Understanding autism and other neurodevelopmental disorders

through experimental translational neurobehavioral models

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Abstract

Neurodevelopmental disorders (NDDs) are highly prevalent and severely debilitating brain illnesses caused by aberrant brain growth and development. Resulting in cognitive, social, motor, language and affective disabilities, common NDDs include autism spectrum disorder (ASD), intellectual disability, communication/speech disorders, motor/tic disorders and attention deficit hyperactivity disorder. Affecting neurogenesis, glia/neuronal proliferation and migration, synapse formation and myelination, aberrant neural development occurs over a substantial period of time. Genetic, epigenetic, and environmental factors play a key role in NDD pathogenesis. Animal models are an indispensable tool to study NDDs. Paralleling clinical findings, we comprehensively evaluate various preclinical tests and models which target key (social, cognitive, motor) neurobehavioral domains of ASD and other common NDDs. Covering both traditional (rodent) and alternative NDD models, we outline the emerging areas of research and emphasize how preclinical models play a key role in gaining translational and mechanistic insights into NDDs and their therapy.

Keywords: neurodevelopmental disorder, model organism, experimental model, preclinical study, translational research

Research highlights:

- Neurodevelopmental disorders are common and widespread psychiatric illnesses

- Autism and other neurodevelopmental deficits often occur in early development

- Animal models are a valuable tool to study autism and other neurodevelopmental disorders

- We parallel clinical and preclinical data to gain a translational perspective of these illnesses

1. Introduction

Neurodevelopmental disorders (NDDs) represent clinically heterogeneous, heritable psychiatric illnesses caused by aberrant brain growth and development (American Psychiatric et al., 2013; Hansen et al., 2013; Homberg et al., 2015). Presenting with motor, cognitive, language and affective disabilities, common NDDs include autism spectrum disorder (ASD), social communication disorders, intellectual disability (ID), attention deficit hyperactivity (ADHD) and motor/tic disorders (Table 1, Fig. 1) (American Psychiatric et al., 2013; Hansen et al., 2013). While NDD symptoms typically emerge during childhood, aberrant neural development usually starts during early embryogenesis (Hu et al., 2014; Sadler, 2006) and continues over a substantial period of time. Affecting neurogenesis, glia/neuronal proliferation and migration, synapse formation and myelination (Fig. 1) (Ding, 2015; Frederick and Stanwood, 2009; Hu et al., 2014; Rice and Barone, 2000), these developmental changes lead to long-lasting behavioral and physiological deficits in both child- and adulthood (Bergner et al., 2010; Buckley et al., 2009; Krishnan, 2005). Depending on the brain structure(s) or the stage of neural development affected, clinical manifestations of NDDs range from specific symptoms to global mental impairments (Table 1) (American Psychiatric et al., 2013; Hansen et al., 2013). In addition, NDDs frequently co-occur (e.g., ADHD with learning disability, ASD with ID) and overlap with other brain disorders, forming a complex spectrum of neuropsychiatric comorbidities (Fig. 1) (Bergner et al., 2010; Buckley et al., 2009; Krishnan, 2005)

NDDs remain a relatively unmet biomedical concern (Bergner et al., 2010; Buckley et al., 2009; Krishnan, 2005) with high prevalence and socio-economic impact (Dykens, 2015). In addition, NDDs cause significant distress and persistent impairments of behavior, memory/learning, social communication, occupational performance and other important daily activities (American Psychiatric et al., 2013; Hansen et al., 2013). Multiple therapeutic approaches to NDDs include pharmacotherapy, behavioral therapy and rehabilitation, such as physical or speech/language therapy (Hansen et al., 2013). However, specific and effective treatments for NDDs are lacking, as we do not know the

biological targets and the exact symptoms, which are also often detected at clinically advanced stages, past the best therapeutic intervention period (Homberg et al., 2015). This, as well as the growing health burden of NDDs (Fig. 2), necessitate further translational research in this field and the development of valid preclinical models, novel biomarkers and therapies.

To address these challenges, the International Stress and Behavior Society (ISBS) has established the Strategic Task Force on NDDs - a team of international experts representing different clinical and preclinical fields (Homberg et al., 2015). Complementing the Panel's recommendations on improving pharmacotherapy of NDDs (Homberg et al., 2015), the present review parallels clinical symptoms of ASD and several other common NDDs with their existing preclinical paradigms, and evaluates various tests and models of animal neurobehavioral development, social behaviors, restricted interests and behavioral perseverations. Covering both traditional (rodent) and alternative models of NDDs, we outline the emerging areas of research and emphasize how preclinical models help gain translational and mechanistic insights into NDDs and their therapy.

2. Animals models of neurodevelopmental disorders

Since a key function of the nervous system is to produce behavior, behavioral analyses provide the most meaningful assessment of the central nervous system (CNS) and its deficits. For example, rodent tests are commonly used to measure neural phenotypes in behavioral genetics, developmental psychobiology, psychopharmacology and neurotoxicology (Buelke-Sam and Kimmel, 1979; Butcher, 1976; Elmazar and Sullivan, 1981; Reiter, 1978; Vorhees et al., 1979). However, because of multiple limitations inherent in experimental modeling of complex human brain disorders (Cachat et al., 2011; Kalueff and Tuohimaa, 2005b; Kalueff et al., 2007e), targeting the entire spectrum of clinical NDDs is impossible (Table 1). Nevertheless, animal paradigms continue to be indispensable for studying the neurobiology of human NDDs (Kalueff et al., 2007e). In general, a good animal model should possess three main attributes: construct validity (conforming to the underlying rationale of the disease), face validity (mimicking some of the characteristics of the

disease) and predictive validity (allowing the prediction of novel disease symptoms, or identification of disease treatments) (Kalueff et al., 2007e; Stewart and Kalueff, 2015). The animal model should also combine genetic tractability, tools to visualize and manipulate neurons *in vivo*, and the ability to translate findings to patients based upon conserved neurobiology. Two major groups of preclinical paradigms merit discussion here. One group is behavioral *tests* which assess NDD-linked phenotypes, and therefore often have high face and predictive validity. The second group represents experimental *models* relevant to NDD pathogenesis (Fig. 2), and therefore possesses high construct validity. Both types of preclinical paradigms can be used complementarily to gain translational and mechanistic insights into NDD pathogenesis (Table 2).

2.1. Tests of rodent neurobehavioral development

Numerous tests for neurobehavioral development in young rodents can be organized into five broad behavioral domains: simple reflexes, sensory function, motor function/coordination, learning/memory and emotionality (Table 3). Simple reflex tests measure behavioral responses that are relatively simple in form, resistant to motivational influences, and often mediated by a small number of sensory and motor neurons. The appearance or disappearance of reflexes from birth is used to assess the rate of maturation of the CNS and differences in the day of appearance or disappearance of reflexes may be used as predictors for NDDs. Tests used to measure sensory development and reactivity assess a wide range of different (e.g., visual, vestibular, auditory and olfactory) systems (Table 3). Differences or abnormalities in rate of sensory development may be indicative of abnormal neuronal pathways associated with NDDs. Furthermore, tests used to assess locomotor activity reflect both exploratory behavior and a state of arousal or "nonspecific excitability" in the context of motor function (Table 3). Proper development of motor coordination can be assessed using numerous tests, such as rotarod and gait analysis, which provide spatial and temporal characteristics of limb movement during locomotion.

Addressing another critical (cognitive) domain, Table 3 outlines learning and memory tests suitable for young rodents, whose immature sensory and motor systems place limitations on their ability to perform certain tasks or express certain learned associations. These tests have been used to assess such aspects of learning and memory as habituation, avoidance, retention, conditioning, and spatial, delayed, discrimination, and reversal learning. Finally, emotionality represents a key neurobehavioral domain often affected during neural development in both animal and clinical studies (Homberg et al., 2015). In general, assessing emotionality in rodents is a difficult task. Four issues are of particular importance to consider: how to measure emotions directly, how to classify emotional states, how to attribute overt behavior to covert emotional states, and how to identify animal models that are good models of human emotional reactions. Several robust tests of emotionality are summarized in Table 3 and have been recently comprehensively evaluated elsewhere (Cryan and Holmes, 2005; Griebel and Holmes, 2013), including altered emotionality in several rodent models of NDDs (Bolivar and Brown, 1994; Branchi and Ricceri, 2002; Martinez-Cue et al., 2006; Ricceri et al., 2007).

2.2. Rodent tests of social behaviors

Social deficits are a common symptom of ASD and many other NDDs. Popular rodent behavioral assays designed to target social behaviors characterize social interaction and communication deficits (Bishop and Lahvis, 2011; Crawley, 2004, 2007; Hunsaker, 2012; Lahvis and Black, 2011; Silverman et al., 2010b). Rodents are particularly suitable to model NDD-associated social deficits since both mice and rats are highly social species with a wide repertoire of social behaviors, including parenting, communal nesting and juvenile play as well as sexual and aggressive behaviors as adults. One of the most popular paradigms, the social interaction test evaluates social responses of the subject mouse directly facing a co-specific (i.e., a freely moving stimulus mouse). Importantly, this also allows a concomitant measurement of ultrasonic vocalizations (USVs) to simultaneously assess rodent social and vocal repertoires. During the social interaction test, mice

typically investigate each other by sniffing (of anogenital regions, heads or the rest of the body), by crawling over/under each other and/or by reciprocal following. This test is easy to perform, and can utilize either same-sex or mixed pairs. Moreover, in both the male-female and female-female social interaction tests, emission of USVs (40-80 kHz) is a consistent robust phenomenon, considered an index of social interest and motivation (Moles et al., 2007; Nyby, 2001; Scattoni et al., 2009). USVs positively correlate with social investigation, such as anogenital sniffing (Moles et al., 2007; Nyby, 1983; Sales, 1972; Scattoni et al., 2011). Digital spectrographic analysis enables the collection of further information on USVs (e.g., waveforms of the calls), classified into several categories based on internal frequency, duration and spectrographic shape (Ey et al., 2013; Roy et al., 2012; Scattoni et al., 2008; Scattoni et al., 2011; Tyzio et al., 2014). Importantly, since mice engage in social interaction as juveniles, these tests are suitable for studying developmental trajectories of social behaviors, which is relevant to modeling NDDs in general.

In behavioral studies, mouse preference for a social (vs. non-social) context, as well their ability to recognize an unfamiliar co-specific (social recognition), are important traits. The social approach task evaluates these two social aspects at two different test phases in the same apparatus (Moy et al., 2004; Nadler et al., 2004; Yang et al., 2011). This test has become extremely popular in phenotyping of ASD mouse models, since it is unbiased to individual variations in behavior of a social stimulus (a stranger mouse confined under small wire cages); is less time-consuming than other related tests (Pearson et al., 2012); can be used in an automated manner; and because mice can be tested at different ages (an opportunity scarcely exploited so far), thus offering the possibility to follow developmental trajectories. However, since the stimulus mouse is contained under a wire cup, the three-chamber social approach apparatus only measures social approach initiated by the subject mouse (also note that the strain of both stimulus and testing mouse can influence the results, and therefore must be carefully considered). This permits the olfactory, auditory and visual contact, avoids sexual and aggressive behaviors, but also prevents a fine-grain evaluation of the social

behaviors and their reciprocity. As already mentioned, various other disorders, both within (e.g., ADHD) and beyond NDD spectrum (e.g., schizophrenia, depression, anxiety), present with social deficits, and a careful dissection of these factors in respective animal assays is necessary. Thus, it is useful to combine the social approach with the social interaction tests (Feyder et al., 2010; Jamain et al., 2008; Peca J et al., 2011; Radyushkin et al., 2009; Schmeisser et al., 2012), as well as to apply tests assessing other behavioral domains (e.g., activity, memory, affect), for a more accurate characterization of rodent social deficits.

