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Extinction after fear memory reactivation fails to eliminate renewal in rats

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Abstract

Retrieving fear memories just prior to extinction has been reported to effectively erase fear memories and prevent fear relapse. The current study examined whether the type of retrieval procedure influences the ability of extinction to impair fear renewal, a form of relapse in which responding to a conditional stimulus (CS) returns outside of the extinction context. Rats first underwent Pavlovian fear conditioning with an auditory CS and footshock unconditional stimulus (US); freezing behavior served as the index of conditioned fear. Twenty-four hours later, the rats underwent a retrieval-extinction procedure. Specifically, 1 h prior to extinction (45 CS-alone trials; 44 for rats receiving a CS reminder), fear memory was retrieved by either a single exposure to the CS alone, the US alone, a CS paired with the US, or exposure to the conditioning context itself. Over the next few days, conditional freezing to the extinguished CS was tested in the extinction and conditioning context in that order (i.e., an ABBA design). In the extinction context, rats that received a CS+US trial before extinction exhibited higher levels of conditional freezing than animals in all other groups, which did not differ from one another. In the renewal context, all groups showed renewal, and none of the reactivation procedures reduced renewal relative to a control group that did not receive a reactivation procedure prior to extinction. These data suggest retrieval-extinction procedures may have limited efficacy in preventing fear renewal.

Keywords

Context; Extinction; Fear; Postretrieval Extinction; Rat; Reconsolidation; Relapse; Renewal

1. Introduction

Fear memories may last a lifetime (Bergstrom, 2016). Even with extensive clinical and pharmaceutical treatments, humans often exhibit relapse of pathological fear and anxiety (Borkovec & Costello, 1993; Hermans et al., 2006; Vervliet et al., 2013a, 2013b; Wicking et al., 2016). Fear relapse can be modeled in the laboratory using Pavlovian fear conditioning

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and extinction (Bouton, 1993, 2002, 2004, 2014; Bouton et al., 2006; Craske et al., 2014; Goode & Maren, 2014; Haaker et al., 2014; Hermans et al., 2006; Kim & Richardson, 2010; Maren & Holmes, 2016; Maren et al., 2013; Vervliet et al., 2013a, 2013b), which may contribute to and interact with fear and anxiety disorders (Careaga et al., 2016; Nees et al., 2015; Ribrough et al., 2016; Smith et al., 2017; Zuj et al. 2016). Specifically, Pavlovian fear conditioning consists of pairing a harmless conditioned stimulus ("CS"; e.g., auditory tone) with a noxious unconditioned stimulus ("US"; e.g., footshock) (Konorski, 1948; Pavlov & Anrep, 1927; Rescorla, 1988). Following one or more pairings in a conditioning chamber, animals will come to express conditioned fear responses (e.g., freezing behavior, autonomic activity) to the CS alone (Fanselow, 1994; Izquierdo et al., 2016; LeDoux, 2000; Maren, 2001). After conditioning, nonreinforced presentations of the CS result in the gradual reduction of fear responses to the CS, a process termed extinction (Bouton et al., 2006; Maren et al., 2013; Myers & Davis, 2007; Pavlov & Anrep, 1927). However, extinguished fear in humans and other animals is known to return under a variety of circumstances (Bouton, 1993, 2002, 2004, 2014; Bouton et al., 2006; Craske et al., 2014; Goode & Maren, 2014; Haaker et al., 2014; Hermans et al., 2006; Kim & Richardson, 2010; Maren & Holmes, 2016; Maren et al., 2013; Vervliet et al., 2013a, 2013b), including after encountering the CS outside of the environment or "context" in which extinction occurred (termed "renewal"; Bouton & Bolles, 1979). Thus, while fear responses to a CS generalize across contexts, extinguished fear responses are context-dependent. Renewal and other relapse phenomena (e.g., shock-induced reinstatement and time-dependent spontaneous recovery of fear) reveal that extinction is not typically a fear-erasing process, rather extinction results in a new competitive memory that is thought to suppress the expression of conditioned fears (Bouton, 1993, 2002, 2004, 2014; Bouton et al., 2006; Maren, 2011). Given that extinction learning is thought to be an important factor in common forms of cognitive-behavioral therapy (e.g., exposure therapy; Graham et al., 2011; Graham & Milad, 2011; Hermans et al., 2006; Kaplan et al., 2011; Wicking et al., 2016), there is considerable interest in identifying new methods to enhance fear extinction and erase pathological fear memories selectively (Dejean et al., 2015; Fitzgerald et al., 2014; Goode & Maren, 2014; Herry et al., 2010; LeDoux, 2015; Maren, 2011; Maren et al., 2013; Maren & Holmes, 2016; Morrison & Ressler, 2014; VanElzakker et al., 2014).

