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Resting-state functional connectivity alterations in obsessive-compulsive disorder

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Abstract

Neuroimaging studies have led to a better characterization of the neuropsychopathology of obsessive-compulsive disorder (OCD). These findings mainly demonstrate disturbances in fronto-striatal circuits as well as impairments in large-scale networks, encompassing fronto-parietal-limbic areas, defined by functionally connected brain regions, reflecting spontaneous brain activity. Nevertheless, there is inconsistency in the reported results. For instance, while some studies point towards increased connectivity between such large-scale networks, others report decreased connectivity. Furthermore, most of these studies employed hypothesis-driven approaches, basing their assumptions on models derived from neurobiological (i.e., animal, lesion) studies and reports from positron emission tomography (PET) studies. Findings from data-driven approaches are scarce, and it is poorly understood whether the findings of the two approaches converge. To tackle these issues, we conducted two studies that represent the core of this thesis.

First, to overcome inconsistencies and to find a consistent and pathologically relevant pattern of connectivity alterations in OCD, we performed a coordinate-based meta-analysis of 18 whole-brain resting-state functional magnetic resonance imaging (fMRI) studies comparing OCD patients and healthy controls (total sample of 541 patients, 572 healthy controls). The meta-analysis resulted in (1) consistent hypoconnectivity within frontoparietal and salience network, and between salience, frontoparietal and default-mode network, and (2) consistent general dysconnectivity (no specific direction of connectivity change) within default-mode and frontoparietal network, as well as between frontoparietal and default-mode, salience network, limbic network, but also with the striatum and thalamus.

Second, we conducted a resting-state fMRI study in a sample of OCD patients and healthy controls and employed independent component and sliding time window analysis to

investigate functional connectivity changes in a data-driven way. We found that (1) the frontoparietal network showed within-network connectivity alterations, mainly between the left and right parts, and (2) dynamic connectivity changes between the left and the right frontoparietal network and between the frontoparietal network and the salience network. Taken together, these results provided evidence for both connectivity alterations between frontoparietal, salience, and default-mode network, reflecting the so-called triple network model of psychopathology in OCD, and alterations in fronto-striatal circuitry. Furthermore, they provide evidence that independent of methodological approaches, findings converge on the frontoparietal network as the main locus of alterations in OCD, underlining the importance of these regions for the pathophysiology of the disorder.

Zusammenfassung

Neuroimaging-Studien haben zu einer besseren Charakterisierung der Neuropsychopathologie der Zwangsstörung (OCD) geführt. Die Ergebnisse dieser Studien zeigen hauptsächlich Störungen in frontostriatalen Schleifen sowie Beeinträchtigungen in großen Netzwerken, die frontoparietal-limbische Areale umfassen, welche durch funktionell verbundene Hirnregionen definiert sind und die spontane Hirnaktivität widerspiegeln. Trotzdem gibt es Inkonsistenzen in den berichteten Ergebnissen. Während einige Studien auf eine erhöhte Konnektivität zwischen solch großen Netzwerken hinweisen, berichten andere von einer verringerten Konnektivität. Darüber hinaus verwendeten die meisten dieser Studien hypothesengetriebene Ansätze, wobei ihre Annahmen auf Modellen beruhten, die aus neurobiologischen (d.h. Tier-, Läsions-) Studien und Positronen-Emissions-Tomographie (PET) -Studien abgeleitet waren. Erkenntnisse aus datengetriebenen Ansätzen sind selten, und es ist unklar, ob die Ergebnisse der beiden Ansätze übereinstimmen. Um diese Probleme anzugehen, haben wir zwei Studien durchgeführt, die den Kern dieser Arbeit darstellen.

Um Inkonsistenzen zu überwinden und ein konsistentes und pathologisch relevantes Muster von Konnektivitätsänderungen bei Zwangsstörungen zu finden, führten wir zunächst eine koordinatenbasierte Metaanalyse von 18 Untersuchungen zur funktionellen Magnetresonanztomographie (fMRI) unter Ruhebedingungen (d.h. ohne Aufgabe) durch, in denen Patienten mit Zwangsstörung und gesunde Kontrollen verglichen wurden (Gesamtstichprobe von 541 Patienten, 572 gesunde Kontrollen). Die Metaanalyse ergab (1) eine konsistente Hypokonnektivität innerhalb des Frontoparietalen- und Salienz-Netzwerks sowie zwischen dem Salienz-, dem Frontoparietalen- und dem Default-Mode-Netzwerk und (2) eine allgemein konsistente Dyskonnektivität (d.h. keine spezifische Richtung der Konnektivitätsänderung) innerhalb des Default-Mode- und des Frontoparietalen-

Netzwerks, sowie zwischen Frontoparietalem- und Default-Mode-Netzwerk, Salienz-Netzwerk, Limbisches-Netzwerk, Striatum und Thalamus.

Zweitens führten wir eine fMRI-Studie unter Ruhebedingungen an einer Stichprobe von OCD-Patienten und gesunden Kontrollpersonen durch und verwendeten eine Unabhängigkeitsnalyse (Independent Component Analysis) und eine sogenannte Sliding Time Window Analyse, um Änderungen der funktionellen Konnektivität datengesteuert zu untersuchen. Die Studie ergab, dass (1) das Frontoparietale-Netzwerk Änderungen der Netzwerkkonnektivität aufwies, hauptsächlich zwischen dem linken und rechten Teil, und (2) dynamische Konnektivitätsänderungen zwischen dem linken und rechten Frontoparietalen-Netzwerk sowie zwischen dem Frontoparietalen-Netzwerk und dem Salienz-Netzwerk.

Zusammengenommen lieferten diese Ergebnisse demnach Hinweise auf Konnektivitätsänderungen zwischen Frontoparietalem-, Salienz- und Default-Mode-Netzwerk, die das sogenannte Triple-Network-Modell der Psychopathologie bei Zwangsstörungen untermauern, sowie auf Änderungen der frontostriatalen Schleifen. Darüber hinaus liefern sie Belege dafür, dass unabhängig von methodischen Ansätzen der Schwerpunkt der Konnektivitätsveränderungen im frontoparietalen Netzwerk bei der Zwangsstörung zu finden ist, was die Bedeutung dieser Regionen für die Pathophysiologie der Erkrankung unterstreicht.

Contents

Abbreviations

ACC – Anterior cingulate cortex

A-SM – Auditory sensory motor network

BG – Basal Ganglia

BOLD – Blood oxygen level-dependent

CBT – Cognitive Behavioral Therapy

CSTC – Cortico-striato-thalamo-cortical

dACC – Dorsal anterior cingulate cortex

DAN – Dorsal attention network

dFNC – Dynamic functional connectivity

dlPFC – Dorsolateral prefrontal cortex

DMN – Default-mode network

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders 5th Revision

DTI – Diffusion Tensor Imaging

ERP – Exposure and response prevention

FPN – Frontoparietal Network

FWE – Family-wise error

GPi – Globus pallidus pars interna

GPe– Globus pallidus pars externa

IBN – Intrinsic brain network

ICA – Independent component analysis

ICD-10 – International Classification of Diseases 10th Revision

iFC – Intrinsic functional connectivity

lFPN – Left frontoparietal network

LIM – Limbic network

MKDA – Multilevel kernel density analysis

MNI – Montreal Neurological Institute

mPFC – Medial prefrontal cortex

MRI – Magnetic Resonance Imaging

MRS – Magnetic resonance spectroscopy

OCD – Obsessive-compulsive disorder

OCI-R – Obsessive Compulsive Inventory Revised

OFC – Orbitofrontal cortex

PCC – Posterior cingulate cortex

PET – Position emission tomography

PFC – Prefrontal cortex

rFPN – Right frontoparietal network

rs-fMRI – Resting-state functional magnetic resonance imaging

SAL – Salience Network

SMA – Supplementary motor area

SNr – Substantia nigra pars reticulata

SPECT – Single-photon emission computed tomography

SSRI – Selective serotonin reuptake inhibitors

STN – Subthalamic nucleus

VIS – Visual network

vMPFC – Ventromedial prefrontal cortex

Y-BOCS – Yale Brown Obsessive Compulsive Scale

$\chi 2$ – Chi-square test

1 | Introduction

1.1. Obsessive-compulsive disorder

The famous inventor and scientist, Nikola Tesla was not only a genius, but also a very peculiar person. For instance, he refused to shake hands and often wore gloves when interacting with people. Human hair was extremely repulsing to him. He loved the number 3 and had many rituals related to this number. For example, he would always walk around a building 3 times before entering, and he would fold 18 napkins before his meal because 18 is divisible by 3. He had an aversion for round objects and could not stand women wearing earrings around him. Had Tesla lived in modern times, he would most certainly be diagnosed with what we now call 'obsessive-compulsive disorder'.

Obsessive-compulsive disorder, in short OCD, is a debilitating psychiatric disorder that is characterized by the presence of unwanted thoughts and images (obsessions) and/or ritualistic behaviors performed frequently (compulsions). More than just 'being neat and organized', OCD is the 4th most common psychiatric disorder with high psychological and financial burden, poor treatment efficacy and high relapse rates. Estimated prevalence of OCD is between 2-3% worldwide (Ruscio et al., 2010). Patients with OCD often have comorbidities including depression and generalized anxiety disorder, which makes it harder to identify disorder-specific changes in the brain. Even with the current cutting-edge technologies, the pathophysiology of the disease is still poorly understood.

1.2. Historical overview

Although there are some records of religious obsessions in the medieval ages, more accurate accounts of obsessive-compulsive symptoms have been described starting from the 17th century. A big part of these descriptions was still in the religious framework and sufferers were viewed as 'possessed' by some external forces and exorcism was used as a preferred treatment method (Salzman and Thaler, 1981).

The shift of OCD into the medical field only started in the 19th century, mainly through the work of pioneer mental health care professionals such as Sigmund Freud and Pierre Janet.

With advances in cognitive psychology, neurobiology and neuroimaging in the 20th century, the understanding of the disorder has improved. OCD is now classified using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases 10th Revision (ICD-10) by mental health care professionals.

1.3. Clinical Characteristics of OCD

1.3.1. Symptoms

The essential elements of the disorder are obsessions and compulsions. Patients with OCD can have either obsessions or compulsions or both. It is more common to have both elements, i.e., only 5% of the subjects have only obsessions or only compulsions (Shavitt et al., 2014). Obsessions are unwanted, recurring thoughts, images or urges. These take shape despite the patients' own will and generate tremendous distress in their daily functioning. Compulsions are ritualistic, repetitive behaviors, usually performed to eliminate the anxiety that obsessions generate. A simple example could be washing the hands compulsively, a behavior related to the fear of contamination. Compulsions are not necessarily bound to the nature of obsessions. Patients might perform certain rituals, i.e., turning on and off the light switch seven times before an exam, because they believe a parent might die otherwise. OCD

is egodystonic, patients typically understand the absurdity of the behavior, however they still carry it out in order to have some momentary relief from anxiety.

Obsessions and compulsions may be present in various forms. Therefore, the disorder is regarded as heterogeneous from a clinical perspective. Studies using factor analysis identified a number of symptom dimensions, including: contamination/cleaning, doubt about harm/checking, symmetry/ordering, and unacceptable thoughts/mental rituals and hoarding (Bloch et al., 2008; Mataix-Cols et al., 2005).

Although OCD can occur at any time in adulthood, it is more common for first symptoms to appear during childhood, in the range of 7.5 to 12.5 years (Geller et al., 1998). There are two onset peaks. The childhood onset OCD is more common in males and usually has symmetry and checking as the most common symptoms (Shafran, 2001). The second peak is in the range of 20-29 years and it is more common in females, with the most frequent symptom being washing (Graybiel and Rauch, 2000).

1.3.2. Etiology

Family and twin studies provide support for strong genetic involvement in OCD. For example, a study by Nestadt et al. (2001) showed that first degree relatives of OCD patients suffer from OCD five times more often than the relatives of healthy controls. Furthermore, in a twin study, Carey & Gottesman demonstrated a higher co-occurrence of obsessive symptoms in monozygotic (87%) than in dizygotic twins (47%) (Carey and Gottesman, 1981). Other indications of the implication of genetic factors come from preclinical studies. For example, Welch and colleagues (2007) have shown that in mice, the deletion of the sapap3 gene, leads to compulsive grooming.

Neurochemistry imbalances are also associated with OCD. Specifically, the efficacy of SSRIs, a class of drugs that selectively inhibit serotonin reuptake (see below), in treating OCD has led to the serotonin hypothesis of OCD. Although not consistently identified,

abnormalities in serotonin transporter 5-HTT have been reported by some studies (Lombardo et al., 2002; Pogarell et al., 2003; Stengler-Wenzke et al., 2004).

Besides genetic factors and neurochemical imbalances, environmental risk factors have also been identified for OCD, including difficulties at birth, stress and traumatic life events (for a review see (Fontenelle and Hasler, 2008)). Interestingly, cases of OCD after streptococcal infection were observed in children, with obsessive symptoms occurring suddenly after the infection, but apparently disappearing after treatment with antibiotics (Vogel, 2018). However, a study by Schrag et al. (2009) found no relationship between streptococcal infection and developing OCD.

These findings suggest that the etiology of OCD is still little understood (Chamberlain et al., 2005).

1.3.3. Treatment

Serotonergic agents are usually the first choice of pharmacotherapy treatment in OCD. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, sertraline, paroxetine, and citalopram are often administered. In addition to the SSRIs, tricyclic antidepressants such as clomipramine are also commonly used. In fact, clomipramine has been proven to be the most effective medication for OCD (Rauch and Jenike, 1998).

Pharmacological treatments are usually combined with psychological therapies. Cognitive behavioral therapy (CBT), more specifically exposure and response prevention (ERP), is widely used to treat OCD (Franklin et al., 2000; Koran et al., 2007). ERP treatment includes finding the distressing and/or fear eliciting stimuli first, and then exposing the patients to them, while preventing them to perform the necessary compulsive actions. For example, a patient who has washing compulsions due to fear of contamination would practice touching the sink without being allowed to wash his hands afterwards. Through such response

prevention, patients eventually realize that their situation is not particularly dangerous, and that their fear decreases in time even when the compulsions are not performed.

The efficacy of ERP is shown to be similar to current drug regimens. Typically, patients show a 40-60% reduction in symptoms in the long term after ERP treatment (Romanelli et al., 2014).

Perhaps somewhat harder to treat, OCD patients with pure obsessional thoughts and without overt compulsions such as washing and checking, can also benefit from the ERP treatment. In this case, the patients would still be exposed to the obsessional thoughts, for instance through an audiotape, and prevented to perform their mental rituals. Freeston and colleagues showed significant improvement in symptoms with this method, and more importantly, in 6 months follow up, patients' symptoms remained stable (Freeston et al., 1997).

Some case studies show that non-invasive alternative methods such as mindfulness can also reduce OCD symptoms (Singh et al., 2004).

For treatment resistant patients, surgical options are also available. For instance, lesions made to cingulate and thalamus as well as deep brain stimulation of the striatum have been shown to be effective for OCD patients (Pittenger, 2017).

1.4. Neurobiology of OCD

Earliest biological accounts of OCD came to light at the end of the 80s and mid 90s, with advances in neuroimaging. Studies started to identify relevant brain regions for OCD during neuroimaging experiments using both rest and task scanning paradigms (Insel and Winslow, 1992). Important evidence arose from studies using imaging modalities such as position emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetic resonance spectroscopy (MRS), which are nuclear medical imaging techniques

that measure for instance glucose metabolism, blood flow and large metabolites in the brain, respectively (Andreasen, 1988; Harris, 1986).

For instance, in a study published in 1987 by Baxter and colleagues, higher metabolism rates were found in the orbitofrontal cortex (OFC) and parts of basal ganglia (BG), specifically in the striatal caudate nuclei of OCD patients compared to healthy controls or depressed patients (Baxter et al., 1987). This finding of higher metabolic rates was replicated by the same group a year later (Baxter et al., 1988) and by Nordahl and colleagues the next year (Nordahl et al., 1989). Change of OFC metabolism was found by many other groups, who also found alterations in additional regions such as thalamus, cingulate gyri, cerebellum, and lateral prefrontal cortex (PFC) (Martinot et al., 1990; Sawle et al., 1991; Swedo et al., 1989). Moreover, pre and post treatment studies identified significant decreases of OFC and caudate metabolism (Baxter et al., 1992; Benkelfat et al., 1990; Swedo et al., 1992) in OCD patients after being treated with pharmacological drugs or CBT. The areas that are commonly found to be affected in OCD namely OFC, cingulate cortex, caudate, and thalamus are highly connected in so called cortico–striato–thalamo–cortical-circuits, in short CSTC circuits, also known as the fronto-striatal system. They were first defined in 1986 by Alexander and colleagues as positive feedback connections from the cortex to basal ganglia structures, and back to the cortex through the thalamus (Alexander et al., 1986). The basal ganglia represent a series of subcortical structures, which include the striatum as an input nucleus, and the globus pallidus pars interna (GPi) and substantia nigra pars reticulata (SNr) as output nuclei (Haber, 2003). Remarkably, these circuits are organized in a topographic manner, with specific cortical functional territories projecting to specific areas in the basal ganglia and thalamus (Parent and Hazrati, 1995). Furthermore, they have been related to specific functions, based on the functional territories they entail (e.g. limbic, motor).

