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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.

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 details 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 × 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

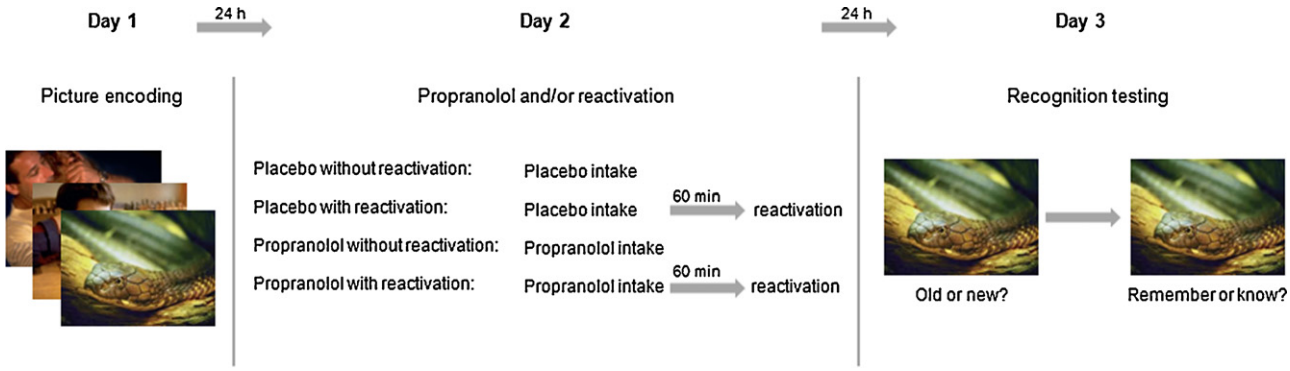

Fig. 1. Illustration of the experimental procedure.

Table 1
Heart rate data at baseline, 60 min after pill intake, and on day 3 before recognition testing.

	Baseline	60 min after pill intake	Day 3
Placebo without reactivation	77.37 ± 2.83	72.50 ± 2.17	74.42 ± 1.96
Placebo with reactivation	78.13 ± 4.57	69.54 ± 3.33	78.83 ± 5.16
Propranolol without reactivation	72.58 ± 3.65	61.08 ± 2.68*	72.79 ± 3.20
Propranolol with reactivation	78.75 ± 3.59	62.08 ± 3.17*	77.92 ± 3.07

Data represent means ± SEM.
* Significantly lower heart rate compared to the placebo groups ($p < .05$).

($F(1,44) = 10.81$, $p < .01$, $\eta^2 = 0.20$). None of our participants showed any signs of negative side effects of the drug.

Propranolol administration before reactivation led to altered memory performance 24 h later (i.e., on day 3), when the drug was not active any more ($p = .59$; Table 1). Whereas participants in the placebo with reactivation, placebo without reactivation, and propranolol without reactivation groups showed better memory (expressed as hit rate minus false alarm rate) for negative compared to neutral pictures (all $p < .005$), this emotional memory enhancement disappeared in participants that had received propranolol before reactivation ($p = .53$, Fig. 2A–D). A drug (placebo vs. propranolol) × reactivation (no-reactivation vs. reactivation) × emotionality (neutral vs. negative) ANOVA and follow-up ANOVAs for neutral and negative pictures revealed that propranolol before reactivation affected specifically the memory for negative pictures (drug × reactivation interaction for negative pictures: $F(1,44) = 4.99$, $p < .05$, $\eta^2 = 0.10$), whereas memory for neutral pictures remained unaffected (drug × reactivation interaction for neutral pictures: $F(1,44) = 0.15$, $p = .70$; drug × reactivation × emotionality interaction: $F(1,44) = 3.67$, $p = .06$, $\eta^2 = 0.08$). As shown in Table 1, the differences in memory accuracy were mainly due to group differences in the percentage of hits. False alarms for negative and neutral pictures were not differentially affected by the drug and/or reactivation (all $p > .23$).

