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THE TEMPORAL DYNAMICS OF ENHANCING A HUMAN DECLARATIVE MEMORY DURING RECONSOLIDATION

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Abstract—When a consolidated memory is reactivated, it can become labile and prone to enhancement or disruption, a process known as reconsolidation. The reconsolidation hypothesis has challenged the traditional view that memories after consolidation are fixed and unchangeable. Recent studies suggest that the mechanisms mediating memory retrieval and the mechanisms that underlie the behavioral expression of memory can be dissociated, offering a new promise for the understanding of human memory persistence. Although reconsolidation studies typically use amnesic agents, it has also been shown that memory can be enhanced by pharmacological agents and real-life events during reconsolidation. Recently, we demonstrated that a mild stressor, cold pressor stress (CPS), can enhance human declarative memory during reconsolidation in a cued-recall test. Here we evaluate whether the recollection of 7- or 20-day-old long-term memories can be improved by exposure to two different neuromodulators: a mild stressor and glucose during reconsolidation. As expected, poor and very poor memory performance was found at the time of memory reactivation (days 6 and 20 after training). CPS during reconsolidation improved the long-term expression of a declarative memory 6 -but not 20-days after training. However, the administration of an oral source of glucose (juice), but not a diet juice, can enhance memory during reconsolidation even 20 days after training. Interestingly, when a recognition test was applied instead of a cued-recall test, memory performance was still robust at both 1 and 3 weeks after training. Here we show that the period in which this memory can be reactivated and become labile largely exceeds the period in which that memory is recalled, proving evidence that conscious access is not needed for reconsolidation. Present results are consistent with dissociation between the mechanisms mediating memory labilization and the mechanisms that underlie the behavioral expression of memory.

Key words: memory modulation, memory enhancement, persistence, reconsolidation, forgetting, memory expression.

INTRODUCTION

Consolidated memories, when reactivated by the presentation of retrieval cues, can return to a labile state and be susceptible to amnesic agents once more, a process known as reconsolidation (Misanin et al., 1968; Sara, 2000b; Alberini, 2007; Nader and Einarsson, 2010; McKenzie and Eichenbaum, 2011; Dudai, 2012). Such a change in the view of fixed and unchangeable long-term memory has led to new interpretations about several mnemonic processes, for instance, the nature of experimental amnesias (Gold, 2006; Miller and Matzel, 2006; Nader and Wang, 2006; Sara and Hars, 2006; Frenkel et al., 2010; Blake et al., 2012; Caffaro et al., 2012).

While most experiments have shown that memory can be disrupted by amnesic agents during memory reconsolidation (Soeter and Kindt, 2011), it has also been shown that memory performance can be enhanced during memory reconsolidation (Sara, 2000a; Alberini, 2011; Dudai, 2012). Indeed, the earliest reports showed reconsolidation enhancement by fructose and cocaine in non-human animals (Rodriguez et al., 1993; Horne et al., 1997). Today, several studies have shown that pharmacological manipulations can enhance memory during reconsolidation (Frenkel et al., 2005b; Tronson and Taylor, 2007; Rodriguez et al., 2012; Tian et al., 2012; Stern and Alberini, 2013). Remarkably, naturalistic events have also been shown to improve memory during reconsolidation. Emotional arousal and stress hormones, including epinephrine and cortisol, are potent modulators of memory processes (Cahill et al., 2003; Sandi and Pinelo-Nava, 2007; McGaugh and Roozendaal, 2009; Wolf, 2009). Like epinephrine, the administration of glucose during memory consolidation has also been employed as an enhancing agent of cognitive functions in humans and non-human animals (Gold, 1986, 2008; Kopf et al., 1993; Manning et al., 1993; Oomura et al., 1993; Messier, 2004). Actually, glucose enhances verbal memory, in both healthy young adult and aged populations (Manning et al., 1993; McNay and Gold, 2002; Messier, 2004; Gold, 2005; Newman et al., 2011).

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Abbreviations: ANOVA, analysis of variance; CPS, cold pressor stress.

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Emotional arousal, mild stress, water deprivation and exposure to glucose and fructose can improve memory after reactivation, showing that real-life events are as effective enhancing factors during reconsolidation as during consolidation (Rodriguez et al., 1999; Cahill et al., 2003; Frenkel et al., 2002, 2005b, 2010; Coccoz et al., 2011; Finn and Roediger, 2011). These findings have raised the possibility of developing new cognitive enhancing protocols in humans with important clinical applications and significant implications for the understanding of human forgetting and memory persistence (Coccoz et al., 2011; Alberini and Chen, 2012).

In the present study, the term forgetting is applied to items that were once retrievable from long-term memory but no longer are, despite using the same retrieval cue in both cases (Wixted, 2007). And the term persistence refers to the retention over time of the information learned, an internal representation that is only, and only sometimes, expressed in overt behavior (Eichenbaum, 2007; Roediger et al., 2007).

Recently, we demonstrated that a mild stressor, cold pressor stress (CPS), can enhance memory during reconsolidation, improving the long-term expression of a human declarative memory (Coccoz et al., 2011). In Coccoz et al. (2011), we used a similar human declarative memory paradigm as in the present study, whose reminder structure allows differentiating between a reactivated labile memory state and a reactivated but non-labile state (Forcato et al., 2009; Coccoz et al., 2011). In fact, only when the memory reactivation procedure involves either a mismatch or a new learning in the new experience, is reconsolidation triggered, allowing memory updating (Pedreira et al., 2004; Rodriguez-Ortiz et al., 2005; Frenkel et al., 2005b; Alberini, 2007; Hupbach et al., 2007; Forcato et al., 2010; Coccoz et al., 2011; Dudai, 2012; Sevenster et al., 2013). We found that, despite poor memory expression at the time of memory reactivation (6 days after training), robust memory expression can be found at testing (day 7) if the CPS administration is specifically concurrent with the reconsolidation phase (Coccoz et al., 2011). Thus, similar to studies in crabs, the behavioral expression of consolidated memories is not required for memory reactivation and labilization (Frenkel et al., 2005a, 2010; Caffaro et al., 2012). These studies added relevant experimental data in favor of the view that there is a dissociation between the mechanisms mediating memory reactivation and those underlying the behavioral expression of memory (Ben et al., 2006; Blake et al., 2012; Caffaro et al., 2012; Rodriguez-Ortiz et al., 2012; Sevenster et al., 2012).

