ELSEVIER

Behavioural Brain Research 132 (2002) 77–84

BEHAVIOURAL BRAIN RESEARCH

www.elsevier.com/locate/bbr

Research report

Humans with hippocampus damage display severe spatial memory impairments in a virtual Morris water task

Robert S. Astur [a,*], Laughlin B. Taylor [b], Adam N. Mamelak [c,d], Linda Philpott [d], Robert J. Sutherland [e]

[a] *Department of Diagnostic Radiology, Yale University, P.O. Box 208042, 330 Cedar Street, New Haven, CT 06520-8042, USA*
[b] *Department of Neuropsychology, Montreal Neurological Institute, Montreal, Québec, Canada H3A 2B4*
[c] *Department of Neurosurgery, Huntington Memorial Hospital, Pasadena, CA 91105, USA*
[d] *Epilepsy and Brain Mapping Program, Huntington Memorial Hospital, Pasadena, CA 91105, USA*
[e] *Department of Psychology and Neuroscience, University of New Mexico, Alburquerque, NM 87131, USA*

Received 16 April 2001; received in revised form 20 September 2001; accepted 20 September 2001

Abstract

For nonhumans, it has been shown that the hippocampus (HPC) is critical for spatial memory. We tested patients with unilateral HPC resections on a virtual analogue of a classic spatial task to assess HPC functioning in nonhumans: the Morris water task. We found that when humans are required to use spatial cues to navigate to a hidden escape platform in a pool, patients with HPC resections display severe impairments in spatial navigation relative to age-matched controls and age-matched patients who have had extra-HPC resections. This effect occurred for every patient tested and was evident regardless of side of surgery. Hence, it is apparent across species and irrespective of which hemisphere is damaged that the human HPC is critical for spatial/relational memory. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Hippocampus; Memory; Spatial; Virtual reality; Human; Morris water task; Epilepsy; Relational memory; Configural memory; Path integration

1. Introduction

The ability to find objects, recall previous locations and navigate throughout the world is dependent upon spatial learning and memory. There is a myriad of converging evidence that suggests that for nonhumans, the hippocampal formation appears to be the critical anatomical structure necessary for these spatial abilities [3,27,28,33,35] (but see Refs. [7,39]). With humans, the data also suggest that the hippocampus is involved in spatial memory. However, it seems that only damage to the right hippocampal formation results in spatial memory impairments [4,6,15,16,31,34].

In examining the tasks used to assess spatial memory across species, there are a number of factors that make comparisons difficult. Specifically, egocentric memory is often examined in human tasks, such as maze learning [6] and object location [34], while allocentric memory is examined in nonhuman tasks, such as the Morris water task [23] and 8-arm radial mazes [29]. In addition, even within species the definition of 'spatial' varies greatly across tasks, such that face recognition [22], memory for abstract designs [16] and egocentric maze learning [6] are all grouped together as tests of spatial memory.

Attempts to reconcile some of these differences have been made in recent reports by Maguire et al. [19] using virtual environments during PET to examine hippocampal contributions during navigation through a virtual town. Their results indicate that both

* Corresponding author. Tel.: +1-203-737-2814; fax: +1-203-785-6534.
E-mail address: rastur@boreas.med.yale.edu (R.S. Astur).

PII: S0166-4328(01)00399-0

hippocampi are active during virtual navigation, but only the right hippocampal activation predicts navigation accuracy. These reports take an important step toward bridging these paradigmatic gaps. However, it is unclear from these studies how patients with hippocampus damage would perform in these virtual tasks. Specifically, the tasks consist of navigating from landmark to landmark and this may not require an allocentric strategy at all. In fact, rats with hippocampus damage are unimpaired in using landmarks to locate a goal [24]. Additionally, the procedure in these studies consists of having a subject learn the virtual environment outside the PET scanner and hence, important information about hippocampal contributions during learning is lost. Lastly, whereas this paradigm has the benefit of mimicking real life navigation, it is unable to be adapted properly for use with nonhumans.

