Fear Extinction as a Model for Translational Neuroscience: Ten Years of Progress

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Abstract

The psychology of extinction has been studied for decades. Approximately 10 years ago, however, there began a concerted effort to understand the neural circuits of extinction of fear conditioning, in both animals and humans. Progress during this period has been facilitated by a high degree of coordination between rodent and human researchers examining fear extinction. Here we review the major advances and highlight new approaches to understanding and exploiting fear extinction. Research in fear extinction could serve as a model for translational research in other areas of behavioral neuroscience.

Contents

INTRODUCTION

Fear extinction refers to the decrement in conditioned fear responses that occurs with repeated presentation of a conditioned fear stimulus that is unreinforced. **Figure 1** shows the number of research publications using the key words "fear extinction" since 1990. Note that the number of animal and human studies increased sharply after 2000, with animal studies preceding human studies by several years. In this review, we start with a brief overview of fundamental psychological concepts of extinction and then review the key factors prior to 2000 that led to the recent increase in fear extinction studies. We then focus on fear extinction research during this past decade, which was facilitated by a rodent-to-human translational approach. Finally, we discuss directions for fear extinction research in the next decade. A comprehensive review of the psychological and neurobiological basis of fear extinction is not possible in this venue. Numerous reviews on molecular mechanisms of extinction, clinical relevance, and inhibition circuitry within the amygdala have recently been published (Etkin et al. 2011, Graham & Milad 2011, Herry et al. 2010, Myers et al. 2011, Pape & Paré 2010, Sotres-Bayon & Quirk 2010).

OVERVIEW OF FEAR EXTINCTION AND ITS PSYCHOLOGICAL BASIS

Initial attempts to understand fear extinction focused on psychological and behavioral phenomena. In the 1920s, Pavlov observed that extinguished appetitive responses in dogs would spontaneously recover with the passage of time, and he proposed that extinction was a special form of inhibition (Pavlov 1927). Despite early theoretical formulations of extinction-related inhibition (Konorski 1967), the search for inhibitory circuits had been largely unsuccessful (Chan et al. 2001, Kimble & Kimble 1970). Research focusing on the behavioral and psychological aspects of conditioning and extinction provided key data upon which contemporary studies on the neural

mechanisms of fear extinction were based. In addition to the passage of time, it was shown that extinguished responding could be renewed with a change in context (Bouton & King 1983) or reinstated with unconditioned stimuli (US; Rescorla & Heth 1975). The phenomena of spontaneous recovery, fear renewal, and reinstatement, as well accelerated reacquisition (Rescorla 2001), have been described in detail over the past decades (reviewed in Bouton & Moody 2004, Rescorla 1988). Together, they constitute strong evidence that extinction does not erase the initial association between the conditioned stimuli (CS) and US but rather forms a new association (CS-No US) that inhibits expression of the conditioned memory.

Context, in particular, is able to gate expression of conditioning versus extinction memory. That is, when an animal is conditioned in one context (context A) and then extinguished in a different context (context B), the extinction memory can be expressed only if the CS is presented in context B. Though "context" is often defined as the physical place, the internal state of the animal can also be considered a context. Also, the passage of time can be viewed as a contextual shift (Bouton et al. 2006).

SETTING THE STAGE FOR FEAR EXTINCTION MECHANISMS

From Avoidance to Fear Conditioning: The Amygdala as a Hub of Fear

Initial animal work on fear extinction in the 1960s to 1980s used active avoidance paradigms. Systemically administered drugs were used to implicate stress hormones, benzodiazepines, and monoamines in extinction (Buresova et al. 1964, Bohus & De Wied 1966, Kokkinidis 1983, Koob et al. 1986). Setting the stage for later molecular work, it was shown that extinction learning required protein synthesis (Flood et al. 1977) and cortical norepinephrine (Mason et al. 1979). Direct manipulations of the brain were few, but lesion and electrical stimulation techniques implicated the septum, prefrontal cortex, striatum, and hippocampus in extinction of avoidance responses (Brennan & Wisniewski 1982, Gralewicz & Gralewicz 1984, Lovely 1975, Sanberg et al. 1979).

Our knowledge of fear-learning circuits advanced rapidly during the 1980s to 1990s. Studies of avoidance learning gave way to more ethologically relevant classically conditioned responses such as freezing and potentiation of startle responses (Blanchard & Blanchard 1969, Chi 1965, Davis & Astrachan 1978). The amygdala became the centerpiece of the fear-conditioning circuit when it was shown that discrete lesions of the amygdala could block the acquisition and expression of conditioned fear responses (Hitchcock & Davis 1986, LeDoux et al. 1984) and that the lateral amygdala received direct input from sensory areas of the thalamus (LeDoux et al. 1985). Neurobiological evidence began to detail how the association between tone and shock is formed and expressed within different subnuclei of the amygdala (Davis 2000, LeDoux 2000, Maren 2005, Sigurdsson et al. 2007).

During the same time, anatomical studies described the connections of the amygdala central nucleus (Ce) with downstream structures implicated in the expression of conditioned fear responses, including the hypothalamus, periaquaductal gray, pons, and other brainstem regions (Applegate et al. 1982, Kapp et al. 1979, LeDoux et al. 1988, Pitkanen et al. 1997, Romanski & LeDoux 1993). Studies during this period also described the inhibitory circuits within the amygdala that were later found to be involved in fear extinction, such as the gamma-aminobutyric acid (GABA)ergic intercalated cells (Nitecka & Ben Ari 1987, Paré & Smith 1993), lateral division of the Ce (Sun & Cassell 1993), and inhibitory cells within the lateral and basolateral nuclei (Mahanty & Sah 1998). Thus, these advances in understanding fear conditioning provided the framework against which to investigate extinction-induced reduction of fear.

Advent of Human Neuroimaging Tools

Concurrent with the advances in rodent fear circuits was the development of functional

Conditioned fear responses: physiological responses exhibited by the organism during conditioning; triggered by the presentation of the conditioned stimulus. Most commonly measured responses include freezing and potentiated startle in rodents and skin conductance and potentiated startle responses in humans

US: unconditioned stimuli

CS: conditioned stimuli

Extinction learning: the start of extinction training, when the organism begins to learn that the CS no longer predicts the US. Also called within-session extinction

Ce: central nucleus of the amygdala

neuroimaging in humans, which began in 1991 with the first functional magnetic resonance imaging (fMRI) study (Belliveau et al. 1991). The initial wave of fMRI studies focused on paradigms involving functional activation of the visual and motor cortices (reviewed in Rosen et al. 1998). With respect to emotional learning, early fMRI studies sought to determine the extent to which rodent models of the amygdala were valid in the human brain. Using a simple differential fear-conditioning paradigm in healthy humans (a blue square as the CS and a mild shock as the US), LaBar et al. (1998) and later Büchel et al. (1999) reported increased amygdala activation in response to the CS+ (CS that is paired with the US) as compared to the CS- (CS that is not paired with the shock). Subsequent fMRI studies using fearful faces as stimuli also showed significant amygdala activation in healthy humans (Breiter et al. 1996, Whalen et al. 1998). These observations were critical for two reasons: (*a*) they provided unequivocal evidence that amygdala function was conserved across species, and (*b*) they validated the use of fMRI for studying fear learning in humans.

