Adolescent Brain Development and Psychopathology: Introduction to the Special Issue

Ellen Leibenluft and Deanna M. Barch

The importance of adolescence to both development and psychopathology cannot be overstated. Developmentally, it is a time of tremendous physiological and behavioral change. Dramatic shifts occur in brain structure (synaptic pruning, increased myelination), function (corticosubcortical connectivity, increased specialization), and neurochemistry (prefrontal GABA [gamma-aminobutyric acid], glutamate, and dopamine neurotransmission) (1). As noted throughout this special issue of Biological Psychiatry, similarly dramatic changes occur in behavior (increased peer orientation, impulsivity, and risk taking), cognition (increased abstraction, social competence), and emotion regulation. And, while research suggests the importance of early neurodevelopment to psychopathology, it has been well documented that a marked upsurge in psychiatric illness, including depression and psychotic disorders, occurs during adolescence (2).

The goal of this special issue is to highlight recent findings on brain development during adolescence and elucidate their relevance to psychopathology. The articles are summarized below, but several overarching themes are worth noting. The first, and least surprising one, concerns the gap between the amount of research that exists on adolescent brain development and psychopathology and the importance of the topic. Indeed, in teaching us about the current literature, each article highlights the critical need for more work, with areas of particularly pressing importance highlighted. Some specific examples are given below, but many more could easily be cited. Second, the behavioral, affective, social, and cognitive phenomena that we see as characteristic of adolescence emerge from a complex interplay between biology and environment, particularly the social environment. Several articles focus on brain mechanisms that mediate, and allow the adolescent to adapt to, evolving peer relationships and family dynamics during this phase of development. Third, the articles underscore that understanding the neural mechanisms of psychiatric illness during adolescence could have far-reaching clinical implications: because adolescence is characterized by marked brain plasticity, there is considerable opportunity for both treatment and prevention.

Finally, while both cross-sectional and longitudinal studies contribute to our growing understanding of why adolescence is a high-risk time for the emergence of psychopathology, some mechanistic questions can only be answered with longitudinal designs, especially those that meet the admittedly high bar of large sample size and dense sampling. As such, these articles highlight the urgent need to conduct and analyze studies that meet or exceed this bar. Notably, the ongoing Adolescent Brain and Cognitive Development (ABCD) Study (3) will be a major contribution in this domain, as it is following children with a host of behavioral, cognitive, affective, social, and neuroimaging measures for >10 years, starting at 9 and 10 years of age. However, while the ABCD Study data are becoming extremely informative, the design of the study is purposefully broad, with brief assessments of many different domains. As highlighted in the this special issue, longitudinal studies with deep phenotyping in focused domains are needed to complement the data being generated by the ABCD Study.

The issue begins with a commentary (1) and 3 articles (4–6) on normative adolescent brain development. Given the complexity of adolescence, Luna et al. (1) emphasize the need for multimodal approaches and longitudinal designs, including those that detect nonlinear trends. The authors suggest methodological approaches to untangling the effects of multiple neural systems, each with its own characteristic normative trajectory. Pfeifer and Allen (4) focus on pubertal mechanisms and their implications for the increased prevalence of depression, anxiety, and nonsuicidal self-injury during adolescence. They note the importance of research on the coevolution of social, pubertal, and neural processes. Next, in a meta-analysis of the neural correlates of emotion regulation in adolescence and early adulthood, Pozzi et al. (5) focus on emotion reactivity and implicit and explicit emotion regulation. While they find intriguing differences between adolescents and young adults in neural processes mediating implicit emotion regulation, their work also reveals an important research gap. Specifically, given the dearth of studies in adolescents, they could not perform age group comparisons on emotion reactivity and explicit emotion regulation. Finally, Andrews et al. (6) note that adolescents’ increased mentalizing and emotion regulation capacities allow them to navigate their increasingly complex and salient social world. They review the literature on the psychological and neural developments that enable such increased social competence, with a particular emphasis on how early interventions might promote health development in this domain.

The next 3 articles (7–9) transition to a more specific focus on psychopathology, particularly mood and anxiety disorders. In their discussion of suicidal thoughts and behaviors and nonsuicidal self-injury, Auerbach et al. (7) summarize a burgeoning literature. They discuss evidence for structural alterations in ventral and orbital prefrontal cortex in these mental health conditions and review functional neuroimaging
research on relevant psychological processes (self-processing, impulsivity/social reward, and emotion processing). They note the challenge of dissociating mechanisms of suicidal thoughts and behaviors and nonsuicidal self-injury from each other and from contributing diagnoses. Nielson et al. (6) present a critical analysis of the data on whether reward processing abnormalities cause and/or predict depression. Meta-analyses of cross-sectional or longitudinal associations find effects whose magnitude is such that they may guide mechanistic studies but are probably not clinically informative. Clinical trials provide limited support for the suggestion that manipulating reward processing impacts depression. However, as the authors review in detail, methodological and theoretical shortcomings in the literature limit the conclusions that can be drawn, and they provide suggestions to guide future research. Finally, Cisler and Herringa (9) focus on posttraumatic stress disorder (PTSD) in adolescents. They underscore the relative paucity of data on PTSD in this age group and review evidence suggesting that while adult and adolescent PTSD may not differ significantly in clinical presentation, there may be important pathophysiological differences. Highlighting yet another important research gap, they note the limited data available to clarify the extent to which trauma-focused cognitive behavioral therapy is effective in adolescents. Cisler and Herringa (9) close with an informative heuristic model of adolescent PTSD that includes domains particularly relevant to this developmental phase—e.g., caregiver response and modeling, cortisol and hormonal response, sleep biology, and the impact of trauma on reward learning.

