Ventromedial Prefrontal Cortex Is Obligatory for Consolidation and Reconsolidation of Object Recognition Memory

Once consolidated, a long-term memory item could regain susceptibility to consolidation blockers, that is, reconsolidate, upon its reactivation. Both consolidation and reconsolidation require protein synthesis, but it is not yet known how similar these processes are in terms of molecular, cellular, and neural circuit mechanisms. Whereas most previous studies focused on aversive conditioning in the amygdala and the hippocampus, here we examine the role of the ventromedial prefrontal cortex (vmPFC) in consolidation and reconsolidation of object recognition memory. Object recognition memory is the ability to discriminate the familiarity of previously encountered objects. We found that microinfusion of the protein synthesis inhibitor anisomycin or the N-methyl-D-aspartate (NMDA) receptor antagonist D,L-2-amino-5-phosphonovaleric acid (APV) into the vmPFC, immediately after training, resulted in impairment of long-term (24 h) but not short-term (3 h) recognition memory. Similarly, microinfusion of anisomycin or APV into the vmPFC immediately after reactivation of the long-term memory impaired recognition memory 24 h, but not 3 h, post-reactivation. These results indicate that both protein synthesis and NMDA receptors are required for consolidation and reconsolidation of recognition memory in the vmPFC.

Keywords: anisomycin, consolidation, NMDA, object recognition memory, reconsolidation, ventromedial prefrontal cortex

Introduction

Memory consolidation refers to the progressive post-acquisition stabilization of the memory trace (Dudai 2002). Ample research has shown that shortly after learning, memory traces are fragile and susceptible to disruption by various agents (Bailey and others 1996; McGaugh 2000; Dudai 2004). It has also been demonstrated that once consolidated, a long-term memory item could be again rendered labile and susceptible to disruption upon its reactivation, in a process dubbed “reconsolidation” (Sara 2000; Nader and others 2000a, 2000b; Eisenberg and others 2003).

Both consolidation and reconsolidation require protein synthesis and share molecular processes and brain circuits, though the neuronal mechanisms involved do not completely overlap (Przybyslawski and Sara 1997; Przybyslawski and others 1999; Nader and others 2000a; Taubenfeld and others 2001; Anokhin and others 2002; Debiec and others 2002; Kida and others 2002; Milekic and Alberini 2002; Pedreira and others 2002; Nader 2003; Duda 2004; Inda and others 2005; Torras-Garcia and others 2005; von Hertzen and Giese 2005).

Most studies of reconsolidation and its affinity to consolidation have so far focused on the role of the amygdala and the hippocampus (Nader and others 2000a; Debiec and others 2002; Kelly and others 2003; Lec and others 2004; Duvarci and others 2005; Wang and others 2005) using mostly aversive conditioning (reviewed in Dudai 2004). Here, we aimed to examine consolidation and potential reconsolidation in a brain region so far unaddressed in this type of studies, the ventromedial prefrontal cortex (vmPFC). The vmPFC is implicated in interrelated “supervisory” attentional functions, including attention to stimulus features and task contingencies (for review, see Dalley and others 2004), and in the storage of long-term memory and plasticity (Jay and others 1995; Taikita and others 1999; Quirk and others 2000; Maroun and Richer-Levin 2003; Santini and others 2004). Specifically, there is evidence to suggest that the prefrontal cortex (PFC) has a role in discrimination of object familiarity. For example, in both primates and rats, lesions of the PFC disrupt performance on familiarity discrimination tasks (Bachevalier and Mishkin 1986; Meunier and others 1997; Ragozzino and others 2002).

Further, we have selected an incidental rather than aversive learning paradigm. Toward that end, we used an object recognition task, which relies on the spontaneous exploratory behavior of the rat (Ennaceur and Delacour 1988). In other studies that compare consolidation and reconsolidation, usually during the consolidation phase a reinforcing stimulus is present, which is absent in the reconsolidation phase, thereby confounding the interpretation of the comparison (Nader 2003). The object recognition task, on the other hand, does not involve an explicit exogenous reinforcer in the consolidation or reconsolidation phases.

