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Review

Genetic and environmental modulation of neurodevelopmental disorders: Translational insights from labs to beds

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ABSTRACT

Neurodevelopmental disorders (NDDs) are a heterogeneous group of prevalent neuropsychiatric illnesses with various degrees of social, cognitive, motor, language and affective deficits. NDDs are caused by aberrant brain development due to genetic and environmental perturbations. Common NDDs include autism spectrum disorder (ASD), intellectual disability, communication/speech disorders, motor/tic disorders and attention deficit hyperactivity disorder. Genetic and epigenetic/environmental factors play a key role in these NDDs with significant societal impact. Given the lack of their efficient therapies, it is important to gain further translational insights into the pathobiology of NDDs. To address these challenges, the International Stress and Behavior Society (ISBS) has established the Strategic Task Force on NDDs. Summarizing the Panel's findings, here we discuss the neurobiological mechanisms of selected common NDDs and a wider NDD+ spectrum of associated neuropsychiatric disorders with developmental trajectories. We also outline the utility of existing preclinical (animal) models for building translational and cross-diagnostic bridges to improve our understanding of various NDDs.

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1. Introduction

Neurodevelopmental disorders (NDDs) are heritable psychiatric illnesses with overt social, motor, cognitive and affective disabilities that are caused by abnormal brain development (Bergner et al., 2010; Buckley et al., 2009; Krishnan, 2005). Although deficits in neurogenesis, glial and neuronal proliferation, migration, synapse formation and myelination occur during early embryogenesis (Ding, 2015; Frederick and Stanwood, 2009; Hu et al., 2014; Rice and Barone, 2000), they evoke lasting behavioral and neurological deficits in NDD children and adults (Homberg et al., 2015; Shen et al., 2016).

NDDs form a heterogeneous group of illnesses with varying severity and clinical manifestations (Fig. 1). One of the most common NDDs is intellectual disability (ID) – a spectrum of impaired mental functions in conceptual (*e.g.*, language, mathematics, memory, knowledge, logic), social (*e.g.*, empathy/compassion, social judgment, communication and interaction skills) and practical (*e.g.*, personal care, occupational responsibilities, hobby) domains (APA, 2013). Communication disorders (CD) present as difficulties with language, speech, phonetic fluency or social communication, including language and speech/sound disorders, childhood-onset stuttering and social (pragmatic) CD (APA, 2013). Attention deficit hyperactivity disorder (ADHD) manifests in inattention and increased hyperactivity-impulsivity (APA, 2013). Specific learning disorder involves difficulties in learning skills, such as reading, writing, spelling or mathematic calculations (APA, 2013). Autism spectrum disorder (ASD) is characterized by persistent reciprocal social deficits in communication and interaction, with restricted, repetitive patterns of behavior, interests or thoughts (APA, 2013). ASD also includes high-functioning autism (Asperger syndrome), Angelman syndrome (AS, characterized by severe ID, seizures, sleep deficits, motor stereotypies and positive emotionality) (Anon., 2013) and X-linked Fragile X syndrome (FXS, caused by mutant Fragile X mental retardation 1 (*FMR1*) gene) with social deficits, ID and stereotypic behaviors (Santoro et al., 2012). Rett syndrome represents another common ASD-related NDD, affecting females and causing stereotyped hand movements, microcephaly (see further), as well as cognitive and social deficits (Neul et al., 2008).

Motor disorders present with impaired execution of motor skills, or repetitive motor behaviors, including developmental coordination and stereotypic movement disorders (APA, 2013) (Fig. 1). Tic disorders are characterized by habitual motor movements or vocalizations which are sudden, rapid, recurrent and non-rhythmic. This group of NDDs includes Tourette's disorder, persistent (chronic) motor or vocal tic disorder, provisional tic disorder, as well as other tics (APA, 2013). Tuberous sclerosis complex (TSC) is characterized by benign brain tumors (tubers), often presenting with ID and varying developmental delays (Curatolo et al., 2015). Structural brain disorders, such as microcephaly and lissencephaly, form a distinct group of NDDs with specific genetic and environmental causes (Hu et al., 2014). Microcephaly, diagnosed as head circumference two standard deviations below the mean for a child's age and sex, often co-occurs with ID and speech delays (Woods et al., 2005). Lissencephaly is a rare genetic disorder that results in a brain lacking gyri and folding, and manifests behaviorally in seizures, hypotonia, and ID resulting from the overall psychomotor impairment (Fry et al., 2014).

Specific environmental factors can also trigger NDD pathogenesis. For example, prenatal exposure to alcohol is a key risk factor for a range of morphological phenotypes and mental retardation collectively referred to as Fetal Alcohol Syndrome (FAS, Fig. 1) (Jones and Smith, 1973). FAS represents the main non-hereditary cause of ID, affecting approximately 2–5% of live births (May et al., 2014). Relatively low doses of alcohol can also affect cognition, behavior and brain morphology (referred to as Fetal Alcohol Spectrum Disorders, FASD), implicating even moderate drinking during pregnancy as a risk for NDD pathogenesis (Hamilton et al., 2010; Rice et al., 2012; Savage and Becher, 2002; Streissguth et al., 1990) (see further).

In general, NDDs are severely debilitating brain illnesses (Fig. 1) with significant societal impact (Dykens, 2015). Given the lack of efficient *targeted* therapies, it is important to gain further translational insights into the pathobiology of these disorders (Homberg et al., 2015). To address this problem, the International Stress and Behavior Society (ISBS) has established the Strategic Task Force on NDDs, an international team of independent clinical and preclinical experts (Homberg et al., 2015). Complementing the Panel's recommendations on improving NDD pharmacotherapy (Homberg et al., 2015) and preclinical behavioral models (Homberg et al., 2016), here we discuss the neurobiological and genetic mechanisms of several common NDDs, and outline further strategic directions of research of their key affected (social, cognitive and motor) domains. This review does not intend to provide a comprehensive coverage of all NDDs, and acknowledges the existing limitations of animal (preclinical) models of these disorders.