One possible method for the selective erasure of maladaptive fear memories involves disrupting memory *reconsolidation*. After conditioning, encountering fear conditioning-related stimuli (the CS, US, and/or conditioned context) can trigger the previously consolidated conditioned memory to enter a labile state that requires reconsolidation (Auber et al., 2013; Clem & Schiller, 2016; Kredlow et al., 2016; Schiller & Phelps, 2011). Behavioral, pharmacological, or neural manipulations during this postretrieval period allows for modification of the fear memory, including weakening or potentially erasing the memory (Auber et al., 2013; Giustino et al., 2016; Kindt et al., 2009; Kindt & van Emmerik, 2016; Lattal & Wood, 2013; Meir Drexler & Wolf, 2016b; Monfils et al., 2009; Nader, 2003, 2015; Nader et al., 2000; Quirk et al., 2010; Schiller et al., 2010; Schwabe et al., 2014; Soeter & Kindt, 2011). Of particular interest, it has been shown that reactivating or retrieving fear memories prior to extinction training can lead to a loss of responding to the CS that does not exhibit renewal, reinstatement, or spontaneous recovery (Monfils et al., 2009). This effect

was time-dependent, such that the retrieval trial was found to enhance extinction only if it preceded normal extinction by 1 or 6 h but not 24 h (i.e., during the "reconsolidation window"; Monfils et al., 2009). Similarly, time-dependent postretrieval extinction has been shown to prevent relapse in humans (Schiller et al., 2010). In these studies, it has been proposed that the CS reminder engages a reconsolidation process that can be disrupted (and the labile memory erased) by extinction trials delivered shortly after memory enters a malleable state (Monfils et al., 2009; Schiller et al., 2010; Schiller & Phelps, 2011).

The possibility that fear memories can be erased has generated enormous excitement in the clinical community (Careaga et al., 2016; Kroes et al., 2016; Post & Kegan, 2017; Quirk et al., 2010; Smith et al., 2017), but the efficacy of "reconsolidation update" procedures in preventing fear relapse is mixed (Auber et al., 2013; Clem & Schiller, 2016; Kredlow et al., 2016; Schiller & Phelps, 2011). A critical variable that has not yet been fully explored might be the procedure used to reactivate the fear memory prior to extinction. For example, reconsolidation windows can be opened by the presentation of the CS alone, the US alone, a conditioned context, or even a conditioning trial (CS+US) and protein synthesis inhibitors delivered after these forms of reactivation lead to impaired retention of conditioned fear memories (Duvarci & Nader, 2004). Moreover, recent work in humans and rats indicates that *weak* US-alone exposure prior to extinction prevents fear reinstatement and spontaneous recovery (Liu et al., 2014; Thompson & Lipp, 2017). However, the relative efficacy of these manipulations in preventing relapse phenomena, including renewal, have not been explored.

In the present study, we examined the efficacy of four different retrieval procedures in preventing fear renewal after extinction. We hypothesized that retrieval procedures that produced prediction errors (CS-, US-, or shock-associated context-alone reminders; Rescorla & Wagner, 1972) would be more effective than a CS+US trial in promoting reconsolidation update and in preventing fear renewal (provided animals were sufficiently extinguished). This hypothesis is based on work by Sevenster and colleagues (2012, 2013, 2014), which highlight the importance of prediction error in engaging reconsolidation (Fernández et al., 2016). Accordingly, rats were conditioned and underwent extinction 1 h after brief or single exposure to the CS, US, a CS+US trial, or the conditioning context; another group of rats did not receive any retrieval procedure to serve as a control. To assess relapse, we tested animals to the extinguished CS outside of the extinction context (renewal). None of the retrieval procedures attenuated fear renewal—in fact, retrieval with a US-alone or CS+US trial facilitated fear expression during renewal. These results challenge the efficacy of retrieval-extinction procedures in preventing fear relapse.

