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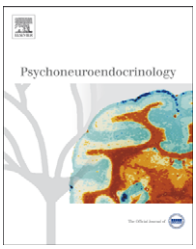

CURT P. RICHTER AWARD PAPER

The link between childhood trauma and depression: Insights from HPA axis studies in humans

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Summary
Childhood trauma is a potent risk factor for developing depression in adulthood, particularly in response to additional stress. We here summarize results from a series of clinical studies suggesting that childhood trauma in humans is associated with sensitization of the neuroendocrine stress response, glucocorticoid resistance, increased central corticotropin-releasing factor (CRF) activity, immune activation, and reduced hippocampal volume, closely paralleling several of the neuroendocrine features of depression. Neuroendocrine changes secondary to early-life stress likely reflect risk to develop depression in response to stress, potentially due to failure of a connected neural circuitry implicated in emotional, neuroendocrine and autonomic control to compensate in response to challenge. However, not all of depression is related to childhood trauma and our results suggest the existence of biologically distinguishable subtypes of depression as a function of childhood trauma that are also responsive to differential treatment. Other risk factors, such as female gender and genetic dispositions, interfere with components of the stress response and further increase vulnerability for depression. Similar associations apply to a spectrum of other psychiatric and medical disorders that frequently coincide with depression and are aggravated by stress. Taken together, this line of evidence demonstrates that psychoneuroendocrine research may ultimately promote optimized clinical care and help prevent the adverse outcomes of childhood trauma.

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1. Introduction

Hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis in major depression is one of the most prominent findings in psychoneuroendocrinology (Arborelius et al., 1999; Nestler et al., 2002). The HPA axis represents the major neuroendocrine stress response system that serves to adapt the organism to change in demand and thereby maintains stability and health (McEwen, 2004). Stress or acute challenge has long been recognized as a potent risk factor for depression, often precipitating the onset of depressive episodes (Hammen et al., 1992; Kendler et al., 1993, 2000). It is conceivable that HPA axis changes in depression may reflect effects of stress and mediate the manifestation of depressive symptoms. However, not every person exposed to stress will develop depression and it is critical to understand sources of individual differences in vulnerability to the pathogenic effects of stress. Thus, preexisting factors known to modulate the organism's ability to compensate in response to emotional challenge might interfere with successful adaptation and convey vulnerability to develop depression.

Epidemiological studies have provided strong evidence that adverse experience during childhood, such as abuse, neglect or loss, is associated with dramatic increases in the risk to develop depression. Edwards et al. (2003) in a CDC study of 8667 adult members of an HMO in the San Diego area reported a strong dose–response relationship between the number of experienced childhood adversities and general mental health problems in adulthood. In the same HMO population, there was a dose–response relationship between the number of experienced childhood adversities and the presence of a depressive episode in the past year or lifetime chronic depression (Chapman et al., 2004). An earlier study in this population found 4-fold increases in the risk of depression in persons with multiple childhood adverse experiences (Felitti et al., 1998). The experience of any childhood adversity increased the risk of attempted suicide in childhood, adolescence or adulthood 2- to 5-fold (Dube et al., 2001). These remarkable studies complemented findings from other landmark studies, including the pioneering studies by Brown and Moran (1994) as well as the seminal McCauley et al. (1997) study demonstrating in a cohort of more than 1900 women from internal medicine practices that childhood, but not adulthood, sexual or physical abuse is associated with increases in depression and anxiety symptoms. Findings of the National Comorbidity Survey (Molnar et al., 2001), the Ontario Health Survey (MacMillan et al., 2001), and a New Zealand community survey (Mullen et al., 1996) have provided concordant findings. A role of childhood trauma in the development of major depression has been confirmed in twin studies (Kendler et al., 1993, 2000; Nelson et al., 2002). In addition to maltreatment, parental loss due to death or separation is also associated with increased risk for depressive disorders (Agid et al., 1999). Of note, individuals with early adverse experience appear to be sensitized to the depressive effects of acute stress in adulthood (Hammen et al., 2000; Dougherty et al., 2004; Kendler et al., 2004). There is also evidence for an interaction between environment and genes, inasmuch as genetic polymorphisms moderate the likelihood of whether or not an individual develops depression in relation to life stress, including early adversity (Caspi et al., 2003; Kaufman et al., 2004, 2006; Kendler et al., 2005; Bradley et al., 2008). It thus appears that interactions between genetic diathesis and environmental influences throughout the lifespan together underlie depression vulnerability in most patients.

The precise mechanism that mediates the effects of early adverse experience on depression risk has been the subject of intense inquiry in translational neuroscience. Studies in rodents and non-human primates have focused on epigenetic modification of phenotypic stress responsiveness as a function of early experience. Results suggest that adverse experience, such as maternal separation or low maternal care, induces persistent structural, functional, and epigenomic changes in neural circuits that are implicated in the integration of cognitive and emotional processing, endocrine–autonomic control, and the regulation of arousal and vigilance. These changes converge in increased endocrine and autonomic reactivity to stress, anxiety-like behavior, anhedonia, cognitive impairment, pain sensitivity, and altered sleep (e.g., reviewed in Ladd et al., 2000; Sánchez et al., 2001; Plotsky et al., 2001; Meaney and Szyf, 2005). In fact, many of the neurobiological and behavioral effects of early-life stress in animal models closely parallel signs and symptoms of major depression. It is therefore conceivable that adverse experience in childhood may indeed be causally associated with developing depression, particularly in response to challenge.

One major question for clinical depression research in the recent years concerned whether childhood adverse experience in humans is associated with neurobiological changes that are similar to those observed animal models and whether these changes are related to depression. To address this question, our group conducted a series of clinical studies. We focused on studying alterations of the HPA axis in subjects with histories of childhood abuse. The central hypothesis underlying these studies was that early adverse experience in humans would lead to sensitization of central stress response systems, particularly corticotropin-releasing factor (CRF) systems, leading to enhanced neuroendocrine, autonomic and behavioral responsiveness to stress as well as altered dynamics of the HPA axis. Such increased stress sensitivity would then lower an individual's threshold to develop depression in relation to further stress.

The current review summarizes results of our studies and presents previously unpublished original data. We further discuss the implications of our results in terms of future research directions and clinical practice. In brief, our results suggest that childhood trauma contributes to the neuroendocrine features of depression, likely reflecting risk to develop depression in response to stress rather than correlates of the illness. Based on an integration of our HPA axis data with results from affective neurosciences, we propose that the primary lesion after childhood trauma is located at the neural systems level and involves failure of a connected neural network to adapt or compensate in response to challenge, leading to exaggerated responses of physiological outflow systems and altered behavior. However, not all forms of depression are associated with childhood adversity and our studies suggest the existence of biologically distinguishable subtypes of depression as a

function of childhood trauma, likely having confounded previous research. These depression subtypes also appear to be responsive to different types of treatment. Given that not all cases with childhood adverse experiences develop depression, potential sources of outcome variability are discussed. Similar associations likely apply to a spectrum of disorders that manifest in relation to stress and often coincide with depression. In the following pages, we summarize the evidence supporting these assumptions.

2. HPA axis studies in individuals with childhood trauma exposure

2.1. Design and definitions

We conducted a series of studies examining the HPA axis in adult women or men with histories of childhood sexual or physical abuse. Because we were interested in determining the contributions of childhood trauma to the neurobiology of depression, we chose a fully balanced study design that would allow us to separate the effects of childhood trauma from the effects of having depression. Thus, we recruited 4 groups, including persons with:

(1) no history of early-life stress and no psychiatric disorder [controls];
(2) a history of childhood abuse without current major depression [risk factor];
(3) a history of childhood abuse and current major depression [risk factor+illness]; and
(4) no history of early-life stress but current major depression [illness variability]. Comparison of the latter 2 groups identifies depression subtypes as a function of early-life stress.

