Available online at www.sciencedirect.com
SCIENCE DIRECT
Biological Psychology 73 (2006) 61–71
BIOLOGICAL PSYCHOLOGY
www.elsevier.com/locate/biopsycho

# Fear extinction in rats: Implications for human brain imaging and anxiety disorders

Mohammed R. Milad [a], Scott L. Rauch [a], Roger K. Pitman [a], Gregory J. Quirk [b,*]

[a] *Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Bldg 149 13th St., Charlestown, MA 02129, USA*
[b] *Department of Physiology, Ponce School of Medicine, PO Box 7004, Ponce, Puerto Rico 00732*

Accepted 4 December 2005
Available online 13 February 2006

**Abstract**

Fear extinction is the decrease in conditioned fear responses that normally occurs when a conditioned stimulus (CS) is repeatedly presented in the absence of the aversive unconditioned stimulus (US). Extinction does not erase the initial CS–US association, but is thought to form a new memory. After extinction training, extinction memory competes with conditioning memory for control of fear expression. Deficits in fear extinction are thought to contribute to post-traumatic stress disorder (PTSD). Herein, we review studies performed in rats showing that the medial prefrontal cortex plays a critical role in the retention and expression of extinction memory. We also review human studies indicating that prefrontal areas homologous to those critical for extinction in rats are structurally and functionally deficient in patients with PTSD. We then discuss how findings from rat studies may allow us to: (1) develop new fear extinction paradigms in humans, (2) make specific predictions as to the location of extinction-related areas in humans, and (3) improve current extinction-based behavioral therapies for anxiety disorders.


*Keywords:* Fear extinction; Rats; Human brain

## 1. Introduction

Pavlovian fear conditioning has been an influential animal model for the study of anxiety disorders (Buchel and Dolan, 2000; Myers and Davis, 2002; Sullivan et al., 2003; Charney, 2004). After repeated pairing of a conditioned stimulus (CS, usually a tone or light) with an unconditioned stimulus (US, usually a footshock), the CS comes to elicit conditioned fear responses such as freezing, increased startle reflexes, autonomic changes, analgesia, and behavioral response suppression (Helmstetter and Bellgowan, 1993; Davis, 1997; Fendt and Fanselow, 1999; LeDoux, 2000). Conditioned fear responses can be extinguished by repeatedly presenting the CS without the US (Pavlov, 1927; Rescorla and Heth, 1975). In certain respects, fear conditioning resembles PTSD (Pitman, 1997; Hamner et al., 1999). For example, a soldier in combat may associate the sound of a helicopter with a severe traumatic event. Years after the war, the sound of the helicopter will continue to induce conditioned fear responses in those veterans who developed PTSD. In PTSD, re-exposure to stimuli associated with the trauma evokes inappropriate fear responses that become disabling and can have devastating consequences on the lives of PTSD sufferers (Pitman et al., 2001; Bremner, 2003).

Exposure therapies used as treatments for anxiety disorders incorporate extinction procedures (Foa, 2000; Rothbaum and Davis, 2003). As with fear extinction in rats, patients with PTSD are exposed to the trauma-associated, conditioned stimuli in the absence of any negative reinforcement (Wald and Taylor, 2003; Taylor et al., 2003). After several sessions of exposure therapy, the majority of patients learn to inhibit their fear responses (Taylor et al., 2003). However, some patients with anxiety disorders fail to respond to exposure therapy (Foa, 2000; van Minnen et al., 2002), suggesting a deficit in extinction learning. Therefore, understanding the neural mechanisms of fear extinction in animals may be fundamental to elucidating the pathophysiology of anxiety disorders, such as PTSD, and could enhance our understanding of the mechanism of action underlying extinction-based therapies (e.g. see Rauch et al., 2003a). In the present review, after briefly outlining what is currently known about the neural mechanisms of fear conditioning, we discuss in detail the involvement of the rat

* Corresponding author. Tel.: +1 787 813 1883; fax: +1 787 844 1980.
*E-mail address:* gjquirk@yahoo.com (G.J. Quirk).

0301-0511/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.biopsycho.2006.01.008

medial prefrontal cortex (mPFC) in the long-term retention and expression of extinction memory. We also consider the homology of prefrontal areas in rats and primates. We then discuss the implications of findings from rat studies of fear extinction with respect to human brain imaging and anxiety disorders. Finally, the potential use of new techniques for the treatment of anxiety disorders in the context of the animal data on fear extinction is considered.

## 2. Neural circuitry of conditioned fear acquisition

A large body of evidence from rodent studies indicates that the amygdala plays a critical role in the acquisition and expression of conditioned fear (Helmstetter, 1992; Fendt and Fanselow, 1999; LeDoux, 2000; Davis and Whalen, 2001; Maren and Quirk, 2004). Fear conditioning to a tone CS potentiates medial geniculate inputs to the lateral nucleus of the amygdala (Quirk et al., 1995; Rogan et al., 1997; Malkani and Rosen, 2000; Bauer et al., 2002), which then excites central nucleus neurons (Collins and Pare, 1999) via indirect projections (Pare et al., 2004). Descending projections from the central nucleus terminate in the brainstem and hypothalamic sites that mediate freezing and autonomic fear responses, respectively (LeDoux et al., 1988). Lesions or pharmacological manipulations of the basolateral amygdala interfere with the acquisition, consolidation, and expression of conditioned fear (Kim and Davis, 1993; Nader and LeDoux, 1999; Moita et al., 2002; Maren and Quirk, 2004). These data support the idea that fear associations are stored in the basolateral amygdala and trigger fear responses via activation of the central nucleus (but see Cahill et al., 1999).

Studies in humans have largely confirmed hypotheses about fear conditioning from the animal studies (LaBar et al., 1998; Orr et al., 2000; Otto et al., 2000; Armony and Dolan, 2002; Cheng et al., 2003; Knight et al., 2004a,b). Fear conditioning reliably increases skin conductance and heart rate responses to the CS (for example, see Orr et al., 2000; Grillon and Ameli, 2001), and this occurs to a greater extent in persons with PTSD (Orr et al., 2000). Positron emission tomography (PET) studies were the first to show that the amygdala is activated during the acquisition of conditioned fear in healthy humans (Furmark et al., 1997; Morris et al., 1998; Fischer et al., 2000). More recently, functional magnetic resonance imaging (fMRI) studies have confirmed the role of the amygdala in conditioned fear (LaBar et al., 1998; Buchel et al., 1999; Armony and Dolan, 2001; Pine et al., 2001; Cheng et al., 2003). Moreover, several imaging studies have shown amygdala activation in response to fearful faces, presented either overtly (Morris et al., 1996; Whalen et al., 2001; Fischer et al., 2003) or covertly (Whalen et al., 1998; Buchel et al., 1998). It remains unclear as to whether these face stimuli are serving as conditioned versus unconditioned stimuli in this context. As predicted by imaging studies, damage to the amygdala in humans interferes with fear conditioning (Bechara et al., 1995; LaBar et al., 1995). Thus, similarities between rat and human findings suggest that the neural mechanisms of fear conditioning are highly conserved across species (Buchel and Dolan, 2000; LeDoux, 2000).

## 3. Neural circuitry of conditioned fear extinction

### 3.1. Extinction as new learning

Pavlov was the first to suggest that extinction does not erase conditioning, based on his observation that extinguished responses spontaneously recovered with the passage of time (Pavlov, 1927). Subsequent studies have confirmed this for conditioned fear; extinguished freezing to a tone CS spontaneously recovers to full strength (Rescorla, 2001; Quirk, 2002), can be reinstated by unsignaled shocks (Rescorla and Heth, 1975; Bouton and Bolles, 1979) or renewed by placing the animal in a context different from the one in which it was extinguished (Bouton and King, 1983). If extinction does not erase conditioning, it must form a new memory (e.g. a CS–no US association) that exists in parallel with conditioning memory and is able to inhibit expression of the conditioned response (Konorski, 1967; Bouton, 1993). This relationship between conditioning and extinction memory is illustrated in Fig. 1. In this scheme, the reduction in conditioned behavior is due to accumulation of extinction, rather than dissipation of conditioning. This suggests the existence of structures or circuits devoted to extinction learning and retention. It also suggests the existence of neurons that increase their activity during extinction in order to inhibit the fear response.

