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REVIEW

Neural Mechanisms of Extinction Learning and Retrieval

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Emotional learning is necessary for individuals to survive and prosper. Once acquired, however, emotional associations are not always expressed. Indeed, the regulation of emotional expression under varying environmental conditions is essential for mental health. The simplest form of emotional regulation is extinction, in which conditioned responding to a stimulus decreases when the reinforcer is omitted. Two decades of research on the neural mechanisms of fear conditioning have laid the groundwork for understanding extinction. In this review, we summarize recent work on the neural mechanisms of extinction learning. Like other forms of learning, extinction occurs in three phases: acquisition, consolidation, and retrieval, each of which depends on specific structures (amygdala, prefrontal cortex, hippocampus) and molecular mechanisms (receptors and signaling pathways). Pharmacological methods to facilitate consolidation and retrieval of extinction, for both aversive and appetitive conditioning, are setting the stage for novel treatments for anxiety disorders and addictions.
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INTRODUCTION

Extinction of classical conditioning has been studied experimentally for almost a century, since Pavlov's classic study of appetitive conditioned responses in dogs (Pavlov, 1927). His observation that extinguished responding to a conditioned stimulus (CS) spontaneously recovers with the passage of time indicated that extinction does not erase the conditioned memory, but is a form of inhibition (Konorski, 1967; Pavlov, 1927). Since then, we have learned that extinguished responses can return following other types of manipulations such as a change in context or presentation of the unconditioned stimulus (Bouton, 1993; Rescorla and Heth, 1975). Such 'uncovering phenomena' confirm that extinction is new learning and raise the question, what are the neural circuits of extinction learning and how do these circuits interact with conditioning memory?

Early investigations of the neural mechanisms of extinction focused on the hippocampus, in accordance with the behavioral inhibition hypothesis of hippocampus popular at the time (Kimble, 1968; Gray, 1972; Rabe and Haddad, 1968). Following this period, psychological research on extinction continued (Bouton and Bolles, 1979; Rescorla, 1988), but neuroscientific investigations lagged (Kimble and Kimble, 1970). The last decade, however, has seen a resurgence of interest in the neural mechanisms of this important form of learning. The reasons for this resurgence are multifold, but three factors stand out. First, impressive gains were made in deciphering the neural mechanisms of classical fear conditioning (LeDoux, 2000; Davis, 2000; Fendt and Fanselow, 1999), which provided an appropriate model system in which to study extinction. For this reason, the most complete understanding of extinction is in the fear system. Second, advances in psychological research on extinction started to converge with neuroscience research. For example, the discovery that extinction was context-specific paralleled the development of spatial mapping theories of the hippocampus (for a review, see Delamater, 2004). Third, and perhaps most importantly, there has been increased use of extinction-based exposure therapies for the treatment of anxiety disorders (Rothbaum and Schwartz, 2002; Wolpe, 1969; Barlow, 1990; Barad, 2005). Exposure therapy is highly effective (Foa, 2006), however, there is the possibility of improving the effectiveness and/or shortening the duration of treatment if extinction learning could be facilitated with pharmacological or other methods (Davis *et al*, 2006b). Here, we review the field of extinction research, emphasizing the phases of extinction learning and the structures involved. An excellent recent review focuses on molecular and pharmacological findings (Myers and Davis, 2007).

Where is 'Extinction Memory'?

Although it may be tempting to identify a single structure as the locus of extinction memory, it is more likely that extinction, like conditioning itself, is distributed across a network of structures. Extinction-related plasticity in each

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structure, however, may not serve identical roles. For example, plasticity in the amygdala may serve to inhibit fear expression, whereas plasticity in the hippocampus or prefrontal cortex may allow for contextual modulation of that inhibition. It is also possible that CS-responsiveness may be inhibited at various sites throughout the sensory processing stream, as suggested by metabolic mapping studies (Bruchey *et al*, 2007).

The involvement of a given structure or molecular process in extinction is likely to be determined by the particular phase of extinction learning in which the animal is engaged. Like other types of learning, extinction occurs in three phases: acquisition, consolidation, and retrieval (Figure 1). Acquisition of extinction is the initial learning that occurs when conditioned responses are declining within an extinction training session. This is followed by a consolidation phase, lasting several hours, in which physiological and molecular processes stabilize a long-term memory for extinction. Subsequent to this, presentation of the extinguished CS triggers retrieval of extinction, as evidenced by low levels of conditioned responding. Poor retrieval of extinction is characterized by high levels of conditioned responding to the extinguished CS, reflecting expression of the original conditioning memory. Poor retrieval of extinction could be due to uncovering phenomena (eg renewal, reinstatement) or to a pathological process that prevents consolidation or recall of extinction. We will now outline what is known concerning the neural mechanisms of each of the three phases of extinction learning, focusing on extinction of conditioned fear. We will then review appetitive extinction, related brain imaging studies in humans, and the attempts to translate extinction research to the clinic.

ACQUISITION OF EXTINCTION

Systemic Studies

Systemic drug studies have attempted to identify the key molecules in the acquisition of extinction. The first molecule implicated in extinction was the *N*-methyl-D-aspartate receptor (NMDAr). Systemic administration of the NMDAr antagonist MK801 prevented extinction (Baker and Azorlosa, 1996; Cox and Westbrook, 1994), but because extinction was carried out over many days with few trials per day, it was not possible to distinguish impairments in acquisition *vs* consolidation. When a massed extinction training design was used, it was observed that systemic NMDAr blockade (with CPP, (±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid) before extinction training did not prevent acquisition of extinction, but did impair retrieval of extinction the following day (Santini *et al*, 2001; Suzuki *et al*, 2004), suggesting a role for NMDArs in consolidation, rather than in acquisition, of extinction. More recently, however, it was shown that a selective antagonist of the Nr2B subunit of the NMDAr, ifenprodil, blocked acquisition of extinction within a session (Sotres-Bayon *et al*, 2007). The discrepancy in findings between ifenprodil and CPP is likely due to the higher affinity of ifenprodil for the Nr2B subunit, in contrast to the higher affinity of CPP for the Nr2A subunit (Lozovaya *et al*, 2004). In addition to having a higher affinity for the Nr2B subunit, ifenprodil does not impair expression of freezing like CPP (Sotres-Bayon *et al*, 2007), and is therefore a better tool for investigating extinction. Thus, it appears that NMDArs are necessary for the acquisition of extinction.

An equally robust blockade of extinction acquisition has been observed with systemic administration of the voltage-gated calcium channel (VGCC) antagonist nifedipine (Cain *et al*, 2002; Barad *et al*, 2004). Together with the NMDA findings, this suggests that calcium currents are required for the initial decrements in responding that occur during an extinction session. Calcium currents operating through Ca^{++}/calmodulin-dependent protein kinase II (CaMKII) have been linked to short-term memory for other types of learning (Rodrigues *et al*, 2004; Irvine *et al*, 2005) and are thought to trigger receptor insertion and other local changes that can support memory acquisition. It is not known, however, if inhibitors of CaMKII (such as KN-62) prevent extinction. A recent study using inducible transgenic techniques showed that inhibition of PKA accelerated acquisition of fear extinction (Isiegas *et al*, 2006), suggesting that some kinase pathways may serve to inhibit extinction.

