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## Post-traumatic stress disorder: review of DSM criteria and functional neuroanatomy

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## **Post-traumatic stress disorder: a review of DSM criteria and functional neuroanatomy**

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## Abstract

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) criteria for post-traumatic stress disorder (PTSD) consists of over twenty possible symptoms that can be divided into six broad categories. These categories correlate with specific brain networks that regulate emotions, behaviors, and autonomic function. Normal functioning of these networks depends on two key regions: the prefrontal cortex and the amygdala. The prefrontal cortex provides top-down executive control over amygdala, whereas the amygdala is critical for threat detection and activation of the ‘fight or flight’ response. Events that trigger extreme and/or prolonged fear can cause persisting dysregulation within the prefrontal-amygdala circuit, resulting in PTSD symptomatology. Studies indicate that effective treatment of PTSD, either psychotherapy or medication, reverses this prefrontal-amygdala dysregulation. This review article summarizes current knowledge and theories available in the medical literature from NCBI’s PubMed database regarding the underlying brain networks involved in PTSD.

## Keywords

post-traumatic stress disorder, PTSD, neuroanatomy, amygdala, prefrontal cortex, network

## Introduction

In 1952, the American Psychiatric Association published the first edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), which included the diagnosis of gross stress reaction (GSR), a condition caused by an identifiable traumatic experience.<sup>1</sup> Events such as “combat” or “civilian catastrophe (fire, earthquake, explosion, etc.)” could cause “great and unusual stress”. Symptoms resulted from the patient’s attempt “to deal with overwhelming fear” and caused a “transient situational personality disturbance”. In DSM-III, gross stress reaction was change to posttraumatic stress disorder (PTSD).<sup>2</sup> According to diagnostic criteria, traumatic events could include the following: a serious threat to the individual’s life or physical integrity, serious threats to the life and safety of others, or the sudden destruction of one’s home or community.

Published in 2014, DSM-5 criteria include more than twenty potential symptoms, which can be divided into 6 broad categories (Table 1). These categories correlate with specific functional brain networks.<sup>3</sup>

Table 1. Summary of DSM 5 Criteria:

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<b>memory symptoms:</b>
intrusive trauma memories
distressing trauma dreams
inability to remember aspects of the trauma
<b>physiological arousal:</b>
hypervigilance, hyperarousal, insomnia
physiological activation to environmental cues
exaggerated startle response
<b>emotional symptoms:</b>
fear to environmental cues
persisting nervousness or anxiety
inability to experience positive emotions
persisting guilt or shame
<b>behavioral symptoms:</b>
avoidance of environmental cues
reactive angry or irritability
impulsive and self-destructive behavior
<b>distorted beliefs:</b>
negative beliefs about oneself or others
distorted beliefs about cause or consequences of trauma
<b>cognitive symptoms:</b>
problems with concentration
dissociative reaction

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## Basic neurobiology

PTSD symptoms develop due to dysfunction in two key brain regions, the amygdala and the prefrontal cortex. The amygdala, a small almond shape structure located in the medial temporal lobe, contains several clusters of neurons. Functional activities attributed to these neurons include environmental threat detection, activation of defensive behaviors ('fight or flight' response), activation of the sympathetic nervous system (SNS), and facilitation of new memory formation.<sup>4</sup> Neurons within the prefrontal cortex (PFC) regulate conscious awareness and volitional control over emotions, attention, memory and behaviors.<sup>5, 6, 7</sup> Functional activity within the PFC can be localized to specific regions as follows: medial PFC regulates emotions and memory, orbital (ventral) PFC regulates behaviors, and lateral PFC regulates attention.<sup>8</sup>

During the initial response to an environmental threat, neurons within the amygdala trigger defensive behaviors and physiological arousal (fear response). Simultaneously, neurons within the medial PFC engage in the conscious assessment of the threat and either suppresses or enhances the fear response.<sup>9,10,11</sup> Functional imaging studies (PET scans and fMRI) in individuals with PTSD show hyper-responsiveness of the amygdala and decreased activity of the medial PFC to potential threats.<sup>12,13</sup> These findings are consistent with the theory that PTSD

symptoms result from hyper-reactivity of the amygdala's fear response and failure of the medial PFC to provide inhibitory feedback.<sup>14,15,16</sup>

