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# Exploring the boundaries of post-retrieval extinction in healthy and anxious individuals

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ABSTRACT

Over a dozen studies have examined the efficacy of post-retrieval extinction (PRE) in healthy adults in the fear conditioning laboratory, with a recent meta-analysis reporting an overall small-moderate effect on attenuating the return of fear compared to standard extinction. The current study was designed to extend PRE effects to a mixed sample of healthy and anxious individuals, explore potential moderators, and examine the benefit of PRE for a memory conditioned over multiple days. Healthy ($n$ = 49) and anxious ($n$ = 43) adults received either one day of acquisition followed by PRE, one day of acquisition followed by extinction, or three days of acquisition followed by PRE. Comparing participants who received one day of acquisition followed by PRE or extinction, no significant effect of PRE was observed on differential skin conductance response reinstatement or reactivity to the conditioned stimulus alone. Anxiety symptoms did not moderate outcomes. There was no difference in return of fear for anxious participants who received three days of acquisition followed by PRE versus one day of acquisition followed by PRE. These results further highlight the variability of findings in the PRE literature and need for further examination of individual difference factors that may moderate PRE effects.

## 1. Introduction

Although exposure-based treatments for anxiety and traumatic stress disorders are generally efficacious (Olatunji, Cisler, & Deacon, 2010; Watts et al., 2013), a number of patients fail to respond or relapse after treatment (Imel, Laska, Jakupcak, & Simpson, 2013; Taylor, Abramowitz, & McKay, 2012). Thus, there is a need for more potent and enduring interventions for these disorders. This has led to a proliferation of studies examining strategies aimed at enhancing extinction learning, with the promise of translation to clinical exposure-based treatments (for review, Kredlow, Eichenbaum, & Otto, 2018). One line of research that has received a considerable amount of recent attention is the enhancement of extinction via the administration of extinction during memory reconsolidation.

Research suggests that memories are not permanent but labile; when an old memory is retrieved it goes through a period of reconsolidation during which it is susceptible to interference and can be modified (for review, Sara, 2000). To harness this process for enhancement of extinction learning, researchers have developed a paradigm called *post-retrieval extinction* (*PRE;* Monfils, Cowansage, Klann, & LeDoux, 2009; Schiller et al., 2010). This paradigm involves a reminder cue to trigger memory destabilization, setting the stage for reconsolidation. The reminder cue is followed by extinction during the reconsolidation window (typically 10 min after the reminder cue). Rather than leading to new memories of safety that compete with the original fear memory, as is the case in standard extinction (Bouton, 2002), PRE is assumed to result in modification of the destabilized original fear memory prior to its reconsolidation. Because the original fear memory has been changed, there should be a reduced likelihood that fear will return due to spontaneous recovery, reinstatement, renewal, or reacquisition (for review, Kredlow, Unger, & Otto, 2016). Theoretically, if PRE were to be successfully translated to the clinic, it would lead to reduced relapse rates after exposure therapy.

Over a dozen studies have examined the efficacy of PRE in healthy adults in the fear conditioning laboratory, with a recent meta-analysis (Kredlow et al., 2016) reporting an overall small-moderate effect size ($g$ = 0.40) on attenuating the return of fear, compared to standard extinction. However, it is unclear whether this paradigm would be effective for individuals with anxiety disorders or posttraumatic stress disorder (PTSD). Indeed, to our knowledge, no studies of laboratory-conditioned fears have examined PRE effects in anxious participants, although in a related paradigm—using propranolol administration to

*Abbreviations:* conditioned stimulus, CS+, CS-; extinction, E; post-retrieval extinction, PRE; skin conductance, SC; skin conductance level, SCL; skin conductance response, SCR; unconditioned stimulus, UCS

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disrupt reconsolidation—higher trait anxiety was associated with reduced reconsolidation disruption (Soeter & Kindt, 2013). Likewise, clinical applications of PRE have been met with only limited and highly variable success, with one study providing no support (Shiban, Brütting, Pauli, & Mühlberger, 2015) and two studies providing partial support for one outcome measure (Maples-Keller et al., 2017; Telch, York, Lancaster, & Monfils, 2017). Accordingly, examination of the role of anxiety in moderating PRE effects is an important next step on the path to more successful translation of PRE strategies to the clinic.

In addition to the role of anxiety, clinical fear is likely to differ from fear conditioned in the laboratory in both the strength of association and the degree of declarative awareness of the fear. Although memory strength has been identified as a potential boundary condition to reconsolidation interference effects (Auber, Tedesco, Jones, Monfils, & Chiamulera, 2013), to our knowledge, no studies of PRE have directly targeted the manipulation of memory strength in human participants. Interestingly, animal studies of reconsolidation blockade have manipulated memory strength and found reconsolidation interference effects (Robinson & Franklin, 2010; Suzuki et al., 2004; Wang, de Oliveira Alvares, & Nader, 2009; Winters, Tucci, & DaCosta-Furtado, 2009). Examining the potential benefit of PRE for strongly conditioned fear memories may provide insight into whether PRE would be effective for the potent and complex fear memories that underlie anxiety and PTSD.

