UNIVERSITY OF CALIFORNIA, SAN DIEGO

Human Declarative Memory and the Medial Temporal Lobe: Evidence from Patients with Medial Temporal Lobe Lesions

A Dissertation submitted in partial satisfaction of the Requirements for the degree Doctor of Philosophy

in

Neurosciences

by

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2008

The Dissertation of Yael Shrager is approved, and it is acceptable in quality and form for publication on microfilm:

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2008

DEDICATION

This dissertation is dedicated to all my friends and family, whose capacity for listening and advising has been invaluable.

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ACKNOWLEDGMENTS

I would like to acknowledge Professor Larry Squire for his invaluable advice and support as the chair of my committee.

I would also like to acknowledge the members of the Squire Laboratory, who made my research more enjoyable and more productive than it would have been as a solitary endeavor. In particular, I thank Peter Bayley, Jennifer Frascino, Sherry Hargrove, Jeff Gold, Brock Kirwan, Christine Smith, Mark Starr, and Leah Swalley for all their time and effort.

Chapter 1, in full, is a reprint of the material as it appears in Journal of Neuroscience, 2006. Shrager, Yael; Gold, Jeffrey J.; Hopkins, Ramona O.; Squire, Larry R. The dissertation author was the primary investigator and author of this paper.

Chapter 2, in full, is a reprint of the material as it appears in Journal of Neuroscience, 2008. Shrager, Yael; Levy, Daniel A.; Hopkins, Ramona O.; Squire, Larry R. The dissertation author was the primary investigator and author of this paper.

Chapter 3, in full, has been submitted for consideration for publication. Shrager, Yael; Kirwan, C. Brock; Squire, Larry R. The dissertation author was the primary investigator and author of this paper.

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ABSTRACT OF THE DISSERTATION

Human Declarative Memory and the Medial Temporal Lobe: Evidence from Patients with Medial Temporal Lobe Lesions

by

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Doctor of Philosophy in Neurosciences

University of California, San Diego, 2008

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The medial temporal lobe supports declarative memory, the capacity to consciously recollect facts and events. This capacity has traditionally been thought to be separable from other perceptual and cognitive functions, as patients with medial temporal lobe lesions exhibit circumscribed impairment in declarative memory. Several current issues surrounding the organization of memory and the medial temporal lobe were addressed in three separate studies. The first study tested whether the medial temporal lobe is necessary for visual perception. Patients with medial temporal lobe damage exhibited intact visual perception, even when perception was challenged with difficult discriminations. The second study tested whether a new

measure of working memory (distraction) that is independent of a traditional measure of working memory (performance of memory-impaired patients with medial temporal lobe damage), would support the long-standing idea that working memory is independent of the medial temporal lobe. The finding was that the method of distraction corresponded with the traditional measure of working memory (performance of memory-impaired patients) and was consistent with the idea that working memory is independent of the medial temporal lobe. The third study tested whether path integration ability (a form of spatial cognition) is dependent on the medial temporal lobe not only when demands are made on long-term memory, but even when performance can be maintained within working memory. Patients with medial temporal lobe damage succeeded in path integration when they could effectively use working memory and were impaired when working memory capacity was exceed and performance depended on long-term memory. It is concluded that the medial temporal lobe supports long-term declarative memory, and that this capacity is separable from other cognitive functions.

INTRODUCTION

The importance of the medial temporal lobe for memory was established in 1957 when Brenda Milner described the profound effects of medial temporal lobe resection on memory in a patient who became known as H.M. (Scoville and Milner, 1957). Subsequently, animal models of human memory impairment identified the anatomical structures that are important for understanding H.M.'s memory impairment: the hippocampal region (hippocampus proper, dentate gyrus, and subicular complex) and the perirhinal, entorhinal, and parahippocampal cortices. These structures comprise the medial temporal lobe memory system (Squire and Zola-Morgan, 1991; Lavenex and Amaral, 2000) (Figure 1).

The medial temporal lobe supports declarative memory (Squire, 1992; Schacter and Tulving, 1994). Declarative memory refers to the capacity to recollect facts and events. Its contents are accessible to conscious recollection. The stored representations are flexible and can guide successful performance in a wide range of conditions. Declarative memory is traditionally thought to be separable from other intellectual and perceptual functions.

Three issues surrounding the function of the medial temporal lobe will be addressed here: 1) whether the medial temporal lobe is necessary for visual perception; 2) whether a measure of working memory that is independent of performance of amnesic patients supports the idea that working memory is independent of the medial temporal lobe; and 3) whether medial temporal lobe

damage impairs spatial cognition (specifically, path integration) when performance can be managed within working memory, as opposed to when demands are made on long-term memory.

CHAPTER 1: Visual Perception

Abstract

A recent proposal that structures of the medial temporal lobe support visual perception in addition to memory challenges the long-standing idea that the ability to acquire new memories is separable from other cognitive and perceptual functions. In four experiments, we have put this proposal to a rigorous test. Six memory-impaired patients with well-characterized lesions of either the hippocampal region or the hippocampal region plus additional medial temporal lobe structures were assessed on difficult tests of visual perceptual discrimination. Across all four experiments, the patients performed as well as controls. The results show that visual perception is intact in memory-impaired patients with damage to the medial temporal lobe even when perception is assessed with challenging tasks. Further, the results support the principle that the ability to acquire new memories is a distinct cerebral function, dissociable from other perceptual and cognitive functions.

Introduction

In 1957 Brenda Milner described the profound effects on memory of bilateral medial temporal lobe resection, which was carried out to relieve severe epilepsy in a patient who became known as H.M. (Scoville and Milner, 1957). This landmark case established that brain structures within the medial temporal lobe are important for memory. Subsequently, animal models of human memory impairment identified the anatomical structures within the medial temporal lobe that are important for understanding H.M.'s memory impairment: the hippocampal region (hippocampus proper, dentate gyrus, and subicular complex), and the perirhinal, entorhinal, and parahippocampal cortices (Squire and Zola-Morgan, 1991; Lavenex and Amaral, 2000). Testing of patient H.M. over the years consistently found intact intellectual and perceptual functions (Milner, 1968; Corkin, 1984), suggesting that medial temporal lobe structures are primarily involved in memory. Accordingly, the fundamental idea was advanced that the ability to acquire new memories is a distinct cerebral function, separable from other perceptual and cognitive functions.

This fundamental principle of brain organization has recently been revisited, as there has been interest in the possibility that the structures of the medial temporal lobe might be involved in visual perception in addition to memory. Initially, work focused on the perirhinal cortex. Some experimental studies with monkeys underscored the role of perirhinal cortex in memory but found no evidence for a role in visual perception (Buffalo et al., 1999; Hampton and Murray, 2002). In contrast, other studies suggested that the perirhinal cortex might be important for perceptual

processing when complex or highly similar visual stimuli are used that have a high degree of feature ambiguity (feature overlap) (Buckley and Gaffan, 1998; Murray and Bussey, 1999; Buckley et al., 2001; Bussey and Saksida, 2002; Bussey et al., 2003).

Yet, it is difficult to test experimental animals for the ability to identify visual stimuli independent of the ability to learn about them, and it has been pointed out that impairments in monkeys that have been attributed to a perceptual deficit could have resulted from impaired learning (Hampton, 2005). In contrast, the distinction between perception and learning is more readily made in studies of humans, because they can be instructed about the requirements of the task. Some studies of patients with large medial temporal lobe lesions, including lesions of the perirhinal cortex, have found intact perceptual abilities (Holdstock et al., 2000; Stark and Squire, 2000; Levy et al., 2005). Yet, it is of interest that recent assessments of a group of memory-impaired patients, with damage reportedly involving either the hippocampus or the hippocampus plus additional medial temporal lobe structures, found significant impairment on tests of perceptual abilities that involved difficult-to-discriminate faces, objects, and scenes (Lee et al., 2005b; Lee et al., 2005a). This newer work, which involved rather complex visual stimuli, raised the possibility that appropriate tests of memory-impaired patients can reveal perceptual deficits that have not been detected by conventional tests of visual perception (Lee, 2005). Thus, these new findings challenge the long-standing idea that memory impairment can occur as a circumscribed disorder and that memory is separable from other cognitive functions. We have re-examined this issue in six patients with damage to the medial temporal

lobe who have been thoroughly characterized, both neuropsychologically and neuroanatomically.

Materials and Methods

Participants. Six memory-impaired patients participated. Four patients (three male) have lesions that are limited to the hippocampus (dentate gyrus, CA fields, and subiculum). G.W. (age = 46 yrs, education = 12 yrs) and R.S. (age = 49 yrs, education = 12 yrs) became amnesic following a drug overdose and associated respiratory failure in 2001 and 1998, respectively. K.E. (age = 64 yrs, education = 13.5 yrs) became amnesic in 2004 following an episode of ischemia associated with kidney failure and toxic shock syndrome. L.J. (age = 68 yrs, education = 12 yrs) became amnesic in 1988 during a 6-month period with no known precipitating event. Her memory impairment has remained stable since that time. Scores for copy and delayed (12 min) reproduction of the Rey-Osterrieth figure (Osterrieth, 1944; maximum score = 36) were 28.3 and 1.5, respectively (controls = 30.3 and 20.6). Recall of a short prose passage after a 12-min delay was 0.3 segments for the patients, 6.4 segments for controls (21 segments maximum). Paired-associate learning of 10 noun-noun pairs across 3 trials was 0, 0.5, 0.8 for patients and 6.0, 7.6, 8.9 for controls. Scores for the Wechsler Adult Intelligence Scale-III (WAIS-III) averaged 104 (R.S. took the WAIS-R), and scores for the Delay subscale of the Wechsler Memory Scale-Revised (WMS-R) averaged 51. Both tests yield means of 100 in the normal population with a standard deviation of 15.

Two patients (both male) have extensive medial temporal lobe lesions as a result of herpes simplex encephalitis (E.P., age = 83 yrs, education = 12 yrs, amnesia onset in 1992; G.P., age = 59 yrs, education = 16 yrs, amnesia onset in 1987). Copy and delayed scores for the Rey-Osterrieth figure were 26.3 and 2.0. Neither patient could recall any of a short prose passage after a 12-min delay (0 segments correct), and paired associate learning scores across 3 trials were 0, 0, and 0. Scores for the WAIS-III averaged 98, and scores for the Delay subscale of the WMS-R averaged 53.

Estimates of medial temporal lobe damage were based on quantitative analysis of magnetic resonance images (MRI) compared to data for 19 controls (K.E., R.S. and G.W.), 11 controls (L.J.), or 4 controls (E.P. and G.P.) (Bayley et al., 2005b; Gold and Squire, 2005). The volume of the full anterior-posterior length of the hippocampus and the parahippocampal gyrus were measured using criteria based on histological analysis of healthy brains (Amaral, 1990; Insausti et al., 1998a; Insausti et al., 1998b). For each patient, the hippocampal and parahippocampal gyrus volumes were divided by the intracranial volume (ICV normalized) to correct for brain size (Gold and Squire, 2005). K.E., L.J., R.S. and G.W. have an average bilateral reduction in hippocampal volume of 49%, 46%, 33% and 48%, respectively (all values more than 3.0 SDs below the control mean). In comparison, the volume of the parahippocampal gyrus (temporopolar cortex, perirhinal, entorhinal, and parahippocampal cortices) is reduced by 17%, -8%, 1% and 12%, respectively (all values within 2 SDs of the control mean). E.P. and G.P. have an average bilateral reduction in hippocampal volume of 97% and 96%, respectively. In addition, E.P. and G.P. have an average

bilateral reduction in the volume of the parahippocampal gyrus of 93% and 92%, respectively, reflecting a complete loss of temporopolar, perirhinal, and entorhinal cortices bilaterally and significant damage to parahippocampal cortex (Bayley et al., 2005b).

