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CHAPTER 2

The Cognitive Neuroscience of Fear Learning

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INTRODUCTION

Fear learning imbues organisms with the ability to use cues in the environment to predict potential dangers and aversive events. The fear acquisition system is rapid, efficient, and persistent, with a sole encounter of a dangerous event potentially being sufficient to form long-lasting fear memories. Using memories of fearful encounters and contexts, the fear system enables the accurate prediction of future danger and recruitment of defensive behaviors. These characteristics provide a strong evolutionary advantage by rendering the need for relearning in the presence of repeated danger unnecessary, thereby minimizing potential exposure to threat. Because environments are never constant, the fear learning system is flexible so that the learning and expression of fear can adapt to changes in environmental circumstance.

The goal of this chapter is to provide a systematic overview of the fear learning literature, intertwining insights from psychological and neuroscientific research. Key findings from animal models and human studies that have advanced the scientific understanding of how fears are acquired and overcome are presented. Finally, we will discuss mechanisms that allow for the extension of simple forms of fear learning to more complex ones, including contextual conditioning, fear generalization to novel stimuli, and social transmission of fear learning.

PAVLOVIAN FEAR CONDITIONING

The predominant methodology by which fear learning is studied—Pavlovian conditioning—was discovered serendipitously by Ivan Pavlov while studying digestion in dogs (Pavlov, 1927). Pavlov noted that the dogs in his laboratory would begin to salivate at the sound of food being prepared, suggesting that the dogs had formed an association between these sounds and the subsequent food presentation. As a methodology, Pavlovian conditioning has been used in the study of learning in an array of species ranging from simple organisms, such as sea slugs (Walters, Carew, & Kandel, 1981) and rats (LeDoux, 2000), up to humans (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998).

In a typical fear-conditioning study, a neutral stimulus (the conditioned stimulus or CS) is predictively associated with an aversive stimulus (the unconditioned stimulus or US), which elicits a natural defensive response from the organism (the unconditioned response or UR). The CS will elicit defensive behavior on its own because it has begun to reliably signal the occurrence of the US. These behaviors are termed the conditioned response (CR) and typically reflect

innate defensive behaviors that prepare the organism for the presence of the US.

Pavlovian conditioning is a highly flexible paradigm that, through minor methodological alterations, can be used to study a multitude of different processes. Although the use of an aversive US (e.g., a foot shock) will recruit defensive behavior, an appetitive US (e.g., a food reward) may initiate approach behavior instead, resulting in appetitive rather than fear conditioning. Similarly, the timing of an aversive US relative to the predictive neutral CS results in either delay or trace conditioning. In delay conditioning, the onset of the US is delayed relative to the CS such that both offset at the same time. Trace conditioning, however, introduces a temporal gap between the offset of the CS and the onset of the US. Although this interval may be shorter in duration than a single second, it requires an organism to create a memory trace of the CS for learning to be successful and is thus more cognitively demanding and reliant on distinct neural substrates. Although most experiments condition subjects to the presentation of explicit foreground cues (cue conditioning), there has been an increasing interest in conditioning to the diffuse background context within which learning occurs (context conditioning). Another important paradigmatic distinction is in the number of cues presented. Animal work most commonly involves the presentation of a single CS that reliably predicts a US, with learning contrasted against a control group of animals that undergo nonassociative learning. Human studies, however, typically rely on a differential conditioning design in which one CS (the CS+) reliably signals the onset of the US, whereas a second CS (the CS–) signals the absence of the US. The use of a within-subjects design in which a second CS acts as a control allows for prodigious cognitive and emotional factors that vary between individuals to be kept constant.

The presence of CRs is taken as confirmation that fear learning has occurred. These typically consist of overt behavioral and physiological responses, which are advantageous in that they provide an index of fear that is readily observable and typically outside of direct conscious control of the research subject (Dillon & LaBar, 2005). The startle reflex, for example, provides a reliable index of the mobilization of fear responding, which is highly conserved across species (Lang, Davis, & Öhman, 2000). In rodents, the startle reflex is typically measured as a whole-body startle, whereas the human response is typically measured from the muscles controlling the eyelids. Startle responses are typically enlarged in the presence of fearful stimuli. Startle responses can be reliably evoked using a sudden loud auditory stimulus, which can be presented along with the CS, making it possible to track potentiated responding across learning trials. Additional behaviors that commonly act as indices of fear learning include freezing behavior in animals and the skin conductance response (SCR) in humans. Freezing is typically formalized as the extent of time that an animal remains immobile during CS presentation. SCR is a phasic increase in skin conductance resulting from sympathetic activation to an arousing stimulus, such as a CS.

Over the years, different models have been proposed to explain how learning occurs in conditioning, such as the Rescorla-Wagner (Rescorla & Wagner, 1972), temporal difference learning (Sutton & Barto, 1981), and Pearce-Hall (Pearce & Hall, 1980) models. A common feature of these models is that they propose that learning occurs when there is a discrepancy between what is predicted by an organism based on sensory cues (the CS) and what actually occurs on a particular trial (the presence or absence of an aversive US). In the first few trials of learning, the occurrence of the US is surprising because the neutral CS has not begun to predict when the US will occur. It is the unexpected occurrence of the US that drives learning by generating an error signal, a discrepancy between what

the organism expected and the outcome that occurred. This error signal is incrementally corrected through subsequent encounters of the CS and US together, resulting in the formation of an association between these two stimuli. The process repeats itself over subsequent trials until the CS becomes a predictor of the US and learning asymptotes because no new information is provided to the organism by the CS and US.

The flexibility and simplicity of Pavlovian conditioning make it a powerful translational tool in understanding how fear is acquired, expressed, and overcome. Through the application of Pavlovian conditioning, researchers have sketched a detailed map of the neural systems that underlie fear learning from simple invertebrate models all the way up to complex psychiatric disorders in humans.

THE BIOLOGY OF FEAR

The Amygdala

The amygdala is a heterogeneous conglomerate of interconnected yet histochemically, morphologically, and functionally diverse nuclei located bilaterally within the medial temporal lobe. The amygdala has rich projections to most other cortical and subcortical structures, with especially strong reciprocal connections to the prefrontal cortex, particularly the orbital and medial regions. Concurrent recordings in orbitofrontal cortex and amygdala, for example, demonstrate that stimulus processing involves a complex iterative flow of information between the two regions (Morrison, Saez, Lau, & Salzman, 2011). Extensive reentrant projections between the amygdala and the rest of the brain exist as far back as primary visual cortex (Amaral, Behniea, & Kelly, 2003; Derryberry & Tucker, 1992; Iwai & Yukie, 1987), making the amygdala well placed to regulate motor and perceptual processes in response to emotional inputs (see Figures 2.1a and 2.1b).

Despite its relatively small size, the amygdala is a highly complex structure, consisting of over a dozen nuclei with extensive internuclear connections (Pape & Paré, 2010; Sah, Faber, Lopez De Armentia, & Power, 2003). Animal studies employing numerous methodologies have been able to dissect the contribution of individual nuclei to the acquisition and expression of fear (Davis & Whalen, 2001; LeDoux, 2000; Paré, Quirk, &

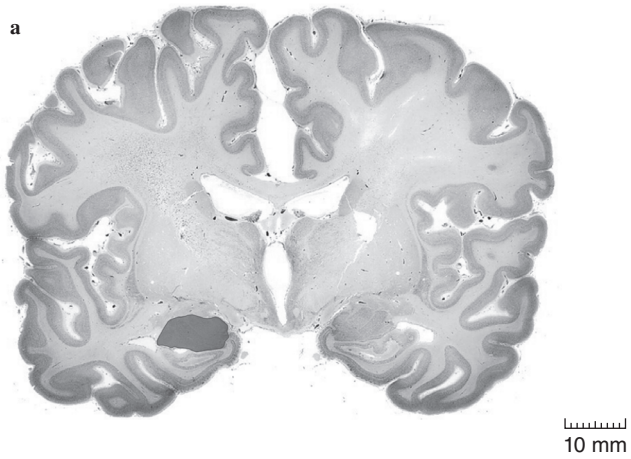

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Figure 2.1a Location of the amygdala (highlighted in red on left) within a Nissl-stained brain slice. Color version of this figure is available at http://onlinelibrary.wiley.com/book/10.1002/9781119170174.

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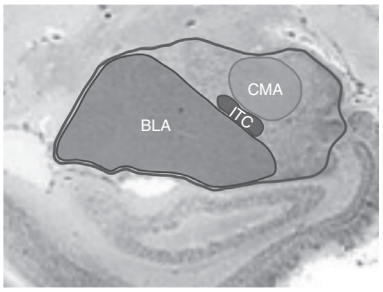

Figure 2.1b An enlarged view of some amygdala subnuclei, highlighting the structures critical for fear conditioning: basolateral complex (BLA; blue), centromedial complex (CMA; green), and intercalated cells (ITC; gray). Color version of this figure is available at http://onlinelibrary.wiley.com/book/10.1002/9781119170174.
SOURCE: Nissl-stained brain slice adapted with permission from Michigan State University Brain Biodiversity Bank (www.brains.rad.msu.edu), supported by the US National Science Foundation and the National Institutes of Health.

LeDoux, 2004; Sigurdsson, Doyère, Cain, & LeDoux, 2007). The lateral, basolateral, and basomedial nuclei, usually grouped into the basolateral complex (BLA), comprise the primary input zone of the amygdala, whereas the central and medial nuclei, collectively the centromedial complex (CMA), are the primary output structures that initiate behavioral responding. A layer of cells that lie between these nuclear complexes, the intercalated cells (ITC), appear to be important in gating the flow of information through the amygdala.

