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Developmental psychoneuroendocrine and psychoneuroimmune pathways from childhood adversity to disease

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Abstract

Childhood adversity has been repeatedly and robustly linked to physical and mental illness across the lifespan. Yet, the biological pathways through which this occurs remain unclear. Functioning of the inflammatory arm of the immune system and the hypothalamic-pituitary-adrenal (HPA)-axis are both hypothesized pathways through which childhood adversity leads to disease. This review provides a novel developmental framework for examining the role of adversity type and timing in inflammatory and HPA-axis functioning. In particular, we identify elements of childhood adversity that are salient to the developing organism: physical threat, disrupted caregiving, and unpredictable environmental conditions. We propose that existing, well-characterized animal models may be useful in differentiating the effects of these adversity elements and review both the animal and human literature that supports these ideas. To support these hypotheses, we also provide a detailed description of the development and structure of both the HPA-axis and the inflammatory arm of the immune system, as well as recent methodological advances in their measurement. Recommendations for future basic, developmental, translational, and clinical research are discussed.

Keywords

childhood adversity; physical abuse; emotional abuse; childhood trauma; adverse childhood events; HPA-axis; cortisol; inflammation; stress

1.1 Introduction

Childhood adversity is a robust risk factor for mental and physical illness (Chapman et al., 2004; Felitti et al., 1998) as well as earlier mortality (Chen et al., 2016). Our understanding of *how* child adversity becomes embedded in biological systems to perpetuate this risk remains limited and would benefit from examination of the potentially distinct consequences of different forms of adversity within a sophisticated developmental framework. Childhood

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adversity is associated with alterations to the body's physiological stress response systems, including the hypothalamic-pituitary-adrenal axis (HPA-axis) (Gunnar & Quevedo, 2007; Heim & Nemeroff, 2001) and the inflammatory arm of the immune system (Carpenter et al., 2010; Danese et al., 2011; Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Slopen, Kubzansky, McLaughlin, & Koenen, 2013; Taylor, Lehman, Kiefe, & Seeman, 2006). Intermediate phenotypes comprised of upregulations in these systems are thought to be central to the pathogenesis of stress-related illness (McEwen, 2013). In particular, the disease risk phenotype includes elevated glucocorticoids and inflammation, yet there are several physiological pathways through which this phenotype can emerge. Notably, the HPA-axis and inflammatory arm of the immune system respond and habituate differently to various types of stressors (Bowers et al., 2008; Kant et al., 1985; Kuhlman et al., 2014; Pacák, 1999; Pacák et al., 1998, 1995; Sheridan and McLaughlin, 2014; Weiner, 1992). Thus, it is possible that subtypes of childhood adversity have distinct physiological pathways that elucidate developmental origins of disease. An emerging literature also suggests childhood trauma exposure during specific phases of development is important to later neurobiological functioning (Andersen et al., 2008; Cowell et al., 2015; Gee and Casey, 2015; Kuhlman et al., 2015), and is critical to our understanding of how biological systems develop under conditions of threat and adversity. To date, the association between adversity and health has predominantly been tested as a dose-response relationship (e.g., Anda et al., 2006; Chapman et al., 2007; Evans et al., 2013; Kessler et al., 2010). This approach limits what we know to the overlap between heterogeneous adversity exposure (See Figure 1), and few studies have considered the role of timing, thus limiting our understanding in the context of human development. Clarifying these gaps in the literature has the potential to inform developmentally-sensitive prevention and intervention strategies that mitigate the negative health sequelae of child adversity exposure across the lifespan.

The purpose of this review is to propose a framework examining adversity type and timing as key distinctions to be made in the link between childhood adversity and lifespan health via alterations to HPA-axis and inflammatory processes during development. To do this, we first provide a basic conceptual framework for HPA-axis and inflammatory stress physiology and their measurement within psychology and psychiatry research. Comprehensive reviews of these systems can be found elsewhere (Black, 2002; Danese and Lewis, 2017; Irwin and Cole, 2011; Weiner, 1992). We then examine three commonly represented elements of adverse childhood experiences, the "biological salience" of these elements, and their potentially distinct physiological consequences. We define biological salience as the component of an adverse experience that is relevant to the organism's successful survival from or adaptation to that stressor. The biologically salient and distinguishable elements of adversity we identify are: physical trauma, disrupted caregiving, and unpredictable environment. The shortage of causal experimental models has been a barrier to understanding type and timing as important factors in physiological and health consequences that accompany childhood adversity exposure. For this reason we identify a candidate animal model that may provide a useful framework for examining health-relevant physiological consequences to each of these biologically salient elements of adversity. We then review the development of the HPA-axis and inflammatory systems with an emphasis on the limited research examining potential periods of sensitivity to adversity exposure.

Finally, because translation of rodent models to human experience is inherently limited, we propose implications and future directions for both animal and human research to investigate the distinct physiological pathways from subtypes of childhood adversity to the intermediate phenotype associated with disease.

1.2 HPA-axis and Inflammatory Physiology: Concepts and Measurement

We focus on the associations between childhood adversity and two peripheral biological systems (HPA-axis and inflammation) that are linked to physical and mental health, have been linked to childhood adversity, can be measured non-invasively in pediatric populations, and can also be measured in ambulatory settings that demonstrate high ecological validity. Coordination of the sympathetic nervous system (SNS), HPA-axis, and the inflammatory arm of the immune system, particularly in response to acute stress, is essential to development, survival, and well-being (Chrousos, 1995; Gunnar and Quevedo, 2007; Lopez-Duran et al., 2009). Under circumstances of acute threat, both the HPA-axis and immune system are activated. See Figure 2 for an illustration of the coordinated HPA-axis and inflammatory response to stress.

1.2.1 The HPA-axis: Methodological approaches—The purpose of the HPA-axis is to maintain homeostasis and promote successful adaptation to environmental stress through a complex hormonal cascade (Aguilera, 2012; Selye, 1950). When structures in the limbic system perceive a threat (e.g., pain, extreme temperatures, aggressor), the paraventricular nucleus (PVN) of the hypothalamus secretes corticotropin releasing hormone (CRH) and vasopressin (AVP) to the anterior pituitary gland (Stratakis and Chrousos, 1995). In response, the pituitary secretes adrenocorticotropin hormone (ACTH). ACTH stimulates the adrenal gland to increase production and release of glucocorticoids (cortisol in humans) (See Gunnar & Vazquez, 2006). Glucocorticoids are essential to the maintenance, duration, and down-regulation of the stress response, regulating CRH secretion from the hypothalamus and ACTH secretion by the pituitary. Glucocorticoid receptors (GRs) are found in cells throughout the body, including those in the brain. Binding of glucocorticoids to GRs in the hippocampus is associated with regulation of the acute stress response (Aguilera, 2012; De Kloet, 1991; Sapolsky et al., 2000; Smith & Vale, 2006).

HPA-axis functioning via glucocorticoid production in humans can be assessed in several ways; commonly via measurement of cortisol in saliva. Repeated measurements of salivary cortisol following acute laboratory stress paradigms have greatly informed our understanding of the HPA-axis. From these repeated measurements, the common approach is to compute a single index of cortisol response magnitude, known as Area Under the Curve (AUC) (Pruessner et al., 2003). If taken frequently enough throughout a stress paradigm, cortisol samples enable the assessment of more than just the overall magnitude of HPA-axis responses to stress, but also acceleration of HPA-axis reactivity and rate of glucocorticoid down-regulation (Kuhlman et al., 2015; Lopez-Duran, Mayer, & Abelson, 2014). In contrast to the AUC approach, these indices provide insight into the temporal dynamics of HPA-axis reactivity to acute stress and potentially the underlying physiological mechanisms that contribute to cortisol synthesis and regulation. For example, acceleration of cortisol increase following stress could reflect the intensity of excitatory input into the axis from the limbic

system, whereas cortisol regulation following peak more likely reflects the density and sensitivity of GRs, primarily in the hippocampus (Sapolsky, Meaney, & McEwen, 1985). A system which quickly returns to baseline cortisol levels after reaching peak is an adaptive response to a mild, acute stressor and likely reflects the density and sensitivity of GRs to shut down the stress response.

Glucocorticoids also fluctuate according to a diurnal pattern. There is a large increase in cortisol in response to waking which is referred to as the cortisol awakening response (CAR) (Federenko et al., 2000). CAR is believed to reflect a mounting of physiological resources to meet the demands of the day (Adam and Gunnar, 2001), and also appears to be a measure of adrenal sensitivity to ACTH (Clow et al., 2010). Healthy, typically-developing humans should demonstrate their highest cortisol concentrations in the morning and their lowest in the evening (Clements, 2012). Abnormally high diurnal cortisol can be an indicator of several dysregulations in the axis; for example, this could indicate chronic hypersecretion of CRH/AVP by the hypothalamus, or hypersecretion of ACTH by the pituitary (Aguilera, 2012), or repeated activation of the acute stress system (Kidd et al., 2014). Abnormally low diurnal cortisol can be an indicator that the hypothalamus has down-regulated secretion of CRF/AVP to the pituitary (Aguilera, 2012), possibly following repeated activation to chronic environmental stress (Heim, Ehlert, & Hellhammer, 2000; Miller, Chen, & Zhou, 2007). Adaptive diurnal functioning of the HPA-axis has implications for other physiological processes such as immune functioning (Heim et al., 2002; Watts-English, Fortson, Gibler, Hooper, & De Bellis, 2006), growth (Kertes et al., 2008), sleep (Buckley and Schatzberg, 2005) and therefore dysregulation may be related to disruptions in these systems as well.

1.2.2 Inflammation: Methodological approaches—Inflammation is a natural, early immune response to pathogens and tissue injury. In response to infection or injury, various types of immune cells, including those in blood (e.g., monocytes, lymphocytes), tissue (e.g., macrophages), and in the brain (e.g., microglia) release pro-inflammatory cytokines (See Black, 2002; Miller et al., 2009 for review). Cytokines are soluble proteins that operate as chemical messengers between cells in the body. They help orchestrate the immune response (e.g., elimination of pathogen, repair any damaged tissue), and thus, the inflammatory response is crucial to healing and survival.

Notably, inflammation also increases in the context of psychosocial stress (Steptoe et al., 2007). When threat is perceived, the SNS releases noradrenaline, which promotes mobilization of stem cells from the bone marrow and activates immune gene transcription within white blood cells, organs, and tissues (Irwin and Cole, 2011). Activation of immune gene transcription leads to the production and release of cytokines. These acute changes are believed to occur adaptively in preparation for potential injuries incurred as a result of acute threat.

The most common way to assess inflammatory processes in humans is to measure concentrations of circulating pro-inflammatory cytokines, such as IL-6 and TNF- α , and systemic markers of inflammation, such as C-reactive protein (CRP), in blood samples. CRP, an acute phase protein synthesized in the liver in response to IL-6, can be a measure of chronic inflammation and concentrations greater than 3.0 mg/L are considered reliably

predictive of cardiovascular disease risk (See Ridker, 2003 for review). Tonic levels of inflammation are typically assessed with a single blood sample collected via venipuncture or dried blood spots (DBS), a relatively non-invasive procedure involving a finger prick and blood drops on specialized filter paper. Repeated blood samples can be collected via an indwelling catheter to capture the inflammatory response to acute stress.

There are several other methods of evaluating inflammatory processes, particularly at the cellular and intra-cellular levels. For instance, acute stress causes myelopoiesis, or the secretion of new immune cells from the bone marrow into circulation (Reader et al., 2015). Myelopoiesis can be measured by enumerating white blood cells before and after exposure to a stimulus. Functions of white blood cells can also be measured in vitro by measuring the production of cytokines following exposure to either a bacterial or anti-inflammatory stimulus (Irwin et al., 2010; Miller et al., 2009). Incubating white blood cells with a bacterial stimulus, such as lipopolysaccharide (LPS), or viral stimulus, and measuring the levels of pro-inflammatory cytokines produced provides a measure of the capacity of immune cells to produce an inflammatory response. GR sensitivity can also be specifically assessed by incubating immune cells with both a microbial stimulus and cortisol, and then quantifying production of pro-inflammatory cytokines.

Measurement limited to circulating peripheral cytokines is often criticized for failing to localize the source of inflammatory cytokines and for being sensitive to several confounding factors, including SES, BMI, age, and sex (M.-F. O'Connor et al., 2009). Further, circulating biomarkers are often temporally sensitive and may fluctuate due to variations in exercise as well as minor colds or infections. Thus, molecular measures of inflammatory functioning of immune cells have also been developed. Individuals vary in the expression of transcription factors associated with inflammation (e.g., NF- κ B) and regulation of inflammation (glucocorticoid receptor) in mRNA of immune cells (Cole, 2008; Cole et al., 2007). Intracellular measures of inflammatory processes may be particularly useful in youth as a predictor of future risk for chronic inflammation. Further, the simultaneous examination of circulating, cellular, and intracellular measurements of inflammatory processes may drive progress in our understanding of environmental and psychological stress on this system.

1.2.3 Coordination between inflammation and the HPA-axis—In addition to activating the HPA-axis, stress also elicits an inflammatory response. A critical role of the HPA-axis is regulation of inflammation. GRs can be found in immune cells and binding of glucocorticoids to the GRs downregulates cytokine production (Silverman et al., 2005). The effective down-regulation of inflammation by glucocorticoids is essential to preventing persistently elevated (Stark et al., 2001). In preclinical models, repeated acute stress has been shown to cause glucocorticoid resistance in immune cells (Avitsur et al., 2009; Engler et al., 2008). Similarly, prolonged or chronic stress in humans can lead to GR insensitivity, meaning that GRs in immune cells are not able to “hear” the inhibitory signals of glucocorticoids (Cohen et al., 2012; Miller et al., 2002).

2.1 Theoretical and empirical support for distinguishing between childhood adversity types

Several overlapping theories have been developed to provide a framework for how childhood adversity confers risk for illness through allostatic load, a process through which an individual's failure to adapt to conditions of repeated or chronic stress leads to wear-and tear on the body (McEwen, 2013; McEwen, 1998). There has also been interest in the aspects of the childhood social environment that drive deteriorations in health (e.g., Risky Families; Repetti, Taylor, & Seeman, 2002), and the biological mechanisms that explain the association between adversity and health (Cole et al., 2012; Danese et al., 2011; Friedman et al., 2015a; Miller et al., 2011). Overall, these theories have concluded that more exposure to adversity exerts pleiotropic effects on health across the lifespan. Indeed, childhood abuse significantly accelerates biological aging (Tyrka et al., 2010) and all-cause mortality (Chen et al., 2016). Existing models have yet to directly examine whether physiological consequences vary across different types of adversity, limiting our understanding of the varying biological salience of different experiences during development. Yet, in the past decade we have developed a much stronger appreciation for the role childhood environments and experiences in the epigenetic regulation of many components of physiological stress response systems (Anacker et al., 2014; Tyrka et al., 2013). Exploring potentially distinct pathways from different types of social environments to at-risk intermediate phenotypes may clarify why the common co-occurrence of different types of adversity is associated with broad and multi-system effects on health and will promote the development of interventions based on specific adversity risk factors.

In this section, we explore whether there are distinct elements of childhood adversity that vary in biological salience and therefore physiological alterations. For example, do adversities that involve physical injury have different physiological consequences than adversities that involve lack of nurturing care or reliable safety and shelter? We propose that childhood adversities vary in the degree to which they involve physical trauma, disruptions in caregiving, and unpredictability. Each of these elements has been identified as salient to the development of the central nervous system with implications for learning and downstream physiological adaptations (Gunnar and Vazquez, 2006; McLaughlin et al., 2014b; Teicher et al., 2003). To better understand the downstream physiological consequences, we consider well-characterized animal models that may serve as useful analogs for these child adversity elements and provide informative causal models for understanding the distinct pathways from different types of developmental stress to disease. Specifically, we highlight three paradigms: repeated social defeat (Avitsur et al., 2001; Reader et al., 2015), maternal separation (Ladd et al., 1996; Roque et al., 2014), and chronic variable stress (CVS) (Herman et al., 1995; Maier and Seligman, 1976; Simpkins and Devine, 2003) (See Table 1). Each of these paradigms has shown evidence that both the HPA-axis and inflammatory response undergo distinct alterations that correspond to diverging behavioral phenotypes. It is possible that each element of adversity (based on the degree of physical threat, caregiving disruption, and unpredictability) differs in biological salience and therefore affects the system differently. In the face of co-occurrence of multiple

adversities, which is more common than not, these effects may converge for multi-systemic vulnerability to disease across the lifespan.

2.2.1 Repeated Social Defeat (RSD) as a model for understanding child adversity involving physical injury

Physical trauma describes experiences that involved actual physical threat, injury, or abuse to the individual. In rodents, the repeated social defeat (RSD) paradigm (Avitsur et al., 2001; Reader et al., 2015) involves placing a large, aggressive rat in the participant rat's cage for 2 hours each day for a week. During these 2-hour episodes, the aggressor rat attacks the subject into submission. RSD causes rodents to release immature, pro-inflammatory immune cells (CD11b+/Ly6C high) into circulation that serve to promote inflammation at the site of injury (Powell et al., 2013). Animals that sustain an injury during attack by the aggressor (Merlot et al., 2003) exhibit glucocorticoid resistant immune cells, systemic increases in glucocorticoids, exaggerated inflammatory responses (Avitsur et al., 2001; Stark et al., 2001), and increases in pro-inflammatory gene expression in immune cells (Powell et al., 2013). In addition, the physiological consequences of exposure to RSD are robustly associated with structural changes (e.g., atrophy, connectivity) to neural systems that modulate threat-sensitivity and anxiety-like behaviors (Reader et al., 2015). And indeed, exposure to RSD leads to anxiety-like behavior in two-thirds of rodents (Golden et al., 2011), and the development of this behavioral phenotype is mediated by immune cell derived IL-6 (Hodes et al., 2014).

Consistent with these animal models, both children (Shackman et al., 2007) and adults (Stein et al., 1996) exposed to physical abuse demonstrate increased risk for anxiety disorders and a wide range of physical and behavioral distress. Thus, we propose that animal models of the physiological consequences of RSD may be useful in understanding the potential effects of childhood adversities involving physical abuse or injury. Based on this proposed translational model, we hypothesize that more physical injury or abuse during childhood would be associated with increased sympathetic innervation of the peripheral stress response systems that serve to promote a rapid and robust response to acute stress. This includes innervation of bone marrow which is necessary for the stimulation of immature, proinflammatory and glucocorticoid resistant monocytes into circulation.

2.2.2 HPA-axis and inflammatory correlates of physical trauma in humans

Physical trauma is often measured in the form of physical punishment or physical abuse. Infants (Bugental et al., 2003) and school-aged children (Kuhlman et al., 2014) exposed to frequent physical punishment demonstrate exaggerated cortisol responses to psychological stress. Exposure to physical abuse is also related to exaggerated HPA-axis responses to acute psychosocial stress (Kuhlman et al., 2015) and to viewing violent films among young adolescents (Ivanov et al., 2011). There is some evidence that basal cortisol is also elevated in youth exposed to physical abuse. For example, youth exposed to sexual abuse, which involves invasive physical contact and often injury, exhibit elevated circulating plasma cortisol compared to controls (Imek et al., 2015), and suicide victims exposed to interpersonal violence as children exhibit elevated CSF cortisol among suicide attempters (Chatzittofis et al., 2013).

Several studies indicate a link between physical trauma and both elevated circulating markers of inflammation and inflammatory diseases (Friedman et al., 2015b). For example, 12-year old children exposed to physical maltreatment by their mothers who also have elevated symptoms of depression have elevated CRP (Danese et al., 2011). Child abuse that results in pediatric traumatic brain injury has also been associated with elevated IL-4, IL-12 (Amick et al., 2001), and IL-8 (Whalen et al., 2000). Similarly, exposure to bullying during childhood and adolescence is associated with elevated CRP during early (Copeland et al., 2014) and middle adulthood (Takizawa et al., 2015), although the documentation of the threat of physical injury versus actual injury are inconsistent. Cumulative childhood maltreatment is associated with exaggerated inflammatory responses to acute stress (Carpenter et al., 2010), however, no study to our knowledge has examined inflammatory responses to acute stress between physically abused and non-abused peers. Taken together, exposure to physical abuse and trauma during childhood exaggerate both inflammatory activity and HPA-axis reactivity to stress until adolescence. Consistent with this hypothesis, childhood physical abuse exposure is associated with a multisystemic biological risk profile (including both HPA-axis and inflammatory markers) (Friedman et al., 2015a). Of note, physical and sexual abuse are not consistently linked with elevated inflammation in adults after accounting for covariates such as BMI and smoking (Bertone-Johnson et al., 2012), suggesting potential behavioral or developmental pathways that may lead from physical trauma to the persistence of inflammation in adulthood (Raposa et al., 2014a).

