sham-controlled including three arms (tRNS, tDCS, and sham). All subjects complete ten treatment sessions (2 sessions per day for 5 days) and 1, 3, 6, 9, and 12 month follow-up sessions. Assessments include Positive and Negative Symptoms Scale (PANSS) and Auditory Hallucinations Rating Scale (AHRS). The twice daily treatments are at least three hours apart. PANSS and AHRS are completed before the 1st treatment, after the last treatment, and at each follow-up.
Results: During a piloting phase, we treated three subjects with tDCS. Treatments were well tolerated. At 1 month subject 1 showed AHRS increases in frequency and salience but decreases in length and loudness (total score increase of 4) with a PANSS total decrease of 2. Subject 2 showed AHRS decreases in all domains (total score decrease of 18) and a PANSS total decrease of 26. Subject 3 has not been seen at 1 month follow-up but reported post treatment AHRS increases in length but decreases in loudness and number of voices (total score decrease of 2) and a PANSS total increase of 2.
Conclusion: Medication refractory AH are common and difficult to treat. Our data suggest that some subjects have a significant response to tDCS while others do not. This may be due to either baseline severity or nature of hallucinations. Additionally, specific sub-symptoms of AH may be more sensitive to tCS as can be seen by the reduction in loudness in all three subjects. As additional subjects are treated a statistical comparison will be be performed to determine whether these findings are statistically significant at a group level.
This work was supported by the Minnesota Veterans Medical Research and Education Foundation and a NARSAD Young Investigator Grant.
ID: 2119290

USING A MOBILE HEALTH APPLICATION TO MONITOR CLINICAL SYMPTOMS AND SIGNS OF RELAPSE IN EARLY PSYCHOSIS

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Background: The early stages of psychotic illness are a critical period for intervention. Mobile health applications offer ecologically valid, data-rich methods of monitoring patients' daily symptoms and functioning, which could alert clinicians to early signs of relapse and facilitate early intervention. We tested a smartphone application that gathers active survey and passive movement/communication data in an outpatient early psychosis (EP) program.
Methods: Early psychosis participants (N=45), ages 14-30, were enrolled from the UC Davis Early Psychosis Programs. Mobile data includes: daily surveys assessing mood, medication adherence, and social contact; weekly surveys assessing basic symptoms; and passive data (number of calls/texts, distance travelled). Repeated models analysis examined longitudinal relationships between mobile data and monthly gold-standard assessments of symptoms (BPRS) and psychosocial functioning (GFR/GFS).
Results: Eighty-six percent of recruited participants were retained in the study over a minimum of 3 months with 76% survey completion. Preliminary data (N=39) indicates associations between weekly surveys and BPRS symptoms (all Ps<0.05): Higher self-reported positive and negative symptoms related to higher BPRS positive and negative symptom scores, and higher self-reported depression and anxiety related to higher BPRS depression/anxiety scores. Additionally, increased self-reported depression, anxiety, visual illusions, impaired tolerance to stress, as well as fewer hours of sleep per night predicted increased BPRS positive symptoms scores one week later.
Conclusion: Results indicate 1) collecting patient-generated data via smartphone device is feasible, 2) patient-generated data closely reflect clinician-rated gold-standard assessments, and 3) weekly assessment of symptoms known to be predictive of relapse may improve early identification of relapse and facilitate early intervention in EP.
ID: 2117007

COMBINING TDCS AND WORKING MEMORY FOCUSED COGNITIVE REMEDIATION: A PROOF OF PRINCIPLE STUDY

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Background: Transcranial direct current stimulation (tDCS) is a non-invasive form of brain stimulation that modulates cortical excitability, and thus, may facilitate learning. The aim of this proof of principle study was to examine the pairing of tDCS with cognitive training in a sample of outpatients with schizophrenia to explore whether this combination enhanced learning. Feasibility and tolerability of repeated, paired administration of these neuromodulation techniques will also be assessed.
Methods: A randomized, sham-controlled design was used to assign participants to a working memory focused cognitive training with either tDCS or sham. Training consisted of 48 1-hour sessions in which participants completed adaptive, computer-based tasks that targeted attention and working memory processes. Beginning in the third week, computer training was augmented with 20 minutes of stimulation (1 mA tDCS/sham) twice a week. Learning was assessed with performance on trained (N-back) and untrained tasks (MATRICS Consensus Cognitive Battery Working Memory and Attention tests). Tolerability was assessed with participant ratings of their physical and emotional experience immediately after and 30 minutes post either tDCS or sham stimulation. Feasibility was assessed with study attendance and attrition.
Results: Of the 15 patients randomized to a condition, 10 (4 sham, 6 tDCS) completed all study procedures. Among the 5 participants who failed to complete the protocol, reasons for withdrawal were unrelated to tDCS stimulation. Participant ratings of emotional and physical distress immediately after and 30 minutes post tDCS or sham stimulation were consistently in the mild range. Between group comparisons will be conducted to determine if recipients of tDCS experienced significantly more distress than those receiving sham stimulation. Between and within-group analyses will be conducted to explore whether cognitive performance is enhanced by tDCS. Results will be reported in terms of effect size.
Conclusion: Results of this study will provide preliminary data regarding the incremental benefit of pairing tDCS with cognitive training as well as the feasibility and tolerability of applying this approach for cognitive rehabilitation purposes with patients with schizophrenia.
ID: 2097197

CLOZAPINE RESPONSE - A NATURALISTIC STUDY OVER 17 YEARS

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Background: In most treatment settings, clozapine continues to be underutilized in patients with schizophrenia who have an inadequate response to other antipsychotic drugs (APDs). The requirement for hematological monitoring presents one barrier to starting clozapine. In addition, a significant number of patients who start on clozapine discontinue it. Many studies, including our own (Davis et al, 2014) suggest that side effects rather than poor efficacy may be the dominant reason for discontinuation. To confirm this, we examined the clozapine response in patients who discontinue and in those who maintain the medication.
Methods: This was an IRB-approved retrospective analysis of data from a clozapine clinic in a Department of Veterans Affairs (DVA) setting. Clinical psychiatrists conducted baseline and follow up assessments using the BPRS. We identified patients on the computerized record system with an ICD diagnostic code of 295 who had been issued clozapine prescriptions for at least 4 weeks. Notes were downloaded and BRPS data extracted. We modeled the temporal trajectory of patients' total BPRS score using linear, locally weighted, and hierarchical regression. All calculations were performed in the R statistical programming language.
Results: A total of 382 patients (90.5% male, 63% service connected) were treated with clozapine for at least 4 weeks. The mean age at the time of clozapine initiation was 49 years (standard deviation 10.3 years). We were able to extract BPRS evaluations for 341 (89%) of these patients. The analysis showed that while the reduction in overall BPRS was already evident at 4 weeks, the pattern of decline continued throughout the initial 6 months, and improvement was maintained for the duration of treatment. Early discontinuers (<1 year) showed similar levels in improvement as late discontinuers (>3 years).
Conclusion: Retrospective, observational data indicate that clozapine-induced improvements generally develop over the initial 6 months and are evident in those who later discontinue clozapine. This underlines the need to identify and mitigate factors driving clozapine discontinuation.
ID: 2115549

ANTIPSYCHOTIC PLASMA CONCENTRATION THERAPEUTIC DRUG MONITORING: A FEASIBILITY STUDY FOR OLANZAPINE AND RISPERIDONE

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Background: Therapeutic drug monitoring (TDM), which examines drug plasma concentrations, is a potentially useful objective tool to aid in the optimisation of antipsychotic prescribing. This study aimed to develop and test a clinically acceptable method for olanzapine and risperidone TDM.
Methods: A non-randomised feasibility study recruiting inpatients from 5 Mental Health Trusts in South-East England was conducted. The intervention comprised: (i) a blood sample taken 12 hours post dose for TDM analysis, 7-14 days after initial drug initiation; (ii) rapid feedback of TDM results to clinicians accompanied by a newly developed algorithm offering interpretation and advice for individual patient antipsychotic dose management. The algorithm was based on target ranges and the time to steady state (olanzapine 20-40ng/mL, 7 days; risperidone 20-60ng/mL, 5 days). A baseline assessment and 6-week follow-up review of clinical notes was conducted to ascertain change in total daily dose of the target drug and to evaluate the TDM process.
Results: Of the 22 consenting participants on olanzapine 19 provided a blood sample, for whom 17 TDM results were made available by the lab, and only 14 remained on olanzapine at study end. Of the 13 consenting participants on risperidone, all provided a blood sample, for whom only 12 TDM results were made available by the lab and only 9 remained on risperidone at the end of the study. There was a mean increase in olanzapine dose of 0.9mg/day (S.D. 2.7, range 0-10) and a mean decrease in risperidone dose of -0.3mg/day (S.D. 2.0, range -4-3). However, only seven (24.1%) participants experienced a dose change, of which only four (13.8%) of the TDM results were confirmed as having been checked by the clinician. Trough level sampling was achieved for all participants for whom data was available, whereas steady state was only achieved for 25/32 (78.1%) participants. Of the 29 TDM results, 16 (55.2%) were reported on within three working days.
Conclusion: TDM can be feasibly implemented as part of routine clinical practice for olanzapine and risperidone. However, the lack of robust supporting evidence for or against antipsychotic TDM has probably led to lack of enthusiasm for and interest in the results. Nevertheless, the advent of less invasive measures and the targeting of patients, who might be more likely to benefit, may facilitate uptake.
ID: 2084491

INDIVIDUAL RESILIENCY TRAINING (IRT) IN NAVIGATE: TRAINING, SUPERVISION, AND FIDELITY ASSESSMENT TO SUPPORT IMPLEMENTATION

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Background: Individualized Resiliency Training (IRT) is a modular, cognitive-behaviorally-based individual intervention for persons recovering from a first episode of psychosis. Its primary aims are to promote recovery by identifying client strengths and resiliency factors, enhance illness self-management and symptom coping, teach skills to facilitate functional recovery, and to help persons achieve and maintain personal goals and wellness. IRT is composed of seven standard modules, as well as seven (optional) individualized modules. The implementation and dissemination of IRT included a comprehensive plan to ensure fidelity and high quality service delivery. In this symposium, we will provide an overview of the IRT implementation plan including a model for training, consultation, and individual clinician fidelity monitoring for the standard and the individualized modules.
Methods: We will review the coordination of training across the sites and the measures to assess competency and complete the certification process.
Results: Data are currently being analyzed on treatment fidelity. Data will be presented on the qualifications of the IRT clinicians trained, fidelity monitoring, and IRT certification.
Conclusion: IRT can be implemented in a large, multi-site study.
ID: 2140924

