Brain Mechanisms of Fear Extinction: Historical Perspectives on the Contribution of Prefrontal Cortex

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What brain regions are involved in regulating behavior when the emotional consequence of a stimulus changes from harmful to harmless? One way to address this question is to study the neural mechanisms underlying extinction of Pavlovian fear conditioning, an important form of emotional regulation that has direct relevance to the treatment of human fear and anxiety disorders. In fear extinction, the capacity of a conditioned stimulus to elicit fear is gradually reduced by repeatedly presenting it in the absence of any aversive consequence. In recent years there has been a dramatic increase in research on the brain mechanisms of fear extinction. One region that has received considerable attention as a component of the brain's extinction circuitry is the medial prefrontal cortex (mPFC). In the present article, we review the historical foundations of the modern notion that the mPFC plays a critical role in emotional regulation, a literature that was largely responsible for studies that explored the role of the mPFC in fear extinction. We also consider the role of the mPFC in a broader neural circuit for extinction that includes the amygdala and hippocampus.

Key Words: Emotion, conditioning, history, amygdala, hippocampus, exposure therapy

The question of how the brain controls and regulates emotional expression is of great interest. Emotional regulation is likely to have evolutionary advantages, especially in highly social animals, such as humans (Darwin 1872). Indeed, society depends on the collective regulation of emotional expression. For example, certain forms of extreme emotional expression are viewed as immoral and/or illegal. The conference represented in this issue of *Biological Psychiatry* focused on a specific and important form of emotion regulation, extinction.

Extinction was first formally studied by the Russian physiologist Ivan Pavlov (Pavlov 1927). In his famous experiments with dogs, a sound was presented just before the delivery of food. At first, the dog only salivated when food was in its mouth. After several repetitions of the sound and food, salivation began to occur at the sound in anticipation of the food. The food was called an unconditioned stimulus (US) and the sound a conditioned stimulus (CS). Accordingly, salivation to the food was designated an unconditioned response (UR) and salivation to the sound a conditioned response (CR). Pavlov then showed that when the CS was repeatedly presented without the US, the ability of the CS to elicit the CR weakened. He called this weakening of the CR experimental extinction.

Although extinction has been studied experimentally for almost a century, it has recently become one of the hottest topics in neuroscience. Part of the reason for this new interest is that several key discoveries have been made that relate extinction to specific brain mechanisms. But not all discoveries about brain mechanisms are equal. What makes discoveries about extinction so important is that the findings have broad clinical significance. Specifically, certain emotional disorders are characterized by a resistance to extinguish learned emotional reactions to anxiogenic stimuli, and sometimes by an avoidance of situations with the potential to induce extinction (Eysenck 1976; Mineka and Ohman 2002; Rothbaum and Davis 2003; Wolpe 1968). Moreover, a major approach to the treatment of emotional disorders involves the promotion of extinction (Barlow 2002; Craske 1999; Foa and Jaycox 1999; Wolpe 1968). Elucidation of the extinction process and how the brain mediates this process could thus lead to better understanding of, and therapies for, emotional disorders.

In this introductory article, we will briefly discuss the nature of extinction and then consider the historical origins of contemporary work on the brain mechanisms of extinction. We concentrate on extinction of learned fear, because much of the recent work on extinction has involved fear conditioning. In discussing the brain mechanisms of extinction, we focus on research that led to the idea that the prefrontal cortex (PFC) plays a key role; however, in considering the contribution of the PFC to extinction we do not mean to minimize the importance of other areas. Thus, we discuss the PFC as a component of a broad fear extinction circuit involving the amygdala and hippocampus, among other areas.

What Is Extinction?

The term extinction is usually used to refer to the weakening of a response to a stimulus that acquired aversive properties through learning. In addition to studying the conditioning and extinction of salivation in response to a CS that predicts food, Pavlov also studied defensive CRs, which were responses elicited by a CS paired with aversive stimulation (Pavlov 1927). In contemporary parlance, defensive conditioning is called fear conditioning. After pairing of the CS and US, usually a tone and shock in rodent studies, the CS elicits freezing behavior and a variety of supporting physiological changes that prepare the organism to deal with the danger being warned about by the CS. With repeated presentations of the nonreinforced CS, these responses dissipate. At this point, the fear response is said to be extinguished. Acquisition and extinction of freezing to a CS is illustrated in Figure 1.

