Alterations in Brain Structure and Function Associated With Post-traumatic Stress Disorder

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Neuroimaging studies in post-traumatic stress disorder (PTSD) have revealed changes in brain structure and function that may underlie the symptoms of PTSD. Two brain areas that have been consistently implicated in PTSD include the hippocampus and prefrontal cortex. Several studies showed that PTSD is associated with reduction in volume of the hippocampus, a brain area involved in learning and memory, as measured with magnetic resonance imaging (MRI). Positron emission tomography (PET) studies showed dysfunction of medial and orbital prefrontal cortex during PTSD symptom provocation and in response to traumatic reminders. Decreased benzodiazepine receptor binding was found in the medial prefrontal cortex as measured with neuroimaging in PTSD. The hippocampus and medial prefrontal cortex play important roles in memory and emotional regulation, and dysfunction in these areas may underlie memory deficits and pathological emotions in PTSD.

Recent studies have shown great promise in applying neuroimaging to the study of posttraumatic stress disorder (PTSD). These studies have shown alterations in structure and function of the hippocampus, a subcortical brain area that mediates declarative memory function, and the medial prefrontal cortex, which is involved in emotional regulation. Changes in these brain areas may underlie symptoms of PTSD.

Neuroimaging studies provide information about the structure and function of the brain. The first radiological studies in trauma patients used pneumoencephalography, which involves the injection of air into the cerebrospinal space, and imaging with the use of simple radiographs. Magnetic resonance imaging (MRI) is a technologically more advanced method of imaging than radiograph-based techniques such as pneumoencephalography. MRI uses a powerful magnet to throw the electrons and protons that make up brain tissue out of their normal patterns, and measures the time it takes for them to return to their normal "resting" state. This "relaxation time" provides information about the content of the tissue, which can be used to create an image of the brain. MRI images are obtained from successive slices that move through the entire volume of the brain a few millimeters at a time. With specialized image processing software on the computer, the outline of individual brain regions can be traced and the volume quantitated. These techniques have provided a wealth of information about brain structure in psychiatric disorders in general, and more recently in the field of PTSD.

Positron emission tomography (PET) can provide measures of brain function as assessed by brain blood flow and metabolism. Glucose is the primary energy source of the brain, and when there is an increase in firing of the neurons in a specific brain region, there is an increase in glucose uptake in that region to meet the demand. Similarly, with increased glucose demand there is an increase of brain blood flow to that region. With a regional increase in neuronal activity (for instance, in the visual cortex following exposure to a bright light), there is a shunting of glucose and blood flow towards that region that can be measured with PET as a measure of brain function. Glucose and water can be made radioactive and injected immediately into the patient for imaging of brain metabolism and blood flow. Brain blood flow is measured with radioactive water H_2[O-15], and brain metabolism with radioactive glucose ([^{18}F]2-fluoro-2-deoxyglucose, or FDG). These substances emit positrons in the course of radioactive decay, which collide with electrons in the brain, creating 2 beams of light that travel away from each other and are detected by the camera. Computers then use this information to reconstruct an image of the brain's metabolism or blood flow patterns.

The first use of neuroimaging in trauma survivors occurred in the aftermath of the Second World War. Pneumoencelography was used in the assessment of concentration camp survivors seeking compensation for disability. Although quantitative methods were not used, the authors did observe abnormalities based on regular radiological interpretation of the studies. The authors reported "[cerebral] atrophy of varying degrees" and "diffuse encephalopathy" in up to 81% of cases, based on their visual interpretation.[1]

More recently advanced technologies of MRI have

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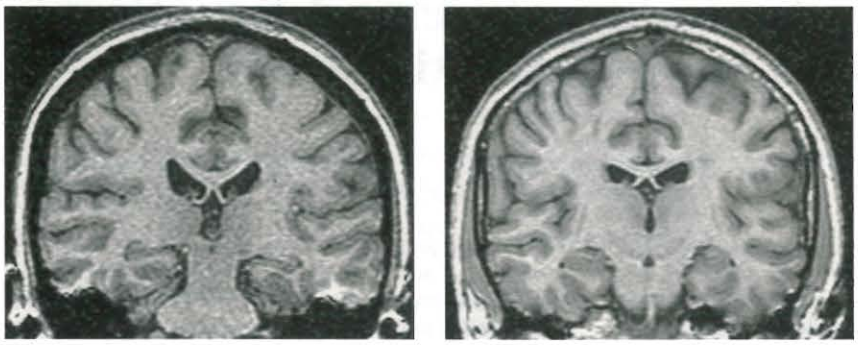