ECT AUGMENTATION IN CLOZAPINE-RESISTANT SCHIZOPHRENIA: ACUTE EFFICACY AND MAINTANCE DATA

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Background: Clozapine is indicated for the treatment of medication-resistant schizophrenia. Nonetheless, up to 70% of patients do not or partially respond to it. Historically, response to clozapine is defined as 20 or 30% reduction in the 4 psychosis items (delusions, hallucinations, disorganization and paranoia) in the Brief Psychiatric Rating Scale (BPRS). In a randomized, controlled, single blind, NIMH-sponsored study we evaluated the efficacy of electroconvulsive therapy (ECT) as an augmentation strategy for the treatment of clozapine-resistant schizophrenia.
Methods: Patients with schizophrenia receiving clozapine with persistent psychotic symptoms (> 12 in the BPRS psychosis subscale (PSS) were included. Patients were randomized to receive 8 weeks of ECT plus clozapine or to continue with clozapine treatment for 8 weeks. Patients in the pharmacotherapy arm, who did not respond after 8 weeks, crossed over to ECT and received the combination treatment for another 8 weeks.. Patients who had 40% reduction in PSS were offered a 6 month period of maintenance ECT with a tapered schedulle of 4 weekly treatments followed by 4 treatments every 2 weeks and monthly treatments for 3 months.
Results: Twenty patients were randomized to receive ECT+clozapine and 19 to continue clozapine pharmacotherapy. The mean age was 39.3 (sd+9.6). The mean BPRS was 46.0 (sd+9.6) and the PSS was 16.5 (sd+3.7). There were no significant differences between groups in race, sex, BPRS scores, and clozapine levels at baseline. Defining response as 20% reduction of the PSS, there were no responders in the pharmacotherapy group, compared to 12 of 20 (60%, $p < 0.001$) in the ECT group. If we define response as 40% reduction, there were no responders in the pharmacotherapy group, compared to 10 of 20 (50%, $p < 0.001$) in the ECT+clozapine group. In the open cross-over phase there were 14 of 19 (73. 3%) responders to ECT+clozapine when response was defined as 20% reduction as the criterion and 9 of 19 (47%) when 40% was used. Fourteen patients were included in the 6-month maintenance phase. Nine of them (64.3%) completed the study and did not relapse. Five patients discontinued the study before the completion of the six months. The combination of ECT and clozapine was well tolerated and no unusual side effects were observed.
Conclusion: These data suggest that the combination of clozapine and ECT is an effective treatment for patients with clozapine-resistant schizophrenia. Maintenance ECT seems to be protective against relapse.
ID: 2091697

PERIPHERAL BDNF LEVELS AND RELAPSE IN SCHIZOPHRENIA

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Background: Understanding the factors that could underlie why patients relapse is an issue of fundamental importance to the treatment of schizophrenia. Moreover, accumulating evidence suggest that impairments in neurodevelopmental processes as a result of genetic and environmental insults lead to the development of schizophrenia pathophysiology. Brain derived neurotrophic factor (BDNF) plays an important role in neurodevelopment and adult brain plasticity. A number of studies including reports our group have shown decrease in peripheral BDNF levels in subjects with schizophrenia. However, it is still unclear whether peripheral BDNF levels contribute to relapse in schizophrenia. In the PROACTIVE study, we tested the hypothesis that a decrease in plasma BDNF levels predicts relapse in schizophrenia.
Methods: Serial plasma BDNF levels were performed on the PROACTIVE sample of three hundred and five patients who are being evaluated for up to 30 months. BDNF levels were measured in the samples collected from all the 8 PROACTIVE sites (a total of 2300 samples) by ELISA.
Results: We obtained BDNF values for 226 of the 305 patients in the study. In addition, 103 subjects had true baseline data, and there were a total of 184 relapses identified from 94 individuals. Our preliminary analysis showed that 58 of 181 patients (32%) had one or more hospitalizations. In addition, lower BDNF was associated with higher risk of hospitalization.
Conclusion: The initial analysis on BDNF and its association with relapse and hospitalizations indicates that peripheral BDNF level could be a potential predictor for relapse in schizophrenia. Since the PROACTIVE data set has a large number of cases with serial blood samples, data analysis and comparison with clinical parameters from the PROACTIVE data set provides the more inclusive a-priori definition of relapse. Such information would be helpful for the long term treatment management of schizophrenia.
ID: 2089073

SCREENING FOR SNARE (SOLUBLE NSF ATTACHMENT PROTEIN RECEPTOR) INHIBITORS AS POTENTIAL DRUGS FOR SCHIZOPHRENIA TREATMENT

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Background: The SNARE complex (syntaxin-SNAP25-VAMP) fuels neurotransmitter release at presynaptic terminals. Converging evidence from clinical and preclinical studies indicates that schizophrenia is associated with aberrant SNARE activity [1,2]. Disrupting the SNARE complex could help treat schizophrenia. Here, we screened for SNARE inhibitors, and further addressed their effect in postmortem brain homogenates from subjects with and without schizophrenia.
Methods: An immunoassay-derived method [1] quantifying syntaxin-SNAP25 interaction in rat cortical lysates was automated for high throughput screening of compounds across 5 different libraries (N=137,028 compounds). Those able to inhibit SNARE formation ≥20%, and meeting dose response criteria, were selected for follow up studies. Postmortem prefrontal cortices (PFC; BA10/47) from 20 schizophrenia and 13 control subjects were collected at the Macedonian/New York State Psychiatric Institute Brain Collection.
Results: The screening study obtained an overall assay Z-factor of 0.78 ± 0.08, supporting the reliability of the screening strategy. Up to 167 compounds were found to inhibit at least 20% of syntaxin-SNAP25 interactions. Only 41 hits met the concentration response requirement in the immunoassay, with IC50 ranging 0.4-228 μM. The best 6 compounds were tested by standard and Far Western blotting assays. Four strongly reduced (65-96%) the immunodensity of the SNARE complex in both immunoblotting techniques. One compound was selected to address SNARE disruption in the PFC of schizophrenia and control subjects. Basal syntaxin-SNAP25 interaction was higher in schizophrenia PFC (24%, p=0.0149). Concentrations of 10 and 100 μM significantly reduced the amount of SNARE interactions in all groups (19-22% and 30-42%, respectively, p<0.0001), although SNARE associations in schizophrenia samples were more resistant to disruption (p=0.0010).
Conclusion: Several compounds have been identified as SNARE inhibitors in rat and human brain lysates. SNARE protein-protein interactions are more abundant and more resistant to chemical disruption in schizophrenia PFC. Future in vivo studies may proof the efficacy of these compounds in the pharmacological management of schizophrenia.
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[1] Barakauskas et al. Neuropsychopharmacology (2010) 35, 1226-1238.
[2] Ramos-Miguel et al., Biol Psychiat. (under review)
[3] Honer et al., Transl Psychiat. (2012) 2, e114.
ID: 2085015

UNDERSTANDING FUNCTIONAL ACTIVATION AND CONNECTIVITY FOLLOWING COGNITIVE REMEDIATION TRAINING IN SCHIZOPHRENIA

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Background: Cognitive remediation training (CRT) for schizophrenia has been shown to improve cognitive and psychosocial functioning, but much is not understood about the neurobiology associated with this intervention. Previous studies have shown that improvements from CRT are associated with changes in prefrontal activation and functional connectivity. However, no study has examined these changes in the same sample. The current study aimed to clarify the neural mechanisms supporting CRT by examining functional activation and connectivity in patients who underwent CRT or a placebo training. We hypothesized that CRT would influence activation in the lateral prefrontal cortex (PFC), and connectivity in the default mode and fronto-parietal networks.
Methods: 26 patients were randomized to undergo either 48 hours of a working memory focused CRT (N=14) or 48 hours of a computer skills training control condition (N=12). Training was conducted at the Minneapolis VA, and was matched for exposure to computers, clinician contact, and intrinsically motivating content. Before and after treatment, patients completed a fMRI scan and cognitive testing. The present analyses focused on a picture 2-back task, and were conducted blind to group status. Changes in functional activation and connectivity were compared between groups at Time 2 versus Time 1 using a GLM and independent components analysis (ICA) respectively. GLM analyses were limited to voxels in the PFC, while ICA examined the default mode network (DMN) and fronto-parietal executive network.
Results: Behavioral findings showed increased 2-back accuracy for the CRT group but not the placebo group. Imaging findings demonstrated neural changes in a group by time interaction for both activation measured in a GLM and connectivity measured by ICA. Changes in functional activation were observed in the left PFC, while connectivity changes were demonstrated in both hypothesized networks. Changes in functional activation in the CRT group correlated with changes in d' scores on the task.
Conclusion: These findings demonstrate that CRT influences both functional activation and connectivity. Further analyses will be required to understand how neural measures relate to cognitive and psychosocial improvements in patients with schizophrenia. Results also support recent meta-analytic findings that show that across modalities, CRT for schizophrenia influences

neural activity in target areas previously shown to be associated with cognitive and socio-emotional dysfunction.
ID: 2088123

ATTENUATION OF KETAMINE-INDUCED IMPAIRMENT IN VERBAL LEARNING AND MEMORY IN HEALTHY VOLUNTEERS BY AN AMPA RECEPTOR POTENTIATOR

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Background: Current treatments fail to address cognitive impairments associated with schizophrenia (CIAS). N-methy-D-aspartate receptor (NMDAR) hypofunction may contribute to the pathophysiology of CIAS. Stimulation of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) may ameliorate NMDAR hypofunction and target CIAS. The AMPAR positive allosteric modulator PF-04958242 attenuated ketamine-induced deficits in a rat spatial working memory (SWM) task and a spatial delayed response task in nonhuman primates. This study aimed to assess whether PF-04958242 would attenuate ketamine-induced impairment in verbal learning, working memory, SWM and psychotomimetic effects in healthy humans.
Methods: 29 healthy men participated in this randomized, 2 period, double-blind, placebo-controlled, crossover study. During each period subjects received placebo or active PF-04958242 (0.35 mg on day 1 followed by 0.25 mg/day on day 2-5). They then underwent a ketamine challenge (racemic ketamine 0.23 mg/kg bolus over one min; and 0.58 mg/kg/hour for ~ 70 min) followed by assessment of cognitive (Hopkins Verbal Learning Test-Revised (HVLT-R), N-back and SWM tasks from Cogstate) and psychotomimetic effects (Positive and Negative Syndrome Scale (PANSS) and the Clinician Administered Dissociative Symptom Scale (CADSS)). The primary efficacy endpoint, mean score of immediate recall trials 2 and 3 in HVLT R on Day 5 (HVLT-R-IR2-3), was analyzed in completers (n=22) with a linear crossover model including period, sequence, and treatment as fixed factors, baseline score as a continuous covariate, and subject as a random effect.
Results: Ketamine resulted in a mean impairment of 2.96 words on the HVLT-R-IR2-3 and induced transient psychotomimetic effects. Treatment with PF-04958242 demonstrated a statistically significant attenuation of ketamine-induced cognitive impairment, resulting in placebo-adjusted mean reduction in ketamine-induced impairment of 0.58 words on HVLT-R-IR2-3 with a 2-sided 90% confidence interval (CI) of (0.04, 1.12) words. Further, PF-04958242 attenuated ketamine-induced impairment on the 2-back and SWM tasks. PF-04958242 had no effect on ketamine-induced PANSS or CADSS scores.
Conclusion: Treatment with PF-04958242 for 5 days significantly attenuated the ketamine-induced cognitive impairment in verbal learning and working memory, suggesting clinical translation of the findings with PF-04958242 in pre-clinical models of NMDAR deficit mediated cognitive disruption.
ID: 2119119