Since NDDs typically have an early onset, behavioral phenotyping targeting the early developmental period is crucial (Bale et al., 2010; Branchi and Ricceri, 2002), although aberrant phenotypes can be present at different developmental stages. For instance, USVs, emitted by mouse pups in response to separation from mother and littermates, are considered a reliable index of pup social motivation (Branchi et al., 2010; Ehret, 2005; Sewell, 1970), suitable for the identification of early communication deficits in ASD mouse models (Wohr and Scattoni, 2013). Pup isolation-induced USVs can reflect aversive affective states, eliciting maternal exploratory and retrieval behaviors (Knutson et al., 2002; Panksepp, 2003; Zippelius and Schleidt, 1956). Usually pups vocalize for a brief period after separation from the nest, and then rapidly habituate. During early postnatal days, USVs follow a clear strain-dependent ontogenetic profile, with a typical peak around Days 5-8, and a progressive decrease afterwards (Elwood and Keeling, 1982; Hahn et al., 1998; Roubertoux et al., 1996). Unusual calling patterns and reduced vocalization rates, sometimes associated with a restricted vocal repertoire (Michetti, 2012), are detected in several genetic mouse models of NDDs (Bozdagi et al., 2010; Romano et al., 2013; Scattoni et al., 2008; Schmeisser et al., 2012; Wohr et al., 2012; Won et al., 2012; Yang et al., 2012). When evaluating development of vocal response, it is crucial to consider potential confounders, as altered body temperature, weight and growth can affect both quantitative and qualitative UVSs (Bozdagi et al., 2010; Hamilton et al., 2011; Romano et al., 2013; Roy et al., 2012; Shair et al., 2003; Veenstra-VanderWeele et al., 2012; Yang et

al., 2012). Overall, pup USV characterization permit identification of an ASD-like phenotype at an early stage of development, in situations when other social or behavioral phenotypes are difficult to obtain.

2.3. Rodent models of repetitive behavior and motor stereotypies

One of the symptoms of ASD and some other NDDs is restricted/repetitive patterns of behavior, interests or activities, manifested by stereotypic motor movements (i.e., repetitive sequences of motor behavior, topographically and morphologically invariant, often rhythmical), inflexible adherence to routines, ritualized patterns and circumscribed or perseverative interest (American Psychiatric et al., 2013). In general, repetitive behaviors can be divided in two classes, roughly indicating 'lower-order' (repetition of movements and stereotypies) and 'higher order' (insistence on sameness, lack of behavioral flexibility, with a distinct cognitive component) responses (Lewis et al., 2007). Although rodents exhibit several spontaneous motor stereotypies (e.g., excessive vertical jumping, back-flipping, circling, digging, chewing), excessive self-grooming behavior has been by far the most well-studied stereotypy in ASD mouse models (Fig. 2), likely because it is a common phenotype with a complex 'patterned' sequential nature, and is easy to measure in rodents (Crawley, 2007; Creese and Iversen, 1975; Kalueff et al., 2007a; Korff and Harvey, 2006; Lewis et al., 2007; McFarlane et al., 2008; Moy et al., 2008; Pogorelov et al., 2005; Turner et al., 2001), also see Table 2.

Recapitulating behavioral perseveration, pathological self-grooming in rodents can also be valuable for examining neural pathways of NDDs (Pearson et al., 2011; Reynolds et al., 2013; Silverman et al., 2010a). For example, ephrins A (ephrin-A ligands), ephrin A receptors (members of the receptor protein-tyrosine kinase superfamily) and their genes are strongly implicated in neural development (Wurzman et al., 2014). Serving as an important membrane-anchored cellular protein, ephrin A modulates neuronal differentiation and synaptic plasticity, and ephrin-A2/A3 receptor double knockout mice display repetitive self-grooming, motor retardation and social deficits,

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recapitulating some clinical symptoms of ASD (Wurzman et al., 2014). Similarly, exaggerated self-grooming is seen in the inbred BTBR mice, displaying callossal agenesis, social deficits and behavioral inflexibility relevant to ASD (Amodeo et al., 2014; Brodkin et al., 2014). Interestingly, cholinergic agents which correct some clinical ASD symptoms (Van Schalkwyk et al., 2015) predictably reduce self-grooming (Amodeo et al., 2014) and other ASD-like behaviors (Karvat and Kimchi, 2014) in BTBR mice, whose self-grooming is also corrected by glutamatergic drugs (Silverman et al., 2012; Silverman et al., 2010a).

Several other candidate 'NDD' genes include the SHANK family - *SHANK1, SHANK2* and *SHANK3* (Guilmatre et al., 2014) modulating synaptic function in the brain. In addition to ASD-like social deficits and repetitive behaviors, *Shank* mutant mice display aberrant grooming (Schmeisser, 2015) including elevated repetitive self-grooming in *Shank1*+/− and −/− (Sungur et al., 2014), *Shank2*−/− (Schmeisser et al., 2012)'(Won et al., 2012) and *Shank3*−/− mice (Peca et al., 2011; Wang et al., 2011; Yang et al., 2012). Ablation of the GABA-synthesizing enzyme glutamic acid decarboxylase (Gad67) also results in mouse ASD-like behavior, including increased self-grooming and cognitive and social deficits (Zhang et al., 2014).

Related to grooming phenotypes, barbering (behavior-induced hair loss, Fig. 2), including both hetero- and self-barbering, can be used to assess repetitive behaviors (Kalueff et al., 2006). Note, however, that stressors and other laboratory environment factors (e.g., poor housing, nutrition/diet, lack of enrichment) may often trigger such behaviors in laboratory rodent colonies (Garner et al., 2011), (Dufour et al., 2010), (Garner et al., 2004), and therefore should be carefully monitored to avoid confusion with NDD-related behaviors. Another rodent paradigm widely used in the context of repetitive behavior is the marble burying test, which measures repetitive behavior related to digging, not correlated with anxiety traits and primarily stimulated by novelty (Thomas et al., 2009). Notably, motor repetitive behaviors, such as self-grooming and marble burying, are often more sensitive (than social responses) in testing different drugs in NDD mouse models (e.g., mGluR5 antagonists

(Silverman et al., 2012; Silverman et al., 2010a) and acetylcholine esterase inhibitors (Amodeo et al., 2014) in BTBR mice), raising the questions of potential differential sensitivity of various NDD phenotypes to drugs.

2.4. Rodent models of restricted interests and behavioral inflexibility

Because ASD patients often follow fixed routines and resist changes (Chen et al., 2009; Frith et al., 1991; Goldman et al., 2009), such restricted interests and behavioral inflexibility can be modeled in rodents by assessing their motivation to explore novel objects and to nose-poke holes in the wall or floor (Elsabbagh et al., 2013). Perseverative exploration of only a limited set of (rather than all) available objects or holes may resemble restricted interests in ASD humans (Moy et al., 2008). Thus, it is possible to model this insistence on sameness in mice by assessing their flexibility to switch from an established habit to a new habit through reversal learning in the T-maze or Morris water maze. Briefly, after establishment of a spatial habit (e.g., reinforcing entries into the left arm of a T-maze or locating the hidden escape platform in one quadrant of a Morris water maze), the experimental set is changed and the mouse is requested to abandon the previously acquired habit and shift to a new location. ASD mouse models displaying repetitive behaviors usually perform well during the acquisition phase, but are generally slower in the acquisition of the new information during the reversal phase (Bader et al., 2011; Gandal et al., 2012; Guariglia and Chadman, 2013; Karvat and Kimchi, 2012; Lee et al., 2013; Moy et al., 2007; Penagarikano et al., 2011; Sala et al., 2013; Sala et al., 2011; Wang et al., 2011; Zhao et al., 2010). Other, more complex and refined rodent attentional set shifting tasks continue to be developed in mice (Colacicco et al., 2002), (Garner et al., 2006) and rats (McAlonan and Brown, 2003) to target cognitive deficits associated ASD, ADHD and other NDDs (Tait et al., 2014), (Scheggia et al., 2014).

2.5. Rodent behavioral tests targeting comorbid traits

Together with core symptoms, NDD patients often present comorbid traits, including seizures, altered emotional and sensory processing, as well as sleep and gastrointestinal deficits (Fassio et al.,

2011; Gilby and O'Brien, 2013; van Steensel et al., 2011; Woolfenden et al., 2012). However, their underlying biological mechanisms remain poorly understood. For example, if comorbid traits are integral to the NDD (Argyropoulos et al., 2013), many of them must also be present in valid NDD mouse models, and assessed as associated symptoms (Crawley, 2007; Roullet and Crawley, 2011). The presence of comorbid phenotypes, such as seizures or altered anxiety levels, may also interfere with spontaneous behavioral responses, thus confounding the interpretations of results (Roullet and Crawley, 2011). Evaluation of comorbid traits (selected on the basis of the information already available on the phenotype or on the basis of the role played by the gene alteration on CNS function) is therefore critical for a fine-grain behavioral characterization of NDD mouse models.

For example, seizures are observed in 8-25% of the ASD population (Hara, 2007; Jeste, 2011; Sansa et al., 2011), and are particularly common in ASD patients with ID (Woolfenden et al., 2012). The presence of seizures can be evaluated in mice using tonic–clonic rating scales or EEG recordings. Seizures can be spontaneous or drug-induced, and once started, interrupt normal activities such as walking, exploring, sniffing and grooming (Morrison et al., 1996). The brain activity recordings permit the evaluation of the neuronal activity and identify the seizures as a spike-wave pattern (Blundell et al., 2009; Chemelli et al., 1999; Zhou et al., 2009). Seizure susceptibility and high levels of seizures have been reported in several ASD mouse models, including *Shank3B*, *CNTNAP2*, *Pten* and *Gabrb3* knockout mice (DeLorey et al., 1998; Peca J et al., 2011; Penagarikano et al., 2011; Zhou et al., 2009). In line with this, some epileptic strains, such as Synapsin I (*Syn1*) and Synapsin II (*Syn2*) knockout mice, show ASD-like traits (Greco et al., 2013), collectively emphasizing the overlap between this NDD and epileptic pathogenesis.

Anxiety is also common in NDD patients (Argyropoulos et al., 2013; Gillott et al., 2001; van Steensel et al., 2011), and standardized mouse assays to measure anxiety-like behaviors are primarily based on approach-avoidance conflicts since mice are nocturnal and avoid lit open novel environments. Currently, the most popular anxiety-related tests include the elevated plus-maze and

light-dark tests, recently reviewed in (Cryan and Holmes, 2005; Griebel and Holmes, 2013). The elevated plus maze consists of two open and two enclosed arms, and the light-dark test represents a two-compartment apparatus with a dark enclosed and an open lit compartments. An unusually high preference for 'protected' closed arms and for 'safe' dark compartment is considered as an excessive anxiety-like trait. Interestingly, several ASD mouse models, such as the *Nlgn2, 5HTT, FMR1, Avpr1b, Shank2, Shank3* and other mice with mutations that may be relevant to autism, show increased anxiety profiles, in addition to at least one other core symptoms (Blundell et al., 2009; Holmes et al., 2003; Peca J et al., 2011; Schmeisser et al., 2012; Spencer et al., 2005; Wersinger et al., 2002; Won et al., 2012).

Finally, mounting evidence suggests early motor abnormalities in ASD neonates and children (Iverson and Braddock, 2013; LeBarton and Iverson, 2013; Phagava et al., 2008) and infants at increased risk for ASD (Leonard et al., 2013). Since motor dysfunction can affect other NDD symptoms, preclinical studies in mouse models have recently addressed this issue by fine-grain characterization of spontaneous motor behavior (De Filippis et al., 2010; Romano et al., 2013). This may be important as a behavioral biomarker of NDD at an early stage of development, when other behavioral phenotypes are difficult to record.

