Early Life Stress

Madeline B. Harms and Seth D. Pollak

Department of Psychology, University of Wisconsin-Madison, Madison, WI, USA

Introduction

Early life, defined here as postnatal life from birth through adolescence, is a developmental period during which individuals are especially sensitive to the biological effects of stress (Lupien, McEwen, Gunnar, & Heim, 2009; though prenatal stress also appears to exert profound influence on health outcomes in offspring, this topic is beyond the scope of this chapter). There is strong evidence that environmental input during early life can program physical, cognitive, and emotional traits to be optimally adaptive for survival and reproduction in that environment (Bock, Rether, Groger, Xie, & Braun, 2014; Nederhof & Schmidt, 2012). Severe early life stress, including famine or war, child abuse and/or neglect, poverty, or exposure to family conflict and violence, has been repeatedly associated with negative cognitive, emotional, and physical health outcomes (Brown, Susser, Lin, Neugebauer, & Gorman, 1995; Eriksson, Räikkönen, & Eriksson, 2014; Kaplan et al., 2001). These adverse experiences appear to lead to changes in the body and brain that can be adaptive in a harsh and traumatic environment. However, these adaptions can increase risk for developing a range of psychiatric disorders and social adjustment problems later in life (Heim & Nemeroff, 2001). The focus of this article is the mechanisms through which early life stress influences neural development and in turn behavioral and psychological outcomes.

Classifying Types of Early Life Stress

The term "stress" has been used to describe different concepts, including both environmental events and individuals' physical and psychological responses to these events. Here, we define stress as activation of bodily and neural systems that respond to potential threats in the environment. We define a "stressor" as "any unpredictable or uncontrollable stimulus that could—potentially—pose a threat to the organism" (Levine & Ursin, 1991). In early childhood, many of the most salient stressors are those that disrupt the attachment bond between a child and

The Wiley Encyclopedia of Health Psychology: Volume 1: Biological Bases of Health Behavior, First Edition.
General Editor: Lee M. Cohen. Volume Editor: Robert H. Paul.

his/her caregiver(s). The establishment and maintenance of an emotional bond between an infant and its mother or parents is believed to "program" emotional and social development throughout the lifespan (Ainsworth, 1962; Bowlby & King, 2004). Adverse experiences that can disrupt this bond include separation from caregivers, neglect, parental psychopathology, and various forms of abuse.

Early life stress has traditionally been characterized in terms of allostatic load, the cost of repeated biological responses to chronic stress exposure (McEwen, 2012) or cumulative risk models, the combination of risks posed by aggregate exposure to multiple stressors (Evans, Li, & Whipple, 2013). These models consider an individual's global exposure to multiple stressors in predicting risk for negative physical or psychological health outcomes. For example, a child who was abused and had an incarcerated parent would be at higher risk than a child who was abused but was not exposed to additional stressors. More recently, some researchers have advocated that subtypes of early life stressors should be categorized in terms of the presence of harmful input, such as caregiver abuse or exposure to violence, and inadequate input, such as caregiver neglect, separation from caregivers, or scarcity of resources (Humphreys & Zeanah, 2015). Subtypes of early life stressors have similarly been characterized in terms of threat or deprivation (McLaughlin & Sheridan, 2016; Pollak, Cicchetti, Homung, & Reed, 2000). In these models, a neglected child has been exposed to qualitatively different types of stressors than a child who has been abused, and we would expect divergent outcomes between the two. However, exposure to multiple subtypes of early life stressors is common (Vachon, Krueger, Rogosch, & Cicchetti, 2015). Although there is some preliminary evidence that these subtypes of stressors may be associated with different neural and behavioral outcomes (Dennison et al., 2017), this is a relatively new idea, and consequently current scientific understanding of these differential pathways is limited.

In terms of human development, more is known about effects of deprivation-related stressors than threat-related stressors. Many of the seminal human studies on neurobehavioral effects of early life stress have stemmed from the Bucharest Early Intervention Project (Zeanah et al., 2003), a randomized controlled trial conducted between 2000 and 2005 that compared foster care as an alternative with institutional care for young Romanian children. In this project, half of a group of 136 children were randomly assigned to high-quality foster care and the other half to remain in institutional care. Children in the intervention group were adopted into foster care between 6 and 31 months of age, and all children were seen for follow-up assessments several times throughout childhood. Findings thus far indicate that early institutionalization leads to profound deficits in many domains of functioning, including cognitive and socioemotional development, brain structure and function, and an elevated incidence of psychological impairment. Children randomized to foster care showed reliably better outcomes in each of these areas than those who remained in institutional care (Nelson et al., 2007). In addition, children who remained in institutional care showed blunted physiological responses to psychosocial stressors compared with children randomized to foster care and to community controls (McLaughlin et al., 2015). As a whole, findings from this project have been interpreted to suggest that the deprivation of a consistent attachment figure in infancy and early childhood is a significant stressor that impairs the optimal development of systems that promote physical and psychological health.

Other forms of early life deprivation, such as caregiver neglect, poverty, and food insecurity, also appear to adversely influence development. Caregiver neglect, defined as a failure to meet children's basic physical needs with respect to clothing, hygiene, food, and/or safety (Leeb, Paulozzi, Melanson, Simon, & Arias, 2008), is one of the most common forms of child maltreatment; it is estimated that 20% of children worldwide experience neglect (World Health

Organization, 2002). Neglect can be similar to institutionalization, in that children who experience severe neglect lack a caregiver that reliably responds to their needs (Bruce, Gunnar, Pears, & Fisher, 2013). Often, these children are placed into foster care families. Also like children who were institutionalized, individuals with a documented history of neglect show dysregulated stress hormone levels (Fisher, Stoolmiller, Gunnar, & Burraston, 2007), as well as deficits in higher-level cognitive function. Poverty is another deprivation-related stressor that has been associated with adverse outcomes in terms of brain development (Brito & Noble, 2014), language development and higher-level cognition (Noble, McCandliss, & Farah, 2007), academic achievement (Hair, Hanson, Wolfe, & Pollak, 2015), and emotion regulation (Kim et al., 2013) by prospective longitudinal studies. While children who are neglected or institutionalized do not reliably have their emotional needs met from their caregiver, children exposed to poverty, especially poverty severe enough to result in food insecurity, may not reliably have their physical needs met. In sum, a child's exposure to uncontrollable, and potentially unpredictable, failure to receive necessary physical and/or emotional stimulation can be characterized as a significant stressor.

In contrast to these deprivation-related stressors, caregiver abuse represents a direct and acute threat to a child's well-being. Children in abusive families may experience physical harm and threat (Bick & Nelson, 2016; Pollak, 2015), which results in chronic stress. Children in these environments may also experience a nonnormative emotional learning environment. While children in abusive families may have their physical needs met, abusive caregivers are often inconsistent in their responses to a child's behavior—sometimes responding in normative ways to their children and other times becoming either extremely reactive or unresponsive to their children (Milner & Robertson, 1989). This type of inconsistency can make it challenging for children to learn environmental contingencies between their own behavior and their caregiver's reactions. In addition, abusive caregivers often provide ambiguous emotional signaling to their children, producing unclear facial and vocal expressions of emotion (Shackman et al., 2010). All these factors likely contribute to significant alterations in emotional, cognitive, and brain development that are well documented in abused individuals (Hanson et al., 2015; Harms, Shannon-Bowen, Hanson, & Pollak, 2017; Hart & Rubia, 2012), as well as their increased risk for developing psychiatric disorders (Heim & Nemeroff, 2001).

In addition to overt maltreatment, less severe and more common forms of early adversity such as disrupted parent–child relationships have also been linked to poorer mental and physical health in adulthood. For example, individuals who grow up in families characterized by high levels of conflict and aggression, relationships that are cold, unsupportive, or neglectful, and chaotic daily lives tend to show more behavioral problems in childhood and poorer health in adulthood (Carroll et al., 2013; Repetti, Robles, & Reynolds, 2011; Repetti, Taylor, & Seeman, 2002). Individuals exposed to these subtler forms of early life stress within the family show problems in emotion processing and social competence, disruptions in stress-responsive biological regulatory systems, and poor health behaviors such as substance abuse (Repetti et al., 2002). In sum, the term "early life stress" encompasses a range of stressors and levels of severity, which poses a challenge for research in this area.

Measurement of Early Life Stress

Another challenge for researchers in early life stress relates to measurement of early adversity. For ethical reasons, the Bucharest Early Intervention Project is the only study using random assignment involving humans that has been conducted to examine the effects of early life

stress. In the majority of studies, children who are exposed to early adversity within the family environment also tend to experience high levels of stress in other domains, such as school-related stress and tension within the neighborhood and community. Thus, it is difficult to isolate how specific sources of early life stress impact children's health and development. However, a number of experimental studies involving rodents provide insight into the specific effects of disrupted caregiver behaviors on offspring.

Most animal studies of stress have either focused on the effects of stress during adulthood or on how early stress influences later neurobehavioral patterns in adults (Malter Cohen et al., 2013). For the most part, rodent models of childhood stress have tended to utilize periods of maternal separation. This approach tends to induce intermittent, rather than chronic stress (i.e., pups are separated from the mother and then reunified). Recently, however, a reliable model of chronic fragmented maternal care, including maltreatment, has been established for rodents. In this model, insufficient bedding and nesting materials in the home cage causes mothers to neglect or even abuse their pups and, in turn, induces early life psychosocial stress in offspring (Baram et al., 2012; Molet, Maras, Avishai-Eliner, & Baram, 2014). In parallel with human studies of maltreatment, this model of early family adversity has been shown to contribute to cognitive and emotional dysfunctions, as well as disrupted brain development (Brunson et al., 2005) and disrupted biological stress responses (Gunn et al., 2013) in offspring.

