Investigating the Pathogenesis of Posttraumatic Stress Disorder With Neuroimaging

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Rapidly evolving brain neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) are proving fruitful in exploring the pathogenesis and pathophysiology of posttraumatic stress disorder (PTSD). Structural abnormalities in PTSD found with MRI include nonspecific white matter lesions and decreased hippocampal volume. These abnormalities may reflect pretrauma vulnerability to develop PTSD, or they may be a consequence of traumatic exposure, PTSD, and/or PTSD sequelae. Functional neuroimaging symptom provocation and cognitive activation paradigms using PET measurement of regional cerebral blood flow have revealed greater activation of the amygdala and anterior paralimbic structures (which are known to be involved in processing negative emotions such as fear), greater deactivation of Broca’s region (motor speech) and other nonlimbic cortical regions, and failure of activation of the cingulate cortex (which possibly plays an inhibitory role) in response to trauma-related stimuli in individuals with PTSD. Functional MRI research has shown the amygdala to be hyperresponsive to fear-related stimuli in this disorder. Research with PET suggests that cortical, notably hippocampal, metabolism is suppressed to a greater extent by pharmacologic stimulation of the noradrenergic system in persons with PTSD. The growth of knowledge concerning the anatomical and neurochemical basis of this important mental disorder will hopefully eventually lead to rational psychological and pharmacologic treatments.

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to the emerging neuroscientific understanding of the pathogenesis of PTSD.

**STRUCTURAL NEUROIMAGING STUDIES**

Magnetic resonance imaging (MRI) is the technique of choice for structural neuroimaging research. The images it yields have been characterized as offering a “living autopsy” of the brain. Structural MRI can be used to identify qualitative gross neuropathologic abnormalities or to quantify the sizes of various structures. Although computed tomographic (CT) scanning has some clinical applications, its relatively inferior soft tissue resolution compared with MRI limits its research utility.

**Neuropathologic Abnormalities**

Using a fluid attenuated inversion recovery pulse sequence not employed in typical MRI studies of PTSD, Canive and colleagues found that 19% of veterans with combat-related PTSD, compared with 0% of healthy controls, showed focal lesions of white matter. Myslobodsky and colleagues reported an incidence of a neurodevelopmental aberration known as cavum septum pellicudum in 50% of PTSD veterans, compared with 14% of normal controls.

**Quantitative Volumetric Studies**

Volumetric studies typically use automated techniques to estimate the overall volume of whole brain, gray matter, white matter, and cerebrospinal fluid. Specific structures are typically quantified via manual tracings using established landmarks, sometimes assisted by semiautomated techniques. These tracings outline the structure’s perimeter on sequential image “slices,” calculate the areas, and then integrate the areas to obtain an estimate of the structure’s volume.

In the single published CT scan study of PTSD, Peters and colleagues found that a higher ventricle:brain ratio and greater global sulcal widening (which suggest loss of brain tissue) were associated with sleep disturbance in former American prisoners of World War II with PTSD symptoms.

Volumetric studies of PTSD employing MRI have focused heavily on the hippocampus, a structure that has been implicated in declarative memory as well as spatial and contextual learning. Studies have found declarative memory impairments in PTSD. The research focus on hippocampus has also been driven by animal research indicating that chronic stress can damage this brain structure.

In the first volumetric MRI study of PTSD, Bremner and colleagues utilized 5-mm MRI slices to measure hippocampal volume in 26 Vietnam combat veterans with PTSD and 22 control subjects (veterans without combat experience) selected to be similar to the patients in age, sex, race, years of education, socioeconomic status, body size, and years of alcohol abuse. The results indicated an 8% decrease in right hippocampal volume in PTSD subjects relative to control subjects (p < .05), with no significant differences for left hippocampus, caudate nucleus, or temporal lobe. Moreover, deficits in short-term verbal memory as measured by the logical memory subscale of the Wechsler Memory Scale-Revised were associated with decreased right hippocampal volume in the PTSD patients (r = 0.64, p < .01).

Gurvits and colleagues reported large reductions in left and right hippocampal volumes (26% and 22%, respectively) in 7 Vietnam veterans with PTSD compared with 7 non-PTSD combat veterans, whose volumes were comparable to 8 normal controls (for an illustration, see Figure 1). There were no statistically significant group differences in the volumes of intracranial cavity, whole brain, ventricles, or amygdala, or in ventricle:brain ratio. There was an inverse relationship between hippocampal volume and self-reported combat exposure severity (Figure 2).