In all studies, early-life traumatic experiences were assessed by structured interview or psychometric rating scales. It should be noted that retrospective self-reports of childhood experiences are certainly not completely accurate and influenced by factors, such as simple forgetting, repression or reporting biases. In general, it is assumed that lack of validity of retrospective self-reports leads to underestimation of the actual occurrence rather than overestimation (Hardt and Rutter, 2004). In our studies, sexual abuse was defined as having been forced to touch another person's intimate parts, having been touched in intimate parts, attempted or completed intercourse. Physical abuse was defined as having been spanked, kicked or choked in a way that left bruises or injuries, having been attacked with a weapon or tied up or locked in a room or a closet. At least one form of abuse must have had occurred before the first menstrual period in women or the age of 13 years in men, given that trauma before maturation has been associated with specific risk for depression (Agid et al., 1999; Maercker et al., 2004).

Assignment to the major depression groups required a diagnosis of current major depression according to criteria of the Diagnostic and Statistical Manual for Mental Disorder 4th Edition (DSM-IV) (APA, 1994). General exclusion criteria were medical illness, lifetime psychosis or bipolar disorder, current substance abuse or eating disorders. All participants were free of medication. All participants were admitted to the General Clinical Research Center of Emory University Hospital as inpatients.

2.2. Pituitary–adrenal and autonomic response to psychosocial stress

The objective of our first study was to determine whether early-life stress in humans is associated with persistent sensitization of the HPA axis and the autonomic nervous system to mild stress in adulthood, thereby contributing to vulnerability to depression (Heim et al., 2000b; Figure 1). For the induction of stress, we employed a standardized psychosocial stress protocol that consists of a public speaking and mental arithmetic task in front of an audience and that has been shown to reliably induce HPA axis and sympathetic activation (Kirschbaum et al., 1993). Blood samples for the determination of plasma adrenocorticotropin (ACTH) and cortisol levels, as well as heart rate measures, were obtained before, during and after the stress induction. In remarkable parallel to results from animal models, women with a history of childhood abuse without and with current major depression exhibited increased ACTH responses to stress compared with controls. Net ACTH response was more than 6-fold greater in abused women with current major depression than in controls. These women also demonstrated increased cortisol and heart rate responses to psychosocial stress. Abused women who were not currently depressed exhibited normal cortisol responses, despite of their increased ACTH response, perhaps suggesting adrenal adaptation to central sensitization as a marker of resilience against depression after early stress. Depressed women without abuse demonstrated normal neuroendocrine responses. Our findings suggest that HPA axis and autonomic nervous system hyperreactivity, presumably due to CRF hypersecretion, may be a persistent consequence of childhood abuse that may contribute to the diathesis for adulthood psychopathology.

As noted above, stress in adulthood is related to the onset of depressive episodes and, moreover, impacts on neuroendocrine activation (Chappell et al., 1986; van Dijken et al., 1993). We therefore used multiple linear regression modeling to estimate the relative role of early adverse experience in predicting neuroendocrine reactivity in women, when controlling for demographic variables, adulthood trauma, life events in the past year and daily hassles in the past month, as well as symptoms of depression and posttraumatic stress disorder (PTSD). Results confirmed that a history of childhood abuse was the strongest predictor of ACTH responsiveness, followed by the number of abuse events, adulthood traumas and depression. An interaction term of childhood and adulthood trauma proved to be the most potent predictor of ACTH responses, suggesting that a history of childhood abuse per se is related to increased stress reactivity, which is further enhanced when additional trauma occurs in adulthood (Heim et al., 2002).

Past depression or concurrent anxiety disorders might have contributed to increased ACTH responsiveness in women with childhood trauma who did not suffer from current depression (Young et al., 1994). It therefore is questionable whether childhood trauma that did not

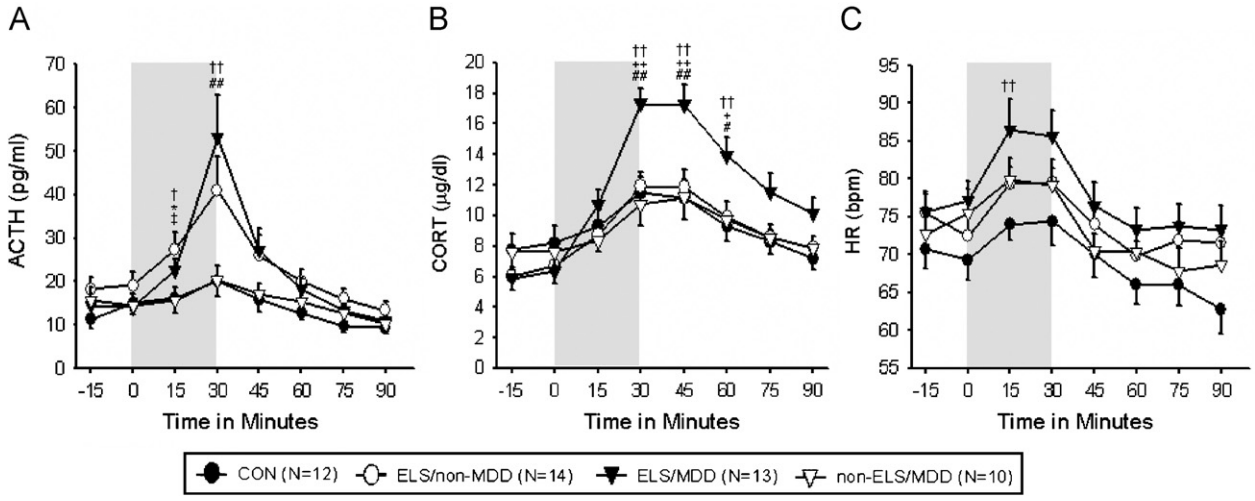

Figure 1 Mean (SE) plasma ACTH (A), plasma cortisol (B), and heart rate responses to psychosocial stress induction in adult women with no history of childhood abuse and no psychiatric disorder (controls), women with a history of childhood sexual and/or physical abuse and no current major depression (ELS/non-MDD), women with a history of childhood sexual and/or physical abuse and current major depression (ELS/MDD), and women with current major depression but no history of significant childhood stress. Reprinted from Heim et al. (2000b).

result in psychopathology might be associated with any discernable biological risk, due to imperfect translation from "external exposure" to "internal lesion". We compared endocrine stress reactivity between never-depressed and depressed women with childhood trauma versus controls. The never-depressed group exhibited markedly increased ACTH responses ($F = 4.9$, df = 1,30, $p < 0.001$), similar to the abused group with depression. This increased response was maintained when controlling for age, race, abuse severity, and adulthood stress. The never-depressed group was free of comorbidity. These findings suggest that childhood trauma is associated with discernable biological risk, even in the absence of lifetime psychopathology [unpublished observation]. It should be noted that a recent study by Carpenter et al. (2007) reported decreased cortisol responses to psychosocial laboratory stress in maltreated men who were never depressed. Sex differences, differences in the type or timing of the trauma, or genetic factors among others might contribute to this inconsistency. Future studies should determine sources of outcome variability in terms of stress reactivity after childhood trauma.

