

REVIEW

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Early life stress and development: potential mechanisms for adverse outcomes



Karen E. Smith*  and Seth D. Pollak

Abstract

Background: Chronic and/or extreme stress in early life, often referred to as early adversity, childhood trauma, or early life stress, has been associated with a wide range of adverse effects on development. However, while early life stress has been linked to negative effects on a number of neural systems, the specific mechanisms through which early life stress influences development and individual differences in children's outcomes are still not well understood.

Main text: The current paper reviews the existing literature on the neurobiological effects of early life stress and their ties to children's psychological and behavioral development.

Conclusions: Early life stress has persistent and pervasive effects on prefrontal–hypothalamic–amygdala and dopaminergic circuits that are at least partially mediated by alterations in hypothalamic–pituitary–adrenal axis function. However, to date, this research has primarily utilized methods of assessment that focus solely on children's event exposures. Incorporating assessment of factors that influence children's interpretation of stressors, along with stressful events, has the potential to provide further insight into the mechanisms contributing to individual differences in neurodevelopmental effects of early life stress. This can aid in further elucidating specific mechanisms through which these neurobiological changes influence development and contribute to risk for psychopathology and health disorders.

Keywords: Early life stress, Early adversity, Neurobiological development, Developmental disorders

Background

Early life experiences represent an important influence on children's neural, behavioral, and psychological development, having long-lasting effects across a wide range of domains [1, 2]. Experience shapes neural plasticity and through this behavior and psychological processes throughout the lifespan [3, 4]. Infancy and early childhood are periods of particularly high rates of synaptic re-growth and remodeling in the brain, during which experience can have long-lasting effects on development [5, 6]. Neuroscience has greatly illuminated our understanding of how both positive and negative early life experiences affect brain development, with implications for children's mental and physical health. In this paper, we review the literature examining the neurobiological

effects of early experiences and discuss where there is a need for further research related to individual differences in children's responses to their early environments.

An early experience that has garnered much attention is that of chronic and/or extreme stress in early life. Experiences of chronic and/or severe stress during early childhood, often also conceptualized as early life stress, childhood adversity, child maltreatment, or childhood trauma, have persistent and pervasive consequences for development [7, 8]. The term stress refers to the psychological response elicited when an individual perceives themselves to be under threat or challenge and is generally beneficial, eliciting a range of behavioral and physiological changes aimed at addressing the perceived threat. However, chronic and/or extreme stress results in extended activation of these psychological, behavioral, and physiological stress response systems leading to dysregulation and negative psychological and behavioral outcomes [9, 10]. Here, we use

* Correspondence: kesmith23@wisc.edu

Department of Psychology and Waisman Center, University of Wisconsin–Madison, 1500 S Highland Blvd, Rm 399, Madison, WI 53705, USA



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the term early life stress broadly to refer to stress occurring in childhood (prior to the age of 18). It is a term which encompasses many different kinds of adverse experiences a child might encounter, including, but not limited to, exposure to toxins, nutritional restriction, abuse, neglect, and limited family resources. Severe and chronic exposure to these types of situations has long-term negative consequences on a wide range of cognitive, emotional, and behavioral processes [11–13]. However, the neural mechanisms supporting these effects are less well understood, and advances in neuroscience are critical for uncovering causal mechanisms linking exposure to early life adverse experiences with well-being across the lifespan.

Below, we review the current state of the literature on the effects of early experiences of stress on neurobiological circuits and the implications these effects have for children's development. We start by introducing two prevalent approaches toward conceptualizing early life stress and its effects on development. We then highlight common findings across these different approaches related to the neural effects of early life stress, with a particular focus on the effects on prefrontal–hippocampal–amygdala and dopaminergic circuits. Finally, we address opportunities for new ways in which to advance our understanding of the mechanisms through which early life stress shapes the developing brain, and in turn children's health outcomes. Together, these data can inform the development of more effective and targeted interventions for at risk children.

Main text

Models for conceptualizing early life stress: elucidating neurobiological mechanisms

Researchers have employed a variety of models aimed at conceptualizing early life stress, with the goal of better elucidating the neurobiological mechanisms through which stress exerts effects on development. While the question of how to best conceptualize early childhood adversity and stress has shifted over time [14, 15], the two predominant models of early life stress fall into the categories of (1) General or “lumping” models, in which various types of stressors are treated as a heterogeneous, broad category, often labeled “adversity,” “early life stress,” or “negative life events” [16–19]; and 2) Specific or “splitting” models, which are based on the premise that different types of adversity each confer specific effects, and links to neurobiological or cognitive systems may be masked by heterogeneous samples [20–22]. Both types of models have provided a wealth of knowledge surrounding early childhood adversity and its effects on development and provided initial insight into some of the potential neurobiological mechanisms underlying these effects. However, there is still much the field does

not understand about what bio-behavioral mechanisms account for individual patterns of developmental change following extreme adversity. In the following sections, we will review the literature supporting general and specific effects of early life stress on neurobiological systems.

Insights from general models

One common general approach to conceptualizing early adversity is that of cumulative measures of adversity. In this approach, individuals are queried about whether they experienced a pre-defined set of potential adverse events in childhood, and their total exposure to events from that list is summed [23, 24]. Examples of these methods include variations on Life Stressors Checklists [25] and the Adverse Child Experiences Scale (ACES) [18, 26]. This approach is based in animal literature that suggests repeated exposure to stress, regardless of type, through chronic activation of stress response systems (i.e., HPA, immune, and autonomic nervous system), alters neural synaptic plasticity leading to cognitive deficits, anxiety, and depressive-like behaviors, and poorer health [9, 27]. Similarly, in humans, cumulative measures of adversity have been linked to differences in hippocampal, PFC, and amygdala volume, and changes in prefrontal–amygdala connectivity [28–30]. These models have also been associated with changes in peripheral stress responses systems, including altered cortisol and autonomic nervous system reactivity to laboratory stressors [31–33], epigenetic changes [34, 35], and increases in markers of inflammatory activity and immune dysregulation [36, 37]. Longitudinal studies tend to provide support for cumulative or general effects [38–40]. A recent longitudinal study from 18 months to mid-adulthood found that cumulative stress rather than physical abuse alone was predictive of adult depressive symptoms [40]. Another study, which followed children from birth to age 37 years, found that childhood stress interacted with current life stress, regardless of type of stressor, to predict diurnal cortisol patterns in adulthood [38]. However, while cumulative models have greatly informed our understanding of the aggregate effects of stress on individuals, they have lacked consistent insight into the neurobiological mechanisms underlying individual differences to children's responses to stress [14]. This suggests that counting types of stressors alone is not sufficient to explain variation in children's development outcomes after early life stress.

Insights from specific methods

Specific models represent a reaction to cumulative models and an attempt to more precisely identify the neurobiological mechanisms linking early experience to development [20, 41]. These approaches are based in

animal models that demonstrate some specificity in the effects of certain types of stressors on neurobiological systems [42, 43]. Based on this evidence, specific models assume that different types of stressors will have distinct and separable effects on developing neural systems. While there are many different variants of this approach [41, 44, 45], an increasingly prevalent one is to conceptualize potential stressors as a lack of expected inputs (i.e., “deprivation”—consisting of things like neglect, food deprivation, and institutionalization) or a presence of direct threat to the child (i.e., “threat”—consisting of things like physical abuse, sexual abuse, and exposure to violence) [46–48].

The rapidly expanding literature taking this approach has provided insight into some of the potential mechanisms supporting the effects of early life stress on development. For example, this literature appears to find more consistent evidence for the association between “threat” and psychopathology being mediated by alterations in stress response systems (including autonomic and HPA reactivity). In contrast, it finds less evidence for the association between “deprivation” and psychopathology being mediated by alterations in stress response systems [49, 50]. However, there are also findings that suggest similar effects of “threat” and “deprivation” experiences on stress response systems and the neural systems supporting them [51–54]. As an example, both threat and deprivation have been linked to negative PFC–amygdala connectivity in late childhood and adolescence [51, 55]. Additionally, both threat experiences such as abuse and deprivation experiences such as neglect have been demonstrated to have specific effects on hippocampal volume [53, 56, 57].

One potential explanation for these commonalities in the effects of different types or categories of stressors is that different types of stressors often co-occur [58, 59]. This co-occurrence creates a number of conceptual issues and makes it difficult to determine if one specific type or dimension of stressor is indeed driving an effect (for extensive discussion see [60]). To illustrate, imagine a study in which a sample of children exposed to physical abuse demonstrate dampened PFC–amygdala connectivity in response to threat. It could be this association is driven by exposure to physical abuse. But, given physical abuse is associated with many other co-occurring risk factors [61–63], it could also be driven by any one of these other risk factors. This makes it difficult to determine what effects are the causal result of just physical abuse, or even if physical abuse itself elicits a neurobiological response. Despite these issues, together general and specific models have provided insight into how early life stress may be shaping neurobiological systems; below, we review commonalities in findings across the two approaches on the development of neurobiological systems.

Neurobiological consequences of early life stress

While strong arguments have been made for using one type of conceptualization over another [14, 15, 47], careful examination of this literature suggests that there are commonalities in findings across the two approaches. Here, we focus on some general recent themes across this literature with implications for human development. Early life stress is consistently associated with altered functioning of the hypothalamic pituitary adrenal (HPA) axis and autonomic nervous system [33, 54, 64]. These systems are critical to facilitating motivated psychological and behavioral responses to the environment, particularly environmental threats and challenges [65, 66]. Additionally, growing evidence suggests that early life stress is associated with alterations in the immune system and inflammatory activity, which is increasingly implicated in producing shifts in individuals’ behavioral responses to their environment [46, 67]. Together, these changes in peripheral physiological systems are critical for facilitating adaptive responses to threat and challenge. In addition, altered activity of these systems is associated with negative mental and physical health consequences after stress exposure [68–70]. The effects of early life stress on these peripheral stress response systems are thought to be a result of altered neural plasticity in circuits integral to stress responses, including the prefrontal cortex (PFC), hippocampus, amygdala, and striatal circuits [15, 71]. There is also a growing corpora of research implicating epigenetic changes in the regulation of many of these effects [34, 72]. Many of these changes have been hypothesized to represent adaptive responses to environments of high threat which become problematic within the broader social context [73, 74]. Below, we review the current state of the literature linking early life stress to altered brain function, and some of the potential hormonal, psychophysiological, neural, and genetic mechanisms thought to support these effects.

Neural consequences of early life stress and their proposed mediating mechanisms

Alterations in prefrontal–hippocampal–amygdala circuits Research in both non-human animals and humans suggests that early life stress is linked to pronounced effects on the development of prefrontal–hippocampal–amygdala circuits. These circuits play an important role in facilitating peripheral stress responses through the release of corticotrophin reducing hormone (CRH) and glucocorticoids and regulation of the autonomic nervous system [9, 75]. Additionally, these circuits are implicated in emotion processing, self-regulation, and memory and learning [76–78]. Rodents exposed to abusive maternal behaviors or maternal separation as pups show decreased dendritic arborization throughout the

PFC and hippocampus [79, 80]. Experiences of chronic restraint stress in adult rodents result in increased dendritic arborization in the amygdala [81, 82], and there is some evidence for similar effects in the amygdala after experiences of stress as pups [83]. In association with these structural changes, rodents demonstrate modifications in synaptic signaling and epigenetic changes in the hippocampus and amygdala [34, 84–86]. These changes in synaptic structure and signaling are thought to produce increased sensitivity to threat in the environment, through decreased regulation of the amygdala by the PFC and hippocampus [87, 88]. Additionally, they have been associated with increased anxiety and depressive-like behaviors in animals after experiences of early life stress [89–92]. Changes in hippocampal synaptic plasticity have also been linked to altered memory and learning processes, with rodents' demonstrating reduced spatial memory [93, 94] and enhanced threat learning [95, 96].