Our previous studies on the modulation of memory expression were based on the hypothesis that, during memory consolidation and reconsolidation, neuromodulators can determine the ability of the memory to guide behavior by either increasing or decreasing its behavioral expression, without affecting its persistence (Frenkel et al., 2005b; Coccoz et al., 2011; Blake et al., 2012; Caffaro et al., 2012a, Frenkel et al., 2010; Smal et al., 2010). The working hypothesis of the present paper is that during memory reconsolidation, neuromodulators can determine the ability of the memory to guide behavior by increasing its conscious access. In light of this, we expect that after forgetting there would be a memory trace that would not be expressed but could be reactivated and labilized by the appropriate reminder. Consequently, we predict that we should be able to recover the behavioral expression of long-term memory if reconsolidation of unrecalled – but reactivated – memory is enhanced. Here we use positive modulation of memory expression during reconsolidation to determine whether 7- or 20-day-old unrecalled memories can be behaviorally re-expressed by two different real-life events presented during memory reconsolidation: a mild stressor and glucose. Results from the present study reveal that a naturalistic mild stressor can enhance reconsolidation, improving the long-term behavioral expression of declarative memories 6 but not 20 days after training. Interestingly, the administration of an oral source of glucose (juice) can enhance memory during reconsolidation even 20 days after training. Consequently, here we show that the period in which a memory can be reactivated and become labile largely exceeds the period in which that memory is consciously accessed. Present results show that memories that cannot be consciously accessed can still be reconsolidated and support the view that it is possible to dissociate memory reactivation-labilization from the behavioral expression of memory.

EXPERIMENTAL PROCEDURES

Each three-session experiment consisted of a *Training Session*, a *Reactivation Session* and a *Testing Session*. The memory paradigm was similar to previous studies except that memory reactivation and testing sessions for CPS (series 1) and glucose (series 2) occurred on days 6 and 7, and days 20 and 21.

Participants

A total of 146 (75 from Buenos Aires University for series 1, and 71 from Universidad Andrés Bello for series 2) healthy undergraduate and graduate students volunteered for the study. Individuals who met any of the following exclusion criteria were excluded from participating: non-native Spanish speaking; current alcohol or substance abuse; tobacco use; cardiac disorders; hypertension; diabetes or treatment with psychotropic medications. All participating healthy volunteers were free of medication except for contraceptive pills ($n = 7$). Their ages ranged from 18 to 35, with a mean of 24. Of the total, 42 subjects were excluded from the data analysis because they drank alcohol during the period of the experiment, wrote the syllables down outside the experimental room, consumed drugs, missed a step in the experimental protocol or did not meet the memory inclusion criteria by the end of the training session. Congruent with previous studies using this memory paradigm, subjects with at least 65% correct responses in the last four training trials (13/20 correct responses in each training trial) were included in the data analysis (Forcato et al., 2007, 2009, 2010; Coccoz et al., 2011; Forcato et al., 2011). All subjects were randomly assigned to groups and tested

individually. Series 1: to reduce the impact of diurnal cortisol level variations, the experiment was performed between noon and 5:00 pm (Cahill et al., 2003). Series 2: the answer booklets used in this study contained a section that requested information about the time and content of their previous meals. These data were not formally analyzed, but established that no participants were fasting and had partaken of some form of meal resulting in an intake of at least 300 kcal 2 h before each memory evaluation. Before participating in the experiment, all subjects signed an informed consent, approved by the Ethic Committees of the Sociedad Argentina de Investigaciones Clínicas, Facultad de Farmacia y Bioquímica (series 1) and the Comité de Bioética de la Universidad Nacional Andres Bello, Chile (series 2).

Experimental room

Experiments were conducted in a dark room using a personal computer. Each subject was provided with earphones and seated facing a monitor. The CPS or glucose treatment was provided in a different room, adjacent to the experimental room.

Experimental series one: the CPS effect

The first series of experiments was intended to evaluate whether already forgotten 6- or 20-day-old memories can be reactivated–labilized using a mild stressor (CPS). We tested the labilization of memory by assessing its potential to be enhanced during reconsolidation (Coccoz et al., 2011). The memory *Reactivation Session* took place 6 or 20 days after training, and one day after that subjects were tested. In control groups named *6d-Testing* and *20d-Testing*, subjects received the training protocol and memory was evaluated 6, 20 or 21 days afterward, coinciding with the *Reactivation Session* of the other control groups. These groups were designed to estimate the performance of the subjects at the time of the reactivation session in the other groups. As in previous studies, we evaluated blood pressure in this series to show that the CPS administration activated the sympathetic nervous system (Velasco et al., 1997; Schwabe and Wolf, 2010; Coccoz et al., 2011).

The paradigm. In essence, participants had to learn a list of five pairs of nonsense syllables, the list was composed of five pairs of nonsense cue–response-syllables in Spanish: **ITE**-OBN, **ASP**-UOD, **FLI**-AIO, **NEB**-FOT, **COS**-GLE (bold type: cue-syllable; regular type: response-syllable) (Fig. 1). The list was presented on the monitor screen. In the first trial, the list was shown and in the successive trials the five cue-syllables were presented and subjects had to write down the corresponding response-syllable. The list was associated with a *specific context* (light projected on a large screen, an image on the monitor screen and a sound coming through the earphones).

