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Early Adversity, Neural Development, and Inflammation

ABSTRACT: *Early adversity is a risk factor for poor mental and physical health. Although altered neural development is believed to be one pathway linking early adversity to psychopathology, it has rarely been considered a pathway linking early adversity to poor physical health. However, this is a viable pathway because the central nervous system is known to interact with the immune system via the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS). In support of this pathway, early adversity has been linked to changes in neural development (particularly of the amygdala, hippocampus, and prefrontal cortex), HPA axis and ANS dysregulation, and higher levels of inflammation. Inflammation, in turn, can be detrimental to physical health when prolonged. In this review, we present these studies and consider how altered neural development may be a pathway by which early adversity increases inflammation and thus risk for adverse physical health outcomes.* © *2015 Wiley Periodicals, Inc.* Dev Psychobiol 57:887–907, 2015.

Keywords: *early adversity; amygdala; hippocampus; prefrontal cortex; hypothalamic-pituitary-adrenal axis; autonomic nervous system; inflammation*

INTRODUCTION

A burgeoning literature suggests that early adverse experiences affect neural development. Compared to non-maltreated children, maltreated children show structural and functional differences in a number of neural regions, including the corpus callosum, amygdala, hippocampus, prefrontal cortex (PFC), and cerebellum, during both childhood and adulthood (Hart & Rubia, 2012; McCrory, De Brito, & Viding, 2012; Pechtel & Pizzagalli, 2011). Given that early adversity increases risk for developing deficits in cognitive functioning and emotion processing and psychiatric disorders (Pechtel & Pizzagalli, 2011; Repetti, Taylor, & Seeman, 2002; Tyrka, Burgers, Philip, Price, & Carpenter, 2013), this area of research has focused on altered neural development as a potential pathway linking early adversity to poor mental health and psychopathology (Frodl & O'Keane, 2013; McCrory, De Brito, & Viding, 2011). However, altered neural development related to early adversity may also contribute to the link between early adversity and adverse physical health outcomes.

Psychosocial stress experienced in early life has a lasting effect on physical health. Adults who had cold, critical, abusive, and/or conflictual familial relationships in early life are more prone to develop obesity, lung disease, cancer, heart disease, and diabetes among other adverse physical health outcomes (Felitti et al., 1998; Miller, Chen, & Parker, 2011; Repetti et al., 2002). To better understand how early adversity comes to affect the development of poor physical health, researchers have focused their attention on underlying mechanisms. Elevated inflammation has emerged as a potential key pathway linking early adversity to poor physical health, as a number of studies have demonstrated a link between

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early adversity and elevated inflammation (Fagundes, Glaser, & Kiecolt-Glaser, 2013; Miller et al., 2011).

Inflammation is a natural, early response of the immune system to pathogens and injured tissue. In response to damaged tissue or infection, immune communication molecules known as pro-inflammatory cytokines, facilitate clearance of the pathogen and injured tissue from the body and promote repair. As such, inflammation is essential to healing and survival. However, prolonged inflammation can be harmful. For example, atherosclerosis is considered a disease rooted in inflammation, as pro-inflammatory cytokines are involved in its initiation and development (Libby, 2006; Pearson et al., 2003). Further, C-reactive protein (CRP), a marker of inflammation, is a robust and reliable predictor of cardiovascular disease with clinical cutoff points indicative of risk (Ridker, 2003). Inflammation has been implicated in a number of other chronic diseases as well, including depression (Raison, Capuron, & Miller, 2006), diabetes (Wellen & Hotamisligil, 2005), hypertension (Harrison et al., 2011), and certain cancers (Coussens & Werb, 2002; Hanahan & Weinberg, 2011; Rakoff-Nahoum, 2006).

The central nervous system and the immune system are known to interact, primarily via the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS) (Irwin & Cole, 2011; Rohleder, 2014). Thus, early adversity-related changes in neural development may have consequences for inflammatory processes and risk for poor health. Accordingly, the aim of this review is to detail how early adversity affects neural development in a manner that may be conducive to inflammation. A number of excellent reviews have synthesized the work on early adversity and neural development, with a focus on how adversity-related alterations in neural development and the HPA axis may increase risk for psychopathology (e.g., Danese & McEwen, 2012; Frodl & O'Keane, 2013; Hart & Rubia, 2012; Loman & Gunnar, 2010; Lupien, McEwen, Gunnar, & Heim, 2009; McCrory et al., 2012). There are also excellent reviews of research on early adversity and inflammation (Fagundes & Way, 2014; Miller et al., 2011), which tend to focus on physiological, molecular, psychosocial, and behavioral functioning as underlying mechanisms for adversity-related changes in inflammatory activity. The goal of this review is to integrate these two areas of work and specifically to highlight the role of neural development as a key pathway through which early adversity may influence downstream inflammatory processes. Thus, we build on past reviews by explicitly detailing the downstream effects of early adversity-related changes in neural development on systemic inflammation (Figure 1).

Although the multiple neurobiological systems interact with one another (as depicted in Figure 1), we focus on the effects of early adversity specifically on top-down regulation of inflammatory processes. More specifically, early adversity has been related to changes in neural regions that are part of a network that regulates HPA and ANS activity in the context of stress. The HPA axis and ANS, in turn, regulate inflammatory processes. As we outline below, altered neural development in these regions can lead to more frequent, prolonged, and/or exaggerated HPA and ANS responses to subsequent psychosocial stress. Over time, such responses can lead to the dysregulation of the HPA axis and ANS. Because the HPA axis and ANS regulate inflammatory processes, their dysregulation over prolonged periods of time can promote inflammation, thereby increasing risk for poor physical health outcomes.

We present evidence for this pathway by first providing an overview of the connection between the central nervous and inflammatory systems, focusing on the amygdala, hippocampus, and PFC. We focus on these regions because they have been widely studied and have been established as key neural regions implicated in stress processes, although other neural regions (e.g., periaqueductal gray of midbrain, hypothalamus) are also implicated in stress processes. Next, we selectively review studies supporting various pieces of the pathway, namely those that have linked early adversity to neural development, HPA axis and ANS functioning, and inflammation. We then integrate these findings and consider how altered neural development might ultimately influence inflammatory processes. We also note the reciprocal relations between neural development and inflammatory processes by briefly describing the role of inflammation on neural development, although this topic is beyond the scope of this article (for reviews on this topic, see Deverman & Patterson, 2009; Musaelyan et al., 2014; Stolp, 2013). Other related topics that are beyond the scope of the present review include glucocorticoids as a mechanism of the effects of early adversity on neural development (Lupien et al., 2009; Tottenham & Sheridan, 2010), and early attachment learning involving the HPA axis and amygdala (Moriceau, Roth, & Sullivan, 2010). We conclude by raising several issues that future research should address in order to advance our understanding of the detrimental effects of early adversity.

