The consolidation of object and context recognition memory involve different regions of the temporal lobe

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These experiments investigated the involvement of several temporal lobe regions in consolidation of recognition memory. Anisomycin, a protein synthesis inhibitor, was infused into the hippocampus, perirhinal cortex, insular cortex, or basolateral amygdala of rats immediately after the sample phase of object or object-in-context recognition memory training. Anisomycin infused into perirhinal or insular cortices blocked long-term (24 h), but not short-term (90 min) object recognition memory. Infusions into the hippocampus or amygdala did not impair object recognition memory. Anisomycin infused into the hippocampus blocked long-term, but not short-term object-in-context recognition memory, whereas infusions administered into the perirhinal cortex, insular cortex, or amygdala did not affect object-in-context recognition memory. These results clearly indicate that distinct regions of the temporal lobe are differentially involved in long-term object and object-in-context recognition memory. Whereas perirhinal and insular cortices are required for consolidation of familiar objects, the hippocampus is necessary for consolidation of contextual information of recognition memory. Altogether, these results suggest that temporal lobe structures are differentially involved in recognition memory consolidation.

A critical aspect of the anterograde amnesic syndrome observed in patient HM and other patients with medial temporal lobe damage is the loss of recognition memory (Scoville and Milner 1957). Recognition memory is the capacity to know that something has been previously experienced, either individual stimuli or whole events (Mandler 1980; Brown and Aggleton 2001). The recognition process is generally considered to be composed of at least two components, one is the judgment of familiarity of items and the other is the recollection of contextual (spatial and/or temporal) information where items were encountered (Brown and Aggleton 2001; Yonelinas et al. 2002).

Earlier studies of amnesia produced by medial temporal lobe ablations in monkeys suggested that combined lesions of the hippocampus and amygdala accounted for severe recognition memory impairment (Mishkin 1978). However, more recent findings showed that recognition impairment was not directly related to damage in those structures but, rather, to damage to the anterior and posterior portions of the perirhinal and entorhinal cortices induced by amygdala and hippocampus aspiration (Murray and Mishkin 1998).

The issue of whether the different regions of the temporal lobe contribute in the same way to familiarity and contextual information of recognition memory remains an issue of considerable controversy. Evidence from animal studies suggests that the perirhinal cortex and the hippocampus contribute differentially to these two components of recognition memory. The findings of many studies suggested that the perirhinal cortex is critically involved in discrimination of familiarity but not in contextual memory, whereas the hippocampus appears to support contextual memory but seems not to be necessary for familiarity discrimination (Ennaceur et al. 1996; Ennaceur and Aggleton 1997; Bussey et al. 1999; Mumbly et al. 2002, 2005; Stupien et al. 2003; Winters et al. 2004). However, as some findings suggest that the hippocampus is involved in object recognition memory as well, the role of the hippocampus in recognition memory remains highly controversial (Broadbent et al. 2004; Rossato et al. 2007; Squire et al. 2007).

Recent findings indicate that the insular cortex is also an important temporal lobe structure involved in consolidation of recognition memory. Muscarinic receptor antagonists infused into the insular cortex known to disrupt taste recognition memory also impair object recognition memory (Bermúdez-Rattoni 2004; Bermúdez-Rattoni et al. 2005).

The present study investigated the specific contributions of these medial temporal lobe structures to object and object-in-context recognition memory consolidation. In order to disrupt consolidation, anisomycin was infused into perirhinal cortex, insular cortex, hippocampus, or basolateral amygdala (BLA) immediately after object or context recognition training and memory was tested 90 min (short-term memory) or 24 h (long-term memory) later.

**Results**

**Experiments for object recognition**

During the training trial (sample phase) the groups exhibited similar time exploring each of the two identical objects (Table 1). A discrimination index was calculated as the difference in time exploring the two objects, expressed as the ratio of the total time spent exploring both objects. Two-way ANOVA indicated no significant differences between groups on the training trials (sample phases) for the groups tested later for short- or long-term memory (see Table 1).
behavior is indicated by a high recognition index (see vehicle-injected groups on Fig. 2B).

