

Neurobiology of PTSD: A Review of Neuroimaging Findings

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Neuroimaging serves as an effective way to investigate the neurocircuitry involved in the development of posttraumatic stress disorder (PTSD).¹⁻³ A number of models describing functional neuroanatomy of PTSD symptom development emerged over the past decade, inspired by both basic animal research and an increasing number of human neuroimaging studies. These models have traditionally conceptualized PTSD as a state of heightened responsivity to threat-

ening stimuli and later as a state of insufficient inhibitory control over-exaggerated threat-sensitivity. They emphasize the centrality of threat-related processing in the pathophysiology of PTSD and therefore account for the “hypersensitivity to threat,” which is highly characteristic of PTSD (such as hypervigilance and hyperarousal). Neuroimaging findings in PTSD lend credence to incorporating “hypersensitivity to threat” within the conceptualization of PTSD, and these findings will be discussed within this review.

It is becoming increasingly apparent, however, that the “hypersensitivity to threat” models do not fully capture the full complexity of PTSD, nor the complexity of changes associated with, trauma exposure and PTSD development. For instance, important phenomena associated with PTSD, such avoidance and numbing, generalization of fear, vulnerability, and resilience factors, all need to be further understood in terms of underlying psychological mechanisms and their neurobiological substrates. The dysfunction of neuronal regions in

PTSD, and the implication this has for the disruption of cognitive and psychological processes, will also be discussed.

This review summarizes the neuroimaging findings pertaining to PTSD and PTSD vulnerability and will focus on a few key regions known to be particularly implicated in PTSD pathophysiology, specifically amygdala, nucleus accumbens (ACC), medial prefrontal cortex (mPFC), and hippocampus. It will first start by reviewing key structural alterations associated with PTSD, and then progress to discussing functional abnormalities, with a particular emphasis on symptom provocation studies, cognitive activation studies, and functional connectivity analyses. Finally, neurochemical differences, as revealed via receptor imaging, will be addressed followed by a discussion of potential future directions for PTSD research.

Different neuroimaging modalities, such as single-photon emission tomography (SPECT), positron emission tomography (PET), magnetic resonance spectroscopy (MRS), magnetic resonance

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imaging (MRI), and functional MRI (fMRI) have all been used in conjunction with PTSD research. This article will incorporate many of these modalities, with a particular emphasis on MRI in the structural section, and fMRI when dealing with functional studies.

STRUCTURAL ABNORMALITIES ASSOCIATED WITH PTSD

Structural neuroimaging studies have originally focused on hippocampal volume in PTSD patients, although emerging evidence suggests structural alterations are also present in other regions. The following section will outline key structural alterations associated with PTSD and PTSD vulnerability focusing on the hippocampus, ACC, and amygdala.

Hippocampus

The hippocampus is a known target for stress hormones,⁴ and abnormalities in hippocampal volumes had been reported in conditions associated with HPA abnormalities like depression and Cushing's

disease.^{5,6} Although PTSD has not been associated with hypercortisolemia, studies of structural brain abnormalities in PTSD have originally focused on the hippocampus, which is also known to be involved in explicit/declarative memory, working memory, episodic/autobiographical memory and contextual learning/memory.^{7,8} Individuals with PTSD perform poorly on neuropsychological memory tasks^{9,10} and are impoverished in their autobiographical memories for positive events.¹¹ A number of structural MRI studies reported decreased hippocampal volumes in individuals with PTSD.^{9,12-15} MRS studies have reported decreased N-acetylaspartate (NAA) levels in the hippocampus, interpreted as reflecting decreased neuronal integrity.^{16,17} Reductions in hippocampal volumes have ranged from 5% to 26%, and have tended to be found bilaterally across studies.¹⁸ It should be noted, however, that a number of studies have not replicated the finding of decreased hippocampal volumes in PTSD.¹⁹⁻²¹ These discrepancies suggest that smaller hippocampi may be restricted to subgroups

of PTSD, may be secondary to comorbid conditions, or that hippocampal pathology may be subtle and not always detectable using standard morphometric MRI procedures.¹⁸ Furthermore, it has not been clear whether reported hippocampal changes are acquired signs of PTSD, or potential predisposing factors. Finally results of a recent meta-analysis further support the presence of smaller hippocampal volumes in PTSD patients relative to controls with and without trauma exposure.²²

