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REVIEW

Stress and Fear Extinction

Stephen Maren*,[1] and Andrew Holmes[2]

[1]Department of Psychology, Institute of Neuroscience, Texas A&M University, College Station, TX, USA; [2]National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, MD, USA

Stress has a critical role in the development and expression of many psychiatric disorders, and is a defining feature of posttraumatic stress disorder (PTSD). Stress also limits the efficacy of behavioral therapies aimed at limiting pathological fear, such as exposure therapy. Here we examine emerging evidence that stress impairs recovery from trauma by impairing fear extinction, a form of learning thought to underlie the suppression of trauma-related fear memories. We describe the major structural and functional abnormalities in brain regions that are particularly vulnerable to stress, including the amygdala, prefrontal cortex, and hippocampus, which may underlie stress-induced impairments in extinction. We also discuss some of the stress-induced neurochemical and molecular alterations in these brain regions that are associated with extinction deficits, and the potential for targeting these changes to prevent or reverse impaired extinction. A better understanding of the neurobiological basis of stress effects on extinction promises to yield novel approaches to improving therapeutic outcomes for PTSD and other anxiety and trauma-related disorders.

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INTRODUCTION

After all, when a stone is dropped into a pond, the water continues quivering even after the stone has sunk to the bottom

Arthur Golden, *Memoirs of a Geisha*

Trauma- and stress-related disorders, including posttraumatic stress disorder (PTSD) (DSM-5, 2013), are among the most prevalent and debilitating neuropsychiatric disorders in the world. These disorders not only seriously undermine the mental health of affected individuals but also levy an enormous public health and economic burden on society at large. The numbers are staggering. In the United States, for example, PTSD has an adult lifetime prevalence of 8%; women (10%) are diagnosed at twice the rate of men (5%) (Kessler *et al*, 1995; 2005). In the United States alone, nearly 25 million people (roughly the population of Texas) will develop PTSD at some point in their lives. Shockingly, the rate of PTSD doubles in military veterans. In the last decade, the prevalence of PTSD in soldiers deployed to Iraq and Afghanistan was nearly 14% and the cost of treating these individuals alone is estimated to be over $3 billion USD per year (Ramchand *et al*, 2008). Children and adolescents also succumb to PTSD after trauma at rates somewhat lower than that experienced by adults (Kessler *et al*, 2012).

Given the exceptional individual and societal costs of PTSD, there has been a considerable effort aimed at understanding the psychological and neurobiological mechanisms underlying this disorder (Liberzon and Sripada, 2008; Mahan and Ressler, 2012; Pitman *et al*, 2012; Goswami *et al*, 2013; Rau *et al*, 2005). This effort has led to enormous gains in understanding not only the brain circuits mediating stress and fear responses in the face of threat, but also those that are involved in dampening fear and anxiety once threats have passed (Ehrlich *et al*, 2009; Pape and Pare, 2010; Milad and Quirk, 2012; Duvarci and Paré, 2014). Indeed, harnessing inhibitory brain circuits to dampen fear in the aftermath of trauma may have a central role in therapeutic interventions for PTSD, including cognitive-behavioral therapies. It is widely believed that promoting the function of these inhibitory brain circuits is critical to developing novel therapeutic interventions for PTSD and other trauma- and stress-related disorders (Yehuda and LeDoux, 2007; Milad and Quirk, 2012; Pitman *et al*, 2012; Singewald *et al*, 2015).

Yet, despite the promise of new therapeutic avenues for treating PTSD, emerging evidence suggests that the heightened stress that accompanies PTSD may hinder the function of fear-dampening inhibitory circuits that are central to behavioral interventions designed to alleviate the syndrome. In this way, trauma-related stress is not only the 'stone dropped in the pond' that drives the development of PTSD

*Correspondence: Dr S Maren, Department of Psychology, Institute for Neuroscience, Texas A&M University, 301 Old Main Drive, College Station, TX 77843-3474, USA, Tel: +1 979 458 7960, Fax: +1 979 458 7911, E-mail: maren@tamu.edu

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but is also an enduring emotional state that 'continues quivering' through the mind and body to maintain PTSD long after trauma.

In the present review, we will consider the neural mechanisms underlying behavioral interventions for trauma- and stress-related disorders, and the modulation of these processes by stress. Our goal is to understand not only how brain circuits involved in the regulation of fear become compromised by stress but also how the impact of stress might be ameliorated to achieve a substantial and lasting therapeutic outcome in patients with PTSD. We rely heavily on work conducted in animal models to elaborate the nature and properties of brain circuits involved in emotional regulation but, where possible, translate this to work in normal human subjects and PTSD patients.

LEARNING AND MEMORY PROCESSES IN TRAUMA-RELATED DISORDERS

Common to all trauma- and stress-related disorders, including PTSD, is the direct or indirect experience (or threat) of death, serious injury, or sexual violence—in other words, experiencing or witnessing a traumatic event precedes the development of PTSD (DSM-5, 2013). Of course, not all individuals that experience or witness trauma develop PTSD—only 10% of individuals that experience trauma will ultimately be diagnosed with PTSD (Kessler *et al*, 1995; Yehuda and LeDoux, 2007). However, for those individuals who develop PTSD, the memory of the traumatic experience—the sights, sounds, smells, and context of the trauma—has a central role in both the development and expression of the disorder (Holmes and Singewald, 2013; Maren *et al*, 2013). Critically, trauma-related stimuli serve as haunting, distressing, and intrusive reminders that force PTSD patients to relive the trauma in waking flashbacks and nightmares as they sleep. Moreover, memories of the trauma lead to avoidance behavior wherein those suffering with PTSD avoid contact with individuals, situations, or places that might recall memories of their traumatic experience. In this way, traumatic memories intrude on everyday life and reap immense suffering in PTSD patients.

Therefore, unlike many neuropsychiatric disorders, PTSD is anchored to particular events and experiences in time. As a result, brain systems important for learning and memory have an essential role in the development and expression of the disorder. In the laboratory, the learning and memory processes that contribute to PTSD can be modeled, at least in part, using aversive learning paradigms such as Pavlovian fear conditioning.

TARGETING MEMORIES AS A THERAPEUTIC INTERVENTION

Fear conditioning is a form of associative learning with a long history as a model of emotional learning and memory processes in both animals and humans (Davis, 1992; Fendt and Fanselow, 1999; LeDoux, 2000; Maren, 2001; Sotres-Bayon *et al*, 2006). For example, in the early part of the 20th century, Watson and Rayner (1920) demonstrated that fear could be learned using classical conditioning procedures in a young boy referred to as 'Little Albert'. After presenting Little Albert with a white rabbit, Watson hammered a suspended steel bar to produce a frighteningly loud noise that caused Little Albert to tremble and cry. After several pairings of the rabbit and the noise, Albert became visibly upset at the sight of the rabbit alone and generalized his 'conditioned emotional reaction' of the rabbit to other white, furry objects (Watson and Rayner, 1920; Maren, 2001). Watson and Rayner (1920) concluded 'it is probable that many of the phobias in psychopathology are true conditioned emotional reactions'.

Twenty years later, Estes and Skinner (1941) developed a quantitative method to measure 'conditioned anxiety states' in rats. They first trained rats in an instrumental procedure to press a lever for a food reinforcer. Once lever-pressing behavior was established, they performed a Pavlovian fear-conditioning procedure in which an auditory conditioned stimulus (CS, a tone) was paired with an aversive electric footshock unconditioned stimulus (US). After fear conditioning, they assessed whether presentation of the tone alone interrupted lever-pressing for food. Indeed, tone presentation resulted in substantial decreases in lever pressing. Estes and Skinner (1941) inferred that lever pressing was interrupted by a conditioned state of anxiety that competed with the motivation to seek food. Importantly, they also found that continuous presentation of the tone in the absence of shock led to extinction, ie, the tone's ability to decrease lever pressing became weaker with CS-alone exposure. However, the extinction of lever pressing was weak and anxiety to the CS returned over the course of 24 h—a phenomenon termed spontaneous recovery.

These early studies revealed that emotional responses and states, including fear and anxiety, could be learned, and supported the notion that the acquisition of fear through conditioning processes might underlie a variety of disorders including specific phobia and PTSD. Indeed, the 'conditioning model of anxiety disorders' became central to the development of behavioral therapies for anxiety disorders. For example, Wolpe (1968) contended that the relief of anxiety centered on the 'deconditioning' of learned fears that underlie states of anxiety in both animals and humans. To this end, Wolpe (1968) developed systematic desensitization, a form of cognitive behavioral therapy that used relaxation methods to inhibit a patient's conditioned anxiety or fear. From a learning theory perspective, systematic desensitization relies on both extinction and counterconditioning, two processes that involve new learning (eg, CS–'no aversive US' and CS–'appetitive US', respectively), which interferes with the expression of conditioned fear. Similarly, exposure therapy, which is an effective treatment for many anxiety, trauma- and stress-related disorders, relies on extinction learning to reduce conditioned fear responses to stimuli that

provoke anxiety and panic (Bouton *et al*, 2001; Rothbaum and Davis, 2003; Craske *et al*, 2008).

THE FRAGILITY OF EXTINCTION

It has long been understood that extinction is less durable than conditioning. Indeed, in his seminal studies of conditioning and extinction learning, Pavlov (1927) described several instances in which conditional responding returned after extinction, including spontaneous recovery and external disinhibition (Figure 1). In the former case, CRs to an extinguished CS returned with the mere passage of time, whereas in the latter case the presentation of novel stimuli reinstated extinguished responding. Consequently, the effectiveness of extinction-based therapies, including exposure therapy, is constrained by phenomena that limit the durability of extinction (Vervliet *et al*, 2013; Goode and Maren, 2014). In addition to spontaneous recovery and external disinhibition, extinguished CRs have also been found to exhibit renewal when the CS is encountered outside the place or 'context' in which extinction training was administered, as well as reinstatement following presentation of the US. These recovery phenomena indicate that extinction does not eliminate the conditioning memory. Rather, it generates a new 'inhibitory' memory (eg, CS–'no US') that competes with the expression of the conditioning memory (Konorski, 1967; Bouton, 1993). This fragility of extinction memories suggests they might be vulnerable to stress, and as we discuss later there is emerging evidence in both animals and humans indicating just that.

