Extending animal models of fear conditioning to humans

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Accepted 25 April 2005
Available online 10 February 2006

Abstract

A goal of fear and anxiety research is to understand how to treat the potentially devastating effects of anxiety disorders in humans. Much of this research utilizes classical fear conditioning, a simple paradigm that has been extensively investigated in animals, helping outline a brain circuitry thought to be responsible for the acquisition, expression and extinction of fear. The findings from non-human animal research have more recently been substantiated and extended in humans, using neuropsychological and neuroimaging methodologies. Research across species concur that the neural correlates of fear conditioning include involvement of the amygdala during all stages of fear learning, and prefrontal areas during the extinction phase. This manuscript reviews how animal models of fear are translated to human behavior, and how some fears are more easily acquired in humans (i.e., social–cultural). Finally, using the knowledge provided by a rich animal literature, we attempt to extend these findings to human models targeted to helping facilitate extinction or abolishment of fears, a trademark of anxiety disorders, by discussing efficacy in modulating the brain circuitry involved in fear conditioning via pharmacological treatments or emotion regulation cognitive strategies.

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Keywords: Emotion; Learning; Amygdala; Prefrontal cortex; Infralimbic; Prelimbic; Acquisition; Extinction; Anxiety disorders; Emotion regulation

1. Introduction

Fear can be characterized by anxiety and agitation due to the expectation of impending danger. Fears can be acquired and expressed in a variety of ways. For example, one can develop a fear of dogs because of previous experiences (i.e., person was earlier bitten by a dog), verbal instructions (i.e., person is told that a dog bites) or mere observation (i.e., person observes a dog biting someone else). Regardless of how the fear was acquired, the person may express similar responses to the presentation of the dog, such as sweating, changes in heart rate, blood pressure and respiration. Fear can serve as an adaptive alert mechanism for the organism. However, fear can also be a detriment as feelings of anxiety persist and have a negative effect on day to day behavior. Therefore, it is important to also understand how fears are diminished, for example, how one stops expressing conditioned responses to the dog by relearning that the dog does not impose any danger. One focus of studies utilizing fear conditioning paradigms is to understand the neural mechanisms that enable acquisition of fear, and perhaps more importantly, the mechanisms that lead to the extinction of fear and decreases in anxiety symptoms.

Much of our knowledge regarding fear and emotion comes from an extensive and elegant animal literature, results that are now being tested and applied in humans using neuropsychological and neuroimaging techniques. The following review briefly discusses fear conditioning as a model paradigm, concentrating on key findings regarding the neural circuitry of both acquisition and extinction in non-human animals, and how we can extend such findings to humans.

2. Acquisition and expression of fear learning

One of the simplest experimental tools for studying fear and anxiety is Pavlovian or classical fear conditioning, based on Ivan Pavlov’s findings that a neutral stimulus can acquire affective properties due to an association with a biologically relevant stimulus (Pavlov and Anrep, 1927). Although there are other forms of aversive learning involving more complex operant or instrumental paradigms (Everitt et al., 2003; Killcross et al., 1997), for purposes of this review, classical conditioning paradigms will primarily be discussed. As described by Rescorla (1988, p. 158) “Pavlovian conditioning
refers to the learning of relation among events that are complexly represented”. This can be illustrated by a typical fear conditioning paradigm, which generally involves presentation of a neutral stimulus such as a tone. Initially, the tone will have little effect on an animal such as a rat. Conditioning occurs when the tone is associated with an aversive stimulus such as a mild foot shock, the unconditioned stimulus (US), which by itself elicits a fear response such as autonomic (i.e., changes in heart rate) and behavioral (i.e., freezing) responses. Through repeated associations, the rat learns that the tone predicts shock and presentation of the tone by itself, a conditioned stimulus (CS), is able to elicit a fear conditioned response (CR). Although most experimental paradigms of fear conditioning make use of repeated pairings between CS and US to achieve conditioning, it is important to note that the CS–US pairing is not essential or sufficient at times for conditioning to occur. Rather what is emphasized is the information that the CS provides about the occurrence of the US (Rescorla, 1988).

