Curr Psychiatry Rep (2015) 17: 90
DOI 10.1007/s11920-015-0625-6

The Preeminence of Early Life Trauma as a Risk Factor for Worsened Long-Term Health Outcomes in Women

Nils C. Westfall[1] · **Charles. B. Nemeroff**[1]

Published online: 18 September 2015

Abstract Early life trauma (ELT) comprises an array of disturbingly common distressing experiences between conception and the beginning of adulthood with numerous and significant potential long-term, even transgenerational, health consequences of great public health concern, including depression, cardiovascular disease, and other psychiatric and medical disorders, and neurobiological, psychological, and behavioral effects which are sufficiently robust to confound many types of biomedical research. The impact of ELT on a woman's health trajectory appears to vary with the specific characteristics of the ELT (e.g., type, number of different types, severity, and timing), the individual (e.g., age, genetics, epigenetics, personality, and cognitive factors), and the individual's environment (e.g., level of social support and ongoing stressors) and to be mediated to a significant extent by persistent changes in a number of biological systems, dysregulation of those governing the stress response chief among them. Growing knowledge of the risk factors and pathophysiological mechanisms by which ELT confers diathesis to various poor health outcomes and the unique treatment–response profiles of women with ELT will lead to much needed improvements in prevention, diagnostic, and therapeutic efforts, including more effective psychotherapy and pharmacotherapy approaches, hopefully making strides toward improvements in the lives of women everywhere and ending countless cycles of intergenerational trauma-associated pathology. This article attempts to broadly summarize the current state of knowledge about the long-term sequelae of ELT for women's health.

Keywords Trauma · Abuse · Stress · Women · Risk factor · Depression · PTSD

Fathers, be good to your daughters
Daughters will love like you do
Girls become lovers who turn into mothers
So mothers, be good to your daughters too
John Mayer

Introduction

Early life trauma (ELT) has undoubtedly been a common experience for many women throughout human history, yet it is only fairly recently that medical professionals have moved beyond only recognizing certain relatively overt, immediate, and short-term effects (e.g., fear, grief, physical trauma, unplanned pregnancy, and STDs), however egregious, to begin to appreciate how ELT can drastically change women's long-term health outcomes. It is more recently still that they have begun to understand how the effects of ELT and trauma during pregnancy experienced by the mother can be passed on to the next generation. Thus, the opportunity to make intentional and substantial advances in the important public health goals of preventing and effectively treating the long-term sequelae of ELT for women and their children is a novel one. There is no time to waste as the numbers of girls in the USA alone who were substantiated by child protective services to have

This article is part of the Topical Collection on *Women's Mental Health*

✉ Nils C. Westfall
nils.westfall@jhsmiami.org

[1] Department of Psychiatry and Behavioral Sciences, Leonard M. Miller School of Medicine, University of Miami, Miami, FL 33136, USA

endured and died of abuse and neglect in 2013 (the latest year for which data are available) were about 345,000 and 500, respectively [1]. As these forms of ELT undoubtedly go unreported or unverified most of the time and there are numerous other types of ELT, such numbers give only a conservative estimate of a fraction of the problem.

Significant interest in the effects of early life experience on later well-being started with Freud's development of psychoanalysis in the early twentieth century [2]. Later, researchers including developmental psychobiologist Seymour Levine [3], endocrinologist Hans Selye [4, 5], and psychologist Harry Harlow [6] used laboratory animal studies to bring science to bear on the issue, providing strong evidence that early life experience profoundly affects development, behavior, and physiological responses to stress in enduring ways and that there are important links between stress and health outcomes. Many preclinical and clinical studies inspired by these pioneers have since shown that ELT is a risk factor for the development in adulthood of numerous serious psychiatric and medical problems, including depression [7], the leading cause of disease burden in women [8] and a leading cause of disability worldwide [9], and cardiovascular disease [10], which is the number one cause of death in the USA [11] and the rest of the world [12]. The complex mechanisms by which ELT contributes to the later development of illness are an active avenue of investigation. Other ongoing lines of inquiry include answering why women may be more resilient to ELT compared to men and why some women develop psychiatric illness and/or loss of function after ELT while a substantial minority do not [13, 14].

Different conceptual frameworks have been proposed to understand how ELT contributes to worsened psychiatric and medical outcomes throughout life including (1) the diathesis–stress model [15], which posits that ELT causes excess activity of stress response regulatory systems (e.g., corticotropin-releasing factor/hypothalamic–pituitary–adrenal (CRF/HPA) axis and sympathoadrenal system), thereby increasing vulnerability to stress-related disease, and (2) the stress sensitization hypothesis [16], which suggests that ELT increases risk of reacting to later stressors with psychopathological symptoms, e.g., depression; sensitive periods [17], the notion that there are certain points in development, each probably corresponding to phases of rapid development in particular brain structures and networks when an individual is especially vulnerable to the deleterious effects of ELT; allostatic load [18, 19], referring to the failure of physiological regulation under chronic stress resulting in secondary health problems; and the psychoanatomical formulation [20], which attempts to explain affective and behavioral symptoms of ELT victims in terms of trauma-induced neuroanatomical changes. The preponderance of evidence currently favors a fusion of them. De Bellis et al. [21] recently proposed the developmental traumatology model, which successfully integrates all of these concepts. Importantly, this model shows how increased unhealthy behaviors associated with ELT help mediate the worsened health outcomes observed in victims.

The specific changes in the stress response systems associated with ELT that overlap with changes observed in certain psychiatric and medical disorders and thus may mediate the increased risk of those disorders after ELT include persistent hypothalamic–pituitary–adrenal (HPA) axis disturbances [22], elevated levels of pro-inflammatory cytokines [23–25], decreases in neurotrophins, disruption of monoamine neurotransmission [17], increased glutamatergic activity [26], reduced hippocampal neurogenesis [27•], and changes in stress-modulating circuits involving prefrontal cortex, cingulate gyrus, amygdala, hippocampus, and others areas [28–30]. It is important to note that the above changes, along with the more direct potential effects of ELT, e.g., traumatic brain injury (TBI), are sufficiently robust that inconsistent controlling for them has likely contributed to various discrepant findings in the literature. For example, because the vast majority of prior studies of major depressive disorder (MDD) did not assess ELT, it has been suggested that some of the main neurobiological findings attributed to depression, such as reduced hippocampal volume, may in fact be consequences of ELT.

Subtypes of ELT include sexual, physical, and emotional abuse; emotional and physical neglect; early loss of or prolonged separation from a parent; being raised by a parent with severe mental illness or substance abuse problems; exposure to war or violence; and bullying before adulthood. The study of the long-term health effects of ELT is rapidly growing more sophisticated and complex as researchers appreciate a growing number of types of ELT and the potential health effects of each, in addition to how the timing of ELTs and their interactions with other risk and protective factors over time affect their impacts.

Important recent findings along these lines include recognition that, although women and men may report approximately an equal overall incidence of ELT in some studies, there are important sex differences in risks for different ELTs (e.g., women report relatively more sexual abuse) [31, 32] and their responses to them; the first potential ELT with long-term health effects may actually occur in the womb [15, 33]; there is strong evidence for ELT-subtype-specific sensitive periods during which children and adolescents are more vulnerable to particular long-term ELT-associated sequelae; verbal and emotional maltreatment early in life may have long-term health effects equally severe to those associated with childhood physical and sexual abuse [31]; bullying, including cyberbullying, in childhood and adolescence is an important and common subtype of ELT [24, 32]; victims of ELT may be predisposed to a unique depression endophenotype that responds differently to treatment of depression in non-victims [34]; and that PTSD reflects enduring and deleterious neurobiological changes in response to acute trauma that various

factors (e.g., ELT, female gender, age, and co-occurring physical injury) predispose one to and that may actually increase the diathesis to PTSD of a woman's offspring [35].

It has long been recognized that the field is challenged by the fact that the data about ELT are largely collected retrospectively and thus are subject to recall bias. Nevertheless, it is important to note that recall bias with regard to ELT is more likely to lead to under-reporting than over-reporting and that retrospective reports of ELT are generally valid for major ELTs that are clearly defined [36]. Furthermore, reports of ELT are quite stable over time [37]. Thus, it appears that retrospective case–control studies of ELT are acceptable second-best alternatives to prospective studies of ELT, which are, of course, far less common. The field has also been challenged by inconsistent findings, many probably resulting from the multifactorial and complex nature of ELT and inconsistent controlling for confounding variables.

This article broadly summarizes the current state of knowledge about the long-term health effects of ELT for women, highlights major recent findings, primarily in human studies involving women due to space considerations, identifying novel risk and protective factors for the development of illness after ELT, and discusses their implications with regard to answering the great need for more effective prevention and treatment approaches for victims.

Psychiatric Consequences of ELT in Women

ELT is associated with increased rates of multiple types of psychopathology in adult women including depressive reactions to stressful life events, self-mutilation, suicidal ideation and behavior, MDD, bipolar disorder, posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), phobias, obsessive compulsive disorder, schizophrenia, eating disorders, personality disorders, substance abuse and smoking, attention deficit hyperactivity disorder (ADHD), cognitive disorders (e.g., impaired executive functioning, visual working memory, emotional processing, receptive language proficiency, and intellectual functioning) and decreased educational achievement, chronic fatigue syndrome, fibromyalgia and other chronic pain syndromes, functional GI disorders (e.g., irritable bowel syndrome), sexual problems, increased rates of inpatient psychiatric admissions, and negative changes in personality, cognitive schema, coping mechanisms, and mood regulation [22, 32, 33, 38–48].

In general, the risk of increased psychopathology and suicidality due to ELT appears to be dose-dependent, increasing with multiple types, frequency, and severity of ELT. The type(s) of ELT that one is exposed and at what time in childhood or adolescence that one is exposed appear to significantly impact whether or not psychopathology will develop and, if so, what type. These findings, along with the recognition of sex differences in responses to ELT, have led to the increasingly validated notion of sensitive periods during which vulnerability to the deleterious enduring effects of ELT on risk for psychiatric problems is heightened in an age-, sex-, and ELT-subtype-specific manner [15, 49, 50], multiple recent examples of which appear below. Interactions between ELTs, protective factors, and risk factors, such as certain gene variants, epigenetic changes, or ongoing life stressors, have also been found to exert significant influences on risk of later manifesting psychiatric illness. The risk and protective factors may interact with ELT and with each other in a complex fashion over time, challenging the development of any simple model of risk and calling for the use of complex computational forecasting methods such as machine learning, which has recently been used to predict risk of non-remitting PTSD [51, 52]. Personality, cognitive factors, coping styles, parenting styles, and psychosocial supports may also mediate the effects of ELT on later psychopathology [22, 42, 44, 47, 53, 54].

It is not yet clear to what extent, if any, differences in rates and types of ELT and their effects may explain why depression is two times as common in women as in men [55] and women attempt suicide about three times more frequently than men [31, 56]. It does appear that women are more likely than men to develop depression following ELT [57]. They are also more susceptible to PTSD, with younger women being more susceptible than older women [58].

It has been speculated that differences between the sexes in response to specific types of ELT could be due to sex genomic, gene–environment interaction, and brain organization differences and differences in the actions of circulating sex steroids on CRH and monoaminergic neurons and/or development given that sex steroids affect the structural plasticity of multiple brain regions involved in mood and stress responsiveness, e.g., amygdala and hippocampus, across the life span [59]. Social, cultural, and other environmental factors could also play roles.