BRAIN CIRCUITS FOR FEAR CONDITIONING AND EXTINCTION

Before considering stress effects on extinction learning, it is important to review the neural circuitry underlying this form of learning. Research over several decades has yielded an impressive corpus of work identifying brain regions and circuits involved in fear conditioning and extinction (Fendt and Fanselow, 1999; LeDoux, 2000; Myers and Davis, 2002; Maren and Quirk, 2004; Quirk and Mueller, 2008; Mahan and Ressler, 2012; Duvarci and Paré, 2014; Herry and Johansen, 2014). Importantly, these circuits are not static, but change over time as memories are consolidated, retrieved, reconsolidated, and updated (Maren, 2011).

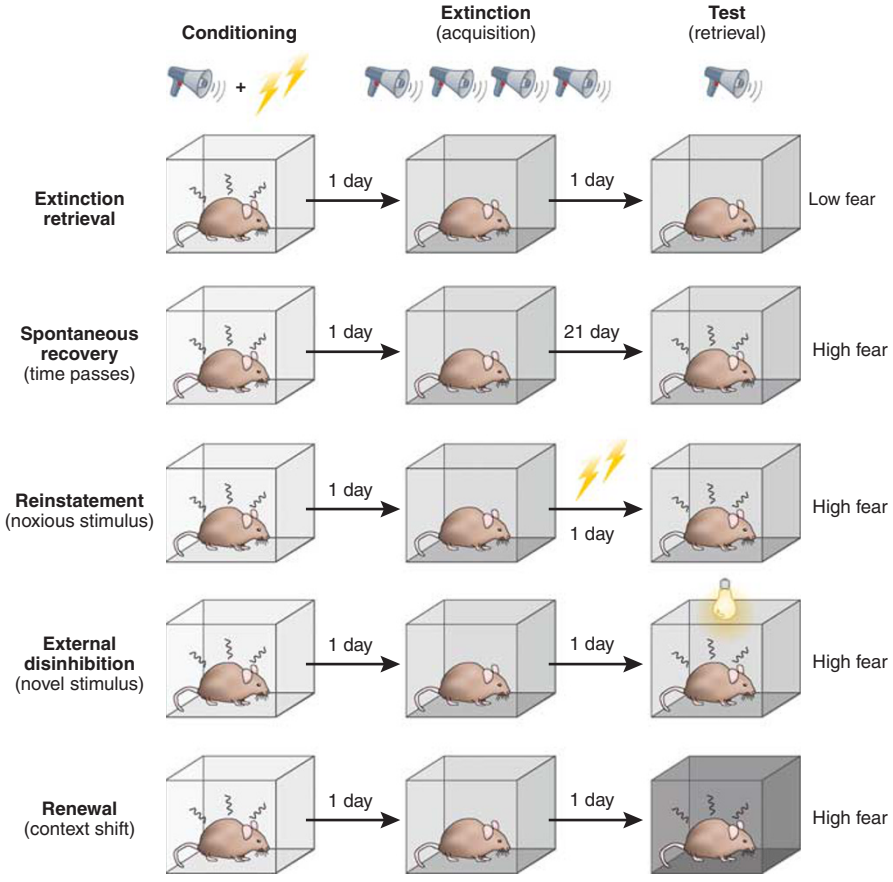

Figure 1. Relapse of fear after extinction. After the extinction of a conditioned fear response, extinction, the expression of conditioned fear is reduced. However, a number of phenomena are associated with the return or relapse of fear responses after extinction. These include (a) spontaneous recovery with the passage of time, (b) external disinhibition after presentation of a novel stimulus, (c) reinstatement after experiencing a noxious event, including the unconditioned stimulus, and (d) renewal after experiencing the conditioned stimulus outside the extinction context.

FEAR, EXTINCTION, AND THE AMYGDALA

At the heart of the emotional learning circuit is the amygdala, a group of heterogeneous nuclei that has an essential role in both fear conditioning and extinction (Maren, 2001; Myers and Davis, 2002; Ehrlich *et al*, 2009; Pape and Pare, 2010; Duvarci and Paré, 2014). Within the amygdala, the basolateral complex (BLA, including the lateral, basolateral, and basomedial nuclei) has been implicated as a critical site of sensory convergence for CSs (eg, tones, odors, or lights), USs (eg, loud noises, orbital shock, or foot shock), as well as contextual information related to the circumstances surrounding the conditioning experience (Herry and Johansen, 2014). The anatomical pathways conveying this information have been well described and involve both cortical and subcortical routes of transmission. For example, auditory and somatosensory information reach many amygdaloid nuclei, but the shortest-latency single-unit responses are obtained in the lateral nucleus via direct projections from the sensory thalamus (eg, medial geniculate nucleus and posterior intralaminar nuclei) (Bordi and LeDoux, 1994). Cortical areas, including the primary auditory cortex and the perirhinal cortex, also convey sensory information to the amygdala and these areas are sufficient for fear conditioning under some conditions (Medina *et al*, 2002).

Most circuit models of fear conditioning posit that sensory convergence and associative synaptic plasticity in the BLA is necessary for many forms of aversive learning and memory. In particular, NMDA receptor-dependent long-term potentiation (LTP) in thalamic and cortical afferents on BLA neurons is critical for fear learning and memory (Maren, 1999; Blair *et al*, 2001; Johansen *et al*, 2011). For instance, early work showed that intra-BLA infusions of the NMDA receptor antagonist D,L-APV (which antagonizes both GluN2A- and GluN2B-containing receptors) prevent the acquisition and expression of fear conditioning (Miserendino *et al*, 1990; Maren *et al*, 1996; Lee and Kim, 1998). In addition, intra-BLA APV also prevents the extinction and reconsolidation of fear (Falls *et al*, 1992; Ben Mamou *et al*, 2006; Zimmerman and Maren, 2010), indicating a broad role for BLA NMDA receptors in fear memory processes. The fear expression deficits produced by APV suggest that decreases in BLA excitability (rather than LTP *per se*) account for deficits in these processes (Maren and Fanselow, 1995; Maren *et al*, 1996). Interestingly, fear expression deficits are not produced by systemic administration of NMDA receptor antagonists, such as Ro 25-6981 and ifenprodil, with selective actions at NMDA receptors containing the GluN2B subunit, whereas these drugs do reliably impair conditioning, extinction, and reconsolidation (Rodrigues *et al*, 2001; Ben Mamou *et al*, 2006; Sotres-Bayon *et al*, 2007; Mathur *et al*, 2009). This suggests GluN2B-containing receptors may have a preferential role in the induction of synaptic plasticity critical for the conditioning, extinction, and reconsolidation of fear memories, whereas other types of NMDA receptor heteromer (eg, containing GluN2A not GluN2B) may have a more general role in regulating excitability and therefore fear expression.

Importantly, the NMDA receptor-dependent processes important for emotional learning and memory are anatomically localized to BLA neurons insofar as infusions of NMDA receptor antagonists into the central nucleus of the amygdala (CeA) spare both fear conditioning and extinction (Zimmerman and Maren, 2010). The importance of BLA synaptic plasticity in conditioned fear is further supported by the observation that AMPA receptors, which are involved in LTP expression, are upregulated in LA neurons after fear conditioning (Rumpel, 2005). Moreover, overexpression of CREB, a transcription factor that promotes synaptic plasticity, in LA neurons increases the probability that they will be incorporated into cellular networks required for the conditioning memory (Han *et al*, 2007). In addition to supporting fear learning, synaptic plasticity in the amygdala is critical for extinction learning.

As noted, extinction is impaired by antagonizing NMDA receptors in the BLA and can be enhanced by NMDA receptor modulators, such as D-cycloserine (Walker *et al*, 2002). In addition, antagonizing brain-derived neurotrophic factor (BDNF) signaling in the amygdala retards the extinction retention (Chhatwal *et al*, 2006). Hence, the intracellular cascades associated with extinction appear to recapitulate, at least in part, those involved in fear conditioning (Tronson *et al*, 2012). For example, extracellular-related kinase (ERK)/mitogen-activated protein kinase (MAPK) activity in the BLA is important for both forms of learning (Herry *et al*, 2006; Merino and Maren, 2006). However, the two forms of learning are likely to involve different degrees or types of plasticity at excitatory and inhibitory synapses (Maren, 2014a). Indeed, extinction appears to involve plasticity at GABAergic synapses in the amygdala that are critical for fear suppression (Chhatwal *et al*, 2005; Trouche *et al*, 2013).

EXTINCTION, CONTEXT, AND THE HIPPOCAMPUS

Although there is ample evidence that synaptic plasticity in the amygdala is critical for encoding conditioning and extinction memories, the amygdala does not act alone. Contexts have multiple roles in the conditioning and extinction of fear (Maren *et al*, 2013). Animals quickly come to learn that aversive stimuli occur in a particular context: for example, explicitly pairing footshock with a context produces a conditioned fear response to that context. This direct context–US association, similar to a CS–US association, is mediated by associative plasticity in the amygdala among hippocampal efferents to the basolateral and basomedial amygdaloid nuclei. In addition, the BLA modulates contextual encoding by the hippocampus, influencing the strength of memories animals form about the context itself (Huff and Rudy, 2004). Furthermore, projections from the BLA to the ventral hippocampus and entorhinal cortex (the major source of cortical afferents to the hippocampus)

modulate both nonassociative (Felix-Ortiz *et al*, 2013) and associative fear (Sparta *et al*, 2014). Hence, bidirectional communication between the amygdala and hippocampus is important in establishing contextual representations.

There is considerable evidence indicating that the hippocampus is critical for establishing contextual representations during fear conditioning and extinction (Fanselow, 2000; Maren, 2001; Rudy *et al*, 2004). Contexts in this regard refer to both exteroceptive and interoceptive information that sets the backdrop for the conditioning and extinction experiences, ie, contexts inform when, where, with whom, and in what internal state an experience occurs. On the one hand, disrupting hippocampal function impairs the formation of contextual representations that are important for contextual fear conditioning. On the other hand, the hippocampus is not essential for contextual fear conditioning in all cases. Animals with pre-training hippocampal lesions acquire conditional freezing to a context normally under some conditions, despite the fact that posttraining lesions are devastating to performance (Maren *et al*, 1997; Frankland *et al*, 1998). Moreover, animals that have encoded and consolidated representations of a to-be-conditioned context exhibit normal context conditioning in the absence of the hippocampus (Young *et al*, 1994). Thus, spared context conditioning after hippocampal damage appears to be mediated by alternate neural systems (Maren *et al*, 1997; Goshen *et al*, 2011); however, if detailed contextual memories are acquired by an intact hippocampal system, the retrieval of those representations is reliant on the hippocampus (Rudy, 2009; Sparks *et al*, 2011). In other words, the hippocampus appears necessary for the encoding and retrieval of detailed contextual representations, whereas other neural systems can mediate the encoding and retrieval of elemental features of context.

