Neuroimaging in Posttraumatic Stress Disorder and Other Stress-related Disorders

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Synopsis

Traumatic stress has a broad range of effects on the brain. Brain areas implicated in the stress response include the amygdala, hippocampus, and prefrontal cortex. Studies in patients with posttraumatic stress disorder (PTSD) and other psychiatric disorders related to stress have replicated findings in animal studies by finding alterations in these brain areas. Brain regions implicated in PTSD also play an important role in memory function, highlighting the important interplay between memory and the traumatic stress response. Abnormalities in these brain areas are hypothesized to underlie symptoms of PTSD and other stress-related psychiatric disorders.

EFFECTS OF TRAUMATIC STRESS ON THE INDIVIDUAL

Traumatic stressors including childhood abuse can lead to posttraumatic stress disorder (PTSD), as well as depression [1,2], substance abuse [3,4], dissociative disorders [5], personality disorders [6,7], and health problems [8]. For many trauma victims, PTSD, which affects about 8% of Americans at some time in their lives [3], may be a life-long problem [9]. However, the development of effective treatments is limited by gaps in knowledge about the underlying neurobiological mechanisms that mediate symptoms of trauma related disorders like PTSD. Until twelve years ago, no brain imaging studies had been performed in patients with PTSD or other stress-related psychiatric disorders. The past decade has seen an explosion of research using brain imaging to assess the effects of traumatic stress on the brain [10]. These studies have implicated the amygdala, hippocampus, and medial prefrontal cortex (including anterior cingulate) in PTSD and other stress related psychiatric disorders. This chapter reviews brain imaging studies looking at the effects of traumatic stress on the brain, and integrates them with basic science findings on the neurosciences of stress.

NEURAL CIRCUITS OF PTSD

PTSD is characterized by specific symptoms, including intrusive thoughts, hyperarousal, flashbacks, nightmares, and sleep disturbances, changes in memory and concentration, and startle responses. Symptoms of PTSD are hypothesized to represent the behavioral manifestation of stress-induced changes in brain structure and function. Stress results in acute and chronic changes in neurochemical systems and specific brain regions, which result in long-term changes in brain “circuits” involved in the stress response [11–14]. Brain regions that are...
Preclinical and clinical studies have shown alterations in memory function following traumatic stress [15] as well as changes in a circuit of brain areas, including hippocampus, amygdala, and medial prefrontal cortex, that mediate alterations in memory [16]. The hippocampus, which is involved in verbal declarative memory, is very sensitive to the effects of stress. Stress in animals has been associated with damage to neurons in the CA3 region of the hippocampus (which may be mediated by hypercortisolemia, decreased brain derived neurotrophic factor, and/or elevated glutamate levels) and inhibition of neurogenesis [17–22].

Antidepressant treatments have been shown to block the effects of stress and to promote neurogenesis [20,23–26]. Animal studies have demonstrated several agents with potentially beneficial effects on stress-induced hippocampal damage. It has been found that phenytoin blocks the effects of stress on the hippocampus, probably through modulation of excitatory amino acid induced neurotoxicity. Other agents, including tianeptine, dihydroepiandosterone (DHEA), and fluoxetine have similar effects [23,24,26,28–33]. These medications may share a common mechanism of action through upregulation of cAMP response element binding protein (CREB), which leads to regulation of expression of specific target genes involved in structural modeling of the hippocampus. Such treatment effects on brain-derived neurotrophic factor (BDNF) and its receptor trkB mRNA can have long-term effects on brain structure and function. There is new evidence that neurogenesis is necessary for the behavioral effects of antidepressants [34,35], although this continues to be a source of debate [32,36].

In addition to the hippocampus, other brain structures have been implicated in a neural circuitry of stress including the amygdala and prefrontal cortex. The amygdala is involved in memory for the emotional valence of events, and plays a critical role in the acquisition of fear responses [37]. The medial prefrontal cortex includes the anterior cingulate gyrus [Brodmann’s area (BA) 32] and subcallosal gyrus (BA 25) as well as the orbitofrontal cortex. Lesion studies demonstrated that the medial prefrontal cortex modulates emotional responsiveness through inhibition of amygdala function [38]. Studies show that neurons of the medial prefrontal cortex play an active role in inhibition of fear responses that are mediated by the amygdala [39,40]. Conditioned fear responses are extinguished following repeated exposure to the conditioned stimulus (in the absence of the unconditioned aversive, e.g., electric shock) stimulus. This inhibition appears to be mediated by medial prefrontal cortical inhibition of amygdala responsiveness. Animal studies also have showed that early stress is associated with a decrease in branching of neurons in the medial prefrontal cortex [41]. The insula also plays a critical role in integrating the physiological stress response.

