The influence of acute stress on the regulation of conditioned fear

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ABSTRACT

Fear learning and regulation is a prominent model for describing the pathogenesis of anxiety disorders and stress-related psychopathology. Fear expression can be modulated using a number of regulatory strategies, including extinction, cognitive emotion regulation, avoidance strategies and reconsolidation. In this review, we examine research investigating the effects of acute stress and stress hormones on these regulatory techniques. We focus on what is known about the impact of stress on the ability to flexibly regulate fear responses that are acquired through Pavlovian fear conditioning. Our primary aim is to explore the impact of stress on fear regulation in humans. Given this, we focus on techniques where stress has been linked to alterations of fear regulation in humans (extinction and emotion regulation), and briefly discuss other techniques (avoidance and reconsolidation) where the impact of stress or stress hormones have been mainly explored in animal models. These investigations reveal that acute stress may impair the persistent inhibition of fear, presumably by altering prefrontal cortex function. Characterizing the effects of stress on fear regulation is critical for understanding the boundaries within which existing regulation strategies are viable in everyday life and can better inform treatment options for those who suffer from anxiety and stress-related psychopathology.

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1. Introduction

Experiencing stress is an inevitable part of daily life that serves a critical role in shaping adaptive behavior. Brief exposure to stress can be a powerful motivating force in both the pursuit of rewards and avoidance of punishment, and can rapidly boost energy stores in times of homeostatic disruption to ensure safety and survival. However, stress exposure and the concomitant neurophysiological response it elicits can also exert detrimental effects on brain regions that facilitate the control and regulation of behavior. These effects are especially relevant for the regulation of fear expression, where top-down regulatory mechanisms are engaged to control emotional responses to threatening stimuli. This process—broadly referred to as 'emotion regulation'—allows an individual to tailor emotional responses and behavior to a dynamic environment (Gross and Thompson, 2007). The capacity to regulate fear responses to threatening cues once the value or significance of such cues change is critical to emotional resilience and health, while deficits in fear regulation capacity strongly predict vulnerability to

an array of affective psychopathology, such as anxiety disorders and depression (Cisler et al., 2010; Johnstone et al., 2007).

Fear responses can be flexibly changed through a broad range of processes that include learning that an aversive stimulus no longer poses a threat, or adopting a strategy to deliberately change the nature of an emotional response. These techniques have been repeatedly shown to inhibit or alter fear expression in the service of generating more adaptive responses that are better aligned with the current state of the environment. Importantly, the adaptive benefits afforded by fear regulation are widely known to rely on intact functioning of the prefrontal cortex (PFC), which supports the inhibition and flexible control of fear (see Hartley and Phelps, 2010 for review). The PFC, however, is also a major target of stress hormones that a growing body of research suggests can markedly impair its function (see Arnsten, 2009 or Holmes and Wellman, 2009; for reviews). This suggests that the flexible control of fear responses to aversive stimuli may be compromised when accompanied or preceded by exposure to stress. Despite the significance of this possibility, stress has remained largely unexplored within the fear regulation literature.

In this review, we examine research investigating the effects of stress and stress hormones on regulatory techniques used to

flexibly control fear responses in humans. Before doing so, it is important to recognize that the constructs of fear and stress are often conflated in the literature due to their behavioral, neural and neurochemical similarities. To clearly differentiate fear expression from that of a stress response in the context of this review, we refer to fear expression as discrete emotional or behavioral responses that occur when an organism detects a threat in its environment, or when it encounters a cue that has predicted danger in the past. In rodents, fear expression is typically measured through defensive behaviors such as freezing, whereas in humans fear is often assessed by recording transient sympathetic nervous system arousal responses (i.e., skin conductance, pupil dilation) in the presence of a threatening stimulus (Critchley et al., 2002, 2013). In contrast, a stress response is operationalized as a more pervasive response that unfolds over a longer timescale and recruits a range of neuromodulatory systems. Unlike transient fear arousal, stressors produce more intense and prolonged response to homeostatic disruptions, eliciting both autonomic and neuroendocrine systems that can exert a broad range of effects on brain function and behavior.

Fear expression can be modulated using a number of regulatory strategies, including extinction learning and retention, cognitive emotion regulation, avoidance strategies and reconsolidation. Extinction learning and retention is the most commonly explored form of fear inhibition and occurs by learning through experience that a stimulus is no longer associated with a threatening outcome. Cognitive emotion regulation refers to a broad range of regulatory strategies that can be used to deliberately alter the nature of an emotional response. Avoidance strategies entail performing certain behaviors in order to prevent the occurrence of an aversive outcome. Finally, interfering with the reconsolidation of fear memories can lead to reductions in fear expression by persistently modifying aversive associations. The neural circuitry underlying each of these forms of fear regulation overlaps with the neural systems that orchestrate both the response to and recovery from stress exposure, rendering these techniques especially sensitive to the effects of stress. Despite the pervasive use of these strategies in research and real-world settings, relatively little is known regarding their efficacy when accompanied or preceded by exposure to stress. Understanding how stress affects these regulatory processes has broad implications both for adaptive daily functioning and for how stress-induced regulatory impairments may lead to or exacerbate affective psychopathology.

Below we discuss what is known about the impact of stress on the ability to flexibly regulate fear responses that are acquired using standard Pavlovian fear conditioning, a fundamental form of associative learning that imbues biologically insignificant cues with aversive value. Given that our primary aim is to explore the impact of stress on fear regulation in humans, we primarily discuss techniques where stress has been linked to alterations of fear regulation in humans (extinction and emotion regulation), although we also briefly mention other techniques (avoidance and reconsolidation) where the impact of stress or stress hormones have been mainly explored in animal models.

We begin by providing a brief overview of the neurobiological mechanisms of acute responses to stress. We then review the behavioral and neural mechanisms underlying Pavlovian fear acquisition and extinction. Our focus in this review is placed primarily on the learning and regulation of cued fear associations, which rely on the amygdala and surrounding brain regions. In the interest of space, we do not cover contextual fear learning and regulation processes, which are known to instead rely on the hippocampus. However, we do mention specific findings from other fear learning procedures when relevant. Since stress may differentially impact different phases of fear conditioning, we discuss the effects of stress and stress hormones on the phases (i.e., learning, consolidation, retrieval) of fear acquisition and extinction by surveying research that has induced stress or administered stress hormones before or concurrently with these phases. We then review the mechanisms of cognitive emotion regulation and the impact of stress in humans. Finally, we briefly review other fear regulation techniques (avoidance and reconsolidation) where the impact of stress and stress hormones have mainly been explored in animal models.

2. The neurobiology of an acute stress response

Stress is induced when real or perceived threats are detected in the environment (Joels et al., 2012). Stressors can emerge from a number of sources that can be generally categorized as physical or psychological in nature. Physical stressors comprise threats to survival such as predatory threats that signal imminent danger, or disruptions to homeostasis such as hunger, sickness or pain. Psychogenic stressors constitute emotional or social threats that may occur through negative social evaluation or severe emotional distress (Dickerson and Kemeny, 2004). Irrespective of their source, stressors are typically characterized by the perception of being novel, unpredictable and, importantly, outside of one's control (Lupien et al., 2007).