Stein and colleagues found a 5% reduction in left hippocampal volume in 21 women who had suffered repeated childhood sexual abuse, 15 of whom had PTSD. Other brain structures were not examined, but the group difference remained significant when adjusted for reference brain slice volume. Left-sided hippocampal volume correlated significantly with dissociative symptom severity but not with explicit memory functioning.
Bremner and colleagues\textsuperscript{12} extended their volumetric MRI research to 17 adult survivors of child physical and sexual abuse, compared with 17 matched, nonabused, healthy subjects. The former had a 12\% smaller left hippocampal volume. There were no group differences in volumes of amygdala, caudate, and temporal lobe.

In contrast to the results of the above studies, De Bellis and colleagues\textsuperscript{13} failed to find hippocampal volume differences in 44 maltreated children and adolescents with PTSD compared with 61 matched, healthy, nonabused controls. There were, however, other brain differences. The PTSD youths had lower overall cerebral volume, lower corpus callosum volume in particular, and greater ventricular and cerebrospinal fluid volumes, all indicative of an underdeveloped or atrophied brain. Moreover, diminished brain volume was significantly associated with both earlier age at onset and longer duration of abuse, as well as with severity of PTSD symptoms.

**Histochemical Studies**

If MRI may be thought of as elucidating the gross anatomy of the living brain, magnetic resonance spectroscopy (MRS) may be thought of as elucidating its histochemistry, albeit in a limited and crude manner. Neurologic interest focuses on its ability to quantify the level of the amino acid N-acetyl aspartate (NAA) in voxels (i.e., small cubes) of brain tissue. Reductions in NAA level are thought to reflect reduced density or viability of neurons.

Two studies have utilized MRS to measure NAA in the brains of PTSD subjects. Schuff and colleagues\textsuperscript{14} found a marginally significant 18\%, and a nonsignificant 6\%, lower NAA level in the right and left hippocampus, respectively, of 7 Vietnam veterans with PTSD compared with 7 healthy, nonveteran control subjects. Other brain areas were not examined. Freeman and colleagues\textsuperscript{15} reported significantly lower NAA in the right and left medial temporal lobes (where the hippocampus and amygdala, among other structures, are located) of 21 PTSD veterans compared with 8 non-PTSD veterans.

**Comments on Structural Neuroimaging Findings in PTSD**

The MRI and MRS studies performed to date document the occurrence of brain abnormalities in at least some individuals with PTSD. These findings are consistent with the increased incidence of neurodevelopmental abnormalities and subtle functional and neurologic impairments that have been found in PTSD in Vietnam veterans and adult women who were sexually abused as children.\textsuperscript{16,17}

With diminished volume or NAA level found in 4 of 5 published studies, the hippocampus stands out as the brain structure of greatest interest in PTSD structural neuroimaging research to date. It also, however, is the structure that has been looked at the most, and investigators tend to find things where they look. Brain structures other than the hippocampus have received less, or even incidental, attention.

Diminished hippocampal volume has also been reported in major depression,\textsuperscript{18,19} which is a common comorbid condition in patients with PTSD. The uncertain regional and diagnostic specificity of observed brain abnormality illustrates how the field of PTSD structural neuroimaging is still in an early stage and awaits the perspective to be offered by the comprehensive study of the structure of the entire brain across a range of mental disorders.

The origin of structural brain abnormalities, and of diminished whole brain and hippocampal volume, in PTSD also remains to be elucidated. With regard to the hippocampus, it is tempting to accept the explanation offered by findings from the animal literature, namely, that stress has damaged this brain structure in persons with PTSD. However, it is important to keep in mind the axiom that correlation does not establish causation. The greatest limitation of published neuroimaging studies of PTSD to date is that all have been cross-sectional and therefore necessarily correliative.

Indeed, there are at least 5 possible alternate explanations of the association between a brain abnormality such as diminished hippocampal volume and PTSD:

1. Preexisting brain abnormality may increase the risk of exposure to a traumatic event capable of causing PTSD. For example, as noted above, the hippocampus is critically involved in declarative memory. Those with a smaller hippocampus (e.g., from birth, perinatal trauma, or adverse development during childhood) may have less ability to...
learn from experience and therefore be less able to avoid dangerous situations. Exposure to traumatic events may thus be increased, with the consequent risk of PTSD.

2. Preexisting abnormality may increase the individual’s vulnerability to developing PTSD after exposure to a traumatic event. For example, failure of extinction of a conditioned response has been postulated in the disorder’s pathogenesis.20 There is some evidence that the hippocampus is involved in the extinction of conditioned responses (reviewed by Falls and Davis21). Individuals with brain abnormalities such as diminished hippocampal volume may be poorer extinguishers of conditioned responses and thereby be more likely to develop chronic PTSD.