With regard to MDD, ELT has previously been associated with earlier onset, increased severity, increased duration, and more comorbidity (e.g., dysthymia, PTSD, GAD, substance abuse, and antisocial personality disorder) [7]. Furthermore, a meta-analysis of 16 epidemiological and 10 clinical studies showed that ELT was associated with an increased risk of developing recurrent (odds ratio (OR) 2.24) and persistent depression (OR 2.34) and an increased probability of depression failing to respond or remit with pharmacotherapy (OR 1.26) or combined psychotherapy–pharmacotherapy (OR 1.9), with a non-significant trend toward decreased responsiveness to psychotherapy [60•]. Myers et al. [61] found positive dose-dependent relationships between number of traumatic events and severity of depression, anxiety, and stress in adulthood.

Tunnard et al. [62] recently completed a cross-sectional study of adult patients with treatment-resistant depression to

identify associations between ELT (i.e., physical, sexual, and emotional abuse; bullying victimization; and traumatic events in childhood), depressive symptomatology, and clinical course. ELT was reported by a full two thirds of the subjects. ELT was associated with earlier age at onset and increased episode persistence and recurrence, risk of having attempted suicide, and risk of having had a psychotic episode. The effects of different types of child abuse on these outcomes appeared to be modality-specific. Of note, because of relevant concerns in the past about potential confounding effects, the association between ELT and suicide risk in treatment-resistant depression did not appear to be mediated by personality disorders.

More specific to suicide, a large retrospective CDC-sponsored cohort study [31] of adult primary care patients showed that there was a robust dose-dependent relationship between ELT and risk of a suicide attempt. The odds ratio for a suicide attempt varied with type of ELT. Interestingly, emotional abuse (OR 5) conferred greater risk than physical (OR 3.4) and sexual abuse (OR 3.4). The OR for a suicide attempt in adulthood ranged from 2.3 in those with one ELT to 29.8 in those with seven or more adverse childhood experiences. The effect may have been partially mediated by factors including depression and substance abuse; however, the association remained significant after controlling for them. The attributable risk fraction for at least one lifetime suicide attempt in the population, which had a 3.8 % lifetime prevalence of suicide attempt, was 67 %, suggesting that ELT has a powerful effect on risk of making a suicide attempt and, therefore, that preventing ELT could have a major impact on the prevalence of attempted suicide.

Importantly, being the victim or perpetrator of bullying increases risk of suicidality and developing depression later in life [24, 32]. Females are at greater risk of suicide attempts/completions due to being victims of bullying. The increased risk is correlated with the severity and frequency of victimization. Females are also at greater risk of suicide if they are bullies themselves. Furthermore, female victims of childhood bullying are more susceptible to developing anxiety disorders, including agoraphobia, GAD, and panic disorder, in adulthood [32].

Khan et al. [63•] recently contributed to the accumulating evidence for multiple early and late sensitive exposure periods in childhood and adolescence when maltreatment maximally impacts risk for MDD, current symptoms of depression, and degree of suicidal ideation in a sex- and modality-specific manner. Their cross-sectional study of 18–25-year-olds to determine the effects of 10 different types of ELT at different ages showed that there were dose-dependent effects of exposure to different types of ELT on risk of the above outcomes. Individuals with histories of ELT and MDD differed most from individuals with ELT without MDD in that they had greater exposure to parental and peer emotional abuse and parental emotional neglect during adolescence. At age 14 years, females were particularly sensitive to peer emotional abuse, which was the most important predictor of a history of MDD and symptoms of depression and was also an important predictor of suicidality. Sexual abuse at age 18 years was the greatest predictor of female suicidality, followed by peer emotional abuse at age 14 years. Emotional neglect at age 12 years was the second most important predictor in females for determining risk for MDD and symptom severity. Emotional neglect at age 3 years and parental verbal abuse at 5–6 years were also significant predictors of depression severity in females.

The results were in line with prior studies showing that ELT confers a greater risk of suicidal ideation and behavior than trauma experienced in adulthood [49] and that PTSD and MDD were equally likely to develop in females abused before the age of 13 years, but PTSD was more likely if abuse occurred later [50]. It has been speculated that such a change in risk with age could partly be due to development of stress coping mechanisms and maturation of the HPA axis [15].

Based on the results of preclinical and clinical studies and the fact that MDD is surely a heterogeneous syndrome, it has been suggested that the decreased responsiveness of victims of ELT to available treatments for MDD may be due to individuals with ELT having a distinct endophenotype of depression [15] defined by important differences in the reactivity of the CRF/HPA axis and other systems known to regulate mood and stress reactivity, such as the serotonin system and various limbic networks. Depressed individuals with histories of ELT may, thus, require a unique treatment approach.

Following prior studies showing associations between ELT and worsened outcomes in bipolar disorder, Etain et al. [64] reported that earlier age of onset, increased number of depressive episodes, increased suicide attempts, and more rapid cycling in bipolar disorder were each significantly associated with at least one subtype of ELT. Interestingly, there was a stronger association between ELT and bipolar disorder symptomatology in females than in males.

Fuller-Thomson and Lewis [65] analyzed cross-sectional data collected in the 2012 Canadian Community Health Survey–Mental Health and showed that in women, physical abuse, sexual abuse, and witnessing parental domestic violence were all associated with an increased risk of ADHD, adding to the growing awareness of the link between ELT and risk of ADHD and other neurocognitive disorders. Although ADHD was more common in men, the association between ELT and ADHD was stronger in women for all types of ELT studied.

It has been previously been shown that women with histories of ELT are characterized by certain deleterious behavioral, personality, cognitive, coping style, and emotional regulation changes that may increase their likelihoods of interpreting life events as distressing and their risks of developing

psychopathology, and these can create barriers to their treatment [39]. Examples include isolativeness, less stable relationships, insecure attachments, mistrustfulness, low self-esteem and other cognitive distortions, emotional lability, and impaired impulse control.

Concordant with prior studies, McElroy and Hevey [47] recently completed a cross-sectional study of Irish adults which revealed that ELT was significantly correlated in a dose-dependent manner with an increased number of perceived stressors in the past year and lower well-being scores. Lower well-being was mostly due to the increase in perceived stressors. In terms of personality, trait emotional intelligence, and coping styles, ELT was positively correlated with increased neuroticism, emotion-focused and distraction coping, and lower levels of trait emotional intelligence, agreeableness, and task-focused coping scores. The findings were interpreted to be consistent with other studies showing more emotion-focused coping and fewer task coping skills in victims of ELT. Higher levels of neuroticism and emotion-focused coping may have partially mediated the association of ELT with the increased number of perceived stressors and lower well-being.

Carvalho Fernando et al. [44] recently found that patients with borderline personality disorder and MDD reported more ELT, had higher levels of emotional dysregulation, used adaptive coping strategies (i.e., cognitive reappraisal) less, and used maladaptive coping strategies (i.e., expressive suppression) more than healthy controls. The strongest associations were between emotional abuse and neglect and emotional dysregulation. The findings supported a mediating effect between childhood emotional abuse and adult borderline symptomatology.

Inspired by prior studies showing that childhood sexual abuse is associated with sexual dysfunction in women, Stephenson et al. [48] observed that there were significant medium- to large-sized effects of childhood sexual abuse on sexual well-being in women presenting with sexual complaints. Women with sexual difficulties who were sexually abused as children exhibited higher levels of sexual distress and weaker links between sexual function and sexual distress than controls.

There is growing evidence that the psychiatric consequences of ELT can be multigenerational, possibly mediated in part via epigenetic effects, adverse effects on the fetus in utero, and changes in maternal behavior postpartum. In trying to understand how alterations of the HPA axis and sympathoadrenal system, two systems often dysregulated in victims of ELT, can have profound impacts on a pregnant woman's offspring, it is instructive to note that multiple prior studies have found that exposure to a depressed mother in utero or in the first months of life is significantly associated with increased cortisol and catecholamine levels in the neonate and infant similar to changes observed in the mother, significant neurobehavioral dysregulation before and after birth, and increased rates of a variety of worsened outcomes (e.g., slower fetal growth rates, lower birth weight, and premature birth) that appear to be mediated to some extent by the former changes [33]. A few recent reports shed further light on the mechanisms by which the effects of a woman's traumatic experiences may be passed to her offspring. Lehrner et al. [66] demonstrated that the adult offspring of female Holocaust survivors with PTSD had lower urinary cortisol excretion and greater glucocorticoid sensitivity as measured by both the lysozyme suppression test and the dexamethasone suppression test compared to controls, providing strong evidence that maternal trauma influences the programming of the HPA axis of offspring, whether through mechanisms that act prior to conception, during pregnancy, or in the postpartum period.

Paralleling this study, Enlow et al. [35] recently reported two related prospective, longitudinal studies with the aim of understanding the effects of maternal PTSD on attachment and later risk of PTSD in the offspring. The first suggested that maternal PTSD symptoms when a child was 6 months old increased the risk of insecure and disorganized mother–infant attachment relationships at 13 months of age. Of note, 57 % of the traumatic events occurred in the mother's childhood or adolescence. In the second study, there was a dose-dependent positive association between insecure attachment in infancy and risk of being diagnosed with PTSD by 17.5 years. Moreover, severity of PTSD at 17.5 years was predicted by a history of disorganized attachment in infancy. Insecure-avoidant and insecure-resistant attachments predicted lifetime PTSD diagnosis in a dose-dependent manner. Risk of developing PTSD was higher in the female offspring than in the male offspring. These results suggest that secure attachments may promote physiological, affective, and behavioral stress regulation and thereby create relative resiliency.

Following from these and other prior studies showing deleterious effects of ELT on mothering behaviors, Juul et al. [67•] found that mothers' histories of ELT were significantly associated with greater tendencies toward neutral affect and decreased cortisol responses during interactions with their 6-month-old infants. Their ELT histories also predicted their lower mean cortisol levels, which partially mediated the associations between their ELTs and neutral affects during mother–infant interactions. These results further implicate dysregulation of the HPA axis in the long-term and transgenerational sequelae of ELT and suggest that mothers with ELT may need treatment specific to their histories of ELT to improve their parenting behaviors and the outcomes of their offspring.

Neurobiological Effects of ELT in Women

The preclinical and clinical evidence that exposure to various ELTs results in persistent alterations in HPA axis activity, a

number of neurotransmitter systems (e.g., CRF, monoamines, and oxytocin), neurotrophins (e.g., brain-derived neurotrophic factor), markers of inflammation, neuroanatomy, and neurophysiology is now quite robust. It is likely that these systems interact in complex ways.

HPA Axis

ELT is associated with a number of persistent alterations in the HPA axis, including the activity of CRF-containing neural circuits [22]. CRF, acting as both a hormone and a neurotransmitter, is a central component of the HPA axis and acts as the main CNS coordinator of the behavioral, autonomic, endocrine, and immune components of the stress response [22]. The specific changes in the HPA axis depend upon the nature of the risk factors involved, the characteristics of the victims (e.g., age, sex, genetics, and epigenetics), and the details (e.g., type, number of types, frequency, duration, and severity) of the ELTs. Persistent dysregulation of the stress response via the enduring effects of ELT on the HPA axis may, in part, explain the increased risk in victims of ELT of developing depression and PTSD, both of which exhibit neurobiological changes that overlap with ELT and both of which are more likely to develop following ELT, particularly in women.

Women with histories of childhood physical abuse have been found to exhibit elevated cerebrospinal fluid (CSF) CRF concentrations. These levels are even greater if more than one type of child abuse occurred or if the abuse occurred later in childhood [34], consistent with the hypotheses that the number of types of abuse is an important risk factor and that there are sensitive periods to ELT. In addition, negative dose–response effects of multiple abuse exposures and duration and severity of abuse have been found for CSF oxytocin levels in adult women [68].