2.3.1 Maternal separation as a model for understanding child adversity involving disrupted caregiving

Disruptions in the caregiving environment include death of a parent, emotional abuse, parental neglect, maternal depression, or low maternal warmth. Pre-clinical animal models have characterized the developmental effects of disruptions in early caregiving through several paradigms, with overlapping physiological consequences. Thus, we propose that maternal separation paradigms may serve as a useful animal model for understanding the unique associations between disruptions in the caregiving environment and HPA-axis and inflammatory functioning.

Repeated and prolonged maternal separation in rodent pups results in exaggerated SNS and HPA-axis responses to stress during adolescence and adulthood (Kalinichev et al., 2002; Plotsky and Meaney, 1993). Yet, maternal separation may be more closely linked to impaired *regulation* of the stress response once initiated whereas physical trauma appears to be linked to exaggerated *activation* of stress response systems. In particular, less naturally occurring maternal licking and grooming behavior immediately following maternal separation corresponds reduced expression of glucocorticoid receptors in the hippocampus that presage increased expression of CRH in the hypothalamus and exaggerated ACTH and glucocorticoid responses to stress in adulthood (Liu et al., 1997). Maternal care in infancy contributes to epigenetic regulation of the glucocorticoid receptor in the hippocampus (Anacker et al., 2014; McGowan et al., 2009) as well as in peripheral immune cells (Miller et al., 2011; Tyrka et al., 2012). This means that animals deprived of maternal nurturing behaviors will demonstrate impaired ability to down-regulate physiological responses to stress once activated. This highlights the importance of the use of analytic and

methodological strategies that differentiate the reactivity and recovery of physiological systems following acute stress (Lopez-Duran et al., 2014).

Within this translational model, we would expect that individuals exposed to various forms of disrupted caregiving would demonstrate impaired HPA-axis negative feedback that can be observed during regulation from CAR, acute stress paradigms, elevated diurnal cortisol, and non-suppression following Dexamethasone administration. Disrupted caregiving may also result in impaired negative feedback within immune cells via increased intracellular inflammatory gene expression and decreased glucocorticoid receptor sensitivity which promotes production of inflammatory cytokines despite the presence of elevated glucocorticoids (Cole et al., 2012).

2.3.2 HPA-axis and inflammatory correlates of disrupted caregiving in humans

Indeed, human studies of different types of disruptions in the caregiving environment fairly consistently observe impaired regulation of the HPA-axis in childhood. For example, social deprivation during early childhood (ages 0–2) is associated with flat diurnal cortisol slopes throughout the day (Koss et al., 2014). In addition, maternal depression is associated with disengaged and negative parenting behaviors (Lovejoy et al., 2000). Maternal depression during early childhood robustly predicts elevated tonic cortisol during middle childhood (Ashman et al., 2002; Essex et al., 2002). Similarly, low maternal warmth during early childhood prospectively predicts impaired down-regulation of cortisol following peak response to acute psychological stress (Kuhlman et al., 2014). And finally, when accounting for other types of early trauma, exposure to emotional abuse was specifically associated with impaired recovery of the HPA-axis to acute psychosocial stress in adolescents (Kuhlman et al., 2015).

This pattern of impaired down-regulation of cortisol also appears to persist into adulthood. For example, adults who lost a parent during childhood demonstrated higher cortisol throughout the day compared with adults who never experienced separation from their parents for longer than two weeks (Nicolson, 2004). Maternal separation during childhood is associated with exaggerated CAR into adulthood (Kumari, Head, Bartley, Stansfeld, & Kivimaki, 2013). Adult men who experienced the loss of a parent via death or desertion during childhood exhibit larger responses to the Dex/CHR test (Tyrka et al., 2008), and adult offspring of Holocaust survivors reporting more exposure to emotional abuse and neglect exhibit elevated urinary cortisol (Yehuda et al., 2000).

Information linking disrupted caregiving and inflammatory functioning is scarce, but still informative. Disrupted caregiving may impair coordination between glucocorticoids and immune cells, such as glucocorticoid insensitivity in immune cells that may contribute to elevated circulating inflammation despite the presence of glucocorticoids (Cole, 2008; Cole et al., 2012). Overall, experiencing multiple types of maltreatment before adulthood was associated with elevated CRP, fibrinogen, and proinflammatory cytokines (Coelho et al., 2014). Consistent with this, total early trauma exposure was associated with elevated CRP, which was driven by exposure to emotional abuse (Rooks et al., 2012). There is also an emerging body of evidence that more chronic childhood stressors such as parent psychopathology (e.g., MDD), low SES, and parent separation are prospectively associated

with elevated inflammation when adolescent girls become depressed, and that inflammatory markers remain elevated even after symptoms recover (Miller and Cole, 2012).

There is significant need to more directly examine the association between disrupted caregiving and long-term functioning of the HPA-axis and inflammatory systems in humans. Disruptions in the caregiving environment during childhood may interfere with the effective down-regulation of glucocorticoid production, including negative feedback following acute stress or pharmacological challenge, diurnal, and tonic regulation of the axis. Some types of disrupted caregiving may be associated with elevated peripheral markers of inflammation. In the context of elevated and poorly-regulated glucocorticoids, the observed heightened markers of inflammation may reflect the presence of glucocorticoid insensitive immune cells.

2.4.1 Chronic Variable Stress (CVS) as a model for understanding child adversity involving unpredictable stress

Exposure to an unpredictable environment during childhood involves experiences that reflect unmet basic physical needs such as poverty, unpredictable access to meals and shelter, exposure to community violence, or singular unpredictable traumatic events (e.g., natural disaster, motor vehicle accident). There are several animal models that explore the physiological and developmental consequences of living in an unpredictable environment that causally contribute to complex behavioral phenotypes such as aggression (Van Loo et al., 2002), impaired learning and memory (Holmes and Wellman, 2009), and anhedonia (Gouirand and Matuszewich, 2005). These models may also provide a useful animal paradigm for understanding the complex HPA-axis and inflammatory consequences of developing in an unpredictable environment.

Unpredictable stress represents a unique challenge to physiological systems within a developmental framework. Following repeated exposure to the same stressor, a developing organism will habituate while becoming sensitized to novel, dissimilar stressors (Simpkiss and Devine, 2003). Chronic variable Stress (CVS) involves exposing rodents to different stressors twice per day for between 15 and 30 days, including social hierarchy disruption, vibrating cage, light-dark reversal, forced swim tests, exposure to extreme temperature (cold), isolation, restraint, and overcrowding (Herman et al., 1995; Simpikiss and Devine, 2003). CVS that includes a combination of both processive (novel environment, forced swim) and systemic (food deprivation, cold exposure) stressors causes global up-regulation of the HPA-axis, including greater CRH mRNA expression in the hypothalamus, elevated basal ACTH and glucocorticoid secretion, increased adrenal gland weight, and decreased glucocorticoid receptor mRNA expression throughout the hippocampus and hypothalamus (Herman et al., 1995). In contrast to maternal deprivation, the decreased glucocorticoid receptor mRNA expression following CVS is global, and thought to result from atrophy following excess glucocorticoid exposure. CVS also causes elevated markers of inflammation including IL-6, IL-1 β , and TNF- α in the hippocampus (Tagliari et al., 2010), but not always in the periphery (Grønli et al., 2005). CVS may lead to neuroinflammation indirectly via atrophy of neural substrates in the limbic system associated with chronic exposure to elevated glucocorticoids. Exposure to CVS also has implications for stress

reactivity later in life, such that CVS causes blunted ACTH secretion following exposure to a familiar stressor and exaggerated ACTH secretion following novel stressors (Simpkiss and Devine, 2003).

Thus, we propose CVS as a plausible translational model for exposure to an unpredictable developmental environment. Based upon this translational model, we expect youth exposed to an unpredictable environment to demonstrate chronic up-regulation of diurnal cortisol, and elevated neuroinflammation that may indirectly increase peripheral inflammatory markers. This may be driven by increased neural sensitivity to novel or ambiguous threat cues in the environment that are sustained by microglia signaling, the inflammatory immune cells within the brain. Targeted inhibition of microglia using minocycline correspond to reductions in peripheral inflammation (Blum et al., 2004; O'Connor et al., 2009). Interestingly, early treatment in rodents with minocycline also appears to mitigate the affective consequences of early infection in adulthood via this neuroinflammatory pathway (Majidi et al., 2016). Unfortunately, methods for examining neuroinflammation directly are limited to animal models (Monnet-Tschudi et al., 2011), and can only be examined in humans using PET and post-mortem assessments (O'Connor et al., 2014). We would also hypothesize that chronic unpredictable stress during childhood would correlate with blunted HPA-axis reactivity to familiar stressors and exaggerated HPA-axis reactivity to novel stressors, yet defining any daily or acute laboratory stress as familiar and novel is much more complex than in controlled animal experiments.

2.4.2 HPA-axis and inflammatory correlates of unpredictable stress during childhood in humans

Studies directly examining unpredictable environments and HPA-axis and inflammatory correlates are scarce, difficult to disentangle, and also illustrative of our argument in favor of examining the role of subtypes of adversity exposure by their biologically salient elements. For example, family adversity, poverty, and minority status operate in opposite directions when predicting HPA-axis function and other indicators of allostatic load (Bush et al., 2011). This may be because family adversity, poverty, and minority status may all involve unpredictability for a developing child, but also vary in degrees of caregiver disruption and physical threat. Another study examining the role of childhood poverty in physiological development found that frequent “adult exits” from the home were associated with elevated cortisol throughout the day during infancy that increased as the child aged (up to age 48 months) (Blair et al., 2011). In contrast, perceived economic insufficiency was also associated with elevated cortisol throughout the day during infancy, but this association diminished with time (Blair et al., 2011). Underscoring the mixed state of the literature, each of these studies identifies distinct associations between different types of adversity that can oppose one another and may be further explained by the biologically salient elements of each adversity.

Living in an unpredictable environment as a child likely promotes upregulation of both diurnal cortisol and peripheral inflammatory markers. For example, poverty is the most thoroughly studied form of unpredictable environment. Low socioeconomic status during childhood predicts a doubling of cumulative morning cortisol well into adulthood (Li et al.,

2007). Living in poverty is associated with elevated cortisol overnight in adolescents (Evans and Kim, 2007). In addition, lower household income, over-crowding and living in rented housing predicted elevated inflammatory markers and disease risk during adulthood (Dowd et al., 2010; Packard et al., 2011), while parent education was not (Dowd et al., 2010). Of course, part of elevated inflammation among children living in poverty occurs through pathways independent of psychosocial stress such as pollution, pathogen exposure, and limited access to healthcare (See Miller and Chen, 2013 for review). Yet having a chaotic home environment appears to show consistent associations with general up-regulation of stress physiology. For example, having a highly chaotic home is associated with heightened and stable morning cortisol over multiple years in early childhood (Laurent et al., 2014) and exposure to violence in the home appears to consistently be linked to elevated cortisol throughout the day (Bair-Merritt et al., 2012). Further, having a chaotic home environment is also a correlate of circulating inflammation in breast cancer survivors beyond the effects of other exposures (Crosswell et al., 2014) and having a father incarcerated at any point in childhood is associated with higher CRP (Boch and Ford, 2015).

So far, it appears that living in an unpredictable environment is associated with a consistent general upregulation of diurnal cortisol and inflammation. The story becomes more complex when considering studies of acute stress responses. For example, living in poverty during childhood was associated with elevated cortisol in anticipation of acute stress in young adults (Sripada et al., 2014). Therefore, it is possible that elevated cortisol throughout the day and circulating inflammation are indicative of a threat sensitive system that activates frequently. Consistent with this idea, several studies have identified neural correlates of physiological responding among youth with an unpredictable childhood environment. In fact, Sripada and colleagues (2014) found that elevated cortisol in individuals who lived in poverty as children was associated with lower connectivity within the default mode network, specifically the connections between the hippocampus, posterior cingulate cortex, and medial prefrontal cortex. Thus, living in an unpredictable environment during childhood may increase neural sensitivity to stress in the environment via attention and vigilance to threat that leads to more frequent activation of stress response systems and less effective regulation of that response by frontal regulatory structures.

2.5.1 Summary of HPA-axis and Inflammatory Correlates of Child Adversity by Subtype

On the surface, it is easy to conclude that most forms of childhood adversity are related to upregulated circulation of glucocorticoids and inflammation. However, the combined interpretation of the existing animal and human literature suggests that there may be distinct underlying processes through which co-occurring elements of childhood adversity lead to a similar intermediate phenotype, elevated inflammation and atypical functioning of the HPA-axis. See Figure 3 for this proposed model. Specifically, physical trauma may be associated with robust activation of the threat response system leading to exaggerated HPA-axis responses to acute stress and elevated inflammation. Disrupted caregiving, in comparison, may be more related to poor down-regulation of glucocorticoids across many contexts and low glucocorticoid sensitivity in both immune cells and the brain. Finally, an unpredictable environment may be particularly associated with elevated basal cortisol and markers of inflammation throughout the day due to increased vigilance of the threat response system

originating from the central nervous system. In practice, this would be reflected by a more frequently activating system throughout the day, rather than a larger response to a single stressor. Empirical examination of these potentially distinct pathways from childhood adversity to disease has the potential to inform our models of pathogenesis, hone assessments of intervention effectiveness at deeper biological levels, and identify distinct points of prevention and intervention for youth exposed to different types of adversity. Inflammatory intervention targets for individuals exposed to childhood trauma are already being developed (Danese and Lewis, 2017). For example, some behavioral interventions effectively reduce proinflammatory gene expression and not necessarily systemic markers (Bower et al., 2014, 2011; Creswell et al., 2012). In contrast, there are several cognitive strategies that mitigate threat sensitivity and therefore the frequency and magnitude of SNS and HPA-axis responses to stress (e.g., Antoni et al., 2000). Yet, the high co-occurrence of different types of adversity and limitations of our existing measures have so far impeded our ability to disentangle these causal pathways in humans.

3.1 Theoretical and Empirical Support for Examining the Role of Childhood Adversity Timing

In addition to neglecting the distinct physiological effects of adversity type, existing models for how early adversity confers risk for poor health, for the most part, do not consider the role of timing of adversity exposure. This limits our understanding of when adversity exposure may have particularly potent and/or long-lasting effects on the maturation and functioning of physiological systems. The HPA-axis and immune system develop significantly in utero (Hostinar and Gunnar, 2013; Simon et al., 2015), and continue to undergo change from the neonatal period through adolescence. Adversity exposure during different periods of development may differentially impact these systems. In this section, we examine the importance of adversity timing on HPA-axis function and inflammatory processes by briefly reviewing what is known about the development of HPA-axis and inflammatory functioning. A number of detailed reviews have previously described development of the HPA-axis (Gunnar and Quevedo, 2007; Gunnar and Donzella, 2002; Hostinar and Gunnar, 2013; Romeo, 2010), and thus, we highlight only major points of development. We also discuss human studies that may inform our understanding of how adversity exposure at specific times in early life might influence the HPA-axis and inflammatory processes. Exposure to different types of adversities at particular points in development may differentially affect the HPA-axis and inflammatory processes. Given the limited literature, we are unable to make these distinctions and instead discuss the possible role of any adversity type.

3.2.1 Development of the HPA-axis

Rodent research indicates that the neonatal period is marked by a stress hyporesponsive period (SHRP), in which neonates exhibit blunted basal and stress-induced corticosterone (Gunnar and Quevedo, 2007; Rosenfeld et al., 1992). Human studies suggest an analogous period of HPA-axis hyporesponsivity that gradually develops over the first year of life (Gunnar and Donzella, 2002). In the first two to three months after birth, the HPA-axis exhibits robust cortisol increases in response to mild perturbations such as physical

examinations (Gunnar et al., 2009a; Larson et al., 1998). The HPA-axis may later transition into a hyporesponsive period. In one longitudinal study, infants mounted a cortisol response to inoculation when 2, 4, and 6 months old, yet the magnitude of the response decreased with age (Lewis and Ramsay, 1995). In another longitudinal study, there was a decrease in cortisol response to inoculation between 2 and 4 months of age, no difference between 4 and 6 months of age, and a subsequent decrease from 6 to 15 months of age (Gunnar et al., 1996a). A lack of cortisol response to other stressors has also been shown among 12 to 24 month olds (Davis and Granger, 2009; Gunnar and Donzella, 2002), and the difficulty in elevating cortisol in response to mild stressors seems to persist through the preschool period (Davis and Granger, 2009). Whether this phenomenon continues throughout childhood up to adolescence remains unclear.

From these studies, it is difficult to definitively determine whether the observed HPA-axis hyporesponsivity is truly a stress hyporesponsive period. Given that infants' mothers accompanied the infant in all of these studies, the findings may reflect increased social buffering of the HPA-axis, particularly by a nurturing caregiver (Hostinar et al., 2014). Supporting this notion, one study found that a responsive caregiver during maternal separation attenuated cortisol responses among 9 month olds (Gunnar et al., 1992). Likewise, studies of 12–18 month olds show that secure attachment is associated with attenuated cortisol responses to fear and physical pain (Ahnert et al., 2004; Gunnar et al., 1996b; Nachmias et al., 1996; Spangler, 1998). Though the HPA-axis has been less studied in middle and late childhood, there is evidence suggesting continued social buffering. In one study, 7–12 year old female youth exhibited an attenuated cortisol response and quicker recovery from social evaluation when reunited with their mothers (Seltzer et al., 2010). Similarly, parental support blunted cortisol responses to social evaluation among 9–10 year old children (Hostinar et al., 2015).

The buffering of the HPA-axis by nurturing caregiving in infancy, and possibly through childhood, is believed to be protective and conducive to optimal development. Infancy and childhood are periods of rapid growth and development, and excessive glucocorticoids can have detrimental effects on development. For instance, the central nervous system undergoes significant development during infancy and childhood (Andersen, 2003; Gao et al., 2015; Huang et al., 2015; Qiu et al., 2015) and is vulnerable to the effects of glucocorticoids (Gunnar, 1998; Lupien et al., 2009). Repeated activation of the HPA-axis in response to mild perturbations that pose no real threat could lead to excessive exposure to glucocorticoids, thereby compromising neural development. Thus, a nurturing caregiver may operate as a safety signal, helping maintain low levels of glucocorticoids and facilitating learning of what stimuli pose real threats.

The HPA-axis again undergoes major change during adolescence and pubertal development, transitioning into a period of increased sensitivity to the environment (Somerville et al., 2010). Unlike the relatively low basal and stress-induced cortisol responses during childhood, basal cortisol increases from childhood to adolescence and is positively associated with pubertal development (Gunnar et al., 2009b; Gunnar and Vazquez, 2006; Hostinar et al., 2015; Legro, 2003; Netherton et al., 2004; Stroud et al., 2009; Törnåge, 2002). In a sample of almost 400 youth aged 7–15 years, for example, diurnal cortisol was

found to positively correlate with pubertal stage (Kiess et al., 1995). Studies of youth have also found that cortisol responses to social stressors increase with age, and are associated with pubertal development (Blumenthal et al., 2014; Gunnar et al., 2009b; Stroud et al., 2009; Sumter et al., 2010; van den Bos et al., 2014). Circadian rhythm and social regulation of the HPA-axis also change during adolescence. In particular, the circadian rhythm has been shown to flatten with increasing age and greater pubertal development, especially among females (Shirtcliff et al., 2012). In contrast to the parental buffering observed in earlier life, parental support no longer buffers cortisol reactivity to stress during adolescence (i.e., 15–16 year olds) (Hostinar et al., 2015). These changes in HPA-axis functioning during adolescence likely serve an adaptive function. Adolescence is marked by increasing autonomy, and as adolescents become increasingly independent, they learn to depend on themselves and peers for survival. From an evolutionary standpoint, it would benefit adolescents to have a hypersensitive HPA-axis that promotes adaptation to potential threats.

