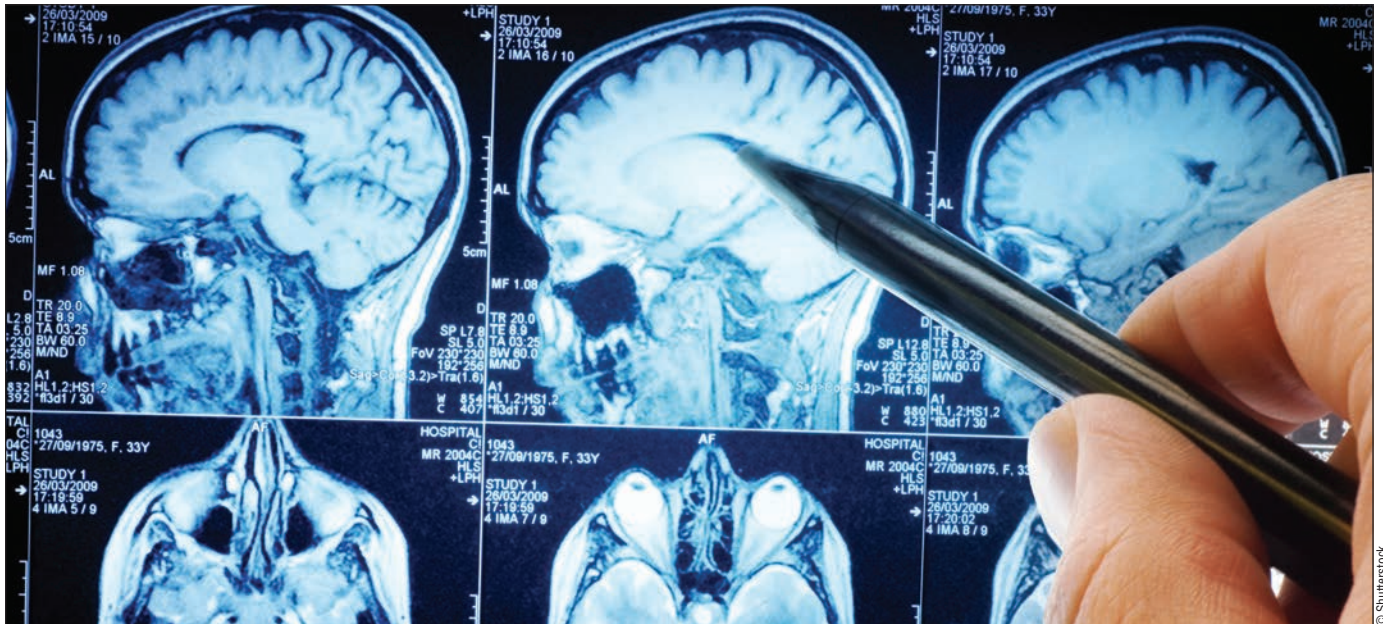


# Brain Imaging Alterations in Posttraumatic Stress Disorder

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## ABSTRACT

Posttraumatic stress disorder (PTSD) is associated with a host of neurobiological changes, including abnormalities in subcortical and cortical structure and func-

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tion. The majority of neuroimaging studies have been motivated by a fear-conditioning perspective to examine neural changes associated with PTSD, with several studies finding alterations in the amygdala, hippocampus, and medial prefrontal cortex. However, not all studies have replicated these findings, suggesting that perhaps more nuanced models of PTSD may be needed to account for the pathophysiology of the disorder. We review neuroimaging findings related to the fear model, encouraging researchers to consider additional factors such as trauma type, age of trauma, and affective neurodynamics. Explicit consideration of these factors may facilitate greater coherence among studies going forward and advance our understanding of the neurobiological alterations associated with PTSD. [*Psychiatr Ann.* 2016;46(9):519-526.]

Posttraumatic stress disorder (PTSD), resulting from a traumatic experience (or set of experiences), is a debilitating disorder with a lifetime prevalence in US adults of approximately 7.8%.<sup>1</sup> PTSD symptoms include avoidance, re-experiencing of the trauma, hyperarousal and hypervigilance, sleep disturbances, and anhedonia. People suffering from PTSD show signs of hypothalamic-pituitary-adrenal (HPA) axis dysregulation, alterations to neural circuits involved in emotional and stress regulation, and heightened fear-potentiated startle responses. This article highlights the current state of neuroimaging research in PTSD, with a particular focus on shortcomings of the “status quo” picture of brain-imaging alterations and how the field

may resolve certain inconsistencies going forward.

