Neuroimaging of Posttraumatic Stress Disorder

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Although there were no published studies using neuroimaging in posttraumatic stress disorder (PTSD) as recently as 5 years ago, since that time there has been a rapid growth of research in this area. This is secondary to a growing appreciation for the neurobiologic contributions to PTSD. In addition, initial studies showed great promise, with several areas of investigation representing direct extensions of basic science research that amplified and extended the knowledge base about the effects of stress on neurobiology.

Neuroimaging studies include all studies that take advantage of radiologic techniques to provide information about the structure and function of the brain. The first radiologic studies in trauma patients used pneumoencephalography, which involves the injection of air into the cerebrospinal space, and imaging with the use of simple x-rays. This technique was applied to World War II concentration camp survivors seeking compensation for disability. The authors reported "cerebral atrophy of varying degrees" and "diffuse encephalopathy" in up to 81% of cases, based on their visual interpretation, although no quantitative measures of atrophy were performed.¹

Magnetic resonance imaging (MRI) is a technologically more advanced method of imaging than x-ray-based techniques such as pneumoencephalography. MRI uses a powerful magnet to throw the electrons and protons, which 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 that can be used to create an image of the brain. MR images are obtained of 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 in successive slices can be traced using a mouse-driven cursor, and the volume within the outlines can be quantitated and converted to real brain volume. These techniques have been shown to be highly reliable in the hands of well-trained operators and have provided a wealth of information about brain structure in psychiatric disorders in general and, more recently, in the field of PTSD.

Studies using MRI in PTSD have measured the volume of the hippocampus, a brain structure involved in learning and memory. This line of research was prompted by studies in animals showing that high levels of cortisol seen during times of stress are associated with damage to the hippocampus.² Glucocorticoids exerted their effect through disruption of cellular metabolism,³ increasing the vulnerability of hippocampal neurons to a variety of insults, including endogenously released excitatory amino acids,⁴ and augmenting extracellular glutamate accumulation.⁵ Stress-induced hippocampal atrophy was also associated with deficits in memory function.⁶

To examine the hypothesis that stress results in hippocampal atrophy and dysfunction in traumatized humans, declarative memory function (thought to be a marker of hippocampal function) was measured in adult male Vietnam combat veterans with PTSD (n = 26) and matched healthy control subjects (n =
PTSD patients had deficits in short-term verbal memory as measured by the Wechsler Memory Scale (WMS)-Logical Component and Selective Reminding Test-Verbal Component with no differences in IQ or visual memory. Other studies also found deficits in verbal declarative memory in Vietnam combat veterans with PTSD and Gulf War veterans with PTSD (Vasterling J, personal communication, February 1998).

Next we used MRI to quantitate hippocampal volume in living human subjects 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 control subjects 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 technique that has been validated by correlating MRI-based volumetrics with hippocampal neuronal numbers obtained from surgical specimens of the hippocampus in patients with epilepsy.

We found an 8% decrease in MRI-based measurement of right hippocampal volume in patients with PTSD (n = 26) in comparison to matched control subjects (n = 22) (1184 versus 1286 mm³; 95% confidence interval [CI] 10-195 mm³) (P < 0.05) (Fig. 1). Images of a typical PTSD patient and a control subject are displayed in Figure 2. Decreases in right hippocampal volume in the PTSD patients were associated with deficits in short-term memory as measured by the WMS-Logical, percent retention subcomponent (r = 0.64; P < 0.05). There was no difference in volume of bilateral left temporal lobe (minus hippocampus) or caudate between patients and control subjects in this study. We have subsequently not found a difference in volume of the amygdala between patients with combat-related PTSD and control subjects. Multiple linear regression, including potential confounders not addressed by the matching methodology, years of alcohol abuse, education, and age, found no significant relationship between these variables and hippocampal volume. Gurvits and colleagues compared hippocampal volume in seven patients with Vietnam combat-related PTSD to seven Vietnam combat veterans without PTSD and eight healthy nonveteran control subjects. The authors found a statistically significant 26% bilateral decrease in hippocampal volume which 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.

