Specialization in the Medial Temporal Lobe for Processing of Objects and Scenes

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ABSTRACT: There has been considerable debate as to whether the hippocampus and perirhinal cortex may subserve both memory and perception. We administered a series of oddity tasks, in which subjects selected the odd stimulus from a visual array, to amnesic patients with either selective hippocampal damage (HC group) or more extensive medial temporal damage, including the perirhinal cortex (MTL group). All patients performed normally when the stimuli could be discriminated using simple visual features, even if faces or complex virtual reality scenes were presented. Both patient groups were, however, severely impaired at scene discrimination when a significant demand was placed on processing spatial information across viewpoint independent representations, while only the MTL group showed a significant deficit in oddity judgments of faces and objects when object viewpoint independent perception was emphasized. These observations provide compelling evidence that the human hippocampus and perirhinal cortex are critical to processes beyond long-term declarative memory and may subserve spatial and object perception, respectively. © 2005 Wiley-Liss, Inc.

KEY WORDS: hippocampus; perirhinal cortex; perception; memory; amnesia

INTRODUCTION

The different medial temporal lobe (MTL) structures, including the hippocampus, entorhinal cortex (EC), perirhinal cortex, and parahippocampal gyrus, are thought to comprise a single long-term declarative memory system (Squire and Zola-Morgan, 1991; Zola-Morgan et al., 1994). Recent studies have, however, challenged this view and suggested that these structures may, in fact, subserve different long-term memory processes. In particular, the perirhinal cortex (BA 35/36) may mediate object recognition on the basis of familiarity and memory for stimulus–stimulus associations, while the hippocampus may subserve memory recollection and navigation (Meunier et al., 1993; Murray et al., 1993; Eacott et al., 1994; Maguire et al., 1997; Buckley and Gaffan, 1998a; Aggleton and Brown, 1999; Burgess et al., 2002; Henson et al., 2003; Winters et al., 2004.

Lately, there has been considerable debate as to whether specific MTL structures may also support the representation and processing of perceptual information beyond the domain of long-term declarative memory (referred to hereafter as "perception"), with the hippocampus and perirhinal cortex contributing to spatial (O'Keefe, 1999; Gaffan, 2001) and object perception (Murray and Bussey, 1999; Buckley et al., 2001; Bussey et al., 2002, 2003) respectively. Animal lesion studies have suggested that the hippocampus is critical for tasks that recruit spatial memory (Morris et al., 1982; Murray et al., 1989, 1993; Hampton et al., 2004). Moreover, both animals (O'Keefe, 1976; Ono et al., 1991, 1993; Wilson and McNaughton, 1993; O'Keefe and Burgess, 1996; O'Keefe et al., 1998; Robertson et al., 1998; Hori et al., 2003) and humans (Ekstrom et al., 2003) possess hippocampal place or spatial-view cells that may signal aspects of spatial location and navigation. On the other hand, perirhinal lesioned monkeys show significant impairments in visual object concurrent discrimination when large stimulus set sizes, multiple distracting stimuli, or different stimulus orientations across trials are employed (Buckley and Gaffan, 1997, 1998b).

One model of perirhinal cortex function (Murray and Bussey, 1999; Bussey and Saksida, 2002; Bussey et al., 2002) proposes that the ventral visual processing stream (Ungerleider and Mishkin, 1982) may culminate in the perirhinal cortex. Thus, caudal inferotemporal cortical regions (e.g., V4, TE/TEO) process simple stimulus features or basic object stimuli, while rostral regions, including the perirhinal cortex, process more complex conjunctions of stimulus features or objects and may underlie object perception. Supporting this view, Bussey et al. (2003) found that monkeys with perirhinal cortex lesions were significantly impaired on the concurrent discrimination of pairs of two-dimensional images when the stimuli were composed of overlapping features, but not when the images possessed unique features.

Although not a specific investigation of the feature conjunction hypothesis, Buckley et al. (2001) also found evidence for a role of the perirhinal cortex in object perception. Monkeys with perirhinal cortex

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TABLE 1.

Mean Structural MRI Scan Ratings (With Standard Deviations), Averaged Across Both Hemispheres

Group	AntTemp	Amyg	PHG	MBCS	LBCS	MBOS	AntHC	LatTemp	PostHC
HC	0.375	0.438	0.438	0.688	0.313	0.125	1.56*	0.438	0.750
	(0.479)	(0.427)	(0.375)	(0.125)	(0.125)	(0.144)	(0.315)	(0.427)	(0.354)
MTL	1.917*	2.667*	2.250*	2.167*	2.083*	2.167*	2.25*	1.083	2.167*
	(0.144)	(0.382)	(0.661)	(1.01)	(0.722)	(0.289)	(0.661)	(0.629)	(0.520)
Control	0.313	0.375	0.188	0.521	0.271	0.333	0.458	0.458	0.271
	(0.284)	(0.483)	(0.188)	(0.291)	(0.310)	(0.289)	(0.382)	(0.411)	(0.361)

AntTemp, the anterior temporal lobe; Amyg, amygdala; PHG, parahippocampal gyrus; MBCS and LBCS, medial and lateral banks of the collateral sulcus; MBOS, medial bank of the occipitotemporal cortex; AntHC and PostHC, anterior and posterior hippocampus; and LatTemp, lateral temporal lobe. Asterisk denotes significant difference in comparison with controls.

ablations were assessed on a series of perceptual discrimination tasks in which subjects had to select the odd stimulus from an array of similar items. The monkeys were impaired on discriminations that placed a significant demand on object perception, in particular, the ability to perceive and identify objects, including faces, from different viewpoints. In contrast, the ability to discriminate objects that were presented from the same viewpoint remained intact, as did oddity judgment on the basis of simple object features (e.g., the perception of differences in color, size, shape).

Evidence for a role of the human MTL in perception comes from a recent study conducted by our laboratory (Lee et al., 2005) in which fine visual discrimination of different stimulus categories was assessed in a group of amnesic patients who had selective hippocampal damage bilaterally (HC group), and another group of amnesics who had larger bilateral MTL lesions (MTL group), including damage to both the hippocampus and perirhinal cortex (Table 1; Fig. 1). Consistent with the idea that the hippocampus and perirhinal cortex may be critical for spatial and object perception, respectively, the HC group demonstrated a selective deficit in the visual discrimination of spatial scenes, while the MTL group were significantly impaired in the discrimination of spatial scenes, faces, and to a lesser extent objects.

While there has been, to our knowledge, no other study that has examined the role of the hippocampus in spatial scene perception, the findings of our recent experiment are in stark contrast to other neuropsychological investigations that have studied the role of the human perirhinal cortex in object perception (Buffalo et al., 1998; Holdstock et al., 2000a). For instance, patients with focal lesions that include the perirhinal cortex are able to match visual stimuli in tasks with minimal declarative memory demand (Buffalo et al., 1998; Holdstock et al., 2000a). Moreover, patients with perirhinal cortex damage have been observed to perform normally on oddity tasks (Stark and Squire, 2000, see also Levy et al., 2005) similar to those used in monkeys (Buckley et al., 2001).

A number of possible reasons may explain these discrepancies, notably (a) that the stimuli used in our original study were not "trial-unique" (i.e., controls might show subtle learning effects not present in our patients) and (b) that the reported effect sizes were extremely small and therefore inconclusive. In addition, it has been proposed that the perceptual deficits observed in our patients could be due to additional atrophy to cortical areas that are known to be involved in the perception of faces and spatial scenes, such as the fusiform face area (FFA; Kanwisher et al., 1997) and the parahippocampal place area (PPA; Epstein and Kanwisher, 1998).

The aims of the current study were, therefore, 2-fold. First, we sought to determine whether the impairment in object perception demonstrated by the MTL group patients in the previous study (Lee et al., 2005) is also evident in the context of oddity tasks used previously in the animal literature (Buckley et al., 2001). Second, we hoped to rule out categorically the possibility that the object and spatial perception deficits observed in our earlier study (Lee et al., 2005) can be accounted for by (a) the use of non-trial-unique stimuli and (b) concomitant atrophy to the FFA and PPA, respectively.

To achieve the first aim, our patients were assessed on oddity tests adapted from a subset of the original tasks used in monkeys (Buckley et al., 2001; Expt. 1). Performance on three of these, color, size, and shape, was not dependent upon the perirhinal cortex in monkeys, while performance on the other two, face and object, was impaired following perirhinal cortex ablation (Buckley et al., 2001). Compared with a previous study (Stark and Squire, 2000) that had used similar tasks, we utilized larger stimulus set sizes on the perirhinal cortex dependent tasks and classified objects into those that were familiar from everyday life and those that were novel, to create two object oddity tasks (novel and familiar object; Fig. 2). Importantly, the stimuli in each condition in Expt. 1 were repeated across 10 blocks of 10 trials. This allowed us to investigate whether the control subjects, but not the patients, would demonstrate learning over multiple presentations of the same stimuli.