Based on the specific microarchitecture of the structures involved and their inhibitory and excitatory projects, a direct and an indirect pathway have been identified, which play a role in action execution or action inhibition, respectively. The direct or "go" pathway starts in the cortex, which projects to the striatum in an excitatory manner, and is followed by striatal inhibitory projections to the GPi and SNr, which – due to this inhibition - can no longer inhibit the thalamus, which is thusly disinhibited, and able to excite the cortex. Therefore, the direct loop promotes the execution of action. The indirect loop on the other hand, which also originates in the cortex and projects to the striatum but is followed by an inhibition of the globus pallidus externa (GPe), which in turn can no longer inhibit the subthalamic nucleus (STN). Thusly disinhibited, the STN then excites GPi and SNr, which send inhibitory projections to thalamus. In the indirect or "no-go" pathway, the thalamus gets inhibited and can no longer project to the cortex, which leads to action inhibition (Figure 1).

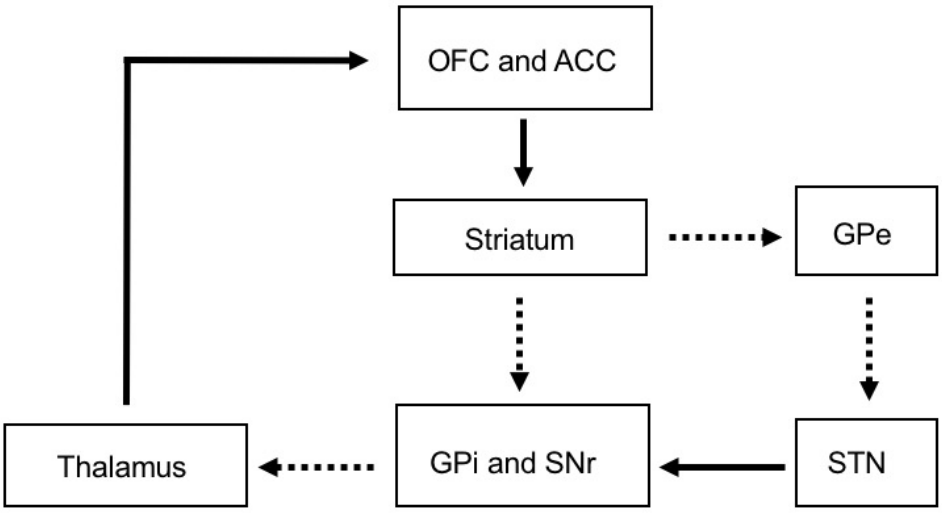

Figure 1. Cortico-striato-thalamo-cortical circuit. Solid arrows indicate excitatory (glutamatergic) and dashed lines indicate inhibitory (GABAergic) pathways. Adapted from Pauls et al. (2014).

The working model of OCD suggests an imbalance between the direct and indirect pathways of CSTC circuits that is mediated by the orbitofrontal subcortical circuit (Saxena and Rauch, 2000). More specifically, a hyperactive direct loop seems to be associated with OCD symptoms. Indeed, OFC, anterior cingulate cortex (ACC), and caudate nuclei have been shown to be involved in the evaluation of the importance of stimuli, habit learning, executive function, error monitoring, and emotional responses to stimuli (Graybiel and Rauch, 2000; Tricomi et al., 2009; Van Veen and Carter, 2002), all of which seemingly impaired in OCD (Ursu et al., 2003). OFC and ACC lesions contribute to the inability of response inhibition (Rosenberg and MacMillan, 2002) and impulse modulation, which again are clearly impaired in OCD. Neurosurgical approaches to the cingulate and thalamus are accompanied by a reduction of OCD symptoms in the treatment refractory patients (Chiocca, 1990). Moreover, animal studies demonstrated that hoarding, a common symptom of OCD, is related to ventromedial striatum, globus pallidus and thalamus which all connect to OFC in the CSTC circuit (Saxena et al., 2001).

Overall, the contribution of OFC in OCD pathophysiology is well supported by studies (Chamberlain et al., 2008; Saxena et al., 1998).

CSTC circuits' dysfunction still remains the prevailing model for OCD pathophysiology after nearly two decades (Saxena and Rauch, 2000), however, recently some changes to this model have been proposed (Milad and Rauch, 2012). Milad and Rauch claimed the classical CSTC model to insufficiently explain the emergence of OCD psychopathology and they revised it, proposing a more detailed version of it, by taking into account the subsystems of CSTC circuits and further regions associated with fear mechanisms. Authors commented that various regions such as amygdala and hippocampus have gained interest for OCD pathophysiology in the recent years. Several studies indicated amygdala dysfunction in OCD (Breiter et al., 1996; Simon et al., 2010) during symptom provocation tasks. In addition, regions that play a role in fear conditioning and extinction such as ventromedial

prefrontal cortex (vmPFC), and dorsal anterior cingulate cortex (dACC) seem to be implicated in OCD pathophysiology too (Adler et al., 2000; Apergis-Schoute et al., 2017). Considering that the above-mentioned therapy approach of ERP is based on the classical concept of extinction (i.e., after successful treatment the conditioned, anxiety provoking character of the stimulus is extinguished, and the stimulus acquires its originally neutral character) the psychopathological relevance of these regions for OCD is highly plausible.

Furthermore, Milad and Rauch argue that the classical CSTC model does not differentiate between subsystems of OFC. For instance, studies showed different functions of lateral OFC and medial OFC, processing negative and positive valence, respectively (Kringelbach and Rolls, 2004). Lastly, early PET studies that found consistent OFC involvement in OCD did not consider these specific functions (Baxter et al., 1996; Saxena and Rauch, 2000).

Overall, Milad and Rauch propose an extended neurobiological model for OCD with three circuits involved: affective, dorsal cognitive, and ventral cognitive circuits (Milad and Rauch, 2012). The affective circuit involves connections between ACC/vmPFC, nucleus accumbens and thalamus, and has been linked to reward processing. The ventral cognitive circuit, shown to be responsible for motor preparation and response inhibition, involves lateral OFC, putamen and thalamus. Finally, the dorsal cognitive circuit originating from the dorsolateral PFC (dlPFC) and projecting through the caudate and thalamus, has been shown to play a role in working memory and executive functions (Figure 2).

In recent years, van den Heuvel et al. (2016) suggested two additional circuits for the OCD neurobiological model, namely a sensorimotor and a fronto-limbic circuit. The former connects the supplementary motor area (SMA), putamen and thalamus, and mediates stimulus-response based habitual behavior. The latter circuit involves connections between vmPFC, amygdala, and thalamus, and processes fear extinction and anxiety.

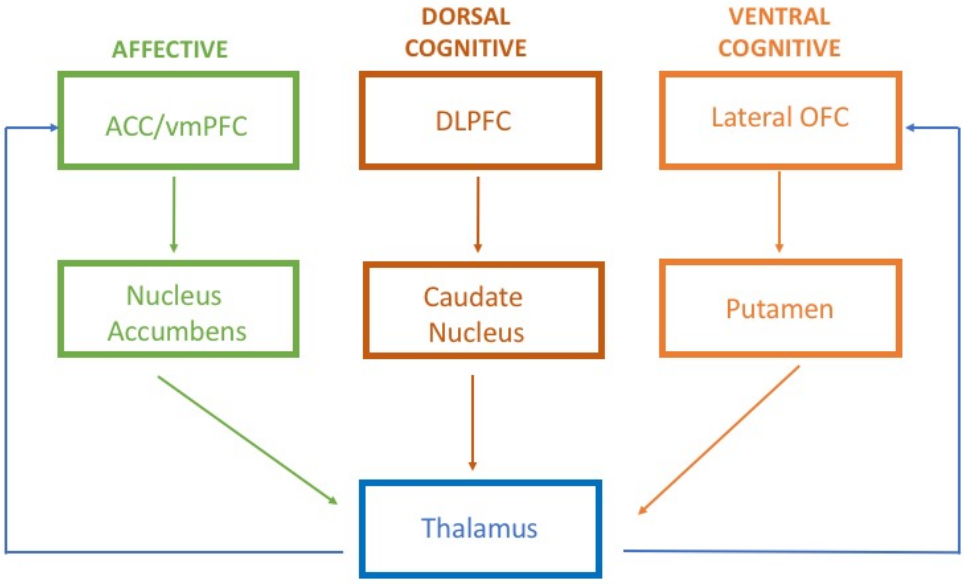

Figure 2. Illustration of pathways and components of cortico-striato-thalamo-cortical circuits implicated in the psychopathology of obsessive-compulsive disorder. ACC: anterior cingulate cortex, vmPFC: ventromedial prefrontal cortex, DLPFC: dorsolateral prefrontal cortex, OFC: orbitofrontal cortex. Modified from Milad and Rauch (2012).

1.5. Functional connectivity of OCD

1.5.1. Resting-state functional magnetic resonance imaging

The human brain can be viewed as a complex network, consisting of regions continuously communicating with each other. One way of measuring these communications is through resting-state functional magnetic resonance imaging (rs-fMRI). In a typical resting-state session, participants are asked to relax and not to think anything particular, while in the scanner. Rs-fMRI measures spontaneous low-frequency fluctuations (<0.1 Hz) of blood-oxygenated-level-dependency (BOLD) signal, reflecting brain activity (Fox and Raichle, 2007).

Biswal and colleagues were the pioneers of functional connectivity, by discovering that during resting-state, the low-frequency fluctuations of the left and right motor cortices of

their participants were highly correlated and did not reflect noise, as previously assumed (Biswal et al., 1995). This finding also demonstrated that the brain is always active, even when the participants are not directly implicated in a certain task.

Brain regions that are temporally dependent - i.e. correlated in their activity - are functionally connected, and functionally connected brain regions, forming spatiotemporal patterns of functional connectivity that organize brain activity at large-scale level are called intrinsic brain networks (IBNs) (Fox and Raichle, 2007). Functional neuroimaging studies consistently identified several IBNs until now. Perhaps the most famous one, the default-mode network (DMN) first identified by Raichle et al. using PET, and later by Grecius et al. using fMRI, consists of medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC) and precuneus (Greicius et al., 2003; Raichle et al., 2001). The DMN reduces its activity during cognitively demanding tasks and is most active during rest, and even shows activity under light sedation (Greicius et al., 2008; Greicius et al., 2003). Furthermore, the DMN has been associated with episodic memories formation, day dreaming, and internal mental processes such as self-processing (Raichle et al., 2001). Another important IBN, the frontoparietal network (FPN), consisting of frontal and parietal regions such as dlPFC and dorsolateral parietal cortex has been linked to goal-oriented behavior (Dodds et al., 2011; Seeley et al., 2007). Also, of interest, the salience network (SAL), including insular cortex and the ACC, has been associated with identifying the saliency of a stimulus and modulation of attentional resources (Palaniyappan and Liddle, 2012; Seeley et al., 2007). Other networks that were consistently found are the visual network (spans over the visual cortex), the auditory network (including auditory cortices), the sensorimotor network (including sensory and motor cortices), and the dorsal attention network (including visual and parietal cortices) (Yeo et al., 2011). IBNs reflect intrinsic brain organization, which has been shown to be stable across different stages of wakefulness, age, and even species (Damoiseaux et al., 2006; Fransson et al., 2007; Greicius et al., 2008; Vincent et al., 2007).

1.5.2. Resting-state fMRI in OCD

Several neuroimaging studies identified functional connectivity abnormalities in OCD with different methods capable of computing functional connectivity such as seed-based functional connectivity and independent component analysis (see Methods for details).

Two putative models of OCD neuropathology have been developed based on findings from seed-based resting-state functional connectivity studies: altered fronto-striatal connectivity and disrupted functional connectivity in large-scale IBNs, specifically in prefrontal-parietal-limbic cortices (Beucke et al., 2014; Goncalves et al., 2017; Pauls et al., 2014).

The former model is supported by many neuroimaging studies (Harrison et al., 2009; Menzies et al., 2008; Posner et al., 2014; Sakai et al., 2011; Saxena et al., 1998; Takagi et al., 2017) and gave rise to the traditional CSTC model of OCD which was previously discussed (see Section 1.4. Neurobiology of OCD), with a particular focus on fronto-striatal projections. Moreover, cognitive functions that rely on this circuit seem to be altered in OCD, which further supports this model (Chamberlain et al., 2005).

The latter model indicates alterations within and between the large-scale IBNs. Of particular interest, DMN, FPN and SAL are commonly reported to be disrupted in OCD (Goncalves et al., 2017; Stern et al., 2012; Zhu et al., 2016). However, these findings are not always consistent. For instance, Stern et al. (2012) showed increased connectivity between anterior insula (part of FPN and SAL) and parts of DMN such as PCC and MPFC. In line with this finding, Posner et al. (2014) also reported increased connectivity between DMN and SAL, specifically between the anterior insula and anterior MFC. On the other hand, Beucke et al. (2014) report decreased connectivity between DMN and SAL.

Beyond seed-based rs-fMRI studies, data-driven methods such as independent component analysis have also been used, albeit scarcer. In more detail, two groups identified connectivity alterations in adult OCD patients using independent component analysis. On the one hand, Fan et al. (2017) divided DMN, SAL and FPN into subsystems. They reported

increased connectivity between SAL and anterior regions of DMN as well as between the SAL and dorsal FPN. On the other hand, Cheng et al. (2013) reported decreased connectivity within the DMN using the same method. These findings appear to be in line with those elicited by seed-based approaches, pointing towards alterations in IBNs, and therefore supporting the second model.

1.6. Aims of the thesis

Studies repeatedly identified dysfunction in important structures included in the CSTC circuits in OCD patients. Recently, rs-fMRI studies reported global connectivity alterations, specifically in the DMN, FPN and SAL.

Based on the literature review mentioned above, the aims of this thesis were three-fold. First, we wanted to identify consistent resting-state network alterations in OCD patients. There have been several studies investigating connectivity alterations in OCD, however, the results are rather inconsistent, probably due to the heterogeneity of the disorder, scanning parameters and other methodological differences between studies, medication, and comorbidities. To achieve this goal, we performed a meta-analysis on 18 resting fMRI studies (overall 541 patients, 572 healthy controls) comparing OCD patients and healthy controls. Meta-analysis is a powerful tool to detect consistent alterations across studies and allows for the identification of such robust connectivity alterations in OCD. Specifically, we used studies that employed a hypothesis-driven approach in investigating functional connectivity alterations in OCD. Based on the accumulated evidence towards alterations reported in CSTC circuits and in triple network model, we hypothesized consistent altered functional connectivity within and between FPN, DMN, SAL and LIM, and between them and subcortical structures such as the striatum and thalamus, in OCD patients compared to healthy controls.

Second, we performed a data-driven analysis on our own OCD patient sample to assess global functional connectivity changes. Due to the scarce literature on data-driven ICA in OCD, we attempted to replicate and extend existing findings. Specifically, we expected to identify alterations in and between DMN, FPN and SAL. Lastly, we investigated the temporal dependency of functional connectivity changes in OCD. In more detail, we used the sliding time window approach, which in comparison to classical static analysis methods allows for the identification of such changes. Based on demonstrated dynamics of IBNs, we hypothesized to find time dependent changes focused mainly on FPN in OCD patients compared to healthy controls.

Together, this thesis aimed to unify the findings of functional connectivity changes in OCD by applying three different analytical approaches and investigating two different data sets. The results of this thesis may provide a more complete and clearer picture on global brain connectivity changes in OCD, and their putative contribution to the pathophysiology of OCD.

2 | Methods

"… all I can say is, that mental action is a function of connections… This much we are surely warranted in accepting; and we have a right to infer that when the continuity of these connections is destroyed, interrupted, or structurally impaired, modification of function must ensue."

-Sir John Batty Tuke, 1894

2.1. A Generic Overview on the Methods

This section provides generic information on the techniques and analysis methods that were used in this thesis. First, the basics of functional magnetic resonance imaging (fMRI) and resting-state are briefly considered, followed by the description of two studies that we performed in order to address the questions asked in this thesis.

2.1.1. Functional MRI – What do we measure?

Functional MRI is a non-invasive imaging technique that measures brain activity. The fMRI method is based on the nuclear magnetic resonance principle. The MRI is basically a magnet that can elicit a very strong magnetic field (e.g. 3T- 60.000 times more than earth's magnetic field) (Jerrolds and Keene, 2009). When subjects are placed in the MR scanner, the water molecules in their body align with the magnetic field of the scanner. Subsequently, when a radio pulse is applied at a certain frequency, these molecules change their alignment from the magnetic field of the scanner to the magnetic field of the radiofrequency. After the pulse, as the molecules return to their initial alignment phase (the scanner's magnetic field), they release a signal which is recorded by the MR scanner. A stronger signal is created where there is more oxygenated blood. fMRI relies on this neurovascular coupling principle, where

there is neural activity, oxygenated blood is provided to the area by the nearby vessels, which is referred to as the hemodynamic response. As oxygenated and deoxygenated hemoglobin have different magnetic properties, change in the ratio of the two leads to signal changes picked up by the fMRI, measured by blood-oxygen-level-dependent (BOLD) contrast (Ogawa et al., 1990).

For many years, fMRI has been used to map brain function, by linking certain functions to specific brain regions. Traditionally, participants were required to complete a task in the scanner. By comparing a baseline condition with such a specific task, it became possible to identify those regions associated with the task (Heeger and Ress, 2002; Linden et al., 1999; Worsley and Friston, 1995). Such studies have led to a much better understanding of brain function, but also of diverse pathological conditions that present with brain function alterations. However, in recent years, one to one mapping of brain region and function became less popular as it became clear that distinct regions in the brain are connected in very complex ways, and that they do not need external stimulation in order to be active. Remarkably, the brain has been found to be intrinsically active (i.e. without being stimulated by a specific task) and this intrinsic activity can also be measured with fMRI.

