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Functional neuroimaging studies of post-traumatic stress disorder

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Abstract

Post-traumatic stress disorder (PTSD) is a significant problem that can affect individuals who have been exposed to a traumatic event or events, such as combat, violent crime or childhood abuse. Over the past several years, neuroimaging studies of PTSD have focused on elucidating the brain circuits that mediate this disorder. In this article, we will briefly introduce some of the methods used in functional neuroimaging studies of PTSD. We will then review functional neuroimaging studies that have reported significant findings in the amygdala, medial prefrontal cortex, hippocampus and insula. Finally, we will suggest future directions for research.

Keywords

amygdala; gyrus cinguli; hippocampus; insula; limbic system; magnetic resonance imaging; MRI; neuroimaging; positron emission tomography; post-traumatic stress disorders

Post-traumatic stress disorder (PTSD) is an anxiety disorder that can develop in individuals who have been exposed to an event or events that involved the threat of death or serious injury and reacted with intense fear, helplessness or horror [1]. Patients with this disorder persistently re-experience their traumatic events in various ways, including intrusive and disturbing recollections, nightmares, flashbacks and distress, and physiological reactivity on exposure to reminders of the event. These individuals often avoid reminders of the traumatic event and experience a restricted range of affect. Finally, patients with PTSD experience hyperarousal, characterized by difficulty sleeping or concentrating, hypervigilance and exaggerated startle response.

A neurocircuitry model of PTSD [2,3] implicates the amygdala, medial prefrontal cortex (mPFC) and hippocampus as dysfunctional in PTSD. According to this model, the amygdala is hyperresponsive, leading to an exaggerated fear response. By contrast, regions of the ventral mPFC (vmPFC; including rostral anterior cingulate cortex [rACC] and ventral medial frontal gyrus) are hyporesponsive and fail to inhibit the amygdala. This hyporesponsivity may also be related to impaired fear extinction in PTSD. Finally, abnormal

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hippocampal function may underlie declarative memory impairments and deficits in identifying safe contexts in PTSD. Emerging evidence suggests that the dorsal anterior cingulate cortex (dACC) may be hyperresponsive in PTSD and may also play a role in this disorder. Although this model did not originally include the insula, recent findings suggest that it may be functionally abnormal in PTSD, as well as in other anxiety disorders [4].

In this article, we will briefly describe the types of methods used in functional neuroimaging studies of PTSD and then summarize relevant findings from these studies. Given the aforementioned neurocircuitry model, we will focus on studies that have reported significant findings in the amygdala, vmPFC, dACC, hippocampus and insula. We will then very briefly review the structural and receptor imaging findings in these brain regions. Finally, we will propose directions for future research in this field.

Methods

In order to investigate the neurocircuitry of PTSD, researchers have used functional MRI (fMRI), SPECT and PET. Although these techniques yield different dependent measures (e.g., blood oxygenation level dependent signal [BOLD] for fMRI and regional cerebral blood flow [rCBF] or regional cerebral metabolic rate for glucose [rCMRglu] for PET), these measures are all thought to be approximate indices of relative regional activity in the brain.

In conjunction with these scanning techniques, researchers typically ask participants to view or listen to emotional (and/or neutral) stimuli or to complete specific cognitive tasks in the scanner. One task that is commonly used to assess the mediating functional neuroanatomy of the symptomatic state is called script-driven imagery [5,6], in which participants are prompted by audiotaped narratives to recall and imagine personal traumatic versus neutral events in the scanner. To examine whether functional abnormalities are specific to processing trauma-related information, researchers often present subjects with emotional stimuli unrelated to their traumatic events, such as fearful facial expressions. Some studies have presented these stimuli overtly while others have used backward masking techniques to prevent conscious processing of the expressions. Other researchers employ cognitive tasks, such as Stroop interference or memory tasks that assess the functional integrity of specific brain regions or circuits of interest in PTSD. Still others study brain activity in patients with PTSD at rest. The reader should keep in mind that the methods vary considerably across the studies reviewed below, and any discrepant results between studies could reflect different methods. Conversely, findings that are consistent across studies despite differing methods may be especially important to note.