To address the possible involvement of PPA and FFA damage in our patients and to extend our previous finding of scene discrimination deficits in our HC group, we administered a series of new trial-unique oddity tasks: face same views, virtual scene same views, face different views, and virtual scene different views (Expt. 2; Fig. 3). Although all four of these tests involved faces and complex virtual reality scenes (processes dependent upon the FFA and PPA, respectively), only two of these tasks, face different views

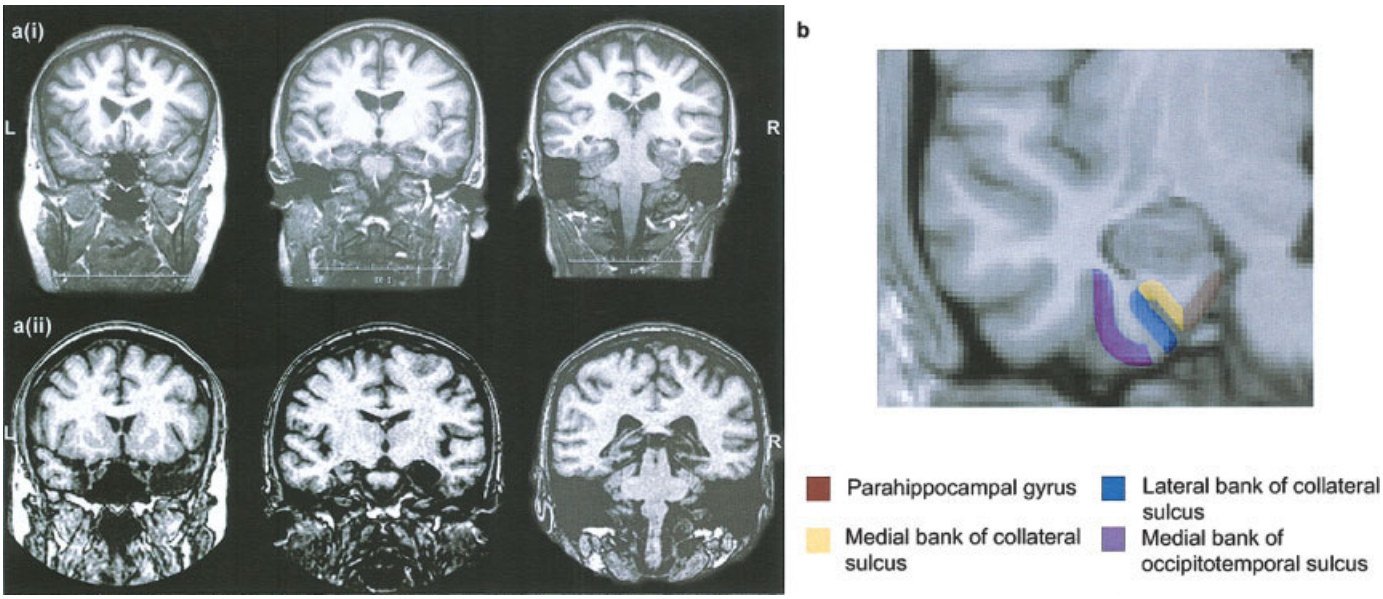

FIGURE 1. **(a) Three brain slices for one representative (i) HC group and (ii) MTL group patient. (b) Schematic diagram outlining the four MTL regions that were rated to assess atrophy to the perirhinal cortex and surrounding regions.**

and virtual scene different views, placed a high demand on face and scene perception (processes that may be more dependent upon the perirhinal cortex and hippocampus, respectively). This is because these two tasks were designed to minimize the use of simple object features and importantly, placed an emphasis on forming viewpoint independent representations of the faces or scenes within each trial. Consequently, we predicted that although the hippocampal and MTL patient groups would perform normally on the face same views and virtual scene same views tasks, both patient groups would have significant problems on the virtual scene different views task. In contrast, only the MTL group would be significantly impaired on the face different views task (similar to the findings in monkeys in Buckley et al., 2001). It is important to note that by using a trial-unique design (i.e., each stimulus was presented only once), we hoped to rule out the contribution of any learning of individual stimuli across trials.

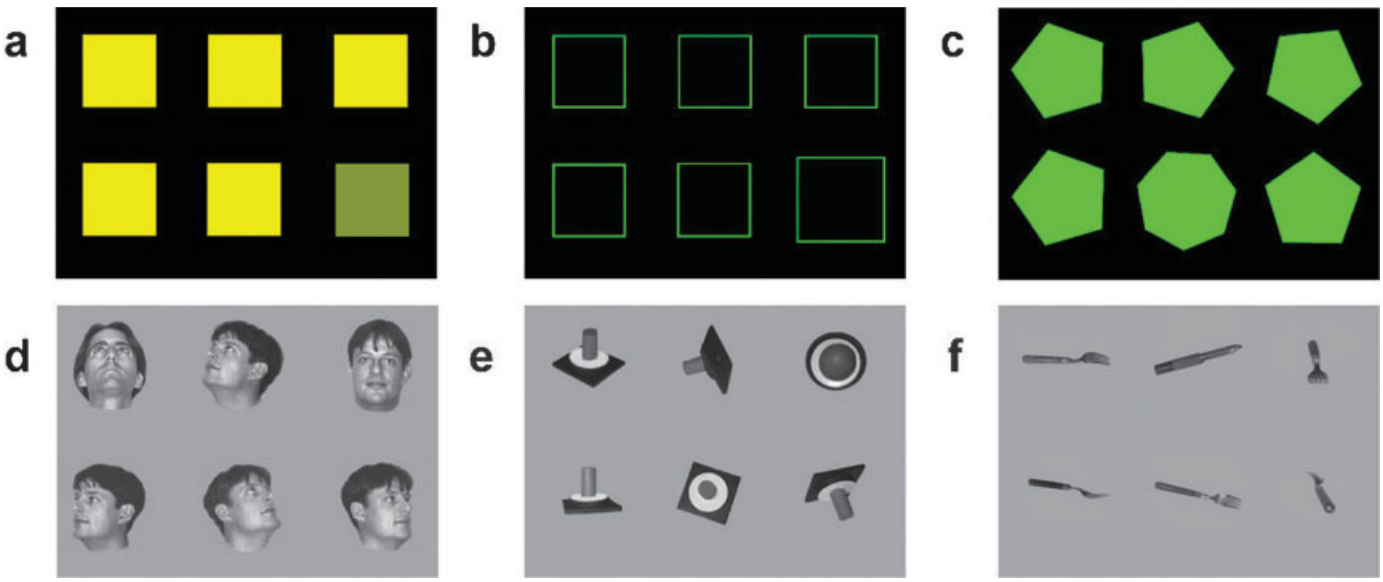

FIGURE 2. **Diagram illustrating a single trial from each task of Expt. 1: (a) color oddity, (b) size oddity, (c) shape oddity, (d) face oddity, (e) novel object oddity, and (f) familiar object oddity.**

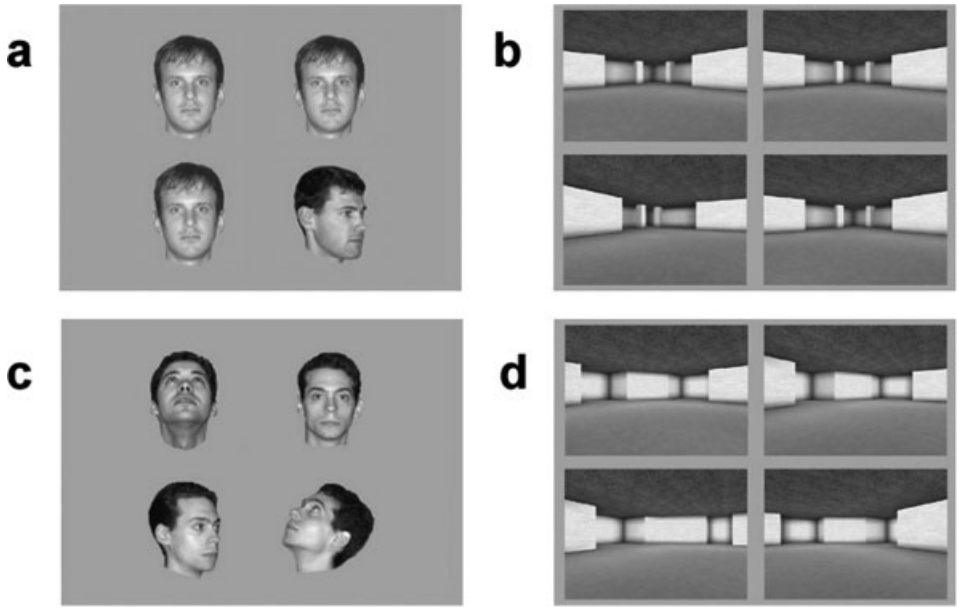

FIGURE 3. Diagram illustrating a single trial from each task of Expt. 2: (a) face same views, (b) scene same views, (c) face different views, and (d) scene different views.

