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Rapid Communication

Inactivation of the dorsal hippocampus or the medial prefrontal cortex impairs retrieval but has differential effect on spatial memory reconsolidation

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ABSTRACT

Active memories can incorporate new information through reconsolidation. However, the notion that memory retrieval is necessary for reconsolidation has been recently challenged. Non-reinforced retrieval induces hippocampus and medial prefrontal cortex (mPFC)-dependent reconsolidation of spatial memory in the Morris water maze (MWM). We found that the effect of protein synthesis inhibition on this process is abolished when retrieval of the learned spatial preference is hindered through mPFC inactivation but not when it is blocked by deactivation of dorsal CA1. Our results do not fully agree with the hypothesis that retrieval is unneeded for reconsolidation. Instead, they support the idea that a hierarchic interaction between the hippocampus and the mPFC controls spatial memory in the MWM, and indicate that this cortex is sufficient to retrieve the information essential to reconsolidate the spatial memory trace, even when the hippocampus is inactivated.

1. Introduction

Retrieval is the process of building mnemonic representations from previously acquired information. Retrieval does not necessarily lead to the behavioral expression of such representations, but it always involves reactivation of the stored memory trace. Over the last twenty years much research has focused on the effects of retrieval on memory persistence. Maybe the most significant outcome of this interest has been the rediscovery and development of the hypothesis firstly proposed by Lewis and coworkers almost half a century ago that memories can become labile during retrieval (Lewis, 1969; Lewis & Maher, 1965; Misanin, Miller, & Lewis, 1968) and in order to persist must undergo a protein synthesis-dependent restabilization procss referred to as reconsolidation (Devietti, Conger, & Kirkpatrick, 1977; Judge & Quartermain, 1982; Mactutus, Riccio & Ferek, 1979; Nader, Schafe, & Le Doux, 2000; Przybyslawski, Roullet, & Sara, 1999; Roullet & Sara, 1998). Reconsolidation has now been described in several species, using behavioral tasks modeling different memory types (Anokhin, Tiunova, & Rose, 2002; Bozon, Davis, & Laroche, 2003; Eisenberg & Dudai, 2004; Forcato et al., 2007; Galluccio, 2005; Hernandez, Sadeghian, & Kelley, 2002; Hupbach, Gomez, Hardt, & Nadel, 2007; Inda, Delgado-García, & Carrión, 2005; Lee, Di Ciano, Thomas, & Everitt, 2005; Pedreira, Pérez-Cuesta, & Maldonado, 2002; Perrin et al., 2007; Sangha, Scheibenstock, & Lukowiak, 2003; Torras-Garcia, Lelong, Tronel, & Sara, 2005; Walker, Brakefield, Hobson, & Stickgold, 2003). However, retrieval is not sufficient for reconsolidation but this process seems to be constrained by a wide range of conditions, including age and strength of the memory trace, length of the retrieval session and detection of contingency or relevant new information during this session (Blaiss & Janak, 2007; Blum, Runyan, & Dash, 2006; Cammarota, Bevilaqua, Medina, & Izquierdo, 2004; Eisenberg & Dudai, 2004; Hernandez & Kelley, 2004; Rossato et al., 2007; Wang, de Oliveira Alvares, & Nader, 2009). In fact, there is currently a major quandary in the field as to whether retrieval is indeed necessary to initiate reconsolidation (Gisquet-Verrier & Riccio, 2012; Otis, Dashew, & Mueller, 2013; Rodriguez-Ortiz, Balderas, Garcia-DeLaTorre, & Bermudez-Rattoni, 2012; Sevenster, Beckers, & Kindt, 2012). This is an important matter inasmuch as it has been frequently suggested that modulation of memory reconsolidation might help anxiety disorder patients to overcome the persistent recollection of distressing events (Centonze, Siracusano, Calabresi, & Bernardi, 2005; Milton & Everitt, 2010; Torregrossa & Taylor, 2013). Previously, we reported that the dorsal hippocampus is involved in spatial memory reconsolidation (Rossato, Bevilaqua, Medina, Izquierdo, & Cammarota, 2006). Here, we investigated whether retrieval of the learned spatial preference is indeed necessary for this process.

