Title

Impairments in precision, rather than spatial strategy, characterize performance on the virtual Morris Water Maze: A case study

Authors

Kolarik, Branden S

Shahlaie, Kiarash

Hassan, Abdul

et al.

Publication Date

2016

DOI

10.1016/j.neuropsychologia.2015.11.013

Peer reviewed

HHS Public Access

Author manuscript

Neuropsychologia. Author manuscript; available in PMC 2017 January 08.

Published in final edited form as:

Neuropsychologia. 2016 January 8; 80: 90–101. doi:10.1016/j.neuropsychologia.2015.11.013.

Impairments in Precision, Rather than Spatial Strategy, Characterize Performance on the Virtual Morris Water Maze: A Case Study

Branden S. Kolarik[1,2], **Kiarash Shahlaie**[3], **Abdul Hassan**[2], **Alyssa A. Borders**[1], **Kyle C. Kaufman**[2], **Gene Gurkoff**[3], **Andy P. Yonelinas**[1], and **Arne D. Ekstrom**[1,2]

[1]Department of Psychology, University of California, Davis, 1 Shields Ave, Davis, CA 95618

[2]Center for Neuroscience, University of California, Davis, 1 Shields Ave, Davis, CA 95618

[3]Department of Neurological Surgery, University of California, Davis, 4860 Y Street Suite 3740, Sacramento, CA 95817

Abstract

Damage to the medial temporal lobes produces profound amnesia, greatly impairing the ability of patients to learn about new associations and events. While studies in rodents suggest a strong link between damage to the hippocampus and the ability to navigate using distal landmarks in a spatial environment, the connection between navigation and memory in humans remains less clear. Past studies on human navigation have provided mixed findings about whether patients with damage to the medial temporal lobes can successfully acquire and navigate new spatial environments, possibly due, in part, to issues related to patient demographics and characterization of medial temporal lobe damage. Here, we report findings from a young, high functioning patient who suffered severe medial temporal lobe damage. Although the patient is densely amnestic, her ability to acquire and utilize new, but coarse, spatial “maps” appears largely intact. Specifically, a novel computational analysis focused on the precision of her spatial search revealed a significant deficit in spatial precision rather than spatial search strategy. These findings argue that an intact hippocampus in humans is not necessary for representing multiple external landmarks during spatial navigation of new environments. We suggest instead that the human hippocampus may store and represent complex high-resolution bindings of features in the environment as part of a larger role in perception, memory, and navigation.

Keywords

Memory; spatial memory; allocentric; cognitive map; MTL lesion; hippocampus; Morris Water Maze

CORRESPONDING AUTHOR: Dr. Arne Ekstrom, Center For Neuroscience and Department of Psychology, University of California, Davis, Davis, CA 95618, adekstrom@ucdavis.edu.

1. Introduction

The ability to navigate is a vital skill for both animals and humans alike. One prominent idea proposed by Edward Tolman, (1948) is that the brain forms a cognitive map that represents a spatial environment in a metric, map-like format (Tolman, 1948). Cognitive Map Theory (CMT) further posits that the hippocampus, a bilateral medial temporal lobe (MTL) structure, is both responsible and necessary for forming map-like representations of the environment (O'Keefe and Nadel, 1978). In particular, CMT argues that navigation combining multiple distal cues to derive locations in space ("allocentric navigation") depends on the hippocampus. In contrast, navigation involving egocentric cues, or locations referenced to one's current position, does not depend on the hippocampus. Support for this idea comes from computational theories based on the neural architecture of the hippocampal formation and the fact that "place cells," neurons that code an animals location, are present in the hippocampus (O'Keefe & Dostrovsky, 1971; Samsonovich & McNaughton, 1997), and alter their firing depending on changes in the location of distal cues (Muller & Kubie, 1987; O'Keefe & Speakman, 1987). Another critical line of support involves the detrimental effect of hippocampal lesions on spatial memory, or more specifically, gross impairments in the ability to find a hidden location via reference to distal landmarks in the environment. (Eichenbaum, Dudchencko, Wood, Shapiro, & Tanila, 1999; Morris, Garrud, Rawlins, & O'Keefe, 1982; White & Wallet, 2000). Thus, two critical lines of research provide support for CMT, the "map-like" nature of place cells and the fact that hippocampal lesions abolish the ability of rodents to find a location based on external landmarks in the environment.

One paradigm extensively used to demonstrate the necessity of the hippocampus to spatial memory is the Morris Water Maze (Morris, 1984; Morris et al., 1982). A basic finding, replicated across numerous studies in rodents, is that lesions to the hippocampus abolish the ability of a rat to find a hidden platform using cues outside of a pool of water (termed allocentric cues). These same lesions, however, do not affect the ability of the rat to find a hidden location using a brightly colored cue card or a familiar trajectory (D'Hooge & De Deyn, 2001; de Hoz, Knox, & Morris, 2003; Morris, 1984; Morris, Garrud, Rawlins, & O'Keefe, 1982; Moser, Moser, Forrest, Andersen, & Morris, 1995; Vorhees & Williams, 2006; Eichenbaum, Stewart, & Morris, 1990 but see Day, Weisand, Sutherland, & Schallert, 1999). These findings suggest that damage to the rodent hippocampus impairs its ability to use allocentric cues to navigate, while leaving egocentric search strategies intact. Partial lesions to the hippocampus, in particular, to the dorsal/posterior hippocampus, similarly significantly impair the ability of the rat to employ an allocentric search strategy based on distal cues outside of the Water Maze (Moser, Moser & Andersen, 1993; Moser et al., 1995). These findings provide support for CMT and suggest that an intact hippocampus is necessary for allocentric spatial navigation.

Extending these findings to humans, though, has been more challenging. Studies in humans using virtual and real analogues of the Morris Water Maze task have shown mixed results, as reviewed in a recent paper (Ekstrom, Arnold, & Iaria, 2014). In one study, consistent with rodent findings, a desktop virtual reality version of the Morris Water Maze was employed in which unilaterally damaged MTL patients and controls navigated a virtual pool to find a hidden goal location. The authors found that MTL patients performed at chance levels on

"probe trials" (in which the hidden platform was removed to allow for a more complete assay of spatial knowledge) (Astur, et al., 2002; see also Bartsch et al., 2010). Additionally, a second study, using a similar paradigm but with patients with lesions more circumscribed to the hippocampus, found above chance yet impaired performance on the virtual Morris Water Maze (Goodrich-Hunsaker, Livingstone, Skelton, & Hopkins, 2010). In a real world analogue of the Morris Water Maze, a recent study again demonstrated impaired, but again, above chance allocentric navigation in a single hippocampally lesioned patient (Banta-Lavenex, Colombo, Ribordy-Lambert, & Lavenex, 2014). Another study that used a real-world analogue of the Morris Water Maze, however, reported no allocentric navigation impairments for patients with damage limited to the hippocampus, although impairments did appear when lesions extended into the parahippocampal cortex (PHC) (Bohbot et al., 1998). Finally, the patient HM, who had some damage to the hippocampus and surrounding cortex, showed no impairment on finding a single hidden target but severely impaired performance on a second location (Bohbot & Corkin, 2007).

There are several potential considerations with previous work in humans, however, warranting further investigation. One issue, which we explore in detail here, is that the analyses used in previous studies of the human Morris Water Maze analogues do not provide a continuous measure of navigation, but rather coarse assessments of spatial memory based on dividing the arena into discrete quadrants. Recent findings, though, suggest that the hippocampus is involved in perceptual precision (Olson, Moore, Stark & Chatterjee, 2006; see also Erez, Lee, & Barense, 2013; Ryan, Moses, Barense, & Rosenbaum, 2013; Warren, Duff, Jensen, Tranel and Cohen, 2012) and a recently proposed alternative theory (which we refer to here as the Precision and Binding Model [PBM]) argues for a role of the hippocampus in spatial precision rather than spatial strategy per se (Yonelinas, 2013). Thus, a more in depth consideration of the precision of trajectories taken through the arena following hippocampal damage could better characterize navigational impairments following MTL damage and possibly help better understand the role of the hippocampus in perceptual precision and navigation.

Another issue regards the focus of medial temporal lobe damage in patients. For example, the patient HM (who was studied in Bohbot & Corkin 2007) had damage primarily to his anterior hippocampus (Annese et al., 2014). Thus, if spatial learning depends more on the posterior hippocampus, as suggested in some rat studies (Moser, Moser, & Andersen, 1993; Moser, Moser, Forrest, Andersen, & Morris, 1995), one might not expect to see deficits in patients with primarily anterior hippocampal damage. Furthermore, many of the patients in the above studies had low- to-average IQs (or in some cases, these data were not reported, i.e., Astur et al. 2002). A lower IQ might make it more challenging to learn environments in VR on a computer as it involves a heavy demand on novel visuo-motor integration. Finally, age could be an important factor as many of the studies above involve participants up to 60 years old. Some reports suggest that older participants have impairments in the ability to use distal cues to navigate (Moffat, Elkins, & Resnick, 2006) and particularly for those with little computer experience, navigating VR could be more challenging.