### THE NEURAL CIRCUITRY OF PTSD: THREAT CONDITIONING CIRCUITRY

Fear conditioning or more accurately “threat conditioning”<sup>2</sup> and extinction perspectives have dominated neuroimaging research on PTSD over the last 2 decades. This ubiquity is due in large part to extensive research on a rodent model of threat learning with known neural circuitry that can be translated to human neuroimaging studies. Pre-clinical research has demonstrated that acquisition of threat memories depends on the amygdala, which mediates a coordinated threat response via its diverse efferent projections.<sup>3</sup> The recall of threat memories is associated with activation of the rodent prelimbic (PL) cortex, associated with more dorsal areas of the primate ventromedial prefrontal cortex (vmPFC), which enhances expression of threat responding via its excitatory projections to the amygdala.<sup>4,5</sup> Threat extinction takes place when a novel association is formed between the threat trigger and safety, resulting in competition between this new memory and the existing conditioned stimulus (CS)-unconditioned stimulus (US) association. Threat extinction occurs via inhibition of amygdala responses by the rodent infralimbic cortex,<sup>5,6</sup> which is associated with more ventral portions of the vmPFC in primates.<sup>7</sup> The neurocircuitry model of PTSD that has emerged from this work<sup>8</sup> (**Figure 1**) posits that symptoms such as hyperarousal and intrusive re-experiencing result from excessive and persistent activation of the amygdala. This amygdala hyperactivity is thought to result from, or be exacerbated by, heightened excitatory input from dorsal aspects of medial PFC and/or ineffective inhibitory input from the vmPFC. Alterations to the function or

structure of the hippocampus, which is anatomically connected to the amygdala and vmPFC, may also contribute to overgeneralization of fear memories or deficiencies in context-dependent learning or memory related to trauma.<sup>8</sup>

In support of this model, studies using positron emission tomography (PET) and functional magnetic reso-

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### *Studies of brain structure provide a complementary perspective on neurobiological disruptions in PTSD.*

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nance imaging (fMRI) have demonstrated elevated amygdala activity in those with PTSD relative to controls, both during rest<sup>9,10</sup> and during threat conditioning and extinction.<sup>11-13</sup> Despite the canonical view that amygdala hyperactivation is central to PTSD, many studies have found no differences between groups, and in some cases found decreased amygdala activation in PTSD across a variety of tasks, including trauma recall or imagery, presentation of negative emotional images, or emotional Stroop tasks.<sup>14,15</sup> Recent meta-analyses of fMRI and PET task data have found increased amygdala activation in PTSD only when including region-of-interest analyses that have specifically targeted this brain region,<sup>16,17</sup> or have failed to find any group differences when the comparison group was matched for trauma experience.<sup>18</sup> This latter finding is consistent with studies showing that trauma exposure results in altered amygdala function and connectivity with prefrontal regions, regardless of the presence of PTSD symptoms.<sup>19,20</sup>

Evidence for decreased vmPFC activation in PTSD is more con-

sistent across these same meta-analyses.<sup>14,16,17</sup> Notably, reduced vmPFC involvement during recall of threat extinction was correlated with reductions in a peripheral physiologic measure of extinction retention,<sup>12</sup> perhaps the most direct evidence linking vmPFC alterations to threat extinction deficits in PTSD (also see Rouge-mont-Bücking et al.<sup>21</sup>). This same study<sup>12</sup> found the opposite relationship for the dorsal anterior cingulate cortex (dACC)—elevated dACC activation in PTSD for extinguished cues was correlated with poorer extinction retention. As with the amygdala, however, evidence for involvement of the dACC and adjacent dorsomedial prefrontal regions in PTSD is equivocal, with meta-analyses concluding that these regions can be both hyperactive<sup>16,22</sup> and hypoactive.<sup>14,18</sup>

Studies of brain structure provide a complementary perspective on neurobiological disruptions in PTSD. A meta-analysis of voxel-based morphometry studies showed consistent gray matter reduction in the anterior hippocampus and rostral cingulate cortex (likely corresponding to rodent PL) in PTSD.<sup>23</sup> A seminal report<sup>24</sup> found reduced hippocampus volume not only in Vietnam veterans who developed PTSD, but also in their nontrauma-exposed twins, suggesting that hippocampus alterations may be a risk factor for the development of PTSD. That report notwithstanding, subsequent meta-analyses across trauma types have shown that trauma exposure in the absence of PTSD is associated with reduced hippocampus volume,<sup>25</sup> and that volumetric reductions in PTSD are of smaller magnitude when the comparison group is matched for trauma exposure.<sup>25,26</sup> Smaller amygdala volume, which has been noted in several studies of PTSD,<sup>26,27</sup> may be specific to hyperarousal symptoms.<sup>28</sup> The lack of asso-