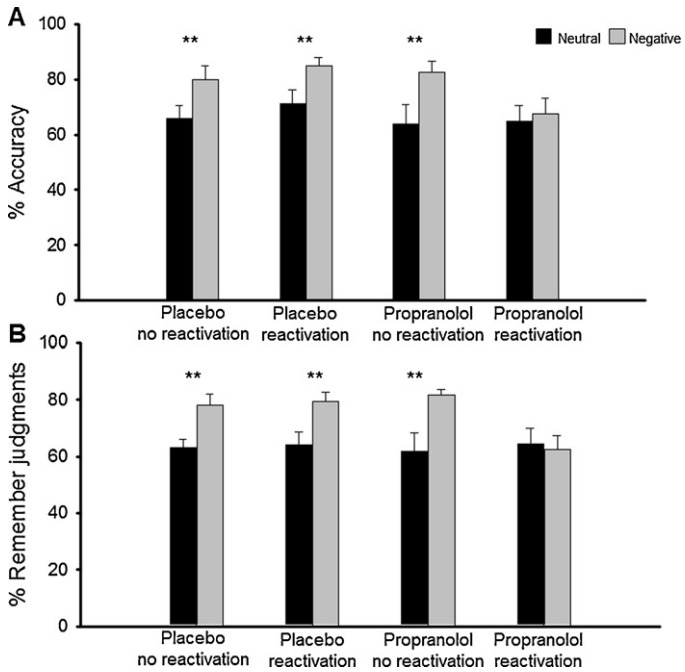

Fig. 2. Influence of reactivation and propranolol on subsequent memory. (A) Recognition performance expressed as percent accuracy (i.e., hit rate – false alarm rate) and (B) subjective feeling of remembering expressed as percent of 'remember' judgments for correctly recognized pictures in the placebo without reactivation, placebo with reactivation, propranolol without reactivation, and propranolol with reactivation groups. Propranolol before memory reactivation on day 2 abolished the emotional memory enhancement and reduced the subjective feeling of remembering for correctly recognized negative pictures on day 3. **$p < .01$. Data represent means ± SEM.

Most importantly, however, propranolol before reactivation altered the nature of remembering (Fig. 2E–H). As expected, participants in the placebo without reactivation group gave significantly more 'remember' judgments for correctly recognized negative pictures than for correctly recognized neutral pictures ($t(11) = 6.08$, $p < .001$, $d = 2.48$), i.e., they remembered the negative pictures more vividly and in more detail. The same was found in the placebo with reactivation group and the propranolol without reactivation group (both $t(11)$, both $p < .01$, both $d > 1.36$), suggesting that memory reactivation per se or propranolol without reactivation did not change the nature of remembering. However, for participants in the propranolol with reactivation group there was no difference in the number of 'remember' judgments associated with neutral and negative pictures ($p = .57$). Compared to the other three groups, 'remember' judgments for correctly recognized negative pictures were reduced by about 25 percent in the participants that had received propranolol before memory reactivation on day 2 (drug × reactivation interaction for negative pictures: $F(1,44) = 8.04$, $p < .01$, $\eta^2 = 0.15$; LSD post hoc tests, all $p < .02$). Again, a drug × reactivation × emotionality ANOVA showed that the effect of propranolol before reactivation was specific for negative pictures (drug × reactivation × emotionality interaction: $F(1,44) = 7.06$, $p = .01$, $\eta^2 = 0.14$); 'remember' judgments for correctly recognized neutral pictures were not affected by propranolol before reactivation (drug × reactivation interaction for neutral pictures: $F(1,44) < 1$, $p = .89$).

Because 'remember' and 'know' responses are complementary, we obtained exactly the opposite pattern of results for 'know' than for 'remember' responses (response type × drug × reactivation × emotionality interaction: $F(1,44) = 6.84$, $p = .012$, $\eta^2 = .14$; see Table 2). In contrast to the other three groups who gave more 'know' judgments for correctly recognized neutral pictures than for correctly recognized negative pictures (all $p \leq .01$), for the propranolol with reactivation group there was no difference in the number of 'know' judgments associated with neutral and negative pictures ($p = .14$). Moreover, participants that had received propranolol before reactivation gave significantly more 'know' responses for negative pictures than participants of the other three groups (drug × reactivation interaction for negative pictures: $F(1,44) = 7.52$, $p < .01$, $\eta^2 = 0.15$; LSD post hoc tests, all $p < .01$). For neutral pictures, there was no influence of propranolol and reactivation on 'know' judgments (drug × reactivation interaction for neutral pictures: $F(1,44) < 1$, $p = .97$; drug × reactivation × emotionality interaction: $F(1,44) = 6.11$, $p = .017$, $\eta^2 = 0.12$).

