Early Life Stress and Neurodevelopment in Adolescence: Implications for Risk and Adaptation

Jonas G. Miller, Rajpreet Chahal, and Ian H. Gotlib

Contents

Abstract An alarming high proportion of youth experience at least one kind of stressor in childhood and/or adolescence. Exposure to early life stress is associated with increased risk for psychopathology, accelerated biological aging, and poor physical health; however, it is important to recognize that not all youth who experience such stress go on to develop difficulties. In fact, resilience, or positive adaptation in the face of adversity, is relatively common. Individual differences in vulnerability or resilience to the effects of early stress may be represented in the brain as specific patterns, profiles, or signatures of neural activation, structure, and connectivity (i.e., neurophenotypes). Whereas neurophenotypes of risk that reflect the deleterious effects of early stress on the developing brain are likely to exacerbate negative outcomes in youth, neurophenotypes of resilience may reduce the risk of experiencing these negative outcomes and instead promote positive functioning. In this chapter we describe our perspective concerning the neurobiological mechanisms and moderators of risk and resilience in adolescence following early life stress and integrate our own work into this framework. We present findings suggesting that exposure to stress in childhood and adolescence is associated with functional and structural alterations in neurobiological systems that are important for social-affective processing and for cognitive control. While some of these neurobiological

J. G. Miller, R. Chahal, and I. H. Gotlib (✉)
Department of Psychology, Stanford University, Stanford, CA, USA
e-mail: jgmiller@stanford.edu; rchahal@stanford.edu; ian.gotlib@stanford.edu

© The Author(s), under exclusive license to Springer Nature Switzerland AG 2022
Curr Topics Behav Neurosci
https://doi.org/10.1007/7854_2022_302

alterations increase risk for psychopathology, they may also help to limit adolescents' sensitivity to subsequent negative experiences. We also discuss person-centered strategies that we believe can advance our understanding of risk and resilience to early stress in adolescents. Finally, we describe ways in which the field can broaden its focus to include a consideration of other types of environmental factors, such as environmental pollutants, in affecting both risk and resilience to stress-related health difficulties in youth.

Keywords Adaptation · Adolescence · Early life stress · MRI · Resilience · Risk

1 Introduction

More than half of youth in the United States are exposed to at least one kind of adverse, stressful experience, such as family violence, poverty, and emotional abuse (McLaughlin et al. 2012). In addition to being highly prevalent, these types of early life stressors carry considerable burden for children and adolescents; indeed, they have been linked to increased risk for psychopathology (Green et al. 2010; LeMoult et al. 2020), accelerated biological aging (Colich et al. 2020; Sosnowski et al. 2020), and poor physical health (Flaherty et al. 2006; Oh et al. 2018). Despite these well-documented adverse effects of early life stress (ELS), not all youth who are exposed to ELS go on to develop difficulties. In fact, resilience, or positive adaptation and decreased vulnerability in the face of adversity (Luthar et al. 2000; Rutter 2006), appears to be quite common (Bonanno and Diminich 2013; Masten 2001). Thus, there are significant individual differences in the psychosocial and neurobiological factors that are involved in vulnerability, and resilience, to the adverse effects of ELS.

Some of these individual differences could be related to variation in the severity, type, duration, and timing of specific events that represent forms of ELS (Cohodes et al. 2020; Malhi et al. 2019), as well as to the presence or absence of both individual- and environment-level protective factors (Holz et al. 2020). Collectively, these various factors may be represented in the brain as specific patterns, profiles, or signatures of neural activation, structure, and connectivity (i.e., neurophenotypes) that confer risk versus resilience. Neurophenotypes of risk that reflect the persistent and deleterious effects of ELS on the developing brain are likely to underpin or exacerbate negative outcomes in children and adolescents. Conversely, neurophenotypes of resilience may reduce the risk of negative outcomes and preserve or promote positive emotional, cognitive, and behavioral functioning following ELS.

There are two main approaches to studying the interplay of ELS, brain development, and risk versus resilience. The first, and most prevalent, approach focuses on the effects of ELS on the brain and examines implications of these relations for child and adolescent well-being (i.e., a mechanism- or mediation-based approach)

(McLaughlin et al. 2020). In other words, this approach considers how the effects of ELS on well-being are explained by or linked to the effects of ELS on brain function and structure. The second, less common, approach focuses on the interactive effects between ELS and neurobiology on well-being (i.e., a moderation-based approach) (Guyer 2020). This approach considers how the specific effects of ELS on well-being (i.e., strength of effects, positive or negative direction) change depending on individual differences in brain function or structure. Although it may seem paradoxical that neurobiological systems can serve both as mechanisms that link ELS to outcomes and as moderators of the effects of ELS, there are at least three reasons to posit that these processes work in concert.

First, although ELS can affect neurobiological functioning and structure, it is important to recognize that neurodevelopment is not shaped solely by early experience. In fact, research suggests that some aspects of neurobiology are highly heritable, and that genetic variation contributes to neurobiological systems that underlie risk for stress-related psychopathology (Fox et al. 2015; Teeuw et al. 2019). This inherent variability may influence the moderation of the effects of ELS on well-being.

Second, there are sensitive periods during which neurobiology is particularly responsive to input from the environment (Dunn et al. 2019; Feldman 2015; Gee 2020). ELS may have more lasting, powerful effects on neurobiological systems when they are undergoing rapid development, as is the case during childhood and adolescence. After the sensitive periods for these systems have passed, additional stressful experiences may have a weaker effect. Importantly, however, these neurobiological systems continue to regulate how children and adolescents perceive and respond to subsequent stressors, potentially moderating their impact on well-being.

Third, it is possible that neurobiological systems that are sensitive to ELS play a role in filtering and encoding information from the environment. Some researchers have posited that reactivity in stress-response systems (e.g., HPA axis, parasympathetic nervous system, and sympathetic nervous system) may help children and adolescents extract and store information about the social environment (Del Giudice et al. 2011). The degree of reactivity in stress-response systems may help to calibrate their long-term functioning (Del Giudice et al. 2011). Importantly, these stress-response systems are regulated by brain regions that are sensitive to ELS (Ulrich-Lai and Herman 2009). Thus, forms of ELS that lead to increased neurobiological reactivity in brain regions important for child and adolescent well-being may also underlie openness and responsiveness to environmental input.

In this chapter we review the current literature in presenting our perspective on the neurobiological mechanisms and moderators of risk and resilience in adolescence following ELS, with particular attention to integrating our own work into this framework. We are conducting an ongoing longitudinal study with a sample of over 200 adolescents to examine the relations among ELS (largely social stress), neurobiology, and adolescent development and well-being. Adolescents in our study completed interviews to assess exposure to 30 different types of stressful events as well as the age at onset of each event. Table 1 shows the types of ELS events and rates of exposure to ELS in our sample. A panel of trained raters coded each

Table 1 Measurement of early life stress

Type of ELS	Examples	Percentage endorsed		
		Total sample (%)	Female (%)	Male (%)
1. Witnessed illness/injury	Caregiver cancer, relative heart attack	48	48	48
2. Moved/family moved in and out	Moving many times, eviction	48	45	53
3. Parental verbal fighting	Nonphysical yelling	39	41	36
4. Death of someone close	Relative to cancer	34	36	31
5. Bullying	Peer name-calling, hitting	33	38	27
6. Divorce	Caregivers separated (legally or non-)	32	32	31
7. Experienced illness/injury	Hospitalized for asthma	30	29	31
8. Witnessed accident	Sibling hit by car	26	26	26
9. Experienced accident	Car crash	22	13	34
10. Family mental illness/substance abuse	Caregiver depression, caregiver alcoholism	19	22	15
11. Separation from family – rehab/foster care/detention	Caregiver in rehab, caregiver in jail	13	14	12
12. Family financial problems	Food/housing insecurity	13	17	8
13. Family legal problems/imprisonment	Sibling DUI arrests, caregiver in prison	12	9	15
14. Separation from family – work/travel	Separation due to work, child going to camp	11	13	9
15. Witnessed community conflict – physical	Robbery, gunshots	10	11	10
16. Domestic violence – physical	Family hitting, throwing objects	9	8	10
17. Attacked by animal	Dog bite	7	5	10
18. Suicide/self-harm of someone close	Classmate suicide, caregiver attempts	7	7	7
19. Neglect	Lack of food/supervision	6	5	7
20. Disaster	Hurricane, tornado, forest fire	5	4	7
21. Witnessed community conflict – verbal	Neighbors yelling/threatening people	5	7	3
22. Physical assault/abuse	Hitting by adult family	5	4	7
23. Emotional abuse	Yelling, threatening by adult family	5	4	7
24. Mugging	Robbery	3	3	4
25. Witnessed live war/terrorism on TV	Live news coverage	3	2	4
26. Sexual assault/abuse	Rape, sexual touching	2	3	0
27. Domestic violence – threats	Family threats of injury	2	3	1

(continued)

Table 1 (continued)

Type of ELS	Examples	Percentage endorsed		
		Total sample (%)	Female (%)	Male (%)
28. Physical assault/abuse – threats	Threat of injury by adult family	2	3	1
29. Sexual assault/abuse of someone close	Rape, sexual touching	1	1	0
30. Kidnapping	Attempted kidnapping, relative kidnapped	1	2	1
Other	Friend moving away, bomb threat at school	7	7	7

Type of ELS presented in order of prevalence of exposure

interview response for stress severity. Here, we discuss ELS as any adversity occurring before or concurrent to the assessment of our participants as adolescents. Recent findings from our study indicate that ELS is associated with anomalous patterns of functional and structural brain outcomes (Chahal et al. 2020b; Colich et al. 2017; Kircanski et al. 2019), and that adolescents who have been exposed to ELS are at greater risk for poor psychosocial outcomes (Humphreys et al. 2019b). Importantly, we are also finding evidence that ELS-related alterations in the brain may confer resilience against adverse outcomes, at least in the short-term (Chahal et al. 2020b; Miller et al. 2020b).

We begin by presenting findings from functional neuroimaging studies suggesting that exposure to ELS is associated with alterations in neurobiological systems that are important for social-affective processing (e.g., amygdala, ventral striatum, orbitofrontal cortex, and medial prefrontal cortex [PFC]) and for cognitive control (e.g., dorsolateral and ventrolateral PFCs, parietal cortices, and the anterior cingulate cortex [ACC]). Next, we review evidence for ELS-related structural alterations in similar regions, particularly the PFC and hippocampus. We then discuss research examining the effects of ELS on functional connections within and between neural circuits (e.g., frontoamygdala circuitry) and on structural properties of white matter tracts (e.g., uncinate fasciculus). Within each section, we focus on findings that point to neurobiological alterations following ELS as potential mechanisms of risk and resilience, but also consider findings that highlight brain-based markers of individual differences in vulnerability, sensitivity, or resilience to the adverse effects of ELS.

