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Review Paper

Strengthening a consolidated memory: The key role of the reconsolidation process

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In memoriam to our science mentor Héctor Maldonado. A true scientist who inspired us with his endless creativity.

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ABSTRACT

The reconsolidation hypothesis posits that the presentation of a specific cue, previously associated with a life event, makes the stored memory pass from a stable to a reactivated state. In this state, memory is again labile and susceptible to different agents, which may either damage or improve the original memory. Such susceptibility decreases over time and leads to a re-stabilization phase known as reconsolidation process. This process has been assigned two biological roles: memory updating, which suggests that destabilization of the original memory allows the integration of new information into the background of the original memory; and memory strengthening, which postulates that the labilization-reconsolidation process strengthens the original memory. The aim of this review is to analyze the strengthening as an improvement obtained only by triggering such process without any other treatment. In our lab, we have demonstrated that when triggering the labilization-reconsolidation process at least once the original memory becomes strengthened and increases its persistence. We have also shown that repeated labilization-reconsolidation processes strengthened the original memory by enlarging its precision, and said reinforced memories were more resistant to interference. Finally, we have shown that the strengthening function is not operative in older memories. We present and discuss both our findings and those of others, trying to reveal the central role of reconsolidation in the modification of stored information.

Contents

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1. Introduction

The study of memory is one of the most challenging and exciting areas of basic and applied neuroscience research. During the twentieth century, the consolidation theory dominated the neurobiological field. Its starting point was the seminal research of Müller and Pilzecker (1900), Müller and Pilzecker (1970), who demonstrated that after an initial phase of fragility, the acquired information is stored in a stable memory which is resistant to disruption by amnesic agents (McGaugh, 2000). Consolidation is a conserved evolutionary process, which has been proved to be present in diverse species, ranging from nematodes to humans, and involving RNA and protein synthesis (McGaugh, 2000; Kandel, 2001). Two levels of description and analysis are commonly used to describe the consolidation process, that is, at the cellular/synaptic and at the brain systems level. Synaptic consolidation refers to process described above, which implies the activation of intracellular signaling cascades, modulation of gene expression, and synthesis of gene products that alter synaptic efficacy in the neural circuit that encodes the memory. Systems consolidation refers to the post-encoding reorganization of long-term memory over distributed brain circuits. The process may last days to years, depending on the memory system and paradigm (Dudai, 2012).

A considerable number of reports show that patients with damage in their medial temporal lobe (MTL) displayed temporally graded retrograde amnesia on declarative memory tasks. A central model that tries to explain this phenomenon is the standard consolidation theory (McClelland et al., 1995; Squire and Alvarez, 1995). This model hypothesize that the hippocampus is only a temporary repository for memory and that the neocortex stores the memory thereafter. However, some evidence that seems to be untenable under this model. More specifically, the effect of MTL lesions affects severely autobiographical episodes and the retrograde temporal gradient for this type of memory is very shallow for memories acquired several decades earlier. Based on these observations and analogous observations in animal models, Nadel and Moscovitch (1997) proposed the multiple-trace theory (MTT). MTT posits that the hippocampus rapidly and obligatorily encodes all episodic information which is encoded in distributed ensembles of HPC neurons, being an index for neurocortical neurons that attend the information, joining them into a coherent representation. The resulting hippocampal-neocortical ensemble constitutes the memory trace for the episode (Dudai, 2012).

In the last years, this theory suffered the impact of the reconsolidation hypothesis. By searching the term *reconsolidation* in *PubMed/Medline,* we were able to identify more than 400 studies published in the last decade, stating its relevance in the field. These studies have shown that by presenting a subject with a specific cue, previously associated with a life event (i.e. training session, episodic memories; Nader et al., 2000; Schiller and Phelps, 2011), the stored memory passes from a stable to a reactivated state. This reactivation implies that the memory is again labile and susceptible to different agents, which, depending on their nature, may either damage or improve the original memory. These studies have also shown that such susceptibility decreases over time and leads to a re-stabilization phase known as reconsolidation process. As well as for consolidation, the reconsolidation process seems to also be a conserved evolutionary process. It has been demonstrated in different paradigms and animals models (Nader and Hardt, 2009; Schiller and Phelps, 2011). These findings suggest that reconsolidation is a general property of memory and is common to different memory systems (Nader and Hardt, 2009; Dudai, 2012).

Many of these studies also seem to show that a memory is reactivated and reconsolidated every time it is retrieved (Nader et al., 2000; Sara, 2000). This fact could represent a real risk because the memory's susceptibility during this process could expose and modify the stored information, which is vital for animals' adaptation to an ever-changing environment. More recently, some researchers have defined some of the constraints present in the process: the strength of the original memory, the age of the memory, the duration of the reminder presentation, the cues included in the reminder structure, and the prediction error during reactivation (Hardt et al., 2010; Dudai, 2012).

Over the last fifteen years, most of the research on reconsolidation has been focused on the cellular and molecular mechanisms and the different neurotransmitters implicated, but little on the biological role of this process. Initially, two nonexclusive functions were proposed for this process (Alberini, 2005): memory updating, which suggests that destabilization of the original memory after the reminder allows the integration of new information into the background of the original memory (Lewis, 1979; Alberini, 2007), and memory strengthening, which postulates that the labilization-reconsolidation process strengthens the original memory (Sara, 2000). This indicates that memory restructuring may include changes not only in content (memory updating), but also in strength (memory strengthening).

Our laboratory began the characterization of the reconsolidation process by using an invertebrate model, the grapsid crab *Neohelice granulata*. In our research, we differentiated the retrieval from the reactivation process and considered that retrieval only evoked the consolidated memory. We found that, during reactivation, the memory is evoked and suffers a change from a stable to a labile state. Under these definitions, we demonstrated that the duration of the reminder and the discrepancy between current and past events (called *mismatch*) are features that constrain the labilization-reconsolidation process (Pedreira and Maldonado, 2003; Pedreira et al., 2004).

