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Behavioral and Neuroanatomical Approaches in Models of Neurodevelopmental Disorders: Opportunities for Translation

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Abstract

Purpose of review—This review highlights the invaluable contribution of *in vivo* rodent models in dissecting the underlying neurobiology for numerous neurodevelopmental disorders. Currently, models are routinely generated with precision genomics and characterized for research on neurodevelopmental disorders. In order to impact translation, outcome measures that are translationally relevant are essential. This review emphasizes the importance of applicable, accurate neurobehavioral and anatomical analyses.

Recent findings—Numerous well-validated assays for testing alterations across behavioral domains with sensitivity and throughput have become important tools for studying the effects of genetic mutations on neurodevelopment. Recent work has highlighted relationships and links between behavioral outcomes and various anatomical metrics from neuroimaging via magnetic resonance. These readouts are biological markers and outcome measures for translational research and will be have important roles for genetic or pharmacologic intervention strategies.

Summary—Combinatorial approaches that leverage translationally relevant behavior and neuroanatomy can be used to develop a platform for assessment of cutting edge preclinical models. Reliable, robust behavioral phenotypes in preclinical model systems, with clustering of brain pathology will lead to well-informed, precise biochemical mechanistic hypotheses. Ultimately, these steadfast workhorse techniques will accelerate the progress of developing and testing targeted treatments for multiple neurodevelopmental disorders.

Keywords

Mouse models; behavior; autism; brain; development; genetics; neurodevelopmental disorder; translation; anatomy

Introduction

Neurodevelopmental disorders (NDDs) are a broad, diverse group neuro-behavioral disorders defined by significant impairments in one or more domains of functioning (e.g.,

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Conflicts of Interest

None

social interactions, cognition, language, motor behaviors). NDDs are prevalent and pervasive lifelong conditions. Deficits can include delays in achieving outcomes and impaired skills or the presentation of atypical behaviors. Although cures (e.g., gene therapy) are not imminent, recent innovations in delivery methods associated with gene products and targeted pharmaceuticals, when combined with evidence-based behavioral interventions, have reinvigorated basic and clinical research. The diagnostic criteria for NDDs, outlined by the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM5), are a group of neurodevelopmental disorders of unknown albeit numerous etiologies with no biological markers. Thus, a diagnosis is defined exclusively by *behavioral* criteria in the distinct domains. The most classic example is intellectual disability (ID), which is diagnosed by deficits in both intellectual and adaptive functioning relative to peers of the same age, sex and socioeconomic group. In addition to the features essential to a diagnosis of ID, challenging behaviors are frequently observed, often resulting from limitations in communicative and behavioral regulation abilities. Although the presence of challenging behaviors are not a part of the ID diagnosis, these behavioral deficits may impede the process of the appropriate ID diagnosis and course of intervention [1].

Autism spectrum disorder (ASD) is another prominent NDD diagnosed by 1) persistent impairments in reciprocal social interaction and deficits in social communication across multiple contexts and 2) repetitive behaviors, with highly fixated, restricted interests and behavioral inflexibility. DSM5 diagnoses include a broader definition of the ASD phenotype than earlier versions to better reflect the current consensus that the causes and clinical presentations of ASD are highly heterogeneous. ASD and Attention-Deficit/Hyperactivity Disorder (ADHD) are frequently co-occurring [2–4]. ADHD is characterized by persistent problems in attention and/or excessive motor restlessness and/or impulsivity that significantly interfere with functioning [5]. Impulsivity also refers to a lack of reflection in the decision-making process. Other NDDs fall into classes of communication or motor disorders, both of which are also heterogeneous. Communication disorders are diagnosed by one or more deficiencies in a wide variety of subdomains such as competence in phonology, morphology, syntax and pragmatics and may adversely affect any or all of these subdomains. Motor disorders are defined by significant delays to reach developmental motor milestones and/or persistent and unusual patterns of typical motor abilities that cause detrimental impact [5, 6].

