Neurobiology of Early-Life Stress

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The seemingly age-old nature-nurture debate has now evolved into an empirically based understanding that stressful experiences, in particular early in an organism’s life, interact with genetic vulnerability in determining risk for the development of several major psychiatric disorders. Increasing evidence from preclinical as well as clinical studies suggests that stress or emotional trauma during development permanently shapes brain circuits that are critically involved in the regulation of stress and emotion. These biological “scars” may then lead to altered behavioral and physiological responsiveness to the environment that ultimately increase the likelihood of adult psychopathology. Indeed, many of the neurobiological consequences of early-life stress (ELS) resemble the established correlates of major depression and anxiety disorders, including posttraumatic stress disorder (PTSD). In this article the relationship between ELS and PTSD is described, the neurobiological effects of ELS in laboratory animals and humans are summarized, and the findings are compared to the neurobiology of PTSD. It appears that the neurobiological effects of ELS may represent...
a “priming” for the development of PTSD in response to subsequent stressors. Implications for the prevention of PTSD after ELS and additional research questions are outlined.

**RELATIONSHIP BETWEEN ELS AND PTSD**

Consideration of the definition of ELS in humans is an appropriate starting point for discussion. In order to define ELS, two main criteria must be considered: the developmental age range that is subsumed under “early-life” and the characteristics of the events that would be considered as “stressful.” There is no such generally agreed upon definition of ELS in humans. Many investigators use an upper age limit to define the early-life criterion, usually between 12 and 18 years. More appropriate approaches refer to the developmental stage by using the onset of sexual maturation, i.e., menarche in females, to more precisely define the early-life period. As for the stress criterion, prevailing models suggest that stress is generally experienced when an individual is confronted with a situation, which is appraised as personally threatening and for which adequate coping resources are unavailable. In addition, threats to physiological homeostasis, such as injury or illness, elicit stress responses. Any such situation occurring within the defined developmental period limit may be classified as ELS in humans. The most salient forms of ELS in humans are sexual, physical, and emotional maltreatment (abuse or neglect) as well as parental loss (death or separation). Other forms of ELS include accidents, physical illness, surgeries, natural disasters, and war or terrorism-related events. Less obvious experiences that pose significant distress on a child include unstable families, inadequate parental care due to mental or physical illness, dysfunctional relationships between parent and child, and poverty. It should be noted that ELS is often complex, inasmuch as various forms of ELS coexist or are associated among each other. Although ELS may be a single event, it more typically occurs as chronic or ongoing adversity in most cases.

How are ELS and PTSD related? Before we answer this question, it must be noted that a traumatic event experienced early in life is surely a form of ELS, but that not all forms of ELS are necessarily traumatic events. More specifically, some, but not all, instances of ELS fulfill the *DSM-IV* A criterion for traumatic events. For example, chronic demands of a child to manage a family household would not meet this criterion, but may well exert pronounced influences on the child’s subsequent vulnerability to stress and PTSD throughout his or her lifespan. One might conceptualize the relationship between ELS and PTSD as being direct or indirect. In the case of the direct relationship, the ELS experience represents the index traumatic episode which fulfills the *DSM-IV* A criterion, to which the PTSD symptoms are related. Rates of PTSD in children with such experiences vary depending on the severity of the trauma and the length of time between the trauma and the assessment. Posttraumatic stress disorder related to childhood trauma can persist into adulthood and may be elicited or aggravated by other events. Indirect relationships between ELS and PTSD occur in at least two ways. First, ELS increases the risk of later trauma that may, in turn, elicit PTSD. For example, emotional neglect is related to an increased risk for traumatic accidents, which often induce PTSD. Second, ELS also increases the risk for the development of PTSD in response to traumas occurring in adulthood (e.g., combat). Such sensitization of responses to trauma has been observed after child abuse experiences, but also after more subtle instances of ELS, e.g., negative parenting style. These latter findings suggest that ELS contributes to the diathesis of PTSD.

There are multiple factors that may influence the manifestation of PTSD in relation to ELS. For example, women are more likely to develop PTSD after ELS than are men, and the effects of ELS on health and adaptation appear to be mediated in part by the extent to which the ELS causes family disruption or dysfunction. It should also be noted that PTSD is hardly the sole consequence of early trauma, but that ELS, in general, is associated with multiple psychopathological and physiopathological outcomes that often coexist with PTSD.

