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Review

From Pavlov to PTSD: The extinction of conditioned fear in rodents, humans, and anxiety disorders

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ABSTRACT

Nearly 100 years ago, Ivan Pavlov demonstrated that dogs could learn to use a neutral cue to predict a biologically relevant event: after repeated predictive pairings, Pavlov's dogs were conditioned to anticipate food at the sound of a bell, which caused them to salivate. Like sustenance, danger is biologically relevant, and neutral cues can take on great salience when they predict a threat to survival. In anxiety disorders such as posttraumatic stress disorder (PTSD), this type of conditioned fear fails to extinguish, and reminders of traumatic events can cause pathological conditioned fear responses for decades after danger has passed. In this review, we use fear conditioning and extinction studies to draw a direct line from Pavlov to PTSD and other anxiety disorders. We explain how rodent studies have informed neuroimaging studies of healthy humans and humans with PTSD. We describe several genes that have been linked to both PTSD and fear conditioning and extinction and explain how abnormalities in fear conditioning or extinction may reflect a general biomarker of anxiety disorders. Finally, we explore drug and neuromodulation treatments that may enhance therapeutic extinction in anxiety disorders.

1. Introduction

In his classical conditioning and extinction experiments, Ivan Pavlov rang a bell (the conditioned stimulus; CS), immediately before giving his dogs food (specifically meat powder, the unconditioned stimulus; US; Pavlov, 1927). On its own, the meat powder made the dogs salivate (the unconditioned response; UR). After repeating this predictive pairing several times, Pavlov's dogs began salivating to the mere sound of the bell—even when no meat powder was presented—making salivation the conditioned response (CR). The sound of the bell predicted something agreeable and biologically valuable: food. However, not all of Pavlov's USs were pleasant, and not all CRs conveyed his dogs' anticipation of something enjoyable. In addition to learning about nourishment sources, it is important for an organism to be able to predict threats to health and safety. For example, when Pavlov repeatedly paired the sound of a metronome (CS) with subsequent application of a small amount of sour-tasting diluted acid (US) onto a dog's tongue, the dog eventually learned the association. Henceforth, upon presentation of the CS alone, the dog exhibited what Pavlov called a "defensive reflex": it shook its head, salivated profusely, and moved its tongue as if to expel a toxic substance, even though no acid was there. A similar process was demonstrated with an 11-month-old child in Watson and Rayner's famous "Little Albert" experiments of 1920. Watson and Rayner paired Albert's touching of a white rat (CS) with a sudden fear-arousing noise (US) made by striking a steel bar behind him (Watson & Rayner, 2000). Upon subsequent presentations of the rat, Albert no longer exhibited his natural curiosity, but rather withdrew his hand. This learned response seemed to generalize to cotton balls, a Santa Claus mask, a brown bunny, and a black fur coat. The Little Albert experiment is an early precursor of what is now known as fear conditioning.

It is not known whether Little Albert subsequently experienced fear around rats and furry objects (if he survived into adulthood at all) or if he was healthy and well-adjusted (Harris, 2011). Of course, modern ethical standards would not allow such a

Abbreviations: 5-HTTLPR, serotonin transporter gene linked polymorphic region; BDNF, brain-derived neurotropic factor; BNST, bed nucleus of the stria terminalis; COMT, catechol-O-methyltransferase; CR, conditioned response; CS+ or CS, conditioned stimulus; CS−, never-conditioned stimulus; dACC, dorsal anterior cingulate cortex; DAT1, dopamine active transporter gene; DCS, D-cycloserine; DRD2, dopamine receptor D2 gene; EMG, electromyography; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; HRR, heart rate response; IED, improvised explosive device; NMDA, N-methyl-D-aspartate; NPSR1, neuropeptide S receptor; OCD, obsessive–compulsive disorder; PET, positron emission tomography; PTSD, posttraumatic stress disorder; rCMRglu, regional cerebral metabolic rate for glucose; SCR, skin conductance response; SRI, serotonin reuptake inhibitor; TMS, transcranial magnetic stimulation; TPH2, tryptophan hydroxylase-2; US, unconditioned stimulus; UR, unconditioned response; vmPFC, ventromedial prefrontal cortex.

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methodology. Still, it is likely that, after the experiment was over, Little Albert encountered other rats or other furry objects in the absence of a loud noise. Eventually, he should have learned that such objects no longer predicted a frightening clang, and his fear response should have declined. This process is known as fear extinction learning. When the CS no longer predicts the US, the conditioned fear response is extinguished.

How do these processes of fear conditioning and fear extinction work? Why is it that with very severe USs, some individuals are burdened by fear and anxiety for decades? The goal of this review is to examine the underlying mechanisms and neurocircuitry of fear conditioning and extinction, as well as to explore how these processes can inform our understanding of anxiety disorders such as posttraumatic stress disorder (PTSD). We will first discuss fear conditioning and extinction in rodents, and then in healthy humans. Finally, we'll discuss fear conditioning and extinction in individuals with PTSD and other anxiety disorders, with an emphasis on how extinction learning relates to treatment.

