CellPress

Neuron
Review

Paradise Lost: The Neurobiological and Clinical Consequences of Child Abuse and Neglect

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http://dx.doi.org/10.1016/j.neuron.2016.01.019

In the past two decades, much evidence has accumulated unequivocally demonstrating that child abuse and neglect is associated with a marked increase in risk for major psychiatric disorders (major depression, bipolar disorder, post-traumatic stress disorder [PTSD], substance and alcohol abuse, and others) and medical disorders (cardiovascular disease, diabetes, irritable bowel syndrome, asthma, and others). Moreover, the course of psychiatric disorders in individuals exposed to childhood maltreatment is more severe. Recently, the biological substrates underlying this diathesis to medical and psychiatric morbidity have been studied. This Review summarizes many of the persistent biological alterations associated with childhood maltreatment including changes in neuroendocrine and neurotransmitter systems and pro-inflammatory cytokines in addition to specific alterations in brain areas associated with mood regulation. Finally, I discuss several candidate gene polymorphisms that interact with childhood maltreatment to modulate vulnerability to major depression and PTSD and epigenetic mechanisms thought to transduce environmental stressors into disease vulnerability.

> "Safety and security don't just happen, they are the result of collective consensus and public investment. We owe our children, the most vulnerable citizens in our society, a life free of violence and fear."—Nelson Mandela

> "The world is a dangerous place, not because of those who do evil, but because of those who look on and do nothing." —Albert Einstein

Introduction

In the last decade, a remarkable concatenation of research findings has accumulated supporting the hypothesis that exposure to early untoward life events (early life stress [ELS]) in the form of child abuse and/or neglect is associated with a marked increase in vulnerability to major psychiatric and other medical disorders including major depression, bipolar disorder, post-traumatic stress disorder (PTSD), alcohol and drug abuse, and perhaps even schizophrenia, as well as obesity, migraines, cardiovascular disease (CVD), diabetes, and others. More recently, the biological and neurobiological consequences of ELS have been scrutinized in order to determine the molecular and cellular mechanisms that mediate the effects of ELS on the aforementioned disease vulnerability. The present Review seeks to succinctly summarize a now vast literature encompassing the epidemiology and clinical course following exposure to ELS, findings utilizing laboratory animal models of ELS, the neuroendocrine and immunological consequences of ELS, and the interaction between ELS and genetic factors in disease vulnerability. In addition, the emerging role of epigenetics is also described. The persistent neurobiological effects of child abuse and neglect, as demonstrated by structural and functional brain imaging, are also summarized. Finally, there is now a burgeoning database concerning the treatment response of patients with mood and anxiety disorders with a history of child abuse and neglect. There is virtually universal agreement that this sizeable subpopulation of patients has a more severe clinical course in terms of symptom severity and age of onset and responds more poorly to pharmacotherapy and/or psychotherapy. A discussion of future research directions concludes this monograph.

A few caveats should be mentioned. First, this is now a vast and rapidly burgeoning field and because of space constraints and the limitations in the number of citations permitted, all of the original research publications could not be included in either the text or the reference list. Second, because our research group has been focused on this area for more than 30 years, there is naturally an over-representation of our own contributions. This is not, in any way, meant to minimize the contributions of other groups. Third, a number of other reviews, many quite comprehensive and lengthy, have appeared and are highly recommended. This includes a recent Institute of Medicine (IOM) report on new directions in child abuse and neglect research (http://www.nap.edu/catalog/18331/new-directions-in-child-abuse-and-neglect-research), as well as reviews from our group, (i.e., Newport et al., 2002; Heim et al., 2008a, 2010; Neigh et al., 2009; Nemeroff and Seligman, 2013; and other leaders in the field, including Bale et al., 2010; Baram et al., 2012; Danese and McEwen, 2012; Teicher and Samson, 2013; Rilling and Young, 2014; Veenstra-VanderWeele and Warren, 2015).

Finally, I wish the reader to appreciate the sea change that has occurred in this area over the last three decades. When we and others first began this work, largely derived from clinical observations and psychoanalytically based principles first promulgated by Freud, there was strong and widespread opposition to the hypothesis that ELS was capable of producing persistent CNS and other long-term biological alterations. Many initial grant

proposals and manuscript submissions were met with great skepticism and disbelief, analogous to the remarkably long time the field came to accept the findings of neurogenesis in the adult mammalian brain. As will be described below, the extant database on the adverse consequences of ELS is now very robust and many of the findings have been widely replicated.

Epidemiology and Clinical Course

As is not unusual in medicine, clinical observations over several decades served as an impetus for well-powered epidemiological and longitudinal cohort studies that have now led to one inexorable conclusion—namely that sexual, physical, and emotional abuse, as well as emotional neglect, leads to a very significant increase in risk in adulthood for mood and anxiety disorders, substance and alcohol abuse, and certain other medical disorders. For the reader who might not recognize the magnitude of this public health problem, it is worthwhile to briefly summarize the latest data on prevalence rates of childhood maltreatment. In 2012, the U.S. Department of Health and Human Services documented 3.4 million referrals to child protective services, representing 686,000 children. Approximately 80% of the maltreatment was perpetuated by one or both parents. In this report, ELS was comprised of neglect (78.3%), physical abuse (18.3%), and sexual abuse (9.3%). Neglect is frequently defined as the failure of a parent or another person with responsibility for the child to provide needed food, clothing, shelter, medical care, or supervision to the degree that the child's health, safety, and well-being are threatened with harm. All authorities agree, however, that the vast majority of cases of child abuse and neglect go unreported. It is also important to note that certain forms of abuse, most notably sexual abuse, occur primarily in the youngest age group. In 2000, 70% of all sexual assaults in the U.S. were committed against children. There are both global regional differences and gender differences in childhood sexual abuse with the highest rates overall in Australia, Africa, and the U.S., with the lowest rates in Asia. Girls exhibited the highest rates of sexual abuse in all regions studied except Africa and South America, where the rates between boys and girls were equal.

In summarizing the large literature on the effects of ELS on risk for adult psychopathology and other medical disorders, the landmark CDC-funded Adverse Childhood Experiences (ACE) epidemiological study provided the findings that, it is not an overstatement to suggest, launched the field (see Anda et al., 2006 for review). This study was comprised of 17,337 adult members of a health maintenance organization (HMO) in San Diego. Assessing eight ELS events including abuse, domestic violence, household substance abuse, parental loss (by incarceration, divorce, and others), the investigators calculated an ACE score as a measure of cumulative ELS to determine the "dose-response" relationship between ELS and adult pathology. The results were striking and conclusive; 64% of the respondents had, at least, one ACE. For those with $\geq$4 ACE events, there was a very significant increase in risk for depression, anxiety, panic attacks, suicide attempts, substance and alcohol abuse, sleep disturbances, obesity, smoking, chronic obstructive pulmonary disease (COPD), and heart disease. A large number of subsequent studies have confirmed and extended these findings. Scott et al. (2010) studied 2,144 individuals ages 16–27 years in New Zealand. ELS was associated with clear increases in PTSD, mood disorders, anxiety disorders, and substance use disorders. Results from the National Comorbidity Study of 9,282 adults were concordant with the ACE study in revealing a dose-response relationship between individual childhood adversities and risk for DSM IV mood, anxiety, disruptive behavior, and substance abuse diagnoses (Green et al., 2010). A prospective cohort study of 676 children with documented physical and sexual abuse or neglect were compared to a matched sample of 520 non-abused and non-neglected children showed a clear increased risk in the ELS cohort for major depression. Moreover, those who developed MDD exhibited higher rates of comorbid disorders including PTSD and substance/alcohol abuse (Widom et al., 2007). These findings are consistent with the findings of Putnam and colleagues (2013), who, further analyzing the National Comorbidity Survey Replication Sample of 9,282 individuals, found that multiple ACEs resulted in complex adult psychopathology, as defined by higher rates of comorbidity and a greater number of symptoms. The Mexican National Comorbidity Survey of 5,826 individuals supported all of the aforementioned findings, namely an increase in mood, anxiety, substance abuse, and externalizing disorders (attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorders) after exposure to family dysfunction and abuse (Benjet et al., 2010).

Several studies have sought to determine the consequences of a single type of ELS on adult psychopathology. A recent meta-analysis by Chen et al. (2010) of 37 studies (17 case-control and 20 cohort) of 3,162,318 participants sought to determine the effects of sexual abuse on lifetime risk for psychiatric disorders. There was a significant association between sexual abuse in both men and women and lifetime diagnosis of an anxiety disorder, depression, eating disorder, PTSD, sleep disorders, and suicide attempts, but not schizophrenia. Maniglio (2010) conducted a systematic review of the effects of sexual abuse in childhood on risk for depression, which was comprised of 60,000 subjects in 160 studies. Their findings indicated that sexual abuse is a significant risk factor for depression.

Bullying has been the focus of recent research, particularly important because this form of ELS has not been included in the vast majority of studies previously conducted. Teicher and Samson (2013) studied parental "verbal aggression" in 554 subjects 18–22 years of age. The untoward effects of this form of ELS was equal to that of those exposed to witnessing domestic violence and non-familial sexual abuse on depression and anxiety and, again, multiple forms of abuse was associated with very large effect sizes. Copeland et al. (2013) reported on 1,420 study participants who were either bullied or engaged in bullying between the ages of 9 and 16 years. In young adulthood, bully victims exhibited increased rates of agoraphobia, generalized anxiety disorder (GAD), and panic disorder, and those who were both bully victims and bulliers exhibited increased rates of MDD, panic disorder, and agoraphobia in women and suicidality in men.

