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Functional neuroimaging in posttraumatic stress disorder

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Abstract

Traumatic stress has a broad range of effects on brain function. Brain areas implicated in the stress response include the amygdala, hippocampus, and prefrontal cortex. Brain studies in patients with posttraumatic stress disorder replicated findings in animal studies by finding alterations in these brain areas. Brain areas implicated in posttraumatic stress disorder play an important role in the stress response as well as memory, highlighting the important interplay between memory and the traumatic stress response. Future studies are required to assess the relationship between recovery from traumatic stress and changes in brain function.

Keywords

depression; stress; PET; PTSD; neuroimaging

Effects of traumatic stress

Traumatic stressors such as early trauma can lead to posttraumatic stress disorder (PTSD), which affects approximately 8% of Americans at some time in their lives [1]. For many trauma victims, PTSD can be a lifelong problem [2]. The development of effective treatments for PTSD is limited by gaps in the knowledge about the underlying brain circuits that mediate symptoms of trauma-related disorders such as PTSD. Recent advances in neuroimaging over the past decade have opened a new window into understanding the changes in functional brain circuitry that underlie PTSD. This paper reviews functional brain imaging studies in the field of PTSD using positron-emission tomography (PET), single photon-emission computed tomography (SPECT) and magnetic resonance imaging (MRI). Studies of PTSD related to early abuse, combat, motor vehicle accident and other forms of traumatic stress will be discussed, with a focus on studies of brain function (as opposed to structure).

Functional neuroimaging techniques

The continuous progress of technology has been beneficial to our understanding of the underlying mechanisms in the brain that cause mental disorders. These techniques include MRI, PET and SPECT [3].

MRI has provided a major technological improvement in the imaging sciences. MRI uses a powerful magnet to throw the electrons that make up brain tissue out of their normal patterns

and measures the time it takes for them to return to their normal 'resting' state. This relaxation time provides information about the content of the tissue, which can be used to create an image of the brain. More recently, MRI has been used to measure brain function, hence the term functional MRI (fMRI). This technique takes advantage of the fact that blood cells have small amounts of the metal heme, which has magnetic properties that can be measured by MRI. With activations of neurons in a specific part of the brain there is an increase in blood flow to that location; this changes the heme concentration in the blood, which is detected by fMRI. Brain function can also be measured with SPECT measurement of [^{99m}Tc] hexamethylpropyleneamine oxime (HMPAO; a marker of brain blood flow) or PET measurement of O-radiolabeled water. PET can also be used to measure brain metabolism (or utilization of sugar) with radioactive glucose ([^{18}F]2-fluoro-2-deoxyglucose [FDG]).

Functional neuroimaging studies can involve subtraction of an active task from a control task, hence a comparison of areas where there are greater differences in response between patients or controls can be made. This can be achieved with fMRI, PET or SPECT. Alternatively, brain metabolism and blood flow can be measured and quantitated using PET. All of these paradigms represent measures of neuronal function and in this paper the term 'function' is used to refer to all of these examples.

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 neurochemical systems and specific brain regions, which result in long-term changes in brain circuits, involved in the stress response [4–7]. Brain regions that are thought to play an important role in PTSD include the hippocampus, amygdala and medial prefrontal cortex (mPFC).

Preclinical and clinical studies have shown alterations in memory function following traumatic stress [8], as well as changes in a circuit of brain areas, including the hippocampus, amygdala and mPFC, which mediate alterations in memory [9]. The hippocampus, an area of the brain involved in verbal declarative memory, is very sensitive to the effects of stress. Stress in animals has been associated with damage to neurons in the CA3 region of the hippocampus (which may be mediated by hypercortisolemia, decreased brain-derived neurotrophic factor [BDNF] and/or elevated glutamate levels) and inhibition of neurogenesis [10–15].

Antidepressant treatments were shown to block the effects of stress and/or promote neurogenesis [13,16–19]. 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 [20]. Other agents, including tianeptine, dihydroepiandrosterone and fluoxetine, have similar effects [16,17,19,21–26]. These

medications may share a common mechanism of action through upregulation of the cAMP response element-binding protein (CREB), that leads to regulation of 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 [27,28], although this continues to be a topic of debate [25,29].