2.6. Rodent models relevant to Tourette syndrome

A common NDD, Tourette syndrome is a highly heritable, early-onset illness (American Psychiatric et al., 2013) characterized by motor and phonic tics - habitual sudden, rapid, recurrent and non-rhythmic movements or vocalizations (Yu et al., 2015). Often comorbid with other NDDs such as ADHD and ASD, clinical Tourette syndrome frequently overlaps with obsessive-compulsive disorder (OCD), anxiety and depression ((APA), 2013; Felling and Singer, 2011). Given excellent recent expert reviews of animal models of Tourette syndrome in this journal (Macri et al., 2013b),(Bronfeld et al., 2013), (Martino and Laviola, 2013), they will be only briefly mentioned here. Several mouse models have recently been proposed as relevant to Tourette syndrome, including DAT-/- mice with

elevated dopaminergic tone, overall hyperactivity and stereotyped self-grooming patterns, which parallel inflexible behavioral actions in Tourette patients (Berridge et al., 2005; Denys et al., 2013). Mutant mice lacking D_{1A} receptors display aberrant behavior including shorter (and more incomplete) grooming episodes with disrupted sequential patterns (Cromwell et al., 1998), potentially relevant to dopaminergic deficits in Tourette syndrome. Other brain neuromediators, including glutamate, serotonin, GABA, norepinephrine (NE) and histamine, play an important role in clinical Tourette's syndrome and its preclinical models (e.g., (Nordstrom et al., 2015), (Macri et al., 2013a), (Rapanelli and Pittenger, 2015)). For example, histidine carboxylase is an enzyme producing histamine from histidine. In line with clinical data implicating mutations in the human histidine decarboxylase (HDC) gene in Tourette syndrome (Castellan Baldan et al., 2014), the *Hdc*-/- mice recapitulate some aspects of this syndrome, including tic-like stereotypic grooming (Xu et al., 2015b). Together with the growing number of animal models of Tourette syndrome and other tic disorders (Macri et al., 2013a), (Godar et al., 2015), (Xu et al., 2015a), this suggests that future translational research will generate significant insights on these NDDs.

2.7. Selected rodent models of attention deficit and hyperactivity

Novel insights into the genetics and neurobiology of ADHD have already benefitted from animal models, and will be discussed here in the context of NDDs. Perhaps, the most robust and easiest ADHD symptom to measure in animal models is motor hyperactivity (hyperlocomotion). The control of hyperactivity is crucially linked to dopamine signalling, and both increased (Antrop et al., 2000; Corkum et al., 2001; Porrino et al., 1983) and decreased dopamine (Giros et al., 1996; Viggiano et al., 2002) can lead to hyperactivity in animal models. Other measurements of ADHD-like behavior, including inattention and increased impulsivity, are more difficult to model (see further), suggesting that most animal paradigms represent "ADHD-like" rather than complete "ADHD" models (Sontag et al., 2010). For example, the spontaneous hypertensive rat (SHR) created by selectively inbreeding rats of the Wistar-Kyoto (WKY) strain (Okamoto and Aoki, 1963) shows face

validity for some aspects of ADHD, including hyperactivity in a novel environment, excessive responses during a fixed interval/extinction schedule and difficulty in operant learning (Mook et al., 1993; Sagvolden, 2000; Wyss et al., 1992). Paralleling core symptoms of ADHD (hyperactivity, impulsivity and inattention), SHR are also less responsive to delayed reinforcement than WKY controls. Their behavioral alterations can be rescued by amphetamine (Myers et al., 1982; Sagvolden et al., 1992)*,* methylphenidate (MPH) (van den Bergh et al., 2006) and the α2-agonist guanfacine (Sagvolden, 2006) providing further links to the human disorder. The SHR also demonstrate construct validity for ADHD, as their behavioral phenotypes are likely caused by altered dopamine signalling. SHR carry a 160-base pair insertion in intron 2 of the DAT gene *Dat/Slc6a3*, possibly affecting its expression in a manner similar to the VNTR seen in human ADHD patients (Vandenbergh et al., 1992). SHR have several abnormalities in cathecholaminergic function, including reduced release of dopamine in the prefrontal cortex, nucleus accumbens and striatum, decreased dopamine turnover in the substantia nigra, ventral tegmentum and frontal cortex (Russell, 2002) and elevated norepinephrine in several brain areas (De Villiers et al., 1995). Nevertheless, despite its excellent attributes, the SHR is not the best ADHD model. For example, the background WKY rat strain is less active (than other rats) and does not perform well on some tasks (van den Bergh et al., 2006) making the behavioral alterations in SHR seem more pronounced. The high blood pressure (hypertension) seen in SHR is not observed in ADHD and could explain some of the behavioral alterations, including changes to learning and memory (Davids et al., 2003). In order to address this issue, a non-hypertensive WKHA strain has been generated by back-crossing SHR rats to the WKY strain. However, while WKHA rats are hyperactive, they do not respond to MPH treatment, suggesting that they may not have predictive validity for ADHD (Hendley and Ohlsson, 1991). In general, despite its limitations, the SHR fulfils many of the criteria needed in an ADHD-like animal model, suggesting that further study may bring even more insights into the etiology of the disease.

Polymorphisms in the DAT gene have been linked to susceptibility for ADHD in a number of clinical studies. The *Dat* knockout (*Dat-/-*) mice show a spectrum of ADHD-like phenotypes including hyperactivity in a novel environment, a reduction of startle response and an impairment of learning and memory (Giros et al., 1996; Sora et al., 1998; Zhuang et al., 2001) (also see details of heterozygous Dat+/- mouse phenotypes in (Kalueff et al., 2007c)). The behavioral symptoms of *Dat-/-* mice can be rescued by both amphetamine and MPH (Gainetdinov et al., 1998). Nevertheless, although DAT is linked to ADHD clinically, *Dat* knockout mice may not represent a good ADHD-like model due to an extreme phenotype, such as a 5-fold increase in dopamine levels in the striatum of these mice coupled to compensatory changes in other dopaminergic signalling pathways. There is also increased activity of tyrosine hydroxylase (Jaber et al., 1999) and down-regulated expression of postsynaptic dopamine D1 and D2 receptors (Gainetdinov et al., 1998). This phenotype is at odds with the presumed pathology of clinical ADHD (which suggests *reduced* dopamine in the prefrontal cortex) and the postulated therapeutic action of many anti-ADHD drugs (including MPH and amphetamine) via DAT. Although the behavioral phenotype of *Dat* knockout mice can also be rescued by SSRIs, non-selective serotonin agonists and 5-HT2A antagonists (Barr et al., 2004), SSRIs are not particularly effective in controlling major disordered symptoms of ADHD clinically. Finally, due to their highly hyperactive phenotype, memory and learning testing is almost impossible to perform in *Dat-/-* mice, which also show unwanted growth retardation and an increased likelihood of premature death (Gainetdinov et al., 1998; Giros et al., 1996). Notably, *Dat* knock-down mice, which only have 10% of normal Dat function, also show hyperactivity, anti-hyperkinetic responses to amphetamine, excessive grooming and tendency to persevere in walking in straight lines (Berridge et al., 2005).

The coloboma mouse has a radiation-induced mutation in the *SNAP25* gene resulting in a 50% reduction of SNAP25-mediated synaptic transmission. Heterozygous coloboma mutant mice (*Cm+/-*) show spontaneous hyperactivity reduced by amphetamine but not MPH (Hess et al., 1996). Coloboma

mutants also display impulsivity and impaired inhibition in a delayed reinforcement task, being unable to wait as long as controls for a larger reward (Bruno et al., 2007). Mutation of *SNAP25* reduces dopamine in the dorsal striatum, increases cortical dopamine and striatal and accumbal norepinephrine (Jones et al., 2001; Raber et al., 1997). Thus, an interaction between these two monoamines' signalling mechanisms seems to be important in coloboma mutants. These mice also seem to have predictive validity for ADHD, since identification of their *SNAP25* mutation led to candidate gene studies that eventually revealed an association between the gene and human ADHD (Brophy et al., 2002). As a caveat, however, *Cm+/-* also have visual problems, while homozygous animals die early in pregnancy, these phenotypes are not associated with ADHD.

Finally, as an example of a developmental toxin that can lead to the symptoms of ADHD, rats lesioned with 6-hydroxydopamine (6-OHDA) on postnatal day 1 show hyperactivity and reduced learning at certain developmental period. 6-OHDA is a neurotoxin that is uptaken by the DAT and NE transporter, and selectively kills both types of neurons. Motor and learning defects of 6-OHDA rats can be rescued by applying amphetamine or MPH. The hyperactivity of 6-OHDA-lesioned animals is accompanied by reduced dopamine in the striatum, prefrontal cortex, midbrain and amygdala, and increased striatal serotonin (Luthman et al., 1989). However, the noradrenergic system does not appear to be altered in these animals. Notably, the behavioral phenotype of 6-OHDA rats normalizes by adulthood, demonstrating the ability of the dopaminergic system to recover from some lesions during early development (Davids et al., 2003).

2.8. Developing translational models of NDDs using non-rodent species

While rodents are an indispensable tool for NDD research (Homberg et al., 2015), other model organisms are gaining popularity in this field. For example, invertebrate models, such as fruit flies (*Drosophila melanogaster*), have traditionally been used in developmental and behavioral genetics, and while out of scope here, are be mentioned for their emerging potential in modeling

NDDs, including ASD and ADHD (see (Kaur et al., 2015; van der Voet et al., 2015; Wise et al., 2015) for details).

Mounting evidence suggests zebrafish (*Danio rerio*) as a valuable translational model (Kalueff et al., 2014a; Stewart et al., 2014a) for behavioral analysis in both larval and adult fish and in-depth characterization of their rich behavioural repertoire (Kalueff et al., 2013; Kalueff et al., 2014b; Stewart et al., 2015a; Stewart et al., 2015d). The large number of mutant strains, as well as the availability of modern genetic, optogenetic and neuroimaging tools (Kalueff et al., 2014a; Kalueff et al., 2014b; Stewart et al., 2015d; Ullmann et al., 2015; Ullmann et al., 2010), make zebrafish an excellent model for studying NDDs. For instance, zebrafish have recently been suggested as a promising model of ASD (Stewart et al., 2014b), especially as fish spent >80% of their time swimming together in shoals (Fig. 2D) and display robust kin recognition and social preference phenotypes (Kalueff et al., 2013). Similar to rodent models, zebrafish also display robust social preference, which can be easily tested in aquatic versions of social interaction and social preference paradigms discussed above for rodents (Fig. 2). Additionally, multiple pharmacological, genetic and environmental manipulations can disrupt zebrafish shoaling behavior (Stewart et al., 2014b). The ability to swim in a stereotypic manner (e.g., corner-to-corner, as after treatment with nicotine, or in tight circles, as after treatment with glutamatergic antagonists ketamine, MK-801 or phencyclidine (Stewart et al., 2015b)), raises the possibility of using zebrafish as models of repetitive behaviors, relevant to motor symptoms of ASD and other NDDs.

