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REVIEW ARTICLE
Neuronal circuits of fear extinction

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Abstract

Fear extinction is a form of inhibitory learning that allows for the adaptive control of conditioned fear responses. Although fear extinction is an active learning process that eventually leads to the formation of a consolidated extinction memory, it is a fragile behavioural state. Fear responses can recover spontaneously or subsequent to environmental influences, such as context changes or stress. Understanding the neuronal substrates of fear extinction is of tremendous clinical relevance, as extinction is the cornerstone of psychological therapy of several anxiety disorders and because the relapse of maladaptative fear and anxiety is a major clinical problem. Recent research has begun to shed light on the molecular and cellular processes underlying fear extinction. In particular, the acquisition, consolidation and expression of extinction memories are thought to be mediated by highly specific neuronal circuits embedded in a large-scale brain network including the amygdala, prefrontal cortex, hippocampus and brain stem. Moreover, recent findings indicate that the neuronal circuitry of extinction is developmentally regulated. Here, we review emerging concepts of the neuronal circuitry of fear extinction, and highlight novel findings suggesting that the fragile phenomenon of extinction can be converted into a permanent erasure of fear memories. Finally, we discuss how research on genetic animal models of impaired extinction can further our understanding of the molecular and genetic bases of human anxiety disorders.

Introduction

In the past decade, increased interest has been directed at understanding the neuronal basis of fear extinction, in part because of its clinical relevance in the context of human anxiety disorders such as phobias and post-traumatic stress disorder (PTSD). In the laboratory, fear extinction is one of the most studied forms of behavioural inhibition. Operationally, fear extinction is defined as a reduction of previously acquired conditioned fear responses as a consequence of non-reinforced presentations of a conditioned stimulus (CS, usually a tone or a light) previously paired with a noxious unconditioned stimulus (US) such as a footshock. The resulting progressive decrease of conditioned fear responses is referred to as extinction learning and can lead to the formation of short- and long-lasting forms of extinction memory. From an historical point of view, research in the extinction field has been largely driven by recurrent questions that are still partially unresolved. The first set of questions relate to the nature of the extinction phenomenon in terms of the underlying associative or non-associative mechanisms. Essentially, they address whether extinction is a new learning of the association between the CS and the absence of US, an unlearning of the original association between the CS and the US, a habituation-like phenomenon or a combination of these mechanisms. Recently, the debate has been gravitating toward temporal and developmental aspects of fear extinction. The general idea is that depending on the developmental state and on the time interval between fear acquisition/reactivation and extinction learning, repeated non-reinforced CS presentations may recruit different extinction mechanisms. A second set of questions concern the nature of the neuronal substrates and the plasticity mechanisms underlying fear extinction. These include the identification of brain structures and neuronal circuits selectively implicated in different phases of extinction (acquisition vs. consolidation), the study of neuronal correlates of extinction memory and the analysis of the underlying molecular mechanisms. The last set of questions are clinically orientated and tackle the fundamental issue as to whether the development of animal models for impaired extinction may help to reveal specific neuronal circuits implicated in the failure to acquire or maintain an extinction memory, and to develop new therapeutic strategies for human anxiety disorders and related psychiatric conditions. In this review, for each of the aforementioned set of questions, we will first briefly outline current knowledge and then discuss recent findings, some of which challenge previously held notions and the current model of fear extinction.

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Fear extinction: new learning or unlearning?

Several behavioural studies have provided compelling evidence indicating that fear extinction reflects new learning rather than the erasure of the original fear memory trace. Learning theorists have long

proposed that extinction entails the development of a second inhibitory association that competes with the original excitatory CS–US association without destroying it (Konorski, 1967). Behaviourally, after extinction has occurred, it has been shown that conditioned fear responses can recover with the simple passage of time (spontaneous fear recovery) (Pavlov, 1927; Brooks & Bouton, 1993), a contextual shift (fear renewal) (Bouton & Bolles, 1979; Bouton & King, 1983) or an exposure to the original US (reinstatement) (Pavlov, 1927; Rescorla & Heth, 1975; Bouton & Peck, 1989; Delamater, 1997). These three paradigms, along with savings of conditioned fear memories (see below), now constitute the gold standard for determining whether a memory has been erased or is being actively suppressed. However, the use of a single read-out (like freezing) to assess memory erasure is likely to be inadequate (Lattal & Stafford, 2008), and more complete analyses will be required to demonstrate memory erasure unequivocally. Recent experimental and theoretical approaches to extinction have emphasized the role of context in the recovery of conditioned fear responses and suggested that the extinction learning process, and therefore extinction memory retrieval, is fundamentally context-dependent (Bouton, 2002, 2004). Therefore, any contextual change after extinction will prevent extinction memory retrieval and precipitate recovery of conditioned fear responses. The strongest support for the notion that extinction involves new learning probably comes from reacquisition experiments demonstrating that after extinction additional CS–US pairings result in the reacquisition of conditioned fear responses at a faster rate than during the initial acquisition (Bouton & Swartzentruber, 1989; Napier *et al.*, 1992). These so-called savings strongly support the idea that the original fear memory has not been erased during extinction. In striking contrast to this hypothesis, an influential learning model postulates that extinction results in the unlearning of the original CS–US association (Rescorla & Wagner, 1972). Although this assumption is not supported by most experimental results, the fact that conditioned fear recovers in most cases to a lesser extent after extinction compared with the original conditioned fear responses may suggest that part of the original memory trace has been erased by extinction (Bouton & King, 1983; Rauhut *et al.*, 2001). Theories of Pavlovian conditioning have postulated that during conditioning, the CS can form associations with separate components of the US such as its sensory and motivational/affective properties (Konorski, 1967; Wagner & Brandon, 1989; Delamater, 1996; Rescorla, 1999). Although this has only been demonstrated in the appetitive domain (for a review see Delamater, 2004), one possible way to reconcile the unlearning vs. new learning hypotheses could be that during fear extinction specific associations between the CS and the US are inhibited whereas others are erased. Finally, non-associative mechanisms have been proposed to explain extinction and spontaneous recovery of conditioned fear responses (Robbins, 1990; Kamprath & Wotjak, 2004). This hypothesis posits that extinction triggers habituation-like processes associated with a loss of CS (Pavlov, 1927; Pearce & Hall, 1980) or US (Rescorla & Heth, 1975) processing or with habituation of the conditioned responses (Hull, 1943). However, the fact that extinction is both CS- and context-dependent (Richards & Sargent, 1983; Kasprow *et al.*, 1984; Bouton, 2002, 2004) is difficult to reconcile with habituation of US processing. Moreover, although it has been argued that the spontaneous recovery of conditioned fear responses after extinction can be explained by a recovery from habituation (McSweeney & Swindell, 2002), the observation that spontaneous recovery often occurs only in a fraction of the animals tested (Herry & Garcia, 2002; Milad & Quirk, 2002; Herry & Mons, 2004) argues against this hypothesis. Recent evidence indicates that habituation of CS processing contributes to extinction under certain conditions. When mice are conditioned with few pairings, habituation-like mechanisms have been demonstrated to account for part of the suppression of fear behaviour during extinction (Kamprath & Wotjak, 2004). Additional evidence that extinction and habituation share common mechanisms is provided by the finding that the CB1 endocannabinoid receptor is required for both processes (Marsicano *et al.*, 2002; Kamprath *et al.*, 2006; for a review see Lafenêtre *et al.*, 2007).

In summary, it seems likely that extinction learning can engage multiple associative and non-associative mechanisms, with the relative contribution of these mechanisms determined by several factors. The next sections discuss two recently identified, dominant factors governing the selection of extinction mechanisms.

Timing-dependence of fear extinction

Recently, the temporal relationship between fear learning, fear retrieval and extinction has attracted considerable attention as a potential determinant of the mechanisms that are engaged during extinction. Findings from these studies may have important clinical implications as they would allow the identification of time windows in which psychological interventions could promote long-lasting extinction of stressful or traumatic events by triggering erasure-like mechanisms.

