Accepted Version
Behavioural Brain Research, 431 (2022) 113962
https://doi.org/10.1016/j.bbr.2022.113962

Rapid decay of spatial memory acquired in rats with ventral hippocampus lesions

Juan M. J. Ramos*

Department of Psychobiology and Mind, Brain and Behavior Research Center (CIMCYC), University of Granada, Granada 18071, Spain

*Corresponding author: Juan M. J. Ramos, Department of Psychobiology, School of Psychology, Campus Cartuja, University of Granada, Granada 18071, Spain.

E-mail address: jmjramos@ugr.es (Juan M. J. Ramos)

Accepted Version - *Behavioural Brain Research*, 431 (2022) 113962
https://doi.org/10.1016/j.bbr.2022.113962

Abstract

Several memory consolidation theories have proposed that following a learning situation the hippocampus gradually stabilizes labile recent memories into long-lasting remote memories. Most work in this field has focused on the dorsal hippocampus (DHip), giving little consideration to a possible contribution by the ventral hippocampus (VHip), particularly when spatial paradigms are used. However, in recent years a growing number of studies have suggested the existence of a functional continuum, related to spatial processing and navigation, along the dorsoventral hippocampal axis. For this reason, in the present study we compare the effect of DHip vs. VHip lesions on long-term spatial memory retention. Using a four-arm plus-shaped maze, rats with lesions in the DHip, VHip or sham-lesioned learned to criterion a place discrimination task based on allothetic cues. During two retraining phases (2 days and 24 days after learning) retention of the spatial information learned during the acquisition phase was evaluated. The main findings revealed no deficit 2 days after learning, but 24 days after learning both lesioned groups showed a profound impairment compared to control animals (expt. 1). In contrast, when rats learned a cue-guided navigation task in the acquisition phase, both lesioned groups performed the two retention tests, 2 days and 24 days after learning, at the same level as the control group (expt. 2). These results suggest not only that the DHip is vital, but also that normal VHip activity is critical during the post-learning period in order for a recent spatial memory to become a stable long-term memory.

Keywords: Spatial memory; Long-term memory; Dorsal hippocampus; Ventral hippocampus; Hippocampal longitudinal axis; Radial maze

1. Introduction

For the memory of an explicit event to persist over time a consolidation process must take place following the learning episode [1, 2]. This process, which in rodents lasts several weeks, is supported by interactions between the hippocampus and neocortical modules and therefore is known as systems consolidation [3, 4]. As a result of systems consolidation a reorganization takes place in the brain circuitry underlying long-term memory, whereby all or part of the initially hippocampus-dependent trace is transferred to neocortex [5-7].

Numerous findings support the critical role of the hippocampus-neocortical interactions during the systems-level consolidation process. First, the type of retrograde amnesia observed in patients following damage to large medial temporal lobe regions or to the hippocampus is frequently temporally graded, with the deficit affecting recent memories while remotely acquired memories are spared [8, 9]. In rodents, a similar form of retrograde amnesia has been observed following hippocampus lesions using non-spatial tasks, for example, contextual fear conditioning [10, 11], social transmission of food preference [12, 13] and trace eyeblink conditioning [14, 15]. Using allocentric spatial tasks the results have been mixed, with some studies showing a flat retrograde amnesia [16-18] and others a graded retrograde amnesia after lesions limited to the hippocampus [19-21]. Second, some studies performed in the water maze have found that lesions to specific regions of the frontal cortex, mainly the anterior cingulate cortex, impaired remote but not recent spatial memory [22-24]. So, the fact that some studies have not found a graded retrograde amnesia following hippocampus lesions, as mentioned above, does not mean that the brain circuits involved in spatial memories are not reorganized during systems-level consolidation. Third, a series of studies has shown time-dependent changes in neural activity at different levels of the hippocampal-neocortical system as the consolidation process progresses. So, results often indicated hippocampal activation during recent but not remote spatial memory retrieval [19, 25, 26]. Complementarily, during remote memory retrieval the hippocampus appears to be deactivated while discrete frontal regions, depending on the type of task being used, are recruited [15, 19, 22, 24-26].

The present study is yet another attempt to explore the contribution of the hippocampus to long-term spatial memory formation. Based mainly on differences in anatomical connectivity and lesions studies, dorsal and ventral subregions have traditionally been considered to be involved in functionally distinct processes, with DHip supporting spatial/contextual memory and VHip being primarily involved in emotion-related behavior [27-29]. For this reason, most studies to date have focused on the dorsal hippocampus [30, 31] and, to the best of our knowledge, no study has yet demonstrated the relevance of the ventral hippocampus in long-term spatial memory retention. In support of this possibility, various studies have shown recently that under certain training conditions the two subregions of the hippocampal dorsoventral axis can act synergically in spatial processing and navigation [32-34]. Furthermore, there are prominent unidirectional and monosynaptic projections, primarily ipsilateral, from the VHip to the prefrontal cortex in rats that could support the necessary interaction between these two regions during the systems consolidation process [35, 36]. Therefore, the primary aim of the two experiments in the present series is to compare the effect of dorsal vs. ventral hippocampal lesions on long-term spatial memory retention. In the two experiments of this study, excitotoxic lesions were made to the DHip or VHip prior to learning and the lesioned animals then learned either a place discrimination task (expt. 1) or a non-allocentric task (expt. 2) until reaching a performance level similar to that of control animals. Since during the post-learning period interaction between the hippocampus and the neocortex is a necessary condition for the normal consolidation of the information, we hypothesize that in hippocampus-damaged animals the retrieval of remote memory should be affected, but not that of recent memory. The main results confirmed these predictions, showing that the ventral hippocampus is significantly involved in long-term allocentric retention, although to a lesser degree than the dorsal region.

2. Material and methods

2.1. Experiment 1: Differential decay over time of allocentric spatial memory acquired in rats with dorsal vs. ventral hippocampus lesions.

Since recent data have suggested a certain cooperation along the dorsoventral hippocampal axis in allocentric learning and memory [34, 37, 38] the main aim of expt. 1 was to compare the effect of DHip vs. VHip damage on the formation of long-term spatial memory, in order to dissociate the contribution of each subregion. Previously, in our lab we have observed that rats with DHip can acquire a place discrimination task in the radial maze if a special training procedure is used that favors behavioral flexibility [30, 31] or when overtraining [39] is employed. In both cases, however, 24 days after acquisition a profound deficit in retention was observed. As far as we know, there is still no data indicating whether the VHip is also necessary for long-term spatial memory retention using an anterograde design. For this reason, in this experiment DHip or VHip-lesioned rats learned a place discrimination task to criterion and two retention tests were administered 2 days and 24 days after learning. Since in the present experiment post-learning interactions between the hippocampus and the neocortex have been disrupted by permanent lesions, we hypothesized that memory formed in VHip lesioned rats would experience an accelerated decay across time if VHip really contributes to long-term stable memory formation during systems consolidation.

2.1.1. Subjects

The subjects were 25 male Wistar rats from Charles River Laboratories (France), randomly assigned to one of the following three groups: DHip-lesioned (n = 8), VHip-lesioned (n = 9) and sham-lesioned (n = 8). Two animals from the DHip-lesioned group did not reach learning criterion during the acquisition period and were eliminated, leaving a total of 6 rats in this group. The animals, initially weighing between 270-290 g, were individually housed in single polycarbonate cages (480 x 265 x 210 mm, Tecniplast, Italy), maintained at a constant temperature of 22 $\pm$ 1° C and under controlled lighting conditions (light on from 8:00 a.m. to 8:00 p.m.). All experimental procedures were performed during the light phase of the cycle and in conformity with the relevant European directive (2010/63 EEC) and Spanish legislation (BOE RD 53/2013). The protocol was approved by the Ethics Committee for animal research of

the University of Granada (protocol number: 01-CEEA-OH-2013) and by the competent authority of the Regional Government of Andalusia (record number: 31/03/2014/57).