Other receptors implicated in the acquisition of extinction are cannabinoid and opioid receptors. Systemic

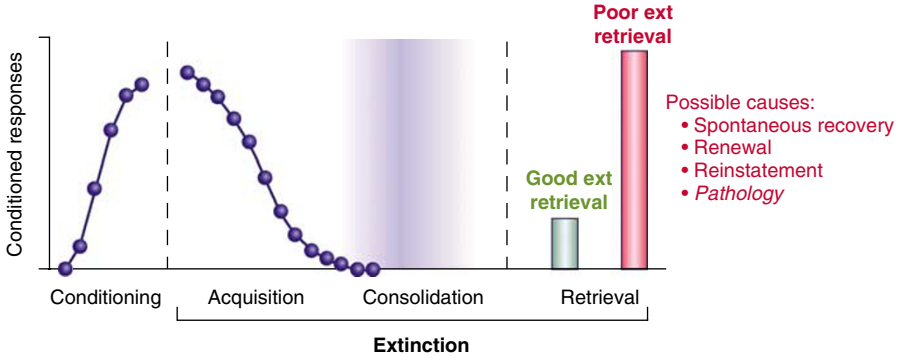


Figure 1 Extinction learning occurs in three phases. Acquisition is characterized by a decrease in conditioned responses to the presentation of a CS without the US. Consolidation is a time-dependent process during which a long-term extinction representation is formed. Retrieval of extinction occurs at a later time, when the CS is re-presented. Good extinction retrieval is characterized by low levels of conditioned responses (green bar), whereas poor extinction retrieval is characterized by high levels of conditioned responses (red bar). Poor retrieval of extinction is normally observed following renewal, reinstatement, spontaneous recovery, or in pathological conditions characterized by extinction failure.

administration of the opioid antagonist naloxone impaired within-session extinction of fear in rats (McNally and Westbrook, 2003). Acquisition of extinction was also slowed by blockade of the cannabinoid CB1 receptor (Marsicano *et al*, 2002; Varvel *et al*, 2005) and accelerated by CB1 agonists or cannabinoid reuptake inhibitors (Chhatwal *et al*, 2005a; Pamplona *et al*, 2006). Increasing levels of the endogenous cannabinoid anandamide appears to accelerate extinction of both fear and spatial memories (Varvel *et al*, 2007), suggesting that manipulating anandamide levels may be clinically useful. Thus, extinction-induced calcium currents may activate downstream kinases, which are modulated by endogenous cannabinoids (Cannich *et al*, 2004) to amplify extinction-related plasticity.

Basolateral Amygdala

Studies on the neurobiology of extinction have been driven by the well-documented circuitry of conditioned fear. The basolateral amygdala (BLA) associates sensory and shock-related inputs and influences central nucleus output neurons, which drive fear expression through descending projections (Pare *et al*, 2004; Davis, 2006; Phelps and LeDoux, 2005). The site of extinction acquisition, however, has been difficult to pinpoint, perhaps because it may be distributed across several structures. Indeed, within-session declines in neural conditioned responses have been observed throughout the fear-conditioning circuit (Quirk *et al*, 1996; Olds *et al*, 1972; Ben Ari and Le Gal, 1974), and it has been argued that extinction may be a habituation-like process (Kamprath and Wotjak, 2004). However, from the point of view of understanding extinction learning, the important question is where is plasticity necessary for the acquisition of extinction?

As lesions of BLA eliminate freezing, it is not practical to use lesions to assess the role of BLA in extinction. Lesions restricted to the basal nuclei of the amygdala, however, do not block the acquisition of conditioned freezing (Nader *et al*, 2001), and also do not prevent extinction (Anglada-Figueroa and Quirk, 2005; Sotres-Bayon *et al*, 2004). This suggests that the basal nuclei are not necessary for extinction; however, it is possible that other structures may have assumed the function of lesioned basal areas. Local infusion of pharmacological agents is a more useful way to study the role of the BLA in the acquisition of extinction. In fact, the BLA was the first structure implicated in extinction, because local infusion of NMDAr antagonists and kinase inhibitors prevented extinction (Falls *et al*, 1992; Lu *et al*, 2001; Lin *et al*, 2003b). In these studies, however, within-session extinction was not assessed and it was therefore not possible to distinguish an effect of the blockers on acquisition *vs* consolidation processes.

Infusion of low-dose muscimol (an inactivating agent) into BLA reduced fear expression during extinction, but did not impair extinction learning as evidenced by normal retrieval of extinction the following day (Akirav *et al*, 2006b). This would appear to suggest that BLA processing is not required for extinction acquisition, although in that study, levels of extinction in controls were very low. Herry *et al* (2006) recently showed that blockade of mitogen-activated protein kinase (MAPk) activity in BLA completely prevented within-session extinction, and that extinction increased levels of pMAPk in BLA. It is not yet known if VGCCs in the BLA are necessary for extinction acquisition, but local blockade of NMDArs (Sotres-Bayon *et al*, 2007) or metabotropic glutamate receptors (Kim *et al*, 2007) in the BLA were recently shown to impair the acquisition of extinction. Cannabinoids modulate glutamatergic and GABAergic transmission in BLA (Azad *et al*, 2003) as well as BLA kinase activity (Cannich *et al*, 2004), but it has yet to be determined if cannabinoid activity in BLA is necessary for extinction. Thus, it is now becoming clear that acquisition of extinction is mediated by calcium-triggered cascades within the BLA.

Periaqueductal Gray

The ventrolateral periaqueductal gray (vlPAG) is a site of expression of fear responses (De Oca *et al*, 1998; LeDoux *et al*, 1988) and is rich in opioid receptors (Atweh and Kuhar, 1983). McNally and co-workers recently suggested that vlPAG opioids are necessary for extinction acquisition. They have shown that blocking μ-opioid receptors with naloxone in the vlPAG prevented acquisition of extinction (McNally *et al*, 2004b, 2005). As naloxone also facilitated acquisition of conditioning (McNally *et al*, 2004a), the authors proposed that opioids signal the current associative strength of the target CS, which is used to calculate the error term in classical learning theory (Rescorla and Wagner, 1972). This is the first theory of extinction acquisition linked to both neuroanatomy and learning theory. A challenge for this model, however, is to determine how opioid signals in the vlPAG communicate the error signal to the amygdala or other sites where conditioning and extinction-related plasticity occurs. In a general sense, extinction of conditioned fear may involve opioids because the omission of an expected shock may be rewarding. This would imply that opioid systems may play different roles in extinction of appetitive *vs* aversive conditioning.

CONSOLIDATION OF EXTINCTION

Like other forms of learning, extinction acquisition is followed by a consolidation phase. Extinction consolidation is supported by two sets of findings: (1) pharmacological agents administered before extinction training do not interfere with extinction acquisition but render the animal unable to recall extinction at a later time (ie intact within-session extinction but deficient between-session extinction), and (2) pharmacological agents administered shortly after extinction training (during the consolidation phase) render the animal unable to recall extinction at a later time. For pre-extinction infusions, it is important to rule out state-dependent learning effects of the drug. This is not a problem for post-training administration of drugs. Consolidation processes could involve activation of molecular cascades triggered by acquisition-induced events or, more interestingly, neuronal activity that initiates during the post-training period to strengthen extinction memory (Routtenberg and Rekart, 2005; Wittenberg and Tsien, 2002; McGaugh, 2000).