Fear conditioning occurs in different species, and similar neural underpinnings are also shared across species (LeDoux, 1996). One common brain region is the amygdala, an almond-shaped structure in the medial temporal lobe that has been previously implicated in processing emotional information such as fear (Aggleton, 2000; Kluver and Bucy, 1937; Weiskrantz, 1956). A potential fear circuitry in the brain has been elaborated primarily in rats, suggesting that the amygdala and its projections may be involved in both the acquisition and expression of conditioned fear (Davis, 1992; LeDoux, 1996; Rosen, 2004; Sarter and Markowitsch, 1985). In simple terms, sensory information from the cortex and thalamus is received by the amygdala which then projects to hypothalamic and brainstem targets that mediate conditioned responses (Amaral, 1986; McDonald, 1998; McDonald et al., 1996; Price, 2003; Swanson and Petrovich, 1998). The lateral nucleus of the amygdala, part of the basolateral complex, is the site of cortical and thalamic inputs (Amaral, 1986; LeDoux et al., 1990; McDonald et al., 1996) and lesions in this region lead to deficits in the acquisition of contingencies that predict aversive outcomes which are capable of causing fear in conditioning paradigms (Campeau and Davis, 1995; Goosens and Maren, 2001; Tazumi and Okaichi, 2002; Wilensky et al., 1999). Further, neuronal cell firing in the lateral nucleus is modulated by nociceptive stimulation and auditory inputs (Romanski et al., 1993) and firing properties are modified during fear conditioning (Quirk et al., 1997, 1995), suggesting a possible integration of CS and US information, although plasticity has been observed in other amygdala subnuclei as well during aversive conditioning (Pascoe and Kapp, 1985a,b). Thus, research suggests that convergence of CS–US information occurs in the lateral nucleus of the amygdala, relayed from cortical inputs that may regulate the learning and expression of affective behaviors (Rosenkranz et al., 2003).

Information processed in the lateral nucleus is further relayed to a different subnucleus of the amygdala, the central nucleus, an output unit of the amygdala (Price and Amaral, 1981; Smith and Pare, 1994). The central nucleus in turn projects to an array of areas responsible for mediating the expression of fear and anxiety (Davis, 1992). Projections to the hypothalamus (Price and Amaral, 1981), for example, may be important for mediating autonomic responses such as skin conductance responses, blood pressure elevation and pupil dilation (see Davis, 2000 for review). Similarly, projections to midbrain nuclei such as the central grey (Hopkins and Holstege, 1978) or ventral tegmental area (Simon et al., 1979) may mediate some behavioral responses such as freezing and attention/vigilance, respectively.

Electrical stimulation of the central nucleus of the amygdala can lead to autonomic and behavioral changes associated with the expression of fear. Increases in blood pressure, for instance, are observed by stimulation of the central nucleus of unanesthetized rats (Tellioğlu et al., 1997). In addition, such stimulation leads to increased arousal and vigilance as measured by cortical electroencephalographic (EEG) activity in rats (Kapp et al., 1994) and rats (Dringenberg and Vanderwolf, 1996). Certain conditioned responses expressed following fear conditioning can also be blocked with lesions of the central nucleus. Changes in the cardiovascular system of rabbits, for example, are no longer observed following specific lesions in the central nucleus of the amygdala (Kapp et al., 1979; McCabe et al., 1992). Decreased freezing is observed in rats that have lesions in the central nucleus pre and post conditioning (Davis, 2000). Lesions of the central nucleus in non-human primates can also lead to reduced expression of fear responses (Kalin et al., 2004). Further, it has been postulated that fear acquisition occurs due to increased activity in the lateral nucleus (in response to CS presentation) which leads to disinhibition of neurons in the central nucleus that then project to brainstem nuclei (Pare et al., 2004). This evidence suggests that the central nucleus of the amygdala is an essential part of a circuitry mediating fear conditioning.