A Clinical Connection to Fear Extinction

It was first proposed in the late 1980s that fear conditioning may serve as an animal model for anxiety disorders, such as posttraumatic stress disorder (PTSD), and could be useful for understanding the underlying psychopathology of anxiety disorders. Pitman and colleagues proposed that PTSD patients hypercondition, i.e., form strong associations between traumatic events and sensory cues present at the time of the trauma (Pitman 1988). These strong associations later become resistant to extinction. Moreover, neuroimaging data that emerged during the late 1990s implicated the amygdala and the ventromedial prefrontal cortex (vmPFC) in the psychopathology of anxiety disorders, which resembled the clinical profile of perseverative fear and anxiety. Positron emission tomography (PET) studies showed decreased prefrontal blood flow in PTSD patients (Bremner et al. 1999, Semple et al. 1996). Furthermore, PTSD patients showed reduced activation of vmPFC, as indicated by fMRI, when recalling traumatic events with the help of script-driven imagery (Shin et al. 1999). Thus, knowledge of fear-learning circuits in rodents provided hypotheses that could be tested in anxiety disorder patients, using contemporary neuroimaging tools.

Initial Research on Fear Extinction Mechanisms: In Search of the Inhibitor

In contrast to fear learning, research on the neurobiology of fear extinction was only just beginning in the 1990s. Harris & Westbrook (1998) confirmed that extinction was a form of inhibition by showing that a beta-carboline antagonist of GABA-A receptors could block the development and expression of extinction. A prescient study by Davis and coworkers (Falls et al. 1992) showed that fear extinction required N-methyl-D-aspartate (NMDA) receptors in the basolateral nucleus of the amygdala (BLA), confirming that extinction was an active form of learning similar to conditioning itself. Initial hints of the involvement of the prefrontal cortex in emotion regulation came from earlier studies showing compulsive-like behavior (disinhibition) in dogs with lesions of the subgenual region of the medial prefrontal cortex (Brutkowski & Mempel 1961) and from monkeys with lesions of orbitofrontal cortex (Butter et al. 1963). Inspired by these early studies, LeDoux and coworkers found that lesions of sensory cortices impaired fear extinction (LeDoux et al. 1989, Teich et al. 1989) and reasoned that sensory areas interacted with frontal or hippocampal cortices to mediate extinction (for review, see Sotres-Bayon et al. 2004).

Anatomical studies appearing at about the same time showed direct projections from the ventral medial prefrontal cortex (vmPFC) to the amygdala (Hurley et al. 1991; McDonald 1991, 1998), in particular to inhibitory areas such as the intercalated cells (Vertes 2004).

fMRI: functional magnetic resonance imaging

CS+: a conditioned stimulus paired with the aversive unconditioned stimulus

CS-: a conditioned stimulus that is not paired with the aversive unconditioned stimulus

PTSD: posttraumatic stress disorder

Ventromedial prefrontal cortex (vmPFC): specific definitions of this region in humans vary from study to study, but broadly speaking, it is within the medial wall of prefrontal cortex that corresponds to Brodmann area (BA) 10m. Some studies refer to BA25 (the subgenual cortex) and parts of BA32 as parts of the vmPFC

PET: positron emission tomography

NMDA: N-methyl-D-aspartate

BLA: basolateral nucleus of the amygdala (including the lateral and basal nuclei)

The first direct evidence for the involvement of the vmPFC in fear extinction came from LeDoux and coworkers (Morgan et al. 1993), who showed that pretraining lesions of the vmPFC had no effect on the acquisition of conditioned fear but impaired fear extinction across days. The authors described the extinction impairment as "emotional perseveration," reminiscent of perseverative conditioned responses in dogs and monkeys with frontal lesions. Davis and coworkers were unable to replicate extinction deficits with lesions of vmPFC or visual cortex (Falls & Davis 1993, Gewirtz et al. 1997), suggesting a possible difference between extinction of freezing versus potentiated startle, or the specific location of the lesions (Sotres-Bayon et al. 2004). Nevertheless, the findings of Morgan et al. (1993) generated interest in prefrontal cortex as an inhibitor in extinction.

THE INHIBITOR FOUND?

Rodent Infralimbic Prefrontal Cortex

In an attempt to resolve the apparent conflict in previous studies assessing vmPFC's role in extinction (Gewirtz et al. 1997, Morgan et al. 1993), Quirk et al. (2000) made lesions of the vmPFC, focusing on the infralimbic (IL) subregion as opposed to the prelimbic (PL) subregion (**Figure 2**). IL lesions did not impair the ability of rats to extinguish conditioned freezing responses within an extinction session, indicating that prefrontal circuits were not necessary for the initial learning of extinction. The following day, however, rats with vmPFC lesions were unable to retrieve their extinction memory at the start of the testing session. Therefore, a distinction was made between the acquisition of extinction and its subsequent retrieval, reflecting behavioral studies showing that retrieval of extinction was regulated by contextual and temporal factors (Bouton 1993, Rescorla 2004). Therefore, dissecting extinction into separate phases of acquisition, consolidation, and retrieval, similar to other types of learning, would be necessary for understanding the neurobiology of extinction (Quirk & Mueller 2008).

Because lesion studies are often difficult to interpret, additional approaches were needed to test the vmPFC hypothesis. Accordingly, Milad & Quirk (2002) used single-cell recording to determine the phase of conditioning and/or extinction training that vmPFC might signal. Paralleling lesion findings, cells in IL did not signal tones during conditioning or extinction phases but did signal tones during the retrieval phase. Furthermore, the magnitude of IL tone responses was inversely correlated with freezing at the retrieval test, consistent with a safety signal. Similar findings have been reported with the activity marker cFos (Hefner et al. 2008, Knapska & Maren 2009) and metabolic mapping methods (Barrett et al. 2003). Moving closer to a test of causality, Milad & Quirk (2002) showed that mimicking IL tone responses with brief microstimulation reduced fear and strengthened extinction (see also Milad et al. 2004). Both recording and stimulation findings were specific to IL and were not observed in the adjacent prelimbic cortex. Taken together, these studies advanced our understanding from a general notion of prefrontal involvement to a specific role of IL plasticity in the retrieval of previously learned extinction. Additional support for a role of vmPFC in extinction came from Garcia and colleagues, who showed that extinction potentiated thalamic and hippocampal inputs to vmPFC (Herry & Garcia 2003) and that extinction memory could be facilitated or impaired by administering high-frequency or low-frequency trains of stimulation, respectively, to vmPFC inputs (Deschaux et al. 2011, Garcia et al. 2008, Herry & Garcia 2002).

Subsequent studies have confirmed the role of IL in the retrieval of extinction using lesions, drug infusions, and stimulation approaches (**Figure 3**) (Akirav & Maroun 2007, Holmes & Wellman 2009, Quirk & Mueller 2008; for recent reviews, see Herry et al. 2010, Sotres-Bayon & Quirk 2010). For a listing of studies prior to 2008 implicating vmPFC in extinction, see Quirk & Mueller (2008). More recent studies implicating IL in extinction are listed in **Table 1**. Extinction

IL: infralimbic prefrontal cortex

PL: prelimbic prefrontal cortex

Table 1 Effects of infralimbic cortex manipulations on memory for fear extinction

