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Review

A review of boundary conditions and variables involved in the prevention of return of fear after post-retrieval extinction

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ABSTRACT

Experimental evidence suggests that the return of fear may be prevented by post-retrieval extinction (PRE), a procedure consisting of extinction training after the presentation of a retrieval cue. However, attempts to replicate these findings have yielded mixed results, with some studies showing diminished fear responses after PRE, whereas others show no effect on the return of fear following this procedure. The discrepancies across studies have been interpreted as evidence that there might be conditions under which PRE is not effective (boundary conditions), but these variables have yet to be fully described. We aimed to provide an overview of PRE in humans. We briefly present the theory and research that originated post-retrieval procedures with a focus on the experimental setup used in human studies. We continue with a compilation of possible experimental boundary conditions along with some questions for future research.

1. Introduction

The pioneering works of Ivan Pavlov (1849–1936) have described an important learning process commonly known as *Pavlovian (or classical) conditioning*. During Pavlovian conditioning, an initially neutral stimulus (*conditioned stimulus*, CS) acquires the function of eliciting responses in the organism (*conditioned responses*, CRs) after being associated with another stimulus that already has eliciting function (*unconditioned stimulus*, US) (Pavlov, 1927). When the US is noxious or potentially harmful, the conditioned responses are characterized by a series of reactions implicated in the detection and response to threat (LeDoux, 2014), such as freezing (Bouton and Bolles, 1980) or physiological arousal of the autonomic nervous systems (Graeff, 2007). In this case, conditioned responses are termed *fear conditioned responses* and the learning process, *fear conditioning* (LeDoux, 2014).

The study of fear conditioning in the laboratory has been widely accepted as a model for understanding and, in some cases, guiding behavioral treatments for psychiatric disorders (LeDoux, 2014). For example, studies on the *extinction* of fear conditioning are thought to contribute for the improvement of treatments for psychiatric disorders characterized by significant fear and anxiety, such as Post-Traumatic Stress Disorder, Obsessive-Compulsive Disorder, and phobias (Foa and McLean, 2016; Kaczkurkin and Foa, 2015). During *extinction*,[1] the CS is repeatedly presented in the absence of the US, which typically results in reduction of conditioned fear responses (Lattal and Lattal, 2012). This experimental setup is thought to be an analog of exposure techniques utilized in clinical settings. Exposure techniques consist of exposing patients to feared situations, objects and images in the absence of aversive or threatening outcomes with the goal of reducing fear reactions to those stimuli (Foa and McLean, 2016; Vervliet et al., 2013).

One of the many challenges in this area is how to maintain fear reduction in the long term (Foa, 2011; Vervliet et al., 2013). Though exposure therapy has received empirical evidence of its efficacy in treating anxiety disorders or patients with a history of traumatic events, it is not uncommon for fear symptoms to return after successful completion of treatment (Foa, 2011; Vervliet et al., 2013). In the laboratory, the return of conditioned responses after extinction (referred to as *return of fear* by Lonsdorf et al., 2017) has been described as occurring, both in rats and in humans, as a function of (1) the passage of time (*spontaneous recovery*, Maren and Chang, 2006; Myers et al., 2006; Norrholm et al., 2008; Pavlov, 1927; Robbins, 1990; Schiller et al., 2008); (2) the presentation of the CS in a different context than the setting in which extinction took place (*renewal*, Alvarez et al., 2007; Bouton and Bolles, 1979a, 1979b; LaBar and Phelps, 2005; Milad et al.,

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[1] In the literature, the term “extinction” has been used to refer either to a procedure (the presentation of the CS without the US after conditioning) or a process (the progressive reduction of the magnitude of the CR due to this procedure) (Catania, 1999; Hermans et al., 2006; Lattal and Lattal, 2012). Here, we chose to use the term as a synonym for the procedure.

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2005; Neumann and Longbottom, 2008; Schiller et al., 2008; Thomas et al., 2003; Westbrook et al., 2002); and (3) the re-exposure to the US alone before testing (*reinstatement*, Bouton and Bolles, 1979b; Milad et al., 2005; Rescorla and Heth, 1975; Schiller et al., 2008; Westbrook et al., 2002).[2]

Recently, it has been shown that the return of fear may be prevented in spontaneous recovery, renewal and reinstatement tests when extinction is conducted shortly after the presentation of a stimulus associated with the initial learning situation (a *retrieval cue*, Monfils et al., 2009; Schiller et al., 2010). Typically, an isolated presentation of the CS before the extinction procedure has been used as a retrieval cue, and the procedure is called *post-retrieval extinction* (Kredlow et al., 2016; Sara, 2000).

Given the potential for developing a behavioral procedure that prevents the return of fear, some laboratories have attempted to replicate these findings with different species. In the case of studies with humans, though some studies were able to demonstrate diminished fear responses after PRE (Agren et al., 2012a; Asthana et al., 2015; Bjorkstrand et al., 2015; Johnson and Casey, 2015; Liu et al., 2014; Oyarzún et al., 2012; Schiller et al., 2010, 2013; Thompson and Lipp, 2017), there are reports of failure in producing these effects (Fricchione et al., 2016; Golkar et al., 2012; Kindt and Soeter, 2013; Klucken et al., 2016; Kredlow et al., 2018; Meir Drexler et al., 2014; Soeter and Kindt, 2011).

The contrasting results obtained across different studies have been discussed as evidence that there might be conditions under which PRE is not effective (Auber et al., 2013). Some of these *boundary conditions*, as well as their possible underlying mechanisms, have been addressed both experimentally and theoretically (Agren, 2014; Beckers and Kindt, 2017; Lee et al., 2017; Nader and Hardt, 2009), but work is still needed to fully understand the variables involved in the long-lasting reduction of fear.

In this paper, we aimed at providing an overview of PRE in humans, focusing our analyses on experiments in which conditioned responses were established experimentally in the laboratory and later exposed to different extinction procedures. We compiled variables that have been experimentally tested as boundary conditions and suggest some questions for future research.

2. Origins of post-retrieval extinction procedures

Post-retrieval extinction procedures originate in experiments on the brain mechanisms of memory (Duncan, 1949; Gordon, 1977; Misanin et al., 1968). In these studies, subjects were exposed to different learning tasks (for example, a classical conditioning procedure) followed by the administration of procedures known to disrupt (amnesic treatments) or enhance performance, such as strong electroconvulsive shocks, hypoxia, hypothermia, inhibitors of protein synthesis, strychnine, and other drugs (Sara, 2000).

Many experiments utilizing amnesic or enhancing treatments have found a time interval during which these procedures are effective in changing behavior. Specifically, amnesic (or enhancing) treatments were shown to be effective when administered shortly after initial learning; when given after a delay (approximately 6 h after learning), no effects were seen on behavior (Duncan, 1949; McGaugh, 1970, 1966). These results led to the memory consolidation hypothesis, which states that there is a time-dependent stabilization of changes in synaptic efficacy following a learning situation and which has received considerable attention in the literature (Nader and Hardt, 2009).

Of importance to the present discussion is a body of evidence showing that amnesic treatments can disrupt behavior even after a long time has elapsed since initial learning, if the treatment is applied shortly after exposing subjects to cues associated with the initial learning experience (*retrieval cues*). Stimuli utilized as retrieval cues include a single presentation of a CS (in the case of fear-conditioning experiments), exposure to the start box and the click of the opening of its door (in studies where subjects had to learn how to cross a complex maze), or other stimuli present at the occasion of learning (for a description of retrieval cues used in different learning paradigms, see Sara, 2000). For example, Misanin et al. (1968) fear-conditioned rats by pairing an auditory stimulus (a loud white noise, CS) with an electrical shock (US), which was followed by strong electroconvulsive shocks at different times following conditioning. Consistent with the consolidation hypothesis, CRs were no longer elicited by the CS when the amnesic treatment was applied immediately after conditioning. Electroconvulsive shocks also diminished CRs when applied 24 h after conditioning if this treatment was immediately preceded by a single presentation of the CS; no effects on the CR were seen when the electroconvulsive shocks were applied 24 h after conditioning, but this procedure was not preceded by the single CS.

The findings of Misanin et al. (1968) were replicated by other studies utilizing several amnesic treatments (Dębiec and Ledoux, 2004; Nader et al., 2000). These data have been interpreted as evidence that putting subjects into contact with retrieval cues can destabilize the memory, requiring a reconsolidation process to be restabilized (Agren, 2014; Beckers and Kindt, 2017; Kredlow et al., 2016; Lee et al., 2017; Nader et al., 2000). For the present discussion, it is noteworthy that some studies demonstrated that post-retrieval amnesic treatments can reduce conditioned responses in a long-lasting way; for example, Dębiec and Ledoux (2004) observed diminished conditioned fear responses one month after this treatment. There is also evidence to suggest that the longer the interval between the retrieval cue and the treatment is, the less behavior will be affected, with intervals longer than 6 h rendering the amnesic treatment completely ineffective (Nader et al., 2000; Sara, 2000). Therefore, experimental data suggest that behavioral responses are more likely to be changed in the 6 h following the presentation of retrieval cues.

The possibility of inhibiting conditioned fear responses in a long-lasting way can have profound clinical implications for the improvement of treatments for emotional disorders, and this potential has been increasingly recognized in the literature (Lee et al., 2017). However, with the exception of a few pharmacological treatments (such as administering propranolol), most interventions utilized after retrieval cues to diminish conditioned responses in animals are not safe for use in humans due to their high toxicity or serious side effects (Beckers and Kindt, 2017). Because of these limitations, some researchers have started to investigate whether behavioral treatments could also result in a long-lasting inhibition of fear responses when applied immediately after the presentation of a retrieval cue.

The first study to demonstrate the effects of behavioral treatments applied immediately after the presentation of a retrieval cue was conducted by Monfils et al. (2009). They exposed rats to parings of an auditory stimulus (a tone, CS) with an electrical shock (US). Twenty-four hours later, they exposed the rats to a retrieval cue consisting of a single presentation of the CS without the US. After this retrieval cue, instead of using pharmacological agents or other amnesic treatments, they conducted an extinction session consisting of several presentations of the CS without the US. The length of the interval between the presentation of the first CS (retrieval cue) and extinction training varied across five groups: 10 min (Group 1), 1 h (Group 2), 6 h (Group 3), 24 h (Group 4) and no interval, i.e., the retrieval cue was immediately followed by extinction training in a session in which the CS was presented every 180 s on average (Group 5). Except for Group 5, rats were removed from the experimental chamber after the retrieval cue and returned to their cages, where they remained during the established

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[2] Like the term extinction, spontaneous recovery, renewal and reinstatement are terms that can either refer to procedures (for example, the presentation of the CS in a context different from where extinction took place, as in renewal) or processes (elicitation of CR after this procedures). These terms will also be used as synonyms for the procedures.

Table 1
Experimental manipulation and timeline in post-retrieval extinction experiments in humans.