The human amygdala has also been implicated in acquisition and expression of fear conditioning. Participants submitted to conditioning procedures, for example, show increased skin conductance responses (SCRs), a measure of arousal that serves as the expressed conditioned response, in the presence of a conditioned stimulus (Hygge and Ohman, 1978; LaBar et al., 1995). Interestingly, this effect has been observed even when the CS+ (stimulus that predicts the occurrence of an aversive US) is masked to prevent conscious awareness (Esteves et al., 1994). Increased SCRs in fear conditioning paradigms are also displayed by amnesic patients, who have an intact amygdala but damage to the hippocampus, even though they are unable to explicitly report which CS was associated with a US (Fried et al., 1997). Patients with unilateral (LaBar et al., 1995) and bilateral lesions of the amygdala (Bechara et al., 1995), however, show the reverse pattern as they fail to exhibit increases in SCR to a CS+ in a fear conditioning paradigm, despite showing explicit knowledge of the contingencies.

The psychophysiological and neuropsychological work is substantiated by recent neuroimaging studies. Functional magnetic resonance imaging methodology (fMRI), for example, allows researchers to investigate the human amygdala’s role in fear learning. Early imaging studies were suggestive of a role for the human amygdala in processing fear-related stimuli,
such as fearful faces (Breiter et al., 1996; Morris et al., 1996), corroborating previous neuropsychological findings of deficits in recognition of fear in facial expressions in patients with bilateral amygdala damage (Adolphs et al., 1995). Two initial studies were instrumental in looking at the amygdala response during acquisition of fear. In 1998, Buchel and colleagues developed a paradigm using faces which allowed them to look at different trials during fear conditioning. Using white noise as the US, they specifically looked at trials that predicted the occurrence (CS+) or absence (CS−) of the US, with a reinforcement rate of 50%. They found bilateral amygdala activation in response to processing of the CS+, which was higher early on during learning and subsequently decreased. At the same time, LaBar et al. (1998) used neutral stimuli (i.e., colored squares) paired (CS+) or unpaired (CS−) with mild shocks, in a paradigm that more closely resembled traditional animal studies. They found activation of the amygdala when comparing CS+ versus CS− acquisition trials. In addition, such activation correlated with the strength of the conditioned response (as measured by SCRs). In both neuroimaging studies, the observed response in the amygdala was temporally graded, consistent with physiological recordings in the rat amygdala (Quirk et al., 1997).

Thus far, much of the research done in humans using fear conditioning has replicated existing animal models. There are disadvantages to human research, however, that are complemented by non-human animal studies. For example, unlike classic animal models of fear conditioning, researchers using both neuropsychological and neuroimaging methodology have encountered difficulties with respect to specificity of lesions (i.e., unilateral versus bilateral lesions, amygdala only versus amygdala and adjacent cortex lesions) and functional anatomy, as fMRI’s resolution is still unable to reliably look at differences between amygdala subnuclei, such as the lateral and central nucleus. Continued progress in neuroimaging techniques, however, has been promising and there is hope that soon more focused acquisition sequences or slice prescriptions will allow investigation of subnuclei within the amygdala. Despite the discrepancy and disadvantages of tools used to study humans compared to methodology used with animals, these tools also afford the opportunity for researchers to ask questions that they could not easily investigate in animals. Such is the case with more social forms of fear learning and emotion regulation strategies, both of which are related to acquisition and extinction of anxiety disorders, respectively.