2. Materials and Methods

2.1. Subjects

Subjects were sixty-four adult male Long-Evans (Blue Spruce) rats (200–225 g) obtained from Harlan Sprague-Dawley (Indianapolis, IN). Subjects were individually housed in a climate-controlled vivarium at the University of Michigan where the present experiment was conducted. Rats were kept on a reverse light (14 h)-dark (10 h) cycle. Food and water were accessible *ad libitum*. Rats were handled once a day for ~1 min for 5 consecutive days prior

to the start of behavior. The University of Michigan Animal Care and Use Committee approved all experimental procedures.

2.2. Behavioral apparatuses

All training and testing procedures occurred in rodent observation chambers (MED-Associates, St. Albans, VT) of identical size (30 × 24 × 21 cm) and construction (Plexiglas ceilings, rear walls, and doors, aluminum side walls, and stainless steel grid floors). Observation chambers were contained within external sound-attenuating cabinets. Grid floors of the observation chambers (consisting of 19 stainless steel rods) were connected to shock sources and solid-state grid scramblers (MED-Associates) for delivering footshock (US). Small speakers were attached to the chambers and provided auditory tones (CS). The observation chambers were also fitted with 15-W house lights and ventilation fans. Each observation chamber rested upon a load-cell platform (connected to load-cell amplifiers) that would respond to cage displacement as a result of a rat's movements (load-cell amplifiers were calibrated to a standardized degree of chamber displacement prior to behavioral training). Load-cell activity output (+/−10 V) was transformed into values of 0–100 and captured every 200 ms using Threshold Activity software (MED-Associates). Smaller values indicated less cage displacement and freezing was quantified as transformed load-cell activity values of ≤10 for 1 s or more.

Sensory features of the chambers were manipulated to obtain three unique contexts (A, B, and C) for the current study. For context A, 1% acetic acid was used to wipe down the chambers (grid floors were dried) and a small volume of the odor was poured into the pans beneath the grid floors. Chamber house lights remained lit, room lights were on, chamber fans were on, cupboard doors encasing the chambers were left open, and rats were transported to and from the chambers in white plastic transport boxes. For context B, 1% ammonium hydroxide was used for the context's odor, chamber house lights were turned off, red room lights were used, chamber fans were turned off, the cupboard doors were closed, and rats were transported in black plastic transport containers. For context C, 10% ethanol served as the chambers' odor, chamber house lights were on, red room lights were used, fans remained off, cupboard doors were left open, and rats were transported in white plastic buckets with a layer of bedding at the bottom.

2.3. Behavioral procedures

A summary of the behavioral procedures is shown in Figure 1. Subjects were randomly assigned to one of five groups: *extinction only* ("*NO REMINDER*"; $n = 12$), *conditioned stimulus reminder* ("CS_R"; $n = 13$), *conditioning context reminder* ("*CONTEXT ALONE*"; $n = 13$), *unconditioned stimulus reminder* ("US_R"; $n = 13$), or *reinforced conditioned stimulus reminder* ("$CS+US_R$"; $n = 13$). Rats were trained and tested in squads of eight (counterbalanced by group assignment when possible).

On day 1, rats were placed in context A and allowed to acclimate for 3 min before the onset of the first CS+US pairing (US onset immediately followed CS offset for all pairings). A 10 s, 2 kHz, 80 dB auditory tone served as the CS, and a 2 s, 1 mA footshock served as the US for both conditioning and retrieval, if involved. For conditioning, rats experienced 5 CS+US

pairings, separated by 58 s interstimulus intervals (ISI's). Rats remained in the chamber for 58 s after the final pairing before being returned to their homecages. On day 2, rats received nonreinforced exposure to context C for 35 min and 30 s (this context would later serve as a renewal context). On day 3, rats were exposed to context A for 5 min, during which rats experienced a retrieval trial based on their respective group assignments. Specifically, after 3 min in the chamber, CS_R, US_R, and $CS+US_R$ rats experienced a single nonreinforced CS, a single US trial alone, or a single CS+US pairing, respectively. *CONTEXT ALONE* rats remained in the chamber for 5 min without reinforcement. *NO REMINDER* rats remained in their homecages during the reminder phase. Rats were returned to their homecages following the reminder. 1 hr after the reminder phase, all rats were extinguished in context B. Extinction consisted of 45 nonreinforced CS alone trials separated by 30 s ISI's. To equate CS exposure, rats that received a CS during the reminder phase received 44 extinction trials. Extinction trials started 3 min after rats were placed in the chambers. The entirety of the extinction session lasted 35 min and 30 s for all groups.