Two articles then discuss behavioral disorders in adolescence, specifically attention-deficit/hyperactivity disorder (ADHD) and substance abuse. Shaw and Sudre (10) focus on the longitudinal trajectory of ADHD—in particular, on potential pathophysiological mechanisms underlying the observation that many, but not all, patients’ ADHD symptoms (particularly hyperactive-impulsive symptoms) diminish during adolescence, and what the implications are of this heterogeneity for prognosis and management. They note that the evidence suggests a significant genetic contribution to both course and onset, but considerably more research is needed on the role of gene × environment interactions in determining course. The authors describe 5 neurodevelopmental models that could account for variation in the longitudinal course of ADHD and the neural changes that one would expect to see under each model. Because most current studies scan subjects only at onset and end point, the authors return to the theme of the need for longitudinal work by noting that testing of these models awaits longitudinal neuroimaging studies with more dense sampling. Regarding substance abuse, Hernandez Mejia et al. (11) focus on one of the most common substance abuse comorbidities among adolescents, nicotine and cannabis. Despite high rates of co-use of these substances, there are few data about the resulting effects. Preliminary findings include that nicotine may mask the cognitive effects of cannabis and atypical hippocampal volume in co-users. Clearly, more research is needed.

The issue concludes with discussions of two important neurodevelopmental disorders: autism and psychosis (specifically, schizophrenia spectrum disorders). Uddin (12) notes the many challenges facing adolescents with autism spectrum disorder (ASD) as they navigate the transition to adult life. These challenges exist because youths with ASD are burdened not only with social deficits but also with executive function deficits that can manifest as inflexible cognition and behavior. Uddin (12) reviews task- and set-shifting studies showing atypical lateral frontoparietal and midcingulo-insular activation in patients with ASD and notes the importance of intrinsic brain network dynamics in supporting cognitive flexibility. To explore the latter, dynamic functional connectivity techniques can be applied to resting-state data to study transitions among brain networks and the degree of variability among functional connections. Further mechanistic research, combined with better measurement and characterization of heterogeneous executive function deficits, can inform novel interventions targeting the inflexibility that compromises the ability of adolescents with ASD to transition to adult life.

In the final article in this issue, Patel et al. (13) focus on adolescent neurodevelopment and vulnerability to psychosis. Both biological and social factors can contribute to adolescent psychosis risk. Disruptions in synaptic pruning and blunting of the normative increase in myelination and fractional anisotropy have been implicated, as has stress associated with multiple role changes relative to one’s family and peers. Patel et al. (13) note that the increased neural plasticity that renders adolescence a high-risk time for the onset of psychosis also creates opportunities for effective intervention. They conclude with a discussion of the literature implicating cannabis in psychosis risk, and note the evidence suggesting markedly different neural effects of two important components of cannabis, Δ9-tetrahydrocannabinol and cannabidiol. Indeed, these two compounds differ so markedly in their neural effects that there is evidence that, in contrast to the apparent psychotogenic effects of Δ9-tetrahydrocannabinol, cannabidiol may decrease psychotic symptoms.

Typically, adolescence is both a joyous and a stressful time for the youths experiencing it and the people that love them. For adolescents burdened with psychiatric illness, social disadvantage, and/or abuse or neglect, this developmental period can pose challenges that feel, at times, insurmountable. In addition, the current coronavirus COVID-19 pandemic impacts disproportionately on adolescents, since pandemic-related social restrictions are occurring at a time when peer relationships are particularly salient to them. The importance of knowledge that ultimately leads to the prevention and treatment of adolescent psychiatric illness has never been more clear. Hopefully, this special issue will inspire and guide more research to that end.

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Article Information
From the Section on Mood Dysregulation and Neuroscience (EL), Intramural Research Program, National Institute of Mental Health, Bethesda, Maryland, and the Departments of Psychological and Brain Sciences, Psychiatry, and Radiology (DMB), Washington University in St. Louis, St. Louis, Missouri.

Address correspondence to Ellen Leibenluft, M.D., at ELiebenluft@sobp.org.

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