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REVIEW ARTICLE

Early life stress and trauma: developmental neuroendocrine aspects of prolonged stress system dysregulation

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Abstract

Experience of early life stress (ELS) and trauma is highly prevalent in the general population and has a high public health impact, as it can trigger a health-related risk cascade and lead to impaired homeostatic balance and elevated cacostatic load even decades later. The prolonged neuropsychobiological impact of ELS can, thus, be conceptualized as a common developmental risk factor for disease associated with increased physical and mental morbidity in later life. ELS during critical periods of brain development with elevated neuroplasticity could exert a programming effect on particular neuronal networks related to the stress response and lead to enduring neuroendocrine alterations, i.e., hyper- or hypoactivation of the stress system, associated with adult hypothalamic-pituitary-adrenal axis and glucocorticoid signaling dysregulation. This paper reviews the pathophysiology of the human stress response and provides evidence from human research on the most acknowledged stress axis-related neuroendocrine pathways exerting the enduring adverse effects of ELS and mediating the cumulative long-term risk of disease vulnerability in adulthood.

Keywords Early life stress · Childhood trauma · Childhood adversity · HPA axis · Autonomic nervous system · Cortisol · Glucocorticoids · Endocrine system

Introduction

The developmental origins hypothesis suggests that the roots of adult disease are to be found among disruptions of physiological developmental processes in early life [1, 2]. The term "early life stress" (ELS) has been used to describe a broad spectrum of adverse exposures during fetal and neonatal life, early and late childhood, and adolescence (e.g., childhood trauma, maltreatment, neglect, separation, abuse, parental loss, and starvation). Experience of such disrupting early life adversities occurs at disturbingly high rates in the general population (over 30–40% of the adult population have experienced some form of ELS) and constitutes a major public health problem [3, 4]. ELS during critical phases of perinatal and juvenile brain development is associated with higher levels of cacostatic load and reduced adaptability to stress in adult life, leading to enhanced vulnerability to disease [5].

Many studies have reported a negative impact of ELS and trauma on adult general mental and physical health-related quality of life. Particularly, a higher risk of psychiatric disorders (e.g., depression, posttraumatic stress disorder, and schizophrenia) and their unfavorable outcomes has been recurrently associated with ELS experience in several retrospective [6–9] but also prospective [10] studies. In addition, risk behavior patterns such as substance use and, especially, tobacco and alcohol consumption are considered significantly increased in individuals with ELS history [11–13]. A recent meta-analysis by Zatti et al. also confirmed the close association of ELS and suicide attempts in later life [14]. Nevertheless, the chronic physical health consequences of childhood adversities may be as substantial as mental health consequences [7, 15]. Several studies and meta-analyses of

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related research point to a distinct association of ELS with cardiovascular, gastrointestinal, neurological, musculoskeletal, pulmonary, and metabolic diseases; chronic inflammatory and pain syndromes; frequency of medical consultations, and number of medical diagnoses [7, 16–21]. These findings indicate that ELS experience not only alters neurobiological systems resulting in an increased risk of mental disorders but may also have a long-lasting effect on a number of organ systems.

ELS rarely occurs as a single event but frequently consists of prolonged or repetitive experience of one or more types of malicious acts. Several negative risk factors may also coexist (e.g., poverty, parental psychopathology, and drug addiction), contributing to a complex milieu of multiple chronic stressors, which calls for specialized assessment [22]. In particular, the seriousness of physical and psychological consequences has often been linked to the number of ELS events experienced [23–26]. In several studies, the number of ELS experiences has been associated with a higher adult risk of psychiatric symptom complexity and severity, psychiatric comorbidities, prescribed psychotropic medication, poor mental and physical quality of life, as well as several physical conditions (e.g., heart disease, asthma, diabetes mellitus, arthritis, chronic spinal pain, and chronic headache) [7, 9, 27–30].

