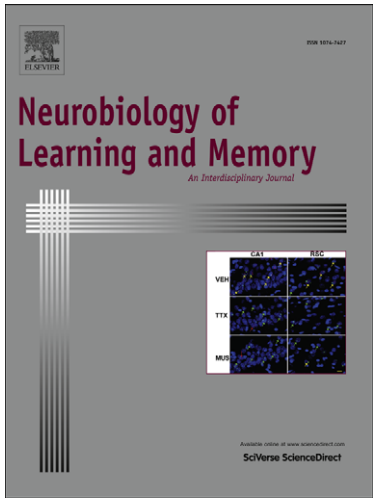

Choline reverses scopolamine-induced memory impairment by improving memory reconsolidation

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Choline reverses scopolamine-induced memory impairment by improving memory reconsolidation

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Abstract

It is widely known that pre-training systemic administration of the muscarinic antagonist scopolamine (SCP) (0.5 mg/kg, i.p.) leads to anterograde memory impairment in retention tests. The administration of the α_7-nicotinic receptor agonist choline (Ch) in the dorsal hippocampus (0.8 µg/hippocampus) immediately after memory reactivation allowed recovery from scopolamine-induced memory impairment. 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 performance effects 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 low doses of SCP is a memory expression failure and not a storage deficit. Therefore, reconsolidation, among other functions, might serve to change memory expression 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.

Research highlights

- Pre-training administration of scopolamine leads to memory impairment.
- Intra-hippocampal administration of choline modulates memory reconsolidation
- Choline reverses scopolamine-induced amnesia by enhancing memory reconsolidation
- Low doses of scopolamine cause memory expression deficit, but not storage impairment
- Reconsolidation could modify the ability of a memory for being expressed later

Keywords

Memory reconsolidation, memory expression, memory retrieval, scopolamine-induced amnesia, cholinergic system

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). Memory consolidation depends on modulation by neurotransmitter systems (McGaugh, 2000; Roozendaal & McGaugh, 2011). Among them, central cholinergic system has been implicated in learning and memory processes, either in invertebrates (Berón de Astrada & Maldonado, 1999; Terazima & Yoshino, 2010; Weinberger, 2006) and vertebrates (Blake, Boccia, Krawczyk, & Baratti, 2011; Boccia, Blake, Acosta, & Baratti, 2004; Boccia, Blake, Acosta, & Baratti, 2006; Boccia, Blake, Krawczyk, & Baratti, 2010; Ortega, del Guante, Prado-Alcalá, & Alemán, 1996; Quirarte et al, 1994; Roldán, Bolaños-Badillo, González-Sánchez, Quirarte, & Prado-Alcalá, 1997), including human subjects, and it seems to be involved in modulation of acquisition, consolidation, reconsolidation, extinction, and retrieval of information (Baratti, Boccia, & Blake, 2009).

Cholinergic blockade by scopolamine (SCP, a muscarinic cholinergic receptor antagonist) before training cause anterograde memory impairment (Berón de Astrada & Maldonado, 1999; Blake et al., 2011; Decker & McGaugh, 1989; Decker, Tran, & McGaugh, 1990; Ohno & Watanabe, 1996; Rush, 1988). This scopolamine-induced memory impairment was also found in human subjects (Frumin, Herekar, & Jarvik, 1976; Ghoneim & Mewaldt 1975; Ghoneim & Mewaldt, 1977; Richardson et al., 1985).

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; Philips, Tzvetkova, Marinesco, & Carew, 2006; Rescorla, 1988). Recovery from amnesia lead us to consider alternative mechanisms for the amnesic treatments, different from impairment of information encoding, i.e. memory expression deficit.

Post-reactivation administration of choline (Ch), a specific α7-nicotinic cholinergic receptor agonist (Albuquerque, Pereira, Alkongdon, & Rogers, 2009) modulates memory reconsolidation, either enhancing or impairing it, depending on training conditions (Boccia et al., 2010). Ch 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).

The present work is aimed to evaluate whether the scopolamine-induced memory impairment is due to storage failure or to memory expression deficits. The results presented here suggest that SCP-induced amnesia is a failure of behavioral expression of the memory, but not absence of memory 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 ºC) 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 Nº 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: Inhibitory avoidance (IA) task

The avoidance behavior was studied in one-trial learning, step-through type (Blake, Boccia, & Baratti, 2008), which utilizes the natural preference of mice for a dark environment. The apparatus consisted of a dark compartment (20cm×20cm×15cm) with a stainless-steel grid floor and a small illuminated platform (5cm×5cm) attached to its front center, elevated 100 cm from the floor (conditioning context) (Blake et al., 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 sec) 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 sec. In the latter case the mouse was immediately removed from the platform and assigned a score of 300 sec (ceiling score). In the retention test session the foot-shock was omitted.

2.3. Drug administrations

Scopolamine hydrochloride (SCP), scopolamine methyl-bromide (mSCP), and Choline bitartrate (Ch) were purchased from Sigma, St Louis, MO. All the drugs were dissolved in sterile saline solution immediately before use. The doses were calculated as the free base. All other agents were of analytical grade and obtained from local commercial sources. The doses of the drugs were determined from previous experiments of our laboratory (Blake et al., 2011; Boccia et al., 2010). SCP and mSCP were injected intraperitoneally (i.p.) (0.1 ml/kg), and 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 sec 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 7). 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.

3. Results

3.1. Pre-training administration of SCP, but not mSCP, causes memory impairment

In the first experiment, three groups of 10 mice each received an injection either of vehicle (Veh), SCP (0.5 mg/kg, i.p.), or mSCP (a quaternary molecule with limited access to central nervous system, 0.5 mg/kg, i.p.), and 20 min later they were trained in the inhibitory avoidance (IA) task. Retention test was performed 2 days after it.

Scopolamine impaired retention performance in the IA task ($p<0.001$, compared with the respective Veh-injected control group) (Fig 1). These results show that pre-training administration of SCP produces memory impairment in our experimental conditions, and confirm previous results. The effects of SCP were centrally mediated, as mSCP did not affect retention latencies at T1.

The following experiments were aimed to determine whether scopolamine-induced memory impairment results from storage or memory expression failure.

3.2. Post-reactivation administration of choline reverses scopolamine-induced memory impairment

This experiment was aimed to determine whether the administration of Ch after the first retention test allowed recovery from scopolamine-induced memory impairment. Four groups of 10 mice each were injected either with Veh or SCP (0.5 mg/kg, i.p.), and 20 minutes after it they were trained in the IA task. The first retention test (T1) was performed 48 h after training. 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 of this experiment are shown in Figure 2. Pre-training administration of SCP impaired performance in T1 ($p<0.001$, compared with the respective Veh-injected group). Choline administered immediately after memory reactivation to mice receiving SCP before training, significantly enhanced retention latencies at T2 ($p<0.001$, comparing SCP-Ch vs. SCP-Veh groups). That is, Ch reversed SCP-induced memory impairment. However, consistent with our previous results (Boccia et al., 2010), Ch caused memory impairment in control mice ($p<0.001$, comparing Veh-Ch vs. Veh-Veh injected groups) (Fig 2).

3.3. The effects of Ch are time-dependent

In the following experiment, four groups of 10 mice each received Veh or SCP (0.5 mg/kg, i.p.), and 20 min after it they were trained in the IA task. 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.

The behavioral procedure and results are shown in Figure 3A. Pre-training administration of SCP induced memory impairment ($p<0.001$, compared with the respective Veh-injected groups). The administration of Ch 3h after memory reactivation did not affect retention latencies, showing that Ch effects are time-dependent (Fig 3A).

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

In the next experiment, four groups of 10 mice each received Veh or SCP (0.5 mg/kg, i.p.), and 20 min after it they were trained in the IA task. 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 hours after it. The behavioral procedure and results are represented in Figure 3B (note that the reactivation session was omitted).

The administration of Ch 48h 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).

3.5. The effects of Ch on memory are not disclosed shortly after memory reactivation

The results shown in the previous experiments suggest that Ch modulates memory reconsolidation. However, to add evidence that the pharmacological actions of Ch are exerted on memory reconsolidation the effects of Ch should not be seen in a retention test performed shortly after retrieval, as was already shown blocking protein synthesis (Nader, Schafe, & LeDoux, 2000) and using NF-κB inhibitors (Boccia et al., 2007).

Four groups of 10 mice each were injected either with Veh or SCP (0.5 mg/kg, i.p.) and 20 min later they were trained in the IA task. The first retention test (T1) was performed 48 h after training. Immediately after the test, mice received a bilateral dHPC infusion of Veh or Ch (0.8 µg/hippocampus). Mice were tested again (T2) 1 h after T1, and (T3) 24 hours after T1. The behavioral procedure and results are shown in Figure 3C.

