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REVIEW

A white paper on a neurodevelopmental framework for drug discovery in autism and other neurodevelopmental disorders

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Abstract
In the last decade there has been a revolution in terms of genetic findings in neurodevelopmental disorders (NDDs), with many discoveries critical for understanding their aetiology and pathophysiology. Clinical trials in single-gene disorders such as fragile X syndrome highlight the challenges of investigating new drug targets in NDDs. Incorporating a developmental perspective into the process of drug development for NDDs could help to overcome some of the current difficulties in identifying and testing new treatments. This paper provides a summary of the proceedings of the 'New Frontiers Meeting' on neurodevelopmental disorders organised by the European College of Neuropsychopharmacology in conjunction with the Innovative Medicines Initiative-sponsored AIMS-2-TRIALS consortium. It brought together experts in developmental genetics, autism, NDDs, and clinical trials from academia and industry, regulators, patient and family associations, and other stakeholders. The meeting sought to provide a platform for focused communication on scientific insights, challenges, and methodologies that might be applicable to the development of CNS treatments from a neurodevelopmental perspective. Multidisciplinary translational consortia to develop basic and clinical research in parallel could be pivotal to advance knowledge in the field. Although implementation of clinical trials for NDDs in paediatric populations is widely acknowledged as essential, safety concerns should guide each aspect of their design. Industry and academia should join forces to improve knowledge of the biology of brain development, identify the optimal timing of interventions, and translate these findings into new drugs, allowing for the needs of users and families, with support from regulatory agencies.

1. Introduction

Neurodevelopmental disorders (NDDs), including autism spectrum disorder (ASD) and intellectual disability (ID), are heterogeneous conditions in which there is a perturbation of brain development. NDDs show varying clinical manifestations and severity and are associated with differing degrees of cognitive and adaptive functioning and disability (Thapar et al., 2017). ASD is defined by persistent deficits in social communication and social interaction across multiple contexts, along with the presence of restricted, repetitive interests and/or behaviours (American Psychiatric Association, 2013). Although prevalence estimates vary substantially across countries and studies, it is estimated that roughly 1% of children have autism worldwide, with increasing rates in recent decades (Lai et al., 2014). ID has an estimated prevalence of 1% and is defined by the presence of childhood-onset impairments in general intellectual abilities that impact adaptive functioning in the conceptual, social or practical domains of life (Maulik et al., 2011). The aetiology of NDDs is multifactorial, with involvement of rare and common genetic variation and environmental factors in their pathophysiology (Kiser et al., 2015).

NDDs affect roughly 120 million people worldwide and are associated with a significant reduction in lifespan as well as high rates of disability, especially in young people (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Hence, there is a pressing need to develop new treatment strategies for NDDs to address unmet needs and to reduce their associated disability. For instance, there is lack of effective pharmacological treatments for ASD core symptoms, which may be significantly impairing for many autistic individuals (Ameis et al., 2018). Despite substantial advances in our understanding of the neurobiol-

ogy of brain disorders and efforts to develop new disorder-modifying compounds, the field of NDDs has encountered a dry pipeline in the past two decades. The failure rate for new drugs targeting CNS disorders is high relative to most of the other areas of drug discovery, especially for so-called disease-modifying drugs (i.e. drugs that aim to alter the course of a disease or condition) (Gribkoff and Kaczmarek, 2017). One of the reasons for this repeated failure may well be the use of clinical categories with insufficient biological validity, given our increasing recognition of the clinical, biological, and aetiological heterogeneity inherent in NDDs and other psychiatric disorders (Loth et al., 2017) and the substantial overlap among disorders (Owen, 2014). Another crucial factor is likely insufficient consideration of the developmental trajectories of mental disorders in clinical trial development (Karmiloff-Smith, 1998).

Understanding the dynamic nature of the pathophysiological mechanisms underlying NDDs and other brain disorders is crucial for the development of effective therapies and preventative strategies (Arango et al., 2018). To date, developmental therapeutic windows have not been sufficiently factored into the processes of design and selection of potential participants for trials testing psychotropic drugs in mental disorders (Marín, 2016). Recent mechanistically driven trials in NDDs such as fragile X syndrome (FXS) have had disappointing phase IIb or III results, despite promising preclinical and early phase trial data, and despite a strong rationale based on sound mechanisms of action (Berry-Kravis et al., 2017b). These studies were conducted in adults and adolescents, and one might wonder whether they should have been conducted in much younger participants, as it may be difficult to reverse decades of atypicalities and the resulting cascade effects with a few months of treatment. There are several examples in medicine beyond the CNS where interventions are effective for disease modification only within a given therapeutic window (e.g. congenital hypothyroidism and myocardial infarction) (Leger et al., 2014; Reed et al., 2017). It is thus possible that patients may have been denied useful drugs because trials were conducted outside of the potential therapeutic window (Parellada, 2013). However, the potential benefits of a drug affecting early neurodevelopmental trajectories also need to be balanced against the uncertainties regarding its long-term effects and the potential risks of such interventions on brain development.

The European College of Neuropsychopharmacology (ECNP) and the AIMS-2-TRIALS consortium jointly organized a 'New Frontiers' meeting in March 2018, which fostered communication among academia, industry, and regulators on how to improve future clinical trials addressing NDDs. The AIMS-2-TRIALS network (https://www.aims-2-trials.eu/) (see Fig. 1) is a consortium funded by the Innovative Medicines Initiative, a large public-private partnership receiving funding support from the EU Horizon 2020 Research and Innovation Programme, the European Federation of Pharmaceutical Industries and Associations (EFPIA), and charity partners, which builds upon the EU-AIMS consortium (Murphy and Spooren, 2012). These consortia are composed of multidisciplinary teams of basic, translational, and clinical researchers from academia and industry seeking to integrate the information provided by cellular assays, animal models, translational science, clinical research, and genomics to develop new evidence-based treatments for ASD (Murphy and Spooren, 2012). These projects aim at developing a precision medicine approach to ASD by better matching treatments to patients through validation of stratification biomarkers and testing novel or repurposed drugs in a Europe-wide clinical trials network (Loth et al., 2014).

This paper aims to provide a general overview of the proceedings and general conclusions derived from this meeting. We will review recent findings from the fields of genetics, neurodevelopment, translational research, and biomarker discovery efforts in NDDs, as well as some of the issues raised by recent drug trial development in single-gene disorders, including the ethical and regulatory challenges of conducting research and clinical trials in young children with NDDs. This review could inform a neurodevelopmental framework for drug discovery and clinical trial implementation for NDDs in the years to come.

2. Lessons learnt from single-gene disorders: fragile X syndrome. Implications for ASD and other NDDs

2.1. Single-gene disorders

Single-gene disorders like fragile X, Rett, Phelan-McDermid, and Angelman syndrome are NDDs associated with a rare variant of large effect that show a distinct behavioural phenotype. Many of these disorders have high rates of intellectual disability and autistic traits, with variable rates of other neuropsychiatric features (Richards et al., 2015; Sanders et al., 2019). However, they are not autism spectrum disorders, and the underlying biology and clinical manifestations may differ from those of nonsyndromic autism. Single-gene disorders have been regarded as a useful venue for drug discovery for ASD and other NDDs, as there is a known genetic cause and clearer pathophysiology that may aid in the development of mechanistically based targets (Arango and Fraguas, 2016). Among them, extensive research on fragile X syndrome (FXS) has been translated into several mechanistically driven clinical trials in the past two decades (Berry-Kravis et al., 2017b). We will briefly discuss the molecular targets identified by this research and some lessons learnt from derived clinical trials in FXS.

2.2. Fragile X syndrome

FXS is a leading cause of inherited intellectual disability and autism. FXS is caused primarily by a trinucleotide repeat disorder [>200 CGG repeats in the 5′ untranslated region of Fmr1 (Fragile X Mental Retardation 1) gene, located on Xq27.3], which leads to transcriptional silencing in the expression of the fragile X mental retardation 1 protein (FMRP) from the 11th week of embryonic development onwards (Colak et al., 2014). Patients with 55 to 200 repeats are considered to carry the premutation, which is associated with the development of fragile X-associated primary ovarian insufficiency (FXPOI), fragile X-associated tremor-ataxia syndrome (FXTAS), and fragile X-associated neuropsychiatric disorders (FXAND), including anxiety and depression (Hagerman et al., 2017; Hagerman et al., 2018). Patients with FXS typically show delays in cognitive develop-

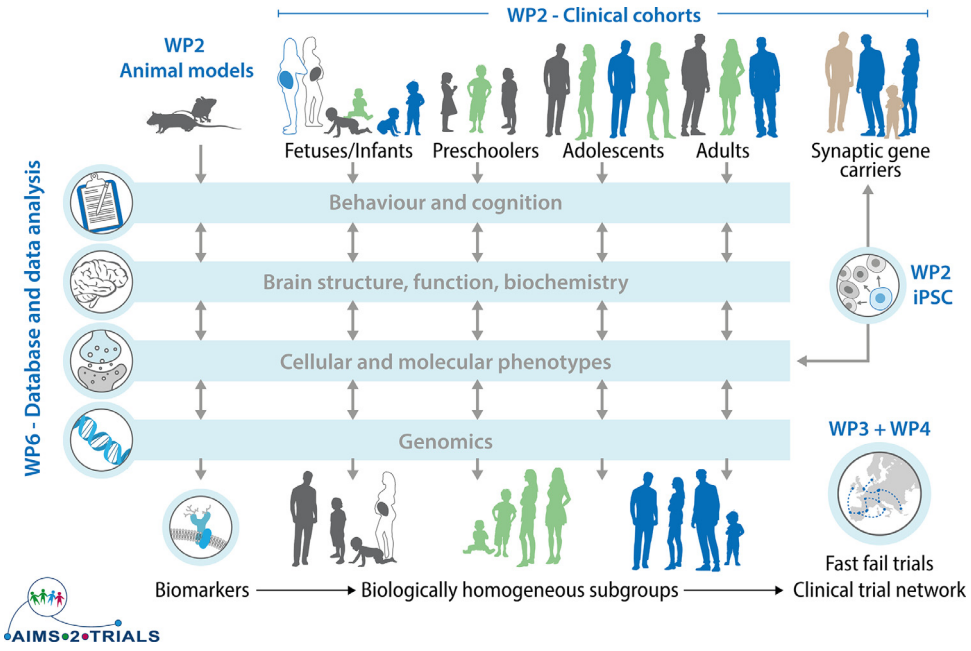

Fig. 1 Overview of AIMS-2-TRIALS approach.
Footnote: Adapted from (Loth et al., 2014). Abbreviations: WP, work-package; iPSC, induced pluripotent stem cells.

ment and intellectual disability, with a relatively consistent cognitive profile —including difficulties in executive functioning, visuospatial skills, working memory and attention, and relative strengths in areas of verbal reasoning and simultaneous processing tasks— along with behavioural problems (Baumgardner et al., 1995; Mazzocco et al., 1993). Despite relative homogeneity in the genetic alteration underlying the condition, FXS and most single-gene disorders are pleiotropic, and the outcome in terms of behaviour, comorbid conditions, and cognitive functioning is variable (Glasson et al., 2020; Hagerman et al., 2017; Sanders et al., 2019), thus demonstrating that, even in monogenic disorders, individual variability is crucial. Although the variance in the FXS phenotype is partially explained by variations in residual levels of FMRP expression, a substantial amount of the variance remains unexplained and could lie in additional genetic, developmental, and environmental factors (Jacquemont et al., 2014).

2.3. Molecular pathways in FXS

FXS is an NDD, and there is intense interest in developmental trajectories in FXS, particularly related to treatments that are initiated early in development (Greiss Hess et al., 2016). In the past few years, studies have revealed mild deficits at different levels, including neuronal migration, and molecular deficits during the early postnatal stage. FMRP is a master regulator of mRNA translation at the synapse (Bagni and Zukin, 2019); it is highly enriched in de novo mutations (Iossifov et al., 2014) and plays a major role in protein synthesis-dependent synaptic homeostasis, synaptic structure and function, and neuroplasticity (Auerbach et al., 2011; Bagni et al., 2012; Darnell et al., 2011). An absence of FMRP leads to dysregulation of a large number of mRNAs encoding presynaptic and postsynaptic proteins, thus suggesting that the concerted alteration of several proteins could underlie the FXS phenotype (Bagni et al., 2012). At the synaptic level, FMRP acts as a translational repressor. In the absence of FMRP there is increased (local) protein synthesis (Bagni and Zukin, 2019). FMRP collaborates in synaptic shaping with other proteins such as cytoplasmic FMRP interacting protein 1 (CYFP1), which regulates translational initiation and actin remodelling. The translational activity of the FMRP/CYFIP1 complex in the brain is modulated by MAP-kinase-interacting kinase (MNK) (Panja et al., 2014). Mutations in CYFP1 affecting the translational regulatory complex or actin polymerisation lead to spinal deficit similar to that found in FXS (De Rubeis et al., 2013; Pathania et al., 2014).

FMRP is involved in the regulation of glutamatergic and GABAergic signalling, ion channels, the BMPR2-cofilin pathway and the endocannabinoid system, among others (Hagerman et al., 2017). Many of these pathways might lead to the inhibitory/excitatory imbalance found in FXS, including alterations in the expression or activity of ion channels and changes in neurotransmitters and receptors (Contractor et al., 2015), which suggests that targeting some of these mechanisms could help rescue the phenotype. FMRP is also required for neural stem and progenitor cell proliferation, differentiation, and survival (Castren, 2016; Patzlaff et al., 2018; Westmark, 2017) and regulates the mRNA encoding the epigenetic regulator Brd4 (Korb et al., 2017). These additional mechanisms could also be involved in the pathophysiology of FXS and underlie some of the phenotypic features of the condition.

FMRP levels seem to be deficient in several brain disorders, including ASD, schizophrenia, mood disorders, and epilepsy (Bernard et al., 2013; Fatemi and Folsom, 2011; Fernandez et al., 2013; Sundberg et al., 2018), and its

targets include many genes and proteins that have been associated with NDDs, including ASD and other neuropsychiatric disorders (Pasciuto and Bagni, 2014). FMRP levels have also been associated with cognitive functioning both in schizophrenia and healthy controls and with age of onset in people with schizophrenia (Kelemen et al., 2013; Kovacs et al., 2013). Common functional variants in genes involved in post-synaptic FMRP regulation such as CYFIP1 and CAMK4 have been associated with autism risk, thus supporting the role of downstream glutamatergic signalling as a molecular link between some syndromic and non-syndromic forms of autism, and their potential for becoming treatment targets (Waltes et al., 2014).

Since FMRP signalling seems to be problematic in other NDDs beyond FXS, studying molecular processes in FXS can help us understand some of the phenotypic commonalities across disorders and improve our knowledge of pathways that can be targeted to guide drug discovery for NDDs. Preclinical studies in FXS have shown that alterations in synaptic function and some aspects of the cognitive and behavioural phenotype might be rescued with both genetic approaches aiming for reactivation of the affected gene and pharmacological strategies aiming to compensate for a lack of FMRP. This has translated into more than 20 clinical trials conducted between 2002 and 2017 in people with FXS (Berry-Kravis et al., 2017b). Despite a solid biological background based on preclinical data, clinical trials targeting FMRP using mGluR5 antagonists and $GABA_B$ receptor agonists did not yield unequivocally positive results in FXS (Berry-Kravis et al., 2017b), highlighting some of the challenges of testing potentially disease-modifying strategies for NDDs.