After examining the patterns of structural and functional brain development that are implicated in risk and resilience, both in the broader literature and in our own study, we discuss potential ways that researchers can more effectively characterize risk- and resilience-related neurobiological factors following ELS that may serve as mechanisms underlying the association between ELS and the subsequent development of psychopathology. We also discuss strategies that can be used to advance our understanding of which adolescents are more likely to be vulnerable, and which

adolescents are more likely to be resilient, to the adverse effects of ELS. In this context, we focus on two specific avenues for future research: (1) integrating neuroimaging with advances in methodology and data science to identify neural circuit-defined biotypes and biomarkers of risk for psychopathology; and (2) using multilevel frameworks that consider neurobiology and ELS embedded in the context of other individual- and environment-level variables.

2 Brain Functional Activation

Amygdala Activation as a Mechanism of the Effects of ELS A growing body of research is demonstrating that ELS is associated with altered functioning of brain regions important for affective and cognitive control processes, such as the PFC, amygdala, and ventral striatum. These alterations appear to underpin both risk and resilience following ELS. One of the most consistent neural abnormalities associated with ELS is hyperactive amygdala reactivity to threatening or salient stimuli, particularly emotional faces (Hein and Monk 2017; Tottenham et al. 2011). Different types of ELS, characterized by both deprivation and threat, have been linked to heightened amygdala activation. For example, compared to family-reared youth, previously-institutionalized youth with a history of psychosocial deprivation exhibit greater amygdala reactivity to emotional faces (Gee et al. 2013); in turn, greater amygdala reactivity to fearful faces was associated with lower levels of social competence (Tottenham et al. 2011). Young adolescents exposed to maltreatment and family violence also demonstrate heightened amygdala reactivity to emotional faces (McCrory et al. 2011). Studies considering specific subdivisions of the amygdala have found that greater exposure to ELS is related to heightened centromedial amygdala reactivity to emotional faces (Suzuki et al. 2014). Similarly, in our own work we found that a cumulative measure of ELS severity was positively associated with right centromedial amygdala reactivity to emotional faces in a community sample of adolescents (Miller et al. 2020b). The centromedial amygdala mediates autonomic, endocrine, and behavioral responses supporting attention to salient stimuli (LeDoux 2007). These aspects of emotional processing may be particularly sensitive to ELS, potentially serving adaptive purposes in stressful contexts (Frankenhuis and de Weerth 2013).

Heightened amygdala activation supports hypervigilance to threat that is important for staying safe in chaotic and dangerous environments, but this neurophenotype could also constitute emotional processes, such as learned fear responses, that increase long-term risk for difficulties (Maren et al. 2013). Indeed, many studies have implicated heightened amygdala reactivity during socioemotional processing in risk for psychopathology in adolescence (Beesdo et al. 2009; Kerestes et al. 2014). Our recent work provided novel evidence that amygdala hyperreactivity also marks risk for accelerated biological aging; specifically, we found that heightened left centromedial amygdala reactivity to emotional faces was associated with more rapid cellular aging, assessed by telomere shortening over 2 years in adolescence

(Miller et al. 2020b). One interpretation of this finding is that centromedial amygdala hyperreactivity may regulate psychological and biological processes involved in accelerated cellular aging, such as negative affect and hypothalamic pituitary adrenal (HPA) axis activation. Although hyper-vigilant amygdala activity may be adaptive in the context of adversity and impeding threat, this neurophenotype may come at the cost of accelerated aging via allostatic load and serve as a risk factor for psychopathology outside of stressful contexts, in which amygdala hyperreactivity is no longer adaptive.

Reward- and Cognitive Control-Related Regions ELS has been also been linked to blunted reactivity in other brain regions that are important for evaluating reward-related stimuli and regions involved in cognitive control. Experiences of emotional neglect have been linked to attenuated ventral striatum reactivity during a monetary reward task which, in turn, predicted and partially mediated subsequent depressive symptoms (Hanson et al. 2015a). Similarly, previously-institutionalized youth have been found to demonstrate lower ventral striatum reactivity to happy faces, which was related to higher depression scores (Goff et al. 2013). The ventral striatum plays a crucial role in attributing value to reward-related stimuli (Berridge 2007); diminished reactivity in this region following ELS may underlie specific types of mental health difficulties, such as reduced anticipation of, and motivation to pursue, reward (Pechtel and Pizzagalli 2011) – a central component of anhedonia commonly observed in depressed individuals (Sherdell et al. 2012; Wu et al. 2017). ELS may also disrupt regions involved in cognitive control of emotion (McLaughlin et al. 2020). Adolescents exposed to violence have decreased dorsal ACC reactivity to fearful faces and reduced dorsomedial PFC and superior frontal gyrus reactivity to neutral faces (Weissman et al. 2020a). Further, decreased dorsal ACC reactivity was found to partially mediate the association between violence exposure and symptoms of psychopathology. This lower activity in cognitive control regions may contribute to the deficits in executive functioning that have been documented in adolescents who have experienced ELS (Pechtel and Pizzagalli 2011), and in individuals with a range of mental health disorders (McTeague et al. 2016).

It is important to note that neurophenotypes that may be implicated in risk for psychopathology have also been documented in asymptomatic individuals following ELS (e.g., van Harmelen et al. 2013), suggesting that other neurobiological factors play a compensatory role in promoting resilience (Teicher et al. 2016). Adaptive functioning in prefrontal regions involved in emotion regulation is an example of a trait-level factor that may contribute to resilience. Consistent with this perspective, dynamic and flexible responses in the ventromedial PFC (vmPFC) during stress induction, marked by initial deactivation followed by increased activation, have been found to be correlated with positive coping responses (Sinha et al. 2016). This flexible neural activity may help to offset sustained activation in other brain regions, including the amygdala, hypothalamus, and insula, that were observed during the stress induction (Sinha et al. 2016). Measures of peripheral nervous system flexibility that are linked to vmPFC functioning, such as high-frequency heart rate variability (Thayer et al. 2012), have also been found to be related to positive

social-emotional competencies in children (Miller et al. 2013; Miller 2018). Although the convergence of these results is intriguing, research examining brain-based functional activation markers of resilience is still in its early stages compared to investigations of the relation between functional brain activation and risk for psychopathology.

Amygdala Activation as a Moderator of the Effects of ELS In addition to being a *mechanism* by which ELS contributes to risk, neural activation in the brain regions described above may also *moderate* the impact of ELS (Schriber and Guyer 2016). For example, amygdala reactivity supports increased engagement with challenging and salient events that, in the context of environmental stressors, often include threat-related cues. Thus, amygdala hyperreactivity supports processes that may increase sensitivity to stressful events, potentially increasing vulnerability to their adverse effects; in contrast, dampened amygdala response supporting decreased sensitivity may contribute to resilience. This pattern of activation would be consistent with the formulation that amygdala functioning is a diathesis for the adverse effects of ELS. Alternatively, there is growing evidence for *differential susceptibility* models, which posit that specific patterns of neurobiological activity indicate increased openness to supportive and adverse environments, both for better and for worse (Boyce 2016). Amygdala hyperreactivity is linked to putative markers of differential susceptibility to environmental influence, such as negative emotionality and increased reactivity in peripheral stress-response systems (Blackford et al. 2013; Ulrich-Lai and Herman 2009).

Consistent with the differential susceptibility model, Gard et al. (2018) demonstrated that increased amygdala reactivity to emotional faces marked differential susceptibility to the presence versus absence of socioeconomic resources, which can be conceptualized as a proxy for exposure to stressors. Specifically, young adult men who exhibited higher amygdala reactivity to emotional faces self-reported the most and the least antisocial behaviors in the context of low and high socioeconomic resources, respectively; conversely, men who had lower amygdala reactivity appeared to be buffered from the association between socioeconomic resources and antisocial behavior. Interestingly, Weissman et al. (2018) found the opposite – that low amygdala reactivity during an emotion introspection task represented increased risk for externalizing problems in the context of increased exposure to community violence. Recent research on brain-based moderators of risk for internalizing symptoms related to ELS has yielded more consistent findings. For example, in a study of previously-institutionalized youth, those who demonstrated decreased amygdala reactivity to parent cues showed reductions in anxiety across 3 years; anxiety symptoms were high and stable over time in those youth who had increased amygdala reactivity (Callaghan et al. 2019). Similarly, in a sample of adolescents exposed to maltreatment, those who decreased amygdala activation during an emotion regulation task showed improvements in depressive symptoms over time (Rodman et al. 2019). These studies demonstrate that amygdala reactivity during affective processing may render some adolescents more or less sensitive to the consequences of ELS and related risk factors; it is still unclear, however, whether

Table 2 Summary of the findings and implications of studies focused on ELS and brain activation in adolescents

Regions	Functional activation alteration following ELS	Implications
Amygdala	Hyperreactivity to salient/threatening stimuli	Hypervigilance that may heighten the adverse effects of ELS on psychopathology, particularly internalizing symptoms
Ventral striatum	Blunted reactivity to monetary and social rewards	Altered reward-related processing
Anterior cingulate cortex and dorsomedial prefrontal cortex	Blunted reactivity to emotional faces	Altered cognitive control of emotion
Ventromedial prefrontal cortex	Unclear	Positive coping that could be important for resilience following ELS

this neurophenotype is a brain-based moderator of environment that conforms more to a diathesis-stress or differential susceptibility model. Further research in this area would help us gain a more comprehensive understanding of why some adolescents do better or more poorly following ELS, and how these individual differences are rooted in the functioning of different brain regions (Guyer 2020).

Table 2 presents a summary of the findings and implications of studies focused on ELS and brain activation in adolescents.