The BLA has been shown through lesion, pharmacological, and electrical stimulation studies in rodents to be vital to fear learning (Davis & Whalen, 2001; LeDoux, 2003). These studies have revealed that sensory information is principally received by the BLA from the thalamus and sensory cortices (Amaral, 1986; LeDoux, Farb, & Ruggiero, 1990), with single neurons within the BLA receiving convergent inputs from sensory, somatosensory, and nociceptive systems (Johansen, Tarpley, LeDoux, & Blair, 2010; Romanski, Clugnet, Bordi, & LeDoux, 1993; Uwano, Nishijo, Ono, & Tamura, 1995). For example, during auditory foot shock conditioning, the BLA receives auditory information from the medial geniculate nucleus of the thalamus (Clugnet & LeDoux, 1990; Romanski & LeDoux, 1992) and the auditory cortex (Li, Stutzmann, & LeDoux, 1996; Romanski & LeDoux, 1992). Information about the painful foot shock US is received by the BLA from the posterior intralaminar nucleus of the thalamus and the insula (Lanuza, Nader, & LeDoux, 2004; Shi & Davis, 1999). The BLA, importantly, not only receives information about the CS and US but also integrates this information by undergoing learning-related plasticity. Plastic changes can be seen in the experience-dependent strengthening of auditory thalamic and cortical synapses on BLA neurons during fear learning (Amano, Duvarci, Popa, & Paré, 2011; Blair, Schafe, Bauer, Rodrigues, & LeDoux, 2001; Johansen, Cain, Ostroff, & LeDoux, 2011; Pape & Paré, 2010). Recordings from individual neurons within the LA nucleus demonstrate firing to the auditory CS and foot shock US stimulation (Maren & Quirk, 2004; Romanski et al., 1993), whereas lesions to the BLA produce severe deficits in the acquisition of fear (Cousens & Otto, 1998; Maren, 1999).

The CMA constitutes the motor interface of the amygdala, providing output to the fear response system through control of the expression of CRs such as freezing, startle, or electrodermal activity. Behavioral responding is achieved through descending projections to the hypothalamus that are important for mediating autonomic responses and other projections to the brainstem, which generate the behavioral expressions of fear (Davis, 1992; Fendt & Fanselow, 1999; LeDoux, 2000; Maren, 2001). Direct electrical stimulation of the CMA produces behavioral

responses in animals that mimic the CRs displayed to the CS (Iwata, Chida, & LeDoux, 1987). Lesions of the CMA are able to abolish CRs such as freezing (Goosens & Maren, 2001; Maren, Aharonov, & Fanselow, 1996) or startle (Campeau & Davis, 1995), demonstrating the critical involvement of the CMA in these behavioral outputs. Importantly, the CMA is the last common structure in the generation of conditioned fear responding. Lesions created downstream of the CMA result in impairments only in specific CRs. Lesions directly to the CMA, however, result in a generalized loss of conditioned responding, suggesting that the CMA is vital in the general expression of fear learning rather than any specific or targeted behavior (LeDoux, Iwata, Cicchetti, & Reis, 1988). This structure also undergoes learning-related plasticity to adaptively engage fear responses in response to learned threat cues.

The borders of the BLA and CMA are separated by a mass of GABAergic inhibitory interneurons called the *intercalated cells* (ITC; Quirk & Mueller, 2008). These cells gate the transmission between the BLA and CMA and are important for the behavioral expression of fear (Asede, Bosch, Lüthi, Ferraguti, & Ehrlich, 2015). Excitatory inputs into the ITC from the BLA and medial prefrontal cortex (mPFC; Amano, Unal, & Paré, 2010; Ehrlich et al., 2009; Likhtik, Popa, Apergis-Schoute, Fidacaro, & Paré, 2008) result in inhibition of CMA output cells. This disinhibition of CMA cells results in disinhibition of the cells' targets and the generation of fear responses.

In the standard anatomical view of fear learning, the BLA receives and integrates sensory information about the CS and US. Projections from BLA to CMA enable the generation of defensive behavior, with the ITC being able to regulate the relationship between BLA and CMA based on inputs from the prefrontal cortex and BLA.

Gamma Oscillations in Fear Learning

In addition to studying how individual neurons and clusters contribute to learning, researchers have investigated the oscillating patterns between and within neural networks and individual structures. Oscillatory synchronization of neuronal activity may provide the mechanism that links anatomically and functionally related brain regions (Singer, 1999). Oscillations in activity have been studied by using electroencephalography (EEG) or local field potentials, with a particular focus on fast oscillations within the gamma band, which are defined as rhythms from ∼25 to 100 Hz (Hughes, 2008). These gamma oscillations are the product of synchronized rhythmic patterns of neuronal spiking and synaptic inhibition and can be entrained by slower theta band (4–10 Hz) activity in response to a stimulus. Gamma oscillations have drawn attention because of their ubiquitous presence across the brain, with recordings in the gamma band readily observed in the cortex and numerous subcortical structures, including the hippocampus (Csicsvari, Jamieson, Wise, & Buzsáki, 2003) and amygdala (Randall, Whittington, & Cunningham, 2011).

Gamma oscillations may provide a fingerprint of a variety of cognitive processes because they are typically observed in cortical and subcortical structures when these are engaged by a cognitive task (Wang, 2010). In terms of fear processing, animal research has associated gamma oscillations with the predictive power of the CS. Headley and Weinberger (2011) recorded gamma oscillations within auditory cortex as rats underwent multiple days of tone conditioning. The authors found that the gamma power induced by the CS during initial acquisition of fear positively predicted the strength of conditioned responding on subsequent days. Other studies indicate that BLA-hippocampal-medial prefrontal circuitry is synchronized by theta

and gamma oscillations during fear and safety manipulations (reviewed in Bocchio & Capogna, 2014). During the retrieval of a conditioned fear memory, theta synchrony is increased across this circuit, leading to increased theta-gamma coupling in the BLA; however, in response to a safety cue (e.g., a CS−), theta and fast gamma power is enhanced in the medial prefrontal cortex, which inhibits the BLA and phase-locks the BLA fast gamma power to medial prefrontal theta. Interestingly, these oscillatory couplings showed a different pattern in individual mice who failed to learn the associations between the cues and aversive reinforcers. Although the subcortical changes are challenging to measure in humans, changes in cortical theta and gamma as measured by scalp EEG also accompany fear acquisition and extinction in humans (Miltner, Braun, Arnold, Witte, & Taub, 1999; Mueller, Panitz, Hermann, & Pizzagalli, 2014). As more becomes understood about how these oscillations relate to conditioning processes and the extent to which they can be altered by neuromodulation techniques, they may provide a useful tool to modulate fear learning and expression in anxiety disorders.

Studies of Fear Conditioning in Humans

Methodological constraints make it difficult to study the role of amygdala nuclei in humans with the level of fine-grained control and direct access that is possible in rodents. Instead, a body of research has developed concerning a small number of neurologic patients who have sustained damage to the amygdala. These patients fall, predominantly, into two categories: individuals who have sustained broader lesions as a result of surgery for the treatment of intractable epilepsy and those with more focal damage as a result of Urbach-Wiethe disease, a genetic disorder that sometimes presents with calcification of the amygdala among other symptoms.

Amygdala Damage in Fear Conditioning Studies: Studies in Temporal Lobectomy Patients

LaBar, LeDoux, Spencer, and Phelps (1995) examined the influence of temporal lobe resection on conditioned fear learning. A group of patients who underwent unilateral temporal lobe resection as a treatment for medically intractable epilepsy was compared to a group of healthy controls. The patient group showed diminished conditioned SCRs following conditioning, consistent with the loss of CRs in animal studies employing lesions of the amygdala. Importantly, SCR responding to the aversive shock was not altered in the patient group, and they were able to report the association between the CS and the US. This spared declarative knowledge about the association of the CS and US suggests a dissociation between the explicit knowledge that these two events are contiguous and associated and the implicit learning of this relationship as reflected in their diminished SCRs to the CS+.

Impaired fear conditioning as a result of temporal lobe resection has been replicated in studies measuring fear-potentiated startle (Weike et al., 2005) and valence ratings (Coppens, Van Paesschen, Vandenbulcke, & Vansteenwegen, 2010) as indices of learning. One difficulty in interpreting the data from studies of individuals who sustained damage to the amygdala as a result of surgery is that the extent of the surgical intervention and the ensuing lesion frequently exceed the amygdala and include surrounding structures. For example, damage frequently includes regions of the hippocampus as well as the amygdala. Additionally, the surgical interventions are overwhelmingly unilateral, leaving the amygdala and surrounding structures intact in the contralateral hemisphere, except in some cases with circumscribed damage in the opposite hemisphere (Phelps et al., 1998). Animal lesions studies, by contrast, have

much finer control over the site and extent of induced lesions.

Amygdala Damage in Fear Conditioning Studies: Studies of Urbach-Wiethe Disease

A second smaller group of patients have been studied who present more focal amygdala lesions as a result of Urbach-Wiethe disease. Although this disease is rare, one of these patients has been instrumental in advancing our understanding of the function of the amygdala in humans because of her almost complete destruction of the amygdala. On testing, patient SM was unable to acquire fear, demonstrating an absence of normal SCR but showing no impairment in her declarative knowledge of the CS-US relationship (Bechara et al., 1995). A reverse behavioral pattern was reported in an individual with hippocampal damage and intact amygdala. This individual was unable to report the CS-US association but showed intact fear learning as indexed by SCR. Taken together, these individuals combined with other cases (Adolphs et al., 2005; Phelps et al., 1998) reiterate the double dissociation of fear learning and declarative knowledge about the CS-US relationship.

