Biological Psychiatry: Celebrating 50 Years

Stress and Neurodevelopment in Adolescent Depression

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Adolescence is a vulnerable time for the onset of depression; it is a developmental period characterized not only by major life transitions and stressors but also by significant brain maturation (1). Consequently, it is essential that psychobiological models of adolescent depression explicitly consider mechanisms by which stress alters neurodevelopment. Contemporary accounts of how stress affects neurodevelopment describe these processes through a prism of "sensitive periods"—that is, distinct periods of heightened plasticity during which environmental factors exert outsized influence on a developing system (2). Brain regions differ in the timing of their sensitive periods, and this hierarchy underlies healthy development; stressful events, including developmentally inappropriate (e.g., premature exposure) or insufficient (e.g., an absence of expected input) experiences, may therefore increase vulnerability to psychiatric illness by altering the developmental programming of brain regions that are associated with affective and cognitive processing (2,3). In this issue of *Biological Psychiatry*, Bartlett *et al.* (4) present evidence consistent with the formulation that stress increases the risk of depression through neurodevelopmental mechanisms by demonstrating that alterations in cortical regions sensitive to stressors occurring during midadolescence predict future depressive symptoms.

The research by Bartlett *et al.* (4) is part of the multiwave Adolescent Development of Emotion and Personality Traits study aimed at identifying and characterizing psychobiological risk factors, precursors, and sequela of first-onset depressive disorders in a sample of adolescent girls (study details available at http://stonybrookadept.com/). In the present investigation, adolescent females were clinically assessed for depression and other psychiatric disorders at 5 waves over 36 months (9 months between each wave); the primary analyses focused on stress and magnetic resonance imaging data obtained at wave 2 as predictors of dysphoria—a cardinal symptom of depressive disorders—at waves 3–5. First, Bartlett *et al.* (4) examined patterns of cortical thickness and surface area that were associated with recent life stress (i.e., in the past 9 months) and found that a higher stress load was associated with cortical thinning in the left precuneus and left postcentral gyrus, as well as a lower surface area in the left superior frontal and right inferior parietal cortices. The authors then used linear mixed effects models to permit individual-level variability while estimating the effect of the morphological metrics from these 4 stress-linked regions on subsequent levels of dysphoria (i.e., waves 3–5). This analysis revealed that cortical thinning of left precuneus predicted subsequent symptoms of dysphoria, even after accounting for previous (i.e., wave 1) and concurrent (i.e., wave 2) symptoms. Finally, in an exploratory mediation analysis, Bartlett *et al.* (4) reported that while the mediative effect was only marginally significant, cortical thickness of the left precuneus nonetheless accounted for 17% of the variance in the association between recent life stress and subsequent dysphoria (i.e., average levels across waves 3–5). Interestingly, cortical thickness of the left precuneus also predicted subsequent levels of lassitude, mania, social anxiety, ill temperament, panic, appetite gain, traumatic intrusions, and suicidality, suggesting that this is a neurophenotype that is specific to mood and anxiety symptoms.

The effects of common life stressors on brain structure in a normative sample reported by Bartlett *et al.* (4) are strikingly similar to those documented in previous studies of individuals exposed to severe stress (5). Importantly, the adolescent females in Bartlett *et al.*'s investigation (4) were not selected on the basis of any risk factors. Considering the broader literature that has focused on samples with more extreme experiences of stress, this is compelling because it suggests that the stressogenic effects of depression are not necessarily caused by toxic levels of stress or maladaptive stress responses that diminish functioning. Rather, normal stress responses—which engage mechanisms of plasticity that are adaptive for neurobiological systems—may lead to depressive disorders in adolescence by influencing neurodevelopmental trajectories.

One prominent theory consistent with this idea is the "stress acceleration" hypothesis, which posits that in conditions of low stress and stability, protracted development is advantageous for individuals to maximize learning from their environments, whereas in conditions of high stress and uncertainty, accelerated development maximizes reproductive success (6). A consequence of accelerated phenotypic development is early termination of plasticity in systems that otherwise would likely benefit from additional input. While prematurely ending a sensitive period may be protective against the influence of negative experiences on brain development, a potential cost is the absence of positive experiences that scaffold optimal development (Figure 1). Thus, it may be through both of these stress-induced alterations in neurodevelopmental trajectories that depressive disorders emerge. More basic and clinical research is needed to test these hypotheses more explicitly and to mechanistically link stress, brain development, and depressive disorders, particularly during adolescence.

Another significant contribution of Bartlett *et al.*'s findings (4) is that they raise the possibility that precuneus thinning is a stress-related neurophenotype of depression. The precuneus

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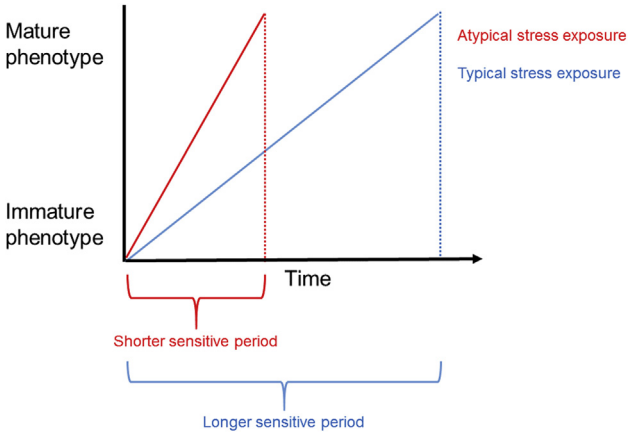