Basolateral Amygdala

As a site of initial acquisition of extinction, it might be expected that the BLA is also a site of extinction consolidation. Augmenting BLA activity after extinction with the GABA-A antagonist bicuculline facilitated extinction in a norepinephrine-dependent manner (Berlau and McGaugh, 2006). This suggests that post-training activity in the amygdala is involved in extinction (but see Akirav *et al*, 2006b). Extinction is known to involve several kinase pathways in the amygdala, such as MAPk (Lu *et al*, 2001; Herry *et al*, 2006) and PI-3 kinase (Lin *et al*, 2003b), as well as immediate early genes cFos and EGR-1 (Herry and Mons, 2004). In each case, interfering with the given pathway prevented consolidation of extinction. Protein synthesis in the BLA is also necessary for extinction (Lin *et al*, 2003b), suggesting that extinction of fear is similar to other forms of extinction learning that rely on protein synthesis for the formation of long-term memory (Berman and Dudai, 2001; Vianna *et al*, 2001; Pedreira and Maldonado, 2003).

However, extinction also activates the phosphatase calcineurin in the BLA, leading to a reversal of conditioning-induced phosphorylation of the transcription factor CREB (Lin *et al*, 2003a). Thus, dephosphorylation of CREB could drive some erasure of original fear memory in the BLA. This finding does not conflict with the existence of uncovering phenomena in extinction, which require that the conditioned memory is maintained in some, but not necessarily all, structures. Recent behavioral data indicate that extinction may indeed erase conditioning, especially when extinction is initiated within minutes of conditioning (Myers *et al*, 2006). Extinction-induced erasure may be a remnant from early stages of development, as extinction of fear in 16-day-old rats results in erasure of conditioning, whereas extinction in 23-day-old rats leaves conditioning intact (Kim and Richardson, 2007a, b).

Recent studies suggest that extinction training leads to structural changes in BLA synapses. Two hours after extinction training, the mRNA for the GABA receptor-binding protein gephyrin is upregulated (Chhatwal *et al*, 2005b). This has the effect of clustering GABA-A receptors in the synaptic cleft for maximal inhibition. At this same time point, mRNA for the neurotrophic factor BDNF is upregulated in BLA (Chhatwal *et al*, 2006). Importantly, rats with lentiviral-induced reduction in BDNF receptors in the BLA can extinguish normally within the session, but are unable to recall extinction the following day (Chhatwal *et al*, 2006), consistent with a role of BLA BDNF in consolidation of extinction. Structural changes following extinction are also suggested by a recent report showing that inhibition of the cell-adhesion molecule PSA-NCAM in the BLA had no effect on within-session extinction, but strengthened extinction memory (Markram *et al*, 2007). Cell adhesion molecules, which stabilize synaptic morphology, are thought to oppose plasticity (Bonfanti, 2006). The same study showed that PSA-NCAM levels in BLA were increased following conditioning, suggesting that conditioning induces morphological changes that oppose extinction. Thus, it appears that extinction-induced calcium currents in BLA trigger molecular cascades and morphological changes responsible for stabilizing extinction memory.

Prefrontal Cortex

One of the earliest observations regarding the neural mechanisms of extinction was that lesions of the ventral medial prefrontal cortex (vmPFC) impaired extinction of conditioned fear (Morgan *et al*, 1993). This study was prompted by earlier findings showing that monkeys with lesions of orbitofrontal cortex showed perseverative response tendencies in extinction (for a review see Sotres-Bayon *et al*, 2006). The vmPFC can modulate fear expression through descending projections to the amygdala, as well as to the amygdala's targets in the brainstem and hypothalamus. A role for the infralimbic region (IL) of the vmPFC in consolidation was suggested by the observation that rats with lesions of IL could acquire extinction within a session, but had difficult retrieving extinction the following day (Quirk *et al*, 2000). Similar findings were observed in other studies employing lesions of vmPFC (Lebron *et al*, 2004; Morgan *et al*, 2003; Weible *et al*, 2000; Fernandez, 2003), but other studies found no effect (Gewirtz *et al*, 1997; Garcia *et al*, 2006; Farinelli *et al*, 2006) (see Table 1 for summary of vmPFC lesion studies).

As permanent lesions can trigger recovery of function by other structures (Anglada-Figueroa and Quirk, 2005), local infusion of inactivating agents is a more reliable method of assessing the role of a structure in extinction. Accordingly, infusion studies of IL show more consistent findings than lesion studies (Table 1). IL infusions of the Na+ channel blocker TTX (Sierra-Mercado *et al*, 2006), NMDAr antagonist CPP (Burgos-Robles *et al*, 2007), protein kinase A inhibitor (Mueller *et al*, 2007), β-adrenergic blocker propranolol P_p-cAMPS (Mueller *et al*, 2007) or protein synthesis blocker anisomycin (Santini *et al*, 2004) do not impair acquisition of extinction, but lead to impaired retrieval of extinction the following day. Control procedures for anisomycin (Santini *et al*, 2004) and CPP (Santini *et al*, 2001) rule out state-dependent learning effects as an explanation for the deficits. A consolidation role of the vmPFC is further suggested by recent findings that infusion of a MAPk inhibitor (Hugues *et al*, 2004, 2006) or NMDAr antagonist (Burgos-Robles *et al*, 2007) immediately after extinction training (but not 2 or 4 h after) impaired subsequent retrieval of extinction (see Table 1 for summary of vmPFC infusion studies). This is further evidence that infusion effects are not due to state-dependent learning, and suggests that consolidation of extinction involves initiation of molecular cascades during the post-training period. This is similar to other forms of learning where post-training NMDAr activity is required for consolidation (McDonald *et al*, 2005; de Lima *et al*, 2005; Shimizu *et al*, 2000).

