The Effects of Childhood Adversity on Stress Response and Its Neurophysiological Mechanisms

Authors: Luo Yu, Xie Jiao, Tan Jiang, Zhang Yu, Luo Yu

Date: 2021-01-11T00:00:00+00:00

Abstract

Childhood adversity significantly increases the risk of individuals developing psychological disorders such as depression and anxiety, and abnormal stress response is an important factor contributing to these disorders. Childhood adversity can affect HPA axis activation, either enhancing or diminishing stress response sensitivity; severe childhood adversity increases individual stress response sensitivity, while mild and moderate childhood adversity may also produce a protective "stress inoculation" effect. The present article elaborates on the mechanisms through which childhood adversity influences stress response from three perspectives: brain function, immune system, and epigenetics. Future research should control for confounding variables and further investigate the effects of different types of childhood adversity on stress response.

Full Text

Preamble

The Influence of Childhood Adversity on Stress Response and Its Neurophysiological Mechanisms

Luo Yu, Xie Jiao, Tan Jiang, Zhang Yu
(School of Psychology, Guizhou Normal University; Stress and Cognition Laboratory, School of Psychology, Guizhou Normal University)

Corresponding author: Luo Yu, E-mail: yuluo@gznu.edu.cn

Abstract

Childhood adversity significantly increases the risk of developing psychological disorders such as depression and anxiety, and abnormal stress responses constitute a key factor in the onset of these conditions. Childhood adversity can affect

hypothalamic-pituitary-adrenal (HPA) axis activation, either enhancing or diminishing stress response sensitivity. While severe childhood adversity tends to increase individual stress reactivity, mild to moderate adversity may produce protective "stress inoculation" effects. This paper elucidates the mechanisms through which childhood adversity influences stress responses from three perspectives: brain function, the immune system, and epigenetics. Future research should control for confounding variables and further investigate how different types of childhood adversity affect stress responses.

Keywords: childhood adversity, stress response, HPA axis, neural mechanisms, inflammation, DNA methylation

1. Introduction

Childhood adversity, also known as adverse childhood experiences (ACE) or childhood trauma (CT), refers to adverse environmental conditions during childhood or adolescence that deviate from developmental expectations and require significant psychological, social, or neurobiological adaptation (McLaughlin, 2016). These experiences primarily include emotional neglect, emotional abuse, physical neglect, physical abuse, sexual abuse, and family dysfunction (such as domestic violence, alcohol abuse, parental separation or divorce), all of which negatively impact individual health and survival (Felitti, 1998). Two primary approaches exist for quantifying childhood adversity. The first is the cumulative risk method, which counts the number of different adversity types experienced to generate a risk score, regardless of the specific type, timing, or severity of the experiences (Evans et al., 2013). For example, a child who has experienced physical abuse, sexual abuse, and domestic violence receives a risk score of 3, as does a child who has experienced poverty, neglect, and maternal depression. This approach implicitly assumes that different adversity types influence development through shared mechanisms. The second approach is a conceptual model proposed by McLaughlin, Sheridan, and Lambert (2014), which classifies adversity along two dimensions: threat exposure and deprivation exposure. Threat exposure encompasses experiences of harm or threat of harm, witnessing community or domestic violence, or chronic physical and sexual abuse. Deprivation exposure refers to the absence of expected environmental inputs during childhood, including family poverty, neglect, parental divorce, or institutional upbringing.

The prevalence of childhood adversity is substantial. Survey data indicate that over half of individuals have experienced at least one form of childhood adversity, with more than one-third reporting at least two types (O' Connor, 2020). The most common forms are emotional and physical neglect, followed by physical abuse (Niu Yi et al., 2014). These adverse physiological and psychological experiences have produced a range of detrimental effects on development.

Extensive research demonstrates that childhood adversity represents a risk factor for numerous psychological and behavioral disorders. Individuals who have

experienced maltreatment, neglect, or poverty during childhood exhibit higher rates of physical and mental health problems compared to those without such experiences, including increased risks for cardiovascular disease (Lim, 2020) and psychiatric conditions such as depression and anxiety (Kong Xinyuan et al., 2020; Aafjes-van Doorn et al., 2019; Simpson et al., 2020; van Draanen, 2020; McFarland et al., 2020; Henry, 2020), poorer cognitive performance (Kalia, 2019; Majer et al., 2010), and difficulties in social relationships (McLaughlin, 2016; Jin Guichun & Wang Youzhi, 2017; Jones et al., 2020).

However, the pathways and mechanisms through which childhood adversity exerts long-term effects on disease onset remain unclear. The stress sensitization model proposes that exposure to adversity during sensitive developmental periods increases future sensitivity to stress, thereby elevating disease risk (Post, 2016). Childhood adversity affects stress-responsive neurons, leading to chronically elevated or suppressed activation of stress systems and altered glucocorticoid secretion. Key factors contributing to long-term homeostatic disruption following childhood adversity include alterations in the HPA axis, autonomic nervous system, immune system and inflammation, oxidative stress, cardiovascular system, gut microbiota, sleep and circadian rhythms, genetics, epigenetics, and brain structure and function. These neurobiological changes increase disease risk and result in elevated physical and psychiatric morbidity later in life (Agorastos et al., 2019). To prevent and treat these disorders and mitigate the adverse effects of childhood trauma, this paper examines how childhood adversity produces long-term psychological and physiological impacts from the perspective of stress response.

The article proceeds in three parts: first, summarizing how childhood adversity influences stress responses; second, exploring the underlying neurophysiological mechanisms; and third, outlining future research directions regarding adversity characteristics, timing, and methodological approaches.

2.1 Measurement and Definition of Childhood Adversity and Stress Response

Childhood adversity encompasses psychological or physical harm and threatening events experienced during childhood or adolescence. Since these experiences occur in the past, their measurement relies primarily on retrospective self-report. The most commonly used instruments include the Childhood Trauma Questionnaire (CTQ) and the Adverse Childhood Experiences (ACE) scale. The CTQ assesses emotional neglect, emotional abuse, physical neglect, physical abuse, and sexual abuse, with a short form version (CTQ-SF) also available (Bernstein et al., 1994). The ACE scale covers a broader range of experiences, including 14 items across three categories: neglect (physical and emotional), abuse (physical, emotional, and sexual), and family dysfunction (alcohol abuse, drug use, domestic violence, parental separation or divorce, mental illness in the family, family suicide, criminal behavior, early parental death, and peer victimization) (Ye Dongqing et al., 2004; Felitti, 1998). These questionnaires capture multiple

facets of childhood adversity, enabling assessment of both the severity of adverse events and differentiation among adversity types, such as physical versus emotional abuse and neglect, as well as material and psychological deprivation. Consequently, they have been widely adopted in the field.