Here, we report findings from a young, high-functioning patient (RT) who experienced dense amnesia following damage to her medial temporal lobe. To better characterize her

medial temporal lobe damage, we employed high-resolution imaging sequences targeting the MTL (Ekstrom et al., 2009), which suggested comparable damage to her anterior and posterior hippocampus. To test ideas related to the precision of navigational trajectories specifically, we examined her navigational paths in more detail than has been done in previous studies using the virtual Morris Water Maze. In most studies, the Morris Water Maze is divided into quadrants and intact spatial memory is defined as searching within the correct quadrant. As shown in Figure 1D, however, this produces an arbitrary division of space that in some cases fails to accurately capture an otherwise fairly accurate path. To address this issue, we analyzed search paths using a sliding window centered on the target location allowing us to better assess the precision of the spatial searches. Our findings reveal that although RT was able to employ a coarse allocentric search strategy to navigate, she did show a significant deficit in the spatial precision of her searches during navigation.

2. Methods

2.1 Participants

2.1.1 Patient—RT, a right-handed female, was 29 years old when testing began. She experienced significant hippocampal damage following a motor vehicle accident 3 years prior to testing. She holds a master's degree in civil engineering, with a total of 19 years of education and a premorbid IQ of 110.

Table 1 contains the results of standardized neuropsychological tests showing that RT meets clinical definition of amnestic. Scores on the California Verbal Learning Test were 2 standard deviations below the mean on short-delay cued recall, delayed recognition, and source recognition discriminability. Furthermore, scores were 1.5 standard deviations below the mean on both short- and long-delay free recall and long-delay cued recall. On the Doors and People Test (Baddeley, Emslie, & Nimmo-Smith, 1994), RT scored in the 25th percentile on general recall, the 1st percentile on recognition, and the 10th percentile on an overall memory score. These scores highlight an amnestic impairment in both recognition and recall with and without a delay, which were at least two standard deviations below her IQ, a standard definition of amnesia (Aly, Ranganath and Yonelinas, 2013).

Figure 1A shows a coronal MPRAGE slice (see MRI Acquisition section for details) highlighting the extent of hippocampal damage. An assessment of the coronal T1-weighted MRI revealed cortical atrophy involving the right frontal and temporal lobes, with a compensatory increase in sulcal spaces, significant volume loss involving the right temporal cortex, temporal stem, and medial structures including the hippocampus, and significant compensatory dilation of the inferior horn of the lateral ventricle. Figure 1B depicts the relative volume of RT's hippocampal subfields relative to 14 control subjects based on a high-resolution sequence targeting her MTL (see MRI Acquisition section for details). The following subfield volumes were significantly below controls: Right anterior CA fields ($z = -3.43$, $p < .001$), left CA3 ($z = -2.30$, $p < .05$), right CA3 ($z = -3.21$, $p < .001$), left CA1 ($z = -2.88$, $p < .01$), right CA1 ($z = -4.5$, $p < .001$), left subiculum ($z = -3.20$, $p < .001$), right subiculum ($z = -5.64$, $p < .0001$), left perirhinal cortex ($z = -3.647$, $p < .001$), right perirhinal cortex ($z = -4.81$, $p < .001$), left parahippocampal cortex ($z = -4.51$, $p < .001$), and right parahippocampal cortex ($z = -5.34$, $p < .0001$). In Table 2, we show the results of employing

the uncal apex to divide the hippocampus into anterior and posterior segments (Poppenk & Moscovitch, 2011). Anterior hippocampus included anterior CA fields and anterior subiculum while posterior hippocampus included CA1, CA2-3/dentate gyrus, and posterior subiculum (Duvernoy, 1998). The patient showed comparable degrees of volume loss in anterior and posterior hippocampus, although damage was approximately twice the amount on the right side across the anterior and posterior hippocampus compared to the left (see Table 2). Considering her overall MTL volume by including entorhinal and perirhinal cortex in anterior segments and posterior parahippocampal cortex in posterior segments suggested numerically greater posterior MTL damage than anterior MTL damage (see Table 2), although this effect was driven by the fact that there was a compensatory gain in entorhinal volume (see Figure 1B). In addition to these subfield volume decreases, assessment of the coronal T2-weighted MRI of the brain focused on the medial temporal lobes, demonstrated atrophy of the right hippocampus, underlying parahippocampal gyrus, and adjacent fusiform and inferior temporal gyri as well as compensatory dilation of the inferior horn of the lateral ventricle Thus, the patient had significant damage to her MTL, which was present in both anterior and posterior areas of the hippocampus and surrounding cortex, with some volume loss in the frontal lobes. Damage to other extra-MTL brain areas was relatively minimal.

2.1.2 Control subjects—Twenty-five University of California, Davis undergraduates (8 Male, mean age 20.2 years) participated for course credit. All participants provided informed consent based on procedures approved by the University of California- Davis Institutional Review Board. We also scanned 14 healthy participants (7 Male), mean age 23.9 years to obtain hippocampal subfield volumes as part of separate studies. We include these subfield volumes to determine the extent of RT's hippocampal-specific atrophy.

2.2.1 MRI Acquisition—MRI scans were collected at the University of California-Davis Imaging Research Center on a 3T Siemens (Erlangen, Germany) Trio equipped with a thirty-two-channel head coil. Structural T1-weighted images were acquired using a three-dimensional MPRAGE pulse sequence with voxel size 1x1x1 mm. High-resolution structural images were acquired using a T2-weighted turbo-spin echo sequence voxel size = 0.4 x 0.4 x 1.9 mm (see Ekstrom et al, 2009). Medial temporal lobe volumes normalized by total intracranial volume were estimated with SIENAX (Smith et al., 2002), part of FSL (Smith et al., 2004).

2.2.2 Experimental Design—Participants performed a virtual reality analog of the Morris Water Maze created in Unity 3d (Unity Technologies, San Francisco). The task was modeled on Astur et al. (2002), which previously demonstrated chance levels of performance in MTL patients on the virtual Morris Water Maze. The task required the participants to explore a virtual reality room presented on a computer screen using keyboard arrow keys to navigate the room in a first-person perspective (Figure 1C). The room was 8 x 8 virtual meters, with 4 unique paintings, unevenly spaced, one on each wall.

Participants were instructed to find a hidden invisible sensor located on the floor of the room. The hidden sensor was a .4 × .4 virtual meter square, occupying 0.25% of the total room area. When the participant virtually walked over the sensor, an on-screen prompt displayed 'You found the hidden sensor' and a 10-second countdown timer started in the

corner of the screen during which time they were able to freely navigate. After the 10 seconds of free navigation, an inter-trial screen was presented and participants clicked on a button to begin the next trial. Participants completed 20 training trials in 5 blocks of 4 trials each. They started from each of 4 locations (arbitrary North, South, East or West) once in each block. On trial 21, unbeknownst to the participant, the sensor was removed, and a probe trial began. On this trial, one of the four start points was randomly chosen and the trial ran just as the training trials. This trial terminated after 30 seconds, at which point the sensor was moved, and the entire procedure was repeated. Following the second probe trial, there were eight trials in which the sensor was visible and the participants simply had to navigate to it. This condition served to control for motivational or motoric deficits in performing the task. Position within the environment was recorded to a text file at a rate of 20 samples per second.

2.3 Data Analysis

Following the past method of analyzing tasks of this nature (i.e. Morris et al., 1982), the room was divided into quadrants using the North-South and East-West axes (Figure 1D). If participants had correctly encoded the location of the sensor, then they should spend significantly more time on the probe trial in the quadrant where the sensor had previously been located. A modified *t*-test procedure was implemented based on the methods described in Crawford and Howell (1998) that allows the comparison of a single case to a sample mean. Modified *t*-tests were calculated individually for the two probe trials (Crawford & Howell, 1998).