Choline effects were not seen in the retention test performed shortly after memory reactivation ($p>0.05$, comparing performance of each group in T2 vs T1, Fig 3C), but reversion of memory impairment was evident in T3 ($p<0.05$ for Veh-Ch, and $p<0.01$ for SCP-Ch, comparing performance of each group at T3 vs T1) (Fig 3C).

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

In this experiment, twelve groups of 10 mice each were injected with Veh or SCP (0.5 mg/kg, i.p.) and 20 min after it they were trained in the IA task. 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 Figure 4.

In order to compare data from groups of mice receiving the same treatment (but in which memory reactivation occurred at different training-T1 intervals), the retention performance in T2 is represented (combining data from this experiment with data from experiment 2). These data are resumed in Figure 5.

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 scopolamine-induced amnesia 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 (Veh-Ch groups) (Fig 4 and 5). In Figure 5, the distance between Veh and Ch curves represent the susceptibility of the memory to the effects of Ch.

3.7. Choline failed to reverse amnesia caused by a high dose of SCP

The last experiment was designed to evaluate whether the reversion of scopolamine-induced memory impairment is also possible if mice received a high dose of SCP. Two groups of mice were injected with vehicle or SCP (5 mg/kg, i.p.) and 20 min after it they were trained in the IA task. The first retention test was performed 48 h after training (T1). Immediately after the test, animals received a bilateral dHPC injection 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 Figure 6.

Post-reactivation administration of Ch failed to reverse scopolamine-induced amnesia in mice receiving a high dose of SCP before training ($p>0.05$, comparing performance on T1 vs T2) (Fig 6).

4. Discussion

It is widely known that pre-training administration of scopolamine (SCP) leads to impaired performance on behavioral tests (Berón de Astrada & Maldonado, 1999; Blake et al., 2011; Decker & McGaugh, 1989; Ohno & Watanabe, 1996; Rush, 1988). If scopolamine is given after training, retrograde amnesia is also produced, suggesting that cholinergic system is necessary for memory consolidation (Berón de Astrada & Maldonado, 1999; Blake et al., 2011; Boccia et al., 2004; Roldán et al., 1997).

Although pre-training and post-training administration of SCP cause memory impairment, the effects seem to be different. Low doses of SCP (even 0.1 mg/kg) are enough to impair memory when administered before training. On the contrary, if the drug is given after training, memory impairment is seen only with very high doses (above 4 mg/kg). Cholinergic system serves to facilitate cue detection and attentional performance (Hasselmo & Stern, 2006; Hasselmo & Sarter, 2011). Therefore, blockade of cholinergic system with pre-training administration of SCP is followed by changes in attentional processes and in information processing, which may alter acquisition of the novel information and may cause subsequent memory impairment. For all these reasons, traditional views considered that SCP impairs acquisition, but not memory consolidation (Ghoneim & Mewaldt, 1975; Rush, 1988; but see Izquierdo, 1989). Along this line, the different effects of pre- and post-training administration of SCP lead to the interpretation that acquisition is more sensitive than consolidation to disruption by cholinergic blockade, and it was proposed that cholinergic muscarinic receptors play different roles on acquisition and consolidation (Blake et al., 2011; Rush, 1988). Nevertheless, the fact that post-training administration of SCP also produces memory impairment shows that consolidation is also affected by cholinergic blockade (Berón de Astrada & Maldonado, 1999; Blake et al., 2011; Roldán et al., 1997). Besides, it must be considered that when SCP is given periferally, the onset of the pharmacological effect is not immediate because the drug needs time to reach the target structure. Thus, when SCP is administered after training, processes occurring during the first seconds (and even minutes) after it are not affected by the drug because it did not reach the pharmacological target yet. On the contrary, if SCP is administered before training, the drug is present in the brain during and after the training session. So, when SCP is given before training, it is not possible to distinguish whether the effects on memory are due to acquisition blockade or to impairment of the early processes occurring during the first seconds after training, that are part of the memory consolidation processes. The question remains unanswered and, for this reason, since SCP impairs acquisition and consolidation processes, we will consider that SCP affects

memory formation. What we do know is that the impairing effects of SCP are centrally mediated and are not due to changes in peripheral autonomic functions, as pre-training administration of mSCP did not affect retention latencies. Previous findings showed that the dose of SCP employed in the present work does not significantly affect exploratory activity (Blake et al., 2011).

Scopolamine-induced memory impairment was suggested for modeling some features of geriatric memory dysfunction and of Alzheimer's disease (AD) memory impairment (Bartus, Dean, Beer, & Lippa, 1982; Ebert & Kirch, 1998; Giacobini, 1990). This was proposed because a mild cholinergic dysfunction occurs in the elderly and at early stages of AD. Further, the magnitude of the reduction in cholinergic system activity is correlated with the degree of cognitive impairment (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 (Neugroschl & Wang, 2011). At early stages of AD, the cholinergic failure is also mild, and the impairment includes forgetting of daily events such as paying bills or taking medications (Neugroschl & Wang, 2011). On the contrary, at advanced stages of AD, the cholinergic dysfunction is profound, 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. For these reasons, it is important to study the consequences of cholinergic system activity blockade on memory processing, and the possibility of reversion of the subsequent dysfunction using the available pharmacological tools.

Several markers of cholinergic activity are reduced in AD (both pre- and post-synaptic) (Quirion, 1993). In particular, cholinergic nicotinic receptors were found to be reduced in 30-40%, mainly due to reduction of the $\alpha_4\beta_2$ subtype, with relative preservation of the α_7-nicotinic receptors (Court et al., 2001; Perry et al., 1995). Thus, α_7-nicotinic receptors can be considered useful for studying the possibility of memory recovery. For this reason, choline (Ch), a specific α_7-nicotinic cholinergic receptor 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-nicotinic receptors, since its effect is completely blocked by the co-administration of the specific α_7-nicotinic receptors 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 sec. 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 sec). In this condition, Ch impairs memory reconsolidation (Boccia et al., 2010).

Throughout the present work, the mice were trained using the intense foot-shock, and animals receiving vehicle before 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 (Boccia et al., 2010). However, animals receiving a pre-training injection of SCP showed impaired performance during T1. In these conditions, post-reactivation administration of Ch enhanced retention performance in subsequent tests. 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-footshock training produced amnesia if administered after high-footshock training. Accordingly, our results are very similar, but in our case Ch was administered immediately after memory reactivation. We can speculate that post-reactivation treatments have important roles in modulating memory processes occurring after retrieval and seem to be very similar, though not identical, to that occurring after learning. The reasons underlying these opposed effects remain undeciphered and could be explained as an example of hormesis (Mattson & Calabrese, 2010). 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).

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 and 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, Miller, & Lewis, 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 SCP-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. Besides, to provide compelling evidence that Ch acts specifically on the mechanisms mediating memory reconsolidation, as opposed to producing nonspecific effects, it is necessary to show that the change does not occur shortly after retrieval, but is observed later (Boccia et al., 2007; Nader et al., 2000). Along this line, we observed that Ch was effective only when T2 was delayed enough from T1.

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 new information 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 Ch on post-retrieval memory processes also depended on the age of the reactivated memory (Baratti, Boccia, Blake, & Acosta, 2008; Boccia et al., 2006; Milekic & Alberini, 2002). Young reactivated memories are more sensitive to modulation than older memories (Alberini, 2005), in accordance with Ribot's law (Ribot, 1881). This fact was clearly demonstrated for protein synthesis inhibitors such as anisomycin or cycloheximide (Milekic & Alberini, 2002; Alberini, 2005). Age-dependence was also demonstrated for the acetylcholine synthesis inhibitor hemicholinium-3 (Boccia et al., 2006). Similar to these results, recent memories were very sensitive to the effects of Ch, but older ones were more resistant. 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. The sensitivity for Ch effects were observed in vehicle-injected and in SCP-receiving mice. That is, in mice receiving the pre-training injection of Veh, Ch caused a strong impairment in recent memories (2-7 days old), but did not impair older ones (21 days old). In mice receiving the pre-training injection of SCP, Ch caused recovery from amnesia of young reactivated memories (2-7 days old), but failed in recovering older ones (21 days old). The fact that Ch effects are dependent on the age of the reactivated memory, suggest that α_7-nicotinic receptors of the hippocampus are involved in post-reactivation memory processes for a limited period of time.

Several observations suggest that the hippocampus contributes to consolidation of memories over long periods (Izquierdo & McGaugh, 2000). Hence, information processing depends on hippocampal function, 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). On the contrary, hippocampal lesions in human beings produce retrograde amnesia of several years (Corkin, 2002; Squire & Wixted, 2011). This difference shows that hippocampal processing of information is more prolonged in humans than in mice. For many events, the elapsed time in mice life is very shorter than the same in humans. A mouse become adult in about 60 days, while it takes about 25 years to men (a relation of about 100-150 times) (Flurkey, Currer, & Harrison, 2007). A mouse model of AD (3xTg) develops cognitive impairment in about 6 months, while AD begins with symptoms at about 70 years in humans (again a relation of about 100-150 times) (Querfurth & LaFerla, 2010). If one assumes that many processes occurring in humans develop about 100-150 times faster in mice, a 7-days-old-memory in mice might represent a memory of about 3 years in men. Therefore, the period of 7 days within which a memory is very susceptible to enhancement by post-reactivation administration of Ch in mice may represent 3 years in humans.

