Fear Models in Animals and Humans

Catherine A. Hartley and Elizabeth A. Phelps

Abstract While fear learning is an adaptive behavior critical to our survival, excessive fear can markedly impair one's ability to function and is a central characteristic of anxiety disorders. In this chapter, we review research detailing the neurobiological mechanisms underpinning fear learning and regulation. We draw on research in both animal models and humans, highlighting developmental research whenever possible. In the first section we review the brain systems that support fear acquisition through both direct experience and social learning. In the second section, we focus on the various means by which learned fears can be lessened, including extinction, cognitive regulation strategies, actively coping with fear, and persistently inhibiting fear through reconsolidation. This basic fear-learning model provides a neuroscientific framework for understanding the role of Pavlovian fear learning in anxiety disorders and suggests potential approaches for treatment.

Keywords Fear • Conditioning • Extinction • Emotion regulation • Anxiety

The ability to recognize and respond to potential sources of harm in the environment is critical for survival. The state of fear that results from the detection of proximal threat serves many important functions. Fear facilitates information gathering through heightened vigilance, enables rapid reactions, and gates learning to promote the long-term retention of salient information. While fear plays a central role in promoting adaptive behavior, excessive fear can markedly impair one's ability to function and is a central characteristic of anxiety disorders. Detailed research examining fear learning in animal models and humans has generated a detailed neuroscientific understanding of how fear responses are acquired. More recent research has begun to elucidate the various methods by which learned fears can be modified or controlled.

This research provides a framework for understanding the neural systems underlying anxiety disorders and may yield novel insights into possible treatments. Of note, the majority of both human and animal studies have examined the acquisition and control of fear in adults, with few examinations of how these learning and regulatory processes might differ in childhood or adolescence. Thus, the bulk of this review will focus on adult studies with reference to pediatric research whenever possible.

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R.A. Vasa and A.K. Roy (eds.), *Pediatric Anxiety Disorders: A Clinical Guide*, Current Clinical Psychiatry,
DOI 10.1007/978-1-4614-6599-7_1,

In this chapter, we review research detailing how fear responses are learned and regulated. In the real world, objects, sounds, or places that are associated with previous traumatic events in our lives can come to elicit fear responses. In addition, humans can readily acquire fears through social means of transmission, such as through verbal instruction or observation of another person's negative experiences. Experimental studies examining Pavlovian cued conditioning, contextual conditioning, and social learning of fear have shed light on the neural mechanisms supporting such fear associations. In the first part of this chapter we review the brain systems linked to fear acquisition. The latter sections of this review focus on the range of techniques by which fears can be lessened, including simple exposure in extinction training, cognitive strategies to regulate fear, developing means to actively cope with fear, and persistently inhibiting the fear by targeting memory reconsolidation.

Fear Acquisition

Below we review experiential and social means by which novel fears may be acquired. Pavlovian cued conditioning and contextual conditioning, respectively, model the processes by which negative affective value may be assigned to a stimulus or context. Fears may also be acquired through observation or explicit instruction. Here we describe each of these means of fear learning and review their neural substrates.

Pavlovian Cued Conditioning

Pavlovian fear conditioning provides an experimental model for the process by which neutral stimuli in the world acquire negative affective value [1]. In a typical Pavlovian fear conditioning paradigm, a neutral stimulus, such as a tone, is paired with an intrinsically aversive unconditioned stimulus (US), such as a shock. The shock elicits a range of unconditioned autonomic, endocrine, and behavioral responses, including freezing in rodents, and increases in skin conductance in humans. After one or more pairings, the previously neutral stimulus, now a conditioned stimulus (CS), acquires the capacity to elicit these fear responses, or conditioned responses (CRs).

Extensive research in animal models has delineated the neural circuits that support Pavlovian fear conditioning (see [2, 3]; Fig. 1). This work highlights the necessary role of the amygdala in acquisition, storage, and expression of fear learning. The amygdala is a heterogenous structure composed of several subnuclei that play distinct roles in fear learning. The lateral nucleus of the amygdala (LA) receives convergent thalamic and cortical projections signaling the presence of the CS and US [4–7]. Pairing of the two stimuli gives rise to synaptic plasticity within the LA [8, 9]. When the CS is then presented alone, the LA activates the central nucleus of the amygdala (CE) [10], which controls the expression of the fear response via projections to brainstem and hypothalamic regions [11]. Distinct cells within the LA maintain the long-term representation of this fear memory [12] and remain responsive to the presentation of a CS even when the behavioral fear response is not expressed. This persistent encoding of the fear association may support the commonly observed return of fears that have been previously diminished through extinction learning [13].

Although studies of fear acquisition have focused primarily on the role of the amygdala, recent evidence in animal models suggests that the prelimbic medial prefrontal cortex is necessary for the expression of learned fear (Fig. 1). Lesions of the prelimbic cortex do not prevent initial fear acquisition or expression [14, 15]; however, pharmacological inactivation of the prelimbic cortex following conditioning disrupts fear expression [16] while prelimbic stimulation increases fear expression [17]. Neurons in prelimbic cortex exhibit sustained responses to CS presentation that parallel the duration

