



## Research report

# Entorhinal cortex lesions impair the use of distal but not proximal landmarks during place navigation in the rat

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**Abstract**

Rats with entorhinal cortex lesions were trained in two versions of the place navigation task in the Morris water maze. In the distal condition, they had to locate the hidden platform on the basis of remote landmarks, while in the proximal condition, they had to rely only on a configuration of proximal objects, placed directly in the pool. Entorhinal rats were impaired in using distal landmarks but were able to use proximal landmarks to navigate toward the platform. These results suggest that the use of distal and proximal landmarks during navigation involves activation of different neural structures. They also suggest, in agreement with previous data, that there are two distinct landmark-processing systems, one devoted to the processing of proximal landmarks and the other to the processing of distal landmarks. © 2004 Elsevier B.V. All rights reserved.

*Keywords:* Entorhinal cortex; Place navigation; Water-maze; Rats

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**1. Introduction**

There is a wealth of data showing the importance of environmental cues in guiding the animals' spatial behavior. In their early theoretical work, O'Keefe and Nadel [21] proposed that perception of distal cues enables an animal to use a mapping strategy during navigation, i.e. a strategy based on a representation encoding spatial relations among cues (allothetic relations). In support of this hypothesis, rats have been repeatedly shown to be able to reach a hidden platform in the Morris water maze from different starting places by relying on the configuration of room cues [17,32]. Consistent with these results are also the findings that manipulation of distal cues disrupts the animals' performance during various spatial tasks [33]. The strong influence exerted by distal cues over navigation and place learning may be related to the fact that they provide a stable spatial frame of reference in the sense that they do not change their relative positions as the animal moves in the environment. In contrast, proximal cues are subject to changes in their relative positions as the animal locomotes. Thus, it may be a

priori more difficult for the animals to build a stable frame of reference by using proximal cues than distal cues. In general, distal landmarks are visual cues located beyond the animal's "working space" whereas proximal landmarks are objects that can be directly approached during exploration.

Behavioral studies indicate that rodents nevertheless are able to integrate proximal landmarks in their spatial representation [2,5,11], therefore, confirming O'Keefe's early assumption that "spatially separated intramaze cues can also serve as place cues" [20]. In addition, several experiments show that active exploration of an environment allows the animal to encode the spatial relationship among proximal landmarks [28,35]. However, it is often reported that it is difficult to train animals in spatial tasks requiring the use of proximal cues [11,12,34]. Such difficulty contrasts with the rapid learning commonly observed in rats trained in spatial navigation based on distal cues (e.g. [14]). Thus, although distal and proximal landmarks can both be used to support mapping strategies, the data suggest that using these two kinds of landmarks involves different mechanisms.

One way to demonstrate the existence of two landmark-processing systems is to show that they are mediated by different brain structures. It is abundantly documented that navigation based on the use of distal landmarks is disrupted by lesions of the hippocampus (e.g. [18]). In contrast, there

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are fewer data reporting the effects of hippocampal lesions on the use of proximal landmarks when they cannot serve as beacons to guide navigation. In a previous study, we tested the ability of rats with hippocampal or parietal cortical lesions to rely on a configuration of proximal or distal landmarks to navigate toward a hidden platform [29]. Hippocampal rats were impaired in using both proximal and distal landmarks whereas parietal rats displayed a navigational deficit only when they had to rely on proximal landmarks. These results suggest that the processing of proximal and distal landmarks is mediated by different brain regions. They are, therefore, compatible with the idea that there are two distinct navigation systems, one based on distant landmarks and the other based on proximal landmarks.

The present study was aimed at further investigating the neural substrate of these two systems. Indeed, they may not be subserved by the hippocampus and the parietal cortex only, but may require the contribution of a larger number of structures. Among the areas possibly involved, the entorhinal cortex must be considered in priority because it has a key function in conveying cortical information to the hippocampus. It receives projections from various cortical areas and sends major input to the hippocampus via the perforant path [3]. Several studies show that damaging the entorhinal cortex produces deficits in various spatial tasks including watermaze tasks [7,10,19,22,31], radial maze tasks [15], and exploration tasks [8,24]. It has to be noted, however, that some other studies have failed to yield deficits [1,9,13,23,27]. Given the pivotal position of the entorhinal cortex between the hippocampus and the cortex, we wished to determine how its function relates to the two navigation systems, namely the system based on distal landmarks and the system based on proximal landmarks.

