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Neural Embedding of Stress Reactivity

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Abstract

A report in this issue of *Nature Neuroscience* demonstrates that stress in infancy leading to altered cortisol levels in childhood culminates in vulnerability to dysregulated affect in adolescent girls by biasing the functional dynamics of core neural regions mediating the generation and regulation of emotional responsiveness.

One of the most intriguing and important questions across psychology, psychiatry and neuroscience is how experience ‘gets under the skin’ to shape individual differences in behavior and risk of mental illness. Early life adversity predicts nearly 45% of childhood-onset and 30% of adult-onset psychopathology¹. Because the treatment of mental illness is expensive and often ineffective, a major goal of research is to prevent its development. Thus, it is important to understand the mechanisms through which early adversity forms a prelude to psychopathology so that therapeutic targets in etiologic chains and predictive biomarkers of risk may be identified.

Research across species has shown that early life stress alters the function of the hypothalamic-pituitary-adrenal (HPA) axis, the central regulator of stress responsiveness. Early life stress is also associated with alterations in the structure, function, and connectivity of a corticolimbic neural circuit, including the amygdala and ventromedial prefrontal cortex (vmPFC), which helps us recognize and react to challenges we encounter by orchestrating adaptive changes in both behavior and physiology. The effects of stress, particularly early in life, on this corticolimbic neural circuit are likely mediated by stress-related alterations in HPA axis function.

A wealth of research in humans and non-human models has demonstrated pleiotropic effects of HPA axis dysregulation on myriad mental and physical health outcomes². Perhaps most relevant to understanding pathways to psychopathology, the hormonal end product of the HPA axis, cortisol, has been linked to variability in the structure and function of the corticolimbic circuit. Exposure to early life stress is associated with blunted diurnal cortisol variation (that is, relative to a normal profile, reduced cortisol on awakening but elevated levels later in the day and a less steep negative slope over the course of the day). Moreover,

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both early adversity and endogenous cortisol concentrations are positively correlated with the magnitude of threat-related amygdala reactivity and amygdala gray matter volume³. In contrast, emerging research in model organisms suggests that chronic adversity and cortisol release result in atrophy of the vmPFC⁴. Complementing these data is growing evidence that the vmPFC is critical in the integration and subsequent top-down regulation of amygdala reactivity and that this modulatory relationship predicts the severity of anxiety and depressive symptoms, as well as variability in diurnal cortisol^{5–7}.

In a study in this issue of *Nature Neuroscience*, Burghy *et al.*⁸ now bridge these biological mechanisms by showing that early life stress increases adolescent symptoms of anxiety and depression and decreases amygdala-vmPFC functional connectivity through adversity-related elevations in childhood cortisol (Fig. 1a). Furthermore, these data emphasize the importance of developmental timing and gender differences in stress-related psychopathology by demonstrating that the changes in functional connectivity predict symptoms in adolescent girls only and are predicted by early, but not later, adversity.

In their study, 57 adolescents from the ongoing Wisconsin Study of Families and Work (<http://www.wsfw.us/>) were recruited into a functional magnetic resonance imaging study assessing the resting-state functional connectivity of the amygdala and vmPFC. Such resting-state measures, wherein subjects are not exposed to explicit triggers such as threatening facial expressions but rather allowed to rest quietly, have emerged as a useful index of general neural circuit architecture, which may represent more trait-like or persistent biases in neural function related to both normal and abnormal behavior⁹. In addition, participants completed self-report measures of current depression, anxiety and life stress, and they provided saliva samples from which basal afternoon cortisol was assayed. These newly collected data were then integrated with earlier measures of infant life stress (represented through a measure of maternal stress) and childhood basal afternoon cortisol. This integration allowed the current set of analyses, wherein Burghy *et al.*⁸ found that in adolescent girls, but not boys, adversity during infancy is positively associated with later childhood cortisol levels, which predict decreased resting-state functional connectivity between the amygdala and vmPFC. Furthermore, this altered amygdala-vmPFC functional connectivity predicts increased symptoms of adolescent anxiety and depression. Interestingly, variability in resting-state functional connectivity and mediation models predicting adolescent anxiety and depression were not related to either recently experienced stressful life events or afternoon basal cortisol levels obtained during adolescence in either gender. The absence of significant association between these more contemporaneous measures suggests the existence of a critical window during development wherein the neural embedding of stress reactivity affects later risk for psychopathology particularly in girls.