3. Traumatic exposure may produce the brain abnormality, and the abnormality may produce the PTSD. For example, as noted above, stress may damage the hippocampus, and a damaged hippocampus, by impairing extinction, may facilitate PTSD.

4. Traumatic exposure may cause the PTSD, and the PTSD may lead to the abnormality. For example, the chronic stress of having PTSD may damage the hippocampus.

5. Traumatic exposure may produce the PTSD, and the PTSD may in turn lead to sequelae or complications that produce the abnormality. For example, alcoholism is a frequent comorbid condition in PTSD, and there is evidence that ethanol damages hippocampal tissue.22,23

Although successful in demonstrating the presence of brain abnormalities in PTSD, the cross-sectional designs of structural neuroimaging studies to date limit their ability to resolve the origin of these abnormalities. The degree to which the currently available data help to clarify the origin of diminished hippocampal volume in PTSD, for example, is the subject of a current debate (see Sapolsky et al.24). Extant studies have generally employed statistical controls for such factors as trauma severity and alcohol intake. More precise control groups will help to free findings from the potential confounds introduced by such factors. Ultimately, prospective studies will be needed that evaluate brain structures of interest prior to and following a traumatic event.

For ethical reasons, studies of the neurologic and psychiatric response to trauma must be naturalistic. However, trauma does not occur in a vacuum. For example, abused children may also suffer from such potentially deleterious factors as neglect, socioeconomic deprivation, and malnutrition. They may also be more likely to inherit abnormalities from behaviorally disordered parents who abuse them. Soldiers with deprived backgrounds, including child abuse, may be more likely to be assigned to combat roles and less well equipped to handle the consequent stress. Dissecting the specific pathogenic influences on the brains of persons with PTSD from a complex web of pretraumatic, peritraumatic, and posttraumatic factors will require scientific ingenuity and persistence.

**FUNCTIONAL NEUROIMAGING STUDIES OF PTSD**

As opposed to CT, MRI, and MRS, which obtain static measures of brain anatomical or chemical structure, functional neuroimaging studies obtain dynamic measurements of brain activity by quantifying regional cerebral blood flow (rCBF) or oxygen or energy consumption. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) use radioisotopes, which during decay lead to the emission of photons that are detected by cameras surrounding the head. Of the 2 techniques, PET offers superior spatial resolution. Functional magnetic resonance imaging (fMRI) does not require radioactive isotopes but rather uses radio frequency pulses within a strong magnetic field to measure subtle changes in signal related to rCBF. This method relies on differences in the signal produced by oxygenated versus deoxygenated hemoglobin and hence is termed the blood oxygenation level dependent (BOLD) method. In all these functional imaging methods, investigators infer that greater signal within a given voxel is related to greater levels of brain activity at that locus.

One or more of the above techniques have been used in conjunction with the symptom provocation or cognitive activation paradigms described below to examine the functional neuroanatomy of PTSD.

**SYMPTOM PROVOCATION PARADIGMS**

In symptom provocation paradigms, researchers measure patterns of rCBF associated with symptomatic versus neutral states. Most functional neuroimaging studies of PTSD to date have been of this type.

Rauch and colleagues25 used PET and script-driven imagery to examine rCBF patterns in a mixed-gender cohort of 8 individuals with PTSD. In separate conditions, subjects were prompted by audiotaped narratives (i.e., scripts) to recall and imagine neutral and traumatic autobiographical events. Heart rate and subjective ratings of negative emotions were higher in the traumatic condition than in the neutral condition. In the traumatic versus control conditions, significant rCBF increases occurred in right medial orbitofrontal cortex, right insular cortex, right anterior temporal pole, anterior cingulate gyrus, right amygdala, right medial temporal cortex, right secondary visual cortex, and bilateral sensorimotor cortex (Figure 3). In addition, rCBF decreases were found in left middle temporal cortex and left inferior frontal cortex (Broca’s motor speech area).22 An important limitation of this study
was the absence of a non-PTSD control group, which prevented concluding whether the observed activations and deactivations are specifically related to PTSD or characterize the responses of trauma-exposed persons regardless of diagnosis.