3.2.2 Timing of adversity and HPA-axis development

Although the HPA-axis seems to develop from infancy into adolescence, periods of greater plasticity may represent times when the HPA-axis is particularly sensitive to environmental input. During these sensitive periods, exposure to adversity may have more profound and/or enduring consequences. The shift from a responsive HPA-axis during the early postnatal months to a relatively hyporesponsive period by 12 months of age may be an important sensitive period. In particular, adversity exposure during the first year of life may interfere with normative development of a hypo-responsive HPA-axis. Consequently, we might observe higher basal cortisol and exaggerated cortisol responses to stress, presumably during the relative hyporesponsive period in typical development.

Consistent with this notion, studies examining the effects of early adversity during the first few years of life have found elevated cortisol at baseline and in response to stress. For instance, mothers with a history of depression and early adversity had infants with higher baseline cortisol (Brand et al., 2010), potentially because depression and early adversity can lead to less attentive or detached parenting (Lovejoy et al., 2000; Pereira et al., 2012). Similarly, maternal emotional withdrawal during the first year of life has been associated with higher baseline cortisol among 1.5-year-old children (Bugental et al., 2003). There is also evidence suggesting adversity exposure during infancy has implications for HPA-axis responses to stress during the HPA-axis hyporesponsive period. Specifically, harsh punishment during the first year of life was associated with higher cortisol responses to the Strange Situation among 1.5-year-olds (Bugental et al., 2003). More direct evidence for the effects of adversity during infancy on the HPA-axis hyporesponsive period comes from a study focusing on the developmental trajectory of HPA-axis reactivity to stress from infancy to toddlerhood (Hibel et al., 2009). In this study, children exposed to interparental violence exhibited a trajectory of increased cortisol responses to challenge tasks from 7 to 24 months of age. By contrast, their non-exposed counterparts exhibited a trajectory of declining cortisol responses.

As noted above, social buffering of the HPA-axis prevents excessive glucocorticoids from having deleterious effects on development. As such, heightened cortisol during the

hypo-responsive period could lead to greater exposure to glucocorticoids. This, in turn, can contribute to glucocorticoid receptor insensitivity over time (Cohen et al., 2012; Miller et al., 2002), although it is not entirely clear whether existing cells become increasingly desensitized over time or new cells with decreased sensitivity enter circulation. Also unclear is whether this glucocorticoid insensitivity is system-wide or specific to particular cells. One possibility is that glucocorticoid receptor insensitivity may disrupt regulation of feedback loops and manifest as continued heightened basal cortisol and delayed recovery from stress later in development. In support of this notion, a study of 7–8 year old children showed that a lifetime history of maternal depression was associated with elevated cortisol; notably, maternal depression during the child's first two years of life was the best predictor of elevated cortisol (Ashman et al., 2002). Adversity exposure during infancy has also been associated with flatter diurnal cortisol slopes and higher cortisol later in the day when levels are typically declining. For instance, maternal depression during the first year of life was related to elevated cortisol in the late afternoon/early evening among 4.5-year-old girls (Belsky et al., 2015), and previously institutionalized toddlers who were recently adopted exhibited a flatter daily decline in cortisol (Koss et al., 2014).

More compelling evidence for the notion that infancy may be a sensitive period during which adversity exposure may result in heightened HPA-axis activity comes from studies of previously institutionalized or maltreated children placed in foster or adoptive care. For instance, 13-month old maltreated children who were placed in foster care following Child Protective Services involvement displayed steeper diurnal cortisol slopes compared to those who remained with their parents, and likely continued to experience maltreatment (Bernard, Butzin-Dozier, Rittenhouse, & Dozier, 2010). The HPA-axis is sensitive to environmental regulation during this period; therefore, an environment with decreased adversity (i.e., foster care) may allow the HPA-axis to function in a manner resembling that of typically developing children (i.e., steeper diurnal slopes). By contrast, previously institutionalized 4.5-year-old children who had been living with their adoptive parents for approximately three years exhibited elevated and prolonged cortisol responses to a challenge task in the presence of their caregiver; never-institutionalized children did not exhibit a cortisol response. Interestingly, both groups of children displayed a cortisol response to the challenge task in the presence of a stranger and their responses did not differ from each other (Fries et al., 2008). As described above, the relative hypo-responsive period of the HPA-axis may be mediated by nurturing caregiving. Given that the previously institutionalized children did not display attenuated cortisol responses in the presence of their caregivers, it is possible that placement in adoptive care may have occurred outside of the developmental period when environmental regulation is able to mitigate the effects of adversity exposure during infancy.

Collectively, these studies point to infancy as a possible sensitive period, especially in the absence of a nurturing caregiver. Yet, examination of the effects of adversity exposure at different ages in a single study is uncommon. The only true experiment to date (McLaughlin et al., 2015) supports the idea of a sensitive period during the first two years of life. In this study, orphan infants were randomized to receive care-as-usual (i.e., prolonged institutionalization) or foster care. At 12 years of age, youth placed in foster care before age two exhibited an enhanced cortisol response, which more closely resembled that of never-

institutionalized children (i.e., controls). Youth in prolonged institutionalization exhibited blunted cortisol responses to psychosocial stress. Similarly, in a study examining the relation between age of first adversity exposure and HPA-axis functioning, adversity exposure prior to age one was related to prolonged cortisol responses to an acute social stressor among adolescents (Kuhlman et al., 2015). Together, these two studies provide more compelling evidence for a sensitive period in which the developing HPA-axis is influenced by the caregiving environment during infancy prior to age 2.

Adversity exposure during middle childhood may also result in elevated cortisol, though the underlying process that results in this intermediate phenotype during this relatively quiescent period is not well understood. In cross-sectional analyses, exposure to inter-parental violence during the last 12 months and family adversity comprising of financial stress, parenting overload, marital conflict, expressions of angry and negative emotions, maternal depression, and harsh parenting, were related to higher levels of total cortisol output among 5-year-old children (Bair-Merritt et al., 2012; Bush et al., 2011). In another study, 8-year-olds exposed to marital violence had higher levels of afternoon cortisol compared to their non-exposed counterparts (Saltzman et al., 2005). These studies assessed adversity exposure and HPA-axis functioning during narrow periods of time. They do not elucidate potentially differing effects of timing of adversity on the HPA-axis. The unique short- and long-term effects of adversity during middle and late childhood on HPA-axis development and functioning are not well understood at this time.

There is a growing number of studies showing significant changes in HPA-axis functioning during adolescence. This suggests that the transition into adolescence and puberty may also be a sensitive period during which adversity exposure can have enduring effects on later HPA-axis functioning. However, adolescence is also a developmental phase characterized by increased sensitivity to the environment, operationalized by increased reactivity (Fuhrmann et al., 2015; e.g., Galván and McGlennen, 2013; Somerville et al., 2010). Thus, it is difficult to discern the enduring role of stressful experiences in functioning of physiological stress response systems in the context of this developmentally normative increase in sensitivity. As autonomy and sexual maturation increase over the course of adolescence, experiences during this transitional period may re-program the HPA-axis in a manner that is adaptive for the given and expected environment. Yet, very little work has been done on how adolescent stress may perturb HPA-axis functioning and development independent of earlier adversity exposure. One study showed that peer victimization within the last three months was associated with lower baseline cortisol among 12-year-olds (Vaillancourt et al., 2008). Likewise, in the context of subsequent acute stress, adversity exposure in the past month was related to blunted cortisol responses to the TSST among 9–12 year olds (Trickett et al., 2014). These cortisol patterns contrast the elevated patterns related to adversity exposure during infancy and childhood, though the reasons for this remain unclear. To our knowledge, there are no studies comparing the effects of adversity exposure during adolescence to those of adversity exposure during different developmental periods. Consequently, more studies are needed to characterize HPA-axis sensitivity to adversity exposure during adolescence.

As highlighted throughout this section, there is a paucity of research examining the role of adversity exposure timing on HPA-axis functioning. The majority of studies to date have

examined early adversity over a broad window of time (i.e., 0–18 years) and HPA-axis functioning in adulthood. A notable exception is a study examining the relation between adversities during different developmental periods and indices of HPA-axis functioning (Bosch et al., 2012). In this study, adversities during prenatal and early postnatal periods were related to heightened cortisol reactivity to a social stressor during adolescence. By contrast, adversity exposure during late childhood (6–11 years), early adolescence (12–13 years), and middle adolescence (14–15 years) was related to total cortisol output, but not cortisol reactivity. More specifically, adversity during late childhood was associated with greater cortisol output, whereas adversity during adolescence were associated with lower cortisol output. These findings are somewhat consistent with the studies reviewed above. It may be that adversity exposure during infancy leads to a hypersensitive HPA-axis whereas adversity exposure during adolescence may lead to hyposecretion of cortisol.

3.3.1 Development of inflammatory processes

Inflammatory processes in early life are distinct from those in adulthood, and may continue to exhibit change into adolescence. The inflammatory response in newborns has been characterized as hyporesponsive. For instance, newborn mice exhibited a decreased inflammatory response to infection compared to adult mice (Wynn et al., 2008). When stimulated with pathogens, monocytes from newborns produced lower levels of IL-6 and TNF- α as adult monocytes (Levy et al., 2004; Pillay et al., 1994; Yan et al., 2004). Localized downregulation of inflammatory cytokines has also been shown. Following traumatic brain injury, newborn mice exhibit lower concentrations of inflammatory cytokines, including anti-inflammatory IL-10, as well as pro-inflammatory IL-1 α and IL-6 compared to control mice without brain injury. This conflicts with the well-characterized neuroinflammation that occurs following traumatic brain injury among adults (Pena et al., 2014; Tajiri et al., 2014). Likewise, in response to LPS, splenic macrophages from newborn mice produced less IL-1 β , IL-6, TNF- α , and IL-12 compared to adult splenic macrophages monocytes (Chelvarajan et al., 2007, 2004). Interestingly, however, an attenuated inflammatory response has not always been observed. Some studies have found that LPS stimulation results in similar levels of TNF- α , IL-6, and IL-8 as in adults (Bernier et al., 2002; Dembinski et al., 2002; Seghaye et al., 1998), which may be an inconsistency that reflects differences in inflammatory sensitivity to different ligands or bacteria across the human lifespan (Levy et al., 2004; Mohamed et al., 2007).

Overall, early innate immunity may be characterized by attenuated inflammatory responses relative to those found in adults. This may protect against excessive inflammation that can compromise development and health. Specifically, inflammatory cytokines play a role in early neural development (Stolp, 2013; Yirmiya and Goshen, 2011), and rodent studies indicate that elevated inflammatory cytokines can have persistent negative effects on brain and behavior. For instance, experimentally-induced systemic inflammation during infancy leads to neuronal loss and delayed myelination for up to a week (Cardoso et al., 2015). Exposure to high levels of inflammation during infancy also has persistent effects on brain and behavior. In particular, systemic inflammation induced during infancy resulted in impaired axonal growth and demyelization, decreased hippocampal neurogenesis, repetitive behaviors, and deficits in social memory during the juvenile period (Lee et al., 2016).

Despite the detrimental effects that high levels of inflammation can have on the developing organism, mounting a robust inflammatory response in some contexts during early development may be adaptive. Innate immunity remains the primary defense against infection, as adaptive immunity takes much longer to develop. As such, having the capacity to mount a robust inflammatory response to particular microbial challenges during the neonatal period likely increases chances of survival.

Innate immunity continues to mature through childhood, although few studies directly test this. In a study of infants, 5-year-olds, 12-year-olds, and adults, PBMC production of IL-12 in response to bacterial challenge was shown to increase with age; however, stimulated production of IL-12 by 12 years of age was still substantially lower than in adults (Upham et al., 2002). Also, IL-12 responses to bacterial challenge in monocytes are positively correlated with age from birth to age 8 years (Härtel et al., 2005).

Studies of inflammatory responses in adolescence have also been relatively uncommon. Given that gonadal hormones are known to modulate immune functioning, inflammatory processes may continue to change throughout adolescence as a function of pubertal development. Circulating immune cells, including macrophages, and lymphoid tissue cells express receptors for gonadal hormones. When bound to androgen receptors, testosterone can downregulate synthesis of proinflammatory cytokines (D'Agostino et al., 1999; Li et al., 1993; Trigunaite et al., 2015), and stimulate secretion of anti-inflammatory cytokines (Liva and Voskuhl, 2001). The modulation of inflammatory processes by estrogen is more complex. Prior work has shown estrogen to be both anti- and pro-inflammatory and its effects may depend on a variety of factors, such as cell type, target organ, estrogen concentration, and expression of estrogen receptors (Straub, 2007). For instance, estrogen has been shown to increase secretion of IL-6 and IL-8 in dendritic cells derived from monocytes (Bengtsson et al., 2004) whereas estrogen receptor- α treatment inhibits TNF- α and IL-6 (Tiwari-Woodruff et al., 2007). In sum, inflammatory processes are immature during infancy, maturing throughout childhood, and interact with gonadal hormones during adolescence.

3.3.2 Timing of adversity and inflammation

The major differences in inflammatory processes among infants, youth, and adults point to the possibility that there are windows of susceptibility during which exposure to adversity may result in differential influences on inflammatory outcomes. Although the association between early adversity exposure and inflammation has been well-documented (See Baumeister et al., 2016; Miller et al., 2011 for review), the vast majority of studies have assessed early adversity exposure across multiple phases of child development, typically spanning infancy through adolescence. Similarly, rodent work focusing on the effects of early adversity on inflammatory markers has typically induced stress during postnatal days 2–20 (Figueiredo et al., 2016; O'Mahony et al., 2009; O'Malley et al., 2011; Roque et al., 2015). Nevertheless, there are studies hinting that the inflammatory consequences of adversity during development may vary as a function of timing of adversity exposure and these associations warrant further investigation.

There is some empirical evidence suggesting that adversity exposure very early in life, from birth to early childhood, may prime immune cells to have a pro-inflammatory tendency, resulting in an intermediate phenotype of enduring elevated inflammation. In particular, rodent studies have demonstrated that early adversity, including maternal separation and early infection, during infancy results in larger, activated microglia, resident immune cells in the brain that secrete inflammatory cytokines (Bilbo, 2013; Gracia-Rubio et al., 2015). Notably, in adulthood, a subsequent stressor can lead these activated microglia to secrete more pro-inflammatory cytokines (Bilbo, 2013). A couple of human studies have similarly shown that adversity very early in life is related to exaggerated inflammatory responses to challenge. For instance, 2-year-old children whose parents reported higher cumulative stress during the child's life exhibited heightened TNF- α responses to an allergen (Wright et al., 2004). Lower SES as indicated by parental occupation during a child's first five years of life has also been associated with exaggerated inflammatory responses to pathogens (Miller et al., 2009). Very early life may be a period during which adversity can program immune cells. Specifically, microglia in the central nervous system and monocytes/macrophages in the periphery may develop a pro-inflammatory tendency (Miller et al., 2011). A more nuanced understanding of these developmental processes and their lifelong health implications may contribute to effective prevention and transdiagnostic intervention targets.

Given that adolescence is another period of significant biological and psychosocial development, adversity during adolescence may prime immune cells and potentially have persistent effects on inflammation. For example, chronic peer stress has been related to enhanced cytokine production in response to bacterial challenge and chronic family stress was related to decreased glucocorticoid receptor sensitivity in immune cells among adolescent females (Ehrlich et al., 2016). Likewise, family chaos has also been associated with greater stimulated proinflammatory cytokine production among 13–16 year old adolescents (Schreier et al., 2014). An intervention study also showed that relative to a waitlist control, a 7-week family-oriented psychosocial intervention implemented among low-SES, 11-year-old youth resulted in lower markers of inflammation when youth were 19-years-old (Miller et al., 2014). This points to the possibility that less adversity during early adolescence may have long-term effects on inflammation.

With the exception of the studies described above examining the effects of adversity on inflammatory processes during relatively narrow windows of time, very few studies explicitly examine the role of timing. One exception is a population-based prospective study of over 4500 youth in which adversity in the past year and a half (i.e., maltreatment, separation from parent) was assessed approximately every 12 months from 18 month to eight years old and inflammation was assessed at ages 10 and 15 (Slopen et al., 2013). Adversity exposure during infancy was related to higher CRP at age 15 but not at age 10, which raises the question of why adversity during infancy would be related to inflammation during mid-adolescence but not late childhood. It could be that early adversity during infancy has long-term effects on inflammation, but that the relation may not emerge until later in life. That is, adversity during infancy may program immune cells to have a pro-inflammatory tendency which would be most readily observable at the intracellular and cellular levels by way of gene expression or in vitro stimulation. Effects of early adversity on circulating markers of inflammation may not become evident until later in life after

repeated activation of these primed and/or exaggerated proinflammatory responses to external stimuli. This remains an open question, as no study to our knowledge has directly tested the effects of early adversity on inflammation measured at multiple levels and during different developmental periods. Two studies have shown that early adversity during childhood and adolescence was related to greater expression of inflammatory-related genes and in vitro stimulation of inflammation, but not to circulating markers of inflammation in adolescents (Miller et al., 2009; Miller and Chen, 2010).

Slopen and colleagues (2013) also found that adversity during middle childhood (6–8 years) was related to higher CRP at both 10 and 15 years. One interpretation of these findings is that adversity during middle childhood has a particular impact on inflammatory processes during youth development. Alternatively, the effects of adversity may be rather short-lived and more proximal measures of adversity may be more predictive of inflammation. The fact that there are multiple interpretations of this finding underscores the importance of probing the role of timing in the inflammatory effects of adversity.

It is also important to consider whether the effects of early adversity on inflammation emerge only in the context of vulnerability factors. In support of this notion, a longitudinal study involving contemporaneous measured early family stress during the first five years of life found that early family stress was indirectly associated with circulating levels of inflammation through adiposity and smoking at 22–25 years of age (Raposa et al., 2014a). Given that inflammatory functioning does not remain static across youth development, it will be important for future studies to prospectively measure timing of adversity exposure and inflammation.

3.4 Summary of HPA-axis and inflammatory correlates of child adversity by timing

The relative immaturity of the HPA-axis and immune systems during infancy and their continued development through childhood and adolescence point to the possibility that functioning of these systems vary according to timing of adversity. In particular, adversity during infancy may result in exaggerated cortisol early in life, which over time could lead to glucocorticoid receptor insensitivity. This may contribute to the persistently elevated cortisol observed past infancy and into childhood. Because binding of cortisol to glucocorticoid receptors on immune cells downregulate inflammation, glucocorticoid receptor insensitivity may also contribute to heightened inflammation that we observe in relation to early adversity. Adversity during adolescence may also be an important time when the social environment becomes biologically embedded, with initial studies showing an association between adversity during adolescence and lower cortisol and elevated inflammation.

There is much that remains to be understood. First, there is a dearth of studies examining adversity in pediatric populations, with the large majority of studies assessing childhood maltreatment retrospectively in adults. Among the pediatric studies that have been published, few have focused on adversity exposure during narrow windows of time and most have been cross-sectional. Thus, from these studies, we do not know whether the observed cortisol and inflammation patterns are due only to recent adversity exposure, the greater perceived subsequent stress (Raposa et al., 2014b), or greater threat reactivity (Chiang et al., 2015) that is associated with childhood adversity exposure. Whether certain patterns persist

over time also remains unknown given the lack of prospective studies. For instance, continued exposure to high cortisol may eventually lead to glucocorticoid insensitivity (Cohen et al., 2012; Miller et al., 2002) and we might observe continued exaggerated and or prolonged elevations in cortisol later in the life course. Alternatively, the brain and body may have a compensatory mechanism that downregulates cortisol secretion after an initial period of hypersecretion (Heim et al., 2000; Miller et al., 2007). To this end, initial investigations in adolescent and young adult samples may be most informative as they may not yet reflect this compensation. An ideal study would involve repeated assessments of inflammatory and neuroendocrine stress reactivity during childhood, adolescence, and multiple times in adulthood to elucidate long-term effects and how timing of adversity may perturb HPA-axis and inflammatory processes throughout the life course.