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2. Materials and methods

2.1. Subjects, surgery and drug infusion procedures

The subjects were experimentally naive male Wistar rats (3 month-old; 280–300 g at the start of the experiments). They were housed in groups of five and maintained at 22–23 °C with free access to food and water under a 12:12 h light/dark cycle (lights on at 06:00 AM). Animals were bilaterally implanted with 22-gauge stainless-steel guide cannulas aimed to the dorsal CA1 region and/or the mPFC (AP −4.2/LL ± 3.0/DV −3.0 and AP + 3.2/LL ± 0.8/DV −4.0, respectively; Paxinos & Watson, 1986) under ketamine/xylazine anesthesia. At the end of surgery, animals were injected with a single dose of meloxicam (0.2 mg/kg) as analgesic and allowed to recover from surgery for at least 4 days before any other procedure. At the time of drug delivery, infusion cannulas were fitted into the guides and injections (1 μl/side) carried out over 60 s with a microinjection pump. 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 last behavioral test, 1 μl of 4% methylene-blue was infused as described above and the extension of the dye 30 min thereafter taken as indication of the diffusion of the drug previously injected.

2.2. Behavioral procedures and data analysis

Behavioral procedures began 5–7 days after surgery. Rats were handled 5 min/day for 3 days prior to training in the hidden-platform version of the MWM. The maze was a matte black circular pool (200 cm in diameter) located in a well-lit white-painted room with several posters and other distal visual stimuli hanging on the walls to provide spatial cues. Concealed two centimeters below the water surface there was a rough textured black escape platform (12 cm in diameter). Training proceeded for 5 days (8 trials/day; 30 s inter-trial interval). A different starting location was used on each trial, which consisted of a swim followed by a 30-s platform sit. This training protocol induces a long-lasting spatial preference (Bonini et al., 2007). Swimming paths were recorded using a video camera mounted above the pool and analyzed with a video tracking and analysis system. A white curtain separated the maze from the room where the computer was set up and the animals housed during the behavioral sessions. All experiments were conducted blind to the treatment condition of the animals and followed the USA National Institutes of Health guidelines for animal care and use. Only data from animals with correct cannula implants were analyzed (185 from a total of 200). Data are expressed as mean ± SEM and were analyzed using Student's *t* test (unpaired) or repeated measures two-way ANOVA followed by Dunnett's multiple comparisons test.

2.3. Drugs

Anisomycin and 5-Aminomethyl-3-hydroxyisoxazole (muscimol) were from Tocris Bioscience or Sigma–Aldrich and were dissolved 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 sterile saline (pH 7.2). The doses used were determined based on pilot experiments and previous studies showing the behavioral effects of each compound.

3. Results

We first investigated the effect of the reversible deactivation of the hippocampus on spatial memory retrieval and reconsolidation. To do that, we trained rats in the MWM and 15 min before a non-reinforced probe test (PT) carried out 24 h after the last training session we inactivated the CA1 region of the dorsal hippocampus by infusing the $GABA_A$ receptor agonist muscimol (MUS; 0.1 μg/

