Neuroimaging findings in post-traumatic stress disorder

Systematic review

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Background Findings from neuroimaging studies complement our understanding of the wide-ranging neurobiological changes in trauma survivors who develop post-traumatic stress disorder (PTSD).

Aims To determine whether neuroimaging studies had identified structural and functional changes specific to PTSD.

Method A review of all functional and structural neuroimaging studies of subjects with PTSD was carried out. Studies were identified using general medical and specific traumatic stress databases and paper searches of current contents and other secondary sources.

Results The most replicated structural finding is hippocampal volume reduction, which may limit the proper evaluation and categorisation of experience. Replicated localised functional changes include increased activation of the amygdala after symptom provocation (which may reflect its role in emotional memory) and decreased activity of Broca's area at the same time (which may explain the difficulty patients have in labelling their experiences).

Conclusions Evidence from neuroimaging studies has suggested areas of the brain that may be damaged by psychological trauma. The clinical implications of these neuroimaging findings need to be investigated further because they challenge traditional therapeutic approaches.

Declaration of interest None.

Psychological reactions to traumatic events such as post-traumatic stress disorder (PTSD) are common and clinically important, with PTSD shown to have a lifetime prevalence in community samples of between 1.3% (Helzer et al, 1987) and 9% (Breslau et al, 1991). Research has confirmed the complex aetiology, epidemiology and symptomatology of PTSD and demonstrated a wide range of neurobiological changes (Friedman, 1997). Neuroimaging techniques provide opportunities to investigate structural and functional brain abnormalities, with the challenge then to integrate ever more complex neurobiological models across many neurochemical systems and structures into a cohesive understanding of PTSD.

This review examines structural and functional studies of the brain and also studies combining both modalities. Symptom and non-symptom provocation paradigms are examined in relation to functional studies, with case reports reviewed separately. Finally, the implications of these findings are discussed.

METHOD

Neuroimaging studies of subjects with PTSD were identified using literature searches of the Medline, Psychlit, Embase and Published International Literature on Traumatic Stress (PILOTS) databases, current contents, recent journal issues, reference lists and secondary sources (e.g. book chapters). A total of 30 published reports were located: 12 reports of brain structure in PTSD and 18 reports of brain function in PTSD (with two of these studies combining the imaging modalities). All English language articles published by August 2001 were included in this review.

RESULTS

Studies of brain structure in patients with PTSD

Computed tomography studies were first to suggest brain abnormalities in PTSD (Table 1) and there have been eight reports on magnetic resonance imaging (MRI) studies in subjects with PTSD (Table 2).

A number of studies have now demonstrated the involvement of the hippocampus in chronic PTSD. Two studies have examined the hippocampus without finding volumetric changes. The first study demonstrated the absence of hippocampal atrophy prior to the onset of PTSD (Bonne et al, 2001). Further, after single-event trauma, hippocampal abnormalities did not occur within 6 months. The second study (De Bellis et al, 1999) demonstrated smaller cerebral volumes and corpus callosum measures but no hippocampal changes in a group of maltreated children.

Possible reasons for the differences in the extent of volume reduction may be the study design (thickness of slices or whether or not the whole brain volume was calculated), the control group utilised, comorbid substance misuse, treatment effects or neurodevelopmental plasticity. In the main, researchers have performed comparative analyses to minimise the effect of other psychiatric disorders, including alcohol and substance misuse.

Sapolsky (1992) has described the sensitivity of hippocampal formation to severe, chronic traumatic stress and perhaps also to elevated glucocorticoids and/or excitatory amino acids, yet many other disorders such as bipolar disorder, schizophrenia, alcohol misuse and dementia are also associated with hippocampal atrophy (McEwen, 1997). Glucocorticoid-induced atrophy would appear to require prolonged or repeated bursts of glucocorticoid excess. However, basal glucocorticoid levels have been shown to be lower than normal in PTSD, perhaps due to enhanced adrenocortical sensitivity to feedback regulation (Yehuda et al, 1991, 1993).