Additional measurements, based on four controls for each patient, were carried out for the insular cortex, fusiform gyrus, frontal lobes, lateral temporal lobes, parietal lobes, and occipital lobes. The only volume reductions in these regions greater than 1.3 SDs of the control mean were the parietal lobe for R.S. (Bayley et al., 2005b), the fusiform gyrus of E.P. and G.P. (54% and 48% reduced, respectively), and the insular cortex of G.P. (65% reduced).

Eight healthy controls (all male; mean age = 70.8 yrs, range = 58 - 84; mean education = 13.4 yrs) participated in the behavioral experiments.

Stimuli. The test stimuli were morphed gray-scale images in each of three stimulus categories: faces, objects, and scenes. Morphed images were created by gradually morphing one distinct gray-scale image into another (e.g., one hat into a different hat or a lemon into a tennis ball) across a 100-step series using computer software (Morpheus Photo Animator, ACD Systems Ltd). One distinct image was labeled 01, the other distinct image was labeled 100, and the intermediate images (02-99) were morphs that progressed from image 01 to image 100.

Experiment 1: Visual Discrimination Learning. Experiment 1 was modeled after Task 1 of Lee et al. (2005a) and consisted of four different tests in each of three stimulus categories (53 trials per test, 12 tests in total). All the images in each test

were derived from the same pair of distinct images. On trials 1-3, two distinct images were presented on the screen (Figure 2a). One of the images was arbitrarily designated as "correct", and participants were asked to indicate on each trial which image they believed to be the correct one. Trials were self-paced, and feedback was provided after each response (a high tone for correct and a low tone for incorrect). On trials 4-53, two morphed images were presented, and participants tried to identify which morphed image was more similar to the distinct image that was designated as correct on trials 1-3. Trials 4-53 were given at five different levels of difficulty (1-5). Thus, trials for level 1 (the easiest level) used images 01-10 and images 91-100 to create 10 image pairs (e.g., image 01 paired with 100; image 02 paired with 99; and so on). Trials for level 5 (the most difficult level) used images 41-50 and images 51-60 to create 10 additional image pairs (e.g., image 41 paired with image 60; image 42 paired with image 59; and so on). The same procedure was followed to create the image pairs for levels 2-4. Two trials from each level of difficulty were presented every 10 trials. The 12 different tests were presented in four different orders across participants, with the constraint that the same stimulus category was never tested more than twice in succession.

Experiment 2: Visual Discrimination. Experiment 2 was modeled after Task 2 of Lee et al. (2005a) and consisted of four different tests in each of three stimulus categories (50 trials per test, 12 tests in total). The images in each test were all derived from the same pair of distinct images. On each trial, a pair of morphed images was presented on the screen below one of the distinct images from which that pair was

derived (Figure 3a). Participants were asked to indicate which of the two morphed images was more similar to the distinct image. Trials were given at five different levels of difficulty (1-5; see Experiment 1 for details on construction of image pairs at each level). Within each test, two trials from each level of difficulty were presented every 10 trials. Trials were self-paced, and feedback was provided on each trial. The 12 different tests were presented in four different orders across participants, with the constraint that the same stimulus category was never tested more than twice consecutively.

Experiment 3: Trial-Unique Visual Discrimination. Experiment 3 consisted of 40 unique trials in each of three stimulus categories (3 tests in total). On each trial, a pair of morphed images was presented on the screen below one of the distinct images from which that pair was derived (Figure 4a). The morphed images for each trial were always derived from a unique pair of distinct images. Participants were asked to indicate which of the two morphed images was more similar to the distinct image. For each stimulus category, 20 trials were given at each of two levels of difficulty (levels 4 and 5; see Experiment 1 for details on construction of image pairs at each level). Five trials from each level of difficulty were presented every 10 trials. Trials were self-paced, and feedback was provided on each trial. The three different tests were presented in four different orders across participants.

Experiment 4: Visual Matching. Experiment 4 consisted of 45 unique trials (15 trials in each of three stimulus categories). On each trial, a target image derived from a unique pair of distinct images was presented at the top of the screen (Figure

5a). This image was randomly selected from images 21 – 80 in the 100-image series. In addition, a single image chosen randomly from the 100-image series was presented below the target image. Participants were asked to match the lower image to the target image by scrolling through the ordered series of 100 morphed images, viewing only one image at a time, and selecting the image that was identical to the target. Trials were self-paced, and feedback was not provided. The 45 trials were presented in four different orders across participants, with the constraint that the same stimulus category was never tested more than three times in succession.

Results

Experiment 1: Visual Discrimination Learning. Figure 2b-d shows scores for controls (CON), patients with hippocampal lesions (H), and patients with large lesions of the medial temporal lobe (MTL) on tests of visual discrimination learning involving faces, objects, and scenes. An analysis of variance (Stimulus Category X Group) revealed an effect of category [$F(2,22) = 7.9$, $P = 0.003$] but no effect of Group ($P = 0.993$) and no interaction ($P = 0.88$). A second analysis of variance that included difficulty level (Stimulus Category X Difficulty Level X Group) also found no effect of Group ($P = 0.96$) and no interactions (all Ps > 0.2). Indeed, none of the 18 possible pairwise comparisons between the patients and controls approached significance (all ts < 1.3, Ps > 0.22). Further, the mean scores of the patient groups were numerically higher than the corresponding score of the control group in 9 of the 18 cases. Despite the normal performance of the patients overall, two scores merit separate mention. In

difficulty levels 1-3 and 5 of the Faces test, patient E.P. in the MTL group obtained low scores (0.78 and 0.53, respectively), because he had difficulty remembering across the 50 trials which face was correct. On difficulty level 1-3, the range of scores for the CON group was 0.65-1.00, and on difficulty level 5, the range of CON scores was 0.58-0.80. An analysis of variance across the five 10-trial blocks within each test revealed a linear contrast of Block ($P < 0.001$) but no effect of Group and no interaction (Ps > 0.1). The linear contrast was found for both controls and patients separately (Ps < 0.06)

Experiment 2: Visual Discrimination. Figure 3b-d shows scores for the three groups (CON, H, MTL) on tests of visual discrimination involving faces, objects, and scenes. An analysis of variance (Stimulus Category X Group) revealed an effect of category [$F(2,22) = 6.0$, $P = 0.008$] but no effect of Group ($P = 0.11$) and no interaction ($P = 0.73$). A second analysis of variance that included difficulty level (Stimulus Category X Difficulty Level X Group) also found no effect of Group ($P = 0.12$) and no interactions involving the group factor (all Ps > 0.4). Further, of 18 possible pairwise comparisons between the patients and controls, the mean scores of the patient groups were numerically better than the corresponding score of the control group in 12 cases. There was only one instance where a patient group performed more poorly than the controls, although the mean difference between groups was small (0.89 vs. 0.95; MTL group vs. CON group, level 4 of Faces, $t[8] = 3.24$, $P = 0.01$). In that condition, the range of scores for the CON group was 0.93-1.0. Another condition that deserves mention is difficulty level 5 of the Faces test, where E.P.

obtained a low score (0.65). On that test, the range of scores for the CON group was 0.68-0.85. An analysis of variance across the five 10-trial blocks within each test (Block X Group) revealed no linear contrast of Block, no effect of Group, and no interaction (*P*s > 0.1).

Experiment 3: Trial-Unique Visual Discrimination. Figure 4b-d shows scores for the three groups (CON, H, MTL) on trial-unique tests of visual discrimination involving faces, objects, and scenes. An analysis of variance (Stimulus Category X Difficulty Level X Group) revealed effects of category [F(2,22) = 8.8, *P* = 0.002] and difficulty level [F(1,11) = 61.2, *P* < 0.001] but no effect of Group (*P* = 0.99) and no interactions (all *P*s > 0.7). Of 12 possible pairwise comparisons between the patients and controls, none approached significance (all *t*s < 1.06, *P*s > 0.3). In addition, the mean scores of the patient groups were numerically better than the corresponding score of the control group in 8 of the 12 cases. Note that level 5 of the Faces test was so difficult that none of the groups scored significantly above chance. When the data analysis was based only on level 4, there was still no effect of group (*P* = 0.92), and the two patient groups both scored numerically above the control mean.

Experiment 4: Visual Matching. Figure 5b shows scores for the three groups (CON, H, MTL) on a test of visual matching involving faces, objects, and scenes. An analysis of variance (Stimulus Category X Group) revealed an effect of category [F(2,22) = 12.5, *P* < 0.001] but no effect of Group (*P* = 0.41) and no interaction (*P* = 0.83). The patient groups scored numerically better (lower) than the control group in all six possible comparisons.

Discussion

Two groups of memory-impaired patients (four with hippocampal lesions and two with large medial temporal lobe lesions) were given four difficult tests of visual perceptual discrimination. With one exception, the two groups performed as well as controls. The exception occurred in difficulty level 4 of the Faces test in Experiment 2, where the two patients with large medial temporal lobe lesions performed a little more poorly than controls (E.P., 0.90; G.P., 0.88; CON, 0.95). Additionally, in three other instances (the Faces test of Experiment 1, difficulty levels 1-3 and 5; the Faces test of Experiment 2, difficulty level 5), patient E.P. obtained scores near the bottom of the control range.

It seems likely that the slightly lower scores in the four just-mentioned conditions were due to severe memory impairment. In Experiment 1, participants had to learn across trials which image was correct. E.P. in particular indicated on a few occasions that he had difficulty remembering the correct image. In Experiment 2, groups of consecutive trials were derived from the same two faces, and participants with intact memory could potentially benefit from what they had encountered on previous trials. Both the patients with large lesions, especially E.P., had to be instructed repeatedly about the task requirements and could have had difficulty retaining information about the stimuli from trial to trial.

It is also possible that E.P.'s somewhat lower performance in Experiments 1 and 2 resulted from a specific difficulty with faces. In earlier studies, E.P. performed

numerically, albeit not significantly, worse than controls on tasks involving complex face stimuli (Stark and Squire, 2000; Levy et al., 2005). Also, E.P. and G.P. were mildly impaired at perceiving certain facial emotions, perhaps due to damage to the amygdala or fusiform gyrus (Schmolck and Squire, 2001). Still, it is interesting that E.P. and G.P. were intact on the Faces tests of Experiments 3 and 4 despite their damage to the fusiform gyrus. Indeed, all the patients performed as well as controls in the Faces tests reported in Experiments 3 and 4, where all the trials were unique, and where learning could not have contributed to performance. It therefore seems most likely that the occasional low performance in Experiments 1 and 2 resulted from impaired learning and memory.