As molecular signatures of extinction consolidation in vmPFC begin to emerge, evidence suggests that there are also physiological signatures. Shortly after extinction training, there is potentiation of evoked potentials (Farinelli *et al*, 2006; Herry and Garcia, 2002; Hugues and Garcia, 2007), and neuronal tone responses (Milad and Quirk, 2002) in the IL. In both cases, the degree of potentiation was correlated with the amount of extinction in a subsequent retrieval test. More recently, it has been shown that high-frequency bursting of IL neurons shortly after extinction predicts retrieval of extinction the following day (Burgos-Robles *et al*, 2007) (Figure 2). NMDA receptors are required

Table 1 Effects of Ventromedial Prefrontal Cortex Manipulations on Extinction Retrieval

	Method	Task	Timing	Retrieval	Reference
Lesions					
	electrolytic	cued fc	pre-cond	impaired	Morgan *et al*, 1993
	electrolytic	cued fc	pre-cond	impaired	Morgan and Ledoux, 1995
	electrolytic	cued fc	pre-cond	no effect	Gewirtz *et al*, 1997
	electrolytic	cued fc	pre-cond	impaired	Quirk *et al*, 2000
	aspiration	eyeblink	pre-cond	impaired	Weible *et al*, 2000
	electrolytic	cued fc	pre-ext	no effect	Morgan *et al*, 2003
	6-OHDA	context fc	pre-cond	impaired	Fernandez Espejo, 2003
	electrolytic	cued fc	pre-cond	impaired	Lebron *et al*, 2004
	excitotoxic: ibotenic acid	cued food cond	pre-cond	impaired	Rhodes and Killcross, 2004
	electrolytic	cued fc	pre-cond	no effect	Farinelli *et al*, 2006
	electrolytic	cued fc	pre-cond	no effect	Garcia *et al*, 2006
	excitotoxic: ibotenic acid	cued food cond	pre-cond	impaired	Rhodes and Killcross, 2007
Infusions					
	muscarinic antagonist: scopolamine	cued food cond	pre-ext	impaired	Maruki *et al*, 2003
	protein synthesis inhibitor: anisomycin	cued fc	pre-ext	impaired	Santini *et al*, 2004
	MAPk inhibitor: PD098059	cued fc	post-ext	impaired	Hugues *et al*, 2004, 2006
	D4 antagonist: L-741,741	cued fc	pre-ext	impaired	Pfeiffer and Fendt, 2006
	inactivation: tetrodotoxin	cued fc	pre-ext	impaired	Sierra-Mercado *et al*, 2006
	inactivation: muscimol	cued fc	pre-ext	enhanced	Akirav *et al*, 2006a
	protein synthesis inhibitor: anisomycin	CTA	pre-ext	impaired	Akirav *et al*, 2006b
	NMDA antagonist: AP5	CTA	pre-ext	no effect	Akirav *et al*, 2006b
	PKA inhibitor: Rp-cAMPS	cued fc	pre-ext	impaired	Mueller *et al*, 2007
	serine/threonine kinase inhibitor: H-7	cued fc	pre-test	impaired	Holahan and Routtenberg, 2007
	NMDA antagonist: CPP	cued fc	pre-ext	impaired	Burgos-Robles *et al*, 2007
	NMDA antagonist: CPP	cued fc	post-ext	impaired	Burgos-Robles *et al*, 2007
	β-adrenergic antagonist: propranolol	cued fc	pre-ext	impaired	Mueller *et al*, 2007
Stimulation					
	vmPFC microstimulation	cued fc	ext	enhanced	Milad and Quirk, 2002
	thalamic inputs to vmPFC	cued fc	pre-ext	enhanced	Herry and Garcia, 2002
	vmPFC microstimulation	cued fc	ext	enhanced	Milad *et al*, 2004
	hippocampal inputs to vmPFC	cued fc	post-ext	enhanced	Farinelli *et al*, 2006

cond, conditioning; CTA, conditioned taste aversion; ext, extinction; fc, fear conditioning.

for both IL bursting and consolidation of extinction (Burgos-Robles *et al*, 2007), suggesting that bursting may trigger calcium currents in IL necessary for stabilizing extinction memory (Quirk *et al*, 2006). Consolidation of extinction can be strengthened by manipulations that augment IL function, such as: (1) long-term potentiation of thalamic (Herry and Garcia, 2002) or hippocampal (Farinelli *et al*, 2006) inputs to IL, (2) local microstimulation of IL (Milad *et al*, 2004; Milad and Quirk, 2002), (3) systemic administration of a metabolic enhancer that augments IL activity (Gonzalez-Lima and Bruchey, 2004), (4) systemic administration of histone deacetylase inhibitors that augment BDNF activity in IL (Bredy *et al*, 2007), and (5) IL infusion of an AMPA receptor potentiator (Zushida *et al*, 2007) (Table 1).

Hippocampus

The role of the hippocampus in consolidation of extinction has been extensively studied in two rodent paradigms in which the hippocampus is also required for conditioning: inhibitory avoidance and contextual fear conditioning. In inhibitory avoidance, the rat learns to refrain from stepping down onto an electrified floor. The advantage of this task is that extinction can be learned in a single trial, thereby facilitating the examination of post-training treatments. Using this paradigm, Izquierdo, Cammorata and co-workers have implicated numerous molecular processes within the hippocampus in the consolidation of extinction. These include NMDArs, MAPks, PKA, SRC tyrosine kinases, gene expression, and protein synthesis (Rossato *et al*, 2006; Bevilaqua *et al*, 2005; Vianna *et al*, 2001, 2003; Szapiro *et al*, 2003). Interestingly, many of these processes are also involved in conditioning and/or recall of the avoidance memory, but some are unique to extinction (Cammarota *et al*, 2005). For contextual fear extinction, the MAPk cascade in the hippocampus is necessary (Fischer *et al*, 2007), as is actin rearrangement (Fischer *et al*, 2004). It has recently been shown that contextual fear extinction involves down regulation of Rac-1 and cyclin-dependent