Contexts also serve as retrieval cues for specific CS–US relationships learned in those contexts and serve to 'set the occasion' for these US relationships (Bouton, 1993). This occasion setting function of context is in particular important for extinction, which is often learned in a context different from that in which conditioning is conducted. In a typical experiment, eg, conditioning (CS–US pairings) would be conducted in one context ('context A') and the following day extinction (CS-alone presentation) would be delivered in a distinct context ('context B'). This is often done so that fear to the CS can be assessed during extinction training without contamination by fear to the conditioning context, ie, when extinction is performed in the conditioning context, fear is elevated on placement in the context before CS presentation. In this way, conditioning and extinction (represented by CS–US and CS–no US memories, respectively) can be disambiguated by the contexts in which they occurred. Similar to fear memories, extinction memories are also tightly bound to the context in which they are learned, such that when an extinguished CS is encountered outside the extinction context, fear will return—a phenomenon that accounts for fear renewal.

There is compelling evidence indicating that the hippocampus is important for the use of contexts to guide retrieval of fear extinction memories that have been formed in particular contexts, eg, hippocampal inactivation impairs fear renewal (Maren and Holt, 2000; Maren *et al*, 2013; Preston and Eichenbaum, 2013). Recent work has also revealed that the context-dependent expression of fear memories after extinction involves hippocampal projections to the amygdala and the medial prefrontal cortex (mPFC). Specifically, neuronal activity (as indexed by expression of the immediate early gene product, Fos) is elevated in hippocampal neurons projecting to the mPFC and the amygdala during fear renewal (Knapska and Maren, 2009). This renewal-related elevation in Fos activity is in particular pronounced in a small population of hippocampal neurons that projects to both the mPFC and BLA (Jin and Maren, 2015). Demonstrating the importance of these pathways to the contextual regulation of fear memories, disconnection of the hippocampus from the mPFC and BLA prevents fear renewal (Orsini *et al*, 2011). Further understanding of these and other neural circuits should help shed light on the basis of the abnormal contextual gating of fear and extinction which, as we discuss later, is evident in patients with PTSD.

mPFC GATING OF FEAR AND EXTINCTION

A growing literature has documented how the mPFC is critical for gating fear expression, in particular after extinction (Quirk and Mueller, 2008; Rozeske *et al*, 2015). Early work revealed that lesions of the mPFC, in particular those encompassing the infralimbic cortex (IL), produced deficits in the retention of extinction (Morgan and LeDoux, 1995; Quirk *et al*, 2000). In these studies, there was substantial spontaneous recovery of conditioned fear responses the day after extinction training in rats with mPFC damage. The effects of mPFC lesions on extinction are most robust in paradigms, including conditioned suppression, in which animals are challenged with competing motivational states, whereas the evidence that mPFC lesions affect extinction retrieval in tasks without ongoing appetitive behavior is less clear-cut (Gewirtz *et al*, 1997; Garcia *et al*, 2006; Chang and Maren, 2010b). Nonetheless, pharmacological (Hugues *et al*, 2006; Sotres-Bayon *et al*, 2007; Laurent and Westbrook, 2008; 2009; Sierra-Mercado *et al*, 2011), electrical (Milad *et al*, 2004) or optogenetic (Do-Monte *et al*, 2015a) manipulations of IL have been found to modulate the acquisition of extinction. In addition, changes in IL spike firing and immediate early gene expression accompany both the acquisition (Milad and Quirk, 2002; Muigg *et al*, 2008; Fitzgerald *et al*, 2014b) and expression (Hefner *et al*, 2008; Knapska and Maren, 2009; Whittle *et al*, 2010; Chang and Maren, 2010b; Knapska *et al*, 2012; Orsini *et al*, 2013) of extinction.

The prevailing view based on these data is that extinction-related plasticity in the IL is involved in establishing extinction memories (Myers and Davis, 2002; Orsini and Maren, 2012). It has been suggested that the IL might gate extinction memories by exciting inhibitory intercalated

neurons (ITC) to suppress amygdala output (Quirk *et al*, 2003; Paré *et al*, 2004; Likhtik *et al*, 2008; Ehrlich *et al*, 2009; Pape and Pare, 2010; Duvarci and Paré, 2014). However, recent findings indicate that the primary functional target of the IL is the BLA rather than the ITCs—consequently, the IL likely modulates amygdala output through the BLA, which in turn recruits the ITCs to suppress fear (Cho *et al*, 2013; Orsini *et al*, 2011; Knapska *et al*, 2012; Strobel *et al*, 2015). An instructional role for the IL, one that entails guiding plastic changes in the BLA that ultimately underlie extinction memories, would be consistent with recent optogenetics experiments showing the IL and IL inputs to the BLA are necessary for the acquisition of a long-term extinction memory, but is not required for the expression of extinction once learned (Do-Monte *et al*, 2015a; Bukalo *et al*, 2015). The IL is not dispensable for extinction expression in all circumstances, however, and may be particularly important when contextual information must be integrated to retrieve an extinction memory (Laurent and Westbrook, 2008; Orsini *et al*, 2011; Knapska *et al*, 2012).

In contrast to the IL, the role of the prelimbic cortex (PL) is to drive the expression of conditional fear (Corcoran and Quirk, 2007; Sotres-Bayon *et al*, 2012). For example, neuronal activity in the PL is positively correlated with conditional freezing behavior (Burgos-Robles *et al*, 2009) and PL neurons exhibit increases in Fos expression after fear retrieval (Knapska and Maren, 2009; Orsini *et al*, 2013). PL interneurons have a crucial role in shaping fear responses, such that reduced activity of parvalbumin-positive interneurons in the PL and anterior cingulate cortex (ACC) leads to the disinhibition of principal cell output to the BLA and an increase in conditional fear (Courtin *et al*, 2014). PL neurons that project to the BLA are also involved in the context-dependent renewal of extinguished fear (Orsini *et al*, 2011; Knapska *et al*, 2012). Interestingly, the role of the PL-BLA pathway in conditional fear expression is highly time dependent. Although recently acquired fear can be attenuated by optogenetically silencing PL inputs to the BLA, PL projections to the paraventricular nucleus of the thalamus must be silenced to inhibit older fear memories (Do-Monte *et al*, 2015b). A final important feature of the PL-BLA and IL-BLA circuits mediating fear and extinction is that they are anatomically and functionally reciprocal. Neuronal projections from the BLA to the PL and IL are recruited to generate fear responses and extinction memories, respectively (Garcia *et al*, 1999; Senn *et al*, 2014). The impressive corpus of data dissecting the prefrontal, hippocampal, and amygdalar circuits that subserve extinction in rodents has greatly informed our understanding of vulnerabilities that may contribute to extinction impairments, such as those associated with stress.

STRESS EFFECTS ON EXTINCTION AND UNDERLYING BRAIN CIRCUITS

Stress has far reaching effects on cognition and emotion in both humans and animals. In the context of trauma-related disorders, such as PTSD, stress may hinder interventions, including exposure therapy, aimed at reducing fear. Indeed, ample evidence reveals that patients with PTSD exhibit extinction impairments and stress exposure impairs extinction in both animals and humans.

STRESS EFFECTS ON EXTINCTION: HUMAN STUDIES

A history of exposure to stress increases risk for developing PTSD after traumas such as combat (Karstoft *et al*, 2015). An abundant literature indicates that stress influences the acquisition and retrieval of extinction in humans (Raio and Phelps, 2015). For example, stress exposure (eg, cold pressor) impairs the extinction (Hartley *et al*, 2014) of a conditioned galvanic skin response. Moreover, stress exposure before retrieval testing impairs the expression of extinction, resulting in a return of conditional responding (Merz *et al*, 2014; Raio *et al*, 2014). Patients with PTSD also exhibit impairments in the acquisition and expression of extinction (Blechert *et al*, 2007; Guthrie and Bryant, 2006; Lissek *et al*, 2005; Orr *et al*, 2000; VanElzakker *et al*, 2014; Wessa and Flor, 2007). After fear conditioning, PTSD patients show heightened conditional responding during extinction training on a variety of psychophysiological measures (eg, heart rate, skin conductance, and acoustic startle) (Blechert *et al*, 2007; Orr *et al*, 2000). The enhanced conditional responding during extinction is often manifest as a loss of differential responding (ie, similarly elevated responses to both the CS+ and CS− relative to controls), which indicates that extinction impairments might reflect overgeneralization of fear (Grillon and Morgan, 1999). In addition to exhibiting larger CRs during extinction training, PTSD patients also have difficulty maintaining extinguished responding over a retention interval, consistent with a deficit in extinction retrieval (Milad *et al*, 2008; 2009). Whether extinction impairments precede PTSD or are a pre-existing trait is unclear. On the one hand, extinction deficits were found in combat-exposed PTSD patients but not their combat-exposed twins who did not have PTSD, suggesting poor extinction was a consequence rather than a cause of PTSD (Milad *et al*, 2008). On the other hand, other work has found impairments in extinction learning are not only present before trauma but predict later risk for developing PTSD (Guthrie and Bryant, 2006).

Another important consideration in dissecting the etiology of extinction impairments in PTSD is the fact that women are more than twice as likely as men to develop the disorder (Glover *et al*, 2015; Shansky, 2015). Women with PTSD also acquire greater levels of conditioned fear than men (Inslicht *et al*, 2013). Although it is uncertain whether this reflects a premorbid trait in women or a differential sex-related response to the disorder, the latter seems more likely given conditional responding is typically greater in healthy male than in female subjects (Milad *et al*, 2010, but see Bentz *et al*, 2013).

The relationship between sex, extinction, and PTSD is also complex. There are recent reports of similar extinction of fear in healthy male and female subjects (Bentz *et al*, 2013; Lebron-Milad *et al*, 2012; Merz *et al*, 2012; Shvil *et al*, 2014). However, sex differences in extinction retrieval can manifest as a function of hormonal contraceptive usage, estrogen status, and menstrual cycle stage in rats (Graham and Milad, 2013, 2014) and also humans, such that men and early-stage women exhibit better recall than mid-cycle women (Milad *et al*, 2006). This picture of sex difference may not necessarily hold in PTSD. For instance, Shvil *et al* (2014) found that male, but not female, patients exhibited poor extinction retrieval in association with elevated activation of the dorsal ACC (dACC), the anatomical analogue of the rodent PL (Milad *et al*, 2009; Shvil *et al*, 2014).

