Imaging in CNS Disease States: PTSD

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Lasting Effects of Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) affects about 8% of Americans at some time in their lives (Kessler et al. 1995). For many trauma victims, PTSD can be a lifelong problem (Saigh and Bremner 1999). The development of effective treatments is limited by gaps in knowledge about the underlying neurobiological mechanisms that mediate symptoms of PTSD. Until 12 years ago, no brain imaging studies had ever been performed in patients with PTSD or other stress related psychiatric disorders. The past decade has seen an explosion of research using brain imaging to assess changes in the brain in PTSD (Bremner 2005). These studies have implicated the amygdala, hippocampus, and the medial prefrontal cortex (including the anterior cingulate) in PTSD and other stress related psychiatric disorders. This chapter reviews brain imaging studies in the field of PTSD, and integrates them with the basic science findings on the neuroscience of stress.

Neural Circuits of PTSD

PTSD is characterized by specific symptoms, including intrusive thoughts, hyperarousal, flashbacks, nightmares, and sleep disturbances, changes in memory and concentration, and startle responses. Symptoms of PTSD are hypothesized to represent the behavioral manifestation of stress-induced changes in brain structure and function. Stress results in acute and chronic changes in the neurochemical systems and specific brain regions, which result in long-term changes in brain "circuits," involved in the stress response (Vermetten and Bremner 2002a, b; Bremner 2002a; Pitman 2001).

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The brain regions that are felt to play an important role in PTSD include the hippocampus, the amygdala, and the medial prefrontal cortex.

Preclinical and clinical studies have shown alterations in memory function in PTSD patients (Elzinga and Bremner 2002), as well as changes in a circuit of brain areas, including the hippocampus, the amygdala, and the medial prefrontal cortex, that mediate alterations in memory (Bremner 2003). The hippocampus, a brain area involved in verbal declarative memory, is very sensitive to the effects of stress. Stress in animals was associated with damage to the neurons in the CA3 region of the hippocampus (which may be mediated by hypercortisolemia, decreased brain derived neurotrophic factor, and/or elevated glutamate levels) and inhibition of neurogenesis (Gould et al. 1998; Magarinos et al. 1996; McEwen et al. 1992; Nibuya et al. 1995; Sapolsky et al. 1990, 1996).

Antidepressant treatments were shown to block the effects of stress and/or promote neurogenesis (Nibuya et al. 1995; Malberg et al. 2000; Czeh et al. 2001; Santarelli et al. 2003; Lucassen et al. 2004). Animal studies have demonstrated several agents with potentially beneficial effects on stress-induced hippocampal damage. It has been found that phenytoin blocks the effects of stress on the hippocampus, probably through modulation of excitatory amino acid induced neurotoxicity.(Watanabe et al. 1992a) Other agents, including tianeptine, dihydroepiandosterone (DHEA), and fluoxetine have similar effects (Malberg et al. 2000; Czeh et al. 2001; Lucassen et al. 2004; Garcia 2002; D'Sa and Duman 2002; Duman et al. 1997, 2001; Duman 2004; McEwen and Chattarji 2004). These medications may share a common mechanism of action through upregulation of the cAMP response element binding protein (CREB) that leads to regulation of the expression of specific target genes involved in structural modeling of the hippocampus. Such treatment effects on BDNF and trkB mRNA, can have long-term effects on brain structure and function. There is new evidence that neurogenesis is necessary for the behavioral effects of antidepressants (Santarelli et al. 2003; Watanabe et al. 1992b) although this continues to be a source of debate (Duman 2004; Henn and Vollmayr 2004).

In addition to the hippocampus, other brain structures including the amygdale and prefrontal cortex have been implicated in a neural circuitry of stress. The amygdala is involved in memory for the emotional valence of events, and plays a critical role in the acquisition of fear responses (Davis 1992). The medial prefrontal cortex includes the anterior cingulate gyrus (Brodmann's area 32) and the subcallosal gyrus (area 25), as well as orbitofrontal cortex. Lesion studies have demonstrated that the medial prefrontal cortex modulates emotional responsiveness through the inhibition of amygdala function (Morgan et al. 1993). Studies show that the neurons of the medial prefrontal cortex play an active role in the inhibition of fear responses that are mediated by the amygdala (Milad and Quirk 2002; Milad et al. 2006). Conditioned fear responses are extinguished following repeated exposure to the conditioned stimulus in the absence of the unconditioned (aversive, e.g., electric shock) stimulus. This inhibition appears to be mediated by the medial prefrontal cortical inhibition of amygdala responsiveness. Animal studies also show that early stress is associated with a decrease in the branching of neurons in the medial prefrontal cortex (Radley et al. 2004).