Method	Task	Extinction memory	Reference
Facilitators			
CB1 receptor agonist	Cued fc	Enhanced	Lin et al. (2009)
BDNF	Cued fc	Enhanced	Peters et al. (2010)
M-type K(+) channel blocker	Cued fc	Enhanced	Santini & Porter (2010)
GABAa antagonist picrotoxin	Cued fc	Enhanced	Thompson et al. (2010)
Microstimulation	Cued fc	Enhanced	Kim et al. (2010)
GABAa antagonist picrotoxin	Cued fc	Enhanced	Chang & Maren (2011)
Histone acetyltransferase	Cued fc	Enhanced	Marek et al. (2011)
Inhibitors			
CB1 receptor antagonist	Cued fc	Impaired	Lin et al. (2009)
Inactivation with muscimol	Context fc	Impaired	Laurent & Westbrook (2009)
D2 antagonist raclopride	Cued fc	Impaired	Mueller et al. (2010)
mGluR5 antagonist MPEP	Cued fc	Impaired	Fontanez-Nuin et al. (2011)
Inactivation with muscimol	Cued fc	Impaired	Sierra-Mercado et al. (2011)

Abbreviations: BDNF, brain-derived neurotrophic factor; CB1, cannabinoid 1; fc, fear conditioning; GABA, gamma-aminobutyric acid; MPEP, 2-methyl-6- phenylethynylpyridine.

memory requires IL activation of NMDA receptors (Burgos-Robles et al. 2007, Sotres-Bayon et al. 2007), protein kinase A (Mueller et al. 2008), MAP kinase (Hugues et al. 2004), cannabinoid receptors (Lin et al. 2009), and protein synthesis (Mueller et al. 2008, Santini et al. 2004). Together, these studies suggest that a calcium-mediated cascade in IL triggers protein kinases and protein synthesis necessary for long-term extinction memory. In addition to tone responding, extinction also increased burst-type firing of IL neurons (Burgos-Robles et al. 2007, Chang et al. 2010) and reversed conditioning-induced depression of intrinsic excitability (Santini et al. 2008). This suggests that extinction-induced potentiation of intrinsic and synaptic mechanisms in IL could increase local plasticity and the impact of IL on its targets. In support of this, the degree of IL bursting is correlated with extinction retrieval (Santini et al. 2008), and pharmacologically augmenting IL excitability strengthens extinction memory (Santini & Porter 2010). Thus, IL rodent data confirmed early observations (Konorski 1967, Pavlov 1927) that extinction does not return the brain to its preconditioning state, but rather potentiates inhibitory circuits. These findings suggest additional ways of augmenting extinction (see Facilitating Extinction in Rodents sidebar).

Translating IL Findings to Humans

Spurred by rodent data, researchers developed numerous ingenious paradigms for assessing fear conditioning and extinction in healthy humans. These included examinations of fear-potentiated startle (Jovanovic et al. 2005, 2006); return of fear phenomena: renewal, reinstatement, and the context dependency of extinction (Hermans et al. 2005, LaBar & Phelps 2005, Milad et al. 2005a, Norrholm et al. 2006, Vansteenwegen et al. 2005, Vervliet et al. 2005); extinction in adolescents (Pine et al. 2001); and the use of virtual reality for generating contextual and cued-conditioned stimuli (Baas et al. 2004, Grillon et al. 2006, Huff et al. 2010). Initial imaging studies focused mostly on within-session extinction learning (e.g., LaBar et al. 1998) and found increased amygdala and orbitofrontal cortex activation during extinction training (Gottfried & Dolan 2004, Knight

et al. 2004). However, rodent data distinguishing recall of extinction from its initial learning called for a multiday conditioning/extinction paradigm in humans.

The Homolog of IL in the Human Brain: Ventromedial Prefrontal Cortex

Phelps and colleagues conducted the first fMRI study to identify a functional homolog of IL in the human brain in a two-day protocol capable of assessing extinction recall (Phelps et al. 2004). They showed that vmPFC increased its activation during recall of extinction in healthy humans, a finding that was later replicated (Kalisch et al. 2006). This suggested that vmPFC might constitute a functional homologue of the rodent IL (see **Figure 2**). We developed and validated a human fear conditioning and extinction paradigm that allowed for contextual manipulation of extinction recall. It also allowed us to compare recall of extinction with recall of conditioning (via the use of extinguished versus unextinguished stimuli) in order to extend the translation of the rodent data to the human brain (Milad et al. 2005a, Rauch et al. 2006). Using this paradigm, we observed vmPFC deactivation during conditioning, which converted to significant activation by the end of extinction learning (Milad et al. 2007b). During extinction recall, the magnitude of vmPFC activation to the extinguished stimulus (relative to the unextinguished stimulus) was positively correlated with the magnitude of extinction retention (Milad et al. 2007b). That is, the stronger the activation of the vmPFC, the more the subject was able to inhibit conditioned responding during extinction recall. Analysis of a separate cohort showed that the thickness of the vmPFC was also correlated with extinction recall (Milad et al. 2005b), a finding that was recently replicated (Hartley et al. 2011). Thus, both structure and function of the human vmPFC positively correlated with the magnitude of extinction memory, similar to rodent IL (**Figure 4**).

FACILITATING EXTINCTION IN RODENTS

The advantage of the rodent model is the ability to deliver drugs systemically or directly into the extinction circuit in an attempt to facilitate extinction. Some of these drugs can then be translated for possible use in humans. Systemic drugs that facilitate extinction (without altering fear expression) include growth factor FGF-2 (Graham & Richardson 2011), adrenergic antagonist yohimbine (Morris & Bouton 2007), NMDA agonist d-cycloserine (Walker et al. 2002), cannabinoids (Lafenetre et al. 2007), histamine (Bonini et al. 2011), estradiol (Milad et al. 2009a), a BDNF receptor agonist (Andero et al. 2011), and corticosterone (Gourley et al. 2009). Many of these agents act within the prefrontal-amygdala extinction circuit (see **Table 1**). The facilitating effect of electrical stimulation of IL (Kim et al. 2010, Vidal-Gonzalez et al. 2006) can be followed up with new optogenetic techniques for activating specific cell types with focal lasers, which are beginning to be used to dissect inhibitory circuits within the amygdala (Ciocchi et al. 2010, Tye et al. 2011). Facilitation of fear extinction may also explain some of the therapeutic effects of electrical deep brain stimulation, which is increasingly used to treat obsessive compulsive disorder (Greenberg et al. 2008, Rodriguez-Romaguera et al. 2010).

OPPOSING EXTINCTION

Rodent Prelimbic Prefrontal Cortex

Lying just dorsal to the IL in rodents is the prelimbic cortex. The idea that PL may be important for expression of conditioned fear has historic precedents in studies with rabbits (McLaughlin et al. 2002) and rodents, using a trace conditioning paradigm (delay between CS and US) (Runyan et al. 2004). For classical auditory fear conditioning (where the CS and US overlap), inactivation of PL reduces fear expression (Corcoran & Quirk 2007, Laurent & Westbrook 2009, Sierra-Mercado et al. 2011). Paralleling these inactivation findings, single PL neurons showed sustained increases in firing rate in response to conditioned tones (Burgos-Robles et al. 2009). The time course of PL activity mirrored that of freezing (**Figure 5*A***) and was excessive in rats showing poor retrieval of extinction. Thus, PL receives a transient fear signal from

Extinction recall: when the organism is presented with the extinguished CS long (e.g., 24–48 hours) after extinction training (also called extinction retention or extinction retrieval). Good recall of extinction, as evidenced by low fear responses, depends on contextual factors

Table 2 Effects of prelimbic cortex manipulations on expression of conditioned fear

Method	Task	Fear expression	Reference
Facilitators			
Microstimulation	Cued fc	Enhanced	Vidal-Gonzalez et al. (2006)
CB1 receptor agonist	Cued fc	Enhanced	Lin et al. (2009)
Inhibitors			
Inactivation with tetrodotoxin	Cued fc	Impaired	Corcoran & Quirk (2007)
Inactivation with muscimol	Context fc	Impaired	Laurent & Westbrook (2009)
Cannabidiol	Context fc	Impaired	Lemos et al. (2010)
Cannabinoid antagonist AM-251	Cued fc	Impaired	Tan et al. (2010)
Site-specific BDNF knockout	Cued fc	Impaired	Choi et al. (2010)
Inactivation with muscimol	Cued fc	Impaired	Sierra-Mercado et al. (2011)

the amygdala and converts it into a sustained signal that returns to the amygdala to sustain fear (see **Figure 5*B***). Finally, microstimulation of PL increased freezing responses to conditioned tones and impaired extinction (Vidal-Gonzalez et al. 2006). These and other recent studies (see **Table 2**) indicate that PL drives conditioned freezing responses and opposes extinction. Thus, the prefrontal cortex is not simply an inhibitor but is able to exert dual control over fear expression via separate modules, each with access to separate sets of inputs and outputs (Sotres-Bayon & Quirk 2010).