The detection of a stressor promotes a broad range of hormonal and neurotransmitter responses that can exert a powerful influence on brain function and behavior (McEwen, 2003). Acute stress exposure rapidly activates the autonomic nervous system through its sympathetic branch that triggers peripheral responses, such as increased respiration, heart rate and blood pressure and allocates metabolic resources to promote defensive behavior (Goldstein, 2003; Ulrich-Lai and Herman, 2009). This response also triggers catecholamine release by way of sympathetic nerves that activate noradrenergic terminals throughout the body, as well as the adrenal medulla that releases adrenaline directly into the bloodstream.

In contrast, the hypothalamic-pituitary-adrenal (HPA) axis elicits neuroendocrine effects that peak at a longer timescale after stress exposure. Activation of the HPA-axis triggers the systemic release of glucocorticoids (cortisol in humans) that can work in a synergistic manner with catecholamines to potentiate their short-lived effects (Ulrich-Lai and Herman, 2009). This is especially so for the effects of stress on modulating emotional learning and memory, as noradrenergic signaling is critical to the enhancing effects of glucocorticoids on memory consolidation and retrieval (Quirarte et al., 1997; Roozendaal et al., 2009). Stressors activate the HPA-axis through the release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus (PVN) of the hypothalamus. When CRH reaches the anterior pituitary gland, it elicits adrenocorticotropic hormone (ACTH) release, which prompts glucocorticoid synthesis in the adrenal glands. Finally, glucocorticoids are released into the bloodstream where they travel and bind to receptors throughout the body and brain (McEwen et al., 1986; DeKloet, 2004; Sapolsky et al., 2000). Glucocorticoid release follows a slower time course than rapidly released catecholamines, peaking 10–20 min after the onset of stress exposure (Sapolsky et al., 2000). Glucocorticoids are often characterized as a recovery hormone that adapts an organism to the neurophysiological changes that occur during stress (Lupien et al., 2007). Collectively, these two systems interact and function in a complementary manner to mobilize energy and help an organism cope with stressful experiences.

Despite the inability of peripheral catecholamines to cross the blood−brain barrier, noradrenaline is projected throughout the brain by way of the locus coeruleus (LC). The LC serves as the brain's

primary source of noradrenaline and shares reciprocal connections with brain regions that are critical to the acquisition and regulation of conditioned fear, such as the amygdala, hippocampus and PFC (Benarroch, 2009). The high proportion of noradrenaline receptors in the amygdala and PFC render these brain regions especially sensitive to the effects of stress (McEwen et al., 1986). Circulating glucocorticoids can influence brain function by readily crossing the blood–brain barrier and binding to high-affinity mineralocorticoid and low-affinity glucocorticoid receptors distributed throughout the amygdala, hippocampus and PFC (Joel et al., 2012; Lupien, 2007). The effects of glucocorticoids include dampening glucose transport within cortical neurons and glia cells, which may further influence brain function by diminishing processing and amplifying the effects of early catecholamine release by slowing their clearance from synaptic space (Grundemann et al., 1998; Ferry et al., 1999; Roozendaal et al., 2002). The release of glucocorticoids is controlled through negative feedback mechanisms housed within the PFC, suggesting that this region is targeted both for glucocorticoid binding under stress and for the regulation of glucocorticoid release (Diorio et al., 1993). Consistent with this, both chronic exposure to stress and affective psychopathology have been shown to be related to deficits in HPA regulation and inhibition (Cacioppo et al., 1998; Nyklicek et al., 2005; Radley et al., 2006).

3. Neurocircuitry of Pavlovian fear acquisition and extinction

Learning to respond appropriately to cues that signal danger is critical to survival and can facilitate adaptive behavior. Pavlovian fear conditioning is often used as a laboratory paradigm to examine how biologically insignificant stimuli can acquire emotional relevance as they come to predict aversive events. In a standard cued Pavlovian fear conditioning paradigm a neutral stimulus, such as a light or tone (conditioned stimulus, or CS), is paired with an innately aversive stimulus, such as an electric shock or noxious odor (unconditioned stimulus, or US) (Pavlov, 1927). The US will automatically elicit an array of physiological, neuroendocrine and behavioral responses consistent with defensive behavior. After a few trials a reinforced CS can come to elicit similar responses to that of the US itself. A long tradition of research in animals and humans has provided an intricate understanding of the behavioral and neural systems underlying aversive learning and regulation.

The amygdala has been shown across species to be critical for the acquisition, storage and expression of conditioned fear (for review, see LeDoux, 2000; Maren, 2001; Davis and Whalen, 2001; Phelps, 2006). The amygdala contains functionally and anatomically distinct nuclei including the lateral (LA), basal (B) and central (CE) nucleus that enables the acquisition and physiological expression of aversive learning. When a CS is presented in conjunction with a US, cortical and thalamic sensory input converge in the lateral amygdala to form the CS-US association. The CE receives this input directly from the LA, or indirectly through the basal or accessory basal (BA) nuclei of the amygdala (collectively referred to as the basolateral amygdala, or BLA) (Krettek and Price, 1978; LeDoux, 2000; PItkanen et al., 1997). The CE serves as a major relay station to brainstem and hypothalamic regions that control threat responses engendered by the US alone (LeDoux, 2000; Maren, 2001; Davis and Whalen, 2001; Pare et al., 2004; Likhtik et al., 2008; Ehlich et al., 2009). Clusters of inhibitory GABAergic interneurons—referred to as the intercalated cell masses—also mediate interactions between the LA and CE by gating fear expression (Millhouse, 1986; Sah et al., 2003; LeDoux, 2007; Ehlich et al., 2009).

The amygdala contains reciprocal connections with surrounding brain regions to integrate sensory information and tailor conditioned fear responses appropriately across different circumstances.

These regions include the insula, which is thought to convey visceral sensory information that is important in pain perception and signaling the internal state of an organism (Shi and Davis, 1999 Craig, 2002); the hippocampus, which is critical for the contextual modulation of fear learning and regulation (Kim and Fanselow, 1992; Phillips and LeDoux, 1992; Maren, 2001; LaBar et al., 2005); the striatum, which is involved in tracking CS reinforcement and the instrumental avoidance of aversive outcomes (LeDoux and Gorman, 2001); and the medial prefrontal cortex, which is partitioned into the prelimbic (PL) and infralimbic (IL) cortex. These subregions are thought to play opposing roles in the expression and regulation of fear responses (Sotres-Bayon and Quirk, 2010; Sierra-Mercado et al., 2011).

The PL is broadly involved in conditioned fear expression and integrating sensory and affective information from somatosensory cortex (Peters et al., 2009; Milad et al., 2007). This brain region is thought to align in a functional manner to that of the human dorsal anterior cingulate cortex (dACC), a region shown to be involved in fear responses to both conditioned (LaBar et al., 1998; Buchel et al., 1998; Knight et al., 2004; Phelps et al., 2004), and unconditioned (Dunsmoor et al., 2008; Knight et al., 2010; Linnman et al., 2011) stimuli. This region has also been shown to be both structurally and functionally associated with individual differences in fear expression in humans, such that physiological arousal responses during fear conditioning correlate positively with dACC volume and activity (Milad et al., 2007; but see Hartley et al., 2011). In contrast, the IL region of the medial prefrontal cortex, (vmPFC, in humans) is critical to the inhibition of fear expression when circumstances become safe (Milad and Quirk, 2012).