## Traumatic memories

Regions critical for the formation and retrieval of autobiographical memory include hippocampus, thalamus and cingulate cortex.<sup>17</sup> Two major projection fibers, the fornix and the cingulum, connect these regions to form a functional circuit (Figure 1). James Papez first demonstrated this circuit in 1937 by injecting rabies virus into the hippocampus of a cat and traced the movement of the virus through the brain (Papez circuit).<sup>18</sup>

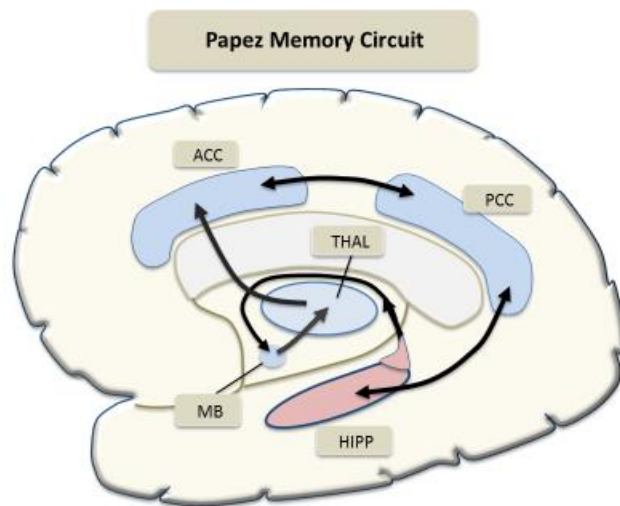


Figure 1: Autobiographical memory circuit (Papez circuit): anterior cingulate cortex (ACC), hippocampus (HIPP), mammillary bodies (MB), posterior cingulate cortex (PCC), thalamus (THAL).

The hippocampus receives information about the environment from sensory cortices via the following pathways: the dorsal and ventral visual streams, the auditory processing stream, and the olfactory tract.<sup>19,20</sup> During periods of wakefulness, the hippocampus facilitates storage of sensory information into short-term memory.<sup>21</sup> The amygdala also receives information from sensory cortices and facilitates long-term memory formation by triggering a state of hyper-arousal, and events that are not emotionally significant will typically be forgotten within four to six weeks.<sup>22,23,24</sup> Preliminary research suggest that medications that block peritraumatic hyper-arousal, such as propranolol, may decrease the risk of PTSD following traumatic events.<sup>25</sup>

Long-term memory consolidation results from new dendritic spine growth and formation of new dendritic connections within regions of the memory network, especially the hippocampus and the anterior cingulate cortex.<sup>26,27</sup> The anterior cingulate cortex projects to the medial PFC, a region that assigns personal meaning and emotional significance to experiences, and controls intentional

retrieval of autobiographical memory (top-down processing).<sup>28,29,30</sup> Another key component of the memory networks is the posterior cingulate cortex, which provides vivid details about past events (i.e. visual images) through direct connections to the medial parietal sensory cortex.<sup>30</sup>

For individuals with PTSD, trauma-related cues trigger intrusive memories through unintentional recall. Functional imaging studies have shown that cues activate the amygdala (bottom-up processing), which in turn activates other components of the memory circuit.<sup>31,32</sup> Vivid sensory flashbacks, consisting of visual images, can be triggered by the activation of sensory cortices (i.e. visual cortex).<sup>33</sup>

Prolonged exposure therapy, which involves reviewing and discussing past trauma, has been shown to reduce intrusive memories.<sup>34</sup> Functional imaging studies indicate that exposure therapy engages medial PFC in self-referential thinking, thereby promoting more rational appraisal of the causes and consequences of traumatic events.<sup>35,36</sup>

Dreams, which occur primarily during REM sleep, activate regions within the memory circuit, including the hippocampus, amygdala, cingulate cortex and secondary sensory cortices.<sup>37</sup> PTSD-related nightmares may activate the sympathetic nervous system resulting in distressful night-time awaking, or may trigger physical activity based on the 'fight or flight' response (punching, kicking).<sup>38,39</sup> Studies indicate that the frequency and intensity of trauma-related dreams decrease with psychotherapy involving dream review and imagery revision, a process that engages the PFC in conscious restructuring of dreams.<sup>40,41</sup>