2. Genetics of neurodevelopmental disorders

NDDs are highly heritable disorders (Bergner et al., 2010; Buckley et al., 2009; Krishnan, 2005). While recent genetic technology has enabled the identification of numerous genes for various NDDs (Hu et al., 2013), their exact pathogenetic mechanisms remain unclear (Zoghbi and Bear, 2012). Our understanding of NDDs is complicated by their polygenic nature and *de novo* mutations in multiple genes (often resulting in similar clinical phenotypes) identified by whole-exome and whole-genome sequencing (Iossifov et al., 2012; Michaelson et al., 2012; O'Roak

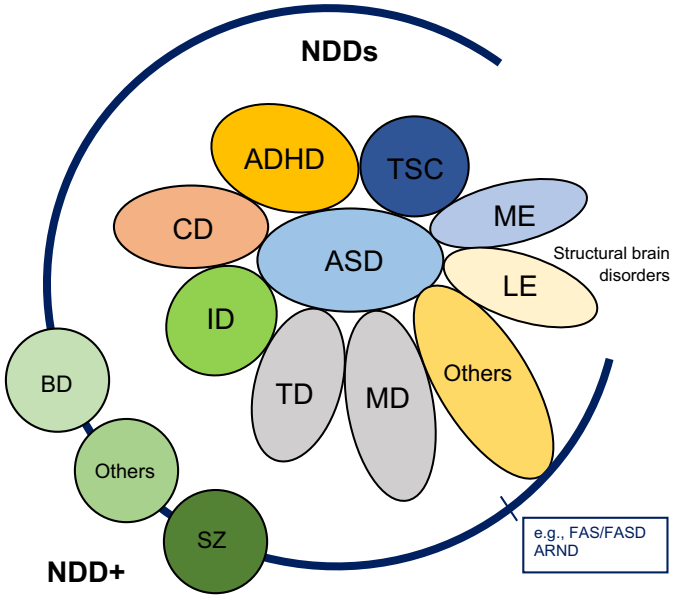

Fig. 1. A general framework of major neurodevelopmental disorders (NDDs) and the larger 'NDD+' spectrum of associated neuropsychiatric illnesses. ASD – autism spectrum disorder, ID – intellectual disability, CD – communication disorder, ADHD – attention deficit hyperactivity disorder, TSC – tuberous sclerosis complex, TD – tic disorders, MD – motor disorders, ME – microcephaly, LE – lissencephaly. Other NDDs include fetal alcohol syndrome (FAS) and related to it fetal alcohol spectrum disorders (FASD) under the 'umbrella' of alcohol-related neurodevelopmental disorder (ARND), as well as not shown here Down, Prader-Willi and Williams syndromes (Table 1). Additional disorders with neurodevelopmental trajectories include bipolar depression (BD) and schizophrenia (SZ), as well as some others, not shown here (*e.g.*, early-onset types of trauma- and stress-related disorders (TSRD)), thereby forming the wider 'NDD+' spectrum.

et al., 2012b; Talkowski et al., 2012). Novel mutations are recurrently seen in such key cellular genes as *CHD8, DYRK1A, GRIN2B* and *PTEN* (O'Roak et al., 2012a), thereby affecting normal growth and development of the brain. Genetic analyses empower the search for candidate genes for NDDs, whose psychiatric symptoms co-occur with other, non-mental phenotypes (*e.g.*, altered facial morphology and cardiac defects) (Benvenuto et al., 2009; Caglayan, 2010). For example, FXS is caused by the expanded CGG repeat in the promoter of the *FMR1* gene (Fu et al., 1991; Verkerk et al., 1991), resulting in distinguishing facial features (Lubs, 1969), ID, speech delay and repetitive behaviors (Belmonte and Bourgeron, 2006; Zoghbi and Bear, 2012). *FMR1* codes for the fragile X mental retardation protein (FMRP), which acts as a negative regulator of mRNA translation in neurons (O'Donnell and Warren, 2002), and its genetic ablation in mice markedly decreases dendritic spine density in the brain – a phenotype also seen in human postmortem FXS samples (Comery et al., 1997; Irwin et al., 2000; O'Donnell and Warren, 2002).

Caused by loss of one copy of the *UBE3A* (Ubiquitin Protein Ligase E3A) gene (Kishino et al., 1997; Malzac et al., 1998; Matsuura et al., 1997), AS-related ID, stereotyped behavior and hyperactivity (Angelman, 1965; Clayton-Smith, 1993) parallel decreased dendritic spine density and impaired long-term potentiation/depression seen in *Ube3a* knockout rodents (Sato and Stryker, 2010; Yashiro et al., 2009). In general, such common deficits in dendritic spine density in NDDs highlights the importance of synaptic processes in neural development (Zoghbi, 2003; Zoghbi and Bear, 2012). For instance, mutations in *SHANK3* (encoding a scaffolding synaptic protein (Naisbitt et al., 1999; Sala et al., 2001; Tu et al., 1999)) cause developmental delay, neonatal hypotonia, decreased socialization and increased stereotypy clinically (Phelan and McDermid, 2012). Similar to SHANK3, the neuroligin and neurexin protein families involved in synaptic scaffolding, are also implicated in ASD (Zoghbi and Bear, 2012). Mutations in the *NEUROLIGIN3* (*NLGN3*) and *NEUROLIGIN4* (*NLGN4*) genes were among the first causative mutations identified in ASD patients (Jamain et al., 2008). In line with this, *Nlgn* knockout mice show specific deficits in excitatory (*Nlgn1*) or inhibitory (*Nlgn2*) synaptic transmission (Chubykin et al., 2007), and social deficits (*nlgn3* and *nlgn4*), a key behavioral symptom of ASD (Jamain et al., 2008; Radyushkin et al., 2009).

Mutations in *MECP2* (encoding the methyl-CpG-binding protein 2, MeCP2) are responsible for the majority of cases of Rett syndrome (Neul et al., 2008), which is highly comorbid with ASD. MeCP2 is abundant in post-mitotic neurons and binds to methylated cytosines in DNA (Lewis et al., 1992; Shahbazian et al., 2002), functioning as both a transcriptional repressor and activator (Chahrour et al., 2008; Tudor et al., 2002). Implication of genes encoding chromatin-modifying enzymes in ASD (De Rubeis et al., 2014b) is not surprising, given the association of *MECP2* with Rett syndrome (Chahrour and Zoghbi, 2007; Hagberg, 2002). Likewise, *Mecp2* mice are a useful model of human Rett syndrome (Chahrour and Zoghbi, 2007; Chen et al., 2001; Guy et al., 2007; Shahbazian et al., 2002), showing aberrant synaptic plasticity and deficient long-term potentiation in genetic knockout (Asaka et al., 2006; Moretti et al., 2006). Interestingly, targeted deletion of *Mecp2* in gamma aminobutyric acid (GABA)-ergic neurons recapitulates many core Rett phenotypes, including reduced GABA-ergic neurotransmission (Chao et al., 2010).