**CHANGES IN BRAIN STRUCTURE IN PTSD AND STRESS RELATED DISORDERS**

Studies have demonstrated several consistent changes in cognition and brain structure associated with PTSD, including verbal declarative memory deficits [15,42–44]. Patients with PTSD secondary to combat [45–49] and childhood abuse [50,51] have been reported to have deficits in verbal declarative memory function based on neuropsychological testing. Using a variety of measures [including the Wechsler Memory Scale (WMS), the visual and verbal components of the Selective Reminding Test, the Auditory Verbal Learning Test, Paired Associate Recall, the California Verbal New Learning Test, and the Rivermead Behavioral Memory Test], investigators have found specific deficits in verbal declarative memory function with a relative sparing of visual memory and IQ [45–49,51–60]. These studies have been conducted in patients with PTSD related to a variety of etiologies including Vietnam combat.
Returning Iraq soldiers were shown to have diminished verbal memory performance compared to their pre-deployment baselines, with greater verbal memory deficits in veterans with high levels of PTSD symptoms [63]. These findings suggest that traumas such as early abuse with associated PTSD result in deficits in verbal declarative memory.

Several studies of PTSD have showed changes in hippocampal volume associated with the disorder. We first demonstrated this in Vietnam veterans with PTSD, who had an 8% reduction in right hippocampal volume based on MRI relative to controls matched for a variety of factors including alcohol abuse and education (p<.05); smaller volume was correlated with deficits in verbal declarative memory function as measured by the WMS (Figure 1) [64]. A second study from our group showed a 12% reduction in mean left hippocampal volume in 17 patients with childhood abuse-related PTSD compared to 17 case-matched controls; this group difference was significant after controlling for confounding factors [65]. Smaller hippocampal volume has been shown to be specific to PTSD within the anxiety disorders, and has not been demonstrated in panic disorder [66]. Gurvits et al. [67] showed bilateral hippocampal volume reductions in combat-related PTSD compared to combat veterans without PTSD and normal controls. Combat severity was correlated with volume reduction. Stein et al. [68] found a 5% reduction in left hippocampal volume. Other studies of PTSD also have found smaller hippocampal volume and/or reductions in N-acetylaspartate (NAA), a marker of neuronal integrity [69–82]. We have reported smaller hippocampal volume in PTSD subjects compared to trauma-exposed non-PTSD subjects [70] while other investigators have observed reductions in both trauma-exposed non-PTSD and trauma-exposed PTSD relative to healthy comparison subjects [83]. Studies in childhood [84–86] PTSD did not find hippocampal volume reduction, although reduced NAA was found in medial prefrontal cortex in childhood PTSD [87]. Although some studies of new onset or recent PTSD have not found changes in hippocampal volume [88,89], others have showed reductions [90]. In a recent meta-analysis, we pooled data from all of the published studies and found smaller hippocampal volume for both the left and the right sides, equally in adult men and women with chronic PTSD, and no change in children [91]. Another recent meta-analysis had similar findings [92]. More recent studies of holocaust survivors with PTSD did not find a reduction in hippocampal volume [93] although subjects who developed PTSD in response to an initial trauma had smaller hippocampal volume compared to those who developed PTSD after repeated trauma, suggesting that a small hippocampal volume may impart vulnerability [94]. Several studies have shown that PTSD patients have deficits in hippocampal activation while performing a verbal declarative memory task [70,75] or a virtual water maze task [95]. Both hippocampal atrophy and hippocampal-based memory deficits reversed with treatment with the selective serotonin reuptake inhibitor (SSRI), paroxetine, which has been shown to promote hippocampal neurogenesis in preclinical studies [96]. We hypothesize that stress-induced hippocampal dysfunction may mediate many of the symptoms of PTSD which are related to memory dysregulation, including both explicit memory deficits as well as fragmentation of memory in abuse survivors. It is unclear at the current time whether these changes are specific to PTSD, whether certain common environmental events (e.g., stress) in different disorders lead to similar brain changes, or whether common genetic traits lead to similar outcomes.

