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FUNCTIONAL NEUROIMAGING STUDIES IN POSTTRAUMATIC STRESS DISORDER: REVIEW OF CURRENT METHODS AND FINDINGS

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Abstract

Posttraumatic stress disorder (PTSD) is an anxiety disorder associated with changes in neural circuitry involving frontal and limbic systems. Altered metabolism in these brain structures after a traumatic event is correlated to PTSD. Developments in the field of neuroimaging have allowed researchers to look at the structural and functional properties of the brain in PTSD. Despite the relative novelty of functional imaging and its application to the field of PTSD, numerous publications have brought to light several of the circuits implied in this disorder. This article summarizes the findings with regard to PTSD in the functional imaging techniques of single-photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). Furthermore, we discuss strengths and weaknesses of the various techniques and studies. Finally, we explore the future potential of functional neuroimaging studies in PTSD.

Keywords

PTSD; PET; fMRI; imaging; hippocampus; amygdala; SPECT; prefrontal cortex

INTRODUCTION

High rates of posttraumatic stress disorder (PTSD), an anxiety disorder caused by the onset of an extreme stressor, are seen across many populations. Examples of such stressors include combat, childhood physical and sexual abuse, motor vehicle accidents (MVAs), rape, and natural disasters. Patients with PTSD often suffer from one or more of the following symptoms: intrusive memories, flashbacks, hypervigilance, sleep disturbance, avoidance of traumatic stimuli, physiological hyperresponsivity, numbing of emotions, and social dysfunction [Bremner and Charney, 1994]. PTSD symptoms in victims or bystanders of a traumatic event have been documented in numerous studies and occur at a rate of approximately 7.8% [Kessler et al., 1995]. A variation in this rate is commonly observed, and may be explained by the differences in traumatic stressors such as trauma type, severity

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of the specific traumatic event, and possibly by individual predisposition to PTSD. Because research in the field of PTSD is in a relatively early stage, much of the neurobiological correlates remain hypothesized or undetermined. The need to address these biological properties is crucial for the development of treatment for a disorder that carries a potentially great social impact.

In recent years, advances in the field of functional neuroimaging have allowed researchers to uncover some of the neural networks believed to be involved in the pathophysiology of PTSD. Imaging techniques such as single-photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) allow for the visualization of activation of specific brain regions by measuring regional cerebral blood flow (rCBF), neuroreceptor density, and blood oxygen levels. Findings suggest that patients with PTSD show altered brain activation in various regions compared to healthy controls. Some of these alterations include a reduced activation of the medial prefrontal cortex (mPFC) and an increase in amygdalar activation in PTSD. Other findings suggest altered functional activity in the hippocampus, parahippocampus, orbito-frontal cortex (OFC), and thalamus, among other regions.

Furthermore, the findings of these studies, research designs, methodologies, and techniques vary to a great extent. The incoherency of the findings between some of the studies may therefore be accounted for by the lack of consistent or repeated paradigms. This review focuses on the functional neuroimaging research conducted to date in PTSD. It covers various techniques (SPECT, PET, and fMRI) that use different kinds of paradigms (resting, active tasks, stimulus presentation) and attempts to create a global overview of the current findings of these studies.

NEUROANATOMY OF PTSD

The pathophysiology of PTSD can be linked to several neurobiological mechanisms related to stress. Preclinical studies that investigated the effects of stress on neural processes such as learning and memory retention were initially used to model PTSD as humans experience it. These studies suggested that an altered fear response mechanism, behavioral sensitization, and failure of the extinction of fear play an important role in the pathophysiology of PTSD [Charney et al., 1993]. Furthermore, it has been shown that patients with PTSD show significant deficits in memory [Bremner et al., 1993, 1995b]. Alterations in memory are correlated with specific brain structures and functional pathways that may be altered and are therefore possibly dysfunctional in patients with PTSD.

The advent of modern structural and functional imaging techniques has opened a great window of opportunity for conducting neurological research in human patients. In the past few years, such techniques have been used to reveal whether the hypotheses about changes in the brain in PTSD, made in the 1990s by Charney et al. [1993] and Bremner et al. [1995a], were accurate. In more recent publications [Bremner, 2003; Charney, 2004] by the same authors, hypotheses supported by preclinical data are discussed in relation to research findings in human subjects. These updates include neural structures, circuits, and functions that are altered in patients with PTSD. Although there is no definitive pathophysiology for PTSD and its biological cause, many theories that have been developed remain closely tied to the mechanisms from the preclinical findings. Four of these mechanisms, which are altered in PTSD, are discussed below.

THE FEAR RESPONSE

Individuals with PTSD commonly experience vivid and intrusive recall of traumatic memories. Furthermore, frequent recall of such memories is part of the diagnostic criteria

for PTSD as summarized in the DSM-IV classification for psychiatric disorders. Alterations in the fear response mechanism are believed to lead to intrusive memories, autonomic hyperarousal, and flashbacks in many patients [Charney, 2004]. Traumatic memories can be elicited via sensory and cognitive (fearful) stimuli that are paired to the traumatic events the individual has experienced. Because patients with PTSD seem to pair their traumatic experience with stimuli that are normally safe, they reexperience their traumatic memories even in a nondangerous situation. Due to the effects of trauma-related stimuli, patients with PTSD display avoidance of such stimuli or numbing of their emotional reactions [Charney, 2004], as described under the C-criteria for PTSD in DSM-IV.

Under normal circumstances, the fear response is an important human adaptation that prepares the body to ready itself in a threatening or dangerous situation. By being able to predict such situations, human beings can adapt their behavior and take on the situation appropriately. The pairing of potentially dangerous stimuli with a response to ready oneself for action can be crucial for survival. Clinically, however, the adaptation takes a different form, in which patients over-generalize danger cues; therefore, they continuously perceive normally nonthreatening situations as dangerous [Charney, 2004]. Cues linked to a traumatic memory, which normally do not elicit fearfulness, can become conditioned and therefore cause autonomic reactions and defensive behavior, even in nonthreatening situations.

Structures involved in the fear response mechanism in humans include the sensory cortex, the dorsal thalamus, the lateral and central nucleus of the amygdala, and the mPFC (including the anterior cingulate) [Charney, 2004]. The anterior cingulate is part of the mPFC, and is discussed separately. Structural abnormalities of the anterior cingulate cortex (ACC) have been reported in patients with PTSD [Rauch et al., 2003; Woodward et al., 2005; Yamasue et al., 2003]. The neurochemical systems that are functional within and communicate between these structures are the glutamate and N-methyl-D-aspartate acid (NMDA) receptors, along with the voltage-gated calcium channels. The main output center for the response to fearful stimuli is the central nucleus of the amygdala, which mediates responses (autonomic, behavioral, and endocrine) related to fear [Charney, 2004].

The lateral amygdala transfers information related to fearful stimuli to the central nucleus, with which it connects directly. Furthermore, long-term potentiation of the lateral amygdala seems to be involved in storing the association between conditioned and unconditioned stimuli, which occurs at high rates in patients with PTSD. Blocking long-term and short-term memory pathways, which are regulated by NMDA receptors and voltage-gated calcium channels in the amygdala, may be a preventive measure against PTSD [Charney, 2004]. NMDA receptors and voltage-gated calcium channel blockers may stop memory potentiation, thus impairing the acquisition of fearful associations.

Information from fearful stimuli is transmitted to the lateral amygdala via two pathways: a short subcortical pathway and a longer cortical pathway. The former pathway, which operates more rapidly and reaches the lateral amygdala directly from the dorsal thalamus, relates to a more instinctual response. The latter pathway incorporates the cortex of the human brain, indicating an involvement of cognition, possibly involved in the assessment of the fearful situation and its context. Furthermore, it allows for the comparison of similar previous experiences, which may lead to a better estimation of the situation at hand [Charney, 2004]. Another structure closely linked in the initial processing of a fearful stimulus, prior to lateral amygdalar activation, is the hippocampus, which is involved in memory and can therefore provide contextual information about a stimulus.