Recently identified risk genes for ID include *SYNGAP1* (encoding the synaptic Ras-GTP activating protein 1) and *SNAP25* (encoding synaptosomal-associated protein 25) regulating synaptic signaling and neurotransmission, respectively (Gosso et al., 2008; Hamdan et al., 2009; Kaufman et al., 2010). *SNAP25* is also a risk locus for ADHD, along with genes encoding proteins involved in dopaminergic and serotonergic neurotransmission, such as dopamine receptors D4 (*DRD4*) and D5 (*DRD5*), dopamine transporter DAT (*SLC6A3*), serotonin transporter (SERT, *SLC6A4*), and serotonin 1B receptor (*HTR1B*) (Gizer et al., 2009; Li et al., 2006). In summary, these and many other examples, including Down, Williams, Prader-Willi and Angelman syndromes and even schizophrenia (Table 1), strongly support the critical role of genetic factors in both clini-

Table 1
Selected genes involved in neurodevelopmental disorders (NDDs). These genes represent those disorders discussed above, and do not serve as an exhaustive list of genetic mutations seen in all the NDDs (Homberg et al., 2015).

Disorder	Genes involves (encoded proteins)	Cellular function
Microcephaly	*CASC5* (Casc5),*CEP152* (Centrosomal protein of 152 kDa), *STIL* (SCL-interrupting locus protein) and others (Genin et al., 2012; Guernsey et al., 2010; Kumar et al., 2008; Roberts et al., 2002)	Centrosome/centriole function; neuroprogenitor proliferation
Lissencephaly	*DCX* (Doublecortin) and *LIS1* (Platelet-activating factor acetylhydrolase IB subunit alpha) (Pilz et al., 1998)	Cortical migration and patterning; neuroprogenitor proliferation
Fragile X syndrome (FXS)	*FMR1* (Fragile X mental retardation protein) (O'Donnell and Warren, 2002)	Negative regulator of mRNA translation
Angelman syndrome (AS)	*UBE3A* (Ubiquitin-protein ligase E3A) (Kishino et al., 1997)	Targets proteins for degradation in the proteasome
Prader-Willi syndrome	*SNORD116* among others (de Smith et al., 2009)	Modifies other small non-coding RNAs
Tuberous sclerosis complex (TSC)	*TSC1* (Hamartin) and *TSC2* (Tuberin) (Crino et al., 2006)	Cellular proliferation *via* mTOR regulation; axon guidance
Williams syndrome	*CLIP2*, *ELN*, *GTF2I*, *GTF2IRD1*, and *LIMK1*, among others (Pringle et al., 1998)	Microtubule organization (*CLIP2*), Transcription (*GTF2I*, *GTF2IRD1*) and brain development (*LIMK1*)
Autism spectrum disorders (ASD)	*NLGN3* (Neuroligin-3), *NLGN4* (Neuroligin-4), *NRXN1* (Neurexin-1) and others (Geschwind and State, 2015; Jamain et al., 2003; Kim et al., 2008)	Synaptic scaffolding and signal transduction
Non-syndromic intellectual disability (ID)	*SYNGAP1* (synaptic Ras-GTP activating protein 1), *SNAP25* (synaptosomal-associated protein 25) and others (Gosso et al., 2008; Hamdan et al., 2009; Kaufman et al., 2010)	Synaptic function and neurotransmission
Attention deficit hyperactivity disorder (ADHD)	*SNAP25* (synaptosomal-associated protein 25), *DRD4* (dopamine receptor D4), *DRD5* (dopamine receptor D5), *SLC6A3* (dopamine transporter), *SLC6A4* (serotonin transporter SERT), *HTR1B* (serotonin receptor 1B) (Gizer et al., 2009; Li et al., 2006)	Neurotransmission
Rett syndrome (RTT)	*MECP2* (Methyl-CpG binding protein 2) (Chahrour and Zoghbi, 2007)	Binding of methylated DNA, modulation of transcription
Down syndrome	Trisomy 21 (~97% of cases) (Antonarakis et al., 2004)	Various
Schizophrenia	Many genes, including the complement component 4 (*C4*) in the *MHC* locus (Homberg et al., 2016; Arnedo et al., 2015)	Neural function and immune regulation

cal NDDs and their genetic animal models, collectively providing important mechanistic insights into pathobiology of NDDs.

3. Environmental factors influencing risk for NDDs

In addition to genetic determinants, a wide range of environmental factors can impact neural development (Fig. 2). Beginning *in utero*, these postconception influences involve the nutritional and physiological (*e.g.*, hormonal or infectious) status of the mother, as well as her lifestyle and use of medications (*e.g.*, selective serotonin reuptake inhibitors, SSRIs or valproate) (Croen et al., 2011; Dominguez-Salas et al., 2012; Lyall et al., 2014). Some of these factors, such as postnatal nutrients, hormones, infections, the microbiome and parenting, potently modulate neural development (Jasarevic et al., 2015; Kofink et al., 2013; O'Donnell et al., 2014), and will be discussed here in detail.

3.1. Pre-natal environmental factors modulating neural development

The placenta transfers nutrients, hormones, drugs and inflammatory factors from the mother to the fetus. For example, placental function affects perfusion of the fetus, and therefore can influence neural development. Nutritional factors, consumed by the mother and relevant for fetal neurodevelopment, include fat-soluble vitamins (*e.g.*, A, D, E), tryptophan and nutrients related to single carbon metabolism (*e.g.*, choline, vitamins B2, B6, B12 and folate) (Dominguez-Salas et al., 2012; Dominguez-Salas et al., 2014). Tryptophan, a food-derived essential amino acid, serves as a precursor of serotonin and melatonin, but is also subject to degradation by indoleamine 2,3-dioxygenase, one of three enzymes catalyzing the first step of the kynurenine pathway of tryptophan degradation. While melatonin is one of the main sources of mitochondrial protection, it acts as antioxidant in the placenta and, as shown in mouse studies, facilitates the transport of folate from maternal circulation through the placentas into the fetus (Fu et al., 2014). Folate deficiency has been associated with neural tube defects (Czeizel and Dudas, 1992) and, as a B-vitamin, is important for CNS cell repair (Iskandar et al., 2010), genome epigenetic modulation (Steegers-Theunissen et al., 2009) and immune mechanisms (Kjer-Nielsen et al., 2012).