4.1 Discussion

This review provides a translational animal-to-human framework from which to disentangle the role of childhood adversity type and timing on health through the HPA-axis and inflammation. Most importantly, the goal of this review is to increase collaboration and communication across researchers using experimental animal models and correlational human models, from basic to clinical and developmental science. We proposed that repeated social defeat (RSD) may be a useful animal analog for understanding the physiological consequences of childhood adversity involving physical trauma and injury, maternal separation may be useful for understanding disrupted caregiving environments, and chronic variable stress (CVS) may be useful for understanding the physiological consequences of living in an unpredictable developmental environment. Here we have reviewed the existing empirical support for the translation of results using these models into children and adults. Overall, there is a tendency for non-specific childhood adversity to be correlated with up-regulated HPA-axis output and elevated inflammation. However, distinct adversity subtypes reveal different underlying biological adaptations. For example, physical abuse and injury may be uniquely associated with exaggerated *activation* of the HPA-axis and inflammatory system during childhood, which persists as elevated inflammation and adrenal insensitivity to ACTH in adulthood. We also find evidence that disruptions in the caregiving environment are associated with impaired glucocorticoid *regulation*, and that repeated exposure to unpredictable stress may be associated with more frequent activation of the stress response systems, perhaps driven by increased neural sensitivity to threat. We also proposed that timing of adversity exposure may contribute to the variation in the effects of adversity on HPA-axis and inflammatory processes. Given the transition into a relative hypo-responsive period of the HPA-axis around the first year of life and major changes in HPA-axis functioning during adolescence, we highlighted these developmental periods as times when adversity may have profound implications for functioning of physiological stress response systems. Likewise, given the reliance of the organism on innate immunity very early in life and the flux of gonadal hormones during puberty, we suggested that adversity during these periods might have greater long-term consequences for inflammatory processes. Some studies begin to support these hypotheses, but to date, many of our translational hypotheses remain untested. The remaining discussion will address avenues for future research that could minimize this gap.

To understand how experiences during development “get under the skin” to promote disease onset and progression later in life, a better understanding of the biological salience of different types of adversity is necessary. The most obvious future direction for this research is to encourage reporting associations between total adversity, adversity timing and subtypes, and health-related biological markers. We know from several large epidemiological studies that childhood adversity predicts lifelong mental and physical illness in a dose-response manner (Caspi et al., 2014; Chapman et al., 2007; Kessler et al., 2010; Vachon, Krueger, Rogosch, & Cicchetti, 2015). A common approach to conducting this research has been to identify individuals with adversity exposure that is above an established health-risk threshold. Yet, a parallel line of experimental research has demonstrated that different types of stress vary in their salience to the key biological systems thought to mediate stress and negative health outcomes (e.g., Dickerson, Gable, Irwin, Aziz, & Kemeny, 2009; Dickerson & Kemeny, 2004; Kuhlman et al., 2014; Lopez-Duran, Hajal, Olson, Felt, & Vazquez, 2009). It is also becoming more and more clear that individuals vary in their sensitivity to stress in the developmental environment (Boyce and Ellis, 2005; Ellis et al., 2005; Ellis and Boyce, 2008; Obradović et al., 2010). Interrogating the role of type and timing of adversity experiences in key physiological domains may offer a more sophisticated look at how adversity contributes to stress sensitivity. To do this, a shift toward the use of large community samples with heterogeneity in child adversity will make detection of distinguishable associations between subtypes more feasible.

Perhaps the largest barrier to the recommendations for future studies in humans is measurement. Currently, there are several measures used to quantify childhood adversity exposure including the Childhood Trauma Questionnaire (Bernstein et al., 2003), Risky Families Questionnaire (Taylor et al., 2004), Early Trauma Inventory (Bremner et al., 2007), STRAIN (Slavich and Epel, 2010), and the LEDS (Brown and Harris, 1989). Many of the existing measures of child adversity and trauma exposure have subscales such as physical abuse, emotional abuse, sexual abuse, neglect, and traumatic events that occur by chance. Given the dramatic increase in information on the biological correlation and consequences of stress exposure, particularly during development, there is a need to develop subtypes of trauma exposure that fit within the biopsychosocial model of health. To date, no measure has developed subscales based on the salience of that event/exposure within a biopsychosocial model. For example, we know that socially-evaluative challenges are particularly salient to the HPA-axis (Dickerson and Kemeny, 2004). Yet, an examination of types of childhood adversity based on their degree of social evaluative threat hasn't been conducted. A central theme of the proposed model is that development of the HPA-axis and inflammatory systems are dynamic, at least until puberty. Until recently there were no measures of child adversity that explicitly aimed to characterize timing of abuse in a child's life. In fact, the Maltreatment and Abuse Chronology of Exposure (MACE) (Teicher and Parigger, 2015) is the first measure to directly assess timing of childhood maltreatment exposure within a developmental framework.

For simplicity, we have proposed that adversity experiences involve a single biologically salient element. This may be true for some adversity experiences during childhood, while others involve multiple biologically salient elements. The next step is to develop a system of measurement for adversity experiences that measure not only the occurrence of events in a

child's life, but also their impact. Within a developmental framework, stress sensitivity is highly dynamic and requires an approach that examines the interaction of type and timing of adversity on biobehavioral outcomes. For example, the first two years of life may be a sensitive period for physiological development, particularly for disruptions in the caregiving environment. There also may be patterns of child adversity that unfold over time in ways that are developmentally and biologically meaningful, which we currently have no standardized method of measuring. Creating measures that reflect the impact of experiences during development may be critical to our understanding of how adversity gets under the skin. In other words, experiences during childhood may be particularly physiologically meaningful if they result in a physical injury, disruption in caregiving, and/or were unpredictable for the child. This framework may then explain why some youth go on to demonstrate trajectories of resilience. For example, parental divorce is an "adverse childhood event," but may not have the same biological salience to the developing child if the subjective quality of the caregiving relationships remains intact. Evidence supporting this notion already exists in maternal buffering of stress, suggesting that nurturing parenting can buffer the effect of other types of stress (Gunnar, 1998; Hagan et al., 2010; Hostinar et al., 2014). Development of reliable and valid assessments of physiologically relevant domains of adversity in a child's life may be more consequential to health outcomes than event checklists with their well-known limitations (Monroe, 2008). This will help the field develop a discourse that goes beyond even the heterogeneity of types of exposure to further examine heterogeneity of psychological experience and biological salience within the same adversity. For example, it would be incorrect to assume that all children exposed to inter-parental violence also experience physical abuse or that their parents are unable to provide nurturing and supportive care. Likewise, experiences of peer bullying during childhood may vary in their psychological and physiological health consequences depending on whether the bullying involved physical threat or injury.

One particular challenge is to disentangle the effects of timing of adversity exposure from those of adversity duration. Individuals with adverse experiences in early life continue to perceive more stress, which may be attributed to how they appraise, select, and respond to their environments (Hazel, Hammen, Brennan, & Najman, 2008; Miller et al., 2011; Raposa et al., 2014). Early adversity such as maltreatment and poverty are often chronic. Consequently, earlier onset of exposure to adversity may simply be a marker of longer duration of adversity. That said, we know that family dynamics change over time (Tsai, Telzer, & Fuligni, 2013), especially from childhood to adolescence (Smetana, Campione-Barr, & Metzger, 2006).

Another area for further research is the use of developmental animal models of stress exposure. Among the proposed translational models presented here, only maternal separation is a developmental model. This is because the large majority of chronic or repeated stress paradigms used in animal models are limited to use with adult animals, thus limiting our understanding of how these paradigms may shape a developing system. And yet, studies on maternal separation and neurobiological effects vary in the exact timing of maternal separation, though it is typically implemented before postnatal day 20. As such, we know relatively little about timing effects within this window of time. In recent years developmental models of early infection, pollution, and impoverished nesting have

demonstrated robust alterations to the inflammatory system via enlarged microglia that have profound effects on memory and behavior (Bilbo and Schwarz, 2012). Indeed, distinct neural networks associated with psychopathology are more sensitive to cortisol and inflammation in children exposed to adversity (Nusslock and Miller, 2015), however these upstream processes are beyond the scope of the present review. In line with our proposed framework, different types of stressors differentially impact neuroplasticity (Teicher & Samson, 2016), specifically in the limbic system (Cohen et al., 2013; Wilson et al., 2015), and specifically with regard to processing of threat and rewards (McLaughlin et al., 2014b). Animal models examining the long-term HPA-axis and inflammatory consequences of different types of repeated stress occurring in different developmental phases would inform many of the questions posed here.

In conjunction with experimental animal models, there is need for funding and interdisciplinary efforts to conduct prospective, longitudinal studies with repeated assessments of adversity and physiological functioning from infancy into adulthood. Ideally, assessments would be relatively close in time (e.g., yearly) so as to minimize recall biases and gain precision in timing of exposure. Childhood adversity accounts for approximately 1/3 of all psychiatric disorders (Kessler et al., 2010) and contributes significantly to chronic physical conditions (Scott et al., 2011). Given continued converging evidence of the contribution of childhood adversity to the global burden of disease, understanding the pathways through which this occurs is of national importance. Identifying timing effects and potential sensitive periods during which adversity may have profound effects on neuroendocrine and inflammatory processes is critical to implementing effective screening within primary care and reveal the optimal time to implement prevention efforts.

Finally, the focused review of the literature provided here suggests the need for novel methodological approaches, such as paradigms designed to test recovery of the stress response system in addition to reactivity, and examination of both the inflammatory and HPA-axis systems in the same sample. A surface level review of the basic physiology demonstrates how dynamically these two systems collaborate (See Figure 2). Understanding how childhood adversity gets under the skin to promote health and disease will be delayed until the measurement of multiple systems becomes the norm rather than the exception. In fact, it may be the degree of covariation between psychological arousal, the HPA-axis, and inflammation that predicts long-term health outcomes. Maltreated youth demonstrate less symmetry between sympathetic and HPA-axis responses to acute stress than non-maltreated youth (Gordis et al., 2008). The timing of covariation of these systems is also of particular importance. Thus within-subject change in cortisol and inflammation over time may be a misunderstood window into how stress leads to diseases such as depression. The predominant approach to understanding psychobiological mechanisms through which stress leads to depression has been between-subjects. At the very least, emerging evidence that psychological and physical stressors have different physiological outcomes suggests that experiences during development contribute to individual differences in how our body responds to stressors. These individual differences may pertain to how robust our physiological response is, or how long it takes to recover. Yet, methods for disentangling exaggerated reactivity from impaired recovery have only recently reached the field (Kuhlman et al., 2015; Lopez-Duran et al., 2014). It is possible that stress leads to

depression when stressors occur before an organism has sufficient time to recover from a preceding stressor. Therefore within-subject differences in the time between stressors may interact with individual differences in stress response patterns to predict future depressive episodes. In support of this idea, the standardized protocols for repeated social defeat and chronic variable stress require repeated administration of the stress paradigm(s) over short periods of time. Presumably, this is because chronic stress paradigms fail if the gap between stressors is too long (Golden et al., 2011). Further testing of this possibility may need to occur outside of a laboratory and involve intensive repeated measures (IRM; See for example Repetti et al., 2015) of ambulatory physiological and psychological reactions and recovery from different types of life events.

4.2 Limitations

This developmental translational model of type and timing of child adversity exposure and peripheral markers of stress physiology is not without its limitations. First, translation of rodent models to humans is never direct. Our intent was to provide a framework to guide our understanding of the physiological consequences of exposure to different types of stress during childhood, which may ultimately inform the role of uniquely human psychological processes on stress. Further, there are some forms of childhood adversity that have no animal model analog. For this reason, and because sexual abuse involves invasive physical contact that may share biological salience with physical threat and injury we have subsumed human literature of the correlates of sexual abuse under physical trauma. Unfortunately, youth exposed to sexual abuse rarely experience this abuse in the absence of other adversities. Further exploration of the pathways outlined in this framework may further explain and contextualize observations that the neurodevelopmental correlates of childhood sexual abuse are different from other types of abuse. Overall, the three proposed animal models lack several important elements of human psychological stress that undoubtedly impact children. For example, physical abuse of children is most commonly perpetrated by their parents or a known adult, while the RSD paradigm makes use of a new intruder each time. Yet, in some ways this limitation allows the use of this model to truly disentangle the social component of developmental stress from the physical component. Another important limitation of the proposed animal models is that RSD and CVS are exclusively used in adult animals, while maternal separation paradigms are exclusively used in infancy. Validation of developmental stress models are needed that more closely approximate elements of childhood adversity and further inform our causal understanding of the role of stress in disease. Finally, we recognize that this model is narrow in developmental and physiological scope. For example, our developmental framework does not address the large and important literature on prenatal programming of the brain and behavior (Glover et al., 2010). We have conceptualized SNS activation as an input to the inflammatory arm of the immune system. There is also wealth of evidence establishing direct pathways between the SNS and physical health (Danese and McEwen, 2012; McLaughlin et al., 2014a; Seeman et al., 2001). Experimental and empirical tests of the proposed pathways will inform inclusion of additional biologically salient elements of developmental adversity, as well as expansion of this model to other systems and developmental periods.

Lastly, we did not review the differential effects of adversity on the brain. Significant and rapid neural development occurs in utero through adolescence, and a growing literature suggests that timing of adversity throughout the lifespan can have differential effects on neural regions (Gee and Casey, 2015; Lupien et al., 2009). More specifically, timing of adversity exposure may differentially affect limbic structures, including the amygdala, hippocampus, and prefrontal cortex. Importantly, these neural substrates are critically involved in stress processes and connected to the biological stress systems. As such, timing effects of adversity on neural development may also have implications for timing effects on more downstream physiological processes (Chiang et al., 2015). A multi-systems approach that includes assessment of the central nervous system, HPA-axis, and inflammatory processes at various time points throughout development may help us identify sensitive periods when adversity exposure may have the most profound effects.

We also have not included a review of the rich literature on genetic risk factors associated with negative health outcomes in children exposed to trauma and adversity. This literature has been thoroughly and carefully reviewed and goes beyond the scope of this review (See for example Nugent et al., 2011; Tyrka et al., 2013). Briefly, there is evidence to support that specific genetic risk factors can predispose an individual to psychopathology in the presence of increasing life stress. Candidate genetic risk factors play functional roles in serotonin transport, activation of the HPA-axis via corticotropin releasing hormone (CRH), glucocorticoid sensitivity, and production of brain derived neurotrophic factors (BDNF). It is notable that each of these identified risk factors has distinct links to functioning of the HPA-axis and inflammatory activity. Thus within the present model, it is likely that some individuals exposed to specific types of adversity during development may be more vulnerable than others. In fact, heterogeneity in adversity exposure in previous samples may explain inconsistent replication of gene-by-environment associations (Kim-Cohen et al., 2006; Munafò et al., 2009). Further, the predominant model to date has been to examine genetic vulnerability to disease in the context of cumulative life stress even though it is more likely that individuals carry genetic vulnerability to specific intermediate phenotypes within a complex system when exposed to relevant life stressors (See for example Tyrka et al., 2009). Pursuit of clarity in the role of type and timing in the HPA-axis and inflammatory processes we have described in this review may provide new avenues for exploring the interaction between genetic risk factors, specific types of adversity, and functioning of key physiological stress systems.

4.3 Conclusions

The purpose of this review was to drive progress in the field by proposing that the challenges of characterizing the impact of childhood adversity on health may be addressed by drawing upon well-characterized animal models through which distinct HPA-axis and inflammatory pathways can be elucidated within a developmental framework. Specifically, we identify the RSD paradigm and its physiological consequences as particularly helpful for understanding physical trauma, the maternal separation/deprivation paradigm for understanding disruptions in the early caregiving environment, and the CVS paradigm for understanding the physiological sequelae of growing up in an unpredictable environment. Exposure to adversity may be especially consequential during infancy and adolescence when major

changes occur in the HPA-axis and inflammatory processes. Different childhood adversities may lead to dysregulated HPA-axis functioning and elevated inflammation via distinct underlying mechanisms and that timing of adversity may contribute to variation in these linkages (See Figure 3). The pursuit of a better characterization of the role of type and timing of adversity warrants further investigation in both animals and humans, and more importantly, the collaboration between researchers in both arenas.

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References

- Adam EK, Gunnar MR. Relationship functioning and home and work demands predict individual differences in diurnal cortisol patterns in women. *Psychoneuroendocrinology*. 2001; 26:189–208. DOI: 10.1016/S0306-4530(00)00045-7 [PubMed: 11087964]
- Aguilera, G. The hypothalamic-pituitary-adrenal axis and neuroendocrine responses to stress. In: Fink, G.Pfaff, D., Levine, J., editors. *Handbook of Neuroendocrinology*. Academic Press; Oxford, UK: 2012. p. 175-196.
- Ahnert L, Gunnar MR, Lamb ME, Barthel M. Transition to child care: associations with infant-mother attachment, infant negative emotion, and cortisol elevations. *Child Dev*. 2004; 75:639.doi: 10.1111/j.1467-8624.2004.00698.x [PubMed: 15144478]
- Amick JE, Yandora KA, Bell MJ, Wisniewski SR, Adelson PD, Carcillo JA, Janesko KL, DeKosky ST, Carlos TM, Clark RS, et al. The Th1 versus Th2 cytokine profile in cerebrospinal fluid after severe traumatic brain injury in infants and children. *Pediatr. Crit. Care Med*. 2001; 2:260–264. [PubMed: 12793952]
- Anacker C, O'Donnell KJ, Meaney MJ. Early life adversity and the epigenetic programming of hypothalamic-pituitary-adrenal function. *Dialogues Clin. Neurosci*. 2014; 16:321–333. [PubMed: 25364283]
- Anda R, Felitti V, Bremner J, Walker J, Whitfield C, Perry B, Dube S, Giles W. The enduring effects of abuse and related adverse experiences in childhood. *Eur. Arch. Psychiatry Clin. Neurosci*. 2006; 256:174–186. DOI: 10.1007/s00406-005-0624-4 [PubMed: 16311898]
- Andersen S, Tomada A, Vincow E, Valente E, Polcari A, Teicher M. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. *J. Neuropsychiatry Clin. Neurosci*. 2008; 20:292–301. DOI: 10.1176/appi.neuropsych.20.3.292 [PubMed: 18806232]
- Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity? *Neurosci. Biobehav. Rev*. 2003; 27:3–18. DOI: 10.1016/S0149-7634(03)00005-8 [PubMed: 12732219]
- Antoni MH, Cruess S, Cruess DG, Kumar M, Lutgendorf S, Ironson G, Dettmer E, Williams J, Klimas N, Fletcher MA, Schneiderman N. Cognitive-behavioral stress management reduces distress and 24-hour urinary free cortisol output among symptomatic HIV-infected gay men. *Ann. Behav. Med*. 2000; 22:29–37. DOI: 10.1007/BF02895165 [PubMed: 10892526]
- Ashman SB, Dawson G, Panagiotides H, Yamada E, Wilkinson C. Stress Hormone Levels of Children of Depressed Mothers. *Dev. Psychopathol*. 2002; 14:333–349. DOI: 10.1017/S0954579402002080 [PubMed: 12030695]
- Avitsur R, Powell N, Padgett DA, Sheridan JF. Social interactions, stress, and immunity. *Immunol. Allergy Clin. North Am*. 2009; 29:285–293. DOI: 10.1016/j.iac.2009.02.006 [PubMed: 19389582]
- Avitsur R, Stark JL, Sheridan JF. Social Stress Induces Glucocorticoid Resistance in Subordinate Animals. *Horm. Behav*. 2001; 39:247–257. DOI: 10.1006/hbeh.2001.1653 [PubMed: 11374910]