Although children can experience a wide range of stressors, such as socioeconomic disadvantage and natural disasters, we primarily draw on studies examining child maltreatment (i.e., abuse and neglect) and other aspects of the family environment, including

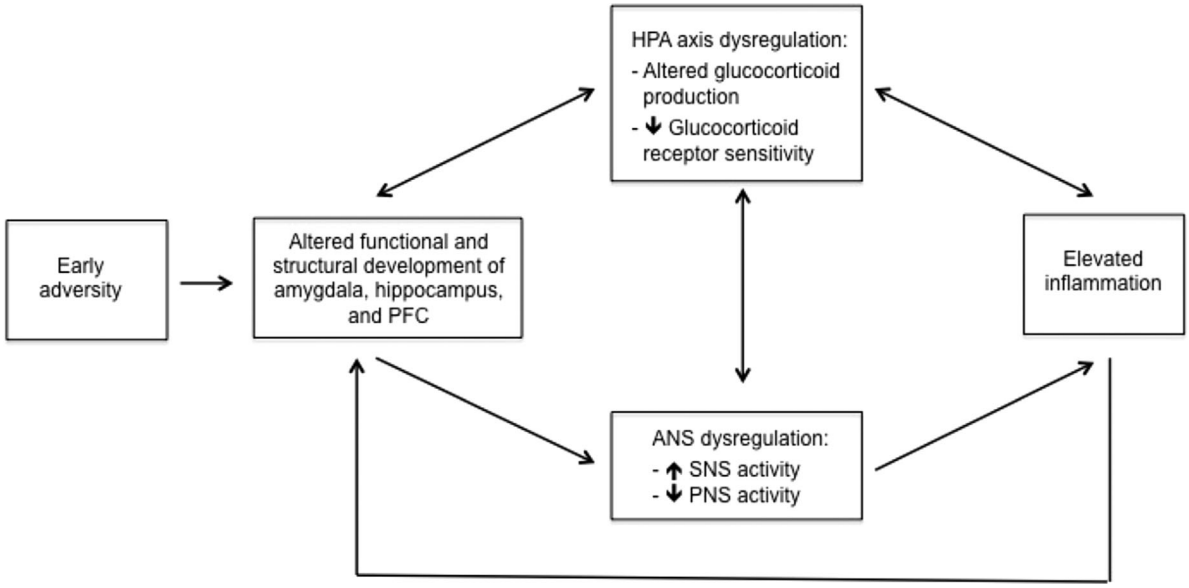

FIGURE 1 Neurodevelopmental pathway by which early adversity may result in elevated inflammation.

family conflict and poor maternal caregiving, given that much of the extant literature on the effects of early life stress on neural development has focused on these types of stressors. Importantly, because these aspects of the family environment are typically enduring and may have long-term effects on physiology (Juster, McEwen, & Lupien, 2010), we focus on early life stress that is chronic. Although we use child maltreatment as the representative construct for understanding the effects of early adversity, our use of "early life stress" and "early adversity" is not confined to child maltreatment, but rather, is used as a broader term that can encompass other chronic psychosocial stressors.

NEURAL REGULATION OF INFLAMMATION

The central nervous system influences inflammatory processes through its regulation of the HPA axis and ANS. Perception of threat initiates the experience of stress, which triggers activation of the HPA axis and sympathetic nervous system (SNS) and withdrawal of the parasympathetic nervous system (PNS). The amygdala, hippocampus, and PFC are key components of the integrated neural network that matches appraisal and interpretation of potentially threatening environmental stimuli to behavioral and biological responses to threat (Fuchs & Flügge, 2003). As such, these neural regions regulate ANS and HPA activity. The HPA axis and ANS, in turn, regulate inflammatory processes.

Central Regulation of the HPA Axis and ANS

The amygdala and hippocampus are particularly important for detecting both physical and psychological threat (e.g., Fanselow & Gale, 2003; LeDoux, 2003). The amygdala plays a critical role in fear-conditioning, which involves pairing novel and initially neutral stimuli with an emotional response. Through such classical conditioning, one learns which aspects of his or her environment are dangerous. Thus, perception of threat activates the amygdala. When threat is perceived, the amygdala triggers the HPA axis and ANS through its projections to the hypothalamus and the brainstem (Gianaros & Sheu, 2009; Herman et al., 2003).

Appraisal of novel, potentially threatening situations is partially a function of learning and memories of past events, including actual aversive experiences and vicarious experiences shared through verbal communication with others (Phelps, 2004). Involved in learning, contextual fear conditioning (Rudy, 1993) and memory (Chadwick, Hassabis, Weiskopf, & Maguire, 2010; Squire, 1992), the hippocampus is crucial for recognizing threat in the environment. Furthermore, the hippocampus interacts with the amygdala to facilitate retrieval of emotionally valenced contextual information (Smith, Stephan, Rugg, & Dolan, 2006), which plays a role in appraisal and reactivity to subsequent contextual stimuli (Maren, Phan, & Liberzon, 2013). As such, the hippocampus can indirectly activate the HPA axis and ANS by modulating amygdala activation (Phelps, 2004). In addition, the hippocampus is directly

involved in inhibiting the HPA axis (Herman et al., 2003), as described in more detail below.

The medial and ventral PFC regions are involved in fear extinction, whereby responses to previously acquired fear dissipate after repeated exposure to a conditioned stimulus in the absence of the unconditioned stimulus (Sotres-Bayon, Cain, & LeDoux, 2006). Thus, medial and ventral PFC activation downregulates amygdala activity, inhibiting responses to acquired fear and other threats (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Quirk, Likhtik, Pelletier, & Paré, 2003; Sotres-Bayon et al., 2006). The medial PFC also connects to and interacts with the hippocampus during retrieval of extinction memory (Maren et al., 2013; Milad et al., 2007; Orsini, Kim, Knapska, & Maren, 2011), an important aspect of appraisal processes. Given amygdalar and hippocampal involvement in threat perception and initiation of HPA and ANS responses to threat, ventral and medial PFC regulation of the amygdala and interactions with the hippocampus may attenuate HPA and ANS responses to stress and/or facilitate physiological recovery from stress. Rich in glucocorticoid receptors, the PFC also plays a role in suppressing the HPA axis (Diorio, Viau, & Meaney, 1993; Sullivan & Gratton, 2002). Interestingly, the PFC has also been shown to exert excitatory control over the HPA axis (Radley, Arias, & Sawchenko, 2006; Wang et al., 2005). Whether the PFC excites or inhibits the HPA axis may depend on the particular area of the PFC and type of stressor (Herman et al., 2003; Herman & Mueller, 2006; Kern et al., 2008; Sullivan & Gratton, 2002).