In addition to the hippocampus, other brain structures have been implicated in a neural circuitry of stress, including the amygdala and prefrontal cortex (PFC). The amygdala is involved in memory for the emotional valence of events and plays a critical role in the acquisition of fear responses [30]. The mPFC includes the anterior cingulate gyrus (Brodmann's area [BA] 32) and subcallosal gyrus (area 25), as well as the orbitofrontal cortex. Lesion studies have demonstrated that the mPFC modulates emotional responsiveness through inhibition of amygdala function [31]. Studies show that neurons of the mPFC play an active role in inhibition of fear responses that are mediated by the amygdala [32,33]. 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 mPFC inhibition of amygdala responsiveness. Animal studies have also shown that early stress is associated with a decrease in branching of neurons in the mPFC [34].

Pharmacological treatment of PTSD

Intervening soon after the trauma event is critical for long-term outcomes, since traumatic memories become indelible and resistant to treatment with time [35]. Pharmacological treatment of chronic PTSD has shown efficacy, originally for imipramine [36], amitriptyline [37] and phenazine [36], and later for brofamine [38], paroxetine [39,40] and sertraline [41]. These medications actually decrease the core symptoms of PTSD. For this reason, selective serotonin-reuptake inhibitors (SSRIs) are now recommended as first-line treatment for PTSD [42–47]. The utility of early treatment is also demonstrated by animal studies, showing that pretreatment before stress with antidepressants reduces chronic behavioral deficits related to stress [48,49]. As reviewed above, antidepressants including both norepinephrine as well as gabapentin and phenytoin, promote neurogenesis in the hippocampus, while stress inhibits neurogenesis [16,17,19,22,24,28,50]. This is important since hippocampal neurogenesis has been shown to be required for an antidepressant response [27].

Functional neuroimaging studies in PTSD

Imaging studies of brain function in PTSD are consistent with dysfunction of the mPFC, amygdala and hippocampus [6,51–57]. The methodology of imaging studies in PTSD is outlined in TABLE 1 and a summary of findings by author and brain region in TABLE 2. Studies of resting blood flow or metabolism with PET and SPECT showed alterations at rest in medial, temporal and dorsolateral PFC, cerebellum, and amygdala [58–60]. Stimulation of the noradrenergic system with yohimbine resulted in activation failure in the dorsolateral prefrontal, temporal, parietal and orbitofrontal cortex, and decreased function in the

hippocampus [60]. 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 activation failure of the mPFC/anterior cingulate, including BA 25 or subcallosal gyrus, area 32 and 24, as measured with PET, SPECT or fMRI (FIGURE 1) [61–75]. Other findings in studies of traumatic-reminder exposure include decreased function in the hippocampus [65], thalamus [64,66], visual-association cortex [64,65,69,70], parietal cortex [65,68,69,76,77] and inferior frontal gyrus [64,65,68,69,73,76,77]. In addition to increased function in amygdala [67,70,76], posterior cingulate [63,65,66,69] and parahippocampal gyri [63,65,67]. Shin and colleagues found a correlation between increased amygdala function and decreased mPFC function with traumatic reminders [70], indicating that a failure of inhibition of the amygdala by the mPFC could account for increased PTSD symptoms with traumatic reminders. Other studies found increased amygdala and parahippocampal function and decreased mPFC function during performance of an attention task [71], increased amygdala function at rest [59], during a working-memory task [78], during recall of traumatic words [79], with exposure to masked, fearful faces [80,81], overtly fearful faces [72], traumatic sounds [67,82] and traumatic scripts [76].

Several studies have examined neural correlates of cognitive tasks in PTSD. During working-memory tasks, patients showed decreased inferior frontal [83] and parietal function [78,83]. Retrieval of emotionally valenced words [84] (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, anterior cingulate and mPFC (BAs 25, 32 and 9), left hippocampus and fusiform gyrus/inferior temporal gyrus, with increased activation in the posterior cingulate, left inferior parietal cortex, left middle frontal gyrus and visual association and motor cortex [85]. Another study found a failure of medial prefrontal cortical/anterior cingulate activation and decreased visual association and parietal cortex function in women who had suffered from abuse and PTSD compared with women who had suffered from abuse without PTSD, during performance of the emotional Stroop task (e.g., naming the color of a word such as ‘rape’) [86]. Shin and colleagues showed increased posterior cingulate and parahippocampal gyrus and decreased medial prefrontal and dorsolateral prefrontal cortical activity during an emotional ‘counting’ Stroop paradigm with fMRI [73].