The changes throughout the PFC, hippocampus, and amygdala and their associated effects on behavior, memory, and learning appear to be at least partially mediated by chronic exposure to CRH and glucocorticoids induced by chronic stress [93, 97–99]. For example, rat pups exposed to chronic stress in the form of fragmented maternal behaviors demonstrate augmented expression of CRH in the hippocampus and memory deficits. Blocking CRH receptors resulted in improved memory performance and prevented dendritic atrophy in the hippocampus [93]. Chronic maternal separation stress in mice is associated with decreases in glucocorticoid receptor mRNA in the brain, especially so in the amygdala, which is in turn associated with alterations in anxiety-like and social behaviors. Restoring the glucocorticoid receptor mRNA deficit in the amygdala reverses the changes in anxiety and social behavior [100]. Additionally, in male mice, enhanced freezing behavior in the context of a conditioned threat paradigm after exposure to fragmented maternal behaviors can be reversed by blocking glucocorticoid receptors [95].

In humans, similar changes in brain structure and function after experiences of stress in childhood are evidenced in the amygdala, PFC, and hippocampus. Indeed, one of the most reliable findings in children exposed to early life stress is reduced hippocampal volume [29, 53, 56]. Reduced hippocampal volume in children exposed to a range of different types of early life stress, including abuse, neglect, and living in poverty, has been linked to increased symptoms of psychopathology [101–104]. Additionally, changes in hippocampal volume are thought to be associated with deficits in learning processes in children who experience early life stress [7, 105, 106]. A growing literature also indicates that early life stress is associated with changes in amygdala and PFC reactivity to emotional stimuli as well as altered connectivity between

the two regions [51, 52, 107]. Cumulative stress, severe neglect from early institutionalization, and abuse have all been associated with heightened amygdala reactivity to emotional images [28, 108, 109]. This heightened reactivity appears to be at least partially a result of altered PFC–amygdala connectivity, leading to increased sensitivity to emotionally salient cues [107, 110, 111]. Indeed, children with a history of maltreatment, which includes emotional, physical, and sexual abuse and emotional and physical neglect, appear to demonstrate atypical connectivity between the amygdala and inferior frontal gyrus [112], and children growing up in poverty is associated with atypical ventrolateral PFC–amygdala connectivity [113]. Longitudinal work suggests that children exposed to various forms of early life stress demonstrate an atypical trajectory of age-related changes in PFC–amygdala connectivity as compared to peers who were not exposed to early life stress [51]. The strength of PFC–amygdala connectivity appears to mediate the relationship between maltreatment exposure and anxiety and depressive symptoms [114, 115]. Structural and functional alterations in PFC–hippocampal–amygdala circuits in individuals exposed to various forms of early life stress suggests that alterations in these circuits play an important role in the relationship between early life stress and its effects on development.

As with non-human animals, there is also evidence that changes in CRH and glucocorticoid function may partially mediate the neural effects described above [34, 54]. Indeed, there is some evidence that humans demonstrate similar epigenetic changes in glucocorticoids to those observed in non-human animals, and these alterations are associated with changes in the hippocampus, symptoms of psychopathology, and altered learning processes [72, 116–118]. Additionally, abnormal hypothalamic pituitary adrenal responsiveness is often observed after a variety of experiences of early life stress, including poverty, family violence, maltreatment, and institutional deprivation, although this varies with age [54, 68]. This, in parallel with the animal literature demonstrating that extended exposure to glucocorticoids leads to hippocampal atrophy and dysregulation of the HPA axis [119, 120], has given rise to the hypothesis that chronic activation of the HPA axis through exposure to severe and/or extended stress leads to neural alterations in the PFC, hippocampus, and amygdala. This in turn produces dysregulation in systems responsible for responding to potential threats and challenges in the environment [64, 71]. This dysregulation of stress response systems can lead to increased risk for both mental and physical health issues [121–123].

The effects of early life stress on PFC–hippocampal–amygdala circuitry are thought to be in part related to alterations in emotion processing produced by the types of early inputs children in high stress environments

experience. Relative to non-maltreated children, children who experience physical abuse have heightened perceptual and physiological sensitivity to angry facial expressions [124, 125] and are more likely to perceive emotional situations as demonstrating anger as early as preschool age [41]. Physically abused children also more readily categorize faces that are morphed between two different emotions as angry [126] and require less perceptual information to identify faces as angry than non-maltreated children [124]. Additionally, physically abused children show biases to angry faces during cognitive tasks. They respond more quickly to angry faces during a Go/No-Go paradigm [22] and seem to require greater cognitive resources to disengage their attention from angry faces, showing delayed disengagement when angry faces served as invalid cues in a selective attention paradigm [127]. Children who are exposed to extreme threat appear to preferentially attend to and identify facial movements that are associated with threat, such as a scowling facial configuration [125, 128–131], and more reliably track the trajectory of facial muscle activations that signal threat [132]. This close attention to cues of anger likely shapes how abused children understand what facial movements mean. For example, one study found that 5-year-old abused children tended to believe that almost any kind of interpersonal situation could result in an adult becoming angry; by contrast, most non-abused children understand that anger is likely in particular interpersonal circumstances [133].

Studies of maltreated children (including those who experience neglect and other forms of abuse) also show less accurate identification of facial emotions in general [41, 131] and particular difficulty identifying positive emotions [134]. In addition, these children demonstrate abnormalities in the expression and regulation of emotions [135]. Neglected children show delays in perceiving emotions in the ways that adults do [41]. Maltreated children also show higher levels of rumination (repeatedly dwelling on past negative experiences), which has been associated with an attention bias to sad faces [136] and may contribute to risk for depressive symptomatology. The combination of difficulties with emotional recognition, expression, and regulation may increase children's risk for a broad range of maladaptive outcomes. For example, misreading others' facial emotion might impair peer interactions, while problematic emotion regulation and expression may contribute to rumination and/or aggressive behavior. The effects of maltreatment on children's recognition of and attention to emotion are thought to, in part, be shaped by the broader environment in which they are raised. Children who grow up in environments where emotional interactions with caregivers are highly atypical have different developmental trajectories than do those growing in more consistently nurturing environments [8]. Parents

from these high-risk families signal emotions unclearly, and express more anger [14, 29, 137, 138]. Together, this suggests that exposure to increased levels of potential threat alters children's perceptual processes such that they become more likely to perceive situations others may not find threatening as threat, likely resulting in extending activation of prefrontal–hippocampal–amygdala circuits and associated peripheral stress response systems.

Alterations in prefrontal–striatal dopaminergic circuits

Recent evidence suggests that early life stress also has a range of negative effects on dopaminergic circuits involved in motivation, specifically those related to reward processing [138, 139]. Animal models of early life stress have been associated with changes in circuits classically implicated in motivation to obtain and pursue rewards, including the ventral striatum, prefrontal cortex, and amygdala [140, 141]. Chronic repeated separation of rodent pups from their mothers alters the number of dopaminergic glial cells, affects rate of cell proliferation and death, and promotes aberrant dopaminergic signaling in the ventral tegmental area and substantia nigra in adulthood [142–144]. Additionally, alterations in maternal care have been associated with reduced connectivity between the PFC and caudate putamen [145] as well as structural and functional alterations in the nucleus accumbens [79, 146]. These changes have been linked to increased anhedonia-like behaviors [147, 148] and altered sensitivity to reward, both hyper- and hyposensitivity depending on the paradigm utilized [149, 150]. As with changes in the hippocampus and amygdala, chronic exposure to glucocorticoids, through interactions with dopaminergic neurons, appears to play an important role in mediating some of these effects [151–153].

In humans, disruptions during reward processing have been observed in the nucleus accumbens, ventral tegmental area, ventral striatum, and PFC after experiences of early life stress [154–157], and these disruptions are associated with depressive and anxiety symptoms in adolescents and adults [158–161] as well as altered reward learning [11, 15]. Specifically, children who experienced maltreatment demonstrate decreased striatal, orbitofrontal cortex, and hippocampal activation during reward learning [157], and children with high early life stress demonstrate decreased activation of the putamen and insula when anticipating future losses [138]. Additionally, in children exposed to early life stress, ventral striatal activation has been demonstrated to mediate variation in reward related learning [162]. Importantly, these circuits are highly connected with both the amygdala and prefrontal cortex, which together play a key role in psychological and behavioral responses to stress, emotional and social learning, and self-regulatory processes [163, 164]. These disruptions likely then place

children at increased risk for maladaptive behaviors, along with negative mental and physical health outcomes later in life.

Summary

Despite the relationships between early life stress and alterations in both PFC–hippocampal–amygdala and dopaminergic reward circuitry outlined above, we still understand relatively little about how these changes are associated with altered learning and behavioral patterns and how they increase risk for mental and physical health disorders and disease. Additionally, it is still unclear which changes are important for different types of health risks and what supports individual differences in children's outcomes after experiences of early life stress. While the frameworks for conceptualizing early life stress outlined above were developed to try and address this question, there are still many findings that are not fully accounted for, suggesting that additional factors may also be critical for shaping children's neurobiological responses to stress.

Promising future approaches to elucidating the mechanisms of early life stress

A commonality across both general and specific models is a focus on identifying types of events a child may or may not be exposed to that meet the criteria of a stressor based on some outside determination (be it criteria set by child protective services for abuse or neglect, economic guidelines for poverty, or researchers determination that one thing represents a stressor over another). But an additional insight into the neurobiological mechanisms underlying the effects of early life stress may lie with an individual child's interpretation or perception of those events. Even in non-human animal models, which do evidence specificity in responses to stress [165, 166], there are a range of individual differences in behavioral responses to the same type of stressor [167]. These individual differences in behavior are supported by different physiological and neural mechanisms [168–170]. Similar variability in response to adverse events is observed in humans across neurobiological stress responses systems [66, 171–173], and this variability has been linked to differential health behaviors and symptoms [174–176].

This range of variability in neurobiological responses to similar types of stressors has led to the proposition that it is not the type or features of an adverse event, but rather the organisms' perception and interpretation of that event, that that has different effects on neurobiological systems [166, 177, 178]. There is now a wealth of research in adults demonstrating that individual variability in neurobiological responses to stress is informed through the assessment of factors that shape perceptions and interpretations of stress [10, 179, 180]. For example,

individual variability in cortisol responses to social speech stress is positively related to how individuals rate their perceived stress during the stressor [175]. Shifts in how humans and animals perceive the controllability and predictability of a stressor will change their physiological responses to that stressor [181–184]. In humans, individual differences in perceptions of control have been linked to differential cortisol responses to acute laboratory stress, differences in brain volume, and differences in brain reactivity to stress in regions including the hippocampus, amygdala, and prefrontal cortex [185–187]. Additionally, perceived adversity, and its associated neurobiological responses, can occur in the absence of any specific identifiable environment event through rumination over previous experience or events or anxiety about future events [188–190]. Recent evidence in children suggests a similarly important role for perception in variability in stress responses. One study utilizing machine learning approaches found that event exposures are not highly predictive of children's outcomes [191] and another found reported exposure to abuse or neglect is more predictive of children's mental health outcomes than exposure identified through court reports [192].