2.1.2. Surgery

An analgesic opioid (buprenorphine, 0.1 mg/kg, i.p., Bupaq®, Richter Pharma AG, Austria) was administered at least 30 min before the anesthesia (sodium pentobarbital, 65 mg/kg, i.p., Sigma Chemical, St. Louis, Missouri). The rats were placed in a David Kopf stereotaxic apparatus (mod. 900, David Kopf Instruments, Tujunga, California) with the incisor bar adjusted so that lambda and bregma were level. When necessary the animals were reinjected with a small amount of pentobarbital to maintain the anesthesia until the end of surgery. The lesioned subjects received bilateral injections of N-methyl-D-aspartic acid (NMDA, Sigma Chemical, PBS, pH 7.4, 0.07 M) through the insertion of a 30-gauge stainless steel cannula in eight sites of the DHip and the VHip in relation to the interaural zero point [40]. Table 1 shows the stereotaxic coordinates used to lesion DHip and VHip. The neurotoxin was administered in a 0.25 µl volume at each site through the cannula attached to a 5 µl Hamilton microsyringe (Teknokroma, Barcelona, Spain). The solution was delivered by a Harvard Apparatus pump set (model 22, Panlab-Harvard Apparatus, Barcelona, Spain), at an infusion rate of 0.1 µl/min. The cannula was left *in situ* for an additional 5 min before being withdrawn. The control group underwent identical surgical procedures, the one exception being that equivalent volumes of phosphate-buffered saline (PBS) were infused into the dorsal or ventral hippocampus. Four hours after surgery each rat was injected with buprenorphine to reduce post-operative pain (0.2 mg/kg, i.p., Bupaq®, Richter Pharma AG, Austria).

2.1.3. Apparatus

The apparatus used was a black Plexiglas four-arm plus-shaped maze built by the University of Granada Technical Services Department. Each arm of the maze measured 60 cm in length x 10 cm in width and was connected to an octagonal central platform 35 cm in diameter. The walls of the central platform were 15 cm in height and the walls of each arm measured 5 cm in

height. The maze was 80 cm from the floor and was located in the middle of an experimental room measuring 3 x 2.8 m. The distance between the various extramaze cues and the maze itself was therefore quite small. Posters on the wall, a window covered in black adhesive plastic, metal shelves and a cabinet were the main extramaze cues used by the rats to learn the task. A schematic diagram of the maze and cues in the testing room has been presented elsewhere [41]. The maze and the cues in the experimental room were illuminated by two tubes, of 100-W each, placed symmetrically on the ceiling and also by one 200-W light bulb hanging from the ceiling 1.2 m above the center of the maze. This provided a high level of illumination (459.8 lux).

2.1.4. Behavioral procedure

The rats were given 10-12 days to recover from the surgery. Following this period, all subjects were put on a food schedule to maintain them at 85-90% of their free-feeding body weight. Beginning on the same day as the food scheduling, all rats were handled on 7 successive days for 10 min each. On the following day behavioral training in the four-arm plus-shaped maze began. Rats were given eight trials per session and one session per day. An animal's training period ended when it reached a learning criterion of at least 14 correct trials over two consecutive days. At the beginning of a trial, the rat was placed at the end of one of the arms used for starting (S, N and E), with its back to the central platform. The order in which the different arms were used for starting was randomized in each daily session. In addition, the frequency with which each animal started from each arm during the training period was the same, and therefore turning left, turning right or going straight was not predictive of reaching the goal arm. During each training trial, two 45-mg food pellets (P.J Noyes Lancaster, NH, USA) were placed in the food cup at the end of the west arm. Identification of the goal arm by smell was prevented by the presence of five inaccessible 45-mg food pellets under each of the four arms. The pellets were placed at the end of each arm, under the food cup, using adhesive tape and they were replaced by fresh ones every 2 days. After a choice was made and the rat passed the mid-way point of the chosen arm with all four of its limbs, the experimenter placed a

wooden cube measuring 10 cm x 10 cm x 10 cm just behind the rat. This way the animal was made to stay at the end of the chosen arm for 8-10 s. Then the rat was picked up and confined in a box for an intertrial interval of 30 s. Between trials the maze was rotated 90° in a clockwise direction in order to prevent the animals from using olfactory signals to reach the goal arm. The floor of the testing room was marked to assure that the position of the maze remained constant in relation to the room cues.

As the animals reached the learning criterion they were put in their respective cages for 2 days and were not tested in any way. Starting on day 2 post-training each animal received retraining on the allocentric spatial task learned during the initial training phase. When the animal again reached the training criterion (at least 14 correct trials over two consecutive days) it was left in its cage until day 24 post-training. Starting on day 24 the animals received a second retraining in the allocentric task learned during the initial training phase, until reaching criterion (14 correct/2 consecutive days). The procedure used during each memory recall test (retention on days 2 and 24 post-learning) was identical to that of training (acquisition). During the 7 days preceding the 24-days remote memory recall test the animals were deprived of food to achieve a weight of 85-90% of their *ad libitum* body weight.

2.1.5. Histology

When the behavioral testing was complete, the rats were given an analgesic opioid (buprenorphine, 0.1 mg/kg, i.p., Bupaq®, Richter Pharma AG, Austria) and 30 min later were injected with a lethal dose of a euthanasia solution (sodium pentobarbital, 180 mg/kg, i.p., Euthoxin®, Fatro Ibérica, S. L., Spain). Animals were perfused intercardially with 0.9% saline, followed by 10% formalin. After extraction from the skull, the brains were post-fixed in 10% formalin for several days and subsequently in 10% formalin-30% sucrose until sectioning. Coronal sections (40 µm) were cut on a cryostat (Leica CM 1850, Leica Microsystems, Germany) and stained with cresyl violet, a Nissl stain.

In order to quantify the extension of the damage in each lesioned rat, regions of cell loss and gliosis identified microscopically were plotted on drawings of coronal sections from the Paxinos and Watson atlas [40]. For each DHip-lesioned rat, the reconstruction of the lesion was based on five coronal sections (anteroposterior levels from interaural zero point: +6.4, +5.7, +4.8, +3.8 and +2.9 mm). Each coronal section was digitized and the lesioned area was calculated by a computer program (ImageJ, http://imagej.nih.gov/ij/). The volume of damage was expressed as a percentage, reflecting the amount of lesioned tissue in proportion to the total volume of the hippocampus measured in 3 normal non-lesioned rats. Similarly, for each VHip-lesioned rat, the reconstruction of the lesion was made based on five coronal sections (anteroposterior levels from interaural zero point: +4.7, +4.2, +3.7, +3.2 and +2.7 mm).

2.1.6. Data analysis

In both the acquisition phase and the retraining phases, the dependent variable was the number of errors before reaching criterion. To compare the performance of the different groups one-way ANOVAs were used. Additionally, a 2-way mixed ANOVA, with group as the between-subject variable and retraining interval as the within-subject variable, was used to analyze the performance during the two retraining periods, on days 2 and 24. Post-hoc Tukey tests for the analysis of simple main effects and interaction were used where appropriate. All analyses were conducted with the Statistica software 8.0 (StatSoft, Tulsa, Oklahoma).

2.2. Experiment 2: Long-term retention of non-allocentric spatial memory acquired in rats with dorsal or ventral hippocampus lesions.

In this experiment the goal was to investigate whether DHip or VHip are necessary for long-term retention of spatial information when the spatial knowledge is acquired in a simple associative manner, i.e. based on a single cue (guidance strategy) and not on complex relationships among allocentric/allothetic cues. This experiment also served as a control experiment in which the locomotion behavior and underlying motivation to learn the task was the same as in the previous experiment. Based on numerous studies that have suggested the

hippocampal memory system is necessary for the performance of allocentric tasks but not of simple associative tasks [42-44], we hypothesized that no retention deficit would be observed in this experiment following dorsal or ventral hippocampal lesions.

2.2.1. Subjects

The subjects were 22 male Wistar rats from Charles River Laboratories (France), randomly assigned to one of the following three groups: DHip-lesioned (n = 7), VHip-lesioned (n = 8) and sham-lesioned (n = 7). The rest of the characteristics were as described in experiment 1.

2.2.2. Surgery, apparatus and histology

As described in experiment 1.

