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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 an unusual degree of coordination between rodent and human researchers examining fear extinction. This successful research program could serve as a model for translational research in other areas of behavioral neuroscience. Here we review the major advances and highlight new approaches to understanding and exploiting fear extinction.

Keywords

Conditioning; prefrontal; cingulate; amygdala; fMRI; anxiety

Introduction

Fear extinction refers to the decrement in conditioned fear responses that occurs with repeated presentation of a conditioned fear stimulus that is unreinforced. Because the neural mechanisms of fear extinction have been examined since the 1960s, 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 appeared (Pape & Paré 2010, Herry et al 2010, Sotres-Bayon & Quirk 2010, Myers et al 2011, Etkin et al 2011). 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 lead to the recent increase in fear extinction studies. Figure 1 shows the number of publications using the key words “fear extinction” since 1990. Note that both animal and human studies exhibited a sharp increase after 2000, with animal

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studies preceding human studies by several years. We focus on fear extinction research during this last decade, which was facilitated by a rodent-to-human translational approach. Lastly, we discuss future directions for fear extinction research in the next decade.

Overview of fear extinction and its psychological basis

Initial attempts to understand fear extinction focused on psychological and behavioral phenomenon. In the 1920's, Pavlov observed that extinguished appetitive responses in dogs would spontaneously recover with the passage of time, and 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 (Kimble & Kimble 1970, Chan et al 2001). 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 (Rescorla & Heth 1975). The phenomena of spontaneous recovery, fear renewal, reinstatement, as well as accelerated re-acquisition (Rescorla 2001) have been described in detail over the past decades (reviewed in Rescorla 1988, Bouton & Moody 2004). Together, they constitute strong evidence that extinction does not erase the initial association between the CS and US but forms a new association (CS-No US) that inhibits expression of the conditioned memory.

Context, in particular, is able to gate expression of conditioning vs. 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 only be expressed if the CS is presented in context B. Though "context" is often defined as the physical place (and all sensory cues present within), it is proposed that 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 1960-80's used the active avoidance paradigms popular at the time. 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 lesions and electrical stimulation implicated the septum, prefrontal cortex, striatum, and hippocampus in extinction of avoidance responses (Lovely 1975, Sanberg et al 1979, Brennan & Wisniewski 1982, Gralewicz & Gralewicz 1984).

Our knowledge of the fear learning circuits advanced rapidly during the 1980-90's. Study of avoidance gave way to more ethologically relevant conditioned responses such as freezing

and potentiation of startle responses (Chi 1965, Blanchard & Blanchard 1969, Davis & Astrachan 1978). The amygdala became the centerpiece of the fear conditioning circuit when it was shown that discrete lesions could block the acquisition and expression of conditioned fear responses (LeDoux et al 1984, Hitchcock & Davis 1986), 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 (LeDoux 2000, Davis 2000, Maren 2005, Sigurdsson et al 2007).

During the same time, anatomical studies described the connections of the amygdala central nucleus with downstream structures implicated in the expression of conditioned fear responses, including the hypothalamus, periaqueductal gray, pons, and other brainstem regions (Kapp et al 1979, Applegate et al 1982, LeDoux et al 1988, Romanski & LeDoux 1993, Pitkanen et al 1997). 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 GABAergic intercalated cells (Nitecka & Ben Ari 1987, Paré & Smith 1993), lateral division of the central nucleus (Sun & Cassell 1993), and inhibitory cells within the lateral and basolateral nuclei (Mahanty & Sah 1998). Thus, the advances in understanding the fear conditioning provided the framework against which to investigate extinction-induced reduction of fear.

Advent of human neuroimaging tools

Paralleling advances in animal work on neural circuits of fear, the field of human neuroimaging was established with the first functional magnetic resonance imaging (fMRI) study published in 1991 (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 whether rodent models of the amygdala in conditioned fear were valid in the human brain. Using a simple differential conditioning paradigm in healthy humans (a blue square as the CS and a mild shock as the US), LaBar et al (1998) (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 CS- (CS that is not paired with the shock). Subsequent fMRI studies using fearful faces as stimuli also resulted in significant amygdala activation in healthy humans (Breiter et al 1996, Whalen et al 1998). These observations were critical for two reasons: 1) they provided unequivocal evidence that amygdala function was conserved across species, and 2) they validated the use of fMRI and cross-species experimental designs for studying fear learning.

