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Review

Parsing neural circuits of fear learning and extinction across basic and clinical neuroscience: towards better translation

Ho Namkung^{1,2}, Kerrie L. Thomas^{6,7}, Jeremy Hall^{6,8}, and Akira Sawa^{1,2,3,4,5*}

Departments of ¹Biomedical Engineering, ²Psychiatry, ³Neuroscience, and ⁴Genetic Medicine

Johns Hopkins University School of Medicine, Baltimore, MD 21287 USA

Department of ⁵Mental Health

Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD 21287 USA

⁶Neuroscience and Mental Health Research Institute, Cardiff University, Cardiff, UK

⁷School of Biosciences, Cardiff University, Cardiff, UK

⁸School of Medicine, Cardiff University, Cardiff, UK

*Corresponding author, Akira Sawa: asawa1@jhmi.edu

Highlights

- Studies of fear learning and extinction have advanced our understanding of the neurobiology of threat and safety learning.

- A review on neural circuits of fear conditioning and extinction across animals and humans enables to identify knowledge gaps to be addressed for better cross-species translation.
- Altered fear conditioning and extinction have been implicated not only in post-traumatic stress disorder (PTSD), but also in other psychiatric and neurological conditions where biological processes in associative learning and memory are affected.
- Our understanding of fear circuits can lay the groundwork for further enhancing clinical benefits in a wide array of brain disorders from both mechanistic and therapeutic viewpoints.

Abstract

Over the past decades, studies of fear learning and extinction have advanced our understanding of the neurobiology of threat and safety learning. Animal studies can provide mechanistic/causal insights into human brain regions and their functional connectivity involved in fear learning and extinction. Findings in humans, conversely, may further enrich our understanding of the neural circuits in animals by providing macroscopic insights at the level of brain-wide networks. Nevertheless, there is still much room for improvement in translation between basic and clinical research on fear learning and extinction. Through the lens of neural circuits, in this article, we aim to review the current knowledge of fear learning and extinction in both animals and humans, and to propose strategies to fill in the current knowledge gap for the purpose of enhancing clinical benefits.

Keywords: fear conditioning, fear extinction, learning and memory, animal, human, translation

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1. Introduction

Over the past decades, the neurobiological basis of fear learning and extinction has been extensively studied in both humans and animals (e.g., non-human primates, rodents, flies, etc.) using fear conditioning paradigms (Anderson and Adolphs, 2014). Reflecting this advance, excellent review articles have recently been reported, most of which focused on molecular or brain circuit mechanisms underlying fear learning and/or extinction (Giustino and Maren, 2015; Greco and Liberzon, 2016; Herry et al., 2010; Johansen et al., 2011; Maren et al., 2013; Myers and Davis, 2007; Sehlmeyer et al., 2009; Tovote et al., 2015). Some review articles have addressed within-/between-species methodological coherence, which is important for translation across basic and clinical research (Flores et al., 2018; Haaker et al., 2019; Lonsdorf et al., 2017; Wotjak, 2019).

The goal of this review is twofold. First, through the lens of neural circuits, we will discuss the knowledge gaps that may interfere with smooth cross-species translation in research of fear conditioning and extinction in particular between rodents and humans (see sub-sections 2, 3, and 4). In particular, we will underscore the topics that have not been fully covered in past literature. Accordingly, we will discuss the insula, which has not been fully studied at the mechanistic levels (sub-section 4.2), and unintended selection bias in the fear conditioning paradigms (sub-section 4.3). We will extend our discussion and highlight subjective feelings of fear (sub-section 4.4).

The second goal is to redirect our discussion on the clinical implication of fear learning and extinction from a classic nosology based on categorical perspectives to recently-emerging

dimensional perspectives. A dimensional approach, represented by the Research Domain Criteria (RDoC) from the National Institute of Mental Health (NIMH), enables pathophysiological processes to be mapped on functional dimensions of the brain. Taking advantage of this perspective, our discussion was extended, beyond post-traumatic stress disorder (PTSD) and anxiety disorders, to other brain conditions not previously reviewed, such as schizophrenia, psychopathy, and Alzheimer's disease (sub-section 5). We will discuss how the knowledge of fear circuitry may contribute to patient stratification of neuropsychiatric disorders beyond their current disease categories, which is followed by mechanistic dissection at molecular, circuitry, and behavioral levels, for novel treatment development (sub-section 6).

2. Foundational knowledge about fear conditioning and extinction

2-1. Overall procedure

Fear can be innate or learned. Innate fear is expressed, with no prior experience or learning, in response to environmental stimuli, including predators, aggressive conspecifics, and sudden proximal encounters (Silva et al., 2016). In contrast, learned fear is expressed as a result of aversive experiences, such as an experience attacked by a dog and food poisoning.

Fear conditioning, a fundamental form of associative learning, has been the most commonly used procedure for inducing learned fear and therefore studying the neural basis of fear learning and memory. In this procedure, subjects learn to associate a (typically biologically-neutral) stimulus (conditioned stimulus, CS) with an aversive stimulus (unconditioned stimulus, US) generally through repeated CS-US pairings (Izquierdo et al., 2016). As a result, the CS acquires emotional salience and alone comes to evoke conditioned fear responses without the US. Note that, while it

has long been debated whether ‘fear’ is a subjective mental state that cannot be studied in non-human animals (e.g., rodents) (LeDoux, 2014; Mobbs et al., 2019), in this article the term ‘fear response(s)’ (see 2.2) is used in a way that collectively describes defense response(s) elicited by threats in both humans and animals, on the basis of a view that these responses capture a central state of fear across species (Anderson and Adolphs, 2014; Fanselow and Pennington, 2018; Mobbs et al., 2019).

Fear conditioning, in principle, involves adaptive processes to signal potential harm to the organism. In research, fear conditioning paradigms enable to fine-tune learning parameters (mostly relevant to the CS and US) in a way that reliably elicits measurable fear responses. They also have the advantage for mechanistic studies that the association is acquired very rapidly – even in a single trial – and retained long, allowing neurobiological changes associated with learning to be investigated in a temporally-controlled manner. Just as fear conditioning is an adaptive procedure, on the other hand, learning to extinguish fear responses when threats are no longer present is also fundamentally adaptive (Dunsmoor et al., 2015). This procedure, referred to as fear extinction, is modeled by repeatedly presenting the CS in the absence of the US, and is the foundation of exposure therapy for pathological fear and anxiety (Dunsmoor et al., 2015; Herry et al., 2010).

2-2. Types of fear conditioning paradigms

Two commonly-adopted fear conditioning paradigms are cued and contextual fear conditioning, which are differentiated by the type of the CS (Curzon et al., 2009; Haaker et al., 2019; Lonsdorf et al., 2017) (**Fig. 1**). In cued fear conditioning, a subject is placed in a conditioning

environment, and then a discrete cue (a cued CS) is delivered to be paired with an aversive event (an US). Despite many selectable discrete cues of different sensory modalities, auditory tones are the most frequently employed CSs in rodent studies, whereas visual cues (e.g., pictures of geometric shapes, differentially-colored lights, and human faces) in human studies (Haaker et al., 2019; Lonsdorf et al., 2017; Wotjak, 2019). Across species, on the other hand, mild electrical stimulation is the most commonly employed US: electric currents through the metal grid floor for rodent and those directly to the skin for humans (Haaker et al., 2019). As a result of CS-US pairings, the subject shows conditioned fear responses even when the cued CS alone is presented. The conditioned fear responses can be measured with a wide range of behavioral and physiological responses. In rodents, percent time frozen during the CS presentation is the most common behavioral outcome measure (Wotjak, 2019). In humans, however, mainly for ethical reasons, the intensity of USs is not strong enough to elicit a remarkable behavioral change. Accordingly, physiological outcome measures are frequently used to index conditioned responses, for which skin conductance responses (SCRs) and fear-potentiated startle (FPS) reflex (eye-blink component) are most common, with those often capturing slightly-different aspects of arousal and expectancy (Constantinou et al., 2021; Haaker et al., 2019; Lonsdorf et al., 2017). Depending on a temporal gap between the CS and US, cued fear conditioning can be further organized into two sub-types (delay and trace) (Curzon et al., 2009; Haaker et al., 2019; Lonsdorf et al., 2017) (**Fig. 1**). In delay fear conditioning, the US is administered to co-terminate with (most common) or immediately after the CS, whereas in trace fear conditioning a time interval is introduced between the termination of the CS and the start of the US. While the trace interval used in rodent studies was as short as 2-5 s or as long as 25-60 s (Curzon et al., 2009), that introduced in human studies ranged from 500 ms to 10 s (Lonsdorf et al., 2017; Sehlmeyer

et al., 2009). Of note, as the trace interval increases, conditioning to the cued CS decreases, whereas conditioning to the training context increases. In trace fear conditioning paradigms, accordingly, conditioned fear responses to the cued CS and the context are often measured separately during retrieval (i.e., cued and contextual retrieval).

In contextual fear conditioning, an aversive event (an US) is given to a subject in a conditioning environment (a contextual CS), without presenting a discrete cue (Curzon et al., 2009; Haaker et al., 2019; Lonsdorf et al., 2017) (**Fig. 1**). Consequently, the subject displays conditioned fear responses during re-exposure to the conditioning environment alone (i.e., the contextual CS alone). Note that a context can be defined as the set of circumstances (e.g., spatial and temporal features, cognitive and social aspects) in which fear conditioning or extinction takes place (Maren et al., 2013). In contrast to discrete cues, accordingly, contexts are complex and multimodal representations that are formed by constitutively binding multisensory and continuous elements into a unified representation. In rodent studies, contexts are manipulated by changing specific features of the physical chambers (e.g., floor textures and odors) in which animals undergo fear conditioning or extinction. On the other hand, in human studies a wide range of settings, which are created by computer background screens, complex images of environments, room illumination, or virtual reality, are employed for manipulating contexts (Lonsdorf et al., 2017).

2-3. Phases of fear learning and memory

Distinct phases of fear learning and memory can be investigated using fear conditioning and extinction paradigms (Lonsdorf et al., 2017; Tovote et al., 2015) (**Fig. 1**). The acquisition of fear

memory is characterized by a gradual increase in conditioned fear responses through CS-US pairings. Labile short-term memory is stabilized over time into a latent long-term memory via consolidation processes (McGaugh, 2000). Subsequently, during the retrieval of fear memory, the consolidated fear memory can be retrieved by re-exposure to the cued CS alone (cued fear conditioning) or the contextual CS alone (contextual fear conditioning). During the retrieval, the extent of fear generalization can also be examined by exposure to a stimulus that resembles the original CS. Note that a certain level of fear generalization is an adaptive process that enables (experience-based) defensive responses to a potential threat in complex environments (Asok et al., 2018). However, generalization can become maladaptive when a safe stimulus that resembles a fearful stimulus is over-interpreted as threatening, as evidenced in some anxiety disorders (Dunsmoor and Paz, 2015; Lissek et al., 2014).

The consolidated fear memory can be modulated by subsequent events (Lonsdorf et al., 2017; Tovote et al., 2015). Upon a brief re-exposure to the CS alone, it can return to a transiently labile state, in which the fear memory requires a reconsolidation process to be re-stabilized (Nader et al., 2000; Schiller et al., 2010). However, if the CS alone is presented repeatedly, fear extinction occurs, which does not erase the original fear memory but instead generates a competing (inhibitory) extinction memory capable of suppressing conditioned fear responses in a context-dependent manner (Bouton, 2004) (**Fig. 1**). Accordingly, the acquisition of extinction memory is characterized by a gradual decrease in conditioned fear responses. Similarly, the extinction memory undergoes a similar but distinct consolidation process (Lin et al., 2003). Subsequently, the consolidated extinction memory can be retrieved by re-exposure to the CS alone, evidenced by low conditioned fear responses. Even after successful fear extinction, it is possible for

conditioned fear responses to reappear through different phenomena of return-of-fear (ROF) that encompass spontaneous recovery, reinstatement, and renewal of fear (**Fig. 1**). Spontaneous recovery of the previously-extinguished conditioned fear responses is often observed after some passage of time. Fear reinstatement also can occur by exposure to the original US or even a different US. Fear renewal can occur by re-exposure to the CS alone in a context other than the extinction context, indicating that fear extinction is context-dependent (Bouton, 2004).