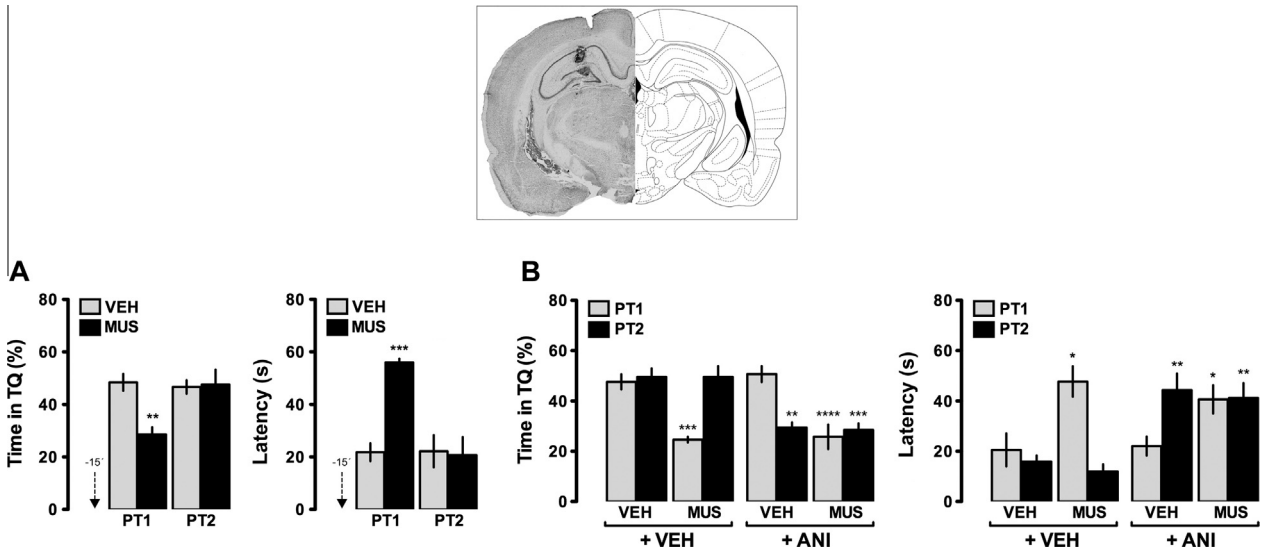

Fig. 1. Pre-test inactivation of the dorsal hippocampus hinders retrieval but does not affect spatial memory reconsolidation. A. Reversible inactivation of the CA1 region of the dorsal hippocampus before a non-reinforced retention test impairs spatial memory retrieval. Animals with cannulas implanted in the CA1 region of the dorsal hippocampus were trained in the spatial version of the MWM during 5 days. Twenty-four hours after the last training session the animals received bilateral intra-CA1 infusions of muscimol (MUS; 0.1 μg/side) and 15 min later were submitted to a probe test in the absence of the escape platform (PT1). A second PT (PT2) was carried out 24 h after PT1; $n = 8$–9 per group, $^{***}p < 0.001$ and $^{**}p < 0.01$ in two-tailed Student's *t*-test. B. Blocking retrieval by inactivating the CA1 region of the dorsal hippocampus does not affect spatial memory reconsolidation in that region. Animals were trained and tested as in A and 15 min before PT1 received bilateral intra-CA1 infusions of VEH or MUS. Immediately after PT1 the animals were given either VEH (+VEH) or the protein synthesis inhibitor anisomycin (160 μg/side; +ANI) in dorsal CA1. Retention was assessed in a second PT (PT2) carried out 24 h later; $n = 6$–11 per group, $^{****}p < 0.0001$, $^{***}p < 0.001$, $^{**}p < 0.01$ and $^{*}p < 0.05$ in Dunnett's multiple comparisons test after repeated measures two-way ANOVA. For Time in TQ during PT1: VEH/+VEH vs MUS/+VEH $q_{(54)} = 4.189$; VEH/+VEH vs MUS/+ANI $q_{(54)} = 4.626$. For Time in TQ during PT2: VEH/+VEH vs VEH/+ANI $q_{(54)} = 3.673$; VEH/+VEH vs MUS/+ANI $q_{(54)} = 4.479$; VEH/+ANI vs MUS/+ANI $q_{(54)} = 0.191$. For Latency during PT1: VEH/+VEH vs MUS/+VEH $q_{(54)} = 3.028$; VEH/+VEH vs MUS/+ANI $q_{(54)} = 2.686$. For Latency during PT2: VEH/+VEH vs VEH/+ANI $q_{(54)} = 3.171$; VEH/+VEH vs MUS/+ANI $q_{(54)} = 3.298$; VEH/+ANI vs MUS/+ANI $q_{(54)} = 0.355$. The photomicrograph shows of a representative Nissl-stained coronal brain section revealing the infusion cannula track terminating in the CA1 region of the dorsal hippocampus.