Translating PL Findings to Humans: Dorsal Anterior Cingulate

Spurred by the PL data in rodents, we reexamined our human structural and functional data for evidence of cortical areas involved in fear expression. As with the vmPFC, both cortical thickness and activation of the dorsal anterior cingulate (dACC) were positively correlated with skin conductance response during the conditioning phase (Milad et al. 2007a; but see Hartley et al. 2011) (see **Figure 4**). The increased responsiveness to conditioned stimuli during fear acquisition was recently replicated in a separate cohort of healthy subjects (Linnman et al. 2011a). Activation of dACC had been noted in previous studies of fear conditioning (Buchel et al. 1998, Cheng et al. 2003, Knight et al. 2004, Phelps et al. 2004), but its significance as a predictor of fear levels was not emphasized. dACC activation has been observed in response to unconditioned stimuli as well as conditioned stimuli. Moreover, dACC was activated by USs consisting of loud noise (Dunsmoor et al. 2008, Knight et al. 2010) and electric shock (Linnman et al. 2011a). Interestingly, omission of an expected shock also activated dACC (Linnman et al. 2011a). These data further support the role of dACC in the expression of conditioned fear in humans, similar to the rodent PL.

Dorsal anterior cingulate (dACC): as with vmPFC, definitions of this brain region vary across studies. Many studies refer to a wide area posterior to the genu of the corpus callosum (BA24) as parts of the dACC. Recent attempts have been made to update the nomenclature of this region, and some refer to this region as the anterior mid-cingulate cortex

ITC: intercalated cells (within the amygdala)

PREFRONTAL CONNECTIVITY WITH AMYGDALA AND HIPPOCAMPUS

Rodent Connectivity

PL and IL cortices can modulate fear expression through descending projections to the amygdala. Whereas PL targets the basal nucleus of the amygdala, IL targets inhibitory areas such as the lateral division of the central nucleus (CeL) and intercalated (ITC) neurons (McDonald 1998, Vertes 2004). Physiological studies support excitatory and inhibitory effects for PL and IL, respectively. PL stimulation excites BLA neurons, which tend to fire at short latencies following PL spikes (Likhtik et al. 2005). In contrast, IL stimulation drives ITC neurons (Amir et al. 2011), which then inhibit Ce output neurons (Royer & Paré 2002). This circuit is consistent with the finding that IL stimulation

reduces the responsiveness of CeL output neurons to BLA or cortical stimulation (Quirk et al. 2003). It is also consistent with resting state functional connectivity in the rat (Liang et al. 2011). Thus, via divergent projections, PL and IL can bidirectionally gate the expression of amygdala-dependent fear memories.

In addition to gating fear expression, recent evidence suggests that IL contributes to extinction-induced plasticity within the amygdala. ITC cells are essential for fear extinction (Jungling et al. 2008, Likhtik et al. 2008) and show extinction-induced potentiation of BLA inputs (Amano et al. 2010). IL activity is essential for the development of this extinction-induced plasticity in ITC (Amano et al. 2010). The cooperativity between IL and inhibitory circuits within the amygdala suggests that successful extinction requires correlated activity between these areas. Pharmacological inactivation of either IL or BLA (including ITCs) prevents the development of stable extinction memory (Laurent et al. 2008, Sierra-Mercado et al. 2011). Indeed, unit recording data suggest that BLA neurons process extinction via reciprocal connectivity with prefrontal and hippocampal areas (Herry et al. 2008, 2010). BLA input is responsible for conditioned fear signaling in PL (Laviolette et al. 2005, Sotres-Bayon et al. 2010), suggesting that neural activity of these two regions may be correlated during conditioned fear expression (see **Figure 5*B***).

The hippocampus plays an essential role in contextual gating of extinction to an explicit CS (Bouton et al. 2006, Ji & Maren 2007) as well as conditioning and extinction of context conditioning (Radulovic & Tronson 2010). The ventral hippocampus (vHPC) projects directly to PL/IL and the BLA and therefore is in a position to modulate fear responses (Hugues & Garcia 2007). Although it is tempting to ask if hippocampal output excites or inhibits fear, there is evidence that the hippocampus may have either effect, depending on the experimental condition examined. Hippocampal inactivation reduces the expression of conditioned fear (Sierra-Mercado et al. 2011) and prevents the renewal of fear after extinction (Hobin et al. 2006, Ji & Maren 2005), both suggesting a role in fear excitation. However, hippocampal inactivation during extinction training leads to poor recall of extinction (Corcoran et al. 2005, Sierra-Mercado et al. 2011), and low-frequency stimulation of vHPC disrupts extinction memory (Hugues & Garcia 2007), suggesting that plasticity in the hippocampal system normally serves to inhibit fear. The necessity of both IL and hippocampus activity for extinction memory suggests that the two structures may work together during recall of extinction.

BOLD: blood oxygen level–dependent

Human Connectivity

Given the striking homology between rodent IL/PL and human vmPFC/dACC, one might also predict cross-species parallels in connectivity. In humans, however, it is more challenging to study subregional connectivity. Limits in the spatial resolution of fMRI make it difficult to accurately subdivide a small structure like the amygdala. Furthermore, the extent to which blood oxygen level–dependent (BOLD) signals represent excitatory versus inhibitory inputs, spiking activity, or local processing is only beginning to be explored (Angenstein et al. 2009). Thus, the understanding of the complex nature of the neural circuits within the amygdala in the human brain is very limited. For the hippocampus, its classical role in contextual conditioning and extinction is studied in animals with multimodal shifts and context changes. Such manipulations are technically challenging within an fMRI scanner. Indeed, an initial study did not report hippocampal activation to manipulations of visual contexts during auditory conditioning (Armony & Dolan 2001). More recent studies using visual contextual manipulations were able to observe hippocampal activations during extinction recall (Kalisch et al. 2006, Lang et al. 2009, Milad et al. 2007b).