There are noteworthy procedural differences between rodent and human paradigms of fear conditioning and extinction (Flores et al., 2018; Haaker et al., 2019; Lonsdorf et al., 2017). Briefly, while rodent studies usually introduce independent sessions of fear memory acquisition and retrieval/extinction with explicit temporal gaps between them (e.g., 24 hr) and with appropriate contextual changes, for practical reasons the vast majority of human studies employ fear memory retrieval/extinction sessions immediately after fear memory acquisition with no temporal delay allowing for fear memory consolidation and sometimes with no appropriate contextual changes. In addition, a substantial number of rodent studies use single-cue paradigms in which the only one CS is paired with the US, whereas human studies usually use discriminative-cue paradigms where one CS (CS+) is paired with the US but another CS (CS-) is not. Furthermore, the reinforcement rates, during fear memory acquisition, usually differ between rodent and human studies, with those being often lower in human studies. These methodological discrepancies represent major cross-species translational challenges (see 4.1), and considerable efforts to address these have recently been made (Flores et al., 2018; Haaker et al., 2019; Lonsdorf et al., 2017).

3. A systematic overview of the neural circuits in fear conditioning and extinction

3.1. Rodent studies

Animal studies allow brain manipulations that are essential to address mechanistic dissection and causality, complementing the limitation of human studies. Brain regions crucial for fear learning and extinction have been traditionally investigated by perturbing specific brain regions at different timepoints in fear conditioning and extinction paradigms (Do Monte et al., 2016; Vaidya et al., 2019). The emergence of optogenetics enables us to functionally characterize the necessity and sufficiency of individual neural circuit elements and their interactions in a brain network within a specific temporal window (Kim et al., 2017). The real-time activity of neural circuits can be longitudinally monitored, using *in vivo* calcium imaging at the single-cell or population level over the course of fear conditioning and extinction (Resendez and Stuber, 2015; Siciliano and Tye, 2019).

Supported by technological advances, the neural circuits recruited in delay and contextual fear conditioning have been under intensive investigation in rodent studies over the past decades. In contrast, there has been relatively a dearth of interest in those engaged in trace fear conditioning. The insertion of a trace interval between the CS and US in trace fear conditioning is thought to impose cognitively demanding processes for learning (e.g., holding the stimulus information in working memory/attention) (Connor and Gould, 2016; Gilmartin et al., 2014a; Han et al., 2003), and therefore recruits brain systems responsible for these processes. Such higher-level cognitive functions are commonly impaired in many brain disorders. Supported by the potential significance in clinical conditions, we here bring and compare the neural circuits in delay, trace, and contextual fear conditioning as well as those in fear extinction in a balanced manner.

3.1.1. Delay fear conditioning

In delay fear conditioning, the amygdala has traditionally been a focal point of research because of its necessary role in both the acquisition and retrieval of conditioned fear responses. In the traditional view, during the acquisition of fear memory, sensory inputs carrying information about the CS and US converge onto principal neurons in a sub-region of the amygdala [the lateral amygdala (LA)], which leads to strengthening of excitatory synapses carrying the CS information (McKernan and Shinnick-Gallagher, 1997; Rogan et al., 1997; Rumpel et al., 2005). This experience-dependent synaptic strengthening subsequently enables the CS alone to activate LA neurons, which eventually influence the central amygdala (CeA) outputs to drive conditioned behavioral and physiological responses via downstream brain regions, such as the periaqueductal gray and hypothalamus (LeDoux et al., 1988). Distinct from this traditional serial model of amygdala information processing, in which emotional processing proceeds in a serial manner from the LA (input) to CeA (output), a parallel information processing model is also gaining significant support, in which the BLA and CeA function independently and in parallel to control distinct aspects of emotional learning (Balleine and Killcross, 2006). According to this model, it is likely that the BLA mediates associations between the CS and sensory properties of the US, whereas the CeA mediates the associations of the CS with emotional properties of the US. Indeed, recent evidence showed that, during fear memory acquisition, a major population of CeA neurons [Protein kinase C- δ -expressing (PKC- δ +) neurons] convey information about the US to the LA and thereby contribute to shaping the synaptic plasticity in the LA, contradicting the serial information flow from the LA to CeA (Yu et al., 2017). Intriguingly, recently-emerging evidence shows that neuromodulation of amygdala circuits also plays crucial roles in fear

memory acquisition. The BLA-projecting ventral tegmental area (VTA) dopamine neurons contribute to fear memory acquisition by signaling the salience of aversive events (Lutas et al., 2019; Tang et al., 2020). Furthermore, BLA-projecting dorsal raphe (DR) serotonergic neurons can facilitate fear memory acquisition by amplifying fear-associated BLA neuronal firing (Sengupta and Holmes, 2019). For more detailed information about the role of amygdala microcircuits in delay fear conditioning, readers are encouraged to read recent review articles thoroughly covering this topic (Duvarci and Pare, 2014; Janak and Tye, 2015b; Krabbe et al., 2018; Tovote et al., 2015).

The medial prefrontal cortex (mPFC) is not necessary for the acquisition of fear memory, but essential for the expression of conditioned fear responses during fear memory retrieval (Corcoran and Quirk, 2007) (**Fig. 2A**). Specifically, the prelimbic cortex (PrL), a sub-region of the mPFC, receives inputs from potential ‘fear neurons’ (i.e., neurons exhibiting a selective increase in CS-evoked activity as a result of fear conditioning) in the basal amygdala (BA) and those from the hippocampus (Ishikawa and Nakamura, 2006; Klavir et al., 2017; Senn et al., 2014; Sotres-Bayon et al., 2012), which in turn drives conditioned fear responses by exerting top-down regulation of downstream circuits including the basolateral amygdala (BLA) (Arruda-Carvalho and Clem, 2014; Do-Monte et al., 2015b) (**Fig. 2A**). The precise temporal control of fear expression is likely to be achieved via a disinhibitory mechanism within the PrL that the phasic inhibition of PrL interneurons disinhibits its projection neurons and synchronizes their firing, leading to fear expression via the downstream targets (Courtin et al., 2014; Cummings and Clem, 2020). Consistently, synchronous 4-Hz oscillations in the PrL-BLA circuits coordinate their functional coupling and control the precise timing of conditioned fear response (Dejean et al.,

2016; Karalis et al., 2016). Notably, the neural circuits recruited for the retrieval of fear memory undergo time- and space-dependent reorganization, in line with systems consolidation of memory: distinctively-reorganized sets of PrL neuronal ensembles are recruited in a time-dependent manner to regulate temporally-switched downstream circuits for the retrieval of fear memory (DeNardo et al., 2019). In accordance with this notion, fear memory retrieval initially depends on PrL-BLA circuits, but likely shifts to PrL-PVT circuits (PVT, the paraventricular nucleus of the thalamus) with the passage of time (Do-Monte et al., 2015b) (**Fig. 2A**).

3.1.2. Trace fear conditioning

In trace fear conditioning, the association of two stimuli separated in time requires to hold a mnemonic ‘trace’ of the first stimulus until the subsequent one occurs. In contrast to delay fear conditioning, accordingly, it is believed that brain systems responsible for bridging the temporally-disconnected stimuli, such as the mPFC, hippocampus, and entorhinal cortex, are recruited for the acquisition of fear memory (Gilmartin et al., 2014a; Kitamura et al., 2015; Raybuck and Lattal, 2014). Within the mPFC, a subset of PrL neurons exhibit sustained increases in firing in response to the CS and throughout the trace interval (Baeg et al., 2001; Gilmartin and McEchron, 2005). Accordingly, the PrL may maintain a neural representation of the CS in working memory during the trace interval, therefore bridging the CS- with US-encoding signals. Supporting this idea, silencing activity of the PrL selectively during the trace interval, but not during the CS or inter-trial interval, impaired the acquisition of fear memory (Gilmartin et al., 2013). Similar to the PrL, activity of the dorsal hippocampus (dCA1) selectively during the trace interval is necessary for the fear memory acquisition (Sellami et al., 2017). Consistently, the entorhinal cortex layer III inputs to the dorsal hippocampus plays a

crucial role in fear memory acquisition (Suh et al., 2011). In contrast to the PrL, however, the dorsal hippocampus does not exhibit persistent activity during the trace interval, but instead involves broad changes in network activity and the emergence of a sparse and temporally stochastic code for stimuli identities (Ahmed et al., 2020). Intriguingly, it is likely that, depending on the length of a trace interval, different neural circuits are recruited for processing temporally-disconnected stimuli: the association across a short trace interval (5 s) relies on the PrL, whereas learning across a longer interval (40 s) becomes dependent on the dorsal hippocampus (Guimaraes et al., 2011). Altogether, the mPFC likely processes working memory-like sustained activity across the trace interval, whereas the dorsal hippocampus encodes learning-related changes in activation to stimuli that probably reflect CS-US temporal information (Connor and Gould, 2016). Of note, there is conflicting evidence showing necessity (Gilmartin et al., 2012; Guimaraes et al., 2011) and unnecessity (Raybuck and Lattal, 2011) of the amygdala in fear memory acquisition, soliciting further systematic efforts to address this discrepancy.

The mPFC and hippocampus play key roles not only in the acquisition, but also in the retrieval of fear memory (**Fig. 2B**). Importantly, their involvement likely undergoes temporal evolution, in accordance with the notion of systems consolidation. Consistent evidence shows that the mPFC is necessary for fear memory retrieval not at a recent time point (1 day after fear acquisition), but at remote time points (30 or 200 days later) (Beeman et al., 2013; Quinn et al., 2008). Supporting this evidence, cells in the mPFC exhibit temporally-graded increase of firing in response to the CS over a period of several weeks after trace fear conditioning, without continued training (Takehara-Nishiuchi and McNaughton, 2008). In contrast, the hippocampus is not necessary for

remote retrieval, but essential for recent retrieval (Beeman et al., 2013; Hall et al., 2001; Quinn et al., 2008). Altogether, it is likely that hippocampal circuits recruited for the retrieval of fear memory gradually become functionally inactive with time, whereas mPFC counterparts become functionally mature with time, in a similar fashion to systems consolidation of contextual fear memory (see 3.1.3) (**Fig. 2B**). Of note, disruption of the hippocampus 1 day after trace fear conditioning did not lead to deficits in fear memory retrieval at a remote time point (30 days later), implying that mPFC-mediated remote retrieval may be independent of hippocampal function (Beeman et al., 2013).

3.1.3. Contextual fear conditioning

Supported by its key roles in episodic memory and spatial representation, the dorsal hippocampus has traditionally been a target of intensive studies of contextual fear conditioning (Maren et al., 2013). Multiple lines of evidence pin down a specific role of the dorsal hippocampus in facilitating the acquisition of contextual fear memory. Notably, disruption of the dorsal hippocampus made before conditioning (i.e., pre-conditioning disruption) does not necessarily eliminate contextual fear acquisition, especially when a pre-exposure to the context (i.e., conditioning chamber) is ensured (Maren et al., 1997; Matus-Amat et al., 2004; Young et al., 1994). This indicates that extra-dorsal hippocampal encoding of simple elemental cues, which collectively constitute a context, is still sufficient for elemental, notwithstanding less efficient, conditioning to occur. With no pre-exposure to the context, furthermore, as the time interval between placement in the context and US-delivery becomes reduced, conditioned fear responses to the context become dampened (Wiltgen et al., 2006). Taken altogether, the dorsal hippocampus has a specific role in encoding contextual representations (i.e., contextual

encoding), but is not necessary for the association of a context and US. Once the context is encoded, the amygdala likely forms the association between the contextual CS and US during the acquisition of fear memory (Fanselow and Kim, 1994; Kochli et al., 2015; Wiltgen et al., 2006; Zelikowsky et al., 2014). Other than the dorsal hippocampus of a traditional focus, recently-emerging evidence underscores recruitment of the ventral hippocampus in contextual fear memory acquisition. The activity of the ventral hippocampal (vCA1) projections to the BA is necessary for contextual fear acquisition, for which selective strengthening of vCA1-BA synapses may represent an associated synaptic change (Jimenez et al., 2020; Kim and Cho, 2020). The ventral hippocampal projections to the PrL also play a necessary role in contextual, but not in (trace) cued, fear memory acquisition, possibly by relaying the current contextual state (Twining et al., 2020). Given an influential previous insight suggesting distinct functional roles for the ventral and dorsal hippocampus, with the ventral hippocampus being associated with motivational and emotional behaviors and the dorsal hippocampus being involved in general cognitive functions (Fanselow and Dong, 2010), more sophisticated studies, which can address the question of how each compartment and their communication play roles in contextual fear memory acquisition, are awaited. Of note, as another brain area crucial for fear memory acquisition when timing (see 3.1.2) and context contribute to threat prediction, the mPFC serves as a potential alternative brain system that compensates for extensive damage to the dorsal hippocampus (Zelikowsky et al., 2013).