During the training trial (sample phase) the groups exhibited similar time exploring each of the two objects (Table 2). Two-way ANOVA indicated no significant differences between groups in sample phase 1 for both conditions; short-term groups ($F_{(7,42)} = 0.90$, NS), or long-term groups ($F_{(7,59)} = 0.91$, NS). Similarly, there were no significant differences in sample phase 2; short-term groups ($F_{(7,42)} = 1.75$, NS), or long-term groups ($F_{(7,59)} = 0.76$, NS).

As can be seen in Figure 2B during retention tests at 90 min, the animals, regardless of their experimental condition, showed a preference for the familiar objects placed in novel contexts. That is, rats microinfused with either vehicle solution or anisomycin showed the expected high recognition index on the short-term memory test. Two-way ANOVA indicated no significant differences between groups ($F_{(7,42)} = 0.23$, NS).

Interestingly, on the long-term memory probe, only animals microinfused with anisomycin in the hippocampus displayed impaired ability to recognize familiar objects in novel contexts. Two-way ANOVA indicated differences between groups ($F_{(7,59)} = 2.39$, $P < 0.05$). Fisher’s post hoc analysis revealed that the group infused with anisomycin into the hippocampus was different from the rest of the groups ($P’s < 0.05$), except to BLA-ANI group. Indicating that the hippocampal treated group showed exclusively long-term context recognition memory impairment (see Fig. 2B).

### Discussion

The present study investigated the contribution of different temporal-lobe regions in the consolidation of the memory for object and object-in-context recognition tasks. These two tasks allow dissociating two important components of recognition memory,
the identity of the object (a whole representation of the stimulus), and the context where it was found. The object recognition task is based on the discrimination of familiarity of the stimuli and for normal performance the subject needs to respond to “what” stimulus was used in the experiment previously. On the other hand, the object-in-context task is based on the association of a specific stimulus with a context and for this, the subject needs to remember “where” the stimulus was first experienced. Conversely, in our object-in-context protocol either the objects or the context are familiar at the test phase; the only novel information is the relation between them.

When the protein synthesis blocker anisomycin was microinfused post-training into the perirhinal or insular cortices, object but not object-in-context memory consolidation was impaired. Conversely, administration of anisomycin into the dorsal hippocampus blocked consolidation of object-in-context, but not object recognition memory. Interestingly, when anisomycin was administered into the BLA, object and object-in-context recognition memory consolidation were unaffected. In none of these regions do anisomycin infusions appear to have effects on short-term object or object-in-context recognition memory.

The ability to recognize a previously experienced stimulus has two components; recollection of the stimulus in the context where it was experienced and a sense of familiarity with the features of that particular stimulus (Eichenbaum et al. 2007). Recognition memory has been linked to a network of medial temporal lobe cortical regions, including the perirhinal, parahippocampal, entorhinal cortices, and the hippocampus (Aggleton and Brown 1999; Malkova and Mishkin 2003; Reed et al. 2004). Recently, it was suggested that these distinct temporal lobe regions are differentially involved in object (discrimination of familiarity) and context (the place where they occur) recognition memory processes (Brown and Aggleton 2001). In this regard, evidence of the participation of these structures in recognition memory consolidation.

The perirhinal cortex is a multimodal association region that is densely interconnected with sensory areas representing many sensory modalities, allowing information exchange between the perirhinal and unimodal cortices (Burwell et al. 1995). This reciprocal connectivity, together with findings of studies that assessed perirhinal participation in recognition memory for different sensory modalities (Otto and Eichenbaum 1992; Suzuki et al. 1993; Buffalo et al. 1999; Gutierrez et al. 2004), support the idea that multiple sensory systems related to stimulus recognition activate the perirhinal cortex (Brown and Aggleton 2001; Murray and Richmond 2001). Thus, association of individual features that represent a stimulus as a whole (within-stimulus association of components) may be represented in the rhinal cortex. Complex associations between stimuli and environment (context) may be represented in the hippocampal formation (Brown and Aggleton 2001).