More recent work has extended these findings by focusing on four cases who presented with damage that was confined to the BLA of the amygdala (Klumpers, Morgan, Terburg, Stein, & van Honk, 2015). Following fear acquisition, control subjects showed a potentiation of their startle response during presentation of the CS+, indicating that fear learning was successful. This effect, however, was absent in the four cases with damage to the BLA. Importantly, there were no significant alterations in defensive responses overall between the two groups of participants. That is, general startle reactions to the auditory probe and US were variable from individual to individual but did not differ between the patients and controls. This sparing of general startle responding is in line with the animal literature, which has found startle responding to depend on the brainstem nuclei, whereas fear potentiated startle depends on intact amygdala processing (Davis, Falls, Campeau, & Kim, 1993; Gallagher, Graham, & Holland, 1990).

Taken as a whole, the study of individuals who have suffered damage to the amygdala because of neurologic disease or surgery have reiterated the importance of the amygdala in fear learning and expression. The development of functional magnetic resonance imaging (fMRI) has made it possible to confirm these findings in healthy individuals. Furthermore, functional imaging in healthy individuals has made it possible to test more nuanced questions and predictions about fear learning arising from animal and patient work.

Human fMRI

As with work in animal models, human studies using fMRI have resonated the critical role for the amygdala in fear learning across sensory modalities and using a variety of aversive stimuli. Significantly increased amygdala responding has been reported in studies pairing the onset of a colored light (Knight, Smith, Cheng, Stein, & Helmstetter, 2004); simple geometric shapes (LaBar et al., 1998; Meier et al., 2014; Merz, Stark, Vaitl, Tabbert, & Wolf, 2013); photographs of human faces posing facial expressions (Lim, Padmala, & Pessoa, 2008); and a variety of other stimuli across modalities with electrical shock US reinforcement. Amygdala responding has also been found in studies that use other types of noxious stimulation, such as painful physical stimulation (Kattoor et al., 2013; Lindner et al., 2015); aversive auditory stimuli (Armony & Dolan, 2002; Hermann, Keck, & Stark, 2014); and CO_2 inductions (Moessnang et al., 2013).

Beyond the amygdala, a network of distributed brain regions is reliably recruited in fear learning. These regions include the primary sensory cortices, anterior cingulate cortex (ACC), hippocampus, insula, thalamus, and prefrontal cortex (LaBar & Cabeza, 2006). Amygdala responding typically decreases over the course of conditioning, whereas activation in ACC and insula remain consistent (Büchel, Morris, Dolan, & Friston, 1998; LaBar et al., 1998; Reinhardt et al., 2010). Declining amygdala activity may be a reflection that the primary role of the amygdala is in the initial acquisition of fear, whereas the ACC and insula are more critically involved in fear expression (see Figure 2.2).

Interestingly, though there is evidence across various modalities that the amygdala is key to fear learning, an effect of amygdala responding is not present in all conditioning studies. In a review of the human fear–conditioning literature, Sehlmeyer and colleagues (2009) identified 44 studies, of which 25 report significant amygdala modulation as a function of CS type. A possible explanation for the lack of amygdala involvement in the other studies may be the preferential involvement of the amygdala in the initial trials of learning, as well as the generally rapid (Breiter et al., 1996) and differential (Wright et al., 2001) habituation of amygdala responding. It has become common to examine amygdala function adjusted for time by, for example, splitting the acquisition phase into early and late components. Indeed, Sehlmeyer et al. (2009) noted that of the 25 studies that did report significant amygdala responding, 19 tested for temporal effects, whereas the 19 studies that did

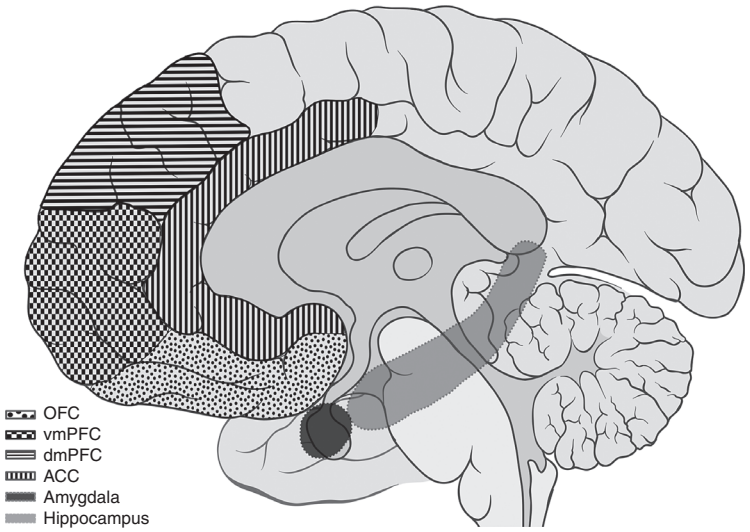

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Figure 2.2 Midsagittal view of the human brain, highlighting key regions involved in conditioned fear learning: orbitofrontal cortex (OFC; light green), ventromedial prefrontal cortex (vmPFC; light blue), dorsomedial prefrontal cortex (dmPFC; darker blue), anterior cingulate cortex (ACC; orange), amygdala (pink), and hippocampus (dark green). Subcortical regions are indicated with dashed boundaries. Color version of this figure is available at http://onlinelibrary.wiley.com/book/10.1002/9781119170174.

SOURCE: Adapted from sagittal brain illustration by Patrick J. Lynch, medical illustrator; C. Carl Jaffe, MD, cardiologist. Creative Commons 2.5 Attribution license: https://creativecommons.org/licenses/by/2.5/.

not report significant amygdala responding during acquisition, only two tested for a temporal interaction on amygdala function. The preponderance of significant amygdala activations in studies that accounted for temporal effects suggests that absence of amygdala activity may not reflect a true absence of responding within the amygdala but may simply be a by-product of the rapid habituation of responding once learning has occurred. As such, it may be necessary to adjust for rapid habituation in order to detect amygdala activity in fear acquisition.

In an attempt to provide an updated map of the network of regions that underlie fear learning, Fullana and colleagues (2016) conducted a meta-analysis of the results from 27 fear-conditioning studies. Reliable activation was detected in ACC, mPFC, anterior insula, and a number of additional cortical regions including the supplementary motor area, dorsolateral PFC, and precuneus. The amygdala did not emerge as one of the regions that was consistently present across studies. The lack of significant activation in the amygdala, however, may be because of a reliance on whole-brain data within this meta-analysis. There are technical difficulties in imaging the amygdala because of its small size and position within the medial temporal lobe. It is therefore typical to examine amygdala responding separately using a region-of-interest approach. Because the meta-analysis by Fullana et al. (2016) relied on whole-brain data, any instances in which a region-of-interest approach was used to examine amygdala responding were neglected.

OVERCOMING FEAR

The ability to acquire and express fear provides a strong adaptive advantage. This advantage, however, could easily become maladaptive if fear is invoked and expressed in situations that do not warrant it. Because the recruitment of defensive behavior carries a metabolic cost for the organism, a counterbalance to fear learning is required that allows for fear responding to diminish or be abolished once it no longer reliably serves an adaptive function. Within the conditioning framework, fear is overcome through the process of extinction wherein a CS that had been paired with an aversive US is now presented alone. After several CS-alone presentations, the organism learns that the CS is no longer a predictor of the US, and conditioned responding subsides.

During extinction, each presentation of a CS without the previously paired US provides the organism with an opportunity to re-encode information about the previously learned CS-US association. In other words, in addition to the original memory that the CS is dangerous, the organism now encodes a new memory that the CS is safe. According to this view (Bouton, 1993, 1994), there now exist two memories that compete for activation: a CS-US memory and a new CS–no US memory. The behavior that is evoked by the presentation of a particular CS depends on which of these two competing memories become active. Recall of the original CS-US memory should result in the deployment of a CR and the return of fear, whereas activation of the newly learned CS–no US memory should lead to inhibition of the CR and extinction maintenance (Bouton, 1993, 2002, 2004; Milad & Quirk, 2002; Myers & Davis, 2002; Pearce, 1994; Quirk, 2002). The activation of the CS-US and CS–no US memories renders the meaning of the conditioned stimulus ambiguous: Although the CS predicts the US during initial fear learning, it no longer does during extinction (Bouton & Ricker, 1994). This "new" learning account of extinction in which the acquisition and extinction memories coexist and compete for

representation has been supported by four phenomena that result in the return of fear following successful extinction.

The first of the return of fear phenomena to be discovered, *spontaneous recovery*, was documented by Pavlov (1927), who noted that extinguished conditioned responses could return after a sufficient passage of time. That is, the mere passage of time may be sufficient for fear responding to once again be elicited by a CS. Fear responding to a CS is said to be *renewed* following extinction if that CS is encountered in the context within which initial fear learning occurred or a novel context that has not been encountered before. Renewal triggers the fear memory rather than the extinction memory trace because encountering the CS in a context that differs from the one within which extinction occurred is thought to release the inhibitory control over fear expression by the extinction context. In conditioning, context refers to the amalgamation of diffuse and continuously present external and internal stimuli that form the backdrop within which fear learning occurs and is usually distinct from the specific cues used as the CS. Fear can be *reinstated* by the unsignaled presentation of the noxious US (or similar stressor), which recovers the latent fear memory when the CS is presented in this stressful context. The fourth phenomenon that indicates that extinction is not the erasure or unlearning of the initial fear memory is *reacquisition*. Reacquisition is tested by presenting additional CS-US pairings following extinction. The presentation of these additional CS-US pairings results in a rapid return of fear, faster than the initial learning, which suggests that the initial memory was spared. The fact that these phenomena can be readily observed following successful and complete extinction of a fear memory strongly suggest that extinction is a distinct learning process, which may recruit different neural structures than the initial fear learning itself.