The present findings agree with a number of other reports of intact visual perception after damage to the medial temporal lobe. Thus, monkeys with lesions of the perirhinal cortex were slow to learn visual discriminations but then performed as well as controls on transfer trials in which the original stimuli were rotated, enlarged, shrunk, presented with color removed, or degraded with masks (Hampton and Murray, 2002). Further, memory-impaired patients with medial temporal lobe lesions also exhibited intact perception, as measured by tests involving complex, abstract designs (Holdstock et al., 2000) and complex, highly similar images (Stark and Squire, 2000; Levy et al., 2005).

In other work, memory-impaired patients with damage reportedly involving the medial temporal lobe (including perirhinal cortex) were impaired on visual perceptual tests of difficult-to-discriminate faces, objects, and scenes (Lee et al.,

2005b; Lee et al., 2005a). A second group of patients with damage reportedly involving the hippocampus was impaired on visual perceptual tests of scenes (Lee et al., 2005b; Lee et al., 2005a). Our Experiments 1 and 2 attempted to duplicate the conditions of the first of these studies (Lee et al., 2005a). Insofar as was possible, we used identical stimuli and tasks, and the difficulty of our tasks was virtually identical to the difficulty of the tasks used in Lee et al. (2005a). Thus, control performance in our Experiment 2 was 0.99 for Levels 1-3, 0.97 for Level 4, and 0.80 for Level 5. In the corresponding experiment in Lee et al. (2005a), the only experiment where control scores were provided, we estimated from their Figure 4 that the control scores were 1.0, 0.98, and 0.81 for Levels 1-3, 4, and 5, respectively.

Across Experiments 1 and 2, our two patients with large medial temporal lobe lesions obtained mean z-scores of –0.60, +0.42, and –0.26 for faces, objects, and scenes, respectively, and our four patients with hippocampal lesions obtained mean z-scores of +0.5, +0.15, and +0.11. As estimated from Figure 3 of the earlier study (Lee et al., 2005a), the z-scores across the two corresponding experiments for three patients with medial temporal lobe lesions averaged -4.8, -2.2, and –7.3 for faces, objects, and scenes, respectively, and the z-scores for four patients with hippocampal lesions averaged 0, -0.13, and –2.1. Notably, in the four cases in which Lee et al. (2005a) reported an overall impairment (MTL group: faces, objects, scenes; H group: scenes), the z-scores obtained by their patients were more than two standard deviations lower than the z-scores obtained by our patients.

In two additional experiments, we used trial-unique stimuli to eliminate entirely any possible contribution of learning to performance of the perceptual tasks. Again, the patients performed as well as controls (MTL group: mean z-score = +0.08; H group: mean z-score = +0.31). Given that we can identify no substantive differences between the materials and procedures that we used and those used by Lee et al. (Lee et al., 2005a), we looked to possible differences in the two patient groups to understand the discrepancy in findings.

The lesions in the patients studied by Lee et al. (Lee et al., 2005b; Lee et al., 2005a) were characterized by visual ratings of magnetic resonance images (4-point or 5-point scales). Ratings based on visual inspection, however, are not the same as quantitative measurements of brain tissue. Additionally, the ratings given for each patient were based on a single coronal section from the anterior hippocampus, posterior hippocampus, amygdala, and lateral temporal lobe, and four coronal sections from the medial temporal lobe cortices (one each from entorhinal cortex, transentorhinal cortex, perirhinal cortex, and the medial bank of the occipitotemporal sulcus). Using single sections to assess damage in these structures leaves a considerable amount of tissue uninspected (see below). Further, even by these incomplete assessments, the damage in some patients extended beyond the brain structures that defined the groups. Indeed, two of the four patients in the hippocampal group had significant (> 2 SDs from the control mean) damage to the parahippocampal gyrus, one of these two had significant damage to the anterior temporal lobe, and one of the three patients in the medial temporal lobe group had

significant damage to the lateral temporal lobe. In the absence of thorough, quantitative assessment of lesions, the possibility remains that there is additional damage outside of the hippocampus (in the case of the hippocampal group) or the medial temporal lobe (in the case of the medial temporal lobe group).

The lesions of the patients in the present study were rigorously measured using quantitative volumetric analysis of magnetic resonance images (Bayley et al., 2005b; Gold and Squire, 2005), using criteria based on histological analyses of healthy brains (Amaral, 1990; Insausti et al., 1998a; Insausti et al., 1998b). For each patient, approximately 60 sections were measured in 1mm intervals rostro-caudally through the medial and lateral temporal lobes. Measurements were taken in every section in which the structure of interest was present, not just in a single section (mean of 29 sections for the hippocampus, 15 for the temporopolar cortex, 30 for the perirhinal cortex, 24 for the entorhinal cortex, 16 for the parahippocampal cortex, and 58 for the lateral temporal lobe). In addition, volumes were calculated for the insular cortex, fusiform gyrus, and the frontal, parietal, and occipital lobes.

Studies with monkeys have reported that damage to the perirhinal cortex impaired performance on difficult perceptual tasks involving complex and highly similar stimuli (Buckley and Gaffan, 1998; Buckley et al., 2001; Bussey and Saksida, 2002; Bussey et al., 2003). As discussed elsewhere (Levy et al., 2005), it is difficult with experimental animals to distinguish between an impaired perceptual ability to identify objects and an impaired ability to learn about those objects. Indeed, a recent review of this literature concluded that impairments in animals that have been

attributed to a perceptual deficit likely resulted from impaired learning (Hampton, 2005; for responses, see (Buckley, 2005; Bussey et al., 2005).

Further, in an earlier study (Levy et al., 2005), patient E.P. performed normally on a difficult visual perceptual discrimination task involving the blending of two unrelated images when learning was not required (Experiment 2a) but then had marked difficulty when an explicit learning requirement was introduced (Experiment 3). Yet, E.P.'s learning problem appeared to impact his performance only a little on the Faces test of Experiment 1 in the current study (where there was an explicit learning requirement) and not at all on the Objects and Scenes tests of Experiment 1. There are a number of differences between the tests of blended stimuli given previously (Levy et al., 2005) and the tests of morphed stimuli given in the current Experiment 1, including the use of practice trials with easy-to-discriminate stimuli in the current experiment. E.P. was apparently better able to label and rehearse the stimuli in the current Experiment 1 than in the earlier study (Levy et al., 2005).

In Experiments 3 and 4, we isolated the process of visual perceptual discrimination by removing the need to learn the correct responses (as could have occurred in Experiment 1) and by using tests in which the stimuli on every trial were derived from a unique pair of images to remove any possible contribution of learning and memory (which could have been a factor in Experiment 2). In these cases, the patients could not be disadvantaged as a result of their poor memory for previous trials. The tasks were perceptually demanding, as indicated by the fact that controls consistently achieved less than maximum scores in the most difficult conditions of

each experiment. In all the conditions of Experiments 3 and 4, the patients performed as well as controls.

In summary, visual discrimination performance was intact despite damage to the hippocampal region or damage to the medial temporal lobe that included the hippocampal region and the perirhinal cortex. Over the past forty years, numerous studies of memory-impaired patients with lesions of the medial temporal lobe have found visual perceptual function to be intact (Milner, 1968; Corkin, 1984; Stark and Squire, 2000; Levy et al., 2005). It was this early work that led to the principle that memory can be severely impaired without impairing other intellectual or perceptual functions. By using more difficult test material than has been used previously, and by testing patients with thoroughly characterized lesions, our study put this principle to a particularly rigorous test. We found that visual perception is intact despite extensive medial temporal lobe damage, even when perception is challenged with difficult tasks involving complex and highly similar images.

Acknowledgments: Chapter 1, in full, is a reprint of the material as it appears in Journal of Neuroscience, 2006. Shrager, Yael; Gold, Jeffrey J.; Hopkins, Ramona O.; Squire, Larry R. The dissertation author was the primary investigator and author of this paper.

CHAPTER 2: Working Memory

Abstract

Working memory has historically been viewed as an active maintenance process that is independent of long-term memory and independent of the medial temporal lobe. Yet, impaired performance across brief time intervals has sometimes been described in amnesic patients with medial temporal lobe damage. These findings raise a fundamental question about how to know when performance depends on working memory and when the capacity for working memory has been exceeded and performance depends on long-term memory. We describe a method for identifying working memory independently of patient performance. We compared patients with medial temporal lobe damage to controls who were given either distraction or no distraction between study and test. In four experiments, we found concordance between the performance of patients and the effect of distraction on controls. The patients were impaired on tasks where distraction had minimal effect on control performance, and the patients were intact on tasks where distraction disrupted control performance. We suggest that the patients were impaired when the task minimally depended on working memory (and instead depended substantially on long-term memory), and they performed well when the task depended substantially on working memory. These findings support the conclusion that working memory (active maintenance) is intact after medial temporal lobe damage.

Introduction

Working memory is a fundamental concept in cognitive neuroscience and psychology, and in these disciplines it has largely replaced the less precise term, short-term memory (Baddeley, 2003). Working memory refers to the capacity to maintain temporarily a limited amount of information in mind, which can then be used to support various cognitive abilities, including learning and reasoning (Baddeley and Hitch, 1974). Historically, working memory (or short-term memory) was distinguished from long-term memory (a large-capacity, stable storage system), and for the past half century this distinction has been fundamental to understanding how the brain has organized its memory functions (Waugh and Norman, 1965; Baddeley and Warrington, 1970). For example, early studies of amnesic patients with medial temporal lobe damage found working memory to be intact despite markedly impaired performance on tasks of long-term memory (Drachman and Arbit, 1966; Milner, 1972). Indeed, in psychological science, one finds the suggestion that what is spared in amnesia provides the best evidence for the construct of working memory as well as a good definition of it (Atkinson and Shiffrin, 1968a; Pashler and Carrier, 1996). The view has been that working memory is independent of the hippocampus and other medial temporal lobe structures, whereas these structures are essential for the formation of long-term memory (Milner, 1972).

These ideas have been challenged recently by the proposal that working memory might sometimes depend on medial temporal lobe structures. Specifically, patients with medial temporal lobe damage were found to be impaired at remembering

information across brief time intervals (Hannula et al., 2006; Nichols et al., 2006; Olson et al., 2006a; Olson et al., 2006b; Hartley et al., 2007). On the one hand, these impairments would seem to require a revision of a long-standing principle of brain organization. On the other hand, the impairments might have occurred because the capacity for working memory was exceeded in these cases (also see discussion in (Hannula et al., 2006; Nichols et al., 2006)). In fact, there is circularity in the way that working memory is traditionally understood (i.e., working memory has been characterized as the kind of memory that is spared in amnesia, but amnesia is also thought to be a condition in which working memory is intact). What is needed is a method for identifying and measuring working memory that is entirely independent of the performance of amnesic patients.

