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CURRENT OPINION

Developmental disorders

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When a child receives a diagnosis of a neurodevelopmental disorder, the first questions posed by the caregivers reflect the tremendous uncertainty surrounding treatment and outcome: 'What is my child's prognosis? Which types of treatments will work most effectively for my child? How can we maximize his/her potential?' Historically, the paucity of evidence regarding mechanisms of disease, diagnostic stratification, and potential treatment targets in these heterogeneous conditions has necessitated answers that are nonspecific and clinically unsatisfying. Decisions regarding treatment targets and intervention strategies rely not on the specific cause or clinical presentation of a child's neurodevelopmental disorder, rather on diagnostic categorization, standardized test scores, and access to services. Over the past several years, however, advances in genetics, animal models, mechanism-driven biomarker development, and targeted intervention design have illuminated the path toward the realization of personalized medicine in neurodevelopmental disorders.

In this issue, these invited articles review the state of the field in neurodevelopmental disorders by focusing not on diagnostic classifications, but on themes that are common across this group of disorders that can provide insight into disease mechanisms and targeted treatments. Ebrahimi-Fakhari and Sahin (pp. 91–102) consider several genetic syndromes that cause autism spectrum disorder (ASD) and intellectual disability, namely, Fragile X syndrome, tuberous sclerosis complex, Angelman syndrome, and Phelan-McDermid syndrome. The authors highlight the remarkable fact that these genetically and phenotypically distinct disorders share common pathways to abnormal brain development, namely, in the dysregulation of synapse formation and structure. This work highlights the theme that is emerging from the genetics of ASD, that there is convergence on molecular and neurodevelopmental pathways, despite extreme genetic heterogeneity in the condition.

Lázaro and Golshani (pp. 103–109) emphasize the high value of mouse models of these high-risk genetic syndromes. Despite being separated by 60 million years of evolution from humans, mouse models have taught us much about the specific molecular, cellular, and circuit-level impairments that lead to the core deficits of ASD, namely, repetitive behaviors and social communication impairments. Although it was not known *a priori* how conserved the brain systems serving social cognition and repetitive behavior were in mice, mice harboring human mutations show remarkable parallels with the human conditions in many cases, including social deficits and repetitive behaviors. After careful characterization of the mouse phenotype, rationally designed treatments for ASD can be tested, with the goal of establishing efficacy at the brain and behavioral level, and understanding mechanisms, both of which would then translate to a targeted treatment for the patient.

The following three clinical articles bridge molecular mechanisms to patients. Jeste, Frohlich and Loo (pp. 110–116) discuss the critical insights that can be gained from electrophysiological biomarkers in ASD and attention deficit hyperactivity disorder (ADHD), not only for diagnosis but also for risk prediction and treatment monitoring. They argue that electrophysiological measures of connectivity and signal complexity may serve as more direct measurements of the underlying mechanism of disease in subpopulations of children within diagnostic categories and may inform risk status before a clinical diagnosis can be made. As we gain a greater understanding of the sensitivity of these biomarkers to both typical and atypical development, outcome measures and treatment response monitoring will be redefined from being purely behavioral to those that combine behavior with measures of brain function. Prediction of atypical development and, more specifically, ASD has become an area of great interest, particularly as behavioral and biological measures of risk can now be quantified in the first

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year of life. Brian, Bryson and Zwaigenbaum (pp. 117–123) provide a timely discussion about early markers of ASD, emphasizing the challenges surrounding optimal timing and strategies in interventions for infants at risk. Greater precision in the prediction of atypical development necessitates more studies in early intervention, both in specific targets and in appropriate outcome measures. Finally, Kasari (pp. 124–129) provides a thought-provoking analysis of the current state of behavioral intervention research in ASD and related developmental disorders. Embracing the theme of individualized treatment, Kasari asserts that behavioral interventions in ASD must evolve from the widespread 'one package' approach (in which children with a range of phenotypes receive the same menu of services) into a modular approach (in which a series of flexible, evidence-based strategies are tailored to the specific needs of a child). She emphasizes the need for rigorous and innovative methodology in clinical trials to test the efficacy of these tailored interventions.

For personalized, or precision, medicine to succeed, patients must be treated based on their specific biological and clinical profile, often informed by the presence of specific causal mutations or complex genetic risk factors. Information from biomarkers and behavioral data can be combined with genetic data to identify the 'subtype' of the disorder, its trajectory, and treatment. The road from gene to mechanism to behavior is being traveled now by many investigators, including studies in rare disorders such as Timothy syndrome [1], tuberous sclerosis complex, and cortical dysplasia-focal epilepsy [2]. A recent example of this is the identification of the contactin-associated protein-like 2 (*CNTNAP2*) mutation in the Amish, recapitulation of the major phenotypes in a mouse model, and recent drug screening that identifies oxytocin pathways as a potential therapeutic avenue in this disorder, with oxytocin treatment reversing the social impairments found in the mouse model of this disorder. One lesson from these studies is that one size does not fit all; treatments may need to be tailored to the specific conditions in which they will be most effective based on model systems data.

Two terms recur throughout these reviews: 'heterogeneity' and 'convergence'. Although seemingly contradictory, they are, in fact, complementary, and they capture the neurobiological essence of neurodevelopmental disorders. Although the causes of these disorders are extremely heterogeneous, a multiplicity of causes seems to lead to convergent disruptions in brain development. A wide range of genetic and environmental factors, and their complex interactions, dysregulate common pathways in ASD and ADHD, pathways that then serve as promising targets for treatment and prevention. However, given the dynamic nature of development and the constant interplay of biology with environment, these common pathways can still result in a wide range of symptoms and phenotypic expression, thereby challenging the implementation of effective treatment strategies.

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Conflicts of interest

There are no conflicts of interest.

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