Rescorla (2004) was one of the first to investigate the influence of the time interval between acquisition and extinction in an appetitive Pavlovian conditioning paradigm in animals. He reported that the strength of spontaneous recovery was inversely correlated with the delay between acquisition and extinction, short delays leading to maximal spontaneous recovery of conditioned responses (Rescorla, 2004). In striking contrast, Myers *et al.* (2006) using the fear-potentiated startle paradigm (FPS) reported that fear extinction initiated 10 min after acquisition leads to memory erasure, as suggested by the lack of spontaneous recovery, renewal and reinstatement of conditioned fear responses. These read-outs were still partially impaired when extinction was initiated 1 h but not 72 h after acquisition (Myers *et al.*, 2006). However, several groups have failed to reproduce these findings albeit under slightly different experimental conditions. For instance, Schiller *et al.* (2008) used conditioned freezing as a read-out in a Pavlovian auditory fear conditioning paradigm with a 12- to 15-min delay between fear acquisition and extinction and found no evidence for weaker spontaneous fear recovery after immediate extinction. This indicates that immediate extinction training after classical fear conditioning may not engage erasure mechanisms. The same conclusion was reached in a recent study using an aversive conditioning paradigm in which suppression of an operant behaviour served as an index of fear (Woods & Bouton, 2008). Maren & Chang (2006) reported that immediate extinction of an auditory CS in a classical fear conditioning paradigm yields poor long-term fear extinction, but rather induces a transient and context-independent suppression of conditioned freezing responses. When the same animals were tested again 48 h later the conditioned freezing responses recovered (Maren & Chang, 2006; Chang & Maren, 2009). The authors concluded that immediate extinction might recruit a context-independent habituation-like mechanism. Human studies using fear measures such as skin-conductance responses or startle amplitude (LaBar & Phelps, 2005; Milad *et al.*, 2005; Alvarez *et al.*, 2007; Schiller *et al.*, 2008) are also mostly inconsistent with the notion that early extinction engages unlearning mechanisms, the only exception being a recent study using the FPS paradigm which showed that immediate extinction is associated with less spontaneous recovery compared with delayed extinction in a discriminative fear conditioning paradigm (Norrholm *et al.*, 2008). Although reasons for discrepancies in these studies are not clear, they

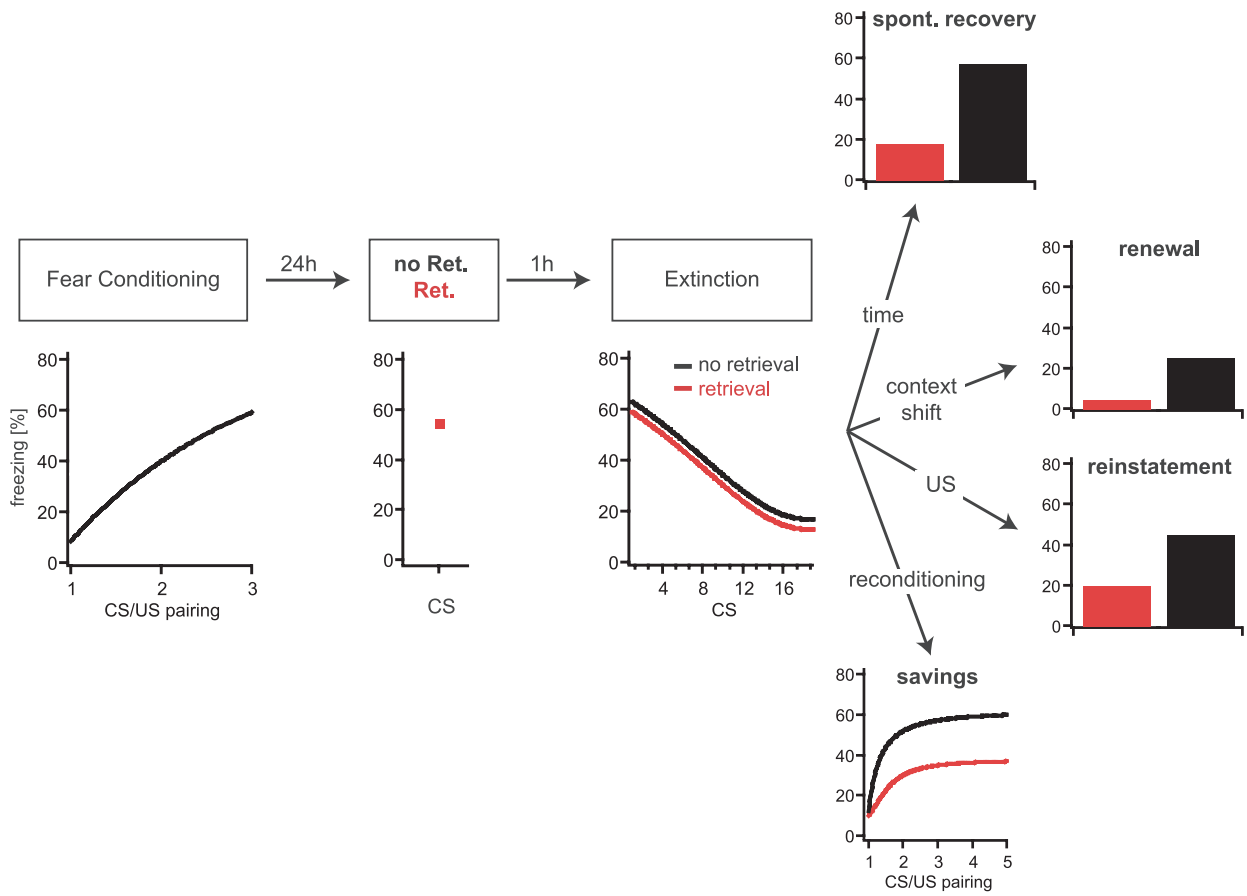

FIG. 1. Extinction initiated during reconsolidation permanently attenuates fear memory. On day 1, rats were fear conditioned using three tone/shock pairings. On day 2, rats were either subjected to a single fear memory retrieval (Ret.) session followed after 1 h by extinction (red), or to extinction in the absence of previous retrieval (black). The acquisition of fear extinction was indistinguishable between the two groups (lines offset for clarity). However, four tests suggest that while fear memory was actively being suppressed in the group without retrieval, the animals with retrieval were biased towards fear memory erasure. Spontaneous recovery was assessed 1 month after extinction. For renewal, extinction was performed in a second context and animals were then exposed to the CS in the original fear conditioning context. Reinstatement was performed employing five unsignalled foot-shocks. Finally, fear memory savings were tested by performing a second fear conditioning session. Adapted from Monfils *et al.* (2009). Reprinted with permission of the American Association for the Advancement of Science.

may involve differences in subjects and behavioural paradigms. Overall, it appears that the time at which extinction is initiated after fear conditioning is not a reliable factor determining the selection of extinction mechanisms.