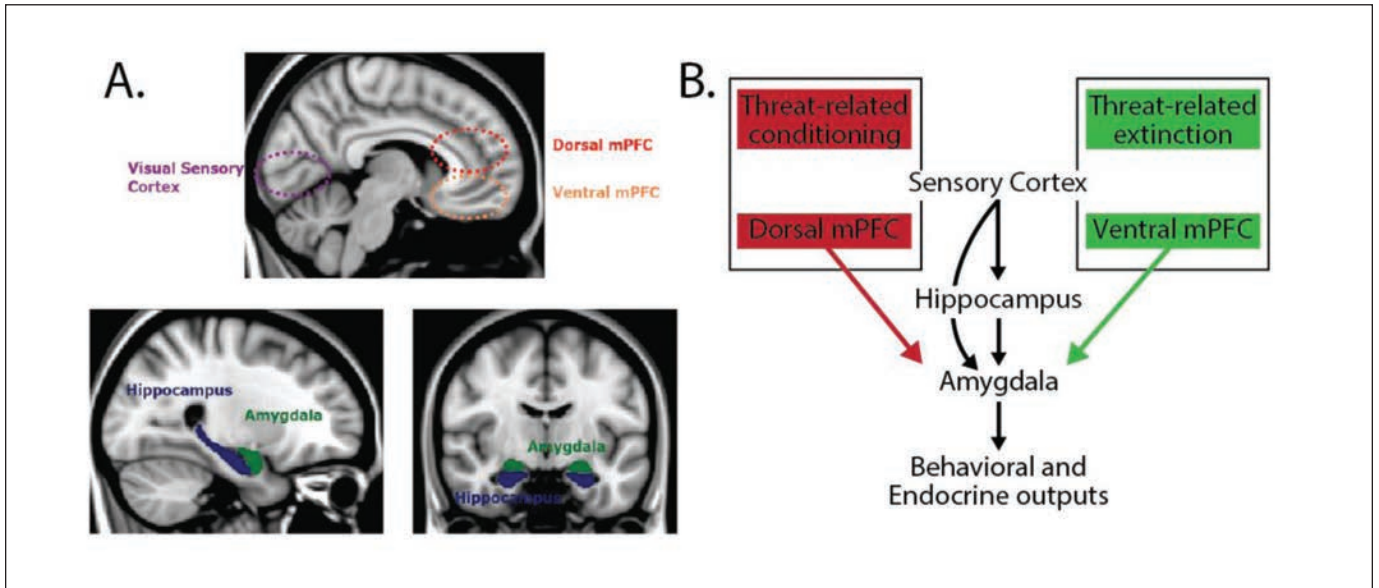


Figure 1. Brain circuitry involved in threat conditioning. (A) Major neural regions include visual sensory cortex, hippocampus, amygdala, and dorsal/ventral medial prefrontal cortex; (B) Circuit diagram indicating pathways by which conditioning and extinction are currently thought to occur.

ciation between amygdala volume and trauma intensity or time since trauma,<sup>27</sup> as well as the finding that amygdala responses to negative stimuli prior to military deployment predicted the subsequent acquisition of PTSD symptoms,<sup>29</sup> has led to the recent suggestion that functional and structural amygdala alterations may be preexisting risk factors for the development of PTSD.<sup>29</sup>

### Shortcomings of the Canonical Neurocircuitry Model of PTSD

This neurocircuitry model of PTSD based on threat conditioning and extinction has grown and persisted in popularity, by now gaining almost canonical status in the field. Although this is not without good reason, several shortcomings of this model suggest the need to develop more nuanced frameworks that can advance efforts aimed at diagnosing, treating, or preventing this disorder.

