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Neuroscience of fear extinction: Implications for assessment and treatment of fear-based and anxiety related disorders

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ABSTRACT

Current exposure-based therapies aimed to reduce pathological fear and anxiety are now amongst the most effective interventions for trauma and anxiety related disorders. Nevertheless, they can be further improved to enhance initial and long-term outcomes. It is now widely accepted that a greater understanding of the neurobiological mechanisms of fear extinction is needed to further develop and identify novel effective targeted treatments as well as prevention strategies for fear-based and anxiety-related disorders. Guided by elegant mechanistic, cellular, and molecular preclinical reports, data from imaging studies are beginning to shape our understanding of how fear is quelled in the human brain. In this article, we briefly review the neural circuits underlying fear extinction in rodents and healthy humans. We then review how these circuits may fail to extinguish fear in patients with anxiety disorders. We end with a discussion examining how fear extinction research may lead to significant advances of current therapeutics for anxiety disorders.

Why fear extinction?

From the viewpoint of basic neuroscience, understanding how our brains learn to fear and how not to fear is an intriguing question. While such a fascination may have been the impetus for the initial wave of preclinical studies conducted in this domain, the rapid advancement of neuroimaging tools and their implementation in studying the psychopathology of anxiety disorders has generated a new translational research approach that merges basic neuroscience and clinical data. This merger has been a work-in-progress over the past decade and thus far has been helpful in advancing our understanding of how fear memories are formed and maintained in the human brain, as well as how such fear memories may be inappropriately expressed and contribute to underlying psychopathology in patients with anxiety disorders.

Pavlovian fear conditioning is one such experimental paradigm that allows for a translational and reverse-translational approach. In this paradigm, subjects learn to form associations between simple cues, such as a black square presented along with a mild electric shock delivered to the fingers of the subject. Subsequent presentations of the black square paired with the more aversive shock can elicit a number of conditioned responses including changes in heart rate and elevation in skin conductance responding. This phase of the experiment is referred to as the fear acquisition phase, as the subject begins to associate the biologically relevant shock with the originally benign square. Repeated presentations of the now conditioned black square (conditioned CS, CS+) without any unconditioned stimuli (US, the electric shock) lead to the gradual diminution, or extinction, of the conditioned response. This is referred to as within-session extinction learning. The memory of this extinction learning can be assessed after a delay (often 24 h later) in a phase referred to as the extinction retention test (between-session extinction). The expression of this extinction memory can be manipulated and gated by varying the context in which fear extinction is first learned and subsequently tested. The context dependent nature of extinction is critical to modulating the expression or inhibition of fear responses.

This model of Pavlovian fear conditioning presents several advantages to study the psychopathology of anxiety disorders. A key feature of some anxiety disorders, and posttraumatic stress disorder (PTSD) in particular, is a failure to appropriately inhibit, or extinguish, fear (Hermans, Craske, Mineka, & Lovibond, 2006; Milad, Rauch, Pitman, & Quirk, 2006; Pitman, Shin, & Rauch,

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2001). Individuals with PTSD or phobic anxiety disorders, such as panic disorder (PD), agoraphobia and social anxiety disorder (SAD), avoid fear-provoking situations and stimuli, or endure them by employing a range of different "safety behaviors" that are designed to protect the individual from harm or negative feared outcomes (Lovibond, Saunders, Weidemann, & Mitchell, 2008). Avoidance and the use of safety behaviors, therefore, prevent patients from challenging unrealistic beliefs and so prevent fear extinction (Lovibond, Mitchell, Minard, Brady, & Menzies, 2009). Hence, the fear extinction model provides a direct measure of what is widely accepted to be a central underlying dysfunction across phobic anxiety disorders and PTSD. Moreover, exposure therapy is based on and parallels an extinction procedure used in animal studies of fear inhibition. In addition to potentially detecting the neural basis for the underlying dysfunction in anxiety disorders, extinction paradigms can also be used as a valid model of the most effective psychological treatment for anxiety disorders and PTSD. Data examining potential differences in fear extinction processes across the anxiety disorders are lacking, and potential areas of overlap and differences between the different disorders have yet to be fully researched. For example, whereas generalized anxiety disorders (GAD) are principally characterized by worry and a generalized nervousness rather than cue-based phobic anxiety, PD with agoraphobia is more clearly a fear-based disorder (Breier, Charney, & Heninger, 1986). It remains unknown if differences in the neurobiology of fear extinction processes are universally present or may underlie such differences in phenomenology across all the anxiety disorders.

Comparisons of animal studies with human neuroimaging studies suggest considerable similarity between the neural structures involved in extinction in the rodent and in the human, highlighting another advantage of the fear extinction model (Delgado, Nearing, Ledoux, & Phelps, 2008). The cross-species validity of the extinction model permits the use of rodents to address questions that are not initially feasible to study in human subjects, while maintaining confidence that such findings can ultimately be translated to the affected human population. For example, animal studies allow researchers to test the effects of novel drugs on extinction and subsequent relapse, as well as the associated neurobiological effects of such drugs on underlying fear neurocircuitry.

