Medial temporal lobe and topographical memory

Zhisen J. Urgolites[a,b], Ramona O. Hopkins[c,d,e], and Larry R. Squire[a,b,f,g,1]

[a]Veterans Affairs San Diego Healthcare System, San Diego, CA 92161; [b]Department of Psychiatry, University of California, San Diego, La Jolla, CA 92093; [c]Department of Psychology, Brigham Young University, Provo, UT 84143; [d]Neuroscience Center, Brigham Young University, Provo, UT 84143; [e]Department of Medicine, Pulmonary and Critical Care Division, Intermountain Medical Center, Murray, UT 84143; [f]Department of Neurosciences, University of California, San Diego, La Jolla, CA 92093; and [g]Department of Psychology, University of California, San Diego, La Jolla, CA 92093

Contributed by Larry R. Squire, June 22, 2017 (sent for review May 31, 2017; reviewed by Howard Eichenbaum and Joseph R. Manns)

There has been interest in the idea that medial temporal lobe (MTL) structures might be especially important for spatial processing and spatial memory. We tested the proposal that the MTL has a specific role in topographical memory as assessed in tasks of scene memory where the viewpoint shifts from study to test. Building on materials used previously for such studies, we administered three different tasks in a total of nine conditions. Participants studied a scene depicting four hills of different shapes and sizes and made a choice among four test images. In the Rotation task, the correct choice depicted the study scene from a shifted perspective. MTL patients succeeded when the study and test images were presented together but failed the moment the study scene was removed (even at a 0-s delay). In the No-Rotation task, the correct choice was a duplicate of the study scene. Patients were impaired to the same extent in the No-Rotation and Rotation tasks after matching for difficulty. Thus, an inability to accommodate changes in viewpoint does not account for patient impairment. In the Nonspatial–Perceptual task, the correct choice depicted the same overall coloring as the study scene. Patients were intact at a 2-s delay but failed at longer, distraction-filled delays. The different results for the spatial and nonspatial tasks are discussed in terms of differences in demand on working memory. We suggest that the difficulty of the spatial tasks rests on the neocortex and on the limitations of working memory, not on the MTL.

hippocampus | spatial memory | working memory | long-term memory

The capacity to form declarative memory depends on the integrity of the hippocampus and related medial temporal lobe (MTL) structures (1, 2). Declarative memory provides for the representation of relationships and permits comparison among items and contexts (3). There has also been interest in the idea that the MTL, and the hippocampus in particular, might have a special role in spatial processing beyond its established role in memory (4, 5). Several studies have reported that patients with damage to the MTL were impaired in various kinds of spatial tasks, even when the burden on memory appeared quite small and when tasks of nonspatial memory appeared less affected (6–9).

In one series of studies, MTL patients were impaired when they needed to appreciate a rotation in viewpoint from one perspective to another (6, 10, 11). For example, participants studied a scene depicting four hills of different shapes and sizes placed at different locations in the scene. They then decided which of four test images depicted the same study scene but now rotated from 15 to 90 degrees (6). MTL patients performed worse than controls even when a brief delay (2 s) intervened between study and test.

A question arises as to whether the impairment reflects a specific difficulty in appreciating the rotation of perspective, or whether an equally severe impairment would be found even if no rotation occurred. A second question is whether the impairment reflects a specific difficulty in processing and remembering spatial layouts or whether the impairment can be understood, not as a spatial memory problem, but as an example of the broad impairment in memory that would be expected after hippocampal damage in tests of either spatial or nonspatial material.

The current study explored these issues using the materials from the earlier study (6), kindly provided by N. Burgess, University College London, London. We administered three different tasks in a total of nine conditions, including the four conditions tested in the earlier study. In all conditions (Fig. 1), participants studied a scene and made a choice among four test images. We first compared the ability to remember spatial layouts with and without a rotation of perspective, using a Rotation task (three conditions) and a No-Rotation task (two conditions). Next, we assessed the ability to remember nonspatial material, using a Nonspatial–Perceptual task (four conditions).