MATERIALS AND METHODS

Subjects

Seven amnesic patients with focal brain lesions, who presented through the Memory Clinic at Addenbrooke's Hospital, Cambridge, UK, or the Wessex Neurological Centre, Southampton General Hospital, UK, participated in this study. All the patients were part of our previous study (Lee et al., 2005) and had structural magnetic resonance imaging (MRI) scans that were rated by two experienced, independent neurologists using a visual rating method. This rating scale is an expansion of a previously developed scale that has been successively validated against volumetric measures (Galton et al., 2001; for a detailed description of the rating methodology, see Lee et al., 2005). On the basis of these scores, the patients were divided into two groups: those that had selective damage to the hippocampus bilaterally ("HC group") and those that had larger MTL lesions ("MTL group"), including damage to the perirhinal cortex as well as some injury to anterior temporal lobe regions (Fig. 1a). Of the four patients that were deemed to be in the HC group (age = 47.8 yrs; education = 15.0 yrs), two had suffered from viral encephalitis, one had anoxia due to status epilepticus, and one suffered carbon monoxide poisoning. Of the three patients who were categorized in the MTL group (age = 67.7 yrs; education = 11.7 yrs), two were viral encephalitis patients and the third suffered traumatic intercerebral bleeding.

The cognitive abilities of the patients were quantified with a series of standardized neuropsychological tests assessing memory and visual perception. In brief, these demonstrated that all patients had severe episodic memory problems, as well as intact perceptual functions. For instance, both patient groups performed poorly on most episodic memory tests such as the logical memory (Stories 1 and 2) immediate recall (mean HC (WMS-R): 26.6%; mean MTL (WMS-III): 22.7%) and delayed recall conditions (mean HC (WMS-R): 6.4%; mean MTL (WMS-III): 3.3%), and the Rey Complex Figure delayed recall condition (mean HC: 19.7%; mean MTL: 10.6%). On the Warrington Recognition Memory Test faces task, the HC group performed normally (mean HC: 93.0%), while the MTL group were severely impaired (mean MTL: 62.7%). Visuoperceptual performance as indicated by tests such as the Benton face test (mean HC: 89.8%; mean MTL: 79.0%), Rey Complex Figure copy (mean HC: 99.3%; mean MTL: 92.1%), and Visual Object Space Perception battery (both groups passed all object and space tests) was normal. The HC group exhibited intact semantic function, while the MTL group was found to be significantly impaired on semantic tests, including Word–Picture matching (mean HC: 100.0%; mean MTL: 88.5%), Naming (mean HC: 98.1%; mean MTL: 67.2%), and the Pyramids and Palm Trees word condition (mean HC: 99.0%; mean MTL: 89.7%).

The greater episodic and semantic memory impairments of the MTL group reflect the larger brain lesions of the patients in this group, in particular, to MTL regions (for scan rating details, see Lee et al., 2005). Given that this study investigated perceptual skills beyond declarative memory, however, any performance differences between the MTL and HC groups are unlikely to reflect differences in these mnemonic abilities. Similarly, since both patient groups possessed intact visual perception as assessed by standard perceptual tests, any experimental task differences cannot be explained by any variations in basic visual perception.

Ten young (age = 47.0 yrs; education = 13.2 yrs) and eleven elderly (age = 66.4 yrs; education = 12.1 yrs) healthy subjects matched to the HC group and the MTL group, respectively, were recruited for Expt. 1, while seven young (age = 48.1 yrs; education = 12.7 yrs) and nine elderly healthy subjects (age = 66.8 yrs; education = 12.1 yrs) were recruited for Expt. 2. There were no significant differences in terms of age and education between the hippocampal patients and their matched controls (Expt. 1: both $t < 0.4$, $P > 0.6$; Expt. 2: both $t < 1.3$, $P > 0.2$) and the MTL patients and their matched controls (Expt. 1: both $t < 0.3$, $P > 0.8$; Expt. 2: both $t < 0.4$, $P > 0.7$). Thus, any task performance differences between the patients and their respective controls could not be attributed to differences in age or education.

Informed consent was received from all subjects and this study received ethical approval from the Cambridge and Southampton Health Authority Local Research Ethics Committees (UK).

Experimental Tasks

The patients were tested either at their own home or at the Wessex Neurological Centre, Southampton General Hospital, UK. All the tests were computerized tasks developed from a subset of the tests used by Buckley et al. (2001) in monkeys and were conducted on a 15″ SVGA LCD touchscreen at 800 × 600 resolution. Subjects were seated in front of the screen so that they could comfortably touch it during testing and were given an opportunity to familiarize themselves with the screen prior to the start of the experimental conditions. Clear instructions were given to the subjects before each task and a few practice trials were also administered so as to ensure that the subjects had understood the instructions. All the tasks were based on an oddity paradigm in which the subjects were instructed to select the odd one out from an array of stimuli, as quickly but as accurately as possible, by touching it with the index finger of their dominant hand. Both response accuracy and response times were recorded.

Experiment 1

Six oddity tasks were used in the first study (Fig. 2): color, size, and shape, on which performance was not dependent on perirhinal cortex in monkeys (Buckley et al., 2001), and face, novel object, and familiar object, on which performance was dependent on perirhinal cortex in monkeys (Buckley et al., 2001). In the original monkey oddity study (Buckley et al., 2001), previously unseen objects and objects with which the monkeys had prior experience were intermixed in the same task, with no significant difference in performance between these two types of object. In all of the Expt. 1 tests, the subjects were presented with six stimuli in two rows of three, five of which were of the same stimulus and one of which was different. On each trial, the positions of each of the six stimuli were randomized between each of the positions in the 2 × 3 array. The six oddity tasks were administered in a counterbalanced order across all the subjects.

Fifty trials were administered for the following tasks.

Color

Six colored squares of dimensions 128 × 128 pixels were presented on a black background (Fig. 2a). Nine colors were used: a base color comprised an equal mix of red and green, and eight alternative colors, four of which differed along the "green" dimension relative to the base color and another four varied in terms of the amount of red they contained. On each trial, either five stimuli were the base color and one stimulus was an alternative color or one stimulus was the base color and the other five stimuli were of an alternative color. A flicker fusion technique was used in human subjects to equate luminance in all six squares.

Size

Six black squares outlined in green were presented on a black background (Fig. 2b). The length of each side was randomly varied from 30 to 128 pixels (99 possible sizes) and in each trial, either five identical smaller squares were shown with one larger square or five identical larger squares were shown with one smaller square. The difference between the two sizes was predetermined at 4, 8, 16, 32, or 64 pixels.

Shape

Six green colored polygons of equal surface area and ranging from 3 to 10 sides were presented on a black background (Fig. 2c). In each trial, five polygons possessed the same number of sides and one polygon either had two more or two less sides. There were six possible pairings in any trial: 3- vs. 5-sided polygons, 4- vs. 6-sided polygons, 5- vs. 7-sided polygons, 6- vs. 8-sided polygons, 7- vs. 9-sided polygons and 8- vs. 10-sided polygons. Furthermore, in each trial, the orientations of the polygons were fixed at a random angle of rotation around a central axis.

For the tasks below, digitized greyscale photographic images (256 levels of gray, 128 × 128 pixels) were presented on a gray background and a total of 100 trials (10 successive blocks of ten trials) were administered for each task. Each stimulus was repeated across the 10 blocks to allow the assessment of learning.

Face

Six images of human faces were presented for each trial (Fig. 2d). A set of 20 unfamiliar (e.g., nonfamous) male faces (all Caucasian aged 20–40 yrs, with short hair, no facial hair, or spectacles) was used and for each of these, six different views were captured: face looking directly ahead; face looking upwards (e.g., head tilted back); face looking 45° to the left; face looking 45° to the right; face looking up and 45° to the left; and finally, face looking up and 45° to the right. In each trial, all six views were represented with five images of different views of one face and one image of one view of another person's face. Each face was presented only once in each block of 10 trials (10 times in total), while across the 100 trials, each face was always randomly paired with another face.

Novel object

Six images of objects uncommon to everyday life were presented for each trial (Fig. 2e). A set of 20 objects was used. Each

object was photographed in five different nonspecific orientations. In each trial, the five views of one object were presented with one view of another object. Furthermore, similar to the face oddity task, each object was presented only once in each block of 10 trials (10 times in total), while across the 100 trials, each object was always randomly paired with another object.

Familiar object

This task was identical to the novel object task except that six images of objects common to everyday life (e.g., kitchen utensils, office stationery) were presented for each trial (Fig. 2f).