Considerable research has been conducted in seeking to determine whether ELS is associated with increased vulnerability for PTSD. In a study of 4,529 male soldiers,

Cabrera et al. (2007) reported that exposure to >2 categories of child adversity (29% of the sample) was associated with a significantly increased risk for PTSD as well as depression. In a study of 1,045 U.S. combat veterans, childhood physical abuse was associated with an increased risk for PTSD as well as depression (Fritch et al., 2010).

The finding that ELS is a major risk factor for suicide is of paramount importance because suicide rates have climbed over the last decade and now represent a top 10 cause of death in the U.S. In 2013, 41,149 suicides were reported in the U.S. Recently, Short and Nemeroff (2014) have reviewed the findings that support the hypothesis that ELS is indeed a major contributor to suicide attempt or completion risk. This conclusion is drawn from multiple studies including the analysis of child sexual abuse in 65,851 subjects contained in 177 studies (Maniglio, 2011), the 8,580 participants in the British Psychiatric Morbidity Survey demonstrating the link between child sexual abuse and suicide attempts (Bebbington et al., 2009), a population of male prisoners (Mandelli et al., 2011), in 6,986 Korean medical students (Jeon et al., 2009), and in 137 patients with treatment-resistant depression (Tunnard et al., 2014).

In the World Mental Health Survey database, collected for 21 countries, ELS was associated with an increased risk for suicide attempt and, more specifically, sexual and physical abuse had the greatest effect, both for onset and persistence of suicidal behavior. Among a group of psychiatric patients with varying diagnoses in France and Italy (n = 587), a significant correlation between childhood trauma and suicidal behavior was observed (Sarchiapone et al., 2009). In a study of 1,488 military personnel and veterans, after controlling for effects of combat exposure and PTSD, childhood trauma exposure was associated with both depressive symptoms and suicidal ideation (Youssef et al., 2013).

The effects of ELS on vulnerability to other psychiatric and medical disorders have been considerably less well studied. There is increasing evidence that ELS increases risk for bipolar disorder and, moreover, worsens its clinical course. Using the National Epidemiological Survey on Alcohol and Related Conditions (n = 33,375), childhood physical and sexual abuse were associated with increased risk for initial onset and recurrent DSM IV manic episodes (Gilman et al., 2015). A recent review of the extant literature indicated that childhood maltreatment is associated with early onset, increased suicidality, and substance abuse in patients with bipolar disorder (Daruy-Filho et al., 2011). In a study of 116 bipolar patients with a high rate (61%) of childhood trauma, those with ELS had a greater number of depressive episodes, total episodes, and attempted suicide (Erten et al., 2014). Patients with bipolar disorder and a history of childhood abuse have a higher rate of suicide attempts and a more severe clinical course when compared to bipolar patients without ELS (Carballo et al., 2008).

The data on ELS and psychotic disorders remains somewhat inconclusive. Bendall et al. (2008) concluded that the then current literature was largely methodologically flawed and the few rigorous studies provided discordant results. Since that time, additional data suggest a relationship between ELS and the development of psychotic disorders. Data from the Adult Psychiatric Morbidity Survey in England of 7,353 individuals found a strong relationship between sexual abuse before the age of 16 years and psychosis (Bebbington et al., 2011). In a case-control and case-sibling comparison study, Heins et al. (2011) reported that childhood trauma was associated with psychotic disorder in a dose-dependent fashion. Finally, there is evidence that child abuse and neglect is associated with an increased risk for bulimia (Sanci et al., 2008), substance abuse (Shin et al., 2010), obesity (Noll et al., 2007), and unintended teenage pregnancy (Bellis et al., 2014).

There is considerable evidence that childhood trauma is associated with a more severe course of depression including chronicity (Wiersma et al., 2009), features of atypical depression (hypersomnia, interpersonal rejection sensitivity, increased appetite, leaden limb paralysis) (Withers et al., 2013), and most importantly a poor outcome to treatment with psychopharmacology and/or psychotherapy (Nanni et al., 2012). This latter finding is described in more detail below.

There is emerging data that the consequences of deprivation/neglect differ substantially from those of threat/abuse. This is an important area of current research (Humphreys and Zeanah, 2015) and some of the neurobiological findings are described below.

Preclinical Models of ELS

This area has also experienced rapid growth with many recent contributions. It is important to note that these laboratory animal paradigms, most notably maternal deprivation, more closely approximate neglect (not abuse) in humans. It is also important to note that although the emphasis here is on the untoward persistent adverse biological consequences of ELS, there is considerable preclinical evidence that early life environmental enrichment, in contrast to ELS, results in long-lasting salutary effects in adulthood, both behavioral and neuroanatomic (Peña et al., 2009). In view of the seminal role of the hypothalamic-pituitary-adrenal (HPA) axis and extra-hypothalamic corticotropin-releasing factor (CRF) circuits in mediating the endocrine, behavioral, immune, and autonomic effects of stress, our early studies focused on the effects of maternal separation on these systems. Brief maternal deprivation, early in life in rats, resulted in increases in basal and stress-induced plasma ACTH concentrations, increases in median eminence CRF concentrations, and downregulation in anterior pituitary CRF-R_1 receptor density. Alterations in both extrahypothalamic CRF concentrations and CRF-R_1 receptor binding were also observed (Ladd et al., 1996). Subsequent studies revealed long-term consequences of maternal separation in adult male rats including elevated cerebrospinal fluid (CSF) CRF concentrations, as well as increased CRF mRNA expression and CRF concentrations in the paraventricular nucleus (PVN), central nucleus of the amygdala, bed nucleus of the stria terminalis, and locus coeruleus (Plotsky et al., 2005). The maternally deprived rats also exhibited escape from suppression of plasma ACTH and corticosterone by the synthetic glucocorticoid dexamethasone (Ladd et al., 2004). Subsequent studies revealed maternal separation effects on brain-derived neurotropic factor (BDNF) expression and processing in the striatum, hippocampus, and ventral tegmental area (Lippmann et al., 2007). Many of these initial findings have been confirmed and extended by others.

Combined ELS in the form of maternal separation and chronic psychosocial stress (chronic subordinate colony housing [CSC]) in mice resulted in elevated CRF mRNA expression in the PVN but reduced plasma corticosterone and a significant increased severity of colitis induced by dextran (Veenema et al., 2008). Studies of the offspring of high versus low maternal licking and grooming in rats revealed shorter dendritic branch length and lower spine density in CA1 cells of low licking and grooming animals, as well as significantly impaired hippocampal long-term potentiation (LTP) and reduced GC and MR receptor density (Champagne et al., 2008). Effects of maternal deprivation on locus coeruleus neuronal activity response to CRF and dendritic morphology have also been observed (Swinny et al., 2010). Yang et al. (2015) recently observed marked effects of repeated stress exposure during the first postnatal week on dendritic development in the dorsal agranular cingulate cortex and prelimbic cortex in neonatal mice, an effect mediated by CRF_1 receptors. Interestingly in a biparental mammal, Degus, paternal deprivation during infancy is associated with lower spine densities in pyramidal neurons in the orbitofrontal cortex (Helmeke et al., 2009).

Finally, our collaborators (e.g., Coplan et al., 1996, 2006, 2011) in the bonnet macaque and our group in rhesus monkeys (Sánchez et al., 2005; Parr et al., 2012) have repeatedly demonstrated persistent neuroendocrine and neurotransmitter and behavioral effects of ELS in non-human primates. In brief, in the bonnet macaques, marked and persistent increases in CSF CRF concentrations, a blunted growth hormone response to clonidine, an increase in body mass index, and alterations in magnetic resonance spectroscopy were observed. In the rhesus monkeys, repeated maternal separations were associated with a flattened diurnal rhythm of cortisol secretion and both increased cortisol reactivity to separation and increased acoustic startle reactivity. Using FDG-PET, maternally deprived subjects exhibited greater regional glucose metabolism in emotional and sensory processing areas (superior temporal sulcus, putamen, thalamus, and inferotemporal cortex) in response to moderate stress.

Endocrinology

Because of the preeminent role of the HPA axis in the regulation of the mammalian stress response, this endocrine system has, understandably, received the most scrutiny relative to others that might potentially be affected by early life trauma. This is an extraordinarily complex area with a substantial number of studies that have documented both increased and decreased HPA axis activity as a consequence of child abuse and neglect. Since publication of a series of studies from our group and our collaborators (Heim et al., 2000, 2001, 2002, 2008b; Carpenter et al., 2004) documenting HPA axis hyperactivity in depressed women and men with ELS (increased ACTH and cortisol responses in The Trier Social Stress Test [TSST] and increased HPA axis activity in the combined dexamethasone-CRF stimulation test) and increased CSF/CRF concentrations in depressed patients and controls exposed to perinatal adversity and perceived adversity in the preteen years, other groups have reported both confirmatory and discrepant findings. Thus, Pesonen et al. (2010) found increased HPA axis activity using the TSST in offspring of Finnish war veterans who were separated from both parents during the war, an intergenerational effect. Fernando et al. (2012) found enhanced baseline and post-dexamethasone cortisol levels in patients with major depression and borderline personality disorder who had a past personal history of childhood trauma. In contrast, several investigators have reported reduced baseline and a blunted HPA axis response to various provocative stimuli in victims of child abuse. This has been observed in victims of bullies assessed at 12 years of age (Ouellet-Morin et al., 2011), in 230 adults without syndromal Axis I psychiatric disorders (Carpenter et al., 2009), and in a similar study of 104 normal women (Voellmin et al., 2015), correlated with parent psychological stress in 8 year olds (Koch et al., 2010) and in patients with personality disorders, though in this latter study CSF CRH levels were elevated (Lee et al., 2012).