In humans involving different types of paradigms the process has been described in procedural, aversive, associative and declarative or episodic memories (see Schiller and Phelps, 2011). The declarative memory, i.e. the conscious recollection of facts and events, is considered as a hallmark of our species (Dudai, 2002). The research on this kind of memory aimed to explore the different processes associated with it. Different reports revealed the presence of the reconsolidation process ranging from autobiographical memories (Schwabe and Wolf, 2009), learn a list of objects (Hupbach et al., 2007, 2009) or verbal stimuli comprised by nouns (Strange et al., 2010). The study of the reconsolidation process using declarative memory paradigms not only supports the universality of some mechanisms, but also opens innovative research lines to find new treatments for traumatic memories (Kindt et al., 2009; Schiller and Phelps, 2011). In this context, our research in humans has aimed to show the existence of a reconsolidation process for declarative memories (Forcato et al., 2007), by characterizing boundary conditions (Forcato et al., 2009) and studying the biological role of this process (Forcato et al., 2010, 2011, 2013).

The aim of this review is to analyze the strengthening function of the reconsolidation process understood as a memory improvement obtained only by triggering such process without any other treatment. We thus present and discuss both our findings and those of others, trying to evidence the central role of reconsolidation in the modification of the stored information and in the fate of a consolidated memory usually doomed to be forgotten.

2. Memory strengthening by the reconsolidation process in animal models

Different researchers have analyzed memory enhancement during the reconsolidation process in animal models by using different

pharmacological agents or modulators which affect the re-stabilization phase (Frenkel et al., 2005; Lee et al., 2006; Carbó Tano et al., 2009). However, other researchers have addressed the strengthening function of reconsolidation by simply triggering the process (Lee, 2008; Inda et al., 2011; Wiltgen and Silva, 2007; de Oliveira Alvares et al., 2012, 2013). These researchers found an increase in the measured response, an increase in memory precision and/or persistence, and a memory more resistant to extinction. Lee (2008) found that a consolidated contextual fear memory could be strengthened by a second learning trial, but only when the consolidated memory was previously reactivated. Intriguingly, impairing memory reactivation with a pharmacological treatment hindered the improvement effect of the second learning trial on the target memory (Lee, 2008). Inda et al. (2011) later found that successive reactivations of young memories (48 h after training), which in turn triggered repeated reconsolidation processes and strengthened the original memory. With the passing of time, older memories (two weeks after training), the repeated presentation of the reminder triggered another memory process: the acquisition of the extinction memory (Inda et al., 2011). Other researchers also found that contextually fear-conditioned animals are good at discriminating between the training context and a novel context, close to the training, but that, in a remote testing session, they then generalize the freezing response to both contexts (Wiltgen and Silva, 2007; de Oliveira Alvares et al., 2012). Based on this, de Oliveira Alvares et al. (2013) tried to determine whether the re-exposure to the training context hinders the aforesaid generalization. To this end, these authors re-exposed the animals briefly to the training context 14 days after training and found that reactivation maintained the specificity for the training context. This lack of generalization could be considered as a consequence of memory strengthening by triggering of the reconsolidation process. These authors proposed that this function prevents the loss of precision, which could be interpreted as a form of memory weakening (De Oliveira Alvares et al., 2013). With the same treatment (a brief re-exposure to the training context 14 days after training), these authors also demonstrated that the memory was reinforced. The animals that had received the treatment showed a sustained freezing response in comparison with non-reexposed animals during a long re-exposure to the training context (i.e. extinction session). These authors concluded that this treatment not only maintains memory precision (fear response to training context), but also increases memory persistence (a robust conditioned response 28 days after training) (De Oliveira Alvares et al., 2013).

3. Strengthening a consolidated declarative memory in humans by the reconsolidation process

The strengthening function of the reconsolidation process creates a new picture for the post-retrieval modification of consolidated memories. In this case, the presentation of the reminder reactivates the consolidated memory and the re-stabilization *per se* modifies the features of such memory. Thus, the occurrence of this phenomenon may modify memory persistence, memory precision or both. In any case, these changes may transform the dynamics and fate of consolidated memories.

3.1. The declarative memory paradigm in humans

To study the declarative memory in humans, we have used a paradigm that included five pairs of non-sense syllables presented in an enriched specific context (image, colored light and music). Each pair was formed by a cue syllable associated with a response syllable. More specifically, each experiment consisted of a training session in which each trial was composed of the context period with diverse stimuli options: for the List 1 the light could be blue or green; the image, three different pictures of cascades; the sound, three different tango melodies. Only one combination of these options (the specific context) was followed by the syllables presentation of List 1 (syllable period). The context period for the List 2 there was two possible options: the light could be green or yellow; the image, a picture of a forest; the sound, three symphonies melodies. Only one combination of these options (the specific context) was followed by the syllables presentation of List 2 (syllable period). The trial which includes the specific context followed by the syllables presentation is termed the actual trial while the others with only context (i.e., without syllables presentation) are called the fake trials. The syllable period 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. Each cue-syllable was taken at random from a list of five pairs. Subjects were given 5 s to write the corresponding response-syllable. Once that period was finished three situations were possible: first, if no syllable was written, the correct one was shown for 4 s; second, if an incorrect syllable was written, it was replaced by the correct one and it was shown for 4 s; and third, if the correct response was given, it stayed for 4 s longer. Immediately after that, another cue-syllable was shown and the process was repeated until the list was over. Altogether an actual trial lasted 51 s (6 s for context period and 45 s for syllable presentation). During the training session, the list of non sense syllables was presented in 10 different trials (in the first trial participants saw the pairs whereas in the other nine trials they completed the pairs and received feedback), a treatment session, in which the reminder and/or the interfering list (a second learning task) was administered, and a testing session, in which memory retention for the target memory was evaluated. Testing session consisted in four cue-recall trials without feedback. To examine in detail the performance at testing, we also categorized the types of errors made during testing in three defined categories: Void-Type error, when no response was written down; Intralist-Type error, when the response syllable was not the right one but belonged to the list; Confusion-Type error, when the response syllable was not included in the list. Based on the type error we defined an improvement in memory precision when the confusion type error diminished, and, an improvement in persistence when the void type error were reduced.

