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### How to cite

RIMMELE, Ulrike et al. Beta-adrenergic Blockade at Memory Encoding, but Not Retrieval, Decreases the Subjective Sense of Recollection. In: Journal of cognitive neuroscience, 2016, vol. 28, n° 6, p. 895–907. doi: 10.1162/jocn\_a\_00941

This publication URL: <https://archive-ouverte.unige.ch/unige:93446>

Publication DOI: [10.1162/jocn\\_a\\_00941](https://doi.org/10.1162/jocn_a_00941)

# Beta-adrenergic Blockade at Memory Encoding, but Not Retrieval, Decreases the Subjective Sense of Recollection

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## Abstract

■ Humans remember emotional events not only better but also exhibit a qualitatively distinct recollective experience—that is, emotion intensifies the subjective vividness of the memory, the sense of reliving the event, and confidence in the accuracy of the memory [Phelps, E. A., & Sharot, T. How (and why) emotion enhances the subjective sense of recollection. *Current Directions in Psychological Science*, 17, 147–152, 2008]. Although it has been demonstrated that activation of the beta-adrenergic system, linked to increases in stress hormone levels and physiological arousal, mediates enhanced emotional memory accuracy, the mechanism underlying the increased subjective sense of recollection is unknown. Behavioral evidence suggests

that increased arousal associated with emotional events, either at encoding or retrieval, underlies their increased subjective sense of recollection. Using a double-blind, placebo-controlled, within-subject design, we showed that reducing arousal at encoding through oral intake of 80-mg of the beta-adrenergic receptor antagonist propranolol decreases the subjective sense of recollection for both negative and neutral stimuli 24 hr later. In contrast, administration of propranolol before memory retrieval did not alter the subjective sense of recollection. These results suggest that the neurohormonal changes underlying increased arousal at the time of memory formation, rather than the time of memory retrieval, modulate the subjective sense of recollection. ■

## INTRODUCTION

Emotion enhances memory accuracy but affects the subjective sense of recollection even more (Phelps & Sharot, 2008). Laboratory studies demonstrate that emotional stimuli are not only remembered better but with an enhanced subjective sense of recollection rather than a feeling of familiarity (Rimmele, Davachi, & Phelps, 2012; Rimmele, Davachi, Petrov, Dougal, & Phelps, 2011; Sharot, Delgado, & Phelps, 2004; Kensinger & Corkin, 2003; Ochsner, 2000). Similarly, emotional real-life events are reexperienced with a greater sense of recollection, vividness, and confidence (Sharot, Martorella, Delgado, & Phelps, 2007; Talarico & Rubin, 2003; Neisser et al., 1996). However, although the enhanced memory accuracy for emotional events has been ascribed to arousal-induced alterations in hormone levels (McGaugh, 2000), the mechanisms underlying the enhanced subjective sense of recollection for emotional stimuli are less understood.

Arousal experienced during the exposure to an emotional event leads to the release of norepinephrine and epinephrine. These hormones influence amygdala function, which modulates the hippocampus during both encoding and consolidation, thus leading to improved

memory for emotional stimuli. This memory modulation hypothesis is supported by findings from pharmacological studies in animals and humans (Murty, Ritchey, Adcock, & LaBar, 2010; Phelps, 2004; McGaugh, 2000, 2002). For example, memory enhancement for emotional stimuli is blocked when propranolol, a beta-adrenergic receptor antagonist that reduces physiological arousal, is administered before encoding (Maheu, Joobers, Beaulieu, & Lupien, 2004; van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998; Cahill, Prins, Weber, & McGaugh, 1994).

Similarly, if propranolol is administered after learning, memory consolidation is less effective (Barseganyan, McGaugh, & Roozendaal, 2014; Roozendaal, Castello, Vedana, Barseganyan, & McGaugh, 2008; Tronel, Feenstra, & Sara, 2004; Sara, Roullet, & Przybyslawski, 1999). In contrast, activation of beta-adrenergic receptors during consolidation helps memory formation (Barseganyan et al., 2014; Roozendaal et al., 2008). These findings suggest that physiological arousal plays a modulatory role in memory formation and later remembering (Phelps, 2006; Dolcos, LaBar, & Cabeza, 2004) via involvement of beta-adrenergic receptors.

Using stimuli that enhance both physiological and subjective arousal (Bradley, Greenwald, Petry, & Lang, 1992), behavioral studies point to the possibility that arousal may not only modulate memory strength but also the subjective sense of recollection. For example, the degree of emotional arousal has been related to memory

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vividness (Reisberg, Heuer, MacLean, & O'Shaughnessy, 1988) and the subjective sense of recollection (Kensinger & Corkin, 2003; Ochsner, 2000). In laboratory studies, the subjective sense of recollection and familiarity have been examined with the remember/know paradigm, in which participants are instructed to provide either a "remember" judgment when the stimulus brings to mind a vivid memory accompanied by details of the encoding episode (i.e., recollection) or a "know" response indicating that the stimulus was recognized, but that the memory is not accompanied by episodic details (i.e., often referred to as item familiarity; Yonelinas, 2002; Rajaram, 1993; Tulving, 1985). Using the remember/know paradigm, Ochsner (2000) found that the subjective experience of recollection is greater for high than medium arousing stimuli and, in turn, greater for medium than low arousing stimuli. This finding was replicated in another study that showed that high arousing negative stimuli (e.g., taboo words) were attributed a higher subjective sense of recollection compared with low arousing negative stimuli (Kensinger & Corkin, 2003).

Two possible mechanisms may underlie modulation of the subjective sense of recollection by arousal. One possibility is that increased arousal at encoding or during consolidation facilitates memory encoding processes and subsequent consolidation. It has been shown that memory for contextual details can drive the subjective recollective experience (Johnson & Raye, 1981). At encoding, arousal may increase attention (Anderson & Phelps, 2001) and perception (Phelps, Ling, & Carrasco, 2006) to the emotional stimulus, resulting in a memory representation that is richer in detail, leading to an increase in the subjective sense of recollection. Additional behavioral evidence points to the possibility that arousal modulates consolidation, and this possibly leads to a heightened subjective sense of recollection. For example, neutral pictures that are encoded in an emotionally arousing versus a neutral context are given more remember responses when retrieved (Anderson, Wais, & Gabrieli, 2006). Furthermore, emotional stimuli that are consolidated for 24 hr versus 5 min after learning are remembered with a heightened subjective sense of recollection (Sharot, Verfaellie, & Yonelinas, 2007).

Another possibility is that emotional arousal may change memory retrieval processes. When emotional versus neutral memories are retrieved, the arousal experienced at encoding is reinstated during retrieval in the brain, notably in the amygdala and the noradrenergic nucleus locus coeruleus (Sterpenich et al., 2006). Sharot et al. (2004) suggested that arousal signals and heightened perceptual fluency at retrieval contribute to the enhanced subjective sense of recollection via activation of the amygdala. In this instance, participants experience memories of emotional stimuli with a heightened subjective sense of recollection, irrespective of memory accuracy. Along with increasing perceptual fluency, arousal at retrieval may lead a person to increase the effort to recall or reconstruct an event.