Twenty-four hours after extinction, half of the rats were tested to the CS in the extinction context (B), while the other half were tested to the CS in the familiar context (C). These testing assignments were counterbalanced across reminder conditions and were swapped out for testing on the following day (i.e., for the second day of testing, rats tested in context B were tested in Context C and vice versa). For each test, five CS-only trials (30 s ISI's) began 3 min after rats were placed in the chambers. The entirety of each test lasted 8 min and 50 s. Twenty-four hours after testing in Context B and C, rats were tested to the CS (identical trials to the previous tests) back in the conditioning context (A).

2.4. Data analysis

Mean percentage freezing (±SEM) served as the dependent variable. Freezing data were collected continuously during each behavioral session. Freezing during the post-CS interstimulus interval served as the primary index of fear to each CS; statistical outcomes for freezing during the CS (not reported) were similar across tests as compared to ISI responding (ISI freezing is often a more reliable measure of fear than freezing during the CS, which is influenced by a head-jerk orienting response; e.g., Holland, 1977, 1980). Data were submitted to analysis of variance (ANOVA). Following a significant overall F ratio, post-hoc comparisons were tested using Fisher's Protected Least Significant Difference (PLSD). Trials for repeated measures/factorial ANOVA correspond to the data shown in the figures, unless noted differently in the Results. No rats were excluded from the analysis.

3. Results

Results are depicted in Figures 2 and 3. Rats exhibited robust conditioning (Fig. 2, "CONDITIONING"), as revealed by a significant main effect of trial [$F_{(5,295)} = 81.978$, $p < 0.0001$]. No group differences in freezing were observed (no main effect of group, no interaction [$Fs < 1$]), indicating the groups acquired similar levels of freezing. Data for the novel context exposure on day 2 is not shown, however no group differences were observed [$Fs < 1$]; freezing was low during the exposure session (mean = 11.638% [±0.735%]), suggesting robust discrimination of contexts A and C. For the reminder phase on day 3 (Fig.

2, “REMINDER”), a main effect of trial [$F_{(3,144)} = 18.368$, $p < 0.0001$] revealed that fear increased throughout the 5 min session in the conditioning context. No group differences were detected [$Fs < 2.5$] (note: *NO REMINDER* rats not included).

During the extinction session (Fig. 2, “EXTINCTION”), there was a significant main effect of trial which reflected the significant decrease in freezing across extinction blocks [$F_{(11,649)} = 71.717$, $p < 0.0001$]. A main effect of group [$F_{(4,59)} = 3.708$, $p < 0.01$] and a group x trial interaction was observed for extinction [$F_{(44,649)} = 2.152$, $p < 0.0001$]. Fisher’s PLSD revealed that $CS+US_R$ rats exhibited significantly more within-session freezing for extinction training as compared to *CONTEXT ALONE* [$p < 0.05$], CS_R [$p < 0.005$], and *NO REMINDER* groups [$p < 0.005$]. Additionally, a separate factorial ANOVA of baseline freezing during extinction revealed a main effect of group [$F_{(4,59)} = 8.916$, $p < 0.0001$]. Post-hoc comparisons showed US_R rats exhibited significantly higher baseline fear as compared to *CONTEXT ALONE* [$p < 0.0001$], CS_R [$p < 0.0001$], and *NO REMINDER* groups [$p < 0.0001$]. Similarly, $CS+US_R$ rats were higher at baseline as compared to *CONTEXT ALONE* [$p < 0.005$], CS_R [$p < 0.005$], and *NO REMINDER* groups [$p < 0.005$]. These data indicate that reminder procedures that include a US significantly enhance freezing in subsequent sessions. However, the groups did not significantly differ during the final extinction block (separate factorial ANOVA: [$Fs < 2.5$]), suggesting that extinction was equivalent despite the higher baseline freezing.