We demonstrated that the presentation of a cue reminder (which included the specific context and a cue syllable without the possibility to write down the response syllable) rendered the target memory labile and susceptible to be interfered by the second task, into a defined time window (defined between 0 and ~6 h after reactivation) (Forcato et al., 2007). The process occurred only when a reminder with this specific structure was presented (Forcato et al., 2009), i.e. the process was triggered only when the mismatch between current and past events was included (Pedreira et al., 2004; Forcato et al., 2009). Thus, the target memory was evoked and its traces remained stable and resistant to amnesic agents only when the reminder consisted of contextual cues (context reminder) or when the subjects were allowed to write down the response syllable (cue-response reminder) (Forcato et al., 2009; Fig. 1A–C).

3.2. Memory persistence is increased by triggering of the labilization-reconsolidation process

Based on that described above, in our lab, we also decided to what extent triggering one or more reconsolidation processes without any other intervention could modify memory strengthening, and consequently, memory persistence (Forcato et al., 2013). To this end, we performed a seven-day experiment including three groups. The treatment was the presentation of varying numbers of cue

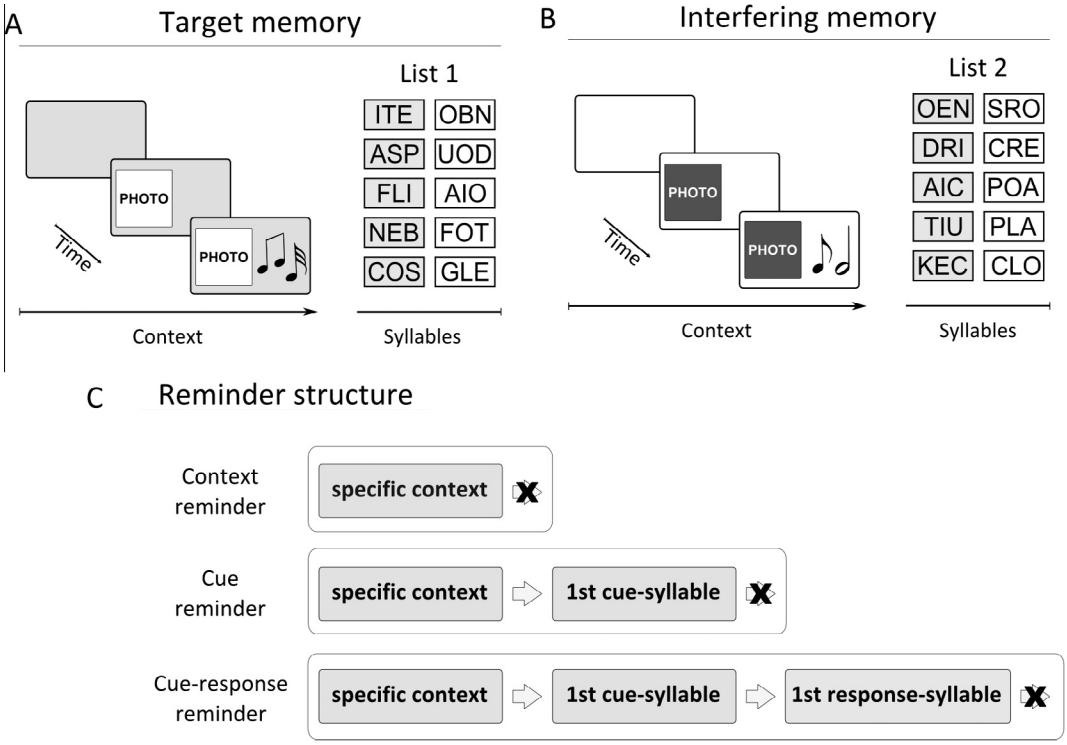


Fig. 1. Experimental protocol. (A) Target Memory: On Day 1, subjects acquired the Target memory. The trial consisted of the context period, i.e. a specific combination of a light (color illumination of the room), image (a picture) and sound (music), and by a syllable period, i.e. 6 s after the stimulus presentation, the five pairs of cue-response syllables (List 1) were presented successively and in random order. (B) Interfering memory: the training of the interfering task (List-2 learning) after the reminder presentation was the same as in A. (C) Types of reminders: the cue reminder (Rc) included the specific context and then one cue syllable was presented after which the trial was abruptly interrupted, thus not allowing the subject to answer with the respective response syllable. The context reminder (Rctx) consisted in the presentation of specific context only and the trial was abruptly interrupted before any syllable presentation. The cue-response reminder (Rw) consisted in the presentation of the specific context, a cue syllable and the opportunity to complete the response. Then, the trial was interrupted. X stands for the full-stop of each type of reminder.

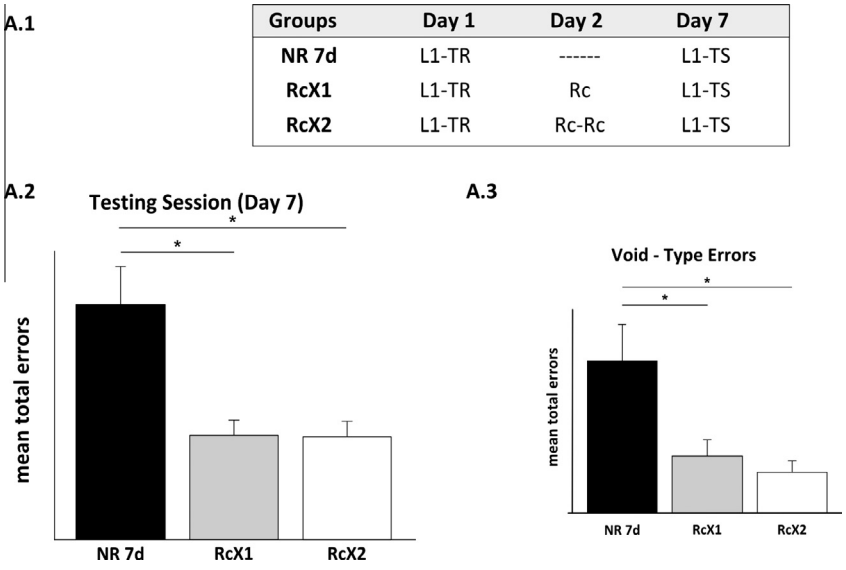


Fig. 2. At least one reminder improves memory persistence. (A.1) Experimental protocol: A three-day experiment. The table shows the experimental groups: no reminder (NR 7d), one cue reminder (RcX1), and two cue reminders (RcX2); L1, List 1; TR, training session; TS, testing session. (A.2) Subjects that had received one (RcX1) or two cue reminders (RcX2) on Day 2 expressed fewer errors on Day 7 than the control group (NR 7d) and were less susceptible to spontaneous decay revealed by the number of void-type errors (A.3). Adapted from Forcato et al. (2013).

