The neurobiological consequences of early stress and childhood maltreatment

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Abstract

Early severe stress and maltreatment produces a cascade of neurobiological events that have the potential to cause enduring changes in brain development. These changes occur on multiple levels, from neurohumoral (especially the hypothalamic–pituitary–adrenal [HPA] axis) to structural and functional. The major structural consequences of early stress include reduced size of the mid-portions of the corpus callosum and attenuated development of the left neocortex, hippocampus, and amygdala. Major functional consequences include increased electrical irritability in limbic structures and reduced functional activity of the cerebellar vermis. There are also gender differences in vulnerability and functional consequences. The neurobiological sequelae of early stress and maltreatment may play a significant role in the emergence of psychiatric disorders during development.

Keywords: Review article; Early adverse experience; Stress; Maltreatment; Child abuse; Trauma; Neglect; Brain development; Corpus callosum; Hippocampus; Amygdala; Limbic system; Glucocorticoid; Cortisol; Hypothalamic pituitary adrenal axis; Laterality; Cerebellum; Vermis; Gender or sex differences; EEG abnormalities; Post-traumatic stress disorder (PTSD); Borderline personality disorder; Mental illness

1. Introduction

Childhood maltreatment is a relatively common adverse experience associated with psychiatric illness and behavioral dysfunction. From the standpoint of neurobiology, exposure to early stress programs the individual to display enhanced stress responsiveness. Early stress also affects important developmental processes, including neurogenesis, synaptic overproduction and pruning, and myelination during specific, sensitive periods. A number of structural and functional neurobiological consequences of early stressful experience have been identified and include reduced corpus callosum size, attenuated development of the left neocortex, hippocampus, and amygdala, enhanced electrical irritability in limbic structures, and reduced functional activity of the cerebellar vermis. Previously, we have discussed how childhood maltreatment, through promoting an alternative neurodevelopmental pathway, may enhance the emergence of psychiatric illness and behavioral dysfunction [1,2]. In this article, we examine the neurobiological consequences of childhood maltreatment reviewing published research and recently completed studies from our laboratory on the electrophysiological, morphological and functional MRI differences between subjects with a history of childhood abuse and healthy controls. These clinical studies reveal important associations but they do not provide information about causality. Hence, relevant preclinical studies are also reviewed that provide evidence for the effects of early stress on the development of these brain regions. Potentially significant gender differences are highlighted. To date, research on the
effects of childhood abuse or early stress on brain development has been predicated on the hypothesis that stressors exert deleterious effects on the neural development. We also summarize in this article an alternative evolutionary hypothesis in which we propose that early stress signals the nascent brain to develop along an alternative pathway adapting itself to survive and reproduce in a malevolent stress-filled world. Clinical research on the association between childhood maltreatment and brain development is a very new area of inquiry. Sample sizes for these pioneering studies are relatively small. Further research will be required to confirm the clinical observations and to begin to test the proposed evolutionary hypothesis.

2. Neurobiological manifestations of early stress and childhood maltreatment

Preclinical studies indicate that brain regions particularly vulnerable to early stressful experience have one or more of the following features: (i) a protracted postnatal development; (ii) a high density of glucocorticoid receptors; and (iii) some degree of postnatal neurogenesis. Section 3 will summarize both preclinical studies that delineate the effects of early stress on specific brain regions and clinical studies demonstrating the effects of childhood maltreatment on the development of these regions in humans.

**Hippocampus.** Preclinical studies have demonstrated the marked vulnerability of the hippocampus to stress [3,4]. This region has a protracted ontogeny, a high density of glucocorticoid receptors ([5,6] but see Ref. [7]), and persistent postnatal neurogenesis [3]. The density of synaptic connections in the hippocampus fluctuates with age [8]. As is true of many regions of the mammalian brain there is a period of postnatal overproduction of axonal and dendritic arborization, synapses and receptors, followed by a postpubertal period of pruning and elimination [9–11]. We have found that early stress seems to prevent the normal peripubertal overproduction of synapses in CA1 and CA3, but does not prevent pruning, which leads to an enduring deficit in overall synaptic density (Andersen et al., unpublished observation).