2.2.3. Behavioral procedure

Unlike the preceding experiment, here the animals had to learn to navigate to the goal arm using as a guide an intramaze cue whose spatial position changed from trial to trial. Therefore, to solve the task successfully the rats had to make use of an S-R association between the intramaze cue and the approach response [45, 46]. In its general aspects the procedure was the same as in expt. 1, except that throughout the initial training phase a piece of sandpaper measuring 10 x 60 cm (roughness reference P50) was on the floor of the variable goal arm. In two of the eight daily training trials the goal arm was positioned in the west, in two trials it was in the east, in two it was in the south and in two it was in the north. At the beginning of each trial the animal was placed in one of the three arms that did not contain the sandpaper. The order in which the different goal arms were used was randomized and it was the same for all animals. Also, the relation between the starting arm and the goal arm was controlled to ensure that at the end of the training period the number of trials in which the goal arm was located to the right, left or opposite the starting arm was the same. This created a situation in which the extramaze information was not relevant and the animal needed to use a ‘guidance’ strategy instead of an

allocentric strategy to effectively solve the spatial problem [42, 45, 46]. Training ended when each animal reached a learning criterion of at least 14 correct trials over two consecutive days.

Once the animals reached the learning criterion two retention tests were applied, 2 days and 24 days after acquisition, in order to evaluate recent and remote memory of the non-allocentric information learned during the acquisition phase. The procedure used during the retraining phases of the experiment was identical to that of the acquisition phase.

2.2.4. Data analyses

As described in experiment 1.

3. Results

3.1. Histological findings

Dorsal hippocampal lesions. The extent of DHip damage was similar in the lesioned groups of expt. 1 and expt. 2. The lesion began at the rostral pole of the DHip with the dentate gyrus and all CA fields were affected at this level (Figure 1). At intermediate levels, specifically at the level of the ventromedial nucleus of the hypothalamus and the mammillary nuclei, the lesion had a similar configuration, with extensive zones showing necrosis or missing tissue in the hippocampal fields CA1-CA3. The most lateral zone of the CA3 field, however, appeared intact in all rats. At this level, in most cases the dentate gyrus was affected but its most medial region appeared intact to varying degrees in most rats. Lesions ended between +3.3 mm and +3.0 mm anterior to the interaural zero point [40], at the beginning of the Sylvius aqueduct. At this level the dorsal hippocampal fields CA1 and CA3 and the dentate gyrus were affected to varying degrees in all the animals. In all the rats the intermediate and ventral regions of the hippocampus remained completely intact. The amount of lesioned tissue, starting from the dorsal pole, in relation to the total volume of the hippocampus, was 42.7 $\pm$ 1.2 % (mean $\pm$ SEM) in expt. 1 and 47.6 $\pm$ 1.3 % in expt. 2.

Ventral hippocampal lesions. In most animals, the lesions began +4.8/+4.6 mm anterior to the interaural zero point and ended +2.5/+2.2 mm anterior to this point [40]. In the rostral region of the lesion, coinciding with the most posterior area of the mammillary bodies of the hypothalamus, extensive cell loss and intense gliosis were observed in CA1-CA3 subfields of the VHip in all the animals, with little variation in the extent of the damage (Figure 1). The most ventral area of the dentate gyrus, however, was spared in most animals. This configuration was maintained throughout all the anteroposterior extension of the lesions. The amount of lesioned tissue, starting from the ventral pole and in relation to the total volume of the hippocampus, was 33.1 $\pm$ 1 % (mean $\pm$ SEM) in expt. 1 and 36.7 $\pm$ 1.1 % in expt. 2. No differences were observed in the extension of the lesion between experiments ($F<1$).

Given that some studies using a genomic-neuroanatomic approach have divided fields CA1 and CA3 into three distinct domains along the longitudinal axis (dorsal, intermediate and ventral), we tried to determine the degree to which the ventral lesions had affected the intermediate hippocampus [47, 48]. To determine the extension of the lesion in the intermediate hippocampus, we selected plates +4.2, +3.7 and +3.2 of the Paxinos and Watson atlas [40], in which the anteroposterior extension of the intermediate hippocampus is represented. At these levels the intermediate-ventral border is approximately level with the dorsal edge of the rhinal fissure [47, 48; see also 28]. It should be noted that, although the genetic-anatomic analyses done by Thompson et al. [47] and by Dong et al. [48] were performed on C57BL/6J mice, the three domains correspond approximately to the septal (dorsal), caudal (intermediate) and temporal (ventral) poles defined in the rat based on connectivity data [49]. Histological results indicated that in our two experiments the ventral region of the intermediate hippocampus was affected in all rats. The mean volume of damaged tissue in the intermediate hippocampus, in relation to its total extension as measured in 3 normal non-lesioned rats, was 23.2 $\pm$ 2.1 % (mean $\pm$ SEM) in expt. 1 and 28.5 $\pm$ 2.3 % in expt. 2. In one animal from expt. 1 and in another from expt. 2, unilateral damage was seen to affect 59% and 63%, respectively, of the total extension of the intermediate hippocampus. In these rats, however, ventral hippocampus

damage presented practically the same extension as in the rest of the animals. Finally, no rat was seen to have sustained damage in the adjacent perirhinal or entorhinal cortices, or in the piriform cortex, in either expt. 1 or expt. 2. Likewise, no damage was apparent in the caudal part of the basolateral and central nuclei of the amygdala. In all the rats of both experiments the septal region of the hippocampus remained completely intact.

3.2. Behavioral findings

3.2.1. Experiment 1

Figure 2A depicts the performance of the DHip, VHip and control groups during the acquisition phase. A one-way ANOVA revealed significant differences in relation to the number of incorrect trials effected before reaching criterion ($F_{2,20} = 14.54$, $p<0.0001$, $\eta^2_p = 0.59$). Post-hoc Tukey tests showed that VHip-lesioned rats learned the task similarly to the controls ($p = 0.99$), while DHip-lesioned rats showed a profound deficit in acquisition, making significantly more errors before reaching criterion than the controls ($p<0.0004$) and also more than the VHip-lesioned rats ($p<0.0004$).

The data obtained during the two retraining periods are depicted in Figure 2B. The main results indicated that the three groups of rats performed the spatial task perfectly 2 days (recent memory) after the end of the acquisition phase, but at 24 days (remote memory) a profound impairment was observed in both lesioned groups, although it was of greater magnitude in DHip-lesioned subjects. These impressions were confirmed by a 2-way mixed ANOVA, with group as the between-subject variable and retraining interval as the within-subject variable, that analyzed the number of errors before reaching criterion during the retraining phases of testing. The results of the ANOVA revealed a significant effect in the factor group ($F_{2,20} = 16.68$, $p<0.0001$, $\eta^2_p = 0.65$), retraining interval ($F_{1,20} = 28.16$, $p<0.0001$, $\eta^2_p = 0.58$) and interaction ($F_{2,20} = 9.23$, $p<0.001$, $\eta^2_p = 0.48$). To analyze the interaction Tukey tests were conducted. During the 2-days recent memory test no significant differences were found in the number of errors before reaching the criterion, in either the DHip (DHip vs. sham, $p = 0.97$) or the VHip-

lesioned group (VHip vs. sham, p = 1.0). Neither were any differences found upon comparing the two lesioned groups (DHip vs. VHip, p = 0.97). In contrast, during the 24-days remote memory test Tukey tests did reveal a profound deficit to criterion in the DHip (DHip vs. sham, p<0.0001) and in the VHip group (VHip vs. sham, p<0.01). Also, DHip-lesioned animals made significantly more errors before reaching criterion than VHip-lesioned rats (DHip vs. VHip-lesioned, p<0.002).

Overall, these results suggest that although rats with DHip and VHip lesions can learn a place discrimination task to the same level of mastery as the sham group and they can retain it 2 days after acquisition, long-term spatial retention is profoundly disrupted in both lesioned groups. These findings also indicate that the deficit is greater in the DHip group than in the VHip group.

3.2.2. Experiment 2

Figure 3A shows the performance during acquisition of the three groups used in this experiment. A one-way ANOVA found no significant differences between the groups in the number of errors before reaching acquisition criterion ($F_{2,19} = 1.43$, p = 0.26).

In Figure 3B the performance of the three groups during the two memory retention tests is shown. A 2-way mixed ANOVA (3 group, between-subject variable x 2 retraining interval, within-subject variable) revealed that lesioned and control groups did not differ significantly in the number of errors to again reach criterion, either 2 days or 24 days after acquisition. The analysis indicated that only the retraining interval factor was significant (group, $F_{2,19} = 1.03$, p = 0.37; retraining interval $F_{1,19} = 36.90$, p<0.0001, $\eta^2_p = 0.66$; interaction $F_{2,19} = 0.51$, p = 0.51). Thus, taken together, in clear contrast with the data of expt. 1, the results of expt. 2 indicate that neither the absence of the DHip nor the absence of the VHip prevent spatial memory acquired using a guidance strategy, from becoming a stable, long-term memory.

