

From Fear Circuit to Recovery: Neural Mechanisms and Interventions in Post-Traumatic Stress Disorder

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Abstract. Post-traumatic stress disorder (PTSD) is a psychiatric condition that develops after exposure to a traumatic event. It is characterized by intrusive memories, avoidance, negative mood changes, and hyperarousal. This paper reviews the main brain mechanisms underlying PTSD and evaluates the effectiveness of current psychological and pharmacological interventions targeting these mechanisms. Diagnostic criteria for PTSD differ between the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the International Classification of Diseases, 11th Revision (ICD-11) systems. They affect how the disorder is identified across studies. At the neural level, PTSD is associated with a dysregulated fear circuit involving amygdala hyperactivity, ventromedial prefrontal cortex hypoactivity, and hippocampal dysfunction. Exposure-based psychotherapy shows strong, consistent evidence of effectiveness and appears to strengthen prefrontal regulation over the amygdala, while pharmacological intervention with propranolol shows more mixed results across individual trials though meta-analytic evidence supports a modest overall benefit. This review argues that psychological and pharmacological approaches converge on the same neural circuit through different mechanisms via gaps in long-term outcome data and treatment accessibility.

Keywords: PTSD, DSM-5, ICD-11, PTSD mechanism

1. Introduction

Today, people know that trauma-related conditions are not purely psychological in the sense of just being about thoughts. They involve measurable, identifiable changes in the brain.

Post-traumatic stress disorder (PTSD) is one of the clearest examples of this.

Along with related conditions such as a subgroup of major depression, borderline personality disorder and dissociative disorders, PTSD belongs to what has been described as a group of trauma spectrum disorders that share a common neurobiological footprint, including notably smaller hippocampal volume, distinguishing them from other psychiatric conditions with similar symptoms but without such a clear trauma link [1]. This suggests that underlying PTSD requires looking not only at behavior and emotion, but at the underlying brain circuitry that produces these symptoms.

The paper first reviews how PTSD is diagnostically defined, then examines the three brain regions most consistently implicated in PTSD, before evaluating the evidence for two major intervention types and discussing the limitations of current research.

2. Definition and diagnostic methods or criteria of PTSD

Post-traumatic stress disorder (PTSD) is a prevailing psychiatric problem among adolescents experiencing exposure to a traumatic event, such as combat, natural disaster or serious accidents. Although the disorder has been recognized over a century, its formal diagnostic criteria have evolved considerably with two major systems which is defining PTSD in notably different ways: the Diagnostic and Statical Manual of Mental Disorders, Fifth Edition (DSM-5) and the International Classification of Diseases, 11th Revision (ICD-11) [2, 3].

The DSM-5 defines PTSD through four symptom categories: intrusion (e.g. involuntary distressing memories or flashbacks), avoidance (e.g. of trauma-related stimuli), negative alterations in cognition and mood (e.g. persistent negative beliefs and emotional numbing), and as well as the alterations in arousal and reactivity (e.g. hypervigilance, exaggerated startle response) [3].

On the other hand, the ICD-11 has a more focused model, which defines PTSD only through three core symptom mechanisms: re-experiencing the trauma in the present, avoidance, and a persistent sense of current threat [4]. It also introduces a completely different diagnosis of Complex PTSD (CPTSD) for prolonged or repeated trauma exposure, adding three "disturbances in self-organization" which is affective dysregulation, negative self-concept, and disturbances in relationships and it is not present in the DSM-5 framework [4].

These structural differences produce measurable discrepancies in practice. In all the large adult samples of Chinese earthquake survivors, ICD-11 criteria yielded a significantly higher PTSD presence than DSM-5 criteria, although there is no significant difference in comorbidity with depression or anxiety [2]. Another study of Chinese adolescents experiencing trauma found there is no significant prevalence difference between the two systems. It suggests the discrepancy may change between age group or population [3]. Together, these findings show that diagnostic classification is not only a labeling exercise. It can significantly affect who is diagnosed to have PTSD.

Understanding these diagnostic differences is important before examining the neural mechanisms underlying PTSD, as the symptom clusters emphasized by each system map onto distinct and identifiable brain circuits. And it will be examined next.

