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Dissociating response systems: Erasing fear from memory

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ABSTRACT

In addition to the extensive evidence in animals, we previously showed that disrupting reconsolidation by noradrenergic blockade produced amnesia for the original fear response in *humans*. Interestingly, the declarative memory for the fear association remained intact. These results asked for a solid replication. Moreover, given the constructive nature of memories, the intact recollection of the fear association could eventually 'rebuild' the fear memory, resulting in the spontaneous recovery of the fear response. Yet, perseverance of the amnesic effects would have substantial clinical implications, as even the most effective treatments for psychiatric disorders display high percentages of relapse. Using a differential fear conditioning procedure in humans, we replicated our previous findings by showing that administering propranolol (*40 mg*) prior to memory reactivation eliminated the startle fear response 24 h later. But most importantly, this effect persisted at one month follow-up. Notably, the propranolol manipulation not only left the declarative memory for the acquired contingency untouched, but also skin conductance discrimination. In addition, a close association between declarative knowledge and skin conductance responses was found. These findings are in line with the supposed double dissociation of fear conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. They support the view that skin conductance conditioning primarily reflects contingency learning, whereas the startle response is a rather specific measure of fear. Furthermore, the results indicate the absence of a causal link between the actual knowledge of a fear association and its fear response, even though they often operate in parallel. Interventions targeting the amygdalar fear memory may be essential in specifically and persistently dampening the emotional impact of fear. From a clinical and ethical perspective, disrupting reconsolidation points to promising interventions persistently erasing fear responses from trauma memory without affecting the actual recollection.

1. Introduction

Memories are fundamentally dynamic processes. They are constructive in nature and always changing (Nader, 2003). The phenomenon of reconsolidation, the stabilization of a memory after retrieval, enables the modification of memory representation (Nader, Schafe, & LeDoux, 2000). Abundant evidence in animals indicates that blockade of the reconsolidation process following memory reactivation, produces amnesia for the original learning (Nader, Schafe, & LeDoux, 2000). Recently, the study of reconsolidation blockade of emotional (fear) memory progressed from animals to humans (Brunet et al., 2008; Kindt, Soeter, & Vervliet, 2009). We demonstrated that oral administration of a β-adrenergic receptor antagonist (*propranolol*) prior to reactivation of a fear memory resulted in amnesia of the fear memory expression in humans 24 h later (Kindt et al., 2009). Interestingly, the propranolol manipulation left the declarative memory for the learned fear association between the conditioned stimulus and its aversive consequence intact, but this knowledge no longer produced a fear response. This remarkable dissociation is clearly in line with the concept of multiple memory systems, involving a distinction between declarative memory (i.e., the conscious recollection of facts and events) and procedural memory, expressed through performance rather than recollection (Squire, 2004). While declarative memory is based on the functional integrity of the hippocampal complex (Squire, Stark, & Clark, 2004), the acquisition and expression of a fear response requires intact amygdala functioning (LeDoux, 2000). Hence, the observed double dissociation of fear conditioning and declarative knowledge relative to the amygdala and hippocampus further highlights the independent function of these two memory systems (LaBar & Cabeza, 2006; Phelps, 2004).

Even though the amygdala and hippocampal complex can operate independently, they also interact in subtle but important ways (LaBar & Cabeza, 2006; Phelps, 2004). For instance, hippocampal-dependent declarative memories can lead to activation of the amygdala, mediating our emotional reactions (Phelps, 2004). Alternatively, disrupting the reconsolidation of the hippocampal

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memory trace or hippocampal-dependent extinction learning can produce amnesia for the amygdalar fear memory (Bouton, 2002; LeDoux, 2000). Since declarative memories are supported by the gradual formation of a more distributed memory network, complete or partial disruption of the hippocampal memory trace could eventually be "reconstructed" (Amaral, Osan, Roesler, & Tort, 2008; Nakazawa et al., 2002), reactivating the emotional (fear) memory accordingly. In a similar vein, extinction learning involves the formation of a new inhibiting hippocampal association that leaves the original fear memory unaffected (Bouton, 2002). Thus, the putative inhibitory role performed by the hippocampus could be essential in the spontaneous recovery of (fear) memory expression (*transient amnesia*). If disrupting reconsolidation of fear memory will be of value for clinical practice, *persistent* rather than transient amnesic effects are desired.