To examine the hypothesis that early stress results in hippocampal atrophy and memory dysfunction, we first looked at memory function in adult survivors of childhood physical and/or sexual abuse with the diagnosis of PTSD and compared them with matched healthy subjects. We found deficits in short-term memory, as measured by the Wechsler Memory Scale (WMS)-Logical Component (verbal memory), for immediate and delayed recall, as well as the Verbal Selective Reminding Test, in the patients with abuse-related PTSD in comparison to control subjects (P < 0.01). Deficits in short-term 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). There was no difference in IQ as measured by the WAIS-R or visual memory as measured by the WMS-Figural Component in early trauma patients in comparison to control subjects. Using MRI we measured hippocampal volume in 17 male and female adults with a history of severe childhood physical and/or sexual abuse and long-term psychiatric consequences in the form of PTSD who were compared with 17 healthy control subjects 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). Multivariate analyses using stepwise linear regression continued to show a significant relationship between PTSD and decreased hippocampal volume when the potential confounders of age, education, and alcohol abuse were entered in the model. There were no significant differences between patients and control subjects for temporal lobe, caudate, or amygdala volumes in this study.
Stoyn and colleagues\textsuperscript{17} found a statistically significant 5% reduction in left hippocampal volume in 21 sexually abused women relative to 21 nonabused female control subjects. 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.

The hippocampus is thought to have an inhibitory effect on corticotropin releasing factor release from the hypothalamus, and chronic stress in animals has been shown to be associated with elevations in CRF. Consistent with this, in a study of Vietnam combat veterans with post-traumatic stress disorder (N = 11) compared with age- and sex-matched healthy subjects (N = 17), there was a significant increase in concentrations of CRF in the cerebrospinal fluid based on lumbar puncture.\textsuperscript{18}

How can it be that a hormonal system that is needed for survival can actually be toxic? During acute stress, it may be more important for the organism to release large amounts of glucocorticoids for survival than to preserve the hippocampus and memory function. Memory dysfunction may not be a problem until later in the lifespan of the organism when it has little impact on that most important event from an evolutionary perspective, passing genetic material on to the next generation.

Some studies,\textsuperscript{16-21} but not others,\textsuperscript{22,23} show decreased cortisol in chronic PTSD. These studies raise the question of how elevated cortisol can represent the etiology of hippocampal atrophy in PTSD. One possibility is that high levels of cortisol at the time of the stressor result in damage to hippocampal neurons which persist for many years after the original trauma leading to reductions in hippocampal volume as measured with MRI.\textsuperscript{24-26} In this scenario, decreased cortisol characterizes the chronic stages of the disorder as a result of adaptation and long-term changes in cortisol regulation. The studies reviewed previously in this article suggest that acute traumatic stress results in hyperactivity of the CRF/hypothalamic-pituitary-adrenal (HFA) system, whereas chronic PTSD may lead
to long-term dysregulation of the HPA/cortisol system. It is also possible that sensitivity of hippocampal glucocorticoid receptors to circulating cortisol represents the critical variable in determining vulnerability to stress-induced hippocampal atrophy. Evidence in support of glucocorticoid-mediated toxicity in humans comes from studies in patients with abnormal elevations of cortisol resulting from Cushing’s disease showing hippocampal atrophy and cognitive memory deficits. However, an alternative hypothesis for hippocampal atrophy is that small hippocampal volume, which is present from birth, is a risk factor for the development of PTSD.

Positron emission tomography (PET) can be used to provide a measure of brain function, measured with 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 after exposure to a bright light), there is a shunting of glucose and blood flow toward that region which can be measured with PET as a “real time” measure of brain function.

The radioactive substances used in PET can be prepared in an on-site cyclotron and injected immediately into the patient for imaging. Brain blood flow is measured with radioactive water (H₂O-15) and brain metabolism with radioactive glucose (¹⁵F]-2-fluoro-2-deoxyglucose, or FDG). These substances emit positrons in the course of radioactive decay, which collide with electrons in the brain creating two beams of light which 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.

Some studies examined resting states of blood flow and metabolism in PTSD. Semple and colleagues studied eight PTSD patients with comorbid substance abuse and eight normal subjects, and found decreased resting blood flow in parietal cortex normalized to whole brain blood flow. Bremner and colleagues found a decrease in resting metabolism measured with PET FDG in temporal cortex. Decreased prefrontal cortical metabolism was not significant in this study after correction for multiple comparisons. Temporal cortex plays an important role in attention and memory, suggesting a possible neural correlate of deficits in memory in patients with PTSD. Findings in patients with comorbid PTSD-substance abuse are not generalizable to other PTSD studies performed to date in which patients do not have a history of current substance abuse.