In support of this hypothesis, electrophysiological recording studies have reported evidence of neuronal changes related to relative familiarity of a visual stimulus in the anterior temporal lobe cortex (entorhinal and perirhinal cortices) (Baylis and Rolls 1987; Brown et al. 1987; Miller et al. 1991). Further, such responses are considerably decreased between the first and second exposure to the same item. This decremented neuronal activity persists for at least one day after stimulation and is specific to a particular item; accordingly, exposure to another novel item induces a normal response. Furthermore, the decrement in neuronal activity persists even if several other items are presented in between (Riches et al. 1991; Fahy et al. 1993; Xiang and Brown 1998). Such findings suggest that the reduced responsiveness in the entorhinal and perirhinal cortices reflects long-term memory processes in those brain regions (Brown and Xiang 1998). This decremented response may allow a better-tuned representation...
Table 2. Recognition indexes on sample phases in context recognition task

|                      | Sample phase 1 | Sample phase 2 |
|----------------------|----------------|----------------|
|                      | (For STM)      | (For LTM)      |
| (A)                  |                |                |
| PRH                  | Vehicle        | Anisomycin     |
| IC                   | 0.47 ± 0.03    | 0.49 ± 0.02    |
| HIP                  | 0.50 ± 0.01    | 0.51 ± 0.02    |
| BLA                  | 0.49 ± 0.02    | 0.50 ± 0.01    |
|                     | 0.53 ± 0.02    | 0.48 ± 0.01    |
|                     | F(7,42) = 0.90  | P = 0.51       |
|                     | F(7,42) = 1.75  | P = 0.12       |
| (B)                  |                |                |
| PRH                  | Vehicle        | Anisomycin     |
| IC                   | 0.47 ± 0.03    | 0.51 ± 0.01    |
| HIP                  | 0.53 ± 0.02    | 0.48 ± 0.01    |
| BLA                  | 0.48 ± 0.02    | 0.51 ± 0.03    |
|                     | F(7,59) = 0.50  | P = 0.76       |
|                     | F(7,59) = 0.61  | P = 0.21       |

Recognition indexes on sample phases expressed as mean ± SEM. (A) Sample phase 1 (two different objects in context 1), and sample phase 2 (two identical objects in context 2) of STM groups. (B) Sample phase 1 (two different objects in context 1), and sample phase 2 (two identical objects in context 2) of LTM groups. Two-way ANOVA showed no differences between groups. See Results section for a detailed statistical description. Only for the purpose of analysis, one of the objects was distinctly selected as “novel” in sample phase 2. Abbreviations are as in Figure 1.

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tionally assess the two components of recognition memory for short- and long-term memory. Additionally, particular memory phases can be evaluated separately. Our findings provide additional information concerning the participation of distinct structures of the temporal lobe required for recognition memory processing, thus making it clear that the hippocampus and the cortex have specific and different roles in long-lasting recognition memory storage.

Materials and Methods

Subjects
Subjects were adult male Wistar rats weighing between 280 and 300 g at the beginning of the experiment. Animals were obtained from the breeding colony of the Institute of Cellular Physiology, UNAM. They were maintained at room temperature (22°C–23°C), under a 12–12 h light-dark schedule, caged individually in a standard acrylic box with food and water freely available. All behavioral protocols were carried out during the light phase. All experiments were performed in accordance with the Ministry of Health, Mexico.

Surgery and microinfusions
Before surgery rats were deeply anesthetized with intraperitoneal injections of ketamine (83.49 mg/kg) and xylazine (8.58 mg/kg). Rats were implanted bilaterally with guide cannulae aimed either at the perirhinal cortex (PRH), (coordinates of the infusion sites from bregma [mm] [Paxinos and Watson 1986]): posterior 3, lateral ± 6.5, ventral 7; insular cortex (IC): anterior 1.2, lateral ± 3.5, ventral 6.5; hippocampus (HIP): posterior 3.6, lateral ± 3.0, ventral 3.3; and basolateral amygdala (BLA): posterior 2.8, lateral ± 5, ventral 8.5. Cannulae were anchored with dental acrylic cement to two surgical screws fixed to the skull. Stylets were inserted into guide cannulae to prevent clogging. Animals were allowed to recuperate for 1 wk before being subjected to behavioral procedures.