## **Physiological regulation**

Individuals with PTSD experience physiological arousal when thinking about past traumatic events or following exposure to trauma-related cues. Neurons within the lateral hypothalamus modulate physiological arousal by activating the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis (neuroendocrine response).<sup>42</sup> Studies have consistently shown physiological hyper-responsiveness, as measured by skin conductance or cardiac physiological, in individuals with PTSD.<sup>43,44</sup>

The amygdala projects to neurons within the lateral hypothalamus through the ventral amygdofugal pathway and stria terminalis, and the medial prefrontal cortex connects to the same neurons by projecting to the bed nucleus of the stria terminalis. The amygdala activates neurons in the lateral hypothalamus, whereas the medial prefrontal cortex either activates or suppresses these same neurons (Figure 2).<sup>45,46,47</sup> Direct bidirectional projection neurons within the amygdofugal pathway and uncinate fasciculus connect the amygdala and medial PFC, and facilitate activity between these two regions. Collectively, the medial prefrontal cortex, the amygdala and the lateral hypothalamus form a physiological regulating network.<sup>42,48,49</sup>

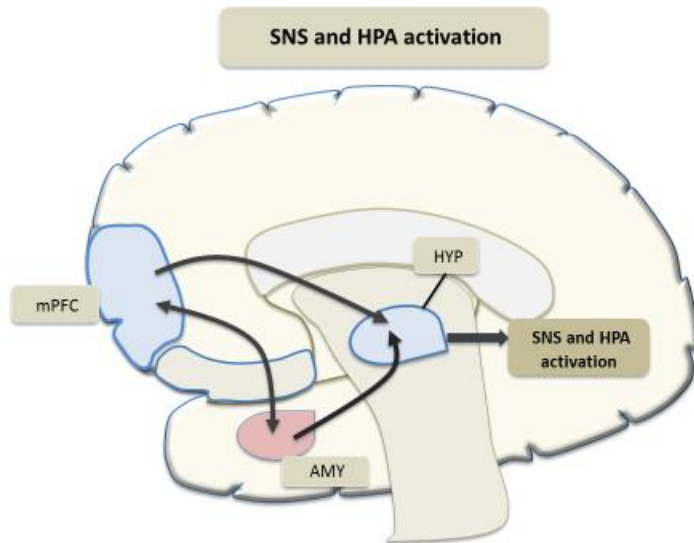


Figure 2: Sympathetic nervous system (SNS) and HPA axis regulation: amygdala (AMY), hypothalamus (HYP), medial prefrontal cortex (mPFC).

Another structure that is critical to physiological arousal is the locus coeruleus (figure 3).<sup>50</sup> This small nucleus located in the brainstem contains most of the brain's norepinephrine producing neurons, with efferents that project throughout the neocortex. Increased release of norepinephrine from the locus coeruleus causes hyper-arousal, hypervigilance and sleep inhibition.<sup>51</sup> Studies indicate that activation of amygdala projections to the locus coeruleus increase release of norepinephrine; whereas medial PFC projections either enhance or suppress norepinephrine release.<sup>51,52,53</sup> Studies in individuals with PTSD have shown increased activity of the locus coeruleus, which can trigger a state of anxious arousal.<sup>54,55</sup> In an attempt to reduce this anxious arousal, patients commonly engage in low stimulation seeking behaviors (social avoidance and isolation).



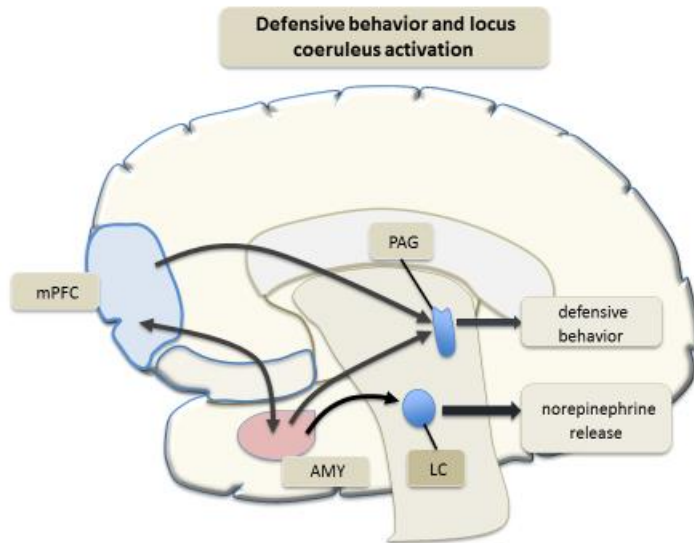


Figure 3: Defensive behavior and LC activation: amygdala (AMY), locus coeruleus (LC), medial prefrontal cortex (mPFC), periaqueductal gray (PAG).