The long-term effects of ELS may, thus, be conceptualized as a common developmental risk factor triggering a health-related risk cascade and mediating cumulative health risk leading to increased physical and mental morbidity and all-cause mortality in later life [1, 3, 23, 31–33]. Furthermore, genetic factors, the specific nature of ELS and particularly its exact timing, presence of caregivers and psychological support, family history of major psychiatric disorders, as well as additional traumatic stress experiences in adulthood may all greatly influence downstream biological pathways and further influence the individual vulnerability for later disease [34]. Although the number of studies assessing the causal relations between ELS and its long-term adverse health-related effects is constantly on the rise, little is known about the exact neurobiological pathways through which ELS is translated into biological health risk.

Among all the systems involved though, the most apparent link between ELS and adult disease is neuroendocrine alterations reflecting a chronic dysregulation of the stress system [34]. This paper reviews the pathophysiology of the human stress response and provides evidence from human research on the most acknowledged stress-related neuroendocrine trajectories, mediating the cumulative long-term risk of disease vulnerability in later life after ELS exposure (cf. Fig. 1).

The biology of stress

Stress, homeostasis, and cacostatic load

The capacity to maintain a state of complex dynamic balance and constant fluctuation around an ideal homeostatic condition (*non-equilibrium homeodynamic state*) serves self-regulation and adaptability of the organism to ongoing challenges [35, 36]. This optimal state is constantly challenged by intrinsic or extrinsic, real or perceived altering conditions or stimuli, defined as stressors. When stressors exceed a certain severity or temporal threshold, perceived stressor-related information initiates a complex stress response, redirecting energy according to the current needs [5, 37–40]. The organism's total response to these ongoing demands is defined as allostatic load and mirrors a state of disharmony. Thus, stress is defined as the state of threatened homeostasis [5, 41].

Repeated, ephemeral, and motivating stress states lead to response habituation and are fairly beneficial, while inadequate, aversive, excessive, or prolonged stress may surpass the natural regulatory capacity and adjustive resources of the organism and majorly affect adaptive responses [5]. Cumulative or excessive stress exposure, especially in developmental stages of particular stress sensitivity and plasticity (e.g., early childhood), but also following a single but extreme stress experience (e.g., traumatic stress) may oversensitize neuroendocrine responses to stress. This can lead to excessive and prolonged activation of the stress system or, in a subgroup of individuals, to chronic hypoactivation of this system and a vulnerable phenotype with disrupted stress reactivity. This chronic condition can result in an altered homeodynamic state, called *allostasis* or, more accurately, *cacostasis* (i.e., *negatively altered homeodynamic state*, *dyshomeostasis*), and accumulated *cacostatic* load which is related to chronic physical and mental morbidity [5]. In the long run, secondary biological alterations with profound and debilitating effects on homeodynamic balance, health, and development are the sequelae of this state [42–46].

The human stress system and the stress response

The human stress system includes central and peripheral components. The central, greatly interconnected components of the stress system are located in the hypothalamus and the brain stem and include the following: (a) the parvocellular neurons of corticotropin-releasing hormone (CRH), (b) the arginine-vasopressin (AVP) neurons of the hypothalamic paraventricular nuclei (PVN), (c) the CRH neurons of the paragigantocellular and parabranchial nuclei of the medulla and the locus coeruleus (LC), (d) the arcuate nucleus proopiomelanocortin-derived peptides alpha-melanocyte-stimulating hormone (MSH) and beta-endorphin, (e) other mostly noradrenergic (NE) cell groups in the medulla and pons (LC/NE system), and (f) the central nuclei of the autonomic nervous system (ANS). The peripheral components of the stress system include (a) the hypothalamic-pituitary-adrenal (HPA) axis and (b) the limbs of the ANS comprising (i) the sympathetic nervous system (SNS) and sympatho-adrenomedullary (SAM) system and (ii) the parasympathetic system (PNS).