4. Discussion

To determine how the DHip vs. VHip contributes to long-term spatial memory retention, lesioned rats learned a spatial task based on allothetic cues in a four-arm plus-shaped maze and then, 2 days and 24 days after learning, retention tests were applied (expt. 1). With respect to initial acquisition, the DHip-lesioned animals exhibited impairment when learning the task, although with overtraining they were able to overcome the deficit and most animals attained a performance level indistinguishable from that of the control group. As for the VHip-lesioned animals, they learned the task at the same rate as the control subjects, with no deficit in acquisition being detected. The most interesting findings of this experiment were obtained during the two post-learning retention tests. While no retention deficit was detected 2 days after the learning, in the remote memory test 24 days after the learning both lesioned groups showed a profound deficit relative to controls. In contrast, in expt. 2, in which the spatial task learned during the acquisition phase was based on a guidance strategy, both lesioned groups performed the two retention tests, 2 days and 24 days after learning, just as well as control animals, with no deficit in retention being found. These results suggest that both DHip and VHip play a critical role in the long-term retention of spatial memories when the spatial information is learned based on allocentric/allothetic cues. However, our data indicate that the deficit in long-term retention is greater in DHip-lesioned than in VHip-lesioned rats.

An initial question raised by this data is what structures have mediated in the acquisition of the allocentric task in the hippocampus-lesioned groups of expt. 1. Given that the rats have partial lesions to the hippocampal dorsoventral axis, one possibility is that each group of rats learned the task with the hippocampal region that remained unlesioned, that is, the DHip-lesioned animals with at least the intact ventral region and the VHip-lesioned animals with at least the dorsal subregion. There is considerable data supporting the idea that both the dorsal and the ventral hippocampus are involved in allocentric processing and navigation. Firstly, some studies have shown that the dorsal and ventral hippocampus can act synergically during spatial navigation. For example, using the reference memory version of the water maze, one study found that small, separate lesions limited to the dorsal or the ventral subregions in mice

(affecting, respectively, 18.9% and 28.5% of the total hippocampal volume) did not result in any deficit in acquisition of the task. However, in a third group of mice, the combination of the two subtotal lesions (dorsal plus ventral) did significantly impair acquisition [50]. Similarly, another recent study in the water maze showed that rats with crossed inactivation (of the DHip in one hemisphere and the VHip in the contralateral hemisphere) performed the task significantly worse than ipsilateral lesioned or sham-operated animals [51]. Thus, both hippocampal subregions normally contribute to allocentric learning. Secondly, studies using single-unit recording techniques have found place cells in both the dorsal and the ventral hippocampus, with both sets of neurons being sensitive to manipulations in the environment's characteristics [52-54]. A critical difference between the two populations of cells is that dorsal place cells present fields that are small in size and have more stable and spatially selective firing fields than ventral place cells [52-54]. Yet, despite the superiority of DHip place cells in spatial processing, a recent study showed that it is possible to extract high resolution spatial information from population activity in the VHip, which suggests that this subregion, in and of itself, is sufficient for generating an accurate representation of the environment [55]. Thirdly, several studies involving rats have observed a high expression of immediate early genes in DHip and VHip, in goal-directed navigation or simply in spatial sampling tasks [56-58]. Although in these studies dorsal expression was higher than ventral, which concords with the acquisition impairment found after DHip lesions in our expt. 1, it is important to note that ventral pyramidal cells did show behaviorally-induced Arc mRNA expression above that of control rats, suggesting an active role of the ventral subregion in spatial navigation [56]. Fourthly and finally, some studies have shown that excitotoxic lesions to the dorsal or ventral hippocampus after acquisition of an allocentric task produced a deficit in retrieval in both lesioned groups [37, 59, 60]. Additionally, using the reference memory version of the water maze task, a study found that lidocaine infusion before a probe trial, in dorsal or ventral hippocampus, disrupted retrieval performance in a similar manner [61]. This data suggests that allocentric learning in an intact brain occurs over a distributed hippocampal network involving

dorsal and ventral subregions and, in consequence, both areas normally contribute to spatial navigation. Overall, the above data suggest that in the lesioned rats of our expt. 1, the functionally intact area of the hippocampus (dorsal in VHip-lesioned rats and ventral in DHip-lesioned rats) can overcome any possible deficit in acquisition. In addition, our data suggest that lesioned animals in expt. 1 probably acquire the task using complex relationships among allothetic cues and not using a simple associative strategy. If they had used a single cue of the experimental room for learning, the lesioned rats of expt. 1 would not have exhibited any deficit in retaining the task 24 days after learning (as in our expt. 2), yet the retention deficit in dorsal and ventral-lesioned rats was profound.

The central finding of this study is the absence of a retention deficit in dorsal and ventral lesioned rats 2 days after learning but a significant deficit 24 days after learning. In DHip-lesioned rats, previous studies have shown a similar deficit in long-term retention using spatial [30, 31, 39] and non-spatial paradigms [62, 63]. However, to the best of our knowledge, the present study is the first to demonstrate intact recent spatial memory but impaired long-term spatial memory in rats with specific damage to the VHip. Yet the deficit in long-term retention was greater in DHip than in VHip-damaged rats. Taken together, our results suggest that although lesioned animals have probably learned the allocentric task with only one subregion of the hippocampus, the persistence of the memory formed requires that both subregions, dorsal and ventral, function normally during a post-learning period. Thus, dorsal and ventral hippocampus does play a critical role in the transformation of this recent memory to a more stable remote state. This interpretation fits with various systems consolidation theories that defend the necessity in rodents of hippocampus-neocortical interactions for days or weeks after learning [3, 4]. In the lesioned animals of expt. 1 this interaction probably occurred in a defective manner due to the pre-training hippocampal damage, resulting in impaired long-term retention. Our data, therefore, show not only that the DHip is vital for the transformation of spatial memory from recent to a more stable remote state but also that the VHip contributes significantly to this process.

The fact that the same rats have been probed twice, 2 days and 24 days after learning, raises an alternative interpretation of our results, different from the one suggested above. It could be that hippocampal lesions disrupted not the systems consolidation process but the spatial memory reconsolidation process that may, presumably, have been triggered by the reactivation of the memory trace at the recent time point (2 days). If so, performance at the remote time point (24 days) would be disrupted as well. However, some studies have demonstrated that there are boundary conditions for the reconsolidation phenomenon [64, 65]. In this regard, first, it has been proposed that one main function of reconsolidation is memory updating [66]. However, in the absence of new information updating is not necessary and some studies, using spatial and non-spatial paradigms, have observed that memory does not undergo reconsolidation if the task was well-learned, as was the case in our first experiment [67-69]. Second, reconsolidation requires new protein synthesis [67, 70]. In relation to this, one study found that the administration of anisomycin in the DHip following reactivation of recent spatial memory did not affect reconsolidation nor did it impair memory performance when a distributed or double massed acquisition procedure was used (strongly acquired memory). For anisomycin to disrupt reconsolidation and affect the performance the reactivation trial would have had to take place 1 week or 1 month after the initial acquisition [71]. Therefore, based on the aforementioned studies and taking into account that our first experiment used a learning procedure leading to an asymptotic level of performance and a well-learned task, it is most likely that the recent memory test 2 days after learning did not trigger a reconsolidation period. So, our results are better interpreted in terms of a disruption of the consolidation and not of the reconsolidation process.