Another important factor for selective engagement of learning vs. unlearning mechanisms during extinction might be the time at which extinction training is initiated after fear reactivation. Once reactivated, consolidated fear memory undergoes a labile phase during which it is sensitive to disruption by protein synthesis inhibitors, a process known as memory reconsolidation (Nader *et al.*, 2000; Sara, 2000). Reconsolidation and extinction processes are similar in that they are initiated upon non-reinforced presentations of the conditioned stimulus and they are CS-specific (Richards & Sargent, 1983; Kasprow *et al.*, 1984; Debiec *et al.*, 2006). The finding that post-reactivation injection of protein synthesis inhibitors is associated with low fear level expression on subsequent tests has been suggested to reflect an enhancement of extinction learning rather than a blockade of reconsolidation process (Myers & Davis, 2002; Fischer *et al.*, 2004). However, this view has been challenged by the observation that post-reactivation injection of protein synthesis inhibitors also prevents spontaneous recovery, renewal or reinstatement of conditioned fear responses, three phenomena that should occur if fear extinction has been enhanced (Duvarci & Nader, 2004; Duvarci *et al.*, 2006). Rather, these results suggest that fear memory has been erased upon reconsolidation blockade and that reconsolidation and extinction are two distinct, experimentally dissociable processes (Eisenberg *et al.*, 2003; Duvarci & Nader, 2004). In a recent study, Monfils *et al.* (2009) thoroughly investigated the relationship between reconsolidation and extinction processes by initiating extinction at different time points after fear memory reactivation (Fig. 1). The authors demonstrated that extinction training initiated during the time window of the reconsolidation process (10 min or 1 h after reactivation) was associated with a lack of spontaneous recovery, renewal or reinstatement of conditioned fear responses. In addition, reacquisition of fear memory upon reconditioning was retarded. When the extinction training was performed outside of the reconsolidation time window (6 h after reactivation), it was associated with recovery of fear in the same four tests. These results are consistent with the view of reconsolidation as an adaptive update mechanism enabling the incorporation of new information into the reactivated memory (Sara, 2000), and strongly support the idea that fear extinction may rely on distinct mechanisms depending on when the extinction training is initiated after fear reactivation. Extinction initiated at the time of fear memory reconsolidation will destabilize the original fear memory trace and recruit erasure-like mechanisms. In contrast, extinction initiated outside this narrow time window leads to the formation of a long-lasting new inhibitory

memory that competes with the original memory trace without destroying it.

Developmental regulation of extinction mechanisms

Another factor that determines which mechanism becomes engaged during extinction is the developmental stage of the animal at the time of behavioural testing. Fear extinction is generally context-dependent in the adult (Bouton, 2004). In contrast, pre-weaning rats do not display contextual fear conditioning (Rudy, 1993; Rudy & Morledge, 1994; Pugh & Rudy, 1996). Therefore, it has been suggested that extinction in juvenile rats may rely on mechanisms distinct from those engaged in adulthood. This hypothesis was first tested in the appetitive domain by Carew & Rudy (1991) who reported a lack of renewal of conditioned responses after extinction in 17-day-old compared with 20-day-old rats. This finding was replicated in the aversive domain by Richardson and colleagues who used auditory and olfactory fear conditioning to show that juvenile 16- to 17-day-old rats do not exhibit spontaneous recovery, renewal or reinstatement of conditioned fear responses after extinction (Kim & Richardson, 2007a,b; Yap & Richardson, 2007). These findings strongly support the view of a developmental switch in extinction mechanisms. During early postnatal development, extinction appears to be permanent and has been suggested to reflect an unlearning process leading to the erasure of conditioned fear memories (Kim & Richardson, 2008). Currently, the neuronal mechanisms underlying the developmental regulation of fear extinction are still poorly understood. Further investigations (see below) could be important to devise novel and specific therapeutic interventions for anxiety and related disorders in children.

Neuronal substrates and plasticity mechanisms underlying fear extinction

This section discusses recent findings extending our knowledge on the neuronal substrates and molecular mechanisms underlying fear extinction in adulthood and in juveniles. For clarity, this part is divided into separate sections covering the neuronal substrates and plasticity mechanisms of acquisition, consolidation and expression, and contextual modulation of fear extinction.

Acquisition of fear extinction

Synaptic signalling and plasticity in the BLA

Over the past decade evidence has accumulated pointing to a critical role of the basolateral amygdala (BLA) in the acquisition phase of extinction. The BLA is composed of several anatomically and functionally distinct nuclei, including the lateral (LA) and basal (BA) nuclei. The LA is known to be a critical site of synaptic plasticity and *N*-methyl-D-aspartate (NMDA) receptor-dependent long-term-potentiation (LTP) during fear learning (Davis, 2000; LeDoux, 2000; Maren, 2001; Maren & Quirk, 2004). However, because of technical difficulties in restricting the local application of drugs to BLA subnuclei, for most of the studies discussed below no claim can be made on the specific contribution of LA and BA. The first study indicating that cellular and synaptic plasticity in the BLA is also implicated in acquisition of extinction was conducted by Falls *et al.* (1992), who demonstrated that intra-BLA injection of the NMDA receptor (NMDAR) antagonist AP5 prevents fear extinction as assessed using the FPS paradigm. Conversely, intra-BLA infusion of the NMDAR partial agonist D-cycloserine facilitates fear extinction (Mao *et al.*, 2006). Using the same paradigm, ERK/MAPK inhibitors injected directly into the BLA also prevent fear extinction (Lu *et al.*, 2001; Lin *et al.*, 2003). However, a major caveat of these studies is the methodological limitation in the FPS paradigm that does not easily allow for discriminating between the acquisition and consolidation phases of extinction. Recent studies, using intra-BLA infusions of glutamate receptor antagonists (including NMDA and mGlu1 receptor antagonists) and ERK/MAPK inhibitors, have unambiguously demonstrated an impairment of extinction acquisition in classical auditory fear conditioning (Herry *et al.*, 2006; Kim *et al.*, 2007; Sotres-Bayon *et al.*, 2007). It is possible that NMDARs might not exclusively be engaged in synaptic plasticity, but could also mediate regular synaptic transmission, for example in GABAergic interneurons (Szinyei *et al.*, 2003), contributing to spatio-temporal dynamics of amygdala network activity. Nevertheless, taken together, these studies strongly suggest that glutamatergic synaptic plasticity in the amygdala is a key component mediating extinction learning.

To date, the pathways and cell types exhibiting NMDAR-dependent synaptic plasticity during extinction acquisition have not been identified. One possibility is that NMDAR-dependent synaptic plasticity occurs at glutamatergic inputs onto local BLA GABAergic interneurons or onto neurons within the intercalated cell masses (ITCs), which are mostly GABAergic and surround the BLA (for a review see Ehrlich *et al.*, 2009). Indeed, NMDAR-dependent LTP has been observed at glutamatergic inputs onto LA (Mahanty & Sah, 1998; Bauer & LeDoux, 2004) and BA (Mahanty & Sah, 1998) interneurons, and at LA and BA afferents onto medial paracapsular ITCs (Royer & Paré, 2002, 2003). However, the relevance of NMDAR-dependent LTP in amygdala inhibitory circuits remains to be determined.

Although additional studies are required for understanding the role of specific amygdala GABAergic circuits in extinction acquisition, there is compelling evidence that enhanced inhibition contributes to the expression of extinction (see below). In addition to plasticity of inhibitory circuits, extinction acquisition might involve plasticity at glutamatergic synaptic inputs onto subpopulations of principal neurons (see below). Finally, consistent with the fact that extinction acquisition is strongly regulated by various neuromodulatory, neuropeptidergic and neuroendocrine systems (for a review see Myers & Davis, 2007), neuromodulation has been shown to regulate amygdala inhibitory circuits at different levels, and to gate activity-dependent plasticity of glutamatergic synaptic transmission (e.g. Shumyatsky *et al.*, 2002; Bissière *et al.*, 2003; Shaban *et al.*, 2006; Tully *et al.*, 2007; Jüngling *et al.*, 2008).