### 3.2. Prefrontal mechanisms of extinction learning

LeDoux and coworkers were the first to suggest that prefrontal inputs to the amygdala might modulate the expression of conditioned fear in extinction (Morgan et al., 1993). They observed that lesions of the ventral medial prefrontal cortex (vmPFC), including the infralimbic (IL, A. 25) and prelimbic (PL, A. 32) areas, had no effect on acquisition of freezing to a tone CS, but impaired extinction. This observation was reminiscent of the perseverative behavior seen in monkeys with prefrontal lesions (Fuster, 1997) and was described as ‘‘emotional perseveration’’ (Morgan et al., 1993). It is important to note, however, that Gewirtz et al. (1997) did not find an effect of vmPFC on the extinction of fear-potentiated startle. The reason for such contradictory findings remains unclear, although it suggests that different behavioral indices of conditioned fear (freezing versus startle) may have different levels of dependence on prefrontal extinction circuits (Sotres-Bayon et al., 2004). Subsequent lesion studies have supported the role of the vmPFC in fear extinction (Morrow

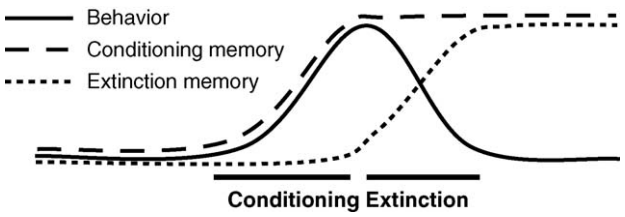


Fig. 1. If extinction does not erase conditioning, then the two must exist simultaneously in the brain of the extinguished animal. This suggests that there are systems in the brain that learn and store fear extinction.

et al., 1999; Weible et al., 2000; Morgan et al., 2003; Fernandez, 2003; Lebron et al., 2004). For example, rats with lesions of the vmPFC are able to extinguish within a session, but are impaired in the recall of extinction 24 h later (Fig. 2A) (Quirk et al., 2000; Lebron et al., 2004). Rats with vmPFC lesions can eventually learn extinction, but they require twice as many days of training to initiate extinction (Lebron et al., 2004), suggesting that vmPFC has a critical role in initiating extinction in across-day training. Thus, vmPFC facilitates rapid consolidation of extinction so that it is available to the animal after a long delay.

Paralleling these lesion findings, single neurons in IL exhibited no tone responses during conditioning or extinction phases of training, but showed robust tone responses the following day when rats were recalling extinction (Milad and Quirk, 2002) (Fig. 2B). Consistent with a role in inhibition of fear, rats with the largest IL tone responses showed the least spontaneous recovery of conditioned freezing. These findings support the extinction-as-new-learning hypothesis, because IL neurons signaled long-term memory for extinction. These findings suggest that consolidation of extinction potentiates inputs to vmPFC; a finding further supported by the recent observation that long-term memory for extinction involves protein synthesis and gene expression in the mPFC (Fig. 3) (Santini et al., 2004; Herry and Mons, 2004). Thus, there is considerable evidence from the animal literature pointing to the vmPFC as a site of consolidation and storage of fear extinction.

### 3.3. Prefrontal mechanisms of extinction expression

In addition to the role of the vmPFC in the retention of fear extinction, there is also evidence indicating that the vmPFC is critical for the expression of extinction. For example, vmPFC activity is inversely correlated with conditioned freezing. This has been shown for single-unit recording (Milad and Quirk, 2002) (Fig. 2C), evoked potentials (Herry and Garcia, 2002) and metabolic activity (Barrett et al., 2003). Furthermore, as shown in Fig. 4A, microstimulation of IL significantly reduced freezing to conditioned tones in rats that were conditioned but not extinguished (Milad and Quirk, 2002; Milad et al., 2004). Thus, these data strongly support the role of the vmPFC in fear inhibition during extinction recall. Indeed, the vmPFC is ideally situated for expression of extinction because it sends robust projections to the amygdala (McDonald, 1998; Vertes, 2004). IL projects strongly to the capsular division of the central nucleus (Ce) (McDonald et al., 1996), which contains GABAergic intercalated cells that inhibit Ce output neurons (Royer et al., 1999). This is true in both rats (McDonald et al., 1996; Sesack et al., 1989) and monkeys (Freedman et al., 2000). Thus, IL could inhibit the expression of fear by inhibiting Ce output cells. In support of this model, stimulation of IL prevents Ce neurons from being activated by basolateral inputs (Quirk et al., 2003) (Fig. 4B). Fig. 4C represents a model demonstrating how IL activation could dampen amygdala output during the expression of extinction memory. Alternatively, however, IL could also modulate the expression of conditioned fear via direct projections to the hypothalamus, periacqueductal gray and other brain stem regions known to be critical for generating conditioned responses (Floyd et al., 2001, 2000; Hurley et al., 1991).

It is important to note that in addition to IL, medial PFC (Cg1), dorsomedial PFC (dmPFC), and dorsolateral PFC (dlPFC) areas have been recently implicated in extinction. Using a deoxyglucose mapping technique in mice, IL together with Cg1, dmPFC, and dlPFC were also activated during extinction recall (Barrett et al., 2003). Moreover, lesions of

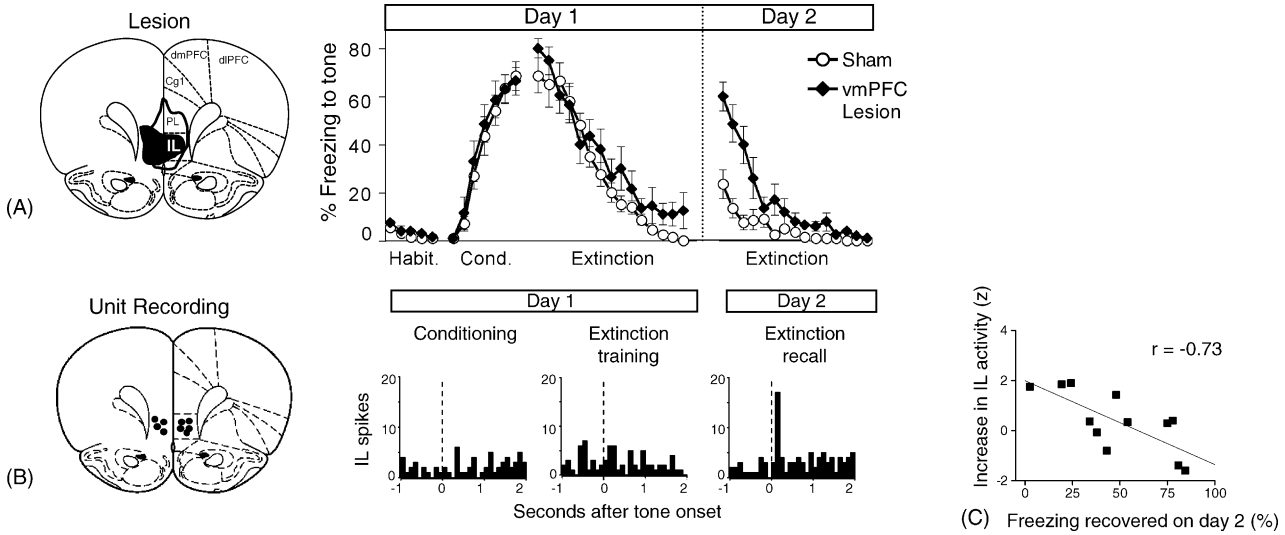


Fig. 2. vmPFC signals extinction memory. (A) Drawing of ventral mPFC lesion (left), consisting of infralimbic (IL) and ventral prelimbic (PL) areas, and freezing to the tone across the 2-day experiment (right). Single-trials are shown. Lesioned rats were able to acquire and extinguish normally on day 1, but spontaneously recovered most of their acquired freezing on day 2 (see Quirk et al., 2000). (B) Location of recording electrodes from IL (left), and firing rate histogram of a typical neuron in IL. IL neurons did not signal the tone during habituation, conditioning, or extinction phases. The next day, however, robust tone responses were seen with a latency of ~100 ms, from the first extinction trial onward (100 ms bins, 10 trials each). (C) The average change in IL tone responses per animal was inversely correlated with spontaneous recovery of freezing on day 2 (see Milad and Quirk, 2002). Cg1, medial prefrontal cortex; dmPFC, dorsomedial PFC; dlPFC, dorsolateral PFC.

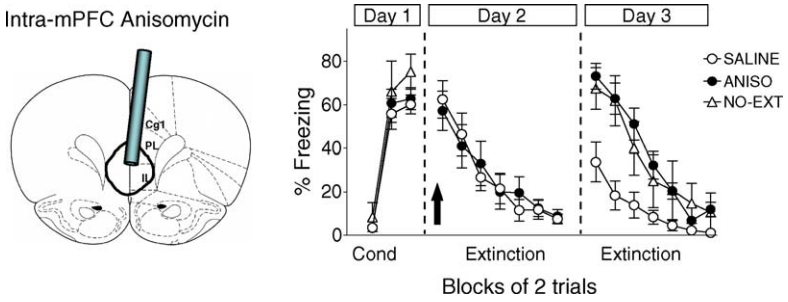


Fig. 3. Long-term memory for fear extinction requires protein synthesis in the vmPFC. Drawing of the location of the infusion site in the vmPFC (left), and freezing to the tone across the 3-day experiment (right). Intra-vmPFC infusions of protein synthesis inhibitor anisomycin (aniso) shortly before extinction training (arrow) did not prevent within-session extinction, but prevented recall of extinction 24 h later. On day 3, the anisomycin group recovered as much freezing as no-extinction controls ($p < 0.05$) (See Santini et al., 2004).

dmPFC in rats retarded the progression of fear extinction across days (Morgan and LeDoux, 1995). Consequently, dmPFC and dlPFC could modulate conditioned freezing via their connections with IL (Conde et al., 1995; Ongur and Price, 2000), or independently of IL via direct projections to the amygdala or its targets (Floyd et al., 2000, 2001).