Functional imaging findings

Amygdala

A widely reported finding in the PTSD literature is that of increased amygdala responsivity in PTSD. Using script-driven imagery, Rauch and colleagues found increased amygdala rCBF during traumatic versus neutral imagery in PTSD [7]; however, this study's lack of a non-PTSD comparison group complicates the interpretation of these findings. Shin and colleagues found increased amygdala activation in response to traumatic versus neutral script-driven imagery in male combat veterans with PTSD compared with those without [8]. However, other studies have found no differences in amygdala activation between trauma-exposed individuals with and without PTSD in response to traumatic versus neutral scripts [9,10].

In addition to scripts, other trauma-related stimuli have been used to study amygdala activation in PTSD. In a SPECT study, Liberzon and colleagues presented combat sounds or white noise to combat veterans with and without PTSD and to combat-unexposed control subjects [11]. Increased left amygdala activation to combat sounds versus white noise was found in the PTSD group only. Pissiota and colleagues also found increased amygdala activation in PTSD to combat sounds compared with neutral sounds, although this study lacked a comparison group without PTSD [12]. Another study exposed combat veterans with and without PTSD to combat-related odors and found increased amygdala activation in the PTSD group relative to the non-PTSD control group [13]. Hendler and colleagues presented backwardly masked combat-related and combat-unrelated images below, near and above recognition thresholds to combat-exposed veterans with and without PTSD [14]. Increased amygdala activation was found in PTSD relative to control subjects across all content and recognition threshold conditions. Protopopescu and colleagues found increased amygdala activation in response to trauma-related versus unrelated words in a PTSD group relative to a trauma-unexposed control group [15]. However, Bremner and colleagues presented combat veterans with and without PTSD with combat-related pictures and sounds during PET scanning and found no differences in amygdala activation between groups [16].

The finding of increased amygdala activation in PTSD has been found to extend to trauma-unrelated emotional material. Rauch and colleagues found that relative to a trauma-exposed control group, individuals with PTSD showed greater amygdala responses to backwardly masked fearful faces than to masked happy faces [17]. Similarly, Bryant and colleagues found greater amygdala activation to masked fearful faces compared with masked neutral faces in individuals with PTSD compared with healthy, trauma-unexposed control participants [18]. Felmingham *et al*. reported increased amygdala activation in response to masked fearful faces in PTSD compared with trauma-exposed and trauma-unexposed control groups [19]. Shin and colleagues presented unmasked facial expressions to subjects during fMRI and found increased amygdala responses to fearful versus happy facial expressions in PTSD subjects relative to trauma-exposed control subjects [20]. Williams and colleagues used a similar task in individuals with PTSD versus a nontraumatized control group and found increased amygdala activation in the fearful versus neutral contrast [21]. Another study using overtly presented facial expressions found greater amygdala responsivity to fearful relative to neutral faces in subjects with PTSD compared with those with PTSD and comorbid depression [22]. Dickie and colleagues used fMRI and a subsequent memory paradigm to test recognition memory for facial expressions presented to subjects with PTSD [23]. They found that PTSD symptom severity positively correlated with left amygdala activation for successfully remembered fearful faces; however, interpretation of these findings is difficult owing to the lack of a control group in the study. Fonzo and colleagues used an emotional face-matching task and found increased amygdala activation in response to fearful versus happy faces in women exposed to intimate partner violence with PTSD relative to trauma-unexposed control subjects [24]. This study also reported less connectivity between the anterior insula, amygdala and anterior cingulate cortex (ACC) in PTSD for this contrast.