2.3. Pharmacological provocation tests

To further explore the mechanisms of neuroendocrine vulnerability to stress in these abused women, we employed standard HPA axis challenge tests, including the CRF stimulation test and the $ACTH_{1-24}$ stimulation test (Heim et al., 2001). Whereas the psychosocial stress test stimulates a stress response involving higher levels of cognitive and emotional processing, several neurotransmitter systems, and endogenous CRF release, the administration of synthetic CRF selectively stimulates ACTH release from the pituitary corticotrophs. Thus, the CRF stimulation test allows for an evaluation of the reactivity of the adenohypophysis to a defined amount of CRF. Changes in pituitary responsiveness to CRF stimulation may reflect CRF receptor changes on corticotrophs due to alterations in the activity of the PVN-median eminence CRF circuit. The administration of high doses of the biologically active $ACTH_{1-24}$ allows for the evaluation of the maximal responsiveness of the adrenal cortex (Heim and Ehlert, 1999). In response to 1 µg/kg ovine CRF stimulation, abused women without depression exhibited increased ACTH responses, similar to their responses in the psychosocial stress test. In contrast, both groups of depressed women with and without childhood trauma histories exhibited a blunted ACTH response to CRF, which is a classic feature of major depression (Holsboer et al., 1984; Gold et al., 1984). In response to 250 µg $ACTH_{1-24}$, abused women without depression secreted less cortisol than all other groups. Both groups of abused women exhibited decreased basal cortisol levels (Heim et al., 2001). Similar hypocortisolism has been observed in non-human primate models of early-life stress (Coplan et al., 1996; Dettling et al., 2002). We interpret our findings as reflecting sensitization of the pituitary and counter-regulative adaptation of the adrenal gland in abused women without current depression. Because cortisol has important inhibitory effects on the central CRF and noradrenergic systems, we believe that relative decreased availability of cortisol, as a consequence of childhood trauma, might facilitate disinhibition of central stress responses. Upon further stress, such women may then repeatedly hypersecrete CRF, eventually resulting in pituitary CRF receptor downregulation and symptoms of depression through CRF effects in extra-hypothalamic circuits.

2.4. Glucocorticoid-mediated feedback regulation

Enhanced stress responsiveness after childhood trauma might further be promoted by changes in glucocorticoid-mediated feedback control of the HPA axis. In an initial

study, we observed increased suppression of cortisol in a low-dose dexamethasone suppression test in abused women with depression and concurrent PTSD (Newport et al., 2004). Such super-suppression indicates enhanced sensitivity of the pituitary to negative feedback and is a prominent finding in PTSD, believed to contribute to stress sensitization (Yehuda, 2006). In fact, the results found in the Newport study might be best attributable to comorbidity with PTSD.

Consideration of glucocorticoid-mediated feedback under conditions of challenge might be particularly relevant to understand altered stress reactivity in depression. Accordingly, the combined dexamethasone/CRF test was developed as an advancement of the simple dexamethasone suppression test. CRF-induced escape from suppression reflects impaired glucocorticoid-mediated feedback control of the HPA axis under conditions of increased hypothalamic drive. The dexamethasone/CRF test is considered to be the most sensitive measure of HPA axis hyperactivity in depression (Heuser et al., 1994), possesses sensitivity to detect familial risk in asymptomatic first-degree relatives of depressed patients (Holsboer et al., 1995; Modell et al., 1998), serves as surrogate marker for treatment response (Ising et al., 2005), and varies with a polymorphism in the FKBP5 gene, a GR-regulating cochaperone of hsp-90, which is also associated with recurrence of depression and antidepressant response (Binder et al., 2004). We sought to determine the effects of childhood abuse on results in the dexamethasone/CRF test in adult men with and without current major depression. Abused men demonstrated markedly increased cortisol responses to dexamethasone/CRF administration when compared with non-abused men, regardless of diagnosis. When stratifying groups by major depression and childhood trauma, only those abused men with current major depression, but not depressed men without childhood trauma demonstrated increased cortisol responses. Increased response was associated with exposure to both sexual and physical abuse and the severity of the abuse (Heim et al., 2008; Figure 2). Importantly, this effect was not attributable to comorbid PTSD. These results suggest that childhood trauma is associated with impaired glucocorticoid-mediated feedback control of the HPA axis during stimulated conditions. The dexamethasone/CRF test appears to be sensitive to detect environmental risk secondary to early-life stress. Similar results have been reported for women with borderline personality disorder (Rinne et al., 2002), suggesting that escape after childhood trauma occurs independent of sex. Of note, we also measured decreased GR binding in cytosol obtained from peripheral mononuclear blood cells (PBMC) of abused women with major depression compared with healthy controls, further suggesting relative glucocorticoid resistance [unpublished observation]. These results concur with reports that early adversity in rodents induces reduced expression of central glucocorticoid receptors (GR) at the epigenomic level, by inducing DNA methylation at a promoter site of the GR gene (Weaver et al., 2004; Meaney and Szyf, 2005). Impaired glucocorticoid effects might contribute to increased stress reactivity and promote symptoms of depression (Pariante, 2004).

2.5. Cerebrospinal fluid (CSF) neuropeptide studies

The above findings of increased stress responsiveness, blunted ACTH response to CRF challenge, and impaired glucocorticoid feedback in individuals with childhood trauma and depression are consistent with increased activation of central nervous system (CNS) CRF systems. CRF neurons integrate information relevant to stress not only at the hypothalamic paraventricular nucleus (PVN), which forms the central component of the HPA axis, but also act in a widespread circuitry throughout the brain, producing autonomic and behavioral responses that parallel signs of stress, depression and anxiety. CRF-1 receptor antagonists or CRF-1 receptor knockouts exhibit attenuated stress

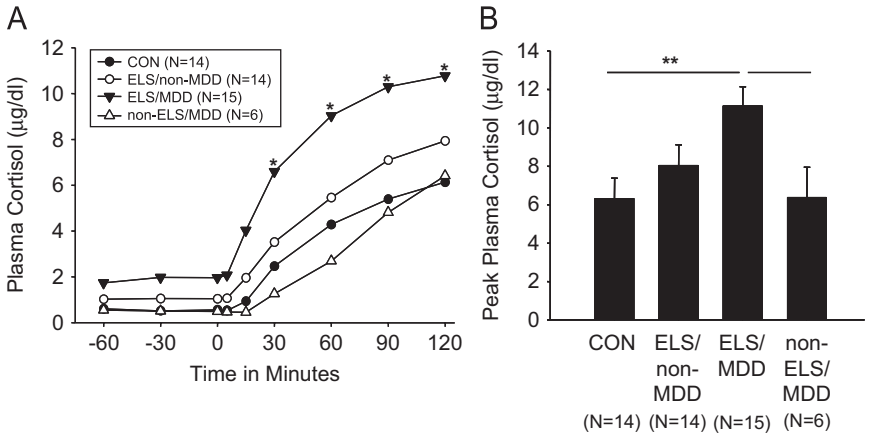

Figure 2 Mean plasma cortisol concentrations in the dexamethasone/CRF test (A) in adult men with no history of childhood abuse and no psychiatric disorder (controls), men with a history of childhood sexual and/or physical abuse and no current major depression (ELS/non-MDD), men with a history of childhood sexual and/or physical abuse and current major depression (ELS/MDD), and men with current major depression but no history of significant childhood stress. (B) Correlation between cortisol escape and abuse severity. Reprinted from Heim et al. (2008).