Neurobiology of Extinction

Investigations of the neural foundation of extinction learning in the animal literature have come to a general consensus that three main structures underlie extinction learning and recall: the amygdala, the prefrontal cortex (PFC), and the hippocampus (Barad, Gean, & Lutz, 2006; Quirk & Mueller, 2008; Sierra-Mercado, Padilla-Coreano, & Quirk, 2011).

As is the case for initial fear acquisition, the BLA appears to be critical in mediating the learning of extinction (Herry, Trifilieff, Micheau, Lüthi, & Mons, 2006; Herry et al., 2008; Sotres-Bayon, Bush, & LeDoux, 2007; Vianna, Coitinho, & Izquierdo, 2004). When recorded directly, BLA neurons exhibit the expected increase in firing during acquisition of fear, with this pattern being reversed during extinction learning (Quirk, Repa, & LeDoux, 1995). Using a GABA-ergic agonist to inactivate the BLA prior to extinction learning, Sierra-Mercado and colleagues (2011) observed reduced fear expression and impaired extinction memory. When these infusions were performed after extinction learning, however, BLA inactivation had no effect on either expression or memory. The BLA, therefore, appears to be required for the initial learning that takes place during extinction but not the subsequent storage and expression of this memory, paralleling the function of the BLA during the initial learning of fear.

In addition to the involvement of the BLA, the ITC may act as a switch during fear extinction, receiving inputs from the PFC and suppressing output neurons in the CMA. Stimulation of PFC neurons in rats appears to directly activate ITC neurons (Berretta, Pantazopoulos, Caldera, Pantazopoulos, & Pare, 2005) and decrease the responsiveness of CMA neurons (Quirk, Likhtik, Pelletier, & Paré, 2003). This direct stimulation of the

PFC, in turn, reduces conditioned freezing in rats, possibly via activation of the ITC (Milad, Vidal-Gonzalez, & Quirk, 2004). The ITC, therefore, appears to act as a regulator of amygdala responding for higher structures such as the PFC.

A role for the ventromedial PFC (vmPFC) was first provided by Morgan, Romanski, and LeDoux (1993). They found that lesions to the vmPFC that were induced prior to conditioning impaired fear extinction, but they did not alter the ability of the animals to acquire conditioned fear. Subsequent work has refined this result, arguing that lesions to the vmPFC do not result in a general impairment of extinction learning but instead cause deficits in the recall of extinction. Rats with lesions to the vmPFC are unable to recall extinction when tested 24 hours after extinction training, demonstrated by the presence of freezing to the CS (Quirk, Russo, Barron, & Lebron, 2000). Convergent evidence has been provided by studies using alternative techniques such as the use of inactivating agents that are infused directly into the PFC of rodents, yielding similar deficiencies in extinction recall (Burgos-Robles, Vidal-Gonzalez, Santini, & Quirk, 2007). Thus, the vmPFC may play a critical role in the consolidation of extinction memories.

Extinction learning can be rescued in the presence of vmPFC lesions, although it proceeds at a slower rate. Lebrón, Milad, and Quirk (2004) demonstrated this effect by first replicating the aforementioned deficits in extinction recall following lesions to the vmPFC. It was then, however, possible to recover extinction learning by exposing rats to further extinction training on subsequent days. Even though this result was obtained through significantly more extinction training, it suggests that it is possible to attain extinction learning despite vmPFC lesions. The vmPFC may, therefore, not be the sole site of extinction memory storage, because recall of extinction memory appears possible in the absence of the vmPFC.

Milad and Quirk (2002) recorded the firing of individual cells in vmPFC while rats acquired and extinguished conditioned fear to a tone cue. In line with the findings in the lesion work, cells in the infralimbic (IL) subdivision of the PFC did not respond during acquisition or extinction, instead firing only when rats recalled the extinction memory the day after acquisition and extinction learning. Interestingly, rats that froze the least—indicating successful extinction—showed the greatest firing rate to the CS in IL. Taking rats that had not undergone extinction, the researchers were able to eliminate freezing behavior by directly stimulating neurons in IL. In other words, it was possible to artificially induce extinction through direct activation of IL neurons. Taken together, these findings lend support to the view that the PFC is involved in the retrieval of extinction memories and furthermore that the vmPFC represents a safety signal for extinguished conditioned stimuli (Greco & Liberzon, 2016).

In addition to these regions that appear to be involved in extinction learning generally, the hippocampus appears to play an essential role in the contextual gating of extinction learning. Temporary (Corcoran, Desmond, Frey, & Maren, 2005; Hobin, Ji, & Maren, 2006) and permanent (Good & Honey, 1991) inactivation of the hippocampus in animal work disrupts the contextual retrieval of fear memories.

These results, in combination with the oscillatory findings discussed in "Gamma Oscillations in Fear Learning," indicate that extinction learning is initiated by the vmPFC and targets the amygdala via oscillatory coupling and neuronal down regulation of CMA output via the ITC cells (as well as direct inhibition of the BLA complex). The amygdala itself encodes this extinction

memory, and the PFC tracks the new safety value of the CS, which is critical for the consolidation of extinction learning. By encoding the contextual cues that envelope extinction learning, the hippocampus is key to the context-dependent retrieval of extinction memories.

Extinction in Human fMRI

Studies using fMRI in human participants have replicated many of the findings from the animal literature. PFC and amygdala activation has been demonstrated in acquisition and extinction, when these two phases of learning were examined together, using simple visual (LaBar et al., 1998) and olfactory (Gottfried & Dolan, 2004) conditioned cues.

Although these results demonstrated the involvement of expected regions in extinction learning, early studies lacked the ability to examine extinction recall because they did not use a multiday design. This concern was addressed by Phelps, Delgado, Nearing, and LeDoux (2004), who examined responding to a CS+ and CS– that had been extinguished on the preceding day, demonstrating significantly increased activation within vmPFC during recall of extinction. This design was extended by Milad and colleagues (2007) by examining extinction recall and acquisition recall in tandem. Participants were conditioned to two distinct CS+ stimuli, with only one of these subsequently undergoing extinction. Results indicated the expected pattern of increased amygdala responding to the two CS+ stimuli during acquisition. The vmPFC, interestingly, showed significant deactivation to the same stimuli. That is, vmPFC activity during the acquisition of fear demonstrated the reverse pattern to that in the amygdala, with responding being greater to the CS– than the CS+. Transitioning into extinction learning, activity in vmPFC flipped, now showing a pattern of greater responding to the CS+ than the CS–. This change in vmPFC responding suggests a similar role for the human vmPFC as in the animal literature in tracking the safety signal of the CS during extinction learning.

Further evidence for the view that vmPFC tracks the safety signal of a CS has come from fear-reversal tasks. In these tasks, participants learn to associate the occurrence of a particular CS+ with the onset and a CS– with the absence of a US. Following learning, the association of the CS and US is reversed so what was initially the CS– now begins to predict the US, and what was the CS+ now signals the absence of the US. Amygdala and striatal responding tracked the fear predictive value of the CS, flipping their response from one stimulus to the other when the contingency with the US changed (Schiller, Levy, Niv, LeDoux, & Phelps, 2008). Consistent with the idea that the vmPFC represents an inhibitory safety signal, activation in the vmPFC tracked the safety value of the stimuli, initially tracking the CS– and then switching to the CS+ when the contingency with the US was reversed.

Removal of Fear: Reconsolidation

Typical extinction processes result in the formation of a new safe memory that leaves the original fear memory intact and capable of again being expressed by return of fear phenomena. Recent years have seen a growing interest in reconsolidation, a process that may provide a means by which fear memories can be permanently altered to become safe, thereby removing the potential for the return of fear phenomena described in the section “Overcoming Fear.” The prevailing view in memory research has been that memory progresses in a unidirectional path from unstable to stable memories that are fixed and become resistant to change through a consolidation process (Alberini & LeDoux, 2013).

The reconsolidation view of memory contends that memories can enter a labile state after retrieval, a state in which they are amenable to change (Schwabe, Nader, & Pruessner, 2014). Reactivated memories then need to undergo a new stabilization process, or reconsolidation, to once again become fixed or stable.

Reconsolidation studies follow a general format wherein participants acquire a fear memory through a standard Pavlovian conditioning paradigm. The following day, the CS+ is present without a US pairing in order to reactivate the fear acquisition memory, thereby rendering it open to change. While the fear memory is in this malleable state, pharmacological or behavioral manipulations are implemented to disrupt reconsolidation. Then, the return of fear to the CS+ is tested on a subsequent day.

Nader, Schafe, and LeDoux (2000) showed that existing fear memories also enter a labile state when retrieved from long-term memory. In this study, an amnesic agent was injected into the amygdala of rats prior to them being reminded of and retrieving an existing memory. Injection of the amnesic agent resulted in an impairment to the existing long-term memory relative to control animals that had not retrieved the existing memory. Moreover, if the amnesic agent was administered 6 hours after reactivation of the existing memory, it had no effect. Collectively, these results suggest that there is a limited window during which retrieved memories can be changed. Subsequent studies have replicated this effect (Debiec & LeDoux, 2004; Taubenfeld, Milekic, Monti, & Alberini, 2001) and extended it to hippocampal-dependent contextual memories (Debiec, LeDoux, & Nader, 2002).