Cutting-edge genetics fast forwards translational science

Stratifying patient phenotypic subgroups and focusing on genetically identifiable populations of individuals with NDDs is a main focus of neurological research. With the advent of next generation sequencing techniques, numerous genetic factors have been shown to confer risk for ASD and ID, with > 100 genes implicated in syndromic ASD cases [7–11] and over 700 genes identified across studies of X-linked, autosomal-dominant and autosomal-recessive ID, which can be used for the molecular diagnosis of ID and ASD [12–14]. Recently, whole exome and targeted sequencing approaches have further clarified the role of 49 different genes as greater than mere “candidate ASD genes,” but mid- to high-confidence genes [7, 15–17]. This past year, 8 novel precision medicine driven mouse models with mutations in two of the highest confidence genes, chromatin helicase domain 8

(*Chd8*) and AT-rich interactive domain 1B (*Arid1b)* debuted for behavioral, cellular, anatomical and molecular characterization studies [18–25]. As our knowledge of genes involved in NDDs, in particular ASD and ID, expands and the number of genes we identify increases, common pathways are emerging. Mechanistically, gene products of *de novo* mutations show strong enrichment for chromatin modifiers and transcriptional regulators (e.g., *CHD8, ARID1B*), embryonically expressed genes (e.g., *TBR1, DYRK1A, PTEN*), cellular signaling pathways (MAPK and Rho-GTPase) and are highly expressed in the postsynaptic density (e.g., *GRIN2B, GABRB3, SHANK3*). Networks constructed using these high-confidence risk genes reveal converging functional pathways in ASD and ID [11, 14, 26, 27].

Behavioral approaches in preclinical mouse models

Basic research into the above common underlying mechanisms of pathology to develop targeted treatment options first requires well-controlled *in vivo* studies in model organisms with a high degree of genetic conservation relative to humans. To date, the most useful models with high construct validity have been mouse models [28, 29]. Although forging definitive links between genetic alterations and complex behavioral impairments (i.e., face validity) is challenging, numerous behavioral assays relevant to the diagnostic domains of ASD, ID, ADHD and motor disorders provide researchers the opportunity to gain insight into how specific genetic mutations impact behavioral features. For one example of complex behavioral assessments, in ASD candidate gene models, social communication deficits can be tested using standard and innovative methods for quantifying behavior relevant to social communication [30–32]. Examples of assays that measure social communication include three-chambered approach, reciprocal dyad interactions, social recognition, social place preference, and ultrasonic vocalizations (USVs). Other assays relevant to DSM5 diagnostic criteria that quantify repetitive behavior and activity, relevant to numerous other NDDs, have revealed high levels of repetitive self-grooming [33–37], circling [38], jumping [39–41], back flipping [42, 43] and/or overall hyperactivity [44–46] in a broad variety of preclinical models. Insistence on sameness and lack of cognitive flexibility in NDDs has been modeled in several rodent models using a few different assays [47, 48]. Below, we highlight the breadth of examinations currently available in one behavioral domain, social behavior, that are utilized for identifying face validity (deficits in social communication) in construct valid genetic models.

Toward beneficial and comprehensive social behavioral phenotyping

Three-chambered approach is an automated and widely used assay that compares time that the subject mouse spends with a novel mouse versus time spent with a non-social inanimate object [49]. A more fine-grained level of detail is collected during the naturalistic reciprocal dyad interactions, where two unfamiliar subjects are placed together in a clean, empty test arena. Interactions are usually examined between sex-and age-matched juveniles and quantified parameters are from a rich history of the established literature [35, 50, 51]. These dyad interactions can also be quantified during male–female social interactions. USV calls, emitted by the sexually motivated male, can also be assessed during these tasks to provide two outcome measures of sociability. USVs are also emitted by rodent pups when separated