HPA Axis and ANS Regulation of Inflammation

Neural processing of stress leads to changes in the HPA axis and ANS. More specifically, perception of threat activates the amygdala, which signals the hypothalamus to secrete corticotrophin releasing hormone (CRH). CRH stimulates the pituitary to secrete adrencorticotrophic hormone, which then stimulates the adrenal cortex to produce and release cortisol. In a negative feedback loop, cortisol binds to glucocorticoid receptors in several brain regions, including the hippocampus, PFC, amygdala, and hypothalamus, suppressing CRH production and the HPA stress response. When bound to glucocorticoid receptors on immune cells, cortisol can suppress transcription of pro-inflammatory genes and subsequent production and release of proinflammatory cytokines (Sternberg, Chrousos, Wilder, & Gold, 1992). Cortisol, then, is anti-inflammatory and protects against negative effects of an exaggerated or sustained inflammatory response (Glezer & Rivest, 2004; Irwin & Cole, 2011; Rohleder, 2011). Indeed, low levels of cortisol have been related to higher systemic levels of inflammatory markers (Kunz-Ebrecht, Mohamed-Ali, Feldman, Kirschbaum, & Steptoe, 2003; Rohleder, 2014). Importantly, in the context of stress, sustained activation of the HPA axis can desensitize glucocorticoid receptors (Avitsur, Stark, & Sheridan, 2001; Cohen et al., 2012; Miller, Cohen, & Ritchey, 2002; Sheridan, Stark, Avitsur, & Padgett, 2000). Consequently, inflammatory cytokines may not to "hear" the signal of cortisol, failing to respond to cortisol's inhibitory signals (Miller et al., 2002; Rohleder, 2011). Desensitized glucocorticoid receptors, then, may also lead to inadequate suppression of inflammation.

Perception of threat also activates the SNS and triggers withdrawal of the PNS. Activation of the amygdala stimulates the neurons in the paraventricular nucleus of the hypothalamus, which projects to sympathetic preganglionic cells in the thoracic spinal cord (Zagon & Smith, 1993) both directly and indirectly via connections to the brainstem. Axons of these cells synapse with those of the adrenal medulla, which secretes the catecholamines, epinephrine and norepinephrine, into systemic circulation. Perception of stress also releases norepinepherine into local microenvironments of vasculature, organs, and tissues via SNS neural fiber innervation (Irwin & Cole, 2011). Norepinephrine, in turn, activates adrenergic receptors. Although the anti- or pro-inflammatory effect of norepinephrine depends on a number of factors, including the adrenergic receptor subtype that it activates, specific tissue, and local concentration of norepinephrine (McNamee et al., 2010; Yang, Lee, Kim, Suh, & Chong, 2012), it can upregulate pro-inflammatory gene expression in monocytes (Cole et al., 2010; Grisanti et al., 2011; Irwin & Cole, 2011). In particular, when bound to $\alpha 2$ and β adrenergic receptors, norepinephrine stimulates NF-κB, a key transcriptional pathway that increases inflammation (Bierhaus et al., 2003). Thus, activation of the SNS in response to stress can increase inflammation.

The paraventricular nucleus also projects directly, and indirectly via connections to the brainstem, to preganglionic neurons of the vagus nerve, the primary nerve of the PNS. Activation of the PNS releases the vagal neurotransmitter acetylcholine. When bound to $\alpha 7$ nicotincic receptors, acetylcholine suppresses pro-inflammatory cytokine production (Abboud, Harwani, & Chapleau, 2012; Rohleder, 2011; Thayer, 2009; Tracey, 2002, 2009). Under tonic conditions, the PNS exerts inhibitory control (Thayer, Ahs, Fredrikson, Sollers III, & Wager, 2012). In the context of stress, parasympathetic activity is typically diminished (Mueller et al., 2012; Thayer, Yamamoto, & Brosschot, 2010; Weber et al., 2010). Thus, low vagal tone and decreased

vagal withdrawal during psychological stress have been associated with increased inflammation (e.g., Haensel, Mills, Nelesen, Ziegler, & Dimsdale, 2008; Thayer & Fischer, 2009; Weber et al., 2010).

In sum, the amygdala, hippocampus, and PFC are central components of the neural network underlying stress processes. Consequently, they can influence inflammatory processes through the HPA axis and ANS. The amygdala and hippocampus are crucial to perceiving and recognizing threat in the environment and can therefore activate biological stress systems. The PFC inhibits biological stress responses by down-regulating amygdala activity. In addition, the hippocampus and PFC play a role in the negative feedback loop of the HPA axis. The HPA axis and ANS can impact inflammatory processes, with the HPA axis and PNS typically exerting anti-inflammatory and the SNS exerting pro-inflammatory effects.

EARLY ADVERSITY AND NEURAL DEVELOPMENT

Experience customizes neural connections and their interactions via synaptic formation and pruning of excess neural connections, a mechanism thought to maximize chances of survival in a given environment (Fox, Levitt, & Nelson III, 2010; Greenough, Black, & Wallace, 1987). Although neural systems and processes are sensitive to experiences throughout the lifespan (Pascual-Leone, Amedi, Fregni, & Merabet, 2005), they may be particularly sensitive to experiences early in life when they undergo significant and rapid development (Lupien et al., 2009). The amygdala, hippocampus, and PFC undergo dramatic changes during childhood and adolescence (Blakemore & Choudhury, 2006; Tottenham & Sheridan, 2010). Therefore, adverse experiences during these periods have been shown to have long-lasting effects on these stress-related neural regions.

Functional Changes

A number of studies have related early adversity to functional changes in the amygdala, hippocampus, and PFC both in childhood and adulthood. Compared to children and adolescents who were never institutionalized, previously institutionalized children and adolescents show greater amygdala responses to threatening interpersonal cues (i.e., fearful and angry faces) (Gee et al., 2013; Maheu et al., 2010; Tottenham et al., 2011). Initial evidence suggests that early adversity may also be related to altered hippocampal and PFC functioning. Specifically, previously institutionalized children have exhibited greater hippocampal reactivity to psychosocial threat (Maheu et al., 2010) and lower glucose metabolism in the hippocampus and PFC (Chugani et al., 2001). Behavioral studies have also shown that early institutionalization is associated with deficits in hippocampal-dependent memory (Bos, Fox, Zeanah, & Nelson III, 2009). Notably, the previously institutionalized children and adolescents of these studies were subsequently adopted, which suggests that the effects of early adversity on amygdala, hippocampal, and PFC functioning persist despite termination of the stressor (Maheu et al., 2010; Tottenham et al., 2011). With the exception of the studies just described, relatively few studies have examined how early adversity impacts PFC and hippocampal functioning in children; more evidence exists for the link between early adversity and altered amygdala functioning in children. Further, these studies have focused on previously institutionalized youth, which represents a relatively extreme case of neglect and caregiver deprivation. Whether these findings generalize to youth experiencing other types of adversity remains unclear. Nevertheless, these studies collectively begin to delineate how early adversity impacts amygdala, hippocampal, and PFC functioning in youth.