An alternative method of using virtual environments to examine hippocampus contributions to spatial learning and memory is to take advantage of the rich paradigms that have been extensively developed for testing rodents. Specifically, one of the most reliable tests used to assess spatial memory in rodents is the Morris water task [23]. In this task, rats are required to use the relationship among distal cues to navigate to a hidden escape platform in a pool of milky water. Normal rats learn to find the platform readily and efficiently. However, rats with hippocampus damage show severe impairments in being able to use a spatial strategy to navigate to this escape platform [24,35]. This task is advantageous in that no single landmark allows for accurate navigation, since the rat must start at different locations within the pool and some landmarks are initially hidden from view, depending on the starting point. Rather, it is utilizing the relationships of the various landmarks in the room that allows for accurate navigation.

To examine the effects of hippocampus damage on navigation in humans, we developed a virtual version of the Morris water task (vMWT) to assess spatial memory in humans with unilateral hippocampal resections [2]. This task is parametrically and directly modeled, in number of trials, relative room dimensions, probe trials, swimming speed and dependent variables, after the Morris water task used in our laboratory to reveal impairments in rats with hippocampus damage [25]. This is advantageous in that we are able to assess not only allocentric memory, but also the learning process. Additionally, because all the parameters are similar, we are better able to make comparisons across species to help form a more unitary picture of the role of the hippocampus in learning and memory. Moreover, this allows for a solitary task to be used to assess hippocampal functioning across species.

2. Materials and methods

2.1. Participants

Our test group consisted of ten patients who had undergone unilateral hippocampal removals (five left-sided, five right-sided) as a component of temporal lobe surgery to treat medically intractable epilepsy. Four of the left hemisphere and two of the right hemisphere patients received a selective amygdalohippocampectomy. The other four patients received an anterior temporal lobectomy. All patients with HPC damage were recruited from the Montreal Neurological Institute and are referred to as the HPC group. In addition, there were six patients that had undergone surgery to remove tumors in areas outside the temporal lobes. These patients were recruited from Huntington Memorial Hospital in Pasadena, CA and are referred to as the tumor group. Lastly, seven age-matched controls, recruited from various personnel at Huntington Memorial Hospital, were tested.

Surgically, the selective amygdalohippocampectomy involves burrowing a hole through the middle temporal sulcus and then aspirating the majority of the amygdala and some HPC. This is carried out to minimize damage to the overlying cortex, although some damage must obviously occur during the burrowing. An anterior temporal lobectomy involves removing the anterior temporal lobe, including the majority of the amygdala, some HPC and the majority of cortex overlying these structures.

2.2. Apparatus

An IBM-compatible computer with a SVGA color monitor was used for testing. Participants navigated through the pool by manipulating a joystick. A speaker connected to the computer was used to provide auditory feedback to the participants.

2.3. Procedure

Participants were told that they would find themselves in a 3-dimensional pool and that their goal would be to escape from the water as quickly as possible. They were told to use the joystick to move around in the pool and that the computer would give them both auditory and visual feedback when they had escaped. The view on the screen was a first-person view, so that if they pushed the joystick to the right, the view on the screen would pan to the right and so on with other joystick movements. There was a 60° field of view of the virtual space, which is approximately the same as the human eye. Participants were told that after completion of a trial, the screen would blank and then they must hit a key on the keyboard to start the next trial.

See Fig. 1 for a possible participant's view of the room from within the pool.

Procedurally, participants started from four different locations (north, south, east, west), five times each for a total of 20 trials. Each block of four trials consisted of one trial from each start location, randomly determined within the block (e.g. Block 1: N W S E; Block 2: S N E W, etc). If the participant swam over the area of the pool where the platform was located, a tone sounded, the platform rose slightly out of the water and a message saying 'Congratulations. You have escaped from the water' was displayed. At this point, the participants were allowed free-swimming movement for 10 s, after which the trial terminated. However, they did not need to move during this time if they so chose. If 60 s elapsed and the participant had not found the platform, the platform was raised out of the pool so that it was visible and the computer made a repetitive beeping noise while scrolling a message 'Time has expired. Please swim toward the platform'. This beeping and scrolling continued until the participant swam to the platform. Once on the platform, the same sequence of congratulatory events occurred as described above. This phase is referred to as 'hidden platform' training.