As already mentioned, exposure to alcohol during pregnancy is a key risk factor in NDDs, such as FAS (Jones and Smith, 1973) and FASD (Hamilton et al., 2010; Rice et al., 2012; Savage and Becher, 2002; Streissguth et al., 1990). Sonic hedgehog (*SHH*) signaling is of special interest in FAS owing to its role in proper craniofacial development. During early neural crest migration, ethanol reduced *Shh* mRNA expression in the chick embryo and caused cell death in cranial neural crest cells, an effect rescued by exogenous *Shh* administration (Ahlgren et al., 2002). FAS and FASD are closely related to the umbrella term "alcohol-related neurodevelopmental disorder" (ARND), representing a facet of NDD pathogenesis associated with history of maternal alcohol exposure (Fig. 1). In addition to rodents, other newly emerging model organisms, such as zebrafish (*Danio rerio*), can be useful to study various aspects of FAS and ARND. For example, zebrafish models link early ethanol effects with aberrant craniofacial morphology (Blader and Strähle, 1998), as well as deficits in social behavior and increased perseveration on a learning task (Parker et al., 2014a; Parker et al., 2014b). These behavioral changes corresponded to altered nicotinic, dopaminergic, serotonergic and μ-opioid receptor gene expression, suggesting that ethanol during development impacts neurotransmitters and receptor expression, causing long-term behavioral effects. The effects of prenatal exposure to ethanol is dependent on the timing of exposure and the dose to which the fetus is exposed, but may also depend on the fetal and maternal

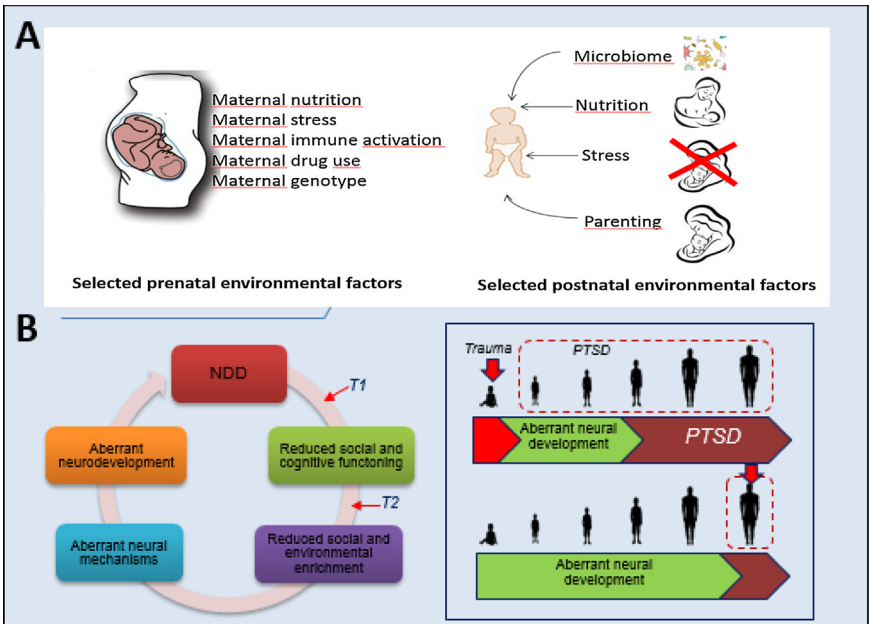

Fig. 2. The role of common environmental factors in pathogenesis of neurodevelopmental disorders (NDDs). Panel A illustrates selected post-conception prenatal and postnatal environmental factors. Prenatal environmental factors of maternal origin either directly cross the placenta, or alter placental function and thereby indirectly alter fetal neural development. The earlier the maternal environmental influences, the more global and diffuse the expected effects on fetal neural development are. Although the newborn/child continues to be exposed to several maternal environmental factors postnatally, the microbiome, stress and the quality of parenting come into play, further shaping neural development. Importantly, all such environmental factors have the potency to increase risk for NDDs. Other potential environmental factors, not shown here but discussed in the text, include early sensory stimulation (*e.g.*, environmental enrichment) and exercise (including both mental/cognitive and physical activity). Panel B summarizes the potential 'vicious' circle of NDD: aberrant neural development evokes behavioral (social, cognitive) deficits from early childhood, which results in deficient social and environmental interactions, necessary for shaping neural plasticity and adaptation in the maturing CNS. As a result, disease-provoked insufficient environmental stimulation may lead to additional impairments of neural development, in turn further worsening the existing NDD. Arrows denote potential treatments, including reducing NDD symptoms in affected individuals (T1) or improving social interactions of others with the patients (T2). Inset: An interesting example of potential complex dual relationship between aberrant neural development, NDDs and other neuropsychiatric disorders, such as post-traumatic stress disorder (PTSD). In one case, an early childhood trauma triggers both an early-onset subtype of PTSD and aberrant neural development (which makes subsequent PTSD worse). Alternatively, the pre-existing aberrant neural development may predispose an individual to an adult-onset subtype of PTSD (*e.g.*, evoked by exposure to a severe trauma as adults). Albeit not the main focus of this review, such dual interplay between NDDs and other brain disorders beyond the NDD spectrum merits further scrutiny in both clinical and preclinical models.

genotype. A screen of alcohol-exposed mutant zebrafish revealed several alcohol-sensitive alleles (Swartz et al., 2014), including the gene encoding platelet derived growth factor receptor α (pgdfra), a mitogen involved with neural crest cell migration and causing craniofacial abnormalities in 63% of heterozygotes after exposure to 1% alcohol. This finding is particularly interesting as it revealed alcohol-induced haploinsufficiency also identified as a potential locus of interest in a GWAS of humans with FAS. Similarly, the PCP gene *vangl2*, which is responsible for neural tube development, is associated with an increased risk of ethanol-induced teratogenesis in heterozygotes, revealing ethanol-induced haploinsufficiency that merits special interest from the NDD/ARND perspective (Swartz et al., 2014).

