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D_1/D_5 dopamine receptors modulate spatial memory formation

Weber C.N. da Silva [a,1], Cristiano C. Köhler [a,b,1], Andressa Radiske [a,b,1], Martín Cammarota [a,b,*]

[a] Laboratório de Neuroquímica & Neurofisiologia da Memória, Centro de Memória, Instituto do Cérebro, Pontifícia Universidade Católica de Rio Grande do Sul (PUCRS), Av. Ipiranga, 6690 – 2nd floor, 90610-000 Porto Alegre, RS, Brazil
[b] Instituto Nacional de Ciência e Tecnologia em Neurociência Translacional, Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Brazil

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ABSTRACT

We investigated the effect of the intra-CA1 administration of the D_1/D_5 receptor antagonist SCH23390 and the D_1/D_5 receptor agonist SKF38393 on spatial memory in the water maze. When given immediately, but not 3 h after training, SCH23390 hindered long-term spatial memory formation without affecting non-spatial memory or the normal functionality of the hippocampus. On the contrary, post-training infusion of SKF38393 enhanced retention and facilitated the spontaneous recovery of the original spatial preference after reversal learning. Our findings demonstrate that hippocampal D_1/D_5 receptors play an essential role in spatial memory processing.

1. Introduction

Dopamine regulates value-based decision-making (Sugrue, Corrado, & Newsome, 2005), and through modulation of the effectiveness and significance of stimuli (Wise, 2004), might induce synaptic plasticity (Lisman & Grace, 2005). In agreement with this hypothesis, D_1 dopamine receptors elicit the onset of the late, protein synthesis-dependent phase of long-term potentiation (LTP) in the hippocampus (Huang & Kandel, 2006), control plasticity -induced protein synthesis (Sajikumar & Frey, 2004), and enhance the persistent storage of hippocampus-dependent memories (Rossato, Bevilaqua, Izquierdo, Medina, & Cammarota, 2009).

The participation of the hippocampus in spatial memory formation has been clearly established (Bird & Burgess, 2008; Leutgeb et al., 2005; Martin & Clark, 2007). Nonetheless, knowledge about the molecular requirements of this process is still incomplete. In particular, information about the role played by the hippocampal dopaminergic system is scarce and originates, mainly, from studies with mutant animals. In this regard, it has been shown that D_1 receptor-knockout mice have spatial learning deficits (El-Ghundi et al., 1999; Granado et al., 2008; Tran et al., 2008), although these mutants also show decreased reactivity to external stimuli, increased locomotion, and deficiencies in initiating movement (Smith et al., 1998), which could reflect compensatory processes resulting from the developmental absence of D_1 receptors (Clifford et al., 1998), and therefore, complicate the interpretation of behavioral data. To circumvent these problems, we analyzed the effect of the intra-hippocampal infusion of well-known D_1/D_5 receptors antagonists and agonists on the retention of the long-term memory (LTM) for a spatial preference in the water maze (WM).

2. Material and methods

2.1. Drugs and statistical analyses

SKF38393 and SCH23390 were from Sigma–Aldrich (St. Louis, MO, USA). They were dissolved in DMSO and stored protected from light at −20 °C until use. Right before that an aliquot was thawed and diluted to working concentration with 0.1% DMSO in saline (pH 7.2). The doses utilized were determined based on previous studies showing the effect of these compounds on learning and memory (Rossato et al., 2009). Data were analyzed by two-tailed Student's *t*-test, repeated measures ANOVA, one-way ANOVA followed by post hoc tests, or the Wilcoxon signed rank test, as appropriate.

2.2. Subjects, surgery and drug infusion procedure

Male Wistar rats (3-month-old, 300–350 g) bought at FEPPS (Fundação Estadual de Produção e Pesquisa em Saúde do Rio

* Corresponding author at: Laboratório de Neuroquímica & Neurofisiologia da Memória, Centro de Memória, Instituto do Cérebro, Pontifícia Universidade Católica de Rio Grande do Sul (PUCRS), Av. Ipiranga, 6690 – 2nd floor, 90610-000 Porto Alegre, RS, Brazil. Fax: +55 51 3320 3312.
E-mail addresses: mcammaro@terra.com.br, martin.cammarota@gmail.com (M. Cammarota).
[1] These authors contributed equally to this work and are cited alphabetically.

