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The dynamic nature of the reconsolidation process and its boundary conditions: Evidence based on human tests

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ABSTRACT

The reconsolidation process is the mechanism by which the strength and/or content of consolidated memories are updated. This process is triggered by the presentation of a reminder (training cues). It is not always possible to trigger the reconsolidation process. For example, memory age and strength are boundary conditions for the reconsolidation process. Here, we investigated the dynamic changes in these conditions. We propose that the boundary conditions of the reconsolidation process are not fixed and vary as a consequence of the interaction between memory features and reminder characteristics. To modify memory properties, participants received a threatening social protocol that improves memory acquisition or a control condition (fake, without social interaction) prior to learning pairs of meaningless syllables. To determine whether a strong young or old declarative memory undergoes the reconsolidation process, we used an interference task (a second list of pairs of meaningless syllables) to disrupt memory re-stabilization. To assess whether the older memory could be strengthened, we repeated the triggering of reconsolidation. Strong young or old memories modulated by a threatening experience could be interfered during reconsolidation and updated (strengthened) by reconsolidation. Rather than being fixed, boundary conditions vary according to the memory features (strong memory), which indicates the dynamic nature of the reconsolidation process. Our findings demonstrate that it is possible to modify these limits by recruiting the reconsolidation process and making it functionally operative again. This novel scenario opens the possibility to new therapeutically approaches that take into account the reconsolidation process.

1. Introduction

The consolidation model states that memory storage implies a passage from a fragile state to a stable form (McGaugh, 2000). However, following the presentation of a memory cue (reminder), consolidated memories become reactivated, followed by a process of re-stabilization, which is referred to as reconsolidation (Dudai, 2012; Lee, 2009; Nader, Schafe, & Le Doux, 2000). A mismatch or prediction error during reactivation is necessary but not sufficient for the occurrence of reconsolidation (Forcato, Argibay, Pedreira, & Maldonado, 2009; Pedreira, Pérez-Cuesta, & Maldonado, 2004; Sevenster, Beckers, & Kindt, 2013, & Kindt, 2014). Memory features, such as strength and age, are crucial boundary conditions that limit the initiation of the reconsolidation process (Baratti, Boccia, Blake, & Acosta, 2008; Eisenberg & Dudai, 2004; Forcato, Fernandez, & Pedreira, 2013; Inda, Muravieva, & Alberini, 2011; Milekic & Alberini, 2002; Suzuki et al., 2004; Wang, de Oliveira Alvares, & Nader, 2009). Thus, strong memories are more resistant to reactivation, and consequently, more resistant to interferences (memory strengthening; Dudai & Eisenberg, 2004; Forcato, Fernandez, & Pedreira, 2014; Morris et al., 2006; Suzuki et al., 2004; Taylor, Olausson, Quinn, & Torregrossa, 2009; Wang et al., 2009; Winters, Tucci, & DaCosta-Furtado, 2009). Moreover, reconsolidation is not triggered when the reactivation stimulus is presented at long intervals after training (memory age; Baratti et al., 2008; Eisenberg & Dudai, 2004; Forcato et al., 2013; Inda et al., 2011; Milekic & Alberini, 2002). In summary, it is possible to differentiate the retrieval from the reactivation process considering that retrieval only evokes the consolidated memory when it is constrained by the boundary conditions (Forcato et al., 2014; Pedreira et al., 2004).

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The reconsolidation process is crucial for the modification of existing memories and is the mechanism by which the strength and/or content of consolidated memories are updated (De Oliveira Alvares et al., 2012, 2013; Forcato, Rodríguez, & Pedreira, 2011; Forcato et al., 2013; Forcato et al., 2014; Inda et al., 2011). Thus, repeated labilization–reconsolidation processes triggered by the presentation of specific reminders increase not only memory precision and persistence but also the resistance to interference during re-stabilization (De Oliveira Alvares et al., 2013; Forcato et al., 2013). Furthermore, the effect of strengthening depends on the age of the memory, in which older memories are more resistant to strengthening (Forcato et al., 2014; Inda et al., 2011).

One topic recurrently considered in reconsolidation studies is the inclusion of the process as the main mechanism to improve therapies for the treatment of anxiety disorders or maladaptive memories (Debiec & Ledoux, 2004; Kindt, Soeter, & Vervliet, 2009; Lee, Di Ciano, Thomas, & Everitt, 2005). The inclusion of this process in novel therapies may represent a crucial change that enables an alternative option in addition to extinction based therapies, which are extensively used in these treatments. The advantage of this change lies in the absence of relapse when extinction is used (Bouton, 2002). However, using these new protocols, it is possible that reconsolidation and extinction are not engaged, and the target fear memory remains in a transitional state (Merlo, Milton, Goozée, Theobald, & Everitt, 2014). Finally, regarding these potential therapies, it is also important to consider that boundary conditions, such as strength, target memory age and the selection of specific parameters in the reactivation process, will be crucial in the design of beneficial therapeutic approaches (Alberini, 2013; Forcato et al., 2013).

Using our declarative memory paradigm (paired associates; Forcato et al., 2007), we have previously demonstrated that the repeated presentation of the reminders cannot labilize or labilize and strengthen an old memory seven days after training. However, the absence of an effect may depend on forgetting, which overshadows memory interference or strengthening (Forcato et al., 2013, 2014). In a recent study (Fernández et al., 2015), we demonstrated how a social threatening event (virtual auditory panel), which was non-specifically related to memory (neutral declarative memory), affects the short- and long-term retention of this neutral declarative memory. In this previous study, we demonstrated that a threatening social situation improves the acquisition and persistence of a strong memory, which prevents the effect of forgetting.

The aim of the present study was to investigate the dynamic changes in the boundary conditions (age and strength) of the reconsolidation process. We proposed that these conditions are not fixed and vary as a consequence of the interaction between memory features and reminder characteristics. We predicted that the changes induced by a threatening social event during an early memory phase modify the memory features, which makes the memory stronger, and creates the possibility to reevaluate the labilization–reconsolidation process under this new condition (Forcato et al., 2013). Thus, we investigated whether a strong young (2 day memory, Experiment 1) or strong old (7 day memory, Experiment 2) declarative memory also undergoes the reconsolidation process and whether it could be strengthened by repeated triggering of the reconsolidation process (Experiment 3). Our findings demonstrate that it is possible to modify these limits by recruiting the reconsolidation process and making it functionally operative again. This possibility of change is relevant for the psychiatric field because it may enable improvements in therapies that use reconsolidation as the main mechanism.

2. Methods and materials

A total of 132 undergraduate and graduate students (77 females and 55 males) from Buenos Aires University (Argentina) participated in the current study. Prior to the experiments, participants provided a written informed consent that was approved by the Ethics Committee of the Review Board of the Sociedad Argentina de Investigación Clínica. The following students were excluded from the experiments: students with cardiovascular and endocrine diseases; students having physical illnesses or being on any kind of medication. Current or lifetime psychopathology or substance abuse was assessed by a clinical psychologist.