2.1.2. Resting-state fMRI

Similar to task-based fMRI studies, resting-state fMRI (rs-fMRI) also relies on the BOLD signal. However, the data is acquired without a task performed in the scanner. The goal of rs-fMRI is to investigate spontaneous low-level fluctuations of the brain (Biswal et al., 1995).

As stated in the Introduction section, these low-level fluctuations provide information about how brain regions communicate with each other forming intrinsic brain networks. These networks can be identified by a temporal correlation of remote brain regions. Regions that are correlated in their activity are called to be ‘functionally connected’. Functional

connectivity can give valuable insight into the intrinsic organization of the brain and furthermore provide information on how this organization differs in psychiatric and neurological disorders.

Earlier studies interpreted low-level fluctuations during rest as noise and there have been ongoing discussions on the neuronal basis of rs-fMRI such as, whether the signal merely reflects physiological processes (i.e., cardiac and respiratory). However, the origin of these oscillations (~0.01 < 0.1 Hz) started to gain meaning in the last decade (Van Essen et al., 2012). Functionally connected regions overlap – at least partially – with anatomical projections, for instance in motor, auditory and visual networks, which further supported the idea that intrinsic brain networks are also implicated in specific types of processing related to the underlying neuroanatomical projections. Moreover, cardiac and respiratory processes seem to exhibit different frequency oscillations than those of intrinsic resting-state networks (Cordes et al., 2001). Remarkably, studies show a strong relationship between oscillations measured with rs-fMRI and recordings of electrophysiological techniques (Nir et al., 2008) and fluctuations in neuronal spiking (Shmuel and Leopold, 2008). Methodological considerations are integrated in the preprocessing steps to eliminate irrelevant signals, for instance by using low-pass filtering and regressing out signals arising from cerebral spinal fluid and white matter. These steps maximize the relevancy of resting-state signals interpreted in the rs-fMRI studies.

IBNs can comprise of regions that are anatomically distal. What is supporting this functional connectivity of remote regions? Several studies investigated the relationship between structural and functional connectivity by combining rs-fMRI and diffusion tensor imaging (DTI) which measures the diffusion of water molecules in the brain (Johansen-Berg and Rushworth, 2009). Results indicate strong similarities between the functional and structural connectivity matrices across whole brain (Skudlarski et al., 2008). Grecius et al. (2009) identified a direct anatomical connection (cingulum bundle) connecting PCC and MFC

which are parts of DMN. Furthermore, van den Heuvel and colleagues (2009) demonstrated that the majority of the IBNs, including DMN, FPN, and SAL, have underlying anatomical connections. These findings suggest a general principle of brain organization relating functional and structural connectivity on a whole brain scale.

There are several ways to analyze rs-fMRI. Two of the most common methods, which are also used in this thesis, are seed-based functional connectivity and independent component analyses. On the one hand, seed-based analyses are performed by correlating the time series of a seed (a region of interest) and the rest of the brain (Biswal et al., 1997; Cordes et al., 2000). This method is more suitable when there is an *a priori* hypothesis, i.e. a relevant region is known to be involved in the process being investigated. The simplicity of this type of analysis and straightforward interpretation of the results make the seed-based method a popular analysis method for rs-fMRI. Independent component analysis (ICA) on the other hand, relies on no hypothesis, and it is completely data-driven. ICA decomposes the data into subcomponents that are statistically independent (Beckmann et al., 2005; Calhoun et al., 2001). These components are characterized by an associated time course and a spatial map that indicates the strength of connectivity. Some components represent pure noise whereas other reflect the established IBNs. In comparison to seed-based methods, ICA is more of a global measure of functional connectivity. Together, seed-based and ICA methods show a strong overlap in the rs-fMRI studies and both support the formation of functionally connected intrinsic brain networks during rest (Van Dijk et al., 2009).

Majority of rs-fMRI studies are based on the assumption that iFC is stationary over time. Usually, the time series in rs-fMRI are averaged across the whole scan to achieve a single correlation coefficient that represents the strength of connectivity. However, with this method, time dependent changes in connectivity may be overlooked, and several studies pointed out that IBNs exhibit dynamic properties (Chang and Glover, 2010; Zalesky et al., 2014). One way of identifying time dependent connectivity changes is through sliding time

window analysis. This method enables us to perform several correlations between two time series by applying a sliding window throughout the resting-state scan, thus, obtaining several correlations and ultimately from these, the peak connectivity between two IBN can be extracted (Franzmeier et al., 2017; Sakoglu et al., 2010).

To sum up, rs-fMRI analyses allow for the investigation of the intrinsic organization of the human brain by characterizing the coherent fluctuations of brain regions. Such methods make it possible to investigate how brain regions communicate with each other, for instance in networks (Biswal et al., 1995; Damoiseaux et al., 2006; De Luca et al., 2006).

Finally, clinical rs-fMRI studies that compare patients and healthy controls provide valuable information on how large-scale brain network organization may differ in psychopathology (Greicius et al., 2007; Greicius et al., 2004; Gürsel et al., 2018; Whitfield-Gabrieli et al., 2009). In the next sections, two rs-fMRI studies are presented that investigate functional connectivity alterations in OCD patients compared to healthy controls.

2.2. Study 1: Meta-analysis of functional connectivity in OCD

The first study's aim was to conduct a meta-analysis in order to identify consistent functional connectivity alterations across fMRI studies that used seed-based functional connectivity approaches to investigate patients with OCD in comparison with healthy controls.

2.2.1. Literature Search and Data Extraction

In the first step, studies that were suitable for the meta-analysis were identified. The literature search was performed using PubMed, Scopus, and PsycNet databases with the query (rest* OR intrinsic) AND connect* AND (OCD OR obsess* OR compuls*) (Figure 3). Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed (Stroup et al., 2000). Cut-off date for the search was July 2016.

Only rs-fMRI studies were included that used whole-brain seed-based intrinsic functional connectivity (iFC) to compare between healthy controls and OCD patients. The studies had to be in the English language and provide information about peak differences in iFC between the two groups. Furthermore, studies were excluded if they did not respect the following: 1. methods other than seed-based iFC (e.g., independent component analysis, graph theory analysis, etc.); 2. did not perform whole-brain analysis (e.g., region of interest analysis); 3. peak coordinates could not be extracted; 4. missing baseline analysis in the case of longitudinal studies.

Following the same approach as Kaiser and colleagues (2015), first seed center coordinates and peak coordinates of significant group differences were extracted from each study and converted to MNI space. Each peak coordinate was marked as hyperconnectivity (representing increased positive or reduced negative connectivity) or hypoconnectivity (representing decreased positive or increased negative connectivity). Second, each peak coordinate was assigned to a brain network based on the anatomical location. Visual (VIS), auditory-sensorimotor (A-SM), dorsal attention (DAN), salience (SAL), limbic (LIM), frontoparietal (FPN), and default-mode network (DMN) templates were used from the whole brain network parcellation of 1000 participants covering cortex, striatum, and cerebellum (Buckner et al., 2011; Choi et al., 2012; Yeo et al., 2011)

In total, 18 studies were selected, that included 541 patients with OCD and 572 healthy controls (see Figure 3 for flow diagram below).

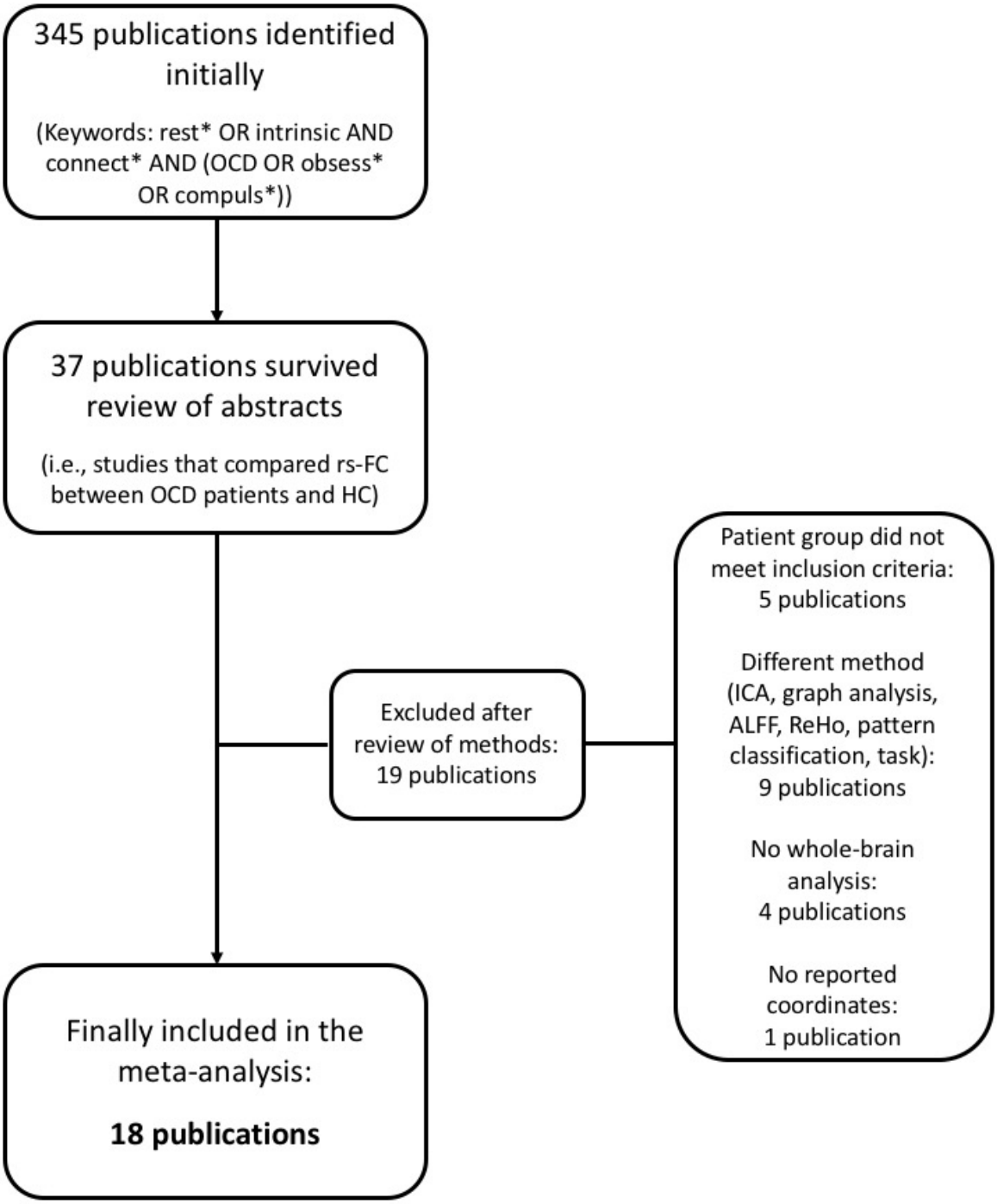

Figure 3. Flow diagram of the literature search of the meta-analysis. The literature search for seed-based rs-fMRI studies yielded a total of 18 publications with a sample of 541 OCD patients and 572 healthy controls. Search keywords and exclusion criteria are shown.

2.2.1. Multilevel kernel density analysis

Coordinate based meta-analysis was performed using the multilevel kernel density (MKDA) toolbox from Wager's lab (http://wagerlab.colorado.edu). In more detail, the method is based on the following:

1. Peak coordinates from each study were convolved with 10mm Gaussian kernel. Due to this, a single study with multiple peaks close to each other would not bias the results. Convolved maps were then binarized, resulting in so-called indicator maps. In an indicator map, each voxel has a value of 1 or 0, representing at least one peak or no peak within the 10 mm radius, respectively.
2. Indicator maps were weighted by sample size and averaged across studies, which resulted in density maps. Each voxel's value in a density map represents the density statistic, which shows the proportion of study contrasts that report at least one peak of functional connectivity difference within the 10mm radius of the voxel.

Two density maps, reflecting the outcome-measure of the meta-analysis, were created per network indicating either hyper- or hypoconnectivity of the network across studies. Consistent hyperconnectivity was calculated by subtracting the hypoconnectivity density map from the hyperconnectivity density map, and correspondingly, consistent hypoconnectivity was calculated by subtracting the hyperconnectivity from the hypoconnectivity density map. Finally, general dysconnectivity was calculated by averaging the two maps (i.e. hypo- and hyperconnectivity).

To establish the significance of the resulting density maps, a Monte Carlo simulation with 15.000 iterations was performed. This step provided a distribution of results, on which the family-wise error (FWE) rate threshold for multiple comparisons was used. Result clusters of significant effects were detected both with height-based threshold (based on density value of that voxel) and extent-based threshold (size of the cluster) (Wager et al., 2007). Results

at $p < .05$ FWE-corrected were reported for both thresholds as they provide complementary information (Kaiser et al., 2015).

2.2.3. Post-hoc analyses

Several post-hoc analyses were performed to control for different factors that could affect the results. First, jackknife analyses were conducted to test if a single study had a disproportionate effect on the results. A jackknife analysis represents the density statistic of every significant meta-analytic result cluster calculated while leaving out one study at a time and then comparing it to the original density statistic using a chi-square ($\chi 2$) test (Etkin and Wager, 2007).

Also, for some networks, some seeds were used more often than others by a larger number of studies, i.e., regions belonging to the CSTC circuits (Harrison et al., 2013; Harrison et al., 2009; Hou et al., 2013; Jung et al., 2013; Posner et al., 2014). To tackle this issue, we calculated the density statistic of each significant result cluster for each region and compared it to the other regions in the same network using a $\chi 2$-test (Kaiser et al., 2015).

We also tested whether clinical factors such as age (adolescent, adult, younger adult, older adult), medication (medicated/ non-medicated), onset type (pre-pubertal, adolescent, adult), symptom severity (mild/moderate/severe) and comorbidity in the form of depression (yes/no) confounded our results. To control for this, we divided the studies into the above-mentioned categories. Then for each category, we calculated the significant cluster and performed $\chi 2$-test to compare density statistic of each result cluster with the other categories in the factor (Kaiser et al., 2015).

2.3. Study 2: Independent component and sliding time window analyses of functional connectivity

The second study's aim was to investigate functional connectivity alterations of IBNs in OCD patients using a data-driven method, and to test whether such alterations are subject to temporal dynamics.

2.3.2. Participants

50 OCD patients and 42 healthy controls matched for age and gender participated in the study. OCD patients were recruited from the Psychosomatic Hospital Windach and Tagesklinik Westend and healthy controls were recruited through online and newspaper advertisements. All participants gave consent according to the Ethical Committee guidelines of Klinikum Rechts der Isar, Technische Universität München. OCD patients were diagnosed based on the DSM-5 criteria. All participants went through 9 minutes of resting-state fMRI scanning with the instruction of keeping awake with eyes closed and not thinking of anything specific. In addition, OCD patients were assessed with relevant clinical questionnaires such as Y-BOCS (Yale-Brown Obsessive-Compulsive Scale) and OCI-R (Obsessive Compulsive Inventory Revised). Details of demographics and clinical characteristics can be seen in Table 3.

2.3.3. MRI Data Acquisition

All images were acquired using 3T Philips scanner with a 32-channel head-coil. T1 weighted high resolution anatomical images used magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence with the parameters: repetition time (TR) = 11.08 ms, echo time (TE) = 5.1 ms, flip angle = 8°, matrix size = 368x318, number of slices = 230, with a resolution of 0.7 × 0.7 × 0.7 mm.

$T2^*$ weighted functional MRI resting-state data images used echo-planar imaging (EPI) with the parameters: TR = 2.7 s, TE = 33 ms, flip angle = 90°, FOV = 192 × 192 × 141 mm, matrix size =96 × 94 × 64 transverse slices with 2.0 mm thickness, covering the entire brain with a resolution of 3 × 3 × 3 mm. In total, 200 whole-brain volumes were recorded.

2.3.4. Data Analysis

2.3.4.1. Data Preprocessing

Functional and structural images were preprocessed using Statistical Parametric Mapping (SPM), version 12 (Wellcome Institute of Cognitive Neurology, London https://www.fil.ion.ucl.ac.uk/spm/). Preprocessing steps included realignment, co-registration of functional image to structural image, normalization to Montreal Neurological Institute (MNI) 2x2x2 mm template, segmentation and smoothing with 6mm Gaussian kernel. Framewise displacement (FD) was used to analyze head motion and was calculated as the sum of the absolute values of the derivatives of the 6 motion parameters obtained from SPM12. One healthy control and one OCD patient were excluded due to excessive head motion (mean FD>0.2mm). No significant differences in mean FD (p=0.73) were found between the remaining healthy controls (mean=0.12, sd=0.03) and OCD patients (mean=0.11, sd=0.04).

2.3.4.2. Independent component analysis and selection of the networks

Independent component analysis (ICA) is a data-driven method that decomposes data into spatially independent networks without *a priori* hypothesis. In order to perform group ICA, the approach from Calhoun et al. (2001) was adapted using the GIFT toolbox (http://icatb.sourceforge.net). First, all the rs-fMRI data of all the participants were concatenated. These multi-subject data were then reduced with principal component

analysis and fed into the algorithm to estimate 20 independent components. 20 components have been chosen as the number has been shown to be sufficient for robust identification of several networks including DMN, FPN and SAL (Di and Biswal, 2014). The analysis was run 20 times to ensure that the components were consistent across analyses.

