Neurobiological and Behavioral Consequences of Exposure to Childhood Traumatic Stress

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9.1 Introduction

The developing brain is a remarkably plastic and dynamic organ. Although the basic possibilities of what it has the potential to become appears to be set by genetic codes, the unique configuration that evolves for each human being is created though a complex process of communication with the environment. In the best circumstances, this ensures a maximal fit between the demands of the environment and the response possibilities available to the individual. However, under conditions of extreme stress, a cascade of events may be initiated that results in aberrations of brain development and subsequent vulnerability to psychopathology.

Our studies focus on the effects of early childhood maltreatment on the developing brain, and the implications for the emergence of psychiatric disorder. We have proposed that early maltreatment produces a cascade of physiological and neurohumoral responses built on the following five fundamental premises. First, that exposure to stress early in life activates stress response systems, and fundamentally alters their molecular organization to modify their sensitivity and response bias. Second, that exposure of the developing brain to stress hormones exerts consequences by affecting gene expression, myelination, neural morphology, neurogenesis and synaptogenesis. Third, that different brain regions vary in their sensitivity, which depends, in part, upon genetics, timing, rate of development, and density of glucocorticoid receptors. Fourth, that there are enduring functional consequences that include attenuated left hemisphere development, decreased right/left hemisphere integration, increased electrical irritability within the limbic system circuits, and diminished functional activity of the cerebellar vermis. Fifth, that there are associated neuropsychiatric consequences and vulnerabilities, which lead to an enhanced risk for the development of posttraumatic stress disorder (PTSD), depression, borderline personality disorder (BPD), dissociative identity disorder (DID), and substance abuse.
Exposure to Stress in Early Life and Stress Response Systems

A series of seminal studies from the laboratories of Plotsky and Meaney have shown that early stress produces enduring changes in the molecular organization of the stress response systems. In essence, stress response systems are programmed by experience to respond more drastically to events later in life. For instance, we are programmed by adverse early experience to have an enhanced cortisol and norepinephrine/adrenaline response to subsequent stressors. The positive aspect of enhanced stress responding is that it facilitates survival in the face of danger and acute injury. The negative effect is that it initiates a variety of processes that promote chronic pathology such as obesity, type II diabetes, cardiac disease, substance abuse, psychiatric illness and accelerated aging [1].

Is It More Than Just Cortisol?

One puzzle in understanding the impact of stress hormones on human brain development is the absence of known neurodevelopmental consequences of childhood treatment with corticosteroids for asthma or arthritis. We suspect that the adverse effects of early stress on human brain development are not simply a consequence of increased exposure to corticosteroids. The suppressive effects of glucocorticoids on cell proliferation appear to occur indirectly via an NMDA receptor-dependent glutamate excitatory pathway. We hypothesize that stress affects brain development via the concerted activation of multiple pillars of the stress response. Norepinephrine, vasopressin and dopamine are released by stress and they synergistically potentiate the excitatory effects of glutamate on NMDA receptors. Hence, concerted activation of multiple systems may have far greater impact than exogenous administration of a single hormone.

This hypothesis is supported by a landmark study from Caspi et al. [2] who identified a very strong gene \times environmental interaction mediating the effects of exposure to early abuse on development of aggressive behavior. Briefly, males with a functional polymorphism associated with low levels of monoamine oxidase-A (MAO-A) expression were more likely to develop antisocial behavior than abused males with a polymorphism associated with high levels of MAO-A expression. This research was based on the hypothesis that MAO-A develops before MAO-B, and serves during early life to buffer the stress-induced overactivation of monoamine systems. Hence, it is likely that stress-induced overactivation of monoamine systems is a key factor, acting alone or in concert with cortisol release, that links exposure to early trauma to enduring effects on brain or behavioral development.
and serotonin), affects crucial steps in postnatal brain development. For example, research in laboratory animals shows that excess exposure to glucocorticoids in early life is associated with reduced brain weight and DNA content, suppression of postnatal neural mitosis of granule cells in the cerebellum and dentate gyrus, alterations in patterns of myelination, and a reduction in dendritic spines in various brain regions. Animals exposed to excessive glucocorticoids also show social behavior changes and deficits in their ability to perform active avoidance tasks.