3. The neural mechanisms of PTSD

3.1. Amygdala hyperactivity

When people experience trauma, the amygdala plays a very important role, because it is the brain area mainly responsible for detecting threats and generating fear response [5]. In PTSD patients, researchers found that the amygdala shows too much activity, not only when facing trauma-related stuff, but also sometimes even for normal stimuli [5]. This means the fear-detecting system in PTSD patients' brain is kind of overreacting and treating things as dangerous when actually they are safe. A meta-analysis combining many neuroimaging studies also confirmed this pattern, showing that PTSD patients consistently have more amygdala activation compared to healthy people, and this pattern was even more specific to PTSD when compared with other anxiety disorders [6]. So people could say, amygdala hyperactivity is probably the most well-established and repeated finding in PTSD brain research, and it explains why patients feel intense fear or panic even in situations that other people would consider harmless.

3.2. vmPFC hypoactivity

If the amygdala is like the alarm system, then the ventromedial prefrontal cortex (vmPFC) is more likely to stop the alarm once the danger has happened. Normally, vmPFC helps to regulate and calm down the amygdala's fear response, especially during the process called fear extinction, when a person learns that a previously scary stimulus is no longer dangerous. However, in PTSD patients, this braking function seems to fail. The same meta-analysis mentioned above found that, unlike other anxiety disorders, PTSD patients specifically show reduced activity in the vmPFC and also in some cingulate cortex regions, and this pattern was unique to PTSD group only [6]. Later reviews further explain that besides functional changes, there are also structural changes happening. For example, some studies noticed reduced gray matter volume in prefrontal regions like dorsolateral and dorsomedial prefrontal cortex (PFC), and this loss of neurons might explain why patients have trouble regulating their emotions and cannot properly turn off the fear response once trauma-related danger is no longer present [5]. So basically, it is not just that the amygdala is too active, but also the brain area that should control it is not working properly, and together these two problems make the fear response very hard to shut down.

3.3. Hippocampal dysfunction

The hippocampus is important because it helps to place memories into correct time and place context. It means that it tells people when and where something happened. In PTSD, many studies observed reduced hippocampal volume, and researchers believe this is related to decreased neurogenesis (the process of making new neurons) as a result of long-term stress exposure [5]. Because the hippocampus is not functioning well, trauma memories may lose their proper tag of being something that happened in the past. This could be one reason why PTSD patients often feel like they are reliving the traumatic event in the present moment, instead of just remembering it as something that already ended. Interestingly, recent circuit-based research using more advanced techniques (like cell-type specific labeling in animal models) also supports the idea that hippocampus works together with amygdala and prefrontal cortex as one connected network during fear memory formation, storage, and extinction, not just as separate regions working alone [7].

3.4. Integrating the three

Combining all the evidence above, this paper can build a picture of PTSD as a problem within one connected fear circuit, involving amygdala, vmPFC and hippocampus together, instead of thinking about these three regions as if they work separately [5, 7]. The amygdala becomes hyperactive and it can generate too much fear response. The vmPFC fails to send inhibitory signals to calm the amygdala down. And the hippocampus, being smaller and less functional, cannot correctly tag traumatic memories with proper time/context information, causing intrusive and present-feeling. However, one important question that is still debated is the direction of causality. For example, does trauma actually cause hippocampal volume to shrink, or do some people already have naturally smaller hippocampus before trauma happens, which then makes them more vulnerable to developing PTSD in the first place? Current evidence cannot really fully answer this question yet, since most studies only measure hippocampal volume after PTSD diagnosis, not before trauma exposure. This means, while the three-region fear circuit model gives a useful and fairly convincing framework for understanding PTSD, it still has some gap, especially about whether these brain changes are the cause or the result of the disorder. This limitation will be discussed more in Section 5.

4. Effectiveness of the current interventions

4.1. Exposure-based psychotherapy

Prolonged exposure (PE) therapy is a psychological treatment for PTSD that has been studied extensively and neuroimaging evidence suggests that it might not only reduce symptoms, but also change patterns of brain functioning. A study using resting-state functional magnetic resonance imaging (fMRI) found that, after doing PE treatment, PTSD patients showed increased functional connectivity between the amygdala which means both basolateral and centromedial subregions and the orbitofrontal cortex and as well as between the hippocampus and medial prefrontal cortex. There is a pattern not seen in trauma-exposed healthy controls. The researchers suggested this stronger connectivity could reflect improved ability of prefrontal regions to inhibit and reappraise threat, and better memory encoding/retrieval, which fits nicely with the circuit model discussed before. In terms of overall effectiveness, not just brain-level change, a meta-analysis of 13 randomized controlled trials (N=658) found PE created a large effect size (Hedges's $g = 1.08$) compared to control conditions. This effect size indicates a substantial clinical advantage for PE-treated patients over those in control conditions, and the treatment benefits were also maintained at follow-up [8]. Taken together, these findings indicate that PE is clinically effective across multiple trials and that its therapeutic effects may be associated with brain-level changes in the amygdala, hippocampus, and prefrontal circuits previously implicated in PTSD.