After these 20 training trials, a probe trial was given in which the platform was removed from the pool and the participant was allowed to search for the platform for 30 s, after which the trial terminated. There was no indication to the participant that the probe trial was in any way different from the previous 20 training trials, until it was completed. After the first probe trial, this testing sequence of 20 training trials followed by a 30-s probe trial was then repeated. Upon completion of this phase of testing, the platform was moved to a different location in the pool and was raised out of the water so that it was visible to the participant. Participants started from four different locations, two times each, for a total of eight trials. This phase is referred to as 'visible platform' training. All events and consequences were identical to those in the hidden platform phase of testing. Participant location in the pool was written to a computer data file at ≈ 10 Hz during each trial. These testing parameters were identical to those used successfully in assessing HPC functioning in rodents in the real Morris water task [25] and these parameters displayed excellent experimental transfer to a virtual environment to assess spatial skills in humans [2].

The probe trials allowed us to examine where in the pool the participant searched for the platform without receiving feedback. The logic is that if the participant was using the spatial cues to locate the platform, they would spend the majority of their swimming during the probe trial in the area of the pool where the platform was located during the hidden platform training. Without attending to the external cues, it was impossible to show a consistent preference for a specific area of the pool. The visible platform trials examined whether there were any motivational, motor or perceptional problems interacting with the 3D nature of the computer program.

3. Results

In examining the latency to find the hidden platform during the 40 training trials, using a repeated measures MANOVA with Trial as the repeating factor, there exists a significant group effect, $F(2, 20) = 4.21$, $P =$

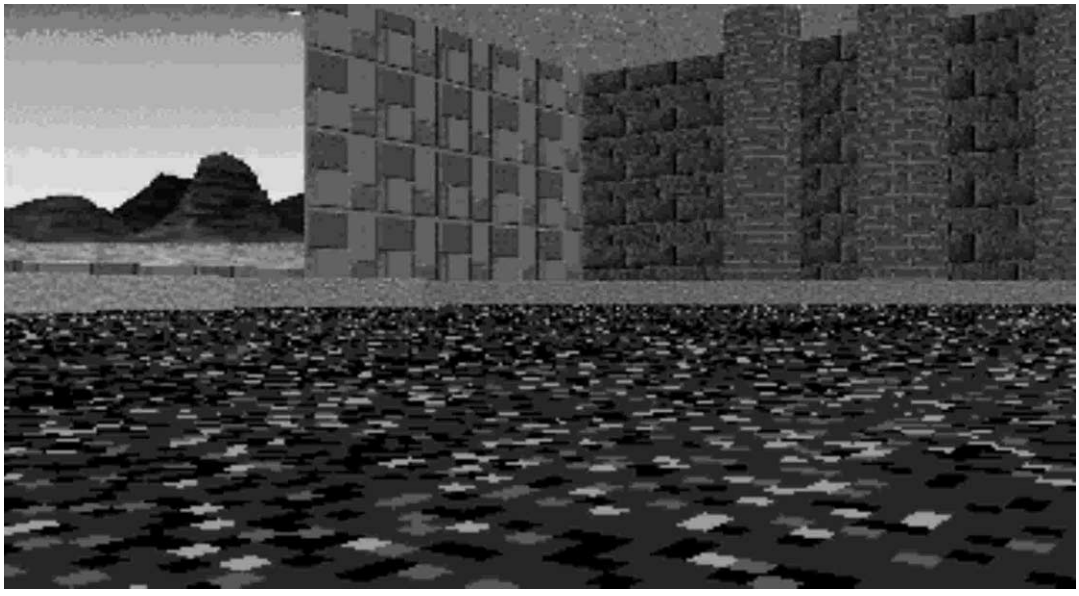

Fig. 1. A view within the virtual pool. The participant is facing the northeast corner where the platform is hidden.