Changes in Brain Structure in PTSD

Studies in PTSD are consistent in the changes in cognition and brain structure. Multiple studies have demonstrated verbal declarative memory deficits in PTSD (Elzinga and Bremner 2002; Buckley et al. 2000; Brewin 2001; Golier and Yehuda 1998). Patients with PTSD secondary to combat (Vasterling et al. 1998; Bremner et al. 1993; Golier et al. 1997; Yehuda et al. 1995; Uddo et al. 1993) and childhood abuse (Bremner et al. 1995a, 2004a) were found to have deficits in verbal declarative memory function based on neuropsychological testing. Studies using a variety of measures (including the Wechsler Memory Scale, the visual and verbal components of the Selective Reminding Test, the Auditory Verbal Learning Test, Paired Associate Recall, the California Verbal New Learning Test, and the Rivermead Behavioral Memory Test), found specific deficits in verbal declarative memory function, with a relative sparing of visual memory and IQ (Vasterling et al. 1998, 2002; Bremner et al. 1993, 1995a; Golier et al. 1997; Yehuda et al. 1995; Uddo et al. 1993; Gilbertson et al. 2001; Jenkins et al. 1998; Moradi et al. 1999; Roca and Freeman 2001; Barrett et al. 1996; Gil et al. 1990; Sachinvala et al. 2000). These studies have been conducted both in patients with PTSD related to Vietnam combat (Vasterling et al. 1998, 2002; Bremner et al. 1993; Golier et al. 1997; Yehuda et al. 1995; Uddo et al. 1993; Gilbertson et al. 2001; Roca and Freeman 2001; Barrett et al. 1996; Sachinvala et al. 2000), rape (Jenkins et al. 1998) the Holocaust (Golier et al. 2002, Yehuda et al. 2005a, b) adults with early childhood abuse (Bremner et al. 1995a), and traumatized children (Moradi et al. 1999). Returning Iraq soldiers were shown to have decreases in verbal memory performance compared to their pre-deployment baselines, with greater verbal memory deficits in veterans with high levels of PTSD symptoms (Vasterling et al. 2006). These studies suggest that traumas such as early abuse with associated PTSD result in deficits in the verbal declarative memory.

Studies have also shown changes in hippocampal volume. Vietnam veterans with PTSD were originally shown to have 8% smaller right hippocampal volume based on MRI relative to controls matched for a variety of factors such as alcohol abuse and education ($p<0.05$); smaller volume was correlated with deficits in verbal declarative memory function as measured with the WMS (Bremner et al. 1995b). A second study from our group showed a 12% reduction in the left hippocampal volume in 17 patients with childhood abuse-related PTSD compared to 17 case-matched controls; this was significant after controlling for confounding factors (Bremner et al. 1997a). Smaller hippocampal volume was shown to be specific to PTSD within the anxiety disorders, and was not seen in panic disorder (Narayan et al. 1999). Gurvits et al. 1996 showed bilateral hippocampal volume reductions in combat-related PTSD compared to combat veterans without PTSD and normal controls. Combat severity was correlated with volume reduction. Stein et al. 1997 found a 5% reduction in the left hippocampal volume. Other studies in PTSD have found smaller hippocampal volume and/or reductions in NAA, a marker of neuronal integrity (Lindauer et al. 2005, 2006, 2004a; Bremner et al. 2003a; Freeman et al.

1998; Gilbertson et al. 2002; Schuff et al. 2001; Villarreal et al. 2002; Shin et al. 2004a; Emdad et al. 2006; Mahmutyazicioglu et al. 2005; Irle et al. 2005; Li et al. 2006; Hedges et al. 2003). Some studies have found smaller hippocampal volume in PTSD subjects compared to trauma exposed non PTSD subjects (Bremner et al. 2003a) while others have not, finding reductions in both trauma exposed non PTSD and trauma exposed PTSD relative to non trauma exposed non PTSD subjects (Winter and Irle 2004). Studies in childhood (De Bellis et al. 1999, 20001; Carrion et al. 2001) PTSD did not find hippocampal volume reduction, although reduced NAA (indicating loss of neuronal integrity) was found in the medial prefrontal cortex in childhood PTSD (De Bellis et al. 2000). Some studies of new onset or recent PTSD did not find changes in hippocampal volume (Bonne et al. 2001; Notestine et al. 2002), while others showed a reduction (Wignall et al. 2004). In a recent meta-analysis, we pooled data from all of the published studies and found smaller hippocampal volume for both the left and the right sides, equally in adult men and women with chronic PTSD, and no change in children (Kitayama et al. 2005). Another recent meta-analysis had similar findings (Smith 2005). More recent studies of holocaust survivors with PTSD did not find a reduction in hippocampal volume (Golier et al. 2005) although PTSD patients who developed PTSD in response to an initial trauma had smaller hippocampal volume compared to those who developed PTSD after repeated trauma, suggesting a possible vulnerability of smaller hippocampal volume (Yehuda et al. 2007). Several studies have shown that PTSD patients have deficits in hippocampal activation while performing a verbal declarative memory task (Bremner et al. 2003a; Shin et al. 2004a) or a virtual water maze task (Astur et al. 2006). Both hippocampal atrophy and hippocampal-based memory deficits reversed with treatment with the SSRI, paroxetine, which has been shown to promote neurogenesis (the growth of neurons) in the hippocampus, in preclinical studies (Vermetten et al. 2003). We hypothesize that stress-induced hippocampal dysfunction may mediate many of the symptoms of PTSD which are related to memory dysregulation, including both explicit memory deficits as well as fragmentation of memory in abuse survivors. It is unclear at the current time whether these changes are specific to PTSD, whether certain common environmental events (e.g., stress) in different disorders lead to similar brain changes, or whether common genetic traits lead to similar outcomes.