Interestingly, in studies of guinea pigs and non-human primates, exposing the pregnant female to a stressful environment induced changes in the HPA axis, immune function, cardiovascular system, and stress- and anxiety-related behaviors of her offspring similar to ELT. Even fairly innocuous stimuli (e.g., strobe light and noise) were found to have profound enduring effects on offspring, opening the possibility that relatively minor maternal abuse could exert significant life-long effects in humans [69].

As with the other effects of ELT, whether or not such changes are reversible is an important question. In rats, the effects of maternal separation on the HPA axis and behavior were reversed by chronic treatment with the SSRI paroxetine but returned after it was stopped [70]. Importantly, in the same model, foster care prevented many of the neurobiological consequences of maternal deprivation [71].

ELT has also been implicated in hyperactivity of the vasopressin system, which may augment the already hyperactive HPA axis and thereby increase vulnerability to the development of depression, anxiety, and hyperresponsiveness to stressful situations [72].

Inflammatory Markers

A recent meta-analysis by Baumeister et al. [73] indicated that ELT has been associated with persistent small but significant elevations in the pro-inflammatory cytokines IL-6, C-reactive protein (CRP), and TNF-α in an ELT-subtype-specific manner. The associations were not mediated by psychiatric illness, age, gender, or BMI. Our own study demonstrated a marked increase in IL-6 levels in response to psychosocial stress in depressed males with a history of ELT, as well as increased DNA binding of the major pro-inflammatory transcription factor NF-κB in peripheral blood mononuclear cells. The magnitudes of the IL-6 and NF-κB rises were correlated with depression severity as assessed with the HAM-D [74].

More recently, Lu et al. [23] found that 13 of 120 cytokines were elevated in MDD patients compared to healthy controls before controlling for ELT. After ELT was controlled for, however, the changes were no longer significant, suggesting that ELT at least partially mediated the effect. Interestingly, cytokine levels could be used to differentiate ELT patients from controls without ELT with an accuracy of 79.5 %. It could not be determined if the elevated cytokine levels were a cause of or predisposing factor to depression because the study did not include a group of healthy patients with ELT.

Highlighting the importance of bullying as an ELT with long-term sequelae, a study by Wolke and Lereya [24] recently showed that being a victim of bullying in childhood and adolescence was associated with elevated CRP in adulthood.

Finally, Levine et al. [25] recently reported that in adults (mean age 73.2 years) randomly selected from the longitudinal Health and Retirement Study, ELT, but not childhood socioeconomic status, childhood health, adult trauma, or low adult socioeconomic status, was associated with elevated inflammatory marker gene expression (i.e., a composite of *COX2/PTGS2*, *IL1B*, and *IL8* expression), demonstrating the long-enduring effects of ELT on the immune system. Childhood trauma significantly exacerbated the effects of low adult socioeconomic status on inflammatory marker gene expression.

These findings, taken together, are of interest because chronic inflammation is associated with the development of a host of serious medical disorders, including a number of chronic autoimmune disorders which are significantly more common in women, and elevated inflammatory factors have been associated with depression and suicidality [74, 75]. Elevated cytokines may contribute to depression and other health problems by affecting the HPA axis, multiple neurotransmitter systems (e.g., dopamine, serotonin, and glutamate), and altering the function of hippocampal neurons, including neurogenesis [76].

Neuroanatomical Changes

A variety of neuroanatomical changes have been found to be associated with ELT. Previously reviewed changes include decreased intracranial volumes; decreased volume of medial prefrontal cortex and reduced gray matter in bilateral insula, anterior cingulate gyrus, orbitofrontal cortex, and caudate; thinning in particular regions of the primary somatosensory cortex; and decreased hippocampal volume [34, 77]. Some of these changes appeared specific to the nature of the trauma, leading to speculation that the anatomical changes, like the changes seen in the stress response system, may be adaptations to ELT. For example, in our study, the thinning observed in the genital representative field of the left somatosensory cortex in women with histories of childhood sexual abuse may be the result of regionally specific neurodevelopmental changes that were protective in the short term while victims were trapped in traumatizing circumstances but that predispose to diminished libido and anorgasmia later in life. Cortical thinning observed in the cingulate and precuneus, areas involved in emotional regulation, self-awareness, self-evaluation, and first-person perspective, which was associated with childhood emotional abuse may similarly have been protective in the short term and deleterious in the long term [77].

Changes in the hippocampus deserve special attention. The hippocampus is a major site for glucocorticoid-mediated negative feedback on HPA axis activity. In addition to being involved in regulation of the HPA axis and stress reactivity, it is integral to memory and learning, including contextual aspects of fear conditioning, and is one of the most plastic regions of the brain, capable of neurogenesis throughout life. Stress and glucocorticoids are both reported to reduce hippocampal volume and neurogenesis [78–80], although the association between stress and impaired hippocampal neurogenesis appears complex [81].

In 18–22-year-old women, hippocampal volume reduction was found to be specifically associated with sexual abuse occurring between 3–5 and 11–13 years (more at 3–5 years than at 11–13 years), whereas frontal cortex volume reduction was associated with sexual abuse occurring between 14 and 16 years of age. Corpus callosum volume was reduced in association with sexual abuse at 9–10 years [17]. Baker et al. [82] found volumetric reductions in right and left anterior cingulate cortex and left insula in healthy adults who experienced ELT between 8 and 17 years, but not in those who experienced ELT between 1 month and 7 years of age. These results lend further credence to the proposition that there are sensitive periods during which there is heightened sensitivity to ELT in an age- and modality-specific manner.

Opel et al. [27•] reported that MDD patients had smaller hippocampal volumes compared to healthy controls. There was an inverse relationship between bilateral hippocampal volumes and ELT scores, as assessed using the Childhood Trauma Questionnaire (CTQ), in both MDD and control subjects. Each CTQ subscale showed similar effects on hippocampal volume. Contrary to some prior studies, the presence and magnitude of depressive symptoms were not associated with hippocampal volumes, suggesting that the decrease in hippocampal size commonly cited in studies of MDD patients may be due to ELT and may be a trait-like risk factor for developing depression (i.e., "limbic scar").

Evidence for a sensitive period in preadolescence specific to amygdala development was recently reported by Pechtel et al. [83]. Correlating Maltreatment and Abuse Chronology of Exposure scale data with brain MRI imaging, they found that right amygdala enlargement in adults was strongly correlated with ELT that occurred between 9 and 10 years of age in a dose-dependent and modality-specific manner. Such a change could contribute to enduring deficits in processing negative stimuli and affect regulation and predispose to psychopathology. The results agreed with some prior studies, but many discrepancies remain in the literature regarding the effects of ELT on amygdala volume and function.

Functional MRI and PET Imaging

Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) imaging are informing the field as to how ELT may lead to enduring changes in the connectivity between different brain regions and the activity of particular critical brain regions that may predispose women to different psychiatric disorders.

Thus, the effects of ELT on the connectivity between the frontal cortex, limbic circuitry, and the HPA axis have been studied. Increased basal cortisol levels in girls were significantly correlated with greater ELT and predicted decreased resting state functional connectivity (rs-FC) between the amygdala and the ventromedial prefrontal cortex (vmPFC) 14 years later. The adolescent amygdala-vmPFC rs-FC, in turn, was inversely correlated with current anxiety and, to a lesser degree, depressive symptoms [84]. These findings are consistent with the hypothesis that ELT can induce changes in the HPA axis which affect cortical-limbic connectivity in an enduring way and contributes to the increased diathesis to anxiety and depression later in life.

Prior studies have demonstrated that ELT is associated with amygdala hyperreactivity in response to emotionally negative stimuli. Recently, Grant et al. [30] used fMRI to study task-based causal connectivity between different amygdalar nuclei and between amgydalar nuclei and other relevant brain regions in response to an unconditioned auditory threat in healthy, mostly female adults with and without histories of ELT. The ELT group showed an aberrant dominance of intra- and extra-amygdaloid pathways facilitated by the central nucleus of the amygdala, which is involved in fear expression, stress-related glucocorticoid output, and autonomic

arousal. These changes may underlie differences in implicit emotional modulation in response to threat, indicating that relative cortical hyperarousal and decreased cortical inhibition of threat detection and/or consolidation of fear memory occur after ELT, and help explain, in part, why individuals exposed to ELT are more susceptible to stress-related psychiatric illness.

Philip et al. [28] recently used fMRI to investigate the differences in regional homogeneity (ReHo) and rs-FC between medication-free, healthy individuals with and without histories of ELT. They found that ReHo in the right inferior parietal lobe and the right superior temporal gyrus was relatively decreased in proportion to ELT severity in victims of ELT. They also found decreased rs-FC between the right inferior parietal lobe and right precuneus/posterior cingulate, left fusiform gyrus, left cerebellar declive, and left caudate. It was speculated that these changes may be related to increased vulnerability to developing depression and PTSD after ELT.

A more recent fMRI study by the same group [29] of the rs-FC differences between healthy subjects with and without ELT in regions highly relevant to the treatment of depression by rTMS showed that subjects with ELT exhibited increased local connectivity with the left middle frontal gyrus and negative connectivity with the left precuneus when seeding the left dorsolateral prefrontal cortex (DLPFC) and negative connectivity to the left precuneus and left inferior parietal lobe when seeding the right DLPFC compared to subjects without ELT. Their results appeared to confirm previous findings of dissociation between executive and default mode networks (DMNs), which are important for self-referential thought, in association with ELT.

A PET study by Miller et al. [85] used [(11)C]McN 5652 to measure regional brain serotonin transporter (5-HTT) binding potential (BP_P) to assess the effects of sexual and physical abuse before the age of 15 and found that adult depressed subjects with these abuse histories had lower 5-HTT BP_P than non-abused depressed subjects in the anterior cingulate, dorsal putamen, amygdala, hippocampus, midbrain, and thalamus. The changes were not mediated by differences in the *5-HTTLPR* polymorphism and were consistent with those found in maternally deprived macaques. The results suggest that ELT causes persistent changes in the serotonergic system and may help explain why victims of ELT are more prone to depression and respond less well to antidepressant pharmacotherapy.

More recently, Oswald et al. [86] completed a PET study of healthy 18–29-year-olds in which they assessed the association between ELT, current level of perceived stress, and the dopamine response, as measured using high specific activity [(11)C]raclopride, to IV amphetamine administration. ELT was positively associated with current level of perceived stress, consistent with prior studies, and each was positively associated in a dose-dependent manner with ventrostriatal dopamine responses to amphetamine, although current stress may have partially mediated the association between ELT and dopamine responsiveness. These results suggest that ELT leads to enhanced mesolimbic sensitivity to psychostimulants, partially through increasing reactivity to later stressors, thereby accounting to some extent for the increased rates of substance use disorders among victims of ELT.

Genetic Factors

Single-nucleotide polymorphisms (SNPs) of several genes have been identified that appear to affect vulnerability to the development of psychopathology (e.g., depression, anxiety, PTSD, suicidality, and prolonged stress response) after ELT exposure including several components of the HPA axis (*CRHR1* [22], *CRFBP* [22], *FKBP5* [87], and *PAC1* [88]), and two involved in the serotonin system (*HTR3A* [89, 90] and *5-HTTLPR* [91]), as well as the brain-derived neurotrophic factor gene *BDNF* [89], which is involved in neuron growth and survival, the stress response, and mood disorders and the oxytocin receptor gene, *OXTR*, thought to play a major role in attachment, trust, social behavior, and stress response modulation [34].