Figure 1. Conceptual model of how stress acceleration may lead to depressive disorders by shortening sensitive periods for developing systems. While prematurely ending a sensitive period may be protective against the influence of negative experiences on brain development, a potential cost is the absence of positive experiences that scaffold optimal development.

is a node of the default mode network (DMN), a functional network whose connectivity patterns undergird higher-order cognition, including affective regulation and self-referential processing. Numerous studies have documented increased functional connectivity of the DMN in depressed adolescents (7), as well as in depressed adults (8), and, further, that this hyperconnectivity is associated with important clinical symptomatology (e.g., rumination). Thus, it may be that stress-induced alterations of precuneus thickness alter the developmental connections of the precuneus with other regions in the DMN, resulting in hyperconnectivity of this circuit in depression. An important direction for future research is to characterize the associations between DMN gray matter morphology and functional connectivity patterns across development and to clarify how stress affects the trajectories of each of these neurophenotypes.

Future studies with prospective designs like the Adolescent Development of Emotion and Personality Traits study that use multimodal neuroimaging and comprehensive assessments of stress at multiple timepoints are needed to elucidate the neurobiological stress mechanisms that contribute to adolescent depression. As Bartlett *et al.* (4) note, inflammatory processes may be especially key to understanding how stress affects neurodevelopment. It is well recognized that life stress activates the immune system by initiating a cascade of inflammatory responses that affect the integrity of the central nervous system, including altering neurotransmitter levels, such as glutamate (9). Indeed, preclinical data have demonstrated that inflammatory signals stimulate glutamate release that, over time, lead to cell apoptosis; thus, glutamatergic excitotoxicity may represent one pathway by which stress exposure results in gray matter loss, measured by cortical thinning and reduced surface area. While Bartlett *et al.* (4) rightly highlight positron emission tomography as an effective method for future studies to use to measure neuroinflammation, less invasive methods, such as magnetic resonance spectroscopy, are capable of measuring the downstream effects of neuroinflammation on neurotransmitter systems and are more amenable for use in adolescents.

Another critical future direction for this line of research is to conduct longitudinal neuroimaging to chart trajectories of cortical (and subcortical) development as a function of stress load and to investigate whether and how stress-related neurodevelopmental trajectories predict longitudinal changes in depressive symptoms. Such approaches have the potential to advance our understanding of depression (and of other psychiatric disorders) by delineating sensitive periods of development during which life stressors affect the maturation of specific brain regions and networks (10). Characterizing longitudinal trajectories of both neurodevelopment and symptomatology will also allow researchers to identify variability in etiologic pathways to depression, which is a necessary first step toward parsing the heterogeneity of depressive disorders into subtypes that have clinical utility (e.g., selecting a treatment for a patient based on their subtype).

Stress is a key nongenomic factor that contributes to nearly all aspects of depression—onset, maintenance, and outcome—and is a driver of neuroplasticity. Bartlett *et al.* (4) present intriguing evidence for the role of stress-sensitive brain regions in the emergence of depressive disorders. While the results of their investigation will need to be replicated in independent samples that include males, these findings add to a growing literature that underscores the importance of stress mechanisms and principles of neurodevelopment in generating psychobiological models of adolescent depression.

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References

1. Breslau J, Gilman SE, Stein BD, Ruder T, Gmelin T, Miller E (2017): Sex differences in recent first-onset depression in an epidemiological sample of adolescents. Transl Psychiatry 7:e1139.
2. Gee DG, Casey BJ (2015): The impact of developmental timing for stress and recovery. Neurobiol Stress 1:184–194.
3. McLaughlin KA, Sheridan MA, Nelson CA (2017): Neglect as a violation of species-expectant experience: Neurodevelopmental consequences. Biol Psychiatry 82:462–471.

4. Bartlett EA, Klein DN, Li K, DeLorenzo C, Kotov R, Perlman G (2019): Depression severity over 27 months in adolescent girls is predicted by stress-linked cortical morphology. Biol Psychiatry 86:769–778.
5. Teicher MH, Samson JA, Anderson CM, Ohashi K (2016): The effects of childhood maltreatment on brain structure, function and connectivity. Nat Rev Neurosci 17:652–666.
6. Callaghan BL, Tottenham N (2016): The stress acceleration hypothesis: Effects of early-life adversity on emotion circuits and behavior. Curr Opin Behav Sci 7:76–81.
7. Ho TC, Connolly CG, Henje Blom E, LeWinn KZ, Strigo IA, Paulus MP, *et al.* (2015): Emotion-dependent functional connectivity of the default mode network in adolescent depression. Biol Psychiatry 78:635–646.
8. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA (2015): Large-scale network dysfunction in major depressive disorder: A meta-analysis of resting-state functional connectivity. JAMA Psychiatry 72:603–611.
9. Miller AH, Maletic V, Raison CL (2009): Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. Biol Psychiatry 65:732–741.
10. Gotlib IH, Ordaz SJ (2016): The importance of assessing neural trajectories in pediatric depression. JAMA Psychiatry 73:9–10.