Initial research on fear extinction mechanisms: In search of the inhibitor

In contrast to fear learning, fear extinction research was only just beginning in the 1990s. Harris and 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 Falls and coworkers (1992) showed that fear extinction required NMDA receptors in the 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 after 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 older studies, LeDoux and coworkers found that lesions of sensory cortices impaired fear extinction (Teich et al 1989, LeDoux 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 appeared showing direct projections from the ventral medial prefrontal cortex (vmPFC) to the amygdala (Hurley et al 1991, McDonald 1991, McDonald 1998), in particular to inhibitory areas such as the intercalated cells (Vertes 2004). The first direct evidence for the involvement of the vmPFC in fear extinction came from Morgan et al. (1993) The authors showed that pre-training lesions of the vmPFC had no effect on the acquisition of conditioned fear but impaired fear extinction across days. Davis and coworkers were unable to replicate extinction deficits with lesions of visual cortex or vmPFC (Falls & Davis 1993, Gewirtz et al 1997), suggesting a possible difference between extinction of freezing vs. potentiated startle, or the specific location of the lesions (Sotres-Bayon et al 2004). Nevertheless, Morgan et al. (1993) generated interest in prefrontal cortex as an inhibitor in extinction.

A clinical connection to fear extinction

It was first proposed in the late 1980's 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 hyper-condition; i.e. form strong associations between traumatic events and sensory cues present at the time trauma (Pitman 1988). These strong associations later become resistant to extinction. Moreover, neuroimaging data that emerged during the late 1990's implicated the amygdala and the vmPFC in the psychopathology of anxiety disorders, which matched the clinical profile of perseverative fear and anxiety. Positron emission tomography (PET) studies showed decreased prefrontal blood flow in PTSD patients (Semple et al 1996, Bremner et al 1999). PTSD patients also 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, an improved understanding of fear learning circuits provided hypotheses which could be tested in humans with contemporary neuroimaging tools, which in turn provided a framework for translational research on fear 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 (Morgan et al 1993, Gewirtz et al 1997), Quirk et al. (2000) made lesions of the vmPFC, focusing on the infralimbic subregion (IL), as opposed to the prelimbic subregion (PL)(see 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.

Thus, 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). Thus, 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). It would no longer be sufficient to simply view extinction as the reversal of a primary conditioning process, but rather a separate process that interacts with conditioning memory.

Because lesion studies are often difficult to interpret, additional approaches were needed to test the vmPFC hypothesis. Accordingly, Milad and Quirk (2002) used single cell recording to determine the phase of conditioning/extinction 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 and Quirk (2002) showed that mimicking IL tone responses with microstimulation reduced fear and strengthened extinction. Both recording and stimulation findings were specific to IL, and were not observed in the adjacent prelimbic cortex. Taken together, these studies redefined the role of vmPFC in extinction, 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 extinction memory could be modulated by administering potentiating or depressing trains of stimulation to vmPFC inputs (Herry & Garcia 2002).

Subsequent studies have confirmed the role of IL in the retrieval of extinction, using lesions, drug infusions, and stimulation approaches (see figure 3) (Akirav & Maroun 2007, Quirk & Mueller 2008, Holmes & Wellman 2009, for recent reviews, see Herry et al 2010, Sotres-Bayon & Quirk 2010). For a listing of studies implicating vmPFC prior to 2008, see Quirk and Mueller (2008). More recent studies specifically of IL are listed here in table 1. Extinction 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 (Santini et al 2004, Mueller et al 2008). 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 increased tone responding, extinction 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 increase 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 (Pavlov 1927, Konorski 1967) that extinction does not return the brain to its pre-conditioning state, but rather potentiates inhibitory circuits.

Translating IL findings to humans

Spurred by rodent data on extinction, 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, Jovanovic et al 2006), return of fear phenomena: renewal, reinstatement, and the context dependency of extinction (Vervliet et al 2005, Vansteenwegen et al 2005, Hermans et al 2005, LaBar & Phelps 2005, Milad et al 2005a, Norrholm et al 2006) extinction in adolescents (Pine et al 2001), and the use of virtual reality (Baas et al 2004, Grillon et al 2006, Huff et al 2010). Regarding brain imaging, initial studies focused mostly on within-session extinction learning (i.e. LaBar et al 1998), and found increased activation of the amygdala and orbitofrontal cortex during extinction training (Gottfried & Dolan 2004, Knight et al 2004). However, the involvement of rodent IL in extinction recall, but not its initial learning, called for a multi-day conditioning paradigm in humans that would distinguish between extinction learning and its subsequent recall.

The homolog of IL in the human brain: Ventromedial prefrontal cortex (vmPFC)

Phelps and colleagues conducted the first fMRI study to identify a functional homolog of IL in the human brain in a two-day paradigm that would assess 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 be 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, and would compare recall of extinction with recall of conditioning (via the use of extinguished vs. unextinguished stimuli), in order to better translate rodent data (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 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 better the ability to inhibit conditioned responding during extinction recall. Analysis of a different cohort showed that, in addition to activation, the thickness of the vmPFC was also correlated with extinction recall (Milad et al 2005b, Hartley et al 2011). Thus, both structure and function of the human vmPFC positively correlate with the magnitude of extinction memory, similar to rat IL (see figure 4).