On days 4 and 5, rats were tested to the CS in a counterbalanced manner in either the extinction context or in the familiar (previously novel; renewal) context. For the test in the extinction context (Fig. 3, “EXTINCTION CONTEXT (ABB)”), repeated measures ANOVA revealed a main effect of trial [$F_{(7,413)} = 27.670$, $p < 0.0001$] as rats increased in freezing after the baseline period. A main effect of group [$F_{(4,59)} = 3.666$ $p < 0.01$] was observed for the extinction test. Similar to extinction training sessions, post-hoc comparisons revealed that $CS+US_R$ rats exhibited significantly more within-session freezing as compared to *CONTEXT ALONE* [$p < 0.01$], CS_R [$p < 0.005$], and *NO REMINDER* groups [$p < 0.005$]. Comparisons of mean post-CS freezing (a mean of ISI’s 1 through 5) during the extinction test vs. mean freezing during the final block of extinction training revealed a significant main effect of trial [$F_{(1,59)} = 10.055$, $p < 0.005$] and group [$F_{(4,59)} = 3.178$, $p < 0.05$]. Post-hoc comparisons indicated that rats exhibited significantly more freezing at test than at the end of extinction training (independent of group assignment; [$p < 0.005$]). Furthermore, $CS+US_R$ rats exhibited significantly more fear across this analysis as compared to CS_R and *NO REMINDER* groups [$ps < 0.005$]. Collectively, these data indicate that rats (independent of group assignment) exhibited some spontaneous recovery when tested in the extinction context, although this recovery was mild: mean freezing across testing was significantly less for all groups (no main effect of group; no trial x group interaction [$Fs < 2.5$]) as compared to the first block of extinction training (repeated measures ANOVA; main effect of trial: [$F_{(1,59)} = 161.322$, $p < 0.0001$]).

For ABC renewal testing (Fig. 3, “RENEWAL CONTEXT (ABC)”), a main effect of trial [$F_{(7,413)} = 38.799$; $p < 0.0001$], a main effect of group [$F_{(4,59)} = 5.214$, $p < 0.005$], and a group x trial interaction [$F_{(28,413)} = 1.929$, $p < 0.005$] were detected. Fisher’s PLSD indicated that $CS+US_R$ rats exhibited significantly more freezing across the ABC renewal

test as compared to *CONTEXT ALONE* [$p < 0.005$], CS_R [$p < 0.001$], and *NO REMINDER* groups [$p < 0.001$]. To assess the extent of ABC renewal (i.e., greater freezing in the ABC vs. ABB conditions), mean freezing across ISI's 1 through 5 of the extinction test and the ABC renewal test were compared using repeated measures ANOVA. A significant main effect of group [$F_{(4,59)} = 6.241$, $p < 0.0005$] was revealed, with Fisher's PLSD further indicating that $CS+US_R$ rats exhibited significantly more freezing across the ISI's of both tests as compared to *CONTEXT ALONE* [$p < 0.0005$], CS_R [$p < 0.0001$], and *NO REMINDER* groups [$p < 0.0001$]. However, we observed no significant main effect of trial or interactions for these comparisons [$Fs < 0.5$], suggesting that the ABC test produced weak renewal when compared to freezing during testing in the extinction context (rats failed to discriminate between context B and C). Although CS_R rats did not exhibit ABC renewal, neither did *CONTEXT ALONE*, *NO REMINDER*, $CS+US_R$, or US_R rats, suggesting no fear erasure by the CS_R procedure, in particular.

Twenty-four hours later, rats were tested to the CS in the conditioning context (ABA renewal; Fig. 3, "RENEWAL CONTEXT (ABA)"), a context in which renewal is more robust (Bouton and Bolles, 1979; Bouton and King, 1983; Harris et al., 2000; Bouton et al., 2006). For the ABA test, a main effect of trial [$F_{(7,413)} = 59.722$, $p < 0.0001$], a main effect of group [$F_{(4,59)} = 10.279$, $p < 0.0001$], and a trial x group interaction [$F_{(28,413)} = 4.987$, $p < 0.0001$] were detected. Post-hoc comparisons showed that US_R and $CS+US_R$ rats exhibited significantly higher fear overall as compared to *CONTEXT ALONE*, *NO REMINDER*, and CS_R rats [$ps < 0.05$]. Interestingly, CS_R and *CONTEXT ALONE* rats also exhibited significantly more fear across ABA testing as compared to *NO REMINDER* rats [$ps < 0.05$]. These differences in part may relate to levels of baseline fear in the conditioning context (however it should be noted that the main effect of trial across testing suggests fear increased generally after the CS). Factorial ANOVA of baseline fear showed a main effect of group [$F_{(4,59)} = 25.342$, $p < 0.0001$]. Post-hoc analyses indicated that *US* and $CS+US_R$ rats exhibited significantly greater baseline fear than all other groups [$ps < 0.0001$], but not between each other. Interestingly, CS_R rats also expressed significantly more freezing during baseline than *CONTEXT ALONE* or *NO REMINDER* rats [$ps < 0.05$].