We have measured the contribution of working memory to normal performance by introducing distraction between study and test in order to interrupt the active maintenance of studied information. We reasoned as follows: If amnesic patients perform well on tasks when they can operate within working memory capacity (that is by active maintenance), then controls given the same tasks should be impaired by distraction between study and test because distraction would disrupt the active maintenance process. Conversely, if amnesic patients perform poorly when their working memory capacity is exceeded, then controls given the same tasks should be minimally affected by distraction between study and test (because performance is now supported more by long-term memory than by active maintenance).

Methods

Participants. Eight patients participated. Two patients (E.P. and G.P., aged 83 and 60, respectively) have severe memory impairment due to viral encephalitis, together with intact perceptual and intellectual functions (Bayley et al., 2006; Shrager et al., 2006). These patients have demonstrated virtually no new learning since the onset of their amnesia, and during repeated testing over many weeks they do not recognize that they have been tested before (Bayley et al., 2005a). Estimates of medial temporal lobe damage were based on quantitative analysis of magnetic resonance (MR) images and data from 4 controls for each patient. E.P. and G.P. have an average bilateral reduction in hippocampal volume of 97% and 96%, respectively. The volume of the parahippocampal gyrus (temporopolar, perirhinal, entorhinal, and parahippocampal cortices) is reduced by 94% and 93%, respectively.

Six patients have damage thought to be limited to the hippocampus and are moderately amnesic. R.S. and J.R.W. participated only in the test of relational information. A.B. participated only in the faces test. A.B. and J.R.W. (aged 66 and 43, respectively) became amnesic after cardiac arrest. G.W. and R.S. (aged 47 and 50, respectively) became amnesic after drug overdoses and associated respiratory failure. K.E. (aged 65) became amnesic after an episode of ischemia associated with kidney failure and toxic shock syndrome. L.J. (the only female; aged 68) became amnesic during a 6-month period in 1988 with no known precipitating event. Her memory impairment has remained stable since that time. Estimates of medial temporal lobe damage were based on quantitative analysis of MR images. K.E., L.J., R.S., G.W.,

and J.R.W. have an average bilateral reduction in hippocampal volume of 49, 46, 33, 48, and 44%, respectively (Bayley et al., 2005b; Gold and Squire, 2005). The volume of the parahippocampal gyrus is reduced by 17, -8, 1, 12, and 6%, respectively (all values within two SDs of the controls mean). A.B. was unable to participate in MR imaging.

Recognition Memory for Names and Faces – Patients versus Controls. The 2 patients with large medial temporal lobe lesions, 4 patients with hippocampal lesions, and 12 age- and education-matched controls were tested for their memory for names and faces. In the names task (only 3 of the hippocampal patients participated), 3 surnames were presented one at a time for 1 second each. After an unfilled delay of 14 seconds, memory was tested with a single probe stimulus that asked participants to decide whether a name was the same as or different from one of the studied names (8 trials/block, 64 total trials). In the faces task, a single face was presented for 1 second. After a delay of 2, 7, or 14 seconds, memory was tested with a single probe stimulus that asked participants to decide whether a face was the same as or different from a studied face (2 sessions, 4 blocks/delay/session presented in pseudorandom order, 8 trials/block, 64 total trials at each delay). The interval between trials was self-paced in all experiments reported here.

Recognition Memory for Names and Faces – Effect of Distraction on Controls. Twelve age- and education-matched controls took the names and the faces tests and on half the trials were distracted during seconds 4 through 7 of the delay. For the distraction, participants counted a series of 10 to 20 rapidly presented names (in the

names condition, each name was presented for 250 ms) or 10 to 20 faces (in the faces condition, each face was presented for 250 ms) and reported their count at the end of the delay (2 blocks/condition, 8 trials/block, 16 total trials for names and 16 for faces). The no-distraction condition also consisted of 16 trials for names and 16 for faces. The 8 blocks (2 each for no distraction and distraction in the names condition, and 2 each in the faces condition) were presented in pseudorandom order.

In designing an appropriate distraction task that will effectively disrupt active maintenance, one can begin by using stimuli of the same type as the studied stimuli. Yet another issue of potential importance is to engage participants in the same domain of working memory (e.g., phonological loop vs. visual sketchpad) that is engaged during study. Because this second criterion might not have been met in our first distraction condition with faces (because participants may have focused on counting the faces, not processing them as faces), we carried out a second distraction condition (faces only), designed to be more relevant to the processing of faces. Ten of the same 12 controls viewed a series of 10 to 20 rapidly presented faces during seconds 4 through 7 of the delay. On half the distraction trials, one of the faces was Bill Clinton (never presented among the first or last three images). Participants indicated at the end of each delay whether they had seen Bill Clinton (2 blocks, 8 trials/block, 16 trials total). The no-distraction condition with faces also consisted of 16 trials (2 blocks, 8 trials/block). The 4 blocks were presented in pseudorandom order.

Recognition Memory for Object Locations – Patients versus Controls. The 2 patients with large medial temporal lobe lesions, 5 patients with hippocampal lesions,

and 12 age- and education-matched controls were tested for object location memory. On each trial, participants studied drawings of 1, 2, 3, 4, or 6 colored objects (Olson et al., 2006b), each presented in 1 cell of a 3X3 grid. Objects were presented one at a time for 1 second each, and no cell was used more than once within a trial. After a delay of 1 or 8 seconds, memory was tested with a single probe stimulus.

Because the probe stimulus for the recognition test always needed to be a combination of one of the studied objects and one of the studied locations, it was not possible to test recognition memory in the 1-object condition (i.e., the correct answer would always be "same"). Thus, on trials where only 1 object was studied, recall of the object and its location was tested. Participants were shown an empty grid and asked to report what object had been presented and in which cell of the grid it had appeared.

On all other trials, one of the studied objects appeared in one of the studied locations, and participants indicated whether the object was in the same location as during study or in a different location. The 1-, 2-, and 3-object conditions were tested in the first of 2 sessions, and the 4- and 6-object conditions were tested in the second session (in each case, 2 blocks/object condition were presented in a pseudorandom order, 8 trials/delay/block**,** 16 total trials at each delay in each object condition).

Recognition Memory for Object Locations – Effect of Distraction on Controls. Eighteen age- and education-matched controls took 2 tests, a 3-object condition and a 6-object condition. On half the trials, they were distracted during seconds 4 through 7 of the delay. For the distraction, participants counted a series of 10 to 20 rapidly

presented black-and-white objects (Snodgrass and Vanderwart, 1980) and reported their count at the end of the delay (2 blocks/condition, 8 trials/block, 16 trials for the 3-object condition and 16 trials for the 6-object condition). The no-distraction condition also consisted of 16 trials for each condition. The 8 blocks (2 each for no distraction and distraction in the 3-object condition, and 2 each in the 6-object condition) were presented in pseudorandom order.

Results

Recognition Memory for Names and Faces. Patients with medial temporal lobe damage and matched controls tried to remember either 3 names or a single face for short time intervals (for details, see Methods). The patients performed as well as controls when they tried to remember 3 names for 14 sec (patients, 94.4% correct; controls, 94.5% correct) (Figure 6a). For faces, performance was good after 2 seconds (patients, 99.1% correct; controls, 98.8% correct) and also 7 seconds (patients, 96.6% correct; controls, 97.8% correct). In contrast, the patients were impaired when asked to remember a single face for 14 seconds (93.2% vs. 98.0% correct; $t_{(16)}$=2.6, p<0.03) (Figure 6a). Average proportion correct, hit, and false alarm scores for each group, together with corresponding standard errors, are presented for all experiments in Supplemental Tables. All results in all the experiments reported here followed the same pattern when analyses were based either on d' scores or on arcsine transformations of the percent correct scores (with the standard correction for 100%

scores: 1-1/(4n), where n = number of trials). Arcsine transformations were used because the scores sometimes deviated from a normal distribution.

The question of interest is whether the impairment found in the faces condition at the 14-second delay reflects impaired working memory or impaired long-term memory. To distinguish between these possibilities, we tested the effect of distraction between study and test on control performance in both the faces condition and the names condition at a 14-second delay. Figure 6b shows that in the names condition performance was affected by distraction (96.4% vs. 87.5% correct, $t_{(11)}$=4.2, p=0.001). In contrast, distraction had no effect in the faces condition (96.4% correct for the no-distraction condition vs. 95.3% correct for the distraction condition). Performance on the distracter (counting) tasks was comparable in the 2 conditions (average count error = 2.8 and 2.5, respectively, $t_{(11)}$=1.4, p=0.19). An additional distracter task in the faces experiment used a task more relevant to the processing of faces (see Methods). Again, distraction had no effect in the faces condition (no distraction = 97.5% correct, vs. distraction = 98.1% correct).

These results reveal a correspondence between the performance of amnesic patients and the effects of distraction on controls. Distraction impaired controls on the names test, presumably because the distraction interfered with an active maintenance process based on rehearsal. Distraction did not affect performance on the faces test, presumably because the information is difficult to maintain actively (rehearse) and must depend on long-term memory shortly after the information is presented (for a similar interpretation of face memory, see (Warrington and Taylor, 1973). We

suggest that amnesic patients were intact when the task was supported by rehearsal (working memory for names) but were impaired in the case of faces when rehearsal was less effective and performance had to depend on long-term memory.

Recognition Memory for Object Locations. It has been suggested that medial temporal lobe structures, particularly the hippocampus, are important for relational memory (Cohen et al., 1999). In the strong version of this view, for tasks involving relational information, medial temporal lobe structures are needed not only for long-term memory but also for working memory (Hannula et al., 2006; Olson et al., 2006b). We tested this idea following the same logic as in the names and faces test. Patients and controls tried to remember 1, 2, 3, 4, or 6 object locations for delays of 1 or 8 seconds. The patients performed as well as controls in all 5 object conditions at the 1-second delay (controls = 90.1% correct, patients = 90.5% correct) and in 4 of the 5 conditions at the 8-second delay (1, 2, 3, and 4 objects; controls = 93.3% correct, patients = 91.3% correct). Group means are shown for each individual condition in Supplementary Tables. The patients were impaired only when trying to remember 6 object locations over an 8-second delay (controls = 71.9% correct, patients = 60.7% correct; $t_{(17)}$=2.7, p<0.02). Figure 7a shows the good performance of the patients when they remembered 3 objects across 8 seconds and their poor performance when they tried to remember 6 objects.

The question of interest is whether the impairment found in the 6-object condition at the 8-second delay reflects impaired working memory or impaired long-term memory. We hypothesized that the performance of patients in the 3-object

condition at 8 seconds was intact because performance in this condition relied on an active maintenance process. Further, we hypothesized that the performance of patients in the 6-object condition at 8 seconds was impaired because now performance relied, at least in part, on long-term memory. Accordingly, following the same logic as in the names and faces tests, we expected distraction to disrupt control performance in the 3-object condition and to disrupt performance much less in the 6-object condition.