3. Acquiring fear through social–cultural means

Animal models of fear conditioning have proven useful in describing the mechanisms underlying human fear conditioning. However, outside the laboratory, humans may acquire most of their fears through social–cultural means, such as social observation and verbal communication (Rachman, 1977). Social–cultural fear learning does not require direct experience of the noxious event predicted by the conditioned stimulus, and thus providing a flexible mode of knowledge-acquisition that is both faster and less risky than Pavlovian conditioning. Whereas the mechanisms underlying fear conditioning are well explored in both humans and non-human animals, much less is known about the mechanisms involved in fear learning via social–cultural means.

Symbolic representations and verbal communication render possible several ways of dispersing information about the emotional significance of objects and events that are unique to humans. Fear responses following verbal instruction have often been reported as being similar to responses observed in traditional fear conditioning experiments (Phelps et al., 2001). Both clinical accounts that retrospectively target the etiology of phobic fears to fear-relevant stimuli (King et al., 1998) and experimental studies involving stimuli ascribed fear provoking qualities through storytelling (Field et al., 2001), reveal that verbal instruction comprises a potent means of fear learning. Also, some studies have shown that participants verbally instructed to expect a shock associated with the presentation of a CS display an arousal response to supraliminal presentations of the CS similar to responses following fear conditioning (Grillon et al., 1991; Phelps et al., 2001).

An interesting and distinct fMRI experiment used a fear conditioning paradigm with interspersed presentations of CS+ and CS−. This study was different from previous fear conditioning imaging experiments (Buchel et al., 1998; LaBar et al., 1998) and from animal models (Davis, 1992; LeDoux, 1996) in that it used verbal instruction to explain the CS–US contingency, rather than some forms of experimental Pavlovian learning, where repeated associations between CS–US strengthen the contingency. Participants were told that one of the CS’s (the CS+) was associated with a possibility of an aversive shock delivery, while another CS (the CS−) was safe. No shock was actually administered during this experiment. In this instructed fear paradigm, activation of the left amygdala was robustly activated when comparing CS+ and CS− trials (Fig. 1), with such activation further correlating with the expression of fear response (as measured by SCR). Consistent with the neuroimaging results, it was found that patients with left, but not right, lateralized amygdala lesions displayed an impaired fear response to a stimulus that was verbally instructed to predict a shock (Funayama et al., 2001). These instructed fear experiments demonstrate that (a) there is an overlap between how fear is processed in the human brain when using abstract representations or aversive stimuli that induce fear and (b) certain types of fear can only be studied in humans rather than animals.

A second means of social communication is observation. Aversive learning through social observation has been documented in a range of species, among them, mice (Kavaliers et al., 2001), cats (John et al., 1968), non-human primates (Mineka et al., 1984) and humans (Hygge and Ohman, 1978; Olsson and Phelps, 2004). These lines of research have established that the expressed emotional distress in a conspecific can serve as a powerful US. In an early experiment, Hygge and Ohman (1978) found that fear responses acquired to a fear-relevant stimulus (e.g. a snake) associated with a confederate’s fear expression were similar to those acquired in Pavlovian fear conditioning paradigms. This finding has now been corroborated by a series of experiments with non-human
primates (e.g., Mineka and Cook, 1993). Similar to classical fear conditioning, these studies have demonstrated rapid, strong, and persistent learning through exposure to a conspecific’s fearful reactions to a fear-relevant stimulus, which has lead Mineka and Cook (1993) to suggest that similar mechanisms support more traditional classical conditioning and vicarious aversive learning.