The quadrant analysis, however, gives little information about the precision of spatial memory. To better assay spatial precision, we calculated the amount of time spent within a sliding window centered on the location of the hidden sensor. For each probe trial, 9 individual precision windows were calculated, each of which was a square ranging from .8 to 4 virtual meters in size (Figure 1D). Each square was centered on the sensor's location. We then calculated the percent of time spent in each of these sliding windows. This allowed us to determine the precision of the spatial memory using non-arbitrary metrics. Modified z-scores that use standard error in the denominator were computed to compare RT to control performance at each of the nine precision windows separately for the two probe trials. These scores give us the likelihood that she belongs to the same population from which our sample was drawn. Because this method naturally inflates the z-score we adjusted our significance threshold appropriately such that our $p_{critical} = .05/\sqrt{N}$, resulting in a critical value of .01 for the following z-score analyses.

We estimated chance performance for the precision analysis using a bootstrapping procedure in which we resampled every control participants' trajectory through the room over the entire session (50 trials), resulting in a series of random trajectories through the environment. This approach calculates every participant's trajectory over all trials, giving a sample of all possible trajectories through the environment regardless of the goal. The 9 precision windows were then imposed on these trajectories, percent of time in each of those windows was calculated, and then the windows shifted by 50 units in either the x or y dimension until the entire area of the room had been covered. This resulted in 1600 separate

calculations for each precision window for each participant, which were then averaged to give an estimate of chance performance. This number represents the likelihood that a participant would spend a given amount of time in a precision window simply by chance. These estimates were confirmed using the first trial of the session where finding the sensor could occur only by chance. Using these estimates, RT's performance can be compared to both controls and chance.

To more precisely characterize the pattern of performance in both RT and controls, we additionally fit functions to the results from our sliding window analysis described above. This allowed us to determine if her precision differed from that of the lowest performing controls. We first fit a linear function to control precision data because a direct path from start to target would result in a linear slope of precision. We then used root-mean-squared-error to determine the fit of a linear function to control participant data and RT. We compared control participants in separate groups (lowest and highest performing controls) based on a median split under the assumption that worse performing participants could have different patterns of precision. This allowed us to assess whether the resulting functions could be used to characterize and compare the patterns of precision drop-off and whether these differed between controls and RT.

3. Results

We first wished to determine whether spatial learning occurred over the training trials in RT and controls. To determine how RT's performance compared to controls at the end of training, we used modified *t*-tests to compare performance on the last trial of each block. Results of this analysis confirm that RT's performance did not differ from controls for the amount of time taken to find the sensor on the last trial of training block 1 ($T_{(24)}$ =.1471, p= n.s) and training block 2 ($T_{(24)}$ =-.174, p =n.s.). These data suggested that by the end of training, RT had learned the location of the hidden sensor as well as controls, although she did show a tendency toward disorientation during training, as indicated by trials in which she failed to find the sensor despite locating it rapidly on the previously trial (Figure 2A).

We next wished to determine the accuracy of RT's path on probe trials compared to both controls and chance performance. Probe trials are helpful to analyze because they provide a full 30 seconds of exploration in which path can be analyzed in greater depth. If RT had knowledge of the hidden location, we would expect most of the searching to be within the quadrant that contained the hidden target. In contrast, if she had no knowledge of the hidden location, we would expect random search trajectories, consistent with Astur et al. (2002) and Bartsch et al. (2010). Figure 2B shows the results of the quadrant analysis. On probe trial 1, RT showed a slight, but not statistically significant impairment ($T_{(24)}$ = -.4655, p =n.s.) relative to controls in the amount of time spent searching the quadrant where the sensor had been located. However, on probe trial 2, RT showed a marked impairment compared to controls ($T_{(24)}$ = −3.9356, p = .0006) and was well below chance in the amount of time spent searching the correct quadrant. Thus, according to the typically employed quadrant analysis, RT showed no impairment on probe location 1 and a profound impairment on probe location 2. These findings are broadly consistent with Bohbot and Corkin's 2007 study with HM, who showed no memory impairment for one spatial location but profound amnesia for the

second location. Together, these findings are compatible with a spatiotemporal memory deficit, rather than an overall spatial memory deficit.

To determine if there were systematic errors in the area searched on the probe trial, we calculated the amount of time spent in each quadrant for RT and controls on both probe trials. We again analyzed probes 1 and 2 trials separately. Figure 2C shows the amount of time RT spent in the correct quadrant, the opposite quadrant, and the two neighboring quadrants to the left and right for each probe. For probe 1, RT spent statistically comparable amounts of time in the correct quadrant relative to controls ($T_{(24)}$ =-.4655, p = n.s.). However, she showed a statistically greater likelihood than controls to search in the right (nearby) quadrant ($T_{(24)}$ = 2.83, p < .01). For Probe 2, RT spent significantly less time in the correct quadrant than controls ($T_{(24)}$ =−4.28, p<.005) and again spent significantly more time in the right quadrant than controls did on average ($T_{(24)}$ = 4.59, p <.0001). Together, these findings suggest a tendency to search within the broad vicinity of the quadrant although overall lacking the precision of control search patterns. This effect was more pronounced for the 2nd compared to 1st probe location, again consistent with the findings from Bohbot and Corkin (2007).

To further investigate the extent to which RT might search within the correct vicinity of the hidden sensor but with less precision than the controls, we performed an analysis using a sliding window centered on the location of the platform (Figure 1D see Section 2.3 *Data Analysis*). Consistent with our finding that she spent more time than controls in the adjacent quadrant, we expected that RT might show some impaired precision even for the first probe trial when an analysis more sensitive to search precision was employed.

The results of this analysis are shown in Figure 3A–B. RT spent significantly less time within the smaller precision windows for both probe 1 [0.64m (z = −5, p<.0001), 1.44m (z = −4.7, p<.0001), 2.56m (z= −4.69, p<.0001), 4.00m (z=−4.55, p<.0001), 5.75m (z= −4.41, p<.0001)] and probe 2 [0.64m (z = −5, p<.0001), 1.44m (z = −5, p<.0001), 2.56m (z= −5, p<.0001), 4.00m (z=−5, p<.0001), 5.75m (z= −5, p<.0001), 7.84m (z=−3.61, p<.005), 10.24m (z= −2.73, p<.01)]. We then tested RT's performance compared to chance. Chance performance was estimated using a bootstrapping procedure in which we resampled every control participants' trajectory through the room over the entire session (50 Trials), resulting in random trajectories through the environment (see Section 2.3 *Data Analysis*). RT was at or below chance performance in 4 of the 5 smallest precision windows on probe trial 1[.64m (z=−219.6, p<.0001), 2.56m (z=−7.54, p<.0001) 4.00m (z=−10.4, p<.0001), 5.75m(z=−5.81, p<.0001)] and on 5 of the 5 smallest precision windows for probe trial 2 [64m (z = −219.6, p<.0001), 1.44m (z = −169, p<.0001), 2.56m (z= −91.39, p<.0001), 4.00m (z=−66.48, p<.0001), 5.75m (z= −55.86, p<.0001)]. Figure 3C–D shows RT's data plotted against chance and is consistent, overall, with comparisons against controls (red asterisks represent precision windows in which she was above chance performance and black asterisks represent precision windows in which RT was at or below chance performance). These results highlight a significant impairment in the precision of RT's spatial memory present on both probe trials compared to controls and chance. Our analysis is consistent, however, with our previous findings in that we find less spatial precision for the second compared to first probe trial.

To further characterize RT's precision deficit compared to controls, we fit linear functions to the data and compared the lowest performing controls to RT (see Section 2.3 *Data Analysis*). The results of the curve fitting analysis are shown in Figure 4B–C. The curve fitting analysis highlights that even the lowest performing half of controls show a slower drop off in their precision compared to chance performance (Figure 4A, best fit is a second order polynomial). Figure 4C–D shows RT's' precision data on probe trials 1 and 2. Because of the dramatic drop-off in precision a third-order polynomial with a steep drop off in precision was required to accurately represent RT's data. To be sure that these results were not a result of averaging control data, we also fit the worst performing control subject. Similar to the average of the lowest performing controls, this subject was fit best by a second-order polynomial. Together, these data suggest that RT 's behavioral performance was quantitatively different from even the lowest performing controls, and was characterized by a steep decline in spatial precision

A final issue we wished to address was whether RT showed impairments on novel start locations as well. The ability to solve the virtual Morris Water Maze from novel start locations is often considered a hallmark of an allocentric spatial search strategy because it involves finding the hidden platform based on a novel view and position relative to the distal cues (Morris et al., 1982). One limitation, however, with investigating this issue using probe trials is that by the time participants perform these trials, they have had fairly extensive experience with different views in the environment from different positions. This could, in principle, facilitate a viewpoint matching strategy consistent with an egocentric search strategy (Wolbers & Wiener, 2014). One way to address the ability to find the hidden platform from a novel location and viewpoint is to look early in learning during acquisition. If patients with MTL damage are able to learn the hidden location from a novel viewpoint, they should be able to do so after even limited experience with the environment. In contrast, a deficit specific to allocentric search strategy should abolish the ability to find the platform on trials involving new viewpoints and positions.