Study info	Design					
Reference	Type of comparison	CSs	Experimental manipulation and timing	Retrieval cue	Test type	Diminished CR in test?
Schiller et al. (2010, Exp.1)	Between	CS+, CS−	Cond → 24 h → (Ret cue → 10 min → Ext) OR (Ret cue → 6 h → Ext) OR (Ext) → 24 h→ Test	1 × CS+ (no US) for 4 s	Spont rec, reinst	Y
Schiller et al. (2010, Exp.2)	Within	CSa+, CSb+, CS−	Cond → 24 h → Ret cue → 10 min → Ext → 24 h → Test	1 × CSa+ (no US), 1 × CS− (4 s each)	Reinst	Y
Soeter and Kindt (2011, exp. IIa and IIb)	Within	CS1+, CS2+, CS−	Cond→ 24 h → Ret cue →10 min → Ext → 24 h → Test	1 × CS1+ (no US), 1 × CS2+ (no US) and 1 × CS− (8 s each)	Spont rec, reinst, recond, gen test	N
Agren et al. (2012)	Between	CS+, CS−	Cond → 24 h→ (Ret cue →10 min → Ext) OR (Ret cue → 6 h → Ext) → 24 h → Test → 48 h → Day 4: Re-test	1 × CS+ (no US) for 120 s	Renewal, reinst	Y
Agren, Furmak et al. (2012)	Between	CS+, CS−	Cond → 24 h → (Ret cue → 10 min → Ext) OR (Ret cue → 6 h → Ext) → 24 h → Test	1 × CS+ (no US) for 120 s	Reinst, recond	Y
Oyarzún et al. (2012)	Within	CSa+, CSb+, NS	Cond → 24 h → Ret cue → 10 min → Ext → 24 h → Test	1 × CSa+ (no US), 1 × CS (no info on duration)	Reinst	Y
Golkar et al. (2012)	Within	CS + r, CS + nr, CS−	Cond → 24 h → Ret cue → 10 min → Ext → 24 h → Test	1 × CSr+ (no US) for 4 s	Reinst	N
Golkar et al. (2012)	Within	CS + r, CS + n, CS−	Cond → 24 h → Ret cue → 10 min → Ext → 24 h → Test	1 × CSr+ (no US) for 4 s	Reinst	N
Kindt and Soeter (2013)	Between	CS1+, CS2−	Cond → 24 h → (Ret cue →10 min → Ext) OR (Ext) → 24 h → Test	1 × CS1, 1 × CS− (8 s each)	Spont rec, reinst, recond	N
Schiller et al. (2013)	Within	CSa+, CSb+, CS−	Cond → 24 h → Ret cue → 10 min → Ext → 24 h → Test	2 × CSa+ (4 s each)	Reinst	Y
Warren et al. (2014)	Between and Within	CSa+, CSb+, CS−	Cond → 24 h → Ret cue → 10 min → Ext → 24 h → Test	1 × CSa+, 1x CS (6 s each)	Spont rec, reinst	N
Steinfurth et al. (2014)	Between	CS+, CS−	Cond → (24 h) OR (7 days) → (Ret cue → 10 min → Ext) OR (Ext) → 24 h → Test	1 × CS+ for 4 s	Reinst	Y
Drexler et al. (2014)	Between	CS1+, CS2−, CS3+, CS4−, CS5−	Cond → 24 h → (Ret cue → Ext in different context) OR (Ext in different context) → 24 h → Test in conditioning context	1 × CS1+ for 30 s without context	Spont rec, renewal	N
Liu et al. (2014, Exp.1)	Between	CS+, CS−	Cond → 24 h → (Ret cue → 10 min → Ext) OR (Ret cue → 24 h → Ext) OR (Ext) → 24 h → Test	1 × weak US (half of the intensity used in cond) for 0.2 s	Spont rec, reinst	Y
Liu et al. (2014, Exp.2)	Between	CS1+, CS2+, CS−	Cond → 24 h → (CS− Ret cue → Ext) OR (US− Ret cue→ Ext) → 24 h → Test	(1 × weak US (half of the intensity used in cond) for 0.2 s) OR (1 × CS1+ for 4 s)	Spont rec, reinst	Y
Liu et al. (2014, Exp.3)	Between	CS1+, CS2+, CS−	Cond → 24 h → (US− Ret cue →10 min→ CS1+ Ext) OR (CS1 and CS2 Ret cue → 10 min → Ext CS1 +) → 24 h → Test	(1 × weak US (half of the intensity used in cond) for 200 ms) OR (1 × CS1+, 1 × CS2+ (for 4 s each))	Spont rec, reinst	Y
Liu et al. (2014, Exp.4)	Between	CS1+, CS2+, CS−	Ext 6–7 months after test (participants from experiment 3)	(1 × weak US (half of the intensity used in cond) for 0.2 s) OR (1 × CS1+, 1 × CS2+ (for 4 s each))	spont rec, reinst	Y
Liu et al. (2014, Exp. 5)	Within	CS1+, CS2+, CS−	Cond → 2 weeks → US Ret cue →10 min → CS1+ Ext → 24 h → Test	1 × weak US (half of the intensity used in cond) for 0.2 s	Spont rec, reinst	Y
Liu et al. (2014, Exp.6)	Within	CS1+, CS2+, CS−	Cond (CS1+ with US1, CS2+ with US2, CS−) → 24 h → (US1 Ret cue → 10 min → Ext) OR (US2 Ret cue →10 min > Ext) → 24 h → Test	1 × weak US1 (half of the intensity used in cond) for 0.2 s	Spont rec, reinst	Y
Johnson and Casey (2015)	Between	CS+, CS−	Cond in context A → 24 h → (Ret cue → 10 min Ext in context B) OR (Ext in context B) → 24 h → (Test in context B)	1 × CS+ (in context B) for 7 s	Reinst	Y
Asthana et al. (2015)	Between	CS+, CS−	Cond → 24 h → (Ret cue → 10 min → Ext) OR (Ext) → 24 h → Test	1 × CS+ for 4 s	Spont rec	Y
Bjorkstrand, Agren, Frik et al. (2016)	Between	CS+, CS−	Re-cond (participants from Agren et al., 2012)	N/A	Recond	Y
Fricchione et al. (2016)	Within	CS + R, CS + NR, CS−	Cond in context A → 24 h → Ret cue → Ext in context B → 24 h → Test in context A → 1 month → Re-test	1 × CS + R for 12 s	Renewal, reinst, spont rec, recond	N
Klucken et al. (2016)	Within	CS + rem, CS + nonrem, CS−	Cond → 24 h → Ret cue → 10 min → Ext → 24 h → Test → 6 months → Day 4: Test	1 × CSr+, 1 × CS− (8 s each)	Reinst	N
Thompson and Lipp (2017)	Between and within	CSa+, CSa−, CSb+, CSb-	Cond → 24 h → (Ret cue → 10 min → Ext) OR (Ext) → 24 h → Test	1 × weak US (half of the intensity used in cond) for 0.2	Spont rec, reinst	Y
Golkar et al. (2017)	Within	CSa+, CSb+, CS−	Cond → 24 h → Ret cue → 10 min → Vic Ext → 24 h → Test	1x CSa+ for 8 s	Reinst	Y

(*continued on next page*)

Table 1 (*continued*)

Study info Reference	Design Type of comparison	CSs	Experimental manipulation and timing	Retrieval cue	Test type	Diminished CR in test?
Agren et al. (2017)	Between	CS+, CS−	Cond → 24 h → (Ret cue → 10 min – in vivo Ext) OR (Ret cue → 6 h – in vivo Ext) OR (Ret cue → 10 min – imaginary Ext) OR (Ret cue → 6 h – imaginary Ext) → 24 h → Test	1 × CS+ for 120 s	Reinst	Y
Kredlow et al. (2018)	Between	CS+, CS−	Cond → 24 h → [(Ret cue → 10 min → Ext) OR (Ext) in **healthy participants**] OR [(Ret cue → 10 min → Ext) OR (Ext) OR (Cond → 24 h → Cond → Ret cue → 10 min → Ext) **in anxious subjects**] → 24 h Test	1 × CS+ for 8 s	Reinst	N

Cond: conditioning; Ext: extinction; Ret cue: retrieval cue; Vic Ext: vicarious extinction; spont rec: spontaneous recovery test; reinst: reinstatement test; gen test: generalization test; recon: reconditioning; Y: yes; N: no.

interval, after which they underwent the extinction training in the experimental chamber. Subsequently, two tests were conducted, 24 h and one month after extinction, in which the CS was presented alone (without the US) and CS-induced freezing (CR) was measured. CRs were diminished in all groups in the first test (24 h after extinction training). However, one month after extinction, only subjects from Groups 1 and 2, whose interval between the retrieval cue and extinction training was 10 min and 1 h, respectively, showed diminished CR; the remaining groups showed a significant return of CR, i.e., spontaneous recovery. Similar results were obtained by conducting the test in a different context than the setting in which extinction took place (renewal test) or presenting the US in isolation before the test (reinstatement test) (Monfils et al., 2009).

3. Post-retrieval extinction in humans

PRE procedures derived from Monfils et al. (2009) were first adapted for humans by (Schiller et al., 2010), who used colored squares displayed on a computer screen as CSs, an electrical shock as US, and skin conductance response as the measure of CRs and URs. Participants were exposed to three experimental phases separated by 24 h: conditioning, extinction and testing. In the first phase, one of two squares was paired with the US in 38% of the trials (CS+), whereas the other square was never paired with the US (CS−). During extinction, participants were divided into three groups (10 min, 6 h, and no reminder groups) and were exposed to 11 CS+ and 11 CS− without the US. Two groups (10 min and 6 h groups) were exposed to an isolated presentation of the CS+ (retrieval cue), followed by an interval of 10 min during which participants watched a TV show episode previously selected by the researchers. After this interval, the 10-min group underwent extinction training (i.e., were exposed to the remaining CSs). The 6-h group received the same treatment as the 10-min group, but extinction was conducted 6 h after the retrieval cue. The remaining groups (no reminder groups) began the session by watching the TV program for 10 min. For half of these subjects, extinction followed immediately after this 10-min period; for the other half, extinction was conducted 6 h after watching the TV show. During the test, all the participants were exposed to 11 presentations of each CS. The results showed that only subjects whose interval between the retrieval cue and extinction was 10 min did not show recovery of conditioned responses. The results were the same after one year, when 19 of the 65 original participants underwent a reinstatement test consisting of four unsignaled presentations of the US, followed by extinction.

Schiller et al. (2010) conducted a second experiment to assess the specificity of CR extinction with the procedure tested in their first experiment, i.e., to test whether interfering with the eliciting function of one CS would affect the eliciting function of another CS associated with the same US. Three CSs (colored squares) were used in a within-subject design. During the conditioning phase, two of three squares (CSa+ and CSb+) were paired with the US (in 38% of presentations), and the third was never paired (CS−). On the following day (extinction phase), participants were exposed to 11 presentations of each of the three CSs without the US. At the start of extinction session, one CSa+ and one CS− were presented (retrieval cues), followed by a 10-min interval, during which participants watched an episode of a TV program; after this interval, participants were exposed to 10 presentations of CSa+ and CS− and 11 presentations of CSb+. Testing occurred on a third day and involved the presentation of four USs (without CS), followed by a 10-min interval, during which participants watched the same television episode as on the previous day, and a new extinction procedure (11 presentations of each of the three CSs alone). Like their first experiment, conditioned responses in the test were only observed when the CSb+ was presented. This set of results suggests that even with humans, the effects of extinction can be enduring if the procedure is conducted after the presentation of a retrieval cue. These data also indicate that the timing of extinction relative to retrieval cues is

Table 2
Stimuli and dependent variables in studies on post-retrieval extinction in humans.

Study info	Stimuli	Measures						
Reference	CS Description/duration	CS is fear-relevant?	US (intensity/duration)	Reinforcement rate (number of pairings)	Number of acquisition trials	Number of extinction trials	Dependent variable (behavioral only)*	Diminished CR in test?
Schiller et al. (2010, Exp.1)	Colored squares/4 s	N	Electrical shocks (10–60 V/200 ms)	38% (6)	16	11	SCR	Y
Schiller et al. (2010, Exp.2)	Colored squares/4 s	N	Electrical shocks (10–60 V/200 ms)	38% (5)	13	11	SCR	Y
Soeter and Kindt (2011, exp. IIa and IIb)	Pictures of spider or gun (CS+), or picture of mug (CS−)/8 s	Y	Electrical shocks (1 mA minimum/2 ms)	80% (4)	5	10	FPS, SCR, Retrospective Expectancy Ratings, Distress ratings	N
Agren et al. (2012)	Photo of lamp lit either in red or blue presented in neutral environment/6 s	N	Electrical shocks (up to 5 mA/500 ms)	100% (16)	16	8	SCR	Y
Agren, Furmak et al. (2012)	Photo of lamp lit either in red or blue presented in neutral environment/6 s	N	Electrical shocks (up to 5 mA/500 ms)	100% (16)	16	8	SCR	Y
Oyarzún et al. (2012)	Colored squares/4 s	N	Loud shrill sounds (98 dB/1.7 or 2.4 s)	38% (6)	16	10	SCR	Y
Golkar et al. (2012, Exp.1)	Fearful male faces/6 s	Y	Electrical shocks (no info/100 ms)	50% (6)	12	12	FPS, SCR	N
Golkar et al. (2012, Exp.2)	Colored squares/6 s	N	Electrical shocks (no info/100 ms)	50% (6)	12	12	SCR	N
Kindt and Soeter (2013)	Pictures of spiders	Y	Electrical shocks (1 mA minimum/2 ms)	75% (6)	8	12	FPS, SCR, Online US-expectancy Ratings	N
Schiller et al. (2013)	Colored squares/6 s	N	Electrical shocks (20–60 V/200 ms)	38% (5)	13	11	SCR	Y
Warren et al. (2014)	Geometric shapes/6 s	N	Air-blast (140 PSI/250 ms)	100% (12)	12	24	FPS, Online US-expectancy Ratings	N
Steinfurth et al. (2014)	Colored squares/4 s	N	Electrical shocks (20–60 V/200 ms)	50% (8)	16	20	SCR	Y
Meir-Drexler et al. (2014)	Pictures of dog, spider, snake, and tiger presented in two zoo frames/8 s	Y	Electrical shocks (no info/100 ms)	75% (12)	16	8	SCR, Online US-expectancy Ratings	N
Liu et al. (2014, Exp.1)	Colored squares/4 s	N	Electrical shocks (5–50 V/200 ms)	38% (6)	16	10	SCR	Y
Liu et al. (2014, Exp.2)	Colored squares/4 s	N	Electrical shocks (5–50 V/200 ms)	38% (6)	16	10	SCR	Y
Liu et al. (2014, Exp.3)	Colored squares/4 s	N	Electrical shocks (5–50 V/200 ms)	38% (6)	16	10	SCR	Y
Liu et al. (2014, Exp.4)	Colored squares/4 s	N	Electrical shocks (5–50 V/200 ms)	N/A	N/A	10	SCR	Y
Liu et al. (2014, Exp. 5)	Colored squares/4 s	N	Electrical shocks (5–50 V/200 ms)	38% (6)	16	10	SCR	Y
Liu et al. (2014, Exp.6)	Colored squares/4 s	N	Electrical shocks (to the right inner wrist and right eyelid) (5–50 V/200 ms)	38% (6)	16	10	SCR	Y
Johnson and Casey (2015)	Picture of blue or yellow windows (CSs) showed on 2 different backgrounds (kitchen or child's room/7 s	N	hybrid of white noise and a 1000-Hz tone + pictures of potentially dangerous animals (fanged snake, spider, snarling dog, shark) (94–102 dB/1 s)	50% (8)	16	16	SCR	Y
Asthana et al. (2015)	Colored squares/4 s	N	Auditory stimulus (code 276 from IADS) (102 dB/2 s)	80% (12)	16	16	SCR	Y
Bjorkstrand, Agren, Frik et al. (2016)	Photo of lamp lit either in red or blue presented in neutral environment/6 s	N	Electrical shocks (up to 5 mA/500 ms)	N/A	N/A	N/A	SCR	Y
Fricchione et al. (2016)	High-definition video clips depicting one of three tarantulas in one of three contexts	Y	Electrical shocks (up to 4 mA/500 ms)	62.5% (5)	8	10	SCR	N

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Table 2 (*continued*)

Study info	Stimuli	Measures						
Reference	CS Description/duration	CS is fear-relevant?	US (intensity/duration)	Reinforcement rate (number of pairings)	Number of acquisition trials	Number of extinction trials	Dependent variable (behavioral only)*	Diminished CR in test?
	(kitchen, bedroom, and office)/12 s (of which, 4 s context only and 8 s CS+ in context)							
Klucken et al. (2016)	Colored squares/8 s	N	Electrical shocks (up to 5 mA/100 ms)	50% (8)	16	11	SCR	N
Thompson and Lipp (2017)	Picture of spider and snake (CSa+ and −); and picture of colored squares (CSb+ and −)/6 s	Y	Electrical shocks (no info/200 ms)	100% (8)	8	10	SCR, Valence rating to CSs	Y
Golkar et al. (2017)	Picure of gun (CS+) and mug (CS−)/8 s	Y	Electrical shocks (minimum 1 mA/2 ms)	No info	10	N/A	FPS	Y
Agren et al. (2017)	Blue or green lamp presented on neutral environment/6 s	N	Electrical shocks (up to 5 mA/100 ms)	100% (16)	16	8	SCR	Y
Kredlow et al. (2018)	Colored shapes (yellow circle or white square)/8 s	N	Electrical shock to the second and third fingers of participants' dominant hand (0.2 to 4 mA/50 pulses per s/500 ms or 1000 ms) and auditory stimulus (scream noise 1 s/95 dB)	60% (6 for weak conditioning group and 18 for strong conditioning group)	10	11	SCR	N

* Only behavioral measures are shown, but note that is some studies, there are neuroimaging or genetic data also. Y: yes; N: no; N/A: not applicable; SCR: skin conductance response; FPS: fear-potentiated startle.

important, with intervals shorter than 6 h allowing for the effect to occur.

