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Activity-dependent signaling: influence on plasticity in circuits controlling fear-related behavior

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Fear regulation is impaired in anxiety and trauma-related disorders. Patients experience heightened fear expression and reduced ability to extinguish fear memories. Because fear regulation is abnormal in these disorders and extinction recapitulates current treatment strategies, understanding the underlying mechanisms is vital for developing new treatments. This is critical because although extinction-based exposure therapy is a mainstay of treatment, relapse is common. We examine recent findings describing changes in network activity and functional connectivity within limbic circuits during fear regulation, and explore how activity-dependent signaling contributes to the neural activity patterns that control fear and anxiety. We review the role of the prototypical activity-dependent molecule, brain-derived neurotrophic factor (BDNF), whose signaling has been critically linked to regulation of fear behavior.

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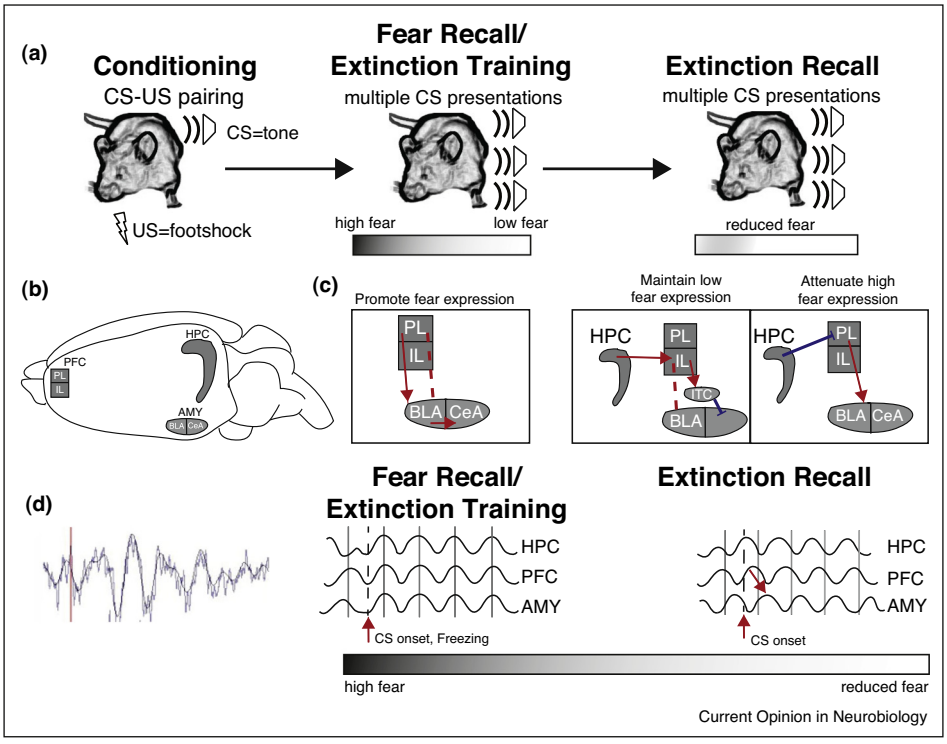
Introduction

Anxiety disorders are common, with an up to 28% lifetime prevalence rate [1]. Post-traumatic stress disorder (PTSD) is a specific anxiety disorder that develops following trauma exposure. Hallmarks of PTSD include re-living the trauma, avoidance of situations resembling the event and hyperarousal. Deficits in fear regulation, including enhanced reactivity to cues linked with the trauma and the inability to reduce those fear responses, are common in PTSD [2]. Given that many people are exposed to trauma while only a small proportion develop PTSD, understanding the biological risk factors is important [3••]. To understand and better treat fear-related disorders, identifying the processes occurring during association of contextual and sensory cues with trauma is also critical [4,5]. Importantly, this learning can be modeled in the laboratory with Pavlovian fear-conditioning, a paradigm in which an aversive unconditioned stimulus (US) footshock is paired with a neutral conditioned stimulus (CS) (Figure 1a). The learned association is evaluated in rodents by measuring the time spent freezing, a behavior indicating high levels of fear. Freezing behavior is used to assess fear learning, recall and extinction. During extinction training, animals are re-exposed to the CS and/or conditioning context in the absence of the US. Repeated exposure results in decreased freezing, indicating successful extinction, that is learning that the CS or context no longer predicts the US. Specificity for the CS–US association is probed by exposing an animal to the original CS (CS+) or a CS never paired with the US (CS−). Animals showing heightened fear towards both CS+ and CS− demonstrate non-specific, or generalized fear. Fear acquisition, recall and extinction represent distinct learning events, which are linked to specific patterns of neural activity and functional connectivity between brain regions in the fear circuitry. We discuss how molecules that sense and respond to changes in neural activity are in a powerful position to control these processes. We specifically focus on the prototypical activity-dependent molecule, brain-derived neurotrophic factor (BDNF), which has been extensively implicated in regulation of fear and anxiety behavior.