The sources of the discordant findings in the literature are an active avenue of investigation. It is now clear that the effects of child abuse and neglect on HPA axis activity are impacted by several factors including, but not limited to:

(1) Nature of early life stress (sexual versus physical versus emotional abuse versus neglect), number of episodes, cumulative period of the adverse events, age at first abuse/neglect, and chronicity
(2) Presence or absence of psychosocial support
(3) Presence of traumatic events in adulthood
(4) Family history of major psychiatric disorders
(5) Genetic and epigenetic factors

In regard to genetics, the modulating role of FKBP5 genotype (see Genetics section below) and CRH receptor gene polymorphisms have already been demonstrated (Tyrka et al., 2009a; Buchmann et al., 2014).

Recently, a comprehensive review has appeared attempting to reconcile the wide range of findings in this area (Strüber et al., 2014). They suggest a two-pathway model to explain the hyper versus hypo activity of the HPA axis after ELS-invoking interactions of the glucocorticoid system with oxytocin pathways (see below) and the serotonergic system.

The past decade has witnessed a remarkable increase in the understanding of the seminal role of oxytocin, a neuropeptide found in the CNS and in the posterior pituitary, in mediating social affiliation, attachment, maternal behavior, intimacy, and trust, in addition to its well-established role in parturition and breast feeding. It is, therefore, not surprising that it has recently been scrutinized as a neural system that might well be affected by ELS. Our initial study of 22 healthy women found a very strong inverse relationship between exposure to maltreatment in childhood and CSF oxytocin concentrations (Heim et al., 2009b). Moreover, the greater the number of adverse exposure categories and the more severe and chronic was the abuse, the lower the CSF oxytocin concentrations. Subsequent work by our group (Myers et al., 2014) examined whether SNP variation in the oxytocin receptor correlated with severity of depression or anxiety and interacted with ELS. In this sample of 653 individuals, a significant effect of oxytocin receptor genotype on anxiety, stress, and depression symptom severity interacting with ELS was observed.

Lastly, it is important to point out the relative dearth of knowledge concerning the effects of ELS on the many other endocrine axes including the hypothalamic-pituitary-gonadal axis and its target hormones estrogen, progesterone, and testosterone, the hypothalamic-pituitary-thyroid axis, and the secretions of growth hormone and prolactin. A strong case can be made to conduct such studies based on both clinical observations (high rates of menstrual cycle irregularities) and hypothyroidism in patients with mood and anxiety disorders.

Inflammation and Risk for Other Medical Disorders

The pioneering Adverse Childhood Experiences (ACE) studies provided the first clear evidence that child abuse and neglect is associated with an increased risk for not only psychiatric disorders, but a variety of medical disorders as well, including ischemic heart disease, cancer, chronic lung disease, skeletal fractures, autoimmune disorders, and liver disease. The risk was directly proportional to the number and magnitude of the ELS (Felitti et al., 1998; Dube et al., 2009). Subsequent studies including meta-analyses have confirmed and extended these observations. In a meta-analysis of 23 studies of 4,640 subjects, sexual abuse was associated with an increased risk for functional gastrointestinal (GI) disorders, chronic pain including chronic pelvic pain, and psychogenic seizures; rape was associated additionally with a risk for fibromyalgia (Paras et al., 2009). In a subsequent meta-analysis of 24 studies of 48,801 subjects, child abuse was associated with neurological and musculoskeletal problems as well as GI, respiratory, cardiovascular, and metabolic disorders (Wegman and Stetler, 2009). The link between ELS and functional GI disorders is supported by the remarkably high rate of sexual and/or physical abuse (66.5%) in female patients referred to a GI clinic at an academic medical center (Leserman et al., 1996). There is also evidence for an increase in headache and more specifically migraine in victims of child abuse and neglect.

Because inflammation has been implicated in the pathogenesis of many of the medical disorders demonstrated to be increased in individuals exposed to ELS, a number of groups have sought to determine the effects of child abuse and neglect on biomarkers of inflammation. Markedly exaggerated interleukin-6 (IL-6) responses to a standard laboratory stressor was observed in depressed men with a history of child abuse and neglect by our group (Pace et al., 2006). Subsequently Danese, Pariente, and their colleagues (Danese et al., 2007, 2008) using the approximately 1,000 subjects in the Dunedin Multidisciplinary Health and Development Study reported that maltreated children exhibit a significant and graded increase in C-reactive protein (CRP) 20 years later, and moreover this effect was independent of more recent life stressors, and adult health and behavior. This effect was particularly robust in depressed individuals with a history of childhood maltreatment, confirming and extending our initial finding described above. This group has subsequently demonstrated significant CRP elevations in depressed and maltreated 12-year-old children compared to depressed only, maltreated only, or controls of the same age (Danese et al., 2011). Subsequent studies have confirmed these seminal findings; Lacey et al. (2013) in a study of 7,642 subjects in the United Kingdom reported that parental separation in childhood was associated with a significant increase in CRP levels at age 44 years. Slopen et al. (2013) found that adverse events prior to 8 years of age predicted increases in inflammatory markers at age 10 years including IL-6 and CRP. Indeed, not only childhood adversity, but prenatal adversity is associated with higher CRP levels in adulthood (Slopen et al., 2015). Particularly relevant to the role of inflammation in the course of medical disorders is the recent report of Crosswell et al. (2014), who found a strong effect of childhood adversity on IL-6 levels in breast cancer survivors, even after controlling for a series of potential confounds such as cancer treatment, age, BMI, ethnicity, and alcohol use. They suggested that such inflammation may contribute to the reportedly poor outcome in depressed breast cancer patients.

Genetics and Epigenetics

Telomeres are DNA-protein complexes located at the ends of linear chromosomes that cap and protect the genome from damage. Inflammation and other factors have previously been shown to reduce telomere length, which has been associated with premature cell shortening and increased morbidity and mortality of age-related diseases. Three studies have assessed the effects of childhood maltreatment on telomere shortening. Tyrka et al. (2009b) studied 31 adults with no past or current major psychiatric disorder and reported that childhood maltreatment was associated with significant telomere shortening. Shalev et al. (2013) studied 236 children in the Environmental-Risk Longitudinal Twin Study. The children exposed to >2 violence exposures exhibited significantly more telomere erosion between age 5 and 10 years. Finally, in a small study of 20 drug-free depressed adult and 20 matched controls, greater adverse childhood experience exposure reduced telomere length in the healthy volunteers without affecting telomerase activity, whereas in the depressed cohort the opposite pattern was observed, namely no change in telomere length but increased telomerase activity (Chen et al., 2014). Other studies have confirmed and extended these observations (Kiecolt-Glaser et al., 2011; O'Donovan et al., 2011; Kananen et al., 2010; Drury et al., 2012).

Because the major psychiatric disorders including bipolar disorder, schizophrenia, major depression, and PTSD all represent "so-called" complex diseases by virtue of both a large genetic and environmental contribution to risk, it is not surprising that the sizeable literature documenting the preeminent role for child abuse and neglect as a major environmental risk factor would drive the field toward investigating gene-environment interactions. The answer to the question as to whether specific genetic polymorphisms could be identified to interact with the now well-established environmental risk factor of childhood maltreatment to mediate risk for the development of mood and anxiety disorders has yielded remarkable results. In fact, because the demonstration of several candidate gene polymorphisms as modifiers of risk for the development of major depression and PTSD in the victims of childhood maltreatment has been so successful, it is truly impossible to review this entire literature in this monograph. There are literally hundreds of reports published in this area and that does not even include the burgeoning epigenetics literature described at the end of this section. Pioneering work in this area has been conducted by Caspi and his collaborators. In a groundbreaking report in *Science* (Caspi et al., 2003), the authors reported that using the Dunedin Multidisciplinary Health and