Therefore, the main point of our work is that reversion of SCP-induced amnesia was a consequence of enhancement of the reconsolidation process by Ch. The memory trace was stored, but did not guide behavior in T1. In other words, the trace was not behaviorally expressed during the first 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.

Interestingly, very similar results were found in invertebrates, using the visual danger stimulus memory model in the crab *Chasmagnatus* (Caffaro, Suárez, Blake, & Delorenzi, 2012). In this work, recovery from SCP-induced amnesia was obtained by improving memory reconsolidation using water deprivation (Frenkel, Maldonado, & Delorenzi, 2005; Frenkel, Suárez, Maldonado, & Delorenzi, 2010).

Altogether, our results support the notion that SCP-induced memory impairment is a consequence of memory expression deficit rather than memory formation impairment.

In our experimental conditions, memory recovery by Ch was only possible in the animals receiving a low dose of SCP, but not when a higher dose was given. This result suggests that recovery from amnesia is not possible when a strong cholinergic blockade is produced during learning or during consolidation. It might be speculated that when a high dose of SCP is given, consolidation is completely blocked and the information is not stored. However, it might be possible that a very weak memory is formed, and higher doses of Ch (or other reconsolidation enhancers) may be needed to reverse the impairment.

From these results, it could be presumed that mild cholinergic dysfunction still allows memory formation, but the stored memory traces fail to be behaviorally expressed. These memories are labilized during the reactivation session, and may be improved through reconsolidation processes, to control behavior in subsequent evaluations. On the contrary, deep cholinergic failure might impair memory formation. Accordingly, memory impairment observed in mild cholinergic failure conditions, as in the elderly and in early stages of AD (Court et al., 2001; Perry et al., 1995), might actually be a symptom of memory expression impairment rather than a real memory loss. Therefore, memories may actually be stored, but remain hidden. If these undisclosed memories are labilized and then enhanced through reconsolidation, one might get behavioral expression of the stored information. This statement would apply at least for recent episodic memories, whose loss is one of the characteristics of mild cognitive impairment and of early stages of AD (Neugroschl & Wang, 2011). In fact, there are no FDA-approved therapies for mild cognitive impairment, and the only approved pharmacological treatment for the early stage of AD is the administration of cholinesterase inhibitors (Hasselmo & LaFerla, 2007; Neugroschl & Wang, 2011).

As was already mentioned, mice receiving SCP before the learning trial performed poorly in the first retention test. However, our results also suggest that a memory trace was stored. This fact is intriguing, and important questions arise from this point. If these animals had stored a memory trace of the task, why they perform poorly in the first retention test? Was this memory trace retrieved during the retention test? Can a memory trace enter in a labile state without being retrieved? Or retrieval is a necessary condition to labilize a memory?

One possibility is that memory labilization can occur independently of memory retrieval. If this were the case, mice performed poorly due to a retrieval deficit. In other words, mice entered the dark compartment because they did not retrieve the information. The other possibility is that memory must be retrieved in order to be labilized. Thus, if retrieval is a necessary condition for memory labilization, one can conclude that mice retrieved the memory trace. But in this case one can assume that memory did not guide behavior, as mice performed poorly. Therefore, if the memory of the task is retrieved but does not guide behavior, which process does it? Do decision-making processes (Bogacz, 2007; Clark, Cools, & Robbins, 2004; Khader et al., 2011) guide behavior and lead mice to enter the dark compartment? These possibilities are represented in figure 8. Unfortunately, the present results do not provide answers for these questions, and we are working to unravel them.

In summary, the results of the present work show that low doses of SCP did not impair memory formation. The stored memory is not expressed during the first retention test

but can be improved by modulating memory reconsolidation with Ch. Once enhanced, memory is expressed in T2. 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.

Acknowledgments

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References

Alberini, C.M. (2005). Mechanisms of memory stabilization: Are consolidation and reconsolidation similar or distinct processes? *Trends in Neuroscience, 28*, 51–56.

Alberini, C. M., Milekic, M. H., & Tronel, S. (2006). Mechanisms of memory stabilization and de-stabilization. *Cellular and Molecular Life Sciences, 63*(9), 999-1008.

Alberini, C. M. (2011). The role of reconsolidation and the dynamic process of long-term memory formation and storage. *Frontiers in Behavioral Neuroscience, 5*, 1-10.

Albuquerque, E. X., Pereira, E. F. R., Alkongdon, M., & Rogers, S. W. (2009). Mammalian nicotinic acetylcholine receptors: from structure to function. *Physiological Reviews, 89*(1), 73-120.

Baratti, C. M., Boccia, M. M., Blake, M. G., & Acosta, G. B. (2008). Reactivated memory of an inhibitory avoidance response in mice is sensitive to a nitric oxide synthase inhibitor. *Neurobiology of Learning and Memory, 89*(4), 426-440.

Baratti, C. M., Boccia, M. M., & Blake, M. G. (2009). Pharmacological effects and behavioral interventions on memory consolidation and reconsolidation. *Brazilian Journal of Medical and Biological Research, 42*(2), 148-154.

Bartus, R. T., Dean, R. L. 3rd, Beer, B., & Lippa, A. S. (1982). The cholinergic hypothesis of geriatric memory dysfunction. *Science, 217*(4558), 408-414.

Berón de Astrada, M., & Maldonado, H. (1999). Two related forms of long-term habituation in the crab Chasmagnathus are differentially affected by scopolamine. *Pharmacology, Biochemistry, and Behavior, 63*(1), 109-118.

Blake, M. G., Boccia, M. M., & Baratti, C. M. (2008). Behavioral differences on memory retrieval between two variants of step-through inhibitory avoidance task in mice. *Neuroscience Letters, 444*(1), 102-105.

Blake, M. G., Boccia, M. M., Krawczyk, M. C., & Baratti, C. M. (2011). Scopolamine prevents retrograde memory interference between two different learning tasks. *Physiology and Behavior, 102*(3-4), 332-337.

Boccia, M. M., Blake, M. G., Acosta, G. B., & Baratti, C. M. (2004). Memory consolidation and reconsolidation of an inhibitory avoidance response in mice. Effects of i.c.v. injections of hemicholinium-3. *Neuroscience, 124*(4), 735-741.

Boccia, M. M., Blake, M. G., Acosta, G. B., & Baratti, C. M. (2006). Post-retrieval effects of icv infusions of hemicholinium in mice are dependent on the age of the original memory. *Learning and Memory, 13*(3), 376-381.

Boccia, M.M., Freudenthal, R., Blake, M.M., de la Fuente, V., Acosta, G.B., Baratti, C.M., & Romano, A. (2007). Activation of hippocampal nuclear factor-κB by retrieval is required for memory reconsolidation. *The Journal of Neuroscience, 27*(49), 13436–13445.

Boccia, M. M., Blake, M. G., Krawczyk, M. C., & Baratti, C. M. (2010). Hippocampal α7 nicotinic receptors modulate memory reconsolidation of an inhibitory avoidance task in mice. *Neuroscience, 171*(2), 531-543.

Bogacz, R. (2007). Optimal decision-making theories: linking neurobiology with behavior. *Trends in Cognitive Sciences, 11*(3), 118-125.

Caffaro, P., Suárez, L. D., Blake, M. G., & Delorenzi, A. (2012). Scopolamine interferes with memory expression without disrupting long-term storage. *Neurobiology of Learning and Memory, submitted to NLM.*

Cahill, L., McGaugh, J. L., & Weinberger, N. M. (2001). The neurobiology of learning and memory: some reminders to remember. *Trends in Neurosciences, 24*(10), 578-581.

Clark, L., Cools, R., & Robbins, T. W. (2004). The neuropsychology of ventral prefrontal cortex: Decision-making and reversal learning. *Brain and Cognition, 55*(1), 41-53.

Corkin, S. (2002). What's new with the amnesic patient H.M.? *Nature Reviews Neuroscience, 3*(2), 153-160.

Court, J., Martin-Ruiz, C., Piggott, M., Spurden, D., Griffiths, M., & Perry, E. (2001). Nicotinic receptor abnormalities in Alzheimer's disease. *Biological Psychiatry, 49*(3), 175-184.

Decker, M. W., & McGaugh, J. L. (1989). Effects of concurrent manipulations of cholinergic and noradrenergic function on learning and retention in mice. *Brain Research, 477*(1-2), 29-37.

Decker, M. W., Tran, T., & McGaugh, J. L. (1990). A comparison of the effects of scopolamine and diazepam on acquisition and retention of inhibitory avoidance in mice. *Psychopharmacology (Berl), 100*(4), 515-521.