Previous findings have also suggested the necessity of an intact hippocampus after learning in order for spatial memory consolidation to occur normally. First, in one representative study, reversible inactivation of the AMPA/kainate receptors of the dorsal hippocampus was maintained chronically for 7 consecutive days, beginning either 1 or 5 days after learning [72]. A memory retention test was applied 16 days after learning, with the hippocampus once again functionally intact. The results revealed a profound deficit in retention, regardless of the day that

inactivation began. In the study by Riedel et al. [72], however, it is unclear if the pharmacological inactivation affected only hippocampus-neocortical interaction or if it might also have affected the very engrams initially stored in the hippocampus [73]. In expt. 1 of our study, though, memory traces are formed in lesioned brains, which are used optimally 2 days later for recent memory retrieval. Thus, the deficit in remote memory observed in our study might be better explained by a deterioration in the process of systems consolidation itself, and not by the lesions affecting the memory traces formed during initial learning, since the memory traces were formed in rats that were already lesioned. Second, in a study by Remondes and Schuman [74] the temporoammonic pathway in rats was damaged from the entorhinal cortex to the CA1 hippocampal area. Lesioned and sham rats were both able to learn the reference spatial memory version of the water maze and exhibited perfect retention 24-h after learning. However, spatial memory formed in lesioned rats decayed over time more rapidly than in controls, as confirmed by a probe test performed 28 days after learning. So, ongoing cortical input conveyed by the temporoammonic pathway is required to maintain a normal hippocampus-neocortex dialogue and consolidate long-term spatial memory. Third, a recent study using a contextual fear conditioning paradigm observed that after optogenetically inhibiting the interaction between dorsal hippocampus and medial prefrontal cortex during training, there was selective disruption in long-term memory retrieval (test days 15 and 22) but no disruption in recent memory (test days 2 and 8 post-training) [75].

Little is known about how the consolidation mechanisms are modulated by post-training hippocampal activity so that remote memory engrams can develop normally. A few recent studies have shed light on this question, suggesting that the nature of memory traces is quite dynamic [6, 76, 77]. In agreement with the foregoing, some studies have shown that during contextual fear conditioning two memory traces are generated, one in the hippocampus and one in specific regions of the cortex, mainly the medial prefrontal cortex [78, 79]. However, although two memory traces are formed quickly during the learning, the neocortical engram is generated in a silent way and cannot be activated by natural recall cues until systems

consolidation occurs [75, 78, 79]. Other studies have shown that silent engram cells in the medial prefrontal cortex, critical for long-term memory, gradually mature in the period of systems consolidation [13, 75, 77]. Furthermore, importantly, this gradual maturation depends directly on post-learning hippocampus activity. Thus, post-training chronic inhibition of the projections from the dentate gyrus engram cells to the medial prefrontal cortex engram cells 1 day after contextual fear conditioning blocked the increase in the dendritic spine density of the silent neocortical engram and, consequently, impaired remote memory retrieval [75, see also 13, 77]. Future studies, however, should directly explore the dynamics of neocortical remote engrams in rats with a defective hippocampus/neocortex interaction during the post-learning period.

In conclusion, our data indicate that although the brain of DHip or VHip-lesioned rats can form memory traces that support recent memory 2 days after learning, remote memory retrieval 24 days after learning was severely affected in these groups. Thus, long-term spatial memory formation requires that both the dorsal and ventral hippocampus function normally during the systems consolidation period. Finally, the present results are among a growing number of studies published in recent years that give the VHip a significant role in spatial cognition. Thus, our findings agree with the recent idea of a progressive gradient from the dorsal to the ventral hippocampus, rather than a strict functional division along the longitudinal hippocampal axis.

Accepted Version - *Behavioural Brain Research*, 431 (2022) 113962
https://doi.org/10.1016/j.bbr.2022.113962

FIGURE 1

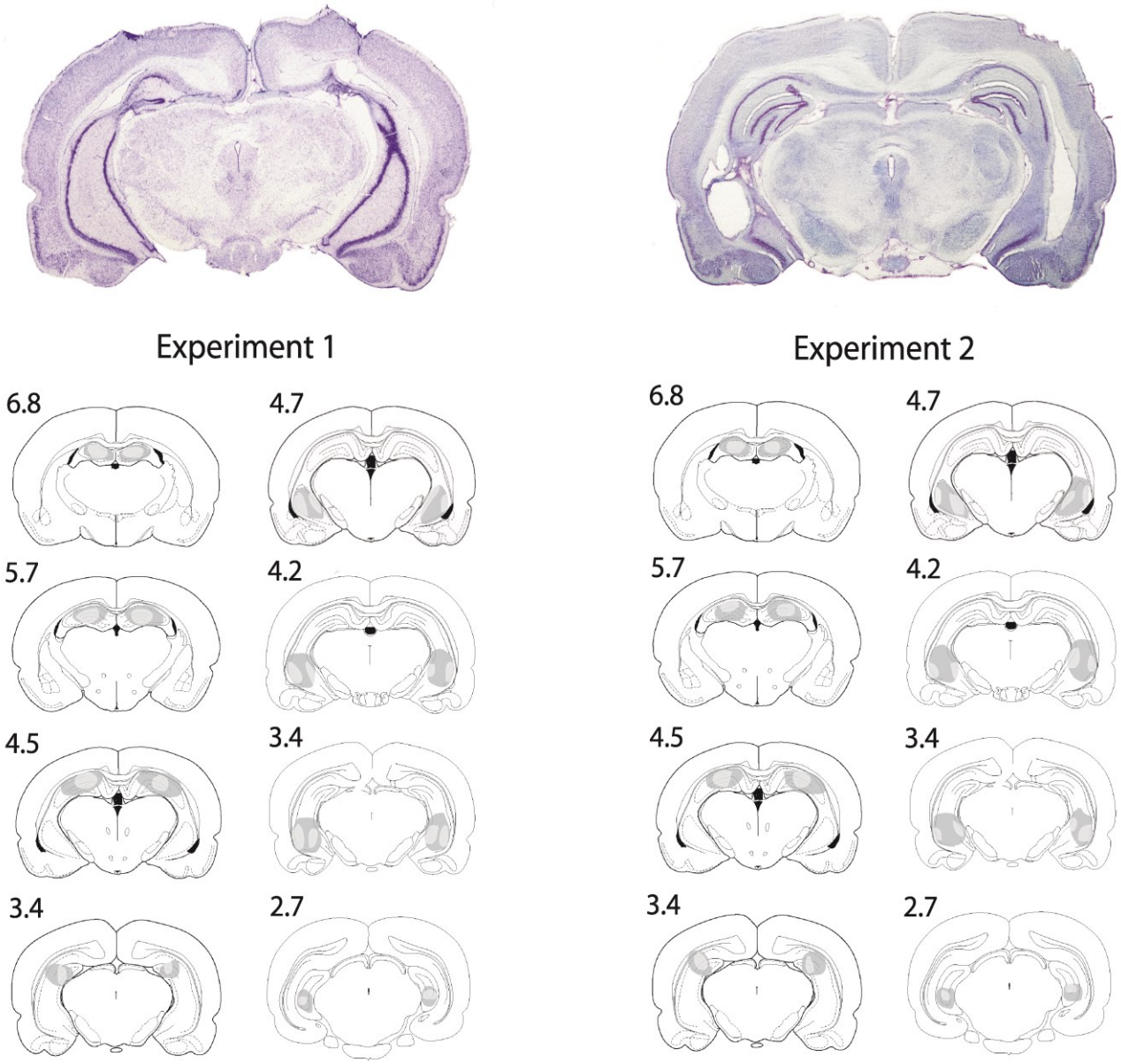

Figure 1. Photomicrographs showing representative lesions and serial reconstruction of the smallest (central white area) and largest (gray) excitotoxic lesions of the dorsal and ventral hippocampus. Anteroposterior coordinates are shown in relation to the interaural zero point [40].