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Grande do Sul, Porto Alegre, Brazil) were used. The animals were housed 5 to a cage and kept with free access to food and water under a 12/12 light/dark cycle, with light onset at 7:00 AM. The temperature of the animal room was maintained at 22–24 °C. To implant them with indwelling cannulas, rats were deeply anesthetized with thiopental (i.p. 30–50 mg/kg) and 22-gauge cannulas stereotaxically aimed to the CA1 region of the dorsal hippocampus (A-4.2, L ± 3.0, V-1.8; Paxinos & Watson, 1986). Animals were allowed to recover from surgery for 4 days before submitting them to any other procedure. At the time of drug delivery, 30-gauge infusion cannulas were tightly fitted into the guides. Infusions (1 μl/side) were carried out over 60 s with an infusion pump and the cannulas were left in place for 60 additional seconds to minimize backflow. The placement of the cannulas was verified postmortem: 2–4 h after the behavioral test, 1 μl of a 4% methylene-blue solution was infused as described above and the extension of the dye 30 min thereafter was taken as an indication of the presumable diffusion of the vehicle or drug previously given to each animal. Only data from animals with correct implants were analyzed (96% of all implanted animals). All experiments were conducted blind to the treatment condition of the animals. Every effort was made to minimize the animal's suffering and to reduce the number of animals used. The "Principles of laboratory animal care" (NIH publication N° 85–23, revised 1996) were strictly followed.

2.3. Training in the spatial version of the water maze (WM)

The WM was a black circular pool (200 cm in diameter) conceptually divided in 4 imaginary quadrants for the purpose of data analysis. The temperature of the water was kept at 21–23 °C. Two centimeters beneath the surface of the water and hidden from the animals' view was a black circular platform (12 cm in diameter) which had a rough surface that allowed rats to climb onto it easily once its presence was detected. The swimming path was evaluated using a video tracking and analysis system. The maze was located in a well-lit white room with several posters and other distal visual stimuli hanging on the walls to provide spatial cues. Rats were handled during 5 min per day for 3 consecutive days prior to training. Animals were trained in the hidden platform (spatial) version of the WM for 5 (long training protocol) or 2 consecutive days (short training protocol), depending on the experiment. On each day, rats received eight consecutive training trials during which the hidden platform was kept in a constant location. A different start location was used on each trial, which consisted of a swim followed by a 30-s stay on the escape platform. The intertrial interval was 30-s. Any rat that did not find the platform within 60-s was guided to it by the experimenter. Drugs were infused at immediately or 3 h after the last trial of each training session. Memory retention was evaluated during a probe test in the absence of the escape platform carried out 24 or 120 h after the last training session. As indicators of memory retention we used the latency to swim over an imaginary annulus (24 cm in diameter) centered at the previous location of the escape platform and/or and the time spent swimming in the target quadrant.

2.4. Reversal learning

Rats were trained in the spatial version of the WM during five days as stated above and, 24 h after the last training session were submitted to eight 60-s long reversal learning trials in which the platform was placed in the opposite quadrant of the pool. Memory retention was evaluated in a probe test carried out 24 or 120 h after the last reversal trial.

2.5. Training in the non-spatial version of the WM

For training in the non-spatial version of the WM, we used the same tank as for training in the spatial version of the task, but heavy black curtains hanged on a ceiling-mounted track were drawn around the maze to occlude distal visual cues. A white plastic disk 10 cm in diameter was mounted on top of the hidden platform to indicate its location. The number of trials and sessions were identical to that for training in the spatial protocol. Drug infusion was performed as stated above.

2.6. Inhibitory avoidance training

Rats were trained in a one-trial, step-down inhibitory avoidance during the light phase of the subjective day (between 9.00 and 11.00 h). The training apparatus was a 50 × 25 × 25 cm plexiglass box with a 5 cm-high, 8 cm-wide and 25 cm-long platform on the left end of a series of bronze bars which made up the floor of the box. For training, animals were gently placed on the platform facing the left rear corner of the training box. When they stepped-down and placed their four paws on the grid, received a 2-s, 0.5 mA scrambled footshock and were immediately withdrawn from the training box. Memory retention was evaluated in a non-reinforced test session carried out 24 h after training. In the test session, the animals were placed back on the training box platform until they eventually stepped down to the grid. The latency to step-down during the test session was taken as an indicator of memory retention.