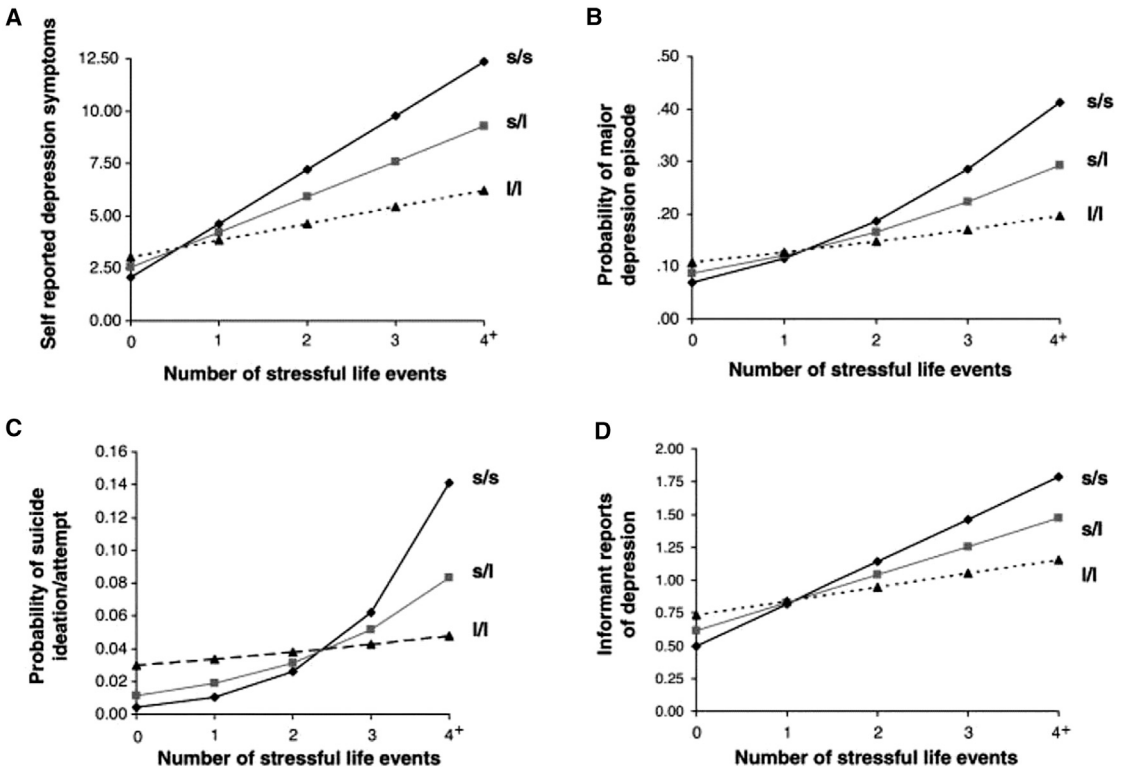

Figure 1. Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene

Results of multiple regression analyses estimating the association between number of stressful life events (between ages 21 and 26 years) and depression outcomes at age 26 as a function of 5-HT T genotype. Among the 146 s/s homozygotes, 43 (29%), 37(25%), 28 (19%), 15 (10%), and 23 (16%) study members experienced zero, one, two, three, and four or more stressful events, respectively. Among the 435 s/l heterozygotes, 141 (32%), 101 (23%), 76 (17%), 49 (11%), and 68 (16%) experienced zero, one, two, three, and four or more stressful events. Among the 264 l/l homozygotes, 79 (29%), 73 (28%), 57 (21%), 26 (10%), and 29 (11%) experienced zero, one, two, three, and four or more stressful events.

(A) Self-reports of depression symptoms. The main effect of 5-HT TLPR (i.e., an effect not conditional on other variables) was marginally significant (b – = 0.96, SE = 0.52, t = 1.86, p = 0.06), the main effect of stressful life events was significant (b = 1.75, SE = 0.23, t = 7.45, p < 0.001), and the interaction between 5-HT TLPR and life events was in the predicted direction (b – = 0.89, SE = 0.37, t = 2.39, p = 0.02). The interaction showed that the effect of life events on self-reports of depression symptoms was stronger among individuals carrying an s allele (b = 2.52, SE = 0.66, t = 3.82, p < 0.001 among s/s homozygotes, and b = 1.71, SE = 0.34, t = 5.02, p < 0.001 among s/l heterozygotes) than among l/l homozygotes (b = 0.77, SE = 0.43, t = 1.79, p = 0.08).

(B) Probability of major depressive episode. The main effect of 5-HT TLPR was not significant (b = –0.15, SE = 0.14, z = 1.07, p = 0.29), the main effect of life events was significant (b = 0.37, SE = 0.06, z = 5.99, p < 0.001), and the G × E was in the predicted direction (b = –0.19, SE = 0.10, z = 1.91, p = 0.056). Life events predicted a diagnosis of major depression among s carriers (b = 0.52, SE = 0.16, z = 3.28, p = 0.001 among s/s homozygotes, and b = 0.39, SE = 0.09, z = 4.24, p < 0.001 among s/l heterozygotes) but not among l/l homozygotes (b = 0.16, SE = 0.13, z = 1.18, p = 0.24).

(C) Probability of suicide ideation or attempt. The main effect of 5-HT TLPR was not significant (b = –0.01, SE = 0.28, z = 0.01, p = 0.99), the main effect of life events was significant (b = 0.51, SE = 0.13, z = 3.96, p < 0.001), and the G × E interaction was in the predicted direction (b= –0.39, SE = 0.20, t = 1.95, p = 0.051). Life events predicted suicide ideation or attempt among s carriers (b = 0.48, SE = 0.29, z = 1.67, p = 0.09 among s/s homozygotes, and b = 0.91, SE = 0.25, z = 3.58, p < 0.001 among s/l heterozygotes) but not among l/l homozygotes (b = 0.13, SE = 0.26, z = 0.49, p = 0.62).

(D) Informant reports of depression. The main effect of 5-HT TLPR was not significant (b = –0.06, SE = 0.06, t = 0.98, p = 0.33), the main effect of life events was significant (b = 0.23, SE = 0.03, t = 8.47, p < 0.001), and the G × E was in the predicted direction (b = –0.11, SE = 0.04, t = 2.54, p < 0.01). The effect of life events on depression was stronger among s carriers (b = 0.39, SE = 0.07, t = 5.23, p < 0.001 among s/s homozygotes, and b = 0.17, SE = 0.04, t = 4.51, p < 0.001 among s/l heterozygotes) than among l/l homozygotes (b = 0.14, SE = 0.05, t = 2.69, p < 0.01). From Caspi et al. (2003). Reprinted with permission from AAAS.

Development Study cohort of 1,037 subjects that had been assessed multiple times from age 3 to adulthood, those who carried one or two copies of the short allele of the serotonin transporter promoter polymorphism exhibited higher rates of adult depression and suicidality when exposed to childhood maltreatment when compared to those long allele homozygotes with equal ELS exposure (Figure 1). Moreover, the number of ELS events accentuated the differences in depressive symptom severity and suicidality between the three genotypes of the serotonin transporter. These findings were not only remarkable for the large effect of the serotonin transporter genotype on vulnerability to depression but because of the observation that in the absence of ELS, serotonin transporter polymorphism had no effect on depression diathesis. It is also important to note that unlike certain SNP findings, this polymorphism is clearly a functional one with reduced serotonin transporter expression in short arm(s) carriers.

These findings have been confirmed in a large number of subsequent studies by Caspi and his collaborators (Uher et al., 2011), our group (Ressler et al., 2011), and others as regards depression vulnerability (Cutuli et al., 2013; Rocha et al., 2015), suicidality (Roy et al., 2007), and in a major meta-analysis (Karg et al., 2011). A number of discordant reports have also

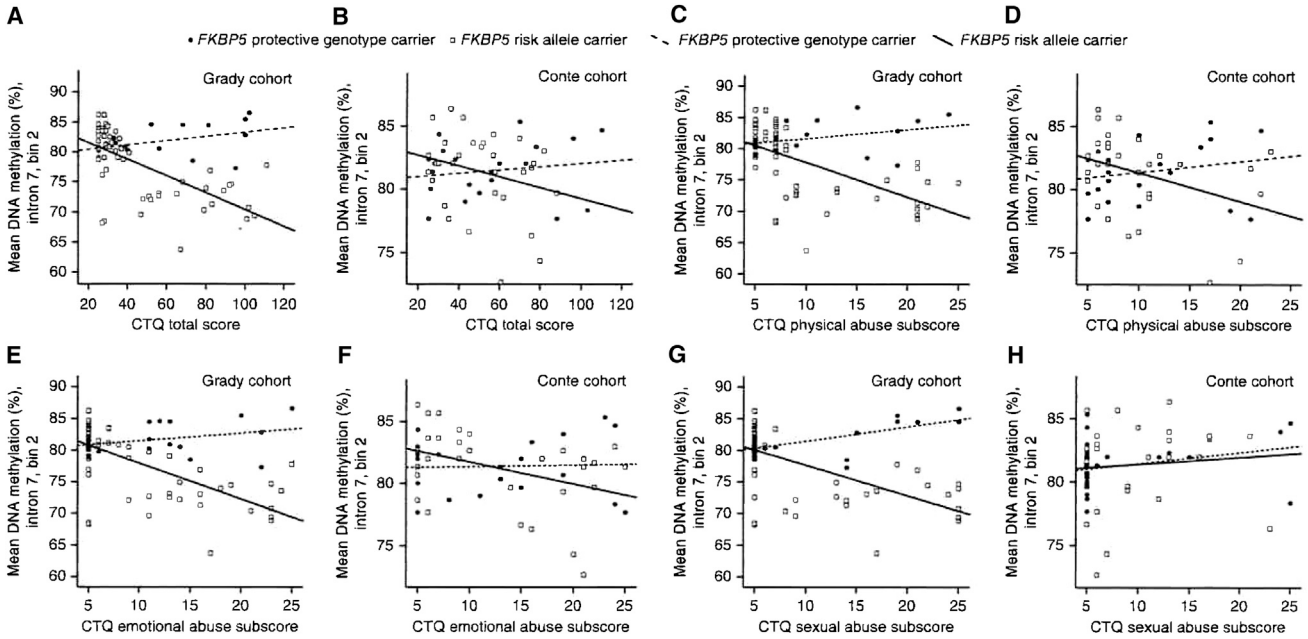

Figure 2. Differential FKBP5 Intron 7 DNA Methylation Depends on Genotype and Trauma Exposure