As the members of episodic memory systems, the neural circuits recruited for the retrieval of contextual fear memory largely overlap with those for trace fear memory (**Fig. 2C**). They are also reminiscent of each other due to inverse temporal contributions of the hippocampus and

mPFC. The dorsal hippocampus is necessary not for remotely-acquired (longer than 30 days), but for recently-acquired (1 day) fear memory (Anagnostaras et al., 1999; Denny et al., 2014; Kim and Fanselow, 1992; Maren et al., 1997; Tanaka et al., 2014). The ventral hippocampus is also crucial at least for recent retrieval of contextual fear memory (Jimenez et al., 2020; Knapska et al., 2012; Xu et al., 2016). In contrast, the mPFC is necessary for fear memory retrieval not at recent time points (1 or 3 days), but at remote time points (18, 36, or 200 days) (Frankland et al., 2004; Quinn et al., 2008). In line with these observations supporting systems consolidation of memory, a recent study suggests that hippocampal neuronal ensembles recruited for contextual memory retrieval gradually become silent with time, whereas mPFC counterparts become functionally mature over time with support from hippocampal inputs (presumably via the medial entorhinal cortex) after being generated during initial conditioning by inputs from both the hippocampal–entorhinal cortex network and the BLA (Kitamura et al., 2017). For both recent and remote retrieval, the amygdala, having inputs from the hippocampus and mPFC, likely serves as a common pathway to drive conditioned fear responses. Of note, an accumulating body of evidence shows that post-conditioning communication between the hippocampus and mPFC for systems consolidation is likely to be mediated by the thalamus. In particular, the reuniens (Re) and rhomboid (Rh) nuclei of the ventral midline thalamus (ReRh), which bidirectionally connect the hippocampus and mPFC (Hoover and Vertes, 2012; Varela et al., 2014), crucially support (off-line) systems consolidation of contextual fear memory, despite no necessity in both recent and remote retrieval (Quet et al., 2020). The anterodorsal thalamic nucleus, having inputs from the hippocampal CA3, may also be a potentially important brain region for systems consolidation of contextual fear memory, given that it becomes more active over the course of systems consolidation (Vetere et al., 2021).

3.1.4. Fear extinction

The neural circuits recruited for fear extinction are also embedded in a large-scale brain network including the amygdala, mPFC, and hippocampus (Herry et al., 2010). During the acquisition of extinction memory, a population of neurons within the BA (so-called ‘extinction neurons’) become responsive to the extinguished CS over the course of repeatedly presenting the CS alone and associated with a low fear state, which is distinct from a population of ‘fear neurons’ within the BA (Herry et al., 2008). Multiple lines of evidence suggest that the acquisition of fear extinction enables remodeling of BLA parvalbumin-expression (PV+) inhibitory interneurons to suppress fear-encoding neurons selectively (i.e., fear neurons), consequently shifting the balance between competitive fear and extinction microcircuits (Davis et al., 2017; Kasugai et al., 2019; Trouche et al., 2013). Interestingly, BLA neurons are critical targets of dopamine whose neuromodulation is known to influence the acquisition of fear extinction. The VTA dopamine neurons are engaged in the acquisition of fear extinction by signaling both prediction errors (by the medial VTA) and salience (by the lateral VTA), consequently exerting a causal role in facilitating fear extinction (Cai et al., 2020; Luo et al., 2018; Salinas-Hernandez et al., 2018). While dopaminergic signaling in the BLA is known to be necessary for the acquisition of fear extinction (Shi et al., 2017), whether and how dopamine selectively targets specific types of neurons to regulate the activity of and reshape amygdala microcircuits for fear extinction, as well as fear conditioning, still need to be answered. Of note, on the basis of a hypothesis that the omission of an expected US may be experienced as a rewarding event, recent evidence proposes that fear extinction may be an appetitive learning process mediated by reward circuits. Indeed, the BLA neuronal ensembles engaged in fear extinction overlap significantly with reward-

responsive neurons in the BLA, with those being mutually interchangeable in driving appetitive behaviors and fear extinction (Zhang et al., 2020). In addition, VTA dopamine neurons encode (potentially reward) predictions error signals upon the US omission (Cai et al., 2020). However, whether those dopamine neurons actually signal ‘reward’ prediction errors that drive appetitive learning further needs to be corroborated by designing a study employing both fear extinction and appetitive learning.

For the expression of learned fear and extinction, according to a contemporary view, the PrL exerts top-down regulation of the amygdala for promoting conditioned fear responses, whereas another sub-region of the mPFC, named the infralimbic cortex (IL), for suppressing fear responses (Burgos-Robles et al., 2009; Giustino and Maren, 2015; Milad and Quirk, 2002; Sierra-Mercado et al., 2011). Notably, there is conflicting evidence in regard to the pathways through which the IL suppresses fear responses during extinction retrieval. Multiple lines of evidence suggest that the IL receives cue- and context-associated inputs from the BA and hippocampus (Hoover and Vertes, 2007; Ishikawa and Nakamura, 2003, 2006; Jay and Witter, 1991; Qin et al., 2021), respectively, which in turn suppresses conditioned fear responses by directly activating intercalated (ITC) neurons, a cluster of inhibitory neurons interspersed between the BLA and CeA, that can produce feed-forward inhibition of CeA outputs (Cho et al., 2013; Likhtik et al., 2008; McDonald et al., 1996; Pinard et al., 2012; Royer et al., 1999) (**Fig. 2D**). In contrast, recent evidence suggests that IL activity affects ITC neurons not directly, but di-synaptically via the BA (Strobel et al., 2015) (**Fig. 2D**). It is possible that, during extinction acquisition, IL-to-BA projections contribute to shaping potentiated BA synapses onto ITC neurons, which can drive feedforward inhibition of the CeA outputs for suppressing fear

responses (Amano et al., 2010). Note that converging evidence implies, during extinction retrieval, the BA can activate ITC neurons without IL inputs (Amano et al., 2010; Bukalo et al., 2015; Do-Monte et al., 2015a) (**Fig. 2D**). While multiple lines of evidence delineates roles of mPFC-amygdala interactions in the retrieval of extinction, roles of the hippocampus and its interactions with the mPFC or amygdala in extinction memory retrieval still remain unclear, and only a few studies are beginning to find some clues. For instance, a recent study shows that the dorsal hippocampus-to-IL pathway essentially mediates extinction memory retrieval (Qin et al., 2021). Of note, the interaction between hippocampus and mPFC for extinction retrieval can also be mediated by a third brain region. Recently-emerging evidence underscores the nucleus reunions (Re), a ventral midline thalamic nucleus that coordinates activity between the mPFC and hippocampus, as a potentially-important brain region in processing contextual information, therefore being essential for the (context-dependent) retrieval, as well as the acquisition, of extinction memory. Specifically, the mPFC-to-Re projections are necessary for both acquisition and retrieval of extinction memory (Ramanathan et al., 2018; Ramanathan and Maren, 2019). How specifically the Re mediates communications between the mPFC and hippocampus for context-dependent fear extinction and fear renewal should be an important subject of future studies.

Fear extinction is a context-dependent learning process – that is, responses to the extinguished CS are suppressed only in the extinction context, but can be renewed in other contexts. Expectedly, a substantial number of studies pin down the hippocampus as a key region of regulating the context dependence of extinction memory, context-dependent renewal of fear in particular. For instance, inactivation of the hippocampus diminishes the renewal of fear

responses to an extinguished CS outside the extinction context, implying deficits in contextual retrieval (Corcoran and Maren, 2001; Hobin et al., 2006; Zelikowsky et al., 2012). Furthermore, interaction of the hippocampus with amygdala is crucially involved in fear renewal after extinction. While the hippocampus regulates context-dependent neuronal activity of the amygdala (Maren and Hobin, 2007), there seem to be at least two major pathways from the hippocampus to amygdala: direct pathway and indirect pathway via the mPFC. Direct ventral hippocampal (and PrL) inputs to the amygdala target neurons activated by fear renewal over those activated by extinction retrieval, presumably promoting contextual retrieval of fear (Kim and Cho, 2017; Knapska et al., 2012). Indirect hippocampal projections to the amygdala can pass via either the PrL or IL. Ventral hippocampal neurons projecting to the PrL are preferentially involved in fear renewal (Wang et al., 2016). Consistently, inactivation of the ventral hippocampus decreases activity of PrL inhibitory neurons, leading to increased spontaneous activity of PrL pyramidal neurons and promoting fear renewal (Sotres-Bayon et al., 2012; Vasquez et al., 2019). Given that the IL is involved in suppressing conditioned fear responses after fear extinction, it may be surprising that ventral hippocampal neurons projecting the IL are also preferentially engaged during fear renewal (Wang et al., 2016). However, a recent study explains a mechanism by which IL-projecting ventral hippocampal neurons affect fear renewal. According to the study, ventral hippocampal projections to the IL can recruit PV+ interneurons to exert feed-forward inhibition of BA-projecting IL pyramidal neurons, consequently countering the expression of fear extinction and promoting fear renewal (Marek et al., 2018). Interestingly, the ventral hippocampal neurons with collaterals to both PrL and BA may play particularly important roles in fear renewal by synchronizing prefrontal-amamygdala circuits (Jin and Maren, 2015). Of note, a recent study shows the formation of two distinct populations of neurons in the

dorsal hippocampus that may determine whether fear is expressed or suppressed in a context-dependent manner after fear extinction (Lacagnina et al., 2019).

3.2. Human studies

Human functional neuroimaging has illuminated human brain systems involved in fear conditioning and extinction. These observations in humans and insights from animal models are complementary to each other. Thus, persistent efforts in comparing the animal and human brain circuits will be indispensable to gaining a clear mechanistic/causal picture drawn by micro- and macro-circuit insights into fear conditioning and extinction. Here, paralleling our review of animal studies, we provide a summary of the human brain correlates of delay, trace, and contextual fear conditioning in healthy individuals, respectively, as well as those of fear extinction.

3.2.1. Delay fear conditioning

According to a substantial number of fMRI studies (Andreatta et al., 2012; Armony and Dolan, 2002; Bach et al., 2011; Buchel et al., 1998; Critchley et al., 2002; Dunsmoor et al., 2008; Eippert et al., 2012; Etkin and Wager, 2007; Fullana et al., 2016; Knight et al., 2004a; Knight et al., 2005; Knight et al., 2009; LaBar et al., 1998; Maier et al., 2012; Marschner et al., 2008; Marsteller et al., 2016; Mechias et al., 2010; Milad et al., 2007a; Savage et al., 2020; Sehlmeyer et al., 2009; Tabbert et al., 2011; Wood et al., 2013; Wood et al., 2012), the most commonly-activated brain regions during delay fear conditioning include the amygdala, anterior cingulate cortex (ACC), and insula. Interestingly, multiple studies show that amygdala responses to the CS+ become diminished over the course of conditioning, possibly indicating a new formation of

the CS-US association in the early acquisition of fear memory (Buchel et al., 1998; LaBar et al., 1998; Marschner et al., 2008). On the other hand, activity of ACC and insula remains more consistent, suggesting their persistent engagement in the expression of fear responses (Buchel et al., 1998; Critchley et al., 2002; Knight et al., 2004a). It should be noted that there has been conflicting evidence in regard to activity of the amygdala, as well as its time-dependent activity profile. Most fundamentally, activity of the amygdala was not reliably captured in some studies (Fullana et al., 2016; Knight et al., 2004a) including a recent large-scale fMRI meta-analysis that further replicates activation of the ACC and insula (Fullana et al., 2016). Moreover, some studies show constant amygdala responses to the CS+ over the course of conditioning (Armony and Dolan, 2002; Bach et al., 2011), and there is also a study suggesting subregion-specific change of the amygdala activity, with the dorsal amygdala showing progressively decreasing activity but the ventral amygdala showing constant activity (Morris et al., 2001). These controversial findings may arise from multiple reasons that include the following: well-known technical challenges in signal detection from this region (Biswal et al., 1996; Boubela et al., 2015; Merboldt et al., 2001; Windischberger et al., 2002) that nevertheless accompany persistent endeavors to overcome (Geissberger et al., 2020; Sladky et al., 2013); methodological differences such as the nature of conditioned stimuli (e.g., angry face vs. neutral face) [refer to the discussion of (Armony and Dolan, 2002)]; sparsely-distributed amygdala neurons responding to the CS+ (threat) and CS- (safety), which often leads to obscuring contrastive fMRI responses to the CS+ vs. CS- in the case of applying spatial filter (i.e., smoothing) (Bach et al., 2011). Regardless, the fact that patients with amygdala lesions show deficits in the acquisition of fear memory still supports its crucial necessity (Bechara et al., 1995; Klumpers et al., 2015).