A comparison of mean post-CS freezing (ISI's 1 through 5) during ABA renewal testing vs. extinction retrieval revealed a main effect of trial [$F_{(1,59)} = 305.061$, $p < 0.0001$], indicating significant renewal of fear (unlike ABC renewal). Additionally, a main effect of group was detected for this comparison [$F_{(4,59)} = 4.013$, $p < 0.01$], however no trial x group interaction was revealed [$F<2$]. Similar to other sessions, post-hoc analyses indicated that $CS+US_R$ rats exhibited significantly more freezing across the extinction and ABA tests as compared to CS_R, *NO REMINDER*, or *CONTEXT ALONE* groups [$ps < 0.05$]. Similarly, US_R rats exhibited more fear as compared to *NO REMINDER* rats [$p < 0.05$]. Collectively, the results indicate that the pre-extinction fear reactivation procedures were not effective in erasing fear, as evident by renewal and lingering baseline fear. Furthermore, these reminders were not any more successful in reducing fear relapse than extinction alone.

4. Discussion

The present study examined the effects of various fear reactivation procedures (CS alone, US alone, a conditioning trial, or conditioned context alone) on extinction and relapse of conditioned fear, particularly renewal. In contrast to what has been reported previously for postretrieval extinction procedures (e.g., Monfils et al., 2009), the current study found that reactivating fear memory prior to extinction training did not prevent fear renewal. Indeed, the observation of robust ABA renewal in all of the groups receiving reminders suggests that the original fear memory was not eliminated by postretrieval extinction. The low levels of fear during retrieval testing and even during the ABC renewal test (while unusual and presumably due to weak discrimination of context B and C) indicate that our effects were not due to a failure of rats to acquire extinction. It is worth noting, the US_R and the $CS{+}US_R$ reminder groups showed enhanced baseline freezing during the extinction session and in the ABA renewal test. This appears to be consistent with the work by Liu and colleagues (2014) in that a strong US reminder impeded context extinction. However, we now show that full extinction of a fear CS shortly after a strong US reminder (or an additional conditioning trial) does not ultimately prevent renewal. $CS{+}US_R$ rats also exhibited more freezing across trials for extinction retrieval and in the ABC renewal session as compared to other groups, but this did not specifically enhance the extent of ABA renewal for this group (however, this could be a ceiling effect). This suggests that $CS{+}US_R$ rats were not necessarily at asymptote following conditioning. Enhanced fear in US_R and $CS{+}US_R$ rats may relate to the immediate extinction deficit (which is observed when animals are extinguished shortly after conditioning trials; Maren, 2014), however this may be due to the additional training trial itself. Interestingly, CS_R rats also exhibited higher baseline fear during ABA renewal, at least when compared to *NO REMINDER* and *CONTEXT ALONE* rats (however, this increase was not as large as $CS{+}US_R$ or US_R rats). It's not fully clear why this may be the case (also, see Chan et al., 2010), but perhaps the isolated CS- retrieval trial in the conditioning context increased fear of the conditioning context by contributing to its ambiguity. All of this considered, the current data do not support the hypothesis that fear reactivation (with or without the original US) before extinction is an effective means of erasing fear and preventing renewal. Conversely, the current data support a model of fear learning in which fear memories are difficult to erase behaviorally, a finding that is consistent with numerous studies documenting relapse after extinction (Bouton, 1993, 2002, 2004, 2014; Bouton et al., 2006; Craske et al., 2014; Goode & Maren, 2014; Haaker et al., 2014; Hermans et al., 2006; Kim & Richardson, 2010; Maren & Holmes, 2016; Maren et al., 2013; Vervliet et al., 2013a, 2013b).