Correlation between intron 7 bin 2, mean methylation, and log-transformed CTQ scores by FKBP5 rs1360780 genotype in the Grady and Conte cohort are shown.
(A) Grady cohort. Risk allele carriers exhibited a strong negative correlation ($R = -0.646$, $p < 0.001$) between methylation and CTQ total load compared with carriers of the protective genotype ($R = 0.414$, $p = 0.078$) (Fisher Z score $= -4.23$, $p < 0.001$).
(B) Conte cohort. Correlation between methylation and total CTQ in risk allele carriers ($R = -0.273$, $p = 0.124$), and in carriers of the protective genotype ($R = 0.153$, $p = 0.485$) (Fisher Z score $= -1.5$, $p = 0.133$).
(C) Grady cohort. Negative correlation was found between methylation and the CTQ physical abuse subscore in risk allele carriers ($R = -0.586$, $p < 0.001$), but not in carriers of the protective genotype ($R = 0.360$, $p = 0.130$) (Fisher Z score $= -4.49$, $p < 0.001$).
(D) Conte cohort. Negative correlation was observed between methylation and the CTQ physical abuse subscore in risk allele carriers ($R = -0.397$, $p = 0.022$), but not in carriers of the protective genotype ($R = 0.246$, $p = 0.258$) (Fisher Z score $= -2.33$, $p = 0.019$).
(E) Grady cohort. Negative correlation was found between methylation and the CTQ emotional abuse subscore in risk allele carriers ($R = -0.685$, $p < 0.001$), but not in carriers of the protective genotype ($R = 0.321$, $p = 0.181$) (Fisher Z score $= -4.1$, $p < 0.001$).
(F) Conte cohort. Negative correlation was found between methylation and the CTQ emotional abuse subscore in risk allele carriers ($R = -0.397$, $p = 0.022$), but not in carriers of the protective genotype ($R = 0.022$, $p = 0.922$) (Fisher Z score $= -1.53$, $p = 0.126$).
(G) Grady cohort. Negative correlation was found between methylation and the CTQ sexual abuse subscore in risk allele carriers ($R = -0.656$, $p < 0.001$), but not in carriers of the protective genotype ($R = 0.599$, $p = 0.007$) (Fisher Z score $= -5.17$, $p < 0.001$).
(H) Conte cohort. Negative correlation was found between methylation and the CTQ sexual abuse subscore in risk allele carriers ($R = 0.118$, $p = 0.514$), and in carriers of the protective genotype ($R = 0.305$, $p = 0.922$) (Fisher Z score $= -0.68$, $p = 0.496$). From Klengel et al. (2013). Reprinted by permission from Macmillan Publishers.

appeared (e.g., Laucht et al., 2009) including a widely publicized meta-analysis (Risch et al., 2009) that concluded that there is no evidence that the serotonin transporter alone or in combination with stressful life events increases risk for depression. Unfortunately, this analysis included "stressful live events," diluting the sample with all stressful events instead of specifically testing the effect of ELS. It also omitted many positive studies published subsequently. Uher and McGuffin (2008) have provided a thoughtful commentary on the controversies in this area with a focus on methodological issues of assessment of ELS, ethnicity, and sample size.

In view of the voluminous database that HPA axis activity is altered in patients with MDD and PTSD and the preeminent role of early adversity in risk for these disorders, it is not surprising that many research groups have sought to determine whether polymorphisms in candidate genes of components of the HPA axis and others that modulate stress responses regulate risk for mood and anxiety disorders by interacting with childhood abuse and neglect in a fashion similar to that described above for the serotonin transporter. Our group and many others have focused on FKBP5, a co-chaperone protein of heat shock protein (hsp) 90, which regulates glucocorticoid receptor sensitivity. Indeed, four SNPs of the FKBP5 gene interact with 70 of child abuse to predict adult PTSD symptoms (Binder et al., 2008). Subsequent work has confirmed and extended these findings (Xie et al., 2010)—individuals homozygous for the minor alleles are particularly sensitive to the depressogenic effects of trauma (Zimmermann et al., 2011) and also interact with childhood trauma to increase suicide attempts (Roy et al., 2010), as well as increase aggressive behavior (Bevilacqua et al., 2012). Polymorphisms in FKBP5 also predict stress reactivity (Zannas et al., 2016). Of particular note is our recent observation (Klengel et al., 2013) that this increased risk to develop PTSD, conferred by the functional polymorphism of the FKBP5 gene, which alters chromatin interaction between the transcription start site and long-range enhancers in the gene, does so by an allele-specific childhood trauma-dependent DNA methylation in function 6C response elements of FKBP5 (Figure 2).

Such findings pave the way for the development of novel antidepressant and anxiolytic agents. Indeed, highly selective inhibitors of FKBP51 have now been developed with antidepressant-like properties in mice (Gaali et al., 2015).

The CRHR1 gene polymorphism has also been extensively studied in view of the evidence that this CNS circuit is hyperactive in MDD. Bradley et al. (2008) reported in two separate cohorts of 422 and 199 subjects, respectively, that specific CRHRI polymorphisms interact with child abuse to predict depressive symptoms in adults. These findings have been confirmed (Heim et al., 2009a) and extended to include risk for suicide attempts (Ben-Efraim et al., 2011). Space constraints preclude any additional detailed discussion of other candidate genes that have been identified as mediating risk for mood disorder or PTSD in victims of child abuse, but they include brain-derived neurotrophic factor (BDNF) Val66 Met polymorphism as described by our group (Gatt et al., 2009) in MDD and bipolar disorder (Miller et al., 2013), which is associated with alterations in subgenual cingulate cortex volume (Gerritsen et al., 2012), as well as the oxytocin receptor gene (Myers et al., 2014; McQuaid et al., 2013) in mediating risk for depression and anxiety, the adrenergic β-2 receptor polymorphism for PTSD (Liberzon et al., 2014), the PAC1 receptor (Ressler et al., 2011), and the opioid receptor-like 1 receptor (Andero et al., 2013) for PTSD and the methylenetetrahydrofolate reductase (MTHFR) polymorphism for MDD (Lok et al., 2013).

The emergence of epigenetics in the last decade as an important part of normal physiology and pathophysiology has been one of the major advances in biomedical science. In brief, epigenetics refers to alterations in gene expression not as a consequence of any change in DNA sequence but instead due to DNA methylation or acetylation, post-translational histone modifications, and small non-coding RNAs. Led by several studies of Meaney (2010) and colleagues, and as summarized comprehensively by Kundakovic and Champagne (2015), there is now overwhelming evidence that epigenetic mechanisms are at the forefront of how early life experiences alter DNA expression, frequently over the lifetime of the organism. Early rodent studies unequivocably demonstrated that maternal care alters gene expression by persistent effects on DNA methylation, associated with a particular phenotype. From these early studies, a molecular model has emerged for how child abuse and neglect can result in increased risk for mood and anxiety disorders. The profound effects of child abuse and neglect on epigenetic regulation of the glucocorticoid receptor (NR3C1) has now been demonstrated in postmortem brain tissue of suicide victims (McGowan et al., 2009) and in peripheral blood leucocytes of patients with bipolar disorder, borderline personality disorder, and major depression (Perroud et al., 2011). Indeed, as noted above, epigenetic mechanisms have been shown to mediate the FKBP5 risk allele for PTSD as a consequence of ELS (Klengel et al., 2013). Recently, Mehta et al. (2013) reported that in PTSD patients with similar trauma exposure, gene expression profiles of those with childhood adverse events were almost completely non-overlapping, from those without ELS, largely accounted for by changes in DNA methylation. A recent comprehensive review by Provençal and Binder (2015) described epigenetic effects pre-conception, and in the prenatal and postnatal periods, and the consequences for psychiatric disease vulnerability.

Brain Imaging

The remarkable advances in structural and, to a somewhat less extent, functional brain imaging methods have now been applied to elucidating the long-lasting effects of childhood maltreatment on the CNS. This work is, to some extent, in its early stages—particularly the fMRI and connectivity studies. It is also potentially confounded by a myriad of variables including determining whether the observed effects are due to early life trauma, subsequent psychiatric symptoms/syndromes, or a combination. Moreover, it appears that different forms of childhood maltreatment, not surprisingly, produce distinct effects on particular brain regions and circuits and the heterogeneity of the patient's past and more recent experience represents another important variable. Finally, the nascent field of imaging genetics has revealed the importance of selective polymorphisms of candidate genes as particularly impactful on provocative fMRI studies of, for example, amygdala responsiveness to fearful stimuli. With these caveats in mind, the emerging data are all congruent in demonstrating persistent structural and functional consequences of ELS on specific CNS structures and circuits. This is not surprising given the demonstration in sensory systems of the consequences of early deprivation, i.e., the seminal studies of Hubel and Wiesel, on the visual cortex after experimental manipulations that removed visual stimulation.

The structural MRI studies can largely be divided into two types—testing of specific hypotheses related to the effects of specific types of abuse or neglect on specific brain regions or circuits and a more ahypothetical approach analogous to the GWAS studies in genetics in which the effects of child abuse and neglect on gray and white matter volumes and on connectivity between specific regions are explored.