Although most work on fear extinction involves learned fear, both innate and acquired fears can be weakened by exposure to the threatening stimulus. We will emphasize extinction of learned fear in this article, because much of the experimental work on extinction has been of this type. From a clinical perspective, however, innate predispositions toward fear are also important, especially in the development of phobias, and exposure therapy (itself a form of extinction) is often used to treat fear pathologies regardless of whether they are clearly due to past learning

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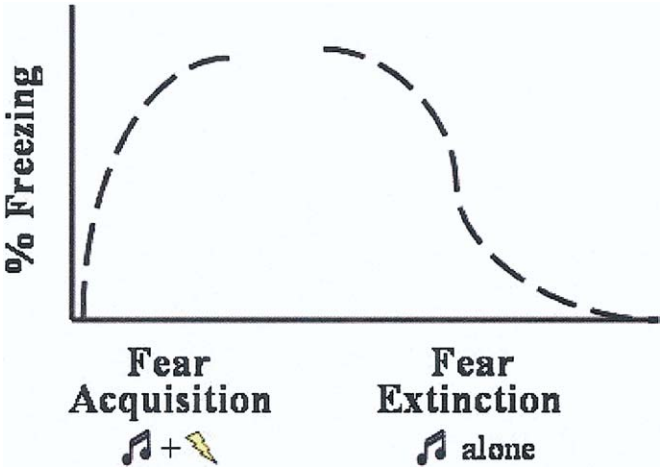

Figure 1. Acquisition and extinction of fear. The percentage of time a rat spends freezing is a common index of fear. Behavioral freezing is illustrated for acquisition (tone + shock) and extinction (tone alone) of conditioned fear to an auditory stimulus. After pairing the tone with the shock, rapid increased freezing is exhibited to the tone. With repeated tone-alone presentations, freezing gradually decreases. In general during fear extinction learning, freezing decreases slowly at first, then fast, and finally slowly again.

(Barlow 2002; Foa and Jaycox 1999; Wolpe 1968). We will consider clinical implications toward the end of this review.

For some time it has been accepted that extinction does not involve forgetting or memory erasure but instead involves new learning that inhibits or overrides past learning (Bouton 2004). Forgetting implies that the fear memory weakens with time in the absence of further training, which is easily ruled out because conditioned fear memories can last a lifetime in rats in the absence of further training (Gale et al 2004). Memory erasure might also be unlikely, given that fear to the CS can return after extinction, an impossibility if extinction caused the deletion of the original CS–US memory trace. For instance, fear to the CS can be recovered after extinction by allowing time to pass (spontaneous recovery; Rescorla 2004), changing contexts (renewal; Bouton 2004), or presenting the US (reinstatement; Rescorla and Heth 1975). Despite this long-held notion, recent work has revived interest in the idea that extinction might sometimes involve memory erasure. Of particular experimental and practical interest is the possibility that fear extinction training might cause erasure shortly after fear acquisition but might cause inhibitory learning once the fear memory is consolidated (Cain et al 2005; Lin et al 2003a, 2003b, 2003c; Myers et al 2006).

How Does the Brain Mediate Extinction?

Given the central role the amygdala plays in fear learning (Davis 1992; Fendt and Fanselow 1999; LeDoux 2000; Paré et al 2004; Sah et al 2003), it is not surprising that contemporary research considers the amygdala to be a key brain region related to extinction, either as a site of critical plasticity or as a site of expression. Indeed, several recent electrophysiological (Hobin et al 2003; Quirk et al 1995, 1997; Repa et al 2001; Rogan et al 1997), molecular (Davis 2002; Lin et al 2003b, 2003c; Marsicano et al 2002; Tang et al 1999), and imaging (Gottfried and Dolan 2004; LaBar et al 1998; Phelps et al 2004) studies implicate the amygdala in fear extinction learning (reviewed in Maren and Quirk 2004; Myers and Davis 2002; Quirk and Gehlert 2003; Sotres-Bayon et al 2004); however, studies showing that damage to cortical areas interferes with extinction (LeDoux et al 1989; Morgan and LeDoux 1995; Morgan et al 1993; Quirk et al 2000; Teich et al 1989; but see Falls and Davis 1993) suggest that amygdala processes alone are not sufficient to account for all aspects of extinction.