Understanding the conditioned fear response in patients with PTSD may provide a tool for uncovering the neurobiological processes that underlie PTSD. By exposing patients to

specific trauma-related stimuli, researchers have measured functional neural processing using techniques such as fMRI, PET, and SPECT.

FAILURE OF FEAR EXTINCTION

The process of fear extinction is closely linked to the conditioning of fear. When a person is exposed to a normally dangerous situation from which no aversive events result, this situation elicits a smaller fear response than before. In patients with PTSD, this process does not occur efficiently, and fear of certain situations fails to extinguish. In military veterans this may be identified by persistent, fearful responses to large, noisy crowds, fireworks, and doors slamming, among other forms of traumatic recall. Therefore, some permanence in fear conditioning in patients is strengthened by a dysfunction in the extinction of fear. Ultimately, this can be the cause of the persistence of the traumatic memories.

The neural mechanisms involved in the extinction of fear greatly overlap with those involved in fear acquisition, as just described. In fact, the main structures involved in the extinction of fear are the medial prefrontal cortex and the amygdala [Quirk and Gehlert, 2003]. NMDA receptors and voltage-gated calcium channels are essential to extinction processes [Charney, 2004]. Other systems include the neuro-transmitters γ-aminobutyric acid (GABA) [Quirk and Gehlert, 2003], norepinephrine [Southwick et al., 1999], and dopamine [Pezze and Feldon, 2004]. During a fearful response of the amygdala, the mPFC is activated and modulates the initial response to the threat. In this manner, fear is contained and managed accordingly. If this prefrontal activation is absent, or occurs to a lesser extent, the amygdala does not receive sufficient inhibitory feedback, resulting in higher autonomic arousal and exaggerated responses, as we see in patients with PTSD [Nutt and Malizia, 2004]. The amygdala–mPFC connection (feedback process) is thought to be mediated by GABA inter-neurons [Charney, 2004], which may be malfunctioning in PTSD.

BEHAVIORAL SENSITIZATION (STRESS SENSITIVITY)

Insomnia, poor concentration, hypervigilance, and exaggerated startle response are traits related to the increased susceptibility to stress of patients with PTSD [Charney et al., 1993]. “Sensitization” may be defined as an increase in a certain response due to the presentation of a specific stimulus. In military veterans with PTSD, for example, a traumatic event, or series of events they witnessed, is thought to cause the onset of PTSD. Patients become more aroused and hypervigilant, among other characteristics, than do healthy individuals when presented with trauma-related stimuli. It is the experience or recurrent experience of traumatic occurrences that facilitates or sensitizes this process. It is therefore possible to state that PTSD is a certain type of behavioral sensitization, in which trauma exposure causes the onset of increased stress sensitivity. Although few human subject studies have investigated these symptoms on a neurobiological level, more advances have been made in preclinical settings [Stam et al., 2000].

The neural circuitry underlying the increased sensitivity to stress is not centralized to a specific anatomical or functional neurological component, because sensitization is a very broad concept and even occurs at cellular levels throughout the body. In patients with PTSD, the (over)sensitization is more vivid in the structures and mechanisms involved in the stress response, as described earlier. An example of this, the glucocorticoid mechanism, is thought to be sensitized in patients with PTSD [Bonne et al., 2003a], making them more susceptible to stress.

MEMORY PROBLEMS ASSOCIATED WITH PTSD

Another trait that is common in patients with PTSD is forgetfulness. Studies that look into the memory deficiencies in PTSD have found significant associations with reductions in

hippocampal volume. The hippocampus has been linked to spatial and episodic memory, stress and emotional regulation, and novelty processing [Geuze et al., 2005]. Lesions of the hippocampus have been found to result in deficiencies of hippocampus-based learning and memory [Scoville and Milner, 2000]. Because patients with PTSD have been found to perform significantly more poorly on neuropsychological memory tasks [Bremner et al., 1993,1995b], studies that have examined hippocampal structure in this population have found smaller hippocampal volumes in patients who have experienced combat trauma, physical and sexual abuse, and childhood sexual abuse [Bremner, 2003]. The findings for hippocampal reductions vary greatly (5–26%), and are found in different areas within this structure depending on the type of trauma. Although many studies that look into hippocampal volume reveal that patients with PTSD show reductions when compared to healthy controls, not all results point in this direction. In fact, one study showed that survivors of recent trauma did not display significant hippocampal volume reductions [Bonne et al., 2001]. Schuff et al. [2001], and Neylan et al. [2003] were also unable to report significant hippocampal volume differences between patients with PTSD and controls. For an extensive review of structural hippocampal volume reductions in PTSD refer to Geuze et al. [2005].

Although changes in hippocampal volume have been found in subjects with PTSD, a causal relationship between a traumatic stressor and hippocampal volume reductions is difficult to prove. In fact, there are two current hypotheses about smaller hippocampal volume. One explanation for a reduced hippocampal volume in PTSD is the neurotoxicity caused by elevated glucocorticoids, reduced brain-derived neurotrophic factor (BDNF), and the inhibition of the regeneration of damaged brain tissue [Bremner, 2002, 2003]. The second hypothesis is that people who have a smaller hippocampus by birth are (genetically) more at risk to develop PTSD. A twin study that provides some evidence for the latter hypothesis indicates that there is a negative correlation between PTSD severity and hippocampal volume in both the patients and their healthy, trauma-unexposed twin's hippocampi [Gilbertson et al., 2002]. Furthermore, several studies suggest that childhood abuse may be a significant contributor to disturbances in hippocampal volume in patients with PTSD during a later stage in their lives [Bremner et al., 2003a]. Ultimately, longitudinal studies in populations regularly exposed to traumatic events may provide evidence of whether hippocampal volume reduces over time or is initially lower in people who get PTSD.

FUNCTIONAL NEUROIMAGING TECHNIQUES

Functional neuroimaging techniques are a relatively recent development in the field of neurological research. There are various ways to measure the activity that takes place in the brain, all based on different principles. Such techniques include SPECT, PET, and fMRI. These three techniques derive brain function indirectly from physiological measures such as cerebral blood flow, blood oxygen levels, and energy consumption [Sassi and Soares, 2003]. The assumption related to these techniques is that glucose metabolism and blood flow, among other parameters, alter when certain brain areas become activated or inhibited. When neural cells fire, their increase in activity requires a restoration of the energy they used. It is thought that the metabolic demands by such neurons result in an increased blood flow to these areas [Jueptner and Weiller, 1995]. Hence, these methods interpret physiological measures to deduce brain activity. Both SPECT and PET make use of rCBF and neuroreceptor concentration, whereas fMRI makes use of the blood oxygen level–dependent (BOLD) signal to show patterns of activity in the brain. Table 1 summarizes studies using various functional imaging techniques in PTSD.

SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY

SPECT is a functional neuroimaging technique that uses γ emitters to measure rCBF changes in the brain. Radiotracers are introduced into the body by means of an injection. A γ camera acquires single-photon projections emitted by radiotracers on a 360° arc to reconstruct activity within a specific region. Because SPECT makes use of only one photon at a time, there is no positional information available about this incoming photon. Lead collimators are used for positioning, because they measure only photons traveling in a specific direction. The cameras that measure rCBF customarily use sodium iodide (NaI) crystals, which are optimized for absorbing the amount of energy released by [Tc-99m] hexamethyl propylene-amine-oxime (140 KeV), a commonly used radio-nuclide in SPECT imaging [Bremner, 2005]. Next to measuring rCBF, SPECT also has applications for measuring neuroreceptor concentration by using a radiotracer such as Iomazenil [I-123].

Advantages of SPECT include the relatively higher availability and its simpler methodology when compared with PET. The equipment to perform SPECT is available in virtually every nuclear medicine department, and γ emitters have a long half-life, making it unnecessary to produce radionuclides on-site. The low cost of the machinery and required substances therefore make SPECT a valuable and accessible neuroimaging technique.

