Early-life stress and adult outcomes: Epigenetic, stress signaling, and structural brain 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 argues that three biological mechanisms (epigenetic modification, stress signaling dysregulation, and structural brain changes) reinforce one another to shape adult outcomes. Across these studies, ELS was found to alter stress-regulating genes through epigenetic changes, disrupt cortisol regulation and neurotransmitter signals, and alter the structure of brain regions (e.g., hippocampus, prefrontal cortex, and amygdala). These mechanisms appear to act as a cascade, although the links between them come largely from rodent studies, while human studies show outcomes consistent with each mechanism. These findings suggest 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 structure, cortisol

Introduction

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 (2,3). Beyond psychiatric outcomes, ELS has also been linked to significant physical health burdens, including cardiovascular disease, cancer, and diabetes (1,3), as well as accelerated biological aging associated with a 21% higher risk of premature mortality (1). 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 (4,5). 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 (4). In comparison to short term stress, chronic stress produces biological alterations that persist into adulthood (6). Although the associations between ELS and adult health outcomes are well established, the biological mechanisms that connect these relationships are still unresolved.

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 (3). This shift moved research beyond understanding the effects of early adversity towards investigating the biological mechanisms that produce these outcomes (4). 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 (5,6). The sympathetic nervous system is a rapid response that releases epinephrine and norepinephrine (6). 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 adrenocorticotropic 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).

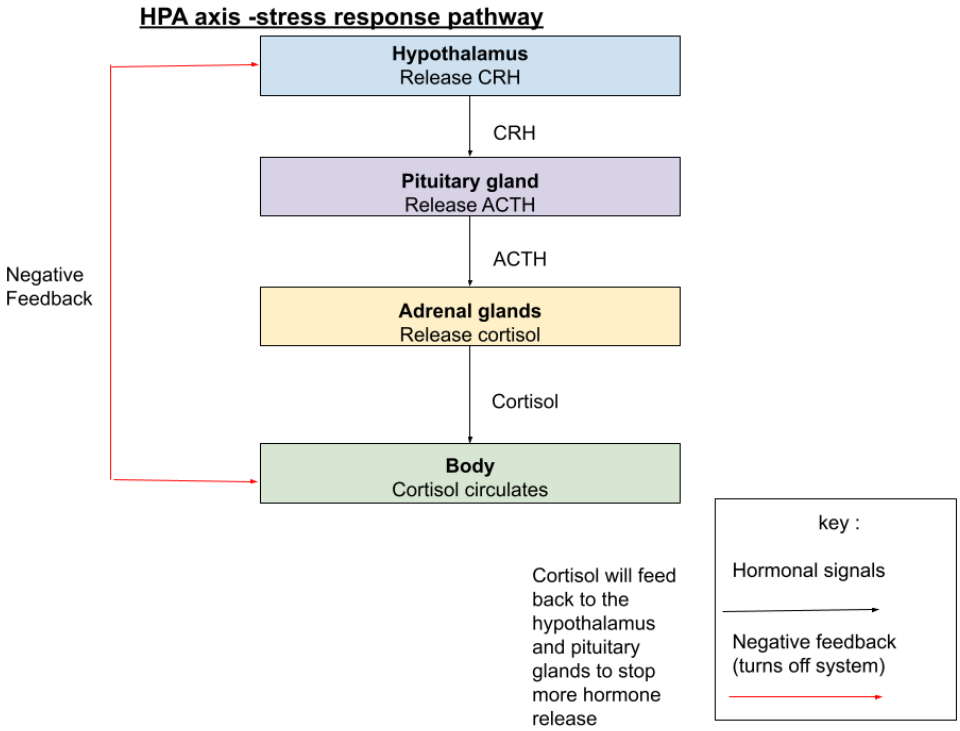


Figure 1. HPA axis response to a stressor. Stressor exposure triggers sequential release of CRH, ACTH, and cortisol. Cortisol provides negative feedback on the hypothalamus and pituitary glands to terminate the response.

