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Long-term effects of childhood abuse on brain and neurobiology

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The "invisible epidemic" of childhood sexual abuse is a major public health problem that is twice as common in women as in men. Women and children are extremely vulnerable to victimization, which makes young girls at especially high risk for victimization by childhood sexual abuse. The sheer magnitude of the problem on a public health scale can be seen by recent nationwide surveys that showed that 16% of women have a history of childhood sexual abuse [1]. This report means that at least one out of every seven women in our society has been the victim of childhood sexual abuse—defined as rape, threat of rape, or unwanted genital fondling—at least once before her eighteenth birthday. Sexual abuse is the most common cause of posttraumatic stress disorder (PTSD) in women, and it affects 10% (approximately 13 million) of women in the country at some time in their lives based on a recent nationwide survey [2]. It also is commonly associated with depression. Little is known about the neurobiology of early childhood abuse.

Early stressors, such as childhood abuse, result in lasting effects on brain systems and circuits that mediate the stress response. These circuits include the hypothalamic-pituitary-adrenal (HPA) axis and norepinephrine systems and brain regions, including the hippocampus, amygdala, and prefrontal cortex [3,4]. Researchers have hypothesized that changes in these circuits and systems lead to symptoms of posttraumatic stress disorder (PTSD) and other stress-related psychiatric disorders, such as depression and dissociative disorders

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[5]. This article reviews the findings in the area of the neurobiology of childhood abuse.

Hypothalamic-pituitary-adrenal axis and early stress

The HPA axis and hippocampus are particularly sensitive to stress. Stress is associated with activation of the HPA axis. Corticotropin-releasing factor (CRF) is released from the hypothalamus, with stimulation of adrenocorticotropin hormone (ACTH) release from the pituitary, which results in glucocorticoid release from the adrenal. This release, in turn, has a negative feedback effect on the axis at the level of the pituitary and central brain sites, including hypothalamus and hippocampus. In addition to its role in triggering the HPA axis, CRF acts centrally to mediate fear-related behaviors [6] and triggers other neurochemical responses to stress, such as the noradrenergic system via the brain stem locus coeruleus [7].

Studies in animals showed that early stress has lasting effects on the HPA axis. During infancy, animals do not demonstrate HPA axis responses to stress; however, infant animals exposed to stressors demonstrate increases in immediate early genes (eg, c-*fos* and nerve growth factor inducible gene) in the paraventricular nucleus of the hypothalamus [8]. These studies demonstrate that a stress-responsive system is present, although it does not invoke the HPA axis at that stage of development. Various early stressors, including maternal deprivation, resulted in increased glucocorticoid response to subsequent stressors [9,10]. Maternally deprived rats had decreased numbers of glucocorticoid receptors, as measured by dexamethasone binding, in the hippocampus, hypothalamus, and frontal cortex [11]. Early postnatal adverse experiences increased hypothalamic CRF mRNA, median eminence CRF content, and stress-induced glucocorticoid [12] and ACTH release [11]. These effects could be mediated by an increase in synthesis of CRH mRNA after stress [13]. In nonhuman primates, adverse early experiences resulted in long-term effects on behaviors and elevated levels of CRF in the cerebrospinal fluid [14]. These observations suggest that early adverse experience permanently affects the HPA axis.

Effects of stress on the hippocampus

The hippocampus, a brain area involved in learning and memory, is particularly sensitive to the effects of stress [15,16]. The hippocampus has an inhibitory effect on the HPA axis [17] so that hippocampal lesions are predicted to result in hypercortisolemia. Psychosocial stress with associated elevated levels of glucocorticoids resulted in decreased dendritic branching and neuronal loss in the CA3 region of the hippocampus [18] and an inhibition of neuronal regeneration [19] in the hippocampus. High levels of glucocorticoids seen with stress also have been associated with deficits in new learning and damage to the hippocampus [20,21].

Brain-derived neurotrophic factor is a recently isolated neuropeptide that has important trophic effects on the hippocampus and other brain regions. Stress resulted in a reduction in brain-derived neurotrophic factor mRNA in the hippocampus. Antidepressant drugs and electroconvulsive therapy increased brain-derived neurotrophic factor levels in the CA3 and CA1 regions of the hippocampus, reversing the effects seen in stress [22]. Serotonin reuptake inhibitors also increase dendritic branching and neurogenesis within the hippocampus [23]. Phenytoin (Dilantin), a medication used to treat epilepsy, inhibits excitatory amino acid transmission and blocks the effects of stress on the hippocampus [24]. These findings have implications for treatment of PTSD and depression and have stimulated clinical trials of these agents to examine their effects on memory and hippocampal volume in PTSD and depression.

The hippocampus demonstrates an unusual capacity for neuronal plasticity and regeneration. In addition to findings previously noted related to the negative effects of stress on neurogenesis, studies recently demonstrated that changes in the environment (eg, social enrichment) can modulate neurogenesis in the dentate gyrus of the hippocampus and slow the normal age-related decline in neurogenesis [25]. These findings may have implications for victims of abuse and emotional neglect.