As previously described, fear conditioning can also occur with both supraliminally and subliminally presented fear-relevant stimuli, suggesting that Pavlovian conditioning is partially independent of cognitive awareness of the CS–US contingency (Ohman and Mineka, 2001). In a recent attempt to compare different kinds of fear learning, Olsson and Phelps (2004) presented subjects with supraliminal and subliminal images of angry faces that previously had been associated with a shock through either direct aversive experience (Pavlovian conditioning), verbal instruction or social observation. During observation learning, participants were asked to watch and learn from a movie displaying a confederate doing a Pavlovian conditioning experiment. In the movie, the confederate received shocks associated with a colored square. The subjects were informed that after the movie, they themselves were going to do a similar experiment involving shocks associated with the same color as in the movie. However, no shocks were administered to the subject during the experiment. The results showed that across learning groups (Pavlovian, verbal instruction and observation) similar levels of fear responses to supraliminal presentations were observed. As predicted, Pavlovian conditioning also produced fear responses to subliminal presentations. Interestingly, observational learning also survived subliminal presentations, whereas the instructed manipulation did not. These findings reinforce the notion that fear learning through observation can be as pervasive as learning through one’s own experience. Moreover, the absence of the same effect in the instructed group lends support to the suggestion that there are partially dissociable systems involved in different forms of emotional learning (Mandel and Bridger, 1973; Ohman and Mineka, 2001). Pavlovian and observational learning are documented across species and are thus likely to be supported by a system that predates the emergence of language.

In a recent fMRI study, the neural correlates involved in observational fear learning were investigated using similar procedures, where participants were asked to watch and learn from a movie displaying a confederate doing a Pavlovian conditioning experiment (Olsson et al., 2004). Whereas the expression of instructed fear predominantly involves the left amygdala (Funayama et al., 2001; Phelps et al., 2001), and Pavlovian conditioning engages the amygdala bilaterally (LaBar et al., 1998; Morris et al., 1998), the results of the observational learning experiment showed that, similar to Pavlovian conditioning, the amygdala was recruited bilaterally during both the observation and the subsequent test stage. This finding supports the behavioral similarities, as noted above, found between observational and Pavlovian fear learning.

4. Extinction of fear

Through animal models and research in humans, we have gained an extensive body of knowledge regarding the neural mechanisms underlying the acquisition and expression of fear. At present, the focus of much research is applying such knowledge to understand how acquired fears can be extinguished. Anxiety disorders, such as phobias and post-traumatic stress disorders for example, are associated with lingering expressions of fear (i.e., autonomic and endocrine system disregulation) often brought about by a stimulus which has been linked with an aversive event or context through learning. Current treatments for anxiety disorders attempt to inhibit these fear responses, making it imperative to understand more about the extinction process to aid in the efficacy of various forms of treatment such as drug and psychotherapy.

Although some learning theories refer to extinction as an unlearning process due to violations of the CS–US contingency (Rescorla and Wagner, 1972), it is usually considered that extinction of fear represents a new type of learning that updates the CS–US contingency to no longer indicate an aversive
prediction, thus inhibiting the expression of the fear response (Bouton, 1993, 2004; Myers and Davis, 2002; Pearce and Bouton, 2001; Wagner, 1981). Early support for the idea that decreases in fear observed during extinction do not represent unlearning come from spontaneous recovery studies that suggest that after a period of time, conditioned fear responses to the cue may return (Robbins, 1990). Further support comes from studies of reinstatement (Dirikx et al., 2004) and renewal (Rodriguez et al., 1999) of fear. These studies suggest that extinction is a process that does not lead to forgetting or unlearning the predictive nature of a CS; instead extinction refers to new inhibitory learning that prevents expression of the conditioned fear.

Evidence from non-human animal research once again implicates the amygdala during extinction of fear learning. Neuronal firing in the lateral nucleus in response to a predictive CS dissipates over time if the US is no longer delivered (Quirk et al., 1995; Repa et al., 2001), although some traces of conditioning still persist (Quirk et al., 1995). This reduction in cell spikes observed in response to a predictive CS during extinction also correlates with behavioral measures of extinction (i.e., attenuation of the CR). Further, disruption of plasticity within the amygdala impairs extinction (Falls et al., 1992; Myers and Davis, 2002).