3.2. Other parental influences

Post-conception maternal stress has a major impact on fetal neural development, especially given mounting evidence that early life stress increases risk to various childhood/adulthood disorders. For instance, maternal stress during pregnancy is associated with an increased incidence of ADHD and ASD, as well as cognitive deficits and emotional/behavioral problems in children later in life (O'Donnell et al., 2009). Animal studies suggest that the neuroendocrine hypothalamic–pituitary–adrenal (HPA) axis is particularly vulnerable to early-life programming by stress and subsequent epigenetic modification of glucocorticoids-related genes (Maccari et al., 2014). Since glucocorticoids promote neuronal survival and differentiation, myelination, dendritic growth and synaptogenesis (Khulan and Drake, 2012), maternal stress can have a substantial impact on fetal neural development and increase the risks for NDDs (Wingenfeld and Wolf, 2011). Pregnancy itself is a risk factor for various brain disorders, such as depression. Because of the detrimental effects of maternal depression on mother and fetus, mothers may receive antidepressant pharmacotherapy during pregnancy, including SSRIs. However, SSRIs readily cross the placenta in both humans and mice (Noorlander et al., 2008) and can alter serotonin homeostasis, thereby affecting neural development. Prenatal SSRI exposure in mice increases anxiety in later life, similar to phenotypes of SERT mutant mice (Ansorge et al., 2004). Clinical studies also report that prenatal SSRI exposure has neurodevelopmental consequences for offspring, ranging from newborn withdrawal symptoms (Moses-Kolko et al., 2005) to delayed motor development, socio-emotional changes (Hanley et al., 2013), ASD (Boukhris et al., 2016; Croen et al., 2011; El Marroun et al., 2014) (but see Castro et al. (2016)) and ADHD (Figueroa, 2010). Given similar neurodevelopmental consequences of prenatal SSRI exposure in rodents (Kepser and Homberg, 2015; Kiryanova et al., 2013), changes in neurotransmitter levels during early brain development may have a major impact on NDD-related phenotypes. Another common example of NDD-relevant prenatal drug exposure is valproic acid. Prescribed for maternal epilepsy and some neuropsychological disorders, this agent significantly increases risk for ASD in humans (Christensen et al., 2013), and its early exposure causes similar ASD-like behavioral deficits in a wide range of animal models, including rodents (Schneider and Przewlocki, 2005), tadpoles (James et al., 2015) and zebrafish (Bailey et al., 2015).

Fetal immune activation (*e.g.*, as a result of maternal infections) may also modulate neural development. These immune interac-

tions are complex, as maternal placenta itself contains natural killer cells and macrophages (Erlebacher, 2013) – the immune cells that can influence the development of the placenta. This, in turn, can affect the fetal microenvironment (*e.g.*, by modulating the perfusion of the fetus) (Marques et al., 2013). Furthermore, cytokines induced by maternal immune activation and maternal antibodies can cross the placenta (Zaretsky et al., 2004), which can exert a negative impact on brain development if the time of exposure overlaps with major processes in neurodevelopment, such as cell migration, axonal elongation and dendritic tree maturation (Bilbo and Schwarz, 2012). While this may increase the risk of NDDs (Depino, 2013) (Capuron and Miller, 2011; Harvey and Boksa, 2012), peripheral activation of the fetal immune system can also modulate the CNS indirectly, by activating the HPA axis (Silverman et al., 2005). Because the blood-brain barrier is not fully developed during the fetal period, larger molecules, such as antibodies, may have greater access to the brain (Diamond et al., 2009). The blood-brain barrier permeability increases as a result of microglia cell activation, infection, trauma or stress, therefore enhancing the risk of exposing the brain to insults and environmental stimuli that affect neural development (Prat et al., 2001).

Another important factor in fetal neural development is maternal genotype. For example, maternal SERT promoter region *5-HTTLPR* genotype affects the development of children, with their neuroimaging phenotypes and cognitive performance differing between the *5-HTTLPR* SS and LL mothers (van der Knaap et al., 2014). Although all children carried the L/S genotype, somatosensory cortex grey matter density and fine motor task performance were greater in children of the SS mothers (van der Knaap et al., 2014). In another human study, familial analyses of the tryptophan hydroxylase 1 gene *TpH1* mutation carriers (that have deficiency in serotonin production in the periphery, but not in the brain) revealed that offspring of mothers carrying *TpH1* mutations exhibited higher ADHD scores and related symptoms than did controls or offspring of fathers with the corresponding *TpH1* mutations (Halmoy et al., 2010). Similarly, mouse fetuses (fully capable of producing serotonin in the brain) conceived by a *TpH1* knockout mother deficient in the peripheral serotonin, had an abnormally shaped cortex (Cote et al., 2007; O'Mahony et al., 2015). Thus, prenatal influences and maternal genotype have profound effects on neural development in offspring, and are therefore highly relevant to NDD pathogenesis.

3.3. Post-natal environmental factors modulating neural development

Microbiome is a key postnatal environmental factor to consider for NDDs, since gestational age, mode of delivery, bacterial environment and use of antibiotics can all influence the composition of the gut microbiota of the newborn (Jasarevic et al., 2015; O'Mahony et al., 2015). For example, bacteria in the gut influence the immune system, as well as tryptophan availability and peripheral monoamine levels (O'Mahony et al., 2015). Germ-free animals exhibit increased plasma tryptophan concentrations which can be normalized by colonization immediately post-weaning (O'Mahony et al., 2015). Germ-free mice show robust changes in the brain, including increased hippocampal serotonin concentrations – an alteration resistant to the subsequent normalization of circulating tryptophan following the introduction of a gut microbiota immediately post-weaning (O'Mahony et al., 2015). Although peripheral tryptophan may be converted to serotonin in the brain, it can also be subject to the indoleamine 2,3-dioxygenase pathway, being converted to kynurenine and therefore becoming unavailable for serotonin synthesis (Yeung et al., 2015). Microbiota influence the kynurenine:tryptophan balance (O'Mahony et al., 2015), and this shift towards kynurenine activates the immune system (Dantzer et al., 2011), thereby indirectly affecting postnatal neural development.

Parenting *per se* also has a major impact on postnatal neural development. A well-known example is the effect of maternal adversity in humans and rodents on development of offspring (Anacker et al., 2014). In humans, childhood maltreatment (often dependent on parent-offspring social interactions) is associated with an increased HPA response to stress (Anacker et al., 2014). In rodents, low maternal grooming of pups increases stress reactivity of the HPA-axis by altering serotonin-dependent epigenetic regulation of glucocorticoid receptors in the hippocampus and the glucocorticoid negative feedback (Anacker, 2014; Anacker et al., 2014). These effects are also accompanied by changes in dendritic morphology of hippocampal pyramidal neurons and pronounced behavioral effects, such as reduced exploration, appetitive behavior and escape from threat, and increased fear-related memories (Anacker et al., 2014) (Champagne et al., 2008).