Results

We first documented an impairment in the Rotation task (Fig. 2). Patients performed as well as controls when they could view the study scene and the test images together [Simultaneous condition, 73.3 ± 5.0% vs. 70.7 ± 4.6% correct; t (15) = 0.39, P = 0.705, Cohen's D = –0.19]. However, the patients were impaired, regardless of the delay, when the study scene was removed before presentation of the test images [0-s delay, 34.3 ± 4.0% vs. 58.7 ± 4.7% correct; t (15) = 3.70, P = 0.002, Cohen's D = 2.00; 2-s delay, 37.1 ± 6.3% vs. 58.0 ± 4.8% correct; t (15) = 2.69, P = 0.017, Cohen's D = 1.31].

We next asked whether the impairment was specifically related to appreciating shifts in perspective, or whether the difficulty might be broader, involving the ability to remember spatial layouts with or without changes in perspective. In the No-Rotation task (Fig. 3), performance was evaluated when the need to account for changes in perspective was removed, and participants needed only to identify the test image that was an exact duplicate of the study scene. The Difficult condition was designed to match the difficulty of the 0-s and 2-s delay conditions of the Rotation task such that controls performed similarly across the three conditions (Figs. 2 and 3). Patients were impaired in the No-Rotation task, both in the Difficult condition [36.2 ± 5.6% vs. 60.7 ± 3.9% correct; t (15) = 3.71, P = 0.002, Cohen's D = 1.92] and in the Easy condition that followed the procedure of the 2-s delay condition of the Rotation task [72.4 ± 4.0% vs. 96.3 ± 1.2% correct; t (14) = 6.45, P < 0.001,

Significance

We investigated the role of the medial temporal lobe (MTL) in topographical memory. Participants studied a scene depicting four hills of different shapes and sizes and made a choice among four test images. MTL patients were impaired in a Rotation condition where the correct choice depicted the study scene from a shifted perspective. Analysis of this impairment in three tasks and a total of nine conditions suggests that the impairment is unrelated to the ability to accommodate shifts in perspectives. We propose that the impairment need not suggest a specific role of the MTL in remembering spatial layouts and that the findings instead reflect a broad impairment in remembering that applies to both spatial and nonspatial material.

Author contributions: Z.J.U. and L.R.S. designed research; Z.J.U. performed research; R.O.H. contributed new reagents/analytic tools; Z.J.U. analyzed data; and Z.J.U. and L.R.S. wrote the paper.

Reviewers: H.E., Boston University; and J.R.M., Emory University.

[1] To whom correspondence should be addressed. Email: lsquire@ucsd.edu.

