

# Propranolol–induced Impairment of Contextual Fear Memory Reconsolidation in Rats: A similar Effect on Weak and Strong Recent and Remote Memories

\*Fatemeh Taherian<sup>1</sup>, Abbas Ali Vafaee<sup>2</sup>, Gholam Hassan Vaezi<sup>1</sup>, Sharaf Eskandarian<sup>1</sup>, Adel Kashefi<sup>2</sup>, Ali Rashidy-Pour<sup>2</sup>

1. Islamic Azad University, Damghan Branch, Damghan, Iran.

2. Laboratory of Learning and Memory, Research Center and Department of Physiology, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran.

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## ABSTRACT

**Introduction:** Previous studies have demonstrated that the  $\beta$ -adrenergic receptor antagonist propranolol impairs fear memory reconsolidation in experimental animals. There are experimental parameters such as the age and the strength of memory that can interact with pharmacological manipulations of memory reconsolidation. In this study, we investigated the ability of the age and the strength of memory to influence the disrupting effects of propranolol on fear memory reconsolidation in rats.

**Methods:** The rats were trained in a contextual fear conditioning using two (weak training) or five (strong training) footshocks (1mA). Propranolol (10mg/kg) injection was immediately followed retrieval of either a one-day recent (weak or strong) or 36-day remote (weak or strong) contextual fear memories.

**Results:** We found that propranolol induced a long-lasting impairment of subsequent expression of recent and remote memories with either weak or strong strength. We also found no memory recovery after a weak reminder shock. Furthermore, no significant differences were found on the amount of memory deficit induced by propranolol among memories with different age and strength.

**Discussion:** Our data suggest that the efficacy of propranolol in impairing fear memory reconsolidation is not limited to the age or strength of the memory.

## 1. Introduction

Reactivation of stabilized memories returns them to a labile state and causes them to undergo extinction or reconsolidation processes. During reconsolidation that requires protein synthesis, the original memory is thought to update or integrate new information into long-term memories (Nadel & Moscovitch, 1997; Nader & Einarsson, 2010). Although the application of protein synthesis inhibitors following memory reactivation interferes with

memory reconsolidation, causing to amnesia, but such manipulations does not always result in to amnesia (Biedenkapp & Rudy, 2004; Cammarota, Bevilaqua, Medina, & Izquierdo, 2004; Pedreira, Pérez-Cuesta, & Maldonado, 2004). One important variable seems to be the age of the memory (Alberini, 2005; Lee, 2009; Nader & Einarsson, 2010). Recent studies have shown that memory age become increasingly less amenable to reconsolidation (Boccia, Blake, Acosta, & Baratti, 2006; Eisenberg & Dudai, 2004; Milekic & Alberini, 2002). Another variable is the strength of the memory. A study has shown that the reconsolidation of stronger

\* Corresponding Author:

Ali Rashidy-Pour, PhD

Laboratory of Learning and Memory, Research Center and Department of Physiology, School of Medicine, Semnan University of Medical Sciences, Semnan, Iran.

Tel/Fax: +98(231)3354186

E-mail: Rashidy-pour@semums.ac.ir

memories are more resistant to disruption by protein inhibitor anisomycin (Suzuki et al., 2004). These findings indicate that the occurrence of memory reconsolidation depends on specific parameters. The experimental conditions such as memory age, and training strength that prevent the occurrence of memory reconsolidation are referred as the boundary conditions (Antoine, Jocelyne, & Serge, 2012; Nader & Einarsson, 2010).

Substantial evidence from animals' studies indicates that the  $\beta$ -adrenergic receptor antagonist propranolol impairs fear memory reconsolidation. It is reported that propranolol administered in combination with memory retrieval disrupts auditory fear conditioning (Dębiec & LeDoux, 2004), contextual fear conditioning (Abrari, Rashidy-Pour, Semnanian, & Fathollahi, 2008; Muravieva & Alberini, 2010), and inhibitory avoidance (Przybylski, Roulet, & Sara, 1999). Furthermore, propranolol has been shown to disrupt the reconsolidation of reward-related memories (Tronson & Taylor, 2007). Human studies have shown that propranolol disrupted reconsolidation of drug-related memory in heroin addicts (Zhao, Zhang, Shi, Epstein, & Lu, 2009), and produced amnesia for the original fear response, remaining intact in the declarative memory for the fear association (Soeter & Kindt, 2012). These findings suggest that  $\beta$ -adrenergic neurotransmission mediates the reconsolidation of several kinds of memories.

