Childhood and Adolescent Neurodevelopmental Disorders

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This issue of the *Journal* brings together a selection of very interesting articles that highlight research efforts focused on developing a better understanding of neurodevelopment-related illnesses. These illnesses tend to emerge during childhood and adolescence, and the disorders covered in this issue include attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), disruptive behavior disorders, and obsessive-compulsive disorder (OCD). To complement the articles that are focused on these illnesses, other research in this issue speaks to critical public health concerns that involve promoting the development of mental health in youth, the effects of early-life parental interventions on brain development in at-risk children, and insights into a linkage between callous-unemotional traits and committing gun-related crimes during adolescence. Also, this issue contains a timely and important piece that draws attention to the challenges in treating patients with alcohol and substance use disorders during the COVID-19 crisis (1).

To set the stage for the focus on childhood and adolescent psychiatric illnesses, we begin with a commentary by Dr. Ricardo Muñoz from Palo Alto University and Dr. Myrna Weissman from Columbia University that presents strategies to promote mental health in youth (2). This instructive commentary is a summary of a 2019 report from the National Academy of Medicine that highlights the need for early detection of psychiatric disorders in youths as a means to enable intervention strategies aimed at prevention. Drs. Muñoz and Weissman urge a focus on identifying and treating high-risk youths and emphasize the importance of fostering integrative approaches to address contributing population- and community-level factors.

The recommendations for promoting mental health in youth are followed by an overview focused on childhood disruptive behavior disorders coauthored by Dr. Essi Viding and Dr. Eamon McCrory, both from University College London. Childhood disruptive behavior disorders, such as oppositional defiant disorder and conduct disorder, are among the most challenging childhood psychiatric disorders, and these authors discuss conceptual and research strategies to better understand factors underlying them (3). Much work is needed in this area, as children with disruptive behavior disorders not only suffer internally and are difficult to treat, but their behavior can have significant negative effects on their families and their communities. With the transition to adulthood, it is not unusual for adolescents with disruptive behavior disorders to meet criteria for antisocial personality disorder. This overview emphasizes the heterogeneous presentation of these disorders as well as the various mechanisms that may underlie them. To better understand these illnesses, the authors underscore the importance of accounting for the complex reciprocal interactions among genetic risk, environmental stressors, temperamental factors, and social context.

Early-Life Parenting Intervention for Brain Function in At-Risk Children

Consistent with the recommendations from the Muñoz and Weissman commentary on improving mental health in children, the article by Valadez et al. (4) assesses the long-term effects of an early-life parenting intervention on brain function in at-risk children. In this study, the parents of high-risk young children were randomly assigned to receive either an early parenting intervention (Attachment and Biobehavioral Catch-Up) or a control intervention. The early adversity experienced by the children in this study put them at risk to develop both externalizing and internalizing disorders. Functional MRI data obtained when the children were, on average, 10 years old demonstrated that when they were presented with maternal cues in the scanner, children in the intervention group had increased activation in various brain regions, including some involved in social cognition. In addition, children with greater activation in these regions tended to have fewer behavioral problems. Although the sample size for this study was small, these findings are important as they begin to suggest the brain mechanisms underlying the positive effects of early-life attachment-focused parenting interventions in at-risk children. In an editorial, Dr. Joan Luby, from Washington University School

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of Medicine in St. Louis, comments on these findings in relation to promoting more positive attachments between parents and children, discussing the importance of understanding the effects of childhood intervention on developing neural systems, and the promise of future experimental treatment designs capitalizing on pre- and postintervention neuroimaging measures (5).

Callous-Unemotional Traits in Adolescent Offenders Linked to Gun Violence

By beginning to identify risk factors in youths that are associated with gun violence, the study by Robertson and colleagues (6) extends the themes discussed by Muñoz and Weissman and is also directly relevant to the overview on disruptive behavior disorders by Drs. Viding and McCrory. The findings are particularly pertinent to conduct disorders as the results demonstrate a linkage between callous-unemotional traits in adolescents and crime-related gun use. Individuals with callous-unemotional traits are characterized as having a lack of empathy and an inability to experience appropriate guilt. And, in DSM-5, callous-unemotional traits are considered to be a component of "limited prosocial emotions," a specifier for the diagnosis of conduct disorder. In studying a large sample of male juvenile offenders for 4 years after their first arrest (N=1,215), the authors found that individuals with callous-unemotional traits were more likely to be carrying and using a gun when subsequently committing crimes. Dr. James Blair, from Boys Town National Research Hospital, provides an editorial that discusses these findings in the context of other factors underlying gun violence and highlights the value of developing a more in-depth understanding of callous-unemotional traits in relation to violence (7). These findings have obvious important public health implications pointing to a readily identifiable personality trait predictive of firearm violence that may be useful in recognizing violence risk and could be explored as a possible intervention target.