For further analyses, independent components from the group ICA algorithm were back-reconstructed to the single-subject space. This step calculates the time courses and spatial maps for each component for single subjects. Spatial maps are shown with a z-map representing the components' functional connectivity. Higher z-values represent stronger connectivity.

In order to determine whether our components reflect the IBNs of interest, seven templates from Yeo and colleagues were used (Yeo et al., 2011). These templates were identified through parcellation of 1000 subjects' brains and they represent robust representations of IBNs. Each component was correlated with these templates one by one, and components showing the highest correlations were chosen as networks of interest.

In the templates from Yeo and colleagues the FPN is provided as a single network. However, group ICA yielded a left and right FPN. We were interested in lateralization effects within FPN, and therefore kept the two components separately as implemented by the group ICA algorithm.

Together, all the analyses were performed on these four networks: left FPN (lFPN), right FPN (rFPN), DMN, SAL.

2.3.4.3. Statistical Analysis

2.3.4.3.1. Demographics and Clinical Characteristics

Comparisons of demographics and clinical characteristics between healthy controls and OCD patients were performed with two-sample t-tests and chi-square test.

2.3.4.3.2. Intra IFC

We first tested for alterations within each IBN of interest, reflecting intra intrinsic functional connectivity (iFC). First, spatial maps were statistically evaluated with one-sample t-test for each group using SPM12 ($p<0.05$, FWE-corrected for multiple comparisons). Second, voxel-wise two sample t-test was performed in order to compare between OCD patients and healthy controls, using age and gender as covariates-of-no-interest. Furthermore, since medication has been shown to affect iFC (Beucke et al., 2013), we also performed control analyses so as to detect the effects of medication. Specifically, we split the patient group into a medicated and a unmedicated subgroups and compared them via voxel-wise two-sample t-test.

2.3.4.3.3. Inter IFC

In the next step, we tested for group differences between the IBNs of interest, reflecting inter iFC. To achieve this, each networks' time course was correlated via pairwise Pearson correlation to the time course of every other network. Correlation coefficients were transformed to z values via Fisher transformation and then entered into two-sample t-test.

2.3.4.3.4. Sliding time window analysis

To measure peak correlations between the networks' time courses, the sliding time window method was applied using Dynamic FNC (dFNC) toolbox in GIFT. Following the approach by Franzmeier and colleagues (2017), a window with a width of 30 repetition time (TR), was overlaid on time courses and shifted in steps of 1 TR. Tapered window was created by convolving the rectangular window with 3mm Gaussian kernel. For each time window, Pearson correlation was calculated between each network's time course to every other network's time course. To measure peak correlation throughout the whole rs-fMRI session, the mean correlation of 10 consecutive time windows was calculated (40 TR's, 108 seconds of MRI acquisition). In order to detect any effect of window selection, the analysis was repeated by calculating the mean correlation with 5 and 15 consecutive time windows. No significant differences were found; therefore, the results are reported based on the previously established time window of 10. To test for group differences, subject specific mean correlations of healthy controls and OCD patients were compared with two-sample t-tests. As we had four components of interest (DMN, lFPN, rFPN, SAL), correlations between the networks were performed 6 times.

3 | Results

3.1. Study 1

18 publications including 541 OCD patients and 572 healthy controls were gathered from the literature search (Table 1). Due to a small number of studies (<3), meta-analysis was only performed for the following IBNs: Default-mode, frontoparietal, salience and limbic networks. The results based on these studies were twofold: The first result revealed hypoconnectivity within and between IBNs, which reflects decreased functional connectivity in OCD patients compared to healthy controls. The second result demonstrated general dysconnectivity within and between IBNs, which reflects consistent abnormal functional connectivity alterations without specific direction in OCD patients compared to healthy controls. No significant hyperconnectivity alterations were found.

Author, year	HC (n)	Mean age HC	OCD (n)	Mean age OCD	Illness duration	Symptom severity (Y-BOCS)	Medicated
Anticevic et al., 2014	66	33	27	36.3	17.3	27.1	yes
Bernstein et al., 2016	13	16	15	15.3	5.7	19.7	yes
Beucke et al., 2013	11	31.9	11	29.1	-	20	no
Beucke et al., 2014	46	30.3	46	30.7	-	20.8	yes
Chen et al., 2016	30	28.1	30	26.2	5.5	23.7	yes
Fitzgerald et al., 2010	18	14.1	18	13.9	3	16.1	yes
Fitzgerald et al., 2011	68	19.8	67	19.7	8.7	20	yes
Harrison et al., 2009	21	26.2	21	28.5	8.7	20.7	yes
Harrison et al., 2013	74	32.7	74	33.1	11.3	21.8	yes
Hou et al., 2013	33	25	33	25.3	6.3	21.1	no
Hou et al., 2014	39	26	39	26.6	3.7	26.7	no
Jang et al., 2010	22	24.3	22	25.1	7.6	21.3	no
Jhung et al., 2014	18	28.2	26	27.2	10.9	22.1	yes
Jung et al., 2013	18	24.8	19	25.8	7.8	20.6	no
Li et al., 2012	20	28.2	20	28.2	6.5	24.8	no
Posner et al., 2014	20	32.6	23	30.9	14.8	25.9	yes
Sakai et al., 2011	23	30.8	20	30.9	-	24.6	yes
Stern et al., 2012	32	28.1	30	25.4	-	22.1	yes

Table 1. Demographic and clinical characteristics of obsessive-compulsive disorder studies included in the rs-fMRI meta-analysis. Y-BOCS = Yale-Brown Obsessive-Compulsive Scale.

3.1.1. Hypoconnectivity

In line with our hypothesis, we found altered functional connectivity in patients in the form of hypoconnectivity. Specifically, we found both within and between iFC alterations for FPN, and SAL.

3.1.1.1. Frontoparietal network

The FPN presented both within network hypoconnectivity and hypoconnectivity with the DMN. Both clusters were located in the dorsolateral prefrontal cortex (dlPFC). (extent-based significance threshold; Table 2, Figure 4, bottom). These results indicate consistently reduced iFC within the FPN and between the FPN and DMN across the studies included in the meta-analysis.

3.1.1.2. Salience network

We found hypoconnectivity within the SAL, peaking in the supramarginal gyrus, a large cluster, which was also part of FPN and DMN. Beyond SAL within-network hypoconnectivity, this cluster also reflected hypoconnectivity between SAL and DMN as well as between SAL and FPN (extent-based significance threshold; Table 2, Figure 4, middle section). These results indicate consistent hypoconnectivity between all three networks of interest, across all studies included in the meta-analysis.

Seed network: Visual (VIS)							
Network had too few seeds for meta-analysis.							
Seed network: Auditory-sensorimotor (A-SM)							
Network had too few seeds for meta-analysis.							
Seed network: Dorsal attention (DAN)							
Network had too few seeds for meta-analysis.							
Seed network: Salience (SAL)							
Effect network	Effect anatomy/region	MNI peak coordinates			Voxels	Maximum P	Threshold (extend/height based)
		x	y	z			
Seed anatomy: insula, prefrontal cortex, striatum							
OCD < HC							
FPN	Right supramarginal gyrus extending to the DMN	52	-40	40	514	0.345	eb
Seed network: Limbic (LIM)							
Seed anatomy: nucleus accumbens, HF, VCN/NA, left OFC, Left IVS							
-							
Seed network: Frontoparietal-executive (FPN)							
Effect network	Effect anatomy/region	MNI peak coordinates			Voxels	Maximum P	Threshold (extend/height based)
		x	y	z			
Seed anatomy: middle temporal gyrus, dorsolateral prefrontal cortex, striatum							
OCD < HC							
FPN	Middle frontal gyrus	-48	16	34	959	0.365	eb
General dysconnectivity in OCD patients							
LIM	Accumbens extending into caudate, thalamus, insula, ACC and OFC	-10	22	-4	3615	0.141	eb
Seed network: Default-mode (DMN)							
Effect network	Effect anatomy/region	MNI peak coordinates			Voxels	Voxels	Threshold (extend/height based)
		x	y	z			
Seed anatomy: cingulate cortex, parietal cortex, prefrontal cortex, striatum, temporal cortex, striatum							
General dysconnectivity in OCD patients							
DMN	ACC	2	42	0	68	0.361	hb
DMN	MPFC	0	44	-2	986	0.299	eb

Table 2. Aberrant intrinsic functional connectivity for each seed network based on Multilevel Kernel Density Meta-Analysis. All reported results are significant for $p<0.05$ FWE-corrected (hb = height-based, eb = extent-based). Labelling of networks was derived from the location of the cluster's peak coordinate. Abbreviations: HC = healthy controls, MNI = Montreal Neurological Institute, OFC = orbitofrontal cortex, IVS= inferior ventral striatum, HF=hippocampal formation, ACC = anterior cingulate cortex, MPFC = medial prefrontal cortex, Maximum P = maximum density value in this cluster (= weighted proportion of studies reporting at least one peak of iFC-difference within 10 mm radius of this voxel), OCD = obsessive-compulsive disorder.

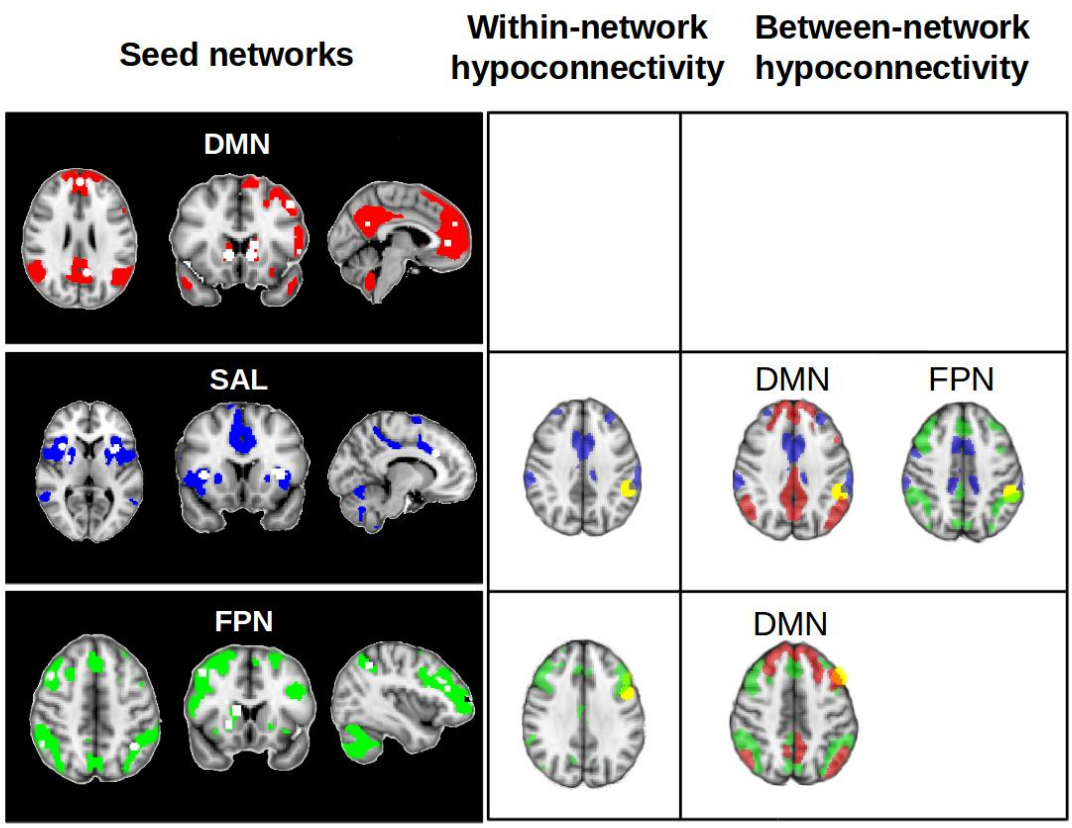

Figure 4. Hypoconnected clusters overlaid on the corresponding seed networks. The left column represents the seed networks (red for DMN, blue for SAL and green for FPN). White spheres represent the anatomical seeds. The middle column represents the within-network connectivity alterations for the respective seed network. The right column represents the between-network connectivity alterations with respect to the seed network. Yellow spheres represent hypoconnectivity clusters.

3.1.2. General Dysconnectivity

Regarding the dysconnectivity findings, our results pointed towards altered functional connectivity within FPN, between FPN and DMN, between FPN and thalamus and between FPN and LIM. Moreover, within dysconnectivity was found in DMN.

3.1.2.1. Default-mode network

The DMN presented within network dysconnectivity located in the ventral medial prefrontal cortex (vmPFC) and anterior cingulate cortex (ACC) (height-based and extent-based significance threshold; Table 2, Figure 5, top).

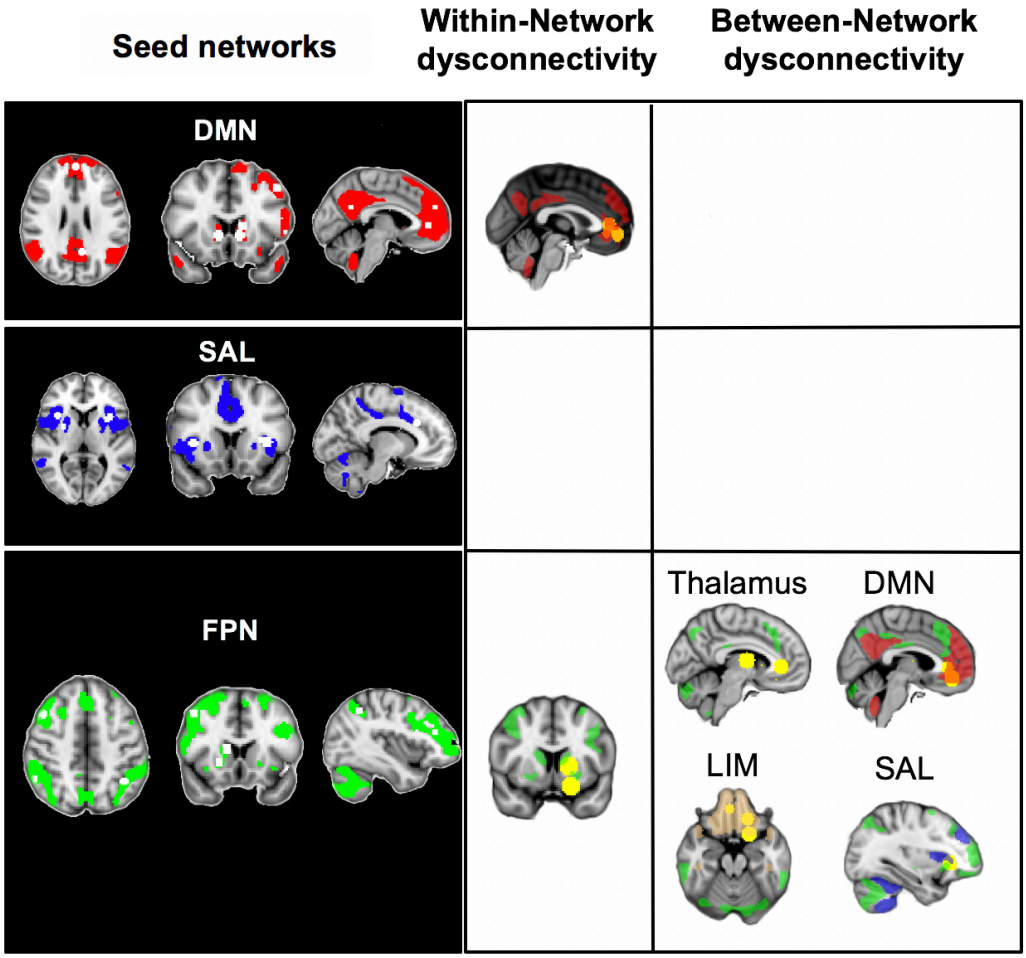

Figure 5. General dysconnectivity clusters overlaid on the corresponding seed networks. The left column represents the seed networks (red for DMN, blue for SAL and green for FPN). White spheres represent the anatomical seeds. The middle column represents the within-network connectivity alterations for the respective seed network. The right column represents the between-network connectivity alterations with respect to the seed network. Yellow spheres represent dysconnectivity clusters.

3.1.2.2. Frontoparietal network

The FPN showed within network general dysconnectivity in the striatum as well as between network dysconnectivity with the DMN (located in vmPFC/ACC), LIM (located in OFC) and SAL (located in insula). Moreover, dysconnectivity with the thalamic dorsomedial nucleus was also found (extent-based significance threshold; Table 2, Figure 5, bottom). These results indicate wide-spread alterations of the FPN with other IBNs and key structures of the CSTC circuits, including the striatum and thalamus (Figure 6).