reminders. On Day 1, subjects learned a list of five pairs of cue-response syllables (training session). On Day 2, one group received one cue reminder whereas another group received two cue reminders separated by a 5-min interval. A no-reminder group, who received no treatment was also included. All subjects underwent testing on Day 7. The performance of each group on Day 7 was estimated as the mean of total errors made when responding to the cue syllables during two testing trials. The results showed that the subjects who had received one or two cue reminders on Day 2 performed better than those who had received

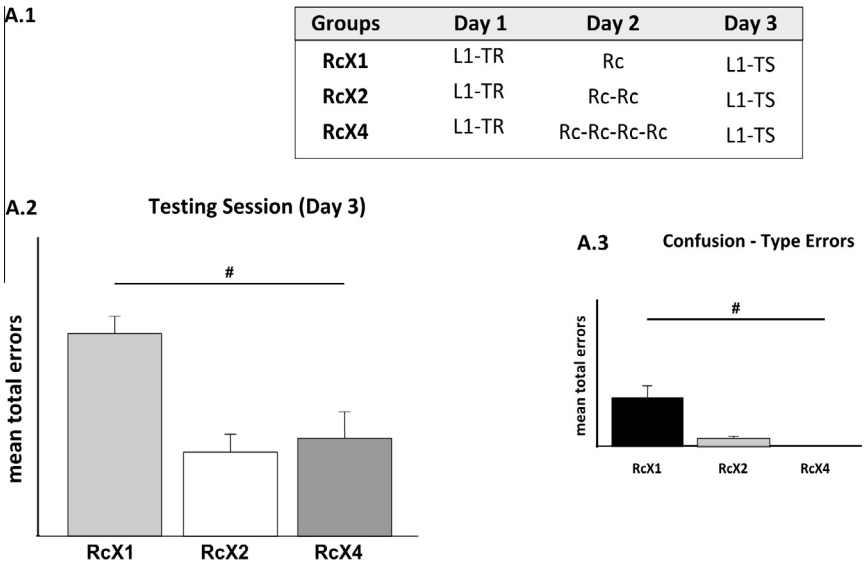


Fig. 3. Memory strengthening by repeated triggering of labilization-reconsolidation. (A.1) Experimental protocol: a three-day experiment. The table shows the experimental groups: one cue reminder (RcX1), two cue reminders (RcX2), four cue reminders (RcX4) and two cue reminders presented 2 h between them (RcX2-2h); L1, List 1; TR, training session; TS, testing session. (A.2) Groups that had received at least two successive cue reminders (RcX2 and RcX4) committed fewer errors than the one that had received only one (RcX1). (A.3) Memory precision is revealed as a reduction in the number of confusion-type errors. Adapted from Forcato et al. (2011).

no reminder. The fewer void-type errors in the groups that had received the treatment on Day 2 suggest that the improvement in memory persistence was reflected by the fact that subjects remembered the whole response syllable (Fig. 2) (Forcato et al., 2013).

To ensure that the strengthening effect was a consequence of labilization-reconsolidation and not just of memory retrieval, we next designed a similar experiment, but used a context reminder (the presentation of contextual cues alone) that only evoked the target memory without triggering the labilization-reconsolidation process. We demonstrated that the presentation of the context-reminder did not affect the performance on Day 7 (Forcato et al., 2013).

We concluded that the strengthening effect depends on the presentation of at least one cue reminder which triggers the labilization-reconsolidation process and improves memory persistence (Forcato et al., 2013).

3.3. Memory precision is increased by repeated triggering of the labilization-reconsolidation process

To evaluate the increase in memory precision, i.e. the other effect of memory strengthening, in another study, we performed a three-day experiment with three groups (Forcato et al., 2011). On Day 1, participants learned the list of cue-response syllables (List 1, training session). On Day 2, one group received one cue reminder, another group received two cue reminders, and the other group received the cue reminder four times. All participants underwent testing on Day 3. The results showed that the participants who had received two or four cue reminders successively on Day 2 performed better than those who had received only one reminder. Moreover, when two or four cue reminders were presented on Day 2, participants made fewer confusion-type errors. The decrease in this error type reflected an increase in memory precision (Fig. 3) (Forcato et al., 2011).

When the cue reminders were given successively in the same treatment session, memory retention was improved as a consequence of a double reactivation (Forcato et al., 2011). Since, in real life, it should be expected that reactivations do not occur necessarily immediately one after the other, we next explored the effect of separate reminder presentations. We demonstrated that the strengthening and increase in precision were observed only when the second cue reminder was presented within the time window of the first triggering of the reconsolidation process (Forcato et al., 2011).

4. How the strengthening function of the reconsolidation process changes the fate of a consolidated memory: its effect on an amnesic agent

The findings described so far in this review demonstrate that the reconsolidation process changes the features of the consolidated memory and that the process *per se* modifies not only the persistence, but also the precision of the target memory.

In another study carried out at our lab, we asked whether the strengthening by reconsolidation modified the strength of the memory making it more resistant to interference. To answer this question, we evaluated the effects of combining repeated reactivations followed by administration of an interfering task (Forcato et al., 2007).

To show the amnesic effect produced by the interfering task on the target memory, we used the retrieval-induced forgetting (RIF) effect. The RIF effect is an observable memory impairment of related material at the time of retrieval. The effect reflects an inhibitory control and suppression of competing memories. Beginning with simple verbal items, it has been shown in a wide range of protocols of verbal and non-verbal materials (Anderson et al., 1994; Anderson and Huddleston, 2012). We argued that the retrieval of a memory can affect the later recall of similar memories. In our experiments, the target memory (List 1) and the interfering memory (List 2) were similar and related by the presence of the context and the task. The RIF effect was evidenced only when the target memory was intact, whereas, when List 2 had interfered with the re-stabilization of the reactivated List 1, the RIF effect was absent (Forcato et al., 2007).