A twin study of Vietnam veterans has helped to clarify the question of whether the hippocampal findings reflect predisposing factors or acquired signs of PTSD. Gilbertson et al studied monozygotic twins discordant for trauma exposure, with and without PTSD, and found that both twins with PTSD and their trauma unexposed twin had smaller hippocampi relative to trauma exposed non-PTSD twins and their co-twin.²³ Moreover, the same group, both PTSD and trauma non-exposed co-twin, showed impaired hippocampus-mediated spatial processing, using a cue configuration task.²⁴ These findings offer compelling evidence for reduced hippocampal size serving as a preexisting and potentially vulnerability or predisposing factor for PTSD.

Anterior Cingulate Cortex

Increasing attention is being devoted to the anterior cingulate cortex (ACC) and the potential role it may play in PTSD.² Significantly, the ACC shares close neuro-anatomical relationships with subcortical components of the "central fear system."²⁵ There is emerging evidence of structural impairment of the ACC associated with PTSD. Manual tracing of the ACC has demonstrated it to be smaller in patients with PTSD, relative to control participants.²⁵ Voxel-based morphometry studies have shown reduced grey matter density in the ACC,²⁶ and a recent meta-analysis of these studies confirmed the presence of significantly smaller anterior cingulate cortex volume in PTSD patients relative

to trauma-exposed controls.²² Kasai et al performed a VBM analysis in the twin cohort in search of structural abnormalities. They found a significant PTSD diagnosis by exposure interaction in the pregenual ACC, such that combat-exposed PTSD twins were found to have lower gray matter density than their combat-unexposed co-twins and lower than the combat-exposed twins without PTSD and their co-twins.²⁷ This supports the inference that pregenual ACC gray matter reduction is likely an acquired sign of PTSD as opposed to a pre-morbid vulnerability factor. In accordance with these structural findings, there is also evidence to suggest that ACC function in PTSD is impaired, and this will be addressed in the following section.

Amygdala

There is equivocal evidence to suggest reduced bilateral amygdala volume is associated with PTSD, as studies differ markedly in results obtained.^{19,28} A meta-analysis, including data from both adults and children with PTSD from different types of trauma, demonstrated some evidence of smaller left amygdala in PTSD subjects compared with healthy controls,²² at the same time highlighting the controversial findings present in the literature. There are a few studies investigating amygdala volume in children with maltreatment-related PTSD, which tend to mirror the inconclusive findings obtained in adults. In one study, no global volume differences between PTSD and control groups were obtained.²¹ In contrast, Carrion et al found a 5.1% reduction in the volume of the amygdala in children with maltreatment-related PTSD compared with healthy controls, although this result became non-significant when scores were adjusted for total brain gray matter.²⁰ A recent meta-analysis investigating amygdala volumes in individuals with childhood maltreatment-related PTSD in both child and adult populations did not find PTSD-related reductions in amygdala volume.²⁹

Insula

The insula is highly interconnected with cortical and limbic regions implicated in PTSD³⁰ and is involved in key processes (eg, emotional processing)³¹ that are linked to PTSD pathophysiology; however, to date, only limited evidence suggests the presence of structural abnormalities in the insula in PTSD. One recent study used voxel-based morphometry (VBM) to explore structural differences in gray or white matter volume between subjects with and without PTSD.³² The PTSD group had lower gray matter density in insula bilaterally as compared with controls. Differences were also obtained in the left hippocampus and left ACC. These results are in accordance with an earlier whole-brain VBM study that showed PTSD subjects had lower gray matter density in the left insula relative to healthy controls.²⁶

FUNCTIONAL STUDIES

Functional neuroimaging studies have the potential to identify regions involved in the pathophysiology of PTSD, due to the altered function of these regions, like mPFC, ACC, and amygdala. It is important to note that functional imaging experiments in individuals with PTSD fall within two categories: those which utilize symptom provocation, and those which rely on cognitive activation probes. Studies utilizing symptom provocation to investigate PTSD do so by employing autobiographical stimuli, which are trauma-related (eg, narrative scripts of personal trauma), or alternatively are more general in nature, employing generally evocative but not necessarily autobiographically relevant pictures and sounds. Such studies were the first to emerge, were the first to provide relatively stable and replicable findings, and are still the most common studies in the PTSD functional neuroimaging literature. In contrast, cognitive activation studies assess specific impairments in neuronal processing associated with PTSD via a neurocognitive task (a “probe”) that is expected to selectively activate neural circuits implicat-

ed in task-related processing. Selectively activating a circuit without eliciting symptoms has a substantial advantage in that this elicits a large number of more general or nonspecific trauma-related responses. Investigators have used cognitive activation strategies to further examine a number of regions implicated in PTSD by symptom provocation studies, such as the mPFC, amygdala, ACC, and hippocampus.

