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Hippocampal α_7-nicotinic cholinergic receptors modulate memory reconsolidation: A potential strategy for recovery from amnesia

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ABSTRACT

When subjects are exposed to new learning experiences, the novel information could be acquired and eventually stored through memory consolidation process. The exposure of mice to a novel experience (a hole-board) after being trained in an inhibitory avoidance apparatus is followed by impaired performance of the avoidance memory in subsequent tests. The same impairing effect is produced when mice are exposed to the novel environment after the reactivation of the avoidance memory. This interfering effect is due to impaired consolidation or reconsolidation of the avoidance memory. The administration of the α_7-nicotinic receptor agonist choline (Ch) in the dorsal hippocampus (0.8 μg/hippocampus) immediately after the inhibitory avoidance memory reactivation, allowed memory recovery. This effect of Ch was time-dependent, and retention performance was not affected in drug-treated mice that were not subjected to memory reactivation, suggesting that the effects on performance are not due to non-specific effects of the drug. The effects of Ch also depended on the age of the reactivated memory. Altogether, our results suggest that Ch exerts its effects by modulating memory reconsolidation, and that the memory impairment induced by new learning is a memory expression failure and not a storage deficit. Therefore, reconsolidation, among other functions, might serve to change whether a memory will be expressed in later tests. Summarizing, our results open new avenues about the behavioral significance and the physiological functions of memory reconsolidation, providing new strategies for recovering memories from some types of amnesia.

1. Introduction

Memory consolidation regards the underlying processes occurring after a learning situation where memory is stabilized and strengthened. New memories are labile and sensitive to disruption before undergoing a series of processes that render the memory representation progressively stable (McGaugh, 1966; McGaugh, 2000; Roozendaal & McGaugh, 2011).

If the information processing were perturbed while consolidation is taking place, the storage could be affected and, as a consequence, the formation of the memory trace could be either enhanced or impaired. Although it was traditionally accepted that once consolidation is complete memories become permanent (Squire & Alvarez, 1995), several studies have shown that when a well consolidated memory is reactivated, it again becomes sensitive to disruption (Lewis, 1979; Misanin, Miller, & Lewis, 1968; Nader, Schafe, & Le Doux, 2000; Przybyslawski & Sara, 1997). Most treatments affecting memory consolidation when given after training are also able to disrupt memories when given after its reactivation. The period of sensitivity triggered after memory reactivation was named reconsolidation (Lewis, 1979; Przybyslawski & Sara, 1997).

Under physiological conditions, memory consolidation and reconsolidation can be interfered by the presentation of novel learning situations (Blake, Boccia, Krawczyk, & Baratti, 2011; Boccia, Blake, Acosta, & Baratti, 2005; Izquierdo, Schroder, Netto, & Medina, 1999; Netto, Dias, & Izquierdo, 1985) or by sleep deprivation (Walker, 2005). The interference could be also produced through pharmacological manipulations, and the drugs administered exert their actions by modulating endogenous processes. In this sense, the administration of agonists or antagonists of neurotransmitter or hormonal receptors (Izquierdo & McGaugh, 2000; Roozendaal & McGaugh, 2011), protein synthesis inhibitors (Davis & Squire, 1984), transcription factors and their blockers (Boccia et al., 2007; Freudenthal et al., 2005) or protein kinase inhibitors (Bernabeu et al., 1997), can enhance or impair memory consolidation and/or reconsolidation.

Among the neurotransmitters, central cholinergic system has been implicated in learning and memory processes, and it seems to be involved in modulation of acquisition, consolidation, reconsolidation, extinction, and retrieval of information (Baratti, Boccia,

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& Blake, 2009). Post-reactivation administration of choline (Ch), a specific α7-nicotinic cholinergic receptor agonist (Albuquerque, Pereira, Alkongdon, & Rogers, 2009) modulates memory reconsolidation of an inhibitory avoidance task, either enhancing or impairing it, depending on training conditions (Blake, Boccia, Krawczyk, & Baratti, 2012; Boccia, Blake, Krawczyk, & Baratti, 2010). Choline impairs memory reconsolidation when mice are trained with a high footshock, but enhances it when animals are trained with a mild footshock (Boccia et al., 2010).

Several studies have shown recovery from memory impairment, suggesting that a hidden memory can be expressed under the appropriate conditions (Cahill, McGaugh, & Weinberger, 2001; Gold, Haycock, Marri, & McGaugh, 1973; Haycock, Gold, Macri, & McGaugh, 1973; Nader & Wang, 2006; Parvez, Stewart, Sangha, & Lukowiak, 2005; Rescorla, 1988). The modulating effect of Ch on memory reconsolidation may be a useful pharmacological tool for recovery from memory impairment (Blake, Boccia, Krawczyk, Delorenzi, & Baratti, 2012). Recovery from amnesia lead us to consider alternative mechanisms for the amnesic treatments, different from impairment of information encoding, i.e. memory expression deficit.

The present work is aimed to evaluate whether the new learning-induced memory impairment is due to storage failure or to memory expression deficits. The results presented here suggest that learning interference causes a failure of behavioral expression of the memory, but not absence of its storage.

2. Materials and methods

2.1. Experimental subjects

CF-1 male mice from our own breeding stock were used (age: 60–70 d; weight: 25–30 g). They were caged in groups of 10 and remained housed throughout the experimental procedures. The mice were kept in a climatized animal room (21–23 °C) maintained on a 12-h light/12-h dark cycle (lights on at 6:00 AM), with ad libitum access to dry food and tap water. Experiments were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publication N° 80–23/96) and local regulations. All efforts were made to minimize animal suffering and to reduce the number of animals used.

2.2. Behavioral procedures

2.2.1. Inhibitory avoidance (IA) task

The avoidance behavior was studied in one-trial learning, step-through type, which utilizes the natural preference of mice for a dark environment. The apparatus consisted of a dark compartment (20 cm × 20 cm × 15 cm) with a stainless-steel grid floor and a small illuminated platform (5 cm × 5 cm) attached to its front center, elevated 100 cm from the floor (conditioning context) (Blake, Boccia, & Baratti, 2008). The mice were not exposed to the apparatus before the learning trial. During training each mouse was placed in the illuminated platform and received a footshock (1.2 mA, 50 Hz, 1 s) as it stepped into the dark compartment. At the times indicated for each experimental group, the retention tests were performed. Each mouse was placed on the platform again and the step-through latency was recorded. The retention test was finished either when the mouse stepped into the dark compartment or failed to cross within 300 s. In the latter case the mouse was immediately removed from the platform and assigned a score of 300 s (ceiling score). In the retention test session the foot-shock was omitted.

2.2.2. The novel environment

In order to expose mice to a novel experience, a hole-board (HB) was used. The apparatus (Ugo Basile Mod. 6650, Comerio, Italy), made of a gray Perspex panel (40 cm × 40 cm × 22 cm), embodies 16 flush mounted tubes of 3 cm of diameter. Each tube has an infrared emitter and a diametrically opposed receiver connected to an automatic counter to register the number of nose-pokes into the holes. During the exposure, each mouse was placed at the center of the apparatus and the number of nose-pokes was automatically registered for 5 min. From one mouse to the next, the hole-board was carefully cleaned with ethanol 70%.