Demo. Before the *Training Session*, all participants were presented with a demo program explaining the instructions of the task. The program consisted of four

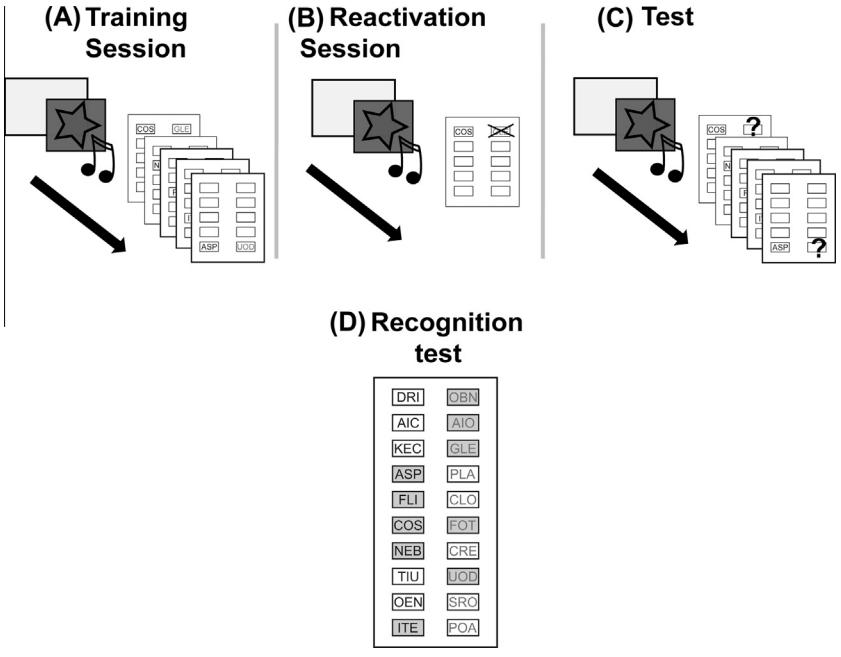

Fig. 1. Experimental design. (A) *Training Session*: included 10 trials with the correct context followed by the list, mixed with 22 fake contexts (in Series 1). Subjects were given 5 s to write down the corresponding response-syllable. Each List was composed of five constant pairs of nonsense cue–response-syllables that appeared on the screen pseudo randomly (see 'Experimental series one: the CPS effect). (B) *Reactivation Session*: had the reminder structure that triggers labilization–reconsolidation, in which the correct context was followed by the presentation of one cue-syllable without allowing the subject to respond with the respective response-syllable. Then, the CPS or glucose treatment was given (see 'Experimental series one: the CPS effect). (C) *Testing Session*: three fake contexts (in series one) and one trial of the list learned on day 1 (see 'Experimental series one: the CPS effect). (D) Recognition test sheet (see 'Recognition test'), the List 1 cue–response syllables are marked gray (now unmatched and placed in pseudo-random order) of the *Training Session*; this mark was absent on subjects' sheet.

trials, similar in structure to the real list but with different pairs of nonsense-syllables associated with a different context.

Training Session (day 1). All participants underwent the same training protocol on day 1 (details in Forcato et al., 2007; Coccoz et al., 2011). Briefly, each training trial (Fig. 1A, left panel) was comprised of a *context period*, where a light–image–sound combination was presented during the syllable presentation to predict the list apparition. This *correct context* combination was followed by a second period, where a series of nonsense-syllables were presented as paired-associates (*the syllable period*). The *syllable period* that followed started with the presentation of a cue-syllable on the left-hand side of the monitor screen and an empty response-box on the right-hand side. Each cue-syllable was taken randomly from a list of five pairs. The first time that the list appeared on the computer screen, the subject tried to memorize each response syllable associated with the matched cue syllable. In the following trials, the list started with the presentation of a cue-syllable from the list on the left-hand side of the monitor screen and an empty response-box on the right, where subjects were given 5 s to write the corresponding response-syllable. There were three situations that could occur during training: (1) if no response syllable was written down, the correct syllable was shown for 4 s, (2) if an incorrect response syllable was written down, it was replaced by the correct syllable and it was shown for 4 s and (3) if the correct response was given, it stayed on the screen for 4 s. Immediately after any of these three situations, another cue-syllable was shown and the process was repeated in semi-random order until the list was over. The actual trial lasted 51 s: 6 s for the Context Period plus 45 s for the syllable period. Throughout the experiment, every time a subject faced a cue-syllable and wrote down a correct response, a correct response was computed. At the beginning of each trial the participants were instructed to press the YES or NO button (the expectancy keys) on the keyboard 3 s after the light–image–sound sequence had started. They were instructed to press YES if the context was previously associated with the List of syllables, NO if the context was not associated with the list (fake trial). Fake trials were initially designed to improve the level of attention during training (Forcato et al., 2007). The training was identical for all subjects: 10 actual trials mixed with 22 fake trials, 32 trials in total.

Reactivation Session (day 6 or 20). The *Reactivation Session* included the reminder that reactivates and labilizes the memory (details in Forcato et al., 2009; Coccoz et al., 2011): it began with the training context and immediately after its presentation – as expected – a cue-syllable appeared on the left-hand side of the monitor screen and the response-box. However, 2 s later a notice displayed on the monitor announced that the session had to be suspended, thus *not allowing the subject to write down the response-syllable in the response-box* (Fig. 1). Immediately, subjects were led to an adjacent room and received the corresponding treatment (Forcato et al., 2009; Coccoz et al., 2011).

Testing Sessions. The testing session consisted of the evaluation of the memory, in a random order, of the five cue–response syllables acquired during training (one trial). The subjects were not informed that there would be a memory test in the last session. The testing session lasted 3 min. Three types of errors can be distinguished in this memory paradigm (Forcato et al., 2009): (1) no response was written down, (2) the response-syllable was not included on the list, (3) the response-syllable was not the right one, but it belonged to the same list. The memory enhancing CPS effects during reconsolidation are not explained by a decrease in a particular type of error (Coccoz et al., 2011).

CPS treatment. The procedure was the same as the one used by Cahill et al. (2003) except that the maximum time for the CPS administration was 1 instead of 3 min, a modification required by the Ethic Committee of the ''Sociedad Argentina de Investigaciones Clínicas'' (CPS groups) (Coccoz et al., 2011). Briefly, subjects immersed their left arm to the elbow in ice-cold (0–4 °C) water and were told that because the procedure could be extremely uncomfortable, they should keep their arms in the water for as long as possible, but not exceed 1 min, and that they could remove their arms at their discretion. Those who kept their left arms in the water for 1 min were instructed at that point to remove their arms from the water. After arm immersion, subjects rested for 3 min with their left arms covered by blankets (details in Coccoz et al., 2011).

Blood pressure evaluation. Blood pressure was measured immediately before and during the CPS with an automatic digital pressure gauge (*Omron Healthcare, model HEM-631int*), the cuff was placed on the wrist of the subject's right arm (details in Coccoz et al., 2011).