There is a growing literature suggesting that the chronicity, developmental timing, and intensity of adversity exposure are important factors shaping the effects of adversity on children [68]. In animal research, the precise timing of when during development a stressor occurs can be tightly controlled, and has demonstrated strong effects as described in a number of recent reviews [46, 68, 193, 194]. However, the developmental period in which adversity occurs is tightly intertwined with the chronicity of adversity (that is, adversity that begins early in a child's life may be longer lasting and chronic than adversity that begins later in a child's life), which also demonstrates profound effects on variability in responses to stress [82, 195]. Children with high scores on the Life Stress Interview (LSI), which quantifies the intensity of children's stress exposure, have smaller amygdala and hippocampal volumes than children exposed to less intense levels of early life stress [29]. Children with high levels of early life stress demonstrate altered activation in circuits involved in value processing during anticipation of rewards and losses [138]. Retrospectively reported severity of early stress exposure in childhood has also been associated with increased dorsal medial PFC responses to a social stressor [196] and altered global connectivity of the ventrolateral PFC [197]. Both severity and amount of maltreatment in children have been linked to epigenetic changes of the glucocorticoid receptor gene [198]. Additionally, variations in intensity of early adversity appears to modulate HPA responses with retrospectively reported intensity of stress, rather than

type of stress, during early childhood being associated with increased levels of cerebrospinal fluid (CSF) CRH [199], and increased cortisol responses to acute social speech stress [200]. Children's rated intensity of adversity also interacts with age to predict cortisol awakening responses [201].

Another potential factor in shaping child development may be features of the early environment such as predictability and contingent responding of caregivers (or, alternatively, chaos and lack of stability) [140, 202]. Parent-child relationships are stereotypically repetitive, highly predictable, and marked by contingent parental responses. In normative contexts, adult caregivers reliably respond to infant cries, comfort a child who is hurt, and provide support to a child who is dysregulated [203, 204]. Lack of predictable and contingent input from caregivers affects children's expectations of the environment, leading to uncertainty and perceptions of vulnerability [11, 137]. While there is limited research directly assessing variation in the predictability of children's environments, there is a growing literature that suggests it has the ability to provide great insight into the mechanisms underlying experiences of early life stress. Longitudinal research assessing early influences on adolescents' externalizing behaviors finds that unpredictability of the environment during childhood, quantified using changes in maternal employment, changes in residence, and changes in cohabitation, is associated with increased externalizing behaviors in adolescence while SES was not related [205]. Recent research in rodents suggests that these observed effects are a result of altered functioning in prefrontal-hippocampal-amygdala circuits, finding that unpredictable maternal inputs are associated with altered connectivity between the medial prefrontal cortex (PFC) and amygdala [91] as well as decreased dendritic arborization in the hippocampus [206] beyond effects produced by types of maternal inputs. These effects are linked to PTSD and depressive-like behaviors as well as deficits in learning [140]. Together, this body of work suggests that variation in the predictability, stability, and/or degree of contingent responding of adult caregivers to the needs of the developing child is a factor in shaping children's responses to adversity through alterations in prefrontal cortical and subcortical stress response circuits. It indicates that assessment of predictability of early environments, along with exposure to negative events, has the potential to provide increased insight into individual differences in the neurobiological effects of early adversity on child development that is not captured when focusing solely on types of adverse events.

Last, increasingly research supports a role for perceived safety in contributing to variations in children's responses to stress. Safety/security in early childhood has been characterized in a variety of different ways, with things such as parental presence/adult "buffering,"

sensitivity, responsivity, and support thought to be cues of safety, and lack of parental input, through isolation, maternal separation, or neglect, or abusive parenting behaviors being cues of lack of safety [207–209]. Cues of safety early in development play an important role in engaging the prefrontal circuits that inhibit threat response circuits, which will have implications for how children perceive and interact with their environment later in life [210]. Indeed, evidence from non-human primate and rodent models supports this finding that early parental presence plays an important role in inhibiting neurobiological threat response systems, with both rodent pups and infant primates demonstrating reduced glucocorticoid release and decreased amygdala activation in the presence of the mother [207, 211]. However, in cases of abusive maternal rearing, maternal presence does not appear to exhibit buffering effects. Under these circumstances, rodent pups and primate infants demonstrate enhanced glucocorticoid responses to stress [207, 212] as well as alterations in both the structure and function of the amygdala and prefrontal cortex [213–215]. From this literature, it is clear that parental presence, a salient early cue of safety, is important to supporting typical development of the neurobiological stress response systems.

There is some evidence indicative of similar early regulatory effects of parental presence on the development of stress response systems in humans [208, 216]. In parallel to the rodent and primate literatures, parental presence has been demonstrated to dampen both cortisol [217, 218] and amygdala reactivity [219] to stress in children. Presentation of parent voice during speech stress has been associated with faster cortisol recovery post-stressor [218], suggesting that parent support does not necessarily need to be physical to buffer children's responses to stress. There is also evidence that early adversity is associated with altered prefrontal-amygdala connectivity, and these alterations have been linked to children's risk for psychopathology [51, 114, 220]. This points to disruptions in the development of these circuits in children lacking early cues of safety that have implications for their behaviors and mental health. However, in cases of adversity where children still receive high levels of support from their parents, these effects are mitigated, with adolescents living in poverty showing altered connectivity in prefrontal cortical networks involved in executive functioning and emotion regulation, but not if they reported having high levels of parent support [221]. Additionally, support provided by other adults or peers may diminish some of the bio-behavioral effects of adversity, with reported social support from family and friends being associated with reduced risk of psychopathology in children who experience maltreatment [222, 223]. This suggests that, at least in humans, individuals outside of the parent-child relationship may

be able to supplement these safety cues when they break down. Consistently incorporating assessment of factors that represent early cues of safety, such as parental support, when studying how children respond to early adversity, has the potential to greatly illuminate the neurobiological mechanisms through which negative environments shape development.

Summary

There is consistent evidence that early life stress exposure changes neural plasticity and function, and these changes have implications for children's mental and physical health across the lifespan. Studies assessing differential effects of events along with timing and intensity of events, predictability and contingency of environmental inputs, and perceptions of safety and social support suggest that these factors differentially shape biological systems involved in stress. Of course, it is the case that there are probably bidirectional effects between exposure to potentially stressful events shaping children's perceptions of their environment in turn resulting in children perceiving their environment as more stressful. For this reason, it may seem like it is easier to establish causality through approaches focusing on identifying events and their associated outcomes. However, while events themselves likely contribute to how children perceive their environment, approaches which focus only on events are missing a multitude of other sources of variation in these perceptions. Further incorporation of factors that may shift how individuals interpret their environment, in combination with event based methods of assessment of stress and rigorous longitudinal studies with assessments at multiple timepoints, has the potential to provide increased insight into the specific neurobiological mechanisms influencing children's development. This type of approach can aid in identifying what may produce resiliency to negative mental and physical health outcomes in children who experience early life stress.

Conclusions

In this article, we have highlighted recent research speaking to the neural mechanisms underlying the effects of early life stress on development. The existing literature supports effects of early life on the development of the prefrontal cortex, hippocampus, hypothalamus, and amygdala, along with communication across those areas, in ways that produces increased vulnerability to mental and physical health disorders later in life. These changes appear to be at least partially mediated through hormonal and neuropeptide alterations in the HPA axis along with interactions with genetic and epigenetic factors. Additionally, there is increasing evidence for a role of dopaminergic reward circuits in these relationships. However, to date, we still lack a good understanding

about how these changes come about, what aspects of the child's environment produces these changes, and, given not all children who experience early life stress develop later psychopathology, what their role is in individual differences in children's outcomes after early life stress.

Abbreviations

PFC: Prefrontal cortex; HPA: Hypothalamic–pituitary–adrenal; CRH: Corticotropin-reducing hormone; CSF: Cerebrospinal fluid

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Authors' contributions

KES and SDP conducted the literature search and wrote the manuscript. All authors approved the final version of the manuscript.

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References

- Pollak SD. Early adversity and mechanisms of plasticity: integrating affective neuroscience with developmental approaches to psychopathology. *Dev Psychopathol.* 2005;17(3):735–52 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16262990>.
- Cicchetti D. Resilience under conditions of extreme stress: a multilevel perspective. *World Psychiatry.* 2010;9(3):145–54.
- Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity? *Neurosci Biobehav Rev.* 2003;27(1–2):3–18.
- Johnson MH. Functional brain development in humans. *Nat Rev Neurosci.* 2001;2(7):475–83 Available from: <http://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=11360036&site=ehost-live>.
- Hill J, Inder TE, Neil J, Dierker D, Harwell J, Van Essen D. Similar patterns of cortical expansion during human development and evolution. *Proc Natl Acad Sci U S A.* 2010;107(29):13135–40 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20624964%5Cn>, <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2919958>.
- Levitt P. Structural and functional maturation of the developing primate brain. *J Pediatr.* 2003;143(4):35–45.
- Pechtel P, Pizzagalli DA. Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology.* 2011;214(1):55–70.
- Pollak SD. Developmental psychopathology: recent advances and future challenges. *World Psychiatry.* 2015;14(3):262–9.
- McEwen BS. The resilient brain: epigenetics, stress and the lifecourse. *Psychoneuroendocrinology.* 2017;83:76 Available from: <https://www.sciencedirect.com/science/article/pii/S0306453017310879>. Cited 2019 Apr 9.