Rats with entorhinal cortex lesions were trained in two versions of the water maze navigation task, similar to those used in the Save and Poucet's study [29]. In the distal condition (Experiment 1), rats had to locate a submerged platform in a water maze by using distal landmarks (room cues). In the proximal condition (Experiment 2), they had to locate the platform by using only proximal landmarks, i.e. objects directly placed in the pool.

## 2. Materials and methods

### 2.1. Subjects

Thirty-one Long Evans black hooded male rats purchased from a commercial supplier (CERJ, Le Genest-St-Isle, France) served as subjects. Upon arrival, the rats weighted between 300 and 325 g and were housed in a room with a natural light/dark cycle. They were initially housed by groups of two but following surgery, they were placed in individual cages (40 cm long × 26 cm wide × 16 cm high). They had free access to food and water throughout the experiment.

In Experiment 1, the rats were arbitrarily assigned to two groups prior to surgery: SHAM-operated rats (SHAM:  $n = 7$ ), and entorhinal cortex-lesioned rats (ENTO:  $n = 9$ ). In Experiment 2, rats were assigned to two groups prior to surgery: SHAM-operated rats (SHAM:  $n = 6$ ), and entorhinal cortex-lesioned rats (ENTO:  $n = 9$ ).

### 2.2. Surgery

Before surgery, rats were deeply anesthetized by injection of sodium pentobarbital (40 mg/kg i.p., Sanofi Santé Animal, Libourne, France) preceded by atropine sulfate (0.25 mg/kg i.p.). Additional injections of ketamine (50 mg/kg i.p., Imalgène, Merial, France) were occasionally made to maintain appropriate anesthesia throughout surgery. The rats were placed in a Kopf stereotaxic apparatus (Kopf Instruments, Tujunga, CA, USA). A midline incision of the scalp was made and the skin and muscles were carefully retracted to expose the skull. Holes were drilled above the target regions. Bilateral lesions of the entorhinal cortex were made by passing a radio-frequency current at the tip of an electrode (70 °C for 15 s; RFG 4, Radionics, Burlington, MA, USA) lowered in the brain at the following coordinates relative to Bregma: AP: -6.8 mm, L: ±4.3 mm and ±5.4 mm; and AP: -8 mm, L: ±5 mm [36]. For each lesion point, the electrode was lowered very slowly until the tip reached the floor of the brain (calvarium) and then raised 1 mm [4]. This position was taken as the dorso-ventral coordinate of the lesion. Due to the posterior curvature of the calvarium, the dorso-ventral coordinate was different for each lesion point, thus allowing to damage the entorhinal cortex along its all extent. SHAM-operated rats were treated the same way as lesioned rats except that no current was passed through the electrode. The skin was sutured and rats received an injection of antibiotic (Terramycine, 60 mg/kg i.m.) as postoperative treatment. They were then placed back in their home cages for recovery. Training began 1 week after surgery.

### 2.3. Histology

At the completion of the experiment, lesioned and SHAM-operated rats received a lethal dose of sodium pentobarbital and were transcardially perfused with a 10% formalin solution. The brains were removed and stored in a 4% formalin solution. Later, coronal and horizontal 40 µm thick sections were made. Every fifth section was mounted and stained with cresyl violet. The slides were observed under the microscope to determine lesion extent.

### 2.4. Apparatus

The apparatus was an elevated circular pool (diameter, 1.40 m; 50 cm above the floor) that was filled with water (to a height of 20 cm) maintained at 18 °C. The water was made opaque by addition of 2 kg of chalk powder. A

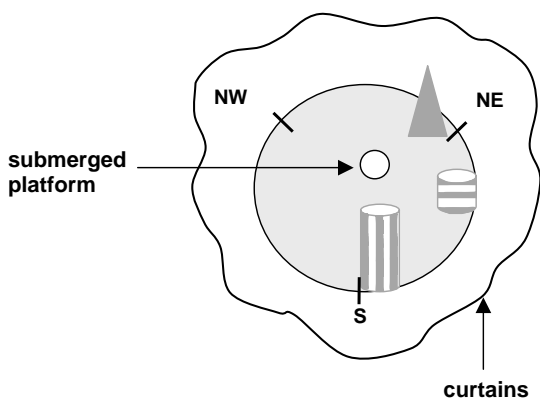


Fig. 1. View from above of the water maze in the proximal condition. Three objects were placed in the pool that was surrounded by curtains. The three cardinal points (NW, S, and NE) correspond to the starting places.