In this study, using contextual fear conditioning, we examined the effects of post-reactivation blockade of  $\beta$ -adrenergic receptors by propranolol on subsequent expression of recent and remote memories acquired under different training paradigms.

## 2. Methods

### 2.1. Animals

Adult male Wistar rats (250–300 g) obtained from the breeding colony of Semnan University of Medical Sciences, Semnan, Iran. The animals were housed five per cage in a room with a natural light cycle and constant temperature ( $24 \pm 20^\circ\text{C}$ ). Food and water were available ad libitum. All experiments were performed between 10:00 and 13:00 h during the light cycle. All procedures were conducted according to the National Institutes of Health Guide for care and use of laboratory animals. 8–12 rats were used per each group.

### 2.2. Drug

Propranolol (Sigma) was dissolved in 0.9% saline (10mg/kg), was injected intraperitoneally at a volume

of 2ml/kg. This dose was chosen based on the previous behavioral studies showing that the drug impairs memory reconsolidation and extinction (Muravieva & Alberini, 2010; Robinson & Franklin, 2010; Rodriguez-Romaguera, Sotres-Bayon, Mueller, & Quirk, 2009).

### 2.3. Behavioral Procedure

Each experiment consisted of three phases: conditioning, memory reactivation session, and testing sessions.

#### 2.3.1. Contextual Fear Conditioning

The apparatus (TSE, Bad Homburg, Germany) and general procedures for contextual fear conditioning have previously been described (Abrari et al., 2008). Contextual fear conditioning took place in a conditioning box. The walls and the ceiling of the box were constructed of clear Plexiglass. The floor of the box was made of 25 stainless steel rods (6 mm in diameter, 12 mm apart) through which footshock (FS) could be delivered from a constant current source. The box was enclosed in a sound attenuating chamber. The chamber was illuminated by a single house light, and cleaned with 5% ethanol before and after utilization. Ventilation fans provided continuous background noise (68 dB) during the experiment. The rats were habituated to the conditioning chamber for 10min each on day 0. On day 1, the rats were placed into the chamber and after 3min received 2FS or 5FS at 120s intervals. Each shock was 1mA and 2s duration. The rats were left in the conditioning box for 30s after termination of the procedure and returned to their home cage.

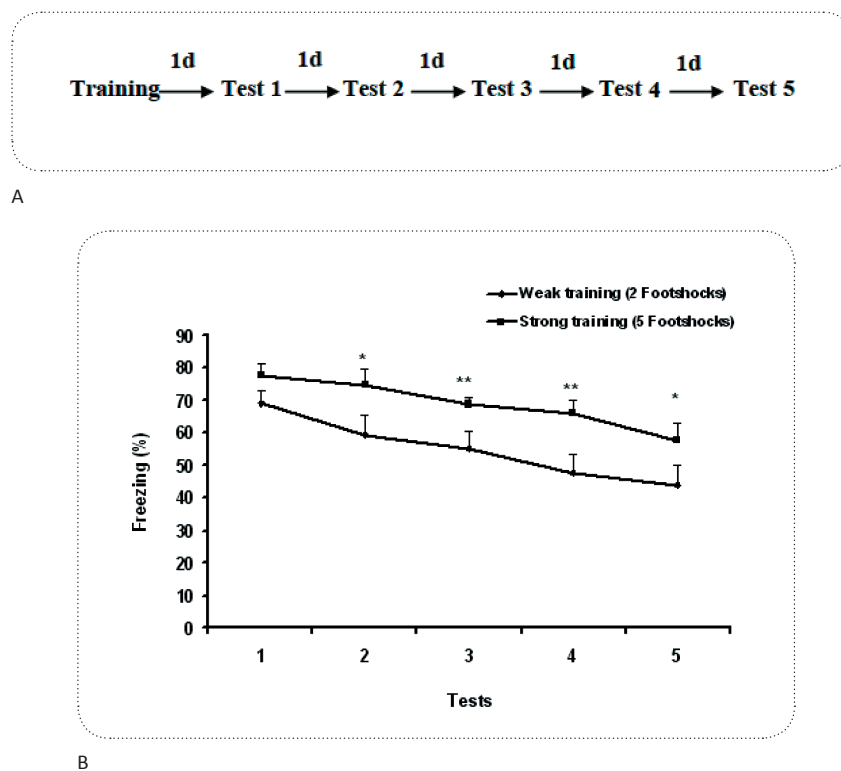
During retention test, the percentage of the time that animal spent freezing (characterized by the absence of all visible movement except respiration) was measured using automated procedures. Such behavior is commonly used as an index of fear in rats (Blanchard & Blanchard, 1969).