10. Sapolsky RM. Stress and the brain: individual variability and the inverted-U. *Nat Neurosci*. 2015;18(10):1344–6 Available from: <http://www.nature.com/doi/10.1038/nn.4109>.
11. Chen Y, Baram TZ. Toward understanding how early-life stress reprograms cognitive and emotional brain networks. *Neuropsychopharmacology*. 2016; 41(1):197–206. <https://doi.org/10.1038/npp.2015.181>.
12. Hughes K, Bellis MA, Hardcastle KA, Sethi D, Butchart A, Mikton C, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health*. 2017;2(8):e356–66 Available from: <https://www.sciencedirect.com/science/article/pii/S2468266717301184>. Cited 2019 Jun 4.
13. Cicchetti D. Socioemotional, personality, and biological development: illustrations from a multilevel developmental psychopathology perspective on child maltreatment. *Annu Rev Psychol*. 2016;67(1):187–211 Available from: <http://www.annualreviews.org/doi/10.1146/annurev-psych-122414-033259>.
14. Palacios-Barrios EE, Hanson JL. Poverty and self-regulation: connecting psychosocial processes, neurobiology, and the risk for psychopathology. *Compr Psychiatry*. 2019;90:52–64 Available from: <https://www.sciencedirect.com/science/article/pii/S0010440X18302141>.
15. Fareri DS, Tottenham N. Effects of early life stress on amygdala and striatal development. *Dev Cogn Neurosci*. 2016;19:233–47. <https://doi.org/10.1016/j.dcn.2016.04.005>.
16. Burghy CA, Stodola DE, Ruttle PL, Molloy EK, Armstrong JM, Oler JA, et al. Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. *Nat Neurosci*. 2012;15(12):1736–41.
17. Winiarski DA, Engel ML, Karnik NS, Brennan PA. Early life stress and childhood aggression: Mediating and moderating effects of child callousness and stress reactivity. *Child Psychiatry Hum Dev*. 2018;49(5):730–9. <https://doi.org/10.1007/s10578-018-0785-9>.
18. Steele H, Bate J, Steele M, Dube SR, Danskin K, Knafo H, et al. Adverse childhood experiences, poverty, and parenting stress. *Can J Behav Sci*. 2016; 48(1):32–8.
19. Steine IM, Winje D, Krystal JH, Bjorvatn B, Milde AM, Grønli J, et al. Cumulative childhood maltreatment and its dose-response relation with adult symptomatology: Findings in a sample of adult survivors of sexual abuse. *Child Abuse Negl*. 2017;65:99–111 Available from: <https://www.sciencedirect.com/science/article/pii/S014521341730008X>. Cited 2019 May 6.
20. McLaughlin KA, Sheridan MA. Beyond cumulative risk: a dimensional approach to childhood adversity. *Curr Dir Psychol Sci*. 2016;25(4):239–45 Available from: <http://journals.sagepub.com/doi/10.1177/0963721416655883>.
21. Humphreys KL, Zeanah CH. Deviations from the expectable environment in early childhood and emerging psychopathology. *Neuropsychopharmacology*. 2015;40(1):154–70 Available from: <http://www.nature.com/articles/npp2014165>. Cited 2019 Apr 12.
22. Pollak SD, Klorman R, Thatcher JE, Cicchetti D. P3b reflects maltreated children's reactions to facial displays of emotion. *Psychophysiology*. 2001; 38(2):267–74 Available from: <https://www.cambridge.org/core/journals/psychophysiology/article/p3b-reflects-maltreated-childrens-reactions-to-facial-displays-of-emotion/66214C16B3D4A65C74B34291FC5A1B36>.
23. Evans GW, Li D, Whipple SS. Cumulative risk and child development. *Psychol Bull*. 2013;139(6):1342–96.
24. Dube SR, Fairweather D, Pearson WS, Felitti VJ, Anda RF, Croft JB. Cumulative childhood stress and autoimmune diseases in adults. *Psychosom Med*. 2009;71(2):243–50 Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3318917&tool=pmcentrez&rendertype=abstract>. Cited 2014 Mar 20.
25. Wethington E, Brown GW, Kessler RC. Interview measurement of stressful life events. In: Cohen S, Kessler RC, Gordon LU, editors. *Measuring stress*. Oxford: Oxford University Press; 1997. p. 59–79.
26. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz A, Edwards VJ, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med*. 1998;14(4):245–58.
27. Ganzel BL, Morris PA, Wethington E. Allostasis and the Human Brain: integrating Models of Stress From the Social and Life Sciences. *Psychol Rev*. 2010;117(1):134–74.
28. Evans GW, Swain JE, King AP, Wang X, Javanbakht A, Ho SS, et al. Childhood Cumulative Risk Exposure and Adult Amygdala Volume and Function. *J Neurosci Res*. 2016;94(6):535–43 Available from: <http://doi.wiley.com/10.1002/jnr.23681>. Cited 2019 Aug 12.
29. Hanson JL, Nacewicz BM, Sutterer MJ, Cayo AA, Schaefer SM, Rudolph KD, et al. Behavioral Problems After Early Life Stress: contributions of the Hippocampus and Amygdala. *Biol Psychiatry*. 2015;77(4):314–23 Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0006322314003515>.
30. Ansell EB, Rando K, Tuit K, Guarnaccia J, Sinha R. Cumulative adversity and smaller gray matter volume in medial prefrontal, anterior cingulate, and insula regions. *Biol Psychiatry*. 2012;72(1):57–64 Available from: <https://www.sciencedirect.com/science/article/pii/S0006322311011930>. Cited 2019 Aug 13.
31. Evans GW, Kim P, Ting AH, Tessler HB, Shannis D. Cumulative risk, maternal responsiveness, and allostatic load among young adolescents. *Dev Psychol*. 2007;43(2):341–51.
32. Blair C, Berry D, Mills-Koonce R, Granger DA. Cumulative effects of early poverty on cortisol in young children: moderation by autonomic nervous system activity. *Psychoneuroendocrinology*. 2013;38(11):2666–75 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23890719>. Cited 2014 Mar 22.
33. Alkon A, Boyce WT, Tran L, Harley KG, Neuhaus J, Eskenazi B. Prenatal adversities and latino children's autonomic nervous system reactivity trajectories from 6 months to 5 years of age. *PLoS One*. 2014;9(1):1–8.
34. Turecki G, Meaney MJ. Effects of the social environment and stress on glucocorticoid receptor gene methylation: a systematic review. *Biol Psychiatry*. 2016;79(2):87–96 Available from: <https://www.sciencedirect.com/science/article/pii/S0006322314009676>. Cited 2019 May 22.
35. Park C, Rosenblat J, Brietzke E, Pan Z, Lee Y, Cao B, et al. Stress, epigenetics and depression: a systematic review. *Neurosci Biobehav Rev*. 2019; Available from: <https://www.sciencedirect.com/science/article/pii/S0149763418309576>. Cited 2019 May 1.
36. O'Donovan A, Neylan TC, Metzler T, Cohen BE. Lifetime exposure to traumatic psychological stress is associated with elevated inflammation in the Heart and Soul Study. *Brain Behav Immun*. 2012;26(4):642–9 Available from: <https://www.sciencedirect.com/science/article/pii/S0889159112000268>. Cited 2019 Aug 13.
37. O'Connor TG, Willoughby MT, Moynihan JA, Messing S, Vallejo Sefair A, Carnahan J, et al. Early childhood risk exposures and inflammation in early adolescence. *Brain Behav Immun*. 2019; Available from: <https://www.sciencedirect.com/science/article/pii/S0889159119304568>. Cited 2019 Aug 13.
38. Young ES, Farrell AK, Carlson EA, Englund MM, Miller GE, Gunnar MR, et al. The dual impact of early and concurrent life stress on adults' diurnal cortisol patterns: a prospective study. *Psychol Sci*. 2019;095679761983366 Available from: <http://journals.sagepub.com/doi/10.1177/0956797619833664>. Cited 2019 Apr 5.
39. Harms MB, Birn R, Provencal N, Wiechmann T, Binder EB, Giakas SW, et al. Early life stress, FK506 binding protein 5 gene (*FKBP5*) methylation, and inhibition-related prefrontal function: A prospective longitudinal study. *Dev Psychopathol*. 2017;29(5):1895–903 Available from: https://www.cambridge.org/core/product/identifier/S095457941700147X/type/journal_article. Cited 2019 Jun 13.
40. Sousa C, Mason WA, Herrenkohl TI, Prince D, Herrenkohl RC, Russo MJ. Direct and indirect effects of child abuse and environmental stress: a lifecourse perspective on adversity and depressive symptoms. *Am J Orthop*. 2018;88(2):180–8 Available from: <http://doi.apa.org/getdoi.cfm?doi=10.1037/ort0000283>. Cited 2019 Jun 13.
41. Pollak SD, Cicchetti D, Hornung K, Reed A. Recognizing emotion in faces: developmental effects of child abuse and neglect. *Dev Psychol*. 2000;36(5): 679–88.
42. Goldstein DS. Adrenal responses to stress. *Cell Mol Neurobiol*. 2010;30(8): 1433–40.
43. Pacák K, Palkovits M. Stressor specificity of central neuroendocrine responses: implications for stress-related disorders. *Endocr Rev*. 2001;22(4): 502–48 Available from: <https://academic.oup.com/edrv/article/22/4/502/2424153>.
44. McLaughlin KA, Sheridan MA, Lambert HK. Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. *Neurosci Biobehav Rev*. 2014;47(11):578–91 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25454359%0A>, <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4308474>.
45. Manly JT, Kim J, Rogosch FA, Cicchetti D. Dimensions of child maltreatment and children's adjustment: contributions of developmental timing and subtype. *Dev Psychopathol*. 2001;13(4):759–82 Available from: <https://www.cambridge.org/core/journals/development-and-psychopathology/article/dimensions-of-child-maltreatment-and-childrens-adjustment-contributions>