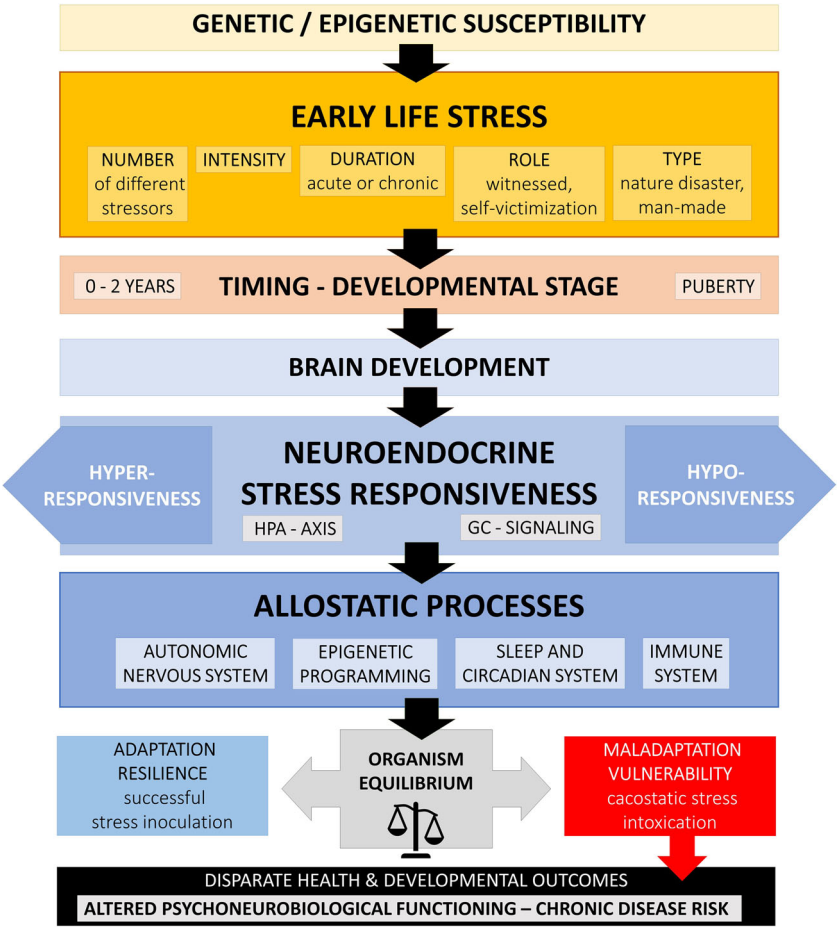

Fig. 1 Schematic model of developmental neuroendocrine aspects of prolonged stress system dysregulation after early life stress exposure

Activation of the stress system through perception of a threat by the limbic system (i.e., PVN) leads to a normally adaptive and time-limited micro-, meso-, and macrophysiologic compensatory response, redirecting energy according to the current needs [5, 37–40]. Together, these responses through different stress effector tissues produce an orchestrated "symphony" enabling a fine-tuned response to challenge in both the central nervous system (CNS) and the somatic periphery [47]. The stress response is remarkably consistent in its qualitative presentation. The principal peripheral effector molecules are the HPA axis-regulated glucocorticoids (GCs) and the SAM-regulated catecholamines (CAs) NE and epinephrine. GCs participate in early direct and non-genomic molecular events as well as in transcriptional cellular procedures [5, 37–41, 48] and are essential to the maintenance, duration, and downregulation of the stress response mainly through GC binding to glucocorticoid receptors (GRs) in the hippocampus [49, 50].