However, animal models have limitations in terms of generalizing results to humans. First, certain types of early life stress that may be unique to humans—such as emotional abuse—cannot be simulated. Rodent models such as the limited bedding/nesting paradigm tend to induce maternal behavior that most closely resembles neglect, but rarely results in physical abuse and obviously cannot approximate emotional abuse. In addition, the fact that rodents are born in litters makes rearing environments fundamentally different between rodents and humans. Several studies have examined early life stress in nonhuman primates, who exhibit similar mother–infant interactions as humans (Nelson & Winslow, 2009). A subset of nonhuman primate mothers do physically abuse their infants, though abuse differs from human families in that it tends to be short lived, confined to an infant's first month of life, and does not co-occur with neglect (Sanchez, 2006). Thus, the specific types of maltreatment environments that human children experience cannot be fully replicated in animal models. Second, rodent and even nonhuman primate models unable to reproduce the rich repertoire of cognitive and emotional behaviors that occur in human development. Third, brain regions mature at different rates and trajectories, which differ across species (Avishai-Eliner, Brunson, Sandman, & Baram, 2002). These differences pose a challenge for researchers who intend to directly compare the age of a developing animal with a specific human age in terms of overall brain development, especially in rodent studies. Due to these limitations, research examining the sequelae of early life stress in humans remains necessary.

Studies involving human subjects typically take either a retrospective or prospective approach to measuring early adversity. Retrospective reports of childhood experiences can be obtained from adults and are therefore a convenient measure in many situations. Some commonly used retrospective measures are questionnaires such as the Childhood Trauma Questionnaire (CTQ) (Bernstein, Fink, Handelsman, & Foote, 1994) and the Adverse Childhood Events Scale (ACES) (Felitti et al., 1998), which ask participants if they experienced maltreatment or negative life events in childhood. Other studies use interview methods, such as the UCLA Life Stress Interview (Hammen, Marks, Mayol, & de Mayo, 1985), which assesses current chronic stress in addition to a retrospective report of childhood stress.

The validity of retrospective reporting of early life stress is debated. A potential confound with this approach is that adults' current levels of stress and/or mood may affect their subjective

feelings regarding their childhood (Colman et al., 2016): for example, current life difficulties may cause them to have a negative bias of their lives as children. In addition, retrospective reports are subject to omission errors (Widom & Morris, 1997), and studies report weak correlations between retrospective reports and prospective measures. For example, in a large longitudinal birth cohort study (Reuben et al., 2016), a prospective measure of adverse experiences that were documented during childhood was only moderately correlated with retrospective reports by adult participants. The accuracy of retrospective reporting may also depend on the types of events that are queried. For example, in this study, higher agreement between prospective and retrospective measurement was reported for objectively adverse events, such as the loss of a parent, than for events involving subjective interpretation, such as emotional abuse. Furthermore, personality traits (neuroticism and agreeableness) were associated with the extent to which retrospective and prospective measurements were congruent. Another important difference between prospective and retrospective measurement is that prospective measures are often objective (e.g., measured through Child Protective Services Records or other informant reports), while retrospective reports are inherently subjective. Indeed, Reuben et al. (2016) found that prospectively measured early life stress best predicted objectively measured health outcomes, while retrospective reports best predicted subjective health outcomes. These associations suggest the possibility for common method bias—i.e., individuals who feel worse about their health also have more negative views regarding their early life experiences. For all these reasons, it is recommended that researchers use prospective measures whenever possible.

Behavioral Sequelae of Early Life Stress

Despite measurement issues, findings from studies using different methods, or involving humans versus animals, show substantial overlap in terms of the neurobehavioral effects of early adversity, including impaired cognitive and emotional development (Lupien et al., 2009). For example, studies involving both rodents (Ivy et al., 2010) and humans (Hanson et al., 2017; Harms, Shannon-Bowen, et al., 2017) have found deficits in learning and memory, along with abnormal development of associated brain regions, following early life stress (Teicher, Tomodo, & Andersen, 2006). Examining emotional development, Malter Cohen et al. (2013) tested parallel models of early life stress in both rodents (limited nesting material) and humans (early institutionalization), reporting evidence that early adversity inhibited the ability to suppress attention toward potentially threatening information in favor of goal-directed action, indicating deficits in fear regulation in both species. These findings have been replicated by many other studies that examined humans or rodents separately (Heim & Nemeroff, 2001; Tottenham & Sheridan, 2010).

Early stress appears to alter threat perception, which can lead to increases in both anxiety and aggressive behavior. In Shackman, Shackman, and Pollak (2007), abused children showed increased attention to visual and auditory anger cues, as indexed by event-related potentials (ERPs) relative to non-abused controls. In addition, the amount of attention children allocated to these threatening emotional stimuli mediated the relationship between physical abuse and child-reported anxiety. In a later study (Shackman & Pollak, 2014), the same researchers showed that a history of maltreatment was also associated with higher levels of negative affect expression and aggression (measured by negative feedback directed toward a putative peer) during a laboratory task. Attention to threat (angry faces) again mediated the relationships between maltreatment and both negative affect and aggression. Thus, over-attending to threat

appears to be a key mechanism through which early stress becomes associated with emotional and behavioral problems.

Behavioral and neuroimaging studies also suggest abnormal reward processing, which integrates emotional and cognitive systems, in individuals exposed to early stress (Birn, Roeber, & Pollak, 2017; Dillon et al., 2009; Goff et al., 2013; Hanson, Hariri, & Williamson, 2015; Mehta et al., 2010; Pechtel & Pizzagalli, 2011; Weller & Fisher, 2013). For example, in an incentive-based learning task, abused children and adolescents did not respond to differences in reward probability, failing to increase their response speed as the chance of winning increased (Guyer et al., 2006). This finding suggests that the abused children were unable to acquire or effectively use information about differing reward probabilities. In addition, studies of risk-taking found reduced exploration behavior, which could have yielded larger rewards, in neglected (Loman et al., 2014) and abused adolescents (Sujan, Humphreys, Ray, & Lee, 2014) relative to control groups. Finally, Harms, Shannon-Bowen, et al. (2017) found deficits in both acquisition and reversal of stimulus–reward associations among adolescents who had been physically abused. Although this is a relatively new area of research, and requires replication in experimental animal research, this emerging evidence suggests that early life stress has profound impacts on reward processing.

Abnormal development in threat sensitivity, emotion regulation, and reward processing may contribute to the association between early adversity and increased risk for a range of psychiatric disorders and behavioral problems (Jaffee, 2017). Early life stress, particularly maltreatment, has been linked to elevated risk for developing major depression (Scott, Smith, & Elis, 2010) and anxiety disorders (Cohen et al., 2006), including PTSD (Breslau et al., 2014), as well as increased levels of suicidal thoughts (Thornberry, Henry, Ireland, & Smith, 2010) and self-injurious behavior (Yates, Tracy, & Luthar, 2008). In addition to higher internalizing symptomatology, victims of maltreatment show increased externalizing problems in adulthood, including higher incidence of antisocial behavior (Johnson & Leff, 1999), and more frequent criminal activity and arrests (Maxfield & Widom, 1996; Thornberry, Henry, Ireland, & Smith, 2010).

Neurobiological Sequelae of Early Life Stress

Early life stress influences an individual's development at multiple levels, including behavior, neurobiology, and the epigenome. To appreciate these influences, it is necessary to understand how organisms respond biologically to stressors in the environment.

The Stress Response

In humans and animals, sophisticated biological systems have evolved to respond to potential threats in the environment. Here, we provide a brief overview of this stress response. An acute stressor activates the hypothalamic–pituitary–adrenal (HPA) axis, which induces the release of corticotropin-releasing hormone (CRH) and vasopressin (AVP) from the hypothalamus and adrenocorticotropic hormone (ACTH) from the pituitary into the blood. This stimulates the release of glucocorticoid (cortisol in humans and corticosterone in rodents) from the adrenal cortex. The HPA axis follows a basal circadian activity rhythm and is regulated by a negative feedback mechanism moderated by corticosteroids that constrain the response of the axis after its activation. This negative feedback mechanism is complex, but briefly, corticosteroids bind to glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) that are expressed

in most bodily tissues and act as transcription factors (Larsson et al., 2012; Sanchez, Arnt, Hyttel, & Moltzen, 1993). GR activation causes a negative feedback loop at several levels of the HPA axis that ends the stress response and the release of cortisol once a threat has been removed (for more information, see Provencal & Binder, 2015).