#### 2.3.2. Memory Reactivation

For memory reactivation, the rats were placed into the same conditioning box for 90s either 1 (recent) or 36 (remote) days later. Immediately after memory reactivation, the rats received saline or propranolol as mentioned below.

#### 2.3.4. Test Sessions

One (Test1), two (Test2), and three (Test3) days after memory reactivation, the rats were returned to the box



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**Figure 1.** The strength of contextual fear memories acquired with two or five footshocks (FS). A: Schematic of the experimental design. Separate groups of rats received 2FS or 5FS. Two days after training, they received extinction sessions. At the end of the extinction session, rats trained with 5FS had significantly more freezing (B). \* $P < 0.05$ , \*\* $P < 0.01$  as compared with weak training at the same test.

for 5min. Memory was assessed and expressed as the percentage of the time that rats spent freezing during 5min. To determine whether memory could reemerge, immediately after Test 3, the rats were exposed to a reminder shock (0.4mA, 1.5s) in a different box and retested one day later (Test 4). To calculate the amount of memory reduction of different groups across testing sessions, the following formula was used: the total time of freezing behavior during first test session minus the total time on the third test session divided by the total time of freezing behavior in the first test session.

### 2.3.5. Extinction

The rats were habituated and trained with 2FS or 5FS as described above. Extinction training was defined as the repetitive exposure to the contextual box in the absence of FS. One day after contextual training, the rats were placed for 5min in the same context and the percentage of the time that animal spent freezing was measured using automated procedures (Test 1). In a similar way, extinction training was performed on four consecutive days after Test 1 (Tests 2-5).

## 2.4. Experiments

### 2.4.1 Experiment 1

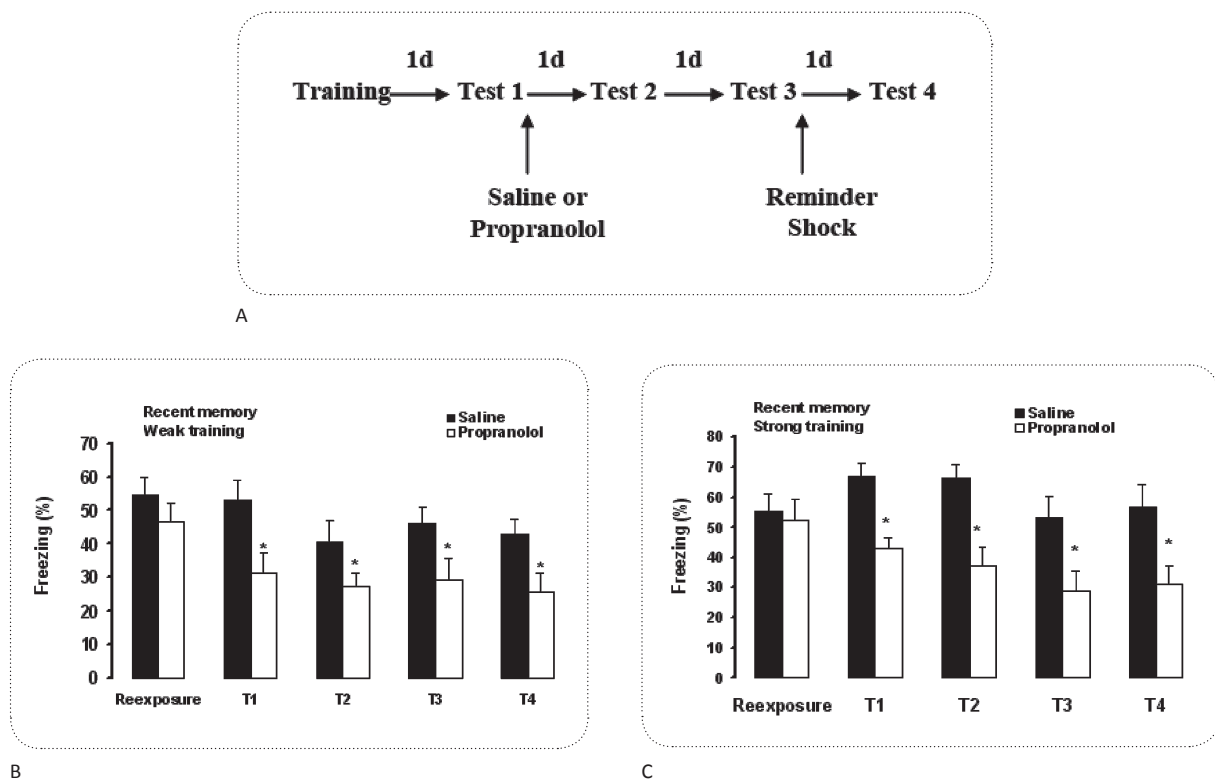
This experiment determined the strength of contextual fear memories acquired with 2FS or 5FS. Separate groups of rats were trained with either 2FS or 5FS and then received multiple extinction trials as mentioned above.