Experiment 2

While the face and object tasks of Expt. 1 involved repeating stimuli in order to assess the possibility of learning, the second study involved four trial-unique oddity tasks (Fig. 3). Thus, any patient deficits in these tasks are unlikely to be explained by difficulties in learning individual stimuli across trials. Performance on two of the tasks, "face same views" and "scene same views," placed a minimal demand on object and spatial scene perception, respectively, since a successful oddity judgment on these tasks was not dependent on the subjects being able to use a complete viewpoint independent representation of a face/scene (e.g., a face same views discrimination could be made by directly matching the four simultaneously presented faces). Subsequently, we predicted that these two tasks were not dependent on the perirhinal cortex or hippocampus. In contrast, object and spatial scene perception were emphasized in the other two tasks, "face different views" and "scene different views," since the subjects were required to use complete three-dimensional representations of faces and scenes within each trial (e.g., be able to identify the same face/scene from different vantage points). In all of these tests, the subjects were presented with four stimuli in two rows of two, three of which were of the same stimulus and one of which was different. On each trial, the positions of each of the four stimuli were randomized between each of the positions in the 2 × 2 array. The four oddity tasks each consisted of 31 trials (with each stimulus only appearing once in each task) and were administered in a counterbalanced order across all the subjects. Via extensive piloting in healthy control subjects, the two different views tasks were matched in terms of difficulty, as were the two same views tasks. It was, however, not possible to match difficulty across the same and different views tasks.

Face same views

Four images of human faces were presented for each trial on a gray background (256 levels of gray, 128 × 128 pixels) (Fig. 3a). A set of 62 unfamiliar (e.g., nonfamous) male faces was used and for each of these, six different views were captured (see Study 1 methods). In each trial, two views were presented, with three images of the same view of one face and one image of a different view of another face. Each face was presented only once and was paired with a second face matched for skin color, similar face structure, hairstyle, and facial hair (all subjects were presented with the same pairings).

Virtual scene same views

Four images of virtual reality scenes were presented for each trial on a gray background (256 levels of gray, 460 × 370 pixels) (Fig. 3b). A set of 62 scenes, created using a commercially available computer game (Deus Ex, Ion Storm L.P., Austin, TX) and a freeware software editor (Deus Ex Software Development Kit v1112f), was used and for each scene, four different views were captured. In each trial, two views were presented, with three images of the same view of one scene and one image of a different view of another scene. Each scene was presented only once and was always paired with the same scene that was similar in appearance and only differed with respect to the dimensions or placement of one or more aspects of the scene (e.g., a wall, window, room cavity).

Face different views

This task was identical to the "face same views" task except that on each trial, three different views of the same face were paired with another view of a different face (Fig. 3c).

Virtual scene different views

This task was identical to the "virtual scene same views" task except that on each trial, three different views of the same scene were paired with another view of a different scene (Fig. 3d).

RESULTS

Experiment 1

The performance accuracy data for the four subject groups on the color, size, shape, face, novel object, and familiar object oddity tasks (shown as percentage error in Fig. 4) were subjected to a repeated measures analysis of variance (ANOVA). A single within-subject factor of "Task" was incorporated with six levels corresponding to the six tasks. Given that the subject groups were structured (i.e., the young controls were chosen to match the hippocampal patients and the elderly controls were selected to match the MTL patients), two between-subject factors, each with two levels, were included: (1) "Health" with the levels Patient (incorporating both patient groups) and Control (incorporating both control groups); and (2) "Lesion Type" with the levels Hippocampal (incorporating the HC group and their matched controls) and MTL (incorporating the MTL group and their matched controls). This analysis showed that the interaction between "Health" and "Lesion Type" was significant ($F(1,24) = 5.997$, $P = 0.022$), suggesting that across all six tasks, the difference between the MTL group and their matched controls was significantly greater than that between the hippocampal patients and their respective controls. To investigate this interaction further, we performed t tests to compare the overall performance of each patient group with their

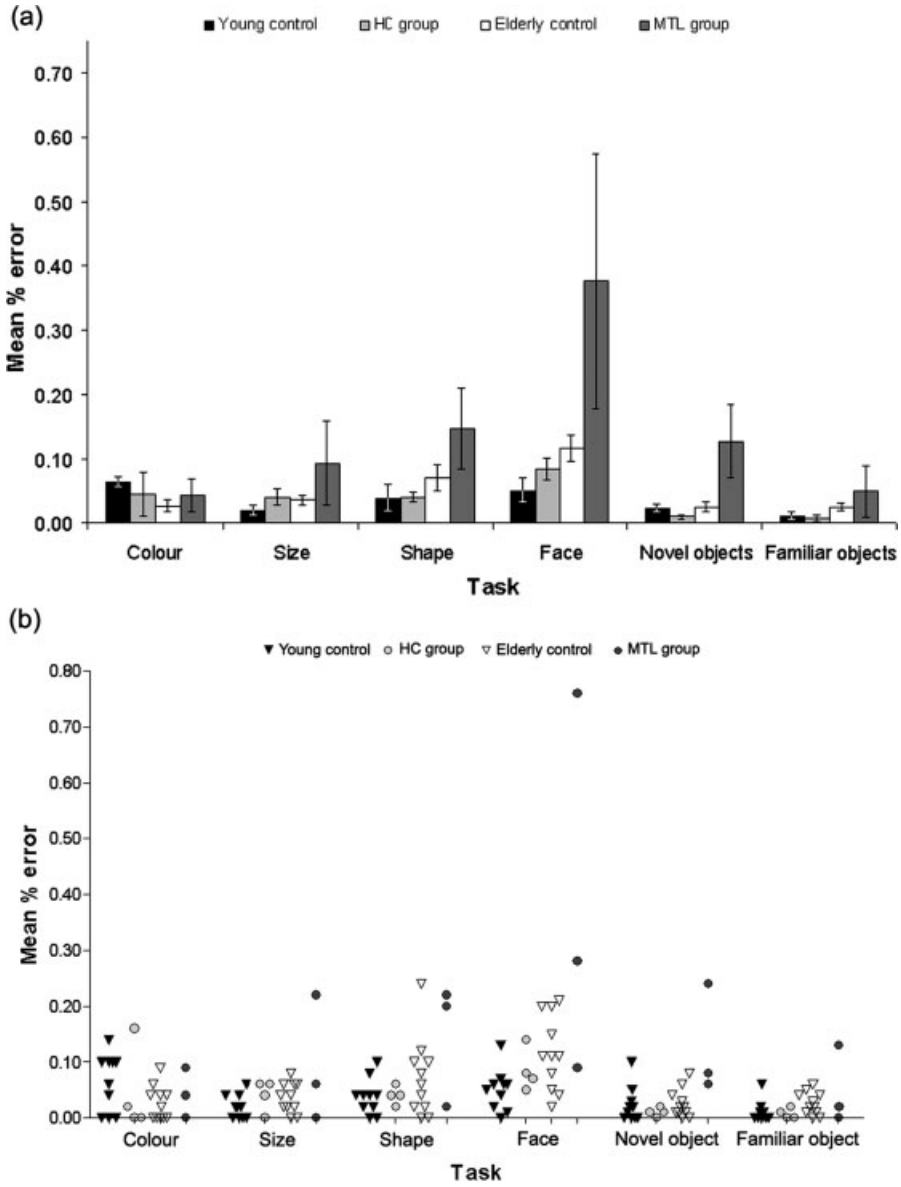

FIGURE 4. (a) Mean percentage error (±standard error) for the four subject groups on the Expt. 1 oddity tasks (chance performance = 75% error; young controls age-matched to HC group, elderly controls age-matched to MTL group). (b) Scores of individual subjects.

own control group. These *t* tests showed that the MTL group performed significantly worse, overall, than their control group ($t(12) = 2.51$, $P = 0.014$, 1-tailed) but the HC group were not significantly impaired, overall, compared with their control group ($t(12) = 0.55$, $P = 0.296$, 1-tailed).