Comparative functional neuroanatomy enables to translate our understanding of brain structure and function across species (**Fig. 2E**). Interpreting human studies in light of rodent studies needs extra caution particularly when concerning the controversy on the human counterpart of the rodent PrL. While the human dorsolateral prefrontal cortex (DLPFC) shares certain functional features with the rodent PrL such as attentional control, anatomical features including cytoarchitecture and connectivity indicate that the BA32 subregion of human ACC (a part of the dorsal ACC, dACC) may be homologous with the rodent PrL (Heilbronner et al., 2016; Hoover and Vertes, 2007; Laubach et al., 2018; van Heukelum et al., 2020). However, at least in the field of fear learning and memory, a prominent view is that the human dACC, considered as a counterpart of the rodent PrL, regulates the expression of fear responses, whereas the human ventromedial prefrontal cortex (VMPFC), regarded as a counterpart of the rodent IL, drives the suppression of fear response (Giustino and Maren, 2015; Milad et al., 2007a; Phelps et al., 2004) (see 3.2.4 for further discussion of the VMPFC). Indeed, in healthy human subjects, the dACC is activated by the CS+, its activation is positively correlated with fear responses, dACC thickness is positively correlated with fear responses during conditioning, and resting metabolism in the dACC positively predicts the acquisition of conditioned fear responses (Linnman et al., 2012b; Milad et al., 2007a). Furthermore, the dACC-amygda functional coupling becomes stronger during the consolidation of fear memory in humans (Feng et al., 2014; Feng et al., 2013). Taken altogether with insights from rodent studies, human studies imply that the formation of the CS-US association involves neuroplasticity in the amygdala and consequent top-down regulation by the dACC onto the amygdala for the appropriate cue-driven expression of conditioned fear responses. Of note, despite its reliable activation, the exact role of the insula in delay fear conditioning, as well as other types of conditioning, remains unknown in both human and rodent

studies. Recognizing this important knowledge gap, therefore, we further discuss about its potential roles in emotional learning and memory in a separately designated section (see 4.2).

3.2.2. Trace fear conditioning

Compared to delay fear conditioning, a relatively small number of studies have focused on understanding the neural circuit basis of trace fear conditioning in humans. Nevertheless, multiple lines of evidence consistently suggest that, during the acquisition of trace fear memory, brain areas essential for associating temporally-separated events, including the hippocampus and DLPFC, are recruited along with the amygdala, ACC, and insula that are engaged in delay fear conditioning (Buchel et al., 1999; Clark and Squire, 1998; Haritha et al., 2013; Knight et al., 2004a). Notably, the DLPFC and anterior insula are activated preferentially during the trace interval compared with all other stimulus periods (Buchel et al., 1999; Knight et al., 2004a), which is further replicated with trace interval-specific activation of the right DLPFC (i.e., right-lateralized) and bilateral insula (Haritha et al., 2013). The DLPFC is well-known to play a crucial role in the maintenance of information by directing attention to internal representations of sensory stimuli (i.e., working memory), as evidenced by the observation of its persistent activity during the retention interval of delayed response tasks (Barbey et al., 2013; Curtis and D'Esposito, 2003). The anterior insula is known to detect emotionally-salient stimuli and then arrange cognitive processes with the DLPFC, such as working memory and attention, for further processing them (Namkung et al., 2017) (see 4.2 for further discussion on the insula). Accordingly, coactivation of the DLPFC and insula during the trace interval likely encodes the maintenance of CS information throughout the trace interval until the occurrence of US. However, the hippocampus is not co-activated along with the DLPFC and insula during the trace

interval, which is not consistent with recent evidence suggesting persistent activity of the hippocampus for the maintenance of working memory (Kaminski et al., 2017). Instead, some studies show that, over the course of trace fear conditioning, activity of the hippocampus becomes diminished (Buchel et al., 1999; Knight et al., 2004a) as does amygdala activation during delay fear conditioning (Buchel et al., 1998; LaBar et al., 1998; Marschner et al., 2008). Of note, activity of the ACC and insula remains consistent.

Preferential activity in the DLPFC during the trace interval bears a close resemblance to that of the rodent PrL. As discussed (3.2.1), although the human dACC is currently believed to be homologous to the rodent PrL in the field, the human DLPFC shares certain functional features with the rodent PrL as exemplified in this case. Accordingly, considerable efforts for more fine functional mapping between human dACC/DLPFC and mouse mPFC subregions will be crucial for enhancing translational insights. Similar to rodent studies, human studies imply that the DLPFC, probably in concert with the anterior insula, maintains a neural representation of the CS in working memory during the trace interval, thereby bridging the CS- with US-encoding signals whose temporal information is processed in the hippocampus particularly in the early stage of conditioning. For the expression of conditioned fear responses, top-down regulation of the dACC onto the amygdala is likely to be exerted.

3.2.3. Contextual fear conditioning

Despite a large number of studies of contextual fear conditioning in rodents, relatively few studies have directly investigated the neural circuit basis of contextual fear conditioning in humans, producing some challenges in cross-species translation. This gap mainly arises from the

challenge in establishing different contexts (CTX+ vs. CTX-) in a functional neuroimaging environment (Maren et al., 2013). Specifically, while in rodent studies contexts can be easily manipulated by changing the animal's physical location (e.g., different chambers) or spatial features (e.g., floor and wall textures), it is much more difficult in human studies to create distinct spatiotemporal contexts while rigorously maintaining experimental control, particularly in a neuroimaging environment (Kroes et al., 2017). Nevertheless, there have been persistent efforts to overcome this inherent difficulty. Several studies used visual cues (e.g., gradual background colors, or pictures of some places) to make a certain contextual representation with no timed-pairing with the US (i.e., temporally-unpredictable US) which is distinct from the timed-pairing of the CS-US in cued fear conditioning, and as a result found the engagement of both the hippocampus and amygdala for the acquisition of contextual fear memory (Lang et al., 2009; Marschner et al., 2008; Pohlack et al., 2012). Multiple studies employed a differential contextual fear conditioning paradigm realized with virtual reality (VR) techniques to create various ecologically valid contexts (Alvarez et al., 2011; Baas et al., 2004; Indovina et al., 2011; Kroes et al., 2017; Neueder et al., 2019), and consistently found the activation of the hippocampus and amygdala during contextual fear acquisition (Alvarez et al., 2008). The activity of the hippocampus and amygdala was further replicated in a recent study employing feature-identical contexts, in which the contexts are constructed with two feature-identical picture stimuli only differing in the arrangement of their context components and therefore more ideally ensure configural, rather than elemental, processing dependent on the hippocampus. Interestingly, integrating cued and contextual fear conditioning in a single paradigm (Grillon et al., 2006) in order to compare roles of the hippocampus and amygdala in each, a comparative study found that the amygdala is activated in both delay (robustly) and contextual (relatively

mildly) fear conditioning, whereas the hippocampus only in contextual fear conditioning, with both showing reduced activity over the course of conditioning (Marschner et al., 2008). These results likely imply that the amygdala plays a general role in the acquisition of fear conditioning, whereas the hippocampus is recruited specifically for contextual processing. It is noteworthy, however, that there is evidence suggesting subregion-specific roles of the hippocampus in contextual fear conditioning: the posterior hippocampus is active preferentially during the early phase of fear acquisition, whereas a more rostro-dorsal hippocampal region during the later phase (Lang et al., 2009). This may indicate that the posterior hippocampus participates in contextual encoding for initial formation of the context-US association, whereas the more rostro-dorsal region in memory consolidation and retrieval. Of note, the ACC and insula display sustained contextual responses over the course of conditioning (Alvarez et al., 2008; Lang et al., 2009; Marschner et al., 2008), probably implying their role in the expression of fear responses as evidenced in cued fear conditioning despite their possible role in contextual encoding.

It is widely accepted that the posterior portions of the human hippocampus correspond to the rodent dorsal hippocampus, while the anterior portions are analogous to the rodent ventral hippocampus (Fanselow and Dong, 2010). In light of these homologies, the findings in human studies may be further interpreted with insights into rodent studies: the human posterior hippocampus (corresponding to the rodent dorsal hippocampus) likely encodes contextual information with which the context-US association is formed at an early phase of conditioning; subsequently, the newly-formed association is consolidated possibly through the interaction between the anterior hippocampus (the rodent ventral hippocampus) and amygdala; contextual fear memory is retrieved and expressed by the top-down regulation of the ACC and anterior

hippocampus. Of note, the exact role of the insula in the acquisition, consolidation, and retrieval of contextual fear memory in both rodents and humans still remains elusive, representing another knowledge gap in the field (see 4.2).

3.2.4. Fear extinction

Supported by its significant clinical implication particularly in posttraumatic stress disorder (PTSD) and anxiety disorders, research of fear extinction has attracted considerable scientific and clinical attention. Multiple lines of early evidence show the recruitment of a network of brain regions, including the VMPFC, hippocampus, amygdala, for fear extinction (Gottfried and Dolan, 2004; Kalisch et al., 2006; Knight et al., 2004b; Milad et al., 2007b; Phelps et al., 2004). Specifically, most of these studies suggested that the amygdala is activated during the acquisition of extinction memory, whereas the VMPFC during the retrieval (24 hr after extinction acquisition). The insula and ACC were also found activated during extinction acquisition and retrieval (Fullana et al., 2018). In some studies employing contextual manipulations, activity of the hippocampus was enhanced during extinction retrieval, and was positively-correlated with activity in the VMPFC, implying the role of a hippocampus-VMPFC network in the context-dependent extinction retrieval (Kalisch et al., 2006; Milad et al., 2007b). The VMPFC was shown to mediate inhibition of the amygdala responses for emotion regulation and extinction retrieval (Delgado et al., 2008; Motzkin et al., 2015), which was further supported by the evidence showing negative functional coupling between the VMPFC and amygdala (Banks et al., 2007; Linnman et al., 2012a). These findings together with insights into rodent studies reached a integrative view that during extinction acquisition a new inhibitory memory is formed in amygdala-centered circuits, and subsequently retrieved by the top-down regulation of the

amygdala by a VMPFC-hippocampus network in a context-dependent manner (as mentioned earlier in 3.2.1, the VMPFC is considered as homologous to the rodent IL). It should be noted that, however, there has been contrasting evidence against this view. Notably, in a recent meta-analysis of fMRI studies, activation of the amygdala during extinction acquisition was undetectable (Fullana et al., 2018), which is reminiscent of the inconsistent amygdala activity in fear memory acquisition during delay fear conditioning. Similarly, this conflicting finding may derive from multiple roots, such as the technical challenges in signal detection from the amygdala and its sparse coding of extinction (see 3.2.1). Considering the necessity of the amygdala in extinction acquisition proven by multiple rodent studies, further research is awaited to reach a resolution. Other than the amygdala, the VMPFC also became subject to some debate in regard to its precise roles including those in fear conditioning and extinction (Barron et al., 2015; Battaglia et al., 2020; Clem and Schiller, 2016; Delgado et al., 2016; Dunsmoor et al., 2019). In the field of fear extinction, a controversy may exist concerning its precise role in extinction acquisition vs. retrieval. Indeed, while some early studies showed activation of the VMPFC during extinction acquisition (Gottfried and Dolan, 2004; Milad et al., 2007b), a recent meta-analysis did not (Fullana et al., 2018). It was pointed out that this discrepancy may arise from some issues including those in experimental designs and/or statistical analysis (Fullana et al., 2018; Morriss et al., 2018). For instance, during extinction acquisition, as the CS+ becomes extinguished and evolved as a safety signal, contrastive neural responses of the VMPFC to the extinguished CS+ (acquired safety) vs. CS- (safety) get diminished and difficult to detect. Determining a clear role for the VMPFC in extinction acquisition vs. retrieval was further complicated by recent studies in rodents showing that extinction retrieval was not dependent on the IL (human VMPFC) (Bukalo et al., 2015; Do-Monte et al., 2015a), thus requiring extra

caution in interpreting fMRI responses of the VMPFC during extinction retrieval. Therefore, persistent efforts in both rodent and human studies, which may include further standardization of experimental protocols and statistical analyses (Lonsdorf et al., 2017; Morriss et al., 2018; Ney et al., 2018), need to be applied to resolve these inconsistencies.