Increased amygdala activity has also been found at rest ([25], but also see [26]) and using neutral stimuli. Using a neutral auditory continuous performance task during PET scanning, Semple and colleagues found greater amygdala blood flow in combat veterans with PTSD and comorbid substance abuse than in a group of healthy control individuals [27]. Shin and colleagues found greater amygdala rCBF (collapsed across memory recall conditions) in firefighters with PTSD compared with those without PTSD [28]. Using fMRI, Bryant and colleagues found greater amygdala responses to targets in an auditory oddball paradigm in subjects with PTSD compared with a nontraumatized control group [29]. Whalley and colleagues scanned individuals using fMRI during a recognition memory task with neutral

images [30]. Results revealed greater left dorsal amygdala activation in response to old versus new images in a group with PTSD compared with both depressed and trauma-exposed control groups. One fMRI study of bank robbery survivors with and without PTSD found that all subjects showed increased amygdala activation in response to negative pictures, but only those subjects with PTSD also demonstrated increased amygdala activation in response to neutral pictures [31]. However, a different study found decreased amygdala responsivity to negative pictures in PTSD compared with trauma-exposed and unexposed control groups [32]. In addition, Strigo *et al.* found no amygdala activation during exposure to pain in PTSD compared with trauma-exposed control subjects [33].

Fear-conditioning paradigms have also demonstrated abnormal amygdala activation in PTSD. Bremner and colleagues used a paradigm involving a fear-acquisition phase, in which a shock was paired with a blue square on a screen, and a control condition, in which subjects received random shocks in the absence of the blue square [34]. Results revealed greater activation in the left amygdala during fear acquisition versus the control condition in a PTSD group compared with a trauma-unexposed control group. Milad and colleagues used a different fear-conditioning paradigm that included a fear-acquisition phase (in which two different colored lights were paired with a shock while a third colored light was not), as well as an extinction learning phase, in which one of the colored lights that was previously paired with the shock now appeared in the absence of the shock (i.e., was extinguished) [35]. Relative to a trauma-exposed control group, the PTSD group showed greater amygdala activation during extinction learning in response to the extinguished light versus the light that had never been paired with shock.

Decreased amygdala activation seems to be associated with resilience to PTSD. Britton and colleagues reported amygdala deactivation in response to traumatic versus neutral scripts in trauma-exposed individuals without PTSD [36]. A PET study scanned individuals 10–29 days after motor vehicle accidents and then assessed PTSD symptoms 3 months later. They found less amygdala activation to trauma versus neutral imagery scripts in these trauma-exposed subjects compared with a group of trauma-unexposed subjects. Only four of the 22 subjects in the trauma-exposed group developed PTSD [37].

Amygdala responsivity has also been positively correlated with PTSD symptom severity [8,12,15,17,23,29,31,38]. In addition, some studies have found a negative correlation between amygdala responses and mPFC activation [8,20], although others have not [21,39]. Lanius and colleagues studied a group of acutely traumatized patients 6 weeks after trauma and found that the strength of resting state connectivity between posterior cingulate cortex/precuneus and right amygdala positively predicted severity of PTSD symptoms [40]. This relationship remained significant after controlling for comorbid depression.

Research has also revealed an association between positive response to cognitive–behavioral therapy (CBT) and decreased amygdala activation [41,42]. In addition, higher pretreatment amygdala activation appears to predict less symptomatic improvement in response to CBT [43].

Importantly, amygdala hyper-responsivity has also been demonstrated to be associated with other anxiety disorders, and therefore may not be specific to PTSD [44]. In addition, as mentioned previously, not all studies have reported increased amygdala activation in PTSD, and these differing results could be due to the fact that amygdala responses can habituate over time, especially in studies using block designs [45]. Averaging amygdala signal over a minute or several minutes (as is commonly carried out during PET or SPECT scans) could reduce the chances of detecting amygdala hyper-responsivity in PTSD [46].