The lateralisation of hippocampal damage has varied, with one possible explanation being changing vulnerability of the hippocampus to stress-induced damage at different developmental stages. The possibility that small hippocampi represent a predisposition to PTSD is not supported by the one study to examine acute PTSD (Bonne et al, 2001) because no change in volume was present acutely or within the

Table 1 Computed tomography studies of patients with post-traumatic stress disorder (PTSD)

Author	Subjects	Control/comparison groups	Diagnostic criteria (method)	Results
Silverman et al, 1989	14 exposed to neurotoxin (pentaborane); 7 with PTSD (7M; 7F)	None	DSM–III (Diagnostic Interview Schedule)	Abnormal VBRs at 1–3 and 18 months post-exposure; no association with PTSD or other diagnosis; abnormal VBRs may be due to neurotoxin
Peters et al, 1990	10 former prisoners of war (all M)	None	Not specified	Increased VBR and sulcal widening associated with sleep disturbances

VBR, ventricular brain ratio; M, male; F, female.

Table 2 Magnetic resonance imaging studies of patients with post-traumatic stress disorder (PTSD)

Author (method)	Subjects	Control/comparison groups	Diagnostic criteria (method)	Results
Myslobodsky et al, 1995	10 CR-PTSD (gender not specified)	10 matched controls	DSM–III (PTSD symptom checklist)	Increased incidence of cavum septum pellucidum (a neurodevelopmental abnormality)
Bremner et al, 1995	26 CR-PTSD (all M)	22 non-CE matched controls (all M)	DSM–III–R (Mississippi Scale for CR-PTSD)	Reduced (R)HC volume, correlates with memory impairment (verbal memory component of Wechsler Memory Scale); no correlation with PTSD symptom severity, dissociation or CE severity
Gurvits et al, 1996	7 CR-PTSD (all M)	7 CE non-PTSD controls (all M); 8 non-CE controls (gender not specified)	DSM–III–R (CAPS)	Bilateral reduction in HC volume with statistically significant correlation between (L)HC volume and CE
Bremner et al, 1997a	17 survivors of CSA and/or physical abuse (12M; 5F)	17 case-matched controls (12M; 5F)	DSM–III–R (Early Trauma Inventory)	Reduced (L)HC volume correlates with abuse duration; trend for larger amygdala in PTSD; reduction in (R)HC not statistically significant
Stein et al, 1997	21 survivors of CSA (all F)	21 non-CSA (all F)	DSM–IV (CAPS)	Reduced (L)HC volume correlates with dissociative symptoms and to lesser extent PTSD symptoms
Canive et al, 1997 (FLAIR sequence)	42 CR-PTSD (all M)	20 controls (all M)	DSM–III–R (CAPS and Mississippi Scale for CR-PTSD)	Focal WMLs in 8 CR-PTSD subjects
De Bellis et al, 1999	44 maltreated children with PTSD (25M; 19F)	61 case-matched non-abused controls (36M; 25F)	DSM–III and DSM–IV (non-standardised measures)	No HC changes; smaller cerebral volumes and total corpus callosum measures correlate with PTSD; cerebral volume correlates with age of onset of trauma and negatively with duration of abuse
Bonne et al, 2001	10 miscellaneous trauma (3M: 7F)	27 TE controls (15M: 12F)	DSM–IV (CAPS at 6 months)	No reduction in HC volume at 1 week or 6 months post-trauma

CR, combat-related; CE, combat-exposed; TE, trauma-exposed; HC, hippocampus; CSA, child sexual abuse; M, male; F, female; (R), right; (L), left; FLAIR, fluid attenuated inversion recovery imaging; CAPS, Clinician Administered PTSD Scale; WML, white matter lesion.

first 6 months. Further, Bremner et al (1995) demonstrated no volume difference between early-onset (before age 8 years) and late-onset (age 8 years or later) abuse.

Canive et al (1997) have uniquely demonstrated focal white matter lesions (WMLs) in eight subjects within a sample of 42 male combat-exposed subjects. Most of the WMLs were identified using the fluid attenuated inversion recovery (FLAIR) imaging sequence, which is not employed in typical MRI studies. The FLAIR sequence causes suppression of the cerebrospinal fluid signal with WML remaining bright, and the absence of the FLAIR imaging sequence may explain why other studies have not replicated this finding.