Figure 5A–D show RT's performance on the fourth training trial on each location. Critically, each of these trials occurred early during learning and involved different starting points than the three preceding trials. Thus, the starting viewpoint was completely novel. Figure 5A–B shows the trajectories RT took on these two trials. RT took a nearly direct path to the correct quadrant for location 1 trial 4, suggesting that she was able to utilize an allocentric search strategy by trial 4. For location 2 trial 4, her path was somewhat less direct (Figure 4B) but still non-random, suggesting some preserved ability to use allocentric cues to remember the target location. As further evidence for intact allocentric searching, RT stated that she used two of the distal cues (the paintings on the wall) to try to locate the hidden area she was searching for.

We then performed an identical precision window analysis on the 4^{th} acquisition trials for locations 1 and 2 (Figure 5C–D). For location 1, she performed above chance for all precision windows [.64m ($z = 14.46$, $p<.0001$), 1.44m ($z = 33.06$, $p<.0001$), 2.56m ($z= 477.74$, $p<.0001$), 4.00m ($z=255.20$, $p<.0001$), 5.75m ($z= 149.9$, $p<.0001$), 7.84m ($z=98.24$, $p<.005$), 10.24m ($z= 70.06$, $p<.01$). 12.96m ($z=50.34$, $p<.0001$), 16.0m($z=41.65$, $p<.0001$)]. For location 2, she was above chance for the 16m window ($z=40.21$, $p<.0001$) and 5.75m

window (z= 10.04, p<.0001) but at or below chance for all other windows. These analyses showed that RT performed significantly above chance in all 9 precision windows on this trial for location 1, but was only above chance on 2 of the larger windows for location 2 (Figure 5D). These results suggest that RT was able to utilize an allocentric search strategy early during learning, although with somewhat impaired spatial precision.

Finally, when looking at the time to reach the sensor on the eight visible training trials, RT performed just as well as controls (z = −1.00, p=.31). This finding indicates that our results cannot be explained by a motor or motivation deficit.

4. Discussion

The results reported here show that on a virtual analog of the Morris Water Maze, a patient with MTL damage showed significant learning of the hidden sensor over training trials, comparable to controls although with some tendency to disorientation. Additionally, using standard analyses for virtual water maze tasks, the quadrant analysis showed that RT performed only slightly below controls on probe trial 1 and well above chance. In contrast, on probe trial 2, performance was impaired relative to controls, with a tendency to incorrectly search the adjacent quadrant rather than the correct one. Overall, these findings are consistent with past studies suggesting at least some intact learning in the virtual Morris Water maze and real-world analogue, the hidden sensor task following MTL damage (Bohbot & Corkin, 2007; Bohbot et al., 1998; Goodrich-Hunsaker et al., 2010). One issue with the quadrant analysis, however, is that it imposes arbitrary boundaries to analyze performance on this task and may miss critical features of the memory impairment (Figure 1D). To address this issue, we used sliding precision windows to analyze the data. We showed that on both probe trials, RT showed a significant impairment relative to controls in the smallest precision windows, while showing equivalent performance in the larger windows. To our knowledge, no past studies of patients with amnesia have employed this approach to address the precision spatial search in Morris Water Maze analogues. These results highlight that, despite being densely amnestic, RT has some intact spatial memory, and that, in particular, the precision of her spatial memory is impaired.

Another issue we addressed was the extent to which RT relied on multiple distal spatial cues to navigate. Could she be using a simple view-matching strategy to find the hidden location? While past studies analyzing search patterns of MTL patients argue against this interpretation (Bohbot & Corkin, 2007; Bohbot et al., 2002), we wished to explore it nonetheless. RT's verbal reports indicated that she employed the paintings on the wall (distal cues) to try to remember the hidden target. We also tested this issue by analyzing her search patterns on early training trials, for which RT would have limited experience with different egocentric viewpoints and thus view-matching strategies would be difficult to employ. Despite the prediction that she would be impaired on trials requiring an allocentric search strategy, RT performed well above chance on all precision windows for location 1 trial number 4 and for the largest precision window for location 2 trial 4. Her trajectories indicated that she navigated more or less directly to the hidden location, and she did not appear to rely on view matching by navigating to a previous start location to get within the vicinity of the hidden target (e.g., Figure 5A). Also, it is important to note that an

explanation that relies on a view-matching strategy would not predict deficits in precision, which all of our analyses revealed, including our analysis of her spatial search on a novel start location. Together, these results show that even with significant MTL damage, RT was able to form and use an allocentric spatial representation to locate the hidden sensor. These findings stand somewhat in contrast with previous findings using the virtual Morris Water Maze (Astur et al., 2002; Bartsch et al., 2010) and instead are consistent with past findings demonstrating that some coarse, simple spatial learning can occur in patients with MTL damage (Bohbot & Corkin, 2007; Bohbot et al., 1998; Goodrich-Hunsaker et al., 2010). Importantly, the current study addresses the specifics of the deficits that do arise following MTL damage. We report that precision of the memory is impaired relative to controls but that simple coarse representations of space are relatively intact, at least for the first location.

Cognitive Map Theory (CMT) postulates that the hippocampus is responsible and necessary for forming a map-like spatial representation useful for navigating an environment using an allocentric spatial strategy. CMT maintains that the hippocampus is part of a memory system particularly tuned for spatial information (Nadel, 1991) and posits that hippocampal damage should lead to severe impairments of successful goal-directed exploratory behavior that involves using multiple distal cues to triangulate location. Rodent studies have shown strong evidence for this theory by demonstrating that, following hippocampal lesions, rats are unable to learn the location of a hidden platform in the water maze and show random search trajectories on probe trials (D'Hooge & De Deyn, 2001; de Hoz et al., 2003; Morris, 1984; Morris et al., 1982; Vorhees & Williams, 2006). This pattern of results has also been observed in humans (Astur et al., 2002; Goodrich-Hunsaker et al., 2010) but only using coarse metrics to assess performance. Thus, these studies could potentially miss a precision deficit, a key aspect of the behavioral results of hippocampal damage. These studies have also involved, in many cases, older adults or lower functioning individuals, who may struggle to master navigation in virtual reality. RT, in contrast, was young and had a high-IQ. We were also able to characterize her hippocampal damage fairly extensively using high-resolution hippocampal imaging (Ekstrom et al., 2009). Our findings demonstrate that, even following MTL damage, a patient with amnesia can still use an allocentric search strategy to navigate the virtual Morris Water Maze, with her deficits best characterized by problems with spatial precision rather than search strategy.

We suggest instead that the Precision and Binding Model (PBM) may be able to better account for the current findings compared to CMT. Specifically, Yonelinas (2013) proposed that the hippocampus plays an important role in perception, working memory, and long-term memory, particularly when a task requires complex high-resolution binding (Yonelinas, 2013). According to this account, the hippocampus is critical for binding together the different aspects that make up an event, and thus it should become increasingly important as tasks require more complex bindings (i.e., binding multiple features together rather than forming simple associations). But in addition, the hippocampus is assumed to be particularly important in supporting the binding of high-resolution information such as the precise color or the precise location of an item, and thus should be more important in tasks that require the binding of high precision information. In support of this idea, Aly et al. (2013) found that patients with hippocampal damage were impaired at detecting subtle perceptual differences in pairs of scene images, but did not show a reduced ability to identify discrete featural

differences between scenes (Aly, Ranganath, & Yonelinas, 2013). The study also used fMRI to measure activity in the hippocampus in this task and found that activity in the hippocampus tracked reported response confidence for accurate perception trials. The authors concluded that the hippocampus plays a role in perception, particularly when high-resolution complex binding is necessary for a task (for a review of the related perception, working memory. and long term memory literatures see Yonelinas, 2013).

Given that performance in the current navigation task requires the binding together of multiple aspects of the environment (i.e., picture1 to picture 2 to a hidden target), one can expect the hippocampus to be involved. This binding effect should become more apparent as more objects encoded in memory, such as having to remember a second hidden location after learning a first hidden location. In addition, the hippocampus should be particularly important in supporting precise memory searches, and thus one can expect navigation impairments to become most pronounced when assessing memory precision, and be less noticeable when less precision is required, as was the case with the current patient. The PBM is consistent with earlier models of navigation such as the CMT model to the extent that it assumes that the hippocampus should be critical in allocentric tasks that require the formation of complex multicomponent representations. But it extends those models by arguing that it is particularly important in supporting memory bindings for the resolution of the information itself, such as precise locations rather than more global spatial information.

