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Exploring How mPFC and Hippocampus Enhance Generalization in PTSD-like Behavior Model

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Abstract. Post Traumatic Stress Disorder (PTSD) patients often show excessive fear generalization to harmless cues. Animal model studies illustrate that, hippocampus and medial prefrontal cortex (mPFC) play important roles in the process of discrimination and generalization of fear memories: as the hippocampus maintain the accuracy of memory through pattern separation and neurogenic mechanisms, mPFC regulates the separation of fear and safe stimuli via the neuroplasticity mechanism mediated by excitatory NMDA receptors. mPFC and hippocampus coordinate emotional valence through the hippocampus-amygdala circuit, achieving the remote updating of memories. If the reconsolidation process of the hippocampus of mPFC's regulation function are unbalanced, the fear memory would remain coarse cortical representation, which increases memory generalization. Understanding these mechanisms would be useful to help conduct the targeted intervention of PTSD, such as promoting the forgetting of the traumatic memories through enhancing the neurogenesis in the hippocampus, and improving the recognition of fear cues through regulating mPFC networks, which could help undermine the symptom of excessive generalization.

Keywords: PTSD, Hippocampus, medial prefrontal cortex, Memory generalization, adult neurogenesis

1. Introduction

Post-Traumatic Stress Disorder (PTSD) is a mental disorder characterized by repeated recollection of traumatic events and high levels of stress [1-3]. PTSD patients often exhibit inappropriate fear response to similar traumatic scenes or stimuli, known as fear overgeneralization [4-9]. This means they could hardly distinguish safe and fear contexts, often mistaking neutral stimuli for threats [1,9,10]. According to research, the hippocampus of PTSD patients often shrinks and shows relations with memory generalization [11]; The function of prefrontal cortex (especially the medial prefrontal cortex and anterior cingulate cortex) is often impaired. These findings indicates that the hippocampus and mPFC plays crucial roles in PTSD memory circuits. Animals models, such as situational fear conditions and social frustration stress, simulates the process of traumatic stress and feat generalization, laying the foundation for the studying related to the molecular and neural mechanisms of the process [1-4,8,12]. Currently, the hippocampus is considered as responsible to the encoding of new environmental information pattern separation; while mPFC is in charge of

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integrating information and induce appropriate fear response [6-9,10,13,14]. They form circuits with emotional brain regions such as the amygdala, collectively determine the expression of fear memories. However, the molecular and circuit mechanisms by which mPFC hippocampus specifically affects memory generalization are still unclear and require further research [1,2].

2. Hippocampus: pattern separation and neurogenesis

The hippocampus, especially dentate gyrus (DG)-CA3 circuit, plays a crucial role in contextual encoding and pattern separation. Through distinguishing and encoding similar environments, the hippocampus allows animals to distinguish traumatic and safe contexts, preventing fear generalization. According to research, hippocampal disorders and the decline of neurogenesis would undermine this distinguishing capability, increasing memory interference and generalization [9,10,13]. According to Besnard et al, adult-born neurons maintain the fidelity of contextual memory details through enhancing pattern separation [4]. Correspondingly, according to Bo Lei et al, hippocampal reconsolidation is needed for recalling remote memories: temporarily suppressing hippocampal (dorsal DG) activities, could prevent the recovery of context-specific fear, leading to sustained fear responses in generalized contexts. In contrast, normal hippocampal reactivation enables “de-generalization”, which restores memory precision [15]. This demonstrates hippocampus reconstructs a new engram during the retrieval of traumatic memories (through neurogenesis) to integrate new information, achieving the update of the memory. In addition, the hippocampus has two memory engram subpopulations defined by different gene expression pathways: Neurons related to Fos could promote memory generalization, while neurons related to Npas4 could enhance memory recognition through local inhibitory network [16]. Overall, the hippocampus improves memory accuracy and suppresses the overgeneralization of traumatic memory through pattern separation and diverse engram mechanisms mediated by newborn neurons [4,7-10,13,14,16,17].

3. Mpfc: recognition of fear memories and generalization controlling

The medial prefrontal cortex (mPFC, including the anterior cingulate cortex (ACC) and the medial prefrontal IL/presympathetic PL region), plays a “gate” role in the regulation of fear and safety information [2,6,7,14]. According to research, IL damage will enhance the generalization of fear contextual memories, interfering the discrimination of safe and dangerous situations; while enhancing activities of PL area would reinforce the expression of fear [6,7,18]. The mPFC has close connections with the hippocampus and the amygdala, playing a vital role in the integration of conditioned fear and discrimination learning [2,7,19]. At the perspective of molecular, mPFC synaptic plasticity is indispensable to the accurate encoding of fear memories [4,20]. According to the newest research, Ca^{2+} signal, modulated by NMDA receptors of excitatory neurons in mPFC, help activate CREB and corresponding acetyltransferase (CBP) pathways, which further help consolidate specific fear memory representations and attenuating generalization responses to harmless stimuli [4,21]. That is to say, the NMDA/CREB pathway in mPFC are helpful for undermining the fear responses to safety cues, thereby achieving the accurate identification of fear memories. Therefore, when mPFC function is insufficient or synaptic plasticity is damaged (such as reduced prefrontal blood flow or metabolism), leading to decreasing abilities to distinguish fear, and increasing generalization [3,14]. To sum up, the mPFC prevents excessive fear responses to safe contexts by regulating excitatory–inhibitory balance and long-term synaptic plasticity [14,20,22].