Neural circuits mediating fear acquisition and its extinction

The neurobiology of fear acquisition is well characterized in rodents and humans (Maren & Quirk, 2004). Briefly, it is widely accepted that the basolateral complex of the amygdala is the main neural structure in which information about the conditioned and unconditioned stimuli converge (Ledoux, 2000). There is also evidence from rodent studies that the prelimbic division of the medial prefrontal cortex is involved in regulating the expression of learned fear (Burgos-Robles, Vidal-Gonzalez, & Quirk, 2009; Burgos-Robles, Vidal-Gonzalez, Santini, & Quirk, 2007; Corcoran & Quirk, 2007). In addition, it has been shown that the central amygdala is a key component in the circuitry devoted to fear acquisition and expression (Duvarci & Pare, 2014). The centromedial subdivision receives inhibitory inputs from other subnuclei of the amygdala including the lateral central amygdala subdivision that gate the expression of fear (Haubensak et al., 2010). Activation of this lateral subdivision of the amygdala is required for fear acquisition, while the basolateral amygdala along with the inhibitory interneurons (intercalated cells) are involved in the acquisition of fear extinction (Ciocchi et al., 2010).

Using functional magnetic resonance imaging (fMRI), it has been shown that humans show robust increases in activity in the amygdala and dorsal anterior cingulate (which appears to be functionally analogous to the rodent prelimbic cortex) during fear acquisition and expression (Knight, Smith, Cheng, Stein, & Helmstetter, 2004; Linnman, Rougemont-Bucking, Beucke, Zeffiro, & Milad, 2011; Milad, Quirk, et al., 2007; Phelps, Delgado, Nearing, & Ledoux, 2004).

Fear extinction, on the other hand, involves interactions between the infralimbic region of the medial prefrontal cortex, the basolateral complex of the amygdala, and the hippocampus (Milad & Quirk, 2012). It is proposed that when an extinguished cue is presented in the extinction training context, the hippocampus activates the infralimbic region, which in turn activates inhibitory interneurons in the basolateral amygdala that inhibit the output neurons in the central amygdala, thus preventing conditioned responding (Herry et al., 2010). In contrast, when the extinguished cue is presented in a context other than the extinction training context, the hippocampus does not activate the infralimbic cortex and central amygdala activity is not inhibited, thus conditioned responding returns (Quirk & Mueller, 2008).

Functional MRI has revealed remarkable preservation of this circuitry between rodents and humans (Milad & Quirk, 2012). Specifically, earlier fMRI studies demonstrated that the amygdala exhibits increased activation to the conditioned stimulus during early extinction training, and this activation decreases across extinction training (LaBar, Gatenby, Gore, Ledoux, & Phelps, 1998; Phelps et al., 2004). Subsequent studies have consistently demonstrated that extinction recall (which inhibits conditioned fear responding) is associated with increased activity in the ventromedial prefrontal cortex (vmPFC) (Kalisch et al., 2006; Milad, Wright, et al., 2007; Phelps et al., 2004), a structure that has been proposed to be the human homolog of the rat infralimbic cortex. Furthermore, it has been shown using structural MRI that extinction recall is positively correlated with the thickness of the vmPFC (Hartley, Fischl, & Phelps, 2011; Milad et al., 2005).

Several studies have also demonstrated evidence for increased hippocampal activity during extinction recall (Kalisch et al., 2006; Milad, Wright, et al., 2007). Furthermore, one study reported increased hippocampal and vmPFC activity during recall in the extinction context, but not in the original conditioning context (Milad, Wright, et al., 2007), supporting the idea that the hippocampus modulates the expression of the extinction memory depending on contextual information. Such data have clear clinical implications, demonstrating a role for effective hippocampal function and detection of context on effectively controlling fear expression in specific contexts. Collectively, there is much evidence suggesting that a distinct neural circuitry involving interactions between the amygdala, vmPFC, and hippocampus underlies the ability to extinguish fear, and that this circuitry has been preserved across evolution.

Is the functional integrity of the fear extinction network impaired across the anxiety disorders?

Structural and functional abnormalities of the brain regions mediating fear extinction has been reported across the anxiety disorders using an ample array of tasks. For example, in symptom provocation studies, it has been shown that blood flow in the medial frontal gyrus is reduced in PTSD participants compared to trauma-exposed controls when exposed to trauma reminders, and medial frontal gyrus blood flow was inversely correlated with changes in amygdala blood flow (Shin et al., 2004). Heightened amygdala (Rauch et al., 2000; Shin et al., 2005) and diminished vmPFC activity (Shin et al., 2005) have also been reported in subjects with PTSD while viewing fearful faces during fMRI, compared to trauma-exposed controls. Similar findings have been reported

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