2. Fear conditioning in rodents

When rodents sense danger, one species-specific behavioral response is to freeze all movement in order to avoid detection by predators. Rodent fear conditioning and extinction studies typically use a foot shock as the US. The fear response is operationalized as the percentage of time a rodent spends engaging in freezing behavior. When a light or tone (CS) repeatedly predicts a foot shock (US) delivered through an electrified metal cage floor, rodents are conditioned to make a CS–US association. Thus, the presence of the CS subsequently triggers freezing, which becomes the CR. Furthermore, when a rodent experiences an aversive US such as shock in a certain context, subsequent re-exposure to that context can cause freezing behavior, even if the shock has not been paired with a discrete CS such as a light or tone. This type of Pavlovian fear conditioning is known as contextual fear conditioning (Rudy, Huff, & Matus-Amat, 2004). When a rodent experiences a sudden loud noise it will startle before freezing, but if that sudden loud noise occurs during the presentation of a danger-associated cue such as a CS or a conditioning context, the startle reflex will be larger. This is known as a fear-potentiated startle and is another commonly used CR (Davis, 2001, chap. 8). The fear-potentiated startle paradigm is advantageous for translational research because it is not species-specific.

Researchers can link conditioned behaviors such as freezing or fear-potentiated startle to brain activity or other fear-based physiological measures. With this simple fear conditioning model, the neurocircuitry of fear learning and extinction has been well delineated (reviewed in more detail in this issue and also Johnson, McGuire, Lazarus, & Palmer, 2012; LeDoux, 2000; Maren, 2001; Rudy, 2008). Here, we will briefly review the neurocircuitry involved in fear conditioning and extinction in rodents (see Fig. 1).

The sensory experiences of the CS and US are processed in the thalamus and somatosensory cortex, as are other sensory experiences. This information reaches the lateral amygdala via one of two routes. A "cortical pathway" relays detailed sensory information through the thalamus to the neocortex and hippocampus before integration and evaluation in the lateral amygdala. However, another pathway forgoes the neocortex in the service of reaction speed. This faster "subcortical pathway" projects a rudimentary sensory representation directly from thalamus to the lateral and central nuclei of the amygdala. The binding together of a conditioned CS–US association is supported by the lateral nucleus of the amygdala, which then projects to the central amygdala, triggering autonomic and behavioral responses such as freezing (Blair, Schafe, Bauer, Rodrigues, & LeDoux, 2001; Pitkanen, 2000) and fear-potentiated startle (Campeau & Davis, 1995). The amygdala is part of a broader neurocircuitry that supports and modulates this process.

Conditioning and extinction of rodent freezing behavior are both modulated by medial prefrontal cortex (mPFC) structures. The more dorsal prelimbic cortex of the rodent is associated with the expression of conditioned fear (Burgos-Robles, Vidal-Gonzalez, & Quirk, 2009). The prelimbic cortex acts as a fear response "accelerator" during conditioning, while the more ventral infralimbic cortex acts as "brakes" during extinction. The infralimbic cortex is necessary for fear conditioning responses to context (Resstel, Joca, Guimarães, & Corrêa, 2006), probably due to its connectivity to hippocampus and amygdala (Bouton, Westbrook, Corcoran, & Maren, 2006; Maren, Phan, & Liberzon, 2013).

The hippocampus serves the function of binding together the disparate sensory and interoceptive elements that form a context into one conjunctive representation (Rudy & O'Reilly, 2001). The rodent hippocampus has connections with both prelimbic and infralimbic cortex and thus provides contextual modulation over fear responses. Furthermore, during exploration of the environment, the hippocampus, along with associated medial temporal cortex, serves as a functional comparator of present and past (stored) experience (VanElzakker, Fevurly, Breindel, & Spencer, 2008). As such, it is vital to the recognition of a context as familiar or the establishment of a context as novel. A related function is its involvement in comparing novel cues to an existing CS, to determine if a CR is appropriate; stimulus generalization is what led Little Albert to be wary of cues that only moderately resembled a white rat. The hippocampus is therefore a crucial structure in determining whether contextual cues are associated with danger or with safety (Maren, 2013; Rudy et al., 2004).

2.1. Extinction in rodents

At the level of behavioral observation, if a conditioned cue (CS) or context is repeatedly presented without subsequent shock (US), the rat will stop freezing in response to the CS. This process of extinction is somewhat tenuous, as its recall is fundamentally context-dependent (Bouton, 2004; Bouton, Westbrook, et al., 2006). That is, once both a CS–US (conditioning) and a CS–noUS (extinction) representation exist, the response relevant to CS–noUS is only expressed in the context in which CS–noUS was learned. Furthermore, reduction of the CR does not necessarily mean that the CS–US association has been broken. This is demonstrated by the phenomena of spontaneous recovery, reinstatement, and renewal. As Pavlov described, spontaneous recovery refers to the fact that, after the passage of time, the CS can recover the ability to elicit an extinguished CR. Reinstatement of an extinguished CR occurs when the US is presented in the absence of the CS; simple exposure to a US, even outside of the conditioning or extinction context or without being paired with any particular cue, can reinstate fear responses to a previously conditioned context or cue. More recent rodent research has also revealed the phenomenon of renewal, which occurs when conditioning and extinction occur in different contexts: a change from the extinction context either back to the conditioning context or into a third context can cause the CR to renew (Bouton, 2004). Therefore, while it may be intuitive to conclude that extinction of the CR represents a fading away of the CS–US association, these three phenomena provide evidence that fear extinction primarily represents a competing memory (Herry et al., 2010) because the CS can still recover the ability to cause a CR without ever being re-paired with the US. This demonstrates that extinction learning represents a new CS–noUS memory trace that competes with and inhibits the existing CS–US memory.

So if extinction represents new learning, how can it give rise to inhibition over a prepotent fear response? There is evidence to