3. Results

To establish whether D_1/D_5 dopamine receptors are necessary for spatial LTM formation, rats were trained in the spatial version of the WM using a 5 day-long training protocol. Bilateral intra-CA1 infusions of the D_1/D_5 receptor antagonist SCH23390 (5 nmol/side), immediately but not 3 h after every daily training session, blocked the decrease in escape latency seen in control animals (Fig. 1A; $F(2, 80) = 5.303$, $p < 0.05$ for treatment; $F(8, 80) = 2.816$, $p < 0.01$ for the interaction between session and treatment). A probe test in the absence of the escape platform carried out 24 h after the last training session confirmed that intra-CA1 administration of SCH23390 impairs spatial memory retention during a limited post-training time window. In this probe test, rats that received SCH23390 immediately after training showed longer latencies to swim over the previous position of the escape platform (Fig. 1B; $F(2, 20) = 4.336$, $p < 0.05$), and spent less time swimming in the target quadrant (Fig. 1C; $F(2, 20) = 9.796$, $p < 0.01$) than animals that received vehicle or were given SCH23390 3 h post-training. SCH23390 did not affect acquisition of the escape response when given immediately after training in the non-spatial version of the WM (Fig. 1E; $F(1, 40) = 3.157$, $p = 0.11$ for treatment; $F(4, 40) = 1.053$, $p = 0.39$ for the interaction between session and treatment). Moreover, animals that received daily intra-CA1 infusions of SCH23390 for 5 days before being trained in inhibitory avoidance, a hippocampus-dependent learning task, learned the avoidance response normally (Fig. 1F; $Z = -2.803$, $p < 0.01$), suggesting that repeated administration of SCH23390 does not affect the functionality of the hippocampal formation.

We next tested the ability of the D_1/D_5 receptor agonist SKF38393 to improve long-term spatial memory. Because the 5 day-long WM training protocol generates a persistent spatial preference lasting more than 30 days (not shown), initially we used a short WM training protocol (see Section 2.3) to avoid possible ceiling effects. When given in dorsal CA1 immediately after training, SKF38393 (45 nmol/side) decreased the time to swim