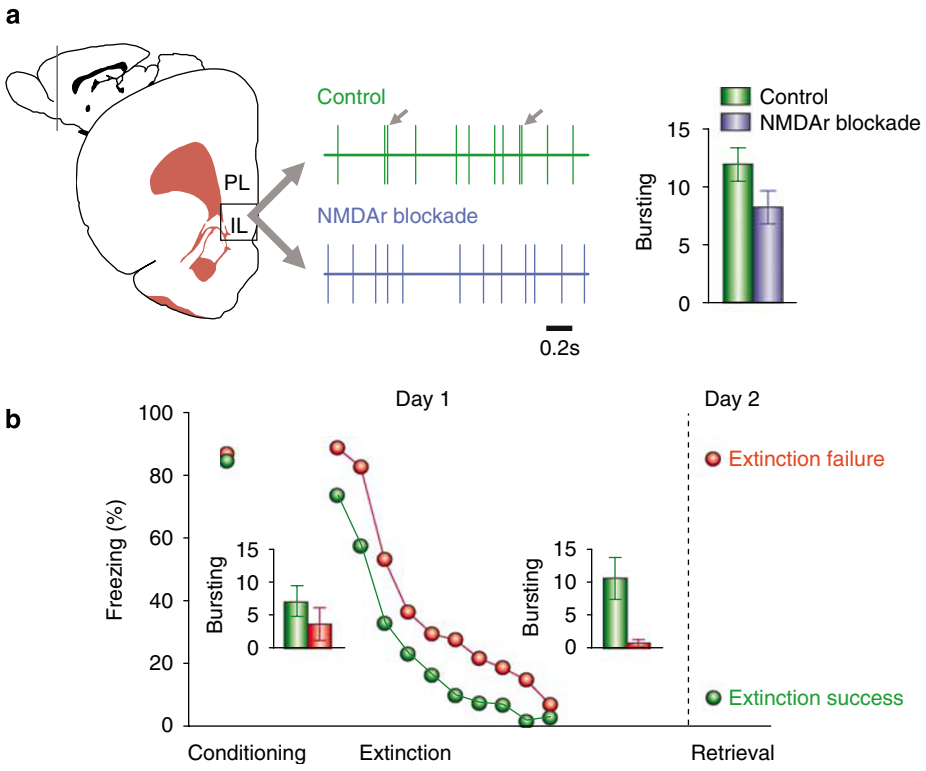


Figure 2 Consolidation of extinction involves NMDAr-mediated bursting in infralimbic (IL) cortex. (a) Action potentials from a single IL neuron before and after systemic injection of CPP, a competitive antagonist the NMDA receptor. CPP did not change the firing rate, but reduced high-frequency bursting, as evidenced by decreased short interspike intervals (20–30 ms). (b) Rats were conditioned to freeze to a tone paired with a shock, and then extinguished (tone alone). The following day, two-third of the rats showed good retrieval of extinction (extinction success), whereas one-third were unable to retrieve extinction (extinction failure). Before extinction, these two groups showed equivalent bursting in IL (bar graph insets), but 30 min after extinction, there was significantly less bursting in the extinction failure group. Thus, post-training IL bursting predicts extinction success and is a physiological signature of extinction consolidation (modified from Burgos-Robles *et al*, 2007).

kinase 5 (Cdk5) (Sananbenesi *et al*, 2007). Consistent with findings in the amygdala (Chhatwal *et al*, 2006), lentiviral inactivation of BDNF in the hippocampus impairs consolidation of fear extinction in a cued fear conditioning paradigm (Heldt *et al*, 2007). Thus, the hippocampus appears to be essential for consolidation of extinction, especially in tasks such as inhibitory avoidance, which require the hippocampus for conditioning.

RETRIEVAL OF EXTINCTION

As discussed above, the retrieval of extinction involves the expression of an inhibitory memory, and is highly context-specific. Accordingly, retrieval of extinction would be expected to activate inhibitory networks, as well as the hippocampus. These retrieval circuits are beginning to be understood for extinction of conditioned fear. Understanding retrieval of extinction is clinically important, because anxiety disorders and relapse of drug abuse are thought to be caused by a failure to retrieve an extinction memory generated in extinction-based treatment (Rauch *et al*, 2006; Kalivas *et al*, 2006).

Inhibitory Networks in the Amygdala

Extinction-induced activation of inhibitory networks suggests the involvement of the inhibitory neurotransmitter GABA in expression of extinction. An early study showed that facilitation of GABA-A activity with systemic injection of an inverse agonist of the benzodiazepine receptor (FG 7142) 'reinstated' conditioned fear after extinction, consistent with a failure to retrieve extinction (Harris and Westbrook, 1998). Importantly, FG 7142 had no effect on fear expression before extinction, suggesting that activation of GABAergic systems is somewhat specific to extinction. Efforts to localize this effect to the amygdala have proved difficult, because inhibition of GABA-A receptors in the amygdala can lead to seizures. Perhaps for this reason, no prior study has examined the effect of GABA-A antagonists (such as bicuculline) on the retrieval of extinction. Several groups have shown that facilitating GABAergic transmission with the GABA-A agonist muscimol in the BLA reduces fear expression (Blair *et al*, 2005; Muller *et al*, 1997; Muller and Fendt, 2006), but this simply confirms lesion studies showing that BLA is essential for expression of conditioned fear. Additional experiments are clearly needed. For example, it would be interesting to know if low levels of fear due to expression of extinction are more dependent on BLA GABA-A receptors than low fear levels due to partial conditioning (eg Jami and Barad, 2004).

Within the amygdala, there are well-defined circuits for inhibition. These include local inhibitory neurons within the BLA and central nucleus of the amygdala, as well as the islands of GABAergic neurons situated between theses two structures known as the intercalated (ITC) cells. ITC cells

receive input from BLA as well as several cortical sites (Pare and Smith, 1998; McDonald *et al*, 1996), and then inhibit central nucleus output neurons (Pare and Smith, 1993; Royer *et al*, 1999). In a similar manner, paracapsular ITC cells surround the BLA and inhibit BLA neurons (Marowsky *et al*, 2005). Thus, ITC cells can be seen as an 'off switch' for the amygdala, activated by cortical input. ITC cells show NMDAr-dependent LTP and LTD following high frequency stimulation of BLA inputs (Royer and Pare, 2002) and could serve as a site of extinction memory. In addition to ITC cells, NMDAr-dependent LTP has also been observed in inhibitory neurons in LA following high-frequency stimulation of thalamic inputs (Bauer and LeDoux, 2004). Thus, extensive local inhibition within the amygdala keeps the firing rate of BLA and central neurons low (Quirk *et al*, 1995; Collins and Pare, 2000; Goosens *et al*, 2003), and could serve as a substrate for expressing and storing extinction (Pare *et al*, 2004).

Cortical Control of Amygdala Inhibition

Cortical inputs to the amygdala provide a mechanism by which contextual, temporal, and mnemonic factors can regulate fear expression. Amygdala ITC cells receive a strong projection from the IL mPFC, in both rodents (McDonald *et al*, 1996) and primates (Chiba *et al*, 2001; Ghashghaei and Barbas, 2002). During extinction retrieval, IL activity is potentiated and is correlated with the extent of extinction retrieval (Milad and Quirk, 2002; Barrett *et al*, 2003; Herry and Garcia, 2002). A potentiated IL output could inhibit amygdala output via activation of ITC cells (Maren and Quirk, 2004; Pare *et al*, 2004). There are several lines of support for this model. Electrical stimulation of IL reduces the responsiveness of central nucleus output neurons to BLA stimulation (Quirk *et al*, 2003), and chemical stimulation of IL activates cFos in the ITC neurons (Berretta *et al*, 2005). Electrical stimulation of IL reduces conditioned fear and strengthens extinction memory (Vidal-Gonzalez *et al*, 2006; Milad and Quirk, 2002; Milad *et al*, 2004), whereas infusion of a broad spectrum kinase inhibitor into mPFC prevents retrieval of extinction (Holahan and Routtenberg, 2007) (Table 1).

During extinction, some neurons in LA (Repa *et al*, 2001) and auditory cortex (Quirk *et al*, 1997) continue to show conditioned responses, despite reduced fear. Extinction-induced inhibition of fear expression at the level of ITC cells, which are downstream from these areas, would effectively prevent fear signals from exiting the BLA (Figure 3). Projections from vmPFC might also activate inhibitory interneurons directly within the BLA or in the pericapsular ITC cells to dampen neuronal responses to conditioned stimuli (Rosenkranz and Grace, 2002; Rosenkranz *et al*, 2003; Marowsky *et al*, 2005). However, anatomical (Smith *et al*, 2000) and physiological (Likhtik *et al*, 2005) findings suggest that vmPFC inputs to BLA are largely excitatory. In addition to the vmPFC, the entorhinal cortex and subiculum project strongly to ITC cells (Canteras and Swanson, 1992; McDonald and Mascagni, 1997), and could participate in regulation of fear responses in extinction. Consistent with this, recent findings have implicated the entorhinal cortex in extinction of inhibitory avoidance (Bevilaqua *et al*, 2006).