- Bair-Merritt MH, Johnson SB, Okelo S, Page G. Intimate partner violence exposure, salivary cortisol, and childhood asthma. *Child Abuse Negl.* 2012; 36:596–601. DOI: 10.1016/j.chiabu.2011.12.002 [PubMed: 22858093]
- Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor- α . *Mol. Psychiatry.* 2016; 21:642.doi: 10.1038/mp.2015.67 [PubMed: 26033244]
- Belsky J, Ruttle PL, Boyce WT, Armstrong JM, Essex MJ. Early adversity, elevated stress physiology, accelerated sexual maturation, and poor health in females. *Dev. Psychol.* 2015; 51:816.doi: 10.1037/dev0000017 [PubMed: 25915592]
- Bengtsson AK, Ryan EJ, Giordano D, Magaletti DM, Clark EA. 17 β -estradiol (E2) modulates cytokine and chemokine expression in human monocyte-derived dendritic cells. *Blood.* 2004; 104:1404.doi: 10.1182/blood-2003-10-3380 [PubMed: 15142882]
- Berner R, Welter P, Brandis M. Cytokine expression of cord and adult blood mononuclear cells in response to *Streptococcus agalactiae*. *Pediatr. Res.* 2002; 51:304. [PubMed: 11861934]
- Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, Stokes J, Handelsman L, Medrano M, Desmond D, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse Negl.* 2003; 27:169–190. DOI: 10.1016/S0145-2134(02)00541-0 [PubMed: 12615092]
- Bertone-Johnson ER, Whitcomb BW, Missmer SA, Karlson EW, Rich-Edwards JW. Inflammation and early-life abuse in women. *Am. J. Prev. Med.* 2012; 43:611–620. DOI: 10.1016/j.amepre.2012.08.014 [PubMed: 23159256]
- Bilbo SD, FRANK A. BEACH AWARD: Programming of Neuroendocrine Function by Early-Life Experience: A Critical Role for the Immune System. *Horm. Behav.* 2013; 63:684.doi: 10.1016/j.yhbeh.2013.02.017 [PubMed: 23474365]
- Bilbo SD, Schwarz JM. The immune system and developmental programming of brain and behavior. *Front. Neuroendocrinol.* 2012; 33:267–286. DOI: 10.1016/j.yfrne.2012.08.006 [PubMed: 22982535]
- Black PH. Stress and the inflammatory response: A review of neurogenic inflammation. *Brain. Behav. Immun.* 2002; 16:622–653. DOI: 10.1016/S0889-1591(02)00021-1 [PubMed: 12480495]
- Blair C, Raver CC, Granger D, Mills-Koonce R, Hibel L. Allostatic and allostatic load in the context of poverty in early childhood. *Dev. Psychopathol.* 2011; 23:845–857. doi:10.1017/S0954579411000344. [PubMed: 21756436]
- Blum D, Chtarto A, Tenenbaum L, Brotchi J, Levivier M. Clinical potential of minocycline for neurodegenerative disorders. *Neurobiol. Dis.* 2004; 17:359–366. DOI: 10.1016/j.nbd.2004.07.012 [PubMed: 15571972]
- Blumenthal H, Leen-Feldner EW, Badour CL, Trainor CD, Babson KA. Pubertal maturation and cortisol level in response to a novel social environment among female adolescents. *J. Adolesc.* 2014; 37:893.doi: 10.1016/j.adolescence.2014.06.005 [PubMed: 25014316]
- Boch SJ, Ford JL. C-Reactive Protein Levels Among US Adults Exposed to Parental Incarceration. *Biol. Res. Nurs.* 2015; 17:574–584. DOI: 10.1177/1099800414564011 [PubMed: 25539769]
- Bosch NM, Riese H, Reijneveld SA, Bakker MP, Verhulst FC, Ormel J, Oldehinkel AJ. Timing matters: Long term effects of adversities from prenatal period up to adolescence on adolescents' cortisol stress response. The TRAILS study. *Psychoneuroendocrinology.* 2012; 37:1439–1447. DOI: 10.1016/j.psyneuen.2012.01.013 [PubMed: 22365483]
- Bower JE, Ganz PA, Irwin MR, Arevalo JMG, Cole SW. Fatigue and gene expression in human leukocytes: Increased NF- κ B and decreased glucocorticoid signaling in breast cancer survivors with persistent fatigue. *Brain. Behav. Immun.* 2011; 25:147–150. DOI: 10.1016/j.bbi.2010.09.010 [PubMed: 20854893]
- Bower JE, Greendale G, Crosswell AD, Garett D, Sternlieb B, Ganz PA, Irwin MR, Olmstead R, Arevalo J, Cole SW. Yoga reduces inflammatory signaling in fatigued breast cancer survivors: A randomized controlled trial. *Psychoneuroendocrinology.* 2014; 43:20–29. DOI: 10.1016/j.psyneuen.2014.01.019 [PubMed: 24703167]

- Bowers SL, Bilbo SD, Dhabhar FS, Nelson RJ. Stressor-specific alterations in corticosterone and immune responses in mice. *Brain. Behav. Immun.* 2008; 22:105–113. DOI: 10.1016/j.bbi.2007.07.012 [PubMed: 17890050]
- Boyce WT, Ellis B. Biological Sensitivity to Context: I. An Evolutionary–developmental Theory of the Origins and Functions of Stress Reactivity. *Dev. Psychopathol.* 2005; 17:271–301. DOI: 10.1017/S0954579405050145 [PubMed: 16761546]
- Brand SR, Brennan PA, Newport DJ, Smith AK, Weiss T, Stowe ZN. The impact of maternal childhood abuse on maternal and infant HPA axis function in the postpartum period. *Psychoneuroendocrinology.* 2010; 35:686–693. DOI: 10.1016/j.psyneuen.2009.10.009 [PubMed: 19931984]
- Bremner JD, Bolus R, Mayer EA. Psychometric properties of the Early Trauma Inventory–Self Report. *J. Nerv. Ment. Dis.* 2007; 195:211–218. DOI: 10.1097/01.nmd.0000243824.84651.6c [PubMed: 17468680]
- Brown, GW., Harris, TO. Life events and illness. Guilford Press; 1989.
- Buckley TM, Schatzberg AF. On the Interactions of the Hypothalamic–Pituitary–Adrenal (HPA) Axis and Sleep: Normal HPA Axis Activity and Circadian Rhythm, Exemplary Sleep Disorders. *J. Clin. Endocrinol. Metab.* 2005; 90:3106–3114. DOI: 10.1210/jc.2004-1056 [PubMed: 15728214]
- Bugental DB, Martorell GA, Barraza V. The hormonal costs of subtle forms of infant maltreatment. *Horm. Behav.* 2003; 43:237–244. DOI: 10.1016/S0018-506X(02)00008-9 [PubMed: 12614655]
- Bush NR, Obradovi J, Adler N, Boyce WT. Kindergarten stressors and cumulative adrenocortical activation: The “first straws” of allostatic load? *Dev. Psychopathol.* 2011; 23:1089–1106. DOI: 10.1017/S0954579411000514 [PubMed: 22018083]
- Cardoso FL, Herz J, Fernandes A, Rocha J, Sepodes B, Brito MA, McGavern DB, Brites D. Systemic inflammation in early neonatal mice induces transient and lasting neurodegenerative effects. *J. Neuroinflammation.* 2015; 12doi: 10.1186/s12974-015-0299-3
- Carpenter LL, Gawuga CE, Tyrka AR, Lee JK, Anderson GM, Price LH. Association between Plasma IL-6 Response to Acute Stress and Early-Life Adversity in Healthy Adults. *Neuropsychopharmacology.* 2010; 35:2617–2623. DOI: 10.1038/npp.2010.159 [PubMed: 20881945]
- Caspi A, Houts RM, Belsky DW, Goldman-Mellor SJ, Harrington H, Israel S, Meier MH, Ramrakha S, Shalev I, Poulton R, Moffitt TE. The p Factor One General Psychopathology Factor in the Structure of Psychiatric Disorders? *Clin. Psychol. Sci.* 2014; 2:119–137. DOI: 10.1177/2167702613497473 [PubMed: 25360393]
- Chapman DP, Dube SR, Anda RF. Adverse childhood events as risk factors for negative mental health outcomes. *Psychiatr. Ann.* 2007; 37:359–364.
- Chapman DP, Whitfield CL, Felitti VJ, Dube SR, Edwards VJ, Anda RF. Adverse childhood experiences and the risk of depressive disorders in adulthood. *J. Affect. Disord.* 2004; 82:217–225. DOI: 10.1016/j.jad.2003.12.013 [PubMed: 15488250]
- Chatzittofis A, Nordström P, Hellström C, Arver S, Åsberg M, Jokinen J. CSF 5-HIAA, cortisol and DHEAS levels in suicide attempters. *Eur. Neuropsychopharmacol.* 2013; 23:1280–1287. DOI: 10.1016/j.euroneuro.2013.02.002 [PubMed: 23453639]
- Chelvarajan L, Popa D, Liu Y, Getchell TV, Stromberg AJ, Bondada S. Molecular mechanisms underlying anti-inflammatory phenotype of neonatal splenic macrophages. *J. Leukoc. Biol.* 2007; 82:403–416. DOI: 10.1189/jlb.0107071 [PubMed: 17495050]
- Chelvarajan RL, Collins SM, Doubinskaia IE, Goes S, Van Willigen J, Flanagan D, de Villiers WJS, Bryson JS, Bondada S. Defective macrophage function in neonates and its impact on unresponsiveness of neonates to polysaccharide antigens. *J. Leukoc. Biol.* 2004; 75:982–994. DOI: 10.1189/jlb.0403179 [PubMed: 14982942]
- Chen E, Turiano NA, Mroczek DK, Miller GE. Association of reports of childhood abuse and all-cause mortality rates in women. *JAMA Psychiatry.* 2016; 73:920–927. DOI: 10.1001/jamapsychiatry.2016.1786 [PubMed: 27540997]
- Chiang JJ, Taylor SE, Bower JE. Early adversity, neural development, and inflammation. *Dev. Psychobiol.* 2015; 57:887.doi: 10.1002/dev.21329 [PubMed: 26369600]

- Chrousos GP. The Hypothalamic–Pituitary–Adrenal Axis and Immune-Mediated Inflammation. *N. Engl. J. Med.* 1995; 332:1351–1363. DOI: 10.1056/NEJM199505183322008 [PubMed: 7715646]
- Clements AD. Salivary cortisol measurement in developmental research: Where do we go from here? *Dev. Psychobiol.* 2012; 55:205–220. DOI: 10.1002/dev.21025 [PubMed: 22488016]
- Clow A, Hucklebridge F, Stalder T, Evans P, Thorn L. The cortisol awakening response: More than a measure of HPA axis function. *Neurosci. Biobehav. Rev.* 2010; 35:97–103. DOI: 10.1016/j.neubiorev.2009.12.011 [PubMed: 20026350]
- Coelho R, Viola TW, Walss-Bass C, Brietzke E, Grassi-Oliveira R. Childhood maltreatment and inflammatory markers: a systematic review. *Acta Psychiatr. Scand.* 2014; 129:180–192. DOI: 10.1111/acps.12217 [PubMed: 24205846]
- Cohen MM, Jing D, Yang RR, Tottenham N, Lee FS, Casey BJ. Early-life stress has persistent effects on amygdala function and development in mice and humans. *Proc. Natl. Acad. Sci.* 2013; 110:18274–18278. DOI: 10.1073/pnas.1310163110 [PubMed: 24145410]
- Cohen S, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, Turner RB. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proc. Natl. Acad. Sci.* 2012; 109:5995–5999. DOI: 10.1073/pnas.1118355109 [PubMed: 22474371]
- Cole SW. Social regulation of leukocyte homeostasis: The role of glucocorticoid sensitivity. *Brain. Behav. Immun.* 2008; 22:1049–1055. DOI: 10.1016/j.bbi.2008.02.006 [PubMed: 18394861]
- Cole SW, Conti G, Arevalo JMG, Ruggiero AM, Heckman JJ, Suomi SJ. Transcriptional modulation of the developing immune system by early life social adversity. *Proc. Natl. Acad. Sci.* 2012; 109:20578–20583. DOI: 10.1073/pnas.1218253109 [PubMed: 23184974]
- Cole SW, Hawkey LC, Arevalo JM, Sung CY, Rose RM, Cacioppo JT. Social regulation of gene expression in human leukocytes. *Genome Biol.* 2007; 8:R189.doi: 10.1186/gb-2007-8-9-r189 [PubMed: 17854483]
- Copeland WE, Wolke D, Lereya ST, Shanahan L, Worthman C, Costello EJ. Childhood bullying involvement predicts low-grade systemic inflammation into adulthood. *Proc. Natl. Acad. Sci.* 2014; 111:7570–7575. DOI: 10.1073/pnas.1323641111 [PubMed: 24821813]
- Cowell RA, Cicchetti D, Rogosch FA, Toth SL. Childhood maltreatment and its effect on neurocognitive functioning: Timing and chronicity matter. *Dev. Psychopathol.* 2015; 27:521.doi: 10.1017/S0954579415000139 [PubMed: 25997769]
- Creswell JD, Irwin MR, Burklund LJ, Lieberman MD, Arevalo JMG, Ma J, Breen EC, Cole SW. Mindfulness-Based Stress Reduction training reduces loneliness and pro-inflammatory gene expression in older adults: A small randomized controlled trial. *Brain. Behav. Immun.* 2012; 26:1095–1101. DOI: 10.1016/j.bbi.2012.07.006 [PubMed: 22820409]
- Crosswell AD, Bower JE, Ganz PA. Childhood Adversity and Inflammation in Breast Cancer Survivors. *Psychosom. Med.* 2014; 76:208–214. DOI: 10.1097/PSY.0000000000000041 [PubMed: 24632893]
- D’Agostino P, Milano S, Barbera C, Di Bella G, La Rosa M, Ferlazzo V, Farruggio R, Miceli DM, Miele M, Castagnetta L, et al. Sex hormones modulate inflammatory mediators produced by macrophages. *Ann. N. Y. Acad. Sci.* 1999; 876:426. [PubMed: 10415638]
- Danese A, Caspi A, Williams B, Ambler A, Sugden K, Mika J, Werts H, Freeman J, Pariante CM, Moffitt TE, Arseneault L. Biological embedding of stress through inflammation processes in childhood. *Mol. Psychiatry.* 2011; 16:244–246. DOI: 10.1038/mp.2010.5 [PubMed: 20157309]
- Danese A, Lewis SJ. Psychoneuroimmunology of early-life stress: The hidden wounds of childhood trauma? *Neuropsychopharmacology.* 2017; 42:99–114. doi: DOI: 10.1038/npp.2016.198 [PubMed: 27629365]
- Danese A, McEwen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiol. Behav.* 2012; 106:29.doi: 10.1016/j.physbeh.2011.08.019 [PubMed: 21888923]
- Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. *Proc. Natl. Acad. Sci.* 2007; 104:1319–1324. DOI: 10.1073/pnas.0610362104 [PubMed: 17229839]
- Davis EP, Granger DA. Developmental differences in infant salivary alpha-amylase and cortisol responses to stress. *Psychoneuroendocrinology.* 2009; 34:795.doi: 10.1016/j.psyneuen.2009.02.001 [PubMed: 19268476]

- De Kloet ER. Brain corticosteroid receptor balance and homeostatic control. *Front. Neuroendocrinol.* 1991; 12:95–164.
- Dembinski J, Behrendt D, Reinsberg J, Bartmann P. Endotoxin-stimulated production of IL-6 and IL-8 is increased in short-term cultures of whole blood from healthy term neonates. *Cytokine.* 2002; 18:116. [PubMed: 12096927]
- Dickerson SS, Gable SL, Irwin MR, Aziz N, Kemeny ME. Social-evaluative threat and proinflammatory cytokine regulation an experimental laboratory investigation. *Psychol. Sci.* 2009; 20:1237–1244. DOI: 10.1111/j.1467-9280.2009.02437.x [PubMed: 19754527]
- Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychol. Bull.* 2004; 130:355–391. DOI: 10.1037/0033-2909.130.3.355 [PubMed: 15122924]
- Dowd JB, Zajacova A, Aiello AE. Predictors of inflammation in US children aged 3–16 years. *Am. J. Prev. Med.* 2010; 39:314–320. DOI: 10.1016/j.amepre.2010.05.014 [PubMed: 20837281]
- Ehrlich KB, Miller GE, Rohleder N, Adam EK. Trajectories of relationship stress and inflammatory processes in adolescence. *Dev. Psychopathol.* 2016; 28:127.doi: 10.1017/S0954579415000334 [PubMed: 25851449]
- Ellis BJ, Boyce WT. Biological sensitivity to context. *Curr. Dir. Psychol. Sci.* 2008; 17:183–187. DOI: 10.1111/j.1467-8721.2008.00571.x
- Ellis BJ, Essex MJ, Boyce WT. Biological sensitivity to context: II. Empirical explorations of an evolutionary–developmental theory. *Dev. Psychopathol.* 2005; 2:303–328. DOI: 10.1017/S0954579405050157
- Engler H, Bailey MT, Engler A, Stiner-Jones LM, Quan N, Sheridan JF. Interleukin-1 receptor type 1-deficient mice fail to develop social stress-associated glucocorticoid resistance in the spleen. *Psychoneuroendocrinology.* 2008; 33:108.doi: 10.1016/j.psyneuen.2007.10.007 [PubMed: 18037570]
- Essex MJ, Klein MH, Cho E, Kalin NH. Maternal stress beginning in infancy may sensitize children to later stress exposure: effects on cortisol and behavior. *Biol. Psychiatry.* 2002; 52:776–784. DOI: 10.1016/S0006-3223(02)01553-6 [PubMed: 12372649]
- Evans GW, Kim P. Childhood Poverty and Health Cumulative Risk Exposure and Stress Dysregulation. *Psychol. Sci.* 2007; 18:953–957. DOI: 10.1111/j.1467-9280.2007.02008.x [PubMed: 17958708]
- Evans GW, Li D, Whipple SS. Cumulative risk and child development. *Psychol. Bull.* 2013; 139:1342.doi: 10.1037/a0031808 [PubMed: 23566018]
- Federenko I, Hellhammer D, Kirschbaum C, Schommer N, Wolf J, Wust S. The cortisol awakening response - normal values and confounds. *Noise Health.* 2000; 2:79–88.
- Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) Study. *Am. J. Prev. Med.* 1998; 14:245–258. DOI: 10.1016/S0749-3797(98)00017-8 [PubMed: 9635069]
- Figueiredo, Í., Frota, PB., da Cunha, DG., da Silva, RR., Canuto, KM., de Andrade, GM., Sousa, N., Moore, SR., Anstead, GM., Alvarez-Leite, JI., et al. *Nutr. Burbank Los Angel. Cty. Calif.*; 2016. Prolonged maternal separation induces undernutrition and systemic inflammation with disrupted hippocampal development in mice.
- Friedman EM, Karlamangla AS, Gruenewald TL, Koretz B, Seeman TE. Early life adversity and adult biological risk profiles. *Psychosom. Med.* 2015a; 77:176–185. DOI: 10.1097/PSY.000000000000147 [PubMed: 25650548]
- Friedman EM, Montez JK, Sheehan CM, Gruenewald TL, Seeman TE. Childhood adversities and adult cardiometabolic health: Does the quantity, timing, and type of adversity matter? *J. Aging Health.* 2015b; 27:1311–1338. DOI: 10.1177/0898264315580122 [PubMed: 25903978]
- Fries ABW, Shirtcliff EA, Pollak SD. Neuroendocrine dysregulation following early social deprivation in children. *Dev. Psychobiol.* 2008; 50:588.doi: 10.1002/dev.20319 [PubMed: 18683181]
- Fuhrmann D, Knoll LJ, Blakemore SJ. Adolescence as a sensitive period of brain development. *Trends Cogn. Sci.* 2015; 19:558. [PubMed: 26419496]