Despite these challenges, emerging data show that the hippocampus and amygdala work together in the context of fear extinction (Kalisch et al. 2006, Lang et al. 2009, Milad et al. 2007b). Importantly, the hippocampus is

fcMRI: resting-state functional connectivity magnetic resonance imaging

PPI: psychophysiological interaction

DTI: diffusion tensor imaging

activated together with the vmPFC during recall of extinction and is sensitive to changes in visual context (Milad et al. 2007b). In addition to the conventional method of analyzing activations and deactivations, various analytic tools are being used in fMRI to examine the functional connectivity between different brain regions. One such tool is resting-state functional connectivity (fcMRI), which examines the temporal oscillations in spontaneous BOLD signals between a selected seed region and the rest of the brain (Buckner & Vincent 2007, Greicius et al. 2003). This analysis is conducted while subjects are not performing any tasks in the fMRI scanner. Although a positive correlation between a seed region and a given structure does not directly indicate anatomical connectivity, some recent studies indicate that results from fcMRI studies are fairly constrained by anatomical connections (Greicius et al. 2009, Van Dijk et al. 2010). Using this tool, recent reports have shown that applying specific seeds to the approximate location of the central (Ce) and basal (BL) nuclei of the amygdala allows for an estimation of connectivity with that region. Accordingly, BL shows greater resting connectivity with vmPFC than with dACC, and Ce shows greater connectivity with dACC than with vmPFC (Etkin et al. 2009, Roy et al. 2009). Consistent with a role in reducing fear, the hippocampus shows greater connectivity with the BL than with Ce (Roy et al. 2009).

Another important fMRI tool for examining interactions between different brain regions is known as psychophysiological interaction (PPI), which is an analysis conducted on task-driven BOLD activations (Friston et al. 1997). This method examines how a behavioral component of the task can modulate interregional coupling during the same task in response to one condition relative to another. Using this tool, we recently showed that there was decreased coupling between the amygdala and the vmPFC, and increased coupling between the amygdala and dACC, when the subjects were shown the extinguished stimulus during extinction recall (Linnman et al. 2011c) (see **Figure 5*C***). These findings support the interstructural relationships observed in rodent studies and demonstrate the need for PPI analysis of extinction circuits throughout different phases of extinction training.

In addition to functional connectivity, studies are beginning to employ diffusion tensor imaging (DTI) as a tool to examine the integrity of the structural connectivity between the amygdala and different subregions of the medial prefrontal cortex. This tool examines white matter fiber tracts based on the diffusion of water molecules along the tracts. The use of DTI to assess the integrity of prefrontal-amygdala connections during fear extinction has yet to be examined. Nonetheless, DTI, as well as fcMRI and PPI, are already being used in emotion-regulation paradigms (i.e., instructing the participants to suppress their emotions in response to a given stimulus). These studies revealed very similar findings to those observed in fear extinction research, namely, the success of emotion regulation appears to be associated with reduced amygdala activation together with increased activation of various prefrontal regions, including the vmPFC (for reviews, see Hartley & Phelps 2010, Kim et al. 2011b).

TESTING THE CIRCUIT IN AN ANXIETY DISORDER

Human neuroimaging findings predicted that fear extinction recall and its associated network would be impaired in PTSD patients (Milad et al. 2006). This hypothesis was recently tested (Milad et al. 2008, 2009b). Consistent with vmPFC dysfunction, PTSD patients showed normal conditioning and within-session extinction but were unable to recall extinction memory the following day (**Figure 6**). Furthermore, this deficit in extinction recall was associated with hypoactivation in the vmPFC and hyperactivation in the dACC in PTSD subjects (Milad et al. 2009b), providing direct support for the prefrontal-amygdala extinction model. Moreover, we recently reported hypoactive vmPFC during the presentation of

the safe (extinction) context during extinction recall in PTSD (Rougemont-Bucking et al. 2011), suggesting that the processing of extinguished cues and extinguished contexts may be impaired in PTSD. Similar observations have been made for schizophrenic subjects (Holt et al. 2009), which suggests that dysfunction in fear extinction circuits might cut across disorders (Graham & Milad 2011, Insel et al. 2010). The model may even be used as a biological marker to predict fear learning and/or fear extinction. It was recently shown that dACC resting metabolism was able to predict fear conditioning and its subsequent extinction (Linnman et al. 2011b,c), and perigenual prefrontal activity was able to predict clinical response to extinction-based therapy for PTSD (Bryant et al. 2008). The ultimate goal, of course, is to facilitate extinction-based therapies (see Impact of Fear Extinction in the Clinic sidebar).

IMPACT OF FEAR EXTINCTION IN THE CLINIC

Research on fear extinction is beginning to show some potential clinical applications. It is now well established that the NMDA receptor partial agonist d-cycloserine, which facilitates extinction in rodents (Davis et al. 2006), augments the clinical response to cognitive behavioral therapy (CBT) for a number of anxiety disorders (for review, see Ganasen et al. 2010). We may soon see additional classes of CBT adjuncts, such as cannabinoids, noradrenergic drugs, and neurotrophic factors, based on promising results from rodent studies (see **Table 1**). Nonpharmacological approaches to facilitating extinction could come from transcranial magnetic stimulation (Boggio et al. 2010) or from simply modifying the timing of extinction sessions. Extinction performed shortly after reactivation of fear memory results in a stronger extinction memory that resists return of fear manipulations in both rats and humans (Monfils et al. 2009, Schiller et al. 2009). Assessment of fear extinction or activity in extinction structures may identify people at risk for anxiety disorders, such as firefighters (Guthrie & Bryant 2006), or those likely to respond to CBT (Bryant et al. 2008, Lonsdorf et al. 2010).

THE NEXT TEN YEARS: WHERE DO WE GO FROM HERE?

The past decade witnessed an expansive growth in the field of fear extinction, with hundreds of publications providing a rich understanding of the neural mechanisms of fear extinction in both rodents and humans. Nonetheless, there is still much to be learned, and new lines of research are extending fear extinction further into psychological and clinical domains.

Extinction Across the Lifespan

Like other forms of learning, the capacity to extinguish varies across the lifespan, and age-related changes in extinction reflect developmental changes in prefrontal-amygdala circuitry. Following early investigations with development of avoidance learning (Myslivecek & Hassmannova 1979), much has been recently learned with auditory fear conditioning. Richardson and colleagues have shown that extinction in preweanling rats violates the "rules" of extinction: It is not context dependent, does not require NMDA receptors, and does not require the prefrontal cortex (reviewed in Kim & Richardson 2010). Instead of potentiating inhibitory systems, early life extinction appears to erase fear memories from the amygdala (Gogolla et al. 2009, Kim & Richardson 2008). During adolescence, extinction again becomes compromised (Esmoris-Arranz et al. 2008), as twice as many training trials are needed to learn extinction and activate the IL (Kim et al. 2011a). Finally, aged rats show impaired extinction coupled with a shift of excitability from IL to PL (Kaczorowski et al. 2011). Developmental aspects of fear extinction have not yet been studied in humans, but it is known that older individuals show decreased awareness of CS-US contingencies that support conditioned fear responses (LaBar et al. 2004). These findings highlight the existance of windows of vulnerability with respect to extinction, but also windows of opportunity for therapeutic intervention if early extinction can erase fear memories before they become a clinical problem.

BDNF: brain-derived neurotrophic factor

Sex Differences in Fear Extinction: From Basic Mechanisms to Clinical Relevance

Sexual dimorphism in the vmPFC, amygdala, hippocampus, and dACC is well documented (Goldstein et al. 2001). Sex hormones such as estradiol and progesterone are known modulators of synaptic plasticity, long-term potentiation, and NMDA receptor function (for review, see Gillies & McArthur 2010). Sex hormones also modulate dendritic spine density within the prefrontal cortex (Hao et al. 2006) and modulate how stress influences the function of the vmPFC and the hippocampus (Maeng et al. 2010, Shansky et al. 2010). From a clinical perspective, women are twice as likely as men to develop anxiety and mood disorders (Breslau et al. 1998, Pigott 2003). In addition, damage to human vmPFC differentially affects men and women: Unilateral right damage produces severe emotional defects in men, whereas unilateral left damage produces severe defects in women (Tranel et al. 2005). Despite these findings, the majority of human studies combined data from male and female subjects, and the majority of animal studies used males. Few studies have directly examined the influence of sex differences and the role of sex hormones on fear extinction.