from their mothers and littermates and reductions in number of neonatal USV emissions have been reported in numerous ASD mouse models [35, 52–55]. Social recognition involves social memory and is commonly examined in rodents through a few different procedures that utilize the innate preference of adult rodents to spend more time with novel over familiar conspecifics. Dysregulation of the oxytocin system has been shown to be relevant for this component of social behavior [56] [57–59] [60]. Social conditioned place preference measures a component of social behavior alongside motivational components. Social place preference arenas pair one of two unique contexts with social interactions for a fixed number of conditioning sessions, during which wildtype control mice develop a place preference to the context associated with social interactions. Given the diversity of social behaviors (e.g., parental investment, mating, cooperation), this task is modifiable to measure motivation for subtypes of social reward and social behavior in models of NDDs [61]. However, one significant challenge to preclinical assays that quantify social behavior is the inability to lesion a brain region and eliminate all social behavior or pharmacologically validate and manipulate the behavior with positive control compounds, as behavioral scientists have been able to for other sophisticated behaviors (e.g., anxiety and benzodiazepines).

Social deficits in genetic mouse models of ASD across mechanisms of action have been reported but with an inconsistency of findings. Deficits in the social behavioral domain have been mild in some cases [62] or in other cases did not fully recapitulate across laboratory environments [63–67]. For a core pillar behavioral domain in ASD diagnosis, this re-emphasizes the need to conduct comprehensive, meticulous and more fine-grained analyses of complex behavioral tasks. Opportunities for the improvement of preclinical research in social behavior include applauding reports that fail to find a social deficit in a genetic mouse model of ASD. In the long run, the NDDs field would benefit from this cautionary approach before labeling a new mouse tool an “autism mouse” based on a mere single of these subtype(s) of behavioral findings that has not been reproduced either intra-or inter laboratory environments.

Key points from our laboratories, which have been successful with reproducibility efforts include a recommendation of using a minimum of two assays in each behavioral domain before making strong conclusions on social or cognitive behavioral phenotypes [68]. This point is especially salient for the social behavioral domain. Sociability is sophisticated and nuanced, much like complex executive learning functions. Moreover, there are numerous components of social behavior for a wide variety of functional outcomes including motivation, learning, dominance, thriving, maternal behavior and sex. Second, and importantly, is that methods employed for behavioral phenotyping of clinically relevant traits are riddled with nuance and should be conducted exclusively by trained technicians with demonstrated proficiency. Finally, to have the utmost translational value, behavioral phenotyping assays should be blinded, unbiased, and highly powered and appropriate age and sex-matched, littermate controls, in both males and females (n = 15–20 per genotype/sex for 2 independent cohorts) to assess behavioral abnormalities, analogous to observed in clinical populations. Other relevant biological variables such as breeding scheme, genetic background, enrichment in home cages and circadian rhythm/time of day should be carefully controlled, adequately considered, and described in severe detail in the methods text. The

importance of procedural and environmental differences often complicates direct comparisons of phenotypic data, however these points are not insurmountable [69, 70]. We and others have reported intra- and inter-laboratory, across time-zones, continents, and seasons replications in mouse models of NDDs [34, 35, 41, 54, 71–73].

Innovative outcome measures for cognition in NDDs

Until recently, cognitive tests for measuring learning and memory in animal models were underdeveloped in complexity, and with most commonly used tests employing rely on rudimentary stimuli and procedures. Most learning tasks are simplistic mazes and/or footshock-based paradigms. This uncritical use of behavioral paradigms may account for the low predictability of mouse models in psychiatric disorders. Newer assays of cognitive abilities for ASD, ID and ADHD include computerized assessments of simple learning, higher order cognitive flexibility, and attention and impulsivity, which are more ideal because they are automated and avoid investigator interference that can have enormous influence on behavioral effects. Automation in preclinical assays is also more analogous to increasingly automated clinical testing for NDDs (e.g., NIH toolbox), and is able to measure multiple domains of cognitive abilities and build upon previously learned rules. Automated touchscreen technology has been employed for tasks of visual discrimination and reversal to identify affected circuits in models with genetic mutations associated with ASD and ID [33, 74].