An animal model that has been applied to studying beneficial early interventions is postnatal handling. Postnatal handling has important effects on the development of behavioral and endocrine responses to stress. For example, daily handling within the first few weeks of life (picking up rat pups and then returning them to their mother) resulted in increased type II glucocorticoid receptor binding, which persisted throughout life. This effect was associated with increased feedback sensitivity to glucocorticoids and reduced glucocorticoid-mediated hippocampal damage in later life [26]. These effects seem to be caused by a type of "stress inoculation" from the mothers' repeated licking of the handled pups [27]. Considered together, these findings suggest that early in the postnatal period a naturally occurring brain plasticity in key neural systems may "program" an organism's biologic response to stressful stimuli.

Noradrenergic systems

Accumulated evidence suggests a relationship between alterations in noradrenergic brain systems and stress [28]. Most noradrenergic cell bodies are located in the locus coeruleus, a nucleus in the dorsal pons region of the brain stem, with a dense network of axons that extend throughout the cerebral cortex and to multiple cortical and subcortical areas, including hippocampus, amygdala, thalamus and hypothalamus, bed nucleus of stria terminalis, nucleus accumbens, and descending projections that synapse at the level of the thoracic spinal cord [29]. Exposure to stressors results in activation of the locus coeruleus, with release of norepinephrine throughout the brain [30]. Acute stressors, such as a cat seeing a dog or another aggressive cat, result in an acute increase in firing of neurons in the locus coeruleus [31], with increased release of norepinephrine in

the hippocampus and medial prefrontal cortex [32]. Chronic stress is associated with potentiated release of norepinephrine in the hippocampus with exposure to subsequent stressors [33].

Early stress is associated with life-long increases in sensitivity of the noradrenergic system [34]. Noradrenergic input stimulates release of CRF from the paraventricular nucleus of the hypothalamus. Maternal separation resulted in an increased release of norepinephrine in the paraventricular nucleus of the hypothalamus. Maternal separation also resulted in a decrease in the alpha-2 autoreceptor of the locus coeruleus [35]. Because the alpha-2 receptor is inhibitory, this effect would be expected to result in an increase in locus coeruleus activity, with increased noradrenergic reactivity. In summary, early stress is associated with lasting increases in noradrenergic responsivity.

Dopaminergic systems

The three major dopaminergic neuronal systems include nigrostriatal (projection from substantia nigra to striatum), mesolimbic (projection from midbrain to nucleus accumbens), and mesocortical/mesoprefrontal (projection from midbrain to prefrontal cortex) systems. Dopamine innervation of the medial prefrontal cortex seems to be particularly vulnerable to even mild and brief stress. Preclinical studies support the fact that acute and chronic stress may have a negative impact on the normal function of the dopaminergic system. Sufficiently low intensity stress (such as that associated with conditioned fear) or brief exposure to stress increases dopamine release and metabolism in the prefrontal cortex in the absence of overt changes in other mesotelencephalic dopamine regions [36]. The medial prefrontal cortex dopamine innervation is preferentially activated by stress compared to mesolimbic and nigrostriatal systems, whereas the mesolimbic dopamine innervation seems to be more sensitive to stress than the striatal dopamine innervation [37]. Intracranial self-stimulation of dopaminergic systems has been used as a model for anhedonia, or decreased pleasure to engage in activities, which suggests that numbing, decreased interest, or being cut off may be related to alterations in dopaminergic systems.

The prefrontal cortex has been suggested to play a role in "working memory" in conjunction with other brain areas, such as hippocampus. A critical range of dopamine turnover is necessary for keeping this "working memory system" active and ready for optimal cognitive functioning [38], a situation that is impaired in situations of extreme or chronic stress [39]. The mesofrontal dopaminergic system also plays a role in emotional responses, selective information processing, and coping with the external world [40,41]. Medial prefrontal cortex has inhibitory inputs to the amygdala that have been hypothesized to play a role in the extinction of fear responses [42]. The area of the effects of early stress on mesofrontal dopamine function is not well developed; however, imaging findings from patients with childhood abuse implicate dysfunction of medial prefrontal cortex.

Serotonin

Most serotonin neurons in the brain area are located in the dorsal raphe (midbrain) with projections to cortical and subcortical areas. Animals exposed to various stressors, including footshock, tail shock, tail pinch, and restraint stress, have produced an increase in serotonin turnover in the medial prefrontal cortex [43,44], nucleus accumbens, amygdala, lateral hypothalamus, and locus coeruleus [45]. Chronic electric shock that produced learned helplessness behavioral deficits was associated with reduced in vivo release of serotonin in frontal cortex [46], which probably reflects a situation in which synthesis is not able to keep pace with demand. In medial prefrontal cortex, the serotonin transport sites showed decreased density in helpless rats as compared to controls but not to nonhelpless rats [47]. Chronic restraint, however, has been shown to result in a decrease in $5HT_{1A}$ binding in the hippocampus [48]. Animals exposed to social stress also had a decrease in binding of $5\text{-}HT_{1A}$ receptors in hippocampus and dentate gyrus and a decrease in $5\text{-}HT_2$ binding in parietal cortex [49].

