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Reconsolidation in a human fear conditioning study: A test of extinction as updating mechanism

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ABSTRACT

Disrupting reconsolidation seems to be a promising approach to dampen the expression of fear memory. Recently, we demonstrated that disrupting reconsolidation by a pharmacological manipulation specifically targeted the emotional expression of memory (i.e., startle response). Here we test in a human differential fear-conditioning paradigm with fear-relevant stimuli whether the spacing of a single unreinforced retrieval trial relative to extinction learning allows for "rewriting" the original fear association, thereby preventing the return of fear. In contrast to previous findings reported by Schiller et al. (2010), who used a single-method for indexing fear (skin conductance response) and fear-irrelevant stimuli, we found that extinction learning within the reconsolidation window did not prevent the recovery of fear on multiple indices of conditioned responding (startle response, skin conductance response and US-expectancy). These conflicting results ask for further critical testing given the potential impact on the field of emotional memory and its application to clinical practice.

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1. Introduction

Emotional memory is considered to lie at the root of anxiety disorders, operationalized as acquired associations between initially neutral or ambiguous stimuli (conditioned stimulus, CS) and intrinsically aversive consequences (unconditioned stimulus, US). People suffering from anxiety disorders feel, think and act as if a feared stimulus (CS) predicts the later occurrence of a negative outcome (US). If the fear memory is crucial in the maintenance of anxiety disorders, repeated presentations of the feared stimulus without any adverse consequence (CS/no-US) should teach the patient that the stimulus is innocuous. Indeed, extinction is still a central element in current cognitive-behavioral therapies for anxiety disorders. Although extinction-like exposure treatments are among the most effective strategies for treating anxiety disorders, a substantial proportion of people experience a relapse even after apparently successful treatment (Craske, 1999). The prevailing view on the return of fear is that extinction can eliminate the fearful responding, but it leaves the original fear memory intact (Bouton, 2002, 2004). Extinction solely involves the formation of a new inhibitory stimulus association (CS/no-US) that competes with the original fear memory (CS–US) (Bouton, 1993; LeDoux, 1995). Once a fear association has been established, the fear memory is held to be forever. In sum, partial or full reappearance of fear may be explained by intact fear memories that resurface.

Insights from neuroscience suggest that it is unnecessarily defeatist to regard the fear memory as irreversible. Animal studies show that fear memory is not inevitably permanent but can change when retrieved. Upon their retrieval, consolidated memories temporarily return into a labile state, requiring de novo protein and RNA synthesis for restabilization (Nader et al., 2000; Sara, 2000; Dudai, 2004; Tronson and Taylor, 2007; Lee, 2009). This process is referred to as reconsolidation and describes a fundamental finding that the retrieval of a previously stable memory renders that memory vulnerable to the disruptive effects of amnestic agents. Disruption of reconsolidation has been demonstrated for pharmacological agents (e.g., anisomycin) either targeting directly the required protein synthesis or indirectly (e.g., propranolol) by inhibiting the noradrenaline-stimulated CREB phosphorylation (Jockers et al., 1998; Chaudhry and Granneman, 1999; Thonberg et al., 2002).

Evidence for disrupting reconsolidation of fear memory recently progressed from animals to humans (Kindt et al., 2009; Soeter and Kindt, 2010, 2011). In a fear-conditioning paradigm, we demonstrated that a β-adrenergic receptor antagonist (i.e., propranolol) administered prior to memory reactivation persistently erased the startle fear responding, while the skin conductance responding and the US expectancy ratings remained unaffected. Although multiple indices of the behavioral expression of conditioned fear (US-expectancy, SCR, and startle response) are usually obtained for reasons of cross-validation, behavioral studies demonstrate that