Opposing extinction

Rodent prelimbic prefrontal cortex

Lying just dorsal to the IL is the prelimbic cortex (PL). The idea that PL may be important for 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 (without a trace), 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 (see figure 5A), and was excessive in rats showing poor retrieval of extinction. Unlike lateral amygdala, PL neurons show sustained tone responses lasting the duration of freezing response, further implicating PL in the generation of freezing. Thus, PL receives a transient fear signal from the amygdala, and converts it into a sustained signal that returns to the amygdala to sustain fear (see figure 5B). 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 (dACC)

Spurred by the rodent findings in PL, we examined our structural and functional data for evidence of cortical areas involved in fear expression. As with vmPFC, both cortical thickness and activation of the dorsal anterior cingulate (dACC) was positively correlated with SCR 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 has been noted in previous studies of fear conditioning (Buchel et al 1998, Cheng et al 2003, Phelps et al 2004, Knight 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. 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, when the subject expected the shock but its delivery was omitted, dACC was also activated (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.

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 inhibits central nucleus output neurons (Royer & Paré 2002). This circuit is consistent with the finding that IL stimulation reduces the responsiveness of central nucleus output neurons to BLA or cortical stimulation (Quirk et al

2003). 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 iplasticity within the amygdala. ITC cells are essential for fear extinction (Likhtik et al 2008, Jungling 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 will require 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 suggests that BLA neurons processes extinction via reciprocal connectivity with prefrontal and hippocampal areas (Herry et al 2008, Herry et al 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 5C).

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 both PL/IL and the BLA and therefore is in a position to modulate fear responses (Hugues & Garcia 2007). While it is tempting to ask if hippocampal output excites fear or inhibits fear, there is evidence that 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 (Ji & Maren 2005, Hobin et al 2006), both suggesting fear excitation. However, 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 inhibits fear. The necessity of both IL and vmPFC activity for extinction memory suggests that the two structures may work together during recall of extinction.

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 and temporal resolution of fMRI make it difficult to subdivide a small structure like the amygdala. Furthermore, the extent to which BOLD signals represent excitatory vs. 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 multi-modal shifts and contexts 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 different visual contextual

manipulations were able to observe hippocampal activations during extinction recall (Kalisch et al 2006, Milad et al 2007b, Lang et al 2009)

Despite these challenges, emerging data show hippocampal and amygdala involvement similar to rodent findings, in the context of fear extinction (Kalisch et al 2006, Milad et al 2007b, Lang et al 2009). Importantly, the hippocampus is 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 signal between a selected seed region and the rest of the brain (Greicius et al 2003, Buckner & Vincent 2007). This analysis is conducted while subjects are not performing any tasks in the fMRI scanner. While 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 used to examine interactions between different brain regions is known as psychophysiological interaction (PPI), an analysis conducted on task-driven BOLD activations (Friston et al 1997). This method examines how a “behavioral” component of the task can modulate inter-regional coupling during the same task. 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 unextinguished stimulus (relative to the extinguished stimulus) during extinction recall (Linnman et al 2011c)(see figure 5C). These findings support inter-structural 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, recent 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 conjunction with various experimental paradigms that examined the neurobiological basis of other types of emotion regulation (i.e. instructing the participants to evaluate and 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

The combined rodent-human extinction 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, Milad et al 2009b). Consistent with vmPFC dysfunction, PTSD patients showed normal conditioning and within-session extinction, but were unable to recall extinction memory the following day (see 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. Similar observations have been made for schizophrenia (Holt et al 2009), suggesting that dysfunction in fear extinction circuits might cut across disorders (Graham and Milad, in press), potentially explaining anxious features of multiple mood and anxiety disorders (Insel et al 2010). The model could be further exploited by recent observations that dACC resting metabolism was able to predict fear conditioning and its subsequent extinction (Linnman et al 2011b, Linnman et al 2011c), and perigenual prefrontal activity was able to predict clinical response to extinction-based therapy for PTSD (Bryant et al 2008).

The next ten years: where do we go from here?

The last decade witnessed an expansive growth in the field of fear extinction with hundreds of publications, providing a rich understanding of the neural mechanisms 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. Despite 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 pre-weanling 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 (Kim & Richardson 2008, Gogolla et al 2009). During adolescence, extinction again becomes compromised (Esmoris-Arranz et al 2008), as twice the number of 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 presence of windows of vulnerability with respect to extinction, but also windows for therapeutic

intervention, if early extinction can erase fear memories before they become a clinical problem.

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, LTP, 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 prospective, women are twice as likely to develop anxiety and mood disorders (Kessler et al., 2005a,b). 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 substantial 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 (Zeidan et al 2011). (Milad et al 2009a, Milad et al 2010). 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 potentially lead to sex-specific treatments for mood and anxiety disorders.