By way of introduction, a dose-dependent relationship has been established between the number of S alleles of the serotonin-transporter-linked polymorphic region (*5-HTTLPR*) of the *5-HTT* gene and the frequency and severity of abuse in conferring risk to later depression. The S allele appears to confer greater risk of depression only in the presence of ELT [38, 92]. There are multiple similar findings with *CRFR1* polymorphisms and additive effects of the *5-HTT* and *CRFR1* risk alleles [22]. These results highlight the sorts of gene × environment and gene × gene × environment interactions that lend great complexity to unraveling the connections between ELT and enduring health effects.

Recent work has confirmed and extended our knowledge of the mediating roles of variants in the CRF receptor gene, *CRHR1*, which has been implicated in anxiety, depression, and suicidality, and the *FKBP5* gene, which codes for FK506 binding protein 5 (FKBP5), a co-chaperone that modulates the receptor binding of glucocorticoids and has been implicated in depression, PTSD, and suicidality, in the diathesis to ELT-associated psychiatric and medical illnesses.

Veenit et al. [93] reported that in adult rats, peripubertal stress was associated with increased CRHR1 messenger RNA (mRNA) expression in the hippocampal CA1 and the central nucleus of the amygdala as well as with increased social and stress-coping behavior deficits. Similar effects of early life stress had previously been noted in animal studies. As in studies of perinatal-stress-exposed laboratory animals, the effects of ELT were attenuated by poststress treatment with a CRHR1 antagonist. The findings further implicated *CRHR1* in mediating diathesis to ELT-associated psychopathology and

added to the literature suggesting that CRHR1 antagonists may be an effective prophylactic strategy against psychopathology in humans exposed to early and late ELT.

Lessard et al. [94] found that a *CRHR1* SNP and an *FKBP5* SNP both mediated the effects of ELT and adult stress on the development of several medical disorders in adults over the course of a 3-year prospective longitudinal study. They appeared to confer risk of illness only in combination with ELT and/or increased adult stress.

Fuge et al. [46] investigated the effect of the interaction between different *CRHR1* polymorphisms and ELT on working memory, as measured by performance on the n-back test, in healthy adults. ELT was inversely correlated with working memory performance. Homozygosity for one allele was associated with markedly worse working memory impairments after ELT than carriers of the other alleles that were examined, suggesting that it conferred greater vulnerability to ELT-associated memory impairment in adulthood, hypothetically by altering the function of the hippocampus. The findings added to those of prior studies showing language, motor skill, working memory, and other cognitive deficits in victims of ELT.

Guillaume et al. [95] recently reported that among individuals with histories of suicide attempts, patients with histories of sexual abuse showed significantly impaired decision-making abilities, as measured by the Iowa Gambling Task (IGT). Sexual abuse and emotional neglect interacted with three *CRHR1* SNPs and one *CRHR2* polymorphism, respectively, to modulate IGT performance, suggesting that the genes moderate the effects of ELT on later decision-making capacity and, hypothetically, risk of suicide.

Laucht et al. [96] found that ELT (CTQ) interacted with two variants of *CRHR1*, one being the *CRHR1* TAT haplotype, to increase symptoms of depression, as measured with the BDI, in young adults. On the contrary, Kranzler et al. [97] reported that the *CRHR1* TAT haplotype conferred a dose-dependent protective effect (OR 0.63 for each allele) against lifetime risk of MDD in African American women with histories of ELT, consistent with some studies, but a higher risk (OR 1.51 in homozygotes) in those without histories of ELT. No interactions between the haplotype and ELT were observed in men or European Americans. The results highlight the possibility that *CRHR1* variants may act as risk or protective factors under different conditions.

An interaction of ELT (CTQ) with a risk allele of *CRHBP*, which encodes a protein that regulates CRF receptor binding, predicted a higher risk of having made a suicide attempt in adult African Americans in a recent study by Roy et al. [98]. They also found an additive effect on increased suicidality of risk alleles of *CRHBP* and *FKBP5* in the same population.

Starr et al. [16] found that adversity prior to 5 years of age increased the tendency to respond to stressors in young adulthood with depression and internalizing symptoms in those with certain *CRHR1* and *5-HTTLPR* variants. High adversity prior to age 5 interacted with the S allele of the *5-HTTLPR* to potentiate the effect of chronic stress on depression and internalizing symptoms in an allelic-dose-dependent manner.

A study by Uddin et al. [88] used data for adult women enrolled in the Detroit Neighborhood Health Study to demonstrate that there were dose-dependent positive correlations between the interaction of a *PAC1* SNP and ELT and both risk of meeting criteria for PTSD and increased PTS severity over the last month. No association between the gene and risk of depression was found, consistent with prior studies. The location of the SNP in a putative estrogen response element may explain why it appears to preferentially confer increased risk of PTSD in women. *PAC1*, which encodes pituitary adenylate cyclase–activating polypeptide 1 receptor type I, has been implicated in regulation of the stress response, adult neurogenesis, and transcriptional control of brain-derived neurotrophic factor (BDNF) and could interact with ELT to effect vulnerability to PTSD in adulthood by disrupting one or more of these functions.

Wankerl et al. [99] recently reported results of a pilot study scrutinizing the interactions between *5-HTTLPR* polymorphisms and environmental adversity by measuring serotonin transporter (SERT) mRNA expression and methylation of the promoter-associated *SERT* CpG island in peripheral blood cells of healthy individuals. Prenatal and early life adversities were associated with decreased SERT mRNA expression in a dose-dependent manner. The effect was additive to the effects of the S allele on SERT mRNA expression and was not mediated by recent stress or methylation of the relevant CpG island. The findings were consistent with findings in laboratory animals and supported a role for serotonergic dysregulation in conferring vulnerability to ELT-associated psychopathology.

Baumann et al. [100] recently contributed to the evidence implicating dysregulation of catecholamine systems in the increased diathesis to stress-associated psychopathology following ELT, reporting that homozygosity for the low-active met allele of the *COMT* gene combined with high ELT was associated with an increase in anxiety sensitivity.

Our group recently identified a new oxytocin receptor SNP associated with increased depression and perceived stress in patients with ELT [61], adding to other studies linking various *OXTR* polymorphisms to ELT-associated psychopathology.

Lok et al. [101] recently reported that an *MTHFR* allele associated with increased oxidative stress and decreased methylation capacity interacted with ELT to significantly increase MDD recurrence over 5.5 years of follow-up of 124 adults with remitted recurrent MDD and increased depression symptomatology in 665 healthy individuals from the general population. ELT group carriers of the allele had hazard ratios for recurrence 2.4 times greater than ELT group non-carriers and had hazard ratios 3.55 times greater than non-ELT group non-carriers.

Oliveira et al. [102] recently reported that the interaction of a *TLR2* rs3804099 TT genotype and a history of childhood

sexual abuse was significantly associated with earlier onset of bipolar disorder as analyzed using a Kaplan–Meier survival curve, suggesting that ELT may increase diathesis to bipolar disorder, in part, by dysregulation of the immune system.

Epigenetic Factors

Epigenetics refers to heritable changes in gene expression (i.e., turning genes "on" or "off") that do not entail alterations in the DNA sequence. Epigenetic mechanisms include DNA methylation, histone acetylation and methylation, non-coding RNAs, and microRNAs [103]. ELT has been associated with a number of epigenetic changes in women.

Altered cytosine methylation of the promoter region of the glucocorticoid receptor gene (*NR3C1*) was found in the hippocampus of adult suicide victims with histories of childhood abuse, but not in those without child abuse. The change leads to decreased expression of the glucocorticoid receptor [104] and so would hypothetically result in decreased negative glucocorticoid feedback on the HPA axis via the hippocampus. The downregulation of the glucocorticoid receptor could be a consequence of a chronically hyperactive stress response and/or an ELT-induced risk factor for hyperreactivity to stress that increases risk of suicidality.

In their study of patients with borderline personality disorder, Martín-Blanco et al. [105] found that there was a significant positive correlation between methylation of *NR3C1* and both physical abuse and greater severity of borderline personality disorder (i.e., symptom scores, self-injury, and number of hospitalizations).

Following a prior study in rodents demonstrating that greater early maternal care was associated with changes in the offspring's HPA axis stress reactivity mediated by alterations in the epigenetic modifications of the *NR3C1* promoter [103], Oberlander et al. [106] conducted a clinical study which revealed that prenatal exposure in the third trimester to a depressed mother was associated with increased methylation of a transcription factor binding site of *NR3C1* and that the increased methylation was associated with heightened HPA axis stress reactivity in the infants at 3 months of age. These results provide compelling evidence that a mother's prenatal mental health and early mothering behaviors exert a significant impact on the stress response systems of her infant via epigenetic mechanisms.

Our group reported that ELT was associated with decreased methylation of a regulatory element of the vulnerability SNP of the *FKBP5* gene [87], which results in increased expression of the FKBP5 protein and attenuated HPA axis negative feedback [107]. This may explain the increased risk of PTSD after ELT associated with this *FKBP5* SNP.

Booij et al. [108] found that physical abuse was associated with increased methylation of the *SERT* promoter in adults. The interaction of homozygosity for the L allele and history of child abuse was associated with greater *SERT* promoter methylation which was inversely correlated with hippocampal volume. SERT mRNA levels did not correlate with methylation level. Decreased hippocampal volume was also associated with MDD diagnosis.

Conclusions that can be drawn about risk for mental illness from epigenetic studies are currently somewhat limited by the realization that epigenetic biomarkers are affected by a myriad of factors (e.g., age, gender, ethnicity, genetic population differences, and cell type), access to brain tissue for epigenetic studies is limited, and the extent to which changes in peripheral epigenetic markers correspond to such changes in the CNS is not well understood and may be variable, although prior studies have shown correspondence between the two [109].

Long-Term Medical Consequences of ELT in Women

ELT is emerging as a major risk factor for numerous serious and chronic medical illnesses and other health problems. For example, ELT is clearly associated in a dose-dependent manner with an increased risk of ischemic heart disease [10], the leading cause of death in both women and men [11, 12]. The mechanisms by which ELT might produce this effect may overlap with those proposed to mediate the increased risk of cardiovascular disease in depressed patients, as reviewed elsewhere [10, 110, 111], and may include those that increase vulnerability to some of the cardiovascular disease risk factors discussed below (e.g., hypertension, metabolic syndrome, and obesity). Interestingly, Zhao et al. [112] recently identified gene × environment interactions between an MAOA polymorphism and physical and emotional abuse that increase the likelihood of subclinical atherosclerosis in middle-aged male twins as measured by brachial flow-mediated dilation using ultrasound.

Suglia et al. [113] recently reported on the results of a nationally representative longitudinal study showing that young adult women with histories of childhood sexual abuse before age 11 years had a significantly higher prevalence (PR 1.43) of hypertension compared to controls. The same effect was not found for other types of abuse or in men. The effect size remained the same but was no longer significant after controlling for obesity, physical activity, smoking, and alcohol consumption indicating that the effect was probably mediated to some extent by differences in health behaviors and other risk factors.

McCarthy-Jones and McCarthy-Jones [114] reported that childhood sexual and physical abuse were each associated with increased BMI and obesity in a dose-dependent manner. Subjects with histories of childhood abuse were, on average,

4.2 BMI units, or 11.16 kg, heavier than subjects without histories of abuse. They also found positive associations between childhood sexual abuse and increased allergies, arthritis, asthma, bladder problems, bone/back/muscle/joint pain, bowel/colon problems, bronchitis/emphysema, cancer, cardiovascular disease, migraine/headaches, skin problems, and stomach ulcer/digestive problems. It appeared that many of these associations might partly be indirectly mediated by BMI, anxiety, or depression.