Stress refers to a series of physiological and psychological responses that occur when homeostasis is threatened, aimed at restoring internal balance (Zhen Zhen et al., 2017). The physiological stress response primarily involves the rapid-acting sympathetic nervous system (SNS) and the slower-acting HPA axis. SNS activation leads to non-specific responses such as increased heart rate, rapid breathing, and elevated blood pressure. HPA axis activation increases cortisol secretion, which constitutes the most important adaptive response to stress, facilitating energy mobilization and maintenance of internal stability. Psychological stress responses include heightened mental tension, anxiety, irritability, and other emotional experiences (Li Wanru & Ku Yixuan, 2020). Human studies typically employ physical, cognitive, emotional, or social-evaluative stressors to induce mild or acute stress responses. Social evaluation represents a common social threat in daily life and constitutes a significant stressor. When social-evaluative threat co-occurs with uncontrollability, it elicits particularly robust stress responses, as exemplified by the Trier Social Stress Test (TSST) (Dickerson & Kemeny, 2004). HPA axis activity has long been considered a critical factor in stress sensitization (Heim et al., 2008). The most commonly used HPA axis indicators include the cortisol awakening response (CAR), diurnal regulation patterns, and cortisol reactivity (Kuhlman et al., 2015), each representing distinct neuroendocrine processes with different biopsychosocial significance (Tsigos & Chrousos, 2002). CAR refers to the surge in cortisol upon awakening, reflecting chronic daily stress and physiological system impact (Fries et al., 2009). Cortisol follows a diurnal rhythm, peaking in the morning and reaching its nadir at night. The gradual decline in cortisol from morning to evening serves as a marker of physiological balance (Tsigos & Chrousos, 2002), and disruption of this diurnal regulation predicts poor health outcomes (Sjögren et al., 2006).

2.2 Effects of Different Childhood Adversities on Stress Response

Previous research examining the impact of childhood adversity on stress responses has yielded inconsistent findings. Most studies indicate that childhood adversity induces long-term hyperactivity of the corticotropin-releasing factor system and alterations in other neurotransmitter systems, resulting in stress response sensitization (Heim & Nemeroff, 2001). In adolescents, stress sensitization due to childhood adversity has been demonstrated across different adversity types (Harkness et al., 2006; La Rocque et al., 2014), with individuals exposed to childhood adversity showing significantly higher cortisol responses following acute stress compared to controls (Shalev et al., 2019). Conversely, other research has found that childhood adversity attenuates stress reactivity. Following

stress exposure, childhood adversity has been associated with reduced HPA axis reactivity (Carpenter et al., 2009; MacMillan et al., 2009; Lovallo, 2011), and individuals with childhood adversity exhibit blunted cortisol responses to social stress (Bunea et al., 2017; Bernard et al., 2017; Frach et al., 2020).

Childhood adversities rarely occur in isolation (Finkelhor et al., 2007), yet most published studies have focused on either a single adversity type, such as parental death (Kaplow et al., 2013) or family poverty (Fuller-Rowell et al., 2012), or have aggregated different adversity types into a single composite category (Gustafsson et al., 2010). These approaches fail to distinguish how different adversity types uniquely influence stress responses. Experiences such as neglect, physical abuse, or natural disasters may affect learning and daily functioning through distinct physiological pathways (Miller et al., 2007). Research has linked early trauma exposure to both heightened and diminished stress reactivity (Peckins et al., 2012; Trickett et al., 2014) and to both elevated and suppressed evening HPA axis activity (Lupien et al., 2009). Exposure to any form of childhood adversity may produce different stress responses, and these divergent outcomes likely stem from the heterogeneity of adversity types.

2.2.1 Effects of Threat Exposure on Stress Response

Threat exposure refers to experiences involving harm or threat of harm. Victims of violence within the past year or adolescents who have witnessed violence exhibit stronger cortisol reactivity under laboratory stress (Peckins et al., 2012), and physical abuse is associated with faster acute stress responses (Kuhlman et al., 2015). Extensive animal research demonstrates that the HPA axis is sensitive to aversive events (Pryce et al., 2002) and that physical danger strongly activates the HPA axis (Miller et al., 2007).

Additional studies have found that childhood experiences of physical, sexual, and emotional abuse correlate with elevated daytime cortisol levels (Cicchetti & Rogosch, 2001), particularly in the afternoon (Bevans et al., 2008). In a study of 138 community youth aged 9 to 16, participants completed a social-evaluative cold pressor task, with four daytime saliva samples collected over two days. Results revealed that witnessing accidents or exposure to natural disasters was associated with altered diurnal cortisol regulation, specifically higher bedtime cortisol concentrations (Kuhlman et al., 2015). Childhood exposure to traumatic events may produce physiological alterations in HPA axis circadian regulation, impairing cortisol downregulation by day' s end (Buckley et al., 2005). However, some maltreated adolescent groups show no abnormalities in cortisol diurnal regulation (MacMillan et al., 2009; Ouellet-Morin et al., 2011). Emotional abuse has also been linked to delayed cortisol recovery following acute stress (Kuhlman et al., 2015). Some studies have found blunted responses to laboratory stress in chronically abused individuals (MacMillan et al., 2009; Ouellet-Morin et al., 2011; Trickett et al., 2014), with childhood physical abuse specifically—not other trauma types—identified as the cause of subsequent blunted cortisol responses (Carpenter et al., 2011).

Overall, threat exposure correlates with HPA axis dysregulation. Experiences involving harm or threat of harm, witnessing community or domestic violence, and chronic physical or sexual abuse produce either blunted or sensitized stress responses. Most studies report impaired cortisol diurnal rhythms with elevated levels throughout the day, though some find no diurnal abnormalities. Delayed stress recovery also associates with threat exposure.

2.2.2 Effects of Deprivation Exposure on Stress Response

Deprivation exposure primarily involves the absence of expected cognitive and developmental environmental inputs. Children from impoverished families exhibit flattened diurnal cortisol rhythms (Fuller-Rowell et al., 2012), lower cortisol reactivity (Sturge-Apple et al., 2012), and positive correlations between poverty and baseline cortisol (Fernald et al., 2008). Children raised in institutional settings show no cortisol decline across the day (Linares et al., 2008). Blunted cortisol responses have also been observed in other deprivation contexts, including exposure to unpredictable natural disasters (Vigil et al., 2010) and transitions from biological to foster families (Bruce et al., 2009), with maltreated children showing significantly lower morning cortisol than non-maltreated peers. Additionally, Meinlschmidt et al. (2005) found that university students with childhood deprivation experiences (e.g., parental separation/divorce, death of close friends or relatives) exhibited significantly reduced post-awakening cortisol responses, an effect more pronounced in individuals with multiple deprivation exposures and without gender differences. A study of pregnant women similarly demonstrated that childhood trauma led to significantly lower baseline cortisol levels upon morning awakening, with cortisol levels negatively correlated with total CTQ scores (Shea et al., 2007). In contrast, Engert et al. (2011) found that children with less parental care showed excessive physiological responses to stress, with increased HPA axis activation and elevated cortisol secretion. Furthermore, adolescents experiencing parental separation, divorce, or chronic parental illness showed enhanced sensitivity to future stressors (Espejo et al., 2007; Starr et al., 2017). Thus, deprivation exposures such as family poverty, parental divorce, or institutional upbringing produce either sensitized or blunted future stress responses, impaired daytime cortisol downregulation, low cortisol awakening responses, and blunted cortisol reactivity.

In summary, no consensus exists regarding whether the severity or type of childhood adversity leads to increased or decreased cortisol secretion and differential stress responses (Krause et al., 2020). These inconsistent findings may result from varying degrees of adversity exposure. Some evidence suggests that mild to moderate childhood adversity may produce protective "stress inoculation" or "steeling" effects, with individuals exposed to low or moderate adversity better equipped to handle subsequent challenges, promoting self-efficacy and reducing negative reactions over time (Seery et al., 2010). Conversely, high-level adversity may overwhelm coping capacities, leading to cumulative effects and chronic HPA axis activation that produce abnormal stress responses.

