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Circuit Dysregulation and Circuit-Based Treatments in Posttraumatic Stress Disorder

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Abstract

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that develops in some individuals in the aftermath of exposure to traumatic events, such as actual or threatened death, serious injury or sexual assault. It has been hypothesized that dysregulations in a number of specific neurocircuits, characterized by heightened responsivity of amygdala, dACC and insula, diminished responsivity of mPFC, impaired hippocampal function and deficits in cortical regions, underlie the development and expression of key PTSD symptoms. Here, we concisely describe three functional neural circuits implicated in PTSD pathophysiology and briefly review selected treatment strategies in the context of these neural circuits. We start with the commonly implicated neurocircuit model, namely, the fear learning and threat detection circuits, and then discuss the context processing circuitry, which plays an important role among others, in fear regulation. We then discuss the emotion regulation circuitry, which can further contribute to PTSD pathophysiology, and conclude with a discussion of the therapeutic approaches that might be targeting dysregulation in these circuits in PTSD patients. Specifically, we discuss how exposure-based treatments might be targeting fear learning circuits, and the pharmacological and brain-stimulation interventions aimed to augment these therapies. Finally, we discuss other pharmacological and cognitive therapeutic approaches that can augment or restore the function of the context processing and emotional regulation circuits.

Introduction

Posttraumatic stress disorder (PTSD) develops in subset of individuals who have been exposed to traumatic events, such as actual or threatened death, serious injury or sexual assault. Such exposure could entail a direct experience of the traumatic event, in-person witnessing of such event, or learning about a traumatic event that occurred to a close individual [1]. Symptom clusters include intrusive reexperiencing symptoms (memories of trauma, nightmares, flashbacks); avoidance of trauma-related thoughts, memories, contexts or cues; negative mood and cognition; and hyperarousal/hypervigilance [1]. In recent years, multiple studies have examined brain regions involved in PTSD symptomatology in an effort to better understand the underlying mechanisms and to develop more effective treatments [2,

3]. In this mini-review, we focus on three key neural circuits that have been implicated in the pathophysiology and symptom development in this disorder, namely, fear learning/threat detection, context processing and emotion regulation circuits. We consider evidence of dysregulation in these circuits in PTSD, and conclude with a discussion of therapeutic approaches that might be targeting these neurocircuits.

1. Fear learning/threat detection circuitry

The most commonly implicated neurocircuit model in PTSD involves the fear-associated learning circuitry [3–7]. In both humans and rodents, fear learning can be examined within the framework of classical (Pavlovian) fear conditioning, where an aversive stimulus (unconditioned stimulus; e.g., electric shock) is paired with a neutral stimulus (conditioned stimulus; e.g., a tone), resulting in the neutral stimulus eliciting a conditioned fear response (increased freezing, fear-potentiated startle, or skin conductance response). The fear-associated learning circuitry also governs fear extinction, a process by which the previously conditioned fear response is extinguished over time, and the cue that was perceived as dangerous, is now perceived as safe. Developing exaggerated fear response to non-threatening cues, or failing to extinguish fear response to cues that no longer signify danger, could contribute to exaggerated fear and recurrence of traumatic memories in PTSD.

The neurocircuitry underlying fear learning contains a number of regions [2, 3, 8, 9], with amygdala as the key structure that receives sensory input from the thalamus and orchestrates response to threatening signals by sending outputs to the hypothalamus, basal ganglia and brainstem. The medial prefrontal cortex (mPFC) is another key region that regulates appropriate fear/safety learning by exerting top-down control on the amygdala [10], with dorsal regions like dorsal anterior cingulate (dACC) being critical to expression of fear and ventromedial region (vmPFC), specifically, playing a key role in later recall of fear extinction [11]. Two key fear learning regions – amygdala and dACC, together with insula/operculum, also constitute important nodes in a more general salience/threat detection system [12]. This system identifies salient cues in the environment [13], and abnormalities within this system can also contribute to PTSD pathophysiology, independent of fear learning [3, 14]. Considering space limitations, the overlap in the key brain regions like amygdala and dACC, and limited empirical data linking the salience system to PTSD, we do not consider it separately here, rather consider them jointly as fear learning/threat detection circuits.