Clinical studies of the effect of early abuse on the hippocampus have provided mixed results. Bremner et al. [12] and Stein [13] have reported a reduction in left hippocampal volume in adults with childhood trauma and a current diagnosis of PTSD or dissociative identity disorder. Driessen et al. [14] observed a 16% reduction bilaterally in hippocampal volume in adult women with borderline personality disorder (BPD) and a history of childhood abuse. In contrast, De Bellis et al. [15] conducted detailed volumetric analysis of the hippocampus in 44 maltreated children with PTSD and 61 healthy controls, which failed to reveal a significant difference in hippocampal volume. Similarly, Carrion et al. [16] failed to observe any difference in hippocampal volume between abused children and healthy controls. Our complete volumetric analysis of the hippocampus in a non-clinical, community sample of 18 late adolescent—early adults (18–22 years of age) with a history of repeated forced sexual abuse accompanied by fear or terror revealed no differences in left or right hippocampal volume when compared with 19 healthy age matched controls. We found no significant associations between hippocampal volume, psychiatric symptomatology, or memory function (Teicher et al., unpublished observation). Only three subjects met criteria for PTSD at the time of assessment, although three others had a prior history. No subjects had a history of drug use or significant alcohol consumption.

One possible explanation for the discrepancies among these observations is that PTSD exerts a gradual effect on hippocampal morphology, such that the adverse effects are not discernable in children or young adults [17]. Another possibility is that reduced hippocampal size may result from alcohol and substance abuse, which often occur in adults with PTSD or childhood abuse histories [18–20]. De Bellis et al. [21] found that adolescent-onset alcohol abuse was associated with decreased hippocampal volume. A further possibility is that reduced hippocampal size is not a result of childhood abuse but is instead a risk factor for the persistence of PTSD into adulthood. This hypothesis is consistent with the recent twin study of Gilbertson et al. [22] who found that combat veterans with persistent PTSD had smaller hippocampi than combat veterans without PTSD. However, the non-trauma exposed identical twins of the combat veterans with PTSD also had reduced hippocampal volumes.

**Amygdala.** The amygdaloid nuclei are among the most sensitive brain structures for the emergence of kindling [23]. Kindling is a process in which repeated intermittent neuronal stimulation produces greater and greater alteration in the excitability of those neurons, eventually resulting in spontaneous electrical discharges, or seizures [24,25]. Kindling results in long-term alterations in neuronal excitability that can have a major impact on behavioral control [25]. Early stress produces an enduring alteration in the subunit composition of the GABA-A supramolecular complex in the amygdala [26], subsequently reducing the density of both central benzodiazepine receptors and high affinity GABA-A receptors [26,27]. In addition, stress results in increased dopamine levels and attenuated serotonin levels in the amygdala and nucleus accumbens [28–30].

Abnormal amygdala or hippocampal development, combined with a diminished density of central benzodiazepine and high affinity GABA-A receptors or alterations in subunit structure, may lead to the emergence of temporal lobe or limbic seizure-like activity [31–34], or ‘limbic irritability’. We created the limbic system checklist-33 (LSCL-33) to rate the occurrence of symptoms that often emerge during temporal lobe seizures (e.g. perceptual distortions, brief hallucinatory events, motor automatisms,
and dissociative phenomena), hypothesizing that the effect of stress on limbic structures may produce these symptoms in the absence of clinical seizures [35]. We found that adult patients with a self-reported history of physical or sexual abuse had increased LSCL-33 scores that were dramatically elevated in patients with a history of combined abuse, both physical and sexual [35]. Subsequently, we found that psychiatrically hospitalized children with a history of abuse had a two-fold increased incidence of clinically significant EEG abnormalities in the frontotemporal region, which consisted of spikes, sharp waves, or paroxysmal slowing, predominantly in the left hemisphere [36].