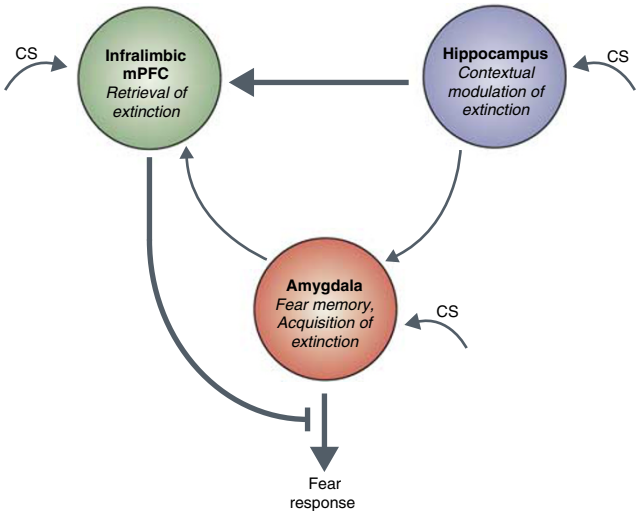


Figure 3 Extinction learning and expression relies on a network of three structures. The amygdala stores both conditioning and extinction memories. CS information enters the amygdala, hippocampus, and IL mPFC. The IL mPFC integrates CS information with contextual information from the hippocampus in order to determine extinction retrieval. In the extinction context, the IL mPFC inhibits amygdala output, to reduce fear. Outside the extinction context, amygdala output is uninhibited.

Although inhibitory influences of mPFC have been emphasized, recent findings suggest that the prelimbic (PL) mPFC *excites* fear expression. Pharmacological inactivation of PL reduces conditioned fear expression (Corcoran and Quirk, 2007a; Blum *et al*, 2006), and microstimulation of PL increases conditioned fear expression (Vidal-Gonzalez *et al*, 2006). During fear conditioning, PL, and IL neurons show opposite response patterns (Gilmartin and McEchron, 2005), and bursting in PL neurons is correlated with acquisition of conditioned fear (Laviolette *et al*, 2005). Similar to extinction, this prefrontal system is responsible for reducing fear under conditions where the stressor is controllable (Baratta *et al*, 2007). PL can augment fear expression via projections to the basal nucleus of the amygdala (Vertes, 2004), which was recently shown to be critical for expression of conditioned fear (Anglada-Figueroa and Quirk, 2005). Thus, PL and IL exert bidirectional control over fear expression, and both likely play a role in extinction retrieval.

Contextual Regulation

Extinguished responses are 'renewed' in contexts other than where extinction occurred. The dependence of extinction retrieval on contextual factors suggests a key role of the hippocampus in the retrieval of extinction (Figure 3). Initial studies examining the effect of lesions of the hippocampus on renewal found no effect (Frohardt *et al*, 2000; Wilson *et al*, 1995), but a more recent study revealed a deficit (Ji and Maren, 2005). This difference may be due to the exact renewal paradigm used (eg ABA *vs* ABC) (Bouton *et al*, 2006), or the possibility of recovery of function by other structures. A clearer picture is emerging from studies using pharmacological inactivation. Inactivating the hippocampus before extinction retrieval prevented renewal

(ie fear was lower than controls) (Corcoran and Maren, 2001, 2004; Hobin *et al*, 2006). Inactivating hippocampus before extinction training lead to poor retrieval of extinction the following day (ie fear was higher than controls) (Corcoran *et al*, 2005). This suggests that activity in the hippocampus is necessary for the renewal of fear in a non-extinction context, and that plasticity in the hippocampus (or its targets) is necessary for retrieval of extinction in an extinction context. Interestingly, similar results are observed with inactivation of the mPFC (Sierra-Mercado *et al*, 2006), suggesting that the mPFC may be an important target of the hippocampus for contextual modulation of extinction retrieval (Hobin *et al*, 2003; Corcoran and Quirk, 2007b).

Support for an amygdala locus of action in the contextual modulation of extinction retrieval comes from work of Maren and co-workers, who showed that the responses of LA neurons to conditioned tones were modulated by context after extinction (Hobin *et al*, 2003). LA tone responses were reduced in the extinction context, compared to a non-extinction context, but there was no contextual modulation of neuronal responses to stimuli that had not been extinguished. A more recent study from this group extended the finding by showing that contextual modulation of LA activity requires the hippocampus (Maren and Hobin, 2007). Similar studies combining unit recording, pharmacological inactivation, and behavioral analyses will be needed to understand the neural mechanisms of contextual modulation of extinction.

IMAGING OF EXTINCTION IN HUMANS

An important goal of extinction research is to translate rodent findings to humans, for future clinical applications. Although previous human imaging studies focused solely on acquisition of conditioned fear (Buchel and Dolan, 2000; LaBar *et al*, 1998), more recent studies have focused on extinction. Following the animal literature, new study designs are allowing researchers to distinguish between extinction acquisition *vs* extinction retrieval by examining subjects both during extinction training as well as 24 h later (Rauch *et al*, 2006; Delgado *et al*, 2006). Paralleling rat findings that the amygdala is necessary for acquisition of extinction, several groups observed amygdala activation during extinction training (Knight *et al*, 2004; Milad *et al*, 2007b; Gottfried and Dolan, 2004; Phelps *et al*, 2004). It is important to note that this activation was observed mid-extinction training, likely reflecting extinction learning rather than simply recall of conditioning. Indeed, in one study, these two processes appear to activate different parts of the amygdala (Knight *et al*, 2004).

During extinction retrieval (24 h after extinction training), several studies have reported significant activation of the vmPFC (Phelps *et al*, 2004; Kalisch *et al*, 2006; Milad *et al*, 2007b). Furthermore, Milad *et al* (2005, 2007b) observed that the amount of extinction retrieved was highly correlated with vmPFC activity and vmPFC thickness. These findings validate the preclinical rodent models of extinction retrieval, and suggest that the vmPFC may be a good target for clinical interventions. Abnormalities in functional connectivity between the prefrontal cortex and amygdala during emotional processing have been reported in humans carrying the short 'S' allele for the serotonin transporter gene (Pezawas *et al*, 2005; Heinz *et al*, 2005) and in mutant mice lacking this gene (Wellman *et al*, 2007), suggesting that there may be a genetic component underlying individual variability in extinction.

In addition to the vmPFC, a network of interconnected structures is emerging that could serve to regulate fear expression. Recent work suggests that the supragenual anterior cingulate may be a functional homologue of the rodent PL (Hariri and Holmes, 2006). This more dorsal region shows structural and functional correlations with acquisition of conditioned fear (Milad *et al*, 2007a), and is overactive in carriers of the serotonin transporter 'S' allele (Pezawas *et al*, 2005). The hippocampus is also activated during extinction retrieval in studies that manipulate context (Kalisch *et al*, 2006; Milad *et al*, 2007b), suggesting that a prefrontal–hippocampal network is involved in contextual modulation of extinction. Although one would expect such a network to inhibit the amygdala, one study found no correlation between vmPFC and amygdala during extinction retrieval (Kalisch *et al*, 2006), whereas two others found a positive correlation (Phelps *et al*, 2004; Milad *et al*, 2007b). Increased activity in the amygdala might represent activation of local inhibitory interneurons, which would be difficult to distinguish from activation of output neurons. Nevertheless, a striking convergence exists between rodent and human literatures on extinction retrieval, and suggests that extinction mechanisms, like fear learning itself, are highly conserved across species.