Thus, we next designed a three-day experiment combining reactivation or repeated reactivations immediately followed by a List 2 learning task. We predicted that the No-RIF effect could be detected because the reconsolidation of the target memory was impaired and that, after confirming the prediction, the

A.1

Groups	Day 1	Day 2	Day 3
RcX1	L1-TR	Rc	L1-TS
RcX1 - L2	L1-TR	Rc 5min L2	L1-TS---L2-TS
RcX2	L1-TR	Rc-Rc	L1-TS
RcX2 - L2	L1-TR	Rc-Rc 5min L2	L1-TS---L2-TS
CT - L2	--------	L2	L2-TS

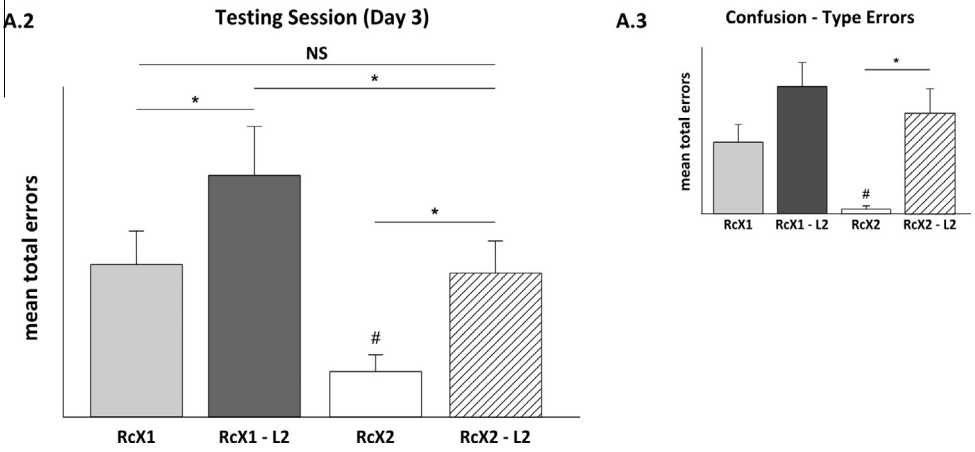


Fig. 4. A memory strengthened by repeated presentation of the cue reminders is more resistant to the interfering task on Day 3. (A.1) Experimental protocol: A three-day experiment. The table shows the experimental groups: one cue reminder (RcX1), one cue reminder and interference (RcX1-L2), two cue reminders (RcX2), two cue reminders and interference (RcX2-L2) and the List-2 control group (CT-L2); L1, List 1; L2, List 2; TR, training session; TS, testing session. (A.2) Subjects that had received two cue reminders successively on Day 2 before learning List 2 committed fewer errors than the other interference group (RcX1-L2) and were similar to those expressed by the Control Group (NR 3d Group). Learning List 2 immediately after the presentation of the cue reminder on Day 2 interfered with the memory for List 1 and two presentations of the cue reminder strengthened the memory. (A.3) The strengthening effect reduced confusion-type errors. Adapted from Forcato et al. (2013).

performance for List1 might reveal the amnesic effect on the target memory (Forcato et al., 2007, 2009).

The experiment included five groups. On Day 1, the subjects of four of these groups received a training session (List 1). On Day 2, one pair of groups received the treatment, which consisted of one cue-reminder presentation, and one of both groups of subjects learned List 2 (interfering list); the other pair received two presentations of the cue reminder, and one of both groups of subjects received the second learning task (List 2). The remaining group learned List 2 only. All subjects received the testing session on Day 3. The results showed No-RIF effect on List-2, confirming the impairment produced by the second task on List 1 memory. However, performance on List 1 showed a significant difference between groups (Fig. 4). The subjects who had received two successive cue reminders on Day 2 performed better than those who received only one reminder and made fewer confusion-type errors, confirming the strengthening effect of repeated reactivations. With respect to the effect of the interference on reconsolidation, each pair (one pair of groups received one and cue reminder the other pair received two cue reminders) revealed the amnesic effect of the interfering task. However, the group that had received two cue reminders immediately following the interfering task and the group that had received one reminder only had similar performances. We concluded that the target memory is strengthened by repeated reactivations, and that, consequently, the interfering list is less effective (Forcato et al., 2013).

4.1. The age of the target memory is a boundary condition for the strengthening function of the reconsolidation process

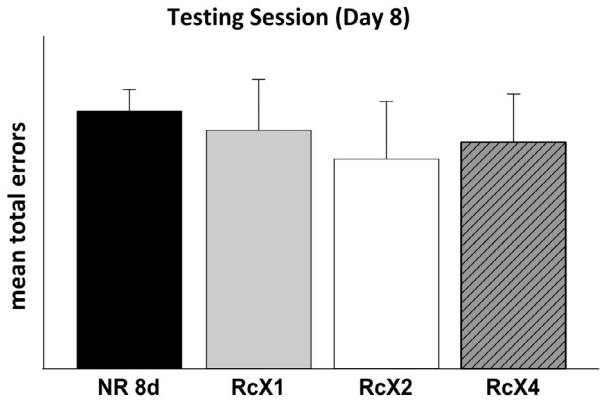
It is also well known that, in some paradigms, the length of the interval between memory acquisition and memory reactivation, which determine the age of the memory, may restrict the labilization of the target memory (Suzuki et al., 2004; Alberini, 2005). We have thus proposed that this boundary condition could be specific for the strengthening function of the reconsolidation process (Forcato et al., 2013). To test this, we analyzed whether remote reactivations by reminder presentations could also strengthen the target memory. To do this, we performed an 8-day experiment where the memory acquisition and memory reactivations were separated by 7 days. On Day 1, subjects learned List 1. On Day 7, three groups received three different treatments: one, two or four cue reminders, whereas a fourth group received no treatment. All subjects were tested on Day 8. All the groups showed the same performance at testing (Fig. 5A1 and A2). Thus, before considering that the strengthening may occur only for younger memories, we evaluated whether any other boundary condition might be at play. We considered that older memories could not be reactivated (Suzuki et al., 2004; Inda et al., 2011). Thus, we used an interfering list after old memory reactivation on Day 7. Subjects learned List 1 on Day 1 and on Day 7, one of the groups received one cue-reminder and after that List 2 training (interfering list). Finally, the fourth group received no treatment on Day 7. All subjects were tested on Day 8. All the subjects showed a similar performance at List-1 testing, hindering a possible amnesic effect.