- of-developmental-timing-and-subtype/2FBEA046C5975B908DE0F0E0C5EE06 DB. Cited 2019 Jun 4.
46. Kuhlman KR, Chiang JJ, Horn S, Bower JE. Developmental psychoneuroendocrine and psychoneuroimmune pathways from childhood adversity to disease. *Neurosci Biobehav Rev.* 2017;80(October 2016):166–84. <https://doi.org/10.1016/j.neubiorev.2017.05.020>.
 47. Sheridan MA, McLaughlin KA. Dimensions of early experience and neural development: deprivation and threat. *Trends Cogn Sci.* 2014;18(11):580–5 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25454359%0A>, <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4308474>.
 48. Amso D, Lynn A. Distinctive mechanisms of adversity and socioeconomic inequality in child development: a review and recommendations for evidence-based policy. *Policy Insights Behav Brain Sci.* 2017;4(2):139–46.
 49. Busso DS, McLaughlin KA, Sheridan MA. Dimensions of adversity, physiological reactivity, and externalizing psychopathology in adolescence: deprivation and threat. *Psychosom Med.* 2017;79(2):162–71 Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L611306772%0Ahttp://dx.doi.org/10.1097/PSY.0000000000000369>.
 50. Platt JM, McLaughlin KA, Luedtke AR, Ahern J, Kaufman AS, Keyes KM. Targeted estimation of the relationship between childhood adversity and fluid intelligence in a US population sample of adolescents. *Am J Epidemiol.* 2018;187(7):1456–66.
 51. Gee DG, Gabard-Durnam LJ, Flannery J, Goff B, Humphreys KL, Telzer EH, et al. Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. *Proc Natl Acad Sci U S A.* 2013; 110(39):15638–43 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24019460>. Cited 2019 Jan 27.
 52. Tottenham N, Sheridan MA. A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. *Front Hum Neurosci.* 2009;3:68 Available from: <http://journal.frontiersin.org/article/10.3389/neuro.09.068.2009/abstract>. Cited 2019 May 8.
 53. Lawson GM, Camins JS, Wisse L, Wu J, Duda JT, Cook PA, et al. Childhood socioeconomic status and childhood maltreatment: distinct associations with brain structure. *PLoS One.* 2017;12(4):1–16.
 54. Koss KJ, Gunnar MR. Annual Research Review: Early adversity, the hypothalamic-pituitary-adrenocortical axis, and child psychopathology. *J Child Psychol Psychiatry.* 2017;59(4):327–46 Available from: <http://doi.wiley.com/10.1111/jcpp.12784>. Cited 2019 May 18.
 55. Peverill M, Sheridan MA, Busso DS, McLaughlin KA. Atypical prefrontal-amygdala circuitry following childhood exposure to abuse: links with adolescent psychopathology. *Child Maltreat.* 2019;107755951985267 Available from: <http://journals.sagepub.com/doi/10.1177/1077559519852676>. Cited 2019 Jun 6.
 56. Teicher MH, Anderson CM, Ohashi K, Khan A, McGreenery CE, Bolger EA, et al. Differential effects of childhood neglect and abuse during sensitive exposure periods on male and female hippocampus. *Neuroimage.* 2018; 169(December 2017):443–52 Available from: <https://doi.org/10.1016/j.neuroimage.2017.12.055>. Cited 2019 Jun 6.
 57. LoPilato AM, Goines K, Addington J, Bearden CE, Cadenhead KS, Cannon TD, et al. Impact of childhood adversity on corticolimbic volumes in youth at clinical high-risk for psychosis. *Schizophr Res.* 2019;213:48–55.
 58. Debowska A, Willmott D, Boduszek D, Jones AD. What do we know about child abuse and neglect patterns of co-occurrence? A systematic review of profiling studies and recommendations for future research. *Child Abuse Negl.* 2017;70:100–11 Available from: <https://www.sciencedirect.com/science/article/pii/S0145213417302405>. Cited 2019 May 17.
 59. Herrenkohl RC, Herrenkohl TI. Assessing a child's experience of multiple maltreatment types: some unfinished business. *J Fam Violence.* 2009;24(7): 485–96 Available from: <http://link.springer.com/10.1007/s10896-009-9247-2>. Cited 2019 May 17.
 60. Smith KE, Pollak SD. Re-thinking concepts and categories for understanding the neurodevelopmental effects of childhood adversity. *Perspect Psychol Sci.* 2020. <https://journals.sagepub.com/doi/full/10.1177/1745691620920725>.
 61. Hamby S, Finkelhor D, Turner H, Ormrod R. The overlap of witnessing partner violence with child maltreatment and other victimizations in a nationally representative survey of youth. *Child Abuse Negl.* 2010;34(10): 734–41 Available from: <https://www.sciencedirect.com/science/article/pii/S0145213410002127>. Cited 2019 May 17.
 62. Witt A, Münzer A, Ganser HG, Fegert JM, Goldbeck L, Plener PL. Experience by children and adolescents of more than one type of maltreatment: association of different classes of maltreatment profiles with clinical outcome variables. *Child Abuse Negl.* 2016;57:1–11 Available from: <https://www.sciencedirect.com/science/article/pii/S0145213416300837#bib0100>. Cited 2019 May 17.
 63. Euser EM, van IJzendoorn MH, Prinzie P, Bakermans-Kranenburg MJ. Elevated child maltreatment rates in immigrant families and the role of socioeconomic differences. *Child Maltreat.* 2011;16(1):63–73 Available from: <http://journals.sagepub.com/doi/10.1177/1077559510385842>. Cited 2019 May 17.
 64. Loman MM, Gunnar MR. Early experience and the development of stress reactivity and regulation in children. *Neurosci Biobehav Rev.* 2010;34(6):867–76 Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2848877&tool=pmcentrez&rendertype=abstract>. Cited 2013 Feb 12.
 65. McEwen BS. What Is the Confusion With Cortisol? *Chronic Stress.* 2019;3: 247054701983364 Available from: <http://journals.sagepub.com/doi/10.1177/2470547019833647>. Cited 2019 Apr 9.
 66. Berntson GG, Cacioppo JT. Heart rate variability: stress and psychiatric conditions. In: *Dynamic Electrocardiography*; 2004. p. 57–64.
 67. Danese A, J Lewis S. Psychoneuroimmunology of early-life stress: the hidden wounds of childhood trauma? *Neuropsychopharmacology.* 2017; 42(1):99–114 Available from: <http://www.nature.com/articles/hpp2016198>. Cited 2019 Apr 25.
 68. Lupien SJ, McEwen BS, Gunnar MR, Heim CM. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci.* 2009; 10(6):434–45.
 69. Gunnar MR, Doom JR, Esposito EA. Psychoneuroendocrinology of stress: normative development and individual differences. In: *Handb child Psychol Dev Sci Vol 3 Socioemotional Process* (7th ed); 2015. p. 106–51.
 70. Fagundes CP, Glaser R, Kiecolt-Glaser JK. Stressful early life experiences and immune dysregulation across the lifespan. *Brain Behav Immun.* 2013;27(1): 8–12 Available from: <https://www.sciencedirect.com/science/article/pii/S0889159112001821>. Cited 2014 Mar 20.
 71. McEwen CA, McEwen BS. Social structure, adversity, toxic stress, and intergenerational poverty: an early childhood model. *Annu Rev Sociol.* 2017; 43:445–72.
 72. Turecki G, Ota VK, Belangero SJ, Jackowski A, Kaufman J. Early life adversity, genomic plasticity, and psychopathology. *Lancet Psychiatry.* 2014;1(6):461–6. [https://doi.org/10.1016/S2215-0366\(14\)00022-4](https://doi.org/10.1016/S2215-0366(14)00022-4).
 73. Boyce WT, Ellis BJ. Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Dev Psychopathol.* 2005;17(2):271–301 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16761546>.
 74. Obradović J, Stamerdahl J, Bush NR, Adler NE, Boyce WT. Biological sensitivity to context : the interactive effects of stress reactivity and family adversity on socioemotional behavior and school readiness. *Child Dev.* 2010;81(1):270–89. Published by: Wiley on behalf of the Society for Research in Child Development Stable. <https://doi.org/10.1111/j.1467-8624.2009.01394.x>.
 75. Thayer JF, Ahs F, Fredrikson M, Sollers JJ III, Wager TD. 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.* 2012; 36(2):747–56 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22178086>. Cited 2013 Mar 7.
 76. McEwen BS, Morrison JH. The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. *Neuron.* 2013;79(1):16–29 Available from: <https://www.sciencedirect.com/science/article/pii/S0896627313005448>. Cited 2019 Jan 27.
 77. Thayer JF, Lane RD. Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. *Neurosci Biobehav Rev.* 2009;33(2):81–8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18771686>. Cited 2014 Mar 22.
 78. Eichenbaum H. Prefrontal-hippocampal interactions in episodic memory. *Nat Rev Neurosci.* 2017;18(9):547–58 Available from: <http://www.nature.com/doi/10.1038/nrn.2017.74>. Cited 2019 Jan 27.
 79. Monroy E, Hernández-Torres E, Floréz G, Flores G. Maternal separation disrupts dendritic morphology of neurons in prefrontal cortex, hippocampus, and nucleus accumbens in male rat offspring. *J Chem Neuroanat.* 2010;40(2):93–101 Available from: <https://www.sciencedirect.com/science/article/pii/S0891061810000748>. Cited 2019 May 27.
 80. Bagot RC, van Hasselt FN, Champagne DL, Meaney MJ, Krugers HJ, Joëls M. Maternal care determines rapid effects of stress mediators on synaptic plasticity in adult rat hippocampal dentate gyrus. *Neurobiol Learn Mem.*

- 2009;92(3):292–300 Available from: <https://www.sciencedirect.com/science/article/pii/S1074742709000677>. Cited 2019 Aug 12.
81. Rodrigues SM, LeDoux JE, Sapolsky RM. The influence of stress hormones on fear circuitry. *Annu Rev Neurosci*. 2009;32(1):289–313 Available from: <http://www.annualreviews.org/doi/10.1146/annurev.neuro.051508.135620>.
82. Vyas A, Mitra R, Rao BSS, Chattarji S. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *J Neurosci*. 2002;22(15):6810–8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12151561>. Cited 2019 May 28.
83. Koe AS, Ashokan A, Mitra R. Short environmental enrichment in adulthood reverses anxiety and basolateral amygdala hypertrophy induced by maternal separation. *Transl Psychiatry*. 2016;6(2):e729 Available from: <http://www.nature.com/articles/tp2015217>. Cited 2019 Aug 12.
84. Brunson KL, Kramér E, Lin B, Chen Y, Colgin LL, Yanagihara TK, et al. Mechanisms of late-onset cognitive decline after early-life stress. *J Neurosci*. 2005;25(41):9328–38.
85. Danielewicz J, Hess G. Early life stress alters synaptic modification range in the rat lateral amygdala. *Behav Brain Res*. 2014;265:32–7 Available from: <https://www.sciencedirect.com/science/article/pii/S0166432814000874>. Cited 2019 Aug 12.
86. Malter Cohen M, Jing D, Yang RR, Tottenham N, Lee FS, Casey BJ. Early-life stress has persistent effects on amygdala function and development in mice and humans. *Proc Natl Acad Sci U S A*. 2013;110(45):18274–8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24145410>. Cited 2019 Aug 12.
87. Malter Cohen M, Tottenham N, Casey BJ. Translational developmental studies of stress on brain and behavior: Implications for adolescent mental health and illness? *Neuroscience*. 2013;249:53–62 Available from: <https://www.sciencedirect.com/science/article/pii/S0306452213000535>. Cited 2019 Aug 13.
88. Taylor SE, Way BM, Seeman TE. Early adversity and adult health outcomes. *Dev Psychopathol*. 2011;23(3):939–54 Available from: https://www.cambridge.org/core/product/identifier/S0954579411000411/type/journal_article. Cited 2019 May 6.
89. Ishikawa J, Nishimura R, Ishikawa A. Early-life stress induces anxiety-like behaviors and activity imbalances in the medial prefrontal cortex and amygdala in adult rats. *Eur J Neurosci*. 2015;41(4):442–53 Available from: <http://doi.wiley.com/10.1111/ejn.12825>. Cited 2019 Aug 12.
90. Wei L, David A, Duman RS, Anisman H, Kaffman A. Early life stress increases anxiety-like behavior in Balbc mice despite a compensatory increase in levels of postnatal maternal care. *Horm Behav*. 2010;57(4–5):396–404 Available from: <https://www.sciencedirect.com/science/article/pii/S0018506X1000019X>. Cited 2019 Aug 12.
91. Bolton JL, Molet J, Regev L, Chen Y, Rismanchi N, Haddad E, et al. Anhedonia following early-life adversity involves aberrant interaction of reward and anxiety circuits and is reversed by partial silencing of amygdala corticotropin-releasing hormone gene. *Biol Psychiatry*. 2018;83(2):137–47 Available from: <https://www.sciencedirect.com/science/article/pii/S000632231731942X>. Cited 2019 May 22.
92. Berman AK, Lott RB, Donaldson ST. Periodic maternal deprivation may modulate offspring anxiety-like behavior through mechanisms involving neuroplasticity in the amygdala. *Brain Res Bull*. 2014;101:7–11 Available from: <https://www.sciencedirect.com/science/article/pii/S0361923013001949>. Cited 2019 Aug 12.
93. Ivy AS, Rex CS, Chen Y, Dubé C, Maras PM, Grigoriadis DE, et al. Hippocampal dysfunction and cognitive impairments provoked by chronic early-life stress involve excessive activation of CRH receptors. *J Neurosci*. 2010;30(39):13005–15 Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2991143&tool=pmcentrez&rendertype=abstract>.
94. Oomen CA, Soeters H, Audureau N, Vermunt L, Van Hasselt FN, Manders EMM, et al. Severe early life stress hampers spatial learning and neurogenesis, but improves hippocampal synaptic plasticity and emotional learning under high-stress conditions in adulthood. *J Neurosci*. 2010;30(19):6635–45.
95. Arp JM, ter Horst JP, Loi M, den Blaauwen J, Bangert E, Fernández G, et al. Blocking glucocorticoid receptors at adolescent age prevents enhanced freezing between repeated cue-exposures after conditioned fear in adult mice raised under chronic early life stress. *Neurobiol Learn Mem*. 2016;133:30–8.
96. Callaghan BL, Richardson R. Maternal separation results in early emergence of adult-like fear and extinction learning in infant rats. *Behav Neurosci*. 2011;125(1):20–8.
97. Tsoory M, Cohen H, Richter-Levin G. Juvenile stress induces a predisposition to either anxiety or depressive-like symptoms following stress in adulthood. *Eur Neuropsychopharmacol*. 2007;17(4):245–56 Available from: <https://www.sciencedirect.com/science/article/pii/S0924977X06001246>. Cited 2019 May 29.
98. Barna I, Bálint E, Baranyi J, Bakos N, Makara GB, Haller J. Gender-specific effect of maternal deprivation on anxiety and corticotropin-releasing hormone mRNA expression in rats. *Brain Res Bull*. 2003;62(2):85–91 Available from: <https://www.sciencedirect.com/science/article/pii/S0361923003002168>. Cited 2019 Jan 27.
99. Vazquez DM, Bailey C, Dent GW, Okimoto DK, Steffek A, López JF, et al. Brain corticotropin-releasing hormone (CRH) circuits in the developing rat: Effect of maternal deprivation. *Brain Res*. 2006;1121(1):83–94 Available from: <https://www.sciencedirect.com/science/article/pii/S0006899306026382>. Cited 2019 Jan 27.
100. Arnett MG, Pan MS, Doak W, Cyr PEP, Muglia LM, Muglia LJ. The role of glucocorticoid receptor-dependent activity in the amygdala central nucleus and reversibility of early-life stress programmed behavior. *Transl Psychiatry*. 2015;5(January):e542.
101. De Brito SA, Mechelli A, Wilke M, Laurens KR, Jones AP, Barker GJ, et al. Size matters: Increased grey matter in boys with conduct problems and callous-unemotional traits. *Brain*. 2009;132(4):843–52 Available from: <https://academic.oup.com/brain/article-lookup/doi/10.1093/brain/awp011>. Cited 2019 Aug 11.
102. Woon FL, Hedges DW. Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. *Hippocampus*. 2008;18(8):729–36.
103. Chen MC, Hamilton JP, Gotlib IH. Decreased hippocampal volume in healthy girls at risk of depression. *Arch Gen Psychiatry*. 2010;67(3):270 Available from: <http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/archgenpsychiatry.2009.202>. Cited 2019 Aug 11.
104. Gorka AX, Hanson JL, Radtke SR, Hariri AR. Reduced hippocampal and medial prefrontal gray matter mediate the association between reported childhood maltreatment and trait anxiety in adulthood and predict sensitivity to future life stress. *Biol Mood Anxiety Disord*. 2014;4(1):12 Available from: <http://biolmoodanxietydisord.biomedcentral.com/articles/10.1186/2045-5380-4-12>. Cited 2019 May 27.
105. Hanson JL, van den Bos W, Roeber BJ, Rudolph KD, Davidson RJ, Pollak SD. Early adversity and learning: implications for typical and atypical behavioral development. *J Child Psychol Psychiatry Allied Discip*. 2017;58(7):770–8.
106. Davis EP, Stout SA, Molet J, Vegetable B, Glynn LM, Sandman CA, et al. Exposure to unpredictable maternal sensory signals influences cognitive development across species. *Proc Natl Acad Sci*. 2017;114(39):10390–5. Available from: <http://www.pnas.org/lookup/doi/10.1073/pnas.1703444114>.
107. VanTieghem MR, Tottenham N. Neurobiological programming of early life stress: functional development of amygdala prefrontal circuitry and vulnerability for stress related psychopathology. *Curr Top Behav Neurosci*. 2018;38:117–36.
108. Tottenham N, Hare TA, Millner A, Gilhooly T, Zevin JD, Casey BJ. Elevated amygdala response to faces following early deprivation. *Dev Sci*. 2011;14(2):190–204 Available from: <http://doi.wiley.com/10.1111/j.1467-7687.2010.00971.x>. Cited 2019 Aug 12.
109. McCrory EJ, De Brito SA, Kelly PA, Bird G, Sebastian CL, Mechelli A, et al. Amygdala activation in maltreated children during pre-attentive emotional processing. *Br J Psychiatry*. 2013;202(4):269–76 Available from: https://www.cambridge.org/core/product/identifier/S0007125000274059/type/journal_article. Cited 2019 Aug 12.
110. Wolf RC, Herringa RJ. Prefrontal–amygdala dysregulation to threat in pediatric posttraumatic stress disorder. *Neuropsychopharmacology*. 2016;41(3):822–31 Available from: <http://www.nature.com/articles/npp2015209>. Cited 2019 Aug 12.
111. Garrett AS, Carrion V, Kletter H, Karchemskiy A, Weems CF, Reiss A. Brain activation to facial expressions in youth with PTSD symptoms. *Depress Anxiety*. 2012;29(5):449–59 Available from: <http://doi.wiley.com/10.1002/da.21892>. Cited 2019 Aug 12.
112. Jedd K, Hunt RH, Cicchetti D, Hunt E, Cowell RA, Rogosch FA, et al. Long-term consequences of childhood maltreatment: altered amygdala functional connectivity. *Dev Psychopathol*. 2015;27(4pt2):1577–89 Available from: https://www.cambridge.org/core/product/identifier/S0954579415000954/type/journal_article. Cited 2019 Aug 12.
113. Kim P, Evans GW, Angstadt M, Ho SS, Sripada CS, Swain JE, et al. Effects of childhood poverty and chronic stress on emotion regulatory brain function

