Animal Models of Fear Relapse

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Abstract

Whereas fear memories are rapidly acquired and enduring over time, extinction memories are slow to form and are susceptible to disruption. Consequently, behavioral therapies that involve extinction learning (e.g., exposure therapy) often produce only temporary suppression of fear and anxiety. This review focuses on the factors that are known to influence the relapse of extinguished fear. Several phenomena associated with the return of fear after extinction are discussed, including renewal, spontaneous recovery, reacquisition, and reinstatement. Additionally, this review describes recent work, which has focused on the role of psychological stress in the relapse of extinguished fear. Recent developments in behavioral and pharmacological research are examined in light of treatment of pathological fear in humans.

Key Words: anxiety; exposure therapy; extinction; fear; PTSD; relapse; resilience; stress

Introduction

More than ever, research in animal models is playing a fundamental role in the development of novel therapies for anxiety. Brain imaging in humans and neuroanatomical studies in animals continue to reveal substantial overlap in the neurobiological systems underlying emotional memories, including conditioned fear memories (Delgado et al. 2008; Herry et al. 2008; Knapska et al. 2012; Kong et al. 2014; Lissek 2012; VanElzakker et al. 2013). Erasing fear memories without disrupting other memory systems remains a heavily coveted end point of behavioral interventions for anxiety disorders (Kindt et al. 2009; Maren 2011; Monfils et al. 2009; Quirk et al. 2010; Schiller et al. 2010). Indeed, behavioral therapies, such as prolonged exposure therapy, typically suppress rather than erase fear memories (Bouton 1988; Maren 2005). The form of learning thought to underlie these therapies—extinction learning—has been found to be rather labile (Bouton 2000; Hermans et al. 2006). As a consequence, fear can readily overpower extinction, and extinguished fear may return under a variety of conditions (Boschen et al. 2009; Bouton 2002; Ji and Maren 2007; Rachman 1979; Rachman 1989; Vervliet et al. 2012). Relapse of extinguished fear poses a considerable challenge to behavioral therapies for fear and anxiety disorders (Boschen et al. 2009; Kindt et al. 2009; Vervliet et al. 2012).

Over the last several decades, Pavlovian fear conditioning has become the gold standard for studying emotional learning and memory in the laboratory (Goswami et al. 2013; LeDoux 2000; Maren 2008; Mineka and Oehlberg 2008; Rasmusson and Charney 1997). Fear conditioning is observed in both humans and animals and is highly amenable to experimental control and investigation. Fear is highly adaptive; it is essential in motivating defensive behavior in the face of threat (Cantor 2009; Ellis 1982; Giske et al. 2013; Öhman and Mineka 2001; Seymour et al. 2004). However, increased conditioned fear is observed in individuals with anxiety disorders, and fear circuits in the brain are thought to mediate and modulate anxiety (Davis 1992; Fanselow and Gale 2003; LeDoux 2012; Zantvoord et al. 2013). In both animals and humans, conditioned fear results from the repeated pairing of a neutral, yet detectable, conditioned stimulus (CS) with an aversive, biologically significant unconditioned stimulus (US) (Delgado et al. 2006; Gunther et al. 1997; Maren 2001). In rodent models, stimuli such as brief tones or lights often serve as CSs, and mild to moderate footshocks most commonly serve as USs. Although footshocks themselves produce an unconditioned response (i.e., a circa-strike "activity burst," including vocalizations; Fanselow 1994), they ultimately engender a conditioned fear state that is associated with a host of fear responses, including freezing (i.e., immobility). In rodents, freezing is a defensive response to an inescapable threat (Bolles 1970; Fanselow 1994; Nissen 1946; Riess 1945) and is a highly reliable index of conditioned fear to the CS (or context; see below). Conditioned fear responses (CRs) also consist of changes in autonomic reactivity, including the release of stress hormones and endogenous opioids (Antov et al. 2013; Davis 1979; Fanselow and Bolles 1979; Fanselow et al. 1989; Kull et al. 2012; Merz et al. 2013a; Przewłocka 1990; Soeter and Kindt 2011). As will be discussed later, pharmacological

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interventions for posttraumatic stress disorder (PTSD) and anxiety often target autonomic responding (Bailey et al. 2013; Cain et al. 2012). Fear acquisition in rodents is remarkably similar to that of the general human population (Galatzer-Levy et al. 2013), allowing Pavlovian fear conditioning to serve as a translational model (Milad and Quirk 2012; VanElzakker et al. 2013).