ACC and mPFC

The ACC is a region that has been activated by many functional neuroimaging studies and has been implicated in different processes involving cognitive-emotion interactions. A variety of evidence supports the existence of functional subdivisions in the ACC, with dorsal ACC supporting cognitive control and error-related processing, while rACC is involved in the assessment of salience of emotional information and the regulation of emotional responses.³³ Reduced activation of the ACC in PTSD patients, relative to both control participants with and without trauma exposure, has been repeatedly shown in a variety of symptom provocation studies. Rauch and colleagues used combat-related, emotionally negative, and neutral pictures paired with verbal descriptions (imagery) in combat veterans with and without PTSD. Combat veterans with PTSD had increased rCBF in ventral anterior cingulate cortex (ACC) and right amygdala when generating mental images of combat-related pictures, but had decreased rCBF in the ACC in the combat image viewing versus neutral image viewing contrast.³⁴ Another study using combat-related pictures and sounds and PET in 10 combat veterans with and 10 without PTSD revealed decreased blood flow in mPFC (area 25) and other areas in response to traumatic pictures and sounds in PTSD patients. However, non-PTSD control subjects activated the anterior cingulate (area 24) to a greater degree than PTSD patients.³⁵ The same group also studied childhood sexual abuse (CSA) subjects (22 women, 10 of whom had PTSD) with

exposure to traumatic and neutral scripts and PET. The PTSD group showed rCBF increases in posterior cingulate (area 31) and superior and middle frontal gyri bilaterally (Brodmann areas 9 and 10). The PTSD group also showed deactivation in the subcallosal anterior cingulate (area 25) and decreased activation in an adjacent portion of anterior cingulate (area 32).³⁵ Using PET and script-driven imagery in 16 subjects with CSA (8 with PTSD), Shin and colleagues also reported deactivation of the medial prefrontal and as well as left inferior frontal (Broca's) areas in the PTSD group.³⁶ We recently reported the results of a [15O] H₂O PET, script-driven imagery study of emotionally evocative and neutral autobiographic events in 16 combat veterans with PTSD (PTSD patients [PP], 15 combat veterans without PTSD (combat controls [CC]), and 14 healthy, age-matched, control subjects (noncombat controls [NC]) that allow to isolate changes that are trauma related (PP versus NC, and CC versus NC) and PTSD specific (PTSD versus CC). Although all subjects deactivated the mPFC and activated the insula for traumatic scripts, the PP deactivated the rostral anterior cingulate cortex (rACC) more than both control groups (CC and NC), but did not demonstrate ventromedial PFC (vmPFC) deactivation observed in controls. The findings observed only in the PTSD group (deactivation of the rACC, and higher vMPFC activity) may reflect neural substrates specific to PTSD.³⁷

Lanius and colleagues reported two fMRI studies where they used a script-driven symptom provocation paradigm. They also observed significantly decreased blood-oxygen-level dependent (BOLD) signal in the ventral ACC (Brodmann area 32) and the thalamus in the PTSD group to both the traumatic and nontraumatic emotional states conditions, suggesting that the earlier neuroimaging findings related to these areas in PTSD may not be specific to traumatic stimuli.^{38,39}

There is also empirical evidence to suggest that reduced activation of the ACC may also be characteristic of pediatric PTSD. To date, the majority of studies have been performed in adult PTSD populations; only limited studies have been performed in children and/or adolescents with PTSD to investigate the neural correlates induced by symptom provocation. One small study examined brain responses during visual perception and imaginary recollection of traumatic reminders of adolescents (12 to 14 years) who developed PTSD versus those who did not after experiencing an earthquake.⁴⁰ Sample size was limited (five with PTSD versus six trauma-exposed PTSD-negative individuals). During earthquake perception relative to neutral perception, the control group showed activation of the ACC, but the PTSD group did not. Additional analyses demonstrated that intergroup differences were significant, providing preliminary evidence that neurobiological alternation of the ACC in adolescence with PTSD are similar to those occurring in adult PTSD populations.⁴⁰