Through this negative feedback mechanism, the HPA system responds very effectively to acute, short-term environmental threats, which were typical throughout most of human evolution. However, the HPA axis is less well equipped to deal with chronic stress. In this context, the negative feedback mechanisms that regulate the stress response can break down, resulting in either hypersensitive or blunted HPA system reactivity. In animal models, early life stress resulting from maternal separation, or from the limited nesting model, tends to lead to hyperreactivity of the HPA axis in adulthood, including increased CRH signaling in response to a stressor and impaired GR-mediated negative feedback (van Bodegom, Homberg, & Henckens, 2017). However, in another model of early life stress, early social deprivation, rodent pups are temporarily separated from their mother and littermates and housed in a novel environment. This more severe stress can decrease stress-induced corticosterone levels in these animals are either blunted or unaffected relative to non-stressed controls (Sandi & Haller, 2015), suggesting reduced HPA sensitivity relative to non-stressed controls. Human findings similarly show variation in the effects of early adversity on HPA axis function. For example, exposure to interparental aggression, corporal punishment, or frequent emotional maternal withdrawal was found to increase baseline (i.e., non-stressed) cortisol levels (Davies, Sturge-Apple, Cicchetti, Manning, & Zale, 2009) and cortisol stress responses (Bugental et al., 2003). In contrast, there is also evidence institutionalization or maltreatment can result in HPA axis hyporeactivity. For example, a recent study showed that childhood maltreatment was associated with decreases in cortisol response during psychosocial stress in adulthood (Grimm et al., 2014). Similarly, studies involving human children exposed to severe neglect, abuse, orphanage/institutional care, or involvement with child protective services report lower basal levels of corticosteroids (Bernard, Zwerling, & Dozier, 2015; Bruce, Fisher, Pears, & Levine, 2009; Gunnar and Donzella, 2002). In general, the literature suggests that more severe early stress is more likely to lead to hypo- versus hypercortisolism.

Inconsistent findings of either increased or decreased stress responsiveness after early adversity might be explained by a trajectory of initial hyperactivation of the HPA axis that progresses to a state of sustained stress hyporeactivity when the stressors are severe and/or chronic (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Pryce, Bettschen, Nanz-Bahr, & Feldon, 2003). HPA hyporeactivity may serve as a compensatory adaptation that protects the organism from deleterious effects of chronic high levels of stress hormones. Initial evidence for this trajectory of HPA axis responsivity resulting from chronic stress has been demonstrated in animal models (Saltzman et al., 2006; Sterlemann et al., 2008). However, more research is needed to investigate mediating and moderating factors that influence how stress affects development of the HPA system.

Early Life Stress and Epigenetics of the Stress Response

Epigenetic mechanisms—changes in gene expression that do not involve changes in the DNA sequence—appear to be important factors that mediate the extent to which early life stress leads to blunting or hypersensitivity of the HPA axis (Conradt, 2017). Although the specific epigenetic modifications that may contribute to differential HPA system trajectories following early stress are not fully understood, the field has made rapid progress in recent years in elucidating how some of these mechanisms operate. For example, we now know that decreases in

GR expression and activation tend to be associated with an increase in the stress response, and this can be explained by epigenetic mechanisms (Provencal & Binder, 2015). DNA methylation, which can function to switch genes between "on" or "off" positions, is one epigenetic mechanism used by cells to regulate gene expression. Stress that occurs during certain developmental sensitive periods may lead to long-term changes in the methylation of genes that regulate the stress response (Zannas, Wiechmann, Gassen, & Binder, 2016). One such gene that has generated recent interest is the FK506 binding protein 5 (FKBP5) gene, which regulates glucocorticoid sensitivity. Childhood maltreatment has been associated with long-term demethylation of this gene (Klengel et al., 2013), which contributes to increased expression of FKBP5 (Harms et al., 2017). Higher expression of FKBP5 appears disrupt the negative feedback mechanism that regulates the HPA axis, resulting in glucocorticoid resistance, higher cortisol levels, and prolonged recovery following exposure to stress (Tyrka, Ridout, & Parade, 2016; Zannas & Binder, 20143). Another important gene that regulates the HPA axis is the glucocorticoid receptor gene, *NR3C1*. This gene shows greater methylation in physically abused children relative to non-maltreated children (Romens, McDonald, Svaren, & Pollak, 2015). A recent study examined the entire human genome in girls exposed to varying levels of childhood stress, finding that girls with high levels of stress exposure showed differential methylation in 122 genes, as well as changes in expression in 12 genes (Papale, Seltzer, Madrid, Pollak, & Alisch, 2018). Several of these genes are known to be involved in the stress response systems, but others serve different regulatory functions throughout the body, suggesting system-wide changes in biological functioning as a result of stress. Thus, early stress in the form of maltreatment appears to induce multiple epigenetic changes in stress response system and beyond that have implications for individuals' biological reactivity to subsequent stress.

Influences of Early Life Stress on Neural Circuitry

In addition to alterations in the stress response, epigenetic changes induced by early life stress appear to play a role in altering brain structure and function following early life stress (Labonte et al., 2012). According to the neurotoxicity hypothesis (Sapolsky, Krey, & McEwen, 1986), chronic glucocorticoid release (induced by extended stress exposure and potential epigenetic modifications that contribute to impaired GR negative feedback) facilitates neurodegenerative processes, resulting in structural changes in the volumes of various brain regions. The brain regions most consistently affected by early life stress include the hippocampus, amygdala, and prefrontal cortex. These regions coordinate learning and memory processes, emotional reactivity, and emotion regulation.

The limbic system, a set of brain regions immediately beneath the cerebral cortex, supports a variety of functions including emotion, motivation, and memory formation. Limbic regions, particularly the hippocampus (facilitating memory formation) and amygdala (facilitating emotional processing), are profoundly affected by early life stress. Studies of hippocampal development in stressed animals provided some of the earliest evidence for effects of chronic stress on the brain, showing decreased branching, reduced length, and atrophy of dendrites in hippocampal neurons among stressed relative to non-stressed rats (e.g., Cook & Wellman, 2004; McEwen, 1999). The limited bedding/nesting model has also been associated with a reduction of synapses and dendritic spines, as well as dendritic atrophy in the hippocampus (Brunson et al., 2005). In humans, structural findings regarding the effects of early life stress on limbic system development are more mixed and tend to involve both hippocampus and amygdala (or finding that early adversity is associated with changes in one region but not the

other). For example, some studies show larger amygdala volumes relative to control groups among previously institutionalized children who were adopted (Mehta et al., 2009; Tottenham, 2010), or smaller hippocampal volumes, with later adopted children showing larger abnormalities (Hodel et al., 2015). However, several studies show no differences in hippocampal (Mehta et al., 2009; Sheridan, Fox, & Zeanah, 2012; Tottenham, Henry, Ireland, & Smith, 2010) or amygdala volumes (Hodel et al., 2015) between previously institutionalized children and controls. Another study that employed detailed hand tracing of amygdala and hippocampus volumes showed that various forms of early life stress (physical abuse, early neglect, or low socioeconomic status) were associated with smaller amygdala and hippocampal volumes (Hanson et al., 2015). Divergent findings in humans could be due to a number of factors, including developmental timing of stress exposure, nonlinear brain development, different effects based on type of stressor, and methodological factors. However, the preponderance of evidence suggests that early stress alters trajectories of limbic brain development, which has implications for memory and emotion processing.

In addition to the limbic system, the prefrontal cortex and its connectivity with the limbic system are affected by early life stress. In animals, maternal separation is associated with long-term changes in prefrontal microstructure (Braun, Lange, Metzger, & Poeggel, 2000; Ovtscharoff & Braun, 2001; Poeggel et al., 2003) in rodents and with decreased medial prefrontal cortex volume in nonhuman primates (Lyons, Parker, Katz, & Schatzberg, 2009; Spinelli et al., 2009). Similarly, in humans, early maltreatment is associated with reduced gray matter volumes in medial prefrontal cortex and anterior cingulate gyrus (Dannlowski et al., 2012; De Brito et al., 2013; Edmiston et al., 2011; Hanson et al., 2010) as well as decreased functional connectivity between medial prefrontal cortex and amygdala (Burghy et al., 2012). Furthermore, a higher number of self-reported adverse childhood experiences have been linked with a smaller volume in regions such as anterior cingulate cortex and caudate that interface with the limbic system and prefrontal cortex (Cohen et al., 2006).

Studies using diffusion tensor imaging (DTI) studies, a method for evaluating structural connectivity through white matter tracts, show that early life stress disrupts microstructural integrity in the brain. Previously institutionalized or neglected children and adolescents show reduced integrity of the uncinate fasciculus (Eluvathingal et al., 2006; Govindan, Behen, Helder, Makki, & Chugani, 2010; Hanson et al., 2013), a white matter tract connecting limbic and frontal lobe regions (Behen et al., 2009). Moreover, several studies have found reduced global white matter volume, disrupted prefrontal white matter organization, or reduced prefrontal cortical thickness (reflecting the width of the cortical gray matter and potential brain atrophy) in children exposed to early deprivation (Eluvathingal et al., 2006; Mehta et al., 2009; Sheridan et al., 2012; McLaughlin et al., 2014). A study that assessed exposure to adverse childhood experiences through self-report found reduced microstructural integrity of the corpus callosum, which connects the two brain hemispheres (Paul et al., 2008). In this study, all participants were free of psychiatric symptoms, suggesting that white matter structure can be impacted by stress even in the absence of psychopathology. Finally, there is evidence that early life stress disrupts the global organization of brain networks—young adults with a history of childhood maltreatment show decreased network centrality in a number of cortical areas relative to non-maltreated individuals (Harms et al., 2017) (Teicher, Anderson, Ohashi, & Polcari, 2014). Decreased network centrality is likely to impair high-level cognitive functions that rely on the integration of information from multiple regions. In sum, various forms of severe early stress appear to alter both fronto-limbic structure and connectivity. These consequences may impact high-level cognitive processes such as emotion regulation and goal-directed behavior.