The timing of adversity exposure may represent another source of contradictory findings. Childhood adversity can both increase and decrease HPA axis activity, but these effects occur at different time points relative to the threatening experience. Shortly after adversity onset, HPA axis activation increases cortisol secretion. Over time, however, compensatory mechanisms may reduce cortisol levels below baseline (Miller et al., 2007). Biologically, this reflects the powerful negative feedback loop regulating the HPA axis, wherein elevated cortisol inhibits corticotropin-releasing hormone and adrenocorticotropic hormone output via glucocorticoid receptors in the hippocampus, hypothalamus, and pituitary (Fries et al., 2005). Since most studies employ cross-sectional designs assessing childhood adversity at different time points, and the HPA axis changes over time, earlier trauma experiences correlate with low cortisol while more recent trauma shows the opposite pattern (Miller et al., 2007).

3 Childhood Adversity and Mental Disorders: The Role of Stress Response

Childhood adversity permanently alters stress responses (Elwenspoek et al., 2020; Hengesch et al., 2018). Chronic activation of the HPA axis and sympathetic-adrenal-medullary (SAM) axis leads to prolonged secretion of stress hormones, resulting in dysregulation of these interdependent stress response systems (Juster Robert-Paul et al., 2010). Altered stress responses constitute one mechanism explaining the relationship between childhood adversity and subsequent psychiatric symptoms such as depression and anxiety (van Nierop et al., 2018). Childhood adversity sensitizes individuals to stressful events, increasing depression risk following life stressors (Starr et al., 2020). Numerous animal and human studies link HPA axis dysregulation—particularly cortisol abnormalities—to major depressive disorder (Ehlert et al., 2001; De Vente et al., 2003). Prospective studies of HPA axis function and depression demonstrate that morning cortisol levels, near the peak of the circadian rhythm, predict depression onset or related symptoms (Halligan et al., 2007; Goodyer et al., 2010). Vrshek-Schallhorn et al. (2013) obtained similar results, showing that cortisol awakening response predicted major depressive episodes one year later. Flattened daytime cortisol slopes mark elevated negative affect such as tension and anger, leading to increased evening cortisol levels (Adam et al., 2006). A review of relationships among childhood adversity, HPA axis function, and disease indicates that HPA axis activity is shaped by individual responses to adversity, with cortisol secretion increasing with subjective distress and contributing to posttraumatic stress disorder development (Miller et al., 2007). Understanding the biological mechanisms through which childhood adversity produces abnormal stress responses is crucial for treating these adverse outcomes.

4.1 Effects of Childhood Adversity on Brain Regions Involved in Stress Response

How does childhood adversity influence stress responses? At the brain level, the amygdala and hippocampus play crucial roles. Children and adolescents exposed to adversity, particularly violence, show reduced hippocampal and amygdala volumes (McLaughlin et al., 2019). Animal research demonstrates that early life stress exerts long-term negative effects on the hippocampus (Watanabe et al., 1992). Following childhood adversity, increased corticotropin-releasing hormone in the hippocampus reduces dendritic spines and branching in hippocampal neurons, a phenomenon that persists with age (Ivy et al., 2010). Reduced hippocampal volume disrupts hippocampal regulation of the HPA axis, which is essential for physiological stress responses (Frodl & O' Keane, 2013). Additionally, childhood exposure to violence correlates with reduced amygdala volume and heightened amygdala reactivity (McLaughlin et al., 2019), with smaller amygdala volume associated with stronger physiological stress reactivity (McLaughlin et al., 2016; Trotman et al., 2018). These structural and functional changes in the amygdala may facilitate rapid threat detection in the environment (McLaughlin & Lambert, 2017; McLaughlin et al., 2014). While adaptive in dangerous environments, these alterations may increase stress vulnerability in safe contexts or when facing less severe stressors.

Reduced hippocampal and amygdala volumes may represent a mechanism underlying stress sensitization, predisposing individuals exposed to childhood adversity to illness. Structural changes in these regions following childhood adversity alter how individuals respond to stressors, thereby increasing disease risk (Weissman et al., 2020). Research has linked smaller hippocampal volume to adult depression (Schmaal et al., 2016), though findings in children and adolescents are inconsistent. Some studies report negative correlations between hippocampal volume and depression in youth (Caetano et al., 2007; MacMaster et al., 2004), while others find no relationship (Rosso et al., 2005) or even positive correlations (Ellis et al., 2019). Similarly, studies examining amygdala volume and depression in children and adolescents have produced mixed results (Caetano et al., 2007; Rosso et al., 2005). Tottenham et al. (2010) found that individuals raised in institutional settings had larger amygdala volumes and higher anxiety levels compared to controls. A review also noted that the effects of childhood adversity on amygdala volume remain inconsistent across studies, possibly due to variations in adversity type, onset, and duration (Hart & Rubia, 2012).

Overall, current research suggests that childhood adversity affects amygdala and hippocampal development, but different adversity types and timing may produce different patterns of volumetric change.

4.2 Effects of Childhood Adversity on the Immune System in Stress Response

Inflammation represents a natural immune response to pathogens and injury, constituting a component of the stress response that is crucial for tissue healing, adaptation, and survival (Glaser et al., 2005). When immune responses become dysregulated, inappropriate or excessive immune reactions can cause tissue damage and inflammation. Acute stress activates pro-inflammatory cytokine secretion through adrenaline and corticotropin-releasing hormone stimulation, helping regulate immune responses (e.g., stimulating acute-phase proteins like C-reactive protein [CRP]) (Steptoe et al., 2007). Pro-inflammatory cytokines stimulate glucocorticoid secretion, which in turn terminates inflammatory responses (Cain et al., 2017). Substantial evidence indicates that the immune system influences brain activity related to stress through peripheral and central immune mechanisms, thereby playing a role in stress, neurobiology, and neuroendocrine responses (Menard et al., 2017). Conversely, dysregulated stress response systems can lead to disinhibited or excessive suppression of inflammatory processes, promoting biological aging, inflammation, or compromised immune health (Gill et al., 2009).

Childhood adversity represents a risk factor for peripheral immune dysregulation and chronic excessive inflammation in adulthood (Kuhlman et al., 2017; Danese et al., 2017a). Maltreated individuals show universally elevated inflammatory biomarkers compared to non-maltreated controls (Baumeister et al., 2016). A study of individuals born in England and Wales found that maltreated children exhibited higher inflammation levels (Danese et al., 2011), with subsequent research supporting and extending these findings to show elevated inflammation in children exposed to adverse events (Slopen et al., 2013; Cicchetti et al., 2015).

Individuals with childhood adversity show enhanced inflammatory responses to laboratory acute psychosocial stress tests (Carpenter et al., 2010; Gouin et al., 2012). HPA axis activation releases glucocorticoids that may disrupt neuroimmune responses, representing a potential mechanism (Agorastos et al., 2019). Thus, the connections among childhood adversity, stress responses, and inflammation are intimate, with childhood adversity influencing immune system responses to subsequent stressors and ultimately affecting a range of psychiatric disorders (Danese et al., 2017b; Misiak et al., 2019).

4.3 Effects of Childhood Adversity on Epigenetics in Stress Response

In recent years, researchers have increasingly focused on relationships between specific candidate genes and environmental factors. Epigenetic mechanisms—including DNA methylation, chromatin remodeling, and abnormal expression of non-coding RNA—modulate genetic polymorphisms and functional loci combinations in stress axes, thereby increasing or decreasing the risk of psychobiological dysregulation following childhood adversity (Skelton et al., 2012; Malan-Müller

et al., 2014). Understanding interactions among environment, genes, and post-adversity gene expression is essential for treating childhood adversity-related disorders.

