

Early-life stress and adult outcomes: Epigenetic, hormonal, and neurodevelopmental mechanisms

Abstract

Early-life stress (ELS) is a leading risk factor for mental and physical health problems in adulthood, but understanding of the underlying biological mechanisms is nascent. Using evidence from human and animal studies, this review examines three biological mechanisms (i.e., epigenetic modification, hormonal dysregulation, and altered brain development) through which ELS influences adult life. Across these studies, ELS was found to alter stress-regulating genes through epigenetic changes, disrupt cortisol regulation through the hypothalamic-pituitary-adrenal (HPA) axis, and affect the development and functioning of brain regions (e.g., hippocampus, prefrontal cortex, and amygdala). Rather than acting independently, these mechanisms reinforce one another in a cascade. Together, these findings demonstrate that early-life stress becomes biologically embedded in ways that persist in adulthood, highlighting the importance of early intervention and further research into whether these changes can be reversed.

Keywords: early-life stress, epigenetics, HPA axis, brain development, cortisol

Introduction(Mulligan, 2025)

Early life stress (ELS) is the leading preventable risk factor for mental illness, with childhood adversities accounting for approximately 29.8% of all adult mental disorders (Kessler et al., 2010; Shonkoff et al., 2012). Beyond psychiatric outcomes, ELS has also been linked to significant physical health burdens, including cardiovascular disease, cancer, and diabetes as well as accelerated biological aging associated with a 21% higher risk of premature mortality (Mulligan, 2025; Shonkoff et al., 2012). ELS refers to exposure to chronic adverse conditions during postnatal development, encompassing but extending beyond the adverse childhood experiences (ACE) framework, which focuses specifically on abuse, neglect, and household dysfunction (Birnie & Baram, 2025; Lee & Jung, 2024). While some literature extends early-life stress to include adolescents, this review focuses primarily on adverse experiences during childhood, specifically rapid and sensitive brain development (Birnie & Baram, 2025). In comparison to short term stress, chronic stress produces biological alterations that persist into adulthood (Mousikou et al., 2023). Although the associations between ELS and adult health outcomes are well established, the biological mechanisms that connect these relationships are still unresolved. Drawing on the evidence from both human and animal studies, this review examines three mechanisms by which ELS contributes to long-term changes in the brain: epigenetics, glucocorticoids/Hypothalamic-Pituitary-Adrenal (HPA) axis dysregulation, and brain development.

Historically, the primary threat to children's health was infectious diseases; however, as the development of vaccines, hygiene, and public health improved, a “new morbidity” of developmental and behavioral difficulties emerged (Shonkoff et al., 2012). This shift moved research beyond understanding the effects of early adversity towards investigating the biological mechanisms that produce these outcomes (Birnie & Baram, 2025). Researchers have consistently shown that ELS is reliably linked to posttraumatic stress disorder, attention deficit hyperactivity disorder, and schizophrenia, among other psychiatric disorders (Kessler et al., 2010; Lee & Jung, 2024). It has also been linked to physical conditions as well, including cardiovascular disease and accelerated biological aging (Lee & Jung, 2024; Mulligan, 2025). While the association between ELS and these outcomes is firmly established, the biological pathways that connect early adversity to lifelong diseases are only beginning to be understood (Lee & Jung, 2024; Pérez et al., 2019). When there is an exposure to a stressor, the body responds in one of two ways, either through the sympathetic nervous system or through the HPA Axis (Lee & Jung, 2024; Mousikou et al., 2023). The sympathetic nervous system is a rapid response that releases epinephrine and norepinephrine (Mousikou et al., 2023). The HPA axis (Figure 1) is a slower-acting hormonal pathway that begins when the hypothalamus releases Corticotropin-Releasing Hormone (CRH). The CRH signals the pituitary gland to release adrenocorticotrophic hormone (ACTH). Once the ACTH reaches the adrenal glands and releases cortisol, the cortisol circulates through the body and provides negative feedback that normally shuts the system off (6).