It is likely that fear extinction involves interactions between cortical and subcortical brain areas, especially interactions between the PFC and amygdala (LeDoux 2000; Morgan et al 1993; Quirk et al 2003; Rosenkranz et al 2003). The basic model is as follows. Circuits within the amygdala are essential to the acquisition of fear learning (auditory fear conditioning; Figure 2). Specifically, the lateral amygdala (LA) is a region where the CS (e.g., a tone) and US (e.g., a shock) converge and thus endow the CS with the capacity to elicit freezing and other related CRs. The LA then communicates with the central nucleus (CE), which controls the expression of fear by way of connections to specific circuits that mediate different response modalities (freezing behavior, autonomic nervous system responses, and endocrine responses). The LA connects with the CE directly and by way of connections to other amygdala areas, including the basal nucleus and the intercalated cell masses (Paré et al 2004). After extinction, the ability of the CS to control CRs by way of communication between the LA and CE is regulated by the ventromedial PFC (vmPFC). Activity between these regions might also be modulated by contextual information provided by the hippocampus. Interestingly, the basal amygdala processes information about the context by way of its reciprocal connections with the hippocampal formation. Although the basal nucleus is not required for fear extinction (Sotres-Bayon et al 2004), it could participate in the contextual modulation of extinction through these connections. Functionally relevant connections in fear extinction are represented between the vmPFC, amygdala, and hippocampus in Figure 3 (auditory fear extinction).

Below, we will consider the origin of the idea that the vmPFC plays a critical role in extinction. We start with a survey of the effects of PFC damage on behavioral regulation (including the

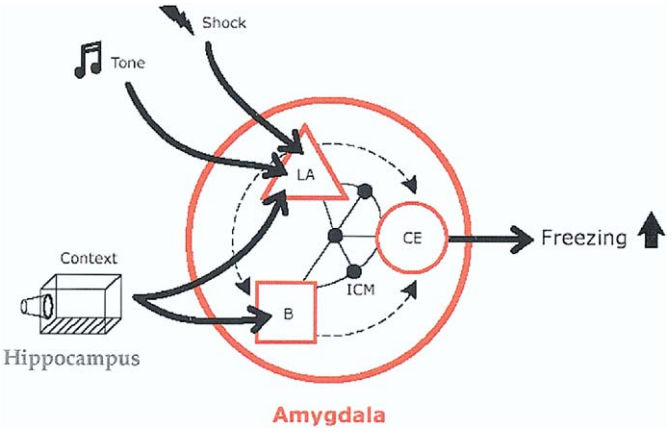

Figure 2. Fear conditioning circuitry. In auditory fear conditioning, animals learn to fear an innocuous tone. By pairing tone and shock, the tone acquires the capacity to elicit defensive reactions, such as freezing (arrow pointing up). Tone and shock stimuli converge in the lateral amygdala (LA), resulting in associative plasticity in the tone–LA pathway. Subsequent presentations of the tone can now activate LA neurons. The LA then communicates with the central nucleus (CE), which controls the expression of fear by way of connections to specific circuits that mediate freezing behavior. The LA connects with CE directly and by way of connections to other amygdala areas, including the intercalated cell masses (ICM), which gate the output, and the basal nucleus (B), which processes contextual information from the hippocampus.

