



# Extinction during reconsolidation eliminates recovery of fear conditioned to fear-irrelevant and fear-relevant stimuli



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## ABSTRACT

Extant literature suggests that extinction training delivered during the memory reconsolidation period is superior to traditional extinction training in the reduction of fear recovery, as it targets the original fear memory trace. At present it is debated whether different types of fear memories are differentially sensitive to behavioral manipulations of reconsolidation. Here, we examined post-reconsolidation recovery of fear as a function of conditioned stimulus (CS) fear-relevance, using the unconditioned stimulus (US) to reactivate and destabilize conditioned fear memories. Participants ( $N = 56$ ; 25 male;  $M = 24.39$  years,  $SD = 7.71$ ) in the US-reactivation and control group underwent differential fear conditioning to fear-relevant (spiders/snakes) and fear-irrelevant (geometric shapes) CSs on Day 1. On Day 2, participants received either reminded (US-reactivation) or non-reminded extinction training. Tests of fear recovery, conducted 24 h later, revealed recovery of differential electrodermal responding to both classes of CSs in the control group, but not in the US-reactivation group. These findings indicate that the US reactivation-extinction procedure eliminated recovery of extinguished responding not only to fear-irrelevant, but also to fear-relevant CSs. Contrasting previous reports, our findings show that post-reconsolidation recovery of conditioned responding is not a function of CS fear-relevance and that persistent reduction of fear, conditioned to fear-relevant CSs, can be achieved through behavioral manipulations of reconsolidation.

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## 1. Introduction

The current focus of human memory reconsolidation research is on developing more efficient methods for long-lasting fear reduction. Research efforts in this area have increased since Schiller et al. (2010) demonstrated that fears, conditioned to fear-irrelevant stimuli (geometric shapes), can be permanently eliminated through safe and non-invasive behavioral interventions that target the memory reconsolidation process. These findings have since been replicated in other studies employing fear-irrelevant stimuli (Agren et al., 2012; Björkstrand et al., 2015; Johnson & Casey, 2015; Liu et al., 2014; Oyarzún et al., 2012; Schiller, Kanen, LeDoux, Monfils, & Phelps, 2013; Steinfurth et al., 2014), but see Golkar, Bellander, Olsson, and Öhman (2012 [experiment 2]) and Klucken et al. (2016). However, disruption of reconsolidation using behavioral interventions has not been demonstrated in studies

employing fear-relevant stimuli (e.g. spiders; Fricchione et al., 2016; Golkar et al., 2012 [experiment 1]; Kindt & Soeter, 2013; Meir Drexler et al., 2014; Soeter & Kindt, 2011 [experiment 2]), leading to speculations that fear, conditioned to fear-relevant stimuli, may not be sensitive to behavioral manipulations of reconsolidation.

Reconsolidation is a time-dependent process that restabilizes reactivated memories (Nader, 2015). The purpose of reconsolidation is to update previously consolidated memories with novel information, in order to facilitate adaptation to the environment (Lee, 2009). Reconsolidation is initiated through reactivation and destabilization of the consolidated memory trace, by presenting cues associated with the original learning (Nader, 2013; Pineyro, Monti, Alfei, Bueno, & Urcelay, 2014). Once reactivated, memories become labile and are open to modification, before they reconsolidate and return to their inactive state (Nader, 2015; Nader, Schafe, & LeDoux, 2000). Although the exact time course of memory reconsolidation is not known, it is believed that reconsolidation is completed within six hours of memory reactivation (Agren et al., 2012; Alberini, 2011; Nader et al., 2000; Schiller et al., 2010).

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Interfering with reconsolidation during this period of lability through administration of pharmacological or behavioral interventions, such as extinction training, may modify the existing memory trace and persistently reduce the recovery of fear (Agren, 2014; Schiller et al., 2010). Conversely, when extinction training is administered without prior memory reactivation, fear may recover in a new context (renewal), after the passage of time (spontaneous recovery) or after re-exposure to the aversive event (reinstatement), as extinction learning involves the acquisition of a new, inhibitory association and not the unlearning of the original fear response (Bouton, 2002).

Reconsolidation studies are typically conducted over the course of three consecutive days and involve differential Pavlovian fear conditioning (e.g. Schiller et al., 2010), whereby a neutral conditioned stimulus (CS+) is paired with an intrinsically aversive stimulus (unconditioned stimulus, US), while another CS is presented by itself (CS-). Future presentations of the CS + result in anticipation of the US, which is reflected in increased differential responding to the CS+, relative to the CS-, on behavioral, verbal, and physiological indices of fear (Lipp, 2006a). During extinction (Day 2), typically delivered 10 min after administration of procedures which are thought to reactive and destabilize fear memories, the CSs are presented without the US until differential responding is extinguished. Successful disruption of reconsolidation is inferred from the absence of differential responding during tests of fear recovery (e.g. Liu et al., 2014; Schiller et al., 2010).