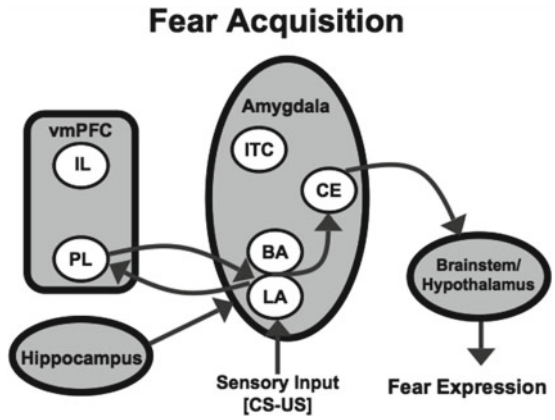

Fig. 1 Neurocircuitry supporting fear acquisition. The lateral nucleus (LA) of the amygdala receives afferent sensory input regarding experienced, observed, or instructed information about the CS–US relationship and is the site of plasticity representing the fear memory during conditioning. The LA and BA are interconnected and both project to the central nucleus (CE), which has outputs to brainstem and hypothalamic regions that control the expression of the CR. Following conditioning, the prelimbic (PL) region of the ventromedial prefrontal cortex (vmPFC) is activated via the BA following CS presentations and drives the expression of conditioned fear. Projections from the hippocampus to the basal nucleus (B) of the amygdala process contextual information during conditioning and may gate fear expression through the CE

of the behavioral freezing response [18], suggesting that the prelimbic cortex drives the expression of conditioned fear. The prelimbic cortex receives inputs from the LA [19] and projects to the basal nucleus of the amygdala (BA), which in turn projects to the CE. Following CS presentation, the prelimbic cortex might transform phasic signals from the LA into sustained prelimbic firing that directly influences fear expression via its CE projections.

Discrimination conditioning paradigms are often used in human fear research. In these paradigms, two conditioned stimuli are presented. These may be auditory tones or more typically, neutral visual stimuli such as colored shapes. Some studies use visual stimuli as CSs that are capable of eliciting fear responses even prior to conditioning (e.g., images of snakes, spider, or fearful faces). These so-called "prepared" stimuli may elicit more robust physiological responses and more persistent conditioned associations [20]. In a discrimination paradigm, one stimulus, the CS+, is paired with a US on a subset of the trials, while the other, the CS− is never paired with shock. Measurable correlates of sympathetic nervous system activity, such as skin conductance responses or pupil dilation, are recorded and assessed for each stimulus. The difference in responding to the threat stimulus (CS+) versus the safety signal (CS−) serves as a measure of the discriminative CR that is assumed to reflect one's degree of threat-specific fear expression.

Studies in humans suggest that the neurocircuitry underlying Pavlovian fear conditioning is conserved across species (see [21] for a review). Both human lesion and neuroimaging studies support the central role of the amygdala in fear conditioning. Patients with both unilateral and bilateral lesions of the amygdala fail to display a conditioned skin conductance response to a reinforced CS [22, 23]. Functional magnetic resonance imaging studies (fMRI) of Pavlovian fear conditioning observed increased blood oxygen level-dependent (BOLD) signal in the amygdala to a conditioned stimulus versus a neutral stimulus [24–27].

In addition to the engagement of the amygdala, fMRI studies of fear conditioning commonly report increases in BOLD activation in the dorsal anterior cingulate cortex (dACC) in response to CS presentation. Both cortical thickness in this region and CS-evoked BOLD activation correlated positively with the magnitude of conditioned fear expression [28], suggesting that the dACC may mediate fear expression in humans. While homology across species is difficult to ascertain, the

authors of this study propose that the dACC may play a similar role in fear expression to the rodent prelimbic region.

Studies in humans examining differences in fear conditioning across development suggest that discrimination between threat and safety stimuli improves with age [29, 30]. An fMRI study examining age effects on discriminative fear conditioning reported that the increased differentiation of the CS+ versus CS− in adults versus adolescents correlated with their recruitment of dlPFC regions during fear conditioning [30]. While not typically proposed to play a key role in fear learning, the authors suggest that the dorsolateral prefrontal cortex (dlPFC) activity in this task may reflect a more general stimulus classification function. In contrast, adolescents showed significant differential activity (CS+>CS−) in the amygdala and hippocampus, while adults did not. Another study comparing discriminative fear learning in healthy versus anxious adolescents found that while both groups showed comparable degrees of discrimination, anxious adolescents displayed higher fear ratings overall, independent of stimulus type [31].

Collectively, convergent evidence in both animal models and humans suggests that the amygdala is necessary for the acquisition, storage, and expression of cued Pavlovian conditioned fear. Furthermore, in both species, prefrontal cortical regions appear to modulate conditioned fear expression.

Contextual Conditioning

While the amygdala is critical for fear learning to specific cues, in many circumstances the learned fear response extends to the larger context in which the aversive event occurred. This contextual fear is adaptive in that the location and circumstances under which dangerous events occur can be as informative about the impending danger as a specific cue that immediately precedes the event. In addition, the same cue may be dangerous in one context (e.g., a gun on a battleground) and safe in another context (e.g., a gun at a sporting store). Context allows one to adaptively modulate the cued-fear response, so it is appropriate to the situation. However, context can comprise many aspects of the environment, and how one interprets the context can be flexible. At times fear of context can generalize excessively, resulting in disorders such as phobias (particularly agoraphobia).

The contextual fear response requires the involvement of the hippocampus (Fig. 1), which is important in encoding contextual aspects of memory more broadly [32]. In rodents, conditioned fear to the context is assessed by placing the animal in a novel cage or context prior to the Pavlovian conditioning protocol and the presentation of the CS–US pairing. After fear conditioning, the animal exhibits not only a conditioned fear response to the CS but also the context in which the conditioning occurred. If amygdala damage follows, the animal fails to show conditioned fear to both the cue and context; however, if damage is localized to the hippocampus, conditioned fear to the CS is intact, but the animal no longer exhibits fear to the context [33]. Interestingly, unlike amygdala lesions, which impair conditioned fear even if damage occurs long after fear conditioning, the impact of hippocampal damage on contextual fear expression diminishes with the amount of time that passes following conditioning. This temporal gradient of retrograde amnesia for contextual fear following hippocampal damage suggests that once the contextual fear memory is fully consolidated, the hippocampus is no longer needed for its expression.

Studies on the development of contextual fear conditioning in rodents suggest pronounced qualitative differences in learning across the lifespan. Both pre-weanling (postnatal day 17, P17) and post-weanling (P24) rats show intact tone shock conditioning; only post-weanling rats exhibited freezing to the conditioning context on the subsequent day [34]. This contextual conditioning deficit is thought to reflect the increased maturation of the hippocampus in the older animals. Furthermore, a recent finding in mice suggests that the expression of contextual fear appears to be temporarily suppressed during adolescence [35]. In this study, contextual fear memories learned during or prior to adolescence were not expressed during this developmental stage; however, these memories reemerge during

adulthood. This temporary suppression of contextual fear expression is proposed to foster the exploratory behavior necessary for the transition from maternal care into independence, which typically occurs during this developmental stage.