Using a similar design, Shin and colleagues used PET to examine rCBF in 16 female survivors of childhood sexual abuse: 8 with PTSD and 8 without PTSD. In separate conditions, subjects were prompted by scripts to recall and imagine neutral and autobiographical abuse events. The PTSD group had greater heart rate responses during personal traumatic imagery than did the comparison group. In the abuse condition, relative to the control conditions, both groups exhibited rCBF increases in medial prefrontal cortex (subcallosal gyrus) and anterior cingulate cortex. However, these increases were significantly greater in the PTSD group than in the comparison group. Only the PTSD group exhibited rCBF decreases in left inferior frontal gyrus (Broca’s area), and only the comparison group exhibited rCBF increases in anterior cingulate gyrus.

Women with histories of childhood sexual abuse were also studied by Bremner and colleagues. In this study, 10 women with PTSD and 12 women without PTSD underwent PET scanning while they listened to scripts describing neutral and abuse events. The abuse versus neutral comparison revealed that, relative to the control group, the PTSD group exhibited greater rCBF increases in posterior cingulate and anterolateral prefrontal cortex. Abuse memories were associated with decreased rCBF in subcallosal gyrus (Brodman’s area 25) and a failure to activate anterior cingulate gyrus. The PTSD group exhibited greater rCBF decreases in several cortical areas, including right hippocampus.

Bremner and colleagues also measured rCBF in 20 Vietnam combat veterans: 10 with PTSD and 10 without PTSD. During scanning, subjects were presented with combat-related and neutral slides and sounds. In the combat versus neutral comparison, the PTSD group exhibited rCBF decreases in medial prefrontal cortex (subcallosal gyrus) and anterior cingulate cortex. A group × condition interaction revealed the following areas with relative decreased rCBF in PTSD and relative increased rCBF in controls: medial prefrontal cortex (subcallosal gyrus), middle temporal gyrus, and thalamus. Areas with relative increased rCBF in PTSD and relative decreased rCBF in controls were inferior parietal lobule, lingual gyrus, cerebellum/pons/parahippocampus, mid-cingulate, and motor cortex.

Cognitive Activation Paradigms

The purpose of cognitive activation paradigms is to examine specific cognitive-behavioral domains and/or brain systems that may be implicated in a certain disorder or condition. Subjects are imaged while performing cognitive tasks that tap the cognitive-behavioral domain and/or brain system of interest. The goal is to determine whether
patients exhibit performance deficits and/or abnormal patterns of brain activation.

Semple and colleagues used PET to measure rCBF in 6 male veterans with PTSD (5 with comorbid substance abuse or dependence) and 7 nonveteran control subjects. Scanning conditions consisted of a resting baseline, a word generation task, and an auditory continuous performance task (CPT) involving tone-volume discrimination. Results revealed that PTSD subjects had greater blood flow than control subjects in orbitofrontal cortex during both cognitive tasks. PTSD subjects exhibited a trend for smaller hippocampal left/right ratios than control subjects in the word generation task. In a more detailed analysis of data collected during the CPT, these investigators reported that subjects with PTSD made more false alarm errors on the CPT and exhibited less blood flow in parietal cortex than did control subjects.

Shin and colleagues studied visual perception and visual mental imagery in 7 combat veterans with PTSD and 7 combat veterans without PTSD. In the perception conditions, subjects viewed and evaluated pictures; in the imagery conditions, subjects imagined and evaluated pictures. Within the perception and imagery conditions, subjects saw neutral, negative, and combat-related pictures. In the combat imagery versus control conditions, the PTSD group exhibited rCBF increases in right amygdala and ventral anterior cingulate gyrus and rCBF decreases in left inferior frontal gyrus (Broca’s area).

Rauch and colleagues sought to measure amygdala responses to threat-related stimuli under conditions in which anterior cingulate cortex (which is thought to inhibit amygdala) was not concurrently activated. During functional MRI, these investigators presented fearful and happy faces temporally masked by neutral faces, a maneuver that has been shown to produce relatively isolated amygdala recruitment. Normal subjects are typically aware of seeing only the neutral faces, although their amygdalae are nevertheless activated by the affectively valenced faces. Rauch and colleagues found that 8 Vietnam combat veterans with PTSD exhibited greater amygdala activation than 8 combat control veterans. Moreover, the magnitude of amygdala activation significantly correlated with PTSD severity. These results suggest that PTSD may be characterized by amygdala hyperresponsivity to general threat-related stimuli, dissociated from medial frontal cortical activation.

Comments on Functional Neuroimaging

Findings in PTSD

Symptom provocation studies of PTSD have revealed activation of amygdala and associated anterior paralimbic regions of the brain. Because these regions are involved in the processing of negative emotion, as well as in the expression of associated autonomic arousal, these results are consistent with a large literature demonstrating increased physiologic responding during traumatic recollections in PTSD (reviewed by Pitman et al.).