Cognitive activation studies have also repeatedly demonstrated ACC to be implicated in the neurocircuitry associated with PTSD. Bremner et al used the modified Stroop task (color Stroop, emotional Stroop, and control task) and [15O] H₂O PET to probe ACC function in 12 women with early CSA-related PTSD and nine CSA women without PTSD. The PTSD group demonstrated a relative decrease in ACC blood flow during the emotional but not the color Stroop task, which elicited increased rCBF in the ACC (BA 24 and 32) in both groups.⁴¹ Shin et al also investigated ACC functioning in 16 Vietnam combat veterans (eight with PTSD) using fMRI and an emotional counting Stroop paradigm. Subjects were asked to count the number of combat-related, generally negative and neutral words while being scanned. In the comparison of combat related to generally negative words, the non-PTSD group showed significant BOLD signal increases in rACC but the PTSD group did not.⁴² In addition, to assess interference processing and inhibitory control, tasks commonly associated with ACC function, a version of the counting Stroop task incorporating only effectively neutral words, also demonstrated hypoactivation of the ACC in patients with PTSD. This task requires participants to count the number of identical words presented on the screen, and to press a button corresponding to the correct number. In the interference condition, the presented word, a numerical value, is an “incorrect” response. This task was performed in 26 trauma exposed men, 13 of whom met diagnosis for PTSD. The PTSD group exhibited less deactivation in subgenual ACC and more deactivation in the insula as compared with controls during interference minus neutral task.⁴³ Taken together, these data provide compelling evidence that functional impairments of the ACC and mPFC are associated with the neurocircuitry implicated in PTSD, and this holds for both symptom provocation and cognitive activations studies.

Amygdala

Another region implicated in the pathophysiology of PTSD is the amygdala. The amygdala is integral to the generation and maintenance of emotional responses, and this has been shown in both animal and human studies.⁴⁴⁻⁴⁶ In one of the first functional imaging symptom provocation studies, Rauch and colleagues⁴⁷ used individualized trauma scripts and [15O] H₂O PET in a small and heterogeneous group of eight PTSD subjects. They demonstrated increased regional cerebral blood flow (rCBF) in anterior paralimbic (right posterior medialorbito frontal cortex [OFC], insular, anterior temporal polar, and medial temporal cortex) and limbic structures (amygdala) in the provoked versus control contrast group. In an ensuing study, our group exposed three groups of subjects (14 combat PTSD subjects, 11 combat-exposed subjects without PTSD, and 11 combat unexposed healthy subjects) to combat sounds or white noise in two counterbalanced sessions and studied rCBF with 99mTc hexamethylpropyleneamine-oxime (HMPAO) SPECT. Only the PTSD group showed increased rCBF in the left amygdaloid region.⁴⁸

Cognitive activation studies have also demonstrated the hyperresponsivity of the amygdala in PTSD. The amygdala is a region implicated in rapidly assessing the salience of emotional and especially threat-related stimuli.⁴⁹ A number of studies have presented fearful faces to individuals with PTSD using various exposure durations, and these have converged upon increased amygdala responsivity in PTSD (especially when stimulus presentation is rapid).⁵⁰⁻⁵² Rauch et al compared amygdala responses in nine PTSD subjects versus eight combat-exposed, non-PTSD subjects using a previously validated masked emotional faces paradigm. Contrasting fearful versus happy masked faces revealed exaggerated amygdala responses in the PTSD subjects. Furthermore, the magnitude of these responses distinguished PTSD subjects with 75% sensitivity and 100% specificity.⁵²