- in adulthood. *Proc Natl Acad Sci*. 2013;110(46):18442–7 Available from: <https://www.pnas.org/content/110/46/18442.short>. Cited 2019 Aug 12.
114. Herringa RJ, Birn RM, Ruttle PL, Burghy CA, Stodola DE, Davidson RJ, et al. Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. *Proc Natl Acad Sci U S A*. 2013;110(47):19119–24 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24191026>. Cited 2019 May 23.
 115. Pagliaccio D, Luby JL, Bogdan R, Agrawal A, Gaffrey MS, Belden AC, et al. Amygdala functional connectivity, HPA axis genetic variation, and life stress in children and relations to anxiety and emotion regulation. *J Abnorm Psychol*. 2015;124(4):817–33. <https://doi.org/10.1037/abn0000094> Available from: <http://ovidsp.ovid.com/ovidweb.cgi?T=J&PAGE=reference&D=emex&NEWS=N&AN=610649746>.
 116. Heim CM, Binder EB. Current research trends in early life stress and depression: review of human studies on sensitive periods, gene-environment interactions, and epigenetics. *Exp Neurol*. 2012;233(1):102–11. <https://doi.org/10.1016/j.expneurol.2011.10.032>.
 117. Champagne FA. Early adversity and developmental outcomes: interaction between genetics, epigenetics, and social experiences across the Life Span. *Perspect Psychol Sci*. 2010;5:564–74.
 118. Papale LA, Seltzer LJ, Madrid A, Pollak SD, Alisch RS. Differentially methylated genes in saliva are linked to childhood stress. *Sci Rep*. 2018;8(1):1–8. <https://doi.org/10.1038/s41598-018-29107-0>.
 119. McEwen BS. Neurobiological and systemic effects of chronic stress. *Chronic Stress*. 2017;1:1–11 Available from: <http://journals.sagepub.com/doi/10.1177/2470547017692328>.
 120. McEwen BS. Redefining neuroendocrinology: epigenetics of brain-body communication over the life course. *Front Neuroendocrinol*. 2018;49:8–30 Available from: <https://www.sciencedirect.com/science/article/pii/S0091302217300687>. Cited 2019 Apr 9.
 121. Silvers JA, Goff B, Gabard-Durnam LJ, Gee DG, Fareri DS, Caldera C, et al. Vigilance, the amygdala, and anxiety in youths with a history of institutional care. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2017;2(6):493–501. <https://doi.org/10.1016/j.bpsc.2017.03.016>.
 122. Nusslock R, Miller GE. Early-life adversity and physical and emotional health across the lifespan: a neuroimmune network hypothesis. *Biol Psychiatry*. 2016;80(1):23–\ Available from: <https://www.sciencedirect.com/science/article/pii/S0006322315004667>. Cited 2019 Apr 25.
 123. Debiec J, Sullivan RM. The neurobiology of safety and threat learning in infancy. *Neurobiol Learn Mem*. 2017;143:49–58. <https://doi.org/10.1016/j.nlm.2016.10.015>.
 124. Pollak SD, Sinha P. Effects of early experience on children's recognition of facial displays of emotion. *Dev Psychol*. 2002;38(5):784–91.
 125. Shackman JE, Pollak SD. Impact of physical maltreatment on the regulation of negative affect and aggression. *Dev Psychopathol*. 2014;26(4):1021–33 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24914736>.
 126. Pollak SD, Kistler DJ. Early experience is associated with the development of categorical representations for facial expressions of emotion. *PNAS*. 2002;99(13):9072–6 Available from: http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&DbFrom=pubmed&Cmd=Link&LinkName=pubmed_pubmed&LinkReadableName=RelatedArticles&IdsFromResult=12072570&ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum.
 127. Pollak SD, Tolley-Schell SA. Selective attention to facial emotion in physically abused children. *J Abnorm Psychol*. 2003;112(3):323–38 Available from: <http://doi.apa.org/getdoi.cfm?doi=10.1037/0021-843X.112.3.323>. Cited 2014 May 26.
 128. Pollak SD, Vardi S, Bechner AMP, Curtin JJ. Physically abused children's regulation of attention in response to hostility. *Child Dev*. 2005;76(5):968–77.
 129. Shackman JE, Shackman AJ, Pollak SD. Physical abuse amplifies attention to threat and increases anxiety in children. *Emotion*. 2007;7(4):838–52 Available from: <http://doi.apa.org/getdoi.cfm?doi=10.1037/1528-3542.7.4.838>. Cited 2019 May 22.
 130. Briggs-Gowan MJ, Pollak SD, Grasso D, Voss J, Mian ND, Zobel E, et al. Attention bias and anxiety in young children exposed to family violence. *J Child Psychol Psychiatry Allied Discip*. 2015;56(11):1194–201.
 131. da Silva Ferreira GC, Crippa JAS, de Lima Osório F. Facial emotion processing and recognition among maltreated children: a systematic literature review. *Front Psychol*. 2014;5:1460 Frontiers Research Foundation.
 132. Pollak SD, Messner M, Kistler DJ, Cohn JF. Development of perceptual expertise in emotion recognition. *Cognition*. 2009;110(2):242–7.
 133. Perlman SB, Kalish CW, Pollak SD. The role of maltreatment experience in children's understanding of the antecedents of emotion. *Cogn Emot*. 2008;22(4):651–70.
 134. Koizumi M, Takagishi H. The relationship between child maltreatment and emotion recognition. *PLoS One*. 2014;9(1):e86093.
 135. Kim-Spoon J, Cicchetti D, Rogosch FA. A longitudinal study of emotion regulation, emotion lability-negativity, and internalizing symptomatology in maltreated and nonmaltreated children. *Child Dev*. 2013;84(2):512–27.
 136. Romens SE, Pollak SD. Emotion regulation predicts attention bias in maltreated children at-risk for depression. *J Child Psychol Psychiatry Allied Discip*. 2012;53(2):120–7.
 137. Harms MB, Shannon Bowen KE, Hanson JL, Pollak SD. Instrumental learning and cognitive flexibility processes are impaired in children exposed to early life stress. *Dev Sci*. 2018;21(4):1–13.
 138. Birn RM, Roeber BJ, Pollak SD. Early childhood stress exposure, reward pathways, and adult decision making. *Proc Natl Acad Sci*. 2017;114(51):13549–54 Available from: <http://www.pnas.org/lookup/doi/10.1073/pnas.1708791114>.
 139. Novick AM, Levandowski ML, Laumann LE, Philip NS, Price LH, Tyrka AR. The effects of early life stress on reward processing. *J Psychiatr Res*. 2018;101:80–103 Available from: <https://www.sciencedirect.com/science/article/pii/S0022395617311068>. Cited 2019 May 21.
 140. Risbrough VB, Glynn LM, Davis EP, Snadman CA, Obenaus A, Stern HS, et al. Does anhedonia presage increased risk of posttraumatic stress disorder. In: Vermetten E, Baker DG, Risbrough VB, editors. *Behavioral Neurobiology of PTSD*. Switzerland: Springer; 2018.
 141. Baram TZ, Davis EP, Obenaus A, Sandman CA, Small SL, Solodkin A, et al. Fragmentation and unpredictability of early-life experience in mental disorders. *Am J Psychiatry*. 2012;169(9):907–15 Available from: <http://psychiatryonline.org/doi/abs/10.1176/appi.ajp.2012.11091347>. Cited 2019 May 21.
 142. Authement ME, Kodangattil JN, Gouty S, Rusnak M, Symes AJ, Cox BM, et al. Histone deacetylase inhibition rescues maternal deprivation-induced GABAergic metaplasticity through restoration of AKAP signaling. *Neuron*. 2015;86(5):1240–52 Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L604772103>. Cited 2019 Sep 16.
 143. Chocyk A, Dudys D, Przyborowska A, Majcher I, Maćkowiak M, Weogonekzony K. Maternal separation affects the number, proliferation and apoptosis of glia cells in the substantia nigra and ventral tegmental area of juvenile rats. *Neuroscience*. 2011;173:1–18.
 144. Chocyk A, Przyborowska A, Dudys D, Majcher I, Maćkowiak M, Wedzony K. The impact of maternal separation on the number of tyrosine hydroxylase-expressing midbrain neurons during different stages of ontogenesis. *Neuroscience*. 2011;182:43–61.
 145. Yan C-G, Rincón-Cortés M, Rainekei C, Sarro E, Colcombe S, Guilfoyle DN, et al. Aberrant development of intrinsic brain activity in a rat model of caregiver maltreatment of offspring. *Transl Psychiatry*. 2017;7(1):e1005 Available from: <http://www.nature.com/articles/tp2016276>. Cited 2019 Aug 13.
 146. Peña CJ, Neugut YD, Calarco CA, Champagne FA. Effects of maternal care on the development of midbrain dopamine pathways and reward-directed behavior in female offspring. *Eur J Neurosci*. 2014;39(6):946–56 Available from: <http://doi.wiley.com/10.1111/ejn.12479>. Cited 2019 Aug 13.
 147. Zhu X, Li T, Peng S, Ma X, Chen X, Zhang X. Maternal deprivation-caused behavioral abnormalities in adult rats relate to a non-methylation-regulated D2 receptor levels in the nucleus accumbens. *Behav Brain Res*. 2010;209(2):281–8 Available from: <https://www.sciencedirect.com/science/article/pii/S0166432810000884>. Cited 2019 Aug 13.
 148. Zhang Y, Zhu X, Bai M, Zhang L, Xue L, Yi J. Maternal deprivation enhances behavioral vulnerability to stress associated with miR-504 expression in nucleus accumbens of rats. *PLoS One*. 2013;8(7):e69934 Available from: <https://dx.plos.org/10.1371/journal.pone.0069934>. Homberg J, editor. Cited 2019 Aug 13.
 149. Rodrigues A-J, Leão P, Carvalho M, Almeida OFX, Sousa N. Potential programming of dopaminergic circuits by early life stress. *Psychopharmacology*. 2011;214(1):107–20 Available from: <http://link.springer.com/10.1007/s00213-010-2085-3>. Cited 2019 Sep 16.
 150. Fone KCF, Porkess MV. Behavioural and neurochemical effects of post-weaning social isolation in rodents—relevance to developmental neuropsychiatric disorders. *Neurosci Biobehav Rev*. 2008;32(6):1087–102 Available from: <https://www.sciencedirect.com/science/article/pii/S0149763408000353>. Cited 2019 Sep 16.