Since the publication of Schiller et al. (2010), several laboratories have begun to investigate PRE in human participants. Table 1 shows the experimental manipulations and timeline of experiments in which the behavior of interest (fear responses) was created in the laboratory and diminished with PRE. These studies have at least three phases, usually separated by a 24-h interval (though this interval has been manipulated in some reports, as discussed in Section 4.2.1). In all studies, the participants underwent differential conditioning procedures in the first phase. In differential conditioning, one or more CSs are paired with the US (CS + s), and there is another CS that is never paired to the US (CS −) (Haaker et al., 2014). Table 2 shows the different stimuli used. As is typical in experiments on Pavlovian conditioning in humans, CSs were visual stimuli (pictures) presented on a computer screen. Mild electrical shocks were the US in all but four studies, which used aversive auditory stimuli, air-blast directed at the larynx, or a hybrid of white noise and pictures of potentially dangerous animals.

Regarding the experimental design, while some experimenters utilized a between-subject design, in which different groups of subjects are exposed to different experimental conditions, there are several studies reporting within-subject design or both within- and between-subject comparisons in the same experiment. In within-subject designs, two CSs are paired, while a third CS is never paired with the US (CS −). In this case, experimental manipulations are conducted with only one CS +, and both CS + s (manipulated and not manipulated) are compared in the test.

In all experiments, PRE procedures were conducted in the second phase (Table 1). Specifically, after a conditioning phase, participants were exposed to extinction, which consisted of several presentations of the CS in the absence of the US. This procedure was preceded by the presentation of a retrieval cue in some groups (or preceded by a retrieval cue for only one of the CS + s in within-subjects design). The interval between the retrieval cue and extinction was usually 10 min. In most studies, a single presentation of the CS alone was used as a retrieval cue. However, very recently, some experimenters have also used a single presentation of the US alone as a retrieval cue (Table 1). As discussed below, these differences in the type, duration and structure of retrieval cues have been shown to influence test results.

One important feature of most PRE studies in humans is that participants are included in the analysis only if they show evidence of conditioning and extinction. The rationale for this procedure is that it is only possible to manipulate a conditioned fear if it exists. Also, it is not possible to assess the return of fear if it has not been diminished at some point (Oyarzún et al., 2012; Schiller et al., 2013, 2010). Furthermore, some degree of extinction learning might need to occur for PRE to result in a long-lasting inhibition of fear. This idea comes from studies that show that pharmacological adjuncts of extinction (such as the administration of D-cyclosterine) are ineffective in preventing return of fear unless there is an optimal degree of within-session safety learning (Hofmann, 2014). Only a few studies do not report excluding subjects because of lack of conditioning or extinction, and some have conducted analyses with both the entire sample and only with subjects fulfilling these criteria (Table 3). Conditioning and extinction are assessed by comparing responses to the CS + with responses to the CS − during the first experimental phase. Greater responses to the CS + in comparison to responses to CS −, as well as an increase in responses to the CS + from the beginning to the end of the session, are interpreted as evidence of fear conditioning. Responses are said to have been extinguished when differences between CS + s and CS − are no longer significant or when results are in the opposite direction of the conditioning (i.e., greater responses to the CS − in comparison with responses to the CS +).

Regarding the test phase, most studies assess fear return by means of a reinstatement procedure in which the US is presented alone several times, followed by presentations of the CS alone. However, it is also common for experimenters to utilize spontaneous recovery (presentations of the CS after some time has passed since extinction) or renewal (presentations of the CS in a different context than the setting where extinction took place) tests. In reinstatement and spontaneous recovery and renewal tests, fear return is assessed by comparing responses to the CSs (CS+s and CS−) at the end of extinction (last trial or a block of trials at the end of the session) with responses to the CSs at the beginning of the test (first trial of first block of trials) or by comparing responses to the different CSs in the test (CS+ vs. CS−) (Fricchione et al., 2016; Golkar et al., 2017, 2012; Thompson and Lipp, 2017). In some cases, only responses to the CS+ at the end of extinction are compared with responses to the CS+ at the beginning of the test (Johnson and Casey, 2015; Meir Drexler et al., 2014; Warren et al., 2014). In other cases, a differential score (CS+ - CS−) at the end of extinction is compared with differential scores at the beginning of the test (Agren et al., 2017, 2012a, 2012b; Liu et al., 2014; Schiller et al., 2010; Soeter and Kindt, 2011; Steinfurth et al., 2014).

There are also studies reporting reconditioning (usually called *reacquisition*) and generalization tests. In reconditioning, the CS is paired again with the US and experimenters assess whether CS+/CS− differentiation occurs again (Agren et al., 2012b). In generalization tests, subjects are presented with visual stimuli that are matched in stimulus category, valence, and arousal with the CSs utilized in the first two phases (conditioning and PRE/extinction) to assess whether reduction of fear conditioned responses generalizes to these stimuli. For example, Soeter and Kindt (2011) conditioned subjects using pictures of a spider (CS1+), a gun (CS2+), and a mug (CS−). In the test, subjects were presented different gun, spider, and mug pictures, and conditioned fear responses to these stimuli were assessed.

4. Possible boundary conditions to post-retrieval extinction in humans

4.1. Subjects’ pre-experimental characteristics

A possible source of variation between studies might be related to the pre-experimental characteristics of participants, such as genetic, demographic, or psychiatric factors. For example, Agren et al. (2012b) explored the effects of genetic characteristics on PRE. Specifically, they assessed whether serotonin- and dopamine-related polymorphisms could affect the results of PRE. They compared two groups, one with a 10-min and another with a 6-h interval between the retrieval cue and extinction. They found that reacquisition one day after extinction was stronger in individuals whose interval between the retrieval cue and extinction was 6 h. In addition, reacquisition in the 6-h group was predominantly present in val/val homozygotes of the functional val158met polymorphism of the catechol O-methyltransferase (COMT) enzyme and in short-allele carriers of the serotonin-transporter length 5-HTTLPR polymorphism. Carriers of the met allele and long-allele homozygotes did not display reacquisition regardless of the timing of extinction. However, a recent study replicating these procedures in a different population did not find the same associations between COMT Val158Met-polymorphism and return of fear (Klucken et al., 2016). By contrast, another study has shown that persistence in reduction of conditioned responses after PRE was present only in the Met-allele carriers of the BDNF val66met polymorphism (Asthana et al., 2015).

Research on the influence of genetic characteristics on PRE shows great potential. Twin studies suggest that fear conditionability is moderately inheritable. In addition, there is evidence from experimental reports that both fear conditioning and extinction are influenced by individual differences in serotonin- and dopamine-related polymorphisms (Garpenstrand et al., 2001; Lonsdorf et al., 2009). There are also studies showing that response systems are differentially affected by genetic characteristics: whereas individual differences in the conditioning and extinction of fear-potentiated startle were associated with polymorphisms in 5-HTTLPR and COMT Val158Met genes, the amount of conditioning and extinction of skin conductance was independent of genotype (Lonsdorf et al., 2009). As pointed out by Klucken et al. (2016), it remains to be seen whether this dissociation between response systems and genotype also applies to the effects PRE.

There has been some exploration of the influence of other pre-experimental characteristics on the effects of PRE such as age and gender. Johnson and Casey (2015) analyzed the differences between adolescents and adults regarding the effects of PRE. Each age group was divided in two subgroups: a group exposed to a retrieval cue 10 min before extinction training and a control group exposed to standard extinction. Adolescents showed diminished extinction learning, but both adolescents and adults showed diminished recovery of fear when a retrieval cue was presented prior to extinction. A recent meta-analysis of PRE found no relation between the age of participants and the direction of the results (Kredlow et al., 2016). Nevertheless, it would be interesting to explore whether the results are the same when older persons are assessed. Additionally, since both conditioning and extinction involving aversive stimuli may be affected by hormones and women's menstrual cycles (Merz et al., 2012; Milad et al., 2010, 2009), some authors have performed exploratory analyses within their samples to determine whether sex could alter the results of PRE, but the results were negative (Liu et al., 2014; Meir Drexler et al., 2014). However, in Liu et al. (2014), the authors did not mention whether the menstrual cycle or contraceptive use was controlled; in Meir Drexler et al. (2014), all women participants used contraceptives but focusing the analysis on one sex might have rendered the sample too small for differences to be detected (19 women divided into two groups). Therefore, further examination of this issue with proper sample size and procedures to control for menstrual cycle or contraceptive use is warranted.

An important boundary condition might be related to the presence of psychiatric symptomatology. A meta-analysis of studies of fear conditioning in human subjects found evidence that individuals with anxiety disorders present increased classical conditioning and take longer to stop responding to conditional stimuli during extinction procedures than do healthy subjects (Lissek et al., 2005). A positive correlation has also been found between chronic anxiety levels, as measured by self-report (Kindt and Soeter, 2013; Spielberger et al., 1970), and an increase in skin conductance responses when CS− is presented after uncontrollable and unpredictable shocks (Kindt et al., 2009; Soeter and Kindt, 2010).

The demonstration of the effects of PRE in clinical populations is especially important if this procedure is to be used in applied situations. However, to the best of our knowledge, there are only a few studies to date exploring this issue. For example, Kredlow et al. (2018) compared the effects of PRE and standard extinction in a mixed sample of healthy and anxious individuals using SCR as a dependent measure. These authors failed to show attenuation of return of fear both in non-anxious and anxious subjects, and no measure of anxiety served as a moderator of the effect of PRE. In another study, subjects reporting a predisposition to being afraid of spiders showed no reduction of return of fear after PRE when the CSs were fear-relevant CSs (Fricchione et al., 2016). Despite these failures to show attenuation of return of fears created in the laboratory, there is evidence that PRE is effective in attenuating pre-existing fear of spiders (Björkstrand et al., 2016). Therefore, the area would certainly benefit from other comparisons between healthy people and psychiatric patients or between two extremes of the same psychiatric disorder (e.g., high vs. low anxious individuals).

4.2. Learning conditions

4.2.1. Time since initial learning

As previously discussed, studies demonstrating long-lasting reduction of fear in humans usually use a three-day procedure in which PRE is conducted one day after conditioning. As such, it is important to ask whether the procedure can be as effective when learning took place after more than 1 day (i.e., when memories are older). In humans, this

Table 3
Participants' information in studies on post-retrieval extinction in humans.