The amygdala itself is important for fear extinction, although probably at a different stage than the PFC (reviewed by Myers and Davis, 2002). Microinjections of NMDA receptors antagonists (Falls et al., 1992; Lee and Kim, 1998; Lin et al., 2003) or protein kinase inhibitors (Lu et al., 2001; Lin et al., 2003) into the amygdala disrupted the extinction of fear-potentiated startle. Paralleling this, microinjection of an NMDA agonist into the amygdala facilitated fear extinction (Walker et al., 2002; Ledgerwood et al., 2003). Given that vmPFC is not involved in the initial acquisition of extinction learning (Quirk et al., 2000), the amygdala may be the critical site for this process (Lin et al., 2003; Knight et al., 2004a,b). Thus, the acquisition and consolidation of fear extinction could involve an interaction between the amygdala and the vmPFC, such that during the consolidation of extinction learning, amygdala to mPFC inputs are potentiated via NMDA and protein synthesis-dependent processes (Santini et al., 2004).

In summary, converging evidence from lesion, recording, stimulation, and molecular studies in rodents strongly implicates the vmPFC in consolidation, retention, and expression of extinction memory. We now explore the implications of this research for understanding extinction in humans.

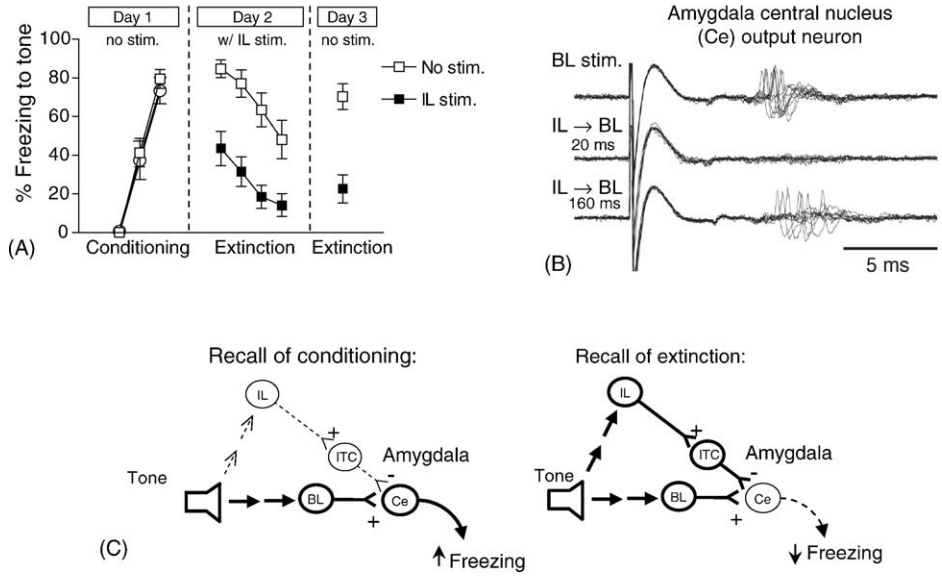


Fig. 4. Stimulation of IL dampens amgydala's output activity. (A) Freezing to the tone in blocks of two trials after a single brief train of IL stimulation was paired with extinction tones on day. Stimulation of IL significantly reduced freezing, and strengthened extinction memory as evidenced by continued low freezing to tones on day 3 (see Milad and Quirk, 2002). (B) In an anesthetized cat, an amygdala central nucleus neuron (Ce) was activated with basolateral (BL) amygdala stimulation (upper trace). Stimulation of IL 20 ms prior to BL stimulation attenuated the Ce response (middle trace). The effect of IL stimulation on Ce response is no longer observed when the interval between IL and BL stimulation is increased (lower trace) (see Quirk et al., 2003). (C) Model of IL–amygdala interactions. During recall of fear conditioning, increased BL output activates Ce neural output to produce fear responses. During extinction recall, parallel activation of IL excites (plus sign) amygdala-intercalated cells (ITC), which dampens (minus sign) Ce output and reduce fear. Boldface and dashed lines indicate increased and decreased activity, respectively. Upward and downward arrows indicate increased and decreased freezing, respectively. CS, conditioned stimulus.

## 4. Fear extinction in humans

The role of the human vmPFC in the inhibition of inappropriate emotional responses is well documented in the literature (Bechara et al., 1999; Manes et al., 2002; Clark et al., 2003). A recent fMRI study showed that humans with high levels of anxiety (due to the expectancy of threat-related stimuli) showed reduced mPFC activity (Bishop et al., 2004). Together with the rodent data, this suggests that the human vmPFC may be required for inhibition of fear responses following extinction.

Most studies of fear conditioning have focused on acquisition rather than extinction (see for example, Fischer et al., 2000; Armony and Dolan, 2001; Phelps et al., 2001; Fischer et al., 2002; Cheng et al., 2003). The few studies that included extinction studied the early phase of extinction, to assess recall of conditioning (e.g. LaBar et al., 1998). One study examining long-term extinction of eye-blink conditioning observed extinction-induced activation in the PFC (Molchan et al., 1994), suggesting the involvement of human PFC in extinction of aversive conditioning. Recently, two important fMRI studies have begun to map the human brain areas involved in extinction. Gottfried and Dolan (2004) showed that the vmPFC and medial orbitofrontal cortex are involved in the extinction of olfactory conditioning. Phelps et al. (2004) showed that vmPFC deactivation was negatively correlated with the extinction recall. That is, the larger the deactivation the poorer the extinction retention whereas the closer the vmPFC activity to baseline, the stronger the extinction memory. It must be noted, however, that conditioned SC responses of the subjects participating in Phelps et al. study showed high fear during the extinction retention test, complicating the interpretation of findings. Nonetheless, Phelps et al. (2004) have provided data clearly implicating the vmPFC in fear extinction.

Behavioral data suggest that mPFC function is compromised in PTSD patients. For example, PTSD subjects show increased perseveration in object-alternation tests that depend on vmPFC (Koenen et al., 2001), and they show deficient extinction in a laboratory setting (Orr et al., 2000; Peri et al., 2000; Rothbaum et al., 2001). It follows, therefore, that patients with anxiety disorders such as PTSD might show dysfunction in mPFC–amygdala circuits.

## 5. Are prefrontal areas homologous in rats and primates?

The nomenclature for the various medial prefrontal regions in the rat differs from that in the primate brain, most likely due to the fact that the prefrontal cortex is more developed in the latter, especially in humans. For example, Brodmann's areas 25 and 32 in the human brain are commonly referred to as subcallosal (SC) and rostral anterior cingulate cortex (rACC), respectively; whereas in the rat, A. 25 and A. 32 are referred to as IL and PL cortices. Even in the rat brain, the same PFC regions have different nomenclature. Therefore, for the purposes of this review, we will refer to the PFC areas of interest in the rat as the following: IL, which is the most ventromedial region of the vmPFC, followed dorsally by PL, Cg1, dmPFC, and dlPFC (depicted in Fig. 2A). In addition, for the human brain, we will refer to the PFC areas of interest as SC and rACC.

To establish homology between human and rat prefrontal areas, anatomists have relied on common inputs/outputs of the prefrontal areas across species. Although it is not surprising to find prefrontal regions in primates that have no homologous counterpart in the rat brain (Ongur and Price, 2000), several medial prefrontal regions appear to be homologous in these species. For example, medial prefrontal regions in both rats and monkeys receive substantial input from the midline thalamic nuclei (Krettek and Price, 1977; Barbas et al., 1991). Furthermore, Price and colleagues have identified a medial prefrontal network that projects to visceral control centers in the periaqueductal gray and the hypothalamus in both the rat and monkey (An et al., 1998; Floyd et al., 2000; Ongur et al., 2003). This network, which includes various subregions of the mPFC such as A. 25, A. 32, A. 24, and A. 12, is thought to be involved in emotion modulation (Carmichael and Price, 1996; Price, 1999; Ongur and Price, 2000; Ongur et al., 2003). Areas 25 and 32 in both rats and primates are reciprocally connected with the amygdala (Barbas et al., 1991; McDonald, 1998; Stefanacci and Amaral, 2002; Vertes, 2004). Finally, rats and monkeys show similar cortico-cortical projections within the medial prefrontal network (Carmichael and Price, 1995; Price, 1999; Ongur and Price, 2000; Stefanacci and Amaral, 2002; Ongur et al., 2003). For example in rats, A. 25 and A. 32 are reciprocally connected with one another, and they are reciprocally connected with dmPFC, dlPFC, Cg1 (McDonald et al., 1996). Cytoarchitectonic analysis also suggests extensive homology between monkey and human prefrontal cortex (Ongur et al., 2003). Thus, it is reasonable to hypothesize that medial prefrontal areas perform similar functions across species.