Preclinical studies have provided evidence that the capability for increased serotonin metabolism during exposure to inescapable stress prevents learned helplessness [50]. Serotonin antagonists produce behavioral deficits that resemble those seen after inescapable shock. Drugs that enhance serotonin neurotransmission (selective serotonin reuptake inhibitors) are effective in reversing the learned helplessness [51]. Preadministration of benzodiazepines or tricyclic antidepressants has been determined to prevent stress-induced decreases in serotonin and the acquisition of behavioral deficits, whereas injection of serotonin (5HT) into the frontal cortex after stress exposure reverses behavioral deficits [52]. In summary, chronic stressors result in long-term alterations in serotonergic function. These findings may have implications for understanding the efficacy of treatment of PTSD with serotonin reuptake inhibitor medications. Current work has not focused on early stressors and serotonergic function. Research is needed in this area.

Endogenous benzodiazepines

Endogenous benzodiazepines also play an important role in stress response and anxiety. Benzodiazepine receptors are present throughout the brain, with the highest concentration in cortical gray matter. Benzodiazepines potentiate and prolong the synaptic actions of the inhibitory neurotransmitter gamma aminobutyric acid (GABA). Central benzodiazepine receptors and GABA receptors are part of the same macromolecular complex. These receptors have distinct binding sites, although they are functionally coupled and regulate each other in an allosteric manner. Agents that block the benzodiazepine receptor increase anxiety, whereas medications such as Valium, which bind to the receptor, result in decreased anxiety. Several studies have shown that chronic stress results in a decrease in benzodiazepine receptor binding in frontal cortex, with some studies

showing a decrease in hippocampus. Studies of early maternal separation also showed reduced benzodiazepine receptor binding in frontal cortex and amygdala and locus coeruleus [51].

Neuropeptides and amino acids

Exposure to stress has marked effects on the activity of a number of other central nervous system (CNS) neuropeptides systems [53]. The neuropeptides that are considered to mediate the response to stress, based on preclinical studies, are CRF, endogenous opioid peptides, neurotensin, somatostatin, cholecystokinin, neuropeptide Y, and others, such as substance P, vasopressin, oxytocin, vasointestinal polypeptide, and thyrotropin-releasing hormone. Neuropeptides account for neurotransmission at a large percentage of synapses in the brain. Because many neuropeptides are hypothalamic pituitary hormones and directly control the secretion of anterior pituitary hormones, they can function as hormones in the hypothalamic-hypophysial portal system and as neurotransmitters in the CNS. Stress is associated with an increase in endogenous opiate release with decreased density of μ-opiate receptors, which may mediate the analgesia associated with stress.

Neurotensin also plays a primary role as a neurotransmitter in the CNS. Neurotensin and its receptor are distributed in hypothalamus, septum, amygdala, and hippocampus, and the receptors are proximal to the cell bodies of origin of the classical neurotransmitters. A role for neurotensin in stress is suggested by the protective effects of centrally administered neurotensin on restraint stress-induced gastric ulcers in rats [54]. Somatostatin (somatotropin release-inhibiting factor) is the major inhibitor of growth hormone secretion. Chronic daily immobilization stress has resulted in an increased basal and stress-induced somatotropin release-inhibiting factor release and decreased growth hormone release. Prolonged increase in somatotropin release-inhibiting factor has been reported to counter an increase in growth hormone releasing factor (GRF) and suppresses growth hormone secretion [55].

Cholecystokinin is an anxiogenic neuropeptide synthesized in the gastrointestinal tract and exerts its effects there and in the brain, which recently has been suggested as a neural substrate for human anxiety. Preclinical data suggest that agonists of cholecystokinin$_B$ produce anxiogenic-like effects, whereas cholecytokinin$_B$ antagonists induce anxiolytic-like responses in several models of anxiety [53]. Neuropeptide Y is one of the most abundant neuropeptides in the brain. It is present in brain stem nuclei, nucleus accumbens, amygdala, hypothalamus, and cerebral cortex. Direct injection of neuropeptide Y in the amygdala has an anxiolytic effect [56] and is protective against restraint stress-induced gastric ulceration in rats [57].

Glutamate plays a role as a neurotransmitter acting via several types of receptors, including the N-methyl-D-aspartate receptor, non–N-methyl-D-aspartate inotropic receptor subtypes, and glutamate receptors. It is involved in long-term synaptic connectivity by initiating long-term potentiation and depression, and it

produces long-lasting changes in synaptic structure and function, neuronal migration, and neuronal viability. Exposure to stress has been shown to increase release of glutamate in the prefrontal cortex and hippocampus [58].

The oxytocin and vasopressin systems play a role in social attachment, which has relevance to early stress. Female subjects that had increased licking and grooming in early life had increased oxytocin receptor binding in the central nucleus of the amygdala, whereas vasopressin binding was increased in male subjects with increased licking and grooming [59].