There are, of course, several limitations that should be noted. First, the small sample size limits the utility of mediation analyses, which likely overestimate the variance in symptoms explained by the biologic measures. Second, the expression of symptoms related to anxiety and depression was not above clinical thresholds for disease diagnosis, and thus the direct relevance of these patterns for treatment and prevention of psychopathology remains to be determined. It is likely that further alterations within the corticolimbic circuit (for example, hippocampal function and connectivity with both the amygdala and vmPFC) would emerge

in individuals with clinical diagnoses of mood and anxiety disorders. Third, diurnal variability in cortisol, which represents a better marker of disordered HPA axis function than a single time-point measure, was not assayed, and thus the extent of dysfunction in this system is unclear. Finally, the relationship between resting-state measures of functional connectivity and the responsiveness of neural circuits to actual provocation, such as that elicited by life stress commonly leading to psychopathology, is uncertain and an area of active inquiry. Presumably, resting-state neural circuit function predicts how the circuit responds to challenge.

Despite these limitations, the work of Burghy *et al.*⁸ provides fertile ground for further speculation regarding the molecular and cellular mechanisms mediating the gender- and developmentally specific neural embedding of stress. Nonhuman primate research has shown that the most rapid rate of amygdala development occurs during infancy, which may represent a critical period during which the amygdala is particularly sensitive to environmental input³. Moreover, females may be more sensitive to early life stress because their amygdala reaches adult-like volume in childhood, whereas in males it grows in volume at least throughout adolescence¹⁰. Estrogen signaling in the amygdala, which can produce anxiogenic and anxiolytic effects mediated through estrogen receptor- α and estrogen receptor- β , respectively, could further contribute to these patterns^{11,12}.

Interestingly, gender-specific evidence of epigenetic regulation related to early adversity has been documented for estrogen receptor- α . Female rats experiencing less maternal care have reduced methylation of the estrogen receptor- α gene and corresponding increased estrogen receptor- α expression in the amygdala¹³. Given that estrogen receptor- α function has been associated with anxiogenic effects and with impaired negative feedback of the HPA axis, adversity during infancy may specifically leave females vulnerable to HPA axis dysregulation, culminating in altered resting-state amygdala-vmPFC functional connectivity and increased symptoms of anxiety and depression. This speculation is particularly intriguing in light of recent evidence that estradiol modulates both vmPFC and amygdala reactivity in women¹⁴. Moreover, gender-specific epigenetic regulation of estrogen receptor- α may magnify more general epigenetic effects occurring in both genders, most notably in the glucocorticoid receptor gene¹⁵, which collectively may leave females particularly vulnerable to HPA axis dysregulation, corticolimbic circuit dysfunction and related risk for psychopathology (Fig. 1b).

Regardless of the molecular mechanisms underlying the findings reported by Burghy *et al.*⁸, their report offers important insight into the neural embedding of stress reactivity and the mechanisms through which early life adversity may precipitate risk for later psychopathology. Perhaps the most important question arising from the present report is whether we can use these findings and those from similar longitudinal research to inform the development of new therapeutic targets (for example, estrogen receptor- α expression in the amygdala) and, more importantly, new markers of risk (for example, genetic polymorphisms predicting greater HPA axis responsiveness) that may ultimately allow the prevention of mood and anxiety disorders and mitigation of their long-term negative impact on individuals, families and societies.

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Figure 1.

Biological pathways linking early life stress to later psychopathology. **(a)** In girls but not boys, a history of maternal stress during infancy predicts heightened basal afternoon cortisol during childhood, which predicts reduced resting- state amygdala-vmPFC functional connectivity during adolescence. Variability in this functional connectivity, in turn, mediates the association between childhood cortisol and adolescent symptoms of anxiety and depression. **(b)** Plausible epigenetic mechanisms contributing to links between early life stress, amygdala-vmPFC connectivity and symptoms of depression and anxiety. The glucocorticoid receptor (GR) is critical for negative feedback of the HPA axis, and increased promoter methylation (red ovals) of the GR gene (*NR3C1*), which results in decreased gene expression, is associated with childhood adversity. Hence epigenetic regulation of the GR may result in impaired negative feedback of the HPA axis that is gender independent. In contrast, childhood adversity may contribute to gender- dependent promoter demethylation (gray ovals) of the estrogen receptor- α (*ESR1*), which results in increased gene expression and, possibly, anxiogenic changes in corticolimbic circuit function. It is further possible that epigenetic regulation of the GR can contribute to these gender-dependent effects through downstream regulation of *ESR1* transcription (dashed lines). In the absence of early adversity, stress-related GR activation may result in downregulation of *ER α* , which

is associated with anxiogenic effects. In contrast, the methylation and subsequent downregulation of *GR* following early adversity leads to increased ER α expression and anxiogenic effects, possibly through alterations of functional connectivity between the amygdala and vmPFC.