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Retrieval per se is not sufficient to trigger reconsolidation of human fear memory

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ABSTRACT

Ample evidence suggests that consolidated memories, upon their retrieval, enter a labile state, in which they might be susceptible to change. It has been proposed that memory labilization allows for the integration of relevant information in the established memory trace (memory updating). Memory labilization and reconsolidation do not necessarily occur when a memory is being reactivated, but only when there is something to be learned during memory retrieval (prediction error). Thus, updating of a fear memory trace should not occur under retrieval conditions in which the outcome is fully predictable (no prediction error). Here, we addressed this issue, using a human differential fear conditioning procedure, by eliminating the very possibility of reinforcement of the reminder cue. A previously established fear memory (picture-shock pairings) was reactivated with shock-electrodes attached (Propranolol group, $n = 18$) or unattached (Propranolol No-Shock Expectation group, $n = 19$). We additionally tested a placebo-control group with the shock-electrodes attached (Placebo group, $n = 18$). Reconsolidation was not triggered when nothing could be learned during the reminder trial, as noradrenergic blockade did not affect expression of the fear memory 24 h later in the Propranolol No-Shock Expectation group. Only when the outcome of the retrieval cue was not fully predictable, propranolol, contrary to placebo, reduced the startle fear response and prevented the return of fear (reinstatement) the following day. In line with previous studies, skin conductance response and shock expectancies were not affected by propranolol. Remarkably, a double dissociation emerged between the emotional (startle response) and more cognitive expression (expectancies, SCR) of the fear memory. Our findings have important implications for reconsolidation blockade as treatment strategy for emotional disorders. First, fear reducing procedures that target the emotional component of fear memory do not necessarily affect the cognitive component and vice versa. Second, mere retrieval of the fear memory is not sufficient to induce its labilization and reconsolidation.

1. Introduction

A dynamic balance between stability and plasticity of memory seems to be crucial for adaptation to an ever-changing environment. Stability of fear memory guarantees a fast response to threat and does not require continuous re-learning, whereas plasticity permits modification of an established memory trace, should conditions require such adaptation (Dudai, 2009). Plasticity of fear memory is also of clinical importance, as it provides a window of opportunity to target unwanted, excessive emotional memories such as those that underlie anxiety disorders (e.g., PTSD). While *consolidation*, the strengthening of a memory trace over time, serves the stability of memory (McGaugh, 1966), the process of *reconsolidation*, the protein-synthesis dependent restabilization of memory upon retrieval, allows for memory modification (Nader, Schafe, & LeDoux, 2000). Reconsolidation is typically demonstrated by the amnesic effects of protein synthesis inhibitors administered before or after memory reactivation (Nader et al., 2000; Pedreira, Pérez-Cuesta, & Maldonado, 2002; Sara, 2000). Recently, we demonstrated that administration of the β-adrenergic receptor antagonist propranolol before memory reactivation disrupted the emotional expression of fear memory (startle fear response) and prevented the return of fear 24 h later, while declarative memory remained intact (Kindt, Soeter, & Vervliet, 2009; Soeter & Kindt, 2010, 2011a, 2011b).

If retrieval per se were sufficient to render a memory trace labile, memory would be hypermalleable. Indeed, it has been suggested that reconsolidation does not necessarily occur when a memory is being reactivated, but only when something can be learned during memory retrieval (memory updating) (Forcato, Argibay, Pedreira, & Maldonado, 2009; Forcato, Rodriguez, Pedreira, & Maldonado, 2010; Lee, 2009; Pedreira, Pérez-Cuesta, &

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Maldonado, 2004). A violation of expectation based on prior learning – the magnitude of the outcome or the outcome itself is not fully predicted (prediction error) – is thus a prerequisite for reconsolidation to take place (Forcato et al., 2009, 2010; Lee, 2009; Pedreira et al., 2004). We hypothesize that when nothing can be learned during memory reactivation (no prediction error), there is no need for the memory to be updated and reconsolidation will not be triggered.

Here we examined in a differential fear conditioning study in humans whether reconsolidation of a previously established fear memory depends on the outcome of the reactivation trial. We applied a reactivation procedure similar to our previous studies (i.e., unreinforced presentation of the feared stimulus) (Kindt et al., 2009; Soeter & Kindt, 2010), but discarded the reactivation trial of prediction error by excluding the very possibility of reinforcement. Briefly, on day 1, fear acquisition was established with use of two spider pictures (Conditioned Stimuli; CS). One of the pictures ($CS1^+$) was followed by an aversive electrical stimulation (Unconditioned Stimulus; US), while the other was not ($CS2^-$). On day 2, participants received propranolol before the fear memory was reactivated with a non-reinforced reminder presentation of the feared stimulus ($CS1^-$-R). During memory retrieval, shock-electrodes were attached in one group (Propranolol group), but not in the other (Propranolol No-Shock Expectation). As such, presentation of the CS1 was supposed to elicit active anticipation of the US in the former group but not in the latter. To test whether the observed effect of the manipulation of shock expectation of the reminder trial was indeed related to a propranolol-induced disruption of reconsolidation, an additional group of participants received a placebo pill before memory reactivation. Similar to the Propranolol group, the shock-electrodes were attached during the reminder presentation in the Placebo group. In all groups, expression of the fear memory was tested 24 h later (day 3). We hypothesize that a reactivation session that is devoid of prediction error (i.e., prior knowledge that the presentation of the feared stimulus ($CS1^-$-R) cannot be followed by shock) will fail to trigger reconsolidation. Noradrenergic blockade will disrupt reconsolidation of a previously acquired fear memory when learning can occur during reactivation. Therefore, we predict that in contrast to both the Propranolol No-SE and the Placebo group, administration of propranolol before memory reactivation will attenuate subsequent expression of the fear memory (startle fear response) in the Propranolol group. In line with our previous studies, declarative memory will remain unaffected (US-expectancies). Given the close association of the skin conductance response (SCR) with declarative knowledge (Hamm & Weike, 2005), noradrenergic blockade will not affect electrodermal responding either.