With regard to the metabolic syndrome, Lee et al. [115] used longitudinal data collected from the 48 contiguous US states in the Biomarker Substudy of MIDUS to seek associations with ELT in adult women. Child abuse was associated with increased numbers of metabolic syndrome symptoms and a dose-dependent increase in probability of a diagnosis of metabolic syndrome. The magnitude of the associations differed by ELT subtype. Possible mediating factors that the authors noted included adult socioeconomic status, maladaptive stress responses, and unhealthy behaviors (e.g., poor sleep quality and stress-induced eating).

Spitzer et al. [116] completed a cross-sectional, case–control study of the association between ELT and multiple sclerosis (MS), a major autoimmune disease that is significantly more common in women. Adjusted odds ratios of subjects with MS reporting emotional abuse, sexual abuse, and emotional neglect were 3.4, 2.2, and 2, respectively, and they also had higher total ELT (CTQ) scores compared to controls. Physical abuse and emotional neglect were also associated with higher relapse rates in MS patients. This same group followed up this study of MS with a cross-sectional, case–control study [117] to identify the effects of ELT on the risk of developing another chronic autoimmune disease that is also more common in women, rheumatoid arthritis. Women with rheumatoid arthritis reported more emotional and physical abuse and had higher ELT (CTQ) scores than the general population. Emotional neglect, sexual abuse, or physical neglect did not differ between the two populations. Adjusted odds ratios of women with rheumatoid arthritis reporting emotional abuse, physical abuse, and emotional neglect compared to the general population were 2.6, 3.2, and 1.9, respectively. In contrast, no relationships between ELT scores and rheumatoid arthritis were found in men. The authors speculated that dysregulation of neuroendocrine–immune networks may mediate the effects of ELT on risk for these autoimmune diseases.

Bertrone-Johnson et al. [118] completed a prospective, longitudinal study which demonstrated that childhood emotional and physical abuse increased the risk of moderate-to-severe premenstrual syndrome in 27–44-year-old women. Risk was highest overall among women reporting chronic abuse of multiple types.

Schüssler-Fiorenza Rose et al. [119] recently used data from a cross-sectional, population-based survey of adults in 14 states and Washington, D.C. completed in 2009 and 2010 to identify a dose-dependent relationship between exposure to child abuse and familial dysfunction and self-reported disability in adulthood that remained significant after controlling for potentially mediating psychiatric and medical conditions. Sexual abuse had the strongest association with disability.

Both Brown et al. [120] and Kelly-Irving et al. [121] reported associations between ELT and premature death. The investigation by the latter group [121] was a prospective cohort study which found a dose-dependent relationship between ELT and premature all-cause mortality.

Bellis et al. [122] analyzed data from a large cross-sectional population-based study in England of 18–69-year-olds to try to elucidate the effects of ELT on the health trajectories of individuals. They identified dose-dependent increases in six different major non-communicable diseases (i.e., cancer, cardiovascular disease, diabetes type 2, stroke, respiratory disease, and liver/digestive disease), any disease, and likelihood of premature death with increasing numbers of ELTs. It was suggested that the effects of ELT on morbidity are likely increasingly masked by age due to increased mortality.

Savolainen et al. [123] used the Helsinki Birth Cohort Study to show that an interaction between temporary separation from both parents in childhood and other traumatic life experiences were associated with a small but significant shortening (about 1.2 %) of leukocyte telomere length, a biomarker of cellular aging, in elderly adults about six decades after the separation event. The authors speculated that the mechanism of shortening may involve a hyperactive HPA axis altering cortisol levels and/or inflammation levels. The study confirms and extends previous observations by other groups [124–126] regarding the effects of ELT on telomere length.

Bradford et al. [127] reported that there were significantly higher rates of general trauma and physical, emotional, and sexual abuse in childhood among adult women with irritable bowel syndrome (IBS) compared to those without, emotional abuse being the strongest predictor of IBS. No such associations were found in men. The associations may have been partially mediated by depression and anxiety. Mediating mechanisms could include stress-induced visceral hypersensitivity, mucosal dysfunction, inflammation, changes in autonomic tone, changes in gastric motility, and HPA axis hypersensitivity.

Based on their findings from a longitudinal case–control study, Jones et al. [128] proposed a model of functional GI disorders (e.g., functional dyspepsia and IBS) in which child abuse sets in motion a cycle of exacerbations of mood disorders repeatedly leading to functional GI symptoms. Child abuse before age 13 years was associated with greater depression, anxiety, neuroticism, and functional GI symptoms in adults; however, the study could not clarify the factors mediating the association between child abuse and functional GI symptoms. They suggested that perhaps child abuse increases neuroticism, which then predisposes individuals to mood and

anxiety disorders and thereby increase risk for functional GI symptoms.

With regard to pregnancy and factors relevant to pregnancy, Leeners et al. [129] found strong associations between a history of childhood sexual abuse and increased risks of pregnant women having fewer prenatal visits, feeling less prepared for labor, smoking (31.7 vs. 9.4 %), having a partner using drugs (10.6 vs. 1.2 %), reporting depression (24.1 vs. 1.8 %) and suicidal ideation (10.6 vs. 0 %), experiencing physical (16.5 vs. 0 %), sexual (12.9 vs. 0 %), and emotional abuse (44.7 vs. 1.7 %), and having more hospitalizations (41.2 vs. 19.4 %) in pregnancy and with higher risks of premature contractions (38.8 vs. 20 %), cervical insufficiency (25.9 vs. 9.4 %), and premature delivery (18.8 vs. 8.2 %) [129–131]. Childhood physical abuse and other adverse childhood experiences also increased risk of premature delivery [131].

Other negative outcomes that have been reported to be associated with ELT in women include increased risk for rape, unintended first pregnancy, and acquiring sexually transmitted diseases [132].

Prevention and Treatment of Psychiatric Disorders in Women with ELT

Prevention

Because victims of ELT are an at-risk group for multiple serious psychiatric disorders, more attention to them is clearly warranted. As the risk factors for developing mental illness after ELT are identified, more and better prevention efforts can be undertaken.

Primary prevention of the development of mental illness after ELT is, of course, preferred and should remain an important goal. Identifying and defining the various types of ELT, including deleterious prenatal events, and their risk factors and developing effective ways of eliminating their impact are central to this.

With regard to bullying and child abuse and neglect, education about their deleterious effects and advocacy for improved parenting skills are critical. These ELTs should, of course, be eliminated, but if a child were identified to have a high risk for developing a particular psychiatric illness after ELT, the parents might be taught how to reduce the risk of ELT exposure or to be more supportive after an ELT in the hopes of decreasing the likelihood of development of psychiatric sequelae. Preclinical, clinical, and epidemiological studies suggest that the consequences of ELT can be attenuated by the availability of a stable home environment and other positive psychosocial supports [14, 133]. Indeed, having a good caregiver is among the most important factors determining whether or not an abused child will have a good developmental outcome [92], a finding observed in foster care environments [53], and the support of remaining family members is similarly critical following loss of a parent due to death or divorce [22]. An enriched environment later in life may attenuate the effects of ELT [22]. Interventions to improve parent–child relationships and communication while decreasing maladaptive parenting behaviors and overprotective parenting styles may reduce the risk of a child becoming a victim of bullying or a bully/victim [134]. Targeting teenage girls who experienced peer or parental emotional abuse, particularly during periods of heightened vulnerability, and fostering social acceptance of teens in their families and peer networks might reduce long-term risk for mental health problems including depression [63•]. Teaching coping and emotion regulation skills to victims of ELT may be important both for the prevention and treatment of psychiatric disorders [44, 47]. Future studies may find that instituting a particular drug therapy or psychotherapy immediately after ELT exposure is effective in preventing the long-term sequelae of ELT. In general, additional suicide prevention efforts in coordination with long-term surveillance may significantly benefit victims of ELT [31, 32].

As for the transgenerational effects of ELT, Enlow et al. [35] concluded that interventions that decrease maternal stress and promote positive mother–child relationships early in development in cases where the mother has PTSD could reduce the risk of her offspring later developing PTSD. Such interventions might be especially effective in populations at high risk of trauma exposure.

Along these lines, Muzik et al. [135] described the results of a pilot uncontrolled open trial of Mom Power, a multimodal, manualized group intervention to improve parenting by mothers with histories of trauma and psychiatric illness (e.g., depression and PTSD) who have young children. The goals are to improve the parent–child relationship and hopefully to prevent the negative impact of maternal psychopathology and traumatic life experiences on family functioning, the parent–child relationship, and attachment. The curriculum is trauma-informed and counteracts engagement hesitancy and mistrust based on trauma-related help-seeking avoidance. The key intervention principles are appreciating the importance of safety, trust building, enhancing self-efficacy through empowerment, and skills building around self-care/mental health, problem-solving, emotion regulation, parenting competence, connecting mothers to community resources, and teaching mothers to engage in treatment. Relationship-focused parenting psychoeducation and support are provided and stress reduction and self-care strategies are taught. Preliminary outcomes for the mothers included decreased symptoms of depression, PTSD, and caregiver helplessness and improvements in caregiver reflectivity. Larger and more rigorous studies will be needed in the future to determine if this or similar interventions are effective.

Treatment

As summarized above, multiple lines of research suggest that patients with histories of ELT and depression may have a distinct endophenotype of depressive disorder that requires unique treatment strategies to produce an optimal outcome [34]. Indeed, only a minority of MDD patients attain remission with initial pharmacotherapy or psychotherapy and response rates for ELT trauma victims are even lower. Further study is clearly necessary to determine the optimal treatment of victims of ELT. Types of therapy that have previously shown some promise for depressed women with histories of ELT include emotion-focused therapy (EFT) and group psychotherapy, with the caveats that group therapy ought to be reserved for women with less severe abuse experiences and symptoms and that disorder-specific treatments are more likely to benefit women with more severe symptoms [39].

In a previous review, Craighead and Nemeroff [39] suggested that psychotherapy may be an essential aspect of treating depression in victims of ELT and offered the following as provisional guidelines regarding psychotherapy for victims of ELT. First of all, the primary therapeutic task is to build a therapeutic alliance around trust and safety because victims of ELT often have disrupted cognitive schema in these regards. Employment of schema-focused therapy may be useful for this purpose. Second, it is essential for the therapist to be aware that it is easy for resensitization to the trauma events and associated stimuli to occur and so extra care should be taken in exploring prior traumatic events. Third, patients with severe symptoms resulting from ELT probably need longer-term therapy rather than acute treatment to achieve meaningful and sustained improvements. In agreement with Carvalho Fernando et al. [44], they suggested that although it may take considerably more time and effort to accomplish, it is of paramount importance for victims of ELT to learn better emotional regulation. To accomplish this goal, Greenberg's Emotion-Focused Therapy and the mindfulness aspects of Linehan's DBT and Mindfulness CBT may be beneficial. In summary, a comprehensive treatment approach for victims of ELT should include psychotherapy with careful exploration of past traumatic events and cognitive reframing that addresses problems surrounding emotional regulation, attachment, and interpersonal relationships in a safe and trusting therapeutic environment. It is important to bear in mind, however, that the majority of patients with MDD and ELT will likely require combination treatment with antidepressants and psychotherapy.

As the neurobiological mechanisms by which ELT contributes to the development of depression are elucidated, new targets for pharmacotherapy will be identified. Future therapies to target dysregulation of the HPA axis may include CRHR1 antagonists, vasopressin V1b receptor antagonists, cortisol synthesis inhibitors, and glucocorticoid receptor antagonists [72, 136]. Results of laboratory animal studies raise hope that future pharmacotherapies will improve the cognitive and functional abilities of victims of ELT in addition to their affective symptoms [137, 138].