responses (Arborelius et al., 1999). Elevated CSF CRF concentrations have been repeatedly reported in patients with major depression [Nemeroff et al., 1984; Bánki et al., 1987; Widerlöv et al., 1988; Hartline et al., 1996). Post-mortem studies reported increased CRF content or mRNA expression was found in the hypothalamic PVN, locus coeruleus and prefrontal cortex (Raadsheer et al., 1994, 1995; Bissette et al., 2003; Merali et al., 2006) of patients with major depression. Increased CSF CRF concentrations as well as regional increases in CRF content and mRNA expression have been reported for rodent and non-human primate models of early-life stress (Coplan et al., 1996; Plotsky et al., 2005). Carpenter et al. (2004) reported that levels of perceived preschool stress-predicted CSF CRF concentrations, more so than symptoms of depression. We therefore measured CSF CRF concentrations in 46 women with and without histories of childhood abuse or major depression. When classifying the women according to abuse type, women who had been physically abused demonstrated higher CSF CRF concentrations than women with no physical abuse experience ($F = 8.866$, df $= 1,45$, $p = 0.004$). Subsequent analyses showed that women who had experienced both sexual and physical abuse had markedly elevated CSF CRF concentrations compared with women with no abuse experience and women with sexual abuse experience alone ($F = 5.382$, df $= 3,45$, $p = 0.003$; Figure 3A). CSF CRF concentrations were correlated with the severity of physical ($r = 0.43$, $p = 0.004$; Figure 3B) and sexual abuse ($r = 0.33$, $p = 0.026$) as well as with the duration of physical ($r = 0.34$, $p = 0.023$) and sexual abuse ($r = 0.29$, $p = 0.050$). When dividing groups according to the age at onset of the abuse, we found that women who had experienced physical or sexual abuse after the age of 6 years demonstrated higher CSF CRF concentrations compared with women who had experienced abuse in early childhood (Figure 3C). We conclude that severe childhood abuse, in particular a combination of sexual and physical abuse in later childhood, contributes to CNS CRF hyperactivity in adult women. These results highlight that trauma features and developmental stage at onset are associated with differential outcomes [unpublished observation].

The neuropeptide oxytocin (OT) has received considerable attention in preclinical and human research for its role in mediating social affiliation, mother–child attachment, social support and trust (Young and Wang, 2004; Kosfeld et al., 2005). OT further has stress-protective effects and decreases amygdala reactivity in humans (Kirsch et al., 2005). Thus, the central OT system may be profoundly impacted by disruption of the caretaker–child relationship during times of heightened plasticity, translating such experiences into vulnerability and disease. Early nurturing experiences induce persistent changes in CNS OT receptor expression in rats (Francis et al., 2000). Nursery-reared rhesus monkeys exhibit decreased CSF OT concentrations compared with mother-reared controls (Winslow et al., 2003). We recently measured markedly decreased CSF OT concentrations women with childhood trauma experiences, providing the first evidence for central

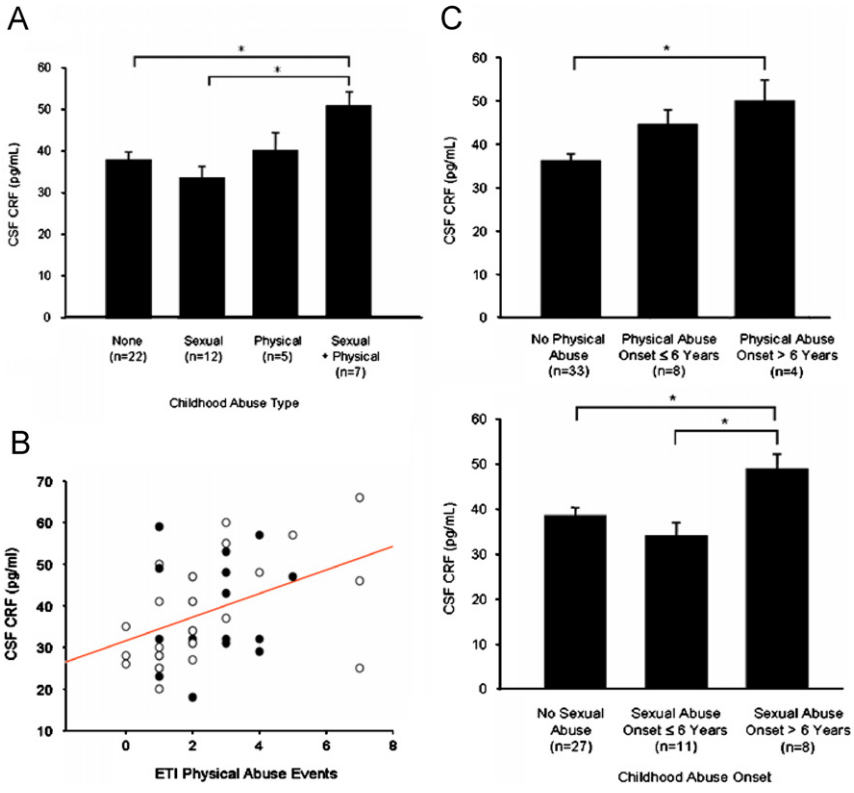

Figure 3 Associations between CSF CRF concentrations and childhood trauma in adult women: (A) CSF CRF concentrations by abuse type, (B) correlation between CSF CRF concentrations and Early Trauma Inventory Physical Abuse Severity Scores, C: CSF CRF concentrations by age of abuse onset (none, 0–6 years, >6 years). For statistics see text.

OT system changes after childhood abuse in humans. (Heim et al., unpublished observation). These results support the hypothesis that early adverse experience may interfere with the development of brain systems implicated in social attachment, which may then lead to decreased resilience against stress and anxiety. Indeed, the mechanism translating early social stress into vulnerability may not simply involve changes in stress-mediating systems, but a disturbed "balance" between stress-mediating and stress-protective neural systems.

2.6. Hippocampal volume

The above endocrine results suggest increased HPA axis reactivity after childhood abuse. The hippocampus is critically involved in the control of the HPA axis as well as explicit memory and contextual aspects of fear conditioning. The hippocampus is also one of the most plastic regions of the brain. Neurogenesis has been demonstrated to occur in adulthood in rodents and non-human primates. Stress and glucocorticoid overexposure have adverse effects on hippocampal neurons, particularly in the CA3 region, including reduction in dendritic branching, loss of dendritic spines and impairment of neurogenesis (Fuchs and Gould, 2000; Nestler et al., 2002). Patients with major depression and PTSD exhibit decreased hippocampal volume (e.g., Sheline et al., 1996; Bremner et al., 2000; Frodl et al., 2002), although findings are not uniformly consistent (e.g., Vakili et al., 2000; Rusch et al., 2001). Reduced hippocampal volume has also been reported in remitted patients with major depression, suggesting that a small hippocampus might be a trait-like risk marker of depression (Neumeister et al., 2005). Interestingly, maternal separation in rodents induces reduced mossy fiber density and impaired neurogenesis in the hippocampus (Huot et al., 2002; Mirescu et al., 2004). Repeated central CRF injection during development also leads to progressive hippocampal volume decreases, independent of glucocorticoids (Brunson et al., 2001). Decreased hippocampal volume has been observed in persons with childhood trauma with and without PTSD (Bremner et al., 1997; Stein et al., 1997). Decreased hippocampal volume in women with borderline personality disorder was found to be associated with early trauma (Driessen et al., 2000). Because hippocampal volume loss was not observed in abused children with PTSD (De Bellis et al., 1999), some have suggested that repeated bursts of cortisol secretion over the course of time may eventually result in smaller hippocampi, because of the well-documented adverse effects of glucocortioids on these neurons. In the light of our endocrine findings, we therefore evaluated whether decreased hippocampal volume in major depression might be associated with histories of child abuse. We found that the left hippocampus in depressed women with childhood abuse was 18% smaller than in non-abused depressed women and 15% smaller than in healthy controls. Depressed women without childhood abuse and controls had similar hippocampal volumes (Vythilingam et al., 2002; Figure 4). It appears that a smaller hippocampal volume in major depression is associated with childhood trauma and is not observed in depressed patients without such trauma, paralleling our neuroendocrine results. Repeated bursts of CRF in response to stress during development and/or increased cortisol reactivity over the course of time may contribute to smaller hippocampi after childhood trauma exposure, leading to further sensitization of the stress responses.