In addition, research suggests that PRE is an amygdala-dependent process (Agren et al., 2012; Björkstrand et al., 2016; Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013) and potentially less effective for more hippocampal-dependent fear memories (Ishii et al., 2012). As the amygdala is involved in implicit aspects of conditioning and the hippocampus is predominantly involved in declarative aspects of conditioning (Bechara et al., 1995; Grillon, 2009), declarative awareness of the conditioned stimulus-unconditioned stimulus (CS-UCS) contingency during conditioning is potentially a sign of more hippocampal-dependent learning (Weike, Schupp, & Hamm, 2007). Our meta-analysis of PRE studies in healthy human samples found that studies using CS-UCS expectancy ratings during acquisition, potentially enhancing CS-UCS contingency awareness and hippocampal-dependence, had smaller effects than studies that did not use expectancy ratings (Kredlow et al., 2016). Given these findings, CS-UCS awareness serves as a useful proxy for hippocampal-dependence of the fear memory that can be easily examined as a moderator of PRE effects.

In summary, the current study was designed to extend the PRE paradigm to the study of anxious participants while also evaluating a number of important boundary conditions that may underlie the strength of PRE effects as they are considered for translation to the clinic. To explore the question of whether PRE is efficacious for stronger fear memories, we tested whether PRE was efficacious for a conditioned fear memory established across three sequential days of conditioning. To explore the question of whether the hippocampal-dependence of the fear memory moderates PRE effects, we examined CS-UCS contingency awareness as a moderator. In sum, potential moderators evaluated in this study include: (1) the role of anxiety/worry, (2) the presence or absence of contingency awareness, and (3) the influence of a greater number of conditioning experiences.

The magnitude of a PRE effect may also be influenced by the success of acquisition and extinction achieved in the fear conditioning procedures. Given that the outcome of interest in PRE studies is return of fear, the PRE paradigm requires that participants first adequately acquire and extinguish a conditioned fear response (Steinfurth et al., 2014). PRE studies have varied considerably in their definitions of "adequate" acquisition and extinction, potentially explaining some of the variability in findings. In order to be consistent with our prior studies, we used the same acquisition criteria as Fricchione et al. (2016) and Spring et al. (2015), which utilized the same differential skin conductance response as the first PRE study conducted by Schiller et al. (2010). To be consistent with prior PRE studies, we applied the extinction criteria from Steinfurth et al. (2014), and confirmed this criteria with the authors (E. Phelps, personal communication, December 11, 2017). We also conducted exploratory analyses using extinction criteria that required maintenance of fear from the end of acquisition to the beginning of extinction, a factor that has not typically been considered in prior studies in this area, but may be important for detecting PRE effects.

## 2. Methods

### 2.1. Participants

Participants were healthy adults ($n$ = 49, recruited from the community and from the undergraduate population) and anxious adults ($n$ = 43, recruited from the community and an anxiety clinic serving both the community and the university). All procedures were approved by the Boston University Institutional Review Board.

**Inclusion criteria.** Healthy and anxious individuals were included if they met the following criteria: (1) between the ages of 18 and 65 and (2) evidenced adequate conditioned responses during acquisition. Adequate conditioned responses were defined as an average unconditioned skin conductance response (SCR averaged across all UCS presentations during acquisition trials) of at least 0.1 microS (untransformed) and an average differential SCR (CS+ minus CS-) across acquisition trials 2–10 of at least 0.1 microS (untransformed; CS + > CS-; Fricchione et al., 2016; Spring et al., 2015). Anxious participants were additionally required to have a Beck Anxiety Inventory (Beck & Steer, 1990) score above 15 (mild to moderate), or a score on the Fear Questionnaire (Marks & Mathews, 1979) above 37 (mild to moderate).

**Exclusion criteria.** Healthy and anxious individuals were excluded if they met any of the following criteria: (1) currently taking anticholinergic medications, clonidine, or benzodiazepines; (2) currently not on a stable dose of psychotropic medication or taking psychotropic medications prn; (3) current medical conditions that contraindicate fear conditioning procedures (e.g., severe heart disease or seizure disorder); (4) pregnancy. Anxious participants were additionally excluded if they: (1) met DSM-5 criteria for any past or present bipolar or psychotic disorder, or substance-related disorder in the last three months (other than caffeine or nicotine use disorder); (2) endorsed current suicidality, homicidality, or self-destructive acts or urges; or (3) were engaged in exposure therapy the week prior to or during study procedures.

### 2.2. Procedures

#### 2.2.1. Screening

All participants completed a brief screening interview; eligible individuals then provided informed consent. Anxious participants completed a diagnostic evaluation with the Anxiety Disorders Interview Schedule for DSM-5 (ADIS-5; Brown & Barlow, 2014) conducted by M.A. level clinicians to evaluate the presence of anxiety and traumatic stress disorders as well as psychiatric inclusion/exclusion criteria. Healthy and anxious individuals who met psychiatric inclusion/exclusion criteria were invited to complete conditioned fear acquisition to determine whether they displayed adequate conditioned responses. All participants were asked to refrain from caffeine and nicotine use 2 h prior to their study visits.

#### 2.2.2. Study design

***Healthy participants.*** On day 1, healthy participants underwent a fear acquisition procedure that involved the use of either a 500-msec. or 1000-msec. shock with or without an additional scream noise as the UCS. Fear acquisition was followed by either post-retrieval extinction (PRE) or extinction (E) on day 2 and a test of reinstatement on day 3. Examination of the UCS design features was part of a secondary study (Kredlow, Orr, & Otto, 2018b). Although the UCS design features for acquisition resulted in different rates of meeting adequate conditioned