Encoding of prediction errors in the vlPAG

During the acquisition of conditioned fear, the dependence of NMDAR-mediated LTP on coincident synaptic input from sensory afferents and postsynaptic depolarization is a good cellular model accounting for coding of CS–US contiguity (for a review see Sah *et al.*, 2008). For extinction acquisition, the mechanisms of plasticity underlying learning about the absence of the US are still unclear. Reinforcement learning theories posit that at the beginning of extinction acquisition, when the animal predicts the occurrence of the US when presented with the CS, a so-called prediction error signal is generated when the US does not occur (Rescorla & Wagner, 1972). Associative learning then occurs as a product of learning rate and the discrepancies (the prediction error) between the expected (the prediction) and obtained outcomes (Rescorla & Wagner, 1972). Prediction error signalling by dopaminergic neurons in the ventral tegmental area is well established in the appetitive domain (for a review see Schultz, 2006). In classical fear conditioning, there is compelling evidence that a similar role might be performed by

mu-opioid receptors (MORs) in the ventro-lateral periaquaeductal gray (vlPAG; McNally & Westbrook, 2006). The vlPAG is rich in opioid receptors and systemic or intra-vlPAG injection of the non-selective opioid receptor antagonist naloxone or the selective MOR antagonist CTAP dose-dependently impairs the acquisition of fear extinction (McNally & Westbrook, 2003; McNally *et al.*, 2004, 2005). Conversely, inhibiting enzymatic degradation of the endogenous opioids accelerates extinction acquisition (McNally, 2005). Based on additional evidence obtained from related learning paradigms involving prediction error signalling, such as Kamin blocking (Kamin, 1968; McNally *et al.*, 2004; Cole & McNally, 2007) and overexpectation (McNally *et al.*, 2004), it has been proposed that vlPAG MORs signal the predicted US, and that the mismatch between this MOR signal and the absence of the US at the onset of extinction training would be necessary to drive the acquisition of extinction (for a review see McNally & Westbrook, 2006). It is intriguing to postulate that while vlPAG MORs encode the prediction error, NMDARs in the BLA are crucial for determining learning rate in fear conditioning (Cole & McNally, 2007, 2008). In the future, it will be of particular interest to use electrophysiological approaches to investigate how MOR-dependent signalling in vlPAG generates a prediction error signal, and how such a signal interacts with synaptic plasticity in the BLA during the acquisition of extinction.

A critical role of the BA

An important step towards understanding the role of the BLA in extinction acquisition is the identification of the subnuclei, circuits and neurons involved. Recent studies using immediate early gene (IEG) analysis, classical lesion approaches or more sophisticated local reversible inactivation have refined the role of distinct amygdala subnuclei during acquisition of extinction. Although NMDAR signalling in the LA may participate in acquisition of extinction (Sotres-Bayon *et al.*, 2007), these studies strongly suggest a critical role for activity in the BA also. It has been shown for instance that extinction training leads to the induction of the IEG *c-fos* in the BA (Herry & Mons, 2004). Conversely, in animal models showing impaired extinction learning *c-fos* induction in the BA is strongly compromised (Muigg *et al.*, 2008; see below). However, pre-training (before fear conditioning) electrical lesions restricted to the BA have no effect on subsequent fear extinction (Sotres-Bayon *et al.*, 2004; Anglada-Figueroa & Quirk, 2005). There are two possible interpretations of these results: either the BA is not necessary for acquisition of extinction, or compensatory mechanisms masked the role of the BA during extinction. Nevertheless, the fact that BA-lesioned animals can still acquire fear extinction suggests that additional structures are implicated. Post-training lesions of the BA have also been conducted, but the fact that this manipulation alters fear expression prevents a firm conclusion about the role of the BA during extinction learning (Anglada-Figueroa & Quirk, 2005). Finally, studies using local reversible inactivation with the $GABA_A$ receptor agonist muscimol have demonstrated that whereas inactivation of the entire amygdala has no effect on extinction learning (Akirav *et al.*, 2006; but see Hart *et al.*, 2009), inactivation restricted to the BA completely blocks acquisition of extinction (Herry *et al.*, 2008). Importantly, memory retrieval and expression were not affected in the latter study, indicating that the BA is required for extinction learning, but not for the storage of extinction memories (Herry *et al.*, 2008).

Which neuronal populations participate in extinction learning, and their properties and functions is still a matter of debate and investigation. First indications came from *in vivo* single unit recordings that established that both the LA and the BA contain distinct cell populations whose activity correlates with high fear levels following auditory fear conditioning (Quirk *et al.*, 1995, 1997; Paré & Collins, 2000; Repa *et al.*, 2001; Goosens *et al.*, 2003; Herry *et al.*, 2008). In particular, one subpopulation of neurons displayed persistent activity throughout extinction learning whereas another showed a decline in conditioned responses upon non-reinforced presentation of the CS (Repa *et al.*, 2001; Herry *et al.*, 2008). It has been suggested that these subpopulations might underlie the encoding and the maintenance of the CS–US association, respectively (Repa *et al.*, 2001). Alternatively, the rapid reversal of neuronal conditioned fear responses during extinction may reflect an erasure of the original CS–US association. The cellular mechanism underlying this erasure could reflect depotentiation of sensory afferent synapses onto LA principal neurons previously potentiated during fear conditioning (Mao *et al.*, 2006; Kim *et al.*, 2007). However, given that fear extinction does not lead to the erasure of the original fear memory under most circumstances, the role of synaptic depotentiation in extinction acquisition remains debatable.

We recently identified a novel cell population specific to the BA which becomes CS-responsive during extinction acquisition ('extinction neurons') (Herry *et al.*, 2008). In concert with another population of BA neurons whose activity correlates with a high fear state ('fear neurons'), activity-switching in these BA circuits is essential for rapid switching between behavioural states (Fig. 2). Extinction neurons may trigger a low fear state by exerting instructive effects on extinction memory consolidation in the medial prefrontal cortex (mPFC; see below). Notably, both 'fear neurons' and 'extinction neurons' project to the mPFC (Herry *et al.*, 2008), suggesting that there could be distinct fear- and extinction-pathways connecting the BA to the mPFC. These distinct neuronal circuits may modulate the transition between high and low fear states by tipping the balance of activity between specific prefrontal circuits as recently suggested (Burgos-Robles *et al.*, 2009). Consistent with the idea of discrete sub-networks of projection neurons interconnecting brain areas involved in extinction, we found that inputs from the mPFC and the hippocampus were differentially targeting 'extinction neurons' and 'fear neurons', respectively (Fig. 2). In addition to specific long-range interactions, extinction neurons could also interact locally with other principal cells or interneurons within the BLA, the central nuclei and/or the ITCs, to reduce fear responses during extinction acquisition and/or to trigger plasticity mediating extinction memory consolidation.

Consolidation and expression of fear extinction

Similar to other forms of learning, acquisition of extinction is followed by a consolidation phase, which lasts several hours and is required to stabilize plastic events into a long-term memory (McGaugh, 2000). As outlined above, extinction learning appears to be mediated by a distributed network of brain areas centred around activity in the BA, while consolidation recruits other circuits and brain areas. The first area found to be implicated in expression of extinction is the mPFC (Morgan *et al.*, 1993). Subsequent studies demonstrated that lesions or inactivation of a subregion of the mPFC, the infralimbic cortex (IL) block retrieval of extinction, but not acquisition (Quirk *et al.*, 2000; Laurent & Westbrook, 2009; for a review see Quirk & Mueller, 2008). In addition, immediate post-training infusions of an NMDAR antagonist (Burgos-Robles *et al.*, 2007) or a MAPK inhibitor (Hugues *et al.*, 2004) impaired the retrieval of extinction. On the physiological level, these findings concur with the fact that a subpopulation of IL neurons shows CS-evoked responses during extinction retrieval, but not during acquisition (Milad & Quirk, 2002), and that neuronal