## 6. Prefrontal cortex and PTSD: deficient extinction?

The current neurocircuitry model of PTSD hypothesizes hyper-responsiveness within the amygdala to threat-related stimuli, with inadequate top-down governance by the vmPFC (Rauch et al., 1998; Pitman et al., 2001; Villarreal and King, 2001; Bremner, 2003; Charney, 2004). This model is supported by converging evidence from multiple laboratories. Patients with PTSD exhibit exaggerated amygdala responses when viewing masked-fearful faces (Rauch et al., 2000) and during the processing of auditory stimuli (Semple et al., 2000). Amygdala hyperactivity has also been observed in PTSD patients during exposure to reminders of traumatic events (Shin et al., 1997; Liberzon et al., 1999; Pissiota et al., 2002; Hendler et al., 2003; Shin et al., 2004).

With regard to the mPFC, an initial symptom provocation study of PTSD using script-driven imagery showed *increased* regional cerebral blood flow (rCBF) in the rACC in PTSD subjects (Rauch et al., 1996). However, the interpretation of this initial study was limited by the absence of a non-PTSD control group. Liberzon et al. (1999) also reported increased rACC

activation in response to trauma-related stimuli in PTSD subjects as well as in non-PTSD controls. In this study, however, no direct contrast between PTSD and non-PTSD subjects was performed. The majority of studies directly comparing PTSD subjects with non-PTSD controls have consistently shown *decreased* activation of mPFC (including the SC, rACC) in PTSD (Bremner et al., 1999a,b; Lanius et al., 2001, 2002; Shin et al., 1999, 2001, 2004). PTSD patients also exhibited attenuated rACC and SC responses to negatively emotionally valenced, trauma-related words (Bremner et al., 2003, 2004; Shin et al., 2004). Recently, Shin and colleagues showed that the decreased mPFC activity in PTSD was inversely correlated with increased amygdala activity (Fig. 5B and C) (Shin et al., 2004), further supporting a failure of top-down control of the amygdala by the vmPFC. In line with this, fMRI and PET data have shown significant inverse correlations between the functional activity of the mPFC and the amygdala (Kim et al., 2003; Dougherty et al., 2004). Fig. 5A summarizes the various imaging studies of PTSD. Note the predominance of studies reporting absent or decreased activation in the medial prefrontal areas. In addition to decreased function, PTSD patients also show volumetric decreases within rACC and SC in PTSD compared to non-PTSD controls (Fig. 6) (Rauch et al., 2003b). Collectively, these data provide strong support for the hypothesis that PTSD is characterized by failure of the mPFC to sufficiently inhibit the amygdala.

## 7. Testing the extinction hypothesis of PTSD

The fact that PTSD subjects show decreased activity in prefrontal areas hypothesized to be involved in extinction retention (based on rodent data) implies deficient extinction retention circuits in the pathophysiology of PTSD. Therefore, it would be timely to combine state of the art imaging techniques with a novel extinction paradigm in order to characterize the neural circuits of fear extinction in healthy humans, and then apply such a paradigm to the study of subjects with PTSD and matched, non-PTSD controls. To maximize the translational impact of these experiments, the conditioning protocol used in the human studies should be closely modeled on existing rat studies. We hypothesize that in normals, vmPFC regions, specifically the rACC and/or the SC, would increase their activity during the recall of fear extinction after a delay, paralleling rat findings (Milad and Quirk, 2002). Furthermore,

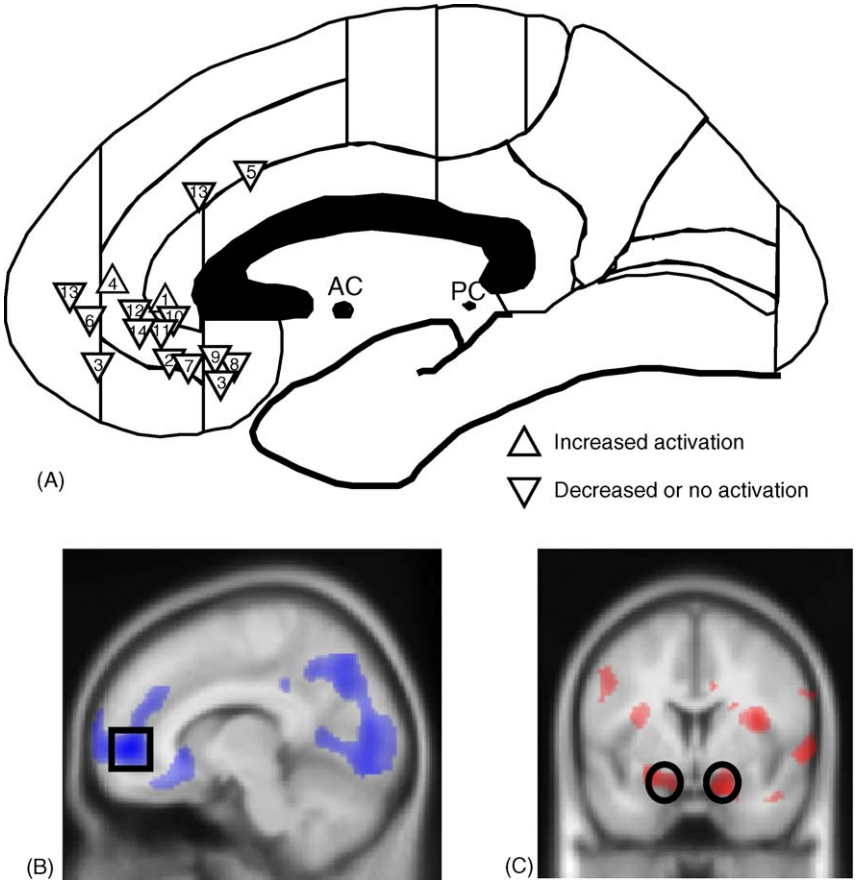


Fig. 5. PTSD patients show dysfunctional PFC-amygdala circuits. (A) Schematic diagram of neuroimaging studies showing dysfunctional mPFC activation. Downward triangles indicate attenuation/or less activation in PTSD, whereas upward triangles indicate increased activation in mPFC. Bolded triangles indicate studies that performed direct comparison of PTSD vs. non-PTSD controls. (B) An example of decreased rCBF in PTSD subjects when exposed to traumatic reminders. (C) The decreased rCBF in mPFC (shown in panel B) was inversely correlated with rCBF changes in the amygdala bilaterally. Significant inverse correlation between right and left amygdala activation and PFC ($r = -0.64$, $r = -0.69$, respectively) (See Shin et al., 2004). *Sources:* 1. Rauch et al. (1996), 2. Lanius et al. (2003), 3. Bremner et al. (2003), 4. Liberzon et al. (1999), 5. Shin et al. (2001), 6. Shin et al. (2004), 7. Lanius et al. (2001), 8. Bremner et al. (1999a), 9. Bremner et al. (1999b), 10. Shin et al. (1999), 11. Liberzon et al. (2003), 12. Semple et al. (2000), 13. Bremner et al. (2004), 14. Shin et al. (2005).

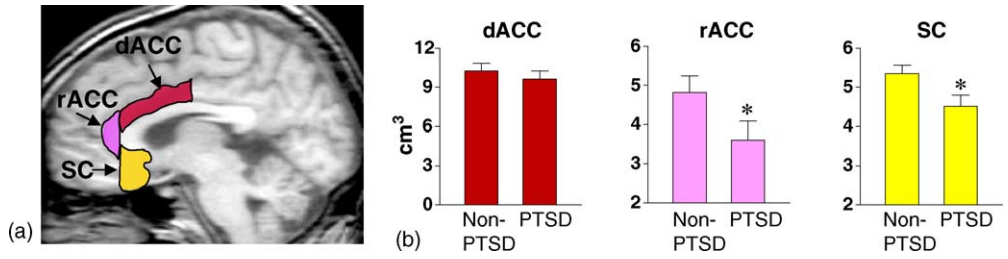


Fig. 6. PTSD subjects show decreased cortical volumes in the rostral anterior cingulate and subcallosal cortex. (a) The parcellation scheme is illustrated on a sample magnetic resonance image. (b) Size of the different subregions of the anterior cingulate cortex in the PTSD subjects and non-PTSD subjects. dACC, dorsal anterior cingulate; rACC, rostral anterior cingulate; SC, subcallosal cortex. $^{*}p < 0.05$ (See Rauch et al., 2003b).

we predict that vmPFC activity during extinction recall would be diminished in patients with anxiety disorders such as PTSD. Such findings would provide the first direct evidence that fear extinction circuits are compromised in a human anxiety disorder. We do acknowledge, however, that fMRI signal does not directly reflect action potentials, but rather local field potentials (Logothetis et al., 2001). Therefore, it is possible that findings to be obtained from fMRI studies may not directly match those obtained by single-unit recordings in rats.

In addition to fMRI, single-unit recording in the human brain could provide valuable data regarding the role of the above prefrontal regions in extinction. Although intracranial recording is ethically problematic in healthy humans, single-unit recording may play a role in the intra-operative evaluation and treatment of some neurological and mental disorders (Benazzouz et al., 2002; Ulbert et al., 2004). Specifically, lesions of sub-territories of the anterior cingulate may be performed as a treatment for major depressive and obsessive-compulsive disorders (OCD) that are refractory to other therapies (Rauch et al., 2005). Using the powerful research tool of single-unit recording prior to the therapeutic resection of rACC and/or SC in patients with depression or OCD could provide unique data with respect to the role of these regions in fear extinction. We predict that recording from these brain regions in humans would show an increase in firing rate to extinguished, but not to unextinguished, conditioned stimuli, thereby providing confirmation of functional neuroimaging data. Moreover, in mental disorders that are characterized by deficient extinction, e.g. PTSD and possibly OCD, such recording might reveal relatively deficient rACC and/or SC firing.