Figure 1. MRI scan of the hippocampus in a normal control (left) and patient with PTSD (right). There is a visible reduction in hippocampal volume in the PTSD patient (right).

been applied to the study of PTSD. MRI studies have measured volume of the hippocampus, a brain structure involved in learning and memory. Animal studies have shown that high levels of glucocorticoids (cortisol in humans) seen in stress are associated with damage to the CA3 region of the hippocampus.[2-4] Glucocorticoids exerted their effect through disruption of cellular metabolism,[5] increasing the vulnerability of hippocampal neurons to a variety of insults, including endogenously released excitatory amino acids[6,7] and augmenting extracellular glutamate accumulation.[8] Stress-induced hippocampal atrophy was also associated with deficits in memory function.[9] Initially deficits in neuropsychological measures of verbal declarative memory function (but not IQ) were found in patients with combat-related PTSD.[10,11] PTSD patients showed deficits on delayed paragraph recall and word list learning, measured with tests (Wechsler Memory Scale Delayed Recall, and Selective Reminding Test) that have been shown to correlate with loss of neurons in the CA3 region of the hippocampus in patients undergoing surgical removal of the hippocampus for the treatment of epilepsy. Other studies also found deficits in verbal declarative memory in Vietnam combat veterans with PTSD[11,12] and Gulf War veterans with PTSD (Vasterling J, personal communication, Feb 31, 1998). We used MRI to quantitate hippocampal volume in patients with a history of traumatic stress and the diagnosis of PTSD. We first looked at hippocampal volume in Vietnam veterans with combat-related PTSD. Healthy controls were matched for age, race, years of alcohol abuse, years of education, height, weight, and socioeconomic status. Measurements of the hippocampus were performed using a reliable technique for measurement of hippocampal volume. We found an 8% decrease in MRI-based measurement of right hippocampal volume in patients with PTSD (n = 26) in comparison to matched controls (n = 22, 1184 vs. 1286 mm^3, 95% confidence interval (CI), 10-195 mm^3, $P < 0.05$). Images of a typical PTSD patient and a control subject are displayed in Fig 1. Decreases in right hippocampal volume in the PTSD patients were associated with deficits in short-term memory as measured by the Wechsler Memory Scale (WMS)-Logical, percent retention subcomponent ($r = 0.64$; $P < 0.05$) (Fig 2). There was no difference in volume of bilateral left temporal lobe (minus hippocampus), amygdala, or caudate between patients and controls in this study.[13] Multivariate analyses continued to show a significant difference between patients and controls controlling for potential confounders. Gurvits et al[14] compared hippocampal volume in 7 patients with Vietnam combat-related PTSD with 7 Vietnam combat veterans without PTSD and 8 healthy nonveteran controls. The authors found a 26% bilateral decrease in hippocampal volume that was statistically significant for both left and right hippocampal volume considered separately. Although subjects were not case-matched for alcohol abuse, there continued to be a significant difference in hippocampal volume after adjusting for years of alcohol abuse using analysis of covariance. There was no difference in ventricular, amygdala, or whole brain volume between the groups. This study also found a significant correlation between level of combat exposure (measured with the Combat Exposure Scale) and hippocampal volume, as well as visual delayed recall errors.

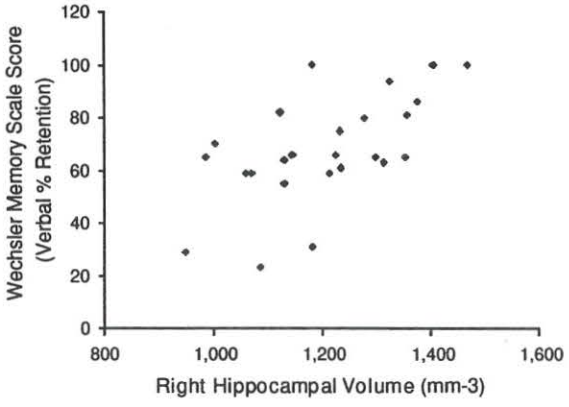

Figure 2. Relationship between hippocampal volume and memory in PTSD. There was a significant correlation between smaller right hippocampal volume and deficits in hippocampal-sensitive measures of verbal declarative memory in patients with combat-related PTSD (delayed recall of paragraph on Wechsler memory scale [$r = .64$; $P < .01$]).

