# Posterior Parahippocampal Place Learning in H.M.

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**ABSTRACT:** In a previous experiment with patients who had undergone unilateral temporal thermocoagulation lesions to alleviate intractable epilepsy, we demonstrated that the right parahippocampal cortex was critical for the performance of a spatial memory task (Bohbot et al. (1998) Neuropsychologia 36:1217–1238). Based on this evidence, we predicted that H.M., whose caudal parahippocampal cortex was structurally intact (Corkin et al. (1997) J Neurosci 17:3964–3979), would be able to learn the spatial memory task. This task was designed to be a human analogue of the Morris water maze in that it measured participants' ability to learn the location of a target, which was an invisible weight sensor placed under a carpet (Bohbot et al. (1998) Neuropsychologia 36:1217–1238). H.M. was first tested with the sensor under a small carpet (162 cm × 150 cm). Then, interspersed with the first sensor location, he was tested with the sensor in a second location, covered by a larger carpet (250 cm × 210 cm). He found the second target location in a direct path on only 10% of the trials. In contrast, when tested on the first sensor location, he walked directly toward the center of the testing area in 19/35 trials and from there found the sensor in a direct path on 15 of the 19 trials (80%). The number of direct hits at the first target location was significantly greater than chance (*P* < 0.0005). An analysis of H.M.'s paths showed that they were characteristic of fast learning, and that he did not rely on egocentric, short-term, or working memory strategies to learn the task. H.M's ability to locate the sensor is remarkable given his severe amnesia and his inability to explicitly recollect the testing episode. These findings underscore the role of the parahippocampal cortex in spatial memory. © 2007 Wiley-Liss, Inc.

**KEY WORDS:** hippocampus; spatial memory; amnesia; place learning; topography

## INTRODUCTION

Bohbot et al. (1998) tested patients with selective thermocoagulation lesions to the medial temporal lobes on the Invisible Sensor Task (IST), a spatial memory measure for humans, designed to be analogous to the Morris water maze (Morris et al., 1987). When recall was measured immediately after learning, patients with damage to the right parahippocampal cortex were able to perform the task normally. In contrast, when recall was tested after a 30-min delay, they were severely impaired.

Patients with lesions to either the left or right hippocampus, leaving the parahippocampal cortex intact, were not impaired on the IST immediately after the task or after a 30-min delay, suggesting that the parahippocampal cortex can support long-term spatial memory (Bohbot et al., 1998). Interestingly, patients with selective lesions to the hippocampus, sparing the parahippocampal cortex, were capable of reaching the target location in a direct path from a new starting position, showing evidence of allocentric spatial memory. In this paper, the parahippocampal cortex is defined as the region of the medial temporal lobe equivalent to areas TF and TH, lining the medial and lateral banks of the collateral sulcus, posterior to the entorhinal and perirhinal cortex. In another study with temporal lobe epilepsy patients, Weniger and Irle (2006) found that those with lesions to the right posterior parahippocampal cortex showed greater impairment in learning a virtual maze relative to control participants and patients with lesions to the anterior medial temporal lobe. This task allowed for both allocentric and egocentric strategies (navigation based on a series of responses from a given starting position). These studies provide evidence that the right parahippocampal cortex plays a pivotal role in spatial memory processes.

Structural MRI scans have shown that H.M.'s posterior parahippocampal gyrus is largely intact bilaterally (Corkin et al., 1997) (Fig. 1). Further, Corkin (2002) showed a significant increase in blood flow in the parahippocampal cortex of H.M. while he encoded pictures during an fMRI session, suggesting that his parahippocampal cortices are functional. We predicted, therefore, that H.M. would successfully learn the IST task, and that the parahippocampal cortex would be instrumental for his long-term spatial memory.

Previous lesion studies showed that the parahippocampal cortex supports learning and memory. Specifically, the left parahippocampal cortex has been shown to play a role in verbal memory (Bogousslavsky et al., 1987), and the right parahippocampal cortex has been linked to way-finding (Habib and Sirigu, 1987; Bohbot et al., 1998; Barrash et al., 2000) as well as other types of spatial memory (Kohler et al., 1998; Bohbot et al., 2000). These studies suggest that the parahippocampal cortex is an essential component of a spatial memory network, and that damage to this region may lead to severe impairments (Bohbot et al., 2004).

**FIGURE 1.** Coronal sections of MRIs illustrating the bilateral medial temporal resection in patient H.M. relative to a normal control (top). In contrast, a posterior section illustrates the intact portion of H.M.'s medial temporal lobes, including part of the hippocampus and most of the parahippocampal cortex shown in relation to images from a control (bottom). Abbreviations: H: Hippocampus, A: amygdala, EC: entorhinal cortex, PR: perirhinal cortex, PH: parahippocampal cortex, cs: collateral sulcus, cer: cerebellum, f: fornix; MMN: medial mammillary nucleus. Image adapted from Figure 5 of Corkin et al., (1997) J Neurosci 17(10):3964–3979.

These impairments may affect other types of memory as well. In a study with epilepsy patients, Weniger et al. (2004) found that lesion size in the parahippocampal cortex was correlated with performance on an associative learning task. Participants with smaller lesions performed significantly better than those with larger lesions, thus showing the importance of the parahippocampal cortex in long-term memory.

