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Vicarious extinction learning during reconsolidation neutralizes fear memory

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ABSTRACT

Background: Previous studies have suggested that fear memories can be updated when recalled, a process referred to as reconsolidation. Given the beneficial effects of model-based safety learning (i.e. vicarious extinction) in preventing the recovery of *short-term fear memory*, we examined whether consolidated *long-term fear memories* could be updated with safety learning accomplished through vicarious extinction learning initiated within the reconsolidation time-window. We assessed this in a final sample of 19 participants that underwent a three-day within-subject fear-conditioning design, using fear-potentiated startle as our primary index of fear learning.
Methods: On day 1, two fear-relevant stimuli (reinforced CSs) were paired with shock (US) and a third stimulus served as a control (CS−). On day 2, one of the two previously reinforced stimuli (the reminded CS) was presented once in order to reactivate the fear memory 10 min before vicarious extinction training was initiated for all CSs. The recovery of the fear memory was tested 24 h later.
Results and conclusion: Vicarious extinction training conducted within the reconsolidation time window specifically prevented the recovery of the reactivated fear memory ($p = 0.03$), while leaving fear-potentiated startle responses to the non-reactivated cue intact ($p = 0.62$). These findings are relevant to both basic and clinical research, suggesting that a safe, non-invasive model-based exposure technique has the potential to enhance the efficiency and durability of anxiolytic therapies.

1. Background

Learning to predict danger by forming associations between threatening events and preceding innocuous cues allows the individual to prepare defense systems to cope with an impending threat in advance of its actual occurrence (Öhman and Mineka, 2001). Although such defensive responses serve adaptive purposes, persistent and excessive fear responses to events that no longer predict danger can develop into pathological anxiety. In fact, such associative learning mechanisms lie at the heart of anxiety, and trauma-related disorders (Mineka & Zinbarg, 2006), which can result from direct experiences such as traumatic events, but also from indirect or vicarious fear learning experiences (Rachman, 1977).

Recent advances suggest that fear memories in humans can be erased by behaviorally disrupting the process of memory reconsolidation (Becker and Kindt, 2016), but there are studies with evidence to the contrary or with limited replication success (Golkar, Bellander, Olsson & Öhman, 2012; Kindt & Soeter, 2013; Klucken, Kruse, Schweckendiek et al., 2016; Soeter & Kindt, 2011; Warren, Anderson, Kwon et al., 2014). Reconsolidation refers to a process during which reactivation of a consolidated fear memory can turn it into a labile state when the memory trace can be changed. The quintessential model to study the mechanisms of associative fear learning and memory is Pavlovian fear conditioning (Briscione, Jovanovic & Norrholm, 2014; Kindt, 2014; Ledoux, 2000; Mineka & Zinbarg, 2006). In the laboratory, the regulation of fear memory is most commonly studied with extinction training; the decrease in fear expression after repeated, safe exposures to the fear-eliciting cue. Extinction-based exposure therapies are among the most effective strategies to treat anxiety, and trauma- and stressor-related disorders, but still a considerable number of patients do not profit from these interventions (Vervliet, Craske & Hermans, 2013). The limitations of extinction-based interventions can be explained by the neuroscience literature on fear

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conditioning and extinction. Animal and human fear-conditioning studies reliably show that an acquired fear response can easily return by memory retrieval techniques such as re-exposure to unsignaled US, i.e., reinstatement; (Bouton & Bolles, 1979; Norrholm, Vervliet, Jovanovic et al., 2008; Rescorla and Heth, 1975), a context change, i.e., renewal; (Bouton, 2004), or testing several weeks later, i.e., spontaneous recovery; (Bouton, 1993). The implication for clinical practice is that the fear symptoms may easily return when confronted with an unexpected aversive situation, when leaving the therapeutic exposure context or simply with the passage of time. A consensus has been reached that extinction learning does not erase the original fear memory. Rather it reflects the formation of a new inhibitory memory, which competes with the earlier formed fear memory. As a consequence, the fear memory remains intact and may resurface, resulting in a return of fear even after originally successful fear extinction. One way to counteract the return of fear is by identifying therapeutic strategies for enhancing inhibitory learning, either pharmacologically or behaviorally, given that this type of learning forms the basis of exposure interventions (Craske, Treanor, Conway et al., 2014). A number of so-called cognitive enhancers have been uncovered, including Yohimbine that increases central noradrenergic transmission or D-cycloserine (DCS), a partial agonist at the glycine site of *N*-methyl-D-aspartate glutamate receptors (Graham, Callaghan & Richardson, 2014; Milad, Rosenbaum & Simon, 2014). The discovery of cognitive enhancers may be promising by accelerating treatment effectiveness, although findings have been inconsistent and effects typically small (Graham et al., 2014; Milad et al., 2014). Importantly, this approach does not necessarily prevent the return of fear since they leave the fear memory intact (Morris & Bouton, 2007). In this context, disrupting the reconsolidation of fear memory has emerged as the most compelling framework because it offers a theoretical way to change the original memory trace.