An example of the former type of study is the Hanson et al. (2012) study of 61 children for whom structural MRI was obtained and executive function was assessed with the clear hypothesis to be tested concerning ELS, executive function and prefrontal cortex volume and connectivity with the anterior cingulate frontal poles. Increased ELS, assessed by the Youth Life Stress Interview, was associated with smaller PFC volumes in both gray and white matter between the anterior cingulate and the frontal poles, a finding also associated with poor executive functioning. Another example is our own study (Heim et al., 2013), which affirmed the hypothesis that victims of sexual abuse would exhibit alterations in the somatosensory area mediating genital sensory signal transduction (BA3), whereas victims of emotional abuse would, in contrast, exhibit atrophy in cortical brain areas mediating emotional processing and self-awareness i.e., anterior cingulate, precuneus, and parahippocampal gyrus (Figures 3 and 4).

The hippocampus has been a major focus of many structural MRI studies for several reasons, including the many reports of volume reduction in patients with major depression, PTSD, and other psychiatric disorders, its role in cognition, an area often reported to be impaired in adult victims of ELS and its rich density of glucocorticoid receptors. In an early study, we reported reduced hippocampal volume in depressed women with a

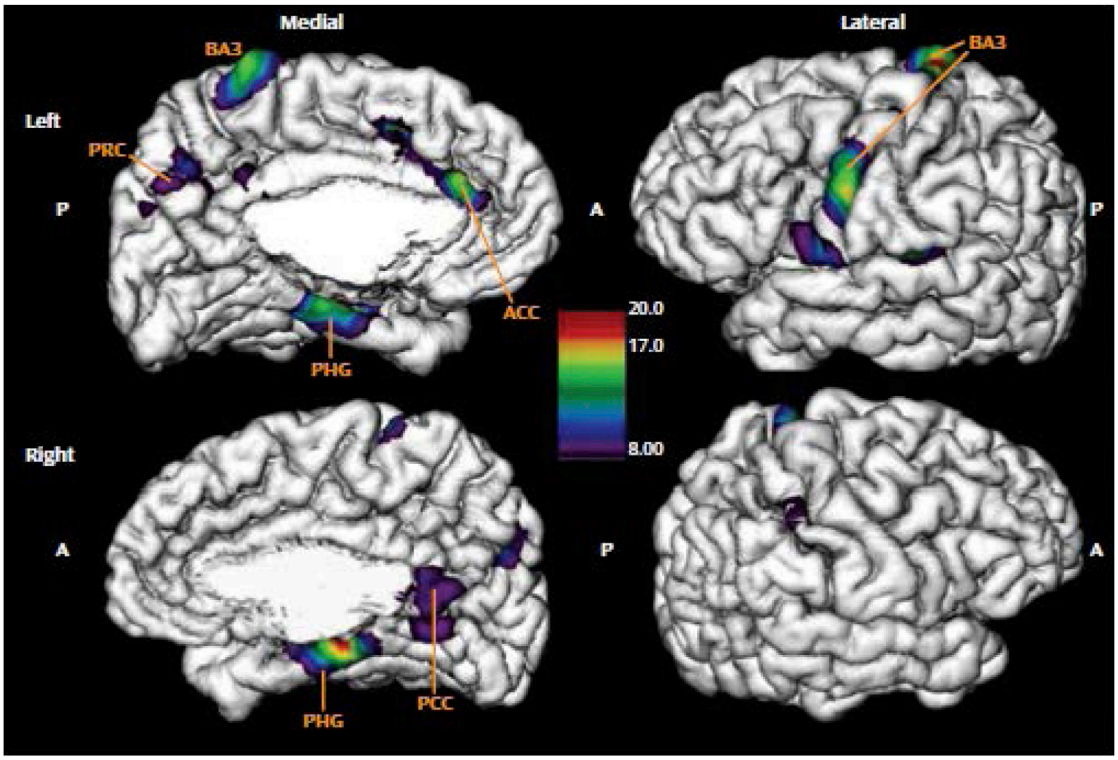

Figure 3. Regression of Childhood Trauma Questionnaire Total Score against Cortical Thickness in Women with and without Childhood Sexual Abuse

Cortical thickness analysis results after regressing Childhood Trauma Questionnaire (CTQ) total score against thickness across the entire cortex. Control variables included age and depression scores. Main effects are seen in the somatosensory cortex in the female genital and mouth area on the left, the parahippocampal gyrus (PHG) bilaterally, the left anterior cingulate cortex (ACC), and the precuneus (PRC) bilaterally. For the precise location of the genital sensory field as identified using fMRI of neural response to stimulation, see Heim et al. (2013). BA3, Brodmann's area 3; PCC, posterior cingulate cortex; A, anterior; p, posterior. The color scale refers to the F values of the linear regression (significance threshold: $F > 4.33$). From Heim et al. (2013). Reprinted with permission from the American Journal of Psychiatry.

history of childhood maltreatment, but not in equally depressed women without ELS (Vythilingam et al., 2002), a finding confirmed by others (Buss et al., 2007; Frodl et al., 2010). Indeed, Opel et al. (2014) recently studied 85 depressed patients and 85 age- and sex-matched healthy controls and using the CTQ and two methods to assess hippocampal volume, concluded that childhood maltreatment and not depression per se was associated with hippocampal atrophy (Figure 5).

The amygdala has been the focus of considerable research in mood and anxiety disorders because of its seminal role in stress responsivity. Consequently, amygdala volume and responsiveness to stressors have been studied in normal volunteers and in individuals exposed to child abuse and neglect. In our study of ELS in non-human primates (Coplan et al., 2014), we observed an increase in amygdala volume in the high ELS (variable foraging demand) group as assessed by MRI. Interestingly, this increase in amygdala volume was associated with elevated CSF CRF concentrations, as well as reduced hippocampal neurogenesis and increased anxiety. Altered amygdala-PFC connectivity also plays a seminal role in the effects of ELS. There is a general consensus that depression is associated with an increased amygdala response to stress, but whether this is due to ELS, depression per se, or a genetic predisposition to mood and anxiety disorders remains unclear. Swartz et al. (2015) studied 232 adolescents 11–15 years and again 2 years later (n = 157). Threat-related amygdala reactivity was associated with a positive family history of depression and/or the severity of stressful life events. These findings suggest that amygdala hyperactivity precedes syndromal mood or anxiety states. Dannlowski et al. (2012) specifically sought to determine the relationship between childhood maltreatment and amygdala responsiveness using the standard emotional face-matching paradigm in 148 healthy subjects. A very strong positive association was found between CTQ scores and amygdala responsiveness and this effect was not confounded by recent life stressors, current depression, or anxiety symptoms or sociodemographic factors (Figure 6).

Not surprisingly, imaging genetic studies have sought to determine whether polymorphisms in candidate genes implicated in mediating the anxiogenic and depressogenic effects of ELS are associated with altered amygdala responses to stress. Indeed, evidence for FKBP5 and mineralocorticoid receptors moderating the effects of ELS on amygdala reactivity have now appeared (White et al., 2012; Bogdan et al., 2012).

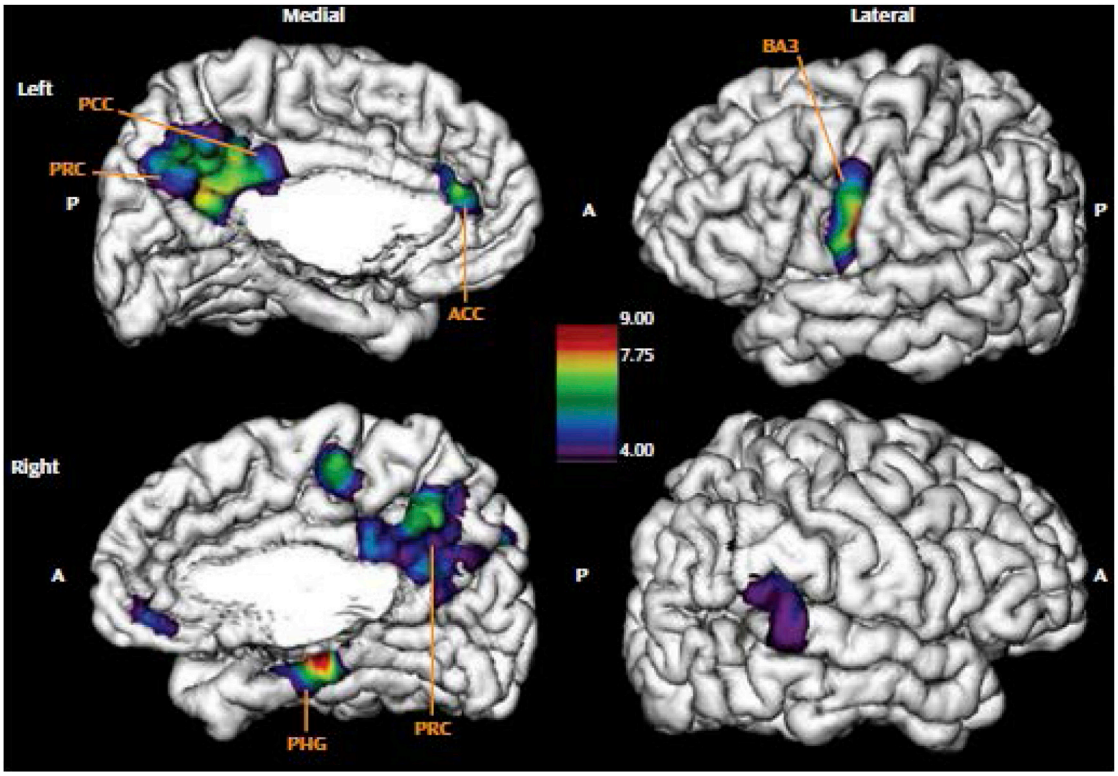

Figure 4. Regression of Childhood Trauma Questionnaire Emotional Abuse Score against Cortical Thickness in Women with and without Childhood Sexual Abuse

Cortical thickness analysis results after regressing Childhood Trauma Questionnaire (CTQ) emotional abuse score against thickness across the entire cortex. Control variables included age, depression, and all other CTQ subscales. Main effects are seen in the left and right precuneus (PRC), left anterior cingulate cortex (ACC), right parahippocampal gyrus (PHG), and left somatosensory cortex in the area of the face. BA3, Brodmann's area 3; PCC, posterior cingulate cortex; A, anterior; p, posterior. The color scale refers to the F values of the linear regression (significance threshold: $F > 4.33$). From Heim et al. (2013). Reprinted with permission from the American Journal of Psychiatry.