Despite the various advantages of SPECT, there are several important drawbacks. The main problem with SPECT is that there is no positional information available about an incoming photon. Lead collimators are used to solve this positional issue, yet result in a decreased sensitivity of images [Lammertsma, 2001]. Furthermore, the spatial resolution of SPECT decreases in accuracy as one measures activities deeper in the brain, due to the attenuation of the signals caused by the various types of tissues between the source and camera. Despite the availability of certain mathematical attenuation corrections, SPECT's accuracy for measuring deep-brain activity remains trivial [Groch and Erwin, 2000]. A final weakness of SPECT is that no isotopes of biological elements emit single photons. Therefore, use of nonspecific radionuclides, such as [Tc-99m], which do not necessarily behave in the same manner as native molecules, results in problems analyzing results [Lammertsma, 2001]. On top of these setbacks is the issue of introducing a radioactive substance into the body via injection, making SPECT an invasive technique.

POSITRON EMISSION TOMOGRAPHY

Instead of acquiring a signal from single photon releasing γ emitters, PET produces functional images of neural activity by acquiring events known as "coincidences." A coincidence occurs when two photons (511 KeV each) are registered at 180° angles by radiation detectors within the PET camera. These photons arise from the collision and annihilation of a positron, which is released from a radioactive isotope, and an electron. Because two photons are emitted, the direction of the photon is known, and a collimator is therefore no longer necessary. These coincidences are then used to generate three-dimensional (3D) maps of the radiotracer's position and concentration in a given area of the brain by means of computer algorithms that calculate brain metabolism or blood flow.

Radiotracers used in PET are labeled with positron emitters and introduced by means of an injection or a gas. Biological molecules that are frequently labeled with positron-emitting radioactive isotopes to form tracers include carbon-11, nitrogen-13, oxygen-15, and fluorine-18. The wide range and specificity of the radiotracers used make PET the most selective and sensitive means of neuroimaging [Lammertsma, 2001]. Signal changes throughout the brain are also more evident with PET than with other neuroimaging methods. fMRI generally shows a 1–2% signal change, whereas PET has a more pronounced change

at approximately 10%. Another advantage of PET is that a collimator is no longer necessary to provide positional information, thus avoiding the loss of sensitivity seen in SPECT.

Difficulties with PET are mainly the financial issues coupled with it. The radiotracers used in PET have a much shorter half-life than those used in SPECT; therefore, they need to be produced by an on-site cyclotron. This expensive process requires advanced machinery and specialized staff, in addition to a high-priced scanner, therefore limiting the availability and use of this technique. Furthermore, the temporal resolution of PET (60–100 s) is very poor when compared to fMRI (<2 s). This is reflected by paradigm design: PET and fMRI use blocked designs and event-related designs, respectively. Finally, like SPECT, PET requires the introduction of a radioactive substance into the human body.

FUNCTIONAL MAGNETIC RESONANCE IMAGING

Unlike SPECT and PET, fMRI does not require the introduction of a radioactive tracer to produce images of neural activation. The human body has its own innate physical properties that provide a tracer. Hemoglobin, or more specifically, the *heme* groups of red blood cells, can act as a type of tracer when exposed to a strong magnetic field. In fMRI, a patient is placed inside a powerful magnetic field (1.5–4 Tesla), and the protons that pass through the magnetic field align themselves. Next, a radio frequency (RF) pulse is sent through the subject that is specific to hydrogen, causing the protons to become excited by absorbing RF energy. As the protons return to their equilibrium state, they emit RF energy that in turn is measured and used to reconstruct an image. In fMRI this process is repeated continuously over the entire stretch of an experiment. Hemoglobin acts as a tracer in fMRI, because it behaves differently depending on its state of oxygenation: Oxyhemoglobin looks different than deoxyhemoglobin in a T2* weighted image due to the presence of a magnetic inhomogeneity. Because neuronal activity results in an increased rate of oxyhemoglobin/deoxyhemoglobin (due to greater rCBF) in the blood flowing through this area, the T2* signal increases. This increase then leads to a more intense MR signal, visible on the reconstructed images. Taken at various points in time, it is possible to observe a pattern of activation in specific regions of interest in response to a task or stimulus, adding a temporal dimension to the 3D capacities of MRI.

fMRI has a significant advantage over the PET and SPECT, in that it does not involve exposure to radiation. Because of this, the imaging process is not only safer but also patients can repeat this process without worrying about overexposure to radioactive substances. Other advantages of fMRI are its high availability in radiology departments, lower cost compared to PET scans, and extremely high anatomical and spatial resolution. Finally, the applications of fMRI are extremely broad, ranging from psychiatric research to clinical diagnosis.

Although the advent of fMRI has been shown to have more advantages with respect to the previously discussed methods, there are some constraints to its approach. The main limitation of fMRI is its reduced temporal resolution, as it measures the changes in rCBF in response to neuronal activity. Since this process occurs approximately 4–6 s after the actual activation of the brain, it measures brain activity with a temporal artifact, unless corrected for during analysis. Furthermore, despite the high resolution of structural MRI (<1 mm), fMRI has a lower resolution at ± 3 mm. Recent developments in the field of PET have resulted in the use of a high-resolution research tomograph (HRRT) scanner, which has a spatial resolution of ± 2 mm, challenging the spatial resolution that MRI offers. Other problems associated with fMRI include the absolute exclusion criteria, such as pacemakers and metallic objects in the body that may eliminate several subjects from a study. Furthermore, the MRI scanner is a very noisy machine that can be uncomfortable and distracting if patients are instructed to perform tasks. Subjects with claustrophobia may also

be difficult to scan, especially because they should not be treated with sedatives if performing tasks or experiencing the effects of stimuli.

FUNCTIONAL NEUROIMAGING PARADIGMS

There are various types of strategies used in measuring functional activity of the brain. The most straightforward way of measuring brain activity is by observing a subject at rest. In PTSD, researchers have used both PET and SPECT to measure rCBF [Bonne et al., 2003b; Mirzaei et al., 2001; Seedat et al., 2004], glucose metabolism [Bremner et al., 1997], and the binding potentials for both benzodiazepine [Bremner et al., 2000; Fujita et al., 2004] and serotonin 1A [Bonne et al., 2005] receptors. Cerebral blood flow, and both receptor availability and affinity are all indirect measures of activity, or potential activity, in the brain. Differences of these variables in persons with PTSD may be helpful in describing the pathophysiology of the disorder.

Activity in the brain can also be observed by having subjects participate in an active task or by exposing them to certain stimuli. When a paradigm includes active tasks, subjects are asked to perform certain activities that elicit a predicted brain response. These tasks are usually designed so that they change neural activities in regions hypothesized to be dysfunctional in PTSD. Such tasks include emotional recall tasks [Pavic et al., 2003], memory recall tasks [Shin et al., 2004b], memory encoding tasks [Bremner et al., 2003b], the counting Stroop task [Shin et al., 2001], the emotional Stroop task [Bremner et al., 2004], and the auditory continuous performance task [ACPT; Semple et al., 1993, 1996, 2000]. Each of these methods measure variables of how well a subject performs a task and what actual neural activity is involved during these tasks. Ideally these two variables show some kind of correlation, so that the brain activity can explain the performance of a task.

In the functional neuroimaging studies of PTSD, paradigms frequently consist of exposure to visual or auditory stimuli related to a specific type of trauma. In this way, neural activity can be studied when subjects are exposed to stimuli reminiscent of their traumatic past. Studies of Vietnam combat veterans have used combat sounds [Bremner et al., 1999b; Liberzon et al., 1999; Pissiota et al., 2002; Zubieta et al., 1999] and combat slides [Bremner et al., 1999b; Hendler et al., 2003] to induce trauma-related stress by symptom provocation. Other studies that include victims of sexual assault or abuse have used personal traumatic scripts [Britton et al., 2005; Gilboa et al., 2004; Lanius et al., 2001, 2002, 2005; Liberzon, 2003; Rauch et al., 1996; Shin et al., 2004a] to elicit an emotional response. Although it is interesting to observe these patients during a state of traumatic recall, it is important to have a baseline with which to compare this activity. This can be done intrapersonally by also measuring activity during a neutral activity or stimulus, or interpersonally, by having a healthy or trauma control group, or a combination of both.