side). As can be seen in Fig. 1A, pre-test MUS blocked retrieval of the learned spatial preference during the first PT ($t_{(15)} = 4.610$, $p < 0.01$ and $t_{(15)} = 9.099$, $p < 0.001$; for time in the target quadrant [Time in TQ] and latency to swim over the previous location of the escape platform [Latency], respectively), but this effect was only transient and spatial memory was completely recovered during a second PT 24 h later. Confirming earlier results (Rossato et al., 2006), the protein synthesis inhibitor anisomycin (ANI; 160 μg/side) hindered subsequent spatial memory retention when given in dorsal CA1 immediately after a PT in the absence of the escape platform. Inhibiting retrieval of the learned spatial preference by infusing MUS in dorsal CA1 15 min before the non-reinforced PT did not affect the amnesia induced by ANI (Fig. 1B; Time in TQ: $F_{(3,27)} = 21.990$, $p < 0.0001$ for treatment and $F_{(3,27)} = 7.652$, $p = 0.0007$ for treatment × session interaction; $q_{(54)} = 4.479$, $p < 0.001$ for VEH/+VEH vs. MUS/+ANI and $q_{(54)} = 0.191$, $p > 0.05$ for VEH/+ANI vs. MUS/+ANI during PT2; Latency: $F_{(3,27)} = 5.290$, $p < 0.005$ for treatment and $F_{(3,27)} = 7.321$, $p = 0.001$ for treatment x session interaction; $q_{(54)} = 3.298$, $p < 0.01$ for VEH/+VEH vs. MUS/+ANI and $q_{(54)} = 0.355$, $p > 0.05$ for VEH/+ANI vs. MUS/+ANI during PT2).

Spatial navigation recruits not only the hippocampus but also several extra-hippocampal structures (Cain & Saucier, 1996). For example, the medial prefrontal cortex (mPFC) plays a significant