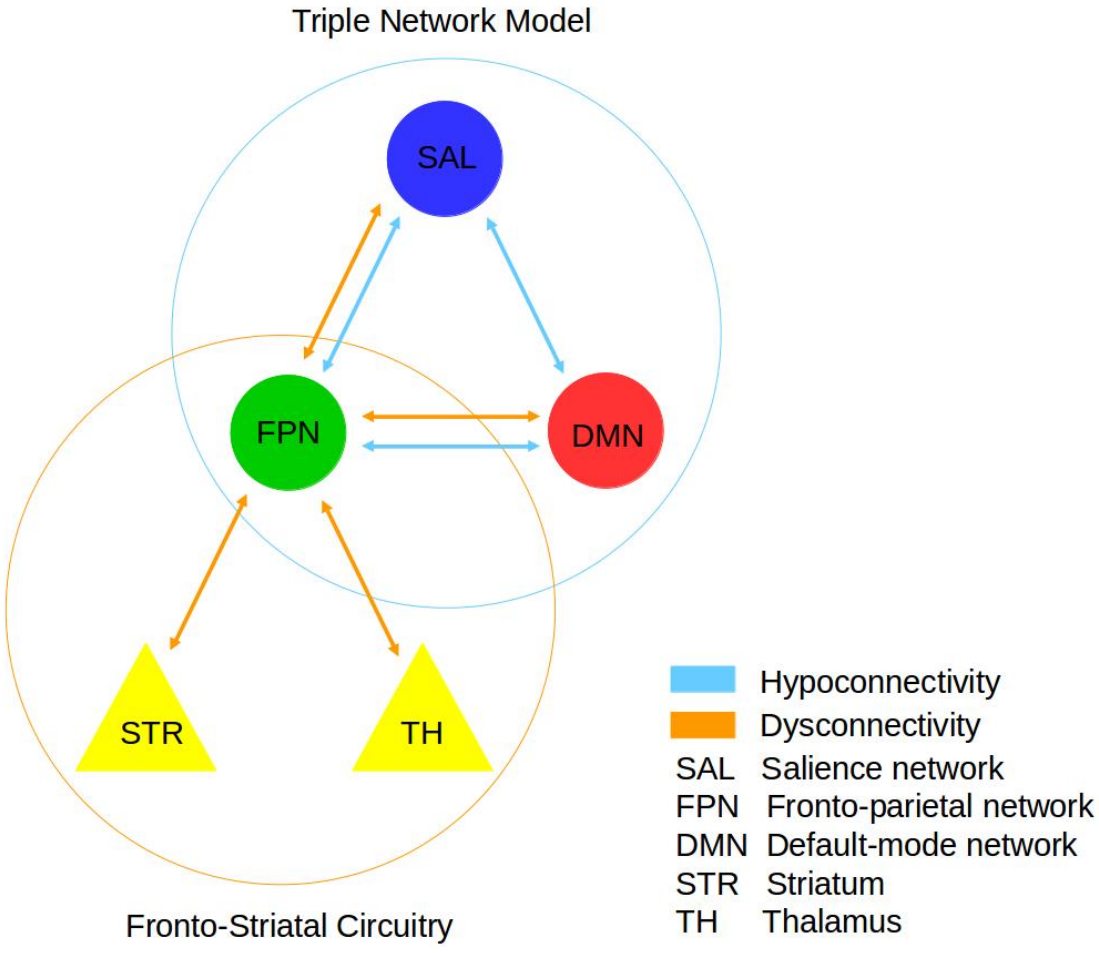

Figure 6. Summary of general dysconnectivity and hypoconnectivity findings in the meta-analysis of seed-based rs-fMRI studies in obsessive-compulsive disorder. Orange circle represents the general unspecific connectivity alterations, which overlap with the regions in the fronto-striatal circuitry. Blue circle represents the reduced connectivity findings of SAL, FPN and DMN, reflecting the validity of the triple network model for OCD. The junction of both findings indicates FPN as a key network of OCD pathophysiology.

3.1.3. Post-hoc analyses

Jackknife analyses showed no effect of a single study on the findings ($p \geq .52$). Additional post-hoc analyses revealed no significant impact of any anatomical region, medication, depression, age of onset, or age. This indicates that the results are robust and not biased by methodological issues.

3.2. Study 2

3.2.1. Sample Characteristics

No significant differences were found between the OCD patients (mean age=34,42 sd=12.07; 16 males) and healthy controls (mean age=35.07, sd=10.04; 19 males) in terms of age (p=0.86) and gender (p=0.51). The demographic and clinical characteristics of the participants are depicted in Table 3.

	Healthy Controls (n = 41)	OCD Patients (n = 49)	p-value
Demographics			
Age, Mean (SD)	35.07 (10.04)	34.42 (12.07)	.86
Gender, Males (%)	19 (46 %)	16 (32 %)	.51
Clinical Characteristics			
Medication (Yes / No)	-	31 / 18	-
Comorbidities	-	22	-
Depression	-	14	-
ADHD	-	4	-
General / Social Anxiety	-	1 / 1	-
Panic Attacks	-	1	-
Borderline	-	1	-
Age of Onset (Mean / Min / Max)		18.3/ 7 / 58	-
Y-BOCS Total, Mean (SD)	-	20.95 (6.1)	-
Y-BOCS Obsessions, Mean	-	10.65 (3.46)	-
Y-BOCS Compulsions Mear	-	10.30 (3.83)	-
OCI-R Total, Mean (SD)	-	27 (10.19)	-
HAM-D, Mean (SD)	-	13.3 (5.46)	-

Table 3. Demographic and clinical characteristics of obsessive-compulsive disorder patients and healthy controls included in the rs-fMRI analysis. Abbreviations: ADHD = Attention Deficit Hyperactive Disorder, Y-BOCS = Yale-Brown Obsessive-Compulsive Scale, OCI-R = Obsessive Compulsive Inventory Revised, HAM-D = Hamilton Depression Rating Scale.

3.2.2. Group ICA

Group ICA yielded 20 components. To determine the corresponding network for each component, we correlated each component with Yeo (2011) templates of interest; 4 components were retained. Correlation coefficients were in the range of 0.30 - 0.44,

indicating a good correlation. Figure 7 shows the spatial maps of the components representing the networks of interest, all components were stable across both groups.

3.2.2.1. Group differences in Intra IFC

First, we tested for within network iFC alterations, reflecting intra iFC. We found increased connectivity in the left FPN located in the superior and middle frontal gyrus in OCD patients compared to healthy controls (cluster-based correction $p<0.01$; cluster size:551, Figure 7, B2, second row). No significant group differences were found for right FPN, SAL and DMN, indicating intra iFC alterations to be restricted to the left FPN.

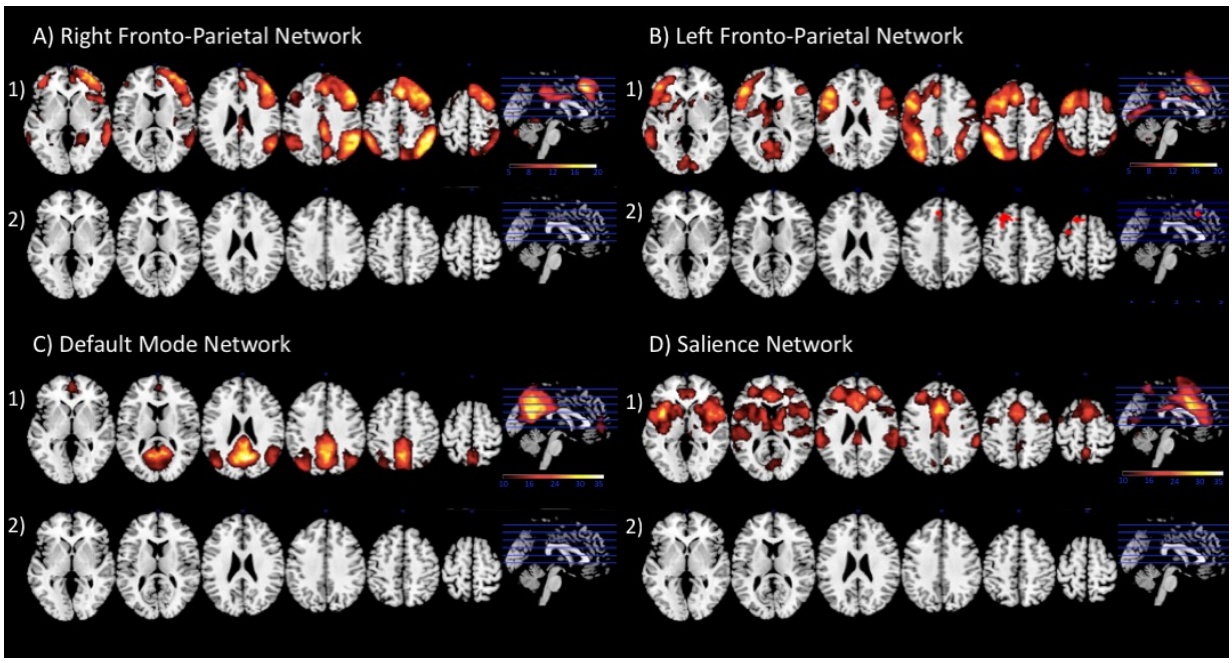

Figure 7. Right and left frontoparietal network, default-mode network & salience network overlaid on MNI template. Axial slices of each network are at the following ascending z-coordinates: 0, 12, 25, 38, 50 & 62. 1) depicts 1-sample t-tests of the respective network for all subjects (FWE, $p<0.05$). The color-scale for rFPN & lFPN are shown for t-values. 2) shows results for the 2-sample t-test between the groups HC and OCD. The red color highlights the changes for OCD>HC. The color scale represents t-values and all maps are corrected with extent threshold ($p < 0.001$; cluster > 111).

3.2.2.2. Group differences in Inter IFC with ICA

Between-network findings indicated decreased connectivity between left and right FPN in OCD patients compared to healthy controls (Figure 8, Table 4, panel A). This result was due to lower positive correlations in the OCD group (correlations HC: 0.498, OCD: 0.342 $p<0.001$). No other group differences were observed.

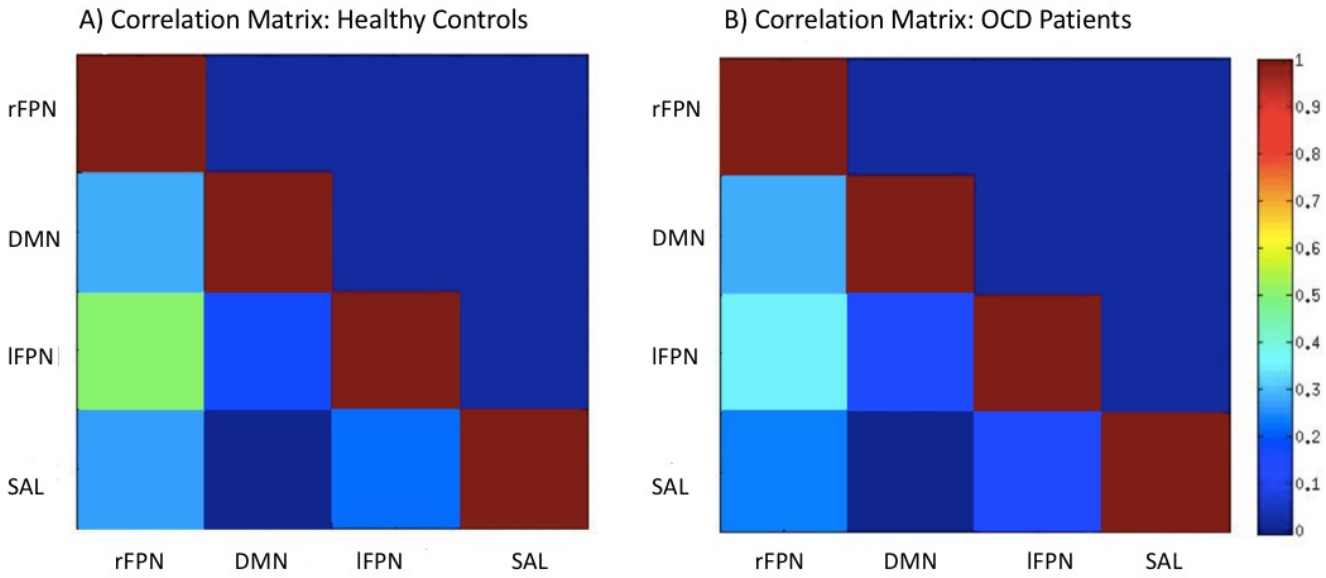

Figure 8. Inter-network iFC matrices for healthy controls and OCD patients. Pairwise Pearson's correlations were performed between the 4 networks of interest. The averaged correlation values of the z-scores are presented here and the colors represent the intensity of the correlations. Abbreviations: r/lFPN=right/left frontoparietal network; DMN=default-mode network; SAL=salience network.

3.2.2.3. Group differences in Inter IFC with Sliding time window analyses

Significant differences were found between left and right FPN and also between left FPN and SAL. More specifically, OCD patients showed decreased functional connectivity for both network pairs. Results were due to lower positive correlations in OCD group (HC: 1.013, OCD: 0.806; HC: 0.732, OCD: 0.561, $p<0.008$, see Table 4 below for details).

	HC (n = 41)	OCD (n = 49)	two-sample t-test direction	p-value
A) Inter-iFC				
rFPN - DMN	0.27	0.28		0.76
rFPN - lFPN	0.49	0.33	HC > OCD	0.0009*
rFPN - SAL	0.25	0.23		0.76
DMN - lFPN	0.15	0.14		0.75
DMN - SAL	-0.02	-0.01		0.76
lFPN - SAL	0.21	0.13		0.08
B) Sliding time window				
rFPN - DMN	0.71	0.77		0.30
rFPN - lFPN	1.01	0.80	HC > OCD	0.0008*
rFPN - SAL	0,74	0.71		0.65
DMN - lFPN	0.59	0.59		0.924
DMN - SAL	0.44	0.45		0.881
lFPN - SAL	0.73	0.55	HC > OCD	0.007*

Table 4. Inter-iFC and Sliding Time Window correlation values between healthy controls and OCD patients. Both correlation values are fisher-z-transformed. IC = Independent component; DMN = Default-mode network; SAL = Salience network; l/rFPN = left/right fronto-parietal network; p-value = from two-sample t-tests reduced to $p < 0.0083$ after Bonferroni correction for 6 t-tests; * = Significance.

4 | Discussion

4.1. Summary of findings

The current thesis investigated functional connectivity alterations in patients with OCD in two separate studies. In the first study, using a coordinate-based meta-analysis of seed-based rs-fMRI studies, we identified consistently altered functional connectivity in large scale brain networks in patients with OCD compared to healthy participants. Specifically, OCD patients showed hypoconnectivity (reduced connectivity) within and between frontoparietal, salience and default-mode networks. Furthermore, this study revealed general dysconnectivity (unspecific directional change) for frontoparietal and default-mode networks, focusing on fronto-cingulate and insular cortices, striatum, and thalamus in patients with OCD.

In the second study, we investigated network based functional connectivity alterations in OCD using a data-driven approach. Based on the mounting evidence of default-mode, frontoparietal, and salience networks alterations that the current literature points out, we focused our analyses on these three networks. By performing one of the most established data-driven approaches, namely ICA, we found increased connectivity within the left frontoparietal network as well as a decreased connectivity between left and right frontoparietal networks. In addition, we performed sliding time window analysis, a novel method which enabled us to identify dynamic connectivity alterations. This revealed decreased connectivity between left and right frontoparietal networks and decreased connectivity between left frontoparietal and salience network.

4.2. Study 1: Meta-analysis of functional connectivity alterations in OCD

The meta-analysis revealed two types of consistent functional connectivity alterations in large scale intrinsic brain networks: hypoconnectivity and general dysconnectivity. Both alteration types affected within and between-network iFC.

4.2.1. Hypoconnectivity

Hypoconnectivity, reflecting reduced iFC in patients compared with healthy controls, was found in the FPN and also between FPN and DMN, both located in a cluster in the dlPFC (Figure 4, bottom, Table 2). Alterations between FPN and DMN have been reported in the literature, although the direction of alteration varies as some studies report hypo- and others hyperconnectivity (see for example the review from Pittenger (2017)). Of note, FPN and DMN connectivity changes have been associated with OCD symptoms (Goncalves et al., 2017). In this sense, a contribution of altered iFC between FPN and DMN to OCD symptomatology could be hypothesized as a disrupted interplay between internal thoughts that are regulated by DMN and goal-oriented behavior that is modulated by FPN (Stern et al., 2012).

Additionally, we found hypoconnectivity within the SAL, between SAL and FPN, and between SAL and DMN. The cluster was located in the supramarginal gyrus (Figure 4, middle section, Table 2). These findings are supported by previous reports of hypoconnectivity between SAL and FPN and between SAL and DMN in OCD patients (Beucke et al., 2014; Harrison et al., 2009; Posner et al., 2014). The SAL encompasses the insular cortices, ACC, and subcortical regions, and is involved in the detection of the saliency of stimuli, as well as directing cognitive and attentional resources (Palaniyappan and Liddle, 2012; Seeley et al., 2007). SAL acts as a switch between internal thoughts or mental processes and external goal-oriented behaviors that are modulated by DMN and

FPN, respectively. Alterations between the SAL, DMN, and FPN have been named the 'triple network model of psychopathology' (Menon, 2011). Disruptions in these networks have been linked to various disorders including depression, ADHD, schizophrenia, autism and frontotemporal dementia (Bressler and Menon, 2010; Manoliu et al., 2013; Manoliu et al., 2014; Menon, 2011; Yuan et al., 2016; Zheng et al., 2015).