4. Discussion

Overall, our results indicate that β-adrenergic blockade after memory reactivation abolished the superior memory for emotional material. Administration of the β-adrenergic antagonist propranolol before memory reactivation reduced specifically the memory accuracy for and the subjective sense of remembering associated with emotional pictures; memory for neutral material was not

Table 2
Accuracies, hit and false alarm rates as well as remember and know judgments in the recognition test on day 3.

	Placebo without reactivation	Placebo with reactivation	Propranolol without reactivation	Propranolol with reactivation
Accuracy (%)				
Neutral	66.0 ± 4.4	71.3 ± 5.0	64.0 ± 7.0	65.0 ± 5.4
Negative	80.0 ± 5.0	85.0 ± 3.0	82.7 ± 4.0	67.7 ± 5.5*
Hits (%)				
Neutral	81.0 ± 3.6	80.0 ± 4.4	82.3 ± 4.9	82.0 ± 3.2
Negative	92.0 ± 2.3	90.7 ± 2.0	92.3 ± 2.3	82.5 ± 2.7*
False alarms (%)				
Neutral	15.0 ± 3.3	8.7 ± 1.9	18.3 ± 3.3	17.0 ± 3.9
Negative	12.0 ± 3.1	5.7 ± 2.0	9.7 ± 2.5	14.8 ± 3.2
Remember (%)				
Neutral	62.9 ± 3.1	64.2 ± 4.5	61.8 ± 6.8	64.3 ± 5.8
Negative	78.3 ± 3.7	79.4 ± 3.3	81.7 ± 2.0	62.5 ± 4.8*
Know (%)				
Neutral	37.1 ± 3.8	35.7 ± 4.3	38.2 ± 6.5	35.7 ± 4.2
Negative	21.8 ± 3.1	19.9 ± 3.5	18.2 ± 1.8	37.5 ± 5.1*

Data represent means ± SEM.
* $p < .05$ (compared to the three other groups).

affected by propranolol. Propranolol alone or memory reactivation without propranolol did not alter emotional memory, suggesting that propranolol disrupted the reconsolidation of emotional episodic memories.

Both, the enhanced accuracy and the increased feeling of remembering that are usually associated with emotionally arousing stimuli are mediated by the amygdala (Cahill et al., 1996; Sharot et al., 2004). According to the memory modulation hypothesis (McGaugh, 2000), emotional arousal-induced noradrenergic activity in the amygdala modulates memory processes in other brain areas such as the hippocampus or the prefrontal cortex. Our results suggest that noradrenergic arousal in the amygdala is not only required for the initial formation of lasting and vivid memories of emotional events but also for the re-stabilization of emotional memories after their reactivation. If the noradrenergic arousal is blocked during reactivation, the amygdala cannot exert its modulatory influence anymore and emotional memories are restored (i.e., reconsolidated) in the same manner as neutral ones.

Previous studies showed that propranolol may block the reconsolidation of conditioned fear memories (Debiec and LeDoux, 2004; Kindt et al., 2009). Our data are in line with these studies but extend them in several ways. We show here for the first time that β-adrenergic blockade during reconsolidation may change the feeling of remembering, i.e., the subjective quality of memory. Interestingly, there is evidence that it is this subjective quality of memory, the vividness of recollection that distinguishes traumatic memories with PTSD from those without PTSD (Berntsen et al., 2003). Moreover, whereas the only studies that showed an effect of propranolol on reconsolidation in humans used amygdala-dependent cue conditioning (Kindt et al., 2009; Soeter and Kindt, 2011) and other studies demonstrated that new learning may alter the reconsolidation of episodic memories (Forcato et al., 2010; Hupbach et al., 2007; Schwabe and Wolf, 2009), this study shows an effect of β-adrenergic blockade on the reconsolidation of hippocampus-dependent episodic memories in humans. One should note that our results are not in conflict with the previous finding that propranolol before fear memory reactivation did not affect the explicit memory for the contingency between unconditioned and conditioned stimulus (Kindt et al., 2009). We do not argue here that propranolol before reactivation impairs episodic memory per se but that it blocks the modulatory influence of the amygdala on the reconsolidation of emotional episodic memories.