www.pnas.org/cgi/doi/10.1073/pnas.1708963114

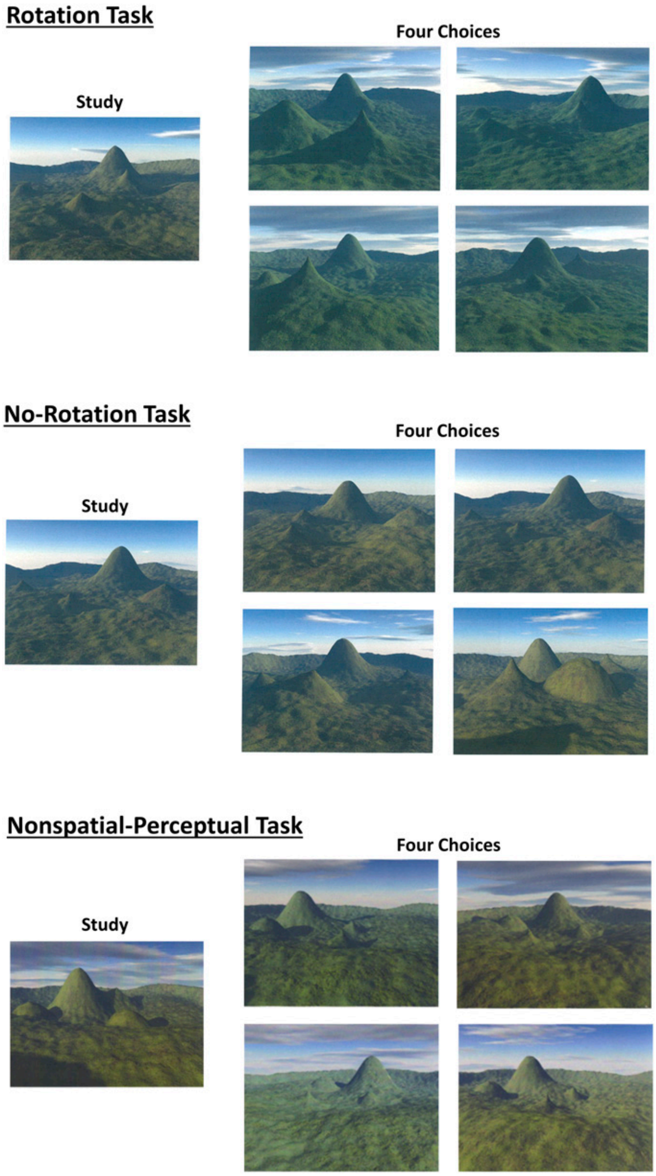

Fig. 1. Sample stimuli for three different tasks. Each image depicts four hills of different shapes and sizes placed at different locations in the scene. For each task, participants studied a scene and made a choice among four test images. In some conditions, the test images were presented together with the study image. In other conditions, the test images were presented after the study image was removed. For the Rotation task, the correct test image depicted a horizontal rotation of the study scene (from 15 to 90 degrees). For the No-Rotation task, the correct test image was a duplicate of the study scene. For the Nonspatial–Perceptual task, the correct test image depicted the same time of day and same time of year as the study scene. For purposes of illustration, the correct test image is in the top right position of each four-image display.

Cohen's D = 3.06]. Note that in the Difficult condition of the No-Rotation task, patients were impaired to the same extent as in the 0-s and 2-s delay conditions of the Rotation task. The scores for controls were within 2.0% of each other in these three conditions, and patients scored from 20.9 to 24.5% below controls. For comparisons among control scores, all *t*s (9) < 0.41, all *p*s > 0.689 (paired *t* tests). Among patient scores, all *t*s (9) < 0.39, all *p*s > 0.707 (paired *t* tests). Thus, patients were similarly impaired with and without the need to appreciate shifts in perspective.

Finally, we asked whether the impairment might involve nonspatial material, in addition to the demonstrated impairment with spatial material. In the Nonspatial–Perceptual task (Fig. 4), participants needed to attend to the coloring in the study scenes and then to select the test image that depicted the same time of day and same time of year as the study scene. Spatial information about the arrangement of the hills was irrelevant. Patients performed similarly to controls, both when the study scene and test images were presented together [Simultaneous condition, 66.7 ± 6.9% vs. 56.0 ± 4.6% correct; t (14) = 1.34, P = 0.200, Cohen's D = −0.68] as well as when the test images were presented 2 s after the study scene was removed [2-s delay condition, 64.4 ± 6.1% vs. 58.0 ± 5.1% correct; t (14) = 0.80, P = 0.439, Cohen's D = −0.41]. When the study–test delays were longer and filled with distraction (Distraction condition), the task was more difficult than at a 2-s delay. For all participants at the 2-s delay, patients and controls, the score was 60.4 ± 3.9% correct. At the longer delays, the score was lower, 41.1 ± 3.6% correct; t(26) = 3.55, P = 0.001. Notably, control performance in the Distraction condition was well above chance [45.5 ± 4.2% correct; t (7) = 4.84, P = 0.002], but patient performance was not [32.5 ± 4.4% correct; t(3) = 1.71, P = 0.186]. Patients performed marginally worse than controls [t (10) = 1.90, P = 0.086, Cohen's D = 1.23].

Note that our study included the four conditions from the earlier study (6) and largely replicated the earlier findings. The single difference was that in our study, performance was intact in the Simultaneous condition of the Rotation task, whereas in the earlier study, performance was intact in only two of the five patients. The interpretation of our results was based on the findings from these four conditions and on the findings from the five additional (and novel) conditions.

Discussion

In all the tasks, participants studied a scene depicting four hills of different shapes and sizes placed at different locations in the scene and made a choice among four test images. In the Rotation task, the correct choice depicted the study scene, but now rotated 15–90 degrees. MTL patients performed as well as controls when the study and test images were presented together, but they were impaired when the test images were presented after the study scene was removed (0-s and 2-s delays) (Fig. 2). In the No-Rotation task, the correct choice was a duplicate of the study scene. When the difficulty of this task was matched to the difficulty of the Rotation task (at the 0-s and 2-s delays), patients were impaired to the same extent as in the Rotation conditions (compare Figs. 2 and 3). In an easier condition that followed the procedure used for the 2-s delay of the Rotation task, patients were also impaired (Fig. 3).