Epigenetics explains relationships between environment and gene transcription, with maternal separation and childhood trauma affecting DNA methylation and subsequent gene expression (Franklin et al., 2010; Agorastos et al., 2019). Research has linked CpG island methylation upstream of the serotonin transporter gene to self-reported childhood trauma in both men and women, with abused males showing significantly increased promoter region CpG island methylation compared to non-abused males (Beach et al., 2010). Furthermore, investigators have examined whether childhood adversity affects candidate genes and downstream epigenetic patterns and their functions. Comparing genome-wide promoter methylation in hippocampal tissue between severely maltreated individuals and controls, they identified 362 differentially methylated promoters, with 248 hypermethylated and 114 hypomethylated, the most significant differences occurring in genes involved in cellular or neuronal plasticity (Labonté et al., 2012).

These findings demonstrate how childhood adversity influences DNA methylation patterns on a genome-wide scale (Labonté et al., 2012; Zannas et al., 2015).

Moreover, growing evidence suggests that childhood adversity may become biologically embedded through accelerated cellular, tissue, and organ aging (Gassen et al., 2017; Zannas et al., 2015; Colich et al., 2019). Specific CpG site DNA methylation patterns serve as effective measures of biological aging (Teschendorff et al., 2013; Marini et al., 2020), with "epigenetic clocks" used to predict accelerated physiological age. When physiological age exceeds chronological age, mortality risk increases (Jovanovic et al., 2017; Marini et al., 2020). A recent study quantifying age acceleration found that exposure to any childhood trauma associated with epigenetic "advancement" of up to six months (Wolf et al., 2018), with children scoring at least one standard deviation above the mean on violence exposure showing twice the epigenetic age acceleration of their peers (Jovanovic et al., 2017). Both threat-related adversities (abuse, domestic violence) and deprivation-related adversities associated with approximately one month of epigenetic age acceleration (Sumner et al., 2019).

With increasing childhood adversity, specific methylation occurs in genes encoding glucocorticoid receptor function, leading to epigenetic age acceleration (Jovanovic et al., 2017; Klengel et al., 2013). However, some studies have reported inconsistent results, observing accelerated pubertal development and cellular aging in threat-exposed but not deprivation-exposed children (Sumner et al., 2019).

In fact, recent research indicates that the epigenetic effects of childhood adversity are primarily determined by the timing of exposure, with adversity experienced during the sensitive period of 0 to 3 years producing more epigenetic changes (Dunn et al., 2019). The epigenetic consequences of childhood adver-

sity and timing effects may be obscured by simple dichotomous classifications of exposed versus unexposed groups. Thus, childhood adversity may alter gene methylation processes by directly or indirectly interfering with normal cellular aging, including gene-specific methylation changes in glucocorticoid receptor function genes that lead to accelerated epigenetic aging. Some studies have found divergent results, necessitating further research to clarify relationships between different adversity types, timing, and epigenetics.

5. Summary and Outlook

Reviewing these findings reveals that childhood adversity influences individual stress responses. Some studies demonstrate that childhood adversity leads to sensitized or blunted stress reactivity, while others show that moderate or low-level adversity may strengthen stress immunity through a "steeling" effect. Childhood adversity can also trigger various psychological disorders—including depression, anxiety, and personality disorders—through altered stress reactivity. At the neural level, childhood adversity affects brain development, producing lasting impacts on stress-related neural substrates such as amygdala and hippocampus structure and function, resulting in either increased or decreased volumes and HPA axis dysregulation. At the immune system level, childhood adversity influences immune responses to subsequent stressors, ultimately affecting a range of psychiatric disorders. From an epigenetic perspective, childhood adversity alters methylation processes by directly or indirectly interfering with normal cellular aging, including gene-specific methylation changes in glucocorticoid receptor function genes that accelerate epigenetic aging. However, different stress responses involve multiple distinct neurobiological circuits, and how childhood adversity affects these circuits requires further investigation.

To date, research examining childhood adversity from a stress perspective remains insufficient, particularly in domestic contexts. Based on existing findings, we propose several directions for future research.

First, the concept of childhood adversity is broad, but its impact depends heavily on characteristics such as severity, duration, frequency, developmental timing, and controllability (Parihar et al., 2011; Parker & Maestripieri, 2011). For instance, common family conflicts have relatively mild effects and may be somewhat controllable for children, potentially fostering resilience. In contrast, events like family poverty, parental divorce, or abuse exert intense effects beyond children' s control, producing negative and enduring consequences (Zhang Huihui et al., 2018). Additionally, these effects vary across individuals, as not all individuals exposed to severe childhood adversity uniformly develop affective, psychotic, or anxiety symptoms (van Nierop et al., 2018). Since current research derives from childhood adversities of varying severity and timing, cross-study comparisons remain challenging. Future research should manipulate and differentiate adversity types and individual differences, incorporating control variables such as resilience and social support to further specify the effects of childhood adversity.

Second, although childhood adversity constitutes a risk factor for psychological disorders, some individuals remain unaffected and show health comparable to the general population. Effective stress responses may play a protective role. An effective stress response is characterized by rapid reactivity during actual stress and quick recovery when the stressor subsides (Roy, 2004), a pattern with adaptive significance (He et al., 2020). Recovery represents another critical consideration: failure to shut down the cortisol system promptly after stimulation may damage health through excessive cortisol secretion (Abercrombie et al., 2006). Since most studies employ cross-sectional designs that cannot capture temporal changes in stress responses among individuals with childhood adversity—such as increases or decreases over time, or response speed—future research should utilize longitudinal designs to examine whether individuals with different childhood adversity profiles show differential stress response effectiveness.

Third, while childhood adversity affects stress responses through multiple mechanisms, the interconnections among these neurobiological pathways should not be overlooked. Research has shown that childhood trauma relates to allele-specific DNA demethylation in functional glucocorticoid response elements of the FKBP5 gene, which in turn associates with reduced glucocorticoid receptor sensitivity in peripheral blood immune cells to lipopolysaccharide-induced interleukin-6 production (Klengel et al., 2013). A study collecting data from over 2,000 participants in the Psychiatric Genomics Consortium PTSD Epigenetics Working Group found that trauma exposure relates to accelerated epigenetic aging in adulthood, with cells protecting and regulating immune responsiveness potentially playing important roles in epigenetic clock adjustments (Wolf et al., 2018). Understanding these connections will facilitate more effective treatment of childhood adversity-related disorders.

Finally, based on an understanding of these mechanisms, targeted interventions can be developed to reduce the negative impacts of childhood adversity. For example, estradiol therapy can reduce cortisol responses to acute stress and prevent HPA axis overactivation (Herrera et al., 2017). Non-invasive transcranial direct current stimulation can reduce post-adversity cortisol responses (Antal et al., 2014). Kotozaki and colleagues tested biofeedback (BFB) as an intervention for adversity-related stress, measuring salivary cortisol as an indicator of BFB effectiveness in stress management skills training. After 28 days of BFB training (5 minutes daily), the intervention group showed significant improvements in psychological test scores and salivary cortisol compared to controls. Furthermore, MRI scans revealed significantly increased regional gray matter volume in the right orbitofrontal cortex, including transgenic regions related to stress reactivity sensitivity (left hippocampus and left subgenual anterior cingulate cortex) (Kotozaki et al., 2014). Thus, interventions using estradiol, non-invasive brain stimulation, and biofeedback can modulate maladaptive stress responses following childhood adversity through different pathways, holding significant value for psychiatric treatment.