	Participants	Inclusion criteria			
Reference	*n* (*n* per group)	Age (range or mean in years)	% females	Psychiatric/medical[*]	Conditioning/extinction
Schiller et al. (2010, Exp. 1)	65 (20–23 per group) 19 in the 1-year test (8–11 per group)	Range 18–48	63%	No info	Successful conditioning and extinction[a]
Schiller et al. (2010, Exp. 2)	18	Range 18–34	55%	No info	Successful conditioning and extinction[a,b]
Soeter and Kindt (2011, exp. IIa and IIb)	40	Range 18–32	72%	Absence of current or previous medical or psychiatric condition contraindicating participation; score < 26 on Anxiety Sensitivity Index (ASI, Peterson and Reiss, 1992)	No info
Agren et al. (2012)	22 (11 per group)	M = 24.0 (SD ± 0.48)	50%	No info	Successful conditioning[c]
Agren, Furmak et al. (2012)	66 (approx. 33 per group)	M = 24.6 (SD ± −4.0)	58%	No info	Successful conditioning[c]
Oyarzún et al. (2012)	17	M = 23.4 (± 5.11)	66%	No history of psychiatric or neurological disease	Successful conditioning and extinction[d]
Golkar et al. (2012, Exp. 1)	19	M = 27.2 (± -9.55)	53%	No info	Analysis with entire sample and with subjects showing successful conditioning and extinction[d]
Golkar et al. (2012, Exp. 2)	15	M = 26.26 (± -7.52)	58%	No info	Analysis with entire sample and with subjects showing successful conditioning and extinction[d]
Kindt and Soeter (2013)	40	Range 18–33	67%	Absence of current or previous medical condition contraindicating participation; ASI < 26	No info
Schiller et al. (2013)	19	Range 18–34	53%	No use of medication for psychiatric or neurological reasons	Measurable SCR on all 3d and successful conditioning and extinction[a,b]
Warren et al. (2014)	55 (10–20 per group)	M = 20.8 (± 1.7)	64%	Absence of current or past psychiatric illness (Structured Clinical Interview for DSM-IV Axis I Disorders, SCID-1, First, 1997) and no use of illicit drug or alcohol abuse or dependency	No info
Steinfurth et al. (2014)	80 (20 per group)	M = 23.21 (± 18–57)	57%	No info	Reliable SCR response during conditioning and successful conditioning and extinction[a]
Drexler et al. (2014)	39 (approx. 20 per group)	Range 19–30	49%	Absence of somatic/endocrine disease, history of psychiatric/neurological treatment or medication use	No info
Liu et al. (2014, Exp.1)	54 (16–19 per group)	Range 18–29	50%	No info	Successful conditioning and extinction[e]
Liu et al. (2014, Exp.2)	36 (18 per group)	Range 17–29	50%	No info	Successful conditioning and extinction[e]
Liu et al. (2014, Exp.3)	37 (18–19 per group)	Range 18–31	57%	No info	Successful conditioning and extinction
Liu et al. (2014, Exp.4)	24 (11–13 per group)	Range 19–29	58%	No info	Successful conditioning and extinction
Liu et al. (2014, Exp. 5)	15	Range 20–27	60%	No info	Successful conditioning and extinction
Liu et al. (2014, Exp.6)	19	Range 21–28	47%	No info	Successful conditioning and extinction
Johnson and Casey (2015)	74 (18–19 per group)	Range 12–17 and 18–32	50%	Absence of hearing impairment, color blindness, diagnosed animal phobias and neurological and psychiatric disorders	Reliable SCR response and successful conditioning[f]
Asthana et al. (2015)	91 (approx. 22 per group)	No info	46%	Absence of neurological or psychiatric illnesses; pregnancy; students with psychology as major	Successful conditioning[g]
Bjorkstrand, Agren, Frik et al. (2016)	20	No info	No info	No info	Successful conditioning
Fricchione et al. (2016)	21	Range 18–28	48%	Presence of Non-phobic fear of spiders (scores above the mean on the Spider Phobia Questionnaire, SPQ-15 (Olatunji et al., 2009) and absence of specific spider phobia criteria; absence of current psychiatric disorders (SCID-I), serious medical or neurological conditions, brain injury, and current or past substance abuse	Successful conditioning[h]
Klucken et al. (2016)	70	M = 23.93 (± −4.15)	55%	Absence of current or past mental illness, chronic diseases, or consumption of psychotropic drugs	Analysis with entire sample and with subjects showing reliable SCRs and successful conditioning[i]
Thompson and Lipp (2017)	56 (28 per group)	M = 23.54 (± −7.05) (experimental group); M = 25.25 (± −8.36) (control group)	55%	Absence of cardiovascular disease, seizure disorder, or pregnancy	No info

(*continued on next page*)

Table 3 (*continued*)

	Participants	Inclusion criteria			
Reference	*n* (*n* per group)	Age (range or mean in years)	% females	Psychiatric/medical[*]	Conditioning/extinction
Golkar et al. (2017)	18	Range 19–23	78%	Absence of medical conditions	Successful conditioning[j]
Agren et al. (2017)	86 (20–23 each group)	Range 19–39	67%	No info	Successful conditioning[c]
Kredlow et al. (2018)	92 (43–49 each group)			Absence of current medical disease contraindicative of fear conditioning, pregnancy, anticholinergic medications, clonidine, benzodiazepines, or psychotropic medications. Half of the sample was composed by healthy adults and the other half by anxious adults (Beck Anxiety Inventory, BAI score > 15 (BAI, (Beck and Steer, 1990) and Fear Questionnaire score > 37 (Marks and Mathews, 1979). Anxious subjects could not have present bipolar or psychotic disorder, substance-related disorder in the last three months (other than caffeine or nicotine use disorder) (ADIS-5, Brown and Barlow, 2014), endorsed current suicidality, homicidality, or self-destructive acts or urges; or be engaged in exposure therapy the week prior to or during study procedures.	Adequate conditioning and extinction[k]

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[*] Psychiatric and/or medical inclusion info is only described when the authors explicitly report having excluded participants base on this data.

[a] Criteria for conditioning and extinction were based on differential responses to the CS+ and CS− during the second half of the conditioning and extinction sessions (averaged), respectively. During conditioning, difference between skin conductance responses to the CS+ and the CS− had to be equal or larger than 0.1 μS. During extinction, this difference had to be smaller than 0.1 μS or in the opposite direction (i.e., CS− > CS+).

[b] Conditioning and extinction to CSa+ and CSb+ had to be equivalent (difference ≤ 0.1 S during conditioning and extinction).

[c] Criteria for conditioning were based on differential responses to the CS+ and CS− during conditioning. Authors calculated difference scores (CS+1 – CS-1, CS+2 - CS-2...CS+16-CS-16). The average delta scores were tested against zero using a one-tailed t-test with statistical cutoff offset at $p < .10$ as the within subject conditioning criterion.

[d] Conditioning and extinction criteria based on differential responses to the CS+s and CS−. Skin conductance responses to CS+s had to be greater than responses to the CS− during conditioning. During extinction, responses to CS+s could not be greater than responses to the CS−.

[e] Criteria for conditioning and extinction were based on differential responses to the CS+ and CS− during conditioning and extinction sessions. During conditioning, subjects had to present more than two delta scores higher than 0.05 μS. During extinction, participants had to present more than two delta scores lower than 0.1 μS.

[f] Responses to the CS+ had to be greater than responses to the CS− during acquisition.

[g] Responses to CS+ had to be greater than responses to the CS− during trials of conditioning. Also, responses to the CS+ during conditioning had to be greater than responses to the CS+ during habituation.

[h] Difference between average responses to both CS+s and average responses to the CS− during conditioning had to be at least 0.1 μS.

[i] Mean differential skin conductance responses (CS+ minus CS−) had to be at least > 02 μS.

[j] Larger differentiation on the last two trials of conditioning than during the first two trials of conditioning for each CS+ relative to the CS−.

[k] The criteria for adequate conditioning were: (1) average unconditioned skin conductance response of at least 0.1 μS (untransformed) and (2) average differential conditioned skin conductance response (CS+ minus CS−) across acquisition trials 2–10 of at least 0.1 μS (untransformed; CS+ > CS−). Criterion for extinction was differential SCR smaller than 0.1 μS (square-root transformed and standardized) in the last four trials of extinction.

has been tested by a study in which participants underwent a differential fear conditioning by pairing electrical shocks (US) with one of two colored squares (CS + s) (Steinfurth et al., 2014). Participants were divided into four groups, two of which underwent traditional extinction 1 or 7 days after conditioning (No Reactivation Day 1 and No Reactivation Day 7, respectively). The other two groups were exposed to the post-retrieval procedure, i.e., a single presentation of the CS+ without the US, followed by extinction, which was conducted 1 or 7 days after initial learning (Reactivation Day 1 and Reactivation Day 7, respectively). On a third day, all groups underwent a reinstatement test. Participants who underwent PRE showed no evidence of fear recovery as measured through SCR, regardless of the age of the memory. In contrast, reinstatement was found in the control groups submitted to traditional extinction 1 or 7 days after conditioning.

Results from Steinfurth et al. (2014) suggest that PRE might be effective in reducing the return of older fears. This is consistent with an experimental study showing the successful reduction of avoidance responses to pictures of spiders after PRE in subjects with a history of fear of spiders (Björkstrand et al., 2016). However, evidence from experimental studies on rodents suggests that other factors might contribute to the effects of PRE in > 1 d old conditioned responses. First, a series of rat studies failed to show reduction of fear with pharmacological blockage of protein synthesis after a retrieval cue when the number of CS-US pairings was increased during conditioning or when the interval between conditioning and post-retrieval pharmacological blockage was prolonged (eight weeks, (Suzuki et al., 2004). However, if the duration of the retrieval cue was increased, then the same procedure was effective in both circumstances. In line with these results, pharmacological blockage of protein synthesis after retrieval cues did not reduce strong conditioned fear in rats 2 or 7 days after conditioning (Wang et al., 2009). As in Suzuki et al. (2004), strong conditioned fear responses were created by increasing the number of CS-US pairing from 1 (weak protocol) to 10 (strong protocol). Importantly, Wang et al. (2009) found that the same pharmacological procedure, when conducted 30 or 60 days after strong conditioning, diminished fear responses (Wang et al., 2009). The implications of these results are that boundary conditions related to the age of a memory interacts with its strength: when the memory is too strong, early interventions does not seem to have an effect, but its resistance to change might be transient.

Another point that should be noted in Steinfurth et al. (2014) is that they did not include procedures to assess the explicit cognitive knowledge of the contingency (such as US-expectancy rating), which can only be acquired in human participants. Only autonomic responses (skin conductance responses) were acquired in order to resemble the methods used in rodent studies that inspired their research (e.g., Clem and Huganir, 2010). As discussed in Section 4.4 (Response Systems), the inclusion of more than one method of assessment of CR, and especially verbal ratings, can change conditioning, extinction, and return of fear. Therefore, it would be important to know whether the results would be the same if multiple indices of conditioning were used.

4.2.2. Reinforcement rate and number of CS-US pairings

The reinforcement rate during conditioning (i.e., the proportion of CS trials ending with the US) has been referred to as a variable that might change the probability of return of fear after PRE (Fricchione et al., 2016; Golkar et al., 2012; Kindt and Soeter, 2013; Oyarzún et al., 2012; Soeter and Kindt, 2011; Warren et al., 2014). This variable has been pointed as a possible explanation for discrepancies across studies because the first two experiments showing diminished return of fear after PRE utilized low reinforcement rates during conditioning (38% in Schiller et al., 2010, and Oyarzún et al., 2012), whereas studies reporting failure to produce these effects were conducted with higher reinforcement rates (75% in Kindt and Soeter, 2013, and 80% in Soeter and Kindt, 2011). In view of this difference, some authors speculated that higher reinforcement rates during conditioning might render the conditional responses more resistant to undergo reconsolidation through PRE, therefore making the return of fear more likely (Oyarzún et al., 2012). However, there are several problems with this hypothesis. First, return of fear after PRE has been shown in studies in which conditioning was conducted with high reinforcement rates (for example, Agren et al., 2012a; Thompson and Lipp, 2017, who utilized a reinforcement rate of 100%; or Asthana et al., 2015, who used 80%). Table 2 shows that there is no apparent relation between reinforcement rate or number of CS-US pairings and fear reduction after PRE.

As pointed out by Golkar et al. (2012), there is no direct evidence that high reinforcement rates actually produced stronger conditioning in experiments on PRE with humans because none of them included an independent measure of conditioning strength, such as resistance to extinction, which is the measure used in animal studies (Suzuki et al., 2004; Wang et al., 2009). In fact, using resistance to extinction as a measure of the strength of a conditioned response would probably weakens this proposal. In Schiller et al. (2010) and Oyarzún et al. (2012), a 38% reinforcement rate was used during conditioning, meaning that CS-US pairings were intermittent and happened in the minority of trials, and both studies found diminished conditioned responses in the test phase. There is experimental data showing that reinforcement rates such as the ones used by Schiller et al. (2010) and Oyarzún et al. (2012) produce conditioned responses that require more extinction trials to reduce. Therefore, these authors used protocols that supposedly produce stronger responses if one considers resistance to extinction a parameter of strength (Bouton, 2004; LaBar et al., 1995; Schiller et al., 2008). Another point regarding the use resistance to extinction as a parameter of conditioning strength is that several studies reporting no return of fear after PRE, only participants who showed evidence of reduction of CR at the end of the extinction phase were; therefore, only subjects who did not present resistance to extinction were included (Oyarzún et al., 2012; Schiller et al., 2013, 2010). Moreover, in animal studies, resistance to extinction is produced by increasing the number of CS-US pairings and not by manipulating the reinforcement rate. For example, Wang et al. (2009) showed that ten CS-US pairings needed more extinction trials for fear to decrease compared to a single CS-US pairing. In humans, the effect of the number of CS-US pairings during conditioning on the return of fear after PRE was manipulated by Kredlow et al. (2018). In this experiment, participants underwent differential conditioning with two CSs (CS+ and CS−), one of which was paired with the US in 60% of the trials (specifically, 6 out of 10 CS+ presentations were paired with the US). For one group of subjects, conditioning was conducted once, whereas other group underwent this conditioning protocol on three consecutive days. These authors failed to show differences between the two groups regarding the return of fear after PRE.

4.2.3. Nature of the CS

Given the possibility of using PRE as a clinical strategy for augmenting behavioral treatments for anxiety disorders, some authors have tried replicating Schiller et al.'s findings utilizing stimuli that resemble clinical situations. As previously described, Schiller et al. (2010) utilized colored squares as CSs, which are thought to be fear-irrelevant and less likely to be associated with anxiety in real life (Golkar et al., 2017, 2012; Kindt et al., 2009; Kindt and Soeter, 2013; Soeter and Kindt, 2011). Some authors utilized fear-relevant stimuli as CSs, such as pictures or high definition video-clips of potentially dangerous animals (tigers, dogs, snakes, spiders) (Fricchione et al., 2016; Golkar et al., 2012; Kindt and Soeter, 2013; Meir Drexler et al., 2014; Soeter and Kindt, 2011), or fearful male faces (Golkar et al., 2012). In these studies, PRE did not prevent return of fear, which led to the hypothesis that the nature of the CS would explain the divergence of results reported (and that PRE was able to prevent return of fear only when CSs were fear-irrelevant) (Fricchione et al., 2016; Kindt and Soeter, 2013; Soeter and Kindt, 2011).