Gene–environment interactions and neural circuitry

Effects of early stress on neural structure and function appear to vary based on genetic factors. Genes involved in regulating serotonin levels and brain-derived neurotrophic factor (BDNF), a moderator of synaptic plasticity, have been shown to moderate the effects of stress on neural circuitry. Some individuals in the population carry "risk alleles" of these genes that increase their neurobiological sensitivity to negative environmental events. In one study, early life stress combined with the HTR3A CC genotype group of the serotonin 3A receptor gene was associated with smaller gray matter volume in hippocampus and frontal cortex and higher negative affect, compared with the T carriers (Gatt, Williams, et al., 2010). In another study, carriers of both BDNF methionine and HTR3A CC risk alleles who were exposed to high levels of early life stress showed elevated emotion-elicited heart rate, as well as right frontal hyperactivation and right parietotemporal hypoactivation in EEG asymmetry, compared with non-risk allele carriers (Gatt, Nemeroff, et al., 2010). These findings reflect gene–environment interactions associated with early stress that may increase the likelihood of developing internalizing psychopathology among risk allele carriers.

Additional Considerations

Additional factors that appear to moderate the effects of early stress on physical and mental health outcomes include developmental timing of stress and sex differences. In addition, we outline promising research addressing prevention and intervention mechanisms that may promote resilience in the face of early adversity.

Developmental Timing of Stress

Evidence suggests that stressors exert different neurobehavioral effects depending on when they occur during an organism's development, and early life stress is generally associated with longer-lasting impacts than stress experienced during adulthood (Lupien et al., 2009). However, in rodents, whose offspring are born relatively immature in terms of neuroendocrine development, there is strong evidence for a stress hyporesponsive period (SHRP) during the first two weeks of postnatal life, in which the HPA axis does not respond, or reacts only minimally, to environmental stressors (Levine, 1994). This period may have evolved to protect the developing brain from the effects of elevated glucocorticoids. There is controversy as to whether such a period exists in humans, though there is evidence that caregivers (when not absent or abusive) provide a strong buffering effect against stress in early childhood (Gunnar & Cheatham, 2003). It should also be noted that, because rodent pups are born less mature but mature at a faster rate than human infants, perinatal stress will impact different stages of development depending on which species is studied (Lupien et al., 2009).

In terms of brain development, stress exposure at different developmental periods is likely to have different impacts because regions mature at different rates (Andersen, 2003). For example, one study found that childhood sexual abuse experienced between 3 and 5 years of age was associated with reduced hippocampal volume, while abuse experienced in adolescence was associated with reduced gray matter volume in the frontal cortex (Andersen & Teicher, 2008). These findings are congruent with the developmental trajectories of these regions, with the hippocampus maturing in early childhood and the prefrontal cortex continuing to develop throughout adolescence (Lupien et al., 2009). Another study found that stress reported in late childhood (ages 8 and up) was associated with smaller anterior cingulated and insula volumes,

while stress reported in early childhood did not impact the volume of these regions (Baker et al., 2013). This finding may be due to changes in the emotional processing of stressful events across development.

Stress experienced during certain developmental periods can show incubation effects, where impacts do not become apparent until later ages: for example, having a mother with maternal depression has been associated with abnormal HPA activity and depressive symptoms in adolescence (Halligan, Hubert, Goodyer, & Murray, 2007). Indeed, a number of mental health problems associated with early life stress tend to surface for the first time in adolescence (Giedd, 2008). Studies show that adolescents are highly vulnerable to psychosocial stress, possibly due to a protracted glucocorticoid response to stress that persists into adulthood (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009; McCormick & Matthews, 2007). For example, chronic variable stress in adolescent rats has been shown to induce long-term alterations in hippocampal structure, cognition, and HPA axis function (Isgor, Kabbaj, Akil, &Watson, 2004). However, most scientific knowledge regarding the impacts of adolescent-specific stress is derived from animals, and more research is needed to determine the long-term impacts of adolescent stress in humans.

Sex Differences

A number of studies suggest that males and females respond differently to developmental stressors, with most evidence indicating that females are more vulnerable to early life stress. Females who experienced trauma, who experienced physical abuse, or whose mothers were depressed during infancy show higher rates of depression, anxiety, and PTSD compared with males (Baker and Shalhoub-Kevorkian, 1999; Macmillan et al., 2001; Pitzer et al., 2011). Sex differences following early life stress are also found in HPA system reactivity. For example, exposure to early trauma has been shown to be positively associated with cortisol response to CRH challenge in men but not in women (DeSantis et al., 2011). This finding suggests that women are more prone to a blunting of the HPA axis as a result of early stress. A recent study involving youth also found that in girls relative to boys, cortisol responses to stress were more highly correlated with genetic risk factors in genes that regulate the HPA axis, suggesting higher susceptibility to "risky" alleles in girls (Pagliaccio et al., 2014). There is also evidence that white matter structure is affected by early stress to a greater extent in females than in males (Paul et al., 2008). Animal models suggest that sex hormones play a role in the diverging neurobiological and behavioral responses to stress that occurs during adolescence between males and females (McCormick & Matthews, 2007). However, more research that specifically examines mechanisms for sex differences in the neurobiological sequelae of early stress is called for. Such research is especially important given that the risk for depression, for which early stress is often a contributing factor, is much higher in females beginning in adolescence (Kessler et al., 2003).

Prevention and Intervention Research

There are promising areas of research addressing prevention and intervention mechanisms to ameliorate negative effects of early life stress on health. Given that stress first affects the HPA system, the most effective prevention and intervention mechanisms should moderate long-term alterations in this system as a result of early stress (Bruce et al., 2013), and two intervention programs so far have been shown to do so. Multidimensional Treatment Foster Care for Preschoolers (MTFC-P) is a preventive intervention that focuses on the use of consistent,

contingent parenting strategies. MTFC-P has been shown to reduce placement disruptions, increase secure attachment-related behaviors (Fisher, Burraston, & Pears, 2005; Fisher & Kim, 2007), and prevent blunting of diurnal cortisol slopes in foster children (Fisher et al., 2007). These positive effects among children may be related to a reduction in caregiver stress resulting from the intervention (Fisher & Stoolmiller, 2008). Another intervention, the Incredible Years Series, was designed to reduce externalizing behaviors by enhancing parenting practices and child social competence among families with preschool-aged children who have siblings convicted for criminal activity. This preventive intervention has been shown to decrease child aggressive behavior (Brotman et al., 2008) and prevent blunted cortisol responses to social challenge (Brotman et al., 2007). Among families with low parental warmth, there is evidence that this intervention reduces child aggression via increased cortisol response, suggesting that HPA axis function mediates the positive impact of this intervention on child behavior (O'Neal et al., 2010).

Throughout infancy, childhood, and adolescence, the body and brain are undergoing dramatic changes and are profoundly shaped by environmental cues. As discussed earlier, many of the deleterious effects of early life stress are associated with a mismatch between the early life environment and later environments that an individual experiences. For example, the adaptations a child develops as a result of institutional care (blunted HPA reactivity, early puberty, preservation of emotional brain systems at the expense of higher-level cognitive systems) may increase their ability to survive long enough to reproduce in a very harsh, deprived environment. Similarly, increased vigilance to threat in the context of physical abuse increases a child's likelihood of avoiding harm in that particular family environment. However, these adaptations can hinder optimal functioning in an adoptive family and resource-rich environment, in school, or at a job later in life, resulting in a higher risk for physical and mental health problems. Stress-exposed individuals tend to exhibit reduced cognitive flexibility, meaning that once a stress-exposed individual learns a specific behavioral strategy during childhood, she/he may persevere with this strategy even if it becomes maladaptive when the environment changes (Harms, Shannon Bowen, et al., 2017). This dilemma presents another potential area for intervention: for children whose adverse environments cannot be fully replaced, perhaps early intermittent exposure to "mismatching" environments may facilitate cognitive and behavioral flexibility in novel situations (Bock et al., 2014). Programs such as Head Start and Boys and Girls Clubs might show positive impacts in part through exposing children from impoverished backgrounds to novel environments. Given the systemic effects of early life stress on physical and mental health outlined above, more research addressing prevention and intervention mechanisms is a profound societal need.

Conclusion

In sum, early life stress takes many forms, but all types of severe early adversity studied thus far have potentially negative impacts on long-term health and development. Early childhood stress influences lifetime physical and psychological health through alterations in the stress response system, the epigenome, and the development of brain circuitry that facilitates cognitive and emotional process. Priorities for future research on early life stress should include an emphasis on prospective measures of stress, longitudinal designs, attention to developmental timing (especially studies that examine adolescent-specific stress), and a focus on prevention and intervention work to mitigate the negative health effects of severe early stress.

Author Biographies

Madeline B. Harms is a visiting assistant professor at Gustavus Adolphus College in St. Peter, MN. She earned her PhD from the Institute of Child Development at the University of Minnesota and then completed a postdoctoral fellowship through the Emotion Training Grant at the University of Wisconsin–Madison. Dr. Harms has published on topics including emotion recognition, executive function development, and the effects of maltreatment on children's learning ability and brain development.

Seth D. Pollak is the College of Letters and Science Distinguished Professor of Psychology and professor of Pediatrics, Anthropology, Neuroscience, and Public Affairs at the University of Wisconsin–Madison. He is also an investigator at the University's Waisman Center for Human Development. Pollak earned dual PhDs from the University of Rochester in brain and cognitive sciences and in child clinical psychology. Professor Pollak has published widely on topics including children's emotional development, the influences of social risk factors on children's brain and behavioral development, and the effects of early experience on children's learning and health. He is a recipient of the American Psychological Association's Distinguished Early Career Award and the Boyd-McCandless Award for Distinguished Contributions to Child Development. Dr. Pollak is a fellow of the American Association for the Advancement of Science and the Association for Psychological Science, as well as a member of the Society for Research in Child Development's Governing Council.