In the present study, we first asked if the vmPFC is obligatory for the consolidation of object recognition memory. This we probed by microinfusing immediately after training the protein synthesis inhibitor anisomycin or the N-methyl-D-aspartate (NMDA) receptor antagonist D,L-2-amino-5-phosphonovaleric acid (APV) into the vmPFC. Next, we asked if the vmPFC is necessary for the reconsolidation of object recognition memory, by microinfusing anisomycin or APV into the vmPFC immediately following the reactivation of the memory. Our results show that the long-term object recognition memory reconsolidates, that the vmPFC is obligatory for both consolidation and reconsolidation, and that protein synthesis and NMDA receptor function are required for both processes.

Materials and Methods

Animals

A total of 124 male Wistar rats (~60 days old, 250–300 g) were used for the experiments. Animals were caged individually at 22 ± 2 °C under 12-h light/dark cycles. Water and food were available ad libitum.

The experiments were approved by the University of Haifa Ethics and Animal Care Committee, and adequate measures were taken to minimize pain or discomfort in accordance with the guidelines laid

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down by the National Institutes of Health in the United States of America regarding the care and use of animals for experimental procedures.

**Drugs**

Anisomycin and APV were from Sigma (St Louis, MO). Anisomycin (100 μg/1 μl) was dissolved in 1 M HCl, diluted in saline, and adjusted to pH 7.5 with NaOH. APV (2.5 μg/1 μl) was dissolved in saline, which was also used as the vehicle control.

**Surgery and Drug Administration**

Rats were anesthetized with 4.8 ml/kg equithesin (2.12% w/v MgSO₄, 10% v/v ethanol, 39.1% v/v propylene glycol, 0.98% w/v sodium pentobarbital, and 4.2% w/v chloral hydrate), restrained in a stereotactic apparatus (David Kopf Instruments, Tujunga, CA), and implanted bilaterally with stainless steel guide cannula (23 gauge, thin wall) aimed at the infralimbic (IL) and prelimbic areas (together compose the vmPFC), anteroposterior, +3 mm relative to bregma; lateral, ±0.05 mm; ventral, −5 mm; Paxinos and Watson 1998). The cannulae were positioned in place with acrylic dental cement and secured by 2 skull screws. A stylos was placed in the guide cannula to prevent clogging. Animals were allowed 1 week to recuperate before being subjected to experimental manipulations.

For microinfusion, the stylos was removed from the guide cannula, and a 28-gauge injection cannula, extending 1.0 mm from the tip of the guide cannula, was inserted. The injection cannula was connected via PE20 tubing to a Hamilton microsyringe driven by a microinfusion pump (CMA/100; Carnegie Medicin, Stockholm, Sweden). Microinfusion was performed bilaterally in a 1-μl volume delivered over 2 min. The injection cannula was left in position before withdrawal for an additional 1 min to minimize dragging of the injected liquid along the injection tract. Two rats were excluded from the experiment for cannula blockade.

**Object Recognition Task**

Object recognition memory is the ability to discriminate the familiarity of previously encountered objects. It was tested in a paradigm based on spontaneous exploration behavior of the rat (Ennaceur and Delacour 1988). If a rat is presented with both a familiar object and a novel object, it will direct more exploration at the novel object. The objects were located in a squared, black open field (50 x 50 x 50 cm) placed under dim light. All the rats were habituated to the experimental apparatus by allowing them to explore it for 10 min twice a day for 5 days in the absence of objects before the experiment was performed. Objects were children’s toys and were fixed to the floor of the open field arena, 10 cm from the walls. From rat to rat, the role (familiar or new object) as well as the relative position of the 2 objects were counterbalanced and randomly permuted. The open field and the objects were cleaned thoroughly between trials with odorous clean wipes. Exploration was defined as sniffing or touching the object with the nose and/or forepaws. Turning around or sitting on the object is not considered as exploratory behavior.