Thereby, the memory of the affect itself may change the mnemonic reconstruction process (Reisberg et al., 1988). Similarly, an arousal response to an emotional stimulus during a recognition test and its influence on attention and perception may lead participants to believe that they are retrieving a vivid memory, independent of any actual mnemonic signal. Previous studies have demonstrated higher false alarm rates, in particular more "remember" false alarm rates for new emotional stimuli (Kapucu, Rotello, Ready, & Seidl, 2008; Dougal, Phelps, & Davachi, 2007; Windmann & Kutas, 2001), suggesting that arousal signals, by themselves, may have some impact on memory judgments. On the neural level, emotion may modulate memory retrieval by enhancing the ability to distinguish between recollection and familiarity through arousal-mediated alterations of activity in brain regions that dissociate recollection and familiarity, for example, hippocampus (Dolcos, LaBar, & Cabeza, 2005).

To understand whether arousal modulates the subjective sense of recollection at encoding or retrieval, this study manipulates physiological arousal by administering 80 mg of propranolol either 90 min before encoding or 90 min before recognition. Consistent with previous studies, we expect that propranolol will reduce physiological arousal as indicated by decreases in heart rate and blood pressure (Cahill et al., 1994). When administered before encoding, propranolol should counteract any arousal-mediated effect on attention and perception at encoding and/or arousal-modulated consolidation processes that may contribute to the subjective sense of recollection. When administered before retrieval, it is expected that propranolol will counteract potential arousal responses to emotional stimuli that may be biasing subjective judgments of recollection.

In addition, we assessed memory for detail (color of frame around image during encoding) to examine how the subjective sense of recollection is related to objective memory for details under propranolol versus placebo. For neutral stimuli, the subjective sense of recollection is accompanied by recollection of a variety of contextual details (Gardiner, Ramponi, & Richardson-Klavehn, 1998; Perfect, Mayes, Downes, & Van Eijk, 1996). In previous studies, we found a dissociation between the subjective sense of recollection and memory for details for emotional versus neutral stimuli. Although "remember" judgments were boosted for negative relative to neutral scenes, "remember" responses for negative versus neutral scenes were less often accompanied by correct memory for some contextual details (Rimmele et al., 2011). Arousal may underlie this effect (Mather, 2007), for example, by impairing binding of the contextual detail to the emotional stimulus during encoding. Consequentially, lowering arousal through administration of propranolol before encoding could abolish the previously found dissociation and result in the same proportion of remember responses for emotional and neutral scenes with correct memory for contextual details.

## METHODS

### Participants

The study sample consisted of 32 healthy participants ( $M = 25.72$ ,  $SE = 0.97$  years, 16 women) recruited from advertisements in the university and general community. All participants provided written informed consent and were paid for their participation. The study was approved by the institutional review board of the Nathan Kline Institute (NKI). Participants were randomly assigned to one of two groups: one group ( $n = 17$ ) received 80 mg propranolol at one of the two learning sessions, and the other group received propranolol ( $n = 15$ ) at one of the two memory retrieval sessions. Age and body mass indices were not different among groups ( $p > .47$ ).

Before participation, all participants underwent a physical examination. To be included in the study, participants were required to be between 18 and 40 years old, have a resting heart rate of at least 55 beats per minute, a systolic blood pressure in the range of 90–160, and a diastolic blood pressure in the range of 60–100. Participants were further required to have clinically normal electrocardiograms. In addition, participants had no evidence of a current diagnosis of psychiatric disorders, any medical condition, or any findings that might increase medical risk associated with participation in the testing procedures, including the administration of propranolol.

Two male participants, both from the group that received propranolol at encoding, were excluded from data analysis because of very poor memory performance in the placebo condition (miss or false alarm rate over 2.5 standard deviations from the mean of all participants in the placebo condition; leaving  $n = 15$  in the group that received propranolol at encoding). Four participants had a 48-hr instead of 24-hr delay between the learning

session and retrieval session in the placebo condition. Exclusion of these participants did not change any effects, therefore they were included in the analyses.

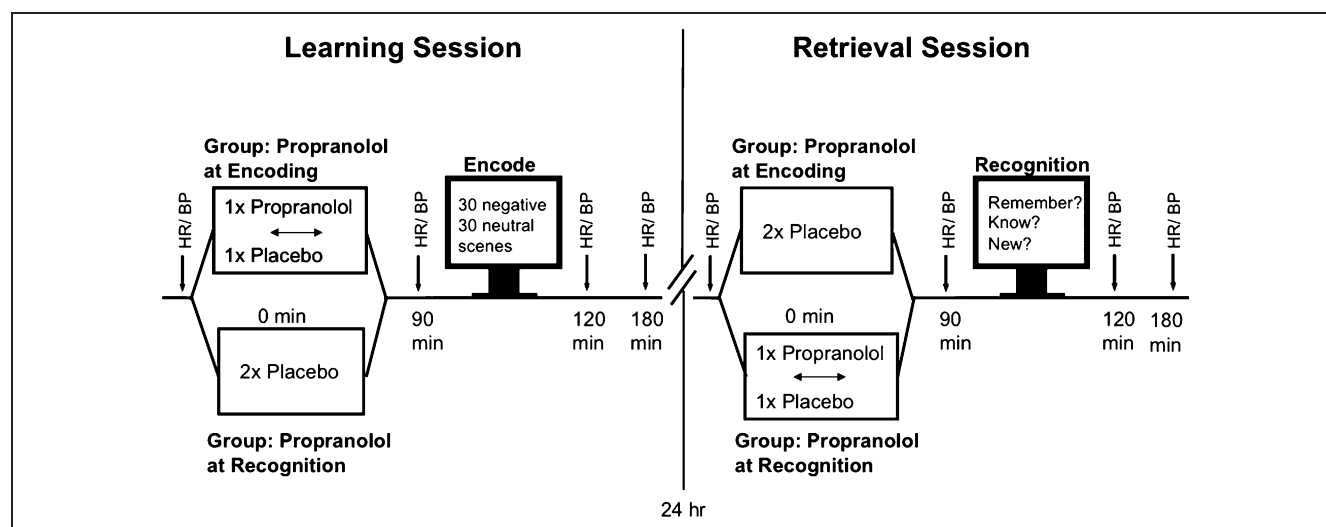
### Stimuli

We divided 240 scenes from the International Affective Picture Set based on their normative ratings provided for emotional arousal and valence (Lang, 1999) into an emotional (arousal:  $M = 5.71$ ,  $SD = 0.74$ , valence:  $M = 2.67$ ,  $SD = 0.83$ ) and a neutral stimulus set (arousal:  $M = 3.81$ ,  $SD = 0.89$ , valence:  $M = 5.78$ ,  $SD = 0.99$ ). During each of the two encoding sessions, 60 scenes (30 neutral, 30 negative) were presented. At each of the test sessions, the studied scenes were intermixed with a set of 60 novel scenes (30 neutral, 30 negative). The scene sets presented at the encoding and testing sessions were counter-balanced across participants and placebo/propranolol condition. For both the emotional and neutral scene sets, approximately two thirds depicted humans, whereas the remaining one third depicted animals and inanimate scenes to an equal degree.