In the ANOVA described above, the three-way interaction between "Health," "Lesion Type," and "Task" was also significant ($F(5,120) = 2.94$, $P = 0.016$). This interaction revealed that the difference between the MTL group performance compared with the old control group and the HC group performance compared with the young control group varied in magnitude across the six tasks. To investigate this further, the results from each individual task were analyzed separately in univariate ANOVAs. For each ANOVA, the same two between-subject factors of "Health" and "Lesion Type" were included with a dependent variable of performance. The interaction between "Health" and "Lesion Type" was significant in the face task ($F(1,24) = 5.25$, $P = 0.031$) and in the novel object task ($F(1,24) = 11.50$, $P = 0.002$), but not in the color, size, shape, or familiar object tasks (all $F(1,24) < 2$, $P > 0.1$). Within each of the two tasks that showed an interaction between "Health" and "Lesion Type," we then performed *t* tests to compare the performance of each patient group with their own control group. In the face task, the MTL patients performed significantly worse than their control group ($t(12) = 2.60$, $P = 0.012$, 1-tailed), while the HC group patients were not significantly different from their control group ($t(12) = 1.59$, $P = 0.070$, 1-tailed). Similarly, in the novel object task,

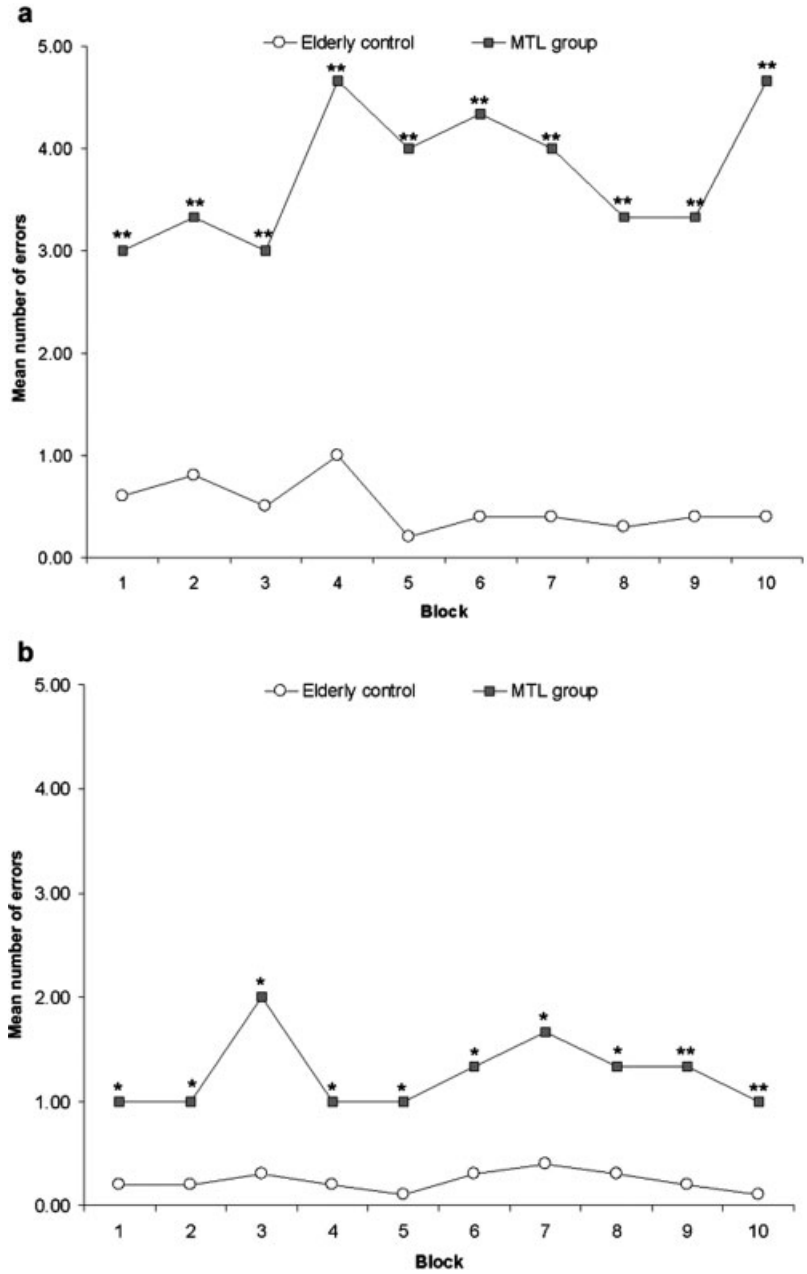

FIGURE 5. Mean percentage error for the MTL patient and elderly control groups across the 10 blocks of the (a) faces and (b) novel objects oddity tasks (Expt. 1). Significant differences between these two subject groups are indicated by asteriks ($*P \leq 0.05$, $**P < 0.01$).

the MTL group were significantly impaired compared with their control group ($t(12) = 3.34$, $P = 0.003$, 1-tailed) but there was no significant difference between the hippocampal patients and their controls ($t(12) = 0.79$, $P = 0.222$, 1-tailed). These t tests demonstrated that the significant interaction between "Health" and "Lesion Type" in the face and novel object tasks arose because the MTL patients were impaired on these tasks, while the hippocampal patients performed within the normal range.

Given that each stimulus in the face and object tasks was presented 10 times across 100 trials (once in each block of 10 trials; see Methods), the profiles of performance of the MTL group and their respective controls throughout the duration of the faces and novel objects conditions were examined further. Within group t tests to compare task accuracy across the first and second halves of these conditions revealed that the elderly control subjects improved marginally across the duration of the face condition (an average of 0.24 fewer errors; $t(9) = 3.09$, $P = 0.013$), but not the novel object condition (an average of 0.06 more errors; $t(9) = 1.15$, $P = 0.279$). In contrast, the MTL group performed similarly throughout the 10 blocks of both these conditions (both $t(2) < 2$; $P > 0.1$). Importantly, however, for both the faces and novel objects conditions, there was a significant difference between the controls and MTL

group even on the first block of 10 trials (both $t(11) > 2$; $P < 0.03$; see Fig. 5). This suggests that it is unlikely that the deficits observed in the MTL group on the faces and novel objects conditions were entirely due to learning present only in the elderly control group.

Experiment 2

The performance accuracy data for the four subject groups on the face same views, virtual scene same views, face different views, and virtual scene different views tasks (shown as percentage error in Fig. 5) were subjected to a similar repeated measures ANOVA, as described earlier. The same two between-subject factors of "Health" and "Lesion Type" were incorporated along with two within-subject factors of "Stimuli" (faces vs. scenes) and "Viewpoint" (same views vs. different views). This analysis showed that there was a significant interaction between "Health," "Lesion Type," "Stimuli," and "Viewpoint" ($F(1,19) = 6.52$, $P = 0.019$). To investigate this further, the results from each individual task were analyzed separately in univariate ANOVAs with the two between-subject factors of "Health" and "Lesion Type" and a dependent variable of performance. The interaction between "Health" and "Lesion Type" was significant in the face different views task ($F(1,23) = 9.74$, $P = 0.006$), and t tests to compare the performance of each patient group with their own control group revealed that this interaction was due to a significant impairment in the MTL group ($t(10) = 4.00$, $P = 0.002$, 1-tailed), but not the HC group ($t(9) < 0.3$, $P = 0.388$, 1-tailed). In contrast, there was no significant "Health" by "Lesion Type" interaction in the face same views, scene same views, and scene different views tasks (all $F(1,23) < 0.4$, $P > 0.5$), indicating that the performance of both patient groups was similar to each other when compared with their respective controls. In the two same views tasks, there was no significant effect of "Health" (both $F(1,23) \leq 4$, $P > 0.05$), and t tests between each patient group and their own control group confirmed that on these two tasks, both patient groups performed within the normal range (both $t < 2$, $P > 0.07$, 1-tailed). On the other hand, the factor of "Health" was significant in the scene different views task ($F(1,23) = 22.68$, $P < 0.0001$) and t tests indicated that both patient groups were significantly impaired on this condition (both $t > 3$, $P < 0.004$, 1-tailed).

It is important to highlight that as all of the tasks in Expt. 2 were trial-unique (no stimulus was presented more than once in each condition; see Methods), it is highly unlikely that the patient deficits on the scene different views task and faces different views task can be explained by the learning of stimuli across trials in the controls only.

DISCUSSION

We have demonstrated that lesions to the human MTL can produce compelling deficits on a series of visual discrimination tasks. Amnesic patients with selective hippocampal lesions or larger MTL lesions, including the perirhinal cortex and hippocampus, were all unimpaired on oddity tasks that were previously shown to be insensitive to perirhinal cortex damage in monkeys (Buckley et al., 2001) and could be solved on the basis of simple features (Expt. 1: color, size, shape). Moreover, these patients exhibited normal performance on tests that involved complex scenes or faces but did not demand viewpoint independent perception (Expt. 2: face same views, scene same views). The MTL group patients, however, performed significantly poorer than age-matched elderly controls on oddity tasks that were susceptible to perirhinal cortex damage in monkeys (Buckley et al., 2001) and emphasized viewpoint independent object perception (Expt. 1: face, novel object, Expt. 2: face different views), whereas the HC group patients performed normally on all of these tasks. It is important to note that the face oddity task in Expt. 2 was more difficult than that in Expt. 1, with all control subjects making more errors in the former. Critically, however, the HC group patients performed within the normal range in both tasks, in fact making fewer errors than their control group on the more difficult version in Expt. 2 (see Fig. 6). Both patient groups demonstrated a significant deficit on an oddity task that placed a high demand on viewpoint independent scene perception (Expt. 2: scene different views).