A discrimination index calculated for each animal was expressed as $T_f / (T_f + T_N)$ ($T_f$ = time spent exploring the familiar object, $T_N$ = time spent exploring the novel object). The amount of time exploring each object was recorded by an observer blind to the treatment. Intact recognition memory on the test phase is reflected in a discrimination score higher than 0.5, which implies greater exploration of the novel object. Four rats were excluded from the experiment for not accumulating a minimum of 25 s of object exploration.

**Consolidation Protocol**

During the sample phase (day 1), each rat was placed in the open field and allowed to explore 2 different objects (A and B) for 5 min. The test phase was given 3 h after the sample trial (short-term retrieval) or 24 h (long-term retrieval; day 2) after the sample trial. During the 5-min test trial, the rat was presented with a duplicate of an object from the sample/reactivation trial and a novel object (A and C). Vehicle, anisomycin, or APV were microinfused into the vmPFC immediately (approximately 2 min) following the reactivation phase on day 2.

**Reconsolidation Protocol**

In the sample phase (day 1), rats were exposed to 2 objects (A and B) for 5 min as described above. Twenty-four hours later (day 2), they were exposed to the same 2 sample objects (A and B) for a 5-min period to reactivate the memory trace. The test phase was given 3 h after the reactivation trial (short-term retrieval) or 24 h (long-term retrieval; day 3) after the reactivation trial. During the 5-min test trial, the rat was presented with a duplicate of an object from the sample/reactivation trial and a novel object (A and C). Vehicle, anisomycin, or APV were microinfused into the vmPFC immediately (approximately 2 min) following the reactivation phase on day 2.

**Histology**

At the completion of the behavioral experiments, animals were anesthetized and microinfused into the vmPFC with 0.5 μl of India ink. Cannula location was examined under a light microscope following Nissl staining. Figure 1 shows schematic drawing of vmPFC cannula placements (coronal view at position 3.20 and 2.70 mm anterior to bregma; Paxinos and Watson 1998). Solid black circles indicate the cannulae tip positions. Four rats were excluded from the experiment for cannula misplacement.

**Statistics**

Differences were determined using between-groups analysis of variance (ANOVA) and $t$-test. All post hoc comparisons were made using the least significant difference multiple comparison test.

**Results**

**Anisomycin and APV Impair Consolidation of Long-Term Object Recognition Memory in the vmPFC, without Affecting Short-Term Recognition Memory**

Animals microinfused with anisomycin (Aniso, $n = 7$) or APV ($n = 9$) into the vmPFC immediately following the sample phase displayed impaired ability to discriminate between the old and new objects in the test, 24 h after the sample (Fig. 2A). ANOVA showed a significant difference between the groups in discrimination index ($F_{2,28} = 10.496, P < 0.001$) on day 2. Post hoc comparisons revealed that the vehicle group ($n = 15$) spent significantly more time exploring the new object compared with the Aniso ($P = 0.002$) and the APV ($P < 0.001$) groups ($t$-test for difference from 0.5 in the vehicle group: $t_{14} = 7.676, P < 0.001$). There was no significant difference in the sample
Figure 2. Consolidation of recognition memory. (A) Animals were exposed to 2 objects for 5 min (day 1; A and B) and immediately afterward were microinfused into the vmPFC with vehicle, anisomycin, or APV. On day 2, rats were reexposed to a familiar object and to a new object (A and C) for 5 min. Data are presented as ratio of the time spent exploring the new object compared with the Aniso (Figure 2B). A time point of 3 h is conventionally considered as short-term memory in behaving animals (McGaugh 1966; Dudai 2004).

All groups explored the new object in the test phase (t test for difference from 0.5 in the vehicle group: \( t_2 = 11.119, P < 0.001 \); Aniso: \( t_2 = 7.177, P < 0.01 \); APV: \( t_2 = 6.779, P < 0.001 \)).