2.4. Lessons learnt from clinical trials in single-gene disorders: implications for ASD and other NDDs

Some conclusions may be drawn from failed clinical trials testing mGluR5 inhibitors and $GABA_B$ agonists for FXS (Berry-Kravis et al., 2017b):

i) Trials testing mGluR5 antagonists for FXS were sufficiently well powered for their main outcome measure and long enough to conclude that they were negative. Clinically active drugs in ASD and other psychiatric conditions show efficacy in treatments shorter than three months in all age groups.
ii) Trials testing mGluR5 antagonists included participants with a broad range of ages (12–40 years), which should have enabled detection of age-related therapeutic benefits within this age range. It cannot be ruled out that mGluR5 antagonists may lead to improvements in developmental trajectory and cognition when tested in very young subjects with longer treatment duration. For drugs with a different mechanism of action such as arbaclofen, a signal was seen in the 5–11 year subgroup (and not in adolescents or adults), which suggests that earlier treatments might be needed for disease modification.
iii) Although trials testing mGluR5 antagonists for FXS were sufficiently powered for their main outcome measures, it is often difficult to complete well-powered RCTs for NDDs with a low prevalence, especially for rare disorders. For instance, in one of largest trials performed using an mGluR5 antagonist in children, adolescents, and adults with FXS, researchers had to screen more than 650 individuals at 24 sites to reach the final sample size. For such conditions, a trade-off may be warranted between the potentially useful data and the insufficient power provided by small trials, which often find signals in multiple post-hoc analyses that cannot be replicated.
iv) Even with relatively large sample sizes, due to different dosage and/or treatment groups, studies may not have enough power for stratification or to conduct secondary analyses assessing additional outcome measures. Alternative approaches or designs for testing dosing strategies or stratification may be required.
v) Results from these trials were also affected by high expectations and placebo effects due to very good results in animal models, although the placebo effect was comparable to that found in other drug trials (Berry-Kravis et al., 2016).

The methodology and design of the trials also highlighted the following key issues:

i) Windows of plasticity: Very young children were not included in these studies, although this may be the only group where effects of disease-modifying strategies on cognition and development can be seen using other interventions (e.g. learning and psychosocial interventions). Well-designed and well-powered studies are required to test this in ASD and other NDDs, although it might difficult to include large numbers of very young children due to safety concerns, difficulties involved in recruitment with narrower inclusion criteria, and average age at diagnosis.
ii) Outcome measures: There is a need to implement age-appropriate objective measures of core phenotypes that are sensitive to change, such as direct assessments of cognition and language that have less subjective variability than caregiver-rated scales and are less affected by placebo response. Biomarkers such as eye-tracking and digital devices (e.g. actigraphs and apps to measure social behaviour) should also be more widely applied in these clinical trials.
iii) Disease modification in NDDs: An appropriate assessment of potentially disease-modifying strategies for NDDs requires implementing longer trials in younger children, combined with learning interventions and cognitive and developmental outcome assessments.
iv) Improved connection between preclinical models and human clinical outcomes: Behaviour and cognition in mice are very remote from human symptoms, hence the need for measures to improve translation (e.g. EEG, fMRI, and other intermediate physiological endpoints). There are divergent views regarding the *Fmr1* knockout mouse model as a translational disease model for FXS. Although the model has been useful for mechanistic and preclinical studies, the variability and small effect size of cognitive deficits and some behavioural phenotypes in the *Fmr1* knockout mouse model may limit its applicability for guiding clinical studies in FXS. Windows of plasticity have also been insufficiently assessed in animal models.
v) Heterogeneity of biology and clinical presentation of NDDs even in single-gene disorders: This suggests that

patient stratification/enrichment procedures (e.g. by including subpopulations with certain clinical features or shared neurobiology) could improve detection of signal efficacy in clinical trials testing some compounds. For instance, a mechanism targeted in clinical trials (i.e. regulation of protein synthesis) was clearly altered and was restored by pharmacological interventions in preclinical models of FXS. It is still unclear, however, to what extent this robust molecular phenotype mechanism contributes to the clinical picture in humans. One study assessed levels of the *de novo* rate of protein synthesis in fibroblasts of 32 patients with FXS and 17 controls and assessed the correlation with clinical symptoms. There was an overall increase in protein synthesis in patients with FXS with an effect size of 0.48. However, one-third of the patients were below the 50th percentile of the normal population, with similar findings in primary neurons of 27 *Fmr1* knockout mice and 20 controls (Jacquemont et al., 2018). This highlights the difficulties of linking molecular mechanisms to the phenotype and supports the notion that, even for single-gene disorders, there may be several pathways and mechanisms contributing to the final complex phenotype. This also suggests that a proportion of individuals with FXS might not benefit from strategies aiming to lower excessive protein synthesis, thus supporting the potential need for stratification approaches based on these kinds of factors for some treatment options.

vi) Challenges of identifying appropriate pharmacological targets for genes with pleiotropic effects through development: Single genes with large effects on brain development and function such as FMRP and SHANK3 are usually master regulators of complex transcriptional networks with a large number of genes, which may contribute to the final phenotype with small individual effects. Studies seeking to identify the transcripts controlled by FMRP have identified candidate mRNAs numbering 100–1000s. However, most studies so far have investigated single or a small set of culprits downstream from FMRP (e.g. MMP9, MAP1b, PSD95, and APP) as potential treatment targets, which may constitute a shortcoming. Similarly, evidence from a recent study assessing the effect of copy number variations (CNVs) on general intelligence in the general population and clinical cohorts assessing 12,000 patients referred for NDDs (CNVs n=1217) suggests that the large effects on cognition and other complex behavioural traits observed for some pathogenic CNVs associated with ASD or ID may be polygenic in nature and result from the sum of the individual effects of several genes, rather than the large effect of a single gene (Huguet et al., 2018). This makes it difficult to establish which and how many genes or mechanisms need to be targeted to reverse the phenotype.

Despite the potential of research in single-gene disorders to identify novel treatment targets to guide drug discovery for NDDs, this approach warrants caution considering the great heterogeneity among NDDs. This means that specific mechanisms altered in single-gene disorders may not always be relevant to other forms of NDDs or nonsyndromic autism, which are biologically and clinically heterogeneous conditions defined by behavioural and cognitive criteria, as opposed to the genetic criteria used to define single-gene disorders. This may limit our ability to develop molecules with a clinically meaningful effect on other NDDs such as nonsyndromic ASD, as previous research in FXS has shown (Jeste and Geschwind, 2016). Moreover, some of the targets identified in studies in single-gene disorders may not be easily 'druggable', as may be the case for Angelman syndrome (Ghosh et al., 2013).

Furthermore, the role of genetic common variation in the aetiology and clinical course of ASD and other NDDs (including phenotypic variability in single-gene disorders) (Gaugler et al., 2014; Klei et al., 2012; Niemi et al., 2018) suggests that drug discovery efforts for NDDs need to integrate these research attempts in single-gene disorders with research addressing common genetic variation to improve the potential for translation of the drug targets identified with this approach (Gandal et al., 2016). This may be especially important considering that rare and common variation could converge on distinct biological processes in ASD, and that genes and pathways affected by common variation may be also amenable to therapeutic modification, as suggested by the finding that successful drug targets for other complex disorders are often supported by common risk variants (Gandal et al., 2016).

3. Pharmacological targets for NDDs

3.1. GABAergic agents

Clinical and biological findings support a role for the GABAergic system in the pathophysiology of different NDDs (Cordeiro et al., 2011; Hagerman et al., 2017). $GABA_A$ (e.g. ganaxolone, alphaxalone, gaboxadol) and $GABA_B$ agonists (e.g. baclofen, arbaclofen) have been tested in preclinical models and some clinical trials for FXS with mixed results (Berry-Kravis et al., 2017b). In FXS clinical trials, those with more severe social deficits and younger children showed the greatest benefits of arbaclofen, thus suggesting that there may be a developmental window (Berry-Kravis et al., 2017a; Berry-Kravis et al., 2012).

Gabaergic compounds have also been tested in ASD in clinical trials that excluded participants with FXS. A phase II 12-week randomised placebo-controlled trial of 150 participants with ASD aged 5–21 years did not detect a significant difference between the arbaclofen and placebo groups in the primary outcome measure (Aberrant Behaviour Checklist (ABC) Lethargy/Social Withdrawal subscale). However, there was a significant improvement in the CGI, and a post-hoc analysis of the VABS II socialisation domain showed a positive effect in participants with no intellectual disability (IQ>70) and in those for whom there was a consistent rater throughout the trial (Veenstra-VanderWeele et al., 2017). Based on these results, two phase II double-blind randomised placebo-controlled multicentre trials have recently been launched, one in the AIMS-2-TRIALS clinical trial network (NCT03682978) and one in the POND network in Canada (NCT03887676) to test arbaclofen in children and adolescents who have ASD with fluent language.

There are also promising results in ASD for bumetanide, a diuretic that enhances GABAergic inhibition by decreasing neuronal chloride concentrations, which showed potential to improve core autism symptoms in a phase II randomised controlled trial (RCT) that warrants replication (Lemonnier et al., 2017). Recently, there has also been increasing interest in the α5 subunit-containing $GABA_A$ receptor as a potential target for treatment of NDDs, with a pilot PET study based on a very small sample, suggesting an α5 subunit-containing $GABA_A$ deficit in ASD (Mendez et al., 2013). However, a larger, more recent study did not replicate this finding (Horder et al., 2018a). A negative allosteric modulator of α5 subunit-containing $GABA_A$ (basmisanil) was tested for treatment of Down syndrome in a phase II RCT (NCT02024789), but did not detect significant efficacy on the primary and secondary endpoints of cognition and functioning relative to placebo in 173 adolescents and young adults (12–30 years of age) (Jacob, 2019). Considering the negative results, a phase II RCT in children aged 6–11 years was terminated (NCT02484703). There are currently ongoing phase I clinical trials testing selective allosteric modulators for ASD (Wulff et al., 2019).

3.2. Glutamatergic agents

Downregulation of mGluRs (mGluR1 and mGluR5) may also be a potential target for therapeutic interventions in NDDs. mGluRs are G-protein-coupled receptors that are involved in synaptic plasticity processes, such as learning and memory, anxiety, and pain perception (Bagni et al., 2012). There have been several targeted treatment trials in FXS using mGluR5 antagonists (e.g. basimglurant and mavoglurant), which were not found to be efficacious after three months of treatment in adolescents or adults (Berry-Kravis et al., 2016; Berry-Kravis et al., 2017b). Although efficacy was not demonstrated in the main behavioural outcome measures (based on questionnaires), mavoglurant did show a biological effect in an eye-tracking paradigm assessing social gaze behaviour (Hessl et al., 2019).

Drugs targeting ionotropic glutamatergic receptors have also been tested in ASD in clinical trials excluding individuals with FXS. Despite some positive results in open-label studies, N-methyl-D-aspartate (NMDA) antagonists such as memantine and amantadine have not demonstrated clinical efficacy on core symptoms of ASD in RCTs (Aman et al., 2017; King et al., 2001). Despite some evidence suggesting that d-cycloserine, a partial glycine agonist of the NMDA receptor, could be useful in improving social deficits in ASD, inconsistent results and limitations of available studies warrant replication in larger samples (Minshawi et al., 2016; Schade and Paulus, 2016; Wink et al., 2017). N-acetylcysteine (NAC) is a glutamatergic modulator with antioxidant and anti-inflammatory properties. RCTs testing NAC as monotherapy or as an add-on to risperidone in ASD have shown some efficacy in reducing irritability, albeit with no overall efficacy for treatment of core symptoms (Dean et al., 2017; Deepmala et al., 2015; Wink et al., 2016). Riluzole, a multimodal glutamate modulator that also inhibits GABA uptake, has shown mixed findings in ASD, with two open-label studies reporting improvements in irritability, while a very small randomised placebo-controlled crossover pilot study in 8 children and young adults with refractory irritability failed to detect significant efficacy (de Boer et al., 2019). A recent study demonstrated that riluzole differentially 'shifts' the prefrontal 'inhibitory index' in autistic adults as compared with controls and modulates abnormalities in functional connectivity (Ajram et al., 2017). A double blind RCT testing riluzole in 60 participants with ASD has been recently completed, and results are currently pending (NCT01661855).

3.3. Serotonergic agents

Hyperserotonaemia (i.e. elevated blood or platelet serotonin levels) can be found in almost 30% of patients with ASD (Gabriele et al., 2014). A study in a large sample of families with ASD including 213 autistic young people, 128 unaffected siblings, and 376 parents and other relatives also found hyperserotonaemia, increased platelet N-acetylserotonin (NAS), and a melatonin deficit in children with ASD and, to a lesser extent, in their relatives, thus supporting the role of a disruption in the serotonin-NAS-melatonin pathway in ASD. The authors found the highest heritability estimates in ASD for NAS, a molecule that is also involved in TrkB activation, immunomodulation, and analgesia (Benabou et al., 2017).

In ASD, acute tryptophan depletion "normalises" the brain activation pattern for response inhibition in functional magnetic resonance imaging (fMRI) (Daly et al., 2014). A proof-of-concept study suggests that the use of tianeptine – a drug that could indirectly enhance selective serotonin reuptake, which also seems to modulate glutamatergic pathways and have direct effects on μ-opioid receptors, and shows low binding affinity for other receptors (McEwen et al., 2010; Samuels et al., 2017) – leads to virtually identical results to those found for acute tryptophan depletion, eliminating case-control differences, and thus supporting a potential for targeting the serotonergic system in ASD (Wichers et al., 2017). A small 12-week crossover RCT in 12 male participants, 4–15 years of age, with ASD who had not responded to or tolerated previous treatments found that tianeptine was associated with greater short-term improvement in irritability versus placebo (Niederhofer et al., 2003). AIMS-2-TRIALS aims to conduct a double-blind placebo-controlled biomarker-stratified "shiftability" fMRI study to establish whether there is a differential response to tianeptine in autistic individuals with and without hyperserotonaemia, for its validation as a candidate stratification biomarker for future trials.

The use of selective serotonin-reuptake inhibitors (SSRI) such as sertraline at very low doses (2.5–5 mg/day) has been found to have an anxiolytic effect in young children with FXS. Additional benefits may be expected in some NDDs considering that SSRIs can stimulate neurogenesis in animal models and humans and increase BDNF (Kraus et al., 2017). A six-month double-blind crossover RCT conducted in young children with FXS (2–6 years of age) did not find a general benefit of sertraline for early expressive language development and global clinical improvement (Greiss Hess et al., 2016). However, there were significant improve-

ments in some cognitive tests and one measure of social participation, and post-hoc analyses did show efficacy in a passive eye-tracking paradigm for receptive language (Yoo et al., 2017), as well as a significant improvement in early expressive language development in those patients who had both FXS and ASD (Greiss Hess et al., 2016).

In ASD, SSRIs have been associated with improvements in repetitive/obsessive behaviours in some small individual RCTs, although larger studies and systematic reviews do not report overall significant efficacy on core symptoms of the condition (Carrasco et al., 2012; Herscu et al., 2020; Williams et al., 2013). A recent RCT found significantly lower scores in obsessive-compulsive behaviours at 16 weeks in young people with ASD treated with fluoxetine relative to placebo. However, the clinical implications of the differences were minimal, and the high dropout rates and lack of significance in models adjusted for baseline imbalances and other potential confounding factors limit the interpretation of these findings (Reddihough et al., 2019).

$5HT1_A$ partial agonism has also been considered a potential target in ASD. A double-blind RCT compared two doses of buspirone and placebo in 166 children, 2–6 years of age, and found that low-dose buspirone (2.5 mg/day) was associated with significant improvement in restrictive and repetitive behaviours, with greater improvement in children who had normal levels of serotonin (Chugani et al., 2016).

3.4. Other neurotransmitter receptors

Drugs targeting other neurotransmitter receptors have also been tested in ASD. These include beta-adrenergic antagonists (e.g. propranolol, with some promising results in previous single-dose studies (Sagar-Ouriaghli et al., 2018) and one ongoing RCT (NCT02871349)), and drugs that reduce dopaminergic transmission such as antipsychotics – some of which are currently approved for treatment of irritability associated with ASD, but show little to no effect on core symptoms (Howes et al., 2018) – and the tyrosine hydroxylase inhibitor L1-79, with some trends toward improvement in social functioning and restrictive repetitive behaviours in an open-label study conducted in adolescent and young adult males with ASD (Rothman et al., 2019) and one RCT currently underway (NCT02947048).