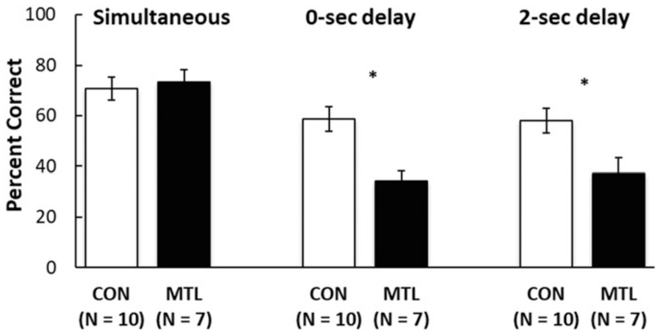

Fig. 2. Rotation task. Participants decided which of the four test images depicted the study scene, albeit viewed from a different perspective. In the Simultaneous condition, the study scene and the four test images were presented together. In the other two conditions, participants studied a scene for 8 s, and the four test images were presented either immediately or 2 s after the study scene was removed. CON, controls; MTL, patients with medial temporal lobe lesions. Error bars show SEs. *P < 0.02.

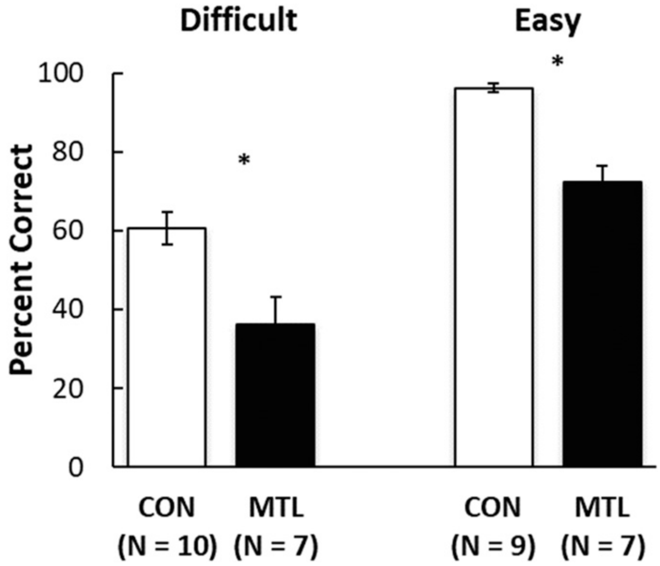

Fig. 3. No-Rotation task. Participants studied a scene and then decided which of four test images was a duplicate of the study scene. In the Difficult condition, the study scene was presented for 1 s, and the test images were presented after a 5-s, task-filled delay. The difficulty of this condition matched the difficulty of the 0-s and 2-s delay conditions in the Rotation task (Fig. 2). The Easy condition followed the procedure of the Rotation task (Fig. 2, *Right*). Specifically, the study scene was presented for 8 s, and the test images were presented 2 s after the study scene was removed. CON, controls; MTL, patients with medial temporal lobe lesions. Error bars show SEs. $^*P < 0.01$.

Last, in the Nonspatial–Perceptual task, the correct choice was the image that, by virtue of its coloring, displayed the same time of day and same time of year as the study scene. The layout of the hills was irrelevant. Patients performed as well as controls when the study and test images were presented together and when the test images were presented 2 s after the study scene was removed (Fig. 4). However, at longer, distraction-filled delays of 5 and 30 s, performance declined in the two groups. Control scores remained above chance, but patient scores did not. Patients performed marginally worse than controls.

Note that patients were similarly impaired in the Rotation task (0-s and 2-s delays, Fig. 2) and in the No-Rotation task (Difficult condition, Fig. 3) when these tasks were matched in difficulty. Thus, patients had no particular difficulty in appreciating changes in viewpoint, and an inability to accommodate shifts in perspective does not account for patient impairment in these tasks. The difficulty exhibited by patients must be related to a feature common to the Rotation and No-Rotation tasks. In an earlier study with a different spatial task that involved long delays and multiple study items (12), MTL patients were also similarly impaired when the viewpoint shifted and when the viewpoint remained stable. The present findings generalize this conclusion to a different task involving short delays and single study items.

