Neural Signature of Reconsolidation Impairments by Propranolol in Humans

Lars Schwabe, Karim Nader, Oliver T. Wolf, Thomas Beaudry, and Jens C. Pruessner

Background: The retrieval of consolidated memories may result in their destabilization, requiring a restabilization process called reconsolidation. During reconsolidation, memories become sensitive to psychological and pharmacological modifications again, thus providing an opportunity to alter unwanted memories. Although such reconsolidation manipulations might open the door to novel treatment approaches for psychiatric disorders such as posttraumatic stress disorder, the brain mechanisms underlying reconsolidation processes in humans are completely unknown. Here, we asked whether a β-adrenergic receptor antagonist might interfere with the reconsolidation of emotional episodic memories and what brain mechanisms are involved in these effects.

Methods: Healthy participants were administered the β-adrenergic receptor antagonist propranolol or a placebo before they reactivated previously learned neutral and emotional material. Recognition memory was tested 24 hours later. Functional magnetic resonance images were collected during reactivation and recognition testing.

Results: Propranolol during reactivation specifically reduced the subsequent memory for emotional pictures; memory for neutral pictures remained unaffected. This emotional memory impairment was associated with significantly increased activity in the amygdala and the hippocampus for correctly recognized pictures at test. Most interestingly, the same structures were active (but not modulated by propranolol) during memory reactivation. Memory reactivation alone or propranolol without reactivation had no effect on subsequent memory.

Conclusions: Our results demonstrate how the consequences of memory reconsolidation processes are represented in the human brain, suggesting that the brain areas that are recruited during reactivation undergo changes in activity that are associated with subsequent memory recall.

Key Words: Amygdala, emotional memory, hippocampus, noradrenaline, propranolol, reconsolidation

Emotionally arousing experiences are usually better remembered than neutral experiences. Although generally adaptive to survival, this emotional memory enhancement may contribute to anxiety disorders such as posttraumatic stress disorder (PTSD) (1). Converging evidence suggests that the superior memory for emotional material is related to arousal-induced noradrenergic activity in the amygdala (2,3). In line with this view, administration of the β-adrenergic receptor antagonist propranolol during or shortly after learning abolishes the emotional enhancement of memory (4,5). First promising findings show that propranolol administered within a few hours after a traumatic event might reduce subsequent trauma memories and PTSD symptoms (6). However, the possibility to modulate the formation of trauma memories by propranolol is limited to a short time-window after the traumatic event (7), during which most individuals will not receive clinical treatment.

Accumulating evidence indicates that consolidated, apparently stable memories might re-enter an unstable state after their reactivation, thus requiring a process of restabilization that is known as reconsolidation (8–12). During reconsolidation, emotional memories become sensitive to amnesic agents, including blockade of β-adrenergic receptors by propranolol (13,14)—again, thus providing a second chance to modify unwanted memories. Despite the potential to reduce traumatic memories, which are a pathological hallmark of PTSD, during reconsolidation, the neural mechanism underlying reconsolidation processes and the impact of propranolol on the reconsolidation of emotional memories in particular is unknown in humans.

To the best of our knowledge, the present study is the first to directly investigate the brain processes associated with reconsolidation processes in humans. To examine the neural correlates of emotional memory reconsolidation impairments by propranolol, we collected functional magnetic resonance images while participants retrieved (i.e., reactivated) previously learned emotional and neutral information under propranolol as well as during a subsequent recognition memory test (Figure 1A). To rule out unspecific effects of memory reactivation or propranolol alone, we included control groups that reactivated memories under placebo or received propranolol without memory reactivation. We hypothesized that memory reactivation under propranolol would reduce subsequent memory for emotional material and that this reconsolidation impairment would be represented at the neural level by altered (i.e., enhanced or reduced) activity in the hippocampus and the amygdala, those brain areas that are crucial for emotional memory formation (15–17). In particular, the emotional memory modulation hypothesis suggests that the emotional memory enhancement is owing to noradrenergic activity in the amygdala, which then modulates memory in the hippocampus (3). Because noradrenergic activity is necessary for enhancing emotional memories but not for forming neutral memories (4,5), the reconsolidation of neutral memories should remain largely unaffected by β-adrenergic receptor blockade during reactivation.