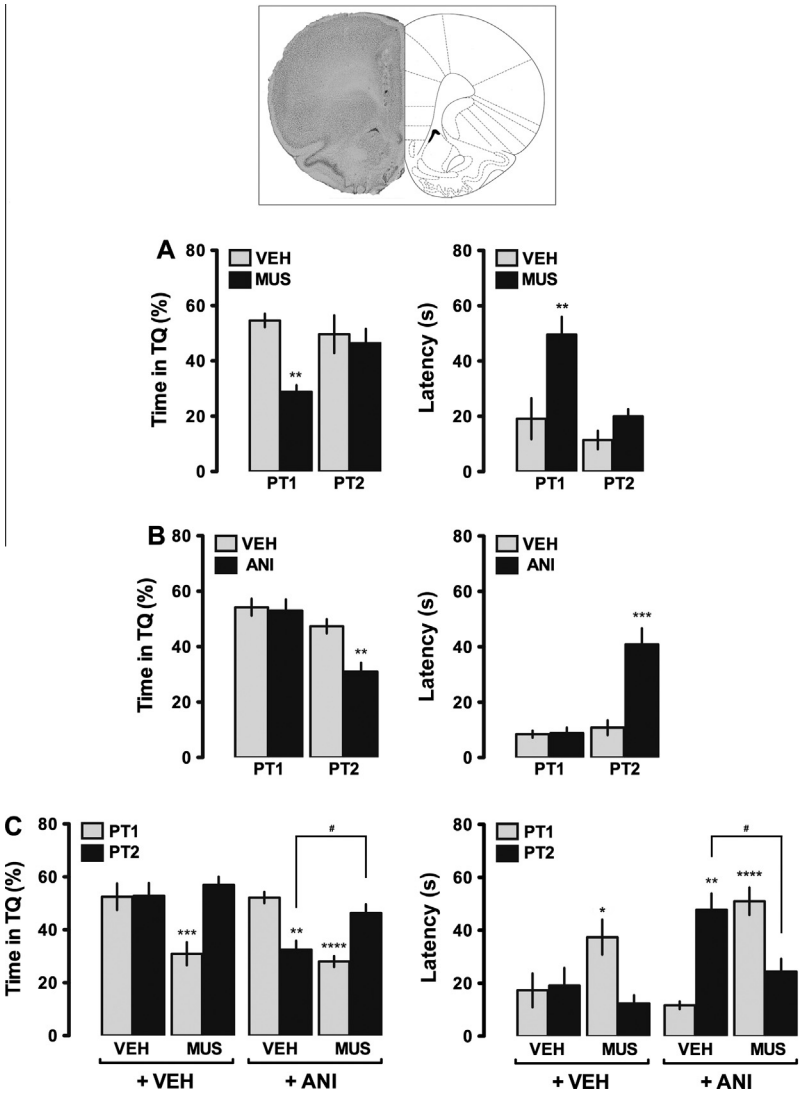

Fig. 2. Spatial memory reconsolidation in the mPFC requires activation of this cortex during the non-reinforced retention test session. A. Reversible inactivation of mPFC before a non-reinforced retention test impairs spatial memory retrieval. Animals with cannulas implanted in mPFC were trained in the spatial version of the MWM during 5 days. Twenty-four hours after the last training session the animals received bilateral intra-mPFC infusions of muscimol (MUS; 0.1 μg/side) and 15 min later were submitted to a probe test in the absence of the escape platform (PT1). A second PT (PT2) was carried out 24 h after PT1; $n = 7$ per group, $^{***}p < 0.001$ and $^{**}p < 0.01$ in two-tailed Student's *t*-test. B. mPFC is necessary for reconsolidation of spatial memory. Animals were trained and tested as in A and immediately after PT1 received bilateral intra-mPFC infusions of VEH or ANI (160 μg/side). Retention was assessed in a second PT (PT2) carried out 24 h later; $n = 8$–10 per group, $^{***}p < 0.001$ and $^{**}p < 0.01$ in two-tailed Student's *t*-test. *C.* Blocking retrieval by inactivating the mPFC impedes the amnesia caused by inhibition of protein synthesis in that cortex after the retention test. Animals were trained and tested as in A and 15 min before PT1 received bilateral intra-mPFC infusions of VEH or MUS (0.1 μg/side). Immediately after PT1 the animals were given either VEH (+VEH) or ANI (160 μg/side; +ANI) in mPFC. Retention was assessed in a second PT (PT2) carried out 24 h later; $n = 7$–13 per group, $^{****}p < 0.0001$, $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$ and $^{\#}p < 0.05$ in Dunnett's multiple comparisons test after repeated measures two-way ANOVA. For Time in TQ during PT1: VEH/+VEH vs MUS/+VEH $q_{(66)} = 4.080$; VEH/+VEH vs MUS/+ANI $q_{(66)} = 5.009$. For Time in TQ during PT2: VEH/+VEH vs VEH/+ANI $q_{(66)} = 3.616$; VEH/+VEH vs MUS/+ANI $q_{(66)} = 1.323$; VEH/+ANI vs MUS/+ANI $q_{(66)} = 2.724$. For Latency during PT1: VEH/+VEH vs MUS/+VEH $q_{(66)} = 2.489$; VEH/+VEH vs MUS/+ANI $q_{(66)} = 4.519$. For Latency during PT2: VEH/+VEH vs VEH/+ANI $q_{(66)} = 3.337$; VEH/+VEH vs MUS/+ANI $q_{(66)} = 0.706$; VEH/+ANI vs MUS/+ANI $q_{(66)} = 3.007$. The photomicrograph shows of a representative Nissl-stained coronal brain section revealing the infusion cannula track terminating in the mPFC.