These disruptions in neural functioning appear to persist into adulthood. For instance, abuse, neglect, and a cold, unsupportive childhood family environment have been associated with greater amygdala reactivity to interpersonal threat-related cues in adults (Dannlowski et al., 2013; Dannlowski et al., 2012; Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006; van Harmelen et al., 2012). Although research on how early adversity may alter hippocampal and PFC functioning in adulthood is scant, preliminary evidence suggests that these relations exist. In one study of 18 adults, childhood maltreatment was associated with greater hippocampal responses to novel, potentially threatening interpersonal cues in adulthood (Edmiston & Blackford, 2013). Behavioral studies offer more support for this link. A history of sexual abuse and greater number of various childhood adverse experiences have been associated with deficits in hippocampal-dependent learning and memory, including short-term, verbal, visual, autobiographical, and global memory scores, slower learning, and reduced persistence during extinction after partial reinforcement (Anda et al., 2006; Navalta, Polcari, Webster, Boghossian, & Teicher, 2006; Patterson, Craske, & Knowlton, 2013). In another study, a cold, harsh, conflict-ridden family environment has been associated with greater right ventrolateral PFC responses to threat-related cues, but this greater PFC activity was correlated with greater rather than decreased amygdala activity, indicating a deficit in PFC

regulation of amygdala responses to threat (Taylor et al., 2006). Together, these studies indicate that changes in amygdala, hippocampal, and PFC functioning resulting from early adversity may be enduring.

Structural Changes

Prior research has also demonstrated an association between early adversity and changes in neural structure during both childhood and adulthood. Neglected and abused children and adolescents have been shown to have greater amygdala volume (Mehta et al., 2009; Tottenham et al., 2010) and smaller anterior cingulate cortex and orbital frontal cortex volume, both subregions of the PFC (De Brito et al., 2013; Hanson et al., 2010; Kelly et al., 2013), compared to children who have not been maltreated. Similarly, irrational punishment, high levels of family conflict, and maternal depressive symptomatology (which is associated with poor maternal care), and cumulative life stress have been associated with larger amygdala and smaller PFC volume in children and adolescents (Edmiston et al., 2011; Hanson et al., 2012; Korgaonkar et al., 2013; Lupien et al., 2011; Whittle et al., 2009). Interestingly, early adversity has not been related to structural changes in the hippocampus during childhood and adolescence (Frodl & O'Keane, 2013; Lupien et al., 2011).

In adulthood, early adversity is related to decreased hippocampal and PFC volume, but not to amygdala volume (Baker et al., 2013; Cohen et al., 2006; Korgaonkar et al., 2013). Healthy adults who experienced neglect and/or abuse in childhood had smaller hippocampal white and gray matter (Chaney et al., 2014; Dannlowski et al., 2012; Frodl, Reinhold, Koutsouleris, Reiser, & Meisenzahl, 2010) and decreased mPFC gray matter (Dannlowski et al., 2012; van Harmelen et al., 2010), compared to their non-maltreated counterparts. Other types of early life stressors including living with a mentally ill family member, exposure to violence, harsh discipline, and parental separation have also been associated with decreased hippocampal and PFC volume in adulthood (Teicher, Anderson, & Polcari, 2012) and PFC volume (Andersen et al., 2008; Cohen et al., 2006; Frodl et al., 2010; Kitayama, Quinn, & Bremner, 2006; Tomoda et al., 2009; Teicher, Anderson, & Polcari, 2012; Treadway et al., 2009).

Overall, evidence suggests that early adversity can lead to persistent functional changes in the amygdala, hippocampus, and PFC. Early adversity also appears to alter neural structure, though some of these effects may be observable only during particular periods of the lifespan. Specifically, changes in amygdala volume as a result of early adversity are apparent earlier in life, but do not seem to persist into adulthood. This may be because early adverse experience precociously engages the amygdala and accelerates its development (for review, see Roozendaal, McEwen, & Chattarji, 2009; Tottenham & Sheridan, 2010). By contrast, the link between early life stress and alterations in hippocampal structural development is not apparent in childhood and adolescence, but seems to emerge in adulthood. Although the mechanisms have yet to be elucidated, it is possible that any effects on pruning of synapses that may lead to decreased hippocampal volume may not be observable until later in life (Andersen & Teicher, 2004, 2009).

Curiously, very few studies have examined the effects of early adversity on the connectivity and interactions of the amygdala, hippocampus, and PFC despite that they collectively regulate responses to stress. An exception is a recent study (Herringa et al., 2013) that found that previous maltreatment was associated with decreased hippocampal-mPFC and amygdala-mPFC connectivity. Although this study offers initial support for the negative effects of early adversity on neural connectivity, only female adolescents were examined. Whether early adversity impacts neural connectivity in children and persists into adulthood is currently unknown.

EARLY ADVERSITY AND HPA AND ANS DYSREGULATION

The preceding section described evidence for the link between early adversity and alterations in the amygdala, hippocampus, and PFC. Given that these regions play an essential role in regulating the HPA axis and ANS, altered development in these regions may lead to altered HPA axis and ANS activity. We would expect, then, that early adversity be related to altered HPA axis and ANS functioning. In this section, we present findings documenting links between early adversity and HPA and ANS dysregulation.

HPA Axis

Because other reviews (e.g., Gunnar & Quevedo, 2007; Repetti, Robles, & Reynolds, 2011) have addressed the effects of early adversity on the HPA axis in detail, we briefly summarize findings. There is compelling evidence that early adversity leads to alterations in HPA functioning in childhood, adolescence, and adulthood. However, the direction of the effect is complex, as studies have documented both hypoactive and hyperactive HPA activity following early adversity. For

instance, children with depressed mothers or who were maltreated have lower basal levels of cortisol and blunted cortisol responses to challenge (Dietz et al., 2013; Fernald, Burke, & Gunnar, 2008; Ouellet-Morin et al., 2011). This blunted pattern of cortisol secretion in response to acute stress is also evident among adolescents and adults who have experienced early life stress (e.g., Carpenter et al., 2007; Carpenter, Shattuck, Tyrka, Geracioti, & Price, 2011; Carpenter et al., 2009; Engert et al., 2010b; Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012; Luecken, Kraft, & Hagan, 2009; MacMillan et al., 2009; Taylor, Karlamangla, Friedman, & Seeman, 2011; Trickett, Gordis, Peckins, & Susman, 2014).