First, although disrupted function and structure of mPFC-amygdalar-hippocampal circuitry is often assumed to reflect maladaptive threat

learning and/or extinction, the studies<sup>8,14,23,26</sup> reviewed above largely reported alterations resulting from other tasks, or involved task-free functional data or structural data agnostic to functional processes. Threat learning and extinction are highly conserved core survival mechanisms shared across species, but humans use overlapping neural circuitry to process a panoply of other “higher-level” activities beyond threat expression and extinction. For example, the vmPFC is a large and functionally heterogeneous region of the brain implicated in self-related processing, projection of oneself into the past or future, processing of reward, and autonomic regulation;<sup>30</sup> the amygdala, although popularly known as the “fear region” of the brain, is also involved in reward conditioning, social interaction, and feeding behavior.<sup>31</sup> Thus, the assumption that observed alterations to this circuitry in PTSD specifically indicate disruptions to threat-learning processes, particularly in the absence of correlations between brain changes and corresponding behavioral or

physiologic alterations (eg, see Milad et al.<sup>12</sup>), is an example of the “reverse inference” fallacy in neuroimaging.<sup>32</sup>

Second, as indicated in the review of functional and structural MRI studies<sup>8,14,23,26</sup> above, involvement of this circuitry is not as consistent as would be expected if these brain regions were solely responsible for the entirety of PTSD. A discussion of this circuitry almost always includes reference to a nearly decade-old meta-analysis of fMRI and PET studies,<sup>14</sup> which has now been cited over 1,300 times, including 242 citations in 2015. However, results from larger and more recently published meta-analyses,<sup>16-18,22</sup> reflecting subsequent advances in fMRI methodology, and including various moderating factors such as type of trauma and nature of comparison group, are more equivocal as discussed above. In particular, amygdala hyperactivation is not consistently observed across functional imaging studies in PTSD; furthermore, amygdala hyperactivity has been associated with a variety of mood and anxiety disorders including

generalized anxiety disorder<sup>33,34</sup> and depression,<sup>35,36</sup> suggesting that amygdala hyperactivity is not specific to PTSD. Additionally, whether people with PTSD are compared to trauma-exposed or trauma-naïve controls critically affects the conclusions of these studies,<sup>17,25</sup> underscoring the critical importance of including both types of control groups to differentiate effects of trauma exposure from those of maladaptive responses to trauma. These recent meta-analyses have also provided evidence for the involvement of additional brain regions in PTSD that have garnered little attention to date. In particular, hyperactivation of the precuneus and adjacent retrosplenial cortex seems to be a robust finding across studies in patients compared to healthy controls.<sup>17,18,22</sup>

Third, and perhaps most significantly, the simplicity and narrow focus of this model on the processing of threat fails to appreciate the complexity of PTSD, which is far more than a disorder of disrupted threat learning and memory. Nonetheless, the field has disproportionately turned to tasks that either target threat learning and extinction or that otherwise attempt to elicit fear or threat responses, eg, through the use of trauma scripts, fearful or angry faces, or trauma-related pictures. The tasks that are used by neuroimaging researchers dictate what neural circuits are likely to be activated, and the results of individual studies and meta-analyses thus do not necessarily reflect a “ground truth” about the neural circuitry central to PTSD.

It goes without saying that PTSD is not a single, homogenous disorder; people with this diagnostic label all fail to respond to traumatic events in an adaptive way, but the extent to which particular symptoms manifest themselves and interfere with daily function can vary widely from patient

to patient. Although this is not a particularly controversial or contested statement, many neuroimaging studies in PTSD fail to incorporate designs or analyses that allow for the identification of neurobiological mechanisms associated with this heterogeneity. The implementation of the Research Domains Criteria<sup>37</sup> may facilitate a

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move of the field in a direction that allows for novel advances in our understanding of the complex and heterogeneous nature of PTSD, contributing to more neurobiologically informed advances in diagnosis, treatment, and prevention.

One way this understanding is being enhanced is through the use of a broader array of functional tasks with behavioral correlates that map onto specific symptoms of PTSD. This approach allows researchers to investigate the neurobiological correlates of diverse symptoms of PTSD beyond heightened fear, and directly relate brain alterations to corresponding behavioral differences. For example, reduced motivation to seek reward and decreased pleasure from reward consumption have both been observed in PTSD,<sup>38</sup> as has reduced ventral striatal activation in response to reward.<sup>39,40</sup> Future work could explore whether this reflects the high comorbidity of PTSD and depression versus a PTSD-specific phenotype. Behavioral, cognitive, and emotional avoidance are central to PTSD and other anxiety disorders;<sup>41</sup> because such avoidance is maladaptive only when it conflicts with the drive to approach desired