It has been argued that failures to replicate the findings from Schiller et al. (2010) with fear-relevant stimuli might be related to stronger conditioning produced by these stimuli. Evidence supporting this hypothesis comes from experimental studies demonstrating that pairing aversive USs with fear-relevant CSs result in conditioning that is more resistant to extinction (Mineka and Öhman, 2002; Öhman et al., 1976; Öhman and Mineka, 2001). However, as pointed out by Golkar et al. (2012), many PRE studies in humans report including only participants who showed evidence of extinction (Golkar et al., 2012; Liu et al., 2014; Oyarzún et al., 2012; Schiller et al., 2013, 2010; Steinfurth et al., 2014). In other studies, return of fear was prevented by PRE using fear-irrelevant stimuli and including the whole sample (i.e., no exclusion of non-extinguishers was reported) (Agren et al., 2012a, 2012b; Asthana et al., 2015). Lastly, there is one report of failure to replicate findings from Schiller et al. (2010) using both fear-relevant and fear-irrelevant stimuli (Golkar et al., 2012), suggesting that the fear-relevant properties of the CS are not sufficient to explain failures to replicate Schiller et al. (2010).

As previously discussed, some measure of conditioning strength is necessary for fear-relevant and fear-irrelevant stimuli in PRE experiments. It is noteworthy that recent data suggest that PRE might work on both fear-relevant and fear-irrelevant stimuli depending on the retrieval cue utilized and the extinction method (Golkar et al., 2017; Thompson and Lipp, 2017). Thompson and Lipp (2017) associated both fear-relevant (pictures of a spider or a snake) and fear-irrelevant (pictures of a blue or yellow square) stimuli with an electrical stimulus (US). Subsequently, subjects were divided into two groups. One group was exposed to a retrieval cue consisting of a presentation of the US at half the physical intensity used during conditioning, followed by a 10-min interval and then extinction training; participants in the other group (control group) were only exposed to extinction training after a 10-min period equivalent to the experimental group. The results showed spontaneous recovery and reinstatement of skin conductance responses to both CSs (fear-relevant and fear-irrelevant) in the control but not in the experimental group. As will be discussed later, this US-retrieval cue procedure has been shown to be effective and to have different effects than the traditional CS-retrieval procedure (see Section 4.3).

In another recent study, Golkar et al. (2017) paired two CSs (CSa+ and CSb+) with an electrical shock (US) and used a third CS, never paired with the US, as a control (CS−). On the second day, one of the previously reinforced CSs (CSa+) was presented once 10 min prior to a vicarious extinction procedure, which consisted of watching a 24-min video depicting a model in front of a computer screen reacting calmly to unreinforced presentations of CS. During the video presentation, subjects were connected to stimulation equipment but were never shocked. The recovery of fear was measured with fear-potentiated startle on the third day. In the test, subjects showed an increase in responses only to the CSb+, which was not presented prior to extinction training.

4.2.4. *Instructions during experimental phases*

Verbal instructions have been shown to establish (Olsson and Phelps, 2004) or extinguish conditioned responses to aversive stimuli (Sevenster et al., 2012a). In addition, there are studies demonstrating that extinction via instructions attenuates return of fear through reinstatement (Sevenster et al., 2012a). A recent study demonstrated that instructions about the CS-US contingency prior to fear conditioning enhanced fear responses during the conditioning and renewal test, whereas information about the absence of CS-US contingency prior to extinction and the test promoted diminished fear responses during these phases; information on the absence of the CS-US contingency only prior to extinction promoted diminished fear responses during this phase but did not prevent return of fear in a renewal test (Javanbakht et al., 2017). In view of this data, it is important to ask whether instructions might change the effects of PRE.

Although information on the instructions given to participants is not always reported, some analyses can be performed. In studies demonstrating no return of fear after PRE, participants were instructed to pay attention to the stimuli (CSs and US) and try to determine the relation between both during conditioning (Kredlow et al., 2018; Liu et al., 2014; Schiller et al., 2010). Experiments reporting negative results usually have more explicit instructions describing that one of the stimuli would be followed by the US (Fricchione et al., 2016; Golkar et al., 2012; Kindt and Soeter, 2013; Soeter and Kindt, 2011). However, there are exceptions, such as Thompson and Lipp, 2017, who told participants that one of the CSs would be followed by the US and were able to prevent return of fear in the test, and Klucken et al. (2016), who told participants only to pay attention to the computer screen and showed negative results. One could ask if explicit instructions rendered conditioning stronger, as there is evidence from experimental studies that conditioned responses are enhanced when verbal instructions regarding CS-US contingencies are presented (Mertens et al., 2016).

In six out of eight studies reporting no reduction return of fear with PRE, participants were asked to “remember what they had learned” at the end of conditioning (Fricchione et al., 2016; Golkar et al., 2012; Kindt and Soeter, 2013; Meir Drexler et al., 2014; Soeter and Kindt, 2011). There are also exceptions here, such as Thompson and Lipp (2017) and Golkar et al. (2017), who showed long-lasting fear reduction, but their procedures are not entirely comparable (specifically, Thompson and Lipp used a US retrieval cue, while Golkar et al. utilized vicarious extinction after memory reactivation). According to Fricchione et al. (2016), asking participants to remember the experimental session allowed for the verbalization of the learning experience. Participants’ recollection was neither confirmed nor denied by the experimenters, but it is possible that asking participants to review the contingences rendered the conditioning more resistant to PRE. As such, future studies should address the differences between PRE when conscious memories are controlled (compared to what happens when one asks or does not ask for conscious recollection).

4.2.5. *Opportunity for verbal covert behavior during PRE*

Studies showing prolonged reduction of fear in humans have relied on extinction training preceded by a retrieval cue. Exposure to a single CS without the US or a single presentation of the US (at half the intensity used in conditioning) have been used as retrieval cues, which are presented 10 min to 6 h before extinction training. Several of these reports describe disconnecting participants from US-delivering devices after the presentation of the retrieval cue and reconnecting the devices just before extinction training. During this interval between the retrieval cue and extinction training, participants were exposed to a television show or video clip (Golkar et al., 2012; Johnson and Casey, 2015; Klucken et al., 2016; Meir Drexler et al., 2014; Oyarzún et al., 2012; Schiller et al., 2013, 2010; Steinfurth et al., 2014) or were offered magazines to read (Golkar et al., 2017; Kindt and Soeter, 2013; Soeter and Kindt, 2011; Thompson and Lipp, 2017). When Schiller et al. (2010, Experiment 1) used an interval of 6 h between the retrieval cue and extinction training, participants watched a television program in the experimental room for 10 min, but no information was given about where they were or what they did for the remainder of the 6 h interval.

These different procedures utilized during the interval between retrieval cue and extinction training might not control for verbal covert behavior that is related to the CS, the US, or the relation between both, which could theoretically change the effects of PRE. For example, some participants might engage in covert verbal behaviors, such as “remembering” the CS, the US, or the CS-US contingency. If this occurs during the manipulated interval, it could maintain (at a covert level) contingencies that are supposed to be experimentally suppressed and change the effects of PRE.

There are experimental data supporting the proposal this proposal. First, classic work has shown that rehearsal, defined as the covert or overt repetition of information, increases the number of stimuli remembered in memory tasks (Atkinson and Shiffrin, 1971; Rundus and Atkinson, 1970). Second, recent studies have demonstrated that conditioned responses take longer to reduce with extinction after the covert repetition of the CS-US contingency (Joos et al., 2013). In line with this research, a relationship between expectancy report and conditional responses has been reported: fear return, measured by the startle response, was higher when subjects were asked to report on a keypad by button-press whether they expected the US after the CS at every presentation of the CS (Warren et al., 2014).

The role of rehearsal in PRE might be especially important when the retrieval cue is a single presentation of the CS. From a procedural point of view, the difference between standard extinction and this PRE procedure is that in the latter, the first and subsequent presentations of the CS are separated by a greater interval during which participants are disconnected from stimulating and assessment devices. Therefore, it is logical to suppose that events occurring during this interval might be relevant for changing the effects of the intervention. Are these changes in experimental context or responses emitted by participants during this interval relevant in determining the function of the first CS presentation? Do events occurring during this interval determine whether the first unreinforced presentation of the CS will be an extinction trial or a trigger for reconsolidation?

The answer to these questions might depend, for example, on the content of what is rehearsed. Rehearsing the CS-US contingency or the US and reactions to it have been shown to maintain or even increase conditioned responses, as measured through US-expectancy rating (Joos et al., 2012a, 2012b), suppression of operant responses (Joos et al., 2013), or skin conductance responses (Davey and Matchett, 1994; Jones and Davey, 1990). Considering these data, one possibility is that thinking about experimental contingencies might increase the probability of return of fear, as rehearsal of the CS-US relation could counteract the prediction error created by the retrieval cue (see Section 4.3 – Retrieval procedures and prediction error). On the other hand, rehearsing only the CS could not prevent extinction in some experiments (Joos et al., 2013) and explicitly instructing participants to imagine that the CS is presented without the US (a procedure called imaginal extinction) has been shown to reduce conditioned responses (Agren et al., 2017). Therefore, it is possible that this type of rehearsal might be innocuous or even augment the effects of PRE. It is noteworthy, however, that finding diminished return of fear in the last case (rehearsing the CS alone) might raise questions about the mechanisms of PRE. If diminished return of fear is found after participants are instructed to rehearse the CS alone, could it be argued that PRE is governed not by memory reconsolidation but simply by enhanced extinction?

Searching for strategies to control, at least partially, these covert behaviors may be a way of investigating the relevance of this variable to the effectiveness of the PRE procedure. From a translational perspective, investigations of the role of verbal covert behavior is important, as repetitive thought – that is, the covert behavior of thinking attentively, repeatedly, and frequently about one's self and one's world – has been associated with anxiety disorders (Segerstrom et al., 2003; Watkins, 2008).

4.3. Retrieval procedures and prediction error

Evidence from studies using pharmacological interventions have shown that it is possible to reduce conditioned responses by changing the parameters or structure of retrieval cues. For example, it has been demonstrated that depending on the history of learning, the retrieval cue does not have to be an exact replica of the CSs used in conditioning (Soeter and Kindt, 2015). Soeter and Kindt (2015) tested this by exposing participants to differential fear conditioning with two CSs, one of which was paired with the US (CS+). For one group of participants, the CS+ and CS− were different pictures of spiders (perceptual group), whereas two stimuli of different categories served as CSs in the other group, specifically, a picture of a spider and a picture of a snake (categorical group). In a second phase of the experiment, both groups were exposed to a retrieval cue followed by administering propranolol. For the perceptual group, the retrieval cue used consisted of the word "SPIDER," while in the categorical group, the retrieval cue was a word referring to the category of the CS+ (that is, the word "SPIDER" for participants whose CS+ was a spider and the word "SNAKE" for participants whose CS+ had been a picture of a snake). The results of this experiment showed that the differential fear-potentiated startle response was eliminated only in the categorical group.

In rats, reduction in conditioned responses was observed when the US was used as a retrieval cue prior to administering a protein synthesis inhibitor (Dębiec et al., 2010). This observation was later replicated in a series of experiments on PRE in humans. Liu et al. (2014) conditioned participants using pictures of colored squares (CSs) and electrical shocks (US) and exposed them 24 h later to the presentation of a retrieval cue followed by extinction. They used a single presentation of the CS (without the US) or a single presentation of the US (at half the intensity utilized in conditioning) as retrieval cues. The results of Exp. 1 showed that a US-retrieval cue before extinction can be as effective as a CS-retrieval cue in reducing fear return in spontaneous and reinstatement tests. These experiments have been replicated very recently in humans using both fear-relevant and fear-irrelevant stimuli as CSs (Thompson and Lipp, 2017).

Other results from Liu et al. (2014, Exp. 2 and 3) demonstrated that the US-retrieval procedure shows some differences in relation to the use of CS as retrieval cues. Specifically, they showed a long-lasting reduction of responses to all CSs previously associated with the US, whereas using a CS as a retrieval cue reduces only responses elicited by that specific CS (Liu et al., 2014, Exp. 2). They also demonstrated that a US retrieval cue before extinction can prevent the return of conditioned responses to all CSs previously associated with it even when extinction was conducted with only one of the CSs (Liu et al., 2014, Exp. 3).

The issue of which properties of the retrieval cue are critical for producing long-lasting reduction of fear after PRE has been increasingly discussed in the literature. One hypothesis, raised to explain why some retrieval cues are more effective than others, comes from classic theories of conditioning (Sevenster et al., 2013). Specifically, these theories state that changes in the strength of conditioned responses depend on the generation of a prediction error, that is, a discrepancy between actual and past events (Rescorla and Wagner, 1972). In line with this theory, some authors have proposed that a retrieval cue would allow post-retrieval intervention to effectively change behavior if it shows that there is something new to be learned (Sevenster et al., 2012b). For this to happen, retrieval conditions cannot have fully predictable outcomes; that is, there must be a certain degree of prediction error.