2.1. Virtual-auditory panel (VAP) protocol

The VAP protocol (Fernández et al., 2015) is an adaptation of the Trier Social Stress Test (TSST) protocol. The VAP protocol used consisted of three phases (Fig. 1A). *Phase 1* was an undemanding attentional task, in which 16 landscape images were shown and participants were asked to rate the images according to their likes. In *Phase 2*, participants had to prepare a speech to advertise themselves as the best candidate for a professional position; this phase lasted 5 min. Finally, in *Phase 3*, the experimenter explained to the participants that a hospital committee was following the presentation online using a webcam. As in the TSST protocol (Kirschbaum, Pirke, & Hellhammer, 1993), after the presentation, participants had to perform an arithmetic task. The experimenter used a pre-recorded ambient sound (different office sounds such as engines, papers, keys, and chairs) as background and a pitch modifier provided with three different voices (virtual panel) that simulated a hospital committee.

The fake VAP (VAPf) consisted of a non-threatening protocol, similar to the VAP but without the main stress component (Dickerson & Kemeny, 2004). In this case, participants were aware that the task was going to be conducted without social interaction. The first two phases were identical to the previous protocol. In contrast, in *Phase 3*, participants had to write down the speech and to resolve the arithmetic task. We included other tasks such as different multiplications, additions or symbol translations, so both protocols lasted the same time. The virtual panel software and the pre-recorded ambient sound were programmed in Cycling'74. Max/msp 5.0 (Fernández et al., 2015).

2.1.1. Measurements

Baseline measurements for the State Trait Anxiety Inventory (STAI), blood pressure, and heart rate were taken before *Phase 1*, blood pressure and heart rate were measured at four different time points: t0 (before *Phase 1*), t1 (after *Phase 2*), t2 (after the speech presentation) and t3 (after the arithmetic task) (Fig. 1A). Skin conductance level (SCL) was recorded during the entire experiment; we defined the SCL baseline level as the continuous measure during *Phase 1* (Fig. 1A). Blood pressure, heart rate and the STAI were measured for the last time at the end of Phase 3 (Fernández et al., 2015).

2.1.1.1. Subjective rating. Cognitive stress and anxiety were measured using the STAI (Spielberger, Gorsuch, & Lushene, 1970) before and after the administration of the procedures (before Phase 1 and 10 min after Phase 3, respectively).

Blood pressure Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) and Heart Rate (HR) were assessed using an Omron HEM 7220 Premium digital Tensiometer (http://omronhealthcare.com/products/7-series-upper-arm-blood-pressure-monitor-bp760). Cardiovascular measurements were taken before Phase 1 (t0), after Phase 1 (t1), at the end of the speech (t2), and at the end of the arithmetical task (t3) (Fig. 1A).

Electrodermal activity was measured along the entire experiment, using an input device with a sine-shaped excitation voltage (±0.5 V) of 50 Hz, derived from the main frequency used in *Psychlab Precision Contact Instruments* (http://www.psychlab.com/). The input device was connected to two Ag/AgCl electrodes of

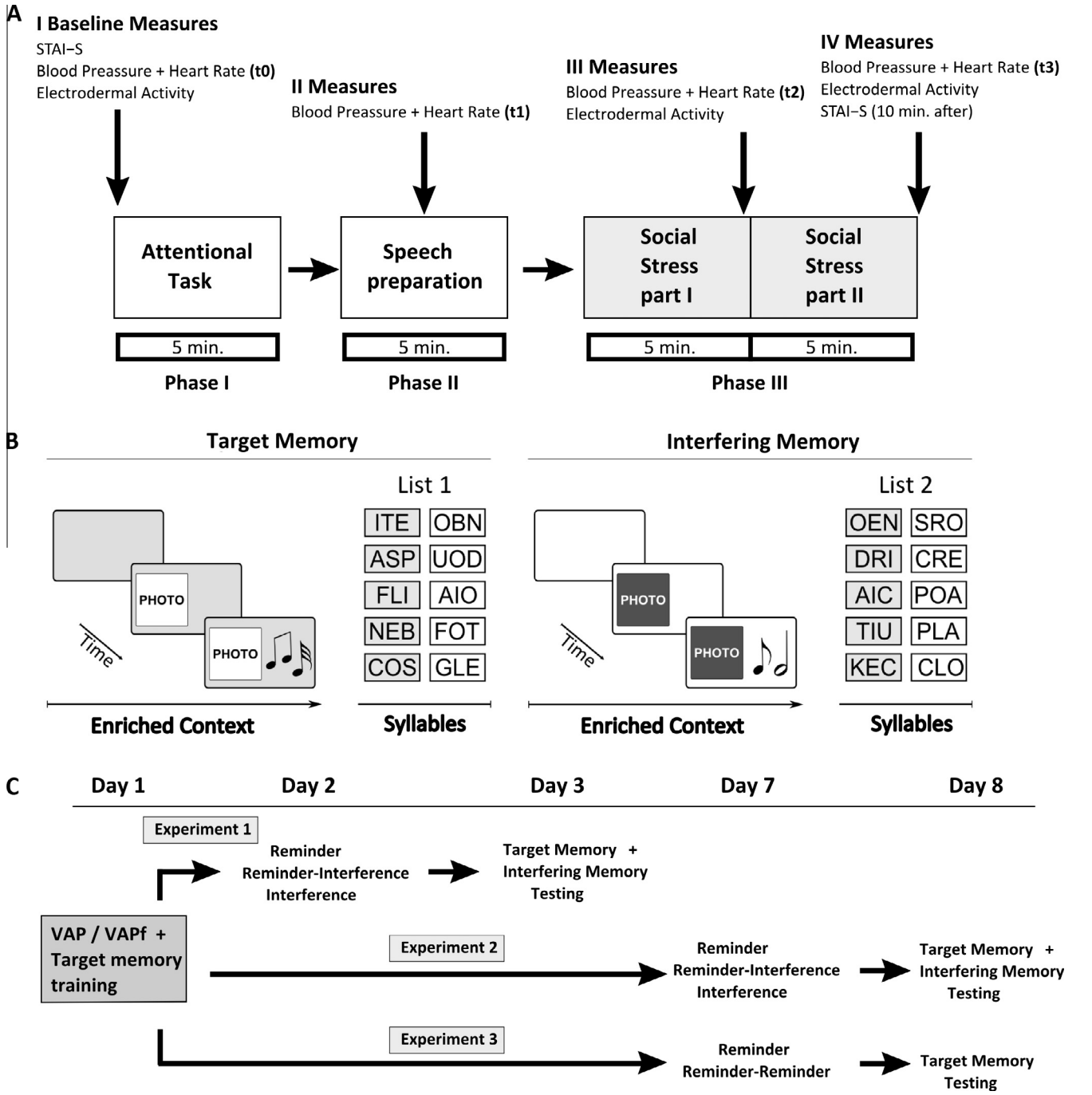


Fig. 1. *(A) Stress protocol.* Schematic diagram showing timing of the tasks and the different measures obtained: Subjective Rating (STAI), cardiovascular activity (blood pressure and heart rate) and sympathetic activity (constant electrodermal activity measurement). Social stress part I refers to the speech in front of an auditory (VAP). VAPf group only writes down the task. Social stress part II stands for the arithmetic task and was conducted as above. The arrows stand for the time when the measures were taken. *(B) Memory task. Target Task:* A trial consisted of the context period, i.e. a specific combination of a light (color illumination of the room), image (a picture) and sound (music), and by a syllable period, i.e. six seconds after the stimulus presentation, the five pairs of cue-response syllables (List 1 as shown) were presented successively 10 times in random order. Testing session consisted in the context formation and only one cue recall trial. *Interfering Task:* Training and testing sessions were conducted as with target memory. *(C) Experimental scheme.* The scheme including the 3 experiments performed in this report was presented in (C).