Subjective assessments. Participants rated on a scale of 0 (''not at all'') to 10 (''very much'') how painful and unpleasant the CPS treatment had been (details in Coccoz et al., 2011).

Experimental groups. Reminder-CPS-7d group. Day 1: subjects received the training session; day 6: the Reminder Session was presented and CPS was administered; day 7: subjects were tested.

Reminder-CPS-21d group. Day 1: subjects received the training session; day 20: the Reminder Session was presented and CPS was administered; day 21: subjects were tested.

Reminder-7d group. Day 1: subjects received the training session, day 6: the Reminder Session was presented; day 7: subjects were tested.

This control was performed to evaluate to what extent the memory enhancements obtained were specific to CPS modulation and not a result of memory labilization *per se*.

6d-Testing and 20d-Testing groups. Day 1: subjects received the training session; day 6 or 20: subjects were tested.

These control groups were performed to estimate the memory level of subjects on day 6 and 20, the time of the retrieval-labilization sessions.

Recognition test

In a different room subjects received a sheet of paper with ten pairs of syllables, five of them were the cue–response syllables acquired during training (the List 1), and the other five pairs had not previously been seen (the List 2, another five pairs of nonsense cue–response syllables in rioplatense Spanish (Forcato et al., 2007)). The cue and response syllables, in the left and right columns respectively, of Lists 1 and 2 were unmatched and placed in a pseudo-random order. Each subject had 5 min to recognize the cue–response syllables that were learned at the *Training Session* and match each of combination with a pen. The proportion of Hits vs. *F* (false recognitions) rates of the five cue–response syllables was analyzed, Hit = recognized paired-associates cue–response syllables acquired during training (List 1)/5 (numbers of pairs learned), and *F* = new and/or old items in incorrect paired-association/5 at the *Testing Session.* Although there are more than five possibilities in this test for *F*, we used 5 in denominator of both *H* and *F* rates, since subjects actually remembered that five is the number of cue–response syllables that were presented in the *Training Session*. Recognition Performance was calculated by subtracting *F* from *H*, where 1 is perfect performance in recognition of the selected items.

Experimental group. Recognition-7d and *Recognition-21d* groups: day 1: subjects received the training session; day 7 or 21: subjects were tested.

Experimental series two: the glucose effect

In this series, we used another natural memory modulator (*Glucose treatment*) to strengthen the reactivated memory during the *Reactivation Session*, 20 days after training, to reveal the unrecalled memory. The paradigm conditions were the same as described above for series one, but in this series of experiments only the correct context was presented (Rodriguez et al., 2012) without the light projected on the large screen. We tested whether the enhancing effect could be revealed in the long term, 21 days after training. In this series, 17 men and 23 women were included. Before their participation in the experiment, subjects signed an informed consent approved by Comité de Bioética de la Universidad Nacional Andres Bello, Chile.

The Reminder Session was performed on day 20. Subjects were led to an adjacent room and asked to wait due to a program ‘‘malfunction’’ (the reminder that trigger memory labilization (see series one, ‘Experimental series one: the CPS effect’)). While waiting, they were offered a glass of commercial peach juice (200 ml, 27 g glucose) and remained in the room drinking it for at least 20 min. Twenty-four hours later subjects were tested as in series one (see training sessions). To ensure that the memory enhancing effects were mediated by glucose, a group of subjects, during the reactivation-labilization session, were offered low-glucose diet peach juice (200 ml, 7, 2 g glucose). Like the experimental group, they were tested 24 h later.

To estimate the level of memory recall on the day of the reactivation-labilization or testing sessions, groups of subjects were tested as above (series one) 20 and 21 days after training, without the reactivation-labilization session.

Experimental groups. Reminder-Juice-21d group. Day 1: subjects received the training session; day 20: the Reminder Session was presented and a glass of commercial peach juice was administered; day 21: subjects were tested.

Reminder–Diet Juice-21d group. Day 1: subjects received the training session; day 20: the Reminder Session was presented and a glass of low-glucose commercial peach juice was administered; day 21: subjects were tested.

20d-Testing and 21d-Testing groups. Day 1: subjects received the training session; day 20 or 21: subjects were tested.

Statistics

The statistical analysis of memory performance was performed according to previous studies (Coccoz et al., 2011). Results were reported as mean and standard errors of the total number of correct responses for the list. Data were analyzed using repeated measures analysis of variance (ANOVA). The between-subjects factor was the experimental groups, the within-subject factor was ‘time of measurement’ the tail end of training (Forcato et al., 2009, 2010) and testing performances of the subjects design was employed (Coccoz et al., 2011). For blood pressure data, a 2×2 design was employed (Schulz et al., 2011) in which the between-subject factors were the experimental groups and the ‘time of measurement’ before and during the CPS treatment measurements. Different post hoc tests were performed using Fisher’s LSD ($\alpha = 0.05$) between groups. An independent sample *t*-test was used to analyze differences from zero in recognition test groups. We analyzed data using STATISTICA (StatSoft 6.0).

RESULTS

Series 1: effects of CPS as a memory modulator

The first series of experiments was intended to evaluate the temporal dynamics of the reactivation-labilization process using a natural mild stressor, CPS. In this series, 29 men and 32 women were included. The experimental groups of this series are described in Experimental series one and summarized in Fig. 2.

Blood pressure. The exposure to the CPS treatment caused a significant rise in diastolic and systolic blood pressure (ANOVA: $F_{1,12} = 31.05$, $P = 0.0001$, diastolic; $F_{1,12} > 22.21$, $P = 0.0005$, systolic). There was no interaction effect between group and time ($F_{1,12} = 0.35$, $P = 0.56$, diastolic; $F_{1,12} = 1.32$, $P = 0.27$, systolic). All groups showed no differences in blood pressure before the treatment ($P > 0.5$), nor did they differ in their blood pressure responses to CPS (all $P > 0.5$). Diastolic blood pressure (mm Hg) (before/during) treatment measures: *Reminder-CPS-7d*, (64.67 ± 3.1; 80.3 ± 2.3); *Reminder-CPS-21d*, (66.8 ± 3.3; 86.20 ± 4.8). Systolic blood pressure (mm Hg) (before/during) treatment: *Reminder-CPS-7d*, (111 ± 3.6; 121.4 ± 2.7); *Reminder-CPS-21d*, (112.20 ± 3.6; 129.4 ± 6.5).