Paradoxically, early adversity has also been linked to exaggerated levels of cortisol secretion. Specifically, neglect and maternal stress and depression, which increase maternal neglect, hostility, and physical assault (Lovejoy, Graczyk, O'Hare, & Neuman, 2000; Turney, 2011), have been associated with higher basal cortisol and cortisol responses to an acute stressor in children (Ashman, Dawson, Panagiotides, Yamada, & Wilkinson, 2002; Essex, Klein, Cho, & Kalin, 2002; Sullivan, Bennet, & Lewis, 2013). High levels of basal and stress-induced cortisol as a result of early adversity are also evident in adulthood (e.g., Engert et al., 2010a; Heim et al., 2000, 2002). For example, maternal separation in childhood has been related to a larger cortisol awakening response and a flatter diurnal cortisol slope (Kumari, Head, Bartley, Stansfeld, & Kivimaki, 2012).

Together, these studies show that early adversity can have enduring effects on HPA function, although research has yet to disentangle factors that lead to different trajectories of HPA functioning. Variation in severity and type of stressors and in methods for assessing HPA functioning across studies may help explain the divergent findings (Dietz et al., 2013; Doom, Cicchetti, & Rogosch, 2014; Struber, Struber, & Rother, 2014). For instance, one study found that adults who were severely maltreated had lower morning cortisol levels whereas moderately maltreated adults had higher cortisol levels (van der Vegt, van der Ende, Kirschbaum, Verhulst, & Tiemeier, 2009). In another study, physical abuse was related to quicker cortisol reactivity to stress whereas emotional abuse was related with delayed cortisol recovery from stress (Kuhlman, Geiss, Vargas, & Lopez-Duran, 2015). Timing of stress and assessment of HPA function may also contribute to the mixed findings, as age and pubertal development can affect HPA function (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009; Romeo, 2010; Stroud et al., 2009). Studies of early adversity that repeatedly assess HPA function through childhood into adulthood can help clarify the effects of early adversity on HPA hyper- and hypo-secretion. Importantly, both exaggerated and blunted cortisol levels generally indicate HPA dysregulation (McEwen, 1998). HPA dysregulation, in turn, can lead to glucocorticoid receptor insensitivity (Miller et al., 2002), a state that may ultimately determine cortisol's anti-inflammatory effects (Cohen et al., 2012). Preliminary evidence suggests that early adversity desensitizes glucocorticoid receptors (Miller & Chen, 2010; Miller et al., 2009), which could explain a state of increased inflammation despite high levels of cortisol among some individuals with a history of early adversity.

ANS

Fewer studies have examined the effects of early adversity on ANS functioning. Nevertheless, those studies suggest that early adversity may affect sympathetic functioning beginning in childhood and persisting into adulthood. Specifically, cross-sectional and longitudinal studies have shown that children exposed to neglect, family stress (e.g., parental depression, anger, and role overload, and financial and parenting stress), and aggressive marital conflict exhibit greater sympathetic activity to laboratory challenges (El-Sheikh, 2005; Ellis, Essex, & Boyce, 2005; Oosterman, De Schipper, Fisher, Dozier, & Schuengel, 2010). As adults, individuals who experienced stress (i.e., abuse, neglect, high levels of family conflict, illness, loss) in early life exhibit increases in heart rate and blood pressure both at rest and in response to acute stress (Gatt et al., 2009; Heim et al., 2000; Larkin, Frazer, & Semenchuk, 1996; Larkin, Frazer, & Wheat, 2011; Lovallo, 2013; Luecken, 1998; Taylor, Lerner, Sage, Lehman, & Seeman, 2004), although not all studies have not found this effect (Larkin et al., 2011; Luecken & Roubinov, 2012).

Early adversity also seems to have an impact on parasympathetic functioning. Marital conflict and negative, hostile, controlling, and cold maternal behavior have been associated with low vagal tone (i.e., the continuous PNS activity under tonic conditions) and decreased vagal withdrawal (i.e., diminished PNS activity under challenging conditions), in infants and children (Calkins, Graziano, Berdan, Keane, & Degnan, 2008; Calkins, Smith, Gill, & Johnson, 1998; Katz, 2007; Moore, 2010; Porter, Wouden-Miller, Silva, & Porter, 2003). The majority of these studies are cross-sectional and examine children age six or younger. The relation between early adversity and parasympathetic functioning in later childhood, adolescence, and adulthood has been less examined. However, initial evidence suggests that early adversity may have a long-lasting

effect on parasympathetic functioning. Two studies of female adolescents found that documented history of maltreatment prospectively predicts lower vagal tone (Miskovic, Schmidt, Georgiades, Boyle, & MacMillan, 2009; Shenk, Noll, Putnam, & Trickett, 2010). Similarly, one study (Dale et al., 2009) found that adult women with a history of abuse exhibited poorer vagal regulation during and immediately after physical stress. The modest evidence necessitates additional investigation to conclude whether early adversity has effects on PNS functioning beyond early childhood and if so, whether it has similar effects on the PNS in males.

In sum, some evidence suggests that early adversity is related to exaggerated SNS activity and poor vagal regulation both in childhood and adulthood. However, such studies are relatively few, and more research is needed to confirm that these associations persist into adulthood. One of the complications in this area of research is the focus on heart rate and blood pressure, which are influenced by both the sympathetic and parasympathetic nervous systems. Studies that use "pure" measures of SNS activity (e.g., pre-ejection period) may clarify the enduring impact of early life stress on this system. Stronger support exists for persistent HPA dysregulation following early adversity, as numerous studies have documented aberrant cortisol levels related to early adversity in youth and adults. Though both hyper and hypo-cortisolism may be indicators of HPA dysregulation, perhaps more important for inflammation is the sensitivity of glucocorticoid receptors, and emerging evidence suggests that early adversity may also render glucocorticoid receptors insensitive.

EARLY ADVERSITY AND INFLAMMATION

The HPA axis and ANS modulate inflammatory processes, as described above. HPA axis and ANS dysregulation resulting from early adversity, then, can affect inflammatory activity. Consequently, early adversity should be related to altered inflammatory activity. In this section, we summarize evidence for this notion.