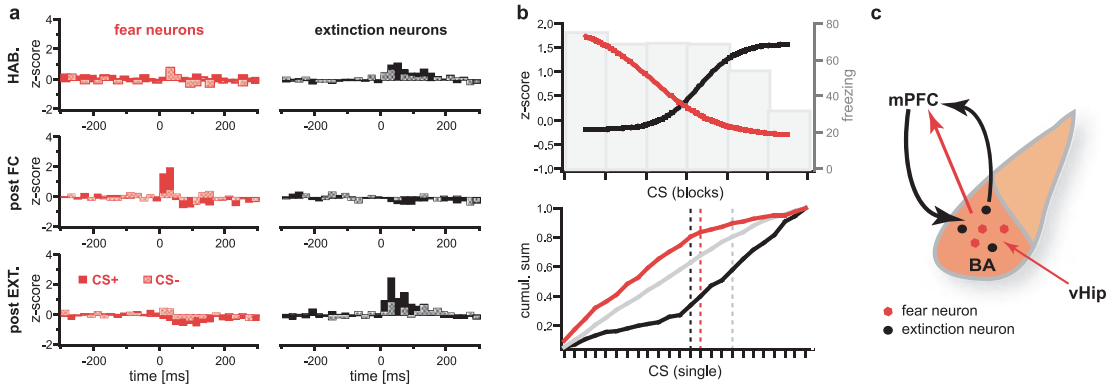

FIG. 2. Distinct subpopulations of BA neurons encode fear and extinction. (a) Fear neurons (red) exhibit a selective increase in CS^+-evoked activity after fear conditioning, which fully reverses after extinction. In contrast, extinction neurons (black) develop CS^+ responses only during extinction. (b) During extinction training, the switch in neuronal activity precedes the behavioural change. Top: activity of fear and extinction neurons (red and black lines) superimposed on freezing behaviour (grey bars). A significant reduction of freezing occurred after the activity scores of the two populations crossed over. Bottom: change-point analysis reveals that the activity of extinction neurons increases one trial before the decrease in fear neuron firing, which is followed by behavioural modification (change-points indicated by dotted lines). (c) Fear and extinction neurons are differentially connected with other brain regions. Fear neurons receive weak input from the ventral hippocampus, and project strongly to the medial prefrontal cortex. In contrast, extinction neurons display strong, bi-directional connectivity selectively with the mPFC. Size of arrows indicates approximate connection strength. Adapted, with permission, from Herry *et al.* (2008).

plasticity in the IL is correlated with behavioural expression of extinction memory (Herry & Garcia, 2002, 2003; Milad & Quirk, 2002). Moreover, micro-stimulation of the IL, but not of the adjacent prelimbic cortex (PL), results in the formation of a stronger extinction memory (Vidal-Gonzalez *et al.*, 2006), further supporting a causal relationship between IL activity and the formation of a long-term extinction memory. Together, these findings strongly implicate the IL in the consolidation and subsequent retrieval of extinction memory, whereas this area does not appear to be involved in the initial acquisition of extinction.

It is thought that the IL inhibits fear expression mainly through its projections to the amygdala, although the details of IL–amygdala interactions are still debated. Support for this model comes from findings that activation of the IL results in inhibition of the medial division of the central amygdala (CEm; Quirk *et al.*, 2003). The CEm is the main output nucleus of the amygdala sending direct projections to brain structures controlling conditioned fear responses, including the ventromedial and lateral hypothalamus and the PAG (Hopkins & Holstege, 1978; Veening *et al.*, 1984; Cassell *et al.*, 1986). Although stimulation of the IL produces inhibition of the CEm (Quirk *et al.*, 2003), this nucleus receives only sparse projections from the IL (McDonald *et al.*, 1996), suggesting that this inhibitory influence is indirect. There is compelling evidence that ITCs, a heterogeneous population of scattered neuronal clusters of inhibitory GABAergic neurons surrounding the BLA (Millhouse, 1986), are a key component of this inhibitory circuit (Paré *et al.*, 2004). The IL sends a robust projection to the medial paracapsular ITCs (mpITCs), which are interspersed between BLA and central nucleus of the amygdala (CEA) (McDonald *et al.*, 1996; Vertes, 2004). These in turn can project to the CEm (Paré & Smith, 1993; Geracitano *et al.*, 2007). Pharmacological disinhibition of the IL induces a large increase in the number of *c-fos*-positive mpITC neurons (Berretta *et al.*, 2005) indicating that their activity can be driven by inputs from the IL. Importantly, Likhtik *et al.* (2008) recently demonstrated that specific ablation of mpITCs after extinction acquisition results in the spontaneous recovery of fear responses. Although this finding provides unambiguous evidence for a role of mpITCs in the expression of extinction, some major questions remain. In particular, it is unclear whether ITCs are simply driven by increased input from IL, or whether activity-dependent plasticity at the level of synaptic inputs to or from ITC neurons is also necessary for the consolidation and expression of fear extinction. Consistent with the latter scenario, BLA inputs to mpITC neurons exhibit NMDAR-dependent bidirectional plasticity (Royer & Paré, 2002, 2003). Such LTP of BLA inputs to ITC neurons could strengthen inhibition of CEm relative to excitation by direct LA inputs. Furthermore, ITCs may integrate different excitatory inputs from the thalamus, BLA and IL to set the level of inhibition onto the CEm during acquisition, expression or retrieval of extinction. Other open questions are raised by recent findings of an unexpected correlation between the lack of behavioural extinction and the activation patterns of distinct ITC subpopulations, as assessed by IEG analysis (Hefner *et al.*, 2008), and the considerable heterogeneity in axonal projection patterns and short-term synaptic plasticity of mpITC neurons (Geracitano *et al.*, 2007). Taken together, these findings support the hypothesis of a topographically organized inhibition amongst ITC neurons (Royer *et al.*, 2000; Paré *et al.*, 2004) and the presence of distinct networks involving different ITC clusters with diverse effects on CEA activity.

In addition to ITCs, local inhibitory circuits within the BLA have been implicated in the expression of fear extinction. This could entail enhanced recruitment of BLA interneurons by afferents from the mPFC (Rosenkranz *et al.*, 2003). However, although IL sends robust projections to the magnocellular subdivision of the BA (Sesack *et al.*, 1989; McDonald *et al.*, 1996), this connectivity appears to be mainly with pyramidal neurons (Likhtik *et al.*, 2005), and the BA does not appear to be necessary for the expression of fear extinction (Angladа-Figueroa & Quirk, 2005; Herry *et al.*, 2008). It is possible, that mPFC afferents to the LA might be directly or indirectly involved in the context-dependent inhibition of CS-evoked activity exhibited by a subpopulation of LA principal neurons (Repa *et al.*, 2001; Hobin *et al.*, 2003; Maren & Hobin, 2007; Herry *et al.*, 2008).

Converging evidence suggests that extinction learning may result in the strengthening of GABAergic synaptic transmission in the BLA. For instance, fear extinction is associated with increased benzodiazepine receptor binding and upregulation of mRNA levels for gephyrin, a structural protein at GABAergic synapses, and for the $GABA_A$ receptor subunits $\alpha 2$ and $\beta 2$, within several hours following extinction learning (Chhatwal *et al.*, 2005; Heldt & Ressler, 2007). Consistent with the notion that extinction is associated with postsynaptic changes in $GABA_A$ receptor trafficking, Lin *et al.* (2009) recently reported that the amplitude of GABAergic miniature inhibitory postsynaptic

currents (mIPSCs) recorded from LA principal neurons was increased after extinction of FPS. The increase in mIPSC amplitude and extinction of FPS were blocked by disruption of the interaction between $GABA_A$ receptors and the associated protein GABARAP, which has been implicated in $GABA_A$ receptor trafficking (for a review see Jacob *et al.*, 2008). Moreover, extinction-associated changes in the expression of the GABA-synthesizing enzyme GAD67 and in the GABA uptake transporter GAT-1 have been reported (Heldt & Ressler, 2007). Thus, extinction might lead to concerted pre- and postsynaptic changes at GABAergic synapses in the BLA. However, given that extinction is highly CS- and context-dependent, it seems unlikely that it should be associated with global changes in GABAergic drive. Indeed, the BLA contains several functionally distinct subtypes of GABAergic interneurons (McDonald, 1982; Rainnie *et al.*, 1993; for a review see Ehrlich *et al.*, 2009). Future studies will have to determine whether extinction affects specific inhibitory circuits that could inhibit BLA principal neurons, or subsets thereof, at distinct levels.