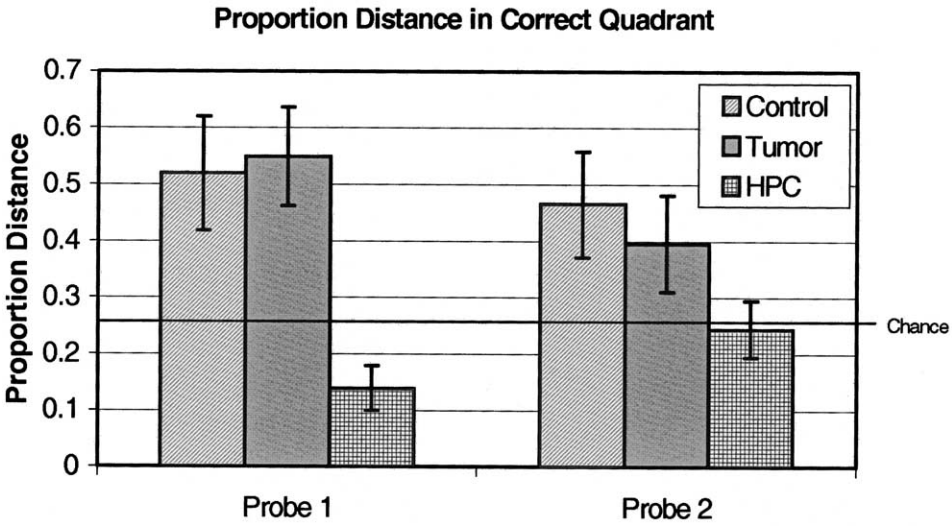

Fig. 2. Proportion distance traveled in the quadrant of the pool where the hidden platform was located for the three groups. For the first probe, the HPC group shows significantly less of a preference than the other two groups. For the second probe, the HPC group again shows significantly less of a preference than the Control group, but the tumor group does not differ from the other two groups.

0.03. Specifically, patients with HPC damage were significantly slower to find the hidden platform than either the tumor group, $F(1, 14) = 6.03$, $P = 0.028$ or the unoperated group, $F(1, 15) = 8.06$, $P = 0.012$. However, the unoperated group and the tumor group did not differ from each other, $F(1, 11) = 0.00$, $P = 0.99$. In addition, during the first probe trial (after training trial 20), in which the platform was removed from the pool, the HPC group spent significantly less of their swim distance in the quadrant of the pool where the platform had previously been located compared to both the tumor group $F(1, 14) = 23.85$, $P < 0.001$ and the unoperated group $F(1, 15) = 17.72$, $P = 0.001$ (Fig. 2). However, the unoperated control group and the tumor group did not differ from each other, $F(1, 11) = 0.05$, $P = 0.99$. For the second probe trial (after training trial 40), again the HPC group spent significantly less of their swim distance in the quadrant of the pool where the platform had previously been positioned compared to the unoperated control group, $F(1, 15) = 7.65$, $P = 0.014$. The tumor group did not significantly differ on this measure from either the HPC group, $F(1, 14) = 2.70$, $P = 0.123$ or from the unoperated group, $F(1, 11) = 0.73$, $P = 0.412$. The swim paths during the first probe trial for the median individual in each group can be seen in Fig. 3. There were no differences between the groups in swimming latency toward the visible platform, $F(2, 20) = 0.95$, $P = 0.40$ or in swim speed during the probe trial, $F(2, 20) = 2.10$, $P = 0.148$. This suggests that all three groups were equally motivated to find the platform and did not have difficulty interacting with the 3D nature of the computer program. In addition, the tumor and the HPC group did not differ in performance of a common visuo-spatial memory task, the Rey–Osterrieth complex figure copy (30.7 vs. 27.8, respectively), $t(9) = 1.67$, $P = 0.129$ or 30–45 min delayed recall (17 vs. 16.2, respectively), $t(9) = 0.27$, $P = 0.792$. This suggests that the observed spatial memory impairments cannot be attributed to a global spatial memory impairment.

By defining a 'spatial' strategy during the probe trial as spending 40% or more of the distance in the quadrant of the pool that contained the platform during training, we note that not a single patient with HPC damage was able to solve this task consistently. A 40% point is reasonable given the experimental results of rats, with bilateral ibotenic acid HPC lesions in the actual Morris water task using identical testing parameters, spent $\approx 33 \pm 7\%$ of their swim distance in the training quadrant during a probe trial [25]. Moreover, patients with left HPC damage showed spatial memory impairments in the probe trials equal to those impairments seen in the patients with the right HPC damage (Probe 1 proportion: left HPC group: mean $= 0.12 \pm 0.05$, right HPC group: mean $= 0.16 \pm 0.07$, $t(8) = 0.41$, $P = 0.35$; Probe 2 proportion, left HPC group: mean $= 0.22 \pm 0.07$, right HPC group: mean $= 0.27 \pm 0.08$, $t(8) = 0.42$, $P = 0.34$).