Functional imaging findings in PTSD, in general, support the notion that amygdala hyperactivation in response to threatening stimuli may account for the exaggerated fear response and persistence of traumatic memories [5, 15–17], while hyperactivation of dACC and insular cortex might contribute to the exaggerated threat detection and fear learning [3, 18]. Furthermore, PTSD has been associated with hyporesponsiveness of the rostral anterior cingulate cortex (rACC) and adjacent vmPFC, which could contribute, to lessened inhibitory input and subsequent hyperactivation of the amygdala [3, 5, 15, 17, 18]. The hypoactivation in mPFC and hyperactivation of the amygdala [19, 20] could, in turn, underlie the impaired extinction recall [3, 16, 21, 22] in PTSD. While this is indeed a plausible hypothesis, it still leaves important questions open, such as: how does this explain emergence of PTSD

symptoms in the absence of trauma cues, or what specific neurobiological process and in what region is the key to PTSD pathophysiology: is it the inhibition in the amygdala, specific deficit in vmPFC, functional connectivity between the two, etc.

Dysregulated fear circuitry might also lead to fear responses to benign stimuli that resemble trauma cues. While the mechanism of fear generalization in general is adaptive and helps to respond to set of stimuli that might have the same consequence (e.g., big wild cats are dangerous, whether it is a lion or a leopard), excessive generalization can lead to pathologic anxiety. Generalization is commonly tested with generalization gradients, where healthy subjects demonstrate a weakening of the fear response to “safer” stimuli [23], while anxiety patients show a less steep degradation, i.e. more fear response to the same stimuli [24–26]. Preliminary results suggest that overgeneralization pattern is also present in PTSD [3, 27–30], and compromised fear neurocircuitry might underlie such overgeneralization [30–32]. Specifically, a decreased connectivity between the basolateral amygdala (BLA) and the mPFC, might play a role as low synchrony between these regions was associated with fear generalization [33]. Indeed, decreased amygdala-vmPFC connectivity has been interpreted as evidence for impaired safety learning in PTSD [29].

2. Context processing circuitry

In the past decade, our laboratory [34], as well as others [35–38], have reported abnormalities in context processing function in PTSD [3]. Context is a set of internal (cognitive and hormonal) and external (environmental and social) factors present during a specific event and affect how the event is perceived and remembered [39, 40]. It is essential for deriving situationally informed meaning from the stimuli around us, thus maintaining cognitive and behavioral flexibility. The hippocampus has been the focus of neurobiological studies on contextual processing [41], as well as its connection with mPFC [40]. Of direct relevance to PTSD, hippocampus-mPFC based contextual processing enables contextual regulation of fear associative learning and retrieval discussed above [40]. Specifically, contextual processing is required to support adaptive fear extinction and renewal, and human research has confirmed the role of the hippocampus-mPFC-amygdala circuitry in both contextual conditioning [42–44] and regulation [45, 46] of fear.

Dysfunction in the contextual processing circuit may lead to inflexible, rigid and inappropriate behavioral responses, contributing to development of various PTSD symptoms [3, 39, 40]. For example, the re-experiencing of the traumatic event and the tendency to avoid reminders of that event may reflect impaired contextual processing, which causes extinguished fear to inappropriately renew in a safe context. A few studies have specifically addressed contextual processing in PTSD, demonstrating that PTSD patients were impaired on contextual processing dependent function – extinction recall, a deficit associated with lesser hippocampal and mPFC activity and greater dACC activity [16]. PTSD patients also showed dACC hyperactivity and vmPFC hypoactivity specifically during contextual processing period [35]. Our laboratory replicated extinction recall findings in vmPFC in PTSD, and further extended it by showing impairment in another context dependent function – fear renewal [34]. Diminished fear renewal was also associated with hypoactive vmPFC and hippocampus, and demonstrated that the deficit in PTSD was not limited to extinction

recall only, but encompassed other context-dependent functions. Recent papers have replicated the impaired contextual learning in PTSD [37], and highlighted the key role of the hippocampus in the etiology of this disorder [38]. Of note, reduced contextual processing was also shown during a non-fear based task, further supporting general contextual processing deficit in PTSD [47].