white painted platform (diameter, 8 cm) was placed inside the pool, 30 cm away from the pool wall. Its top surface was 1 cm below the surface of the water and was, therefore, invisible to the animals. The whole apparatus was illuminated by a circular 40 W neon placed directly above the pool. A camera was positioned above the pool. In all conditions, a radio station tuned to an FM broadcasting was fixed to the ceiling in a central position relative to the apparatus and displayed background noise >70 dB to mask non controlled directional sounds during learning. In the distal condition, the pool was located in the middle of a room containing numerous extra-maze landmarks such as doors, cupboards, shelves, pieces of equipment, etc. In the proximal condition, the curtains were maintained and three large distinct objects were placed inside the pool: a gray and white vertically striped cylinder (diameter, 16 cm; height, 41 cm), a gray and white horizontally striped cylinder (diameter, 11 cm; height, 61 cm) and a gray cone (base diameter, 19 cm, top diameter, 4.5 cm, height, 45 cm). These objects were placed against the pool wall and the platform placed 40 cm away from the pool wall (Fig. 1).

### 2.5. Behavioral procedure

Two independent groups of rats were trained in the distal condition (Experiment 1) and in the proximal condition (Experiment 2), respectively. In the two conditions, a typical trial consisted of releasing gently an animal, its head facing the wall, from one of four (distal condition) or three peripheral starting points (proximal condition). Once in the water, rats swim until they eventually come across and climb on the escape platform. When a rat did not reach the platform within 60 s, it was gently guided by the hand towards the goal. The animals were allowed to stay for 20 s on the platform to rest between trials. After their last daily trial, rats were dried in a towel and put back in their home cage. For probe trials, the platform was

removed and the rats were allowed to swim until 60 s have elapsed.

*Experiment 1:* In the distal condition, the platform remained at the same place relative to the room frame of reference. Rats received four trials a day for 15 days. They were released from four different starting points in pseudo-random order (N, S, E, and W). After all trials had been run on day 15, each rat was given a probe trial with the platform removed in order to examine place responses to the platform position.

*Experiment 2:* In the proximal condition, opaque curtains surrounded the apparatus and three objects were placed in the pool. To neutralize the possible influence of extra-maze landmarks, both the object-set and the platform were rotated 120° in arbitrary directions relative to the center of the pool from day to day. Three starting places were used, two of them being located next to an object, the third being away (Fig. 1). Rats were given six trials a day for 10 days. After all trials had been run on day 10, each rat was given a probe trial with the platform removed.

### 2.6. Data analysis

All trials were processed on line by a tracking system (View Point, Champagne-au-Mont-D'or, France). This system produced files consisting in series of pairs of integer numbers (from 0 to 512) which represented the X–Y position coordinates of the rat during the trials. Sampling was done at 25 Hz (i.e. 40 ms). The files were then stored in a computer for off-line analysis. Custom-written computer programs allowed to extract the raw data for each navigation trial and to calculate escape latency (the time required to find the platform), swim speed and total distance swam to the platform. For the probe trial, we calculated the amount of time spent in the area where the platform was located during training (the “goal area” defined as a 20 cm diameter circle centered on the former platform location) and in three equivalent circles in the pool (Opposite, Adjacent right, and Adjacent left areas). In addition, navigational performance in the probe trial of the distal condition in Experiment 1 was evaluated by measuring the time spent in a peripheral annulus (30 cm wide).