We also note that PBM makes slightly different predictions from other theoretical conceptualizations of the hippocampus, such as relational memory theory (Cohen & Eichenbaum, 1991; Eichenbaum & Cohen, 2014; Eichenbaum, Otto, & Cohen, 1992). As with the PBM, relational memory theory assumes that the hippocampus is important for relating or ‘binding together’ the various features or objects that make up an environment. The PBM, though, argues that the hippocampus is most critical for the binding of high-resolution features, and so will not be equally involved in all tasks that involve memory for relations. PBM can thus account for the current results because in learning the location of the hidden sensor, the precise location of the small target needed to be bound to external cues (paintings) around the room. Additionally, performance for the second location was worse than the first location, suggesting a deficit that arose when the demand to bind spatial and temporal information was increased. Thus, PBM appears to most naturally account for RT’s combined perceptual precision and complex binding deficit, at least compared to CMT and relational memory theory.

One potential limitation with our study is that RT’s hippocampal damage, like many amnestic patients, was incomplete. It is possible that either some intact anterior (Feigenbaum & Morris, 2004) or posterior hippocampal tissue (Moser et al., 1995) could support some residual allocentric navigation abilities. For example, one theoretical proposal suggests that the posterior hippocampus is more involved in precise spatial details as part of a larger role in storing accurate cognitive maps while the anterior hippocampus may be more important for storing coarse contextual details and emotional processing (Fanselow & Dong, 2010; Nadel, Hoscheidt, & Ryan, 2013). While our findings cannot rule out the possibility that some residual hippocampal tissue accounts for RT’s intact, yet imprecise, allocentric navigational abilities, we believe that such models would predict disproportionate precision

loss following greater posterior than anterior damage. RT's pattern of damage, however, did not differ as a function of anterior vs. posterior hippocampus, and thus our findings do not appear completely consistent with the predictions of this model either. Furthermore, RT's search pattern was significantly more impaired for finding a second versus first location, which is consistent with spatiotemporal deficits in amnestics noted in past reports (Bohbot & Corkin, 2007) and PBM. Anterior versus posterior conceptualizations of hippocampal function, however, would not appear to provide a clear account of why her precision would be worse for a second location. Finally, it is also noteworthy that RT was densely amnestic, performing well below normal on most memory tasks, yet showing some intact navigational abilities. Theories postulating differences in function for anterior versus posterior hippocampus would seem to best account for the dense amnesia based on greater damage to anterior than posterior hippocampus, although RT showed comparable degrees of damage to both her anterior and posterior hippocampus. Thus, while we cannot rule out the idea that some intact posterior hippocampus accounted for her preserved coarse, yet impaired precise, spatial memory abilities, her overall pattern of results do not seem to naturally fit into this account either.

In addition to PBM, we believe that our data are also consistent with some parts of Multiple Trace Theory (MTT) (Moscovitch et al., 2005). MTT states that the hippocampus is necessary to store traces of episodic memories and that recollecting these memories in vivid detail requires the hippocampus. In contrast, semantic or 'gist' memories can be supported by extrahippocampal structures. MTT states that hippocampal damage would result in the loss of vivid episodic memories but that semantic or extrahippocampally dependent memory will be spared. Our data closely reflect this idea with a few key differences. First, RT showed relatively spared spatial memory on probe trial 1 when analyzed with the standard quadrant analysis. In order to remember the correct quadrant, details such as the locations of the paintings on the wall relative to the target are required. Using the standard analysis, RT performed just as well as controls for the first location, suggesting that some details were encoded. However, the precision of the relation between the target and the distal cues was impaired as was the ability to bind spatial and temporal information as evidenced in the significant performance drop on location 2. So together, our results potentially extend MTT by suggesting that the hippocampus plays a role in the precision and binding of episodic details. Transformation Theory (Winocur, Moscovitch and Sekeres, 2007; Winocur, Moscovitch and Bontempi, 2010) can be seen as an extension of MTT and suggests that initially, all memories are dependent on the hippocampus, but that during consolidation, a memory is transformed into a fundamentally different form that is less detailed and more 'gist-like'. This transformed memory can be maintained independent of the hippocampus but contains little detail about an episode, while a hippocampally-dependent memory still remains that contains the rich contextual details. PBM differs from this account in that it does not assume hippocampal dependence for all memories initially. PBM maintains that simple, less precise memories can be encoded independent of the hippocampus from the onset.

Past studies using remote spatial memory also support the idea that allocentric spatial memory is intact following damage to the medial temporal lobe. In one study with the patient EP, who experienced extensive hippocampal and medial temporal lobe damage as

the result of a viral infection, although his ability to encode and retrieve new information was greatly impaired, his ability to navigate neighborhoods from his childhood was almost completely intact (Teng & Squire, 1999). In another study by Rosenbaum et al, the patient KC was able to describe new paths and trajectories through his neighborhood, which he had lived in since he was a child, although, consistent with amnesia, the details were lacking in his descriptions (Rosenbaum, Gao, Richards, Black, & Moscovitch, 2005; Rosenbaum et al., 2000; Rosenbaum, Cassidy, & Herdman, 2015). Finally, a study from Maguire et al. in an amnestic taxi driver revealed the ability to use major roads to successful mentally navigate to new locations, although his ability to use minor roads was impaired relative to controls (Maguire, Nannery, & Spiers, 2006). Importantly, though, all of these reports involved well-learned spatial memories from the patient's past, all of which could be supported, in principle, by cortical areas acquiring this information gradually over time (Squire, Stark, & Clark, 2004). While this idea has been challenged (Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004; Gilboa et al., 2006; Martin, de Hoz, & Morris, 2005), no study, to our knowledge, has demonstrated intact allocentric spatial search strategy in a patient with MTL damage for a recently encoded spatial environment.

Past work has also frequently associated the hippocampal circuitry with a function termed pattern completion/separation (Marr, 1971; for a review, see Rolls and Kesner, 2006). This work suggests that the hippocampal circuitry tends to "complete" similar information into the same trace in some circumstances and "separate" overlapping information into different traces (i.e., Bakker et al, 2008). In the case of our patient, because she has a pronounced deficit in remembering a specific location during navigation, it could be that she has trouble pattern separating this trace from other nearby locations she experienced. This could also, in principle, explain why she has more trouble remembering a second location. On closer inspection, though, a pattern separation/completion does not provide a complete account of our findings, either. A pattern separation account might suggest that the patient would tend to have trouble differentiating location 1 from location 2, and thus search for location 1 when she should be searching for location 2. Her search pattern for location 2, however, did not show this evidence of perseverance (Figure 2C); instead, she tended to search near location 2 just less precisely than controls. Further experiments will be needed to explore this possibility in more depth.

Together, our results from patient RT suggest that the hippocampus may not always be necessary for forming map-like allocentric spatial memories, but may have a more complex role in the binding of multi-item high-resolution information in support of episodic memory. One idea proposed in the field of human spatial navigation is that other brain areas may, in some instances, can support allocentric knowledge, such as retrosplenial cortex, parietal cortex, prefrontal cortex, and parahippocampal cortex (Ekstrom et al., 2014). One possibility is that these networks may be difficult to access following hippocampal damage unless alternative strategies are specifically trained and emphasized (Tse et al., 2011). If it is the case that patient RT is utilizing other brain regions for allocentric navigation, this could in turn arise from her high intellectual functioning, which may relate to higher flexibility in terms of network contributions to behavior (Bassett & Gazzaniga, 2011). Future studies involving greater numbers of patients with damage to the MTL, particularly more complete damage of the hippocampus proper, will be needed to more fully investigate this possibility.

This will allow a more complete adjudication between competing conceptualizations of human hippocampal function during navigation.

Acknowledgments

The authors are indebted to the patient RT for contributing extensively to this work and would also like to thank Lindsay Vass for helpful comments on this manuscript. The authors also wish to acknowledge support from the Emil Barth Award (ADE and KS), NIH/NINDS grants NS093052 and NS076856 (ADE), and NIH/NIMS grants MH59352 and MH083734 (APY).

References

Aly M, Ranganath C, Yonelinas AP. Detecting changes in scenes: the hippocampus is critical for strength-based perception. Neuron. 2013; 78(6):1127–1137.10.1016/j.neuron.2013.04.018 [PubMed: 23791201]

Annese J, Schenker-Ahmed NM, Bartsch H, Maechler P, Sheh C, Thomas N, Corkin S. Postmortem examination of patient H.M.'s brain based on histological sectioning and digital 3D reconstruction. Nat Commun. 2014; 5:3122.10.1038/ncomms4122 [PubMed: 24473151]

Astur R, Laughling T, Mamelak A, Philpott L, Sutherland R. Humans with hippocampus damage display severe spatial memory impairments in a virtual Morris water task. Behav Brain Res. 2002; 132:77–84. [PubMed: 11853860]

Baddeley, AD.; Emslie, H.; Nimmo-Smith, I. Doors and people: A test of visual and verbal recall and recognition. Thames Valley Test Company; 1994.