- Galván A, McGlennen KM. Enhanced striatal sensitivity to aversive reinforcement in adolescents versus adults. *J. Cogn. Neurosci.* 2013; 25:284–296. DOI: 10.1162/jocn_a_00326 [PubMed: 23163417]
- Gao W, Alcauter S, Smith JK, Gilmore J, Lin W. Development of human brain cortical network architecture during infancy. *Brain Struct. Funct.* 2015; 220:1173. doi: 10.1007/s00429-014-0710-3 [PubMed: 24469153]
- Gee DG, Casey BJ. The impact of developmental timing for stress and recovery. *Neurobiol. Stress.* 2015; 1:184. doi: 10.1016/j.yenstr.2015.02.001 [PubMed: 25798454]
- Glover V, O'Connor TG, O'Donnell K. Prenatal stress and the programming of the HPA axis. *Neurosci. Biobehav. Rev.* 2010; 35:17. doi: 10.1016/j.neubiorev.2009.11.008 [PubMed: 19914282]
- Golden SA, Iii HEC, Berton O, Russo SJ. A standardized protocol for repeated social defeat stress in mice. *Nat. Protoc.* 2011; 6:1183–1191. DOI: 10.1038/nprot.2011.361 [PubMed: 21799487]
- Gordis EB, Granger DA, Susman EJ, Trickett PK. Salivary alpha amylase–cortisol asymmetry in maltreated youth. *Horm. Behav.* 2008; 53:96–103. DOI: 10.1016/j.yhbeh.2007.09.002 [PubMed: 17945232]
- Gouirand AM, Matuszewich L. The effects of chronic unpredictable stress on male rats in the water maze. *Physiol. Behav.* 2005; 86:21–31. DOI: 10.1016/j.physbeh.2005.06.027 [PubMed: 16099481]
- Gracia-Rubio I, Moscoso-Castro M, Pozo OJ, Marcos J, Nadal R, Valverde O. Maternal separation induces neuroinflammation and long-lasting emotional alterations in mice. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 2015; 65:104. doi: 10.1016/j.pnpbp.2015.09.00 [PubMed: 26382758]
- Grønli J, Murison R, Fiske E, Bjorvatn B, Sørensen E, Portas CM, Ursin R. Effects of chronic mild stress on sexual behavior, locomotor activity and consumption of sucrose and saccharine solutions. *Physiol. Behav.* 2005; 84:571–577. DOI: 10.1016/j.physbeh.2005.02.007 [PubMed: 15811392]
- Gunnar M, Quevedo K. The neurobiology of stress and development. *Annu. Rev. Psychol.* 2007; 58:145–173. DOI: 10.1146/annurev.psych.58.110405.085605 [PubMed: 16903808]
- Gunnar MR. Quality of early care and buffering of neuroendocrine stress reactions: Potential effects on the developing human brain. *Prev. Med.* 1998; 27:208–211. DOI: 10.1006/pmed.1998.0276 [PubMed: 9578997]
- Gunnar MR, Brodersen L, Krueger K, Rigatuso J. Dampening of adrenocortical responses during infancy: normative changes and individual differences. *Child Dev.* 1996a; 67:877. [PubMed: 8706532]
- Gunnar MR, Brodersen L, Nachmias M, Buss K, Rigatuso J. Stress reactivity and attachment security. *Dev. Psychobiol.* 1996b; 29:191. doi: 10.1002/(SICI)1098-2302(199604)29:3<191::AID-DEV1>3.0.CO;2-M [PubMed: 8666128]
- Gunnar MR, Donzella B. Social regulation of the cortisol levels in early human development. *Psychoneuroendocrinology.* 2002; 27:199–220. DOI: 10.1016/S0306-4530(01)00045-2 [PubMed: 11750779]
- Gunnar MR, Larson MC, Hertsgaard L, Harris ML, Brodersen L. The stressfulness of separation among nine-month-old infants: effects of social context variables and infant temperament. *Child Dev.* 1992; 63:290. [PubMed: 1611934]
- Gunnar MR, Talge NM, Herrera A. Stressor paradigms in developmental studies: what does and does not work to produce mean increases in salivary cortisol. *Psychoneuroendocrinology.* 2009a; 34:953–967. DOI: 10.1016/j.psyneuen.2009.02.010 [PubMed: 19321267]
- Gunnar, MR., Vazquez, D. Stress neurobiology and developmental psychopathology. In: Cicchetti, D., Cohen, DJ., editors. *Developmental Psychopathology, Vol 2: Developmental Neuroscience.* 2. John Wiley & Sons Inc; Hoboken, NJ, US: 2006. p. 533-577.
- Gunnar MR, Wewerka S, Frenn K, Long JD, Griggs C. Developmental changes in hypothalamus-pituitary-adrenal activity over the transition to adolescence: normative changes and associations with puberty. *Dev. Psychopathol.* 2009b; 21:69–85. DOI: 10.1017/S0954579409000054 [PubMed: 19144223]
- Hagan MJ, Roubinov DS, Gress-Smith J, Luecken LJ, Sandler IN, Wolchik S. Positive parenting during childhood moderates the impact of recent negative events on cortisol activity in parentally

bereaved youth. *Psychopharmacology (Berl.)*. 2010; 214:231–238. DOI: 10.1007/s00213-010-1889-5 [PubMed: 20521029]

- Härtel C, Adam N, Strunk T, Temming P, Müller-Steinhardt M, Schultz C. Cytokine responses correlate differentially with age in infancy and early childhood. *Clin. Exp. Immunol.* 2005; 142:446.doi: 10.1111/j.1365-2249.2005.02928.x [PubMed: 16297156]
- Heim C, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology*. 2000; 25:1–35. [PubMed: 10633533]
- Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol. Psychiatry*. 2001; 49:1023–1039. DOI: 10.1016/S0006-3223(01)01157-X [PubMed: 11430844]
- Heim C, Newport DJ, Wagner D, Wilcox MM, Miller AH, Nemeroff CB. The role of early adverse experience and adulthood stress in the prediction of neuroendocrine stress reactivity in women: a multiple regression analysis. *Depress. Anxiety*. 2002; 15:117–125. DOI: 10.1002/da.10015 [PubMed: 12001180]
- Herman JP, Adams D, Prewitt C. Regulatory Changes in Neuroendocrine Stress-Integrative Circuitry Produced by a Variable Stress Paradigm. *Neuroendocrinology*. 1995; 61:180–190. DOI: 10.1159/000126839 [PubMed: 7753337]
- Hibel LC, Granger DA, Blair C, Cox MJ, The Family Life Project Key Investigators 3 6 5 7. Intimate partner violence moderates the association between mother-infant adrenocortical activity across an emotional challenge. *J. Fam. Psychol.* 2009 Oct.23:615–625. 2009. DOI: 10.1037/a0016323 [PubMed: 19803598]
- Hodes GE, Pfau ML, Leboeuf M, Golden SA, Christoffel DJ, Bregman D, Rebusi N, Heshmati M, Aleyasin H, Warren BL, et al. Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. *Proc. Natl. Acad. Sci. U. S. A.* 2014; 111:16136.doi: 10.1073/pnas.1415191111 [PubMed: 25331895]
- Holmes A, Wellman CL. Stress-induced prefrontal reorganization and executive dysfunction in rodents. *Neurosci. Biobehav. Rev.* 2009; 33:773–783. DOI: 10.1016/j.neubiorev.2008.11.005 [PubMed: 19111570]
- Hostinar CE, Gunnar MR. Future directions in the study of social relationships as regulators of the HPA axis across development. *J. Clin. Child Adolesc. Psychol.* 2013; 42:564.doi: 10.1080/15374416.2013.804387 [PubMed: 23746193]
- Hostinar CE, Johnson AE, Gunnar MR. Early social deprivation and the social buffering of cortisol stress responses in late childhood: An experimental study. *Dev. Psychol.* 2015; 51:1597.doi: 10.1037/dev0000029 [PubMed: 26322485]
- Hostinar CE, Sullivan RM, Gunnar MR. Psychobiological mechanisms underlying the social buffering of the hypothalamic–pituitary–adrenocortical axis: A review of animal models and human studies across development. *Psychol. Bull.* 2014; 140:256–282. DOI: 10.1037/a0032671 [PubMed: 23607429]
- Huang H, Shu N, Mishra V, Jeon T, Chalak L, Wang ZJ, Rollins N, Gong G, Cheng H, Peng Y, et al. Development of human brain structural networks through infancy and childhood. *Cereb. Cortex*. 2015; 25:1389.doi: 10.1093/cercor/bht335 [PubMed: 24335033]
- Irwin MR, Carrillo C, Olmstead R. Sleep loss activates cellular markers of inflammation: Sex differences. *Brain. Behav. Immun.* 2010; 24:54–57. DOI: 10.1016/j.bbi.2009.06.001 [PubMed: 19520155]
- Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. *Nat. Rev. Immunol.* 2011; 11:625.doi: 10.1038/nri3042 [PubMed: 21818124]
- Ivanov I, Yehuda R, Greenblatt E, Davidow J, Makotkine I, Alfi L, Newcorn JH. The effect of trauma on stress reactivity in aggressive youth. *Psychiatry Res.* 2011; 189:396–402. DOI: 10.1016/j.psychres.2011.05.046 [PubMed: 21684014]
- Kalinichev M, Easterling KW, Plotsky PM, Holtzman SG. Long-lasting changes in stress-induced corticosterone response and anxiety-like behaviors as a consequence of neonatal maternal separation in Long–Evans rats. *Pharmacol. Biochem. Behav.* 2002; 73:131–140. DOI: 10.1016/S0091-3057(02)00781-5 [PubMed: 12076732]

- Kant GJ, Eggleston T, Landman-Roberts L. Habituation to repeated stress is stressor specific. *Pharmacol. Biochem. Behav.* 1985; 22:631–634. DOI: 10.1016/0091-3057(85)90286-2 [PubMed: 2986182]
- Kertes DA, Gunnar MR, Madsen NJ, Long JD. Early deprivation and home basal cortisol levels: A study of internationally adopted children. *Dev. Psychopathol.* 2008; 20:473–491. DOI: 10.1017/S0954579408000230 [PubMed: 18423090]
- Kessler RC, McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM, Aguilar-Gaxiola S, Alhamzawi AO, Alonso J, Angermeyer M, Benjet C, Bromet E, Chatterji S, Girolamo G de, Demyttenaere K, Fayyad J, Florescu S, Gal G, Gureje O, Haro JM, Hu C, Karam EG, Kawakami N, Lee S, Lépine J-P, Ormel J, Posada-Villa J, Sagar R, Tsang A, Üstün TB, Vassilev S, Viana MC, Williams DR. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *Br. J. Psychiatry.* 2010; 197:378–385. DOI: 10.1192/bjp.bp.110.080499 [PubMed: 21037215]
- Kidd T, Carvalho LA, Steptoe A. The relationship between cortisol responses to laboratory stress and cortisol profiles in daily life. *Biol. Psychol.* 2014; 99:34–40. DOI: 10.1016/j.biopsycho.2014.02.010 [PubMed: 24582772]
- Kiess W, Meidert A, Dressendörfer RA, Schriever K, Kessler U, König A, Schwarz HP, Strasburger CJ. Salivary cortisol levels throughout childhood and adolescence: relation with age, pubertal stage, and weight. *Pediatr. Res.* 1995; 37:502. doi: 10.1203/00006450-199504000-00020 [PubMed: 7596692]
- Kim-Cohen J, Caspi A, Taylor A, Williams B, Newcombe R, Craig IW, Moffitt TE. MAOA, maltreatment, and gene–environment interaction predicting children’s mental health: new evidence and a meta-analysis. *Mol. Psychiatry.* 2006; 11:903–913. DOI: 10.1038/sj.mp.4001851 [PubMed: 16801953]
- Koss KJ, Hostinar CE, Donzella B, Gunnar MR. Social deprivation and the HPA axis in early development. *Psychoneuroendocrinology.* 2014; 50:1–13. DOI: 10.1016/j.psyneuen.2014.07.028 [PubMed: 25150507]
- Kuhlman KR, Geiss EG, Vargas I, Lopez-Duran NL. Differential associations between childhood trauma subtypes and adolescent HPA-axis functioning. *Psychoneuroendocrinology.* 2015a; 54:103–114. DOI: 10.1016/j.psyneuen.2015.01.020 [PubMed: 25704913]
- Kuhlman KR, Olson SL, Lopez-Duran NL. The development of preadolescent internalizing symptoms: examining the interplay between parenting and neuroendocrine stress reactivity. *Dev. Psychobiol.* 2014; 56:908–923. DOI: 10.1002/dev.21166 [PubMed: 24009085]
- Kuhlman KR, Vargas I, Geiss EG, Lopez-Duran NL. Age of trauma onset and HPA Axis dysregulation among trauma-exposed youth. *J. Trauma. Stress.* 2015b; 28doi: 10.1002/jts.22054/full
- Kumari M, Head J, Bartley M, Stansfeld S, Kivimäki M. Maternal separation in childhood and diurnal cortisol patterns in mid-life: findings from the Whitehall II study. *Psychol. Med.* 2013; 43:633–643. DOI: 10.1017/S0033291712001353 [PubMed: 22785027]
- Ladd CO, Owens MJ, Nemeroff CB. Persistent changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation. *Endocrinology.* 1996; 137:1212. [PubMed: 8625891]
- Larson MC, White BP, Cochran A, Donzella B, Gunnar M. Dampening of the cortisol response to handling at 3 months in human infants and its relation to sleep, circadian cortisol activity, and behavioral distress. *Dev. Psychobiol.* 1998; 33:327. [PubMed: 9846236]
- Laurent HK, Neiderhiser JM, Natsuaki MN, Shaw DS, Fisher PA, Reiss D, Leve LD. Stress system development from age 4.5 to 6: family environment predictors and adjustment implications of HPA activity stability versus change. *Dev. Psychobiol.* 2014; 56:340–354. DOI: 10.1002/dev.21103 [PubMed: 23400689]
- Lee JH, Espinera AR, Chen D, Choi K-E, Caslin AY, Won S, Pecoraro V, Xu G-Y, Wei L, Yu SP. Neonatal inflammatory pain and systemic inflammatory responses as possible environmental factors in the development of autism spectrum disorder of juvenile rats. *J. Neuroinflammation.* 2016; 13doi: 10.1186/s12974-016-0575-x
- Legro RS. Urinary Free Cortisol Increases in Adolescent Caucasian Females during Perimenarche. *J. Clin. Endocrinol. Metab.* 2003; 88:215–219. DOI: 10.1210/jc.2002-020256 [PubMed: 12519855]

- Levy O, Zarembek KA, Roy RM, Cywes C, Godowski PJ, Wessels MR. Selective impairment of TLR-mediated innate immunity in human newborns: neonatal blood plasma reduces monocyte TNF- α induction by bacterial lipopeptides, lipopolysaccharide, and imiquimod, but preserves the response to R-848. *J. Immunol. Baltim. Md* 1950. 2004; 173:4627.
- Lewis M, Ramsay DS. Developmental change in infants' responses to stress. *Child Dev.* 1995; 66:657. [PubMed: 7789193]
- Li L, Power C, Kelly S, Kirschbaum C, Hertzman C. Life-time socio-economic position and cortisol patterns in mid-life. *Psychoneuroendocrinology.* 2007; 32:824–833. DOI: 10.1016/j.psyneuen.2007.05.014 [PubMed: 17644268]
- Li ZG, Danis VA, Brooks PM. Effect of gonadal steroids on the production of IL-1 and IL-6 by blood mononuclear cells in vitro. *Clin. Exp. Rheumatol.* 1993; 11:157. [PubMed: 8508557]
- Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A, Sharma S, Pearson D, Plotsky PM, Meaney MJ. Maternal Care, Hippocampal Glucocorticoid Receptors, and Hypothalamic-Pituitary-Adrenal Responses to Stress. *Science.* 1997; 277:1659–1662. DOI: 10.1126/science.277.5332.1659 [PubMed: 9287218]
- Liva SM, Voskuhl RR. Testosterone acts directly on CD4+ T lymphocytes to increase IL-10 production. *J. Immunol. Baltim. Md* 1950. 2001; 167:2060.
- Lopez-Duran NL, Hajal NJ, Olson SL, Felt BT, Vazquez DM. Individual differences in cortisol responses to fear and frustration during middle childhood. *J. Exp. Child Psychol.* 2009a; 103:285–295. DOI: 10.1016/j.jecp.2009.03.008 [PubMed: 19410263]
- Lopez-Duran NL, Mayer SE, Abelson JL. Modeling neuroendocrine stress reactivity in salivary cortisol: adjusting for peak latency variability. *Stress.* 2014; 17:285–295. DOI: 10.3109/10253890.2014.915517 [PubMed: 24754834]
- Lopez-Duran NL, Olson SA, Felt B, Vazquez DM. An Integrative Approach to the Neurophysiology of Emotion Regulation: The Case of Social Withdrawal. *Biopsychosoc. Regul. Process. Dev. Child. Behav. Probl.* 2009b; 57
- Lovejoy MC, Graczyk PA, O'Hare E, Neuman G. Maternal depression and parenting behavior: a meta-analytic review. *Clin. Psychol. Rev.* 2000; 20:561. [PubMed: 10860167]
- Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat. Rev. Neurosci.* 2009; 10:434–445. DOI: 10.1038/nrn2639 [PubMed: 19401723]
- Maier SF, Seligman ME. Learned helplessness: Theory and evidence. *J. Exp. Psychol. Gen.* 1976; 105:3–46. DOI: 10.1037/0096-3445.105.1.3
- Majidi J, Kosari-Nasab M, Salari A-A. Developmental minocycline treatment reverses the effects of neonatal immune activation on anxiety- and depression-like behaviors, hippocampal inflammation, and HPA axis activity in adult mice. *Brain Res. Bull.* 2016; 120:1–13. DOI: 10.1016/j.brainresbull.2015.10.009 [PubMed: 26521068]
- McEwen BS. The Brain on Stress Toward an Integrative Approach to Brain, Body, and Behavior. *Perspect. Psychol. Sci.* 2013; 8:673–675. DOI: 10.1177/1745691613506907 [PubMed: 25221612]
- McEwen BS. Stress, Adaptation, and Disease: Allostasis and Allostatic Load. *Ann. N. Y. Acad. Sci.* 1998; 840:33–44. DOI: 10.1111/j.1749-6632.1998.tb09546.x [PubMed: 9629234]
- McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, Turecki G, Meaney MJ. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat. Neurosci.* 2009; 12:342–348. DOI: 10.1038/nn.2270 [PubMed: 19234457]
- McLaughlin KA, Sheridan MA, Alves S, Mendes WB. Child maltreatment and autonomic nervous system reactivity: identifying dysregulated stress reactivity patterns by using the biopsychosocial model of challenge and threat. *Psychosom. Med.* 2014a; 76:538.doi: 10.1097/PSY.000000000000098 [PubMed: 25170753]
- McLaughlin KA, Sheridan MA, Lambert HK. Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. *Neurosci. Biobehav. Rev.* 2014b; 47:578.doi: 10.1016/j.neubiorev.2014.10.012 [PubMed: 25454359]