In humans, finding independent conditioned fear effects for cue and context in the laboratory is somewhat difficult. The experimental setting is itself a strong context, and the use of techniques like brain imaging does not permit alterations of the actual context (i.e., the MRI machine). As a result, most investigations in humans examine the impact of context on cued conditioned fear expression. One such study, using images of two rooms as contexts and the colors of a light in the rooms as cues (CS+ and CS−), demonstrated that cued fear learned in one context and extinguished in another shows renewal upon reintroduction to the fear context [36]. However, there is evidence for enhanced fear to the context in conditioning paradigms where there is no distinct predictive cue CS [37, 38], and neuroimaging studies assessing the effect of context independent of cue report enhanced activation of the hippocampus [38, 39]. More recently, virtual reality techniques, similar to those that have been used in exposure therapy treatments for phobias [40], have been used to examine contextual fear in humans [38, 41]. Manipulating the context with virtual reality has enabled the independent assessment of cue and contextual fear-learning effects in a single learning paradigm in humans [42], revealing that contextual fear is acquired more rapidly than cued fear and that conducting cued-fear extinction in the acquisition context impedes extinction learning.

Social Learning of Fear

Although Pavlovian fear conditioning is a powerful model for understanding fear across species, it requires direct experience with an aversive event. In humans, many of our fears are learned through social means without direct aversive experience. For instance, a common phobia is fear of germs. Although science tells us germs exist, our perceptual systems do not detect them. Nevertheless, by learning about germs and their consequences through verbal instruction from parents and others, we routinely take preventative steps to diminish their potentially harmful effects. For some, this symbolic knowledge of the dangers of germs results in unwarranted fear and excessive preventative measures. This is an example where learning fear through social communication can result in a robust fear response and psychopathology.

In general, learning fears through social communication is adaptive in that one does not need to have painful experiences to know about potential threats. Social fear learning also expands the range of stimuli and events that can be associated with potential aversive outcomes. There are two primary means of social fear learning. The first, verbal instruction, is dependent on language and is unique to humans. The second is learning through direct observation of conspecifics in aversive circumstances. Observational fear learning has been shown to occur in some nonhuman primates and a few other vertebrates, such as birds and rodents (see [43] for a review).

In a typical instructed fear study, a participant is told she/he might receive a shock when presented a neutral stimulus (the instructed CS). This symbolic communication of threat has been shown to lead to robust fears that are difficult to distinguish from those learned through direct aversive experience [44]. One of the few differences is that Pavlovian CS's biologically "prepared" by evolution to yield more lasting fear responses (e.g., spiders, snakes, angry faces) will continue to show fear expression when presented subliminally (see [20] for a review). In contrast, awareness of the presentation of the instructed CS is necessary for the expression of instructed fear [45]. Although it is unlikely the amygdala is the site of storage for the symbolic representation underlying instructed fear, the amygdala seems to be necessary for instructed fear expression. An fMRI study of instructed fear in which subjects were told which stimulus carried the threat of shock (CS+) and which was safe (CS−) reported activation of the left amygdala in response to threat versus safe conditions that correlated with the

degree of fear expression [46]. A study examining the effect of right versus left temporal lobectomy on instructed fear learning found that lesions of the left, but not right, amygdala result in impaired expression of instructed fear [47]. This left hemisphere lateralization of instructed fear is consistent with left hemisphere representation of language more broadly. Unlike instructed fear, Pavlovian conditioned fear has been shown to involve both the right and left amygdala [23, 48].

Like instructed fear, observational fear leads to robust fear responses that are difficult to distinguish from Pavlovian conditioning. However, observational fear appears to be more similar in some ways to Pavlovian fear than instructed fear in that its expression is intact with subliminal presentation [45]. Furthermore, although being told about potential dangers may not result in an emotional response unless danger is imminent, observing a conspecific in an aversive circumstance can lead to an empathetic emotional response in the perceiver. For example, Olsson and colleagues [49] showed participants a video of a confederate undergoing a Pavlovian fear conditioning paradigm to serve as a model for the procedures the participant would experience in the following session. This comprised the learning phase. When observing the confederate receiving a shock, the participants showed an increase in skin conductance and bilateral amygdala activation indicating an emotional response during the observational fear learning. Consistent with observational fear, the participants also showed a fear response to the observational CS in the later test session, along with bilateral activation of the amygdala. Because there is a fear response during learning, as well as later expression of observational fear, it appears the observation itself acts as a social US, similar to a direct US, such as shock. Interestingly the strength of expression of observational fear correlated with activation during the learning phase in the insula, anterior cingulate cortex, and medial prefrontal cortex, regions that have been implicated in empathy and mentalizing about others [50, 51].

Control of Fear

Research on the neural mechanisms underlying fear learning provides insight in to the mechanisms underlying anxiety disorders in humans. However, translation of this knowledge into more effective treatment of fear-related anxiety disorders requires a better understanding of how learned fears can be diminished. Recent research in both humans and animal models has highlighted several means by which conditioned fear can be diminished. In this section, we describe the neural mechanisms underlying four fear-reduction techniques, extinction, cognitive regulation, active coping, and reconsolidation (Fig. 2).