Once a stimulus has acquired aversive value, defensive responses can be inhibited or controlled using a number of regulatory methods. Among the most widely studied of these is extinction training, which comprises the foundation of exposure therapy, a therapeutic technique used by clinicians to treat symptoms of anxiety disorders. During extinction learning, conditioned threat responses gradually diminish after a CS that previously signaled danger is repeatedly presented in the absence of the US (Pavlov, 1927). The development of this new, safe association relies on active learning processes, and in contrast to some early learning models (Rescorla and Wagner, 1972), does not constitute the elimination of the original CS-US association (Bouton, 2004). Evidence that extinction is an active learning process comes from research across species that demonstrates how fear expression toward an extinguished CS can re-emerge over time (spontaneous recovery), by introducing the original aversive learning context (renewal) or after unexpected presentations of the US (reinstatement) (for review, see: Bouton, 2004).

Converging evidence from electrophysiological, pharmacological and lesion studies in rodents suggests a critical role for the amygdala in extinction learning and consolidation. Plasticity within the LA and BA is thought to facilitate extinction learning by diminishing CS-related activity when US reinforcement is omitted (Quirk et al., 1997; Myers and Davis, 2007; Hobin et al., 2003). However, a distinct population of these neurons has been found to remain responsive during extinction learning (Repa et al., 2001), supporting the notion that the CS-US association is maintained. Recent research in rodents has also identified specific cell populations within the BA that are only responsive to the CS during extinction training and that correlate with behavioral extinction performance (Herry et al., 2008). Collectively, this suggests that the amygdala plays an active role in extinction learning by modulating fear expression in the presence of an extinguished CS by way of functionally distinct neuronal populations. However, extinction learning also involves reciprocal interactions between the amygdala and the PL and IL subregions of the vmPFC, which can

differentially influence fear expression (see Herry et al., 2010; Milad and Quirk, 2012, for recent reviews).

The PL promotes fear expression through reciprocal connections with the (BLA) amygdala, which provides signals regarding the presence of a threat. These signals are thought to become amplified within the PL before projecting back to amygdala nuclei that then relay these signals to output regions that engender fear expression (Milad and Quirk, 2012). Consistent with this, firing rates of PL neurons intensify in the presence of an aversive CS in a manner related to assays of fear expression (i.e., freezing) (Burgos-Robles et al., 2009). Stimulation of the PL subregion enhances fear expression to CSs and slows extinction learning (Vidal-Gonzalez et al., 2006), while inactivation the PL leads to reduced fear expression to an aversive CS (Corcoran and Quirk, 2007; Sierra-Mercado et al., 2011).

Conversely, the IL plays a critical role in fear inhibition and regulation. Recent research in rodents has suggested that during extinction learning, these functionally distinct cell populations in the LA and BA may signal the presence of a 'safe' CS to the IL region of the vmPFC, which can then feedback to this same population of neurons (Repa et al., 2001; Herry et al., 2008; Burgos-Robles et al., 2009). The IL can then suppress fear expression by inhibiting the CE directly (Quirk et al., 2003) or indirectly through the ITCs that surround the BA and LA and project heavily to the CE (Pare et al., 2004; Millhouse, 1986; McDonald, 1998; Vertes, 2004). The IL can also activate local inhibitory interneurons in the LA to gate fear expression (Rosenkranz et al., 2003). Finally, the hippocampus also plays an important role by providing contextual modulation of extinction learning (Milad and Quirk, 2012).

Although extinction training serves as a useful paradigm to model safety learning, the viability of extinction training as a therapeutic option for treating affective disorders depends critically on the extent to which this learning is retained and later utilized when cues are again encountered. Research across species has demonstrated a critical role for the IL of the vmPFC in the retention and retrieval of extinction learning (Akirav and Maroun, 2007; Quirk and Mueller, 2008; Holmes and Wellman, 2009; Sotres-Bayon and Quirk, 2010; Milad and Qirk, 2012). In rodents, IL activity correlates with levels of extinction retrieval (Milad and Quirk, 2012) and stimulating the IL inhibits fear expression and strengthens extinction retrieval (Milad et al., 2004). In contrast, inactivation of IL circuits leads to deficits in extinction retrieval (Sierra-Mercado et al., 2011). Neuroimaging work in humans is largely consistent with these findings. During extinction learning, vmPFC activity increases (Phelps et al., 2004) and correlates with the magnitude of later extinction retention (Milad et al., 2007). The vmPFC is also active during extinction retrieval (Phelps et al., 2004; Kalisch et al., 2006) and the volume of cortical tissue in this region has been shown to be positively associated with the magnitude of extinction retrieval (Hartley et al., 2011), confirming an important role across species for this region in the successful retrieval of extinction training.

4. The influence of stress on Pavlovian fear acquisition and extinction

4.1. Acquisition and consolidation

Although the primary focus of this review is the impact of stress on regulating fear responses to aversive stimuli, the influence of stress on the acquisition and storage of fear associations has implications for future attempts to regulate responses to these acquired fears. As outlined earlier, the acquisition and storage of Pavlovian fear conditioning primarily depends on the amygdala. The amygdala's central role in modulating aversive learning and expression means it is also positioned to respond in a highly sensitive manner to stress and stress hormones. Specifically, noradrenergic release during acute stress enhances amygdala function (Tully et al., 2007; McGaugh, 2004) and works in concert with circulating glucocorticoids to modulate the learning and consolidation of aversive associations (see LeDoux, 2000; Rodrigues et al., 2009 or Roozendaal et al., 2009 for review). Research in animals has demonstrated that exposure to stress facilitates the acquisition of cued fear learning as measured by within-session performance (Wilson et al., 1975; Shors et al., 1992; Shors, 2001). Noradrenaline appears to be critical to this enhancement as blocking noradrenaline in the amygdala before training impairs the acquisition of cued fear conditioning (Bush et al., 2010). This does not appear to be the case for glucocorticoids since studies have found blocking their release does not affect the initial fear acquisition performance (Jin et al., 2007; Rodrigues and Sapolsky, 2009).