3 Brain Structure

Prefrontal and Limbic Structural Alterations as Mechanisms of ELS Another brain-based variable implicated as a mechanism and/or moderator of the association between ELS and risk/resilience for psychopathology is brain structure. Human neuroimaging studies have consistently found that ELS is associated with structural alterations of PFC and limbic regions that are important for multiple forms of emotional processing and are implicated in the development of mental health problems. PFC regions that undergo protracted development may be particularly vulnerable to the effects of ELS. For example, the orbitofrontal cortex (OFC), which plays an important role in emotion, motivation, and psychopathology (Rolls 2019), is one of the last brain regions to mature in humans (Toga et al. 2006), and research suggests that the development of this region is affected by exposure to ELS. Adolescents who experience physical abuse and child maltreatment have been found to have smaller OFC volumes than do typically-developing adolescents (De Brito et al. 2013; Hanson et al. 2010). Research with adults has also found that the cumulative number of stressful life events experienced is associated with smaller volume in the OFC, as well as in regions that are implicated in salience processing, including the insula and ACC (Ansell et al. 2012). Compared to a control

group of adolescents who were reared by their biological families, post-institutionalized youth with a history of psychosocial deprivation were found to demonstrate broad, global reductions in gray matter volume and more specific reductions in PFC and hippocampal volume (Hodel et al. 2015). In turn, ELS-related reductions in prefrontal and hippocampus volume in adolescents have been associated with social difficulties and behavioral problems (Hanson et al. 2010, 2015b). ELS has also been linked to cortical development in community samples exposed to a range of more normative ELS events. For example, in a study of adolescent girls, recent common life stress was associated with thinner parietal cortices which, in turn, predicted the future development of depressive symptoms (Bartlett et al. 2019).

Although ELS has been linked to volumetric reductions across a number of cortical regions and the hippocampus, some studies suggest that ELS is related to *larger* amygdala volume. Previously-institutionalized youth have been found to have larger amygdala volume than a comparison group of adolescents without a history of institutionalization (Mehta et al. 2009); prolonged institutional rearing in early life (i.e., later adoption) has also been found to be associated with larger amygdala volume (Tottenham et al. 2010). It is worth noting, however, that other studies have failed to find an effect of institutionalization on amygdala volume in youth (Sheridan et al. 2012), and that other studies have linked violence exposure and a cumulative measure of ELS exposure with smaller, not larger, amygdala volume (Hanson et al. 2015b; Weissman et al. 2020b). These inconsistencies in the literature on amygdala volume are somewhat surprising given the relatively consistent effects of ELS on amygdala functional activation (Teicher et al. 2016).

Our group posited that some of these discrepancies in findings across studies may be due, in part, to sex differences. In our community sample of adolescents, we found that self-reported experiences of childhood neglect were associated with larger right amygdala volume in boys but not in girls (Roth et al. 2018); further, larger right amygdala volume mediated the association between greater childhood neglect and more severe anxiety symptoms in boys. These sex differences mirror findings of recent research that neglect has stronger associations with hippocampal volume in males, whereas threat-related experiences are more strongly correlated with hippocampal volume in females (Teicher et al. 2018). Sex-specific effects of ELS on brain development in adolescence may be mediated by sex hormones. More specifically, the amygdala is rich in glucocorticoid and androgen receptors (LeDoux 2007; Martini and Melcangi 1991), and amygdala volume in adolescent boys has been positively associated with circulating levels of testosterone (Neufang et al. 2009). ELS may lead to atypical coupling of stress and sex hormones in adolescents, although research on the nature of this effect has yielded inconsistent findings (Dismukes et al. 2015; King et al. 2020; Ruttle et al. 2015). Nevertheless, it is possible that neuroendocrine functioning mediates sexual dimorphic effects of ELS on amygdala volume as well as on other brain structures, but further research is clearly needed.

Discrepancies in the literature concerning amygdala volume could also be related to differences in the timing of assessments or in the ages of participants across

studies. Weems et al. (2015) found that, compared to same-age healthy control adolescents, younger participants exposed to trauma had smaller right amygdala volume, but older participants exposed to trauma had larger right amygdala volume. Interestingly, associations between higher ELS and smaller amygdala volume have been found in samples of participants who were, on average, in early adolescence (Hanson et al. 2015b; Weissman et al. 2020a; but see Tottenham et al. 2010 for an exception), whereas Mehta et al. (2009) found that ELS was associated with larger amygdala volume in middle adolescence. In general, the amygdala increases in volume during adolescence (Scherf et al. 2013); longitudinal studies are necessary to determine whether this developmental trajectory of the amygdala is altered following exposure to ELS. ELS may be associated with a trajectory characterized by relatively smaller amygdala volume in early adolescence but relatively larger amygdala volume later in adolescence, and it is possible that this trajectory is related to pubertal development more strongly than to age. Pubertal stage and levels of circulating testosterone have been found to be associated with larger amygdala volume (Neufang et al. 2009); further, we have observed pubertal shifts in the effects of ELS on other neurobiological outcomes, such as the cortisol awakening response (King et al. 2017).

Brain Structure in Relation to Types and Timing of ELS Beyond degree of ELS severity, number of ELS events, or comparing individuals with and without a history of ELS, researchers are increasingly considering the effects of different forms of ELS on alterations in brain structure (Everaerd et al. 2016). For example, we have used a person-centered approach (i.e., latent class analysis) to identify unique subgroups of adolescents exposed to particular combinations of ELS experiences, and examined whether this approach provided novel information about ELS-related effects on hippocampal volume (King et al. 2019). The hippocampus is rich in glucocorticoid receptors and plays a role in the regulation of stress responding (Jacobson and Sapolsky 1991). Exposure to glucocorticoids as a result of stress can disrupt synaptogenesis and neurogenesis, thereby leading to alterations in hippocampal volume (Andersen and Teicher 2008). In our community sample of adolescents, taking a person-centered approach to measuring ELS yielded three different subgroups that were distinguished by experiences of family instability (e.g., parental divorce, separation from family) and victimization (e.g., maltreatment). The largest subgroup was composed of adolescents who experienced less exposure to both experiences of family instability and victimization; adolescents in the second largest subgroup experienced high levels of family instability, and the smallest subgroup was characterized by direct victimization experiences. These subgroupings were similar to those identified in prior work with a high-risk sample of young children (Hagan et al. 2016). In our community sample, adolescents in the subgroup characterized by direct victimization had smaller bilateral hippocampal volume than did adolescents in the subgroup characterized by low exposure to family instability and victimization. These findings are consistent with findings from cumulative severity and extreme-group models of ELS suggesting that hippocampal volume is specifically sensitive to threatening experiences (Sheridan and

McLaughlin 2014). Importantly, however, King et al. (2019) found that using a person-centered approach to modeling ELS explained more variation in hippocampal volume than did using a cumulative measure of ELS, highlighting the need for research explicitly considering the advantages and disadvantages in using different approaches to modeling ELS.

In addition to examining combinations of different types of ELS, it will also be important to consider the timing of ELS exposure, given that there may be sensitive periods of development during which neurobiology is particularly malleable and shaped by experiences of ELS (Dunn et al. 2019; Feldman 2015; Gee 2020). Specifically, we found that more severe stressful experiences in early childhood (through 5 years of age), but not in late childhood (age 6 years and older), were associated with smaller hippocampal volume in early adolescence (Humphreys et al. 2019a). Importantly, stress in early childhood outperformed a cumulative measure of stress severity in predicting hippocampal volume. These findings add to a growing body of research underscoring the importance of ELS experiences in childhood for brain development, and particularly the hippocampus region (Luby et al. 2016).

Brain Structure as a Moderator of the Effects of ELS Compared to research examining the relation between ELS and structural alterations in the brain, there are fewer studies that have assessed structural markers of individual differences in susceptibility, vulnerability, and resilience to ELS in adolescents (i.e., treating brain structure as a moderator). In a study of Mexican-origin adolescents, Schriber et al. (2017) found that larger hippocampal volume was a marker of differential susceptibility. Specifically, in adolescents with larger hippocampal volume, community violence and family connectedness were associated with more and less severe depressive symptoms, respectively; in contrast, these factors were not associated with depressive symptoms in adolescents with smaller hippocampal volume. Deane et al. (2020) focused on sensitivity to the adverse effects of maternal aggression, which could be a proxy for common family-related stressors. Assessing individual differences in cortical thinning at three timepoints across adolescence, Deane et al. (2020) found that adolescents with less cortical thinning were more susceptible to both the adverse and the positive effects of higher and low maternal aggression, respectively, on their well-being. Although more research is needed, these early findings suggest that larger hippocampal volume and reduced cortical thinning mark heightened sensitivity to both negative and positive experiences during adolescence.

Table 3 presents a summary of the findings and implications of studies focused on ELS and brain structure in adolescents.

4 Brain Circuits

Functional connections between the amygdala and regions of the PFC constitute a critical circuit for socioemotional processing (Banks et al. 2007; Phelps et al. 2004). Several studies have reported altered amygdala-prefrontal functional connectivity

Table 3 Summary of the findings and implications of studies focused on ELS and brain structure in adolescents

Regions	Structural alteration following ELS	Implications
Prefrontal and parietal cortices	Reduced volume, increased cortical thinning	Increased risk for psychopathology, but may also indicate reduced plasticity and sensitivity to negative and positive experiences in adolescence
Hippocampus	Reduced volume	Increased risk for psychopathology, but may also indicate reduced plasticity and sensitivity to negative and positive experiences in adolescence
Amygdala	Unclear; may be sex-, age-, or pubertal development-specific	Altered emotion processing implicated in risk for psychopathology

following ELS (see review by VanTieghem and Tottenham 2018). Children and adolescents who had been exposed to trauma (e.g., physical abuse, neglect, domestic violence, sexual abuse) have been shown to exhibit weaker negative connectivity between the pregenual ACC and amygdala than do non-trauma-exposed youth when viewing and labeling facial emotions in the presence of emotional distractor words; further, lower connectivity was associated with poorer performance on this emotional conflict task (Marusak et al. 2015). These findings suggest that heightened emotional reactivity following ELS (as shown via activation studies of amygdala) is not properly modulated by prefrontal regions, leading to difficulties in emotion regulation.