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4. Collective mechanism of mpfc-hippocampus-amygdala

The formation and expression of fear memories are depended on multiple brain regions, including mPFC, hippocampus, and amygdala [1,2]. According to Bo Lei et al, mPFC can not only form engrams for itself, but could also simultaneously modulate the activities of the hippocampus and BLA (basal amygdala) through projection [2,7,15]. To be specific, during the retrieval of a newly formed engram by the hippocampus, mPFC regulate the activities of the amygdala and the hippocampus through projection, integrating contextual information and emotional valence (encoded by the amygdala) [2,7,19]. Based on experimental evidence, memories' "de-generalization" would be disrupted if the simultaneous activation of mPFC and the hippocampus-amygdala circuit is interrupted during remote memory retrieval stage, leading to wide generalization of fear memories [7,8,13,15]. Similarly, human and animal research illustrate that ACC (part of mPFC)'s projection to vHPC could directly regulate fear generalization: Inhibiting ACC or vHPC neuronal activities using chemical or optogenetics methods could significantly decrease generalization of remote conditioned fear memories in similar contexts; In contrast, activate this pathway could enhance the generalization of early memories [7,23]. These results demonstrate that, the activity state of the mPFC-hippocampal circuit determines the accuracy of fear memory [2,7,19]. If mPFC-hippocampus-BLA are coordinated and consistent, memory will return to a specific context; On the contrary, a broken network leads to sustained erroneous generalization [8,9,23].

5. Causal chain integration

In summary, PTSD-like generalization could be seen as a result of a multi-level mechanism synergy: traumatic learning is initially encoded by the hippocampus into the memory system, and then mPFC stores contextual clues [2,13]; During remote recall, the hippocampus must be reactivated to build new engrams, integrating current context and old traumatic memories. This process of reconsolidation is depended on the protein synthesis and the regeneration of hippocampal neurons. If the hippocampus is disrupted during re-engagement, the memory is fixed at the cortical level, leading to the generalization of fear towards similar situations [7,8]. mPFC functions in two ways during this process: on one hand, its excitatory plasticity could ensure the specific encoding of memories (NMDAR/CREB mediated synaptic remodeling promotes inhibition of safe stimuli) [20]; on the other hand, its projection pathways with the hippocampus and the amygdala help integrate emotional and spatial information [7,23,24]. When mPFC functions abnormally, (such as abnormal inhibitory neuron activity or decreased circuit inhibition ability), this balance is disrupted, which amplifies the erroneous generalization signal [14,17,20]. Therefore, from memory encoding to reconsolidation, the hippocampal pattern separation and mPFC's discriminative regulation together determine whether the memory is accurate recalled or overgeneralized [6,10,13].

6. Prospects and therapeutic potential

Based on the above mechanism, new research and treatment directions can be proposed. First, enhancing hippocampal neurogenesis or promoting "forgetting" of traumatic memory is a potential strategy: for example, interventions such as NMDA receptor antagonist memantine or exercise can promote the formation of hippocampal new neurons and accelerate the declining of old fear memories; In the social frustration stress (PTSD like model), the treatment with memantine significantly weakened the avoidance memory of aggressors and anxious behavior [9,12,13]. Second, drugs or neural regulatory techniques targeting the synaptic plasticity of mPFC can

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reinforce fear discrimination ability, such as increasing mPFC activity through transcranial magnetic stimulation and using small molecules with positive NMDA/CREB signaling to assist memory reconsolidation [14,24,25]. Third, specific circuit intervention strategies are worth to be explored. ACC–vHPC circuit is an important pathway that is in charge for regulating memory generalization [23,26], and "switching off" this pathway can avoid overgeneralization, suggesting that this circuit may become a target. Furthermore, gender difference, time scales (short-term vs. long term memory), and other factors on the generalization mechanism should also be considered [4,7,23]. In conclusion, the understanding of hippocampal-mPFC interaction mechanism provides electrophysiological, molecular, and behavioral intervention targets for PTSD, such as combining behavioral therapy with memory consolidation interventions (such as drug interventions during recall), which may be more effective in correcting generalized patterns of traumatic memory.

7. Conclusion

Hippocampus and mPFC regulate the accuracy of fear memory through their respective and collective neural mechanisms [1,2]. The hippocampus relies on pattern separation and new engrams (regulated by neurogenesis) to maintain contextual specificity of memory [4,16], while mPFC relies on synaptic plasticity (NMDAR/CREB/CBP pathway) to reduce fear responses to safe stimuli [10,13,20,24]. The two coordinate with each other through multiple pathways, enabling memory to generalize during recall; On the contrary, once the hippocampus or mPFC functions abnormally, fear memory will remain generalized for a long time [7,8,19,20]. Deeper understandings about these pathological causal chains not only demonstrates the fundamental principles of PTSD memory generalization, but also paves the way for future therapy design, such as reducing traumatic memory generalization by promoting neurogenesis or regulating prefrontal function [4,9,12,23]. The research prospects in this field are broad, and it is expected to provide more accurate diagnostic indicators and personalized intervention strategies for PTSD patients.

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