Several studies have found smaller anterior cingulate volumes based on MRI measurements in PTSD [97–99], including women with abuse and PTSD [91]. One study found a reduction in the ratio of NAA to creatinine (Cr) measured with magnetic resonance spectroscopy [79], while another found a decrease in gray matter density [100]. An important question is whether these effects are reversible with treatment. Other findings related to volumetrics include smaller volumes of the corpus callosum in neglected children [101] and adults with PTSD [102]. One
study showed smaller volumes of the insula with voxel-based morphometry [103]. A study in twins found smaller volumes of the cavum septum pellucidum [104].

FUNCTIONAL NEUROIMAGING STUDIES IN PTSD

Imaging studies of brain function in PTSD implicate dysfunction of the medial prefrontal cortex, amygdala, and hippocampus [13,105–111]. Methodologies used in imaging studies of PTSD are outlined in Table 1 and a summary of findings by author and brain region appears in Table 2. Studies of resting cerebral blood flow or metabolism with positron emission tomography (PET) and single photon emission tomography (SPECT) have showed alterations at rest in the medial prefrontal, temporal, and dorsolateral prefrontal cortices, cerebellum, and amygdala [112–114]. Stimulation of the noradrenergic system with yohimbine resulted in a failure of activation in the dorsolateral prefrontal, temporal, parietal and orbitofrontal cortex, and decreased function in the hippocampus [114]. Exposure to traumatic reminders in the form of traumatic slides and/or sounds or traumatic scripts have been associated with an increase in PTSD symptoms, decreased cerebral blood flow and/or a failure of activation in the medial prefrontal cortex/anterior cingulate, including BA 25, or subcallosal gyrus, BA 32 and BA 24, as measured with PET, SPECT or functional MRI (fMRI) [115–129] (Figure 2). Other findings in studies of traumatic reminder exposure include decreased function in the hippocampus [119], thalamus [118,120], visual association cortex [118,119,123,124], parietal cortex [119, 122,123,130,131], and inferior frontal gyrus [118,119,122,123,127,130,131], and increased function in the amygdala [121,124,130], posterior cingulate [117,119,120,123], and parahippocampal gyrus [117,119,121]. Shin and colleagues [124], found a correlation between increased amygdala function and decreased medial prefrontal function with traumatic reminders indicating that a failure of inhibition of the amygdala by the medial prefrontal cortex could account for increased PTSD symptoms with traumatic reminders. Other studies have found increased amygdala and parahippocampal function and decreased medial prefrontal function during the performance of an attention task [125], and increased amygdala function at rest [113], during a working memory task [132], during recall of traumatic words [133], and with exposure to masked fearful faces [134,135], overt fearful faces [126], traumatic sounds [121,136], and traumatic scripts [130].

Several studies have examined neural correlates of cognitive tasks in PTSD. During working memory tasks patients showed decreased inferior frontal [137] and parietal function [132, 137]. Retrieval of emotionally valenced words [138] (e.g., “rape-mutilate”) in women with PTSD from early abuse resulted in decreases in blood flow in an extensive area that included orbitofrontal cortex, anterior cingulate, and medial prefrontal cortex (BA 9, 25, and 32), 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 [139]. Another study found a failure of medial prefrontal cortical/anterior cingulate activation and decreased visual association and parietal cortex function during performance of the emotional Stroop task (i.e., naming the color of a word such as “rape”) in women with PTSD who were abused relative to abused women without PTSD [140]. Shin and colleagues [127] showed increased posterior cingulate and parahippocampal gyrus and decreased medial prefrontal and dorsolateral prefrontal during an emotional “counting” Stroop paradigm with fMRI.

Declarative memory tasks have been used as specific probes of hippocampal function in PTSD. We measured brain activation with a paragraph encoding task in conjunction with $^{15}$O-water PET measurements of cerebral blood flow. Women with PTSD and a history of abuse showed a failure of hippocampal activation during the memory task relative to control subjects [70]. Women with PTSD who had been abused also had smaller hippocampal volumes as measured with MRI relative to both abused women without PTSD and non-abused, non-PTSD women.
The failure of hippocampal activation was significant after controlling for differences in hippocampal volume as well as accuracy of encoding. Shin and colleagues [75] also found a failure of hippocampal activation with a memory stem completion task in PTSD.

