

Amygdala, Medial Prefrontal Cortex, and Hippocampal Function in PTSD

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ABSTRACT: The last decade of neuroimaging research has yielded important information concerning the structure, neurochemistry, and function of the amygdala, medial prefrontal cortex, and hippocampus in posttraumatic stress disorder (PTSD). Neuroimaging research reviewed in this article reveals heightened amygdala responsivity in PTSD during symptomatic states and during the processing of trauma-unrelated affective information. Importantly, amygdala responsivity is positively associated with symptom severity in PTSD. In contrast, medial prefrontal cortex appears to be volumetrically smaller and is hyporesponsive during symptomatic states and the performance of emotional cognitive tasks in PTSD. Medial prefrontal cortex responsivity is inversely associated with PTSD symptom severity. Lastly, the reviewed research suggests diminished volumes, neuronal integrity, and functional integrity of the hippocampus in PTSD. Remaining research questions and related future directions are presented.

KEYWORDS: anterior cingulate; posttraumatic stress disorder; fMRI; PET; neuroimaging

INTRODUCTION

Over the past decade, neuroimaging techniques have been critical to the process of identifying key brain systems in the pathophysiology of posttraumatic stress disorder (PTSD). In the current article, we will describe three brain regions of interest in PTSD and review a functional neurocircuitry model of PTSD. Next, we will review findings from studies using magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), functional MRI (fMRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) that bear on the structure, neurochemistry,

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and function of the three brain regions. Finally, we will offer a few suggestions for future research in this area.

BRAIN REGIONS OF INTEREST IN PTSD

Research in basic science and functional neuroimaging has helped to identify three brain regions that may be involved in the pathophysiology of PTSD: the amygdala, medial prefrontal cortex, and hippocampus. The amygdala is involved in the assessment of threat-related stimuli and/or biologically relevant ambiguity¹⁻³ and is necessary for the process of fear conditioning.^{1,4} Given that individuals with PTSD are hypervigilant concerning potential threat in the environment and that they show relatively heightened acquisition of conditioned fear in the laboratory,^{5,6} many researchers have hypothesized that the amygdala is hyperresponsive in this disorder. Indeed, as will be reviewed in the following text, functional neuroimaging studies have provided evidence for amygdala hyperresponsivity in PTSD.

A second region of interest is the medial prefrontal cortex, which includes the anterior cingulate cortex, subcallosal cortex, and medial frontal gyrus. Medial prefrontal cortex is well connected to the amygdala in primates,⁷⁻¹⁰ and is involved in the process of extinction of fear conditioning and the retention of extinction.¹¹⁻¹³ Extinction does not occur normally when medial prefrontal cortex is damaged.^{12,13} Individuals with PTSD exhibit persistent inappropriate fear responses in daily life and diminished extinction of conditioned fear responses in the laboratory,^{5,14} leading to the hypothesis that medial prefrontal cortex may be impaired in this disorder. As we will show in this article, neuroimaging studies have reported reduced cortical volumes and neuronal integrity, as well as decreased function in medial prefrontal structures in this disorder.

A third region of interest is the hippocampus, which is involved in explicit memory processes and in the encoding of context during fear conditioning.¹⁵⁻¹⁷ Importantly, the hippocampus appears to interact with the amygdala during the encoding of emotional memories,^{18,19} a process that is highly relevant to the study of trauma and PTSD. In animals, hippocampal cell damage and memory impairment can result from extreme stressors and high levels of stress-related hormones.²⁰⁻²² As we will show, PTSD has been associated with memory impairment as well as reduced hippocampal volumes and abnormal hippocampal function.

One neurocircuitry model of PTSD posits that the amygdala is hyperresponsive, medial prefrontal cortex is hypo-responsive, and medial prefrontal cortex and the hippocampus fail to inhibit the amygdala. Other related models have been described elsewhere.²³⁻²⁵ In the following text, we will review the results of structural, neurochemical, and functional neuroimaging studies of the amygdala, medial prefrontal cortex, and hippocampus in PTSD.