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 ¹⁵O-water measurement of brain blood flow. Women with abuse and PTSD showed a failure of hippocampal activation during the memory task relative to controls [87]. In this study, women who had suffered abuse and were diagnosed with PTSD also had smaller hippocampal volume measured with MRI relative to both women with abuse without PTSD and nonabused non-PTSD women. The failure of hippocampal activation was significant after controlling differences in hippocampal volume as well as accuracy of encoding. Shin and colleagues also found a failure of hippocampal activation with a memory stem completion task in PTSD [88]. Astur and colleagues found deficits in hippocampal activation in PTSD with a computerized underwater maze task [103].

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 subjects underwent PET measurement of cerebral blood flow and psychophysiology measurement of heart rate and skin conductance (SC) 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 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]). During extinction subjects were again exposed to the blue squares (CS) without shock (active extinction). On a second day, 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 SC responses to CS exposure during the active versus the control conditions in all subjects. There was increased SC for PTSD during the first CS-UCS presentation. Extinction of fear was associated with increased SC responses to CS exposure during the active versus the control conditions in all subjects. When PTSD and non-PTSD subjects were examined separately, SC levels were significantly elevated in non-PTSD subjects undergoing extinction following the active compared with the control condition during session one. PTSD subjects showed activation of the bilateral amygdala during fear acquisition compared with the control condition (FIGURE 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 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 bilateral superior temporal gyrus (BA 22), cerebellum, bilateral inferior frontal gyrus (BA 44, 45) and posterior cingulate (BA 24). Fear acquisition was associated with decreased function in mPFC, visual association cortex and medial temporal cortex, inferior parietal lobule and other areas. Extinction of fear responses was associated with decreased function in the orbitofrontal and mPFC (including subcallosal gyrus, BA 25 and anterior cingulate, BA 32), 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 extinction (increased blood flow in amygdala correlated with decreased blood flow in mPFC) in all subjects (correlation coefficient $[r] = -0.48$; $p = 0.05$). 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 medial prefrontal blood flow during extinction and anxiety as measured with the Panic Attack Symptom Scale during extinction in the PTSD group, which was only significant after correction for multiple comparisons ($r = -0.90$; $p = 0.006$) [89]. 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 overactive amygdala and a failure of mPFC to extinguish, or shut off, the amygdala when the acute threat is no longer present.

We have tested the hypothesis that patients with trauma-related psychiatric disorders, which have been described as 'trauma spectrum' disorders [5], have common abnormalities in specific brain areas, including the amygdala, mPFC and hippocampus. These disorders include abuse-related PTSD, depression associated with early abuse, borderline personality disorder (BPD) associated with early abuse and dissociative identity disorder (DID) with early abuse. To test this hypothesis we exposed traumatized women with and without BPD to the stress of a script outlining a personally upsetting abandonment scene in conjunction with PET imaging of the brain [90]. Women with BPD exhibited a relative failure of medial prefrontal activation during abandonment scripts compared with non-BPD females. Women with BPD and abuse had increased psychophysiological responses to abandonment scripts relative to trauma scripts, while women with PTSD and abuse had the opposite pattern [91], indicating differential responding in these two disorders in spite of the common exposure to early abuse. Studies of structural MRI have also shown smaller hippocampal volume across several trauma spectrum disorders, including abuse-related PTSD [87,92], DID with early abuse [93], BPD with early abuse [94] and depression with early abuse [95].

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

Effects of pharmacotherapy on brain function & structure in PTSD

We have begun to assess the effects of pharmacotherapy on brain structure and function in PTSD [96]. 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 [20]. We studied nine patients with PTSD in an open-label trial before and after treatment with phenytoin. Phenytoin resulted in a significant improvement in PTSD symptoms [97]. It also resulted in increases in both right hippocampal volume and hemisphere volume [98]. 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 [99] and a decrease in Cortisol responsiveness to a stressful cognitive challenge [100]. 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 [101]. Another study assessed resting brain blood flow with SPECT^{99mTc} HMPAO before and after 8 weeks of open-label treatment with the SSRI Citalopram, in 11 adult patients with PTSD. Treatment resulted in a decrease in left medial temporal cortex blood flow. Decreased PTSD symptoms as measured with the Clinician Administered PTSD Scale were correlated with increased function in the mPFC [102].