Finally, a large number of studies using structural MRI have scrutinized gray and white matter volumes in patients with ELS. Space constraints preclude a comprehensive review of all of the findings. In a study of 256 healthy Australians without psychopathology, ELS was associated with reduced anterior cingulate cortex and caudate nuclei volumes (Cohen et al., 2006). Similar findings were reported by Thomaes et al. (2010) in child abuse-related PTSD, namely reduced anterior cingulate, as well as orbitofrontal and hippocampal volumes. Several additional studies of adolescents and adults without psychopathology (Edmiston et al., 2011), as well as those with substance use disorders (Van Dam et al., 2014) and psychotic disorders (Sheffield et al., 2013) and a recent meta-analysis reported widespread reductions in gray matter volumes in ELS victims in several brain regions including the prefrontal cortex, hippocampus, parahippocampus, stratum, and orbitofrontal cortex (Lim et al., 2014). Teicher et al. (2014) utilized high-resolution T1-weighted MRI in 265 unmedicated 18–25 year olds classified as maltreated (n = 142) or not maltreated (n = 123) to assess network connectivity. Childhood maltreatment was associated with marked changes in the cortical network architecture of young adults with striking effects in the left anterior cingulate, right occipital and left temporal poles, and the right medial frontal gyrus.

Treatment Implications

Although there are fewer datasets available regarding the question as to how child abuse and neglect impacts treatment response, the available evidence suggests that ELS results in a significantly poorer response to both pharmacotherapy and psychotherapy in patients with depression. In an early study of 107 depressed adolescents, Barbe et al., (2004) reported that childhood sexual abuse was a negative predictor of response to cognitive-behavior therapy (CBT). Vitriol et al. (2009) studied 87 women with severe depression and a history of childhood trauma who were randomized to a 3 month course of brief psychodynamic psychotherapy (BPP) or standard supportive psychotherapy. Patients also received psychopharmacological treatment. The BPP, focused on the childhood trauma, was superior in efficacy at 3 and 6 months. Klein et al. (2009) reported that in a study of 808 patients with chronic depression, ELS predicted poor response to antidepressants including sertraline, escitalopram, bupropion, venlafaxine, or mirtazapine, an observation previously reported by Nemeroff et al. (2003) in chronically depressed patients treated with nefazodone. Miniati et al. (2010) reported that a history of emotional or physical abuse in a study of 312 depressed outpatients predicted a significantly longer time to remission and a higher percentage of those patients required

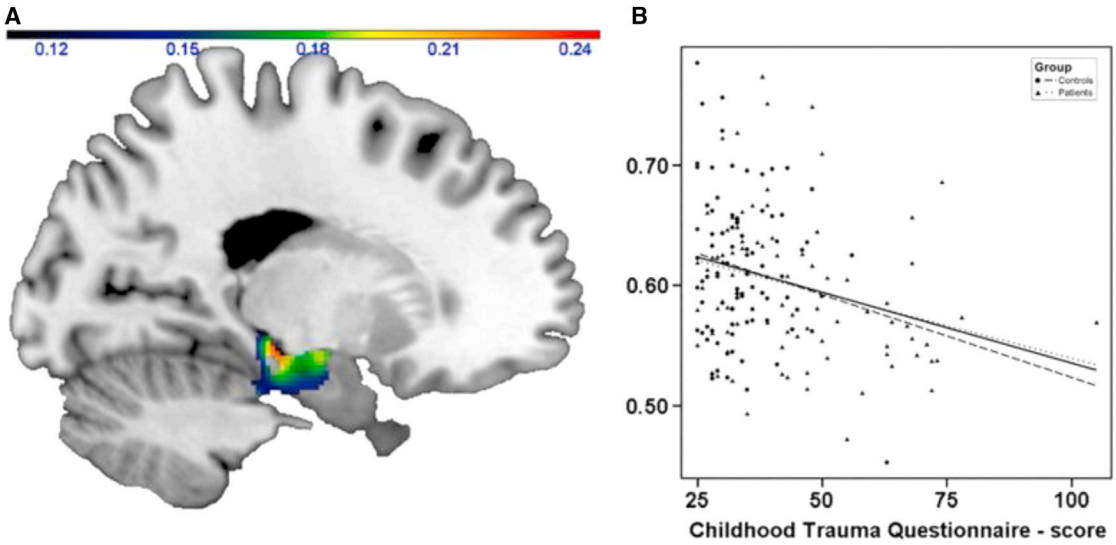

Figure 5. Effect of Childhood Maltreatment on Hippocampal Gray Matter Volume in the Entire Study Sample
(A) Coronal view (x = 0.75, 14) depicting gray matter volume negatively associated with Childhood Trauma Questionnaire (CTQ) scores; color bar, negative correlation coefficient r. (B) Scatter plot depicting gray matter volume at x = 0.75, 14; y = 0.75, 10; z = 0.75, 24 correlated with CTQ scores within the entire sample. Dotted lines: regression slopes of patients and controls separately; continuous line: regression slope in the entire sample. From Opel et al. (2014). Reprinted by permission from Macmillan Publishers.

antidepressant augmentation. More recently, Grote et al. (2012) reported a poorer outcome in depressed pregnant women with a history of childhood trauma treated with Interpersonal Therapy for Depression (IPT) at 3 months post-baseline. However, discordant findings have also appeared. Johnstone et al. (2009) reported that although abuse did not predict antidepressant response in 195 depressed outpatients, having a neglectful father or an overprotective mother did predict a poorer response. This highlights the importance of intra-familial relationships. Nanni et al. (2012) conducted a meta-analysis of ten clinical trials and concluded that childhood maltreatment is associated with significantly poorer response and remission rates to pharmacotherapy, psychotherapy, and the combination (Figure 7). These findings suggest that depression in patients with a history of ELS is a fundamentally distinct biological endophenotype with a corresponding difference in response to conventional treatments.

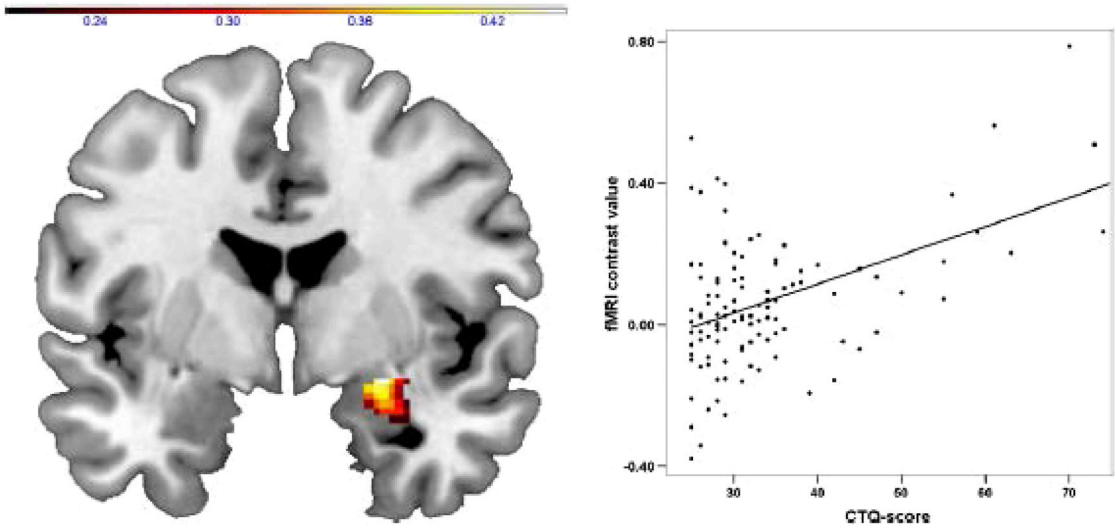

Figure 6. Childhood maltreatment, Childhood Trauma Questionnaire Scores, Is Positively Associated with Right Amygdala Responsiveness to Negative Facial Expressions
Left: coronal view (y = −2) depicting amygdala responsiveness modulated by Childhood Trauma Questionnaire (CTQ) scores. For display reasons, the statistical threshold was set to p < 01, uncorrected. Color bar, correlation coefficient r. Right: scatter plot depicting the positive correlation (r = 0.456, p < .0001) of the mean cluster activation values (left) and CTQ scores. From Dannlowski et al. (2012). Reprinted with permission from Elsevier.