Despite the evidence that lesions to the parahippocampal cortex cause disruptions in memory, some investigators have argued that the deficit occurs due to restricted output from the hippocampus to surrounding cortical areas (Von Cramon et al., 1988). Contrary to this claim, researchers have provided evidence that spatial memory can occur despite a lesion to the hippocampus, suggesting that the parahippocampal cortex plays a role above and beyond being a simple gateway to the hippocampus (Bohbot et al., 1998).

It was only with advances in functional neuroimaging that the parahippocampal cortex has reclaimed attention (Aguirre et al., 1996), with a focus on its participation in spatial memory. Functional magnetic resonance imaging (fMRI) studies have demonstrated the importance of the parahippocampal cortex when viewing scenes (Stern et al., 1996; Epstein and Kanwisher, 1998). In a region of interest analysis, Epstein and Kanwisher (1998) showed that the parahippocampal cortex responded best to rooms with furniture and rooms without furniture, and least to objects and faces. Importantly, imaging studies using fMRI (Aguirre et al., 1996) and positron emission tomography (Ghaem et al., 1997; Maguire, 1997) have also shown that the parahippocampal cortex is highly active in navigation tasks. With fMRI, Rosenbaum et al. (2004) found increased levels of activation in the parahippocampal cortex when encoding spatial information about environmental land-

marks. Brewer et al. (1998) correlated subsequent memory for places represented in pictures, with the activity elicited in the parahippocampal cortex. Parahippocampal activity was higher for pictures that would be subsequently remembered than it was for pictures that would be subsequently forgotten.

Similarly, lesion studies in monkeys have provided evidence for the participation of the parahippocampal cortex in spatial memory (Malkova and Mishkin, 2003), whereby monkeys were severely impaired at a task that required memory for two locations. This study showed that monkeys with ibotenate hippocampal lesions performed normally on the task, thus ruling out the possibility that a simple functional deactivation of the hippocampus was the cause of the behavioral deficits consequent to the parahippocampal lesion.

Based on the evidence that H.M.'s caudal parahippocampal gyrus was bilaterally intact, we wanted to investigate his ability to acquire spatial memories. We predicted that he would be capable of learning the location of the sensor in the IST despite his dense amnesia. Then, we further investigated whether his learning would be limited to short-term memory which is known to be intact, or whether his spatial learning extended to long-term memory. We examined whether the task was acquired slowly or rapidly, and whether his spatial memory was allocentric or egocentric. Synaptic modifications occur rapidly in the medial temporal lobes during acquisition of associative tasks (Wilson and McNaughton, 1993; Naya et al., 2001) relative to the slow acquisition occurring in other parts of the brain, such as the caudate nucleus (Packard and McGaugh, 1996). Further, our prior research showed that the parahippocampal cortex dependent spatial learning was fast, allocentric, and long-term (Bohbot et al., 1998). Consequently, rapid allocentric spatial learning in H.M. would be consistent with acquisition dependent on the parahippocampal cortex. We tested H.M. after several delays, including a 24-h delay, to assess his long-term memory. If he were to show evidence of long-term retention it would suggest that long-term memory can be supported by the parahippocampal cortex. In addition, we asked whether H.M. was capable of learning multiple spatial locations in a single room, or whether his learning was limited to a single location. In sum, our objective in the current study was to investigate whether H.M.'s performance on the IST was indicative of rapid learning, greater than would be expected by chance, and whether his performance was characterized by allocentric long-term memory.

## MATERIALS AND METHODS

Participants included patient H.M. and three healthy control participants. H.M. was 72 yr old at the time of testing. He had 12 yr of education and had undergone bilateral medial temporal resection in 1953 in an attempt to alleviate his intractable epilepsy (Scoville and Milner, 1957). While it was originally believed that complete ablation of the medial temporal lobes had been performed during the surgical procedure, Corkin et al. (1997) found that H.M.'s posterior medial

temporal lobe region, including his parahippocampal cortex (Fig. 1) and posterior hippocampus, was intact, though the remaining hippocampal tissue was shriveled and likely deafferented. Damaged areas included the medial temporal polar cortex, most of the amygdaloid complex, partial or entire entorhinal cortex, and approximately half of the hippocampus. Portions of the ventral perirhinal and parahippocampal cortices were spared.

## Control Participants

Three control participants (2 women, 1 man) matched to H.M. for age (mean, 71.3 ± 1.5) and education (mean, 12 ± 0) participated in the study. They had no known history of psychiatric or neurological disorders.

## Procedure

The IST is a dry version of the Morris water maze adapted for humans. As a one-trial learning task, it measures participants' ability to learn the location of an invisible weight sensor (10 cm × 10 cm) placed under a carpet. Stepping on the sensor will trigger a distally located sound box to alert participants that they have located it successfully. The carpet was placed in a room filled with objects and cues, such as desks, chairs, shelves, and a door, which could have been used for orientation.