The source of the impairment in the Rotation and No-Rotation tasks, and what is common to the two tasks, could be a difficulty related to the remembering of spatial layouts. Alternatively, the impairment could reflect a broader difficulty in remembering that applies to spatial as well as nonspatial material. The findings from the Nonspatial–Perceptual task (Fig. 4) illuminate the matter. In this task, patients performed well at a 2-s delay, but they scored at chance at the longer, distraction-filled delays and marginally worse than controls (Fig. 4). Thus, in this instance, patients had difficulty when the task required them only to notice the overall coloring of a scene and did not require them to appreciate the spatial relationships among features in the scene. This finding shows that the impairment involves both spatial and nonspatial material.

Interestingly, the impairment in the spatial tasks was more severe than the impairment in the nonspatial tasks. Patients performed well at the 2-s delay in the Nonspatial–Perceptual task, whereas they were impaired even at a 0-s delay in the Rotation task (and at a 2-s delay in both the Rotation and No-Rotation tasks). We propose that the material to be remembered in the Rotation and No-Rotation tasks (remembering the shapes and sizes of four hills and their relations) exceeded working memory capacity and made a greater demand on working memory than the material used for the Nonspatial–Perceptual task (remembering the overall coloring of the study scene). In this view, the difficulty of the spatial tasks rests on the neocortex and on the limitations of working memory, not on the MTL. The findings need not suggest a special role of the MTL in topographical memory.

Note that the retention interval is not the key factor determining whether MTL patients succeed or fail at memory tasks. The important factors are the capacity of working memory and the effect of attention, i.e., the amount of material that can be held in mind and how successfully it can be attended to and rehearsed. Patients with MTL damage typically exhibit intact working memory (13–15), but they routinely fail memory tests (even at very short retention intervals) when the amount of material to be remembered exceeds what can be held in working memory.

In the Rotation task, patients failed the moment that the study image was removed (0-s delay). This result is reminiscent of the impairment found after MTL lesions in tasks of object discrimination and paired-associate learning, where a memory impairment appeared in the absence of any retention interval due to the complexity and quantity of the test material (16, 17). In contrast, performance in the Nonspatial–Perceptual task was intact, even after a 2-s delay, likely because the information that needed to be maintained (overall coloring) could be managed for a short time by working memory. However, when the longer, distraction-filled delays challenged the ability to attend to and maintain this information, then performance failed. Studies involving spatial and nonspatial stimuli should take into account differences in the complexity of the materials to be remembered and differences in their burden on working memory.

We suggest that the impairments reported here reflect a broad deficit in the ability to remember and that differences in demand on working memory across test materials account for the different results in the spatial and nonspatial tasks. Thus, the different results reflect the functions of neocortex and the organization of working memory, not the functions of the MTL. The two spatial

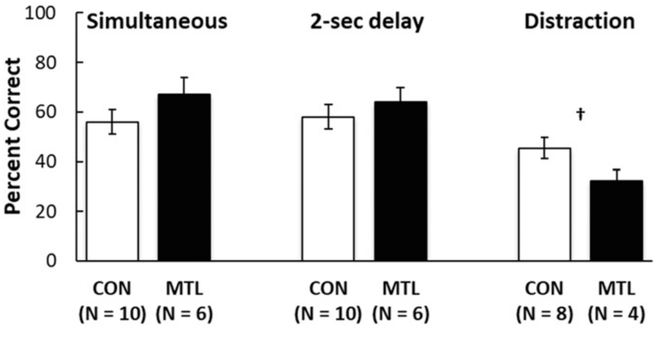

Fig. 4. Nonspatial–Perceptual task. Participants studied a scene and decided which of four test images depicted the same time of day and the same time of year as the study scene. In the Simultaneous condition, the study scene and the four test images were presented together. In the 2-s delay condition, the study scene was presented for 8 s, and the test images were presented 2 s after the study scene was removed. In the Distraction condition, the study scene was presented for 8 s, and the test images were presented after distraction-filled delays of 5 and 30 s (data combined). CON, controls; MTL, patients with medial temporal lobe lesions. Error bars show SEs. $^{\dagger}P = 0.086$.

tasks placed a heavy burden on working memory, such that performance needed to depend on long-term memory (and the MTL), even at a 0-s delay. For the nonspatial task, working memory could support performance for a few seconds, and performance depended on long-term memory only after distraction-filled delays.