This latter study implicates the dACC as a neural correlate of impaired extinction, which is consistent with the widely replicated observation of dACC hyperactivity in PTSD patients responding to a fearful stimulus (Pitman *et al*, 2012). Other reliable findings in PTSD have been an increased BOLD response to a fear challenge in the amygdala and a corresponding reduction in the activation of the ventromedial PFC (vmPFC, the human analogue of the rodent IL) and the hippocampus (Pitman *et al*, 2012). Although there have been fewer studies of neural activation specifically during extinction tasks in PTSD patients, Milad *et al* (2009) found impaired extinction retrieval was associated with decreased BOLD responses in the vmPFC. Thus, current data imply dysregulation of hippocampo–prefrontal–amygdala circuits in PTSD, characterized by over activity of fear-generating brain regions and a difficulty engaging circuits normally involved in the inhibition of conditional fear.

Interestingly, recent work suggests that it may not necessarily be a loss of inhibitory regulation *per se* that characterizes network changes in PTSD, but rather a loss of context-appropriate engagement of this inhibitory mechanism (Garfinkel *et al*, 2014; Maren *et al*, 2013; Rougemont-Bücking *et al*, 2011). This idea has emerged from studying PTSD patients for neural correlates of the contextual regulation of extinguished fear, a phenomenon that recruits hippocampal and prefrontal cortical circuits to regulate fear expression by the amygdala (Maren *et al*, 2013; Orsini and Maren, 2012). Recent work showed that PTSD patients exhibited deficits in extinction retrieval, as previously reported, but were also impaired in renewing their fear outside of the extinction context (Garfinkel *et al*, 2014). This is a surprising outcome insofar as a loss of inhibitory control hypothesized to accompany PTSD would be expected to increase fear to an extinguished CS not only in the extinction context but in any context the CS is encountered. Impaired renewal in PTSD suggests that patients might have hippocampal dysregulation, given the aforementioned work in rodents implicating this region in renewal. Indeed, in addition to the reduced vmPFC activity and heightened amygdala activity reported in prior studies of extinction, PTSD patients exhibited weaker hippocampal activation to the CS− during renewal, relative to combat-exposed controls (Garfinkel *et al*, 2014). These provocative findings suggest that a major cause of deficient extinction in PTSD patients is the inability to use contextual information to determine when and where it is appropriate to express fear.

STRESS EFFECTS ON EXTINCTION: ANIMAL MODELS

Beginning with evidence that extinction is disrupted in rats and mice subjected to forced swim or restraint (Izquierdo *et al*, 2006; Miracle *et al*, 2006), extinction deficits have been

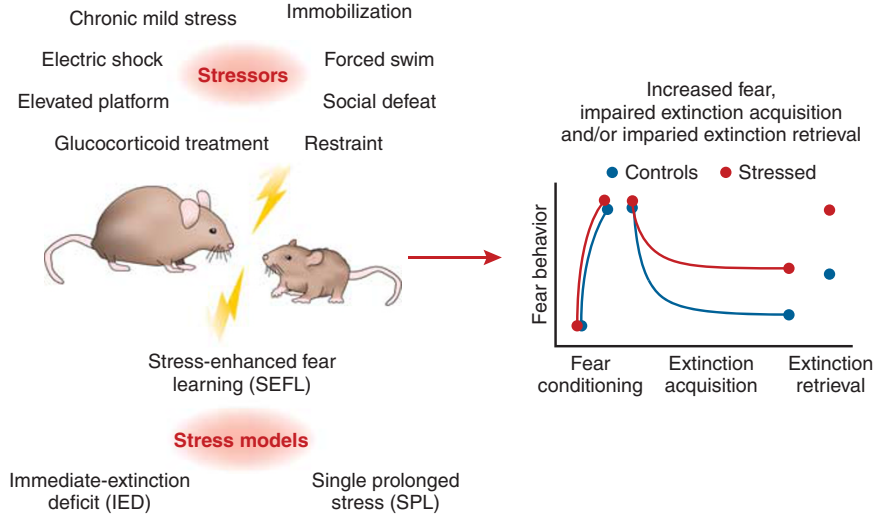

Figure 2. Stressors and stress models affecting fear extinction in rodents. A range of established stressors, applied singly or in combination, either acutely or chronically, has been shown to cause impairments in extinction acquisition or retrieval, sometimes in association with increased fear. Abnormalities in fear and extinction are also found after rodents are subjected to the stress-enhanced fear learning (SEFL) (Rau *et al*, 2005), single-prolonged stress (SPL) (Yamamoto *et al*, 2009), and immediate-extinction deficit (IED) (Maren, 2014b) models of stress.

reported following exposure to various types of stressor, both acute and chronic. These include maternal separation, predator exposure, social defeat and isolation, and elevated platform exposure (for a cartoon summary, see Figure 2) (Andero *et al*, 2011; Chauveau *et al*, 2012; Clay *et al*, 2011; Deschaux *et al*, 2013; Dubreucq *et al*, 2012; Ganon-Elazar and Akirav, 2013; Garcia *et al*, 2008; Goswami *et al*, 2010; Green *et al*, 2011; Ishikawa *et al*, 2012; Judo *et al*, 2010; Knox *et al*, 2012a; Long and Fanselow, 2012; Matsumoto *et al*, 2008; Matsumoto *et al*, 2013; Saito *et al*, 2012; Saito *et al*, 2013; Segev *et al*, 2013; Toledo-Rodriguez *et al*, 2012; Wilber *et al*, 2011; Wilson *et al*, 2013; Yamamoto *et al*, 2008; Yamamoto *et al*, 2009; Zhang and Rosenkranz, 2013; Zheng *et al*, 2013; Skelly *et al*, 2015). Extinction deficits after stress are typically, although not always, manifest as decreases in within-session reductions in conditional responding as well as deficits in the retention of extinction across sessions (ie, extinction retrieval deficits). Echoing the aforementioned sex differences in extinction in human subjects, stress effects on extinction have also been reported to be sex dependent. For example, the same chronic (restraint) stress regimen that impairs extinction in males tends to facilitate extinction in females (Baran *et al*, 2009, but see (Xiong *et al*, 2014). Of course, more work is required to further explore sex differences in stress effects on extinction given that the majority of work has been done in males.

Recent studies have examined whether extinction is affected by exposure to stress regimens that produce other PTSD relevant phenotypes in rodents. In the 'single prolonged stress' or SPS procedure, animals receive several stressors (restraint, forced swim, and ether anesthesia) in a single session followed by a 1-week period of quiescence. This procedure causes a dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis that mirrors that seen in PTSD patients, and produces several behavioral changes that model aspects of PTSD. SPS is also associated with impairments in extinction retention (but not fear conditioning) to both shock-paired contexts (Yamamoto *et al*, 2008) and auditory CSs (Knox *et al*, 2012a). Rats experiencing SPS before fear conditioning and extinction also exhibit greater levels of fear renewal, suggestive of a stress-induced sensitization of fear responding (Knox *et al*, 2012a). As noted below, SPS-induced deficits in extinction can be prevented by various pharmacological interventions.

Interestingly, in cases where a stress manipulation elevates conditional fear, this fear remains extinction resistant, even when the fear response to the original stressor has itself been successfully extinguished. For example, Long and Fanselow (2012) and Rau *et al* (2005) have described an enhancement of fear conditioning they term 'stress-enhanced fear learning' (SEFL) that is resistant to extinction. In this procedure, rats are first submitted to a series of 15 footshocks in a distinct context. One to 7 days later, animals receive a fear-conditioning procedure consisting of either a single un-signaled shock or tone-shock pairing in a novel context. With both procedures, prior shock exposure greatly potentiates or sensitizes the conditional fear response that is acquired during the second learning experience. However, extinguishing fear to the trauma context (the first context) does not eliminate SEFL (Long and Fanselow, 2012). Hence, the capacity of shock exposure to facilitate subsequent fear conditioning does not depend on associations between the trauma context and shock, rather it is mediated by a non-associative sensitization of fear that is resistant to extinction.

Stress-induced impairments in extinction learning are also manifest when extinction occurs soon after fear conditioning (Maren, 2014b). For example, Maren and Chang (2006) submitted rats to an extinction procedure either 15 min or 1 day after a standard, 5-trial auditory fear-conditioning session. Both groups of rats exhibited decrements in conditioned freezing during extinction training, but only rats in the delayed-extinction condition maintained this decrement in freezing over a 24-h retention interval. Rats extinguished 15 min after fear conditioning exhibited a near-complete spontaneous recovery of fear the following day; they showed little evidence of extinction retrieval. This 'immediate extinction deficit' (IED) has been confirmed in both rats and mice after either context or cued fear conditioning (Chang and Maren, 2009; Kim *et al*, 2010; Macpherson *et al*, 2013; Stafford *et al*, 2013). Interestingly, Maren and Chang (2006) found that recently shocked animals exhibited high levels of sensitized fear in the minutes before extinction training (which was manifest as high baseline, pre-CS freezing behavior), suggesting that prevailing fear at the time of extinction training impairs the acquisition of long-term extinction memories (Chang and Maren, 2009). Indeed, delayed extinction is also impaired if a shock reminder is delivered minutes before extinction training (Maren and Chang, 2006). It has been argued that the IED is a prime example of stress interfering with extinction-mediating processes—in this case, the stress of recently experienced fear conditioning (Maren, 2014b). Consistent with this notion, IEDs are associated with neural abnormalities that are analogous to those produced by other, more 'explicit' stressors, a set of findings we discuss in more detail later.

GENETIC MODERATION OF RISK FOR PTSD

Risk for stress- and trauma-related conditions is, as with other neuropsychiatric disorders, moderated by genetic factors. The results of twin and family studies estimate a significant heritable contribution to PTSD and there is an ongoing search for the specific genes involved (Hettema *et al*, 2003; Pitman *et al*, 2012). Interestingly, a number of the plausible genetic candidates identified to date encode for proteins in the same neurotransmitter and molecular systems that have been shown to regulate the effects of stress on extinction (summarized in Figure 3).