OVERVIEW OF RECENT FAILURES IN SCHIZOPHRENIA CLINICAL TRIALS - A DRUG INDUSTRY PERSPECTIVE

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Background: Over the past few years, several drugs with novel mechanisms-of-action have not achieved their primary end-points in clinical trials in schizophrenic patients. This talk will review the outcome of these failed trials, and the preclinical studies used to support them, and describe the potential impact of these results on future drug development for schizophrenia.
Methods: Publicly available information was gathered on the results of clinical trials in schizophrenia and the preclinical studies used to support them.
Results: Drugs with a variety of novel mechanisms-of-action (e.g., PDE10 inhibition, mGlu2/3 agonist activity, GlyT1 inhibition, α7-nicotinic agonist activity) failed to reach their primary efficacy measures in placebo-controlled, double-blind trials in schizophrenic patients. Overlapping yet distinct preclinical data packages supported these trials. The predictive validity of the preclinical data must be reevaluated in the context of our increasing knowledge of the pathophysiology of schizophrenia and the limits of our knowledge of central target engagement. The results of these clinical trials will help us modify our preclinical assays, selection of novel targets, and future clinical trials for schizophrenia.
Conclusion: When examined in the context of a changing internal and external environment, the inability of potential novel treatments to demonstrate efficacy in schizophrenic patients will force dramatic changes to the way future research (both preclinical and clinical) is conducted in the pursuit of improved treatments for schizophrenia.
ID: 2090173

SUBTYPING SCHIZOPHRENIA BY TREATMENT RESPONSE: REFINING CRITERIA

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Background: We have recently proposed that subtyping schizophrenia based on treatment response represents an ecologically valid means of differentiating at least three forms of the illness (Antipsychotic Responsive; Clozapine Responsive; Clozapine Resistant). Using such a strategy as a framework, we can then employ a multi-faceted approach (genetic, imaging, neurochemical, electrophysiological, clinical) in examining similarities and differences between groups.
Methods: Data extracted from our own studies, as well as others, are examined, with a specific focus on current evidence, practice patterns, and response across different measures of outcome.
Results: A review of evidence suggests criteria for subtyping can be further refined, with recommendations including: 1) removal of illness duration and reference to functioning; 2) focus on positive symptoms. In addition, we propose simplification of response threshold criteria and the underlying rationale. How this approach aligns with other strategies for subtyping schizophrenia will be addressed.
Conclusion: Schizophrenia is now routinely referred to as heterogeneous, but to date the field has struggled in distinguishing variants. Subtyping by clinical response provides a means of pursuing this notion further, and in this context we suggest refining criteria to a) align with current evidence, and b) permit a strategy that can be embraced by both clinicians and researchers. The approach is not without its challenges and these will also be outlined.
ID: 2093967

TREATING FIRST EPISODE PSYCHOSIS WITHIN A TRANSITIONAL CARE CLINIC

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Background: Early intervention in psychosis may minimize disease-related functional disability. Because of this, First Episode Psychosis (FEP) programs are being developed to engage and treat individuals early in the illness course. The NIMH-funded RAISE Initiative has established recommendations for key components of early psychosis programs, including identification of individuals early in their illness, engagement of these individuals in treatment, and age- and phase-specific treatment of psychosis. Transitional Care Clinics (TCCs) use intensive engagement to decrease psychiatric recidivism for individuals being discharged from psychiatric inpatient or emergency services. Data from our TCC in San Antonio, Texas indicate that the TCC has decreased hospital recidivism from approximately 13% to 9% in patients it has treated. Although not focused on FEP, approximately 6% of our TCC patients meet criteria for FEP. Given the age- and phase-specific needs of FEP patients, and the challenges of engaging FEP patients in care, we hypothesized that FEP patients at our TCC would exhibit poorer treatment engagement and higher hospital recidivism rates than non-FEP patients referred to the TCC. A secondary goal of this study was to examine predictors of treatment engagement among FEP patients.
Methods: We used a chart-review methodology. Charts of 60 FEP patients and 60 non-FEP patients were coded by two independent raters, blind to study hypotheses, using a structured review rubric. Treatment engagement was operationalized in terms of attendance at scheduled TCC appointments (with prescribers, social workers, psychotherapists, and/or in-home mental health providers). Based on the literature and available data, predictor variables included family involvement in care and comorbid drug use.
Results: Initial data analyses provide preliminary support for the study hypothesis. Compared to non FEP-patients, FEP patients showed poorer treatment engagement on some, but not all measures of engagement.
Conclusion: Post-acute transitional psychiatric treatment provides an opportunity to engage FEP patients in care, but, as with typical FEP programs, it may be necessary to integrate age- and phase-specific interventions within transitional services.
ID: 2118584

REMEDIATION OF SOCIAL COGNITIVE BIAS IN SCHIZOPHRENIA

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Background: A growing literature shows that it may be possible to improve social functioning in schizophrenia by way of social cognitive training. The bulk of this research emphasizes remediation of social cognitive deficits. Less attention has been played to decreasing social cognitive biases that negatively effect social functioning, including hostile attributional bias, self-referential bias, and jumping-to-conclusions bias. Those interventions that do target bias typically use face-to-face in-person training. The current project describes initial testing of an intervention designed to decrease social cognitive bias in schizophrenia via in-home iPad-based training.
Methods: Following research on debiasing in social psychology, we developed a 30-day intervention that first activates biases by increasing self-relevant processing, and then increases awareness of, and control over biases. In a proof-of-of concept trial, 26 individuals with schizophrenia completed either a bias-activation or non bias-activation version of the training. Based on this trial, we added a debiasing component to the intervention. In a subsequent blinded, randomized, controlled trial (RCT), 36 patients received either 24 sessions of 15-minute in-home debiasing training or an equal amount of a computer game control intervention. Telephone support was provided to maximize adherence and to support engagement in the debiasing intervention. Outcomes were assessed in terms of feasibility and performance on measures of social cognitive capacity and bias.
Results: The proof-of-concept trial showed statistically significant increases across all bias domains among patients receiving bias engagement versus those who did not. RCT results showed good feasibility and modest but promising effects on social cognition in the treatment versus control conditions.
Conclusion: These initial findings indicate that in-home iPad-based training can be used to engage and decrease social cognitive biases in schizophrenia. More work is needed to strengthen the intervention's ability to increase patients' awareness of their own biases and to dampen the effect of these biases on social cognitive responding.
ID: 2118428

ASSISTING PRESCRIBERS' EFFORTS WITHIN THE RAISE-ETP STUDY TO OPTIMIZE PHARMACOTHERAPY FOR FIRST EPISODE SCHIZOPHRENIA

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Background: Most prescribers see few patients with first episode schizophrenia and few community clinicians have the time to keep abreast of research findings about the specialized treatment needs of this patient subgroup. Compared with medication treatment for multi-episode patients, the suggested sequence and optimal dosing of medications differs for first episode patients. Core requirements for NAVIGATE medication treatment were that it 1) incorporated research findings about the specialized medication approaches needed for patients with early phase schizophrenia-spectrum disorders and 2) be tailored to individual needs and preferences.
Methods: A panel of experts reviewed the literature and existing treatment guidelines and developed suggested NAVIGATE guidelines for medication selection, dosing and side effect management. NAVIGATE medication treatment was guided by COMPASS, a computer clinical decision-making tool using a measurement-based care approach that was developed for NAVIGATE and was available to NAVIGATE prescribers and patients on a secure website. COMPASS facilitated patient-prescriber communication through direct patient input of information about symptoms, side effects, treatment preferences and other issues into the system. These data then guided prescribers in their sessions with patients. COMPASS also provided guidance about evidence-based medication strategies that informed patient - prescriber decision making about medication treatment.
Results: COMPASS-guided treatment was successfully employed at all 17 NAVIGATE sites. During the course of the study, patients completed 3939 self assessments. Over time, patients reported significant reductions in symptoms (e.g. depression and anxiety), side effects (e.g. sedation) and functional difficulties and less need to change their medication regimes. Attitudes to medications changed significantly in several areas: patients reported having less trouble taking medications and more assessment that they had an illness needing medication treatment. There were no significant changes over time in fears about the medications or the belief that people who take medications are stigmatized by society.
Conclusion: Our data suggest that use of computer decision support systems for the treatment of early phase schizophrenia is feasible at community treatment facilities. These systems offer the possibility of patients at community centers receiving treatment guided by the most current research findings and guidelines.
ID: 2117823

A RANDOMIZED DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL OF PREGNENOLONE FOR NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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Background: Pregnenolone is a neurosteroid found in high concentrations in the brain. Several small proof-of-concept studies have indicated the potential beneficial effects of pregnenolone, particularly fornegative symptoms. This study further investigated the use of pregnenolone as augmentation of antipsychotic medication in patients with schizophrenia.
Methods: Following 2 weeks of single-blind placebo lead-in, 100 patients with schizophrenia or schizoaffective disorder with negative symptoms on stable antipsychotic treatment were randomized 2:1 to oral pregnenolone or placebo. Subjects receiving pregnenolone were titrated over 5 weeks from 100 mg/d to 500 mg/d, and maintained on medication for 14 weeks. Symptom assessments occurred every 4 weeks with cognition measured at baseline, 8 weeks, and end of study utilizing the IntegNeuro battery. Safety measures included adverse events, vital signs, and clinical labs. The primary outcome was negative symptoms as assessed by the SANS and the PANSS negative symptom subscale with a mixed effects models for repeated measures (MMRM) analysis.
Results: With pregnenolone treatment, mean PANSS negative symptom subscale was significantly lower compared to placebo (17.2 vs. 19.5, P=0.047) at week 12 as assessed by MMRM. This statistically significant difference was not maintained at week 16. An ANCOVA model which included baseline value showed similar benefit of pregnenolone at week 16 (16.5 vs. 18.7, P=0.0498). The SANS total score did not show a difference between treatment groups at any time point in either model. Significantly more subjects on pregnenolone showed a 20% or greater improvement from baseline to week 16 on the PANSS negative symptoms subscale than placebo subjects (Chi-square test, P=0.0012); there was trend toward significance in this analysis for the SANS total score. The benefit of pregnenolone demonstrated a medium effect size (0.37-0.42). There was no change in positive, anxiety, or depressive symptoms. Pregnenolone was well tolerated with a higher completion rate than placebo. Adverse events were no higher for any body system category for pregnenolone than for placebo. There was no clinically significant change in weight, movement disorder rating scales, or clinical laboratory values.
Conclusion: This study showed in some but not all analyses that pregnenolone has benefit for negative symptoms of schizophrenia. These results need to be further studied in larger, controlled clinical trials.
ID: 2096230