In addition to the hippocampus, other brain structures have been implicated in a neural circuitry of stress, including the amygdala and the prefrontal cortex. The amygdala is involved in memory for the emotional valence of events, and plays a critical role in the acquisition of fear responses. The medial prefrontal cortex includes the anterior cingulate gyrus (Brodmann's area 32) and the subcallosal gyrus (area 25), as well as the orbitofrontal cortex. Lesion studies have demonstrated that the medial prefrontal cortex modulates emotional responsiveness through the inhibition of amygdala function. Conditioned fear responses are extinguished following repeated exposure to the conditioned stimulus (in the absence of the unconditioned (aversive, e.g., electric shock) stimulus. This inhibition appears to be mediated by the medial prefrontal cortical inhibition of amygdala responsiveness. The insula plays a critical role in integrating the physiological stress response.

Animal studies also show that early stress is associated with a decrease in the branching of neurons in the medial prefrontal cortex (Radley et al. 2004). Several studies have found smaller anterior cingulate volume based on MRI measurements in PTSD (Rauch et al. 2003; Yamasue et al. 2003; Woodward et al. 2006), including women with abuse and PTSD (Kitayama et al. 2005). One study found a reduction in NAA/Cr measured with MRS (Mahmutyazicioglu et al. 2005), while another found a decrease in gray matter density (Corbo et al. 2005). An important question is whether these effects are reversible with treatment. Other findings related to volumetrics include smaller volumes of the corpus callosum in neglected children (Teicher et al. 2004) and adults with PTSD (Villarreal et al. 2004). One study showed a smaller volume of the insula with voxel based morphometry (Chen et al. 2006). A study in twins found smaller volume of the cavum septum pellucidum (May et al. 2004).

Functional Neuroimaging Studies in PTSD

Imaging studies of brain function in PTSD are consistent with dysfunction of the medial prefrontal cortex, the amygdala, and the hippocampus (Pitman 2001; Liberzon and Phan 2003; Liberzon and Martis 2006; Liberzon et al. 2003; Bremner 1998; Bremner 2002b; Rauch et al. 2006; Cannistraro and Rauch 2003). The methodology of imaging studies in PTSD is outlined in Table 1 and a summary of findings by the author, and brain region in Table 2. Studies of resting blood flow or metabolism with PET and SPECT showed alterations at rest in the medial prefrontal, temporal, and dorsolateral prefrontal cortex, the cerebellum, and the amygdala (Bonne et al. 2003; Chung et al. 2006; Bremner et al. 1997b). Stimulation of the noradrenergic system with yohimbine resulted in a failure of activation in the dorsolateral prefrontal, temporal, parietal and orbitofrontal cortex, and decreased function in the hippocampus (Bremner et al. 1997b). Exposure to traumatic reminders in the form of traumatic slides and/or sounds or traumatic scripts was associated with an increase in PTSD symptoms, decreased blood flow and/or failure of activation in the medial prefrontal cortex/anterior cingulate, including Brodmann's area 25, or subcallosal gyrus, area 32 and 24, as measured with PET, SPECT or fMRI (Britton et al. 2005; Yang et al. 2004; Bremner et al. 1999a, b; Lanius et al. 2001, 2003; Liberzon et al. 1999; Shin et al. 1999, 1997, 2001, 2004b, 2005; Semple et al. 2000; Lindauer et al. 2004b; Phan et al. 2006) (Fig. 1). Other findings in studies of traumatic reminder exposure include decreased function in the hippocampus (Bremner et al. 1999b), the thalamus (Lanius et al. 2001, 2003), the visual association cortex (Lanius et al. 2003; Bremner et al. 1999b; Shin et al. 1997, 2004b), the parietal cortex (Bremner et al. 1999b; Shin et al. 1997, 1999; Rauch et al. 1996; Sakamoto et al. 2005), and the inferior frontal gyrus (Lanius et al. 2003; Bremner et al. 1999b; Shin et al. 1997, 1999, 2001; Rauch et al. 1996; Sakamoto et al. 2005), and increased function in the amygdala (Liberzon et al. 1999; Shin et al. 2004b; wv2001; Shin et al. 1997), and the parahippocampal gyrus (Bremner et al. 1999a, b;