The neurobiology of early stress in children

The few studies of the effects of early stress on neurobiology conducted in clinical populations of traumatized children generally have been consistent with findings from animal studies. Research in traumatized children has been complicated by issues related to psychiatric diagnosis and assessment of trauma [60]. Some studies have not specifically examined psychiatric diagnosis, whereas other studies have focused on children with trauma and depression and still other studies have focused on children with trauma and PTSD. In the author's view, the issues of diagnosis are important in this area. Not all children develop a psychopathologic condition after exposure to abuse, and the author hypothesizes that stress-induced changes in neurobiology underlie the development of psychiatric symptoms [4,5].

Studies in adults with a history of early childhood abuse and the diagnosis of PTSD have been consistent with long-term changes in HPA axis, hippocampal morphology, and hippocampal-based memory function [4]. An increase in cerebrospinal fluid concentrations of CRF was shown in adult patients with combat-related PTSD compared to healthy controls [61]. Consistent with increased levels of CRF, combat-related PTSD patients had a blunted ACTH response to CRF challenge [62], although adult women with PTSD showed the opposite response [63]. Some studies in adults with chronic PTSD [64], but not others [65], found decreased levels of cortisol in 24-hour urine specimens. Other findings in combat-related PTSD include increased suppression of cortisol with low-dose (0.5 mg) dexamethasone [66] and increased number of glucocorticoid receptors on peripheral lymphocytes [67]. Sexually abused girls (in whom effects of specific psychiatric diagnosis was not examined) had blunted ACTH response to CRF [68], whereas women with childhood abuse-related PTSD had hypercortisolemia [69]. Another study of traumatized children in which the diagnosis of PTSD was established showed increased levels of cortisol measured in 24-hour urine specimens [70]. Emotionally neglected children from a Romanian orphanage had elevated cortisol levels over a diurnal period compared to controls [71]. Maltreated school-aged children with clinical level internalizing problems had elevated cortisol compared to controls [72]. Adult women with a history of childhood abuse showed increased suppression of cortisol with low-dose (0.5 mg) dexamethasone [73]. Preliminary data from Bremner et al in women with PTSD

related to early childhood sexual abuse showed decreased baseline cortisol and increased baseline ACTH based on 24-hour diurnal assessments of plasma, blunted ACTH response to CRF, no difference in cortisol response to ACTH and CRF challenge, and exaggerated cortisol response to stressors (traumatic stressors [74] more than neutral cognitive stressors [75]) relative to controls.

Few studies have examined noradrenergic function related to childhood abuse. Studies have found increased noradrenergic function in adults with PTSD [76]. Studies in children with abuse in which diagnosis of PTSD was not established found increased catecholamines in 24-hour urine specimens (including norepinephrine, epinephrine, and dopamine) [77]. Studies in children with the diagnosis of PTSD are also consistent with elevations in catecholamine [70]. These findings are consistent with animal studies that show increased noradrenergic activity after early stress.

Another important outcome of childhood abuse is depression. Hypercortisolemia is a well-replicated finding in a subgroup of patients with depression. Depressed patients also showed increased rates of nonsuppression on the dexamethasone suppression test (consistent with excessive levels of cortisol in the periphery), elevated CRF levels in cerebrospinal fluid [78], and blunted ACTH response to CRF challenge (consistent with excessive CRF release) [79]. Findings in adolescents with depression are less clear, with a smaller number of patients exhibiting hypercortisolemia, which may be specific to nighttime cortisol levels [80–83]. These discrepant findings may be related to the fact that hypercortisolemia is more common in patients with trauma histories [84]. In a study of ACTH response to CRF challenge in children with depression with and without a history of childhood abuse, children with depression and abuse had an increased ACTH response to CRF challenge compared to children with depression without abuse. These children were in a chaotic environment at the time of the study, which indicates that the ongoing stressor may have played a role in the potentiation of the ACTH response to CRF [85]. Adult women with depression and a history of early childhood abuse had an increased cortisol response to a stressful cognitive challenge relative to controls [86] and a blunted ACTH response to CRF challenge [87].

Childhood abuse also has been associated with changes in central brain function. Several studies have shown alterations in electroencephalogram measures of brain activity in children with various traumas who were not selected for diagnosis compared to healthy children. Approximately half of the children in these studies had a psychiatric diagnosis. Abnormalities were located in the anterior frontal cortex and temporal lobe and were localized to the left hemisphere [88,89].