Individual variability in fear extinction: Biomarkers

Traditionally, behavioral neuroscience has emphasized average behavior, however, 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 BDNF in the hippocampus (Heldt et al 2007, Peters et al 2010). Consistent with animal models, humans expressing a SNP 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 (Pezawas et al 2005, Hariri et al 2006). In both of these cases, a *reverse translation* approach was used to develop mouse models of the human polymorphism (Wellman et al 2007, Soliman et al 2010). Both of these mice exhibited impaired fear extinction, as well as deficits 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 (PACAP) (Ressler et al 2011).

Another emerging approach for understanding individual differences in extinction is to compare existing strains of inbred mice or rats. Fear extinction deficits in one particular strain of mouse (129S1) can be reversed with a dietary manipulation that restored the balance of activity in IL vs.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 can predict subsequent extinction recall (Linnman et al 2011c).

Conclusion

We have shown how translational research in the past 10 years has moved fear extinction from a primarily psychological concept to a specific circuit conserved across species. Human neuroimaging is sometimes criticized as being too descriptive and lacking mechanistic explanations. Animal models, while mechanistic, are often viewed as too simplistic for modeling psychiatric disorders, and therefore not relevant. Though there is some validity to these criticisms, we have shown how combining both approaches in a translational research program mitigates the limitations of each approach alone. Perhaps more than other fields 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, to test 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 fear.

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BOX 1 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 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), estrogen (Milad et al 2009a), a BDNF receptor agonist (Andero et al 2011), and corticosterone (Gourley et al 2009). Many of these act within prefrontal-amygdala extinction circuit (see table 1). The facilitating effect of electrical stimulation of IL (Vidal-Gonzalez et al 2006, Kim et al 2010) can be followed up with new optogenetic techniques for activating specific cell types with focal lasers, which is 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 (DBS), which is increasingly used to treat obsessive compulsive disorder (Greenberg et al 2008, Rodriguez-Romaguera et al 2010).

BOX 2 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 rodent studies (see table 1). Non-pharmacological approaches to facilitating extinction could come from transcranial magnetic stimulation (TMS) (Boggio et al 2010), or 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).

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 connect to inhibitory centers within the amygdala, whereas PL/dACC connect 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 directions

- 1- How does extinction circuitry and psychology change as we age?
- 2- How are the neural mechanisms that mediate fear extinction different in “his” and “her” brains?
- 3- How does sleep (or the lack thereof) affect with 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 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?

Figure 1.

Exponential increase in fear extinction studies within the last decade. Number of peer-reviewed studies identified with 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 cortex (PL) and human dorsal anterior cingulate cortex (dACC) increase fear expression and oppose extinction, while the rodent infralimbic cortex (IL) and human ventromedial prefrontal cortex inhibit fear expression and promote extinction.

Figure 3.

Summary of rodent findings for PL and IL prefrontal cortex. **A-C:** Divergent findings suggest that PL activity increases fear expression. **D-F:** Parallel data suggest that IL inhibits fear expression and strengthens extinction recall (**D,E,F**). 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).

**Fear acquisition is correlated with dACC thickness (A)
and activity (B,C)**

**Fear extinction is correlated with vmPFC thickness (D)
and activity (E,F)**

Figure 4.

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

activity and freezing (bin: 3 sec). **B.** Left: Schematic illustrating reciprocal connections between PL and the BLA. Transient tone response emanating from BLA trigger sustained tone responses in PL that feedback to BLA and drive fear. 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 BLA drive PL. **C.** Psychophysiological interaction (PPI) analysis during extinction recall in healthy humans. During recall of a non-extinguished stimulus, increased coupling of the neural activity of the amygdala (seed) with the dACC (red circle) was observed, and reduced functional coupling between the amygdala (seed) and vmPFC (green circle) was observed (adapted from Linnman et al. (2011c)).

Figure 6.

In PTSD, reduced extinction recall is associated with failure to activate vmPFC and increased activation of dACC. **A.** Skin conductance responses 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.** fMRI data using a contrast of extinguished vs. unextinguished conditioned stimuli in PTSD vs. Controls during extinction recall, showing hypoactivation of the vmPFC (green circle) and a trend toward hyperactivation of dACC (red circle) in PTSD relative to controls. Adapted from Milad et al. (2009b)

Table 1

Effects of infralimbic cortex manipulations on memory for fear extinction

Method	Task	Ext. memory	Reference
<i>Facilitators</i>			
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
<i>Inhibitors</i>			
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

Table 2

Effects of prelimbic cortex manipulations on fear expression

Method	Task	Retrieval	Reference
<i>Facilitators</i>			
microstimulation	cued fc	enhanced	Vidal-Gonzalez et al., 2006
CB1 receptor agonist	cued fc	enhanced	Lin et al., 2009
<i>Inhibitors</i>			
inactivation with TTX	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