References

Ainsworth, M. D. (1962). The effects of maternal deprivation: A review of findings and controversy in the context of research strategy. *Public Health Papers*, *14*, 97–165.

Andersen, S. L. (2003). Trajectories of brain development: Point of vulnerability or window of opportunity? *Neuroscience and Biobehavioral Reviews*, *27*, 3–18.

Anderson, S. L., & Teicher, M. H. (2008). Stress, sensitive periods, and maturational events in adolescent depression. *Trends in Neurosciences*, *31*(4), 183–191. doi:10.1016/j.tins.2008.01.004

Avishai-Eliner, S., Brunson, K. L., Sandman, C. A., & Baram, T. Z. (2002). Stressed-out, or in (utero)? *Trends in Neurosciences*, *25*(10), 518–524.

Baker, A., & Shalhoub-Kevorkian, N. (1999). Effects of political and military traumas on children: The Palestinian case. *Clinical Psychology Review*, *19*(8), 935–950.

Baker LM, Williams LM, Korgaonkar MS, Cohen RA, Heaps JM, & Paul RH. (2013). Impact of early vs. late childhood early life stress on brain morphometrics. *Brain Imaging Behaviour*, *7*(2), 196–203.

Baram, T. Z., Davis, E. P., Obenaus, A., Sandman, C. A., Small, S. L., Solodkin, A., & Stern, H. (2012). Fragmentation and unpredictability of early-life experience in mental disorders. *American Journal of Psychiatry*, *169*, 907–915. doi:10.1176/appi.ajp.2012.11091347

Behen, M. E., Muzik, O., Saporta, A. S. D., Wilson, B. J., Pai, D., Hua, J., & Chugani, H. T. (2009). Abnormal fronto-striatal connectivity in children with histories of early deprivation: A diffusion tensor imaging study. *Brain Imaging and Behavior*, *3*, 292–297. https://doi.org/10.1007/s11682-009-9071-6

Bernard, K., Zwerling, J., & Dozier, M. (2015). Effects of early adversity on young children's diurnal cortisol rhythms and externalizing behavior. *Developmental Psychobiology*, *57*, 935–947. doi:10.1002/dev.21324

Bernstein, D. P., Fink, L., Handelsman, L., & Foote, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *American Journal of Psychiatry*, *151*(8), 1132–1136.

Bick, J., & Nelson, C. A. (2016). Early adverse experiences and the developing brain. *Neuropsychopharmacology*, *41*(1), 177–196. doi:10.1038/npp.2015.252

Birn, R. M., Roeber, B. J., & Pollak, S. D. (2017). Early childhood stress exposure, reward pathways, and adult decision making. *PNAS*, *114*(51), 13549–13554. https://doi.org/10.1073/pnas.1708791114

Bock, J., Rether, K., Groger, N., Xie, L., & Braun, K. (2014). Perinatal programming of emotional brain circuits: An integrative view from systems to molecules. *Frontiers in Neuroscience*, *8*, 11. doi:10.3389/fnins.2014.00011 eCollection 2014

Bowlby, J., & King, P. (2004). *Fifty years of attachment theory: Recollections of Donald Winnicott and John Bowbly*. London: Karnac Books.

Braun, K., Lange, E., Metzger, M., & Poeggel, G. (2000). Maternal separation followed by early social deprivation affects the development of monoaminergic fiber systems in the medial prefrontal cortex of Octoden degus. *Neuroscience*, *95*(1), 309–318.

Breslau, N., Koenen, K. C., Luo, Z., Agnew-Blais, J., Swanson, S., & Houts, R. M. (2014). Childhood maltreatment, juvenile disorders and adult post-traumatic stress disorder: A prospective investigation. *Psychological Medicine*, *44*(9), 1937–1945.

Brito, N. H., & Noble, K. G. (2014). Socioeconomic status and structural brain development. *Frontiers in Neuroscience*, *8*, 276. doi:10.3389/fnins.2014.00276

Brotman, L. M., Gouley, K. K., Huang, K. Y., Kamboukos, D., Fratto, C., & Pine, D. S. (2007). Effects of a psychosocial family-based preventive intervention on cortisol response to a social challenge in preschoolers at high risk for antisocial behavior. *Archives of General Psychiatry*, *64*, 1172–1179.

Brotman, L. M., Gouley, K. K., Huang, K. Y., Rosenfelt, A., O'Neal, C., Klein, R. G., & Shrout, P. (2008). Preventive intervention for preschoolers at high risk for antisocial behavior: Long-term effects on child physical aggression and parenting practices. *Journal of Clinical Child and Adolescent Psychology*, *37*, 386–396.

Brown, A. S., Susser, E. S., Lin, S. P., Neugebauer, R., & Gorman, J. M. (1995). Increased risk of affective disorders in males after second trimester prenatal exposure to the Dutch hunger winter of 1944-45. *The British Journal of Psychiatry*, *166*, 601–606.

Bruce, J., Fisher, P. A., Pears, K. C., & Levine, S. (2009). Morning cortisol Levels in preschool-aged foster children: Differential effects of maltreatment type. *Developmental Psychobiology*, *51*, 14–23. doi:10.1002/dev.20333

Bruce, J., Gunnar, M. R., Pears, K. C., & Fisher, P. A. (2013). Early adverse care, stress neurobiology, and prevention science: Lessons learned. *Prevention Science*, *14*(3), 247–256.

Brunson, K. L., Kramar, E., Lin, B., Chen, Y., Colgin, L. L., Yanagihara, T. K., … Baram, T. Z. (2005). Mechanisms of late-onset cognitive decline after early-life stress. *The Journal of Neuroscience*, *25*, 9328–9338. doi:10.1523/JNEUROSCI.2281-05.2005

Bugental, D. B., Martorell, G. A., & Barraza, V. (2003). The hormonal costs of subtle forms of infant maltreatment. *Hormones and Behavior*, *43*(1), 237–244.

Burghy, C. A., Stodola, D. E., Ruttle, P. L., Molloy, E. K., Armstrong, J. M., Oler, J. A., … Birn, R. M. (2012). Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. *Nature Neuroscience*, *15*(12), 1736–1741.

Carroll, J. E., Gruenewald, T. L., Taylor, S. E., Janicki-Deverts, D., Matthews, K. A., & Seeman, T. E. (2013). Childhood abuse, parental warmth, and adult multisystem biological risk in the Coronary Artery Risk Development in Young Adults study. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(42), 17149–17153. doi:10.1073/pnas.1315458110

Cohen, R. A., Grieve, S., Hoth, K. F., Paul, R. H., Sweet, L., Tate, D., … Williams, L. M. (2006). Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. *Biological Psychiatry*, *59*(10), 975–982.

Colman, I., Kingsbury, M., Garad, Y., Zeng, Y., Naicker, K., … Thompson, A. H. (2016). Consistency in adult reporting of adverse childhood experiences. *Psychological Medicine*, *46*(3), 543–549. https://doi.org/10.1017/S0033291715002032

Conradt, E. (2017). Using principles of behavioral epigenetics to advance research on early-life stress. *Child Development Perspectives*, *11*, 107–112. doi:10.1111/cdep.12219

Cook, S. C., & Wellman, C. L. (2004). Chronic stress alters dendritic morphology in rat medial prefrontal cortex. *Journal of Neurobiology*, *60*(2), 236–248.

Dannlowski, U., Stuhrmann, A., Beutelmann, V., Zwanzger, P., Lenzen, T., Grotegard, D., … Kugel, H. (2012). Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biological Psychiatry*, *71*(4), 286–293.

Davies, P. T., Sturge-Apple, M. L., Cicchetti, D., Manning, L. G., & Zale, E. (2009). Children's patterns of emotional reactivity to conflict as explanatory mechanisms in links between interpartner aggression and child physiological functioning. *Journal of Child Psychology and Psychiatry*, *50*, 1384–1391. doi:10.1111/j.1469-7610.2009.02154.x

De Brito, S. A., Viding, E., Sebastian, C. L., Kelly, P. A., Mechelli, A., Maris, H., & McCrory, E. J. (2013). Reduced orbitofrontal and temporal grey matter in a community sample of maltreated children. *Journal of Child Psychology and Psychiatry*, *54*(1), 105–112. doi:10.1111/j.1469-7610.2012.02597.x

Dennison, M. J., Rosen, M. L., Sambrook, K. A., Jenness, J. L., Sheridan, M. A., & McLaughlin, K. A. (2017). Differential associations of distinct forms of childhood adversity with neurobehavioral measures of reward processing: A developmental pathway to depression. *Child Development*.

DeSantis, S. M., Baker, N. L., Back, S. E., Spratt, E., Ciolino, J. D., Moran-Santa Maria, M., … Brady, K. T. (2011). Gender differences in the effect of early life trauma on hypothalamic-pituitary-adrenal axis functioning. *Depression and Anxiety*, *28*(5), 383–392.

Dillon, D. G., Holmes, A. J., Birk, J. L., Brooks, N., Lyons-Ruth, K., & Pizzagalli, D. A. (2009). Childhood adversity is associated with left basal ganglia dysfunction during reward anticipation in adulthood. *Biological Psychiatry*, *66*, 206–213.