20 mm × 16 mm. The electrodes were located in the intermediate phalanges of the index and middle fingers of the non-dominant hand. Data were analyzed with Matlab (Mathworks Inc. Sherborn, MA, USA) and Ledalab (Benedek & Kaernbach, 2010).

2.2. Memory protocol

On Day 1, subjects learned a list of five pairs of meaningless syllables (List 1) in an enriched specific context (image, colored light and music; Forcato et al., 2007). Each pair was formed by a cue syllable associated with a response syllable (Fig. 1B). During the training session, the list was presented in 10 trials. Only the subjects that achieved at least 65% of correct responses during the last four training trials were included. During the reactivation session (Fig. 1C), one or seven days after training (Day 2 or Day 7, respectively), subjects received one, two or no reminder presentations. The reminder was formed by the specific context and a cue-syllable immediately followed by an interruption message without

any opportunity to complete the target (Forcato et al., 2009). The interference groups learned an interference task (List 2, Fig. 1B) after the reminder, which consisted of another set of five pairs of meaningless syllables in a different enriched context. The testing session took place 3 or 8 days after List 1 training (Day 3 or Day 8, respectively) and consisted of 2 trials. Errors made at testing were classified as: Void-type errors (blank responses) associated with memory persistence, Confusion-type errors (writing a non-existent response syllable) associated with memory precision, and Intralist-type errors (writing response syllables for a different cue syllable; Forcato et al., 2013). The scheme including the 3 experiments performed in this report is presented in Fig. 1C.

2.2.1. Amnesic effect

Considering that memories are integrated into complex associative networks, we further used the retrieval-induced forgetting effect as an alternative method to reveal the amnesic effect of the interference task (List 2) on the target memory reconsolidation (List 1; Anderson, Bjork, & Bjork, 1994). This effect implies that the retrieval of a target memory could temporary block the retrieval of related memories. Because List 1 and List 2 share elements (room, experimenter, same way of presenting stimuli), it is expected that they interact during retrieval. Thus, if the List 1 memory is intact (it does not undergo through the reconsolidation process), its retrieval temporally interferes with the retrieval of List 2 when it is tested immediately after target memory (Retrieval-Induced Forgetting – RIF-, high number of errors for List 2 testing). Otherwise, if List 1 is impaired (memory reconsolidation was interfered), its retrieval does not interfere with List 2 retrieval (no-RIF, fewer errors for List 2 testing; Forcato et al., 2007).

2.3. Experimental groups

2.3.1. Experiment 1 (n = 12)

A total of 72 participants (24 ± 2.1 years old) randomly assigned in six groups were included in Experiment 1. On Day 1, the Reminder/Interference-VAP, noReminder/Interference-VAP and Reminder-VAP groups received the VAP and then learned List 1. The Reminder-VAPf and Reminder/Interference-VAPf groups received the VAPf before List 1 training. On Day 2, the Reminder/Interference-VAPf and Reminder/Interference-VAP groups received the reminder and then learned the interference task. The Reminder-VAP and the Reminder-VAPf groups received the reminder without interference task training whereas the noReminder/Interference-VAP. We also included an Interference-Control group which only learned List 2 to evaluate the List 2 performance at testing session. The inclusion of this group allowed us to evaluate the RIF-effect (by the comparison of List 2 performance in the different groups of the experiment). On Day 3, all groups were tested on List 1 and then the groups that had learned the interference task on Day 2 were tested on the interference task.

2.3.2. Experiment 2 (n=12)

A total of 48 participants (23 ± 2.6 years old) randomly assigned in four groups were included in Experiment 2. On Day 1, three groups received the VAP before List 1 training, and one group learned only List 1. Seven days after training (Day 7), the Reminder-VAP and Reminder/Interference-VAP groups received the reminder and then the Reminder/Interference-VAP group learned the interference task. The noReminder/Interference-VAP group learned only List 2 on Day 7. The Interference-Control group learned only the interference task. On Day 8, all groups were tested on List 1 and then on List 2.

2.3.3. Experiment 3 (n=12)

A total of 36 participants (24 ± 2.5 years old) randomly assigned in three groups were included in Experiment 3. On Day 1, all groups received the VAP before List 1 training. Seven days after training (Day 7), subjects received one or two reminders (Reminderx1-VAP and Reminderx2-VAP groups, respectively) or no-reminder (Control-VAP). On Day 8, all groups were tested on List 1.

2.4. Statistical Analysis

2.4.1. STAI

The STAI is reported as the mean score difference in each participant at the end of Phase 3 and before the attentional task (Phase 1). Data were analyzed using one-way analysis of variance (ANOVA), followed by LSD post-hoc comparisons (FISHER, $\alpha = 0.05$) when necessary.

2.4.2. Blood pressure and heart rate

A mean cardiovascular value (t0, t1, t2, t3) was reported (mm/HG, BPM). Data were analyzed using repeated measures ANOVA (Group × Time). When the interaction was significant, simple effects were performed followed by LSD comparisons when appropriate. When sphericity was not accomplished, Greenhouse–Geisser correction was applied.

2.4.3. Electrodermal activity

It is reported as the mean SCL (μS) in each participant during the baseline attentional task (Phase 1) and during stress induction (Phase 3). The use of the mean SCL is supported by the stationary time series of the signal and the low variability between points (Fernández et al., 2015). Data were analyzed using repeated-measures ANOVA (Group × Time). Interaction, post-hoc comparisons and sphericity were treated as with blood pressure and heart rate measurements.

2.4.4. Neutral declarative memory (List 1 and Interference task)

The Training session is reported as the mean number of errors per training trial and was analyzed with repeated-measures ANOVA. The Testing session was first analyzed with one-way ANOVA and followed by post-hoc comparisons (FISHER, $\alpha = 0.05$). We also studied the different types of errors (Forcato et al., 2013). Void-, Confusion- and Intralist-type errors are reported as the mean number of errors and were analyzed with one-way ANOVA, followed by LSD post-hoc comparisons ($\alpha = 0.05$).

3. Results

3.1. Experiment 1

3.1.1. Memory task

The goal of Experiment 1 was to determine whether a strong declarative memory acquired under social stress passes through the reconsolidation process. We compared groups that received the virtual auditory panel (VAP) protocol or the fake protocol (VAPf), the reminder or no reminder, and the interference or no interference task (Fig. 2A).