There was no significant difference between the groups in discrimination index in the sample phase (\( F_{2,15} < 1 \), NS) or in the test phase, 3 h after the microinfusion (\( F_{2,15} < 1 \), NS). Furthermore, there was no significant difference between the groups in their total exploration time during the sample (\( F_{2,28} < 1 \), NS) or the test (\( F_{2,28} < 1 \), NS) phase. Thus, protein synthesis and NMDA function in the vmPFC are not required for short-term recognition memory.

In order to demonstrate that long-term memory consolidation is not impaired when the time between the sample phase and the infusion is delayed, rats were microinfused with the drugs into the vmPFC following exposure to the arena with no objects. Thus, in the sample phase (day 1), rats were exposed to 2 objects (A and B) for 5 min. Twenty-four hours later (day 2), they were exposed to the open field for a 5-min period, with no objects in the arena. Immediately afterward, rats were infused with vehicle (n = 8), anisomycin (n = 6), or APV (n = 6) into the vmPFC and were tested on day 3. All groups showed significant preference to explore more the new object in the test phase (t test for difference from 0.5 in the vehicle group: \( t_5 = 8.668, P < 0.001 \); Aniso: \( t_5 = 10.847, P < 0.01 \); APV: \( t_5 = 5.646, P = 0.01 \); Fig. 2C).

Table 1

<table>
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<th>Figure</th>
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<td>33.3 ± 5.1</td>
<td>39.6 ± 3.9</td>
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Note: Data are presented as means ± standard error of the mean.
There was no significant difference between the groups in discrimination index in the sample phase ($F_{2,17} < 1$, NS) or in the test phase 24 h after the microinfusion ($F_{2,17} < 1$, NS). Furthermore, there was no significant difference between the groups in their total exploration time during the sample ($F_{2,17} < 1$, NS) or the test ($F_{2,17} < 1$, NS) phase.

Anisomycin and APV Impair Reconsolidation of Long-Term Object Recognition Memory in the vmPFC, without Affecting Post-Reactivation Short-Term Recognition Memory

We have shown in Figure 2C that microinfusing the drugs after exposure to the arena with no objects did not affect memory consolidation. Next, we aimed to examine whether microinfusing the drugs immediately following reactivation of the memory trace with objects in the arena would affect memory reconsolidation. Thus, animals were microinfused with vehicle ($n = 7$), anisomycin (Aniso, $n = 7$), or APV ($n = 6$) into the vmPFC immediately following reactivation on day 2 (Fig. 3A). ANOVA unveiled a significant difference between the groups in discrimination index in the test on day 3 ($F_{2,18} = 8.219, P = 0.003$). Post hoc comparisons revealed that the vehicle group spent significantly more time exploring the new object compared with the Aniso ($P = 0.001$) and the APV ($P = 0.009$) groups ($t$-test for difference from 0.5 in the vehicle group: $t_6 = 5.309, P = 0.002$).

There was no significant difference between the groups in discrimination index on day 1 ($F_{2,18} < 1$, NS) or day 2 ($F_{2,18} < 1$, NS). Furthermore, there was no significant difference between the groups in their total exploration time during the sample ($F_{2,18} < 1$, NS), reactivation ($F_{2,18} < 1$, NS), or test ($F_{2,18} < 1$, NS) phase.

We further examined the involvement of NMDA receptors in the vmPFC in post-reactivation short-term memory. Animals were vmPFC microinfused with vehicle ($n = 6$), anisomycin ($n = 5$), or APV ($n = 6$) immediately following the reactivation phase (Fig. 3B). After 3 h, rats were reexposed to a familiar object and to a new object (A and C) for 5 min. All groups explored the new object in the test phase ($t$-test for difference from 0.5 in the vehicle group: $t_6 = 8.556, P < 0.001$; Aniso group: $t_5 = 10.811, P < 0.001$; APV group: $t_6 = 7.16, P < 0.01$).