4.2. Pharmacological intervention: propranolol

Propranolol works through a very different logic compared to psychotherapy. Instead of primarily promoting new safety learning, as PE does, propranolol aims to interfere with the reconsolidation of reactivated traumatic memories by modulating noradrenergic activity (like PE does), it tries to block the biological process of memory reconsolidation itself, using its effect on noradrenergic receptors. However, the evidence here is a bit more mixed than for PE. In one well-designed double-blind randomized controlled trial (RCT) with 66 chronic PTSD patients, both the propranolol group and the placebo group showed similar symptom reduction (about 39% vs. 35%). There was no significant treatment difference between them [9]. Considered in isolation, this finding may suggest that propranolol does not produce a clear advantage over placebo. However, when this trial was pooled with six other RCTs in a recent meta-analysis, propranolol was associated with a statistically significant improvement in PTSD symptoms, with low heterogeneity across studies. It suggests the effect is valid even though individual trials do not always reach significance.

4.3. Conditions for optimal effectiveness of PE and propranolol

Because PE and propranolol have not been directly compared in the same head-to-head trial, it is more appropriate to consider the conditions under which each approach may be most beneficial. Propranolol's mechanism depends on disrupting memory reconsolidation, so its effect may be more relevant in early intervention, shortly after a traumatic event, before the fear memory becomes deeply consolidated, though the studies reviewed here actually tested it in patients with chronic and established PTSD. PE on the other hand works through new learning rather than erasing old memory, so it can be applied regardless of how long ago the trauma happened, but it requires the patient to actively engage with trauma-related memories over multiple sessions, which not everyone can tolerate. In this sense, the two approaches are more complementary than competing. Both seem

to converge on regulating the same amygdala, vmPFC, hippocampus circuit discussed before, just through different mechanisms (new learning vs. memory disruption).

5. Discussion and suggestion

5.1. Strengths and limitations of the current findings

The three-region fear circuit model discussed above is supported by substantial evidence, but important limitations remain, particularly in relation to individual variability. The largest neuroimaging study on PTSD to date, combining 1,868 subjects across 16 cohorts worldwide, did confirm smaller hippocampal volume in PTSD patients, but the effect size was actually quite small (Cohen's $d = -0.17$), and the parallel finding for amygdala volume ($d = -0.11$) did not even survive correction for multiple comparisons [10]. This tells that although the smaller hippocampus in PTSD finding is statistically real when combining nearly 2,000 people together, the effect at an individual level is quite small and inconsistent, which explains why so many smaller and earlier studies can produce conflicting results. This raises important questions about whether these brain markers can meaningfully inform clinical assessment for individual patients, even if they remain valuable for understanding PTSD mechanisms at the group level.

5.2. Gaps in the current intervention research

One clear gap concerns long-term outcomes. Most of these studies mentioned above, including the PE and propranolol trials, are mainly focused on outcomes at post-treatment or a few months follow-up. However, data on whether these benefits are maintained over several years remain limited, making it difficult to determine whether these interventions produce sustained recovery or mainly short-term symptom relief.

A separate but equally important gap is possible for newer treatments like methylenedioxymethamphetamine (MDMA)-assisted therapy (MDMA-AT). This means that, even if MDMA-AT proves effective in clinical trials, its real-world implementation may be constrained by limited accessibility, high costs, and substantial workforce training requirements, which could prevent many patients from receiving the treatment. Its treatment protocol requires a co-therapist dyad model. It means every patient needs about 40 hours therapy time from two therapists and 80 hours total [11]. This means that even if the treatment is effective in trials, the real-world accessibility, cost, and workforce training requirements can be the barriers to prevent patients from actually getting recovered.

6. Conclusion

This paper provides the answer to two connected questions: what are the main brain mechanisms behind PTSD and how effective are current interventions in targeting them.

PTSD symptoms appear to arise from dysfunction within a specific fear circuit where amygdala hyperactivity generates an exaggerated threat response, vmPFC hypoactivity fails to regulate the response, and hippocampal dysfunction disrupts the proper contextual tagging of memories. Therefore leads to trauma that makes people feel as though it is happening in the present rather than the past. Although this three-region model is well supported by neuroimaging evidence, it is not without limitations, especially around individual variability and unresolved questions about whether some of these brain changes are a cause or a consequence of trauma exposure.

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