METHODS

We performed a MEDLINE indexed search using the following combination of keywords: “PTSD *and* functional imaging,” “PTSD *and* SPECT,” “PTSD *and* PET,” and “PTSD *and* functional MRI.” The database was filtered through abstract analysis to include only publications that used human subjects, were published in the English language, and were not submitted as reviews or case reports. The final database comprised 45 publications ranging from 1993 to 2005 (only articles published before 1 May 2005 were included). Although functional differences have been reported in many neurological structures in PTSD studies, we focused our interpretations on several regions of interest that are closely related to the presentation of PTSD symptoms. These structures are the amygdala, mPFC (including the ACC, OFC, and the medial prefrontal cortex proper), hippocampus, parahippocampus, and thalamus.

RESULTS

SYMPTOM PROVOCATION PARADIGMS

The most widely used paradigm to measure differences in neural activation between patients with PTSD and healthy controls is symptom provocation. Various stimuli, including pictures, sounds, and autobiographical scripts, have been used to trigger neural responses.

By exposing patients with PTSD to images and sounds related to their traumatic experiences, it is possible to elicit activity in brain regions related to their symptoms. Three studies using combat sounds were carried out using SPECT technetium-99m hexamethyl propylenamine oxime (Tc-99m HMPAO) in veterans with combat-related trauma. Zubieta et al. [1999] found increases in the blood flow of the mPFC, and Liberzon et al. [1999] reported increased cerebral perfusion in both the left amygdala and left nucleus accumbens. In another study, the latter author found a reduced ratio of cortical/subcortical perfusion [Liberzon et al., 1996] but did not include a control population. Table 2 summarizes PTSD studies using SPECT.

PET studies have also adapted audio and visual stimuli related to combat situations. Pissiota et al. [2002] reported increased rCBF in the right amygdala and the right sensorimotor cortex between neutral and traumatic sound presentation in veterans with combat-related PTSD. This study did not include any controls; therefore, results are only comparable between conditions. When presenting combat sounds and pictures to Vietnam veterans with combat-related PTSD, Bremner et al. [1999b] found decreased mPFC (including the ACC) perfusion and increased rCBF in regions involved in visuospatial processing compared to that in healthy controls. A study using visual images of combat situations [Shin et al., 1997] found increased rCBF in both the right amygdala and the ventral part of the anterior cingulate gyrus. The presentation of traumatic slides in fMRI studies has been applied to a group of Israeli soldiers [Hendler et al., 2003] and survivors of a severe earthquake [Yang et al., 2004]. In the combat-trauma group, a significant increase in amygdalar activity was found. On the contrary, the study by Yang et al., did not reveal any alterations in the amygdala, but did reveal decreased mPFC activation accompanied by more prominent parahippocampal and cerebellar activity. Table 3 summarizes region of interest findings in PET and fMRI studies of PTSD.

Another method of provoking PTSD symptoms that is widely used in functional neuroimaging studies in PTSD is the presentation of autobiographical scripts related to a subject's traumatic experiences. Results from SPECT (Tc-99mHMPAO) studies by Pagani et al. [2005] and Lindauer et al. [2004] indicated different rCBF patterns in patients with PTSD compared to healthy controls. The former research found increased blood flow in the right hemisphere of patients with mixed civilian trauma, whereas the latter found a significantly decreased rCBF in the medial frontal gyrus, accompanied by an increase in right cuneus perfusion in police officers.

Similar paradigms using PETwere also successful in reporting altered neural activity in PTSD. In a recent study in which veterans with combat-related PTSD were scanned using H_2O^{15} while they listened to scripts, Britton et al. [2005] found a relatively greater rostral ACC deactivation. Liberzon [2003] replicated this finding in a similar patient population and also noted reduced amygdala activation in these patients. In other studies, changes in rCBF were found in patients with PTSD related to childhood sexual abuse. Bremner et al. [1999a] also found a failure of activation in the ACC in this group using PET (H_2O^{15}). Furthermore, decreased blood flow was reported in the right hippocampus and visual association cortex, whereas the motor cortex and posterior cingulate showed increased activity patterns. In a similar PET $[O^{15}]CO_2$ paradigm, Shin et al. [1999] found altered rCBF in the mPFC

(increases in the OFC, decreases in the ACC), increased perfusion in the anterior temporal poles, and reduced blood flow in the parahippocampal and left inferior frontal gyri. A more recent study [Shin et al., 2004a] also noted reduced activation in the medial frontal gyrus of combat veterans with PTSD. Furthermore, cerebral perfusion was higher in the amygdala for patients with PTSD. Finally, Rauch et al. [1996] found evidence for increased blood flow using PET $[O^{15}]CO_2$ in various limbic, paralimbic, and visual areas, whereas no activations were reported for the hippocampus, dorsolateral prefrontal cortex, or thalamus. This last study, however, did not use any type of control group without PTSD symptoms.

Autobiographical scripts have also been adapted for paradigms using fMRI. Two studies by Lanius et al. [2001, 2003b] have found reduced activity in the mPFC and thalamus of patients with trauma related to sexual abuse and MVAs. Furthermore, these studies found decreased OFC [Lanius et al., 2001] and parahippocampal activity [Lanius et al., 2003b]. Patients with PTSD who show dissociative responses to autobiographical scripts were reported to show decreased parahippocampal activation and heightened mPFC responses.

Functional connectivity analyses of PET and fMRI studies using autobiographical scripts have revealed differential functional activation patterns in patients with mixed civilian-trauma-based PTSD. Gilboa et al. [2004], using PET (H_2O^{15}), found no differences in memory retrieval networks (including the hippocampus and right prefrontal cortex) between patients and healthy subjects. Alterations were found in the networks related to autonomic and emotional control in PTSD, with influences of structures such as the amygdala and ACC. Using fMRI, Lanius et al. [2004] found different connectivity maps, with patients showing enhanced patterns in the right hemisphere, in regions such as the posterior cingulate gyrus, caudate, and parietal and occipital lobes. Another fMRI study by the same group, focusing on patients with dissociative PTSD symptoms [Lanius et al., 2005] found greater activation in neural networks involved in representing bodily states. Structures found to show altered presentations in this network include the right middle frontal gyrus, superior temporal gyrus, right insula, right cuneus, and left parietal lobe.

The neural response to the presentation of emotionally valenced faces has also been used to compare healthy controls to patients with PTSD. Shin et al. [2005] used an fMRI paradigm where fearful, happy, and neutral faces were presented to patients who had experienced different types of trauma. Patients with PTSD showed heightened amygdalar responses, accompanied by diminished mPFC activity, when compared to healthy controls. In an earlier study of combat veterans, Rauch et al. [2000] used fMRI while presenting faces expressing the same emotions but using a masking technique. Similarly, exaggerated responses of the amygdala were found; yet no alterations were observed in the mPFC between patients and controls.

As with emotional faces, emotionally laden words have also resulted in altered brain activity in fMRI studies of patients with PTSD. Sexually and physically abused patients with PTSD were found to show differential amygdala activity by Protopopescu et al. [2005]. More specifically, amygdalar activation was more pronounced and less capable of habituating to trauma-related negative words. In a study wherein Vietnam veterans were exposed to various words (combat, general negative, neutral) while performing a counting Stroop task [Shin et al., 2001], a failure of rostral ACC activation was observed in patients with combat-related PTSD. Furthermore, significantly greater activity was seen in the hippocampus, parahippocampus, and thalamus of these patients. Finally, Driessen et al. [2004] presented traumatic words and generally negative words to patients with borderline personality disorder (BPD), with and without comorbid PTSD. Patients with BPD and PTSD showed more pronounced amygdalar, parahippocampal, and cerebellar activity. The OFC showed smaller activation in patients with PTSD than in individuals diagnosed solely with BPD.