Methods and Materials

Participants

Fifty-two healthy right-handed participants (18 to 30 years old; 26 men, 26 women) with normal or corrected-to-normal vision were randomly assigned to one of four experimental groups (n =

From the Douglas Mental Health Institute and Department of Psychiatry (LS, TB, JCP); Department of Psychology (KN, JCP), McGill University, Montreal, Canada; and the Department of Cognitive Psychology (LS, OTW), Ruhr-University Bochum, Bochum, Germany.

Address correspondence to Lars Schwabe, Ph.D., Ruhr-University Bochum, Department of Cognitive Psychology, 44780 Bochum, Germany; E-mail: Lars.Schwabe@ruhr-uni-bochum.de.

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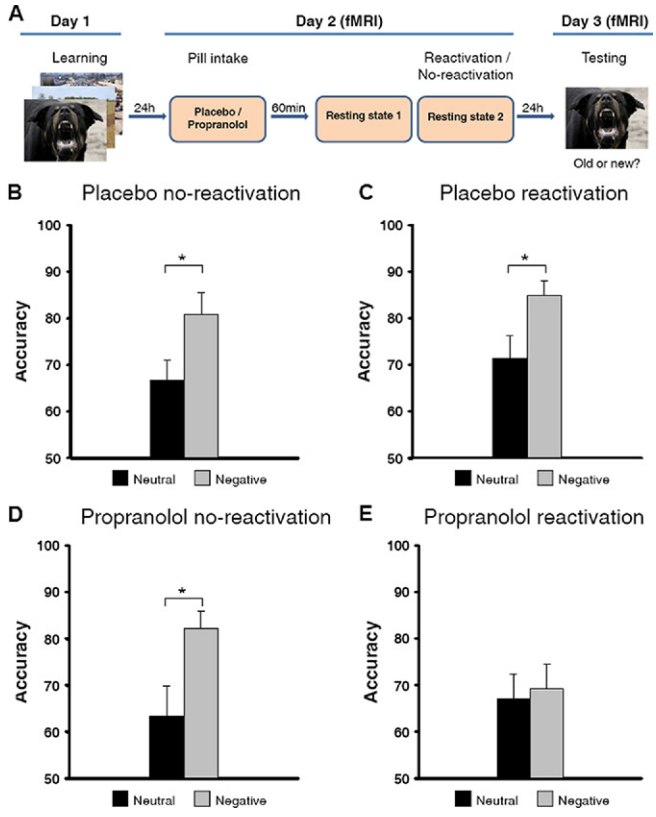

Figure 1. Reconsolidation impairment by propranolol. **(A)** Procedure: volunteers learned a number of neutral and emotional pictures (example image shown is representative of International Affective Picture System images used for this study). Twenty-four hours later, they took a placebo or the β blocker propranolol (40 mg) before they underwent two resting state scans. During the second "resting state" scan, one-half of the participants reactivated the learned pictures. Again 24 h later, all participants completed a recognition memory test in the scanner. **(B)** Participants that received a placebo without memory reactivation had better memory for negative than for neutral pictures. **(C** and **D)** This emotional memory enhancement remained unchanged by memory reactivation under placebo or propranolol administration without memory reactivation. **(E)** Propranolol administered before memory reactivation abolished the emotional memory enhancement. Accuracy = hit rate – false alarm rate. Error bars show mean and SEM; $n = 51$, $^*p < .01$. fMRI, functional magnetic resonance imaging.