References

Aafjes-van Doorn, K., Kamsteeg, C., & Silberschatz, G. (2020). Cognitive mediators of the relationship between adverse childhood experiences and adult psychopathology: a systematic review. *Development and psychopathology, 32*(3), 1017-1029.

Abercrombie, H. C., Speck, N. S., & Monticelli, R. M. (2006). Endogenous cortisol elevations are related to memory facilitation only in individuals who are emotionally aroused. *Psychoneuroendocrinology, 31*(2), 187-196.

Adam, E. K., Hawkley, L. C., Kudielka, B. M., & Cacioppo, J. T. (2006). Day-to-day dynamics of experience–cortisol associations in a population-based sample of older adults. *Proceedings of the National Academy of Sciences, 103*(45), 17058-17063.

Agorastos, A., Pervanidou, P., Chrousos, G. P., & Baker, D. G. (2019). Developmental trajectories of early life stress and trauma: a narrative review on neurobiological aspects beyond stress system dysregulation. *Frontiers in psychiatry, 10*, 118.

Antal, A., Fischer, T., Saiote, C., Miller, R., Chaieb, L., Wang, D. J., ···& Kirschbaum, C. (2014). Transcranial electrical stimulation modifies the neuronal response to psychosocial stress exposure. *Human brain mapping, 35*(8), 3755-3765.

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C. M., & Mondelli, V. (2016). Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. *Molecular psychiatry, 21*(5), 642-649.

Beach, S. R., Brody, G. H., Todorov, A. A., Gunter, T. D., & Philibert, R. A. (2010). Methylation at SLC6A4 is linked to family history of child abuse: an examination of the Iowa Adoptee sample. *American journal of medical genetics. Part B, Neuropsychiatric genetics: the official publication of the International Society of Psychiatric Genetics, 153*(2), 710-713.

Bernard, K., Frost, A., Bennett, C. B., & Lindhiem, O. (2017). Maltreatment and diurnal cortisol regulation: A meta-analysis. *Psychoneuroendocrinology, 78*, 57-67.

Bernstein, D. P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., ···& Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *The American journal of psychiatry.*

Bevans, K., Cerbone, A., & Overstreet, S. (2008). Relations between recurrent trauma exposure and recent life stress and salivary cortisol among children. *Development and psychopathology, 20*(1), 257-272.

Buckley, T. M., & Schatzberg, A. F. (2005). On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: normal HPA axis

activity and circadian rhythm, exemplary sleep disorders. *The Journal of Clinical Endocrinology & Metabolism, 90*(5), 3106-3114.

Bunea, I. M., Szentágotai-Tătar, A., & Miu, A. C. (2017). Early-life adversity and cortisol response to social stress: a meta-analysis. *Translational psychiatry, 7*(12), 1-8.

Bruce, J., Fisher, P. A., Pears, K. C., & Levine, S. (2009). Morning cortisol levels in preschool-aged foster children: Differential effects of maltreatment type. *Developmental Psychobiology: The Journal of the International Society for Developmental Psychobiology, 51*(1), 14-23.

Caetano, S. C., Fonseca, M., Hatch, J. P., Olvera, R. L., Nicoletti, M., Hunter, K., ···& Soares, J. C. (2007). Medial temporal lobe abnormalities in pediatric unipolar depression. *Neuroscience letters, 427*(3), 142-147.

Cain, D. W., & Cidlowski, J. A. (2017). Immune regulation by glucocorticoids. *Nature Reviews Immunology, 17*(4), 233-247.

Carpenter, L. L., Tyrka, A. R., Ross, N. S., Khoury, L., Anderson, G. M., & Price, L. H. (2009). Effect of childhood emotional abuse and age on cortisol responsivity in adulthood. *Biological psychiatry, 66*(1), 69-75.

Carpenter, L. L., Gawuga, C. E., Tyrka, A. R., Lee, J. K., Anderson, G. M., & Price, L. H. (2010). Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. *Neuropsychopharmacology, 35*(13), 2617-2623.

Carpenter, L. L., Shattuck, T. T., Tyrka, A. R., Geracioti, T. D., & Price, L. H. (2011). Effect of childhood physical abuse on cortisol stress response. *Psychopharmacology, 214*(1), 367-375.

Cicchetti, D., & Rogosch, F. A. (2001). Diverse patterns of neuroendocrine activity in maltreated children. *Development and psychopathology, 13*(3), 677-693.

Cicchetti, D., Handley, E. D., & Rogosch, F. A. (2015). Child maltreatment, inflammation, and internalizing symptoms: investigating the roles of c-reactive protein, gene variation, and neuroendocrine regulation. *Development & Psychopathology, 27*(02), 553-566.

Colich, N. L., Platt, J. M., Keyes, K. M., Sumner, J. A., Allen, N. B., & McLaughlin, K. A. (2019). Earlier age at menarche as a transdiagnostic mechanism linking childhood trauma with multiple forms of psychopathology in adolescent girls. *Psychological medicine, 50*(7), 1090-1098.

Danese, A., Caspi, A., Williams, B., Ambler, A., Sugden, K., Mika, J., ···& Arseneault, L. (2011). Biological embedding of stress through inflammation processes in childhood. *Molecular psychiatry, 16*(3), 244-246.

Danese, A., & Lewis, S. J. (2017a). Psychoneuroimmunology of early-life stress: the hidden wounds of childhood trauma?. *Neuropsychopharmacology, 42*(1),

99-114.

Danese, A., & Baldwin, J. R. (2017b). Hidden wounds? Inflammatory links between childhood trauma and psychopathology. *Annual review of psychology, 68*, 517-544.

De Vente, W., Olff, M., Van Amsterdam, J. G. C., Kamphuis, J. H., & Emmelkamp, P. M. G. (2003). Physiological differences between burnout patients and healthy controls: blood pressure, heart rate, and cortisol responses. *Occupational and environmental medicine, 60*(suppl 1), i54-i61.

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychological bulletin, 130*(3), 355-391.

Dunn, E. C., Soare, T. W., Zhu, Y., Simpkin, A. J., Suderman, M. J., Klengel, T., ···& Relton, C. L. (2019). Sensitive periods for the effect of childhood adversity on DNA methylation: results from a prospective, longitudinal study. *Biological psychiatry, 85*(10), 838-849.

Ehlert, U., Gaab, J., & Heinrichs, M. (2001). Psychoneuroendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: the role of the hypothalamus–pituitary–adrenal axis. *Biological psychology, 57*(1-3), 141-152.

Ellis, R., Fernandes, A., Simmons, J. G., Mundy, L., Patton, G., Allen, N. B., & Whittle, S. (2019). Relationships between adrenarcheal hormones, hippocampal volumes and depressive symptoms in children. *Psychoneuroendocrinology, 104*, 55-63.

Elwenspoek, M. M., Hengesch, X., Leenen, F. A., Sias, K., Fernandes, S. B., Schaan, V. K., ···& Vögele, C. (2020). Glucocorticoid receptor signaling in leukocytes after early life adversity. *Development and psychopathology, 32*(3), 901-912.

Engert, V., Efanov, S. I., Dedovic, K., Dagher, A., & Pruessner, J. C. (2011). Increased cortisol awakening response and afternoon/evening cortisol output in healthy young adults with low early life parental care. *Psychopharmacology, 214*(1), 261-268.