One PET (H_2O^{15}) study [Bremner et al., 2005] also investigated the altered neural responses to fearful stimuli using a Pavlovian fear-conditioning paradigm, where a visual presentation (conditioned stimulus) was paired an electric shock (unconditioned stimulus). Bremner et al. found that patients with PTSD showed exaggerated left amygdala activation during the fear acquisition phase, whereas reduced mPFC and ACC function were found during the fear extinction phase relative to controls.

ACTIVE TASK PARADIGMS

Task paradigms are also commonly used to elicit neural activation in patients with PTSD. One task applied to PET functional imaging techniques in PTSD is the auditory continuous performance task (ACPT) by Semple. In a study in which they used this paradigm, Semple et al. [1993] found a significantly increased blood flow in the OFC and a reduced left/right hippocampal perfusion ratio in the PTSD group. In a similar study by the same authors, reductions in rCBF were found in the parietal cortex. A more recent study by Semple et al. [2000] revealed increased rCBF in the right amygdala, left parahippocampal gyrus, and the occipital cortex when patients were performing the ACPT task. Furthermore, patients with PTSD showed reduced frontal cortex and anterior cingulate activity compared to healthy controls. All of the subjects in these studies were veterans with combat-related PTSD and a history of substance abuse. The former two studies used H_2O^{15} radiotracers, whereas the latter introduced ^{15}O-butanol.

Other functional imaging studies in subjects with PTSD make use of tasks that target memory. Bremner et al. [2003a] used a paragraph-encoding task to measure the performance of patients' verbal declarative memory and its neural correlates. Results from this PET (H_2O^{15}) study in women who experienced childhood sexual abuse show a failure in left hippocampal activation, accompanied by a decreased blood flow in the OFC and cerebellum. Another PET (H_2O^{15}) study by the same authors, using an emotional word retrieval task [Bremner et al., 2003b], replicated the findings regarding the left hippocampus and OFC in women with PTSD related to childhood sexual abuse. Furthermore, reduced blood flow was found in the medial prefrontal cortex (including the anterior cingulate) and the inferior temporal gyrus. Increased activity was reported in the posterior cingulate, left inferior parietal cortex, left middle frontal gyrus, and visual association cortex. Shin et al. [2004b], introducing the radiotracer [^{15}O]CO_2, reported different findings regarding hippocampal activity during the retrieval of nonemotional words: Bilateral activation of the hippocampus was found to be greater in patients with PTSD. Using a working memory task and applying a functional connectivity analysis in a PET (H_2O^{15}) study, Shaw et al. [2002] revealed significantly altered memory network connections in patients with PTSD. More specifically, reduced activation was found in the inferior medial frontal lobe, right inferior temporal gyrus, and bilaterally in the middle frontal gyri; increased rCBF was found in the inferior parietal lobes and the left precentral gyrus.

RESTING PARADIGMS

Several studies used resting paradigms to measure cerebral perfusion, receptor binding, and cerebral glucose metabolism. Three of these studies used SPECT to analyze cerebral perfusion in PTSD. In the first reported study, Lucey et al. [1997], using 99m-TcHMPAO, found a decreased rCBF in the superior frontal cortex and the right caudate. Furthermore, no changes were reported in the cerebellum, medial frontal cortex, and thalamus. Mirzaei et al. [2001], using the same radiotracer, found an increase in left hemisphere rCBF in patients with PTSD who survived torture episodes. The most recent results, reported by Bonne et al. [2003b], using 99m-Tc HMPAO, found decreased activity in the right precentral, superior temporal, and fusiform gyri, accompanied by increased rCBF in the cerebellum. Both male and female subjects were included, all having experienced civilian trauma.

Studies using SPECT to measure receptor-binding affinity in patients with PTSD had inconsistent findings. According to Bremner et al. [2000], benzodiazepine receptor binding was reduced in the pre-frontal cortex in patients with Vietnam combat–related PTSD. Fujita et al. [2004] applied a similar paradigm to Gulf War veterans and found no differences in receptor binding. Both studies used an [^{123}I]Iomazenil radiotracer. Furthermore, serotonin receptor 1A (5HT1AR) binding was also found to be unaltered in patients with PTSD with mixed trauma types, using the [^{18}F]FCWAY radiotracer [Bonne et al., 2005].

In a PET study by Bremner et al. [1997], glucose metabolism in response to the administration of the α_2-AR antagonist, yohimbine, was measured in Vietnam veterans with a history of combat-related PTSD. Metabolic rates were decreased in the OFC, temporal cortex, and the parietal cortex using ^{18}F-fluorodeoxy-glucose (FDG). Furthermore, the PTSD group showed significant decreases in hippocampal glucose metabolism in response to yohimbine administration. It is also interesting to note that the metabolism of the temporal cortex was reduced during placebo administration (rest state).

DISCUSSION

The findings of the studies summarized in the previous section indicate several trends in neural correlates of PTSD, permitting us to create a model of this disorder. Two of the most recurrent findings in patients with PTSD, using PET, fMRI, and SPECT are decreased medial prefrontal cortex and increased amygdalar activation. On the other hand, inconsistent findings have been tied to regions such as the hippocampus and the adjacent parahippocampal gyrus. These inconsistencies could be the result of a wide variation of parameters in different studies, and of the complex nature of PTSD.

Altered function in the amygdala is frequently discussed in the clinical presentation of PTSD. Studies using symptom provocation paradigms and active tasks have both found an increased amygdalar activation pattern in patients with PTSD compared to healthy controls. Symptom provocation studies target the fear response mechanism, in which the amygdala is thought to play a pivotal role. Stimuli successfully used in these paradigms include combat sounds [Liberzon et al., 1999] and images [Hendler et al., 2003; Shin et al., 1997], emotional faces [Rauch et al., 2000; Shin et al., 2005], emotional words [Protopopescu et al., 2005], and traumatic scripts [Shin et al., 2004a]. Furthermore, studies using active tasks found amygdala activation when subjects were instructed to perform an auditory continuous performance task [Semple et al., 2000], explicit memory recall tasks [Shin et al., 2004b], and active trauma recall [Driessen et al., 2004]. On the whole, the amygdala appears to be more active in patients with PTSD. This hyperactivation is thought to be the reason for a failure of the extinction to fearful stimuli, a common component of the clinical presentation of PTSD [Bremner et al., 1995a].

Another common finding in studies measuring neural activity in PTSD is a hypoactivation of the mPFC, which includes the OFC (Brodmann's area 11), the ACC (Brodmann's area 32), and mPFC proper (Brodmann's areas 9 and 25). Symptom provocation paradigms that found this trend for the latter two regions in patients with PTSD made use of traumatic sounds and images [Bremner et al., 1999b; Yang et al., 2004], emotional faces [Shin et al., 2005], and traumatic scripts [Bremner et al., 1999a; Britton et al., 2005; Lanius et al., 2001; Liberzon et al., 2003; Lindauer et al., 2004; Shin et al., 1999, 2004]. Furthermore, studies using active tasks found relative mPFC deactivation when subjects were instructed to perform an auditory continuous performance task [Semple et al., 2000], memory tasks [Bremner et al., 2003b; Lanius et al., 2003B], or a counting Stroop task using combat words [Shin et al., 2001]. Similarly, studies using resting paradigms [Bremner et al., 1997], symptom provocation [Driessen et al., 2004; Lanius et al., 2001] and active memory tasks

also found OFC dysfunction. Studies using SPECT to measure benzodiazepine receptor binding affinity have found both reductions [Bremner et al., 2000] and unchanged [Fujita et al., 2004] binding in the mPFC of war veterans. The latter finding was related to Gulf War veterans, whereas the former included veterans from the Vietnam era. An alteration in benzodiazepine receptors is thought to be involved in causing PTSD symptoms such as elevated levels of anxiety.