Three separate studies have provided evidence for a failure to activate anterior cingulate/medial frontal cortex during symptom provocation in PTSD patients. This finding is interesting in light of the fact that these regions may play a role in the extinction of conditioned fear responses and may perform a compensatory role in the regulation of emotion. Cognitive activation studies have provided further evidence for higher amygdala responsivity in PTSD. This pattern of findings suggests that PTSD may be accompanied by a hyperresponsive amygdala and an underresponsive medial prefrontal cortex that fails to inhibit it.

Although neuroimaging studies of PTSD have yielded some consistent results, this literature is also plagued by several inconsistencies. For example, although it is a highly salient finding in some studies, amygdala activation has not been confirmed in the majority of symptom provocation studies. Lack of amygdala activation may be due to several factors, including the small size of the structure, imperfect spatial and temporal resolution, and small sample sizes. The presence of inconsistencies in the literature should not be too surprising given that scanning methods differed greatly between studies.

Ligand Studies

Ligand studies involve tagging bioactive compounds, e.g., neurotransmitters or drugs, with radioisotopes to create “tracers,” administering them to subjects, and then measuring the brain locations of their emissions via PET or SPECT to determine the structural and functional state of receptors.

In a SPECT study with the tracer $^{123}$I-iomazenil, Bremner and colleagues measured brain benzodiazepine receptor binding in 13 Vietnam veterans with PTSD and 13 normal control subjects. Lower binding was found in the PTSD subjects in frontal cortex (Brodmann’s area 9). The investigators noted that this finding is consistent with preclinical studies showing decreased benzodiazepine binding in the frontal cortex of chronically stressed animals. They also commented that this finding may be related to the decreased activity in adjacent cingulate cortex found in symptom provocation studies of PTSD (see above).

Given the lively interest in catecholamine, indolamine, opioid and other peptide, hypothalamic-adrenal-cortical, and other neurohormonal systems in PTSD, ligand neuroimaging studies of this disorder may be expected to proliferate in the future as the necessary tracers are developed.

DISCUSSION

Metcalfe and Jacobs have distinguished between an amygdala-centered (anterior paralimbic) emotional, “hot” memory system and a hippocampus-centered (posterior
paralimbic) cognitive, “cool” memory system. These authors have theorized that the “hot” amygdala system is actively involved in the pathogenesis of PTSD. As noted above, PTSD symptoms may be conceptualized as the products of fear conditioning. The role of the amygdala in this process has been amply demonstrated in preclinical research.

Findings of diminished hippocampal volume in structural neuroimaging studies of PTSD suggest that the “cool” memory system may be underactive in this disorder. This has yet to be confirmed in functional neuroimaging studies of the hippocampus. As noted above, one of the roles of the hippocampus may be to facilitate the extinction of conditioned emotional responses. Meanwhile functional neuroimaging studies have documented underactivity of cingulate cortex in PTSD, which as noted above is a structure that also may facilitate extinction.

The alternate possible origins of structural brain abnormalities outlined above also apply to functional abnormalities in PTSD. For example, if the amygdala is overactive and/or overresponsive in PTSD, as the neuroimaging data suggest, the cross-sectional studies conducted to date cannot resolve the competing possibilities that this organ has been sensitized by the trauma or by the PTSD on the one hand, or that a preexisting sensitive amygdala increased the individual’s vulnerability to develop PTSD following traumatic exposure on the other hand. Thus, longitudinal, twin, at-risk, and other creative designs will also be required to clarify the results of functional neuroimaging studies of PTSD.

The implications of the neuroimaging findings reviewed above depend on which of the various possible explanations of the association between an observed abnormality and PTSD is supported in further research. If a structural or functional brain abnormality is antecedent, its explanations of the association between an observed abnormality and PTSD is supported in further research. If a structural or functional brain abnormality is antecedent, its implications may be more straightforward. For example, if the amygdala is overactive and/or overresponsive in PTSD, as the neuroimaging data suggest, the cross-sectional studies conducted to date cannot resolve the competing possibilities that this organ has been sensitized by the trauma or by the PTSD on the one hand, or that a preexisting sensitive amygdala increased the individual’s vulnerability to develop PTSD following traumatic exposure on the other hand. Thus, longitudinal, twin, at-risk, and other creative designs will also be required to clarify the results of functional neuroimaging studies of PTSD.

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Drug name: yohimbine (Aphrodyne and others).

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