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Review

Stress and adolescence: vulnerability and opportunity during a sensitive window of development

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Abstract

Adolescence is a period of dynamic change across multiple systems. Concurrent maturation of neural, biological, and psychosocial functioning renders adolescence a time of heightened sensitivity to both negative and positive experiences. Here, we review recent literature across these domains, discuss risk and opportunity in the context of ongoing neural development, and highlight promising directions for future research. Finally, we propose that conceptualizing adolescence as a sensitive window during which plasticity across multiple systems is enhanced may support the identification of links between experience, neurodevelopment, and psychopathology.

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Introduction

Adolescence, typically defined as the developmental stage that begins with the onset of puberty and ends when individuals reach adulthood [1], is a unique time of neural, behavioral, and biological flux. This developmental period is characterized by a distinct increase in brain plasticity, pubertal maturation, and shifts in behavior, such as increased independence and attention to peer relationships [2]. The emergence of psychopathology also peaks in adolescence [3], with youth who have been exposed to stressful life events at elevated risk for developing psychopathology [4]. Understanding how stressors experienced prior to and during the dynamic adolescent period affect neurodevelopmental trajectories, behavior, and mental health is of critical importance to efforts that aim to optimize interventions based on developmental stage.

Here, we review and discuss recent evidence suggesting that stressors exert differential influences on neurodevelopment and behavior during adolescence. In addition to heightened risk during adolescence, we consider how adolescence also confers unique opportunities for resilience, such as the buffering effects of a positive social environment. Finally, we explore promising directions for extending our understanding of the ways in which specific dimensions of stress may impact developmental change across systems during adolescence.

The hypothalamic-pituitary-adrenal axis during adolescence

Adolescence is a period of significant physiological maturation, including of the hypothalamic-pituitary-adrenal (HPA) axis. Enhanced plasticity of the HPA axis during adolescence is one potential pathway through which stress exposure may exert long-lasting effects, but also may represent a window of opportunity for resilience. The HPA axis is responsible for regulating the body's acute stress response, via the release of glucocorticoid hormones. Prolonged exposure to glucocorticoid hormones can lead to cumulative changes in neural structure and may mediate the association between stress exposure and brain structure and function [5,6]. Both heightened and blunted cortisol responses have been associated with stress exposure, underscoring the complexity of the effects that stress exerts on the neuroendocrine system [7]. Age and developmental stage are important factors contributing to this complexity. During adolescence, the onset of puberty triggers a cascade of hormonal changes that affect systems throughout the body [8–10], including the HPA axis. In rodents, the acute hormonal stress response lasts about twice as long in adolescent animals than in adults, possibly due to modulation by gonadal hormones [11]. Furthermore, in contrast to adult rodents whose hormonal stress responses habituated to chronic stress exposure, exposure to chronic stressors resulted in repeatedly heightened responses in adolescent rodents [9]. These adolescent-specific shifts in HPA signaling indicate that adolescence is a period of plasticity for the HPA axis, during which it is likely that the upstream regulators of the hormonal stress response

are undergoing maturation and adaptation to conditions of the current environment.

Although childhood stress can have effects that last into adulthood [12], not all children exposed to stress develop psychopathology [4], and development provides unique opportunities for resilience. Recent evidence highlights a particular phenomenon that may facilitate reshaping specifically during adolescence. Although early childhood is known to be a particularly potent period for sculpting stress reactivity [7,13,14], recent findings suggest that adolescence may represent a second developmental stage during which increased plasticity of the HPA axis facilitates recalibration based on the current environment [15,16]. Youth exposed to institutionalization in early childhood and later adopted into stable families showed a more blunted cortisol response in early puberty relative to never-institutionalized peers. However, youth previously exposed to institutionalization demonstrated longitudinal increases in cortisol response over the course of puberty, such that their cortisol responses did not differ from never-institutionalized youth by later puberty [15,16]. Critically, recalibration is dependent on a shift from the early adverse environment to a more predictable, less harsh environment during adolescence [16], and the precise role that such recalibration may play in later wellbeing remains unclear [17,18]. Evidence of pubertal recalibration is consistent with the possibility that neuroendocrine maturation confers HPA axis plasticity in adolescence, during which positive environmental input such as supportive caregiving may facilitate adaptive reshaping.