2.3. Drug administrations

Choline bitartrate (Ch) was purchased from Sigma, St. Louis, MO. The drug was dissolved in sterile saline solution immediately before use, and the dose was calculated as the free base. All other agents were of analytical grade and obtained from local commercial sources. The dose of the drug (0.8 μg/hippocampus) was determined from previous experiments of our laboratory (Blake et al., 2012; Boccia et al., 2010). Ch was injected bilaterally in the dorsal hippocampus (dHPC) (0.5 μl/hippocampus). Experiments were carried out in a blinded fashion with regard to drug treatments.

2.4. Intra-dorsal-hippocampal (dHPC) Injections

Mice were prepared (Boccia et al., 2010) for the dHPC injections of vehicle or drug solutions 48 h before training, so that a minimum of time was necessary for injection, which was administered under light ether anesthesia in a stereotaxic instrument. The preliminary surgery was also performed under ether anesthesia and consisted of an incision of the scalp. Two holes were drilled in the skull without perforating the brain, at the following stereotaxic coordinates AP: −1.50 mm posterior to bregma, L/R + 1.20 mm from the midsagital suture and DV: −1.75 mm from a flat skull surface (Franklin & Paxinos, 1997), in order to bilaterally infuse the drugs after recovery. The skull was covered with bone wax and the mouse was returned to its home cage. Injections lasted 90 s and were driven by hand through a 30-gauge blunt stainless steel needle attached to a 5 μl Hamilton syringe with PE-10 tubing. The volume of each intrahippocampal infusion was 0.5 μl.

The accuracy of dHPC injections was determined by histological determination of the needle position on an animal-by-animal basis. For this purpose, the brains of injected animals were dissected, fixed in 4% parafomaldehide/buffer phosphate saline, and stored in 30% sucrose. They were then cut into 25 μm coronal sections with a cryostat. The deepest position of the needle was superimposed on serial coronal maps (Franklin & Paxinos, 1997). Coronal sections containing the deepest reach of the needle were Nissl stained to estimate the damage produced during the procedure (Fig. 1). Animals were excluded from the statistical analysis if the infusions caused excessive damage to the targeted structure or if the needle tips extended outside the target structure.

2.5. Data analysis

Data are expressed as median latencies (sec) to step-through and interquartile ranges during the retention test and were analyzed, when appropriate, with the nonparametric analysis of variance of Kruskal–Wallis. The differences between groups were estimated by individual Mann–Whitney U tests (two-tailed) (Siegel, 1956). In all cases, $p < 0.05$ values were considered significant.

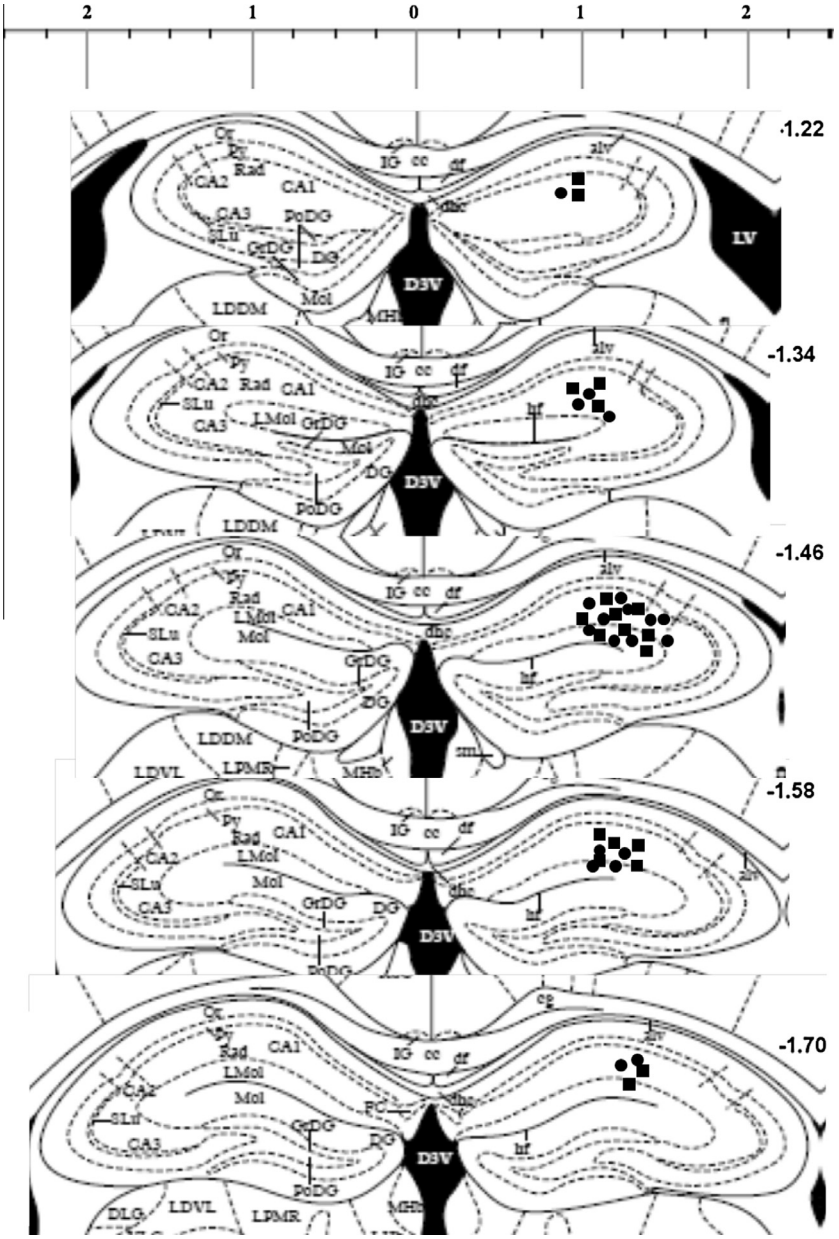

Fig. 1. Coronal brain images adapted from the atlas of Franklin and Paxinos (1997), indicating location of the injections in the hippocampus corresponding to experiment 1 (● SS ■ Ch).

3. Results

3.1. Effects of post-reactivation administration of choline on new learning-induced memory consolidation impairment

3.1.1. Post-reactivation administration of choline reverses new learning-induced memory impairment

This experiment was aimed to determine whether the administration of Ch after the first retention test allowed recovery from new learning-induced memory impairment. Four groups of 10 mice each were trained in the IA task. Immediately after it, two of the groups were exposed to the HB for 5 min, and the other two groups were returned to the home cages. The first retention test (T1) was performed 48 h after training. Immediately after this test, mice received a bilateral dHPC infusion of Veh or Ch (0.8 μg/hippocampus). Mice were tested again (T2) 24 h after T1.