## 3. Results

### 3.1. Histology

Extent of damage to the entorhinal cortex was determined by examining cresyl violet-stained sections. All rats sustained extensive bilateral lesions of the entorhinal cortex [3]. The subiculum, presubiculum, and the hippocampus were totally spared in all rats. Lesions slightly encroached upon the parasubiculum, medially, and the perirhinal cortex, laterally, both at the most ventral level of the lesion in most rats. Fig. 2 shows a reconstruction of the smallest and largest

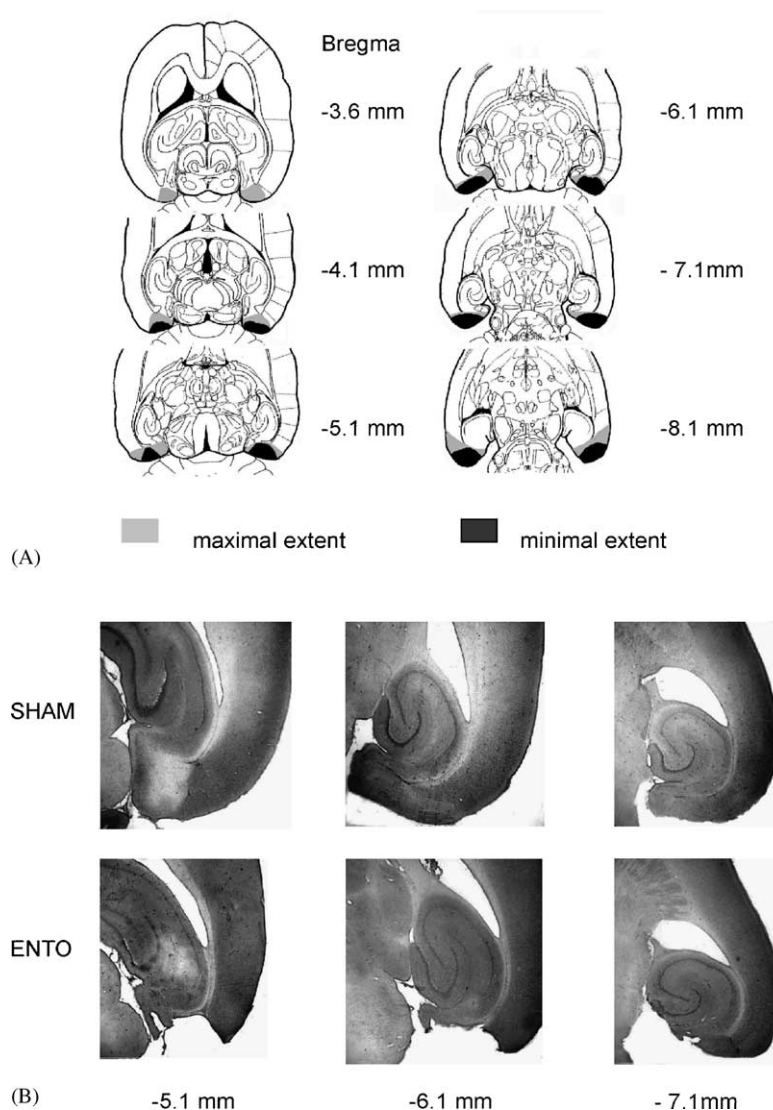


Fig. 2. (A) Series of horizontal sections showing maximal (light shading) and minimal (dark shading) extent of bilateral entorhinal lesions. Redrawn after Paxinos and Watson (1986) [25]. (B) Photomicrographs of cresyl violet-stained horizontal sections showing intact entorhinal area in SHAM-operated rats and representative damaged entorhinal area in lesioned rats at three levels relative to Bregma.

lesion extent. Are also shown representative examples of sections drawn from a rat with entorhinal damage.

### 3.2. Behavior

#### 3.2.1. Experiment 1: distal condition

**3.2.1.1. Training.** The time-course of latencies in the two groups is shown in Fig. 3A. A two-way analysis of variance revealed a main effect of Group ( $F(1, 14) = 195.02$ ,  $P < 0.001$ ), Session ( $F(14, 196) = 33.03$ ,  $P < 0.001$ ), and a significant Group  $\times$  Session interaction ( $F(14, 196) = 2.28$ ,  $P < 0.01$ ). Detailed analyses ( $t$ -tests) indicated that, except in Session 1 and Session 2, ENTO animals displayed higher latencies than SHAM animals throughout learning (all  $P < 0.05$ ). The ENTO rats swam a greater distance to the

platform than SHAM rats (mean distance averaged across all trials: SHAM, 342.48 cm, ENTO, 733.74 cm;  $t$ -test:  $t(14) = 8.72$ ,  $P < 0.0001$ ). ENTO and SHAM rats displayed similar swim speed (mean speed averaged across all trials: SHAM, 22.76 cm/s, ENTO, 22.84 cm/s;  $t$ -test:  $t(14) = -1.14$ ,  $P > 0.05$ ).