Table 1 Published functional imaging studies in PTSD-methods

Authors	Study population	Sample size	Control group	Sample size	Imaging methods	Active condition	Control
Rauch et al. (1996)	Mixed PTSD	8	None	0	PET O-15	Combat scripts	Neutral scripts
Semple (1996)	Combat PTSD+SA	6	Healthy subjects	6	PET FDG	Continuous performance test	Rest
Bremner et al. (1997a, b)	Combat-related PTSD	10	Healthy subjects	10	PET FDG	Yohimbine	Placebo
Shin et al. (1997)	Combat-related PTSD	7	Combat veterans without PTSD	7	PET O-15	Trauma imagery/ perception	Neg/neutral image/ perception
Bremner et al. (1999a)	Combat-related PTSD	10	Combat veterans without PTSD	10	PET O-15	Combat slides/sounds	Neutral slides/ sounds
Bremner et al. (1999b)	Women with abuse-related PTSD	10	Abused women without PTSD	12	PET O-15	Abuse scripts	Neutral scripts
Shin et al. (1999)	Women with abuse-related PTSD	8	Abused women without PTSD	8	PET O-15	Abuse scripts	Neutral scripts
Liberzon et al. (1999)	Combat-related PTSD	14	Healthy subjects/ combat controls	14/11	SPECT HMPAO	Combat sounds	White noise
Zubieta (1999)	Combat-related PTSD	12	Combat veterans without PTSD, healthy subjects	11/12	SPECT HMPAO	Combat sounds	White noise
Rauch et al. (2000)	Combat-related PTSD	8	Combat veterans without PTSD	8	fMRI	Masked fearful faces	Masked happy faces
Semple et al. (2000)	Combat PTSD+SA	6	Healthy subjects	7	PET O-15	Continuous performance test	Rest
Shin et al. (2001)	Combat-related PTSD	8	Combat veterans without PTSD	8	fMRI	Counting stroop-combat	Stroop general negative

Lanius et al. (2001)	Mixed civilian (SA or MVA)	9	Traumatized non-PTSD	9	fMRI	Traumatic scripts	Resting state
Pissiota et al. (2002)	Combat PTSD	7	None	0	PET	Traumatic sounds	Neutral sounds
Lanius et al. (2003)	Mixed civilian (SA or MVA)	10	Traumatized non-PTSD	10	fMRI	Sad, anxious, trauma script	Resting state
Bremner et al. (2003a)	Women with abuse-related PTSD	10	Healthy women	11	PET O-15	Trauma related word recall	Shallow encoding
Bremner et al. (2003b)	Women with abuse-related PTSD	10	Women with abuse without PTSD	12	PET O-15	Memory task	Shallow encoding
Clark et al. (2003)	Civilian PTSD	10	Healthy subjects	10	PET O-15	Working memory task	Fixed target
Bonne et al. (2003)	Civilian PTSD	11	Trauma controls/ healthy controls	17/11	SPECT HMPAO	Resting state	
Bremner et al. (2005a, b)	Women with abuse-related PTSD	8	Healthy subjects	11	PET O-15	Fear conditioning	Unpaired CS-US
Bremner et al. (2004a, b, c)	Women with abuse-related PTSD	12	Women with abuse without PTSD	9	PET O-15	Emotional stroop	Neutral stroop
Shin et al. (2004a, b)	Vietnam combat related PTSD	17	Vietnam veterans without PTSD	19	PET O-15	Traumatic scripts	Neutral scripts
Shin et al. (2004b)	Firefighters with PTSD	8	Firefighters without PTSD	8	PET O-15	Memory task	Shallow encoding
Lindauer et al. (2004a, b)	Policemen with PTSD	15	Policemen without PTSD	15	SPECT HMPAO	Traumatic scripts	Neutral scripts

(continued)

Table 1 (continued)