PRIME: A NEUROSCIENCE-INFORMED MOBILE APP INTERVENTION TO TREAT REWARD PROCESSING IMPAIRMENTS AND IMPROVE QUALITY OF LIFE IN RECENT ONSET SCHIZOPHRENIA

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Background: Recent data suggests that negative symptoms, and amotivation in particular, are the single most important factor affecting functional disability in schizophrenia and undermining quality of life. This presentation will focus on a novel approach to treating reward processing deficits using a newly developed Personalized Real-time Intervention for Motivational Enhancement (PRIME), a mobile app for young people with schizophrenia. PRIME promotes reward anticipation and drive, and encourages enhanced-motivated behavior across social, work/school, and health domains.
Methods: Forty participants with recent-onset schizophrenia (RO; ages 16-30, within 5 years of diagnosis) will be randomly assigned to receive either PRIME or Treatment As Usual/Wait-list. Participants will complete a series of clinical assessments and a laboratory-based reward-learning task at the pre and post-treatment assessment. In addition, we will recruit an age-matched healthy comparison group to investigate the extent to which PRIME-related improvements improve functioning to levels of people without schizophrenia.
Results: We will present the results from the first 20 participants with pre and post treatment data, as well as the results from group and individual interviews conducted with users during the design phase of the study. Preliminary results demonstrate that after 3-months of using PRIME, participants experienced improved global functioning ($t = -4.11$, $p < .05$), enhanced behavioral drive ($t = 5.00$, $p = .10$), and less severe negative symptoms (4.00, $p < .05$).
Conclusion: To the best of our knowledge, this is the first study to demonstrate the benefit of a translational intervention targeting motivational deficits to improve negative symptoms in young people with schizophrenia.
ID: 2119338

THE RAISE-ETP STUDY DESIGN, RESEARCH AND IMPLEMENTATION MODEL

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Background: The National Institute of Mental Health (NIMH) mandate to evaluate an integrated intervention for the treatment of first-episode psychosis (FEP) that could be delivered in non-academic community treatment settings in the United States drove the design and conduct of the RAISE-ETP study.
Methods: Thirty- four sites in 21 states were selected that did not have formal FEP programs but were willing to create such a program and to provide team-based care. Sites, rather than individual patients, were randomly assigned to provide either the integrated treatment (NAVIGATE) or usual care (Community Care). Training was provided to all sites regarding recruitment, engagement and retention of FEP clients, as well as research procedures. NAVIGATE site intervention teams received further initial training and ongoing supervision/consultation in providing treatment. Treatment and follow-up assessment continued for at least two years following study entry. Because the study was conducted at sites without trained clinical research assessors, clinical assessments were completed by centralized clinical assessors using live two-way video. Assessors were masked to site and study design. The primary outcome measure is change in the Heinrichs Carpenter Quality of Life Scale. Secondary outcomes include symptomatology assessed by the Positive and Negative Syndrome Scale and the Calgary Depression Rating Scale and service use to assess cost.
Results: All sites invited to participate agreed to their random assignment after learning it. Four hundred four clients entered the RAISE-ETP protocol. At enrollment, all participated in the live two-way video assessment.
Conclusion: Site randomization had the advantages of limiting training of intervention teams to half of the sites and avoiding the risk that a novel intervention will influence treatment of those not assigned to it. No sites refused participation after learning of their assignment. Further, participants did not have to agree to random treatment allocation. Use of live video assessment by centralized raters allowed conduct of the study at community sites without trained clinical assessors and insured that assessments

were masked to treatment condition. The RAISE-ETP study demonstrates that rigorous research can be conducted in the context of community treatment facilities in the United State.
ID: 2089463

RISPERIDONE LONG-ACTING INJECTION VS. ORAL RISPERIDONE: ANALYSIS OF RELAPSE AND REHOSPITALIZATION CONTROLLING FOR SWITCHING IN A PRAGMATIC TRIAL

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Background: There were no significant differences in relapse or hospitalization between long-acting injectable (LAI) risperidone(RIS) and oral second generation antipsychotics(SGA) in the PROACTIVE study, consistent with other studies. Randomization to LAI-RIS could entail both change in route of administration and antipsychotic. For those already receiving oral RIS, randomization entailed only change in route of administration. Study of this subgroup provides a more precise test of the hypothesis that the LAI route of administration reduces risk of relapse.
Methods: 305 subjects at 8 academic centers were randomly assigned to LAI-RIS or oral SGA; 105 were receiving oral RIS at enrollment. Open treatment lasted up to 30 months. Subjects had confirmed diagnoses of schizophrenia or schizoaffective disorder, were living in the community for at least 4 weeks and were at least moderately ill (CGI >4). Masked Master Raters assessed symptoms via live video connection. Relapse and/or hospitalization for symptom exacerbation was determined by a masked Relapse Monitoring Board. We used Cox regression analysis to assess time to first relapse and hospitalization.
Results: There were significant differences in the proportion of subjects receiving oral RIS by site, they were younger at first hospitalization and had higher SANS Affective Flattening and Asociality/Anhedonia. Within the RIS cohort, LAI-RIS subjects had poorer global Scale of Functioning than oral subjects. There were no significant differences in time to relapse or hospitalization.
Conclusion: Comparing LAI-RIS to oral RIS controls for possible confounds. Only route of administration varies between the treatment groups and treatment with LAI does not involve medication change. This analysis is comparable to studies in the 1970s that compared comparing oral and LAI fluphenazine. There were differences between the RIS cohort and those who received other antipsychotics; they were younger at first hospitalization and had more negative symptoms. Further, the percentage of patients receiving RIS at the 8 sites varied significantly from 21% to 57%. None of these differences were reflected in treatment group differences within the RIS cohort. The RIS cohort findings are consistent with the findings for the full cohort - no significant differences in time to relapse or hospitalization in a 30-month trial.
ID: 2089107

EARLY INCREASE IN APPETITE - A PREDICTOR OF RESPONSE TO ANTIPSYCHOTICS

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Background: Several studies report an association between clinical improvement and metabolic side-effects with antipsychotics. Patients commonly report an increase in appetite on antipsychotic treatment, which could account for metabolic side-effects. Moreover, appetite disturbances are seen in untreated psychosis. It has not been systematically examined if appetite changes predict antipsychotic treatment response.
Methods: 100 adult patients with psychosis, initiated on antipsychotic treatment alone, were assessed on Brief Psychiatric Rating Scale (BPRS), Visual Analogue Scale for appetite, anthropometric measurements (weight, waist circumference, body mass index) and serum lipid profile and fasting blood sugar, at baseline, first follow-up [2-4weeks (n=72)] and at second follow-up [8-12weeks (n=39)].
Results: Risperidone (65.3%) and Olanzapine (16.7%) were the commonest antipsychotics prescribed. Early (2-4weeks) increase in appetite had a significant correlation with BPRS score reduction at first ($r=0.39;p<0.01$) and second ($r=0.32;p<0.05$) follow-ups. On forward-stepwise-multiple-linear-regression analysis, early (2-4weeks) increase in appetite and triglyceride levels ($R2=0.257;p=0.003$) together predicted 26% variance in treatment response (BPRS score reduction) at first follow-up. Those with reduced appetite (VAS<0) at baseline (n=43) were compared with the rest (n=29). The reduced appetite group had higher baseline BPRS scores ($t=2.408;p=0.019$) and greater mean reduction in BPRS scores at first follow-up ($t=2.316;p=0.023$). Patients who reported an increase in appetite, during follow-up (n=48) were compared with those who reported no increase (n=24). The former group had a significantly greater reduction in BPRS scores ($t=3.37;p<0.01$) at follow-up.
Conclusion: Our study found - a) reduced appetite was associated with higher illness severity at baseline and a greater mean improvement on follow-up; b) an increase in appetite on treatment predicted greater symptomatic improvement. Possibly, common neural pathways mediate psychopathology, appetite changes, and antipsychotic response. Further examination is warranted to elucidate the interaction between appetite regulating pathways and psychosis.
ID: 2118065

EFFICACY OF BREXPIPRAZOLE (OPC-34712) IN ACUTE SCHIZOPHRENIA: RESULTS OF TWO POOLED PIVOTAL STUDIES

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Background: Brexpiprazole is a rationally designed serotonin-dopamine activity modulator that is currently under review by the FDA as monotherapy for schizophrenia and adjunctive treatment for MDD. The efficacy, safety, and tolerability of brexpiprazole were evaluated in patients with acute schizophrenia, based on pooled data from two pivotal phase III studies.
Methods: Patients with acute schizophrenia were randomized to treatment with fixed daily doses of brexpiprazole or placebo for 6 weeks (Study 1 [NCT01396421]: brexpiprazole 4mg, 2mg, 0.25mg, or placebo [2:2:1:2]; Study 2 [NCT01393613]: brexpiprazole 4mg, 2mg, 1mg, or placebo [3:3:2:3]). The primary efficacy endpoint was change in PANSS total score from baseline to week 6; key secondary endpoint was the change in CGI-S score at week 6. Pooled efficacy analyses were conducted using MMRM, including treatment, visit, site, and treatment-by-visit interaction as fixed effects, and baseline score-by-visit as covariate. The 0.25mg group and the 1mg group were included to establish a non-effective/minimally effective dose range of brexpiprazole.

Results: Pooled brexpiprazole 4mg (n=359) and 2mg (n=359) were each superior to placebo (n=358) in change from baseline in PANSS total score at week 6 (least square mean difference [LSMD] to placebo: -6.69, p<0.0001 and -5.46, p=0.0004, respectively). Results of the key secondary endpoint supported the primary results. Brexpiprazole 0.25mg (n=87) and brexpiprazole 1mg (n=117) showed numerical improvement over placebo at week 6 for the primary endpoint (LSMD: −2.89, p=0.2910 and LSMD: −3.37, p=0.1588, respectively). A total of 8.2% (30/364), 7.1% (26/368), 9.2% (11/120), and 13.3% (12/90) brexpiprazole-treated patients (4mg, 2mg, 1mg, and 0.25mg, respectively) vs 14.7% (54/368) placebo-treated patients discontinued due to adverse events. The incidences of insomnia and agitation in the brexpiprazole treatment groups were similar or lower than those observed in the placebo group. For akathisia, the incidences were 6.9%, 4.6%, 4.2% and 0% in the brexpiprazole 4mg, 2mg, 1mg, and 0,25mg groups, respectively, vs 4.6% in the placebo group.
Conclusion: Data from two adequate and well-controlled clinical studies provide evidence that brexpiprazole is efficacious and safe in treating patients with acute schizophrenia. All doses of brexpiprazole were well tolerated, with notably low levels of akathisia and sedation.
ID: 2089994

THETA BURST TRANSCRANIAL MAGNETIC STIMULATION FOR AUDITORY VERBAL HALLUCINATIONS; NEGATIVE FINDINGS FROM A LARGE DOUBLE BLIND TRIAL