In normal development, there is a period characterized by reductions in basal corticosteroid levels called the “stress hyporesponsive period.” This period likely exists to protect the developing brain from the effects of minor stressors. However, certain stressors such as maternal deprivation appear to override this effect.

9.4
Differential Sensitivity to the Effects of Stress in Various Brain Regions

In general, the regions of brain most vulnerable to the effects of early stress are those that develop slowly during the postnatal period and have a high density of glucocorticoid receptors. These include the hippocampus, the corpus callosum, the cerebellar vermis, and the cerebral cortex. Postnatal neurogenesis, evident in

Fig. 9.1.  [author, please provide short caption]
the human hippocampus, and debated in other brain regions, is an additional factor that may lead to stress-sensitivity.

9.4.1 Hippocampus

In preclinical studies of the hippocampus, exposure to stress or corticosteroids can suppress production of new granule cells, and can alter the morphology or even lead to the death of pyramidal cells. Stress also suppresses the production of new granule cells. Imaging studies of adults with a history of childhood abuse have consistently reported hippocampal volume reduction, particularly on the left side.

The hippocampus is known to be critical for memory storage and retrieval and is most likely critical for the generation of dissociative states. Both the hippocampus and the parahippocampal gyrus also appear to play a role in the pathophysiology of generalized anxiety and panic disorder, probably stimulated by noradrenergic activity originating in the locus coeruleus. Lastly, serotonergic projections from the median raphe nuclei to the hippocampus play an important role in establishing an individual's level of overall behavioral inhibition. Thus, alterations in hippocampal development may affect anxiogenic, dissociative, amnestic and disinhibitory aspects of the PTSD response.

The potential effect of childhood abuse on hippocampal volume has led to a consistent inconsistency in the imaging literature. Currently, there are four studies of hippocampal volume in adults with a history of childhood abuse with diagnoses of PTSD, DID, major depression, or BPD [3, 4, 5, 6]. In all of these studies (total \( n = 80 \) abused and 73 healthy controls) there was a significant volume reduction in the hippocampus, which ranged from 5% to 16%, and was left-sided in three studies and bilateral in one. In contrast, there have been three separate studies of hippocampal volume in children with history of abuse and current symptoms of PTSD (total \( n = 96 \) abused and 153 healthy controls) [7, 8, 9]. In none of these studies was there a significant difference in hippocampal volume between abused and control children.

There are several possible explanations. One possibility is that PTSD exerts a very gradual effect on hippocampal morphology so that the adverse effects are not discernable in children or adolescents [10]. Another possibility is that reduced hippocampal size may be an artifact of the high levels of alcohol and substance abuse that often occurs in adults with PTSD. Indeed De Bellis et al. found that adolescent-onset alcohol abuse was associated with decreased hippocampal volume. Another intriguing possibility is that reduced hippocampal size may not be a result of childhood abuse or even a risk factor for the emergence of PTSD, but may be a risk factor for the persistence of PTSD into adulthood.

We have hypothesized that the effects of early experience on the hippocampus may be quite delayed and emerged as a consequence of neuromaturational changes [11] (see sidebar). This possibility was explored by performing volumetric analyses of the hippocampus in a group of 21 young adult (18–22 years of age) collegiate females with a history of repeated childhood sexual abuse (CSA) and 15...
sociodemographically comparable healthy controls. None of the subjects had a history of substance abuse, and CSA subjects were selected without regard to psychiatric diagnosis, and most subjects did not have a current axis I diagnosis. Hence, this population was far healthier than previously reported abuse samples used in imaging studies. Overall, we found that there was an 8% reduction in hippocampal volume, bilaterally. Loss of hippocampal volume in CSA subjects was not related to past or current history of depression or PTSD. This supports the hypothesis that the effects of CSA on hippocampal volume become manifest by late adolescence or early adulthood, and are not an artifact of substance abuse, a gradual consequence of PTSD, or a preexisting abnormality increasing risk for the development or persistence of PTSD.