Another notable finding to emerge has been that the influence of certain genes on risk for PTSD is in turn dependent on the amount of stress an individual has experienced in his/her life, especially during childhood. In an exemplar of this kind of interaction, variation in

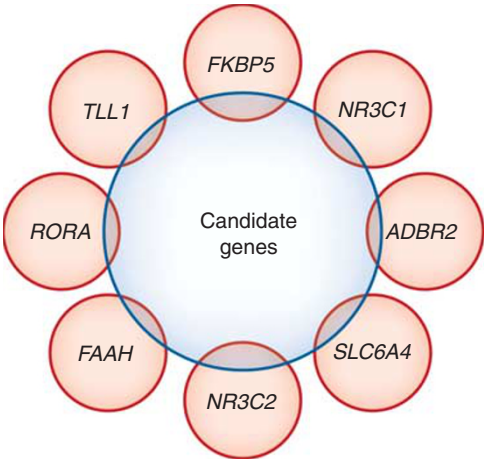

Figure 3. Candidate gene variants moderating stress-related risk for posttraumatic stress disorder (PTSD). A number of human genetic variants have been found to interact with exposure to stress and trauma, often in childhood, to moderate risk for PTSD. To date, these have included the serotonin transporter (*SL6A4*) (Caspi *et al*, 2010; Xie *et al*, 2012), FK506-binding protein 51 (*FKBP5*) (Zannas and Binder, 2014), adenylate cyclase-activating polypeptide receptor (*ADCYAP1*) (Dias *et al*, 2013), and the β-adrenergic receptor (*ADBR2*) (Liberzon *et al*, 2014). Although they have not yet been studied for their potential interaction with stress, variants in the Tolloid-Like 1 Gene (*TLL1*) (Xie *et al*, 2013), retinoid-related orphan receptor alpha gene (*RORA*) (Logue *et al*, 2013) and fatty acid amide hydrolase (*FAAH*) (Dincheva, 2015; Gunduz-Cinar *et al*, 2013b) genes have been recently associated with PTSD or PTSD-related personality traits, including fear extinction and stress-reactivity.

the FK506-binding protein 51 gene (*FKBP5*) predicts the occurrence of PTSD symptoms in adults as a function of the severity of abuse suffered during childhood (Binder *et al*, 2008). Further studies have suggested that *FKBP5* likely moderates the impact of stress by regulating the function of a key stress-regulating molecule, the glucocorticoid receptor (GR) (Zannas and Binder, 2014). A related recent finding is that epigenetic modification of the GR gene (*NR3C1*) associates with PTSD prevalence in male Rwandan genocide survivors (Vukojevic *et al*, 2014). Another interesting link to the GR is the nomination of the β2-adrenergic receptor gene (*ADRB2*) as a moderator of the lasting effects of stress on risk for PTSD. From an examination of almost 4000 genetic candidates, Liberzon *et al* (2014) identified a variant in the promoter region of *ADRB2* that was associated with rates of PTSD in male and female patients that had experienced childhood adversity. As we discuss at greater length later, there is growing preclinical evidence of interactions between the GR and β2-adrenergic receptor in fear extinction and its mediation by stress.

A number of genes have been linked to stress moderation of PTSD via functional effects on the extinction circuit. For instance, a polymorphism in the *SLC6A4* gene, encoding the serotonin transporter, is associated with increased risk for PTSD and depression in individuals with a history of exposure to traumatic life events (Caspi *et al*, 2010; Xie *et al*, 2012). A series of elegant studies by Fisher and Hariri (2012), employing functional magnetic resonance imaging, has documented greater amygdala activation and lesser connectivity between the amygdala and vmPFC, to threat in individuals carrying the 'risk' *SLC6A4* variant. In a similar vein, a variant in the gene encoding the adenylate cyclase-activating polypeptide receptor (PAC1R, *ADCYAP1*) predicts PTSD in women from highly traumatized backgrounds (Dias and Ressler, 2013) in concert with heightened threat activation of the amygdala and hippocampus, and poorer functional connectivity between these two brain regions (Stevens *et al*, 2014). Effects on these extinction-mediating regions suggest these genes may affect extinction itself. Although additional studies will be needed to firmly establish this link, there is preliminary evidence that these and related variants affect fear and fear extinction in humans and rodents (Dias *et al*, 2013; Hartley *et al*, 2012; Lonsdorf *et al*, 2009).

Among the various functional neural abnormalities detected in traumatized populations, the amygdala response to threat currently represents the most credible neural marker for genetic effects on the extinction circuit. Genes found to predict variant in amygdala reactivity to threat include the aforementioned PTSD-associated *FKBP5* as well as the *NR3C2* gene encoding the glucocorticoid-activated mineralocorticoid (MR) receptor (Bogdan *et al*, 2012; White *et al*, 2012). Another example is the gene for fatty acid amide hydrolase (*FAAH*), an enzyme that controls the degradation of the endocannabinoid (eCB), anandamide. *FAAH* gene variation predicts not only amygdala threat reactivity and habituation, but also vmPFC–amygdala coupling, trait anxiety levels, and fear extinction (Dincheva, 2015; Gunduz-Cinar *et al*, 2013b; Hariri *et al*, 2009). These findings also have a translational dimension given, as we discuss later, the eCB system, and the amygdala FAAH activity specifically has a key role in regulating fear extinction and the effects of stress in rodents (Gunduz-Cinar *et al*, 2013a).

In the coming months and years, multiple novel candidate genes moderating PTSD groups will likely be nominated by large-scale genome-wide association studies of PTSD currently underway. The initial findings from these studies are already encouraging, revealing previously unknown associations between PTSD and the retinoid-related orphan receptor-*α*gene (*RORA*) (Logue *et al*, 2013) and genetic loci near the Tolloid-like 1 gene (*TLL1*) (Xie *et al*, 2013). This approach will be complemented by preclinical studies of PTSD-relevant phenotypes in rodents, including impaired fear extinction.

Echoing the significant genetic contribution to risk for PTSD in humans, the efficacy of extinction memory formation in rats has a sizeable (greater than one third) heritable component (Shumake *et al*, 2014). There have been attempts to model individual differences in fear extinction both within and between rodent strains and lines to establish neural and genetic correlates of extinction (for further discussion, see Holmes and Singewald, 2013). Some investigators have studied correlates of extinction differences that are evident within ostensibly homogeneous populations of

animals within a single genetic strain (Bush *et al*, 2007; Shumake *et al*, 2014). This approach has proven valuable to defining the functional contributions of prefrontal, amygdalar, and hippocampal regions to extinction by showing how neuronal activity in these areas correlates with how well individual animals or subgroups extinguish (Burgos-Robles *et al*, 2009; Burgos-Robles *et al*, 2007; Herry and Mons, 2004; Peters *et al*, 2010). Another useful method has been to exploit marked differences in fear extinction that have been described across different strains of rats and mice (Camp *et al*, 2009; Chang and Maren, 2010b; Hefner *et al*, 2008).

How naturally occurring variation in extinction efficacy in rodent populations relates to variation in sensitivity to the effects of stress is not well understood, but a number of findings are consistent with a close relationship between the two domains. For example, strain comparisons have found that certain strains of inbred mice exhibiting impaired extinction also show GR abnormalities and dysregulated neuroendocrine responses to stress challenge (Camp *et al*, 2012). Another finding of note has been that rodent lines that have been bred for learned helplessness induced by repeated inescapable stress (Shumake *et al*, 2005) or other stress-related phenotypes, including high contextual fear (Ponder *et al*, 2007) and unconditioned anxiety-like behavior (Muigg *et al*, 2008), show impairments in extinction. The implication from these findings is that there may be common genetic factors influencing a collection of stress-related phenotypes that encompass fear extinction.

EXTINCTION AND STRESS IN DEVELOPING ANIMALS

We earlier made the point that genetic influences on PTSD symptoms and circuits are often linked to stress experienced during childhood. In fact, most cases of stress-related disorders emerge during childhood and adolescence (Kessler *et al*, 2005). Some have posited that this reflects heightened vulnerability stemming from the protracted developmental maturation of corticolimbic systems regulating stress and emotion. The human PFC matures relatively late in development (Giedd and Rapoport, 2010), whereas the amygdala shows exaggerated reactivity to threat in fear-prone adolescent subjects (Blackford and Pine, 2012). How these ontogenetic changes affect extinction and stress effects on extinction could have important implications not only for understanding the pathophysiology of stress-related disorders in children and adolescents, but could also inform decisions about how extinction-based CBT treatments can be best employed in young people. If extinction-based approaches are relatively ineffective in adolescents, then should alternate treatments be considered for this age group? Moreover, if stress shifts the development trajectory of extinction efficacy, does a young patient's history of stressful life events need to be factored into treatment decisions?

In addressing these questions, there is growing evidence that the nature and underlying neural basis of fear and fear extinction also varies profoundly across early development in rodents (Figure 4) (for excellent recent reviews, see Callaghan *et al*, 2013; Landers and Sullivan, 2012; Pattwell *et al*, 2013; Shechner *et al*, 2014). In their third postnatal week, rats and mice show greater reductions in fear after extinction than adults, potentially reflecting an extinction-induced erasure of the original fear memory (Kim and Richardson, 2007). These age-related differences are associated with developmental differences in the extinction circuitry. BLA principal neurons dramatically increase their arborization and spine density during the first postnatal month (Ryan *et al*, 2014), whereas parvalbumin-positive interneurons in the BLA exhibit more extracellular matrix structures, known as perineuronal nets, at the age when extinction becomes adult-like (Gogolla *et al*, 2009). Demonstrating the functional importance of these perineuronal nets, their removal via intra-BLA infusion of chondroitinase ABC or chronic fluoxetine treatment recapitulates an infantile form of extinction in adults (Gogolla *et al*, 2009; Karpova *et al*, 2012).

A related finding is that mutants lacking the extracellular matrix protein, reelin, show a developmental prolongation of infant-like extinction, which extends into the postweaning period (Iafrati *et al*, 2013). The deficient extinction phenotype in this mutant is associated with impaired dendritic spine density and synaptic plasticity (LTP) in the mPFC (see also Fitzgerald *et al*, 2015a) and is reversed by a single, systemic administration of either ketamine or a GluN2B NMDA receptor antagonist (Ro 25-6981) (Iafrati *et al*, 2013). These observations would suggest that functional immaturity of the mPFC might contribute to infant-like extinction. In support of this idea, extinction increases phosphorylated MAPK in the mPFC of adult but not infant rats, and inactivating the infant mPFC does not impair extinction, as it does in adults (Kim *et al*, 2009).

Rather strikingly, extinction continues to show dynamic changes as development continues. Following a transient period soon after weaning during which extinction demonstrates adult-like properties (erasure resistance), fear memories in adolescent animals show heightened fear or extinction resistance (Hefner and Holmes, 2007; McCallum *et al*, 2010; Pattwell *et al*, 2012). Similarly, human adolescents also show poorer fear extinction retrieval as compared with adults and with younger children (Pattwell *et al*, 2012), indicating the developmental trajectory of extinction is conserved. Deficits in extinction in adolescent rats are associated with the attenuation of mPFC (specifically IL) activation and plasticity, and can be prevented by activating NMDA receptors via D-cycloserine treatment (Kim *et al*, 2009; Pattwell *et al*, 2012). This relative hypofunction of the adolescent mPFC echoes the finding, discussed in greater length later, that the mPFC is a major target for the deleterious effects of stress on extinction in adults.