### 2.4.2. Experiment 2

This experiment investigated the effect of propranolol on the reconsolidation of the 2FS or the 5FS recent fear memory. The animals were randomly assigned into two experimental groups (saline or propranolol) for each memory and trained as described above. Immediately after reactivation, the rats received saline and propranolol. Retention was tested as previously described.

### 2.4.3. Experiment 3

This experiment examined the effect of propranolol on the reconsolidation of the 2FS or the 5FS remote fear memory. The animals were randomly assigned to



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**Figure 2.** Post-reactivation administration of propranolol impairs reconsolidation of recent contextual fear memories with either weak or strong strength. **A:** Schematic of the experimental design. Rats received either two or five footshocks. One day after training, the memory was reactivated with exposure of rats into the same conditioning box for 90s and immediately followed by saline or propranolol injections. Long-term memory was tested one (Test1), two (Test2), and three (Test3) days after memory reactivation. Propranolol impaired long-term memory with either weak (B) or strong strength (C). Application of a weak reminder shock did not recover the original memory. \* $P < 0.05$ , \*\* $P < 0.01$  as compared with saline-treated animals at the same test.

two experimental groups (saline or propranolol) for each memory. This experiment was identical to Experiment 2; however, memory reactivation was occurred 36 days after training.

#### 2.4.4. Experiment 4

This experiment determined whether the effect of propranolol on fear memory reconsolidation was reactivation dependent. Eight separate groups of rats (four groups for recent and four groups for remote memories) were exposed to 2FS or 5FS and received saline or propranolol following memory reactivation (one or 36 days after training) and tested one day later.