Researchers have provided evidence of a mediating role of amygdala-prefrontal circuitry in the association between ELS and psychopathology in adolescence. Adolescents who experienced childhood maltreatment (e.g., physical and sexual abuse, physical and emotional neglect) have been shown to have weaker resting-state connectivity between the amygdala and subgenual ACC; importantly, this amygdala-prefrontal alteration mediated the association between ELS and internalizing symptoms at age 18, such that weaker connectivity contributed to higher levels of symptoms (Herringa et al. 2013). Weaker resting-state amygdala-ACC connectivity in ELS-exposed children and adolescents has also been shown to predict higher anxiety symptoms 1 year later (Pagliaccio et al. 2015). The long-term impact of ELS on amygdala-PFC connectivity and stress response has also been documented in adults. Young adult males who reported a history of ELS, specifically childhood abuse, showed weaker resting-state functional connectivity between the pregenual ACC and amygdala; these adults also exhibited higher levels of state anxiety following a psychosocial stress task (Fang et al. 2012). Similarly, young adults with history of childhood maltreatment have been found to exhibit atypical connectivity between the amygdala and inferior frontal gyrus when processing threat-related emotional stimuli (Jedd et al. 2015).

Importantly, the *Stress Acceleration Hypothesis* posits that fronto-limbic circuitry develops at an accelerated rate following ELS as a temporary adaptation to adversity

(Callaghan and Tottenham 2016; Herzberg and Gunnar 2020). For example, adolescents who were exposed to maternal deprivation were found to have more mature (i.e., negative) amygdala-prefrontal functional connectivity; further, this neural pattern was related to fewer symptoms of anxiety and, thus, may be characterized as being adaptive (Gee et al. 2013). In addition, previously-institutionalized youth have been shown to have stronger functional connectivity between prefrontal and limbic regions during aversive learning than do typically-developing youth (Silvers et al. 2016); stronger connectivity also predicted improvement in anxiety symptoms. Finally, negative prefrontal-amygdala connectivity has been found to be stronger in adolescents with ELS, a pattern that was also associated with lower internalizing symptoms. Recently, we similarly demonstrated that adolescents who were exposed to more severe ELS exhibited negative prefrontal-amygdala connectivity during socioemotional processing (Colich et al. 2017; Miller et al. 2020b); further, this neurophenotype predicted slower biological aging over 2 years, assessed by telomere shortening and pubertal tempo (Miller et al. 2020b). The protective associations of negative prefrontal-amygdala connectivity were strongest in adolescents who had been exposed to more severe ELS, suggesting that this neurophenotype confers some positive adaptation following ELS. We also recently found that adolescents with more exposure to ELS exhibited greater age-related changes in white matter pathways connecting the frontal lobes to limbic, temporal, and parietal regions; further, higher fiber density and cross-section of the uncinate fasciculus, which connects frontal and limbic regions, was associated with lower levels of internalizing problems in mid-adolescence (Chahal et al. 2020b). We should note, however, that in these studies we conducted cross-sectional analyses and found that adolescents exposed to ELS have more "mature"-appearing neurophenotypes that are often accompanied by fewer symptoms of psychopathology. No study has yet examined longitudinally the development of brain functional or structural connections in the context of ELS to investigate whether neural alterations remain throughout development, or alternatively, whether lower-ELS youth eventually "catch up" with their more ELS-exposed peers.

Although less common than research examining fronto-limbic connectivity, some studies also suggest that reward circuitry is altered in ELS. Lower functional connectivity between the ventral tegmental area and hippocampus, as well as between the substantia nigra and hippocampus, has been reported in adolescents who were exposed to threat-related forms of ELS (Marusak et al. 2017). Another study found that post-institutionalized youth exhibited higher functional connectivity between the ventral striatum and anterior medial PFC, a neural pattern that was also related to greater social problems (Fareri et al. 2017). Finally, Herzberg and Gunnar (2020) posited that accelerated fronto-limbic circuit development may come at the cost of delayed reward circuit development, although this formulation has not yet been tested longitudinally.

ELS has also been linked to alterations in the executive control network (ECN). The ECN includes frontoparietal brain regions and supports executive functioning skills (Cole and Schneider 2007). Stress experienced in the first year of life has been associated with greater resting intra-regional synchronization of activity in the left

Table 4 Summary of the findings and implications of studies focused on ELS and brain circuits in adolescents

Regions	Circuit alteration following ELS	Implications
Prefrontal-amygdala	Mixed evidence with studies reporting either weaker or stronger negative connectivity	Dysregulated emotional reactivity
Fronto-parietal-temporal (executive control network)	Weaker positive connectivity	Poor executive functioning abilities (e.g., attention); potentially exacerbates risk for physical and mental health problems
Striatal-frontal-limbic (reward network)	Unclear	Altered emotion processing implicated in risk for psychopathology

prefrontal cortex in young children, and this pattern of brain activity was associated with poorer cognitive control ability (Demir-Lira et al. 2016). In a study that compared adolescents with a history of severe child abuse with a healthy control group, participants exposed to child abuse demonstrated reduced functional connectivity in the ECN network when engaging in a sustained attention task, a neural pattern related to poorer performance on the task (Hart et al. 2017). Taken together, ELS may contribute to abnormal functional connectivity within the ECN and between the ECN and other regions, potentially impeding the development of executive functions that help buffer against the development of psychopathology.

In addition to possibly being altered following ELS, recent research on moderator effects indicates that functional connectivity within the ECN may be a source of resilience. Higher resting-state ECN connectivity appears to buffer adolescents against cardiometabolic risks associated with exposure to violence in the community (Miller et al. 2018). Similarly, we are finding that higher ECN connectivity buffers against risk for internalizing problems during the COVID-19 pandemic in adolescents who previously reported being in more advanced stages of puberty relative to their same-age peers (Chahal et al. 2021); further, ELS was associated with more advanced puberty in females, a finding consistent with results of past research with adolescents exposed to maltreatment (Mendle et al. 2011). Taken together, it appears that neural circuits that support executive functioning contribute to resilience against physical and mental health problems in adolescents who may otherwise be at risk (e.g., those exposed to ELS).

Table 4 presents a summary of the findings and implications of studies focused on ELS and brain circuits in adolescents.

5 Common Themes Across ELS Research on Function, Structure, and Circuits

The literature shows that across various samples, across measures of ELS, and across neuroimaging methods, exposure to ELS is associated with altered brain development in adolescence. ELS may have selective strengthening and downregulatory effects on different neural systems. ELS is linked not only to neurophenotypes that underlie increased engagement with and processing of emotionally salient stimuli (Hein and Monk 2017; Humphreys et al. 2019a; Teicher et al. 2018), but also to blunted reward-processing (Hanson et al. 2015a) and to decreased activation and connectivity in regions important for executive functioning (Chahal et al. 2020c; Weissman et al. 2020a). The combination of these neural alterations following ELS may support psychological processes that serve as core mechanisms that link ELS to multiple forms of psychopathology.

Many of the observed associations both in the broader literature and in our own study are consistent with the stress acceleration hypothesis – that ELS can lead to faster maturation of neural regions and circuits implicated in affective processing (Callaghan and Tottenham 2016). For example, ELS has been linked to amygdala hyperreactivity to salient and threatening stimuli (Hein and Monk 2017; Suzuki et al. 2014; Tottenham et al. 2011), to negative prefrontal-amygdala functional connectivity (Colich et al. 2017; Gee et al. 2013; Miller et al. 2020b), to increased integrity in fronto-limbic white matter tracts (Chahal et al. 2020b; Kircanski et al. 2019), and to cortical thinning and reduced gray matter (Bartlett et al. 2019; Hanson et al. 2010). Although these outcomes may reflect more mature neurophenotypes in adolescence, they may also vary in whether they confer risk or resilience (short-term) following ELS (Aghajani et al. 2014; Callaghan and Tottenham 2016; Gee et al. 2013). More mature functional and structural connections between frontal and limbic regions may confer resilience to adverse outcomes following ELS (Chahal et al. 2020b; Gee et al. 2013; Miller et al. 2020b), whereas amygdala hyperreactivity and accelerated cortical maturation may contribute to elevated risk for ELS-related difficulties (Bartlett et al. 2019; Hanson et al. 2010; Tottenham et al. 2011). Further research is necessary to clarify when and for whom ELS leads to neurophenotypes that reflect accelerated maturation that supports resilience versus vulnerability.

One potential consequence of ELS-related acceleration in neurodevelopment is an earlier reduction in plasticity (Callaghan and Tottenham 2016). Interestingly, some of the brain-based moderators of sensitivity to environmental influence are affected by ELS. For example, smaller hippocampal volume and greater cortical thinning following ELS may indicate more mature development in these systems, with implications for increased risk for psychopathology (Bartlett et al. 2019; Hanson et al. 2015b), but may also indicate reduced sensitivity to environmental influence (Deane et al. 2020; Schriber et al. 2017). This relative insensitivity to the environment may represent a developmental adaptation following ELS that helps to reduce vulnerability to subsequent adverse experiences during adolescence (i.e., plasticity) that may exacerbate difficulties. Indeed, research with nonhuman primates

suggests that ELS places a limit on reactivity to subsequent stressors (Parker et al. 2006). Conversely, reduced sensitivity/plasticity may also render some adolescents less open to the benefits that can be derived from subsequent positive, supportive experiences. It is important to note, however, that this interpretation is speculative given that few studies have focused on brain-based moderators of ELS and related experiences. Indeed, research on brain-based resilience in general is a relatively recent undertaking compared to research on ELS-related mechanisms of risk. More studies are urgently needed to increase our understanding of whether putative neurophenotypes of resilience serve as compensatory factors that help to offset ELS-related risk, or whether they act as protective moderators that buffer against the adverse effects of ELS.