Imaging studies of amygdala volume in abuse survivors with PTSD by Bremner et al. [12], Stein [13] and De Bellis et al. [15] failed to reveal any differences in volume in comparison with controls. However, Driessen et al. [14] reported an 8% reduction in bilateral amygdaloid volume in women with a history of childhood abuse and a diagnosis of BPD. We are currently in the process of analyzing amygdala volume in young adults (18–22) years of age recruited from the community with a history of repeated sexual abuse. Results from the first 33 subjects measured revealed an 8.4% reduction in the size of the left amygdala (p < 0.02), which inversely correlated with self-report ratings of depression and irritability (Teicher et al., unpublished observation). Unlike the subjects of the previous studies, our sample demonstrated a low incidence of PTSD or psychopathology more generally, despite their substantial history of abuse. Because amygdala over-activation maybe a critical factor in PTSD [37], a plausible explanation for our observation is that a smaller amygdala may provide protection from the emergence of PTSD following childhood trauma, or may facilitate recovery from PTSD. Further study of the amygdala with respect to early stress and clinical psychopathology is required.

Corpus callosum and hemispheric integration. Myelinated regions such as the corpus callosum are also potentially susceptible to the impacts of early exposure to high levels of stress hormones, which suppress glial cell division critical for myelination [38]. Pioneering studies by Victor Denenberg and colleagues [39] and Juraska and Kopcik [40] showed that the size of the corpus callosum was affected by early experience, and that the effects were gender-dependent. Brief handling (a beneficial stimulus that increases maternal attention [41, 42]) resulted in larger and more regularly shaped corpus callosum in male but not female rats [39]. Rats of both sexes reared in a complex environment had larger and more unmyelinated axons than isolated rats. In females early environment affected the number of myelinated axons, while in males rearing environment affected the diameter of the myelinated axons [40]. Sanchez et al. [43] reported that male Rhesus monkeys raised individually in the laboratory from 2 to 12 months had smaller corpus callosum that monkeys reared in a semi-natural environment. Cynader et al. [44] found that the normal bi-directional transfer of information between the hemispheres through the corpus callosum was affected by early experience in kittens. In the extreme circumstance when visual information only reached one hemisphere communication between the right and left visual cortex became entirely unidirectional [44].

Teicher et al. [45] provided the first indication that childhood trauma may affect the development of the corpus callosum in humans. We found a marked reduction in the middle portions of the corpus callosum in child psychiatric inpatients (especially boys) with a substantiated history of abuse or neglect versus contrast controls. This observation was replicated and extended in an important study by De Bellis et al. [15], who showed that reduced corpus callosum size was the most significant anatomical finding observed in children with a history of abuse and PTSD. Similar to our study, males were more affected than females. More recently, we found in a comparison study of 28 psychiatrically hospitalized abused children, 23 psychiatrically hospitalized children without abuse, and 115 healthy controls, that the corpus callosum of boys was particularly vulnerable to the effects of neglect while the corpus callosum of girls appeared to be more susceptible to the adverse effects of sexual abuse [46]. These results are quite interesting but should be regarded as only preliminary given the relatively small sample of abused children.

Reduced size of the corpus callosum has been associated with diminished communication between the cortical hemispheres [47]. In a probe auditory evoked potential study of laterality and integration of memory, Schiffer et al. [48] demonstrated that adults with a history of childhood trauma have a dramatic difference in hemispheric activation during recollection of a neutral memory and a disturbing memory. Probe auditory evoked potentials provide a convenient means of assessing lateralized hemispheric activity. In this paradigm, subjects listening to bilateral audible clicks while engaged in a cognitive task. Evoked potential responses are recorded and summated to assess the relative degree of right and left hemisphere response (N1-P2 amplitude) over auditory cortex [49]. Papanicolaou et al. [49] has shown that the probe evoked response is attenuated if the hemisphere is actively engaged in another task. Evoked potential assessment of hemispheric activation has been found to be in excellent agreement with the determination of hemispheric activation using regional cerebral blood flow (rCBF) measures [50]. In Schiffer’s study subjects silently but actively engaged in the sequential recall of a neutral work or school memory and then a disturbing childhood memory [48]. Normal controls demonstrated equal probe evoked amplitudes between hemispheres on both tasks. In contrast, the subjects with a history of trauma showed a marked suppression of the evoked potential response over the left hemisphere during recall of the neutral memory, while demonstrating a suppressed evoked potential response over the right hemisphere during recall of the disturbing memory. These results suggest that while normal controls utilized both
hemispheres in both tasks, subjects with a history of childhood trauma show a marked lateralization of hemispheric processing which shifted dramatically between the two tasks.