These findings suggest that PTSD is associated with increased amygdala responsivity to threat-related (but not necessarily trauma-related) stimuli. Another group used a similar masked emotional faces paradigm to examine 13 subjects with acute, rather than chronic PTSD.⁵⁰ There was a positive correlation between the severity of PTSD and the difference in amygdala responses between masked fearful and happy faces. These findings suggest that functional abnormalities in brain responses to emotional stimuli observed in chronic PTSD might be apparent already in the acute phase. In a recent study, Bryant et al exposed 15 patients with PTSD and 15 age and sex-matched non-traumatized controls to fearful stimuli (16.7 ms) followed by a 163.3 ms neutral mask. They found significantly greater left amygdala activity in the PTSD relative to the control group.⁵³

Regarding overt presentation of fearful faces, heightened amygdala activity does not appear to be particularly robust during this type of processing of fear stimuli, although differences have been obtained in some studies.⁵¹ In one study, Shin et al used overtly presented emotional facial expressions and fMRI to compare BOLD responses in 13 men with PTSD and 13 trauma-exposed men without PTSD. The PTSD group showed increased amygdala responses and decreased mPFC responses to overt fearful (versus happy) facial expressions.⁵⁴ The amygdala is known to be involved with the rapid assessment of threat, and so it appears amygdala-related hyperactivation associated with PTSD is more sensitive to subliminal exposure durations in the region of 12-30 ms. Overt, longer duration exposure might lead to signal that integrates repeated stimulation and the habituation processes, and thus it might be less sensitive in picking up changes involving a specific process.

Insula

The insula is a large cortical structure composed of anatomical subdivisions that have distinct major afferent and efferent projec-

tions; the anterior insula connects reciprocally with the amygdala, while the posterior insula connects reciprocally with the secondary primary sensory cortex and receives input from ventral posterior thalamic nuclei. The insula likely cannot be viewed as a single entity, as the anatomical subdivisions are thought to provide the basis for functional sub-regions. Meta-analysis of Wager and Barrett⁵⁵ suggests that the ventral anterior insula is important for core affect and associated consciousness of subjective feelings.⁵⁶ The dorsal anterior insula is thought to be involved in developing and updating motivational states, in autobiographical memory,⁵⁷ cognitive control, elicit affective processing, and pain.⁵⁵ In contrast, the posterior insula, including SII and portions of parietal operculum, are particularly specialized to convey homeostatic information such as pain, temperature, and sensual touch.⁵⁸

Abnormal functioning of the insula has been linked to anxiety, with hyperactivation of the anterior insula demonstrated in highly anxious individuals when anticipating the arrival of aversive stimuli.⁵⁹ Imaging studies specifically within PTSD populations have implicated the insula as one of the key regions involved in PTSD, particularly in regard to the anterior insula. For example, symptom provocation experiments have shown that during script-driven imagery with traumatic scripts (relative to neutral scripts), individuals with PTSD had higher anterior insula activation.⁶⁰ This occurs in the region previously shown to be involved in interoceptive awareness of psychological and emotional states⁶¹ and autobiographical memory.⁵⁷ Interestingly, a study investigating the influence of comorbid depression on the neurocorrelates of traumatic imagery found that individuals with PTSD but without comorbid depression had higher insula activation relative to a PTSD group with comorbid depression.⁶²

Functional Connectivity Analyses

The introduction of functional connectivity studies reflects a growing awareness

that complicated brain processes rely on the orchestrated interactions of distributed brain networks, rather than, or in addition to, activation of individual brain regions. Consequently functional connectivity analysis, which refers to the application of specific statistical methods to functional neuroimaging data sets to identify correlated brain activity across various regions,^{63,64} is a particularly relevant and useful technique. Several recent studies have applied functional connectivity analysis to neuroimaging studies of PTSD. Gilboa et al studied 20 individuals with a history of civilian trauma (10 with PTSD), using symptom provocation (autobiographical trauma-related and neutral scripts) and [15O] H₂O PET. A multivariate analysis technique (partial least squares) was used to identify brain regions whose activity covaried with two reference (“seed”) voxels, one in right PFC (BA 10) and the other in right amygdala. Amygdala activity was found to significantly influence activity in the visual cortex, subcallosal gyrus, and anterior cingulate in the PTSD subjects but not in the trauma-exposed controls.⁶⁵ These findings indicate that blood flow measures reflect influence of the amygdala on medial frontal regions in PTSD, rather than a failure of mPFC inhibition of the amygdala. In addition, correlational analyses did not lend support for the failure of inhibition of the ACC over the amygdala.