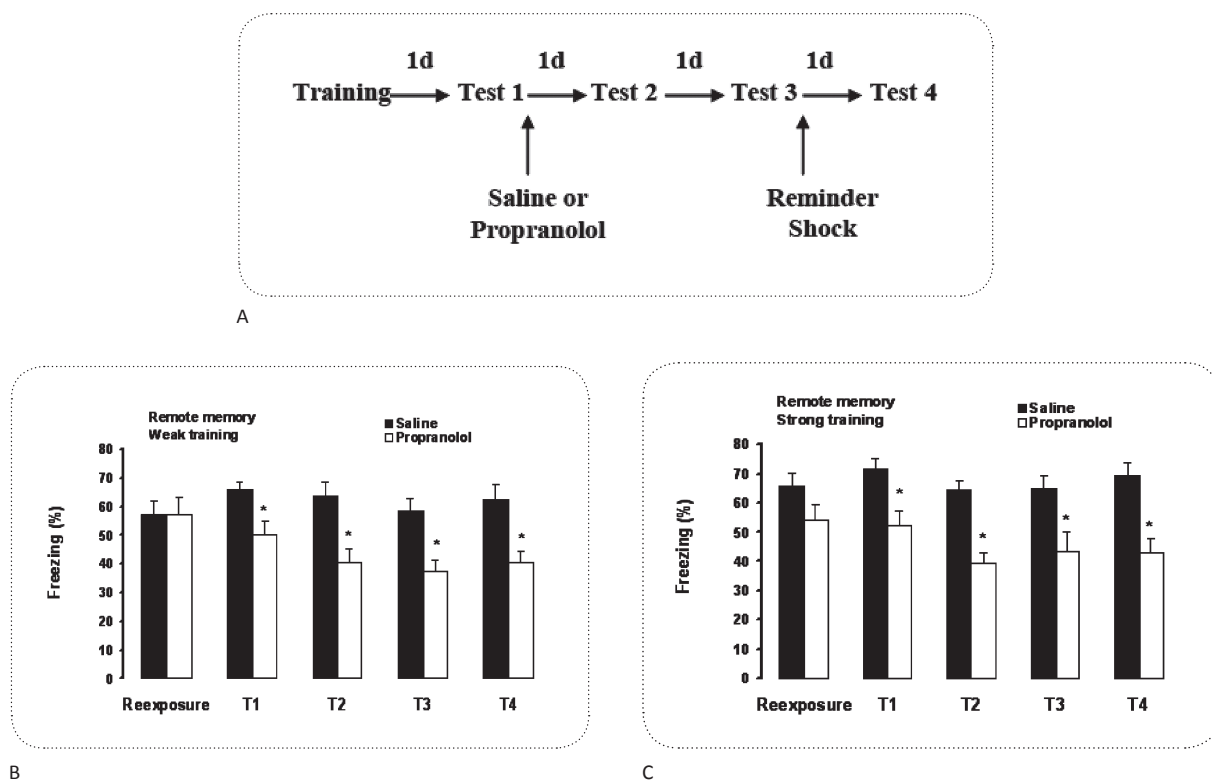
#### 2.5. Statistical Analysis

The data were expressed as a means  $\pm$  SEM and analyzed with one-way or two-way analysis of variance (ANOVA). Post-hoc or two-independent groups' comparisons were performed using student's t-test. Values of  $P < 0.05$  were considered significant.

### 3. Results

#### 3.1. Experiment 1: Contextual Fear Memory Acquired with 5FS was Stronger than with 2FS

We found that the strength of contextual fear memories acquired with 5FS was stronger than with 2FS. Separate groups of rats were conditioned with either 2FS or 5FS and then received multiple extinction trials in several sessions (Fig. 1). A two-way ANOVA comparing freezing scores of across group and testes revealed a significant effect of group (2FS:  $F(1,22)=6.54$ ,  $P=0.018$ ; 5FS:  $F(1,18)=15.23$ ,  $P=0.0001$ ), a significant effect of test (2FS:  $F(2,44)=3.6$ ,  $P=0.041$ ; 5FS:  $F(2,36)=8.22$ ,  $P=0.001$ ), and no test  $\times$  treatment interaction (2FS:  $F(2,44)=0.66$ ,  $P=0.52$ ; 5FS:  $F(2,36)=0.3$ ,  $P=0.74$ ). Post-hoc comparison showed that compared with the 5FS group, the 2FS froze significantly less during Test 2 ( $P < 0.05$ ), Test 3 ( $P < 0.01$ ), and Test 4 ( $P < 0.01$ ), and Test 5 ( $P < 0.05$ ). This indicates that the 5FS memory was stronger than the 2FS memory.



**Figure 3.** Post-reactivation administration of propranolol impairs reconsolidation of remote contextual fear memories with either weak or strong strength. A: Schematic of the experimental design. Rats received either two or five footshocks. 36 days after training, the memory was reactivated with exposure of rats into the same conditioning box for 90s and immediately followed by saline or propranolol injections. Long-term memory was tested one (Test1), two (Test2), and three (Test3) days after memory reactivation. Propranolol impaired long-term memory with either weak (B) or strong (C) strength. Application of a weak reminder shock did not recover the original memory. \* $P < 0.05$ , \*\* $P < 0.01$  as compared with saline-treated animals at the same test.

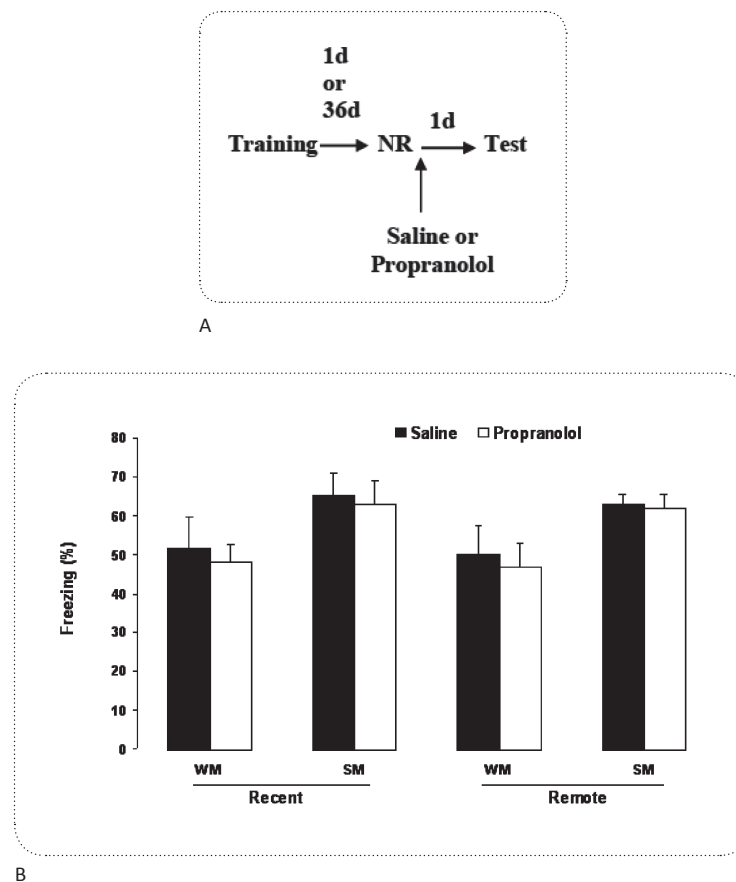
### 3.2. Propranolol Impairs the Reconsolidation of Recent Memories with either Weak or Strong strength