Cerebellar vermis. A brain region that should also be particularly sensitive to the effects of early maltreatment is the cerebellar vermis, which shows the greatest increase in size of any brain region during the postnatal period [51]. Like the hippocampus, the CV may produce granule cells postnatally [52]. The vermis also has the highest density of glucocorticoid receptors during development, exceeding that of the hippocampus [53], and may be particularly vulnerable to the effects of stress hormones [54,55]. The pioneering social isolation rearing experiments of Harry Harlow provided insight into the role of the cerebellar vermis in emotional development. Monkeys raised in isolation are profoundly affected by their emotional neglect [56,57]. However, studies by Mason and Harlow [58], and Prescott [59], demonstrated that vestibular stimulation from a rocking wire monkey surrogate markedly attenuated the adverse effects of rearing without maternal contact. The vermis is a major target of the vestibular nuclei, and is a primary region for multimodal sensory integration [60].

Isolation reared monkeys with behavioral disturbances have epileptiform spike and sharp-wave activity in their fastigial nucleus (output nucleus of the cerebellar vermis) and hippocampus [61]. This provides an intriguing parallel to the observation of abnormal EEG activity in children or adults with abuse histories [36,62,63]. The cerebellar vermis appears to play a role in the control of epilepsy or limbic activation. Preclinical [64,65] and clinical studies [66,67] have found that electrical stimulation of the vermis suppresses the onset and spread of seizures.

Anderson et al. [68] studied the association between activity in the cerebellar vermis, assessed with T2 relaxometry, and symptoms of limbic irritability. T2 relaxometry provides a non-invasive indication of resting regional cerebral blood volume [69,70]. In this study, we found a substantial correlation between T2 relaxation time and the degree of limbic irritability on the LSCL-33 in both healthy young adult controls and young adults with a history of repeated sexual abuse. However, at any level of limbic symptomatology, there was a marked decrease in relative perfusion of the vermis in the individuals with the abuse history, indicative of a functional impairment in the activity of the cerebellar vermis.

Cerebral cortex. Early stress influences cortical development, including cerebral lateralization and prefrontal maturation. The neocortex develops slowly through cyclic processes of reorganization [71]. Delayed myelination of the corpus callosum enables the hemispheres to develop relatively independently of one another. Of all cortical regions, the prefrontal cortex has the most delayed ontogeny, such that major projections to the prefrontal cortex myelinate primarily between adolescence and the third decade of life [72–74]. The prefrontal cortex also has a relatively high density of glucocorticoid receptors [75], and dopamine projections to the prefrontal cortex are specifically activated by stress [76–78]. The prefrontal cortex, in turn, exerts inhibitory effects on all of the major monoamine projections to subcortical regions and serves to limit their response to stress and exerts inhibitory feedback control on the HPA [75,79].

Early experience exerts marked effect on behavioral and neurochemical lateralization in laboratory animals, which are gender dimorphic [80–83]. Early in development, stress exerts a widespread effect on the neuroaxis [84]. As the prefrontal cortex matures, response to stress becomes more restrictive [84] due to the inhibitory influence of the prefrontal cortex on other regions [79]. We have postulated that early stress activates the developing prefrontal cortex, altering its development and producing precocious maturation but stunted final capacity [85].

Several clinical studies suggest that early maltreatment alters cortical neuronal development in humans. In our study of the effects of childhood trauma on the development of the left versus right hemisphere we used EEG coherence to assess cortical maturation and differentiation [71,86,87]. We found that the left cortex of 15 healthy right-handed pediatric controls was more developed than their right cortex, consistent with is known about the anatomy of the dominant hemisphere [45,88]. However, in 15 pediatric psychiatric inpatients with a documented history of abuse, EEG coherence indicated that their right hemispheres were significantly more developed than their left, even though all the subjects were right-handed. Furthermore, coherence measures indicated that the right hemisphere of abused subjects had developed to the same degree as the right hemisphere of controls, while the left hemisphere of the abused subjects lagged substantially behind the left hemisphere of healthy controls [45,88].