Studies using proton magnetic resonance spectroscopy in patients with PTSD

Proton magnetic resonance spectroscopy (MRS) can provide information about alterations in N-acetyl aspartate (NAA) and choline-containing compounds in the human brain without the radiation

exposure of positron emission tomography (PET) on single photon emission computed tomography (SPECT) but with lower sensitivity. Two studies have utilised this technique (Table 3) to measure NAA in subjects with PTSD. Schuff *et al* (1997) utilised both MRI and proton MRS to measure hippocampal volume and changes in NAA. An 18% reduction in right hippocampal NAA compared with a 6% reduction in right hippocampal volume suggests that NAA is a more sensitive measure of neuronal loss than volume changes. Although this study does not answer whether the NAA changes were pre-existing or a consequence of trauma rather than PTSD *per se*, the second study (Freeman *et al*, 1998) suggests that it correlated with PTSD. Decreased NAA has been demonstrated in other disorders, such as early-onset schizophrenia (Bertolino *et al*, 1996), temporal lobe epilepsy (Ende *et al*, 1997) and Alzheimer's disease (MacKay *et al*, 1996).

Studies of brain function in patients with PTSD

Most functional brain imaging studies in PTSD have used either PET or SPECT, which involve the detection of radiation-emitting radioisotopes to measure regional cerebral metabolism or blood flow. Functional MRI determines regional brain activation by detecting changes in blood oxygenation level and has a better spatial resolution than PET or SPECT.

The majority of studies employed a symptom provocation paradigm because measuring brain function at rest poses the problem of controlling the range of possible mental states. Studies have concentrated upon traumatic memory as a central component in PTSD because the presence of intrusive symptoms compellingly points to PTSD as the diagnosis. The one study to employ a non-symptom provocation paradigm (Lucey *et al*, 1997) used SPECT to study three groups with anxiety-related disorders: PTSD, obsessive–compulsive disorder (OCD) and agoraphobia with panic disorder (see Table 5). One study utilised a pharmacological challenge and is discussed separately below (Bremner *et al*, 1997*b*).

Pharmacological challenge study

Bremner *et al* (1997*b*) administered the α_2-antagonist yohimbine in a pharmacological challenge symptom provocation paradigm (Table 4). Yohimbine has been shown to provoke an exaggerated behavioural and biochemical responsiveness in subjects with PTSD (Southwick *et al*, 1993) and panic disorder (Charney *et al*, 1987*a*) but not in patients with other mental disorders (Charney *et al*, 1987*b*; Glazer *et al*, 1987; Rasmussen *et al*, 1987; Heninger *et al*, 1988). Bremner *et al* demonstrated that yohimbine administration correlated with increased anxiety symptoms in patients with PTSD but not in controls. Patients with yohimbine-induced panic attack (approximately 60%) had significantly reduced hippocampal and neocortical metabolism, suggesting enhanced noradrenaline release in subjects with PTSD after yohimbine administration.

Symptom provocation studies using PET

The majority of PET studies (six reports) provoked intrusive symptoms by using personalised trauma scripts or trauma-related sounds or pictures (Table 4), and one group examined changes during the performance of cognitive tasks (Semple *et al*, 1993, 1996, 2000).

Symptom provocation studies using SPECT

Only three SPECT studies have examined subjects with PTSD after symptom provocation (Table 5). Liberzon *et al* have conducted a SPECT study of subjects with combat-related PTSD and reported key findings in two papers (Liberzon *et al*, 1999; Zubieta *et al*, 1999) and one case report (Liberzon *et al*, 1996/97). They report separately on a specific analysis of the activity of the medial prefrontal cortex, which is thought to modulate the fear response (Zubieta *et al*, 1999). An increased regional cerebral blood flow (rCBF) was found in the medial prefrontal cortex in subjects with PTSD during provocation, although no statistically significant association was found with peripheral measures. The different findings may reflect the fact that the subjects were from the same cohort but the region-of-interest analysis was derived from a different cohort of normal controls. The anatomical region sampled for the region-of-interest analysis was more rostral than the anterior cingulate