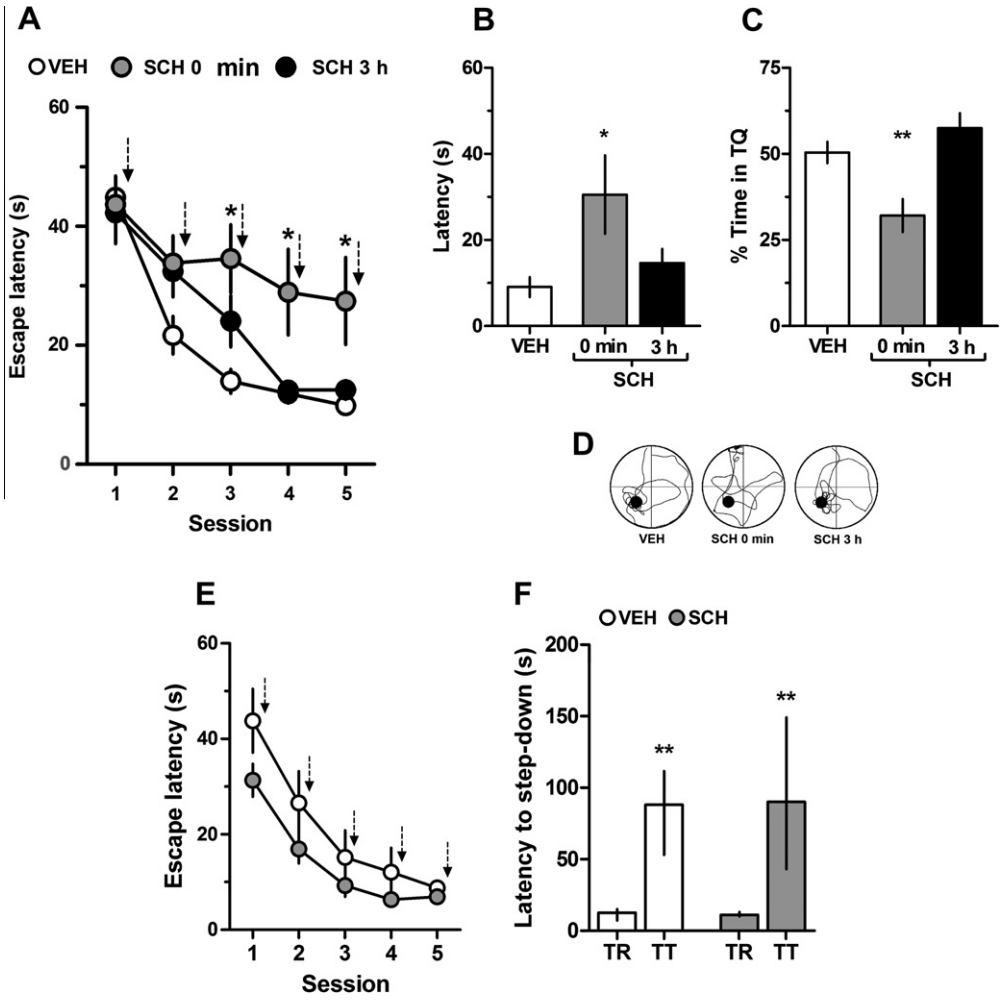

Fig. 1. Intra-CA1 infusion of SCH23390 blocks long-term spatial memory formation. (A) Mean escape latency during training in the spatial version of the WM (5 day-long training protocol) for rats given vehicle (VEH) or the D_1/D_5 receptor antagonist SCH23390 (SCH) in dorsal CA1 immediately or 3 h after each training session. Arrows indicate the moments of drug infusion. Data are presented in blocks of eight trials as mean ± SEM; $n = 7–9$ per group; * $p < 0.05$ in repeated measures ANOVA. (B) Latency to swim over the previous location of the escape platform, and (C) mean time spent in the target quadrant (TQ) during a 60-s probe test carried out 24 h after the last WM training session for the animals showed in A. Data are presented as mean ± SEM. * $p < 0.05$ and ** $p < 0.01$ vs VEH in Dunnett's test after ANOVA. (D) Representative swimming paths during the 60-s probe test for the animals showed in A, B and C. (E) Mean escape latency during training in the non-spatial version of the WM for rats given VEH or SCH in dorsal CA1 immediately after each training session. Data are presented in blocks of eight trials as mean ± SEM; $n = 7–9$ per group. (F) Step-down latencies during training (TR) and retention test (TT) sessions in an inhibitory avoidance learning task for animals that had received daily intra-CA1 infusions of VEH or SCH (5 nmol/side) during 5 days. The training session was carried out 24 h after the last injection. Data are presented as median ± interquartile range; $n = 7–8$ per group, ** $p < 0.01$ vs TR in Wilcoxon signed rank test.

over the previous location of the escape platform (Fig. 2B; $t(13) = 2.743$, $p < 0.05$), and increased the time spent in the target quadrant (Fig. 2C; $t(13) = 3.312$, $p < 0.001$) during a probe test carried out 120 h after the last training session indicating that it improves spatial memory retention. To further evaluate this hypothesis, we trained animals in the spatial version of the WM using the 5 days-long training protocol. Immediately or 3 h after each training session, rats received SKF38393 in dorsal CA1 and, one day after the last training session, were submitted to eight consecutive reversal learning trials to extinguish the original spatial preference (Lattal, Honarvar, & Abel, 2004; Xu, Zhu, Contractor, & Heinemann, 2009). As can be seen in Fig. 3, SKF38393-treated animals normally extinguished the original spatial preference (Fig. 3A; $F(7, 287) = 20.630$, $p < 0.001$ for the session; $F(14, 287) = 0.935$, $p = 0.52$ for the interaction between treatment and session). Extinction was still evident 24 h after the last reversal training trial (Fig. 3C; $F(5, 86) = 0.564$, $p = 0.73$). However, when tested 120 h after reversal learning, the animals that had received SKF38393 immediately but not 3 h after each training session, spontaneously recovered the original preference (Fig. 3D; $F(5, 86) = 6.362$, $p < 0.001$), showing the existence of savings of the initial spatial engram, and therefore confirming that early post-training activation of D_1/D_5 receptors enhances spatial memory retention.