4. Towards better cross-species translation

Fear conditioning and extinction paradigms provide illuminating translational models for understanding and treating a wide range of brain disorders including posttraumatic stress disorder (PTSD) and anxiety disorders. A key prerequisite for realizing and further enhancing their clinical benefits is to facilitate cross-species translation particularly across rodents and humans. Before introducing how fear conditioning and extinction are implicated in the etiology and pathophysiology of many brain disorders, we discuss potential knowledge gaps that may interfere with smooth cross-species translation in research of fear conditioning and extinction.

4.1. Taking into account methodological disparities

Some fundamental gaps arise from methodological disparities that are inherent to experimental protocols in rodent and human studies. Recently, considerable efforts have been made to raise awareness in regard to the potential consequences of methodological discrepancies within and between species (Haaker et al., 2019; Lonsdorf et al., 2017; Wotjak, 2019). In this sub-section, therefore, we highlight and extend several points covered previously. Briefly, essential elements that constitute fear conditioning and extinction paradigms are mostly shared across species (e.g., CS and US), but are species-specific in some cases (e.g., instruction about the US for human participants). These species-specific elements, as well as some divergent settings in presenting

species-shared elements, may entail the recruitment of different neural circuit mechanisms that can confound trans-species inferences of experimental results. Accordingly, considerable efforts could be placed on maximally unifying methodological/procedural discrepancies in a way that modifies current animal protocols to better capture realistic circumstances in which human fear learning occurs. For example, typically delay fear conditioning paradigms in animals have been most extensively adopted to investigate fear learning and, in a clinical context, the pathophysiology of many brain disorders relevant to fear and anxiety. However, the unambiguous US-predicting CS, which is realized through 100% CS-US contingency with no temporal complexity, may construct an artificial situation and does not reflect realistic circumstances in human fear learning that in general involve a higher order of probabilistic and temporal complexity (Lissek et al., 2006).

From a translational viewpoint, devising modified protocols in a way to enhance uncertainty/temporal complexity and consequently better capture processes underlying human fear learning may be indispensable to gaining practically-translatable mechanistic insights, as exemplified in a recent study applying probabilistic fear conditioning paradigms in animals to illuminate a role of midbrain dopamine neurons in regulating threat uncertainty and fear generalization (Jo et al., 2018). Admittedly, however, alignment of protocols can only be achieved to a certain degree because of inherent differences in experimental demands in animals and humans (Haaker et al., 2019). Therefore, identifying the extent to which mechanistic inferences can be valid from animals to humans (or vice versa) in the maximally-aligned condition will be critical to avoid any misinterpretation.

We also note the difficulty of approaching the amygdala in human fMRI studies, which may underlie some inconsistency among reports (Geissberger et al., 2020). In particular, addressing its sub-regions is almost impossible in humans (Kolada et al., 2017). Given that the amygdala is a core brain system of fear circuitry, technical improvement of human brain imaging is warranted (Bielski et al., 2021; Tyszka and Pauli, 2016).

4.2. Paying attention to a crucial, but underexplored, brain region: the insula

Consistent evidence of human fMRI studies highlighted the insular cortex, the insula in short, as a brain region crucially engaged in fear learning and memory. Nevertheless, it is surprising to identify that, in contrast to other brain regions involved, such as the amygdala, hippocampus, and mPFC, the precise role of the insula in aversive learning and memory has not been systematically studied yet in rodents, in which its causal/mechanistic contribution can be investigated.

Fortunately, along with a recent surge of interest in both the human and animal insula (Gogolla, 2017; Namkung et al., 2017), this knowledge gap is coming on researcher's radars, as evidenced by recently-increasing efforts (Casanova et al., 2018; de Paiva et al., 2021; Gehrlach et al., 2019; Shi et al., 2020; Shiba et al., 2017). In this sub-section, we briefly review the previous literature and discuss future research direction to better understand the precise role of the insula in aversive learning and memory. The human insula can be roughly subdivided into posterior and anterior sections, with each having different cytoarchitectonic features, connectivity, and functions (Gogolla, 2017; Namkung et al., 2017). Similarly, the existence of two major sub-divisions has recently been identified in rodents based on remarkably-distinct connectivity profiles along the antero-posterior insular axis (Gehrlach et al., 2020), which further supports the homology between the human and rodent insula. In rodents, research of the insula in fear learning and

memory has primarily focused on characterizing the posterior insula. In a recent study, while neurons in the posterior insula are activated in response to foot shocks, their inactivation during delay or contextual fear acquisition had no subsequent impact on fear responses during fear memory retrieval (Gehrlach et al., 2019), which not only indicates no necessity of the posterior insula in delay-cued and contextual fear memory acquisition, but also replicates some early studies (Lanuza et al., 2004; Shi and Davis, 1999). Furthermore, post-training lesions or protein synthesis inhibition of the posterior insula prevented conditioned fear responses during fear memory retrieval in delay, but not in contextual, fear conditioning, indicating a crucial role in memory consolidation or retrieval selectively in delay fear conditioning (Brunzell and Kim, 2001; Casanova et al., 2016; de Paiva et al., 2021; Shi and Davis, 1999). It should be noted that post-training lesions do not allow us to differentiate necessity of the posterior insula in consolidation and/or retrieval, thus encouraging further study employing tools with better temporal resolutions, such as optogenetics and chemogenetics. To our best knowledge, no study has directly interrogated a role of the posterior insula in trace fear conditioning.

Other than the posterior insula, a few studies have directly investigated a role of the anterior insula in fear conditioning and extinction in rodents. Some studies showed that activity of relatively anterior portions of the insula (still not rostral insula with the only agranular architecture) is essential for fear memory consolidation in delay and contextual fear conditioning, with no impact on pain perception (Alves et al., 2013; Shi et al., 2020). Furthermore, inhibition of the same regions during extinction acquisition facilitated fear extinction. However, conflicting evidence also exists showing no necessity of the anterior insula in fear memory consolidation in both delay and contextual fear conditioning (de Paiva et al.,

2021). Therefore, substantial efforts should be placed not only to address conflicting findings, but also to understand the precise role of the anterior insula in each type and phase of fear conditioning and extinction. As highlighted in human fMRI studies, as a core component of the fear or extinction network, the anterior insula is one of the most reliably-activated brain regions in almost all types of fear conditioning and extinction. To pin down its precise mechanistic roles in fear learning and memory, we should go beyond the mere loss-of-function research of local insular circuits, but instead have to acquire a network level of understanding in each type and phase of fear conditioning and extinction. Given that the anterior insula stands at a network ‘hub’ that integrates sensory, emotional, cognitive, and motivational signals, deconstructing its roles along each neural pathway is particularly important. For example, in human trace fear conditioning (see 3.2.2), it was identified that coactivation of the DLPFC and anterior insula occurred preferentially during the trace interval, compared to other stimulus periods. This observation may lead us to hypothesize their crucial role in working memory-like functions, and subsequently test this hypothesis by optogenetically-manipulating and monitoring activity of neuronal pathways between the PrL (the functional counterpart of the human DLPFC) and anterior insula selectively during the trace interval, in comparison to during other stimulus periods. Meanwhile, given that the anterior insula and amygdala have strong anatomical connection and functional correlation particularly in emotional dimensions, we can also dissect the precise role of this pathway in each phase of trace fear conditioning, which may be functionally-discriminable from that of the anterior insula-DLPFC pathway.

4.3. Recognizing unintended selection bias in the fear conditioning paradigms

Some other important knowledge gaps may derive from an unintended selection bias in the fear conditioning paradigms. As mentioned, the neural circuit mechanisms entailed in trace fear conditioning have not been well explored in rodents, compared with those in delay and contextual fear conditioning. In trace fear conditioning, the insertion of a temporal gap between a CS and an US enables to investigate the neurobiological basis of the associative learning of temporally discontinuous (i.e., separated) events that we frequently encounter in reality but cannot be captured by a rudimentary delay fear conditioning paradigm (Gilmartin et al., 2014b; Raybuck and Lattal, 2014). Moreover, trace fear conditioning requires brain regions including the prefrontal cortex and hippocampus that are not only responsible for higher cognitive functions (e.g., working memory and attention) but also frequently impaired in many brain disorders (Gilmartin et al., 2014b; Gilmartin and Helmstetter, 2010; McEchron et al., 1998).

In human studies, on the other hand, relatively little research has investigated the neural basis of contextual fear conditioning. As mentioned previously, the primary reason may be because of the inherent difficulty in establishing different contexts in a fMRI scanner suite (Maren et al., 2013). A key advantage of applying contextual fear conditioning may be to capture how the brain encodes learning and memory of temporally uncertain threats in an adaptive manner. Therefore, it can serve as a great paradigm to capture a key component of pathological (maladaptive) anxiety (i.e., an overestimation of uncertain threats), compared with delay fear conditioning where the use of an unambiguous predictor does not faithfully capture such an uncertain component (Grupe and Nitschke, 2013; Lissek et al., 2006; Pulcu and Browning, 2019). Given the significance and challenge in creating distinct contexts in a neuroimaging room while rigorously maintaining experimental control, more vigorous employment of immersive VR in

contextual fear conditioning and fear extinction paradigms is encouraged, particularly with the utility of VR headset, which helps increase the feeling of being immersed in a virtual environment and removed from the present physical location (Sanchez-Vives and Slater, 2005). It was reported that only a handful of contextual fear conditioning studies have thus far incorporated VR headsets (Kroes et al., 2017). Considerable efforts to augment immersive VR-adopted research, including the commercial release of VR headsets specialized for the purpose (Kroes et al., 2017), will be helpful.

4.4. Dissecting the neurobiological basis of subjective feelings of fear

Fear can be viewed as an integrative, multi-dimensional state whose key constructs encompass externally-observable survival responses and subjective feelings, with those constructs not necessarily being mutually exclusive (LeDoux and Hofmann, 2018; Mobbs et al., 2019). In animals subject to fear conditioning and extinction, the measurement of freezing has long been the gold standard of quantifying externally-observable survival responses as a key behavioral correlate of learned fear. However, it has often been argued that studying the neural basis of fear only via externally-observable survival responses may not be sufficient to understand some integral parts of fear, including subjective feelings of fear in particular (Mobbs et al., 2019). Dissecting the neurobiological basis of subjective feelings of fear can contribute to obtaining a more complete mechanistic understanding of how emotions arise in neural circuits. It is also a challenging, but indispensable, component in realizing better intervention particularly for mood-associated dimensions across many brain disorders. In humans, subjective feelings are frequently assessed by some form of self-reporting: participants typically provide either a verbal or a non-verbal report of information to which they have introspective access (LeDoux and Hofmann,

2018). In non-verbal animals, however, non-verbal reporting is the only option. From translational viewpoints, therefore, establishing a trans-species, non-verbal readout for quantitative and objective assessments of subjective emotional experience is critical for exploring its neurobiological basis.

Facial expressions are emerging as particularly promising, trans-species readouts of subjective emotional states. Charles Darwin suggested that facial expressions are evolutionarily well-conserved across species and the richest source of information about emotional states in both animals and humans (Darwin, 1872). Substantial efforts have already been made to identify and correlate facial expressions with emotional states in numerous organisms including humans, monkeys, horses, sheep, dogs, and rodents (Bloom and Friedman, 2013; Ekman, 1992; Fureix et al., 2012; Parr et al., 2005). Of note, recent break-throughs in machine-vision and -learning approaches analyzing facial expressions have made a huge leap toward reliable quantification of subjective emotional states even in rodents (Dolensek et al., 2020). It has long been considered that conscious, subjective emotional states are not realized solely by subcortical circuits that drive externally-observable survival responses in animals, but crucially by an assembly of cortical circuits with subcortical inputs to them (Mobbs et al., 2019). Indeed, human neuroimaging studies proposed several key cortical bases of subjective feeling states, including the anterior insula which is known to integrate interceptive signals into subjective feeling states (Craig, 2009; Namkung et al., 2017). In line with this, single neurons in the anterior insula of mice have been shown to be closely correlated with specific emotional facial expressions. Moreover, optogenetic manipulation of their activity directly affected specific emotional facial expressions, altogether supporting the eligibility of facial expressions as promising, trans-species

readouts of subjective emotional states (Dolensek et al., 2020). Supported by facial expressions as reliable readouts, therefore, fear conditioning and extinction may serve as critical tools to study the neurobiological basis of subjective feelings of learned fear in both physiological and pathophysiological conditions, although we should take into account a pitfall that humans can pose facial expressions even in the absence of an underlying emotion (i.e., not genuine facial expressions).