Amygdala

There is currently no clear evidence for abnormal amygdala volumes in PTSD. One study reported smaller amygdala volumes in a cohort of breast cancer survivors with intrusive recollections compared to survivors without intrusive recollections, but none of the participants met diagnostic criteria for PTSD.²⁶

Amygdala hyperresponsivity in PTSD has been reported during the presentation of personalized traumatic narratives^{27,28} and cues,²⁹ combat sounds,^{30,31} combat photographs,^{32,33} and trauma-related words.³⁴ Importantly, a recent PET study has shown amygdala hyperresponsivity during acquisition of fear conditioning in abuse survivors with PTSD.³⁵ In PTSD, the amygdala also appears to show exaggerated responses to trauma-unrelated affective material, such as fearful facial expressions,^{36–38} as well as during neutral auditory oddball and continuous performance tasks.^{39,40} Whether amygdala activation declines over repeated presentations of affective stimuli in PTSD is currently unclear.^{34,37,38} Amygdala activation has been shown to be positively correlated with PTSD symptom severity^{27,28,34,41} and self-reported anxiety.^{31,42} As will be mentioned in a later section, there is some evidence for a correlation between amygdala and medial prefrontal cortex function in PTSD, although the direction of this correlation remains undetermined.^{28,37,38,43}

It is important to note that several functional neuroimaging studies have failed to find any amygdala activation during symptomatic states in PTSD.^{44–48} Failure to replicate this finding may be due to relatively poor spatial and temporal resolution (e.g., in SPECT and PET), type II error associated with small sample sizes, and/or inadequate symptom provocation.

In summary, functional neuroimaging studies of PTSD have provided evidence in support of heightened amygdala responsivity to both traumatic reminders and more general affective stimuli. In addition, five independent studies have reported a positive relationship between PTSD symptom severity and amygdala activation.

Medial Prefrontal Cortex

Several morphometric MRI studies have reported decreased volumes of frontal cortex in PTSD,^{49–51} but only four such studies have examined medial prefrontal cortex specifically. Anterior cingulate volumes appear to be smaller in PTSD compared to trauma-exposed control groups.^{52–54} In addition, one study has reported possible shape differences in the anterior cingulate in PTSD.⁵⁵ Diminished volumes of anterior cingulate cortex do not appear to be attributable to alcohol use or total brain volume.⁵⁴ Two studies have reported that severity of PTSD is inversely correlated with anterior cingulate cortex volume.^{53,54}

Neurochemistry studies have provided data consistent with medial prefrontal cortex abnormalities. One recent MRS study has revealed lower N-acetyl aspartate (NAA)/creatine ratios in pregenual anterior cingulate cortex in maltreated children and adolescents with PTSD,⁵⁶ suggesting the possibility of decreased neuronal integrity in that region. According to one case report, NAA/creatine ratios in a maltreated boy with PTSD increased following successful treatment with clonidine.⁵⁷ However, another MRS study failed to replicate altered NAA/creatine ratios in PTSD, but instead found higher choline/creatine and myoinositol/creatine levels in the anterior cingulate cortex in PTSD, which may be suggestive of glial cell proliferation rather than neuronal loss.⁵⁸ One study using SPECT and [¹²³I] iomazenil reported lower benzodiazepine receptor binding in anterior medial prefrontal cortex in combat veterans with PTSD,⁵⁹ although a subsequent study failed to replicate this finding.⁶⁰

Functional neuroimaging studies have also yielded findings consistent with decreased activation and/or a failure to activate medial prefrontal cortex, including anterior cingulate cortex and medial frontal gyrus, in PTSD. This finding has been reported during the presentation of traumatic narratives,^{28,44,45,48,61,62} negative trauma-unrelated narratives,⁶³ combat pictures and/or sounds,^{47,64} fearful facial expressions,^{37,38} and during the performance of emotional Stroop interference tasks,^{65,66} an auditory continuous performance task,⁴⁰ and an emotional word retrieval task.⁶⁷ Extinction after fear conditioning has been associated with diminished activation in anterior cingulate cortex in PTSD.³⁵ Four studies have reported that medial prefrontal cortex activation is inversely related to PTSD symptom severity,^{28,37,38,61} such that smaller medial prefrontal cortex activation is associated with greater symptom severity. Two treatment studies have reported a relationship between symptomatic response to serotonin reuptake inhibitors and increased activation of medial prefrontal cortical regions.^{68,69}