The Reminder-VAP group exhibited significantly fewer errors compared with the Reminder/Interference-VAP group regarding target memory testing (Fig. 2B, $F_{4,55} = 11.19$, $P < 0.001$, LSD post-hoc comparison $P < 0.001$). The same pattern of results was identified for the fake VAP groups (Reminder-VAPf and Reminder/Interference-VAPf, $P < 0.001$). The noReminder/Interference-VAP group also exhibited a significantly increased number of errors at testing compared with the Reminder-VAP group (respectively,

A

Groups	Day 1	Day 2	Day 3
Reminder-VAP	Training	R	Testing
Reminder/Interference-VAP	Training	R -- Interference	Testing
noReminder/Interference-VAP	Training	Interference	Testing
Reminder-VAPf	Training	Interference	Testing
Reminder/Interference-VAPf	Training	R -- Interference	Testing
Control-Interference	----	Interference	Testing

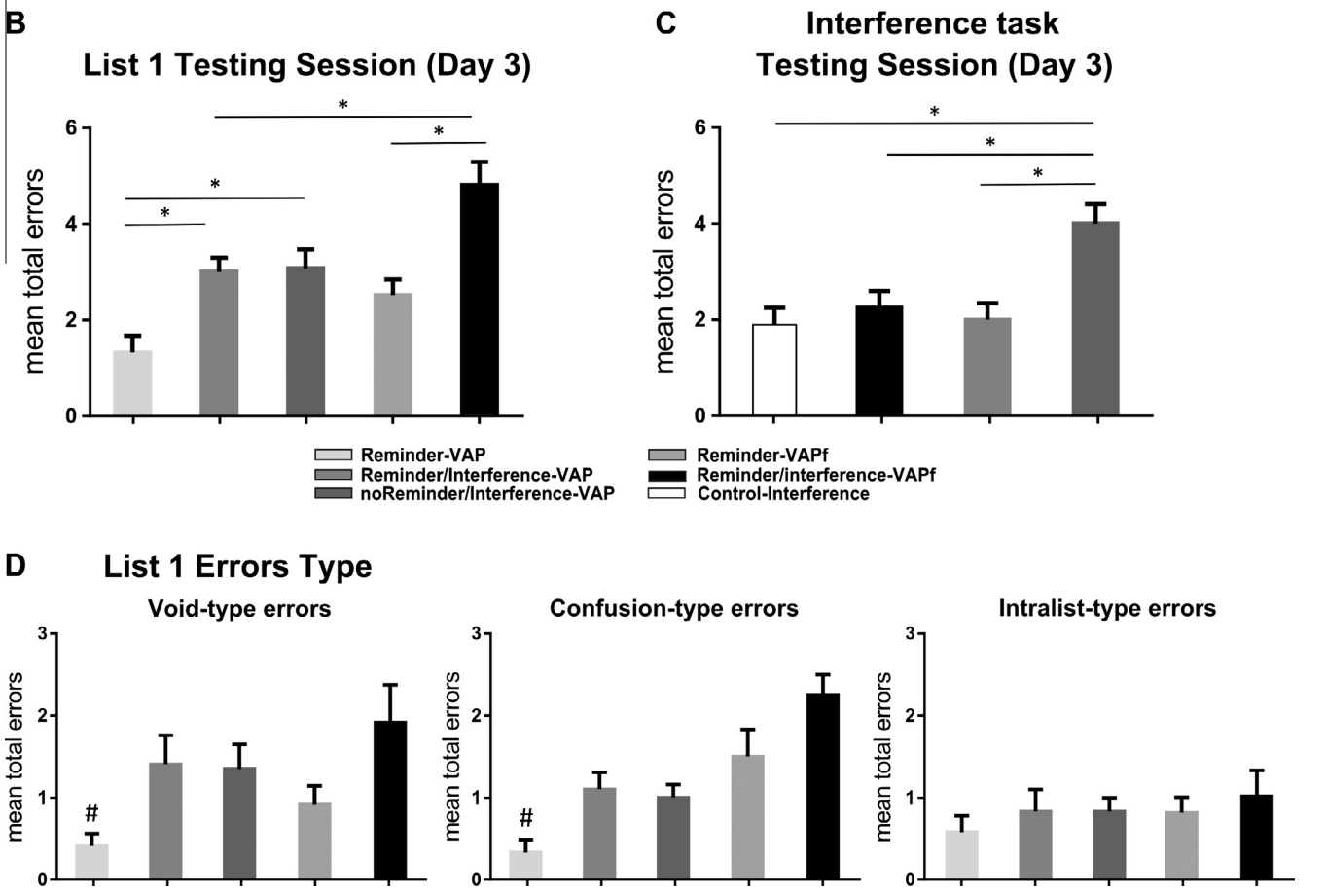


Fig. 2. Experiment 1. A strong memory acquired under stress can be labilized and impaired with an interference task prior the presentation of a reminder on Day 2 ($n = 12$). (A) Experimental protocol. A three-day experiment. VAP and VAPf stands for the stress and control protocols and R for the reminder. (B) Target memory testing session. Mean number of total errors ± SEM on Day 3, $^{*}P < 0.05$. (C) Interference task testing session. Mean number of total errors ± SEM on Day 3 for the interference task, $^{*}P < 0.05$. (D) Error type. Symbols as above.

$P < 0.005$). Thus, to determine if the increased number of errors in the groups that received the interference task was a result of an impairment effect on memory re-stabilization or to simultaneous retrieval interference of related memories, we evaluated the interference task performance at testing (Fig. 2C). When similar tasks are learned, memories interact at retrieval (Retrieval-Induced Forgetting – RIF-high number of errors for List 2 testing; Anderson et al., 1994; Forcato et al., 2007). However, if the target memory is impaired, there is no-RIF effect on the related memory. Fig. 2C shows that the Reminder/Interference-VAP and the Reminder/Interference-VAPf groups did not make a significant number of errors when the interference task was compared with the Interference-Control group that was only trained and tested for that task (no-RIF, one-way ANOVA $F_{3,44} = 7.37$, $P < 0.005$, LSD post-hoc comparison all $P > 0.05$). In contrast, the noReminder/Interference-VAP group made a significantly increased number of errors compared with the Interference-Control group, showing the presence of an RIF effect ($P < 0.001$).

Fig. 2B shows that the groups that received the VAP protocol had better performance at the target memory testing compared with the groups that received the same treatment of reminder and interference but the VAPf protocol instead (Fig. 2B, one-way ANOVA $F_{4,55} = 11.19$, $P < 0.001$, LSD post-hoc comparison Reminder-VAP vs. Reminder-VAPf groups $P < 0.05$; Reminder/Interference-VAP vs. Reminder/Interference-VAPf groups $P < 0.001$). Moreover, the Reminder-VAP group made fewer errors in the target task testing compared with the other groups (all $P < 0.005$). Regarding the error type made at testing, the

Reminder-VAP group made fewer Void-type and Confusion-type errors compared with the other groups (Fig. 2D, one-way ANOVA $F_{4,55} = 9.34$, $P < 0.0001$, LSD post-hoc comparison all $P < 0.05$). No significant differences were identified for the Intralist-type errors ($P > 0.05$).