During fear conditioning, animals encode not only an association between the CS and US but also an association between the context in which they occur and the US (i.e., identified as context fear) (Fanselow 1980; Maren et al. 2013). Importantly, conditioned fear to the CS generalizes across contexts, unlike that of extinction (see below). Contexts include the physical environment surrounding the animal (exteroceptive contexts), as well as the animal's internal states of being (interoceptive contexts) (Maren et al. 2013). In rodent models, exteroceptive contexts are created with distinct cage odors, changes in the texture of the testing platform, and alterations in background lighting and noise. Interoceptive contexts are inherently subjective to the animal and may consist of unconscious components. Interoceptive contexts include (but are not limited to) states of arousal, drug states, states of deprivation, and temporal states (Bouton 1993; Bouton 2002; Bouton et al. 1990; Cunningham 1979; Davidson 1993; Järbe et al. 1981; Richardson et al. 1986; Servatius and Beck 2005). Context fear is elicited by the exteroceptive context in which the aversive US occurs and is particularly strong with unsignaled USs (i.e., contextual fear conditioning) (Fanselow and Bolles 1979; Waddell et al. 2006).

In contrast to conditioning, extinction is a procedure in which the contingency between the CS and US is degraded by presenting the CS alone many times without the aversive footshock. Context fear associated with the US can also be extinguished by placing the subject in the conditioned context in the absence of any aversive US (refer to Maren et al. 2013). As a result, animals learn that the CS (or context) no longer predicts the aversive US (Bouton 2004; Chang et al. 2009; Hermans et al. 2006; Lolordo and Rescorla 1966; Pavlov 1927), thereby reducing conditioned fear. Extinction has been shown to engage distinct neural circuits that act on and interact with the neural circuits involved in conditioning (Courtin et al. 2014; Herry et al. 2010; Maren 2011; Milad et al. 2006b; Myers and Davis 2002; Orsini et al. 2013). Interestingly, these neural circuits are active during the suppression of fear in humans (Delamater and Westbrook 2014; Milad and Quirk 2012; Milad et al. 2006b). As such, fear extinction in rodents has been argued to model exposure therapy in humans (Bouton 1988; Hofmann 2007; Milad and Quirk 2012). Exposure therapy is used to treat a variety of anxiety disorders, including PTSD (Cahill et al. 2006; Foa 2011; McLean and Foa 2011; Motraghi et al. 2014; Powers et al. 2010; Rauch et al. 2012; Rothbaum and Swartz 2002). Certain cues are thought to be more readily associated with the aversive US, and subsequently, these cues may be resistant to extinction under certain conditions (though this has been met with controversy; Mineka and Öhman 2002; Lueken et al. 2011). Overall, fear-relevant cues in humans (e.g., a picture of a spider or snake) have been shown to be difficult to extinguish (McNally 1986; Öhman et al. 1975a; Öhman et al. 1975b).

Although extinction-based therapies such as exposure therapy are effective at suppressing fear, the long-term efficacy of these treatments is challenged by the propensity of extinguished fear to relapse (Bouton 1988; Rachman 1979; Rachman 1989; Rodriguez et al. 1999; Vervliet et al. 2012). Understanding the nature and causes of fear relapse is essential to developing effective therapeutic interventions in patients with anxiety disorders. In this review, we will focus on the behavioral mechanisms involved in relapse of extinguished fear, taking care to translate work in animal models to humans. Additionally, this review will highlight strategies that are known to enhance the retention of extinction.

Extinction Retention: A Vulnerable Process

Pavlov (1927) was the first to note that extinction procedures produce only a temporary loss of conditioned responding. For example, he observed that presenting a novel stimulus after extinction caused a reemergence of the CR (external disinhibition); moreover, the mere passage of time after extinction resulted in a return of the CR (spontaneous recovery). In the context of aversive conditioning, these and other phenomena indicate that extinction procedures do not erase fear memories; rather, they lead to a new memory that inhibits the representation of the US (thereby reducing conditioned responding) (Bouton 1993; Konorski 1967; Maren 2011; Quirk 2002). The reemergence of fear is clearly inimical to the aims of therapy and is unpleasant for the patient (Vervliet et al. 2012; Vervliet et al. 2013); unrelenting and unmanaged anxiety is certainly not without health risks (Baganz and Blakely 2013; Hou and Baldwin 2012; Kemp and Quintana 2013). In the following sections, we review four fundamental fear relapse phenomena: renewal, spontaneous recovery, reacquisition, and reinstatement. Although each phenomenon is discussed in light of animal research, these forms of fear relapse have also been identified in humans (Hermans et al. 2005; Vervliet et al. 2012; Vervliet et al. 2013). In later sections, we will examine how particular stressors may modulate extinguished fear and how stress factors may relate to relapse of fear in general.