6 Future Directions

One intriguing direction for the field is to apply more person-centered methodologies to define brain-based biotypes. Brain-based biotyping is a relatively novel concept that involves examining patterns of resting-state (or task-based) functional connectivity (within and between networks) to determine whether subgroups of individuals can be identified at the neural level. Figure 1 presents a visual summary of the brain-based biotyping approach and how it might reveal otherwise undetected heterogeneity in a sample of adolescents exposed to ELS (e.g., who is more or less likely to develop symptoms of psychopathology). Biotyping can be accomplished by selecting regions of interest in candidate networks (e.g., default mode, salience, cognitive control networks) and testing whether individuals with different subtypes of disorders differ in their neural signatures (Williams 2017). A second approach to biotyping is utilizing data-driven techniques to parse neurophysiological patterns, rather than examining differences in a priori groups; this approach allows researchers to distinguish neural patterns that may otherwise be masked by group-averaged approaches (e.g., Chahal et al. 2020d; Price et al. 2017). For example, subtypes of adult depression have been identified based on heterogeneous connectivity-based profiles using the Subgroup Group Iterative Multiple Model Estimation (S-GIMME; Gates et al. 2017). Further, a community sample of adolescents have been parsed using S-GIMME into two ventral affective network biotypes that differ in the past, current, and future internalizing symptoms (Chahal et al. 2020d). Importantly, S-GIMME is an unsupervised approach that examines directed functional connections between regions of interest and uses Walktrap (Pons and Latapy 2006), a community detection algorithm, to identify subgroups of individuals with shared patterns of directed connectivity. Because no symptom information is required beforehand, this approach relies entirely on brain-derived information to search for connectivity-based subgroups that can later be compared on external variables. Therefore, biotyping has great potential for use in research examining ELS risk and resilience, as it can reveal brain-based differences that may be related to different

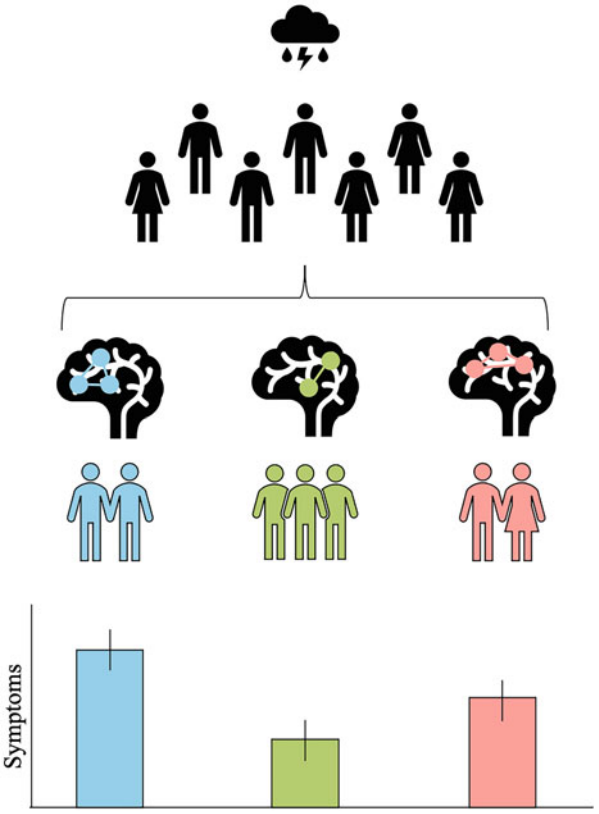

Fig. 1 The utility of biotyping in uncovering brain-based susceptibility to psychopathology following early life stress. Brain-based biotyping utilizes functional brain imaging data to determine whether there are heterogeneous patterns of neural connectivity in the sample. This approach has shown promise in uncovering different patterns of neural circuitry interactions that are associated with current and future symptom levels (e.g., Chahal et al. 2020d). When applied to a sample of participants exposed to early life stress, this approach reveals distinct neural biotypes that show differential levels of susceptibility to psychopathology (e.g., Chahal et al. revise and resubmit). This figure has been adapted with permission from Chahal et al. (2020a)

types or duration of ELS, and to differences in susceptibility to adversity with regard to psychopathology, without any prior model information.

To date, however, only two studies have investigated biotypes in the context of ELS. One study found that adolescents with high violence exposure were more likely to belong to a connectivity-based subgroup (i.e., biotype) that showed few shared connections and low network density of the salience and default mode networks, compared to adolescents who were not exposed to violence (Goetschius et al. 2020). In the second study, we examined the utility of biotyping in understanding resilience to psychopathology following ELS (Chahal et al. revise and resubmit). We first identified regions of the executive control network, given its involvement in adolescent psychopathology (Chahal et al. 2020a). We then tested whether we could identify connectivity subgroups, based on similarities in directed functional connections within the ECN. We found three separable ECN subgroups, and then tested whether these subgroups differed in the association between ELS severity and depression, in order to examine whether there are susceptible or resilient brain-based groups. Interestingly, we found that one ECN connectivity subgroup, consisting of 25% of the sample and characterized by more directed connections between frontoparietal brain regions, did not show an association between ELS and

general psychopathology (based on a latent factor score of six psychopathology measures). This ECN subgroup could be characterized as resilient, given that those participants were protected from ELS effects. In contrast, in the other two subgroups there were strong positive associations between ELS and psychopathology (i.e., risk groups). Importantly, we found that differences in risk and resilience could not be uncovered by raw correlation values that are typically used in connectivity studies. These findings highlight the importance of examining biotypes to understand individual differences in the sequelae of ELS. The community detection approach is blind to information about symptoms and ELS exposure; thus, the resulting subgroups represent meaningful partitions of psychological processes.

Finally, we believe it is important for researchers to adopt theoretical perspectives and use methodological approaches that conceptualize ELS as being embedded in the context of other types of environmental factors. For example, ELS often co-occurs with different physical environmental factors, such as environmental pollutants, that are also implicated in the development of neurobiological systems important for risk and resilience (Olvera Alvarez et al. 2018). Few studies of ELS and brain development have considered pollutants, despite recent calls for more research both on the effects of pollutants on psychological development (Trentacosta et al. 2016) and on the joint, synergistic effects of ELS and pollutants on neurobiology and health (Olvera Alvarez et al. 2018). Interestingly, many of the adverse effects of ELS and environmental pollutants appear to be mediated through similar neurobiological pathways, such as chronic activation of stress-response systems (Thomson 2019). Our own work with adolescents suggests that living in areas with higher concentrations of air pollution is associated with increased biological reactivity to social stress (i.e., increased autonomic and HPA axis reactivity to lab-based stress test), a link that we found to be magnified in adolescents who were experiencing high levels of psychosocial stress in the form of internalizing difficulties (Miller et al. 2019, 2020a). In addition, we recently found that for adolescents living in psychologically controlling families, higher levels of drinking water contaminants were associated with increases in depressive symptoms over 2 years (Manczak et al. 2020). Taken together, these findings highlight the interplay of psychosocial and physical environmental factors in influencing risk and resilience to psychopathology. More research on adolescent brain development is needed that considers exposure to physical environmental and psychosocial factors that are more closely related to ELS, such as experiences of deprivation and threat.

7 Conclusions

The studies we discuss in this chapter converge to suggest that exposure to ELS organizes and consolidates brain development in a manner that places adolescents at risk for experiencing psychopathology and other kinds of negative health outcomes. The field is making considerable progress in identifying specific brain-based pathways that link ELS to subsequent problems in mental and physical health.

Nevertheless, not all adolescents are equally sensitive or vulnerable to the adverse effects of ELS on well-being. The complex coordination of ELS and neurobiology that underlies individual differences in risk and resilience is only beginning to be considered by researchers in the area of developmental neuroscience. Methodological advances in our modeling of ELS and neurobiology, as well as a consideration of ELS in the context of other risk- and resilience-promoting factors, will advance our understanding of mechanisms, of early detection of high-risk adolescents, and of efforts to develop targeted preventions and interventions aimed at fostering resilience.

Acknowledgements Preparation of this paper was supported by the National Institutes of Health (Grants R37MH101495 to IHG and F32MH120975 to RC), the Klingenstein Third Generation Foundation (RC), and the Stanford Center on Longevity (JGM).

References

Aghajani M, Veer IM, van Lang NDJ, Meens PHF, van den Bulk BG, Rombouts S, Vermeiren R, van der Wee NJA (2014) Altered white-matter architecture in treatment-naive adolescents with clinical depression. Psychol Med 44(11):2287–2298. https://doi.org/10.1017/S0033291713003000

Andersen SL, Teicher MH (2008) Stress, sensitive periods and maturational events in adolescent depression. Trends Neurosci 31(4):183–191. https://doi.org/10.1016/j.tins.2008.01.004

Ansell EB, Rando K, Tuit K, Guarnaccia J, Sinha R (2012) Cumulative adversity and smaller gray matter volume in medial prefrontal, anterior cingulate, and insula regions. Biol Psychiatry 72(1):57–64. https://doi.org/10.1016/j.biopsych.2011.11.022

Banks SJ, Eddy KT, Angstadt M, Nathan PJ, Phan KL (2007) Amygdala-frontal connectivity during emotion regulation. Soc Cogn Affect Neurosci 2(4):303–312. https://doi.org/10.1093/scan/nsm029

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(10):769–778. https://doi.org/10.1016/j.biopsych.2019.04.027

Beesdo K, Lau JYF, Guyer AE, McClure-Tone EB, Monk CS, Nelson EE, Fromm SJ, Goldwin MA, Wittchen H-U, Leibenluft E, Ernst M, Pine DS (2009) Common and distinct amygdala-function perturbations in depressed vs anxious adolescents. Arch Gen Psychiatry 66(3):275–285. https://doi.org/10.1001/archgenpsychiatry.2008.545

Berridge KC (2007) The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology 191(3):391–431. https://doi.org/10.1007/s00213-006-0578-x

Blackford JU, Allen AH, Cowan RL, Avery SN (2013) Amygdala and hippocampus fail to habituate to faces in individuals with an inhibited temperament. Soc Cogn Affect Neurosci 8(2):143–150. https://doi.org/10.1093/scan/nsr078

Bonanno GA, Diminich ED (2013) Annual research review: positive adjustment to adversity--trajectories of minimal-impact resilience and emergent resilience. J Child Psychol Psychiatry 54(4):378–401. https://doi.org/10.1111/jcpp.12021

Boyce WT (2016) Differential susceptibility of the developing brain to contextual adversity and stress. Neuropsychopharmacology 41(1):142–162. https://doi.org/10.1038/npp.2015.294

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. https://doi.org/10.1016/j.cobeha.2015.11.018

Callaghan BL, Gee DG, Gabard-Durnam L, Telzer EH, Humphreys KL, Goff B, Shapiro M, Flannery J, Lumian DS, Fareri DS, Caldera C, Tottenham N (2019) Decreased amygdala reactivity to parent cues protects against anxiety following early adversity: an examination across 3 years. Biol Psychiatry Cogn Neurosci Neuroimaging 4(7):664–671. https://doi.org/10.1016/j.bpsc.2019.02.001

Chahal R, Gotlib IH, Guyer AE (2020a) Brain network connectivity and the heterogeneity of depression in adolescence: a precision mental health perspective. J Child Psychol Psychiatry 61(12):1282–1298. https://doi.org/10.1111/jcpp.13250

Chahal R, Kirshenbaum JS, Ho TC, Mastrovito D, Gotlib IH (2020b) Greater age-related changes in white matter morphometry following early life stress: associations with internalizing problems in adolescence. Dev Cogn Neurosci 47:100899. https://doi.org/10.1016/j.dcn.2020.100899