There were no significant differences between the groups at the training of the target task or the interference task (repeated-measures ANOVA, List 1 $F_{4,55} = 2.41$, $P > 0.05$; interference task $F_{3,43} = 0.88$, Fig. S1). In addition, there was no group by trial interaction (List 1, $F_{32,440} = 0.98$ $P > 0.5$; interference task $F_{24,344} = 1.15$, $P = 0.27$).

Similar to our previous report, declarative memory improvement was associated with an unrelated threatening event during acquisition (the VAP protocol induced a significant increase in subjective stress and the sympatho-adrenal-medullary -SYM-response). Despite its strength, the strong memory may be labilized and interfered, without changes in the parameters of the reactivation session. Nevertheless, the interference is less effective and the memory is preserved by the enhancement produced by the threatening situation.

3.1.2. Cognitive and physiological measurements

The VAP groups exhibited significant SYM axis activation and cognitive stress following the administration of the protocol compared with the VAPf (Table 1). The VAP protocol induced an increase in cardiovascular and electrodermal activity. The VAP groups also exhibited a significantly increased in the STAI score compared with the other three VAPf-groups, which suggests an increase in subjective stress (Table 1).

3.2. Experiment 2

3.2.1. Memory task

The goal of Experiment 2 was to determine whether the reconsolidation process occurs in an older memory. The reactivation session occurred seven days after training (Day 7). On Day 1, three groups received the VAP, prior to the List 1 training. On Day 7, the Reminder-VAP and Reminder/Interference-VAP groups received the reminder. The Reminder/Interference-VAP, the noReminder/Interference-VAP, and the interference task control (Interference-Control) groups subsequently received the interference task. All subjects were tested for Lists 1 and 2 on Day 8 (Fig. 3A).

The Reminder/Interference-VAP and noReminder/Interference-VAP groups made significantly more errors at the List 1 testing (Day 8) compared with the Reminder-VAP group (Fig. 3B, one-way ANOVA $F_{2,33} = 8.13$, $P < 0.001$; LSD post-hoc comparison $P < 0.001$ and $P < 0.005$, respectively).

The evaluation of the interference memory demonstrated that the Reminder/Interference-VAP and Interference-Control groups made a similar number of errors (Fig. 3C one-way ANOVA $F_{2,33} = 13.81$, $P < 0.001$; LSD post-hoc comparison $P = 0.57$). This finding indicated the absence of RIF. In contrast, the noReminder/Interference-VAP group made significantly more errors compared with noReminder/Interference-VAP and noReminder/Interference groups, which indicates the presence of RIF ($P < 0.005$ and $P < 0.0001$, respectively). Similar to Experiment 1, these findings suggest that the interference task training following the reminder presentation (Reminder/Interference-VAP) impaired the reconsolidation of the old declarative memory (List 1), and the interference task training in the absence of the reminder only inhibited the retrieval of the target memory (noReminder/Interference-VAP).

Regarding the error type, the Reminder-VAP group made significantly fewer Void-type and Confusion-type errors compared with the other two groups (Fig. 3D, one-way ANOVA $F_{2,33} = 6.29$, $P < 0.0005$ and $F_{2,33} = 5.65$, $P < 0.05$, respectively; LSD post-hoc comparison, all $P < 0.005$). No differences were identified for the Intralist-type errors ($P > 0.05$). Repeated-measures ANOVA indicated there were no significant differences between the groups for List 1 for the interference task training (Fig. S1; $F_{2,33} = 0.02$, $P = 0.98$ and $F_{2,33} = 2.14$, $P = 0.14$, respectively), as well as no group by trial interaction ($F_{16,264} = 0.58$, $P = 0.89$ and $F_{16,264} = 1.06$, $P = 0.39$, respectively).

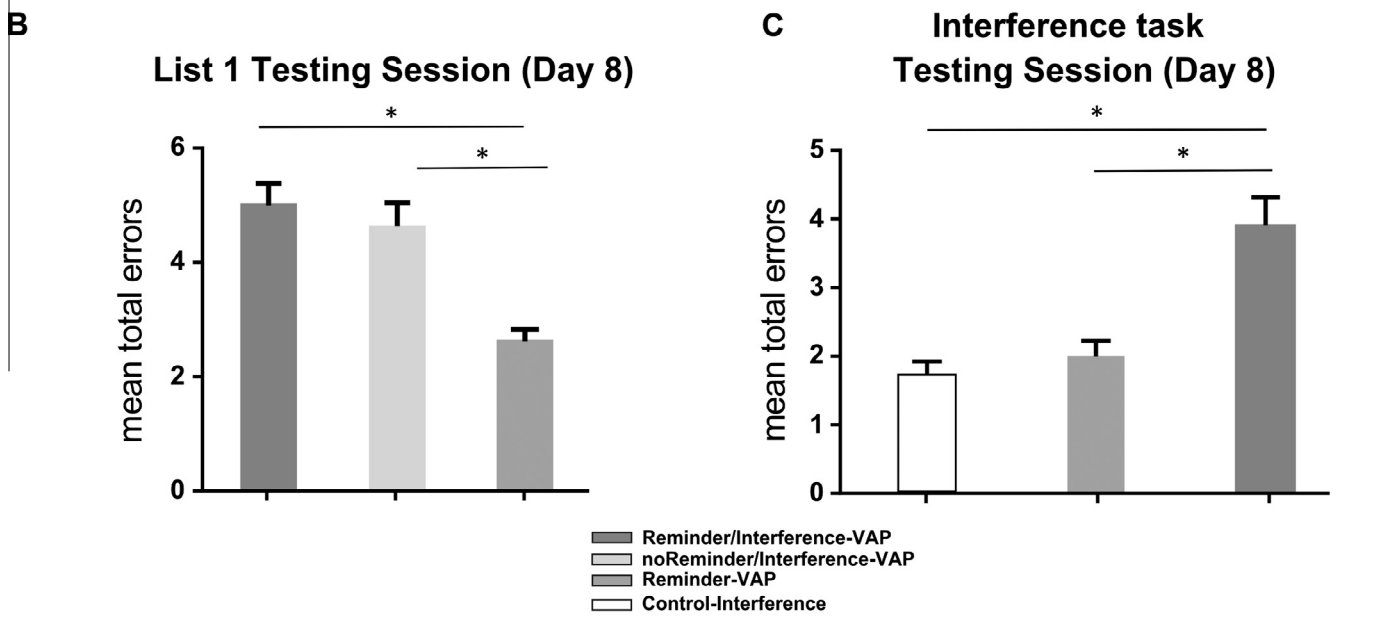
Table 1
Cognitive and physiological measures for the Experiment 1. Cardiovascular activity at different time points (t0, t1, t2, t3). Mean SBP (mm HG), Mean DBP (mm HG) and Mean HR (BPM), Mean Subjective Rating difference and SCL (μS) (± SEM) at 4 different time points for the three groups. The *F* and effect size reported corresponds to the group × time interaction of a repeated measures ANOVA. SE stands for simple effects.