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Background: Auditory verbal hallucinations (AVH) are a characteristic symptom of schizophrenia, which are resistant to antipsychotic medication in 25% of patients. Previous studies have investigated repetitive transcranial magnetic stimulation (rTMS) to the left temporoparietal region as a non-invasive treatment for refractory AVH, with positive results. Recent studies with large sample sizes could not replicate efficacy of 1-Hz rTMS compared to placebo. A new stimulation protocol using continuous theta burst rTMS (TB-rTMS) showed high efficacy in open label studies, but was not tested in a double blind fashion.
Methods: In a double-blind study, seventy-six patients with AVH were randomly allocated to either TB-rTMS or placebo treatment. The TB-rTMS group received 10 TB-rTMS treatments over the left temporoparietal cortex. The placebo group received 10 treatments of sham stimulation. Severity of AVH was assessed using the Positive and Negative Symptom Scale (PANSS), Auditory Hallucinations Rating Scale (AHRS) and Psychotic Symptom Rating Scale (PSYRATS) before treatment, directly after treatment, and during follow-up one month later. Adverse events were assessed after treatment and during follow-up using a selection of the Global Index of Safety (GIS).
Results: Twelve patients dropped out before the end of the study. All patients had remained blind to treatment allocation as confirmed in a mean score of 80% who at end of study thought to have had real TMS in either group. In the remaining 64 AVH improved significantly after treatment in both groups as measured by both the PSYRATS (p<.01) and the AHRS (p<.00), while AVH severity as measured by the PANSS did not show significant changes after treatment in either treatment group. However, improvement was not different in the TB-rTMS group as compared to placebo treatment. TB-rTMS did not cause significantly more adverse events compared to placebo.
Conclusion: These results suggest a placebo effect of continuous TB-rTMS on the left temporoparietal region and highlight the importance of double blind trials to assess efficacy of new treatments.
ID: 2072193

A PRAGMATIC ANALYSIS COMPARING ONCE-MONTHLY PALIPERIDONE PALMITATE VERSUS DAILY ORAL ANTIPSYCHOTIC TREATMENT IN PATIENTS WITH SCHIZOPHRENIA

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Background: Patients with schizophrenia are at increased risk for institutionalization and may require specific, targeted treatment approaches. The PRIDE (Paliperidone palmitate Research In Demonstrating Effectiveness) study compared once-monthly injectable paliperidone palmitate (PP) to daily oral antipsychotics (OAs) in patients with schizophrenia (NCT01157351). Its design reflects real-world aspects of schizophrenia patients. This pragmatic analysis assessed cumulative treatment failures (TFs) over the full study period.
Methods: In PRIDE, a 15-month prospective, open-label, event monitoring board-blinded study, subjects with schizophrenia were randomly assigned to flexibly dosed PP (78-234 mg) or a daily OA (from a preselected group of 7 commonly prescribed OAs). TF was defined as arrest/incarceration, psychiatric hospitalization, suicide, discontinuation due to inadequate efficacy or safety/tolerability, treatment supplementation due to inadequate efficacy, or an increase in psychiatric services to prevent imminent psychiatric hospitalization. Multiple TFs from the same subject were analyzed as recurrent events using a proportional intensity model with treatment group as a fixed factor.
Results: Cumulative TFs, arrests/incarcerations, or psychiatric hospitalizations were significantly lower with PP vs OA during the study period (Table). Most common treatment-emergent adverse events (TEAEs) for PP and OA, respectively, were injection-site pain (18.6%, 0%), insomnia (18.6%, 12.4%), increased weight (13.3%, 7.3%), akathisia (11.5%, 7.8%), and anxiety (11.1%, 8.3%). TEAEs leading to treatment discontinuation occurred in 12.4% vs 8.7% (PP vs OA) of subjects, and serious TEAEs occurred in 18.6% vs 24.3% of subjects. One death (considered unlikely related to study medication) was reported in the PP group.
Conclusion: PP had a more robust treatment effect vs OA as assessed by mean cumulative number of events and institutionalizations over the 15-month period. These results inform therapeutic risk:benefit comparisons of PP and OA treatment options and public health decision making.
ID: 2085881

ADHERENCE TO ANTIPSYCHOTIC MEDICATION LEADS TO IMPROVED INSIGHT INTO THE NEED FOR THE MEDICATION AFTER AN INITIAL EPISODE OF SCHIZOPHRENIA

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	PP (n=226)	OA (n=218)	P value
Completed 15 months of study follow-up, %	41.2	40.4	—
Average number of events per subject during the 15-month treatment period			
Any TF events	1.09	1.51	<0.001
Arrests/incarcerations	0.72	1.00	0.004
Psychiatric hospitalizations	0.17	0.31	0.009

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Background: Insight into the need for antipsychotic medication is associated with medication adherence in schizophrenia.
Methods: The temporal relationships between insight and adherence were examined in patients with a recent first schizophrenia episode in the context of a randomized controlled trial at the UCLA Aftercare Research Program (N=83) that involved risperidone in oral and long-acting injectable (RLAI) formulations. Each patient's adherence was rated on a 1-5 scale based on timeliness of injections for RLAI, and on pill counts, which were verified with plasma levels, MEMS®, patient reports, and psychiatrist judgments for oral medication. Average adherence scores were computed for the period after an initial period of stabilization (baseline) to the 6-month point, and for months 7-12. Awareness of having a mental disorder, and in particular awareness of the need for antipsychotic medication, was assessed using the Scale for Unawareness of Mental Disorder-Revised (SUMD-R) at baseline and every 6 months during the randomized medication follow-through period.
Results: Awareness of the need for medication at baseline was not significantly associated with medication adherence over the next 6 months (r=.20, N=50, p=.17). However, adherence during the first 6 months following baseline was associated with awareness of the need for medication at the 6 and 12 month points (r=.40, N=49, p=.005, and r=.42, N=38, p=.01, respectively). The correlations between adherence and awareness of the need for medication were examined for evidence consistent with possible causal relationships using cross-lagged panel design analyses. For the oral risperidone group, these analyses suggest that adherence during months 1-6 might have led to greater levels of awareness of the need for medication at the 6 month point, not that better initial awareness led to better adherence during the later 7-12 month interval (z=2.0, N=19, P=.03). Significant suggestive directional effects could not be established for the RLAI group.
Conclusion: Awareness of the efficacy and need for antipsychotic medication is often cited as a predictor of subsequent medication adherence. However, the picture might not be so straightforward because a period of adherence to oral medication might be necessary to gain such awareness of the need for antipsychotic medication. In addition, in the RLAI group, the high degree of adherence obscured any significant correlational relationships with awareness of the need for medication.
ID: 2077861

ADJUNCTIVE MINOCYCLINE IN CLOZAPINE TREATED SCHIZOPHRENIA PATIENTS: IMPROVEMENTS IN GENERAL HEALTH AND WELL-BEING

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Background: Clozapine is the most effective antipsychotic treatment for chronic and treatment resistant patients diagnosed with schizophrenia. However, there is no evidence base for treatment selection in patients who are partially responsive to clozapine treatment. Accumulating preclinical and clinical has suggested minocycline may be effective for adjunctive treatment of schizophrenia.
Methods: A 10 week, randomized, double-blind, placebo controlled study of adjunct minocycline (100 mg BID) compared to placebo in 50 participants stabilized, but only partially responsive to clozapine, was completed. A secondary aim of the study was to assess study participants' quality of life and perceived health quality through completion of the Psychological General Well-Being Schedule (PGWB), the Short Form-36 Health Survey (SF-36), the Personal and Social Performance Scale (PSP), and the Patient Global Impression (PGI) at several time points throughout the study.
Results: 29 participants were assigned to minocycline and 23 to placebo. Two participants assigned to minocycline discontinued early, while all others completed the trial. Patients did not differ on demographic variables, clozapine dose or clozapine blood level at baseline. On the PGWB, there was no significant improvement on the composite score, but the general health dimension showed a tendency toward improvement among minocycline patients (minocycline-placebo difference 0.94 ± SE 0.48, p=0.057). The SF-36 showed no significant difference in the total score between the treatment groups, however minocycline treated patients showed an improvement in the emotional well-being construct at the completion of the study (minocycline-placebo difference= 6.38 ± SE 3.03, p=0.041). The PSP showed no significant difference in the total score between the treatment groups, but minocycline treated patients showed a significant improvement in the socially useful activities domain (minocycline-placebo difference= -0.24 ± SE 0.12, p=0.048). There was no significant difference found on the PGI between the two treatment groups.
Conclusion: Modest improvements were noted in general health, emotional well-being and engagement in socially useful activities with minocycline in a treatment resistant and chronically ill population. Larger studies are needed to confirm and better understand these findings in order to improve available treatment options in patients diagnosed with chronic and treatment resistant schizophrenia.
ID: 2085662

SWITCHING TO CLOZAPINE USING IMMEDIATE VS. GRADUAL ANTIPSYCHOTIC DISCONTINUATION: A PILOT, DOUBLE-BLIND, RANDOMIZED CONTROLLED TRIAL

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Background: While the issue of clozapine titration has frequently been addressed because of its numerous and potentially severe side effects, no study as of yet has assessed the comparability of gradual vs. immediate antipsychotic discontinuation in switching to clozapine.
Methods: This study represents a pilot, 8-week, double-blind, randomized controlled trial. Patients who met the following criteria were included in the study: (1) outpatients with schizophrenia or schizoaffective disorder; and (2) candidacy for a trial of clozapine, defined as an inadequate clinical response to > two antipsychotics and/or intolerable side effects. Patients were randomly assigned to immediate discontinuation (prior antipsychotics were discontinued at baseline) or gradual discontinuation (prior antipsychotics were reduced by 25% each week). For each group, clozapine was gradually increased to 300 mg/day. The following assessments were completed at baseline, week 1, 2, 3, 4, and 8: the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression - Severity scale (CGI-S), Calgary

Depression Scale for Schizophrenia (CDSS), Drug Attitude Inventory, and Schedule for the Assessment of Insight (SAI) for efficacy; side effect measures included the Simpson-Angus Scale, Barnes Akathisia Rating Scale, Abnormal Involuntary Movement Scale, and the UKU Side Effect Rating Scale.
Results: A total of 32 patients were enrolled; 15 and 17 patients were assigned to the immediate and gradual discontinuation group, respectively. Three patients in the gradual discontinuation group discontinued the study due to side effects. While significant improvements were observed in the BPRS total, CGI-S, CDSS and SAI total scores after the switch to clozapine ($P<0.05$), no significant differences were found on any efficacy or side effect measure between groups ($P\geq0.05$).
Conclusion: The findings indicate that (1) a switch to clozapine improved psychopathology in patients with treatment-resistant schizophrenia and (2) immediate and gradual antipsychotic discontinuation strategies are comparable with regard to efficacy and safety when switching to clozapine in patients with schizophrenia. Due to the small sample size, larger-scale trials are needed to confirm the findings.
ID: 2083476