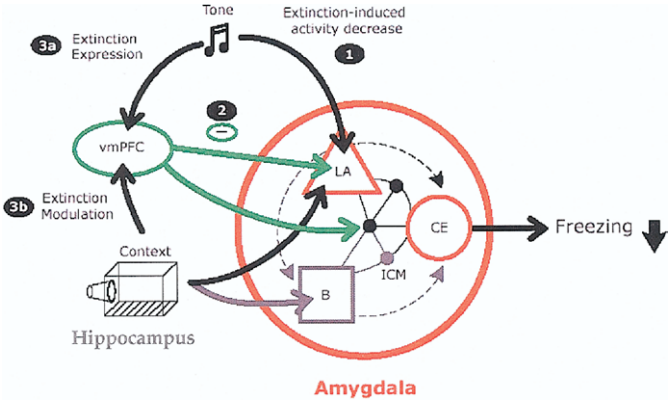

Figure 3. Fear extinction: neural model. In fear extinction, tone-alone presentations result in a reduced expression of the previously learned conditioned response, reflected as gradual reduction in freezing behavior (arrow pointing down). Ultimately, the central nucleus (CE) of the amygdala controls the expression of fear by way of connections to specific neural circuits that mediate freezing behavior. This model depicts the role the amygdala, ventromedial prefrontal cortex (vmPFC), and hippocampus play in three hypothetical stages of fear extinction. 1) In the early stage, after fear acquisition, tone-alone presentations cause some amygdala neurons to decrease their firing rate, through fear learning reversal and/or new inhibitory learning. 2) Next, at some point during consolidation of extinction, the inhibitory memory trace between the vmPFC and the lateral amygdala (LA) and/or intercalated cell masses (ICM) is established (mPFC-mediated amygdala inhibition; green arrows and minus sign). 3a) Third, after extinction learning, when the animal is required to retrieve the already-consolidated extinction memory, the vmPFC suppresses activity in the amygdala through inhibition of LA neurons and/or activation of the inhibitory ICM, resulting in a rapid decrease in freezing. 3b) At the same time, hippocampus-based contextual memory modulates neural activity of the vmPFC and/or LA, but not through basal amygdala (B; grey; Sotres-Bayon et al 2004), during extinction expression to regulate the animal's behavioral response (i.e., decrease freezing) if in the appropriate environment. For simplicity, we omitted two other connections that could be relevant: vmPFC connections to B and projections from vmPFC to CE.

regulation of emotional behavior) and then consider how this research tradition informed studies of fear extinction. We will briefly reconsider the interactive role of the vmPFC, amygdala, and hippocampus in extinction at the end of the article. Contributions of the PFC, amygdala, and hippocampus to fear extinction are surveyed in more depth in other articles in this issue (PFC: Quirk et al 2006; amygdala: Barad et al 2006; hippocampus: Bouton et al 2006).

Effects of PFC Damage on Behavioral Regulation

Evidence of the effects of brain damage on behavioral regulation can be traced back to the late 19th century. Jackson (1888) proposed that "higher" brain regions exert inhibitory control over the "lower" brain regions. According to Jackson, when higher centers are damaged, the inhibitory influence is removed from lower levels, revealing impulsive, instinctive, or, in some cases, maladaptive behaviors (Finger 2001). Evidence supporting this idea came from anecdotal reports, such as the famous case of Phineas Gage (Harlow 1848; Harlow 1868). Gage survived a railroad explosion that forced an iron bar completely through his head. The bar entered below his cheek and exited through his forehead, destroying most of the front of his brain, especially damaging the anterior part of his frontal lobe. By all accounts, Gage was an exemplary citizen before the accident but turned impulsive, restless, and disrespectful afterward. As noted by his physician, the accident unleashed "animal passions" in Gage (Harlow 1868).

Subsequent studies in animals showed that dramatic changes in emotional behavior followed frontal lobe damage (Bianchi 1895, 1922; Jacobsen 1935). In contrast to Gage, these studies most commonly reported a weakening or blunting of emotional reactivity. On the basis of such observations, Moniz (1936) attempted to treat anxious and aggressive patients by frontal leucotomy, a surgical procedure whereby fibers connecting the most anterior part of the frontal lobe—the PFC—to the rest of the brain were sectioned. Shortly after Moniz reported his procedure, Freeman championed prefrontal lobotomies (PFC removal: fibers and cell bodies) in the United States (Freeman and Watts 1942), leading to approximately 1000 surgeries per year in the 1940s to treat emotional disorders as varied as psychosis, depression, and even "criminality." The common finding after frontal lobotomy was that patients were generally less emotional—an outcome that sometimes alleviated presurgical symptoms but often at the expense of personality traits. So-called psychosurgery continued to be used into the 1960s (Finger 2001; Mark and Ervin 1970) but then ceased because of ethical concerns (Valenstein 1980) and the development of less-invasive treatments. These gross manipulations demonstrated the PFCs involvement in emotion. More specific manipulations done later helped to better define the function of PFC subregions, as we discuss in the following paragraphs.