Subjective assessments. Participants rated on a scale from 0 (‘‘not at all’’) to 10 (‘‘very much’’) how painful and unpleasant the CPS treatment had been. As expected, all participants that were exposed to CPS rated the treatment as painful and unpleasant (*Reminder-CPS-7d*, 7.72 ± 0.48; *Reminder-CPS-21d*, 9.15 ± 0.38) ($P = 0.07$).

CPS and memory performance. In order to determine the degree of uniformity of the performances at paired-associate trainings throughout the *Training Session*, we compared the mean of correct responses for the last four actual trials of the training, termed the *Training Tail* (Fig. 2). Repeated measures ANOVA of the tail end of training compared to testing (Forcato et al., 2007; Coccoz et al., 2011) revealed a significant group effect ($F_{4,37} = 7.36$; $P < 0.0002$) and an interaction effect between groups and trials ($F_{4,37} = 10.91$; $P < 0.00001$); post hoc analyses showed no significant differences in correct responses between groups in the *Training Tail* (all $P > 0.38$); the *6d-Testing*, *20d-Testing*, *Reminder-7d* and *Reminder-CPS-d21* groups showed a patent decrease at testing compared with the *Training Tail*; (all $P < 0.00001$). Significant differences between both *6d-Testing* and *Reminder-7d* groups, and *20d-Testing* group (all $P < 0.001$) at *Testing Session* were found, displaying a fall in performance at testing between 1 and 3 weeks after training. In the *Reminder-CPS-7d*, a smaller decrease in performance at testing compared with its *training tail* was found ($P < 0.01$) and, remarkably, this group showed significantly more correct responses

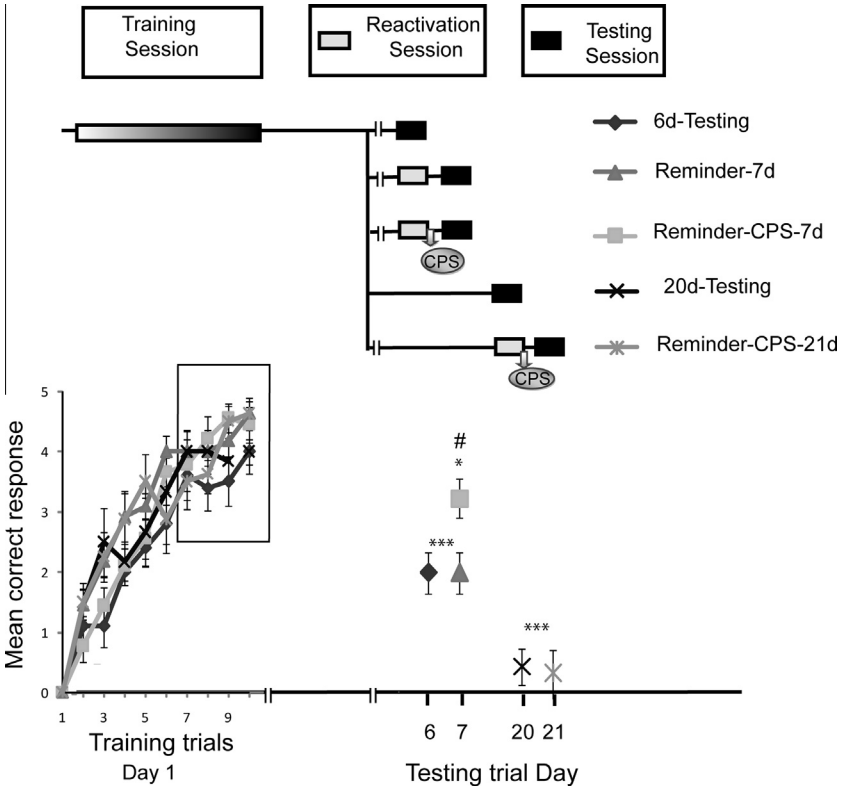

Fig. 2. The memory enhancing effects of CPS administration during reconsolidation were obtained 7 days but not 21 days after training. Experimental design: the *6d-Testing* ($n = 8$) and the *20d-Testing* ($n = 11$) groups underwent the *Testing Session* without a prior *Reactivation Session*. The *Reminder-CPS-7d* group ($n = 8$) had the reminder structure that triggers labilization–reconsolidation that triggers labilization–reconsolidation on day 6, in which the correct context was followed by the presentation of one cue-syllable without allowing the subject to respond with the respective response-syllable. Then, the CPS treatment was given. The testing session occurred on day 7. *Reminder-CPS-21d* ($n = 6$) was like the *Reminder-CPS-7d* group except that the reminder and testing sessions occurred on day 20 and 21. The *Reminder-7d* group had the reminder structure that triggers labilization–reconsolidation but no CPS treatment. The testing session occurred on day 7 ($n = 8$). During the *Training Session* (day 1) all groups received 10 actual trials (mean correct responses ± SEM), the last four of which are shown in the box (tail of training). During the *Testing Session* (mean of correct responses ± SEM) only the *Reminder-CPS-7Day* group made significantly more correct responses compared to the other one-week control groups *6d-testing* and *Reminder-7d*; the *Reminder-CPS-21d* and the *20d-Testing* groups displayed a lower performance 3 weeks after training. (∗) Significant differences at testing compared to the *training tail*, $^{*}P < 0.01$, $^{***}P < 0.0002$; (#) Significant differences at testing compared to the three control groups, $^{\#}P < 0.02$.

compared to all other groups during testing (all $P < 0.012$), including the *Reminder-CPS-21d* group, which showed as poor performance as the *20d-Testing* group ($P = 0.80$). Simply stated, the group with the *Reactivation Session* and the CPS treatment showed memory enhancements on day 7 but not on day 21 after training.