Insight into disrupting reconsolidation of fear memory has emerged from several different species and paradigms (Nader, 2015). In humans, disrupting reconsolidation with the noradrenergic β-blocker propranolol HCl neutralized the fear memory (Kindt, Soeter & Vervliet, 2009; Sevenster et al., 2012b, 2013, 2014b; Soeter & Kindt, 2010; Soeter & Kindt, 2012; 2015b), while leaving the declarative knowledge about the memory intact, and has been shown to produce comparable effects on behavioral approach tendencies in a subclinical population of spider fearful individuals (Soeter & Kindt, 2015a). The use of purely behavioral interventions to target the process of memory reconsolidation in humans was sparked by the work of Schiller and colleagues (2010), suggesting that extinction training initiated after a memory reactivation can reduce the recovery of fear. Although there have been replications of this effect (Agren et al., 2012; Schiller, Kanen, Ledoux, Monfils & Phelps, 2013), the field has also been hampered with full or partial replication failures suggesting that this effect is fragile and sensitive to procedural differences (Golkar et al., 2012; Kindt & Soeter, 2013; Klucken et al., 2016; Soeter & Kindt, 2011; Warren et al., 2014). Moreover, and in contrast to alternative pharmacological interventions to disrupt reconsolidation (e.g. Kindt et al., 2009), the effects of extinction training within the reconsolidation window have been restricted by a number of factors. First, successful demonstrations have used fear-irrelevant stimuli, such as geometrical figures. However, anxiety disorders do not tend to be associated with fear-irrelevant stimuli (e.g., geometric figures), but with objects and situations related to survival threats (i.e., fear-relevant stimuli) (Öhman and Mineka, 2001). Second, the effects of disrupting memory reconsolidation have been observed using skin conductance responses (SCRs), which reflect the increase in general sympathetic arousal and is highly sensitive to attentional processes (Filion, Dawson, Schell et al., 1991). Alternative measures, such as the fear-potentiated startle (FPS), a reliable enhancement of the startle reflex when an organism is in a state of fear (Davis, 2006), is more valence specific (Lang, Bradley & Cuthbert, 1998) and effects of attention or CS–US expectancy are considered smaller than emotional effects (e.g.Bocker, Baas, Kenemans & Verbaten, 2004). Additionally, FPS taps directly into the amygdala (Davis, 2006) and provides a unique tool to more directly link non-human animal and human research (e.g. Briscione et al., 2014). Therefore, the effects of disrupting reconsolidation using the FPS may be advantageous over SCR.

To address the limitations in previous research, we conducted a reconsolidation experiment using fear-relevant stimuli as CSs and FPS as the index of fear learning. Capitalizing on the efficiency of model-based safety learning (i.e. vicarious extinction) in preventing the recovery of short-term fear memory (Golkar, Castro & Olsson, 2015a; Golkar, Haaker, Selbing & Olsson, 2015b; Golkar, Selbing, Flygare, Öhman & Olsson, 2013), we examined whether consolidated long-term fear memory can be updated with vicarious extinction learning initiated within the reconsolidation time-window. Vicarious extinction learning is a model-based exposure technique in which another individual – the learning model – acts calmly in the presence of a fear-eliciting stimulus. It is used as part of exposure treatments of fears and phobias in which the client views the therapist who approaches and interacts with the threat stimulus before the patient is directly exposed to it (Seligman and Wuyek, 2005). Experimentally, vicarious extinction learning has been shown to outperform traditional, direct extinction in preventing the return of short-term fear memory (Golkar et al., 2013). To this end, we used a within-subjects design, in which the memory of one of two fear conditioned stimuli was reactivated through a reminder trial prior to vicarious extinction learning. Testing occurred across three consecutive days, involving differential conditioning on Day 1, reactivation of one previously reinforced CS (reminded CS), followed by vicarious extinction learning on Day 2, and a reinstatement test for fear recovery on Day 3. Based on the beneficial effects of vicarious extinction in previous work (Golkar et al., 2015a; 2015b; 2013), we hypothesized that differential FPS responses to the reminded CS would be diminished, but that differential FPS responses would recover to the non-reminded CS on the third day of testing.

2. Methods

2.1. Participants

To estimate the sample size, we performed a power analysis based on the results of Schiller et al. (2010) and used a threshold of 90% sensitivity (1−beta = 0.90) and a significance level of $\alpha = 0.05$. This yielded a required sample size of 19. Given that fear recovery cannot be assessed when fear responses are not successfully acquired, previous work have excluded participants that failed to acquire a fear response (Agren et al., 2012; Klucken, 2016; Schiller et al., 2010; Schiller et al., 2013). Therefore, we recruited forty-six undergraduate students from the University of Amsterdam of which thirty-five completed all three days of the study. Two participants were excluded after medical screening and one participant was excluded due to a technical failure to administer the reinstatement shocks at Day 3, leaving 32 participants for the analysis. Similar to the practice of previous studies (Agren et al., 2012; Klucken et al., 2016; Schiller et al., 2010; Schiller et al., 2013) we excluded participants (n = 14) that failed to acquire fear conditioning (see supplementary figure S1 for a graphical illustration of the data for the whole sample (N = 32). Successful acquisition was defined as larger differentiation on the last two trials of acquisition (post-learning) than during the first two trials