For microinfusions, styllets were removed and a 30-gauge infusion needle was inserted extending 2.0 mm from the tip of each guide cannula. The infusion needle was connected via polyethylene tubing to a 10 µL Hamilton microsyringe driven by a microinfusion pump (Cole Palmer Instruments). In all cases, infusions were performed over a minute and the injector was left in place for an additional minute to allow complete diffusion. For IC, PRH, and HIP the injected volume was 1 µL per hemisphere; for BLA the injected volume was 0.5 µL per hemisphere. Microinjections of vehicle solution served as the control.

Drugs
The protein synthesis inhibitor anisomycin was purchased from Sigma (St. Louis). The drug was dissolved in equimolar HCl and adjusted to 120 mg/ml, pH 7.4 in vehicle solution (ACSF [mM]: 125 NaCl, 5 KCl, 1.25 NaH2PO4, H2O, 1.5 MgSO4, 7 H2O, 26 NaHCO3, 10 glucose, 2.5 CaCl 2). The dose of anisomycin was chosen according to previous studies indicating that doses between 100 and 125 µg/µL were effective in inhibiting protein synthesis in more than 90% indistinctly of the infused structure (Rosenblum et al. 1993; Morris et al. 2006; Canal et al. 2007) the volume was chosen according to a previous study that shows that 1 µL of ink into the cortex spreads 1 mm on average (Berman et al. 2000).

Apparatus

Object recognition memory experiments, one square arena made of gray-painted wood with the floor covered with sawdust was used (40 × 40 × 40 cm). On object-in-context recognition memory experiments, we used two arenas with different physical features. A similar gray square arena served as one of the contexts, and a circular arena made of red plastic material (40 cm in height × 40 cm in diameter) was used as the other context. For both arenas, some irregular figures made of cardboard were placed in the walls to serve as spatial landmarks, and the floor was covered with sawdust.

The arenas were placed in the same dim-light illuminated room. A video camera was mounted above the open-field arenas and all test sessions were recorded. The objects to be discriminated were white glass bulbs (6 cm in diameter and 11 cm in length) and transparent glass jars (5.5 cm in diameter and 5 cm in height). All objects were fixed to the floor at the back corners of the arena (10 cm from walls) with Velcro to prevent them from being displaced by the rats. To avoid olfactory cues, objects were thoroughly cleaned with 70% ethanol and the sawdust was stirred after each trial.

Behavioral procedures
For each session, animals were transported from the vivarium to the experimental room 2 h before the beginning of each session, and were left in the experimental room for an additional 2 h at the end of each session, in order to avoid stress conditions that could affect the performance or consolidation of the tasks.

For all experiments, contexts, objects and their relative positions were counterbalanced. All experiments were carried out in independent groups. Exploration was considered as pointing the nose toward an object at a distance of less than 1 cm and/or touching it with the nose. Turning around or sitting on the objects was not considered as exploratory behavior. Rats that showed a total exploration time <10 s on either training or testing were discarded from further analysis.

Object recognition memory task
For five consecutive days animals were handled for a minute, and immediately after positioned into the open-field arena without any objects for 3 min. On the sample phase, rats were placed in the arena facing the wall opposite the objects for 10 min and were allowed to freely explore two identical objects (either two light bulbs or two jars [A1 and A2]). Memory was tested either 90 min (short-term memory) or 24 h later (long-term memory). On memory test, rats were allowed to explore freely one copy of the previously presented object (familiar, A1) together with a new one (B) for 3 min. Vehicle or anisomycin was microinjected immediately after the sample phase (see Fig. 1A). The groups tested for STM were: PRH-VEH (n = 4), IC-VEH (n = 6), HIP-VEH (n = 8), BLA-VEH (n = 7); PRH-ANI (n = 7), IC-ANI (n = 5), HIP-ANI (n = 5), BLA-ANI (n = 8). The groups used for LTM were: PRH-VEH (n = 9), IC-VEH (n = 11), HIP-VEH (n = 9), BLA-VEH (n = 8); PRH-ANI (n = 10), IC-ANI (n = 11), HIP-ANI (n = 12), BLA-ANI (n = 6).

