



β -Adrenergic blockade during reactivation reduces the subjective feeling of remembering associated with emotional episodic memories

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ABSTRACT

In contrast to neutral events, emotionally arousing events often are remembered vividly and with great detail. Although generally adaptive to survival, this emotional memory enhancement may contribute to psychopathology. Blocking the arousal-related noradrenergic activity with a β blocker shortly after learning prevents the emotional enhancement of memory. In the present experiment, we tested in 48 healthy subjects whether the administration of the β blocker propranolol before the reactivation of already consolidated emotional episodic memories may interfere with their reconsolidation and, thus, reduce the subsequent feeling of remembering associated with these memories. Our results show that propranolol before reactivation abolished the superior memory for emotional relative to neutral stimuli and decreased 'remember' judgments for emotional items, suggesting that β -adrenergic blockade during reactivation made emotional memories comparable to neutral memories.

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1. Introduction

Reactivating apparently stable, consolidated memories may render them unstable again, so that a process of reconsolidation is needed to stabilize them anew (Dudai, 2006; Lewis et al., 1968; Nader and Hardt, 2009). During reconsolidation, memories can be updated by incorporating new experiences (Forcato et al., 2007; Hupbach et al., 2007; Schiller et al., 2010) or modified by amnesic agents (Eisenberg and Dudai, 2004; Kindt et al., 2009; Nader et al., 2000). Such reconsolidation manipulations provide an opportunity to alter unwanted memories and thus a pathological hallmark of several psychiatric disorders, including post-traumatic stress disorder (PTSD).

The overly strong memory for traumatic events that is characteristic for PTSD (American Psychiatric Association, 1994) can be seen as an extreme form of the otherwise adaptive memory enhancement for emotional events. Emotionally arousing events are usually very well remembered and this emotional memory enhancement is mediated by noradrenergic activity in the amygdala (McGaugh, 2000; Phelps and LeDoux, 2005). The overstimulation of endogenous stress hormone systems due to an extremely stressful event

mediates an over-consolidation of the event, resulting in a lasting trauma memory (Pitman, 1989). Emotional arousal, however, leads not necessarily to memories that are particularly accurate (emotion may sometimes even increase false alarm rates; e.g. Johansson et al., 2004; Kapucu et al., 2008) but rather to memories that are particularly vivid and associated with a strong subjective feeling of remembering (Ochsner, 2000; Sharot et al., 2004; Talarico and Rubin, 2003). Most likely, it is this vividness, this subjective sense of remembering that makes memory so painful in PTSD.

Blocking the arousal associated with emotional events by a β -adrenergic antagonist shortly after encoding prevents the emotional memory enhancement in healthy subjects (Cahill et al., 1994) and may reduce the risk for PTSD in individuals that have experienced a potentially traumatic event (Pitman et al., 2002). Although these data are promising, their clinical applicability may be limited as these effects are confined to a relatively short window after an event has happened (Ji et al., 2003), during which most people will not receive a clinical treatment. However, if reactivated memories are sensitive to similar manipulations as new memories, β -adrenergic blockade after memory reactivation should affect the reconsolidation of emotional memories and, thus, abolish the emotional memory enhancement a considerable time after the original memory was created. Support for this idea comes from rodent and human studies showing that β -adrenergic blockade during the reactivation of a conditioned fear may reduce the subsequent fear memory (Debiec and LeDoux, 2004; Kindt et al., 2009; Soeter and Kindt, 2011).

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In the present experiment, we hypothesized that the administration of the β -adrenergic antagonist propranolol before memory reactivation would reduce the subjective feeling of remembering associated with emotional episodic memories. We used the ‘remember/know’ procedure to assess the subjective sense of remembering neutral and emotionally arousing episodic memories. Participants were asked to indicate whether a previously presented stimulus evokes specific, vivid memories of its occurrence (‘remembering’) or whether they cannot recollect any specific aspects of its presentation (‘knowing’). According to the dual-process theory of recognition memory (Yonelinas, 2002), ‘remembering’ and ‘knowing’ reflect two distinct processes that engage separable neural networks (Henson et al., 1999; Wheeler and Buckner, 2004). In particular, the amygdala, which processes emotional arousal (Kensinger and Corkin, 2004), is implicated in ‘remembering’ but not in ‘knowing’ emotional stimuli (Sharot et al., 2004).

2. Methods

2.1. Participants and design

In a double-blind, placebo-controlled, between-subjects design, 48 healthy young university students from Montreal (24 men, 24 women; age: $M = 20.98$ years, $SEM = 0.35$ years) were randomly assigned to one of four experimental groups: (i) placebo without reactivation, (ii) placebo with reactivation, (iii) propranolol without reactivation, and (iv) propranolol with reactivation. Participation was limited to those between 18 and 30 years of age, without medication intake, with no reported history of any psychiatric or neurological disorders. Psychology students were excluded from participation in order to avoid any biasing effects of prior knowledge. Participants were debriefed about the purpose of the study at the end of the experiment. This sample is part of a larger neuroimaging project on reconsolidation processes in humans (Schwabe et al., 2012). All participants provided written informed consent in accordance with procedures approved by the Institutional Review Board of the Medical Faculty at McGill University (Reg.-Nr. A04-M46-08A).

2.2. Stimulus material

Stimulus material consisted of 50 neutral and 50 negative pictures taken from the International Affective Picture System (IAPS; Lang et al., 1988) based on their normative arousal (neutral: $M = 3.09$, $SEM = 0.10$; negative: $M = 6.01$, $SEM = 0.10$) and valence scores (neutral: $M = 5.10$, $SEM = 0.05$; negative: $M = 2.31$, $SEM = 0.09$). The IAPS numbers of the used pictures are listed in Appendix A.