Considerations for complex behavioral phenotypes

For many of these complex behavioral assays outlined above, the ultimate goal is to identify disease-relevant endpoints that are robust, reliable, and reproducible, and that can be employed to evaluate potential novel therapeutic agents. The impact of a competing or confounding behavior on the behavioral endpoints listed above cannot be understated. For example, mutations can cause physical impairments that limit a subject's ability to perform a task. Genetic mutations relevant to ASD and ID that caused physical defects (e.g., smaller body weights) include the most common copy number variant in ASD, 16p11.2 deletions [38]. Motor defects in ASD models including hypo- [33, 34] and hyper-locomotion [44–46, 75–77] can also have consequences on the behavioral outcome of interest by competing or preventing the subject from engaging in the tasks of core symptomology testing. Just as it is important to understand the limitations of a behavioral task itself, it is important to investigate, acknowledge, and report the limitations of the rodent model being tested so as not to be shortsighted in the interpretations and applications of the data.

Neuroanatomical approaches in preclinical model systems

In conjunction to behaviorally relevant outcome measures, the search for biomarkers of NDDs has grown and heavily relied upon visualizing the brain in an effort to understand the neurodevelopmental differences in preclinical genetic models and to determine if those neuroanatomical alterations can be reversed or corrected [78, 79]. Neuroanatomical indices of pathology in preclinical models of NDDs have successfully identified phenotypes with cellular resolution, using techniques such as histology [80, 81], two photon microscopy [79],

and electron microscopy [82]. Mesoscopic resolution can be obtained with computed tomography (CT) [83, 84], positron emission tomography (PET) [85], and magnetic resonance imaging (MRI) [86, 87]. While the benefits of examining the brain at the cellular resolution are self-evident, such as visualization of processes and/or counting of the cell numbers, the lack of whole brain coverage often makes these techniques less than idyllic for NDDs, for which the behavior dysfunction is unlikely to be the result of a single localized brain region, highlighted by numerous clinical imaging studies in ASD, Fragile X and Prader-Willi syndromes [88–97].

MRI focused neuroanatomical phenotyping

The ability of MRI-based techniques to encompass multiple brain regions and circuits in a single study is highly advantageous to illustrate causal insults resulting of genetic mutations in a developed, living system. This comprehensive level of whole brain data collection provides a unique opportunity for neurodevelopmental research. Moreover, once methodologies are in place and optimized, MRI provides large datasets with efficiency, throughput and sensitivity [98]. Over the past decade, our collaborative laboratories have shown that most mouse models exhibiting behavioral phenotypes also have prominent detectable neuroanatomical phenotypes [55, 99–102]. The non-invasive nature of MRI also means that it can be performed repeatedly to track disease progression and loss of skills and/or symptom onset (or regression by reversals of brain phenotypes), extremely beneficial to neurodevelopmental research [103]. A broad variety of imaging sequences can be used to look at differential components of neurodevelopment. For example, diffusion tensor imaging (DTI) infers differences in the tissue microstructure throughout the brain and is extremely sensitive to differences in the white matter [104]. Preclinical studies using unbiased MRI in mouse models of NDDs have allowed for rapid whole brain phenotyping that alludes to future mechanistic hypothesis focused research with the aforementioned cellular resolution techniques. Because of this necessity in the genetic mouse model field, MRI assessments of the brain in NDDs have become a staple of the diagnostic battery used to comprehensively phenotype novel mouse models of NDDs.

With over 700 genes implicated in NDDs and greater than 250 mouse models generated to study ASD alone [106, 107], the demand is pronounced for high-throughput, quality, consistent, optimized and informative MRI scans. Our laboratory group at the Mouse Imaging Centre (MICe) has pioneered this advanced platform of mouse imaging and developed techniques to scan up to 16 mice in a single MRI session [86, 87], which has helped to maintain and scan the consistent stream of NDD relevant mouse models. Additional improvements to MRI systems such as higher fields or cryogen-cooled coils will help to enhance both the image quality and throughput even further in the near future [78].