Edmiston, E. E., Wang, F., Mazure, C. M., Guiney, J., Sinha, R., Mayes, L. C., & Blumberg, H. P. (2011). Corticostriatal-limbic gray matter morphology in adolescents with self-reported exposure to childhood maltreatment. *Archives of Pediatrics & Adolescent Medicine*, *165*(12), 1069–1077. doi:10.1001/archpediatrics.2011.565

Eluvathingal, T. J., Chugani, H. T., Behen, M. E., Csaba, J., Muzik, O., Maqbook, M., … Makki, M. (2006). Abnormal brain connectivity in children after early severe socioemotional deprivation: A diffusion tensor imaging study. *Pediatrics*, *117*(6), 2093–2100. doi:10.1542/peds.2005-1727

Eriksson, M., Räikkönen, K., & Eriksson, J. G. (2014). Early life stress and later health outcomes—Findings from the Helsinki Birth Cohort Study. *American Journal of Human Biology*, *26*, 111–116.

Evans, G. W., Li, D., & Whipple, S. S. (2013). Cumulative risk and child development. *Psychological Bulletin*, *139*, 1342–1396.

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., … Marks, J. S. (1998). Household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) Study. *American Journal of Preventive Medicine*, *14*(4), 245–258.

Fisher, P. A., Burraston, B., & Pears, K. C. (2005). The Early Intervention Foster Care Program: Permanent placement outcomes from a randomized trial. *Child Maltreatment*, *10*, 61–71.

Fisher, P. A., & Kim, H. K. (2007). Intervention effects on foster preschoolers' attachment-related behaviors from a randomized trial. *Prevention Science*, *8*, 161–170.

Fisher, P. A., & Stoolmiller, M. (2008). Intervention effects on foster parent stress: Associations with child cortisol levels. *Development and Psychopathology*, *20*, 1003–1021.

Fisher, P. A., Stoolmiller, M., Gunnar, M. R., & Burraston, B. O. (2007). Effects of a therapeutic intervention for foster preschoolers on diurnal cortisol activity. *Psychoneuroendicronology*, *32*(8-10), 892–905.

Fries, E., Hesse, J., Hellhammer, J., & Hellhammer, D. H. (2005). A new view on hypocortisolism. *Psychoneuroendocrinology*, *30*, 1010–1016. doi:10.1016/j.psyneuen.2005.04.006

Gatt, J. M., Nemeroff, C. B., Schofield, P. R., Paul, R. H., Clark, C. R., Gordon, E., & Williams, L. M. (2010b). Early life stress combined with serotonin 3A receptor and brain-derived neurotrophic factor valine 66 to methionine genotypes impacts emotional brain and arousal correlates of risk for depression. *Biological Psychiatry*, *68*(9), 818–824.

Gatt, J. M., Williams, L. M., Schofield, P. R., Dobson-Stone, C., Paul, R. H., Grieve, S. M., … Nemeroff, C. B. (2010). Impact of the HTR3A gene with early life trauma on emotional brain networks and depressed mood. *Depression and Anxiety*, *27*(8), 752–759. doi:10.1002/da.20726

Giedd, J. N. (2008). The teen brain: insights from neuroimaging. *Journal of Adolescent Health*, *42*(4), 335–343.

Goff, B., Gee, D. G., Telzer, E. H., Humphreys, K. L., Gabard-Durnam, L., Flannery, J., & Tottenham, N. (2013). Reduced nucleus accumbens reactivity and adolescent depression Following early-life stress. *Journal of Neuroscience*, *249*, 129–138.

Govindan, R. M., Behen, M. E., Helder, E., Makki, M. I., & Chugani, H. T. (2010). Altered water diffusivity in cortical association tracts in children with early deprivation identified with Tract-Based Spatial Statistics (TBSS). *Cerebral Cortex*, *20*(3), 561–569.

Grimm, S., Pestke, K., Feeser, M., Aust, S., Weigand, A., Wang, J., … Bajbouj, M. (2014). Early life stress modulates oxytocin effects on limbic system during acute psychosocial stress. *Social Cognitive and Affective Neuroscience*, *9*, 1828–1835. doi:10.1093/scan/nsu020

Gunn, B. G., Cunningham, L., Cooper, M. A., Corteen, N. L., Seifi, M., Swinny, J. D., … Belelli, D. (2013). Dysfunctional astrocytic and synaptic regulation of hypothalamic glutamatergic transmission in a mouse model of early-life adversity: Relevance to neurosteroids and programming of the stress response. *The Journal of Neuroscience*, *33*(50), 19534–19554.

Gunnar, M. R., & Cheatham, C. L. (2003). Brain and behavior interfaces: stress and the developing brain. *Infant Mental Health Journal*, *24*, 195–211.

Gunnar, M. R., & Donzella, B. (2002). Social regulation of the cortisol levels in early human development. *Psychoneuroendocrinology*, *27*, 199–220. doi:10.1016/S0306-4530(01)00045-2

Gunnar, M. R., Wewerka, S., Frenn, K., Long, J. D., & Griggs, C. (2009). Developmental changes in hypothalamus-pituitary-adrenal activity over the transition to adolescence: Normative changes and associations with puberty. *Development and Psychopathology*, *21*, 69–85.

Guyer, A. E., Kaufman, J., Hodgdon, H. B., Masten, C. L., Jazbec, S., Pine, D. S., & Ernst, M. (2006). Behavioral alterations in reward system function: The role of childhood maltreatment and psychopathology. *Journal of the American Academy of Child & Adolescent Psychiatry*, *45*(9), 1059–1067.

Hair, N. L., Hanson, J. L., Wolfe, B. L., & Pollak, S. D. (2015). Association of child poverty, brain development, and academic achievement. *JAMA Pediatrics*, *169*(9), 822–829. doi:10.1001/jamapediatrics.2015.1475

Halligan, S. L., Herbert, J., Goodyer, I., & Murray, L. (2007). Disturbances in morning cortisol secretion in association with maternal postnatal depression predict subsequent depressive symptomatology in adolescents. *Biological Psychiatry*, *62*, 40–46.

Hammen, C., Marks, T., Mayol, A., & de Mayo, R. (1985). Depressive self-schemas, life stress, and vulnerability to depression. *Journal of Abnormal Psychology*, *94*, 308–319. doi:10.1037/0021-843X.94.3.308

Hanson, J. L., Adluru, N., Chung, M. K., Alexander, A. L., Davidson, R. J., & Pollak, S. D. (2013). Early neglect is associated with alterations in white matter integrity and cognitive functioning. *Child Development*, *84*(5), 1566–1578. http://doi.org/10.1111/cdev.12069

Hanson, J. L., Bos, W., Roeber, B. J., Rudolph, K. D., Davidson, R. J., & Pollak, S. D. (2017). Early adversity and learning: Implications for typical and atypical behavioral development. *Journal of Child Psychology and Psychiatry*, *58*(7), 770–778. doi:10.1111/jcpp.12694

Hanson, J. L., Chung, M. K., Avants, B. B., Shirtcliff, E. A., Gee, J. C., Davidson, R. J., & Pollak, S. D. (2010). Early stress is associated with alterations in the orbitofrontal cortex: A tensor-based morphometry investigation of brain structure and behavioral risk. *The Journal of Neuroscience*, *30*(22), 7466–7472. http://doi.org/10.1523/JNEUROSCI.0859-10.2010

Hanson, J. L., Nacewicz, B. M., Sutterer, M. J., Cayo, A. A., Schaefer, S. M., Rudolph, K. D., Shirtcliff, E. A., Pollak, S. D., & Davidson, R. J. (2015). Behavioral problems after early life stress: contributions of the hippocampus and amygdala. *Biological psychiatry*, *77*(4), 314–323. https://doi.org/10.1016/j.biopsych.2014.04.020

Harms, M. B., Birn, R., Provencal, N., Wiechmann, T., Binder, E. B., Giakas, S. W., Roeber, B. J., & Pollak, S. D. (2017). Early life stress, FK506 binding protein 5 gene (FKBP5) methylation, and

inhibition-related prefrontal function: A prospective longitudinal study. *Development and psychopathology*, *29*(5), 1895–1903.

Harms, M. B., Shannon-Bowen, K., Hanson, J. D., & Pollak, S. D. (2017). Instrumental learning and cognitive flexibility are impaired in children exposed to early life stress. *Developmental Science*, *21*(4), e12596. doi:10.1111/desc.12596

Hart, H., & Rubia, K. (2012). Neuroimaging of child abuse: a critical review. *Frontiers in Human Neuroscience*, *6*(52). doi:10.3389/fnhum.2012.00052 eCollection 2012

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biological Psychiatry*, *49*, 1023–1039.

Hodel, A. S., Hunt, R. H., Cowell, R. A., van den Heuvel, S. E., Gunnar, M. E., & Thomas, K. M. (2015). Duration of early adversity and structural brain development in post-institutionalized adolescents. *NeuroImage*, *105*, 112–119.

Humphreys, K. L., & Zeanah, C. H. (2015). Deviations from the expectable environment in early childhood and emerging psychopathology. *Neuropsychopharmacology Reviews*, *40*, 154–170. doi:10.1038/npp.2014.165

Isgor, C., Kabbaj, M., Akil, H., & Watson, S. J. (2004). Delayed effects of chronic variable stress during peripubertal-juvenile period on hippocampal morphology and on cognitive and stress axis functions in rats. *Hippocampus*, *14*, 636–648.

Ivy, A. S., Rex, C. S., Chen, Y., Dube, C., Maras, P. M., Grigoriadis, D. E., … Baram, T. Z. (2010). Hippocampal dysfunction and cognitive impairments provoked by chronic early-life stress involve excessive activation of CRH receptors. *Journal of Neuroscience*, *30*(39), 13005–13015. https://doi.org/10.1523/JNEUROSCI.1784-10.2010

Jaffee, S. R. (2017). Child maltreatment and risk for psychopathology in childhood and adulthood. *Annual Review of Clinical Psychology*, *13*, 525–551. https://doi.org/10.1146/annurev-clinpsy-032816-045005

Johnson, J. L., & Leff, M. (1999). Children of substance abusers: Overview of research findings. *Pediatrics*, *103*(2), 1085–1099.