Table 3 Functional magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) studies in patients with post-traumatic stress disorder (PTSD)

Author (tracer used)	Subjects	Controls/comparators	Design/method of provocation	Diagnostic criteria (method)	Results
Schuff *et al*, 1997 (proton MRS and MRI)	7 CR-PTSD (6 M; 1 F); 5 of the 7 completed both scans	7 non-veteran controls (gender not specified)	Measurement of NAA	Not specified	Reduced (R)HC NAA (greater than reduced (R)HC volume)
Freeman *et al*, 1998 (proton MRS)	21 CR-PTSD	8 CE-PTSD	Measurement of NAA/creatine ratio	DSM–IV (CAPS and SCID)	Decreased NAA/creatine ratios in the medial temporal lobes bilaterally, with (R) significantly lower than (L)
Rauch *et al*, 2000 (functional MRI)	8 CR-PTSD (all M)	8 CE non-PTSD (all M)	Masked face paradigm	DSM–IV (CAPS)	Exaggerated automatic amygdalar response to threat-related stimuli

CR, combat-related; CE, combat-exposed; M, male; F, female; (R), right; (L), left; SCID, Structured Clinical Interview for DSM–IV; CAPS, Clinician Administered PTSD Scale; NAA, *N*-acetyl aspartate; HC, hippocampus.

Table 4 Positron emission tomography (PET) studies of patients with post-traumatic stress disorder (PTSD)

Author (tracer used)	Subjects	Controls/ comparison groups	Design/method of provocation	Diagnostic criteria (method)	Results
Semple et al, 1993 (^{15}O-H$_2$O)	6 CR-PTSD (all M; 5 with SA)	7 controls (all M with SM)	Auditory continuous performance task, word generation task	Not specified	Increased rCBF in orbitofrontal cortex
Rauch et al, 1996 (^{15}O-CO$_2$)	8 miscellaneous trauma 'physiological responders' (2M; 6F)	No controls (within-subject design)	Personal traumatic script	DSM–III–R (SCID)	Increased rCBF in (R) limbic, paralimbic and (R) secondary visual areas; decreased rCBF in Broca's area ((L) inferior frontal cortex) and (L) middle temporal cortex
Semple et al, 1996 (^{15}O-H$_2$O)	8 CR-PTSD (all M with CA)	8 controls (all M with CA)	Auditory attentional task	DSM–III–R (Mississippi Scale for CR-PTSD)	Decreased parietal rCBF during attentional tasks
Bremner et al, 1997b (^{18}F-FDG and MRI)	10 CR-PTSD (all M)	10 non-CE controls (all M)	Yohimbine administration	DSM–III–R (Mississippi Scale for CR-PTSD)	Increased noradrenaline release in subjects with PTSD after yohimbine; correlates with decreased metabolism in PTSD in hippocampus and neocortical regions and increased metabolism in controls
Shin et al, 1997a,b (^{15}O-CO$_2$)	7 CR-PTSD (all M)	7 CE non-PTSD controls (all M) (significant age difference between groups)	CR pictures (viewed and personally generated mental images)	DSM–III–R (CAPS)	Increased rCBF in anterior cingulate gyrus and (R) amygdala during mental imagery; decreased rCBF in Broca's area when viewing combat pictures
Rauch et al, 1997 (^{15}O-CO$_2$)	8 miscellaneous PTSD (2M; 6F)	7 simple phobia (1M; 6F); 8 OCD (5M; 3F); no controls	Personal trauma script	DSM–III–R (SCID)	Increased rCBF in paralimbic belt ((R) frontal and subcortical nuclei) in anxiety disorders
Bremner et al, 1999a (^{15}O-H$_2$O)	10 CR-PTSD (all M)	10 CE non-PTSD (all M)	Sound and visual images of CR trauma	DSM–IV (SCID)	Decreased rCBF in medial prefrontal cortex; increased rCBF in anterior cingulate in non-PTSD subjects; no amygdalar activation
Bremner et al, 1999b (^{15}O-H$_2$O)	10 CSA-related PTSD (all F)	12 CSA non-PTSD (all F)	Personal trauma script	DSM–IV (SCID)	Increased rCBF of posterior cingulate, motor cortex and prefrontal cortex; decreased rCBF in visual association cortex, inferior temporal gyrus, anterior cingulate, (R) hippocampus and supramarginal gyrus; no amygdalar activation
Shin et al, 1999 (^{15}O-CO$_2$)	8 CSA-related PTSD (all F)	8 CSA non-PTSD (all F)	Personal trauma scripts and trauma imagery	DSM–III–R (CAPS)	Increased rCBF in orbitofrontal cortex and anterior temporal poles; decreased rCBF in bilateral anterior frontal regions and (L) inferior frontal gyrus; no amygdalar activation
Semple et al, 2000 (^{15}O-butanol)	7 CR-PTSD (all M) with CA	6 normal controls (all M)	Auditory attentional task	Not specified	Increased rCBF in (R) amygdala and (L) parahippocampal gyrus during performance tasks; decreased rCBF in frontal cortex at rest and during attentional tasks