3. Emotion regulation circuitry

In addition to changes in fear associated learning and context processing circuitry, abnormalities in one's ability to control and modulate emotions can also contribute to PTSD pathophysiology [3]. Emotional regulation is a critical component of an adaptive behavior and healthy well-being, and the most well-studied strategy of such regulation in the cognitive domain is reappraisal, where one reinterprets the emotional significance of an event [48, 49]. Other cognitive regulation strategies exist, but clearly require further research, including re-allocation of attention away from emotional stimuli, suppression of expression of an emotion, distraction [50], and distancing, i.e. taking a third-person perspective [51]. Reappraisal of negative stimuli has been associated with increased activation of dorsolateral, ventrolateral and dorsomedial prefrontal cortex (PFC), and decreased activation of medial orbitofrontal cortex and the amygdala [52] – findings that were confirmed by a recent meta-analysis [53]. Accordingly, a model had been proposed whereby regions of the PFC maintain cognitive control by selecting stimulus interpretation, whereas decreased amygdala activation reflects the top-down modulation of the emotional salience of the stimuli [53–55]. It is important to highlight that "emotion regulation" is not a single unified circuitry but rather a set of circuits that share common and also unique regions, depending on the specific function that is performed. For example, redirecting attention might involve dorsal parietal (unique) and dorsolateral PFC (common) regions, while reappraisal might involve dorsolateral PFC (common) and dorsomedial PFC (unique) regions [52].

Diminished ability to properly regulate emotions might be contributing to symptomatology of PTSD, as well as other psychiatric disorders [56]. For example, it has been reported that PTSD symptoms are associated with greater use of suppression and less use of reappraisal to down-regulate emotions [57]. In a study that examined volitional regulation of emotional response to negative pictures in PTSD, all trauma- exposed subjects demonstrated diminished down-regulation of emotional response [58]. However, in a more recent study of veterans with combat-related PTSD, we reported lower dorsolateral PFC activation specifically in PTSD patients during down-regulation of negative affect, as compared to trauma-exposed controls [59]. Similarly, deficits in other executive function (e.g., attention, inhibitory function) that are often seen in PTSD also relate to dysfunction within dorsal prefrontal networks and are exacerbated within emotional or trauma-related context [60]. The notion that prefrontal deficits may contribute to the development or maintenance of PTSD is also consistent with the more general idea of imbalanced interaction between the dorsal and ventral cortical systems that can contribute to psychiatric disorders [61].

4. Circuit-based treatments

The identification of the neural circuits that might be dysregulated in PTSD lays the groundwork for treatment development that aims to target these circuits. The comprehensive review of all treatment options for PTSD is beyond the scope of this manuscript, thus in the following paragraphs we focus on selected treatments and the neural circuits they might be targeting. The existing evidence-based first line treatments for PTSD include exposure therapy, as well as two selective serotonin reuptake inhibitors (SSRIs): sertraline and paroxetine [62]. Both sertraline and paroxetine had been FDA approved for PTSD treatment [63], however, they were developed initially as “me too” products, and while some hypothetical links to specific circuits can be proposed (see below), there are no sufficient empirical data to link their efficacy to a specific neural circuitry. Similarly, the development of exposure therapy treatments was not neurocircuitry-based originally, but its effectiveness can be more readily traced to its effects within specific neural circuits. Insofar fear extinction is an active component of exposure-based therapies, these therapies are likely active in the fear circuitry, employing mechanisms of fear inhibition that might enhance “fear off” circuits within amygdala, or may be accompanied by enhanced inhibitory control of the PFC over the amygdala [6]. Similarly, exposure treatment might be also decreasing overgeneralized fear by reducing fear reactivity to stimuli resembling features of the traumatic encounter [28, 30].