Although multiple studies have used symptom provocation with traumatic scripts or similar designs, little has been done in the area of fear conditioning in PTSD. To that end, we studied women with a history of severe childhood sexual abuse and the diagnosis of current PTSD (N=8) and women without childhood abuse or PTSD (N=11). All subjects underwent PET measurements of cerebral blood flow and psychophysiological measurements of heart rate and skin conductance during habituation, acquisition and extinction conditions, on a single day, with scanning during a control condition on another day separated by one week from the active condition. During habituation, subjects were repeatedly exposed to a blue square on a screen [conditioned stimulus (CS)], during active fear acquisition exposure to the blue square (CS) was paired with an electric shock to the forearm [unconditioned stimulus (UCS)], and during extinction subjects were again exposed to the blue squares (CS) without shock (“active” extinction). On a second day, subjects went through the same procedure with electric shocks delivered randomly when the blue square was not present (unpaired CS-UCS). Acquisition of fear was associated with increased skin conductance responses to CS exposure during the active versus the control conditions in all subjects. There was increased skin conductance response for PTSD during the first CS-UCS presentation. Extinction of fear was associated with increased skin conductance responses to CS exposure during the active versus the control conditions in all subjects. When PTSD and non-PTSD subjects were examined separately, skin conductance response levels were significantly elevated in non-PTSD subjects undergoing extinction following the active compared to the control condition during session one. PTSD subjects showed activation of the bilateral amygdala during fear acquisition compared to the control condition (Figure 3). Non-PTSD subjects showed an area of activation in the region of the left amygdala. When PTSD subjects and control subjects were directly compared, PTSD subjects showed greater activation of the left amygdala during the fear conditioning condition (pairing of US and CS) relative to the random shock control than healthy women. Other areas that showed increased activation with fear acquisition in PTSD included bilateral superior temporal gyrus (BA 22), cerebellum, bilateral inferior frontal gyrus (BA 44, 45) and posterior cingulate (BA 24). Fear acquisition was associated with decreased function in medial prefrontal cortex, visual association cortex, and medial temporal cortex, inferior parietal lobule function, and other areas. 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), visual association cortex, and other areas in the PTSD subjects, but not in the controls. Amygdala blood flow with fear acquisition was negatively correlated with medial prefrontal blood flow with fear extinction (increased blood flow in amygdala correlated with decreased blood flow in medial prefrontal cortex) in all subjects (r = -0.48; p<.05). Increased amygdala blood flow with fear acquisition was positively correlated with PTSD (r=0.45), anxiety (r=0.44) and dissociative (r=0.80) symptom levels in PTSD (but not non-PTSD) subjects. There was a negative correlation between medial prefrontal blood flow during extinction and anxiety as measured with the Panic Attack Symptom Scale (PASS) during extinction in the PTSD group only, which was significant after correction for multiple comparisons (r = -0.90; p=0.006) [141]. This study was consistent with increased amygdala function with fear acquisition, and decreased medial prefrontal (anterior cingulate) function during extinction in PTSD. This is consistent with the model of an overactive amygdala and a failure of the medial prefrontal cortex to extinguish the amygdala when the acute threat is no longer present.

We have tested the hypothesis that patients with trauma-related psychiatric disorders, which have been described as “trauma spectrum” disorders [12], share in common abnormalities in specific brain areas, including the amygdala, medial prefrontal cortex, and hippocampus. These
disorders include abuse-related PTSD, depression associated with early abuse, borderline personality disorder (BPD) associated with early abuse, and Dissociative Identity Disorder (DID) with early abuse. To test this hypothesis, we exposed traumatized women with and without BPD to the stress of a script outlining a personally upsetting abandonment scene in conjunction with PET imaging of the brain [142]. Women with BPD exhibited a relative failure of medial prefrontal activation during abandonment scripts compared to non-BPD subjects. Women with BPD and abuse had increased psychophysiological responses to abandonment scripts relative to trauma scripts, while women with PTSD and abuse had the opposite pattern [143], indicating differential responses in these two disorders in spite of the common exposure to early abuse. Studies of structural MRI have also shown smaller hippocampal volume across several trauma spectrum disorders, including abuse-related PTSD [65,70], DID with early abuse [144], BPD with early abuse [145,146], and depression with early abuse [147].

Few studies have involved imaging of receptors in the brain in PTSD. This study used single photon emission computed tomography (SPECT) to show a decrease in benzodiazepine receptor binding in the frontal cortex in combat-related PTSD.