Medial prefrontal cortex

Functional neuroimaging studies have typically reported less activation or even deactivation in vmPFC regions during traumatic script-driven imagery in PTSD. In a PET study, Bremner and colleagues reported that compared with childhood sexual abuse survivors without PTSD, those with PTSD failed to activate the rACC in response to traumatic versus neutral scripts [9]. Shin and colleagues found less rACC activation in response to traumatic versus neutral scripts in survivors of childhood sexual abuse with PTSD versus those without [47]. Lanius and colleagues found decreased rACC and medial frontal gyrus activation in a traumatic versus baseline imagery condition in PTSD compared with traumatized individuals without PTSD [10]. Shin and colleagues found less activation in the medial frontal gyrus in male combat veterans and female nurse veterans with PTSD relative to those without [8]. Furthermore, within the PTSD group, rCBF in this region was negatively correlated both with PTSD symptom severity and rCBF in the amygdala. Using SPECT, Lindauer and colleagues found lower activation in the medial frontal gyrus in response to traumatic versus neutral scripts in trauma-exposed police officers with PTSD compared with those without [48]. Britton and colleagues found greater rACC deactivation in combat veterans with PTSD in response to traumatic/stressful scripts compared with combat veterans without PTSD and combatunexposed individuals [36]. In addition, within the PTSD group, dorsomedial prefrontal cortex activation was negatively correlated with PTSD symptom severity. Finally, Lanius and colleagues found less rACC activation in response to trauma imagery versus baseline in a group of individuals with PTSD compared with a group of individuals with PTSD and comorbid major depression [49].

Several studies have probed vmPFC function in PTSD using trauma-related stimuli other than scripts. One PET study found decreased rACC blood flow in response to combat-related versus neutral images in combat-exposed individuals with PTSD relative to those without PTSD [50]. Bremner and colleagues reported decreased vmPFC blood flow in response to combat-related versus neutral audio–visual stimuli in combat veterans with PTSD relative to veterans without PTSD [16]. Using fMRI and an emotional counting Stroop task, Shin and colleagues found that relative to combat veterans without PTSD, combat veterans with PTSD failed to activate rACC in the combat-related versus generally negative word condition [51]. Yang and colleagues presented trauma-related and neutral pictures to adolescents with PTSD and trauma-exposed control subjects [52]. They found decreased ACC activation in response to trauma-related versus neutral pictures in the PTSD group relative to the control group. Hou and colleagues also reported decreased ACC activation in response to trauma-related versus neutral pictures in mining accident survivors with PTSD relative to those without PTSD [53].

Decreased vmPFC activation has also been demonstrated using emotional, trauma-unrelated stimuli, such as faces. Using fMRI, Shin and colleagues presented unmasked happy and fearful facial expressions to subjects with PTSD and trauma-exposed subjects without PTSD [20]. Diminished rACC, vmPFC and dorsal mPFC responses to fearful versus happy expressions were found in the PTSD group relative to trauma-exposed control subjects. rACC activation was negatively correlated with PTSD symptom severity. Williams and colleagues found reduced activation in the mPFC and dorsal portions of the ACC to overtly presented fearful versus neutral facial expressions in individuals with PTSD relative to healthy, trauma-unexposed control subjects [21]. Kemp and colleagues compared individuals with PTSD with and without comorbid depression and found decreased mPFC responsivity to fearful versus neutral facial expressions in subjects with PTSD and comorbid depression compared with those with PTSD alone [22]. Kim and colleagues studied subway fire survivors with PTSD and healthy comparison individuals using a same–different judgment task with task-irrelevant neutral and emotional face distracters [54]. In the fearful versus neutral face contrast, significantly diminished rACC activation was found in the

PTSD compared with the control group. Furthermore, within the PTSD group, a negative correlation was found between rACC activation and PTSD symptom severity. Dickie and colleagues used a subsequent memory paradigm and found a negative correlation between PTSD symptom severity and vmPFC activation in response to forgotten faces [23].

Studies using nonfacial emotional stimuli have shown similar results. Lanius and colleagues found decreased ACC activation in response to scripts describing sad and anxious personal events in PTSD relative to trauma-exposed subjects without PTSD [55]. Bremner and colleagues found decreased rCBF in the rACC and subcallosal cortex during retrieval of deeply encoded negative versus neutral words in PTSD relative to trauma-unexposed healthy control subjects [56]. In a different study, the same group reported decreased rCBF in the ACC during an emotional Stroop task in women with PTSD relative to trauma-exposed women without PTSD [57]. One study measured rCBF in combat veterans with and without PTSD, as well as trauma-unexposed control subjects while they viewed aversive and neutral pictures. Relative to the trauma-unexposed control group, the PTSD group deactivated the vmPFC in response to negative versus neutral pictures, but no significant differences were found between trauma-exposed groups [32].