Espejo, E. P., Hammen, C. L., Connolly, N. P., Brennan, P. A., Najman, J. M., & Bor, W. (2007). Stress sensitization and adolescent depressive severity as a function of childhood adversity: a link to anxiety disorders. *Journal of abnormal child psychology, 35*(2), 287-299.

Evans, G. W., Li, D., & Whipple, S. S. (2013). Cumulative risk and child development. *Psychological bulletin, 139*(6), 1342-1382.

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., & Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse

Childhood Experiences (ACE) Study. *American journal of preventive medicine, 14*(4), 245-258.

Fernald, L. C., Burke, H. M., & Gunnar, M. R. (2008). Salivary cortisol levels in children of low-income women with high depressive symptomatology. *Development and Psychopathology, 20*(2), 423-436.

Finkelhor, D., Ormrod, R. K., & Turner, H. A. (2007). Poly-victimization: A neglected component in child victimization. *Child abuse & neglect, 31*(1), 7-26.

Frach, L., Tierling, S., Schwaiger, M., Moser, D., Heinrichs, M., Hengstler, J. G., ···& Kumsta, R. (2020). The mediating role of KITLG DNA methylation in the association between childhood adversity and cortisol stress reactivity does not replicate in monocytes. *Psychoneuroendocrinology, 116*, 104653.

Franklin, T. B., Russig, H., Weiss, I. C., Gräff, J., Linder, N., Michalon, A., ··· & Mansuy, I. M. (2010). Epigenetic transmission of the impact of early stress across generations. *Biological psychiatry, 68*(5), 408-415.

Fries, E., Hesse, J., Hellhammer, J., & Hellhammer, D. H. (2005). A new view on hypocortisolism. *Psychoneuroendocrinology, 30*(10), 1010-1016.

Fries, E., Dettenborn, L., & Kirschbaum, C. (2009). The cortisol awakening response (CAR): facts and future directions. *International journal of Psychophysiology, 72*(1), 67-73.

Frodl, T., & O' Keane, V. (2013). How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. *Neurobiology of disease, 52*, 24-37.

Fuller-Rowell, T. E., Doan, S. N., & Eccles, J. S. (2012). Differential effects of perceived discrimination on the diurnal cortisol rhythm of African Americans and Whites. *Psychoneuroendocrinology, 37*(1), 107-118.

Gassen, N. C., Chrousos, G. P., Binder, E. B., & Zannas, A. S. (2017). Life stress, glucocorticoid signaling, and the aging epigenome: implications for aging-related diseases. *Neuroscience & Biobehavioral Reviews, 74*, 356-365.

Gill, J. M., Saligan, L., Woods, S., & Page, G. (2009). PTSD is associated with an excess of inflammatory immune activities. *Perspectives in psychiatric care, 45*(4), 262-277.

Glaser, R., & Kiecolt-Glaser, J. K. (2005). Stress-induced immune dysfunction: implications for health. *Nature Reviews Immunology, 5*(3), 243-251.

Goodyer, I. M., Croudace, T., Dudbridge, F., Ban, M., & Herbert, J. (2010). Polymorphisms in BDNF (Val66Met) and 5-HTTLPR, morning cortisol and subsequent depression in at-risk adolescents. *The British journal of psychiatry, 197*(5), 365-371.

Gouin, J. P., Glaser, R., Malarkey, W. B., Beversdorf, D., & Kiecolt-Glaser, J. K. (2012). Childhood abuse and inflammatory responses to daily stressors.

Annals of Behavioral Medicine, 44(2), 287-292.

Gustafsson, P. E., Anckarsäter, H., Lichtenstein, P., Nelson, N., & Gustafsson, P. A. (2010). Does quantity have a quality all its own? Cumulative adversity and up-and down-regulation of circadian salivary cortisol levels in healthy children. *Psychoneuroendocrinology, 35*(9), 1410-1415.

Halligan, S. L., Herbert, J., Goodyer, I., & Murray, L. (2007). Disturbances in morning cortisol secretion in association with maternal postnatal depression predict subsequent depressive symptomatology in adolescents. *Biological psychiatry, 62*(1), 40-46.

Harkness, K. L., Bruce, A. E., & Lumley, M. N. (2006). The role of childhood abuse and neglect in the sensitization to stressful life events in adolescent depression. *Journal of abnormal psychology, 115*(4), 730-741.

Hart, H., & Rubia, K. (2012). Neuroimaging of child abuse: a critical review. *Frontiers in human neuroscience, 6*, 52.

He, Y., Fan, J., & Yang, J. (2020). An efficient acute stress response in Chinese individuals with high interdependent self-construal. *Anxiety, Stress, & Coping, 33*(5), 1-14.

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biological psychiatry, 49*(12), 1023-1039.

Heim, C., Newport, D. J., Mletzko, T., Miller, A. H., & Nemeroff, C. B. (2008). The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology, 33*(6), 693-710.

Hengesch, X., Elwenspoek, M. M., Schaan, V. K., Larra, M. F., Finke, J. B., Zhang, X., ···& Schächinger, H. (2018). Blunted endocrine response to a combined physical-cognitive stressor in adults with early life adversity. *Child Abuse & Neglect, 85*, 137-144.

Henry, B. F. (2020). Typologies of adversity in childhood & adulthood as determinants of mental health & substance use disorders of adults incarcerated in US prisons. *Child abuse & neglect, 99*, 104251.

Herrera, A. Y., Hodis, H. N., Mack, W. J., & Mather, M. (2017). Estradiol therapy after menopause mitigates effects of stress on cortisol and working memory. *The Journal of Clinical Endocrinology & Metabolism, 102*(12), 4457-4466.

Ivy, A. S., Rex, C. S., Chen, Y., Dubé, C., Maras, P. M., Grigoriadis, D. E., ···& Baram, T. Z. (2010). Hippocampal dysfunction and cognitive impairments provoked by chronic early-life stress involve excessive activation of CRH receptors. *Journal of Neuroscience, 30*(39), 13005-13015.

Jones, M. S., Burge, S. W., Sharp, S. F., & McLeod, D. A. (2020). Childhood adversity, mental health, and the perpetration of physical violence in the adult

intimate relationships of women prisoners: a life course approach. *Child Abuse & Neglect, 101*, 104237.

Jovanovic, T., Vance, L. A., Cross, D., Knight, A. K., Kilaru, V., Michopoulos, V., ···& Smith, A. K. (2017). Exposure to violence accelerates epigenetic aging in children. *Scientific reports, 7*(1), 1-7.

Juster, R. P., McEwen, B. S., & Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience & Biobehavioral Reviews, 35*(1), 2-16.

Kalia, V., & Knauft, K. (2020). Emotion regulation strategies modulate the effect of adverse childhood experiences on perceived chronic stress with implications for cognitive flexibility. *Plos one, 15*(6), e0235412.

Kaplow, J. B., Shapiro, D. N., Wardecker, B. M., Howell, K. H., Abelson, J. L., Worthman, C. M., & Prossin, A. R. (2013). Psychological and environmental correlates of HPA axis functioning in parentally bereaved children: Preliminary findings. *Journal of traumatic stress, 26*(2), 233-240.

Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J. C., Pariante, C. M., ···& Binder, E. B. (2013). Allele-specific FKBP5 DNA demethylation mediates gene–childhood trauma interactions. *Nature neuroscience, 16*(1), 33-41.