## 8. Prefrontal cortex and amygdala in PTSD: where is the pathology?

Whereas most studies of PTSD suggest deficient top-down control of the amygdala by the vmPFC, one recent report on the functional connectivity of the mPFC and the amygdala in PTSD implied an excessive ‘‘bottom-up’’ influence of the amygdala over the mPFC (Gilboa et al., 2004), This suggests that the primary pathology in PTSD might be located in the amygdala. This proposition is consistent with the findings of Rauch et al. (2000) showing amygdala hyperactivity in PTSD subjects in response to the presentation of masked fearful faces, even when relatively dissociated from the top-down inhibition of the mPFC. Indeed, inhibition of the mPFC by the amygdala has been demonstrated in rats (Garcia et al., 1999). It is therefore reasonable to hypothesize that amygdala hyperresponsivity may be the primary abnormality in PTSD, and that deficient mPFC responses are secondary.

Although initial attempts to characterize amygdalo–frontal interactions have focused on data gathered during a single scanning session, longitudinal studies may be important to perform. For instance, a developmental perspective might suggest that early deficiencies in mPFC efficacy could lead to the development of dysregulated amygdala, or conversely that amygdala irritability in early life might impair mPFC maturation. In this context, it is noteworthy that youths with behaviorally inhibited temperaments, a risk factor for developing anxiety disorders, exhibit exaggerated amygdala responses to novel versus familiar stimuli (Schwartz et al., 2003), and that children and adolescents with PTSD secondary to maltreatment show diminished *N*-acetylaspartate (a marker of neuronal health) in ACC (De Bellis et al., 2000).

## 9. Stimulation of prefrontal cortex in PTSD: could it facilitate extinction memory?

Whether anxiety disorders stem from too much ‘‘bottom-up’’ amygdala activation or too little ‘‘top-down’’ inhibitory control, facilitation of mPFC activity might be effective in controlling an overactive amygdala. The effectiveness of IL stimulation in reducing conditioned fear responses in rats raises the intriguing possibility of using an analogous approach to ameliorating symptoms in patients with anxiety disorders such as PTSD. Deep brain stimulation (DBS) has been used in the treatment of OCD with encouraging initial results (Nuttin et al., 2003; Kopell et al., 2004). It is conceivable that DBS could be used to stimulate mPFC regions that appear to be hypoactive in PTSD. However, DBS is highly invasive and is currently only being administered as a continuous/chronic, rather than intermittent, form of treatment.

Alternatively, the use of repetitive transcranial magnetic stimulation (rTMS) in conjunction with exposure therapy might serve to strengthen extinction memory (Milad and Quirk, 2002). TMS has been investigated for the treatment of depression (Eschweiler et al., 2000) with promising results. A PET analysis of TMS of the left PFC in depressed patients demonstrated that high frequency stimulation (10–20 Hz) significantly enhanced rCBF bilaterally in various relevant

brain regions, including the PFC and other paralimbic areas (Speer et al., 2000). Interestingly, Cohen et al. (2004) recently reported that rTMS targeting the dlPFC produced therapeutic effects in PTSD subjects. However, given that stimulation of the vmPFC in rats was only effective when it was paired with conditioned stimuli (Milad and Quirk, 2002; Milad et al., 2004), rTMS might be significantly more effective when paired with traumatic reminders.

One possible limitation of rTMS is that it may not penetrate sufficiently to reach deep structures such as the vmPFC. However, mapping of prefrontal structures involved in extinction might reveal additional (dorsal) areas that might be more amenable to direct manipulation by rTMS. It is even plausible to hypothesize that the different subregions of the mPFC might signal extinction memory at different phases of training or latencies with respect to the presentation of the traumatic stimuli. Therefore, a thorough characterization of the involvement of these regions in extinction memory could eventually lead to more sophisticated rTMS scenarios with multiple sites and timings, in order to more closely simulate neural processing of fear extinction.

## 10. Concluding remarks

PTSD is a disorder that is characterized by the pathological acquisition, expression, and persistence of learned fear associations. A fuller understanding of the rat and human networks that mediate extinction may be essential to elucidating the pathophysiology of PTSD as well as the mechanism of action of certain extinction-based therapies. Rat studies identifying the brain regions involved in extinction retention will guide hypotheses regarding regions of interest in future neuroimaging experiments. Conversely, regions implicated by human imaging experiments in mental health and disorder can be more thoroughly interrogated in rats. Finally, once the relevant neuroanatomic and neurophysiologic parallels between rats and humans are well-characterized, translational research opportunities may emerge to develop new treatments based upon facilitating extinction retention. Beyond PTSD, this approach could conceivably serve as a model for the study and treatment of other anxiety and mood disorders.

## References


An, X., Bandler, R., Ongur, D., Price, J.L., 1998. Prefrontal cortical projections to longitudinal columns in the midbrain periaqueductal gray in macaque monkeys. Journal of Comparative Neurology 401, 455–479.

Armony, J.L., Dolan, R.J., 2001. Modulation of auditory neural responses by a visual context in human fear conditioning. Neuroreport 12, 3407–3411.

Armony, J.L., Dolan, R.J., 2002. Modulation of spatial attention by fear-conditioned stimuli: an event-related fMRI study. Neuropsychologia 40, 817–826.

Barbas, H., Henion, T.H., Dermon, C.R., 1991. Diverse thalamic projections to the prefrontal cortex in the rhesus monkey. Journal of Comparative Neurology 313, 65–94.

Barrett, D., Shumake, J., Jones, D., Gonzalez-Lima, F., 2003. Metabolic mapping of mouse brain activity after extinction of a conditioned emotional response. Journal of Neuroscience 23, 5740–5749.

Bauer, E.P., Schafe, G.E., LeDoux, J.E., 2002. NMDA receptors and L-type voltage-gated calcium channels contribute to long-term potentiation and different components of fear memory formation in the lateral amygdala. Journal of Neuroscience 22, 5239–5249.

Bechara, A., Damasio, H., Damasio, A.R., Lee, G.P., 1999. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. Journal of Neuroscience 19, 5473–5481.

Bechara, A., Tranel, D., Damasio, H., Adolphs, R., Rockland, C., Damasio, A.R., 1995. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. Science 269, 1115–1118.

Benazzouz, A., Breit, S., Koudsie, A., Pollak, P., Krack, P., Benabid, A.L., 2002. Intraoperative microrecordings of the subthalamic nucleus in Parkinson's disease. Movement Disorders 17 (Suppl. 3), S145–S149.

Bishop, S., Duncan, J., Brett, M., Lawrence, A.D., 2004. Prefrontal cortical function and anxiety: controlling attention to threat-related stimuli. Nature Neuroscience 7, 184–188.

Bouton, M.E., 1993. Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. Psychological Bulletin 114, 80–99.

Bouton, M.E., Bolles, R.C., 1979. Role of conditioned contextual stimuli in reinstatement of extinguished fear. Journal of Experimental Psychology-Animal Behavior Processes 5, 368–378.

Bouton, M.E., King, D.A., 1983. Contextual control of the extinction of conditioned fear: tests for the associative value of the context. Journal of Experimental Psychology-Animal Behavior Processes 9, 248–265.

Bremner, J.D., 2003. Functional neuroanatomical correlates of traumatic stress revisited 7 years later, this time with data. Psychopharmacological Bulletin 37, 6–25.

Bremner, J.D., Narayan, M., Staib, L.H., Southwick, S.M., McGlashan, T., Charney, D.S., 1999a. Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. American Journal of Psychiatry 156, 1787–1795.

Bremner, J.D., Staib, L.H., Kaloupek, D., Southwick, S.M., Soufer, R., Charney, D.S., 1999b. Neural correlates of exposure to traumatic pictures and sound in Vietnam combat veterans with and without posttraumatic stress disorder: a positron emission tomography study. Biological Psychiatry 45, 806–816.

Bremner, J.D., Vermetten, E., Vythilingam, M., Afzal, N., Schmahl, C., Elzinga, B., Charney, D.S., 2004. Neural correlates of the classic color and emotional stroop in women with abuse-related posttraumatic stress disorder. Biological Psychiatry 55, 612–620.

Bremner, J.D., Vythilingam, M., Vermetten, E., Southwick, S.M., McGlashan, T., Staib, L.H., Soufer, R., Charney, D.S., 2003. Neural correlates of declarative memory for emotionally valenced words in women with posttraumatic stress disorder related to early childhood sexual abuse. Biological Psychiatry 53, 879–889.

Buchel, C., Dolan, R.J., 2000. Classical fear conditioning in functional neuroimaging. Current Opinion in Neurobiology 10, 219–223.

Buchel, C., Dolan, R.J., Armony, J.L., Friston, K.J., 1999. Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. Journal of Neuroscience 19, 10869–10876.