Stress and stress hormones strongly influence the consolidation of cued fear learning. Glucocorticoids play an essential role in this process by interacting with noradrenaline in the amygdala to promote enhanced storage of aversive associations (Ferry et al., 1999; Roozendaal et al., 2002). Stress induced prior to training leads to enhanced consolidation of aversive learning as measured by later retrieval (Conrad et al., 1999; Rau et al., 2005; Rau and Fanselow, 2009). Stress (Hui et al., 2006) or glucocorticoid administration (Hui et al., 2004) directly after fear conditioning enhances the consolidation of aversive associations, while blocking glucocorticoid release impairs its consolidation (Jin et al., 2007; Rodrigues and Sapolsky, 2009). Interestingly, blocking noradrenergic activity after cued aversive learning training does not impair the consolidation of fear learning (Bush et al., 2010; Debiec and LeDoux, 2004; Lee et al., 2001), suggesting that noradrenergic release during training alone is sufficient to facilitate consolidation. However, noradrenergic activity appears to be necessary for the enhancing effects of stress-induced glucocorticoids on fear learning as blocking noradrenaline during concurrent administration of glucocorticoids into the amygdala impairs cued fear memory enhancements seen with glucocorticoid adminstration alone (Roozendaal et al., 2006). This is consistent with the notion that noradrenergic signaling in the amygdala facilitates the acquisition (i.e., within-session performance) of fear learning independently of glucocorticoids, while the consolidation of such learning relies critically on glucocorticoid activity that works synergistically with noradrenaline (Rodrigues et al., 2009).

Surprisingly few studies have examined the effects of stress on cued fear learning in humans. One study showed that stress induced an hour before fear conditioning facilitated acquisition in male participants but not females (Jackson et al., 2006). Another reported that high levels of endogenous glucocorticoids (i.e., cortisol) after stress enhanced fear memory consolidation as measured by retrieval one day later (Zorawski et al., 2006). A recent study in men (Antov et al., 2013) demonstrated that stress administered prior to fear conditioning did not alter fear acquisition relative to non-stressed controls. Although group differences did not emerge, the interval of time between the stressor and fear conditioning task did influence the effects of stress hormones on conditioned responses as measured by skin conductance. Specifically, stress administered 10 min before fear conditioning resulted in a positive association between conditioned responses and features of sympathetic nervous system arousal (i.e., blood pressure increase), consistent with the rapid noradrenergic effects typically reported directly after stress exposure. In contrast, conditioning after a longer delay of 50 min led to a negative association between conditioned responses and cortisol, suggesting that HPA-axis responses at longer timescales may facilitate the recovery of a

stressful experience by attenuating fear responses, as has been suggested previously (see Hermans et al., 2014 for review).

4.2. Extinction learning

Despite significant progress identifying the temporal and contextual factors that influence the learning and retention of extinction, limited studies have investigated the effects of stress on this form of fear inhibition, especially in humans. Research in non-human animals, however, has provided some insight into how these processes, along with the neural circuits that support them, may be affected by acute stress. These studies are reviewed below, followed by research assessing these effects in humans.

As mentioned earlier, while Pavlovian fear acquisition largely depends on the amygdala, extinction requires the interaction of the amydala and regions of the PFC, specifically the IL subregion. Stress exposure is sufficient to produce neuronal alterations (i.e., dentritic retraction) in IL neurons (Izquierdo et al., 2006), and impair plasticity between the mPFC and amygdala in rodents (Maroun and Richter-Levin, 2003). Consistent with this, stress exposure prior to extinction training has been shown to impair learning (Izquierdo et al., 2006; Akirav and Maroun, 2007; Maroun and Richter-Levin, 2003), although reports have been mixed as some studies have showed intact extinction learning performance after stress (Miracle et al., 2006; Garcia et al., 2008; Knox et al., 2012).

Complete blockade of noradrenaline through lesions of the locus coeruleus or its primary projection pathways impair the extinction of conditioned fear responses, suggesting optimal levels of noradrenaline play a critical role in extinction learning (Mason and Fibiger, 1979; McCormick and Thompson, 1982). Systemic blockade of beta-adrenergic activity using propranolol has been shown to facilitate extinction learning by attenuating conditioned fear responses (Cain et al., 2004; Rodriguez-Romaguera et al., 2009), whereas propranolol infused directly into the IL does not affect within-session extinction learning performance (Mueller et al., 2008), suggesting that dampening noradrenergic responses during extinction training is most effective when it has access to beta-adrenergic receptors in the amygdala. Interestingly, enhancing noradrenergic activity systemically with yohimbine prior to extinction learning has also been shown to attenuate conditioned fear responses during extinction, however, recent research suggests these effects are variable and may be strongly modulated by genetic background, contextual variables, or how fear responses are measured (Holmes and Quirk, 2010).

Finally, the acute effects of glucocorticoids on extinction learning are mixed. For example, a single dose of glucocorticoids administered in rodents led to prolonged expansion of basolateral amygdala neurons that correlated with increased anxiety-like behavior (Mitra and Sapolsky, 2008), suggesting it might also impair or slow extinction learning. Research in rodents has shown that in the amygdala elevated levels of circulating cortisol can bind to GRs within the CE leading to increased excitability (Karst et al., 2005) and dendritic hypertrophy (Mitra and Sapolsky, 2008). In the presence of an extinguished CS, these changes could potentially enhance fear expression by disrupting inhibitory circuits locally within the amygdala. Glucocorticoid exposure also leads to dendritic retraction and reduced plasticity in the IL region of the PFC in rodents (Wellman and Holmes, 2009). This work suggests that stress or glucocorticoid exposure may lead to disruptions in the vmPFC's dense projections to inhibitory interneurons in the amygdala, which gate fear expression in the presence of an extinguished CS. However, studies that have administered glucocorticoids alone to animals prior to extinction training have found limited effects extinction learning performance (Barrett and Gonzalez-Lima, 2004; Yang et al., 2006), suggesting more

research is needed to fully characterize the effects of these hormones on within-session extinction training performance.

Few studies have assessed the effects of acute stress on extinction processes in humans. One investigation reported that using the cold-pressor task (CPT; a painful ice-water submersion technique) before extinction training led to impairments in fear memory retrieval at the start of an extinction training session, a finding that was only seen in male participants (Bentz et al., 2013). Due to both the failure to retrieve the original fear association, and poor overall extinction performance, the effects of stress on extinction learning and retrieval, respectively, could not be assessed. Another study recently showed that male participants who were stressed using the CPT directly before a fear conditioning task displayed resistance to extinction training that followed (Antov et al., 2013).

4.3. Extinction consolidation and retrieval

In animals, repeated or chronic stress consistently has been shown to impair extinction retention even after intact training (Miracle et al., 2006; Garcia et al., 2008; Knox et al., 2012; Wilber et al., 2011). A recent study in rats showed that a single episode of acute stress induced directly before an extinction retention test led to retrieval deficits and the re-emergence of extinguished fear (Deschaux et al., 2013). Such retrieval deficits have been linked to IL dysfunction since lesioning the IL region of the vmPFC in rodents has been shown to produce extinction retrieval deficits that are comparable to those seen after stress induction (Farrell et al., 2010). Impairments in extinction retention have also been documented in animal populations bred for high trait-anxiety (Muigg et al., 2008).