One of the most consistent and well-documented effects of PFC damage is perseveration (Luria 1969, 1973; Milner 1964; Teuber 1964). That is, humans and animals with PFC lesions are unable to switch their behavioral choices when situations change. For example, Milner (1964) had PFC-damaged patients and control subjects sort cards on the basis of objects that varied on several dimensions: shape (circles, squares, triangles), color (red, blue, green), and number (one, two, or three objects). Over a sequence of trials, one dimension (e.g., shape) was the correct sorting principle. Then the rule would change (to color or number). Control subjects readily learned to switch; patients with PFC damaged did not. Interestingly, Milner noted that PFC-damaged patients were aware of the perseverative errors they committed but were unable to modify their strategy.

Animal studies also found perseverative errors in other reversal tasks. For instance, in some studies, monkeys were first trained to receive a reward when they chose one of two stimuli, and then the reward was switched to the other stimulus. Control subjects readily switched, but monkeys with damage to the PFC continued to respond to the previously rewarded stimulus (Butter 1969; Butter et al 1963; Deuel and Mishkin 1977; Iversen and Mishkin 1970; Jones and Mishkin 1972; Mishkin 1964). Subsequent lesion studies in monkeys (Dias et al 1996; Roberts and Wallis 2000; Wallis et al 2001) and humans (Fellows and Farah 2003; Hornak et al 2004) isolated the region of the PFC involved in such reward-related perseverative errors. In these studies, damage to the dorsolateral PFC impaired the ability to alternate between rules irrespective of their reward value, whereas damage to the vmPFC impaired the ability to switch to the appropriate behavioral choice when reward information changed. Consistent with these findings, unit recording studies showed that activity changes in vmPFC neurons as reward changes (Rolls 1999; Thorpe et al 1983). Because reward and punishment are emotionally significant stimuli, the findings are consistent with the idea that the vmPFC is especially involved in emotional regulation. This notion is also supported by recent studies showing that patients with damage to the vmPFC are impaired in

using emotional information to guide decision making (Damasio 1994; Damasio and van Hoesen 1983). Today, the ventromedial areas of the PFC are generally believed to be involved in adjusting behavior on the basis of emotional/motivational, including social, cues (for recent reviews see Bechara et al 2000; Rolls 1996, 1999).

Although the dorsolateral PFC was not found to play a critical role in behavioral regulation that involved processing of emotionally significant stimuli, it turned out to be the region most responsible for other effects observed after PFC damage (Fuster 1989; Goldman-Rakic 1987; Luria 1966, 1973; Milner 1964; Nauta 1971). Monkeys and humans with damage to dorsolateral PFC lack behavioral flexibility in tasks in which information has to be held in working memory temporarily for the purpose of making choices and decisions (Arnsten 1998; D'Esposito et al 2000; Smith and Jonides 1999). The dorsolateral PFC is in fact believed to play a key role in working memory and executive functions (see Miller and Cohen 2001). Deficits in cognitive processes, such as working memory and executive control, are believed to also underlie poor performance in tasks like card sorting, as discussed above. Because working memory and executive functions are generally considered "cognitive" in nature, whereas processing of reward and punishment are considered "emotional," it is widely assumed that dorsolateral and ventromedial areas of the PFC are involved in cognitive and emotional functions, respectively. It should be noted, however, that the distinction is not crystal clear because the cognitive tasks in animal studies are learned through reward or punishment of behavior.

In summary, the PFC seems to be necessary for rapidly readjusting behavioral responses to stimuli. The dorsolateral PFC allows flexibility of thought and behavior in response to changing information and rules. The ventromedial areas of the PFC are involved in adjusting behavior on the basis of emotional cues. In each case, PFC damage produces perseverative tendencies that compromise the ability of the organism to adapt to changing situations.