Does Early Stress Exert a Delayed Effect on the Hippocampus?

Using a rodent model, Andersen and Teicher [11] found that early stress prior to weaning (days 2–20) prevented the expected prepubertal overproduction of synapses in hippocampal regions CA1 and CA3, but does not prevent pruning. This combination of underproduction and normal pruning produced a net deficit in synaptic connections that was not apparent even at puberty (day 40), but was prominent by early adulthood (day 60). This suggests that early life stress may affect a brain region in a way that is not immediately apparent on a gross morphological level, but may become apparent with continued maturation.

9.4.2 Corpus Callosum

Myelinated regions, such as the corpus callosum, also appear to be vulnerable to the effects of early exposure to trauma. Elevated levels of stress hormones suppress the glial cell division critical for myelination. Monkeys reared in isolating environments show attenuation in development and diminished volume in the corpus callosum, which is associated with deficits in learning. In humans, Teicher and colleagues were the first to suggest that alterations in corpus callosum may be associated with exposure to early abuse after finding that the midsagittal area of the corpus callosum was reduced in psychiatrically ill children with a history of abuse or neglect relative to nonabused psychiatrically ill controls (see [12] for review). De Bellis et al. showed more definitively, in two separate studies, that corpus callosum area was reduced in abused children with PTSD relative to healthy controls [8, 9]. Indeed, reduced area of the midportions of the corpus callosum was the most prominent anatomical abnormality found in abused children suffering from PTSD. Subsequent work from our laboratory has shown that corpus callosum abnormalities in girls were more likely to be associated with a history of sexual abuse, whereas in boys, abnormalities were associated with neglect [13].

Reductions in size of corpus callosum appear to affect communications between cerebral hemispheres, possibly leading to an attenuated degree of integration. In adults with a history of trauma, Schiffer et al. [14] showed a marked suppression of [AQ3] electroencephalography (EEG) evoked potential response over the left
hemisphere (indicative of left hemisphere processing) during recall of neutral memories, which shifted dramatically to a marked suppression of evoked responses over the right hemisphere (indicative of right hemisphere activation) during recall of traumatic memories. In adults with no trauma history, both hemispheres were equally involved in processing either type of memory. These results suggest that exposure to early trauma is associated with increased hemispheric laterality and decreased hemispheric integration.

9.4.3 Cerebral Cortex

Maturation in the neocortex occurs slowly, and the delayed myelination of the corpus callosum allows the two hemispheres to develop relatively independently. Language and motor laterization is mostly set by the age of 5 years through a process that begins in utero. During the first few months of life, the right hemisphere shows more dendritic outgrowth than the left, and develops more rapidly. By 5 or 6 months of age, dendritic growth in the left hemisphere surpasses the right, which continues over the next 2 years. Between 3 and 6 years of age, growth in the right hemisphere speeds up and helps provide the components of prosody that peak between 5 and 6 years. Specialization for perception of human faces in the right hemisphere emerges between 8 and 13 years.

In the cortex, the two cerebral hemispheres are specialized to a great degree with respect to information processing. The left hemisphere is usually associated with the perception and expression of language, is logical and analytical, and is somewhat more intricate in its development than the right. The right hemisphere plays a central role in the perception and expression of emotion, particularly negative emotion. The two hemispheres are connected through the corpus callosum, and the anterior and posterior commissures. To ensure optimal functioning, the two hemispheres need to interact closely. Of importance is the fact that the normal bidirectional flow of information through the corpus callosum can be altered by early experience.