In normal physiology, glucocorticoid levels regularly fluctuate, influencing the activation of the two main stress hormone receptors (8). The two main stress hormone receptors that are incorporated into the system are mineralocorticoid (MR) and glucocorticoid (GR) receptors (8). MR activates at low, everyday cortisol levels where it promotes stability and excitability in neurons to allow the brain to be ready and responsive (8). GR is primarily activated at high, stress-level cortisol concentrations, when cortisol enters the brain in large amounts and GR exerts suppressive, regulatory effects (8).

Epigenetic modification refers to a chemical change that alters gene expression (9). 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 (1,9).

The stress response is especially vulnerable to disruptions during the early development (4). Early life is a period of rapid, tightly regulated brain development, involving processes such as synaptogenesis, synapse pruning, and myelination (5). 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 (5). To study these mechanisms directly, researchers often use animal models given the ethical and practical implications of deliberately exposing

human infants to stress (4). Through these animal studies, researchers can use controlled designs and monitor specimens longitudinally across their entire lifespan (4,5). 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 (5). Although each of these mechanisms has been studied individually, they are rarely examined as an interconnected system. Drawing on the evidence from both human and animal studies, this review argues that three mechanisms—epigenetic modification, stress signaling dysregulation, and structural brain changes—reinforce one another, which helps explain why early-life stress produces lasting and wide-ranging effects such as impaired stress regulation and psychiatric vulnerability.

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 modification.

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 (5,8). 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 (5,8).

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 (5). 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 (5,9). ELS can also alter microRNAs, which help regulate genes important to brain development (10). In rates, 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 (10).

Scientists can estimate biological age using “epigenetic clocks,” tools that predict age based on DNA methylation patterns in specific sites within the genome (1). When the biological age exceeds chronological age, this is known as epigenetic age acceleration (EAA) (1). Studies have shown that exposure to ELS can contribute to EAA

in a dose-response manner (1). 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 (1). 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 (1). 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 (1). Overall, early stress leaves lasting chemical marks on stress-related genes (GR, Fkbp5, Drd1a) that persist into adulthood. These chemical marks are where the cascade begins. Because reduced GR expression weakens the negative feedback loop, these epigenetic changes set up the stress signaling dysregulation.

Stress signaling dysregulation.

When ELS occurs during the stress hyporesponsive period, the HPA axis can be easily disrupted by abnormally high cortisol (5). In rodent studies, limited bedding exposure produced elevated ACTH and glucocorticoids, enlarged adrenal glands, and a dysfunctional negative feedback loop (5). In a 37-year longitudinal human 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 (11). This suggests that early exposure to cortisol may eventually create a stress system that under-responds, rather than one that over-respond. 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 (6). 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 (5). This inflammatory state may impair immune responses and could even contribute to cancer (5).

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 (5,9). 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 (5). Finally, the serotonin system is particularly significant, as it transmits signals and helps shape brain development (5). ELS reduces serotonin transporter expression and alters serotonin signaling, changes associated with depression (5,9). Early stress disrupts the stress system in two ways: cortisol regulation, which is elevated early but blunted in adulthood, and neurotransmitter signaling, including norepinephrine, dopamine, and serotonin. Cortisol disruption affects growth and immunity, while neurotransmitter changes affect mood and reward. The prolonged cortisol elevation that occurs early on also connects to the next mechanism, as chronic glucocorticoid exposure drives the structural brain changes.

Structural brain changes.

Beyond epigenetic and stress signaling changes, ELS can reshape a person's brain structure. In adult rodent models, chronic stress causes structural changes in certain regions, shrinking the hippocampus and prefrontal cortex through neuronal atrophy, while the amygdala expands (8).