Pathophysiology of the stress response

Traumatic and long-term stress exposure is considered to lead to sustainable alterations in stress regulation and psychophysiological reactivity [1, 3, 15, 19, 23, 31–33, 51–53], impaired GC signaling [54–56], and changes in ANS function, the HPA axis, and the SAM system [57, 58]. Previous results have pointed to a particularly crucial role of GC signaling in the pathophysiology of chronic stress. Insufficient glucocorticoid signaling, although through dysregulations at different levels (resulting from either hyper- or hypoactivation of the HPA axis), may have similar devastating effects on the organisms' physiology [55]. Such effects may be related to the particular role of GC signaling in the regulation of the immune system and the ANS [54]. The typical example of chronic hyperactivation of the stress system is observed in melancholic depression [5, 48], with chronic hypersecretion of CRH/AVP by the hypothalamus and hypersecretion of ACTH by the pituitary [49], resulting in repeated activation of the stress system and increased peripheral cortisol levels due to an insensitive negative GC feedback of the HPA axis loop [59]. Similarly, other conditions, such as anorexia nervosa, obsessive–compulsive disorder, panic disorder, alcohol withdrawal, excessive exercising, poorly controlled diabetes mellitus, and hyperthyroidism among others, may also be associated with increased cortisol levels through hyperactivation of the HPA axis [60]. On the other hand, repeated or chronic stress may also result in hypoactivation of the HPA axis (rather than sustained

activation), with lower peripheral cortisol levels, possibly reflecting a compensatory physiologic adaptation [56, 60, 61]. Patients with atypical depression, chronic fatigue syndrome, fibromyalgia, hypothyroidism, nicotine withdrawal syndrome, and PTSD fall into this category. This diminished secretion seems to be the result of a negative feedback hypersensitivity of GCs associated with an upregulated leukocyte GR number and sensitivity [62–66], downregulated secretion of CRF/AVP to the pituitary [49], or a long-lasting dropping of glucocorticoid catabolism to increase the persistence of active cortisol in the liver and kidney without elevation of circulating levels [67]. These effects appear even greater in individuals with ELS history, suggesting a developmental programming through GC signaling.

ELS and the stress system

Preclinical and clinical studies have shown that ELS can irreversibly disrupt central neurobiological systems crucial for growth and puberty in the most vulnerable periods of human development and, thus, lead to long-lasting altered neuroendocrine stress responses [64, 68, 69]. Because of their pivotal role in the regulation of the dynamic stress response, the HPA axis and ANS have received the closest scrutiny in relation to other systems that may be longitudinally affected by ELS [34, 70]. However, progress in this research area is hampered by the complex and often conflicting associations found between markers of HPA axis function (i.e., both increased and decreased HPA axis activity) and ELS [5, 70], as well as the broad definition of ELS (i.e., broad time window of 0–18 years of age). For example, ELS has been repeatedly positively associated with HPA axis hyperactivity not only in adults with depression and PTSD but also in healthy individuals (e.g., increased peripheral cortisol and dehydroepiandrosterone-DHEA levels, enhanced CAR, increased ACTH and cortisol responses to psychosocial stress or endocrine challenges) [71–80], while several studies have reported HPA axis hypoactivity (e.g., reduced peripheral cortisol levels and blunted cortisol responses to psychosocial stress) in similar populations and study designs [81–85]. Therefore, several factors may have influenced study results, such as the exact subtype of trauma, gender, and the assessment of phasic (e.g., diurnal saliva cortisol and cortisol reactivity to challenge) versus tonic cortisol values (e.g., hair cortisol) [86, 87]. However, probably the most important factor modulating the impact of ELS in later HPA axis activity is its exact timing.

Timing of ELS and HPA axis development

Although the HPA axis develops continuously from infancy to adolescence and adulthood, specific periods of greater plasticity may also represent periods of greater vulnerability and, very likely, profound and enduring consequences [88]. In conjunction with the HPA axis, amygdala, and hippocampus development, there are also evolving non-linear patterns until the age of 25 years, with specific gender differences [89–91]. Accordingly, several findings suggest a differential impact of ELS according to specific developmental age of exposure.