Each scene was presented inside a colored frame (either yellow, red, blue, or green). Colors were counter-balanced across neutral and negative scenes and across the sets for encoding and test. The framed stimuli were shown on a 15-in. computer monitor, scaled to screen size.

### Design and Procedure

A randomized, placebo-controlled, double-blind, within-subject, cross-over design was used (Figure 1). Each participant was tested in two conditions (propranolol vs. placebo) with the treatment order balanced across participants.



**Figure 1.** Each participant was assigned to one of two groups (80 mg propranolol at encoding vs. 80 mg propranolol at recognition) and then tested in two conditions (propranolol vs. placebo) with the treatment order balanced across participants. Each condition included a learning session followed 24 hr later by a retrieval session. After a washout period of a minimum of 7 days, the learning and retrieval sessions were repeated with the same participant with another set of scenes, this time with participants receiving the treatment they had not received the first time. To control for a decrease in physiological arousal after propranolol, heart rate (HR) and blood pressure (BP) were assessed four times during each session.

The two conditions for a participant were separated by an interval of at least 7 days. Each condition included a learning session followed 24 hr later by a retrieval session. In the learning session, participants were presented emotional and neutral scenes. In the retrieval session, participants carried out a surprise memory test that assessed (1) recognition and subjective recollection for the presented scenes and (2) recognition of the frame color for correctly recognized scenes. Half of the participants ( $n = 15$ ) received propranolol (80 mg) at one of the learning sessions and placebo at the other learning session and the two retrieval sessions; half of the participants ( $n = 15$ ) received propranolol at one retrieval session and placebo at the other retrieval session and the two learning sessions. Learning and retrieval took place between 90 and 120 min after medication or placebo administration, respectively, when propranolol has been shown to be at peak levels and affect memory processes (Maheu et al., 2004). After a washout period of a minimum of 7 days, the procedure was repeated with the same participant with another set of scenes, this time with participants receiving the treatment they had not received the first time. Participants were instructed to refrain from intense physical exercise and food and drink other than water for 3 hr before medication or placebo administration. Every pill was administered with a granola bar. The participants and the research team conducting the experiment were blind to whether placebo or propranolol was administered.

### *Physiological Measures*

Autonomic responses to propranolol were assessed by measures of heart rate and blood pressure obtained and monitored by medical and nursing staff at NKI not involved in other study procedures, so as to maintain blinding. These measures were obtained immediately before propranolol/placebo administration and 90, 120, and 180 min after administration of propranolol/placebo. At the end of each session, participants were asked to indicate whether they thought that they had received propranolol or placebo during this session.

### *Memory Testing*

In the learning session, participants encoded 30 emotional and 30 neutral scenes. Each trial consisted of a 6000-msec presentation of a scene surrounded by a colored frame. For each trial, participants were instructed to judge whether the frame color appeared in the scene or not by pressing one of two response keys. After each scene presentation, a white fixation cross was shown for 2000 msec. The stimuli were presented pseudorandomly in three blocks of 20 scenes with no more than three consecutive negative or neutral scenes. A practice version of the task was administered to each participant

before the actual experimental procedure to ensure that he or she understood the task.

In the retrieval session, which took place 24 hr after encoding session, a self-paced memory test was administered to assess the subjective sense of recollection for scenes and memory for frame color.

**Scene recognition.** For each scene, the subjective experience of recollection was assessed by asking for remember/know (R/K) judgments. Before the recognition test, participants were trained to make R/K judgments (Rajaram, 1993). In short, participants were asked to respond R when they could recollect any aspect of the study time, K if they knew that the scene was previously presented but they could not recollect it, and N if the scene was never seen. After reading the detailed instructions, participants explained the meaning of R and K judgments in their own words. During the practice trials, participants indicated why they provided R or K responses to a scene. The recognition test was administered once it was determined that the participant correctly understood the instructions, that is, they gave an R judgment to a scene when it brought back to mind a specific detail from the episodic context in which the scene had been experienced, such as a sensory detail, a thought, or a feeling.

During the recognition test, the 60 previously presented scenes were shown again, without the frame color, randomly intermixed with an equal number of novel scenes. For each scene, participants had to make an R/K/N judgment of their recognition memory. Each scene was presented for 2000 msec. Scenes were presented pseudorandomly in six blocks of 20 scenes each with no more than three consecutive negative or neutral scenes.

**Frame color recognition.** For each scene that was given an R or K response, participants had to choose the frame color (out of the four) that had surrounded the scene during the study or indicate that they did not know the frame color (this option was given to minimize guessing). The four color options and the "I don't know" option appeared underneath the scene, labeled numerically (1–5) to indicate the corresponding keystroke.

### **Data Analysis**

First, the effect of propranolol on raw R and K scores as well as on corrected recognition scores ( $R_{\text{hit rate}} - R_{\text{false alarm rate}}$  and  $K_{\text{hit rate}} - K_{\text{false alarm rate}}$ ) was analyzed. Then recollection and familiarity scores were computed according to the model of Yonelinas (2001; Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998). In particular, the subjective sense of recollection was computed by subtracting  $R_{\text{false alarm rate}}$  from  $R_{\text{hit rate}}$ , and then dividing by the proportion that a participant could have given a correct R response ( $1 - R_{\text{false alarm rate}}$ ). Familiarity ( $Fd'$ )



was computed in two steps. First the probability of correctly responding  $K$  to an old item ( $F_{old}$ ) and the probability of incorrectly responding  $K$  to a new item ( $F_{new}$ ) were calculated. Second, these two values ( $F_{old}$  and  $F_{new}$ ) were used to calculate  $Fd'$  using  $d'$  tables. Thereby,  $F_{old}$  and  $F_{new}$  take into account that a  $K$  response can be given only when an item is familiar but not recollected, that is,  $F_{old} = K_{old}/(1 - R_{old})$  and  $F_{new} = K_{new}/(1 - R_{new})$ . All memory variables were analyzed with a 2 (emotion/neutral)  $\times$  2 (propranolol/placebo)  $\times$  2 (group: propranolol at encoding group/propranolol at retrieval) mixed-design ANOVAs. Analyses for heart rate, blood pressure, and subjective arousal included time as an additional factor representing the different time points of measurements during the sessions. Significant ANOVA effects were further investigated with follow-up ANOVAs within each group and pairwise contrasts using  $t$  tests. An alpha level of .05 was used for all statistical tests.