151. Campioni MR, Xu M, McGehee DS. Stress-induced changes in nucleus accumbens glutamate synaptic plasticity. *J Neurophysiol*. 2009;101(6):3192–8.
152. Kim S, Kwok S, Mayes LC, Potenza MN, Rutherford HJV, Strathearn L. Early adverse experience and substance addiction: dopamine, oxytocin, and glucocorticoid pathways. *Ann N Y Acad Sci*. 2017;1394:74–91 Blackwell Publishing Inc.
153. Leão P, Sousa JC, Oliveira M, Silva R, Almeida OFX, Sousa N. Programming effects of antenatal dexamethasone in the developing mesolimbic pathways. *Synapse*. 2007;61(1):40–9 Available from: <http://doi.wiley.com/10.1002/syn.20341>. Cited 2019 Sep 16.
154. Dennison MJ, Rosen ML, Sambrook KA, Jenness JL, Sheridan MA, McLaughlin KA. Differential associations of distinct forms of childhood adversity with neurobehavioral measures of reward processing: a developmental pathway to depression. *Child Dev*. 2017;90(1):96–113 Available from: <http://doi.wiley.com/10.1111/cdev.13011>.
155. Marusak HA, Hatfield JR, Thomason ME, Rabinak CA. Reduced ventral tegmental area–hippocampal connectivity in children and adolescents exposed to early threat. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2017;2:130–7.
156. Mehta MA, Gore-Langton E, Golembo N, Colvert E, Williams SCR, Sonuga-Barke EJ. Hyporesponsive reward anticipation in the basal ganglia following severe institutional deprivation early in life. *J Cogn Neurosci*. 2010;22(10):2316–25 Available from: NS.
157. Gerin MI, Puetz VB, Blair RJR, White S, Sethi A, Hoffmann F, et al. A neurocomputational investigation of reinforcement-based decision making as a candidate latent vulnerability mechanism in maltreated children. *Dev Psychopathol*. 2017;29(5):1689–705.
158. Hanson JL, Knodt AR, Brigidi BD, Hariri AR. Heightened connectivity between the ventral striatum and medial prefrontal cortex as a biomarker for stress-related psychopathology: understanding interactive effects of early and more recent stress. *Psychol Med*. 2017;48(11):1–9 Available from: https://www.cambridge.org/core/product/identifier/S0033291717003348/type/journal_article. Cited 2019 Aug 7.
159. Nikolova YS, Bogdan R, Brigidi BD, Hariri AR. Ventral striatum reactivity to reward and recent life stress interact to predict positive affect. *Biol Psychiatry*. 2012;72(2):157–63 Available from: <https://www.sciencedirect.com/science/article/pii/S0006322312002624>. Cited 2019 Aug 12.
160. Goff B, Gee DG, Telzer EH, Humphreys KL, Gabard-Durnam L, Flannery J, et al. Reduced nucleus accumbens reactivity and adolescent depression following early-life stress. *Neuroscience*. 2013;249:129–38 Available from: <https://www.sciencedirect.com/science/article/pii/S0306452212011918>. Cited 2019 Aug 12.
161. Corral-Frias NS, Nikolova YS, Michalski LJ, Baranger DAA, Hariri AR, Bogdan R. Stress-related anhedonia is associated with ventral striatum reactivity to reward and transdiagnostic psychiatric symptomatology. *Psychol Med*. 2015;45(12):2605–17 Available from: https://www.cambridge.org/core/product/identifier/S0033291715000525/type/journal_article. Cited 2019 Aug 12.
162. Kamkar NH, Lewis DJ, van den Bos W, Morton JB. Ventral striatal activity links adversity and reward processing in children. *Dev Cogn Neurosci*. 2017;26:20–7.
163. Berridge KC, Kringelbach ML. Neuroscience of affect: brain mechanisms of pleasure and displeasure. *Curr Opin Neurobiol*. 2013; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23375169>. Cited 2013 Mar 6.
164. Ledoux JE, Daw ND. Surviving threats: Neural circuit and computational implications of a new taxonomy of defensive behaviour. *Nat Rev Neurosci*. 2018;19(5):269–82.
165. Kemeny ME. The Psychobiology of Stress. *Curr Dir Psychol Sci*. 2003;12(4):124–30.
166. Goldstein DS, McEwen BS. Allostasis, homeostasis, and the nature of stress. *Stress*. 2002;5:55–8.
167. Korte SM, Koolhaas JM, Wingfield JC, McEwen BS. The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. *Neurosci Biobehav Rev*. 2005;29(1):3–38 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15652252>.
168. de Boer SF, van der Vegt BJ, Koolhaas JM. Individual variation in aggression of feral rodent strains: a standard for the genetics of aggression and violence? *Behav Genet*. 2003;33(5):485–501 Available from: <http://link.springer.com/10.1023/A:1025766415159>. Cited 2019 Jun 2.
169. Carere C, Groothuis TG, Möstl E, Daan S, Koolhaas J. Fecal corticosteroids in a territorial bird selected for different personalities: daily rhythm and the response to social stress. *Horm Behav*. 2003;43(5):540–8 Available from: <https://www.sciencedirect.com/science/article/pii/S0018506X03000655>. Cited 2019 Jun 2.
170. Verbeek ME, De Goede P, Drent PJ, Wiepkema PR. Individual behavioral characteristics and dominance in aviary groups of great tits. *Behaviour*. 1999;136:23–48 Available from: <https://www.jstor.org/stable/pdf/4535592.pdf>. Cited 2019 Jun 2.
171. Cohen S, Hamrick N. Stable individual differences in physiological response to stressors: implications for stress-elicited changes in immune related health. *Brain Behav Immun*. 2003;17(6):407–14 Available from: <https://www.sciencedirect.com/science/article/pii/S0889159103001107>. Cited 2019 Jun 2.
172. Manuck SB, Cohen S, Rabin BS, Muldoon MF, Bachen EA. Individual differences in cellular immune response to stress. *Psychol Sci*. 1991;2(2):111–5 Available from: <http://journals.sagepub.com/doi/10.1111/j.1467-9280.1991.tb00110.x>. Cited 2019 Jun 2.
173. Pruessner JC, Dedovic K, Khalili-Mahani N, Engert V, Pruessner M, Buss C, et al. Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biol Psychiatry*. 2008;63(2):234–40 Available from: <https://www.sciencedirect.com/science/article/pii/S0006322307004350>. Cited 2019 Jun 2.
174. Buchanan TW, Preston SD. Stress leads to prosocial action in immediate need situations. *Front Behav Neurosci*. 2014;8:5 Available from: <http://journal.frontiersin.org/article/10.3389/fnbeh.2014.00005/abstract>. Cited 2019 Feb 9.
175. Roy MP, Kirschbaum C, Steptoe A. Psychological, cardiovascular, and metabolic correlates of individual differences in cortisol stress recovery in young men. *Psychoneuroendocrinology*. 2001;26(4):375–91 Available from: <https://www.sciencedirect.com/science/article/pii/S0306453000000615>. Cited 2019 Jun 2.
176. Vedhara K, Hyde J, Gilchrist I, Tytherleigh M, Plummer S. Acute stress, memory, attention and cortisol. *Psychoneuroendocrinology*. 2000;25(6):535–49 Available from: <https://www.sciencedirect.com/science/article/pii/S0306453000000081>. Cited 2019 Jun 2.
177. McEwen BS. Resilience of the brain and body. *Stress Physiol Biochem Pathol*. 2019;19–33 Available from: <https://www.sciencedirect.com/science/article/pii/B9780128131466000023>. Cited 2019 Apr 9.
178. Brosschot JF, Verkuil B, Thayer JF. Exposed to events that never happen: generalized unsafety, the default stress response, and prolonged autonomic activity. *Neurosci Biobehav Rev*. 2017;74:287–96 Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0149763416300380>.
179. Peters A, McEwen BS, Friston KJ. Uncertainty and stress: why it causes diseases and how it is mastered by the brain. *Prog Neurobiol*. 2017;156:164–88. <https://doi.org/10.1016/j.pneurobio.2017.05.004>.
180. Brosschot JF, Verkuil B, Thayer JF. Generalized unsafety theory of stress: unsafe environments and conditions, and the default stress response. *Int J Environ Res Public Health*. 2018;15(3):1–27.
181. Henry J. Biological basis of the stress response. *Integr Physiol Behav Sci*. 1992;27(1):66–83.
182. Mormede P, Dantzer R, Michaud B, Kelley KW, Le Moal M. Influence of stressor predictability and behavioral control on lymphocyte reactivity, antibody responses and neuroendocrine activation in rats. *Physiol Behav*. 1988;43(5):577–83.
183. Muller MJ. Will it hurt less if I believe I can control it? Influence of actual and perceived control on perceived pain intensity in healthy male individuals: A randomized controlled study. *J Behav Med*. 2012;35:529–37.
184. Bollini AM, Walker EF, Hamann S, Kestler L. The influence of perceived control and locus of control on the cortisol and subjective responses to stress. *Biol Psychol*. 2004;67:245–60.
185. Pruessner JC, Baldwin MW, Dedovic K, Renwick R, Mahani NK, Lord C, et al. Self-esteem, locus of control, hippocampal volume, and cortisol regulation in young and old adulthood. *Neuroimage*. 2005;28(4):815–26 Available from: <https://www.sciencedirect.com/science/article/pii/S1053811905004210>. Cited 2019 Jun 11.
186. Harnett NG, Wheelock MD, Wood KH, Ladnier JC, Mrug S, Knight DC. Affective state and locus of control modulate the neural response to threat. *Neuroimage*. 2015;121:217–26 Available from: <https://www.sciencedirect.com/science/article/pii/S105381191500645X>. Cited 2019 Jun 11.
187. Hashimoto T, Takeuchi H, Taki Y, Sekiguchi A, Nouchi R, Kotozaki Y, et al. Neuroanatomical correlates of the sense of control: gray and white matter volumes associated with an internal locus of control. *Neuroimage*. 2015;119:146–51 Available from: <https://www.sciencedirect.com/science/article/pii/S1053811915005662>. Cited 2019 Jun 11.