Other environmental factors, including environmental enrichment (EE) and exercise, have been investigated as potential interventions for NDDs in animal models. For example, in a rat ASD model involving prenatal valproic acid exposure, EE reversed many ASD-like phenotypes, including repetitive behaviors, decreased social interactions and increased anxiety (Schneider et al., 2006). The restricted and repetitive behaviors seen in ASD may be particularly modifiable by EE (Lewis et al., 2007; Reynolds et al., 2013). Exercise also has beneficial effects on neural function and neuroplasticity, and may confer resistance to stressful stimuli occurring during crucial developmental periods (Levine, 2005; Pietropaolo et al., 2008). For example, symptoms of ADHD show some improvement following bouts of exercise, and scheduled exercise along with EE has been proposed as an adjuvant treatment for ADHD (Halperin and Healey, 2011). Clearly, future studies should continue to investigate the remediation of NDDs by environmental factors including EE and exercise in both clinical and preclinical settings, as these may offer cost-effective benefits for the patients.

4. Emerging translational challenges

Taken together, mounting evidence summarized here demonstrates a complex interplay between genetic and environmental factors underlying NDD pathogenesis in both clinical and preclinical studies (Figs. 1 and 2). The issue of how well animal models translate into clinical NDDs and other brain disorders has already been comprehensively discussed in the literature (including recent reviews of the scope, validity and challenges of translation of preclinical models (Kalueff et al., 2008; Kalueff et al., 2007; Nestler and Hyman, 2010; Stewart and Kalueff, 2015; van der Staay, 2006; van der Staay et al., 2009)), and will not be addressed here. Fully recognizing the existing limitations of animal NDD models, the ISBS Task Force has emphasized several strategies to address the existing challenges in this field of biological psychiatry. Identified by the Panel as critical areas of research to build translational and cross-diagnostic bridges, these studies can improve markedly our understanding of NDD neurobiology.

4.1. Improving the pharmacotherapy of NDDs: understanding molecular targets

Although varying in the central and genetic causes or in their clinical symptoms, NDDs can respond to drug therapies that target discrete deficits (Table 2) (Homberg et al., 2015). The degree of genetic anomalies and brain pathology underlying NDDs determine the potential targets for pharmacotherapy. For example, comparable cognitive improvements are less likely for NDDs associated with severely underdeveloped brain regions, such as FAS

Table 2
Selected drugs used to treat common neurodevelopmental disorders (see Homberg et al. (2015)) for details).

Drugs	Main profile and mechanism of action	Disorders treated
Risperidone (Risperdal)	Atypical antipsychotic, blocks D2 and 5-HT2A receptors	Tics, ASD
Haloperidol (Haldol)	Typical antipsychotic (neuroleptic), blocks D2 receptors	Tics
Clonidine (Catapres)	Sympatolytic α2 adrenergic- and imidazoline receptor agonist	Tics, ADHD
Atomoxetine (Strattera)	Non-stimulant norepinephrine reuptake inhibitor	ADHD
Methylphenidat (Ritalin)	Stimulant, dopamine-norepinephrine reuptake inhibitor	ADHD
Ziprasidone (Geodon)	Blocker ofdopamine/serotonin receptors and monoamine reuptake	ASD
Buspirone (Buspar)	Anxiolytic, serotonin 5-HT1A receptor partial agonist	ADHD, ASD
Amphetamine (Adderal)	Stimulant, monoamine reuptake inhibitor	ADHD
Dextroamphetamine (Dexedrine)	Stimulant, monoamine reuptake inhibitor	ADHD
SSRIs	Antidepressants, selective serotonin reuptake inhibitors	ASD, ADHD

or microcephaly (Dobyns, 1987). The prognosis of pharmacotherapy is better for NDDs caused by subtler neural changes that affect the function of local, well-defined neural circuits. Likewise, targeting dysfunction in long-term plasticity, including both synapse strengthening *via* long-term potentiation and weakening by long-term depression, appears to be rather efficient (Malenka and Nicoll, 1999). In some cases, an effective therapy may involve drugs given to infants or young children (Hanley, 2004), thereby requiring a well-timed diagnosis. Pharmacotherapies that target disrupted equilibrium of neurotransmitter systems also offer promise for NDDs, since drugs that counter such imbalances affect ongoing neural circuit dynamics rather than established gross anatomical abnormalities. Examples of therapeutic strategies in this category include the use of GABA antagonists for Down syndrome (Fernandez et al., 2007), mGluR antagonists for FXS (Bear et al., 2004), and norepinephrine reuptake inhibitors for Rett syndrome (Roux et al., 2007; Zanella et al., 2008). Finally, functional homeostatic mechanisms may contribute to the rebalancing of neurotransmitter function after drug therapy (Fernandez et al., 2007), and different therapeutic strategies for NDDs may be required at different stages of life (Homberg et al., 2015). Thus, a major task is to find a critical 'core' deficit among multiple neurological processes at a sensitive time window in NDDs, and then quickly adjust their pharmacotherapy accordingly.