Kotozaki, Y., Takeuchi, H., Sekiguchi, A., Yamamoto, Y., Shinada, T., Araki, T., ···& Kawashima, R. (2014). Biofeedback-based training for stress management in daily hassles: an intervention study. *Brain and behavior, 4*(4), 566-579.

Krause, B. J., Artigas, R., Sciolla, A. F., & Hamilton, J. (2020). Epigenetic mechanisms activated by childhood adversity. *Epigenomics, 12*(14), 1239-1255.

Kuhlman, K. R., Geiss, E. G., Vargas, I., & Lopez-Duran, N. L. (2015). Differential associations between childhood trauma subtypes and adolescent HPA-axis functioning. *Psychoneuroendocrinology, 54*, 103-114.

Kuhlman, K. R., Chiang, J. J., Horn, S., & Bower, J. E. (2017). Developmental psychoneuroendocrine and psychoneuroimmune pathways from childhood adversity to disease. *Neuroscience & Biobehavioral Reviews, 80*, 31-44.

La Rocque, C. L., Harkness, K. L., & Bagby, R. M. (2014). The differential relation of childhood maltreatment to stress sensitization in adolescent and young adult depression. *Journal of adolescence, 37*(6), 871-882.

Lim, G. B. (2020). Childhood adversity is associated with cardiovascular disease in later life. *Nature Reviews Cardiology, 17*(7), 384-384.

Linares, L. O., Stovall-McClough, K. C., Li, M., Morin, N., Silva, R., Albert, A., & Cloitre, M. (2008). Salivary cortisol in foster children: a pilot study. *Child abuse & neglect*.

Lovallo, W. R. (2011). Do low levels of stress reactivity signal poor states of health?. *Biological psychology, 86*(2), 132-139.

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature reviews neuroscience, 10*(6), 434-445.

MacMaster, F. P., & Kusumakar, V. (2004). Hippocampal volume in early onset depression. *BMC medicine, 2*(1), 2.

MacMillan, H. L., Georgiades, K., Duku, E. K., Shea, A., Steiner, M., Niec, A., ···& Walsh, C. A. (2009). Cortisol response to stress in female youths exposed to childhood maltreatment: results of the youth mood project. *Biological psychiatry, 66*(1), 62-68.

Majer, M., Nater, U. M., Lin, J. M. S., Capuron, L., & Reeves, W. C. (2010). Association of childhood trauma with cognitive function in healthy adults: a pilot study. *BMC neurology, 10*(1), 61.

McFarland, D. C., Nelson, C., & Miller, A. H. (2020). Early childhood adversity in adult patients with metastatic lung cancer: Cross-sectional analysis of symptom burden and inflammation. *Brain, behavior, and immunity, 90*, 167-174.

Malan-Müller, S., Seedat, S., & Hemmings, S. M. J. (2014). Understanding posttraumatic stress disorder: insights from the methylome. *Genes, Brain and Behavior, 13*(1), 52-68.

Marini, S., Davis, K. A., Soare, T. W., Zhu, Y., Suderman, M. J., Simpkin, A. J., ···& Dunn, E. C. (2020). Adversity exposure during sensitive periods predicts accelerated epigenetic aging in children. *Psychoneuroendocrinology, 113*, 104544.

McLaughlin, K. A., Sheridan, M. A., & Lambert, H. K. (2014). Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. *Neuroscience & Biobehavioral Reviews, 47*, 578-591.

McLaughlin, K. A., & Sheridan, M. A. (2016). Beyond cumulative risk: A dimensional approach to childhood adversity. *Current directions in psychological science, 25*(4), 239-245.

McLaughlin, K. A., & Lambert, H. K. (2017). Child trauma exposure and psychopathology: mechanisms of risk and resilience. *Current opinion in psychology, 14*, 29-34.

McLaughlin, K. A., Weissman, D., & Bitrán, D. (2019). Childhood adversity and neural development: a systematic review. *Annual review of developmental psychology, 1*, 277-312.

Meinlschmidt, G., & Heim, C. (2005). Decreased cortisol awakening response after early experience. *Psychoneuroendocrinology, 30*(6), 568-576.

Menard, C., Pfau, M. L., Hodes, G. E., Kana, V., Wang, V. X., Bouchard, S., ···& Russo, S. J. (2017). Immune and neuroendocrine mechanisms of stress vulnerability and resilience. *Neuropsychopharmacology, 42*(1), 62-80.

Miller, G. E., Chen, E., & Zhou, E. S. (2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. *Psychological bulletin, 133*(1), 25-45.

Misiak, B., Frydecka, D., Stanczykiewicz, B., & Samochowiec, J. (2019). Peripheral Markers of Immune Response in Major Psychiatric Disorders: Where Are We Now and Where Do We Want to Be?. *Frontiers in psychiatry, 10*, 5.

O' Connor, M., Slopen, N., Becares, L., Burgner, D., Williams, D. R., & Priest, N. (2020). Inequalities in the distribution of childhood adversity from birth to 11 years. *Academic pediatrics, 20*(5), 609-618.

Ouellet-Morin, I., Odgers, C. L., Danese, A., Bowes, L., Shakoor, S., Papadopoulos, A. S., ···& Arseneault, L. (2011). Blunted cortisol responses to stress signal social and behavioral problems among maltreated/bullied 12-year-old children. *Biological psychiatry, 70*(11), 1016-1023.

Parihar, V. K., Hattiangady, B., Kuruba, R., Shuai, B., & Shetty, A. K. (2011). Predictable chronic mild stress improves mood, hippocampal neurogenesis and memory. *Molecular psychiatry, 16*(2), 171-183.

Parker, K. J., & Maestripieri, D. (2011). Identifying key features of early stressful experiences that produce stress vulnerability and resilience in primates. *Neuroscience & Biobehavioral Reviews, 35*(7), 1466-1483.

Peckins, M. K., Dockray, S., Eckenrode, J. L., Heaton, J., & Susman, E. J. (2012). The longitudinal impact of exposure to violence on cortisol reactivity in adolescents. *Journal of Adolescent Health, 51*(4), 366-372.

Post, R. M. (2016). Epigenetic basis of sensitization to stress, affective episodes, and stimulants: implications for illness progression and prevention. *Bipolar disorders, 18*(4), 315-324.

Pryce, C. R., Ruedi-Bettschen, D., Dettling, A. C., & Feldon, J. (2002). Early life stress: long-term physiological impact in rodents and primates. *Physiology, 17*(4), 150-155.

Rosso, I. M., Cintron, C. M., Steingard, R. J., Renshaw, P. F., Young, A. D., & Yurgelun-Todd, D. A. (2005). Amygdala and hippocampus volumes in pediatric major depression. *Biological psychiatry, 57*(1), 21-26.

Roy, M. P. (2004). Patterns of cortisol reactivity to laboratory stress. *Hormones and Behavior, 46*(5), 618-627.

Schmaal, L., Veltman, D. J., van Erp, T. G., Sämann, P. G., Frodl, T., Jahanshad, N., ···& Vernooij, M. W. (2016). Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. *Molecular psychiatry, 21*(6), 806-812.

Seery, M. D., Holman, E. A., & Silver, R. C. (2010). Whatever does not kill us: cumulative lifetime adversity, vulnerability, and resilience. *Journal of personality and social psychology, 99*(6), 1025-1041.