Although a majority of studies have reported relatively diminished activation of medial prefrontal cortical regions in PTSD, a few studies have yielded discrepant results, such as both increased and decreased activation in this region^{39,70} or increased activation.^{27,71,72} Possible explanations for such discrepancies may lie in the imaging techniques used or in the dissociative state of the participants. With regard to the latter, patients with PTSD who dissociated during traumatic narratives had greater activation in medial prefrontal cortex than control subjects,⁷³ whereas patients who did not dissociate had relatively less activation in this region than control subjects.⁴⁴ Thus, future studies ought to take into account the dissociative state of the participant.

In summary, there is evidence for structural, neurochemical, and functional abnormalities in medial prefrontal cortex, including anterior cingulate and medial frontal gyrus, in PTSD. The most prevalent functional neuroimaging finding is that of a relatively diminished responsivity in medial prefrontal cortex. Four studies have reported an inverse correlation between activation in this region and PTSD symptom severity. Additional research is needed to

determine the relationship between the structural and functional findings in medial prefrontal cortex in this disorder.

Amygdala/Medial Prefrontal Cortex Interactions

Given that current functional neurocircuitry models of PTSD posit relationships between brain systems, recent functional neuroimaging studies have used correlational and other more complex multivariate analyses to test these models.^{74–76} Four published studies have examined the relationship between the amygdala and medial prefrontal cortex in PTSD. A recent PET study²⁸ involving traumatic script-driven imagery in veterans with chronic PTSD found that regional cerebral blood flow (rCBF) changes in medial frontal gyrus were significantly inversely related to rCBF changes in bilateral amygdala. Specifically, as rCBF changes in medial frontal gyrus decreased, rCBF changes in amygdala increased. Similar results were reported in an fMRI study involving the presentation of fearful and happy facial expressions in combat veterans and firefighters with chronic PTSD.³⁷ These findings suggest a reciprocal relationship between medial prefrontal cortex and amygdala function in PTSD, although the direction of causality remains undetermined. In contrast, a recent fMRI study that used fearful versus neutral facial expressions to study patients with more acute PTSD reported a positive correlation between amygdala and anterior cingulate responses. Finally, a PET study⁴³ of traumatic imagery implementing partial least squares and structural equation modeling found a positive relationship between the amygdala and anterior cingulate and posterior subcallosal cortex. Thus, although all four studies report a significant relationship between amygdala and medial prefrontal cortex, the direction of this relationship differs across studies. One possible account for this difference may lie in the chronicity of the participants' PTSD; duration of PTSD (or time since trauma) appears to be longer in the studies reporting an inverse relationship between amygdala and medial prefrontal cortex compared to those studies reporting a positive relationship. Future research will benefit from a direct and more thorough examination of the relationship between amygdala and medial prefrontal cortex in acute versus chronic PTSD.

Hippocampus

A majority of neuroimaging studies of the hippocampus in PTSD have assessed hippocampal structure and neurochemistry. The predominant finding is of decreased hippocampal volumes in PTSD, compared to either trauma-exposed control subjects^{77–79} or trauma-unexposed healthy subjects.^{77,80–85} In addition, MRS studies of PTSD have reported decreased NAA in the hippocampus, suggesting decreased neuronal integrity.^{86–90} Furthermore, hippocampal

volumes have been inversely associated with verbal memory deficits,⁸⁰ combat exposure severity,⁷⁸ dissociative symptom severity,^{77,82} depression severity,⁸³ and PTSD symptom severity.^{77,79,83} A study of hippocampal volumes in monozygotic twins, discordant for trauma exposure, reported that trauma-unexposed co-twins of veterans with PTSD had smaller hippocampal volumes compared to unexposed co-twins of veterans without PTSD.⁷⁹ In addition, PTSD symptom severity in the exposed twin was inversely correlated with hippocampal volume in both the exposed and unexposed identical co-twin. These findings are consistent with the hypothesis that smaller hippocampal volume is a preexisting risk factor for the development of pathological stress responses. Other recent data suggest that hippocampal volumes may increase with successful treatment with paroxetine in PTSD.⁹¹