Extinction

Extinction refers to the gradual decrease in fear expression that typically occurs when a conditioned stimulus is repeatedly presented without aversive reinforcement [1, 13]. This decrease reflects the occurrence of a new learned association that the CS that was once predictive of threat is now safe. The formation of an extinction memory does not overwrite the initial fear association between the CS and this aversive outcome, as evidenced by the fact that fear expression can return following extinction under a number of circumstances (see review by [13]). The term renewal refers to the return of fear following reexposure to the context in which an extinguished fear memory was initially learned. Reinstatement is the return of expression of an extinguished fear that occurs after the unsignalled presentation of the aversive unconditioned stimulus. Spontaneous recovery refers to the increase in fear expression that typically occurs following extinction with the mere passage of time. These situations in which extinguished fear reemerges suggest that extinction memory and the original fear memory

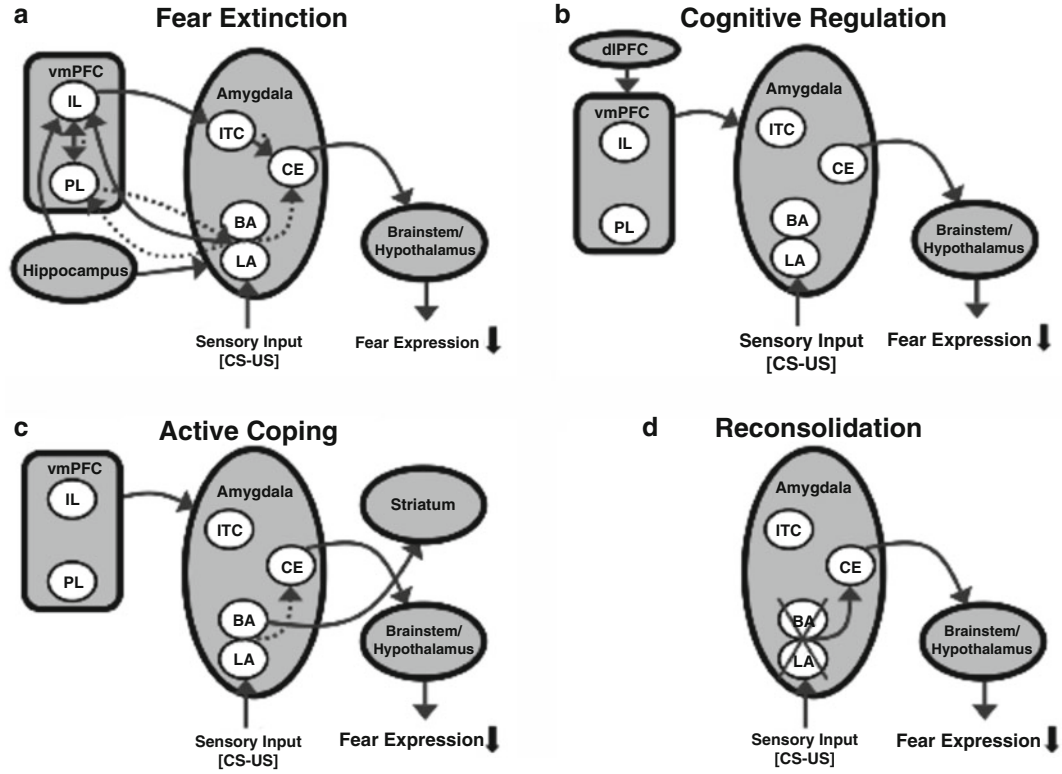

Fig. 2 Neural mechanisms of changing conditioned fear. (**a**) During fear extinction learning and consolidation, connections are established between the infralimbic (IL) subregion of the vmPFC and the inhibitory intercalated (ITC) cell masses, which inhibit activity in the CE. During extinction recall, these connections are activated, inhibiting fear expression. The IL and PL inhibit one another, mediating the competition between the fear and extinction memory for expression. Contextual modulation of extinction expression is mediated by projections from the hippocampus to the vmPFC and/or LA. (**b**) During cognitive regulation, the dorsolateral prefrontal cortex (dlPFC) regulates fear expression through projections to the vmPFC, which in turn inhibits amygdala activity. (**c**) During active coping, information from the LA is routed not to the CE, which drives fear expression, but to the B, which in turn projects to the striatum. The striatum is thought to reinforce instrumental action taken during instrumental learning. Following active coping, changes occur in the vmPFC such that it is activated by subsequent exposure to a stressor, inhibiting the fear response. (**d**) Reconsolidation diminishes conditioned fear expression through alteration of the original CS–US association stored in the LA

are engaged in a competition to determine which controls the behavior of the organism, a view that is consistent with our current understanding of the neurocircuitry supporting fear extinction.

Studies in animal models have made substantial progress in clarifying the neural circuits that underlie extinction learning (Fig. 2a). This research suggests that the acquisition of initial extinction learning, like the original fear memory, depends upon the amygdala. Pharmacological blockade of NMDA and glutamate signaling or mitogen-activated protein kinase (MAPk) activity within the basal and lateral nuclei or basolateral amygdala complex (BLA) impairs extinction learning [52–54]. BLA synapses appear to exhibit plastic changes following extinction training that support the consolidation of the extinction memory [55–58].

While the amygdala appears necessary for the initial acquisition of extinction learning, the ventromedial prefrontal cortex (vmPFC) plays a critical role in both the consolidation and retrieval of extinction memory (see [59] for a review) (Fig. 2a). While not essential for the initial acquisition of extinction learning [15], evidence from electrophysiological, pharmacological inactivation, and lesion studies implicates the infralimbic region (IL) of the vmPFC as a site of extinction consolidation [15, 60–62].

Following initial learning, the retrieval of extinction memory is mediated by the IL, which inhibits conditioned fear expression via its projections to the intercalated cell masses (ITC) within the amygdala, which in turn have inhibitory projections to the CE [63–65]. Projections from the hippocampus to the vmPFC and the amygdala appear to mediate the context-dependent expression of extinction [66, 67], providing information that determines whether extinction learning is retrieved or the original fear memory returns (see [13] for a review).