Summary & conclusions

Traumatic stress has a broad range of effects on brain function. Brain areas implicated in the stress response include the amygdala, hippocampus and PFC. 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 neurogenesis in the hippocampus may be central to the efficacy of antidepressants. Studies in patients with PTSD show alterations in brain areas implicated in animal studies, including the amygdala, hippocampus and PFC. Increased amygdala activation with acquisition of fear responses and a failure of the mPFC 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 promotion of memory and increased hippocampal volume in PTSD. Future studies are needed to assess neural mechanisms in treatment responses in PTSD. In addition, studies need to move beyond assessments of brain function and examine areas such as neuroreceptor binding and changes in brain chemicals (e.g., with magnetic resonance spectroscopy).

Expert commentary

Functional neuroimaging studies have identified abnormalities in brain function in PTSD, including increased amygdala function and decreased medial prefrontal and hippocampal function.

These brain abnormalities likely underlie a failure to extinguish traumatic memories.

Almost no studies have examined the effects of antidepressants on brain function or the relationship between recovery from traumatic stress and changes in brain function.

Future studies will assess the effects of treatments on brain function and the relationship between natural recovery from trauma and changes in brain function.

Five-year view

The past decade has seen remarkable progress in the field of functional brain imaging. We have gone from literally no published studies in the field 10 years ago, to the current situation where there is an ever-expanding number of publications. Most of the studies to date have appropriately examined the effects of stimulating PTSD symptoms on brain function. These studies have used scripts of traumatic events or trauma-related slides and sounds to provoke symptoms that are specific to that particular person's trauma. This was an appropriate place for the field to start, being the most salient to understanding the core clinical presentation of PTSD. After that wave of initial studies, investigators started to look at neural correlates of abnormal cognition in PTSD, such as neural correlates of deficits in verbal declarative memory, or other paradigms, such as inhibition of responsiveness with emotional Stroop paradigms. Studies have just begun to examine neural correlates of classic fear conditioning, or the effects of treatment on brain function. I predict that 5 years from now there will be many more studies of this type. In addition, changes in brain chemicals and neuroreceptor binding will be better understood; a topic which has received essentially no attention up to this point.

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Key issues

- Functional imaging with functional magnetic resonance imaging, positron emission tomography and single photon-emission computed tomography can be used to identify brain circuits that underlie symptoms of posttraumatic stress disorder (PTSD).
- PTSD is associated with increased amygdala function and decreased function in the medial prefrontal cortex and hippocampus.
- Antidepressants promote neurogenesis in the hippocampus and increase hippocampal volume in PTSD patients.
- Future studies are needed to assess the effects of antidepressants on brain function in PTSD.

Figure 1. Decreased medial prefrontal function with exposure to combat related slides and sounds

There was a decrease in function in the mPFC in combat veterans with PTSD relative to combat veterans without PTSD with exposure to traumatic combat material. Reprinted from [63] with permission from the Society of Biological Psychiatry.

BA: Brodmann's Area; mPFC: Medial prefrontal cortex; PTSD: Posttraumatic stress disorder.

Figure 2. Increased amygdala function during acquisition of conditioned fear responses in women with early childhood abuse and posttraumatic stress disorder

Yellow areas represent bilateral amygdala activation. There was greater amygdala activation with acquisition of fear responses (pairing of conditioned stimulus and unconditioned stimulus) in posttraumatic stress disorder compared with controls. Reprinted with permission from [89].

Table 1

Published functional imaging studies in posttraumatic stress disorders.