	Means (±SE) of the cognitive and physiological measures					
	Experiment 1					
	Reminder-VAPf	Reminder/ Interference-VAPf	Reminder-VAP	Reminder/ Interference-VAP	noReminder /Interference-VAP	
SBP (mm HG)						
t0	108.75 (1.75)	107.33 (2.42)	106.20 (1.21)	108.71 (2.72)	108 (2.68)	$F(12,165) = 9.08$, $p < 0.001$
t1	103.41 (2.86)	96 (2.5)	100.12 (0.82)	98.33 (3.10)	101.16 (1.50)	SE VAP group $_{t2}$ $p < 0.001$; $_{t3}$ $p < 0.001$
t2	**97.25 (1.39)**	**97.5 (2.02)**	**116.22 (1.34)**	**116.5 (2.75)**	**114.08 (2.71)**	LSD all $p < 0.001$
t3	**96.59 (1.58)**	**95.16 (1.72)**	**113.58 (1.31)**	**114.16 (2.61)**	**110.85 (1.93)**	SE time VAP $_{t1-t2} < 0.001$
DBP (mm HG)						
t0	73,75 (1.38)	74.5 (1.1)	74.10 (1.96)	74.10 (2.46)	75.25 (2.07)	$F(12,165) = 9.08$, $p < 0.001$
t1	70.33 (1.66)	70.9 (1.72)	69.02 (0.71)	68.16 (1.42)	70.41 (1.53)	SE VAP group $_{t2}$ $p < 0.001$; $_{t3}$ $p < 0.001$
t2	**71.3 (1.50)**	**70.5 (1.8)**	**79 (0.97)**	**78.6 (1.21)**	**79.25 (1.34)**	LSD all $p < 0.001$
t3	**69.25 (1.49)**	**68.1 (1.45)**	**78.55 (0.96)**	**77.69 (1.12)**	**78.66 (1.68)**	SE time VAP $_{t1-t2} < 0.001$
HR (BPM)						
t0	79.25 (1.17)	77.5 (2.21)	77.59 (1.32)	78.83 (1.45)	78.5 (2.38)	$F(12, 165) = 2.74$, $p < 0.005$
t1	75 (1.60)	73.91 (1.70)	74.63 (1.01)	75.91 (1.36)	75 (1.53)	LSD all $p < 0.001$
t2	**75 (1.35)**	**75.33 (1.49)**	**83.10 (1.26)**	**80.93 (1.27)**	**81.21 (2.72)**	SE VAP group $_{t2}$ $p < 0.005$; $_{t3}$ $p < 0.005$
t3	**70.1 (1.14)**	**71 (1.34)**	**82.16 (1.33)**	**80.41 (1.28)**	**80.75 (3.01)**	SE time VAP $_{t1-t2} < 0.005$
STAI						
Score	−0.08 (0.36)	0.83 (0.34)	−1.63 (0.28)	−1.16 (0.42)	−1.33 (0.49)	$F(4, 55) = 5.96$, $p < 0.001$, LSD all $p < 0.001$
SCL (μS)						
Phase I	3.78 (0.22)	3.64 (0.28)	3.94 (0.23)	3.52 (0.30)	3.72 (0.34)	$F(4, 55) = 12.23$, $p < 0.001$
Phase III	**3.76 (0.23)**	**3.19 (0.28)**	**5.574 (0.22)**	**4.99 (0.49)**	**5.32 (0.51)**	SE VAP $p < 0.001$; SE VAP time $_{I-III}$ $p < 0.001$

The bold type reflect the statistical significant differences.

A

Groups	Day 1	Day 7	Day 8
Reminder/Interference-VAP	Training	R -- Interference	Testing
noReminder/Interference-VAP	Training	Interference	Testing
Reminder-VAP	Training	R	Testing
Control-Interference	--------	Interference	Testing



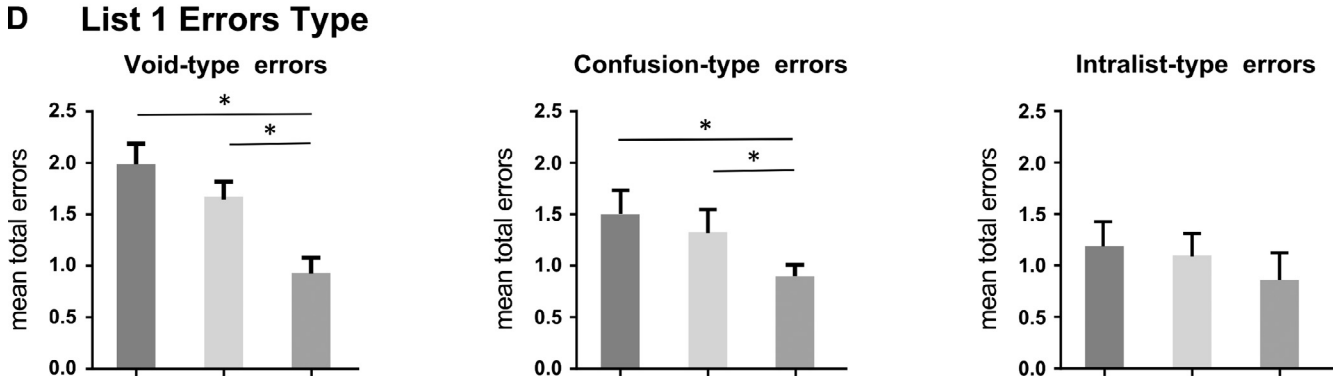


Fig. 3. Experiment 2: A strong-old memory acquired under stress can be labilized and impaired by an interference task ($n = 12$). (A) Experimental protocol. A three-day experiment, symbols as in Experiment 1. (B) Target memory testing session. Mean number of total errors ± SEM on Day 8, $^{*}P < 0.05$. (C) Interference task testing session. Mean number of total errors ± SEM on Day 8 for the interference task. (D) Error type. Symbols as above.

Taken together, these findings demonstrate that an unrelated threatening event improved a neutral declarative memory during acquisition. As a consequence, this strong memory was preserved for a longer period of time and the forgetting effect was reduced. Moreover, this strong old memory may be labilized and interfered by a second learning task. These findings indicated that for a 7 day memory, age is not a boundary condition for the reconsolidation process in this experimental condition (Forcato et al., 2013, 2014).

3.2.2. Cognitive and physiological measures

The groups exhibited the same profile as in Experiment 1. There was no difference between the VAP groups during stress induction (Table 2).

3.3. Experiment 3

3.3.1. Memory task

To determine how old memories acquired close to a threatening situation may be strengthened by repeated labilization–reconsolidation processes, we conducted a three-day experiment using three groups (Fig. 4A). On Day 1, the subjects received the VAP protocol prior to learning List 1. On Day 7, two groups received one or two reminders (Reminderx1-VAP and Reminderx2-VAP, respectively), and the remaining group received no treatment on Day 7 (Control-VAP). List 1-memory was evaluated on Day 8 (Fig. 4A).