**NEUROBIOLOGY OF ELS**

By what mechanisms does ELS exert such pronounced and long-lasting effects on adaptation and health? Such effects have been hypothesized to be due to the plasticity of the developing central nervous system. Although certain sensory input is required for normal development of certain brain areas, some regions may be particularly sensitive to adverse experiences, which may lead to major, sometimes irreversible, abnormalities. Based on this understanding, it is conceivable that stress or emotional trauma during
development may permanently “pro-
gram” the very same brain circuits that 
are critically involved in the regulation 
of stress and emotion, resulting in 
heightened responses to subsequent 
stress and the development of disor-
ders, such as PTSD.

**Stress Response Systems**

Multiple neurotransmitter systems in various brain 
regions participate in the regulation of the mam-
malian stress response. In brief, the stress response 
includes activation of two major peripheral outflow 
systems, the sympathetic 
division of the autonomic nervous system and the 
hypothalamic-pituitary-adrenal (HPA) axis, both of 
which adapt the organism to the changing demand. 
Sympathoadrenal activation results in increased 
release of epinephrine and norepinephrine from the 
adrenal medulla, increased release of norepinephrine 
from the sympathetic nerve endings and 
changes in blood flow to a variety of organs, reflecting an alarm reaction that 
allows optimal coping. Activation of the 
HPA axis results in increased secretion of glucocorticoids from the adrenal cor-
tex, which—via binding to glucocorticoid receptors (GR) and mineralocorti-
oid receptors (MR)—exert manifold effects on metabolism, the immune sys-
tem, and the brain. These physiological 
changes are associated with behavioral 
changes, such as fear and anxiety, sup-
pression of food intake, reproductive 
behavior, and sleep, as well as fight or 
flight behaviors among other coping 
behaviors. The preeminent neurotransmitter believed to coordinate these vari-
ous stress response elements into one 
integrated coping reaction is corti-
cotropin-releasing factor (CRF). Direct 
central nervous system administration 
of CRF to laboratory animals produces 
HPA axis and sympathetic activation 
as well as the array of behavioral 
changes that resemble the signs of 
stress, whereas treatment with 
CRF receptor antagonists or 
CRF-1 receptor knockouts exhibit attenuation of the 
stress response.

This fundamental role of CRF in the coordination of 
the stress responses is made 
possible by the strategic distribution of 
CRF neurons and/or their receptors in the 
brain regions that mediate 
cognitive, emotional, neu-
roendocrine, and autonomic 
processes. These include the 
cerebral cortex, amygdala, 
hippocampus, hypothalamus, and brain stem. In these 
brain regions, CRF interacts 
with other neurotransmitters 
that modulate the stress 
response. In particular, a 
feed forward cascade 

tween central nervous system 
CRF systems and norepinephrine 
neurons originating in the locus coeruleus has been described that mediates many of 
the anxiogenic effects of stress. Serot-
onergic and GABAergic neurons also 
interact with CRF systems. Other neuro-
transmitters, such as neuropeptide Y and 
oxycort, appear to counteract the effects 
of CRF in the stress response. Alter-
ations of all of these neurotransmitters 
systems have been implicated in mood and 
consultation disorders, including 
PTSD.10-12 In sum, any disruption in the 
organization or function of these circuits as 
a consequence of ELS would likely 
compromise successful adaptation to 
therapeutic stress and promote symptoms or 
syndromes related to stress.

**Studies in Laboratory Animals**

Much of what we know about the 
long-term effects of ELS was obtained 
from laboratory animal studies that 
allow for a controlled experimental 
variation of the early environment during 
development. One frequently used 
animal model of ELS is maternal 
separation. In one model, rat pups are 
removed from their dams for 180 min/d 
on postnatal days 2 to 14. Control 
conditions include pups that are removed 
from the cage daily for 15 minutes on 
postnatal days 2 to 14 and/or pups that 
were reared under normal animal facility 
conditions. After postnatal day 14, 
pups are subjected to routine care and the 
long-term consequences are studied 
after postnatal day 60, which defines 
adolescence.13 Adult rats exposed to 
maternal separation exhibit increased 
responsiveness to a variety of stressors 
as compared to control rats. For example, 
maternally separated rats show up to 3-fold increases of corticosterone 
(ACTH) and corticosterone responses to 
airpuff startle. This sensitization of 
the HPA axis is observed throughout the 
lifespan of these animals. These 
maternally separated rats also develop 
marked behavioral changes, including 
increased anxiety-like behavior and 
anhedonia, and increased alcohol 
consultation as well.14-16 