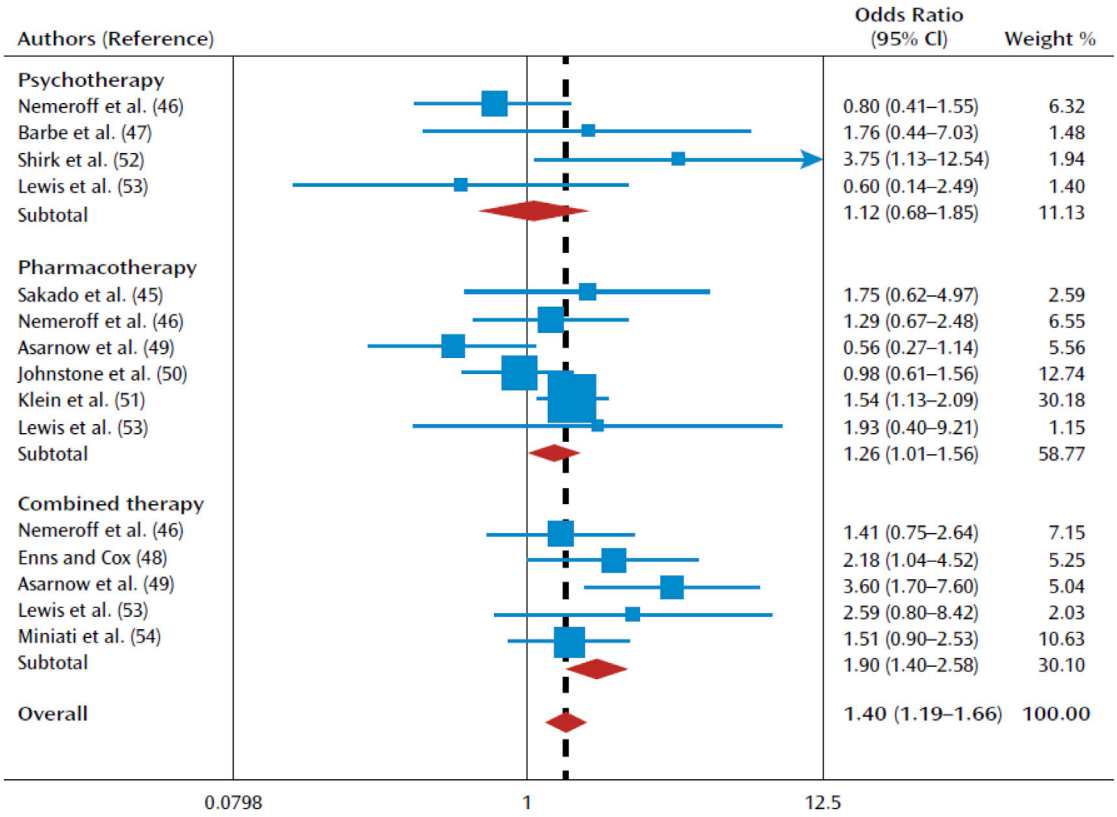

Figure 7. Meta-analysis of Clinical Trials Investigating the Association between Childhood Maltreatment and Treatment Outcome of Depression

Based on the evidence of homogeneous distributions of effect sizes within treatment groups, we present here the results of fixed-effects model meta-analyses for different treatment groups. The overall effect size across treatment groups was estimated with a random-effects model meta-analysis with the following study weights: Nemeroff (psychotherapy): 7.88; Barbe: 2.78; Shirk: 3.49; Lewis (psychotherapy): 2.65; Sakado: 4.36; Nemeroff (pharmacotherapy): 8.03; Asarnow (pharmacotherapy): 7.32; Johnstone: 10.96; Klein: 14.09; Lewis (pharmacotherapy): 2.25; Nemeroff (combined therapy): 8.42; Enns: 7.07; Asarnow (combined therapy): 6.90; Lewis (combined therapy): 3.61; and Miniati: 10.18. The red diamonds show the combined effect sizes for studies concerned with psychotherapy, pharmacotherapy, and combined therapy, as well as the overall effect size of the meta-analysis (top to bottom). From Nanni et al. (2012). Reprinted with permission from the American Journal of Psychiatry.

Very few studies have sought to determine the effects of ELS on treatment response in other psychiatric disorders. Cloitre et al. (2010) studied 104 women with PTSD related to childhood abuse randomly assigned to a treatment combining an initial preparatory phase of Skills Training in Affect and Interpersonal Regulation (STAIR) followed by exposure, compared to supportive counseling followed by cognitive or skills training, followed by supportive counseling. The STAIR + exposure treatment was superior in efficacy. Foa et al. (2013) randomized adolescent girls with sexual abuse-related PTSD to prolonged exposure therapy versus supportive counseling. The prolonged exposure treatment was significantly more effective in PTSD symptom severity and several secondary measures.

Discussion

Instead of rehashing all of the findings described in this Review, the most propitious use of this space is to describe the most pressing unanswered questions related to the neurobiological effects of early life trauma. However, before doing so, it is worth noting that although there is, not surprisingly, some discordant findings in this now vast and ever growing literature, it is striking as to how much concordance there is, in terms of the gene × environment interaction studies, several of the biological marker findings, e.g., inflammation, and perhaps of greatest interest in the studies documenting the devastating effects of child abuse and neglect on the risk and course of mood and anxiety disorders and their negative impact on treatment response. In spite of this considerable progress, many critical questions remain unanswered:

(1) In view of the rapid rate of brain development in the first few years of life, how does the timing of early life adverse events, their magnitude (number of events, severity, and specific chronicity), and type impact on the developing CNS? This speaks to the importance of specific sensitive periods. These variables undoubtedly contribute to some of the discordant findings, most notably HPA axis activity and brain imaging findings. There is emerging data that the type of abuse/neglect has specific neurobiological consequences (Pechtel et al., 2014; Teicher et al., 2006).

(2) What are the precise biological mechanisms that transduce child abuse and neglect into vulnerability to

disease? More specifically, how does early life trauma interact with multiple risk alleles (e.g., FKBP5, CRHR1, BDNF, PAC1, OXTR1, etc.) to increase vulnerability to mood and anxiety disorders?

(3) It is clear that early life trauma is associated with an increased risk, not only for major psychiatric disorders, but for several major medical disorders including ischemic heart disease, diabetes, irritable bowel syndrome, asthma, and others? What are the mechanisms and gene-environment interactions that mediate these effects? Some of these vulnerabilities are likely mediated by engagement of victims of child abuse and neglect in unhealthy behaviors including smoking, illicit drug use, and lack of exercise. However, there is evidence that the risk for these medical disorders in this population cannot be explained by these factors alone. It has been suggested that the increase in inflammatory markers in victims of ELS is a major etiological factor in this process and clearly additional research in this area is needed.

(4) The clear recognition that patients with major depression (and other severe psychiatric syndromes) who have a history of ELS exhibit a very much poorer response to psychotherapy, pharmacotherapy, and their combination further suggests that such individuals possess a unique endophenotype that requires a novel therapeutic strategy. To that end, studies enriched with ELS patients are urgently needed. Moreover, a number of treatment strategies are ready to be explored in this population including CRHR1 antagonists, vasopressin V1b receptor antagonists, and others based on the extant findings. For example, would oxytocin receptor agonists benefit such patients? Should these strategies be employed as monotherapies or as adjunctive treatments?

(5) Would interventions, either psychotherapeutically or pharmacologically, immediately after detection of child abuse/neglect prevent the development of depression, PTSD, and other psychiatric syndromes? Would such treatment prevent the neurobiological consequences of early life trauma?

(6) Are the biological consequences of ELS reversible? More specifically, are the structural and functional imaging alterations, changes in HPA axis activity, increased inflammation, reduction in telomere length, epigenetic marks, and other findings preventable and/or reversible with treatment?

(7) Prevention of child abuse and neglect must become a national and, indeed, international priority. This should take the form of national campaigns and widespread educational fora with special attention to high-risk populations, including teenage parents, victims of child abuse themselves, and others. Implementation of successful prevention programs such as the Nurses Home Visiting Program (Olds et al., 1986, 1997) could likely have a remarkable positive effect.

(8) What are the biological mechanisms that mediate the increased risk for obesity, diabetes, cardiovascular disease, and other medical disorders in patients exposed to childhood maltreatment?

(9) Family history is a well-documented risk for mood and anxiety disorders but has not been well studied as a mediating factor in the effects of child abuse and neglect.

These open questions highlight the complexity of the interactions between environment, experience, and biology and underscore that concerted efforts across medical and research disciplines will be needed to further advance the field. Despite the multiple unknowns and current methodological limitations, I hope that this Review serves to illustrate, at least in brush strokes, how numerous clinical and basic studies have contributed to establish the now widely accepted idea that adverse early life experiences can elicit profound effects on the development and function of the nervous system.

SUPPLEMENTAL INFORMATION

Supplemental Information includes financial disclosures and can be found with this article online at http://dx.doi.org/10.1016/j.neuron.2016.01.019.

ACKNOWLEDGMENTS

C.B.N.'s research is supported by grants from the NIH (MH-094759, DA-031201, and DA-034589). A full disclosure of interests is included in the Supplemental Information.

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