Bakker A, Kirwan CB, Miller M, Stark CE. Pattern separation in the human hippocampal CA3 and dentate gyrus. Science. 2008; 319(5870):1640–2. [PubMed: 18356518]

Banta-Lavenex P, Colombo F, Ribordy-Lambert F, Lavenex P. The human hippocampus beyond the cognitive map: Evidence from a densely amnesic patient. Frontiers in Human Neuroscience. 2014; 8(711):1–18. [PubMed: 24474914]

Bartsch T, Schonfeld R, Muller FJ, Alfke K, Leplow B, Aldenhoff J, Koch JM. Focal lesions of human hippocampal CA1 neurons in transient global amnesia impair place memory. Science. 2010; 328(5984):1412–1415.10.1126/science.1188160 [PubMed: 20538952]

Bassett DS, Gazzaniga MS. Understanding complexity in the human brain. Trends Cogn Sci. 2011; 15(5):200–209.10.1016/j.tics.2011.03.006 [PubMed: 21497128]

Bohbot VD, Corkin S. Posterior parahippocampal place learning in H.M. Hippocampus. 2007; 17(9): 863–872.10.1002/hipo.20313 [PubMed: 17598157]

Bohbot VD, Jech R, Ruzicka E, Nadel L, Kalina M, Stepankova K, Bures J. Rat spatial memory tasks adapted for humans: characterization in subjects with intact brain and subjects with selective medial temporal lobe thermal lesions. Physiol Res. 2002; 51(Suppl 1):S49–65. [PubMed: 12479786]

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):1217–1238. [PubMed: 9842767]

Crawford JR, Howell DC. Comparing an Individual's Test Score Against Norms Derived from Small Samples. The Clinical Neuorpsychologist. 1998; 12(4):482–486.

Cohen NJ, Eichenbaum H. The theory that wouldn't die: a critical look at the spatial mapping theory of hippocampal function. Hippocampus. 1991; 1(3):265–268.10.1002/hipo.450010312 [PubMed: 1669304]

Day LB, Weisand M, Sutherland RJ, Schallert T. The hippocampus is not necessary for a place response but may be necessary for pliancy. Behav Neurosci. 1999; 113(5):914–924. [PubMed: 10571475]

D'Hooge R, De Deyn PP. Applications of the Morris water maze in the study of learning and memory. Brain Res Brain Res Rev. 2001; 36(1):60–90. [PubMed: 11516773]

de Hoz L, Knox J, Morris RG. Longitudinal axis of the hippocampus: both septal and temporal poles of the hippocampus support water maze spatial learning depending on the training protocol. Hippocampus. 2003; 13(5):587–603.10.1002/hipo.10079 [PubMed: 12921349]

Duvernoy, HM. The Human Hippocampus: Functional Anatomy, Vascularization, and Serial Sections with MRI. Berlin: Springer; 1998.

Eichenbaum H, Cohen NJ. Can We Reconcile the Declarative Memory and Spatial Navigation Views on Hippocampal Function? Neuron. 2014; 83(4):764–770. [PubMed: 25144874]

Eichenbaum H, Dudchencko P, Wood E, Shapiro M, Tanila H. The hippocampus, memory, and place cells: Is it spatial memory or a memory space? Neuron. 1999; 23(2):209–226. [PubMed: 10399928]

Eichenbaum H, Otto T, Cohen NJ. The hippocampus--what does it do? Behavioral and Neural Biology. 1992; 57(1):2–36. [PubMed: 1567331]

Eichenbaum H, Stewart C, Morris RG. Hippocampal representation in place learning. J Neurosci. 1990; 10(11):3531–3542. [PubMed: 2230943]

Ekstrom AD, Arnold AE, Iaria G. A critical review of the allocentric spatial representation and its neural underpinnings: Toward a network-based perspective. Frontiers in Human Neuroscience. 2014

Ekstrom AD, Bazih AJ, Suthana NA, Al-Hakim R, Ogura K, Zeineh M, Bookheimer SY. Advances in high-resolution imaging and computational unfolding of the human hippocampus. Neuroimage. 2009; 19:19.

Erez J, Lee AC, Barense MD. It does not look odd to me: perceptual impairments and eye movements in amnesic patients with medial temporal lobe damage. Neuropsychologia. 2013; 51(1):168–180.10.1016/j.neuropsychologia.2012.11.003 [PubMed: 23154380]

Fanselow MS, Dong HW. Are the dorsal and ventral hippocampus functionally distinct structures? Neuron. 2010; 65(1):7–19.10.1016/j.neuron.2009.11.031 [PubMed: 20152109]

Feigenbaum JD, Morris RG. Allocentric versus egocentric spatial memory after unilateral temporal lobectomy in humans. Neuropsychology. 2004; 18(3):462–472. doi:10.1037/. [PubMed: 15291724]

Gilboa A, Winocur G, Grady CL, Hevenor SJ, Moscovitch M. Remembering our past: functional neuroanatomy of recollection of recent and very remote personal events. Cereb Cortex. 2004; 14(11):1214–1225.10.1093/cercor/bhh082 [PubMed: 15166099]

Gilboa A, Winocur G, Rosenbaum RS, Poreh A, Gao F, Black SE, Moscovitch M. Hippocampal contributions to recollection in retrograde and anterograde amnesia. Hippocampus. 2006; 16(11): 966–980.10.1002/hipo.20226 [PubMed: 17039487]

Goodrich-Hunsaker NJ, Livingstone SA, Skelton RW, Hopkins RO. Spatial deficits in a virtual water maze in amnesic participants with hippocampal damage. Hippocampus. 2010; 20(4):481–491.10.1002/hipo.20651 [PubMed: 19554566]

Maguire EA, Nannery R, Spiers HJ. Navigation around London by a taxi driver with bilateral hippocampal lesions. Brain. 2006; 129(Pt 11):2894–2907. 129/11/2894 [pii]. 10.1093/brain/awl286 [PubMed: 17071921]

Marr D. Simple memoyr: A theory for archicortex. Phil Trans R Soc Lond B. 1971; 262:23–81. [PubMed: 4399412]

Martin SJ, de Hoz L, Morris RG. Retrograde amnesia: neither partial nor complete hippocampal lesions in rats result in preferential sparing of remote spatial memory, even after reminding. Neuropsychologia. 2005; 43(4):609–624.10.1016/j.neuropsychologia.2004.07.007 [PubMed: 15716151]

Moffat SD, Elkins W, Resnick SM. Age differences in the neural systems supporting human allocentric spatial navigation. Neurobiology of aging. 2006; 27(7):965–972.10.1016/j.neurobiolaging.2005.05.011 [PubMed: 15982787]

Morris R. Developments of a water-maze procedure for studying spatial learning in the rat. J Neurosci Methods. 1984; 11(1):47–60. [PubMed: 6471907]

Morris RGM, Garrud P, Rawlins JNP, O'Keefe J. Place navigation impaired in rats with hippocampal lesions. Nature. 1982; 297:681–683. [PubMed: 7088155]

Moscovitch M, Rosenbaum RS, Gilboa A, Addis DR, Westmacott R, Grady C, Nadel L. Functional neuroanatomy of remote episodic, semantic and spatial memoyr: A unified account based on mulitple trace theory. Journal of Anatomy. 2005; 207:35–66. [PubMed: 16011544]

Moser E, Moser MB, Andersen P. Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. J Neurosci. 1993; 13(9): 3916–3925. [PubMed: 8366351]

Moser MB, Moser EI, Forrest E, Andersen P, Morris RG. Spatial learning with a minislab in the dorsal hippocampus. Proc Natl Acad Sci U S A. 1995; 92(21):9697–9701. [PubMed: 7568200]

Muller RU, Kubie JL. The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. J Neurosci. 1987; 7(7):1951–1968. [PubMed: 3612226]

Nadel L. The hippocampus and space revisited. Hippocampus. 1991; 1(3):221–229. [PubMed: 1669368]

Nadel L, Hoscheidt S, Ryan LR. Spatial cognition and the hippocampus: the anterior-posterior axis. J Cogn Neurosci. 2013; 25(1):22–28.10.1162/jocn_a_00313 [PubMed: 23198887]

O'Keefe J, Dostrovsky J. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res. 1971; 34(1):171–175. [PubMed: 5124915]

O'Keefe, J.; Nadel, J. The Hippocampus as a Cognitive Map. Oxford University Press; 1978.