To test these predictions, we next tested the effect of distraction between study and test on control performance in both the 3-object condition and the 6-object condition at an 8-second delay. Figure 7b shows that in the 3-object condition performance was markedly affected by distraction (91.3% vs. 67.4% correct, paired $t_{(17)}$=6.6, p<0.001). Distraction also affected performance in the 6-object condition (73.6% vs. 65.6% correct, paired $t_{(17)}$=2.2, p<0.05), albeit much less than in the 3-object condition. Importantly, there was a Number of Objects X Distraction interaction ($F_{(1,17)}$ = 6.8, p < .02), indicating that the effect of distraction was greater in the 3-object condition than in the 6-object condition. It is also important that there was no floor effect in the two distraction conditions. Thus, all group means were above chance (50%, ps < 0.05), and 50% was well outside of the 95% confidence interval for each condition (for the 3-object distraction condition, 67.4% ± 7.4%; for the 6-object distraction condition, 65.6% ± 6.1%). Performance on the distracter (counting) task was comparable for the 3-object and 6-object conditions (average count error = 2.2 and 2.3, respectively, $t_{(17)}$=0.4, p=0.68).

Still another way to consider the data from the distraction experiment with object locations is to look at the benefit afforded by the use of working memory. That is, one can consider the distraction conditions as a baseline, showing how controls perform when they would have difficulty using working memory. Then, one can ask how performance improves when controls are allowed to use working memory. In the 3-object condition, the benefit is quite large (improvement from 67.4% to 91.3%), whereas in the 6-object condition, the benefit is minimal (improvement from 65.6% to 73.6%). We interpret this pattern of results to mean that performance in the 3-object condition depended substantially on working memory but that, in the 6-object condition, performance depended mainly on long-term memory.

As with names and faces, these results reveal a correspondence between the performance of amnesic patients and the effects of distraction on controls. Distraction impaired controls to a greater degree in the 3-object condition than in the 6-object condition. Presumably, performance in the 3-object condition depended substantially on rehearsal, and distraction interfered with active maintenance of what had been presented. In contrast, distraction had only a modest effect on the 6-object condition, because what was presented exceeded working memory capacity, and performance relied substantially on long-term memory. The important finding was that distraction impaired performance in the 3-object condition significantly more than in the 6-object condition.

We suggest that amnesic patients were intact in the 3-object condition because the task was supported primarily by working memory (rehearsal), and they were

impaired in the 6-object condition because, while working memory likely contributed to some extent, rehearsal was not sufficient to support good performance.

Discussion

In four different tasks (memory for names, faces, 3 object locations, and 6 object locations), we found concordance between the performance of patients with medial temporal lobe damage and the effect of distraction on controls. The patients were intact on tasks where distraction disrupted control performance, and the patients were impaired on tasks where distraction minimally affected control performance. These findings suggest that an active maintenance process (working memory) contributed substantially to control performance when patients performed well and less so or not at all when patients were impaired. These results suggest that the active maintenance process is intact after medial temporal lobe damage. It is true that patients with medial temporal lobe damage can be impaired at remembering some kinds of stimuli after quite brief delays, even when no stimuli intervene between study and test (Hannula et al., 2006; Nichols et al., 2006; Olson et al., 2006a; Olson et al., 2006b; Hartley et al., 2007; Ezzyat and Olson, 2008). However, we suggest that these findings reflect an early dependence on long-term memory, not an impairment in working memory. Working memory is limited by its low capacity and by the ease with which information can be actively maintained through rehearsal. The length of the study-test interval is not the important factor.

Our findings also address the suggestion that relational memory is critically dependent on the medial temporal lobe, regardless whether performance depends on long-term memory or working memory. The strong version of this view holds that patients with medial temporal lobe damage should be impaired in maintaining relational information even over short delays (Olson et al., 2006b). Contrary to this idea, we found that patients with hippocampal damage, and even the two patients with extensive medial temporal lobe damage, successfully maintained up to 6 object-location associations (relational information) for 1 second and up to 4 object-location associations for 8 seconds. We suggest that relational information can be maintained as long as the material is amenable to rehearsal and does not exceed the capacity of working memory.

Despite similarity in the tasks, the performance of our patients differed in some respects from the performance of patients in previous studies (Nichols et al., 2006; Olson et al., 2006a; Olson et al., 2006b). In the faces test, our patients performed as well as controls at the 2-second and 7-second delays and were impaired only at the 14-second delay. In an earlier study (Nichols et al., 2006), patients were impaired at the 7-second delay and performed numerically worse than our patients at that delay. In another study of memory for faces, patients were impaired when trying to remember a single face for 4 seconds (Olson et al., 2006a). In the object location test, our patients performed well at remembering up to 6 object locations for 1 second and up to 4 object locations for 8 seconds. In an earlier study (Olson et al., 2006b), patients were

impaired when remembering 3 object locations for 1 second (in one of 2 experiments) and for 8 seconds (in 2 of 2 experiments).

Differences between patient groups might account for these differences in severity of impairment. The damage in our patients was measured using quantitative volumetric analysis of MR images (Bayley et al., 2005b; Gold and Squire, 2005). The damage in the earlier studies resulted from a variety of etiologies and reportedly included diencephalic (Nichols et al., 2006) and medial temporal lobe structures (Nichols et al., 2006; Olson et al., 2006a; Olson et al., 2006b). Descriptions of the damage were based on visual inspection of MR images, or on etiology in the absence of MRI evidence. In the absence of quantitative measurements, the possibility remains that the patients had additional damage.

It is also possible that differences in testing procedure or in the construction of test stimuli could account for the modest differences between our study and the earlier ones. First, the faces in Olson et al. (2006a) were presented without hair, which can make face recognition rather difficult. Our faces were presented with hair (as in Nichols et al., 2006). In addition, in Olson et al. (2006b), there was not a subject-paced pause between trials (instead, there was a 0.5-second intertrial interval). In our experience, amnesic patients can become confused about what they are supposed to do, or whether they are in the study phase or the test phase. Therefore, we included a pause between trials, so that the patients would not be disadvantaged in their knowledge about the task compared to controls. This difference in procedure might

explain why our patients performed a little better than the patients in Olson et al. (2006b).

Using a measure of working memory that is unrelated to the effects of medial temporal lobe damage, we have resolved a circularity inherent in the working memory construct. The findings support a brain-based distinction between working memory and long-term memory, as well as the idea that working memory is independent of medial temporal lobe structures. We suggest that working memory depends on persistent activity in distributed regions of neocortex, including frontal, lateral temporal, and parietal cortical areas that are known to be important in the perception and initial processing of new information (Fuster, 2003; Postle, 2006).

Acknowledgments: Chapter 2, in full, is a reprint of the material as it appears in Journal of Neuroscience, 2008. Shrager, Yael; Levy, Daniel A.; Hopkins, Ramona O.; Squire, Larry R. The dissertation author was the primary investigator and author of this paper.

CHAPTER 3: Path Integration

Abstract

The hippocampus and entorhinal cortex have been linked to both memory functions and to spatial cognition, but it has been unclear how these ideas relate to each other. An important part of spatial cognition is path integration (the ability to keep track of a reference location using self-motion cues), and it has been suggested that the path integrator resides in the hippocampus or entorhinal cortex. Patients with hippocampal lesions or larger lesions that also included entorhinal cortex were led on paths while blindfolded (up to 15 meters in length) and were asked to actively maintain the path in mind. Patients pointed to and estimated their distance from the start location as accurately as controls. A rotation condition confirmed that performance was based on path integration. When demands on long-term memory were increased, patients were impaired. Thus, in humans the hippocampus and entorhinal cortex are not essential for path integration.

Introduction

For several decades, two influential ideas have been central to discussions about the function of the hippocampus, entorhinal cortex, and related medial temporal lobe structures. One perspective emphasizes the importance of these structures for memory (Scoville and Milner, 1957; Squire et al., 2004), and the other emphasizes their importance for spatial cognition (O'Keefe and Nadel, 1978; Etienne and Jeffery, 2004; McNaughton et al., 2006). An important aspect of spatial cognition is the capacity for path integration, that is, the ability to use internal cues during movement (i.e., self-motion cues) to keep track of a reference location (Etienne and Jeffery, 2004; McNaughton et al., 2006). Yet, keeping track of a reference location requires memory. Accordingly, it has been unclear how proposals about memory and proposals about spatial cognition relate to each other.

The view that medial temporal lobe structures are important for memory makes a key distinction between what is termed short-term (or working) memory and long-term memory. Working memory (that is, the ability to hold information actively in mind, for example, a short list of digits) is independent of medial temporal lobe structures (Drachman and Arbit, 1966; Atkinson and Shiffrin, 1968b), whereas long-term memory is critically dependent on these structures. Accordingly, patients with hippocampal or entorhinal damage should perform poorly on memory tasks only when demands are made on long-term memory. If instead a task could be performed within the span of working memory, then patients should succeed despite damage to the

hippocampus or entorhinal cortex. This idea applies even to tasks that require spatial cognition, such as path integration.

In contrast, the idea that the hippocampus and entorhinal cortex are important for path integration includes the suggestion that the path integrator is located in these structures (Etienne and Jeffery, 2004; McNaughton et al., 2006). First, the rat hippocampus contains place cells, cells that exhibit activity specific to an animal's location in space (O'Keefe and Dostrovsky, 1971). Second, grid cells were recently discovered in rat entorhinal cortex, upstream from hippocampal place cells. Grid cells exhibit a grid-like structure of place fields that repeat at regular intervals across the environment, suggesting that major steps in computing spatial location information occur in entorhinal cortex, immediately afferent to the hippocampus (Fyhn et al., 2004; Hafting et al., 2005). Accordingly, it is possible that patients with damage to the hippocampus or entorhinal cortex would be impaired at path integration. Further, the impairment should occur whether or not demands are made on long-term memory (i.e., the distinction between working memory and long-term memory is not germane). We have tested these ideas by asking whether the hippocampus and entorhinal cortex are essential for path integration even when the task can be managed within the span of working memory.

Methods

Participants: Five memory-impaired patients (mean age = 66, 1 female) and seven matched controls (mean age = 69, 2 females) were tested for their path

integration ability. Two patients are profoundly amnesic and have large, well-characterized lesions of the medial temporal lobe, including all of the hippocampus, all of the entorhinal cortex, all of the perirhinal cortex, and the majority of the parahippocampal cortex (E.P. and G.P.). These patients have demonstrated virtually no new learning since the onset of their amnesia, and during repeated testing over many weeks they do not recognize that they have been tested before (Bayley et al., 2005a). Three patients are moderately amnesic and have well-characterized lesions limited to the hippocampus (K.E., L.J., and G.W.).

Condition 1: Standard: Participants wore a blindfold and noise-canceling earphones, and verbal instructions were transmitted through the earphones. Participants were led on 16 paths (8 involving 1 turn, 8 involving 2 turns) in a 2.4 × 4.3 m (8 x 14 ft) space (Figure 8). Mean path length was 4.3 m (14.2 ft). Because the patients have impaired long-term memory, we intended to use paths short enough that they might be actively maintained in mind (i.e., they should not exceed working memory capacity) and could be traversed in approximately 30 seconds. Participants were encouraged to actively maintain the paths in mind during each trial. Ensuring that the task could be performed within the span of working memory was essential so that the memory-impaired patients would not be disadvantaged by their long-term memory deficits.