Taking into account the similar performances for List 1 and the large number of errors made by the group receiving no treatment, we proposed that the forgetting effect (as a consequence of the passing of time) overshadowed any amnesic effect. We confirmed this possible interpretation by comparing the performance of two groups that learned List 1 on Day 1: one group was evaluated on Day 3 and the other on Day 8. The forgetting effect was reflected in the large number of errors made by the group evaluated on Day 8. We concluded that two processes could coexist in this experimental protocol: the effect of interference on the re-stabilization of the target memory, and forgetting because of the mere passing of time (Forcato et al., 2013). However, to determine whether older memories can be reactivated, we decided to perform

A.1

Groups	Day 1	Day 7	Day 8
NR 8d	L1-TR	------	L1-TS
RcX1	L1-TR	Rc	L1-TS
RcX2	L1-TR	Rc-Rc	L1-TS
RcX4	L1-TR	Rc-Rc-Rc-Rc	L1-TS

A.2



B.1

Groups	Day 1	Day 7	Day 8
GL-NR 8d	L1-TR	------	L1-TS
GL-RcX1 - L2	L1-TR	Rc 5min ----- L2	L1-TS---L2-TS
GL-CT - L2	-----	L2	L2-TS

B.2

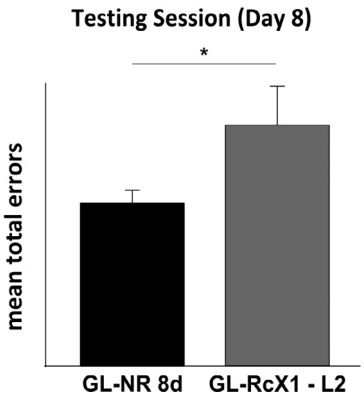


Fig. 5. The reconsolidation of an older memory. (A.1) Repeated labilizations do not strengthen an older memory. Experimental protocol: A three-day experiment. The table shows the experimental groups: no reminder (NR 8d), one cue reminder (RcX1), two cue reminders (RcX2), four cue reminders (RcX4); L1, List 1; TR, training session; TS, testing session. (A.2) Two or four cue reminders presented on Day 7 do not improve memory retention on Day 8. Adapted from Forcato et al. (2013). (B) An older memory could be reactivated and interfered. Experimental protocol: a three-day experiment. The table shows the experimental groups: Good Learners No Reminder (GL-NR 8d), Good Learners who received one cue reminder and the interfering task (GL-RcX1-L2) and Good Learners List-2 Control Group (GL-Ct-L2); L1, List 1; L2, List 2; TR, training session; TS, testing session. A.2) Only subjects that performed better at training (Day 1) revealed the amnesic effect of the interference (List 2) on the target memory (List 1), revealing the amnesic effect of the interfering task on the reconsolidation of an older memory.

a supplementary analysis of the data trying to separate the effect of both factors, i.e. the interference on reconsolidation and forgetting. To this end, we re-analyzed the data of this eight-day experiment including in the group only the very good learners, that is, the subjects whose performance was 85% or over at training. We expected that under this condition, the effect of forgetting would be minimized, enabling the evaluation of the effect of the interference. The analysis of the good learner performance at the testing session showed a very different result profile. Under this condition, an amnesic effect was revealed for List 1 at testing (Fig. 5B1 and B2). An amnesic effect was detected in the groups including only good learners. However, when we applied the same sort of analysis (including only the good learners) for the groups that had received a different number of cue reminders on Day 7, the performance at testing was the same between groups. The strengthening effect was not present despite the inclusion of the good learners. Based on the above, we proposed that the older target memory could be reactivated, but that the repeated reactivations performed 7 days after acquisition did not modify the strength of the memory. We concluded that the age of the memory is a boundary condition for the strengthening function of the reconsolidation process.

5. General discussion

The main findings described above can be summarized in three points. First, triggering at least once the labilization-reconsolidation process strengthens the original memory and maintains it available for longer periods of time. In fact, one of the first reports in the topic (Sara, 2000) postulated that the reconsolidation process implies a recapitulation of different steps of consolidation and results in the modification of the stored information, specifically in memory strength. Thus, our results are in agreement with this initial description of the term *reconsolidation*. Second, repeated labilization-reconsolidation processes strengthen the original memory, and the simple recall has no effect on memory persistence or precision. More interestingly is the fact that reinforced memories are more resistant to interference. Finally, the strengthening via reconsolidation is not operative in older memories. We proposed two possible explanations for this last result: either the memory is not labilized seven days after training, or forgetting overshadows any other effect on the target memory. To minimize the forgetting effect, we analyzed only the data of very good learners and the effect of interference became present under this condition. We concluded that the memory could be reactivated; however, no effect of repeated labilization-reconsolidation was observable on Day 8.

Based on the above, we propose that the strengthening function of the reconsolidation process is a key factor which transforms the fate of memories depending on the memory features and the boundary conditions that determine the occurrence of such process.