Several studies have shown that 
maternal separation leads to changes in 
subsequent maternal behavior, eg, 
prolonged latency to retrieve pups after 
reunion and decreased licking behavior, 
and that altered reactivity to stress is 
likely determined by these variations in 
maternal behavior and not by the 
separation per se.14,17-19 Subsequent studies 
have explored the neurobiological 
underpinnings of increased vulnerability 
to stress related to maternal separation 
or lack of maternal care. In these 
research, alterations in the multiple neurocircuits 
that participate and interact in the
control of the stress responses have been identified. Findings include increased activity and sensitization of CRF neurons in hypothalamic and limbic regions, decreased glucocorticoid receptor density in the hippocampus and prefrontal cortex, increased mineralocorticoid receptors in the hippocampus, decreased neurogenesis in the dentate gyrus of the hippocampus, increased locus coeruleus noradrenergic activity as well as decreased GABA/central benzodiazepine receptor binding, decreased oxytocin receptor binding (in females), and decreased neuropeptide Y concentrations in selected brain regions. These changes likely underlie behaviors of increased stress, anxiety and depression, and may converge into sensitization of neuroendocrine and autonomic responses to environmental events.

Some studies on the long-term consequences of ELS in non-human primates have also focused on variations in maternal behavior during infancy. In one model, adult bonnet macaques that were reared by mothers exposed to unpredictable conditions with respect to food access over 3 months (resulting in diminished perception of security and a reduction of maternal care in the infants) exhibit stable traits of anxiety as well as significantly elevated cerebrospinal fluid CRF concentrations, but decreased cerebrospinal fluid cortisol concentrations, when compared to control groups. These primates further develop sensitization of the noradrenergic system and serotonergic dysfunction as identified in pharmacological challenge tests as well as behavioral sensitization to fear stimuli. Thus, ELS induces manifold changes in multiple neurocircuits that are involved in neuroendocrine, autonomic, and behavioral responses to stress. If similar changes also occurred in humans exposed to ELS, these changes might indeed confer an enhanced risk for PTSD and other disorders as well.

**Studies in Humans**

Only a limited number of clinical studies on the neurobiological consequences of ELS have been published to date. The majority of these studies have recruited children or adult women with a history of childhood sexual or physical abuse. Studies in children with early adversity provided convincing (but sometimes conflicting) evidence for neuroendocrine, autonomic, neurochemical and neuroanatomical abnormalities. Findings include alterations of diurnal rhythms of cortisol, altered peripheral catecholamine levels and cardiovascular (re-) activity as well as altered responses to standard HPA and serotonin challenge tests. There is also evidence for abnormalities in brain electrical activity, indicative of changes in cognitive processing of emotional stimuli and structural brain development. The available findings also suggest that the neurobiological state of maltreated children is variable and influenced by multiple factors, e.g., type, age at onset, and duration of the adverse events, time elapsed since the events, ongoing adversity or concomitant stresses, and concurrent psychopathology. Nevertheless, many of the findings parallel results from animal models of ELS and are compatible with altered stress responsiveness and enhanced risk for maladaptation later in life.

Only a limited number of retrospective studies have evaluated the long-term effects of ELS in adults. Women with a history of childhood sexual abuse and current PTSD exhibit increased 24h urinary cortisol excretion. In another study, women with a history of childhood sexual abuse (with and without psychiatric disorder) had normal basal morning cortisol concentrations, but were more sensitive to the suppressive effects of dexamethasone on HPA axis activity. Other studies found decreased basal plasma cortisol concentrations in abused women. The variance in these data may reflect methodological differences. It is also possible that increased 24h urinary cortisol excretion reflects enhanced fluctuation of cortisol release in relation to stresses throughout the day in abused women with PTSD, though cortisol levels may be low under basal conditions.

In view of the compelling evidence from laboratory animal studies for long-term sensitization of the HPA axis after ELS, it appears important to evaluate neuroendocrine responsiveness in adult humans exposed to ELS. Women with a history of childhood sexual or physical abuse with and without current depression were exposed to a mild psychosocial laboratory stress (consisting of a public speech and mental arithmetic task) and markedly increased plasma ACTH responses were observed in abused women when compared to controls and depressed women without ELS. Corticotropin responses in abused women were more than 6 fold higher than in controls and were correlated with current severity of symptoms of depression and PTSD. Depressed women with a history of abuse also demonstrated increased cortisol responses as compared to all other groups.