Chahal R, Kirshenbaum JS, Miller JG, Ho TC, Gotlib IH (2020c) Higher executive control network coherence buffers against puberty-related increases in internalizing symptoms during the COVID-19 pandemic. Biol Psychiatry Cogn Neurosci Neuroimaging. https://doi.org/10.1016/j.bpsc.2020.08.010

Chahal R, Weissman DG, Hallquist MN, Robins RW, Hastings PD, Guyer AE (2020d) Neural connectivity biotypes: associations with internalizing problems throughout adolescence. Psychol Med 1–11. https://doi.org/10.1017/S003329172000149X

Chahal R, Kirshenbaum JS, Miller JG, Ho TC, Gotlib IH (2021) Higher executive control network coherence buffers against puberty-related increases in internalizing symptoms during the COVID-19 pandemic. Biol Psychiatry Cogn Neurosci Neuroimaging 6(1):79–88. https://doi.org/10.1016/j.bpsc.2020.08.010

Chahal R, Ho TC, Kirshenbaum JS, Miller JG, Gotlib IH (revise and resubmit) Neural subgroups based on executive control and default mode networks predict longitudinal changes in internalizing and externalizing symptoms during puberty

Cohodes EM, Kitt ER, Baskin-Sommers A, Gee DG (2020) Influences of early-life stress on frontolimbic circuitry: harnessing a dimensional approach to elucidate the effects of heterogeneity in stress exposure. Dev Psychobiol. https://doi.org/10.1002/dev.21969

Cole MW, Schneider W (2007) The cognitive control network: integrated cortical regions with dissociable functions. NeuroImage 37(1):343–360. https://doi.org/10.1016/j.neuroimage.2007.03.071

Colich NL, Williams ES, Ho TC, King LS, Humphreys KL, Price AN, Ordaz SJ, Gotlib IH (2017) The association between early life stress and prefrontal cortex activation during implicit emotion regulation is moderated by sex in early adolescence. Dev Psychopathol 29(5):1851–1864. https://doi.org/10.1017/S0954579417001444

Colich NL, Rosen ML, Williams ES, McLaughlin KA (2020) Biological aging in childhood and adolescence following experiences of threat and deprivation: a systematic review and meta-analysis. Psychol Bull 146(9):721–764. https://doi.org/10.1037/bul0000270

De Brito SA, Viding E, Sebastian CL, Kelly PA, Mechelli A, Maris H, McCrory EJ (2013) Reduced orbitofrontal and temporal grey matter in a community sample of maltreated children. J Child Psychol Psychiatry 54(1):105–112. https://doi.org/10.1111/j.1469-7610.2012.02597.x

Deane C, Vijayakumar N, Allen NB, Schwartz O, Simmons JG, Bousman CA, Pantelis C, Whittle S (2020) Parenting × brain development interactions as predictors of adolescent depressive symptoms and well-being: differential susceptibility or diathesis-stress? Dev Psychopathol 32(1):139–150. https://doi.org/10.1017/S0954579418001475

Del Giudice M, Ellis BJ, Shirtcliff EA (2011) The adaptive calibration model of stress responsivity. Neurosci Biobehav Rev 35(7):1562–1592. https://doi.org/10.1016/j.neubiorev.2010.11.007

Demir-Lira ÖE, Voss JL, O'Neil JT, Briggs-Gowan MJ, Wakschlag LS, Booth JR (2016) Early-life stress exposure associated with altered prefrontal resting-state fMRI connectivity in young children. Dev Cogn Neurosci 19:107–114. https://doi.org/10.1016/j.dcn.2016.02.003

Dismukes AR, Johnson MM, Vitacco MJ, Iturri F, Shirtcliff EA (2015) Coupling of the HPA and HPG axes in the context of early life adversity in incarcerated male adolescents. Dev Psychobiol 57(6):705–718. https://doi.org/10.1002/dev.21231

Dunn EC, Soare TW, Zhu Y, Simpkin AJ, Suderman MJ, Klengel T, Smith ADAC, Ressler KJ, Relton CL (2019) Sensitive periods for the effect of childhood adversity on DNA methylation: results from a prospective, longitudinal study. Biol Psychiatry 85(10):838–849. https://doi.org/10.1016/j.biopsych.2018.12.023

Everaerd D, Klumpers F, Zwiers M, Guadalupe T, Franke B, van Oostrom I, Schene A, Fernández G, Tendolkar I (2016) Childhood abuse and deprivation are associated with distinct sex-dependent differences in brain morphology. Neuropsychopharmacology 41(7):1716–1723. https://doi.org/10.1038/npp.2015.344

Fang P, Zeng L-L, Shen H, Wang L, Li B, Liu L, Hu D (2012) Increased cortical-limbic anatomical network connectivity in major depression revealed by diffusion tensor imaging. PLoS One 7(9). https://doi.org/10.1371/journal.pone.0045972

Fareri DS, Gabard-Durnam L, Goff B, Flannery J, Gee DG, Lumian DS, Caldera C, Tottenham N (2017) Altered ventral striatal–medial prefrontal cortex resting-state connectivity mediates adolescent social problems after early institutional care. Dev Psychopathol 29(5):1865–1876. https://doi.org/10.1017/S0954579417001456

Feldman R (2015) Sensitive periods in human social development: new insights from research on oxytocin, synchrony, and high-risk parenting. Dev Psychopathol 27(2):369–395. https://doi.org/10.1017/S0954579415000048

Flaherty EG, Thompson R, Litrownik AJ, Theodore A, English DJ, Black MM, Wike T, Whimper L, Runyan DK, Dubowitz H (2006) Effect of early childhood adversity on child health. Arch Pediatr Adolesc Med 160(12):1232–1238. https://doi.org/10.1001/archpedi.160.12.1232

Fox AS, Oler JA, Shackman AJ, Shelton SE, Raveendran M, McKay DR, Converse AK, Alexander A, Davidson RJ, Blangero J, Rogers J, Kalin NH (2015) Intergenerational neural mediators of early-life anxious temperament. Proc Natl Acad Sci 112(29):9118–9122. https://doi.org/10.1073/pnas.1508593112

Frankenhuis WE, de Weerth C (2013) Does early-life exposure to stress shape or impair cognition? Curr Dir Psychol Sci 22(5):407–412. https://doi.org/10.1177/0963721413484324

Gard AM, Shaw DS, Forbes EE, Hyde LW (2018) Amygdala reactivity as a marker of differential susceptibility to socioeconomic resources during early adulthood. Dev Psychol 54(12):2341–2355. https://doi.org/10.1037/dev0000600

Gates KM, Lane ST, Varangis E, Giovanello K, Guiskewicz K (2017) Unsupervised classification during time-series model building. Multivar Behav Res 52(2):129–148. https://doi.org/10.1080/00273171.2016.1256187

Gee DG (2020) Caregiving influences on emotional learning and regulation: applying a sensitive period model. Curr Opin Behav Sci 36:177–184. https://doi.org/10.1016/j.cobeha.2020.11.003

Gee DG, Gabard-Durnam LJ, Flannery J, Goff B, Humphreys KL, Telzer EH, Hare TA, Bookheimer SY, Tottenham N (2013) Early developmental emergence of human amygdala–prefrontal connectivity after maternal deprivation. Proc Natl Acad Sci 110(39):15638–15643. https://doi.org/10.1073/pnas.1307893110

Goetschius LG, Hein TC, McLanahan SS, Brooks-Gunn J, McLoyd VC, Dotterer HL, Lopez-Duran N, Mitchell C, Hyde LW, Monk CS, Beltz AM (2020) Association of childhood violence exposure with adolescent neural network density. JAMA Netw Open 3(9). https://doi.org/10.1001/jamanetworkopen.2020.17850

Goff B, Gee DG, Telzer EH, Humphreys KL, Gabard-Durnam L, Flannery J, Tottenham N (2013) Reduced nucleus accumbens reactivity and adolescent depression following early-life stress. Neuroscience 249:129–138. https://doi.org/10.1016/j.neuroscience.2012.12.010

Green JG, McLaughlin KA, Berglund PA, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC (2010) Childhood adversities and adult psychiatric disorders in the National Comorbidity Survey Replication I: associations with first onset of DSM-IV disorders. Arch Gen Psychiatry 67(2):113–123. https://doi.org/10.1001/archgenpsychiatry.2009.186

Guyer AE (2020) Adolescent psychopathology: the role of brain-based diatheses, sensitivities, and susceptibilities. Child Dev Perspect 14(2):104–109. https://doi.org/10.1111/cdep.12365

Hagan MJ, Sulik MJ, Lieberman AF (2016) Traumatic life events and psychopathology in a high risk, ethnically diverse sample of young children: a person-Centered approach. J Abnorm Child Psychol 44(5):833–844. https://doi.org/10.1007/s10802-015-0078-8

Hanson JL, Chung MK, Avants BB, Shirtcliff EA, Gee JC, Davidson RJ, Pollak SD (2010) Early stress is associated with alterations in the orbitofrontal cortex: a tensor-based morphometry investigation of brain structure and Behavioral risk. J Neurosci 30(22):7466–7472. https://doi.org/10.1523/JNEUROSCI.0859-10.2010

Hanson JL, Hariri AR, Williamson DE (2015a) Blunted ventral striatum development in adolescence reflects emotional neglect and predicts depressive symptoms. Biol Psychiatry 78(9): 598–605. https://doi.org/10.1016/j.biopsych.2015.05.010

Hanson JL, Nacewicz BM, Sutterer MJ, Cayo AA, Schaefer SM, Rudolph KD, Shirtcliff EA, Pollak SD, Davidson RJ (2015b) Behavioral problems after early life stress: contributions of the hippocampus and amygdala. Biol Psychiatry 77(4):314–323. https://doi.org/10.1016/j.biopsych.2014.04.020

Hart H, Lim L, Mehta MA, Chatzieffraimidou A, Curtis C, Xu X, Breen G, Simmons A, Mirza K, Rubia K (2017) Reduced functional connectivity of fronto-parietal sustained attention networks in severe childhood abuse. PLoS One 12(11):e0188744. https://doi.org/10.1371/journal.pone.0188744

Hein TC, Monk CS (2017) Research review: neural response to threat in children, adolescents, and adults after child maltreatment - a quantitative meta-analysis. J Child Psychol Psychiatry 58(3): 222–230. https://doi.org/10.1111/jcpp.12651