Studies have begun to use PET during pharmacologic and cognitive provocation of PTSD symptom states to identify neural correlates of PTSD symptomatology and of traumatic remembrance in PTSD. We used PET and FDG in the measurement of cerebral glucose metabolic rate after administration of yohimbine and placebo in Vietnam combat veterans with PTSD and healthy control subjects. Increased noradrenergic function has been hypothesized to underlie many of the symptoms of PTSD. Administration of the alpha-2 antagonist, yohimbine, which stimulates brain norepinephrine release, resulted in increased PTSD symptoms and anxiety among the PTSD group. Norepinephrine has a U-shaped curve type of effect on brain function, with lower levels of release causing an increase in metabolism while high levels of release actually cause a decrease in metabolism. We hypothesized that yohimbine would cause a relative decrease in metabolism in patients with PTSD in cortical brain areas which 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 control subjects, with PTSD showing a pattern of decreased and normal subjects a pattern of increased metabolism in these areas (Fig. 3). PTSD patients (but not normal subjects) had decreased hippocampal metabolism with yohimbine. These findings are consistent with an increased release of norepinephrine in the brain following yohimbine in PTSD.

Several studies have now used PET H₂O to look at brain blood flow during cognitive challenge to provoke PTSD symptoms and traumatic remembrance. Rauch and colleagues used PET and H₂O to look at blood flow during exposure to traumatic and neutral scripts in a group of eight 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 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. We 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) demonstrated a decrease in blood flow in the medial prefrontal cortex (Brodmann area 25, or subcallosal gyrus) and middle temporal cortex (auditory cortex) during exposure to combat-related slides and sounds. These areas are known to modulate emotion and fear responsiveness through inhibition of amygdala responsiveness. Dysfunction of the medial prefrontal and middle temporal cortical areas may represent a neural correlate of a failure of extinction to fearful stimuli in PTSD. Exposure to combat slides resulted in differences in blood flow response between PTSD and non-PTSD in two.
limbic regions, lingual gyrus (posterior parahippocampus) and mid-cingulate, as well as left inferior parietal and left motor cortex, and dorsal pons. PTSD patients in general showed a pattern of increased blood flow in these areas, and non-PTSD showed no change or decreased blood flow. Shin and colleagues used PET and H$_2$O$^{[18]}$O 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 control subjects (N = 7). This study found increased blood flow in anterior cingulate during combat versus neutral imagery in PTSD. Blood flow was also increased in right amygdala during combat imagery versus exposure to combat-related pictures in PTSD, whereas control subjects, but not patients, had increased blood flow in orbitofrontal and medial prefrontal cortex during these conditions; patients had a pattern of increase in blood flow in orbitofrontal that failed to reach the more conservative level of statistical significance. Patients, but not control subjects, also had decreased blood flow in middle temporal and left inferior frontal cortex during exposure to traumatic mental imagery.

All PET blood flow studies of symptom provocation performed to date have found a relative decrease in middle temporal blood flow with combat slides and sounds in PTSD patients. The middle temporal cortex also plays a role in the extinction of fear through inhibition of amygdala function. In addition, these studies found differences in several adjacent medial prefrontal areas. The parahippocampus was also found to activate with traumatic reminders in all of these PET activation studies. In our study, it involved a posterior portion of the parahippocampus, the lingual gyrus, which has been specifically implicated in visual processing. The cingulate was found to activate in all studies, an area of mid-cingulate in our subjects and anterior cingulate in the other studies. Cingulate is a limbic region involved in memory, emotion, and attention in the service of selection for action. The fact that some brain regions did not show activation in all of the studies reviewed above may be explainable by differences in study populations, study setting, and tasks involved in each study. The brain is sensitive to the type of behavioral task, and subtle differences in behavioral task will result in differences in brain activation patterns. Future research may show that traumatic exposure involves specific regions, regardless of the task, whereas other regions are task-specific. For instance, some groups, but not others, found activation in amygdala and a decrease in left inferior frontal gyrus activity with traumatic exposure. These findings were seen only with traumatic imagery, however, and not with presentation of traumatic pictures. The findings may be specific to the generation of mental images of the traumatic event and not reproducible during presentation of pictures of traumatic events or with exposure to the combination of traumatic pictures and sounds.

In summary, there are now four replicated...
studies showing hippocampal atrophy 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 (not reviewed here in detail) is also consistent with a failure of hippocampal activation during the performance of memory tasks in women with childhood sexual abuse-related PTSD. PET studies are consistent with differences in metabolic response to noradrenergic challenge, with PTSD showing a pattern of decrease and normal subjects increase in cerebral cortical and hippocampal metabolism, which is consistent with potentiation of central noradrenergic responsiveness in PTSD. PET studies using cognitive activation studies with traumatic slides and sounds, or traumatic scripts, have implicated several areas, including medial prefrontal and orbitofrontal cortex, cingulate, temporal and parietal cortex, visual association cortex, and amygdala. Future studies are required to more definitively identify neural correlates of traumatic remembrance and symptom exacerbation in PTSD.

REFERENCES


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