Neural maturation during adolescence

Neural plasticity is also heightened during adolescence, conferring greater sensitivity to both positive and negative environmental exposures [19–21]. Brain structure and function undergo substantial change during adolescence, likely owing in part to morphological changes such as synaptic pruning and myelination [22–25]. The brain matures in a region-specific and nonlinear manner, with some regions such as the hippocampus and amygdala reaching a mature state earlier than cortical regions, which continue to develop into adulthood [22,26]. Regions that undergo protracted development, such as the association cortex, may remain in a more plastic state during adolescence [20,26–28] and thus be more sensitive to environmental inputs during this time [19,29,30]. Prefrontal and limbic regions also have high densities of glucocorticoid receptors [6], and hormonal stress responses may interact with ongoing neurodevelopmental processes in ways that produce stress-associated changes in these regions during adolescence.

Although adolescence is posited to be a sensitive period for the development of the association cortex and corresponding higher-order cognitive and affective processes [28], previous research has almost exclusively relied on animal models to examine molecular mechanisms of sensitive period onset and offset because it is challenging to identify biological hallmarks of a sensitive period in a noninvasive manner [31–34]. However, innovative work recently tested for changes in the excitatory to inhibitory neurotransmission ratio, which has been linked with sensitive period closure, in adolescents. The researchers used data from a sample of adults to generate a model that distinguished neural connectivity patterns associated with increased inhibitory neurotransmission among adults taking benzodiazepines [35]. Applying this model to a developmental sample of youth, results showed a gradual reduction in the ratio of excitatory to inhibitory patterns in association cortex across adolescence, aligning with past animal work on molecular properties that characterize the closing of sensitive periods [31–34]. These findings support the idea that adolescence represents a unique window of development, such that disruptions in expected inputs (such as predictable and nurturing social relationships) might exert heightened effects on the developing cortex.

A growing body of research has identified potential mechanisms by which stress exposure affects the developing brain and risk for psychopathology. Stress experienced in childhood can heighten sensitivity to future stressors, thereby increasing the likelihood of developing stress-related psychopathology in adolescence [36,37]. Recent evidence indicates that variation in subcortical brain volumes and fronto-amygdala functional connectivity may contribute to such effects of stress sensitization [38,39]. While the possible relation between stress sensitization and sensitive periods of plasticity has yet to be elucidated, sensitization effects may be particularly strong when the subsequent stress exposure occurs during periods of increased plasticity, such as adolescence. Another potential mechanism by which stress exposure may influence functioning is via more rapid neurobiological maturation [40,41], which parallels evidence of acceleration in pubertal development and cellular aging after stress [42,43]. Youth previously exposed to childhood stress display more mature patterns of connectivity between limbic and prefrontal regions [44–48,82], although the extent to which effects of acceleration may be specific to stress characterized by threat [42,49,50] or to corticolimbic circuitry [46] is less clear. Such 'stress acceleration' may reflect an adaptive response to meet the demands of a harsh early environment [40,51]. Consistent with the idea that more rapid corticolimbic neural maturation may confer some initial benefit following stress exposure, youth who exhibited more mature patterns of corticolimbic connectivity also had lower internalizing symptoms [44,82] and slower telomere shortening and pubertal tempo [47]. However, the ways in which changes in the timing

of circuit development — including potential alteration of the timing or trajectory of an adolescent sensitive period — may be linked with later psychopathology is not yet clear.

The social environment during adolescence

In part due to dynamic changes in neurobiological development and pubertal maturation, youth become more highly attuned to the social environment as they enter adolescence [2,52], with peer relationships playing a central role in adolescent wellbeing [53–55]. This increased sensitivity to the social environment represents a distinct shift from childhood and may mark a period during which social stressors exert disproportionate effects relative to other stages of life. Indeed, adolescents are particularly susceptible to social risks and peer rejection, which in turn are associated with depressive symptoms [56].

Alongside the burgeoning importance of peer relations, stress and support at the family level continue to play a critical role in adolescence. Although adolescents are more attuned to social stressors [56], they are also more sensitive to positive social experiences such as social approval and supportive caregiving [57,58]. Indeed, sensitivity to supportive caregiving is heightened in adolescence and associated with increased reward responsiveness and better mental health, even for adolescents who experienced intense psychosocial stress during childhood [57]. Supportive caregiving can buffer against the effects of social stressors such as peer victimization on mood and behavior [59] and may also exert protective effects at the neural level. Several recent studies suggest that supportive caregiving buffers against stress-associated changes in neural connectivity [60] and fronto-amygdala structural development [61] and may attenuate anxiety via cortical activation during adolescence [62]. These effects of supportive caregiving on adolescent mental health and neurodevelopment indicate that parent and caregiver relationships continue to be of great importance for adolescent wellbeing, despite emerging independence and a shift toward increased salience of peer relationships. Together, this body of work emphasizes that adolescence may be a sensitive window for heightened importance of the social environment, including both positive effects of supportive caregiving and more deleterious effects of social stressors such as peer victimization.