Some studies implementing neutral stimuli have found evidence of diminished vmPFC activation in PTSD. Semple and colleagues found less blood flow in the ACC/medial frontal gyrus during an auditory continuous performance task in individuals with PTSD and a history of substance abuse compared with healthy, trauma-unexposed individuals [27]. Moores and colleagues found diminished ACC activation in a PTSD group relative to a trauma-unexposed control group during verbal working memory updating [58]. In a group of motor vehicle accident survivors, most of whom did not develop PTSD, Osuch and colleagues found greater rCBF at rest in rACC relative to trauma-unexposed control subjects [37]. This could suggest that increased activation in this area is a protective factor against developing PTSD.

Decreased vmPFC in PTSD has also been reported in the context of fear conditioning. Bremner and colleagues found decreased rACC and subcallosal cortex activation during extinction in women with PTSD compared with trauma-unexposed control subjects [34]. In a study conducted by Milad and colleagues, subjects underwent fear conditioning, extinction and then on a separate day, extinction recall, in which the previously extinguished conditioned stimuli were presented again in the absence of the shock [35]. This study reported decreased vmPFC activation during extinction recall in PTSD subjects relative to trauma-exposed control subjects.

Activation in the vmPFC has been found to inversely correlate with PTSD symptom severity [8,20,21,23,36,54,59]. Some treatment studies have reported a positive association between symptomatic improvement and increases in vmPFC activation [41,42,60,61]. However, Bryant and colleagues found that individuals with PTSD who did not respond well to CBT had significantly greater pretreatment rACC activation in response to masked fearful versus neutral facial expressions than those who did respond [43]. The researchers speculated that the masked stimulus presentation used in this study may have resulted in this counterintuitive finding.

Although many studies have found evidence suggesting that regions of the vmPFC are hyporesponsive in PTSD, several other studies have not. Using SPECT, Liberzon and colleagues found equivalent ACC activation during the presentation of combat sounds versus white noise in combat veterans with PTSD, combat veterans without PTSD and combat-unexposed healthy control subjects [11]. Zubieta and colleagues also used SPECT with combat sounds and found increased mPFC activation in individuals with combat-

related PTSD relative to combat and healthy control subjects [62]. Another study found greater vmPFC activation in response to unconsciously processed fearful versus neutral faces in a PTSD group compared with a healthy control group, which may suggest that decreased vmPFC responsivity in PTSD is limited to conscious fear processing [18]. Greater rACC activation has also been reported in PTSD relative to trauma-unexposed control subjects during an auditory oddball paradigm [29] and a response-inhibition task [63]. Another study found a significant positive correlation between PTSD symptom severity and rACC activation in response to combat-related versus neutral photos [64]. Finally, two SPECT studies have produced findings of increased perfusion in ACC at rest in PTSD compared with trauma-unexposed healthy control subjects [25,65], and Bonne and colleagues found no difference in resting ACC perfusion between PTSD, trauma-exposed non-PTSD, and trauma-unexposed groups [66].

Most of the previous findings of relatively diminished mPFC activation in PTSD were located in ventral portions of this brain region. By contrast, some studies have suggested that dorsal regions of the ACC may have normal or increased responsivity in PTSD. Exaggerated dACC activation has been observed during fear conditioning [34,35], interference tasks [51,67], emotional and auditory oddball tasks [29,68], as well as at rest [26]. Fonzo and colleagues found greater dACC activation in response to male versus female faces in female survivors of intimate partner violence with PTSD compared with trauma-unexposed comparison females [24]. In addition, dACC activation was positively correlated with hyperarousal symptoms. Shin and colleagues found increased rCMRglu in dACC, not only in combat veterans with PTSD but also in their identical, combat-unexposed co-twins without PTSD, suggesting that elevated dACC activation could be a familial risk factor for PTSD [26]. In addition, rCMRglu in the dACC was positively correlated with PTSD symptom severity.