Stress hormones play a pivotal role in facilitating the consolidation of extinction learning in both the amygdala and IL. For example, noradrenergic administration in the BLA facilitates extinction memory by boosting consolidation (Berlau and McGaugh, 2006). In the IL, direct infusions of propranolol before training impairs later extinction retrieval without affecting within-session performance, supporting the critical role of the IL in extinction retrieval. In contrast, propranolol administered directly into the IL after extinction training does not affect later retrieval, suggesting it leaves consolidation intact (Mueller et al., 2008). This discrepancy is thought to be due to pre-training reductions in arousal, which may disrupt extinction learning by reducing the salience of conditioned stimuli, subsequently impairing consolidation. Conversely, intact noradrenergic signaling during extinction training itself may be enough to enable consolidation despite reductions in arousal directly after training (Mueller and Cahill, 2010).

Administration of glucocorticoid agonists before or after initial extinction training enhances extinction retention (Cai et al., 2006; Yang et al., 2006), while blocking glucocorticoid activity impairs its consolidation (Barrett and Gonzalez-Lima, 2004; Yang et al., 2006). Repeated glucocorticoid exposure, which leads to down-regulation of glucocorticoid release, has been shown to impair the retention of extinction memory (Gourley et al., 2008), suggesting that as in other forms of memory consolidation, glucocorticoids play a critical role in the storage of extinction learning.

In humans, less work has assessed the effects of stress on extinction retention and retrieval. A recent investigation of extinction retrieval in women at different stages of their menstrual cycles revealed that extinction recall is better when preceded by stress in mid-cycling women with high estradiol status whereas the opposite was true of early cycling woman with low estradiol status (Antov and Stockhorst, 2014). This study highlights the importance of expanding investigations to assess how endogenous sex and

stress hormones may interact and work synergistically or in opposition during emotional learning processes.

We have recently demonstrated that inducing acute stress using the CPT in humans impaired extinction retrieval relative to non-stressed controls 24 h after intact fear learning and extinction training, irrespective of gender (Raio et al., 2014). Interestingly, conditioned responses across the extinction retrieval session were positively correlated with cortisol in both conditions. Although speculative, these results may be related to the abundance of glucocorticoid receptors in both the amygdala and vmPFC, making these regions especially sensitive to stress. Given the vmPFC's crucial role in extinction retrieval, dysfunction of this region or its connectivity to the amygdala is the most likely candidate by which stress might lead to extinction retrieval deficits. Consistent with this hypothesis, recent work in humans has shown that functional connectivity between the amygdala and vmPFC is disrupted after CPT stress exposure (Clewett et al., 2013).

Based on the animal and human work reviewed above, stress exposure appears to influence extinction processes differently depending on the phase at which stress is induced and extinction performance is assessed. Stress can impair the acquisition of extinction learning by potentially disrupting the inhibition of conditioned fear responses. Likewise, stress hormones can impair the retrieval of extinction memory after intact learning. In contrast, stress and stress hormones can enhance the consolidation and storage of intact extinction training, leading to stronger retrieval when later tested. These findings are generally consistent with the broader role of stress hormones in enhancing memory consolidation but impairing memory retrieval. They also suggest that patient populations marked by anxiety or stress-related psychopathology may be most vulnerable to extinction learning and retrieval deficits but that administration of stress hormones before or after extinction training may strengthen extinction memory. Extant research in humans testing these predictions is reviewed below.

4.4. Extinction processes in stress-related psychopathology

A larger body of research has examined extinction-related processes in human patient populations marked by affective and stress-related psychopathology. Research in panic disorder patients (Michael et al., 2007) and those diagnosed with post-traumatic stress disorder (PTSD) have consistently demonstrated impairments at extinguishing conditioned fear responses (Orr et al., 2000; Peri et al., 2000; Blechert et al., 2007; Wessa and Flor, 2007; Norrholm et al., 2011). In the majority of these investigations this deficit appeared to be related to a failure to inhibit responses to a previously threatening CS + that currently signals safety (Orr et al., 2000; Peri et al., 2000; Blechert et al., 2007; Norrholm et al., 2011).

Deficits in the retrieval of extinction after intact training have also been reported in patients with PTSD (Milad et al., 2008, 2009). Furthermore, the failure to inhibit fear responses has recently been reported to be associated with higher levels of PTSD-related symptoms (Milad et al., 2009; Norrholm et al., 2011; Sijbrandij et al., 2013). It is thought that these impairments may arise from dysregulation in the circuitry supporting extinction processes, namely enhanced amygdala and dACC activity in combination with diminished vmPFC activity (Rauch et al., 2006; Shin et al., 2004; Liberzon and Martis, 2006; Milad et al., 2008, 2009; Jovanovic and Norholm, 2011). Consistent with this, neuroimaging research in healthy humans assessing the neural circuits supporting the extinction of aversive learning has shown that the integrity of reciprocal connections between the amygdala and vmPFC predict levels of trait-like anxiety (Kim et al., 2009, 2011), suggesting that dysfunction within amygdala-prefrontal circuits may contribute to

stress-induced vulnerabilities to inhibit fear. Other functional neuroimaging studies assessing stress in healthy humans have reported increases in dACC activity and decreases in hippocampal and medial/orbitofrontal regions during or after stress exposure (see Dedovic et al., 2009, for review). Collectively, these studies provide a compelling marker of vulnerability to anxiety and trauma-related psychopathology under conditions of stress.

Notably, the same stress hormone (i.e., cortisol) that has been found in healthy humans to correlate positively with conditioned responses during extinction retrieval (Raio et al., 2014) has been shown to exert different effects in anxiety patients. Specifically, glucocorticoid administration was found to reduce trauma-related memory retrieval and symptoms in PTSD patients (Aerni et al., 2004; Suris et al., 2010) and reduce subjective and physiological measures of fear in phobic patients who were given glucocorticoids prior to exposure therapy (Soravia et al., 2006; de Quervain et al., 2011). Consistent with the broader role in memory enhancement, glucocorticoid administration prior to safety learning may later reduce anxiety and fear responses by bolstering initial extinction learning and consolidation within the amygdala and vmPFC. The precise mechanism underlying the immediate reduction of fear expression is less clear, but is thought to be related to glucocorticoids impairing the retrieval of previously acquired aversive associations (de Quervain and Margraf, 2008). Interestingly, the therapeutic effects of glucocorticoids in these reports provided benefits to anxiety patients only, indicating that glucocorticoids may be most effective in patients suffering from stress-related psychopathology. This is consistent with clinical research work showing that the hypersensitivity of glucocorticoids in PTSD patients leads to reductions in basal cortisol levels (Yehuda, 2009). Therefore, anxiety populations may benefit from exogenous glucocorticoid administration because it promotes optimal glucocorticoid levels that lead to stronger inhibition of fear responses and more robust consolidation of safety learning.

5. Cognitive regulation of fear

When an aversive outcome is imminent, cognitive strategies can be used to assert control over emotional responses. These techniques—referred to as *cognitive* emotion regulation—are unique to humans and denote any regulatory strategy used intentionally to generate a more adaptive emotional response (Gross, 1998; Gross and Thompson, 2007). They include shifting attention away from aversive aspects of a stimulus, changing the meaning of a stimulus (i.e., reappraisal), or altering the expression of an emotional response (for reviews, see Gross and Thompson, 2007; Gross, 2013). Recruiting cognitive strategies to deliberately change the way a stimulus is evaluated has been shown to effectively reduce the subjective (Gross, 1998; Shurick et al., 2012), physiological (Gross and Thompson, 2007; Delgado et al., 2008; Shurick et al., 2012) and neural components (Ochsner et al., 2012; Hartley and Phelps, 2010; Schiller and Delgado, 2010) of emotion. In humans, using cognitive control to change emotional responses is commonly used due it its unique capacity to be deployed at will in a variety of circumstances.