Renewal

A fundamental observation concerning extinction is that it is context-specific (Bouton and Bolles 1979; Bouton and Nelson 1994). That is, when an extinguished CS is encountered outside of the extinction context, renewal of conditional responding occurs (Bouton 2004; Bouton and King 1983; Bouton and Ricker 1994; Neumann and Longbottom 2008; Polack et al. 2013; Vervliet et al. 2013). Renewal of fear to an extinguished CS can occur when the CS is presented outside either the exteroceptive or interoceptive context of extinction (Maren et al. 2013; Maren 2014). Renewal of fear

is ordinarily strongest when the extinguished CS is presented back in the conditioning context (extinction and conditioning often occur in separate contexts; Maren 2014). Hence, although fear memories readily generalize across contexts, extinction learning is characteristically limited to the context in which the extinction memory was formed (Bouton 2004; Maren 2014; Rosas et al. 2013). Thus, renewal of fear is a major challenge for clinicians. Suppression of fear in a therapist's office may not readily translate to other environments in the patient's life (Mystkowski et al. 2002; Rodriguez et al. 1999). Further compounding the issue, renewal is not limited to a single change in context; renewal of fear can occur across multiple extinction sessions in several distinct contexts (Bouton et al. 2006). Renewal of fear can also occur when the animal experiences the CS in a novel environment (Neumann and Kitlertsirivatana 2010; Maren 2014) or in a familiar environment where the animal has never experienced the CS (Polack et al. 2013). In both cases, renewal appears to be mediated by an unexpected occurrence of the CS in any given context. Renewal of fear has received considerable attention over the last decade, and several important brain structures have been identified in the regulation of renewal (Lissek et al. 2013; Maren 2011; Maren et al. 2013; Maren 2014; Zelikowsky et al. 2013a). Given the importance of contextual information in fear responding, renewal is thought to interact with other known forms of fear relapse.

Spontaneous Recovery

An extinguished response to a CS also returns merely with the passage of time, a phenomenon termed spontaneous recovery (Bouton 1993, Rescorla 1997; Leung and Westbrook 2010; Rescorla 2004; Pavlov 1927). In this case, a change in temporal context (i.e., a form of interoceptive context) has been suggested to account for the return of fear (Bouton 1993). By this view, recent events may be more strongly associated with one another than with temporally distant ones (Bouton 1988; Bouton 1993; Rescorla 2004), suggesting that renewal processes may interact with spontaneous recovery (Bouton 2002; Bouton 2004). Indeed, presentation of a reminder cue of the extinction context prior to testing attenuates relapse of fear in animal models of renewal or spontaneous recovery (Brooks and Bouton 1993; Brooks and Bouton 1994). Clearly spontaneous recovery is a major obstacle in treatment of pathological fear, as routine and ongoing therapeutic interventions may not be practical or feasible for the patient. If implemented with respect to time, other strategies that are known to reduce or prevent renewal may be useful in curbing spontaneous recovery.

Reacquisition

Another phenomenon that restores conditioned responding is administering additional conditioning trials after extinction (Bouton 2002; Kehoe and Macrae 1997; Napier et al. 1992; Rescorla 2001), a phenomenon known as reacquisition. After extinction, pairing the CS and US once again rapidly restores conditional responding under the majority of circumstances (Bouton 2002). However, in some cases, the reacquisition of fear to an extinguished CS is slow (Bouton 1986). This is particularly true when reacquisition trials occur in a unique extinction context. For this reason, Bouton (2002) has argued that rate of reacquisition may depend upon the presence of contextual cues associated with conditioning or extinction, noting that when cues for extinction are removed (and replaced with cues for the conditioning context), reacquisition of CR is far more rapid. Thus, similar to spontaneous recovery, reacquisition interacts with contextual information and also reflects the context-dependence of extinction memories. Interestingly, intermittent CS-US pairings alongside CS-alone presentations can, if implemented correctly, deepen extinction and weaken the possibility of reacquisition of fear in the wake of the extinction procedure (Bouton 2002; also see Ricker and Bouton 1996). Through this design, postextinction presentation of a CS-US pairing may call on memories of extinction, rather than of conditioning, and thereby may result in a weakening of reacquisition. Even with this paradigm, however, some reacquisition of fear is likely to occur (Bouton 2002).