Fig. 3B displays representative trajectories of rats in the two groups at the end of training (Session 15). Visual examination of these trajectories showed that SHAM-operated rats reached the platform by using fairly straight paths from the several starting places. In contrast, entorhinal rats adopted a different strategy, by swimming at a fixed distance from the wall (corresponding to the distance of the platform), until they encountered it. To confirm the use of this navigational strategy, we analyzed the time the animals spent in a peripheral 30 cm-wide annulus relative to the central part of the

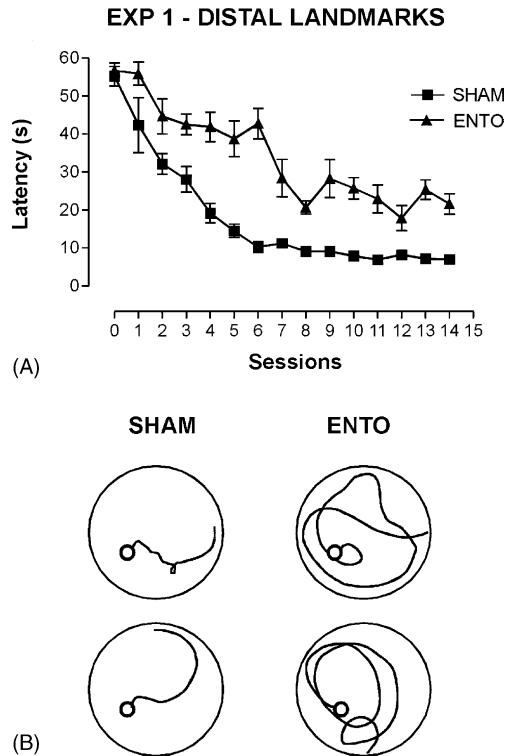


Fig. 3. Experiment 1: distal condition. (A) Mean escape latency (±S.E.M.) during acquisition of the place navigation task. (B) Two examples of trajectories for each group at the end of acquisition.

water maze (which contained the platform) during the probe trial. It was expected that entorhinal rats would spend more time in the peripheral part than in the central part of the pool.

**3.2.1.2. Probe trial.** Fig. 4A shows the time spent in the “goal area” and the averaged time spent in three other geometrically equivalent areas during a 60 s probe trial with no platform. SHAM-operated rats spent more time in the goal area relative to the other areas ( $t(6) = 7.49$ ,  $P < 0.001$ ) whereas entorhinal rats did not display such a preference ( $t(8) = -1.47$ ,  $P > 0.05$ ) indicating that they were impaired in place learning. Comparison of the time spent in a peripheral annulus with the time spent in the central area of the pool revealed that, as shown on Fig. 4B, entorhinal rats exhibited a significant bias toward the peripheral area ( $t(8) = 4.4$ ,  $P < 0.01$ ) whereas SHAM-operated rats did not exhibit such a bias ( $t(6) = 0.3$ ,  $P > 0.05$ ). Confirming visual examination of the trajectories, this indicates that the rats used a looping strategy to search for the platform.

Overall, our results indicate that entorhinal rats were strongly impaired relative to SHAM-operated rats in navigation and place learning based on distal landmarks. At the end of training, entorhinal rats were shown to adopt a looping strategy that allowed them to reach the platform independently of distal landmarks. This suggests that they