Recognition test. Despite showing low memory performance when using cue-syllable recall tests, subjects show very high detection of the learnt *training syllables* – when asked to recognize the paired associations (Fig. 1D) – (9.50 ± 0. 34 and 9.33 ± 0.21 out of 10 syllables from List 1 (see 'Experimental series one: the CPS effect') for the *6d-Recognition* and *20d-Recognition* groups respectively. Remarkably, the proportion of Hits vs. *F* rates of the five cue–response syllables analyzed showed that each group has values different from zero: Hit = 0.80 ± 0.10 and $F = 0.20 \pm 0.102$; $H–F = 0.60 \pm 0.21$ for the *6d-Recognition* group ($t_5 = 3$, 32, $P < 0.02$); Hit = 0.73 ± 0.08 and $F = 0.20 \pm 0.09$; $H–F = 0.53 \pm 0.16$ for the *20d-Recognition* group ($t_5 = 2.90$, $P < 0.03$).

This high performance in recognition tasks suggests that even after 21 days of training, remote memory that is not consciously assessed in the cue-syllable recall tests can still be recalled via recognition. To attain recognition 3 weeks after training, the memory needs to persist, raising the possibility that the original memory could be reactivated and labilized at the *Reminder Session*. However, CPS treatment, while capable of enhancing memory during reconsolidation 6 days after training, was no longer able to improve it 20 days after training. The following experiment was intended to evaluate whether glucose, which is known to influence cognitive functioning and enhance memory consolidation in humans and non-human animals, can positively modulate this memory during memory reconsolidation, even 3 weeks after training.

Oral administration of a glucose juice during reconsolidation and memory performance

The experimental groups of this series are described in 'Experimental series two: the glucose effect' and summarized in Fig. 3. Repeated measures analysis of variance (ANOVA) of the tail end of training compared to testing revealed a significant group effect ($F_{3,36} = 9.87$; $P < 0.00001$) an interaction effect between groups and trials ($F_{3,36} = 3.523$; $P < 0.024$) (Fig. 3); post hoc analyses showed no significant differences in correct responses between groups in the *training tail* (all $P > 0.14$) and all groups showed a significant decrease at testing compared to the *training tail* ($P < 0.00001$). Post-hoc analysis which focused on the *Testing Session* showed no significant differences between *20d-Testing*,

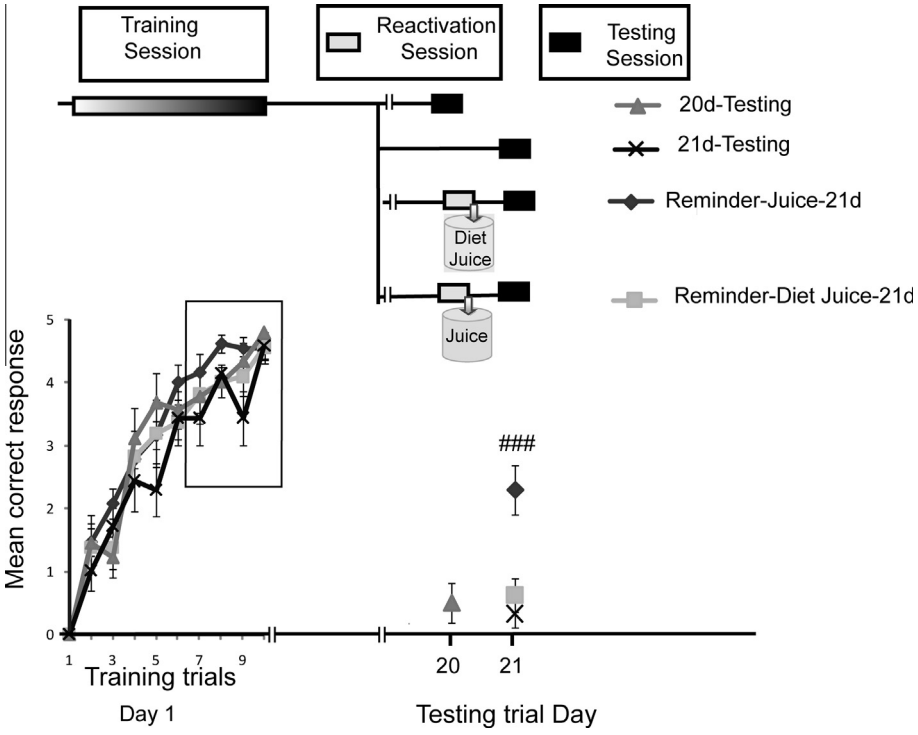

Fig. 3. Glucose administration during reconsolidation enhances memory three weeks after training (Series two, see 'Experimental series two: the glucose effect'). Experimental design: the *Reminder-Juice-21d* group ($n = 13$) included the reminder structure that triggers labilization–reconsolidation followed by drinking the glucose juice on day 20. The testing session was performed 24 h after reactivation. The *Reminder-Diet Juice-21d* group ($n = 11$) had the same structure as the previous one but diet juice replaced glucose juice. The *20d-Testing* ($n = 9$) and the *21d-Testing* ($n = 7$) groups had the *Testing Session* without a prior *Reactivation Session*. During the *Training Session* (day 1) all groups received 10 trials (Mean correct responses ± SEM), the last four of which are shown in the box (tail of training). During the *Testing Session* (mean of correct responses ± SEM on day 21) only the *Reminder-Diet Juice-21d* group made significantly more correct responses compared to *Reminder-Diet Juice-21d*, the*20d-Testing* and *21d-Testing* groups. (#) Significant differences at testing compared to the three control groups, $^{###}P < 0.0001$.

21d-Testing and *Reminder-Diet Juice-21d* groups (all $P > 0.45$). Remarkably, the *Reminder-Juice-21d* group demonstrated significantly more correct responses at testing compared to the other groups (all $P < 0.0001$). It must be noted that on days 20 and 21, the performance was very low in control groups (0.67 ± 0.34 and 0.43 ± 0.38 cue–response syllables respectively), suggesting that most of the syllables were already forgotten, but memory expression was significantly increased (to 2.31 ± 0.28) when the high-glucose juice was administrated after memory reactivation.