CR, combat-related; CE, combat-exposed; SM, substance misuse; CA, cocaine and alcohol misuse; CSA, child sexual abuse; M, male; F, female; (R), right; (L), left; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ^{15}O-CO$_2$, ^{15}O-labelled CO$_2$; ^{15}O-H$_2$O, ^{15}O-labelled H$_2$O; ^{15}O-butanol, ^{15}O-labelled butanol; SCID, Structured Clinical Interview for DSM–IV; MRI, magnetic resonance imaging; CAPS, Clinician Administered PTSD Scale; rCBF, regional cerebral blood flow; OCD, obsessive–compulsive disorder.

Table 5 Single photon emission computed tomography (SPECT) studies in patients with post-traumatic stress disorder (PTSD)

Author (tracer used)	Subjects	Controls/ comparison groups	Design/method of provocation	Diagnostic criteria (method)	Results
Lucey et al, 1997 (^{99m}TcHMPAO)	16 PTSD (14M; 2F) (miscellaneous trauma)	15 OCD (8M; 7F); 15 agoraphobia with panic (8M; 7F); 15 controls (8M; 7F)	Non-symptom provocation	DSM–III–R (Impact of Event Scale)	Reduced rCBF in caudate and superior frontal cortex in PTSD and OCD; reduced caudate rCBF correlates with depression and PTSD severity
Liberzon et al, 1999 (^{99m}TcHMPAO)	14 CR-PTSD (all M)	11 CE non-PTSD (all M); 14 controls (all M)	Audiotape of combat sounds	DSM–III–R (SCID)	Activation of (L) amygdala in PTSD; activation of anterior cingulate and medial prefrontal cortex in all three groups
Zubieta et al, 1999 (^{99m}TcHMPAO)	12 CR-PTSD (all M)	11 CE non-PTSD (all M); 12 controls (all M)	Audiotape of combat sounds	DSM–III–R (SCID)	Activation of medial prefrontal cortex in PTSD only
Bremner et al, 2000 (^{123}I-iomazenil)	13 CR-PTSD (all M)	13 case-matched controls (all M)	Measurement of benzodiazepine receptor binding	DSM–IV (SCID)	PTSD subjects had 41% lower distribution volumes in the prefrontal cortex (i.e. lower benzodiazepine receptor binding)

OCD, obsessive–compulsive disorder; rCBF, regional cerebral blood flow; CR, combat-related; CE, combat-exposed; M, male; F, female; (R), right; (L), left; ^{99m}TcHMPAO, 99m-technetium-d,l-hexamethylpropyleneamine oxide; SCID, Structured Clinical Interview for DSM–IV.

region examined by Liberzon *et al* (1999).

Functional MRI studies

Rauch *et al* (2000) conducted a functional MRI study applying a validated method for measuring automatic amygdala responses to general threat-related stimuli using a masked face paradigm (Whalen *et al*, 1998*b*). The magnitude of amygdala response distinguished subjects with PTSD from those without PTSD with 75% sensitivity and 100% specificity (Table 3).