Authors	Study population	Sample size	Control group	Sample size	Imaging methods	Active condition	Control
Yang et al. (2004)	Children – earthquake related PTS	5	Children – earthquake – non-PTSD	6	fMRI	Earthquake pictures/ images	Neutral pictures/ imagery
Shin et al. (2005)	Firefighters+VN combat with PTS	13	Trauma exposed without PTSD	13	fMRI	Overt fearful faces	Neutral overt faces
Armony et al. (2005)	Acute PTSD – MVA	13	None	0	fMRI	Masked fearful faces	Masked happy faces
Sakamoto et al. (2005)	Mixed civilian PTSD	16	Healthy subjects	16	fMRI	Masked traumatic images	Masked neutral images
Protopopescu et al. (2005)	Sexual/physical abuse PTSD	11	Healthy subjects	21	fMRI	Traumatic word recall	Neutral word recall
Bryant et al. (2005)	Civilian PTSD	14	Healthy controls	14	fMRI	Oddball working memory	
Britton et al. (2005)	Combat PTSD	16	Combat controls/ Healthy controls	15/14	PET O-15	Traumatic scripts	Neutral scripts
Chung et al. (2006)	Civilian PTSD	23	Healthy controls	46	SPECT HMPAO	Resting state	None
Phan et al. (2006)	Vietnam combat related PTSD	16	Combat controls/ healthy subjects	15/15	PET	Negative pictures	Control pictures
Astur et al. (2006)	Civilian PTSD	12	Healthy controls	12	fMRI	Virtual water maze	Visual condition

Table 2 A summary of results of published functional imaging studies of the neural circuitry of PTSD

Authors	Hippocampus	Parahippocampus	Amygdala	mPFC AC (32/24/25)	mPFC OBF (11)	Anteromedial	Dorsolateral PFC (MFG 6)	Dorsolater PFC (IFG)	Posterior cingulate	Sup.temp (2)	Middletemp (21)	Inf. tempfusiform	Insula	Motor cortex	Sensor cortex	Visual association	Precune cuneus	Parietal (IPL)	ParietalSMG (40)	Cerebellum	Thalamus
Rauch et al. (1996)			↑	↑	↑			↓			↓		↑					↓			
Semple (1996)																		↓			
Bremner et al.																					
(1997a, b) (baseline)	NC	NC	NC	NC	NC		↓			↓				NC	NC	NC		NC		NC	NC
(activation)	↓	NC	NC	NC	↓		↓			↓				NC	NC	NC		↓		NC	NC
Shin et al. (1997)																					
(perc v neg)								↓L	↑								↑		↓R		
(imagery v neg)						↓		↓			↑					↓	↓			↑	
(perc v neu)				↓			↓														
(imagery v neu)				↑						↓								↓			
Bremner et al. (1999a)		↑		↓					↑		↓			↑				↑		↑	
Bremner et al. (1999b)	↓R	↑		↓	↓	↑	↑	↓R	↑	↑		↓R	↓R	↑	↓	↓			↓R	↓	
Shin et al. (1999)		↓L		↓	↑	↓	↓	↓	↓	↑								↓R			
Liberzon et al. (1999)			↑																		
Zubieta (1999)				NC		↑														NC	NC
Rauch et al. (2000)			↑	NC								NC									
Semple et al. (2000)		↑	↑	↓				↓								↑				↓	
Shin et al. (2001)	↑	↑		↓			↓	↓	↑	↑		↓	↑				↑	↑			
Lanius et al. (2001)				↓		↓															↓

(continued)

Table 2 (continued)

Authors	Hippocampus	Parahippocampus	Amygdala	mPFC AC (32/24/25)	mPFC OBF (11)	Anteromedial	Dorsolateral PFC (MFG 6)	Dorsolater PFC (IFG)	Posterior cingulate	Sup.temp (2)	Middletemp (21)	Inf. temptusiform	Insula	Motor cortex	Sensor cortex	Visual association	Precune cuneus	Parietal (IPL)	ParietalSMG (40)	Cerebellum	Thalamus
Pissiota et al. (2002)			→	→			→	→						←						→	←
Lanius et al. (2003)				→			→	→	←			→		→		→	→				
Bremner et al. (2003a, b)	→				→		→		→	→		→		→		→		→		→	
Bremner et al. (2003b)	→																				
Clark et al. (2003)							→					→						→			
Bonne et al. (2003)								→	→	→		→	→	→	→	→	→	→		→	
Bremner et al. (2005a, b)		→	→	→	→		→	→	→	→			→	→	→	→	→	→		→	→
Bremner et al. (2004a, b, c)				→			→														
Shin et al. (2004a, b)		→		→	→					→						→					
Shin et al. (2004b)	→				→							→					←				
Lindauer et al. (2004a, b)				→																	
Yang et al. (2004)		→		→												→				→	
Shin et al. (2005)			→	→																	
Armony et al. (2005)			→																		
Sakamoto et al. (2005)							→							→						→	