Anatomical Terminology of Medial PFC Divisions

The human and animal research reviewed above suggests that ventral and medial areas of the PFC are necessary for adjusting behavior when the emotional relevance of a stimulus changes. Fear extinction is exactly such a situation. Once a CS no longer predicts danger, it is important to stop treating it as dangerous. It thus makes sense that the ventral or medial PFC might be involved in fear extinction. Before considering the evidence implicating this region in extinction, it is important to briefly discuss what defines this region.

Most of the evidence reviewed so far has involved human and nonhuman primate studies; however, studies of fear extinction have typically involved rodents. Although exact homologies between the PFC in primates and other mammals are difficult to draw, it is generally believed that the ventral and medial areas of the PFC are more similar across mammals than the dorsal and lateral areas (Povinelli and Preuss 1995; Preuss 1995).

The term medial PFC (mPFC) loosely refers to a collection of brain regions in the frontal lobe extending down the medial wall of the hemispheres to the base of the frontal lobe. Some of the key regions include the anterior cingulate, infralimbic, prelimbic, and medial orbital cortex. Medial PFC is sometimes used to refer to all of these and sometimes only some. When the term *vmPFC* is used, it sometimes refers to the infralimbic, prelimbic, and medial orbital areas, though in some studies it only refers to medial orbital or only to infralimbic and prelimbic cortices. One should carefully determine what a particular investigator has in mind when these terms are used. We will attempt to be as precise as possible below.

Contributions of PFC Areas to Fear Extinction

How did medial areas of the PFC come to be implicated in fear extinction? This view has its origins in several studies performed in the late 1980s and early 1990s. The first two studies we will consider did not study mPFC at all but instead sensory areas of cortex. LeDoux et al (1989) found that extensive damage to the visual cortex had no effect on conditioning of fear responses to a visual CS; however, extinction was disrupted (but see Falls and Davis 1993). The same year, Teich et al (1989) showed that auditory cortex lesions interfered with extinction of auditory fear conditioning. It was viewed as unlikely that damage to sensory cortex disrupted the mechanism of extinction itself. Just as the amygdala had emerged as a key structure of the acquisition of fear conditioning regardless of the sensory modality of the CS, it was thought that there might also be a universal system that mediates extinction, independent of the sensory modality of the CS.

What might that system involve? In considering this question, Morgan et al (1993) drew upon the extensive literature reviewed above implicating the ventral and medial PFC in emotional regulation. Studies previously examining this issue provided some support, but others failed to find an effect (Divac et al 1984; Frysztak and Neafsey 1991). Morgan and colleagues therefore re-examined the issue. They found that lesions of the mPFC (including the ventral part of the anterior cingulate cortex, as well as the infralimbic and prelimbic cortex) resulted in resistance to extinction. That is, animals with such lesions required many more nonreinforced CS presentations to extinguish freezing elicited by the CS. In an effort to relate their findings to human and nonhuman primate literature, Morgan and colleagues referred to the resistance to extinction as "emotional perseveration."

In a set of follow-up studies, Morgan and LeDoux (1995) pinpointed the infralimbic/prelimbic region as the key mPFC area involved in extinction. Animals with damage restricted to this region showed the same resistance to extinction produced by the larger lesions in the previous study. Studies by Quirk and colleagues then refined the conclusion further, emphasizing the importance of the infralimbic region (Milad and Quirk 2002; Quirk et al 2000). Although the mPFC has been implicated in extinction in a variety of other studies (Barrett et al 2003; Garcia et al 1999; Herry and Garcia 2002, 2003; Herry and Mons 2004; Herry et al 1999; Lebron et al 2004; Morrow et al 1999; Rosenkranz et al 2003; Santini et al 2004), one study failed to find an effect (Gewirtz et al 1997), possibly owing to the measurement of startle rather than freezing. It is possible that freezing and startle differ in terms of their cortical (visual cortex [Falls and Davis 1993] and mPFC [Gerwitz et al 1997]) dependence for extinction. Furthermore, in contrast to the effects of damage to the mPFC, animals with damage to the ventrolateral PFC (lateral orbital cortex) exhibited reduced fear reactivity to contextual stimuli associated with conditioning but did not show deficits in extinction (Morgan and LeDoux 1999).