Dudai, Y. (2006). Reconsolidation: the advantage of being refocused. *Current Opinion in Neurobiology, 16*(2), 174-178.

Ebert, U., & Kirch, W. (1998). Scopolamine model of dementia: electroencephalogram findings and cognitive performance. *European Journal of Clinical Investigation, 28*(11), 944-949.

Flurkey, K., Currer, J.M., & Harrison, D.E. (2007). The mouse in aging research. In J.G. Fox (Ed.), *The mouse in biomedical research* (pp. 637-672). Burlington: Elsevier.

Francis, P. T., Palmer, A. M., Snape, M., & Wilcock, G. K. (1999). The cholinergic hypothesis of Alzheimer's disease: a review of progress. *Journal of Neurology, Neurosurgery, and Psychiatry, 66*(2), 137-147.

Franklin, K. B. J., & Paxinos, G. (1997). *The mouse brain in stereotaxic coordinates*. London: Academic Press.

Frenkel, L., Maldonado, H., & Delorenzi, A. (2005). Memory strengthening by a real-life episode during reconsolidation: an outcome of water deprivation via brain angiotensin II. *European Journal of Neuroscience, 22*(7), 1757-1766.

Frenkel, L., Suarez, L. D., Maldonado, H., & Delorenzi, A. (2010). Angiotensin modulates long-term memory expression but not long-term memory storage in the crab Chasmagnathus. *Neurobiology of Learning and Memory, 94*(4), 509-520.

Frumin, M. J., Herekar, V. R., & Jarvik, M. E. (1976). Amnesic actions of diazepam and scopolamine in man. *Anesthesiology, 45*(4), 406-412.

Ghoneim, M. M., & Mewaldt, S. P. (1975). Effects of diazepam and scopolamine on storage, retrieval and organizational processes in memory. *Psychopharmacologia, 44*(3), 257-262.

Ghoneim, M. M., & Mewaldt, S. P. (1977). Studies on human memory: the interactions of diazepam, scopolamine, and physostigmine. *Psychopharmacology (Berl), 52*(1), 1-6.

Giacobini, E. (1990). Cholinergic receptors in human brain: effects of aging and Alzheimer disease. *Journal of Neuroscience Research, 27*(4), 548-560.

Gold, P. E., Haycock, J. W., Marri, J., & McGaugh, J. L. (1973). Retrograde amnesia and the "reminder effect": an alternative interpretation. *Science, 180*(4091), 1199-1201.

Gold, P.E., & van Buskirk, R. (1976) Effects of posttrial hormone injections on memory processes. *Hormones and Behavior, 7*(4), 509-517.

Hasselmo, M.E., & Stern, C.E. (2006). Mechanisms underlying working memory for novel information. *Trends in Cognitive Sciences, 10*(11), 487-493.

Hasselmo, M.E., & Sarter, M. (2011). Modes and models of forebrain cholinergic neuromodulation of cognition. *Neuropsychopharmacology, 36*(1), 52-73.

Haycock, J. W., Gold, P. E., Macri, J., & McGaugh, J. L. (1973). Noncontingent footshock attenuation of retrograde amnesia: a generalization effect. *Physiology and Behavior, 11*(1), 99-102.

Izquierdo, I. (1989). Mechanism of action of scopolamine as an amnestic. *Trends in Pharmacological Sciences, 10*(5), 175-177.

Izquierdo, I., & McGaugh, J.L. (2000). Behavioural pharmacology and its contribution to the molecular basis of memory consolidation. *Behavioural Pharmacology, 11*(7-8), 517-534.

Khader, P. H., Pachur, T., Meier, S., Bien, S., Jost, K., & Rösler, F. (2011). Memory-based decision-making with heuristics: evidence for a controlled activation of memory representations. *Journal of Cognitive Neuroscience, 23*(11), 3540-3554.

Mattson, M.P., & Calabrese, E.J. (2010). *Hormesis. A revolution in Biology, Toxicology and Medicine*. New York: Springer.

McGaugh, J. L. (1966). Time-dependent processes in memory storage. *Science, 153*(3742), 1351-1358.

McGaugh, J. L. (2000). Memory - a century of consolidation. *Science, 287*(5451), 248-251.

Milekic, M. H., & Alberini, C. M. (2002). Temporally graded requirement for protein synthesis following memory reactivation. *Neuron, 36*(3), 521-525.

Misanin, J. R., Miller, R. R., & Lewis, D. J. (1968). Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. *Science, 160*(3827), 554-555.

Myers, K. M., & Davis, M. (2002). Behavioral and neural analysis of extinction. *Neuron, 36*(4), 567-584.

Nader, K., Schafe, G.E., & Le Doux, J.E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature, 406*(6797), 722-726.

Nader, K., & Wang, S. H. (2006). Fading in. *Learning and Memory, 13*(5), 530-535.

Neugroschl, J., & Wang, S. (2011). Alzheimer's disease: diagnosis and treatment across the spectrum of disease severity. *Mt Sinai Journal of Medicine, 78*(4), 596-612.

Ohno, M., & Watanabe, S. (1996). Interactive processing between glutamatergic and cholinergic systems involved in inhibitory avoidance learning of rats. *European Journal of Pharmacology, 312*(2), 145-147.

Ortega, A., del Guante, M. A., Prado-Alcalá, R. A., & Alemán, V. (1996). Changes in rat brain muscarinic receptors after inhibitory avoidance learning. *Life Sciences, 58*(9), 799-809.

Parvez, K., Stewart, O., Sangha, S., & Lukowiak, K. (2005). Boosting intermediate-term into long-term memory. *Journal of Experimental Biology, 208*(Pt 8), 1525-1536.

Perry, E. K., Morris, C. M., Court, J. A., Cheng, A., Fairbairn, A. F., McKeith, I. G., Irving, D., Brown, A., & Perry, R. H. (1995). Alteration in nicotine binding sites in Parkinson's disease, Lewy body dementia and Alzheimer's disease: possible index of early neuropathology. *Neuroscience, 64*(2), 385-395.

Philips, G. T., Tzvetkova, E. I., Marinesco, S., & Carew, T. J. (2006). Latent memory for sensitization in Aplysia. *Learning and Memory, 13*(2), 224-229.

Przybyslawski, J., & Sara, S. J. (1997). Reconsolidation of memory after its reactivation. *Behavioural Brain Research, 84*(1-2), 241-246.

Querfurth, H.W., & LaFerla, F.M. (2010). Alzheimer's Disease. *The New England Journal of Medicine, 362*(4), 329-344.

Quirarte, G. L., Cruz-Morales, S. E., Cepeda, A., Garcia-Montanez, M., Roldán-Roldán, G., & Prado-Alcalá, R. A. (1994). Effects of central muscarinic blockade on passive avoidance: anterograde amnesia, state dependency, or both? *Behavioral and Neural Biology, 62*(1), 15-20.

Quirion, R. (1993). Cholinergic markers in Alzheimer disease and autoregulation of acetycholine release. *Journal of Psychiatry and Neuroscience, 18*(5), 226-234.

Rescorla, R. A. (1988). Behavioral studies of Pavlovian conditioning. *Annual Review of Neuroscience, 11*, 329-352

Ribot, T. (1881). *Les maladies de la memoire*. Appleton-Century-Crofts, New York.

Richardson, J. S., Miller, P. S., Lemay, J. S., Jyu, C. A., Neil, S. G., Kilduff, C. J., & Keegan, D. L. (1985). Mental dysfunction and the blockade of muscarinic receptors in the brains of the normal elderly. *Progress in Neuro-psychopharmacology and Biological Psychiatry, 9*(5-6), 651-654.

Roldán, G., Bolaños-Badillo, E., González-Sánchez, H., Quirarte, G. L., & Prado-Alcalá, R. A. (1997). Selective M1 muscarinic receptor antagonists disrupt memory consolidation of inhibitory avoidance in rats. *Neuroscience Letters, 230*(2), 93-96.

Roozendaal, B., & McGaugh, J. L. (2011). Memory modulation. *Behavioral Neuroscience, 125*(6), 797-824.

Rush, D. K. (1988). Scopolamine amnesia of passive avoidance: a deficit of information acquisition. *Behavioral and Neural Biology, 50*(3), 255-274

Siegel, S. (1956). *Non-parametric statistics for the behavioral sciences*. New York: McGraw-Hill.

Squire, L. R. (2006). Lost forever or temporarily misplaced? The long debate about the nature of memory impairment. *Learning and Memory, 13*(5), 522-529.

Squire, L.R., & Wixted, J.T. (2011). The cognitive neuroscience of human memory since H.M. *Annual Review of Neuroscience, 34*, 259-288.

Terazima, E., & Yoshino, M. (2010). Modulatory action of acetylcholine on the Na+-dependent action potentials in Kenyon cells isolated from the mushroom body of the cricket brain. *Journal of Insect Physiology, 56*(12), 1746-1754.

Tronson, N. C., & Taylor, J. R. (2007). Molecular mechanisms of memory reconsolidation. *Nature Reviews Neuroscience, 8*(4), 262-275.