Buchel, C., Morris, J., Dolan, R.J., Friston, K.J., 1998. Brain systems mediating aversive conditioning: an event-related fMRI study. Neuron 20, 947–957.

Cahill, L., Weinberger, N.M., Roozendaal, B., McGaugh, J.L., 1999. Is the amygdala a locus of "conditioned fear"? Some questions and caveats. Neuron 23, 227–228.

Carmichael, S.T., Price, J.L., 1995. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. Journal of Comparative Neurology 363, 615–641.

Carmichael, S.T., Price, J.L., 1996. Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. Journal of Comparative Neurology 371, 179–207.

Charney, D.S., 2004. Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. American Journal of Psychiatry 161, 195–216.

Cheng, D.T., Knight, D.C., Smith, C.N., Stein, E.A., Helmstetter, F.J., 2003. Functional MRI of human amygdala activity during Pavlovian fear con-

ditioning: stimulus processing versus response expression. Behavioral Neuroscience 117, 3–10.

Clark, L., Manes, F., Antoun, N., Sahakian, B.J., Robbins, T.W., 2003. The contributions of lesion laterality and lesion volume to decision-making impairment following frontal lobe damage. Neuropsychologia 41, 1474–1483.

Cohen, H., Kaplan, Z., Kotler, M., Kouperman, I., Moisa, R., Grisaru, N., 2004. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: a double-blind, placebo-controlled study. American Journal of Psychiatry 161, 515–524.

Collins, D.R., Pare, D., 1999. Reciprocal changes in the firing probability of lateral and central medial amygdala neurons. Journal of Neuroscience 19, 836–844.

Conde, F., Maire-Lepoivre, E., Audinat, E., Crepel, F., 1995. Afferent connections of the medial frontal cortex of the rat. II. Cortical and subcortical afferents. Journal of Comparative Neurology 352, 567–593.

Davis, M., 1997. Neurobiology of fear responses: the role of the amygdala. Journal of Neuropsychiatry and Clinical Neuroscience 9, 382–402.

Davis, M., Whalen, P.J., 2001. The amygdala: vigilance and emotion. Molecular Psychiatry 6, 13–34.

De Bellis, M.D., Keshavan, M.S., Spencer, S., Hall, J., 2000. *N*-Acetylaspartate concentration in the anterior cingulate of maltreated children and adolescents with PTSD. American Journal of Psychiatry 157, 1175–1177.

Dougherty, D.D., Rauch, S.L., Deckersbach, T., Marci, C., Loh, R., Shin, L.M., Alpert, N.M., Fischman, A.J., Fava, M., 2004. Ventromedial prefrontal cortex and amygdala dysfunction during an anger induction PET study in patients with depression with anger attacks. Archives of General Psychiatry 61, 795–804.

Eschweiler, G.W., Wegerer, C., Schlotter, W., Spandl, C., Stevens, A., Bartels, M., Buchkremer, G., 2000. Left prefrontal activation predicts therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) in major depression. Psychiatry Research 99, 161–172.

Falls, W.A., Miserendino, M.J., Davis, M., 1992. Extinction of fear-potentiated startle: blockade by infusion of an NMDA antagonist into the amygdala. Journal of Neuroscience 12, 854–863.

Fendt, M., Fanselow, M.S., 1999. The neuroanatomical and neurochemical basis of conditioned fear. Neuroscience and Biobehavioral Reviews 23, 743–760.

Fernandez, E.E., 2003. Prefrontocortical dopamine loss in rats delays long-term extinction of contextual conditioned fear, and reduces social interaction without affecting short-term social interaction memory. Neuropsychopharmacology 28, 490–498.

Fischer, H., Andersson, J.L., Furmark, T., Fredrikson, M., 2000. Fear conditioning and brain activity: a positron emission tomography study in humans. Behavioral Neuroscience 114, 671–680.

Fischer, H., Andersson, J.L., Furmark, T., Wik, G., Fredrikson, M., 2002. Right-sided human prefrontal brain activation during acquisition of conditioned fear. Emotion 2, 233–241.

Fischer, H., Wright, C.I., Whalen, P.J., McInerney, S.C., Shin, L.M., Rauch, S.L., 2003. Brain habituation during repeated exposure to fearful and neutral faces: a functional MRI study. Brain Research Bulletin 59, 387–392.

Floyd, N.S., Price, J.L., Ferry, A.T., Keay, K.A., Bandler, R., 2000. Orbitomedial prefrontal cortical projections to distinct longitudinal columns of the periaqueductal gray in the rat. Journal of Comparative Neurology 422, 556–578.

Floyd, N.S., Price, J.L., Ferry, A.T., Keay, K.A., Bandler, R., 2001. Orbitomedial prefrontal cortical projections to hypothalamus in the rat. Journal of Comparative Neurology 432, 307–328.

Foa, E.B., 2000. Psychosocial treatment of posttraumatic stress disorder. Journal of Clinical Psychiatry 61 (Suppl. 5), 43–48.

Freedman, L.J., Insel, T.R., Smith, Y., 2000. Subcortical projections of area 25 (subgenual cortex) of the macaque monkey. Journal of Comparative Neurology 421, 172–188.

Furmark, T., Fischer, H., Wik, G., Larsson, M., Fredrikson, M., 1997. The amygdala and individual differences in human fear conditioning. Neuroreport 8, 3957–3960.

Fuster, J., 1997. The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe. Lippincott Williams & Wilkins, Baltimore.

Garcia, R., Vouimba, R.M., Baudry, M., Thompson, R.F., 1999. The amygdala modulates prefrontal cortex activity relative to conditioned fear. Nature 402, 294–296.

Gewirtz, J.C., Falls, W.A., Davis, M., 1997. Normal conditioned inhibition and extinction of freezing and fear-potentiated startle following electrolytic lesions of medical prefrontal cortex in rats. Behavioral Neuroscience 111, 712–726.

Gilboa, A., Shalev, A.Y., Laor, L., Lester, H., Louzoun, Y., Chisin, R., Bonne, O., 2004. Functional connectivity of the prefrontal cortex and the amygdala in posttraumatic stress disorder. Biological Psychiatry 55, 263–272.

Grillon, C., Ameli, R., 2001. Conditioned inhibition of fear-potentiated startle and skin conductance in humans. Psychophysiology 38, 807–815.

Gottfried, J.A., Dolan, R.J., 2004. Human orbitofrontal cortex mediates extinction learning while accessing conditioned representations of value. Nature Neuroscience 7, 1144–1152.

Hamner, M.B., Lorberbaum, J.P., George, M.S., 1999. Potential role of the anterior cingulate cortex in PTSD: review and hypothesis. Depress Anxiety 9, 1–14.

Helmstetter, F.J., 1992. The amygdala is essential for the expression of conditional hypoalgesia. Behavioral Neuroscience 106, 518–528.

Helmstetter, F.J., Bellgowan, P.S., 1993. Lesions of the amygdala block conditional hypoalgesia on the tail flick test. Brain Research 612, 253–257.

Hendler, T., Rotshtein, P., Yeshurun, Y., Weizmann, T., Kahn, I., Ben Bashat, D., Malach, R., Bleich, A., 2003. Sensing the invisible: differential sensitivity of visual cortex and amygdala to traumatic context. Neuroimage 19, 587–600.

Herry, C., Garcia, R., 2002. Prefrontal cortex long-term potentiation, but not long-term depression, is associated with the maintenance of extinction of learned fear in mice. Journal of Neuroscience 22, 577–583.

Herry, C., Mons, N., 2004. Resistance to extinction is associated with impaired immediate early gene induction in medial prefrontal cortex and amygdala. European Journal of Neuroscience 20, 781–790.

Hurley, K.M., Herbert, H., Moga, M.M., Saper, C.B., 1991. Efferent projections of the infralimbic cortex of the rat. Journal of Comparative Neurology 308, 249–276.

Kim, H., Somerville, L.H., Johnstone, T., Alexander, A.L., Whalen, P.J., 2003. Inverse amygdala and medial prefrontal cortex responses to surprised faces. Neuroreport 14, 2317–2322.

Kim, M., Davis, M., 1993. Electrolytic lesions of the amygdala block acquisition and expression of fear-potentiated startle even with extensive training but do not prevent reacquisition. Behavioral Neuroscience 107, 580–595.

Knight, D.C., Cheng, D.T., Smith, C.N., Stein, E.A., Helmstetter, F.J., 2004a. Neural substrates mediating human delay and trace fear conditioning. Journal of Neuroscience 24, 218–228.

Knight, D.C., Smith, C.N., Cheng, D.T., Stein, E.A., Helmstetter, F.J., 2004b. Amygdala and hippocampal activity during acquisition and extinction of human fear conditioning. Cognitive Affect Behavioral Neuroscience 4, 317–325.

Koenen, K.C., Driver, K.L., Oscar-Berman, M., Wolfe, J., Folsom, S., Huang, M.T., Schlesinger, L., 2001. Measures of prefrontal system dysfunction in posttraumatic stress disorder. Brain Cognition 45, 64–78.

Konorski, J., 1967. Integrative Activity of the Brain. University of Chicago Press, Chicago.