Several studies have suggested a relationship or direct functional link between the amygdala and the mPFC regions discussed here. In fact, four functional imaging studies [Driessen et al., 2004; Semple et al., 2000; Shin et al., 2004a, 2005] have found a decrease in mPFC activity and a simultaneous hyperactivation of the amygdala simultaneously in patients with PTSD. It is thought that the mPFC provides a system of negative feedback to the amygdala, regulating its activation during emotional and fearful conditions: An increase in mPFC activity inhibits activation of the amygdala, whereas a decrease in mPFC activity, as found in numerous imaging studies in PTSD, seems to be connected to increased, or unchecked, amygdalar activity.

Although there is significant agreement about the connection of mPFC and amygdalar activity among the functional imaging studies, some findings point in different directions. Gilboa et al. [2004] reported a parallel increase in mPFC and amygdalar activity, for example. Conversely, another study reported parallel hypoactivation of these structures in a group of combat veterans with PTSD [Liberzon et al., 2003]. Other PTSD studies report no changes in amygdalar [Bremner et al., 1999a,b; Britton et al., 2005; Lanius et al., 2001, 2002, 2003b; Yang et al., 2004] or mPFC [Bonne et al., 2005; Semple et al., 1996] activity. One possible explanation for the lack of amygdalar activation in two of these studies [Britton et al., 2005; Lanius et al., 2001] is the use of traumatic scripts (internally generated stimuli as opposed to externally generated sounds or images). Yang et al. [2004] attributed their lack of amygdalar activation to paradigm design and small sample size ($n = 11$). The fact that Rauch et al. [2000] did not observe any mPFC changes is difficult to explain. In a more recent symptom provocation study using the presentation of emotional faces, activity in the mPFC was significantly reduced in patients with PTSD [Shin et al., 2005]. Furthermore, studies using combat pictures [Bremner et al., 1999b] and slides related to natural disaster [Yang et al., 2004] found significantly reduced activation of the mPFC. One possibility for the lack of results in the study by Rauch et al. [2000] could be the presentation of masked emotional faces, a practice not employed by studies showing reduced mPFC activity. Semple et al. [1996] also failed to find a difference in mPFC activity, yet they did manage to do so in a more recent study using a similar auditory continuous performance task paradigm. Finally, Lanius et al. [2002] found an increase in mPFC/ACC region, as opposed to the decreased activation trend. A possible explanation for this is the exclusive participation of subjects with dissociative responses to fearful stimuli, as we discuss further on. In a SPECT study, Zubieta et al. [1999] also reported an increased mPFC activity and hypothesized hyperactive dysfunction of the mPFC.

Inconsistencies are far from uncommon in neuroimaging studies of PTSD. For instance, findings in the hippocampus and parahippocampus are highly inconsistent when considered both individually and compared to each other. The parahippocampal gyrus, a region anatomically adjacent to the hippocampus, is liaison for many neocortical projections from the hippocampus and also the source of most afferents to the hippocampus. Activity in these structures is therefore related and can be compared to a certain extent. Despite their functional relationship in one of the limbic pathways, results in functional imaging studies of PTSD appear to be altered regarding these regions, because the majority of findings suggest a decrease in hippocampal functioning alongside increased parahippocampal

activity. When we look at these results more closely, however, it is possible to find trends of neural activity disruption in PTSD.

The hippocampus plays a critical role in the consolidation of novel memories of facts and events. Several studies have shown that patients with chronic PTSD perform significantly more poorly on hippocampal-based memory and learning tasks [Bremner et al., 1993, 1995b]. Starting from this premise, a multitude of studies have explored the hippocampal structure of patients with PTSD. A review by Geuze et al. [2005] summarized the 14 MRI-based hippocampal volume reduction studies in PTSD as being inconsistent, because both reductions and insignificant differences were observed. Studies reporting differences in the functional properties of the hippocampus have similarly presented consistency issues. Altered hippocampal function was reported mostly in paradigms that employ memory to elicit hippocampal activity. PET studies by Bremner et al. using declarative memory tasks [Bremner et al., 2003a,b] and script-driven imagery [Bremner et al., 1999a] have shown a failure or reduced activation of the hippocampus. In addition, Shin et al. [2004b] demonstrated reduced hippocampal activation using PET during a word-stem completion task. On the contrary, in the only known fMRI study to report hippocampal dysfunction, Shin et al. [2001] found increased hippocampal activity during a counting Stroop task that uses emotionally valenced words. Finally, using a resting paradigm, Bremner et al. [1997] observed reduced hippocampal functioning when administering the α_2 receptor-antagonist yohimbine. In conclusion, reduced activation of the hippocampus is found in patients with PTSD during memory-related tasks, whereas studies using tasks with emotional content report inconsistent findings.

The parahippocampal gyrus is to a great extent functionally related to the hippocampus. The majority of findings related to this structure show a trend of increased activity, which could contradict the theory of memory deficits in PTSD. The parahippocampus is an extensive neural structure with a large functional diversity. In analyzing the studies that specified the precise location of altered parahippocampal functioning, we can attempt to derive several interesting conclusions. The studies that suggest decreased parahippocampal functioning [Lanius et al., 2002, 2003b] refer to more specific regions such as the entorhinal and perirhinal cortices (Brodmann's areas 28 and 35, respectively). The entorhinal cortex has been found to be one of the major afferents to the hippocampus. Results for these specific regions reported a decrease in activity in patients with PTSD. Both regions are found to be functionally related to emotion, memory, and association of these memories. Another region, anatomically different but functionally similar to these areas, the retrosplenial cortex, is situated in the posterior cingulate cortex (Brodmann's area 30). This region is also involved as an intermediary between the hippocampus and more cortical areas, and findings from the same studies show reduced activation in patients with PTSD.

On the other hand, three studies that reported increases in parahippocampal activity referred more specifically to the more posterior-oriented lingual gyrus [Brodmann's area 19; Bremner et al., 1999a,b; Shin et al., 2001; Yang et al., 2004]. This specific region has previously been linked to visuospatial processing and visual association. A possible explanation for the increased activity of this area, and perhaps other regions of the parahippocampus, is that it may facilitate or trigger flashbacks and intrusive thoughts. The fact that some studies report the specific areas within a region of interest enables us to make the distinctions found above. Other studies unfortunately did not report their results in great detail, making it difficult to trace the trend within the parahippocampus. It is therefore important to note that a future direction in the field of neuroimaging should be a common way of reporting results, paying close attention to the level of detail. This includes a more specific categorization of parahippocampal structures and a better understanding of the role these play in various networks.

A less documented finding in functional neuroimaging studies is the involvement of the thalamus in patients with PTSD. The thalamus is an important relay station for the transmission of external sensory information to different areas of the cerebral cortex and limbic system, where this information is processed. Target regions include the frontal cortex, cingulate gyrus, amygdala, and hippocampus, all of which are closely related to the neural networks hypothesized to be active in PTSD. Two studies by Lanius et al. [2001, 2004] using traumatic script-driven imagery and another using traumatic memory recall [Lanius et al., 2003b] report decreased thalamic activity. The disruption in thalamic activity could lead to several of the traits displayed by the clinical presentation of PTSD. Due to its functional nature, a disruption in activity of the thalamus could lead to the misinterpretation of external stimuli. It is important to note, however, that the only research group that found altered activity in PTSD with regard to the thalamus, used fMRI as opposed to SPECT or PET. Furthermore, this particular group uses a 4 Tesla MRI scanner as opposed to the more conventional (and lower resolution) 1.5 and 3 Tesla scanners. Due to the importance of the thalamus in relaying sensory information to higher cortical regions, it is a region of interest in PTSD research that deserves and requires further investigation.