Recently, Fan and colleagues (2017) also reported triple network alterations in OCD patients. In this study, the authors divided DMN and FPN into subsystems in their analyses and reported functional connectivity changes between SAL and subsystems of DMN and FPN, respectively. In more detail, the authors found connectivity alterations between the anterior part of DMN (mPFC and ACC) and SAL, along with dorsal FPN (superior parietal gyrus and superior frontal gyrus) and SAL. The results from this study are in line with our own findings of aberrant functional connectivity between DMN and SAL and between FPN and SAL.

Switching between internal processes and goal-oriented behavior requires a healthy modulation of these three networks. Disruption in the communication of the triple networks may potentially provide a neural basis for obsessive-compulsive behavioral patterns, explaining why patients are unable to detach from obsessive thoughts.

As previously stated, the triple network model has been reported in several psychiatric disorders (Buckholtz and Meyer-Lindenberg, 2012; Menon, 2011). Such common connectivity alterations in large scale networks may therefore reflect a general marker of psychopathology. This hypothesis has been confirmed by a recent meta-analysis which investigated resting-state data in 8 different psychiatric disorders, including OCD, based on a total sample size of 8298 patients and 8165 healthy controls (Sha et al., 2019). Partly similar to the present findings this meta-analysis showed hypoconnectivity between FPN and SAL and DMN and ventral SAL, as well as a hyperconnectivity between the DMN and FPN and between the DMN and dorsal SAL. Hence, these findings once more illustrate

alterations in the triple network in the context of various psychiatric disorders. The authors conclude from their findings that the network disruption might represent a marker of illness progression, cognitive deterioration, or even genetic susceptibility of the respective psychiatric disorders. However, alterations between the networks can take various forms (increased/ decreased iFC), which do not appear to be consistent across different psychiatric disorders, indeed not even consistent in OCD (i.e., both hypo- and hyperconnectivity have been reported for DMN-FPN (see for example the review from Pittenger (2017)). Different alteration patterns in distinct psychiatric disorders or distinct subgroups of one disorder may therefore reflect disorder/ disorder-subgroup specificity (see for instance associations between FPN-DMN altered iFC and symptoms in (Goncalves et al., 2017)).

4.2.2. General dysconnectivity

General dysconnectivity, reflecting altered iFC without specifying the direction of change, was found for FPN and DMN. Specifically, for FPN, the results were in the fronto-cingulate areas, striatum and thalamus (Figure 5, bottom).

FPN alterations are common findings in the OCD literature. Alterations in both within FPN and between FPN and other networks have been reported. For instance, a study that employed graph theory approach by Gottlich et al. (2014), showed increased connectivity within FPN in unmedicated OCD patients. In our findings, the cluster of alteration within the FPN was located in the striatum and included the left putamen and the left caudate (Figure 5, bottom). Basal ganglia structures, especially the striatum, have been repeatedly shown to be involved in OCD. Nonetheless, the findings from recent fMRI studies are not consistent regarding the type of alterations. For instance, some studies reported increased connectivity between striatum and other regions (Hou et al., 2013; Posner et al., 2014), while others found decreased connectivity in the same areas (Gottlich et al., 2014; Vaghi et

al., 2017). These mixed imaging studies may explain our general unspecific dysconnectivity findings.

Interestingly, although most of the findings point towards hyperconnectivity between the striatum and frontal regions (Gottlich et al., 2014; Harrison et al., 2009; Vaghi et al., 2017), there are also alternate findings, which suggest that medication may have an effect on these results. For instance, Beucke and colleagues (2013) reported decreased ventral striatum connectivity in medicated OCD patients in comparison to unmedicated OCD patients.

We also identified dysconnectivity between FPN and the thalamus, mainly located in dorsomedial and ventral anterior nuclei (Figure 5, bottom, Table 2). Thalamus dysfunction in OCD has been shown by many studies (Fitzgerald et al., 2011; Perani et al., 1995) and specifically the dorsomedial nucleus has been shown to play an important role in the pathogenesis of OCD (Modell et al., 1989). It is possible that thalamus dysfunction might contribute to disturbances in the cortico-striato-thalamic circuits (CSTC). Such contribution is possible in two ways: (1) the thalamus has reciprocal connections with the cortex, reflecting so-called cortico-thalamic circuits that can influence different functional cortical areas, which in turn project to the striatum – reflecting the input structure of the basal ganglia - (Haber and Calzavara, 2009), and (2) the thalamus is a key structure of the CSTC circuits, which relays feedback to the cortex (Alexander et al., 1986).

With reference to between-network general dysconnectivity, the results revealed aberrant functional connectivity between FPN and several networks such as DMN, LIM and SAL (Figure 5, bottom Table 2). The cluster for FPN-LIM dysconnectivity was located in the orbitofrontal cortex (OFC). Gottlich et al. (2014) found similar results in their study and also associated this iFC alteration to cognitive deficits, emotion processing, and reward in OCD.

These general dysconnectivity results were mostly located within frontal and between frontal and subcortical areas. As these structures – in particular OFC, ACC, vmPFC,

striatum, and thalamus – are part of the CSTC circuits (Pauls et al., 2014), our findings are in line with the most accepted pathophysiological model of OCD. As detailed in the Introduction section of this thesis, CSTC circuits represent positive feedback loops between cortical regions including OFC, ACC, PFC and basal ganglia structures such as the striatum and pallidum through the thalamus (Alexander et al., 1986; Haber, 2003; Milad and Rauch, 2012), and are organized in a parallel but largely segregated way. Through direct and indirect pathways of the CSTC circuits, action/movement/behavior initiation or inhibition occurs, respectively (Benarroch, 2016; Pauls et al., 2014). In OCD, an imbalance between the direct and indirect pathways that could contribute to symptom generation or maintenance has been hypothesized (Pauls et al., 2014; Saxena et al., 2004).

To summarize, our meta-analysis showed both hypoconnectivity and general dysconnectivity within and between intrinsic brain networks, contributing to the idea of the validity of the triple network model in OCD, and adding further support for aberrant CSTC circuits in OCD, mainly focused on fronto-striatal and fronto-thalamic circuits. The triple network model displays an abnormal relationship between salience, default-mode and frontoparietal networks, which might reflect impairments in switching between obsessions/compulsions and goal directed behavior. Furthermore, altered CSTC circuits indicate a dysregulation in the inhibition of intrusive thoughts and compulsive actions. Remarkably, the frontoparietal network appears to be the common element in both pathophysiological models, further stressing the relevancy of these areas in OCD (Figure 6). These findings of connectivity alterations appear to be robust, as they were not biased by age, illness duration or medication, as shown by post-hoc analyses.

4.3. Study 2: Intrinsic brain network alterations in OCD: Insights from independent component and sliding time window analyses

Group ICA results revealed both intra and inter network connectivity alterations focused on within and between FPN, as well as between FPN and SAL.

Regarding the intra network findings, we found increased connectivity in OCD patients in the left FPN, mainly in the superior and middle frontal gyrus (Figure 7, B2, Table 2). Similar results were reported previously. For instance, Göttlich and colleagues (2014) employed a graph theory approach and found increased connectivity in the FPN located in middle frontal gyrus in OCD patients. Moreover, Anticevic et al. (2014) also reported alterations in the superior, middle and inferior gyri in patients with OCD. These findings, therefore, suggest consistent FPN alterations, mainly in middle frontal gyrus, as they have been shown with distinct analysis frameworks and in independent samples.

Regarding the inter iFC network findings, we found reduced connectivity between left and right FPN (Figure 8, Table 4, panel A). FPN alterations are frequently reported in OCD functional connectivity studies (Gürsel et al., 2018). This network is involved in regulating goal oriented meaningful behavior, and attention. Alterations in FPN might explain some of the symptoms of OCD such as difficulties in task switching or response inhibition (Abramovitch et al., 2013; Remijnse et al., 2006).

In the second part of the study, we investigated dynamic functional connectivity alterations. The majority of fMRI studies make the assumption that intrinsic brain network connectivity is constant over time and the analyses are usually performed by averaging the signal over the whole resting-state experiment duration. This is a convenient but over simplistic way of looking into the complex dynamics of brain activity (Deco et al., 2013). Recent studies have shown time varying changes in functional connectivity, specifically fluctuations over time

between different network pairs (Hutchison et al., 2013; Jones et al., 2012; Zalesky et al., 2014). In order to integrate time dependent changes in our data which might not be captured with the traditional analyses, we performed sliding time window approach, which enabled the identification of peak connectivity changes between intrinsic brain networks. This method demonstrated reduced connectivity between left and right FPN, further supporting the inter-iFC findings, and also reduced connectivity between left FPN and SAL (Table 4, panel B). These findings are in line with the results of the first study (Gürsel et al., 2018) and other reports of reduced connectivity between FPN and SAL in OCD patients (Harrison et al., 2009). However, they extend previous findings by demonstrating that within FPN and FPN-SAL iFC alterations are also dynamic in nature.

4.4. Limitations

The studies included in this thesis have several limitations. Regarding the first study, we restricted the meta-analysis to whole-brain seed-based rs-fMRI studies. Specifically, we excluded independent component analyses, graph theory analyses, regional homogeneity, or Granger causality. Based on such exclusions, we restricted our search to hypothesis-driven approaches (i.e., seed-based analyses), which might have resulted in a more prominent depiction of CSTC circuits' alterations. Next, the meta-analysis focused on seed regions (i.e., regions of interest yielded by previous studies or models of OCD psychopathology) and related networks. Based on common models of psychopathology, some seed regions were used more often than others, which might have led to an overrepresentation of some networks. For example, the largest number of included studies contained seeds in the fronto-striatal system. We attempted to control for these issues with jackknife analyses, however we cannot completely exclude a bias of overrepresentation. Finally, the meta-analysis was limited to rs-fMRI data, and did not, one the one hand,

account for structural alterations – which are also common in OCD (Rus et al., 2017) - or attempt to converge structural and functional alterations.

Regarding the second study, the ICA identified 20 independent components. However, a higher number of components (i.e., 75 ICs) generates more detailed networks, reflecting subcomponents (i.e., anterior, posterior, superior and ventral parts of the networks), which might be used to identify more fine-grained connectivity patters. However, we only focused here on three networks of interest (DMN, SAL and FPN) for which a predefined component number of 20 was sufficient. Regarding the time window analysis, time dependent analysis of resting-state fMRI is susceptible to noise. We employed rigid preprocessing steps and a relatively larger size of window (with 81s duration) to minimize such effects. Lastly, we used a heterogeneous sample of patients in our study, which might mask some of the specific connectivity patterns seen in subgroups. In more detail, several factors can have an effect on iFC ranging from symptom profile (Jhung et al., 2014), illness duration (Ping et al., 2013) to medication status (Beucke et al., 2013). To tackle this last issue, we split the patient group into two subgroups based on medication and compared them. We found no evidence of different alteration patterns of iFC between the two groups, suggesting FPN alterations as a robust marker for OCD.

4.5. Outlook and Concluding Remarks

To sum up, this thesis investigated functional connectivity alterations in OCD with two separate studies. In the first study, we identified consistently altered functional connectivity in several regions with a network analysis, by investigating 18 studies that involved a large number of patients and healthy controls. In the second study, we employed a data-driven approach without *a priori* hypotheses in our own sample. Taken together, these studies' findings provide support for the classical neurobiological model of OCD, namely they point

towards alterations along the CSTC circuits, and demonstrate that the triple network model of psychopathology also applies to OCD.

Collectively, the results of both studies indicate the FPN as the main locus of alteration in OCD. Remarkably, as demonstrated through different analyses with different samples, FPN alterations seem to be very robust, regardless of the analysis method, sample or heterogeneity of the disorder.

In order to understand the importance of FPN regions in OCD, it is crucial to evaluate its functional implications. The FPN is involved in a variety of executive functions, but crucially, it has a role in cognitive flexibility such as set shifting and response inhibition. Response inhibition can be measured by simple Go/No-Go or stop-signal tasks in which the participant needs to withhold a response intermittently. Inhibitory impairments have been reported in OCD by many studies (Aycicegi et al., 2003; Bannon et al., 2002; Rosenberg et al., 1997) and even more importantly, these impairments were associated with structural changes in frontal and parietal regions (Menzies et al., 2007). Impairments in set shifting have been also commonly reported (Hymas et al., 1991; Okasha et al., 2000). Together, these results indicate a rigid cognitive pattern – i.e., lack of flexibility – in OCD patients, reflecting an impairment in basic cognitive functioning. Furthermore, this thesis demonstrates alterations not only within FPN but also between FPN and various regions including subcortical areas such as striatum and thalamus. Speculatively, due to such altered connectivity patterns between the FPN and several other 'relay' structures in the brain, such basic functional impairment in executive functioning could spread to several other functional areas, leading to a very heterogeneous clinical tableau, as seen in OCD patients.

Regarding OCD heterogeneity, several studies report that a large variety of symptoms often start in childhood or adolescence (Nestadt et al., 2000; Ruscio et al., 2010). The field could benefit from research approaches using longitudinal studies in order to investigate how brain changes occur in different stages of the disorder, and whether different symptom

profiles can be identified. It is known from some fMRI studies on OCD patients, for instance during a symptom provocation task in which the patients are presented with stimuli that target their symptoms subtypes, that specific activations can be identified in different regions for distinct subgroups (Mataix-Cols et al., 2004). Future research is needed to identify whether symptom specific neural mechanisms exist in OCD and whether treatments can be developed that target specific regions corresponding to distinct symptom dimensions. This complicated and heterogenous disorder should be further investigated by integrating findings from brain structure, function, as well as genetics and cellular alterations. Technological improvements now allow scientists to employ multimodal imaging for example using a hybrid PET/MR scanner. Such a technique allows observations not only for brain structure and function but also for neuromodulatory systems, which have been shown to be involved in OCD pathophysiology.

6 | References

Abramovitch, A., Abramowitz, J.S., Mittelman, A., 2013. The neuropsychology of adult obsessive-compulsive disorder: a meta-analysis. Clin Psychol Rev 33, 1163-1171.

Adler, C.M., McDonough-Ryan, P., Sax, K.W., Holland, S.K., Arndt, S., Strakowski, S.M., 2000. fMRI of neuronal activation with symptom provocation in unmedicated patients with obsessive compulsive disorder. J Psychiatr Res 34, 317-324.

Alexander, G.E., DeLong, M.R., Strick, P.L., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9, 357-381.

Andreasen, N.C., 1988. Brain imaging: Applications in psychiatry. Science 239, 1381-1388.

Anticevic, A., Hu, S., Zhang, S., Savic, A., Billingslea, E., Wasylink, S., Repovs, G., Cole, M.W., Bednarski, S., Krystal, J.H., Bloch, M.H., Li, C.S., Pittenger, C., 2014. Global resting-state functional magnetic resonance imaging analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder. Biol Psychiatry 75, 595-605.

Apergis-Schoute, A.M., Gillan, C.M., Fineberg, N.A., Fernandez-Egea, E., Sahakian, B.J., Robbins, T.W., 2017. Neural basis of impaired safety signaling in obsessive compulsive disorder. Proceedings of the National Academy of Sciences 114, 3216-3221.

Aycicegi, A., Dinn, W.M., Harris, C.L., Erkmen, H., 2003. Neuropsychological function in obsessive-compulsive disorder: effects of comorbid conditions on task performance. European psychiatry 18, 241-248.

Bannon, S., Gonsalvez, C.J., Croft, R.J., Boyce, P.M., 2002. Response inhibition deficits in obsessive-compulsive disorder. Psychiatry Res 110, 165-174.

Baxter, L.R., Jr., Phelps, M.E., Mazziotta, J.C., Guze, B.H., Schwartz, J.M., Selin, C.E., 1987. Local cerebral glucose metabolic rates in obsessive-compulsive disorder. A comparison with rates in unipolar depression and in normal controls. Arch Gen Psychiatry 44, 211-218.

Baxter, L.R., Jr., Saxena, S., Brody, A.L., Ackermann, R.F., Colgan, M., Schwartz, J.M., Allen-Martinez, Z., Fuster, J.M., Phelps, M.E., 1996. Brain Mediation of

Obsessive-Compulsive Disorder Symptoms: Evidence From Functional Brain Imaging Studies in the Human and Nonhuman Primate. Semin Clin Neuropsychiatry 1, 32-47.

Baxter, L.R., Jr., Schwartz, J.M., Mazziotta, J.C., Phelps, M.E., Pahl, J.J., Guze, B.H., Fairbanks, L., 1988. Cerebral glucose metabolic rates in nondepressed patients with obsessive-compulsive disorder. Am J Psychiatry 145, 1560-1563.

Baxter, L.R., Schwartz, J.M., Bergman, K.S., Szuba, M.P., Guze, B.H., Mazziotta, J.C., Alazraki, A., Selin, C.E., Ferng, H.-K., Munford, P., 1992. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Archives of general psychiatry 49, 681-689.

Beckmann, C.F., DeLuca, M., Devlin, J.T., Smith, S.M., 2005. Investigations into resting-state connectivity using independent component analysis. Philosophical Transactions of the Royal Society B: Biological Sciences 360, 1001-1013.

Benarroch, E.E., 2016. Intrinsic circuits of the striatum: Complexity and clinical correlations. Neurology 86, 1531-1542.

Benkelfat, C., Nordahl, T.E., Semple, W.E., King, A.C., Murphy, D.L., Cohen, R.M., 1990. Local cerebral glucose metabolic rates in obsessive-compulsive disorder. Patients treated with clomipramine. Arch Gen Psychiatry 47, 840-848.