While understanding developmental shifts in the role of peers and family is crucial to clarifying the effects of stress exposure during adolescence, individual variation in neural function remains important to consider and may moderate associations between stress exposure and cognitive and emotional state. Indeed, individual variation in ventral striatal and amygdalar activation during anticipation of a social reward moderated the effects of family conflict on psychopathology [63], suggesting that individual neural sensitivity to social context plays an important role in linking the effects of social stressors with psychopathology. Sensitivity to social context may also be a pathway through which stressors experienced in adolescence impact processes such as emotion regulation that have been closely tied to psychopathology. For example, one recent study found that for girls with heightened sensitivity to social rejection, less effective recruitment of key neural regions involved in emotion regulation was associated with a history of more peer victimization [64]. These findings support the formulation that individual differences in susceptibility [65] may moderate the extent to which social context influences emotion regulation and mental health during adolescence.

Directions for future research in the study of stress during adolescence

Despite remarkable advances in the science of adolescent development and stress, there remain important questions about the ways in which stress impacts adolescent wellbeing. Research examining how specific dimensions of stress exposure differentially impact neurodevelopment and mental health may aid in elucidating the range of outcomes following stress [13,66]. Frameworks identifying certain features of stress exposure as particularly salient, such as threat and deprivation [67] or unpredictability [68], have already proved fruitful in understanding how the brain may be shaped by distinct aspects of stress exposure. Leveraging such theoretical advances in conjunction with examining timing-specific effects [66,69,70] may yield a richer understanding of associations between dimensions of stress exposure in adolescence and the emergence of psychopathology.

Further parsing associations between stress exposure, neurobiological development, and psychosocial functioning will require a clearer understanding of the timing of sensitive periods throughout development. As sensitive periods represent times when neural regions or circuits are tuning their function in an experience-expectant manner, identifying the timing and duration of sensitive periods for key neural circuits and functions is critical for advancing knowledge of how to optimally prevent and treat stress-related psychopathology [19,30,71,72]. Moreover, specific dimensions of stress may be particularly impactful when experienced during specific stages of development (e.g. during a sensitive period for a given circuit or region) [66]. Thus, more thoroughly phenotyping how the environment interacts with sensitive periods may further elucidate the nature of heterogeneity in developmental outcomes following stress.

In addition to theory-driven advances in how stress exposure affects the adolescent brain, there have been recent advances in approaches to modeling complex change during developmental periods such as adolescence. Analytical methods such as structural equation modeling and generalized additive modeling may more accurately capture complex region-specific nonlinear neural maturational trajectories, as well as associations with biological and environmental factors [28,49]. In parallel, usage of unsupervised learning methods such as similarity network fusion, latent profile analysis, and sparse canonical correlation analysis may help to identify latent patterns that characterize subgroups of individuals [73,74] or multivariate links between network connectivity and psychopathology [75,76]. Data-driven, circuit-based approaches that move beyond region-of-interest investigations [77,78] will lead to a more encompassing view of the complex effects of stress on neurodevelopment and have the additional benefit of reducing bias in results [79]. Finally, the advent of large, multisite, open-source, longitudinal studies such as the Adolescent Brain Cognitive Development Study [80,81] will facilitate the identification of robust, generalizable patterns of neurodevelopment through adolescence. Such methodological advancements allow a more precise mapping of neurodevelopmental trajectories and parsing of co-occurrences between brain, environmental exposures, and psychopathology during adolescence.

Conclusions

Adolescence is a highly dynamic period characterized by both vulnerability and opportunity. Here, we review recent evidence that adolescence represents a sensitive window during which maturational change in neuroendocrine systems, neurodevelopment, and social sensitivity render youth uniquely attuned to stress and support. Conceptualizing adolescence as a sensitive window during which plasticity is increased across multiple systems and metrics may aid in more clearly unraveling links between environmental exposures, neurodevelopment, and risk for psychopathology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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