outcomes, future studies should explore the neural basis of approach-avoidance conflict in PTSD.<sup>42</sup> A recent magnetoencephalography study found reduced early prefrontal activity and subsequently enhanced visual cortical processing for trauma-related words, suggesting a neural mechanism associated with the prominent clinical feature of hypervigilance for trauma-relevant stimuli.<sup>43</sup> Finally, despite the criticisms detailed above, it is important to note that threat conditioning and extinction clearly play an important role in PTSD that deserves further exploration. Recent research has targeted two specific processes with direct clinical relevance: (1) threat generalization, or the “spreading” of physiologic/self-reported threat responding to safe cues that are perceptually similar;<sup>44,45</sup> and (2) contextually appropriate modulation of threat expression.<sup>13</sup> These studies provide a more nuanced perspective on the role of altered threat learning, memory, and extinction in PTSD.

In addition to targeting different symptoms through the use of diverse tasks, the field of biological psychiatry will continue to benefit from studies whose analytic strategies make explicit use of phenotypic heterogeneity, rather than treating all participants with PTSD as belonging to a single homogeneous group. One strategy gaining favor recently has been to examine continuous variability in different symptom clusters, and to identify brain regions or circuits in which activation, connectivity, or structure is associated with distinct symptoms. Studies adopting this approach have identified specific relationships between hyperarousal symptoms and reduced amygdala volume;<sup>28</sup> re-experiencing symptoms and resting-state hippocampal connectivity;<sup>46</sup> hyperarousal symptoms, altered mPFC-amygdala connectivity, re-experiencing symptoms, and

hippocampus-insula connectivity, both during an emotional Stroop task;<sup>47</sup> and hyperarousal/re-experiencing symptoms and elevated activation in distinct vmPFC regions during unpredictable threat anticipation.<sup>48</sup>

In summary, although functional and structural imaging studies do indicate alterations to mPFC-amygdalar-hippocampal circuitry in PTSD, there are some inconsistencies in the involvement of this circuitry across studies. Due to the frequent use of a nontrauma-exposed control group, many of the observed changes may reflect normative responses to trauma rather than pathologic changes associated with PTSD. Furthermore, disrupted function, structure, or connectivity of this circuitry should not necessarily be taken as evidence that a threat conditioning and extinction perspective provides a complete explanatory model for the complex and heterogeneous nature of PTSD. Future research on the neurobiology of this disorder will benefit from tasks that target the broad range of functional impairments in PTSD, and analytic methods that link particular symptom clusters or phenotypes to corresponding brain changes in regions including, but not limited to, the mPFC, amygdala, and hippocampus.

### AFFECTIVE NEURODYNAMICS

A key symptom of PTSD is hypervigilance, in which anticipation of threat is sustained and ongoing in the absence of any evidence that such vigilance is still necessary. Heightened anticipation of aversive outcomes and sustained fear is central to many anxiety disorders<sup>49,50</sup> and both human and rodent models suggest this is associated with activity of the extended amygdala, including the bed nucleus of the stria terminalis<sup>51</sup> and the prefrontal cortex.<sup>52</sup> For example, sustained conditioned threat responses in rodent

PL neurons are associated both with threat expression to a conditioned stimulus as well as a failure to extinguish CS-US associations.<sup>53</sup> Although there is accruing evidence for abnormalities in the duration of amygdala and ventral striatal activity in people with depression,<sup>54-56</sup> neuroimaging studies to date have not explicitly examined the affective neurodynamics of cortical or subcortical circuits in PTSD. These parameters can include the amplitude, duration, and speed of onset of affective and neural responses to environmental stimuli. Such approaches explicitly attempting to parse psychological and neurobiological processes into these temporal dynamic parameters may yield more replicable results and more accurately capture the neural processes underlying PTSD.

### IMPORTANCE OF TRAUMA TYPE AND DEVELOPMENTAL CONSIDERATIONS

An important consideration for all research on PTSD, including neuroimaging studies, is the type of trauma encountered and the possibility that different types of trauma exposure may result in divergent clinical and neurobiological profiles.<sup>57</sup> The brain is likely to respond in different ways to a specific and isolated traumatic event, such as an automobile accident or witnessing a homicide, versus multiple acute traumatic events that take place in a chronically stressful environment, as is the case for combat veterans or someone in an abusive relationship. To date, there have been almost no neuroimaging studies to include trauma type as a potential explanatory factor. One recent diffusion tensor imaging (DTI) study compared veterans and civilians with and without PTSD in a 2 × 2 design, and found white matter microstructural alterations in the posterior cingulum

for civilians but not for veterans with PTSD.<sup>58</sup> The authors concluded that differences in trauma type may account for discrepancies in past DTI studies, although it is difficult to draw firm conclusions on the basis of this single study.