Kopell, B.H., Greenberg, B., Rezai, A.R., 2004. Deep brain stimulation for psychiatric disorders. Journal of Clinical Neurophysiology 21, 51–67.

Krettek, J.E., Price, J.L., 1977. The cortical projections of the mediodorsal nucleus and adjacent thalamic nuclei in the rat. Journal of Comparative Neurology 171, 157–191.

LaBar, K.S., Gatenby, J.C., Gore, J.C., LeDoux, J.E., Phelps, E.A., 1998. Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. Neuron 20, 937–945.

LaBar, K.S., LeDoux, J.E., Spencer, D.D., Phelps, E.A., 1995. Impaired fear conditioning following unilateral temporal lobectomy in humans. Journal of Neuroscience 15, 6846–6855.

Lanius, R.A., Williamson, P.C., Boksman, K., Densmore, M., Gupta, M., Neufeld, R.W., Gati, J.S., Menon, R.S., 2002. Brain activation during script-driven imagery induced dissociative responses in PTSD: a functional

magnetic resonance imaging investigation. Biological Psychiatry 52, 305–311.

Lanius, R.A., Williamson, P.C., Densmore, M., Boksman, K., Gupta, M.A., Neufeld, R.W., Gati, J.S., Menon, R.S., 2001. Neural correlates of traumatic memories in posttraumatic stress disorder: a functional MRI investigation. American Journal of Psychiatry 158, 1920–1922.

Lebron, K., Milad, M.R., Quirk, G.J., 2004. Delayed recall of fear extinction in rats with lesions of ventral medial prefrontal cortex. Learn Memory 11, 544–548.

Ledgerwood, L., Richardson, R., Cranney, J., 2003. Effects of D-cycloserine on extinction of conditioned freezing. Behavioral Neuroscience 117, 341–349.

LeDoux, J.E., 2000. Emotion circuits in the brain. Annual Review of Neuroscience 23, 155–184.

LeDoux, J.E., Iwata, J., Cicchetti, P., Reis, D.J., 1988. Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. Journal of Neuroscience 8, 2517–2529.

Lee, H., Kim, J.J., 1998. Amygdalar NMDA receptors are critical for new fear learning in previously fear-conditioned rats. Journal of Neuroscience 18, 8444–8454.

Liberzon, I., Taylor, S.F., Amdur, R., Jung, T.D., Chamberlain, K.R., Minoshima, S., Koeppe, R.A., Fig, L.M., 1999. Brain activation in PTSD in response to trauma-related stimuli. Biological Psychiatry 45, 817–826.

Lin, C.H., Yeh, S.H., Lu, H.Y., Gean, P.W., 2003. The similarities and diversities of signal pathways leading to consolidation of conditioning and consolidation of extinction of fear memory. Journal of Neuroscience 23, 8310–8317.

Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., Oeltermann, A., 2001. Neurophysiological investigation of the basis of the fMRI signal. Nature 412, 150–157.

Lu, K.T., Walker, D.L., Davis, M., 2001. Mitogen-activated protein kinase cascade in the basolateral nucleus of amygdala is involved in extinction of fear-potentiated startle. Journal of Neuroscience 21, RC162.

Malkani, S., Rosen, J.B., 2000. Specific induction of early growth response gene 1 in the lateral nucleus of the amygdala following contextual fear conditioning in rats. Neuroscience 97, 693–702.

Manes, F., Sahakian, B., Clark, L., Rogers, R., Antoun, N., Aitken, M., Robbins, T., 2002. Decision-making processes following damage to the prefrontal cortex. Brain 125, 624–639.

Maren, S., Quirk, G.J., 2004. Neuronal signaling of fear memory. Natural Review of Neuroscience 5, 844–852.

McDonald, A.J., 1998. Cortical pathways to the mammalian amygdala. Progress in Neurobiology 55, 257–332.

McDonald, A.J., Mascagni, F., Guo, L., 1996. Projections of the medial and lateral prefrontal cortices to the amygdala: a Phaseolus vulgaris leucoagglutinin study in the rat. Neuroscience 71, 55–75.

Milad, M.R., Quirk, G.J., 2002. Neurons in medial prefrontal cortex signal memory for fear extinction. Nature 420, 70–74.

Milad, M.R., Vidal-Gonzalez, I., Quirk, G.J., 2004. Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner. Behavioral Neuroscience 118, 389–395.

Moita, M.A., Lamprecht, R., Nader, K., LeDoux, J.E., 2002. A-kinase anchoring proteins in amygdala are involved in auditory fear memory. Nature Neuroscience 5, 837–838.

Molchan, S.E., Sunderland, T., McIntosh, A.R., Herscovitch, P., Schreurs, B.G., 1994. A functional anatomical study of associative learning in humans. Proceedings of the National Academy of Sciences of the United States of America 91, 8122–8126.

Morgan, M.A., LeDoux, J.E., 1995. Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. Behavioral Neuroscience 109, 681–688.

Morgan, M.A., Romanski, L.M., LeDoux, J.E., 1993. Extinction of emotional learning: contribution of medial prefrontal cortex. Neuroscience Letters 163, 109–113.

Morgan, M.A., Schulkin, J., LeDoux, J.E., 2003. Ventral medial prefrontal cortex and emotional perseveration: the memory for prior extinction training. Behavioural Brain Research 146, 121–130.

Morris, J.S., Frith, C.D., Perrett, D.I., Rowland, D., Young, A.W., Calder, A.J., Dolan, R.J., 1996. A differential neural response in the human amygdala to fearful and happy facial expressions. Nature 383, 812–815.

Morris, J.S., Ohman, A., Dolan, R.J., 1998. Conscious and unconscious emotional learning in the human amygdala. Nature 393, 467–470.

Morrow, B.A., Elsworth, J.D., Rasmusson, A.M., Roth, R.H., 1999. The role of mesoprefrontal dopamine neurons in the acquisition and expression of conditioned fear in the rat. Neuroscience 92, 553–564.

Myers, K.M., Davis, M., 2002. Behavioral and neural analysis of extinction. Neuron 36, 567–584.

Nader, K., LeDoux, J.E., 1999. Inhibition of the mesoamygdala dopaminergic pathway impairs the retrieval of conditioned fear associations. Behavioral Neuroscience 113, 891–901.

Nuttin, B., Gybels, J., Cosyns, P., Gabriels, L., Meyerson, B., Andreewitch, S., Rasmussen, S.A., Greenberg, B., Friehs, G., Rezai, A.R., Montgomery, E., Malone, D., Fins, J.J., 2003. Deep brain stimulation for psychiatric disorders. Neurosurgery Clinics of North America 14, xv–xvi.

Ongur, D., Ferry, A.T., Price, J.L., 2003. Architectonic subdivision of the human orbital and medial prefrontal cortex. Journal of Comparative Neurology 460, 425–449.

Ongur, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cerebral Cortex 10, 206–219.

Orr, S.P., Metzger, L.J., Lasko, N.B., Macklin, M.L., Peri, T., Pitman, R.K., 2000. De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. Journal of Abnormal Psychology 109, 290–298.

Otto, T., Cousens, G., Herzog, C., 2000. Behavioral and neuropsychological foundations of olfactory fear conditioning. Behavioural Brain Research 110, 119–128.

Pare, D., Quirk, G.J., LeDoux, J.E., 2004. New vistas on amygdala networks in conditioned fear. Journal of Neurophysiology 92, 1–9.

Pavlov, I., 1927. Conditioned Reflexes. Oxford University Press, London.

Peri, T., Ben Shakhar, G., Orr, S.P., Shalev, A.Y., 2000. Psychophysiologic assessment of aversive conditioning in posttraumatic stress disorder. Biological Psychiatry 47, 512–519.

Phelps, E.A., O'Connor, K.J., Gatenby, J.C., Gore, J.C., Grillon, C., Davis, M., 2001. Activation of the left amygdala to a cognitive representation of fear. Nature Neuroscience 4, 437–441.

Phelps, E.A., Delgado, M.R., Nearing, K.I., LeDoux, J.E., 2004. Extinction learning in humans: role of the amygdala and vmPFC. Neuron 43, 897–905.

Pine, D.S., Fyer, A., Grun, J., Phelps, E.A., Szeszko, P.R., Koda, V., Li, W., Ardekani, B., Maguire, E.A., Burgess, N., Bilder, R.M., 2001. Methods for developmental studies of fear conditioning circuitry. Biological Psychiatry 50, 225–228.

Pissiota, A., Frans, O., Fernandez, M., von Knorring, L., Fischer, H., Fredrikson, M., 2002. Neurofunctional correlates of posttraumatic stress disorder: a PET symptom provocation study. European Archives of Psychiatry and Clinical Neuroscience 252, 68–75.

Pitman, R.K., 1997. Overview of biological themes in PTSD. Annales of the New York Academy of Sciences 821, 1–9.

Pitman, R.K., Shin, L.M., Rauch, S.L., 2001. Investigating the pathogenesis of posttraumatic stress disorder with neuroimaging. Journal of Clinical Psychiatry 62 (Suppl. 17), 47–54.

Price, J.L., 1999. Prefrontal cortical networks related to visceral function and mood. Annales of the New York Academy of Sciences 877, 383–396.