THE EFFECT OF COGNITIVE REMEDIATION ON THEORY OF MIND IN SCHIZOPHRENIA: A MULTIPLE CASE STUDY

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Background: Previous studies have shown that in patients with schizophrenia, cognition predicts social cognition skills and social cognition plays a mediator role in the relationship between cognition and social functioning. Deficits in theory of mind (ToM), an important area of social cognition, are common in patients with schizophrenia and may be a key target in cognitive remediation studies.The effect of a top-down cognitive remediation approach -targeting several cognitive domains and metacognition - on ToM is still unknown.
Methods: This multiple case study included four male patients with a DSM-IV diagnosis of schizophrenia (illness duration range: 3 to 9 years), who all presented with cognitive and social cognitive deficits at baseline (age range: 24 to 33 years old). Cognitive remediation lasted approximately three months with the Computerised Interactive Remediation of Cognition - Training for Schizophrenia (CIRCuiTS), French version. ToM was assessed with the Combined stories task at baseline, immediately after therapy (3 months post-baseline), and at two follow-up points (6 months post-baseline n=3; 1 year, n=2). A reliable change index (RCI) was calculated for each patient for each evaluation. A RCI is statistically significant if the score is superior to 1.96.
Results: Immediately after therapy, all four patients showed increased performance in ToM but this was not significant (RCI: patient 1=1.310, patient 2=1.529, patient 3=0.655, patient 4=1.092). Six months post-baseline, the results again showed improvements compared to baseline (RCI: patient 1=1.747, patient 2=3.494*, patient 3=Not available, patient 4=1.747). One year post-baseline, one patient showed a significant increased performance compared to baseline (RCI: patient 1=0.437, patient 2=2.184*, patient 3, 4 = Not available).
Conclusion: These results provide evidence that in patients with ToM and cognitive deficits, it is possible to increase ToM skills and that for some individuals it is consistent and can reach significance (*) a considerable time post therapy. These improvements were achieved using a cognitive remediation approach that trains cognitive and metacognitive processing and provides patients with strategies for applying these trained processes in daily life. This cognitive remediation program could indirectly affect ToM abilities by improving the cognitive skills necessary for ToM, or directly through the emphasis on strategy and metacognition in CIRCuiTS.
Grant: Canadian Institutes of Health Research (fellowship)
ID: 2087525

COMPENSATORY COGNITIVE TRAINING FOR PEOPLE WITH SEVERE MENTAL ILLNESS IN SUPPORTED EMPLOYMENT

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Background: Treatments for cognitive impairment and unemployment associated with severe mental illness are urgently needed. We tested a 12-week, manualized, Compensatory Cognitive Training (CCT) intervention targeting prospective memory, attention, learning/memory, and executive functioning in the context of supported employment, the evidence based practice for people with severe mental illness who want to return to work.
Methods: 136 unemployed, work-seeking outpatients with schizophrenia (n=51), bipolar disorder (n=35), or major depression (n=50) were randomized to receive supported employment plus CCT or enhanced supported employment, which matched the CCT condition for therapist contact. Assessments of neuropsychological performance, functional capacity, psychiatric symptom severity, and self-reported functioning and quality of life were administered at baseline and post-treatment; work outcomes were collected for two years.
Results: ANCOVAs controlling for baseline performance demonstrated significant CCT-associated effects on measures of learning ($p=0.042$), financial capacity ($p=0.020$), depressive symptom severity ($p=0.011$), and self-reported everyday functioning ($p=0.021$). There were also significant positive effects of CCT on working memory and functional capacity for participants with schizophrenia, and on general psychiatric symptom severity and quality of life for those with bipolar disorder. Fifty-three percent of the participants obtained competitive work, but there were no differences in work attainment, weeks worked, or wages earned between the CCT and the enhanced supported employment group.
Conclusion: Compensatory Cognitive Training has the potential to improve cognitive performance, functional skills, psychiatric symptom severity, and self-rated functioning and quality of life in people with severe mental illness. Receiving CCT did not result in better work outcomes, suggesting that supported employment can result in job placements regardless of cognitive status.
ID: 2119174

COMPENSATORY COGNITIVE TRAINING FOR PEOPLE WITH SCHIZOPHRENIA: RECENT RESULTS AND MOBILE APP DEVELOPMENT

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Background: Cognitive impairment is associated with poor everyday functioning and disability in people with schizophrenia. We have examined cognitive and functional capacity outcomes following a 12-week Compensatory Cognitive Training (CCT) intervention targeting prospective memory, attention, learning, and executive functioning; we are currently pilot-testing a self-administered mobile application version of the intervention.
Methods: Our most recent trials of CCT have included 58 unemployed outpatients with schizophrenia or schizoaffective disorder receiving supported employment and 27 outpatients with first episode schizophrenia. The MATRICS Consensus Cognitive Battery (MCCB) and the UCSD Performance-Based Skills Assessment - Brief were administered as measures of cognition and functional capacity, respectively, at baseline and post-treatment in both studies. Our mobile application pilot testing will include 18 supported employment clients with schizophrenia.
Results: ANCOVAs controlling for baseline performance revealed that CCT was differentially associated with greater improvement in working memory (p=.043), learning (p=.035), and functional capacity (p=.044) performance in the supported employment group, and greater improvements in the MCCB Composite score (p=.002), processing speed (Trail Making, part A, p=.032), and social cognition (p=.041) in the first episode group. Pilot testing of the CCT mobile application will result in data regarding feasibility and acceptability, as well as frequency and amount of use.
Conclusion: CCT has the potential to improve cognitive performance and functional capacity in outpatients with early and chronic schizophrenia. It is possible that we can improve access to CCT by offering it as a self-administered mobile application.
ID: 2089426

ITI-007, A FIRST-IN-CLASS INVESTIGATIONAL NEW DRUG FOR THE TREATMENT OF SCHIZOPHRENIA: RATIONALE FOR DOSE SELECTION FOR A PHASE 3 CLINICAL TRIAL

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Background: Blockade of dopamine (DA) receptors is thought to mediate antipsychotic efficacy while excessive blockade of DA receptors can lead to extrapyramidal side effects (EPS). Modulation of serotonin by 5-HT2A receptor antagonism and reuptake inhibition may contribute to improving psychosis and mood. Modulation of glutamate may contribute to improving psychosis, negative symptoms and cognition. ITI-007 represents a new approach with serotonergic, dopaminergic and glutamatergic modulation. Nonclinical and clinical translational data were reviewed to select doses for a Phase 3 program of ITI-007 in schizophrenia.
Methods: ITI-007 was evaluated using conditioned avoidance response (CAR) to predict antipsychotic efficacy, a step-down latency assay to predict EPS, and in vivo microdialysis to measure DA concentrations and turnover preclinically. Positron emission tomography (PET) was measured in healthy human volunteers to determine 5-HT2A and D2 receptor and serotonin transporter occupancy. A Phase 2 trial in patients with acute schizophrenia was conducted.
Results: ITI-007 significantly inhibited CAR with an ED50 of 1.5 mg/kg translating to a projected human dose of about 17 mg. No haloperidol-like frank catalepsy is observed with ITI-007 even at doses up to and including 30 mg/kg (projected 340 mg human dose). Mesocortical selectivity of ITI-007 was demonstrated using in vivo microdialysis; 3 mg/kg ITI-007 significantly increased extracellular concentrations of DA in the prefrontal cortex with lesser effects in the striatum. These data indicate an efficacious human dose around 20 - 40 mg ITI-007. In the PET study, a dose of 20 mg ITI-007 demonstrated a peak of about 20% striatal D2- receptor occupancy, with essentially full cortical 5-HT2A receptor occupancy achieved at 10 mg ITI-007. This would put the striatal D2 receptor occupancy for ITI-007 lower than that of the majority of approved antipsychotic drugs. Rather than test this hypothesis, doses with higher projected striatal D2 receptor occupancy were tested in a Phase 2 schizophrenia trial. A dose of 60 mg ITI-007 (projected ~ 50% occupancy), but not 120 mg ITI-007 (projected ~70% occupancy), demonstrated antipsychotic efficacy.
Conclusion: Based on the translational data that indicate efficacy at relatively lower levels of striatal D2 occupancy, a dose of 40 mg ITI-007 will be tested in a Phase 3 clinical trial in addition to 60 mg ITI-007 that was shown previously to be effective as an antipsychotic.
ID: 2119800

ITI-007, A FIRST-IN-CLASS INVESTIGATIONAL NEW DRUG FOR THE TREATMENT OF SCHIZOPHRENIA: PHASE 2 CLINICAL TRIAL EFFICACY AND SECONDARY ANALYSES

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Background: ITI-007 is a first-in-class new molecular entity in development for the treatment of schizophrenia and other neuropsychiatric disorders. As a modulator of serotonin, dopamine, and glutamate, ITI-007 addresses a broad range of symptoms beyond acute psychosis with a favorable safety profile.
Methods: ITI-007 was evaluated in a Phase 2 randomized, double-blind, placebo- and active-controlled clinical trial. Subjects with schizophrenia (N=335) were randomized to receive 60 mg or 120 mg ITI-007, 4 mg risperidone or placebo. The primary endpoint was change from baseline on the Positive and Negative Syndrome Scale (PANSS) total score. Secondary endpoints included PANSS Subscales and Factors and the Calgary Depression Scale for Schizophrenia (CDSS). Pre-specified analyses were conducted in a subgroup of patients exhibiting prominent negative symptoms at baseline and in a subgroup of patients with comorbid depression. Safety endpoints included assessment of motor function and clinical laboratory assessments of prolactin and metabolic parameters (e.g., insulin, glucose, cholesterol and triglycerides).
Results: ITI-007 60 mg demonstrated a statistically significant reduction in the change from baseline on PANSS total scores compared to placebo, meeting the objective of the study. Risperidone also significantly separated from placebo, demonstrating assay sensitivity, but 120 mg ITI-007 did not separate from placebo. Unlike risperidone, ITI-007 did not increase motor side effects, prolactin levels or metabolic parameters. ITI-007 60 mg significantly reduced positive symptoms as measured by the PANSS Positive Symptom Subscale and Factor. On the PANSS Negative Symptom Subscale and Factor, ITI-007 60 mg improved negative symptoms numerically more than risperidone or placebo in a subgroup of patients with prominent negative symptoms, whereas risperidone worsened negative symptoms compared to placebo. In patients with schizophrenia and co-morbid depression at baseline, ITI-007 60 mg significantly reduced symptoms of depression and symptoms of psychosis. A post-hoc analysis showed a robust and statistically significant improvement of the Pro-social Factor of the PANSS by ITI-007 60 mg, consistent with improved social function.
Conclusion: The dose of 60 mg ITI-007 demonstrated antipsychotic efficacy with a differentiating efficacy and safety profile in comparison to risperidone. ITI-007 is currently in Phase 3 clinical development for the treatment of schizophrenia.
ID: 2191190