Thus, abused women without depression showed mild adrenal dysfunction, given their elevated ACTH, but normal cortisol responses. Depressed women without ELS showed normal HPA axis responses. Increased stress sensitivity may thus be related to a mixed state of depression and anxiety, including PTSD, which develops after early trauma and is pathophysiologically distinct from depression without ELS. Multiple regression analyses revealed that the effects of child abuse on ACTH responses to stress persisted after controlling for...
age, socioeconomic status, ethnicity, adulthood stress, and psychiatric symptoms. The interaction term of the childhood and adulthood trauma was the most significant predictor of ACTH responses, suggesting that a history of child abuse, per se, is related to increased neuroendocrine stress reactivity, which is further enhanced when additional trauma is experienced in adulthood.34

To further elucidate the mechanisms of HPA axis dysfunction in these women, we administered standard endocrine challenge tests to the aforementioned population. Similar to their responses in the stress test, abused women without depression exhibited increased ACTH responses to exogenous ovine CRF, whereas both groups of women with depression, with or without abuse, exhibited blunted ACTH responses that are typical for depression.31 The blunted responses likely reflect pituitary CRF receptor down-regulation due to chronic CRF hypersecretion. Indeed, we found an inverse relationship between cerebrospinal fluid CRF and vasopressin concentrations and ACTH responses to exogenous CRF in these women (Newport et al., submitted manuscript). Increased endogenous CRF and vasopressin may thus have contributed to the enhanced response in the psychosocial stress test in abused women with depression. Underscoring our initial observation that ELS in the absence of depression is associated with mild adrenal dysfunction, we observed decreased cortisol levels throughout a standard ACTH(1-24) stimulation test in these women, whereas abused women with current depression (and PTSD) showed pronounced responses relative to their decreased basal cortisol levels.31 Possibly reflective of a relative lack of the suppressive effects of cortisol on immune functions in abused women, we also found elevated plasma levels of the pro-inflammatory cytokine, interleukin-6, that were related to self-reported symptoms of pain and fatigue (Heim et al., unpublished observation).

Concordant with a feed forward cascade between central CRF and noradrenergic systems, elevated 24h urinary norepinephrine excretion was reported in abused women with PTSD.79 In addition, increased heart rate or blood pressure responses have been observed during stress induction in adults with early parental loss and women with a history of child abuse,33,35 as well as during mental imagery of abuse experiences in abused women with PTSD,36 suggesting increased autonomic reactivity. Regarding serotonergic function, a history of child abuse was found to be correlated with blunted prolactin responses to the partial serotonin agonist, meta-chlorophenylpiperazine (m-CPP), in women.32,37 Whether GABAergic or other stress-buffering neurotransmitter systems are altered after ELS in adult humans is unknown.

Magnetic resonance imaging studies have evaluated structural changes of the hippocampus in subjects with ELS. The hippocampus is one of the most plastic regions of the brain, with neurogenesis demonstrated to occur in adulthood in rodents and non-human primates. The hippocampus is also involved in the control of the HPA axis, in explicit memory, and in contextual aspects of fear conditioning. Impaired neurogenesis in the hippocampus has been observed in animal models of ELS.16 Alterations of the hippocampus as a function of ELS may thus contribute to heightened stress reactivity and vulnerability to depression and anxiety, including PTSD. There is evidence for decreased hippocampal volumes in adults with histories of ELS with or without PTSD.38-40 We have recently demonstrated that decreased hippocampal volume in major depression is associated with a history of child abuse and does not occur in depressed women without ELS, which mirrors our neuroendocrine findings.41 It is unclear which neurobiological mechanisms may contribute to the decreased hippocampal volume in humans after ELS. Because hippocampal volume loss was not observed in abused children with PTSD,42 some have suggested that repeated bursts of cortisol secretion over the course of time may eventually result in smaller hippocampi, because of the well-documented adverse effects of glucocorticoids on these neurons. A recent laboratory animal study also suggests that enhanced CRF secretion during development may contribute to progressive hippocampal volume loss, independent of the effects of glucocorticoids.43 Positron emission tomography studies have revealed functional changes of frontal cortical regions that are involved in emotional processing during script-driven mental imagery of personal abuse experiences in abused women with PTSD relative to abused women without PTSD.44,45

The concatenation of findings from clinical studies suggest that ELS is associated with marked long-term neurobiological changes in humans, which are comparable to those described in a sizable number of preclinical studies. Dysfunctional neurotransmission and changes in corticolimbic pathways appear to be asso-
associated with altered neuroendocrine and autonomic stress responsiveness and may, in concert, underlie an enhanced risk for the development of psychopathology related to ELS, including PTSD.