One of the most vulnerable periods in CNS development is infancy and early childhood (0–2 years of age) [44, 88, 92, 93]. Animal and human research implies that the HPA axis, after an initial hyperresponsive period, may later transition into a stress hyporesponsive period (SHRP) with blunted basal and stress-induced cortisol [88, 92, 94, 95]. Several longitudinal studies indicate that stress responses in early childhood decrease with age throughout the preschool period [88, 94–96]. There are several studies demonstrating that these findings might reflect a particular social buffering of the HPA axis (i.e., blunted response) by a nurturing caregiver, who may operate as a safety signal and help maintain low GC levels [97–99]. Interestingly, in a recent review, Struber et al. have also proposed important interactions of GC signaling with oxytocin pathways, which may, in part, explain some of results in early childhood [100]. Collectively, these findings suggest that the shift from a hyper- to a relatively hyporesponsive stress axis during the first 2 years of life within the first 2 years of age may be an important stress-sensitive period, especially in the absence of a nurturing caregiver [92]. ELS accompanied by heightened cortisol during the hyporesponsive period could lead to greater exposure to glucocorticoids and, in turn, to glucocorticoid receptor insensitivity over time, affecting the physiological development of a hyporesponsive HPA axis [88, 101]. Studies from Kuhlman et al. [87, 102] confirm that ELS exposure prior to the age of 2 years was associated with prolonged cortisol responses to an acute social stressor among adolescents. Similarly, in their longitudinal orphan study, McLaughlin et al. [103] reported that youth who had been placed in foster care before the age of 2 showed similar cortisol responses to never-institutionalized children, while youth in prolonged institutionalization exhibited blunted cortisol responses to psychosocial stress. These findings support the hypothesis of a particularly high sensitivity and plasticity during the first 2 years of life.

Another particularly sensitive and vulnerable period is the later developmental stage of adolescence/puberty, which signifies a new major change in HPA axis activity, transitioning from hyporesponsivity to a period of increased activity [88, 104–106] with continuously higher basal [95, 99, 107, 108] and reactive [95, 107, 109–111] cortisol levels. Interestingly, during this developmental stage, parental support does not seem to buffer HPA axis reactivity in humans [99]. However, the autonomy and sexual maturation characterizing this period in humans may reprogram HPA axis reactivity for the new challenges in interaction with sex and environmental

cues [102]. The individual, but also gender-specific onset of gonadal hormone production (pubertal maturation completed around the age of 16 years), plays a pivotal role in stress and HPA axis reactivity, since estrogen secretion suppresses HPA axis hyperactivity in women [112]. Some human studies on ELS during adolescence reported lower baseline cortisol [113] and blunted cortisol responses to psychosocial stress [114], hence pointing to an opposite effect of ELS on HPA axis basal activity and reactivity than in infancy.

Taken together, ELS during the first hyposensitive 2 years of life may lead to a hyperactivity and hyperresponsiveness of the HPA axis and ELS during the hyperactive phase of adolescence to a hypoactive and hyporesponsive HPA axis [88]. The study by Bosch et al. [115] confirms this hypothesis by reporting a particular association between adversities in the first year of life, but not late childhood or adolescence, and heightened cortisol reactivity later in life. In addition, they reported greater cortisol output later in life after experience of adversities during childhood, but lower cortisol output after experience of adversities in adolescence. These age-related differences in HPA axis activity and reactivity seem also to be reflected in the specific risk of developing a mental disorder. Accordingly, after traumatization in early childhood, the risk of developing major depressive disorder in adulthood equals the risk of developing PTSD, while after traumatization in adolescence, the risk of PTSD is greater than that of depression [6].

Interplay between the HPA axis and the ANS

Normally, the HPA axis and the ANS are closely interconnected at several neuroendocrine levels and their activity shows some degree of analogy and complementarity throughout the body. The HPA axis and the ANS are increasingly studied together [116], as integrated and interrelated components of an internal neural regulation system (central autonomic network, CAN). Dysregulation of the central autonomic network [117–119] may affect downstream autonomic core centers, from the prefrontal cortex (PFC) via the amygdala and the hypothalamus to the brain stem, thereby altering peripheral ANS activity and overall stress responsiveness [118, 120, 121]. Accordingly, findings suggest that the appropriate regulation of the HPA axis depends, at least in part, on the ANS, especially on vagal influences [122]. On the other hand, ANS activity is heavily implicated in the development of trauma- and stress-related pathophysiological alterations. The significant overlap of the fear/arousal circuitry with the CAN [123] could, at least in part, be responsible for autonomic dysregulation after ELS or trauma exposure [124]. The high comorbidity of stress- and trauma-related psychiatric disorders with cardiovascular disease [125–130] confirms an important pathophysiological link between these disorders and autonomic control [131–133].