Central acting adrenergic agents, such as prazosin and clonidine, block the effects of norepinephrine in the neocortex. These agents can decrease hyper-vigilance and improve sleep in PTSD.<sup>56</sup> Additionally, the practice of biofeedback or mindfulness-based meditation may reduce autonomic arousal and improve PTSD symptoms by down-regulating amygdala activity and improve prefrontal-amygdala functional intergration.<sup>57,58,59</sup>

### Defensive motor response

Activation of neurons within the periaqueductal gray matter and the nucleus reticularis pontis caudalis (brainstem nuclei) can generate rapid defensive motor responses (figure 3). In animal studies, stimulation of neurons within periaqueductal gray matter can trigger jumping, running, freezing, and increased overall muscle tone.<sup>60</sup> In one recent functional MRI study, increased activity of periaqueductal gray matter was demonstrated in individual with PTSD.<sup>61</sup> Stimulation of the nucleus reticularis pontis caudalis triggers the acoustic startle reflex with rapid onset of body defensive posture; a reaction that has been shown to be hyper-responsive with PTSD.<sup>62,63</sup> The amygdala sends direct projections to the periaqueductal gray matter and the nucleus reticularis pontis caudalis, and potentiates these defensive responses.<sup>64,65,66</sup>

### Behavioral symptoms

Behavioral changes, such as impulsivity and reactive anger, are common following severe emotional trauma and reflect dysfunction of brain regions that modulates behavior. Studies have shown that the nucleus accumbens (NA), a small group of neurons within the basal forebrain, plays a critical role in behavioral control and impulsivity.<sup>67</sup> The nucleus accumbens acts an

interface between the amygdala, the orbital PFC and the motor cortex (Figure 4). Collectively these regions form a network that regulates social behavior. This network can be summarized as follows: the orbital PFC sends bidirectional projecting fibers to the amygdala through uncinate fasciculus, both the orbital PFC and the amygdala send direct projection fibers to the nucleus accumbens (NA), and the nucleus accumbens connects to the supplementary motor cortex through the thalamus.<sup>68,69,70</sup>

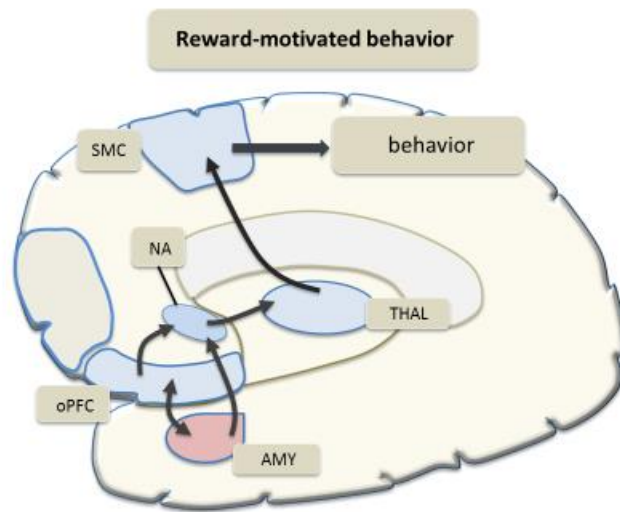


Figure 4: Regulation of reward-motivated behavior: amygdala (AMY), nucleus accumbens (NA), orbital prefrontal cortex (oPFC), supplementary motor cortices (SMC), thalamus (THAL).