188. Ottaviani C, Thayer JF, Verkuil B, Lonigro A, Medea B, Couyoumdjian A, et al. Physiological concomitants of perseverative cognition: a systematic review and meta-analysis. *Psychol Bull.* 2016;142(3):231–59.
189. Paulesu E, Sambugaro E, Torti T, Danelli L, Ferri F, Scialfa G, et al. Neural correlates of worry in generalized anxiety disorder and in normal controls: a functional MRI study. *Psychol Med.* 2010;40(1):117–24 Available from: https://www.cambridge.org/core/product/identifier/S0033291709005649/type/journal_article. Cited 2019 May 21.
190. Hilt LM, Pollak SD. Characterizing the ruminative process in young adolescents. *J Clin Child Adolesc Psychol.* 2013;42(4):519–30 Available from: <http://www.tandfonline.com/doi/abs/10.1080/15374416.2013.764825>. Cited 2019 Aug 1.
191. Salganik MJ, Lundberg I, Kindel AT, Ahearn CE, Al-Ghoneim K, Almaatoug A, et al. Measuring the predictability of life outcomes with a scientific mass collaboration. *Proc Natl Acad Sci.* 2020;201915006 Available from: <http://www.pnas.org/content/early/2020/03/24/1915006117.abstract>.
192. Danese A, Widom CS, et al. *Nat Hum Behav.* 2020. <https://doi.org/10.1038/s41562-020-0880-3>.
193. Andersen SL. Exposure to early adversity: Points of cross-species translation that can lead to improved understanding of depression. *Dev Psychopathol.* 2015;27(02):477–91 Available from: http://www.journals.cambridge.org/abstract_S0954579415000103. Cited 2019 Apr 1.
194. Teicher MH, Samson JA. Annual Research Review: Enduring neurobiological effects of childhood abuse and neglect. *J Child Psychol Psychiatry Allied Discip.* 2016;57(3):241–66.
195. Danese A, McEwen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiol Behav.* 2012;106(1):29–39. <https://doi.org/10.1016/j.physbeh.2011.08.019>.
196. van Harmelen A-L, Hauber K, Gunther Moor B, Spinhoven P, Boon AE, Crone EA, et al. Childhood emotional maltreatment severity is associated with dorsal medial prefrontal cortex responsivity to social exclusion in young adults. *PLoS One.* 2014;9(1):e85107 Available from: <http://dx.plos.org/10.1371/journal.pone.0085107>. Hoshi Y, editor. Cited 2019 May 28.
197. Cisler JM, James GA, Tripathi S, Mletzko T, Heim C, Hu XP, et al. Differential functional connectivity within an emotion regulation neural network among individuals resilient and susceptible to the depressogenic effects of early life stress. *Psychol Med.* 2013;43(3):507–18 Available from: https://www.cambridge.org/core/product/identifier/S0033291712001390/type/journal_article. Cited 2019 May 28.
198. Perroud N, Paoloni-Giacobino A, Prada P, Olié E, Salzmann A, Nicastro R, et al. Increased methylation of glucocorticoid receptor gene (NR3C1) in adults with a history of childhood maltreatment: a link with the severity and type of trauma. *Transl Psychiatry.* 2011;1(12):e59 \.
199. Carpenter LL, Tyrka AR, McDougle CJ, Malison RT, Owens MJ, Nemeroff CB, et al. Cerebrospinal fluid corticotropin-releasing factor and perceived early-life stress in depressed patients and healthy control subjects. *Neuropsychopharmacology.* 2004;29(4):777–84 Available from: <http://www.nature.com/articles/1300375>. Cited 2019 May 27.
200. Ouellet-Morin I, Robitaille M-P, Langevin S, Cantave C, Brendgen M, Lupien SJ. Enduring effect of childhood maltreatment on cortisol and heart rate responses to stress: The moderating role of severity of experiences. *Dev Psychopathol.* 2019; 31(02):497–508 Available from: https://www.cambridge.org/core/product/identifier/S0954579418000123/type/journal_article. Cited 2019 Jun 4.
201. King LS, Colich NL, LeMoult J, Humphreys KL, Ordaz SJ, Price AN, et al. The impact of the severity of early life stress on diurnal cortisol: The role of puberty. *Psychoneuroendocrinology.* 2017;77:68–74 Available from: <https://www.sciencedirect.com.ezproxy.library.wisc.edu/science/article/pii/S030645301630498X>. Cited 2019 May 27.
202. Glynn LM, Baram TZ. The influence of unpredictable, fragmented parental signals on the developing brain. *Front Neuroendocrinol.* 2019;100736 Available from: <https://www.sciencedirect.com/science/article/pii/S0091302218301006>. Cited 2019 May 21.
203. Hallers-Haalboom ET, Groeneveld MG, van Berkel SR, Endendijk JJ, van der Pol LD, Linting M, et al. Mothers' and fathers' sensitivity with their two children: a longitudinal study from infancy to early childhood. *Dev Psychol.* 2017;53(5):860–72 Available from: <http://doi.apa.org/getdoi.cfm?doi=10.1037/dev0000293>. Cited 2019 May 27.
204. Fisher PA, Frenkel TI, Noll LK, Berry M, Yockelson M. Promoting healthy child development via a two-generation translational neuroscience framework: the filming interactions to nurture development video coaching program. *Child Dev Perspect.* 2016;10(4):251–6 Available from: <http://doi.wiley.com/10.1111/cdep.12195>. Cited 2019 May 27.
205. Doom JR, Vanzomeren-Dohm AA, Simpson JA. Early unpredictability predicts increased adolescent externalizing behaviors and substance use: a life history perspective. *Dev Psychopathol.* 2016;28(4pt2):1505–16 Available from: https://www.cambridge.org/core/product/identifier/S0954579415001169/type/journal_article. Cited 2019 May 21.
206. Molet J, Maras PM, Kinney-Lang E, Harris NG, Rashid F, Ivy AS, et al. MRI uncovers disrupted hippocampal microstructure that underlies memory impairments after early-life adversity. *Hippocampus.* 2016; 26(12):1618–32 Available from: <http://doi.wiley.com/10.1002/hipo.22661>. Cited 2019 May 22.
207. Sanchez MM, McCormack KM, Howell BR. Social buffering of stress responses in nonhuman primates: maternal regulation of the development of emotional regulatory brain circuits. *Soc Neurosci.* 2015;10(5):512–26.
208. Gunnar MR, Hostinar CE, Sanchez MM, Tottenham N, Sullivan RM. Parental buffering of fear and stress neurobiology: reviewing parallels across rodent, monkey, and human models. *Soc Neurosci.* 2015;10(5):474–8. <https://doi.org/10.1080/17470919.2015.1070198>.
209. Callaghan BL, Tottenham N. The neuro-environmental loop of plasticity: a cross-species analysis of parental effects on emotion circuitry development following typical and adverse caregiving. *Neuropsychopharmacology.* 2016; 41(1):163–76 Available from: <http://www.nature.com/articles/hpp2015204>. Cited 2019 May 27.
210. Porges SW. Making the world safe for our children: Down-regulating defence and up-regulating social engagement to “optimise” the human experience. *Child Aust.* 2015;40(2):114–23.
211. Sullivan RM, Opendak M. Developmental and neurobehavioral transitions in survival circuits. *Curr Opin Behav Sci.* 2018;24:50–5 Available from: <https://doi.org/10.1016/j.cobeha.2018.03.005>.
212. Moriceau S, Shionoya K, Jakubs K, Sullivan R. Early-life stress disrupts attachment learning: The role of amygdala corticosterone, locus ceruleus corticotropin releasing hormone, and olfactory bulb norepinephrine. *J Neurosci.* 2009;29(50):15754–5 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12716958>. Cited 2019 May 22.
213. Nephew BC, Huang W, Poirier GL, Payne L, King JA. Altered neural connectivity in adult female rats exposed to early life social stress. *Behav Brain Res.* 2017;316:225–33 Available from: <https://www.sciencedirect.com/science/article/pii/S0166432816305691>. Cited 2019 May 23.
214. Rincón-Cortés M, Sullivan RM. Emergence of social behavior deficit, blunted corticolimbic activity and adult depression-like behavior in a rodent model of maternal maltreatment. *Transl Psychiatry* 2016 610. 2016;6(10):e930 Available from: <http://www.nature.com/articles/tp2016205>. Cited 2019 May 23.
215. Spinelli S, Chefer S, Suomi SJ, Higley JD, Barr CS, Stein E. Early-life stress induces long-term morphologic changes in primate brain. *Arch Gen Psychiatry.* 2009;66(6):658 Available from: <http://archgenpsychiatry.com/article.aspx?doi=10.1001/archgenpsychiatry.2009.52>. Cited 2019 May 23.
216. Tottenham N. Social scaffolding of human amygdala-mPFC circuit development. *Soc Neurosci.* 2015;10(5):489–99 Available from: <http://www.tandfonline.com/doi/full/10.1080/17470919.2015.1087424>. Cited 2019 May 22.
217. Hostinar CE, Johnson AE, Gunnar MR. Early social deprivation and the social buffering of cortisol stress responses in late childhood: an experimental study. *Dev Psychol.* 2015;51(11):1597–608 Available from: <http://doi.apa.org/getdoi.cfm?doi=10.1037/dev0000029>. Cited 2019 May 6.
218. Seltzer LJ, Ziegler TE, Pollak SD. Social vocalizations can release oxytocin in humans. *Proc R Soc B Biol Sci.* 2010;277(1694):2661–6 Available from: <http://www.royalsocietypublishing.org/doi/10.1098/rspb.2010.0567>. Cited 2019 May 23.
219. Gee DG, Gabard-Durnam L, Telzer EH, Humphreys KL, Goff B, Shapiro M, et al. Maternal buffering of human amygdala-prefrontal circuitry during childhood but not during adolescence. *Psychol Sci.* 2014;25(11):2067–78 Available from: <http://journals.sagepub.com/doi/10.1177/0956797614550878>. Cited 2019 May 22.
220. Fan Y, Herrera-Melendez AL, Pestke K, Feeser M, Aust S, Otte C, et al. Early life stress modulates amygdala-prefrontal functional connectivity: implications for oxytocin effects. *Hum Brain Mapp.* 2014;35(10):5328–39 Available from: <http://doi.wiley.com/10.1002/hbm.22553>. Cited 2019 May 23.
221. Brody GH, Yu T, Nusslock R, Barton AW, Miller GE, Chen E, et al. The protective effects of supportive parenting on the relationship between adolescent poverty and resting-state functional brain connectivity during

- adulthood. *Psychol Sci.* 2019;095679761984798 Available from: <http://journals.sagepub.com/doi/10.1177/0956797619847989>. Cited 2019 May 28.
222. McLafferty M, O'Neill S, Armour C, Murphy S, Bunting B. The mediating role of various types of social networks on psychopathology following adverse childhood experiences. *J Affect Disord.* 2018;238:547–53 Available from: <https://www.sciencedirect.com/science/article/pii/S0165032718306207>. Cited 2019 May 6.
223. van Harmelen A-L, Gibson JL, St Clair MC, Owens M, Brodbeck J, Dunn V, et al. Friendships and family support reduce subsequent depressive symptoms in at-risk adolescents. *PLoS One.* 2016;11(5):e0153715 Available from: <https://dx.plos.org/10.1371/journal.pone.0153715>. Alway SE, editor. Cited 2019 May 22.

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