## RESULTS

### Heart Rate, Blood Pressure, and Subjective Arousal

Propranolol effectively lowered heart rate and systolic blood pressure (Figure 2). Although baseline levels at the beginning of the sessions did not differ between the placebo and the propranolol condition ( $p > .12$  for all comparisons), heart rate and blood pressure significantly decreased after propranolol administration, at the time of both encoding or retrieval testing (90–120 min after medication administration; heart rate:  $F(1, 28) = 42.84, p < .001$  for Propranolol/placebo main effect;  $F(3, 84) = 14.21; p < .001$  for Propranolol/placebo  $\times$  Time interaction; systolic blood pressure:  $F(1, 28) = 27.68, p < .001$  for Propranolol/placebo main effect;  $F(3, 84) = 5.55; p < .01$  for Propranolol/placebo  $\times$  Time interaction). In addition, propranolol lowered diastolic systolic blood pressure ( $F(1, 28) = 4.63, p < .05$ , for Propranolol main effect). Heart rate and blood pressure were similarly affected by propranolol in both groups (all  $ps > .12$ ). Heart rate and blood pressure did not differ between the three sessions, during which placebo was administered (all  $ps > .10$ ).

Participants were not able to correctly identify whether they had received an active agent or placebo between the session during which they received propranolol and its respective placebo session ( $\chi^2$  test;  $p > .10$ ).

### Encoding

Propranolol did not affect RTs at encoding (all  $ps > .45$ ). The group that received propranolol at encoding showed similar RTs as the group that received propranolol at retrieval ( $p > .19$ , for main effect of Group). Participants took significantly longer to judge whether the color of the frame appeared in negative scenes ( $M = 2702$  msec,  $SE = 82$  msec) than in neutral scenes ( $M = 2422$  msec,

$SE = 70$  msec;  $F(1, 28) = 51.72, p < .001$ , for main effect of “emotional/neutral”).

## Memory for Scenes

### Corrected Recognition Rates

Propranolol affected  $R_{hit\ rate} - R_{false\ alarm\ rate}$  differentially when it was administered at encoding versus retrieval (Propranolol/placebo  $\times$  Group interaction in  $2 \times 2 \times 2$  ANOVA:  $F(1, 28) = 6.54, p = .016$ ) but had no effect on emotional versus neutral corrected  $R$  scores (main effect of Emotion:  $F(1, 28) = 41.75, p < .001$ ; Emotion  $\times$  Propranolol/placebo interaction  $p > .12$ ). Propranolol administration at encoding markedly reduced corrected  $R$  scores for both emotional (placebo:  $M = 0.60, SE = 0.04$ , propranolol:  $M = 0.45, SE = 0.06$ ) and neutral scenes (placebo:  $M = 0.45, SE = 0.06$ , propranolol:  $M = 0.34, SE = 0.05$ ; main effect of Propranolol:  $F(1, 14) = 9.06, p = .009$  in the  $2 \times 2$  follow-up ANOVA for the group that received propranolol at encoding). In contrast, when propranolol was administered at retrieval, it had no effect on corrected  $R$  scores ( $p > .22$  for all comparisons).

Propranolol did not affect corrected  $K$  scores ( $K_{hit\ rate} - K_{false\ alarm\ rates}$ ;  $p > .14$  for all comparisons in the  $2 \times 2 \times 2$  ANOVA), whereas participants showed higher  $K_{hit\ rate} - K_{false\ alarm\ rates}$  for emotional versus neutral scenes (main effect of Emotional/neutral:  $F(1, 28) = 15.91, p < .01$ ).

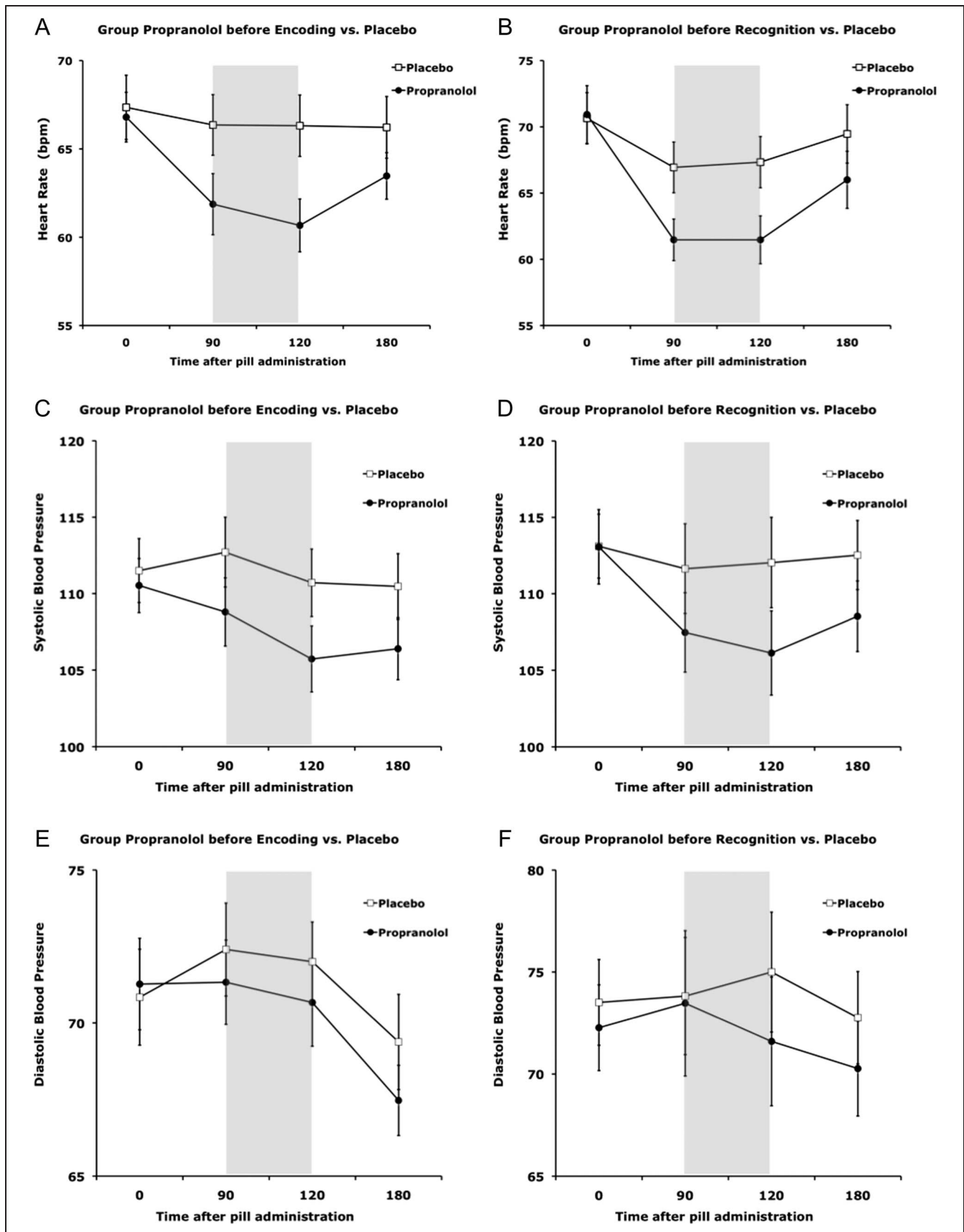
### Raw Remember and Know Responses

Raw remember and know responses are summarized in Table 1.