Chronic stress and elevated glucocorticoids cause neuronal atrophy in the hippocampus, exhibited by retracting dendrites and losing spines (8). Chronic stress also suppresses hippocampal neurogenesis (8). This could potentially underlie the memory deficit that has been associated with long-term cortisol exposure (8). Moreover, chronic stress causes the amygdala, which governs threat detection and emotional responses, to expand, with dendrites growing rather than retracting (8). Studies specifically suggest that early adversity makes the amygdala more reactive to threats, as it is densely packed with stress hormone receptors during a sensitive developmental window (12). 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 (12). The combination of a shrunken hippocampus and an enlarged amygdala may help explain the anxiety, hypervigilance, and emotional dysregulation commonly seen in adulthood after early chronic stress and trauma (8,12). 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 (8). With early adversity, the amygdala-PFC connection weakens or develops abnormally, impairing emotion regulation (12).

Beyond broadly stress-responsive regions, sensory systems develop early and remain highly plastic, making them vulnerable to disruption (13). Moreover, 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 (13). In one human study of 52 young adults (22 who witnessed domestic violence and 30 comparison participants), those who witnessed domestic violence during childhood showed reduced gray matter volume and cortical thinning in visual regions, including a 6.1% reduction in the right lingual gyrus (14). These findings indicate that ELS does not affect the brain uniformly, as the sensory regions involved in processing a particular adverse experience appear especially susceptible to change (13,14). Early stress therefore reshapes both stress-responsive regions and the sensory regions that process adverse experiences. As the final step in the cascade, these structural changes may contribute to the impaired emotion regulation and psychiatric vulnerability observed in adults exposed to ELS.

Discussion

The evidence reviewed suggests that early-life stress affects adult outcomes through three mechanisms that reinforce one another. Epigenetic changes such as GR gene methylation reduce the receptors needed for negative feedback, prolonged cortisol elevation (5,8). This prolonged exposure is associated with structural changes in the hippocampus, prefrontal cortex, and amygdala that may impair memory and emotion regulation (8,12). However, the evidence differs across these links. The mechanism steps, from caregiving to GR methylation and from glucocorticoid exposure to dendrite

changes, come largely from rodent studies (5,8). Human studies instead show outcome consistent with each mechanism, including accelerated epigenetic aging after childhood sexual abuse (1), blunted adult cortisol response (11), and altered amygdala reactivity and visual cortex volume (12,14). No study reviewed here trace all three steps in the same individuals, so the cascade remains a well-supported model rather than a directly demonstrated pathway.

There are also several factors, including timing, caregiving environment, and genetics, that influence how strongly ELS affects these mechanisms. Timing matters because stress during the stress hyporesponsive period disrupts the HPA axis while it is still being programmed (5). Consistent with this, early childhood stress predicts blunted adult cortisol responses more strongly than cumulative lifetime stress (11). The caregiving environment can also buffer these effects. Because maternal care regulates GR expression through DNA methylation and histone acetylation, supportive caregiving may protect the stress-regulating gene described earlier (5,8). In addition, stable caregiver relationships are among the strongest protectors against toxic stress (3). Finally, genetic variation contributes to these differences, as certain genotypes can make individuals more vulnerable to the effects of ELS (5,9).

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 and structural changes appear at least partially reversible, interventions timed to sensitive developmental windows may help reduce the lasting effects of ELS (1,8). 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 (3).

Conclusion

In summary, this review argues that early-life stress influences adult outcomes through three mechanisms that reinforce one another: epigenetic modification, stress signaling dysregulation, and structural brain changes. 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. Stress signaling dysregulation disrupts both cortisol regulation and neurotransmitter systems, with lasting effects on physical growth, immunity, and mood and reward processing. Structural brain changes reshape key regions, shrinking the hippocampus and prefrontal cortex while enlarging the amygdala, potentially impairing memory and emotion regulation. Although the link between these mechanisms rests largely on rodent evidence, the biological changes produced by early-life stress appear to persist 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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