There was no significant difference between the groups in discrimination index in the sample ($F_{2,14} < 1$, NS), reactivation ($F_{2,14} < 1$, NS), or test phase 3 h after the microinfusion ($F_{2,14} = 2.689$, NS). Furthermore, there was no significant difference between the groups in their total exploration time during the sample ($F_{2,14} < 1$, NS), reactivation ($F_{2,14} < 1$, NS), or test ($F_{2,14} < 1$, NS) phase. Thus, protein synthesis and NMDA function in the vmPFC are not required for short-term postreactivation recognition memory.

To determine the upper limit of the time window of reconsolidation, we exposed rats to 2 objects for 5 min (A and B, sample phase). Twenty-four hours later (day 2), rats were exposed to the same 2 sample objects (A and B) for a 5-min period to reactivate the memory trace. Three hours following the reactivation in day 2, animals were vmPFC microinfused...
with vehicle, anisomycin, or APV (n = 7 each). On day 3, rats were reexposed to a familiar object and to a new object (A and C) for 5 min. All the groups explored the new object in the test phase (Fig. 3C). f-test for difference from 0.5 in the vehicle group: t0 = 4.041, P = 0.002; Aniso: t0 = 7.716, P < 0.001; APV: t0 = 3.43, P = 0.014.

There was no significant difference between the groups in discrimination index on day 1 (F2,18 < 1, NS), day 2 (F2,18 = 1.59, NS), or day 3 (F2,18 = 1.355, NS). Thus, 3 h following reactivation, the memory trace is no longer susceptible to disruption by protein synthesis and NMDA blockers.

Importantly, because both drugs had no effect on reconsolidation using this time window, the effects of the drugs on consolidation and reconsolidation cannot be attributed to neurotoxicity or general impairment. Furthermore, there was no significant difference between the groups in their total exploration time during the sample (F2,18 < 1, NS), reactivation (F2,18 < 1, NS), or test (F2,18 < 1, NS) phase. Thus, protein synthesis and NMDA function in the vmPFC are not required for short-term post-reactivation recognition memory.

Discussion

In this paper, we show that the vmPFC is required for consolidation of long-term visually guided recognition memory in the rat, that this memory undergoes reconsolidation upon its reactivation, and that the vmPFC is also required for the reconsolidation process. Our data further suggest that protein synthesis and NMDA receptors are required for both consolidation and reconsolidation of recognition memory in the vmPFC. The fact that anisomycin and APV infused 3 h following reactivation had no effect on reconsolidation strongly suggests that the blocking effects of the drugs used in this study should not be attributed to neurotoxicity or general impairment. Infusion sites were located in the vmPFC, mainly in the IL subdivision; yet, although we used a small infusion volume (0.5 µl/side), the drugs may have spread to adjacent areas.

Importantly, we showed that exposure to the objects and not merely the arena is necessary for the drugs to affect memory. Thus, when the time between the sample phase and the infusion is delayed, long-term memory consolidation is not affected. However, when animals were exposed to the arena with objects (i.e., reactivation of the memory trace) and then infused with the drugs, long-term memory reconsolidation was impaired. Thus, this supports that memory consolidation can in fact be compromised if the same sample phase is reintroduced.

Blocking protein synthesis and NMDA receptors in vmPFC immediately after the sample phase resulted in failure to discriminate the old from the new object 24 h later. This disruption of the consolidation phase is congruent with other studies, mostly in monkeys, indicating a role for the medial PFC in object recognition memory (Bachevalier and Mishkin 1986; Meunier and others 1997; Giovannini and others 1998; Parker and others 1998; Rainer and Miller 2000; Ragozzino and others 2002; Xiang and Brown 2004). Our data, however, are incongruent with other studies in which medial PFC lesions in the rat had no effect on performance in object recognition task (Ennaceur and others 1997; Mitchell and Laiacona 1998; Mogensen and others 2004). It should be noted, nevertheless, that the lesions performed in those above-mentioned studies usually did not include the IL cortex, and the rats were tested only shortly (less than 3 h) after the exposure to the sample. Yet, although we find that vmPFC is critical for object recognition memory, clearly other brain regions, particularly the perirhinal cortex, also play a critical role in this type of task (Murray and Richmond 2001; Holscher and Rolls 2002; Winters and Bussey 2005).