BIAS AND DEFICIT IN SOCIAL COGNITION

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Background: Poor social functioning is a hallmark of schizophrenia. Oxytocin (OXT) a nonapeptide hormone produced by the brain has been implicated in social behavior and social cognitive functions. Our research on oxytocin has moved us to conceptualize social cognitive impairments as composed of bias (e.g., self-referential bias, and jumping to conclusions related to positive symptoms) and deficit (e.g., emotion perception impairments related to negative symptoms). OXT administration may have positive effects for patients with social cognitive deficits but negative effects for patients with social cognitive bias. We have tested interventions to focus separately on each of these domains.
Methods: In Study 1, we randomized 50 patients with persistent negative symptoms to MOtiVation Enhancement Treatment (MOVE) or treatment as usual (TAU) for 9 months. MOVE is a multi-component set of interventions including in vivo in home training for deficits in emotional processing and emotional expression, in addition to behavioral activation and skill building approaches to address a broad range of negative symptom expression and social impairment. Assessments were conducted at baseline and every 3 months during treatment. In Study 2, we randomized 28 patients to a version of Social Cognition and Interaction Training delivered daily (15 min /day) on a tablet computer (SCIT-T) or to a waiting list control condition. The SCIT-T intervention involved a debiasing skill of seeing all social situations from three perspectives—that of My-fault Mary (sad, guilty, self-blaming), Blaming Bill (angry, suspicious, blames others), and Easy Eddie (calm, non blaming). Assessments were conducted at baseline, after 1 month of treatment and at one month follow up. Waiting list patients received SCIT-T after their post-waiting list assessment.
Results: Results of study 1 demonstrated improvements in negative symptoms including social impairment for patients in MOVE versus TAU but not until the 9 month time point. Results of Study 2 indicated decreases in bias with repeated remediation.
Conclusion: Perhaps addressing both bias and deficit in one intervention or combining OXT with psychosocial treatments could lead to greater improvements in social cognition for individuals with schizophrenia. More research is needed on the potential for OXT to increase social cognitive bias among patients with prominent positive symptoms.
ID: 2087459

A RANDOMIZED PILOT STUDY OF MOTIVATION ENHANCEMENT THERAPY (MOVE)

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Background: Among individuals with schizophrenia, those who have persistent and clinically significant negative symptoms (PNS) including restricted affect, diminished emotional range, poverty of speech, decreased motivation and interests, diminished sense of purpose and diminished social drive typically have the poorest functional outcomes and quality of life. The NIMH-MATRICS Consensus Statement on Negative Symptoms indicated that these symptoms represent an unmet therapeutic need for large numbers of individuals with schizophrenia. While aspects of negative symptoms may be lessened with existing evidence-based practices, no model addresses the entire constellation of PNS.
Methods: 51 patients with PNS were randomized into one of two groups for a period of 9 months: 1) MOtiVation and Engagement (MOVE) Program or 2) Treatment as usual. MOVE is a home based, manual-driven, multi-modal treatment that employs a number of cognitive and behavioral principles to address the broad range of factors contributing to PNS and their functional consequences. Components of MOVE include: Environmental supports and the organization of belongings to prompt task initiation and persistence, in-vivo skills training to ameliorate deficits and encourage appropriate interaction with individuals in the client's environment, cognitive behavioral techniques to address self-defeating attitudes that mediate the relationship between negative symptoms and functional outcomes, in-vivo training in emotional processing to address affective blunting and problems in identifying emotions, and specific techniques to address the deficits in anticipatory pleasure experienced by individuals with PNS. Patients were assessed at baseline and each 3 months with multiple measures of negative symptoms.
Results: Repeated measures analyses of variance for mixed models indicate significant Group by Time effects for the Negative Symptom Assessment (NSA; $p<.02$) and the Clinical Assessment Interview for Negative Symptoms (CAINS $p<.04$). Group differences were not significant until 9 months of treatment and were not significant for the Brief Negative Symptom Scale (BNSS). Treatment gains in MOVE primarily reflected improvements in socialization and motivation rather than expression.
Conclusion: Further investigation of a comprehensive treatment for PNS, such as MOVE, is warranted.
ID: 2088976

SOURCES OF PUBLICATION BIAS

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Background: Publication bias is a common and serious problem in Medicine and Psychiatry is not free of it. There are several sources of publication bias, including those emerging from intentional and unintentional causes.
Methods: Systematic review of sources of publication bias in Psychiatry, looking into major conditions such as schizophrenia, bipolar disorder and depression. Searches in NIMH clinicaltrials.gov database, Cochrane, and PubMed.
Results: Publication bias may be as high as 70% when considered in a broad sense. Psychiatry is not worse than other areas of Medicine. The most common sources of publication bias in Psychiatry are: 1) study incompletion 2) failed study 3) negative study 4) duplication and unjustified post-hoc analyses 5) protocol violations leading to lack of power or unreliability 6) unwarranted conclusions
Conclusion: There are several sources of publication bias, including the failure to submit negative studies for publication due to sponsor concerns (typically but not exclusively in the industry), or because authors feel unhappy about the results, and/or editors trying to raise their Impact factors may be less keen to publish those studies. Many studies are discontinued before the planed number of patients are enrolled, leading to lack of power and unsubmission. Another type of bias is the repeated publication of positive studies (by subanalyzing, pooling, and combining data subsets). Methods to detect publication bias exist and potential solutions exist too.
ID: 2119029

INTERACTIVE TECHNOLOGY AND COGNITIVE TREATMENTS FOR SCHIZOPHRENIA

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Background: Recent cognitive science advances now permit treatment development for schizophrenia that is guided by an understanding of underlying neural system impairments. Among these impairments, deficits in general cognition, social cognition, and motivated behavior are critical factors in long-term outcome that have often not been addressed by conventional interventions.
Methods: Automated cognitive training methods that target cognitive operations, socio-affective processes, and motivation have been developed based on the basic science of learning, cortical plasticity, and reward and motivated behavior. We have recently integrated these methods with advances

in interactive software development and innovations in mobile health platforms. We have initiated randomized trials in both first-episode patients and in those with persistent illness that focus on: 1) The use of iPads and Facetime to perform remote assessments and cognitive training interventions to individuals in distant locations; 2) The development of a mobile app incorporating 1:1 remote coaching and social networking that is explicitly designed to harness intrinsic motivational processes to improve health-promoting behavior in young people with schizophrenia.
Results: Interim data indicate that it these methods show good acceptability, feasibility, and tolerability as well as strong patient adherance. Assessments performed remotely show acceptable reliability with those performed in person. On average, participants train for 2.5 hours per week. Mobile app users access the app an average of once per day, and require less than 15 minutes of direct coaching per day. They report goal achievement at 80%. They cite the social networking aspects as a particularly rewarding feature.
Conclusion: Initial data indicate that these approaches show potential to increase cost-effectiveness, accessibility, and scalability of interventions, while increasing autonomy, competence and social support. In addition, these approaches permit real-time quantification of patients' symptoms, adherence, and progress, allowing for continuous dynamic customization of rehabilitation support and the delivery of true "personalized psychiatry".
ID: 2090262

PREVALENCE OF CATATONIA DIAGNOSIS IN SCHIZOPHRENIA AND TREATMENT WITH MINOCYCLINE

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Background: Catatonia is a frequently encountered, psychomotor syndrome, often unrecognized and poorly treated with antipsychotics. It has been erroneously associated as occurring most frequently within schizophrenia. With DSM-5, catatonia is treated as a separate entity and necessary criteria for its diagnosis have been advanced. In our study, we examined the incidence of catatonia and its response to minocycline in a population suffering refractory schizophrenia and schizoaffective disorder. Some preliminary evidence suggests that minocycline may be effective for catatonia.
Methods: 52 participants with persistent positive symptoms of schizophrenia and schizoaffective disorder, despite adequate clozapine dosing, were randomized to receive adjunct minocycline (100 mg BID) (N=29) or placebo (N=23). Catatonia was assessed at baseline and endpoint in this 10 week study using the Bush-Francis Catatonia Rating Scale (BFCRS). We examined BFCRS scores and subfactorsin the catatonia and non catatonia groups and also examined changes in BFCRS scores during treatment in the clinical trial.
Results: At baseline, we identified 3/51(5.8%) that met DSM-5 criteria for catatonia. In the DSM-5 diagnosed catatonia group total scores on the BFCRS were significantly higher (9.00 ± 3.00 vs. 0.8333 ± 1.48, p=0.0028) compared to the noncatatonic patients. DSM-5 diagnosed patients scored significantly higher in the subfactors but no difference was seen in the repetitive movements subfactor. Overall, there were no significant differences seen in BFCRS scores between minocycline and placebo groups (BPRS total score, p=0.38), however within patient changes in the two catatonia patients assigned to minocycline showed moderate to robust improvements. One patient had fluctuating improvements of 13-28% in total BPRS and the second catatonic patient had an 18% improvement in the total SANS. The catatonic patient in the placebo group had no changes in symptoms.
Conclusion: In our study we find approximately a 6% rate of catatonia in a treatment resistant schizophrenia population treated with clozapine. Catatonia patients (N=2) in the minocycline group had improvements while the one patient treated with placebo remained unchanged. With the new diagnostic criteria for catatonia in the DSM-5 more attention may be paid to this diagnosis. Minocycline may be effective however definitive studies are needed to determine its efficacy and to determine if treatments for catatonia may cut across diagnostic boundaries.
ID: 2093218

IMPACT OF TECHNOLOGY AND SOCIAL TRENDS AT THE SITE LEVEL: WHAT ARE THE IMPLICATIONS FOR INVESTIGATORS?

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Background: Computerized tests, ongoing monitoring of adherence and the use of electronic devices for data collection are only a few of the many new technologies that are coming into use in clinical trials. The inclusion of these technologies provides unique challenges while at the same time offering new possibilities for data gathering. This presentation will discuss the site's role in the implementation and use of these technologies in trials with individuals who have schizophrenia.
Methods: A review of current, and potential future, technologies used at the site level.
Results: This presentation will explore the site's perspective on the evolving use
of technology in clinical trials for schizophrenia.
Conclusion: Technology holds the promise of changing the way that clinical data is gathered in clinical trials for schizophrenia. This presentation provides an overview of the investigator and research staff's perspective in the implementation and use of these newer methods.
ID: 2124291

ADJUNCTIVE RALOXIFENE TREATMENT IMPROVES ATTENTION AND MEMORY IN MEN AND WOMEN WITH SCHIZOPHRENIA

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Background: There is increasing clinical and molecular evidence for the role of hormones and specifically estrogen and its receptor in schizophrenia. A selective estrogen receptor modulator, raloxifene, stimulates estrogen-like activity in brain and can improve cognition in older adults. The present study tested the extent to which adjunctive raloxifene treatment improved cognition and reduced symptoms in young to middle age men and women with schizophrenia.