Kaplan, G. A., Turrell, G., Lynch, J. W., Everson, S. A., Helkala, E. L., & Salonen, J. T. (2001). Childhood socioeconomic position and cognitive function in adulthood. *International Journal of Epidemiology*, *30*, 256–263.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., … National Comorbidity Survey Replication. (2003). The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). *JAMA*, *289*, 3095–3105.

Kim, P., Evans, G. W., Angstadt, M., Shaun Ho, S., Sripada, C. S., Swain, J. E., … Phan, K. L. (2013). Effects of childhood poverty and chronic stress on emotion regulatory brain function in adulthood. *PNAS*, *110*(46), 18442–18447. https://doi.org/10.1073/pnas.1308240110

Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J. C., Pariante, C. M., … Binder, E. B. (2013). Allele-specific *FKBP5* DNA demethylation mediates gene–childhood trauma interactions. *Nature Neuroscience*, *16*, 33–41. https://doi.org/10.1038/nn.3275

Labonté, B., Suderman, M., Maussion, G., Navaro, L., Yerko, V., Mahar, I., … Turecki, G. (2012). Genome-wide epigenetic regulation by early-life trauma. *Archives of General Psychiatry*, *69*(7), 722–731. doi:10.1001/archgenpsychiatry.2011.2287

Larsson, L., Thorbert-Mros, S., Rymo, L., & Berglundh, T. (2012). Influence of epigenetic modifications of the interleukin-10 promoter on IL10 gene expression. *European Journal of Oral Sciences*, *120*, 14–20.

Leeb, R. T., Paulozzi, L., Melanson, C., Simon, T., & Arias, I. (2008). *Child Maltreatment Surveillance: Uniform Definitions for Public Health and Recommended Data Elements, Version 1.0*. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.

Levine, S. (1994). The ontogeny of the hypothalamic-pituitary-adrenal axis. The influence of maternal factors. *Annals of the New York Academy of Sciences*, *746*, 275–288.

Levine, S., & Ursin, H. (1991). What is stress? In M. R. Brown, G. F. Koob, & C. Rivier (Eds.), *Stress: Neurobiology and neuroendocrinology* (Vol. *1991*, pp. 3–21). New York: Marcel Dekker.

Loman, M. M., Johnson, A. E., Quevedo, K., Lafavor, T. L., & Gunnar, M. R. (2014). Risk-taking and sensation-seeking propensity in postinstitutionalized early adolescents. *Journal of Child Psychology and Psychiatry*, *55*, 1145–1152.

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews Neuroscience*, *10*, 434–445. doi:10.1038/nrn2639

Lyons, D. M., Afarian, H., Schatzberg, A. F., Sawyer-Glover, A., & Moseley, M. E. (2002). Experience-dependent asymmetric variation in primate prefrontal morphology. *Behavioural brain research*, *136*(1), 51–59. https://doi.org/10.1016/s0166-4328(02)00100-6

MacMillan, H. L., Fleming, J. E., Streiner, D. L., Lin, E., Boyle, M. H., Jamieson, E., … Beardslee, W. R. (2001). Childhood abuse and lifetime psychopathology in a community sample. *The American Journal of Psychiatry*, *158*, 1878–1883.

Malter Cohen, M., Jing, D., Yang, R. R., Tottenham, N., Lee, F. S., & Casey, B. J. (2013). Early-life stress has persistent effects on amygdala function and development in mice and humans. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(45), 18274–18278.

Maxfield, M. G., & Widom, C. S. (1996). The cycle of violence: Revisited 6 years later. *Archives of Pediatrics & Adolescent Medicine*, *150*(4), 390–395. doi:10.1001/archpedi.1996.02170290056009

McCormick, C. M., & Mathews, I. Z. (2007). HPA function in adolescence: role of sex hormones in its regulation and the enduring consequences of exposure to stressors. *Pharmacology, Biochemistry, and Behavior*, *86*, 220–233.

McEwen, B. S. (1999). Stress and hippocampal plasticity. *Annual Review of Neuroscience*, *22*, 105–122.

McEwen, B. S. (2012). Brain on stress: How the social environment gets under the skin. *Proceedings of the National Academy of Sciences, USA*, *109*, 17180–17185.

McLaughlin, K. A., & Sheridan, M. A. (2016). Beyond cumulative risk: A dimensional approach to childhood adversity. *Current Directions in Science*, *25*(4), 239–245.

McLaughlin, K. A., Sheridan, M. A., Tibu, F., Fox, N. A., Zeanah, C. H., & Nelson, C. A. (2015). Causal effects of the early caregiving environment on development of stress response systems in children. *Proceedings of the National Academy of Sciences*, *112*(8), 5637–5642.

McLaughlin, K. A., Sheridan, M. A., Winter, W., Fox, N. A., Zeanah, C. H., & Nelson, C. A. (2014). Widespread reductions in cortical thickness following severe early-life deprivation: a neurodevelopmental pathway to attention-deficit/hyperactivity disorder. *Biological psychiatry*, *76*(8), 629–638. https://doi.org/10.1016/j.biopsych.2013.08.016

Mehta, M. A., Gore-Langton, E., Golembo, N., Colvert, E., Williams, S. C., & Sonuga-Barke, E. (2010). Hyporesponsive reward anticipation in the basal ganglia following severe institutional deprivation early in life. *Journal of Cognitive Neuroscience*, *22*(10), 2316–2325. http://doi.org/10.1162/jocn.2009.21394

Milner, J. S., & Robertson, K. R. (1989). Inconsistent response patterns and the prediction of child maltreatment. *Child Abuse & Neglect*, *13*(1), 59–64.

Molet, J., Maras, P. M., Avishai-Eliner, S., & Baram, T. Z. (2014). Naturalistic rodent models of chronic early-life stress. *Developmental Psychobiology*, *56*(8), 1675–1688. doi:10.1002/dev.21230

Nederhof, E., & Schmidt, M. V. (2012). Mismatch or cumulative stress: Toward an integrated hypothesis of programming effects. *Physiology & Behavior*, *106*, 691–700. doi:10.1016/j.physbeh.2011.12.008

Nelson, E. C., & Winslow, J. T. (2009). Non-human primates: Model animals for developmental psychopathology. *Neuropsychopharmacology Reviews*, *34*, 90–105.

Nelson, C. A., III, Zeanah, C. H., Fox, N. A., Marshall, P. J., Smyke, A. T., & Guthrie, D. (2007). Cognitive recovery in socially deprived young children: The Bucharest Early Intervention Project. *Science*, *318*(5858), 1937–2940.

Noble, K. G., McCandliss, B. D., & Farah, M. J. (2007). Socioeconomic gradients predict individual differences in neurocognitive abilities. *Developmental Science*, *10*(4), 464–480.

O'Neal, C. R., Brotman, L. M., Huang, K. Y., Gouley, K. K., Kamboukos, D., Calzada, E. J., & Pine, D. S. (2010). Understanding relations among early family environment, cortisol response, and child aggression via a prevention experiment. *Child Development*, *81*, 290–305.

Ovtscharoff, W., & Braun, K. (2001). Maternal separation and social isolation modulate the postnatal development of synaptic composition in the infralimbic cortex of Octodon degus. *Neuroscience*, *104*(1), 33–40.

Pagliaccio, D., Luby, J. L., Bogdan, R., Agrawal, A., Gaffrey, M. S., Belden, A. C., … Barch, D. M. (2014). Stress-system genes and life stress predict cortisol levels and amygdala and hippocampal volumes in children. *Neuropsychopharmacology*, *39*(5), 1245–1253. doi:10.1038/npp.2013.327

Papale, L., Seltzer, L. J., Madrid, A., Pollak, S. D., & Alisch, R. S. (2018). Differentially methylated genes in saliva are linked to childhood stress. *Scientific Reports*, *8*, 10785. doi:10.1038/s41598-018-29107-0

Paul, R., Henry, L., Grieve, S. M., Guilmette, T. J., Niaura, R., Bryant, R., … Gordon, E. (2008). The relationship between early life stress and microstructural integrity of the corpus callosum in a non-clinical population. *Neuropsychiatric Disease and Treatment*, *4*(1), 103–201.

Pechtel, P., & Pizzagalli, D. A. (2011). Effects of early life stress on cognitive and affective function: An integrated review of human literature. *Psychopharmacology*, *214*(1), 55–70.

Pitzer, M., Jennen-Steinmetz, C., Esser, G., Schmidt, M. H., & Laucht, M. (2011). Prediction of preadolescent depressive symptoms from child temperament, maternal distress, and gender: Results of a prospective, longitudinal study. *Journal of Developmental and Behavioral Pediatrics*, *32*(1), 18–26. doi:10.1097/DBP.0b013e3181f4a474

Poeggel, G., Helmeke, C., Abraham, A., Schwabe, T., Friedrich, P., & Braun, K. (2003). Juvenile emotional experience alters synaptic composition in the rodent cortex, hippocampus, and lateral amygdala. *Proceedings of the National Academy of Sciences*, *100*(26), 16137–16142. doi:10.1073/pnas.2434663100

Pollak, S. D. (2015). Multilevel developmental approaches to understanding the effects of child maltreatment: Recent advances and future challenges. *Development and Psychopathology*, *27*(4, Pt. 2), 1387–1397.