Reinstatement

Encountering the US in absence of the CS after extinction has been shown to reinstate fear responding to the CS (Bouton and Bolles 1979; Rescorla and Heth 1975; Westbrook et al. 2002). Reinstatement can occur with either a strong or weak US (i.e., a footshock of a smaller amplitude than that utilized in conditioning). Additionally, the reinstating US is often unsignaled (unlike reacquisition), but reinstatement can occur with a signaled US (i.e., presentation of a cue other than the CS with the US; Bouton and Bolles 1979). According to one view, presentation of the US might reinstate fear by serving as a retrieval cue for the conditioning memory. Alternatively, context-US associations might summate with fear to the CS to promote conditional responding (Bouton 1993; Bouton 2002; Bouton and King 1983). Evidence that reinstatement occurs only in the context in which unsignaled USs are delivered is consistent with this view (Bouton 1984; Bouton 1988; Bouton 1993; Bouton and Bolles 1979; Bouton and King 1983). However, Westbrook and colleagues (2002) argue that reinstatement is not always context specific. In this study, Westbrook and colleagues (2002) extinguished two distinct CSs (termed CS1 and CS2) in two separate contexts (conditioning occurred in context A, CS1 was extinguished in context B, and CS2 was extinguished in context C; letters correspond to unique contexts). Later, rats received a footshock (US) reminder in context B (but not C) and were subsequently tested for retention of extinction in a separate neutral context (context D). Rats exhibited more fear to CS1 than to CS2

when tested in D, suggesting that reinstatement is not context specific. This stimulus-specific reinstatement of fear across contexts appears to be independent of renewal of fear (Westbrook et al. 2002; see also Holland 1990). The notion that reinstatement can be observed outside of the context in which the US reminder is presented will become important for other reinstatement studies described in this manuscript (e.g., Morris et al. 2005a; Morris et al. 2005b).

In some respects, reinstatement may be determined by the mere aversiveness of the US, such that the fear state induced by an unsignaled US reminds the animal of the state of fear at the time of conditioning, thereby facilitating fear responding. As such, other aversive fear-inducing stimuli might yield reinstatement to the CS. Indeed, the concept of reinstatement in recent years has grown to include other "aversive triggers" of fear responding to the CS. For example, presentation of an unextinguished CS (which induces fear) reinstates fear to a different, extinguished CS (Halladay et al. 2012). Moreover, recent exposure to a conditioned context (i.e., a "dangerous" context) has been shown to reinstate fear to an extinguished CS in a separate context (Morris et al. 2005a; Morris et al. 2005b). Low levels of context fear prior to CS presentation in the testing context do not negate this effect. This work by Morris and colleagues (2005a) suggests, in contrast to Bouton (2002), that reinstatement can occur in a context different from the context in which fear was induced (e.g., via exposure to separate dangerous context) (also refer to Westbrook et al. 2002). Conceivably, the mechanisms of these two forms of reinstatement are different insofar as US-induced reinstatement appears to be context dependent, whereas the reinstatement that follows fear induction is not. That said, both footshocks and dangerous contexts are stressful, and stress may therefore play a role in reinstatement of fear (Jacobs and Nadel 1985). Stress clearly confers susceptibility to anxiety disorders (Callaghan et al. 2013; Cohen et al. 2013; Green et al. 2011; Timmermans et al. 2013), though less is known about the role of stress in relapse. Moreover, stress systems in the brain are known to overlap and interact with fear circuitry (Asan et al. 2013; Tye et al. 2011). As such, examining the role that stress might play in the relapse of fear is of fundamental importance in understanding and preventing relapse.

Stress and Fear Relapse

Stress is precipitated by a variety of stimuli, can exert a multitude of physiological effects, and may exhibit both facilitatory and inhibitory effects on fear memory depending on the nature of the stressor and the task at hand (Akirav and Maroun 2013; Baratta et al. 2007; Kim and Diamond 2002; Roth et al. 2012; Sanders et al. 2010; Sapolsky 2003; Trammell and Clore 2013; Wideman et al. 2013). Stress can even alter the memory systems involved in solving the task (Goodman et al. 2012; Packard and Goodman 2012). Moreover, the extent to which an animal has control over the stressor ultimately affects the consequence of stress on behavioral performance (Baratta et al. 2007; Christianson et al. 2013; Kubala et al. 2012; Maier et al. 2006). Recently, Hartley and colleagues (2013) demonstrated in humans that inescapable stress impairs extinction, while controllable stress actually reduces spontaneous recovery. As such, understanding the consequences of stress on fear relapse requires an appreciation of the type and time-course of the stress (i.e., physical vs. psychological, acute vs. chronic vs. intermittent, controllable vs. uncontrollable, etc.), as well as its physiological effect on the animal.