Case reports involving functional neuroimaging

Levin *et al* (1999) report on one subject from an ongoing SPECT study utilising the same provocation paradigm as Rauch *et al* (1996). Subjects were scanned before and after successful treatment for PTSD. After treatment there were two areas of increased activity: the anterior cingulate cortex and the left frontal lobe. The treatment was eye movement desensitisation and reprocessing (EMDR; Shapiro, 1996) but the subject of this report was also on a selective serotonin reuptake inhibitor throughout the study. The authors state that these changes were consistent with summed data from four out of six subjects in their ongoing study.

Profound memory deficits were demonstrated in a case report of a man after a second traumatic event triggering memories of a fatal accident he witnessed as a child. A PET scan revealed hypoperfusion in memory-sensitive regions such as the hippocampal formation and temporal lobe (Markowitsch *et al*, 1998). Liberzon *et al* (1996/97) report one patient who experienced a flashback after provocation while being scanned. There was greater uptake in subcortical regions, especially the thalamus, in comparison with cortical regions.

Summary of functional findings

Many of the functional neuroimaging studies have suggested abnormalities of limbic and paralimbic areas during symptom provocation and cognitive activation studies. This supports the suggested role of these areas in mediating emotional arousal in normal anxiety (Benkelfat *et al*, 1996), across a range of disorders (Rauch *et al*, 1995) and in trauma-exposed non-PTSD groups. These changes are therefore not specific to PTSD. Hyperperfusion of limbic and paralimbic areas may be a result of stress-induced long-term potentiation of the monosynaptic N-methyl-D-aspartate (NMDA)-mediated pathway between the amygdala and the periacqueductal grey (Davidson & Sutton, 1995; Adamec, 1997). The NMDA receptors are thought to be activated to produce long-term memories of events when sufficient glutamate is released as a result of the stress (Glue *et al*, 1993).

Amygdalar activation may be detected more easily during the processing of fear-related stimuli (Breiter *et al*, 1996; Morris *et al*, 1996; Whalen *et al*, 1998*a*). Inconsistent findings of amygdala activation may reflect the nature of the trauma, and the greater emotional responsiveness to personal narratives of traumatic events (Rauch *et al*, 1996) rather than to generalised trauma-related pictures and images (Shin *et al*, 1997*a*,*b*) or to generalised combat sounds (Bremner *et al*, 1999*a*). For example, Shin *et al* (1997*b*) found increased activation of the amygdala in PTSD only during combat imagery, despite both the imagery and combat perception conditions being rated as of equal significance and causing equal arousal. In addition, the failure to demonstrate amygdalar activation may be due to its involvement in encoding an event's emotional significance but not in the recall of the event *per se* (Cahill *et al*, 1996).

The role of the amygdala was investigated in subjects with probable Alzheimer's disease who experienced the 1995 earthquake in Kobe, Japan (Ikeda *et al*, 1998; Mori *et al*, 1999; Kazui *et al*, 2000). Memories of the earthquake were examined as an index of emotional memory. Subjects remembered their personal experience rather than the context of the earthquake, and emotional memory correlated with normalised amygdalar volume (via MRI) irrespective of generalised brain atrophy and cognitive impairments.

Increased automatic amygdalar responsiveness to stimuli (cognitive activation or masked face paradigm) has been shown to be accompanied by decreased activity of the prefrontal cortex, which has a role in

the encoding and retrieval of verbal memories. Lower benzodiazepine receptor binding in the prefrontal cortex might mean that PTSD causes a down-regulation of benzodiazepine receptor binding or that pre-trauma low levels of benzodiazepine receptor binding in the prefrontal cortex might increase the risk of developing PTSD after traumatic events (Bremner et al, 2000).

Although needing replication, the study by Levin et al (1999) suggests that successful treatment may not only reduce amygdala activity but also may involve activation of structures implicated in the modulation of fight/flight reactions to perceived threat, and perhaps the differentiation of real from imagined threat. Increased perfusion of the thalamus during a flashback (Liberzon et al, 1996/97) supports its suggested role in the generation of dissociative symptoms in PTSD (Krystal et al, 1995).