Summarizing and finding trends in the results of the functional imaging studies to date remain a complicated issue. One possible explanation underlying discrepancies among the various studies lies in the actual design of the paradigms used to measure neural activity in patients with PTSD. According to our current research, 45 studies published used functional neuroimaging techniques in PTSD research. These studies make use of a wide range of methodologies: measuring resting brain activity, presenting a wide range of stimuli, and using active tasks performed by a subject. Within these main groupings there are further distinctions to be made, such as the type of stimulus (auditory, visual, trauma script, personal script), type of task (active recall, counting Stroop task, auditory continuous performance task), and type of tracer used in PET or SPECT studies. Due to this variation, difficulties arise when comparing data across different studies.

Another issue that confounds comparison is a wide array of subjects in specific studies and when comparing different studies, including patients with a broad trauma spectrum and of different sexes. It is important to distinguish between trauma types, such as trauma caused by MVAs, sexual assault, combat situations, natural disasters, and so forth. This could be one reason behind the inconsistency in hippocampal activation. Furthermore, studies have shown significant differences in properties between the male and female brain [Goldstein et al., 2001]. PTSD is a complex anxiety disorder with foundations in an extensive neural circuitry. By examining patients with a common traumatic history and sex it is possible to analyze neural activity with higher precision, and potential differences between the groups can be brought to light.

In addition to the different traumas that cause the onset of PTSD, the clinical presentation of symptoms also varies between patients. Recently, it has been hypothesized that there are two main categories of PTSD symptoms, closely related to the criteria that make up the disorder. Whereas some patients tend to be hyperaroused, others show numbing in response to fearful situations. This latter often have moments of dissociation, as opposed to the former, who tend to be hypervigilant and experience flashbacks of their trauma. In a study performed by Lanius et al. [2005], functional connectivity was measured using fMRI in both dissociated and flashback PTSD groups. The findings indicate a different neural connectivity between the two groups, with the dissociated group showing greater connectivity in the left inferior frontal gyrus, an area previously found to be related to the determination of self-relevance of emotional statements [Lanius et al., 2005]. Moreover, in a case report of a married couple involved in an MVA, Lanius et al. [2003a] clearly presented a case for different types of PTSD. The husband responded to a traumatic script about the accident in a state of

hyperarousal, whereas his wife became numb and frozen. Because there is a possible difference in brain activation patterns between the flashback and dissociated PTSD groups, comparing these two groups of patients may lead to distortions in the outcome of a study.

An interesting observation can also be drawn from the discrepancy in abnormalities between functional versus structural neuroimaging. Although functional neuroimaging demonstrates abnormalities in the mPFC (including ACC) and amygdalar circuit, structural MRI studies have exclusively focused on the hippocampus, but not on the amygdala. Functional neuroimaging studies suggest that there are clear differences in metabolic acticity in the mPFC–amygdala circuit; therefore, it would be interesting to investigate further whether patients with PTSD show structural differences with respect to their amygdalae.

Another important issue that needs to be raised is that one may wonder whether the abnormalities found in functional neuroimaging studies are specific to PTSD. Similar findings have also been reported in other studies, targeting other anxiety disorders, such as obsessive–compulsive disorder [Nakao et al., 2005], panic disorder [van den Heuvel et al., 2005], and generalized social phobia [Phan et al., 2005]. We must be careful, however, in assuming similarity with these other anxiety disorders due to the specificity of the experimental designs. Studies that target patients with PTSD use different experimental designs, with content specific to the disorder. For example, script-driven imagery for patients with PTSD differs from that used for patients with other anxiety disorders. In turn, this may elicit different, disease-specific brain activation patterns.

FUTURE DIRECTIONS

Functional neuroimaging studies that use SPECT, PET, and fMRI have opened up a new window to uncover the mechanisms behind PTSD. The most consistent finding in many research studies to date is a relative decrease in mPFC activity, and increased amygdalar activation. Although no conclusive evidence exists, a functional relationship between the two regions is hypothesized, which is altered in PTSD. The role of the hippocampus and parahippocampal gyrus in PTSD is ambiguous, despite several studies that support the involvement both in structural and functional studies. The numerous variations between the studies discussed and the complexity of PTSD symptomatology are potential causes for the inconsistent findings to date. More comprehensive meta-analyses of the findings across functional imaging studies in PTSD could be benefited by paradigm conformation. With a standard set of guidelines for subject inclusion, scanning procedures, stimulus presentation, tasks and other variables, results may become more comparable. Correspondingly, setting guidelines risks limiting novel methods and ultimately novel results, potentially impeding progress in uncovering the neural mechanisms underlying PTSD. As the research base deepens, the number of studies increases, facilitating comparison. Ultimately this may lead to more frequent and consistent trends. In conclusion, many advances have been made in the fields of neurobiology and neuroimaging of PTSD, but further research is imperative to further approach the neurobiological correlates of this complex and diverse disorder.

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TABLE 1

Methods of functional neuroimaging studies in PTSD

Study	Year	Population	Sample Size	Control Group	Sample Size	Imaging Method	Active Condition	Control Condition
SPECT								
Pagani, M	2005	Assaultive & Non-Assaultive PTSD	20	Assaultive & Non-Assaultive without PTSD	27	HMPAO	Traumatic Scripts	-
Lindauer, RJL	2004	Police Officers with PTSD	15	Police Officers without PTSD	15	HMPAO	Traumatic Scripts	Neutral Scripts
Fujita, M	2004	Combat-related PTSD	19	Non-deployed, healthy veterans	19	[^{123}I]Iomazenil	Rest	-
Bonne, O	2003	Mised Vivilian PTSD	11	Mixed Civilian Trauma without PTSD/ Healthy	17/11	HMPAO	Rest	-
Mirzaei, S	2001	Torture Survivors with PTSD	8	Healthy subjects	8	HMPAO	Rest	-
Bremner, JD	2000	Combat-related PTSD	13	Healthy subjects	13	[^{123}I]Iomazenil	Rest	-
Zubieta, JK	1999	Combat-related PTSD	12	Veterans without PTSD/Healthy	11/12	HMPAO	Combat Sounds	White Noise
Liberzon, I	1999	Combat-related PTSD	14	Veterans without PTSD/Healthy	14/11	HMPAO	Combat Sounds	White Noise
Lucey, JV	1997	Unspecified	16	Healthy subjects	15	HMPAO	Rest	-
PET								
Britton, JC	2005	Combat-related PTSD	15	Healthy subjects	14	[^{15}O]H_2O	Traumatic/ Stress Scripts	Neutral Scripts
Bonne, O	2005	Abuse Related PTSD	12	Healthy subjects	11	[^{18}F]FCWAY	Rest	-
Bremner, JD	2004	Childhood Sexual Abuse with PTSD	12	Childhood Sexual Abuse without PTSD	9	[^{15}O]H_2O	Emotional Stroop	Color Stroop/Neutral Control
Shin, LM	2004a	Firefighters with PTSD	8	Firefighters without PTSD	8	[O^{15}]CO_2	Explicit Memory Recall Tasks	Baseline Task
Shin, LM	2004b	Combat-related PTSD	17	Combat veterans without PTSD	19	[O^{15}]CO_2	Traumatic Scripts	Neutral Scripts
Gilboa, A	2004	Civilian Trauma PTSD	14	Civilian Tuauma, no PTSD	12	[^{15}O]H_2O	Traumatic Scripts	Neutral Scripts
Bremner, JD	2003a	Childhood Sexual Abuse with PTSD	10	Healthy subjects	11	[^{15}O]H_2O	Emotional Word Retrieval	Neutral Word Retrieval
Bremner, JD	2003b	Childhood Sexual Abuse with PTSD	10	Childhood Sexual Abuse without PTSD	12/11	[^{15}O]H_2O	Memory- encoding Task	Attention task
Liberzon, I	2003	Combat-related PTSD	16	Combat veterans without PTSD/Healthy	15/15	[^{15}O]H_2O	Traumatic/ Stress Scripts	Neutral Scripts
Shaw, ME	2002	Mixed PTSD	10	Healthy subjects	10	[^{15}O]H_2O	Working Memory Task	-
Semple, WE	2000	Combat-related PTSD + Substance Abuse	7	Healthy subjects	6	^{15}Q-Butanol	Auditory Continuous Performance Task	Rest