At the end of each path, participants stepped onto a platform raised 5 cm above the floor and equipped with handlebars to insure the stability of the participants. After a short delay (10-17 seconds), participants were asked to point to their start location

(mean trial length = 33.4 seconds). Two independent raters measured the direction in which participants pointed (measurements were taken to the nearest degree from a grid beneath the platform, mean inter-rater error = 4°). The pointing direction was then recorded in degrees for each trial, where 0° indicated perfect performance. For each participant, we derived the circular mean (mean pointing direction) and a measure of variability across the 16 trials. On each trial, participants began in a different start location, and the path ended in a different location. Participants were blindfolded at the start location but before the platform was moved to the next end location. Further, the handlebars were always in line with the final path direction taken by the participant and thus did not provide information about where the path started.

Condition 2: Longer paths: The two patients with large medial temporal lobe lesions (E.P. and G.P.) and four controls were given a test of path integration using longer paths (Figure 8). Participants again wore a blindfold and noise-canceling earphones, and they were led on 8 different paths in an outdoor open space. Each path involved 2 turns, and traversal of the path resembled a natural walk (path length = 15 m). At the end of the path, participants used handlebars for support (held in place by one of the experimenters) and pointed to their start location (mean trial length = 29.7 seconds).

Condition 3: Distance: The same twelve participants as in condition 1 wore a blindfold and earphones and were led on 8 paths, similar to those in the standard condition (4 involving 1 turn, 4 involving 2 turns). Half the paths (2 involving 1 turn, 2 involving 2 turns) ended only a short distance from the start location (mean = 1.6

m), and half the paths (2 involving 1 turn, 2 involving 2 turns) ended a longer distance from the start (mean = 4.0 m). At the end of the path, participants stepped onto the platform and after a short delay (similar in length to the delay in condition 1) were asked to estimate in feet the distance between their current location and the start location. The mean trial length was 32.1 seconds.

Condition 4: Rotation: The twelve participants from condition 1 again wore a blindfold and earphones and were led to the platform along 16 new paths (mirror images of the paths in the standard condition). Immediately after they stepped onto the platform, a remotely controlled motor within the platform slowly rotated the participant for a distance of 190° at a low speed (~14°/sec). Pilot experiments indicated that at this rotation speed participants had difficulty knowing how far they had been rotated. Mean trial length matched that of the standard condition (32.4 seconds).

Condition 5: Delay & Distraction: All participants (from condition 1) wore a blindfold and earphones and were led on 16 paths (the same as in the standard condition but in a different order). Immediately after stepping onto the platform, participants were instructed to remain stationary while engaging in 1 to 3 tasks of mental navigation. For each task, they were first asked to imagine themselves facing an initial heading direction (N, S, E, or W). They then carried out mentally a sequence of 3 instructions (e.g., turn 90° right and take a step, turn 90° left and take a step, turn 90° left and take a step). They then reported their final heading direction (N, S, E, or

W). At the end of this filled delay, participants pointed to the start location of the path. The average trial length was 1 minute, 10 seconds.

Results

Condition 1: Standard: Participants were led on 16 different paths (Figure 8) and at the end of each path were asked to point to their start location (mean trial length = 33.4 seconds). Circular statistics (Batschelet, 1981) revealed that both groups exhibited a significant (Moore's test, $p < 0.05$) and similar (Rank-Sum test, $p > 0.1$) pointing direction (controls = 4°, patients = -4°, Figure 9a) and that for each group the pointing direction did not differ from the correct direction (0°) (V-test, ps > 0.1). The dispersion of individual mean scores (that is, the extent to which the individual means in each group clustered around that group's mean) was also similar for controls and patients (Nonparametric Test for Dispersion, $p > 0.1$). Further, each individual participant exhibited a significant pointing direction. Notably, the two patients with large lesions that include all of the hippocampus and entorhinal cortex (E.P. and G.P.) exhibited pointing directions that were well within control range (E.P. = -10° and G.P. = -7°, control range = -14° to 20°).

To quantify the variability within individual participants, we next averaged for each group the standard deviations of the 16 pointing responses made by each individual. Figure 9c shows that the individual variability of controls and patients was nearly identical (controls = 30.5, patients = 31.3). The variability of patients E.P. and G.P. was well within control range (E.P. = 40.6 and G.P. = 37.0, control range = 14.0

to 66.6). To determine whether participants were in fact engaged in path integration, we asked the two most severely memory-impaired patients (E.P. and G.P.) and four controls immediately after they pointed how they had accomplished the task. All subjects uniformly described trying to keep track of their position in space as they moved, continually updating their position relative to the start point. There was no hint that anyone tried to do post-walk calculations of any kind.

Condition 2: Longer paths: In the standard condition, we showed that path integration could be accomplished despite damage to the hippocampus or the hippocampus plus entorhinal cortex. We next asked whether path integration might be impaired if the task were more demanding, albeit still manageable within working memory. The two patients with large medial temporal lobe lesions (E.P. and G.P.) and four controls were led in an outdoor space on 8 paths that were nearly four times longer than the paths in condition 1 (15 m in this condition vs. 4.3 m in condition 1) and that more closely resembled a natural walk. The mean trial time was 29.7 seconds. The mean pointing direction and individual variability for controls was 9° and 35.0 (Figure 9b,d). For E.P. and G.P., the mean pointing direction was -17° and -13°, and the individual variability was 24.3 and 29.9, respectively. Both patients were well within the range of the controls with respect to both pointing direction (-15° to 34°) and individual variability (24.1 to 47.0).

Condition 3: Distance: In a third condition, we tested the ability of participants to estimate the distance between the start location and the end location. The five patients and seven controls who participated in condition 1 made similar estimates.

For the 4 shorter paths (mean = 1.6 m), patients estimated a distance of 1.9 m, and controls estimated a distance of 1.5 m; for the 4 longer paths (mean 4.0 m), patients estimated a distance of 2.9 m and controls estimated a distance of 2.7 m (ts < 1.1, ps > 0.3). Further, for each group, the estimates for the 4 shorter distances were smaller than the estimates for the 4 longer distances (ts > 4.0, ps < 0.02).

Condition 4: Rotation: In another condition (rotation), we tested whether participants were in fact performing path integration by using internal cues, rather than by relying on external cues beyond experimental control (mean trial length = 32.4 seconds). Pilot experiments indicated that during rotation participants had difficulty knowing how far they had been turned. We therefore expected that if participants were in fact relying on path integration (internal cues) to point to their starting location, then they would have difficulty when a rotation was introduced into the standard condition (condition 1). The results confirmed that performance was substantially compromised in the rotation condition. First, neither group exhibited a significant pointing direction (Moore's test, ps > 0.1, Figure 10a). Second, for both groups, the variability of each individual's performance was markedly increased as compared to the standard condition (again, measured as the standard deviation of each individual's 16 pointing directions: controls = 61.5 in the rotation condition vs. 30.5 in the standard condition; patients = 54.9 vs. 31.3, ts > 3.1, ps < 0.04, Figure 10b). Third, the marked variability in individual performance was similar for the two groups (61.5 vs. 54.9, $t_{(10)} < 0.7$, $p > 0.5$).

Condition 5: Delay & Distraction: In a final condition (distraction), we increased the long-term memory demands of the task by increasing the duration of each trial (modeled after the trials in the standard condition) and by introducing distraction during the longer delay (total trial length = 1 minute 10 seconds). The controls performed as well in the distraction condition as in the standard condition (mean pointing direction = 1° in the distraction condition vs. 4° in the standard condition) (Figure 11a). As in the standard condition, controls also had a significant pointing direction (Moore's test, $p < 0.05$) that was not different from 0° (V-test, $p > 0.1$). Further, for the control group, the variability of individual pointing directions in the distraction condition (30.1) was no greater than the variability of individual pointing directions in the standard condition (30.5) (compare Figure 11b to Figure 9c). In contrast, the patients had difficulty in the distraction condition. On the one hand, they did exhibit a significant pointing direction (Moore's test, $p < 0.05$; mean pointing direction = -14° in the distraction condition vs. -4° in the standard condition) that was not different from 0° (V-test, $p > 0.1$) and not different from the mean pointing direction of controls (-14° vs. 1°, rank-sum test, $p > 0.1$) (Figure 11a). On the other hand, by this measure, 5 of the 6 patients performed more poorly in the distraction condition than in the standard condition. For example, E.P.'s pointing direction was quite poor (-42°, compared to -10° in the standard condition). More importantly, distraction dramatically increased the variability of individual patient performance across the 16 trials (57.1 in the distraction condition vs. 31.3 in the standard condition, $t > 2.9$, $p < 0.05$, compare Figure 11b to Figure 9c). E.P.'s variability was 77.0, G.P.'s

was 67.4, and both values were outside the range of controls (16.7 to 58.0). Further, an ANOVA of the individual variability scores for the standard and distraction conditions revealed a Group X Condition interaction ($F > 11.0$, $p < 0.01$), indicating that the patients were more affected by distraction than the controls.

To illustrate more dramatically the severity of memory impairment in E.P. and G.P., we asked them several minutes after testing to describe paths they had walked and to describe the task they had been engaged in. Neither patient could remember anything of what they had been doing and suggested they had been "in conversation" (E.P.) or "looking at objects" (G.P.). These observations make clear that when E.P. and G.P. succeeded in the navigation tasks described here, they succeeded by maintaining the start location in working memory.

Discussion

We have shown that patients with lesions limited to the hippocampus as well as patients with larger lesions that include the entorhinal cortex can path integrate as well as controls on paths up to 15 meters in length and involving 1 or 2 turns. After being led on a path, and while deprived of external cues, the patients pointed as accurately as controls to their start location. They also estimated as accurately as controls the distance between the start and end locations. Performance of both groups was disrupted in the rotation condition, indicating that participants were engaged in path integration and not using any external cues in the environment. Lastly,

introducing a long-term memory requirement to the path integration task impaired the performance of the patients.

By intention, the paths used in our study were relatively short (involving 1 or 2 turns and a duration of less than 35 seconds) so that they might be maintained within working memory. It is possible that an impairment in path integration would have been detected if we had not been limited by the memory impairment of the patients and had been able to test much more complex paths. Still, if the hippocampus and entorhinal cortex were essential for path integration, one would have expected the patients to have some difficulty as soon as their paths involved turning and moving across a reasonable distance. Instead, we found that performance was entirely intact for paths as long as 15 meters that involved up to two turns.

Our data are therefore difficult to reconcile with the view that the hippocampus and entorhinal cortex are essential sites where computations necessary for path integration are carried out. There is no doubt that cells with distinct spatial properties are found in both hippocampus and entorhinal cortex (O'Keefe and Dostrovsky, 1971; Fyhn et al., 2004; Hafting et al., 2005) and that these cells can represent detailed spatial information as well as many other relevant features of ongoing behavioral episodes in service of memory function (Wood et al., 1999). Nonetheless, our results suggest that in humans these structures do not perform computations essential for path integration. A recent study using functional MRI found that hippocampal activation correlated with path integration accuracy in healthy volunteers (Wolbers et al., 2007). We suggest that damage to the hippocampus would not impair performance on this

task so long as the task did not exceed the span of working memory. Our findings are not inconsistent with the possibility that the computations underlying path integration are carried out in parallel at more than one site (including the medial temporal lobe), but the findings rule out the idea that the medial temporal lobe is the only site that can carry out these computations.