Beucke, J.C., Sepulcre, J., Eldaief, M.C., Sebold, M., Kathmann, N., Kaufmann, C., 2014. Default mode network subsystem alterations in obsessive-compulsive disorder. Br J Psychiatry 205, 376-382.

Beucke, J.C., Sepulcre, J., Talukdar, T., Linnman, C., Zschenderlein, K., Endrass, T., Kaufmann, C., Kathmann, N., 2013. Abnormally high degree connectivity of the orbitofrontal cortex in obsessive-compulsive disorder. JAMA Psychiatry 70, 619-629.

Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 34, 537-541.

Biswal, B.B., Van Kylen, J., Hyde, J.S., 1997. Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. NMR Biomed 10, 165-170.

Bloch, M.H., Landeros-Weisenberger, A., Rosario, M.C., Pittenger, C., Leckman, J.F., 2008. Meta-analysis of the symptom structure of obsessive-compulsive disorder. Am J Psychiatry 165, 1532-1542.

Breiter, H.C., Rauch, S.L., Kwong, K.K., Baker, J.R., Weisskoff, R.M., Kennedy, D.N., Kendrick, A.D., Davis, T.L., Jiang, A., Cohen, M.S., Stern, C.E., Belliveau, J.W., Baer, L., O'Sullivan, R.L., Savage, C.R., Jenike, M.A., Rosen, B.R., 1996. Functional magnetic resonance imaging of symptom provocation in obsessive-compulsive disorder. Arch Gen Psychiatry 53, 595-606.

Bressler, S.L., Menon, V., 2010. Large-scale brain networks in cognition: emerging methods and principles. Trends Cogn Sci 14, 277-290.

Buckholtz, J.W., Meyer-Lindenberg, A., 2012. Psychopathology and the human connectome: toward a transdiagnostic model of risk for mental illness. Neuron 74, 990-1004.

Buckner, R.L., Krienen, F.M., Castellanos, A., Diaz, J.C., Yeo, B.T., 2011. The organization of the human cerebellum estimated by intrinsic functional connectivity. J Neurophysiol 106, 2322-2345.

Calhoun, V.D., Adali, T., Pearlson, G.D., Pekar, J.J., 2001. Spatial and temporal independent component analysis of functional MRI data containing a pair of task-related waveforms. Hum Brain Mapp 13, 43-53.

Carey, G., Gottesman, I.J.R.P., New York, 1981. Twin and family studies of anxiety, phobic and obsessive disorders In Klein DF, Rabkin JG (editor) Anxiety New research and Changing Concepts.

Chamberlain, S.R., Blackwell, A.D., Fineberg, N.A., Robbins, T.W., Sahakian, B.J., 2005. The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. Neurosci Biobehav Rev 29, 399-419.

Chamberlain, S.R., Menzies, L., Hampshire, A., Suckling, J., Fineberg, N.A., del Campo, N., Aitken, M., Craig, K., Owen, A.M., Bullmore, E.T., 2008. Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. Science 321, 421-422.

Chang, C., Glover, G.H., 2010. Time-frequency dynamics of resting-state brain connectivity measured with fMRI. Neuroimage 50, 81-98.

Cheng, Y., Xu, J., Nie, B., Luo, C., Yang, T., Li, H., Lu, J., Xu, L., Shan, B., Xu, X., 2013. Abnormal resting-state activities and functional connectivities of the anterior and the posterior cortexes in medication-naive patients with obsessive-compulsive disorder. PLoS One 8, e67478.

Chiocca, E.A., 1990. Neurosurgical therapy of obsessive-compulsive disorder. Obsessive-compulsive disorders: theory and management, 283-289.

Choi, E.Y., Yeo, B.T., Buckner, R.L., 2012. The organization of the human striatum estimated by intrinsic functional connectivity. J Neurophysiol 108, 2242-2263.

Cordes, D., Haughton, V.M., Arfanakis, K., Carew, J.D., Turski, P.A., Moritz, C.H., Quigley, M.A., Meyerand, M.E., 2001. Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. AJNR Am J Neuroradiol 22, 1326-1333.

Cordes, D., Haughton, V.M., Arfanakis, K., Wendt, G.J., Turski, P.A., Moritz, C.H., Quigley, M.A., Meyerand, M.E., 2000. Mapping functionally related regions of brain with functional connectivity MR imaging. AJNR Am J Neuroradiol 21, 1636-1644.

Damoiseaux, J.S., Rombouts, S.A., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M., Beckmann, C.F., 2006. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A 103, 13848-13853.

De Luca, M., Beckmann, C.F., De Stefano, N., Matthews, P.M., Smith, S.M., 2006. fMRI resting state networks define distinct modes of long-distance interactions in the human brain. Neuroimage 29, 1359-1367.

Deco, G., Jirsa, V.K., McIntosh, A.R., 2013. Resting brains never rest: computational insights into potential cognitive architectures. Trends in neurosciences 36, 268-274.

Di, X., Biswal, B.B., 2014. Modulatory interactions between the default mode network and task positive networks in resting-state. PeerJ 2, e367.

Dodds, C.M., Morein-Zamir, S., Robbins, T.W., 2011. Dissociating inhibition, attention, and response control in the frontoparietal network using functional magnetic resonance imaging. Cereb Cortex 21, 1155-1165.

Etkin, A., Wager, T.D., 2007. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry 164, 1476-1488.

Fan, J., Zhong, M., Gan, J., Liu, W., Niu, C., Liao, H., Zhang, H., Yi, J., Chan, R.C.K., Tan, C., Zhu, X., 2017. Altered connectivity within and between the default mode, central executive, and salience networks in obsessive-compulsive disorder. J Affect Disord 223, 106-114.

Fitzgerald, K.D., Welsh, R.C., Stern, E.R., Angstadt, M., Hanna, G.L., Abelson, J.L., Taylor, S.F., 2011. Developmental alterations of frontal-striatal-thalamic connectivity in obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry 50, 938-948 e933.

Fontenelle, L.F., Hasler, G., 2008. The analytical epidemiology of obsessive–compulsive disorder: risk factors and correlates. Progress in Neuro-Psychopharmacology and Biological Psychiatry 32, 1-15.

Fox, M.D., Raichle, M.E., 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 8, 700-711.

Franklin, M.E., Abramowitz, J.S., Kozak, M.J., Levitt, J.T., Foa, E.B., 2000. Effectiveness of exposure and ritual prevention for obsessive-compulsive disorder: randomized compared with nonrandomized samples. J Consult Clin Psychol 68, 594-602.

Fransson, P., Skiold, B., Horsch, S., Nordell, A., Blennow, M., Lagercrantz, H., Aden, U., 2007. Resting-state networks in the infant brain. Proc Natl Acad Sci U S A 104, 15531-15536.

Franzmeier, N., Buerger, K., Teipel, S., Stern, Y., Dichgans, M., Ewers, M., Alzheimer's Disease Neuroimaging, I., 2017. Cognitive reserve moderates the association between functional network anti-correlations and memory in MCI. Neurobiol Aging 50, 152-162.

Freeston, M.H., Ladouceur, R., Gagnon, F., Thibodeau, N., Rhéaume, J., Letarte, H., Bujold, A., 1997. Cognitive—behavioral treatment of obsessive thoughts: A controlled study. Journal of Consulting and Clinical Psychology 65, 405.

Geller, D.A., Biederman, J., Jones, J., Shapiro, S., Schwartz, S., Park, K.S., 1998. Obsessive-compulsive disorder in children and adolescents: a review. Harv Rev Psychiatry 5, 260-273.

Goncalves, O.F., Soares, J.M., Carvalho, S., Leite, J., Ganho-Avila, A., Fernandes-Goncalves, A., Pocinho, F., Carracedo, A., Sampaio, A., 2017. Patterns of Default Mode Network Deactivation in Obsessive Compulsive Disorder. Sci Rep 7, 44468.

Gottlich, M., Kramer, U.M., Kordon, A., Hohagen, F., Zurowski, B., 2014. Decreased limbic and increased fronto-parietal connectivity in unmedicated patients with obsessive-compulsive disorder. Hum Brain Mapp 35, 5617-5632.

Graybiel, A.M., Rauch, S.L., 2000. Toward a neurobiology of obsessive-compulsive disorder. Neuron 28, 343-347.

Greicius, M.D., Flores, B.H., Menon, V., Glover, G.H., Solvason, H.B., Kenna, H., Reiss, A.L., Schatzberg, A.F., 2007. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol Psychiatry 62, 429-437.

Greicius, M.D., Kiviniemi, V., Tervonen, O., Vainionpaa, V., Alahuhta, S., Reiss, A.L., Menon, V., 2008. Persistent default-mode network connectivity during light sedation. Hum Brain Mapp 29, 839-847.

Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A 100, 253-258.

Greicius, M.D., Srivastava, G., Reiss, A.L., Menon, V., 2004. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci U S A 101, 4637-4642.

Greicius, M.D., Supekar, K., Menon, V., Dougherty, R.F., 2009. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb Cortex 19, 72-78.

Gürsel, D.A., Avram, M., Sorg, C., Brandl, F., Koch, K., 2018. Frontoparietal areas link impairments of large-scale intrinsic brain networks with aberrant fronto-striatal interactions in OCD: a meta-analysis of resting-state functional connectivity. Neurosci Biobehav Rev 87, 151-160.

Haber, S.N., 2003. The primate basal ganglia: parallel and integrative networks. J Chem Neuroanat 26, 317-330.

Haber, S.N., Calzavara, R., 2009. The cortico-basal ganglia integrative network: the role of the thalamus. Brain Res Bull 78, 69-74.

Harris, R.K., 1986. Nuclear magnetic resonance spectroscopy.

Harrison, B.J., Pujol, J., Cardoner, N., Deus, J., Alonso, P., Lopez-Sola, M., Contreras-Rodriguez, O., Real, E., Segalas, C., Blanco-Hinojo, L., Menchon, J.M., Soriano-Mas, C., 2013. Brain corticostriatal systems and the major clinical symptom dimensions of obsessive-compulsive disorder. Biol Psychiatry 73, 321-328.

Harrison, B.J., Soriano-Mas, C., Pujol, J., Ortiz, H., Lopez-Sola, M., Hernandez-Ribas, R., Deus, J., Alonso, P., Yucel, M., Pantelis, C., Menchon, J.M., Cardoner, N., 2009. Altered corticostriatal functional connectivity in obsessive-compulsive disorder. Arch Gen Psychiatry 66, 1189-1200.

Heeger, D.J., Ress, D., 2002. What does fMRI tell us about neuronal activity? Nat Rev Neurosci 3, 142-151.

Hou, J., Song, L., Zhang, W., Wu, W., Wang, J., Zhou, D., Qu, W., Guo, J., Gu, S., He, M., Xie, B., Li, H., 2013. Morphologic and functional connectivity alterations of corticostriatal and default mode network in treatment-naive patients with obsessive-compulsive disorder. PLoS One 8, e83931.

Hutchison, R.M., Womelsdorf, T., Gati, J.S., Everling, S., Menon, R.S., 2013. Resting-state networks show dynamic functional connectivity in awake humans and anesthetized macaques. Human brain mapping 34, 2154-2177.

Hymas, N., Lees, A., Bolton, D., Epps, K., Head, D., 1991. The neurology of obsessional slowness. Brain 114 (Pt 5), 2203-2233.

Insel, T.R., Winslow, J.T., 1992. Neurobiology of obsessive compulsive disorder. Psychiatr Clin North Am 15, 813-824.

Jerrolds, J., Keene, S., 2009. MRI safety at 3T versus 1.5 T. Internet J World Health Soc Politics 6.

Jhung, K., Ku, J., Kim, S.J., Lee, H., Kim, K.R., An, S.K., Kim, S.I., Yoon, K.J., Lee, E., 2014. Distinct functional connectivity of limbic network in the washing type obsessive-compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry 53, 149-155.

Johansen-Berg, H., Rushworth, M.F., 2009. Using diffusion imaging to study human connectional anatomy. Annual review of neuroscience 32, 75-94.

Jones, D.T., Vemuri, P., Murphy, M.C., Gunter, J.L., Senjem, M.L., Machulda, M.M., Przybelski, S.A., Gregg, B.E., Kantarci, K., Knopman, D.S., 2012. Non-stationarity in the "resting brain's" modular architecture. PloS one 7, e39731.

Jung, W.H., Kang, D.H., Kim, E., Shin, K.S., Jang, J.H., Kwon, J.S., 2013. Abnormal corticostriatal-limbic functional connectivity in obsessive-compulsive disorder during reward processing and resting-state. Neuroimage Clin 3, 27-38.

Kaiser, R.H., Andrews-Hanna, J.R., Wager, T.D., Pizzagalli, D.A., 2015. Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. JAMA Psychiatry 72, 603-611.

Koran, L.M., Hanna, G.L., Hollander, E., Nestadt, G., Simpson, H.B., American Psychiatric, A., 2007. Practice guideline for the treatment of patients with obsessive-compulsive disorder. Am J Psychiatry 164, 5-53.

Kringelbach, M.L., Rolls, E.T., 2004. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog Neurobiol 72, 341-372.

Linden, D.E., Prvulovic, D., Formisano, E., Völlinger, M., Zanella, F.E., Goebel, R., Dierks, T., 1999. The functional neuroanatomy of target detection: an fMRI study of visual and auditory oddball tasks. Cerebral Cortex 9, 815-823.

Lombardo, I., Simpson, H., Slifstein, M., Huang, Y., Hwang, D., Mawlawi, O., Martinez, D., Gelbard, I., Abi-Dargham, A., Van Heertum, R., 2002. Measurement of the 5-

HT transporter in patients with OCD with C-11-(+) McN-5652, JOURNAL OF NUCLEAR MEDICINE. SOC NUCLEAR MEDICINE INC 1850 SAMUEL MORSE DR, RESTON, VA 20190-5316 USA, pp. 16P-16P.

Manoliu, A., Riedl, V., Doll, A., Bauml, J.G., Muhlau, M., Schwerthoffer, D., Scherr, M., Zimmer, C., Forstl, H., Bauml, J., Wohlschlager, A.M., Koch, K., Sorg, C., 2013. Insular Dysfunction Reflects Altered Between-Network Connectivity and Severity of Negative Symptoms in Schizophrenia during Psychotic Remission. Front Hum Neurosci 7, 216.

Manoliu, A., Riedl, V., Zherdin, A., Muhlau, M., Schwerthoffer, D., Scherr, M., Peters, H., Zimmer, C., Forstl, H., Bauml, J., Wohlschlager, A.M., Sorg, C., 2014. Aberrant dependence of default mode/central executive network interactions on anterior insular salience network activity in schizophrenia. Schizophr Bull 40, 428-437.

Martinot, J.L., Allilaire, J.F., Mazoyer, B.M., Hantouche, E., Huret, J.D., Legaut-Demare, F., Deslauriers, A.G., Hardy, P., Pappata, S., Baron, J.C., et al., 1990. Obsessive-compulsive disorder: a clinical, neuropsychological and positron emission tomography study. Acta Psychiatr Scand 82, 233-242.

Mataix-Cols, D., Rosario-Campos, M.C., Leckman, J.F., 2005. A multidimensional model of obsessive-compulsive disorder. Am J Psychiatry 162, 228-238.

Mataix-Cols, D., Wooderson, S., Lawrence, N., Brammer, M.J., Speckens, A., Phillips, M.L., 2004. Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. Arch Gen Psychiatry 61, 564-576.

Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci 15, 483-506.

Menzies, L., Achard, S., Chamberlain, S.R., Fineberg, N., Chen, C.H., del Campo, N., Sahakian, B.J., Robbins, T.W., Bullmore, E., 2007. Neurocognitive endophenotypes of obsessive-compulsive disorder. Brain 130, 3223-3236.

Menzies, L., Chamberlain, S.R., Laird, A.R., Thelen, S.M., Sahakian, B.J., Bullmore, E.T., 2008. Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. Neurosci Biobehav Rev 32, 525-549.

Milad, M.R., Rauch, S.L., 2012. Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. Trends Cogn Sci 16, 43-51.

Modell, J.G., Mountz, J.M., Curtis, G.C., Greden, J.F., 1989. Neurophysiologic dysfunction in basal ganglia/limbic striatal and thalamocortical circuits as a pathogenetic mechanism of obsessive-compulsive disorder. J Neuropsychiatry Clin Neurosci 1, 27-36.

Nestadt, G., Samuels, J., Riddle, M., Bienvenu, O.J., 3rd, Liang, K.Y., LaBuda, M., Walkup, J., Grados, M., Hoehn-Saric, R., 2000. A family study of obsessive-compulsive disorder. Arch Gen Psychiatry 57, 358-363.

Nestadt, G., Samuels, J., Riddle, M.A., Liang, K.Y., Bienvenu, O.J., Hoehn-Saric, R., Grados, M., Cullen, B., 2001. The relationship between obsessive-compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD Family Study. Psychol Med 31, 481-487.

Nir, Y., Mukamel, R., Dinstein, I., Privman, E., Harel, M., Fisch, L., Gelbard-Sagiv, H., Kipervasser, S., Andelman, F., Neufeld, M.Y., Kramer, U., Arieli, A., Fried, I., Malach, R., 2008. Interhemispheric correlations of slow spontaneous neuronal fluctuations revealed in human sensory cortex. Nat Neurosci 11, 1100-1108.