Physical stressors are commonly used in rodents (Heinrichs and Koob 2006) and include footshock, restraint stress, forced swim, nutrient deprivation, and loud noise. Certainly, physical stressors are not without psychological implications; physical stressors are merely differentiated from psychological stressors based on the source of the stress. In contrast, psychological stressors do not place physical strain on the animal's body and include predator odor exposure, social isolation, prolonged elevation, dangerous context exposure, and distress vocalizations (Deschaux et al. 2012; Fleshner et al. 2004; Hu et al. 2014; McNeal et al. 2014; Morris et al. 2005a; Wallace and Rosen 2000). Psychological stressors may also include exposure to novel stimuli and contexts, as well as associative unexpectancy (i.e., an unexpected occurrence of an extinguished CS in a familiar context; Maren 2014). Introduction or elimination of conspecifics can yield psychosocial stress (Huhman 2006). Psychosocial stressors include social defeat, chronic subordinate colony housing, and maternal deprivation (Fraga et al. 2014; Papciak et al. 2013; Uschold-Schmidt et al. 2013). Although all of the aforementioned stressors are specific to rodent models, analogs of these stressors are implemented in human research, particularly psychological and psychosocial stressors (Björkqvist 2001; Campbell and Ehlert 2012; Hartley et al. 2013; Maner et al. 2008; Schultheiss et al. 2005). Worth noting is that stress responding can also be induced pharmacologically or via electrical stimulation of anxiogenic regions of the brain (Kellet and Kokkinidis 2004; Morris et al. 2005b).

Psychological stressors in rodents have garnered considerable attention in recent years, driven in part by the important role played by psychological stress in the psychopathology of human anxiety disorders. Several studies now highlight the potential risk of fear relapse in the wake of psychological stress. Deschaux and colleagues (2012) demonstrated a return of fear to an extinguished CS after a 30-minute exposure of rats to an elevated platform. The relapse of fear in these rats was blocked by chronic administration of the antidepressant, fluoxetine (administration of fluoxetine occurred over 20 consecutive days; refer to Deschaux et al. 2012). As discussed earlier, Morris and colleagues (2005a) induced relapse of extinguished fear in rats simply by briefly exposing the animals to a dangerous context. This effect was blocked with the beta-adrenergic antagonist propranolol (Morris et al. 2005b). Additionally, Morris and colleagues (2005b) demonstrated that artificial induction of adrenergic activity with acute systemic administration of epinephrine replicated

the effects of exposure to the dangerous context. Thus, reinstatement of fear to an extinguished CS may be related to the stress engendered by other unsignaled footshocks or fear in general (Halladay et al. 2012; McCarty and Kopin 1978; Morris et al. 2005b). By this view, any aversive experience might result in the reinstatement of extinguished fear. Whether stress-induced relapse and reinstatement are mediated by overlapping neural structures has yet to be fully explored. If there is overlap, behavioral and pharmacological strategies that curb reinstatement may also attenuate stress-induced relapse. Likewise, stress reduction techniques may be key to reducing vulnerabilities to fear relapse. The effect of physical stress on fear responding in the aftermath of extinction has gone largely unexplored, though a similar pattern is expected as with psychological stressors. Nonassociative mechanisms that accompany stress should also be explored with regards to relapse.

Stress prior to conditioning has been shown to facilitate fear learning in rodents and to make fear responding more resistant to attenuation under certain conditions (Corley et al. 2012; Long and Fanselow 2012; Maren and Chang 2006; Rau et al. 2005; Rau and Fanselow 2009; Rodrigues et al. 2009). Additionally, stress prior to extinction (but after conditioning) can also impair the acquisition of extinction (Adamec et al. 2006; Maren and Chang 2006; Maren 2013). In rodents, the experience of aversive stress prior to conditioning can impair the retention of extinction memories in retrieval tests. For example, single prolonged stress prior to conditioning has been shown to enhance the renewal of fear in extinguished rats (Knox et al. 2012). Additionally, extinguished context fear is poorly retained in rats that have undergone a single prolonged stress procedure prior to the context conditioning procedure (Yamamoto et al. 2008). Similarly, Goswami and colleagues (2010) showed that exposure to predator threat prior to fear conditioning weakened the acquisition and recall of extinction in a cohort of Lewis rats (described as "PTSD-like"). These PTSD-like rats were shown to exhibit low levels of exploratory behavior on an elevated plus maze. Interestingly, Goswami and colleagues (2010) demonstrated that this impairment in extinction retention was not observed in rats that had previously exhibited high levels of exploratory behavior on the elevated plus maze (i.e., "resilient" rats). In humans, a similar pattern exists in both the facilitation of conditioning and the weakening of extinction through stress (Milad et al. 2008; Peri et al. 2000; Robinson et al. 2013; VanElzakker et al. 2013).

Early life stressors long before fear conditioning may also contribute to the susceptibility of fear relapse. Acute maternal deprivation has been shown to foster a propensity for relapse of fear in young rat pups (Cowan et al. 2013). Interestingly, infant pups under standard rearing conditions exhibit a degree of resistance to relapse; fear fails to reinstate or renew in these rats (but see Revillo et al. 2013). However, the lifelong implications of acute maternal deprivation on fear responding remain unclear. That said, prenatal stress (i.e., stress in pregnant rats) has even been found to reduce the retention of extinction of offspring trained later in life (Green et al. 2011).