Given the lasting impact of childhood stress on later risk for developing PTSD, understanding how stress might differentially affect extinction as a function of age remains an outstanding question for future work. Pioneering

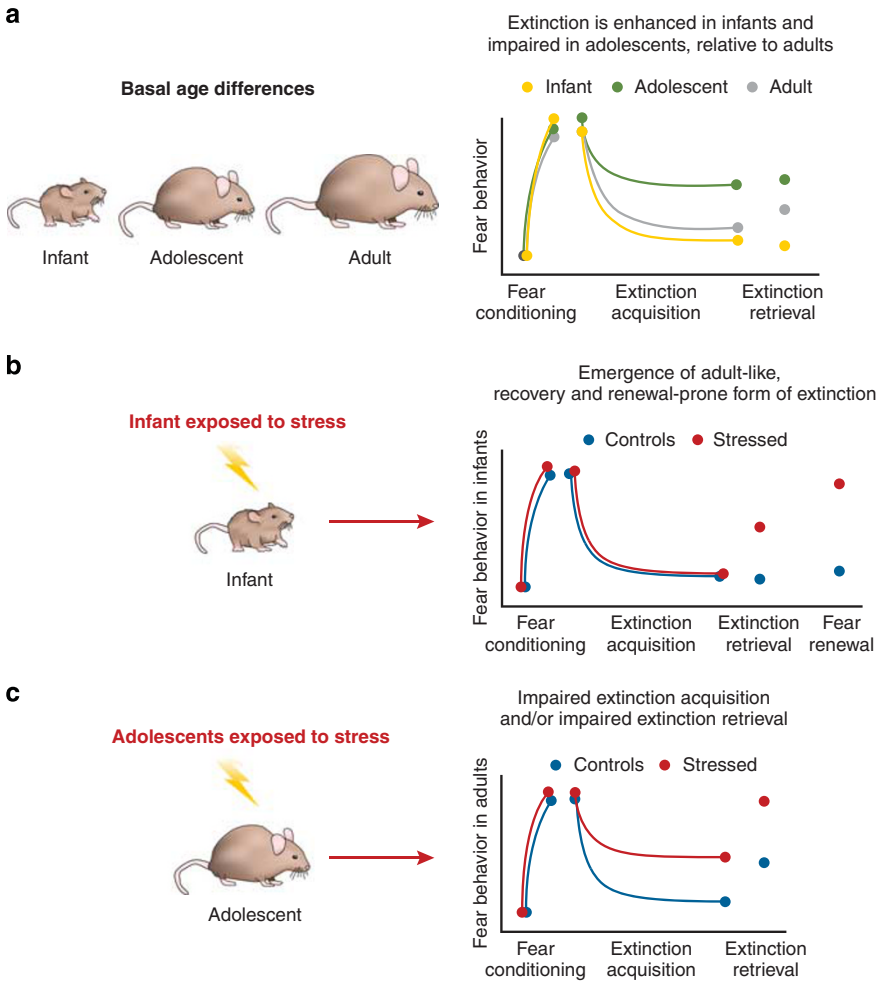

Figure 4. Effects of stress on fear extinction in infant and adolescent rodents. (a) At preweaning ages, infant rodents exhibit an erasure-like form of extinction that is less prone to spontaneous recovery and context-renewal than extinction in post-weaning animals (Kim and Richardson, 2007). (b) Exposing infants to stressors leads to the emergence of the adult form of extinction at preweaning (Callaghan *et al*, 2013). (c) Adolescent rats exposed to chronic stress typically show impaired extinction when tested as adults (Ishikawa *et al*, 2012; Judo *et al*, 2010; Toledo-Rodriguez *et al*, 2012), although there is preliminary evidence that acute stress in adolescence can facilitate extinction (Schayek and Maroun, 2014).

preclinical efforts in this regard, Callaghan and Richardson (2012, 2014) and Cowan *et al* (2013) have shown that infant (pre-weaning) rats subjected to acute or repeated maternal separation (or corticosterone treatment) show the adult-like, rather than infantile, form of extinction (Figure 4). These observations suggest that stress early in life can catalyze the normal developmental ontogeny of extinction. However, the situation may be more complex in adolescence. One recent study found that acute elevated platform stress in postweaning rats facilitated extinction retrieval (Schayek and Maroun, 2014), which is distinct from the stress-impairing effect of stress in adults. However, in other studies that subject adolescents to repeated stressors (eg, predator odor, elevated platform, social instability, social isolation, or footshock), elevated fear or impaired extinction was evident during extinction training when the animals were later tested in young adulthood (Figure 4) (Ishikawa *et al*, 2012; Judo *et al*, 2010; McCormick *et al*, 2013; Toledo-Rodriguez *et al*, 2012; Naert 2011; Skelly *et al*, 2015). Thus, the nature, chronicity, and precise timing of stress exposure in adolescents may be important factors determining how stress alters extinction.

STRESS EFFECTS ON EXTINCTION CIRCUITRY

The effects of stress on fear extinction are mediated, at least in part, by structural and functional alterations within extinction circuits. Here we focus on some of the stress-related abnormalities that have been detected within the prefrontal, hippocampal, and amygdala nodes of the extinction circuitry (for a comprehensive review, see McEwen and Morrison, 2013).

With regards to the amygdala, a series of influential studies by Chattarji and coworkers has shown that chronic immobilization stress leads to dendritic hypertrophy of BLA principal neurons (Mitra *et al*, 2005; Padival *et al*, 2013; Vyas *et al*, 2006; Vyas *et al*, 2002), mimicking the BLA

dendritic hypertrophy in animals with innate extinction deficits (Camp *et al*, 2012). However, dendritic expansion of BLA neurons does not always parallel deficient extinction. Acute elevated platform stress impairs extinction and causes dendritic retraction (Grillo *et al*, 2015; Maroun *et al*, 2013). A more consistent observation across acute and chronic stressors is increased BLA spinogenesis, which can manifest either immediately after stress or following a period of incubation (Maroun *et al*, 2013; Mitra *et al*, 2005).

Stress-induced spinogenesis at BLA neurons is accompanied by increased neuronal excitability, NMDAR-mediated synaptic responsivity and plasticity (LTP), as well as elevated levels of BDNF, with a parallel decrease seen in synaptic inhibition (Chauveau *et al*, 2012; Lakshminarasimhan and Chattarji, 2012; Maroun and Richter-Levin, 2003; Rosenkranz *et al*, 2010; Suvrathan *et al*, 2014). Impaired extinction resulting from exposure to chronic stress in adolescence or adulthood has also been associated with increased BLA, CeA, and hippocampal immediate-early gene (c-Fos) activity and metabolism (2-deoxyglucose) (Hoffman *et al*, 2014; Toledo-Rodriguez *et al*, 2012). In addition, the extinction-impairing SEFL model alters the BLA expression of glutamate and plasticity-associated genes, including the glutamate transporter, EAAT1, and specific glycine α2 and somatostatin type-2 receptors (Ponomarev *et al*, 2010). Taken together, these findings are consistent with a stress-induced shift towards greater excitability, at least a subpopulation, of BLA neurons that results in a bias toward sustained fear and weakened extinction (Roozendaal *et al*, 2009). In agreement with such a scheme, neuropeptide S injected into the LA was recently shown to reverse stress-induced synaptic hyperexcitability and the attendant extinction deficits caused by acute immobilization stress (Chauveau *et al*, 2012).

The impact of stress is not limited to the amygdala, but encompasses the wider neural circuitry mediating extinction. Of particular note, stress leads to structural and functional changes in mPFC and hippocampal regions known to interact with the amygdala in regulating extinction. However, in contrast to the dendritic hypertrophy seen at BLA neurons after stress, stress leads to the loss of dendritic material at mPFC and hippocampal neurons (Leuner and Gould, 2010). Remarkably, even a brief history of swim stress causes dendritic retraction at principal IL neurons and deficits in extinction (Holmes and Wellman, 2009; Izquierdo *et al*, 2006). These observations suggest that in agreement with the known importance of the IL for extinction discussed earlier, stress impairment of extinction could be a result of a loss of function in the IL. Indeed, restoring plasticity in the mPFC, via BDNF infusions, can promote extinction and rescue effects of stress (Graybeal *et al*, 2011; Peters *et al*, 2010). However, the contribution of the IL may not be so straightforward. Damaging the IL can prevent the impairing effects of stress (Farrell *et al*, 2010), implying the IL must be intact at the time of stress in order to drive the neural alterations that ultimately manifest as deficits in extinction.

Electrophysiological recordings of the activity of mPFC neurons during extinction reveal a significant blunting of IL (and PL) neuronal firing in chronically restrained rats exhibiting impaired extinction retrieval (Wilber *et al*, 2011). Similarly, extinction deficits evident during immediate extinction training are accompanied by attenuated mPFC neuronal burst firing as well as IL hypoactivation (indexed by IEG expression) (Chang *et al*, 2010a; Kim *et al*, 2010; Stafford *et al*, 2013). Moreover, pharmacological manipulations that rescue IEDs, including picrotoxin and D-cycloserine, do so in concert with an increase in mPFC neuronal activity (Chang and Maren, 2011). Taken together, these various lines of evidence are consistent with the view that stress influences extinction, at least in part, by interfering with mPFC, although the precise locus of these effects is still not fully clear (Holmes and Wellman, 2009).

One relevant site of neural adaptations induced by stress is at the level of functional connections between the mPFC and BLA. Studies by Maroun and colleagues, and others have demonstrated how extinction deficits produced by acute elevated platform stress are tied to the disruption of synaptic plasticity (LTP) in the mPFC-BLA pathway (Maroun, 2006; Maroun and Richter-Levin, 2003; Richter-Levin and Maroun, 2010; see also Rocher *et al*, 2004). Interestingly, the same stressor was recently found to enhance mPFC-BLA plasticity in adolescent rats, providing another example of how the neural consequences of stress differ as a function of age (Schayek and Maroun, 2014). In adults, stress-induced plasticity changes in mPFC-BLA pathway are associated with multiple of molecular abnormalities in the mPFC. Among these, stressors including maternal separation, SPS, and chronic corticosterone treatment have been shown to cause extinction deficits that are accompanied by the loss of mPFC levels of glutamate and glutamine, and reductions in the mPFC expression of NMDARs (GluN1 and GluN2B) and L-α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid receptors (AMPAR, GluA2/3) (Gourley *et al*, 2009; Knox *et al*, 2010; Wilber *et al*, 2009). This apparent loss of prefrontal glutamate signaling contrasts with the hyperglutamatergic profile of the stressed BLA.