H.M. and the control participants were tested on two sensor locations, location 1 (L1) and location 2 (L2), in the following order: L1, L2, L1 and again 5 months later L1, L2, L1. For each sensor location, multiple trials were administered at various delay intervals (Table 1), ranging from immediately after a trial to 24 h between two consecutive trials. The two sensor locations were located in the same room. Participants were first tested with the sensor under a small blue carpet (162 cm × 150 cm). On the first trial, H.M. and control participants had to find the sensor by chance (i.e., the experimenter did not demonstrate the sensor location). Subsequently, multiple trials were administered at various delay intervals. Immediately before each trial, the experimenter triggered the sensor by stepping on it while participants looked the other way. The experimenter asked H.M. whether he remembered ever hearing this sound before, and regardless of his answer, he was asked to find the place under the carpet that would produce the sound. Since the sound itself was produced by a distally located box, it could not be used to localize the sensor. Control participants were asked to find the place under the carpet that would produce the sound. To test the memory capacity for sensor locations, after location 1, participants were tested on a second sensor location which was covered by a larger black carpet (250 cm × 210 cm). Importantly, both carpets covered both sensor locations. Participants were tested again on location 1 in order to assess whether the experience with sensor location 2 had an impact on performance with sensor location 1. This manipulation resulted in a greater number of trials for location 1. We repeated the procedure after a 5-month interval. H.M. was

*TABLE 1.*

*Number of Trials Performed by H.M.*

| Sensor location | Visit I | | | Visit II | | | No. of direct hits/total | |
|---|---|---|---|---|---|---|---|---|
| | L1 | L2 | L1 | L1 | L2 | L1 | L1 | L2 |
| Immediate | 1 | 2 | 0 | 6 | 1 | 0 | 3/7 | 0/3 |
| 10-s delay in dark | 2 | 1 | 0 | 9 | 4 | 1 | 5/12 | 1/5 |
| 15 min | 0 | 0 | 0 | 1 | 0 | 0 | 1/1 | 0/0 |
| 30 min | 1 | 1 | 0 | 3 | 1 | 0 | 1/4 | 0/2 |
| 60 min | 1 | 1 | 0 | 2 | 1 | 0 | 1/3 | 0/2 |
| 24 h | 1 | 1 | 1 | 4 | 1 | 1 | 5/7 | 0/2 |
| 5 months | 0 | 0 | 0 | 1 | 1 | 0 | 1/1 | 0/1 |
| No. of direct hits/total | 5/6 | 1/6 | 1/1 | 11/26 | 0/9 | 0/2 | 17/35 | 1/15 |

Total number of trials that H.M. performed over 9 test days on two separate visits to the laboratory (Visit I and Visit II) shown by delay interval. The table does not include the first trial to location 1 and the first trial to location 2 during which H.M. had to find the target by trial and error, as in our previous study (the sensor location is not demonstrated but has to be found by searching for it). The two visits were separated by a 5-month delay interval. During each visit, sensor location 1 (L1) was presented first, then sensor location 2 (L2) and sensor location 1 (L1) again, therefore, tests for location 2 never occurred during the delay interval of location 1, except for the 24-h delay interval. The various delay intervals were intermixed within testing for a given location. The number of direct hits to sensor locations 1 and 2 are indicated in the last row.

retested once again on sensor locations 1 and 2 and then location 1 again, using the same procedure that was used initially (referred to as Visits I and II in Table 1).

The methods and analysis of H.M.'s performance were modified from those previously used (Bohbot et al., 1998). Since H.M. walked very slowly with the help of a walker, the path to the sensor, rather than latency, was used as the measure of learning for all participants. H.M. was not urged to find the sensor as quickly as he could, but instead he was asked to find the place under the carpet that would produce a sound if stepped on. To accommodate H.M. and minimize fatigue, he was not asked to move to randomly distributed starting locations. Instead, he was asked to start from anywhere around the two edges of the carpet, opposite the walls. Consequently, many trials began from roughly the same start location. H.M. was highly motivated in his search. Manual tracings of H.M.'s trajectories were collected live and a videotape of H.M. was used to later verify the trajectories and characterize the paths.

## Analysis

The paths to the sensor were first characterized as going towards the center first, a characteristic of experienced participants, or going along a side first, a characteristic of naive participants (Fig. 2). In a second step, the paths were characterized

FIGURE 2. Performance of H.M. and three matched control participants while attempting to find the first sensor location of the Invisible Sensor Task. The diagrams illustrate the types of paths used. The proportion of corresponding paths is indicated for H.M. or the controls with and without experience. The total number of trials performed for the controls was 3 (one trial per participant) without experience; 27 trials were administered after the controls had gained experience; and 35 trials were administered to H.M. for the sensor location 1. Shaded area indicates an unusual proportion of direct paths to the target by patient H.M., which resembles that of experienced controls.

as search or direct. A path was considered to be direct if the participant reached it in a straight line or if the participant made one or two turns before reaching the sensor. A path that contained more than two turns was considered a search. Consequently, four patterns characterized the paths to the sensor (Fig. 2). (1) Side first/search: Participants first walked along the side of the carpet, and searched for the sensor. (2) Side first/direct: Participants first walked along the side of the carpet, and found the sensor with two turns or fewer. (3) Center first/search: Participants first headed towards the center of the carpet, and searched for the sensor. (4) Center first/direct: Participants first headed towards the center of the carpet, and found the sensor with two turns or fewer.