Despite the numerous advantages of zebrafish for developmental neuroscience, there are currently very few ADHD-related models in zebrafish. Hyperactivity is arguably the easiest ADHD-related phenotype to assess in zebrafish, presenting as increased distance travelled, velocity and movement frequency/duration in both adult (Blaser et al., 2009; Lopez-Patino et al., 2008) and larval fish (Chen et al., 2011; Norton, 2011; Saili et al., 2012; Seibt et al., 2010). Even fewer studies targeted impulsivity and inattention in zebrafish, most likely reflecting challenges of designing

specific tests (Parker et al., 2012) and the general under-appreciation of zebrafish as a behavioral model of NDDs. Several successes, however, indicate the growing potential of zebrafish models of ADHD. For example, morpholino-mediated inhibition of *nr4a2,* an ADHD-linked dopaminergic orphan nuclear receptor (Saili et al., 2012)*,* during development leads to permanent hyperactivity (Blin et al., 2008). A recently developed 5-choice serial reaction time task (5CSRTT) can measure impulsivity in zebrafish similar to rodents (Parker et al., 2014b; Parker et al., 2014c; Parker et al., 2012). To analyze the role of ADHD-linked genes in zebrafish phenotypes, the *latrophilin 3.1* (*lphn3.1*) gene has been comprehensively evaluated during zebrafish development (Lange et al., 2012b). *LPHN3* is an orphan adhesion-G protein-coupled receptor whose gene contains a variation that conveys a risk haplotype for ADHD (Arcos-Burgos et al., 2010). *latrophilin3.1* represents a zebrafish homolog of human *LPHN3*, expressed in the brain up to 6 dpf. The reduction of its function during zebrafish development by injecting morpholinos results in hyperactive phenotype of the morphants, also displaying more bursts of acceleration (increased motor impulsivity) – the two ADHD-like phenotypes rescued by anti-ADHD drugs MPH and atomoxetine (Lange et al., 2012b) (Fig. 2). Together with some other recent interesting genetic models (e.g., (Huang et al., 2015)), this illustrates the growing utility of zebrafish in modelling ADHD and other NDDs.

Chick models are also gaining popularity in neurodevelopmental research, especially since they display robust social, motor and cognitive phenotypes relevant to clinical NNDs (Fig. 2E) and demonstrate critical disease 'susceptibility' windows during the neural development (Koshiba et al., 2013a; Mimura et al., 2013; Mimura, 2013). For example, chicks display high preference for social groups (like rodents), and emit social vocalizations (e.g., 'alarm' and 'joy' calls when isolated or meeting peers, respectively (Koshiba et al., 2013c)). Social environment is particularly important for chicken normal behaviors and their overall sensitivity to environmental stressors (Koshiba et al., 2013a; Mimura et al., 2013; Mimura, 2013). For example, deficit of peer rearing affects monoaminergic systems in young chicks, evoking depressive-like behaviors (Koshiba, 2013;

Shirakawa, 2013b) and suppressing forebrain growth around critical susceptible age (Koshiba et al., 2013a).

Non-human primate models, such as those based on common marmoset (*Callithrix jacchus*), represent another promising area of NDD research (Fig. 2E). Marmosets display rich vocal communication with approximately 10 types of 'calls', likely representing (based on contexts) positive or negative emotional states (Koshiba et al., 2011; Koshiba et al., 2013b). Together with parallel assessment of vocalizations and behaviors, the socio-behavioral trajectories in marmosets have recently been studied using multivariate repression. For example, such analyses revealed important time windows around weaning, critical for establishing normal social and motor behaviors, also showing pathological hyperactivity in marmosets if reared without adequate social environment (Koshiba et al., 2013b). Light-induced disruption of the young marmoset circadian rhythm affects their adult behaviors, leading to more 'hyperactive' patterns of social and motor activity (Koshiba et al., 2015b; Senoo et al., 2011) (also see the link between marmoset emotional responses, body temperature (Karino, 2015; Koshiba, 2013; Shirakawa, 2013a) and hormones (Koshiba et al., 2011), Fig. 2E).

3. Selected emerging translational questions

A complex, systems biology-based approach that parallels clinical studies, preclinical animal models, biomarker discovery and mechanistically-driven *in-vitro* research is becoming increasingly critical for improving our understanding of brain disorders and their therapies (Cryan and Slattery, 2007; Kalueff and Stewart, 2015; Kalueff et al., 2015; Kalueff et al., 2007d; Redei et al., 2001; Stewart and Kalueff, 2015). As outlined here, marked progress in studying NDDs has been achieved through translational analyses using preclinical (animal) models and tests (Table 1) (Homberg et al., 2015). However, more work is needed in order to fully understand the pathobiology of NDDs. For example, while the opportunity of targeted genetic manipulations in mice resulted in significant advances in our understanding of genetics and biology of NDDs, the availability of genetically altered

rat models (especially due to the development of modern gene-editing approaches, such CRISPR-Cas9 or Zinc-Finger Nuclease (ZFN) technologies) may significantly further the progress in the field (Kaneko and Mashimo, 2015), (Parker et al., 2014a). Beyond their obvious advantage of larger size, rats have a wider range of well established complex behavioral paradigms (compared to mice), particularly critical to evaluate fine behaviors, cognitive function and emotionality, critical for NDD research (Parker et al., 2014a). The Panel recognizes the importance of genetically modified rats in studying a wide spectrum of NDDs and other brain disorders (Kalueff et al., 2010). Several additional, emerging challenges can be relevant to building translational bridges in this field. Thus, while we may not be able to provide definite answers to these questions at present, their discussion can benefit future studies of NDDs.

3.1. Making research more translational: from lab to bedside

Discussion of translational NDD models would be incomplete without mentioning clinical studies utilizing behavioral approaches and biomarkers similar to those developed for rodents, zebrafish, chicks and non-human primates (see above). One interesting example of such translational bridge is "reverse translation", or "bedside to bench", experiment performed in patients with psychiatric disorders (schizophrenia and bipolar disorder) by analysing their behavioural pattern of activity and directly comparing them with the behavioral pattern of mutant mice (e.g., hyperactive DAT knockouts) recorded in similar conditions (Perry et al., 2009), (Perry et al., 2010). Such *translational* angle is also important given the need to develop 'early' and 'very early' behavioral and physiological biomarkers of clinical NDDs. For instance, multivariate analyses of neurological development across age in normal infants vs. infants with aberrant neural development shows correlation of physiological biomarkers (blood and brain imaging data) with specific behavioral phenotypes, such as head control and rolling behavior (Fig. 2F) (Koshiba et al., 2015a). This raises the possibility of using such phenotypes as potential 'early' behavioral biomarkers of NDDs (Koshiba et al., 2015a), crucial in the absence of other, more complex behaviors to aid diagnostics. This is

particularly important because early neural development represents a critical window for maximizing the success of therapeutic intervention. Finally, the development of video-tracking and other behavior-recording methods (e.g., those utilizing smart phones (Mimura et al., 2015)) to study older children and adults further fosters NDD research and extraction of novel behavioural biomarkers (Fig. 2F).

3.2. Moving from single- to poly-phenotype models

As already mentioned, the majority of NDDs are multi-factorial brain illnesses with many genetic and environmental determinants. Therefore, a conceptual approach deconstructing these disorders into simpler and easily quantifiable phenotypic units ('endophenotypes') is a reasonable strategy (Gottesman and Gould, 2003; Gould and Gottesman, 2006; Lenzenweger, 2013). The endophenotype concept has been successful in dissecting various brain disorders, their overlapping and unique symptoms, as well as candidate biomarkers and genes across the disorder spectrum (Courtet et al., 2011; Crossley et al., 2014; Ikeda et al., 2013; Ivleva et al., 2010); also see (Kalueff et al., 2008b; Kalueff and Stewart, 2015; Kalueff et al., 2015; LaPorte et al., 2010; Stewart and Kalueff, 2015) for detailed discussion. Recognizing that multiple phenotypes can be shared by several distinct disorders, such strategy is in line with the recently suggested research domain criteria, RDOCs (Casey et al., 2013; Cuthbert and Insel, 2010; Insel et al., 2010; Insel, 2014) that target phenotypic dimensions, rather than categories, of psychiatric diagnoses (Gottesman and McGue, in press; Kalueff et al., 2015). However, in parsing individual endophenotypes *across* and *within* the disorders in both clinical and preclinical models, the predominant focus of biological psychiatry continues to be narrow and phenotype-centered (Ditzen et al., 2012; Filiou et al., 2011; Gormanns et al., 2011; Kalueff et al., 2008b; Maccarrone et al., 2013). From a conceptual standpoint, if a CNS disorder consists of several distinct endophenotypes A, B and C, then focusing on clinical and preclinical models or tests that target more than one endophenotype (e.g., A and B or A, B and C) is better than using experimental models or clinical studies that assess only one. Using ASD as an example, an animal model is likely

more valid if it assesses both social deficits and behavior perseverations, as compared to a model with only one aberrant phenotype. A growing number of studies are already embracing this approach, monitoring several distinct endophenotypes of a disorder and discovering their biomarkers and potential treatments (Amodeo et al., 2014; Burket et al., 2013; Kalueff et al., 2015; Pearson et al., 2011; Reynolds et al., 2013; Silverman et al., 2010a) (Fig. 4). The main challenge, however, is that it may be insufficient to dissect 'unique' molecular mechanisms of endophenotypes A, B and C from their 'shared' pathways (e.g., A+B or B+C) because, as suggested recently (Kalueff et al., 2014c; Kalueff et al., 2015), principally novel genetic and molecular 'cross-talk' pathways may underlie the pathogenetic coupling of such endophenotypes (e.g., 'A<->B' or 'B<->C') without affecting each endophenotype *per se* (Fig. 4). Remaining to yet be established, the putative mechanisms by which such novel classes of genes act, may include synchronizing or synergizing several distinct disordered processes (Stewart et al., 2015c). Applying this concept to NDDs, it is possible that in clinical or experimental ASD, social deficits can be pathogenetically linked to repetitive behaviors via cross-talk molecular mechanisms. Likewise, in addition to its hallmark symptoms - hyperactivity and attention deficit – ADHD may rely on additional molecular networks integrating the two endophenotypes together, thus making it the single well-defined clinical disorder. Complementing current theories of NDDs, the pathological linkage between several distinct disordered endophenotypes, in addition to focusing on them separately or in combination, merit further scrutiny (Fig. 4). For example, this can be achieved by applying a network-based 'cloud' approach to modeling NDDs, where individual endophenotypes (as well as biomarkers and disorders) are not only assessed in clinical and preclinical studies individually or in combinations, but are assessed by novel linkages between them (Fig. 4). Based on this rationale, clinical cases with two synchronized phenotypes (e.g., repetitive behaviors and social deficits in ASD) may demonstrate a stronger (and, therefore, more debilitating or treatment-resistant) NDD, compared to cases when core endophenotypes are expressed in less organized manner (Fig 4, therefore, implying their weaker pathogenetic integration and less

pronounced overall pathogenesis). Clearly, this necessitates further integrative clinical studies and respective innovative preclinical models of NDD pathogenesis.

3.3. Monoamines as neurotrophic factors: lessons from serotonin

While brain neurotransmitters play a key role in NDDs, it is often overlooked that in early development they also act as neurotrophic factors (Homberg et al., 2010). As one illustrative example, consider the serotonergic system − a target of many pharmaceutical agents (e.g., antidepressants and antipsychotics) used to treat NDDs, with multiple genetic polymorphisms conferring the risks for NDDs (Lesch and Waider, 2012). Although the precise role of serotonin in NDDs is not fully understood, it mediates aversive processing (Deakin and Graeff, 1991), behavioral inhibition (Cools et al., 2008) and social behavior (Kiser et al., 2012), which are often affected in NDDs. The common underlying function of serotonin may be the modulation of sensitivity to environmental stimuli (Homberg, 2012), a role mostly ascribed to serotonin acting as a neurotransmitter. However, serotonin also acts as an important neurotrophic factor during early development (Gaspar et al., 2003), and may shape brain circuits involved in these processes. The latter function is likely to be critical for NDDs.