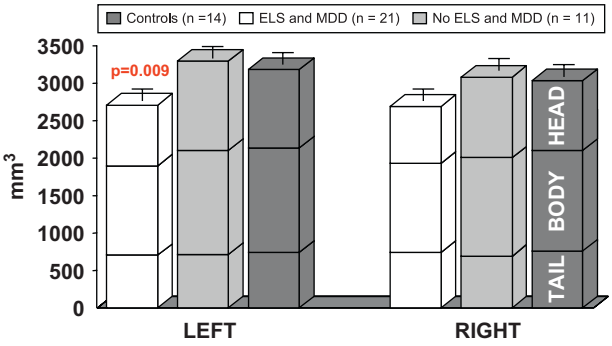

Figure 4 Mean hippocampal volume in depressed women with and without childhood physical and/or sexual abuse and healthy subjects. Reprinted from Vythilingam et al. (2002).

3. Comparison with findings in depression

Taken together, our findings suggest that early adverse experience in humans is associated with various neuroendocrine and neuroanatomical changes that are comparable to those described in animal models. These changes include sensitization of neuroendocrine and autonomic responses to stress, altered dynamics of pituitary and adrenal response to selective challenge, CRF-induced escape of cortisol from dexamethasone suppression, increased CNS CRF and decreased OT activity, as well as decreased hippocampal volume. Several of these changes strikingly resemble the established features of major depression reported in the literature (Arborelius et al., 1999; Nestler et al., 2002; Heim et al., 2004), although there are some exceptions: It should be noted that low adrenocortical activity, as observed in abused women, is dissimilar to the hypercortisolemia that has classically been associated with melancholic or psychotic major depression (e.g., Gillespie and Nemeroff, 2005; Keller et al., 2006). However, decreased rather than increased cortisol secretion has been reported for patients with nonpsychotic forms of major depression (Posener et al., 2000), major depression and comorbid PTSD (Oquendo et al., 2003) as well as atypical depression (Anisman et al., 1999). Super-suppression of cortisol in response to a low-dose of dexamethsone, as observed in abused women with depression and comorbid PTSD, is a classical feature of PTSD and does not seem to be related to early-life stress per se (Yehuda, 2006). It can be stated that the specific neurobiological consequences of childhood trauma likely converge into sensitization to stress. These changes are not present in depressed patients without childhood trauma histories. It thus appears that several of the established features of major depression reported in the literature, in fact, are secondary to early-life stress and likely represent risk to develop depression, especially in response to stress, rather than reflecting correlates of the disease itself.

4. Are there neural network changes after childhood trauma?

It is well-known that the endocrine, autonomic and behavioral components of the stress response are concerted in a widespread neuronal circuitry, including the prefrontal cortex, hippocampus, amygdala, and brainstem regions (Feldman et al., 1995; Arborelius et al., 1999; Nestler et al., 2002). Findings from animal models provide firm evidence for multiple changes in these circuits that occur as a consequence of early-life stress (e.g., Ladd et al., 2000; Sánchez et al., 2001; Meaney and Szyf, 2005). Our findings of increased neuroendocrine and autonomic stress responsiveness would therefore suggest that childhood trauma in humans results in changes at the neural systems level and failure of a network of critical circuits to compensate in response to challenge.

Indeed, psychological studies provide indirect support for functional CNS changes after childhood trauma in humans. Pollak and Kistler (2002) evaluated whether experiences of child abuse might influence the development of basic CNS functions, such as the perception and recognition of emotional stimuli. It was found that the childhood abuse was associated with a change in the children's perceptual preferences and also altered the discriminative abilities that influence how children categorize facial expressions. Specifically, abused children showed a preference for the recognition of angry faces and were more likely to categorize ambiguous faces as angry compared with controls. Unfortunately, the study did not employ functional brain imaging methods to evaluate neuronal correlates of altered emotional processing in these children. A recent study reported that adult healthy persons with moderate childhood family stress exhibited increased amygdala activation during emotional labeling of angry faces as well as an abnormal relationship between ventrolateral prefrontal cortical/insular activation and amygdala responses (Taylor et al., 2006). Of note, the insula has been implicated in interoception and regulation of autonomic arousal and neuroendocrine responses to psychological stress (Craig, 2003; Wang et al., 2005). Electroencephalographic studies further corroborate cortical–limbic dysfunction and impaired connectivity after childhood trauma in young adults (Teicher et al., 2003). In addition, a PET study found that poor parental care in healthy subjects was associated with increased CNS dopaminergic responses to arithmetic stress, which were correlated with cortisol responses (Pruessner et al., 2004).

Independent research from the field of affective neurosciences suggests that there are discernable neural markers of trait-like depression risk that operate within a connected neural network and become distinguishable during emotional challenge (Mayberg, 2003). For example, decreases in medial frontal/orbital cortex (mF10/oF11) and increases in anterior cingulate (CG24) cerebral blood flow in response to sad mood challenge were found to be present in sick and remitted patients as well as in never-depressed persons with temperamental or familial risk factors of depression (Keightley et al., 2003; Kruger et al., 2003, 2006; Mayberg, 2003; Zald et al., 2002). The prefrontal cortex is involved in neuroendocrine control and, in turn, is influenced by glucocorticoids. Remarkably, these areas overlap with neural markers of genetic risk factors that moderate the relationship between childhood trauma and depression (see below). There is also recent evidence for separable neural markers of resilience in subjects with familial risk for depression (Kruger et al., 2006). Taken together, functional neuroimaging studies are needed to better understand the neural network basis of the relationship between childhood trauma, neuroendocrine stress sensitization and vulnerability to depression in humans.

5. Subtypes of depression as a function of childhood trauma

Clearly not all forms of depression are associated with childhood trauma. Our previous research suggests that several of the neuroendocrine features of depression described in the literature are secondary to childhood trauma and likely reflect risk to develop depression in response to stress. These changes were not present in depressed patients without childhood trauma experience. Therefore, our results would suggest that there are biologically distinct subtypes of depression as a function of childhood trauma. This insight has seminal implications for depression research and the classification of depressive disorders.

Previous neurobiological depression research did not control for the effects of childhood trauma. Given the high prevalence of childhood trauma among depressed patients (and the general population), it is conceivable that previous studies included patients (and controls) with significant childhood adverse experience, but the effects of these experiences were not separated from those of depression. Depending on the distribution of childhood adverse experience across patient and control groups, previous findings on the neurobiology of depression might be significantly confounded, which might also explain discrepant findings across studies. For example, when subdividing our study groups only based on presence or absence of major depression, there are no significant effects regarding stress responsiveness and hippocampal volume data. As for the dexamethasone/CRF test, there is a moderate effect for depression. However, when stratifying groups based on childhood trauma and major depression, highly significant effects emerge, with only depressed patients with childhood trauma, but not depressed patients without such experiences, demonstrating changes in stress response systems (see Heim et al., 2004, 2008). Similar findings were independently reported for depressed children (Kaufman et al., 1997) and women with borderline personality disorder (Rinne et al., 2002), with and without childhood abuse histories.