Herringa RJ, Birn RM, Ruttle PL, Burghy CA, Stodola DE, Davidson RJ, Essex MJ (2013) Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. Proc Natl Acad Sci 110(47):19119–19124. https://doi.org/10.1073/pnas.1310766110

Herzberg MP, Gunnar MR (2020) Early life stress and brain function: activity and connectivity associated with processing emotion and reward. NeuroImage 209:116493. https://doi.org/10.1016/j.neuroimage.2019.116493

Hodel AS, Hunt RH, Cowell RA, Van Den Heuvel SE, Gunnar MR, Thomas KM (2015) Duration of early adversity and structural brain development in post-institutionalized adolescents. NeuroImage 105:112–119. https://doi.org/10.1016/j.neuroimage.2014.10.020

Holz NE, Tost H, Meyer-Lindenberg A (2020) Resilience and the brain: a key role for regulatory circuits linked to social stress and support. Mol Psychiatry 25(2):379–396. https://doi.org/10.1038/s41380-019-0551-9

Humphreys KL, King LS, Sacchet MD, Camacho MC, Colich NL, Ordaz SJ, Ho TC, Gotlib IH (2019a) Evidence for a sensitive period in the effects of early life stress on hippocampal volume. Dev Sci 22(3):e12775. https://doi.org/10.1111/desc.12775

Humphreys KL, Watts EL, Dennis EL, King LS, Thompson PM, Gotlib IH (2019b) Stressful life events, ADHD symptoms, and brain structure in early adolescence. J Abnorm Child Psychol 47(3):421–432. https://doi.org/10.1007/s10802-018-0443-5

Jacobson L, Sapolsky R (1991) The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. Endocr Rev 12(2):118–134. https://doi.org/10.1210/edrv-12-2-118

Jedd K, Hunt RH, Cicchetti D, Hunt E, Cowell R, Rogosch F, Toth S, Thomas KM (2015) Long-term consequences of childhood maltreatment: altered amygdala functional connectivity. Dev Psychopathol 27(4 0 2):1577–1589. https://doi.org/10.1017/S0954579415000954

Kerestes R, Davey CG, Stephanou K, Whittle S, Harrison BJ (2014) Functional brain imaging studies of youth depression: a systematic review. Neuroimage Clin 4:209–231. https://doi.org/10.1016/j.nicl.2013.11.009

King LS, Colich NL, LeMoult J, Humphreys KL, Ordaz SJ, Price AN, Gotlib IH (2017) The impact of the severity of early life stress on diurnal cortisol: the role of puberty. Psychoneuroendocrinology 77:68–74. https://doi.org/10.1016/j.psyneuen.2016.11.024

King LS, Humphreys KL, Camacho MC, Gotlib IH (2019) A person-centered approach to the assessment of early life stress: associations with the volume of stress-sensitive brain regions in early adolescence. Dev Psychopathol 31(2):643–655. https://doi.org/10.1017/S0954579418000184

King LS, Graber MG, Colich NL, Gotlib IH (2020) Associations of waking cortisol with DHEA and testosterone across the pubertal transition: effects of threat-related early life stress. Psychoneuroendocrinology 115:104651. https://doi.org/10.1016/j.psyneuen.2020.104651

Kircanski K, Sisk LM, Ho TC, Humphreys KL, King LS, Colich NL, Ordaz SJ, Gotlib IH (2019) Early life stress, cortisol, frontolimbic connectivity, and depressive symptoms during puberty. Dev Psychopathol 31(3):1011–1022. https://doi.org/10.1017/S0954579419000555

LeDoux J (2007) The amygdala. Curr Biol 17(20):R868–R874. https://doi.org/10.1016/j.cub.2007.08.005

LeMoult J, Humphreys KL, Tracy A, Hoffmeister J-A, Ip E, Gotlib IH (2020) Meta-analysis: exposure to early life stress and risk for depression in childhood and adolescence. J Am Acad Child Adolesc Psychiatry 59(7):842–855. https://doi.org/10.1016/j.jaac.2019.10.011

Luby JL, Belden A, Harms MP, Tillman R, Barch DM (2016) Preschool is a sensitive period for the influence of maternal support on the trajectory of hippocampal development. Proc Natl Acad Sci 113(20):5742–5747. https://doi.org/10.1073/pnas.1601443113

Luthar SS, Cicchetti D, Becker B (2000) The construct of resilience: a critical evaluation and guidelines for future work. Child Dev 71(3):543–562. https://doi.org/10.1111/1467-8624.00164

Malhi GS, Das P, Bell E, Mattingly G, Mannie Z (2019) Modelling resilience in adolescence and adversity: a novel framework to inform research and practice. Transl Psychiatry 9(1):1–16. https://doi.org/10.1038/s41398-019-0651-y

Manczak EM, Miller JG, Gotlib IH (2020) Water contaminant levels interact with parenting environment to predict development of depressive symptoms in adolescents. Dev Sci 23(1):e12838. https://doi.org/10.1111/desc.12838

Maren S, Phan KL, Liberzon I (2013) The contextual brain: implications for fear conditioning, extinction and psychopathology. Nat Rev Neurosci 14(6):417–428. https://doi.org/10.1038/nrn3492

Martini L, Melcangi RC (1991) Androgen metabolism in the brain. J Steroid Biochem Mol Biol 39(5B):819–828. https://doi.org/10.1016/0960-0760(91)90031-y

Marusak HA, Martin KR, Etkin A, Thomason ME (2015) Childhood trauma exposure disrupts the automatic regulation of emotional processing. Neuropsychopharmacology 40(5):1250–1258. https://doi.org/10.1038/npp.2014.311

Marusak HA, Hatfield JRB, Thomason ME, Rabinak CA (2017) Reduced ventral tegmental area–hippocampal connectivity in children and adolescents exposed to early threat. Biol Psychiatry Cogn Neurosci Neuroimaging 2(2):130–137. https://doi.org/10.1016/j.bpsc.2016.11.002

Masten AS (2001) Ordinary magic. Resilience processes in development. Am Psychol 56(3):227–238. https://doi.org/10.1037//0003-066x.56.3.227

McCrory EJ, De Brito SA, Sebastian CL, Mechelli A, Bird G, Kelly PA, Viding E (2011) Heightened neural reactivity to threat in child victims of family violence. Curr Biol 21(23):R947–R948. https://doi.org/10.1016/j.cub.2011.10.015

McLaughlin KA, Greif Green J, Gruber MJ, Sampson NA, Zaslavsky AM, Kessler RC (2012) Childhood adversities and first onset of psychiatric disorders in a national sample of US adolescents. Arch Gen Psychiatry 69(11):1151–1160. https://doi.org/10.1001/archgenpsychiatry.2011.2277

McLaughlin KA, Colich NL, Rodman AM, Weissman DG (2020) Mechanisms linking childhood trauma exposure and psychopathology: a transdiagnostic model of risk and resilience. BMC Med 18(1):96. https://doi.org/10.1186/s12916-020-01561-6

McTeague LM, Goodkind MS, Etkin A (2016) Transdiagnostic impairment of cognitive control in mental illness. J Psychiatr Res 83:37–46. https://doi.org/10.1016/j.jpsychires.2016.08.001

Mehta MA, Golembo NI, Nosarti C, Colvert E, Mota A, Williams SCR, Rutter M, Sonuga-Barke EJS (2009) Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian adoptees study pilot. J Child Psychol Psychiatry 50(8):943–951. https://doi.org/10.1111/j.1469-7610.2009.02084.x

Mendle J, Leve LD, Van Ryzin M, Natsuaki MN, Ge X (2011) Associations between early life stress, child maltreatment, and pubertal development among girls in foster care. J Res Adolesc 21(4):871–880. https://doi.org/10.1111/j.1532-7795.2011.00746.x

Miller JG (2018) Physiological mechanisms of prosociality. Curr Opin Psychol 20:50–54. https://doi.org/10.1016/j.copsyc.2017.08.018

Miller JG, Chocol C, Nuselovici JN, Utendale WT, Simard M, Hastings PD (2013) Children's dynamic RSA change during anger and its relations with parenting, temperament, and control of aggression. Biol Psychol 92(2):417–425. https://doi.org/10.1016/j.biopsycho.2012.12.005

Miller GE, Chen E, Armstrong CC, Carroll AL, Ozturk S, Rydland KJ, Brody GH, Parrish TB, Nusslock R (2018) Functional connectivity in central executive network protects youth against cardiometabolic risks linked with neighborhood violence. Proc Natl Acad Sci 115(47): 12063–12068. https://doi.org/10.1073/pnas.1810067115

Miller JG, Gillette JS, Manczak EM, Kircanski K, Gotlib IH (2019) Fine particle air pollution and physiological reactivity to social stress in adolescence: the moderating role of anxiety and depression. Psychosom Med 81(7):641–648. https://doi.org/10.1097/PSY.0000000000000714

Miller JG, Gillette JS, Kircanski K, LeMoult J, Gotlib IH (2020a) Air pollution is associated with elevated HPA-Axis response to stress in anxious adolescent girls. Compr Psychoneuroendocrinol 4:100015. https://doi.org/10.1016/j.cpnec.2020.100015

Miller JG, Ho TC, Humphreys KL, King LS, Foland-Ross LC, Colich NL, Ordaz SJ, Lin J, Gotlib IH (2020b) Early life stress, frontoamygdala connectivity, and biological aging in adolescence: a longitudinal investigation. Cereb Cortex 30(7):4269–4280. https://doi.org/10.1093/cercor/bhaa057

Neufang S, Specht K, Hausmann M, Güntürkün O, Herpertz-Dahlmann B, Fink GR, Konrad K (2009) Sex differences and the impact of steroid hormones on the developing human brain. Cereb Cortex 19(2):464–473. https://doi.org/10.1093/cercor/bhn100

Oh DL, Jerman P, Silvério Marques S, Koita K, Purewal Boparai SK, Burke Harris N, Bucci M (2018) Systematic review of pediatric health outcomes associated with childhood adversity. BMC Pediatr 18(1):83. https://doi.org/10.1186/s12887-018-1037-7

Olvera Alvarez HA, Kubzansky LD, Campen MJ, Slavich GM (2018) Early life stress, air pollution, inflammation, and disease: an integrative review and immunologic model of social-environmental adversity and lifespan health. Neurosci Biobehav Rev 92:226–242. https://doi.org/10.1016/j.neubiorev.2018.06.002