Serotonin is first generated in the developing brain at mid-gestation, by serotonergic neurons in the raphe nuclei of the brainstem, mediated by the neuronal isoform tryptophan hydroxylase 2 (TPH2) (Gaspar et al., 2003). Serotonin is synthesized from the essential amino acid tryptophan and packed into vesicles by vesicular monoamine transporter (VMAT), whereas SERT is responsible for the reuptake of serotonin into the presynaptic nerve terminal, and thereby determines synaptic serotonin levels (Kriegebaum et al., 2010). During development, circulating serotonin of gastrointestinal, placental and maternal origins produced by peripheral isoform TpH1 penetrate into the developing brain (Bonnin and Levitt, 2011). There it influences developmental processes, including cell division, differentiation and migration (Gaspar et al., 2003). These developmental processes may also involve non-serotonergic neurons, since SERT is transiently expressed in non-

serotonergic cells in the brain during development (Homberg et al., 2010). Indeed, SERT is expressed in specific sets of glutamatergic neurons in the thalamus and in thalamocortical projection neurons, as well as in prefrontal cortex and hippocampus, and takes up extrasynaptic serotonin during perinatal CNS development, until approximately P14 (corresponding to the third trimester of human pregnancy) (Gaspar et al., 2003). This serotonin is expected to be derived from serotonin-producing raphe neurons traveling a long distance in the developing brain (Kullyev et al., 2010). The role of SERT in glutamatergic thalamocortical neurons is particularly well established, as SERT regulates sensory map architecture (Chen et al., 2015). For example, knockout of SERT in these neurons causes lasting alterations in thalamocortical axon patterning, spatial organizations of cortical neurons and dendritic arborization in sensory cortex (Gaspar et al., 2003). These developmental effects of serotonin are specific for non-serotonergic neurons, since SERT knockdown in serotonin-producing neurons does not impair barrel maps (Chen et al., 2015). Likewise, excessive serotonin levels in SERT knockout rats is associated with disrupted topographic patterning of both the barrel and visual cortex (Cases et al., 1996; Miceli et al., 2013; Murphy and Lesch, 2008; Persico et al., 2001). In addition, the outgrowth of raphe neurons to the prefrontal cortex and cortical layering are altered in SERT knockout rodents (Altamura et al., 2007; Witteveen et al., 2013). Behaviorally, SERT knockout is consistently associated with anxiety-like behavior (Kalueff et al., 2010) and impaired social interactions (Kiser et al., 2012), symptoms that are key to NDDs. In contrast, behavioral inhibition is reduced in rodents lacking SERT (Holmes et al., 2002; Homberg et al., 2007a). Thus, there is strong but indirect evidence that serotonergic genetic variance modulates neurodevelopmental processes involved in the pathogenesis of NDDs. In rodents, administration of SSRIs during pregnancy and during the first 2 postnatal weeks reduces social play in rats and alters sensory processing, cortical wiring and myelin sheet formation (Simpson et al., 2011; Xu et al., 2004). These findings resemble those associated with ASD (Deoni et al., 2015; Zikopoulos and Barbas, 2010) and SERT in rodents (Homberg et al., 2007b). SSRI exposure decreases cortical dendritic arbor

complexity prenatally (Chameau et al., 2009; Smit-Rigter et al., 2012) while during P2-P11 it decreases dendritic complexity in the prefrontal cortex and evokes anxiety-like behavior (Rebello et al., 2014) (similar to SERT knockout rodents (Kalueff et al., 2010)). Thus, further research is needed to examine both the neurotransmitter and neurotrophic roles of serotonin and other brain neuromediators in NDD pathogenesis.

3.4. Understanding gene-environment correlations and environmental enrichment

Another problem to address in future translational studies is the potentially self-perpetuating nature of NDDs (Fig. 2B). For example, since aberrant neural development often results in debilitating NDD behavioral symptoms (e.g., social, cognitive or motor deficits) from early childhood, this disrupts normal social and affective interactions of an affected individual with their social environment (Fig. 2C). Accordingly, this can increase risks of the environment becoming more adverse for affected individuals. Because healthy social/environmental stimulation is important for shaping neural plasticity in maturing brain and for developing efficient behavioral adaptations from early age, the evoked social/environmental adversity may further impair neural development, worsening the existing NDD by creating a pathogenetic 'vicious circle' (Fig. 2). The recognition that the individual's exposure to the environment can be a function of their genotype, called Gene-Environment *correlations* (Jaffee and Price, 2007), is relatively recent in biological psychiatry. Conceptually, it complements the widely accepted notion of Gene x Environment *interactions* (GxE), which reflect how genotypes modify the sensitivity to environmental factors (Duncan et al., 2014; Kalueff et al., 2007d; Le Strat et al., 2009). Highly relevant to NDD pathogenesis, the Gene-Environment correlations (Fig. 2C) may have multiple clinical implications. For example, correcting behavioral strategies (e.g., pharmacologically or behaviorally) in ASD or ID children can improve their interaction with social environment at a 'critical' early age. Moreover, educating parents and peers on how to best deal with special needs patients can improve their integration into the society, therefore reducing 'early' environmental adversity. Collectively, this may not only improve clinical

symptoms of the existing NDD, but, in parallel, prevent the risks of additional (e.g., stress/adversity-triggered) neurodevelopmental deficits (Fig. 2C). From a practical standpoint, a potential strategy to target Gene-Environment *correlations* in experimental models of NDDs can involve correlational analyses of social components displayed by multiple individuals in social interactions. Improvement of software tools to analyze social interactions of multiple animals in detail (e.g., assessing social components sequentially with a high time- and space- resolution) may significantly empower the assessment of Gene-Environment *correlations* in biological experiments. As the concept of Gene-Environment *correlations* is gaining more recognition in neuropsychiatry (Jaffee and Price, 2007), the development of their experimental preclinical models may represent an important and novel strategic direction of NDD research (Homberg et al., 2015).

Paralleling clinical data on positive effects of cognitive and behavioral therapy in various NDDs (e.g., (Morand-Beaulieu et al., 2015), (Boyer et al., 2015)), the ability of early environmental interventions to reverse or rescue aberrant phenotypes in animal models of NDDs is particularly interesting (Nithianantharajah and Hannan, 2006). For example, *Fmr1*-knockout mice, a model of FXS, display hyperactivity and a lack of habituation that is rescued in animals raised in an enriched environment (Restivo et al., 2005). In mice deficient for *Mecp2*, a genetic model of Rett syndrome, early environmental enrichment rescued memory deficits, motor coordination and anxiety-like behaviors in a sex-specific manner (Lonetti et al., 2010), whereas environmental enrichment reversed the increase in repetitive self-grooming behavior in BTBR mice (Reynolds et al., 2013). Taken together, these preclinical studies further support the need to investigate a possible role for environmental treatments in alleviating the symptoms of NDDs.
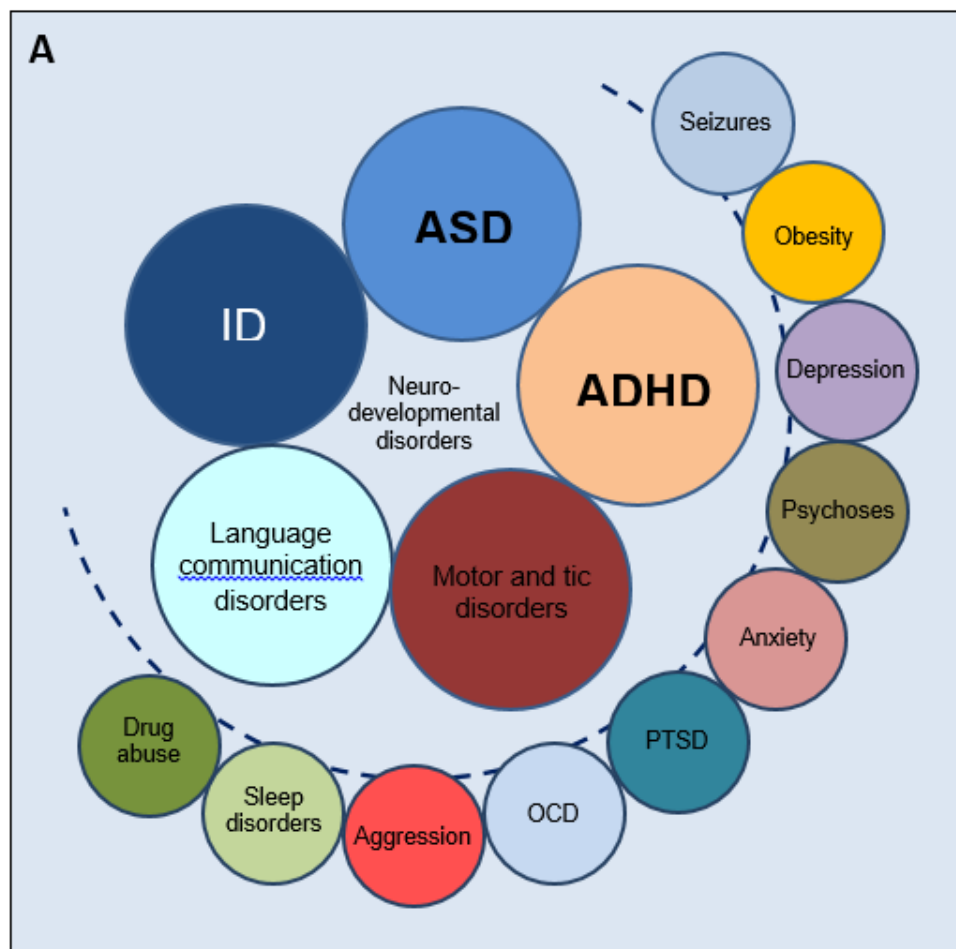
4. Conclusion

In summary, while NDDs are triggered by aberrant neural development, their pathogenesis involves a complex interplay between developmental, genetic, endocrine, immune and neural abnormalities. The extensive research covered here illustrates the existing challenges in identifying

the neurobiological basis as well as clarifying susceptibility, resilience and strategies for novel effective treatments of NDDs.

As already emphasized, both traditional 'rodent' mouse and rat models (extensively used in NDD research) are also increasingly complemented by the growing spectrum of alternative model organisms, including zebrafish, chicks and non-human primates. Overall, experimental animal models are critical to increase our understanding of NDDs, including studying behavior, neuronal morphology and gene expression patterns across developmental stages before and during the manifestation of disorders-related symptoms (Homberg et al., 2015). In addition, preclinical models permit the functional assessment of the impact of genes and gene networks at the level of genetic, synaptic and neuronal networks of cognition, behavior and neural systems. Paralleling clinical findings, such models begin to play a more critical role in gaining translational and mechanistic insights into NDD pathogenesis.

Figure 1. The spectrum nature of neurodevelopmental disorders (NDDs). Panel A presents the spectrum of neurodevelopmental and other associated disorders. **Panel B** shows phenotypic domain structure and heritability of common NDDs (red – reduced, green – increased; also see Table 1). ASD – autism spectrum disorder, ID – intellectual disabilities, ADHD – attention deficit hyperactivity disorder, OCD – obsessive compulsive disorder, PTSD – post-traumatic stress disorder. **Panel C** summarizes the temporal dynamics of key neuronal processes related to neural development. **Panel D** illustrates typical onset of selected common neurodevelopmental disorders.