4. Discussion

In this study, we trained rats in the spatial version of the WM and gave them intra-CA1 infusions of the D_1/D_5 receptor antagonist SCH23390 or of the D_1/D_5 receptor agonist SKF38393 at different post-training times. We found that SCH23390 impaired while SKF38393 enhanced long-term spatial memory only when given immediately but not 3 h after training. Control experiments indicate that this was not due to unspecific behavioral alterations, drug lingering effects, or permanent hippocampal impairment. Moreover, after reversal learning, the extinguished spatial preference recovered spontaneously with the passage of time only in those animals that received SKF38393 right after training. Together, our results demonstrate that hippocampal D_1/D_5 receptors are necessary for spatial LTM formation during a restricted post-training

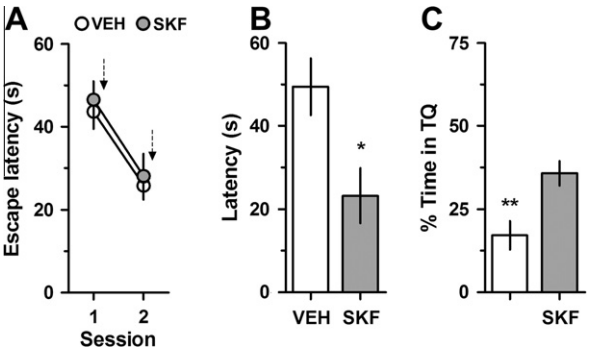

Fig. 2. Intra-CA1 infusion of SKF38393 enhances long-term spatial memory retention. (A) Mean escape latency during training in the spatial version of the WM (2 day-long training protocol) for rats given vehicle (VEH) or the D_1/D_5 receptor agonist SKF38393 (SKF) in dorsal CA1 immediately after each training session. Arrows indicate the moments of drug infusion. Data are presented in blocks of eight trials as mean ± SEM; n = 7–8 per group. (B) Latency to swim over the previous location of the escape platform and (C) mean time spent in the target quadrant (TQ) during a 60-s probe test carried out 120 h after the last training session in the WM for animals showed in A. Data are presented as mean ± SEM. * $p < 0.05$ and ** $p < 0.01$ in Student's t-test.

time window lasting less than 3 h, and that pharmacological manipulation of these receptors can increase retention.

The idea that dopamine modulates spatial learning is prevalent. Previous studies showed that systemic or intra-accumbens injections of the non-specific dopaminergic antagonist haloperidol impair acquisition of the spatial version of the WM (Ploeger, Spruijt, & Cools 1992; Ploeger, Spruijt, & Cools 1994), and that aging-related performance deficits in this task are associated with a decrease in medial frontal cortex dopamine levels (Lee et al., 1994) and improved by systemic administration of D_1 receptor agonists (Hersi, Rowe, Gaudreau, & Quirion, 1995). Indeed, D_1 receptor-deficient mutant mice failed to develop a reliable spatial preference in the WM (Karasinska, George, El-Ghundi, Fletcher, & O'Dowd, 2000) and subcutaneous administration of the D_2 receptor antagonist sulpiride enhanced retention of both the spatial and non-spatial version of the maze (Setlow & McGaugh, 2000), while intra-peritoneal injection of SCH23390 blocked acquisition of the spatial memory trace (Stuchlik, Rehakova, Telensky, & Vales, 2007). However, although lesions experiments suggest that functional meso-hippocampal dopaminergic connections are essential for place navigation in the WM (Gasbarri, Sulli, Innocenzi, Pacitti, & Brioni, 1996; Wisman, Sahin, Maingay, Leanza, & Kirik, 2008), and neurochemical changes that normally happen in the hippocampus after spatial learning do not occur in D_1 receptor mutant mice (Xing et al., 2010), ours is the first report to directly demonstrate the involvement of hippocampal D_1 receptors in the formation of long-term spatial memory in the WM. Our results are partially at odds with those reported by O'Carroll, Martin, Sandin, Frenguelli and Morris (2006) showing that pre- but not post-training intra-hippocampal administration of SCH23390 affects memory for a delayed matching-to-place (DMP) paradigm in the WM. Differences between the learning tasks employed might account for these discrepancies (Cain, Saucier, Hall, Hargreaves, & Boon, 1996). In contrast to the classic version of the WM used in our experiments, the DMP WM utilized by O'Carroll et al. (2006) involved 8 days of drug-free