5. Fear conditioning and extinction in neurological and psychiatric disorders: the focus on neural circuits

Fear conditioning and extinction paradigms have been extensively used to investigate the neurobiology of associative learning and memory, which are impaired in a wide array of psychiatric and neurological disorders. Focusing on certain emotional dimensions associated with fear, a substantial number of studies have been conducted for post-traumatic stress disorder (PTSD) and anxiety disorders, mainly due to the direct relevance of fear conditioning and extinction to the etiology and pathophysiology as well as potential treatment of these conditions. However, fear conditioning and extinction paradigms also have their clinical utility in other psychiatric and neurological conditions where neural and molecular processes involved in associative learning and memory are affected. We here summarize, through the lens of neural circuits, multiple categories of brain disorders in which investigations of fear conditioning and extinction hold promise for advancing the understanding of pathophysiology with potential for therapeutic benefits (**Fig. S1**).

5.1. PTSD

As the index traumatic experience in PTSD is easily regarded as an explicit conditioning episode, PTSD has frequently been conceptualized in the framework of fear learning and memory (VanElzakker et al., 2014). Even though an traumatic event that can contribute to the development of PTSD is typically much more aversive than an US employed in human experimental settings, similar underlying processes involved in fear conditioning paradigms have proven to be valuable in understanding neural circuit mechanisms of PTSD. A series of fMRI studies have been conducted to capture an abnormal pattern of brain activity in patients with PTSD who undergo a delay fear conditioning-extinction procedure. While persistent and exaggerated fear response, a central feature of PTSD, is seemingly predictive of hyperactivation of the fear network including the amygdala, unexpectedly divergent findings have emerged thus far. A recent meta-analysis of fMRI studies found increased activation of the amygdala, along with the ACC and insula, during fear memory acquisition in PTSD (Suarez-Jimenez et al., 2020), in line with a positron emission tomography (PET) study (Bremner et al., 2005). In contrast, some studies have reported reduced activity of the amygdala when trauma-related pictures were used as the US during the acquisition of delay fear conditioning (Diener et al., 2016). Furthermore, no change in amygdala activation during fear acquisition has been reported (Garfinkel et al., 2014; Milad et al., 2009). Of note, these inconsistent findings may reflect the well-recognized heterogeneity within the diagnosis of PTSD (Neria, 2021). Other than the perspective of abnormal fear learning, deficits in extinction learning have also been proposed as a central mechanism of persistently heightened fear responses in PTSD (Liberzon and Abelson, 2016; Neria, 2021). Supportively, enhanced activation of the amygdala during extinction acquisition (Milad et al., 2009; Suarez-Jimenez et al., 2020) and extinction retrieval (Garfinkel et al., 2014; Suarez-Jimenez et al., 2020) has been reported in patients with PTSD who exhibit

heightened fear responses during extinction retrieval. Furthermore, reduced activation of the VMPFC and hippocampus in patients with PTSD has been reported during extinction retrieval (Milad et al., 2009; Rougemont-Bucking et al., 2011; Suarez-Jimenez et al., 2020). As mentioned earlier, it is believed that, during extinction retrieval, the VMPFC in concert with the hippocampus suppresses fear responses by top-down inhibition of the amygdala in a context-dependent manner. Accordingly, the dysregulation of the VMPFC-hippocampus network also leads to impairment in (context-dependent) fear renewal (Garfinkel et al., 2014). Collectively, dysregulation of the amygdala, probably arising from dysfunctional VMPFC-hippocampal network in PTSD, likely underlies a failure to inhibit fear responses to the CS that no longer yields an aversive outcome in a context-dependent manner.

5.2. Anxiety disorders

Patients with specific phobia (SP) show excessive and persistent fear of a specific object, situation, or activity that is generally not harmful (e.g., dogs, flying, small spaces, etc.). According to the biological preparedness theory which is one of the most influential ideas in explaining the origin of SP, certain classes of stimuli are biologically-prepared for fear learning because of their particular importance for survival throughout our evolution (Ahs et al., 2018; de Silva et al., 1977; Seligman, 2016). Supported by its direct relevance to the etiology and maintenance, the neural circuits recruited in fear learning and extinction have been studied in patients with SP. Two independent surveys, which comprehensively analyzed the papers published before 2012, consistently pinned down hyperactivation of the fear network of the amygdala, ACC, and insula mostly to phobia-relevant (vs. phobia-irrelevant) stimuli in SP patients, most of whom were patients with small animal phobia (Del Casale et al., 2012; Linares

et al., 2012). The hyperactivation of the amygdala and insula has further been replicated in a recent meta-analysis of fMRI studies (Penate et al., 2017), along with the DLPFC that was also overactivated to spider pictures in patients with spider phobia (Wiemer et al., 2015). Collectively, evidence is binding to suggest that an over-attribution of salience to a phobia-relevant stimulus mediated by the anterior insula and ACC (together constituting the key nodes in the salience network) occupies executive resource through the DLPFC (a key node of the central executive network) to drive the amygdala-mediated fear response in patients with SP (Menon and Uddin, 2010; Namkung et al., 2017). Interestingly, a recent study showed, in patients with spider phobia, that repeated exposure to spider stimuli attenuates the amygdala reactivity, and the degree of attenuation predicts subsequent avoidance to spider pictures, with larger attenuation predicting less avoidance (Bjorkstrand et al., 2020). Other than the SP, the neural circuits of fear learning and extinction have also been impaired in other types of anxiety disorders. In contrast to SP, for instance, neural responses to fear-associated stimuli are not likely to be apparent in patients with generalized anxiety disorder (GAD). Patients with GAD showed less discriminative activation in the VMPFC to safety- versus danger-signaling stimuli during the acquisition of fear memory in delay fear conditioning (Britton et al., 2013; Cha et al., 2014; Greenberg et al., 2013). Similarly, patients with GAD showed indiscriminately increased amygdala activation to the safety- and danger-signaling stimuli (Nitschke et al., 2009). Given that the VMPFC specifically encodes safety-, but not danger-, signaling stimuli (Marstaller et al., 2017; Raber et al., 2019; Schiller et al., 2008), dysfunction of the VMPFC can result in a failure to inhibit amygdala activity in response to safety-signaling stimuli, contributing to fear generalization in GAD. The neural circuits of threat and safety learning have also been implicated in social anxiety disorders (SAD). Multiple lines of evidence reported hyperactivation

of the amygdala, ACC, and insula, in response to socio-emotional stimuli (e.g., fearful faces) in SAD patients (Etkin and Wager, 2007; Evans et al., 2008; Phan et al., 2006; Prater et al., 2013; Schneider et al., 1999; Stein et al., 2002; Veit et al., 2002), despite no replication in a recent study (Marin et al., 2020). In regard to safety learning, patients with SAD displayed diminished activation of the VMPFC to safety- vs. threat-signaling stimuli, which is a finding broadly observed across a wide range of anxiety disorders (Marin et al., 2020; Marin et al., 2017). These findings imply that dysfunction of the fear network likely contributes to overactivation to socio-emotional stimuli, whose maintenance may arise from impaired safety learning of discriminating safety from threat stimuli.

5.3. Schizophrenia (SZ)

Studies of fear conditioning and extinction have been applied to studying the neurobiology of aberrant learning and memory in SZ. Notably, Bleuler's earliest description of SZ emphasized alterations in association formation as a core element of the condition resulting in associated emotional changes, and molecular genetic studies implicate synaptic processes of relevance to associative learning in the etiology of the condition (Bleuler and Bleuler, 1986; Hall et al., 2015; Peralta and Cuesta, 2011). Studies of fear conditioning represent one means to probe the impacts of changes in associative learning in SZ (Hall et al., 2009). Impairment in fear extinction has been reported in patients with SZ using a delay fear conditioning-fear extinction procedure, with patients showing reduced VMPFC activation, along with elevated fear responses, during extinction memory retrieval (Holt et al., 2012; Holt et al., 2009). Furthermore, SZ patients show aberrant functional coupling between the VMPFC and hippocampus, with the abnormality being correlated with the severity of paranoid delusions (Godsil et al., 2013). Amygdala hyperactivity

and altered midbrain activation have also been associated with paranoid symptoms in SZ (Pinkham et al., 2015; Romaniuk et al., 2010). There is also evidence that genetic risk factors for SZ, including copy number variants, impact molecular pathways involved in fear extinction (Clifton et al., 2017). These findings can be integrated in the interpretation that dysregulation of fear circuitry including the amygdala, possibly affected by VMPFC-hippocampal dysfunction, may underlie deficits in inhibiting fear responses in response to safety-signaling stimuli, contributing to persistence of paranoid ideation, a core symptomatic dimension of SZ (Clifton et al., 2017; Fletcher and Frith, 2009; Griffin and Fletcher, 2017). Of note, the aberrant response to a safety-signaling stimulus can be manifest as impaired fear generalization that has recently been reported in psychotic illness (Tuominen et al., 2021).

5.4. Psychopathy

Fear conditioning paradigms provide a route for understanding the neurobiological basis of abnormal fear processing observed in patients with psychopathy who lack the capability to anticipate punishment and are deficient in autonomic responding in anticipation of threatening events (Hare et al., 1978). In some studies of delay fear conditioning, while the patients acquired knowledge about the association between the CS and US, they were not able to learn emotional significance of the association (Birbaumer et al., 2005), in accordance with the notion of emotional detachment in psychopathy (Patrick et al., 1993). fMRI studies have shown an abnormal reduction in the activities of multiple brain regions including the amygdala, insula, and ACC in psychopaths during fear memory acquisition in delay fear conditioning (Birbaumer et al., 2005; Veit et al., 2002). Given that the network composed of these regions plays a key role in processing emotional valence of stimuli in an anticipatory manner (Bush et al., 2000; Goodkind

et al., 2012; Janak and Tye, 2015b, a; Namkung et al., 2017), dysfunction of this network can result in a failure in emotional prediction in patients categorized as psychopathy (Birbaumer et al., 2005). Of note, a recent study argued that impairment in emotional prediction is observable only in a subset of patients with psychopathy, implying the heterogeneity within the diagnosis (Schultz et al., 2016).

5.5. Alzheimer's disease (AD)

AD involves pathologically-progressive alterations of brain structures, including (but not limited to) the amygdala and hippocampus, which are crucially involved in fear learning and extinction. Of note, medial temporal lobe structures such as the hippocampus are differentially impacted early in the disease. Accordingly, deficits in fear memory acquisition are observed not only in delay fear conditioning (Hamann et al., 2002; Hoefer et al., 2008), but also in trace fear conditioning (Woodruff-Pak et al., 1990; Woodruff-Pak et al., 1996) in AD patients. As AD is a progressive disease with pre-symptomatic stages spanning many years, it is particularly important to identify diagnostic and prognostic biomarkers (Jack et al., 2013). A recent study comparing three groups of healthy elderly, subjects with amnesic mild cognitive impairment (aMCI) that often precedes AD, and patients with AD tested a potential utility of (delay) fear conditioning-extinction paradigm as a prognostic biomarker for the pathological progression (Nasrouei et al., 2020). Intriguingly, a gradient of diminished acquisition of fear and extinction memory has been observed from healthy elderly to subjects with aMCI to patients with AD (Nasrouei et al., 2020). Notably, these progressive alterations were most evidently represented in self-report measures (valence and US-expectancy ratings) indexing certain aspects of conditioned fear responses, with a slightly weaker contrast in skin conductance response. These

results likely reflect the progressive damage to specific brain regions implicated in AD, including the amygdala and hippocampus, as well as associated cortical circuitry (Poulin et al., 2011; Sabuncu et al., 2011), therefore suggesting that declining of fear conditioning and extinction (particularly captured by self-reported measures) may serve as useful prognostic biomarkers for AD onset (Nasrouei et al., 2020). Nevertheless, these findings need to be further replicated in large independent cohorts.