The Reminderx2-VAP group made fewer errors at List 1 testing compared with the Reminderx1-VAP and Control-VAP groups (Fig. 4B, one-way ANOVA $F_{2,33} = 3.39$, $P < 0.05$: LSD post-hoc

Table 2
Cognitive and physiological measures for the Experiment 2 and 3. Cardiovascular activity at different time points (t0, t1, t2, t3). Mean SBP (mm HG), Mean DBP (mm HG) and Mean HR (BPM), Mean Subjective Rating difference and SCL (μS). Symbols as in Table 1.

	Means (±SE) of the cognitive and physiological measures							
	Experiment 2				Experiment 3			
	Reminder/ Interference-VAP	noReminder/ Interference-VAP	Reminder-VAP		Reminderx2-VAP	Reminderx1-VAP	Control-VAP	
SBP (mm HG)								
t0	109.75 (1.28)	107.33 (1.96)	110.10 (3.20)	$F(6,99)=0.187$	108.83 (1.65)	112.75 (2.07)	109.35 (2.03)	$F(6,99) = 0.462$
t1	100.25 (1.05)	98.25 (2.16)	100.10 (2.27)	$p = 0.98$	98.91 (1.73)	102.16 (1.50)	102.23 (1.67)	$p = 0.83$
t2	**115.66 (1.96)**	**112.58 (0.99)**	**115.54 (2.92)**	SE time $_{t1-t2}$ $p < 0.001$	**113.25 (1.52)**	**116.16 (2.63)**	**116.52 (2.50)**	SE time $_{t1-t2}$ $p < 0.001$
t3	111 (0.90)	108.42 (1.75)	112 (2.54)		110 (2.26)	112.21 (2.34)	112.94 (1.89)	
DBP (mm HG)								
t0	74.58 (1.94)	73.08 (1.58)	75.36 (0.85)	$F(6,99)=0.838$	73.58 (2.29)	74.16 (1.60)	75.35 (1.21)	$F(6.99)=1.50$
t1	68.91 (1.75)	66.91 (1.17)	69.55 (1.71)	$p = 0.54$	71.66 (1.88)	71.33 (1.33)	67.52 (1.28)	$p = 0.16$
t2	**78.68 (1.23)**	**78.08 (1.16)**	**81.36 (2.71)**	SE time $_{t1-t2}$ $p < 0.001$	**79.5 (1.96)**	**79.23 (1.34)**	**80.35 (1.89)**	SE time $_{t1-t2}$ $p < 0.001$
t3	79.16 (1.54)	77.08 (1.89)	80.54 (1.55)		80.66 (1.83)	78.33 (1.71)	79.17 (1.33)	
HR (BPM)								
t0	81.10 (2.03)	82 (3.58)	81.54 (2.02)	$F(6,99)=0.43$	81.08 (1.53)	79.25 (1.69)	80.76 (1.31)	$F(6,99)=0.128$
t1	74.66 (1.83)	75.5 (2.01)	76.36 (2.41)	$p = 0.86$	78.41 (2.70)	75.41 (2.57)	78 (1.82)	$p = 0.99$
t2	**83 (1.61)**	**81.41 (2.30)**	**80.81 (3.16)**	SE time $_{t1-t2}$ $p < 0.005$	**84 (1.89)**	**80.08 (1.49)**	**83.35 (2.80)**	SE time $_{t1-t2}$ $p < 0.005$
t3	81 (1.15)	80.75 (1.16)	82.09 (2.20)		84.66 (2.47)	81.41 (1.51)	84 (2.35)	
STAI								
Score	−1.33 (0.25)	−1.08 (0.23)	−1.09 (0.31)	$F(2, 33)=0.263$. $p = 0.76$	−1.17 (0.20)	−1.25 (0.25)	−1.08 (0.20)	$F(2, 31)=0.232$, $p = 0.79$
SCL (μS)								
Phase I	3.38 (0.40)	3.49 (0.34)	4.05 (0.49)	$F(2,33)=0.251$; $p = 0.50$	3.83 (0.41)	4.02 (0.49)	3.76 (0.34)	$F(2,33)=0.551$; $p = 0.85$
Phase III	**4.98 (0.43)**	**5.18 (0.45)**	**5.45 (0.61)**	SE VAP time $_{I-III}$ $p < 0.001$	5.33 (0.66)	5.91 (0.48)	5.29 (0.39)	SE time VAP I–III $p < 0.001$

The bold type reflect the statistical significant differences.

A

Groups	Day 1	Day 7	Day 8
Reminderx2-VAP	Training	R-R	Testing
Reminderx1-VAP	Training	R	Testing
Control-VAP	Training	---	Testing