Shalev, I., Hastings, W. J., Etzel, L., Israel, S., Russell, M. A., Hendrick, K. A., ···& Siegel, S. R. (2019). Early-life adversity is associated with differential gene expression in response to acute psychological stress: preliminary findings. *bioRxiv*, 727180.

Shea, A. K., Streiner, D. L., Fleming, A., Kamath, M. V., Broad, K., & Steiner, M. (2007). The effect of depression, anxiety and early trauma on the cortisol awakening response during pregnancy: preliminary results. *Psychoneuroendocrinology, 32*(8-10), 1013-1020.

Simpson, J., Helliwell, B., Varese, F., & Powell, P. (2020). Self-disgust mediates the relationship between childhood adversities and psychosis. *British Journal of Clinical Psychology, 59*(2), 260-275.

Sjögren, E., Leanderson, P., & Kristenson, M. (2006). Diurnal saliva cortisol levels and relations to psychosocial factors in a population sample of middle-aged Swedish men and women. *International Journal of Behavioral Medicine, 13*(3), 193-200.

Skelton, K., Ressler, K. J., Norrholm, S. D., Jovanovic, T., & Bradley-Davino, B. (2012). PTSD and gene variants: new pathways and new thinking. *Neuropharmacology, 62*(2), 628-637.

Slopen, N., Kubzansky, L. D., McLaughlin, K. A., & Koenen, K. C. (2013). Childhood adversity and inflammatory processes in youth: a prospective study. *Psychoneuroendocrinology, 38*(2), 188-200.

Starr, L. R., Dienes, K., Stroud, C. B., Shaw, Z. A., Li, Y. I., & Mlawer, F., et al. (2017). Childhood adversity moderates the influence of proximal episodic stress on the cortisol awakening response and depressive symptoms in adolescents. *Development and Psychopathology, 29*(05), 1877-1893.

Starr, L. R., Stroud, C. B., Shaw, Z. A., & Vrshek-Schallhorn, S. (2020). Stress sensitization to depression following childhood adversity: Moderation by HPA axis and serotonergic multilocus profile scores. *Development and Psychopathology, 32*(1), 1-15.

Steptoe, A., Hamer, M., & Chida, Y. (2007). The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. *Brain, behavior, and immunity, 21*(7), 901-912.

Sturge-Apple, M. L., Davies, P. T., Cicchetti, D., & Manning, L. G. (2012). Interparental violence, maternal emotional unavailability and children' s cortisol functioning in family contexts. *Developmental psychology, 48*(1), 237-249.

Sumner, J. A., Colich, N. L., Uddin, M., Armstrong, D., & McLaughlin, K. A. (2019). Early experiences of threat, but not deprivation, are associated with

accelerated biological aging in children and adolescents. *Biological psychiatry, 85*(3), 268-278.

Teschendorff, A. E., West, J., & Beck, S. (2013). Age-associated epigenetic drift: implications, and a case of epigenetic thrift?. *Human molecular genetics, 22*(R1), R7-R15.

Trickett, P. K., Gordis, E., Peckins, M. K., & Susman, E. J. (2014). Stress reactivity in maltreated and comparison male and female young adolescents. *Child Maltreatment, 19*(1), 27-37.

Tottenham, N., Hare, T. A., Quinn, B. T., McCarry, T. W., Nurse, M., Gilhooly, T., ···& Thomas, K. M. (2010). Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Developmental science, 13*(1), 46-61.

Trotman, G. P., Gianaros, P. J., Veldhuijzen van Zanten, J. J., Williams, S. E., & Ginty, A. T. (2019). Increased stressor-evoked cardiovascular reactivity is associated with reduced amygdala and hippocampus volume. *Psychophysiology, 56*(1), e13277.

Tsigos, C., & Chrousos, G. P. (2002). Hypothalamic–pituitary–adrenal axis, neuroendocrine factors and stress. *Journal of psychosomatic research, 53*(4), 865-871.

van Draanen, J. (2020). Unique roles of childhood poverty and adversity in the development of lifetime co-occurring disorder. *SSM-population health, 10*, 100540.

van Nierop, M., Lecei, A., Myin-Germeys, I., Collip, D., Viechtbauer, W., Jacobs, N., ···& van Winkel, R. (2018). Stress reactivity links childhood trauma exposure to an admixture of depressive, anxiety, and psychosis symptoms. *Psychiatry Research, 260*, 451-457.

Vigil, J. M., Geary, D. C., Granger, D. A., & Flinn, M. V. (2010). Sex differences in salivary cortisol, alpha-amylase, and psychological functioning following Hurricane Katrina. *Child Development, 81*(4), 1228-1240.

Vrshek-Schallhorn, S., Doane, L. D., Mineka, S., Zinbarg, R. E., Craske, M. G., & Adam, E. K. (2013). The cortisol awakening response predicts major depression: predictive stability over a 4-year follow-up and effect of depression history. *Psychological medicine, 43*(3), 483-493.

Watanabe, Y., Gould, E., & McEwen, B. S. (1992). Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain research, 588*(2), 341-345.

Weissman, D. G., Lambert, H. K., Rodman, A. M., Peverill, M., Sheridan, M. A., & McLaughlin, K. A. (2020). Reduced hippocampal and amygdala volume as a mechanism underlying stress sensitization to depression following childhood trauma. *Depression and anxiety, 37*(9), 916-925.

Wolf, E. J., Maniates, H., Nugent, N., Maihofer, A. X., Armstrong, D., Ratanatharathorn, A., ···& Logue, M. W. (2018). Traumatic stress and accelerated DNA methylation age: a meta-analysis. *Psychoneuroendocrinology, 92*, 123-134.

Zannas, A. S., Arloth, J., Carrillo-Roa, T., Iurato, S., Röh, S., Ressler, K. J., ···& Mehta, D. (2015). Lifetime stress accelerates epigenetic aging in an urban, African American cohort: relevance of glucocorticoid signaling. *Genome biology, 16*(1), 1-12.

Jin Guichun, & Wang Youzhi. (2017). The influence of childhood psychological abuse on aggressive behavior: The multiple mediating roles of perceived social support and personality traits. *Chinese Journal of Clinical Psychology, 25*(4).

Kong Xinyuan, Wang Xiang, Fang Shulin, He Jiayue, Zhang Panwen, & Luo Xingwei, et al. (2020). The relationship between childhood trauma and depression in college students: The mediating role of alexithymia. *Journal of Clinical Psychiatry, 30*(4), 247-249.

Li Wanru, & Ku Yixuan. (2020). The physiological and psychological mechanisms of acute stress affecting working memory. *Advances in Psychological Science, 28*(9), 1508-1524.

Niu Yi, Xue Yunzhen, Li Wentao, & Cao Yanmei. (2014). Childhood abuse experiences among college students and their relationship with family factors. *China Journal of Health Psychology, 22*(12), 1900-1903.

Ye Dongqing, Yao Jie, & Dong Maxia. (2004). Research status of adverse childhood experiences. *Chinese Journal of Disease Control & Prevention, 8*(6), 483-485.

Zhen Zhen, Qin Shaozheng, Zhu Ruida, Feng Chunliang, & Liu Chao. (2017). Exploring the brain mechanisms of stress and its impact on social decision-making. *Journal of Beijing Normal University (Natural Science), 53*(3), 372-378.

Zhang Huihui, & Zhang Liang. (2018). The impact of early stress on emotion regulation and its neural mechanisms. *Advances in Psychological Science, 26*(7), 1193-1203.

Note: Figure translations are in progress. See original paper for figures.