## Statistics

To assess whether the proportion of direct paths performed by H.M. were statistically significant, we have to assess the population probability, which in turn is used to calculate the binomial probability. The population probability ($P$) is based on the width of H.M.'s path (width of two feet + width of two sides of the walker = 30 cm), multiplied by two (for both sides of the sensor) and divided by the width of the search area perpendicular to the path (width of the small carpet = 162 cm, $P = 0.37$ and width of the larger carpet = 250 cm, $P = 0.24$). The binomial probability makes use of two assumptions. (1) H.M. took very small steps and consequently covered all areas in his path. (2) It assumes that H.M. walked perpendicular to the length of the carpet and that he did not walk sideways. In reality, H.M. occasionally found the target while walking at an angle and did not take very small steps, so overall, our estimate is conservative. Calculating the binomial probabil-

ity requires the population probability ($P$), the number of observations ($N$), and the number of direct paths ($R$).

$$\text{Binomial Probability} = \frac{N!}{R!(N-R!)} P^R (1-P)^{N-R}$$

## RESULTS

After one trial, control participants found the sensor directly on 45/51 trials (90%) for locations 1 and 2. H.M. found the sensor directly on 17/35 trials (50%) for location 1 and 1/15 (10%) for location 2. In this case, H.M.'s performance on the IST was very poor. The question we sought to answer in this analysis, however, was whether his performance could be attributed to chance, or whether he was demonstrating preserved spatial memory.

### Search Strategies

We previously reported that control participants and patients with small thermocoagulation lesions to the hippocampus and/or parahippocampal cortex who were naive to this task typically searched for the sensor in a strategic manner (Bohbot et al., 1998, 2002). Examples of their strategies include going along one edge of the carpet and zigzagging around, or circling around the area (for example, see Fig. 2, "side first/search"). After one trial, participants immediately went to the sensor in a straight line, walking away from the edge of the carpet (for example, see Fig. 2, "center first"). In the present experiment, the data were comparable, showing that on the very first trial, none of the control participants walked directly towards the center of the carpet. Instead, they always started their search at the edge (Fig. 2). On subsequent trials, after gaining experience with the task, control participants walked directly towards the center (for locations 1 and 2). Thus, going along the edge of the carpet (side first) was characteristic of naive participants who planned a search strategy, whereas going straight toward the center of the carpet was characteristic of experienced participants. When H.M. was tested on the first sensor location, about 50% of his paths reflected a planned search characteristic of naive participants, whereas 50% of his trials were characteristic of experienced participants (Fig. 2). Planning a search strategy was the logical thing to do in the case of H.M., who presumably believed that he was being tested on the IST for the first time, every time (confirmed during debriefing after every trial). It is also worth noting that H.M.'s global amnesia did not interfere with his attempt to find the sensor on trials in which he initially walked directly toward the center of the carpet. Consequently, further exploration was warranted on the particular trials in which his performance was characteristic of experienced participants (the "center first" trials). We asked two questions: While heading for the center, towards the target location, how many times did H.M. find the sensor directly? And, how many times did he get lost on the way?
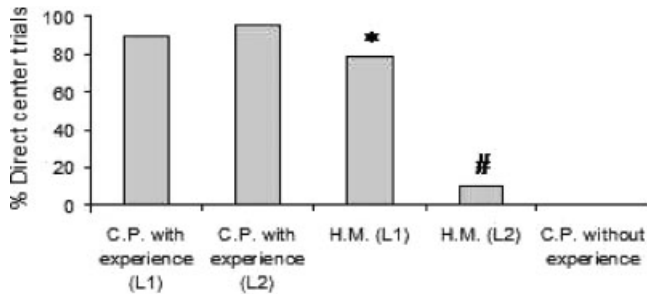
FIGURE 3.    Proportion of direct paths to the sensor over total center trials. On a subset of the "center first" trials, characteristic of experienced control participants, H.M. found the sensor to the first location (L1) in a direct path 15/19 times (80%). *$P <$ 0.0005. For the second sensor location (L2), H.M. walked in a direct path only 1/10 center trials (10%). #$P = 0.94$, n.s. The results show a difference between performance for the first sensor location, where H.M.'s performance was significantly above chance levels, and the second sensor location, where he performed at chance levels. Control participants with experience found the sensor directly on 18/20 (90%) center trials for sensor location 1 and 22/23 (96%) center trials for sensor location 2.

*Location 1.* H.M. went directly toward the center of the carpet in 19/35 trials (about 50%). Of the 19 "center first" trials, H.M. found the sensor in a direct path 15/19 times or 80% (Fig. 3). The binomial probability of hitting the sensor directly 15/19 times, based on a population probability of 0.37, is $P <$ 0.0005. Thus, the proportion of H.M.'s successful sensor detections was much higher than would be expected by chance.

*Location 2.* H.M. went directly toward the center of the carpet on 10/15 trials (about 67%). Of these 10 "center first" trials, H.M. found the sensor in a direct path 1/10 times or 10% (Fig. 3). The binomial probability of hitting the sensor directly 1/10 times, based on a population probability of 0.24 in the larger carpet, was $P = 0.94$, n.s. We can conclude, therefore, that H.M.'s hits, when attempting to find sensor location 2, indicate chance performance. This result contrasts dramatically with his superior performance when sensor location 1 was the target.

## Rapid Learning

Analysis of the distribution of direct paths to the target showed that H.M. reached the target directly on five of the first six trials he performed (Table 1, Visit I, bottom row). This result is evidence of rapid learning.

## Long-Term Spatial Memory

H.M.'s direct paths to location 1 were examined according to the delay interval between a hit and the trial immediately preceding it. Here we found evidence of long-term memory formation: over 60% of his hits were made after a 24-h delay. Therefore, based on this finding, we can safely exclude the possibility that H.M. was using a short-term memory strategy (Fig. 4 and Table 1).