In this human fear conditioning study, we replicated and extended our previous study (Kindt et al., 2009) by testing whether *disrupting the reconsolidation process by noradrenergic blockade would persistently reduce the fear response from its memory*. In order to maximize the likelihood of fear memory expression, we included two well-established retrieval techniques, that is, the administration of *reminder shocks* on both day 3 and during follow-up, and a *long-term* test one month later. Participants were subjected to a differential fear conditioning procedure including different phases: *fear acquisition* (day 1), *memory reactivation* (day 2), *extinction* followed by a *reinstatement* procedure and a *test* phase (day 3), and a *follow-up session* including an additional extinction, reinstatement and test phase one month later (day 30) (Fig. 1A). Fear conditioning typically involves the pairing of an initially neutral conditioned stimulus (CS^+) with an intrinsically aversive unconditioned stimulus (US) (e.g., an electric shock). The conditioned fear response (CR) was measured as potentiation of the *eyeblink startle reflex* to a loud noise by electromyography (EMG) of the right orbicularis oculi muscle. Stronger startle response to the loud noise during the fear-conditioned stimulus (CS^+) as compared to the control stimulus (CS^-) reflects the fearful state of the participant elicited by the feared stimulus (CS^+). Potentiation of the startle blink response is only observed during aversive fear conditioning (Weike, Schupp, & Hamm, 2007). Neurally, it reflects the influence of direct and indirect connections from the amygdala to the primary startle-reflex pathway in the brainstem (Davis & Whalen, 2001). *Declarative knowledge* of the fear association was measured through online US-expectancy ratings during each CS presentation within 5 s after stimulus onset. In addition, *skin conductance responses* were obtained as an objective measure of expectancy learning. Note, however, that SCR discrimination is not only observed for aversive but also for nonaversive conditioning. It primarily reflects the more cognitive level of contingency learning (i.e., declarative knowledge) (Weike et al., 2007). Reconsolidation of the fear memory was manipulated by the systemic administration of propranolol, double-blind placebo controlled. To determine whether the effect of propranolol required active retrieval of the fear memory, propranolol was administered to another fear-conditioned group without reactivation of the memory.

We hypothesized that disrupting reconsolidation by noradrenergic blockade would result in the persistent weakening of the *startle fear response*, while leaving the *declarative memory* for the fear association intact. Given the close association between declarative knowledge and electrodermal activity (Hamm & Weike, 2005), we reasoned that β-adrenergic blockade during memory reactivation would not sort any effect on *skin conductance* conditioning. Salivary alpha amylase (sAA) and blood pressure levels were obtained to ensure the propranolol manipulation exerted its intended physiological effect. US evaluation and state anxiety were assessed to test whether the expected reduction in startle responses could be explained by any general effects of propranolol on these variables.

2. Materials and methods

2.1. Subjects

Sixty undergraduate students (15 men, 45 women) from the University of Amsterdam ranging in the age of 18 to 46 years (mean ± SD age, 20.4 ± 3.8 years) participated in the study. All participants reported to be free from any current or previous medical or psychiatric condition that would contraindicate taking a single 40 mg oral dose of propranolol hydrochloride (i.e., pregnancy; seizure disorder; respiratory disorder; cardiovascular disease; diabetes; liver-/kidney disorder; previous adverse reaction to a β-blocker; use of another β-blocker; use of medication that could involve potentially dangerous interactions with propranolol; depression; or psychosis). To be eligible for participation, blood pressure had to be ⩾90/60 mm Hg during medical screening as

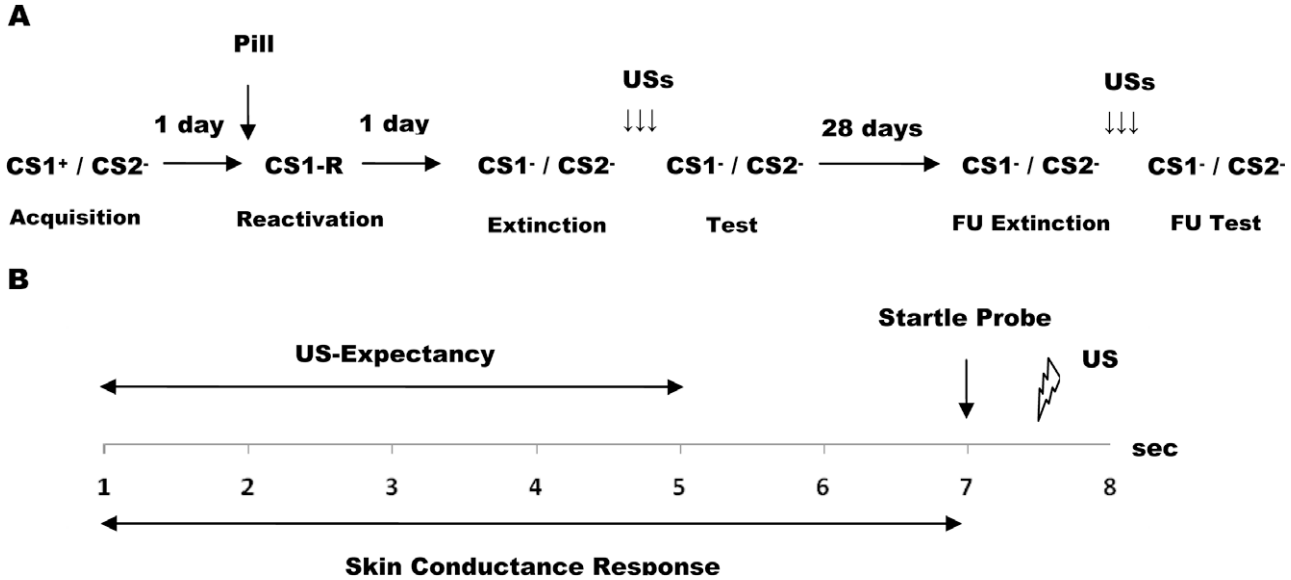

Fig. 1. Schematic of the experimental design (**A**) and the $CS1^+$ conditioning trial (**B**). In the $CS1^-$, $CS2^-$ and CS1-R trials, no US was delivered.