Failures to observe the postretrieval extinction effect have been reported in both animals (Chan et al., 2010; Ishii et al., 2012) and humans (Golkar et al., 2012; Kindt & Soeter, 2013; Klucken et al., 2016; Meir Drexler et al., 2014; Soeter & Kindt, 2011). A recent meta-analysis of these and similar studies found that the effects of postretrieval extinction on relapse in animals are typically small and often nonsignificant (Kredlow et al., 2016), which is in line with the current data. That said, in cases where postretrieval extinction was successful, Kredlow and colleagues (2016) found housing conditions and the timing of retention testing to be important factors in the effect. Specifically, the authors found that

housing conditions were a significant moderator of postretrieval extinction, such that group housing appeared to reduce the efficacy of postretrieval extinction. It is not yet clear what may mediate this effect, although it may relate to social transfer of fear (Knapska et al., 2010; Nowak et al., 2013). Animals were individually housed in the present study. Kredlow and colleagues (2016) also found that postretrieval extinction was significantly more effective in studies with longer time intervals (roughly a week or more) between extinction's end and testing for relapse. The current study examined relapse one to three days after extinction, so it is possible that a longer retention interval would have revealed a renewal deficit. Nonetheless, others have reported significant effects of postretrieval extinction when testing occurred 24 h after extinction (Auber et al., 2013; Kredlow et al., 2016). The timing following postretrieval extinction is an area of ongoing discussion (Auber et al., 2013).

Of course, it is possible that weaker fear memories are more susceptible to postretrieval extinction. In the current study, rats underwent five training trials with a 2 sec, 1 mA footshock US. Similarly, Ishii and colleagues (2012), who failed to see fear erasure using postretrieval extinction in mice, utilized six training trials with a 2 sec, 0.75 mA footshock US. Moreover, stress-enhanced fear learning has been found to be resistant to reconsolidation blockade techniques (Hoffman et al., 2015). To our knowledge, all of the currently published studies on the effects of postretrieval extinction on fear relapse in rats and mice—outside of the mouse study of Clem & Huganir (2010)—utilized fewer and weaker US intensities as compared to the present study. However, US intensities and trials are often weaker in studies involving mice. In humans, fear conditioning studies are often considered less aversive when compared to rodent studies. Human participants may experience fewer conditioning trials and select for the intensity of their own shock (Sehlmeyer et al. 2009). Interestingly, Kredlow and colleagues (2016) observed trending effects for US intensity (not duration) as a potential moderator of the postretrieval extinction effect in animals, however, this trended towards greater efficacy of postretrieval extinction with higher intensity USs. That said, once group housing was controlled for, this effect of US intensity was no longer predictive of the effect. Ultimately, it is not yet clear if strong US intensities (and stronger fear memories) account for the various effects of postretrieval extinction on relapse.

Another possible explanation for the current results is that the conditioning context prevented the animals from processing the reminders or that the reactivation procedure failed to produce reconsolidation (Sevenster et al., 2012, 2013, 2014). However, other groups have used the conditioning context during the reactivation phase (albeit some with success in preventing relapse and some without). It is worth noting that Chan and colleagues (2010) tested retrieval in the conditioning context or in a novel (but habituated) context and both ended without successful prevention of fear relapse (also, see Ishii et al. 2012).

As Kredlow and colleagues (2016) highlight, significant moderators of postretrieval extinction efficacy were not consistent across the domains of animal studies of fear and appetitive relapse and human fear relapse studies. In contrast to the animal work, they found significant effects (small to moderate) overall for postretrieval extinction in humans. However, no positive effect was observed in human studies of fear renewal. While these findings concord with the current data, it should be noted that there are fewer studies

examining the effects of postretrieval extinction on fear renewal in humans as compared to fear reinstatement for example. Perhaps certain forms of relapse (such as reinstatement) are more amendable to the procedure.