The amygdala promotes impulsivity by enhancing “motor readiness” to respond to external situations, whereas the orbital PFC normally suppresses impulsivity by modulating amygdala and nucleus accumbens activity.<sup>71,72,73</sup> In human studies, damage to the orbital PFC triggers significant change in social behavior, with an increase in risk-taking, aggressiveness, and impulsivity.<sup>74,75</sup> Recent studies have demonstrated changes in functional activity and volume of the orbital PFC in patients with PTSD, which may explain the reactive aggression that occurs with this disorder.<sup>76,77,78,79</sup>

## Emotional symptoms

The insular cortex, a region involved with introspective emotional awareness, receives ascending peripheral viscerosensory projections via the thalamus, and direct projections from the amygdala (Figure 5).<sup>80,81,82,83</sup> Functional imaging studies suggest that activation of the amygdala-insula circuit generates feelings of fear and anger, and over-activity of this circuit may cause generalized fear, anger and decreased positive emotions in PTSD.<sup>84,85,86</sup>

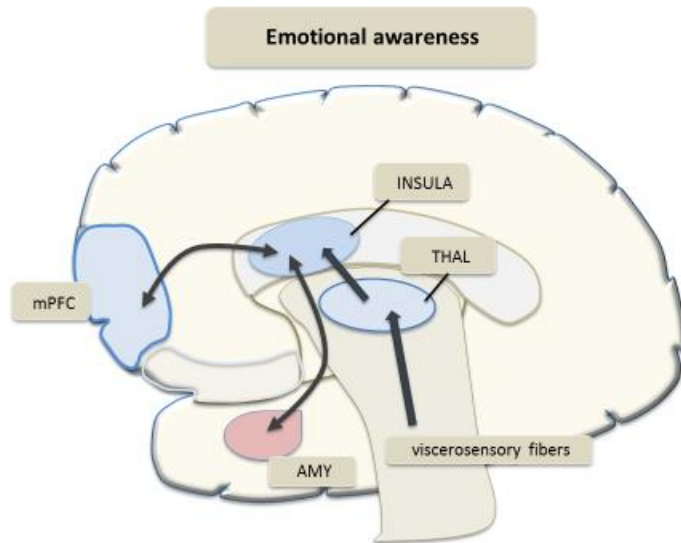


Figure 5: Emotional awareness: amygdala (AMY), insula cortex, medial prefrontal cortex (mPFC), thalamus (THAL).

The insular cortex has strong bidirectional connections with the medial prefrontal cortex, a region that controls self-referential thinking and effortful regulation of emotions.<sup>80,81,83,87,88,89,90</sup> Studies have indicated that activation of the amygdala-insula circuit suppresses medial PFC activity and impacts emotional regulation.<sup>85,86</sup> Therefore, impairment of emotional regulation seen with PTSD may result from overactivity of the amygdala-insula circuit.<sup>86</sup> Exposure psychotherapy and selective serotonin reuptake inhibitors (SSRIs) have been shown to increase PFC activity with improved emotional regulation in individuals with PTSD.<sup>91,92,93,94</sup>

The experience of anxiety and nervousness can be triggered by activation of the sympathetic nervous system (SNS).<sup>95</sup> Viscerosensory feedback of SNS activity occurs through fibers that project to the insular cortex via the thalamus. In PTSD, anxiety and nervousness occur in the context of SNS arousal to trauma-related cues. As a potential treatment option, one recent study showed a decrease in SNS activation to traumatic memories, as measured by skin conductance and heart rate response, in patients treated with propranolol.<sup>96</sup> However, no data on symptom response was provided in this study.

## Conclusion

Post-traumatic stress disorder can be conceptualized as a syndrome that results from prefrontal-amygdala dysregulation.<sup>13,14,15,97,98</sup> Although the nomenclature is often inconsistent and can be confusing, knowledge of basic neuroanatomy is important in understanding symptom patterns and for the treatment of PTSD.

PTSD symptoms can be grouped into categories based on distinct functional networks. A key structure in these networks is the amygdala. The amygdala has been called the ‘reptilian’ or ‘primal’ brain because of its critical role in activation of the fight or flight response.<sup>99,100</sup> The amygdala becomes over-active and hyper-responsive following severe life-threatening trauma or trauma that threatens the integrity of the self (e.g., sexual assault). Imaging studies indicate that overactivity of the amygdala causes down-regulation of prefrontal cortical regions, especially the medial and orbital PFC.

Recent functional imaging studies indicate that effective treatment of PTSD leads to a decrease in amygdala hyper-responsiveness and an increase in prefrontal cortical activity. Understanding these functional changes may help with the discovery of new treatment options and lead to the development of therapies aimed at prevention of PTSD after severe trauma.

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