We found that the impairing effects of propranolol following recent memory reactivation did not depend on the strength of the memory. All groups of rats exhibited similar levels of freezing during 90s reactivation phase (Fig. 2). However, systemic propranolol following recent memory reactivation impaired subsequent expression of the recent memory acquired either with weak or strong training (Fig. 2B and C). A two-way ANOVA comparing freezing scores of across treatment and testes revealed a significant effect of treatment (2FS:  $F(1,22)=6.54$ ,  $P=0.018$ ; 5FS:  $F(1,18)=15.23$ ,  $P=0.0001$ ), a significant effect of test (2FS:  $F(2,44)=3.6$ ,  $P=0.041$ ; 5FS:  $F(2,36)=8.22$ ,  $P=0.001$ ), and no test  $\times$  treatment interaction (2FS:  $F(2,44)=0.66$ ,  $P=0.52$ ; 5FS:  $F(2,36)=0.3$ ,  $P=0.74$ ). Post-hoc comparison showed that compared with saline, propranolol-treated rats froze significantly less during Test 1 (2FS:  $P=0.015$ , 5FS:  $P=0.001$ ), Test 2 (2FS:  $P=0.036$ , 5FS:  $P=0.001$ ), and Test

3 (2FS:  $P=0.015$ ; 5FS:  $P=0.017$ ). Application of a weak reminder shock did not recover the original memory.

### 3.3. Propranolol Disrupts the Reconsolidation of Remote Memories with either Weak or Strong Strength

All groups of rats exhibited similar levels of freezing during 90s reactivation phase (Fig. 3). However, systemic propranolol following remote memory reactivation impaired subsequent expression of the remote memory acquired either with weak or strong training (Fig. 3B and C). A two-way ANOVA comparing freezing scores of across treatment and testes revealed a significant effect of treatment (2FS:  $F(1,18)=6.32$ ,  $P=0.022$ ; 5FS:  $F(1,18)=9.38$ ,  $P=0.007$ ), a significant effect of test (2FS:  $F(2,36)=6.93$ ,  $P=0.003$ ; 5FS:  $F(2,36)=7.96$ ,  $P=0.001$ ), and no test  $\times$  treatment interaction (2FS:  $F(2,36)=1.15$ ,  $P=0.32$ ; 5FS:  $F(2,36)=1.3$ ,  $P=0.28$ ). Post-hoc comparison showed that compared with saline, propranolol-treated rats froze significantly less during Test 1 (2FS:  $P=0.015$ , 5FS:  $P=0.01$ ), Test



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**Figure 4.** Propranolol does not impair retention of non-reactivated fear memories. A: Schematic of the experimental design. Rats received two or five footshocks. 1 or 36 days after training, saline or propranolol was injected in the absence of memory reactivation and tested one day later. Propranolol did not impair long-term memory in any experimental groups (B). NR: No-reattivation.

2 (2FS:  $P=0.046$ , 5FS:  $P=0.001$ ), and Test 3 (2FS:  $P=0.012$ ; 5FS:  $P=0.019$ ). Application of a weak reminder shock did not recover the original memory.

We also found no significant differences on the amount of memory deficit induced by propranolol between recent or remote memories with either weak or strong strength ( $F(3,38)=1.8$ ,  $P=0.16$ ) (data not shown).

### 3.4. Propranolol does not Disrupt the Reconsolidation of Recent or Remote Memories in the Absence of Memory Reactivation

Fig. 4 shows the freezing levels of different groups injected with the saline or propranolol either 1 (recent) or 36 (remote) days after training in the absence of memory reactivation (Test 1), and tested one day later. For recent memory, the freezing levels of rats that received propranolol in the absence of memory reactivation were not different from that of the saline group (2FS:  $t_{16}=0.37$ ,  $P=0.71$ ; 5FS:  $t_{16}=0.28$ ,  $P=0.80$ ). Similar results were

obtained for remote memory (2FS:  $t_{16}=0.32$ ,  $P=0.75$ ; 5FS:  $t_{16}=0.15$ ,  $P=0.89$ ).