Protopopescu et al. (2005)			↑																		
Bryant et al. (2005)			↑	↑				↑							↑				↑	↓	
Britton et al. (2005)			↓	↓									↓								
Chung et al. (2006)	↑	↑	↑				↓			↓								↓			
Phan et al. (2006)			↓	↓																	
Astur et al. (2006)	↓																				
Decreased Function	6	1	2	16	4	3	10	8	1	4	2	3	3	3	1	5	3	5	2	4	2
Increased Function	2	7	11	3	2	2	2	2	6	6	1	1	3	4	2	3	3	3	1	6	0

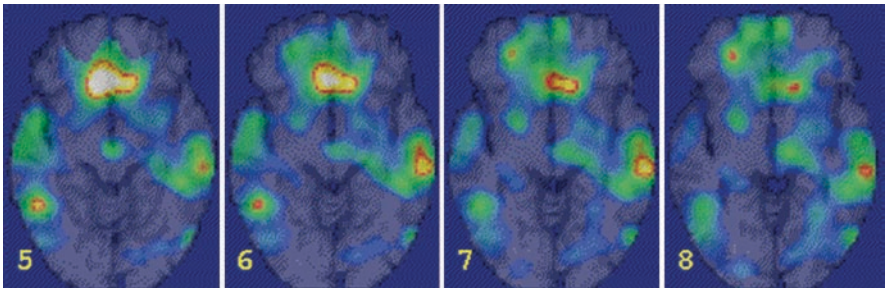

Fig. 1 Hippocampal volume on MRI in PTSD. There was smaller hippocampal volume in a representative patient with PTSD (*right*) relative to a non PTSD subject (*left*)

Liberzon et al. 1999). Shin et al. 2004b found a correlation between the increased amygdala function and the decreased medial prefrontal function with traumatic reminders, indicating that a failure of inhibition of the amygdala by the medial prefrontal cortex could account for increased PTSD symptoms with traumatic reminders. Other studies found increased amygdala and parahippocampal function and decreased medial prefrontal function during performance of an attention task (Semple et al. 2000), and increased amygdala function at rest (Chung et al. 2006), during a working memory task (Bryant et al. 2005), during recall of traumatic words (Protopopescu et al. 2005), with exposure to masked fearful faces (Rauch et al. 2000; Armony et al. 2005), overt fearful faces (Shin et al. 2005), traumatic sounds (Liberzon et al. 1999; Pissiota et al. 2002), and traumatic scripts (Rauch et al. 1996).

Several studies have examined neural correlates of cognitive tasks in PTSD. During working memory tasks, patients showed decreased inferior frontal (Clark et al. 2003) and parietal function (Bryant et al. 2005; Clark et al. 2003). Retrieval of emotionally valenced words (Bremner et al. 2001) (e.g., "rape-mutilate") in women with PTSD from early abuse resulted in decreases in blood flow in an extensive area which included the orbitofrontal cortex, the anterior cingulate, and the medial prefrontal cortex (Brodmann's areas 25, 32, 9), the left hippocampus, and the fusiform gyrus/inferior temporal gyrus, with increased activation in the posterior cingulate, the left inferior parietal cortex, the left middle frontal gyrus, and the visual association and motor cortex (Bremner et al. 2003b). Another study found a failure of the medial prefrontal cortical/anterior cingulate activation, and decreased visual association and parietal cortex function in women with abuse and PTSD, relative to women with abuse without PTSD, during performance of the emotional Stroop task (i.e., naming the color of a word such as "rape") (Bremner et al. 2004b). Shin et al. 2001 showed an increased posterior cingulate and parahippocampal gyrus and a decreased medial prefrontal and dorsolateral prefrontal during an emotional "counting" Stroop paradigm with fMRI.

Studies have also used declarative memory tasks as specific probes of hippocampal function. We measured brain activation with a paragraph encoding task in conjunction with PET O-15 water measurement of brain blood flow. Women with abuse and PTSD showed a failure of hippocampal activation during the memory task, relative

to controls (Bremner et al. 2003a). Women with abuse and PTSD in this study also had smaller hippocampal volume measured with MRI, relative to both women with abuse without PTSD and non-abused non-PTSD women. The failure of hippocampal activation was significant after controlling differences in hippocampal volume as well as accuracy of encoding. Shin et al. 2004a also found a failure of hippocampal activation with a memory stem completion task in PTSD.