Lanius et al used functional connectivity analyses on data gathered during fMRI script-driven symptom provocation experiments in 11 subjects with PTSD from sexual abuse/assault or motor vehicle accident (MVA), and 13 trauma-exposed subjects without PTSD. Connectivity maps for right ACC showed greater correlations in PTSD subjects (versus controls) in the right posterior cingulate cortex (PCC) (BA 29), right caudate, right parietal lobe (BA 7 and 40), and right occipital lobe (BA 19). Subjects without PTSD had greater correlations of ACC with left superior frontal gyrus (BA 9), left anterior ACC (BA 32), left striatum (caudate), left parietal lobe (BA 40 and 43),

and left insula (BA 13).⁶⁶ These findings are intriguing; however, our understanding of functional neural networks both in health and disease is still very limited. As methods for the analysis of functional connectivity continue to develop, and the knowledge base regarding coordinated activation of brain regions grows, these approaches will likely play an increasingly important role in delineating functional relationships between regions implicated in the pathophysiology of PTSD.

Receptor Imaging

Insight into which regions differ in activity as a function of PTSD can be gauged with fMRI, as BOLD signal is likely to reflect changes in neuronal firing or postsynaptic activity. In contrast, differences that may exist in functional neurochemistry between those with and without PTSD can be gauged using *in vivo* receptor imaging. Only a few studies to date have used receptor imaging to investigate neurotransmitter abnormalities associated with PTSD. Previous research in both animals and humans has implicated GABA, the principle inhibitory neurotransmitter within the brain, to be involved in both the pathogenesis and pathophysiology of PTSD.^{67,68} In a recent study, Geuze et al used [11C]flumazenil and PET to assess differences in the benzodiazepine-GABAA receptor complex in veterans with and without PTSD.⁶⁹ Geuze et al found reduced binding potential of [11C]flumazenil in veterans with PTSD relative to control veterans without PTSD, specifically in the hippocampus, thalamus, and throughout the cortex, including the frontal, temporal, parietal, and occipital cortex.⁶⁹ This suggests that these specific regions may be associated with pre-morbid differences in the composition/expression of GABAA-benzodiazepines receptors in PTSD patients, or a disease-induced modulation and/or downregulation of the GABAA receptor complex. Consistent with this study is a previous [123I]iomazenil SPECT study in Vietnam veterans, which also found decreased volume of distribu-

tion of [123I]iomazenil in the prefrontal cortex in Vietnam veterans with PTSD relative to healthy controls.⁷⁰ It should be noted, however, that another study also using [123I]iomazenil and SPECT was unable to find any differences in volume distribution of [123I]iomazenil between Gulf War veterans with and without PTSD.⁷¹

In a recent study, our group investigated altered mu-opioid receptor binding in PTSD using PET and the selective mu-opioid radiotracer [11C] carfentanil.⁷² We had previously demonstrated endogenous opioids to be involved in inhibiting and modulating emotional responses in healthy humans,⁷³ and this was the first study to provide direct evidence of alterations in mu-opioid receptor in vivo availability in PTSD. We demonstrated significant differences in the regional mu-opioid receptor BP2 between both the trauma-exposed groups and normal controls, as well as between PTSD patients and trauma exposed individuals who did not develop PTSD. These differences between the groups indicate mu-opioid receptor alterations arising from trauma can be differentiated from those specifically associated with PTSD. Changes were principally located in limbic forebrain and cortical regions known to be involved in emotion regulation, which likely reflect adaptive changes resulting from trauma exposure or stress, as well as maladaptive alterations associated with PTSD pathophysiology.⁷²

Both receptor imaging and fMRI approaches have implicated similar brain regions in the pathophysiology of PTSD (eg, prefrontal cortex, amygdala, and hippocampus), yet reconciling the findings of these two methodologies poses a challenge. The receptor imaging data suggests decreased GABA binding potential in prefrontal regions in PTSD, suggesting potentially lower inhibitory tone, and therefore, enhanced reactivity. In contrast, the fMRI data indicates hypoactivation of cortical regions (specifically mPFC) associated with PTSD. Alternatively, if the decreased GABA binding potential reflects a decreased number of GABA receptors on the inhibitory interneurons, this could