role in navigation efficiency by controlling the reactivation of spatial information maintained in the hippocampus (Jo et al., 2007). This cortex is also involved in retrieving information about where events occurred (DeVito & Eichenbaum, 2010) and participates in error detection and executive control (Euston, Gruber, & McNaughton, 2012). We found that intra-mPFC infusion of MUS (0.1 μg/side) 15 min before a non-reinforced PT performed 24 h after the last MWM training session impaired spatial memory retrieval in that PT but not in a second one carried out 24 h later (Fig. 2A, PT1; $t_{(12)} = 7.638$, $p < 0.001$ for Time in TQ and $t_{(12)} = 3.087$, $p < 0.01$ for Latency). Besides, when given in the mPFC immediately after retrieval, ANI (160 μg/side) hindered memory persistence (Fig. 2B, PT2; $t_{(16)} = 3.829$, $p < 0.01$ for Time in TQ and $t_{(16)} = 4.868$, $p < 0.001$ for Latency), indicating that the mPFC is necessary not only for retrieval but also for reconsolidation of spatial memory. Pre-PT intra-mPFC administration of MUS abolished the amnesic effect of the post-PT intra-mPFC infusion of ANI (Fig. 2C; Time in TQ: $F_{(3,33)} = 6.556$, $p = 0.0013$ for treatment and $F_{(3,33)} = 14.670$, $p < 0.0001$ for treatment × session interaction; $q_{(66)} = 1.323$, $p > 0.05$ for VEH/+VEH vs. MUS/+ANI and $q_{(66)} = 2.724$, $p < 0.05$ for VEH/+ANI vs. MUS/+ANI during PT2; Latency: $F_{(3,33)} = 4.002$, $p < 0.015$ for treatment and $F_{(3,33)} = 17.339$, $p < 0.0001$ for treatment × session interaction; $q_{(66)} = 0.706$, $p > 0.05$ for VEH/+VEH vs. MUS/+ANI and $q_{(66)} = 3.007$, $p < 0.05$ for VEH/+ANI vs. MUS/+ANI during PT2). Moreover, pre-PT intra-mPFC infusion of MUS also impeded the amnesia caused by giving ANI in dorsal CA1 immediately after that same PT (Fig. 3A; Time in TQ: $F_{(3,33)} = 4.284$, $p = 0.0117$ for treatment and $F_{(3,33)} = 16.990$, $p < 0.0001$ for treatment × session interaction; $q_{(66)} = 0.571$, $p > 0.05$ for VEH/+VEH vs. MUS/+ANI and $q_{(66)} = 4.550$, $p < 0.0001$ for VEH/+ANI vs. MUS/+ANI during PT2; Latency: $F_{(3,33)} = 13.870$, $p < 0.0001$ for treatment and $F_{(3,33)} = 24.320$, $p < 0.0001$ for treatment × session interaction; $q_{(66)} = 1.754$, $p > 0.05$ for VEH/+VEH vs. MUS/+ANI and $q_{(66)} = 4.006$, $p < 0.0001$ for VEH/+ANI vs. MUS/+ANI during PT2). On the contrary, blocking spatial memory retrieval by infusing MUS in dorsal CA1 had no effect on the amnesia induced by the post-PT intra-mPFC administration of ANI (Fig. 3B; Time in TQ: $F_{(3,27)} = 16.940$, $p < 0.0001$ for treatment and $F_{(3,27)} = 7.393$, $p = 0.0009$ for treatment x session interaction; $q_{(54)} = 4.330$, $p < 0.001$ for VEH/+VEH vs. MUS/+ANI and $q_{(54)} = 0.726$, $p > 0.05$ for VEH/+ANI vs. MUS/+ANI during PT2; Latency: $F_{(3,27)} = 21.660$, $p < 0.0001$ for treatment and $F_{(3,27)} = 18.110$, $p < 0.0001$ for treatment × session interaction; $q_{(54)} = 5.821$, $p < 0.0001$ for VEH/+VEH vs. MUS/+ANI and $q_{(54)} = 0.318$, $p > 0.05$ for VEH/+ANI vs. MUS/+ANI during PT2).

4. Discussion

Our results confirm that the hippocampus is necessary for retrieval of a spatial preference in the MWM, and indicate that the mPFC is engaged during this process. This last observation is in agreement with findings showing that the mPFC is required