Although multiple studies have used symptom provocation with traumatic scripts or similar designs, little has been done in the area of fear conditioning in PTSD. To that end, we studied women with a history of severe childhood sexual abuse and the diagnosis of current PTSD ($N=8$), and women without childhood abuse or PTSD ($N=11$). All the subjects underwent positron emission tomographic (PET) measurement of cerebral blood flow and psychophysiology measurement of heart rate and skin conductance during habituation, acquisition and extinction conditions on a single day, with scanning during a control condition on another day separated by 1 week from the active condition. During habituation the subjects were repeatedly exposed to a blue square on a screen (conditioned stimulus (CS)); during active fear acquisition, exposure to the blue square (CS) was paired with an electric shock to the forearm (unconditioned stimulus (UCS)); and during extinction, subjects were again exposed to the blue squares (CS) without shock ("active" extinction). On the second day, the subjects went through the same procedure with electric shocks delivered randomly when the blue square was not present (unpaired CS–UCS). Acquisition of fear was associated with increased skin conductance (SC) responses to CS exposure during the active versus the control conditions in all the subjects. There was increased SC for PTSD during the first CS–UCS presentation. Extinction of fear was associated with increased skin conductance (SC) responses to CS exposure during the active versus the control conditions, in all the subjects. When PTSD and non-PTSD subjects were examined separately, the SC levels were significantly elevated in non-PTSD subjects undergoing extinction of fear following the active compared to the control condition during session one. PTSD subjects showed activation of the bilateral amygdala during fear acquisition compared to the control condition (Fig. 2). Non-PTSD subjects showed an area of activation in the region of the left amygdala. When PTSD subjects and control subjects were directly compared, PTSD subjects showed a greater activation of the left amygdala during the fear conditioning condition (pairing of US and CS) relative to the random shock control than healthy women. Other areas that showed increased activation with fear acquisition in PTSD included the bilateral superior temporal gyrus (Brodmann's Area (BA) 22), cerebellum, bilateral inferior frontal gyrus (BA 44, 45) and the posterior cingulate (BA) 24). Fear acquisition was associated with decreased function in the medial prefrontal cortex, the visual association cortex, and the medial temporal cortex, the inferior parietal lobule function, and other areas. Extinction of fear responses was associated with decreased function in the orbitofrontal and medial prefrontal cortex (including subcallosal gyrus, BA 25, and anterior cingulate BA 32), the visual association cortex, and other areas in the PTSD subjects, but not in the controls. Amygdala blood flow with fear acquisition was negatively correlated with medial prefrontal blood flow with fear

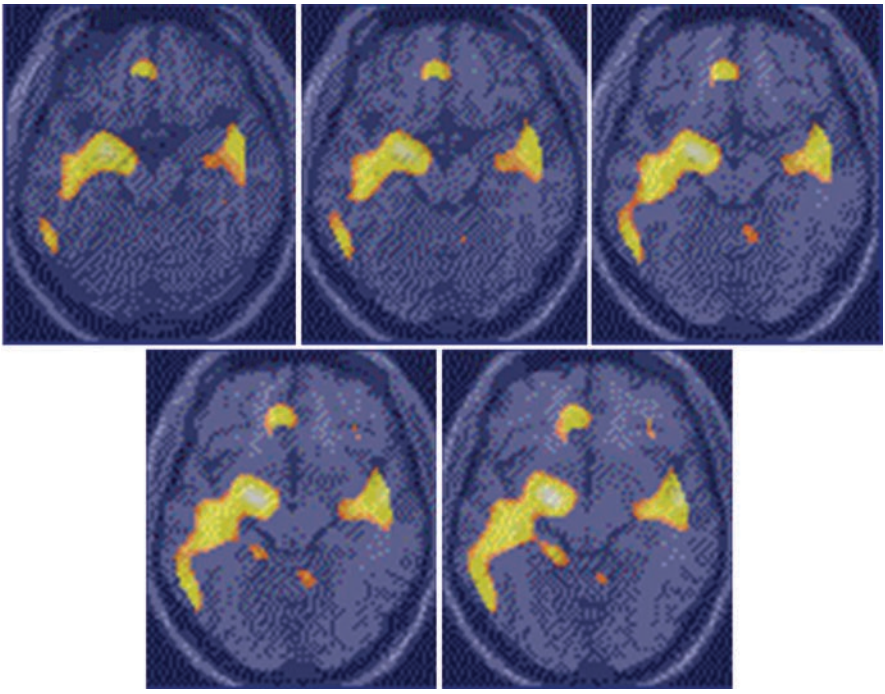

Fig. 2 Medial prefrontal dysfunction in PTSD. There was a failure of medial prefrontal activation in a group of combat veterans with PTSD compared to combat veterans without PTSD during exposure to traumatic combat related slides and sounds (*yellow* area in prefrontal cortex)