4. Discussion

The current results indicate that, in humans, spatial learning/memory impairments in a virtual Morris water task occur following unilateral HPC removal and are independent of the side removed. Moreover, because the tumor and hippocampal group do not differ on the Rey–Osterrieth complex figure copy and recall task, this result cannot be attributed to a global learning/memory impairment.

Interestingly, this spatial learning/memory impairment does not seem to be lateralized. The patients with left HPC damage showed spatial learning/memory impairments in this task equal to those impairments seen in the patients with the right HPC damage. This is atypical for learning/memory performance following surgical excision for epilepsy. More specifically, there is a plethora of studies that suggest that it should be lateralized. For example, excisions to the left hemisphere are usually followed by verbal memory impairments for stimuli, such as prose [9] or words [14,16]. However, following right hemisphere excisions, one usually observes spatial memory impairments for maze learning [6], spatial locations [4,34], face recognition [22] or abstract designs [15,16,31,37]. Accordingly, one would expect performance in the vMWT to be unaffected by left HPC damage, but we did not observe this result. Note that this is not an issue of statistical power. Whereas, there were only five patients each in the left and right HPC groups, the critical observation here is that none of the five patients with left HPC resections could solve the task. Their percent distance in the quadrant of the pool where the platform had previously been located was $12 \pm 5\%$ during the first probe trial and $22 \pm 7\%$ during the second probe (recall chance performance is 25%). Hence, this is not a trend that does not reach statistical significance simply due to a low *N*. Rather, the patients with left HPC resections display spatial learning/memory impairments in this task.

Functional imaging data tend to be in agreement with the data reported here. Specifically, Maguire et al. reported both right and left HPC activation during navigation in a virtual environment using PET, depending on which subtraction they used [19]. Aguirre et al. [1] reported bilateral parahippocampal activation in virtual navigation using fMRI while Gron et al. [13] reported bilateral HPC activation for men and right HPC activation for women in a virtual maze. Hence, it seems that not only is there bilateral involvement of the HPC in these virtual tasks, but the results of the current study suggest that hippocampus by itself cannot sustain accurate navigation. Additionally, another explanation for the lack of a laterality effect in our task could be that the participants were utilizing both linguistic and visuo-spatial strategies to solve this task and that neither strategy alone was sufficient to solve the task. Hence, damage to either the left or right HPC impairs performance.

In deciphering the reported laterality effects following unilateral hippocampal resections, it may be that the left and right HPC function precisely in the same manner and it is the damage to the overlying cortex that determine the observed deficits. Because the left HPC receives inputs from association cortex that is involved in linguistic processes [8], impairments in that domain are observed following damage to it. Accordingly, because the right HPC receives inputs from association cortex that is essential for spatial or abstract processing, damage to it results in impairments at those levels. Hence, the domain specificity of deficits after left or right medial temporal lobe excisions may be based upon lateralized specificity of the overlying rhinal and association cortex and the HPC may be functionally symmetrical. This view is consistent with the dissociations after damage to HPC versus rhinal cortex in nonhuman primates [26]. Thus, damage to left or right HPC could generate relational memory deficits irrespective of stimulus type, whereas damage to left or right rhinal and association cortex determines the type of information that is affected (e.g. linguistic or visuo-spatial information). Functional imaging studies, as well as extensions of the current study, should be able to elaborate these laterality issues further.

There are fundamental differences in performing a virtual version of the task compared to a real spatial navigation task. When performing the virtual version, there are minimal vestibular inputs that can help during