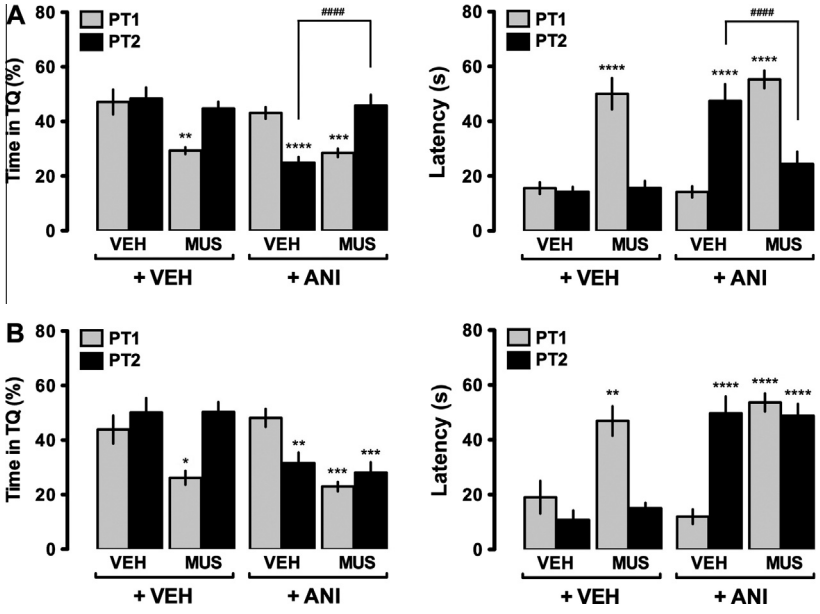

Fig. 3. Spatial memory reconsolidation in the hippocampus requires activation of the mPFC during the non-reinforced retention test session. A. Blocking retrieval by inactivating the mPFC impedes the amnesia caused by inhibition of protein synthesis in the CA1 region of the dorsal hippocampus after the retention test. Animals with cannulas implanted in dorsal CA1 and the mPFC were trained in the spatial version of the MWM during 5 days. Twenty-four hours after the last training session the animals received bilateral intra-mPFC infusions of muscimol (MUS; 0.1 μg/side) and 15 min later were submitted to a probe test in the absence of the escape platform (PT1). Immediately after PT1 the animals were given either VEH (+VEH) or the protein synthesis inhibitor anisomycin (160 μg/side; +ANI) in dorsal CA1. Retention was assessed in a second PT (PT2) carried out 24 h later; $n = 7$–15 per group. $^{****}p < 0.0001$, $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$ and $^{\#\#\#\#}p < 0.0001$ in Dunnett's multiple comparisons test after repeated measures two-way ANOVA. For Time in TQ during PT1: VEH/+VEH vs MUS/+VEH $q_{(66)} = 3.438$; VEH/+VEH vs MUS/+ANI $q_{(66)} = 4.259$. For Time in TQ during PT2: VEH/+VEH vs VEH/+ANI $q_{(66)} = 4.507$; VEH/+VEH vs MUS/+ANI $q_{(66)} = 0.571$; VEH/+ANI vs MUS/+ANI $q_{(66)} = 4.550$. For Latency during PT1: VEH/+VEH vs MUS/+VEH $q_{(66)} = 5.244$; VEH/+VEH vs MUS/+ANI $q_{(66)} = 7.148$. For Latency during PT2: VEH/+VEH vs VEH/+ANI $q_{(66)} = 5.027$; VEH/+VEH vs MUS/+ANI $q_{(66)} = 1.754$; VEH/+ANI vs MUS/+ANI $q_{(66)} = 4.006$. B. Blocking retrieval by inactivating the CA1 region of the dorsal hippocampus does not impede the amnesia caused by inhibition of protein synthesis in the mPFC after the retention test. Animals with cannulas implanted in dorsal CA1 and the mPFC were trained in the spatial version of the MWM during 5 days. Twenty-four hours after the last training session the animals received bilateral intra-CA1 infusions of muscimol (MUS; 0.1 μg/side) and 15 min later were submitted to a probe test in the absence of the escape platform (PT1). Immediately after PT1 the animals were given either VEH (+VEH) or the protein synthesis inhibitor anisomycin (160 μg/side; +ANI) in mPFC. Retention was assessed in a second PT (PT2) carried out 24 h later; $n = 6$–12 per group. $^{****}p < 0.0001$, $^{***}p < 0.001$, $^{**}p < 0.01$ and $^{*}p < 0.05$ in Dunnett's multiple comparisons test after repeated measures two-way ANOVA. For Time in TQ during PT1: VEH/+VEH vs MUS/+VEH $q_{(54)} = 3.009$; VEH/+VEH vs MUS/+ANI $q_{(54)} = 4.099$. For Time in TQ during PT2: VEH/+VEH vs VEH/+ANI $q_{(54)} = 3.271$; VEH/+VEH vs MUS/+ANI $q_{(54)} = 4.330$; VEH/+ANI vs MUS/+ANI $q_{(54)} = 0.726$. For Latency during PT1: VEH/+VEH vs MUS/+VEH $q_{(54)} = 3.789$; VEH/+VEH vs MUS/+ANI $q_{(54)} = 5.359$. For Latency during PT2: VEH/+VEH vs VEH/+ANI $q_{(54)} = 5.503$; VEH/+VEH vs MUS/+ANI $q_{(54)} = 5.821$; VEH/+ANI vs MUS/+ANI $q_{(54)} = 0.318$.