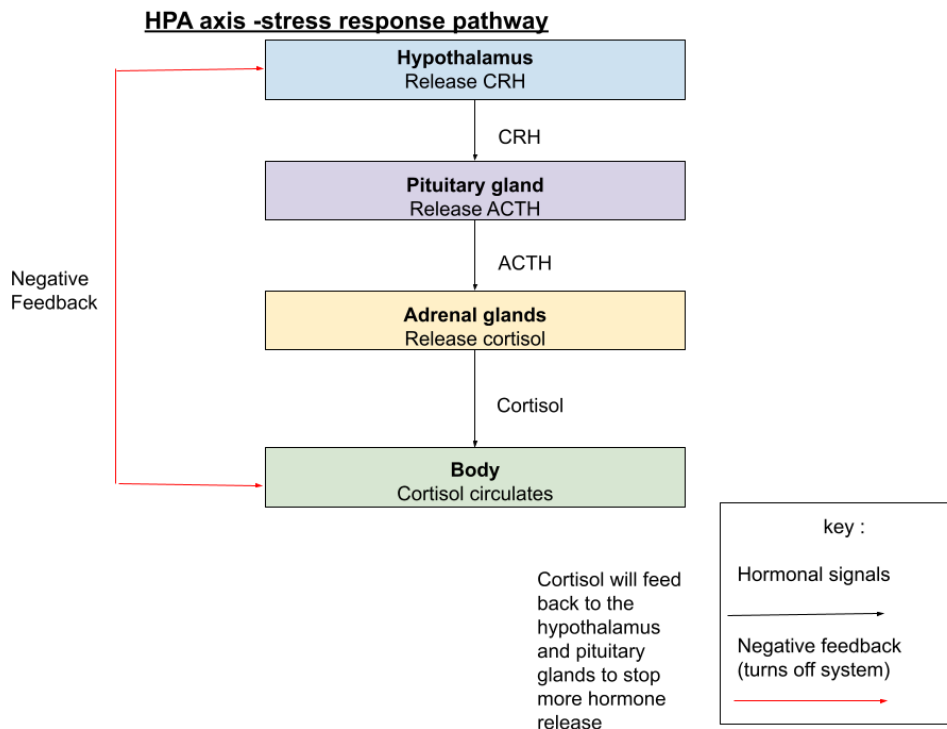


Figure 1. HPA axis response to a stressor. Stressor exposure triggers sequential release of CRH, ACTH, and cortisol. Cortisol provides negative feedback on the hypothalamus and pituitary glands to terminate the response.

In normal physiology, glucocorticoid levels regularly fluctuate, influencing the activation of the two main stress hormone receptors (McEwen et al., 2016). The two main stress hormone receptors that are incorporated into the system are mineralocorticoid (MR) and glucocorticoid (GR) receptors (McEwen et al., 2016). MR activates at low, everyday cortisol levels where it promotes stability and excitability in neurons to allow the brain to be ready and responsive (McEwen et al., 2016). GR activates only at high, stress-level cortisol concentrations, where it crosses into the brain and exerts suppressive, regulatory effects (McEwen et al., 2016).

The stress response is especially vulnerable to disruptions during the early development (Birnie & Baram, 2025). Early life is a period of rapid, tightly regulated brain development, involving processes such as synaptogenesis, synapse pruning, and myelination (Lee & Jung, 2024). During this period, the brain passes through a stress hyporesponsive period, a naturally low-cortisol window that protects the developing brain but is also highly sensitive to rising cortisol levels (Lee & Jung, 2024). To study these mechanisms directly, researchers often use animal models given the ethical and practical implications of deliberately exposing human infants to stress (Birnie & Baram, 2025). Through these animal studies, researchers can use controlled designs and monitor specimens longitudinally across their entire lifespan (Birnie & Baram, 2025; Lee & Jung, 2024). These findings can then be connected to human data to help validate the use of animal models and use evidence from animal and human studies (Lee & Jung, 2024). Although each of these mechanisms has been studied individually, they

are rarely examined as an interconnected system. This review synthesizes evidence across epigenetic, hormonal, and neurodevelopmental pathways to understand how early-life stress influences adult outcomes. The following section outlines how the studies within this review were identified and chosen.

Methods

Articles for this review were identified through searches of the PubMed database using the terms “early-life stress,” “stress,” “epigenetics,” “HPA axis,” “hippocampus,” and “adverse childhood experiences (ACE)”. Each term was searched individually rather than in combination. Initial searches were filtered to review articles to better understand the broader scope of the field. Later searches were expanded to include original research studies and experiments, providing primary evidence for specific mechanisms across both human and animal studies. Articles were included if they addressed the effects of early-life stress on brain development, the role of early caregiving, or structural and functional changes in specific brain regions such as the hippocampus and amygdala. In total, 14 articles met these criteria and were included in this review.

Results

Epigenetic changes.

Epigenetic modification refers to a chemical change that alters gene expression (Cheng et al., 2022). The three most commonly studied types are DNA methylation, histone modification, and non-coding RNA. DNA methylation is a chemical “mute button” at CpG sites that reduces expression. Histone modification changes the proteins that DNA wraps around. Lastly, non-coding RNA is the molecule that blocks gene translation without changing the DNA itself (Cheng et al., 2022; Mulligan, 2025). In rodent models of naturally varying maternal care, poor maternal care is linked to increased methylation of the glucocorticoid receptor (GR) gene, which reduces GR expression in the hippocampus and impairs the negative feedback loop that normally shuts off the stress response (Lee & Jung, 2024; McEwen et al., 2016). In contrast, positive maternal care (e.g., licking and grooming) increases GR expression through histone acetylation, demonstrating that the quality of caregiving shapes “stress gene” regulation in both directions (Lee & Jung, 2024; McEwen et al., 2016).