Three experiments from the same laboratory support this hypothesis (Sevenster et al., 2014, 2013, 2012b). In one study, participants underwent differential conditioning in which one of two pictures of spiders (CSs) was associated with an electrical shock (US) (Sevenster et al., 2012b). In a second phase of the experiment, participants were exposed to a retrieval cue consisting of one presentation of the CS without the US, followed by the administration of propranolol. For one group of participants (Propranolol group), the retrieval cue was conducted with shock electrodes attached, which is the usual procedure and is thought to induce prediction error, since a shock was to be expected based on the conditioning phase. For a second group, shock electrodes were not attached, and participants were instructed that the CS+ would not be followed by US (Propranolol No-Shock Expectation). This procedure was conducted to promote a situation in which the absence of US was unsurprising. There was also a third group, which was exposed to the retrieval cue with shock, but this was followed by the administration of a placebo (Placebo group). In line with their hypothesis, only the Propranolol group showed no fear-potentiated startle responses when exposed to presentations of the CS without the US 24 h later.

These authors expanded these results in another experiment in which two groups of participants were conditioned by associating one of two pictures (CSs) with an electrical shock (US) in all trials (100% reinforcement rate), and participants were explicitly instructed that the CS would be followed by the US (Sevenster et al., 2013). On the second day, both groups were presented with a retrieval cue followed by the administration of propranolol. For one group, however, the retrieval cue was a single presentation of the CS+ without the US (negative PE group), whereas the other was exposed to a presentation of the CS+ with the US, as with conditioning (no PE group). Experimenters also tested a third group (positive PE group), for which conditioning was conducted by pairing the CS with the US in 33% of trials and by giving verbal instructions that did not describe which of the two CSs would be followed by a shock. For this group, the retrieval cue was a single presentation of the CS with the US. All participants were exposed to a test on a third day on which the CS was presented without the US several times, which was followed by a reinstatement test. According to the hypothesis that prediction error is necessary for post-retrieval amnesia to occur, the negative PE group should present diminished return of fear in the test, since the omission of the US during the retrieval cue consisted in a mismatch between actual and past events. They also predicted that the positive PE group would not show fear responses in the test because the partial reinforcement rate used in conditioning would not induce asymptotic learning and, as such, a reinforced presentation of the CS on Day 2 should generate additional learning. In accordance with these predictions, participants' US-expectancy ratings, measured at each presentation of the CS, decreased from the end of conditioning to the beginning of the test in the negative PE group, increased in the positive PE group, and remained similar in the no-PE group. Furthermore, only the no-PE group showed return of fear.

A third experiment from the same group was designed to test if different degrees of mismatch between conditioning, and the retrieval cue would change the results. In this study, participants were fear-conditioned with a 50% rate of reinforcement in which CSs were paired on all even trials but not odd ones. Therefore, USs could be expected at every other trial. On Day 2, participants received either one, two or four presentations of the CS without the US, followed by the administration of propranolol. On Day 3, when CS was presented, attenuation of fear was observed in the group presented with the CS twice. These results suggest that retrieval cues are effective only when they induce an optimal degree of expectancy violation. Moreover, the transition from insufficient prediction error to sufficient prediction error appears to be subtle (Sevenster et al., 2014).

The results from studies in rats have also supported the notion that some degree of discrepancy between retrieval cues and the original learning condition are required for a persistent attenuation of fear to be observed in the test. In these studies, changes in the parameters of training and retrieval cues, such as the timing of the US relative to the CS offset or the removal of the US during CS presentation, have been shown to result in drug-induced amnesia (Alfei et al., 2015; Díaz-Mataix et al., 2013; Pedreira et al., 2004).

To the best of our knowledge, there are no reports in which the role of prediction error was directly tested in humans using PRE procedures, as the studies from Sevenster and colleagues were conducted using pharmacological interventions after the retrieval cue. However, some authors analyzed that differences between the stimuli during conditioning and when used as retrieval cues might be a possible source of failure in studies showing persistent fear reduction with PRE (Agren, 2014; Golkar et al., 2012). For example, Golkar et al. (2012) raised the possibility that retrieval cues consisting of nonpaired presentations of the CS prior to extinction were more likely to avoid return of fear if conditioning was done at a high reinforcement rate. This is because one nonpaired presentation of a CS after a history of 100% CS-US pairings would represent a greater mismatch than the same nonpaired presentation after a history of intermittent and infrequent pairings. However, as Golkar et al. (2012) pointed out, this hypothesis is at odds with the fact that several studies demonstrating no return of fear have utilized low reinforcement rates during conditioning (Liu et al., 2014; Schiller et al., 2013, 2010) (see Table 2). Another possible source of mismatch between the retrieval procedure and conditioning could be the duration of the CS. For example, Agren et al. (2012a,b), who showed no return of fear after PRE, used a 120 s presentation of the CS without the US as a retrieval cue (in conditioning, CSs had a 6 s duration). Nevertheless, most studies demonstrating no return of fear have used the exact same duration for CSs during conditioning and retrieval procedures (Johnson and Casey, 2015, 2015; Liu et al., 2014; Schiller et al., 2013, 2010; Steinfurth et al., 2014).

Some authors have pointed out that an analysis of the relation between prediction error and return of fear after PRE should consider the strength of the conditioning. According to this view, the amount of prediction error (i.e., the amount of discrepancy between the retrieval cue and the history of conditioning) might have to be greater when conditioning is stronger (Exton-McGuinness et al., 2015; Fricchione et al., 2016). However, as discussed previously, confirmation of this hypothesis requires experimenters to present some sort of independent measure of strength. Future work should address this issue.

In sum, work is still needed to confirm this hypothesis and the limits of prediction error on the prevention of fear after PRE. Future studies should directly test the relation between the degree of similarity between retrieval cues and the history of conditioning. In addition, measures of strength also appear to be necessary here to make comparisons between the degree of prediction error and the amount of fear reduction. Lastly, it is necessary to consider the role of verbal instruction in prediction error.

4.4. *Response systems*

Several methods have been used to measure conditioned responses in humans, including skin conductance responses (SCR), fear-potentiated startle (FPS),[3] US expectancy ratings,[4] valence ratings,[5] and reaction-time tasks (ratings) (Haaker et al., 2014). Although these measures can covary, there is evidence to suggest that they do not necessarily work in conjunction (Kindt and Soeter, 2013). For example, conditioning of SCR was demonstrated with both aversive and non-aversive USs (electrical shock and a vibrotactile stimulus, respectively), whereas FPS was only observed when the US was aversive (Hamm and Vaitl, 1996). Another difference between SCR and FPS is that the conditioning of SCR was demonstrated only in participants that could describe the CS-US contingency (i.e., contingency-aware participants), whereas participants showed FPS conditioning in both aware and unaware participants (Hamm and Vaitl, 1996; Weike et al., 2007). There is also evidence of a dissociation between US-expectancy ratings and FPS. One example is a study analyzing the extinction and

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[3] Fear-potentiated startle is measured through electromyographic activity (EMG) of the orbicularis oculi muscle (Kindt and Soeter, 2013; Vervliet et al., 2013). In this type of measure, it is necessary to present not only the CS and the US (usually an image and an electrical stimulus, respectively) but also a startle stimulus, which in many studies is a brief sound stimulus (for example, 95 dB of white noise lasting 50 ms, as used by Weike et al. (2007). The startle stimulus, when presented, produces a blink response of a certain magnitude and latency. This stimulus is presented either alone or superimposed on the CS. Next, the difference between the blinking magnitude in the absence and presence of the CS is estimated. If the magnitude of the blink response to the startle stimulus is greater when superimposed on the CS, a response elicitation is considered to have occurred (Kindt & Soeter, 2013; Weike et al., 2007).

[4] US-expectancy rating is assessed by presenting a scale whose values reflect the degree of certainty that a CS will be followed by a US. For example, in Kindt and Soeter (2013), in the presence of the CS, a scale appeared on a computer screen, ranging from −5 (certainty that the US would not occur) to +5 (certainty of the presentation of the US), and the subjects were asked to choose the scale value that corresponded to their belief that a CS would be followed by a US.

[5] Valence rating is assessed by presenting a scale whose value reflects the degree of pleasantness (or unpleasantness) of a stimulus. For example, in Thompson and Lipp (2017), participants were shown a 9-point scale (from 1 [unpleasant] to 9 [pleasant]) and were asked to rate the CS and US at different times throughout the experiment.

reinstatement of Pavlovian conditioning in which FPS responses and US-expectancy ratings were measured (Norrholm et al., 2006). In this study, though almost the entire sample indicated not to be expecting the US to follow the CS, nearly half of the participants still showed FPS in the final trials of extinction. Lastly, some studies have shown that administering propranolol prior to the presentation of a retrieval cue prevented the return of FPS responses but not skin conductance responses or US-expectancy ratings (Kindt et al., 2009; Soeter and Kindt, 2011, 2010).

Given this evidence of dissociations between response systems, some authors have questioned whether PRE might have the same effects on different measures of learning (Kindt and Soeter, 2013). Moreover, it has also been questioned whether the presence of multiple measures can change the results of PRE (Golkar et al., 2012; Kindt and Soeter, 2013; Oyarzún et al., 2012; Warren et al., 2014).

In most studies on PRE, conditioned responses have been assessed through skin conductance response (SCR), but some experiments have also utilized fear-potentiated startle (FPS), retrospective or online US-expectancy ratings, or distress or valence ratings. Usually, only one measure was used, but some studies reported acquiring multiple measures (see Table 2). Diminished return of fear after PRE has been seen almost exclusively when SCR were utilized as a single measure. However, there have been failures to show diminished return of fear when only SCR was used. One study demonstrating diminished returned of fear with FPS was by Golkar et al. (2017), who used vicarious extinction after presentation of a retrieval cue. All other studies with FPS combined this measure with ratings and sometimes SCR, and the results were negative. The only study with multiple measures of CR demonstrating long-lasting return of fear was Thompson and Lipp (2017), who associated both fear-relevant and fear-irrelevant pictures (CSs) with an electrical shock (US). The following day, they exposed one group of participants to a US-retrieval cue prior to extinction and another group to traditional extinction. The return of skin conductance responses in spontaneous recovery and reinstatement tests were observed only for the group exposed to traditional extinction. However, no differences between groups were found regarding CS-valence, with both groups rating CS + s as more negative than CS − s.

Failures to show diminished return of fear with FPS have been argued to be associated with two variables. First, when assessing FPS, some studies (Kindt and Soeter, 2013; Soeter and Kindt, 2010) utilized a 104 dB sound as startle stimuli. Some authors have argued this stimulus is intrinsically aversive, and its presence therefore might have created a more threatening environment, increasing contextual conditioning and preventing fear attenuation (Oyarzún et al., 2012). Another point relates to the fact that FPS was associated with the US-expectancy rating in several studies. There is evidence that the presence of a keypad for online assessment of US-expectancy enhances acquisition, spontaneous recovery, and reinstatement of FPS (Warren et al., 2014). Warren et al. (2014) examined the effects of PRE in the presence or absence of a three-button response keypad to report participant US-expectancy during each trial. They used a spontaneous recovery test followed by a reinstatement test. Online expectancy ratings enhanced the degree of FPS in both the acquisition and extinction phases. However, all groups displayed some level of spontaneous recovery of FPS, with keypad groups showing a greater degree of recovery.

In sum, skin conductance responses appear to be more sensitive to PRE than FPS, but this effect was not found in most studies with multiple measures of CR. In addition, failure to show persistent reduction in conditioned responses has also been reported in studies using only SCR as a dependent measure. There are studies showing long-lasting reduction of conditioned responses with FPS and when multiple measures were used (SCR and valence-ratings), but this was achieved through vicarious extinction or using the US as a retrieval cue (Golkar et al., 2017; Thompson and Lipp, 2017). As such, it appears that different post-retrieval procedures can engage different response systems (Kredlow et al., 2018).

5. Summary and conclusions

Recent studies suggest that extinction may have long-lasting effects when preceded by the presentation of a stimulus that was present when conditioning occurred (*retrieval cue*). This stimulus can be the CS itself or the US and is effective in preventing return of fear only when presented 10 min to 6 h before extinction. When combined in a meta-analysis, the results from human studies show small-to-moderate effects for preventing the return of a CR relative to standard extinction procedures using the above procedures (Kredlow et al., 2016). However, there have been some failures to replicate these results, and these have been interpreted as evidence that there might be conditions under which this procedure is thought not to be effective.

Variables identified as possible boundary conditions include pre-experimental characteristics of participants (genetic or psychiatric), conditions thought to produce stronger conditioning (time since initial learning, the percentage and/or number of CS-US pairings, the nature of CS, or the instruction during experimental phases), the retrieval procedures (the type of retrieval cue and the likelihood of generating prediction error), and the response systems assessed. Experimental data also suggest that experimental studies should address the possible effect of rehearsal and other covert behaviors on the experimental phases that could also change the effects of PRE. Further systematic testing of these boundary conditions seems important. When testing the hypothesis that certain conditions produce stronger conditioning, it would be important to show some form of independent measure of strength (resistance to extinction, for example) in accordance with the proposal of Golkar et al. (2012).

Uncovering boundary conditions is important because critical differences between clinical disorders and laboratory experiments include many of the factors that have been highlighted. In PTSD or phobias, patients present conditioning that supposedly is stronger (due to intense USs), is associated with more complex CSs (and more CSs), and there is usually a longer period between initial learning and treatment (for example, PTSD requires symptoms to be present for at least one month). To use the knowledge gained from these studies to improve treatments as applied in these situations, it will be necessary to thoroughly analyze the behavioral manipulations that are needed to prevent the return of fear.

Conflicts of interest

None.

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References

Agren, T., 2014. Human reconsolidation: a reactivation and update. Brain Res. Bull. 105, 70–82. https://doi.org/10.1016/j.brainresbull.2013.12.010.