Accepted Version - *Behavioural Brain Research*, 431 (2022) 113962
https://doi.org/10.1016/j.bbr.2022.113962

FIGURE 2

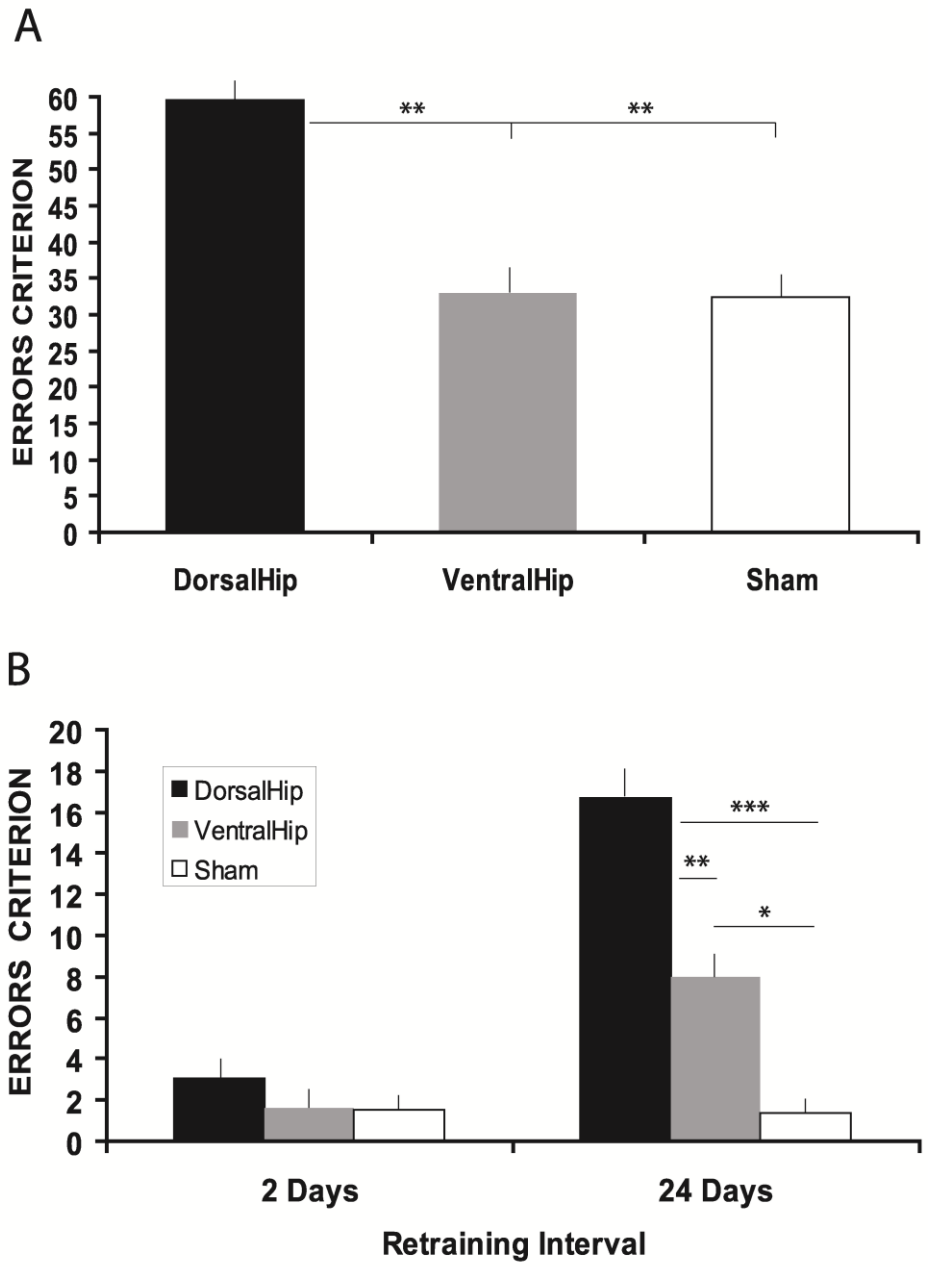

Figure 2. Experiment 1. A) Acquisition of a spatial reference memory task in a four-arm plus-shaped maze: Mean (±SEM) number of errors before criterion for the DHip, VHip and control groups during the training (acquisition) phase of testing. B) Retraining: Mean (±SEM) number of errors before criterion for the DHip, VHip and control groups during the 2-days and the 24-days memory recall tests. *** $p<0.0001$, ** from $p<0.01$ to $p<0.001$; * from $p<0.05$ to $p<0.01$.

FIGURE 3

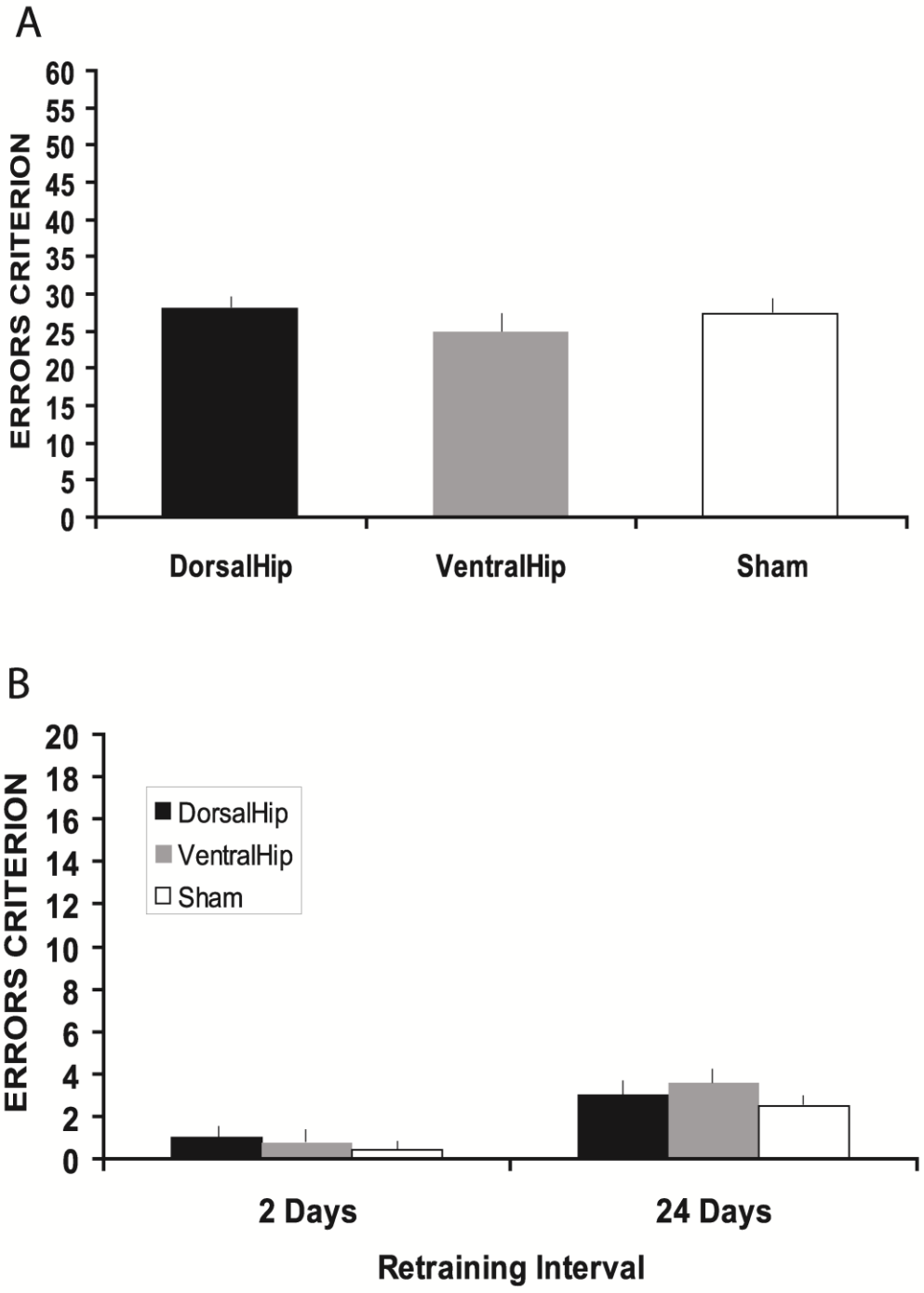

Figure 3. Experiment 2. A) Acquisition of a cue-guided navigation task in a four-arm plus-shaped maze: Mean (±SEM) number of errors before criterion for the DHip, VHip and control groups during the training phase (acquisition) of testing. B) Retraining: Mean (±SEM) number of errors before criterion for the DHip, VHip and control groups during the 2-days and the 24-days memory recall tests.

Acknowledgements

This work was supported by a grant from the Spanish Subdirección General de Proyectos de Investigación, Ministerio de Economía y Competitividad (Madrid, Spain) and the European Regional Development Fund – ERDF (PSI2013-41098-P). The author declares no conflict of interest. We thank Alexia Weninger for editing the language of the manuscript.

References

[1] J.L. McClelland, B.L. McNaughton, R.C. O'Reilly, Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory, Psychol. Rev. 102 (1995) 419-457.

[2] S-H. Wang, R.G.M. Morris, Hippocampal-neocortical interactions in memory formation, consolidation, and reconsolidation, Ann. Rev. Psychol. 61 (2010) 49-79.