The absence of increased anterior cingulate activation over comparison groups may be associated with the inability of people with PTSD to extinguish fear. It is thought to play a major role in the assignment of motivational significance and is associated with non-specific anxiety states being activated in procaine-induced fear (Ketter et al, 1996), imagery of aversive stimuli (Kosslyn et al, 1996) and healthy individuals recollecting sad events (Whalen et al, 1998a). The increased activation of the posterior cingulate (Bremner et al, 1999b) may relate to its suggested role in the emotional processing of distressing material (Fischer et al, 1996).

A replicated finding has been the deactivation of Broca's area, the area of the brain thought to be responsible for applying semantic representations to personal experience to allow its communication or description (Rauch et al, 1996; Shin et al, 1997b). This would appear to be consistent with subjects with PTSD having difficulty in cognitively restructuring their traumatic experience.

The modality of re-experiencing phenomena will have a bearing on regional brain activation. The mental imagery in the study by Rauch et al (1996) was predominantly visual, causing increased rCBF in the secondary visual cortex, a finding not found by Shin et al (1997a,b, 1999) because the re-experiencing phenomena in their study were predominantly tactile. These findings serve to illustrate that different types of trauma cause different emotional reactions; trauma memories are not uniform and activation of brain regions will vary. Further, hypoperfusion of the left inferior frontal gyrus in PTSD (Shin et al 1997a,b, 1999) may reflect the nature of intrusive thoughts because the frontal regions are implicated in effortful recall (Schacter et al, 1996), whereas intrusive phenomena are effortless and may therefore lead to hypoperfusion.

DISCUSSION

Neuroimaging is a powerful method to examine the links among structural and functional brain changes, psychopathology and findings from other neurobiological research in traumatised individuals. However, neuroimaging in PTSD is only just emerging from its infancy, with only 30 published reports as of August 2001. Results are far from uniform but the degree of consensus at this early stage is encouraging. Research in the trauma field is fraught with difficulties; one inherent difficulty in all trauma research is the choice of population to be studied. Research studies have tended to examine homogeneous and highly selected trauma populations. Eighteen of these reports (67%; 18/30) were conducted solely on combat veterans and 73% (254/356) of all scanned subjects were male. Furthermore, combat veterans (58%; 219/377) and survivors of childhood physical and sexual abuse (27%; 101/377) accounted for 85% of all subjects recruited to neuroimaging studies. It is vital that future research into the neurobiology of PTSD attempts to incorporate a wider spectrum of trauma.

The triggers causing intrusive thoughts or flashbacks are personal and often idiosyncratic. Research provocation paradigms need to be able to reflect this and if they do not then researchers may be studying different phenomena. The similarity between generalised combat sounds and a self-generated narrative of a fatal motor vehicle accident in which an individual was at fault have little in common and may explain why there was a failure to show amygdalar activation when generalised combat sounds were used rather than personalised trauma scripts. To expect uniform activation of the brain in different trauma populations with varying provoking stimuli is to suggest that all traumas have similar effects and trigger the same symptoms.

The failure of studies to include control or comparison groups (of trauma-exposed subjects without PTSD) leaves the possibility that the observed changes are due to trauma exposure as opposed to PTSD itself. However, there are demonstrated biological changes following trauma exposure that are associated with PTSD and not simply with the trauma exposure per se (Yehuda & McFarlane, 1995). The neurobiology of PTSD is a progressive state of modification and a cross-sectional perspective cannot answer some of the fundamental questions. Could a pre-existing brain abnormality predispose to PTSD or to exposure to trauma, thereby identifying at-risk individuals? Alternatively, could the trauma exposure rather than PTSD be responsible for the demonstrated structural and functional changes (Sapolsky, 2000)? Only one study has examined neuroimaging changes in individuals with acute PTSD and this suggests that no abnormality existed prior to the development of PTSD (Bonne et al, 2001). Furthermore, are there identifiable trait effects (defining the underlying disease process) as opposed to state effects (reflecting the symptom severity)? Only the latter have been investigated so far in PTSD.