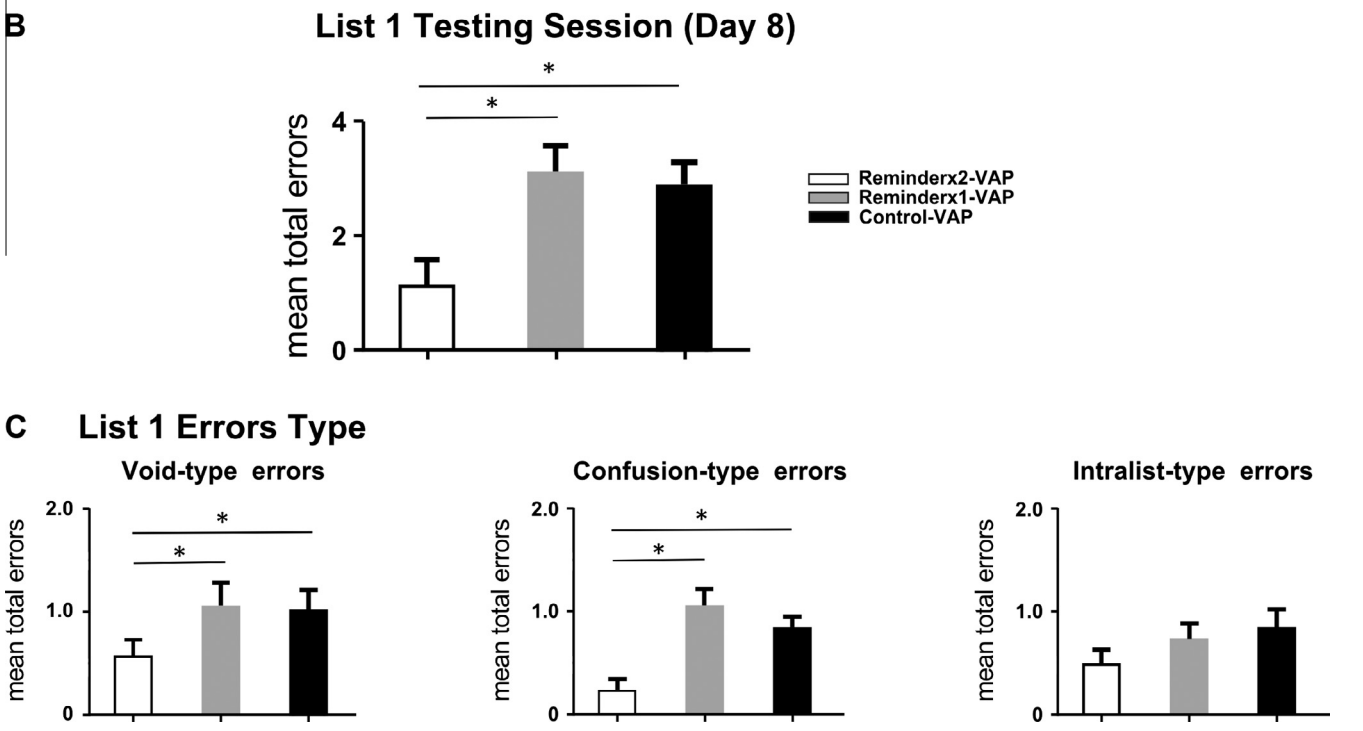


Fig. 4. Experiment 3. Two reminders on Day 7 strength a strong old memory ($n = 12$). (A) Experimental protocol. A three-day experiment, symbols as in Experiment 1 and 2. (B) Target memory testing session. Mean number of total errors ± SEM on Day 8, * $P < 0.05$. (C) Interference task testing session. Mean number of total errors ± SEM on Day 8 for the interference task. (D) *Error type*. Symbols as above.

comparison $P < 0.05$ and $P < 0.05$, respectively). We subsequently analyzed the types of errors made during testing (Fig. 4C). The Reminderx2-VAP group exhibited a significantly lower number of Void- and Confusion-type errors compared with the other two groups ($F_{2,33} = 3.64$, $P < 0.05$ and $F_{2,33} = 4.88$, $P < 0.01$, respectively; LSD post-hoc comparison all $P < 0.05$ and all $P < 0.005$, respectively). No significant differences were identified for the Intralist-type errors ($P > 0.05$).

Repeated-measures ANOVA indicated there were no significant differences between the groups at training (Fig. S1, $F_{2,33} = 0.58$, $P = 0.57$), as well as no group by trial interaction ($F_{16,264} = 1,12$, $P = 0.34$).

These findings demonstrate that a strong old memory may be strengthened by the triggering of two consecutive labilization–re consolidation processes. These findings also support the idea that for a strong memory, the strengthening function of the reconsolidation process is not constrained by the age of the memory, which thus changes the dynamics of the process (Forcato et al., 2013).

3.3.2. Cognitive and physiological measures

Similar to Experiments 1 and 2, the VAP protocol exhibited a similar profile regarding the physiological and cognitive measures (Table 2).

4. Discussion

Following the reappearance of the reconsolidation process, three topics have been recurrently considered in the search for its therapeutic use: its boundary conditions, role and profound characterization in humans (Alberini, 2005, 2013; Corlett, Krystal, Taylor, & Fletcher, 2009; Dudai, 2012; Hardt, Einarsson, & Nader, 2010). Using a declarative memory paradigm, we analyzed how two boundary conditions, as age and strength, affect the reconsolidation function. To resemble everyday life, in these experiments the acquisition of the task during a social threatening situation (Fernández et al., 2015) results in the formation of a strong memory. This strong memory becomes more persistent as a consequence of the improvement during acquisition that counteracted with the effect of forgetting (Fernández et al., 2015). Here, we demonstrated that strong young memories passed through the reconsolidation process and were more resistant to interference (Experiment 1). Moreover, the reconsolidation of strong old memories was impaired by the presentation of a reminder followed by an interference task (Experiment 2). These memories were also strengthened by repeated triggering of the labilization–reconsolidation process, which recovered its updating function (Experiment 3). The analysis of the types of errors indicated that the stress prior to acquisition or the strengthening by repeated labilization–reconsolidation processes improved memory precision and persistence (Forcato et al., 2013).

A boundary condition emerges when a reminder fails to reactivate a target memory. In relation to the boundary conditions analyzed in this report, other studies with animal models have demonstrated the influence of memory strength on memory reconsolidation. In these cases, it was mandatory to modify

the parameters of the reminder to trigger memory reconsolidation (Suzuki et al., 2004; Wang et al., 2009). Thus, using a strong training protocol, it was necessary to change the reminder duration or the moment when it was presented to reactivate the memory. The age of a memory also affects the reconsolidation process. The interval between the training and the reminder session determines the occurrence of the process (Inda et al., 2011; Milekic & Alberini, 2002). It has also been demonstrated that memory strengthening by repeated labilization–reconsolidation processes is constrained by the passage of time, which changes from the reconsolidation to extinction of older memories (Inda et al., 2011).

Nevertheless, these boundary conditions have scarcely been investigated using human memory paradigms or analyzing the reconsolidation functions. Our findings shed light on the boundary conditions, as well as the role of the reconsolidation function. In a previous report (Forcato et al., 2013), we have demonstrated that strengthening is not active in old memories, and old memories are resistant to interference. In this previous study, the simple passage of time induced a forgetting process, which may overshadow memory impairment and strengthening. In this report, we reversed these results by changing the memory features (memory strength). We demonstrate that strong old memories modulated by a threatening experience prior to acquisition could be interfered during the reconsolidation process and updated by repeated reconsolidation processes. Thus, we demonstrated that rather than being permanent, the boundary conditions change as a consequence of the interaction between memory features and reminder characteristics, which indicates the dynamic nature of this process. Consistent with this interpretation, Coccoz, Maldonado, and Delorenzi (2011) have demonstrated that an old declarative memory may be improved when it is reactivated 6 days after training and a mild stressor is applied.

In this context, the reconsolidation process may offer potential translational applications. First, the reconsolidation process may represent the mechanism of psychopathology formation and maintenance (Alberini, 2013). Second, in coincidence with the reconsolidation boundary conditions, it is now accepted that factors such as the duration of untreated psychopathology and the severity of symptoms are important characteristics that compromise treatment outcome. Longer periods between the appearance of symptoms (age of psychopathology) and their severity (strength of psychopathology) are significant predictors of relapse (Blom et al., 2007; Eisen et al., 2013; Farooq, Large, Nielssen, & Waheed, 2009; Lambert, Karow, Leucht, Schimmelmann, & Naber, 2010; Van Os, Jones, Sham, Bebbington, & Murray, 1998). More specifically, Cognitive Behavioral Therapy (CBT) is a therapeutic framework that includes several techniques that target the dysfunctional cognitive and behavioral elements (cognition, behavior and emotion) of psychiatric disturbances to achieve symptom change. The way in which individuals cognitively structure their experiences is considered to exert a prime influence on their emotion and behavior. CBT predicts that changes in the declarative/semantic systems causally lead to changes in behaviors and emotions (Beck & Haigh, 2014). This concept implies an updating of the declarative content of the experience. Memory age and strength result in boundary conditions for the reconsolidation process and potentially for symptomatology remission. Changes in the boundary conditions indicate the dynamic nature of the reconsolidation process. Our findings demonstrate that it is possible to modify these limits. Thus, the reconsolidation process and its functions are again operative. This novel scenario enables the possibility to consider the role of the declarative/semantic system in the improvement of CBT.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.nlm.2016.03.001.

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