3.5. Oxytocin and vasopressin

Oxytocin and vasopressin are neuropeptides that are involved in regulation of social behaviour in mammals. Treatment with intranasal oxytocin has so far yielded mixed findings in ASD and other NDDs, with great inter-individual variability of efficacy on measures of social cognition and behaviour and negative findings on most measures of social cognition and interaction in meta-analyses (Alvares et al., 2017; Keech et al., 2018; Leppanen et al., 2017; Ooi et al., 2017). Although a recent study suggests that oxytocin may improve social abilities in ASD, with the greatest effects found in participants with lower pre-treatment oxytocin blood levels (Parker et al., 2017), an even more recent RCT in 103 adult participants with high-functioning ASD did not detect a significant effect of oxytocin on social reciprocity as the main outcome measure and failed to replicate such an association between baseline oxytocin levels and treatment efficacy (Yamasue et al., 2018). Similarly, another recent RCT conducted in 40 adult males with ASD did not detect significant efficacy of 4 weeks of multi-dose intranasal oxytocin on core social symptoms, despite some improvements in secondary outcome measures (Bernaerts et al., 2020). A recent meta-analysis does not report overall efficacy of oxytocin in reducing restrictive and repetitive behaviour in ASD (Zhou et al., 2020).

Balovaptan, an orally available competitive antagonist of the vasopressin 1a (V1a) receptor with high specificity for V1a, V2, and oxytocin receptors, has been recently tested in the VANILLA trial, a 12-week phase II trial conducted in 223 men with ASD and IQ $\geq$70. Although balovaptan did not show a significant effect on the main outcome measure (Social Responsiveness Scale-2), it was associated with clinically meaningful and dose-dependent improvements in adaptive behaviour (especially in socialisation and communication scores) (Bolognani et al., 2019). Balovaptan was being tested in a phase III RCT in adults (NCT03504917), a phase II RCT in children and adolescents 5–17 years of age (NCT02901431), and a phase Ib open-label study in very young children (ages 2–4; NCT04049578). However, the three RCTs were recently terminated due to negative findings at 24 weeks in the paediatric phase II study and results of a futility analysis suggesting that the adult study is highly unlikely to meet the pre-defined primary objective.

Intranasal arginine vasopressin (AVP) has also been recently found to improve social abilities in a phase II 4-week double-blind randomised placebo-controlled study conducted in 30 children (age range 6–9.5 years) with ASD, with very large effect sizes. Treatment with AVP was also associated with improvements in anxiety and repetitive behaviours. Pre-treatment AVP blood concentrations were associated with efficacy in social communication, that is, patients with higher blood levels of AVP at baseline benefited the most from intranasal vasopressin, a finding that could seem counterintuitive and warrants replication (Parker et al., 2019).

3.6. Other treatment targets

Additional molecules with a potential for treatment of NDDs include trofinetide, a glypromate (GPE) analogue of the neuropeptide insulin growth factor-1 (IGF-1), with positive results in animal models of NDDs (Deacon et al., 2015) and promising results in clinical trials in Rett syndrome (Glaze et al., 2017; Kaufmann et al., 2016) and FXS (Hagerman et al., 2017). A small RCT in Phelan-McDermid syndrome and an open-label study in Rett syndrome also report potential benefits of treatment with recombinant human IGF-1 (mecasermin) (Kolevzon et al., 2014). Nevertheless, caution is needed considering the widespread developmental effects of IGF-1 (Werner and LeRoith, 2014; Wrigley et al., 2017) and given the uncertainties regarding the potential side effects of longer-term use at early ages on brain and other system development. The potential to translate such targeted treatments based on animal models

or proof-of-concept studies of single-gene disorders to other NDDs, including nonsyndromic autism, may be also limited.

Metformin is also regarded as a potentially useful treatment of NDDs due its effects on different pathways, including downregulation of the insulin/IGF-1 signalling pathway and a decrease in mTOR activity and inflammation (Barzilai et al., 2016). An open-label study in 7 patients with FXS, 4–60 years of age, assessing low-dose metformin to treat obesity in the Prader-Willi phenotype, found parent-reported improvements in behaviour and language abilities in most patients (Dy et al., 2018). Minocycline is an antibiotic of the tetracycline class that also has antioxidant, anti-inflammatory, and antiapoptotic properties and slows translation of some proteins (Hagerman et al., 2017). In a double-blind crossover RCT in FXS, minocycline was associated with significant clinical improvement (Leigh et al., 2013) and a significant effect on event potentials, which was associated with an improvement in habituation (Schneider et al., 2013).

HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase inhibitors (e.g. simvastatin and lovastatin) inhibit RAS proteins and indirectly dampen activation of the ERK (extracellular-signal-regulated kinase) signalling pathway (Berry-Kravis et al., 2017b). Lovastatin has been found to reverse some phenotypes in animal models of FXS and Angelman syndrome (Chung et al., 2018; Hagerman et al., 2017), as well as to improve behavioural symptoms such as hyperactivity in an open-label study in 15 adolescents and adults with FXS (Caku et al., 2014). Simvastatin has been found to improve hyperactivity and irritability as an add-on to risperidone in a 10-week double-blind randomised placebo-controlled study conducted in 70 drug-naïve children with ASD aged 4–12 (Moazen-Zadeh et al., 2018). A recent 12-week randomised placebo-controlled study conducted in 30 children with neurofibromatosis 1 and ASD showed a significant effect of simvastatin on several neuroimaging measures affecting brain areas previously involved in neurofibromatosis I pathophysiology and social cognition networks. The study was not powered to test effectiveness and did not detect significant efficacy of simvastatin on autism symptoms (Stivaros et al., 2018).

Glycogen synthase kinase-3 β (GSK-3β) is involved in protein synthesis regulation and in the regulation of synaptic plasticity mechanisms such as NMDA receptor-dependent long-term potentiation and depression (Peineau et al., 2008). GSK-3β inhibition has been found to rescue some of the phenotypic characteristics of the Fmr1 model of FXS (Guo et al., 2012). Chronic treatment with lithium, which can inhibit GSK-3β, has been associated with reversion of multiple phenotypes in preclinical studies in FXS, with positive results in some behavioural measures in an open-label trial in humans (Berry-Kravis et al., 2017b). Treatment with lithium was also associated with clinical improvement in Phelan-McDermid syndrome in two adolescents with ASD and a mutation or microdeletion of SHANK3 inducing a premature stop codon in exon 21 and showing regression and catatonia features (Serret et al., 2015) and in one adult male with intellectual disability, atypical bipolar disorder, and regressive features with a truncating mutation in SHANK3 (Egger et al., 2017). Screening of 202 compounds in neurons derived from induced pluripotent stem cells (iPSCs) found that lithium and valproic acid showed the greatest efficacy in increasing SHANK3 levels and corrected SHANK3 haploinsufficiency phenotypes *in cellulo*. The subsequent administration of lithium to one 12-year-old patient with a de novo truncating mutation in SHANK3, mild intellectual disability, and autistic, regressive, and bipolar features was associated with improvement in bipolar and autism symptom severity (Darville et al., 2016). A recently completed RCT tested tideglusib – a potent, selective, irreversible GSK-3 inhibitor, which has been previously tested for Alzheimer's disease in phase II trials – in 83 adolescents with ASD (NCT02586935).

The endocannabinoid system is a key modulator of several processes that are affected in NDDs such as synaptic plasticity, cognition, anxiety, nociception, and seizure susceptibility (Busquets-Garcia et al., 2013). Many families report benefits of cannabidiol tinctures in children with FXS, and there are very preliminary data based on a case series suggesting potential benefits for anxiety and social skills (Tartaglia et al., 2019). There are also promising preclinical and clinical data in ASD (Fusar-Poli et al., 2020; Poleg et al., 2019), with a recent open-label study reporting efficacy for treating comorbid symptoms (Barchel et al., 2018), warranting replication in the near future. There are currently two ongoing RCTs testing cannabinoids in ASD (NCT02956226, and NCT03202303). Another related set of compounds are fatty acid amide hydrolase (FAAH) inhibitors, which modulate anandamide signalling and have been shown to have anxiolytic effects and improve social and repetitive behaviours in rodents (Zamberletti, Gabaglio, Parolaro, 2017). There is currently one ongoing study utilising an FAAH inhibitor in adolescents and adults with ASD (NCT03664232).

Recent genetic studies and animal models suggest the involvement of ion channels in the aetiology and pathophysiology of some forms of ASD and other NDDs (Sanders et al., 2018; Schmunk and Gargus, 2013; Yi et al., 2016). Despite current challenges for ion channel structure-based drug design for brain disorders, including target specificity and selectivity, half-life and volume of distribution, and challenges in crossing the brain-blood barrier, some molecules with a potential to selectively target specific ion channels that merit further research include biologics such as venom-derived peptides and targeted monoclonal and engineered antibodies (Wulff et al., 2019).

Additional potentially effective supplements may also target alternative pathways. For instance, sulforaphane, a phytochemical derived from cruciferous vegetables such as broccoli, upregulates heat-shock proteins, with effects on immune, oxidative, and inflammatory pathways. In a randomised placebo-controlled double-blind study in young men 13–27 years of age with moderate-severe ASD, sulforaphane was associated with significantly greater improvements in social interaction, verbal communication, and abnormal behaviour than placebo (Singh et al., 2014). There are currently several ongoing or recently completed trials testing sulforaphane in ASD (e.g. NCT02879110 and NCT02677051).

Table 1 shows a summary of potential pharmacological targets for NDDs based on the available preclinical and clinical evidence (Berry-Kravis et al., 2017b; Green and Garg, 2018; Hagerman et al., 2017).

Table 1 Pharmacological targets for neurodevelopmental disorders.

Mechanism	Examples
Glutamatergic transmission	• mGluR5 negative allosteric modulators: mavoglurant • NMDA receptor partial agonists: d-cycloserine • Glutamate modulators: N-acetylcysteine, riluzole
Blockers of pathways between mGluR and protein translation	• HMG-CoA reductase inhibitors (lovastatin, simvastatin) • GSK-3β inhibitors: lithium, tideglusib
GABAergic transmission	• $GABA_A$ agonists: alphaxalone, gaboxadol, ganaxolone • $GABA_A$ α5 receptor positive and negative allosteric modulators • $GABA_B$ agonists or positive modulators: baclofen, arbaclofen ■ Acamprosate ($GABA_A$ and $GABA_B$ agonist) • GABA enhancement: bumetanide (NKCC1 chloride-importer inhibitor)
Serotonin	SSRIs, SSREs (tianeptine), 5-HT_1 partial agonists (buspirone)
Neuropeptides involved in regulation of social behaviour	• Oxytocin • Vasopressin, vasopressin receptor antagonists (balovaptan)
Insulin signalling, growth and neurotrophic factors	Metformin, IGF-1 (trofinetide, mecasermin), minocycline
Endocannabinoid signalling	Cannabidiol

Abbreviations: 5HT, serotonin; GABA, gamma aminobutyric acid; GSK-3β, glycogen synthase kinase-3 β; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; IGF, insulin-like growth factor; mGluR, metabotropic glutamate receptor; NMDA, N-methyl-D-aspartate; SSRE, serotonin selective reuptake enhancer; SSRI, serotonin selective reuptake inhibitor.

4. How genetics might inform drug discovery for neurodevelopmental disorders

4.1. Gene discovery and genetic architecture of autism and other NDDs

Unlike later-onset disorders such as schizophrenia, for which dozens of highly significant variants with small individual effect sizes have been identified in genome-wide association studies (GWAS) (Schizophrenia Working Group of the Psychiatric Genomics, 2014), the most dramatic recent progress in gene discovery with regard to ASD and other NDDs has been the investigation of often *de novo* (spontaneous) germline genetic alterations. These mutations tend to have relatively large biological effects, presumably in part as a consequence of the fact that natural selection has a limited window to act, thus allowing for large impacts on early developmental stages and very early clinical manifestations that would otherwise be selected out of the population over generations (Sanders et al., 2015; Sestan and State, 2018).

This is not to suggest that common small effect variation does not contribute to ASD and other NDDs. With recent substantial increases in cohort sizes, the first replicable genome-wide significant common alleles have now been confirmed in ASD (Grove et al., 2019). Indeed, the distribution of types and population frequencies of genetic variation – that is, the so-called allelic architecture – of NDDs can be viewed as a continuum. Some NDDs are known to be caused by mutations in single genes (e.g. Rett syndrome, FXS, tuberous sclerosis). More common, heterogeneous, early-onset NDDs, including ASD, Tourette syndrome (Wang et al., 2018; Willsey et al., 2017), and epilepsy (Epi et al., 2013; Kearney, 2014), have all been found to involve both rare mutations of large effect and common alleles of small effect, with a relatively greater contribution by the former when compared with later-onset NDDs. Here, for example in schizophrenia, the contribution of polygenic inheritance of common alleles of small effect is particularly prominent (Marshall et al., 2017; Singh et al., 2016).

Over the last decade, the contribution of de novo mutations to ASD has been a seminal observation, one which presaged the current era of reliable and systematic identification of genes and genomic risk intervals (Levy et al., 2011; Marshall et al., 2008; Pinto et al., 2010; Sanders et al., 2011; Sebat et al., 2007). Between 5% and 10% of affected individuals in simplex families carry at least one de novo copy number variation (CNV) (Marshall et al., 2008), an increase or decrease in the number of copies of a (typically sub-microscopic) genomic interval (Marshall et al., 2008). The risk attributable to many of these rare de novo risk CNVs, often encompassing multiple genes, are at least an order of magnitude larger than common ASD risk alleles (Grove et al., 2019; Levy et al., 2011; Sanders et al., 2011). Many of these alterations, including CNVs mapping to regions 1q21.1, 3q39, 7q11.23, 15q11.2–13, 15q13.2-q13.3, 16p11.2, and 22q11.2, have been convincingly replicated (Sanders et al., 2015; Willsey and State, 2015).

More recently, whole exome sequencing (WES) studies have confirmed that *de novo* coding single nucleotide variants (SNVs) also contribute to the risk for NDDs and are a powerful approach to identifying risk genes (De Rubeis et al., 2014; Klei et al., 2012; Neale et al., 2012;

O'Roak et al., 2012; Sanders et al., 2015; Satterstrom et al., 2019). Individuals with ASD show a significantly higher number of *de novo* loss-of-function (LoF) or likely gene disrupting (LGD) mutations (stop codons, canonical splice-site mutations, and frameshift mutations) relative to their siblings, with no significant differences in the rate of *de novo* mutations as a whole. This suggests that the observed increased frequency of these specific types of events in ASD-affected individuals is attributable to their contributing risk. At present, more than 100 individual genes and loci have been identified that exceed statistical thresholds for high-confidence ASD risk via the study of rare *de novo* mutations mapping to the coding region of the genome (Sanders et al., 2015; Satterstrom et al., 2019). De novo coding variants have also been found to contribute to other NDDs such as Tourette syndrome with overall effect sizes similar to those seen in recent studies of ASD (Wang et al., 2018; Willsey et al., 2017).

Most recently, whole genome sequencing (WGS) studies show that the effect size of the contribution of noncoding variation to autism risk is modest relative to that of de novo LGD variants (Werling et al., 2018). However, despite a smaller magnitude of effects, very recent data based on a 'de novo risk score' suggest that noncoding mutations affecting evolutionarily conserved sites in promoter regions contribute to ASD (An et al., 2018).

To date, the most important consequence of the discovery of ASD risk genes carrying large-effect mutations has been their contribution to illuminating the biology and pathophysiology of ASD. There is little question that the task of elaborating the path from genes to mechanisms is more straightforward in the laboratory when examining a single coding mutation carrying substantial risk, versus attempts to model dozens or hundreds of alleles simultaneously. In fact, the observed impact of a single high-confidence ASD risk gene (De Rubeis et al., 2014) exceeds the cumulative contribution of the top decile of polygenic risk for schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics, 2014). In contrast, when one considers overall population risk for ASD, common small effect mutations carry the vast majority of the impact. To some degree, this is a consequence of the fact that most population risk is carried by individuals who show no symptoms of the disease or disorder. In ASD, currently somewhere in the neighbourhood of 10–30% of the unselected clinical population is accounted for by rare, large effect mutations (Vorstman et al., 2017). This percentage is higher in female clinical populations, individuals with co-morbid seizures and dysmorphic features, those with a lower intelligence quotient (IQ), and in individuals from families in which there is a relatively greater number of unaffected siblings (Sanders et al., 2015).