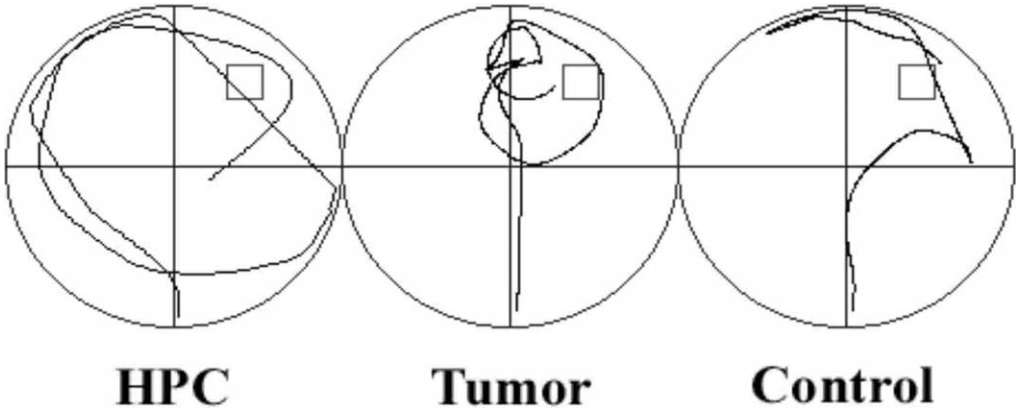

Fig. 3. Probe trial swim paths from the first probe trial of the median individual in each group, as determined by probe trial performance. Note the lack of a preference for the correct quadrant by the individual from the HPC group.

navigation and vestibular information has been shown to be important for rodents to navigate efficiently [5,20,30]. However, whereas the vestibular inputs are minimal, there still exists optokinetic (i.e. visual motion) information that can be utilized by the participants. Indeed, it has been shown that place cells in the hippocampus are sensitive to both vestibular information and optokinetic information [32]. Moreover, it is well known in the virtual reality world that motion sickness and vertigo can be induced using optokinetic information. Hence, the optokinetic information has a strong interaction with the vestibular systems. These points notwithstanding, all groups are equally deprived of such sources of information, so it is not as if the vestibular information that is obtained by moving through an actual environment is necessary to solve this task. Nonetheless, it may be that the patients with hippocampus damage are lacking a mechanism to integrate the optokinetic information with the landmark and relational information. This, in turn, may impair their ability to utilize path integration or cognitive mapping strategies.

In choosing a control group, the ideal group to compare with the HPC group would be a group that has had surgery to treat their intractable seizures that involves removed structures in the temporal lobe other than HPC. However, such a group simply does not exist. In using surgical methods to treat epilepsy, the main epilepigenic structure in the temporal lobe is the HPC. Hence, no epilepsy neurosurgeon would operate on temporal lobe without the intention of removing HPC. Given that the amygdala has an established role in epilepsy and is prone to an epileptic model called kindling [12], the amygdala is also routinely removed. This leaves us with the question of what an ideal control group would be. Initial attempts were made to test patients who were epileptic and who had resections of brain structures exterior to temporal lobe, such as parietal or frontal resections. However, the first group of patients tested had seizures either immediately prior to or during testing. Immediately after a seizure (i.e. post-ictally), patients are often disoriented and confused and conservatively, any data collected within 12 h after a seizure are not good indicators of normal performance. Thus, it became quickly apparent that this group was not going to be a good control group. Hence, the tumor group was chosen. They had all undergone brain surgery and had rather substantial volumes of brain tissue removed. So, whereas they were not consistent in terms of the surgeries that they had undergone, they acted as a proper control group in that they were age-matched, had parts of their cortex removed and are now neurologically healthy.

Although the HPC is the main structure targeted in these surgeries, it is critical to point out that all the HPC patients tested also had the majority of their amygdala removed as well as some of the overlying cortex (i.e. perirhinal cortex). Hence, it is not clear whether these impairments are a result of damage to the HPC, the amygdala, perirhinal cortex or to some combination of these. However, the literature on the neural bases of spatial memory suggests a converging story that the amygdala is probably not involved in spatial navigation. Specifically, it has been shown that in rodents, there are no impairments in the Morris water task following amygdala damage [36]. Furthermore, there have been numerous reports of various dissociations involving HPC and amygdala functioning [21,25], suggesting that they do not subserve the same functions. Rather, the amygdala seems to have a more accepted role of being involved in memory for emotional stimuli [18,38] or various stimulus–reward associations [10,17]. Correspondingly, it also seems that perirhinal cortex is not involved in spatial navigation, but rather is involved in object memory [11,36]. Nonetheless, it must be kept in mind that these data are the result of HPC + overlying cortex resections and conclusions about the specific contributions of each structure must await further experimentation.

In other attempts to bridge the paradigmatic gap between the rodent and human tests, Bohbot et al. [4] created a real life analogue of the Morris water task using a hidden sensor under a carpet as a goal. They report that humans with damage to either the left or right hippocampus proper displayed no impairments in their task, but they observed impairments in three patients with right parahippocampal excisions. However, their test differed from the actual Morris water task in that the one-trial learning and latency to find the sensor is the only dependent variable reported. Hence, the strategy being utilized by the subjects cannot be determined due to the lack of a probe trial or reports of navigation speed (e.g. were the three patients with right parahippocampal excisions simply walking more slowly?). Regardless, their data are inconsistent with the rodent literature that implicates the hippocampus as critical for accurate navigation in the Morris water task.