Nordahl, T.E., Benkelfat, C., Semple, W.E., Gross, M., King, A.C., Cohen, R.M., 1989. Cerebral glucose metabolic rates in obsessive compulsive disorder. Neuropsychopharmacology 2, 23-28.

Ogawa, S., Lee, T.M., Kay, A.R., Tank, D.W., 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A 87, 9868-9872.

Okasha, A., Rafaat, M., Mahallawy, N., El Nahas, G., El Dawla, A.S., Sayed, M., El Kholi, S., 2000. Cognitive dysfunction in obsessive-compulsive disorder. Acta Psychiatr Scand 101, 281-285.

Palaniyappan, L., Liddle, P.F., 2012. Does the salience network play a cardinal role in psychosis? An emerging hypothesis of insular dysfunction. J Psychiatry Neurosci 37, 17-27.

Parent, A., Hazrati, L.N., 1995. Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. Brain Res Brain Res Rev 20, 91-127.

Pauls, D.L., Abramovitch, A., Rauch, S.L., Geller, D.A., 2014. Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective. Nat Rev Neurosci 15, 410-424.

Perani, D., Colombo, C., Bressi, S., Bonfanti, A., Grassi, F., Scarone, S., Bellodi, L., Smeraldi, E., Fazio, F., 1995. [18 F] FDG PET Study in Obsessive–Compulsive

Disorder: A Clinical/Metabolic Correlation Study after Treatment. The British Journal of Psychiatry 166, 244-250.

Ping, L., Su-Fang, L., Hai-Ying, H., Zhang-Ye, D., Jia, L., Zhi-Hua, G., Hong-Fang, X., Yu-Feng, Z., Zhan-Jiang, L., 2013. Abnormal Spontaneous Neural Activity in Obsessive-Compulsive Disorder: A Resting-State Functional Magnetic Resonance Imaging Study. PLoS One 8, e67262.

Pittenger, C., 2017. Obsessive-Compulsive Disorder: Phenomenology, Pathophysiology, and Treatment. Oxford University Press.

Pogarell, O., Hamann, C., Popperl, G., Juckel, G., Chouker, M., Zaudig, M., Riedel, M., Moller, H.J., Hegerl, U., Tatsch, K., 2003. Elevated brain serotonin transporter availability in patients with obsessive-compulsive disorder. Biol Psychiatry 54, 1406-1413.

Posner, J., Marsh, R., Maia, T.V., Peterson, B.S., Gruber, A., Simpson, H.B., 2014. Reduced functional connectivity within the limbic cortico-striato-thalamo-cortical loop in unmedicated adults with obsessive-compulsive disorder. Hum Brain Mapp 35, 2852-2860.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc Natl Acad Sci U S A 98, 676-682.

Rauch, S.L., Jenike, M.A., 1998. Pharmacological treatment of obsessive compulsive disorder. A guide to treatments that work, 358-376.

Remijnse, P.L., Nielen, M.M., van Balkom, A.J., Cath, D.C., van Oppen, P., Uylings, H.B., Veltman, D.J., 2006. Reduced orbitofrontal-striatal activity on a reversal learning task in obsessive-compulsive disorder. Arch Gen Psychiatry 63, 1225-1236.

Romanelli, R.J., Wu, F.M., Gamba, R., Mojtabai, R., Segal, J.B., 2014. Behavioral therapy and serotonin reuptake inhibitor pharmacotherapy in the treatment of obsessive–compulsive disorder: A systematic review and meta-analysis of head-to-head randomized controlled trials. Depression and Anxiety 31, 641-652.

Rosenberg, D.R., Dick, E.L., O'Hearn, K.M., Sweeney, J.A., 1997. Response-inhibition deficits in obsessive-compulsive disorder: an indicator of dysfunction in frontostriatal circuits. J Psychiatry Neurosci 22, 29-38.

Rosenberg, D.R., MacMillan, S., 2002. Imaging and neurocircuitry of OCD. Neuropsychopharmacology. The 5th generation of progress, 1621-1646.

Rus, O.G., Reess, T.J., Wagner, G., Zaudig, M., Zimmer, C., Koch, K., 2017. Hypogyrification in obsessive-compulsive disorder. Psychol Med 47, 1053-1061.

Ruscio, A.M., Stein, D.J., Chiu, W.T., Kessler, R.C., 2010. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry 15, 53-63.

Sakai, Y., Narumoto, J., Nishida, S., Nakamae, T., Yamada, K., Nishimura, T., Fukui, K., 2011. Corticostriatal functional connectivity in non-medicated patients with obsessive-compulsive disorder. Eur Psychiatry 26, 463-469.

Sakoglu, U., Pearlson, G.D., Kiehl, K.A., Wang, Y.M., Michael, A.M., Calhoun, V.D., 2010. A method for evaluating dynamic functional network connectivity and task-modulation: application to schizophrenia. MAGMA 23, 351-366.

Salzman, L., Thaler, F.H., 1981. Obsessive-compulsive disorders: a review of the literature. Am J Psychiatry 138, 286-296.

Sawle, G.V., Hymas, N.F., Lees, A.J., Frackowiak, R.S., 1991. Obsessional slowness. Functional studies with positron emission tomography. Brain 114 (Pt 5), 2191-2202.

Saxena, S., Bota, R.G., Brody, A.L., 2001. Brain-behavior relationships in obsessive-compulsive disorder. Semin Clin Neuropsychiatry 6, 82-101.

Saxena, S., Brody, A.L., Maidment, K.M., Smith, E.C., Zohrabi, N., Katz, E., Baker, S.K., Baxter, L.R., Jr., 2004. Cerebral glucose metabolism in obsessive-compulsive hoarding. Am J Psychiatry 161, 1038-1048.

Saxena, S., Brody, A.L., Schwartz, J.M., Baxter, L.R., 1998. Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. Br J Psychiatry Suppl, 26-37.

Saxena, S., Rauch, S.L., 2000. Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. Psychiatr Clin North Am 23, 563-586.

Schrag, A., Gilbert, R., Giovannoni, G., Robertson, M., Metcalfe, C., Ben-Shlomo, Y., 2009. Streptococcal infection, Tourette syndrome, and OCD: is there a connection? Neurology 73, 1256-1263.

Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27, 2349-2356.

Sha, Z., Wager, T.D., Mechelli, A., He, Y., 2019. Common Dysfunction of Large-Scale Neurocognitive Networks Across Psychiatric Disorders. Biological psychiatry 85, 379-388.

Shafran, R., 2001. Obsessive-compulsive disorder in children and adolescents. Child Psychology and Psychiatry Review 6, 50-58.

Shavitt, R.G., de Mathis, M.A., Oki, F., Ferrao, Y.A., Fontenelle, L.F., Torres, A.R., Diniz, J.B., Costa, D.L., do Rosario, M.C., Hoexter, M.Q., Miguel, E.C., Simpson, H.B., 2014. Phenomenology of OCD: lessons from a large multicenter study and implications for ICD-11. J Psychiatr Res 57, 141-148.

Shmuel, A., Leopold, D.A., 2008. Neuronal correlates of spontaneous fluctuations in fMRI signals in monkey visual cortex: Implications for functional connectivity at rest. Hum Brain Mapp 29, 751-761.

Simon, D., Kaufmann, C., Musch, K., Kischkel, E., Kathmann, N., 2010. Fronto-striato-limbic hyperactivation in obsessive-compulsive disorder during individually tailored symptom provocation. Psychophysiology 47, 728-738.

Singh, N.N., Wahler, R.G., Winton, A.S., Adkins, A.D., Group, M.R., 2004. A mindfulness-based treatment of obsessive-compulsive disorder. Clinical Case Studies 3, 275-287.

Skudlarski, P., Jagannathan, K., Calhoun, V.D., Hampson, M., Skudlarska, B.A., Pearlson, G., 2008. Measuring brain connectivity: diffusion tensor imaging validates resting state temporal correlations. Neuroimage 43, 554-561.

Stengler-Wenzke, K., Muller, U., Angermeyer, M.C., Sabri, O., Hesse, S., 2004. Reduced serotonin transporter-availability in obsessive-compulsive disorder (OCD). Eur Arch Psychiatry Clin Neurosci 254, 252-255.

Stern, E.R., Fitzgerald, K.D., Welsh, R.C., Abelson, J.L., Taylor, S.F., 2012. Resting-state functional connectivity between fronto-parietal and default mode networks in obsessive-compulsive disorder. PLoS One 7, e36356.

Stroup, D.F., Berlin, J.A., Morton, S.C., Olkin, I., Williamson, G.D., Rennie, D., Moher, D., Becker, B.J., Sipe, T.A., Thacker, S.B., 2000. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283, 2008-2012.

Swedo, S.E., Pietrini, P., Leonard, H.L., Schapiro, M.B., Rettew, D.C., Goldberger, E.L., Rapoport, S.I., Rapoport, J.L., Grady, C.L., 1992. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Revisualization during pharmacotherapy. Arch Gen Psychiatry 49, 690-694.

Swedo, S.E., Schapiro, M.B., Grady, C.L., Cheslow, D.L., Leonard, H.L., Kumar, A., Friedland, R., Rapoport, S.I., Rapoport, J.L., 1989. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Arch Gen Psychiatry 46, 518-523.

Takagi, Y., Sakai, Y., Lisi, G., Yahata, N., Abe, Y., Nishida, S., Nakamae, T., Morimoto, J., Kawato, M., Narumoto, J., Tanaka, S.C., 2017. A Neural Marker of Obsessive-Compulsive Disorder from Whole-Brain Functional Connectivity. Sci Rep 7, 7538.

Tricomi, E., Balleine, B.W., O'Doherty, J.P., 2009. A specific role for posterior dorsolateral striatum in human habit learning. Eur J Neurosci 29, 2225-2232.

Ursu, S., Stenger, V.A., Shear, M.K., Jones, M.R., Carter, C.S., 2003. Overactive action monitoring in obsessive-compulsive disorder: evidence from functional magnetic resonance imaging. Psychol Sci 14, 347-353.

Vaghi, M.M., Vertes, P.E., Kitzbichler, M.G., Apergis-Schoute, A.M., van der Flier, F.E., Fineberg, N.A., Sule, A., Zaman, R., Voon, V., Kundu, P., Bullmore, E.T., Robbins, T.W., 2017. Specific Frontostriatal Circuits for Impaired Cognitive Flexibility and Goal-Directed Planning in Obsessive-Compulsive Disorder: Evidence From Resting-State Functional Connectivity. Biol Psychiatry 81, 708-717.

van den Heuvel, M.P., Mandl, R.C., Kahn, R.S., Hulshoff Pol, H.E., 2009. Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. Hum Brain Mapp 30, 3127-3141.

van den Heuvel, O.A., van Wingen, G., Soriano-Mas, C., Alonso, P., Chamberlain, S.R., Nakamae, T., Denys, D., Goudriaan, A.E., Veltman, D.J., 2016. Brain circuitry of compulsivity. Eur Neuropsychopharmacol 26, 810-827.

Van Dijk, K.R., Hedden, T., Venkataraman, A., Evans, K.C., Lazar, S.W., Buckner, R.L., 2009. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. Journal of neurophysiology 103, 297-321.

Van Essen, D.C., Ugurbil, K., Auerbach, E., Barch, D., Behrens, T.E., Bucholz, R., Chang, A., Chen, L., Corbetta, M., Curtiss, S.W., Della Penna, S., Feinberg, D., Glasser, M.F., Harel, N., Heath, A.C., Larson-Prior, L., Marcus, D., Michalareas, G., Moeller, S., Oostenveld, R., Petersen, S.E., Prior, F., Schlaggar, B.L., Smith, S.M., Snyder, A.Z., Xu, J., Yacoub, E., Consortium, W.U.-M.H., 2012. The Human Connectome Project: a data acquisition perspective. Neuroimage 62, 2222-2231.

Van Veen, V., Carter, C.S., 2002. The anterior cingulate as a conflict monitor: fMRI and ERP studies. Physiology & behavior 77, 477-482.

Vincent, J.L., Patel, G.H., Fox, M.D., Snyder, A.Z., Baker, J.T., Van Essen, D.C., Zempel, J.M., Snyder, L.H., Corbetta, M., Raichle, M.E., 2007. Intrinsic functional architecture in the anaesthetized monkey brain. Nature 447, 83-86.

Vogel, L., 2018. Growing consensus on link between strep and obsessive-compulsive disorder. CMAJ 190, E86-E87.

Wager, T.D., Lindquist, M., Kaplan, L., 2007. Meta-analysis of functional neuroimaging data: current and future directions. Soc Cogn Affect Neurosci 2, 150-158.

Welch, J.M., Lu, J., Rodriguiz, R.M., Trotta, N.C., Peca, J., Ding, J.D., Feliciano, C., Chen, M., Adams, J.P., Luo, J., Dudek, S.M., Weinberg, R.J., Calakos, N., Wetsel, W.C., Feng, G., 2007. Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. Nature 448, 894-900.

Whitfield-Gabrieli, S., Thermenos, H.W., Milanovic, S., Tsuang, M.T., Faraone, S.V., McCarley, R.W., Shenton, M.E., Green, A.I., Nieto-Castanon, A., LaViolette, P., Wojcik, J., Gabrieli, J.D., Seidman, L.J., 2009. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc Natl Acad Sci U S A 106, 1279-1284.

Worsley, K.J., Friston, K.J., 1995. Analysis of fMRI time-series revisited--again. Neuroimage 2, 173-181.

Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zollei, L., Polimeni, J.R., Fischl, B., Liu, H., Buckner, R.L., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 106, 1125-1165.

Yuan, K., Qin, W., Yu, D., Bi, Y., Xing, L., Jin, C., Tian, J., 2016. Core brain networks interactions and cognitive control in internet gaming disorder individuals in late adolescence/early adulthood. Brain Struct Funct 221, 1427-1442.

Zalesky, A., Fornito, A., Cocchi, L., Gollo, L.L., Breakspear, M., 2014. Time-resolved resting-state brain networks. Proc Natl Acad Sci U S A 111, 10341-10346.

Zheng, H., Xu, L., Xie, F., Guo, X., Zhang, J., Yao, L., Wu, X., 2015. The Altered Triple Networks Interaction in Depression under Resting State Based on Graph Theory. Biomed Res Int 2015, 386326.

Zhu, Y., Fan, Q., Zhang, H., Qiu, J., Tan, L., Xiao, Z., Tong, S., Chen, J., Li, Y., 2016. Altered intrinsic insular activity predicts symptom severity in unmedicated obsessive-compulsive disorder patients: a resting state functional magnetic resonance imaging study. BMC Psychiatry 16, 104.

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8 | List of Figures and Tables

9 | Publications

1. **Gürsel, D.A.**, Avram, M., Sorg, C., Brandl, F. and Koch, K., 2018. Frontoparietal areas link impairments of large-scale intrinsic brain networks with aberrant fronto-striatal interactions in OCD: a meta-analysis of resting-state functional connectivity. *Neuroscience & Biobehavioral Reviews*, *87*, pp.151-160.

2. **Gürsel, D.A**., Reinholz L., Bremer B., Schmitz-Koep B., Avram M., Koch K., 2019. Frontoparietal and Salience Network Alterations in Obsessive-Compulsive Disorder: Insights from independent component and sliding time window analyses, *Journal of Psychiatry & Neuroscience (under review)*.

3. Calza J., **Gürsel D.A.**, Schmitz-Koep B., Bremer B., Reinholz L., Berberitz G., Koch K., 2019, Altered cortico-striatal functional connectivity during resting-state in obsessive-compulsive disorder, *Frontiers in Psychiatry.*

4. Boedhoe P.S.W., Rooij D., Hoogman M., …, **Gürsel D.A.**, … & van den Heuvel O., 2019, Subcortical brain volume, regional cortical thickness and cortical surface area variations across attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD), *Biological Psychiatry.*

5. Kong, X., Boedhoe, P.S., …, **Gürsel D.A.**, & Francks C., 2019, Mapping Cortical and Subcortical Asymmetry in Obsessive-Compulsive Disorder: Findings from the ENIGMA Consortium, *Biological Psychiatry.*

6. Brandl, F., Avram, M., Weise, B., Shang, J., Simões, B., Bertram, T., Ayala, D.H., Penzel, N., **Gürsel, D.A.**, Bäuml, J. and Wohlschläger, A.M., 2018. Specific substantial dysconnectivity in schizophrenia A transdiagnostic multimodal meta-analysis of resting-state functional and structural MRI studies. *Biological Psychiatry.*

7. Reess, T.J., Rus, O.G., **Gürsel, D.A.**, Schmitz-Koep, B., Wagner, G., Berberich, G. and Koch, K., 2018. Network-based decoupling of local gyrification in obsessive-compulsive disorder. *Human brain mapping*, *39*(8), pp.3216-3226.

8. Koch, K., Reess, T.J., Rus, O.G., **Gürsel, D.A.**, Wagner, G., Berberich, G. and Zimmer, C., 2018. Increased default mode network connectivity in obsessive–compulsive disorder during reward processing. *Frontiers in Psychiatry*, *9*, p.254.

9. Reess, T.J., Rus, O.G., **Gürsel, D.A.**, Schmitz-Koep, B., Wagner, G., Berberich, G. and Koch, K., 2018. Association between hippocampus volume and symptom profiles in obsessive–compulsive disorder. *NeuroImage: Clinical*, *17*, pp.474-480.