The prefrontal cortex has the most delayed ontogeny of any brain region. Myelination of major projections to the prefrontal cortex only begins in adolescence and then continues well into the third decade of life. The prefrontal cortex also has a relatively high density of glucocorticoid receptors. Dopamine projections to this area are specifically activated by stress. In turn, the prefrontal cortex exerts inhibitory effects on all of the major monoamine projections to subcortical regions and serves to limit their response to stress. While stress exerts a widespread effect on the brain regions early in development, we found that this response becomes more restricted as the prefrontal cortex matures. We have theorized that early exposure to stress may produce precocious maturation of the prefrontal cortex, leading to signs of early maturation (e.g., the AQ4 “parentified child”), but may also arrest the development of this region and prevent it from reaching its full adult capacity.

Examination of cortical development in abused children with major psychopathology have reported: (a) increased levels of right hemisphere EEG coherence,
indicative of delayed or attenuated maturation [15]; (b) loss of white matter volume and total volume of the prefrontal cortex [9]; (c) loss of normal left–right asymmetry in the frontal cortex [7]; (d) a reduction in the ratio of N-acetylaspartate to creatine in the anterior cingulate cortex, which is a marker for neuronal loss or dysfunction; and (e) alterations in gray matter volume of the superior temporal gyrus (see [12] for citations).

We have recently analyzed the effects of repeated exposure to sexual abuse on regional gray matter volume (GMV) in young adult females ($n = 23$ abused and 14 healthy controls) using voxel-based morphometry, and compared these results to a group of young adults with exposure to intense parental verbal abuse ($n = 10$ abused and 13 healthy controls). Young adults with a history of repeated sexual abuse had a highly significant and very selective reduction (17%) in GMV of the right visual cortex (Brodmann’s Area 17 and 18). In contrast, young adults with exposure to severe parental verbal abuse had a significant and selective reduction (15%) of GMV in the right superior temporal gyrus (Brodmann’s Area 42). The superior temporal gyrus is believed to be a key anatomical substrate for speech, language and communication. Together these studies strongly suggest that early maltreatment alters neuronal development of the neocortex, and may target primary sensory regions as well as prefrontal regions.

9.4.4 Cerebellar Vermis

The cerebellar vermis (also called arbor vitae or tree of life) is a midline structure that separates and connects the cerebellar hemispheres. It consists of a gray matter region with highly complex lobular architecture and a major white matter fiber tract. Also, residing in the vermis are the intrinsic fastigial nuclei, which provide output projections from the vermis.

Interestingly, the vermis increases in size to a greater degree during the postnatal period than any other brain region and, like the hippocampus, may continue to produce new granule cells after birth. Further, studies comparing brain regions in identical twins indicates that the vermis differs most between twins, suggesting that it may be most susceptible to the effects of early experience. During early postnatal development the vermis in rodents has a higher density of glucocorticoid receptors than the hippocampus, and some studies suggest that in primates it continues to have a higher density.

Studies from our group [16] have shown that increased basal cerebral blood volume in the vermis is associated with symptoms of limbic irritability in both healthy young adult controls and in individuals with abuse history. However, in individuals with an abuse history, there was an overall decrease in relative perfusion (see [12]). It is known that vermal stimulation can be used to suppress seizure activity. It is also known that the vermis is involved in regulation of affect, attention, eye-movement control, and components of sensorimotor integration and postural regulation. Thus, stress-induced functional abnormalities in the vermis may contribute to our understanding of the sequelae of exposure to early trauma.
New Insights into the Cerebellar Vermis as a Stress-Sensitive Region

Our interest in the vermis and its contribution to the effects of early stress followed, in part, from seminal studies conducted by Harlow, Mason and Prescott. Briefly, Harlow showed the critical importance of early experience in his studies in which monkeys were raised in isolation with wire-mesh- or terry-cloth-covered surrogate mothers. Isolation-reared monkeys were often violent and had highly deviant social relationships. Mason found that some of the effects of isolation rearing could be ameliorated if the surrogate mother was on a pivot that provided rocking motions. This led Prescott to write about the importance of the vestibular and proprioceptive systems to normal development, and to theorize about the importance of the cerebellar vermis, which receives major projections from these systems.