## Allocentric Memory

The starting locations of the direct paths to location 1 showed that H.M. was not using a strategy related to his start position or body position (e.g. "one step forward and turn right") but instead was using allocentric memory based on the external environment (Fig. 5).

## DISCUSSION

The purpose of this study was to investigate whether H.M. could learn the IST, a task that requires the parahippocampal cortex, which is spared in his brain. We attempted to categorize his performance in terms of fast or slow acquisition, short-term or long-term memory, and egocentric or allocentric memory. H.M. was asked to walk to a sensor hidden under a carpet at several different locations. The sensor produced a noise when stepped on, but it was not possible to localize it by sight or touch. Our findings revealed that H.M. was indeed able to learn the task, and that his learning was characteristic of a rapid learning and memory system, and that it was long-term and allocentric. Here, we summarize the different aspects of H.M.'s performance, including his search strategies, his capacity for fast learning, long-term memory, allocentric memory, and memory for one location but not two. Then we describe the role of the parahippocampal cortex in spatial memory compared to other brain regions, and how the findings relate to previous research.

### Search Strategies

In about half of the trials, H.M. used search strategies characteristic of experienced participants, going straight toward the
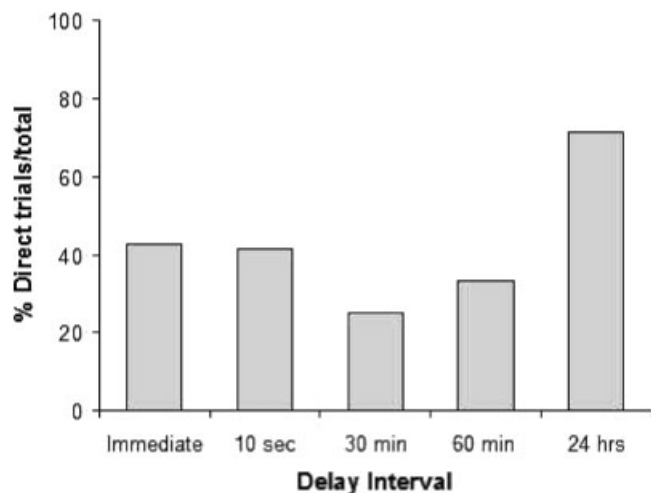


FIGURE 4.    H.M.'s direct paths grouped by delay interval, showing that H.M. went directly to the sensor across a large range of delay intervals including after a 24-h delay. This result is strong evidence that his performance was grounded in long-term memory and not short-term memory strategies. The 10-s delay interval was spent in total darkness. In addition to the trials shown, H.M. was tested once with a 15-min delay interval and once with a 5-month delay interval; in both cases, H.M. traversed a direct path to the target.
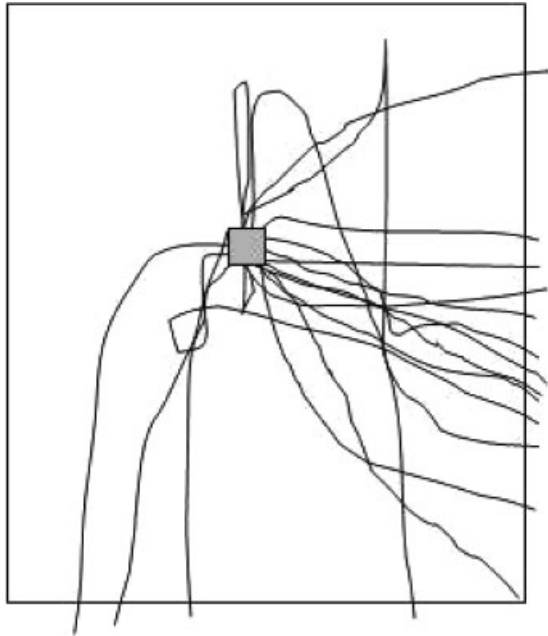
**FIGURE 5.** Path overlay of H.M.'s 17 direct paths to the sensor location 1 (15 paths going first towards the center, and two paths first going towards the edge). Importantly, the target was reached from several different directions, suggesting that H.M. used an allocentric spatial strategy. Grey box: sensor location 1.

center of the carpet. In the other half of the trials, he used search strategies characteristic of naive participants, going along the side of the carpet first. Bohbot et al. (2002) showed that planning a search for the sensor was undisrupted in patients with unilateral hippocampal and/or parahippocampal damage, indicating that this process relies on other areas of the brain. In other words, on the very first trial, the search strategies of patients with damage to the hippocampus and/or parahippocampal cortex were identical to the strategies used by control participants (Bohbot et al., 2002). Because the prefrontal cortex is known to be critical for executive functions such as planning (Miller and Cohen, 2001), Bohbot et al. (2002) suggested that the prefrontal cortex is a brain area critical for planning an effective search strategy for the IST. Further, H.M. performed normally on tasks requiring a functional prefrontal cortex such as the Wisconsin Card Sorting Test (Milner, 1982; Corkin, 2002). Considering this evidence, together with the fact that H.M. has global amnesia and could not remember being tested on this task before each trial, it would be logical for him to adopt the strategy characteristic of naive participants ("side first"), one that would have recruited the prefrontal cortex for planning. Thus, it is possible that H.M.'s global amnesia, together with his sufficient planning abilities, may have interfered with his ability to access his knowledge of the sensor location, encouraging him to use the side first search strategy. The fact that H.M. walked directly towards the sensor on half the trials is interesting and warranted detailed examination. For this reason, H.M.'s performance on the "center first" trials was assessed independently, and we examined the frequencies of trials where

H.M. found the target directly and the trials where he missed and had to search for the target.