## 4. Discussion

The present study investigated whether the impairing effects of propranolol on fear memory reconsolidation depend on the age as well as the strength of memory. We found that systemic injections of propranolol disrupt the reconsolidation of recent and remote memories acquired either with weak or strong training conditions. In both conditions, memory retention was not reinstated by a reminder shock in a different context, indicating that loss of memory is likely not due to extinction but rather reconsolidation disruption. Furthermore, the disruptive effect of propranolol was contingent upon reactivation. In fact, when propranolol was injected 1 or 36 days after training in the absence of memory reactivation, no effect was found on either recent or remote memories. This indicates that memory reactivation is required for the disruptive effect of propranolol on fear memory recon-

solidation. Our findings are in agreement with previous studies that demonstrated an impairment of contextual fear memory reconsolidation by post-retrieval systemic as well as intra-cerebral injections of propranolol (Abrari et al., 2008; Muravieva & Alberini, 2010). Similar effects of propranolol on reconsolidation of other types of memory have been reported in animals and human (Diergaarde, Schoffelmeer, & De Vries, 2006; Przybyslawski et al., 1999; Robinson & Franklin, 2010; Zhao et al., 2011). Furthermore, our findings demonstrate that the reconsolidation of both recent and remote contextual fear memories with either weak or strong strength requires  $\beta$ -adrenergic neurotransmission.

What mechanisms are involved in the effect of the post-retrieval administration of propranolol? Propranolol is a synthetic  $\beta$ -adrenergic receptor blocker that crosses the blood-brain and thus acts on both peripheral as well as central  $\beta$ -adrenergic receptors. It blocks the action of epinephrine and norepinephrine on both  $\beta$ 1- and  $\beta$ 2-adrenergic receptors. Norepinephrine and epinephrine play a key role in learning and memory processes, as evidenced by post-training increases in epinephrine, and noradrenalin release (Tomie, Tirado, Yu, & Pohorecky, 2004). Immediate post-training systemic injections of epinephrine or norepinephrine to rats enhance memory of aversively motivated inhibitory avoidance training (Gold & Van Buskirk, 1976; Roozendaal, Carmi, & McGaugh, 1996). More importantly, a blockade of  $\beta$ -adrenoceptors in the amygdala prevented memory enhancement induced by systemic injections of epinephrine (Liang, Juler, & McGaugh, 1986), indicating that epinephrine effects on memory consolidation are critically depend on the noradrenergic activation of the amygdala.  $\beta$ -adrenoceptor is coupled with the Gs protein, which activates adenylyl cyclase, catalysing the formation of cyclic adenosine monophosphate (cAMP) and activates protein kinase A and the cAMP response element binding protein (CREB, a transcription factor). The agents that disrupt the activity of CREB specifically block the formation of long-term memory, whereas the agents that increase the amount or activity of the transcription factor accelerate the process, indicating that CREB plays a key role in long-term memory formation (Yin & Tully, 1996). Post-reactivation amnesia was found in the present and other studies (Abrari et al., 2008; Diergaarde et al., 2006; Muravieva & Alberini, 2010; Robinson & Franklin, 2010; Zhao et al., 2011) by  $\beta$ -receptor blockade suggests that intracellular mechanisms involved the same second messenger pathways as involved in memory consolidation and formation.

Which parts of the brain were affected by post-retrieval administration of propranolol? Hippocampus and some cortical regions are important components of the sys-

tem involved in the reconsolidation of contextual fear memory. A recent study mapped brain regions involved in the recall of recent (day-old) and remote (month-old) memory in mice. This study showed that hippocampus was strongly activated only during recall of the contextual recent memory. In contrast, a number of different cortical regions were strongly activated only following recall of the same remote memory (Frankland, Bontempi, Talton, Kaczmarek, & Silva, 2004). A more recent study, using functional magnetic resonance imaging, showed that propranolol administration before memory reactivation reduces subsequent expression of emotional, but not neutral pictures. This emotional memory impairment was associated with significantly increased activity in the amygdala and the hippocampus for pictures that were correctly recognized at test. Most interestingly, the same structures were active (but not modulated by propranolol) during memory reactivation (Schwabe, Nader, Wolf, Beaudry, & Pruessner, 2011). Thus, we can hypothesize that the impairing effects of propranolol on fear memory reconsolidation, at least in part, might be mediated through blockade of  $\beta$ -adrenergic located in these regions.