Cortical and Subcortical Brain Measures in ADHD, ASD, and OCD

In an article by Boedhoe et al. (8), data from the Enhancing Neuroimaging Genetics Through Meta-Analysis (ENIGMA) consortium are presented suggesting various structural brain differences across different ages for patients with ADHD, ASD, and OCD. A major aim of the study was to characterize the shared and unique structural brain alterations across these diagnoses and across different stages of development. The authors were motivated to examine these disorders together as they are all neurodevelopmental disorders that share some clinical features with one another; are hypothesized to have some shared pathophysiology, such as deficits in inhibitory control; can be comorbid; and typically begin during childhood and adolescence. Using the largest data set analyzed to date, it was somewhat surprising that no significant shared alterations were found among these disorders and that the findings that were observed were, in general, characterized by small effect sizes. In relation to diagnosis-specific findings, children and adolescents with ADHD were found to have smaller intracranial volumes than control subjects or patients with OCD and ASD. In addition, adults with ASD were found to have thicker frontal cortices compared with adult control subjects and the other patient groups. No specific OCD structural brain alterations were found. Dr. Graeme Fairchild, from the University of Bath, discusses the findings from this large study in more detail (9), commenting on methodologic issues and emphasizing the importance of the findings in relation to age in that various alterations that were identified within a diagnosis were not found to be consistent across childhood, adolescence, and adulthood. In addition to Fairchild's editorial, it is important to keep in mind recent issues that call for caution in relation to the interpretation of MRI findings focused on disease-related structural alterations. For example, Weinberger and Radulescu (10, 11) emphasize that MRI measurements are indirect measures of brain tissue and that there are numerous potentially confounding factors that affect the MRI signal in ways that could appear to be "true" structural differences. Based on this, these authors suggest that reports involving such data use the following type of phrase: "differences in MRI measurements possibly related to…," rather than claiming that the MRI assessments necessarily reflect "true" structural differences.

Neural Correlates Associated With Heterogeneity in Adolescents With ADHD

ADHD is highly heterogeneous, with major subtypes considered to be inattentive, hyperactive/impulsive, or a combination of both, and various pathophysiological processes are thought to underlie these different presentations. The study by Shen et al. (12) also used MRI measurements to infer relations between regional gray matter volumes and different affected psychological, cognitive, and motivational processes in youths with ADHD. The cognitive deficits associated with ADHD are in the domains of executive function and working memory, attention, and response inhibition. Individuals with ADHD also have alterations in reward-related processes that manifest as motivational issues, such that these individuals tend to prefer smaller short-term rewards at the expense of delaying their gratification for larger, more valuable rewards (greater delay discounting). In this study, the authors first used a large community sample, not selected for ADHD, to assess measures of gray matter volume in relation to dimensional measures of the cognitive and motivational constructs relevant to ADHD symptoms. Genotyping data were also available from this sample, allowing for an understanding of the genetic associations with these findings. Importantly, the findings regarding reductions in gray matter were then validated in a clinical sample comparing youths with ADHD and control subjects. In the large community sample, measures of inattention were associated with reduced gray matter volumes in two brain clusters, one in the prefrontal cortex (PFC) that comprised the ventromedial PFC, the dorsal anterior cingulate cortex, and the anterior insula, and another in the posterior occipital cortex, including regions of the cuneus

and calcarine sulcus. Increased errors in working memory were associated with reduced gray matter measures in the posterior occipital cluster, and deficits in delay discounting were associated with reductions in both the prefrontal and occipital clusters. Polygenic risk scores were computed and were found to be associated with higher ADHD symptoms and decreased measures of gray matter volume in the posterior occipital cluster. Gray matter reductions in both clusters were also found in the clinical sample but, interestingly, were found to be significant only for individuals with the ADHD inattentive subtype. It also appeared that the measurements of gray matter volumes in both the PFC and occipital clusters did not differ between medicated patients and control subjects. Taken together, the regions implicated suggest ADHD-related involvement of the visual attention network and that the posterior occipital cortex may be a common substrate related to the cognitive and psychological processes that contribute to the heterogeneous presentations of ADHD.

Candidate Genes Relevant to ADHD: Combining Rare Copy Number Variations (CNVs) With Animal Model Data

Although ADHD is highly heritable, as with other psychiatric illnesses, its genetics are proving to be very complex. Most studies have focused on understanding the contribution of commonly occurring genetic variations, such as single-nucleotide polymorphisms, in relation to ADHD, and less emphasis has been placed on rare CNVs, on which there are much more limited data. Harich and colleagues (13) use data combining clinical studies identifying ADHD-related CNVs with animal models implicating specific genes in mediating the phenotypic components of ADHD, and with other various databases. The aim is to use CNVs to home in on potential candidate genes as they relate to molecular systems and biological processes potentially relevant to ADHD. The authors also used methods to implicate protein modules that may be involved in mediating the effects of the implicated genetic alterations. The winnowing method used in this study allowed for a prioritization of 26 gene candidates from an initial list of 2,241 possible genes. Interestingly, this approach demonstrated convergence between CNV and common genetic variant studies, as both strategies identified *POLR3C* and *RBFOX1* as candidates. These genes are interesting possibilities in relation to this neurodevelopmental disorder, as *POLR3C* is also implicated in ASD and *RBFOX1* is involved in the regulation of genes associated with neuronal development. Dr. Anita Thapar, from Cardiff University, provides an informative editorial that discusses the potential importance of studying rare CNVs that have large phenotypic effects, reviews current data pertaining to the genetics of ADHD, and emphasizes the need to explore these genetic leads in animal models to establish causal validity (14).

Conclusions

In conclusion, this issue of the *Journal* provides an opportunity for our readership to learn in detail about issues relevant to further understanding and treating neurodevelopmental psychiatric disorders. These disorders begin in childhood and adolescence, and a better understanding of their mechanisms and pathophysiologies will inform the development of novel early-life interventions. An important article in this issue provides an example of the potential impact of early-life interventions, demonstrating the long-term effects of a parenting intervention on brain function in at-risk children. The neuroimaging and genetic findings presented in this issue are particularly relevant to ADHD and provide new ideas about targeting specific brain regions and genes for further study and as possible treatment targets. Finally, the article linking callous-unemotional traits in adolescence to gun-related criminal behavior offers insights into a risk factor that deserves considerably more attention from the standpoints of research and the prevention of adolescent criminal behavior.

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