The current experiment utilized converging sources of information across species and within experimental paradigms to assess HPC function in humans. Using the vMWT, we observed striking impairments in every patient with unilateral HPC damage. Moreover, this impairment did not seem to be sensitive to side of surgery. These results are the first to use a nonhuman paradigm to reveal allocentric learning/memory impairments in humans with hippocampus damage and this is consistent with those reported in the literature. This is advantageous in that it utilizes a virtual analogue of a classic nonhuman memory task to assess the integrity of HPC functioning in humans and hence, experiments can be designed to test similar factors both in nonhu-

mans and humans. Accordingly, as in nonhumans, the HPC in humans is critical for spatial/relational memory. Further experimentation is underway to decipher whether the observed deficits are based on problems with allocentric representations as opposed to path integration. Moreover, functional imaging will allow for better assessment of the role of the intact hippocampal system in this task.

Acknowledgements

We wish to thank Brenda Milner and Joelle Crane for their invaluable contributions to this project. This work was partially funded by a Minority Biomedical Research Support and Student Research Allocation Committee award to RSA.

References

[1] Aguirre GK, Detre JA, Alsop DC, D'Esposito M. The parahippocampus subserves topographical learning in man. Cereb Cort 1996;6:823–9.
[2] Astur RS, Ortiz ML, Sutherland RJ. A characterization of performance by men and women in a virtual Morris water task: a large and reliable sex difference. Behav Brain Res 1998;93:185–90.
[3] Bingman V. Unimpaired acquisition of spatial reference memory, but impaired homing performance in hippocampal ablated pigeons. Behav Brain Res 1988;27:179–88.
[4] Bohbot VD, Kalina M, Stepankova K, Spackova N, Petrides M, Nadel L. Spatial memory deficits in patients with lesions to the right hippocampus and to the right parahippocampal cortex. Neuropsychologia 1998;36(11):1217–38.
[5] Chapuis N, Krimm M, de Waele C, Vibert N, Berthoz A. Effect of post-training unilateral labyrinthectomy in a spatial orientation task by guinea pigs. Behav Brain Res 1992;51:115–26.
[6] Corkin S. Tactually-guided maze learning in man: effects of unilateral cortical excisions and bilateral hippocampal lesions. Neuropsychologia 1965;3:339–51.
[7] Day LB, Weisend MP, Sutherland RJ, Schallert T. The hippocampus is not necessary for a place response but may be necessary for pliancy. Behav Neurosci 1999;113(5):914–24.
[8] Duvernoy HM. The Human Hippocampus. Berlin, Germany: Springer Press, 1998.
[9] Frisk V, Milner B. The role of the left hippocampal region in the acquisition and retention of story content. Neuropsychologia 1990;28:349–59.
[10] Gaffan D, Gaffan EA, Harrison S. Visual–visual associative learning and reward-association learning in monkeys: the role of the amygdala. J Neurosci 1989;9:558–64.
[11] Glenn MJ, Mumby DG. Perirhinal cortex lesions do not impair allocentric spatial working memory in rats. Behav Neurosci 1998;112:1353–65.
[12] Goddard GV, McIntyre D. Some properties of a lasting epileptogenic trace kindled by repeated electrical stimulation of the amygdala in mammals. In: Laitinen LV, Livingston KE, editors. Surgical Approaches in Psychiatry. Baltimore: University Park Press, 1973.
[13] Gron G, Wunderlich AP, Spitzer M, Tomczak R, Riepe MW. Brain activation during human navigation: gender-different 10 neural networks as substrate of performance. Nat Neurosci 2000;3(4):404–8.
[14] Jones M. Imagery as a mnemonic aid after left temporal lobectomy: contrast between material-specific and generalized memory disorders. Neuropsychologia 1974;12:21–30.