The behavioral procedure and results of this experiment are shown in Fig. 2. Post-training exposure to the HB impaired performance in T1 ($p < 0.001$, compared with the respective non-exposed group). Choline administered immediately after memory reactivation to mice exposed to the HB after training, significantly enhanced retention latencies at T2 ($p < 0.01$, compared with the non-exposed group). That is, Ch reversed the new learning-induced memory impairment. However, consistent with our previous results (Boccia et al., 2010), Ch caused memory impairment in control mice ($p < 0.001$, compared with the vehicle-injected group) (Fig. 2).

3.1.2. The effects of Ch are time-dependent

In the following experiment, four groups of 10 mice each were trained in the IA task. Immediately after it, two of the groups were exposed to the HB for 5 min, and the other two groups were returned to the home cages. The first retention test (T1) was performed 48 h after training. Three hours after T1, mice received a bilateral dHPC infusion of Veh or Ch (0.8 μg/hippocampus). Mice were tested again (T2) 24 h after T1.

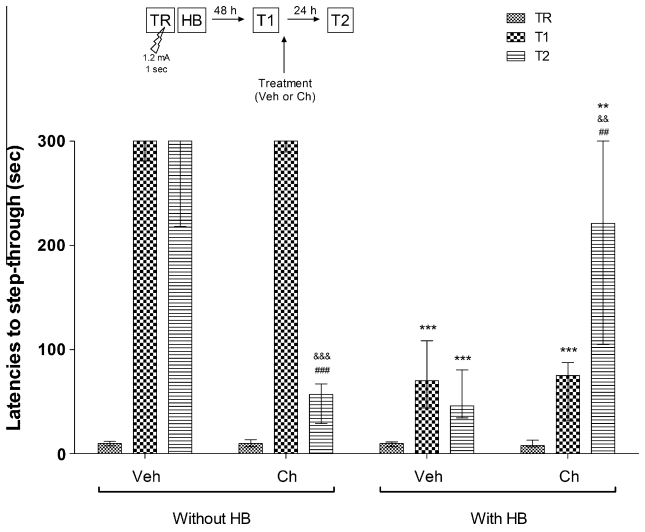

Fig. 2. Effects of Ch on retention performance of mice exposed or not to the novel environment (HB) immediately after training. Choline (0.8 μg/hippocampus) was given immediately after T1. The behavioral protocol is represented above the graph. Each bar represents the median and interquartile range ($n = 10$ mice/group). TR: training session, T1-2: retention tests. $^{***}p < 0.001$, $^{**}p < 0.01$, compared with the corresponding test of the respective group not exposed to the HB; &&& $p < 0.001$, && $p < 0.01$, compared with the corresponding test of the respective Veh-injected group; ### $p < 0.001$, ## $p < 0.01$, comparing T1 vs. T2 of the same group.

The behavioral procedure and results are shown in Fig. 3A. Post-training exposure to the HB impaired performance in T1 ($p < 0.001$, compared with the respective non-exposed group). The administration of Ch 3 h after memory reactivation did not affect retention latencies, showing that Ch effects are time-dependent (Fig. 3A).

3.1.3. Ch effects are observed only if the avoidance memory was reactivated

In the next experiment, four groups of 10 mice each were trained in the IA task. Immediately after it, two of the groups were exposed to the HB for 5 min, and the other two groups were returned to the home cages. Forty-eight hours after training, mice received a bilateral dHPC infusion either of Veh or Ch (0.8 μg/hippocampus). The first retention test (T1) was performed 24 h after the infusion. The behavioral procedure and results are represented in Fig. 3B (note that the reactivation session was omitted).

The administration of Ch 48 h after training without memory reactivation, did not affect retention performance ($p > 0.05$ comparing animals injected with Ch with each respective Veh-injected group) (Fig. 3B).

3.1.4. Choline effects depends on the age of the reactivated memory

In this experiment, twelve groups of 10 mice each were trained in the IA task. Immediately after it, half of the groups were exposed to the HB for 5 min, and the other groups were returned to the home cages. The first retention test (T1) was performed 7, 14 or 21 days after training, depending on the experimental group. Immediately after the test, mice received a bilateral dHPC infusion of Veh or Ch (0.8 μg/hippocampus). Mice were tested again (T2) 24 h after T1. The behavioral procedure and results are shown in Fig. 4.

A resuming graph was included (Fig. 5) in order to compare data from groups of mice receiving the same treatment (but in which memory reactivation occurred at different training-T1 intervals). In this figure, only the retention performance in T2 is represented (combining data from this experiment with data from experiment 2).

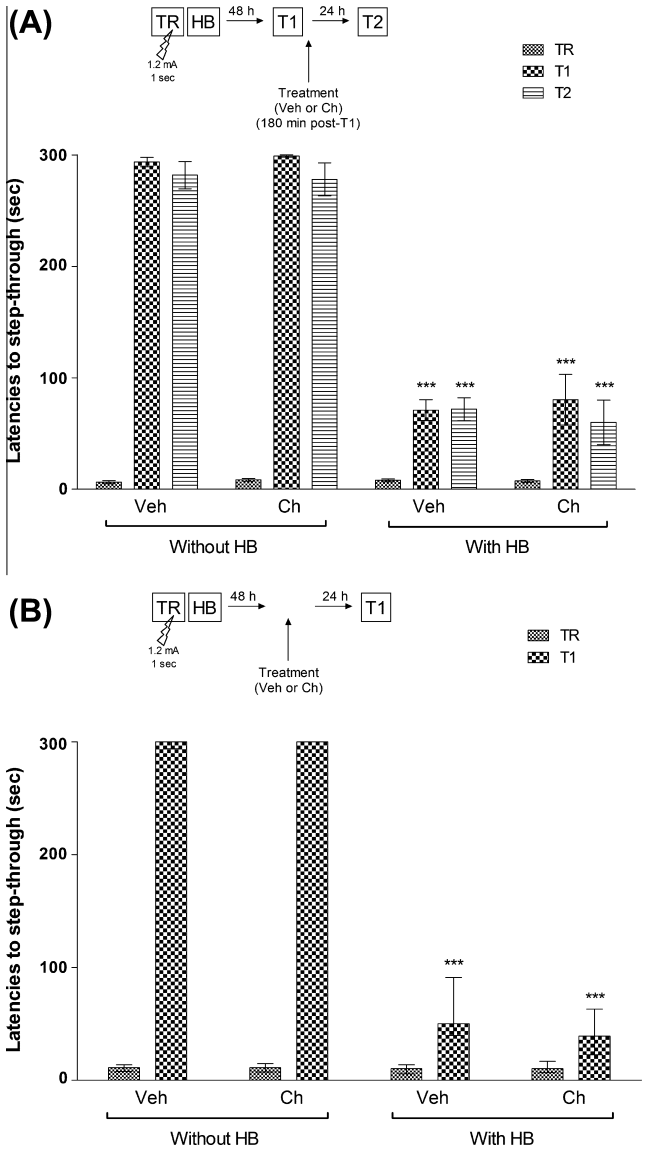

Fig. 3. Effects of Ch on retention performance of mice exposed or not to the novel environment (HB) immediately after training. Choline (0.8 μg/hippocampus) was given: (A) 3 h after T1, (B) 48 h after training, in absence of memory reactivation. The behavioral protocol is represented above each pannel. Each bar represents the median and interquartile range ($n = 10$ mice/group). TR: training session, T1-2: retention tests. $^{***}p < 0.001$, compared with the corresponding test of the respective group not exposed to the HB.