Study	Year	Population	Sample Size	Control Group	Sample Size	Imaging Method	Active Condition	Control Condition
Bremner, JD	1999a	Childhood Sexual Abuse with PTSD	10	Childhood Sexual Abuse without PTSD	12	$[^{15}O]H_2O$	Trauma Imagery/ Perception	Neutral Imagery & Perception
Bremner, JD	1999b	Combat-related PTSD	10	Combat veterans without PTSD	10	$[^{15}O]H_2O$	Combat Sounds & Slides	Neutral Sounds & Slides
Shin, LM	1999	Childhood Sexual Abuse with PTSD	8	Childhood Sexual Abuse without PTSD	8	$[^{15}O]CO_2$	Traumatic Scripts	Neutral Scripts
Shin, LM	1997	Combat-related PTSD	7	Combat veterans without PTSD	7	$[O^{15}]CO_2$	Combat Imagery/Perception	Negative & Neutral Imagery/ Perception
Bremner, JD	1997	Combat-related PTSD	10	Healthy subjects	10	$[^{18}F]FDG$	Yohimbine Administration	Placebo Administration
Semple, WE	1996	Combat-related PTSD + Substance Abuse	8	Healthy subjects	8	$[^{15}O]H_2O$	Auditory Continuous Performance Task	Rest
Semple, WE	1993	Combat-related PTSD + Substance Abuse	6	Healthy subjects	7	$[^{15}O]H_2O$	Auditory Continuous Performance Task	Rest
fMRI								
Lanius RA	2005	Sexual Abuse & MVA PTSD (dissociative/ reliving)	10/11	Sexual Abuse & MVA without PTSD	10	fMRI	Traumatic Script-Driven Imagery	Neutral Script-Driven Imagery
Shin LM	2005	Combat-related/ Firefighters with PTSD	13	Combat-veterans/ Firefighters without PTSD	13	fMRI	Fearful & Happy Faces	Neutral Faces
Protopopescu, X	2005	Sexual & physical Assault with PTSD	11	Healthy subjects	21	fMRI	Negative/Anxiety & Positive Words	Neutral Words
Yang, P	2004	Natural Disaster with PTSD	5	Natural Disaster without PTSD	6	fMRI	Traumatic Slides	Neutral Slides
Driessen, M	2004	Traumatized BPD Patients with PTSD	6	Traumatized BPD Patients without PTSD	6	fMRI	Active Trauma Recall	Active Non- trauma Recall
Lanius, RA	2004	Sexual Abuse & MVA PTSD	11	Sexual Abuse & MVA without PTSD	13	fMRI	Traumatic Script-Driven Imagery	Neutral Script-Driven Imagery
Hendler, T	2003	Combat-related PTSD	10	Combat veterans without PTSD	11	fMRI	Combat Slides	Non-Combat Slides
Lanius, RA	2003b	Sexual Abuse & MVA PTSD	10	Sexual Abuse & MVA without PTSD	10	fMRI	Traumatic/Sad/ anxious Memory Recall	Neutral Memory Recall
Lanius, RA	2002	Sexual Abuse with PTSD	7	Sexual Abuse & MVA without PTSD	10	fMRI	Traumatic Script- Driven Imagery	-
Shin, LM	2001	Combat-related PTSD	8	Combat veterans without PTSD	8	fMRI	Counting Stroop (Combat Words)	Counting Stroop (Neutral Words)
Lanius, RA	2001	Sexual Abuse & MVA PTSD	9	Sexual Abuse & MVA without PTSD	9	fMRI	Traumatic Script-Driven Imagery	Neutral Script-Driven Imagery
Rauch, SL	2000	Combat-related PTSD	8	Combat veterans without PTSD	8	fMRI	Masked Fearful Faces	Masked Happy Faces

SPECT: Single Photon Emission Computed Tomography; PET: Positron Emission Tomography; fMRI: Functional Magnetic Resonance Imaging; PTSD: Posttraumatic Stress Disorder; MVA: Motor Vechicle Accident; BPD: Borderline Personality Disorder; Tc-^{99}-ECD: 99mTc ethylene dicysteinate; FDG: Fluorodeoxyglucose; HMPAO: 99mTc hexamethyl-propyleneamine oxime.

TABLE 2

Main findings of SPECT studies in PTSD

Study	Year	Measure	Main findings
Pagani et al.	2005	rCBF	↑ Right hemisphere blood flow
Lindauer et al.	2004	rCBF	↓ Medial frontal gyrus, ↑ right cuneus
Fujita et al.	2004	BZR	No difference in BZR levels between groups
Bonne et al.	2003b	rCBF	↑ Cerebellum; ↓ right precentral, superior temporal, and fusiform gyri
Mirzaei et al.	2001	rCBF	↑ Left-hemisphere blood flow
Bremner et al.	2000	BZR	↓ Distribution volume in the prefrontal cortex
Zubieta et al.	1999	rCBF	↑ Prefrontal cortex
Liberzon et al.	1999	rCBF	↑ Left amygdala, left nucleus accumbens
Lucey et al.	1997	rCBF	↓ Superior frontal cortex, right caudate; = medial frontal cortex, cerebellum, thalamus

This table illustrates the differences in activity uncovered using SPECT in patients with PTSD.

rCBF regional cerebral blood flow; BZR, benzodiazepine receptors; ↑, activity increase; ↓, activity decrease;=, no change in activity.

TABLE 3

Region of interest findings of PET and fMRI studies in PTSD

Study	Year	Measure	Hippocampus	Parahippocampus	Amygdala	mPFC/ACC	mPFC/OFC	Thalamus
Britton et al.	2005	rCBF			=	↓		
Shin et al.	2004a	rCBF	↑		↑			
Bremner et al.	2003a	rCBF	↓L			↓	↓	
Bremner et al.	2003b	rCBF	↓L				↓	
Semple et al.	2000	rCBF		↑	↑	↓		
Bremner et al.	1999a	rCBF		↑		↓		
Bremner et al.	1999b	rCBF	↓R	↑		↓	↓	
Shin et al.	1999	rCBF		↑		↓	↑	
Shin et al.	1997	rCBF			↑			
Bremner et al.	1997	GMB	↓	=	=	=	↓	=
Semple et al.	1996	rCBF				=		
Semple et al.	1993	rCBF					↑	
FMRI								
Shin et al.	2005	BOLD			↑	↓		
Protopopescu et al.	2005	BOLD			↑			
Yang et al.	2004	BOLD		↑	=	↓		
Driessen et al.	2004	BOLD		↑	↑		↓	
Lanius et al.	2004	BOLD						↓
Hendler et al.	2003	BOLD			↑			
Lanius et al.	2003b	BOLD		↓		↓		↓
Lanius et al.	2002	BOLD		↓		↑		=
Shin et al.	2001	BOLD	↑	↑		↓		↑
Lanius et al.	2001	BOLD			=	↓	↓	↓
Rauch et al.	2000	BOLD			↑	=		

This table illustrates the differences in activity of specific regions of interest in patients with PTSD.

Bremmer et al., 2004: measure=rCBF; ↑ R mPFC/ACC.

Shin et al., 2004b: measure=rCBF; ↑ Amygdala; ↓ mPFC/ACC.

mPFC/ACC, medial prefrontal cortex/anterior cingulated cortex; OFC, orbitofrontal cortex; rCBF, regional cerebral blood flow; BOLD, blood oxygen level–dependent signal; GMB, glucose metabolism; ↑, activity increase; ↓, activity decrease; =, no change in activity; R, right; L, left.