Consistent with the idea that post-traumatic stress disorder (PTSD) is caused by a failure to consolidate and retrieve memory for extinction, these same areas appear to be dysfunctional in PTSD. Subjects with PTSD due to various etiologies show reduced vmPFC volume and activity, together with increased activity in the amygdala (Bremner, 2006; Shin *et al*, 2006; Liberzon and Martis, 2006) (see Box 1). A recent meta-analysis showed that the prefrontal areas deficient in PTSD correspond to the same areas implicated in extinction (Milad *et al*, 2006). The hippocampus also shows decreased volume and activity in PTSD (Bremner, 2006; Shin *et al*, 2006; Gilbertson *et al*, 2002), consistent with the hypothesis that contextual modulation of extinction is compromised. Thus, optimal functioning in the hippocampal–prefrontal–amygdala network may be critical for normal emotional regulation, and may even determine certain personality traits (Rauch *et al*, 2005; Quirk and Beer, 2006; Hariri *et al*, 2006).

EXTINCTION OF APPETITIVE RESPONSES

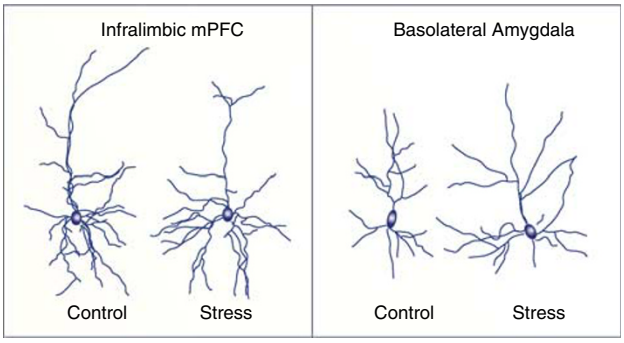
Relative to fear extinction, there are few studies on the neural mechanisms of appetitive extinction. The available evidence, however, indicates that appetitive extinction also involves the BLA and vmPFC. Classic work in monkeys (Weiskrantz, 1956) and more recent work in rats (Burns *et al*, 1999) has shown that lesions of the BLA impair extinction of conditioned responding for food rewards, suggesting that the BLA is necessary for acquisition of extinction in appetitive tasks. A similar finding was recently reported for pharmacological inactivation of the caudal BLA (McLaughlin and Floresco, 2007). In apparent contrast

to these findings, BLA lesions in monkeys enhanced extinction of an appetitive instrumental response (Izquierdo and Murray, 2005). In that study, however, BLA lesions also impaired expression of the conditioned response at the start of extinction, making it difficult to interpret extinction deficits. As with conditioned fear, the central nucleus of the amygdala is necessary for expression of conditioned appetitive responses, acquired through both classical (Lee *et al*, 2005) and instrumental (Knapska *et al*, 2006) conditioning. Thus, there is good agreement across affective modalities as to the involvement of the amygdala in extinction.

The vmPFC and orbital cortex were originally implicated in extinction in early appetitive studies (Butter *et al*, 1963; Sotres-Bayon *et al*, 2006). More recent studies in rodents using classical appetitive conditioning have re-examined the effects of vmPFC lesions. Similar to conditioned fear, lesions of vmPFC did not impair within-session extinction, but impaired retrieval of extinction the following day, as evidenced by increased spontaneous recovery (Rhodes and Killcross, 2004) and increased renewal (Rhodes and Killcross, 2007). Consistent with these findings, infusions of the muscarinic antagonist scopalamine into the vmPFC before extinction of lever pressing for food left within-session extinction intact, but impaired extinction retrieval the following day (Maruki *et al*, 2003). As with extinction of fear (Hugues *et al*, 2007) extinction of appetitive behavior triggers norepinephrine efflux in vmPFC (Mingote *et al*, 2004), which could explain the deficits in extinction retrieval following forebrain depletion of norepinephrine (Mason and Iversen, 1977). A role of the vmPFC in retrieval of appetitive extinction suggests that vmPFC may modulate return of drug-seeking behavior following extinction (Kalivas *et al*, 2006).

Box 1 Extinction and Stress

Does stress impair extinction? This is obviously an important question, as many mental disorders are compounded by high levels of chronic stress, which could impede extinction-based therapies. Recent morphological evidence suggests that stress may impair extinction. Chronic stress (daily restraint over a period of 7–20 days) decreases dendritic branching and spine count in the hippocampus (McEwen, 2001) and mPFC (Radley *et al*, 2004, 2006; Cook and Wellman, 2004; Brown *et al*, 2005), but increases dendritic branching and spine count in the BLA (Mitra *et al*, 2005; Vyas *et al*, 2002, 2006) (see Box 2 figure). This pattern of effects would be expected to increase conditioning and impair extinction. Accordingly, chronic stress has been reported to impair recall of extinction (Miracle *et al*, 2006), but, because the stress was induced before conditioning, it was not possible to distinguish the effects of stress on conditioning *vs* extinction. Morphological analysis of prefrontal alterations has been limited to the PL mPFC, even though the IL mPFC is the structure more implicated in extinction. Thus, additional studies are needed that focus on IL, and induce stress after conditioning, but before extinction. In this regard, a recent study showed that 3 days of forced swim stress induced dendritic retraction specific to IL, and impaired the acquisition of extinction (Izquierdo *et al*, 2006).



Inset: IL cells adapted from Izquierdo *et al* (2006) and basolateral amygdala cells adapted from Vyas *et al* (2002).

CLINICAL IMPLICATIONS

Anxiety disorders are among the most commonly diagnosed mental health problems (Breslau *et al*, 2004), and are often treated with extinction-based exposure therapies (Foa, 2006; Hermans *et al*, 2005; Garakani *et al*, 2006). In patients with PTSD, deficits in fear extinction are observed (Peri *et al*, 2000; Orr *et al*, 2000), and are thought to contribute to the persistence of this disorder (Charney *et al*, 1993). Therefore, overcoming these deficits by enhancing current therapeutic treatments with pharmacological adjuncts could accelerate and strengthen extinction (Anderson and Insel, 2006). A

Table 2 Pharmacological Enhancers of Extinction (Systemic)

	Drug	Action	Reference
Preclinical			
	DCS	partial NMDAr agonist	Walker *et al*, 2002
	methylene blue	metabolic enhancer	Gonzalez-Lima and Bruchey, 2004
	yohimbine	noradrenergic 2r antagonist	Cain *et al*, 2004
	sulpiride	dopamine D2r antagonist	Ponnusamy *et al*, 2005
	AM-404	cannabinoid reuptake inhibitor	Chhatwal *et al*, 2005a
	WIN 55,212-2	cannabinoid receptor agonist	Pamplona *et al*, 2006
	dexamethasone	glucocorticoid receptor agonist	Yang *et al*, 2006
	PEPA	AMPA receptor potentiator	Zushida *et al*, 2007
Clinical			
	DCS	partial NMDAr agonist	Ressler *et al*, 2004; Hofmann *et al*, 2006
	cortisol	endogenous glucocorticoid	Soravia *et al*, 2006

number of pharmacological agents have been shown to enhance extinction in animals, and translational studies in humans are beginning to bear fruit.