A growing number of studies suggest that throughout the lifespan, individuals maltreated in childhood experience greater inflammatory activity, both tonically and in response to psychosocial stress, in the absence of microbial threat and disease. For example, in one prospective study (Slopen, Kubzansky, McLaughlin, & Koenen, 2013), mothers reported whether their children experienced any socially adverse events (i.e., taken into foster care, physically hurt by someone, sexually abused, separated from either parent) in the previous 12–18 months every year for the first eight years of their children's lives. Children's levels of circulating interleukin-6, a pro-inflammatory molecule, and CRP, were then assessed at ages 10 and 15. Cumulative adverse events were associated with greater levels of inflammation in both childhood and adolescence. Similarly, childhood bullying was prospectively related to higher levels of circulating levels of CRP in childhood and adolescence (Copeland et al., 2014). Such prospective studies of early adversity and inflammation are rare, and some studies have not found a link between early adversity and circulating markers of inflammation in plasma (e.g., Miller & Chen, 2010). Nevertheless, the longitudinal studies (Copeland et al., 2014; Slopen et al., 2013) described offer strong support for the link between early adversity and inflammation in youth given that they employed a prospective design and included large samples ($n > 1000$) and repeated assessments of adversity throughout childhood.

Studies of adults with a history of early adversity have more consistently shown that early adversity is associated with heightened inflammation. As adults, people who were raised in a cold, conflictual family environment (e.g., harsh discipline, maternal rejection) or experienced child maltreatment or caregiver changes have greater circulating levels of CRP, as demonstrated cross-sectionally (Kiecolt-Glaser et al., 2011; Schrepf, Markon, & Lutgendorf, 2014; Taylor, Lehman, Kiefe, & Seeman, 2006). When challenged, adults with a history of early adversity exhibit an exaggerated inflammatory response. Specifically, adults who experienced childhood maltreatment compared to those who did not had greater increases in circulating concentrations of interleukin-6 in response to a laboratory social stressor (Carpenter et al., 2010; Pace et al., 2006) and to daily stress (Gouin, Glaser, Malarkey, Beversdorf, & Kiecolt-Glaser, 2012). The majority of these studies rely on retrospective reports of early life experiences, raising the concern of recall biases. However, prospective studies with repeated assessments of early adversity using parental reports, child reports, and behavioral observations have also found that early adversity is related to greater circulating levels of inflammatory markers in adulthood (Copeland et al., 2014; Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Lacey, Kumari, & Bartley, 2014; Matthews, Chang, Thurston, & Bromberger, 2014). These studies offer compelling evidence that early adversity is related to heightened inflammation in adulthood.

FROM ALTERED NEURAL DEVELOPMENT TO INCREASED INFLAMMATION

Thus far, we have described how the central nervous system links to inflammatory processes and have

reviewed past studies showing associations between early adversity and altered neural development, HPA axis and ANS dysregulation, and increased inflammation. But exactly how might adversity-related alterations in neural development increase inflammatory activity? Based on the lines of research reviewed above, we consider the downstream effects of altered neural development on systemic inflammation in this section.

As described above, the amygdala and hippocampus are involved in detecting and recognizing threat in the environment. Thus, a hypersensitive amygdala and deficits in hippocampal-dependent learning and memory processes resulting from early life stress can lead to more frequent detection of threat in the environment. Behavioral studies have supported this notion, showing that children who were maltreated or perceived less warmth and acceptance from their parents appraised their environment as more threatening (Davies & Cicchetti, 2004; Pollak & Kistler, 2002) and perceived more social stress in their adolescent years (Raposa, Hammen, Brennan, O'Callaghan, & Najman, 2014).

Because perception of threat activates physiological stress systems (Gaab, Rohleder, Nater, & Ehlert, 2005), the functional alterations in the amygdala and hippocampus may be accompanied by repeated, exaggerated, and/or prolonged activation of the biological stress systems. Moreover, given that the mPFC downregulates amygdala activity, early adversity that disrupts mPFC function and its connectivity to the amygdala could potentially lead to inadequate inhibition of amygdala activity. This would further sustain prolonged and/or exaggerated responses to threat. Consistent with this notion, greater amygdala activity has been related to greater HPA axis and SNS activity, and to lesser PNS activity (Muscatell & Eisenberger, 2012; Thayer et al., 2012; Urry et al., 2006). By contrast, increased activity in the mPFC has been related to lower levels of cortisol (Kern et al., 2008), decreased blood pressure and heart rate (Hänsel & von Känel, 2008; Kern et al., 2008; Pruessner et al., 2008; Verberne & Owens, 1998; Wager et al., 2009), and increased vagal activity (Lane et al., 2009; Thayer et al., 2012). Moreover, a stronger coupling of the medial PFC and the amygdala is predictive of a steeper decline in the daily rhythm of cortisol (Urry et al., 2006), which is believed to be more adaptive.

Structural changes in the brain may also alter HPA function, although the mechanisms are not entirely clear. Support for this notion comes primarily from studies on animals and on patients sustaining brain damage or lesions. Hippocampal lesions or damage in rodents and humans results in elevated basal levels of glucocorticoids (Fendler, Karmos, & Telegdy, 1961; Knigge, 1961), disrupts the diurnal rhythm of glucocorticoids (Buchanan, Kern, Allen, Tranel, & Kirschbaum, 2004; Fischette, Komisaruk, Edinger, Feder, & Siegel, 1980; Herman & Mueller, 2006), and delays HPA recovery after stress (Herman, Cullinan, Morano, Akil, & Watson, 1995; Magarinos, Somoza, & De Nicola, 1987; Sapolsky, Armanini, Sutton, & Plotsky, 1989). Human studies of non-clinical samples have also shown that smaller hippocampal volume is related to a disrupted diurnal pattern of cortisol (Buchanan et al., 2004; Pruessner et al., 2010). Similarly, animal studies show that damage or lesions to the mPFC can result in an enhanced HPA response to acute stress (Brake et al., 2000; Diorio et al., 1993; Figueiredo, Bruestle, Bodie, Dolgas, & Herman, 2003; Herman & Cullinan, 1997). Decreased PFC volume has also been associated with a failure to suppress cortisol responses to dexamethasone challenge (MacLullich et al., 2006), and higher levels of cortisol at bedtime when cortisol levels should be approaching their nadir (Carrion, Weems, Richert, Hoffman, & Reiss, 2010). Taken together, these studies show that decreased hippocampal and PFC volume can disrupt HPA axis functioning. Whether alterations in hippocampal and PFC structure affects ANS function is currently unclear. Nevertheless, to the extent that neural structure underlies neural function, smaller hippocampal and PFC volume may also affect ANS activity.