In summary, persistent and exaggerated fear responses are core clinical features of PTSD and anxiety disorders, for which fear conditioning and extinction paradigms not only allow for studying their neurobiological underpinnings, but also provide a cornerstone of exposure therapy. Fear conditioning and extinction paradigms are also relevant as a part of behavioral dimensions in other brain conditions (e.g., SZ, psychopathy, and AD). Although these paradigms may not capture the central features of these conditions, the dimensional approach such as RDoC (see the **Introduction** section) will utilize the knowledge for better patient stratification beyond their current disease categories, which is followed by mechanistic dissection at molecular, circuitry, and behavioral levels, for novel treatment development. This will be discussed further in the next sub-section.

6. Towards enhancing clinical benefits of fear conditioning and extinction

We have thus far reviewed that fear conditioning and extinction paradigms can greatly enrich our understanding of their relevant neural circuits across basic and clinical research. In this section, we discuss how this understanding can lay the groundwork for further enhancing clinical benefits

in a wide range of brain disorders. The discussions are approached from two angles: mechanism and therapy.

6.1. The application of fear conditioning and extinction paradigms for mechanistic understanding of disease

Despite significant efforts for the treatment of neuropsychiatric conditions, there have been relatively few advances in therapeutics. The heterogeneity among patients within the same diagnosis often leads to inconsistent treatment outcomes, and challenges the biological validity of existing categorical approaches in clinical nosology (Namkung et al., 2018; O'Donovan and Owen, 2016). Alternatively, a dimensional approach enables pathophysiological processes to be mapped on functional dimensions of the brain, thereby providing a framework for mechanism-based reclassification of brain disorders (Namkung et al., 2018; O'Donovan and Owen, 2016). In particular, RDoC provides a framework constructed by fundamental circuit-based behavioral dimensions that can cut across traditional diagnostic categories (Cuthbert, 2014; Insel et al., 2010).

The acute threat (fear) and potential threat (anxiety) are the major constructs of a particular RDoC domain, named negative valence systems, for which fear conditioning and extinction paradigms can serve as powerful routes to dissect neurobiological mechanisms particularly starting from the neural circuit level. As each type/phase of fear conditioning and extinction involves well-characterized sets of neural circuits, the systematic mapping of brain disorders onto a circuit-defined framework can enable stratifying a clinical population beyond their current disease categories (**Fig. 3**). Once this functional circuit-based stratification is achieved, we can

then extend our exploration of their pathophysiological mechanisms to the genetic, molecular, synaptic, and cellular levels. Discovering a central pathophysiological molecular pathway of relevance to pathogenic factors (e.g., genetic risk factors) may be particularly important in dissecting the overall pathological cascade from the pathogenesis to pathophysiology and symptomatic phenotypes (Namkung et al., 2018). A well-appreciated approach for causal inference on key intermediate (molecular) pathways in clinical research, as well as epidemiology, is Mendelian randomization (MR) (Lawlor et al., 2008; Namkung et al., 2018; Swerdlow et al., 2012). Supported by recent advances in multi-institutional genome-wide association studies (GWAS) and gene expression profiling, application of MR in neuropsychiatric research is becoming more promising, in which a genetic variant [e.g., a SNP)] is used as an instrumental variable to test for the causative effect of an exposure (e.g., gene expression) on an outcome (phenotype) (Lawlor et al., 2008; Namkung et al., 2018).

The molecular pathways can be back-translated into animal models for mechanistic validation. Causality between a molecular target and behavioral pattern in fear conditioning/extinction can be addressed in animal models that allow for invasive manipulations. In parallel, the pathophysiological mechanisms that underlie the causality can also be addressed. Thus, animal models have been appreciated in any medical research. However, it is difficult and unlikely that an animal model can recapitulate all human clinical features of psychiatric illnesses (Monteggia et al., 2018). To reconcile this limitation, investigators have recently applied a dimensional approach (e.g., RDoC) to characterize rodent (mouse and rat) models for the mechanistic understanding of psychiatric illnesses. Fear conditioning and extinction not only provide reliable measures that are translatable across species, but also constitute key dimensions that are impaired

in a wide array of neuropsychiatric disorders including PTSD and anxiety disorders. Classically, rodent models of deficient fear conditioning and/or extinction (e.g., 129S1/SvImJ mice, HAB rats and mice) have been used to understand genetic involvement, neurobiology, and pathophysiology of the core clinical features in PTSD and anxiety disorders (Hefner et al., 2008; Landgraf and Wigger, 2002; Sartori et al., 2011). More recently, mouse models that utilize the information of psychiatric genetics have emerged (e.g., knock-in mice expressing the variant brain-derived neurotrophic factor (BDNF) (Soliman et al., 2010). More details are described in

Table 1.

Taken altogether, our understanding of the neural circuits of fear conditioning and extinction can build a promising framework for patient stratification, in which pathophysiological mechanisms of dysfunctional dimensions common to multiple brain disorders can be dissected at multi-layers starting from genetics, molecular and cellular mediators, and circuitry, to behavior.

6.2. The use of fear conditioning and extinction paradigms for better therapeutic intervention

There have been considerable efforts to target fear circuits via potential molecular pathways particularly in PTSD and anxiety disorders. For example, the antibiotic and partial N-methyl-D-aspartate (NMDA) agonist D-cycloserine is a representative medication to enhance exposure therapy in patients with PTSD (de Kleine et al., 2012; Rothbaum et al., 2014) and those with anxiety disorders (Hofmann et al., 2006; Otto et al., 2010; Ressler et al., 2004). The rationale behind the use of D-cycloserine and other glutamatergic modulators in concert with exposure therapy is to enhance glutamatergic signaling in the PFC that in theory can facilitate fear extinction (Sheynin and Liberzon, 2017). Nevertheless, a recent meta-analysis has reported that

the clinical benefits of using D-cycloserine in conjunction with exposure therapy are relatively small and may easily dissipate over time in patients with PTSD and those with anxiety disorders (Mataix-Cols et al., 2017). This may be partly because a subset of patients was not carefully selected from the viewpoint of neurobiological mechanisms for the treatment, and/or because the optimal molecular drug target may not have been chosen. In addition to the glutamatergic pathway, other neurotransmitters and neuromodulators regulate fear circuits. These include gamma-aminobutyric acid (GABA), serotonin, dopamine, noradrenaline, and endocannabinoids. The efforts of exploring therapeutic effects of these on fear extinction deficits in PTSD and anxiety disorders are ongoing (Abdallah et al., 2019; Bukalo et al., 2014; Sartori and Singewald, 2019).

SZ-associated genetic variants have been shown to be enriched for those associated with NMDA receptor-mediated signaling pathways that play a central role in associative learning (Hall et al., 2015). Indeed, converging evidence has linked hypofunction of NMDA receptors with both cognitive abnormalities and psychotic symptoms in SZ (Goff and Coyle, 2001; Javitt et al., 2012). Accordingly, whether D-cycloserine can enhance cognitive behavioral therapy (CBT) for delusions in patients with SZ has been tested (Diminich et al., 2020; Gottlieb et al., 2011). Interestingly, while D-cycloserine in combination with CBT did not improve delusions compared to placebo during treatment, there was some improvement of delusions at 3-month follow-up, despite the need for replication (Diminich et al., 2020). Therefore, further work is required to demonstrate its therapeutic efficacy in relevant clinical conditions including PTSD and SZ, for which longitudinal monitoring of the neural circuits engaged in fear extinction, as well as physiological/behavioral responses, can serve as an objective marker. Targeting the modulation

of non-glutamatergic systems for fear extinction deficits is also ongoing. For example, an antipsychotic medicine brexpiprazole facilitates fear extinction (Bjorkholm et al., 2017; Sartori and Singewald, 2019).

In parallel with these endeavors for pharmacological interventions, considerable efforts are being made to improve psychological interventions, such as CBT, for PTSD and other conditions characterized by altered fear learning (Beck, 2005; Porto et al., 2009). While psychotherapeutic interventions have been devised based on psychological theories and clinical effects, its mechanistic understanding is indispensable to appropriately choosing a parallel pharmacotherapy, providing outcome measures, and helping the development of new treatment protocols (Linden, 2008). Multiple lines of evidence have reported that CBT exerts its therapeutic effects on certain symptoms (e.g., anxiety-associated symptoms) in a wide range of psychiatric conditions, including PTSD, anxiety, SZ, and obsessive-compulsive disorder (OCD), by affecting brain regions in the fear and extinction network (Brooks and Stein, 2015; Gottlich et al., 2015; Kumari et al., 2009; Marwood et al., 2018). Accordingly, longitudinal fMRI studies of psychotherapeutic effects on fear and extinction circuits relevant to certain symptoms can serve as an objective neurobiological measure that can be integrated with patient-reported subjective measures to improve the design of psychotherapy for relevant brain disorders (Marwood et al., 2018). Of particular note, psychotherapeutic effects on emotional memories may be significantly enhanced within a specific time window. As introduced earlier, a consolidated memory can return to a transiently labile state, in which the fear memory requires a reconsolidation process to be re-stabilized. This reconsolidation window is a temporary opportunity in which pharmacological and psychotherapeutic interventions can be applied to target the unstable

memory. Indeed, considerable evidence reported that extinction (i.e., exposure) training during the reconsolidation window, temporally opened by memory reactivation, prevented the return of fear (Bjorkstrand et al., 2016; Schiller et al., 2010), which may be further enhanced by post-retrieval treatment with propranolol, a non-selective β -adrenergic receptor antagonist, as shown in both healthy subjects and clinical populations including those with PTSD (Brunet et al., 2008; Kindt et al., 2009; Soeter and Kindt, 2010).

7. Conclusion

In summary, fear conditioning and extinction paradigms offer powerful routes for investigating the neurobiological basis of learning, memory, and behavior. To realize its full translational potential, further efforts are required to align animal and human studies of fear conditioning studies, and to improve mechanism-guided therapeutic interventions. Once achieved, we anticipate further insights will be gained not only into human behavior but also into the neurobiology of neuropsychiatric disorders characterized by altered associative fear learning.

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Figure Legends**Fig. 1. Types and phases of fear conditioning and extinction.**

A. Rodent fear conditioning and extinction paradigms. Two commonly-adopted fear conditioning paradigms are cued (delay and trace) and contextual fear conditioning (FC), which are differentiated by the nature of the conditioned stimulus (CS). Cued fear conditioning uses a discrete cue as the (cued) CS (e.g., a tone), whereas contextual fear conditioning has a conditioning environment as the (contextual) CS (i.e., a conditioning chamber). Cued fear conditioning can be subdivided into delay and trace fear conditioning, depending on a temporal gap between the CS and unconditioned stimulus (US). In delay fear conditioning, the US is administered to co-terminate with or immediately after the CS, whereas in trace fear conditioning a time interval is introduced between the termination of the CS and the start of the US. Fear memory undergoes the distinct phases of acquisition, consolidation, and retrieval. Fear extinction occurs if the CS alone is presented repeatedly without the US after fear conditioning. Fear extinction memory also undergoes the distinct phases of acquisition, consolidation, and retrieval. Even after successful fear extinction, it is possible for conditioned fear responses to reappear through different phenomena of return-of-fear (ROF) that encompass fear renewal, fear reinstatement, and spontaneous recovery. Fear renewal can occur by re-exposure to the CS alone in a context other than the extinction context. Fear reinstatement also can occur by exposure to the original US or even a different US. Spontaneous recovery of the previously-extinguished conditioned fear responses is often observed after some passage of time.