Table 1. Volume of the Hippocampus (mm3) in Abuse Patients and Controls

	Patients (n = 17)		Controls (n = 17)			
Brain Region	*Mean*	*SD*	*Mean*	*SD*	*F*	*P value*
Left Hippocampus	1,050	152	1,193	142	8.07	0.0077
Right Hippocampus	1,062	169	1,116	190	0.74	0.40
Mean Hippocampus	1,056	160	1,155	160	3.57	0.07

Abbreviations: SD, standard deviation; F, F-statistic associated with analysis of variance.

Studies using populations of abuse survivors also showed memory deficits and smaller hippocampal volume in PTSD patients. Deficits in verbal declarative memory function in patients with childhood abuse-related PTSD were found based on similar measures to those used for combat veterans. Deficits in verbal declarative memory in the childhood abuse patients were significantly correlated with level of abuse as measured with the composite severity score on the Early Trauma Inventory ($r = -0.48$; $P < 0.05$).[15] Using MRI, we measured hippocampal volume in 17 male and female adults with a history of severe childhood physical and/or sexual abuse and PTSD, who were compared with 17 healthy controls matched on a case-by-case basis for age, sex, handedness, race, years of education, and years of alcohol abuse. There was a 12% reduction in left hippocampal volume in the patients with abuse-related PTSD in relation to comparison subjects, which was statistically significant ($P < 0.05$). A 3.8% reduction in volume of the right hippocampus was not significant (Table 1). Multivariate analyses using stepwise linear regression continued to show a significant relationship between PTSD and decreased hippocampal volume after controlling for differences in potential confounders not accounted for by the matching strategy. There were no significant differences between patients and controls for temporal lobe, caudate, or amygdala volumes in this study.[16]

Stein and colleagues[17] found a statistically significant 5% reduction in left hippocampal volume in 21 sexually abused women relative to 21 nonabused female controls. Hippocampal atrophy in this study was correlated with level of dissociative symptomatology in the abused women ($r = -0.73$; $P < 0.05$). Most (although not all) of the abused women had a current diagnosis of PTSD. In summary, there are now 4 replicated studies showing smaller volume of the hippocampus in PTSD, and several studies showing deficits in verbal declarative memory function.

Various hypotheses have been advanced to explain hippocampal volume reduction in PTSD.[18,19] High levels of glucocorticoids seen in stress may lead to atrophy or neuronal loss in the hippocampus in PTSD patients. Evidence in support of glucocorticoid mediated toxicity in humans comes from studies in patients with abnormal elevations of cortisol because of Cushing's disease showing hippocampal atrophy and cognitive memory deficits.[20] Elevated concentrations of corticotropin releasing factor (CRF) in the cerebrospinal fluid of patients with PTSD[21] and blunted adrenocorticotrophic hormone (ACTH) response to CRF[22] are consistent with excessive activity of the hypothalamic-pituitary-adrenal (HPA) axis. The hippocampus has an inhibitory effect on release of CRF from the hypothalamus in PTSD,[23] and elevated levels of CRF support the hypothesis of hippocampal dysfunction in PTSD. Peripheral levels of cortisol were not, however, consistently elevated, and several studies actually found lower cortisol levels in chronic PTSD[24] (although emerging data in acute PTSD are more consistent with hypercortisolemia).[25] Studies looking at rape survivors used measures of cortisol obtained 12 to 48 hours or more after the trauma,[26] and these cannot be viewed as true reflections of cortisol release at the time of the trauma. These studies found that previous trauma history was associated with low cortisol 12 to 48 hours after rape, however, cortisol levels did not predict the development of PTSD. We have hypothesized that cortisol release at the time of the stressor, or differences in glucocorticoid receptor sensitivity, may result in hippocampal damage in PTSD with associated volume reduction.[27] Other factors besides glucocorticoids may represent the cause of hippocampal volume reduction in PTSD. Stress was associated with decreased levels of brain-derived neurotrophic factor (BDNF), which may also play a role in hippocampal damage. An alternative hypothesis for hippocampal volume reduction is that small hippocampal volume, which is present from birth, is a risk factor for the development of PTSD. Regardless of the cause, the marked deficits in declarative memory as measured with tests that have been validated against neuronal loss is consistent with a functionally significant deficit in hippocampal function. Consistent with hippocampal dysfunction are preliminary results from our group showing a failure of hippocampal activation measured with PET during verbal memory tasks in PTSD.