Finally, although the mPFC may inhibit the expression of conditioned fear through its control over the ITCs and/or the BLA, this could also be accomplished through alternative routes involving, for example, direct projections to the lateral capsular subdivision of the CEA (McDonald, 1998) or to the hypothalamus and the brain stem (Fisk & Wyss, 2000; Floyd *et al.*, 2000). Future studies should be designed to test the validity of these different circuit models as well as to determine the integration of different components mediating consolidation of fear extinction.

Contextual modulation of fear extinction

Fear extinction is strongly modulated by contextual elements (Bouton, 2002, 2004). Given the involvement of the hippocampus in the formation of contextual representations (Kim & Fanselow, 1992; Phillips & LeDoux, 1992), numerous studies have thoroughly investigated its role in the contextual modulation of fear extinction (for reviews see Bouton *et al.*, 2006; Ji & Maren, 2007). The main questions addressed so far relate to participation of the hippocampus in encoding the context-specificity of extinction, and its role in the context-dependent retrieval of fear after extinction.

Context specificity coding was evaluated by Corcoran *et al.* (2005) using acute pre-extinction inactivation of the dorsal hippocampus with muscimol. Whereas extinction acquisition was delayed, rats were unable to express fear extinction when tested the next day in the same or in a different context. This effect has been suggested to reflect an involvement of the hippocampus in the contextual encoding and context-dependent retrieval of the extinction memory, but not in the encoding of extinction *per se* (Corcoran *et al.*, 2005). These findings are consistent with human functional magnetic resonance imaging data showing that retrieval of extinction memory was associated with an activation of the hippocampus in concert with the ventral mPFC (Kalisch *et al.*, 2006; Milad *et al.*, 2007).

Additionally, the hippocampus has a critical role in the context-dependent renewal of extinguished fear memories. Acute pharmacological inactivation by local injection of muscimol into the dorsal or ventral hippocampus prior to testing completely prevented context-dependent renewal of conditioned fear when tested in a novel context (Corcoran & Maren, 2001; Hobin *et al.*, 2006), but not in the fear conditioning context (Corcoran & Maren, 2004). In contrast, pre-conditioning electrolytic lesions of the dorsal hippocampus also interfered with fear renewal in the conditioning context (Ji & Maren, 2005). This indicates that the type of manipulation (lesion vs. inactivation) or the timing of the manipulation (pre-conditioning vs. pre-test) play a critical role. Using single unit recordings in the LA, Hobin *et al.* (2003) demonstrated that renewal of conditioned fear responses was associated with an increase in CS-evoked neuronal activity. These renewal-associated neuronal responses were abolished by inactivation of the dorsal hippocampus (Maren & Hobin, 2007).

Furthermore, several human studies also support a role of the hippocampus in context-dependent retrieval of fear after extinction. For example, recovery of conditioned fear responses after extinction is context- and CS-specific (LaBar & Phelps, 2005; Schiller *et al.*, 2008), and patients with selective bilateral atrophy of the hippocampus do not exhibit context-dependent recovery of fear responses following reinstatement (LaBar & Phelps, 2005). Collectively, these findings suggest an important role for the hippocampus in controlling the context-dependency of extinguished fear responses in both humans and animals. Interestingly, acute pre-testing inactivation of the hippocampus does not abolish extinction, but rather renders extinction behaviour context-independent and impairs context-dependent renewal of conditioned fear responses. Accordingly, it has been proposed that the contextualization of previously acquired fear memories upon extinction training might reflect a more general principle governing the interaction between different memories in the sense that memories become contextualized by a second learning episode (Harris *et al.*, 2000; Bouton, 2004).

What might be the neuronal circuitry by which the hippocampus triggers the context-dependent renewal of conditioned fear responses? One possibility is that the hippocampus regulates neuronal activity in the amygdala indirectly via its strong projections to the mPFC (Hoover & Vertes, 2007). Indeed, renewal of conditioned fear responses is associated with opposite changes in *c-fos* expression in IL and PL (Knapska & Maren, 2009). Alternatively, or in addition, the hippocampus might exert contextual control of conditioned fear behaviour through direct projections to the amygdala. Consistent with this scenario, we recently found that BA neurons exhibiting context-dependent renewal of neuronal conditioned responses (i.e. 'fear neurons'), but not BA 'extinction neurons', receive strong hippocampal inputs (Herry *et al.*, 2008). Moreover, hippocampal inputs to the BA have been shown to exhibit NMDAR-dependent LTP (Maren & Fanselow, 1995). Thus, these data strongly suggest that hippocampal inputs onto specific subpopulations of BLA neurons contribute to the context-dependent renewal of conditioned fear responses.

Mechanisms of extinction in juveniles

As mentioned earlier, fear extinction is developmentally regulated and results in the formation of a permanent extinction memory in juvenile rats and mice younger than about 3 weeks. In contrast to adult animals, extinguished fear responses do not exhibit spontaneous recovery, context-dependent renewal or reinstatement (Kim & Richardson, 2007a,b; Yap & Richardson, 2007; Gogolla *et al.*, 2009), strongly suggesting that extinction training leads to unlearning or erasure of the conditioned fear response. Mechanistically, extinction in juveniles seems to be based on mechanisms and circuits which overlap with the adult, but which also display distinct features. As in adults, extinction in juveniles is an active process requiring an intact BLA (Kim & Richardson, 2008) and depends on NMDAR and MOR activation (Langton *et al.*, 2007; Kim & Richardson, 2009). However, extinction in juveniles is mPFC-independent (Kim *et al.*, 2009), and is insensitive to pharmacological treatments that reduce the efficiency of GABAergic transmission (Kim & Richardson, 2007b). This suggests that extinction in juveniles might involve distinct plasticity mechanisms in different BLA micro-circuits. In particular, the role of inhibitory circuits appears to be developmentally regulated.

This is very reminiscent of the developmental regulation of neuronal circuit plasticity in visual cortex. There, the development of inhibitory circuits containing parvalbumin-positive interneurons marks the opening and closure of critical periods, during which environmental manipulations, such as eye closure, can have profound effects on circuit organization and function (for a review see Hensch, 2005). Recently, we found in analogy to visual cortex that the formation of perineuronal nets (PNNs), an organized form of extracellular matrix around parvalbumin-positive interneurons (Berardi *et al.*, 2003; Hensch, 2005), coincides with the switch of extinction mechanisms to the adult phenotype (Gogolla *et al.*, 2009). Interestingly, enzymatic degradation of PNNs in the BLA of adult animals re-enabled the erasure of conditioned fear memories by extinction training, but only if PNNs were degraded before fear conditioning (Gogolla *et al.*, 2009). Thus, in adults, PNNs appear to actively protect conditioned fear memories from extinction-induced erasure, allowing extinction memories to coexist with previously acquired fear memories, both of which can be retrieved in a context-dependent manner. In juveniles, contextualization cannot occur because extinction induces the erasure of fear memories. Consistent with the proposed role of the mPFC and the hippocampus in the contextualization of extinction memories (Hobin *et al.*, 2003, 2006), connections between the BLA and these brain areas continue to develop up to several months after birth (Bouwmeester *et al.*, 2002; Cunningham *et al.*, 2002). Thus, the developmental regulation of amygdala circuit function underlying extinction-induced memory erasure enables juvenile animals to adhere to the most recently learned information, a strategy that might increase chances of survival.