In line with our results, by studying episodic memories, Wichert et al. (2011) analyzed whether the possibility to alter retrieved memories depended on the age of such memories. Their paradigm consisted in learning a set of pictures (emotional and neutral) and recalling them 1, 7, or 28 days later. Immediately after reactivation, the volunteers learned a second set of pictures. These authors found that the reactivation *per se* enhanced 28-day-old memories. In accordance with our results of increased memory persistence (Fig. 2), they showed that strengthening by reconsolidation could occur under specific parametric conditions. When they analyzed the effect of the interfering task, the new pictures interfered with 1-day-old and 28-day-old memories but not with 7-day-old memories. Based on our results, we interpreted these findings as a consequence of the interaction between two opposite processes at the time window of lability: strengthening by reconsolidation and an amnesic effect resulting from the use of the interference pictures. The authors also argued that the combination of these effects could depend on the age of the memory (Wichert et al., 2011). In another report, Wichert et al. (2012) evaluated the impact of multiple reactivations on the amnesic effect of the interfering task. Their experimental design included the presentation of one to three extra

reminders distributed in different days. Their results showed that even after multiple reactivations, memories remained susceptible to the amnesic effect of the interfering task. In accordance with their previous report, these authors found no evidence of strengthening when the test was performed 7 days after training (Wichert et al., 2012).

5.1. Memory improvement during reconsolidation: the effect of different modulators during the time window of the process

Memories may not only be strengthened via mere memory reactivation and its re-stabilization. The labile state after reactivation opens a window of fragility where different agents may enhance the memory. Thus, it is possible to use different pharmacological treatments to enhance the memory during its re-stabilization (Lee et al., 2006; Carbó Tano et al., 2009). Then, in our lab, we also decided to use our paradigm with pharmacological interventions. Based on the importance of the GABAergic system in different memory processes (Makkar et al., 2010), and more specifically in the reconsolidation process in very different animal models (Bustos et al., 2006; Carbó Tano et al., 2009), our hypothesis was that the role of such system is evolutionarily conserved and thus involved in the reconsolidation of the declarative memory in humans. Thus, using our paradigm, we analyzed the effect of benzodiazepines on the reconsolidation process of the declarative memory (Rodríguez et al., 2013). The verbal memory was labilized by a reminder presentation 24 h after acquisition, and then a placebo capsule or 0.25 mg clonazepam was administered. The verbal memory was evaluated on Day 3. The volunteers who had received 0.25 mg clonazepam after the cue reminder showed memory improvement, whereas no improvement was observed in the absence of the reminder presentation, or when the memory was only evoked or when the memory was evaluated at a short-term test. These results indicate that a similar dose of benzodiazepine, commonly prescribed to treat anxiety, positively modulates a neutral declarative memory. This effect on a memory generated by a neutral verbal task might be considered a collateral effect on other memories when the treatment is aimed to treat anxiety disorders. These results are at odds with other results using aversive paradigms in animal models where agonists of the GABAergic system show a detrimental effect on reactivated memories (Bustos et al., 2006; Carbó Tano et al., 2009). In line with these paradoxical results, Corlett et al. (2013) administered ketamine (an N-methyl-d-aspartate (NMDA) subtype of glutamate receptor antagonist) after memory reactivation. Based on the clearly described role of this type of receptor in learning and memory (Finnie and Nader, 2012) where NMDA antagonists usually show an amnesic effect, Corlett et al. analyzed its effect during a fear memory reconsolidation. On Day 1, the participants were conditioned using by an auditory fear conditioning, on Day 2, they received the placebo or ketamine after memory reactivation once the conditioned stimulus (CS) was presented, and on Day 3, they went through an extinction session (repeated presentations of the conditioned stimulus) and reinstatement protocol unconditioned stimulus presentation (Bouton, 2004). Participants showed an increased conditioned response in the group that had received the CS followed by ketamine (Corlett et al., 2013).

Considering the well-known effect of stress on memory processes, Coccoz et al. (2011) evaluated the impact of a mild stressor that had shown an effect on memory processing in other paradigms (Cahill et al., 2003; Smeets et al., 2008) on the verbal learning paradigm. Six days after training, these authors presented the reminder followed by a cold pressor stress. When they evaluated the memory on Day 7, they observed memory retention when the cold pressor stress was concurrent with the labile-memory state. They concluded that a mild stressor could enhance the reconsolidation process (Coccoz et al., 2011).

5.2. Translational applications of the reconsolidation process

The knowledge about reconsolidation opens at least two possible translational applications of the process. First, cognitive neuroscience and its insight into problems in psychiatry (Eysenck, 1976; Gordon, 1981) have led to the characterization of many of the symptoms of mental illness as pathologies of memory formation, maintenance, and utilization (Halligan and David, 2001). In this framework, the reconsolidation process could not only be the mechanism of some psychopathologies (Corlett et al., 2009), but also open a new therapeutic window (Taylor et al., 2009; Debiec, 2012). The reconsolidation process has been proposed as a new tool for the design of new therapies for the treatment of different anxiety disorders, drug addiction and maladaptive memories (Debiec and LeDoux, 2004; Lee et al., 2005; Kindt et al., 2009). For these potential therapies, boundary conditions, such as strength, target memory age and choosing specific parameters in the reactivation process will be crucial in the design of beneficial therapeutic approaches (Alberini, 2013; Forcato et al., 2013). It has also been described that the most salient memories would be spontaneously reactivated when undergoing repeated reconsolidation processes, which in turn would increase their fixity (Rasch et al., 2007). Under these conditions, in emotional disorders, such as anxiety, depression, and post-traumatic stress disorders, the extreme fixity of these memories may compromise the possibility of reactivation and/or memory updating under therapeutic conditions (Alberini, 2007). However, there are a few examples where these kinds of protocols have shown promising results. Using propanolol (a β-adrenergic antagonist), which is used to interfere reconsolidation in animal models and humans (Przybyslawski and Sara, 1997; Kindt et al., 2009), Saladin et al. (2013) impaired the reconsolidation of drug memory in cocaine abusers. Participants were exposed to cocaine cues (videos showing cocaine use and direct cues like false bags of cocaine or a crack pipe for crack cocaine users). Then, the authors repeated this presentation 15 min after, and at the end of the second presentation participants received a pill of propanolol or placebo. The authors found a significantly lower drug craving score in the subjects of the propanolol group 24 h after reactivation, but not a week later (Saladin et al., 2013). In another study, Xue et al. (2012) used the extinction procedure to disrupt reconsolidation (Schiller et al., 2010; Agren et al., 2012). Heroin addicts on withdrawal were exposed to a reactivation-exposure procedure. The reactivation consisted in the presentation of a 5-min video with drug-related cues. The control group watched neutral images. Then, the extinction session consisted of a 60-min exposure to heroin cues. A lower heroin-craving score was found in the group that had watched the video with drug-related images and had received the extinction session 24 h after the treatment. The effect remained the same after 30 and 180 days. Based on these promising results, the authors concluded that it seems feasible to design new therapies (Xue et al., 2012).