Consistent with these animal studies, recent human imaging studies using fear conditioning protocols similar to animal research show that mPFC activity changes during extinction in humans (Gottfried and Dolan 2004; Phelps et al 2004). Although equation of the exact areas is not possible in the human and animal work, the rough correspondence is striking. For a com-

prehensive review of neural substrates of extinction in humans, see Phelps et al (2006), in this issue.

There have been considerable advances in our understanding of the role of the vmPFC in fear extinction since the original finding more than 10 years ago; however, recent findings are beyond the scope of this review. We will consider these advances when proposing a broad neural circuit model for fear extinction below (Figure 3). For a comprehensive review of prefrontal mechanisms in extinction of conditioned fear, see Quirk et al (2006), in this issue.

A General Overview of the Fear Extinction Circuitry

Converging evidence has identified three brain regions that are important for fear extinction: the vmPFC, amygdala, and hippocampus. Particularly influential has been the view that the mPFC regulates the expression of fear by inhibiting the amygdala (Davidson 2002; Drevets 1999; LeDoux 1996; Quirk and Gehlert 2003; Sotres-Bayon et al 2004). A couple of theories have emerged to account for this regulation (Berretta et al 2005; Quirk et al 2003; Rosenkranz et al 2003). The vmPFC, especially the infralimbic cortex, seems to encode an important aspect of long-term extinction (Milad and Quirk 2002; Milad et al 2004; Quirk et al 2000; Santini et al 2004) and might directly suppress the firing of amygdala neurons after extinction; however, the details of this regulation are still debated (for review see Sotres-Bayon et al 2004). In brief, extinction could involve either mPFC activation of inhibitory LA interneurons (Rosenkranz et al 2003) or mPFC activation of inhibitory projections from the intercalated cell masses to the CE (Quirk et al 2003).

The amygdala, a critical site of fear learning plasticity, might also be a critical site of extinction learning plasticity and/or might be inhibited by other regions and thus be necessary for the expression of extinction. This is supported by studies showing that 1) manipulation of molecules in the amygdala affects fear extinction (Chhatwal et al 2005b; Falls et al 1992; Ledgerwood et al 2003; Lin et al 2003b, 2003c; Lu et al 2001; Marsicano et al 2002; Walker et al 2002); and 2) that amygdala activity changes during extinction (Gottfried and Dolan 2004; Herry and Mons 2004; LaBar et al 1998; Maren and Quirk 2004; Phelps et al 2004; Quirk et al 1997; Repa et al 2001; Rogan et al 1997).

The hippocampus is not required for cue fear extinction; however, it seems to play an important role in the contextual modulation of extinction after renewal (Corcoran and Maren 2001; Ji and Maren 2005; but see Frohardt et al 2000; Wilson et al 1995) or reinstatement (Frohardt et al 2000; Wilson et al 1995). The hippocampus has strong reciprocal connections with the mPFC and the basal amygdala nucleus. Nonetheless, it is not yet clear which of these connections is important for the contextual modulation of extinction.

Thus, the mPFC, amygdala, and hippocampus seem to interactively coordinate the encoding and expression of fear extinction. These three structures might have distinct interactions at different fear extinction stages. We propose three different chronological stages in which one or several of these brain regions might be crucial. This model intends to synthesize the accumulated evidence implicating each of these structures in fear extinction and recent work suggesting that extinction training might cause erasure shortly after fear acquisition but might cause inhibitory learning once the fear memory is consolidated (Cain et al 2005; Lin et al 2003a, 2003b; Myers et al 2006) (see Figure 3).

There have been considerable advances in recent years regarding the brain regions responsible for fear extinction; however, much more remains to be understood about the detailed mechanisms by which these three brain regions contribute to extinction. The rapid progress offers hope that the mechanisms will be understood, which could then offer new treatments for clinical problems related to fear and anxiety.