Materials and Methods

Participants. Seven memory-impaired patients participated, six with bilateral lesions thought to be limited to the hippocampus (CA fields, dentate gyrus, and subicular complex) and one with larger medial temporal lobe lesions (Table 1). Patients D.A., R.S., and G.W. became amnesic in 2011, 1998, and 2001, respectively, following a drug overdose and associated respiratory failure. J.R.W. became amnesic in 1990 following an anoxic episode associated with cardiac arrest. K.E. became amnesic in 2004 after an episode of ischemia associated with kidney failure and toxic shock syndrome. L.J. (the only female) became amnesic during a 6-mo period in 1988 with no known precipitating event. Her memory impairment has been stable since that time.

Estimates of MTL damage were based on quantitative analysis of magnetic resonance (MR) images from 19 age-matched, healthy males for K.E., R.S., G.W., and J.R.W., 11 age-matched, healthy females for patient L.J. (18), and 8 younger healthy males for D.A. Patients D.A., K.E., L.J., R.S., G.W., and J.R.W. have an average bilateral reduction in hippocampal volume of 35, 49, 46, 33, 48, and 44%, respectively (all values at least 2.9 SDs from the control mean). On the basis of two patients (L.M. and W.H.) with similar bilateral volume loss in the hippocampus for whom detailed postmortem neurohistological information was obtained (19), the degree of volume loss in these four patients may reflect nearly complete loss of hippocampal neurons. The volume of the parahippocampal gyrus (temporopolar, perirhinal, entorhinal, and parahippocampal cortices) is reduced by −5, 11, −5, 10, 12, and −17%, respectively (all values within 2 SDs of the control mean). The minus values indicate volumes that were larger for a patient than for controls. These values are based on published guidelines for identifying the boundaries of the parahippocampal gyrus (20, 21).

One patient (G.P.) has severe memory impairment resulting from viral encephalitis in 1987. During repeated testing over many weeks he did not recognize that he had been tested before (22). G.P. has an average bilateral reduction in hippocampal volume of 96%. The volume of the parahippocampal gyrus is reduced by 94%. Eight coronal magnetic resonance images from each patient, together with detailed descriptions of the lesions, can be found elsewhere (16). One patient (K.E.) did not complete the Nonspatial–Perceptual task. Two additional patients did not complete the 5-s and 30-s delay conditions of this task.

Ten healthy controls (three females) also participated (mean age = 62.2 ± 3.9 y; mean education = 13.6 ± 0.5 y). One participant did not complete the Easy condition of the No-Rotation task. Two participants did not complete the 5-s and 30-s delays of the Nonspatial–Perceptual task. All procedures were approved by the Institutional Review Board at the University of California, San Diego, and participants gave written informed consent before participation.

Experimental Design. The stimuli were scenes depicting four hills of varying shapes and sizes placed at different locations in the scene (Fig. 1). These stimuli were used in an earlier study (6) and were generously provided to us in four test booklets. Using these materials, we constructed three different tasks involving a total of nine conditions: a Rotation task (three conditions), a No-Rotation task (two conditions), and a Nonspatial–Perceptual task (four conditions). Every condition began with three practice trials (with feedback), followed by15 test trials without feedback. On each test trial, participants studied a scene and made a choice among four test images. Participants had 60 s to respond, and the mean response time across conditions was 14.5 s.

Four of the nine conditions were as in the earlier study (6) and were tested on the same day using Booklets 1–4 (the Simultaneous and 2-s delay conditions of both the Rotation and Nonspatial–Perceptual tasks). Five new conditions were also constructed (Rotation task, 0-s delay condition; No-Rotation task, Difficult and Easy conditions; Nonspatial–Perceptual task, 5-s and 30-s delay conditions). The first two of these new conditions (Rotation task, 0-s delay; and No-Rotation task, Difficult) were given on the same day, an average of 6 mo after the first four tests. The third new condition (No-Rotation task, Easy) was given an average of 11 mo after the first four tests. The remaining two new conditions (Nonspatial–Perceptual task, 5-s; and 30-s delays with distraction) were given an average of 30 and 31 mo after the first four tests. Participants were tested once in each condition.

Rotation Task. Participants studied a scene and decided which of four test images depicted the same study scene but now rotated by 15, 30, 45, 60, 75, or 90 degrees (Fig. 1, *Top*). Across 15 trials, each kind of rotation was tested either two or three times. The three incorrect choices differed from the correct choice with respect to the shapes and sizes of the hills, the distance between hills, or the locations of the hills, as described previously (6).