Propranolol affected  $R_{hit\ rate}$  differently in the group that received propranolol at encoding versus the group that received propranolol at retrieval (Propranolol/placebo  $\times$  Group interaction in a 2 (propranolol/placebo)  $\times$  2 (Emotional/neutral)  $\times$  2 (Group: propranolol at encoding/propranolol at retrieval) ANOVA,  $F(1, 28) = 6.447, p = .017$ ). Propranolol versus placebo lowered  $R_{hit\ rate}$  (main effect of Propranolol/placebo:  $F(1, 28) = 8.62, p < .01$ ). As expected,  $R_{hit\ rate}$  was higher for Emotional than neutral scenes (main effect of Emotional/neutral:  $F(1, 28) = 50.09, p < .001$ ).

Most importantly, propranolol lowered  $R_{hit\ rate}$  for both emotional and neutral scenes in the group that had received propranolol at encoding ( $F(1, 14) = 10.085, p < .01$  for main effect of Propranolol/placebo in a 2 (emotional/neutral)  $\times$  2 (Propranolol/placebo) follow-up ANOVA), but not in the group that received propranolol at retrieval (all  $ps > .22$ ).

In addition, propranolol reduced  $R_{false\ alarm\ rate}$  compared with placebo (main effect of Propranolol/placebo:  $F(1, 28) = 5.05, p < .05$  in a  $2 \times 2 \times 2$  ANOVA).  $R_{false\ alarm\ rates}$  were marginally higher for new emotional compared with new neutral items (main effect of Emotional/neutral:  $F(1, 28) = 3.61, p = .068$  in a  $2 \times 2 \times 2$  ANOVA).



**Figure 2.** Propranolol (80 mg) administered 90 min before encoding (A, C, E) or 90 min before recognition testing (B, D, F) significantly lowered participants' heart rate (A, B) and systolic blood pressure (C, D) during encoding or recognition respectively of emotional and neutral images (gray bars) compared with placebo (mean of the three placebo sessions per group depicted).

**Table 1.** Proportion of Remember and Know Responses of Old and New Emotional and Neutral Items after Placebo Administration or Propranolol Administration at Either Encoding or Retrieval (Mean  $\pm$  SEM)

	Remember Responses								Know Responses							
	Hits				False Alarms				Hits				False Alarms			
	Emotional		Neutral		Emotional		Neutral		Emotional		Neutral		Emotional		Neutral	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Placebo control for propranolol at encoding	.63*	.04	.46*	.06	.03	.01	.02	.01	.24	.04	.29	.04	.09	.01	.08	.02
Propranolol at encoding	.47*	.06	.35*	.05	.02	.01	.01	.005	.33	.06	.31	.05	.08	.02	.06	.03
Placebo control for propranolol at retrieval	.70	.04	.46	.06	.02	.01	.01	.005	.18	.03	.28	.05	.06	.02	.07	.02
Propranolol at retrieval	.67	.04	.48	.04	.004	.003	.002	.002	.19	.03	.30	.03	.07	.02	.07	.02

\*Significant differences between placebo and propranolol ( $p < .05$ ).

However, neither emotion nor propranolol significantly affected  $R_{\text{false alarm rates}}$  when  $2 \times 2$  ANOVAs were run separately for the group that received propranolol at encoding and the group that received propranolol at retrieval (all  $ps > .09$ ).

Although emotion significantly affected  $K_{\text{hit rate}}$  (main effect of emotional/neutral:  $F(1, 28) = 13.04, p < .01$ ), propranolol did not influence  $K_{\text{hit rate}}$  (main effect of propranolol/placebo and its interactions  $ps > .09$  in a  $2 \times 2 \times 2$  ANOVA).  $K_{\text{false alarm rates}}$  were neither affected by emotion, propranolol, nor group (all  $ps > .28$  in a  $2 \times 2 \times 2$  ANOVA).

### Recollection and Familiarity

Paralleling the results on  $R_{\text{hit rate}}$ , propranolol affected the subjective sense of recollection ( $R_{\text{hit rate}} - R_{\text{false alarm rate}} / (1 - R_{\text{false alarm rate}})$ ) differently in the group that received propranolol at encoding versus the group that received propranolol at retrieval (Propranolol/placebo  $\times$  Group interaction in  $2 \times 2 \times 2$  ANOVA,  $F(1, 28) = 6.55, p = .016$ ). Similar to the main effect on  $R_{\text{hit rate}}$ , there was a main effect of Propranolol/placebo on recollection ( $F(1, 28) = 6.40, p = .017$ ). As expected, emotional scenes were remembered with a heightened sense of recollection compared with neutral scenes (main effect of Emotion:  $F(1, 28) = 40.81, p < .001$ ; Figure 3).

Crucially, propranolol lowered the subjective sense of recollection for both emotional (placebo:  $M = 0.60, SE = 0.03$ , propranolol:  $M = 0.45, SE = 0.06$ ) and neutral scenes (placebo:  $M = 0.45, SE = 0.06$ , propranolol:  $M = 0.34, SE = 0.05$ ) only in the group that received propranolol at encoding (main effect of Propranolol  $F(1, 14) = 9.00, p = .01$  in a  $2 \times 2$  ANOVA), but not when it was administered at retrieval (all  $ps > .25$ ; Figure 3).

Familiarity ( $Fd'$ ) scores were neither affected by Emotion, Propranolol, nor Group (all  $ps > .14$  in a  $2 \times 2 \times 2$  ANOVA; Figure 4).