With respect to these findings, some studies have reported increased ANS activity in adults with ELS exposure. For example, Otte et al. [134] have shown increased CA responses to psychological stress in police academy recruits with ELS history, while O'Hare et al. [135] reported a strong association between ELS experience and syncope frequency in adulthood. However, the number of adult ELS-exposed studies is limited in relation to the numerous studies assessing ANS activity in adult PTSD patients and pointing to an increased sympathetic and/or decreased vagal activity as a sequel of trauma [136].

Lately, several pediatric studies have sought to shed some light on the interplay between the HPA axis and the ANS after ELS. De Bellis et al. have reported significantly higher 24-h urinary concentrations of CAs and their metabolites but similar responses to CRH injection in sexually abused girls relative to matched controls [137]. In another pediatric study, Gordis et al. [138] reported an asymmetry between concentrations of salivary alpha-amylase (sAA), an indicator of SNS functioning, and cortisol reactivity to a social stressor, with maltreated youth showing no associations between the peripheral biomarkers of HPA axis and SNS activity. Pervanidou et al. [139] reported a successive normalization of cortisol levels but a continuous increase of CA levels after 6 months of trauma exposure in children with PTSD following a motor vehicle accident, suggesting a lifted cortisol-mediated restraint on the catecholaminergic response in limbic structures (e.g., locus coeruleus and other brain stem centers), resulting in enhanced ANS activity. With respect to these findings, Pervanidou [56] has proposed a progressive divergence of HPA axis and ANS activity following ELS, which may represent another potential pathophysiological pathway leading to the long-term impact of ELS and the preservation of symptoms over the years. Hence, the low cortisol levels and enhanced ANS activity found in adult PTSD patients and some ELS exposed individuals may represent a late event in the natural history of stress-axis divergence in trauma-related disorders [140].

The stress system and immune axis

The central and peripheral limbs of the stress system and the immune axis are implicated in a very complex, two-way neuroimmunoendocrine interplay [141–143], which implicates the immune system in stress resilience, influencing peripheral and central stress-related neurobiological and neuroendocrine responses [144]. Acute stress-related adrenergic and CRH-peptidergic stimulation activates the secretion of proinflammatory cytokines, which coordinate further immune responses (e.g., stimulation of systemic acute-phase proteins, such as C-reactive protein, CRP) [45, 145]. Proinflammatory cytokines also stimulate the secretion of GCs, while GCs, in turn, help terminate the inflammatory response [143, 146–148]. A dysregulated stress response could, thus, lead

to a dysregulation of inflammatory feedback mechanisms, thereby promoting biological aging and the development of inflammatory-related or immunosuppressed medical conditions [54, 64, 149–151].

ELS has therefore been increasingly associated with peripheral immune dysregulation and long-term, low-grade inflammatory excess, leading to a proinflammatory phenotype and an increased risk of disease with immune origin in adulthood [19, 33, 88, 152–156]. Although the precise underlying mechanisms involved are still not completely understood [141], the two major limbs of the stress system may play a crucial role. On the one hand, an ELS-related ANS dysregulation with compromised vagal activity could directly enhance inflammation via direct vagal efferent effects of autonomic brain regions [157–159]. On the other hand, ELS-related HPA axis dysregulation could affect GR-mediated transcriptional and post-transcriptional responses of immune-related genes and result in reduced recovery capability [54, 160]. Human and preclinical research has confirmed GC resistance and insensitivity in immune cells and, thus, altered inhibitory signaling of GCs [101, 161] following repeated acute and/or chronic stress [162, 163].