Investigations into the neural mechanisms underlying the cognitive regulation of emotion most commonly implicate the lateral PFC, specifically the dorsolateral and ventrolateral PFC (dlPFC and vlPFC, respectively), along with medial regions, such as the vmPFC and dorsomedial PFC (dmPFC), as more highly active when participants utilize regulatory strategies relative to when they do not (for reviews, see: Hartley and Phelps, 2010; Schiller and Delgado, 2010; Ochsner et al., 2012). This pattern of increased prefrontal activity is often coupled with decreased activity in the amygdala during the reappraisal of aversive or threatening stimuli

(Delgado et al., 2008; Oschner and Gross, 2002). Collectively, this work has led to a provisional model of cognitive emotion regulation in which the dlPFC—consistent with its broader role in executive function—facilitates the online maintenance and manipulation of information needed for reappraisal to take place, while activity in the amygdala diminishes as the emotional significance of regulated stimuli dampen. The inhibitory nature of this PFC-amygdala relationship is thought to be mediated by the vmPFC (Delgado et al., 2008; Ochsner et al., 2012) suggesting a mechanism through which dlPFC activity could modulate amygdala activity during cognitive regulation (Hartley and Phelps, 2010; Ochsner and Gross, 2007; Schiller and Delgado, 2010).

Cognitive emotion regulation relies on a number of higher-level executive functions including intact working memory, used to maintain representations of relevant information during emotion regulation; response inhibition, which can facilitate the inhibition of automatic responses to threatening cues; and cognitive flexibility, which enables one to adopt different strategies to foster more adaptive responses (Hofmann et al., 2012). However, emerging work across species suggests that these processes—and the prefrontal brain regions on which they depend—are highly sensitive to the detrimental effects of acute stress. Specifically, these impairments are thought to arise from excessive levels of stress hormones, which have been shown in animals to disrupt neuronal activity (i.e., alter firing rates) and lead to a broad range of cognitive impairments (Arnsten et al., 1998, 2009; Murphy et al., 1996).

The PFC relies on a delicate balance of catecholamines such as noradrenaline and dopamine, which each exert an inverted U-shaped influence on lateral PFC physiology and function in which optimal levels facilitate neuronal firing patters and PFC-dependent task performance, while supraoptimal levels—such as those that may be reached during or after stress exposure—lead to impairments. Research in humans is consistent with this: brief exposure to stress has been shown to impair executive functions including working memory capacity (Duncko et al., 2009; Elzinga and Roelofs, 2005; Luethi et al., 2009; Roozendaal et al., 2004; Schoofs et al., 2009), cognitive flexibility (Alexander et al., 2007; Plessow et al., 2011), and goal-directed behavior (Otto et al., 2013), and leads to metabolic reduction in areas selective to emotion regulation, including the vmPFC (Kern et al., 2008) and the dlPFC (Qin et al., 2009). Conversely, stress enhances the functioning of a broad network of brain regions that are innervated by catecholamine and glucocorticoid inputs, such as the amygdala, hypothalamus, insula and dorsal anterior cingulate (Hermans et al., 2014, for review). Collectively, these findings suggest that under the stressful conditions when we are most likely to engage in deliberate forms of cognitive emotion regulation is precisely when the resources supporting these techniques may be compromised. Evidence for this has already been demonstrated in anxiety disorder patients that consistently show impairments using cognitive regulation strategies in the laboratory (Mennin et al., 2005; Cisler et al., 2010), as well as individuals with high trait anxiety (Indovina et al., 2011; Lissek et al., 2005). This is consistent with research showing that negative affect is related to the failure to exercise self-regulatory control over thoughts and behavior (Baumeister and Heatherton, 1996; Heatherton and Wagner, 2011).

Based on this research, a recent study in our laboratory tested the hypothesis that cognitive emotion regulation would be impaired after exposure to stress (Raio et al., 2013). After a fear-conditioning task where physiological arousal was measured as an index of fear, participants were trained to re-appraise an aversive CS and re-structure the fear-conditioning task overall in a less threatening manner. One day later, participants either underwent a physiological stressor (i.e., CPT) or a control task, before repeating the fear-conditioning task, this time with instructions to utilize their newly acquired regulation skills. The CPT elicited greater stress responses as measured by self-report, as well as increases in salivary alpha-amylase and cortisol, markers of noradrenergic and HPA-axis activity, respectively. Stressed participants exhibited marked impairments regulating both physiological and self-reported fear responses to the aversive CS and showed comparable fear responses to the previous day prior to regulation training. In contrast, controls showed reductions in both assays of fear expression.

Stress may exert detrimental effects on the capacity to cognitively regulate fear responses through a number of potential mechanisms. In our study, we found a positive association between alpha-amylase and fear responses after stress, suggesting that the effects of noradrenergic activity on the brain regions that support the regulation of fear may be one possible mechanism by which cognitive fear regulation is impaired. Excessive levels of noradrenaline released after stress can target brain regions that support cognitive emotion regulation, including the amygdala, vmPFC and dorsolateral PFC (see: Arnsten, 2009; or, Hermans et al., 2014, for review). Noradrenaline exerts regionally specific effects on the brain due to various receptor subtype availability (Berridge and Waterhouse, 2003). For example, alpha-2 adrenergic receptors, which are densely distributed throughout the lateral PFC, have a high affinity for noradrenaline. Moderate levels of noradrenaline during emotional arousal therefore lead to optimal occupancy in the PFC of these high affinity alpha-2 receptors, facilitating cognitive function (Arnsten and Goldman-Rakic, 1985; Wang et al., 2007). However, higher levels of noradrenaline release as seen during stress exposure is thought to engage lower affinity alpha-1 and beta-adrenergic receptor subtypes that impair prefrontal function (Birnbaum et al., 1999; Ramos et al., 2005) but strengthen activity in the amygdala (McGaugh, 2004). Glucocorticoids can also function in a synergistic manner with noradrenaline to exacerbate its effects in PFC (Ferry et al., 1999; Roozendaal et al., 2004; Grundemann et al., 1998; Arnsten, 2009). Therefore, it is possible that both noradrenergic and glucocorticoid responses to acute stress, and the interacting influence they exert in the brain, serve as a potential mechanism for the impact of stress on the cognitive control of fear.