There is growing evidence to suggest that fear extinction may differ between the sexes and that extinction consolidation may be modulated by sex hormones. Indeed, sex differences in emotional memories have consistently been documented in rodents and humans (reviewed in Andreano & Cahill 2009). Recent evidence from rodents and naturally cycling women suggests that fluctuations in the menstrual cycle alter extinction retention (Milad et al. 2009a, 2010; Zeidan et al. 2011). Moreover, exogenous estradiol administration facilitates extinction (Chang et al. 2009, Milad et al. 2009a, Zeidan et al. 2011). Future research in this domain could be informative in describing the mechanistic differences between "his and her" brains in processing fear extinction. Such research could potentially explain the increased prevalence of PTSD in women and lead to sex-specific treatments for mood and anxiety disorders.

Individual Variability in Fear Extinction: Biomarkers

Traditionally, behavioral neuroscience has emphasized average behavior; however, research on individual variability in fear extinction could potentially explain why some individuals are prone to develop anxiety disorders (Bush et al. 2007). Failure to recall extinction in rats is correlated with decreased excitability in IL neurons (Burgos-Robles et al. 2007, Santini et al. 2008) and decreased brain-derived neurotrophic factor (BDNF) in the hippocampus (Heldt et al. 2007, Peters et al. 2010). Consistent with animal models, humans expressing a single-nucleotide polymorphism correlated with decreased BDNF release (Val66Met) show impaired fear extinction (Soliman et al. 2010) and increased response to social stressors (Shalev et al. 2009). The serotonin transporter short allele is also associated with increased risk for anxiety as well as decreased vmPFC-amygdala connectivity (Hariri et al. 2006, Pezawas et al. 2005). In both of these cases, a reverse translation approach was used to develop mouse models of the human polymorphism (Soliman et al. 2010, Wellman et al. 2007). Both BDNF and serotonin transporter–deficient mice exhibited impaired fear extinction as well as alterations in prefrontal cortex. Such a combined rodent-human approach will be particularly useful in investigating the newest genetic biomarkers of PTSD: the stress-related gene FKBP5 (Binder et al. 2008) and the estrogen-sensitive pituitary adenylate cyclase-activating polypeptide (Ressler et al. 2011).

Another emerging approach is to compare extinction across existing strains of inbred mice or rats. Fear extinction deficits in one particular mouse (129S1) can be reversed with a dietary manipulation that restores the balance of activity in IL versus PL (Hefner et al. 2008, Whittle et al. 2010). A subset of Lewis rats shows impaired fear extinction, but only after exposure

to a predator (Goswami et al. 2010), providing an animal model of how traumatic experiences can reveal underlying susceptibilities to extinction failure. Gene knockout techniques have been used to discover new molecules involved in fear extinction, including zinc transporter (Martel et al. 2010), protease nexin-1 (Meins et al. 2010), and metabotropic glutamate receptors (Goddyn et al. 2008, Xu et al. 2009). Thus, the function of candidate genes derived from patients, inbred rodents strains, or knockout studies can be assessed within the prefrontal-amygdala circuits that control fear extinction. Of particular interest will be the extent to which genetic factors contribute to dACC resting metabolism, which has been shown to predict extinction recall (Linnman et al. 2011c).

CONCLUSION

We have shown how translational research in the past 10 years has moved fear extinction from a psychological concept to the activity of a specific circuit that appears to be conserved across species. Human neuroimaging is sometimes criticized as being too descriptive and lacking mechanistic explanations. Animal models, although mechanistic, are often viewed as too simplistic for modeling psychiatric disorders and therefore not relevant. Although both of these criticisms are valid to some extent, we have shown how combining both approaches in a translational research program mitigates the limitations of each approach alone. Perhaps more than other areas of psychology, conditioned fear provides for specific hypotheses in both rodents and humans, which can be tested with new techniques to correlate behavior with neural structure and function. The animal studies allowed us to identify the circuits of fear extinction, characterize molecular machinery, and test ways to manipulate the circuit. The neuroimaging approach allowed for translation of those findings to the human brain, testing specific hypotheses about extinction and its role in anxiety disorders. Continuing parallel lines of fear extinction research in rodents and humans could lead to novel therapeutic approaches for strengthening extinction and help us learn how our brains overcome our fears.

SUMMARY POINTS

1. Rodent research on fear extinction in the past 10 years has made great progress in generating specific hypotheses about neural circuits, which are being tested in humans with neuroimaging.
2. The rodent infralimbic cortex is important for fear extinction recall and is homologous to the human ventromedial prefrontal cortex. The rodent prelimbic cortex is important for fear expression and is homologous to the human dorsal anterior cingulate cortex.
3. IL/vmPFC connects to inhibitory centers within the amygdala, whereas PL/dACC connects to excitatory areas within the amygdala.
4. Activity in PL (rodents) or dACC (humans) can predict the extent of subsequent extinction learning.
5. Failure to properly activate the vmPFC and dACC in humans results in inappropriate fear expression and is observed in anxiety disorders.

FUTURE ISSUES

1. How do extinction circuitry and psychology change as we age?
2. How do the neural mechanisms that mediate fear extinction differ in "his" and "her" brains?
3. How does sleep (or the lack thereof) affect the consolidation of the fear extinction memory?
4. Do successful treatments of psychiatric disorders return fear extinction circuits to a healthy state?
5. Can the capacity to extinguish fear predict clinical response to CBT or itself be predicted with biological markers?
6. Do deficits in fear extinction cut across existing classifications of mood and anxiety disorders?

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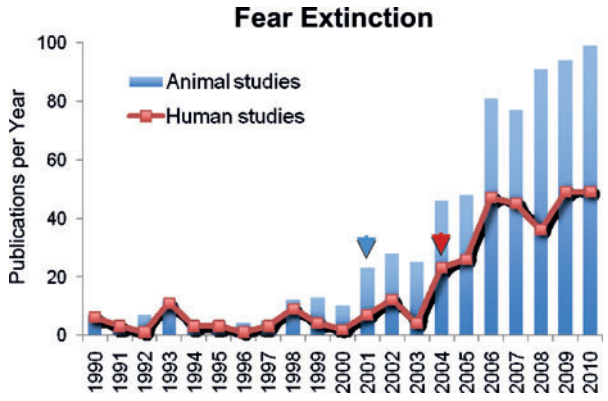

Figure 1

Fear extinction studies have increased exponentially within the past decade. **Figure 1** illustrates the number of peer-reviewed studies identified with the key terms "fear" and "extinction" in PubMed in the past 20 years. Note that the increase in animal studies (*blue bars*, *blue arrow*) began several years prior to the increase in human studies (*orange line*, *orange arrow*).

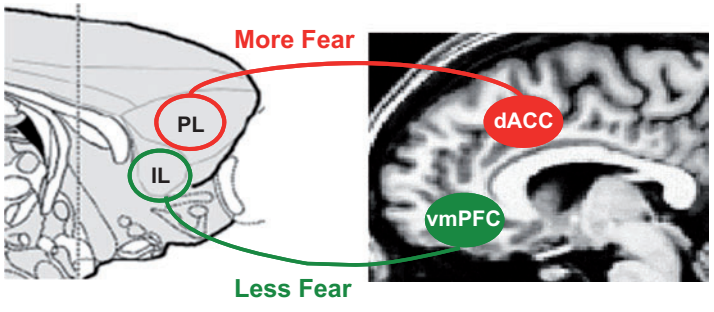

Figure 2

Homologous prefrontal structures in rodent and human brain that modulate fear expression. The rodent prelimbic (PL) cortex and human dorsal anterior cingulate (dACC) cortex increase fear expression and oppose extinction, whereas the rodent infralimbic (IL) cortex and human ventromedial prefrontal cortex (vmPFC) inhibit fear expression and promote extinction.