With the recent accumulation of very large patient cohorts numbering in the tens of thousands, a genome-wide meta-analysis has identified five genome-wide significant loci associated with ASD, as well as seven additional loci shared with other phenotypes (i.e. schizophrenia, major depression, and educational attainment) (Grove et al., 2019). As expected, these studies confirmed the very modest individual risks associated with individual alleles. Importantly, however, while common variation confers smaller biological effects, it is very likely that common alleles are acting as important modulators of relevant phenotypes even in individuals carrying large-effect mutations (Bourgeron, 2015; State and Levitt, 2011). Polygenic risk could thus help to explain the pleiotropy of individual developmental outcomes found in individuals with ASD, even for those showing the same high-effect mutation.

The finding already of more than 100 risk genes and regions underscores the tremendous genetic heterogeneity of ASD and other common NDDs, thus raising critical questions regarding how one can conceptualise moving from molecules to therapies. With the early recognition that there were likely to be hundreds of gene targets to be identified (Levy et al., 2011; Sanders et al., 2011), there was attendant concern that this suggested ASD might require a similarly overwhelming number of distinct treatment approaches. However, as discussed below in more detail, this observation does not necessarily dictate the need to develop specific drugs for each affected gene, as both the structural variation and single-gene mutations identified so far seem to converge on a much smaller and coherent set of neurodevelopmental, molecular, cellular, and anatomical pathways (Geschwind and State, 2015; Sestan and State, 2018; State and Levitt, 2011). These genetic alterations likely perturb critical neurodevelopmental processes in different ways, thus suggesting that the specific neurodevelopmental mechanisms, and not only the individual genes, could become important targets for intervention.

Previous research on other genetically heterogeneous conditions such as cancer set an example on how to identify informative subgroups by clustering together patients with mutations in genes converging on downstream pathways (Hofree et al., 2013). Network-based stratification approaches can thus help to identify genetically driven molecular subgroups of NDDs that may show differing biological or clinical profiles (e.g. differing severity or comorbidities). Such approaches require big data that are both 'broad' (i.e. based on large samples) and 'deep' (i.e. multiple levels of data acquired for each individual), as well as highly advanced bioinformatics techniques, which are essential to identify developmental brain gene interaction networks associated with different phenotypic characteristics, and to facilitate translation from gene discovery to the underlying molecular and biological pathways (Lombardo et al., 2019).

4.2. Leveraging genomics to develop novel treatments for NDDs

Table 2 shows some of the challenges of translating genetic findings in NDDs to the development of new treatment targets.

It has been estimated that selecting genetically supported targets could double the drug development success rate (Nelson et al., 2015). Large-effect mutations provide avenues for the development of therapeutics through three main mechanisms: i) targeting the mutation, ii) identifying protective factors, and iii) improving knowledge of the underlying pathophysiology of NDDs. However, drug discovery efforts for NDDs also need to account for common genetic variation (including the effects of putative protective alleles), considering its crucial role in the aetiology and phenotypic variability in clinical manifestations and clinical course of ASD and other NDDs, even in carriers of

Table 2 Challenges of drug discovery for neurodevelopmental disorders.

Challenges for gene discovery and its application for drug discovery in NDDs

- Genetic heterogeneity of NDDs at three different levels (phenotypic, locus, and allelic)
- Biological pleiotropy: Identical mutations may lead to a broad range of phenotypes (e.g. epilepsy, intellectual disability, schizophrenia, and specific language impairment).
- Indirect relationship between DNA changes and behavioural manifestations of the disorder
- Challenges of incorporating genetic findings into the process of new drug development for NDDs:
  - Broad outcomes complicate risk-benefit analysis
  - Very early liability
  - Lack of direct access to the human brain

Challenges for translational research in NDD

- There is great heterogeneity of neuropsychiatric disorder labels in terms of aetiology and neurobiology.
- NDDs and other neuropsychiatric disorders are the result of dysfunction of large complex networks.
- The pathophysiology of NDDs is still mostly unknown and may be different at different developmental stages.
- Some symptomatic manifestations are uniquely human, thus limiting the applicability of animal models.
- Indications so far have comprised target symptom domains or phenotypes that are complex, multidimensional phenotypes.
- The function of some molecular targets is pleiotropic, especially during early neurodevelopmental stages

Methodological challenges of clinical trials in NDDs

- Identification of specific targets for each time point during development
- Timing of interventions
- Optimal duration of interventions
- Optimal duration of follow-up
- Pleiotropy of outcomes in NDDs
- Biological construct validity of current diagnostic categories
- Distance between initial insult and behavioural phenotype, which may be also the consequence of homeostatic changes to the initial event and ongoing functional deficits
- Identification of appropriate and valid biomarkers, with potential for bidirectional translation between animal and human models
- Use of outcome measures that are mechanistically plausible, valid, reliable, and meaningful (for patients, caregivers, and clinicians)
- Adequate quantification of dose and intensity of concomitant interventions (e.g. behavioural interventions)
- High placebo response rates in paediatric trials
- Operational challenges of multicentre clinical trials for relatively rare disorders
  - Sample sizes
  - Identification of appropriate clinical sites with experience in the field
  - Training in critical scales that are quite comprehensive and complicated
  - Standardisation and quality assessment across sites, including reliability assessments
  - Standardisation of EEG procedures and other multisite biomarker paradigms
  - Assessment and support of treatment adherence over time
  - Differences in standard of care and healthcare systems across countries, potentially underlying differences in treatment as usual received by participants

Ethical and regulatory challenges of clinical trials in NDDs

- Trade-off between safety concerns and equality
- Ability of parents or legal guardians to consent on behalf of their children or other vulnerable populations (e.g. people with intellectual disability)
- Balance between potential risks associated with clinical trial participation and risks of testing new treatments in non-controlled settings
- Lack of consistent criteria among ethics review boards
- Ethical concerns about preventive and very early pharmacological strategies
- Limited experience of ethical bodies and regulatory agencies with preventive and very early pharmacological strategies
- Identification of valid outcome measures for regulators, including valid biomarkers

Abbreviations: EEG, electroencephalography; NDDs, neurodevelopmental disorders

large-effect mutations (Gaugler et al., 2014; Klei et al., 2012; Niemi et al., 2018).

i) Targeting the mutation

Despite the important caveats noted above, over just the last several years, it has become increasingly plausible to directly target the specific causal rare large-effect mutation, including those identified for single-gene NDDs and more common forms of ASD. The notion that one could directly edit the mutation or otherwise intervene at the level of the risk gene has gone from a distant hope to a realistic expectation in the last few years –in part because of the development of improved viral gene delivery, antisense oligonucleotide and CRISPR/Cas9 technology– as well as related approaches that allow for targeting a specific mutation at the gene level without leaving a DNA "scar" (Cox et al., 2017; Matharu et al., 2019). In fact, gene targeting has already been used successfully to treat a devastating very early onset neurological disorder, spinal muscular atrophy (SMA). Both intrathecal injection of an AAV vector with a normal copy of the SMN (Survival Motor Neuron) gene and use of antisense oligonucleotides have led to markedly improved outcomes (Finkel et al., 2017; Mendell et al., 2017). Similar approaches are currently being considered for single-gene NDDs such as Angelman syndrome (Meng et al., 2015) and MECP2 duplication syndrome (Sztainberg et al., 2015). There are other recent examples, for instance in the study of SCN1A mutations, suggesting the usefulness of antisense transcripts (Hsiao et al., 2016). For ASD, due to rare genetic LGD mutations with large effect sizes, these advances will undoubtedly spur attempts at gene therapy – raising a wide range of both practical as well as ethical considerations in the not-too-distant future.

ii) Identifying protective factors

The identification of protective factors via mid/high-throughput drug or small molecule screening offers an alternative strategy to identify novel therapeutics in the absence of a thorough understanding of pathophysiology. One promising approach in this regard relies on unbiased screens that seek to rescue a physiological or behavioural phenotype observed in a model system recapitulating high impact mutation(s). For example, a recent analysis of more than 500 diverse neuroactive compounds in a mutant zebrafish model of the recessive form of autism caused by loss-of-function mutations in the Contactin-Associated Protein-like 2 (CNTNAP2) gene found that oestrogens suppressed a highly reproducible mutant behavioural phenotype (Hoffman et al., 2016). Clearly, such an approach would be most promising if such screens identified rescue strategies that applied to not just one, but multiple, apparently functionally diverse, risk genes/mutations simultaneously (Willsey et al., 2018).

A similar idea motivates additional large-scale genomic studies. It is conceivable that as cohort sizes increase, studies may be able to address genomic buffering/resilience in the face of a known pathological mutation. The observation that individuals with the same causative or high-risk variant may have widely varying outcomes, along with evidence that common and rare variation combine to determine risk in the individual, suggests that both protective and risk alleles are present in the genome. There are currently major challenges to identifying these factors given the individual rarity of known high-risk mutations for common forms of ASD. Gathering enough cases to be able to discern an association of protective alleles with confidence is a very real obstacle. However, these types of experimental designs may prove initially useful in investigating protective genetic factors in the context of relatively common monogenic syndromes such as FXS.

iii) Improving knowledge of the underlying pathophysiology at the molecular, cellular and circuit level

The most widely applied recent effort at rational therapeutics development for NDDs has relied on the classic approach of starting with a genetic mutation, elaborating a molecular pathway, and targeting the hypothesised mechanism. For example, the observation that fragile X mutations in model systems altered synaptic protein synthesis and implicated mGluR5 receptors in mediating this effect led to multiple studies of therapeutic compounds. As discussed above, the disappointing results of the related trials may well have been a consequence of poor timing. However, another confound involves the distinction between the downstream biology of a risk gene and the attendant pathophysiological mechanisms. Many of the genes identified as contributing to ASD risk are biologically pleiotropic. Consequently, the identification of a highly valid and quite interesting developmental, molecular, physiological or behavioural phenotype in a model (e.g. rodent) system may or may not point to a biological function that is relevant to the human disorder (Sestan and State, 2018; Willsey et al., 2018). The complexity of the search space between a risk mutation and the relevant pathological mechanisms in ASD is not a consequence of pleiotropy alone. The complexity of brain development both anatomically and temporally complicates the picture considerably, as does the observation of male predominance in ASD.

Perhaps ironically, the tremendous genetic heterogeneity observed in ASD (and other early onset NDDs) may be a key to elaborating its pathophysiology and distinguishing that from the overall biology of risk genes. It is certainly reasonable to hypothesise that, in order to lead to the shared phenotypic features of ASD in the human population, groups of overtly functionally distinct ASD risk genes are likely to show convergence in the path from gene to complex behaviours. The first efforts to find such points of convergence focused on protein function, narrowing in on the importance of synaptic structure and function (Zoghbi, 2003). With ongoing gene discovery, such early observations have held up well, with multiple studies pointing to the synapse as well as to chromatin remodelling and transcriptional regulation as critical aspects of ASD biology (De Rubeis et al., 2014; Geschwind and State, 2015; O'Roak et al., 2012; Pinto et al., 2014). Such approaches have also highlighted a nexus between single-gene NDDs and more common forms of ASD. Targets of fragile X mental retardation protein (FMRP) have been repeatedly shown to be enriched for ASD risk genes (De Rubeis et al., 2014; Iossifov et al., 2012).

Alternative approaches to searching for points of convergence have focussed not only on what genes do, but when and where they may be acting to increase ASD risk – i.e. spatiotemporal convergence (Parikshak et al., 2013; Willsey et al., 2013; Willsey and State, 2015). This

is motivated by a desire to place specific mutations in a relevant developmental context, which in turn may inform windows of opportunity for specific treatments and help to identify dynamic targets for intervention. Based in part on co-expression network data from the BrainSpan developmental transcriptome, which maps gene expression from early foetal to late adult life in typically developing brains (www.brainspan.org), multiple groups have found that sets of ASD risk genes converge in mid-foetal prefrontal cortical development in the human brain, specifically in glutamatergic neurons (Chang et al., 2015; Parikshak et al., 2013; Polioudakis et al., 2019; State and Sestan, 2012; Willsey et al., 2013). These studies have shown modest disagreement regarding the importance of deep (Willsey, Sanders et al. 2013) versus more superficial (Parikshak, Luo et al. 2013) cortical layers. As gene discovery has progressed and larger gene sets have been discovered, these findings have been validated, and additional brain regions and time windows, including in the striatum and in early postnatal development, have also begun to emerge (Geschwind and State, 2015; Sestan and State, 2018). This information could be applied to the identification of dynamic targets for intervention by facilitating either a) focussed and temporospatially highly specific investigations of single genes in specific cell types, developmental stages, and brain regions or b) the study of mutations in different genes converging on a specific temporospatial window.

5. Neurodevelopment: a therapeutic window

Human brain development spans more than two decades, with events occurring at earlier stages showing greater long-term effects. Pathological genetic variations in interaction with environmental factors during sensitive developmental periods has long-term consequences on brain function that may lead to the development of neuropsychiatric disorders (Marín, 2016). Each developmental stage needs to be completed before going on to the following one, which suggests that failing to achieve critical biological neurodevelopmental milestones at very early stages may have a cascade effect thereafter, and the brain may thus show atypical development over time (Veenstra-VanderWeele and Warren, 2015). This has clear implications, insofar as the brain is considered a dynamic target during development, and a decision needs to be made not only regarding where but also when (temporally during neurodevelopment) to intervene to reshape brain development and normalise its functioning. Interventions aiming to prevent the onset of brain disorders should thus take into account critical periods and developmental windows of plasticity and vulnerability (Marín, 2016).

Critical and sensitive periods are time windows when the brain undergoes greater changes and neurobiological plasticity is increased. Genetic or environmental risk factors acting during these periods and prompting even subtle changes in gene expression, neuronal activity, or circuit development are likely to have a significant impact on developmental trajectories, thus leading to NDDs (Meredith, 2015). For instance, recent experiments in mice reveal that pyramidal neuron activity regulates interneuron survival in a critical window during early postnatal development, at least in part by negatively modulating PTEN signalling. This regulation of interneuron survival helps to establish the normal proportion of inhibitory and excitatory cortical neurons (Wong et al., 2018). This ratio seems to be stable across cortical regions and species (DeFelipe et al., 2002), while disruptions in the inhibitory-excitatory balance seem to be common to several brain disorders, including ASD (LeBlanc and Fagiolini, 2011; Marín, 2012),

Studies in two animal models of NDDs highlight the importance of considering temporospatial specificities of developmental changes to guide targeted treatments:

5.1. CNTNAP2

Genetic variation in CNTNAP2 has been linked to autism, as well as to other neurological and neurodevelopmental disorders such as epilepsy and schizophrenia (Alarcon et al., 2008; Bakkaloglu et al., 2008; Chiocchetti et al., 2015; Poot, 2015; Vernes et al., 2008). The CNTNAP2 gene encodes the contactin-associated protein-like 2 (Caspr2), which plays an important role in neurodevelopment (Poliak et al., 1999). Caspr2 controls the clustering of potassium channels in the juxtaparanodes of myelinated axons in the brain, and it has been associated with the physiological properties of white matter conductivity, especially due to its effects on excitatory conduction. Single axon recordings at the corpus callosum in Cntnap2 mutant mice show abnormal axonal action potential prolongation, which leads to increased postsynaptic excitatory activity, reduced long-range synchronisation, and overexcitation, relative to wild type mice (Scott et al., 2019). This parallels the phenotype in humans and affects all axons in the brain, thus suggesting a spatially widespread effect.