It must be noted that our findings are not in disagreement with previous studies, particularly those suggesting escape in the dexamethasone/CRF test as a major of depression. In our studies, we artificially recruited MDD and control groups to create extremes of high versus low exposure to childhood trauma within groups. These groups by definition are not representative of the general depressed population in terms of childhood trauma exposure. Recruitment based on the presence or absence of major depression in previous studies likely resulted in representative distribution of early-life

stress in patients with major depression (more) and controls (less), which then plausibly could have contributed to escape in the depressed groups. Only by artificially creating groups with and without a certain risk factor, we could demonstrate that this risk factor, i.e. early trauma, contributes to escape. This does not hamper the validity of findings that depressed patients with natural distribution of childhood trauma exhibit escape. Therefore, our findings are actually not in disagreement with previous studies, in the opposite, they provide additional information what factors might contribute to the ''escape'' observed in the general population of depressed people. Early-life stress is certainly not the only factor contributing to HPA axis dysregulation in depression, but likely interacts with other risk factors, such as genotype variations and gender (see below).

This issue also applies to other research areas, such as research on risk factors of depression. For example, the observed preponderance of women in depression might be due to gender differences in the prevalence of early-life stress (Weiss et al., 1999). The potency of acute life stress as a risk factor of depression depends on the presence or absence of childhood adversity (Hammen et al., 2000; Dougherty et al., 2004). In addition, symptom patterns and clinical course of depression may vary as a function of childhood trauma. For example, childhood trauma has been consistently associated with early onset of depression (Young et al., 1997; Bernet and Stein, 1999; Gladstone et al., 2004) as well as larger numbers of episodes or more chronic depression, respectively (Bernet and Stein, 1999; Zlotnick et al., 1995, 2001). In fact, biological and symptom patterns as a consequence of childhood trauma might span across DSM diagnostic categories, providing insight into the nature of comorbidity in depression, for example with anxiety disorders and substance abuse (Bernet and Stein, 1999; Molnar et al., 2001).

These considerations have important relevance for the classification of depressive disorders. Depressive disorders are clearly characterized by substantial variability in terms of clinical presentation, onset, course, neurobiological alterations, and treatment response, suggesting a heterogeneous group of etiologically distinct disorders. Historically, a binary model of depression prevailed over many years that distinguished between endogenous/psychotic and reactive/neurotic subtypes of depression. Unitarian positions, in contrast, assumed that different manifestations of depression are located along a continuum of a single subtype with a ''psychobiological final common pathway'' (Akiskal and McKinney, 1973). With DSM-III, a purely descriptive classification based on phenomenology was introduced, supposedly representing a research-based medical model rather than a clinical-based biopsychosocial model (Wilson, 1993). It has been argued that this current classification has obscured depression research and failed to produce uniform neurobiological findings or predictors of treatment response, and that paradigms of different subtypes of depression should be empirically tested using clinical, etiological, neurobiological and genetic variables (Parker, 2000). Given our findings on different neurobiological subtypes of depression as a function of childhood adverse experience, we suggest that developmental factors should be considered when deriving new depression models. A new typology of depression, based on genetic factors, developmental pathways, and neurobiological patterns might lead towards improved diagnosis and treatment, and the identification of predictors of treatment response.

6. Childhood trauma and treatment response in depression

There are only very few predictors of treatment response in depression. For example, childhood adverse experience has been associated with decreased responsiveness to pharmacological treatment in patients with dysthymia and depression (Hayden and Klein, 2001; Kaplan and Klinetob, 2000). Childhood adversity has further been related to higher likelihood of relapse after initial remission of depression (Lara et al., 2000). We were interested in investigating whether childhood trauma might be associated with differential effectiveness of different types of treatment in depressed patients (Nemeroff et al., 2003). To address this question, we had the opportunity to reanalyze data from a large multi-center treatment trial comparing the effectiveness of either pharmacological treatment (nefazodone) or psychotherapy (Cognitive Behavioral Analysis System of Psychotherapy), or the combination of both (Keller et al., 2000). In the original study, the effects of the antidepressant and psychotherapy alone were equal and significantly less effective than the combination treatment (Keller et al., 2000). When subdividing the treatment groups based on presence or absence of childhood trauma, we found marked differences in terms of treatment success (Figure 5). Among chronically depressed patients with no history of early trauma, combination treatment was most effective in attaining remission compared with nefazodone and psychotherapy. In contrast, in chronically depressed patients with early-life trauma, remission rates were significantly higher for psychotherapy alone versus nefazodone.

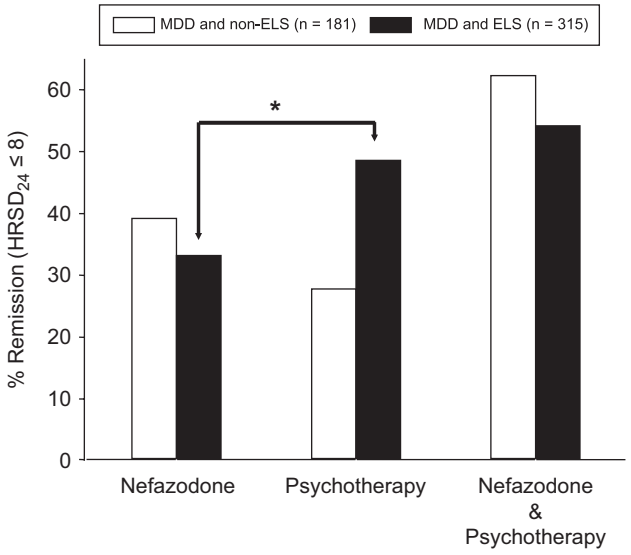

Figure 5 Remission rates as a function of treatment type and early adverse life events in patients with chronic forms of major depression. Reprinted from Nemeroff et al. (2003).

The combination treatment did not have any further advantage over psychotherapy alone. The likelihood to achieve remission in psychotherapy versus nefazodone was two times higher for depressed patients with childhood trauma and three times higher specifically for those with parental loss (Nemeroff et al., 2003). These findings suggest that psychotherapy might be an essential element of treatment for depressed patients with childhood trauma. Of note, in a subsequent cross-over phase, it was shown that chronically depressed patients who did not respond to either monotherapy, benefited from being switched to the other treatment (Schatzberg et al., 2005).

Such differential treatment effects might occur due to variability in neurobiological pathways to depression, which might be differentially affected by drugs or psychotherapy (Mayberg, 2003). Interestingly, there is evidence from PET studies that depressed patients who respond to cognitive behavioral therapy have different brain changes in response to treatment than patients who respond to drug (Goldapple et al., 2004). Multivariate analyses revealed that these responder groups already had different neural activation patterns before treatment (Seminowicz et al., 2004). Areas of difference between these groups overlapped with areas identified as risk markers of depression (Mayberg, 2003). Future studies should evaluate whether childhood trauma is associated with ''treatment response-specific'' neuronal activation patterns.