Growing evidence suggests that following extinction, distinct amygdala–prefrontal subnetworks control whether extinction memory or fear memory is expressed (see [68] for a review). A recent study demonstrated that distinct populations of cells within the BA are responsive to CS presentation during fear expression and extinction retrieval and that this region mediates the switches between these high and low fear states [69]. The BA is proposed to drive or inhibit fear expression in concert with the PL and IL prefrontal regions, respectively [68]. Further research is required to elucidate the detailed dynamics of this competition for behavioral control; however, this model suggests how the same CS may give rise to opposing behavioral responses depending on the available information about the contextual circumstances.

Studies in rodents have highlighted pronounced changes in extinction learning across development. Following extinction learning, post-weanling rats (24 days old) exhibit contextual renewal, spontaneous recovery, and reinstatement of conditioned fear, suggesting the existence of competing threat and safety memories; however, pre-weanling animals show none of these fear reemergence phenomena [70–72]. Unlike in adults, extinction learning in these pre-weanling animals does not recruit the vmPFC [73] but instead appears to overwrite the initial fear memory within the amygdala [72, 74]. This suggests that early-life extinction may yield fear erasure, suggesting a developmental window of opportunity for the treatment of fears acquired early in life. In contrast, adolescent rats show impaired retention of extinction learning [75, 76], suggesting that adolescence may represent a period of vulnerability to persistent fear.

An early functional neuroimaging study of extinction learning in humans [27] used a two-day paradigm in which subjects learned to discriminate between a visual CS+ and CS− on day one and then immediately underwent extinction, during which the CS+ was no longer paired with shock. On day two, subjects returned for a second extinction session to assess the retention of their extinction learning. This study reported increases in BOLD signal in a subgenual anterior cingulate/vmPFC region during initial extinction learning, as well as a corresponding decrease in amygdala BOLD activation. Further increases in vmPFC BOLD activation were observed during extinction recall on the following day [27]. Subsequent fMRI studies of extinction have also reported increased activation in the vmPFC during extinction retrieval [77, 78]. Furthermore, both the magnitude of vmPFC BOLD signal and the thickness of the cortex in this region have been found to correlate with the degree of extinction retrieval [78–80]. These findings suggest that this subgenual ACC/vmPFC region may be a human homologue of the rodent IL region and may directly inhibit fear expression via projections to the amygdala.

Studies in humans corroborate the role of the hippocampus in the context-dependent retrieval of extinction [77, 78]. Using a paradigm in which extinction learning is associated with a distinct visually identifiable context, increases in hippocampal BOLD activation were reported during extinction retrieval [77, 78]. Consistent with the evidence that the hippocampus mediates the context-dependent recall of extinction via connections with the vmPFC, hippocampal BOLD activation correlated positively with vmPFC activation [78]. Finally, individuals with hippocampal lesions show impaired context-dependent fear reinstatement [81], a finding that parallels observations in rodents [82].

In summary, studies examining extinction learning in humans have been largely consistent with the findings in animal models, suggesting that the underlying neurocircuitry is conserved across species.

Extinction-based techniques are commonly employed in cognitive-behavioral therapy to treat anxiety disorders. Exposure therapy involves establishing prolonged contact with the specific stimuli, thoughts, or experiences that elicit anxiety in a safe context [83]. As the current models of extinction

suggest, this process may result in the formation of a new safety memory that may override the expression of the fear memory. Thus, the ability to acquire and consolidate extinction learning may be critical for successful treatment. Consistent with this notion, a recent study reported that degree of extinction retention between exposure sessions predicted the long-term efficacy of treatment at reducing anxiety symptoms [84]. Furthermore, exposure therapy outcomes are improved by the administration of D-cycloserine, a drug that enhances extinction learning [85, 86]. A number of pharmacological agents have been identified that facilitate extinction learning in rodents [87], suggesting promise for the development of drug treatments that enhance the efficacy of exposure therapy.

Cognitive Regulation

While research in animal models has critically informed our understanding of how fear is attenuated during extinction, humans also regularly use an array of cognitive regulatory techniques to modulate emotional responses. Cognitive regulation refers to a range of automatic and intentional mechanisms by which thoughts are used to change emotions [88, 89]. Prominent theories propose that emotional responses arise when we attend to a stimulus and judge it to be motivationally significant [90, 91]. These models suggest that our allocation of attention and the manner in which we ascribe meaning to an event can be important determinants of our emotional experiences. Accordingly, recent studies in humans have demonstrated that intentional cognitive regulation techniques can be used to diminish negative emotional responses and have suggested a provisional model of the neurocircuitry underlying these effects [92, 93].

An early neuroimaging study of cognitive emotion regulation examined whether changes in our appraisal of a potentially unpleasant stimulus could diminish negative emotional responses [94]; see also [95]. In this study, participants viewed images with negative emotional content and were instructed to reinterpret the scene in a more positive manner, reducing their emotional response. For example, a participant viewing an image of a grieving man might instead interpret the scene as depicting a man shedding tears of joy at wedding. This "reappraisal" technique, in which the individual changes the affective significance of a stimulus, also reduced subjects' ratings of negative affect [94]. This study provided a preliminary outline of the neural mechanisms underlying the cognitive regulation of negative affect. The neuroimaging data showed that during reappraisal of the negative scenes, in comparison to simply attending to them, BOLD activation in the amygdala decreased, while activation in both dorsolateral (dlPFC) and ventrolateral (vlPFC) prefrontal cortex increased [94].

Several subsequent studies employing similar cognitive regulation techniques have observed reductions in self-reports and physiological measures of negative affect evoked by diverse stimuli including unpleasant pictures and films (see [93] for a review) and even aversion to monetary loss [96, 97]. Those studies that conducted functional imaging of these tasks largely confirm the provisional neurocircuitry described above, in which regulation evokes an increase in BOLD activation in dlPFC and/or vlPFC accompanied by a decrease in amygdala activity that mirrors the associated decrease in negative affect (see [93, 98] (Fig. 2b)). The interpretation of this pattern of activation is that engagement of the dlPFC reflects executive control processes involved in carrying out the cognitive strategy, while the vlPFC is involved in the selection of the novel emotional interpretation of the stimulus [92, 98]. The reduction in amygdala activation is typically interpreted as evidence of successful deployment of a top-down control process that changes the affective value of the stimulus and the associated measure of negative affect. However, one neuroanatomical conflict with this model is that the dorsolateral prefrontal cortex does not have direct projections to the amygdala [5, 99]. One suggestion is that ventromedial prefrontal regions may mediate the reduction in amygdala activity via strong projections to this region [100, 101]. Thus, cognitive regulation may recruit the same vmPFC–amygdala neurocircuitry implicated in attenuating fear following extinction learning.