In addition, much of the focus of research in extinction has been on the mechanisms that inhibit amygdala subnuclei and the CA1, with areas in the prefrontal cortex (PFC) possibly mediating or regulating amygdala activity. For example, the infralimbic region of rat medial PFC, an area with strong projections to the amygdala (McDonald et al., 1996; Sesack et al., 1989), has been shown to inhibit both lateral (Rosenkranz and Grace, 2002, 2003) and central nucleus (Quirk et al., 2003), and when stimulated leads to reductions in CR expression (Milad and Quirk, 2002). Interestingly, neurons in rat infralimbic region are unresponsive to a predictive CS during acquisition and subsequent extinction. Instead, they respond primarily to a predictive CS presented 24 h later, perhaps reflecting retention of the extinction memory (Milad and Quirk, 2002). This result is substantiated by lesion studies demonstrating successful extinction in rats with medial PFC lesions, but poor recall of extinction memory during a subsequent session 24 h later (Lebron et al., 2004; Morgan et al., 1993). Further, a correlation between medial PFC activity and extinction recall was also found 24 h post-acquisition (Herry and Garcia, 2002, 2003). This suggests that medial PFC may be involved in the maintenance or retention and subsequent recall of extinction memory (Pare et al., 2004).

Although animal models of extinction learning have highlighted the role of structures such as the amygdala and PFC regions in extinction learning, substantially less research exists in humans. In previous imaging experiments, extinction was difficult to measure due to rapid increases in amygdala activity (Buchel et al., 1999, 1998; LaBar et al., 1998) and the fact that the US was presented continuously following each presentation of a CS during acquisition, which leads to very rapid extinction in humans (LaBar et al., 1998). Recently, a few neuroimaging studies have implicated the human amygdala (Gottfried and Dolan, 2004; Knight et al., 2004) and PFC (Gottfried and Dolan, 2004) involvement in human extinction studies, using paradigms that involved either reforcer inflation of the US (Gottfried and Dolan, 2004) or between-subject comparisons of CS+ exposed and control participants (Knight et al., 2004).

In a human extinction paradigm designed to mirror experimental paradigms in the non-human animal literature, two predictive stimuli either paired (CS+) or not (CS−) with shock were used (Pfaff et al., 2004). With the intention of slowing down the extinction process, only some of the CS+ presentations were paired with the US during acquisition (a partial reinforcement design). The acquisition phase was immediately followed by an extinction session (day 1 extinction), where subsequent presentations of CS+ were not paired with US, and a second extinction session roughly 24 h later (day 2 extinction). The physiological expression of fear (measured by SCRs) was, not surprisingly, significantly higher for CS+ compared to CS− trials during the acquisition phase. The strength of the CR, however diminished over extinction trials (specifically during the late trials of day 1 extinction and during day 2 extinction). Brain activation patterns showed robust and increased activation in the amygdala when comparing CS+ trials during acquisition with CS+ trials during day 1 extinction (Fig. 2A). Amygdala activity further correlated with the CR during day 1 extinction, suggesting greater differential amygdala activity predicts greater extinction.