As fear is expressed on the verbal, behavioral, and physiological level (Lang, 1985), several methods exist to measure conditioned fear. The most commonly employed measure in humans is electrodermal activity (skin conductance responses, SCRs) which increases during conditioning as a result of increased sweat gland activity (Boucsein, 2012; Dawson, Schell, & Filion, 2007). Fear learning is also reflected on verbal indices of conditioned responding, such as increased negative valence of the reinforced CS+ (De Houwer, Thomas, & Baeyens, 2001). Physiological and verbal indices of fear learning are said to be governed by dissociable implicit (non-conscious) and explicit (conscious) processes respectively (LaBar & Cabeza, 2006; Schultz, Balderston, Geiger, & Helmstetter, 2013; but see; Sevenster, Beckers, & Kindt, 2012) and are differentially sensitive to manipulations of reconsolidation (e.g. Kindt & Soeter, 2013; Soeter & Kindt, 2010). By measuring multiple indices of conditioned responding, we can obtain a comprehensive understanding of processes underlying fear learning and fear reduction (Lipp, 2006a).

Extant literature indicates that post-reactivation extinction training is superior to extinction training alone in achieving lasting reduction of fear (Agren et al., 2012; Björkstrand et al., 2015; Liu et al., 2014; Schiller et al., 2010). However, at present, it is unknown whether all types of fear memories are sensitive to behavioral manipulations of reconsolidation. Relative to fear-irrelevant CSs, phylogenetically fear-relevant CSs, such as snakes, show superior conditioning which resists extinction (Mineka & Öhman, 2002). Accordingly, it is possible that fears conditioned to different classes of stimuli may be differentially sensitive to behavioral manipulations of reconsolidation. However, conclusive evidence is lacking, as past research has either employed only fear-relevant or fear-irrelevant CSs (e.g. Fricchione et al., 2016; Golkar et al., 2012; Kindt & Soeter, 2013). Cross-study comparisons are problematic, due to methodological variations, such as the reinforcement rate employed during fear conditioning, number of acquisition trials, type and duration of the US or the memory reactivation procedure (for reviews see Auber, Tedesco, Jones, Monfils, & Chiamulera, 2013; Finnie & Nader, 2012; Kredlow, Unger, & Otto, 2016).

Differences across memory reactivation procedures deserve

further consideration, as successful reactivation and destabilization of memories is a prerequisite for memory reconsolidation (Pineyro et al., 2014). The vast majority of past fear conditioning research (e.g. Golkar et al., 2012; Kindt & Soeter, 2013; Schiller et al., 2010) has employed an unreinforced presentation of the previously conditioned CS + to reactivate fear memories (“CS-reactivation”). The success of this and other reactivation procedures is constrained by a number of boundary conditions. These include, but are not limited to, the age, strength and type of memory to be reactivated, type of reactivation procedure, and the ‘prediction error’ generated by the reactivating stimulus (for reviews of boundary conditions and prediction errors, please see Auber et al., 2013; Exton-McGuinness, Lee, & Reichelt, 2015; Fernández, Boccia, & Pedreira, 2016; Finnie & Nader, 2012; Lee, 2009).

The term ‘prediction error’ in reconsolidation research refers to a mismatch between past learning history, and actual events that are of relevance to prior learning and contain novel information that warrants updating or modification of memories (Exton-McGuinness et al., 2015; Fernández et al., 2016; Lee, 2009). An example of a manipulation that can generate a prediction error would be a change to the temporal CS-US relationship, by presenting the US 20 s earlier or later than expected, based on the trained CS-US interval (Díaz-Mataix, Ruiz Martínez, Schafe, LeDoux, & Doyère, 2013). An unreinforced presentation of the previously conditioned CS + may also generate a prediction error, for instance when the duration of the CS presentation is increased, relative to training conditions (Agren et al., 2012). It has also been observed that CS-reactivation may trigger memory reconsolidation when the consequences of the CS are not fully predictable, for instance following training on a partial reinforcement schedule (Oyarzún et al., 2012; Schiller et al., 2010), but see Golkar et al. (2012); Kindt and Soeter (2013). Overall, extinction training subsequent to CS-reactivation is more likely to disrupt the reconsolidation of fears conditioned to fear-irrelevant CSs (e.g. Schiller et al., 2010) than of those conditioned to fear-relevant CSs (Kindt & Soeter, 2013). There are several reasons as to why the CS-reactivation procedure may fail to destabilize these fear memories.

Briefly, it has been proposed that the strength of conditioned fears varies across training protocols. For instance, training with fear-relevant CSs is thought to result in strong fear associations which are resistant to extinction (Mineka & Öhman, 2002) and to behavioral manipulations of reconsolidation (Kindt & Soeter, 2013; Soeter & Kindt, 2011). It is also conceivable that the mere absence of the US during CS-reactivation does not create the prediction error necessary to facilitate behavioral manipulations of reconsolidation, even though the reactivation procedure is capable of supporting pharmacological manipulations (see Soeter & Kindt, 2011 for a comparison of these methods). It should be noted that there are a number of additional factors which may determine whether a manipulation results in memory destabilization. A comprehensive review of these factors is, however, beyond the scope of this paper. Readers interested in differences in prediction errors across memory types, training conditions, and computational models of associative learning may wish to consult Fernández et al. (2016); Holland and Schiffrino (2016); or Schultz and Dickinson (2000).

Due to the mixed results from studies which used CS-reactivation, we employed a reactivation procedure that consisted of a single presentation of the US, at half the physical intensity used during acquisition (“US-reactivation”). This procedure has been successfully employed in past research (Liu et al., 2014), albeit only with fear-irrelevant CSs. Relative to CS-reactivation, the present reactivation procedure may be more likely to generate a prediction error, due to the mismatch between the actual and expected US intensity, as well as due to the unsignalled presentation of the US, in the absence of the CS. Based on previous reports, US-reactivation

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