O'Keefe J, Speakman A. Single unit activity in the rat hippocampus during a spatial memory task. Experimental brain research. 1987; 68(1):1–27. [PubMed: 3691688]

Olson IR, Moore KS, Stark M, Chatterjee A. Visual working memory is impaired when the medial temporal lobe is damaged. J Cogn Neurosci. 2006; 18(7):1087–1097. [PubMed: 16839283]

Poppenk J, Moscovitch M. A hippocampal marker of recollection memory ability among healthy young adults: contributions of posterior and anterior segments. Neuron. 2011; 72(6):931–937.10.1016/j.neuron.2011.10.014 [PubMed: 22196329]

Rolls ET, Kesner RP. A computational theory of hippocampal function, and empirical tests of the theory. Progress in Neurobiology. 2006; 79:1–48. [PubMed: 16781044]

Rosenbaum RS, Cassidy BN, Herdman KA. Patterns of preserved and impaired spatial memory in a case of developmental amnesia. Front Hum Neurosci. 2015; 9:196.10.3389/fnhum.2015.00196 [PubMed: 26029074]

Rosenbaum RS, Gao F, Richards B, Black SE, Moscovitch M. "Where to?" remote memory for spatial relations and landmark identity in former taxi drivers with Alzheimer's disease and encephalitis. J Cogn Neurosci. 2005; 17(3):446–462.10.1162/0898929053279496 [PubMed: 15814004]

Rosenbaum RS, Priselac S, Kohler S, Black SE, Gao F, Nadel L, Moscovitch M. Remote spatial memory in an amnesic person with extensive bilateral hippocampal lesions. Nature neuroscience. 2000; 3(10):1044–1048.10.1038/79867 [PubMed: 11017178]

Ryan JD, Moses SN, Barense M, Rosenbaum RS. Intact learning of new relations in amnesia as achieved through unitization. J Neurosci. 2013; 33(23):9601–9613.10.1523/JNEUROSCI.0169-13.2013 [PubMed: 23739957]

Samsonovich A, McNaughton BL. Path integration and cognitive mapping in a continuous attractor neural network model. J Neurosci. 1997; 17(15):5900–5920. [PubMed: 9221787]

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Matthews PM. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 2004; 23(Suppl 1):S208–219.10.1016/j.neuroimage.2004.07.051 [PubMed: 15501092]

Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, De Stefano N. Accurate, Robust, and Automated Longitudinal and Cross-Sectional Brain Change Analysis. Neuroimage. 2002; 17(1):479–489.10.1006/nimg.2002.1040 [PubMed: 12482100]

Squire LR, Stark CE, Clark RE. The medial temporal lobe. Annu Rev Neurosci. 2004; 27:279–306. [PubMed: 15217334]

Teng E, Squire LR. Memory for places learned long ago is intact after hippocampal damage. Nature. 1999; 400(6745):675–677.10.1038/23276 [PubMed: 10458163]

Tolman E. Cognitive maps in rats and men. The Psychological Review. 1948; 55(4):189–208. [PubMed: 18870876]

Tse D, Takeuchi T, Kakeyama M, Kajii Y, Okuno H, Tohyama C, Morris RG. Schema-dependent gene activation and memory encoding in neocortex. Science. 2011; 333(6044):891–895.10.1126/science.1205274 [PubMed: 21737703]

Vorhees CV, Williams MT. Morris water maze: procedures for assessing spatial and related forms of learning and memory. Nat Protoc. 2006; 1(2):848–858.10.1038/nprot.2006.116 [PubMed: 17406317]

Warren D, Duff M, Jensen U, Tranel D, Cohen N. Hiding in plain view: Lesions of the medial temporal lobe impair online representation. Hippocampus. 2012; 22:1577–1588. [PubMed: 22180166]

White N, Wallet P. Doral hippocampal function in unreinforced spatial learning. Hippocampus. 2000; 10:226–235. [PubMed: 10902892]

Winocur G, Moscovitch M, Bontempi B. Memory formation and long-term retention in humans and animals: Convergence towards a transformation account of hippocampal–neocortical interactions. Neuropsychologia. 2010; 48(8):2339–56. [PubMed: 20430044]

Winocur G, Moscovitch M, Sekeres M. Memory consolidation or transformation: context manipulation and hippocampal representations of memory. Nature Neuroscience. 2007; 10(5):555–557. [PubMed: 17396121]

Wolbers T, Wiener JM. Challenges in identifying the neural mechanisms that support spatial navigation: the impact of spatial scale. Frontiers in Human Neuroscience. 2014; 8(571):1–12. [PubMed: 24474914]

Yonelinas AP. The hippocampus supports high-resolution binding in the service of perception, working memory and long-term memory. Behav Brain Res. 2013; 254:34–44.10.1016/j.bbr.2013.05.030 [PubMed: 23721964]

Highlights

- We test an amnestic patient with medial temporal lobe damage on virtual navigation
- Novel analysis reveals that precision of her memory was impaired
- Her ability to use distal cues to navigate was largely intact
- Our findings support models implicating the hippocampus in high-resolution binding

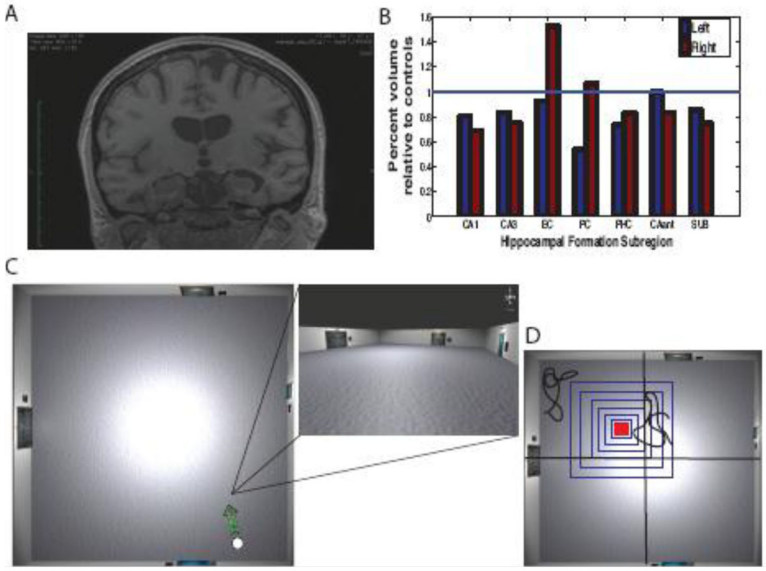

Figure 1.

Patient characteristics and experimental design. A. T1-weighted structural MRI of patient RT highlighting significant volume loss in the medial temporal lobes including the hippocampus. B. Relative normalized hippocampal subfield volumes of patient RT compared to 14 controls subjects. C. Virtual room schematic with first-person perspective. D. Illustration of standard quadrant analysis procedure and the precision window analysis used in the current study.

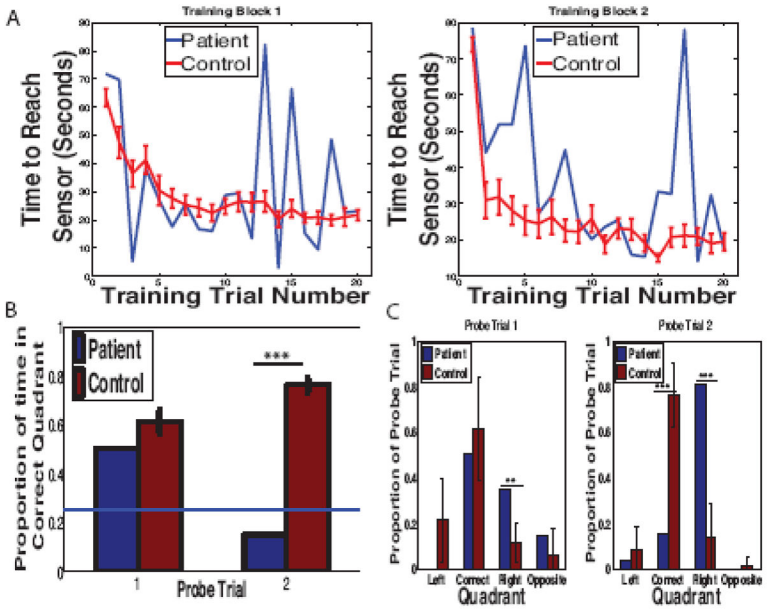

Figure 2.