The Rotation task was given in three conditions (Simultaneous, 0-s delay, and 2-s delay). In the Simultaneous condition (using Booklet 1), the study scene and the four test images were presented together. In the 0-s delay condition, the study scene was presented for 8 s, and the four test images were presented immediately after the study scene was removed. The 0-s delay condition used the same materials as the Simultaneous condition (Booklet 1), albeit 6 mo later. In the 2-s delay condition (using Booklet 2), the study scene was presented for 8 s, and the four test images were presented 2 s after the study scene was removed.

No-Rotation Task. Participants first studied a scene and then decided which of four test images was a duplicate of the study scene (i.e., without a change in perspective) (Fig. 1, *Middle*). The No-Rotation task was given in two conditions (Difficult and Easy). Importantly, the Difficult condition was designed to match the difficulty of the Rotation task (0-s and 2-s delay conditions). In this way, the results for the No-Rotation and Rotation tasks could be properly compared. The study scene was presented for 1 s, and four test images were presented 5 s after the study scene was removed. During the delay, participants saw a different display of four hills and pointed at them in order, from shortest to tallest. The shorter study time (1 s), the longer delay (5 s), and the interpolated task were designed to challenge working memory and weaken performance such that controls performed similarly on the No-Rotation task and the Rotation task (0-s and 2-s delays). The Easy condition followed the procedure used in the Rotation task (2-s delay). The study scene was presented for 8 s, and the four test images were presented 2 s after the study scene was removed.

The Difficult and Easy conditions were created from the material used for the 2-s delay condition of the Rotation task by modifying Booklet 2. For the Difficult condition, one test image from each trial of the Rotation task was duplicated to serve as the study scene for that trial. Accordingly, on every trial, the study scene and the correct choice were duplicates. The Easy condition was constructed the same way, except that a different test image was duplicated to serve as the study scene on each trial. For both the Rotation and No-Rotation tasks, participants needed in effect to remember not a single picture so much as a set of spatial relations among the hills of each image.

Nonspatial–Perceptual Task. Participants studied a scene and decided which of four test images depicted the same time of day and the same time of year as

Table 1. Characteristics of memory-impaired patients

				WMS-R				
Patient	Age (years)	Education (years)	WAIS-III IQ	Attention	Verbal	Visual	General	Delay
D.A.	32	12	95	104	90	91	90	56
K.E.	73	13.5	108	114	64	84	72	55
L.J.	77	12	101	105	83	60	69	<50
R.S.	58	12	99	99	85	81	82	<50
J.R.W.	51	12	90	87	65	95	70	<50
G.W.	55	12	108	105	65	86	70	<50
G.P.	68	16	98	102	79	62	66	50

WAIS-III is the Wechsler Adult Intelligence Scale-III and the WMS-R is the Wechsler Memory Scale-Revised. The WMS-R does not provide numerical scores for individuals who score <50. IQ scores for R.S. and J.R.W. are from the WAIS-Revised, and the IQ score for D.A. is from the WAIS-IV.

the study scene (Fig. 1, *Bottom*). Participants were instructed to make their judgments based, for example, on the overall coloring and to ignore spatial information. Spatial information was irrelevant, and remembering spatial information about the hills (or the direction of shadows) could not support performance. The Nonspatial–Perceptual task was given in four conditions (Simultaneous and at 2-s, 5-s, and 30-s delays). In the Simultaneous condition (using Booklet 3), the study scene and the four test images were presented together. In the 2-s delay condition (using Booklet 4), the study scene was presented for 8 s, and the four test images were presented 2 s after the study scene was removed. The 5-s and 30-s delays served as Distraction conditions to create a situation where working memory would be challenged, and performance would likely depend on long-term memory.

There was no intention to match the difficulty of these Distraction conditions to the difficulty of any other condition. The data from the two Distraction conditions were combined. In both cases, the study scene was presented for 8 s, and the four test images were presented after the study scene was removed. During the 5-s delay, participants saw a different display of four hills and pointed at them in order, from shortest to tallest. The 30-s delay was filled with conversation. These two Distraction conditions used the same materials as the Simultaneous condition (Booklet 3), albeit 30–31 mo later and with a 1-mo interval between the two conditions. Note that although we reused booklets in this study, the interval between conditions that used the same booklets was a minimum of 1 mo and as long as 30 mo.