Among strategies targeting fear circuits, pharmacological interventions with compounds like d-cycloserine, a partial NMDA agonist, in combination with exposure therapy, have been shown to facilitate fear extinction in phobic patients [64]. The rational behind the use of d-cycloserine and other glutamatergic modulators in conjunction with exposure therapy is that enhancing glutamatergic signal in the PFC could theoretically facilitate extinction, however, further work is required to demonstrate their efficacy in PTSD [65, 66]. Interestingly, it was recently suggested that the cannabinoid system might serve as a novel promising target for facilitating extinction learning and extinction recall – an idea that warrants further development and clinical testing [67]. Another avenue targeting fear-learning circuits, taken by some investigators is to try and prevent fear learning or consolidation of fear memory in the first place by the administration of agents, such as beta-blocker propranolol [68] or hydrocortisone [69] in the immediate aftermath of trauma. While initial reports had been promising, some subsequent studies failed to replicate positive effects [e.g. 70], suggesting that further research is required. Finally, transcarnial magnetic stimulation (TMS) was also suggested to be potentially an effective and well-tolerated treatment [71], although larger studies with well controlled comparison groups are clearly required.

Targeting the context processing circuitry and specifically, mPFC and hippocampal functions, is another potential therapeutic avenue in PTSD. Glutamatergic modulators like ketamine (NMDA antagonist that increases glutamate release) might affect prefrontal function more generally, improving contextual processing. While the efficacy of ketamine for treatment of depression has been reported [72], its efficacy in PTSD treatment is currently being examined. More specific to hippocampus, behavioral exercise or other manipulations aimed at increasing BDNF-TrkB signaling or hippocampal neurogenesis might improve pattern separation and hippocampal function and ultimately, improve

contextual processing and help to modulate fear responses in PTSD [30]. Interestingly, if adult neurogenesis in the dentate gyrus enhances contextual processing in hippocampus by improving one's ability to separate harm from safety [73, 74], this might explain at least partially the therapeutic efficacy of antidepressants shown to enhance hippocampal neurogenesis [75], in treatment of PTSD symptoms. Conducting extinction training across different contexts [e.g., 76], is another potential strategy to enhance contextual processing and hippocampo-prefrontal function, with some data suggesting that sleep quality might be an important variable in this process [77]. Finally, recent reports on the efficacy of mindfulness-based therapies suggest that focusing on immediate physiological and spatial context might be beneficial in "exercising" context awareness [78].

Lastly, different psychotherapies (from prolonged exposure, through cognitive therapy and to mindfulness-based therapies) contain, to a varying degree, an "emotional regulation", "reframing" or "taking perspective" components, which recruit emotion regulation neurocircuitry. For example, in *cognitive therapy*, conscious, volitional effort is used to reappraise situation [79]. Similarly, *attentional control* that re-directs attention (in mindfulness-based therapies), also engages executive function/emotional regulation constructs [61]. Mindfulness therapies that focus on somatic cues (e.g., breathing and heart rate) on the other hand, might be engaging contextual circuitry that integrates somatic cues into internal context representation.

Interestingly, it is possible that some of the pharmacological approaches also modify emotion regulation neurocircuitry. Ketamine enhancement of glutamate signal in PFC could affect prefrontal executive function, and MacNamara et al. have recently reported the neural correlates of pharmacological treatment with SSRIs [80]. They showed that treatment with the SSRI, paroxetine, increased activation of dorsolateral PFC and supplementary motor area during a reappraisal task. It was also shown that patients with less activation of prefrontal regions implicated in emotion regulation would benefit more from this first-line treatment for PTSD [80]. While these findings are preliminary and require further confirmation, they suggest that at least part of the treatment mechanism of SSRIs is mediated by changes in the emotion regulation circuitry. Finally, it was suggested that in addition to targeting explicit (volitional) emotion regulation, treatments should also address implicit (automatic) forms of regulation [81]. Such implicit processes are believed to be engaged automatically without explicit volitional effort, they do not require instructions, effort or awareness, and were proposed to be critical for patients' well-being in everyday life [81].