PET has shown functional abnormalities in patients with PTSD. Semple and colleagues[28] studied 8 PTSD patients with comorbid substance abuse and 8 normal subjects and found decreased resting blood flow in parietal cortex normalized to whole brain blood flow. Findings in patients with comorbid PTSD-substance abuse

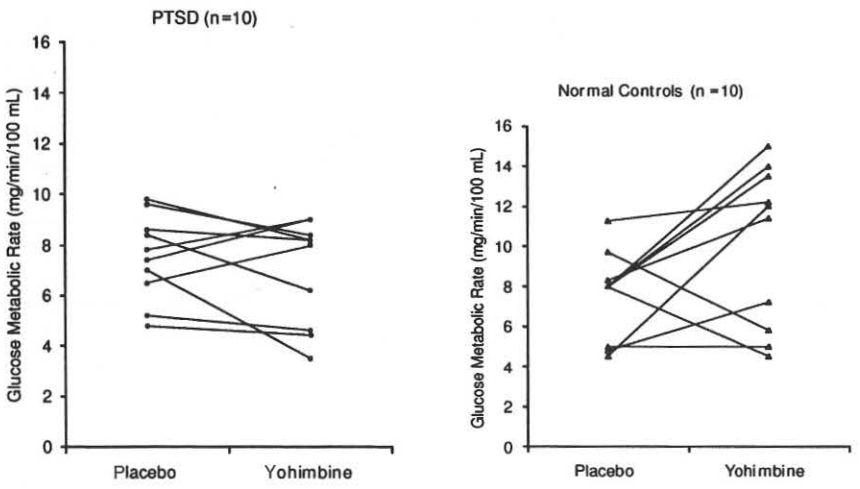

Figure 3. Metabolic response to yohimbine and placebo in orbitofrontal cortex in PTSD patients (left) and controls (right). There was significant difference in metabolic response to yohimbine, with controls increasing metabolism, and PTSD patients showing a pattern of decrease.

are not generalizable to other PTSD studies performed to date, in which patients do not have a history of current substance abuse. Bremner and colleagues[29] found a decrease in resting metabolism measured with PET FDG in temporal and prefrontal cortex in 10 combat veterans with PTSD compared with 10 healthy subjects.

PET has also been used to study neural correlates of symptom provocation in PTSD. Bremner et al[29] used PET and FDG in the measurement of cerebral glucose metabolic rate after administration of the alpha-2 noradrenergic receptor antagonist, yohimbine (which stimulates norepinephrine release in the brain and provokes symptoms of PTSD), and placebo in 10 Vietnam combat veterans with PTSD and 10 healthy controls. Norepinephrine has a U-shaped curve type of effect on brain function, with lower levels of release causing an increase in metabolism, whereas very high levels of release actually cause a decrease in metabolism.[30] We hypothesized that yohimbine would cause a relative decrease in metabolism in patients with PTSD in cortical brain areas that receive noradrenergic innervation. Consistent with this hypothesis, yohimbine resulted in differences in metabolism in orbitofrontal, temporal, parietal, and prefrontal cortex, in PTSD patients relative to controls, with PTSD showing a pattern of decreased and normals a pattern of increased metabolism in these areas (Fig 3). PTSD patients (but not normals) had decreased hippocampal metabolism with yohimbine.[29] These findings are consistent with an increased release of norepinephrine in the brain after yohimbine in PTSD.

Several studies have now used PET $H_20[150]$ to look at brain blood flow during cognitive challenge to provoke PTSD symptoms and traumatic remembrance. Rauch and colleagues[31] used PET and $H_20[150]$ to look at blood flow during exposure to traumatic and neutral scripts in a group of 8 patients with PTSD related to a variety of different traumas. Exposure to traumatic scripts resulted in an increase in brain blood flow in limbic regions (right amygdala, insula, orbitofrontal cortex, and anterior cingulate), and decreased blood flow in the middle temporal and left inferior frontal cortex. This study did not have a control group, and therefore does not permit conclusions about the specificity of findings to PTSD. Bremner et al[32] studied 10 Vietnam veterans with PTSD and 10 Vietnam veterans without PTSD during exposure to combat-related and neutral slides and sounds. Vietnam veterans with combat-related PTSD (but not non-PTSD) showed a decrease in blood flow in the medial prefrontal cortex (Brodmann's area 25, or subcallosal gyrus) and middle temporal cortex (auditory cortex) during exposure to combat-related slides and sounds. Exposure to combat slides resulted in differences in blood flow response between PTSD and non-PTSD in lingual gyrus (posterior parahippocampus), and posterior cingulate, as well as the left inferior parietal and left motor cortex, and the dorsal pons. PTSD patients in general showed a pattern of increased blood flow in these areas, and non-PTSD patients showed no change or decreased blood flow. Shin et al[33] used PET and $H_20[^{15}0]$ during exposure to neutral and combat trauma related pictures (without sounds) and neutral and combat-related mental imagery in patients with PTSD (n = 7) and healthy combat exposed controls (n = 7). This study found increased blood flow in anterior cingulate during combat versus neutral imagery in PTSD. Blood flow was also increased in the right amygdala during combat imagery versus exposure to combat-related pictures in PTSD, whereas controls (but not patients) had increased blood flow in the orbitofrontal and medial prefrontal cortex during these conditions. Patients (but not controls) also had decreased blood flow in the middle temporal and left inferior frontal cortex during exposure to traumatic mental imagery. This study did not, however, involve a comparison of patients with controls.