Activation was also observed in the subgenual cingulate cortex, part of the ventromedial PFC and a region suggested to be analogous to the infralimbic and prelimbic regions of rat medial PFC (Kim et al., 2003). This pattern of activation was characterized by a depression in the blood-oxygen-level-dependent (BOLD) response during acquisition CS+ trials (relative to the CS− trials and rest). A relative increase in the BOLD response (i.e., a decreased depression) was then observed as extinction learning progressed in both day 1 and day 2 extinction. Furthermore, a correlation was observed between the magnitude of the increased BOLD response in the subgenual anterior cingulate activation at the beginning of day 2 extinction and the extinction of conditioned fear (as measured by SCR) during day 1 extinction (Fig. 2B). The correlation suggested that participants who were able to better extinguish their fears during day 1, showed a more positive change in activity within the subgenual region during the beginning of day 2 extinction, consistent with the proposal that the ventromedial PFC may play a role in the retention of extinction learning (Milad and Quirk, 2002). These results are in agreement with Milad and Quirk (2002), as the medial PFC response was predictive of extinction learning after a 24 h retention period. However, in their study Milad and Quirk (2002) found increasing activity in medial PFC in rats in response to a CS (relative to the preceding baseline), while in this imaging study (Pfaff et al., 2004) an initial decrease to CS+ trials was observed during acquisition which diminished as extinction progressed. This disparity may arise from difference in species, locus of
activity (i.e., rat infralimbic cortex and human analogue perhaps including infralimbic and prelimbic aspects) and paradigm design (i.e., the inclusion of two CS predictors). Further, it is worthy to note that while researchers have a good grasp on the correlation between increases in BOLD response and neural activity, there is still uncertainty about what decreases in BOLD responses may represent. Corroborating the human findings, however, Garcia et al. (1999) used a conditioned inhibition paradigm in mice and found a depression in the response to the CS+ in the prelimbic cortex that diminished as the CS+ become less predictive of the US (after induction of a conditioned inhibitor, the CS−). This pattern of response mirrored the results shown in humans by Phelps et al. (2004).

5. Facilitation of extinction

An important goal of clinical interventions of anxiety disorders is to facilitate extinction of fear. More recently, research has suggested that incorporation of pharmacological or cognitive treatments, combined with psychotherapy, can aid in extinction learning. In terms of pharmacological manipulations, N-methyl-D-aspartate (NMDA) glutamatergic receptors have continuously been associated with learning (for recent reviews see Lynch, 2004; Nakazawa et al., 2004; Walker and Davis, 2004), specifically in the amygdala (Maren, 1999; Pare, 2004), thus it is no surprise that it has also been linked to extinction learning (Myers and Davis, 2002; Richardson et al., 2004). For example, using fear potentiated startle as a measure,
Falls et al. (1992) showed that extinction is blocked when NMDA antagonists are infused into the rat amygdala before extinction. In contrast, application of D-cycloserine, an NMDA partial agonist, seems to facilitate extinction. Walker et al. (2002) used systemic administration or direct infusions into the amygdala, 2 days after the initial CS–US pairings occurred. Using potentiated startle as a measure of fear, it was shown that administration of D-cycloserine facilitated extinction as measured by less fear to the CS compared to a control group (Walker et al., 2002). Similar results were observed when D-cycloserine was administered post a brief extinction period, and tested again 2 days later, suggesting that the pharmacological treatment may be important during the consolidation of a new extinction memory (Ledgerwood et al., 2003).

The findings and potential benefit of these animal experiments suggest possible treatment for patients suffering from anxiety disorders. Currently, research is attempting to integrate the use of D-cycloserine with psychotherapy to improve the efficacy of treatment. In one study, n-cycloserine was administered to phobic patients suffering from acrophobia (fear of heights) undergoing behavioral exposure therapy (Ressler et al., 2004). The efficacy of the drug was displayed by the observation of faster reductions in symptoms in patients that were treated with therapy in conjunction with n-cycloserine as opposed to placebo. This facilitation in extinction learning was observed within the treatment environment (virtual reality behavioral exposure), as well as by decreases in post-treatment skin conductance responses and overall better scores in scales measuring day to day acrophobia symptoms. Further research is needed to completely understand the effects of D-cycloserine in humans and its variations. For example, one study found poor evidence of the benefits of n-cycloserine using a post-traumatic stress disorder population (Heresco-Levy et al., 2002), although it is worthy to note that no behavioral therapy was used in conjunction with drug application. Thus, there is optimism for future research using n-cycloserine and behavioral therapies to aid extinction learning.