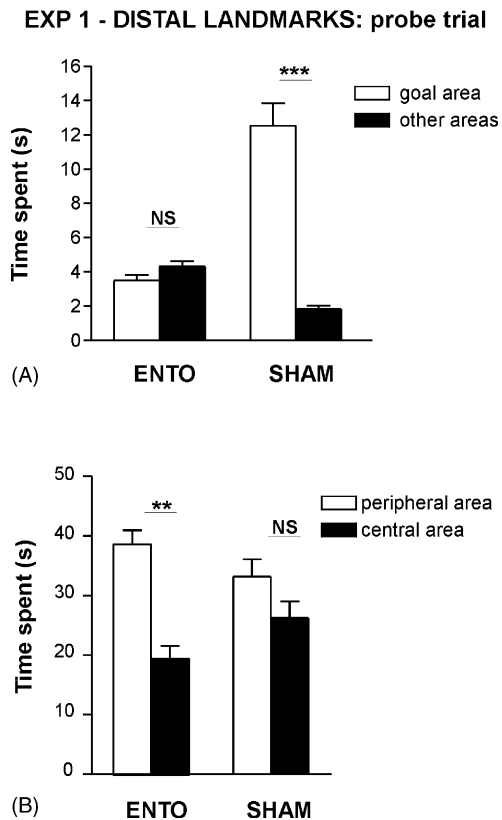


Fig. 4. Experiment 1: probe trial. (A) Mean time spent (±S.E.M.) in the goal area as compared with three other equivalent areas. (B) Mean time spent (±S.E.M.) in a peripheral annulus as compared with a central area. Asterisks indicate significant difference: \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ ; NS: non significant.

were not able to use distal landmarks but instead used the apparatus itself as a cue.

### 3.2.2. Experiment 2: proximal condition

**3.2.2.1. Training.** Rats were required to use three objects placed in the pool to navigate toward the platform from different starting points. The influence of the distal environment was limited by placing an opaque curtain around the pool and by rotating the objects and platform between sessions. The time-course of latencies in entorhinal and SHAM-operated rats is shown in Fig. 5A. A two-way analysis of variance revealed that the two groups learned the task and did not differ from each other (Group:  $F(1, 13) = 1.68$ ,  $P > 0.05$ ; Session:  $F(9, 117) = 43.35$ ,  $P < 0.001$ ; Group  $\times$  Session:  $F(9, 117) = 0.83$ ,  $P > 0.05$ ). In addition, the two groups swam a similar distance to the platform (mean distance averaged across all trials: SHAM, 560.33 cm, ENTO, 435.49 cm;  $t$ -test:  $t(13) = 1.93$ ;  $P > 0.05$ ) and swim speed (mean speed averaged across all trials: SHAM, 16.88 cm/s, ENTO, 18.36 cm/s;  $t$ -test:  $t(13) = 1.17$ ;  $P > 0.05$ ). Note that both entorhinal- and SHAM-lesioned rats displayed more circuitous paths in the proximal condition than in the distal condition to reach the

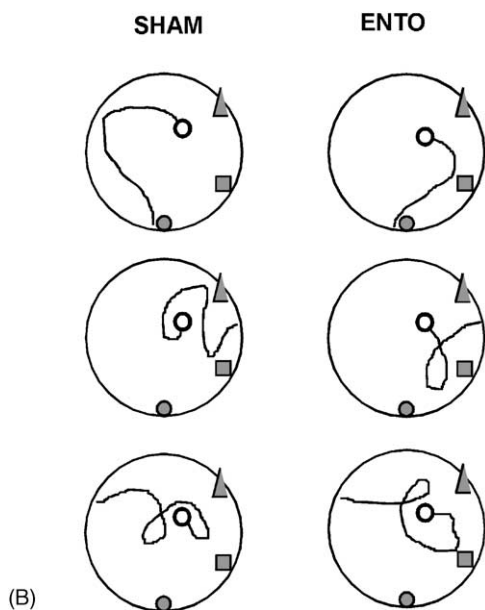
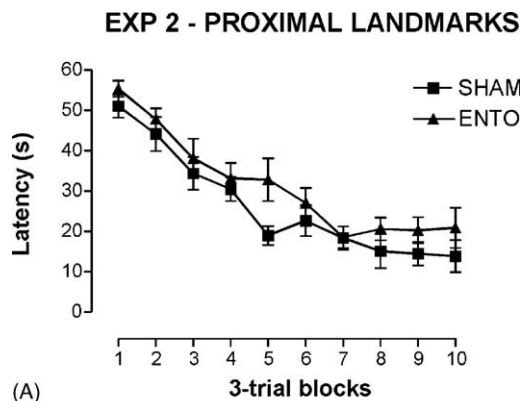