In rodents, some phenotypic characteristics show differential developmental expressivity, such as alterations in grooming behaviour, repetitive and stereotyped motor behaviour, and loss of control, which do not appear until the sixth week of life, when myelination is mostly completed in mice (Scott et al., 2019). Connections between the cortex and basal ganglia are crucial for grooming behaviour, and it has been reported that chronic, but not acute, stimulation of corticostriatal connections may lead to repetitive behaviours (Ahmari et al., 2013). In Cntnap2 mutant mice, these connections are chronically overexcited at earlier neurodevelopmental stages, thus eventually facilitating development of repetitive motor behaviour when the axons become myelinated. Considering the developmental mechanisms that seem to be involved, it would not be expected that providing Caspr2 shortly before the onset of the first clinical manifestations would be efficacious to rescue the phenotype. In order for this strategy to be effective, Caspr2 should be provided when these connections are being built (i.e. in early pregnancy). Indeed, deficient Caspr2 may no longer be excessively important for later intervention, since it has triggered but is not the underlying factor in the current problem. The effect of CNTPA2 seems therefore to be spatially widespread but dependent on timing.

5.2. ERBB4

ERBB4 sets an example of spatial specificity. In the cortex, ERBB4 is specifically expressed in fast spiking interneurons, and it plays an essential role in their wiring (Fazzari et al., 2010). Genetic variation in ERBB4 has been linked to intellectual disability and schizophrenia (Walsh et al., 2008). Primary synaptic deficits secondary to loss of ERBB4 translate into complex and unexpected network abnormalities that are not a direct result of the primary genetic insult, and the resulting phenotype can only be understood from a neurodevelopmental perspective. In Erbb4 mutants, the primary genetic insult leads to decreased excitatory synapses projecting to parvalbumin interneurons. However, this does not lead to decreased inhibitory function, since there is a homeostatic reaction to the loss of synapses by pyramidal cells, which increase their firing rate, thus leading to increased excitatory drive to parvalbumin interneurons. Although this increased excitation in the cortex could, at least theoretically, lead to epilepsy, there is a subsequent homeostatic response because parvalbumin interneurons also increase their firing rate, which translates into increased inhibition. After these homeostatic processes, the balance can be restored during neurodevelopment, but this balance is fairly dysfunctional (as it is currently set at a higher level, with every cell, both excitatory and inhibitory, firing at a higher rate), thus leading to the subsequent difficulties that underlie the final phenotype.

These processes have important functional consequences with a potential for translation, since this might be measured in humans by assessing alterations in gamma synchronisation. In freely moving Erbb4 mutants, there is an increase in gamma oscillations in the hippocampus, thus supporting the notion that the system has been reset to increased gamma oscillations, which mirror the “baseline noise” that the system has acquired to compensate for the difficulties (Del Pino et al., 2013). Alterations in gamma synchronisation are not associated with a specific pattern of cognitive difficulties, which would also support their potential role as a common underpinning of different NDDs (Cho et al., 2006; Kikuchi et al., 2011).

Both examples suggest that primary synaptic deficits might translate into complex and unexpected network abnormalities, and the resulting phenotype can only be understood from a neurodevelopmental perspective. Developmental brain alterations lead to cascading defects due to normal homeostatic mechanisms underpinning the dysfunction that eventually leads to the clinical phenotype. Clinical and cognitive manifestations of NDDs might be thus the result of the initial genetic or environmental insult, the homeostatic developmental response to the initial insult (including compensatory and cascading effects), and ongoing functional deficits. The original problem in the brain leads to mechanisms to compensate for early abnormalities, sometimes successfully, but sometimes leading to an unstable balance. To develop effective treatments for NDDs we need to i) consider timing and decide at which point we want to reset the balance, as this point might no longer be directly linked to the original problem, and allowing for the fact that each brain region may have multiple critical periods with differing biological underpinnings and that timing of critical periods may differ across circuits within the same region (Meredith, 2015), ii) use animal models, which help determine the spatial and temporal points where we need to intervene and apply targeted interventions, although they need to be validated and translated to human models, and iii) focus on brain circuits rather than on a single pathway, since this is how we can relate brain abnormalities to specific functions and behaviours.

6. Developmental trajectories in ASD as phenotypes with a potential to guide treatment strategies for NDDs

6.1. Developmental trajectories of ASD in childhood, adolescence, and adulthood

NDDs are conditions set off by an atypical response to aberrant structural or functional brain development that occurs even before birth, which prompts atypical neurodevelopmental trajectories. Developmental pathways may be shared across different NDDs (e.g. ASD, ID, single-gene disorders) and other neuropsychiatric disorders, which seems to reflect common vulnerabilities and could underlie high rates of co-occurrence (Johnson et al., 2015). Some behavioural manifestations of NDDs seem to reflect a delay in specific developmental trajectories (e.g. transient delays in acquisition of gross motor milestones in some children with ASD and other NDDs), while others may be the consequence of deviant trajectories (such as sensory processing atypicalities in some children with ASD) (Johnson et al., 2015).

Converging evidence based on longitudinal studies supports the heterogeneity of developmental trajectories in children diagnosed with ASD from early childhood through adolescence and adulthood (Anderson et al., 2014; Baghdadli et al., 2012; McGovern and Sigman, 2005; Seltzer et al., 2004). A large study in more than 421 preschool children aged 2–4 years newly diagnosed with autism reported heterogeneous developmental trajectories in ASD in childhood, with improvements in adaptive functioning found in 20% of the sample during this period, and greater stability of autism symptom trajectories (Szatmari et al., 2015). Another study identified six typical trajectories of social, communication, and repetitive behaviour functioning from childhood to adolescence in young people with ASD, again with great heterogeneity in developmental pathways. Although children with less severe symptoms at first diagnosis showed more rapid improvements, there was also a subgroup of 10% of children with the most severe social deficits at baseline, who also showed significant improvement in their social trajectories over time (Fountain et al., 2012).

The most replicated predictors of outcome in ASD in adulthood seem to be language development and cognitive ability, but there are some inconsistencies regarding other variables (Howlin et al., 2014; Magiati et al., 2014). Although long-term outcomes are poor for a significant proportion of people with ASD (Howlin, 2003), extensive work is currently underway to characterise those with “optimal outcomes” (i.e. those who no longer meet diagnostic crite-

ria for ASD over time), including assessments of the effect of interventions on developmental trajectories and outcomes (Anderson et al., 2014; Fein et al., 2013; Moulton et al., 2016; Orinstein et al., 2015; Troyb et al., 2014).

Available neuroimaging studies suggest that brain development atypicalities in ASD follow complex trajectories, rather than a constant, linear deviation from typically developing (TD) individuals, with differing trajectories for changes in cortical surface area and thickness over time. Studies have thus reported, on average, increased brain volumes during the first few years of life, with accelerated growth trajectories of grey and white matter volume, and cortical surface area in several regions (Courchesne et al., 2007; Hazlett et al., 2011; Redcay and Courchesne, 2005), especially affecting frontal and temporal areas (Carper et al., 2002). During later childhood and adolescence, there seems to be, on average, a slowing of brain growth and increased cortical thinning, with an inconsistent trajectory versus TD individuals, such that no case-control differences in whole brain volume are usually found in adults (Hernandez et al., 2015; Zielinski et al., 2014). However, some atypicalities affecting specific regions remain dynamic well into adulthood, and several cross-sectional and longitudinal studies have reported greater age-dependent reductions in brain volumes and cortical thinning affecting temporal and parietal areas during adolescence and early adulthood in ASD relative to TD individuals (Lange et al., 2015; Wallace et al., 2010; Wallace et al., 2015; Zielinski et al., 2014). On the contrary, findings for surface area suggest comparable growth rates in both populations, or even a smaller decline in these brain regions in ASD during this period (Mensen et al., 2017; Wallace et al., 2015). Along those lines, a recent cross-sectional mega-analysis using a large sample from the ENIGMA ASD working group aged 2–64 years found alterations in cortical thickness affecting the striatum, frontal, and temporal cortices – albeit with small effect sizes – with a developmental peak in these regions (i.e. the greatest differences relative to TD individuals) found around adolescence, while no significant differences in cortical surface area were found for any region (van Rooij et al., 2018).

There also seem to be age-dependent inconsistencies in patterns of atypical resting-state functional connectivity in cross-sectional studies, which supports the notion of developmental changes in these processes across the lifespan in people with ASD (Dajani and Uddin, 2016; Farrant and Uddin, 2016; Nomi and Uddin, 2015). In keeping with this, a very recent longitudinal study has also reported atypical developmental trajectories of some resting-state networks (i.e. the default mode network and the central executive network) in young people with ASD during adolescence (Lawrence et al., 2019).

Taken together, the available evidence suggests that age modulates the trajectories of brain structure and function atypicalities, which calls for a developmental approach to neuroimaging studies in ASD (Hernandez et al., 2015). Reviews also highlight the great inconsistency of findings across studies, which may be a consequence of the neurobiological heterogeneity of the condition, small effects, variable age of the cohorts assessed, and differing developmental trajectories among people with a diagnosis of ASD, and support the use of dimensional measures, strategies to identify more homogeneous subgroups, and new statistical multivariate approaches (Ecker et al., 2013; Hernandez et al., 2015).

6.2. Developmental trajectories in infants with increased likelihood of ASD

The study of infants and toddlers with increased likelihood of NDDs may improve our understanding of pathways into the disorder and developmental windows for intervention (Johnson et al., 2015). Most of these studies have been conducted in siblings of children with ASD, who show a 10- to 20-fold increase in the likelihood of presenting ASD (Hansen et al., 2019; Ozonoff et al., 2011; Sandin et al., 2014), and can be identified prenatally and followed-up from birth (Varcin and Jeste, 2017). Initial studies considered the increased likelihood sample quite homogeneously, but there has been increasing interest in identifying variables that might help to stratify infants with increased likelihood and to identify their potentially underlying biology to guide targeted therapies (Loth et al., 2016a). Early interventions in infants with increased likelihood, applied before onset of defining symptoms of ASD, could be associated with improvements in social communication skill development and possibly also some ASD symptoms (Green et al., 2017; Whitehouse et al., 2019). Nevertheless, it should be noted that siblings of children with ASD may also show other neurodevelopmental outcomes (including ADHD, ID, or language or psychomotor developmental delays) (Charman et al., 2017), which suggests that some of the identified likelihood markers may be predictive of broader developmental phenotypes, rather than of a categorical diagnosis of ASD.

Prospective studies in toddlers and infants with increased likelihood suggest that the defining behavioural manifestations of ASD (i.e. abnormalities in social communication and repetitive behaviour) unfold in the second year of life and consolidate between 18 and 36 months of age, although some features could be identified earlier (Sacrey et al., 2015; Varcin and Jeste, 2017). Some of the early signs that can be identified during the first two years of life in infants with increased likelihood who later receive a diagnosis of ASD include delays or atypicalities in expressive and receptive language acquisition, gross and fine motor skills and gestures, gaze patterns and social attention, sensory processing, repetitive behaviours, and emotional dysregulation (Johnson et al., 2015; Jones et al., 2014; Piven et al., 2017; Varcin and Jeste, 2017). Combinations of some of these behavioural markers at age 18 months have been found to be predictive of a later diagnosis of ASD (Chawarska et al., 2014). Atypicalities in social visual engagement (including preferential attention to biological motion and preferential attention to others' eyes) during the first few months of life could constitute a promising early developmental marker, considering that they can be detected at pre-symptomatic stages, are minimally influenced by learning, and are predictive not only of a categorical diagnosis of ASD, but also of other dimensional developmental outcomes (Constantino et al., 2017; Jones et al., 2008; Klin et al., 2009; Klin et al., 2015). In a prospective eye-tracking study, toddlers with increased likelihood who later received a diagnosis of ASD initially showed levels of eye fixation similar

to those found in TD individuals at 2 months of age, but presented a significant decline from 2 to 6 months of age, thus supporting the notion that this may be an important developmental window (Jones and Klin, 2013).

Brain imaging studies have reported atypical patterns in brain morphometry, and structural and functional connectivity during the first year of life in individuals with increased likelihood who later received a diagnosis of ASD (Varcin and Jeste, 2017; Wolff et al., 2018), including atypicalities in the microstructural organisation of white matter tracts and atypical morphological features affecting the corpus callosum, subcortical structures, extra-axial cerebrospinal fluid, and the cerebellum, among other regions (Elison et al., 2013; Emerson et al., 2017; Lewis et al., 2017; Pote et al., 2019; Shen et al., 2013; Wolff et al., 2012). A recent study found that infants with high familial likelihood of ASD who later received a diagnosis of ASD at 24 months show hyperexpansion of cortical surface area between 6 and 12 months of age, preceding brain volume overgrowth between 12 and 24 months of age, and that brain overgrowth is associated with severity of social deficits. A deep learning algorithm based primarily on neuroimaging variables (mostly surface area) was found to accurately predict a diagnosis of ASD in this sample (Hazlett et al., 2017).

EEG, fMRI, and near-infrared spectroscopy (fNIRS) studies also report atypical resting-state patterns or patterns of activation associated with exposure to social stimuli or human voices in infants with increased likelihood who later receive a diagnosis of ASD (Lloyd-Fox *et al.*, 2018; Varcin and Jeste, 2017; Varcin and Nelson, 2016). For instance, a recent prospective study assessing neural responses to auditory repetition at age 8 months has reported an EEG pattern suggesting cortical hyperreactivity in infants with increased likelihood with a later diagnosis of ASD, also associated with dimensional measures of social communication and language development across the whole sample with high likelihood (Kolesnik et al., 2019). Very recent data-driven analyses of the longitudinal trajectories of EEG power measurements from ages 3 to 36 months in infants at low and high likelihood for ASD suggest that trajectories during the first postnatal year, along with delta and gamma frequency power trajectories, may be useful to differentiate autism outcomes (Gabard-Durnam et al., 2019), thus supporting their role as potential stratification biomarkers for ASD.

Although some research is currently being conducted in foetuses and neonates with increased likelihood (Ciarrusta et al., 2019), most of the information on prenatal developmental trajectories in autism is still based on animal models or retrospective studies. A systematic review found an association between some alterations in ultrasound measurements, including nuchal thickness and ventricle enlargement, with a later diagnosis of ASD in some studies, although data were sparse and controversial (Fulceri et al., 2018). A small prospective ultrasound study did not show significant differences in macroscopic prenatal head or body growth between foetuses with high and low likelihood (Unwin et al., 2016). Very recently, AIMS-2-TRIALS has reported that neonates at increased likelihood of developing ASD have higher levels of local functional connectivity and dysmaturation of interconnected regions responsible for processing higher-order social information. This suggests that atypical development of functional connectivity patterns affecting these regions could constitute a vulnerability mechanism for autism (Ciarrusta et al., 2019). Further longitudinal research using safe methods (e.g. MRI and MRS) that allow for more accurate assessment of brain development and developmental pathways to ASD is warranted in this population. This longitudinal research, in combination with data obtained from other samples with increased likelihood of NDDs, could be critical to understanding the cascading effects of genetic and environmental risk factors on early brain development and to identifying stratification biomarkers that precede onset of clinical symptoms, so as to guide early interventions.

6.3. Implications of developmental trajectories for drug discovery and clinical trial development in NDDs

The study of the natural history and prognostic factors of ASD and other NDDs may be essential to identify plasticity windows and optimise treatment strategies. Clinical, cognitive, and neurobiological heterogeneity of developmental trajectories of NDDs has clear implications for the development of therapeutic strategies, since interventions (including drugs) for each kind of trajectory may differ in terms of targets, efficacy, and tolerability. Although the biological underpinnings of differing developmental trajectories in ASD and other NDDs are still unknown, developmental trajectories of these conditions could constitute important phenotypes for genetic studies, biomarker discovery, and stratification (Lord et al., 2015). A deep phenotypic characterisation of these developmental trajectories may also help to identify more homogeneous subgroups within NDDs and facilitate drug discovery for these conditions (Loth et al., 2016a).

Another implication pertains to the need for developmentally sensitive outcome measures in clinical trials for NDDs. For instance, there is a dearth of appropriate standardised measures of social communication to assess longitudinal changes in children with NDDs in the context of clinical trials (Bishop et al., 2019). Appropriate measurement of social communication in NDDs should focus on skill development, rather than on deficits, and enable detection of changes independent of language and cognitive development, while allowing for age-expected and non-linear improvements, as well as for heterogeneous developmental trajectories of different symptom dimensions. Although adaptive functioning scales such as the Vineland Adaptive behavior Scales (VABS) are more developmentally appropriate than other standardised measures, they may have some limitations with respect to capturing changes (Bishop et al., 2019). There is also a need for cognitive measures that are equally suitable and meaningful across the lifespan, with sufficient sensitivity across the complete intellectual ability range (Loth and Evans, 2019).