Given that the HPA axis and ANS regulate inflammatory processes, we would expect that stress-related changes in neural function and structure would relate to inflammation. To date, only two human studies to our knowledge have examined the link between neural activity during stressful situations and inflammation. In the first study, greater activity in the dorsal anterior cingulate during a social exclusion task were associated with greater stress-induced increases in the soluble receptor for tumor necrosis factor-α (sTNF-RII), a marker of inflammation, assessed in oral fluids (Slavich, Way, Eisenberger, & Taylor, 2010). In a more recent study, greater amygdala activity during negative social evaluation was related to greater stress-induced increases in plasma IL-6 (Muscatell et al., 2015). These studies together provide initial evidence that the amygdala and PFC are related to stress-related inflammatory processes. Future work should substantiate these findings, in addition to clarifying the roles of early adversity and HPA axis and ANS function in these links.

Early adversity-related alterations in neural function may promote more frequent detection of threat and prolonged and/or exaggerated responses to threat, which can lead to sustained HPA and SNS activation and PNS withdrawal. Early adversity related decreased hippocampal and PFC volume may also interfere with the negative feedback loop of the HPA axis, resulting

in higher levels of cortisol. Over time, these biological states can promote inflammation. Given that sympathetic activity can upregulate inflammatory processes and parasympathetic activity can downregulate inflammatory processes, exaggerated and sustained activation of the SNS and sustained PNS withdrawal can contribute to increases in inflammation. Although cortisol typically has anti-inflammatory effects, prolonged exposure to stress, presumably accompanied by sustained activation of the HPA axis, can desensitize glucocorticoid receptors, which could result in inadequate suppression of inflammation (Cohen et al., 2012).

Although the studies described in the present review collectively suggest that early adversity related changes in the development of the amygdala, hippocampus, and mPFC may mediate the early adversity-inflammation association, no study to date has actually incorporated assessment of all the neurobiological systems; therefore, empirical support for this pathway is currently nonexistent. However, studies are beginning to chart this pathway by using gene expression in immune cells as a window into the dynamics between early adversity-related alterations in neuroendocrine and immune functioning. In one study (Cole et al., 2012), compared to rhesus macaques that were maternally-reared, those that were peer-reared exhibited greater inflammatory gene expression, and greater activity of CREB transcription factors, which play an essential role in the effects of the SNS. Interestingly, there was no evidence of decreased glucocorticoid signaling. Similarly, in a study of human adults (Miller et al., 2009), low socioeconomic status during childhood, which is often associated with a harsh family environment (Dodge, Pettit, & Bates, 1994; Pinderhughes, Dodge, Zelli, Bates, & Pettit, 2000), was also related to greater inflammatory gene expression and CREB signaling. In this study, lower socioeconomic status was also related to decreased glucocorticoid receptor signaling. Further support that increased inflammation resulting from early adversity may be mediated by decreased glucocorticoid receptor sensitivity comes from a longitudinal study of female adolescents raised in either a harsh or nurturing family environment (Miller & Chen, 2010). In addition to circulating levels of pro-inflammatory cytokines, this study examined the capacity of immune cells to mount an inflammatory response to microbial challenge in vitro (i.e., stimulated production of pro-inflammatory cytokines). Harsh family climate related changes in circulating levels of inflammation were not observed. Over time, however, the white blood cells of those raised in a harsh family climate exhibited increasingly exaggerated inflammatory responses to bacterial stimuli and greater resistance to the anti-inflammatory effects of cortisol in vitro. This suggests that early adversity may lead immune cells to develop a pro-inflammatory tendency relatively early in life, which may contribute to a chronic pro-inflammatory state later in life (Miller et al., 2011). Collectively, this study and those examining gene expression in relation to early adversity offer initial evidence that early adversity may upregulate SNS activity and desensitize glucocorticoid receptors to increase inflammation and are an important step towards understanding the role of alterations in neural development in the early adversity-inflammation link. Assessing neural structure and function in similar such studies is a critical next step in this line of work.

INFLAMMATORY REGULATION OF NEURAL DEVELOPMENT

The main focus of the present review is to consider the implications of altered neural development related to early adversity for peripheral inflammatory processes. Nevertheless, the bidirectional interactions between neural and inflammatory processes require consideration of the role that inflammatory processes play in neural development.

Inflammatory cytokines and other immune molecules play a critical role in various aspects of neural development, including neural plasticity, neurogenesis, dendrite development, and hippocampal long-term potentiation (Gilmore, Jarskog, Vadlamudi, & Lauder, 2004; Stolp, 2013; Yirmiya & Goshen, 2011). Thus, increased inflammation during early life when both the central nervous and immune systems are developing can have long-lasting detrimental effects on cognitive functioning and behavior and increase risk for developmental neuropsychiatric disorders, including schizophrenia and autism spectrum disorder (Meyer, Feldon, & Dammann, 2011; Yirmiya & Goshen, 2011). For instance, rodent experimental studies show that neonatal and postnatal infection can prime microglia, immune cells located in the brain, to secrete more inflammatory molecules; therefore, when the immune system is subsequently activated, the heightened levels of inflammatory molecules interfere with learning and memory (Bilbo, 2013). Similarly, LPS- and PolyI:C-induced inflammation in the absence of infection in pregnant mothers alters inflammatory cytokines in the fetal brain (Smith, Li, Garbett, Mirnics, & Patterson, 2007; Garay, Hsiao, Patterson, & McAllister, 2013). These changes can produce neuroanatomical, neurochemical, behavioral, and cognitive changes implicated in schizophrenia and autism in offspring. More specifically, they can disrupt dopamine and GABA systems,

social interactions, working memory, selective attention, and sensorimotor gating (Feigenson, Kusnecov, & Silverstein, 2014; Malkova, Yu, Hsiao, Moore, & Patterson, 2012; Meyer & Feldon, 2009, 2012). Whether early life psychological stress-induced inflammation has similar effects is not entirely clear.

In human studies, endotoxin- and thyphoid-induced increases in systemic inflammation have been shown to affect neural substrates, particularly those underlying socio-emotional processes. Increased inflammation has been related to increased amygdala and subgenual anterior cingulate cortex activation to socially threatening stimuli (Harrison et al., 2009; Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012). Greater amygdala activation to social threat, in turn, was correlated with increased feelings of social disconnection (Inagaki et al., 2012), and greater subgenual anterior cingulate cortex activation was correlated with greater mood deterioration (Harrison et al., 2009). Social disconnection, negative affect, and a lack of positive affect, have also been shown to upregulate inflammation (Chiang et al., 2015; Howren, Lamkin, & Suls, 2009; Jaremka et al., 2013; Steptoe, O'Donnell, Badrick, Kumari, & Marmot, 2008). Whether early adversity influences these associations has not yet been determined.