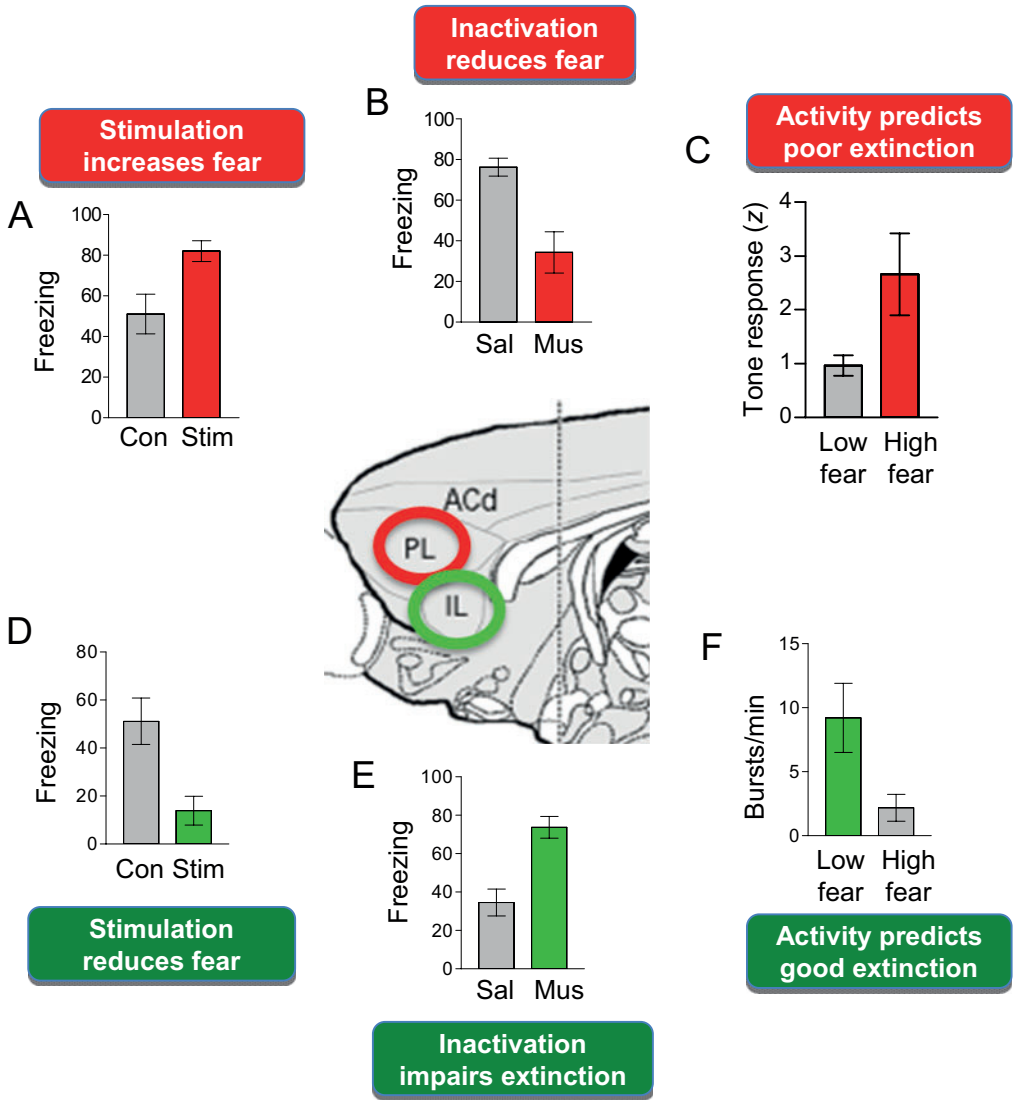

Figure 3

Summary of rodent findings for PL and IL prefrontal cortex. (*A*, *B*, *C*) Divergent findings suggest that PL activity increases fear expression. (*D*, *E*, *F*) Parallel data suggest that IL inhibits fear expression and strengthens extinction recall. Data adapted from previously published studies: (*A*, *D*) Vidal-Gonzalez et al. (2006), see also Kim et al. (2010); (*B*, *E*) Sierra-Mercado et al. (2011), see also Laurent & Westbrook (2009); (*C*) Burgos-Robles et al. (2009); (*F*) Burgos-Robles et al. (2007), see also Chang et al. (2010).