Circuit and network activity in limbic regions influences fear and anxiety behavior

Studies in animals and humans suggest that changes in plasticity underlie function in amygdala (AMY)–prefrontal cortex (PFC)–hippocampus (HPC) fear circuits [3••,6] (Figure 1b). AMY is the fear acquisition and expression hub, while PFC critically controls fear inhibition and extinction. Within PFC, regional differences in fear regulation between infralimbic (IL) and prelimbic (PL) subdivisions are noted. Specifically, IL activation enhances extinction, while PL promotes fear expression [7•,8,9]. HPC modulates AMY and PFC activity, and provides contextual information about the fear memory. Regulation of fear behavior depends on coordinated activity and communication between these regions. As PFC plasticity in IL and PL is critical for fear regulation, communication between these regions and AMY has been extensively investigated (Figure 1c). Research suggests that the opposing effects of IL and PL are mediated by differences in their respective connections with AMY [7•]. Specifically, IL projects to the intercalated cell masses (ITCs) and lateral division of the central nucleus,

Figure 1



Behavioral fear paradigms and their anatomical and physiological correlates. **(a)** Behavioral paradigms for fear learning and memory. Rodents learn to associate a neutral tone (conditioned stimulus, CS) with an aversive outcome, a footshock (unconditioned stimulus, US). Learning for this association is measured by cessation of movement (freezing). Memory for the association is measured at a later time point during which the CS is presented in the absence of the US. During the fear recall trial, the animal expresses high freezing/fear, displaying its memory for the CS–US pairing. As extinction trials (CS exposure without the US) progress, the animal learns that the CS no longer predicts the US, and freezing decreases. Memory for extinction can be tested in a subsequent session by assessing freezing to the CS during an extinction recall session. **(b)** Structural representation of the areas important in fear learning. The hippocampus (HPC), prefrontal cortex (PFC), and amygdala (AMY) are the main interconnected regions of the fear circuit. The AMY regions depicted include basolateral (BLA), central nucleus (CeA) and the intercalcated cells (ITCs). PFC is divided into prelimbic (PL) and infralimbic (IL) subdivisions. **(c)** Circuits active during extinction learning and extinction recall. During states of high fear during the fear recall/extinction training session PL activates BLA neurons, leading to excitatory output from CeA and fear expression. Activation of 2 pathways inhibits fear expression during extinction recall. To inhibit fear expression, HPC activates IL, which projects to the GABAergic ITC neurons and inhibits fear output from CeA. To decrease activity of the extinction fear expression circuit, the HPC inhibits PL, leading to an indirect decrease of CeA output. **(d)** The physiological activity correlated with fear memory and learning. Left, an example of a raw LFP trace with data filtered between 1 and 12 Hz to display the increase in theta activity following freezing behavior. During states of high fear theta frequency activity is synchronized across the fear circuit. During extinction recall, there is less theta synchrony in response to the CS. In addition, theta phase activity in PFC leads the AMY, which is hypothesized to be a signal of learned safety (see text).

which contain GABAergic neurons that inhibit output neurons of central amygdala (CeA). Alternatively, PL promotes fear by activating basolateral amygdala (BLA) neurons. The BLA stores the CS–US association, and BLA neurons project to and excite CeA. IL and PL also have reciprocal connections with AMY and HPC that modulate fear expression. Recent studies combining retrograde tracer techniques with immediate early gene activation in discrete projections from BLA to HPC and PFC provided new insight about circuit connectivity during fear recall and extinction [10•,11]. Specifically, these findings showed that a subpopulation of BLA to PL projection neurons become active during states of high fear, while BLA to IL projections are selectively recruited during extinction. Supporting studies demonstrated that BLA cells projecting to PL exhibit firing patterns induced by plasticity in conditioned mice, while BLA-IL cells show these changes only following extinction [10•]. These findings support the idea that cellular plasticity is required for interregional communication that regulates both fear acquisition and its extinction.

New technologies, including optogenetics, now allow researchers to directly activate or inhibit cell type specific populations, and such studies manipulating AMY and PFC cells have increased our understanding of mechanisms controlling fear regulation [10•,12,13,14••,15]. Investigations into the role of interneurons highlighted