B

Major affected behavioral domains

Disorders	Language	Social interest	Repetitive behavior	Cognitive function	Locomotor activity
Communication	↓				
ID	↓	↓		↓	
ASD	↓	↓	↑		
ADHD			↑	↓	↑
Motor/Tic			↑		

Heritability estimates

High

Medium

Low

Communication   ID   ASD   ADHD   Tics

C

Neurodevelopmental events

Proliferation

Migration

Synapse formation

Myelination

Neurogenesis

Prenatal   Days   Weeks   Months   Years

Postnatal (*continues into adulthood)

D

ASD, Tic disorders, ID, Communication disorders

ADHD

<1 year   1-6   6-13   13-19   20-25   >25 years

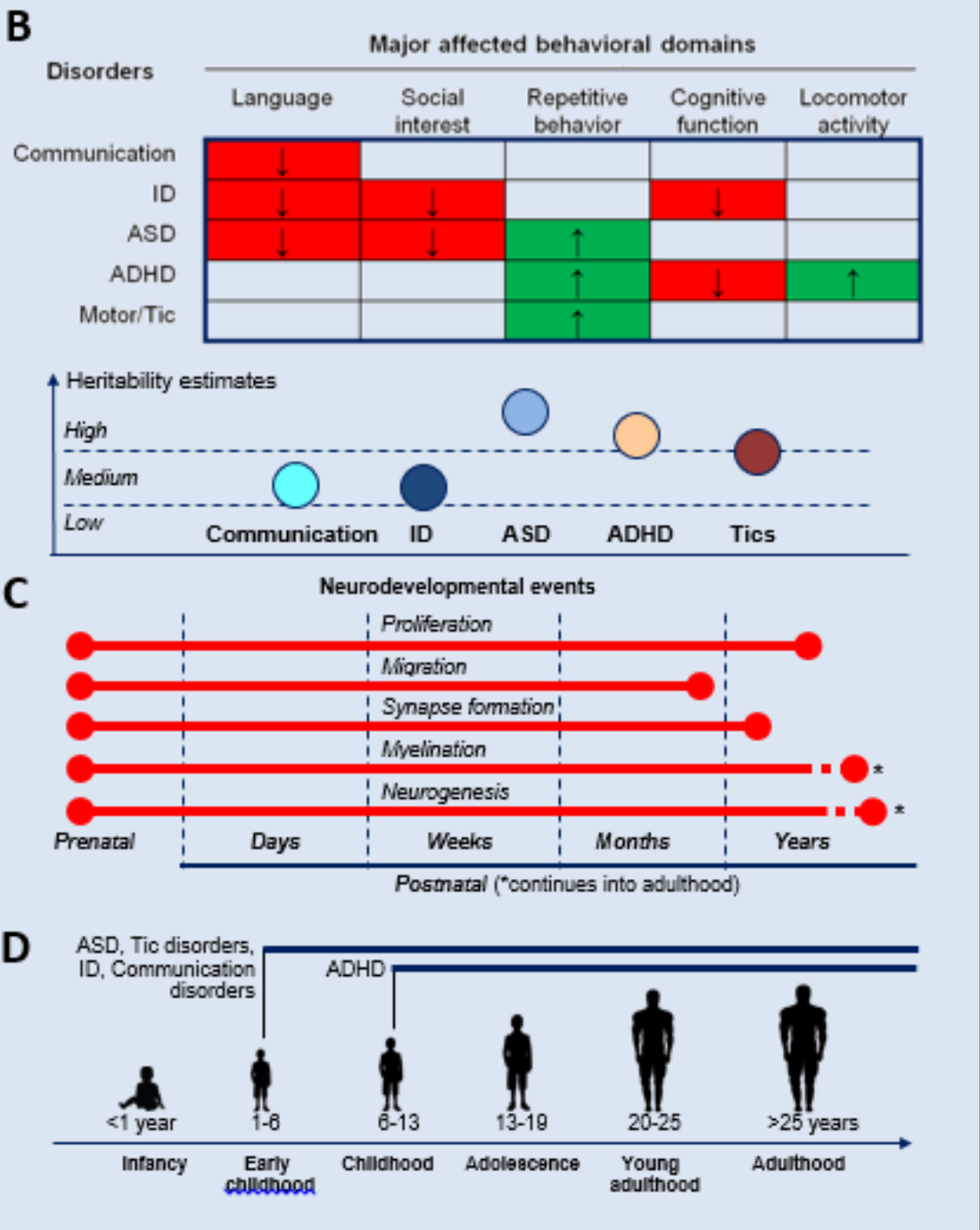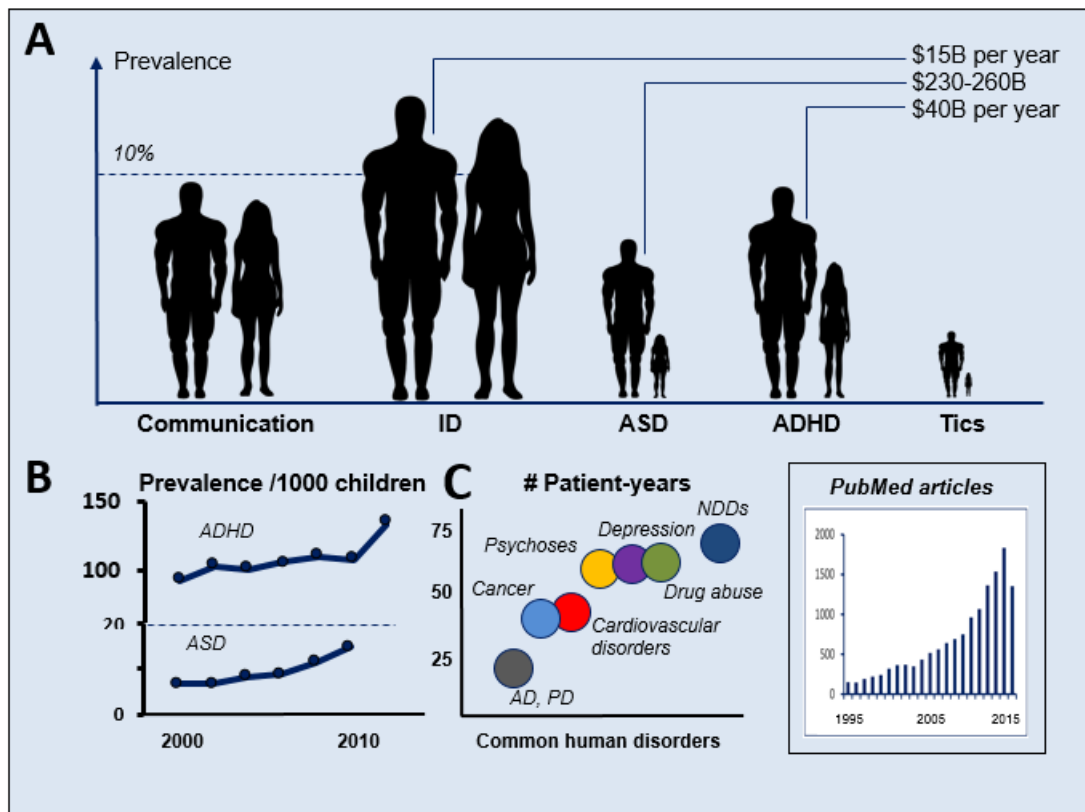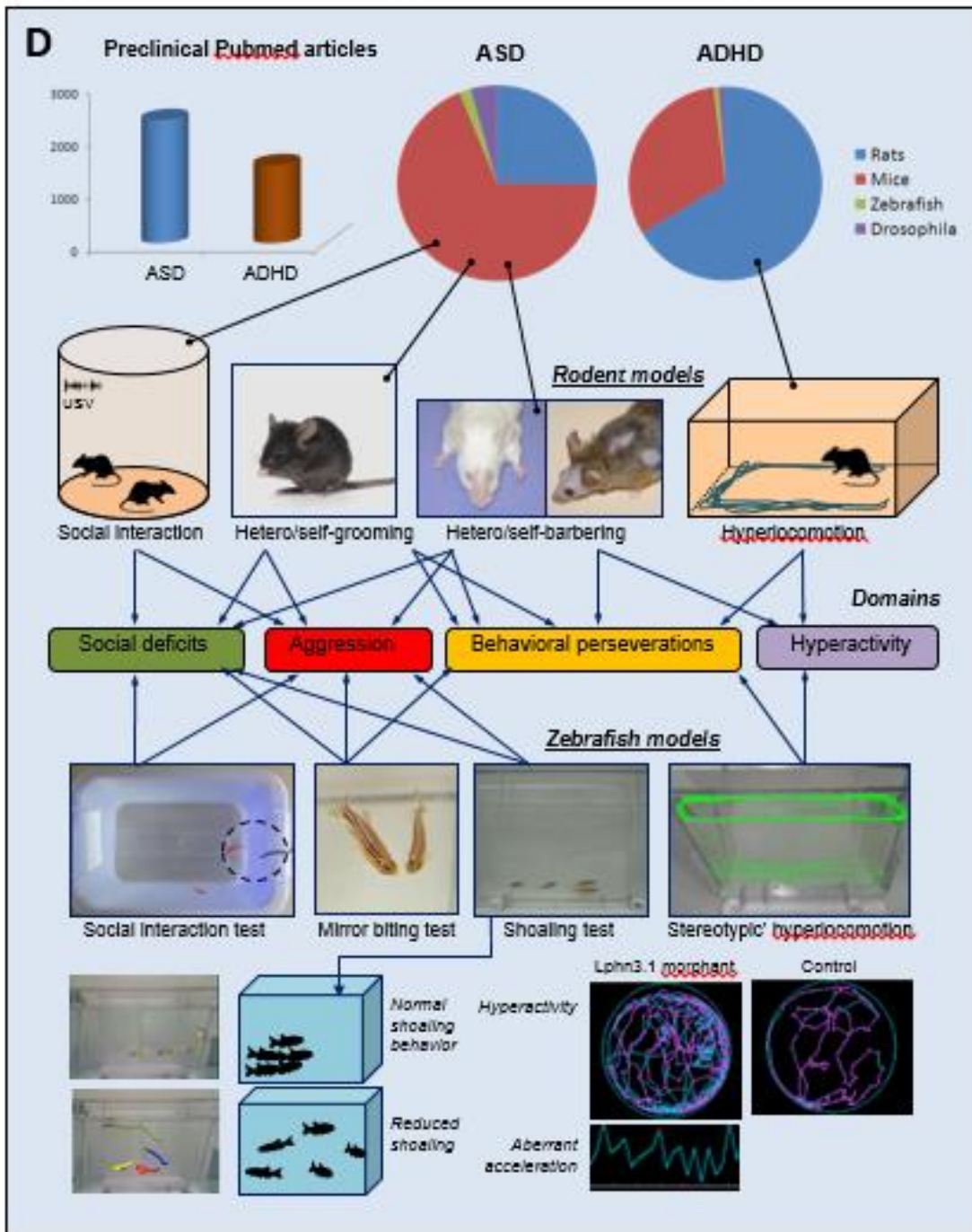Infancy   Early childhood   Childhood   Adolescence   Young adulthood   Adulthood