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the different response systems do not necessarily act in concert (e.g., Hamm and Weike, 2005; Weike et al., 2005; Soeter and Kindt, 2010, 2011). Electrodermal conditioning seems to primarily reflect anticipatory arousal, irrespective of the valence of the anticipated stimulus (Hamm and Vaitl, 1996; Weike et al., 2007), whereas human startle responding is considered to be a reliable and specific index of fear that operates more independently from the cognitive level of fear learning (Hamm and Weike, 2005). Indeed, in our studies the SCR corresponded with the US expectancies ratings (Soeter and Kindt, 2010, 2011). The previous findings that the β-adrenergic blocker specifically affected the emotional expression of fear memory (i.e., startle response) do not imply that reconsolidation cannot be targeted at a more cognitive level. Post-retrieval interference by behavioral manipulation (e.g., new learning) has been found with numerous memory tasks including declarative and procedural memory in humans (Walker et al., 2003; Hupbach et al., 2007; Forcato et al., 2007, 2009; Strange et al., 2010). However, reconsolidation does not necessarily occur when memory is being reactivated, but only when there is something to be learned (i.e., informational value) during memory retrieval (Lee, 2009; Sevenster et al., submitted for publication). A violation based upon prior learning is supposed to be a necessary condition for reconsolidation, meaning that the magnitude of the outcome or the outcome itself is not being fully predicted (i.e., prediction error) (Pedreira et al., 2004; Forcato et al., 2009; Lee, 2009). In our previous studies, the *single* unreinforced reactivation trial appeared to be sufficient for updating the emotional expression of fear memory but prevented learning about the CS–US contingency (Kindt et al., 2009; Soeter and Kindt, 2010, 2011). Apparently, the various memory expressions of a single learned association call for different reactivation conditions.

Recently, a behavioral approach targeting the reconsolidation of fear memory demonstrated that *multiple* unreinforced presentations allowed for updating of threat anticipation in humans (Schiller et al., 2010). That is, an *extinction procedure* performed within the window of reconsolidation resulted in the persistent erasure of the skin conductance response. Obviously, a *behavioral* procedure is preferred over *pharmacological* manipulations provided that similar effects can be obtained for the emotional expression of fear memory (i.e., startle response). In a recent within-subject study with two reinforced stimuli (CSs^+) and one unreinforced stimulus (CS^-), we failed to replicate the finding that extinction within the reconsolidation window updates the reactivated fear memory (Soeter and Kindt, 2011). The Schiller et al. study and the Soeter–Kindt study diverged in several ways, with the most notable differences being the assessment of conditioned responding (single-method *vs.* multi-method of indexing fear, resp.) and the conditioned stimuli (geometric figures *vs.* fear-relevant stimuli, resp.). We employed fear-relevant stimuli because they lead to a superior conditioning of aversive associations and are especially resistant to extinction learning compared with fear-irrelevant cues (Mineka and Öhman, 2002; Lang et al., 2005). Providing that anxiety disorders do not tend to be associated with fear-irrelevant stimuli (e.g., geometric figures) but rather with objects and situations related to survival threats (i.e., fear-relevant stimuli) (Mineka and Öhman, 2002), we are specifically interested in targeting stronger fear memory. Although Schiller et al. demonstrated the effects in two experiments, one between-subject and one within-subject design, the effects are rather small and only demonstrated for a non-specific measure of fear (i.e., skin conductance responding). Given the potential impact on the field of emotional memory and its application to clinical practice, this finding asks for further critical testing in a more simple between-subject design and a specific measure of fear (i.e., startle fear responding; Hamm and Weike, 2005; Weike et al., 2007; but see Lipp et al., 2001, 2003; Mallan and Lipp, 2007).

Table 1
Mean values (SD) of the reported spider fear, trait anxiety, anxiety sensitivity, shock intensity and US evaluation for the *Reactivation–Extinction* and *Extinction–Only* condition.