There was an inverse correlation between choline effects and the age of the reactivated memory. That is, the older the memory became, the less susceptible it was to choline effects. Recovery from new learning-induced memory impairment was almost complete for 2-days-old memories. However, the effect diminished for older memories, being no longer observed for 21 days old memories. Interesting, the age-dependence was also observed for the impairment effect of Ch in control groups (Figs. 4 and 5). In Fig. 5, the gap between Veh and Ch curves represents the susceptibility of the memory to the effects of Ch.

3.2. Effects of post-reactivation administration of choline on new learning-induced memory reconsolidation impairment

In the previous set of experiments, the exposure to the HB was performed immediately after the training session of the IA task.

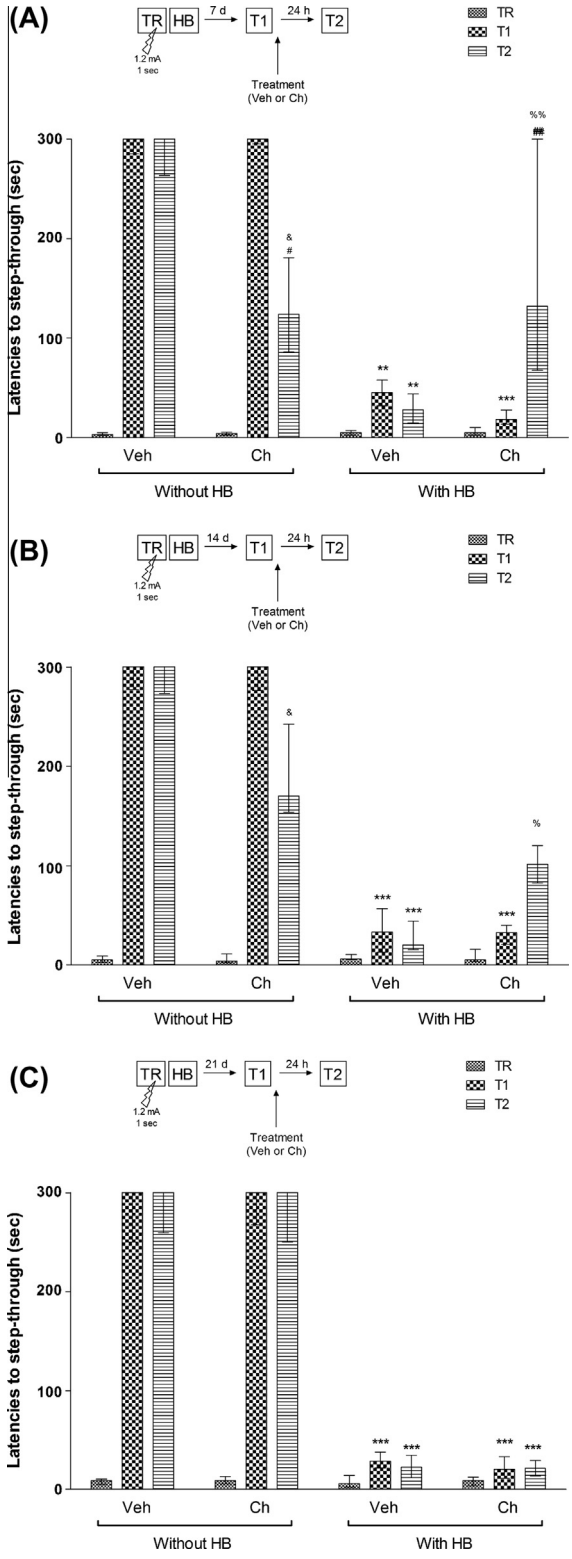

Fig. 4. Effects of Ch on retention performance of mice exposed or not to the novel environment (HB) immediately after training. Choline (0.8 μg/hippocampus) was given immediately after T1. The first retention test was performed (A) 7 days, (B) 14 days, and (C) 21 days after training. The behavioral protocol is represented above each pannel. Each bar represents the median and interquartile range (n = 10 mice/group). TR: training session, T1-2: retention tests. $^{**}p < 0.01$, $^{***}p < 0.001$, in all cases compared with the corresponding test of the respective group not exposed to the HB; & $p < 0.05$, compared with the corresponding test of the respective Veh-injected group; # $p < 0.05$, ## $p < 0.01$, comparing T1 vs. T2 of same group; % $p < 0.05$, %% $p < 0.01$, comparing with the corresponding test of the group reactivated 21 days after training (that is, comparing T2 of panels A and B, with panel C).

This implies that the exposure to novelty affected memory consolidation. The next set of experiments was designed considering that when the novel environment is presented after the first retention test, memory reconsolidation is impaired.

3.2.1. Choline also reverses new learning-induced memory reconsolidation impairment

Four groups of 10 mice each were trained in the IA task. The first retention test (T1) was performed 48 h after training, and immediately after it, two of the groups were exposed to the HB for 5 min, and the other two groups were returned to the home cages. A second retention test (T2) was performed 24 h after T1. Immediately after T2, mice received a bilateral dHPC infusion of Veh or Ch (0.8 μg/hippocampus). Mice were tested again (T3) 24 h after T2.

The results are presented in Fig. 6. Post-T1 exposure to the HB led to memory reconsolidation impairment ($p < 0.001$, comparing performance in T2 of groups exposed vs. not exposed to the HB). Choline administered immediately after T2 to mice that were exposed to the HB after T1, significantly increased retention latencies at T3 ($p < 0.01$). That is, Ch reversed the new learning-induced memory reconsolidation impairment. However, consistent with the results of experiment 1, Ch caused memory impairment in control mice ($p < 0.01$).

3.2.2. The effects of Ch are time-dependent

In the following experiment, four groups of 10 mice each were trained in the IA task, and the first retention test was performed 48 h after training. Immediately after T1, two of the groups were exposed to the HB for 5 min, and the other two groups were returned to the home cages. The second retention test (T2) was performed 24 h after T1. Three hours after T2, mice received a bilateral dHPC infusion of Veh or Ch (0.8 μg/hippocampus). Mice were tested again (T3) 24 h after T2.

The behavioral procedure and results are shown in Fig. 7A. Post-T1 exposure to the HB impaired performance in T2 ($p < 0.001$, compared with the respective non-exposed group). The administration of Ch 3 h after memory reactivation did not affect retention latencies, showing that Ch effects are time-dependent (Fig. 7A).