### Order Effects

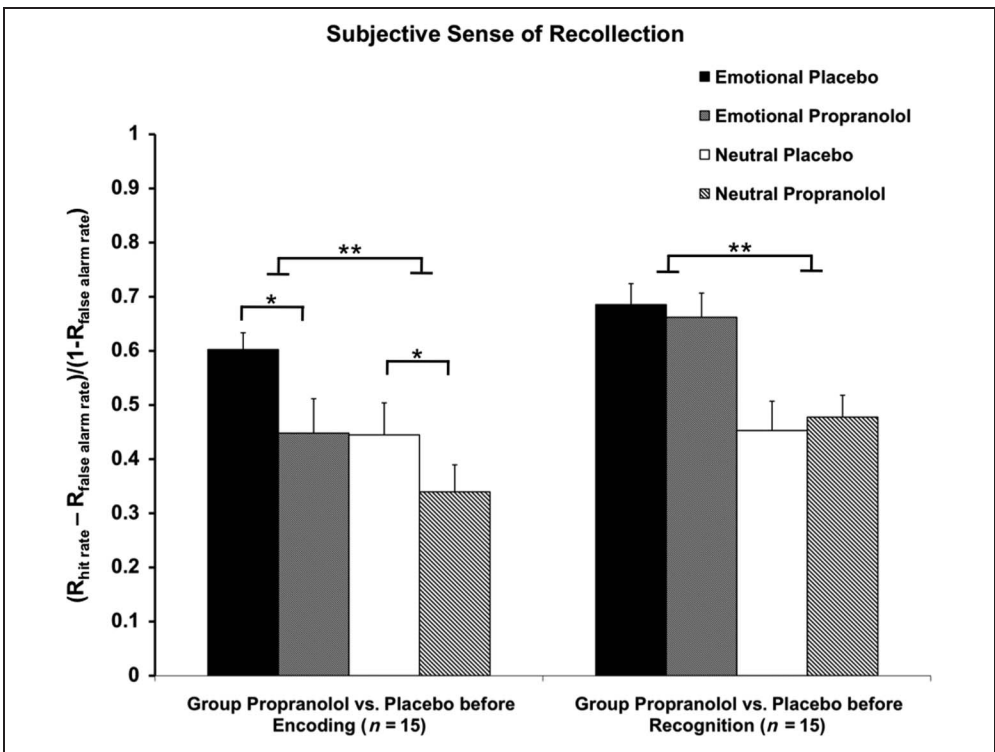
One limitation of our design is that participants may have anticipated a memory test during the second phase of participation. To examine whether there were order effects modulating the observed propranolol effects, we ran 2 (Propranolol/placebo)  $\times$  2 (Emotional/neutral)  $\times$  2 (Group: propranolol at encoding/propranolol at retrieval)  $\times$  2 (Order: first condition propranolol/second condition propranolol) ANOVAs for  $R_{\text{hit rate}}$ ,  $R_{\text{false alarm rate}}$ , and the subjective sense of recollection ( $R_{\text{hit rate}} - R_{\text{false alarm rate}} / (1 - R_{\text{false alarm rate}})$ ).

For  $R_{\text{hit rate}}$  and  $R_{\text{false alarm rate}}$ , we found no significant main effect or interaction of order (all  $ps > .10$ ). Interestingly, however, propranolol affected the subjective sense of recollection ( $R_{\text{hit rate}} - R_{\text{false alarm rate}} / (1 - R_{\text{false alarm rate}})$ ) for emotional versus neutral stimuli differently depending on whether it had been administered in the first or the second phase of participation ( $F(1, 26) = 4.50, p < .05$  for Emotion  $\times$  Propranolol/placebo  $\times$  Order interaction in the  $2 \times 2 \times 2 \times 2$  ANOVA).

Analogous to our main data analyses, we ran 2 (Propranolol/placebo)  $\times$  2 (Emotional/neutral)  $\times$  2 (Order) follow-up ANOVAs separately for the group that received propranolol at encoding and the group that received propranolol at retrieval. In the group that received propranolol at encoding, no effects of order emerged (all  $ps > .46$ ). However, for the group that had received propranolol at retrieval, propranolol affected the subjective sense of recollection for emotional versus neutral stimuli differently depending whether it had been taken in the first or second condition ( $F(1, 13) = 5.91, p < .05$  for Propranolol/placebo  $\times$  Emotion  $\times$  Order effect in the  $2 \times 2 \times 2$



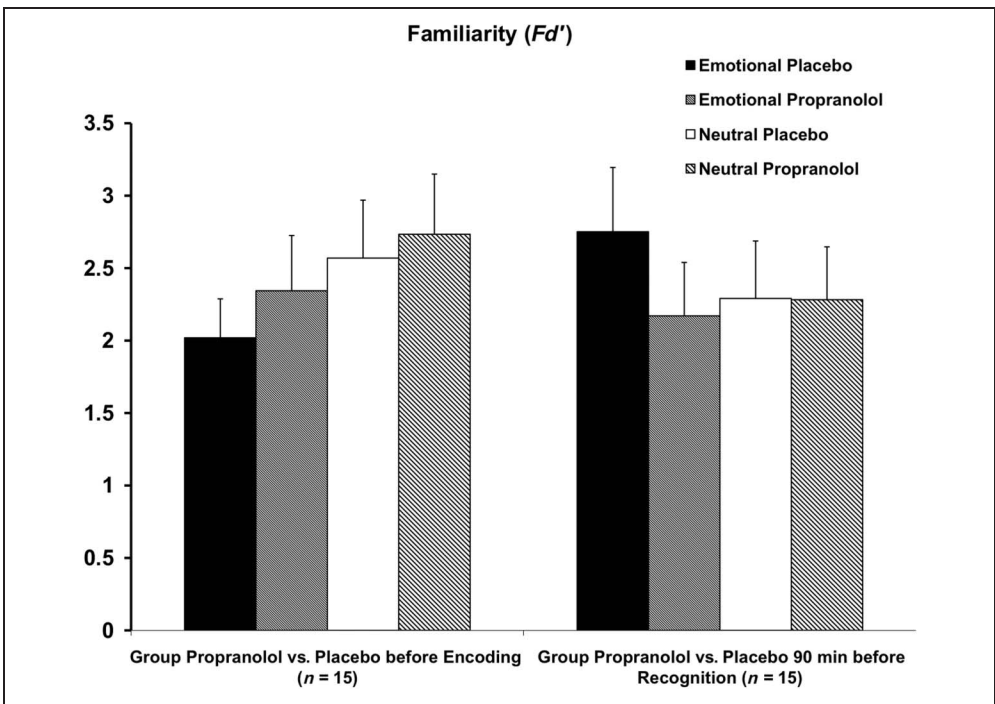
**Figure 3.** Propranolol given 90 min before encoding, but not before recognition, significantly reduced the subjective sense of recollection ( $R_{\text{hit rate}} - R_{\text{false alarm rate}} / (1 - R_{\text{false alarm rate}})$ ) for both emotional and neutral scenes 24 hr later.  $*p < .05$ .  $**p < .01$ .



ANOVA). Two additional 2 (Propranolol/placebo)  $\times$  2 (Emotional/neutral) follow-up ANOVAs separated for the order of propranolol administration within the group that received propranolol at retrieval, revealed a marginal Emotion  $\times$  Propranolol/placebo interaction ( $F(1, 6) = 4.04, p = .09$ ) for participants that received propranolol during the second phase of participation at retrieval. When

participants were given propranolol at retrieval at the second round of participation, during which they might have anticipated a memory test, propranolol significantly lowered the subjective sense of recollection for emotional ( $M = 0.60, SE = 0.08$  after propranolol vs.  $M = 0.68, SE = 0.06$  after placebo  $t(6) = 2.56, p < .05$ ), but not neutral stimuli (all  $ps > .23$ ). In contrast, propranolol did not

**Figure 4.** Propranolol given 90 min before encoding or recognition had no effect on familiarity for both emotional and neutral scenes 24 hr later.



affect the subjective sense of recollection when it was administered during the first round of participation at retrieval (all  $p$ s > .26).