De Bellis et al. [89] used single voxel proton magnetic resonance spectroscopy to measure the relative concentration of N-acetylaspartate (NAA) and creatine in the anterior cingulate cortex as an index of neuronal density and viability [90–92]. Eleven children and adolescents who met DSM-IV criteria for PTSD secondary to maltreatment were compared to 11 healthy matched comparison subjects. There was a significant reduction in the ratio of NAA to creatine in the abused subjects with PTSD, suggesting neuronal loss and dysfunction in this region [89]. Recently, Carrion et al. [16] assessed frontal lobe asymmetry in 24 children (7–14 years of age) with a history of trauma and PTSD symptoms and compared them to historical controls. The abused children had attenuated frontal lobe asymmetry and smaller total brain and cerebral volumes than controls [16]. Overall, these studies suggest that the developing human neocortex may be rather vulnerable to the effects of abuse and maltreatment.
3. Functional manifestations of early stress and childhood maltreatment

What are the functional consequences of stress-related effects on the development of the hippocampus, amygdala, corpus callosum, cerebral cortex and cerebellar vermis? To better understand the potential effects of stress on a functional and behavioral level, we will briefly review the functional aspects of these brain regions.

Hippocampus. The hippocampus is known to play a critical role in encoding and the retrieval of episodic information [93] and has been implicated in the generation of dissociative states [94,95]. The hippocampus and parahippocampal gyrus may also play a significant role in the pathophysiology of generalized anxiety and panic disorders [96–98], which may arise from excess noradrenergic influences from the locus coeruleus on the hippocampus. In addition, the septal area and hippocampus may be crucial components of the behavioral inhibitory system, which acts to arrest ongoing behavior when it is environmentally inappropriate [99]. Serotonergic projections from the median raphe nuclei to the hippocampus presumably play an important role in establishing an individual’s overall level of behavioral inhibition [99]. Therefore, alterations in hippocampal development may subserve the amnestic, dissociative, anxiogenic, and disinhibitory aspects of PTSD. As noted above, early severe stress may be associated with reduced synaptic numbers in the hippocampal region. While this phenomenon may explain some difficulties in memory retrieval associated with traumatic events, Stein’s study [13] suggests that hippocampal alterations may be more associated with dissociative symptomatology than problems with declarative memory.

Amygdala. The amygdala appears to play a crucial role in fear conditioning and in the control of aggressive, oral, and sexual behaviors [100]. Episodic dyscontrol and impulsive violence may be due to irritable foci in the amygdaloid nuclei [100]. This region may also be involved in the formation and recollection of emotional memory, the learning of non-verbal motor patterns, and the triggering of fight-or-flight responses [101]. Excessive amygdaloid activation has been proposed to play a crucial role in the development of PTSD [37,102–105] and in major depression [106].

Temporolimbic seizures. Seizure foci producing partial complex seizures are often localized to limbic structures in the temporal lobe. Both hippocampal sclerosis (characterized by neuronal loss in the dentate nucleus and in the CA1 and CA4 sectors of the hippocampus) and amygdaloid damage have been observed in a significant proportion of patients with TLE [107,108]. One controversial, potential consequence of abnormalities in temporal lobe electrophysiology may be a tendency toward aggressive behavior. For example, Bach-Y-Rita [109], in a study of 130 violent patients with histories of childhood deprivation, parental psychiatric illness, and family violence, found that one half of all patients receiving EEGs showed abnormalities, particularly temporal spikes.

EEG abnormalities may be a significant risk factor for suicidal ideation or attempts. One of the earliest studies on the physiological determinants of suicide reported a strong association between paroxysmal EEG disturbances and suicidal ideation, suicide attempts, and assaultive—destructive behavior [110,111]. The risk of completed suicide is 4–5 times greater in epileptics than among non-epileptic patients and may be 25 times greater in patients with temporal lobe epilepsy [112,113]. As many as one third of all epileptic patients have attempted suicide at some point in their life [114,115], and suicide risk is substantially greater for epileptic patients than patients with other medical disorders producing a comparable degree of handicap or disability [116].