Although others have demonstrated that postretrieval extinction can prevent fear relapse in animals (Auchter et al., 2017; Baker et al., 2013; Clem & Huganir, 2010; Flavell et al., 2011; Jones et al., 2013; Jones & Monfils, 2016; Monfils et al., 2009; Olshavsky et al., 2013; Rao-Ruiz et al., 2011; Shumake & Monfils, 2015) and in humans (Agren et al., 2012a, 2012b, 2017; Björkstrand et al., 2015; Golkar et al., 2017; Liu et al., 2014; Meir Drexler et al., 2014; Meir Drexler & Wolf, 2016a; Oyarzún et al., 2012; Schiller et al., 2010, 2013; Thompson & Lipp, 2017), it is important to consider that *prevention* of relapse may not equate to *erasure* of the fear memory. For example, a well-trained extinction memory may be able to outcompete a fear memory for expression, without the fear memory necessarily being eliminated (Lattal & Wood, 2013). Furthermore, it should be noted that there are existing studies demonstrating an *increase* in the degree of relapse as a result of postretrieval extinction (Chan et al., 2010; although that was not the case in the current data; also, see Auber et al., 2013 for comparison). Ultimately, we found that multiple forms of retrieval failed to generate postretrieval extinction impairments on renewal, suggesting that there are limits to the efficacy of these procedures in preventing fear relapse (Auber et al., 2013; Kredlow et al., 2016; Nader & Einarsson, 2010).

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Highlights

- Conditioned stimulus (CS) retrieval 1h prior to extinction did not prevent fear renewal.
- Pre-extinction exposure to the conditioning context did not disrupt fear renewal.
- Unconditioned stimulus (US) exposure prior to extinction enhanced baseline fear but did not eliminate renewal.
- A conditioning trial prior to extinction enhanced fear across training but did not block renewal.

Figure 1.
Behavioral design.

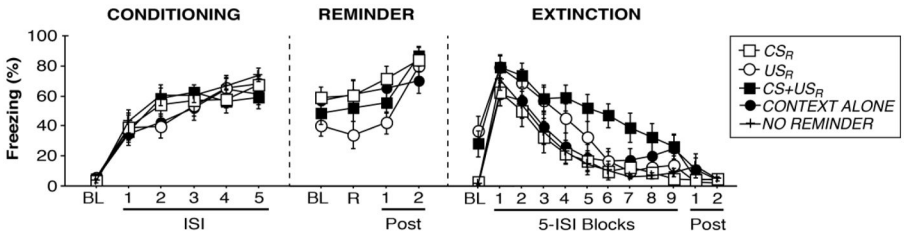

Figure 2.

Effects of pre-extinction fear reactivation on fear extinction. CONDITIONING: Mean freezing (%) during a 3-min baseline period ('BL') followed by five interstimulus intervals ('ISI'; 58 s each) separating conditioning trials (CS+US). REMINDER: Mean freezing (%) during a 3-min baseline period, during a 10-s window starting at the onset of a fear reminder ('R'), followed by freezing across the final two minutes in the chamber ('Post'; note: Post 2 is 50 s). EXTINCTION: Mean freezing (%) during a 3-min baseline period, during forty-five extinction (CS-no-US) trials (broken up into nine 5-ISI blocks with each ISI spanning 30 s each; note: the fifth ISI of block 9 is 1 min), and during each minute remaining in the chamber ('Post'). Rats that received CS retrieval during the reminder phase experienced 44 extinction trials (freezing was measured across equivalent time points).

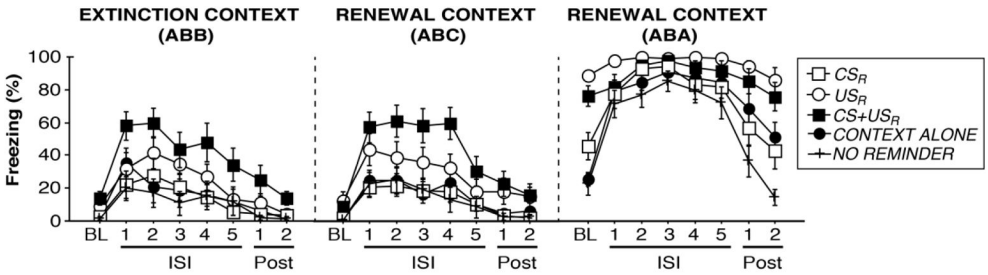

Figure 3.

Effects of pre-extinction fear reactivation on fear renewal. EXTINCTION CONTEXT (ABB): Mean freezing (%) during a 3-min baseline, during five ISI's (ISI 1–4 are 30 s each, ISI 5 spans 1 min) separating testing trials (CS-), and during each minute remaining in the extinction context. RENEWAL CONTEXT (ABC): Mean freezing (%) across trials in the familiar context (trials are identical to testing in the extinction context). RENEWAL CONTEXT (ABA): Mean freezing (%) across trials in the conditioning context (trials are identical to testing in the extinction context).