Individual Differences and Susceptibility to Relapse

Anxiety disorders exist throughout the world, but certain groups are preferentially affected. For example, women have an increased risk of clinical anxiety and PTSD compared with men (Foa and Street 2001; Kobayashi et al. 2012). Sex differences are observed in animal models of fear conditioning and extinction, as well as in stress responding (Farrell et al. 2013; Gupta et al. 2001; Lebron-Milad et al. 2013; Lynch et al. 2013; Maren et al. 1994; Merz et al. 2013a; Merz et al. 2013b; Milad et al. 2009). Humans exhibit a similar pattern, albeit with fewer consistencies across studies (Milad et al. 2006a). Nevertheless, it stands to reason that susceptibility of relapse may differ between sexes. Indeed, female rats are more likely to exhibit renewal of fear (Baker-Andresen et al. 2013). Chronic stress prior to conditioning preferentially impairs the recall of extinction memories in male rats, but not female rats; however, unstressed female rats appear to not extinguish as robustly as males (Baran et al. 2009).

The developmental stage of the animal can also have a profound impact on the nature of fear acquisition and expression of extinguished fear (Callaghan and Richardson 2013; Campbell and Ampuero 1985; Kim and Richardson 2007a; Kim and Richardson 2007b; Kim and Richardson 2010; Mactutus et al. 1982; Sanders 2011). Stress responding can vary widely across development in both humans and animals, suggesting that the occurrence of relapse may interact with developmental stages (Green and McCormick 2013; Revillo et al. 2013; Takahashi et al. 1991; Wright et al. 2012). For example, postweanling rats as young as a few weeks old are capable of renewal, spontaneous recovery, and reinstatement, whereas preweanling rats are known to exhibit resistance to relapse of conditioned fear (Kim and Richardson 2010; but see Revillo et al. 2013). Adolescent rats are particularly susceptible to fear relapse when compared with preadolescent and adult rats (Baker et al. 2013). To combat this susceptibility, Baker and colleagues (2013) have shown that a CS-alone presentation (i.e., a retrieval trial) prior to or following extinction training reduced the risk of subsequent renewal in the adolescent rats. Interestingly, Sanders (2011) demonstrated a deficit in renewal of extinguished fear in aged mice (17 months). This impairment in renewal may be related to the weakening of contextual gating systems in the aging mouse brain.

These studies suggest that strategies of relapse prevention should be targeted to susceptible groups accordingly. Drug treatments in humans must certainly be mindful of developmental stages in children and adolescents (Huemer et al. 2010). Furthermore, future work should ascertain how sex differences interact with developmental stages across the lifespan. Several genes are associated with an increased risk for PTSD and other anxiety disorders (Almli et al. 2014; El-Kordi et al. 2013; Erhardt and Spoormaker 2013; Felmingham et al. 2013; Norrholm et al. 2013; Wilker et al. 2013), and these genes may also predispose individuals to

relapse. In addition, epigenetic mechanisms of stress and psychopathology have received considerable attention in recent years (Maddox et al. 2013; Norrholm et al. 2013; Zovkic et al. 2013), and these factors might also confer individual differences in fear extinction and relapse. Indeed, some individuals extinguish fear rapidly and exhibit resilience in the face of stress (Franklin et al. 2012; Jovanovic and Ressler 2010; Galatzer-Levy et al. 2013). Insight into what contributes to resiliency, both in terms of behavior and brain function, may offer a means to reduce susceptibility of fear relapse in others.

Strategies to Prevent Relapse

To this point, we have discussed factors that influence the return of extinguished fear. We will now describe classic and contemporary strategies that may combat relapse of fear.

Optimizing Behavioral Therapy

Several studies indicate that the magnitude and duration of fear reduction after extinction relates to the amount of extinction training (Cain et al. 2003; Denniston et al. 2003; Orinstein et al. 2010). Extinction learning is slowly acquired, and limited training leads to rapid fear relapse. Thus, animals undergoing massed extinction trials often experience several hundred consecutive CS-alone presentations (Laborda and Miller 2013; Urcelay et al. 2009). As is often the case in procedures for massed extinction, the intertrial interval may be of short duration, which may in actuality weaken the extinction memory (Li and Westbrook 2008). Spaced trials may offer greater protection from fear relapse than with massed trials (Li and Westbrook 2008; Urcelay et al. 2009). As mentioned earlier, spaced trial procedures across multiple points in time may buffer against spontaneous recovery by supporting multiple temporal contexts with which extinction training is associated (Bouton 2002; Tsao and Craske 2000; Urcelay et al. 2009). The greater efficacy of spaced versus massed extinction trials continues to be explored (Li and Westbrook 2008; also see Fitzgerald et al. 2013).