Similarly in rodents, glucocorticoid exposure from ELS alters methylation of the *Fkbp5* gene, which regulates GR sensitivity, and this change is associated with increased anxiety in adulthood (Lee & Jung, 2024). Additionally, ELS, specifically maternal separation combined with social isolation, increases methylation of the *Drd1a* gene, which encodes the dopamine D1 receptor in the nucleus accumbens. This silences the gene and reduces reward signaling, contributing to depressive symptoms that persists in adulthood (Cheng et al., 2022; Lee & Jung, 2024). ELS can also alter microRNAs, which help regulate genes important to brain development. Maternal separation caused lasting increases in miR-132 and miR-124 in the prefrontal cortex that were present early in development and still detectable in adulthood (Callaghan & Richardson, 2013).

Scientists can estimate biological age using “epigenetic clocks,” tools that predict age based on DNA methylation patterns in specific sites within the genome (Mulligan,

2025). When the biological age exceeds chronological age, this is known as epigenetic age acceleration (EAA) (Mulligan, 2025). Studies have shown that exposure to ELS can contribute to EAA in a dose-response situation (3). For example, women who experienced childhood sexual abuse had approximately 3.4 years of accelerated biological aging by their forties compared to women who had not experienced childhood sexual abuse (Mulligan, 2025). EAA carries significant health consequences: for every five years of age acceleration, there is a 21% higher risk of all-cause mortality, as well as an increased risk of cardiovascular disease, cancer, and diabetes (Mulligan, 2025). However, a human pilot study found a 2.5 year reduction in epigenetic age following a protocol aimed at regenerating the thymus, an immune organ that shrinks with age, suggesting that EAA may be at least partially reversible (Mulligan, 2025).

Hormonal dysregulation.

When ELS occurs during the stress hyporesponsive period, the HPA axis can be easily disrupted by abnormally high cortisol (Lee & Jung, 2024; Young et al., 2021). In rodent studies, limited bedding exposure produced elevated ACTH and glucocorticoids, enlarged adrenal glands, and a dysfunctional negative feedback loop (Lee & Jung, 2024). Beyond internal changes, chronic cortisol elevation suppresses the growth hormone, thyroid, and gonadal axes, leading to stunted growth, delayed puberty, and metabolic changes such as insulin resistance (Mousikou et al., 2023). ELS also disrupts immune function. Chronic HPA activation is associated with persistent inflammation, including elevated inflammatory cytokines and increased activity of microglia, the brain's immune cells (Lee & Jung, 2024). This inflammatory state may impair immune responses and could even contribute to cancer (Lee & Jung, 2024).

ELS also disrupts several neurotransmitter systems including norepinephrine, dopamine, and serotonin. The norepinephrine system, which governs rapid arousal, becomes over-responsive after chronic stress, showing increased excitability (Cheng et al., 2022; Lee & Jung, 2024). The dopamine system, which is the reward and motivation system, is disrupted through the *Drd1a* silencing described previously, along with changes to the mesocortical circuit that contribute to vulnerability to addiction and psychosis (Lee & Jung, 2024). Finally, the serotonin system is particularly significant, as it transmits signals and helps shape brain development (Lee & Jung, 2024). ELS reduces serotonin transporter expression and alters serotonin signaling, changes associated with depression (Cheng et al., 2022; Lee & Jung, 2024). Human evidence supports these mechanisms (Young et al., 2021). In a 37-year longitudinal study of 112 individuals, early-life stress predicted blunted adult cortisol responses more strongly than cumulative lifetime stress, indicating that early life is a uniquely sensitive window for HPA programming (Young et al., 2021).

Altered brain development.

Beyond hormonal and genetic changes, ELS can reshape a person's physical brain structure. Chronic stress causes structural changes in certain regions, shrinking the hippocampus and prefrontal cortex through neuronal atrophy, while the amygdala expands (McEwen et al., 2016).