The observation that even a mild stressor can render cognitive emotion regulation less effective is especially striking considering that these techniques are used pervasively in clinical contexts to treat an array of psychological disorders. Cognitive reappraisal and restructuring comprise some of the primary principles underlying for Cognitive-Behavioral Therapy (CBT), a therapeutic technique often referred to as the 'gold-standard' for treating an array of psychological dysfunction, including anxiety and trauma-related disorders (Beck and Emery, 1985; Beck and Dozois, 2011; Butler et al., 2006; Hofmann et al., 2008). However, we note that our stress manipulation took place after only one session of training, whereas the majority of CBT treatment plans are instituted over an extended period of time (e.g., 12–24 weeks) (Butler et al., 2006). Stress likely has more limited effects of cognitive emotion regulation as training continues and is practiced over time, therefore we do not argue that cognitive regulation does not have utility in clinical settings, only that its vulnerability to acute stress in the early stages of training should be considered. Additionally, it is important to note that there are multiple components to CBT for which our study was not designed or capable of testing, such the social support garnered from therapeutic relationships, as well as a broad range of restructuring techniques inherent in CBT, which include encouraging patients to recognize and correct automatic thoughts that may be irrational or maladaptive to promote more adaptive emotional responses. It is possible the combination of all of these components might lead to CBT being more resistant to

stress even while the specific reappraisal components use in our task are notably impaired under stress.

6. Additional techniques: avoidance and reconsolidation

6.1. Avoidance strategies

Although the majority of fear regulation techniques involve changing the value associated with an aversive stimulus, adopting a course of action or inhibiting a response in order to avoid an aversive outcome can also control fear responses. One such method of this is referred to as active avoidance learning, which comprises a more complex learning process that involves both Pavlovian and instrumental components for regulating fear. During active avoidance learning, one must learn to first associate a CS with an aversive outcome before learning how to use a specific action to either avoid or terminate the presence of a threatening CS (see Cain et al., 2010, for review). Importantly, it has been shown that active avoidance (Moscarello and LeDoux, 2013) and similar active, stressor controllability paradigms (e.g., Cain and LeDoux, 2007; Baratta et al., 2007) can lead to fear reduction in the presence of a CS even when the avoidance action is no longer available. In this way, these forms of avoidance do not just regulate fear in the moment, but can be viewed as more lasting fear regulation techniques that may also change the value of the CS in future encounters.

Research in rodents has revealed that the amygdala is critical to active avoidance learning (LeDoux and Gorman, 2001; Gabriel et al., 2003), specifically to the initial Pavlovian stage of learning. As discussed earlier, the convergence of the CS-US association occurs through plasticity in the LA and this input projects to the CE, which outputs to brainstem and hypothalamic regions that mediate fear expression and defensive responses. As avoidance training commences, projections from the PFC are thought to inhibit conditioned fear expression, which allow the performance of instrumental avoidance responses (see Cain et al., 2010 for review). Evidence for this comes from rodent studies showing that lesions to the IL leads to excessive fear responses and impaired avoidance learning, with opposite results emerging from lesions of the CE (Moscarello and LeDoux, 2013). The BA can also receive input from the LA and, importantly, has direct projections to the nucleus accumbens (NA), which modulates goal-directed instrumental behavior, enabling avoidance behavior (LeDoux and Gorman, 2001). Amorapanth et al. (2000) found that LA lesions disrupted both the Pavlovian and instrumental stage of avoidance learning. Lesions of the CE preserved avoidance learning but impaired the initial expression of conditioned responses (i.e. freezing), whereas lesions to the B led to opposite results, suggesting that pathways through the B are critical to signaling striatal circuits that facilitate avoidance learning. Neuroimaging research in humans also supports a role of the striatum in learning to avoid aversive outcomes. Participants who learned to terminate the presence of a threatening CS using a button press showed reduced levels of physiological fear arousal and amygdala activation coupled with greater activation of the striatum, pointing to a role for the striatum in aversive avoidance learning (Delgado et al., 2009).

Interestingly, the initial fear response to an aversive CS has been shown to impair the ability to mount an instrumental response to avoid it (Choi and LeDoux, 2003), suggesting higher sensitivity to acute stress may impair the ability to adopt action-related coping strategies to control fear. Choi and LeDoux (2003) had rodents learn to perform an instrumental shuttling response in the presence of a CS to avoid an imminent electric shock. A specific subset of 'non-learners' were unable to perform this avoidance response because of high levels of conditioned fear responses (i.e., freezing). However, after lesions to the CE, these animals were capable of adopting the avoidance strategy, indicating that excessive fear expression can impair the capacity to perform actions that promote safety and reduce fear. This implies that higher levels of trait anxiety or acute exposure to stress may impair the capacity to acquire or retain avoidance strategies when confronted with threat.

Of the limited studies that have directly assessed the effects of stress or stress hormones on avoidance learning, most have examined passive (i.e., inhibitory) avoidance learning. In contrast to active avoidance processes that require the use of an instrumental response to prevent or terminate an aversive outcome, passive avoidance requires the suppression of an innate behavior in order to successfully avoid an aversive outcome. A common way to test passive avoidance is to measure the latency with which an animal crosses from a naturally preferred darkened chamber that has been paired with shock to a less preferred bright chamber that the animal has learned to associate with safety. Passive avoidance involves the amygdala as well as the hippocampus due to the contextual nature of the task (Ogren and Stiedl, 2010).

As with other forms of aversive learning, passive avoidance is dependent on stress hormones to facilitate learning and consolidation. For example, blocking noradrenaline systemically or within the LA or B after avoidance training disrupts its consolidation as measured by weaker subsequent retention (Ferry and McGaugh, 1999; Gallagher et al., 1977; Liang et al., 1986; Quirarte et al., 1997). In contrast, enhancing noradrenaline after avoidance training enhances its retention (McGaugh et al., 2002; McIntyre et al., 2002). Furthermore, infusion of glucocorticoid agonists into the LA directly after training on a fear avoidance and escape task enhances subsequent retention, while GR antagonists infused prior to training impaired retention. Notably, infusions at either time point into the CE had no effect on memory retrieval (Roozendaal and McGaugh, 1997).

The effect of acute stress on passive avoidance was recently tested in rodents. Before training, animals were classified into high, medium and low anxiety based on the elevated plus-maze test; subsequently, half of the mice in each group then underwent an acute stress manipulation. Stress altered avoidance performance in the high anxiety group only. Specifically, stressed males showed enhanced avoidance as measured by longer latencies to enter a darkened chamber previously paired with shock, while stressed females showed marked impairments in avoidance learning (Navarro-Francés and Arenas, 2014).

Although more research is required to understand the effects of stress on avoidance strategies, avoidant behaviors are common among anxiety patients (Eifert and Forsyth, 2007; Craske and Barlow, 1988; Sprang and LaJoie, 2009), suggesting that stress may enhance well-practiced avoidance strategies. It should be noted that although avoiding an aversive outcome may attenuate fear responses, the habitual avoidance of fearful situations may also prevent one from confronting aversive stimuli and engaging in extinction processes, which can be detrimental to the treatment of anxiety symptoms. Therefore, while stress may hinder the initiation of avoidance behavior during learning, overuse of avoidance strategies may lead to habitual, potentially maladaptive avoidance behaviors that are facilitated by stress.