The study of developmental trajectories in populations with increased likelihood for NDDs may also enable identification of likelihood biomarkers, which could potentially help to estimate the likelihood of developing ASD before onset of the first behavioural manifestations of the condition in order to implement earlier interventions (Loth et al.,

2016a). This information may also help to identify sensitive periods for intervention and biological mechanisms underlying likelihood, with a potential to become treatment targets. The identification of variables that might help to stratify infants with increased likelihood and the study of their underlying biology may help to guide targeted therapies at earlier developmental stages (Loth et al., 2016a).

7. Translational approaches to advance treatment of neurodevelopmental disorders

7.1. Translational studies for drug development in brain disorders

Translational studies in neuroscience aim to bridge the gap between preclinical models and clinically relevant endpoints in patient samples. These studies focus on component processes and circuit-dependent behaviours that seek to link behavioural assays in animals to the targeted symptoms in patients. An ideal translational medicine study for NDDs should i) be based on a good knowledge of the neurobiology underlying the target disorder and symptoms, ii) use appropriate key outcome measures related to mechanisms, with demonstrated effects in valid animal models, iii) include biomarkers and other objective outcome measures that demonstrate effects on involved mechanisms, iv) have predictive validity, and v) be of short duration with a small sample size. Overall, a translational medicine study should ideally enable an early go/no-go decision. However, clinical trials in the real world face considerable challenges to implementing this approach, especially in the field of brain disorders.

Table 2 summarises some of the challenges of developing translational research in NDDs. Potential ways of addressing these challenges include: i) dissecting complex phenotypes (e.g. deficits in social communication and cognition) and diagnostic entities, by assessing bio-behavioural domains or factors that can link specific neural circuits to behavioural manifestations and component behaviours, including the study of intermediate phenotypes such as neurocognition and brain measures (e.g. resting-state functional connectivity (Elton et al., 2016; Tang et al., 2020)), ii) demonstrating efficacy on key neural circuits or specific behavioural tests assessing key behavioural functions, iii) use of genetic enrichment or stratification strategies, and iv) promoting observational studies to carefully characterise the longitudinal course of the illness and identify potentially useful biomarkers.

Early clinical development in psychiatry should include exploratory studies (i.e. proof-of-mechanism and proof-of-concept studies) to characterise target engagement, physiological modulation of circuits, and disease-relevant pharmacology including safety. For instance, for new compounds targeting negative symptoms of schizophrenia, proof-of-mechanism studies using biomarkers such as reward-based learning and reward-based effortful behaviour could facilitate an early no-go decision (Strauss et al., 2014). Clinical trials in the field should also take into account the fact that most CNS disorders are not static and that pharmacological abnormalities involved in the disorder may change over time. For some NDDs, there may be multiple and differing points of intervention during development, and efficacy and objectives of the intervention (e.g. disease modification, delay in progression, and functional rescue) could vary depending on the timing of the intervention.

For ASD, the core symptom domain of impaired social communication could be dissected into multiple potentially underlying bio-behavioural dimensions and functions, such as social attention, processing of facial information, reward processing, emotional reactivity, and cognitive control (Neuhaus et al., 2010). Social attention can be investigated using distal and proximal biomarkers of social communication such as eye-tracking tasks or tasks assessing complex social perception (e.g. reading the mind in the eyes test and affective speech recognition). Early developmental phases for a compound targeting impaired social communication in autism might thus include eye-tracking tasks (e.g. assessment of biological motion detection and preference, human activity, static face scanning, and complex social scenes), which could provide useful mechanistic information on behaviours.

These tasks were used to test a novel vasopressin 1a (V1a) receptor antagonist (RG7713) in a single-dose randomised placebo-controlled crossover proof-of-mechanism study in 19 adult patients with high-functioning autism (Umbricht et al., 2017). Single-dose treatment with the active compound was associated with increased gaze orientation to biological motion (ES=0.8). This information suggested a potential role for this mechanism of action in the management of social communication deficits in ASD and enabled a rapid go decision for further studies testing other V1a receptor antagonists. The question whether these short-term changes in the eye-tracking paradigm after treatment could translate into clinical changes in the longer term was tested in the VANILLA study (see above). The authors found that balovaptan (another V1a receptor antagonist) had a consistent effect on socialisation and communication, thus confirming that the minor effect initially found for the biomarker could also be clinically meaningful (Bolognani et al., 2019).

7.2. The need for developmental animal models for NDDs with a potential for translation

Experimental studies in preclinical models of NDDs are required to improve knowledge of their pathophysiology. These studies may aid the development of better treatments by helping to define changes in activity of different neuromodulators, brain structure, and function associated with treatments, characterise developmental plasticity windows for treatment, assess pharmacokinetics and pharmacodynamics of drugs in developing individuals, and evaluate appropriate duration of treatments. To achieve this, animal models should show appropriate face validity (i.e. strong analogies to the human endophenotypes), construct validity (i.e. the same biological dysfunction that causes the human condition, such as a gene mutation, molecular mechanism, or abnormality in brain structure or function),

and predictive validity (i.e. similar responses to preventive or therapeutic interventions to those found in humans) (Silverman et al., 2010). Animal models for NDDs thus need to show behavioural and neurodevelopmental characteristics that reasonably reflect some aspects of the human phenotype (Bethea and Sikich, 2007; Sukoff Rizzo and Crawley, 2017). In neuroscience, the translatability of animal models can be lower than in other areas of medicine, due to the intrinsic difficulties of translating some behavioural manifestations that are purely human (Loth et al., 2016a). Therefore, there is a pressing need for animal models that use task batteries and biomarkers translatable from animals to humans, including adequate cross-matching of cognitive and behavioural domains and readouts that can be translated across species (Damiano et al., 2014). These endeavours require close cooperation between basic and clinical neuroscientists working in the field of NDDs (Kazdoba et al., 2016b), as well as among preclinical laboratories to assess the quantitative stability of behavioural assays and the validity of animal models (Murphy and Spooren, 2012).

In neuroscience, murine models are frequently used to assess cellular and molecular changes and mechanisms of treatments. In the case of ASD, most animal studies have been conducted in mice. Like humans, rodents (mice and rats) are social species that seek contact with others and display a wide array of social behaviours, including reciprocal social interactions, parenting, mating, and aggressive behaviours (Kazdoba et al., 2016b). Different groups have developed a comprehensive set of assays in mice for assessment of social interaction (e.g. measures of social approach, reciprocal social interactions, and social preference), social communication (e.g. measures of olfactory habituation and ultrasonic vocalisations), as well as restricted (e.g. perseveration in spatial tasks) and repetitive behaviours (e.g. motor stereotypies such as circling and vertical jumping, or repetitive behaviours such as self-grooming and digging), with varying face validity (Crawley, 2012; Silverman et al., 2010). Several paradigms that allow for assessing associated symptoms of autism have also been developed, including cognitive tasks and anxiety (Silverman et al., 2010).

There are several categories of animal models for ASD and other NDDs: i) genetically modified models (e.g. knockout models) showing mutations analogous to those found in single-gene disorders associated with high rates of ASD or NDDs (e.g. FXS or SHANK3), or mutations affecting genes involved in processes that are associated with NDDs (e.g. synaptic cell-adhesion proteins, signalling and developmental proteins, neurotransmitters and receptors, etc.; see (Kazdoba et al., 2016a) for a review), ii) models after ablation of some brain areas (e.g. amygdala or anterior cingulate cortex), and iii) models based on environmental insults (e.g. models obtained by manipulating maternal factors, such as prenatal valproate exposure, or models of virus infection and maternal immune activation) (Patterson, 2011).

Murine models of ASD reproduce different behavioural manifestations of the autism phenotype and some of its neuroanatomical and microstructural features (Crawley, 2012; Kazdoba et al., 2016b; Patterson, 2011; Silverman et al., 2010; Varghese et al., 2017). Most studies conducted so far have focussed on only one genetic, neuronal, or behavioural pattern rather than on complex screening. However, as NDDs are complex, multifactorial conditions that are polygenic in nature, combinations of data from different animal models could be needed to deepen our understanding of the neurobiology of ASD and other NDDs. For instance, combinations of data provided by different knockout models for single-gene disorders can provide invaluable information on the different pathways potentially involved in NDDs. Among them, knockout models comprising mutations in cell surface adhesion glycoproteins (e.g. NEUROLIGIN3, SHANK3, and CNTNAP2) and animal models of FXS or tuberous sclerosis hold great potential for translatability (Crawley, 2012). In addition to knockout genetic models of ASD, some inbred mouse strains (e.g. BTBR mice) could also constitute appropriate models of idiopathic autism, because they display well-replicated social deficits and repetitive behaviours (Kazdoba et al., 2016b). However, their applicability might be diminished to some extent due to different strains that are too genetically similar to each other. To address this, the Collaborative Cross line of mice (bred from eight different mouse strains) offers new opportunities to mimic the polygenic nature of NDDs beyond single-gene/single-genetic-background models, thus potentially facilitating the quantification of developmental effects across multiple genetic backgrounds (Molenhuis et al., 2018; Sukoff Rizzo and Crawley, 2017).

Despite their advantages, it seems unlikely that rodent models could fully capture all of the neurodevelopmental and behavioural abnormalities present in autism. It has been proposed that non-human primates (NHP) could help to overcome some of the limitations of rodent models, considering their greater similarity to humans. The costs and ethical dilemmas of research conducted in NHP must however also be factored into the equation (Nelson and Winslow, 2009). Additional models with a potential for translation, include studies in flies, zebrafish, rats, and iPSCs, among others (Damiano et al., 2014; Loth et al., 2016a). iPSCs offer a unique opportunity to better understand the molecular underpinnings of ASD by enabling connection and integration of *in vitro* (e.g. cell proliferation, differentiation, and growth, synaptic structure and function, neural network activity) with *in vivo* (e.g. genetic, neuroimaging, behavioural, clinical, cognitive) measures for a particular person (Courchesne et al., 2019). Studies conducted in iPSCs derived from autistic people with brain overgrowth or enlargement found excess proliferation and cell cycle acceleration of neural progenitor cells as a shared feature, with subsequent disruption in multiple foetal age processes of neuronal and synaptic development and early dysfunction in neural networks, and heterogeneity in synaptogenesis defects (Marchetto et al., 2017; Mariani et al., 2015), reviewed in Courchesne et al. (2019). One of these studies found that IGF-1 was able to rescue some of these phenotypes *in vitro*, thus strengthening the rationale for the potential usefulness of IGF-1 in ASD (Marchetto et al., 2017). Additional studies in iPSCs also suggest that glial dysfunction may also be involved in autism pathophysiology by disrupting neuronal development and point to interleukins as potential drug targets for some forms of nonsyndromic autism (Russo et al., 2018).

Furthermore, drug discovery for NDDs requires developmentally sensitive animal models. This depends on identification of developmental stages analogous to those involved in the human phenotype and careful assessment of periods where processes relevant to ASD occur in those models (e.g. synaptogenesis, synapse refinement, and integration of networks). Although advances in the field might be hampered to some extent by differences in some of these processes across species (Bethea and Sikich, 2007), an increasing number of studies conducted in animal models provide invaluable information on critical and sensitive periods, including the effect of multiple or sequential disruption within these periods, the effect of variations in spatiotemporal gene expression on this disruption, and potential compensatory mechanisms at the circuit or behavioural level (see Meredith, 2015 for a review). These studies also provide several examples of plasticity windows in animal models of NDDs, which are very important for translation. These examples show that rescue of some behavioural features with pharmacological interventions occurs only during certain time windows or sensitive/critical periods, and they support the notion that treatments applied at stages of increased sensitivity may have long-lasting effects on development that may not be detected if applied outside these time windows (Bethea and Sikich, 2007; Meredith, 2015). For instance, there are several examples in animal models of genetic syndromes, such as FXS and Down syndrome, showing that the administration of a pharmacological agent may reverse some abnormalities in brain structure and function and behaviour only when it occurs at early postnatal developmental stages, while the same pharmacological agent may not be effective if applied at later stages (Gatto and Broadie, 2008; McBride et al., 2005; Stagni et al., 2015; Su et al., 2011).

Other studies have assessed the effect of prenatal treatments on phenotypes of NDDs (Meredith, 2015). For instance, in two rodent models of autism (i.e. the Fmr1-mouse model of FXS and valproate pre-treated pregnant rats), maternal pre-treatment with bumetanide one day before delivery was found to rescue some of the later behavioural and electrophysiological phenotypes in offspring (Tyzio et al., 2014). It should however be noted that treatment with bumetanide has also been associated with long-lasting developmental effects (i.e. permanent decreases in excitatory transmission and sensorimotor gating deficits, similar to those described in schizophrenia) when administered to wild type control mice during cortical development, possibly due to the role of GABA-mediated depolarisation in regulating the cortical inhibitory-excitatory imbalance during this period (Wang and Kriegstein, 2011). These examples illustrate that taking timing of critical periods into account could improve efficacy of therapeutic agents if applied in analogous developmental periods in humans, but they also highlight the potential for long-term side effects of early developmental interventions, which warrants cautionary approaches to such interventions (Meredith, 2015).

Bearing this information in mind, AIMS-2-TRIALS aims to conduct preclinical and clinical studies in parallel by assessing six bio-behavioural dimensions (e.g. social processes, reward, predictability, emotional reactivity, sensory processing, and cognition) fundamental to ASD and its co-occurring features at different levels (i.e. brain circuit, cellular, molecular, and genetic) across species. The consortium adopts a dimensional, transdiagnostic, and developmental approach, by assessing developmental trajectories of these dimensions across diagnostic boundaries. Cross-dimension analyses will also help identify developmental correlations between different dimensions. Animal models will also be used (together with data from foetuses and toddlers with increased likelihood of NDDs) to assess the role of critical periods of brain development in NDDs.

7.3. The search for biomarkers of neurodevelopmental disorders

Drug discovery efforts for clinically and biologically heterogeneous conditions such as ASD and other NDDs may be substantially aided by implementing biomarker-based approaches. Such approaches may help to identify pathways and potential drug targets relevant to specific subgroups by constraining heterogeneity, guide stratified preventive and therapeutic interventions, and optimise assessment of molecular drug effects on relevant biological variables and therapeutic response.

A biomarker is defined as a variable "that can be objectively measured and assessed as an indicator of normal biological processes, pathological process, or biological response to a therapeutic intervention" (Biomarkers Definitions Working Group, 2001). Validation of a particular biomarker requires establishing that it is accurate (i.e. sensitive and specific), biologically plausible, and reliable relative to a certain clinical endpoint, as well as precise (i.e. reproducible across different settings) (Biomarkers Definitions Working Group, 2001). According to a proposed taxonomy, biomarkers for neuropsychiatric disorders including NDDs can be roughly classified into six categories: i) risk, ii) diagnosis or trait, iii) state or acuity, iv) stage, v) treatment response, and vi) prognosis (Davis et al., 2015). From a practical perspective, except for (ii), most of these kinds of biomarkers may aid classification of individuals into more homogeneous subgroups relevant to prediction or to assessment of preventive and therapeutic interventions, and could thus belong into an operationalised category of *stratification* biomarkers.

7.3.1. Stratification biomarkers for NDDs

Stratification aims to identify more biologically homogeneous subgroups of NDDs based on neuroimaging, molecular, and biochemical variables. These subgroups are expected to have differing aetiologies and/or clinical manifestations relative to other subgroups. Stratification approaches can thus help to narrow the intrinsic heterogeneity of NDDs, and facilitate identification of potential pharmacological targets and development of clinical trials adopting a precision medicine approach (Loth et al., 2016b). Identification of stratification biomarkers for NDDs requires multimodal deep phenotyping of participants from childhood through adulthood and alternative approaches to traditional case-control designs, including hierarchical clustering and normative modelling of neuroimaging data. One approach to stratification involves splitting samples based on demographic or clinical variables (e.g. sex, developmental levels, cognition, and comorbidity) and assessing their potential

neurobiological correlates. As an alternative, unsupervised data-driven methods could enable stratification based on neuroimaging or electrophysiological biomarkers or network-based stratification based on genetic or molecular profiles (Loth et al., 2016b; Wolfers et al., 2019).