Studies in adult survivors of childhood abuse also are consistent with abnormalities of the hippocampus. Neuropsychological tests of long-term memory function, such as the verbal Selective Reminding Test and percent retention during paragraph recall on the Wechsler Memory Scale can be used as probes of hippocampal function. Bremner et al [90] found deficits in verbal declarative memory as measured by the Wechsler Memory Scale and verbal Selective Reminding Test in

patients with childhood physical and sexual abuse in comparison to controls. Deficits in verbal memory in the childhood abuse patients were significantly correlated with severity of childhood sexual abuse. Several studies showed similar deficits in verbal declarative memory tasks, including paragraph delayed recall and word list learning, in patients with depression [91] (a common outcome of early abuse), which is reversible with antidepressant treatment [92]. High levels of cortisol seen during depressive episodes were correlated with deficits in memory and cognition, and memory deficits associated with depressive episodes improved when cortisol levels were lowered after successful treatment [93].

Based on the animal studies there was a rationale to measure hippocampal volume in patient with PTSD and depression. An initial study used MRI volumetric techniques to show an 8% reduction in hippocampal volume in patients with combat-related PTSD compared to controls [94]. In a second study that compared 17 patients with PTSD related to early childhood abuse to 17 case-matched controls, there was a 12% reduction in left hippocampal volume ($P < 0.05$) [95]. Two other published studies showed hippocampal volume reduction, one in combat-related PTSD [96] and a second in women with early sexual abuse, most of whom met criteria for PTSD [97]. The author recently found a reduction in bilateral hippocampal volume in women with early childhood sexual abuse and PTSD, relative to abused women without PTSD and non-abused women without PTSD [98]. In a study of children with abuse-related PTSD there was a smaller intracranial and cerebral volume, with no reduction in hippocampal volume [99] and no change in hippocampal volume over a 2-year time period [100]. Adults with new-onset PTSD showed no difference in hippocampal volume relative to controls [101]. MRI studies in adult depression showed smaller hippocampal volume in adults with depression [102]. Recently the author found that smaller left hippocampal volume was only seen in women with depression and a history of childhood abuse but not in depressed women without childhood abuse [103]. These studies suggest that chronicity of PTSD illness may determine hippocampal volume reduction. Similarly, chronicity of depression has been associated with a degree of hippocampal atrophy.

Neuroimaging studies of childhood abuse

Neuroimaging studies have provided a map for the neural circuitry of early childhood abuse [3]. The development of animal models for early stress has provided a model for the neural circuitry of the lasting effects of childhood abuse (Fig. 1). These studies have implicated the hippocampus, a brain area involved in new learning and memory. The medial prefrontal cortex also has been implicated in the stress response. Medial prefrontal cortex in the human consists of several related areas, including orbitofrontal cortex, anterior cingulate (area 25-subcallosal gyrus, and area 32), and anterior prefrontal cortex (area 9). Lesions of the medial prefrontal cortex in animals resulted in a failure of inhibition of amygdala function [42]. Given the role of the amygdala in fear response, these findings led

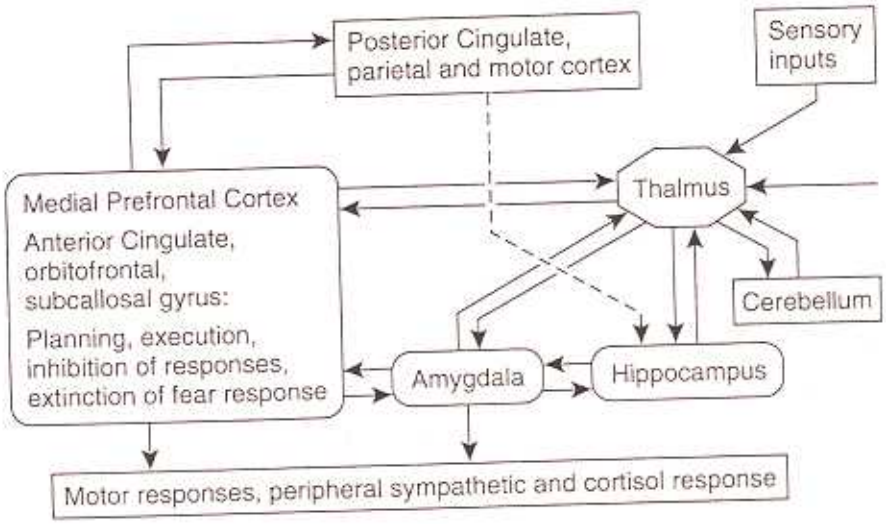

Fig. 1. Neural circuitry of childhood abuse-related PTSD. Stress has detrimental effects on the hippocampus, which plays a role in learning and memory. The hippocampus has connections with the amygdala, which plays a critical role in fear acquisition. The medial prefrontal cortex is hypothesized to inhibit amygdale function during the extinction of fear, and dysfunction in this region plays a role in a failure of extinction in PTSD.

to the hypothesis that medial prefrontal cortex mediates extinction of fear responses. Human subjects with lesions of the prefrontal cortex showed dysfunction of normal emotions and an inability to relate in social situations that require correct interpretation of the emotional expressions of others [104]. These findings suggest that dysfunction of medial prefrontal cortex may play a role in pathologic emotions that sometimes follow exposure to extreme stressors, such as childhood sexual abuse. Other regions, including posterior cingulate, parietal and motor cortex, and cerebellum, are functionally related to anterolateral prefrontal cortex (superior and middle frontal gyri), which mediates visuospatial processing that is critical to survival in life-threatening situations. The author has hypothesized that the excessive vigilance seen in persons with PTSD is associated with increased demands on brain areas involved in visuospatial aspects of memory function and planning of response to potentially threatening stimuli.