3.2.3. Ch effects are observed only if the avoidance memory was reactivated immediately before the drug infusion

In the next experiment, four groups of 10 mice each were trained in the IA task, and the first retention test was performed 48 h after training. Immediately after T1, two of the groups were exposed to the HB for 5 min, and the other two groups were returned to the home cages. Twenty-four hours after T1, mice received a bilateral dHPC infusion either of Veh or Ch (0.8 μg/hippocampus). The final retention test (T2) was performed 24 h after the injection. The behavioral procedure and results are represented in Fig. 7B (note that the reactivation session preceding the injection of Ch was omitted).

The administration of Ch in absence of memory reactivation did not affect retention performance ($p > 0.05$ comparing animals injected with Ch with each respective Veh-injected group) (Fig. 7B).

4. Discussion

When subjects are exposed to different learning situations, some of the experiences can produce interferences in the information processing of others (Müller & Pilzecker, 1900). When mice are exposed to a HB after being trained in the IA task, an interfering effect is observed between these two learning situations (Blake et al., 2011; Boccia et al., 2005). The sole exposure to the novel situation and the mere perception of the novelty are not sufficient conditions to cause the interference between the two behavioral tasks:

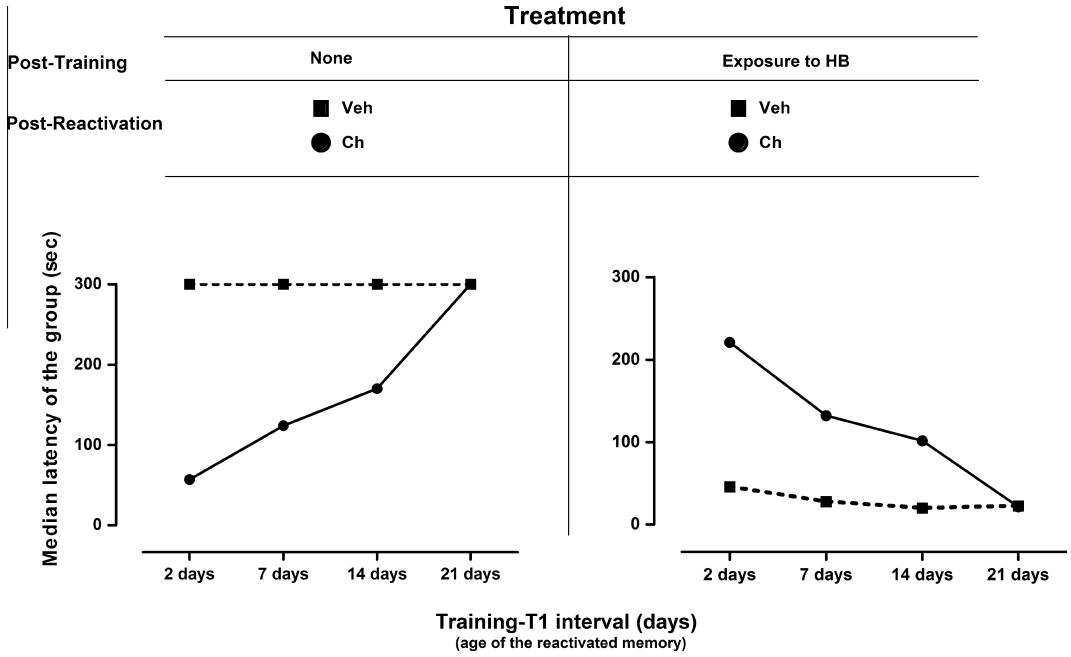

Fig. 5. Effects of Ch on retention performance of mice exposed or not to the novel environment (HB) immediately after training, for different TR-T1 intervals. Vehicle (dashed lines) or choline (solid lines) (0.8 μg/hippocampus) were given immediately after T1. The first retention test was performed 2, 7, 14 or 21 days after training. Only median latencies at T2 are represented (data collected from Figs. 2 and 4). Each point represents the median ($n = 10$ mice/group).

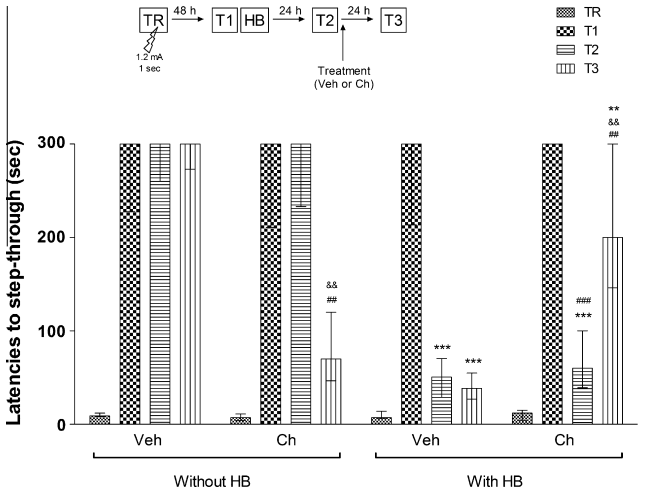

Fig. 6. Effects of Ch on retention performance of mice exposed or not to the novel environment (HB) immediately after the first retention test. Choline (0.8 μg/hippocampus) was given immediately after T2. The behavioral protocol is represented above the graph. Each bar represents the median and interquartile range ($n = 10$ mice/group). TR: training session, T1-3: retention tests. $^{**}p < 0.01$, $^{***}p < 0.001$, compared with the corresponding test of the respective group not exposed to the HB; && $p < 0.01$, compared with the corresponding test of the respective Veh-injected group; ### $p < 0.001$, ## $p < 0.01$, comparing each test with the immediate previous test of the same group.

the interference is produced only if the interfering task is learned (Blake et al., 2011). In fact, this new learning-induced interference is produced if the information of the novel environment is acquired while consolidation of the avoidance memory is taking place (Blake et al., 2011; Boccia et al., 2005). Although the ultimate reasons for this interference remain not completely understood, it is possible that both tasks share common molecular resources (Martínez, Alen, Ballarini, Moncada, & Viola, 2012). Therefore, memory traces for both tasks may compete for their stabilization, showing a possible underlying mechanism for the retrograde interference (Martínez et al., 2012). Along this line, if the acquisition of the information of the second task is blocked, the memory trace of the first task does not need to compete for the molecular resources, and the interference is not observed (Blake et al., 2011).

"Amnesia" is the clinical or experimental condition in which a subject is unable to demonstrate a memory (Squire, 2006). It refers to a specific, acquired difficulty in learning new information and/or remembering information from the past (Butters, Delis, & Lucas, 1995). Of course, if the individual did not store information, no memory was formed, and, therefore, amnesia occurs. However, it may happen that the memory was in fact stored, but for some reason the individual fails to express it; that is, the memory cannot take control of behavior (Squire, 2006). The capability of memories to guide behavior was named "memory expression" (Izquierdo & Medina, 1993). This capability can be modified by modulation, depending on the history of each memory.