Fig. 5. Experiment 2: proximal condition. (A) Mean escape latency ( $\pm$ S.E.M.) during acquisition of the place learning task. (B) Three examples of trajectories for each group at the end of acquisition.

platform (Fig. 5B). In particular, they frequently swam by the objects before they search for the goal. This suggests that navigation in the proximal condition resulted from an interaction between exploratory activity and goal-directed behavior. However, because it is possible that the two groups differed in using this strategy, we analyzed the amount of contacts made by the animals with the objects during navigation. The presence of the animal in a 5 cm large annulus around the objects was computed at the asymptotic level of performance (Sessions 7–10). The comparison yielded no difference between ENTO and SHAM rats (mean number of contacts per trial averaged across Sessions 7–10: SHAM, 2.5; ENTO, 2.3;  $t$ -test:  $t(13) = 0.77$ ,  $P > 0.05$ ), thus indicating that the groups used similar navigation strategy.

**3.2.2.2. Probe trial.** Fig. 6 (right) shows the time spent in the goal area and the averaged time spent in three other equivalent areas during a 60 s probe trial with no platform. Both SHAM-operated and entorhinal rats spent more time

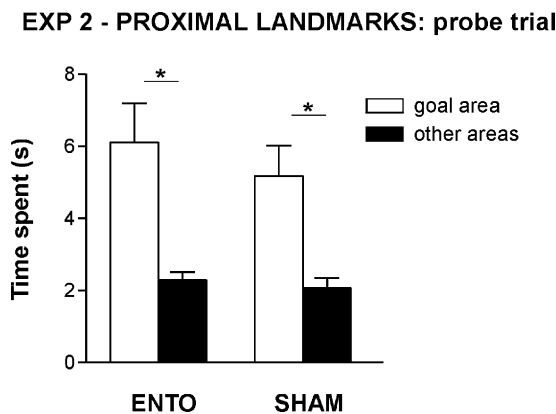


Fig. 6. Experiment 2: probe trial. Mean time spent ( $\pm$ S.E.M.) in the goal area as compared with three other equivalent areas.

in the goal area than in the others (SHAM:  $t(5) = 3.46$ ,  $P = 0.018$ ; ENTO:  $t(8) = 2.93$ ,  $P = 0.019$ ) indicating that entorhinal lesions did not affect place learning in the proximal condition.

#### 4. Discussion

Rats with entorhinal cortex lesions were trained in two versions of the place navigation task in the water maze. In the distal condition (Experiment 1), rats had to locate the hidden platform by using remote landmarks while in the proximal condition (Experiment 2), they had to use three proximal objects placed directly in the pool. We found that lesions of the entorhinal cortex disrupted place navigation in the distal condition but not in the proximal condition.

Studies of rats with entorhinal lesions in spatial memory tasks have generated conflicting results (see [1] for a discussion). The importance and the role of the entorhinal cortex thus remains equivocal. Whether the entorhinal cortex is a simple relay between the neocortex and the hippocampus or mediate specific mnemonic functions remains an open question. Our results are compatible with the latter possibility and suggest that the entorhinal cortex plays a specific role in spatial memory. Generally, the deficits induced by entorhinal cortex lesions are different from those induced by hippocampal lesions or neocortical lesions (for example [4,15]). Thus, damaging the entorhinal cortex is not simply a way to disrupt hippocampal functioning but results in deficits reflecting proper function. It is likely, however, that this structure mediates multiple functions due to the great variety of inputs that converge onto it from different parts of the brain.

More specifically, the results of the present study suggest that the entorhinal cortex plays a role in the processing of distal landmarks but is not involved when the animal has to perform place navigation based on proximal landmarks. They are consistent with a number of studies showing that lesions restricted to or including the entorhinal cortex affect