The hippocampus and its connections to the mPFC also undergo signs of functional downregulation in response to stress. For instance, postnatal footshock stress attenuates extinction-related ERK phosphorylation in the CA1 subregion of the hippocampus and the mPFC, and leads to a loss of LTP in the hippocampal-mPFC pathway that can be rescued by systemic treatment with D-cycloserine (Ishikawa *et al*, 2012; Judo *et al*, 2010). In addition, exposure to the extinction-disrupting SEFL model leads to decreased synaptic efficacy in the dorsal hippocampus (Deschaux *et al*, 2014; Spennato *et al*, 2008). Extinction deficits produced by chronic mild stress (Cerqueira *et al*, 2007; Garcia *et al*, 2008) or footshock (Ishikawa *et al*, 2012; Koseki *et al*, 2009) are paralleled by a decrease in hippocampal–PL transmission. Moreover, extinction deficits can be mimicked by low-frequency stimulation of the dorsal hippocampus (Garcia *et al*, 2008) and high-frequency hippocampal stimulation can

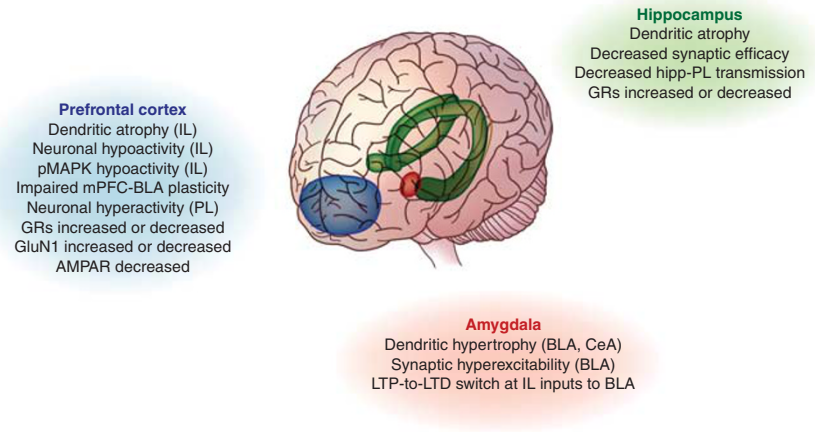

Figure 5. Stress-induced changes in fear extinction-mediating brain regions. Stress produces a range of morphological, electrophysiological and molecular changes in the prefrontal cortex, hippocampus, and amygdala that parallel extinction abnormalities. BLA, basolateral nucleus of the amygdala; CeA, central nucleus of the amygdala; IL, infralimbic cortex; PL, prelimbic cortex.

prevent SEFL-induced extinction deficits (Deschaux *et al*, 2014) in a manner that requires concurrent activation of the mPFC (Deschaux *et al*, 2011). These studies suggest a potential causal role for impaired hippocampal recruitment in stress-impaired extinction.

In sum, current findings paint a picture of amygdala hyperexcitability coupled with loss of important sources of input from hippocampal and prefrontal areas in extinction-impaired stressed animals (Figure 5). We next turn to some of the major molecular events that underlie these system-level changes.

STRESS, GLUCOCORTICOIDS, AND EXTINCTION

A defining feature of stress is the mobilization of glucocorticoids (cortisol in humans and corticosterone in rodents). Glucocorticoids activate MRs and GRs in extinction-mediating brain regions and there is growing indications of a connection, albeit complex, between glucocorticoids and extinction.

Chronically elevating glucocorticoids in pregnant rats through repeated corticosterone administration (or restraint) impairs extinction and decreases GR expression in the mPFC and hippocampus among other regions, when offspring are subsequently examined as adults (Bingham *et al*, 2013; Green *et al*, 2011). Other work has shown that repeated administration of corticosterone in adult rats leads to the loss of NMDARs and AMPARs in the mPFC and again disrupts extinction (Gourley *et al*, 2009). These stress-related losses in prefrontal and hippocampal glucocorticoids and glutamate signaling may contribute to the impaired capacity for forming extinction memories. This notion concurs with the observation that mouse strains exhibiting poor extinction have a pre-existing loss of hippocampal GRs (Camp *et al*, 2012) or forebrain MRs (Ter Horst *et al*, 2012). There are, however, examples in which disruption to extinction following exposure to stressors such as maternal separation and exposure to SPS correlate with increases in mPFC and hippocampal GR expression (Knox *et al*, 2012a; Knox *et al*, 2012b; Wilber *et al*, 2009). Moreover, blocking the SPS-induced upregulation of GRs in these areas by treating rats with the anticonvulsant phenytoin effectively prevents the emergence of extinction deficits (George *et al*, 2015).

One interpretation of these seemingly contradictory findings is that extinction may be sensitive to the deviations from normal GR signaling, with either increases or decreases being sufficient to disrupt behavior. Indeed, although some of the aforementioned studies (eg, George *et al*, 2015) suggest that preventing corticohippocampal GR upregulation may be able to prevent stress from impairing extinction, the formation of extinction memories is also known to require glucocorticoids. In a variety of experimental designs, acute administration of exogenous corticosterone or the synthetic glucocorticoid, dexamethasone, facilitates extinction in rats and certain mouse strains (Abrari *et al*, 2008; Brinks *et al*, 2009; Cai *et al*, 2006; Ninomiya *et al*, 2010; Yang *et al*, 2006; Yang *et al*, 2007). Conversely, blocking the synthesis of corticosterone synthesis (with metyrapone) produces deficits in extinction (Barrett and Gonzalez-Lima, 2004; Blundell *et al*, 2011; Yang *et al*, 2006; Yang *et al*, 2007, but see Clay *et al*, 2011).

The bidirectional modulation of extinction by glucocorticoids likely involves the amygdala given the effects of systemic treatments can be recapitulated by direct delivery into the BLA. Microinfusion of the GR agonist (RU28362) or the GR antagonist (mifepristone) into the BLA before extinction training leads to facilitation and impairment in extinction, respectively (Yang *et al*, 2006). In addition, the extinction-facilitating effects of systemically administered dexamethasone are prevented by blocking (with AP5 or MK-801) NMDARs in the BLA (Yang *et al*, 2007), a finding which further implicates the BLA as a key site of glucocorticoid action and suggests that GRs regulate glutamatergic plasticity in this region. Importantly, plasticity-promoting

actions of GR signaling in the BLA are not limited to the formation of extinction memory. In the same studies showing that pre-extinction corticosterone treatment improves extinction, the same treatment given before fear conditioning produces stronger, extinction-resistant fear memory (Brinks *et al*, 2009). This is entirely in agreement with the well-established role GRs have in enhancing emotional memories (Roozendaal and McGaugh, 2011).

From a clinical standpoint, the use of GR-acting drugs as a novel treatment for PTSD has attracted considerable attention (see Figure 6 for a putative model of how GR and NMDA receptor agonists might act). Phobic patients administered the synthetic glucocorticoid (hydrocortisone) before exposure therapy showed improved therapeutic outcome at follow-up (de Quervain *et al*, 2011; Soravia *et al*, 2006). Preliminary work with the same drug in PTSD patients has thus far been negative (Suris *et al*, 2010), but the results of larger clinical trials are expected in the near future (Yehuda *et al*, 2010) (see clinicaltrials.gov identifier NCT01090518).

STRESS, eCBS, AND EXTINCTION

Recent evidence indicates that glucocorticoids transduce their effects on fear in part through the modulation of eCBs. Stress and glucocorticoids rapidly increase eCBs in extinction-mediating regions such as the BLA and, in turn, eCBs regulate glucocorticoids and the HPA axis to create a functional feedback loop (Hill *et al*, 2010b). The ability of glucocorticoids (via systemic corticosterone, dexamethasone, or intra-BLA RU28362) to enhance fear memory is occluded by blockade of CB1R (via AM251) in the BLA or hippocampus (Atsak *et al*, 2014; Atsak *et al*, 2012; Campolongo *et al*, 2009; de Oliveira Alvares *et al*, 2010). Moreover, fear memory enhancement achieved by activating CB1R in the BLA (with WIN55,212-2) is not prevented by blocking GRs (via RU38486), which is consistent with GR being upstream of eCBs (Atsak *et al*, 2014). However, the finding that the corticosterone synthesis inhibitor metyrapone blocks the enhancement of fear memory by CB1R agonists (Campolongo *et al*, 2013) suggests that GRs and eCBs likely interact in a more complex, bidirectional manner.

The contribution of eCBs to glucocorticoid-mediated extinction remains to be determined but is a question of significant interest given recent findings. First, improvements in extinction are found after augmenting eCBs levels by inhibiting uptake or reducing degradation of anandamide via FAAH inhibition or point mutation (Chhatwal *et al*, 2005; de Oliveira Alvares *et al*, 2008; Dincheva, 2015; Gunduz-Cinar *et al*, 2013b; Pamplona *et al*, 2006). Second, the rapid release of corticotropin-releasing hormone (CRH), acting through the CRHR1 receptor, has recently been identified as a mechanism that, by suppressing FAAH activity, causes reductions in BLA anandamide levels that precede, and are independent of, the mobilization of glucocorticoids (Gray *et al*, 2015). These opposing, temporally