2. Materials and methods

2.1. Participants

Sixty (19 male; 41 female) healthy undergraduate students participated in the study, ranging in age between 18 and 30 years, with a mean age of 21.08 years (SD = 2.61). All participants were free from any condition contraindicative to the administration of 40 mg propranolol (see Soeter & Kindt, 2010). Participants received either partial course credit or a small amount of money (€ 35, –) for their participation. All participants gave informed consent and were notified that they could withdraw from participation at any time. The study had full ethical approval. Participants were assigned to the Propranolol group (n = 20, 7 male), the Propranolol No-Shock Expectation (No-SE) group (n = 20, 6 male) or the Placebo group (n = 20, 5 male) with the restriction that groups were matched on gender and Spider Phobia Questionnaire (SPQ) scores.

2.2. Apparatus

2.2.1. Stimuli

The Conditioned Stimuli (CS) consisted of two different images depicting spiders (IAPS, nr 1200; 1201). Electrical stimulation was delivered through a pair of Ag electrodes of 20 by 25 mm with a fixed inter-electrode mid-distance of 45 mm. Shock deliverance was controlled by a Digitimer DS7A constant current stimulator (Hertfordshire, UK). Between the electrodes and the skin a conductive gel (Signa, Parker) was applied.

2.2.2. Fear potentiated startle (FPS)

Startle response was measured through electromyography (EMG) of the right orbicularis oculi muscle. Two 5-mm Ag/AgCl electrodes filled with a conductive gel (Signa, Parker) were positioned approximately 1 cm under the pupil and 1 cm below the lateral canthus, respectively; a ground electrode was placed on the forehead, 1 cm below hairline (Blumenthal et al., 2005). Acoustic stimuli were presented binaurally through headphones (Sennheiser, model HD 25-1 II). The EMG signal was sampled at 1000 Hz and amplified in two stages. The input stage had an input resistance of 10 MOhm, a frequency response of DC-1500 Hz and an amplification factor of 200. A 50 Hz notch filter was used to reduce interference of the mains noise. The second stage amplified the signal with a variable amplification factor of 0–100× and integrated the signal. The raw EMG data were band-pass filtered (28–500 Hz, Butterworth, 4th order (Blumenthal et al., 2005)) to obtain the cleanest possible data without affecting response amplitude. Peak blink amplitude was determined in a 30–150 ms interval following probe onset.

2.2.3. Skin conductance response (SCR)

Electrodermal activity was measured using an input device with a sine-shaped excitation voltage (7.5 V) of 50 Hz, which was derived from the mains frequency. Two Ag/AgCl electrodes of 20 by 16 mm were attached with adhesive tape to the medial phalanges of the first and third fingers of the non-preferred hand. The signal from the input device was led through a signal-conditioning amplifier and the analog output was digitized at 100 Hz by a 16-bit AD-converter (National Instruments, NI-6224). Startle response and electrodermal activity were recorded with the software program VSSRP98. Electrodermal responding to the CS was calculated by subtracting the baseline (2 s before stimulus onset) from the maximum score during the 0–7 s window after CS onset. This is a well-established approach of examining electrodermal reactivity and has been used extensively in human psychophysiological research (Milad, Orr, Pitman, & Rauch, 2005; Orr et al., 2000; Pineles, Orr, & Orr, 2009).

2.2.4. Subjective distress ratings

Subjective distress was measured online during each image presentation, on an 11-point scale ranging from 'not distressed at all' (0) to 'very distressed' (10). The scale was placed at the bottom of the screen below the CS picture. Participants rated distress levels by shifting the cursor on the scale with use of the mouse and confirmed their ratings by pushing the left mouse button within 7 s following stimulus onset.

2.2.5. US-expectancy ratings

Participants were asked to complete a graph representing the evolution of their US-expectancies during the experiment. US expectancy was depicted on the *Y*-axis ranging from 'at that moment, I very strongly expected a shock' (5), through 'I didn't know what to expect' (0) to 'at that moment, I very strongly expected no shock' (−5). On the *X*-axis the different experimental phases were