Conclusions

There is rapidly growing appreciation of ELT as comprising an array of distressing experiences between conception and the beginning of adulthood with a multitude of potential long-term, even transgenerational, health consequences of great public health concern (e.g., depression and cardiovascular disease). The neurobiological, psychological, and behavioral effects are also sufficient, if overlooked, to potentially confound many types of ongoing biomedical research. Certain effects previously attributed to diseases were, in fact, likely due to ELT.

The impact of ELT on a woman's long-term health trajectory varies with the type, number of different types, severity, frequency, and timing of the ELT, the characteristics of the individual (e.g., age, genetics, epigenetics, and personality), and the individual's environment (e.g., level of social support and ongoing stressors) and is likely mediated to a significant extent by persistent changes in a number of biological systems, dysregulation of those governing the stress response preeminent among them. ELTs may be most likely to precipitate persistent deleterious health outcomes when they occur during particular sensitive periods in development. Female sex appears to increase the likelihood of suffering particular ELTs, such as sexual abuse, and the development of certain health problems (e.g., depression and PTSD) in adulthood after ELT, relative to men. The reasons for the relatively increased diathesis of women to certain health problems after ELT remain obscure.

The emerging transgenerational effects of ELT obviously carry special implications for female victims of ELT who are pregnant or have the potential to become so and those whose parents experienced ELT. The burgeoning knowledge of the effects of ELT and stress during pregnancy on women and their children will hopefully have positive effects in the social, forensic, and public health realms including greater protection from abuse, better advocacy for victims of abuse, and greater availability of targeted services for mothers with histories of ELT and/or mental illness and their children.

Growing knowledge of the risk factors and pathophysiological mechanisms for the development of health problems after ELT will lead to improved prevention, diagnostic, and treatment efforts, including more effective psychotherapeutic approaches and medications, hopefully making great improvements in the lives of women everywhere and ending countless cycles of intergenerational trauma-associated pathology. The need for prospective, longitudinal studies and controlled, blinded trials that examine the effects of specific

subtypes of ELT during particular times in childhood and adolescence is great. Also critically important is the need to consistently control for the potentially confounding effects of ELT whenever appropriate to improve the consistency and reliability of disease-related results reported in the literature. Given that there are many risk and protective factors with complex interactions determining total risk of various health problems after ELT, advanced quantitative forecasting methods such as machine learning may emerge as important tools for determining the likelihoods of various health outcomes in victims of ELT.

At the present time, it is important to use the available prevention strategies, heighten our vigilance in identifying victims of ELT to ensure needed help is directed to them, and appreciate that victims of ELT are likely to have more medical and psychiatric comorbidities and different treatment needs compared to non-victims.

Compliance with Ethics Guidelines

Conflict of Interest Nils C. Westfall declares no conflict of interest.

Charles. B. Nemeroff consults for Xhale, Takeda, SK Pharma, Shire, Roche, Lilly, Mitsubishi Tanabe Pharma Development America, Taisho Pharmaceutical Inc., and Lundbeck. He is a stockholder in Opko, Antares, Xhale, Celgene, Seattle Genetics and Abbvie. He serves on the scientific advisory boards of the American Foundation for Suicide Prevention (AFSP), CeNeRx BioPharma (2012), the National Alliance for Research on Schizophrenia and Depression (NARSAD), Xhale, PharmaNeuroBoost (2012), Clintara, the Anxiety Disorders Association of America (ADAA), and Skyland Trail. He serves on the board of directors for AFSP, Skyland Trail, Gratitude America, and ADAA. He receives income in excess of $10,000 from Clintara, American Psychiatric Publishing, and Xhale. He holds two patents: Method and devices for transdermal delivery of lithium (US 6,375,990B1) and Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2). None of these activities present a conflict with the current article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. U.S. Department of Health and Human Services, Administration for Children and Families, Administration on Children, Youth and Families, Children's Bureau. Child maltreatment 2013. 2015. http://www.acf.hhs.gov/programs/cb/research-data-technology/statistics-research/child-maltreatment. Accessed 13 June 2015.
2. Freud S. Vorlesungen zur einführung in die psychoanalyse. Leipzig: Internationaler Psychoanalytischer Verlag; 1920.
3. Levine S. Infantile experience and resistance to physiological stress. Science. 1957;126(3270):405.
4. Selye H. A syndrome produced by diverse nocuous agents. Nature. 1936;138(3479):32.
5. Szabo S, Tache Y, Somogyi A. The legacy of Hans Selye and the origins of stress research: a retrospective 75 years after his landmark brief "letter" to the editor of nature. Stress. 2012;15(5):472–8.
6. Harlow HF, Dodsworth RO, Harlow MK. Total social isolation in monkeys. Proc Natl Acad Sci. 1965;54(1):90–7.
7. Widom CS, DuMont K, Czaja SJ. A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. Arch Gen Psychiatry. 2007;64(1):49–56.
8. WHO. The global burden of disease: 2004 update. 2008. http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf?ua=1. Accessed 8 June 2015.
9. WHO. Depression fact sheet. 2012. http://www.who.int/mediacentre/factsheets/fs369/en/. Accessed 8 June 2015.
10. Dong M, Giles WH, Felitti VJ, Dube SR, Williams JE, Chapman DP, et al. Insights into causal pathways for ischemic heart disease: adverse childhood experiences study. Circulation. 2004;110(13):1761–6.
11. CDC, NCHS. Underlying Cause of Death 1999–2013. In: CDC WONDER Online Database. 2015. http://wonder.cdc.gov/ucd-icd10.html. Accessed 9 June 2015.
12. WHO. Cardiovascular disease fact sheet. 2015. http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed 8 June 2015.
13. McGloin JM, Widom CS. Resilience among abused and neglected children grown up. Dev Psychopathol. 2001;13(4):1021–38.
14. DuMont KA, Widom CS, Czaja SJ. Predictors of resilience in abused and neglected children grown-up: the role of individual and neighborhood characteristics. Child Abuse Negl. 2007;31(3):255–74.
15. Neigh GN, Gillespie CF, Nemeroff CB. The neurobiological toll of child abuse and neglect. Trauma Violence Abuse. 2009;10(4):389–410.
16. Starr LR, Hammen C, Conway CC, Raposa E, Brennan PA. Sensitizing effect of early adversity on depressive reactions to later proximal stress: moderation by polymorphisms in serotonin transporter and corticotropin releasing hormone receptor genes in a 20-year longitudinal study. Dev Psychopathol. 2014;26(4 Pt 2):1241–54.
17. Andersen SL, Tomada A, Vincow ES, Valente E, Polcari A, Teicher MH. Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. J Neuropsychiatry Clin Neurosci. 2008;20(3):292–301.
18. Katz DA, Sprang G, Cooke C. The cost of chronic stress in childhood: understanding and applying the concept of allostatic load. Psychodyn Psychiatry. 2012;40(3):469–80.
19. Danese A, McEwen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiol Behav. 2012;106(1):29–39.
20. Vela RM. The effect of severe stress on early brain development, attachment, and emotions: a psychoanatomical formulation. Psychiatr Clin N Am. 2014;37(4):519–34.
21. De Bellis MD, Zisk A. The biological effects of childhood trauma. Child Adolesc Psychiatr Clin N Am. 2014;23(2):185–222. vii.
22. Heim C, Shugart M, Craighead WE, Nemeroff CB. Neurobiological and psychiatric consequences of child abuse and neglect. Dev Psychobiol. 2010;52(7):671–90.
23. Lu S, Peng H, Wang L, Vasish S, Zhang Y, Gao W, et al. Elevated specific peripheral cytokines found in major depressive disorder patients with childhood trauma exposure: a cytokine antibody array analysis. Compr Psychiatry. 2013;54(7):953–61.

24. Wolke D, Lereya ST. Long-term effects of bullying. Arch Dis Child. 2015. doi:10.1136/archdischild-2014-306667.
25. Levine ME, Cole SW, Weir DR, Crimmins EM. Childhood and later life stressors and increased inflammatory gene expression at older ages. Soc Sci Med. 2015;130:16–22.
26. Mathew SJ, Shungu DC, Mao X, Smith EL, Perera GM, Kegeles LS, et al. A magnetic resonance spectroscopic imaging study of adult nonhuman primates exposed to early-life stressors. Biol Psychiatry. 2003;54(7):727–35.
27.• Opel N, Redlich R, Zwanzger P, Grotegerd D, Arolt V, Heindel W, et al. Hippocampal atrophy in major depression: a function of childhood maltreatment rather than diagnosis? Neuropsychopharmacology. 2014;39(12):2723–31. **The authors reported an inverse relationship between bilateral hippocampal volumes and ELT (CTQ) scores in both patients with MDD and in healthy controls. Each CTQ subscale showed similar effects on hippocampal volume. Contrary to some prior studies, the presence and magnitude of depressive symptoms were not associated with hippocampal volumes, suggesting that the decrease in hippocampal size commonly cited in studies of MDD patients may be due to ELT to some extent. This study highlighted the importance of ELT as an important potential confounder in the study of affective disorders and lent support to the hypotheses that depressed patients with histories of ELT may be a distinct clinical subtype with a common set of neurobiological alterations and that hippocampal volume loss after ELT may be a trait-like risk factor for developing depression.**
28. Philip NS, Kuras YI, Valentine TR, Sweet LH, Tyrca AR, Price LH, et al. Regional homogeneity and resting state functional connectivity: associations with exposure to early life stress. Psychiatry Res. 2013;214(3):247–53.
29. Philip NS, Valentine TR, Sweet LH, Tyrka AR, Price LH, Carpenter LL. Early life stress impacts dorslateral prefrontal cortex functional connectivity in healthy adults: informing future studies of antidepressant treatment. J Psychiatr Res. 2014;52:63–9.
30. Grant MM, Wood K, Sreenivasan K, Wheelock M, White D, Thomas J, et al. Influence of early life stress on intra- and extra-amygdaloid causal connectivity. Neuropsychopharmacology. 2015;40(7):1782–93.
31. Dube SR, Anda RF, Felitti VJ, Chapman DP, Williamson DF, Giles WH. Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: findings from the Adverse Childhood Experiences Study. JAMA. 2001;286(24):3089–96.
32. Short ATO, Nemeroff CB. Early life trauma and suicide. In: Hudzik TJ, Cannon KE, editors. Suicide: phenomenology and biology. Switzerland: Springer International Publishing; 2014. doi:10.1007/978-3-319-09964-4_11.
33. Field T, Diego M, Hernandez-Reif M. Prenatal depression effects on the fetus and newborn: a review. Infant Behav Dev. 2006;29(3):445–5.
34. Heim C, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology. 2008;33(6):693–710.
35. Enlow MB, Egeland B, Carlson E, Blood E, Wright RJ. Mother-infant attachment and the intergenerational transmission of post-traumatic stress disorder. Dev Psychopathol. 2014;26(1):41–65.
36. Hardt J, Rutter M. Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. J Child Psychol Psychiatry. 2004;45(2):260–73.
37. Yancura LA, Aldwin CM. Stability and change in retrospective reports of childhood experiences over a 5-year period: findings from the Davis Longitudinal Study. Psychol Aging. 2009;24(3):715–21.
38. Kendler KS, Kuhn JW, Prescott CA. Childhood sexual abuse, stressful life events and risk for major depression in women. Psychol Med. 2004;34(8):1475–82.
39. Craighead WE, Nemeroff CB. The impact of early trauma on response to psychotherapy. Clin Neurosci Res. 2005;4:405–11.
40. Widom CS, Czaja SJ, Paris J. A prospective investigation of borderline personality disorder in abused and neglected children followed up into adulthood. J Pers Disord. 2009;23(5):433–46.
41. Noll JG, Shenk CE, Yeh MT, Ji J, Putnam FW, Trickett PK. Receptive language and educational attainment for sexually abused females. Pediatrics. 2010;126(3):e615–22.
42. Gould F, Clarke J, Heim C, Harvey PD, Majer M, Nemeroff CB. The effects of child abuse and neglect on cognitive functioning in adulthood. J Psychiatr Res. 2012;46(4):500–6.
43. Perna G, Alciati A, Prestia D, Torti T, Nemeroff B. Is there a link between child abuse and neglect and anxiety disorders? Minerva Psichiatr. 2013;54(2):137–48.
44. Carvalho Fernando S, Beblo T, Schlosser N, Terfehr K, Otte C, Lowe B, et al. The impact of self-reported childhood trauma on emotion regulation in borderline personality disorder and major depression. J Trauma Dissociation. 2014;15(4):384–401.
45. Cohen LJ, Tanis T, Bhattacharjee R, Nesci C, Halmi W, Galynker I. Are there differential relationships between different types of childhood maltreatment and different types of adult personality pathology? Psychiatry Res. 2014;215(1):192–201.
46. Fuge P, Aust S, Fan Y, Weigand A, Gärtner M, Feeser M, et al. Interaction of early life stress and corticotropin-releasing hormone receptor gene: effects on working memory. Biol Psychiatry. 2014;76(11):888–94.
47. McElroy S, Hevey D. Relationship between adverse early experiences, stressors, psychosocial resources and wellbeing. Child Abuse Negl. 2014;38(1):65–75.
48. Stephenson KR, Pulverman CS, Meston CM. Assessing the association between childhood sexual abuse and adult sexual experiences in women with sexual difficulties. J Trauma Stress. 2014;27(3):274–82.
49. McCauley J, Kern DE, Kolodner K, Dill L, Schroeder AF, DeChant HK, et al. Clinical characteristics of women with a history of childhood abuse: unhealed wounds. JAMA. 1997;277(17):1362–8.
50. Maercker A, Michael T, Fehm L, Becker ES, Margraf J. Age of traumatisation as a predictor of post-traumatic stress disorder or major depression in young women. Br J Psychiatry. 2004;184:482–7.
51. Galatzer-Levy IR, Karstoft KI, Statnikov A, Shalev AY. Quantitative forecasting of PTSD from early trauma responses: a machine learning application. J Psychiatr Res. 2014;59:68–76.
52. Karstoft KI, Galatzer-Levy IR, Statnikov A, Li Z, Shalev AY. Bridging a translational gap: using machine learning to improve the prediction of PTSD. BMC Psychiatry. 2015;16(15):30.
53. Kessler RC, Pecora PJ, Williams J, Hiripi E, O'Brien K, English D, et al. Effects of enhanced foster care on the long-term physical and mental health of foster care alumni. Arch Gen Psychiatry. 2008;65(6):625–33.
54. Aust S, Stasch J, Jentschke S, Hartwig EA, Koelsch S, Heuser I, et al. Differential effects of early life stress on hippocampus and amygdala volume as a function of emotional abilities. Hippocampus. 2014;24(9):1094–101.
55. Grigoriadis S, Robinson GE. Gender issues in depression. Ann Clin Psychiatry. 2007;19(4):247–55.
56. Mościcki EK. Gender differences in completed and attempted suicides. Ann Epidemiol. 1994;4(2):152–8.