[3] P.W. Frankland, B. Bontempi, The organization of recent and remote memories, Nat. Rev. Neurosci. 6 (2005) 119-130.

[4] L.R. Squire, L. Genzel, J.T. Wixted, R.G. Morris, Memory consolidation, Cold Spring Harb. Perspect. Biol. 7 (2015) a021766.

[5] Y. Dudai, A. Karni, J. Born, The consolidation and transformation of memory, Neuron 88 (2015) 20-32.

[6] S. Tonegawa, M.D. Morrissey, T. Kitamura, The role of engram cells in the systems consolidation of memory, Nat. Rev. Neurosci. 19 (2018) 485-498.

[7] M. Moscovitch, R. Cabeza, G. Winocur, L. Nadel, Episodic memory and beyond: the hippocampus and neocortex in transformation, Annu. Rev. Psychol. 67 (2016) 105-134.

[8] N. Kapur, D.J. Brooks, Temporally specific retrograde amnesia in two cases of discrete bilateral hippocampal pathology, Hippocampus 9 (1999) 247-254.

[9] C.B. Kirwan, P.J. Bayley, V.V. Galván, L.R. Squire, Detailed recollection of remote autobiographical memory after damage to the medial temporal lobe, Proc. Natl. Acad. Sci. 105 (2008) 2676-2680.

[10] K.K. Tayler, K.Z. Tanaka, L.G. Reijmers, B.J. Wiltgen, Reactivation of neural ensembles during the retrieval of recent and remote memory, Curr. Biol. 23 (2013) 99-106.

[11] G. Winocur, M.J. Sekeres, M.A. Binns, M. Moscovitch, Hippocampal lesions produce both nongraded and temporally graded retrograde amnesia in the same rat, Hippocampus 28 (2013) 330-341.

[12] R.E. Clark, N.J. Broadbent, S.M. Zola, L.R. Squire, Anterograde amnesia and temporally graded retrograde amnesia for a nonspatial memory task after lesions of hippocampus and subiculum, J. Neurosci. 22 (2002) 4663-4669.

[13] E. Lesburgueres, O. Gobbo, S. Alaux-Cantin, A. Hambucken, P. Trifilieff, B. Bontempi, Early tagging of cortical networks is required for the formation of enduring associative memory, Science 331 (2011) 924-928.

[14] K. Takehara, S. Kawahara, Y. Kirino, Time-dependent reorganization of the brain components underlying memory retention in trace eyeblink conditioning, J. Neurosci. 23 (2003) 9897-9905.

[15] K. Takehara-Nishiuchi, B.L. McNaughton, Spontaneous changes of neocortical code for associative memory during consolidation, Science 322 (2008) 960-963.

[16] R.E. Clark, N.J. Broadbent, L.R. Squire, Impaired remote spatial memory after hippocampal lesions despite extensive training beginning early in life, Hippocampus 15 (2005) 340-346.

[17] S.J. Martin, L. de Hoz, R.G.M. Morris, Retrograde amnesia: neither partial nor complete hippocampal lesions in rats result in preferential sparing of remote spatial memory, even after reminding, Neuropsychologia 43 (2005) 609-624.

[18] A.C. Ocampo, L.R. Squire, R.E. Clark, Hippocampal area CA1 and remote memory in rats, Learn. Mem. 24 (2017) 563-568.

[19] T. Maviel, T.P. Durkin, F. Menzaghi, B. Bontempi, Sites of neocortical reorganization critical for remote spatial memory, Science 305 (2004) 96-99.

[20] G. Winocur, M. Moscovitch, S. Fogel, R.S. Rosenbaum, M. Sekeres, Preserved spatial memory after hippocampal lesions: effects of extensive experience in a complex environment, Nat. Neurosci. 8 (2005) 273-275.

[21] S. Gaskin, M. Tardif, D.G. Mumby, Pattern of retrograde amnesia for recent and remote incidental spatial learning in rats, Hippocampus 19 (2009) 1212-1221.

[22] P.W. Frankland, B. Bontempi, L.E. Talton, L. Kaczmarek, A.J. Silva, The involvement of the anterior cingulate cortex in remote contextual fear memory, Science 304 (2004) 881-883.

[23] J. Lopez, K. Herbeaux, B. Cosquer, M. Engeln, C. Muller, C. Lazarus, C. Kelche, B. Bontempi, J-C. Cassel, A. Pereira de Vasconcelos, Context-dependent modulation of hippocampal and cortical recruitment during remote spatial memory retrieval, Hippocampus, 22 (2012) 827-841.

[24] C.M. Teixeira, S.R. Pomedli, H.R. Maei, N. Kee, P.W. Frankland, Involvement of the anterior cingulate cortex in he expression of remote spatial memory, J. Neurosci. 26 (2006) 7555-7564.

[25] B. Bontempi, C. Laurent-Demir, C. Destrade, R. Jaffard, Time-dependent reorganization of brain circuitry underlying long-term memory storage, Nature 400 (1999) 671-675.

[26] D.N. Barry, A.N. Coogan, S. Commins, The time course of systems consolidation of spatial memory from recent to remote retention: a comparison of the immediate early genes Zif268, c-Fos and Arc, Neurobiol. Learn. Mem. 128 (2016) 46-55.

[27] D.M. Bannerman, R. Sprengel, D.J. Sanderson, S.B. McHugh, N.P. Rawlins, H. Monyer, P.H. Seeburg, Hippocampal synaptic plasticity, spatial memory and anxiety, Nat. Rev. Neurosci. 15 (2014) 181-192.

[28] M.S. Fanselow, H-W. Dong, Are the dorsal and ventral hippocampus functionally distinct structures? Neuron 65 (2010) 7-19.

[29] M.A. Kheirbek, K.C. Klemenhagen, A. Sahay, R. Hen, Differential control of learning and anxiety along the dorsoventral axis of the dentate gyrus, Neuron 77 (2013) 955-968.

[30] J.M.J. Ramos, Long-term spatial memory in rats with hippocampal lesions, Eur. J. Neurosci. 12 (2000) 3375-3384.

[31] J.M.J. Ramos, Hippocampal damage impairs long-term spatial memory in rats: comparison between electrolytic and neurotoxic lesions, Physiol. Behav. 93 (2008) 1078-1085.

[32] S. Ruediger, D. Spirig, F. Donato, P. Caroni, Goal-oriented searching mediated by ventral hippocampus early in trial-and-error learning, Nat. Neurosci. 15 (2012) 1563-1571.

[33] S. Riaz, A. Schumacher, S. Sivagurunathan, M. van der Meer, R. Ito, Ventral, but not dorsal, hippocampus inactivation impairs reward memory expression and retrieval in contexts defined by proximal cues, Hippocampus 27 (2017) 822-836.

[34] M. Contreras, T. Pelc, M. Llofriu, A. Weitzenfeld, J-M. Fellous, The ventral hippocampus is involved in multi-goal obstacle-rich spatial navigation, Hippocampus 28 (2018) 853-866.

[35] T.M. Jay, M.P. Witter, Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of Phaseolus vulgaris-leucoagglutinin, J. Comp. Neurol. 313 (1991) 574-586.

[36] W.B. Hoover, R.P. Vertes, Anatomical analysis of afferent projections to the medial prefrontal cortex in the rat, Brain Struct. Funct. 2012 (2007) 149-179.

[37] J.M.J. Ramos, I. Morón, Ventral hippocampus lesions and allocentric spatial memory in the radial maze: anterograde and retrograde deficits, Behav. Brain Res. 417 (2022) 113620.

[38] B.A. Strange, M.P. Witter, E.S. Lein, E.I. Moser, Functional organization of the hippocampal longitudinal axis, Nat. Rev. Neurosci. 15 (2014) 655-669.

[39] J.M.J. Ramos, Retention of spatial information in hippocampally damaged rats overtrained on a cartographic task, Brain Res. 879 (2000) 200-203.

[40] G. Paxinos, D. Watson, The Rat Brain in Stereotaxic Coordinates, fourth ed., Academic Press, New York, 1998.

[41] J.M.J. Ramos, Influence of the shape of the experimental room on spatial learning in the rat, Physiol. Behav. 70 (2000) 351-357.

[42] J. O'Keefe, L. Nadel, The Hippocampus as a Cognitive Map, Oxford Univesity Press, New York, 1978.