Rocking motion clearly has a dramatic effect on emotional state, and this is likely a consequence of vestibular projections to the vermis, which in turn has projections to the limbic system via the fastigial nucleus. Indeed, stimulation of this vermal–fastigial pathway can even suppress seizure activity within the limbic system. The vermis also plays an important role in regulating blood flow to the body and brain, which needs be constantly adjusted to cope with postural change, and this system has projections to the locus coeruleus, substantia nigra and ventral tegmental area, through which it modulates the release of dopamine and norepinephrine.

Abnormalities in the cerebellar vermis have recently been reported to be associated with various psychiatric disorders, including manic depressive illness, schizophrenia, autism and attention deficit/hyperactivity disorder (ADHD). These maladies emerge from genetic and prenatal factors, not childhood mistreatment, but the fact that vermal anomalies seem to sit at the core of so many psychiatric conditions suggests that this region plays a critical role in mental health. Lesions in the cerebellar vermis in childhood appear to be associated with mutism that can last from weeks to months, and sustained symptoms of affective instability.

The vermis appears to be affected by all known drugs of abuse, is also affected by anticonvulsants, mood-stabilizers and lithium, and may be the primary target of the putative antiaddictive drug ibogaine. Taken together, these results suggest that the vermis may mediate a variety of neurobehavioral consequences of early exposure to stress or trauma and that the vermis is an important region for regulation of emotional health.

9.5 Neuropsychiatric Consequences and Psychopathology

As outlined above, exposure to early trauma is associated with diminished development of the left hemisphere, including the neocortex and hippocampus, reduced size of the corpus callosum, and attenuated activity in the cerebellar vermis. These stress-induced alterations result from a cascade of physiological and neurohumoral responses, and then go on, in turn, to create vulnerabilities to a variety of emotional and behavioral pathologies. Included among these are depressive disorders, PTSD, DID, ADHD, BPD and substance abuse.
In our studies, 43% of young adults with a history of abuse had current or recurrent episodes of major depression. In addition to the psychosocial effects of childhood maltreatment, the cascade of neurobiological events described above is likely to shape brain development so as to create vulnerabilities to this disorder. Depression is known to be associated with alterations in the glucocorticoid system, and is often characterized by hypersecretion of CRF, hypercortisolemia, and diminished feedback regulation of cortisol. As described above, exposure to early trauma enhances CRF neuronal activity and sensitizes the brain to the effects of exposure to subsequent stressors. Moreover, exposure to chronic nonspecific stressors may result in downregulation of CRF receptors, dysregulation of cortisol rhythms and the emergence of symptoms of depression.

We have also found in animal studies that exposure to early stress is associated with an enduring reduction in serotonin turnover in the amygdala and nucleus accumbens, which may also predispose to the development of depression. Recently, there has been considerable interest in the possible role of hippocampal neurogenesis in the emergence of depression and response to antidepressants. Stress can markedly suppress hippocampal neurogenesis, and individuals exposed to early stress may be particularly vulnerable if their stress response systems become programmed to respond in an overly robust manner to subsequent stressors.

Caspì and colleagues [17] made the seminal finding that a functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene moderated the influence of stressful life events on risk of developing depression. Individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism, who were exposed to three or more adverse life events exhibited more depressive symptoms, diagnosable depression, and suicidality than individuals homozygous for the long allele. This study shows the potential importance of genetic factors in modulating vulnerability to the effects of stress.

Adults with major depression and history of childhood stress may respond differently to treatments than depressed adults with less stressful childhoods. Nemeroff and colleagues [18] found that depressed subjects with history of early abuse responded preferentially to CBASP, a kind of cognitive–behavioral psychotherapy. Subjects with no early abuse history had a more favorable response to an antidepressant monotherapy, and had their best overall response to a combination of medication plus CBASP.