Extinction in multiple contexts has been argued to facilitate suppression of fear in future encounters with the CS (Balooch et al. 2013; Chelonis et al. 1999; Gunther et al. 1998). This strategy has been argued to be particularly effective at reducing renewal. This has come with mixed results, however (Fitzgerald et al. 2013). Recent experiments suggest that extinction in multiple contexts is not always successful in preventing renewal (Bouton et al. 2006). Pairing massed extinction with extinction in multiple contexts may help foster greater fear suppression than with either strategy alone (Laborda and Miller 2013; Vervliet et al. 2013). Interestingly, by extinguishing renewed fear as a result of an extinguished CS presentation in a novel context, rats exhibit resistance to subsequent renewal of fear when the CS is presented in the conditioning context (Holmes and Westbrook 2013). Although contexts are distinct for experimental animals, several features and cues in the contexts are often shared among different testing chambers and contexts. During times of high risk of relapse, presentation of retrieval (reminder) cues of the extinction experience may foster resilience against renewal and spontaneous recovery or against relapse in general (Bouton 2000; Brooks and Bouton 1993; Brooks and Bouton 1994; Culver et al. 2011; Dibbets et al. 2008; Dibbets et al. 2013). As a preventative measure, it has been proposed that having patients consciously identify similarities between the extinction context and other environments may prove helpful in preventing relapse (Bouton 2002).

Enriched environments are known to offer protection against the negative effects of stress (Baldini et al. 2013; Mitra and Sapolsky 2009). In turn, supportive and enriched environments may offer protection against stress-induced relapse. Additionally, voluntary exercise has been shown to foster resilience in animals (Fox et al. 2008; Salem et al. 2009; but see Hare et al. 2012). In rodents, voluntary exercise most often comes in the form of wheel running. With more time spent on an exercise wheel, uncontrollable stress exerts less of a negative impact on the animal (Greenwood et al. 2005). Thus, voluntary exercise may help buffer stress-induced fear relapse.

Time of day effects can also play a role in the acquisition and retention of extinction. Recent work in humans highlighted a deepening of extinction simply through training subjects in the morning as opposed to evening sessions (Pace-Schott et al. 2013). In rodent behavioral work, experimenters should be mindful of renewal effects that may occur as a result of irregularity in the time of day at testing. Although patients may be reluctant to entertain the idea, habituation to the US has also been argued to potentially reduce the risk of fear relapse to CS (Rauhut et al. 2001). Other work in humans suggests that merely observing others undergoing extinction can provide some protective effects (Golkar et al. 2013). Interestingly, postexposure sleep appears to enhance long-term fear reduction (Kleim et al. 2013). In another sleep study, Wixted (2013) described a means by which fear can be extinguished during sleep by exposing subjects to odor cues during sleep. In combination with other extinction strategies, these and other novel procedures may offer greater protection against relapse; however, that remains to be demonstrated.

Behavioral interventions for PTSD in humans are often implemented immediately following trauma (Agorastos et al. 2011; Kearns et al. 2012; Roberts et al. 2009). In recent years, the efficacy of immediate extinction procedures has come under question. In some instances, immediate extinction has been found to be robust and effective in preventing relapse (Myers et al. 2006); there's even some evidence that these procedures are capable of erasing the original fear memory (Maren 2011; Monfils et al. 2009). On the other hand, immediate extinction after conditioning is often ineffective in long-term suppression of fear in rodents (Archbold et al. 2010; Chang and Maren 2009; Maren 2011; Maren 2013; Maren and Chang 2006). In general, delayed extinction has been shown to be far more effective in humans in preventing relapse in renewal and spontaneous recovery paradigms

(Huff et al. 2009). Similarly, Archbold and colleagues (2013) found spontaneous recovery in rats to be more pronounced shortly after extinction training (i.e., between 1 and 4 hours postextinction) when compared with later time points (i.e., 8 to 24 hours postextinction). Long-term consolidation of the extinction memories may account for the reduction in spontaneous recovery at the later time points (Archbold et al. 2013). Distributing extinction training across a wide array of time points may deepen extinction (Gershman et al. 2013), and this notion is supported by clinical work in humans (Rowe and Craske 1998; Tsao and Craske 2000).