6.2. Reconsolidation

Since the fear regulation techniques discussed above can be vulnerable to the effects of acute stress, as well as other contextual and temporal factors, emerging research in animals and humans has examined the interference or blockade of fear memory reconsolidation as a putative alternative to change fear. Normative models of memory suggest that immediately after learning, there is window of time in which newly encoded information is susceptible

to interference. However, recent research suggests that memories must undergo an additional phase of consolidation each time they are reactivated, a restabilization process referred to as *reconsolidation*. Since it is often not feasible to interfere with the initial consolidation of traumatic experiences, interfering with reconsolidation offers the possibility of altering traumatic memories in a more permanent manner. In a typical reconsolidation paradigm, after an aversive association is acquired and consolidated, a time-dependent reconsolidation window is induced by a single presentation of the CS, which is thought to reactivate the aversive memory. A variety of behavioral or pharmacological manipulations can then be used during the presumed reconsolidation window to alter memory re-storage before later testing for the conditioned responses in the presence of the CS.

Research in humans (Schiller et al., 2009, 2014; Steinfurth et al., 2014; see Schiller and Phelps, 2011 for review) and animals (Nader et al., 2000; Monfils et al., 2009; Einarsson and Nader, 2012; Hong et al., 2013) has now demonstrated that disrupting or interfering with reconsolidation leads to the persistent modification of amygdala-dependent aversive associations. Recent research in rodents suggests that interfering with the reconsolidation of aversive association induces plasticity in the LA (Monfils et al., 2009; Clem and Huganir, 2010) and in humans, reconsolidation of fear memory leads to diminished BOLD responses in the amygdala (Agren et al., 2012) and a failure to involve vmPFC mechanisms typically seen in standard extinction learning and retrieval process (Schiller et al., 2014), providing evidence that reconsolidation interference may target the original aversive memory trace.

The effects of stress and stress hormones on reconsolidation processes have remained relatively unexplored, however, some recent investigations have begun to characterize these effects. In animals, administration of propranolol directly into the amygdala after a threatening association is reactivated impairs the reconsolidation of cued (Debiec and LeDoux, 2004) and contextual fear (Abrari et al., 2009) as well as memory of avoidance training (Przybyslawski et al., 1999), whereas increasing noradrenaline after reactivation can enhance its later retrieval (Debiec et al., 2011). This is consistent with research in humans that has reported attenuated fear-related symptoms when PTSD or trauma victims are administered propranolol after the reactivation of traumatic memories (Brunet et al., 2008; Orr et al., 2000; Pitman and Delahanty, 2005; Pitman et al., 2002).

Blocking glucocorticoid release in the amygdala immediately (but not 6 h) after an aversive fear memory is reactivated impairs the subsequent retrieval of the aversive association but leaves within-session responses intact, an effect seen for memories that were both 1 or 10 days old (Jin et al., 2007). Similar effects were shown in an inhibitory avoidance task where systemic glucocorticoid antagonists were administered after fear memory reactivation (Taubenfeld et al., 2009; Nikzad et al., 2011). Glucocorticoid administration directly after fear memory retrieval has also been shown to impair the subsequent retrieval of aversive associations, however, rather than impairing reconsolidation this effects appeared to be the result of enhancing extinction consolidation (Cai et al., 2006).

While the impact of acute stress on the reconsolidation process is relatively unexplored, there is evidence suggesting that the strength of the aversive US during initial fear acquisition can modulate the later susceptibility to interventions used to target reconsolidation (Suzuki et al., 2004; Finsterwald and Alberini, 2014). The effect of stress on fear memory reconsolidation has not been formally tested in humans. However, a recent study reported that across six different studies assessing how propranolol administration before or after fear memory retrieval might disrupt the reconsolidation of fear memory, individuals who reported higher levels of trait anxiety were more resistant to the effects of reconsolidation interference. This suggests that individuals who are most vulnerable to the effects of stress may be less responsive to fear memory disruption using this technique (Soeter and Kindt, 2013).

7. Conclusion

From minor daily annoyances to deeply traumatic events, stressful experiences constitute an undeniable aspect of daily life. Reports on the profound impact that stress has on mental and physical health are pervasive throughout the scientific community, leading to widespread interest in understanding how to reduce stress and promote emotional control. Accordingly, empirical studies investigating emotion regulation have grown exponentially over the last two decades, reflecting mounting interest within the field (Gross, 2013). Despite the broad scientific interest in understanding how emotions are regulated, however, the notion that stress may be detrimental to emotional control has been relatively overlooked within this literature. Consequently, the effects of stress on the capacity to flexibly control emotional responses have remained largely unexplored. The studies reviewed here offer some initial insight into understanding how acute stress exposure affects the inhibition and control of conditioned fear.

The research discussed in this review used Pavlovian fear conditioning as a basis for understanding the effects of stress on the regulation of fear. Since the neural circuitry underlying fear learning is highly conserved across species, we can use animal models as a basis for understanding how stress may influence this circuitry in humans as well. Our investigation of extinction and cognitive regulation reveals robust effects of stress impairing the persistent inhibition of fear, presumably by altering prefrontal cortex function. Although less is known concerning the impact of stress on the persistent fear reduction observed with avoidance and reconsolidation, it is possible these fear regulation techniques are less vulnerable to the negative consequences of stress since they rely less on the inhibitory mechanisms involved in extinction and cognitive regulation.

It is important to note that the behavioral and neural research covered in this review focused mainly on brief exposure to stress, rather than chronic exposure. Although the immediate effects of acute stress can exert detrimental effects on the brain regions critical to the regulation of fear responses, chronic exposure to stress can trigger more systemic neuroendocrine changes. For example, chronic stress can lead to dysfunctional regulation of the HPA-axis, resulting in a flattened diurnal cycle of cortisol release, such as that seen in depressives and PTSD (Young et al., 1994; Yehuda, 2009). It can also lead to more profound structural and functional changes in brain regions critical to autonomic and HPA-axis related regulation (i.e., amygdala and hippocampus) that can lead to suppression of synaptic plasticity and neurogenesis in these regions (see McEwen, 2003 for review). Collectively, chronic stress produces what has been referred to as allostatic load, creating an overwhelming demand on the neural circuits that mediate appropriate responses and recovery from stress.

Fear learning and regulation is a prominent model for describing the pathogenesis of anxiety disorders and stress-related psychopathology. Stress has been shown to play a critical role in the etiology, exacerbation and treatment of affective psychopathology suggesting close interplay between the two. Accordingly, research has shown that individuals with anxiety or depression show a broad range of abnormalities in controlling fear-related responses, suggesting that deficits in emotion regulation may be linked to neurobiological differences in response to stress. The considerable overlap in stress and fear-related neurocircuitry is one likely

explanation for why fear regulation impairments emerge in populations marked by stress. However, it should be noted that although the interaction between stress and fear circuitry undoubtedly exist and similar mechanisms may be at play, there is likely to be a large degree of heterogeneity in terms of how acute stress may alter fear regulation in clinical populations depending on their individual diagnoses. Gaining a clearer understanding of how stress affects the regulation of fear is critical to assess the efficacy of these techniques in clinical populations and inform better treatment options for populations with stress-related psychopathology.

Acknowledgments

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