### 9.5.2 Posttraumatic Stress Disorder

Most children exposed to traumatic events never develop PTSD. Deblinger et al. found that only 6.9% of psychiatrically hospitalized children with physical abuse and 20.7% with sexual abuse history met diagnostic criteria for PTSD. Famularo and colleagues found that only 35% of severely maltreated and...
psychologically traumatized children who were removed from parental custody due to the trauma actually met strict criteria for PTSD. This is not necessarily a matter of resilience. Kiser et al. found that abused children and adolescents who did not develop PTSD actually exhibited more anxiety, depression, externalizing behaviors and more overall problems than children who did. Similarly, Glod et al. found that psychiatrically hospitalized abused children without PTSD had more agitated and disrupted sleep than abused children with PTSD. These findings suggest that the PTSD criteria formulated and validated in adults does not necessarily adequately describe the psychiatric impact of exposure to childhood trauma, and does not necessarily identify those children most adversely affected by trauma.

While exposure to early trauma does not necessarily produce disturbances that fit adult criteria for PTSD, early exposure to trauma primes the brain to be more-susceptible to a PTSD response when later trauma strikes. Enhanced risk may be related to CRF neuronal overactivity. Molecular alterations within the amygdala and locus coeruleus may produce limbic irritability or kindling, induce sympa-

What Constitutes a Childhood Trauma?

Several investigators have recently reported surprisingly strong effects of emotional abuse or neglect on their measures of interest, often eclipsing the effects of sexual abuse. Bernet and colleagues found that the severity of childhood trauma, most notably emotional abuse, was directly related to age of onset, course and severity of major depression in adulthood. DID, which includes multiple personality disorder and related conditions, is often assumed to result from childhood sexual trauma. However, recent studies show that neglect and exposure to emotional maltreatment are much stronger predictors than exposure to sexual abuse. We have recently analyzed results from a sample of 564 young adults (18–22 years of age) regarding childhood experiences and ratings of psychiatric symptoms. Across all of the measures of interest verbal abuse was associated with somewhat larger effect sizes (more deleterious outcomes) than witnessing domestic violence, and substantially greater effect sizes than familial physical abuse. However, witnessing of domestic violence and physical abuse can qualify in DSM-IV as a category A (1) traumatic event necessary for the diagnosis of PTSD, while exposure to verbal abuse cannot. The focus of the traumatic exposure criteria is on threats to the physical integrity of self or others. We wonder, particularly in children, if threats to ones mental integrity and sense of self can be equally traumatizing. Certainly, torture experts know the significance of verbal abuse and other forms of emotional abuse that threaten the mental integrity of an individual, rather than just their physical integrity as enshrined in the A (1) criteria.

Our results are consonant with the observations of Bremner and colleagues, who found that emotional abuse items, such as being often shouted at, appeared to substantially increase risk for PTSD. They suggest that the specific role of emotional abuse has yet to be determined, and, research is needed to evaluate if emotional abuse is causative, or if it contributes to the development of PTSD through association with other forms of abuse.
thetic hyperarousal, enhance fear or startle reactions, augment fight or flight re-
sponses, or promote the emergence of memories associated with the event. Disso-
ciative and amnestic components of PTSD may be facilitated by stress-induced al-
terations in hippocampal functioning.

9.5.3 Attention-Deficit/Hyperactivity Disorder

At least three investigators have now reported that children with a history of abuse also show elevated rates of symptoms of ADHD. In our studies, about 30% of children with severe abuse histories meet criteria for ADHD. However, based on acti-
graph recording we found that children with classical ADHD were about 25% more active than controls while abused children meeting ADHD criteria were only 11% more active than controls [19]. This led us to hypothesize that early abuse can produce symptoms of overactivity and inattention that resemble ADHD, but that this is distinct from the actual disorder. Syndromic overlap may occur if early abuse affects functional activity of the cerebellar vermis, as a reduc-
tion in the size of the cerebellar vermis appears to be the most consistent anatom-
ical abnormality found in ADHD. A second mechanism leading to syndromic over-
lap may be reduced size in the midportions of the corpus callosum, which occurs with early abuse or neglect and has been associated with increased rates of impul-
se behavior.