In a study that followed up on findings of reduced hippocampal volume in abuse-related PTSD, the author measured hippocampal function and structure in childhood abuse-related PTSD. Hippocampal function during the performance of hippocampal-based verbal declarative memory tasks was measured using positron emission tomography (PET) and [^{15}O]H $_2$O in women with a history of early childhood sexual abuse with and without PTSD. Hippocampal volume was measured with MRI in three subject groups: women with early childhood sexual abuse and PTSD, women with early abuse without PTSD, and women without early abuse or PTSD. A failure of hippocampal activation ($F = 14.94$; $df = 1.20$; $P < 0.001$) and 16% smaller volume of the hippocampus was seen in women with abuse and PTSD compared to women with abuse without PTSD (Fig. 2). Abused women with PTSD also had a 19% smaller hippocampal volume relative to women without abuse or PTSD [98]. These results are consistent with the

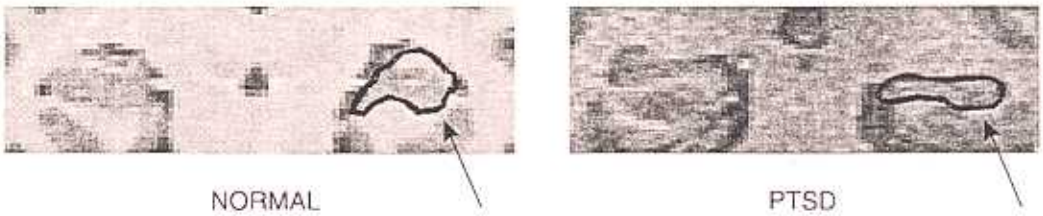

Fig. 2. MRI of the hippopcampus in a normal individual and a patient with PTSD. There is a visible reduction in hippocampal volume in the patient with PTSD.

hypothesis that early abuse with associated PTSD results in deficits in hippocampal function and structure, possibly through damage to hippocampal neurons.

Functional neuroimaging studies have been performed in childhood abuse-related PTSD to map out the neural circuitry of abuse-related PTSD. These studies are consistent with dysfunction in a network of related brain areas, including medial prefrontal cortex and hippocampus. The author measured brain blood flow with PET and [^{15}O]H $_2$O during exposure to personalized scripts of childhood sexual abuse. Twenty-two women with a history of childhood sexual abuse underwent injection of $H_2[^{15}O]$ followed by PET imaging of the brain while listening to neutral and traumatic (personalized childhood sexual abuse events) scripts. Brain blood flow during exposure to traumatic versus neutral scripts was compared between sexually abused women with and without PTSD. Memories of childhood sexual abuse were associated with greater increases in blood flow in portions of anterior prefrontal cortex (superior and middle frontal gyri: areas 6 and 9), posterior cingulate (area 31), and motor cortex in sexually abused women with PTSD compared to sexually abused women without PTSD. Abuse memories were associated with alterations in blood flow in medial prefrontal cortex, decreased blood flow in subcallosal gyrus area 25, and a failure of activation in anterior cingulated area 32. There was also decreased blood flow in right hippocampus, fusiform/inferior temporal gyrus, supramarginal gyrus, and visual association cortex in women with PTSD relative to women without PTSD [105].

- This study replicated findings of decreased function in medial prefrontal cortex and increased function in posterior cingulate in combat-related PTSD during exposure to combat-related slides and sounds [106]. Shin et al [107] studied eight women with childhood sexual abuse and PTSD and eight women with abuse without PTSD using PET during exposure to script-driven imagery of childhood abuse. The authors found increases in orbitofrontal cortex and anterior temporal pole in both groups of subjects, with greater increases in these areas in the PTSD group. Patients with PTSD showed a relative failure of anterior cingulate activation compared to controls. The patients with PTSD (but not controls) showed decreased blood flow in anteromedial portions of prefrontal cortex and left inferior frontal gyrus.

These studies have relied on specific traumatic cues to activate personalized traumatic memories of childhood abuse and PTSD symptoms in patients with PTSD. Another method to probe neural circuits in PTSD is to assess neural

correlates of retrieval of emotionally valenced declarative memory. In this type of paradigm, instead of using a traditional declarative memory task, such as retrieval of word pairs such as "gold-west," which has been the standard of memory research for several decades, words with emotional valence, such as "stench-fear," are used [108]. Although there has been relatively little research on retrieval of emotionally valenced words, it is of interest from the standpoint of PTSD as a method for activating neural pathways relevant to trauma and memory. If patients with PTSD demonstrate a pattern of brain activation during retrieval of emotionally valenced declarative memory that is similar to that seen during exposure to other tasks that stimulate brain networks mediating PTSD symptoms, such as exposure to personalized scripts of childhood trauma or exposure to trauma-related pictures and sounds, then that would provide convergent evidence for dysfunction of a specific neural circuit in the processing of emotional memory in PTSD.