13/group): placebo no-reactivation, placebo reactivation, propranolol no-reactivation, and propranolol reactivation. The imaging data of one participant are missing due to technical problems. The Institutional Review Board of McGill University approved the study protocol, and written informed consent was obtained from all participants.

Stimuli

Stimuli consisted of 50 neutral and 50 negative pictures taken from the International Affective Picture System (18), on the basis of their standard scores for emotional arousal and valence. To ensure that pictures were indeed experienced as neutral and emotionally arousing, respectively, participants rated all pictures with respect to valence and arousal on 0–100 scales with the endpoints "very negative" versus "very positive" and "very calm" versus "very aroused," respectively. In retrospect, ratings of participants confirmed the classification of the pictures as neutral and negative, respectively: neutral pictures were rated as neutral (mean [M] = 52.6, SEM = .6), and negative pictures were rated as negative (M = 21.1, SEM = 1.1) [$F(1,48) = 799.79$, $p < .001$, $\eta^2 = .94$]. Negative pictures were experienced as significantly more arousing (M = 67.1, SEM = 1.4) than neutral pictures (M = 30.1, SEM = 2.2) [$F(1,48) = 221.63$, $p < .001$, $\eta^2 = .82$]. There were no significant differences between experimental groups in the valence and arousal ratings (all $p > .15$).

Pictures were subdivided into two sets, each consisting of 25 neutral and 25 negative pictures. Picture sets were matched according to the normative valence and arousal scores, complexity, and semantic categories (e.g., human/animal attack, mutilation, neutral faces, objects). The two picture sets used during learning and as new pictures in the recognition test were counterbalanced across participants.

Procedure

Participants were tested on 3 consecutive days: Day 1, learning outside the scanner; Day 2, pill intake and memory reactivation inside the scanner; Day 3, recognition testing inside the scanner (Figure 1A). On Day 1, participants saw 25 neutral and 25 negative pictures presented in randomized order and were asked to memorize these pictures. Each picture was presented for 2 sec. To control for possible group differences in encoding, an immediate free recall test was given after picture presentation. In this free recall test, participants described verbally all pictures they could remember in as much detail as possible, and the experimenter checked on a list the pictures that were remembered. If it was unclear to which pictures the participants were referring, the experimenter asked the participants for more details.

Twenty-four hours later, participants received a placebo or a propranolol pill (40 mg; Teva, Sellersville, Pennsylvania), depending on the experimental condition. To verify the action of the drug, heart rate measurements were taken immediately before as well as every 10 min in the hour after the drug intake (participants were not told about their heart rates). Sixty minutes after the drug intake, participants underwent two 10-min resting state scans during which they fixated on a cross presented at the center of a screen. After the first resting state scan, participants in the reactivation conditions were explicitly reminded of the learning session on Day 1. The experimenter asked them to remember the pictures they had seen on the previous day in as much detail as possible while they were fixating on the cross. We decided not to cue the memory of the learned pictures explicitly, because that would have complicated the interpretation of group differences in memory performance on Day 3 significantly. In particular, the presentation of the pictures from Day 1 in a recognition test or a cued-recall test would have represented another learning trial, which would have made comparisons between the reactivation and no-reactivation groups impossible. Although relearning processes might occur during retrieval also without external cuing (19), such relearning processes might have been more pronounced if the original learning material would have been presented again during reactivation. Furthermore, a free recall test was hardly possible in the scanner. However, in a brief interview after scanning, all participants in the reactivation conditions confirmed that they concentrated on the previously learned pictures and that they could remember many of them.

The 70-min interval between drug intake and reactivation was used, to be consistent with previous studies that have used propranolol to modify reconsolidation of fear conditioning in humans (13). This interval also coincides with the pharmacodynamics of propranolol (20) and ensured that peak propranolol levels were reached shortly after memory reactivation. Participants in the no-reactivation conditions received no reminder of the learned pictures; for them there was no difference between the resting state scans. Experimental day 2 took place in another building, in another