A recent study directly examined whether intentional cognitive regulatory strategies and fear extinction share overlapping neural substrates [102]. In this study, participants viewed conditioned stimuli that were colored squares while instructed to either attend to their natural response or regulate these responses by generating a pleasant mental image of something soothing in nature associated with the CS color. Conditioned responses in the regulation condition were significantly lower than when participants simply attended to their anticipatory responses. This reduction in fear was accompanied by decreased amygdala activity and increased activity in both the dlPFC and a region of the vmPFC that, when compared to a previous study of extinction learning, overlapped with a region activated during extinction. Furthermore, activity in the vmPFC was correlated with that of the amygdala and dlPFC, providing further evidence that dlPFC inhibition of amygdala activity is mediated by the vmPFC. Thus, despite the fact that the regulation of fear through the use of cognitive strategies may be unique to humans, this suggests that cognitive fear regulation recruits the same vmPFC–amygdala extinction circuitry that is evolutionarily conserved across species.

Few studies have examined the use of cognitive regulation strategies to reduce negative affect in individuals with anxiety disorders [103, 104]. However, two recent neuroimaging studies highlight differences in the functioning of the neurocircuitry supporting cognitive regulation between patients and healthy individuals. In these studies [105, 106], cognitive regulation of emotional responses to negative stimuli (negative self-beliefs and physical and social threat-related images) was effective in reducing both ratings of negative affect and neural activity in the amygdala in both healthy controls and patients with social anxiety disorder. However, activity in prefrontal regions differed between controls and patients. While controls show robust early activity in dlPFC and vmPFC that decreased over trials, patients displayed increases in these regions across time with both smaller and later peaks. Furthermore, analysis of regions correlated with amygdala activity during regulation revealed a greater extent of the dlPFC inversely correlated with amygdala activity in controls than in patients [106].

Cognitive therapy techniques taught in a clinical context encourage individuals with anxiety or depression to overcome their biases toward negative situational appraisals, thus diminishing their corresponding negative emotional responses [107]. Experimental studies of cognitive regulation in the laboratory delineate the neural pathways through which this regulation takes place. While the deployment of cognitive regulation techniques may be improved through instruction and practice, the efficacy of treatment of fear-related disorders via cognitive therapy may depend on the functional and structural integrity of the prefrontal–amygdala regulatory neurocircuitry [108]. The structural integrity of the white matter tract that comprises this inhibitory pathway varies between individuals and is inversely correlated with trait anxiety [109]. Such individual variation may contribute significantly to the heterogeneity in individual responses to clinical cognitive interventions.

Active Coping

To date, experimental research on the control of fear has focused primarily on how cognitive processes, such as implicit safety learning during extinction or intentional cognitive regulation, can alter fear expression. However, a common means by which we regulate our emotions in everyday life is through the performance of actions that improve our emotional state. The term “active coping” can refer to any action taken to mitigate or avoid aversive experiences or to bring about a positive experience.

Actively coping with a fear-eliciting stimulus requires a sequence of distinct learning processes. First, one must learn that a stimulus or a context poses a threat via the formation of a Pavlovian fear association. Next, the exercise of control over the fear-eliciting situation requires that one learn an action that can be taken to avoid or escape the feared stimulus. Finally, recent research suggests that neural changes occurring following the exercise of control over a stressor diminish subsequent fear

expression [110] and buffer the effects of future exposure to uncontrollable stressors [111]. Through these processes, active coping enables the modulation of fear responses to both present and future aversive situations.

Relative to other fear-reduction techniques, our understanding of the neural substrates that support actively coping with fear is rudimentary. However, existing studies provide a provisional model of the neural circuits involved in each stage of the active coping process (Fig. 2c). As described above, once a Pavlovian fear memory has been learned, the presentation of a conditioned stimulus activates the LA, which in turn activates the CE, triggering fear expression via descending projections to the brainstem and hypothalamus. Evidence that an alternative amygdala pathway plays a critical role in instrumental learning phase comes from a study employing an escape from fear (EFF) task, in which an instrumental response terminates exposure to a tone CS that was previously paired with shock [112]. This study showed that lesions to the CE impaired the expression of the Pavlovian conditioned freezing response. Lesions to the BA prevented the acquisition of an EFF avoidance response. Lesions to the LA prevent both fear expression and instrumental learning, suggesting that the LA plays a critical role in both Pavlovian and instrumental learning. The LA projects to the BA, which in turn has striatal projections that play a key role in instrumental reinforcement learning [113]. Engaging the LA–BA pathway likely guides instrumental learning in the EFF task by providing conditioned reinforcement signals that motivate the avoidance response.

In contrast, engagement of the LA–CE pathway, which drives fear expression, may prevent the performance of active coping behavior. In an active avoidance task in which rats had to learn to shuttle across a chamber in order to avoid a shock [114], post-training lesions of the CE had no effect on shuttling behavior in animals that had learned to avoid the shock. Surprisingly, in animals that had not learned to consistently avoid the shock, lesions to the CE revealed that they had indeed learned the avoidance contingency. When the CE-mediated freezing response was disengaged, these animals were then able to perform the avoidance response. This suggests that excessive fear may impair active coping by preferentially engaging defensive Pavlovian responses.