Other methodological issues would include the standardisation of image acquisition (and analysis) and a consensus on methodologies (e.g. type of trauma population, type of symptom provocation and method of diagnosis). In addition, studies controlling for past and current treatment and the presence or absence of comorbidity are needed to determine the relative contributions. This would allow the pooling of data or a meta-analysis that would compensate for individually small studies.

Neuroimaging studies in PTSD have suggested a number of brain regions meriting further attention. Key regional abnormalities, their replicability and the possible significance of each finding are described in Table 6. Findings to support the proposed right-hemisphere lateralisation of post-trauma symptoms are inconsistent, with no neuroimaging study in PTSD examining the role of dominance (studies have chosen to study dextrals) or gender on this proposed laterality. For example, gender differences have been demonstrated in studies of self-induced dysphoria (Whalen et al, 1998b), with bilateral activation in women and predominantly left-sided activation in men.

Table 6 Central findings of neuroimaging studies

Finding	Replicability[1]
Decreased hippocampal volume	+++[2]
Increased amygdala activity	+++[2]
Decreased Broca's area (left inferior cortex) activity	+[2]
Hemispheric lateralisation	+++[2]
Decreased anterior cingulate cortex activation	++[2]
Decreased N-acetyl aspartate in medial temporal regions	+
Activation in visual cortex	+[2]

1. Replicability was rated as follows: (+) two, (++) three and (+++) four or more studies.
2. Inconsistent findings.

Treatment implications

Neuroimaging findings suggest that after psychological trauma biological changes are not restricted to dysregulation of neurochemical systems but involve alterations in brain function and structure. The challenge for clinicians is to employ therapies for patients with PTSD that prevent, halt or reverse these changes. Functional brain changes after successful treatment have been demonstrated in other conditions (Schwartz *et al*, 1996) and preliminary data suggest that the same is true for patients with PTSD (Levin *et al*, 1999). One possible target is the demonstrated hippocampal damage. The hippocampus may be unique in the brain in its ability to regenerate neurons (Gould *et al*, 1998), with agents such as phenytoin potentially able to reverse stress-activated hippocampal atrophy (Watanabe *et al*, 1992). Silver *et al* (1991) have suggested that anticonvulsants may reduce limbic kindling in PTSD, thereby preventing progression of symptoms, but this has yet to be tested in clinical trials in subjects with acute post-traumatic reactions.

Perhaps one of the least expected early findings is the hypoperfusion of Broca's area when trauma-related memories are provoked. Broca's area is necessary for the labelling of emotions, therefore its deactivation under symptom provocation would explain why patients with PTSD can experience intense emotions without being able to label and understand them. This marries clinically with survivors often describing an inability to put their experience into words – it is, in effect, 'unspeakable'. Therefore, the ability of psychological treatment, especially 'talking therapies', may be compromised during some phases of the disorder. Therapies incorporating exposure have proven efficacy for the treatment of PTSD (van Etten & Taylor, 1998) and this may be because they can target all sensory modalities and not just their semantic representations. Alternatively, their potency may be explained by the preclinical finding that the reactivation of memory allows its disruption (Nader *et al*, 2000). Importantly, the reactivation of memory does not require it to be put into communicable language.

The strategies and findings of published neuroimaging studies in PTSD provide a framework for future research, not just in neuroimaging but for clinical trials of historically accepted treatments for trauma survivors. Future neuroimaging studies need to develop protocols to investigate state and trait effects in a range of traumatic events and to study treatment-naïve subjects. Pre- and post-treatment studies also need to be completed to assess the full effectiveness of clinical strategies.

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CLINICAL IMPLICATIONS

■ More work is needed to identify treatments that reverse the demonstrated functional and structural regional brain changes.

■ The effectiveness of psychological treatments, especially 'talking therapies', may be compromised by underactivity of Broca's area when individuals are accessing traumatic material.

■ Possible right-hemispheric lateralisation may explain the 'timeless' quality of traumatic memories.

LIMITATIONS

■ The majority of studies are restricted to highly selected and homogeneous samples.

■ Many of the studies lacked a control or comparison group and therefore did not exclude the possibility that observed changes are the result of exposure to the trauma itself rather than to post-traumatic stress disorder.

■ Unpublished studies are not discussed.

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