Study	PTSD study population		Control group		n	Imaging methods	Active condition	Control	Ref.
Rauch	Mixed	8	None	8	0	PET ¹⁵⁰	Combat scripts	Neutral scripts	[76]
Sample	Combat plus SA	6	Healthy subjects	6	6	PET FDG	Continuous performance task	Rest	[104]
Bremner	Combat related	10	Healthy subjects	10	10	PET FDG	Yohimbine	Placebo	[60]
Shin	Combat related	7	Combat veterans without PTSD	7	7	PET ¹⁵⁰	Trauma imagery/perception	Negative/neutral image/perception	[69]
Bremner	Combat related	10	Combat veterans without PTSD	10	10	PET ¹⁵⁰	Combat slides/sounds	Neutral slides/sounds	[63]
Bremner	Women with abuse	10	Abused women without PTSD	10	12	PET ¹⁵⁰	Abuse scripts	Neutral scripts	[65]
Shin	Women with abuse	8	Abused women without PTSD	8	8	PET ¹⁵⁰	Abuse scripts	Neutral scripts	[68]
Liberzon	Combat related	14	Healthy subjects/combat controls	14/11	14/11	SPECT HMPAO	Combat sounds	White noise	[67]
Zubieta	Combat related	12	Combat veterans without PTSD, healthy controls	12	11/12	SPECT HMPAO	Combat sounds	White noise	[105]
Rauch	Combat related	8	Combat veterans without PTSD	8	8	fMRI	Masked fearful faces	Masked happy faces	[80]
Sample	Combat plus SA	6	Healthy	6	7	PET ¹⁵⁰ butanol	Continuous performance task	Rest	[71]
Shin	Combat related	8	Combat veterans without PTSD	8	8	fMRI	Counting Stroop combat	Stroop general negative	[73]
Lanius	Mixed civilian (SA or MVA)	9	Traumatized non-PTSD	9	9	fMRI	Traumatic scripts	Resting state	[66]
Pissiota	Combat related	7	None	7	0	PET	Traumatic sounds	Neutral sounds	[82]
Lanius	Mixed civilian (SA or MVA)	10	Traumatized non-PTSD	10	10	fMRI	Sad, anxious, trauma scripts	Resting state	[64]
Bremner	Women with abuse	10	Healthy women	10	11	PET ¹⁵⁰	Trauma-related word recall	Shallow encoding	[85]
Bremner	Women with abuse	10	Women with abuse without PTSD	10	12	PET ¹⁵⁰	Memory task	Shallow encoding	[87]
Clark	Civilian	10	Healthy	10	10	PET ¹⁵⁰	Working-memory task	Fixed target	[83]
Bonne	Civilian	11	Trauma/healthy	11	17/11	SPECT HMPAO	Resting state	NA	[58]
Bremner	Women with abuse	8	Healthy	8	11	PET ¹⁵⁰	Fear conditioning	Unpaired CS-US	[89]
Bremner	Women with abuse	12	Women with abuse without PTSD	12	9	PET ¹⁵⁰	Emotional Stroop	Neutral Stroop	[86]
Shin	Vietnam combat related	17	Vietnam veterans without PTSD	17	19	PET ¹⁵⁰	Traumatic scripts	Neutral scripts	[70]
Shin	Firefighters	8	Firefighters without PTSD	8	8	PET ¹⁵⁰	Memory task	Shallow encoding	[88]
Lindauer	Policemen	15	Policemen without PTSD	15	15	SPECT HMPAO	Traumatic scripts	Neutral scripts	[74]
Yang	Children, earthquake related	5	Children, earthquake related, non-PTSD	5	6	fMRI	Earthquake pictures/imagery	Neutral pictures/imagery	[62]
Shin	Firefighters plus Vietnam combat	13	Trauma exposed without PTSD	13	13	fMRI	Overtly fearful faces	Neutral overt faces	[72]

Study	PTSD study population	n	Control group	n	Imaging methods	Active condition	Control	Ref.
Armony	Acute PTSD-MVA	13	None	0	fMRI	Masked fearful faces	Masked happy faces	[81]
Sakamoto	Mixed civilian	16	Healthy	16	fMRI	Masked traumatic images	Masked neutral images	[77]
Protopopescu	Sexual/physical abuse	11	Healthy	21	fMRI	Traumatic word recall	Neutral word recall	[79]
Bryant	Civilian	14	Healthy	14	fMRI	Oddball working memory	Background stimuli	[78]
Britton	Combat	16	Combat/healthy	15/14	PET ¹⁵ O	Traumatic scripts	Neutral scripts	[61]
Chung	Civilian	23	Healthy controls	46	SPECT HMPAO	Resting state	None	[59]
Phan	Vietnam combat related	16	Combat/healthy	15/15	PET	Negative pictures	Control pictures	[75]
Astur	Civilian	12	Healthy	12	fMRI	Virtual water maze	Visual condition	[103]

CS: Conditioned stimulus; FDG: 2-fluoro-2-deoxyglucose; fMRI: Functional magnetic resonance imaging; HMPAO: Hexamethylpropyleneamine oxime; MVA: Motor vehicle accident; NA: Not applicable; PET: Positron emission tomography; PTSD: Posttraumatic stress disorder; SA: Substance abuse; SPECT: Single photon-emission computed tomography; US: Unconditioned stimulus.