9.5.4 Borderline Personality Disorder

Pioneering studies by Stone and by Herman and colleagues revealed a strong asso-
ciation between early abuse and the development of BPD. We have theorized at length how different abuse-associated alterations in brain morphology or function can account for the diverse array of symptoms seen in subjects with BPD [20]. Our discoveries that abused patients show diminished right–left hemisphere integra-
tion and a smaller corpus callosum suggest a possible model for the emergence of borderline features in this population. This polarized hemispheric dominance could cause the rapid shifting of emotions from positive in one state to resound-
ingly negative in another. Further, limbic irritability could lead to increased aggres-
sion and, combined with the polarized hemispheric dominance, to an increased risk for suicide and self-destructive behavior. Previous research has shown higher rates of temporal lobe–limbic system dysfunction in borderline patients. Specifi-
cally, patients with BPD have been shown to have a higher incidence of EEG abnor-
malities (38% compared to 13% in dysthymic patients), and increased EEG sharp wave abnormalities (41% compared to 5% in unipolar depressed patients). We have found that children and adolescents with confirmed abuse histories have markedly increased incidence of EEG abnormalities and symptoms suggestive of temporal lobe epilepsy. Self-destructive behavior, mood fluctuations, and susceptibility to
brief psychotic states may also result from stress-induced alteration in dopamine and serotonin levels in the amygdala and nucleus accumbens.

9.5.5 Dissociative Identity Disorder

Another disorder sometimes reported both by patients with a trauma history and by patients with borderline personality disorder is DID. In one report, 23% of subjects with DID showed grossly abnormal EEG results with paroxysmal spike and sharp waves, which is between five and ten times the average rate found in populations of psychiatric ill patients. Another study reported DID patients showed an extreme degree of left hemisphere activation. We propose that DID may arise from an extreme attenuation of hemispheric integration that results in abrupt changes in personality when activation is shifted from the left to the right hemisphere dominant mode. Abnormal hippocampal development may facilitate the generation of dissociative states, which may be triggered or exacerbated by the presence of temporal lobe epilepsy.

9.5.6 Substance Abuse

Individuals who have been exposed to childhood physical and sexual abuse are at risk for a wide range of adjustment difficulties including substance use and abuse, both during adolescence and in later life. Several studies have assessed the relative risk and have identified factors that may influence risk. The association between early maltreatment and alcohol or drug use may manifest at an alarmingly young age. Abuse was associated with more than a 3-fold increase in the odds that alcohol/cigarette experimentation had occurred, and more than a 12-fold increase in the odds that marijuana use or regular drinking had occurred by 10 years of age. For eighth graders, combined sexual and physical abuse was associated with a twofold greater risk of light to moderate drinking and an almost eightfold increase in risk of heavy drinking. Holmes found that early sexual abuse increased by more than 12-fold the risk of early initiation of parenteral drug abuse. Fergusen et al. found that CSA involving attempted/completed intercourse was associated with 2.7-fold increased risk of alcohol abuse/dependence and a 6.6-fold increased risk of substance abuse/dependence.

In our survey of 537 college students, there was an association between limbic irritability ratings and the amount of substance abuse they reported. In fact, limbic irritability ratings correlated more strongly with self-reported rates of substance abuse than did ratings of depression, anxiety or anger–irritability. Limbic irritability ratings were markedly increased by exposure to childhood trauma, and correlated with measures of regional blood flow into the cerebellar vermis [16].

There are compelling reasons to hypothesize that the vermis plays a role in modulating response to addictive drugs. Through its fastigial projections to the ventral tegmental area and the locus coeruleus, the vermis exerts strong effects on the
turnover of dopamine and norepinephrine in the caudate and nucleus accumbens. The vermis receives direct monoamine projections from the midbrain and has dopamine receptors and transporters. Moreover, virtually all drugs of abuse are known to affect the vermis, and the antiaddictive agent, ibogaine, exerts profound effects here. In addition, ADHD is a serious risk factor for the development of substance abuse disorders, and given that the most consistently reported anatomical abnormality in ADHD is reduced vermal size, the vermis is likely involved in regulating substance use and abuse. Together, these findings suggest that early traumatic stress may enhance risk for later substance abuse by fostering limbic irritability and inadequate vermal development. Early stress may also increase risk for substance abuse by sensitizing the dopamine system, and by programming stress response systems to overreact to exposure to subsequent stressors.