Animal models of impaired extinction: evidence for extinction circuitry dysfunction

Impaired extinction of fear memories is thought to contribute to the development and persistence of anxiety disorders including phobias, PTSD and panic (e.g. Rosen & Schulkin, 1998; Lissek *et al.*, 2005; Anderson & Insel, 2006; Mineka & Zinbarg, 2006; Rauch *et al.*, 2006; Milad *et al.*, 2008). Currently, a substantial proportion of anxiety patients do not respond effectively to standard treatments to inhibit pathological fear responses, including extinction-based cognitive behavioural therapy and pharmacotherapy (Pull, 2007). For the development of novel therapeutic strategies to promote fear extinction processes selectively, a better understanding of mechanisms underlying pathologically impaired fear extinction is necessary. Animal models mimicking impaired fear extinction could provide this insight and open avenues for therapeutic strategies applicable to human pathology (Yehuda *et al.*, 2006). There is considerable genetic as well as environmental (e.g. psychological trauma, stress) contribution to individual variability in the risk for anxiety disorders (True *et al.*, 1993; Kendler, 2001; Yehuda & LeDoux, 2007), although the genes involved in resistance to extinction are not known. Interestingly, stress elicits structural changes in key areas implicated in extinction, such as the mPFC (Holmes & Wellman, 2009), amygdala (Vyas *et al.*, 2002; Roozendaal *et al.*, 2009) and hippocampus (Watanabe *et al.*, 1992). Both stress and genetic differences were exploited to generate rodent models displaying impaired extinction. Indeed, in these animal models, more persistent fear responses can be observed after exposure to different stressors (e.g. Izquierdo *et al.*, 2006; Miracle *et al.*, 2006; Mitra & Sapolsky, 2009; Yamamoto *et al.*, 2008; Baran *et al.*, 2009), in animals acutely selected according to their individual differences in extinction (Herry & Mons, 2004; Bush *et al.*, 2007), after selective breeding (Ponder *et al.*, 2007; Muigg *et al.*, 2008; Lopez-Aumatell *et al.*, 2009; see also Shumake *et al.*, 2005; Wrubel *et al.*, 2007) or in naturally occurring extinction-deficient mouse strains (Falls *et al.*, 1997; Stiedl *et al.*, 1999; McCaughran *et al.*, 2000; Waddell *et al.*, 2004; Hefner *et al.*, 2008; Camp *et al.*, 2009), and following different genetic manipulations (e.g. Marsicano *et al.*, 2002; Wellman *et al.*, 2007). Extinction deficits were apparent in some models during the acquisition and/or during retrieval of extinction and were seen in contextual and/or cued fear extinction.

Insight into the neuronal correlates of extinction failure in these models comes mainly from IEG mapping studies. It has been shown previously that the molecular events which underlie synaptic plasticity accompanying extinction learning and retrieval require activation of specific signalling cascades, including expression of IEGs (Morrow *et al.*, 1999; Nader *et al.*, 2000; Hall *et al.*, 2001). Of these IEGs, mainly *c-fos* (Kovacs, 1998; Hoffman & Lyo, 2002; Singewald, 2007) and *Zif268* (*Egr1*; Davis *et al.*, 2003; Lee *et al.*, 2004; Amin *et al.*, 2006; Jenkins *et al.*, 2006; Schulte *et al.*, 2006) have been used to label activated neurons in widespread regions of the brain, including cortical and amygdala regions.

From these studies, it is emerging that resistance to extinction is associated with distinct alterations in activation of IEGs in prefrontal-limbic circuits important in fear extinction. Specifically, hypoactivation of the IL is associated with extinction deficits. This was observed in 129S1 mice, a strain with pronounced deficits in fear extinction learning and retrieval (Hefner *et al.*, 2008; Camp *et al.*, 2009), and in acutely selected mice showing impaired extinction retrieval and re-extinction learning (Herry & Mons, 2004) (Table 1). Furthermore, HAB rats, a model of pathological anxiety (Landgraf *et al.*, 2007) with impaired extinction acquisition and retrieval (Muigg *et al.*, 2008), display a similar hypoactivation of the IL with a prolonged extinction learning session (Table 1), which may already involve extinction consolidation. In contrast, extinguishing control animals from all these studies showed robust activation in the IL (Herry & Mons, 2004; Muigg *et al.*, 2008; Hefner *et al.*, 2008; see also Knapska & Maren, 2009). These findings support the notion that activity of IL neurons is correlated with and necessary for extinction consolidation and expression, and suggest a common failure to appropriately activate IL neurons in animal models of impaired fear extinction. Furthermore, they show intriguing parallels between deficient activation of the IL in rodent models and of homologous brain regions in humans implicated in resistance to extinction in anxiety disorders including PTSD, panic and specific phobia (reviewed in Rauch *et al.*, 2006; Hofmann, 2007; Quirk & Mueller, 2008; see also Michael *et al.*, 2007; Milad *et al.*, 2008).

It has been suggested that PL activation is associated with a resistance to induce fear extinction learning (Gilmartin & McEchron, 2005; Vidal-Gonzalez *et al.*, 2006; Corcoran & Quirk, 2007). To date there is no evidence for enhanced PL activation in animal models displaying impaired extinction (Table 1). However, thus far IEG mapping has only been performed in response to multiple CS presentations during extinction training (Muigg *et al.*, 2008) or retrieval (Herry & Mons, 2004; Hefner *et al.*, 2008). This has the caveat that it may result in a ceiling effect in PL activation, obscuring subtle differences in the activation of neurons in this area. Indeed, preliminary results using only one CS presentation in extinction retrieval revealed enhanced PL activation in non-extinguishing 129S1 compared with extinguishing C57BL/6 mice (Whittle *et al.*, 2009). In keeping with the idea that fear extinction may require down-regulation of PL activity, in a recent study, Burgos-Robles *et al.* (2009) demonstrated that in rats exhibiting good extinction memory, CS-evoked activity in PL was low, whereas animals exhibiting poor extinction memory showed persistent CS-evoked activity in PL.

Another common observation is that resistance to extinction is associated with altered activation in specific amygdala regions. As

TABLE 1. Immediate early gene responses in animal models of impaired fear extinction

	HAB vs. LAB rats (Muigg *et al.*, 2008)	129S1 vs. C57BL/6 (Hefner *et al.*, 2008)	C57BL/6 mice individual differences (Herry & Mons, 2004)
Paradigm:	Auditory fear conditioning	Auditory fear conditioning	Auditory fear conditioning
Behavioural extinction deficits	Impaired extinction learning, higher fear in retrieval	No extinction learning, higher fear in retrieval	Higher fear in retrieval, impaired re-extinction learning
IEG staining following:	Extinction learning	Extinction retrieval (performed 24 h following extinction training)	Extinction retrieval (performed 7 days following 2nd extinction training)
IEG:	*c-fos*	*c-fos*, *Zif268*	*c-fos*, *Zif268*
mPFC			
PL	↔	↔↑*	↓
IL	↓	↓	↓
AMY			
LA	↓	↓	↓
BA	↓	↓	↓
ITC*	ND	↓	ND
mITC	ND	↑	ND
lITC	ND	↔	ND
CEm	↑	↑	ND

AMY, amygdala; BA, basal amygdala; CEm, medial division of central amygdala; IL, infralimbic cortex; lITC, lateral paracapsular intercalated cell mass; mITC, medial paracapsular intercalated cell mass; ITC, intercalated cell nucleus; LA, lateral amygdala; mPFC, medial prefrontal cortex; PL, prelimbic cortex; ↔, no change; ↑, enhanced immediate-early gene response; ↓, reduced immediate-early gene response; ND, not determined. *Preliminary result from Whittle *et al.* (2009).