Some previous studies suggested that strong memories may initially be resistant to reconsolidation-blocking treatments; they become once again labile after prolonged disuse. A recent study has shown that a weak memory for a drug-place association (4 pairings) underwent reconsolidation when reactivated 1 day after training. Propranolol disrupted reconsolidation for this memory. However, when the number of drug-place pairings was increased to 8, propranolol disrupted reconsolidation if memory was reactivated 30 days, but not 1-day after training (Robinson & Franklin, 2010). Similarly, it has been shown that strong fear auditory memory (10 tone-shock pairings) did not undergo reconsolidation 2 or 7 days after training. However, 30 or 60 days after training to memory reactivation, the memory was underwent reconsolidation and disrupted by anisomycin infused into the basolateral amygdala (Wang, de Oliveira Alvarés, & Nader, 2009). These findings suggest that boundary conditions induced by the strength of memory can be decreased over time. Furthermore, the disruptive effect of anisomycin on contextual fear conditioning can be influenced by the strength of memory. Increasing the strength of memory, the resistance of these fear memories to disruption was increased by anisomycin. In addition to the strength of memory, the age of memory also affects reconsolidation. Memories become increasingly resistant to disruption with age, as older memories become less amenable to reconsolidation and they could be rendered labile again only if the reactivation phase was prolonged (Antoine et al., 2012; Nader & Einarsson, 2010). More-

over, it has been also reported that blocking reconsolidation of older contextual fear memory requires larger doses of amnesic treatment (Bustos, Maldonado, & Molina, 2008). One possible mechanism for disruption of the old memory resilience is the increased distribution of memory trace over the brain areas (Nadel & Moscovitch, 1997). Another mechanism might be the reorganization of the memory trace, so that memory become less dependent from hippocampus while increasingly more dependent on cortical representation (Squire & Bayley, 2007).

Regarding contextual fear memory age, there are contradictory reports on reduced vulnerability to systemic and intra-hippocampal pharmacological manipulations. For example, a recent study reported more resistance of contextual fear memory to anisomycin infusions with age (Suzuki et al., 2004), while others found no more resistance with age (Frankland et al., 2006). The later study showed that post-reactivation of protein synthesis in the hippocampus disrupted reconsolidation of recent by ANI (1-day-old), but not remote (36-day-old), the contextual memories in mice. However, reconsolidation of remote (36-day-old) memories could be blocked by anisomycin, if the duration of the reactivation session was extended from 2.5 to 15 min (Frankland et al., 2006). Similarly, an earlier study examining contextual fear memory in rats found that intra-hippocampal infusions of anisomycin blocked reconsolidation of both recent (1-day-old) and remote (i.e., 45-day-old) memory (Debiec, LeDoux, & Nader, 2002), suggesting that the memory continues to be sensitive to hippocampal reconsolidation challenges over time.

Our findings that systemic administration of propranolol impairs the reconsolidation of contextual fear memory regardless to the age and strength of memory are inconsistent with the studies showing more stability and less susceptibility of memories to the disruption by pharmacological agents with age (Boccia et al., 2006; Eisenberg & Dudai, 2004; Milekic & Alberini, 2002), but confirm the studies found no more resistance with age (Debiec et al., 2002; Frankland et al., 2006). The mechanisms that lead to such discrepancies are not clear. One possible mechanism is that the impact of memory age and strength on reconsolidation susceptibility may vary as a function of the activation of endogenous hormonal systems and the nature of the memory (i.e; emotional, traumatic, spatial). Emotional arousal play an important role in encoding and reconsolidation of emotional-related memories in animals and humans (Cahill, Prins, Weber, & McGaugh, 1994; Soeter & Kindt, 2011), so that blocking the arousal associated with emotional events by  $\beta$ -adrenergic antagonist shortly after encoding or during the memory reactivation may reduce the subsequent fear

memory (Cahill et al., 1994; Dębiec & LeDoux, 2004; Kindt, Soeter, & Vervliet, 2009; Soeter & Kindt, 2011). On the basis of our results, it seems that reactivation of both recent and remote contextual fear memories with either weak or strong strength elicits emotional arousal and, consequently,  $\beta$ -adrenergic transmission which, in turn, may play an important role in the reconsolidation of contextual fear memory at recent and remote time points.

In conclusion, pharmacological manipulations of the reconsolidation process might open the door to novel treatment approaches for traumatic or drug-related memories. However, the boundary conditions on reconsolidation such as the age and the strength of memory may make these memories enormously resistant to pharmacological intervention. Our findings provide important evidence that systemic injections of propranolol impair the reconsolidation of contextual fear memory at recent and remote time points irrespective to the strength of memory. Systemic injections are valuable if the drug have a clinical relevance. Thus, propranolol could be a potential drug for treatment of traumatic or drug-related memories with different age (history) and strength in PTSD, addicted patients, and other mental disorders that have an emotional memory.

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