4.2. Expanding NDD spectra beyond traditional diagnostic categories: understanding clinical targets across disorders

Recently developed and promoted by NIMH *research diagnostic criteria* (RDOCs) (Insel et al., 2010) emphasize the importance of pathobiological mechanisms and aberrant traits across multiple disorders. This approach aims to lay a firmer foundation for discovering the distal etiology of brain diseases, which are presently only recognized by their clinical depictions in the DSM and the ICD. Various psychiatric disorders have recently been reconsidered in the context of neural development, as genetic risk and environmental factors may jointly predispose an individual to pathogenesis *beyond* traditional NDDs, such as depression, anxiety and schizophrenia. For example, early studies have identified an increase in minor physical abnormalities in adult patients with major depression (Lohr et al., 1997), suggesting some neurodevelopmental origin of depressive symptoms. Although subsequent studies did not replicate these findings (Tenyi et al., 2004), recent hypotheses of depression pathogenesis recognize the importance of early environmental modulation and developmental trajectories in adult affective states (Ansorge et al., 2007). For instance, risks from genes related to monoaminergic neurotransmission and neurotrophic factors, such as BDNF, may be combined with aversive environmental conditions during development, to increase depression risk (Homberg et al., 2014). Likewise, the neurodevelopmental hypothesis of schizophrenia has gained traction recently, especially as genetic association studies have revealed significant risk overlap with ASD and ID in networks related to chromatin remodeling and synaptic connectivity (Homberg et al., 2016; Fromer et al., 2014; McCarthy et al., 2014). Subsequent meta-analysis also revealed significant co-morbidity between ASD and schizophrenia (Chisholm et al., 2015). Genetic schizophrenia risks involve common variation across the genome, particularly in the major histocompatibility complex (MHC) region and the complement component 4 (Sekar et al., 2016; Stefansson et al., 2009). Genetic predisposition and environmental factors affecting brain development therefore encompass schizophrenia risk, suggesting that NDDs represent, in fact, a much wider 'NDD+' spectrum of abnormalities (Nour and Howes, 2015; Owen et al., 2011) (Fig. 1).

Individuals exposed to intense trauma are also at significant risk for developing post-traumatic stress disorder (PTSD) or other trauma- and stressor-related disorders (TSRDs) (Hoffman et al., 2011; Thomas et al., 2010; Zoladz and Diamond, 2013). Childhood abuse/trauma can result in an early-onset PTSD, suggesting that this subset of TSRDs may be related to NDDs (Anda et al., 2006; Bremner et al., 2003; Penza et al., 2003). TSRDs are difficult to treat because stress interacts with vulnerability factors (Ehlers et al., 2004; Kleim et al., 2013; Reynolds and Brewin, 1998; Reynolds and Brewin, 1999), differentially affecting traumatized individuals (Heim and Nemeroff, 2009; Nemeroff et al., 2006; Newport and Nemeroff, 2000; Reynolds and Brewin, 1998). Neurodevelopmental deficits (*e.g.*, reduced hippocampal volume) *per se* may predispose individuals to PTSD (Bremner et al., 2003; Nemeroff et al., 2006), with 'early' traumas making it more treatment-resistant (Marshall et al., 1998). Thus, neurodevelopmental factors may play a dual role in TSRDs: while some stressors may induce them at young age (thereby influencing neural development), other stressors can trigger pathogenesis in vulnerable adults with pre-existing neurodevelopmental abnormalities (Fig. 2) (Diamond et al., 2007; Pitman et al., 2012; Shalev et al., 2008; Zoladz and Diamond, 2013). For example, individual responses to trauma are influenced by a history of childhood abuse or neglect (Anda et al., 2006; Bremner et al., 2003; Penza et al., 2003), causing neuroendocrine deficits and dysfunction of forebrain structures (*e.g.*, the hippocampus and prefrontal cortex (Bremner, 2003; Bremner, 2007; Vermetten et al., 2003)), and sensitizing vulnerable individuals to respond more strongly to stress in adulthood (Marshall et al., 1998; Pariante and Lightman, 2008). A recent animal PTSD model utilizes a 1-month daily inescapable confinement of rats close to a cat, combined with daily social stress (Zoladz et al., 2012; Zoladz et al., 2015). Using this and other preclinical TSRD models (Daskalakis et al., 2013; Pitman et al., 2012) can be particularly interesting in neurodevelopmental contexts – *e.g.*, assessing how trauma in mothers affects neural development of offspring, or how early stress in pups alters their adult NDD-related behaviors. Moreover, in addition to NDD-promoting impact of early traumas, it is also possible that, under certain circumstances, such exposure can also increase resistance (somewhat similar to how vaccinations boost the immune system). Therefore, the fine balance between NDD-triggering and protec-

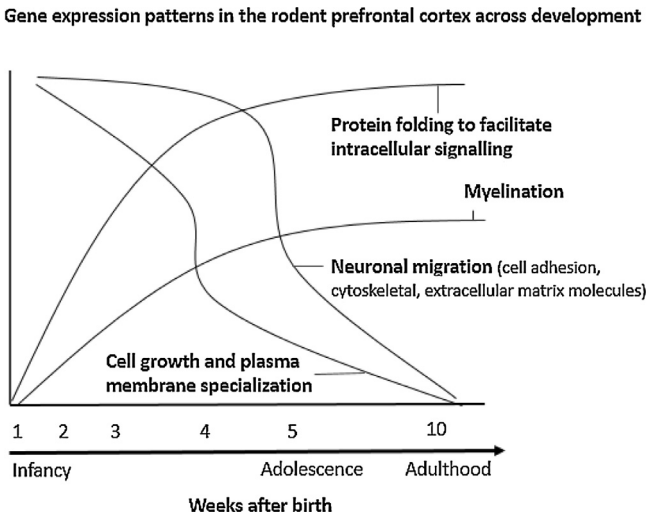

Fig. 3. Clustering of differentially expressed genes in the developing cortex of rodents. This diagram show typical patterns of gene expression clusters against time in postnatal weeks, grouped into "umbrella" categories (adapted from Semeralul et al. (2006)) and complemented with findings from Xu et al. (2014)). This graph illustrates that gene expression patterns change markedly across development, rendering gene expression data at only one single time point uninformative.

tive impacts of early life experiences merits further scrutiny in both clinical and pre-clinical studies. Accordingly, more 'spectrum-based' integrative animal models to target this growing 'NDD+' group may be needed (Kalueff and Murphy, 2007; Stewart and Kalueff, 2015).