Quirk, G.J., 2002. Memory for extinction of conditioned fear is long-lasting and persists following spontaneous recovery. Learn Memory 9, 402–407.

Quirk, G.J., Likhtik, E., Pelletier, J.G., Pare, D., 2003. Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. Journal of Neuroscience 23, 8800–8807.

Quirk, G.J., Repa, C., LeDoux, J.E., 1995. Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: parallel recordings in the freely behaving rat. Neuron 15, 1029–1039.

Quirk, G.J., Russo, G.K., Barron, J.L., Lebron, K., 2000. The role of ventromedial prefrontal cortex in the recovery of extinguished fear. Journal of Neuroscience 20, 6225–6231.

Rauch, S.L., Greenberg, B.D., Cosgrove, G.R., 2005. Neurosurgical treatments and deep brain stimulation. In: Sadock, B.J., Sadock, V. (Eds.), Comprehensive Textbook of Psychiatry. 8th ed. Lippincott, Williams & Wilkens, Philadelphia/Baltimore.

Rauch, S.L., Shin, L.M., Wright, C.I., 2003a. Neuroimaging studies of amygdala function in anxiety disorders. Annales of the New York Academy of Sciences 985, 389–410.

Rauch, S.L., Shin, L.M., Whalen, P.J., Pitman, R.K., 1998. Neuroimaging and the neuroanatomy of PTSD. CNS Spectrums 3 (Suppl. 2), 30–41.

Rauch, S.L., Shin, L.M., Segal, E., Pitman, R.K., Carson, M.A., McMullin, K., Whalen, P.J., Makris, N., 2003b. Selectively reduced regional cortical volumes in post-traumatic stress disorder. Neuroreport 14, 913–916.

Rauch, S.L., van der Kolk, B.A., Fisler, R.E., Alpert, N.M., Orr, S.P., Savage, C.R., Fischman, A.J., Jenike, M.A., Pitman, R.K., 1996. A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. Archives of General Psychiatry 53, 380–387.

Rauch, S.L., Whalen, P.J., Shin, L.M., McInerney, S.C., Macklin, M.L., Lasko, N.B., Orr, S.P., Pitman, R.K., 2000. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. Biological Psychiatry 47, 769–776.

Rescorla, R.A., 2001. Retraining of extinguished Pavlovian stimuli. Journal of Experimental Psychology-Animal Behavior Processes 27, 115–124.

Rescorla, R.A., Heth, C.D., 1975. Reinstatement of fear to an extinguished conditioned stimulus. Journal of Experimental Psychology-Animal Behavior Processes 1, 88–96.

Rogan, M.T., Staubli, U.V., LeDoux, J.E., 1997. Fear conditioning induces associative long-term potentiation in the amygdala. Nature 390, 604–607.

Rothbaum, B.O., Davis, M., 2003. Applying learning principles to the treatment of post-trauma reactions. Annales of the New York Academy of Sciences 1008, 112–121.

Rothbaum, B.O., Kozak, M.J., Foa, E.B., Whitaker, D.J., 2001. Posttraumatic stress disorder in rape victims: autonomic habituation to auditory stimuli. Journal of Traumatic Stress 14, 283–293.

Royer, S., Martina, M., Pare, D., 1999. An inhibitory interface gates impulse traffic between the input and output stations of the amygdala. Journal of Neuroscience 19, 10575–10583.

Santini, E., Ge, H., Ren, K., Pena de Ortiz, S., Quirk, G.J., 2004. Consolidation of fear extinction requires protein synthesis in the medial prefrontal cortex. Journal of Neuroscience 24, 5704–5710.

Schwartz, C.E., Wright, C.I., Shin, L.M., Kagan, J., Rauch, S.L., 2003. Inhibited and uninhibited infants ''grown up'': adult amygdalar response to novelty. Science 300, 1952–1953.

Semple, W.E., Goyer, P.F., McCormick, R., Donovan, B., Muzic Jr., R.F., Rugle, L., McCutcheon, K., Lewis, C., Liebling, D., Kowaliw, S., Vapenik, K., Semple, M.A., Flener, C.R., Schulz, S.C., 2000. Higher brain blood flow at amygdala and lower frontal cortex blood flow in PTSD patients with comorbid cocaine and alcohol abuse compared with normals. Psychiatry 63, 65–74.

Sesack, S.R., Deutch, A.Y., Roth, R.H., Bunney, B.S., 1989. Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with Phaseolus vulgaris leucoagglutinin. Journal of Comparative Neurology 290, 213–242.

Shin, L.M., Kosslyn, S.M., McNally, R.J., Alpert, N.M., Thompson, W.L., Rauch, S.L., Macklin, M.L., Pitman, R.K., 1997. Visual imagery and perception in posttraumatic stress disorder. A positron emission tomographic investigation. Archives of General Psychiatry 54, 233–241.

Shin, L.M., McNally, R.J., Kosslyn, S.M., Thompson, W.L., Rauch, S.L., Alpert, N.M., Metzger, L.J., Lasko, N.B., Orr, S.P., Pitman, R.K., 1999. Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: a PET investigation. American Journal of Psychiatry 156, 575–584.

Shin, L.M., Orr, S.P., Carson, M.A., Rauch, S.L., Macklin, M.L., Lasko, N.B., Peters, P.M., Metzger, L.J., Dougherty, D.D., Cannistraro, P.A., Alpert, N.M., Fischman, A.J., Pitman, R.K., 2004. Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. Archives of General Psychiatry 61, 168–176.

Shin, L.M., Whalen, P.J., Pitman, R.K., Bush, G., Macklin, M.L., Lasko, N.B., Orr, S.P., McInerney, S.C., Rauch, S.L., 2001. An fMRI study of anterior cingulate function in posttraumatic stress disorder. Biological Psychiatry 50, 932–942.

Shin, L.M., Wright, C.I., Cannistraro, P.A., Wedig, M.M., McMullin, K., Martis, B., Macklin, M.L., Lasko, N.B., Cavanagh, S.R., Krangel, T.S., Orr, S.P., Pitman, R.K., Whalen, P.J., Rauch, S.L., 2005. An fMRI study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. Archives of General Psychiatry 62, 273–281.

Speer, A.M., Kimbrell, T.A., Wassermann, E.M., Repella, D., Willis, M.W., Herscovitch, P., Post, R.M., 2000. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. Biological Psychiatry 48, 1133–1141.

Sotres-Bayon, F., Bush, D.E., LeDoux, J.E., 2004. Emotional perseveration: an update on prefrontal-amygdala interactions in fear extinction. Learn Memory 11, 525–535.

Stefanacci, L., Amaral, D.G., 2002. Some observations on cortical inputs to the macaque monkey amygdala: an anterograde tracing study. Journal of Comparative Neurology 451, 301–323.

Sullivan, G.M., Apergis, J., Gorman, J.M., LeDoux, J.E., 2003. Rodent doxapram model of panic: behavioral effects and c-Fos immunoreactivity in the amygdala. Biological Psychiatry 53, 863–870.

Taylor, S., Thordarson, D.S., Maxfield, L., Fedoroff, I.C., Lovell, K., Ogrodniczuk, J., 2003. Comparative efficacy, speed, and adverse effects of three PTSD treatments: exposure therapy, EMDR, and relaxation training. Journal of Consulting and Clinical Psychology 71, 330–338.

Ulbert, I., Magloczky, Z., Eross, L., Czirjak, S., Vajda, J., Bognar, L., Toth, S., Szabo, Z., Halasz, P., Fabo, D., Halgren, E., Freund, T.F., Karmos, G., 2004. In vivo laminar electrophysiology co-registered with histology in the hippocampus of patients with temporal lobe epilepsy. Experimental Neurology 187, 310–318.

van Minnen, A., Wessel, I., Dijkstra, T., Roelofs, K., 2002. Changes in PTSD patients' narratives during prolonged exposure therapy: a replication and extension. Journal of Traumatic Stress 15, 255–258.

Vertes, R.P., 2004. Differential projections of the infralimbic and prelimbic cortex in the rat. Synapse 51, 32–58.

Villarreal, G., King, C.Y., 2001. Brain imaging in posttraumatic stress disorder. Seminar of Clinical Neuropsychiatry 6, 131–145.

Wald, J., Taylor, S., 2003. Preliminary research on the efficacy of virtual reality exposure therapy to treat driving phobia. Cyberpsychological Behaviour 6, 459–465.

Walker, D.L., Ressler, K.J., Lu, K.T., Davis, M., 2002. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. Journal of Neuroscience 22, 2343–2351.

Weible, A.P., McEchron, M.D., Disterhoft, J.F., 2000. Cortical involvement in acquisition and extinction of trace eyeblink conditioning. Behavioral Neuroscience 114, 1058–1067.

Whalen, P.J., Rauch, S.L., Etcoff, N.L., McInerney, S.C., Lee, M.B., Jenike, M.A., 1998. Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. Journal of Neuroscience 18, 411–418.

Whalen, P.J., Shin, L.M., McInerney, S.C., Fischer, H., Wright, C.I., Rauch, S.L., 2001. A functional MRI study of human amygdala responses to facial expressions of fear versus anger. Emotion 1, 70–83.