B. Human fear conditioning and extinction paradigms are similar to rodent ones, except for several remarkable differences. While rodent studies usually introduce independent sessions of fear memory acquisition and retrieval/extinction with explicit temporal gaps between them (e.g.,

24 hr) and with appropriate contextual changes, for practical reasons the vast majority of human studies employ fear memory retrieval/extinction sessions immediately after fear memory acquisition with no temporal delay allowing for fear memory consolidation and sometimes with no appropriate contextual changes. In addition, a substantial number of rodent studies use single-cue paradigms in which the only one CS is paired with US, whereas human studies usually use discriminative-cue paradigms where one CS (CS+) is paired with USs but another CS (CS-) is not. Furthermore, the reinforcement rates, during fear memory acquisition, usually differ between rodent and human studies, with those being often lower in human studies

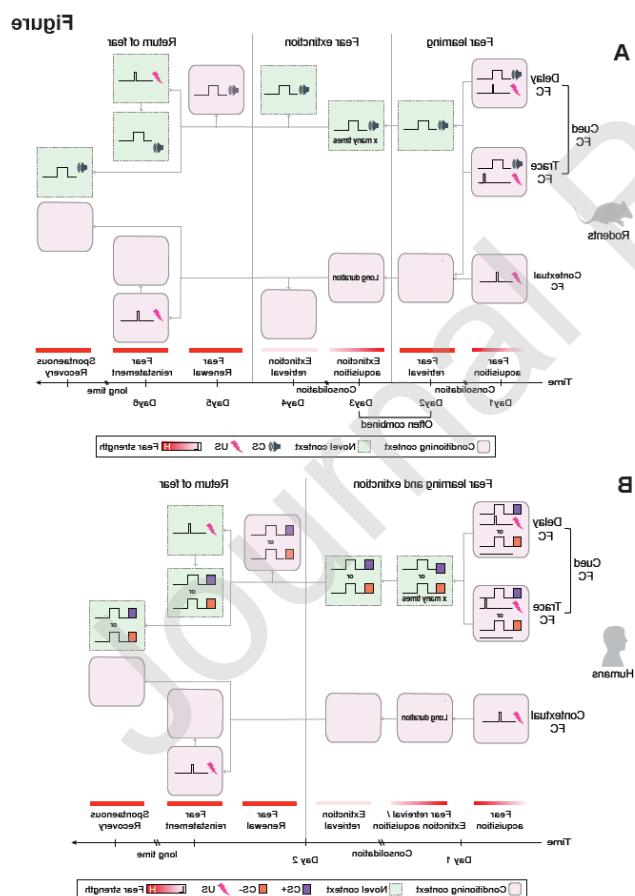


Fig. 2. A schematic of the neural circuits recruited for the retrieval fear and extinction memory.

- A.** Depending on the type of fear conditioning, different neural circuits are recruited for the retrieval of recent and remote fear memory. In delay fear conditioning, the prelimbic cortex (PrL), a sub-region of the medial prefrontal cortex (mPFC), receives cue-associated inputs from the basal amygdala (BA), and in turn drives conditioned fear responses by exerting top-down regulation of downstream circuits including the basolateral amygdala (BLA). With the passage of time, fear memory retrieval, which initially depends on PrL-BLA, likely shifts to PrL-PVT circuits (PVT, the paraventricular nucleus of the thalamus).
- B.** In trace fear conditioning, it is currently thought that the hippocampus (HP) is recruited for the retrieval of recent fear memory possibly by interacting with the BA. However, with the passage of time, HP circuits recruited for the recent retrieval of fear memory gradually become functionally inactive, whereas mPFC counterparts become functionally mature for the remote retrieval of fear memory, in line with systems consolidation of memory.
- C.** In contextual fear conditioning, during the retrieval of recent fear memory, the HP encodes contextual inputs, and in turn drives conditioned fear responses through the regulation of downstream circuits including the BLA. Over time, hippocampal neuronal ensembles recruited for the retrieval of recent contextual fear memory gradually become silent, whereas mPFC counterparts become functionally mature with support from hippocampal inputs, in a similar fashion to systems consolidation of trace fear memory. AMG: amygdala; IN: input; OUT: output.
- D.** During the retrieval of extinction memory, the infralimbic cortex (IL) of mPFC receives cue- and context-associated inputs from the BA and HP, respectively, and then suppresses fear

responses by activating intercalated (ITC) cells, a cluster of inhibitory neurons interspersed between the BLA and central amygdala (CeA), producing feed-forward inhibition of CeA outputs. In addition, BA inputs onto ITC cells become potentiated over the acquisition of extinction memory, thus additionally driving feedforward inhibition of the CeA outputs. AMG: amygdala; IN: input; OUT: output.

E. Comparative functional neuroanatomy enables us to translate our understanding of brain structure and function across species. VMPFC: ventromedial prefrontal cortex; DLPFC: dorsolateral prefrontal cortex; dACC: dorsal anterior cingulate cortex; INS: insula.

Figure 2

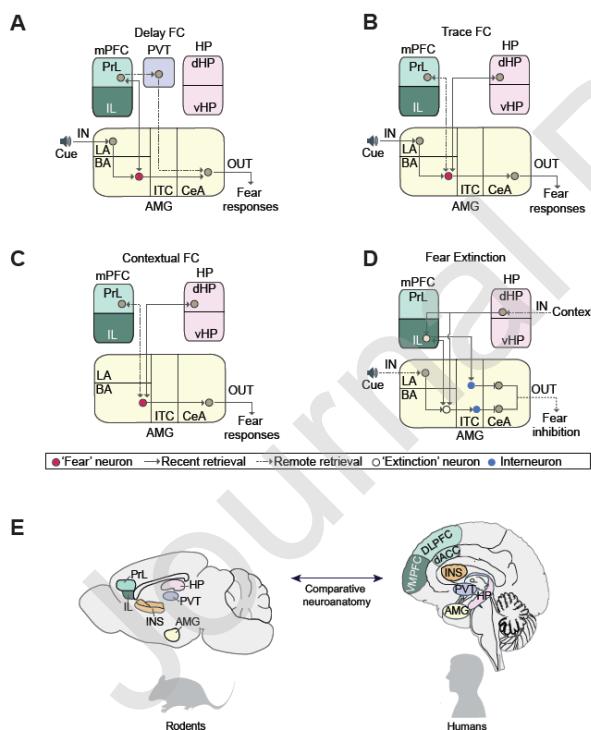


Fig. 3. Strategies for better mechanistic studies and therapeutic intervention.

Patients with brain disorders may be re-stratified based on the patterns of their dysfunction in fear conditioning and extinction, regardless of their current disease categories. We can then explore their common pathophysiological mechanisms at the genetic, molecular, synaptic/cellular, and circuit levels. Discovering a key pathophysiological molecular pathway, in association with pathogenic factors (e.g., genetic risks), may be particularly important from a drug discovery viewpoint. Once promising molecular candidates are found, the information can be back-translated, via comparative neuroanatomy, into animal models where pathophysiological mechanisms at the cellular, and circuit levels can further be dissected with their causal links. SZ: schizophrenia; PTSD: post-traumatic stress disorder; AD: Alzheimer's disease; MDD: major depressive disorder.

Figure 3

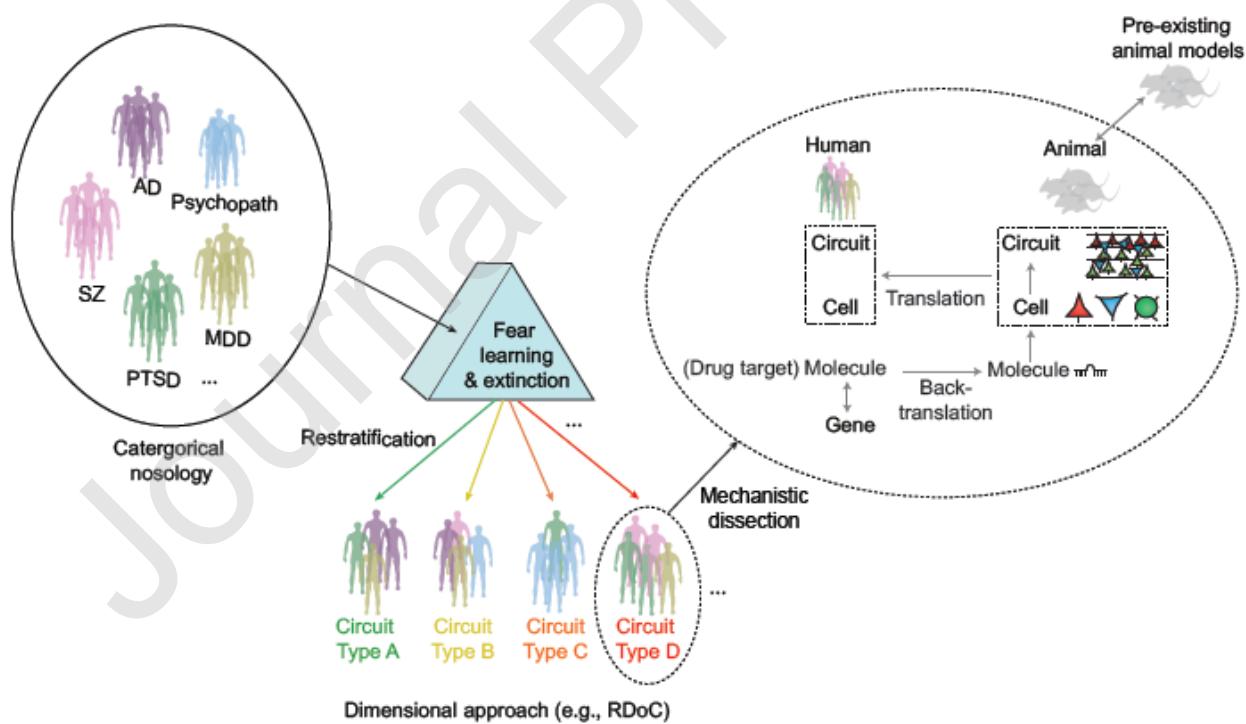


Fig. S1. A brief summary of aberrant brain activity in brain disorders.

Patients with brain disorders may be re-stratified based on the patterns of their dysfunction in fear conditioning and extinction, regardless of their current disease categories. Accordingly, the presentation based on the classical disease categories may be revisited and revised. Nevertheless, representative observations from the current literatures are summarized in the panels. AMG: amygdala; dACC: dorsal anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; HP: hippocampus; INS: insula; VMPFC: ventromedial prefrontal cortex.

Table 1. Representative rodent models of deficient fear conditioning and/or extinction.

CA1: CA1 area of the hippocampus; CeM: medial part of the central nucleus of the amygdala; CG: cingulate cortex; Imp: medial paracapsular intercalated cell mass; KI: knock-in; KO: knock-out; pAKT: phosphorylation of AKT (a.k.a. PKB, protein kinase B); PN: pyramidal neuron; BDNF: brain-derived neurotrophic factor; and 5-HTT: serotonin transporter.

Model type	Model name	Behavior	Neural circuit	References
Phenotype-driven	129S1/SvImJ	Extinction acquisition ↓ Extinction retrieval ↓ Fear generalization ↑	IL, BLA: activity ↓ PrL, CeA, Imp: activity ↑	(Camp et al., 2012; Fitzgerald et al., 2014; Hefner et al., 2008)
	High anxiety-related behavior (HAB) rats	Extinction acquisition ↓ Extinction retrieval ↓	IL, CG, BLA: activity ↓ CeM: activity ↑	(Muigg et al., 2008)
	HAB mice	Fear memory retrieval ↑ Remote extinction acquisition ↓ Spontaneous recovery ↑		(Sartori et al., 2011; Yen et al., 2012)
Genetic risk model	Variant BDNF-expressing KI mice	Extinction acquisition ↓	VMPFC (IL): activity ↓ vCA1-to-PrL: adaptation ↓	(Giza et al., 2018; Soliman et al., 2010)
	5-HTT KO mice	Extinction retrieval ↓	IL: activity ↓ CeL: activity ↑ BLA and IL: dendritic dysmorphology of PNs LA-mPFC: abnormal coupling	(Narayanan et al., 2011; Nietzer et al., 2011; Shan et al., 2018; Wellman et al., 2007)
Stress model	Restraint	Extinction acquisition ↓ Extinction retrieval ↓	IL: activity ↓ PrL: activity ↑ LA: excitatory synaptic activity ↑ mPFC: dendritic dysmorphology of PNs	(Chauveau et al., 2012; Cook and Wellman, 2004; Miracle et al., 2006; Wilber et al., 2011)
	Elevated platform	Extinction acquisition ↓ Extinction retrieval ↓	CA1: impaired synaptic plasticity BLA-to-mPFC: impaired synaptic plasticity VMPFC-to-BLA: impaired synaptic plasticity BLA: dendritic dysmorphology of PNs	(Maroun, 2006; Maroun et al., 2013; Maroun and Richter-Levin, 2003)
	Social defeat	Extinction acquisition ↓ Extinction retrieval ↓	PFC: activity ↑ LA-mPFC: abnormal coupling	(Lisboa et al., 2018; Narayanan et al., 2011; Wohleb et al., 2011)
	Forced swim	Extinction acquisition ↓	IL: dendritic dysmorphology	(Izquierdo et al., 2006)
Gene x environment model	5-HTT KO x social defeat stress	Extinction acquisition ↓ Extinction retrieval ↓	LA-mPFC: abnormal coupling	(Narayanan et al., 2011)