Summary of results of published functional imaging studies of the neural circuitry of posttraumatic stress disorder.

Table 2

Study	Ref	Thalamus	Cerebellum	Perical (SNrG; BA: 40)	Parietal (IPL)	Precuneus	Visual association cortex	Sensory cortex	Motor cortex	Insula	Inferior temporal Islandform	Middle temporal (BA: 21)	Superotemporal (BA: 22)	Posterior cingulate (BA: 31)	Disrupted PFC (IFC)	Disrupted PFC (MFG/BA: 6/46)	Anterior cingulate (BA: 9,10)	mPFC ORF (BA:11)	mPFC-AC (BA:32,24,25)	Amygdala	Parahippocampus	Hippocampus
Rauch (1996)	[70]				↗					↓		↗			↑			↓	↓	↓		
Sample (1996)																						
Bremner(1997)-baseline - activation	[60]	NC	NC		NC		NC	NC	NC				↗			↑		NC	NC	NC	NC	↑
	[60]																					
	[60]																					
	[60]																					
Shin (1997) - perception negative - imagery vs negative - perception vs neutral - imagery vs neutral	[63]								↓			↑				↑			↓			
	[63]												↗						↓			
	[63]																					
	[63]																					
Bremner(1999)	[65]				↓IR		↗	↗	↑	↓IR	↓IR		↓	↑					↑		↓	
Bremner(1999)	[68]												↓	↓	↓IR	↓	↓	↑	↑		↓IR	
Shin (1999)	[67]													↑	↑	↑	↑	↓	↑		↓L	
Liberson (1999)	[105]	NC	NC																	↓		
Zubeau (1999)	[80]										NC						↓		NC			
Rauch (2000)	[71]				↑		↗												NC	↓		
Sample (2000)	[62]									↓	↑		↓					↗	↗	↓	↑	
Shin (2001)	[69]	↑												↓	↗	↗		↗	↗	↑	↑	
Lamus(2001)	[82]								↑								↗		↗			
Pissioti (2002)	[64]	↗					↗													↓		
Lamus (2003)	[85]								↑		↑				↗	↗		↗				
Bremner (2003)	[87]													↓		↓		↑			↗	
Bremner (2003)	[83]																					↗
Clark (2003)	[58]								↑		↑		↓									
Bonne (2003)	[89]								↗	↑			↑							↑	↑	
Bremner (2005)	[86]									↗			↑	↓	↓				↗			
Bremner (2004)	[70]						↗							↑					↗			

Study	Hippocampus	Parahippocampus	Amygdala	mPFC/AC (BA32,4,25)	mPFC/ORB (BA11)	Anteromedial (BA9,10)	Dorsolateral PFC (BA9,46)	Dorsolateral PFC (PFC)	Posterior cingulate (BA31)	Supratemporal (BA22)	Middle temporal (BA21)	Inferior temporal Island	Insula	Motor cortex	Sensory cortex	Visual association cortex	Precuneus	Parietal (PPL)	Parietal (SMG; BA40)	Cerebellum	Thalamus	Ref.
Shin (2004)				↑								↑										[88]
Shin (2004)																						[72]
Lindner (2004)																						[62]
Yang (2004)																						[72]
Shin (2005)																						[81]
Armory (2005)																						
Sakamoto (2005)																						[77]
Protopopescu (2005)																						[79]
Byant (2005)																						[78]
Barton (2005)																						[61]
Chang (2006)																						[59]
Phan (2006)																						[75]
Axtur (2006)																						[103]
Decreased function	+++++/-	+++++	+++++++	+++++++/+	++/-+	-	-/-+++	-/+	+++	+++	+	++/-	+++	++/-	+	-/+	++/-	++++	+	++/-	++	
Increased function																						

AC: Anterior cingulate; BA: Brodmann's area; IPL: Inferior parietal lobe; L: Left; MFG: Medial fusiform gyrus; mPFC: Medial prefrontal cortex; OBF: Orbitofrontal; NC: No change; R: Right; SMG: Supra marginal gyrus.