Sleep and the circadian system

The human circadian system (CS) enables the temporal organization and coordination of numerous physiologic processes [164], such as the diurnal rhythmicity of the HPA axis and ANS activity [165–168]. The central and peripheral CS synchronizes hypothalamic CRH- and AVP-secreting neurons, influences adrenal sensitivity to ACTH, stimulates circadian GC hormone secretion, and displays a peripheral 24-h rhythm of target tissue sensitivity to GCs through circadian acetylation and deacetylation of the GRs and peripheral clock gene expression [165, 169–173]. The CS also modulates ANS activity through projections to preautonomic hypothalamic neurons and is essential for the physiologic autonomic diurnal fluctuations seen in humans [174–176].

Recent research has focused on a potential causal role of sleep and circadian disruption in the development of the long-term cacostatic effects of trauma exposure [177–179]. Circadian disruption represents a critical loss of the strict temporal order at different organizational levels and introduces a breakdown of harmonious functioning of internal biological systems [180–182], which may sensitize individuals to stress and increase their vulnerability to stress-related disorders [183, 184]. Acute and chronic physical and/or psychological stress affects the CNS sleep centers [185–188] and can cause both immediate and long-lasting sleep disruption [189–191], which may, in turn, enhance maladaptive stress regulation [192]. Some animal [193], and numerous human, studies have repeatedly confirmed that ELS is independently associated with enduring adult sleep disruption including global sleep pathology (i.e., insomnia), as well as specific types of sleep problems, most likely in a dose-response manner [194–205]. Sleep and circadian disruption occurring after trauma exposure could thus represent a core pathway mediating the enduring neurobiological correlates of ELS through stress system dysregulation [177, 178, 190, 206–208].

Genetics and epigenetics

Human genetic background, environmental influence, DNA methylation (methylome), and gene expression profiles (transcriptome) are all integral to our understanding of stress-related disorders, as their interaction modulates functional sites controlling the human stress axis and may, hence, increase or decrease the risk of psychobiological maladjustment after exposure to ELS [209, 210].

Gene × environment interactions of gene polymorphisms may influence the acute effects of trauma and modulate long-term risk of disease development. After the first groundbreaking studies on the interaction of ELS with monoamine oxidase A (MAOA) and the promoter region of the serotonin transporter (5-HTTLPR) functional polymorphisms predicting adult outcomes by Caspi et al. [211, 212], more recent studies point to a vital role of further genes involved in HPA axis function and GC sensitivity, in conjunction with exposure to ELS [213]. The two key genes implicated to date are the CRH-releasing hormone receptor 1 (CRHR1) and the GC response elements of the FKBP5 co-chaperone gene [213, 214]. The interaction of ELS with specific single nucleotide polymorphisms (SNPs) of the FKBP5 gene predicts the level of adult PTSD symptoms [215] probably through an allele-specific demethylation in the GC response elements of FKBP5 leading to a resistance of tissues to GCs [216]. Additional studies confirmed that minor alleles of FKBP5 are particularly sensitive and interact with ELS to increase aggressive behavior [217], suicide attempts [218], and depression [219]. The CRHR1 gene plays an important role in the initiation and termination of the stress response as it influences sensitivity of the negative feedback loop of cortisol. The interaction of ELS with specific CRHR1 polymorphisms increased the risk of adult depression and adult suicide attempts [220–222]. Finally, imaging studies investigated the potential interaction of specific polymorphisms in candidate genes and ELS with brain development [223]. A number of studies proposed a moderating effect of FKBP5 [224–226] and mineralocorticoid receptor genotypes [227] on amygdala volume, reactivity, and connectivity of adult individuals with ELS experience, thus implicating HPA axis-related genes in brain development.