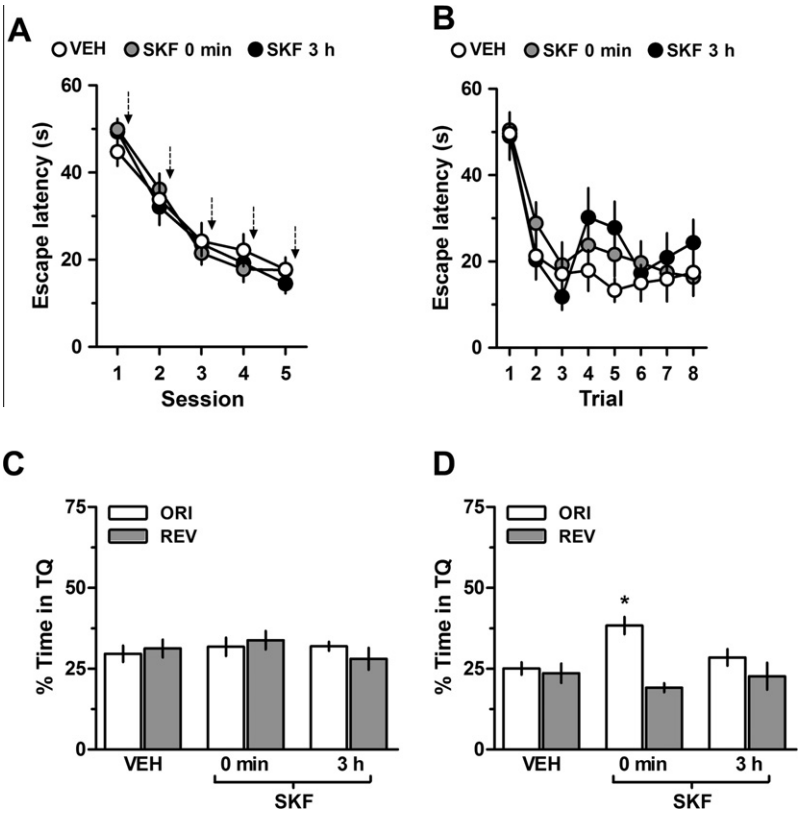

Fig. 3. Posttraining intra-CA1 infusion of SKF38393 facilitates spontaneous recovery of the original spatial preference following reversal learning. (A) Mean escape latency during training in the spatial version of the WM (5 day-long training protocol) for rats given vehicle (VEH) or the D_1/D_5 receptor agonist SKF38393 (SKF) in dorsal CA1 immediately or 3 h after each training session. Arrows indicate the moments of drug infusion. Data are presented in blocks of 8 trials as mean ± SEM; n = 14–17 per group. (B) Mean escape latency during reversal learning training (carried out 24 h after the last WM training session) for animals shown in A. (C and D) Mean time spent in the target quadrant (TQ) of the training phase (ORI) and reversal learning (REV) during a 60-s probe test carried out 24 h (C) or 120 h (D) after reversal learning; * $p < 0.05$ in ANOVA followed by Bonferroni's test.

pre-training during which the hidden escape platform was located in different locations within the pool. So, it is not clear what type or phase of memory processing these authors were assessing in their experiments. Moreover, since they evaluated retention at 6 h after training, a time too short to be sure that the trace was actually being retrieved from LTM, it is also unclear whether they were analyzing the role of dopamine receptors on LTM, or instead, on short-term memory (STM) retention.

At this stage, we can only speculate about the biochemical and physiological mechanisms controlled by hippocampal D_1/D_5 receptors during spatial memory formation. In this respect, it is known that dopamine enhances dendritic protein synthesis in hippocampal neurons (Smith, Starck, Roberts, & Schuman, 2005), maybe interacting with brain-derived neurotrophic factor (BDNF)-regulated signaling pathways, particularly those mediated by activation of extracellular signal-regulated kinases (ERK) 1/2 (Yoshii & Constantine-Paton, 2010). Indeed, contrary to wild-type animals, D_1 receptor mutant mice, which are unable to acquire a long-term spatial preference in the WM, do not show spatial learning-induced activation of ERK1/2 signaling in the hippocampus (Xing et al., 2010). Interestingly, it has been recently suggested (Moncada, Ballarini, Martinez, Frey, & Viola, 2011; Moncada & Viola 2007) that hippocampal dopamine D_1/D_5 receptors are required to induce the synthesis of plasticity-related proteins able to convert the STM trace resulting from a weak training event, like that generated by a single WM training session, into a long-lasting engram through interaction with synaptic tags, as originally proposed by Frey and Morris (1998). Experiments to evaluate whether a mechanism such as that operates to ensure the persistent storage of spatial memory in the hippocampus are currently being performed.

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