To date, the majority of the reconsolidation work has been carried out in the animal literature (reviewed in Dudai, 2012), with only recent translation of this phenomenon to human studies. Building on animal work that demonstrated the effectiveness of amnesic agents in modifying retrieved memories, Kindt, Soeter, and Vervliet (2009) sought to test the malleability of human memories during the reconsolidation window that had been established in the animal literature. To achieve this aim, healthy individuals were fear conditioned, with this fear reactivated 24 hours later using a single presentation of the CS+. Importantly, participants were administered the beta-blocker propranolol prior to reactivating their acquisition memory. Participants then returned 24 hours later and underwent extinction of the acquired fear, as well as a reinstatement procedure to examine what effects propranolol and reactivation had on the return of fear. Participants who were administered a placebo demonstrated increased responding to the CS+ at the start of extinction and following reinstatement. Critically, propranolol administration and reactivation of the fear memory abolished these effects, with participants demonstrating a complete absence of fear responding to the CS+ during extinction and after reinstatement. Importantly, the authors examined a group of participants who were administered propranolol but who did not undergo reactivation of the fear memory. This manipulation did not alter fear memory, showing the necessity of reactivation in rendering the fear memory labile. Reduced fear responding has also been demonstrated when propranolol was administered after, rather than prior to, reactivation (Soeter & Kindt, 2012).

An alternative approach that has leveraged reconsolidation that does not rely on the use of drug administration is the implementation of extinction processes during the labile stage of a reactivated memory. In a behavioral study using rats, Monfils, Cowansage, Klann, and LeDoux (2009) demonstrated that presenting fear extinction within the reconsolidation window of a labile CS memory is able to

prevent the return of fear during renewal, reinstatement, and spontaneous recovery. This finding was translated to human participants by Schiller and colleagues (2010), who found that participants who underwent extinction 10 minutes after reactivation of a fear memory—within the labile window of the memory—showed no return of fear when tested 24 hours later. These results are in stark contrast to participants who did not reactive their fear memories or underwent extinction outside the labile window of the memory and showed the expected return of fear pattern. Impressively, the effects of successful reactivation and extinction persisted for a full year after testing.

Agren, Engman, et al. (2012) set out to examine the brain regions involved in the attenuation of fear as a result of extinction during reactivation. Participants underwent extinction 10 minutes or 6 hours after reactivation of an acquisition memory. Fear memory was assessed in a renewal test on the following day, and in a reinstatement test 3 days after reactivation. Consistent with previous behavioral work, extinction conducted 10 minutes after reactivation prevented the return of fear. Additionally, activity in the amygdala was significantly lower during renewal testing than in participants who were extinguished 6 hours after reactivation. Examining the involvement of the PFC, Schiller and colleagues (2013) noted the expected engagement of the PFC to CS+ stimuli that were not reactivated but an absence of PFC responding to CS+ stimuli that were activated prior to extinction training. It may be this absence of PFC activity that allows for more permanent alteration of the original fear memory within the amygdala.

Although some subsequent studies have replicated these findings (Agren, Furmark, Eriksson, & Fredrikson, 2012; Oyarzún et al., 2012), others have found that a single reminder reactivation prior to extinction is not effective in diminishing fear (Golkar, Bellander, Olsson, & Öhman, 2012; Kindt & Soeter, 2013). Furthermore, the results from other reconsolidation studies have recently been called into question. In an attempt to replicate early reconsolidation work in the motor learning domain by Walker, Brakefield, Hobson, and Stickgold (2003), Hardwicke, Taqi, and Shanks (2016) were unable to replicate the expected effect of reminders on memory stability. Namely, providing participants with a reminder of a finger sequence that they had learned on a previous day did not appear to render this memory labile to change, despite multiple attempts at replication. Attempts to extend and further understand this failure to replicate indicated that, rather than making the original memory labile, the reminder effect appears to have strengthened the original memory, making it more resistant to change. Although these experiments did not use a fear memory paradigm, they do raise questions about the replicability and universality of the existing memory reconsolidation findings as they apply to fear learning. Given the limited number of studies that have been done to date, it is still too early to determine if these failures to replicate are caused by methodological differences between studies or if they represent a limitation of the robustness of extinction in human reactivation work. Because the application of reconsolidation theory to fear learning is in a nascent stage, replications and extensions of existing findings are likely to reshape our understanding of the effectiveness and boundary conditions of reconsolidation as it is applied to the formation and modification of existing fear memories.

FEAR BEYOND THE CS

The evolutionary advantage provided by the fear learning system would be stunted if fear associations were strictly fixed to the particular characteristics of the CS exemplar to which initial learning occurred. Environments are under constant flux, making it unlikely that future encounters of a CS will be identical to those during initial fear acquisition. The fear-learning system needs to be flexible to adapt to these potential changes. Two processes that demonstrate the flexibility of conditioning are context conditioning and the generalization of conditioned associations. Context conditioning enables an organism to include representations of the environment in which learning has occurred. Generalization promotes the spread of fear to other cues that conceptually or perceptually resemble those encountered during the initial learning. Both of these phenomena represent an extension of the initial learning beyond the CS-US association.

Learning to Fear the Context

The concept of context is not consistently defined in the literature, but a broad and generally accepted view is that context is formed from the internal (cognitive and physiological) and external (environmental and social) backdrop within which fear acquisition occurs. Unlike the discrete cues that form a CS, contexts are typically multisensory, diffuse, and continuously present (Maren, Phan, & Liberzon, 2013). Importantly, contextual representations are more than the sum of their parts. That is, although a contextual representation is formed from the elements that they encompass, the context as a whole can be distinguished from the individual elements. For example, although an office consists of certain elements (a desk, chair, filing cabinet), the office context exists as a gestalt representation of these constituent elements existing in a specific unified representation.

Two important processes underlie learning in a context: context encoding and context conditioning. The former refers to the encoding of a representation of the context, which may be necessary for conditioning to the context to be possible. The latter process—context conditioning—is the association of this contextual representation with the occurrence of an aversive stimulus. The necessity of context encoding can be easily demonstrated by presenting shocks immediately on placing animals in a chamber. These animals fail to show conditioning to the chamber context because there is insufficient time for the context to be encoded (Fanselow, 1990). If there is sufficient time for context encoding to occur prior to the presentation of the shock, then context conditioning is learned.

Contexts in conditioning are examined in two primary ways. First, contexts can act as an occasion setter or memory modulator. That is, the context in which a CS is encountered determines how an organism responds to that discrete CS. As discussed in the previous section, encountering a fear conditioned CS in the context in which conditioning occurred can result in the recall of the fear association and the elicitation of a conditioned response. Although fear acquisition may be partly context dependent, context exerts a more powerful influence over extinction learning.

Second, contexts can act as a cue for the US in their own right, even in the absence of an explicit CS. Presenting unpleasant USs in one context renders it dangerous, whereas another context in which no USs are encountered will be deemed as safe. In this case, the spatial context itself is capable of

eliciting fear behavior on its own. A context that has been conditioned can then interact with a discrete cue, resulting in summation or retardation effects. For example, an animal that receives foot shocks within a context will show freezing within that context in subsequent testing in absence of the foot shocks, suggesting a fear response to the context (Fanselow, 1980). When a discrete CS that elicits a fear response is tested within a context that also elicits a fear response, a summation of the two separate fear states can result in exaggerated freezing behavior (Polack, Laborda, & Miller, 2013).

Learning to Fear the Context: Neurobiological Basis

The hippocampus has been the main focus of research aimed at trying to understand the brain systems that allow for context conditioning because of the essential role of the hippocampus in spatial representation and memory formation in animals and humans (Ekstrom et al., 2003; Morris, Garrud, Rawlins, & O'Keefe, 1982; Squire, 1992). Animal work has confirmed the necessity of the hippocampus in tasks that involve learning and remembering fearful contexts (for a review see Holland & Bouton, 1999). Lesions of the hippocampus in rodents produce deficits in freezing behavior during exposure to a conditioned context but spared defensive behavior when exposed to an explicit fear cue (Phillips & LeDoux, 1992; Selden, Everitt, Jarrard, & Robbins, 1991). Importantly, intact amygdala function is required for successful association of the conditioned fear context (Fanselow & Poulos, 2005; LeDoux, 2000; Maren & Quirk, 2004).

The extent to which context conditioning depends on or is able to continue in the absence of the hippocampus remains an unanswered question. This is best exemplified by spared contextual fear learning when hippocampal damage precedes conditioning (Frankland, Cestari, Filipkowski, McDonald, & Silva, 1998; Wiltgen, Sanders, Anagnostaras, Sage, & Fanselow, 2006) or when rats are exposed to the to-be-feared conditioned context prior to learning, which eliminates the effects of hippocampal lesions on context learning (Biedenkapp & Rudy, 2007). Rats with hippocampal damage also continue to show an immediate-shock deficit, similarly to control animals, with reduced learning when the interval between placement in the shock context and the shock are too short. These results suggest that the involvement of the hippocampus in contextual fear learning is temporally limited and wanes over time. This latter effect is suggested by the finding that deficits in fear behavior resulting from hippocampal lesions are most robust when lesions are made soon (1 day) after contextual fear learning but are minimal when the lesion is made at a later time (> 30 days; Kim & Fanselow, 1992). This finding, however, has been called into question by recent work that has found that hippocampal lesions profoundly impair contextual fear conditioning even when these lesions were made 100 days following learning, with this impairment being reproduced across a variety of task designs and lesion sizes (Broadbent & Clark, 2013). The reason for these discrepancies is presently unknown, with one difficulty of this line of research being that the failure to observe hippocampal activation during context conditioning does not necessarily rule out hippocampal involvement (Holland & Bouton, 1999). Although the nature of temporal dynamics of hippocampal involvement in conditioning will need further work to be properly charted, the general importance of the hippocampus in context learning remains unchallenged.