To our knowledge, our study is the first to assess the effects of bilateral hippocampal and entorhinal damage on path integration that also untangles the spatial demands of the task from its potential demands on long-term memory. A few studies have examined the effect of lesions on path integration ability but have yielded mixed results. In one study, patients with right temporal lobe lesions who were led along a path were impaired at estimating direction (but not distance) information (Worsley et al., 2001). However, in these cases the lateral temporal lobe was extensively damaged (inferior and middle temporal gyrus). In another study, rats with hippocampal lesions exhibited normal path integration ability (Alyan and McNaughton, 1999). In two other studies, rats with lesions of the hippocampus or entorhinal cortex were impaired at path integration (Maaswinkel et al., 1999; Parron and Save, 2004). None of the rodent studies reported the time needed to accomplish each trial, though it seems likely that the trials in some cases may have been relatively short. Still, the possibility remains that in rats these tasks placed demands on long-term memory. Additionally, it is possible that there are substantive species differences between humans and rodents, such that the more developed neocortex in humans might be capable of supporting

path integration, whereas in rodents the hippocampus and entorhinal cortex might be more important.

Our data support the view that medial temporal lobe structures are important for long-term memory and not for the spatial computations needed for path integration, so long as performance can be supported by working memory. It is possible that path integration is accomplished in parallel at more than one site (e.g., both in the medial temporal lobe and in parietal cortex), with the result that damage to the medial temporal lobe would leave path integration intact. Alternatively, the computations necessary for path integration may be carried out upstream of the medial temporal lobe, perhaps in parietal cortex, inasmuch as damage to the parietal cortex impairs performance on a variety of spatial tasks in rats, monkeys, and humans (Mesulam, 1981; Kolb and Walkey, 1987; Save and Moghaddam, 1996). Further, cells exhibiting activity specific to a particular path (a sequence of left and right turns through an environment) have been found in rat parietal cortex (Nitz, 2006). By this view, spatial information from cortex arrives at the medial temporal lobe, like information from other modalities (for example, visual and auditory information), and the medial temporal lobe then carries out the operation of transforming perception into long-term memory.

Acknowledgments: Chapter 3, in full, has been submitted for consideration for publication. Shrager, Yael; Kirwan, C. Brock; Squire, Larry R. The dissertation author was the primary investigator and author of this paper.

CONCLUSIONS

For the past 50 years, the medial temporal lobe has been known to support memory (Scoville and Milner, 1957). Testing of patients and animals with medial temporal lobe damage has consistently found long-term memory impairment, while other perceptual and cognitive functions remain intact. Here, I have described experiments showing that 1) visual perception is independent of the medial temporal lobe; 2) working memory can be identified independently of the performance of amnesic patients, and when this is done, working memory is found to be independent of the medial temporal lobe; and 3) path integration, a form of spatial cognition, is independent of the hippocampus and entorhinal cortex when information can be maintained within working memory, but path integration depends on these structures when demands are made on long-term memory.

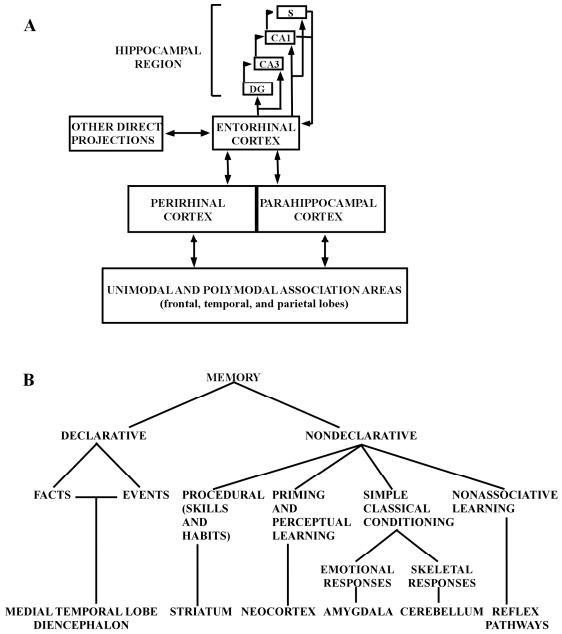

Figure 1. a) A schematic view of the medial temporal lobe memory system for declarative memory, which is composed of the hippocampal region together with the perirhinal, entorhinal, and parahippocampal cortices. From Manns and Squire, 2002. The hippocampal region is composed of the dentate gyrus (DG), the CA fields and the subiculum (S). **b)** A taxonomy of mammalian long-term memory systems. The taxonomy lists the brain structures thought to be especially important for each form of declarative and nondeclarative memory. In addition to its central role in emotional learning, the amygdala is able to modulate the strength of both declarative and nondeclarative memory. From (Squire and Knowlton, 2000)

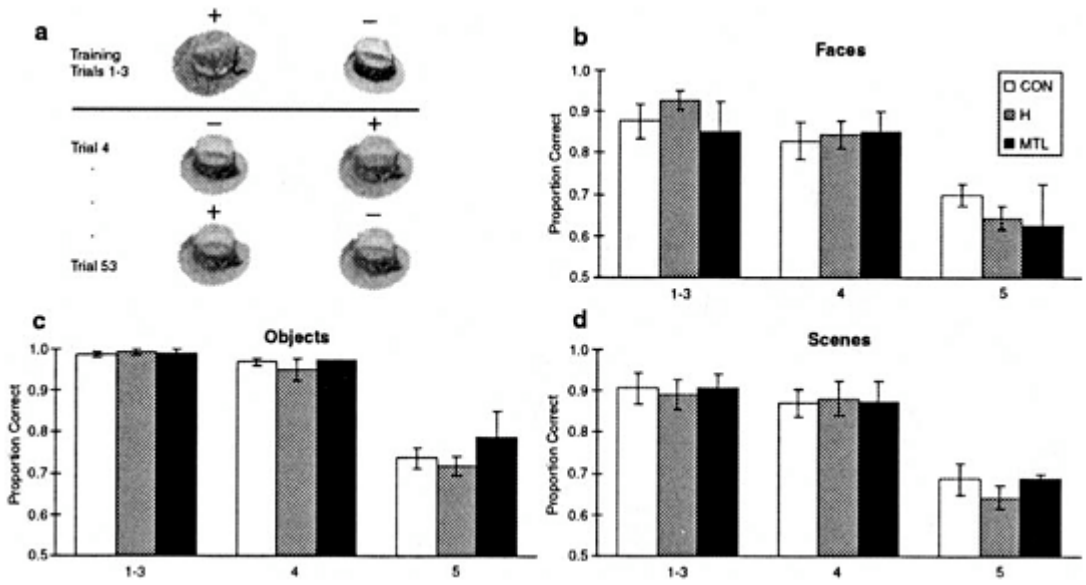

Figure 2. Visual discrimination learning. **a)** The task. On trials 1 – 3, two distinct images were presented. Participants were asked to indicate which image they believed to be "correct" (here identified by a +), and feedback was provided after each choice. For trials 4 – 53, participants saw two morphed images, each of which was intermediate to the images in trials 1 – 3. On each trial, participants chose the image that appeared more similar to the correct image. **b – d)** Proportion correct scores for the H group (n = 4), the MTL group (n = 2), and the CON group (n = 8) on four different tests in each of three categories: **b)** faces; **c)** objects; **d)** scenes. Trials were given at five different levels of difficulty (1 – 5), and scroes are shown for levels 1 – 3, level 4, and level 5. Error bars indicate standard error.

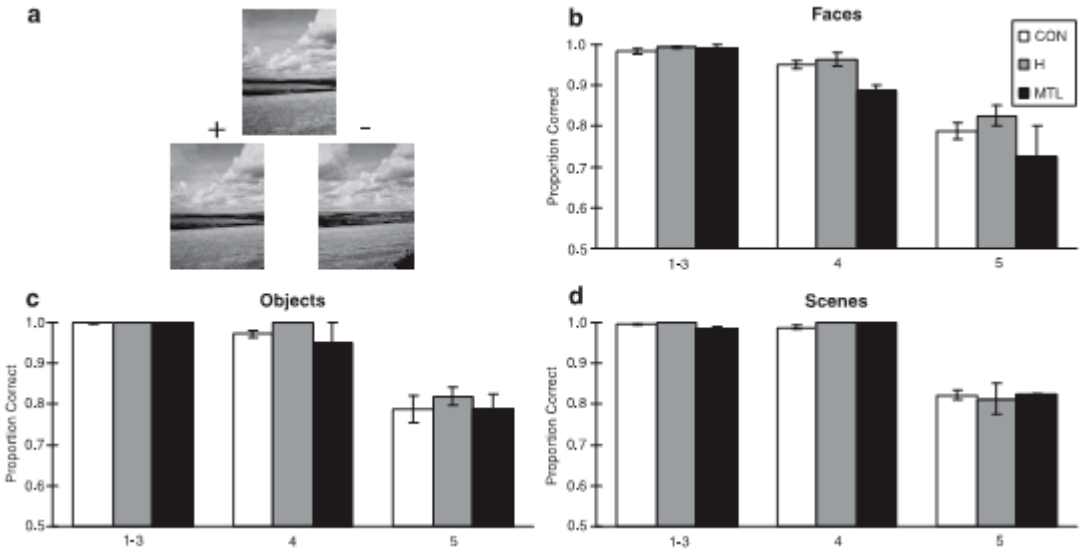

Figure 3. Visual discrimination. **a)** The task. On each trial, two morphed images were presented below a single distinct image. Participants were asked to choose the lower image (here identified by a +) that appeared more similar to the upper image. **b – d)** Proportion correct scores for the H groups (n = 4), the MTL groups (n = 2), and the CON group (n = 8) on four different tests in each of three categories: **b)** faces; **c)** objects; **d)** scenes (50 trials per test). The morphed images presented in each tests of 50 trials were all derived from the same two source images (See Chapter 1 Methods). Trials were given at five different levels of difficulty (1 – 5), and scores are shown for levels 1 – 3, level 4, and level 5. Error bars indicate standard error.