[43] R.J. McDonald, N.M. White, A triple dissociation of memory systems: hippocampus, amygdala and dorsal striatum, Behav. Neurosci. 107 (1993) 3-22.

[44] J.M.J. Ramos, Profound retrograde but absence of anterograde amnesia for cued place learning in rats with hippocampal lesions, Behav. Brain Res. 236 (2013) 102-109.

[45] M.G. Packard, R. Hirsh, N.M. White, Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: evidence for multiple memory systems, J. Neurosci. 9 (1989) 1465-1472.

[46] R.J. McDonald, N.S. Hong, How does a specific learning and memory system in the mammalian brain gain control of behavior? Hippocampus 23 (2013) 1084-1102.

[47] C.L. Thompson, S.D. Pathak, A. Jeromin, L.L. Ng, C.R. MacPherson, M.T. Mortrud, A. Cusick, Z.L. Riley, S.M. Sunkin, A. Bernard, et al., Genomic anatomy of the hippocampus, Neuron 26 (2008) 1010-1021.

[48] H.W. Dong, L.W. Swanson, L. Chen, M.S. Fanselow, A.W. Toga, Genomic-anatomic evidence for distinct functional domains in hippocampal field CA1, Proc. Natl. Acad. Sci. U.S.A. 106 (2009) 11794-11799.

[49] L.W. Swanson, W.M. Cowan, An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat, J. Comp. Neurol. 172 (1977) 49-84.

[50] J. Hauser, L.H. Llano López, J. Feldon, P.A. Gargiulo, B.K. Yee, Small lesions of the dorsal or ventral hippocampus subregions are associated with distinct impairments in working memory and reference memory retrieval, and combining them attenuates the acquisition rate of spatial reference memory, Hippocampus 30 (2020) 938-957.

[51] S.L. Lee, D. Lew, V. Wickenheisser, E.J. Markus, 2019. Interdependence between dorsal and ventral hippocampus during spatial navigation. Brain Behav. 9, e01410.

[52] M.W. Jung, S.I. Wiener, B.L. McNaughton, Comparison of spatial firing characteristics of units in dorsal and ventral hippocampus of the rat, J. Neurosci. 14 (1994) 7347-7356.

[53] A.P. Maurer, S.R. Vanrhoads, G.R. Sutherland, P. Lipa, B.L. McNaughton, Self-motion and the origin of differential spatial scaling along the septo-temporal axis of the hippocampus, Hippocampus 15 (2005) 841-852.

[54] K.B. Kjelstrup, T. Solstad, V.H. Brun, T. Hafting, S. Leutgeb, M.P. Witter, E. Moser, M-B. Moser, Finite scale of spatial representation in the hippocampus, Science 321 (2008) 140-143.

[55] A.T. Keinath, M.E. Wang, E.G. Wann, R.K. Yuan, J.T. Dudman, I.A. Muzzio, Precise spatial coding is preserved along the longitudinal hippocampal axis, Hippocampus 24 (2014) 1533-1548.

[56] M.K. Chawla, V.L. Sutherland, K. Olson, B.L. McNaughton, C.A. Barnes, Behavior-driven arc expression is reduced in all ventral hippocampal subfields compared to CA1, CA3, and dentate gyrus in rat dorsal hippocampus, Hippocampus 28 (2018) 178-185.

[57] J.Q. Lee, A.M. Demchuk, E. Morgan, R. McHugh, B.L. McNaughton, R.J. Sutherland, R.J. McDonald, Place navigation in the Morris water task results in greater nuclear Arc mRNA expression in dorsal compared to ventral CA1, Hippocampus 29 (2019) 1133-1138.

[58] Z. Beer, C. Chwiesko, M.M. Sauvage, Processing of spatial and non-spatial information reveals functional homogeneity along the dorso-ventral axis of CA3, but not CA1, Neurobiol. Learn. Mem. 111 (2014) 56-64.

[59] M.B. Moser, E.I. Moser, Distributed encoding and retrieval of spatial memory in the hippocampus, J. Neurosci. 18 (1998) 7535-7542.

[60] L. de Hoz, S.J. Martin, Double dissociation between the contributions of the septal and temporal hippocampus to spatial learning: the role of prior experience, Hippocampus 24 (2014) 990-1005.

[61] M. Loureiro, L. Lecourtier, M. Engeln, J. Lopez, B. Cosquer, K. Geiger, C. Kelche, J-C. Cassel, A. Pereira de Vasconcelos, The ventral hippocampus is necessary for expressing a spatial memory, Brain Struct. Funct. 217 (2012) 93-106.

[62] N. Vnek, L.A. Rothblat, The hippocampus and long-term object memory in the rat, J. Neurosci. 16 (1996) 2780-2787.

[63] M. Zelikowsky, S. Bissiere, M.S. Fanselow, Contextual fear memories formed in the absence of the dorsal hippocampus decay across time, J. Neurosci. 32 (2012) 3393-3397.

[64] Y. Dudai, Reconsolidation: the advantage of being refocused, Curr. Opin. Neurobiol. 16 (2006) 174-178.

[65] S. McKenzie, H. Eichenbaum, Consolidation and reconsolidation: two lives of memories? Neuron 71 (2011) 224-233.

[66] J.I. Rossato, L.R. Bevilaqua, J.H. Medina, I. Izquierdo, M. Cammarota, Retrieval induces hippocampal-dependent reconsolidation of spatial memory, Learn. Mem. 13 (2006) 431-440.

[67] R.G. Morris, J. Inglis, J.A. Ainge, H.J. Olverman, J. Tulloch, Y. Dudai, P.A. Kelly, Memory reconsolidation: sensitivity of spatial memory to inhibition of protein synthesis in dorsal hippocampus during encoding and retrieval, Neuron 50 (2006) 479-489.

[68] C.J. Rodriguez-Ortiz, V. De la Cruz, R. Gutierrez, F. Bermudez-Rattoni, Protein synthesis underlies post-retrieval memory consolidation to a restricted degree only when updated information is obtained, Learn. Mem. 12 (2005) 533-537.

[69] B.D. Winters, M.C. Tucci, M. DaCosta-Furtado, Older and stronger object memories are selectively destabilized by reactivation in the presence of new information, Learn. Mem. 16 (2009) 545-553.

[70] K. Nader, Memory traces unbound, Trends Neurosci. 26 (2003) 65-72.

[71] X. De Jaeger, J. Courtey, M. Brus, J. Artinian, H. Villain, E. Bacquié, P. Roullet, Characterization of spatial memory reconsolidation, Learn. Mem. 21 (2014) 316-324.

[72] G. Riedel, J. Micheau, A.G. Lam, E.L. Rolof, S.J. Martin, H. Bridge, L. de Hoz, B. Poeschel, J. McCulloch, R.G. Morris, Reversible neural inactivation reveals hippocampal participation in several memory processes, Nat. Neurosci. 2 (1999) 898-905.

[73] L. Nadel, M. Moscovitch, Memory consolidation, retrograde amnesia and the hippocampal complex, Curr. Opin. Neurobiol. 7 (1997) 217-227.

[74] M. Remondes, E.M. Schuman, Role for a cortical input to hippocampal area CA1 in the consolidation of a long-term memory, Nature 431 (2004) 699-703.

[75] T. Kitamura, S.K. Ogawa, D.S. Roy, T. Okuyama, M.D. Morrissey, L.M. Smith, R.L. Redondo, S. Tonegawa, Engrams and circuits crucial for systems consolidation of a memory, Science 356 (2017) 73-78.

[76] S.A. Josselyn, S. Tonegawa, Memory engrams: recalling the past and imagining the future, Science 367 (2020) eaaw4325.

[77] L. Restivo, G. Vetere, B. Bontempi, M. Ammassari-Teule, The formation of recent and remote memory is associated with time-dependent formation of dendritic spines in the hippocampus and anterior cingulate cortex, J. Neurosci. 29 (2009) 8206-8214.

[78] K.Z. Tanaka, A. Pevzner, A.B. Hamidi, Y. Nakazawa, J. Graham, B.J. Wiltgen, Cortical representations are reinstated by the hippocampus during memory retrieval, Neuron 84 (2014) 347-354.

[79] K.K. Cowansage, T. Shuman, B.C. Dillingham, A. Chang, P Golshani, M. Mayford, Direct reactivation of a coherent neocortical memory of context, Neuron 84 (2014) 432-441.