Bremner and colleagues have used PET to study cerebral blood flow correlates of exposure to personalized scripts of childhood sexual abuse in women with histor-

ies of childhood abuse with (n = 10) and without (n = 12) PTSD. PTSD women showed decreased blood flow in the medial prefrontal cortex (area 25) and failure of activation in anterior cingulate, with increased blood flow in the posterior cingulate and motor cortex (replicating findings in combat-related PTSD) and the anterolateral prefrontal cortex. PTSD women also had decreased blood flow in the right hippocampus, parietal, and visual association cortex (Bremner et al, unpublished data, Dec 20, 1998).

These findings point to a network of related regions as mediating symptoms of PTSD. Two or more PET studies performed to date showed increased activation in posterior cingulate and motor cortex, failure of activation in the anterior cingulate and decreased blood flow in the medial prefrontal cortex (area 25, or subcallosal gyrus), the hippocampus, middle temporal cortex, and visual association cortex with traumatic stimuli in PTSD. The posterior cingulate plays an important role in visuospatial processing[34,35] and is therefore an important component of preparation for coping with a physical threat. The posterior cingulate has functional connections with the hippocampus and adjacent cortex, which led to its original classification as part of the "limbic brain".[36] PTSD may represent a dysfunction in the brain's response to coping with stress and potential threat, which involves excessive recruitment in brain areas responsible for visuospatial processing, attention, and memory, in addition to attaching an effective valence to stimuli. Motor cortex activation may represent the neural correlate of preparation for action (ie "fight or flight").[37] The hippocampus is involved in declarative memory as well as contextual fear.[38] The motor, parietal, visual association cortex, and posterior cingulate are involved in a functional network with connections to portions of the prefrontal cortex (middle frontal gyrus).[39]

A number of PET studies have now implicated the medial prefrontal cortex in both normal and pathological responses to stress and emotion. In the 2 PET studies conducted by Bremner and colleagues there was a failure of activation of the anterior cingulate and decreased blood flow in the medial prefrontal cortex (subcallosal gyrus) during exposure to traumatic stimuli in PTSD. A third study by Bremner and colleagues using symptom provocation with yohimbine showed a failure of activation in the medial and orbitofrontal cortex in PTSD. PET studies in normal subjects, using a variety of paradigms to stimulate intense emotions, have consistently shown activation of the anterior cingulate (areas 32 and 24). Human subjects with lesions of medial prefrontal cortical areas (eg the famous case of Phineas Gage[40]) have deficits in interpretation of emotional situations that are accompanied by impairments in social relatedness. Lesions of this area in animals result in impairments in mounting the peripheral glucocorticoid and sympathetic response to stress.[34,35,41]

Findings from imaging studies may also be relevant to the failure of extinction to fear responding that is characteristic of PTSD and other anxiety disorders. After the development of conditioned fear, as in the pairing of a neutral stimulus (bright light, the conditioned stimulus) with a fear-inducing stimulus (electric shock, the unconditioned stimulus), repeated exposure to the conditioned stimulus alone normally results in the gradual loss of fear responding. The phenomenon is known as extinction to conditioned fear and is mediated by the central nucleus of the amygdala.[42,43] The extinguished memory is rapidly reversible after reexposure to the conditioned-unconditioned stimulus pairing even up to 1 year after the original period of fear conditioning, suggesting that the fear response did not disappear, but was merely inhibited. Recent evidence suggests that extinction is mediated by cortical inhibition of amygdala responsiveness. The medial prefrontal cortex (area 25) or the adjacent medial prefrontal regions (anterior cingulate, area 24 and 32, and orbitofrontal cortex) have inhibitory connections to the amygdala[34,35,44] that play a role in extinction of fear responding,[45,46] an important component of the symptom profile of PTSD. PET studies in PTSD during traumatic reminders reveiwed above showed decreased blood flow of the medial prefrontal cortex (area 25), with failure of activation of the anterior cingulate and medial orbitofrontal cortex. Based on these findings, we previously argued that the anterior cingulate (area 32) activation represents a "normal" brain response to traumatic stimuli that serves to inhibit feelings of fearfulness when there is no true threat. Failure of activation in this area and/or decreased blood flow in the adjacent medial prefrontal cortex (area 25) in PTSD may lead to increased fearfulness that is not appropriate for the context, a behavioral response that is highly characteristic of patients with PTSD.