Figure 2. The growing clinical and preclinical importance of neurodevelopmental disorders (NDDs). Panel A demonstrates global prevalence of NDDs and their costs (USA, $B per year; Center for Disease Control/CDC, 2014). **Panel B** shows rapid growths in occurrence of NDDs, such as ASD and ADHD, in the last decade (ASD data represent prevalence in 8 year olds (2015) and ADHD data represent prevalence in children 3-17 years old (Bloom et al., 2013)). **Panel C** shows the relative 'health burden' of NDDs and other common human disorders, calculated as year-patients since the disorders' onset and based on average life expectancy of 80 years (AD – Alzheimer's disease, PD – Parkinson's disease). Note that NDDs are among the most impactful disorders. Inset: the rapidly expanding biomedical research on NDDs in the last 20 years, based on Pubmed article search for 'neurodevelopmental' (December 2015). **Panel D** shows popular model organisms used in translational research on NDDs, and relevance of rodent and zebrafish behaviors to various phenotypic domains of these disorders. Rodent models of NDDs have been extensively discussed in the text. Note overt social, locomotor and repetitive (e.g., grooming, hetero- and self-barbering (Kalueff et al., 2007a; Kalueff et al., 2006)) behaviors in rodents. Illustrating the value of zebrafish models for NDDs, the bottom left section shows normal and aberrant ASD-like zebrafish shoaling behaviors (Stewart et al., 2014b). Botom right section illustrates an ADHD-related zebrafish model based on morphants with rediced fucntion of *lphn3*.1 gene encoding latrophilin 3 (note overall baseline hyperactivity associated with impulsive-like acceleation bursts, accompanied by reduced and mislaced dopaminergic neurons in the ventral diencephalon) (Lange et al., 2012a, c). **Panel E** illustrates social and cognitive behavioral tests used in preclinical NDD models based on domestic chicks (Koshiba et al., 2013a; Koshiba et al., 2013c; Koshiba, 2013; Mimura et al., 2013; Mimura, 2013; Shirakawa, 2013b) and common marmosets (Karino, 2015; Koshiba et al., 2011; Koshiba et al., 2015b; Koshiba et al., 2013b; Senoo et al., 2011; Shirakawa, 2013a). Paralleling human clinical studies in preterm infants and juveniles (Koshiba et al., 2015a; Koshiba et al., 2013b; Koshiba, 2013), such models can also enhance biomarker discovery. For example, the posterior-lateral forebrain

serotonin metabolite, 5-hydroxyindolacetic acid (5HIAA), correlates with chick freezing behavior (Koshiba, 2013; Shirakawa, 2013a), whereas emotional phenotypes in common marmosets correlate with venous blood progesterone in female adult common marmosets (Koshiba et al., 2011). **Panel F** illustrates several examples of clinical models of NDDs based on behavioral analyses (similar to those developed for non-human model organisms), including studying head control and body rolling in normal and neurologically affected infants or using computer games in older children (top row) (Koshiba et al., 2013b) and behavioral video-tracking of social and locomotor activity in normal vs. autistic 2-year old children (bottom row), image courtesy of Noldus IT (Netherlands).

D Preclinical Pubmed articles

ASD   ADHD

Legend: Rats, Mice, Zebrafish, Drosophila

Rodent models

USV

Social interaction — Hetero/self-grooming — Hetero/self-barbering — Hyperlocomotion

Domains

Social deficits | Aggression | Behavioral perseverations | Hyperactivity

Zebrafish models

Social interaction test — Mirror biting test — Shoaling test — Stereotypic' hyperlocomotion

Normal shoaling behavior

Reduced shoaling

Hyperactivity

Aberrant acceleration

Lphn3.1 morphant   Control

E Chick models: social isolation

Typical chick group behavior

Isolation > Group

Brain 5-HIAA

Distress vocalizations

escape zone / Others / Center / g-move zone

Freezing behavior

Primate models: common marmoset social interaction

emotional index

[μg/mL] progesterone

F Clinical models: infants and children

Rolling over behavior
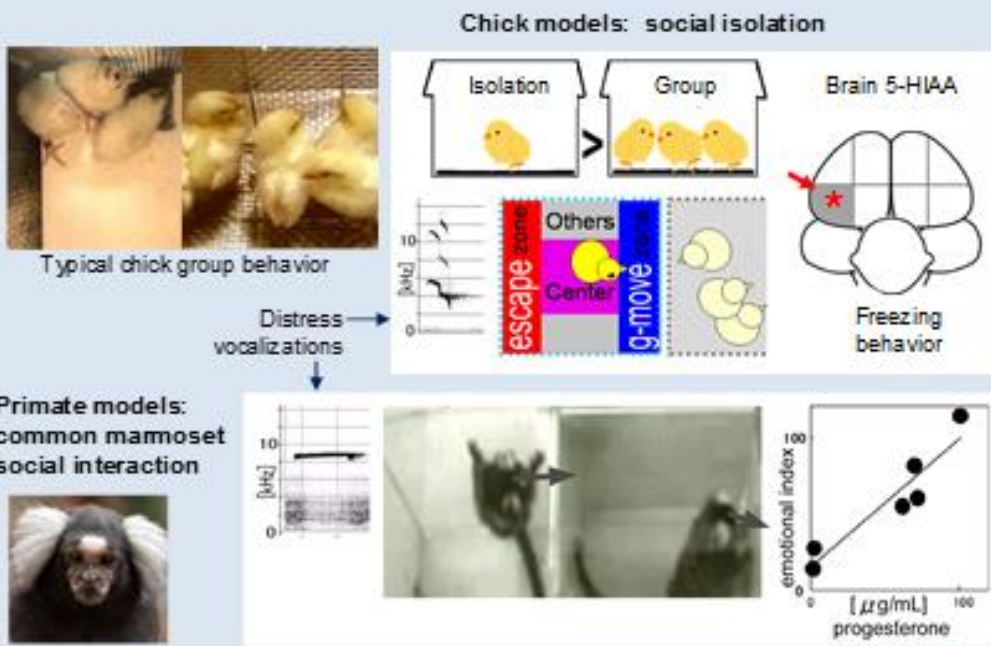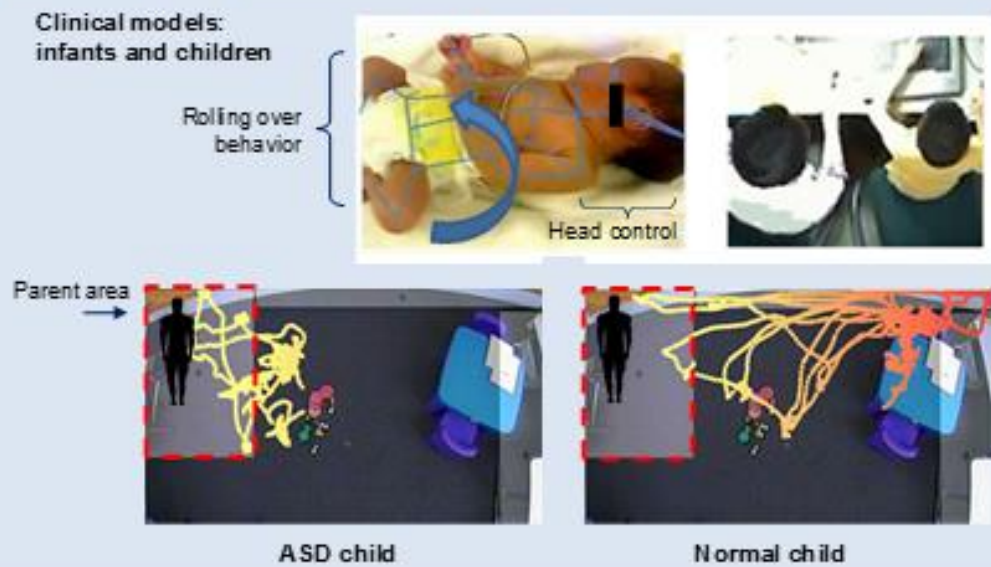
Head control

Parent area

ASD child

Normal child

Figure 3. The concepts of Gene x Environment interactions (GxE) and Gene-Environment correlations (G-E), as well as their potential implications for NDDs and their experimental animal models.
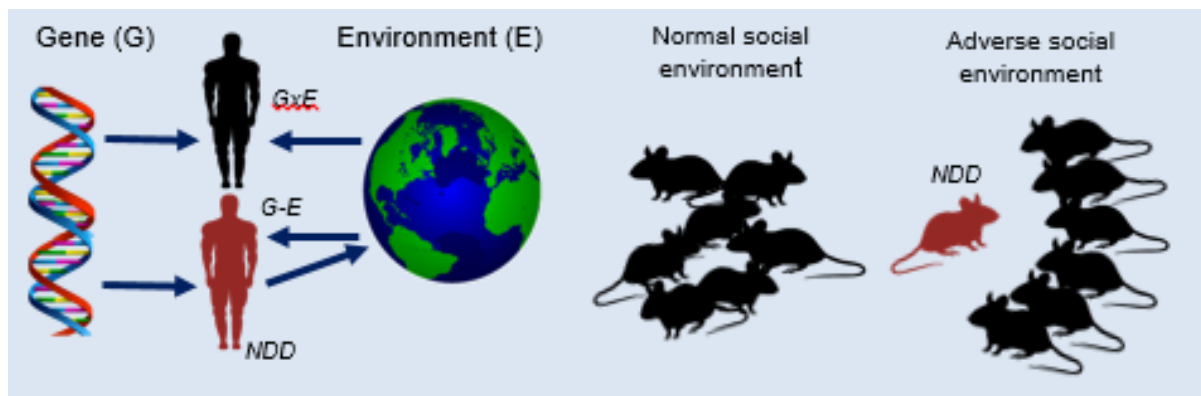
Figure 4. The proposed 'integrative' strategy for modeling of neurodevelopmental disorders (NDDs). NDDs usually consist of several 'core' symptoms (endophenotypes, e.g., A and B). **Panel A** shows 'early' experimental models of brain disorders that focus on targeting individual endophenotypes A or B, and more recent complex models examining several endophenotype and their respective biomarkers in parallel (A+B vs. A vs. B). As an example here, we use the mouse autism-like behaviors (endophenotype A – behavioral perseverations/self-grooming, endophenotype B – social deficit). In addition, we suggest that a network-like 'cloud' approach must be used to link disordered endophenotypes between themselves (i.e., A<->B vs. A+B vs. A vs. B), in order to identify their "interplay" genes and biomarkers, in addition to those 'unique' and 'shared' between them. For example, a disorder with stronger synchronization of endophenotypes A and B is likely to be more severe and treatment-resistant, as compared to a disease with similar 'amplitude' of endophenotypes, but the lack of their correlation. **Panel B** illustrates the importance of tracking the activity of all proposed genetic networks across ontogenesis, as different subgroups of genes (A-specific, B-specific, and 'interplay' A<->B genes may show distinct pattern of gene activity/expression (Y-axis) during neural development (X-axis). Circles represent the severity of phenotype expression (note that subtypes of severe NDDs may include cases of mild but tightly coordinated disordered endophenotypes, as well as strongly affected but relatively moderately coordinated/overlapping endophenotypes).
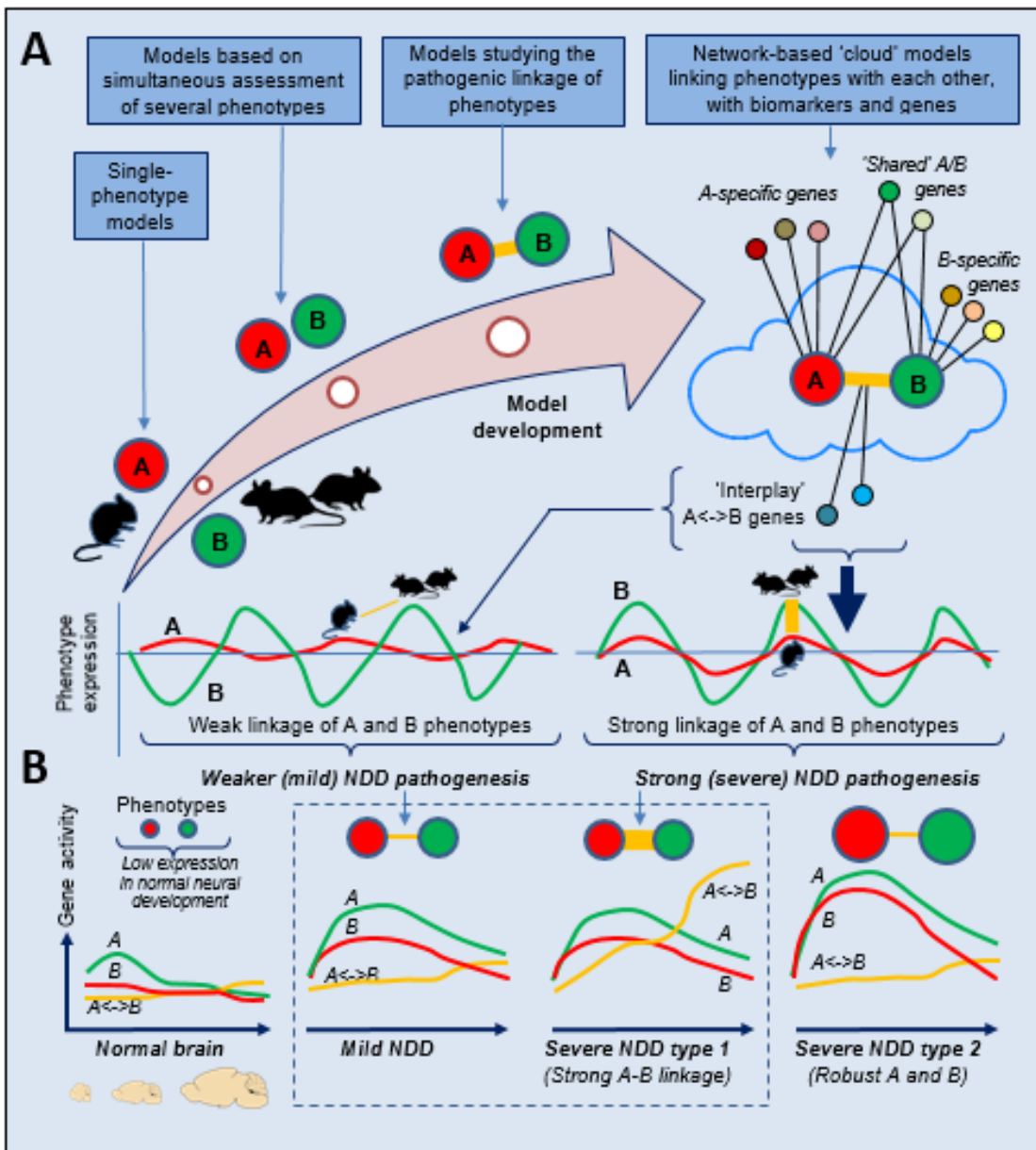
A