4.3. Tracing NDDs across the lifespan: understanding potential therapeutic windows

Other important emerging questions are how the brain develops under healthy conditions, and how this goes awry in NDDs. The former needs to be clear by establishing the latter. As brain development is driven by a complex interplay of genetic and environmental determinants (Devlin and Scherer, 2012; State, 2011), animal models are particularly useful for tracing neural development across developmental stages. For example, micro-array gene expression and high-throughput RNA-sequencing of the mouse brain across developmental stages, from infancy (postnatal day P7), adolescence (P28) to adulthood (P70), show that the overall increase in gene expression from infancy to adolescence, decreases in adulthood (Semeralul et al., 2006; Xu et al., 2014); see Fig. 3 for an overview of gene expression changes across development. The adolescent brain has the most active gene expression, especially of regulatory genes and transcription factors critical for neurogenesis, differentiation, glial lineage determination and circadian rhythm regulation. Compared to infant brains, adolescent and adult brains also show a drastic increase in myelin basic protein-coding gene expression (Xu et al., 2014). During infancy and adolescence, gene expression related to axon repulsion and attraction show opposite trends, as axon attraction is activated at the embryonic stage and declines postnatally (Xu et al., 2014). Animal studies can detail developmental processes in neurons, astrocytes, microglia, endothelial cells, pericytes and various maturation states of oligodendrocytes, given that the major brain cell classes differ in their developmental processes. In the P7 mouse cortex, RNA sequencing reveals many new cell type-enriched genes and splicing isoforms, substantially enhancing our understanding of brain developmental processes (http://web.stanford.edu/group/barres_lab/brain_rnaseq.html). Novel long non-coding RNAs (lncRNAs) were also identified in proliferating neural stem cells, differentiating progenitors and newborn neurons, which overlapped with neurogenic genes and shared a nearly identical expression pattern (Aprea et al., 2013). This suggests that lncRNAs control corticogenesis by tuning the expression of nearby cell fate determinants. Finally, during cortical development, a group of novel small non-coding RNAs (sncRNAs) is associated with much higher editing events at late postnatal stages (P7, P14, P28), implicating sncRNA editing in fine tuning of gene expression during the formation of complicated synaptic connections at postnatal stages (Yao et al., 2012). Empowered by the availability of in-vivo animal models, such approaches may help improve our understanding of neurodevelopmental trajectories in the healthy brain as well as in NDDs. Clearly, studying gene expression at the end point/time of disease manifestation, is insufficient to understand what goes wrong during development. This necessitates systematic studies generating timelines for genetic or environmental NDD animal models and may reveal time windows responsive to early interventions that reduce successive abnormal neurodevelopmental processes.

4.4. The role of epigenetic modulation: bridging genetic and pharmacological therapies

As both genetic and environmental factors impose risk for NDDs, epigenetic enzymes and modification rapidly emerge as potential avenues for investigation of biological mechanisms and novel pharmacological therapies. Indeed, mutations in specific epigenetic enzymes may cause some NDDs (*e.g.*, mutations in *MECP2* in Rett syndrome) (Amir et al., 1999). Recent genome-wide studies have identified *de novo* mutations in numerous genes involved in chromatin modification present in patients with ASD (Bourgeron, 2015; De Rubeis et al., 2014a). Other genes identified in these same studies include synaptic organization proteins, and it is possible that these two biological networks may be more closely related than previously assumed. For example, the chromatin-modifying gene *CHD8*, which is associated with ASD, modulates the transcription of other ASD risk genes during neural development (Cotney et al., 2015). Given the involvement of environmental factors in the etiology of NDDs, epigenetic alterations occurring during early life, from gestation to adolescence and young adulthood, may confer increased or decreased risk for these disorders (Cotney et al., 2015). For example, as whole-genome sequencing becomes more economically viable, mutations in non-coding, regulatory regions in ASD patients have been observed recently (Turner et al., 2016). Additionally, ASD patients show differential expression of lncRNAs compared to controls (Wang et al., 2015). The notion of transgenerational epigenetic effects, where risk for a disease may be passed along outside of traditional genetic encoding, may also play a role in NDD risk. For example, prenatal nicotine exposure in rodents causes hyperactivity that resembles ADHD, and this phenotype is inherited (presumably, epigenetically) until at least the third generation *via* the maternal lineage (Zhu et al., 2014). Further exploration of epigenetic enzymes, transgenerational effects, and regulatory regions of the genome can shed additional light on the pathogenesis of complex NDDs.

5. Conclusion

In summary, various genetic and environmental risk factors predispose to NDDs, affecting both the brain development and its mature functioning. Despite the growing scientific inquiry into the pathogenesis of NDDs, their etiology and effective treatment strategies remain unclear. NDDs also significantly overlap with other prevalent psychiatric disorders, including schizophrenia, depression and PTSD, possibly representing an even broader 'NDD+' spectrum of brain maladies resulting from developmental pertur-

bations (Fig. 1). Continued effort into improving pharmacotherapy and identifying genetic and environmental risk factors for NDDs will implicate novel biological pathways and, hopefully, improve clinical outcomes. As many genetic and environmental factors influence neural development, they can do so both independently and in interaction. Thus, environmental factors can impinge on genotype-driven divergent neural development at varying time points, both pre- and postnatally. While it is not feasible to address in one experiment all possible genotype x environment x time interactions, this complexity must be considered when interpreting clinical or experimental neurobehavioral data.

The ultimate goals of understanding the etiology of NDDs are to direct treatments at neurodevelopmental deficits, to apply them during a most sensitive time window, and/or early enough in order to prevent or reduce aberrant neural development. Since genes and environmental factors often act prenatally, this may also require 'very early' diagnostic and therapeutic intervention, such as treatment of the mother during pregnancy. However, like using prenatal SSRIs to alleviate maternal depression and protect the fetus for glucocorticoid-mediates changes in neural development (Homberg et al., 2010; Kepser and Homberg, 2015), this may also result in a catch-22 situation with side effects of the remedy overweighting its therapeutic action. Therefore, finding the appropriate intervention before disease symptoms are displayed is not trivial, and must be considered from neurodevelopmental perspective, in addition to other (primary) goals of therapeutic treatment.

On a positive note, children and adults suffering from NDDs may also have their strong phenotypic characteristics. Therefore, rather than only correcting NDD deficits, augmenting the patients' strengths may provide an alternative strategy to increase a patient's well-being. However, this aspect is particularly environment-dependent. For instance, while ASD patients have difficulties with complex information integration, they perform very well when focusing on a task. Likewise, while ADHD children have difficulties in sitting still in the class room, as adults they can do well as managers who have to multitask. Thus, rather than fitting them with the 'standard' environment shaped for the majority of the human population, the ISBS Panel recognizes that providing the special NDD patients with an environment that fosters their capacities may not only down-play their limitations, but also benefits the society, as well as reduces negative (*e.g.*, stress-related) influences, thereby indirectly further alleviating some aspects of NDD pathobiology. Collectively, this emphasizes (for both animal and human research) the need to consider disorder-related symptoms in the 'personalized' context of the specific environment of individual patients. In addition, it is becoming critical to test the efficacy of environmental adjustments (as a supplement to other interventions) to enhance the capacities of those that are inflicted by aberrant neural development.

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