In experimental approaches, memory cannot be directly measured, but is inferred from a change in behavior (Cahill et al., 2001). The animal is expected to show a specific change in behavior, from which memory will be inferred. This specific response is what will be actually measured and finally taken as a signal of the presence of memory. Therefore, amnesia is suspected when an experimental subject does not change its behavior in the expected way. The experimental research on amnesia normally used pharmacological tools. However, to resemble an everyday situation, throughout this work we used a physiological approach to induce memory deficits: the interference between learning situations (Blake et al., 2011; Boccia et al., 2005). When a subject is successively exposed to various learning situations, the individual may experience troubles in processing the recently acquired information if that processing is interfered by presenting new information. Hence, if an individual is presented with two consecutive learning situations, learning the information provided by the second task may interfere with the processing of the information contained in the first, affecting the eventual expression of the corresponding memory. That is, the individual will show amnesia for the information contained in the first learning task (Blake et al., 2011; Boccia et al., 2005).

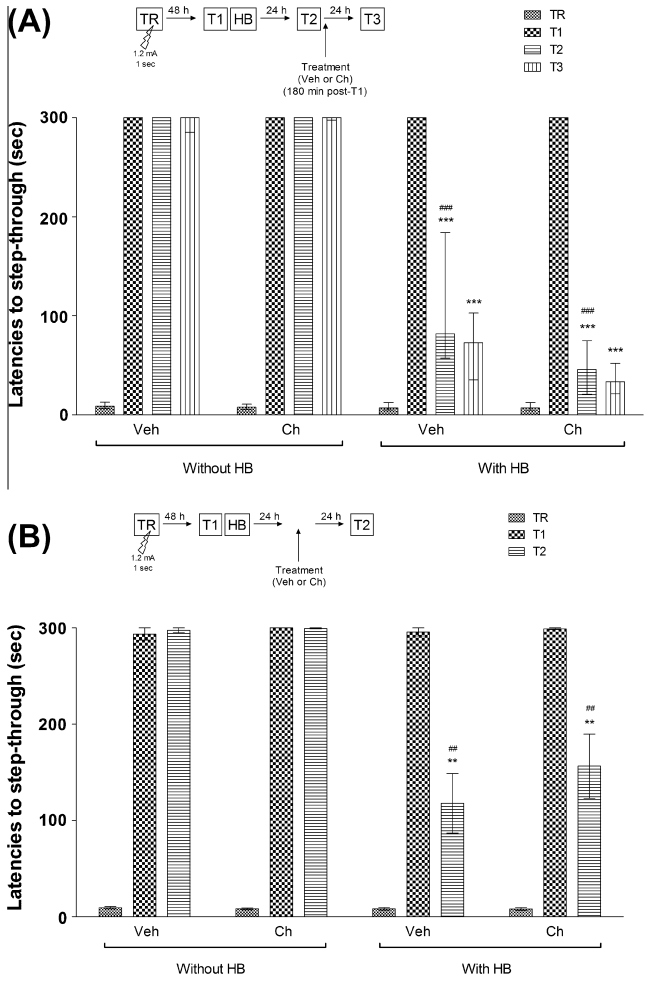

Fig. 7. Effects of Ch on retention performance of mice exposed or not to the novel environment (HB) immediately after the first retention test. Choline (0.8 μg/hippocampus) was given: (A) 3 h after T2, (B) 48 h after T1, in absence of memory reactivation. The behavioral protocol is represented above each pannel. Each bar represents the median and interquartile range ($n = 10$ mice/group). TR: training session, T1-3: retention tests. $^{**}p < 0.01$, $^{***}p < 0.001$, compared with the corresponding test of the respective group not exposed to the HB; ### $p < 0.001$, ## $p < 0.01$, comparing T1 vs. T2 of the same group.

In our experimental conditions, as no drug is administered before or after the training session, one can be sure that no long-term effect of any drug is acting during the first retention test.

Many clinical conditions include varying degrees of amnesia (Kopelman, 2002). In such cases it is not easy to decide whether this amnesia is due to a disappearance of the memories or the memories are still stored but the individual fails to express them. During normal aging, there is a progressive decline in some cognitive abilities, including increasing difficulty to access memories (Neugroschl & Wang, 2011; Querfurth & LaFerla, 2010). The observed degree of cognitive decline in elderly patients correlates well with the magnitude of the reduction of the central cholinergic activity (Bartus, Dean, Beer, & Lippa, 1982; Francis, Palmer, Snape, & Wilcock, 1999). Geriatric mild cognitive impairment is characterized by episodic memory impairment such as forgetting details of a recently viewed movie or conversations, which correlates with a slight reduction in cholinergic activity. If the cholinergic deficit worsens, the cognitive manifestations become more pronounced. A mild cholinergic failure is also observed during the early stages of Alzheimer's disease (Neugroschl & Wang, 2011; Querfurth & LaFerla, 2010). In this case, the memory impairment includes events of daily life, and the individual forgets to pay bills, or stops taking their medication. On the contrary, at advanced stages of AD, the cholinergic dysfunction is profound and covers other neurochemical systems besides cholinergic, and there is also an important loss of cortical neurons. As the disease become severe, semantic and procedural memories progressively deteriorate and other behavioral disturbances are evident (Neugroschl & Wang, 2011; Querfurth & LaFerla, 2010). For these reasons, it is important to study the possibility of reversion of the memory dysfunction using the available pharmacological tools.

Some markers of cholinergic activity are reduced in AD (both pre- and post-synaptic) (Quirion, 1993). In particular, cholinergic nicotinic receptors (nAChRs) were found to be reduced in 30–40%, mainly due to reduction of $\alpha_4\beta_2$, with relative preservation of the α_7 subtype (Court et al., 2001; Perry et al., 1995).

Several studies have shown recovery from memory impairment, suggesting that a hidden memory can be expressed under the appropriate conditions (Squire, 2006). Taking into account that some types of amnesia are not due to a loss of information, but to an inability to evoke memory, α_7-nAChRs can be considered useful for studying the possibility of memory recovery. For this reason, choline (Ch), a specific α_7-nAChRs agonist (Albuquerque et al., 2009), was administered after the first retention test in order to modulate post-reactivation memory processes (Boccia et al., 2010). Despite Ch participates as a precursor of acetylcholine synthesis, and may modify cholinergic activity in different ways, the effects of post-reactivation administration of Ch on memory are likely due to its binding to α_7-nAChRs, since its effect is completely blocked by the co-administration of the specific α_7-nAChRs antagonist methyllicaconitine (Boccia et al., 2010).

It was previously found that the effects of Ch on memory reconsolidation of the inhibitory avoidance response depend on training conditions (Boccia et al., 2010). If a weak foot-shock is used during the training procedure, retention latencies are about 120 s. In these conditions, Ch enhances memory reconsolidation if given in the hippocampus after memory reactivation. On the contrary, if a strong training procedure is employed (an intense foot-shock), animals perform during the retention test with latencies at the ceiling (300 s). In this condition, Ch impairs memory reconsolidation (Boccia et al., 2010).