Agren, T., Björkstrand, J., Fredrikson, M., 2017. Disruption of human fear reconsolidation using imaginal and in vivo extinction. Behav. Brain Res. 319, 9–15. https://doi.org/10.1016/j.bbr.2016.11.014.

Agren, T., Engman, J., Frick, A., Björkstrand, J., Larsson, E.-M., Furmak, T., Fredrikson, M., 2012a. Disruption of reconsolidation erases a fear memory trace in the human amygdala. Science 337, 1550–1552. https://doi.org/10.1126/science.1223006.

Agren, T., Furmark, T., Eriksson, E., Fredrikson, M., 2012b. Human fear reconsolidation and allelic differences in serotonergic and dopaminergic genes. Transl. Psychiatry 2, e76. https://doi.org/10.1038/tp.2012.5.

Alfei, J.M., Ferrer Monti, R.I., Molina, V.A., Bueno, A.M., Urcelay, G.P., 2015. Prediction error and trace dominance determine the fate of fear memories after post-training manipulations. Learn. Mem. 22, 385–400. https://doi.org/10.1101/lm.038513.115.

Alvarez, R.P., Johnson, L., Grillon, C., 2007. Contextual-specificity of short-delay extinction in humans: renewal of fear-potentiated startle in a virtual environment. Learn. Mem. 14, 247–253. https://doi.org/10.1101/lm.493707.

Asthana, M.K., Brunhuber, B., Mühlberger, A., Reif, A., Schneider, S., Herrmann, M.J., 2015. Preventing the return of fear using reconsolidation update mechanisms depends on the met-allele of the brain derived neurotrophic factor Val66Met polymorphism. Int. J. Neuropsychopharmacol. pyv137. https://doi.org/10.1093/ijnp/pyv137.

Atkinson, R.C., Shiffrin, R.M., 1971. The control processes of short-term memory. Sci. Am. 224, 82–94.

Auber, A., Tedesco, V., Jones, C.E., Monfils, M.-H., Chiamulera, C., 2013. Post-retrieval extinction as reconsolidation interference: methodological issues or boundary conditions? Psychopharmacology (Berl.) 226, 631–647. https://doi.org/10.1007/s00213-013-3004-1.

Beck, A.T., Steer, R.A., 1990. Beck Anxiety Inventory. The Psychological Press, San Antonio.

Beckers, T., Kindt, M., 2017. Memory reconsolidation interference as an emerging treatment for emotional disorders: strengths, limitations, challenges, and opportunities. Annu. Rev. Clin. Psychol. 13, 99–121. https://doi.org/10.1146/annurev-clinpsy-032816-045209.

Björkstrand, J., Agren, T., Åhs, F., Frick, A., Larsson, E.-M., Hjorth, O., Furmark, T., Fredrikson, M., 2016. Disrupting reconsolidation attenuates long-term fear memory in the human amygdala and facilitates approach behavior. Curr. Biol. 26, 2690–2695. https://doi.org/10.1016/j.cub.2016.08.022.

Bjorkstrand, J., Agren, T., Frick, A., Engman, J., Larsson, E.-M., Furmark, T., Fredrikson, M., 2015. Disruption of memory reconsolidation erases a fear memory trace in the human amygdala: an 18-month follow-up. PLOS ONE 10, e0129393. https://doi.org/10.1371/journal.pone.0129393.

Bouton, M.E., 2004. Context and behavioral processes in extinction. Learn. Mem. 11, 485–494.

Bouton, M.E., Bolles, R.C., 1980. Conditioned fear assessed by freezing and by the suppression of three different baselines. Anim. Learn. Behav. 8, 429–434.

Bouton, M.E., Bolles, R.C., 1979a. Contextual control of extinction of conditioned fear. Learn. Motiv. 10, 445–466.

Bouton, M.E., Bolles, R.C., 1979b. Role of conditioned contextual stimuli in reinstatement of extinguished fear. J. Exp. Psychol. Anim. Behav. Process. 5, 368.

Brown, T.A., Barlow, D.H., 2014. Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5L): Client Interview Schedule. Oxford University Press, Oxford; New York.

Catania, A.C., 1999. Aprendizagem: Comportamento, linguagem e cognição, 4th ed. ArtMed, Porto Alegre.

Clem, R.L., Huganir, R.L., 2010. Calcium-permeable AMPA receptor dynamics mediate fear memory erasure. Science 330, 1108–1112. https://doi.org/10.1126/science.1195298.

Davey, G.C., Matchett, G., 1994. Unconditioned stimulus rehearsal and the retention and enhancement of differential “fear” conditioning: effects of trait and state anxiety. J. Abnorm. Psychol. 103, 708.

Dębiec, J., Díaz-Mataix, L., Bush, D.E.A., Doyère, V., LeDoux, J.E., 2010. The amygdala encodes specific sensory features of an aversive reinforcer. Nat. Neurosci. 13, 536–537. https://doi.org/10.1038/nn.2520.

Dębiec, J., Ledoux, J.E., 2004. Disruption of reconsolidation but not consolidation of auditory fear conditioning by noradrenergic blockade in the amygdala. Neuroscience 129, 267–272. https://doi.org/10.1016/j.neuroscience.2004.08.018.

Díaz-Mataix, L., Ruiz Martinez, R.C., Schafe, G.E., LeDoux, J.E., Doyère, V., 2013. Detection of a temporal error triggers reconsolidation of amygdala-dependent memories. Curr. Biol. 23, 467–472. https://doi.org/10.1016/j.cub.2013.01.053.

Duncan, C.P., 1949. The retroactive effect of electroshock on learning. J. Comp. Physiol. Psychol. 42, 32–44.

Exton-McGuinness, M.T.J., Lee, J.L.C., Reichelt, A.C., 2015. Updating memories—the role of prediction errors in memory reconsolidation. Behav. Brain Res. 278, 375–384. https://doi.org/10.1016/j.bbr.2014.10.011.

First, M.B., 1997. Structured Clinical Interview for the DSM-IV Axis I Disorders: SCID-I/P, Version 2.0. Biometrics Research Dept., New York State Psychiatric Institute, New York.

Foa, E.B., 2011. Prolonged exposure therapy: past, present, and future. Depress. Anxiety 28, 1043–1047. https://doi.org/10.1002/da.20907.

Foa, E.B., McLean, C.P., 2016. The efficacy of exposure therapy for anxiety-related disorders and its underlying mechanisms: the case of OCD and PTSD. Annu. Rev. Clin. Psychol. 12, 1–28. https://doi.org/10.1146/annurev-clinpsy-021815-093533.

Fricchione, J., Greenberg, M.S., Spring, J., Wood, N., Mueller-Pfeiffer, C., Milad, M.R., Pitman, R.K., Orr, S.P., 2016. Delayed extinction fails to reduce skin conductance reactivity to fear-conditioned stimuli: delayed extinction fails to reduce reactivity. Psychophysiology 53, 1343–1351. https://doi.org/10.1111/psyp.12687.

Garpenstrand, H., Annas, P., Ekblom, J., Oreland, L., Fredrikson, M., 2001. Human fear conditioning is related to dopaminergic and serotonergic biological markers. Behav. Neurosci. 115, 358–364. https://doi.org/10.1037//0735-7044.115.2.358.

Golkar, A., Bellander, M., Olsson, A., Öhman, A., 2012. Are fear memories erasable?-reconsolidation of learned fear with fear-relevant and fear-irrelevant stimuli. Front. Behav. Neurosci. 6. https://doi.org/10.3389/fnbeh.2012.00080.

Golkar, A., Tjaden, C., Kindt, M., 2017. Vicarious extinction learning during reconsolidation neutralizes fear memory. Behav. Res. Ther. 92, 87–93. https://doi.org/10.1016/j.brat.2017.02.004.

Gordon, W.C., 1977. Susceptibility of a reactivated memory to the effects of strychnine: a time-dependent phenomenon. Physiol. Behav. 18, 95–99.

Graeff, F.G., 2007. Ansiedade experimental humana. Rev. Psiquiatr. Clínica São Paulo 34, 251–253.

Haaker, J., Golkar, A., Hermans, D., Lonsdorf, T.B., 2014. A review on human reinstatement studies: an overview and methodological challenges. Learn. Mem. 21, 424–440. https://doi.org/10.1101/lm.036053.114.

Hamm, A.O., Vaitl, D., 1996. Affective learning: awareness and aversion. Psychophysiology 33, 698–710.

Hermans, D., Craske, M.G., Mineka, S., Lovibond, P.F., 2006. Extinction in human fear conditioning. Biol. Psychiatry 60, 361–368. https://doi.org/10.1016/j.biopsych.2005.10.006.

Hofmann, S.G., 2014. D-cycloserine for treating anxiety disorders: making good exposures better and bad exposures worse. Depress. Anxiety 31, 175–177. https://doi.org/10.1002/da.22257.

Javanbakht, A., Duval, E.R., Cisneros, M.E., Taylor, S.F., Kessler, D., Liberzon, I., 2017. Instructed fear learning, extinction, and recall: additive effects of cognitive information on emotional learning of fear. Cogn. Emot. 31, 980–987. https://doi.org/10.1080/02699931.2016.1169997.

Johnson, D.C., Casey, B.J., 2015. Extinction during memory reconsolidation blocks recovery of fear in adolescents. Sci. Rep. 5. https://doi.org/10.1038/srep08863.

Jones, T., Davey, G.C.L., 1990. The effects of cued UCS rehearsal on the retention of differential “fear” conditioning: an experimental analogue of the “worry” process. Behav. Res. Ther. 28, 159–164.

Joos, E., Vansteenwegen, D., Hermans, D., 2012a. Post-acquisition repetitive thought in fear conditioning: an experimental investigation of the effect of CS-US-rehearsal. J. Behav. Ther. Exp. Psychiatry 43, 737–744. https://doi.org/10.1016/j.jbtep.2011.10.011.

Joos, E., Vansteenwegen, D., Hermans, D., 2012b. Repetitive thought about an aversive learning experience maintains conditioned responding. J. Exp. Psychopathol. 3, jep.020811. https://doi.org/10.5127/jep.020811.

Joos, E., Vansteenwegen, D., Vervliet, B., Hermans, D., 2013. Repeated activation of a CS-US-contingency memory results in sustained conditioned responding. Front. Psychol. 4. https://doi.org/10.3389/fpsyg.2013.00305.

Kaczkurkin, A.N., Foa, E.B., 2015. Cognitive-behavioral therapy for anxiety disorders: an update on the empirical evidence. Dialogues Clin. Neurosci. 17, 337.

Kindt, M., Soeter, M., 2013. Reconsolidation in a human fear conditioning study: a test of extinction as updating mechanism. Biol. Psychol. 92, 43–50. https://doi.org/10.1016/j.biopsycho.2011.09.016.

Kindt, M., Soeter, M., Vervliet, B., 2009. Beyond extinction: erasing human fear responses and preventing the return of fear. Nat. Neurosci. 12, 256–258. https://doi.org/10.1038/nn.2271.

Klucken, T., Kruse, O., Schweckendiek, J., Kuepper, Y., Mueller, E.M., Hennig, J., Stark, R., 2016. No evidence for blocking the return of fear by disrupting reconsolidation prior to extinction learning. Cortex 79, 112–122. https://doi.org/10.1016/j.cortex.2016.03.015.

Kredlow, M.A., Orr, S.P., Otto, M.W., 2018. Exploring the boundaries of post-retrieval extinction in healthy and anxious individuals. Behav. Res. Ther. 108, 45–57. https://doi.org/10.1016/j.brat.2018.06.010.

Kredlow, M.A., Unger, L.D., Otto, M.W., 2016. Harnessing reconsolidation to weaken fear and appetitive memories: a meta-analysis of post-retrieval extinction effects. Psychol. Bull. 142, 314–336. https://doi.org/10.1037/bul0000034.

LaBar, K.S., LeDoux, J.E., Spencer, D.D., Phelps, E.A., 1995. Impaired fear conditioning following unilateral temporal lobectomy in humans. J. Neurosci. 15, 6846–6855.

LaBar, K.S., Phelps, E.A., 2005. Reinstatement of conditioned fear in humans is context dependent and impaired in amnesia. Behav. Neurosci. 119, 677–686. https://doi.org/10.1037/0735-7044.119.3.677.

Lattal, K.M., Lattal, K.A., 2012. Facets of Pavlovian and operant extinction. Behav. Processes 90, 1–8. https://doi.org/10.1016/j.beproc.2012.03.009.

LeDoux, J.E., 2014. Coming to terms with fear. Proc. Natl. Acad. Sci. 111, 2871–2878. https://doi.org/10.1073/pnas.1400335111.

Lee, J.L.C., Nader, K., Schiller, D., 2017. An update on memory reconsolidation updating. Trends Cogn. Sci. 21, 531–545. https://doi.org/10.1016/j.tics.2017.04.006.

Lissek, S., Powers, A.S., McClure, E.B., Phelps, E.A., Woldehawariat, G., Grillon, C., Pine, D.S., 2005. Classical fear conditioning in the anxiety disorders: a meta-analysis. Behav. Res. Ther. 43, 1391–1424. https://doi.org/10.1016/j.brat.2004.10.007.

Liu, J., Zhao, L., Xue, Y., Shi, J., Suo, L., Luo, Y., Chai, B., Yang, C., Fang, Q., Zhang, Y., Bao, Y., Pickens, C.L., Lu, L., 2014. An unconditioned stimulus retrieval extinction procedure to prevent the return of fear memory. Biol. Psychiatry 76, 895–901. https://doi.org/10.1016/j.biopsych.2014.03.027.