These findings underscore the fact that inflammation also influences neural development and processes. How increased inflammation following early psychological stress may affect neural development remains incompletely understood. Yet the fact that there are bidirectional effects of the CNS and immune systems makes plausible the notion that early adversity may create a cycle of dysregulation in these neurobiological systems.

FUTURE DIRECTIONS

The present review considered how alterations in neural development associated with early adversity may lead to increased inflammation. Past work has contributed significantly to our understanding of how early adversity might affect inflammatory processes and therefore physical health, but a number of issues remain.

Longitudinal Assessment of Multiple Systems

The majority of studies examining early adversity and neurobiological systems have been cross-sectional. Moreover, to our knowledge, there are no studies to date that have examined changes in neural development as a mechanism linking early adversity and increased inflammation. Thus, longitudinal investigations of early adversity involving repeated assessment of neural structure and functioning and markers of the HPA axis, ANS, and inflammation are needed. An integrative approach in a prospective design would help elucidate how early stressful experiences affect developmental trajectories of neurobiological systems that ultimately culminate in increased inflammation and greater risk for poor health. It would be relatively easy to add assessment of the HPA axis, SNS, and inflammatory processes to neuroimaging studies that examine the effects of early adversity on neural development. Cortisol and α-amylase, a digestive enzyme secreted by salivary glands that are under SNS control, can be assessed via saliva samples, whereas assessment of inflammatory markers such as CRP can be assessed from dried blood spots (DBS) (McDade, Burhop, & Dohnal, 2004). Both saliva sampling and DBS collection are relatively non-invasive procedures. In fact, DBS requires no medical personnel and has been used routinely to perform medical screening tests in infants. Additionally, assaying saliva samples for cortisol and α-amylase and DBS for CRP is relatively inexpensive.

Neural Connectivity

Studies of the effects of early adversity on connectivity between the amygdala, hippocampus, and mPFC are uncommon, despite the fact that these connections are implicated in contextual learning memory processes pertinent to fear conditioning and extinction (Maren et al., 2013; Stein et al., 2007). Given that memory and fear extinction are believed to play a role in appraisal and reactivity to subsequent contextual stimuli, alterations in connectivity among the amygdala, hippocampus, and PFC and their functional interactions may have implications for HPA and ANS activity during subsequent stress, and ultimately, for inflammatory processes. A research priority for next studies, then, is to investigate the effects of early adversity on amygdala-hippocampal-PFC structural and functional connectivity and their impact on HPA, ANS, and inflammatory processes.

Sensitive Periods

The impact of child maltreatment on neural development may depend on timing of exposure of maltreatment and the temporal development of specific neural regions (Lupien et al., 2009; Payne, Machado, Bliwise, & Bachevalier, 2010). The amygdala, hippocampus, and PFC all undergo significant development during childhood and adolescence, but specific periods of rapid development differ across these regions. The amygdala and hippocampus undergo rapid development earlier in childhood (Tottenham & Sheridan, 2010), whereas the PFC undergoes significant reorganization during adolescence (Blakemore & Choudhury, 2006). As a result,

exposure to stress during these periods may have differential effects on the different neural regions. Indeed, early adversity during late (8–17 years) rather than early (1 month–7 years) childhood has been associated with smaller PFC volume whereas early adversity during early childhood has been associated with smaller hippocampal volume (Andersen et al., 2008; Baker et al., 2012). Determining whether early stressful experiences during particular developmental stages have differential and/or additive effects on neurobiological systems can help determine optimal times to intervene.

Severity of Early Adversity

A particular gap in the literature concerns the effects of normal variation in parenting on neurobiological systems. Past studies have almost exclusively focused on traumatic events and severe forms of maltreatment (i.e., physical, emotional, and sexual abuse and neglect). Yet, most children do not experience severe forms of maltreatment, but may nevertheless experience negative relationships with their parents and other stressors (e.g., Felitti et al., 1998; Repetti et al., 2002). For instance, spanking without use of any objects is a common form of discipline in the United States (Zolotor, Theodore, Runyan, Chang, & Laskey, 2011). Rodent studies suggest that typical variations in parenting (i.e., licking and grooming) can lead to differences in the expression of hippocampal glucocorticoid receptors and the ability to induce synaptic potentiation, thereby affecting HPA and hippocampal functioning (van Hasselt et al., 2012; Weaver et al., 2004). Similarly, in a human study, corporal punishment not considered physical abuse was associated with structural alterations in the anterior cingulate cortex (Tomoda et al., 2009). Thus, further investigation of particular aspects of normative parenting that adversely affect neurobiological systems is warranted.

Genetic Factors

The role that genetics play in these processes and which polymorphisms might contribute to the development of stress-related neurobiological vulnerabilities that may culminate in inflammation are beginning to be elucidated. Single nucleotide polymorphisms in the BDNF and serotonin transporter genes have been found to moderate vulnerability to alterations in developing neurobiological systems as a result of early adversity. BDNF is critical for neuronal growth and survival, supports learning and memory, and plays an important role in inflammatory processes. As a result, the Met allele, which leads to lower levels of BDNF secretion relative to the Val allele, may enhance vulnerability to the neural and inflammatory effects of early adversity. Indeed, Met carriers with a history of early life stress have smaller hippocampal, amygdala, and anterior cingulate cortical volumes compared to homozygous Val carriers with a history of early life stress (Carballedo et al., 2013; Gatt et al., 2009; Gerritsen et al., 2011). Whether greater levels of inflammation are exhibited among Met carriers compared to Val carriers remains to be seen.

The serotonin transporter gene, which regulates transportation of the neurotransmitter serotonin, may also increase vulnerability to the negative neural effects of early life stress. Depressed S allele carriers who experienced early adversity in the form of emotional neglect were found to have smaller hippocampal and prefrontal cortical volumes compared to those with either a genetic or environmental risk factor (Frodl et al., 2010). As work on genetics progresses, additional genetic polymorphisms that unduly differentiate vulnerability to early family adversity are likely to be identified.

CONCLUSION

Alterations in neural development of the amygdala, hippocampus, and PFC may be a key pathway linking early adversity to not only poor mental health, but also to greater inflammation and subsequent poor physical health. Separate lines of work together support this hypothesis, as described in this review. Specifically, studies have begun to document links between early adversity and alterations in functional and structural development of the amygdala, hippocampus, and PFC, HPA and ANS functioning, and inflammatory processes. Based on these data and on known anatomical connections and physiological regulations among these neurobiological systems, we conclude that altered neural development resulting from early adversity likely ultimately increases inflammation and risk for poor health outcomes in adulthood.

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