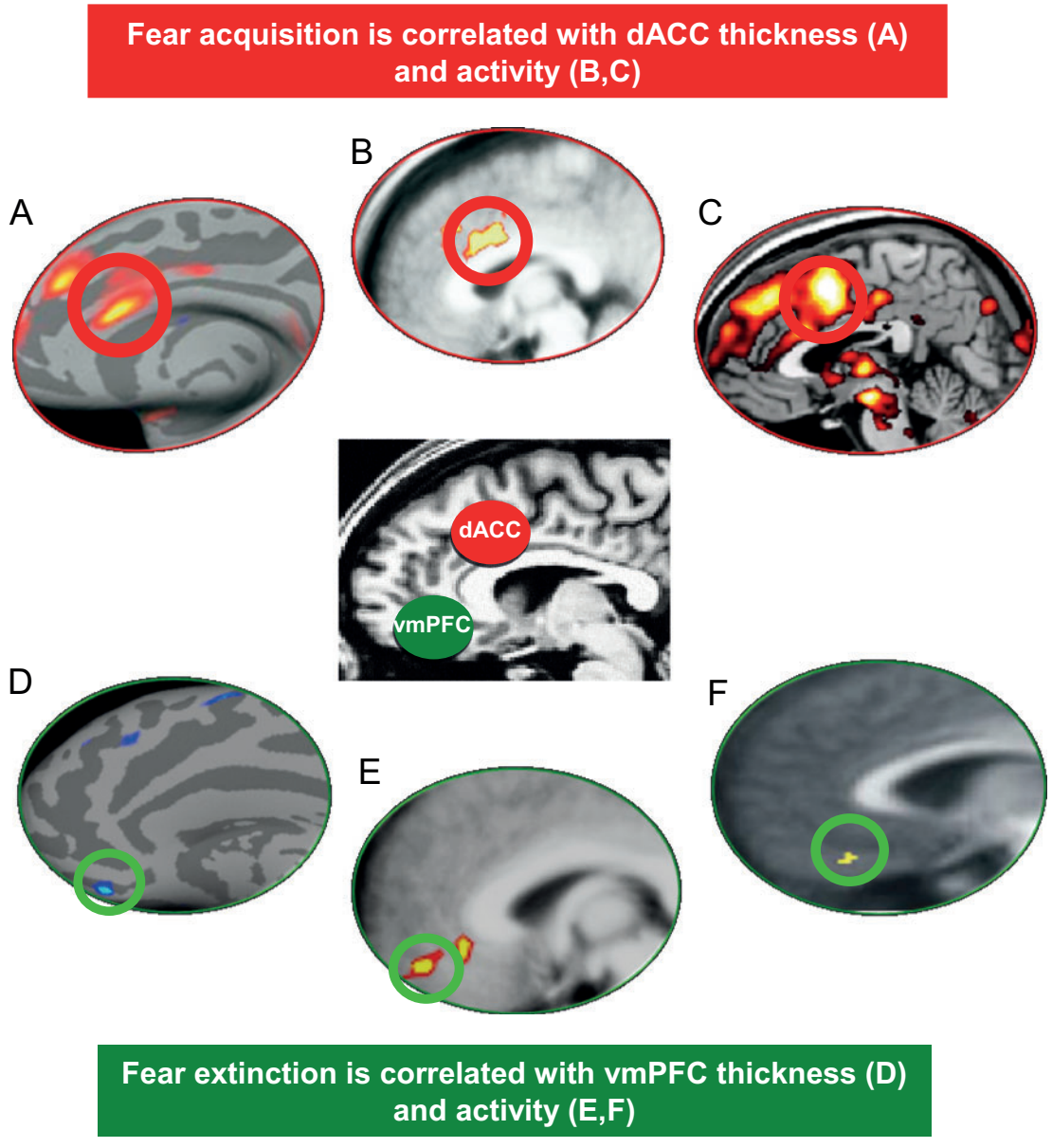

Figure 4

Summary of neuroimaging research demonstrating that the dACC (*A*, *B*, *C*) regulates fear acquisition, and vmPFC (*D*, *E*, *F*) regulates fear extinction, in healthy humans. From (*A*, *B*) Milad et al. (2007a); (*C*) Linnman et al. (2011b); (*D*) Milad et al. (2005b); (*E*) Milad et al. (2007b); (*F*) Kalisch et al. 2006.

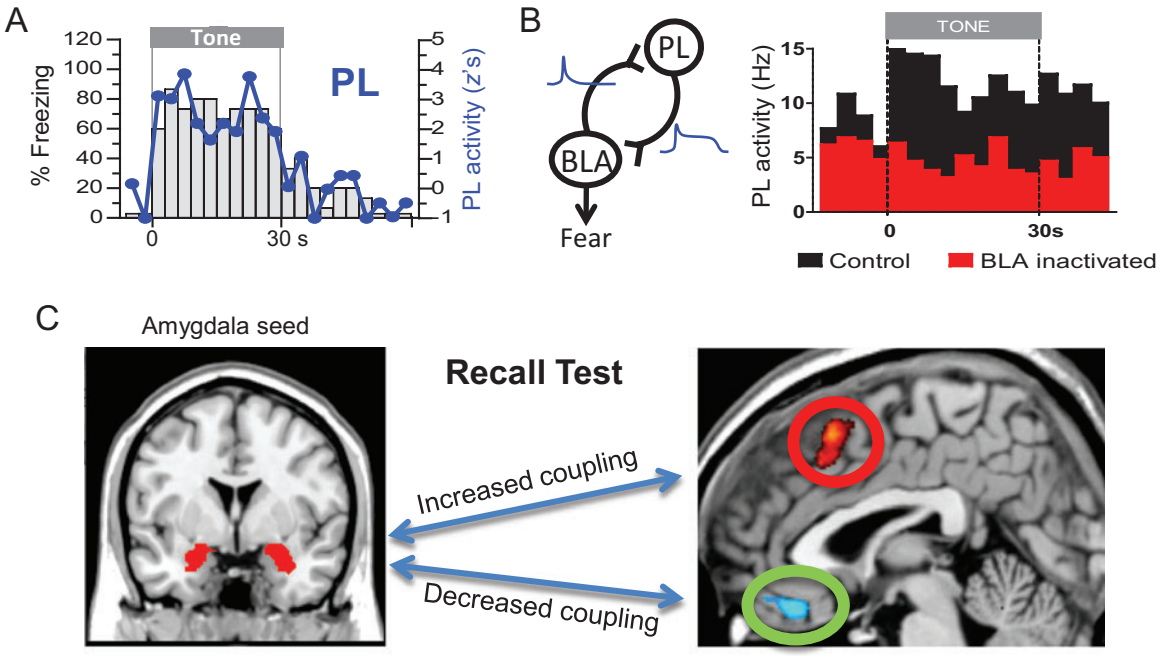

Figure 5

Prefrontal-amygdala interaction in rodents and humans. (*A*) The tone response of a single PL neuron (*blue line*, *z*-score) superimposed upon the rat's freezing to the tone (*gray bars*) (adapted from Burgos-Robles et al. 2009). Note the high correlation between time courses of PL activity and freezing (bin: 3 sec). (*B*, *left*) Schematic illustrating reciprocal connections between PL and the BLA. Transient tone response (*blue line*) emanating from BLA trigger sustained tone responses in PL that feedback to BLA and drive fear. (*B*, *right*) Perievent time histogram showing a conditioned tone response of a PL neuron under control conditions (*black bars*) and after inactivation of BLA with infusion of muscimol (*red bars*). Fear signals in PL are driven by BLA. (*C*) Psychophysiological interaction analysis during a recall test in healthy humans. One day after extinction training, increased coupling was observed between amygdala activity (*seed*) and the dACC (*red circle*), and reduced coupling was observed between the amgydala (*seed*) and vmPFC (*green circle*) (adapted from Linnman et al. 2011c).

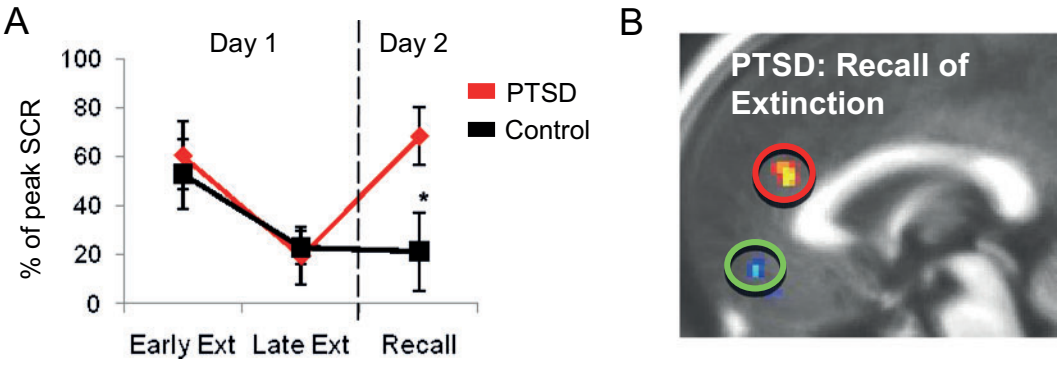

Figure 6

In posttraumatic stress disorder (PTSD), reduced extinction recall is associated with failure to activate ventromedial prefrontal cortex (vmPFC) and increased activation of dorsal anterior cingulate (dACC). (*A*) Skin conductance responses (SCRs) normalized to peak acquisition levels show intact fear learning [indexed in early extinction (early ext)], intact extinction learning (late ext), but impaired extinction recall (day 2) relative to controls. (*B*) Functional magnetic resonance imaging data using a contrast of extinguished versus unextinguished conditioned stimuli during extinction recall, showing hypoactivation of the vmPFC (*green circle*) and a trend toward hyperactivation of dACC (*red circle*) in individuals with PTSD relative to controls. Adapted from Milad et al. (2009b).

Annual Review of Psychology
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Contents

Neuroscience Methods

Indexes

Errata

An online log of corrections to *Annual Review of Psychology* articles may be found at http://psych.AnnualReviews.org/errata.shtml