Stratification biomarkers may not be specific to ASD, but cut across several diagnostic categories. That is, a biological variable associated with atypicalities in some of the bio-behavioural dimensions affected in ASD such as reward processing, emotional reactivity, or social cognition could be associated with dimensional symptom severity across several diagnostic categories (Loth et al., 2016a). In this regard, transdiagnostic approaches might help to address heterogeneity in NDDs and beyond and also improve our understanding of the biological underpinnings of some of their clinical manifestations, as well as common neurodevelopmental, physical, and psychiatric comorbidities (Lombardo et al., 2019).

There are several types of stratification biomarkers depending on their intended purposes (e.g. risk, prognostic, predictive, target engagement, and surrogate outcomes). From a clinical point of view, stratification biomarkers may be especially useful if they have prognostic value – i.e. they provide information on the evolution or outcome of a particular (untreated) condition, which requires longitudinal designs with at least three time points so as to appropriately appraise developmental trajectories of clinical, cognitive, functional, or neuroimaging variables (Loth et al., 2014) – or if they are predictive of response to particular treatments. Several RCTs have assessed whether biological variables (e.g. oxytocin levels) might influence treatment effects and could be used as stratification biomarkers, so far with mixed results. The AIMS-2-TRIALS project is currently exploring whether hyperserotonaemia could be a useful stratification variable for testing pharmacological strategies targeting the serotonergic system (see Section 4).

Risk biomarkers are variables that may help to predict the likelihood of an individual developing a NDD before onset of the first clinical manifestations. While diagnostic biomarkers reflect the presence of a specific condition, risk biomarkers are associated with the transition from an asymptomatic state to the condition (Davis et al., 2015). Risk biomarkers can become stratification biomarkers by allowing identification of different developmental pathways to the condition. For NDDs, two designs allow for identification of risk biomarkers: i) longitudinal studies in infants at increased familial likelihood for ASD (see Section 3 for further details) and ii) longitudinal population-based studies with infants followed from birth to age of first diagnosis. Most studies have used the first approach, since identification of "prodromal" subgroups in population samples requires very large sample sizes, and they incur very high costs due to the low numbers of children who develop ASD in these cohorts (Loth et al., 2016a).

Additional stratification biomarkers that might be useful for drug discovery and clinical trials include target engagement or surrogate endpoint biomarkers. Target engagement biomarkers provide evidence that an intervention is influencing an intended neurobiological process, and they enable stratification based on subgroups with different molecular responses to a particular treatment, while surrogate endpoint biomarkers are variables intended to substitute a clinical endpoint (Amur et al., 2015). The EU-AIMS consortium has discovered examples of biomarkers with a potential for target validation in ASD. Magnetic resonance spectroscopy studies (MRS) conducted in the NLGN3 knockout rat model of ASD and in adults with idiopathic autism have reported alterations in the balance between excitatory and inhibitory transmission, with reduced glutamate levels in the basal ganglia in both species (Baudouin et al., 2012; Horder et al., 2014; Horder et al., 2018b). In humans, this phenotype could emerge during foetal life, with pilot evidence supporting alterations in glutamate levels in the foetal brain. A recent multimodal study using MRS and fMRI found that single-dose treatment with riluzole, a repurposed compound with a widespread effect on glutamate-GABA transmission, showed opposite effects on the prefrontal cortex inhibitory index in individuals with ASD relative to TD individuals. Riluzole was also associated with elimination of baseline case-control differences in resting-state functional connectivity (Ajram et al., 2017). These findings suggest that variations in glutamate/GABA levels, as measured with MRS, could constitute useful stratification biomarkers for future clinical trials in ASD and provides further support for the notion that drugs targeting GABAergic or glutamatergic signalling may be useful pharmacological strategies for ASD.

7.4. The potential of brain imaging and electrophysiological studies in drug discovery for NDDs

As shown above, brain imaging studies, including fMRI and MRS, may advance and accelerate innovative pharmacological interventions by helping to identify potential pathways and mechanisms to target, provide proof of target engagement, establish dose-response relationships of interventions, define surrogate endpoint biomarkers by identifying biological signatures of efficacy and side effects, and stratify ASD/ID populations into biologically more homogeneous subgroups (Borsook et al., 2011).

Electrophysiological assessments, including EEG, also hold great promise for identification of stratification biomarkers for NDDs, considering their low cost, high accessibility, and objectivity of measurement. In this concern, the EMA and the FDA have supported the N170 event-related potential as a prognostic biomarker for adaptive social functioning in ASD, with a potential use as a stratification factor in clinical trials (https://www.ema.europa.eu/en/documents/other/letter-support-n170-erp-prognostic-biomarker-adaptive-social-functioning-its-potential-stratify_en.pdf).

Multimodal biomarkers (e.g. combination of fMRI, MRS, and EEG data) may be especially suitable here to improve prognostic and predictive value. For instance, abnormalities in gamma band oscillations in EEG may reflect an excitatory/inhibitory imbalance but do not identify whether this imbalance is the result of increased glutamatergic or reduced GABAergic signalling. Complementary information provided by MRS could thus guide individual

interpretation of results and selection of a drug profile that is expected to be more effective in a particular individual (e.g. GABA agonists vs glutamate receptor antagonists) (Loth et al., 2016a). Novel and powerful multivariate statistical techniques, including machine learning, may help to integrate this multimodal information into complex "biomarker systems" to improve stratification (Ecker et al., 2013).

7.5. The need for systems biology and bioinformatics for biomarker and drug discovery for NDDs

The integration of multi-omics data (e.g. genomics, epigenomics, transcriptomics, proteomics, interactomics, metabolomics) and their complex networks of interactions through development with multidimensional longitudinal deep phenotyping data in human cohorts in heterogeneous conditions like ASD and other NDDs using systems biology and integrative approaches require highly advanced bioinformatics (Parikshak et al., 2015). Systems biology works by combining mathematical models with experimental models that provide *in silico*, *in vitro*, and *in vivo* high-throughput datasets to account for the multifactorial nature of biological systems and the hierarchy, emergence, and robustness inherent in them, and provide understanding of synergistic effects and compensatory responses within the system (Alawieh et al., 2012). Such approaches are essential to prioritise potential disease mechanisms and drug targets (Gandal et al., 2016). In the case of NDDs, studies of gene co-expression, protein-protein interactions, enrichment for transcription factors, specificity for cell type, tissue, and developmental period, and integration with other disease-risk genes may be of special interest (Gandal et al., 2016; Parikshak et al., 2015). Bioinformatics approaches to NDDs need to account for the ever-increasing amounts of available data, resources, and novel techniques relevant to these conditions, and leverage findings from different models (e.g. cell cultures, brain organoids, *Drosophila*, zebrafish, rodents, NPH, and iPSCs) (Sanders et al., 2019). This requires strong computational infrastructure and simulation software tools (Alawieh et al., 2012).

High-throughput computing, biology, and screening approaches may help to identify clinically and biologically meaningful subgroups, establish relevant endophenotypes, and facilitate drug repositioning and repurposing. For instance, a very recent integrative genomic analysis has enabled identification of a convergent molecular subtype of ASD by integrating genome-wide measures of mRNA expression, miRNA expression, DNA methylation, and histone acetylation from ASD and control brains (Ramaswami et al., 2020). Knowledge-based bioinformatics has also enabled identification of a set of miRNAs that may act as putative autism biomarkers (Shen et al., 2016). A pharmacoinformatics network analysis of results from the NIH-funded PsychENCODE project (comprising data on different neuropsychiatric conditions including autism), whose aim was to identify druggable targets that control neurogenic transcriptional networks, found that valproic acid and other psychotropic drugs may directly affect these networks by acting on chromatic remodelling complexes, transcription factors, and other epigenetic markers (Higgins et al., 2019). High-throughput screening of molecules in neurons derived from iPSCs was also able to identify lithium and divalproex as molecules with a potential to increase SHANK3 levels, which was later tested *in cellulo* and *in vivo*, leading to clinically significant improvement in one patient with Phelan-McDermid syndrome (Darville et al., 2016); see Section 2. These are some examples that highlight the potential of bioinformatics to guide stratification and identification of drug targets, but also the challenges encountered when addressing the complexity and heterogeneity of NDDs.

7.6. Future lines of translational research and biomarker discovery for NDDs

Some of the future lines of research in the field include i) studying the effect of common genetic variation and environmental risk factors and their interaction on developmental outcomes in NDDs, ii) assessment of populations that have not been studied previously (e.g. foetuses with increased likelihood of ASD, preschoolers, or patients with ASD and comorbid epilepsy, ID, and/or ADHD) iii) increase in the numbers of cohorts of individuals with specific genetic disorders, such as SHANK3 and NRXN1, which might enable specific clinical trials in these forms of syndromic autism, iv) study of rodent models using a developmental perspective to assess the effect of interventions at developmental timepoints equivalent to those of humans, v) validation of the identified biomarkers in clinical trials, and vi) development of proof-of-concept "shiftability" (i.e. target engagement) studies, which might enable early identification of signals of change/efficacy, thus taking compounds to fast-fail trials.

The AIMS-2-TRIALS consortium will try to address some of these pending questions by conducting validation studies for stratification biomarkers in ASD and developing and implementing a Europe-wide Clinical Trial Network run to high clinical standards, with the support of the industry and charities. AIMS-2-TRIALS conducts target engagement studies and fast-fail clinical trials testing novel or repurposed compounds. The consortium is currently conducting a proof-of-network trial testing arbaclofen in ASD (see Section 2) and incorporating EEG as a potential predictive biomarker. To improve outcome assessment, the project works with the IMI-funded RADAR-CNS (https://www.radar-cns.org/), whose aim is to develop new objective outcome measures sensitive to change that might augment structured clinical assessments, including wearable devices to monitor the real-life environment (e.g. heart rate, social activity) and experience sampling.

8. Ethical and regulatory aspects of drug discovery for earlier stages of neurodevelopment

8.1. Ethical implications of conducting research in very young children

An argument can be made for clinical trials in NDDs to be conducted first in very young children, once safety has

been established. This does not pertain only to clinical trials testing pharmacological treatments, although there is usually less debate regarding psychosocial interventions, even if few published studies testing those have explicitly examined safety. Such an argument would be supported by the following: i) a trade-off between ethics and equality, ii) the possibility to achieve better long-term developmental outcomes if we start early, and iii) the presence of developmental differences in treatment targets and the subsequent need for temporospatial targeted interventions (Simonoff, 2018). From an ethical perspective, some concerns may limit the possibility of developing clinical trials in very young people with NDDs. They include inability to consent, which would be also applicable to adults with intellectual disability, and uncertainty whether parents are always able to give consent for their children. Nevertheless, the ethical process of clinical trials ensures that the treatment has been appropriately offered and that patients are safeguarded when parents are consenting for their children. Furthermore, patients with NDDs belong to a vulnerable population and seem to be more prone to experiencing some adverse events (Howes et al., 2018), which may be the consequence of biological differences, unpredictability of effects (especially if previous studies have been based on adult samples), and greater risk of harm. In addition, it may be difficult to collect self-reports of adverse events in this population. We also need to take into consideration the trade-off between outcome severity in NDDs in the absence of intervention and uncertainties regarding the long-term effects of some pharmacological interventions that affect development, especially drug targets with widespread developmental effects (e.g. IGF-1). Developmental side effects may be difficult to recognise, as they may not be acute but rather impact a person's development. This concern should be considered especially when managing conditions that are not life-threatening.

Despite the potential risks, equality should be also factored into the equation. Children have an equal right to receive evidence-based interventions that have been robustly evaluated and to participate in clinical trials. They also have the right to the best possible outcome, which calls for specific testing of treatment strategies to identify the best option for this age group, as suggested by studies on child leukaemia. If studies are conducted only in adults, we may be looking at the wrong effect and testing the wrong intervention, which may result in failure to identify potentially useful interventions because they have been tested in the wrong population. For instance, inconsistency in findings of functional connectivity in ASD, with hypoconnectivity in adolescents and adults and hyperconnectivity in children, suggests differences in developmental trajectories over time (Uddin, 2015), which could affect response to treatment.

In addition, parents may want to try new treatments outside of a trial context, which increases the risk of use of ineffective and potentially harmful treatments and may stand in the way of utilising evidence-based interventions. In this regard, an online survey found that 2% of parents of young children with ASD reported using potentially harmful therapies in the EU (Salomone et al., 2015). The best way to prevent this would be to offer participation in experimental interventions through clinical trial participation. Moreover, there are also some benefits of clinical trial participation: the experimental arm is designed and usually expected to be at least as effective as treatment as usual, there is a careful assessment and monitoring of benefits and adverse effects, and other previously undetected conditions might be identified, which means that there may be better outcomes for those participating in clinical trials, even for those on placebo (Siafis et al., 2020).

To minimise potential risks, clinical trials should take into account biological differences, including pharmacokinetics, pharmacodynamics, and other physiological aspects that may underlie child-specific adverse events in other areas of medicine (e.g. Reye's syndrome associated with aspirin use). Although we may not yet be aware of those side effects, data from earlier clinical trials could also be used for earlier identification of this kind of adverse effects. Further evidence is required regarding normal development of receptors in humans and sensitive periods of intervention. Examples from other areas of medicine such as inborn errors of metabolism (Potter et al., 2013), hearing and visual impairment (Hensch, 2005), and age-dependent differences in bone marrow transplant outcomes in Hurler syndrome (Poe et al., 2014) support the notion that intervening early may improve long-term outcomes and that some alterations may not be completely reversed if intervention comes too late. Low quality of previous studies should be addressed in future trials, especially those testing psychosocial interventions, which have usually been limited by lack of clear blinding or allocation methods, use of inappropriate outcome measures, or insufficient power (French and Kennedy, 2018). Some adjustments may be required to conduct clinical trials for NDDs in young children, including how to manage placebo effects, establishing optimal duration, and identifying what kind of design may be more suitable in this age group (see Table 2).

8.2. Regulatory aspects of conducting research at earlier stages of neurodevelopment

Regulation of medicines aims at protecting and promoting public health. Dangerous or ineffective medicines should not be allowed into the market, while evidence for potentially useful drugs should be generated in a timely manner. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) provides an ethical and regulatory framework for conducting paediatric research, and EU and US regulatory agencies have developed specific regulations governing clinical trial development in paediatric populations (Stoyanova-Beninska et al., 2011). However, although there has been a substantial increase in the numbers of pharmacological trials and drug authorisations for paediatric populations in the past few years in the EU, there has been little change in the number of molecules approved for brain disorders in the same period (Nordenmalm et al., 2018; Tomasi et al., 2017).

8.2.1. The EU perspective

The EU Regulation on Paediatric Medicines – Regulation (EC) 1902/2006 amending Regulation 1901/2006 – was developed to stimulate research in paediatric patients, and came

into force in January 2007 (Tomasi et al., 2017). A Paediatric Committee (PDCO) meets regularly at the European Medicines Agency (EMA) and is in charge of implementing most aspects of the Regulation, which combines obligations and incentives. New medicines for children must be developed according to a Paediatric Investigation Plan (PIP) pre-approved by the PDCO, and there are market incentives if the PIP is implemented (i.e. generics are delayed for six months and exclusivity is increased for two years for orphan drugs). The proposed PIP must be submitted to the PDCO at the end of phase I human studies and is binding for the sponsor developing the product. Amendments to the PIP can be made throughout the procedure (e.g. to take into account findings from ongoing studies as they become available). Companies can no longer claim that they are not interested in studying a certain indication for paediatric subjects, although a waiver may be granted in some circumstances (e.g. adult-only disease, lack of expected significant benefit).