The object recognition index was calculated as follows: time of exploration of novel object (n) / (time of exploration of novel object + time of exploration of familiar object + time of exploration of novel object) (Ennaceur and Delacour 1988). A recognition index equal to 0.5 reflects no preference for any of the objects. An index higher than 0.5 shows preferences for novel objects.

Object-in-context recognition memory task
For five consecutive days animals were handled for 1 min, and immediately after habituated to both contexts (90 min apart) without any objects for 3 min. On sample phase 1, rats were placed in one of the arenas (context 1) facing the wall opposite to
the objects and were allowed to explore two different objects (one light bulb and one jar [A1 and B1]) for 10 min. Sample phase 2 was conducted 24 h later, rats were placed in context 2 together with two identical objects (copies of one of the previously presented objects, i.e., either two light bulbs or two jars [A2 and A3]) and were allowed to explore the objects for 10 min. Memory was tested 90 min (short-term memory) or 24 h (long-term memory) later. On the memory test, rats were reintroduced to context 2 and were allowed to explore freely for 3 min one copy of the previously presented object in context 2 (A2) together with a copy of one of the objects previously presented in context 1 but not presented in context 2 (B2). Vehicle or anisomycin was microinjected immediately after sample phase 2 in order to assess consolidation of familiar objects presented in a novel context (see Fig. 2A). The groups tested for STM were: PRH-VEH (n = 7), IC-VEH (n = 5), HIP-VEH (n = 7), BLA-VEH (n = 7); PRH-ANI (n = 7), IC-ANI (n = 5), HIP-ANI (n = 7), BLA-ANI (n = 5). For LTM the groups used were: PRH-VEH (n = 10), IC-VEH (n = 6), HIP-VEH (n = 6), BLA-VEH (n = 8); PRH-ANI (n = 11), IC-ANI (n = 9), HIP-ANI (n = 8), BLA-ANI (n = 9). Context recognition indexes were calculated as follows: time of exploration of familiar object in novel context/time of exploration of familiar object in familiar context. A recognition index equal to 0.5 reflects no preference for any of the objects. An index higher than 0.5 shows a preference for familiar objects in novel contexts.

In the protocol designed for object-in-context recognition memory assessment, one of the objects was presented twice before the retention test, while the other was presented just once, raising the possibility of one of the objects becoming more familiar. To discard the possibility that one object may become more familiar than the other on the retention test, we conducted the following control experiment.

On sample phase 1, rats were placed in one of the arenas (context 1) facing the wall opposite the objects and allowing them to explore two different objects (a light bulb and a jar [A1 and B1]) for 10 min. Sample phase 2 was conducted 24 h later, rats were placed in context 2 with two copies of one of the familiar objects (either two light bulbs or two jars [A2 and A3]) and were allowed to explore the objects for 10 min. Retention was tested 24 h after sample phase 2 (long-term memory test). During the retention test, rats were reintroduced to context 1 and were allowed to explore freely for 3 min one copy of each of the previously presented objects (A1, B1).

Under these conditions, we expected that rats would explore equally the two objects either in sample phases or in memory test, because there are not any novelty components for discrimination. One-sample t-test showed that the sample phases and memory test were not different from the 0.5 score (chance level) P > 0.05 (n = 14, data not shown).

Histology
At the end of the experiments, animals were overdosed with sodium pentobarbital, and perfused with 0.9% saline. The brains were removed and stored at 4°C in buffered 4% paraformaldehyde solution for 24 h. The brains were then stored in a 30% sucrose/phosphate buffer (0.1 M) solution for five days. Frozen sections (40 μm) were collected and stained with Cresyl violet and examined by light microscopy in order to establish injector tips placement. All animals included in the analysis had the needle tips in the cerebral region of interest. Figure 3 shows representative microphotographs of the injection placements.

Statistical analysis
Although the memory test was recorded for a total time of 3 min, for the context recognition task only the first minute was used for statistical analysis, since it has been reported that novel object discrimination is more evident during the first minute (Dix and Aggleton 1999; Mumby et al. 2002). The analysis for the object recognition task included the whole 3 min. Two-way ANOVA (drug × brain area) was used to assess behavioral data. Mean ± SEM recognition indexes were used for comparisons between groups. A probability level of P < 0.05 was accepted as statistical significance.

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