Hippocampus

Findings regarding hippocampal responsivity in PTSD have been mixed. Bremner and colleagues used script-driven imagery during PET and found decreased hippocampal activation in the traumatic versus neutral contrast in survivors of childhood sexual abuse with PTSD relative to those without PTSD [9]. Decreased activation in this region has also been demonstrated using memory tasks with neutral and emotional stimuli. Bremner and colleagues found decreased left hippocampal activation in PTSD relative to a trauma-exposed control group during encoding of neutral verbal passages; furthermore, this finding remained significant when researchers controlled for hippocampal volume [69]. This group also found that relative to healthy, trauma-unexposed individuals, childhood sexual abuse survivors with PTSD showed decreased left hippocampal blood flow during emotional versus neutral word retrieval [56]. A PET study of the recollection of deeply versus shallowly encoded neutral words revealed less hippocampal activation in firefighters with PTSD compared with firefighters without PTSD [28]. Astur and colleagues employed a virtual water maze task in fMRI and found reduced right hippocampal activation in individuals with PTSD compared with a healthy, trauma-unexposed comparison group [70]. A negative correlation between symptom severity and hippocampal activation was also reported. Another study found decreased hippocampal responsivity during verbal working memory updating in individuals with PTSD compared with a healthy control group [58]. During retrieval of neutral word pairs, Geuze and colleagues reported less activation in the hippocampus during the retrieval of paired associates in veterans with PTSD compared with those without PTSD [71]. Molina and colleagues studied combat veterans with and without PTSD and reported reduced rCMRglu in the hippocampus at rest in PTSD [72]. Decreased hippocampal activation has also been reported in PTSD during fear extinction recall [35]. Finally, Peres and colleagues reported increased left hippocampal activation in response to

traumatic scripts following treatment with psychotherapy in patients with subthreshold PTSD, suggesting that this abnormality normalizes with treatment [42].

By contrast, other studies have found evidence of increased hippocampal activation in PTSD. Although Shin and colleagues found diminished hippocampal activation in PTSD during the recollection of deeply versus shallowly encoded neutral words, when all conditions were averaged and groups were compared, the PTSD group showed greater hippocampal rCBF than the control group [28]. Furthermore, within the PTSD group, symptom severity was positively correlated with rCBF in the hippocampus. In a group of motor vehicle accident survivors resilient to PTSD who underwent script-driven imagery during PET, Osuch and colleagues found decreased hippocampal blood flow in the traumatic versus neutral contrast compared with healthy unexposed control subjects [37]. Werner and colleagues reported increased hippocampal activation during encoding of face–occupation associations in a PTSD group relative to a healthy control group [73]. Whalley and colleagues showed subjects neutral target images superimposed over emotional or neutral background images and later tested recognition memory for the neutral target images during fMRI [30]. They found greater hippocampal responsivity during the recognition of neutral targets that had been learned with emotional versus neutral backgrounds in PTSD compared with depressed subjects and trauma-exposed control subjects. Hippocampal hyper-responsivity has also been demonstrated during a continuous performance task [27], encoding of neutral word pairs [71] and face–profession name pairs [73], deep encoding and correct recognition of trauma-related words [74], as well as and at rest [65]. Positive correlations between hippocampal activation and symptom severity have also been found [28,75]. Overall, it seems that the direction of hippocampal functional abnormalities depends in part on the type of tasks and analyses employed.

Insula

Several studies have reported increased activation in the insula in PTSD. Using SPECT and script-driven imagery, Lindauer and colleagues demonstrated increased activation in the right insula to trauma-related scripts in individuals with PTSD compared with trauma-exposed control subjects [76]. Lanius and colleagues used script-driven imagery during fMRI to compare activation patterns in PTSD subjects with and without major depression [49]. After controlling for differences in PTSD severity between groups, greater left insula activation to trauma-related imagery was found in the group with PTSD compared with the group with both PTSD and depression. Increased insula activation has also been found in response to trauma-related odors in combat veterans with PTSD compared with veterans without PTSD [13].