Optogenetics as a research method has provided a powerful new tool in studying

the functional role of individual neurons to contextual fear memories. Using a combination of genetics and optics, the optogenetic method makes it possible to control and monitor the activity of individual neurons in real time. Liu and colleagues (2012) demonstrated that it is possible to induce freezing behavior in mice by reactivating hippocampal neurons that were activated during fear conditioning. To achieve this, the researchers first identified the populations of hippocampal neurons activated during fear conditioning. It was then possible to induce freezing behavior in a novel context by using an optogenetic light to activate the neurons that were tagged during learning. The induction of freezing behavior was not seen in control animals that were initially fear conditioned to a different context or when different cell populations were activated. Together, these findings indicate that the artificial activation of neurons within the hippocampus that contribute to a fear memory engram is sufficient for the recall of that memory and behavioral fear expression.

A number of other regions appear to contribute to successful context conditioning. Integrity of the entorhinal cortex, which forms the primary cortical input to the hippocampus, appears to be required for normal background contextual conditioning (Majchrzak et al., 2006). Anterior cingulate and medial PFC lesions have been found to interfere with remote but not recent context memory (Frankland, Bontempi, Talton, Kaczmarek, & Silva, 2004; Quinn, Ma, Tinsley, Koch, & Fanselow, 2008). Tasks that use complex contexts also appear to rely on the PFC (Gilmartin & Helmstetter, 2010; Zhao et al., 2005), perhaps because of its role in binding spatiotemporal features in attention or working memory. Together, these results suggest the involvement of a wider network in the formation of contextual fear memories that act together with—and possibly in the absence of—the hippocampus to enable the acquisition of contextual fear memories.

Investigations of context conditioning in humans are constrained by the limitations of the laboratory and neuroimaging testing environments. In animals, contextual learning relies on multimodal shifts and immersive changes to contextual environments that physically move the animal from one testing chamber to another. Such manipulations are difficult to carry out in controlled human laboratories and within the physical confines of the MRI scanner. Indeed, early attempts failed to find hippocampal activation to changes in a background screen color during tone conditioning (Armony & Dolan, 2001). More recent human fMRI studies have confirmed the involvement of the amygdala and the hippocampus in context-conditioning tasks using colored screen backgrounds (Lang et al., 2009), pictures of real rooms (Alvarez et al., 2008), and virtual environments (Marschner, Kalisch, Vervliet, Vansteenwegen, & Büchel, 2008).

A promising technological development that may advance future studies into the influence of contexts in conditioning is the use of virtual reality (VR). VR enables the construction of rich and immersive environments without requiring alterations to the physical lab environment. To date, VR has been effectively applied in a number of fear-conditioning studies (Åhs, Dunsmoor, Zielinski, & LaBar, 2015; Baas, Nugent, Lissek, Pine, & Grillon, 2004; Dunsmoor, Åhs, Zielinski, & LaBar, 2014; Glotzbach, Ewald, Andreatta, Pauli, & Mühlberger, 2012; Huff et al., 2011). For example, Dunsmoor, Åhs, et al. (2014) demonstrated that extinction conducted in multiple VR contexts is resistant to reinstatement of fear. Participants who were exposed to multiple contexts showed diminished startle responses relative to those

who were extinguished in either the acquisition or a novel context alone. Åhs, Dunsmoor, et al. (2015) similarly leveraged the power of VR manipulations by testing the influence of spatial proximity in fear conditioning. CS stimuli were manipulated so as to appear in either close or distant spatial proximity to the participant. Interestingly, startle responding showed delayed extinction and significantly increased subsequent recall for CS+ stimuli that were presented in near egocentric space compared to those presented in far space relative to the participant.

In examining brain responding, Alvarez and colleagues (2008) were able to replicate the involvement of the amygdala and hippocampus in contextual conditioning using VR environments. Significantly greater activity was observed for contexts that had been paired with a negative US relative to those that had not. Furthermore, context conditioning was associated with activity in a number of other regions including anterior insula, parahippocampal, orbitofrontal, inferior frontal, and parietal cortices. Together with the behavioral results previously discussed, these findings provide strong support for the use of VR in manipulating contextual and other cues, such as personal distance, which may be difficult to otherwise manipulate in a human laboratory.

When Not to Fear the Context: Contextual Regulation of Extinction

Unlike initial fear learning, extinction of fear appears to be particularly sensitive to shifts of context, with a change from the extinction context to another one being a potent means by which fear can be renewed. The context-dependent expression of fear following extinction, when the meaning of the CS is ambiguous, appears to be based on the gating of CS-US and CS–no US associations that are encoded in the amygdala. The hippocampus appears to be critical for gating these memories. Pharmacological inactivation of the hippocampus in animal studies results in reduced renewal of fear in response to an extinguished CS when it is encountered in a novel context (Maren & Hobin, 2007).

Direct recording of neuronal activity in animals indicates that different interdigitated populations of neurons within the amygdala respond either during the expression of extinction or during the renewal of fear (Herry et al., 2008). Interestingly, neurons that responded to extinction received inputs from the mPFC, whereas those firing to the renewal of fear received inputs from the hippocampus. Neurons in the BLA demonstrate context dependence in that the reduction of responding that occurs during extinction is reversed, with a return of CS-elicited firing being present when an extinguished CS is presented outside of the extinction context (Herry et al., 2008). This pattern of renewed firing within the amygdala appears to depend on input from the hippocampus (Maren & Hobin, 2007).

Milad and colleagues (2007) used contextual discrimination to show that the vmPFC and hippocampus are engaged during the retrieval of extinction memory. Moreover, increased activity in these regions correlated with the behavioral expression of extinction memories. Individuals who showed greatest suppression of conditioned responding also had greater vmPFC and hippocampal activity than those who showed less extinction learning. When responses to the conditioned stimuli were examined, vmPFC was found to be hyperactive in response to the CS+ during extinction learning, particular in late stages, but showed a pattern of hypoactivity to the CS+ during acquisition.

Åhs, Kragel, Zielinski, Brady, and LaBar (2015) sought to understand how context influences whether fear is renewed or extinction is recalled. Participants acquired and

extinguished fears in separate VR contexts, returning on a subsequent day to test for recall and renewal by encountering the CSs in both environments. Consistent with fear renewal, enhanced SCR responding to the CS+ was present in the acquisition context. At the neural level, a significant relationship emerged between hippocampal and amygdala activation, with this relationship being fully mediated by the dmPFC. By contrast, participants showed diminished SCRs in the extinction context, consistent with extinction maintenance. Examining the neural correlates, the authors observed that the vmPFC partially mediated the relationship between the hippocampus and the amygdala. The neural level results highlight the context-specific involvement of the dmPFC in fear renewal and vmPFC in extinction recall. Furthermore, they suggest a complex interplay between these frontal structures and the amygdala and hippocampus in determining whether fear renewal or extinction recall occurs within a particular context. These results are generally consistent with the results from the animal models at the neural circuit level, implying a conservation of function across species.

Fear Generalization

Generalization of fear is an important aspect of the fear learning system. Generalization allows for an organism to extend what is learned about a specific predictive cue to other similar cues. This extension of fear beyond the initially learned CS makes it possible to avoid potentially negative outcomes that follow cues that differ in some dimension from those encountered during initial learning. For example, it may be adaptive to extend the learning that a particular Doberman is dangerous to other dogs of that breed. If responding to a fear-conditioned stimulus was specific to only the particular stimulus that was encountered during learning, the organism would be at a strong disadvantage in a dynamic environment where a feared object is unlikely to assume the exact same form from one encounter to the next. Being able to extend fear learning beyond the specific stimuli encountered during learning would provide an adaptive advantage by removing the need to relearn aversive encounters for stimuli that resemble the CS. Following a bite from a particularly vicious Doberman, for example, it may be wise to avoid other similarly sized dogs in the future. This generalization, however, could become maladaptive if it is generalized too broadly, encompassing safe stimuli that pose no actual threat. It has been suggested that generalization of conditioned fear is an important factor in the development and maintenance of anxiety disorders (Lissek, 2012; Mineka & Zinbarg, 2006).

Ghosh and Chattarji (2015) investigated the specific role of the amygdala in fear generalization by building on the finding that increasing the intensity of the US results in greater generalization of fear in rodents (Baldi, Lorenzini, & Bucherelli, 2004). Rats were conditioned to discriminate between two tones that acted as the CS+ and CS–. Recording within the lateral nucleus of the amygdala, the authors identified neurons that selectively increased their firing to the CS+ but not the CS– as a result of conditioning. These cue-specific cells constituted 42% of all the recorded units. A second group of neurons altered their firing as a consequence of learning but responded equally to the CS+ and CS–. These generalized cells constituted about 6% of all recorded units. The remainder of the recorded cells (52%) showed no change in their firing as a result of fear learning.