explain overall higher inhibitory tone in the mPFC. Furthermore, although BOLD activity likely reflects overall neuronal activity within a particular region, changes both in inhibitory and excitatory neurotransmission can contribute to the overall BOLD output. Thus, the changes in one particular neurotransmitter system should not be interpreted as defining the overall changes in BOLD signal. Moreover, given the complex interconnectivity of the PFC, its heterogeneity, and its broad functionality, it is possible that PTSD is associated with both increased and decreased activity within distinct regions of the PFC. To date, receptor imaging in PTSD has focused on inhibitory systems (GABA and opioids) and a focus for future research on glutamatergic (excitatory) systems, as well as other neurotransmitters/neuromodulators implicated in PTSD, such as serotonin,⁷⁴ central catecholamines,⁷⁵ and corticotrophin-releasing hormone,⁷⁶ will further help elucidate the molecular basis of altered brain function associated with PTSD.

Treatment Studies and PTSD

There is a growing appreciation that biomarkers that predict treatment response have the potential to significantly advance treatment of PTSD, and that neuroimaging is one of the key methodologies in search of those biomarkers. Moreover, insight into brain changes that occur after treatment can help elucidate the biological mechanisms involved. Consequently, treatment studies in PTSD patients that utilize neuroimaging are a rapidly growing area, although, only very limited evidence has been published so far. In one study, 14 treatment-seeking participants who were survivors of interpersonal violence ($n = 9$) or motor vehicle accidents ($n = 5$) received eight once-weekly sessions of CBT.⁷⁷ Prior to treatment, participants viewed rapidly presented faces (fear and neutral) in a backwards masked paradigm. Increased bilateral amygdala activity during fear processing prior to treatment was associated with poor response to CBT. Prior evidence suggests that adequate management of anxiety during therapy is required for CBT

to be efficacious, despite CBT requiring activation of fear networks.⁷⁸ Larger studies, using a variety of treatment strategies, can help reveal the generalizability and reliability of these findings.

SUMMARY OF NEUROIMAGING STUDIES IN PTSD

The studies reviewed above involve different cohorts (combat and CSA-related PTSD), different paradigms (symptom provocation versus cognitive activation), and different modalities (fMRI, PET, and SPECT) to assess structural, functional, and receptor alterations associated with PTSD. Despite these variations, the findings repeatedly converge on a number of key structures such as the amygdala, ACC, mPFC, insula, and hippocampus. Taken together, the findings lend tentative support to a neurocircuitry model that emphasizes the role of dysregulation in threat-related processing in PTSD. According to this model, trauma exposure sets off a cascade of neural changes that culminates in a state of amygdala hyperresponsivity to trauma reminiscent and other threat-related stimuli that mediates symptoms of hyperarousal and vigilance associated with PTSD. The model also proposes associated inadequate top-down control by the mPFC and ACC that maintains and perpetuates the state of amygdala hyperresponsivity, and also helps mediate the failure to suppress attention to trauma-related stimuli. Consistent with this model, several studies have demonstrated reduced activation of the mPFC (BA 10 and 11) and ACC (BA 32) in PTSD subjects compared with traumatized controls.^{36,38,39,42,79} Other studies have reported increased responsivity of the amygdaloid region,^{45,47,52} although some have not.^{36,39,79} Although conceptualizing of PTSD-related pathophysiology as emphasizing the role of threat-related processing has some empirical support, there is clearly a need for a broader conceptualization of the processes implicated in the disorder. This is because deficits in threat-related processing explain only some aspects of PTSD, and

other significant manifestations of PTSD remain unexplained by this model. These include emotional numbing, generalization of vigilance and avoidance from the initial traumatic event to other less closely related events, sensitization, and finally vulnerability and resilience factors.

To understand these complex phenomena, future neuroimaging research needs to focus on additional relevant mechanisms that may assist in understanding the complex phenomenology of PTSD such as fear conditioning and cognitive-emotion interactions. For example, behavioral and emotional avoidance associated with PTSD may be manifestations of underlying emotion dysregulation. The mPFC is a region known to be involved in emotion regulation,⁸⁰ and evidence suggests that emotion regulation may be disrupted in PTSD. Posttraumatic stress symptoms have been associated with dysfunctional emotional processing strategies, such as impulse-control difficulties, limited access to effective emotion regulation strategies, and lack of emotional clarity.⁸¹

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