9.6 Perspectives

The brain is a very malleable organ engineered to be sculpted by experience. Exposure to severe stress during childhood has probably been a routine occurrence throughout the natural history of Homo sapiens. It seems unlikely that the changes we see in the brain that result from exposure to early stress are simply forms of damage to a brain that has never evolved to cope with early stress. Rather, we postulate exposure to early stress initiates a cascade of responses that cause the brain to follow an alternative developmental pathway that molds the brain to be exquisitely suited to the demands of the environment in which it predicts it will find itself [15]. Hence, the neurobiological responses that we, and others, have observed may be perfectly natural and adaptive modifications in brain structure and functioned triggered by certain forms and levels of stress during key periods of development. In this way, the brain may match its wiring and configuration to the environment that it expects to survive and reproduce in.

If an individual is born into a harsh and aggressive environment, it will be crucial for him to maintain a heightened sense of vigilance that will alert him to the first signs of danger. It will be important for him to have the ability to mobilize an intense fight or flight response and to react quickly to environmental challenge with a strong aggressive response to facilitate survival. Alterations in the amygdala and limbic irritability may enhance the fight or flight response and aggression. Hippocampal alterations and changes in CRF receptor density and neuronal activity may augment corticosteroid responses. Further, hippocampal abnormalities may facilitate the emergence of dissociation as a psychic defensive maneuver against stress. Diminished left hemisphere maturation, reduced corpus callosum size and attenuated left hemisphere integration may substantially increase an individual’s capacity to react rapidly and shift into an angry aggressive state when threatened with danger or loss. Diminished development of the cerebellar vermis may be essential for the maintenance of this state of limbic irritability, hyperar-
ousal and sympathetic activation. Lastly, enduring alterations that occur in messenger RNA levels for vasopressin and oxytocin as consequence of exposure to early stress may predispose to patterns of sexual behavioral and mating practices that foster reproductive success in a malevolent world [15].

However, these alterations may not be optimal for survival in a more benign environment, where impulsive responses, aggressive actions or dissociative states put the individual at a disadvantage in settings where cooperative problem-solving responses are needed. Moreover, the mismatch between brain responsiveness and environmental demands may lead to psychiatric conditions such as depression, PTSD, ADHD, BPD, DID, or problems with substance abuse.

What if the individual were to continue to exist in a hostile, aggressive environment to which his brain is optimally suited? It appears that this alternative developmental pathway would likely permit the individual to survive longer and to compete more successfully than would be possible without these adaptations. However, as McEwen [1] has reported, repeated glucocorticoid and catecholamine mobilization comes with a severe physical cost. Over time, these stress-induced responses create an “allostatic load” that further stresses the system and can accelerate physical disease processes, such as cardiovascular disease, diabetes and obesity. Thus, eventually, the alternative developmental pathway would probably lead to chronic illness and premature death. However, these disease processes emerge slowly, usually long after we have passed though our primary reproductive stage (which is what matters from an evolutionary perspective), and may go unnoticed in circumstances where life expectancies are relatively short.

Thus, although we are exquisitely created to be maximally adapted to the world into which we are born, the fact that we are mobile and that life circumstances may change means that many individuals struggle with neurobiological coping responses that are ill-suited to their realities. For these individuals optimal mental and physical health may require a dramatic change in our neurobiology. To what degree can we achieve this? Efforts to reduce exposure to stressors early in life are one preventative approach. Efforts to attenuate or modulate stress responses following early life exposure to trauma may be another. What remains to be determined is the degree to which early stress-associated alterations in brain structure or function can be reversed, and if so, by what means. It is our next challenge to seek answers to this question.

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