Pollak, S. D., Cicchetti, D., Hornung, K., & Reed, A. (2000). Recognizing emotion in faces: Developmental effects of child abuse and neglect. *Developmental Psychology*, *36*(5), 679–688. doi:10.1037/0012-1649.36.5.679

Provencal, N., & Binder, E. B. (2015). The effects of early life stress on the epigenome: From the womb to adulthood and even before. *Experimental Neurology*, *268*, 10–20. doi:10.1016/j.expneurol.2014.09.001

Pryce, C. R., Bettschen, D., Nanz-Bahr, N. I., & Feldon, J. (2003). Comparison of the effects of early handling and early deprivation on conditioned stimulus, context, and spatial learning and memory in adult rats. *Behavioral Neuroscience*, *117*, 883–893. doi:10.1037/0735-7044.117.5.883

Repetti, R. L., Robles, T. F., & Reynolds, B. (2011). Allostatic processes in the family. *Development and Psychopathology*, *23*(3), 921–938.

Repetti, R. L., Taylor, S. E., & Seeman, T. E. (2002). Risky families: Family social environments and the mental and physical health of offspring. *Psychological Bulletin*, *128*(2), 330–366.

Reuben, A., Moffitt, T. E., Caspi, A., Belsky, D. W., Harrington, H., Schroeder, F., … Danese, A. (2016). Lest we forget: comparing retrospective and prospective assessments of adverse childhood experiences in the prediction of adult health. *Journal of Child Psychology and Psychiatry*, *57*(10), 1103–1112.

Romens, S. E., McDonald, J., Svaren, J., & Pollak, S. D. (2015). Associations between early life stress and gene methylation in children. *Child Development*, *86*, 303–309. doi:10.1111/cdev.12270

Saltzman, W., Hogan, B. K., & Abbott, D. H. (2006). Diminished cortisol levels in subordinate female marmosets are associated with altered central drive to the hypothalamic-pituitary-adrenal axis. *Biological psychiatry*, *60*(8), 843–849. https://doi.org/10.1016/j.biopsych.2005.12.006

Sanchez, C., Arnt, J., Hyttel, J., & Moltzen, E. K. (1993). The role of serotonergic mechanisms in inhibition of isolation-induced aggression in male mice. *Psychopharmacology*, *110*, 53–59.

Sanchez, M. M. (2006). The impact of early adverse care on HPA axis development. Nonhuman primate models. *Hormones and Behavior*, *50*, 623–631.

Sandi, C., & Haller, J. (2015). Stress and the social brain: Behavioural effects and neurobiological mechanisms. *Nature Reviews. Neuroscience*, *16*, 290–304. doi:10.1038/nrn3918

Sapolsky, R. M., Krey, L. C., & McEwen, B. S. (1986). The neuroendocrinology of stress and aging: The glucocorticoid cascade hypothesis. *Endocrinology Review*, *7*(3), 284–301.

Scott, K. M., Smith, D. R., & Ellis, P. M. (2010). Prospectively ascertained child maltreatment and its association with DSM-IV mental disorders in young adults. *Archives of General Psychiatry*, *67*(7), 712–719. doi:10.1001/archgenpsychiatry.2010.71

Shackman, J. E., Fatani, S., Camras, L. A., Berkowtiz, M. J., Bachorowski, J., & Pollak, S. D. (2010). Emotion expression among abusive mothers is associated with their children's emotion processing and problem behaviours. *Cognition and Emotion*, *24*(8), 1421–1430. https://doi.org/10.1080/02699930903399376

Shackman, J. E., & Pollak, S. D. (2014). Impact of physical maltreatment on the regulation of negative affect and aggression. *Development and Psychopathology*, *26*, 1021–1033. doi:10.1017/S0954579414000546

Shackman, J. E., Shackman, A. J., & Pollak, S. D. (2007). Physical abuse amplifies attention to threat and increases anxiety in children. *Emotion*, *7*(4), 838–852.

Sheridan, M. A., Fox, N. A., & Zeanah, C. H. (2012). Variation in neural development as a result of exposure to institutionalization early in childhood. *Proceedings of the National Academy of Sciences*, *109*(32), 12927–12932. http://doi.org/10.1073/pnas.1200041109/-/DCSupplemental

Spinelli, S., Chefer, S., Suomi, S. J., Higley, J. D., Barr, C. S., & Stein, E. (2009). Early-life stress induces long-term morphologic changes in primate brain. *Archives of General Psychiatry*, *66*(6), 658–665. doi:10.1001/archgenpsychiatry.2009.52

Sterlemann, V., Ganea, K., Liebl, C., Harbich, D., Alam, S., Holsboer, F., … Schmidt, M. V. (2008). Long-term behavioral and neuroendocrine alterations following chronic social stress in mice: Implications for stress-related disorders. *Hormones and Behavior*, *53*(2), 386–394.

Sujan, A. C., Humphreys, K. L., Ray, L. A., & Lee, S. S. (2014). Differential association of child abuse with self-reported versus laboratory-based impulsivity and risk-taking in young adulthood. *Child Maltreatment*, *19*, 145–155.

Teicher, M. H., Anderson, C. M., Ohashi, K., & Polcari, A. (2014). Childhood maltreatment: Altered network centrality of cingulate, precuneus, temporal pole and insula. *Biological Psychiatry*, *76*(4), 297–305. http://doi.org/10.1016/j.biopsych.2013.09.016

Teicher, M. H., Tomoda, A., & Andersen, S. L. (2006). Neurobiological consequences of early stress and childhood maltreatment: Are results from human and animal studies comparable? *Annals of the New York Academy of Sciences*, *1071*, 313–323.

Thornberry, T. P., Henry, K. L., Ireland, T. O., & Smith, C. A. (2010). The causal impact of childhood-limited maltreatment and adolescent maltreatment on early adult adjustment. *The Journal of Adolescent Health*, *46*(4), 359–365.

Tottenham, N., Hare, T. A., Quinn, B. T., McCarry, T. W., Nurse, M., Gilhooly, T., Millner, A., Galvan, A., Davidson, M. C., Eigsti, I. M., Thomas, K. M., Freed, P. J., Booma, E. S., Gunnar, M. R., Altemus, M., Aronson, J., & Casey, B. J. (2010). Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Developmental science*, *13*(1), 46–61. https://doi.org/10.1111/j.1467-7687.2009.00852.x

Tottenham, N., & Sheridan, M. A. (2010). A review of adversity, the amygdala and the hippocampus: A consideration of developmental timing. *Frontiers in Human Neuroscience*, *3*, 68. doi:10.3389/neuro.09.068.2009 eCollection 2009

Tyrka, A. R., Ridout, K. R., & Parade, S. H. (2016). Childhood adversity and epigenetic regulation of glucocorticoid signaling genes: Associations in children and adults. *Development and Psychopathology*, *28*, 1319–1331. https://doi.org/10.1017/S0954579416000870

UN World Health Organization (WHO). (2002). World report on violence and health, ISBN 92 4 154561 5. Retrieved from https://www.refworld.org/docid/54aa8f744.html

Vachon, D. D., Krueger, R. F., Rogosch, F. A., & Cicchetti, D. (2015). Assessment of the harmful psychiatric and behavioral effects of different forms of child maltreatment. *JAMA Psychiatry*, *72*(11), 1135–1142. doi:10.1001/jamapsychiatry.2015.1792

Van Bodegom, M., Homberg, J. R., & Henckens, M. J. A. G. (2017). Modulation of the hypothalamic-pituitary-adrenal axis by early life stress exposure. *Frontiers in Cellular Neuroscience*, *11*, 87. doi:10.3389/fncel.2017.00087

Weller, J. A., & Fisher, P. A. (2013). Decision-making deficits among maltreated children. *Child Maltreatment*, *18*(3), 184–194.

Widom, C. S., & Morris, S. (1997). Accuracy of adult recollections of childhood victimization, part 2: childhood sexual abuse. *Psychological Assessment*, *9*(1), 34–46. https://doi.org/10.1037/1040-3590.9.1.34

Yates, T. M., Tracy, A. J., & Luthar, S. S. (2008). Nonsuicidal self-injury among "privileged" youths: Longitudinal and cross-sectional approaches to developmental process. *Journal of Consulting and Clinical Psychology*, *76*(1), 52–62.

Zannas, A., Wiechmann, T., Gassen, N., & Binder, E. B. (2016). Gene–stress–epigenetic regulation of *FKBP5*: Clinical and translational implications. *Neuropsychopharmacology*, *41*, 261–274. https://doi.org/10.1038/npp.2015.235

Zannas, A. S., & Binder, E. B. (2014). Gene–environment interactions at the FKBP5 locus: sensitive periods, mechanisms and pleiotropism. *Genes, Brain, and Behavior*, *13*, 25–37.

Zeanah, C. H., Nelson, C. A., Fox, N. A., Smyke, A. T., Marshall, P., Parker, S. W., & Koga, S. (2003). *Development and Psychopathology*, *15*(4), 885–907.

Suggested Reading

Heim, C., & Binder, E. B. (2012). Current research trends in early life stress and depression: Review of human studies on sensitive periods, gene–environment interactions, and epigenetics. *Experimental Neurology*, *233*(1), 102–111. doi:10.1016/j.expneurol.2011.10.032

Hostinar, C. E., & Gunnar, M. R. (2013). The developmental effects of early life stress: An overview of current theoretical frameworks. *Current Directions in Psychological Science*, *22*, 400–406. doi:10.1177/0963721413488889

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behavior and cognition. *Nature Reviews Neuroscience*, *10*, 434–445. doi:10.1038/nrn2639