Considering that the oddity tasks in this study did not place an explicit demand on long-term declarative memory, our findings may be interpreted in a number of ways. One explanation is that an impairment in visual short-term memory may underlie the patient deficits. This is because each oddity discrimination required the subjects to fixate on each stimulus in a presented array sequentially. Thus, when more complex stimuli were involved (e.g., faces and scenes presented from different viewpoints), it is conceivable that a greater demand was placed on visual working memory maintenance to enable comparisons across images. Further investigations will be required to investigate this possibility, although it is important to note that MTL lesions are not commonly associated with generic working memory difficulties (Cave and Squire, 1992; Rempel-Clower et al., 1996; see, however Ranganath and D'Esposito, 2001; Ranganath and Blumenfeld, in press). An alternative explanation is that while the patients may suffer from difficulties in object and/or scene working memory, these problems may, in fact, reflect a primary deficit in perception for these stimulus categories, for instance, the processing of feature conjunctions (Murray and Bussey, 1999; Bussey and Saksida, 2002; Bussey et al., 2002) or the formation of viewpoint independent stimulus representations (Buckley et al., 2001). This account would predict difficulties in tasks involving the types of stimuli reported here, irrespective of whether any significant demands are placed on working or long-term memory.

The Role of the Perirhinal Cortex in Object Perception

The present findings differ from those of earlier studies that failed to observe a deficit in patients with perirhinal cortex damage on simultaneous and short delay conditions in visual

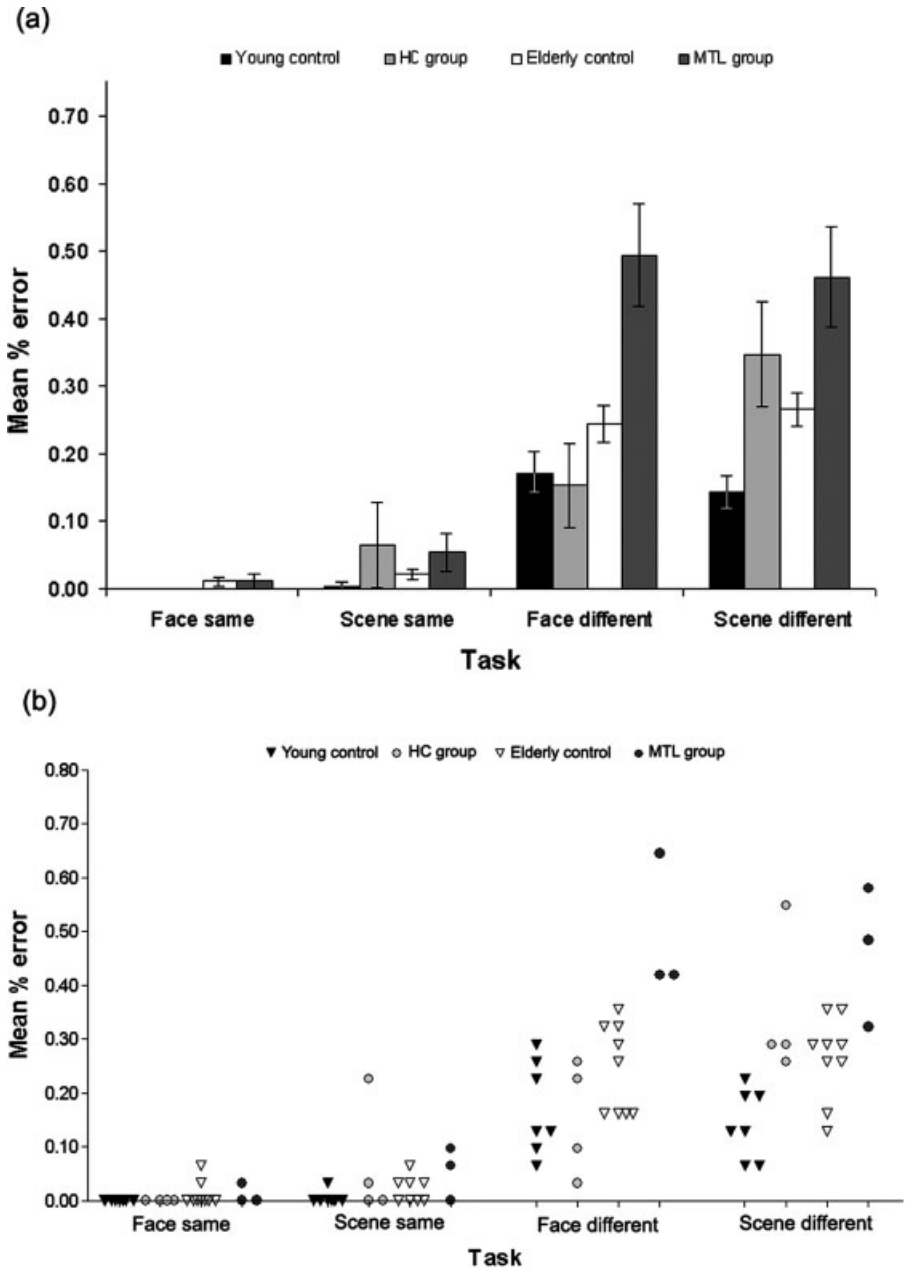

FIGURE 6. (a) Mean percentage error (±standard error) for the four subject groups on the Expt. 2 oddity tasks (chance performance = 75% error; young controls age-matched to HC group, elderly controls age-matched to MTL group). (b) Scores of individual subjects.

matching to sample tasks (Buffalo et al., 1998; Holdstock et al., 2000a). It is possible that these earlier studies used stimuli (e.g., two-dimensional abstract patterns of varying shapes, colors, and lines) that placed an insufficient demand on the types of perceptual processes that have been attributed to the perirhinal cortex in monkeys (Buckley et al., 2001; Bussey and Saksida, 2002; Bussey et al., 2002, 2003). Consequently, the patients reported in these articles could have solved the tasks primarily on the basis of simple feature discrimination, just as our patients here were able to perform difficult color, size, and shape oddity judgments. Importantly, both patient groups in this study also performed normally on standard tests of perception (e.g., Benton face task, VOSP battery), suggesting that these tasks are not dependent on the lesioned MTL structures in these patients. This may also explain why, to date, there has been limited evidence from the neuropsychological literature to suggest that MTL damage in humans can lead to difficulties in perception (for review, see Lee et al., in press).

This explanation, however, cannot reconcile the findings of the present study with a previous experiment that used similar oddity tasks and yet failed to find impairments in their patients on object discrimination (Stark and Squire, 2000). Two factors

probably contribute to this disparity. First, the aforementioned study (Stark and Squire, 2000) used a combination of novel and familiar objects in their object oddity tasks. As demonstrated here, this can have a significant effect on the discrimination of objects: the MTL group was significantly impaired on the face and novel object oddity tasks, but not the familiar object task in Expt. 1. One possible explanation for this finding is that semantic knowledge about the highly familiar objects (of which existing perceptual representations may be a critical component) facilitated performance on the familiar object task, leading to faster response times and significantly improved task accuracy. In support of this, there have been recent reports that semantic knowledge can influence performance on visual processing tasks, for example, by aiding the perception of object silhouettes (Hovius et al., 2003) or impeding performance on a visual search task if the target and distractor items are semantically associated (Moores et al., 2003).

A second contributory factor to the disparity between the present experiment and a previous study (Stark and Squire, 2000) that used similar tasks is the difference in stimulus set size. The tasks in Expt. 1 comprised 10 stimulus-unique trials (a set of 20 items, each randomly paired with another). In contrast, 62 stimuli were used in each task of Expt. 2 to create 31 stimulus-unique trials. In the previous investigation (Stark and Squire, 2000), only sets of 10 stimuli were used. It has been demonstrated that employing a large stimulus set size is critical for eliciting impairment in visual concurrent discrimination tasks in monkeys with perirhinal cortex ablations (Buckley and Gaffan, 1997); the successful discrimination of items within a larger set may require more precise perceptual representations, for example, due to a higher degree of feature overlap between stimuli across trials (Buckley and Gaffan, 1997; Buckley, in press; Hampton, in press).

Since the performance of all subject groups on the novel object task was comparable or better than that on the color, shape, and size oddity tasks (Expt. 1), the observed MTL group impairment on the novel object and face tasks cannot be only due to their increased difficulty. In terms of learning, the elderly group did demonstrate a very small performance improvement across the faces condition (a decrease of one quarter of an error over 100 trials). This, however, cannot explain entirely the MTL group deficits, since (a) the elderly control group's performance did not improve across the duration of the novel objects condition; (b) in both the faces and novel objects conditions there was a significant difference between the MTL group and their respective controls from the very first 10-trial block of the tasks (see Fig. 5); and finally, (c) the finding of a MTL group deficit in face oddity judgment in Expt. 1 was replicated in Expt. 2 in which no stimulus was presented more than once in each condition.