These apparently contradictory effects of Ch on memory reconsolidation depending on the training conditions resemble to those reported by Gold and Van Buskirk (1976). In that case, a dose of epinephrine that enhanced retention performance after low-foot-shock training produced amnesia if administered after high-foot-shock training. The reasons underlying these opposed effects remain undeciphered and could be explained as an example of hormesis (Mattson & Calabrese, 2010). Accordingly, results obtained following choline administration are very similar, but Ch was administered immediately after memory reactivation. We can speculate that post-reactivation processes have important roles in modulating information processing occurring after retrieval and seem to be very similar, though not identical, to that occurring after learning (Lee, 2010; Lee, Everitt, & Thomas, 2004; Milekic, Pollonini, & Alberini, 2007; Tronel, Milekic, & Alberini, 2005). So, the post-reactivation administration of Ch probably modifies the physiological balance of neurotransmitter systems by activating α_7-nAChRs, thus affecting the modulation of information processing. Therefore, the opposite effects caused by the administration of Ch after memory reactivation, depending on training conditions, may be considered as a manifestation of its modulatory effects on memory reconsolidation (Boccia et al., 2010).

Throughout the present work, the mice were trained using the intense foot-shock, and animals that were not exposed to the HB after the training session performed during the first retention test (T1) with latencies at the ceiling. In these mice, Ch exerted impairing effects on memory reconsolidation, confirming previous results

(Blake et al., 2012; Boccia et al., 2010). However, animals exposed to the novel environment (the HB) after the learning trial, showed impaired performance during T1 (Fig. 2). In these conditions, post-reactivation administration of Ch enhanced retention performance in the subsequent test. Specific controls are needed to assume that a post-retrieval treatment affects memory reconsolidation processes. Since the reminder that induce reconsolidation is also a part of the cues presented during training, but the unconditioned stimulus (US) is not presented after the conditioned stimulus (CS), new information is available for being learned and other processes emerge as candidates for explaining any post-retrieval effect, like extinction (Myers & Davis, 2002). Standard controls determine that retention performance should not be affected if the treatment is administered in absence of memory reactivation or showing that the post-retrieval treatment needs to be given before the end of a temporal window to be effective (Alberini, 2011; Alberini, Milekic, & Tronel, 2006; Dudai, 2006; Misanin et al., 1968; Przybyslawski & Sara, 1997; Tronson & Taylor, 2007). However, none of these controls can completely discard that a new learning process is occurring, and that it is the actual responsible for performance in subsequent tests.

In our experimental conditions, recovery from new learning-induced memory impairment was produced by post-retrieval memory enhancement by Ch. This recovery depended on memory reactivation, and only occurred if the treatment was administered within a temporal window (Fig. 3). Since no repetition of CS–US pairing is presented during the memory reactivation session, the improved performance may not be attributed to retraining or to new learning, because the new information presented during T1 should lead to learn that CS is not followed by US (Squire, 2006). All these facts suggest that the effects of Ch are exerted on memory reconsolidation.

The modulatory effects of post-reactivation treatments on post-retrieval memory processes depend on the age of the reactivated memory. Young reactivated memories are more sensitive to modulation than older ones (Alberini, 2005), in accordance with Ribot's law (Ribot, 1881). This fact was clearly demonstrated for protein synthesis inhibitors such as anisomycin or cycloheximide (Alberini, 2005; Milekic & Alberini, 2002). Age-dependence was also shown for the acetylcholine synthesis inhibitor hemicholinium-3 (Boccia, Blake, Acosta, & Baratti, 2006), and also for Ch (Blake et al., 2012). Similar to these results, recent memories were very sensitive to the effects of Ch, but older ones were more resistant (Figs. 4 and 5). In the present study, we show evidence that recent memories (2–7 days old) are labile but remote ones (14–21 days old) become progressively insensitive to Ch administration, confirming and extending previous findings. The sensitivity to Ch effects were observed either in mice exposed or non-exposed to the HB. That is, in control mice (not exposed to the HB), Ch caused a strong impairment in recent memories (2–7 days old), but did not impair older ones (21 days old). In mice exposed to the HB, Ch caused recovery from amnesia of young reactivated memories (2–7 days old), but failed in recovering older ones (21 days old). This age-dependency suggest that α_7-nAChRs of the hippocampus are involved in post-reactivation memory processes for a limited period of time (see Fig. 5).

Therefore, reversion of new learning-induced amnesia was a consequence of enhancement of the reconsolidation process by Ch. The memory trace was stored, but was unable to guide behavior in the retention test performed before the administration of Ch. In other words, the trace was not behaviorally expressed during this retention test. This memory was, however, labilized by the reactivation session, and by improving memory reconsolidation using Ch, memory was expressed in T2. Therefore, reconsolidation processes might serve to change memory expression in later tests, among other functions.

Very similar results were obtained when novelty presentation was used to impair memory reconsolidation. In this set of experiments, the avoidance memory follows two successive reconsolidation sessions, that is, memory was interfered twice. In this case, all the mice performed during T1 with retention latencies at the ceiling (300 s). Exposure to the HB immediately after T1 led to memory impairment in T2, confirming previous results (Boccia et al., 2005). The post-T2 administration of Ch in the hippocampus allowed recovery of the impaired memory in the mice exposed to the HB, and caused memory impairment in the non-exposed mice (Figs. 6 and 7). This means that the exposure to the novel environment after the first memory reactivation impaired memory reconsolidation, but did not erase the memory trace. This memory trace remained unexpressed until the second modulation of memory reconsolidation, by α_7-nAChRs, allowed it to be expressed in a later test. Therefore, memory reconsolidation may serve to assign new behavioral meanings to previously stored information determining to what degree a memory will control behavior later (that is, modifying its strength).

Although memory consolidation and reconsolidation share some features, they also have many differences deserving attention. There is increasing evidence for different molecular markers elicited by both processes (Lee, 2010; Lee et al., 2004; Milekic et al., 2007; Tronel et al., 2005), and it was proposed that when a memory is reactivated, the new information is linked to the old information via consolidation (Tronel et al., 2005), and reconsolidation could not be a re-storage, but serve to change the strength of the memory (Lee, 2010). The results of the second set of experiments (Section 3.2, shown in Figs. 6 and 7) are in accordance with the idea that reconsolidation allow the change in the strength with which a memory is expressed (that is the ability of the memory to control behavior in subsequent tests) (Izquierdo & Medina, 1993). Hence, after reactivation, the avoidance memory can be modulated more than just once, either increasing or decreasing its strength by using a new learning situation or by the administration of choline (Fig. 6).

Information processing depends on hippocampal formation, which contributes to consolidation of memories over long periods (Izquierdo & McGaugh, 2000), but the temporal dependence is different among species. Hippocampal lesions in mice cause retrograde amnesia for events occurring a few hours prior to the damage (Izquierdo & McGaugh, 2000), but in human beings produce retrograde amnesia of several years (Corkin, 2002; Squire & Wixted, 2011), showing that hippocampal involvement in information processing in humans lasts more time than in mice. For many events, the elapsed time in mice life is very shorter than the same in humans, with a relation of about 100–150 times for many processes (Flurkey, Currer, & Harrison, 2007). Therefore, the period of 7 days within which a memory is very sensitive to enhancement by post-reactivation administration of Ch in mice may represent 100–150 more times in humans (about 3 years).