Another way to facilitate extinction learning, which is more common in humans, is the use cognitive strategies to regulate emotion. As observed by previous descriptions of how fear can be acquired through more social–cultural means, such as instruction (Phelps et al., 2001) or observation (Olsson and Phelps, 2004), humans possess different capabilities which allows them to acquire fear, and therefore perhaps can also facilitate in the extinction or regulation of fear. Recent studies have aimed to understand how humans can attempt to regulate their emotional responses by using cognitive strategies, in turn modulating brain regions involved in emotional processing such as the amygdala and PFC (Gross, 2002; Ochsner and Gross, 2004). For example, Schaefer et al. (2002) presented unpleasant pictures to participants while they either maintained their emotional response to the stimulus or passively viewed the pictures. After the stimulus presentation, affective ratings about participant’s current emotional status were acquired. Higher behavioral ratings were observed for negative pictures while participants maintained their emotional reaction as opposed to when they just passively viewed the stimulus, a result that was mirrored in the amygdala in an fMRI experiment, where greater activity was observed during maintenance of negative emotional feelings.

Another study by Ochsner et al. (2002) investigated the neural correlates of reappraisal, a type of cognitive strategy that proposes that an individual can change their emotional reaction by reevaluating the situation in a less negative context (Gross, 2002). In this study, participants viewed emotionally negative pictures (e.g., woman crying on steps of church) and were asked to either “attend” or “reappraise” the stimulus. Participants were asked to let themselves experience whatever came to mind (e.g., a funeral) and respond naturally during “attend” trials. In contrast, participants were trained to reinterpret the picture in a less negative context (e.g., the woman is crying at a wedding) so that they no longer felt negative about it during “reappraisal” trials. The reappraisal technique was successful in reducing the emotional reaction to the negative stimulus, as expressed by a reduced affective rating during “reappraisal” trials. The neuroimaging data revealed increases in activity during “reappraisal” in left PFC, while decreases were documented in both the amygdala and ventral areas of the frontal cortex. Thus, the use of cognitive strategies appears to modulate the subjective expression of emotions (i.e., self-ratings) and the underlying brain circuitry involved in emotional processing (i.e., amygdala, PFC).

Investigations of extinction in fear conditioning studies and neuroimaging studies of emotion regulation both suggest modulation of amygdala activity (Ochsner et al., 2002; Schaefer et al., 2002). A recent study has attempted to more closely examine the effects of cognitive emotion regulation strategies in fear acquisition through classical conditioning (Delgado et al., 2004). Using a fear conditioning paradigm with two predictive colored squares (CS+ and CS−) and two instructions (“attend” and “reappraise”), it was hypothesized that cognitive emotion regulation strategies would be successful in decreasing the CR, or expression of fear (as measured by SCR) and would modulate brain systems involved in extinction. Participants were instructed to either attend to their natural feelings (i.e., “I may receive a shock” upon seeing an “attend” CS+) or think of something calming in nature that was specific to the color of the square (i.e., upon seeing a blue square, a “reappraise” CS+ trial, participants would think of the ocean). Application of cognitive emotion regulation strategies was successful in decreasing the expression of conditioned fear, as suggested by decreased SCRs to “reappraisal” versus “attend” CS+ trials. Further, decreased amygdala activation and increased ventromedial PFC activation were observed, similar to previous human extinction studies (Phelps et al., 2004), suggesting that the use of cognitive strategies may also facilitate the extinction process.

6. Summary

Fear conditioning has been used as a model paradigm to investigate the neural circuitry of emotional learning across species. Animal models of fear conditioning have examined the neural pathways of fear acquisition and extinction from stimulus input to response output. These models have provided
clear hypotheses for the investigation of the neural systems of fear learning and extinction in humans. Behavioral, neuropsycho- physiological and neuroimaging research in humans have confirmed and extended these animal models to social–cultural means of learning (e.g., language and observation) and cognitive strategies that can be used to regulate emotion (e.g., cognitive behavioral therapy). These new frontiers in human research of fear and anxiety will hopefully lead to new hypotheses that can be tested in animals to increase or develop new ways to efficaciously decrease the impact of maladaptive fear in everyday life.

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