Chronic stress and elevated glucocorticoids cause neuronal atrophy in the hippocampus, exhibited by retracting dendrites and losing spines (McEwen et al., 2016). Chronic stress also suppresses hippocampal neurogenesis (McEwen et al., 2016). This could potentially underlie the memory deficit that has been associated with long-term cortisol exposure (McEwen et al., 2016). Moreover, chronic stress causes the amygdala, which governs threat detection and emotional responses, to expand, with dendrites growing rather than retracting (McEwen et al., 2016). Early adversity also makes the amygdala more reactive to threats, as it is densely packed with stress hormone receptors during a sensitive developmental window (VanTieghem & Tottenham, 2017). Human studies report similar effects. For example, previously institutionalized youth (ages 7-16) are more likely to display heightened, adult-like amygdala reactivity compared to non-institutionalized youth (VanTieghem & Tottenham, 2017). The combination of a shrunken hippocampus and an enlarged amygdala can explain the anxiety, hypervigilance, and emotional dysregulation commonly seen in adulthood after early chronic stress and trauma (McEwen et al., 2016; VanTieghem & Tottenham, 2017). Similar to the hippocampus, the prefrontal cortex (PFC) also shrinks under chronic stress, with dendrites retracting; this shrinkage is reversible in young (3-month-old) rats but becomes less reversible with age (McEwen et al., 2016; VanTieghem & Tottenham, 2017). With early adversity, the amygdala-PFC connection weakens or develops abnormally, impairing emotion regulation (VanTieghem & Tottenham, 2017).

Beyond broadly stress-responsive regions, sensory systems develop early and remain highly plastic, making them vulnerable to disruption (Tomoda et al., 2025). For example, the type of ELS appears to shape which brain regions are affected, with harsh corporal punishment, childhood sexual abuse, and parental verbal abuse each linked to distinct structural changes (Tomoda et al., 2025). In one human study [add number of participants], young adults who witnessed domestic violence during childhood showed reduced gray matter volume and cortical thinning in visual regions, with a reduction of approximately 6% in the right lingual gyrus (Tomoda et al., 2012). Together, these findings suggest that ELS does not affect the brain uniformly; rather, the specific sensory regions that process adverse experiences are the most altered by this.

Discussion

The evidence reviewed supports the notion that early-life stress influences adult outcomes through three biological mechanisms that work together in an integrated system. Epigenetic changes such as GR gene methylation reduces the receptors needed to regulate the HPA axis, leading to prolonged cortisol elevation (Lee & Jung, 2024; McEwen et al., 2016). This continued cortisol elevation then reshapes the physical structure of the brain, shrinking the hippocampus and prefrontal cortex while enlarging the amygdala (McEwen et al., 2016). Ultimately, these structural changes may impair memory and emotion regulation, potentially increasing vulnerability to psychiatric disorders in adulthood (McEwen et al., 2016; VanTieghem & Tottenham, 2017). These mechanisms reinforce one another, which helps explain why early-life stress produces lasting and wide-ranging effects.

However, not all individuals exposed to ELS develop the same outcomes. Several factors, including timing, caregiving environment, and genetics [explain why

these factors moderate the effect of ELS on the outcomes here]. Recent research also suggests unpredictability of adversity plays a role. The timing of stress plays an important role in brain development, which is most sensitive during early windows (Lee & Jung, 2024). Stress during early childhood has been shown to predict adult cortisol dysregulation more strongly than stress experienced later in life (Lee & Jung, 2024; Young et al., 2021). The caregiving environment can also shape outcomes, as supportive and responsive caregiving can decrease the effects of ELS, while stable caregiver relationships are among the strongest protectors against toxic stress (McEwen et al., 2016; Shonkoff et al., 2012). Finally, genetic variation contributes to these differences, as certain genotypes can make individuals more vulnerable to the effects of ELS (Cheng et al., 2022; Lee & Jung, 2024).

There are several limitations to consider. First, much of the mechanistic evidence comes from animal models, specifically rodents, and may not fully translate to human development. Second, there are relatively few longitudinal human studies, which are necessary to verify that early-life stress produces lasting effects across the lifespan. Third, the definition of early-life stress varies across studies, ranging from specific forms of abuse to broadened adversities, which makes it difficult to compare findings. These mechanisms have specific implications for treatment and prevention. Because some epigenetic changes appear at least partially reversible, interventions timed to sensitive developmental windows may help reduce the lasting effects of ELS (McEwen et al., 2016). In addition, because the quality of caregiving can influence stress-gene regulation, supporting a stable and responsive caregiver may act as a biologically useful form of prevention (McEwen et al., 2016; Shonkoff et al., 2012).

Conclusion

In summary, this review examined the biological mechanisms through which early-life stress influences adult outcomes, focusing on epigenetic modification, HPA axis dysregulation, and altered brain development. Epigenetic modification has been shown to produce lasting chemical changes to stress-regulating genes, altering how the body responds to stress and accelerating biological aging. Dysregulation of the HPA axis disrupts the body's ability to control cortisol levels, with lasting effects on the brain, physical growth, immune function, and neurotransmitter systems. Altered brain development physically reshapes key regions in the brain, shrinking the hippocampus and prefrontal cortex while enlarging the amygdala, potentially impairing memory and emotion regulation. Together, early-life stress produces significant biological changes that continue into adulthood, reinforcing the importance of early prevention and intervention as a public health priority. Future research should investigate whether ELS-related biological changes can be reversed, and how these mechanisms can be applied to develop effective prevention and public health intervention systems.

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