To elucidate how generalization of cue stimuli is represented in the amygdala, the authors tested a second group of rats with a US set to double the intensity of the weak

US, which has been shown to result in generalization of the CS+ (Baldi et al., 2004). This change in the intensity of the US shifted the firing profile of the recorded cells to be more generalized than was observed for the weak US. The proportion of cue-specific cells (cells that fired more for the CS+ than the CS–) did not change significantly. Importantly, however, the proportion of cells that exhibited generalized firing to the CS+ and CS– increased significantly from a mere 6% for a weak US up to a 30% of all cells when the intensity of the US had been increased. Separate behavioral and neuronal indices of generalization confirmed the increased generalization of the CS+.

Work has begun to translate the findings in animal works to the human domain. In these studies, a simple visual stimulus consisting of a circle (Lissek et al., 2008) or a square (Hajcak et al., 2009) is differentially fear conditioned. Fear responses are then examined in response to the feared CS and to a series of generalized stimuli that vary in perceptual similarity to the CS. The generalized stimuli were created by altering the size of the CS by parametrically increasing or decreasing it. Quantified using the fear-potentiated startle reflex, fear expression varied in magnitude as the generalized stimuli decreased in similarity to the CS+.

Extending this paradigm to neuroimaging, Greenberg, Carlson, Cha, Hajcak, and Mujica-Parodi (2013) found a number of regions that tracked the conditioned fear gradient. The insula, ACC, supplementary motor cortex, and caudate showed increasing activation as generalization stimuli were more similar to the CS+. Interestingly, the vmPFC showed a reverse pattern, with increasing activation as the generalization stimuli grew more dissimilar to the CS+. Using a similar paradigm of generalized visual stimuli, Lissek and colleagues (2014) replicated the positive gradient in bilateral insula to stimuli that resemble the CS+ and the negative gradient in vmPFC to stimuli that differ from the CS+.

The reliance on simple sensory stimuli such as simple shapes affords a great level of control over the stimuli and an easy means of creating generalized stimuli. This approach, however, comes at the cost of ecological validity. Fear-learning situations outside of the lab are predominantly defined by complex stimuli that consist of multiple dimensions that will resemble other stimuli not only along sensory dimensions such as color or size but also categorical concepts such as "dog" or "mugger." Recent work has begun to reflect this complexity by using complex stimuli that vary on categorical dimensions rather than a single sensory feature.

Dunsmoor, Prince, Murty, Kragel, and LaBar (2011) used images of a face posing varying intensities of fearful emotional expression, ranging from a neutral face to a face with a highly fearful expression to investigate the generalization of fear learning along a continuum of emotional intensity. The expression intermediate between these two endpoints acted as the CS+ and was paired with an electric shock. Brain activity in the insula, thalamus, and striatum was enhanced to the generalized stimuli that displayed high levels of fear after, but importantly not prior to, conditioning to the intermediate CS+. These results were interesting because they revealed a bias toward high-intensity stimuli that resembled the CS+ along a gradient of emotional intensity rather than a gradient of perceptual similarity.

In another study, Dunsmoor, Kragel, Martin, and LaBar (2014) examined whether aversive learning is able to modulate the representation and responding to category concepts. Participants were conditioned to exemplars drawn from two superordinate categories: animals or tools. The individual member stimuli from within these two categories varied in their level of typicality of the category to which they belonged.

For example, a picture of a dog or cow served as highly typical examples of animals, whereas a starfish or armadillo rated low in typicality. During fear conditioning, one stimulus category served as the CS+, whereas the other served as a CS–. A number of regions showed increased responding to CS+ trials compared to CS– including the amygdala, hippocampus, insula, and anterior cingulate cortex. Consistent with the results from extinction learning studies, activity within vmPFC as well as the posterior cingulate cortex showed increased responding to the CS– relative to the CS+, confirming the sensitivity of these regions to safety signaling. Typicality of the individual members of the tool and animal categories modulated hippocampal activity, with exemplars that were viewed as more typical of their category showing greater activity in the hippocampus than exemplars that were less typical. Furthermore, there was significant coupling between the hippocampus and the amygdala, which declined as the experiment progressed. Because US reinforcement was not determined by typicality but instead by category membership of the stimuli, increased responding within the hippocampus and functional coupling with the amygdala may reflect the mechanism by which category-level representations generalize from typical to atypical members of that category.

Findings from studies investigating generalization show that learning to fear a specific CS+ results in fear associations not only to that particular stimulus but also a spreading of responding to stimuli that are similar in perceptual features or categorical membership. This generalization of fear responding is reflected at the neural level with increased responding along the generalization within a number of key regions, including the amygdala, and generalized responding within vmPFC is consistent with its tracking of a safety signal.

LEARNING FEAR FROM OTHERS

The direct experience of aversive events is a potent way to form fear associations, but it is not the only means by which fears can be learned. Social transmission of fear provides an important alternative by which fear can be expressed, transmitted, and acquired without direct exposure to a threat.

Rachman (1977) proposed that there are three means by which individuals attain fear. The first of these is the direct pathway, discussed thus far, where the CS and US are directly experienced together. The second is a vicarious pathway where individuals can learn by observing others' experience of the CS and US. The third pathway involves communicating information about the CS and US using language, without any experience of the relationship between these two stimuli.

The opportunity to learn fear associations from others removes the potentially dangerous requirement of directly experiencing a potentially harmful event. Given this adaptive function of social learning, it is unsurprising that social learning of fear has been demonstrated in numerous animals, ranging from birds (Cornell, Marzluff, & Pecoraro, 2012), mice (Jeon & Shin, 2011), wallabies (Griffin & Evans, 2003), and primates (Mineka & Cook, 1993). Cook and Mineka (1989) and colleagues, for example, exposed cage-reared monkeys to either movies or live presentations of a model monkey reacting fearfully to fear-relevant (snake) and fear-irrelevant objects (toy) objects. A single experience of observing a model reacting fearfully was sufficient to produce robust fear learning, which persisted for several months.

The neural processes that form the basis of social learning have only begun to be investigated in human and nonhuman animals. Jeon and colleagues (2010) found that mice successfully developed freezing

behavior by observing other mice receiving repetitive foot shocks. Inactivation of the ACC and the parafascicular and mediodorsal thalamic nuclei, which form the medial pain system (thought to comprise the affective components of pain) resulted in significantly reduced observational fear learning. Importantly, inactivation of these regions did not influence direct fear learning, and inactivation of the thalamic nuclei that form the sensory pain system had no effect on social fear learning, even though this inactivation resulted in reduced pain response behavior in the animals. These results are consistent with experiments relying on direct experience of pain, which find that the ACC is necessary to encode the affective aspect—or the "aversiveness"—of nociception (Johansen, Fields, & Manning, 2001). Taken together, these patterns of deficit following inactivation of the affective and sensory pain systems suggests that the ACC and the aforementioned thalamic nuclei may be uniquely necessary for social learning to be established.

Although the ACC appeared to be necessary for the acquisition of social fear, inactivation of the ACC was not detrimental to the expression of existing social fear memories. This is in contrast to the amygdala, in which inactivation disrupted acquisition and the subsequent expression of observed fear. Additionally, activity of intact ACC and amygdala were synchronized at theta rhythm frequency during learning, which may represent the neuronal communication that is necessary for social learning to occur, with the amygdala ultimately being necessary for the expression of socially and directly acquired fear.

One difficulty in understanding the specific role of the ACC in social learning is the polyglot nature of the ACC, with the structure implicated myriad cognitive processes (Ebitz & Hayden, 2016). Although prevailing views tend to focus on the involvement of the ACC in error detection, reward processing, and acting as a corrective device, it is also reliably implicated in nociceptive and social cognitive processes that may form the basis of its role in social learning. The consistency with which ACC responding, particularly within a dorsal region, is activated by pain has led some researchers to argue that the dorsal ACC is selective for pain processing (Lieberman & Eisenberger, 2015). Though this specificity for pain processing over other cognitive functions has been challenged as overly selective by others (Wager et al., 2016), it highlights the strong evidence, spanning techniques and species, that exists linking the ACC to pain processing (Hutchison, Davis, Lozano, Tasker, & Dostrovsky, 1999; Iwata et al., 2005; Koyama, Tanaka, & Mikami, 1998; Price, 2000). The involvement of the ACC in pain processing is, however, insufficient to explain the greater role for the ACC in social fear learning, given that direct fear learning similarly involves pain perception. Rather, it may be the social cognitive processes subserved by the ACC that provide a necessary and unique contribution when learning from others. The ACC responds not only to the direct experience of pain but also responds when we observe others experiencing pain (Yesudas & Lee, 2015). Furthermore, the perception of pain in others appears to be at least partially distinct from the direct experience of pain, because the observation of vicarious pain invokes activation within the ACC that is, at least partially, distinct from activation when pain is experienced directly (Jackson, Rainville, & Decety, 2006; Morrison & Downing, 2007). The distinct processing of vicarious pain foreshadows the involvement of the ACC in mentalizing (Frith & Frith, 2006), the ability to infer others' mental states (theory of mind), and empathy (Saarela et al., 2006). The involvement of the ACC in the ability to empathize another's experience of pain by inferring their mental

and affective states, and tying this internal representation of others' pain with an informative cue, may be what makes it possible to learn from others. Because this is a recent area of interest in the fear-learning literature, there remains much to be understood about how it is that we learn from others and in what ways this form of learning is more effective or constrained relative to direct learning.