DISCUSSION

A key finding of this study is that the low memory performance found in cue-recall testing 6 or 20 days after training due to forgetting (Wixted, 2007) resulted from a lack of conscious access and not from a storage deficit. Memory persistence was revealed by the fact that a recognition strategy, as expected, allowed the subjects to retrieve the memory that was otherwise unexpressed during cued-recall. As is largely recognized in retrieving memories through recall and perceptual recognition (Tulving and Schacter, 1990; Eichenbaum, 2007), the difference in retrieval success through cue-recall reflects impairment in conscious access with intact recognition. Nonetheless, the capacity of the memory to be reactivated by the presentation of the reminder endured for at least three weeks after training, even while the subjects showed no conscious access to the memory during cued-recall. Thus, the main finding of this study is that conscious access is not required for a memory to be reactivated and become labile by a specific reminder.

Physiological findings were in accordance with the working hypothesis of the present study. Our results show that poor and very poor memory expression can be found at both reactivation times (days 6 and 20 after training) and at both testing sessions (days 7 and 21) in all groups that were designed as controls. In line with our previous study (Coccoz et al., 2011), robust memory expression was shown at testing when the CPS administration was concurrent with the retrieved-labile memory state on day 6. However, the mild stressor was not effective when memory was reactivated–labilized 20 days after training. Remarkably, the oral administration of a glucose juice after the *Reminder Session*, but not a diet juice, was able to induce an increase in memory expression 24 h later, showing that this declarative memory can in fact be reactivated, become labile and improved even if it is not consciously accessed 20 days after training.

In the first series of experimental results (Fig. 2), the groups which were designed to estimate the performance of the subjects at the time of the reactivation session in the other groups showed low memory performance 6 days after training, and very low performance 20 days after training. We reproduced our previous findings on days 6 and 7 (Coccoz et al., 2011), showing that the mild stressor presented immediately after memory reactivation-labilization induces an increase in memory expression at testing, i.e., when the CPS administration was concurrent with the retrieved-labile memory state. On the other hand, no enhanced performance at testing was shown in the *Reminder-7d* control group, where the mild stressor was not present. We have previously shown that this enhancing effect depends on the mild stressor – as warm water is ineffective – and is reconsolidation-specific (Coccoz et al., 2011) because (a) it needs time to develop (Pedreira et al., 2004; Frenkel et al., 2005a; Alberini, 2007; Boccia et al., 2007; Nader and Einarsson, 2010; Schiller et al., 2010; Dudai, 2012), as the increase in memory expression is displayed long after but not shortly after the reactivation session, and (b) the reminder structure can determine whether the memory is to be retrieved but not labilized, in which case enhanced memory expression at testing does not take place (Forcato et al., 2009, 2010; Coccoz et al., 2011). In an attempt to elucidate whether an already forgotten memory can be reactivated–labilized even 20 days after training, here we show that the administration of glucose, but not CPS, following the *Reactivation Session* can enhance memory performance.

Stressors, emotional arousal and stress hormones are known to modulate memory processes, inducing either positive or negative effects (McGaugh, 2000; Lupien et al., 2002, 2007; Rimmele et al., 2003; Anderson et al., 2006; Sandi and Pinelo-Nava, 2007; Luethi et al., 2008; McGaugh and Roozendaal, 2009; Schwabe and Wolf, 2010). CPS is a widely used technique in neuroscience research that induces a mild stress response which has been demonstrated to modulate memory consolidation (Cahill et al., 2003; Smeets et al., 2008) and reconsolidation (Schwabe and Wolf, 2010; Coccoz et al., 2011; Hupbach and Fieman, 2012). Glucose drinks are also known to influence cognitive functions and enhance memory in humans and animals for several aversive and non aversive tasks (Benton and Owens, 1993; Benton and Nabb, 2003; Gold, 1986, 2005, 2008; Morris, 2008). Indeed, glucose enhances verbal memory in humans, including healthy young adults and the aged, as well as in individuals with Down syndrome and Alzheimer's disease (Manning et al., 1993; McNay and Gold, 2002; Messier, 2004; Gold, 2005).

In the second series of experiments (Fig. 3), the 20-Day Testing and 21-Day Testing groups, designed to estimate the performance of the subjects at the time of the reactivation session (day 20) and when no reactivation-labilization session is performed (day 21) showed very low memory performance, levels of almost complete forgetfulness. However, an increase in memory expression was shown at testing (day 21) when the juice was administered immediately after the *Reminder Session* (day 20), which can reactivate and make the memory labile. The enhancing memory effect is specific to the administration of glucose, as the *Reminder-Diet Juice-21d* group, which differs only in the glucose content of the drink they consumed, showed very low performance at testing. Although additional research is needed to positively correlate the memory reconsolidation enhancements with an increase in blood glucose, results clearly show that the enhancing effect only occurs following the oral intake of juice instead of

diet juice, suggesting that glucose induces an increase in long-term memory expression when administered during memory reconsolidation. In this experimental series, the training protocol did not include the fake contexts. It was previously shown that with or without fake contexts, the reminder that triggers reconsolidation is maintained (Coccoz et al., 2011; Rodriguez et al., 2012). Although fake trials were designed to increase attention, glucose administration after memory reactivation, unlike CPS 20 days after training, was effective in improving this cue–response memory even without fake contexts during training. These enhancing effects of glucose as a potent memory modulator have been reported in several memory models across phyla, suggesting that glucose plays a key role in regulating several memory processes, including memory reconsolidation (Rodriguez et al., 1999; Besnard et al., 2012). Extensive studies show that glucose may also be an important mediator of epinephrine effects on memory (Gold, 1986, 2008; Manning et al., 1993; Messier, 2004; Newman et al., 2011). An increase in circulating glucose levels can occur during a variety of stressful situations, and several studies show that peripheral and central administration of glucose enhances memory (Gold, 2008). Indeed, the enhancement of memory by glucose remains intact in the presence of adrenergic antagonists (Gold, 1986). In short, several reports suggest that a rise in blood glucose levels subsequent to epinephrine released in stressful circumstances may mediate the effects of the hormone on memory (Gold, 2008). Accordingly, the norepinephrine response to the cold pressor test is positively related to an increase in plasma glucose (Flaa et al., 2008), leading to the suggestion that this increase in blood glucose is also a key factor in the memory enhancing effects of CPS treatment (Gold, 2008; McGaugh and Roozendaal, 2009). Understanding why glucose, but not CPS, can enhance memory 20 days after training requires further research, but it may be related to the magnitude of the response elicited by the mild stressor used here (CPS, 1 min maximum). It is possible that stronger stressors used in other memory studies (CPS, 3 min, Cahill et al., 2003; Schwabe and Wolf, 2010) may show comparable effects to those found for glucose three weeks after training. In addition, the dose–response effects of sugar on both new and old memories may be different between consolidation and reconsolidation (Rodriguez et al., 1999). Further research is required to resolve these issues. Even though discussions about the relationship between different kinds of memory enhancers and the different temporal windows to reactivate and labilize this declarative memory are pertinent, the present and previous results consistently show a clear dissociation between (a) the capacity of a memory to be reactivated by specific reminders and (b) the probability of such a memory being consciously accessed (Ben et al., 2006; Frenkel et al., 2010; Caffaro et al., 2012; Rodriguez-Ortiz et al., 2012; Sevenster et al., 2012).