The experience of control over a stressor that occurs during active coping appears to foster resilience to subsequent stressors, reducing fear-related behavior even in future uncontrollable situations [111]. Studies demonstrating this effect used a triadic design, in which rats were first exposed to escapable shock, yoked inescapable shock of identical intensity and duration of that experienced by a paired individual in the escapable condition, but that could not be escaped, or a control condition involving no shock exposure. One week later, these animals underwent fear conditioning [110]. Exposure to inescapable stress increased conditioned fear in comparison to control animals. However, surprisingly, animals exposed to controllable shock exhibited less fear than animals with no prior shock exposure, suggesting the experience of controllable stress inhibited subsequent fear. Evidence suggests that the vmPFC mediates the effects of prior behavioral control on future stressor-evoked behavior. Inactivation of the vmPFC during controllable stress or during exposure to a subsequent stressor negates the effects of controllability on later behavior [115, 116]. Either the vmPFC or an afferent input region appears to detect when a stressor is under an organism's instrumental control and, in turn, inhibits the physiological and behavioral effects of uncontrollable stress [115]. Furthermore, the experience of controllable stress appears to give rise to long-term changes in the vmPFC that enable it to be activated during subsequent uncontrollable stress, regulating the behavioral response [117]. The IL subregion of the vmPFC is activated by controllable stress [118] and may later inhibit the CE directly, mitigating fear expression [116].

Consistent with this notion that control over stressors engages the same vmPFC–amygdala pathway active during extinction retrieval, active coping appears to prevent the spontaneous recovery of fear [110, 119]. In one such demonstration [119], animals first were fear conditioned; then one group of animals learned an EFF response, terminating exposure to a tone CS, while a second group received yoked tone exposure, essentially undergoing classic extinction. Both groups showed reduced fear during their respective learning phase; however, in a subsequent retrieval test, the extinction group

showed the typical recovery of fear, while the group that had learned an active coping response did not. A major shortcoming of the extinction-based therapies that are typically used to treat fear-related anxiety is that extinguished fears often reemerge. This finding suggests that therapeutic approaches employing active coping techniques may yield a more lasting reduction in fear.

Few studies have explored fear reduction through active coping in humans; however, the preliminary data suggest that the underlying neurocircuitry is shared across species. An fMRI study examining the neural substrates of avoidance learning found that when subjects learned to avoid a shock by performing a key press during CS presentation, performance of this response led to an increase in striatal activation, as well as a decrease in amygdala activation that was accompanied by a reduction in fear expression [120].

Given that the avoidance of fear-eliciting situations is a hallmark of anxiety disorders, the notion that avoidance behaviors might foster resilience might appear counterintuitive and warrants clarification. Avoidance of a stressor can occur through either a passive or active route. A passive avoidance response involves withdrawal from threat, preventing encounters with a fear-eliciting stimulus through the suppression of thoughts or behavior, akin to the freezing response displayed by rodents. In contrast, an organism may show a proactive exploratory avoidance response, attempting to escape or "disarm" a present threat through action. Evidence from studies in rodents suggests that individuals may show stable biases toward active or passive coping styles [121], and a recent study suggests that a bias toward active or passive fear responses may be determined by the function of an intra-amygdalar circuit [122]. While cognitive-behavioral therapy often aims to reduce avoidance behavior, research suggests that the active type of avoidance response may be adaptive, yielding long-term resilience. Thus, it may be that forms of avoidance behavior that engage the individual in action to directly mitigate the aversiveness of a feared object or situation have beneficial consequences. An important area for future investigation is to examine the effect of active versus passive coping responses (including active avoidance behavior) in humans to clarify its effects on subsequent fear expression.

Reconsolidation

All of the techniques to diminish fear described above control the fear response through inhibition of the amygdala via the prefrontal cortex. Although these techniques can be very effective, they leave the amygdala's fear representation largely intact. As described earlier in the section on extinction, one consequence is that the fear can return under a range of circumstances. In the clinic, this intact fear representation may be an important factor linked to the potential for relapse following successful treatment. Due to this limitation, there has been growing interest in emerging techniques to target the amygdala's fear representation by influencing memory reconsolidation.

Reconsolidation refers to a process by which a previously consolidated memory is brought back to a fragile or labile state when retrieved and requires a second consolidation process, or reconsolidation, for re-storage. For most of the last century, the standard model of memory suggested that immediately after information is learned, it is fragile and prone to disruption because the synaptic processes that form the memory require time. This memory formation process is called consolidation. However, once a memory has been fully consolidated, it was assumed that the memory was stable and no longer prone to disruption. New learning about a stimulus could create a second memory trace, but the original memory trace was still intact. Over the last decade, however, there has been renewed interest in the notion that every time a memory is retrieved, it is once again in a fragile state and requires a second consolidation process, or reconsolidation, and new synaptic plasticity to once again become stable. If memory is fragile after retrieval, this provides a second opportunity to potentially disrupt or permanently alter the memory before it is reconsolidated. In the case of fear memories, this provides an avenue to alter the original fear memory, as opposed to inhibit its expression (Fig. 2d).

Initial evidence for fear memory reconsolidation was provided in a seminal study by Nader and colleagues [123]. As mentioned earlier, the LA is thought to be the site of fear memory storage. Nader and colleagues hypothesized that if fear memory reconsolidation requires new synaptic plasticity, which requires protein synthesis, then injecting a protein synthesis inhibitor into the LA after retrieval should prevent reconsolidation and permanently alter the original fear memory. To test this, they conditioned rats to fear a tone CS. After initial consolidation of this fear memory, the rats were exposed to the tone again to reactivate the memory. This was immediately followed by administration of the protein synthesis inhibitor anisomycin into the lateral amygdala. A day later, the conditioned fear response was assessed. The rats that received the injection immediately after cue retrieval showed reduced expression of conditioned fear in comparison to rats receiving placebo, no reminder and injection of the drug, or injection of the drug 6 h after the reminder cue when the reconsolidation process was complete.

Since this study, there have been hundreds of studies in nonhuman animals investigating the mechanisms of fear memory reconsolidation. This research has basically supported these initial findings suggesting that the original fear memory is significantly altered by targeting reconsolidation, although some important distinctions in both the temporal molecular requirements and the brain regions involved in reconsolidation and initial consolidation have emerged (see [124] for a review).