for spatial navigation when allocentric information is degraded (Jo & Choi, 2014), and corroborates a report published while this manuscript was in preparation (Cholvin et al., in press). Our data also confirm earlier findings showing that the hippocampus participates in the reconsolidation of spatial memory in the MWM (Bonini et al., 2007; Da Silva et al., 2008; Rossato et al., 2006) and demonstrate the functional role of the mPFC in this process. One conclusion that can be drawn from our experiments is that the hippocampus and the mPFC are involved in different aspects of memory retrieval, which is indeed necessary for reconsolidation of a learned spatial preference in the MWM. The first premise of this assertion is in keeping with previous theoretical considerations (Preston & Eichenbaum, 2013), but the second one does not concur with recent reports showing that retrieval is unneeded to trigger the reconsolidation of other types of representations (Ben-Mamou, Gamache, & Nader, 2006; Milton et al., 2013; Santoyo-Zedillo, Rodriguez-Ortiz, Chavez-Marchetta, Bermudez-Rattoni, & Balderas, 2014). However, it must be borne in mind that despite the careful combination of drugs acting on several neurotransmitter or neuromodulatory systems at different times before and after the reactivation test, those studies entailed the analysis of a single brain region and, maybe, were unable to fully grasp the anatomical and functional complexity of memory retrieval, which engages the hierarchical participation and interaction of many brain structures (Henson & Gagnepain, 2010). The existence of such hierarchic organization for the case of spatial memory in the MWM is indicated by the fact that blocking retrieval by temporary inactivation of the mPFC hindered the amnesic effect of post-test ANI not only in that cortex but also in the hippocampus, whereas hampering retrieval by deactivating the hippocampus had not effect on the amnesia induced by inhibiting protein synthesis in any of these two regions. The main suggestion of our work is that spatial memory retrieval requires the reactivation of a distributed network that includes the hippocampus, and that without this mPFC-mediated reactivation, reconsolidation cannot occur. Indeed, there is ample evidence that the hippocampus and the mPFC interact during spatial memory processing (Churchwell & Kesner, 2011; Gordon, 2011; Lee & Kesner, 2003) and it has been suggested that the mPFC exerts top-down control of memory retrieval by influencing hippocampal activity (Anderson & Levy, 2009; Munakata et al., 2011). Preliminary results from our lab indicate that blocking NMDA receptors in the hippocampus prevents spatial memory retrieval but not reconsolidation, suggesting that mPFC-mediated reactivation of memory circuits in the hippocampus does not engage these receptors. In any case, it seems plausible to assume that retrieval of a spatial preference in the MWM requires more than just the reactivation of a hippocampal spatial map. This map would be worthless if the animals were unable to recognize where they are and what they have to look for when reintroduced into the maze or if, once there, they were incapable of forming a suitable representation and planning an escape strategy.

There is ample evidence that the mPFC is vital for these functions and also for setting up memory reactivation and monitoring the contents of the reactivated engram (Cholvin et al., 2013; Preston & Eichenbaum, 2013; Sakai, 2003; Yang, Shi, Wang, Peng, & Li, 2014). The hypothesis that retrieval is not necessary for reconsolidation is inconsistent with findings showing that spatial memory reconsolidation happens only after non-reinforced reactivation (Morris et al., 2006; Rossato et al., 2006) which, in turn, are in agreement with the broadly accepted idea that discrepancy between the animal's prediction and what actually occurs during the reactivation session is essential to induce reconsolidation (Diaz-Mataix, Martinez, Schafe, LeDoux, & Doyere, 2013; Pedreira, Pérez-Cuesta, & Maldonado, 2004; Sevenster et al., 2012). Predictions demand the construction of anticipatory mnemonic representations of the past (i.e. memory retrieval); it goes without saying that realization that a prediction was incorrect requires the same.

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