In rodents, extinction of fear is enhanced by several classes of systemically applied drugs (Table 2). With respect to monoaminergic systems, the dopamine D2 receptor antagonist sulpiride (Ponnusamy *et al*, 2005) and the α2-adrenoceptor antagonist yohimbine (Cain *et al*, 2004; Morris and Bouton, 2007) facilitate extinction. A general metabolic enhancer, methylene blue, has also been shown to facilitate fear extinction (Wrubel *et al*, 2007; Gonzalez-Lima and Bruchey, 2004), likely by enhancing extinction-induced activity in the vmPFC. The best studied extinction facilitator is the NMDAr partial agonist D-cycloserine (DCS), which has been shown to accelerate and strengthen extinction of fear in several laboratories (Weber *et al*, 2007; Woods and Bouton, 2006; Mao *et al*, 2006; Lee *et al*, 2006; Parnas *et al*, 2005; Walker *et al*, 2002; Ledgerwood *et al*, 2003). Intracerebral infusions indicate that the site of action of DCS is in the BLA (Walker *et al*, 2002; Ledgerwood *et al*, 2003), in agreement with the effects of NMDAr antagonists in the BLA (Falls *et al*, 1992; Sotres-Bayon *et al*, 2007). DCS may also act in IL, which is a site of NMDAr-dependent consolidation of extinction (Burgos-Robles *et al*, 2007). With respect to appetitive learning, DCS facilitated extinction of drug-seeking behavior in rats (Botreau *et al*, 2006), suggesting that DCS could be used in conjunction with extinction-based treatments for addiction (see Box 2).

In humans, DCS has already been shown to augment therapeutic responses to therapies for acrophobia (Ressler *et al*, 2004) and social anxiety (Hofmann *et al*, 2006), suggesting that it may be useful as an adjunct to exposure therapy. Recent studies, however, found no effect of DCS in therapy for spider phobia (Guastella *et al*, 2007b) or on fear extinction itself (Guastella *et al*, 2007a). Other possible limitations of DCS have been recently documented in rodents, including CS nonspecificity and tolerance following repeated administration of DCS (Ledgerwood *et al*, 2005; Parnas *et al*, 2005). Thus, while promising, additional clinical trials with DCS are needed to determine its efficacy as an adjunct to therapy.

Drugs in addition to DCS have been shown to enhance extinction in rodents, and might be useful in humans (Table 2). These include AM404, an inhibitor of endocannabinoid breakdown and reuptake (Chhatwal *et al*, 2005a), RB101(S), an inhibitor of enkephalin-degrading enzymes (McNally, 2005), and PEPA, a potentiator of AMPA receptors (Zushida *et al*, 2007). A particularly exciting new avenue of study involves the glucocorticoids, which have been recently shown to facilitate fear extinction in rats (Yang *et al*, 2006, 2007). It has been known for some time that PTSD sufferers have reduced circulating levels of cortisol (Yehuda, 2001), suggesting that corticosteroids may have a protective effect. In fact, repeated cortisol treatments administered before exposure therapy augmented the therapeutic response in social phobia and spider phobia (Soravia *et al*, 2006). Moreover, patients with spider phobia continued to express reduced fear during exposure therapy 48 h following treatment with cortisol (Soravia *et al*, 2006), suggesting that extinction consolidation was enhanced. Thus, the use of glucocorticoid treatments to enhance therapeutic outcomes warrants further study.

Box 2 Extinction *vs* Reconsolidation

Extinction involves reactivation of the conditioning memory. An increasing number of studies over the past 7 years indicates that reactivation of a memory initiates a 'reconsolidation' process necessary for maintenance of the conditioning memory (Nader *et al*, 2000; Tronson and Taylor, 2007; Dudai, 2002). Reconsolidation requires many of the same cellular processes as extinction, such as protein synthesis, NMDA receptors, β-adrenergic receptors, protein kinase A, and MAPk (for reviews, see Miller and Sweatt, 2006; Alberini, 2005). This raises the question: which process predominates in an extinction session, and how might they interact? Converging findings from conditioned fear studies in several species suggest that the process that predominates depends on the duration of the re-exposure to the conditioned stimulus (Sangha *et al*, 2003; Pedreira and Maldonado, 2003; Eisenberg *et al*, 2003; Suzuki *et al*, 2004). If re-exposure is very short (without accompanying extinction), reconsolidation will predominate and blockers will cause low levels of fear (impaired reconsolidation). If re-exposure is long enough to induce extinction, extinction will predominate and blockers will cause high levels of fear (impaired extinction). Thus, an extinction session may initially trigger reconsolidation, but this leads to consolidation of extinction as the session progresses. It should be noted, however, that reconsolidation processes can occur despite extinction, suggesting that these two processes can occur independently of one another (Duvarci *et al*, 2006).

From a clinical perspective, both reconsolidation and extinction could be pharmacologically manipulated to reduce the exaggerated fear responses seen in anxiety disorders. The intent would be to impair reconsolidation or facilitate extinction. Extinction can be facilitated with the NMDA partial agonist DCS (see main text), whereas reconsolidation can be impaired with the β-adrenergic receptor blocker propranolol (Debiec and LeDoux, 2004). Both of these drugs are in various stages of clinical testing (Davis *et al*, 2006a; Brunet *et al*, 2007). However, the interaction between reconsolidation and extinction could result in undesirable effects, depending on the duration of re-exposure (see Box 1 table). With a short re-exposure, DCS was recently shown to increase fear in rats, presumably by strengthening reconsolidation (Lee *et al*, 2006). Similarly, propranolol was shown to impair extinction of conditioned fear in mice (Cain *et al*, 2004), resulting in high fear. Thus, the duration of exposure must be carefully coordinated with the drug used and the particular memory process that is being targeted.

Duration of CS re-exposure determines treatment outcome

Intent	CS exposure	Drug	Outcome
Impair reconsolidation	Short →	Propranolol →	Low fear
	Unintended: *Long* →	*Propranolol* →	*High fear*
Enhance extinction	Long →	DCS →	Low fear
	Unintended: *Short* →	*DCS* →	*High fear*

CONCLUSIONS

Neuroscientific research on extinction has advanced rapidly over the past decade, uncovering the neural mechanisms that regulate this form of learning. The processes of acquisition, consolidation, and retrieval of extinction require the interplay of several key structures, including the BLA, infralimbic prefrontal cortex, and hippocampus. Parallel findings are emerging from studies of extinction of appetitive responses, suggesting the existence of a general circuit for extinction. Of particular importance is the determination of the mechanisms regulating extinction consolidation and retrieval. Pharmacological agents that

facilitate extinction consolidation and retrieval could serve as adjuncts to cognitive behavioral therapy for anxiety disorders and addiction, offering a novel treatment strategy for enhancing therapeutic outcome.

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