Results of learning and standard quadrant analyses. A. Plot of the time for RT (blue) and controls (red) to reach the hidden sensor on training trials for location 1 (left) and location 2 (right). Error bars are SEM. B. Results of the traditional quadrant analysis for probe trials 1 and 2. Error bars are SEM, blue line represents chance performance. C. Analysis of errors made on probe trials 1 and 2 plotted as the percent of time spent in a given quadrant. Error bars are standard deviation, black bars are comparisons in which modified t-tests showed RT significantly differed from controls.

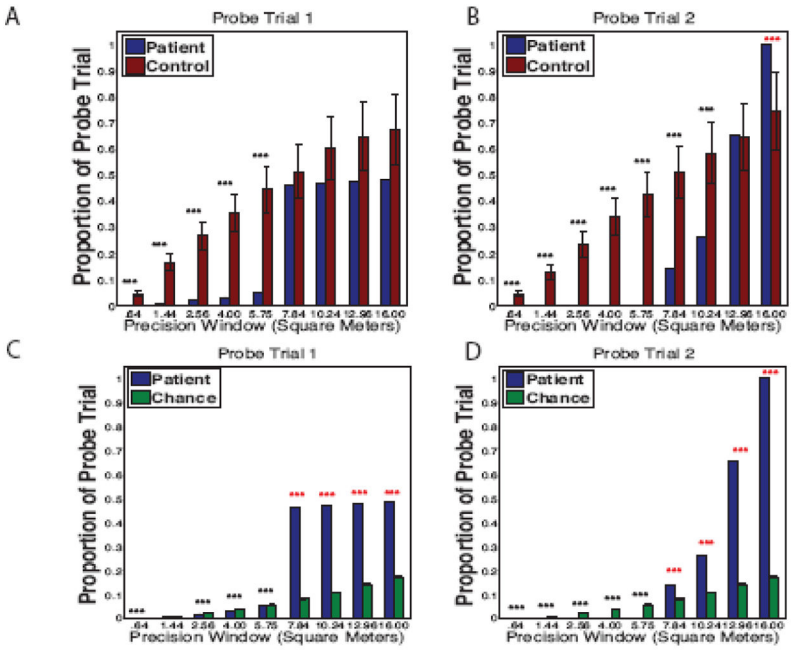

Figure 3.

Results of precision analysis comparing RT to controls and chance. A–B. Proportion of probe trials spent in each of the 9 precision windows for RT compared to controls. Error bars are SEM, black asterisks indicate comparisons where RT was significantly below controls (z-scores). C–D. Proportion of probe trials spent in each of the 9 precision windows for RT compared to chance performance. Error bars are SEM, black asterisks indicate comparisons where RT was significantly at or below chance, red asterisks indicate comparisons where RT was significantly above chance (z-scores).

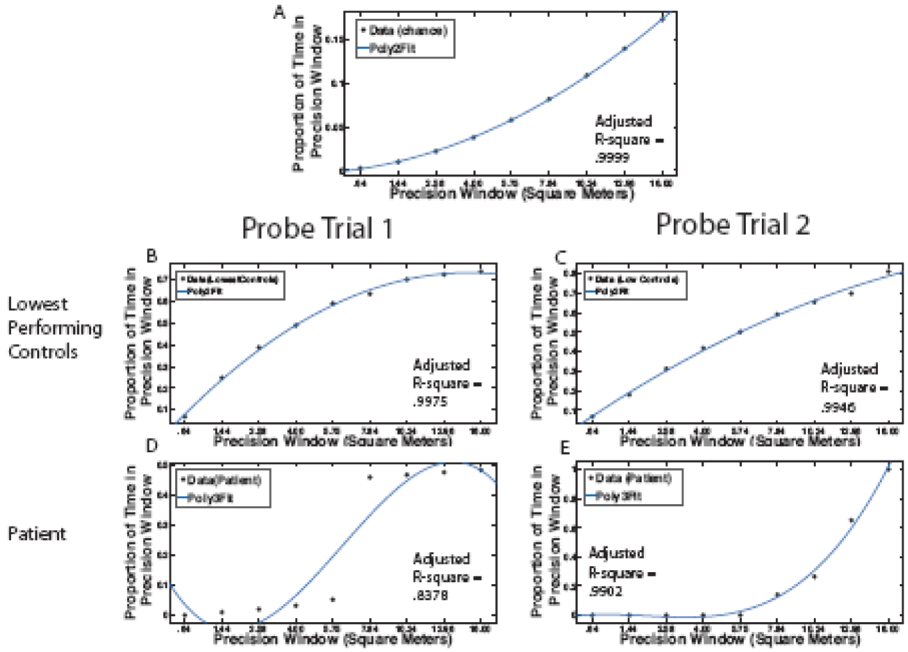

Figure 4.

Curve fitting analysis. A. Best fitting function for chance precision analysis across all control participants. B–C. Curve fitting plots for the lowest performing half of controls fit, with second-order polynomials showing that lowest performing control precision drop-off is less steep than estimated chance. D–E. Curve-fitting plots for RT fit with a third-order polynomial showing the steep drop in precision for the smaller search windows.

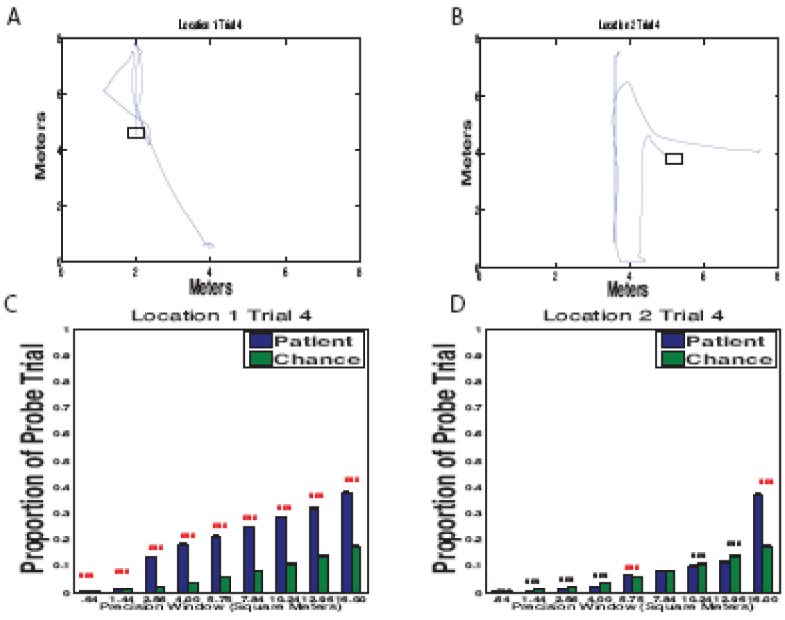

Figure 5.

Allocentric learning trial analysis. A–B. RT's trajectories for the fourth trial for both location 1 and location 2. C–D. Precision analysis on the two trajectories above compared to chance performance. Error bars are SEM, red asterisks indicate comparisons where RT is significantly at or below chance, black asterisks indicate comparisons where RT is significantly above chance.

Table 1

Neuropsychological test scores for patient RT.

Test	Raw Score	Normed Score
Intellectual Function		
Shipley-2	110	1.6 (z)
WTAR	35	103
Anterograde Memory		
WMS-IV		Standard Score
Visual Reproduction 1	35	8
Visual Reproduction 2	17	6
WMS-R		Index Score (Z- Score)
Verbal Memory	73	99
Visual Memory	62	116
General Memory	135	105
Delayed Recall	76	94
Attention/Concentration	74	104
CVLT-IV		Z-Score
Total Trials 1–5	41	35 (T-score)
Short Delay Free Recall	8	−1.5
Short Delay Cued Recall	8	−2
Long Delay Free Recall	9	−1.5
Long Delay Cued Recall	9	−1.5
Delayed Recognition Hits	13	−2
Source Recognition Discriminability (d′)	2.4	−2
Doors and People	Scaled	Percentile
Recall	8	25th
Recognition	4	1st
Overall	5	10th

WTAR= Wechsler Test of Adult Reading, WMS-IV = Wechsler Memory Scale IV, WMS-R = Wechsler Memory Scale-Revised, CVLT-IV = California Verbal Learning Test IV.

Table 2

Patient RT gray matter volume loss relative to controls. Percent volume loss for anterior and posterior MTL (hippocampus + parahippocampal cortex + perirhinal cortex + entorhinal cortex + subiculum) and hippocampus (hippocampus + subiculum).

		Left	Right
MTL	Anterior	20.25	−.006
	Posterior	15.95	25.54
Hippocampus	Anterior	13.81	27.78
	Posterior	12.36	28.31