Weinberger, N. M. (2006). Food for thought: honeybee foraging, memory, and acetylcholine. *Sci STKE, 2006*(336), pe23.

Figure legends

Fig. 1. Effect of the pre-training administration of SCP on retention performance. SCP (0.5 mg/kg, i.p.) and mSCP (0.5 mg/kg, i.p.) were administered 20 min before training. The behavioral protocol is represented above the graph. Each bar represents the median and interquartile range (n=10 mice/group). TR: training session, T1: retention test. *** p<0.001, compared with the Veh-injected group.

Fig. 2. Effects of Ch on retention performance of mice receiving SCP (0.5 mg/kg, i.p.) 20 min before 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, compared with the corresponding test of the respective Veh-injected group; ### p<0.001, comparing T1 vs. T2 of each group.

Fig. 3. Effects of Ch on retention performance of mice receiving SCP (0.5 mg/kg, i.p.) 20 min before training. Choline (0.8 µg/hippocampus) was given: (A) 3 hours after T1, (B) 48 hours after training, in absence of memory reactivation, and (C) immediately after T1, but T2 was performed 1 hour after T1. 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<0.05, ** p<0.01, *** p<0.001, in all cases compared vs. the corresponding Veh-injected group; ## p<0.01, comparing T2 vs. T3 of each group; &&& p<0.001, comparing T3 of SCP-Veh vs. T3 of SCP-Ch groups.

Fig. 4. Effects of Ch on retention performance of mice receiving SCP (0.5 mg/kg, i.p.) 20 min before 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 both cases compared vs. the corresponding Veh-injected group; ### p<0.001, comparing T1 vs. T2 of each group.

Fig. 5. Effects of Ch on retention performance of mice receiving Vehicle or SCP (0.5 mg/kg, i.p.) 20 min before 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 figures 2 and 4). Each point represents the median (n=10 mice/group).

Fig. 6. Effects of Ch on retention performance of mice receiving a high dose of SCP (5 mg/kg, i.p.) 20 min before 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. *** $p<0.001$, compared with the corresponding test of the Veh-injected group.

Fig. 7. Coronal brain images adapted from the atlas of Franklin and Paxinos (1997), indicating location of the injections in the hippocampus corresponding to experiment 7 (● SS ■ Ch 0.80 µg/hippocampus).

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 let to this memory control its behavior. All these steps are necessary, and any failure can cause a poor performance.