### Memory Scores After Exclusion of the Four Participants with a 48-hr instead of 24-hr Delay

The data were additionally analyzed without the four participants that had a 48-hr instead of a 24-hr interval between the learning and the retrieval session. In all four participants, the 48-hr delay concerned the placebo condition in the group that had received propranolol at encoding. Similar to the full data set, when excluding these participants, propranolol lowered  $R_{\text{hit rate}}$  for both emotional ( $M = 0.44$ ,  $SE = 0.07$  vs. placebo:  $M = 0.64$ ,  $SE = 0.04$ ) and neutral scenes ( $M = 0.33$ ,  $SE = 0.06$  vs. placebo:  $M = 0.50$ ,  $SE = 0.07$ ,  $F(1, 10) = 13.36$ ,  $p < .01$  for main effect of Propranolol/placebo in a  $2 \times 2$  follow-up ANOVA). Likewise, the subjective sense of recollection was reduced in the propranolol condition for both emotional ( $M = 0.41$ ,  $SE = 0.08$  vs. placebo:  $M = 0.61$ ,  $SE = 0.04$ ) and neutral scenes ( $M = 0.32$ ,  $SE = 0.06$  vs. placebo:  $M = 0.48$ ,  $SE = 0.07$ ;  $F(1, 10) = 13.20$ ,  $p < .01$  for main effect of Propranolol/placebo in a  $2 \times 2$  follow-up ANOVA).

### Memory Accuracy for the Color of the Frame

Memory for the color of the frame around the presented scenes was assessed using two measures. First, we assessed memory between the color of the frame and the scenes collapsed across R and K responses for the scenes. Second, we assessed the memory for the color of the frame with respect to R responses. To assess veridical memory and avoid guessing, participants had been given the choice to respond "I don't know" when they did not know the color of the frame.

Correct identification of the previously presented color of the frame (indexed by recognized scenes with correct color attribution given an R or K response) was significantly better for neutral scenes ( $M = 0.27$ ,  $SE = 0.02$ ) compared with negative scenes ( $M = 0.23$ ,  $SE = 0.02$ ),  $F(1, 28) = 6.42$ ,  $p < .05$ , for main effect of emotion), replicating previous findings (Mackenzie, Powell, & Donaldson, 2015; Rimmele et al., 2011). Irrespective of the emotionality of the scenes, the proportion of recognized scenes with correct color frame was not affected by propranolol ( $p > .14$  for main effect of Propranolol/placebo and Propranolol/placebo  $\times$  Emotion interaction).

In general, memory for color of the frame was rather low in respect to R responses. For example, 25% of all participants showed 6% or less of emotional or neutral R responses with correct color memory of the frame in the placebo condition. Nevertheless, including all participants, a  $2$  (negative/neutral)  $\times 2$  (propranolol/placebo)  $\times 2$  (group: propranolol at encoding/group propranolol at

retrieval) ANOVA showed that a lower proportion of negative ( $M = 0.23$ ,  $SE = 0.02$ ) versus neutral scenes ( $M = 0.29$ ,  $SE = 0.02$ ), given a correct R response were accompanied by correct color attribution ( $F(1, 28) = 8.10$ ,  $p < .01$ , for main effect of emotion). Propranolol had no effect on the proportion of R responses with correct memory for the color of the frame ( $p > .70$  for main effect of Propranolol/placebo and Propranolol/placebo  $\times$  Emotion interaction). Follow-up comparisons showed that the main effect of emotion was driven by a significant difference of less emotional ( $M = 0.22$ ,  $SE = 0.03$ ) than neutral R response with correct color identification after placebo ( $M = 0.29$ ,  $SE = 0.04$ ;  $t(29) = 2.00$ ,  $p = .05$ ), but not after propranolol ( $p > .21$ ). Because there was no main effect or interaction of group, we did not run follow-up ANOVAs separately for each group.

## DISCUSSION

Replicating previous observations demonstrating that emotional events are remembered with a heightened sense of recollection (Rimmele et al., 2011, 2012; Sharot & Yonelinas, 2008; Dolcos et al., 2005; Sharot & Phelps, 2004; Kensinger & Corkin, 2003; Ochsner, 2000), our study participants were more likely to exhibit a rich recollective experience for negative than neutral scenes, as indicated by a higher  $R_{\text{hit rate}}$  as well as higher recollection score for negative stimuli. Importantly, we showed that blocking physiological arousal with 80 mg of the beta-adrenergic antagonist propranolol 90 min before encoding diminished the subjective sense of recollection for both emotional and neutral stimuli. In contrast, administering propranolol 90 min before testing recognition did not influence the subjective sense of recollection. These findings suggest that physiological arousal during memory formation rather than memory retrieval contributes to the subjective sense of recollection.

Similar to our findings, previous pharmacological studies reported impaired subjective sense of recollection, but no effect on familiarity after administration of the benzodiazepine lorazepam (Curran, Barrow, Weingartner, Lader, & Bernik, 1995; Curran, Gardiner, Java, & Allen, 1993) or a stronger impairment in the subjective sense of recollection than familiarity after midazolam (Hirshman, Fisher, Henthorn, Arndt, & Passannante, 2002). Of note, the impairment in the subjective sense of recollection after lorazepam was correlated with the state of arousal at encoding (Curran et al., 1993). Similar to propranolol, benzodiazepines have been shown to decrease physiological arousal, for example, lower heart rate or plasma norepinephrine levels (Tulen & Man in't Veld, 1998; Tulen et al., 1994; Tulen, Moleman, Boomsma, van Steenis, & van den Heuvel, 1991; Duka, Ackenhil, Noderer, Doenicke, & Dorow, 1986). Moreover, there is evidence that the GABAergic and noradrenergic systems interact in the brain in modulating memory (Intorini-Collison, Castellano, & McGaugh, 1994). Thus, it is possible that benzodiazepines

through their stimulating action on inhibitory GABA receptors modify noradrenergic transmission in the brain and similar to propranolol decrease physiological arousal as well as the subjective sense of recollection.