Methods: Ninety-five patients with a diagnosis of schizophrenia or schizoaffective disorder were recruited into a dual-site, thirteen week, randomized, double-blind, placebo-controlled, crossover trial of adjunctive raloxifene treatment in addition to their usual antipsychotic medications. Symptom severity and cognition in the domains of working memory, attention/processing speed, language and verbal memory were assessed at baseline, six, and thirteen weeks.
Results: Analyses of the initial six-week phase of the study using a parallel groups design (with 39 patients receiving placebo and 40 receiving raloxifene) revealed that adjunctive raloxifene treatment showed significant improvement relative to placebo in memory and attention/processing speed. There was no reduction in symptom severity with raloxifene treatment compared to placebo. There were also significant carryover effects, suggesting some cognitive benefits are sustained even after raloxifene withdrawal. Analysis of the 13-week crossover data revealed significant improvement with raloxifene only in attention/processing speed.
Conclusion: This is the first study to show that daily, oral adjunctive raloxifene treatment at 120 mg/day has beneficial effects in attention/processing speed and memory for both men and women with schizophrenia. Thus, raloxifene may be useful as an adjunctive treatment for cognitive deficits associated with schizophrenia.
ID: 2070696

OXYTOCIN FOR SCHIZOPHRENIA: A RANDOMIZED CONTROLLED TRIAL

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Background: Both human and animal studies have found that the neuropeptide oxytocin (OXT) is involved in regulating affiliative behaviors, including sexual behavior, mother-infant and adult-adult pair-bond formation. Social dysfunction is among the most disruptive outcomes of schizophrenia. Intranasal OXT administration has been reported to have pro-social effects in patients with autism spectrum disorders and with schizophrenia. The aim of this study was to examine the effectiveness of intranasal administration of OXT alone, and of OXT combined with social skills training in the treatment of social dysfunction in patients with schizophrenia.
Methods: Using a 2X2 design, we conducted a randomized, double blind, placebo-controlled, 3 week trial testing the effect of intranasal OXT (24IU X3/d) or placebo in combination with social skills training or supportive psychotherapy. Subjects were 48 patients with schizophrenia with significant impairment of their social abilities, stabilized on anti-psychotics. The primary outcome measure was a structured assessment of social interaction, done by video-taping interviews with schizophrenia patients and then having raters blinded to treatment status assessing the quality of the social interactions, specifically focusing on gaze to experimenter's face, vocalization (patient's vocal output, positive/negative tone, and fluent speech) and affect, body tone, movements, and other non-verbal signals.
Results: The study has been completed; we are cleaning up the database and will soon break the blind. Data will be presented.
Conclusion: We hypothesized that while each treatment would be effective separately, the combination of social skills training with OXT treatment will demonstrate a distinct pro-social advantage compared to OXT or placebo alone.
ID: 2118300

CHARACTERISTICS, PHARMACOTHERAPY, AND TREATMENT OUTCOMES OF A LARGE COHORT OF PATIENTS WITH TREATMENT-RESISTANT PSYCHOSIS

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Background: Treatment-resistant psychosis is a challenge to psychiatry and a substantial burden to health-care systems. The province of British Columbia in Canada has publicly funded, universal health care, and patients with treatment-resistant psychosis may receive care in a specialized residential program. Between 1993 and 2011, 663 patients were admitted to this program; this cohort contains one of the largest known series of patients with treatment-resistant schizoaffective disorder.
Methods: All patients were evaluated by a psychiatrist, social worker, pharmacist, nurse, general physician, and neuropsychologist. Records from previous hospital admissions were reviewed and all information was presented at a multidisciplinary conference. This resulted in a consensus DSM-III-R or DSM-IV diagnosis and a detailed treatment plan. Ratings of symptoms and functioning at admission and discharge included the Positive and Negative Syndrome Scale (PANSS), the Global Assessment of Functioning Scale, the Social and Occupational Functioning Scale, and the Clinical Global Impression of Severity. A research psychologist compiled all data by means of chart review.
Results: Patients who did not complete treatment or had a diagnosis other than schizophrenia (SZ), schizoaffective (SZA) or mood disorder (MD) were excluded; the following describes 551 included patients (SZ = 63%, SZA = 29%, MD = 8%). More than half were male (59%), and the mean duration of hospitalization was 30 weeks. The proportion receiving clozapine increased from 21% at admission to 61% at discharge. Those with a MD were less likely to receive clozapine than either SZ or SZA (SZ = 64%, SZA = 61%, MD = 41%). In each diagnostic group, both antipsychotic polypharmacy and the ratio of prescribed to defined daily dose (PDD/DDD) of antipsychotic medication decreased during hospital stay (polypharmacy: SZ: 52% to 16%, SZA: 52% to 14%, MD: 43% to 0%; PDD/DDD: SZ: 2.1 to 1.6, SZA: 2.1 to 1.4, MD: 1.6 to 1.1). The use of mood stabilizers declined in all groups, but antidepressant use declined only in SZ and SZA. Mean total PANSS score declined in all diagnostic groups, but most in MD, least in SZ, and intermediate in SZA.
Conclusion: In an intensive inpatient program for treatment-resistant psychosis, aggregate improvement occurred despite global reduction in medications, while clozapine use nearly tripled. Lower total antipsychotic dose correlated with greater improvement at discharge.
ID: 2117303

PSYCHOSOCIAL TREATMENT PRIOR TO IDENTIFICATION OF CLINICAL HIGH RISK STATUS: CHARACTERISTICS OF THE NORTH AMERICAN PRODROME LONGITUDINAL STUDY (NAPLS)-2 COHORT

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USA; 11. Psychiatry, Institute of Genomic Medicine, Univrsity of California, San Diego, La Jolla, CA, USA; 12. Psychology and Psychiatry, Emory University, Atlanta, GA, USA

Background: Referrals to studies of individuals at clinical high risk (CHR) for psychosis typically accompany a new or worsening complaint or psychosis-specific help seeking. Yet, a majority of these individuals have sought professional help prior to study entry. Our aims were to 1) characterize psychosocial treatment histories of a large CHR population recruited from 8 North American sites between 2008 and 2013 and 2) compare rates of treatment with the NAPLS-1 1998-2005 cohort.
Methods: Detailed treatment histories were collected for 743 (97%) of the NAPLS-2 cohort of 765 identified at CHR with the Structured Interview for Prodromal Syndromes (SIPS). Results were compared with those for the NAPLS-1 cohort.
Results: Eighty percent reported prior treatment (range across sites: 75-96%) compared to 82% in NAPLS-1. NAPLS-2 participants who reported prior treatment received a mean of 46 (SD = 90) sessions over 79 weeks, or 1.5 years. Therapies included supportive (53%, M= 42 sessions), school counseling (17%, M= 60 sessions), case management (13%, M= 22 sessions), cognitive behavioral (11%, M= 28 sessions), family (11%, M= 27 sessions), interpersonal (7%, M= 45 sessions), stress management (3%, M= 14 sessions), and psychodynamic (2%, M= 20 sessions).
Conclusion: In spite of changes in services and public awareness, the rates of prior treatment of participants recruited for CHR research remain strikingly similar to those of an earlier cohort. The high rates of not only recent but historical help-seeking in CHR youth emphasize the potential for even earlier screening and intervention and the need to identify effective treatments and implement them with fidelity in community settings.
ID: 2119159

POOR MEDICATION ADHERENCE OF SCHIZOPHRENIA IN CHINA: RESULTS FROM A MULTICENTER SURVEY

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Background: Non-adherence to antipsychotics is a global issue in schizophrenia treatment which related to more relapse, poorer functioning and worse outcome. This study aimed to (a). Investigate non-adherence rate during the year after hospital discharge among patients with schizophrenia in China, and (b). Explore the risk factors associated with non-adherence.
Methods: It was a retrospective observational investigation without any interventions. Nine hundreds and ninety two schizophrenic inpatients aged 18 to 65 years discharged with recovery/improvement condition between September 2011 and February 2012 from 10 mental health hospitals in China were included in this study. In the end of the year after discharge, we interviewed those enrolled subjects by telephone to collect information about non-adherence and possible risk factors using a homemade questionnaire. Adherence was graded into three levels based on medication taking behavior, (1)adherence: adherence to prescription most of the time, non-adherence time < 2 months or continuously without drug < 2 weeks; (2) moderate non-adherence: adherence to prescription in half of the time, 2 months ≤ non-adherence time < 6 months or 2 weeks ≤ continuously without drug < 2 months; (3) severe non-adherence: almost not adherence to prescription, non-adherence time ≥ 6 months or continuously without drug ≥ 2 months.
Results: Of 992 enrolled subjects, 88.3% (876/992) completed the questionnaire. In which, 38.1% were non-adherence(17.4% were moderate non-adherence and 20.7% were severe non-adherence). Qualitative analysis showed about 30% of the respondents had negative attitude towards medication treatment. The most mentioned reason of the 333 non-adherence patients was "there was no need to take drugs at all" (28.1%); 24.2% thought that drugs could be stopped when symptoms improved, 14.3% didn't adherence because of adverse events. In logistic regression analysis, the top three factors associating with adherence were "positive attitude to medication treatment"(OR=5.434, 95%CI 3.617-8.164), "visiting hospital after discharge" (OR=2.782, 95%CI 1.770-4.374) and "good family environment"(OR=2.492, 95%CI 1.375-4.514).
Conclusion: In our study, 38.1% of patients didn't adherence to their prescriptions. The most important factor associated with non-adherence was negative attitude towards medication treatment. Further research investigating intervention to correct negative attitudes and improve adherence is warranted.
ID: 2117392

TESTING THE RESULTS OF RISK-BASED DATA-MONITORING ALGORITHMS FOR THE PANSS: WHAT IS THE PREDICTIVE ABILITY OF THIS APPROACH GIVEN EMPIRICAL RESULTS IN A POOLED SAMPLE FROM EIGHT PHASE III SCHIZOPHRENIA TRIALS?

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Background: Increasingly academic and industry researchers have been using scale specific algorithms - pre-set rules of item association - to evaluate psychometric study data for risks associated with rater error. Rater error is a significant source of variance in clinical trials and the data-monitoring process is designed to detect problematic scale use and provide correct during the course of a trial. These rules were developed using the factor structures of the instrument (e.g., Marder et al, 1997) wherein, for example, items that measure aspects of given factor should be scored in a particular manner given directionality and magnitude of comparable items. If the direction and magnitude of two items is sufficiently inconsistent, it is referred to as a "violation". The purpose of this study was to use ROC analysis to evaluate the sensitivity of such algorithms to detect the risk of problematic administration of the PANSS in clinical trials.
Methods: ROC analysis was used to determine the true-positive rate, or how sensitive the data-monitoring algorithms are in the detection of problematic data where it existed. The monitoring algorithms split the sample into binary data that contained item relationships containing violations of the scale logic indicative of rater error and those that did not. R 3.1.1 statistical software was used to conduct the ROC analysis and data was considered against the background of dichotomized empirical results from the trials, i.e., if the presence of violation was verified through contact with the rater.
Results: Pooled data (n=4096) from eight Phase III schizophrenia trials that had been subject to in-study data-monitoring was used for this analysis. The true positive rate was found to be in the very good range GLM (AUC = .81) given the model parameters RF (AUC =1).
Conclusion: These results suggest that algorithms designed to detect the error in the PANSS, in their current characterization, appear to have strong predictive power to determine risk of rater error in clinical trials for schizophrenia. The results of improving rater accuracy in-study can lead to better differentiation between drug and placebo and serve to mitigate the risk of both Type-I and Type-II error.
ID: 2119492