## Rapid Learning

H.M.'s performance on the center first trials with the first IST location was significantly better than chance, with 80% direct hits. Direct paths to the target were found in five out of the first six trials, which is evidence of rapid learning. If H.M. had learned the location of the sensor gradually, we would have seen a greater number of misses and searches early on, and direct hits would have been observed in a later phase of training. Clearly, this was not the case. Rapid learning is a characteristic of the medial temporal lobes, as opposed to slowly acquired stimulus response learning or habit formation dependent on the striatum (Packard and McGaugh, 1996). These results are consistent with findings from previous work showing that the parahippocampal cortex, but not the hippocampus, is critical for rapid learning of the sensor location on the IST (Bohbot et al., 1998).

## Long-Term Memory

An analysis of performance on the "center first" trials revealed successful learning of location 1, with evidence of significant long-term memory. It also appeared that, on these trials, he was not using a working or short-term memory strategy because the number of direct hits occurred throughout a range of delay intervals, including delays of 24 h. If H.M. had used a short-term memory or working memory strategy, a filled delay interval of a few minutes would have been sufficient to disrupt performance. This was not the case. Thus, these results suggest that H.M. was relying on a form of long-term spatial memory that is likely dependent on the parahippocampal cortex as suggested by our earlier work (Bohbot et al., 1998).

## Allocentric Spatial Memory

The various direct paths to the target that originated from different starting locations showed that H.M. was not using an egocentric memory strategy (i.e., he was not using a sequence of body turns from a single starting point). If he had, we would have observed that all of the direct hits originated from a single starting point and all of the misses with starting points in other locations. Figure 5 indicates otherwise, suggesting that H.M.'s long-term memory was based on allocentric spatial information.

## Memory for One Location but Not Two

H.M.'s performance on the first IST location was significantly better than chance (with 80% direct hits). When tested on the second sensor location, H.M. hit the target location directly on only 10% of the "center first" trials, indicating chance performance. Based on his remarkable performance in finding sensor location 1, it was surprising that he was unable to learn the location of the second sensor. Important methodological factors should be considered when analyzing these
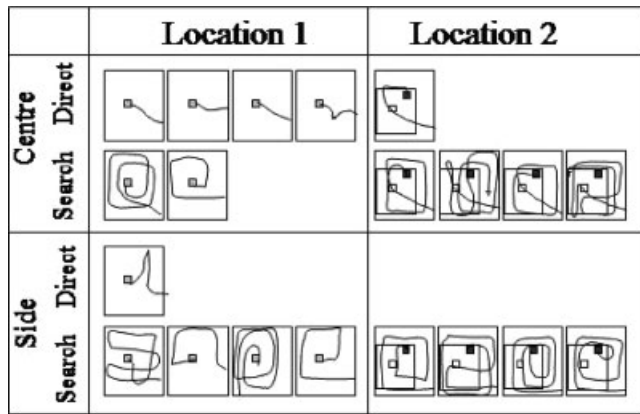
FIGURE 6. Exemplars of the trajectories traversed by H.M. when searching for locations 1 and 2. The larger outer squares represent the search area. The inner larger square shown for location 2 represents the location of the carpet previously used for location 1 that was not present during the actual testing (note the different scaling used to depict trajectories in locations 1 and 2). The small squares represent the positions of the target locations relative to the search area; grey: sensor location 1; white: old sensor location 1 not present during the actual testing of sensor location 2; black: sensor location 2. The first four observations of each category are reported except when fewer observations were made throughout testing. Note that all the center trials in location 2 show that H.M. first crosses the old location 1. One of the two center search trial for location 1 shows that H.M. had just missed the sensor. The center direct path to location 2 illustrates the criterion whereby two turns or fewer were used to categorize the search as direct. However, based on his overall performance, it is thought that the direct hit to location 2 occurred by chance.

results. Administration of the IST with sensor locations 1 and 2 occurred in the same room and in roughly the same area (about 1 m away from each other) (i.e., both carpets covered both sensor locations). This method tested the capacity of the parahippocampal memory system in terms of number of invisible locations that could be learned in a given room. The results indicated that H.M. could learn only one invisible sensor location with the present experimental design. It is unclear, however, whether similar results would have been obtained if the carpets had been placed in different rooms or in different areas of a single room. Seeing that the carpets overlapped in the present experiment, sensor location 1 may have caused interference in learning sensor location 2. For example, after accidentally hitting sensor location 2 on a particular trial, H.M. spontaneously volunteered the thought that the sensor had been moved, even though he could not remember having been tested on the task before (when hitting the sensor he said, "It moved!"). Further, he pointed toward sensor location 1 when we asked him where the sensor had been before. In fact, while searching for location 2, H.M. crossed location 1 directly on 5/5 (100%) center trials in the first visit and 1/6 (17%) center trials in the second visit, suggesting that location 1 indeed interfered with learning of location 2 (Fig. 6). H.M.'s search for location 1 when tested on location 2 may help explain why he adopted center trials despite a clear impairment at finding sensor location 2. The reduction in location 1 crossings when

searching for location 2, in H.M.'s second visit, may be indicative of extinction of memory for location 1 while performing the search for location 2. If we consider the fact that H.M. found the sensor directly five times in the first six trials in location 1 (before being exposed to location 2), it is also possible that testing of location 2 later interfered with location 1 to some degree. The ability to learn only a single location has been observed before in an object location study of the style "A not B" with patients with amnesia due to early Alzheimer's, closed head injury, aneurism, or anoxia (Schacter et al., 1986). In that experiment, amnesic patients were able to learn the location of a single object in a room, but were unable to learn a second object location, instead searching for the second location in the old place. In summary, H.M. did not exhibit learning of the second sensor location, but this failure may have been caused by interference from learning of the first sensor location, consistent with his global amnesia.