- McLaughlin KA, Sheridan MA, Tibu F, Fox NA, Zeanah CH, Nelson CA. Causal effects of the early caregiving environment on development of stress response systems in children. *Proc. Natl. Acad. Sci.* 2015; 112:5637–5642. DOI: 10.1073/pnas.1423363112 [PubMed: 25902515]
- Merlot E, Moze E, Dantzer R, Neveu PJ. Importance of fighting in the immune effects of social defeat. *Physiol. Behav.* 2003; 80:351–357. [PubMed: 14637235]
- Miller AH, Maletic V, Raison CL. Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression. *Biol. Psychiatry, Social Stresses and Depression.* 2009; 65:732–741. DOI: 10.1016/j.biopsych.2008.11.029
- Miller GE, Brody GH, Yu T, Chen E. A family-oriented psychosocial intervention reduces inflammation in low-SES African American youth. *Proc. Natl. Acad. Sci.* 2014; 111:11287–11292. DOI: 10.1073/pnas.1406578111 [PubMed: 25049403]
- Miller GE, Chen E. The Biological Residue of Childhood Poverty. *Child Dev. Perspect.* 2013; 7:67–73. DOI: 10.1111/cdep.12021 [PubMed: 24032051]
- Miller GE, Chen E. Harsh Family Climate in Early Life Presages the Emergence of a Proinflammatory Phenotype in Adolescence. *Psychol. Sci.* 2010; doi: 10.1177/0956797610370161
- Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF, Cole S, Kobor MS. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. *Proc. Natl. Acad. Sci.* 2009; 106:14716–14721. DOI: 10.1073/pnas.0902971106 [PubMed: 19617551]
- Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. *Psychol. Bull.* 2011; 137:959–997. DOI: 10.1037/a0024768 [PubMed: 21787044]
- Miller GE, Chen E, Zhou ES. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychol. Bull.* 2007; 133:25–45. [PubMed: 17201569]
- Miller GE, Cohen S, Ritchey AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: A glucocorticoid-resistance model. *Health Psychol.* 2002; 21:531–541. DOI: 10.1037/0278-6133.21.6.531 [PubMed: 12433005]
- Miller GE, Cole SW. Clustering of Depression and Inflammation in Adolescents Previously Exposed to Childhood Adversity. *Biol. Psychiatry, Endocrinology, Epigenetics, Extinction, and Early Life Traumatization.* 2012; 72:34–40. DOI: 10.1016/j.biopsych.2012.02.034
- Mohamed MA, Cunningham-Rundles S, Dean CR, Hammad TA, Nesin M. Levels of pro-inflammatory cytokines produced from cord blood in-vitro are pathogen dependent and increased in comparison to adult controls. *Cytokine.* 2007; 39:171. [PubMed: 17884557]
- Monnet-Tschudi F, Defaux A, Braissant O, Cagnon L, Zurich M-G. Methods to assess neuroinflammation. *Curr. Protoc. Toxicol.* Chapter 12, Unit12.19. 2011; doi: 10.1002/0471140856.tx1219s50
- Monroe SM. Modern approaches to conceptualizing and measuring human life stress. *Annu. Rev. Clin. Psychol.* 2008; 4:33. doi: 10.1146/annurev.clinpsy.4.022007.141207 [PubMed: 17716038]
- Munafò MR, Durrant C, Lewis G, Flint J. Gene × Environment Interactions at the Serotonin Transporter Locus. *Biol. Psychiatry, Epigenetic Mechanisms in Psychiatry.* 2009; 65:211–219. DOI: 10.1016/j.biopsych.2008.06.009
- Nachmias M, Gunnar M, Mangelsdorf S, Parritz RH, Buss K. Behavioral inhibition and stress reactivity: the moderating role of attachment security. *Child Dev.* 1996; 67:508. [PubMed: 8625725]
- Netherton C, Goodyer I, Tamplin A, Herbert J. Salivary cortisol and dehydroepiandrosterone in relation to puberty and gender. *Psychoneuroendocrinology.* 2004; 29:125–140. DOI: 10.1016/S0306-4530(02)00150-6 [PubMed: 14604596]
- Nicolson NA. Childhood parental loss and cortisol levels in adult men. *Psychoneuroendocrinology.* 2004; 29:1012–1018. DOI: 10.1016/j.psychneuen.2003.09.005 [PubMed: 15219652]
- Nugent NR, Tyrka AR, Carpenter LL, Price LH. Gene–environment interactions: early life stress and risk for depressive and anxiety disorders. *Psychopharmacology (Berl.).* 2011; 214:175–196. DOI: 10.1007/s00213-010-2151-x [PubMed: 21225419]

- Nusslock R, Miller GE. Early-Life Adversity and Physical and Emotional Health Across the Lifespan: A Neuroimmune Network Hypothesis. *Biol. Psychiatry*. 2015; doi: 10.1016/j.biopsych.2015.05.017
- Obradovi J, Bush NR, Stamperdahl J, Adler NE, Boyce WT. Biological Sensitivity to Context: The Interactive Effects of Stress Reactivity and Family Adversity on Socioemotional Behavior and School Readiness. *Child Dev*. 2010; 81:270–289. DOI: 10.1111/j.1467-8624.2009.01394.x [PubMed: 20331667]
- O'Connor JC, Lawson MA, André C, Moreau M, Lestage J, Castanon N, Kelley KW, Dantzer R. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. *Mol. Psychiatry*. 2009; 14:511–522. DOI: 10.1038/sj.mp.4002148 [PubMed: 18195714]
- O'Connor M-F, Bower JE, Cho HJ, Creswell JD, Dimitrov S, Hamby ME, Hoyt MA, Martin JL, Robles TF, Sloan EK, Thomas KS, Irwin MR. To assess, to control, to exclude: Effects of biobehavioral factors on circulating inflammatory markers. *Brain. Behav. Immun*. 2009; 23:887–897. DOI: 10.1016/j.bbi.2009.04.005 [PubMed: 19389469]
- O'Connor TG, Moynihan JA, Caserta MT. Annual Research Review: The neuroinflammation hypothesis for stress and psychopathology in children – developmental psychoneuroimmunology. *J. Child Psychol. Psychiatry*. 2014; 55:615–631. DOI: 10.1111/jcpp.12187 [PubMed: 24372371]
- O'Mahony SM, Marchesi JR, Scully P, Codling C, Ceolho AM, Quigley EM, Cryan JF, Dinan TG. Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses. *Biol. Psychiatry*. 2009; 65:263. doi: 10.1016/j.biopsych.2008.06.026
- O'Malley D, Liston M, Hyland NP, Dinan TG, Cryan JF. Colonic soluble mediators from the maternal separation model of irritable bowel syndrome activate submucosal neurons via an interleukin-6-dependent mechanism. *Am. J. Physiol. Gastrointest. Liver Physiol*. 2011; 300:G241. doi: 10.1152/ajpgi.00385.2010 [PubMed: 21109592]
- Pacák K. Stressor-specific activation of the hypothalamic-pituitary-adrenocortical axis. *Physiol. Res. Sci. Bohemoslov*. 1999; 49:S11–7.
- Pacák K, Palkovits M, Kvetnanský R, Yadid G, Kopin IJ, Goldstein DS. Effects of various stressors on in vivo norepinephrine release in the hypothalamic paraventricular nucleus and on the pituitary-adrenocortical axis. *Ann. N. Y. Acad. Sci*. 1995; 771:115–130. [PubMed: 8597392]
- Pacák K, Palkovits M, Yadid G, Kvetnansky R, Kopin IJ, Goldstein DS. Heterogeneous neurochemical responses to different stressors: a test of Selye's doctrine of nonspecificity. *Am. J. Physiol. - Regul. Integr. Comp. Physiol*. 1998; 275:R1247–R1255.
- Packard CJ, Bezlyak V, McLean JS, Batty DG, Ford I, Burns H, Cavanagh J, Deans KA, Henderson M, McGinty A, et al. Early life socioeconomic adversity is associated in adult life with chronic inflammation, carotid atherosclerosis, poorer lung function and decreased cognitive performance: a cross-sectional, population-based study. 2011; doi: 10.1186/1471-2458-11-42
- Pena ID, Sanberg PR, Acosta S, Tajiri N, Lin S-Z, Borlongan CV. Stem cells and G-CSF for treating neuroinflammation in traumatic brain injury: aging as a comorbidity factor. *J. Neurosurg. Sci*. 2014; 58:145. [PubMed: 24844175]
- Pereira J, Vickers K, Atkinson L, Gonzalez A, Wekerle C, Levitan R. Parenting stress mediates between maternal maltreatment history and maternal sensitivity in a community sample. *Child Abuse Negl*. 2012; 36:433. doi: 10.1016/j.chiabu.2012.01.006 [PubMed: 22633056]
- Pillay V, Savage N, Laburn H. Circulating cytokine concentrations and cytokine production by monocytes from newborn babies and adults. *Pflüg. Arch*. 1994; 428:197–201.
- Plotsky PM, Meaney MJ. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Mol. Brain Res*. 1993; 18:195–200. DOI: 10.1016/0169-328X(93)90189-V [PubMed: 8497182]
- Powell ND, Sloan EK, Bailey MT, Arevalo JMG, Miller GE, Chen E, Kobor MS, Reader BF, Sheridan JF, Cole SW. Social stress up-regulates inflammatory gene expression in the leukocyte transcriptome via β -adrenergic induction of myelopoiesis. *Proc. Natl. Acad. Sci*. 2013; 110:16574–16579. DOI: 10.1073/pnas.1310655110 [PubMed: 24062448]

- Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology*. 2003; 28:916–931. DOI: 10.1016/S0306-4530(02)00108-7 [PubMed: 12892658]
- Qiu A, Mori S, Miller MI. Diffusion tensor imaging for understanding brain development in early life. *Annu. Rev. Psychol.* 2015; 66:853. doi: 10.1146/annurev-psych-010814-015340 [PubMed: 25559117]
- Raposa EB, Bower JE, Hammen CL, Najman JM, Brennan PA. A Developmental Pathway From Early Life Stress to Inflammation The Role of Negative Health Behaviors. *Psychol. Sci.* 2014a; 25:1268–1274. DOI: 10.1177/0956797614530570 [PubMed: 24760142]
- Raposa EB, Hammen CL, Brennan PA, O’Callaghan F, Najman JM. Early adversity and health outcomes in young adulthood: the role of ongoing stress. *Health Psychol.* 2014b; 33:410. doi: 10.1037/a0032752 [PubMed: 23730716]
- Reader BF, Jarrett BL, McKim DB, Wohleb ES, Godbout JP, Sheridan JF. Peripheral and central effects of repeated social defeat stress: Monocyte trafficking, microglial activation, and anxiety. *Neuroscience*. 2015; 289:429–442. DOI: 10.1016/j.neuroscience.2015.01.001 [PubMed: 25596319]
- Repetti RL, Reynolds BM, Sears MS. Families Under the Microscope: Repeated Sampling of Perceptions, Experiences, Biology, and Behavior. *J. Marriage Fam.* 2015; 77:126–146. DOI: 10.1111/jomf.12143
- Repetti RL, Taylor SE, Seeman TE. Risky families: Family social environments and the mental and physical health of offspring. *Psychol. Bull.* 2002 Mar.128:330–366. 2002. DOI: 10.1037/0033-2909.128.2.330 [PubMed: 11931522]
- Ridker PM. Clinical Application of C-Reactive Protein for Cardiovascular Disease Detection and Prevention. *Circulation*. 2003; 107:363–369. DOI: 10.1161/01.CIR.0000053730.47739.3C [PubMed: 12551853]
- Romeo RD. Adolescence: a central event in shaping stress reactivity. *Dev. Psychobiol.* 2010; 52:244. doi: 10.1002/dev.20437 [PubMed: 20175102]
- Rooks C, Veledar E, Goldberg J, Bremner JD, Vaccarino V. Early Trauma and Inflammation: Role of Familial Factors in a Study of Twins. *Psychosom. Med.* 2012; 74:146–152. DOI: 10.1097/PSY.0b013e318240a7d8 [PubMed: 22286843]
- Roque A, Ochoa-Zarzosa A, Torner L. Maternal separation activates microglial cells and induces an inflammatory response in the hippocampus of male rat pups, independently of hypothalamic and peripheral cytokine levels. *Brain. Behav. Immun.* 2015; doi: 10.1016/j.bbi.2015.09.017
- Roque S, Mesquita AR, Palha JA, Sousa N, Correia-Neves M. The behavioral and immunological impact of maternal separation: a matter of timing. *Front. Behav. Neurosci.* 2014; 8:192. doi: 10.3389/fnbeh.2014.00192 [PubMed: 24904343]
- Rosenfeld P, Suchecki D, Levine S. Multifactorial regulation of the hypothalamic-pituitary-adrenal axis during development. *Neurosci. Biobehav. Rev.* 1992; 16:553. [PubMed: 1480351]
- Saltzman KM, Holden GW, Holahan CJ. The psychobiology of children exposed to marital violence. *J. Clin. Child Adolesc. Psychol.* 2005; 34:129–139. DOI: 10.1207/s15374424jccp3401_12 [PubMed: 15677287]
- Sapolsky RM, Meaney MJ, McEwen BS. The development of the glucocorticoid receptor system in the rat limbic brain. III. Negative-feedback regulation. *Dev. Brain Res.* 1985; 18:169–173. DOI: 10.1016/0165-3806(85)90261-5
- Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr. Rev.* 2000; 21:55–89. DOI: 10.1210/er.21.1.55 [PubMed: 10696570]
- Schreier HM, Roy LB, Frimer LT, Chen E. Family chaos and adolescent inflammatory profiles: the moderating role of socioeconomic status. *Psychosom. Med.* 2014; 76:460. doi:10.1097/PSY.000000000000078. [PubMed: 24979577]
- Scott KM, Von Korff M, Angermeyer MC, et al. Association of childhood adversities and early-onset mental disorders with adult-onset chronic physical conditions. *Arch. Gen. Psychiatry.* 2011; 68:838–844. DOI: 10.1001/archgenpsychiatry.2011.77 [PubMed: 21810647]

- Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proc. Natl. Acad. Sci.* 2001; 98:4770–4775. DOI: 10.1073/pnas.081072698 [PubMed: 11287659]
- Seghaye MC, Heyl W, Grabitz RG, Schumacher K, von Bernuth G, Rath W, Duchateau J. The production of pro-and anti-inflammatory cytokines in neonates assessed by stimulated whole cord blood culture and by plasma levels at birth. *Biol. Neonate.* 1998; 73:220. [PubMed: 9551188]
- Seltzer LJ, Ziegler TE, Pollak SD. Social vocalizations can release oxytocin in humans. *Proc. R. Soc. B Biol. Sci.* 2010; 277:2661. doi: 10.1098/rspb.2010.0567
- Selye H. The physiology and pathology of exposure to stress. *Montr. Acta Medica Publ.* 1950
- Shackman JE, Shackman AJ, Pollak SD. Physical abuse amplifies attention to threat and increases anxiety in children. *Emot. Wash. DC.* 2007; 7:838. doi: 10.1037/1528-3542.7.4.838
- Sheridan MA, McLaughlin KA. Dimensions of early experience and neural development: deprivation and threat. *Trends Cogn. Sci.* 2014; 18:580–585. DOI: 10.1016/j.tics.2014.09.001 [PubMed: 25305194]
- Shirtcliff EA, Allison AL, Armstrong JM, Slattery MJ, Kalin NH, Essex MJ. Longitudinal stability and developmental properties of salivary cortisol levels and circadian rhythms from childhood to adolescence. *Dev. Psychobiol.* 2012; 54:493–502. DOI: 10.1002/dev.20607 [PubMed: 21953537]
- Silverman MN, Pearce BD, Biron CA, Miller AH. Immune modulation of the hypothalamic-pituitary-adrenal (HPA) axis during viral infection. *Viral Immunol.* 2005; 18:41. doi: 10.1089/vim.2005.18.41 [PubMed: 15802953]
- Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. *Proc. R. Soc. B Biol. Sci.* 2015; 282:doi: 10.1098/rspb.2014.3085
- Simpkiss JL, Devine DP. Responses of the HPA axis after chronic variable stress: effects of novel and familiar stressors. *Neuroendocrinol. Lett.* 2003; 24:97–103. [PubMed: 12743542]
- im ek , Yüksel T, Kaplan , Uysal C, Alaca R. Examining the levels of BDNF and cortisol in children and adolescent victims of sexual abuse-a preliminary study. *Compr. Psychiatry.* 2015; 61:23. doi: 10.1016/j.comppsy.2015.04.013 [PubMed: 25982069]
- Slavich, GM., Epel, ES. The Stress and Adversity Inventory (STRAIN): An automated system for assessing cumulative stress exposure. *Los Angel. Univ. Calif; Los Angel.* 2010.
- Slopen N, Kubzansky LD, McLaughlin KA, Koenen KC. Childhood adversity and inflammatory processes in youth: A prospective study. *Psychoneuroendocrinology.* 2013; 38:188–200. DOI: 10.1016/j.psyneuen.2012.05.013 [PubMed: 22727478]
- Smith SM, Vale WW. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. *Dialogues Clin. Neurosci.* 2006; 8:383–395. [PubMed: 17290797]
- Somerville LH, Jones RM, Casey BJ. A time of change: Behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. *Brain Cogn., Adolescent Brain Development: Current Themes and Future Directions.* 2010; 72:124–133. DOI: 10.1016/j.bandc.2009.07.003
- Spangler G. Emotional and adrenocortical responses of infants to the strange situation: The differential function of emotional expression. *Int. J. Behav. Dev.* 1998; 22:681–706.
- Sripada RK, Swain JE, Evans GW, Welsh RC, Liberzon I. Childhood Poverty and Stress Reactivity Are Associated with Aberrant Functional Connectivity in Default Mode Network. *Neuropsychopharmacology.* 2014; 39:2244–2251. DOI: 10.1038/npp.2014.75 [PubMed: 24675708]
- Stark JL, Avitsur R, Padgett DA, Campbell KA, Beck FM, Sheridan JF. Social stress induces glucocorticoid resistance in macrophages. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2001; 280:R1799–805. [PubMed: 11353685]
- Stein MB, Walker JR, Anderson G, Hazen AL, Ross CA, Eldridge G, Forde DR. Childhood physical and sexual abuse in patients with anxiety disorders and in a community sample. *Am. J. Psychiatry.* 1996; 153:275. doi: 10.1176/ajp.153.2.275 [PubMed: 8561213]
- Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain. Behav. Immun.* 2007; 21:901–912. DOI: 10.1016/j.bbi.2007.03.011 [PubMed: 17475444]

- Stolp HB. Neuropoietic cytokines in normal brain development and neurodevelopmental disorders. *Mol. Cell. Neurosci.* 2013; 53:63.doi: 10.1016/j.mcn.2012.08.009 [PubMed: 22926235]
- Stratakis CA, Chrousos GP. Neuroendocrinology and pathophysiology of the stress system. *Ann. N. Y. Acad. Sci.* 1995; 771:1–18. [PubMed: 8597390]
- Straub RH. The complex role of estrogens in inflammation. *Endocr. Rev.* 2007; 28:521.doi: 10.1210/er.2007-0001 [PubMed: 17640948]
- Stroud LR, Foster E, Papandonatos GD, Handwerger K, Granger DA, Kivlighan KT, Niaura R. Stress response and the adolescent transition: Performance versus peer rejection stressors. *Dev. Psychopathol.* 2009; 21:47.doi: 10.1017/S0954579409000042 [PubMed: 19144222]
- Sumter SR, Bokhorst CL, Miers AC, Van Pelt J, Westenberg PM. Age and puberty differences in stress responses during a public speaking task: Do adolescents grow more sensitive to social evaluation? *Psychoneuroendocrinology.* 2010; 35:1510–1516. DOI: 10.1016/j.psyneuen.2010.05.004 [PubMed: 20541871]
- Tagliari B, Tagliari AP, Schmitz F, Cunha AAda, Dalmaz C, Wyse ATS. Chronic Variable Stress Alters Inflammatory and Cholinergic Parameters in Hippocampus of Rats. *Neurochem. Res.* 2010; 36:487–493. DOI: 10.1007/s11064-010-0367-0 [PubMed: 21184279]
- Tajiri N, Acosta SA, Shahaduzzaman M, Ishikawa H, Shinozuka K, Pabon M, Hernandez-Ontiveros D, Kim DW, Metcalf C, Staples M, et al. Intravenous transplants of human adipose-derived stem cell protect the brain from traumatic brain injury-induced neurodegeneration and motor and cognitive impairments: cell graft biodistribution and soluble factors in young and aged rats. *J. Neurosci. Off. J. Soc. Neurosci.* 2014; 34:313.doi: 10.1523/JNEUROSCI.2425-13.2014
- Takizawa R, Danese A, Maughan B, Arseneault L. Bullying victimization in childhood predicts inflammation and obesity at mid-life: a five-decade birth cohort study. *Psychol. Med.* 2015; 45:2705–2715. DOI: 10.1017/S0033291715000653 [PubMed: 25988703]
- Taylor SE, Lehman BJ, Kiefe CI, Seeman TE. Relationship of early life stress and psychological functioning to adult C-reactive protein in the coronary artery risk development in young adults study. *Biol. Psychiatry.* 2006; 60:819–824. DOI: 10.1016/j.biopsych.2006.03.016 [PubMed: 16712805]
- Taylor SE, Lerner JS, Sage RM, Lehman BJ, Seeman TE. Early Environment, Emotions, Responses to Stress, and Health. *J. Pers.* 2004; 72:1365–1394. DOI: 10.1111/j.1467-6494.2004.00300.x [PubMed: 15509286]
- Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM. The neurobiological consequences of early stress and childhood maltreatment. *Neurosci. Biobehav. Rev. Brain Development, Sex Differences and Stress: Implications for Psychopathology.* 2003; 27:33–44. DOI: 10.1016/S0149-7634(03)00007-1
- Teicher MH, Parigger A. The “Maltreatment and Abuse Chronology of Exposure” (MACE) Scale for the Retrospective Assessment of Abuse and Neglect During Development. *PLoS ONE.* 2015; 10:e0117423.doi: 10.1371/journal.pone.0117423 [PubMed: 25714856]
- Tiwari-Woodruff S, Morales LBJ, Lee R, Voskuhl RR. Differential neuroprotective and antiinflammatory effects of estrogen receptor (ER) α and ER β ligand treatment. *Proc. Natl. Acad. Sci. U. S. A.* 2007; 104:14813.doi: 10.1073/pnas.0703783104 [PubMed: 17785421]
- Törnhaage CJ. Reference values for morning salivary cortisol concentrations in healthy school-aged children. *J. Pediatr. Endocrinol. Metab. JPEM.* 2002; 15:197. [PubMed: 11874185]
- Trickett PK, Gordis E, Peckins MK, Susman EJ. Stress reactivity in maltreated and comparison male and female young adolescents. *Child Maltreat.* 2014; doi: 10.1177/1077559513520466
- Trigunait A, Dimo J, Jørgensen TN. Suppressive effects of androgens on the immune system. *Cell. Immunol.* 2015; 294:87.doi: 10.1016/j.cellimm.2015.02.004 [PubMed: 25708485]
- Tyrka AR, Burgers DE, Philip NS, Price LH, Carpenter LL. The neurobiological correlates of childhood adversity and implications for treatment. *Acta Psychiatr. Scand.* 2013; 128:434–447. DOI: 10.1111/acps.12143 [PubMed: 23662634]
- Tyrka AR, Price LH, Gelernter J, Schepker C, Anderson GM, Carpenter LL. Interaction of childhood maltreatment with the corticotropin-releasing hormone receptor gene: Effects on hypothalamic-pituitary-adrenal axis reactivity. *Biol. Psychiatry, The Persisting Neurobiological Impact of Early Childhood Trauma.* 2009; 66:681–685. DOI: 10.1016/j.biopsych.2009.05.012