BPD is associated with childhood sexual abuse in 52% to 71% of cases [148]. BPD is associated feelings of internal emptiness and fear of abandonment and is often accompanied by self-destructive behaviors such as self-cutting. There are large overlaps in the neurobiological correlates of BPD and PTSD [149,150]. Similar to PTSD, BPD is associated with reductions in hippocampal volume [80,145,146] and a functional dysregulation of the prefrontal-limbic axis [142,149,151–156], which may underlie the affective dysregulation seen in both BPD and PTSD.

In summary, these studies are consistent with dysfunction of a circuit involving the medial prefrontal cortex, dorsolateral prefrontal cortex, hippocampus, and amygdala, in PTSD patients that we hypothesize underlie symptoms of PTSD and other stress-related psychiatric conditions.

**EFFECTS OF PHARMACOTHERAPY ON BRAIN FUNCTION AND STRUCTURE IN PTSD**

We have begun to assess the effects of pharmacotherapy on brain structure and function in PTSD, and recently have evaluated the effects of phenytoin on brain structure and function [157]. Studies in animals have showed that phenytoin, which is used in the treatment of epilepsy and is known to modulate glutamatergic function, blocks the effects of stress on the hippocampus [27]. We studied 9 patients with PTSD in an open-label function before and after treatment with phenytoin. Phenytoin resulted in significant improvement in PTSD symptoms [158], and further resulted in increases in both right hippocampal volume and right hemisphere volume [159]. These findings indicate that phenytoin has an effect on symptoms as well as brain structure in PTSD patients. In a second study, patients with PTSD were shown to have an increase in hippocampal volume and memory function with paroxetine [96], and a decrease in cortisol responsiveness to a stressful cognitive challenge [160]. One case report showed decreased inferior frontal, prefrontal, and insula blood flow measured with PET in response to war-related sounds. These changes normalized with successful treatment with the SSRI fluoxetine [161]. Another study assessed resting cerebral blood flow with SPECT Tc-99m HMPAO before and after 8 weeks of open-label treatment with the SSRI citalopram in 11 adult patients with PTSD. Treatment resulted in a decrease in left medial temporal cortex blood flow; decreased PTSD symptoms as measured with the Clinician-Administered PTSD Scale (CAPS) were correlated with increased function in the medial prefrontal cortex [162].
SUMMARY AND CONCLUSIONS

Traumatic stress has a broad range of effects on brain function. Brain areas implicated in the stress response include the amygdala, hippocampus, and prefrontal cortex. These regions also play a critical role in memory, highlighting the important interplay between memory and the traumatic stress response. Preclinical studies show that stress affects these brain areas. Furthermore, antidepressants have effects on the hippocampus that counteract the effects of stress. In fact, promotion of nerve growth (neurogenesis) in the hippocampus may be central to the efficacy of the antidepressants. Studies in patients with PTSD show alterations in brain areas implicated in animal studies, including the amygdala, hippocampus, and prefrontal cortex. Increased amygdala activation with acquisition of fear responses, and a failure of the medial prefrontal cortex to properly mediate extinction, are hypothesized to underlie symptoms of PTSD. Treatments that are efficacious for PTSD show a promotion of neurogenesis in animal studies, as well as promotion of memory and increased hippocampal volume in PTSD. Future studies are needed to assess neural mechanisms in treatment response in PTSD. In addition, studies need to move beyond assessments of brain function and to examine areas such as neurotransmitter binding and changes in brain chemicals (e.g., with MR spectroscopy).

LITERATURE CITED


Neuroimaging Clin N Am. Author manuscript; available in PMC 2009 August 19.


Figure 1.
Hippocampal volume on MRI in PTSD. Smaller hippocampal volume in a representative patient with PTSD (right) relative to a non PTSD subject (left).
Figure 2. Medial prefrontal dysfunction in PTSD. There was a failure of medial prefrontal activation in a group of combat veterans with PTSD compared to combat veterans without PTSD during exposure to traumatic combat related slides and sounds (yellow area in prefrontal cortex)
Figure 3.
Amygdala activation during acquisition of fear learning in PTSD. There was an increase in amygdala activation during acquisition of conditioned fear learning in women with PTSD related to early childhood abuse. Yellow areas in the amygdala show areas of increased blood flow during acquisition of fear learning in the group of women with abuse-related PTSD as a group. Women with abuse-related PTSD had greater increases of amygdala activation during fear learning than women without PTSD.
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