Hemispheric laterality. It is well known that the two cerebral hemispheres are highly specialized in their information processing abilities. It is usually the case that the left hemisphere is specialized for the perception and expression of language and for logical and analytical thought. The left hemisphere is slightly more intricate in its development and is usually dominant in a variety of tasks. In contrast, the right hemisphere plays a role in the perception and expression of emotion, particularly negative or unpleasant emotion [117–121]. Hemispheric dominance and the degree and direction of lateralized function are controlled by genetic, hormonal and experiential factors [82,83,122,123]. The two hemispheres need to interact closely with each other [124] and are connected through the corpus callosum, and the anterior and posterior commissures. Cynader et al. [44] has shown in kittens that the normal bidirectional flow of information from the right and left hemispheres through the corpus callosum can be affected by early experience. In extreme circumstances, the corpus callosum can be so affected that communication becomes entirely unidirectional. We have hypothesized that early stress exerts a strong effect on the degree of right–left hemispheric integration [48,85,125].

The innervation patterns of neurotransmitter systems in the rat and human brain are lateralized [126–128], and the degree and direction of these laterality differences may have important consequences on behavior. For example, we have observed that right > left asymmetries in serotonin and dopamine projections to the amygdala and prefrontal cortex, respectively, were much more highly correlated with levels of anxiety then actual transmitter levels [129]. Early stress alters the development of monoamine neurotransmitters and affects their degree of laterality [28,80].

Cerebellar vermis. Recently, there has been increasing awareness of the critical role played by the cerebellum in attention, language, cognition and affect [60,130–135]. Cognitive, linguistic, social behavioral, and emotional disruptions appear to be the primary clinical manifestation of cerebellar and vermal lesions [132,134,136,137].
Phylogenetic evidence suggests that expansion of the cerebellar hemispheres during the last million years parallels the dramatic evolutionary increase in the size of the frontal lobes [52,138]. The cerebellum, while occupying only 10–20% of brain volume, contains more than half of all neurons in the brain [139].

A convergence of new data suggests that abnormalities in the cerebellar vermis may be involved in a wide array of psychiatric disorders, including: schizophrenia [136, 140–145]; autism [146–148]; ADHD [149–151]; and both bipolar and unipolar depression [152–155]. The cerebellar vermis exerts strong modulatory effects on the locus coeruleus, ventral tegmental area, and substantia nigra, which are cell body regions for the primary norepinephrine and dopamine projections [156–158]. The cerebellum possesses a high density of glucocorticoid receptors [7,159,160] and CRF receptors [161] and appears to play a critical role in mediating response to stress [162–165]. Finally, the cerebellum modulates not only the systemic circulation but also profoundly influences rCBF, and initiates long-term neuroprotection of the brain from ischemic injury independent of its effects on blood flow [166].

Following Harlow’s pioneering experiments demonstrating the deleterious effects of maternal separation and early isolation in monkeys [56,57], Mason and Berkson [58] showed that swinging-wire surrogate mothers greatly diminished the degree of behavioral pathology (e.g. aggression and self-stimulation) seen in adult primates raised in isolation. Prescott [167], based on this observation, suggested that proprioceptive and vestibular stimulation was the protective factor, and Berman [168] found that lesions of the vermis, which receives major input from the locus coeruleus, ventral tegmental area, and substantia nigra, which are cell body regions for the primary norepinephrine and dopamine projections [156–158].

In symptom manifestation [175], and sex differences in rates of major depression [176]. We propose that gender-related differences in the emergence of certain psychiatric disorders, such as BPD, stem from the interaction of three factors: (1) sex differences in the nature of adverse early experience; (2) sexually dimorphic effects of early experience on brain development; and (3) sex differences in brain laterality and hormonal milieu [2]. First, individuals may be more or less likely to experience particular types of maltreatment depending on their sex. In the case of BPD, a major risk factor for its development is sexual abuse by a male non-caretaker [177], and girls are at substantially greater risk for sexual abuse by males [178]. Hence, gender may affect the nature of early adverse experience.

Second, early adverse experience may yield different neurobiological manifestations in the different sexes. For instance, our findings indicate that sexual abuse is associated with diminished corpus callosum size in girls, while diminished corpus callosum size in boys is associated with neglect [46]. Animal studies further indicate that early experience specifically affects the number of corpus callosum axons in females, but predominantly affects only the diameter of corpus callosum axons in males [40]. Hence, there may be marked gender differences in the nature, timing and extent of corpus callosum vulnerability.