- Tyrka AR, Price LH, Kao H-T, Porton B, Marsella SA, Carpenter LL. Childhood maltreatment and telomere shortening: preliminary support for an effect of early stress on cellular aging. *Biol. Psychiatry*. 2010; 67:531–534. DOI: 10.1016/j.biopsych.2009.08.014 [PubMed: 19828140]
- Tyrka AR, Price LH, Marsit C, Walters OC, Carpenter LL. Childhood adversity and epigenetic modulation of the leukocyte glucocorticoid receptor: Preliminary findings in healthy adults. *PLoS ONE*. 2012; 7:e30148.doi: 10.1371/journal.pone.0030148 [PubMed: 22295073]
- Tyrka AR, Wier L, Price LH, Ross N, Anderson GM, Wilkinson CW, Carpenter LL. Childhood parental loss and adult hypothalamic-pituitary-adrenal function. *Biol. Psychiatry*. 2008; 63:1147–1154. DOI: 10.1016/j.biopsych.2008.01.011 [PubMed: 18339361]
- Upham JW, Lee PT, Holt BJ, Heaton T, Prescott SL, Sharp MJ, Sly PD, Holt PG. Development of Interleukin-12-Producing Capacity throughout Childhood. *Infect. Immun*. 2002; 70:6583.doi: 10.1128/IAI.70.12.6583.6588.2002 [PubMed: 12438328]
- Vachon DD, Krueger RF, Rogosch FA, Cicchetti D. Assessment of the harmful psychiatric and behavioral effects of different forms of child maltreatment. *JAMA Psychiatry*. 2015; 72:1135–1142. DOI: 10.1001/jamapsychiatry.2015.1792 [PubMed: 26465073]
- Vaillancourt T, Duku E, Decatanzaro D, Macmillan H, Muir C, Schmidt LA. Variation in hypothalamic-pituitary-adrenal axis activity among bullied and non-bullied children. *Aggress. Behav*. 2008; 34:294–305. DOI: 10.1002/ab.20240 [PubMed: 18161876]
- van den Bos E, de Rooij M, Miers AC, Bokhorst CL, Westenberg PM. Adolescents' increasing stress response to social evaluation: pubertal effects on cortisol and alpha-amylase during public speaking. *Child Dev*. 2014; 85:220.doi: 10.1111/cdev.12118 [PubMed: 23638912]
- Van Loo PLP, Kruitwagen CLJJ, Koolhaas JM, Van de Weerd HA, Van Zutphen LFM, Baumans V. Influence of cage enrichment on aggressive behaviour and physiological parameters in male mice. *Appl. Anim. Behav. Sci*. 2002; 76:65–81. DOI: 10.1016/S0168-1591(01)00200-3
- Watts-English T, Fortson BL, Gibler N, Hooper SR, De Bellis MD. The psychobiology of maltreatment in childhood. *J. Soc. Issues*. 2006; 62:717–736. DOI: 10.1111/j.1540-4560.2006.00484.x
- Weiner, H. *Perturbing the organism: The biology of stressful experience*. University of Chicago Press; 1992.
- Whalen MJ, Carlos TM, Kochanek PM, Wisniewski SR, Bell MJ, Clark RS, DeKosky ST, Marion DW, Adelson PD. Interleukin-8 is increased in cerebrospinal fluid of children with severe head injury. *Crit. Care Med*. 2000; 28:929–934. [PubMed: 10809261]
- Wilson MA, Grillo CA, Fadel JR, Reagan LP. Stress as a one-armed bandit: Differential effects of stress paradigms on the morphology, neurochemistry and behavior in the rodent amygdala. *Neurobiol. Stress, Stress Resilience*. 2015; 1:195–208. DOI: 10.1016/j.ynstr.2015.06.001
- Wright RJ, Finn P, Contreras JP, Cohen S, Wright RO, Staudenmayer J, Wand M, Perkins D, Weiss ST, Gold DR. Chronic caregiver stress and IgE expression, allergen-induced proliferation, and cytokine profiles in a birth cohort predisposed to atopy. *J. Allergy Clin. Immunol*. 2004; 113:1051.doi: 10.1016/j.jaci.2004.03.032 [PubMed: 15208584]
- Wynn JL, Scumpia PO, Winfield RD, Delano MJ, Kelly-Scumpia K, Barker T, Ungaro R, Levy O, Moldawer LL. Defective innate immunity predisposes murine neonates to poor sepsis outcome but is reversed by TLR agonists. *Blood*. 2008; 112:1750.doi: 10.1182/blood-2008-01-130500 [PubMed: 18591384]
- Yan SR, Qing G, Byers DM, Stadnyk AW, Al-Hertani W, Bortolussi R. Role of MyD88 in Diminished Tumor Necrosis Factor Alpha Production by Newborn Mononuclear Cells in Response to Lipopolysaccharide. *Infect. Immun*. 2004; 72:1223.doi: 10.1128/IAI.72.3.1223-1229.2004 [PubMed: 14977922]
- Yehuda R, Bierer LM, Schmeidler J, Aferiat DH, Breslau I, Dolan S. Low cortisol and risk for PTSD in adult offspring of holocaust survivors. *Am. J. Psychiatry*. 2000; 157:1252.doi: 10.1176/appi.ajp.157.8.1252 [PubMed: 10910787]
- Yirmiya R, Goshen I. Immune modulation of learning, memory, neural plasticity and neurogenesis. *Brain. Behav. Immun*. 2011; 25:181–213. DOI: 10.1016/j.bbi.2010.10.015 [PubMed: 20970492]

Highlights

- Physical trauma, disrupted caregiving, & unpredictability have unique developmental implications
- RSD may be a useful animal analog for childhood adversity involving physical trauma
- Maternal separation may be useful for understanding disrupted caregiving
- CVS may be useful for understanding living in an unpredictable developmental environment
- Infancy and pubertal may be sensitive periods for childhood adversity exposure

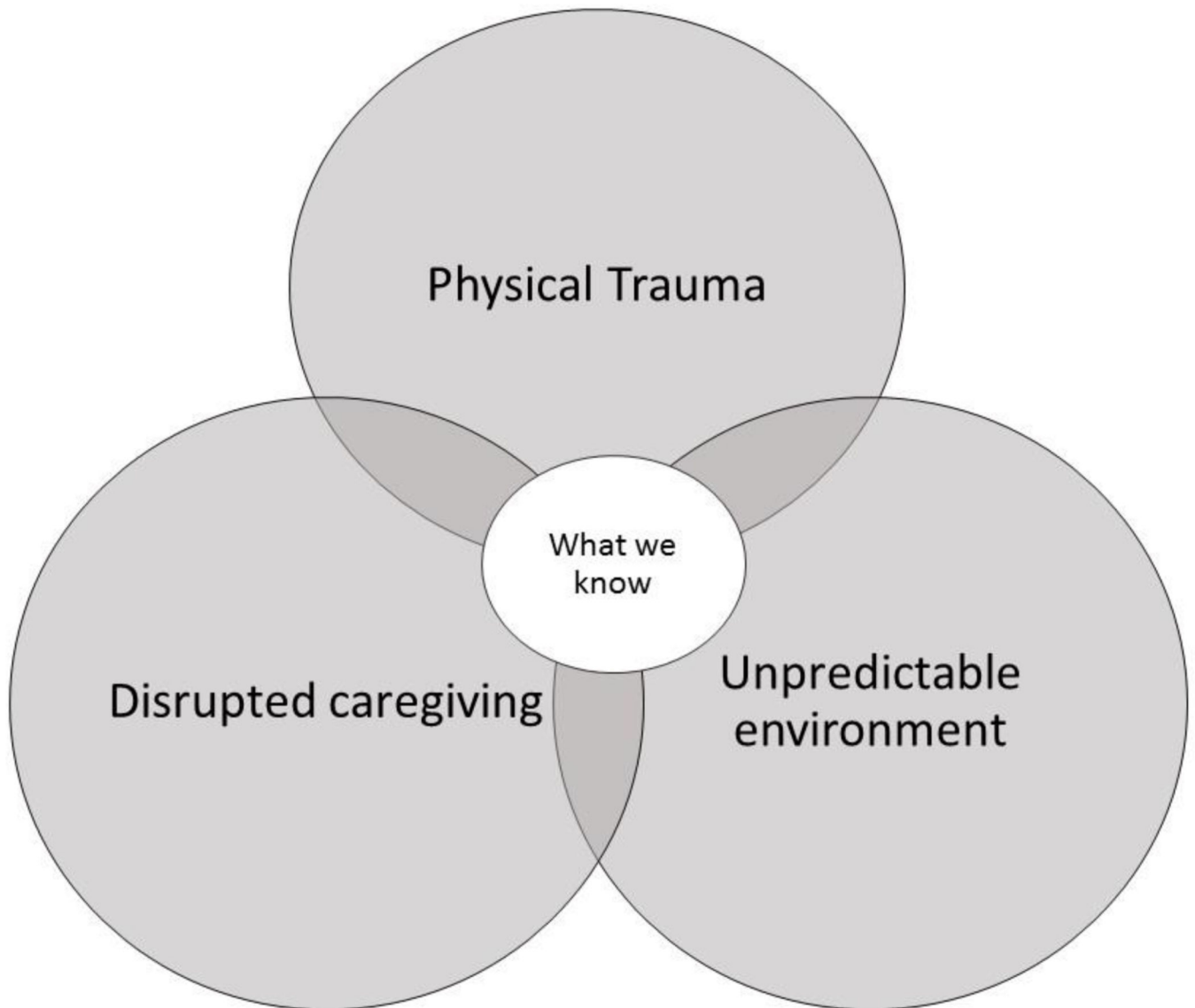


Figure 1. Dose-response models of childhood adversity limit what we know

Predominant dose-response models of childhood adversity exposure have limited our understanding of the peripheral biological consequences of childhood adversity to the overlap between different elements of stressful experiences.

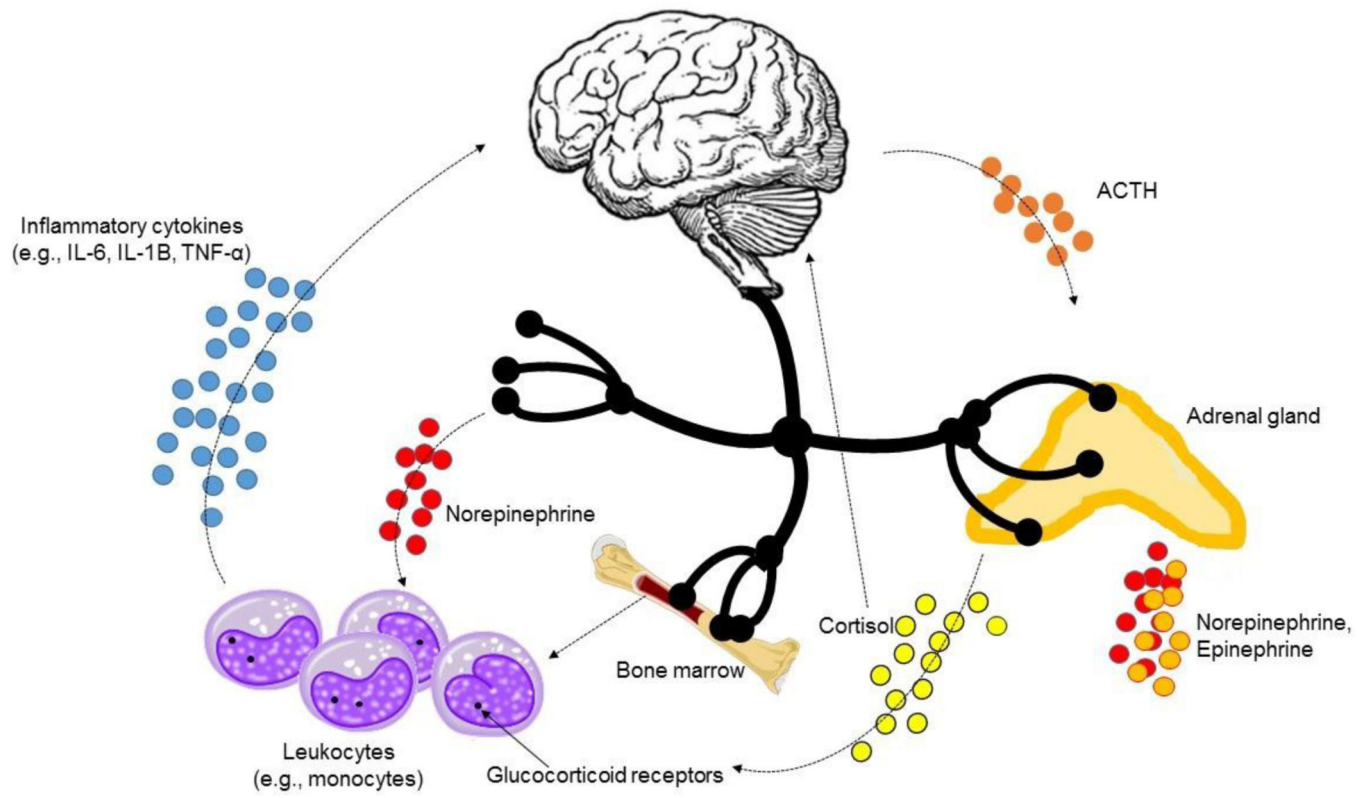
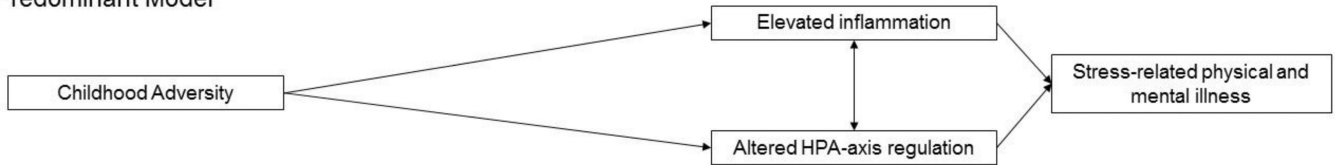


Figure 2. Coordinated hypothalamic-pituitary-adrenal axis (HPA-axis) and inflammatory response to stress

Predominant Model



Proposed Model

Biologically salient adversity elements

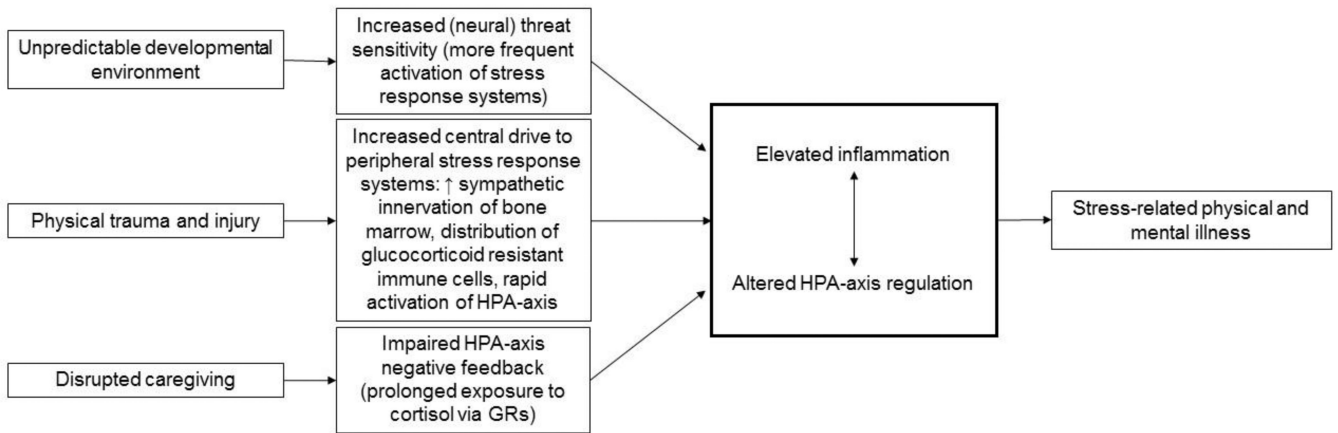


Figure 3. Proposed biobehavioral pathways from elements of adversity to stress-related disease

Table 1

Proposed pathways from subtypes of childhood adversity to inflammatory and neuroendocrine dysregulation.

Biologically Salient Adversity Element	Childhood Adversity	Potential Animal Model	Potential Mechanisms	Hypothesized Physiological Consequences
Physical Trauma	<ul style="list-style-type: none"> - Physical abuse - Major physical injury 	Repeated Social Defeat (RSD)	<ul style="list-style-type: none"> - Increased sympathetic innervation of bone marrow and tissue - Exaggerated central activation peripheral systems 	<ul style="list-style-type: none"> - Exaggerated HPA-axis, and inflammatory response to acute stress
Disrupted Caregiving	<ul style="list-style-type: none"> - Parental loss - Parental separation - Low maternal warmth - Emotional abuse 	Maternal separation/deprivation	<ul style="list-style-type: none"> - Decreased central and peripheral glucocorticoid sensitivity 	<ul style="list-style-type: none"> - Delayed physiological recovery from stress - Prolonged exposure to glucocorticoids
Unpredictable	<ul style="list-style-type: none"> - Community violence/war - Motor vehicle accident - Natural disaster - Extreme poverty 	Chronic Variable Stress (CVS)	<ul style="list-style-type: none"> - Increased neural sensitivity to environmental threat 	<ul style="list-style-type: none"> - More frequent activation of physiological stress systems - Elevated diurnal cortisol and circulating inflammation

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