Altogether, our results support the notion that new learning-induced memory impairment is a consequence of memory expression deficit rather than memory formation impairment. In addition, it could be presumed that information processing from novelty did not block memory formation, but that the stored memory traces fail to be behaviorally expressed after the exposure to novelty. Therefore, memory was actually stored, but remains hidden. In any case, this hiding memory failed in controlling behavior (as performance was impaired in the retention test), but was labilized by this test (as was modulated by activating the α_7-nAChRs with Ch).

In our interpretation, "memory expression deficit" is different from "memory retrieval deficit" (see Fig. 8). Memory retrieval is the access, selection, reactivation or reconstruction of an internal representation (Dudai, 2002), but memory expression means this

internal representation effectively taking control of behavior (Izquierdo & Medina, 1993). In Fig. 2, for example, it can be observed that retention latencies during T1 of mice exposed to the HB after training was about 50–100 s. This is very different from the expected for an amnesic animal, which is expected to behave as if it was never trained; that is, an amnesic subject is expected to perform during the test similar to the behavior during the training session (with latencies of about 10 s). Hence, it might be concluded that the avoidance memory was indeed retrieved during T1, but failed to fully control behavior. Thus, we propose that what was impaired is not actually the retrieval process, but the memory expression instead. Therefore, if the avoidance memory is retrieved but does not control behavior, it can be concluded that some other process determine the behavioral output. Decision-making processes (Bogacz, 2007; Clark, Cools, & Robbins, 2004; Khader et al., 2011) might appear as a promising candidate to explain such findings. These decision-making processes might determine whether a memory will be expressed, and to what degree. Our interpretation of the processes is represented in Fig. 8. To obtain a good performance in a retention test, memory had to be successfully stored, it must persist during a certain time, and it has to be efficiently retrieved, although not necessarily consciously, as can be inferred from the experiments evaluating posthypnotic amnesia (reviewed in Kihlstrom, 1997). All these steps are necessary, and any failure can cause a poor performance. But it is not sufficient. During the test the animal may retrieve the memory we are assessing, but the animal may also evaluate other possibilities that could take control of behavior (instincts, information provided by other memories). Furthermore, the decision of the experimental subject may be influenced by several other systems (anxiety, stress, motivation, etc.), all determining the behavioral output, i.e., determining whether the animal allow this memory to guide its behavior.

In the figure, the dashed line between memory storage and labilization represents the possibility of labilizing a memory independently of its retrieval. More important, the memory reconsolidation loop represents that memory could be modulated many times, as was done in the experiments corresponding to the set 3.2 (see Figs. 6 and 7), and that memory reconsolidation is the process allowing the change in its capability to control behavior in the future, contributing to the dynamics and malleability of memory.

In summary, the results of the present work show that novelty presentation did not impair memory storage. The stored memory is not expressed during the retention test but can be improved by modulating memory reconsolidation with Ch. Once enhanced,

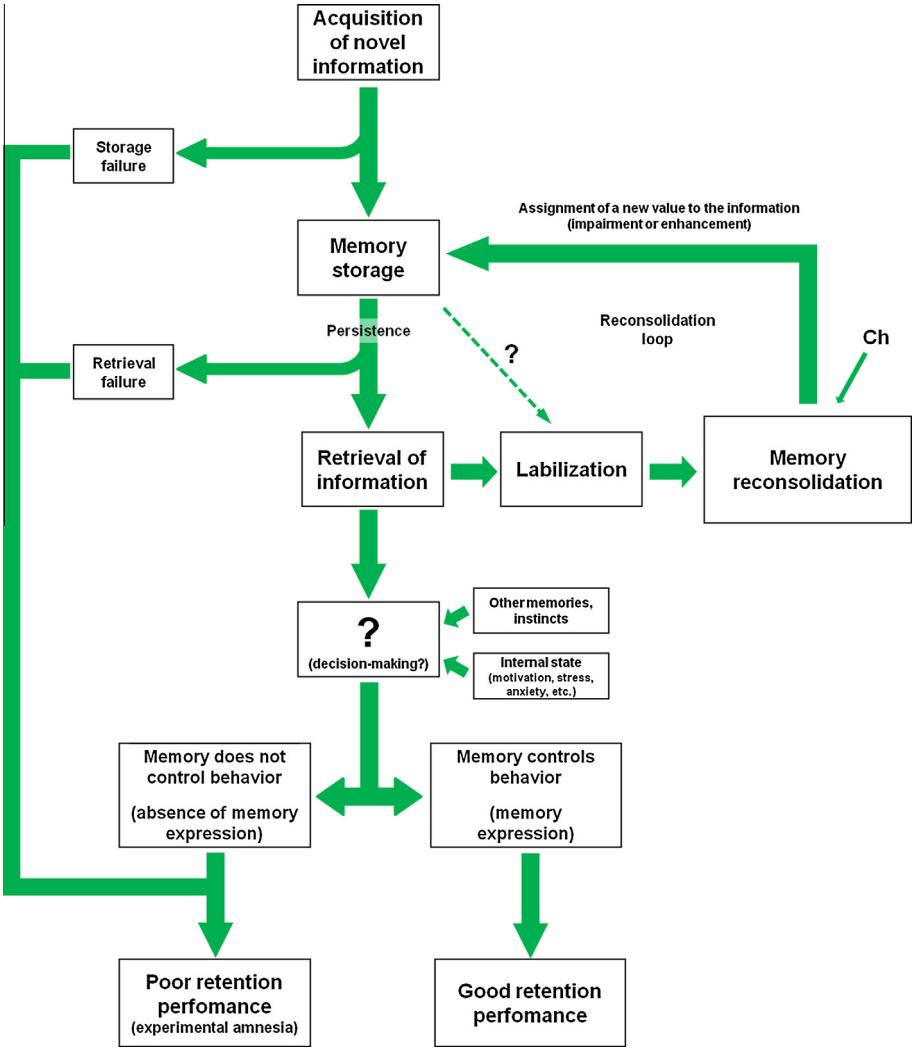

Fig. 8. Proposed sequence of events determining retention performance. To obtain a good performance in a retention test, memory had to be successfully stored, efficiently retrieved, and after evaluation of other possibilities, the animal must allow this memory to control its behavior. In our interpretation, decision-making could be the process performing such evaluation of all the possibilities, and finally determine the degree of memory expression. There is only one path leading to memory expression. All these steps are necessary, and any failure can cause a poor performance (see the text).

memory is expressed in a later test. Therefore, our results open new avenues about the behavioral significance and the physiological functions of memory reconsolidation. In addition, they provide new strategies for recovering memories from some types of amnesia.

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