The author recently used PET in the examination of neural correlates of retrieval of emotionally valenced declarative memory in 10 women with a history of childhood sexual abuse and the diagnosis of PTSD and 11 women without abuse or PTSD. The author hypothesized that retrieval of emotionally valenced words would result in an altered pattern of brain activation in patients with PTSD similar to that seen in previous studies of exposure to cues of personalized traumatic memories. Specifically the author hypothesized that retrieval of emotionally valenced words in patients with PTSD relative to patients without PTSD would result in decreased blood flow in medial prefrontal cortex (subcallosal gyrus and other parts of anterior cingulate), hippocampus, and fusiform gyrus/inferior temporal cortex, with increased blood flow in posterior cingulate, motor and parietal cortex, and dorsolateral prefrontal cortex. During retrieval of emotionally valenced word pairs, patients with PTSD showed greater decreases in blood flow in an extensive area that included orbitofrontal cortex, anterior cingulate, and medial prefrontal cortex (Brodmann's areas 25, 32, 9), left hippocampus, and fusiform gyrus/inferior temporal gyrus, with increased activation in posterior cingulate, left inferior parietal cortex, left middle frontal gyrus, and visual association and motor cortex. There were no differences in patterns of brain activation during retrieval of neutral word pairs between patients and controls. These findings were similar to previous imaging studies in PTSD from the author's group using trauma-specific stimuli for symptom provocation, adding further supportive evidence for a dysfunctional network of brain areas involved in memory, including hippocampus, medial prefrontal cortex and cingulate, in PTSD (Bremner et al, unpublished data, 2002).

Other studies have used MRI to examine structural changes in other brain areas besides the hippocampus in childhood abuse. One study used single voxel proton magnetic resonance spectroscopy to measure relative concentration of N-acetylaspartate and creatinine (a marker of neuronal viability) in the anterior cingulate of 11 children with maltreatment-related PTSD and 11 controls. The authors found a reduction in the ratio of N-acetylaspartate to creatinine in PTSD relative to controls [109]. Studies also have found smaller brain size and smaller size of the corpus callosum in children with abuse and PTSD relative to controls

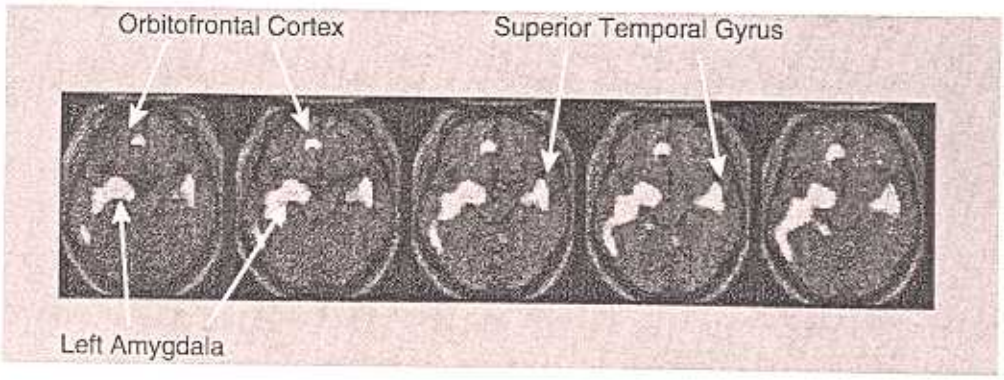

Fig. 3. Areas of increased blood flow with fear acquisition versus control in PTSD. There was increased blood flow in the bilateral amygdala in the control with PTSD. Although controls also had amygdala activation, contrasts showed greater activation in the left amygdala compared to controls. White areas represent areas of relatively greater increase in blood flow with paired versus unpaired US-CS in women with PTSD alone. $Z < 3.09$; $P < 0.001$.

[99]. In a study of abused children in whom diagnosis was not specified, there was an increase in T2 relaxation time in the cerebellar vermis, which suggested dysfunction in this brain region [110].

The author developed a method for assessing neural correlates of fear conditioning in abuse-related PTSD. In the fear-conditioning paradigm, pairing of a light with a shock leads to a fear reaction to the light alone, an effect mediated by the amygdala. Women with early childhood sexual abuse-related PTSD (n = 8) and women without abuse or PTSD (n = 11) underwent measurement of psychophysiologic responding and PET measurement of cerebral blood flow during habituation, acquisition, and extinction of conditioned fear. During habituation, subjects were exposed to a blue square on a screen, 4 seconds in duration, for eight times at regular intervals over 90 seconds. During acquisition, exposure to the blue square was paired with an electric shock

Table 1
Published functional and structural imaging studies in abuse-related PTSD methods