Regarding the temporal window to reactivate and labilize the memory, our results suggest that even 20-day-old unrecalled memory can undergo reconsolidation, suggesting that the time window for reconsolidation largely exceeds the time for conscious recall of a forgotten memory. Given that subjects were still able to recognize the syllables in a recognition test three weeks after training *(Recognition test),* it remains unknown whether reconsolidation can still occur several months after training, when recognition tests also fail to disclose the memory.

In the present and previous studies, all control groups showed the expected low memory performance 1 or 3 weeks after training due to the natural process of forgetting (Wixted, 2004, 2007; Coccoz et al., 2011). However, the memory of pairs of nonsense cue–response-syllables must persist to be reactivated, become labile and then expressed at a subsequent testing session if the enhancing factor is contingent upon the reconsolidation process. Congruent with the enhancing effects on memory expression obtained in Experimental Series one and two, the recognition test showed that high performance, even after 21 days of training, can be achieved if a different route of accessing the same information is used (Tulving and Schacter, 1990; Craik, 2007; Eichenbaum, 2007). Consequently, the capability of the cue–response syllable memory to be consciously accessed at the testing session may be modulated by naturalistic agents such as CPS or glucose during reconsolidation. In this sense, the ‘‘strength’’ of memory traces would refer to how accessible they are during testing sessions, yet their capability to be reactivated and become labile by specific remainders remains unaffected even if the memory is not consciously accessed. This is congruent with previous seminal notions in the neuroscience of memory that have proposed that memories must first be reactivated, and then a subsequent process will determine whether they can or cannot be behaviorally expressed (Tulving, 1983). The enhancement of reconsolidation that improves the behavioral expression of long-term memory shown here might be due to changes in decision making processes that intervene between the reactivated memories and the behavioral response; i.e., the reinforcement of processes that are critical for long-term memory expression (Dudai and Eisenberg, 2004). Accordingly, it has been shown that amnesic effects in fear memories during reconsolidation would target the behavioral expression of the emotional components of fear memory, but do not necessarily affect the cognitive component (Kindt et al., 2009; Sevenster et al., 2012, 2013; Soeter and Kindt, 2010). Therefore, although it is well-established that the absence of memory expression is largely insufficient to imply that unexpressed memory traces are lost (Gold et al., 1973; Lewis, 1976; Cahill et al., 2001; Gold, 2006; Philips et al., 2006; Eichenbaum, 2007), our present and recent reconsolidation studies support the view that memory expression is not a requirement for long-term memories to be reactivated and labilized; i.e., *memory expression* is not a boundary condition for reconsolidation (Frenkel et al., 2005b, 2010; Coccoz et al., 2011; Blake et al., 2012; Caffaro et al., 2012; Dudai, 2012). Indeed, the fact that the period in which a memory, which was once retrievable, can be reactivated

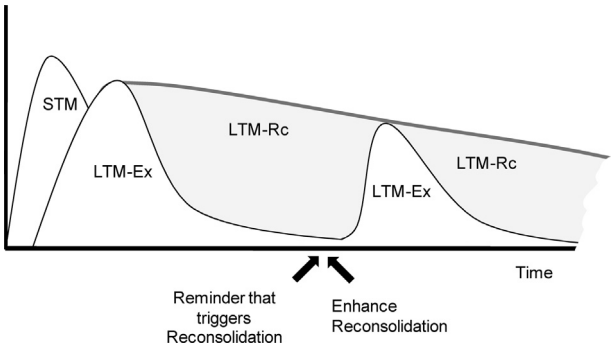

Fig. 4. Proposed model in which memories can be reactivated and labilized even after being unrecalled or forgotten. Schematic diagram describing the decaf of memory performance of a consolidated memory due to the natural process of forgetting (**LTM-Ex**: LTM defined as *lasting change in behavior resulting from previous experience* (Dudai, 2002). However, despite being unexpressed, memory can persist and be reactivated–labilized for reminders that triggers reconsolidation (**LTM-Rc**: LTM defined as *the retention over time of experience internal representations, or the capacity to reactivate such representations* (Dudai, 2002). If reconsolidation is enhanced, LTM-Ex can be recovered.

and became labile largely exceeds the period in which the memory can be consciously accessed, when the same retrieval cues are used (Fig. 4 outlines our proposal), would add new features to the concepts of memory persistence and forgetting (Tulving and Schacter, 1990; Wixted, 2004, 2007; Eichenbaum, 2007; Bekinschtein et al., 2008).

CONCLUSION

Here we show evidence suggesting that conscious access is not required for a memory to be reactivated and become labile by a specific reminder. Our present and previous results are in line with studies that show a dissociation between the mechanisms mediating memory reactivation and labilization, and the mechanisms that underlie the behavioral expression of memory (Frenkel et al., 2005b, 2010; Ben et al., 2006; Coccoz et al., 2011; Caffaro et al., 2012; Finn et al., 2012; Rodriguez-Ortiz et al., 2012; Sevenster et al., 2012). This study may provide relevant insights into the nature of memory enhancing effects on human memory during reconsolidation, where unexpressed memories can be reactivated and positively modulated by concurrent experiences. This finding might have significant implications both for the understanding of declarative memory persistence in humans (Tulving and Schacter, 1990; Eichenbaum, 2007; Henke, 2010) and for the design of novel strategies to enhance memory in the general population and in patients with mild cognitive impairment.

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