**COMPARISON OF THE NEUROBIOLOGY OF ELS AND PTSD**

The neurobiology of PTSD is reviewed in this issue (page 30). We therefore briefly compare selected findings on the neurobiology of ELS and PTSD. It should be noted that several studies of ELS have recruited subjects with early trauma who fulfill diagnostic criteria for PTSD, and several studies on the neurobiology of PTSD have recruited patients with index traumatic events in childhood and/or adulthood, making it very difficult to distinguish the effects of ELS from the features of PTSD. As difficult as it may be, it is of paramount importance to begin to understand in what ways ELS enhances vulnerability to PTSD later in life.

Perhaps the most prominent finding in the neurobiology of ELS is the persistent sensitization of the stress response as observed in both preclinical and clinical studies. In our research, pituitary and adrenocortical responses to standardized psychosocial laboratory stress were most pronounced in women with child abuse, who also had symptoms of PTSD and/or depression. It has long been suggested that the HPA axis is sensitized to stress in PTSD based on clinical observations and HPA axis findings. Many of the central nervous system features of PTSD are also quite compatible with increased stress reactivity and remarkably parallel the effects of ELS in animal models or human studies. These include central nervous system CRF neuronal hyperactivity, norepinephrine sensitization and serotonergic dysfunction, decreased central benzodiazepine receptor binding and decreased neuropeptide Y availability, as well as structural and functional changes in brain circuits relevant to stress and emotion.

Surprisingly few studies have evaluated responses in the CRF stimulation test in PTSD. Blunted ACTH responses increased ACTH and cortisol responses to CRF stimulation in women with PTSD. When trying to integrate these seemingly disparate findings, it is important to consider comorbid diagnoses and the type/timing of trauma experiences. Only 2 of the 13 women with PTSD in the Rasmusson study suffered from current major depression and these findings, therefore, compare well with our finding of increased ACTH responses to CRF stimulation in non-depressed women with prepubertal abuse, some of whom had PTSD. The Rasmusson study predominantly enrolled women who had experienced mixed types of trauma during puberty, adolescence, or adulthood (9 of 13 women were 12 years or older at the time of the trauma). All four of the

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**Figure.** Hypothetical model on the relationship between early-life stress and later pathology. Alterations of the various components of the stress response systems, as a consequence of early-life stress, may result in complex effects that ultimately trigger PTSD and other symptoms after additional trauma. Relatively decreased cortisol output shortly before a given stressor/truma in adulthood may have a permissive effect toward the activation of an already sensitized feed-forward cascade between the CRF and noradrenergic systems. Alterations in protective neurotransmitter systems and increased cytokine release may further accelerate this cascade. The activation pattern may lead toward the three symptom clusters of PTSD as well as coexisting mental disorders.

CNS = central nervous system; GR = glucocorticoid receptor; CRF = corticotropin-releasing factor; MR = mineralocorticoid receptor; NE = norepinephrine.
women with earlier childhood trauma also experienced later trauma. The study sample is, therefore, quite different from our sample. Furthermore, the results are inconclusive with respect to specific correlates of early adversities in the presence or absence of PTSD, though cortisol responses were inversely correlated with the age at the first trauma. Clearly, the present findings are certainly difficult to integrate and further research is warranted. At the current stage, the findings may best support a model, in which ELS and PTSD are associated with sensitization of ACTH responses to CRF, which evolves into dysregulation and blunted responses on exposure to additional chronic stresses and the development of depression.

Perhaps the most intriguing similarities between the neurobiology of ELS and PTSD are found at the adrenocortical level. Initially seemingly paradoxical, decreased basal cortisol secretion has been demonstrated in PTSD in many studies, which occurs in the context of enhanced negative feedback sensitivity. There is now also evidence for decreased adrenocortical responsiveness in combat veterans with PTSD, which may contribute to the low basal cortisol levels in PTSD. Similar alterations have been found in some animal models and human studies of ELS, including low basal cortisol levels in nonhuman primates and women with child abuse experiences, increased feedback inhibition of the HPA axis in women with child abuse, and decreased adrenocortical reactivity relative to increased central reactivity. A similar dissociation has been reported for transgenic mice expressing antisense RNA against the GR. In humans, the MR antagonist spironolactone increases cortisol (but not ACTH) responses in the combined dexamethasone/CRF test, suggesting that MR have direct effects on adrenal responsiveness. In rodents, ELS alters the hippocampal MR/GR ratio, leading to increased MR and decreased GR expression. This constellation of findings may promote low basal cortisol levels and increased central stress reactivity. On the other hand, Rasmusson et al. in their recent study, reported increased cortisol responses to ACTH(1-24) in a group of women with mixed traumas and PTSD. This finding is actually not dissimilar from our findings in women with early abuse and depression (and PTSD), who had quite pronounced net cortisol responses to ACTH, relative to their decreased basal cortisol levels. Based on the current data, it may be suggested that some forms of ELS initially induce low adrenocortical activity, perhaps reflecting a peripheral adaptation to central hyperactivity. While initially adaptive, this peripheral change may pose a vulnerability factor to subsequent stress, due to the multiple effects of glucocorticoids on the brain and behavior, and may set the stage for PTSD, which then is associated with further dysregulation of stress responses.