Third, there are significant sex differences in brain laterality and hormonal milieu. The degree of hemispheric specialization for language functions differs in a sex-dependent fashion [179–181]. Right-handed males typically show strong left hemisphere specialization while a substantial number of right-handed females demonstrate bilateral representation [180,181]. We suspect that the greater bilateral linguistic capacity and reduced hemispheric dominance in women facilitates switching between right and left hemisphere polarized states, enhancing their capacity for affective instability and splitting in the emergence of BPD. In contrast, we suspect that strong left hemisphere specialization and diminished corpus callosum development in maltreated males serves to further separate thought from affect and social awareness, and may facilitate the development of alexithymia or antisocial personality disorder [182]. There are also significant sex differences with respect to hormonal influences on development. We have postulated that limbic electrical irritability stemming from early abuse is a significant predisposing factor for development of BPD and other psychiatric syndromes [2]. Estrogen exerts a substantial epileptogenic effect on limbic structures, particularly when they are already sensitized [183]. Progesterone and its metabolites inhibit kindling and seizure activity [183] but may produce depression [183]. Testosterone and dihydrotestosterone exerts antiseizure effects through inhibition of glutaminergic NMDA receptors [183]. Hence, sex-related hormonal differences across

4. Sex differences

The relationship between sex differences and early experience is complex, such that the relative contributions of social and biological forces resist clarification. We may examine this issue through the example of BPD. The vast majority of patients diagnosed with BPD are women [172, 173]. This observation has generated a number of conflicting explanations, involving differing cultural expectations of male and female behavior [173,174], gender differences
development may yield substantial effects on the neurobiological manifestations of childhood maltreatment.

5. Reframing the effects of early stress from an evolutionary perspective

Initially, our view was that early stress evoked a cascade of neurohumoral and neurotransmitter effects that produced enduring deleterious alterations in brain structure and function. Within this narrow perspective, we viewed excessive stress as simply a toxic agent that interfered with the normal progression of brain development, yielding a somewhat altered and impaired brain [35,36,48,88,184,185]. Further, we postulated that the neuropsychiatric consequences associated with early exposure to stress were due to this form of developmental insult [2,85,184,185]. This point of view has now been articulated by several other authors [12,15,186–189].

More recently, we have come to re-evaluate this initial view [1,190]. We postulate instead that these alterations in neurodevelopment represent an alternative, adaptive developmental pathway. Stress-induced developmental modifications, triggered by the nature of experience during critical, sensitive stages, are designed to allow the individual to adapt to high levels of life-long stress or deprivation that may be signaled by early stressful experience. If an individual is born into a malevolent and stress-filled world, the manifestations of early stressful experience on later development may serve an adaptive purpose, enabling the individual to mobilize intense fight-flight responses or react aggressively to challenge. On the other hand, these alterations are not optimal for survival and reproductive success in a more benign environment.

In short, we propose that the brain goes through a sensitive period in postnatal life in which exposure to high levels of stress hormones select for an alternative pathway of development that occurs through a cascade of neurobiological effects. That is, exposure to significant stressors during a sensitive developmental period causes the brain to develop along a stress-responsive pathway. Further, we hypothesize that exposure to corticosteroids is a crucial factor in organizing the brain to develop in this manner. Seckel and colleagues [191–193] have also postulated that glucocorticoids exert an organizing effect on development. They have proposed that late prenatal exposure to glucocorticoids produces low-birth weight infants, and exerts an organizing effect on the human fetus to produce an enduring elevation in corticosteroid levels accompanied by a substantially increased risk for the development of cardiovascular disease and type-II diabetes. In our hypothesis, postnatal neglect or other maltreatment serves to elicit a cascade of stress responses that organizes the brain to develop along a specific pathway selected to facilitate reproductive success and survival in a world of deprivation and strife. This pathway, however, is costly as it is associated with an increased risk of developing serious medical and psychiatric disorders and is unnecessary and maladaptive in a more benign environment.

As we stated earlier, the work reviewed here is of a preliminary nature. These findings require further study and replication. Future work should widen its focus to the effects of emotional maltreatment and the impact of corporal punishment in addition to abuse. New imaging techniques, such as diffusion tensor imaging which provides information about white matter structures, will be useful tools in clarifying this area of study. Finally, an important challenge that remains is the study of the impact of treatment and the potential reversibility of altered neurodevelopment.

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