[15] Jones-Gotman M. Right hippocampal excision impairs learning and recall of a list of abstract designs. Neuropsychologia 1986;24:659–70.
[16] Jones-Gotman M, Zatorre RJ, Olivier A, Andermann F, Cendes F, Staunton H, McMackin D, Siegel AM, Wieser HG. Learning and retention of words and designs following excision from medial or lateral temporal-lobe structures. Neuropsychologia 1997;35(7):963–73.
[17] Kentridge RW, Shaw C, Aggleton JP. Amygdaloid lesion and stimulus–reward associations in the rat. Behav Brain Res 1991;42:57–66.
[18] LeDoux JE, Cicchetti P, Xagoraris A, Romanski M. The lateral amygdaloid nucleus: sensory interface of the amygdala in fear conditioning. J Neurosci 1990;10:1062–9.
[19] Maguire EA, Burgess N, Donnett JG, Frackowiak RSJ, Frith CD, O'Keefe J. Knowing where and getting there: a human navigation network. Science 1998;280:921–4.
[20] Martin GM, Harley CW, Smith AR, Hoyles ES, Hynes CA. Spatial disorientation blocks reliable goal location on a plus-maze but does not prevent goal location in the Morris water task. J Exp Psychol: ABP 1987;23:183–93.
[21] McDonald RJ, White NM. A triple dissociation of memory systems: hippocampus, amygdala, and dorsal striatum. Behav Neurosci 1993;107(1):3–22.
[22] Milner B. Visual recognition and recall after right temporal-lobe excision in man. Neuropsychologia 1968;6:191–209.
[23] Morris RGM. Spatial localization does not require the presence of local cues. Learn Motiv 1981;12:239–69.
[24] Morris RGM, Garrud P, Rawlins JP, O'Keefe J. Place navigation in rats with hippocampal lesions. Nature 1982;297:681–3.
[25] Mumby DG, Astur RS, Weisend MP, Sutherland RJ. Retrograde amnesia and selective damage to the hippocampal formation: memory for places and object discriminations. Behav Brain Res 1999;106:97–107.
[26] Murray EA, Mishkin M. Visual recognition in monkeys following rhinal cortical ablations combined with either amygdalectomy or hippocampectomy. J Neurosci 1986;6:1991–2003.
[27] O'Keefe JA, Dostrovsky J. The hippocampus as a spatial map: preliminary evidence from unit activity in freely moving rats. Brain Res 1971;34:171–5.
[28] O'Keefe JA, Nadel L. The Hippocampus as a Cognitive Map. Oxford: Clarendon Press, 1978.
[29] Olton DS, Becker JT, Handelmann GE. Hippocampus, space, and memory. Behav Brain Sci 1979;2:313–66.
[30] Ossenkopp KP, Hargreaves EL. Spatial learning in an enclosed eight-arm maze in rats with sodium arsinilate-induced labryinthectomies. Behav Neural Biol 1993;59:253–7.
[31] Pigott S, Milner B. Memory for different aspects of complex visual scenes after unilateral-temporal or frontal-lobe resection. Neuropsychologia 1993;13:1–15.
[32] Sharp PE, Blair HT, Etkin D, Tzanetos DB. Influences of vestibular and visual motion information on the spatial firing patterns of hippocampal place cells. J Neurosci 1995;15(1):173–89.
[33] Sherry DF, Jacobs LF, Gaulin SJ. Spatial memory and adaptive specialization of the hippocampus. Trends Neurosci 1993;15(8):298–303.
[34] Smith ML, Milner B. The role of the right hippocampus in the recall of spatial memory. Neuropsychologia 1981;19:781–93.

[35] Sutherland RJ, Whishaw IQ, Kolb B. Spatial mapping: definitive disruption by hippocampal and frontal cortex damage in the rat. Neurosci Letts 1982;31:271–6.
[36] Sutherland RJ, McDonald RJ. Hippocampus, amygdala, and memory deficits in rats. Behav Brain Res 1990;37:57–79.
[37] Taylor LB. Localisation of cerebral lesions by psychological testing. Clin Neurosurg 1969;16:269–87.
[38] Weiskrantz L. Behavioral changes associated with ablation of the amygdaloid complex in monkeys. J Comp Physiol Psychol 1956;49:381–91.
[39] Whishaw IQ, Cassel JC, Jarrard LE. Rats with fimbria-fornix lesions display a place response in a swimming pool: a dissociation between getting there and knowing where. J Neurosci 1995;15:5779–88.