navigation when the rat has to rely on remote landmarks [7,10,19,22,31]. In contrast, very few studies have investigated the role of the entorhinal cortex in the use of proximal landmarks in navigation. Among those, Oswald and Good [22] and Oswald et al. [23] have trained rats in two navigation tasks based on the use of a single intramaze landmark or extramaze landmarks. Oswald et al. [23] found that entorhinal cortex damage did not produce deficits in any task except when rats, previously trained to use a single landmark, were required to learn the platform location on the basis of distal landmarks with the single landmark still available but made irrelevant for place learning. This led the authors to propose an interpretation in terms of a role of the entorhinal cortex in attentional processes for cue selection rather than in spatial navigation. In contrast, the results of the present study indicate that radiofrequency entorhinal cortex lesions resulted in a dissociation between two navigation systems, one based on the use of distal landmarks and the other based on proximal landmarks. However, it is difficult to compare the present results with those of Oswald et al. due to notable differences in training procedures. One of these differences is that we used a configuration of intramaze landmarks whereas Oswald et al. [23] examined the control exerted by a single intramaze landmark. A single landmark or a configuration of landmarks may activate different navigational strategies based on heading vectors or multiple allocentric spatial relationships, respectively [26]. In the present study, it was expected that combination of multiple intramaze landmarks and variable starting places would encourage the animal to adopt a mapping strategy. This hypothesis is supported by the fact that hippocampal damage impaired navigation based on a configuration of intramaze landmarks [29] whereas it has been shown that navigation by heading vectors does not depend on the hippocampus [26]. Thus, in both the proximal and distal conditions, the animals relied on a mapping strategy to locate the platform. Our results, therefore, suggest that the mapping strategy can be mediated by different neural structures according to the distance of landmarks.

The present results complement previous data that suggest a different role for the hippocampus and the parietal cortex in the processing of spatial landmarks. Rats with hippocampal damage were found to be impaired in both distal and proximal conditions whereas rats with parietal cortex damage had deficits in the proximal condition only [29]. Here, we show that rats with entorhinal cortex damage affects navigation in the distal condition only, confirming the existence of two parallel systems subserved by different neural substrates. One system is devoted to the processing of proximal landmarks, i.e. objects that are placed in the animal's behavioral space, and requires activation of the parietal cortex. The other system is devoted to the processing of distal landmarks and requires the entorhinal cortex. The two systems converge on the hippocampus which may, therefore, play a role in managing the interaction between the use of proximal landmarks and the use of distal landmarks. This is a

function that is necessary for adaptive and flexible behavior. Interestingly, the hypothesis of two distinct landmark processing systems is also supported by unit recording studies of hippocampal place cells and thalamic head direction cells in the rat. These studies suggest that, at the neural level, the processing of proximal landmarks can also be dissociated from that of distal landmarks [6,37], thus indicating that these two systems involve larger networks of structures that remained to be determined.

One important issue is to understand what makes the difference between using proximal and distal landmarks for place learning and navigation. Although these two systems have undoubtedly similar aspects (the animal has to process the allocentric spatial relationships between environmental landmarks to locate the platform), there must be some fundamental differences that account for separate neural implementation. One difference is that distal landmarks are of greater efficiency in guiding navigation because they provide the animal with stable directional information as well as useful positional information. In contrast, proximal landmarks seem to provide more precise positional information than distal cues but much poorer directional information. Another complementary aspect relates to the mechanisms that allow formation of a spatial representation on the basis of either kind of landmarks. Because motion parallax effects are strong for proximal landmarks, we assume that the animal needs to actively integrate allothetic (visual) and idiothetic information in order to build an allocentric representation of their environment. Such integration might be less crucial or less difficult when forming a representation based on distal landmarks. As it has been hypothesized previously, the parietal cortex could play an important role in this process [30]. Overall, we propose that information provided by distal landmarks is processed by the entorhinal–hippocampal circuitry and information provided by proximal landmarks is processed by the parietal–hippocampal circuitry.

Assuming that there are distinct systems dealing with the processing of proximal landmarks and distal landmarks, respectively, the idea of distinguishing a far and a near space in the animal's surrounding is appealing. Although there is no evident physical border between the two kinds of spaces, our results do suggest that the existence of two landmark-processing systems has some functional importance and adaptive value for the rats. Interestingly the concepts of far and near space have been extensively used in primates. Far space is defined as the space beyond hand-reaching (extrapersonal) and near space as the space within hand-reaching (peripersonal). Clinical, neuropsychological and neurophysiological evidence suggests that the primate brain contains distinct representations of far and near space [16]. In the rat, the data are compatible with the hypothesis of the existence of two landmark processing systems, one devoted to near space and the other to far space, whose functional and neuroanatomical organization remains to be determined.

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