	Reactivation–Extinction	Extinction–Only	*t*-Test
Spider fear	5.3 (5.1)	5.9 (5.3)	$t(38) < 1$
Trait anxiety	34.9 (7.4)	34.7 (7.5)	$t(38) < 1$
Anxiety sensitivity	8.7 (5.0)	8.5 (4.1)	$t(38) < 1$
Shock intensity	18.3 (11.3)	16.0 (11.5)	$t(38) < 1$
US evaluation	−2.5 (1.1)	−2.6 (1.7)	$t(38) < 1$

Here, we tested whether unreinforced extinction trials provided during the reconsolidation window prevents the return of extinguished fear, using a between-subject fear-conditioning design with only two fear-relevant stimuli. Testing included different phases across three consecutive days each separated by 24 h. During fear acquisition (day 1), one of two fear-relevant stimuli ($CS1^+$) was repeatedly paired with an aversive electric stimulus (US), while the other fear-relevant stimulus ($CS2^-$) was not (i.e., pictures of spiders; IAPS numbers 1200–1201) (Lang et al., 2005). Assignment of the slides as $CS1^+$ and $CS2^-$ was counterbalanced across participants. On day 2, all participants were exposed to extinction training in which the feared CS1 was presented without the unconditioned stimulus. In the *Reactivation–Extinction* condition, the fear memory was reactivated 10 min before extinction training, using a single presentation of an unreinforced CS1 (Schiller et al., 2010). The other *Extinction – Only* condition was not reminded of the previously acquired fear association before extinction training. Memory retention ($CS1^-$ *vs.* $CS2^-$) was tested 24 h later (day 3). In order to trigger the original fear memory, *reminder shocks* were administered following *re*-extinction learning (i.e., day 3). The absence of a fear response by the behavioral provocation (i.e., reinstatement) suggests, but cannot prove, the absence of the underlying fear association. Rapid *re*acquisition of fear was therefore further investigated as a measure of savings of the original fear association. The conditioned fear response (CR) was measured as potentiation of the eyeblink startle reflex to a loud noise by electromyography of the right orbicularis oculi muscle. Skin conductance responses and online US-expectancy ratings were obtained to assess the anticipation of threat (Weike et al., 2007) (i.e., declarative knowledge).

2. Materials and methods

2.1. Participants

Forty undergraduate students (13 men, 27 women) from the University of Amsterdam ranging in the age of 18–33 years (mean ± SD age, 21.1 ± 3.0 years) participated in the study. All participants were assessed to be free from any current or previous medical condition that would contraindicate participation (i.e., pregnancy; seizure disorder; cardiovascular disease). An additional exclusion criterion contained a score ≥26 on the Anxiety Sensitivity Index (ASI; Peterson and Reiss, 1992). Participants were randomly assigned to one of two conditions with the restriction that conditions were matched on Trait Anxiety (STAI-T) (Spielberger et al., 1970), Spider Phobic Questionnaire (SPQ) (Klorman et al., 1974), and ASI scores as close as possible (see Table 1). Participants received either partial course credits or were paid a small amount (€32, –) for their participation in the experiment.

The ethical committee of the University of Amsterdam approved the study and informed consent was obtained from all participants.

2.2. Apparatus and materials

2.2.1. Stimuli

In order to strengthen the fear association during acquisition, fear relevant stimuli served as CSs (i.e., pictures of spiders; IAPS numbers 1200–1201) (Lang et al., 2005). The slides were 200 mm high and 270 mm wide and were presented in the middle of a black screen on a 19-in. computer monitor. One of the slides ($CS1^+$) was followed by an US (75% of the presentations), while the other slide ($CS2^-$) was not. Assignment of the slides as $CS1^+$ and $CS2^-$ was counterbalanced across participants. Both the $CS1^+$ and $CS2^-$ stimuli were presented for 8 s. The startle probe was presented 7 s after CS onset and was followed by the US ($CS1^+$) 500 ms later (i.e., at 7.5 s). An electric stimulus with duration of 2 ms, delivered to the wrist of the non-preferred hand, served as US. Delivery of the electric stimulus was controlled

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