8.2.2. The American perspective

Since 1979, when the subsection "Pediatric Use" was added to drug labelling, various regulations have encouraged the development of paediatric research in the US. In 2002, the Best Pharmaceuticals for Children Act (BPCA) provided a financial incentive to companies to voluntarily conduct paediatric studies, and the FDA and NIH partnered to obtain information to support labelling of off-patent products used in children (e.g. lithium). In 2003, the Pediatric Research Equity Act (PREA) came into force and required companies to assess the safety and effectiveness of certain drugs and biological products in the paediatric population for approval. If paediatric studies are conducted, the results must be included on the label even if the study has failed. Paediatric studies with orphan status are exempt from requirements. In the past, paediatric labels could take more than 10–15 years from the initial approval, since sponsors tended to wait until the approval was available in adults. Since 2012, FDA asks for the initial Pediatric Study Plan (iPSP; the US analogue of the PIP) to be submitted much earlier (between phases II and III), and in some cases they may ask for studies in children to be conducted earlier than planned.

There are two main differences between the EU and the US systems: 1) the PIP has to be submitted to the EMA at the end of phase I studies (earlier than in the FDA, where this may be submitted later), 2) contrary to the FDA, the EMA does not approve clinical trials; individual member states do, which sometimes makes harmonisation difficult. However, there are periodic teleconferences between EMA and FDA to exchange views on paediatric plans, which helps to achieve a more homogeneous approach internationally.

8.2.3. Key considerations for conducting studies in paediatric samples from a regulatory perspective

Regulatory changes in both the US and Europe have effectively encouraged paediatric trials of drugs already in development for adults. An alternative question concerns drugs whose mechanisms of action and hence their effects may vary depending on the stage of brain development (e.g. drugs that may be effective in the paediatric but not the adult population). In these instances, it should be considered whether clinical trials should first be conducted in paediatric samples. Paediatric trials should be conducted as soon as possible for drugs addressing an unmet clinical need in this population, if well-explored safety concerns appear proportionate and manageable within the context of the clinical trial, and if there are sufficient exploratory data suggesting efficacy that can inform the design of a valid clinical trial (de Andres-Trelles, 2015). A case-by-case approach may be required, and sometimes establishing direct communication between the sponsor and the regulatory agencies may accelerate the process, as that might help determine the best way to approach a particular question.

The following general aspects should be considered in deciding when to conduct paediatric clinical trials: disease onset, clinical manifestations, and general course of the illness over time, taking into account the potential developmental windows and nature of the intervention. In view of these aspects, there are three possible scenarios:

1) Mainly or exclusively paediatric diseases (e.g. NDDs): the complete drug development programme may be implemented in children after initial phase I safety and tolerability studies in adults. This is customary in ADHD, for which paediatric data are needed for the initial approval, and should probably be the case for ASD, although some sponsors prefer to conduct the initial trials in adults. With ASD, although symptoms are similar regardless of age, it is not unreasonable to assume that there may be a critical developmental window for intervention (e.g. considering sensitive periods for language and social development), which can be missed if studies are conducted only in adults.
2) Serious diseases with limited therapeutic options in both adults and children: early development in children should also be considered.
3) Other diseases (i.e. lack of medical need likely to be met by the drug): development in children should start when adult studies are well advanced. For safety reasons, these studies might be even conducted during the post-marketing phase of the adult medicine.

Recent treatments for rare diseases represent an example of the FDA regulatory framework for conducting clinical trials only in paediatric populations for very specific conditions. Cerliponase alfa, an enzyme replacement therapy for CLN2 disease using recombinant TPP1, delivered via intracerebroventricular infusion, was found to attenuate the progression of the disease (Schulz et al., 2018). Approval for recombinant TPP1 was granted after a single open-label safety and efficacy study in 24 children aged 3 or older with mild to moderate CLN2 followed by open-label extension, thanks to positive results in very good animal models (TTP1-knockout mice and TTP1-null mutation dogs). For spinal muscular atrophy (SMA), the intrathecal administration of an antisense oligonucleotide (2′-O-(2-methoxyethyl) antisense nucleotide; nusinersen) binding to SMN2 pre-mRNA to promote inclusion of exon 7 in the mRNA transcript led to the production of higher levels of functional SMN protein. Evidence of the effectiveness of nusinersen leading to initial FDA approval was based on a single well-designed double-blind sham-controlled multicentre trial in infantile-onset SMA with a very stringent statistical threshold, which found a clinically meaningful benefit for motor milestone development that was inconsistent with the natural course of the disease (Finkel et al., 2017). Additional supportive open-

Table 3 Take-home messages for implementing a neurodevelopmental framework for drug discovery in neurodevelopmental disorders.

1. Improved knowledge of the genetic factors and temporospatial dynamics of dysfunctions leading to NDDs

- Ongoing **gene discovery** is required including new data on **large-effect** mutations and **common** polymorphisms associated with increased risk for NDDs, as well as discovery of **putative protective alleles**, which might enable an alternative approach to treatment development.
- There is a need to account for the **spatial and temporal convergence of pathways** leading to early neurodevelopmental deviance or dysfunction, so as to identify **dynamic targets, therapeutic windows**, and **optimal strategies** for each sensitive developmental period.
- Additional **"omics" data** (e.g. transcriptomics and proteomics) and **multidimensional models** (e.g. iPSCs, organoids, zebrafish, xenopus, non-human primates, and genome engineering tools such as CRISPR) may be required to increase the spatial and temporal resolution of these analyses. Analysis of such high-throughput data requires application of **systems biology** and **network-based** and **integrative approaches,** with support of **highly advanced bioinformatics** and **computational biology.**
- The study of **large-effect mutations** and **single-gene disorders** may aid drug discovery by identifying **new therapeutic targets** with potential relevance for other NDDs. Drug discovery for NDDs also requires consideration of **genetic common variation**, on account of its essential role in the aetiology and clinical course of ASD and other NDDs.
- **Single-gene disorders** highlight the challenges of drug discovery in NDDs. Despite a sound mechanistically-driven approach, the **timing of an intervention** could underlie some of the negative results obtained so far.
- Both a **bottom-up** and a **top-down** approach to drug development for NDDs may be required.
- Mechanisms that merit further research are the role of **environmental factors** and **epigenetics**, the presence of a **female protective effect** for NDDs, and **immune dysregulation**.

2. Use of valid outcome measures and biomarkers based on solid translational approaches

- **Developmentally sensitive, reliable, reproducible, sensitive,** and **specific outcome measures** in association with biologically sound measures are needed in the field of drug development for NDDs. There is a need for **objective** outcome measures that are also **sensitive to change** (e.g. language sampling paradigms).
- **Digital medicine,** including remote monitoring, actigraphy, ecological momentary assessments, and other objective assessments could help to improve clinical measurements. **Artificial intelligence** and **machine learning** can contribute to the analysis and interpretation of big data, and improve biomarker identification and development of prediction tools.
- Dialogue with user groups, advocates, and families is required to co-construct relevant outcome variables, including identification of **clinically meaningful outcome variables** that are important to people with NDDs and their families, including measures of **quality of life**.
- Despite advances in the field, **biomarker discovery** with potential for translation is still required. Optimal biomarkers need to be replicated and should be **feasible, acceptable**, and **valid** in this age range. **Functional connectivity, eye-tracking paradigms, event-related potentials,** and other **EEG** measures are promising surrogate biomarkers that are currently being incorporated into clinical trials in ASD.
- Biomarker discovery in NDDs should allow for **developmental trajectories** of each biomarker relative to typically developing individuals and establish cut-offs for stratification tailored to each developmental stage.
- **International multidisciplinary consortia** might provide added value and increase efficiency of biomarker discovery by developing relevant preclinical and clinical models in parallel, with constant crosstalk between different research approaches.
- Incorporation of better biomarkers with neurodevelopmental relevance into preclinical and clinical drug development can also help **accelerate regulatory assessment** of CNS products by providing a **better understanding of the mechanisms of action** of novel drugs. Biomarkers make it possible to confirm clear drug **target engagement** and could help to establish **dosing** and to **stratify** participants.
- **Observational, longitudinal studies** including **deep intermediate phenotyping** may be required for understanding the pathophysiological changes and the longitudinal course of NDDs and to identify and validate appropriate biomarkers. To this end, there is a need to **move beyond case-control designs** to try to identify subpopulations that are more biologically homogeneous.
- **Translational approaches should look beyond animal models** to also include other dimensions and processes (molecular, iPSCs). Basic cellular and rodent models need to demonstrate reliability and validity.

3. Quantification and optimisation of timing, dosing, and duration of pharmacological and concomitant psychosocial interventions for NDDs

- An ability to **reject ineffective drugs early in clinical development** is essential to advancement in the field.

(*continued on next page*)

Table 3 (*continued*)

- Research is needed on **optimal timing, duration,** and **dosing of interventions** in clinical trials for NDDs. Duration of trials may need to be adjusted depending on the timing of the intervention, the type of intervention, and the outcome measure assessed (e.g. cognition or language). Longer follow-ups may be required to measure clinically relevant outcomes for NDDs (e.g. ASD studies), and even more so to achieve changes in developmental trajectories.
- Strategies are required to **measure dosing of already available efficacious strategies** (e.g. behavioural interventions for ASD).
- **Negative findings** should be published.
- **Clinical trials are needed in toddlers and preschool children**. It is critically (and ethically) important to conduct rigorous research in these age groups where the benefits of potentially disease-modifying strategies may be maximised. Objective outcome measures and biomarker discovery efforts should especially focus on this population.

4. Foster communication with regulatory agencies, ethical bodies, and key stakeholders

- A **joint effort** by clinicians, academics, and industry leaders is needed to increase knowledge of the neurobiology of normal and atypical neurodevelopment that might translate into new, targeted treatments that can be implemented at earlier developmental stages. **Multidisciplinary** and **multisectorial** cooperation is required. **Large-scale translational consortia** supporting cooperation of academic groups and industry are needed, as are other cooperative networks including other entities with relevant expertise in NDDs.
- A shift in the focus towards preventive strategies and interventions at earlier stages of development requires the **involvement of regulatory bodies, advocacy groups,** and other **interested stakeholders**, along with a **rigorous ethical approach**. It is crucial to develop research that is **meaningful** for people with NDDs and their caregivers and that takes into account their needs and expectations.
- **Experts by experience** and **advocacy groups** should be involved from the outset in the **decision-making** process for development of targeted drugs for NDDs, both by academia and industry, as well as by regulatory agencies. They may have highly valuable input regarding the development of clinically meaningful and pragmatic **outcome measures**, selection of assessment **methods, prioritisation** of interests, and **design** and **implementation** of clinical trials.
- A **joint effort** from academia, industry, and user/parent/advocacy organisations, with the support of regulatory bodies, may facilitate **clinical trial development** and **targeted and precise recruitment to bespoke trials across multiple clinical centres.**
- There is a need for **more consistent ethical** and **regulatory guidelines** for paediatric studies of drugs for NDDs.
- Clinical trials could be conducted **first in children and adolescents** if there is a **good rationale** for doing so and if there are **good safety data**. Considering the difficulties of "paediatric first" (or "paediatric only") programmes, it is advisable to establish an **early dialogue with regulatory agencies** and provide evidence from additional currently available studies to enable decisions on a case-by-case basis.
- **Early communication with regulatory agencies** to obtain **tailored advice** on the qualification of innovative methods, appropriate biomarkers, and clinical trial development can also enable a more robust assessment of the risk-benefit balance, increase the replicability of methods and findings, and speed up the translation of findings to the clinical field.

5. Methodological considerations

- It will probably take **more than one medication** to treat NDDs, starting at a very young age.
- **Trade-off of sample sizes**. While small sample sizes increase quality, larger numbers may be required to detect an effect, especially for a heterogeneous condition and a single main outcome measure. This requires a careful balance between both factors.
- There is a need to assess the impact of **environmental** and **protective factors** to incorporate them into effective treatments for NDDs (e.g. maternal responsiveness or environmental toxicity, epigenetic changes). This could include **optimisation of the environmental response** to atypical functional and structural brain development.
- Considering that **multimodal interventions** are rather the rule in clinical settings, future trials should test **synergies** and **potentiation effects** between psychosocial (e.g. early behaviour interventions or learning paradigms) and pharmacological strategies targeting similar core symptoms, especially during sensitive developmental periods.
- **Cost-effectiveness studies** are required using appropriate outcome measures (considering that QALYs are excessively tailored to physical disability and may not capture the challenges faced by people with NDDs) and a lifelong approach (since short-term benefits may be less relevant to these disorders).
- Considering the great **heterogeneity** of NDDs, a **precision approach** to intervention research is needed so as to identify **mediators** and **moderators** of treatment response, which will probably require substantially larger sample sizes.
- The role of **serendipity** and **genetic-driven repurposing** based on drug/disorder genetic hallmarks needs to be considered when developing new treatments for NDDs. It may be useful to test multiple indications from the beginning, as many of the pathways that we aim to target may be shared by different disorders. However, this might be problematic for obtaining funding and regulatory approval.

Abbreviations: ASD, autism spectrum disorders; CRISPR, clustered regularly interspaced short palindromic repeats, EEG, electroencephalography; iPSCs, induced pluripotent stem cells; *NDDs, neurodevelopmental disorders; QALYs, quality-adjusted life years*

label data in older patients (later-onset patients) provided support for a more global indication for SMA in general.

Additional factors that should be considered when developing paediatric research from a regulatory perspective include whether the treatment is exclusively symptomatic or has the potential to address the underlying pathophysiology of the disease, the need for comprehensive exploratory phases including proof-of-concept and proof-of-mechanism studies, thus ensuring proper target engagement at the proposed doses, and incorporation of biomarkers into the drug development plan, which may add to the validity of the conclusions and contribute to explaining discrepant results or outliers, thus constituting critical stratification factors to enrich samples by increasing homogeneity or biological specificity (see Table 3).

9. Take-home messages for implementing a neurodevelopmental framework for drug discovery and improvement of clinical trials in brain disorders

Table 3 shows a summary of the take-home messages for implementing a neurodevelopmental framework for drug discovery and clinical trial development in NDDs and other brain disorders derived from the meeting.

Conclusions

A neurodevelopmental framework for drug discovery may improve treatment of NDDs and other brain disorders and contribute to implementing a preventive approach to mental health (Arango et al., 2018). In the last decade, there have been substantial advances in terms of genetic findings and translational research on NDDs, with many critical discoveries in their aetiology and pathophysiology, which could guide new drug development. The study of the temporospatial dynamics of molecular-level brain dysfunction during early stages of development is warranted. This could inform different levels and stages of tailored interventions, including psychopharmacological approaches, to counteract early dysfunction or its homeostatic consequences and prevent their subsequent functional and morbid consequences, especially during sensitive neurodevelopmental periods.

Research conducted in single-gene disorders such as fragile X syndrome paves the way for further studies in the field and supports the notion that timing of interventions may be crucial. The inclusion of younger participants in clinical trials for NDDs seems to be warranted, but prudence and safety are naturally the overriding considerations. Thus, drugs should be tested first in paediatric populations only when there is good rationale for doing so, and only after careful preclinical and phase I studies to ensure maximum participant safety. Close cooperation with regulatory agencies is recommended to facilitate this process. User and advocacy groups and other key stakeholders must be incorporated into the process of drug development from its earliest stages to ensure that the clinical trial design addresses their needs and that clinically meaningful outcome measures are used. In clinical trials for NDDs, identification and practical implementation of reliable, valid, and sensitive outcome measures, including stratification biomarkers, is still required. Observational studies might provide essential clues on the temporal course of the pathophysiology of these conditions and contribute to the identification of potential biomarkers. A “4P’s” approach (participatory, personalised, predictive and pre-emptive) (Green and Garg, 2018; Insel, 2007) to intervention is needed in order to foster development of new treatments for NDDs and other brain disorders and improve the care and outcomes of those living with these disabling conditions.

Contributors

This work was based on the presentations given during the 2018 ECNP New Frontiers Meeting. C. M. Díaz-Caneja wrote a first draft of the manuscript, which was subsequently reviewed and edited by the rest of the authors. All authors contributed to and have approved the final manuscript.

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