Increased insula activation has also been found in studies using emotional, trauma-unrelated stimuli. Bremner and colleagues used PET to study rCBF associated with the retrieval of emotional and neutral word pairs in women with early childhood sexual abuse-related PTSD and nontraumatized women [56]. Greater insula activation during negative word retrieval was found in the PTSD group relative to the control group. Simmons and colleagues found increased insula activation during the anticipation of negative versus positive images in women with intimate partner violence-related PTSD compared with healthy, trauma-unexposed control subjects [77]. The same group found increased activation of the insula while processing fearful (and angry) versus happy facial expressions in women with intimate partner violence-related PTSD relative to trauma-unexposed control subjects [24]. Another study found increased insula recruitment in PTSD relative to both trauma-exposed and depressed control groups when retrieving neutral items that had been encoded in emotional relative to neutral contexts [30]. Increased insula activation in PTSD has also been found during an emotional counting Stroop task [51] and during encoding of face–profession associations [73].

Exposure to painful stimuli has also been reported to increase insula activation in PTSD. Geuze and colleagues found that combat veterans with PTSD demonstrated greater bilateral insula responsivity to painful heat stimulation than combat-exposed control subjects [78]. In another study of pain processing in PTSD, Strigo and colleagues found that women with PTSD related to intimate partner violence showed greater insula activation during painful stimulation compared with trauma-unexposed women without PTSD [33]. However, after repeated exposure to the temperature stimulation, PTSD subjects exhibited decreased insula activation relative to the comparison group.

Some studies have reported a positive correlation between activation in the insula and symptom severity [59,63,75]. A recent voxel-wise meta-ana lysis confirmed the finding of greater insular activation in PTSD and other anxiety disorders [44]. However, several studies have reported no group differences or relatively decreased insular activation in PTSD (e.g., [9,32,47,57,58,72]).

Structural imaging findings

Although not the main focus of this article, structural findings in PTSD have generally been consistent with functional findings (see [79,80] for recent reviews of this literature). Relatively few studies have examined amygdala volumes in PTSD. Although two have found trends for smaller amygdala volumes in PTSD [81,82], others have not [83–88]. Several studies have found decreased ACC volumes in PTSD [89–93]. Kasai and colleagues found decreased gray matter densities in the rACC of combat veterans with PTSD but not in their identical twins, suggesting that this abnormality may be an acquired sign of the disorder [93]. Decreased hippocampal volumes have been found in some [28,69,81–83,87,94–103], but not all, studies [84,86,104–108]. Hippocampal volumes in PTSD have also been found to inversely correlate with measures of symptom severity [69,87,96]. The results of one study suggest that decreased hippocampal volumes may be a familial risk factor for PTSD [87], but further research is needed to clarify this issue.

Although some functional neuroimaging studies have statistically controlled for the volumes of relevant brain structures (e.g., [28,69]), most studies have not used structural information to inform the interpretation of functional findings. Additional research is needed to determine how functional abnormalities may be related to volumetric abnormalities in PTSD.

Receptor imaging findings

Relatively few studies have studied receptor-binding differences associated with PTSD. One study used PET and ^{11}C-carfentanil and reported decreased μ-opioid receptor-binding potential in the amygdala and ACC in PTSD compared with a healthy comparison group [109]. Another PET study found decreased [^{11}C]flumazenil binding in the left amygdala in combat veterans with PTSD compared with those without the disorder [110], although two other studies did not report this effect [111,112]. Decreased benzodiazepine-receptor binding has been found in the mPFC in some [111,113], but not all, studies [112]. Finally, one study used PET and found diminished [^{11}C]flumazenil binding in the hippocampus and the bilateral insular cortex in trauma-exposed individuals with versus without PTSD, suggesting decreased benzodiazepine-$GABA_A$ function in the disorder [110].