Models based on simultaneous assessment of several phenotypes

Models studying the pathogenic linkage of phenotypes

Network-based 'cloud' models linking phenotypes with each other, with biomarkers and genes

Single-phenotype models

A-specific genes

'Shared' A/B genes

B-specific genes

A   B

Model development

'Interplay' A<->B genes

Phenotype expression

A

B

Weak linkage of A and B phenotypes

B

A

Strong linkage of A and B phenotypes

B

Weaker (mild) NDD pathogenesis

Strong (severe) NDD pathogenesis

Gene activity

Phenotypes

Low expression in normal neural development

A
B
A<->B

Normal brain

A
B
A<->B

Mild NDD

A<->B
A
B

Severe NDD type 1
(Strong A-B linkage)

A
B
A<->B

Severe NDD type 2
(Robust A and B)

39

Table 1. Neurodevelopmental disorders currently listed in Diagnostic Statistical Manual (DSM-5) (American Psychiatric et al., 2013)**, also see Table 2**

Disorders and their main symptoms	Availability of animal models
Intellectual Disabilities (ID) – impairment of mental functions in conceptual (language, reading, writing, mathematics, memory, insight, knowledge, interpretation), social (empathy, compassion, social judgment, communication and interaction skills, amicability, harmony) and practical (personal care, school and/or occupational responsibilities and organization, financial management, entertainment, hobby) aspects, including: Intellectual Disability (Intellectual Developmental Disorder), Global Developmental Delay, Unspecified Intellectual Disability (Intellectual Developmental Disorder)	+
Communication Disorders (CD) – difficulties in language, speech, phonetic fluency or social communication, including: Language Disorder, Speech Sound Disorder, Childhood-Onset Fluency Disorder (Stuttering), Social (Pragmatic) Communication Disorder, Unspecified Communication Disorder	Not feasible
Autism Spectrum Disorder (ASD) - persistent reciprocal social deficits (communication and interaction), and restricted, repetitive patterns of behavior, interests or thoughts	+
Attention-Deficit/Hyperactivity Disorder (ADHD) - a pattern of inattention and/or hyperactivity-impulsivity, including: ADHD, Other Specified and Unspecified ADHD	+
Specific Learning Disorder - difficulties learning skills like reading, writing, spelling, mathematic calculations, etc.	Not feasible
Motor Disorders (MD) – impairments of execution of coordinated motor skills, or repetitive motor behaviors, including: Developmental Coordination Disorder, Stereotypic Movement Disorder	+
Tic Disorders (TD) - habitual motor movements or vocalizations which are sudden, rapid, recurrent and non-rhythmic, including: Tourette's Disorder, Persistent (Chronic) Motor or Vocal Tic Disorder, Provisional Tic Disorder, Other Specified and Unspecified Tic Disorders	+
Other Neurodevelopmental Disorders	?

Table 2. Selected animal (rodent) models of neurodevelopmental disorders, abbreviations as in Table 1 (also see Fig. 2 and Table 3) (Homberg et al., 2015).

Animal (rodent) model	Ease to perform	Throug hput	Affected domain/phenotype	Clinical relevance
Social interaction test	++	+	Social deficit*/**	Social deficit in ASD
Social preference test	++	+	Social deficit*	Social deficit in ASD
Social recognition	+	+	Social deficit*	Social deficit in ASD, ID
Open field test	+++	+++	Hyperlocomotion*	Hyperactivity in ADHD
Homecage observation	++	+	Hyperlocomotion*	Hyperactivity in ADHD
Various memory tests	++	+	Cognitive deficits*	Cognitive deficits in ID and ADHD
Various attention tests	+	+	Attention deficits	Attention deficits in ADHD
Various impulsivity tests	+	+	Increased impulsivity	Increased impulsivity in ADHD
Self-grooming test	+++	+++	Increased grooming	Behavioral perseverations in ASD, TD
Hetero-grooming	++	+	Aberrant grooming	Social deficits in ASD, ID
Self-barbering test	++	+	Hair-loss (barbering)	Behavioral perseverations in ASD, TD
Hetero-barbering	++	+	Hair-loss (barbering)	Social deficits in ASD, ID
Open field test	+++	+++	Increased stereotypies*	Behavioral perseverations in ASD
Aggression test	++	+	Increased aggression**	Aggression in ID, ADHD
Marble burying test	+++	+++	Increased burying	Behavioral perseverations in ASD
Homecage observation	++	+	Increased stereotypies*	Behavioral perseverations in ASD
Startle test	+++	+++	Aberrant startle*	Altered cognition in ADHD and ID
Ultrasonic vocalizations	+	++	Aberrant vocalization	Social deficits in ASD, ID or CD

* denotes the availability of similar tests in alternative model organisms, such as zebrafish (Fig. 2)

** also see shoaling test and mirror biting test in zebrafish (Green et al., 2012; Miller et al., 2013) (Fig. 2D)

Table 3. Tests used to measure the neural development and behavior of young rodents (Homberg et al., 2015).

Tests	System measured	Age of testing	Referen-ces
Simple Reflexes			
Pupillary constriction	Sensorimotor	PND12 to appearance	(Crofton, 1992)
Salivation	Sensorimotor	PND2 to appearance	(Crofton, 1992)
Lacrimation	Sensorimotor	PND2 to appearance	(Crofton, 1992)
Acoustic startle	Auditory, Motor	PND6 to appearance	(Fox, 1965)
Forelimb grasp reflex	Somatic, Motor	PND2 to appearance	(Blaney et al., 2013; Fox, 1965)
Hindlimb grasp reflex	Somatic, Motor	PND2 to appearance	(Amendola et al., 2004; Blaney et al., 2013; Fox, 1965)
Loss of crossed-extensor reflex	Somatic, Motor	PND2 to disappearance	(Blaney et al., 2013; Fox, 1965)
Loss of rooting response	Somatic, Motor	PND2 to disappearance	(Fox, 1965; Roubertoux et al., 1987)
Vibrissae response	Somatic, Motor	PND2 to appearance	(Amendola et al., 2004; Blaney et al., 2013; Fox, 1965)
Sensory and motor			
Reflex modification	Visual, Auditory, Olfactory, Somatic	PND 14-onwards	(Wecker et al., 1985)
Cliff avoidance	Visual: depth perception	PND 14-onwards	(Fox, 1965)
Visual placing test	Visual, motor coordination	PND14-onwards	(Pinto and Enroth-Cugell, 2000)
Olfactory discrimination	Olfaction	After weaning	(Brown and Willner, 1983)
Swimming test	Vestibular, Neuromotor coordination	After weaning	(Kalueff et al., 2004)

Negative geotaxis	Vestibular, Neuromotor coordination	PND2-onwards	(Blaney et al., 2013; Fox, 1965)
Surface righting	Vestibular, Neuromotor coordination	PND 2-onwards	(Amendola et al., 2004; Fox, 1965)
Mid-air righting	Vestibular, Neuromotor coordination	PND2-onwards	(Fox, 1965)
Hindlimb splay	Vestibular, Neuromotor coordination	PND2-onwards	(Broxup et al., 1989; Moser et al., 1988)
Gait analysis	Neuromotor coordination	After weaning	(Wooley et al., 2005)
Rotarod, accelerod	Neuromotor coordination	After weaning	(Van Raamsdonk et al., 2005)
Horizontal rod test	Vestibular, Neuromotor coordination	After weaning	(Kalueff et al., 2008a)
Forelimb grip strength test	Neuromotor coordination, muscle strength	PND2-onwards	(Blaney et al., 2013)
Nest building test	Neuromotor coordination	After weaning	(Kalueff et al., 2007b)
Rope climbing test	Neuromotor coordination, muscle strength	After weaning	(Kalueff et al., 2007b)
Vertical screen test	Neuromotor coordination, muscle strength	After weaning	(Kalueff et al., 2004)
Self-grooming test	Neuromotor coordination, muscle strength	After weaning	(Kalueff and Tuohimaa, 2004a, 2005a)
Open Field	Locomotor activity	PND12-onwards	(Alleva et al., 1985; Blaney et al., 2013)

Cognitive tests

Olfactory conditioning	Learning and memory	PND6 onwards	(Sullivan and Wilson, 1995)
Neonatal T-maze	Learning and memory	PND9-onwards	(Nagy et al., 1976)
Hebb Williams Maze	Learning and memory	After weaning	(Hebb and Williams, 1946; Pritchett and Mulder, 2004)
Morris water maze	Learning and memory	After weaning	(Morris, 1984)
Passive avoidance test	Learning and memory	After weaning	(Cuomo et al., 1996)
Active avoidance test	Learning and memory	After weaning	(McNamara et al., 1977)
Operant conditioning schedules	Learning and memory	After weaning	(Cuomo et al., 1996)
Homing test	Learning and memory	PND14-onwards	(Alleva et al., 1985; Fox, 1965)
Object recognition test	Learning and memory	PND22-onwards	(Blaney et al., 2013)

Social/ Emotional

Ultrasonic vocalization	Anxiety, sociability	PND2-onwards	(Bolivar and Brown, 1994; Scattoni et al., 2009)
Elevated plus maze	Anxiety	After weaning	(Cuomo et al., 1996)
Black and white transition test	Anxiety	After weaning	(Crawley, 1981)
Social interaction test	Anxiety, sociability	After weaning	(Crawley, 1981)
Self-grooming analysis	Anxiety, repetitive behavior	After weaning	(Kalueff et al., 2007a; Kalueff and Tuohimaa, 2004b)
Suok test	Anxiety, motorisensory integration	After weaning	(Kalueff et al., 2008a; Kalueff and Tuohimaa, 2005b)
Social preference test	Sociability	After weaning	(Ricceri et al., 2007; Silverman and Crawley, 2014)

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