Since the MTL group possessed atrophy to temporal lobe regions beyond the perirhinal cortex, it is important to evaluate how these areas may potentially contribute to the observed deficit in object/face oddity judgment. One possible argument is that the MTL group patients' impairment may be primarily due to damage to higher processing visual areas such as area TE or the FFA (Kanwisher et al., 1997). There are, however, a number of concrete reasons to argue against this possibility.

First, structural scan ratings (see Methods; Table 1) revealed no significant difference between the MTL group and a healthy control group on a lateral temporal lobe rating. While it is currently unclear what region in the human brain corresponds to area TE, as first identified in the macaque brain (Von Bonin and Bailey, 1947; Seltzer and Pandya, 1978), area TE in macaques is known to occupy the inferior and middle temporal gyri, the latter of which was included in our lateral temporal lobe rating. In fact, two of the three MTL group patients were adjudged to have no additional lateral temporal lobe atrophy in comparison with a control group, and yet these patients were impaired on the novel object and face oddity tasks in Expt. 1 and the face different views task in Expt. 2.

Second, although the MTL group did have significant damage to a medial inferior temporal lobe region adjacent to the perirhinal cortex (i.e., medial bank of the occipitotemporal sulcus, see Methods), their performance profile on the oddity tasks do not match existing knowledge of the effects of damage to area TE in nonhuman primates. It has been demonstrated that lesions to area TE in monkeys disrupts fine color discrimination (Buckley et al., 1997). Furthermore, single-unit recordings have suggested that cells in this region represent moderately complex visual features, such as those in the simple feature oddity tasks (Expt. 1), but not objects (Tanaka, 1996). In the current study, the MTL group patients were not impaired on the simple feature oddity tasks, including judgments for color oddity, implicating intact functioning of area TE. This mirrors the original findings of Buckley et al. (2001) who found that performance on simple feature oddity tasks was not disrupted following perirhinal cortex ablations in monkeys.

Third, and more importantly, we found in the present study that the MTL group patients performed within the normal range on a task that involved faces but did not place a demand on viewpoint independent perception (Expt. 2: face same views). A similar finding has been reported in monkeys with perirhinal lesions (Buckley et al., 2001). These results underline the notion that lesions to perirhinal cortex do not cause a general perceptual deficit and argue against the possibility that the observed deficits are due to damage to regions more posterior in the temporal lobe, such as the FFA in humans. Moreover, the MTL group patients do not suffer from symptoms such as prosopagnosia that are often associated with lesions to the FFA (Barton et al., 2002). It is important to note, however, that all subject groups performed at or close to ceiling on the face same views task. It is possible, therefore, that a more difficult version of this task may lead to deficits in the MTL patient group.

Given that the MTL patients have larger lesions compared with the HC group (see Table 1), one possible explanation is that it is the increased damage to the hippocampus, rather than other MTL structures, that is causing the additional MTL group deficits in face and novel object oddity judgment. Evidence against this suggestion comes from a recent study in our group (Lee et al., unpublished observations) in which the same oddity battery in Expt. 1 was administered to patients with

semantic dementia (SD), a condition associated with progressive, cross-modal loss of semantic knowledge (Warrington, 1975; Snowden et al., 1989; Hodges et al., 1992) and disproportionate atrophy to the perirhinal cortex compared with other MTL structures (Davies et al., 2004), and patients with Alzheimer's disease (AD), who typically have less atrophic perirhinal cortex but severe damage to the hippocampus (Davies et al., 2004). It was found that the SD patients demonstrated a similar performance profile to the MTL group (impaired object, but not simple feature, perception). In contrast, the AD patients performed well on all tasks in spite of possessing hippocampal atrophy, an identical pattern to that seen in the HC group reported here. These findings suggest that damage to the perirhinal cortex is likely to underlie the MTL group deficits observed in the current study, rather than the larger hippocampal lesions in these patients. It is important to note, however, that similar to SD patients, the MTL patients in the present study possessed significant damage to the anterior temporal lobe (Table 1). Although the perirhinal cortex is known to extend into the temporal pole in humans (Insausti et al., 1998), it is currently impossible to clarify the possible contribution of other anterior temporal lobe regions to the perceptual processes that have been attributed to the perirhinal cortex in monkeys, and to determine whether these regions may also be critical for these processes.

Given the replicability of the findings across different patient groups, plus the striking convergence in the behavioral patterns seen in human patients and monkeys with perirhinal cortex involvement, it seems reasonable to hypothesize that the perirhinal cortex may be critically involved in object perception. As described in the Introduction, one model of perirhinal cortex function (Murray and Bussey, 1999) is that it processes complex conjunctions of object features (i.e., representation of complete objects), while more caudal regions such as area TE/TEO and V4 process moderately complex conjunctions (e.g., Tanaka, 1996, 2003) and simple features. Although there has been support for this model from recent monkey lesion (Bussey et al., 2002, 2003) and computational modeling (Bussey and Saksida, 2002) studies, the precise details of this view remain to be determined. For example, it is uncertain how the perirhinal cortex may, as the suggested apex of the ventral processing stream, exert top–down influence on earlier regions such as area V4. With respect to our present data, it is not obvious how the ability to process complex conjunctions of features contributes to the perception and identification of objects from multiple viewpoints, as assessed in the oddity tasks. There are, however, indications that the object perception impairments in our patients cannot be explained entirely by an impairment in forming viewpoint independent representations of objects. For instance, in Lee et al. (2005) the same MTL group patients had a deficit in the discrimination of faces, and to a lesser extent objects, that were blended to various degrees but did not place a demand on viewpoint independent perception. Furthermore, we have data to suggest that when the degree of feature overlap between two stimuli is controlled systematically, it is possible to observe deficits in the discrimination of two-dimensional stimuli when the level of feature overlap is high but not when it is low (Lee et al., in press; Barense et al., 2004).

One important question is whether the neural mechanisms that mediate object perception in the perirhinal cortex are similar to those that underlie the declarative memory functions of this region, for example, recognition on the basis of familiarity and memory for stimulus–stimulus associations (Meunier et al., 1993; Murray et al., 1993; Eacott et al., 1994; Buckley and Gaffan, 1998a; Aggleton and Brown, 1999; Henson et al., 2003). Although our two patient groups demonstrated similar levels of performance on immediate and delayed recall of a story and complex figure (see Methods), their scores on tests of recognition memory were discrepant: the HC group showed normal performance on the recognition memory test for faces (mean score = 91.2%), while the MTL group were significantly impaired (mean score = 62.0%). This result is consistent with the view that familiarity-based processes that might support recognition memory but not recall are dependent upon nonhippocampal regions such as the perirhinal cortex (Meunier et al., 1993; Murray et al., 1993; Eacott et al., 1994; Buckley and Gaffan, 1998a; Aggleton and Brown, 1999; Henson et al., 2003; Henson, in press). Importantly, however, the finding of impaired perceptual processing of novel faces in our current study and poor recognition memory for faces does not necessarily mean that these deficits are caused by the same neural impairment.

Some indication of whether the same neuronal mechanisms underlie both perceptual and declarative memory processes in the perirhinal cortex come from nonhuman primate electrophysiological studies. These have demonstrated that there are perirhinal neurons that decrease their firing in response to subsequent presentations of unfamiliar objects (Brown et al., 1987; Li et al., 1993; Sobotka and Ringo, 1993), and it has been suggested that this mechanism may constitute the neural basis of recognition memory (for review, see Brown and Xiang, 1998). There are also, however, neurons that possess stimulus-specificity but do not exhibit decremental response patterns (Xiang and Brown, 1998), and moreover, studies have shown that recognition memory can be dissociated from the decremental response properties of some perirhinal neurons (Sobotka and Ringo, 1996). This suggests that there may be a variety of neural mechanisms that make distinct contributions to the mnemonic and perceptual processes that the perirhinal cortex has been suggested to subserve.

The Role of the Hippocampus in Spatial Perception

Both amnesic patient groups showed significant difficulties making oddity judgments for scenes when they were required to perceive the spatial arrangement of a virtual room using the information available from different views (Expt. 2: virtual scene different views). This observation converges with findings from our previous study in which we found that hippocampal damage resulted in a significant impairment in the visual discrimination of pairs of spatial scene images that were blended

to create different levels of feature overlap (Lee et al., 2005). Importantly, the use of trial-unique tasks in the current study (Expt. 2) rules out the possibility that the reported deficit in spatial perception in these patients is due to learning effects that were present in the controls but not the patients (a possible confounding factor in our earlier study, Lee et al., 2005). Thus, this demonstration of a striking, and selective, deficit in scene discrimination across two separate studies supports the suggestion that the human hippocampus may play a critical role in space perception.