Conclusions

The last two decades of affective neuroscience research have yielded important information concerning the structure and function of neural circuits in PTSD. Findings often demonstrate heightened responsivity of amygdala, dACC and insula, diminished responsivity of mPFC, as well as impaired hippocampal function and possibly deficits in cortical regions responsible for executive function and emotional regulation. Functionally, these findings can be segregated to fear circuitry, context-processing circuitry and executive function/emotion regulation circuitry (Table 1). This is not to say that aberrations in other networks might not exist (reward circuitry [82], for example); however, to date, these data are limited and it has

not been shown that these abnormalities can account for key aspects of PTSD. Thus, more research is needed to support their role in the development of PTSD.

Many other key questions await further study. For instance, it is unknown whether the described changes are preexisting risk factors or they are markers of the disorder itself; longitudinal studies will be required to address this question [83]. Similarly, the heterogeneity of PTSD symptomatology raises the question whether different pathophysiological processes are contributing to “subgroups” within PTSD, or whether PTSD with and without comorbid disorders have different underlying pathophysiology [2].

Understanding the neural mechanisms of PTSD, have been already instrumental in understanding key mechanism involved in therapeutic efficacy, and will be essential for the development of new therapeutic avenues. The use of d-cycloserine or endocannabinoids to enhance extinction training, or the use of ketamine or novel psychotherapeutic approaches to enhance prefrontal function, or the development of strategies to improve adult neurogenesis and contextual processing in hippocampus – all were assisted by improved understanding of specific neural circuits involvement in PTSD. Future studies can take advantage of novel circuit-based approaches (e.g., genetic and viral tools, optogenetics and advanced in-vivo imaging techniques) to characterize cellular and molecular mechanisms and to address the role of both local microcircuits and long-range projection pathways within defined neurocircuits that are dysregulated in PTSD [84]. Future studies could also test how environmental factors such as childhood background and trauma load interact with the discussed neurocircuits, to examine questions of vulnerability and resilience to trauma exposure [6].

Lastly, in the future, targeted treatments will aim to alleviate PTSD symptoms through the modulation of specific dysregulated circuit activity, for instance, by enhancing extinction learning or improving contextualization of fear memories. Better understanding of the specific circuits and their contribution to PTSD pathophysiology – for example, what specific processes within hippocampus (pattern separation vs. pattern completion vs. both), and what subfields of hippocampus are involved, will better define targets for behavioral and pharmacological interventions. Further, it will promote personalized treatment approaches, allow preventive strategies development, and ultimately improve treatment matching and response rate by incorporating this information into pre- and post-treatment assessments.

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Table 1

Summary of reviewed circuit dysregulation in PTSD

	Amy	Insula	dACC	Hpc	vmPFC	dlPFC	vlPFC	Conn
Fear learning	↑ [5, 15–17]		↑ [18]		↓ [3, 5, 15, 17, 18]			
Threat detection	↑ [3, 17]	↑ [3, 18]	↑ [3, 35]					↑ [3, 14]
Emotional regulation	↑ [52] (sec)				↓ [3]	↓ [3, 59]	↓ [3]	
Context Processing	↑ [3, 34] (sec)	↑ [3, 34] (sec)	↑ [3, 16, 34, 35] (sec)	↓ [3, 16, 34, 40]	↓ [3, 16, 34, 35, 40]			↓ [3, 14]

Note: Arrows indicate greater or less activation in PTSD compared to healthy controls. Amy = Amygdala; dACC = dorsal anterior cingulate; Hpc = Hippocampus; vmPFC, dlPFC, vlPFC = ventromedial, dorsolateral, ventrolateral prefrontal cortex; Conn = Connectivity; sec = secondary (accompanied by smaller arrows).