In the interaction of ELS with specific genotypes, epigenetic modifications play a crucial role, as they regulate functional expression of genes by decreasing, silencing, or increasing gene expression [228, 229]. The installment of

such epigenetic marks in the transcriptome by early developmental challenges may play a central role in the long-term biological trajectories of ELS through programming effects in stress reactivity [92, 230, 231] and represents a critical factor explaining interindividual variation in vulnerability or resilience. There is accumulating evidence of gene programming and epigenetic regulation of specific genes in the aftermath of trauma in humans [232–235]. However, gene expression profiles of PTSD patients with and without ELS are 98% non-overlapping [236], suggesting that DNA methylation changes may have a much greater impact during early life and possibly reflect differences in the pathophysiology of PTSD. ELS experience has been especially associated with epigenetic changes and altered gene expression profiles in stress system-related genes in the CNS (e.g., the hippocampus and amygdala) [237–240]. In particular, several GC signaling-related genes (e.g., GR gene promoter 1F) are subject to stress- and trauma-related epigenetic regulation throughout life and may be useful as future biomarkers [241, 242]. For example, ELS experience is related to postmortem changes in hippocampal neuron-specific GR (NR3C1) promoter DNA methylation status, implying distinct epigenetic ELS effects on hippocampal GR expression [243]. Maternal stress during pregnancy has been associated with epigenetic hypermethylation of the promoter and exon 1F of the human GR gene Nr3c1 and related elevated cortisol stress reactivity in the offspring [244]. On the other hand, in a genome-wide blood DNA methylation analysis, a locus in the Kit ligand gene (KITLG; cg27512205) was shown to strongly modulate the relation between ELS and cortisol stress reactivity [245]. Finally, cross-sectional, large-scale methylation studies have indicated significant ELS-related differences in methylation of a large proportion of genes responsible for HPA axis regulation [246].

Imaging findings

ELS has been associated with remarkable structural and functional brain changes even decades later [213, 223, 247, 248] through alterations in brain development affecting behavioral, cognitive, emotional, and physiologic responses [34, 249]. The two brain structures particularly frequently reported to be impaired in adult victims of ELS are the amygdala and the hippocampus, strongly indicating the vital prefrontal-limbic gray matter effects of ELS. The hippocampus has a special importance due to its role in cognition and its rich density in GR, and the amygdala because of its pivotal role in stress responsivity. Numerous reports and meta-analytic studies confirm the association of ELS with reduced hippocampal volume in adulthood [223, 247, 250–254]. Concerning study results as regards the volumetric effect of ELS on the amygdala, findings are inconclusive [247, 250, 251, 255–258]. However, with respect to amygdala responsiveness, ELS has been repeatedly associated with facial threat- or negative emotion-related amygdala hyperresponsiveness [223, 247, 259, 260], implying that the risk of adult depression after ELS could be actually mediated by this preceding amygdala hyperactivity [259, 261].

Conclusions

Coordination of the stress system is essential to development, survival, and well-being [5, 41]. The continuum of ELS-provoked aftermath extends from healthy adaptation with high resilience to severe maladjustment with increased physical and mental morbidity in later life. Despite the resilience of many abused children, ELS is highly prevalent in the general population and can, thus, be conceptualized as a common developmental risk factor for disease with high public health impact. ELS during critical phases of perinatal and juvenile brain development with elevated neuroplasticity is associated with impaired homeodynamic balance, elevated cacostatic load, and reduced adaptability to stress in adult life, consequently leading to enhanced vulnerability. ELS disrupts developmental programming of the related neural circuitry and results in alterations in neuroendocrine (re-)activity, i.e., hyper- or hypoactivation of the stress system, associated with the adult HPA axis, glucocorticoid signaling, and ANS dysregulation with related structural and molecular changes both in the brain and in peripheral tissues. Although most studies support a causal relationship between ELS and psychobiological maladjustment in later life, the exact developmental course of such changes and its temporal coincidence have not yet been fully elucidated. Understanding the pathways susceptible to disruption following ELS exposure could provide new insights into the neuroendocrine trajectories linking toxic stress during developmental stages of childhood and adolescence to adult maladjustment. Screening strategies for ELS and trauma therefore need to be improved, in order to better identify an individual's risk level for disease development and/or help predict his or her response to treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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