57. Weiss EL, Longhurst JG, Mazure CM. Childhood sexual abuse as a risk factor for depression in women: psychosocial and neurobiological correlates. Am J Psychiatry. 1999;156(6):816–28.
58. Breslau N, Davis GC, Andreski P, Peterson EL, Schultz LR. Sex differences in posttraumatic stress disorder. Arch Gen Psychiatry. 1997;54(11):1044–8.
59. Heim C, Nemeroff CB. Neurobiology of posttraumatic stress disorder. CNS Spectr. 2009;14(1 Suppl 1):13–24.
60.• Nanni V, Uher R, Danese A. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. Am J Psychiatry. 2012;169(2):141–51. **The authors completed a meta-analysis of 16 epidemiological and 10 clinical studies published before December 31, 2010 regarding the effects of ELT on recurrence, persistence, and responsiveness to treatment of depression, showing that ELT was associated with increased risk of developing recurrent (OR 2.24) and persistent depression (OR 2.34) and an increased probability of depression failing to respond or remit with pharmacotherapy (1.26) or combined treatment (OR 1.9) in depressed individuals with histories of ELT compared to depressed individuals without histories of ELT. There was a nonsignificant trend toward decreased responsiveness to psychotherapy in depressed patients with histories of ELT relative to those without. The lack of placebo controlled clinical trials limited the conclusions that could be drawn regarding the effectiveness of treatment of depression in victims of ELT.**
61. Myers AJ, Williams L, Gatt JM, McAuley-Clark EZ, Dobson-Stone C, Schofield PR, et al. Variation in the oxytocin receptor gene is associated with increased risk for anxiety, stress and depression in individuals with a history of exposure to early life stress. J Psychiatr Res. 2014;59:93–100.
62. Tunnard C, Rane LJ, Wooderson SC, Markopoulou K, Poon L, Fekadu A, Juruena M, Cleare AJ. The impact of child adversity on suicidality and clinical course in treatment-resistant depression. J Affect Disord. 2014;152–4:122–130.
63.• Khan A, McCormack HC, Bolger EA, McGreenery CE, Vitaliano G, Polcari A, et al. Childhood maltreatment, depression, and suicidal ideation: critical importance of parental and peer emotional abuse during developmental sensitive periods in males and females. Front Psychiatry. 2015;6:42. **The authors conducted a cross-sectional study of 18–25 year olds to determine the effects of 10 different types of ELT occurring at different ages, providing robust evidence for modality-specific sensitive exposure periods when maltreatment maximally impacts risk for MDD, current symptoms of depression, and degree of suicidal ideation. The results highlighted the relative importance of peer and parental emotional maltreatment – insults often assumed to be significantly less noxious than physical and sexual abuse – among the various types of ELTs in terms of conferring risk of psychopathology. They also supported the hypothesis that there are early and late sensitive periods and that experiencing specific types of ELT during particular sensitive periods may be as or more important than cumulative stress exposure. The generalizability of the results to victims of ELT older than 25 years old was limited by the narrow age range of the subjects, a problem that should be addressed in future studies.**
64. Etain B, Aas M, Andreassen OA, Lorentzen S, Dieset I, Gard S, et al. Childhood trauma is associated with severe clinical characteristics of bipolar disorders. J Clin Psychiatry. 2013;74(10):991–8.
65. Fuller-Thomson E, Lewis DA. The relationship between early adversities and attention deficit/hyperactivity disorder. Child Abuse Negl. 2015. doi:10.1016/j.chiabu.2015.03.005.
66. Lehrner A, Bierer LM, Passarelli V, Pratchett LC, Flory JD, Bader HN, et al. Maternal PTSD associates with greater glucocorticoid sensitivity in offspring of Holocaust survivors. Psychoneuroendocrinology. 2014;40:213–20.
67.• Juul SH, Hendrix C, Robinson B, Stowe ZN, Newport DJ, Brennan PA, et al. Maternal early-life trauma and affective parenting style: the mediating role of HPA-axis function. Arch Womens Ment Health. 2015. doi:10.1007/s00737-015-0528-x. **The authors found that a mother's history of ELT was significantly associated with a greater tendency toward exhibiting a neutral affect and a decreased cortisol response during interactions with her 6-month-old infant. The tendency toward exhibiting neutral affect during mother-infant interactions was partially mediated by the mother's mean cortisol level, which was inversely related to her history of ELT. Past or present symptoms of depression did not mediate these associations. The results add to the growing literature demonstrating the deleterious effects of ELT on mothering behaviors, demonstrate that some of these effects may be mediated by persistent changes in the HPA axis, and suggest that some of these effects on the outcomes of her offspring act independently of any diagnosable psychopathology (e.g. depression, PTSD) that she may have and so require separate targeted interventions.**
68. Heim C, Young LJ, Newport DJ, Mletzko T, Miller AH, Nemeroff CB. Lower CSF oxytocin concentrations in women with a history of childhood abuse. Mol Psychiatry. 2009;14(10):954–8.
69. Kapoor A, Matthews SG. Short periods of prenatal stress affect growth, behaviour and hypothalamo-pituitary-adrenal axis activity in male guinea pig offspring. J Physiol. 2005;566(Pt 3):967–77.
70. Huot RL, Thrivikraman KV, Meaney MJ, Plotsky PM. Development of adult ethanol preference and anxiety as a consequence of neonatal maternal separation in Long Evans rats and reversal with antidepressant treatment. Psychopharmacology (Berlin). 2001;158(4):366–73.
71. Huot RL, Gonzalez ME, Ladd CO, Thrivikraman KV, Plotsky PM. Foster litters prevent hypothalamic-pituitary-adrenal axis sensitization mediated by neonatal maternal separation. Psychoneuroendocrinology. 2004;29(2):279–89.
72. Beurel E, Nemeroff CB. Interaction of stress, corticotropin-releasing factor, arginine vasopressin and behaviour. Curr Top Behav Neurosci. 2014;18:67–80.
73. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Mol Psychiatry. 2015. doi:10.1038/mp.2015.67.
74. Pace TWW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, et al. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. Am J Psychiatry. 2006;163(9):1630–3.
75. Cattaneo A, Macchi F, Plazzotta G, Veronica B, Bocchio-Chiavetto L, Riva MA, et al. Inflammation and neuronal plasticity: a link between childhood trauma and depression pathogenesis. Front Cell Neurosci. 2015;9:40.
76. Currier MB, Nemeroff CB. Depression as a risk factor for cancer: from pathophysiological advances to treatment implications. Annu Rev Med. 2014;65:203–21.
77. Heim CM, Mayberg HS, Mletzko T, Nemeroff CB, Pruessner JC. Decreased cortical representation of genital somatosensory field after childhood sexual abuse. Am J Psychiatry. 2013;170(6):616–23.
78. Gould E, Tanapat P, McEwen BS, Flügge G, Fuchs E. Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. Proc Natl Acad Sci U S A. 1998;95(6):3168–71.
79. Tanapat P, Galea LA, Gould E. Stress inhibits the proliferation of granule cell precursors in the developing dentate gyrus. Int J Dev Neurosci. 1998;16(3-4):235–9.

80. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev. 2000;21(1): 55–89.
81. Hanson ND, Owens MJ, Nemeroff CB. Depression, antidepressants, and neurogenesis: a critical reappraisal. Neuropsychopharmacology. 2011;36(13):2589–602.
82. Baker LM, Williams LM, Korgaonkar MS, Cohen RA, Heaps JM, Paul RH. Impact of early vs. late childhood early life stress on brain morphometrics. Brain Imaging Behav. 2013;7(2):196–203.
83. Pechtel P, Lyons-Ruth K, Anderson CM, Teicher MH. Sensitive periods of amygdala development: the role of maltreatment in preadolescence. Neuroimage. 2014;97:236–44.
84. Burghy CA, Stodola DE, Ruttle PL, Molloy EK, Armstrong JM, Oler JA, et al. Developmental pathways to amygdala-prefrontal function and internalizing symptoms in adolescence. Nat Neurosci. 2012;15(12):1736–41.
85. Miller JM, Kinnally EL, Ogden RT, Oquendo MA, Mann JJ, Parsey RV. Reported childhood abuse is associated with low serotonin transporter binding in vivo in major depressive disorder. Synapse. 2009;63(7):565–73.
86. Oswald LM, Wand GS, Kuwabara H, Wong DF, Zhu S, Brasic JR. History of childhood adversity is positively associated with ventral striatal dopamine responses to amphetamine. Psychopharmacology (Berlin). 2014;231(12):2417–33.
87. Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, et al. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA. 2008;299(11):1291–305.
88. Uddin M, Chang SC, Zhang C, Ressler K, Mercer KB, Galea S, et al. ADCYAP1R1genotype, posttraumatic stress disorder, and depression among women exposed to childhood maltreatment. Depress Anxiety. 2013;30(3):251–8.
89. Gatt JM, Nemeroff CB, Schofield PR, Paul RH, Clark CR, Gordon E, et al. Early life stress combined with serotonin 3A receptor and brain-derived neurotrophic factor valine 66 to methionine genotypes impacts emotional brain and arousal correlates of risk for depression. Biol Psychiatry. 2010;68(9):818–24.
90. Gatt JM, Williams LM, Schofield PR, Dobson-Stone C, Paul RH, Grieve SM, et al. Impact of the HTR3A gene with early life trauma on emotional brain networks and depressed mood. Depress Anxiety. 2010;27(8):752–9.
91. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science. 2003;301(5631):386–9.
92. Kaufman J, Heinrich C. Exposure to violence and early childhood trauma. In: Zeanah C, editor. Handbook of infant mental health. New York: Guilford Press; 2000. p. 195–207.
93. Veenit V, Riccio O, Sandi C. CRHR1 links peripuberty stress with deficits in social and stress-coping behaviors. J Psychiatr Res. 2014;53:1–7.
94. Lessard J, Holman EA. FKBP5 and CRHR1 polymorphisms moderate the stress-physical health association in a national sample. Health Psychol. 2014;33(9):1046–56.
95. Guillaume S, Perroud N, Jollant F, Jaussent I, Olié E, Malafosse A, et al. HPA axis genes may modulate the effect of childhood adversities on decision-making in suicide attempters. J Psychiatr Res. 2013;47(2):259–65.
96. Laucht M, Treutlein J, Blomeyer D, Buchmann AF, Schmidt MH, Esser G, et al. Interactive effects of corticotropin-releasing hormone receptor 1 gene and childhood adversity on depressive symptoms in young adults: findings from a longitudinal study. Eur Neuropsychopharmacol. 2013;23(5):358–67.
97. Kranzler HR, Feinn R, Nelson EC, Covault J, Anton RF, Farrer L, et al. A CRHR1 haplotype moderates the effect of adverse childhood experiences on lifetime risk of major depressive episode in African-American women. Am J Med Genet B Neuropsychiatr Genet. 2011;156B(8):960–8.
98. Roy A, Hodgkinson CA, Deluca V, Goldman D, Enoch MA. Two HPA axis genes, CRHBP and FKBP5, interact with childhood trauma to increase the risk for suicidal behavior. J Psychiatr Res. 2012;46(1):72–9.
99. Wankerl M, Miller R, Kirschbaum C, Hennig J, Stalder T, Alexander N. Effects of genetic and early environmental risk factors for depression on serotonin transporter expression and methylation profiles. Transl Psychiatry. 2015;4, e402.
100. Baumann C, Klauke B, Weber H, Domschke K, Zwanzger P, Pauli P, et al. The interaction of early life experiences with COMT val158met affects anxiety sensitivity. Genes Brain Behav. 2013;12(8):821–9.
101. Lok A, Bockting CLH, Koeter MWJ, Snieder H, Assies J, Mocking RJT, et al. Interaction between the MTHFR C677T polymorphism and traumatic childhood events predicts. Transl Psychiatry. 2013;3, e288.
102. Oliveira J, Etain B, Lajnef M, Hamdani N, Bennabi M, Bengoufa D, et al. Combined effect of TLR2 gene polymorphism and early life stress on the age at onset of bipolar disorders. PLoS ONE. 2015;10(3), e0119702.
103. Szyf M, Weaver I, Meaney M. Maternal care, the epigenome and phenotypic differences in behavior. Reprod Toxicol. 2007;24(1): 9–19.
104. McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. Nat Neurosci. 2009;12(3):342–8.
105. Martín-Blanco A, Ferrer M, Soler J, Salazar J, Vega D, Andión O, et al. Association between methylation of the glucocorticoid receptor gene, childhood maltreatment, and clinical severity in borderline personality disorder. J Psychiatr Res. 2014;57:34–40.
106. Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics. 2008;3(2):97–106.
107. Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariante CM, et al. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat Neurosci. 2013;16(1):33–41.
108. Booij L, Szyf M, Carballedo A, Frey E-M, Morris D, Dymov S, et al. DNA methylation of the serotonin transporter gene in peripheral cells and stress-related changes in hippocampal volume: a study in depressed patients and healthy controls. PLoS ONE. 2015;10(3), e0119061.
109. Nemeroff CB, Binder E. The preeminent role of childhood abuse and neglect in vulnerability to major psychiatric disorders: toward elucidating the underlying neurobiological mechanisms. J Am Acad Child Adolesc Psychiatry. 2014;53(4):395–7.
110. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. Biol Psychiatry. 2003;54(3):227–40.
111. Nemeroff CB, Goldschmidt-Clermont PJ. Heartache and heartbreak–the link between depression and cardiovascular disease. Nat Rev Cardiol. 2012;9(9):526–39.
112. Zhao J, Bremner JD, Goldberg J, Quyyumi AA, Vaccarino V. Monoamine oxidase A genotype, childhood trauma, and subclinical atherosclerosis: a twin study. Psychosom Med. 2013;75(5): 471–7.
113. Suglia SF, Clark CJ, Boynton-Jarrett R, Kressin NR, Koenen KC. Child maltreatment and hypertension in young adulthood. BMC Public Health. 2014;14:1149.
114. McCarthy-Jones S, McCarthy-Jones R. Body mass index and anxiety/depression as mediators of the effects of child sexual and

physical abuse on physical health disorders in women. Child Abuse Negl. 2014;38(12):2007–20.
115. Lee C, Tsenkova V, Carr D. Childhood trauma and metabolic syndrome in men and women. Soc Sci Med. 2014;105:122–30.
116. Spitzer C, Bouchain M, Winkler LY, Wingenfeld K, Gold SM, Grabe HJ, et al. Childhood trauma in multiple sclerosis: a case-control study. Psychosom Med. 2012;74(3):312–8.
117. Spitzer C, Wegert S, Wollenhaupt J, Wingenfeld K, Barnow S, Grabe HJ. Gender-specific association between childhood trauma and rheumatoid arthritis: a case-control study. J Psychosom Res. 2013;74(4):296–300.
118. Bertone-Johnson ER, Whitcomb BW, Missmer SA, Manson JE, Hankinson SE, Rich-Edwards JW. Early life emotional, physical, and sexual abuse and the development of premenstrual syndrome: a longitudinal study. J Womens Health (Larchmt). 2014;23(9):729–39.
119. Schüssler-Fiorenza Rose SM, Xie D, Stineman M. Adverse childhood experiences and disability in US adults. PM R. 2014;6(8):670–80.
120. Brown DW, Anda RF, Tiemeier H, Felitti VJ, Edwards VJ, Croft JB, et al. Adverse childhood experiences and the risk of premature mortality. Am J Prev Med. 2009;37(5):389–96.
121. Kelly-Irving M, Lepage B, Dedieu D, Bartley M, Blane D, Grosclaude P, et al. Adverse childhood experiences and premature all-cause mortality. Eur J Epidemiol. 2013;28(9):721–34.
122. Bellis MA, Hughes K, Leckenby N, Hardcastle KA, Perkins C, Lowey H. Measuring mortality and the burden of adult disease associated with adverse childhood experiences in England: a national survey. J Public Health (Oxf). 2014. doi:10.1093/pubmed/fdu065.
123. Savolainen K, Eriksson JG, Kananen L, Kajantie E, Pesonen A, Raikkonen K. Associations between early life stress, self-reported traumatic experiences across the lifespan and leukocyte telomere length in elderly adults. Biol Psychol. 2014;97:35–42.
124. Tyrka AR, Price LH, Kao HT, Porton B, Marsella SA, Carpenter LL. Childhood maltreatment and telomere shortening: preliminary support for an effect of early stress on cellular aging. Biol Psychiatry. 2010;67(6):531–4.
125. Entringer S, Epel ES, Kumsta R, Lin J, Hellhammer DH, Blackburn EH, et al. Stress exposure in intrauterine life is associated with shorter telomere length in young adulthood. Proc Natl Acad Sci U S A. 2011;108(33):e513–8.
126. O'Donovan A, Epel E, Lin J, Wolkowitz O, Cohen B, Maguen S, et al. Childhood trauma associated with short leukocyte telomere length in posttraumatic stress disorder. Biol Psychiatry. 2011;70(5):465–71.
127. Bradford K, Shih W, Videlock EJ, Presson AP, Naliboff BD, Mayer EA, et al. Association between early adverse life events and irritable bowel syndrome. Clin Gastroenterol Hepatol. 2012;10(4):385–90.e1-3.
128. Jones MP, Oudenhove LV, Koloski N, Tack J, Talley NJ. Early life factors initiate a 'vicious circle' of affective and gastrointestinal symptoms: a longitudinal study. United Eur Gastroenterol J. 2013;1(5):394–402.
129. Leeners B, Stiller R, Block E, Görres G, Rath W, Tschudin S. Prenatal care in adult women exposed to childhood sexual abuse. J Perinat Med. 2013;41(4):365–74.
130. Leeners B, Stiller R, Block E, Görres G, Rath W. Pregnancy complications in women with childhood sexual abuse experiences. J Psychosom Res. 2010;69(5):503–10.
131. Leeners B, Rath W, Block E, Görres G, Tschudin S. Risk factors for unfavorable pregnancy outcome in women with adverse childhood experiences. J Perinat Med. 2014;42(2):171–8.
132. Dube SR, Felitti VJ, Dong M, Giles WH, Anda RF. The impact of adverse childhood experiences on health problems: evidence from four birth cohorts dating back to 1900. Prev Med. 2003;37(3):268–77.
133. Kaufman J, Yang BZ, Douglas-Palumberi H, Houshyar S, Lipschitz D, Krystal JH, et al. Social supports and serotonin transporter gene moderate depression in maltreated children. Proc Natl Acad Sci U S A. 2004;101(49):17316–21.
134. Lereya ST, Samara M, Wolke D. Parenting behavior and the risk of becoming a victim and a bully/victim: a meta-analysis study. Child Abuse Negl. 2013;37(12):1091–108.
135. Muzik M, Rosenblum KL, Alfafara EA, Schuster MM, Miller NM, Waddell RM, et al. Mom Power: preliminary outcomes of a group intervention to improve mental health and parenting among high-risk mothers. Arch Womens Ment Health. 2015. doi:10.1007/s00737-014-0490-z.
136. Ozbolt LB, Nemeroff CB. HPA axis modulation in the treatment of mood disorders. In: Schoepf D, editor. Psychiatric disorders – new frontiers in affective disorders. 2013; doi:10.5772/51600.
137. Couto FS, Batalha VL, Valadas JS, Data-Franca J, Ribeiro JA, Lopes LV. Escitalopram improves memory deficits induced by maternal separation in the rat. Eur J Pharmacol. 2012;695(1–3):71–5.
138. Garcia VA, Hirotsu C, Matos G, Alvarenga T, Pires GN, Kapczinski F, et al. Modafinil ameliorates cognitive deficits induced by maternal separation and sleep deprivation. Behav Brain Res. 2013;253:274–9.