discussed above, extinction acquisition in control animals is associated with increased levels of the IEG *c-fos* in the BA (Herry & Mons, 2004) and with the activation of distinct cell populations within LA and BA (Repa *et al.*, 2001; Herry *et al.*, 2008). In contrast, in animal models of impaired fear extinction, LA and BA appear to be hypoactivated, as assessed by *c-fos* and *Zif268* expression (Table 1). It remains to be shown whether the hypoactivation in the BA reflects attenuated recruitment of 'extinction neurons' identified in this area (Herry *et al.*, 2008). The other population of amydala neurons with an intruiging pattern of dysregulation are the ITCs. Quantification of the IEG *Zif268* in non-extinguishing 129S1 mice revealed a differential regulation of specific ITC clusters (Table 1). While the mpITCs become hyperactivated, there is no change in activation of the lateral paracapsular cluster, when compared with extinguishing C57BL/6 mice (Hefner *et al.*, 2008). In addition, preliminary results show a hypoactivation of the main ITC nucleus in extinction-deficient 129S1 mice (Whittle *et al.*, 2009). These findings suggest functional heterogeneity among the different ITC clusters (i.e. mpITC and main ITC) located along the internal capsule. It is possible that this differential activation pattern results from a topographically organized inhibition among clusters in the ventromedial direction (Royer *et al.*, 2000; Paré *et al.*, 2004). That differential activation of ITC clusters in the intermediate capsule may be relevant for extinction is consistent with the finding that their specific ablation results in extinction retrieval deficits (Likhtik *et al.*, 2008). Interestingly, within the CEA, hyperactivation has been observed particularly in the output station, the CEm, in animal models of impaired fear extinction (Hefner *et al.*, 2008; Muigg *et al.*, 2008). This is unlikely to be a result of only higher freezing levels (e.g. Frank *et al.*, 2006), as there is no difference in *c-fos* expression in CEA or BA when animals with different levels of conditioned freezing were compared without being subjected to extinction training (Skorzewska *et al.*, 2007). This suggests that differences in IEG expression between control and extinction-impaired animals reflect extinction-related plastic changes in neural circuits. Hyperactivity of CEA neurons in HAB rats has been shown to be attenuated after chronic treatment with selective serotonin re-uptake inhibitors (Muigg *et al.*, 2007), although whether this intervention facilitates fear extinction has not been studied. Enhanced CEA activation is congruent with observations in anxiety disorders including PTSD, social anxiety disorder and specific phobia showing amygdala hyper-responsivity (Rauch *et al.*, 2003; Etkin & Wager, 2007), which is reversed by successful therapeutic intervention (e.g. Goossens *et al.*, 2007; Schienle *et al.*, 2007).

Taken together, IEG mapping studies provide evidence that aberrant activation in specific neuronal populations of the mPFC–amygdala circuit is linked to deficits in extinction learning and/or retrieval. Importantly, main findings revealed in rodent models of impaired extinction (hypoactivation in the IL and hyperactivation in the CEA) are congruent with findings in imaging studies of patients suffering from anxiety disorders including PTSD (Milad *et al.*, 2006), underlining the high translational value of animal models in this field. The major advantage of animal IEG mapping studies is the much higher spatial resolution, which provides detailed information about extinction circuitries at the cellular level. In the future, it will be important to determine the dynamics and connectivity of neurons and circuits that show dysfunctional activation by electrophysiological and tracing studies in animal models of impaired extinction. Furthermore, molecular analyses including genomics, transcriptomics and proteomics (e.g. Yamamoto *et al.*, 2008) can be used to generate hypotheses about the molecular and genetic underpinnings of fear extinction failure. As a number of extinction-facilitating drugs including D-cycloserine and yohimbine have been identified (for a review Quirk & Mueller, 2008), an important next step will be to use these drugs to study long-term control of extinction in animal models and reveal the circuits, neurons and molecular pathways that are modulated. The information gained in such studies will hopefully reveal new targets and approaches for more efficient extinction-based therapies applicable to humans suffering from anxiety disorders.

Conclusions

Fear extinction is an adaptive form of learning allowing for inhibiting the expression of conditioned fear behaviour in response to altered environmental contingencies. Failure of extinction can lead to

excessive and inappropriate fear and anxiety behaviour as seen in certain forms of anxiety disorders such as PTSD. Accumulating evidence indicates that extinction involves new learning resulting in the formation of a long-term extinction memory. Phenomena such as spontaneous recovery, reinstatement and context-dependent fear renewal strongly argue for the notion that extinction does not lead to the destruction of a previously acquired fear memory, but that fear and extinction memories coexist with each other. Recent work reviewed here indicates that extinction memories are acquired, stored and retrieved within the same brain areas as fear memories albeit involving distinct neuronal circuits.

A general emerging concept is that the various phases of extinction learning involve close interactions between different brain areas including the brain stem (vlPAG), amygdala, distinct subdivisions of the mPFC and the hippocampus (Bouton *et al.*, 2006; Quirk & Mueller, 2008; Burgos-Robles *et al.*, 2009). There seems to be a temporal sequence by which these brain areas contribute to distinct phases of extinction. Whereas the vlPAG and the BLA play an important role during the initial acquisition phase, consolidation of extinction memory requires the IL, and possibly a down-regulation of PL activity. Expression of the extinction memory again depends on the amygdala, although on other cell types and circuits than those involved in the acquisition phase. Interactions between the different brain areas are mediated by specific neuronal subcircuits as illustrated by the opposite role of two distinct subpopulations of BA principal neurons in the acquisition of fear and extinction memory (Herry *et al.*, 2008), and by the specific role of the GABAergic ITCs in the expression of extinction (Likhtik *et al.*, 2008). Most probably, a similar degree of specificity also exists in other brain areas. Undoubtedly, addressing this question will be facilitated by state-of-the-art molecular genetic tools that allow for the functional and anatomical analysis of defined subpopulations of neurons and for specifically manipulating interactions between brain areas within large-scale networks in behaving animals (for reviews see Gradinaru *et al.*, 2007; Luo *et al.*, 2008).

A second major advance of recent work on fear extinction is the fact that the mechanisms underlying extinction strongly depend on the developmental state of the animal and on its recent experience. Whereas in adult animals, extinction training does not erase a previously acquired fear memory, but rather results in the context-dependent suppression of fear behaviour, in juvenile animals the same behavioural paradigm induces unlearning or erasure of the fear memory (Kim & Richardson, 2008). The mechanisms underlying extinction-induced fear memory erasure and its behavioural implications for juvenile animals are beginning to be elucidated (Kim & Richardson, 2007a; Langton *et al.*, 2007; Kim *et al.*, 2009). Importantly, these mechanisms remain dormant throughout life, because they can be re-activated in adults (Gogolla *et al.*, 2009), opening potential therapeutic avenues. Another successful approach in inducing unlearning or erasure of fear memories entails the precise timing of extinction training within a defined time period after exposing the animal to a CS reminder (Monfils *et al.*, 2009). It appears that the brief period during which fear memories become malleable during reconsolidation can be exploited to target and erase specific fear memories. Future studies are necessary to determine whether the basic principles that determine if fear memories are erased or merely suppressed in animals can be translated to humans.

Finally, we have discussed the potential of using genetic animal models to tackle the mechanisms underlying extinction failure. Genetic mouse models of impaired extinction offer the unique possibility to link functional and molecular studies to address the genetic bases of extinction, and extinction failure, at the level of defined neuronal circuits. Results from these models will provide invaluable information that can be compared and integrated with genomic and functional data obtained from humans and may impart novel therapeutic strategies for the treatment of anxiety disorders.

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Abbreviations

BA, basal nucleus of the amygdala; BLA, basolateral amygdaloid complex; CEA, central nucleus of the amygdala; CEm, medial subdivision of the central amygdala; CS, conditioned stimulus; FPS, fear-potentiated startle paradigm; IEG, immediate early gene; IL, infralimbic cortex; ITCs, intercalated cell masses; LA, lateral nucleus of the amygdala; LTP, long-term potentiation; mIPSC, miniature inhibitory postsynaptic current; MOR, mu-opioid receptor; mPFC, medial prefrontal cortex; mpITC, medial paracapsular intercalated cell mass; NMDA, *N*-methyl-D-aspartate; NMDAR, *N*-methyl-D-aspartate receptor; PL, prelimbic cortex; PNN, perineuronal net; PTSD, post-traumatic stress disorder; US, unconditioned stimulus; vlPAG, ventro-lateral periaquaeductal gray.

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