## Memory and the Parahippocampal Cortex

Previous studies (Bohbot et al., 1998) suggest that the parahippocampal cortex may be the brain region responsible for sustaining long-term allocentric memory of the IST location 1 in H.M. This conclusion stems from the result that patients with selective unilateral lesions to the right hippocampus, including two patients with damage that extended into the posterior hippocampus, learned the IST at a 30-min delay, whereas patients with additional damage to the parahippocampal cortex did not. This suggested that the parahippocampal cortex and not the posterior hippocampus in H.M. may be responsible for learning the IST. While the task administered to H.M. and the patients with unilateral lesions was the same, we made minor methodological changes for H.M., such as the size of the search area, which could have influenced the strategies available, and hence the brain areas recruited in solving the task. Still, when tested on the delayed IST, the search pattern of patients with selective lesions to the right hippocampus, sparing the parahippocampal cortex, was similar to H.M.'s direct hits to location 1 (i.e., center first/direct). On the other hand, the search pattern of patients with parahippocampal damage was qualitatively very different: they typically went directly to the correct quadrant, and then searched for the sensor by circling around in the quadrant. This would correspond closest to the center first/search in the current study, except that H.M. never limited himself to a given quadrant. Consequently, the search patterns in H.M. resemble more closely those of patients with lesions to the right hippocampus that spared the parahippocampal cortex.

Strong evidence supporting parahippocampal place learning in H.M. comes from two other lines of research. First, H.M. scored normally on a picture recognition test (Freed et al., 1987; Freed and Corkin, 1988), a task known to require the parahippocampal cortex (Brewer et al., 1998). Second, H.M. correctly reproduced the layout of the house he had moved into after his operation (Corkin, 2002), also known to require the parahippocampal cortex (Shelton and Gabrieli, 2002). These two lines of evidence will be discussed in turn.

In 1987, Freed et al. reported that H.M. was able to learn and recognize complex photographs containing animals, buildings, interiors, people, nature, and single objects (Freed et al., 1987; Freed and Corkin, 1988). In this task, H.M. was given longer encoding times than were allotted to controls (20 s instead of 1 s) in order to make his initial recognition performance comparable to theirs. Using Yes/No decisions and forced-choice recognition, H.M. exhibited normal forgetting at delay intervals of 10 min, 72 h, 1 week, and 6 months. Later, Reed et al. (1997) showed that patient E.P., who had extensive damage to the medial temporal lobes and lateral temporal cortices, including major damage to the parahippocampal cortex, was severely impaired on a picture recognition task despite extended encoding times, thus suggesting that the parahippocampal cortex may have been responsible for the residual mnemonic function in H.M. (Reed et al., 1997). This conclusion is consistent with fMRI studies showing that the parahippocampal cortex is critical for viewing and encoding scenes (Stern et al., 1996; Brewer et al., 1998; Epstein and Kanwisher, 1998).

Corkin (2002) showed H.M.'s drawings of the layout of a house he lived in after the onset of his amnesia. Notably, the relation among the rooms in his drawing was accurate. Evidence from brain damaged patients suggests that the parahippocampal cortex may have subserved this function. For example, patients with damage to the mesial temporo-occipital gyrus that included the parahippocampal cortex had difficulties in perceiving the globality of drawings of complex scenes. They could not find the way to their room in the hospital and they were unable to draw a floor plan (Habib and Sirigu, 1987). Further, fMRI studies of human virtual navigation find consistent activation of the parahippocampal cortex (Aguirre et al., 1996; Shelton and Gabrieli, 2002), supporting the proposal that the parahippocampal cortex in H.M. could have been responsible for the acquisition of the layout of his house. Altogether, several lines of evidence suggest that the parahippocampal cortex was responsible for H.M.'s successful navigation towards the target sensor in our IST.

## Other Memory Systems

While the parahippocampal cortex may have been critical to learn various locations, our data suggest that it is limited in that role. Maguire and Cipolotti (1998) showed that a severely amnesic patient with Pick's disease who had severely atrophied temporal lobes, particularly on the left, showed normal recall of familiar routes. The patient could also learn new routes through a complex virtual reality town, a task that had previously shown activation of the hippocampus in normal participants (Maguire et al., 1998). The researchers concluded that topographical learning relies on a brain module independent of areas that support memory for faces and designs.