Figure 1

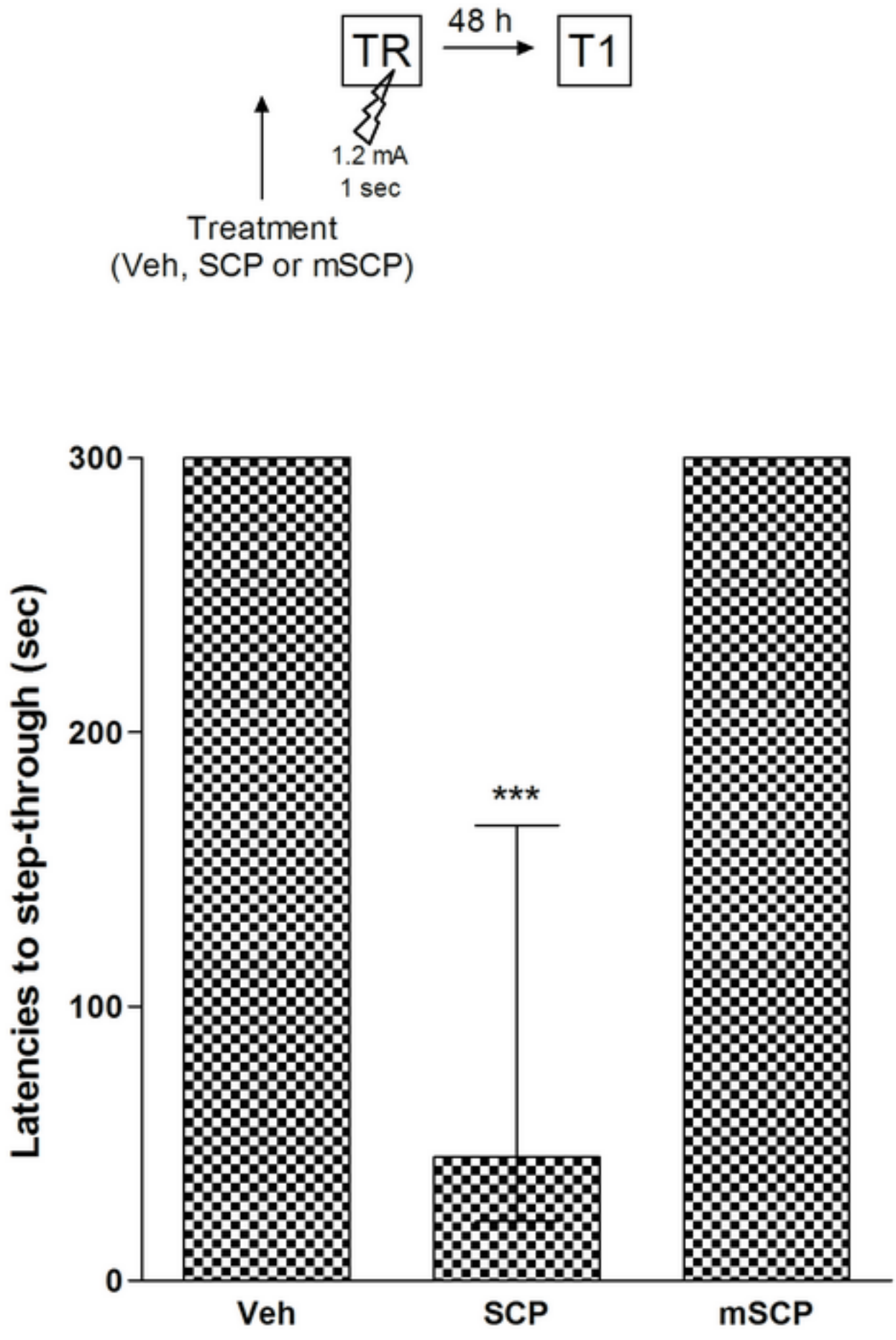


Figure 2

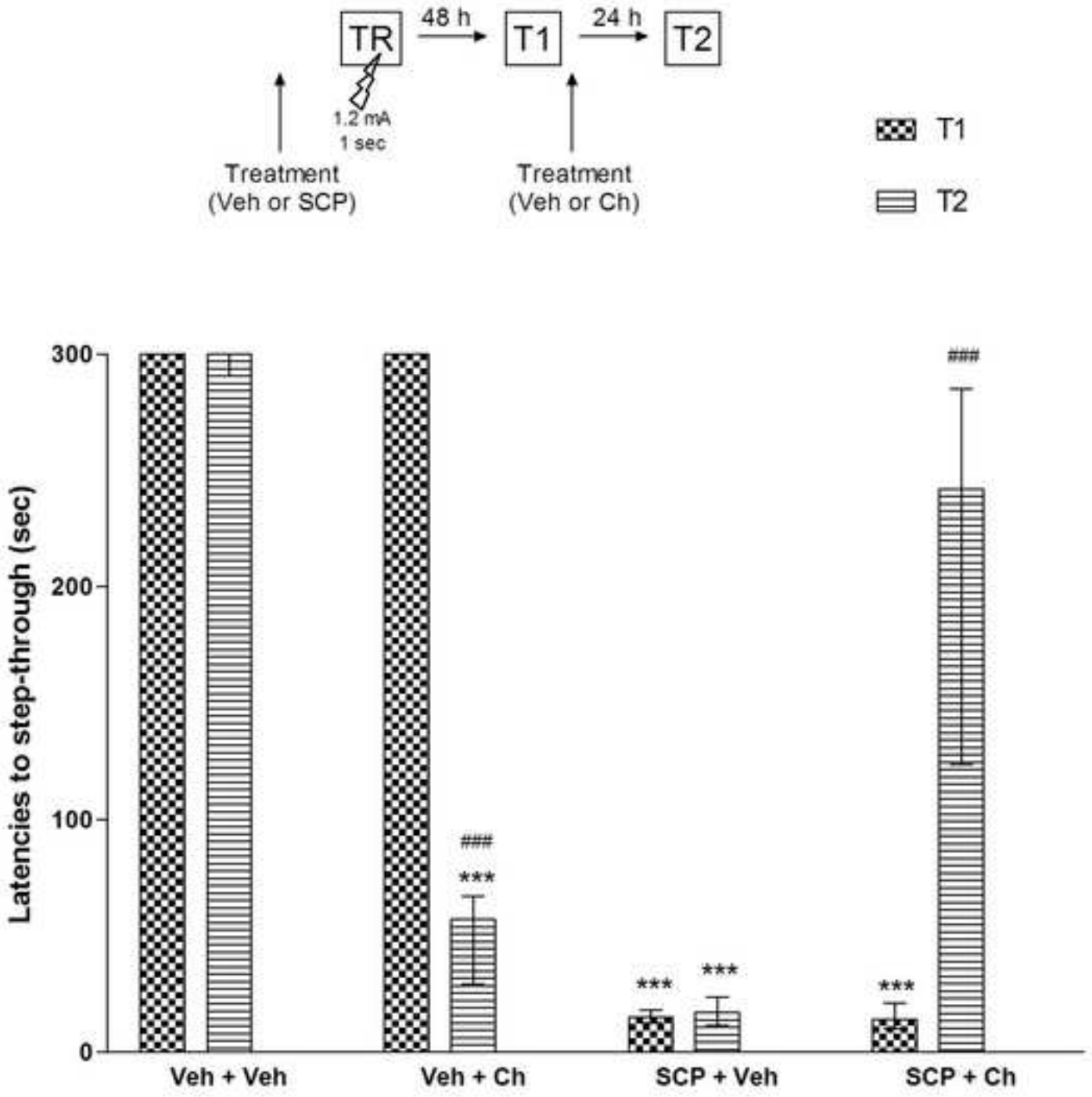


Figure 3

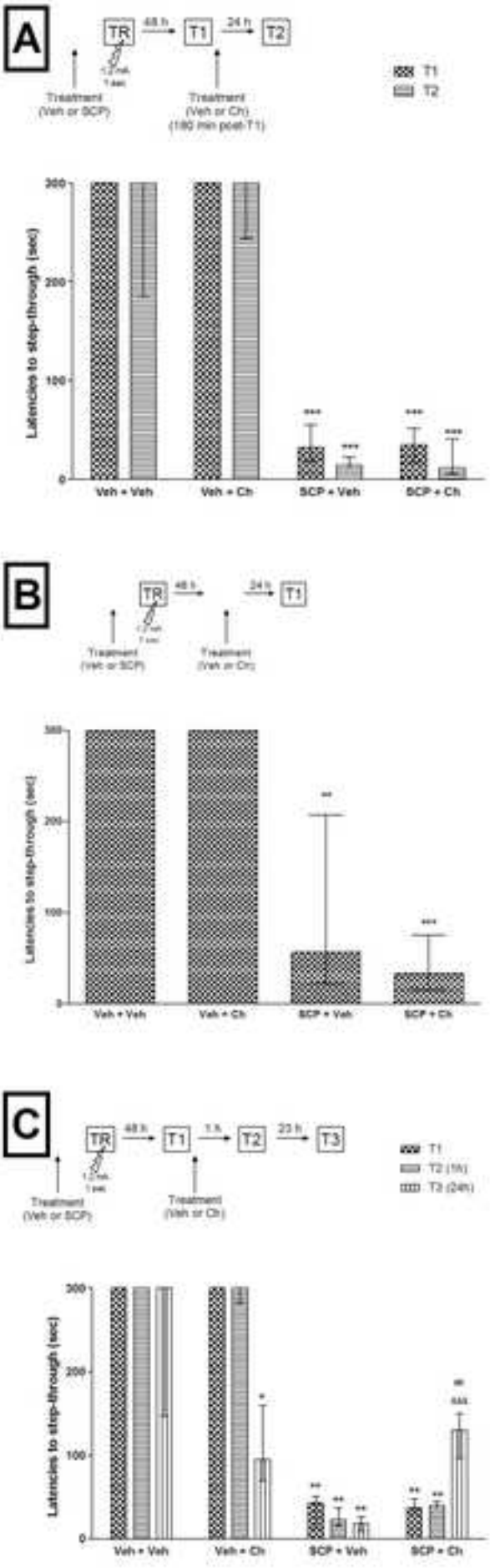


Figure 4

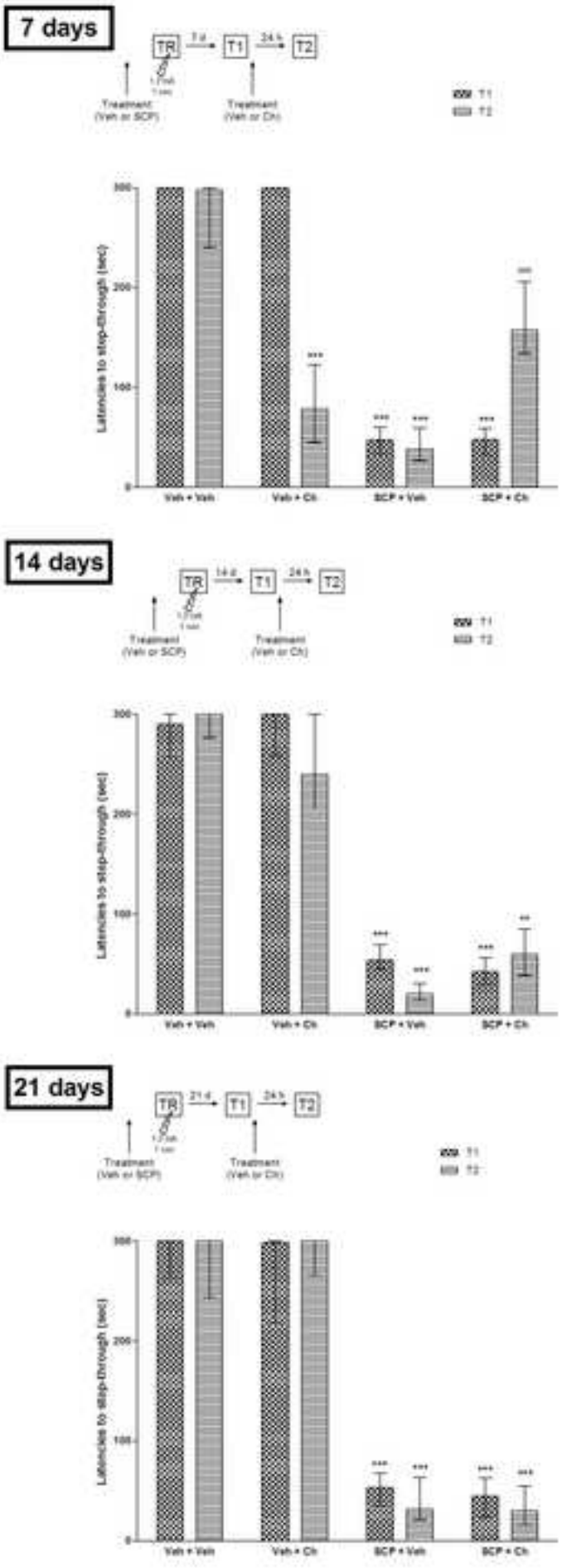


Figure 5

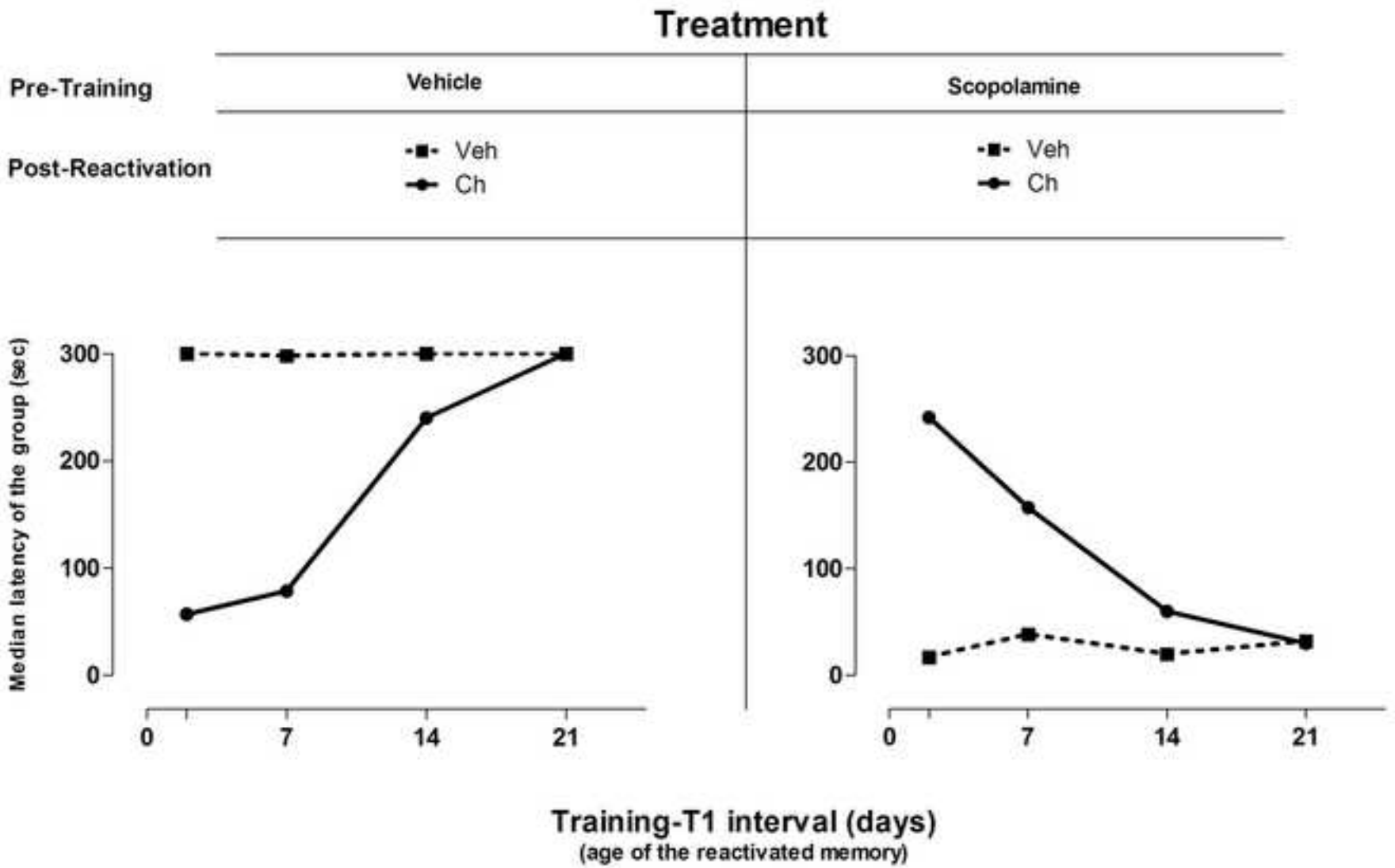


Figure 6

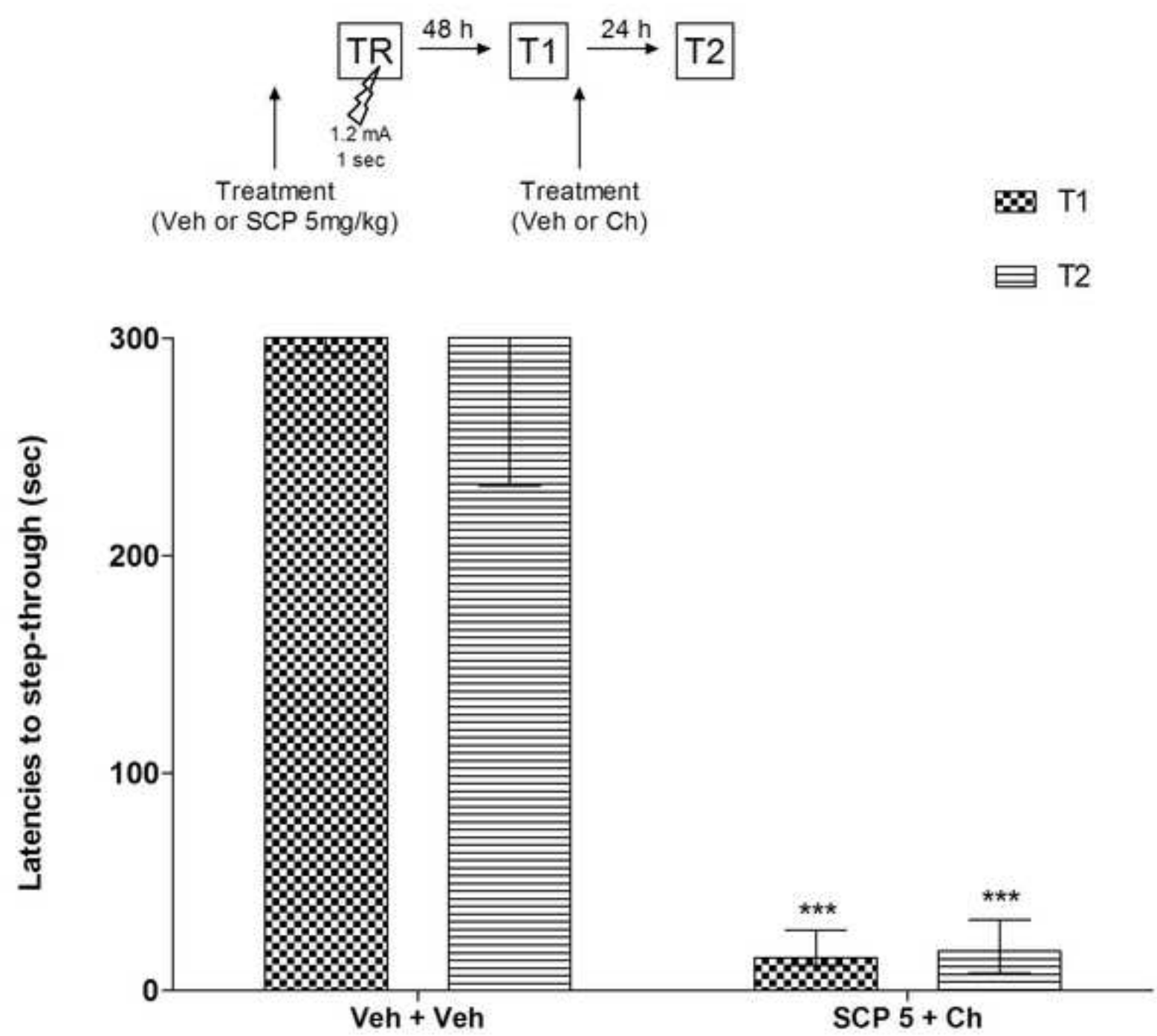


Figure 7

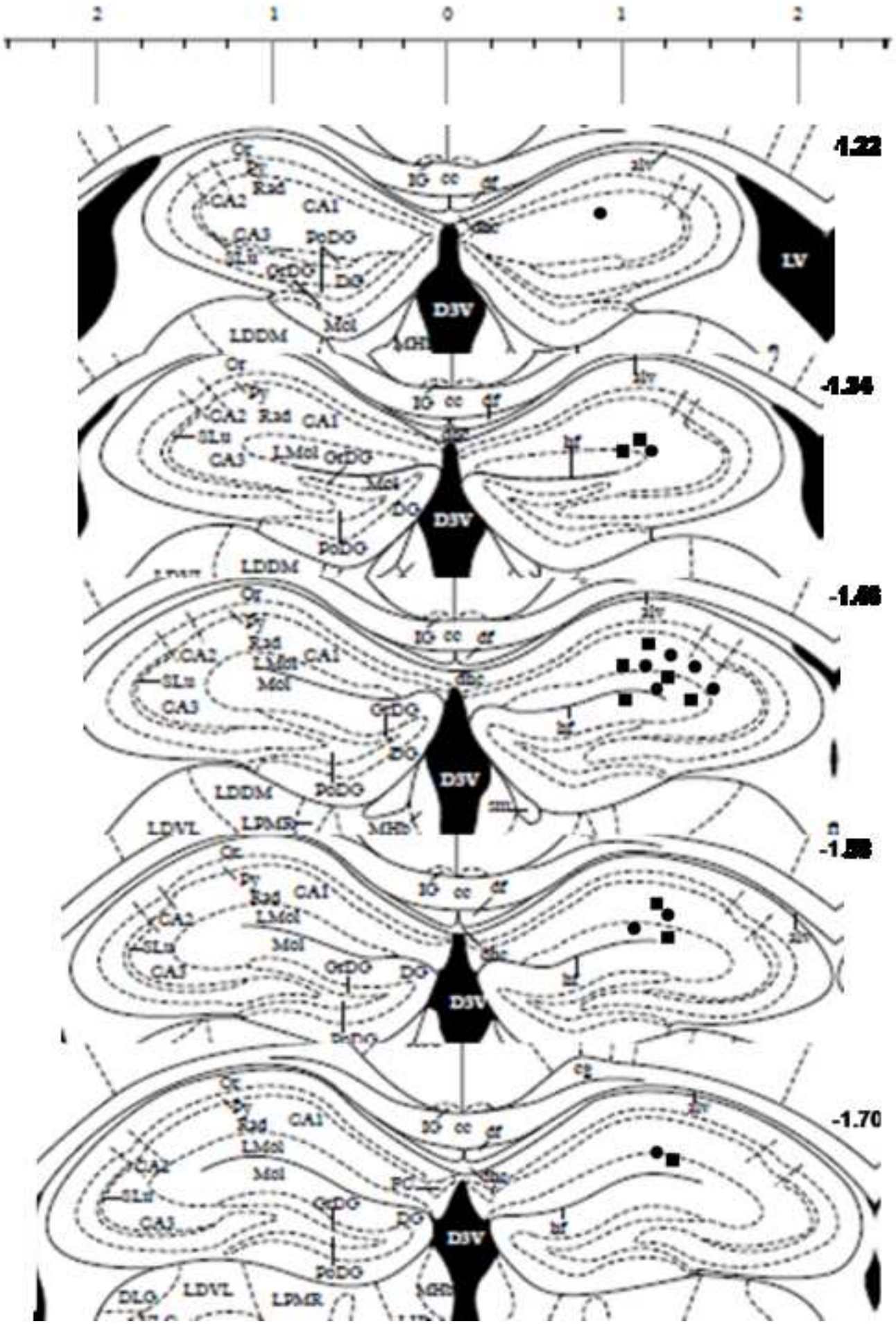
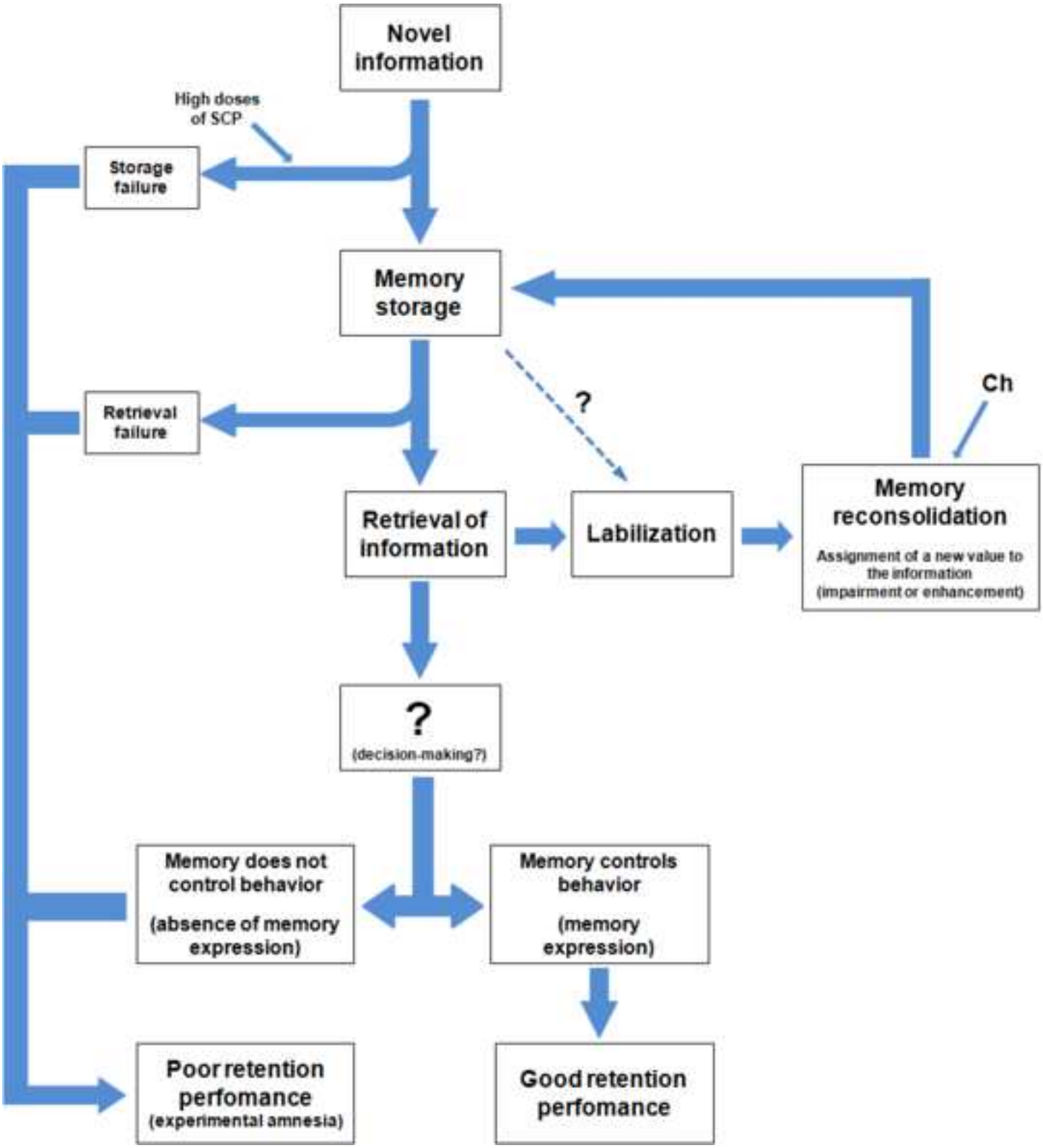
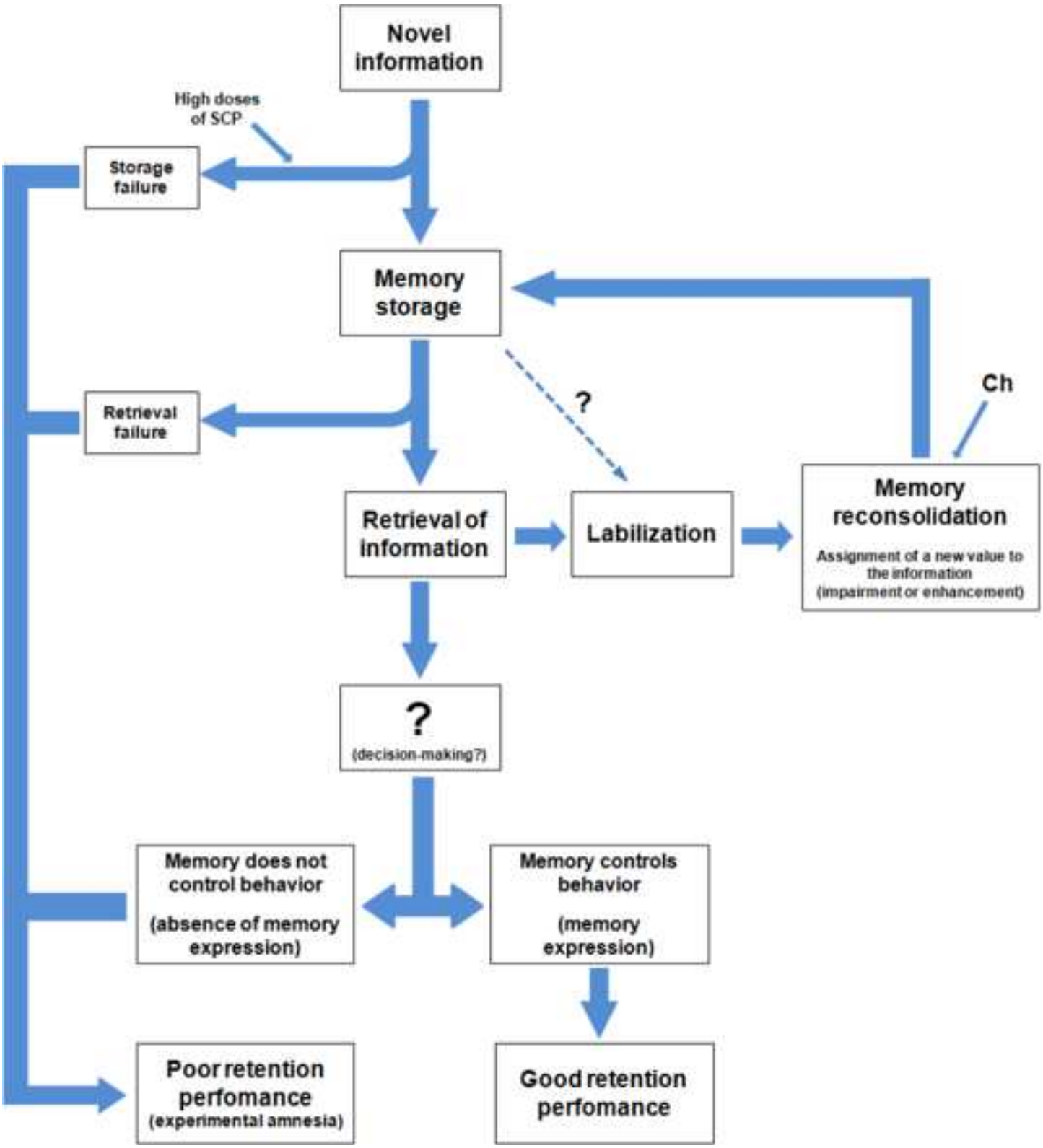


Figure 8




Novel information
High doses of SCP
Storage failure
Memory storage
Retrieval failure
?
Ch
Retrieval of information
Labilization
Memory reconsolidation
Assignment of a new value to the information (impairment or enhancement)
?
(decision-making?)
Memory does not control behavior
(absence of memory expression)
Memory controls behavior
(memory expression)
Poor retention perfomance
(experimental amnesia)
Good retention perfomance

- Pre-training administration of scopolamine leads to memory impairment.
- Intra-hippocampal administration of choline modulates memory reconsolidation
- Choline reverses scopolamine-induced amnesia by enhancing memory reconsolidation
- Low doses of scopolamine cause memory expression deficit, but not storage impairment
- Reconsolidation could modify the ability of a memory for being expressed later