Moving forward the most relevant and informative studies are going to be multi-modal combinations of several techniques including genomic analysis, behavioral phenotyping, global physiological outputs and neuroanatomical imaging.

Multi-modal phenotyping in next generation genetic mouse models

Advances in next generation genomic technology have greatly improved diagnostic capabilities for NDDs and have discovered consistent mutations across the heterogeneity, vigorously contributing to the growing preclinical models of NDDs pool. These studies have identified genes that regulate large gene networks, which end up regulating and affecting numerous postulated mechanisms of action including synaptic development, neuronal function, modulation of transcription process, chromatin remodeling, calcium signaling, and cellular signaling pathways. One example from whole exome sequences clarified the role of the chromodomain helicase DNA binding protein-8 (*CHD8*), with over 15 various mutations in this single gene confirmed to contribute to ASD [108–111].

Now, as the genetic models become available, our group has paved the way for a focused effort to comprehensively define the anatomical phenotype in an unbiased, hypothesis-generating effort that will contrast and compare differences across these models [99]. In collaboration with prominent behavioral scientists, we have spearheaded an effort to correlate neuroanatomical differences with behavioral metrics, which allows for powerful inferences and biochemical hypotheses to be pursued for any given study. In fact, showing direct relationships and links amongst behavior and any of our numerous MRI readouts (e.g., regional volume, DTI, cortical thickness) can be used as biological markers, outcome measures, and may define targets for genetic or pharmacologic intervention.

Recently, we jointly applied behavioral and neuroanatomical phenotyping on the *Chd8+/del5* model of *CHD8* mutation in ASD. We observed embryonic lethality in the homozygous subjects and global macrocephaly, cognitive behavioral deficits, cortical cytoarchitecture anomalies and atypical neurogenesis. Cognitive behavioral deficits were observed in two standard assays of learning and memory, the novel object recognition task and contextual fear conditioning. Since the behavioral and structural MRI analyses were performed in the same subject cohort, detected increases in absolute volume of the cortex, hippocampus, and amygdala were correlated with deficits (i.e., reduced freezing) in fear conditioning [19]. These additional correlations provide two complimentary clinically relevant outcome measures, which are desperately in demand for pharmaceutical development in NDDs. Other advantages of cross model phenotyping are to highlight brain regions or behavioral domains of interest and decipher previously unknown underlying neural networks. Our efforts of combining behavior with neuroanatomy will aid stratification efforts for NDDs, which will ultimately lead to an increased diagnostic specificity and streamlined therapeutic development.

Summary and Conclusions

Recent advances in neuroscience have fostered a shift in thinking as to how various clinical disorders and behaviors are mediated, with evidence pointing to subtle alterations across multiple brain regions, neurotransmitter systems, and synaptic processes that converge as neural circuits. While it is tempting to proceed with technological advances that allow us to examine and manipulate single cells, for neurodevelopmental disorders, a systems level approach is necessary and will be heavily relied upon for therapeutic development strategies.

As the number of sophisticated tools increases, we must not forget that there is no replacement for behavioral and neuroanatomical outcomes, the clinically relevant tools that continue to drive translational research forward.

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Key Bullet Points

- Next generation technology has generated an abundance of precise novel genetic mouse models that are essential for research on neurodevelopmental disorders (NDD).
- Translational outcome measures, such as behavior and brain anatomy, are leading numerous discoveries of the underlying NDD neurobiology via the new mouse models.
- Behavioral domains core to NDD are complex and require multiple assays for accurate interpretation.
- Linking behavioral outcomes with neuroanatomical metrics will inform mechanistic hypotheses and therapeutic targets.
- Systems level approaches will be heavily relied upon for therapeutic development, as biological markers and outcome measures.