In contrast to its effects on consolidation of long-term memory, blocking protein synthesis or NMDA receptors did not impair performance 3 h after the sample or the reactivation phase. The fact that anisomycin did not affect the performance in the test corresponds with many studies showing that short-term memory is independent of protein synthesis (McGaugh 2000; Kandel 2001). The preference for the new object during the 3-h test demonstrates that short-term memory is intact and that the drug did not have any nonspecific effects on long-term memory. Further support to our findings comes from studies showing that NMDA antagonists impair consolidation of long-term memory, but not short-term memory, using conditioned taste aversion (Ferreira and others 2002), fear conditioning (Kim and others 2002), and spatial learning (Steele and Morris 1999). Moreover, it has been shown that NMDA receptors are required for consolidation and reconsolidation of an odor-reward association task (Tronel and Sara 2003; Torras-Garcia and others 2005). It has been recently proposed that in order to demonstrate that a behavioral impairment is attributable to consolidation blockade, and not nonspecific effects of a manipulation, intact short-term memory must be demonstrated (Dudai 2004; also see, Duvarci and Nader 2004).

In other studies, in which NMDA receptor antagonist was injected systemically (de Lima and others 2005) or directly to the perirhinal cortex (Winters and Bussey 2005) or the hippocampus (Baker and Kim 2002), it impaired short-term object recognition memory 1.5 and 3 h after the sample. Hence, together with previous studies showing that lesions of the medial PFC (Ennaceur and others 1997) or the anteromedial PFC (Mogensen and others 2004) do not impair short-term object recognition memory, our results may suggest that short-term object recognition memory is not dependent on the vmPFC.

Our results (as well as those of Tronel and Sara 2003) further support that NMDA receptors are involved in memory consolidation processes taking place after the initial acquisition. Tsien and others (Shimizu and others 2000; Wittenberg and Tsien 2002) have suggested the “synaptic reentry reinforcement” hypothesis according to which neuronal ensembles involved in initial learning are continually reactivated and undergo “multiple round” of synaptic reinforcement. This synaptic reinforcement is NMDA receptor dependent, so that the NMDAs within the circuit to be reinforced would be periodically reactivated to reinitiate the consolidation process.

Whereas we show that intact long-term consolidation and reconsolidation recognition memory require protein synthesis and NMDA function, other studies on reconsolidation and object recognition memory have shown the involvement of other molecular mechanisms. Specifically, Kelly and others (2003) have shown that rapid activation of the mitogen-activated protein kinase pathway occurs in the entorhinal-hippocampal circuitry in association with both consolidation and reconsolidation of recognition memory. Bozon and others (2003) have shown that when a consolidated memory for objects is recalled, zif268 mutant mice are impaired in long-term but not short-term recognition memory.
Summary

An important advantage of the object recognition task is that it is basically incidental in nature and relies on the rat’s innate exploratory behavior, without involving an explicit exogenous reinforcer. In other studies that compare consolidation and reconsolidation, usually during the consolidation phase a re-inforcing stimulus is present, which is absent in the reconsolidation phase, thereby confounding the interpretation of the comparison (Nader 2003). Further, most reconsolidation studies use exogenous aversive stimuli (Nader 2003; Dudai 2004), which are lacking in the recognition paradigm. Our study hence contributes to the generalization of the reconsolidation phenomenon over a wide spectrum of memory paradigms. The present study also indicates that consolidation and reconsolidation of recognition memory share a brain region (PFC) and molecular mechanisms (protein synthesis, NMDA receptor function). We cannot yet conclude, however, whether the two processes are mechanistically or functionally identical and also whether reconsolidation is a distinct memory phase (Dudai and Eisenberg 2004; Lee and others 2004; Alberini 2005).

Notes

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