The reconsolidation process may also be of use in other therapeutic approaches. More specifically, if reconsolidation serves to update or strengthen memories, its inclusion in new protocols could be a novel behavioral strategy for cognitive rehabilitation. Memory rehabilitation programs are typically focused on teaching retrieval strategies (different sensory aids, diary use, etc) and learning strategies (errorless learning, distributed practice and vanishing cues) (Wilson, 2008). The reconsolidation framework may allow, not only upgrading the existing techniques (i.e. how and when is efficient to reactivate a memory), but also developing new ones based on the proper use of reminder cues that are known

to trigger the strengthening function of reconsolidation. Under these new protocols, patients would be able to improve their memory in everyday life.

A key topic in the Education field is related to maximizing students' retention of learned information. One technique that has shown to be highly effective is the use of testing (Potts and Shanks, 2012). In this context, the evaluation of the learned information without feedback could be considered as a form of reactivation. Following this line of thinking, Karpicke and Roediger (2008) evaluated the effects of repeated learning or repeated retrieval without feedback on a long-term retention test a week after initial learning. Using foreign language vocabulary -word pairs-, they examined the contributions of repeated study and repeated testing by comparing three dropout conditions once an item was successfully recalled: dropout condition 1 involved dropping the item from but still include it in the tests; dropout condition 2 involved dropping the item from the tests but including it in the study; and finally dropout condition 3 involved dropping the item from both the study and the test. The results showed that repeated study after learning had no effect on delayed recall, but that repeated testing enhanced the target memory (Karpicke and Roediger, 2008). Thus, we consider this report to be a good example of a testing procedure that complies with the necessary conditions to reactivate the learned information. However it is important to remark the difference between the testing effects and the strengthening function proposed for the reconsolidation process based on our results. The single reminder cue used in these experiments does not include the target item and is capable to reactivate the whole memory (the entire pairs of syllables). This effect is revealed by a generalized interference (new learning after the reactivation) over the original memory. Even tough, within the Testing Effect literature, a full retrieval session (testing) of the entire list of cue-target associations, was observed to immunize the original memory from interference (Potts and Shanks, 2012) or updating with new information (Finn and Roediger III, 2013).These differences could be related to the paradigms and the type of reminder session used.

5.3. Strengthening function in the framework of system consolidation

The reconsolidation process can be defined in different ways. Some authors consider that reconsolidation does not represent a new process, but a manifestation of lingering consolidation. Thus, under this point of view, the concept of *reconsolidation* expands the concept of consolidation (Dudai and Eisenberg, 2004). In this model, a later round of consolidation is initiated by the reactivation of a consolidated memory, which transiently destabilizes the long-term memory (Dudai, 2012). In this framework, it could be possible to analyze reconsolidation either as a process included in the synaptic consolidation (defined as the process by which information is transformed into a long-term form at local nodes in the neural circuits that encode the memory) or as a system consolidation (defined as an internal representation that is converted into a long-term form and reorganized over distributed brain circuits) (Dudai, 2012). For the latter, two different theories have been proposed: the standard consolidation theory (McClelland et al., 1995; Squire and Alvarez, 1995), which assumes that the hippocampus is only a temporary storage area for memory and that the neocortex stores memories thereafter, and the multiple trace theory (Nadel and Moscovitch, 1997), which proposes that the hippocampal complex encodes episodic information that is encoded in distributed assemblies of such neurons binding them into a coherent representation. However, since the trace is commonly reactivated in an altered context, a newly encoded hippocampal trace is formed, and this new trace is joined with the pre-existing one. Consequently, multiple traces share some or all the information about the initial episode.

At this point it is important to analyze the results exposed in this review under these two models. The differences obtained in our research for younger and older memories, can be explained under these two theories. Under the first theory, if the reconsolidation process is associated with the initial area of storage, the reinforcement by triggering the reconsolidation process is possible only when the memory is dependent on the hippocampus. For older memories, when the memory trace becomes more independent of the hippocampal activity, the strengthening by repeated reminder presentations is no longer operative. Under the second theory, younger memories formed by single traces could be reinforced by the reconsolidation process; however, older memories could include multiple traces and the possibility of reinforcement is weakened. However, the possibility to interfere the re-stabilization with a new learning is still open.

6. Conclusions and remarks

Based on all the research described above regarding reconsolidation of declarative memories in humans, we conclude that such memories do not go through reconsolidation every time they are retrieved. Different boundary conditions for the process determine whether the labilization-reconsolidation is triggered or not. In this respect, the comparison between current and past events (mismatch) seems to be a necessary condition that guides memory updating (Dudai, 2012). We have demonstrated that the biological role of the process is likely to involve the modification, updating, or strengthening of a consolidated memory, and that the mismatch is a central key boundary condition for the process (Forcato et al., 2010, 2011, 2013). With respect to the strengthening function, we have shown that triggering once is enough to reinforce the target memory at a long-term test. However, under nearer test conditions, the effect is only evidenced after a second triggering in the time window of the first. This result could be interpreted as the consequence of the overlapping of the molecular cascades associated with the re-stabilization of the memory trace. Thus, future experiments may show different degrees of effectiveness of the interfering list if it is administered after two reactivations separated by longer than 5 min, where the overlapping of the molecular cascade is diminished.

Finally, the malleability of the memories after retrieval has been documented by cognitive psychology (Schacter et al., 2000). In this framework, the appearance of the reconsolidation hypothesis offers a plausible process to modify the acquired information. The two proposed functions for the process comply with such plasticity as postulated by cognitive psychology and which brings together the cognitive and neurobiological point of view of memory processes (Hardt et al., 2010). Based on all the above, we consider the strengthening function a key factor in the role of reconsolidation in the fate of declarative memories in humans.

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