Lonsdorf, T.B., Menz, M.M., Andreatta, M., Fullana, M.A., Golkar, A., Haaker, J., Heitland, I., Hermann, A., Kuhn, M., Kruse, O., Meir Drexler, S., Meulders, A., Nees, F., Pittig, A., Richter, J., Römer, S., Shiban, Y., Schmitz, A., Straube, B., Vervliet, B., Wendt, J., Baas, J.M.P., Merz, C.J., 2017. Don’t fear “fear conditioning”: methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. Neurosci. Biobehav. Rev. 77, 247–285. https://doi.org/10.1016/j.neubiorev.2017.02.026.

Lonsdorf, T.B., Weike, A.I., Nikamo, P., Schalling, M., Hamm, A.O., Öhman, A., 2009. Genetic gating of human fear learning and extinction: possible implications for gene-environment interaction in anxiety disorder. Psychol. Sci. 20, 198–206.

Maren, S., Chang, C., 2006. Recent fear is resistant to extinction. Proc. Natl. Acad. Sci. 103, 18020–18025.

Marks, I.M., Mathews, A.M., 1979. Brief standard self-rating for phobic patients. Behav. Res. Ther. 17, 263–267.

McGaugh, J.L., 1970. Strychnine effects on discrimination learning in mice: effects of dose and time of administration. Physiol. Behav. 5, 1437–1442.

McGaugh, J.L., 1966. Time-dependent processes in memory storage. Science 153, 1351–1358.

Meir Drexler, S., Merz, C.J., Hamacher-Dang, T.C., Marquardt, V., Fritsch, N., Otto, T., Wolf, O.T., 2014. Effects of postretrieval-extinction learning on return of contextually controlled cued fear. Behav. Neurosci. 128, 474–481. https://doi.org/10.1037/a0036688.

Mertens, G., Kuhn, M., Raes, A.K., Kalisch, R., De Houwer, J., Lonsdorf, T.B., 2016. Fear expression and return of fear following threat instruction with or without direct contingency experience. Cogn. Emot. 30, 968–984. https://doi.org/10.1080/02699931.2015.1038219.

Merz, C.J., Tabbert, K., Schweckendiek, J., Klucken, T., Vaitl, D., Stark, R., Wolf, O.T., 2012. Neuronal correlates of extinction learning are modulated by sex hormones. Soc. Cogn. Affect. Neurosci. 7, 819–830. https://doi.org/10.1093/scan/nsr063.

Milad, M.R., Igoe, S.A., Lebron-Milad, K., Novales, J.E., 2009. Estrous cycle phase and gonadal hormones influence conditioned fear extinction. Neuroscience 164, 887–895. https://doi.org/10.1016/j.neuroscience.2009.09.011.

Milad, M.R., Orr, S.P., Pitman, R.K., Rauch, S.L., 2005. Context modulation of memory for fear extinction in humans. Psychophysiology 42, 456–464. https://doi.org/10.1111/j.1469-8986.2005.00302.x.

Milad, M.R., Zeidan, M.A., Contero, A., Pitman, R.K., Klibanski, A., Rauch, S.L., Goldstein, J.M., 2010. The influence of gonadal hormones on conditioned fear extinction in healthy humans. Neuroscience 168, 652–658. https://doi.org/10.1016/j.neuroscience.2010.04.030.

Mineka, S., Öhman, A., 2002. Phobias and preparedness: the selective, automatic, and encapsulated nature of fear. Biol. Psychiatry 53, 927–937.

Misanin, J.R., Miller, R.R., Lewis, D.J., 1968. Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. Science 160, 554–555.

Monfils, M.-H., Cowansage, K.K., Klann, E., LeDoux, J.E., 2009. Extinction-reconsolidation boundaries: key to persistent attenuation of fear memories. Science 324, 951–955. https://doi.org/10.1126/science.1167975.

Myers, K.M., Ressler, K.J., Davis, M., 2006. Different mechanisms of fear extinction dependent on length of time since fear acquisition. Learn. Mem. 13, 216–223.

Nader, K., Hardt, O., 2009. A single standard for memory: the case for reconsolidation. Nat. Rev. Neurosci. 10, 224–234. https://doi.org/10.1038/nrn2590.

Nader, K., Schafe, G.E., LeDoux, J.E., 2000. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature 406, 722–726.

Neumann, D.L., Longbottom, P.L., 2008. The renewal of extinguished conditioned fear with fear-relevant and fear-irrelevant stimuli by a context change after extinction. Behav. Res. Ther. 46, 188–206. https://doi.org/10.1016/j.brat.2007.12.004.

Norrholm, S.D., Jovanovic, T., Vervliet, B., Myers, K.M., Davis, M., Rothbaum, B.O., Duncan, E.J., 2006. Conditioned fear extinction and reinstatement in a human fear-potentiated startle paradigm. Learn. Mem. 13, 681–685. https://doi.org/10.1101/lm.393906.

Norrholm, S.D., Vervliet, B., Jovanovic, T., Boshoven, W., Myers, K.M., Davis, M., Rothbaum, B., Duncan, E.J., 2008. Timing of extinction relative to acquisition: a parametric analysis of fear extinction in humans. Behav. Neurosci. 122, 1016–1030. https://doi.org/10.1037/a0012604.

Öhman, A., Fredriksson, M., Hugdahl, K., Rimmö, P.-A., 1976. The premise of equipotentiality in human classical conditioning: conditioned electrodermal responses to potentially phobic stimuli. J. Exp. Psychol. Gen. 105, 313.

Öhman, A., Mineka, S., 2001. Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. Psychol. Rev. 108, 483–522. https://doi.org/10.1037//0033-295X.108.3.483.

Olatunji, B.O., Woods, C.M., de Jong, P.J., Teachman, B.A., Sawchuk, C.N., David, B., 2009. Development and initial validation of an abbreviated Spider Phobia Questionnaire using item response theory. Behav. Ther. 40, 114–130.

Olsson, A., Phelps, E.A., 2004. Learned fear of "unseen" faces after Pavlovian, observational, and instructed fear. Psychol. Sci. 15, 822–828.

Oyarzún, J.P., Lopez-Barroso, D., Fuentemilla, L., Cucurell, D., Pedraza, C., Rodriguez-Fornells, A., de Diego-Balaguer, R., 2012. Updating fearful memories with extinction training during reconsolidation: a human study using auditory aversive stimuli. PLoS ONE 7, e38849. https://doi.org/10.1371/journal.pone.0038849.

Pavlov, I., 1927. Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex (Translated and edited by GV Anrep). Oxford University Press, London.

Pedreira, M.E., Pérez-Cuesta, L.M., Maldonado, H., 2004. Mismatch between what is expected and what actually occurs triggers memory reconsolidation or extinction. Learn. Mem. 11, 579–585.

Peterson, R.A., Reiss, S., 1992. Anxiety Sensitivity Index Manual. International Diagnostic Systems, Worthington, OH.

Rescorla, R.A., Heth, C.D., 1975. Reinstatement of fear to an extinguished conditioned stimulus. J. Exp. Psychol. Anim. Behav. Process. 1, 88.

Rescorla, R.A., Wagner, A.R., 1972. A Theory of Pavlovian conditioning: variations in the effectiveness of reinforcement and nonreinforcement. In: Black, A.H., Prokasy, W.E. (Eds.), Classical Conditioning II: Current Research and Theory. Appleton-Century-Crofts, New York, pp. 64–99.

Robbins, S.J., 1990. Mechanisms underlying spontaneous recovery in autoshaping. J. Exp. Psychol. Anim. Behav. Process. 16, 235.

Rundus, D., Atkinson, R.C., 1970. Rehearsal processes in free recall: a procedure for direct observation. J. Verbal Learn. Verbal Behav. 9, 99–105.

Sara, S.J., 2000. Retrieval and reconsolidation: toward a neurobiology of remembering. Learn. Mem. 7, 73–84. https://doi.org/10.1101/lm.7.2.73.

Schiller, D., Cain, C.K., Curley, N.G., Schwartz, J.S., Stern, S.A., LeDoux, J.E., Phelps, E.A., 2008. Evidence for recovery of fear following immediate extinction in rats and humans. Learn. Mem. 15, 394–402. https://doi.org/10.1101/lm.909208.

Schiller, D., Kanen, J.W., LeDoux, J.E., Monfils, M.-H., Phelps, E.A., 2013. Extinction during reconsolidation of threat memory diminishes prefrontal cortex involvement. Proc. Natl. Acad. Sci. 110, 20040–20045. https://doi.org/10.1073/pnas.1320322110.

Schiller, D., Monfils, M.-H., Raio, C.M., Johnson, D.C., LeDoux, J.E., Phelps, E.A., 2010. Preventing the return of fear in humans using reconsolidation update mechanisms. Nature 463, 49–53. https://doi.org/10.1038/nature08637.

Segerstrom, S.C., Stanton, A.L., Alden, L.E., Shortridge, B.E., 2003. A multidimensional structure for repetitive thought: what's on your mind, and how, and how much? J. Pers. Soc. Psychol. 85, 909–921. https://doi.org/10.1037/0022-3514.85.5.909.

Sevenster, D., Beckers, T., Kindt, M., 2014. Prediction error demarcates the transition from retrieval, to reconsolidation, to new learning. Learn. Mem. 21, 580–584. https://doi.org/10.1101/lm.035493.114.

Sevenster, D., Beckers, T., Kindt, M., 2013. Prediction error governs pharmacologically induced amnesia for learned fear. Science 339, 830–833. https://doi.org/10.1126/science.1231357.

Sevenster, D., Beckers, T., Kindt, M., 2012a. Instructed extinction differentially affects the emotional and cognitive expression of associative fear memory: instructed extinction of startle response and SCR. Psychophysiology 49, 1426–1435. https://doi.org/10.1111/j.1469-8986.2012.01450.x.

Sevenster, D., Beckers, T., Kindt, M., 2012b. Retrieval per se is not sufficient to trigger reconsolidation of human fear memory. Neurobiol. Learn. Mem. 97, 338–345. https://doi.org/10.1016/j.nlm.2012.01.009.

Soeter, M., Kindt, M., 2015. Retrieval cues that trigger reconsolidation of associative fear memory are not necessarily an exact replica of the original learning experience. Front. Behav. Neurosci. 9. https://doi.org/10.3389/fnbeh.2015.00122.

Soeter, M., Kindt, M., 2011. Disrupting reconsolidation: pharmacological and behavioral manipulations. Learn. Mem. 18, 357–366. https://doi.org/10.1101/lm.2148511.

Soeter, M., Kindt, M., 2010. Dissociating response systems: erasing fear from memory. Neurobiol. Learn. Mem. 94, 30–41. https://doi.org/10.1016/j.nlm.2010.03.004.

Spielberger, C.D., Gorsuch, R.L., Lusthene, R.E., 1970. Manual for the State-Trait Anxiety Inventory. Consulting Psychologists, Palo Alto.

Steinfurth, E.C.K., Kanen, J.W., Raio, C.M., Clem, R.L., Huganir, R.L., Phelps, E.A., 2014. Young and old Pavlovian fear memories can be modified with extinction training during reconsolidation in humans. Learn. Mem. 21, 338–341. https://doi.org/10.1101/lm.033589.113.

Suzuki, A., Josselyn, S.A., Frankland, P.W., Masushige, S., Silva, A.J., Kida, S., 2004. Memory reconsolidation and extinction have distinct temporal and biochemical signatures. J. Neurosci. 24, 4787–4795. https://doi.org/10.1523/JNEUROSCI.5491-03.2004.

Thomas, B.L., Larsen, N., Ayres, J.J., 2003. Role of context similarity in ABA, ABC, and AAB renewal paradigms: implications for theories of renewal and for treating human phobias. Learn. Motiv. 34, 410–436. https://doi.org/10.1016/S0023-9690(03)00037-7.

Thompson, A., Lipp, O.V., 2017. Extinction during reconsolidation eliminates recovery of fear conditioned to fear-irrelevant and fear-relevant stimuli. Behav. Res. Ther. 92, 1–10. https://doi.org/10.1016/j.brat.2017.01.017.

Vervliet, B., Craske, M.G., Hermans, D., 2013. Fear extinction and relapse: state of the art. Annu. Rev. Clin. Psychol. 9, 215–248. https://doi.org/10.1146/annurev-clinpsy-050212-185542.

Wang, S.-H., de Oliveira Alvares, L., Nader, K., 2009. Cellular and systems mechanisms of memory strength as a constraint on auditory fear reconsolidation. Nat. Neurosci. 12, 905–912. https://doi.org/10.1038/nn.2350.

Warren, V.T., Anderson, K.M., Kwon, C., Bosshardt, L., Jovanovic, T., Bradley, B., Norrholm, S.D., 2014. Human fear extinction and return of fear using reconsolidation update mechanisms: the contribution of on-line expectancy ratings. Neurobiol. Learn. Mem. 113, 165–173. https://doi.org/10.1016/j.nlm.2013.10.014.

Watkins, E.R., 2008. Constructive and unconstructive repetitive thought. Psychol. Bull. 134, 163–206. https://doi.org/10.1037/0033-2909.134.2.163.

Weike, A.I., Schupp, H.T., Hamm, A.O., 2007. Fear acquisition requires awareness in trace but not delay conditioning. Psychophysiology 44. https://doi.org/10.1111/j.1469-8986.2006.00469.x.

Westbrook, R.F., Iordanova, M., McNally, G., Richardson, R., Harris, J.A., 2002. Reinstatement of fear to an extinguished conditioned stimulus: two roles for context. J. Exp. Psychol. Anim. Behav. Process. 28, 97–110. https://doi.org/10.1037//0097-7403.28.1.97.