In humans, however, there has been less success in demonstrating fear disruption by targeting reconsolidation. A primary reason is that the protein synthesis inhibitors typically used to target reconsolidation in other species have not been verified as safe for use in humans. In an effort to introduce a safe pharmacological intervention, Debiec and LeDoux [125] examined whether propranolol, a beta-adrenergic blocker that has been shown disrupt some forms of amygdala-dependent consolidation [126], would also disrupt fear memory reconsolidation. Propranolol is commonly prescribed to help with stage fright and has also been used in treating high blood pressure. Using both systemic and intra-amygdala injections in rats, they showed administering propranolol immediately after fear memory reactivation abolished the conditioned fear response at later test. Unfortunately, studies examining the efficacy of propranolol in human fear memory reconsolidation have been mixed. In an initial attempt, Brunet and colleagues [127] administered propranolol after the retrieval of traumatic memories in patients suffering from post-traumatic stress disorder (PTSD). Although at later test these patients showed some evidence of diminished physiological fear responses when cued with these memories, this manipulation did not have a lasting impact on PTSD symptoms. In a laboratory Pavlovian paradigm examining the influence of propranolol administration after reactivation on later fear expression found only a transitory reduction of later fear expression (see [128] for a discussion). Finally, a series of studies examining the impact of propranolol administration prior to cued-fear memory reactivation found some evidence that later fear expression was impaired but only for a limited range of fear assessments [129]. In these studies, however, it is possible that the administration of propranolol prior to fear memory reactivation disrupts a mechanism of fear expression, as opposed to reconsolidation [130].

Given some of the difficulties of using pharmacological manipulations to target fear memory reconsolidation in humans, a recent series of studies have used a different approach. These studies take advantage of the potential adaptive function of reconsolidation. If the purpose of reconsolidation is to update old memories with new relevant information available at the time of retrieval, then it is possible that introducing new information during the reconsolidation process will alter the original memory and have a lasting impact on the memory expression. This basic effect was demonstrated in humans in a clever series of studies on motor memory, in which introducing a new motor sequence after reminding participants of a previously learned motor sequence impaired later memory for the older sequence [131]. In fear learning, this behavioral interference of reconsolidation effect has been observed in mice [132], rats [133], and humans [134] using extinction training precisely timed to coincide with memory reconsolidation to interfere with the original fear memory. The primary difference between using extinction training to update the fear memory during reconsolidation and standard

extinction training is the timing. Fear memory reconsolidation is initiated by the retrieval or reactivation of the fear cue. After reactivation, it takes somewhere between 3 and 10 min for the reconsolidation process to begin [133, 134]. If extinction training begins too early, both the return of the fear response and indicators of synaptic plasticity within the LA [133] are consistent with standard extinction training. However, if extinction training is slightly delayed until the reconsolidation process has begun, the fear does not return, in contrast to standard extinction. In addition, changes in the LA under this behavioral interference protocol suggest learning-induced plasticity consistent with reconsolidation [133]. In humans, it has been shown that this diminished fear response with behavioral interference of reconsolidation is apparent even after a year [134]. More recently, in an examination of the molecular mechanisms underlying this effect, Clem and Huganir [132] demonstrated that the behavioral interference of reconsolidation might be linked to calcium-permeable AMPA receptor dynamics within the LA.

Although research on reconsolidation in humans is just emerging, it provides an exciting avenue for future research because it potentially eliminates the necessity for prefrontal inhibition of the amygdala. Variation in function of the amygdala–prefrontal pathway has been linked to both the recovery of fear following extinction and PTSD [135]. As of yet, the efficacy of these techniques has not been investigated in clinical interventions, and there may be significant limitations, such as the ability to target specific memories. However, if these techniques prove to be clinically useful, fear reconsolidation research has the potential to yield more lasting and effective treatments of anxiety disorders.

Conclusion

Through cross-species research in animal models and in humans, we have obtained a detailed model of the neurobiological underpinnings of fear learning. As described above, the amygdala plays an important role in cued, contextual, and social means of fear acquisition, highlighting its central role in fear acquisition and expression. Additionally, the hippocampus modulates the acquisition and expression of fear to a context. Drawing upon this detailed neurobiological model of fear conditioning, research in the past decade on fear extinction has delineated how safety learning following conditioning activates a prefrontal–amygdala pathway, inhibiting fear expression [59]. This inhibitory circuit is also modulated by contextual information relayed via the hippocampus. Notably, cognitive regulation and active coping, means of fear regulation that differ substantially from extinction, also recruit this phylogenetically shared inhibitory pathway [136, 137]. However, as these methods inhibit intact fear memories that can return under certain circumstances, they may all yield a transitory attenuation of fear. Recent work on reconsolidation suggests that pharmacological or behavioral interference with a fear memory following retrieval may permanently alter its representation, suggesting a mechanism for long-term prevention of fear recovery [128].

A central goal of fear research is to understand the origins of pathological anxiety in humans. Fear conditioning serves as an experimental model for the real-world associative learning that causes stimuli in our environment to evoke negative affective responses. Excessive generalization or poor regulation of such learning is proposed to underlie the persistent fear that characterizes anxiety disorders [138] and may contribute to the biased decision-making associated with these clinical conditions [139]. While neuroscientific fear research has outlined the mechanisms modulating fear expression in the typical “average” individual, one important question that remains poorly understood is what gives rise to the substantial variation between individuals in fear acquisition and regulation. Future research elucidating how variation in both the genetic and experiential background of the individual shapes the neurocircuitry governing fear learning will play a critical role in translating fear research from the laboratory to clinical treatment methods. Furthermore, the small body of research on the developmental

trajectory of fear learning and regulation indicates that there are important qualitative differences in these processes across development. An improved understanding of the development of fear conditioning will be a necessary step toward understanding the origins of vulnerability to and resilience against anxiety disorders across the lifespan.

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