An alternative explanation for our results is that propranolol reduced the retrieval (i.e. reactivation) rather than the reconsolidation of emotional memories on experimental day 2 (Kroes et al., 2010). We consider this possibility less likely because we administered propranolol 60 min before memory reactivation so that peak levels were reached 30 min *after* reactivation (Gilman and Goodman, 1996; Paterson et al., 1970), i.e., during the reconsolidation window (Nader and Hardt, 2009). Nevertheless, our heart rate data indicated that propranolol was already active during reactivation. Therefore, effects on memory reactivation cannot be completely ruled out. However, even if propranolol affected the reactivation of emotional memories, the reactivation-dependent effect of propranolol on emotional memory was lasting. It became apparent in the recognition test 24 h after reactivation, when the drug was not active anymore. Thus, β-adrenergic blockade during and/or after reactivation has most likely changed the reconsolidation of the reactivated emotional memories, possibly in combination with impairing effects on secondary encoding processes (Nadel and Moscovitch, 1997).

Same as earlier studies on episodic memory reconsolidation (Hupbach et al., 2007, 2009), we did not quantify the memory reactivation on day 2. Although this might be considered a limitation of the present study, it is important to note that the lack of a behavioral quantification of reactivation, does not question our interpretation because none of the potential outcomes, i.e., comparable, enhanced or impaired reactivation in the propranolol group relative to the placebo group, would be in conflict with our argumentation. Comparable memory reactivation in the placebo and propranolol groups would be the expected scenario that would obviously not question the conclusion that propranolol affected the reconsolidation of the emotional episodic memories. If memory reactivation was enhanced in the propranolol group this would speak for an even stronger reconsolidation effect which could turn a stronger memory on day 2 into a weaker memory on the following day. If memory reactivation was reduced in the propranolol group this would still not question our conclusion because the participants that did not at all reactivate the memories on day 2 had better memory on day 3 than the propranolol with reactivation group.

Another limitation of the present study might be seen in the fact that we gave different memory tests on day 1 and day 3, thus making a direct comparison of memory performance on day 1 and day 3 difficult. We used a free recall test, instead of a recognition test, on Day 1 because a recognition test would have been another learning trial in which the presentation of 'lures' (i.e., new pictures) could have interfered with the original memory. Moreover, it is to be noted, however, that memory performance on day 1 was just a control for potential encoding differences between groups and that we did not intend to compare memory performance between day 1 and day 3 but group differences in memory on day 3.

In sum, our data show that the administration of a β-adrenergic antagonist before memory reactivation abolished the superior memory for and the vivid recollection of emotionally arousing stimuli. We suggest that these results are related to a blockade of modulatory influences of arousal-related amygdala activity on the reconsolidation of emotional memories. Overly strong emotional (traumatic) memories are the pathological hallmark of PTSD and these strong memories have been attributed to the action of hormones and neurotransmitters that are released during the traumatic experience on memory formation. Our findings support recent attempts to treat such traumatic memories with β-adrenergic antagonists at the time of their controlled reactivation (Brunet et al., 2008) and indicate that such treatment may not only reduce the accuracy but also the distressing vividness of these memories.

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Appendix A.

IAPS numbers of pictures presented on day 1 and/or day 3.
Set 1

Neutral	Negative
2191	1052
2214	1111
2396	1300
2487	2095
2495	2703
2620	3000
2840	3015
2870	3016
6150	3100
7000	3120
7002	3140
7004	3170
7020	3180
7031	3266
7037	3550
7055	6212
7056	6313
7090	6350
7140	6560
7207	8230
7217	9040
7503	9120
7547	9425
7590	9430
7705	9911

Set 2

Neutral	Negative
2215	1040
2514	1220
2570	2205
2850	2800
2880	3010
2890	3030
7006	3060
7010	3101
7025	3150
7035	3160
7039	3225
7053	3350
7059	3500
7130	6210
7175	6243
7185	6540
7190	6570
7205	6940
7491	9265
7500	9300
7504	9410
7560	9428
7595	9435
7620	9452
8311	9570

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