Consistent with previous findings (Kroes, Strange, & Dolan, 2010; Hurlmann et al., 2005; Maheu et al., 2004; Strange, Hurlmann, & Dolan, 2003), propranolol decreased physiological arousal in our study, as indicated by lower heart rate and blood pressure assessed 90 and 120 min after administration of the beta-adrenergic antagonist. When learning took place during this time of decreased physiological arousal (propranolol vs. placebo given 90 min before encoding), participants remembered emotional and neutral stimuli 24 hr later with a decreased subjective sense of recollection. The fact that higher degrees of affect and arousal have been related to increased memory vividness (Reisberg et al., 1988) and a stronger subjective sense of recollection in previous behavioral studies (Kensinger & Corkin, 2003; Ochsner, 2000) fits well with our finding that a decrease in arousal as a result of beta blockade lowers the subjective sense of recollection. Possibly, propranolol counteracts arousal-induced changes of initial stimulus processing at encoding. At encoding, emotionally arousing stimuli attract attention (MacKay et al., 2004; Anderson & Phelps, 2001; Fox, Russo, Bowles, & Dutton, 2001; Ohman, Flykt, & Esteves, 2001) and enhance perception (Bocanegra & Zeelenberg, 2009; Phelps et al., 2006). Attention at encoding specifically supports recollection (Kensinger, Clarke, & Corkin, 2003; Yonelinas, 2001). In addition, arousal at encoding is associated with enhanced perceptual vividness predicting increased memory vividness (Todd, Talmi, Schmitz, Susskind, & Anderson, 2012). Given these results, an arousal-mediated decrement of attention and perception during encoding after propranolol administration may have contributed to diminishing the subjective sense of recollection in the current study.

Another possible explanation for the reduced subjective sense of recollection in the group that received propranolol before encoding is that propranolol affected memory consolidation. Previous studies show that the enhanced recollective experience for emotional compared with neutral stimuli increases over time (Sharot & Yonelinas, 2008; Sharot, Verfaellie, et al., 2007). This finding suggests that emotion elicits a mechanism that modulates memory consolidation of the recollective experience, possibly by increased physiological arousal during consolidation. Because blood pressure and heart rate were back to normal levels only 3 hr after propranolol administration (i.e., 1–1.5 hr after encoding), a decrease in physiological arousal during initial memory consolidation could have counteracted arousal-mediated memory consolidation processes resulting in lower subjective recollection in the group that received propranolol at encoding. On the contrary, prior studies have shown that postlearning arousal selectively enhances familiarity, rather than recollection of neutral information presented

beforehand (McCullough & Yonelinas, 2013; Schwarze, Bingel, & Sommer, 2012; Yonelinas, Parks, Koen, Jorgenson, & Mendoza, 2011). Thus, future studies are needed to determine the role of physiological arousal during encoding versus consolidation and its relation to the subjective recollective experience.

It is of interest that propranolol decreased the subjective sense of recollection for both emotional and neutral stimuli. One explanation of this finding is that propranolol at encoding may have lowered arousal to emotional as well as to the neutral stimuli. The mean arousal ratings for neutral stimuli ( $M = 3.81$ ,  $SD = 0.89$ ) in our study show that neutral stimuli are experienced as somewhat arousing, which could have been decreased by propranolol. Given that increased arousal at encoding is associated with an increased subjective sense of recollection (Anderson, Wais, et al., 2006; Anderson, Yamaguchi, Grabski, & Lacka, 2006; Kensinger & Corkin, 2003; Ochsner, 2000), a propranolol-induced decrease in arousal during encoding of neutral as well as emotional stimuli might have lowered the subjective sense of recollection for both types of stimuli 24 hr later. In addition, propranolol has been found to lower attention during encoding not only to emotional but also to neutral stimuli (De Martino, Strange, & Dolan, 2008), a further factor that might explain the main effect of propranolol on decreasing the subjective sense of recollection for both emotional and neutral stimuli.

Propranolol given 90 min before recognition testing had no significant influence on the subjective sense of recollection for emotional and neutral stimuli encoded 24 hr earlier. This finding implies that arousal during memory retrieval does not affect the subjective sense of recollection, which is inconsistent with the hypothesis that the increased subjective sense of recollection typically found for emotional stimuli, is due to increased arousal at retrieval enhancing perceptual fluency (Sharot et al., 2004) or changing the mnemonic reconstruction process (Reisberg et al., 1988). The finding that propranolol at encoding, but not retrieval, decreased the subjective sense of recollection provides evidence that physiological arousal especially impacts the formation of subjectively vivid memories. However, in a small proportion of participants ( $n = 7$ ), when propranolol was administered at retrieval at the second round of participation, the subjective sense of recollection was decreased after propranolol versus placebo for emotional, but not neutral scenes. Future studies with a larger sample should determine whether anticipation of a memory test, as it could be the case in the second round of participation, might influence the effects of propranolol on retrieval.

In line with previous findings (Mackenzie et al., 2015; Rimmele et al., 2011), memory for the color of the frame that surrounded the scenes during encoding was lower for negative than neutral scenes given a correct *R* response. This disadvantage for contextual details for recollected

emotional scenes was marginally significant after placebo, but absent following propranolol administration. Given the low memory of contextual details in our task, future studies should examine whether propranolol, with its concurrent reduction in arousal, may influence the trade-off in memory of central versus peripheral details with more easy tasks. A potential mechanism thereof may be a propranolol-linked broader attentional focus of emotional negatively valenced stimuli at encoding, including that of peripheral scene detail, resulting in better memory for peripheral details when propranolol is active during encoding (Mather, 2007; Reisberg & Heuer, 2004; Heuer & Reisberg, 1992).

In summary, our data show that decreasing physiological arousal through administration of the beta-adrenergic receptor blocker propranolol at memory encoding, but not at retrieval, decreases the subjective sense of recollection. This finding suggests a biological mechanism that underlies the formation of memories with a qualitatively distinct recollective experience, that is, physiological arousal via activation of beta-adrenergic receptors at the time of encoding and consolidation results in the formation of memories with a stronger subjective sense of recollection. On the neural level, activities in the amygdala and hippocampus during encoding have been related to a strong subjective sense of recollection for emotionally arousing stimuli (Dolcos et al., 2004; Kensinger & Corkin, 2004). In addition, amygdala and visual cortex activation at encoding is related to enhanced perceptual and mnemonic vividness for emotional scenes (Todd, Schmitz, Susskind, & Anderson, 2013; Todd et al., 2012). Evidence from animal and human studies further suggests that the amygdala modulates other brain regions, in particular the hippocampus and visual cortex during emotional memory formation (Todd et al., 2012, 2013; Richardson, Strange, & Dolan, 2004; Kilpatrick & Cahill, 2003; McGaugh, 2002). Pharmacological studies showed that this modulation depends on activation of beta-adrenergic receptors (McGaugh, Cahill, & Roozendaal, 1996). For example, propranolol administration in humans reduces amygdala activity during emotional encoding and amygdala–hippocampal interactions that are linked to emotional memory (van Stegeren et al., 2005; Strange & Dolan, 2004). On this background, together with our data, we suggest that a noradrenergic mechanism involving amygdala–hippocampal interactions and amygdala–visual cortex interactions may play a role in modulating the formation of emotional memories with a strong subjective sense of recollection.

## Acknowledgments

This research was supported by NIH Grant MH062104 to E. A. P. and by grants from the Swiss National Science Foundation (PZ00P1\_137126), the German Research Foundation (DFG RI 1894/2-1), and the European Community Seventh Framework Programme (FP7/2007-2013, FP7/2007-2011) under Grant Agreement 334360 to U. R.

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