Pagliaccio D, Luby JL, Bogdan R, Agrawal A, Gaffrey MS, Belden AC, Botteron KN, Harms MP, Barch DM (2015) Amygdala functional connectivity, HPA axis genetic variation, and life stress in children and relations to anxiety and emotion regulation. J Abnorm Psychol 124(4):817–833. https://doi.org/10.1037/abn0000094

Parker KJ, Buckmaster CL, Sundlass K, Schatzberg AF, Lyons DM (2006) Maternal mediation, stress inoculation, and the development of neuroendocrine stress resistance in primates. Proc Natl Acad Sci 103(8):3000–3005. https://doi.org/10.1073/pnas.0506571103

Pechtel P, Pizzagalli DA (2011) Effects of early life stress on cognitive and affective function: an integrated review of human literature. Psychopharmacology 214(1):55–70. https://doi.org/10.1007/s00213-010-2009-2

Phelps EA, Delgado MR, Nearing KI, LeDoux JE (2004) Extinction learning in humans: role of the amygdala and vmPFC. Neuron 43(6):897–905. https://doi.org/10.1016/j.neuron.2004.08.042

Pons P, Latapy M (2006) Computing communities in large networks using random walks. J Graph Algorithms Applications, arXiv:physics/0512106

Price RB, Lane S, Gates K, Kraynak TE, Horner MS, Thase ME, Siegle GJ (2017) Parsing heterogeneity in the brain connectivity of depressed and healthy adults during positive mood. Biol Psychiatry 81(4):347–357. https://doi.org/10.1016/j.biopsych.2016.06.023

Rodman AM, Jenness JL, Weissman DG, Pine DS, McLaughlin KA (2019) Neurobiological markers of resilience to depression following childhood maltreatment: the role of neural circuits supporting the cognitive control of emotion. Biol Psychiatry 86(6):464–473. https://doi.org/10.1016/j.biopsych.2019.04.033

Rolls ET (2019) The orbitofrontal cortex and emotion in health and disease, including depression. Neuropsychologia 128:14–43. https://doi.org/10.1016/j.neuropsychologia.2017.09.021
Roth MC, Humphreys KL, King LS, Gotlib IH (2018) Self-reported neglect, amygdala volume, and symptoms of anxiety in adolescent boys. Child Abuse Negl 80:80–89. https://doi.org/10.1016/j.chiabu.2018.03.016
Rutter M (2006) Implications of resilience concepts for scientific understanding. Ann N Y Acad Sci 1094:1–12. https://doi.org/10.1196/annals.1376.002
Ruttle PL, Shirtcliff EA, Armstrong JM, Klein MH, Essex MJ (2015) Neuroendocrine coupling across adolescence and the longitudinal influence of early life stress. Dev Psychobiol 57(6): 688–704. https://doi.org/10.1002/dev.21138
Scherf KS, Smyth JM, Delgado MR (2013) The amygdala: an agent of change in adolescent neural networks. Horm Behav 64(2):298–313. https://doi.org/10.1016/j.yhbeh.2013.05.011
Schriber RA, Guyer AE (2016) Adolescent neurobiological susceptibility to social context. Dev Cogn Neurosci 19:1–18. https://doi.org/10.1016/j.dcn.2015.12.009
Schriber RA, Anbari Z, Robins RW, Conger RD, Hastings PD, Guyer AE (2017) Hippocampal volume as an amplifier of the effect of social context on adolescent depression. Clin Psychol Sci 5(4):632–649. https://doi.org/10.1177/2167702617699277
Sherdell L, Waugh CE, Gotlib IH (2012) Anticipatory pleasure predicts motivation for reward in major depression. J Abnorm Psychol 121(1):51–60. https://doi.org/10.1037/a0024945
Sheridan MA, McLaughlin KA (2014) Dimensions of early experience and neural development: deprivation and threat. Trends Cogn Sci 18(11):580–585. https://doi.org/10.1016/j.tics.2014.09.001
Sheridan MA, Fox NA, Zeanah CH, McLaughlin KA, Nelson CA (2012) Variation in neural development as a result of exposure to institutionalization early in childhood. Proc Natl Acad Sci U S A 109(32):12927–12932. https://doi.org/10.1073/pnas.1200041109
Silvers JA, Lumian DS, Gabard-Durnam L, Gee DG, Goff B, Fareri DS, Caldera C, Flannery J, Telzer EH, Humphreys KL, Tottenham N (2016) Previous institutionalization is followed by broader amygdala–hippocampal–PFC network connectivity during aversive learning in human development. J Neurosci 36(24):6420–6430. https://doi.org/10.1523/JNEUROSCI.0038-16.2016
Sinha R, Lacadie CM, Constable RT, Seo D (2016) Dynamic neural activity during stress signals resilient coping. Proc Natl Acad Sci. https://doi.org/10.1073/pnas.1600965113
Sosnowski DW, Kliewer W, Valrie CR, Winter MA, Serpell Z, Amstadter AB (2020) The association between adverse childhood experiences and child telomere length: examining self-regulation as a Behavioral mediator. Child Dev 92(2). https://doi.org/10.1111/cdev.13441
Suzuki H, Luby JL, Botteron KN, Dietrich R, McAvoy MP, Barch DM (2014) Early life stress and trauma and enhanced limbic activation to emotionally valenced faces in depressed and healthy children. J Am Acad Child Adolesc Psychiatry 53(7):800–813.e10. https://doi.org/10.1016/j.jaac.2014.04.013
Teeuw J, Brouwer RM, Guimarães JPOFT, Brandner P, Koenis MMG, Swagerman SC, Verwoert M, Boomsma DI, Hulshoff Pol HE (2019) Genetic and environmental influences on functional connectivity within and between canonical cortical resting-state networks throughout adolescent development in boys and girls. NeuroImage 202:116073. https://doi.org/10.1016/j.neuroimage.2019.116073
Teicher MH, Samson JA, Anderson CM, Ohashi K (2016) The effects of childhood maltreatment on brain structure, function and connectivity. Nat Rev Neurosci 17(10):652–666. https://doi.org/10.1038/nrn.2016.111
Teicher MH, Anderson CM, Ohashi K, Khan A, McGreenery CE, Bolger EA, Rohan ML, Vitaliano GD (2018) Differential effects of childhood neglect and abuse during sensitive exposure periods on male and female hippocampus. NeuroImage 169:443–452. https://doi.org/10.1016/j.neuroimage.2017.12.055
Thayer JF, Ahs F, Fredrikson M, Sollers JJ, Wager TD (2012) A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress

and health. Neurosci Biobehav Rev 36(2):747–756. https://doi.org/10.1016/j.neubiorev.2011.11.009

Thomson EM (2019) Air pollution, stress, and allostatic load: linking systemic and central nervous system impacts. J Alzheimers Dis 69(3):597–614. https://doi.org/10.3233/JAD-190015

Toga AW, Thompson PM, Sowell ER (2006) Mapping brain maturation. Trends Neurosci 29(3):148–159. https://doi.org/10.1016/j.tins.2006.01.007

Tottenham N, Hare TA, Quinn BT, McCarry TW, Nurse M, Gilhooly T, Milner A, Galvan A, Davidson MC, Eigsti I-M, Thomas KM, Freed P, Booma ES, Gunnar M, Altemus M, Aronson J, Casey B (2010) Prolonged institutional rearing is associated with atypically larger amygdala volume and difficulties in emotion regulation. Dev Sci 13(1):46. https://doi.org/10.1111/j.1467-7687.2009.00852.x

Tottenham N, Hare TA, Millner A, Gilhooly T, Zevin J, Casey BJ (2011) Elevated amygdala response to faces following early deprivation. Dev Sci 14(2):190–204. https://doi.org/10.1111/j.1467-7687.2010.00971.x

Trentacosta CJ, Davis-Kean P, Mitchell C, Hyde L, Dolinoy D (2016) Environmental contaminants and child development. Child Dev Perspect 10(4):228–233. https://doi.org/10.1111/cdep.12191

Ulrich-Lai YM, Herman JP (2009) Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci 10(6):397–409. https://doi.org/10.1038/nrn2647

van Harmelen A-L, van Tol M-J, Demenescu LR, van der Wee NJA, Veltman DJ, Aleman A, van Buchem MA, Spinhoven P, Penninx BWJH, Elzinga BM (2013) Enhanced amygdala reactivity to emotional faces in adults reporting childhood emotional maltreatment. Soc Cogn Affect Neurosci 8(4):362–369. https://doi.org/10.1093/scan/nss007

VanTieghem MR, Tottenham N (2018) Neurobiological programming of early life stress: functional development of amygdala-prefrontal circuitry and vulnerability for stress-related psychopathology. Curr Top Behav Neurosci 38:117–136. https://doi.org/10.1007/7854_2016_42

Weems CF, Klabunde M, Russell JD, Reiss AL, Carrión VG (2015) Post-traumatic stress and age variation in amygdala volumes among youth exposed to trauma. Soc Cogn Affect Neurosci 10(12):1661–1667. https://doi.org/10.1093/scan/nsv053

Weissman DG, Gelardi KL, Conger RD, Robins RW, Hastings PD, Guyer AE (2018) Adolescent externalizing problems: contributions of community crime exposure and neural function during emotion introspection in Mexican-origin youth. J Res Adolesc 28(2):551–563. https://doi.org/10.1111/jora.12358

Weissman DG, Jenness JL, Colich NL, Miller AB, Sambrook KA, Sheridan MA, McLaughlin KA (2020a) Altered neural processing of threat-related information in children and adolescents exposed to violence: a transdiagnostic mechanism contributing to the emergence of psychopathology. J Am Acad Child Adolesc Psychiatry 59(11):1274–1284. https://doi.org/10.1016/j.jaac.2019.08.471

Weissman DG, Lambert HK, Rodman AM, Peverill M, Sheridan MA, McLaughlin KA (2020b) Reduced hippocampal and amygdala volume as a mechanism underlying stress sensitization to depression following childhood trauma. Depress Anxiety 37(9):916–925. https://doi.org/10.1002/da.23062

Williams LM (2017) Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation. Depress Anxiety 34(1):9–24. https://doi.org/10.1002/da.22556

Wu H, Mata J, Furman DJ, Whitmer AJ, Gotlib IH, Thompson RJ (2017) Anticipatory and consummatory pleasure and displeasure in major depressive disorder: an experience sampling study. J Abnorm Psychol 126(2):149–159. https://doi.org/10.1037/abn0000244