Expert commentary

Although some findings have been mixed, functional neuroimaging research has generally supported the hypothesis that the amygdala is hyperresponsive in PTSD, while rostral and ventral portions of the mPFC are hyporesponsive. Emerging evidence suggests that the

dACC and insula may be hyperresponsive in PTSD, although these abnormalities have also been found in other anxiety disorders [4,44]. Hippocampal functional abnormalities have also been reported, although the direction of the abnormality tends to vary, perhaps depending on the methods used. Functional abnormalities in the hippocampus may be related to volumetric abnormalities, although at least two studies suggest that group differences in hippocampal function remain significant after controlling for hippocampal volumes [28,69]. The direction of the findings reviewed above may also be affected by whether a study used a trauma-exposed or unexposed control group. Studies in which trauma-unexposed control groups are used cannot determine with certainty whether abnormalities are attributable to PTSD or trauma exposure.

A few limitations of this type of research should be noted. Although the technology is continually advancing, functional neuroimaging techniques have limited spatial resolution, making differentiating between very small bordering structures difficult. The temporal resolution of functional neuroimaging ranges from several seconds (fMRI–BOLD) to several minutes (PET–rCMRglu); none of the methods discussed in this article can assess brain responses on the order of milliseconds after stimulus presentation. The high comorbidity rate between PTSD and other disorders (e.g., depression) is another issue. While it may seem methodologically rigorous to exclude individuals with comorbid disorders, this practice would limit the generalizability of findings to the greater population of individuals with anxiety disorders. In the future, psychiatric control groups should be used when possible in order to address this issue. Finally, it is important to note that at the current time, functional neuroimaging cannot be utilized for diagnosing individual patients. PTSD and non-PTSD groups tend to overlap on dependent measures of brain activation, and functional neuroimaging does not currently have the specificity and sensitivity needed to be a reliable diagnostic tool for this disorder. Although this is important to acknowledge, most imaging studies of PTSD have been conducted in order to better understand the underlying neurocircuitry of this disorder rather than to develop a diagnostic tool. Further advances in technology and data analysis will be necessary to address these limitations.

Five-year view

Although functional neuroimaging studies of PTSD have produced vast amounts of information about the disorder over the last two decades, many aspects of its neurocircuitry remain incompletely researched and understood. One important direction for future research would be to use biomarkers to predict treatment response in PTSD. Research indicates that different PTSD symptom profiles may have different neural signatures. For example, individuals with dissociative symptoms exhibit increased mPFC during traumatic imagery [114] and viewing of overtly presented fearful faces [115]. An eventual goal of this research would be to use neurocircuitry profiles to determine what form of treatment would be most appropriate for individual patients. Another important future direction would be to determine the origin of functional abnormalities – that is, do they represent familial risk factors for developing PTSD or are they acquired signs that occur after its appearance? If amygdala hyper-responsivity, for example, is found to be a familial trait that increases an individual's risk for developing PTSD, then it could potentially be used to screen individuals who are likely to experience trauma, such as military and police officer recruits. However, if amygdala hyper-responsivity is found to be an acquired characteristic of PTSD, it could become the target of treatments and a potential biologic marker of symptomatic improvement. It should be noted that the field is, in general, searching for biological markers in anxiety and mood disorders, and the amygdala and mPFC have simply been logical places to start. In addition, even if such biological markers for PTSD are found, they may not be as effective as other clinical data that are more easily and cost-effectively obtained. Continued research is needed to better understand the roles of the brain regions involved in the

neurocircuitry of PTSD and to clarify the origin and potential clinical implications of their functional abnormalities.

Key issues

- Post-traumatic stress disorder (PTSD) is an anxiety disorder that can affect individuals exposed to traumatic events. Patients with this disorder persistently re-experience their traumatic events, avoid reminders of the traumatic event and experience hyperarousal symptoms.
- Many studies support the hypothesis that the amygdala is hyperresponsive in PTSD while rostral and ventral portions of the medial prefrontal cortex are hyporesponsive.
- The dorsal anterior cingulate cortex and insula appear to be hyperresponsive in PTSD, as well as in other anxiety disorders.
- The hippocampus also appears to function abnormally in PTSD, although the direction of the abnormality tends to vary depending on the methods used.
- One line of future research should attempt to use these biomarkers to predict treatment response in PTSD.
- A second line of future research should determine whether these functional abnormalities are familial risk factors or acquired characteristics of PTSD.

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