extinction (increased blood flow in the amygdala correlated with decreased blood flow in the medial prefrontal cortex) in all the subjects ($r = -0.48$; $p < 0.05$). Increased amygdala blood flow with fear acquisition was positively correlated with PTSD ($r = 0.45$), anxiety ($r = 0.44$) and dissociative ($r = 0.80$) symptom levels in PTSD (but not non-PTSD) subjects. There was a negative correlation between the medial prefrontal blood flow during extinction and anxiety as measured with the PASS during extinction in the PTSD group only which was significant after correction for multiple comparisons ($r = -0.90$; $p = 0.006$) (Bremner et al. 2005a). This study was consistent with increased amygdala function with fear acquisition, and decreased medial prefrontal (anterior cingulate) function during extinction in PTSD. This is consistent with the model of an over active amygdala and a failure of medial prefrontal cortex to extinguish, or shut off, the amygdala, when the acute threat is no longer present.

Few studies have involved imaging of receptors in the brain in PTSD. One study used single photon emission computed tomography (SPECT) to show a decrease in benzodiazepine receptor binding in the frontal cortex in Vietnam combat-related PTSD (Bremner et al. 2000). Another study of Gulf War-related PTSD showed a negative correlation between childhood trauma and right superior temporal gyrus benzodiazepine receptor binding (Fujita et al. 2004).

In summary, these studies are consistent with dysfunction of a circuit involving the medial prefrontal cortex, the dorsolateral prefrontal cortex, and the hippocampus and the amygdala, in PTSD patients that we hypothesize underlie symptoms of PTSD.

Effects of Pharmacotherapy on Brain Function and Structure in PTSD

We have begun to assess the effects of pharmacotherapy on brain structure and function in PTSD (Bremner and Vermetten 2004). We recently assessed the effects of phenytoin on brain structure and function. Studies in animals show that phenytoin, which is used in the treatment of epilepsy and is known to modulate glutamatergic function, blocks the effects of stress on the hippocampus (Watanabe et al. 1992a). We studied nine patients with PTSD in an open label function before and after treatment with phenytoin. Phenytoin resulted in a significant improvement in PTSD symptoms (Bremner et al. 2004c). Phenytoin also resulted in increases in both right hippocampal volume and right hemisphere volume (Bremner et al. 2005b). These findings indicate that phenytoin has an effect on PTSD symptoms as well as brain structure in PTSD patients. In a second study, patients with PTSD were shown to have an increase in hippocampal volume and memory function with paroxetine (Vermetten et al. 2003), and a decrease in cortisol responsiveness to a stressful cognitive challenge (Vermetten et al. 2006). One case report showed decreased inferior frontal, prefrontal, and insula blood flow measured with PET in response to war related sounds. These changes normalized with successful treatment with the SSRI fluoxetine (Fernandez et al. 2001). Another study assessed resting brain blood flow with SPECT Tc-99m HMPAO before and after 8 weeks of open label treatment with the SSRI citalopram in 11 adult patients with PTSD. The treatment resulted in a decrease in the left medial temporal cortex blood flow; decreased PTSD symptoms as measured with the CAPS were correlated with increased function in the medial prefrontal cortex (Seedat et al. 2003).

Summary and Conclusions

Brain imaging studies have shown that PTSD is associated with changes in brain function and structure. Brain areas implicated in the stress response include the amygdala, the hippocampus, and the prefrontal cortex. These brain areas also play a critical role in memory, highlighting the important interplay between memory and the traumatic stress response. Preclinical studies show that stress affects these brain areas. Furthermore, antidepressants have effects on the hippocampus that counteract the effects of stress. In fact, promotion of nerve growth (neurogenesis) in the hippocampus may be central to the efficacy of the antidepressants. Studies in patients with posttraumatic stress disorder (PTSD) show alterations in brain areas

implicated in animal studies, including the amygdala, the hippocampus, and the prefrontal cortex. Increased amygdala activation with acquisition of fear responses, and a failure of the medial prefrontal cortex to properly mediate extinction are hypothesized to underlie symptoms of PTSD. Treatments that are efficacious for PTSD show a promotion of neurogenesis in animal studies as well as a promotion of memory and increased hippocampal volume in PTSD. Future studies are needed to assess neural mechanisms in treatment response in PTSD. In addition, studies need to move beyond assessments of brain function and to examine areas such as neuroreceptor binding and changes in brain chemicals (e.g., with MRS).

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