7. Sources of outcome variability after childhood trauma

Clearly, not all individuals exposed to early-life adversity go on to develop major depression, even upon further stress or challenge. Therefore, moderating effects of dispositional factors, such as gender and genes, must be considered.

7.1. Sex differences

Major depression is twice as common in women as in men (Young, 1998; Weiss et al., 1999). This sex difference may reflect higher rates of early adversities in girls relative to boys. However, according to the National Child Abuse and Neglect Data System, boys experience 48.5% of all incidents of child abuse. Girls more frequently experience sexual abuse, whereas boys are more likely to suffer physical abuse or neglect. It is thus possible that sex differences in the exposure to different types of trauma might contribute to differential vulnerability to depression in adulthood. In addition, there might be sex differences in the response to childhood trauma. Notably, women are more likely than men to develop depression in relation to child abuse (Weiss et al., 1999). Rodents studies suggest that females generally exhibit greater magnitude and duration of HPA axis responses to stress than males (Rhodes and Rubin, 1999), though findings in humans are not entirely consistent (Young, 1998; Kudielka and Kirschbaum, 2005). Sex differences in neuroendocrine stress responses have previously been attributed to direct effects of circulating estrogen on CRF neurons. For example, chronic estradiol treatment of ovariectomized rats enhances CRF mRNA expression in the PVN and increases ACTH/corticosterone responses to stress (Swanson and Simmons, 1989; Burgess and Handa, 1992). Short-term estradiol treatment of adult men induces increased ACTH, cortisol and NE responses to psychosocial stress (Kirschbaum et al., 1996). Estrogen receptor mRNA has been localized in parvocellular CRF neurons of the PVN and there is evidence for an estrogen-responsive portion of the promoter region of the human CRF gene, which confers estrogen enhancement of CRF expression in CV-1 transfected cells (Vamvakopoulos and Chrousos, 1993). Sex steroids also interact with other neurotransmitter systems involved in the stress response, such as the serotonin system (Bethea et al., 2002; Smith et al., 2004). Progesterone has also been implicated in modulating these systems (Centeno et al., 2007). However, sex differences in HPA responses to stress have now also been observed in humans, independent of acute gonadal steroid effects (Roca et al., 2005). Other factors that might determine sex differences in the stress response therefore include genomic differences, organizational differences in brain structures or developmentally programmed effects of gonadal steroids (Kudielka and Kirschbaum, 2005; McEwen, 2001; Roca et al., 2005). Of note, sex steroids play a role in lifelong structural plasticity of several brain regions, including areas involved in stress responsiveness, i.e. the hippocampus and amygdala (McEwen, 2001). Functional imaging studies identified sex differences in the brain's response to fear stimuli (Schienle et al., 2005; Williams et al., 2005). Such processes may eventually converge into the basis of sex differences in the long-term neurobiological consequences of childhood trauma that translate into differential risk for psychopathology. Accordingly, female rhesus monkeys repeatedly separated from their mothers between 3 and 6 months of age exhibited increased cortisol responses to subsequent separation and flattened basal cortisol cycles at later ages. These changes were not observed in male macaques (Sánchez et al., 2005). Scrutinizing the neurobiological basis of sex differences in the pathological effects of childhood trauma will be an important area of future research.

7.2. Genetic factors

In addition to gender, the effects of childhood trauma on later vulnerability to stress and disease are also moderated by genotype. A recent study has provided particular insight into such interactions: In a prospective-longitudinal study of a representative birth cohort in New Zealand, Caspi et al. (2003) found that a common functional polymorphism in the promoter region of the serotonin transporter gene, 5HTTLPR, significantly moderated the effects of stressful life events on depression. Of the 481 subjects, 17% were homozygous for the short allele (s/s), 51% had one short and one long allele (s/l) and 32% were homozygous for the long allele (l/l). There was a graded moderating effect of the genotype (s/s$>$ s/l$>$ l/l) on the presence of depressive symptoms, diagnosable depression, and suicidality in relation to life stress, including child maltreatment. Thus, carriers of the l/l allele form were resilient to the depressogenic effects of life stress. The effect has been replicated in a recent twin study (Kendler et al., 2005) as well as in maltreated children (Kaufman et al., 2004, 2006). In the latter studies, depression risk as a function of child

maltreatment and 5HTTLPR status was further modified by social support and a polymorphism in the brain-derived neurotrophic factor (BDNF) gene. Interestingly, in a recent study in a large inner city population, our group identified haplotypes in the CRF-1 receptor gene that convey risk versus resilience against the depressive effects of childhood trauma, providing substantial support for the CRF hypothesis of depression (Bradley et al., 2008).

These gene–environment interactions likely reflect genetic moderation of the brain's functional response to stress, including early-life stress, which translates into depression. Of note, individuals with one or two copies of the s allele also exhibit traits of anxiety (Lesch et al., 1996), increased risk to develop depression after tryptophan depletion (Neumeister et al., 2002), and increased amygdala responses to frightening faces (Hariri et al., 2002, 2005; Pezawas et al., 2005; Munafò et al., 2007). In the Pezawas study, morphometrical analyses revealed reduced gray matter volume in s allele carriers in amygdala and cingulate regions, which form a feedback circuit during processing of negative emotion. Short allele carriers showed relative uncoupling of this circuit when processing fearful faces. This deficit was associated with temperamental anxiety (Pezawas et al., 2005). It is conceivable that these genotype-related alterations underlie individual differences in the susceptibility to develop neuroendocrine stress sensitization and depression related to childhood trauma. Accordingly, a recent study in rhesus macaques reported that childhood stress was associated with increased ACTH responses to stress and relative hypocortisolemia; however, this effect was only present in female monkeys who were also 5HTTLPR s allele carriers (Barr et al., 2004). These findings suggest multiple interactions between childhood stress, gender and genotype in determining vulnerability to stress and depression. Interactions between childhood stress, gender and genotype at the brain level are an important area of future research.

8. Spectrum of disorders associated with childhood trauma

The neurobiological consequences of childhood trauma may also promote the development of a spectrum of psychiatric and medical disorders that are aggravated by stress and frequently coincide with depression. Many of these disorders have been associated with increased rates of childhood trauma in the literature. These include anxiety disorders, PTSD, and substance abuse disorders (e.g., Bremner et al., 1993; McCauley et al., 1997), chronic fatigue syndrome (Heim et al., 2006), fibromyalgia and other chronic pain syndromes (Imbierowicz and Egle, 2003; Heim et al., 1998), functional gastrointestinal disorders (Drossman et al., 1990), and cardiovascular disease (Dong et al., 2004). These disorders appear to be part of a spectrum of disorders that share the central feature of enhanced stress and emotional reactivity, likely facilitated by childhood trauma. Of note, patients with functional gastrointestinal disorders are differentially responsive to psychotherapy versus pharmacotherapy, as a function of childhood sexual abuse exposure (Drossman et al., 2003; Creed et al., 2005), similar to our previous findings in depression (Nemeroff et al., 2003).