Studies are using neuroimaging to examine central benzodiazepine receptor function in anxiety disorders. Animal studies showed that chronic stress leads to a decrease in benzodiazepine receptor binding in frontal cortex. Our group and others have developed methods for quantitation of benzodiazepine receptor binding in living human brain using both PET and single photon emission tomography (SPECT). We used SPECT with [^{123}I]Iomazenil to quantitate benzodiazepine receptor binding in patients with panic disorder and controls. This study found a reduction in benzodiazepine receptor binding in left hippocampus and precuneus in panic disorder. Elevated levels of panic anxiety were correlated with decreased binding in the frontal cortex (Bremner et al, unpublished data, Jan 12, 1999). Using similar methods we recently found a decrease in benzodiazepine receptor binding in medial prefrontal cortex (Brodmann's area 9) in 13 patients with combat-related PTSD compared with 13 case-matched healthy controls (Bremner et al, unpublished data, Dec 2, 1998) (Fig 4). These findings were consistent with animal studies of stress showing decreased binding in the frontal lobe.

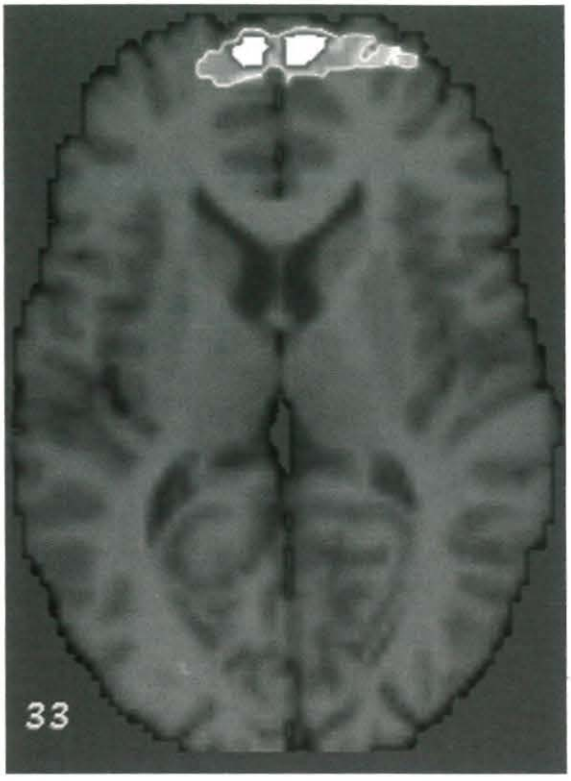

Figure 4. Statistical parametric map overlaid on an MRI for demonstration of anatomical detail showing area of decreased benzodiazepine receptor binding in combat-related PTSD (n = 13) compared with case-matched healthy controls (n = 13). A decrease was found in medial prefrontal cortex (area 9) (z score > 3.00; $P < .001$).

Neuroimaging has made great progress in recent years in mapping out changes in brain function and structure in PTSD. Four replicated studies have shown smaller volume of the hippocampus based on MRI in PTSD. Deficits in verbal declarative memory support a role for dysfunction of this area. Preliminary PET blood flow data from our site are also consistent with a failure of hippocampal activation during the performance of memory tasks in women with childhood sexual abuse-related PTSD. Functional imaging studies of symptom provocation were consistent with dysfunction of both the hippocampus and medial prefrontal cortex in PTSD. Dysfunction of the hippocampus may underlie memory deficits in PTSD, whereas medial prefrontal cortical dysfunction may represent the mechanism of a failure of extinction to fear responding and emotional dysregulation in PTSD. A decrease in benzodiazepine receptor binding in medial prefrontal cortex may contribute to increased anxiety and other pathological emotions in PTSD. Future studies should apply specific probes of brain areas implicated in PTSD, including hippocampus and medial prefrontal cortex, as well as quantitative measures of neuroreceptor binding in PTSD.

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