Work in humans has found equivalent levels of learning, as indexed by SCR, when fear was acquired through direct experience, social observation, and verbal instruction (Olsson & Phelps, 2004). Expanding these behavioral results to brain imaging, Olsson, Nearing, and Phelps (2007) found a pattern of activation similar to that observed in the classical fear conditioning studies discussed previously. Participants in this study learned to associate CSs with aversive outcomes in two ways: by viewing a video of another person undergoing fear acquisition and separately by verbal instruction of the contingencies between a CS and US. The former examined if fear can be learned through the observation of a conspecific undergoing conditioning, and the latter provided a test of whether fear can be acquired through abstract language transmission. Importantly, neuroimaging results replicated the canonical observation of amygdala responding during fear acquisition and expression in both social learning tasks. Additionally, activation was also observed within the ACC and anterior insula, consistent with existing links between these two regions and the anticipation and experience of pain (Koyama, McHaffie, Laurienti, & Coghill, 2005; Lieberman & Eisenberger, 2015; Simmons, Matthews, Stein, & Paulus, 2004), as well as autonomic arousal (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005). Interestingly, activity within these regions was greater during the instructed conditioning phase when participants were expecting shocks, though none were delivered, than the observation phase, when participants did not anticipate shocks. This relative difference in activity between the two conditions may reflect the difference in anticipated pain and arousal between these two experimental phases.

One striking difference in neural activation between the two tasks was the significant activity observed within the anterior medial PFC (amPFC) during the observation task, which was absent in the instructed fear phase. The amPFC has been linked to a number of higher-order social and cognitive processes, including person perception and mentalizing (Amodio & Frith, 2006). Increased activation of the amPFC during the social observation stage may, therefore, be a reflection the attribution of mental states to the observed individual, which may be necessary for learning to be possible. That is, it may not be possible to acquire fear through the observation of others without the recruitment of empathy and an attribution of mental states that enable individuals to infer what the observed model is learning and what physical states, such as pain or discomfort, they may be experiencing.

Findings to date suggest that fear acquired through social observation relies on learning that is supported by neural processes similar to those underlying directly experienced fear conditioning. This is evidenced by similar patterns of behavioral and psychophysiological responding and the necessity of the amygdala across the two forms of learning. Research to date has implicated a number of additional structures that appear to underlie cognitive processes, such as mentalizing and affective pain, which may uniquely contribute to social learning.

Instructed Fear Learning

In addition to learning through experience and by observing others, humans possess

the unique ability to learn through language. Whereas fear learning through direct experience and social observation involves sensory representation of the stimuli involved, language conveys abstract information about the stimuli, forcing the receiver to rely on past experiences and internally generated imagery.

Exploring the effectiveness of fear acquired through direct experience, social observation, and instructed learning, Olsson and Phelps (2004) found comparable fear responses, as assessed using SCR, across the three means of learning. In order to map the neural mechanisms that underlie instructed fear learning, Phelps and colleagues (2001) provided participants with explicit instructions that they may receive a shock when shown the CS+, but not when shown the CS–. Results indicated robust activation in the left amygdala to CS+, consistent with the vital involvement of the amygdala in Pavlovian fear learning. Activation of the left insular cortex additionally correlated with SCR. Activity within the insula is present during Pavlovian conditioning and is key to conveying a cortical representation of pain to the amygdala (Shi & Davis, 1999). As such, the insula may be recruited by the expectation of the US, which may be necessary for the amygdala-mediated fear learning to occur.

A formal meta-analysis of 10 instructed fear studies revealed reliable activation within the dorsomedial PFC (dmPFC) (Mechias, Etkin, & Kalisch, 2010). Less-consistent activation was also observed within the insula and dorsal ACC, with activation in these two regions also being present when the authors examined studies of uninstructed Pavlovian conditioning. The findings from this meta-analytic work suggest that the dmPFC may be uniquely involved in instructed fear, providing support for the view that the dmPFC is involved in conscious threat appraisal (Kalisch & Gerlicher, 2014; Maier et al., 2012).

Neuroimaging work by Atlas, Doll, Li, Daw, and Phelps (2016) demonstrated an important dissociation between frontal regions and the amygdala in their involvement in fear learning. Brain activity was recorded in two groups of participants as they completed a reversal learning paradigm using photographs of human faces. In this paradigm, the stimuli that served as the CS+ and CS– would swap every 20 trials so that the stimulus that previously served as CS+ now acted as the CS– and vice versa. Importantly, the participants in the study were split into two groups: One group was instructed explicitly which stimulus would predict the shock at the start of the experiment and after every contingency reversal, but the other group was not provided with any explicit information and would rely entirely on reinforcement history. Examining the neural activation, the authors found that the amygdala was uninfluenced by instruction, instead relying on reinforcement history alone. Activity in the striatum, vmPFC, and orbitofrontal cortex (OFC), however, updated immediately following instruction, with no experience of the new CS+-US relationship being necessary to alter responding in these regions. These findings demonstrate an important divergence of the neural structures underlying fear learning. The amygdala appeared impervious to verbal instructions and contingency awareness, a finding consistent with models that paint the amygdala as evolutionarily impervious to cognitive interference (Öhman & Mineka, 2001). This apparent tendency of the amygdala to respond to environmental cues without regard to cognitive knowledge may provide vigilance to potential danger consistent with an evolutionary role as a threat detector. It is possible, however, that this vigilance may also prove maladaptive in situations in

which cognitive knowledge should override amygdala processing. A better understanding of how knowledge can shape fear learning and how the relationship between amygdala responding and frontal regions can be mediated may provide an avenue for the development of more effective and targeted interventions for disorders characterized by persisted or maladaptive fear.

FUTURE DIRECTIONS

Much has been learned to date about the neural and psychological factors that underpin fear learning. Despite the large body of knowledge that has been developed so far there remain many unanswered questions and opportunities for future research.

Genetic Influences on Human Fear Learning

Behavioral genetic work suggests that fear conditioning is moderately heritable, with approximately one-third of the variability in SCR during fear learning explained in a twin study (Hettema, Annas, Neale, Kendler, & Fredrikson, 2003). In tandem, cognitive genetic work has begun to identify common genetic variants that influence the functioning of neural systems implicated in fear learning. For example, variation in the human serotonin transporter gene has been repeatedly associated with amygdala function (Munafò, Brown, & Hariri, 2008), with early work linking the same variant with amygdala function during conditioning (Klucken et al., 2015). Though similar associations with fear learning have been noted for variation in BDNF (Lonsdorf, Haaker, & Kalisch, 2014; Lonsdorf et al., 2010) and COMT (Agren, Furmark, et al., 2012; Wendt et al., 2014), there have been failures to replicate existing effects (for example, see Torrents-Rodas et al., 2012). Further research with sufficiently large sample sizes is needed to replicate and expand on existing findings.

Individual Differences in Fear Learning

Most of the advances in our understanding of fear learning have focused on commonalities, that is, the circuits and behaviors that are consistent across studies. Inter-individual differences in fear conditioning, however, are common, and they appear to be stable over time (Zeidan et al., 2012) and heritable (Hettema et al., 2003). This stability and heritability suggests that the individual behavioral differences may be a reflection of alterations at the neural level. Although work has begun to unravel the factors that drive individual variation, such as the relationship between amygdala activity and individual differences in SCR (e.g., MacNamara et al., 2015), there is at present a paucity of evidence. The importance of understanding factors that drive individual differences is that they may provide biomarkers for resilience or vulnerability for disorders associated with the fear-learning system such as anxiety (Lissek et al., 2005) or post-traumatic stress disorder (VanElzakker, Dahlgren, Davis, Dubois, & Shin, 2014).

CONCLUSION

Much has been learned about the neuroscience and psychology of fear learning since Pavlov's initial observation. Animal studies employing lesions, direct neural recordings, and, more recently, optogenetic manipulations have provided a highly detailed map of the neural structures that form the basis of the fear learning system. The interplay of nuclei that form the amygdala in generating fear memories and behavioral responses has been mapped in high detail. Similarly, much has

been learned about the function of prefrontal and hippocampal inputs into this system to enable extinction and contextual regulation of fear memories.

Spurred by the advent of functional brain imaging, this work has been translated to human participants. A large body of work has replicated the vital role of the amygdala, PFC, and hippocampus in the acquisition, extinction, and generalization of conditioned fear. The basic fear-learning processes have also been extended to understand how we learn fear from others through observation and language.

Though much has been learned to date, there remain many questions that need to be answered. For example, are the neural mechanisms that make it possible to extinguish fear consistent across extinction through direct experience and extinction obtained by observing others? Similarly, although research has begun to test the utility of reconsolidation as a means to permanently alter fear memories, future work will need to test the parameters under which reconsolidation is able to permanently alter fear memories and the boundary limits within which it operates. Studies thus far have focused on altering discrete CS during the reconsolidation window, but it may be possible to alter fear memories by additionally modifying contextual memories in order to strengthen extinction recall. Future research will be needed to answer these and the many other open questions on how fear learning operates in humans and animal models.

LIST OF ABBREVIATIONS

CS	Conditioned stimulus
US	Unconditioned stimulus
UR	Unconditioned response
CR	Conditioned response
BLA	Basolateral complex of the amygdala
CMA	Centromedial complex of the amygdala
ITC	Intercalated cells
SCR	Skin conductance response
fMRI	Functional magnetic resonance imaging
ACC	Anterior cingulate cortex
PFC	Prefrontal cortex
vmPFC	Vental medial prefrontal cortex
dlPFC	Dorsolateral prefrontal cortex
dmPFC	Dorsomedial prefrontal cortex
amPFC	Anterior medial prefrontal cortex
IL	Infralimbic subdivision of the prefrontal cortex
VR	Virtual reality

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