H.M.'s intact caudate nucleus might have supported his ability to learn the layout of his house. A navigation study from Bohbot's laboratory (Iaria et al., 2003) showed that healthy young individuals spontaneously use either spatial or nonspatial strategies that depend on the hippocampal and caudate mem-

ory systems, respectively. The caudate nucleus is described as a slow learning system (Packard and McGaugh, 1996) that becomes engaged during the repetition of rewarded stimulus–response associations (Packard and Knowlton, 2002; White and McDonald, 2002; Bohbot et al., 2004). In other words, the caudate nucleus will contribute to habit formation of repeated successful behavioral responses. Assuming that H.M. had repeated opportunities to learn the layout of his new house by following the same route over and over again, for several years, one would expect that response learning dependent on the caudate nucleus would have emerged. The caudate nucleus receives major anatomical inputs from the parahippocampal cortex (Suzuki, 1996), and is, therefore, in an optimal position to form habits of spatial memories (Bohbot et al., 2004). Nevertheless, caudate nucleus-based response learning (which has been characterized as a type of stimulus–response learning based on reward) cannot account for learning the sensor location in the present study for several reasons: (1) No stimuli pointed directly to the target. (2) H.M. could have used an egocentric response strategy (i.e., a series of responses based on his starting position), but if he had, all of the target hits would have been achieved from a single starting point, which was not the case. Instead, by reaching the target from multiple different starting positions, H.M. showed evidence of allocentric spatial memory. (3) Stimulus–response learning occurs with repeated exposure to the stimuli and successful response behavior, which requires repeated trials (Packard and McGaugh, 1996). Instead, H.M. learned the task in one trial. While the caudate nucleus is a candidate for learning the IST via stimulus–response learning, the data suggest otherwise.

## Parahippocampal Versus Hippocampal Representation of Space

The results of the present study, together with prior reports, suggest that the hippocampus and parahippocampal cortex both support allocentric spatial memory (Holdstock et al., 2000), but important differences in the roles of these brain structures have been identified. First, the current study demonstrated that the parahippocampal cortex plays a limited role in spatial memory, because H.M. was able to learn one but not two sensor locations. In this case, H.M.'s impaired episodic memory (Scoville and Milner, 1957; Corkin, 1984, 2002) leads to interference from sensor location 1, when he attempted to learn sensor location 2. Another important difference between the role of the hippocampus and parahippocampal cortex can be appreciated in the functional imaging literature. While the parahippocampal cortex was activated in fMRI studies of navigation (Aguirre et al., 1996), tasks that required the development of novel routes, hence tapping into the participant's cognitive map, required the hippocampus (Maguire et al., 1998). Further, Hartley et al., (2003) found that activity in the left hippocampus positively correlated with wayfinding accuracy. When participants were tested on a navigational task that allowed for spatial as well as nonspatial strategies, only the participants who spontaneously chose the spatial strategies, coding

for the relation between landmarks, showed significant activity in the hippocampus (Iaria et al., 2003). King et al. (2002, 2004) concluded that the hippocampus is critical when viewpoint independence is necessary. Consistent with this view, in an fMRI study with virtual navigation, Wolbers and Buchel (2005) showed that the hippocampus was activated when participants had to integrate novel information with an existing memory representation. Interestingly, while Ekstrom et al. (2003) recorded place sensitive neurons in the human hippocampus during virtual navigation, neurons recorded in the parahippocampal cortex responded more to views of target landmarks as opposed to views of people or background view. Though learning the IST requires allocentric spatial memory, it involves learning the location of a single target with respect to the room landmarks. Accordingly, a viewpoint specific spatial strategy dependent on the parahippocampal cortex may be sufficient to solve the IST task with a single target location (Bohbot et al., 2004), but not two (Malkova and Mishkin, 2003). This should be distinguished from an egocentric strategy, where, by virtue of being small, the sensor would have been missed by a slight deviation from the path, for example, due to different starting positions. These findings are in line with an fMRI study in which participants previously exposed to a virtual route containing objects showed significantly greater activity in the parahippocampal cortex to objects with spatial relevance than to presentation of objects without spatial relevance (Janzen and van Turennout, 2004). In that experiment, the objects with spatial relevance were those strategically located in places where a navigational decision had to be made, as opposed to objects placed at nondecisional points. Interestingly, the increase in fMRI signal in the parahippocampal cortex to navigationally relevant objects occurred for forgotten as well as remembered objects, regardless of the ability to consciously recollect having seen the object. This result is interesting in light of the fact that in our study, H.M. could not explicitly remember having learned the sensor task, and our finding is consistent with the proposal that the hippocampus is critical for recollective recognition that depends on episodic memory (Holdstock et al., 2005; Aggleton and Brown, 2006).

In summary, studies in the literature suggest that the hippocampus becomes necessary when recollective memory for spatial relationships is used to build a cognitive map of the environment (O'Keefe and Nadel, 1978), whereas the parahippocampal contribution to allocentric spatial memory is viewpoint specific, such as that of a picture or a scene.

## SUMMARY

In conclusion, the present experiment revealed that H.M.'s performance on the IST location 1 was better than would be expected by chance, with 80% direct hits at finding the location of the sensor, when considering his performance on the "center first" trials characteristic of experienced participants. An analysis of H.M.'s paths showed that he did not rely on egocentric, short-term memory, or working memory strategies to learn the task, but rather his learning was characterized by fast learning. It is unclear whether his impairment in learning the second location resulted from the increased difficulty of the task, or from interference from the first sensor location. The place learning he displayed on the IST is at odds with his severe amnesia and his inability to explicitly recollect the episode. These findings suggest that allocentric place learning, which may be dependent on the parahippocampal cortex, does not require conscious recollection.

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