Clinical Implications

Understanding the neural mechanisms of Pavlovian fear extinction is likely to have important implications for the treatment of humans with fear and anxiety disorders. Cognitive–behavior therapy (CBT) in humans is based on extinction and typically involves exposure to fear-eliciting cues in a safe setting (Barlow 2002; Foa and Jaycox 1999; Wolpe 1968). Cognitive–behavior therapy is widely used today and remains one of the most effective therapies for pathological anxiety, such as phobias, panic, and posttraumatic stress disorder (Craske 1999; Foa et al 2002). A broad goal of extinction research is to develop treatments that will accelerate CBT and make its effects longer lasting. Already researchers have proposed several methods of improving CBT, based on recent animal fear extinction research. For instance, the discovery that infralimbic PFC neurons signal extinction memory led to the suggestion that transcranial magnetic stimulation might improve CBT (Milad and Quirk 2002). Research unraveling the molecular cascade specific to extinction has led to the suggestion that drugs such as d-cycloserine (Ressler et al 2004), yohimbine (Cain et al 2004), cannabinoid receptor 1 agonists (Chhatwal et al 2005a; Marsicano et al 2002), and L-type calcium channel agonists (Cain et al 2002) might facilitate CBT. Alternatively, this research has also identified some common drugs often taken in conjunction with CBT that might actually impair extinction and that should be avoided at least during therapy (benzodiazepines [Bouton et al 1990] and β-blockers [Cain et al 2004]). Moreover, an interesting possibility not yet studied is that drugs designed to specifically interfere with hippocampus-dependent context learning but not extinction might lead to longer-lasting CBT because return of fear is often context dependent (Bouton and King 1983; Corcoran and Maren 2001). For a comprehensive review of treatment in clinical populations, see Foa et al (2006) in this issue.

Future Considerations

The brain mechanisms of emotional regulation have been a topic of interest for centuries, and for good reason. Emotional regulation is critical for adapting to change and for the maintenance of stable social groups. Pavlovian fear extinction is a particularly important, and relatively simple, form of emotional regulation.

Future research will undoubtedly seek to understand how the PFC, amygdala, and hippocampus interact to fully encode the extinction memory and coordinate its expression. These brain regions might make unique contributions to particular phases in the extinction process (acquisition, consolidation, retrieval). Thus, besides spatially dissociating which subregions within these structures are necessary, temporally isolating when they contribute will provide a better understanding of how extinction occurs. For instance, there are strong interconnections between the hippocampus and the basal nucleus of the amygdala (B); however, we recently showed that B is not required for extinction learning or spontaneous recovery (Sotres-Bayon et al 2004). Given the hippocampus' role in contextual modulation of extinction, an obvious question is whether or not B is necessary for other extinction-related phenomena like renewal or reinstatement. If

not, perhaps the hippocampus exerts its modulation by way of the PFC, by direct connections to the LA (Hobin et al 2003; Sotres-Bayon et al 2004), or by other indirect pathways connecting these areas.

Another set of major questions concerns the exact nature of the roles the PFC and amygdala play in fear extinction. The PFC has a long history in emotional regulation, including extinction, but its precise role in fear extinction learning is still a matter of debate. Animals with vmPFC lesions learn extinction acutely and show savings of extinction learning, despite large deficits in the initial recall of long-term extinction (Quirk et al 2000). One possibility is that PFC lesion effects can be revealed by more subtle tests like retraining (Morgan et al 2003) or that the PFC might be necessary for conditioned fear acquisition (Baeg et al 2001; Frysztak and Neafsey 1991; Laviolette et al 2005). Another possibility is that the PFC learns generally that stimulus contingencies can change and uses this experience to accelerate emotional suppression during future experiences. On the other hand, the amygdala is an obvious place to look for fear extinction–related changes, given its known role in fear learning and expression. Indeed, during extinction, the responses of many cells return to activity levels observed before fear learning (Repa et al 2001). It is not yet clear, however, which subregions of the amygdala are important for extinction, whether plasticity of glutamate or γ-aminobutyric acid transmission is important, or whether this plasticity involves potentiation (long-term potentiation) or depression (long-term depression and/or depotentiation) of synaptic connections. These and other questions regarding the brain mechanisms of fear extinction are likely to be intensely studied in future years, given the importance of this process to normal human behavior and especially to the treatment of pathological anxiety.

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