It is plausible that altered interactions between endocrine and immune systems contribute to risk for fatigue, pain, cardiovascular disease and other disorders after childhood stress. Specifically, the combination of increased stress responsiveness with insufficient glucocorticoid signaling due to glucocorticoid receptor deficiency might have adverse effects in target systems that are regulated by glucocorticoids (Heim et al., 2000a; Raison and Miller, 2003). Stress is known to induce immune activation through increased sympathetic and decreased parasympathetic activation, resulting in activation of the transcription factor, nuclear factor (NF)-κB, with subsequent increases in the secretion of pro-inflammatory cytokines, such as tumor necrosis factor-a, interleukin (IL)-1 and IL-6. These cytokines regulate cellular immunity, mediate fatigue and pain, and further stimulate brain pathways involved in stress, depression and anxiety, including CRF neuronal systems. Glucocorticoids released during stress serve to inhibit activation of NF-κB via GR-mediated signaling, in order to help cytokines return to baseline levels and prevent pathogenic effects of exaggerated cytokine secretion (see Raison and Miller, 2003; Raison et al., 2006). Given that childhood trauma is associated with increased autonomic stress responses, on the one hand, and insufficient glucocorticoid signaling, on the other hand, it is plausible that persons with histories of childhood trauma might exhibit exaggerated immune responsiveness. In support of this hypothesis, we observed increased plasma IL-6 responses to CRF stimulation in women with histories of childhood abuse [unpublished observation]. Recently, we also measured increased activation of NF-κB in peripheral mononuclear blood cells in response to psychosocial stress induction in adult men with major depression and increased early-life stress levels compared with controls. Accordingly, these men also exhibited elevated plasma IL-6 concentrations at 90 min after the stressor. These findings are consistent with impaired regulatory glucocorticoid signaling (Pace et al., 2006). Enhanced cytokine activation might further promote depression and anxiety, as well as somatic disorders, i.e. chronic fatigue syndrome, chronic pain, and cardiovascular disease.

9. Conclusion

We summarized findings of clinical studies conducted over the past several years on the neuroendocrine consequences of childhood trauma and their relationship to major depression. These studies suggest that childhood trauma is associated with persistent sensitization of the stress responses as well as altered dynamics of the HPA axis, which in turn are related to symptoms of depression. In fact, several of the classical neuroendocrine findings reported in the literature for patients with major depression appear to be secondary to early-life stress, likely representing psychobiological risk for the development of depression in response to stress. Other risk factors, such as female gender and genetic dispositions, may interfere with components of the stress response and thereby further increase vulnerability to depression in relation to childhood trauma. Phenotypic vulnerability is likely manifested at the brain level, involving cortical, limbic and brainstem circuits.

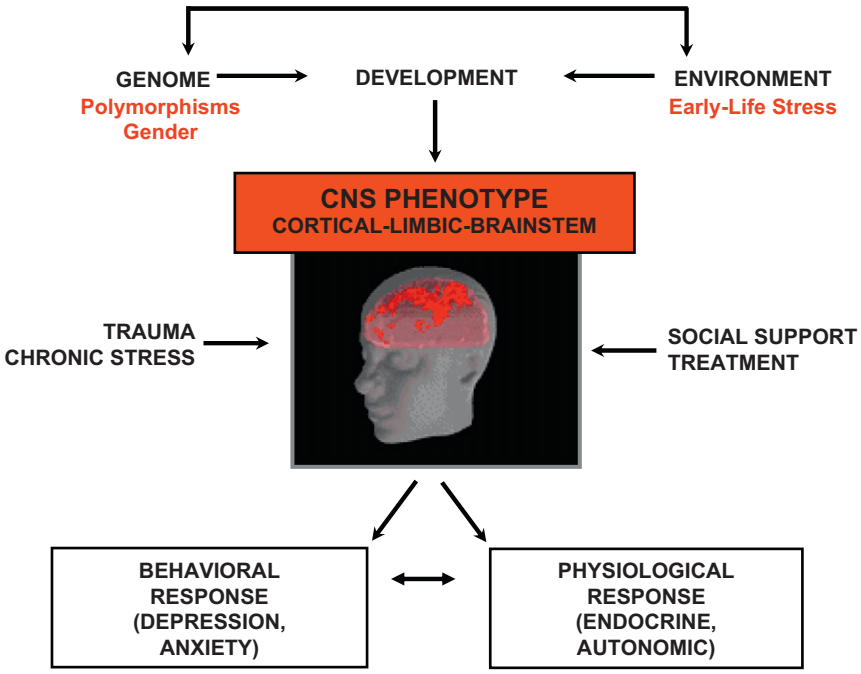

Figure 6 A working model. Genetic disposition and early-life stress interact in shaping a vulnerable phenotype with changes in cortical–limbic–brainstem circuits. Upon stress or trauma, maladaption in these circuits leads to increased endocrine–autonomic and behavioral–emotional responses. Social support and successful treatments modify the stress responses system in different components.

Successful treatments normalize this circuitry in different modules. There are subgroups of depression that are biologically distinct, dependent on the presence or absence of childhood trauma (interacting with other risk factors), which are responsive to different types of treatments. Successful treatments likely modify components of a connected neural network, modified by early-life stress, resulting in normalization of neuroendocrine responsiveness and behavior (Figure 6).

In conclusion, more than 800,000 cases of child maltreatment are reported in the United States each year, with approximately 85% of cases unreported (Edwards et al., 2003). These children have a lifelong increased risk to develop depression, anxiety and other disorders. Future research should further elucidate the neural and molecular basis of increased risk after childhood trauma, and integrate these mechanisms with neuroendocrine features and clinical symptoms. Interactions between genetic dispositions and environmental factors in inducing neurobiological vulnerability should be studied. Particular emphasis should be given to studying differential impact of different types of traumas at different developmental stages, in order to identify precise targets as well as developmental windows of opportunity for prevention of adverse outcomes after childhood trauma exposure. Longitudinal studies are needed to meet this goal. It might be necessary in the future to reevaluate current approaches in the classification of depressive disorders. New typologies that address developmental pathways, together with genetic risk, neurobiological patterns and associated symptom constellations, might significantly enhance research progress on the causes of depression and lead to optimized treatment selections. Our results demonstrate that integrative psychoneuroendocrine research can ultimately contribute to improved clinical care.

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Conflict of interest

Christine Heim: Dr. Heim received research grants from the National Alliance for Research on Schizophrenia and Depression (NARSAD), Anxiety Disorders Association of America (ADAA), Eli Lilly, Novartis, National Institutes of Health (NIH), and Centers for Disease Control & Prevention (CDC).

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Charles B. Nemeroff: In the past 3 years, Dr. Nemeroff consulted to, served on the Speakers' Bureau and/or Board of Directors, has been a grant recipient, and/or owned equity in one or more of the following: Abbott Laboratories, Acadia Pharmaceuticals, American Foundation for Suicide Prevention (AFSP), American Psychiatric Institute for Research and Educations (APIRE), AstraZeneca, BMC-JR LLC, Bristol-Myers-Squibb, CeNeRx, Corcept, Cypress Biosciences, Cyberonics, Eli Lilly, Entrepreneur's Fund, Forest Laboratories, George West Mental Health Foundation, GlaxoSmithKline, i3 DLN, Janssen Pharmaceutica, Lundbeck, National Alliance for Research on Schizophrenia and Depression (NARSAD), Neuronetics, NIMH, NFMH, NovaDel Pharma, Otsuka, Pfizer Pharmaceuticals, Quintiles, Reevax, UCB Pharma, Wyeth-Ayerst. Currently, Dr. Nemeroff serves on the Scientific Advisory Board for Astra-Zeneca, Johnson & Johnson, Pharma Neuroboost, Forest Laboratories, Quintiles and NARSAD. He is a grant recipient from NIH, NARSAD and AFSP. He serves on the Board of Directors of AFSP, APIRE, NovaDel Pharmaceuticals and the George West Mental Health Foundation. He owns equity in CeNeRx and Reevax. He owns stock or stock options in Corcept, Cypress Biosciences and NovaDel.

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