Statistical analyses were based on independent *t* tests for comparisons between groups, paired *t* tests for comparisons within groups (when the same individuals were tested across conditions), and one-sample *t* tests for comparisons against chance performance.

ACKNOWLEDGMENTS. We thank Neil Burgess for generously providing test booklets and test instructions and for his comments on an early draft of this manuscript. We also thank Jennifer Frascino for assistance and Christine Smith for helpful comments. This work was supported by the Medical Research Service of the Department of Veterans Affairs (Award 5I01CX000359), by the National Institute of Mental Health (Grant 24600), and by NIH Training Grants (5T32AG000216 and 5T32MH020002, to Z.J.U.).

1. Squire LR, Zola-Morgan S (1991) The medial temporal lobe memory system. *Science* 253:1380–1386.
2. Eichenbaum H, Cohen NJ (2001) *From Conditioning to Conscious Recollection: Memory Systems of the Brain* (Oxford Univ Press, New York).
3. Eichenbaum H, Cohen NJ, Otto T, Wible C (1991) Memory representation in the hippocampus: Functional domain and functional organization. *Memory: Organization and Locus of Change*, eds Squire LR, et al. (Academic Press, New York), pp 163–204.
4. Bird CM, Burgess N (2008) The hippocampus and memory: Insights from spatial processing. *Nat Rev Neurosci* 9:182–194.
5. Maguire EA, Mullally SL (2013) The hippocampus: A manifesto for change. *J Exp Psychol Gen* 142:1180–1189.
6. Hartley T, et al. (2007) The hippocampus is required for short-term topographical memory in humans. *Hippocampus* 17:34–48.
7. Lee AC, et al. (2005) Specialization in the medial temporal lobe for processing of objects and scenes. *Hippocampus* 15:782–797.
8. Hannula DE, Tranel D, Cohen NJ (2006) The long and the short of it: Relational memory impairments in amnesia, even at short lags. *J Neurosci* 26:8352–8359.
9. Olson IR, Page K, Moore KS, Chatterjee A, Verfaellie M (2006) Working memory for conjunctions relies on the medial temporal lobe. *J Neurosci* 26:4596–4601.
10. King JA, Burgess N, Hartley T, Vargha-Khadem F, O'Keefe J (2002) Human hippocampus and viewpoint dependence in spatial memory. *Hippocampus* 12:811–820.
11. King JA, Trinkler I, Hartley T, Vargha-Khadem F, Burgess N (2004) The hippocampal role in spatial memory and the familiarity–recollection distinction: a case study. *Neuropsychology* 18:405–417.
12. Shrager Y, Bayley PJ, Bontempi B, Hopkins RO, Squire LR (2007) Spatial memory and the human hippocampus. *Proc Natl Acad Sci USA* 104:2961–2966.
13. Baddeley AD, Warrington EK (1970) Amnesia and the distinction between long- and short-term memory. *J Verb Learn Verb Beh* 9:176–189.
14. Baddeley A, Jarrold C, Vargha-Khadem F (2011) Working memory and the hippocampus. *J Cogn Neurosci* 23:3855–3861.
15. Jeneson A, Squire LR (2011) Working memory, long-term memory, and medial temporal lobe function. *Learn Mem* 19:15–25.
16. Knutson AR, Hopkins RO, Squire LR (2013) A pencil rescues impaired performance on a visual discrimination task in patients with medial temporal lobe lesions. *Learn Mem* 20:607–610.
17. Musen G, Shimamura AP, Squire LR (1990) Intact text-specific reading skill in amnesia. *J Exp Psychol Learn Mem Cog* 6:1068–1076.
18. Gold JJ, Squire LR (2005) Quantifying medial temporal lobe damage in memory-impaired patients. *Hippocampus* 15:79–85.
19. Rempel-Clower NL, Zola SM, Squire LR, Amaral DG (1996) Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. *J Neurosci* 16:5233–5255.
20. Insausti R, et al. (1998) MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. *Am J Neuroradiol* 19:659–671.
21. Franko E, Insausti AM, Artacho-Perula E, Insausti R, Chavoix C (2014) Identification of the human medial temporal lobe regions on magnetic resonance images. *Hum Brain Mapp* 35:248–256.
22. Bayley PJ, Frascino JC, Squire LR (2005) Robust habit learning in the absence of awareness and independent of the medial temporal lobe. *Nature* 436:550–553.