Pharmacotherapeutic Interventions

Pharmacological therapies often coincide with behavioral interventions of anxiety disorders (Choi et al. 2010; Davis et al. 2006; de Kleine et al. 2013; Dunlop et al. 2012; Hetrick et al. 2010). Several pharmacological strategies have been identified that are known to facilitate extinction learning in animals (for a recent review, see Fitzgerald et al. 2013). In combination with behavioral therapies, these strategies may offer greater protection from relapse (Foa et al. 2002). Recently, a single L-dopa administration was shown to be effective in preventing renewal of fear in rats (Haaker et al. 2013). As mentioned, acute propranolol administration in the wake of a stressful exposure to a dangerous context has been shown to prevent relapse of fear (Morris et al. 2005b). In modulating glucocorticoid signaling, cannabinoids may offer protection in the form of enhanced extinction learning (de Bitencourt et al. 2013; Ganon-Elazar and Akirav 2012; Rabinak and Phan 2013). Systemic administration of the cholinergic antagonist scopolamine has been found to reduce renewal of fear in low doses, perhaps through disruption of both hippocampal activity and normal context-dependent encoding of extinction (Zelikowsky et al. 2013b). D-Cycloserine has also shown some efficacy in reducing anxiety (Bouton et al. 2008), although its effects on extinction are mixed (Fitzgerald et al. 2013). In patients with generalized anxiety disorder, chronic administration of the melatonergic antidepressant, agomelatine, has been found to be efficacious in reducing relapse (Stein et al. 2012). In the future, more uncommon molecular targets might pave the way for future relapse therapies. For example, global increases of magnesium levels in the brain have been shown to improve extinction retention (Abumaria et al. 2011). Pharmacologically enhanced brain-derived neurotrophic factor signaling in the brains of female mice attenuates renewal of fear (Baker-Andresen et al. 2013). In another study in rats, systemic injection of fibroblast growth factor-2 has been shown to also offer protection against renewal (Graham and Richardson 2010).

Deep Brain Stimulation

Specific regions of the prefrontal cortex (PFC) in rodents and humans have been implicated in fear suppression and resilience (Courtin et al. 2014; Maier et al. 2006), and the PFC has an important role in extinction (Chang and Maren 2011; Herry 2010; Likhtik et al. 2005; Likhtik et al. 2014; Maren 2011; Maroun 2013; Milad et al. 2007; Sotres-Bavon et al. 2012). Stress is thought to perturb these areas of the PFC (Akirav and Maroun 2007; Maier and Watkins 2010; McEwen and Morrison 2013), and one strategy for facilitating extinction involves functional activation of the PFC. By artificially stimulating these regions, resilience in the face of stress might be encouraged, possibly offering a means of relapse prevention. In most cases, artificial stimulation in the brain has been examined only in light of facilitating the extinction process, rather than observing whether its use results in a more resilient form of extinction. That said, others have begun to elucidate the significance of cortical stimulation in relapse prevention. High-frequency stimulation in the PFC of rats has been shown to be effective in preventing reemergence of extinguished fear as a result of a subconditioning procedure (Zheng et al. 2013). Subconditioning involves pairing the US once again with the CS after conditioning; however, the US is dramatically weaker. In turn, the postextinction subconditioning procedure will not initiate reconditioning of fear to the CS but will impair the retention of extinction in future tests. Unlike chronic fluoxetine administration in a separate experiment from the same laboratory, Zheng and colleagues (2013) demonstrated that high-frequency stimulation of the PFC did not buffer against acute stress-induced relapse elicited by exposure to an elevated platform (Deschaux et al. 2012). Cortical stimulation may not be entirely effective alone, but combinative strategies (i.e., behavioral training in conjunction with stimulation) may prove fruitful. Moreover, high-frequency stimulation is not the only method by which resilience may be produced. In a trace-conditioning paradigm, pairing extinction training with low-frequency stimulation in anterior cingulate cortex (a technique that is known to reduce neural excitability and ultimately induce long-term depression) reduced spontaneous recovery in primates (Klavir et al. 2012). Lastly, there is even evidence that peripheral vagus nerve stimulation coinciding with extinction training can facilitate rapid fear suppression (Peña et al. 2013).

Conclusions

The relapse of fear after exposure therapy is a major challenge for clinical interventions for fear and anxiety (Vervliet et al. 2012). Although we have focused on fear recovery phenomena in isolation of one another, it is important to consider that the conditions that precipitate these phenomena might be concurrently experienced to produce additive or super-additive effects on relapse. For example, experiencing both a passage of time with a change in context after extinction (i.e., a paradigm including both spontaneous recovery and renewal components) might result in a particularly strong relapse of fear (Laborda and Miller 2013). Consistent with these ideas, emerging evidence suggests that relapse phenomena (such as

spontaneous recovery or reinstatement, for example) may be mediated by separate neural mechanisms (Ma et al. 2012) and in turn may require alternative modes of intervention. Critically, our understanding of these relapse phenomena has been notably advanced by the study of Pavlovian fear conditioning and extinction in rodents, which provide a unique and unparalleled opportunity for concurrent behavioral and neural analyses. Nonetheless, more work is clearly needed to understand the myriad of factors that cause fear to return in anxious brains.

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