Several studies, however, have not replicated the finding of smaller hippocampal volumes in PTSD.^{49-51,92-94} Prospective longitudinal studies with up to a 2-year follow-up period have found no significant decline in hippocampal volumes over time in PTSD.^{95,96} These mixed results have suggested that smaller hippocampal volumes may occur in only some subgroups (e.g., adults with chronic PTSD, but see also Ref. 84), or that they may be secondary to comorbid conditions (e.g., depression or alcohol dependence), or that hippocampal pathology may be relatively subtle and not readily detectable by morphometric MRI procedures. Indeed, one recent study reported decreased hippocampal region NAA in the absence of volumetric changes in veterans with PTSD.⁸⁹

A few neuroimaging studies in the literature have examined hippocampal function in PTSD. Early studies reported lower activity in this region during symptomatic states^{45,48} and after the administration of yohimbine.⁴⁶ Cognitive activation studies of PTSD have reported a failure to activate the hippocampus during the encoding of neutral verbal passages⁷⁷ and during the recollection of emotional words⁶⁷ and neutral words.⁹⁷ However, the latter study also found that diminished hippocampal activation in PTSD was due to greater hippocampal blood flow in the baseline condition, as well as across conditions.⁹⁷ In addition, blood flow in the hippocampus and parahippocampal gyrus was significantly positively correlated with symptom severity. This finding appears to be consistent with reports of higher activity in the hippocampal region at rest and during an auditory continuous performance task,^{40,71} as well as the positive correlation between flashback intensity and rCBF in the left perihippocampal region in patients with chronic PTSD.⁹⁸

In summary, the majority of studies has found decreased hippocampal volume or decreased hippocampal NAA levels in PTSD. Functional neuroimaging studies are more mixed, with reports of both a failure to activate the hippocampus during cognitive tasks and increased hippocampal activation at rest or across tasks. Across studies, greater PTSD symptom severity has been associated with smaller hippocampal volumes and elevated hippocampal/parahippocampal blood flow. Correlations between hippocampal volumes

and hippocampal blood flow have been assessed, but were not found to be significant.^{77,97} Additional studies with larger sample sizes will be needed to adequately explore the relationship between hippocampal structure and function in PTSD.

CONCLUSIONS

The neuroimaging research reviewed above provides evidence for heightened responsivity of the amygdala, diminished responsivity of the medial prefrontal cortex, as well as a functional relationship between these two regions. In addition, there is evidence for diminished hippocampal volumes and neuronal integrity, as well as impaired hippocampal function in PTSD.

Although the last decade of research has yielded much important information, many issues concerning brain function in PTSD remain unaddressed. For example, whether brain structure, chemistry, and function are similar at early versus late stages of the disorder is currently unknown; future research ought to examine and directly compare cohorts of acute and chronic PTSD. In addition, whether brain abnormalities identified thus far are preexisting risk factors for the development of PTSD after trauma or whether they are a marker of the disorder itself is unclear, and prospective longitudinal research designs or twin studies are needed to address this issue. It will also be important to further explore the relationship between volumetric changes and functional changes in the hippocampus and medial prefrontal cortex. Furthermore, we currently know very little about the specificity of brain abnormalities to PTSD versus comorbid disorders or other anxiety disorders, and future studies will need to compare subgroups of PTSD with and without comorbid disorders and/or use psychiatric control groups. Whether brain abnormalities described in the literature resolve with effective treatment also needs further exploration. Additional studies should examine brain structure and function in patients before and after treatment with medications or cognitive behavioral therapy. Finally, the functional relationship between brain structures in PTSD requires further study, and additional research should use new cognitive paradigms that simultaneously probe the regions of interest, as well as correlational or multivariate data-analytic techniques.

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