The classification of pictures as neutral and negative, respectively, was confirmed by participants’ valence and arousal ratings, which were given on a scale from 0 (“not at all positive/arousing”) to 100 (“very positive/arousing”) at the end of the experiment: negative pictures (arousal ($M \pm SEM$): 67.43 ± 1.35 ; valence: 21.12 ± 7.96) were experienced as significantly more arousing and less positive than neutral pictures (arousal: 30.17 ± 2.34 ; valence: 52.39 ± 0.57 ; both $t(47) > 13.81$, both $p < .001$, both $d > 3.98$).

2.3. Procedure

Participants were tested on three consecutive days, 24 h apart: day 1, learning; day 2, pill intake and memory reactivation; and day 3, recognition testing (Fig. 1). On day 1, participants saw 25 neutral and 25 negative pictures in randomized order on a computer screen, each picture for 2 s. After picture presentation, we gave

an immediate free recall test to control for possible group differences in picture encoding.

The procedure on day 2 differed for the four experimental groups. Depending on the group, participants received a placebo pill or the β -adrenergic antagonist propranolol (40 mg). Heart rate measurements were taken to verify the action of the drug. Sixty minutes after pill intake, participants in the reactivation groups were reminded of the pictures they had seen the day before. They were asked to concentrate on these pictures and to try to remember them in as much detail as possible. Specifically, participants received the following instruction: “Do you remember the pictures that you saw yesterday? – Please try to remember the neutral and negative pictures you saw in the slideshow yesterday. Try to recall all the pictures that you saw yesterday in as much detail as possible! We will ask you questions about the pictures later on.” This reactivation procedure is similar to those used in earlier studies showing that a subtle reminder is sufficient to trigger reconsolidation processes in episodic memory (Hupbach et al., 2007, 2009). Participants in the no-reactivation groups were just reading newspapers after pill intake (as were participants in the reactivation conditions until reactivation); they did not receive a reminder. In addition, these groups were tested in a different experimental room on day 2 than on day 1 to avoid spontaneous memory reactivation by the learning context (Hupbach et al., 2008). The 60-min interval between pill intake and reactivation was chosen to ensure that propranolol reaches peak levels at about 30 min after reactivation (Gilman and Goodman, 1996; Paterson et al., 1970), when reconsolidation is supposed to take place (Nader and Hardt, 2009).

On day 3, all participants completed a recognition memory test in which they were presented the 50 pictures they had seen on day 1 and 50 new IAPS pictures (25 neutral, 25 negative) that were matched for complexity and semantic category. Participants were instructed to decide whether they confidently recognized a picture as having been presented during encoding on day 1 (‘old’) or whether it was ‘new’. In line with the two-step instruction suggested by previous studies (Eldridge et al., 2002, 2005; Otten, 2006), participants were then asked to indicate for each recognized picture if they consciously recollected, i.e., ‘remembered’, its occurrence on day 1 or if they simply ‘knew’ that the picture was presented on day 1 because it felt familiar.

3. Results

In line with previous studies showing that emotion enhances memory encoding (Dolcos et al., 2004; Kensinger and Schacter, 2006), participants recalled significantly more negative pictures ($M \pm SEM$: 15.06 ± 0.48 pictures) than neutral pictures (10.40 ± 0.47 pictures) in the immediate free recall test on day 1 ($F(1,44) = 131.48$, $p < .001$, $\eta^2 = 0.75$). There were no group differences in immediate free recall performance ($F(1,44) < 1$, $p = .85$), suggesting that groups did not differ in picture encoding.

The time a memory takes to reconsolidate is shorter than for consolidation (Nader, 2003). Therefore, in order to maximize the chances of detecting an effect on reconsolidation with propranolol, we administered propranolol at a time prior to reactivation on day 2. Significant decreases in heart rate after pill intake on day 2 verified the action of propranolol (drug \times time point of measurement interaction: $F(1,44) = 10.23$, $p < .01$, $\eta^2 = 0.19$). As shown in Table 1, groups did not differ before pill intake ($p = .47$), yet participants that were administered propranolol had significantly lower heart rate than participants in the placebo groups 60 min after pill intake

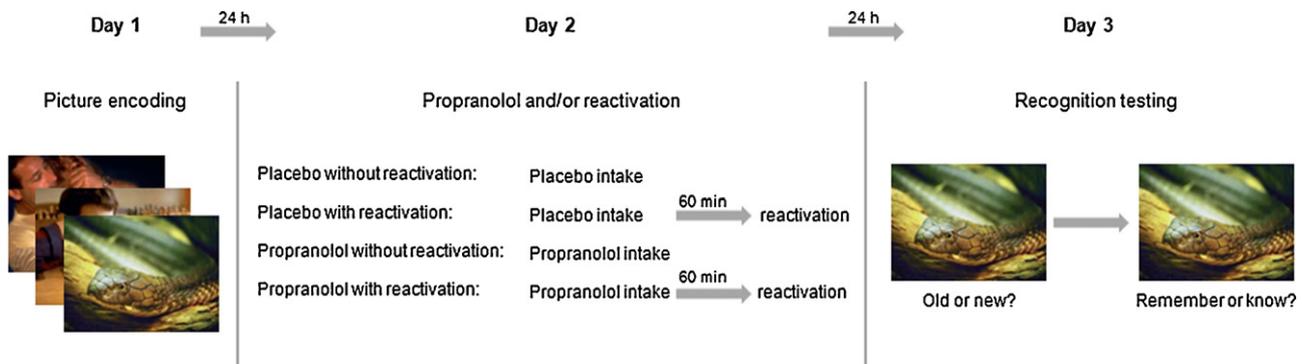


Fig. 1. Illustration of the experimental procedure.

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