Based on these findings, it is conceivable that the specific alterations of the various components of the stress response systems that occur as a consequence of ELS may result in complex effects that ultimately trigger PTSD symptoms after additional trauma. For example, glucocorticoids do not only feedback on the hippocampus and hypothalamus to decrease hypothalamic CRF secretion and HPA axis activation, but also exert negative feedback effects on CRF-induced activation of the locus coeruleus noradrenergic cells. Relatively decreased cortisol output, as a consequence of ELS, shortly before a given trauma may thus have a permissive effect toward the activation of an already sensitized feed-forward cascade between the CRF and noradrenergic systems. Enhanced CRF and norepinephrine release, in concert with altered hippocampal function due to ELS, would drive the HPA axis, resulting in enhanced ACTH responses, but relatively subnormal cortisol responses. Low cortisol responses (perhaps in concert with sustained cytokine responses) may result in failure to shutdown the central nervous system responses and may lead to a perpetuation of CRF-noradrenergic activation. Alterations in protective neurotransmitter systems, as a consequence of ELS, may further accelerate this cascade. Corticotropin-releasing factor and norepinephrine are implicated in enhanced encoding of traumatic emotional memories and facilitation of fear conditioning, as well as increased vigilance and arousal, including increased startle responses, leading toward the three symptom clusters of PTSD. Indeed, increased autonomic activity and low cortisol secretion directly after the trauma are significant predictors of the development of PTSD. Administration of hydrocortisone during trauma effectively prevents PTSD in humans at least in one study. We propose that early adversity is an important factor in the induction of such "biological priming" in genetically vulnerable individuals, providing a neurobiological mechanism for the evidence of an indirect relationship between ELS and PTSD (Figure, page 23).
CONCLUSION AND FUTURE DIRECTIONS

We have described possible relationships between early adverse experience and PTSD. We found that ELS, if not directly inducing PTSD, may indirectly increase the risk for PTSD in response to further traumas. Findings from both preclinical and clinical studies were summarized demonstrating that ELS induces persistent changes in neurobiological stress response systems, many of which parallel those of mood and anxiety disorders, including PTSD. We have hypothesized that the neurobiological effects of ELS may represent a "biological priming" for the development of PTSD. Other risk factors, such as genetic disposition and female, may interfere with components of the stress response and thereby further increase vulnerability to PTSD related to ELS, i.e., ELS-related sensitization of the CRF-nora-drenergic system could be enhanced in women versus men due to direct stimulatory effects of estrogens on CRF messenger RNA expression via an estrogen-responsive portion of the promoter region of the human CRF gene.

Future research should elucidate the interactions of the stress-mediating and protective neurotransmitter systems, as well as the effects of peripheral hormones (e.g., glucocorticoids, estrogens) on these systems, in the mediation of the adverse outcomes of ELS. Based on this understanding, novel strategies that directly target and reverse the neurobiological effects of ELS could be derived to prevent PTSD and other stress-related disorders in victims of ELS. Such prevention strategies might include selective CRF-receptor antagonists, noradrenergic blockers and neuropeptide Y agonists, but also agents that normalize cortisol secretion and MR/GR function. Recently, it was also shown that stress inoculation training results in significant reduction of HPA axis responses to psychosocial stress, suggesting that cognitive-behavioral stress management may be useful in the prevention of stress-related disorders after ELS. The dramatic number of reported cases of child abuse and neglect in the United States, together with the increasing evidence for severe and sustained effects of ELS on the brain and behavior, call for a rapid evaluation of intervention strategies in order to prevent adverse health outcomes and maladaptation throughout the lifespan of these individuals.

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