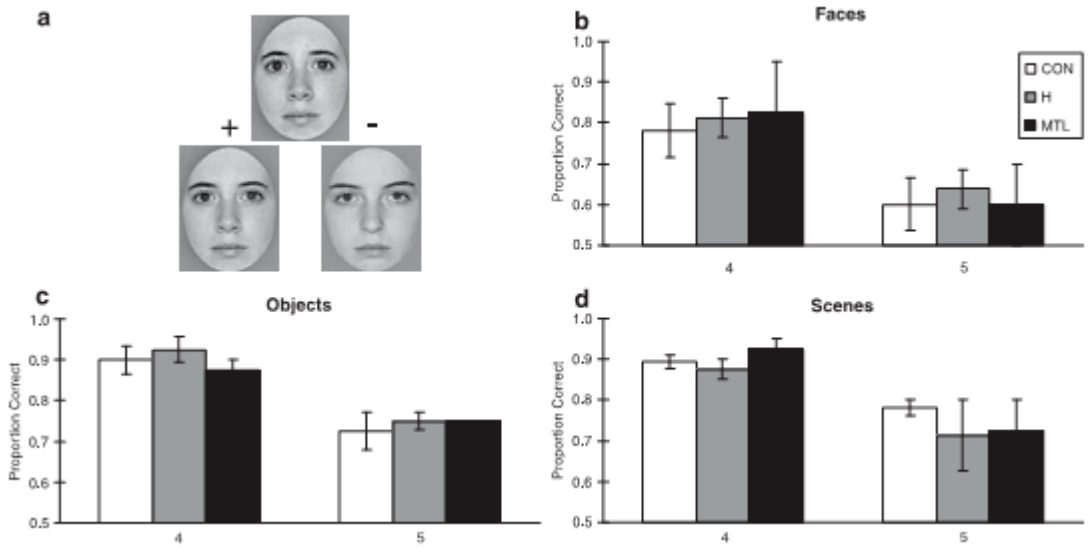

Figure 4. Trial-unique visual discrimination. **a)** The task. On each of 120 unique trials, two morphed images were presented below a single distinct image. Participants were asked to choose the lower image (here identified by a +) that appeared more similar to the upper image. **b – d)** Proportion correct scores for the H group (n = 4), the MTL group (n = 2), and the CON group (n = 8) on one test in each of three categories: **b)** faces; **c)** objects; **d)** scenes (40 trials per test). The morphed images presented in each test were all derived from different source images (See Chapter 1 Methods). Trials were given at two different levels of difficulty (4 and 5). Error bars indicate standard error.

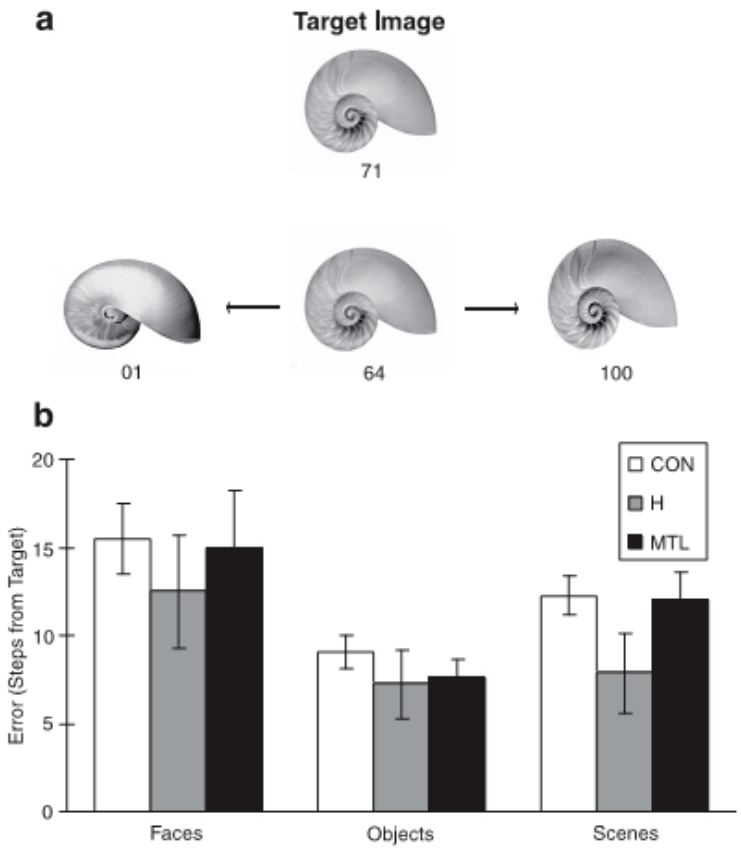

Figure 5. Visual matching. **a)** The task. On each of 45 unique trials, a target image was presented above a single image. Both images were derived from a unique pair of distinct images (images 01 and 100). In the case illustrated, the target image is number 71 in the 01 - 100 series, and the bottom image is image number 64 from the same series. Participants were asked to scroll through the ordered series of 100 images (image 01 – 100) and to try to match the lower image to the target. Image numbers did not appear during testing. **b)** Error scores (number of steps from the target) for the H group (n = 4), the MTL group (n = 2), and the CON group (n = 8) on trials involving faces, objects, and scenes (15 trials per category). Error bars indicate standard error.

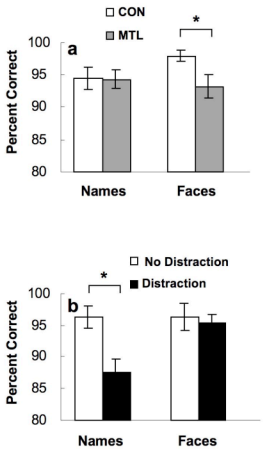

Figure 6. Memory for Names and Faces. **a)** Twelve controls (CON) and patients with medial temporal lobe damage (MTL) tried to remember 3 names for 14 seconds (Names, n = 5 patients) or a single face for 14 seconds (Faces, n = 6 patients). **b)** Twelve controls (CON) were tested in both the Names condition and the Faces condition with and without a distraction task during the 14-second delay. Error bars indicate standard error. Asterisks indicate $p < 0.05$.

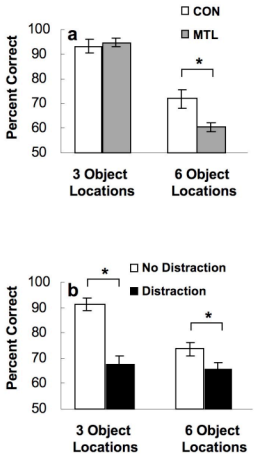

Figure 7. Memory for Object Locations. **a)** Twelve controls (CON) and 7 patients with medial temporal lobe damage (MTL) tried to remember 3 object locations or 6 object locations for 8 seconds (16 trials/condition). **b)** Eighteen controls (CON) tried to remember 3 or 6 object locations with or without a distraction task during the delay (16 trials/condition, 64 trials total). Error bars indicate standard error. Asterisks indicate $p < 0.05$.

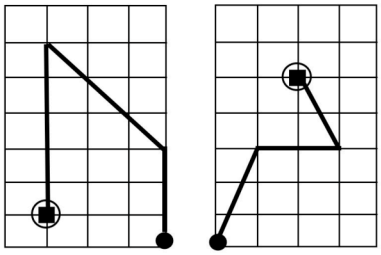

Figure 8. Sample routes. In each of five conditions, blindfolded participants were led in an indoor 2.4 × 4.3 m area (conditions 1, 3, 4, and 5) or in an outdoor 5 x 15 m open area (condition 2) along paths that ended at a circular platform (small circle around ■, there was not a platform in condition 2). In conditions 1, 3, 4, and 5, half the routes involved one turn, and half involved two turns. In condition 2, all routes involved 2 turns. ● = start; ■ = finish. In conditions 1 and 2 (16 and 8 trials, respectively), participants pointed to the start location shortly after stepping onto the platform (mean interval from start = 33.4 and 29.7 sec, respectively). In condition 3 (8 trials), participants walked a path and, shortly after stepping onto the platform, estimated their distance from the start location (mean interval from start = 32.1 sec). In condition 4 (16 trials), participants walked a path, stepped onto the platform, and then pointed to the start location after being rotated 190° at 14°/sec (mean interval from start = 32.4 sec). In condition 5 (16 trials), participants walked a path, stepped onto the platform, and then pointed to the start location after being engaged in an unrelated task of mental navigation (mean interval from start = 1 min, 10 sec).

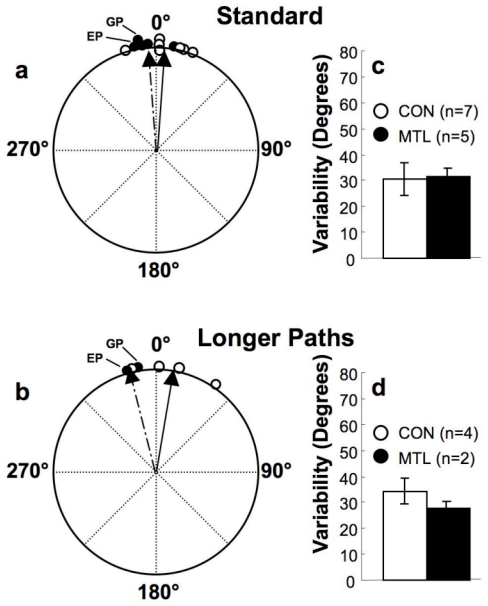

Figure 9. a, b) Circular means of each participant's 16 **(a)** or 8 **(b)** pointing directions in conditions 1 and 2, respectively, for patients with damage to the medial temporal lobe (MTL, filled circles) and controls (CON, unfilled circles). 0° indicates the correct direction. Group pointing directions are also indicated (solid arrow = CON; broken arrow = MTL). Shorter arrows denote greater variability (dispersion) in the group's pointing direction (following Moore's test for non-uniformity [Batschelet, 1981]). The standard deviation of pointing directions around each participant's circular mean was calculated, and the individual standard deviations were then averaged for each group (individual variability) (**c, d)**. Brackets indicate standard error.

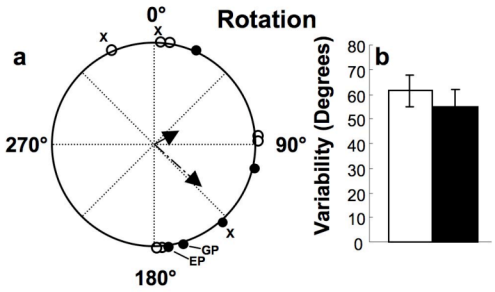

Figure 10. a) Circular means of each participant's 16 pointing directions in condition 4 (rotation) for patients with damage to the medial temporal lobe (MTL, filled circles) and controls (CON, unfilled circles). 0° indicates the correct direction. Group pointing directions are also indicated (solid arrow = CON; broken arrow = MTL). 'X' indicates individuals who did not exhibit a significant point direction. Individual variability for each group is shown in **b**. Brackets indicate standard error.

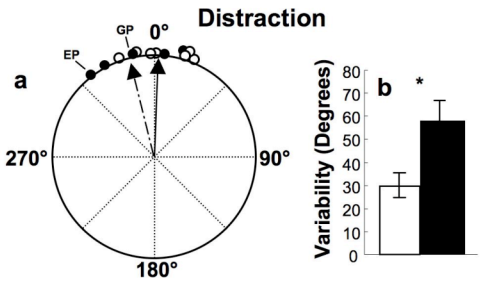

Figure 11. a) Circular means of each participant's 16 pointing directions in condition 5 (delay & distraction) for patients with damage to the medial temporal lobe (MTL, filled circles) and controls (CON, unfilled circles). 0° indicates the correct direction. Group pointing directions are also indicated (solid arrow = CON; broken arrow = MTL). Individual variability for each group is shown in **b**. Asterisk (*) indicates $p < 0.05$. Brackets indicate standard error.

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