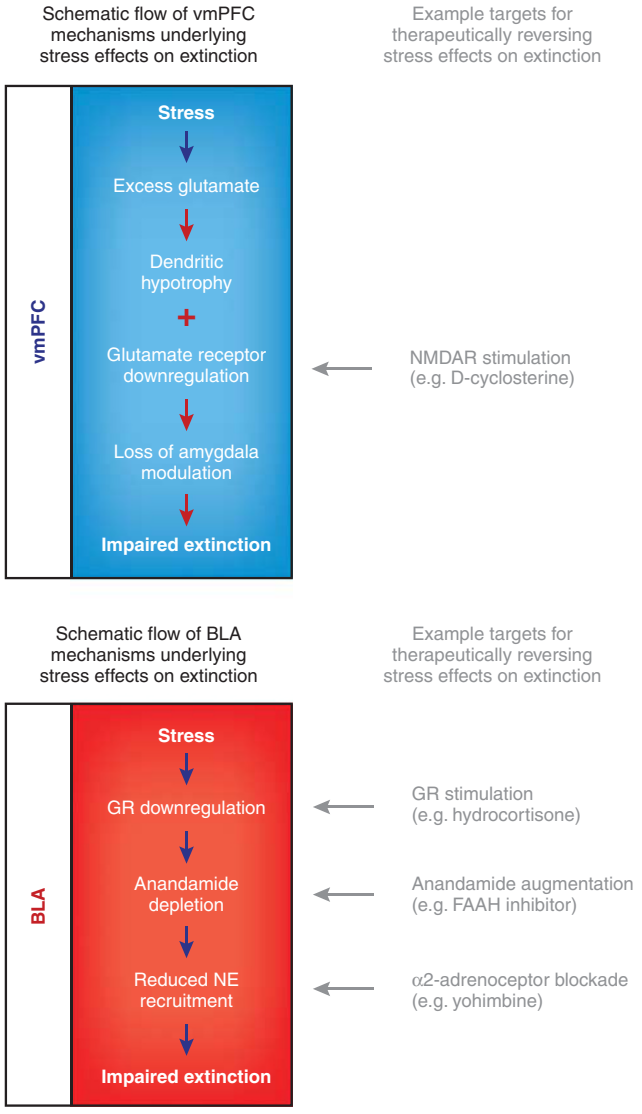

Figure 6. Putative schematic flow of mechanism in the ventromedial prefrontal cortex (vmPFC) and basolateral nucleus of the amygdala (BLA) underlying stress-induced extinction deficits. In the vmPFC, stress has been shown to cause excess glutamate and associated dendritic hypotrophy and downregulation of glutamate receptors. These adaptations could lead to loss of vmPFC modulation of the amygdala and a resulting impairment in extinction that may be prevented by stimulating NMDA receptors using, eg, D-cycloserine. In the BLA, GR downregulation and anandamide depletion is seen after stress, which could in turn lead to reduced engagement of noradrenergic transmission and deficient extinction. There may be multiple points of intervention to reverse this cascade, including stimulating GRs or elevating anandamide with hydrocortisone and FAAH inhibitors, respectively, or blocking α2-adrenoceptors with yohimbine to increase BLA noradrenaline. BLA, basolateral amygdala; NE, norepinephrine; GR, glucocorticoid receptor; vmPFC, ventromedial prefrontal cortex.

dissociated effects of CRH and glucocorticoids on BLA anandamide could impact stress-induced deficits in extinction in important ways that will require further work to parse. A corollary question is whether the pro-extinction efficacy of putative eCB-augmenting treatments in PTSD varies as a function of prior stress history and the functional

status of an individual's glucocorticoid system. In normal human subjects, acute pre-extinction administration of dronabinol, a synthetic version of Δ9-tetrahydrocannabinol (Rabinak *et al*, 2013b), or cannabidiol (Das *et al*, 2013), a compound with FAAH-inhibiting properties (Leweke *et al*, 2012), improves extinction retrieval coincident with enhanced recruitment of the vmPFC–amygdala circuit (Rabinak *et al*, 2013a). How these beneficial effects are impacted by stress remains to be clarified, but we offer an heuristic model for how FAAH inhibitors could combat stress effects on extinction in Figure 6.

STRESS, NOREPINEPHRINE, AND EXTINCTION

The norepinephrine (NE) system provides a further functional link between glucocorticoids and eCBs. Noradrenergic activity in the BLA, acting through the β-adrenoceptor (β-AR), promotes fear memory and the ability of both glucocorticoids and eCBs to enhance fear memory requires the activity of BLA β-ARs (ie, they are prevented by the β-AR blocker propranolol) (Atsak *et al*, 2014; Roozendaal *et al*, 2009). On the basis of these observations, some authors suggest that glucocorticoids trigger eCBs to inhibit GABAergic interneurons, which in turn disinhibit NE release onto β-ARs and increases the sensitivity of principal BLA neurons to NE input (Hill and McEwen, 2010a; Morena and Campolongo, 2014). This mechanistic scheme could account for the aforementioned interaction between β-AR gene variation, childhood stress, and risk for PTSD (Liberzon *et al*, 2014).

The β-AR has also received significant attention clinically as a potential therapeutic for extinction and the β-AR antagonist propranolol has shown some efficacy as an adjunct to exposure therapy, although the results remain preliminary (Brunet *et al*, 2014). The mechanism by which propranolol would augment extinction remains unclear. Given that extinction is an active learning process requiring the activation of principal BLA 'extinction' neurons (Herry *et al*, 2010), blockade of β-ARs would presumably interfere with noradrenergic (as well as glucocorticoid) mediation of extinction. This is borne out by experimental studies in normal human subjects (Bos *et al*, 2012), which have reported extinction impairments following administration of propranolol (Mueller *et al*, 2008). However, it may be that under stressful conditions, elevated noradrenergic signaling impedes extinction learning, an effect that might be counteracted by propranolol. Indeed, propranolol has recently been shown to stabilize stress-induced changes in PFC firing and attenuate the immediate extinction deficit (Fitzgerald *et al*, 2015b).

By the same logic, augmenting noradrenergic activity at the time of extinction memory formation would be expected to promote extinction. In support of this, yohimbine, an α2-adrenoceptor antagonist that increases NE release, promotes extinction in some preclinical studies (Davis *et al*, 2008; Holmes and Quirk, 2010; Janak and Corbit, 2011). Yohimbine has also been found to improve the efficacy of exposure therapy in patients with claustrophobic and social anxiety disorder (Powers *et al*, 2009; Smits *et al*, 2014), with studies in PTSD sufferers currently underway (clinicaltrials.gov identifier NCT01031979) (see Figure 6 for a model of how yohimbine might act to reverse stress-impaired extinction). Again, a caveat is that the efficacy of manipulations that enhance or limit noradrenergic transmission may critically depend on the basal state of NE transmission at the time of the intervention. For example, under stressful conditions and elevated NE transmission it might be expected that a noradrenergic agonist might impair (rather than promote) extinction by exacerbating the deleterious influence of stress on extinction. That is, it is likely that an inverted-U function defines optimal NE signaling for extinction learning and stress may shift this function in a way that alters the efficacy of noradrenergic modulators.

Future directions and clinical implications

The last decade has witnessed remarkable progress that has broadened our understanding of the brain mechanisms for extinction-based therapies and the vulnerabilities of these mechanisms to stress. The challenges, of course, are to develop strategies to dampen stress-induced impairments in extinction, as well as to deepen the endurance and generalization of extinction memories once formed. As we have seen, there are now several pharmacological cognitive enhancers for PTSD (Singewald *et al*, 2014; Bukalo *et al*, 2014) and many of these compounds facilitate extinction learning (Fitzgerald *et al*, 2014a) (Figure 6). Moreover, there are ongoing efforts to improve behavioral therapies by incorporating extinction reminders, eg, to limit relapse of fear after therapy (Vervliet *et al*, 2013). Yet, in the end, extinction-based therapies will always be limited by the impermanence of this form of learning. Ultimately, a more effective approach might be the targeted erasure of traumatic memories—at least the emotional components of traumatic memories central to PTSD. Interestingly, this approach has met with success in both animals and people.

In the first study of its kind, Monfils *et al* (2009) examined whether delivering extinction trials soon after reactivating a fear memory would produce a more enduring loss of fear by impairing the reconsolidation of that information. They found that delivering extinction trials from 10 min to 1 h after a single CS reminder (itself an extinction trial) resulted in loss of conditional responding that showed less spontaneous recovery, renewal, and reinstatement than that obtained after a standard extinction procedure. A similar effect has been described in healthy humans (Schiller *et al*, 2010). In both cases, it has been argued that the retrieval-extinction procedure may produce a more enduring loss of fear by preventing memory reconsolidation, thereby effectively erasing the fear memory. Indeed, there is evidence to suggest, at least in animals, that changes in glutamate

receptors at BLA synapses may account for the loss of conditional responding (Clem and Huganir, 2010; Monfils *et al*, 2009). That said, this retrieval-extinction procedure has not always proved effective at eliminating fear relapse (Chan *et al*, 2010; Costanzi *et al*, 2011) and extinction administered soon after conditioning (when fear memories are in an active state) fails to yield long-term extinction (Macpherson *et al*, 2013; Maren and Chang, 2006; Stafford *et al*, 2013). Moreover, it is difficult to know whether a manipulation truly erased fear memory or produced a particularly deep extinction (Lattal and Wood, 2013). Clearly, further work is required to understand the conditions under which memories might be erased by extinction procedures (Auber *et al*, 2013).

In addition to behavioral procedures, pharmacological manipulations have been used to target the reconsolidation of fear memories as previously described (Nader and Hardt, 2009). Of these, the most promising manipulation for use in humans is propranolol (Kindt *et al*, 2009; Pitman *et al*, 2006). For example, Kindt *et al* (2009) found that fear memories (indexed by startle) in healthy humans could be erased (ie, the CR failed to reinstate) by reactivating the fear memory under propranolol. Much of this work has been interpreted in terms of propranolol's properties as a protein synthesis inhibitor to disrupt the reconsolidation of reactivated fear memories (Otis *et al*, 2015; Soeter and Kindt, 2011). Despite the early promise in healthy humans, results have been underwhelming in clinical populations studied to date (Wood *et al*, 2015) (additional data are pending, see clinicaltrials.gov identifier NCT01127568). One possibility is that propranolol or retrieval-extinction procedures, which have typically been tested in isolation, might be particularly effective if administered together.

Of course, it has been argued that extinction memories are not necessarily impermanent (Lattal and Wood, 2013). By this view, either enhanced extinction or reconsolidation failure could account for the enduring loss of fear after a variety of behavioral or pharmacological manipulations. From this perspective, molecular strategies to strengthen extinction memory hold promise for achieving lasting suppression of conditional fear. In this regard, there is considerable interest in the possibility that epigenetic modifications can sustain long-term extinction memories. For example, some very recent work indicates that specific histone deacetylase (HDAC) inhibitors can facilitate the consolidation of fear extinction (Bowers *et al*, 2015; Stafford *et al*, 2012; Whittle *et al*, 2013; Pizzimenti and Lattal, 2015). Moreover, HDAC2-targeted inhibitors coupled with memory reactivation and extinction can lead to persistent loss of even remote fear memories that are normally resistant to updating (Gräff *et al*, 2014). This suggests that memory reactivation coupled with extinction procedures and memory-promoting adjuncts may hold the key for establishing deep extinction memories that are resistant to fear relapse.

There is clearly much yet to learn about the conditions that dampen the deleterious effects of stress on extinction, promote and deepen extinction memories, and erase unwanted fears. Ultimately, it can be said that the field has made considerable progress on all fronts, producing important mechanistic information on extinction learning that is being translated to human clinical trials and novel therapies. The clinical implications of this progress are enormous; there is no doubt that this work will herald a new era of neurobiologically informed pharmacotherapies to revolutionize the treatment of stress and trauma-related disorders.

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