Another less frequently discussed factor that is related to trauma type is the age at which trauma occurred. Data suggest that age at the time of trauma influences what type of disorder is likely to result, such that early trauma (before age 13 years) among girls confers higher risk for the later development of depression versus PTSD,<sup>59,60</sup> whereas trauma during puberty confers higher risk of development of an anxiety disorder.<sup>61</sup> Furthermore, at a basic level, it is not known whether the age at which trauma occurs has any impact on treatment outcome or whether a specific treatment approach will have greater efficacy.<sup>62</sup> The human brain is an amazingly plastic organ, but the exact neurobiological impact of trauma at early versus later stages of development (eg, while the brain is still undergoing substantial maturation vs after the majority of maturation has occurred) has not been specified. Given evidence that the timing of trauma appears to have an impact on HPA axis function, investigators have suggested that trauma timing may impact hippocampal and pituitary structure and function,<sup>63</sup> overall cerebral volume,<sup>64</sup> as well as lateral PFC dysfunction given a role for the PFC in hippocampal regulation.<sup>59</sup> However, large-scale neuroscientific studies examining such timing effects have not been undertaken (or statistically accounted for). Diagnostically, studies examining the psychiatric impact of trauma early in life have found that these people go on to develop PTSD or major depressive disorder.<sup>65</sup> However, future studies attempting to examine the neural impact of early life

stress must fully control for age of trauma as well as current disorder status. This will require research that uses a 2 × 2 design in which age of trauma (early vs late) and current disorder status (PTSD vs healthy control) are controlled for. These types of designs will go a long way to address issues related to specificity of the neural mechanisms underlying PTSD.

In addition to scientific questions regarding brain responses to different kinds of trauma and the effects of trauma timing on brain structure and function, there are critically important policy implications at stake. To the general public, PTSD is a condition most typically associated with war. PTSD became a formal diagnosis in *DSM-III*<sup>66</sup> due to the efforts of the veterans' group Vietnam Veterans Against the War and a small group of supportive psychiatrists,<sup>67</sup> and the recent wars in Iraq and Afghanistan have again brought the disorder to the forefront of public attention. Although the number of US war veterans who have been affected by PTSD stands at a staggering 1.4 million, this number pales in comparison to the approximately 17 million US civilians who have suffered from the disorder,<sup>68</sup> many of them due to physical and sexual abuse suffered during childhood or as adults. Congressional legislation reinforces the public perception of PTSD as a condition of war; of 161 PTSD-specific bills introduced between 1989 and 2009, 91% of explicit mentions to PTSD focused exclusively on military populations, compared to 5% that focused exclusively on civilian PTSD.<sup>69</sup> As it is often the case that funding of military-specific issues eventually benefits the public more broadly, an advanced understanding of the neurobiology of combat-related trauma may come to benefit all people suffering from PTSD. It may also be the case, however, that after dedicating the lion's share of funding and attention to research on a rela-

tive minority of cases, this knowledge is ultimately revealed to be of little relevance for PTSD resulting from different types of trauma. This is an empirical question, and we do not yet have the evidence to conclude whether the neurobiology of combat-related PTSD is the same, similar, or completely different in nature from PTSD resulting from accidents, disasters, or physical and sexual assault in civilian populations. Although the practical challenges of addressing these questions are substantial, the potential implications make this a critical issue to tackle in future work.

## CONCLUSION

Our understanding of the neural mechanisms underlying the pathophysiology of PTSD has advanced substantially since the advent of neuroimaging. Abnormalities in cortical and subcortical circuits including the medial PFC, hippocampus, and amygdala appear to be at the heart of brain abnormalities underlying PTSD. Given the normative function of this circuitry, these abnormalities likely contribute to difficulties in emotional and stress regulation observed in PTSD. Most neuroimaging studies to date have used a threat-conditioning model of PTSD, due to its face validity and clear translation to animal models. Despite the utility of this approach and the substantial data it has garnered, researchers should continue to investigate alternative perspectives that may more fully explain the diverse and heterogeneous nature of PTSD. In particular, additional temporal, developmental, and trauma type considerations may help facilitate coherence across studies and advance a more nuanced understanding of the neurobiological alterations associated with PTSD.

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