Authors	Study population	Sample size	Control group	Sample size	Imaging methods	Active condition	Control
Bremner [106]	Women with abuse-related PTSD	10	Abused women without PTSD	12	PET O-15 function	Abuse scripts	Neutral scripts
Shin [107]	Women with abuse-related PTSD	8	Abused women without PTSD	8	PET O-15 function	Abuse scripts	Neutral scripts
Bremner [95]	Women with abuse-related PTSD	16	Healthy women	16	MRI structure	N/A	
Stein [97]	Abused women, mixed diagnoses	21	Healthy women	21	MRI structure	N/A	
De Bellis [99]	Abused children with PTSD	44	Healthy children	61	MRI structure	N/A	
Anderson [110]	Abused children, mixed diagnoses	8	Healthy children	16	MRI T2 relaxation	N/A	

Table 2
A summary of results of published functional imaging studies of the neural circuitry of abuse-related PTSD

Authors	Hippocampus	Parahippocam	Amygdala	mPFC AC (32/24/25)	mPFC OBF (11)	Anteromedial (9,10)	Dorsolateral PFC (MFG 6,46)	Dorsolateral PFC (IFG)	Posterior cingulate
Bremner 99b	↓R	↑		↓	↓	↑	↑	↓R	↑
Shin 99		↓L		↓	↑	↓	↓	↓	↓
Bremner 97	↓L		NC						
Stein 97	↓L								
De Bellis 99	NC								
Anderson 02									

Abbreviations: Inf, inferior; Sup, superior; PFC, prefrontal cortex; OBF, orbitofrontal cortex; ILP, inferior parietal lobule; SMG, supramarginal gyrus.

Table 2 (*continued*)

Authors	Sup. temp (22	Inf. temp fusiform	Insula	Motor cortex	Senso cortex	Visual associal	Parietal (IPL)	Parietal SMG (40)	Cerebellum	Corpus callosum	Whole brain
Bremner 99b	↑	↓R	↓R	↑	↓	↓		↓R	↓		
Shin 99	↑						↓R				
Bremner 97											
Stein 97											
De Bellis 99										↓	↓
Anderson 02									↓		

to the forearm. With extinction, subjects were again exposed to the blue squares without shock. On a second day, subjects went through the same procedure with random electric shocks (an equal number as on day 1) during the "acquisition" phase. The control paradigm was identical to the acquisition of conditioned fear paradigm, with the exception that subjects underwent scanning during sensitization trials instead of acquisition of conditioned fear trials for scans three and four. Subjects underwent sensitization trials, which involved exposure to conditioned stimulus (blue square) and random electric shocks not paired with the conditioned stimulus. Patients with PTSD and control subjects showed activation of the amygdala with acquisition of conditioned fear (pairing of unconditional stimulus [US] and conditional stimulus [CS]) relative to the control condition ($P < 0.005$). Greater left amygdala activation during fear conditioning was seen in patients with PTSD relative to comparison subjects (Fig. 3). Extinction of fear responses was associated with decreased function in the orbitofrontal and medial prefrontal cortex (including subcallosal gyrus, BA 25, and anterior cingulate BA 32) in the patients with PTSD but not in the controls. Extinction of fear responding was associated with a greater decrease in medial prefrontal function (anterior cingulate, BA 25,32,24) in patients with PTSD compared to controls. These findings are consistent with increased amygdala function in PTSD.

In summary, several studies have examined the effects of childhood abuse on the brain (Tables 1, 2). Two studies found smaller hippocampal volume in adults with early abuse and PTSD, whereas one study in children with abuse and PTSD did not find such an effect. One functional imaging study found a failure of hippocampal activation with verbal declarative memory encoding tasks in abuse-related PTSD. Differences in the results of the studies may be related to the chronicity of abuse and PTSD. One study in children with PTSD did find smaller brain volume and corpus callosum volume with increased ventricular size, whereas a study in children who were not selected for diagnosis found alterations in the cerebellum. Studies in adults have not found smaller brain volume. Functional imaging studies of the neural circuitry of PTSD in adults with PTSD related to early abuse found reduced function in anterior cingulate/medial prefrontal cortex, with some studies finding reduced hippocampal function. A single spectroscopy study in children with abuse-related PTSD was consistent with decreased neuronal integrity in anterior cingulate. These studies are consistent with alterations in medial prefrontal cortex and hippocampus being associated with early childhood abuse and the diagnosis of PTSD. Future studies are required to assess the longitudinal course of brain changes related to abuse and to examine other aspects of the effects of childhood abuse on the brain.

Summary

Early stress is associated with long-term alterations in brain circuits and systems that mediate the stress response. Early stressors have lasting effects on

the HPA axis and norepinephrine systems. Other brain systems that are involved include benzodiazepine, opiate, dopaminergic, and various neuropeptide systems. These neurochemical systems modulate function in brain regions, including the hippocampus, amygdala, and prefrontal cortex. Long-term alterations in these brain regions are hypothesized to play a role in the maintenance of PTSD, depression, and other psychiatric symptoms after childhood abuse.

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