This contrasts with recent investigations that propose that it is the neighboring parahippocampal cortex, more specifically the PPA (Epstein and Kanwisher, 1998), that is crucial for processing spatial information, for example, the layout and appearance of spatial scenes (Epstein et al., 1999). One possibility is that the deficits in spatial perception observed in our amnesic patients may be caused by additional damage to the PPA rather than hippocampal dysfunction. Two pieces of evidence seem to rule out this possibility. First, both the HC and MTL patient groups performed within the normal range on a task that involved complex images of virtual scenes, but could be solved using simple features (e.g., size of a wall; Expt. 2: virtual scenes same views). This suggests that the patients did not have a deficit in perceiving scenes per se, but rather had difficulties making judgments that required processing spatial information about the room layout. Second, none of the patients had damage that was obviously near or in the PPA, and there was no significant difference between the controls and patients in any structural rating other than that for the hippocampus (including an anterior parahippocampal gyrus region). Consequently, one may conclude that both the hippocampus and parahippocampal cortex are important for spatial perception, although further studies will be needed to clarify the differential roles played by these two regions.

Our observation of an impairment in discriminating different, but not same, views scenes following hippocampal damage supports and expands upon recent studies by King et al. (2002, 2004), which found that a single hippocampal lesion patient was only mildly impaired at recognizing object locations that were viewed from the same viewpoint as that during the learning phase, but was severely impaired when the object locations were viewed from a different viewpoint from that at learning. Our study suggests that the deficits reported by King et al. (2002, 2004) can be evident in a task without an overt declarative memory component and that hippocampal damage may lead to deficits in perceiving, as well as remembering, spatial scenes. It is important to note that the hippocampal case reported by King et al. (2002, 2004) was able to perform mental rotation of single objects and that our hippocampal patients were able to perform oddity judgments of different views faces (Expts. 1 and 2) and objects (Expt. 1). This reinforces the idea that the deficits observed in our patients are unlikely to be due to a fundamental deficit in mental rotation. Rather, it appears that patients with hippocampal damage may be unable to use viewpoint independent representations of spatial scenes, often referred to as allocentric representations (e.g., see Aguirre and D'Esposito, 1999; Holdstock et al., 2000b; Burgess et al., 2001; Bohbot et al., 2004; Feigenbaum and Morris, 2004; King et al., 2004).

It is important to highlight that while the present study has demonstrated impaired allocentric scene perception in patients with damage to the hippocampus, it is unlikely that this deficit can account entirely for the spatial memory and perception deficits often seen following hippocampal dysfunction in humans and nonhuman primates. For instance, in our previous study, both the HC and MTL patient groups were significantly impaired in a scene discrimination task that did not require allocentric scene perception (Lee et al., 2005). Also, hippocampal dysfunction in monkeys, by means of fornix transection, can result in deficits in learning conjunctions of spatial information: for example, the association between tail orientation, length, and spatial location of tadpoles within a two-dimensional scene (Buckley et al., 2004). In addition to this, recent functional neuroimaging studies have demonstrated activity in the hippocampus during memory tasks for spatial configuration, on which successful performance also does not depend on allocentric processing (e.g., Duzel et al., 2003; Pihlajamaki et al., 2004).

The possibility of perceptual deficits following hippocampal damage raises the question as to what the functional consequences may be for patients in everyday life. Given that we have demonstrated that patients with hippocampal damage are able to discriminate scenes presented from the same view, it is likely that any difficulties in real life will only be evident in the rare circumstances where the patients are, for example, exposed to multiple environments that are highly similar. One controversial suggestion is that the mnemonic deficits commonly seen after hippocampal damage (Tulving and Markowitsch, 1998; Spiers et al., 2001) may actually be the result of a primary deficit in spatial perception (Horel, 1978; Gaffan, 2001;). While the current study clearly indicates a contributory role for the hippocampus in processing spatial information, it does not necessarily mean that this is the sole role of the hippocampus in memory and perception. For example, it is difficult to see how deficits in the recall of a prose passage can be caused by such spatial difficulties. Given the broader profile of amnesia, therefore, it seems possible that the deficits described here reflect a more general impairment in relational or associative processing, of which computing relationships between the objects and features constituting a scene is a part (Eichenbaum et al., 1992, 1994; Cohen et al., 1999; Eichenbaum and Cohen, 2002). Critically, however, the latter process is thought to be specific to memory, involving binding perceptually distinct items (e.g., objects) into long-term memory representations (Eichenbaum et al., 1992, 1994; Eichenbaum and Cohen, 2002). One suggestion, therefore, is that the patient deficits in the scene different views task may actually be a reflection of long-term relational memory difficulties. For example, it is conceivable that within each trial, the healthy controls may have benefited from the ability to encode the spatial relations within each scene into long-term declarative memory (i.e., "memory facilitated perception"). Further studies will be required to explore the exact

details of this idea further and hopefully clarify what aspects of relational and/or spatial processing are dependent upon the hippocampus. In addition, it will be important to determine whether these types of processing can be extended beyond the domain of long-term declarative memory, as indicated by our recent studies.

In summary, we have demonstrated that lesions to the human perirhinal cortex can lead to difficulties in object, including face, oddity judgment, while lesions to the human hippocampus can cause difficulties in scene oddity judgment. Contrary to existing literature proposing a selective role for the human MTL in long-term declarative memory (Buffalo et al., 1998; Tulving and Markowitsch, 1998; Holdstock et al., 2000a; Spiers et al., 2001), this data confirms a broader role for the perirhinal cortex and hippocampus that extends to very short-term visual working memory at least, and possibly also perceptual processing, strongly supporting and extending recent findings from the nonhuman primate literature.

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REFERENCES

Aggleton JP, Brown MW. 1999. Episodic memory, amnesia and the hippocampal-anterior thalamic axis. Behav Brain Sci 22:425–489.

Aguirre GK, D'Esposito M. 1999. Topographical disorientation: a synthesis and taxonomy. Brain 122(Part 9):1613–1628.

Barense MD, Bussey TJ, Lee ACH, Rogers TT, Saksida LM, Murray EA, Hodges JR, Graham KS. 2004. Differentiating the components of the medical temporal lobe: a critical role of feature ambiguity. Soc Neurosci Abst 201.13.

Barton JJ, Press DZ, Keenan JP, O'Connor M. 2002. Lesions of the fusiform face area impair perception of facial configuration in prosopagnosia. Neurology 58:71–78.

Bohbot VD, Iaria G, Petrides M. 2004. Hippocampal function and spatial memory: evidence from functional neuroimaging in healthy participants and performance of patients with medial temporal lobe resections. Neuropsychology 18:418–425.

Brown MW, Xiang JZ. 1998. Recognition memory: neuronal substrates of the judgement of prior occurrence. Prog Neurobiol 55:149–189.

Brown MW, Wilson FA, Riches IP. 1987. Neuronal evidence that inferomedial temporal cortex is more important than hippocampus in certain processes underlying recognition memory. Brain Res 409:158–162.

Buckley MJ. The role of the perirhinal cortex and hippocampus in learning, memory, and perception. Q J Exp Psychol B, in press.

Buckley MJ, Gaffan D. 1997. Impairment of visual object-discrimination learning after perirhinal cortex ablation. Behav Neurosci 111: 467–475.

Buckley MJ, Gaffan D. 1998a. Perirhinal cortex ablation impairs configural learning and paired-associate learning equally. Neuropsychologia 36:535–546.

Buckley MJ, Gaffan D. 1998b. Learning and transfer of object-reward associations and the role of the perirhinal cortex. Behav Neurosci 112:1–9.

Buckley MJ, Gaffan D, Murray EA. 1997. Functional double dissociation between two inferior temporal cortical areas: perirhinal cortex versus middle temporal gyrus. J Neurophysiol 77:587–598.

Buckley MJ, Booth MC, Rolls ET, Gaffan D. 2001. Selective perceptual impairments after perirhinal cortex ablation. J Neurosci 21:9824–9836.

Buckley MJ, Charles DP, Browning PG, Gaffan D. 2004. Learning and retrieval of concurrently presented spatial discrimination tasks: role of the fornix. Behav Neurosci 118:138–149.

Buffalo EA, Reber PJ, Squire LR. 1998. The human perirhinal cortex and recognition memory. Hippocampus 8:330–339.

Burgess N, Becker S, King JA, O'Keefe J. 2001. Memory for events and their spatial context: models and experiments. Philos Trans Roy Soc Lond B Biol Sci 356:1493–1503.

Burgess N, Maguire EA, O'Keefe J. 2002. The human hippocampus and spatial and episodic memory. Neuron 35:625–641.

Bussey TJ, Saksida LM. 2002. The organization of visual object representations: a connectionist model of effects of lesions in perirhinal cortex. Eur J Neurosci 15:355–364.

Bussey TJ, Saksida LM, Murray EA. 2002. Perirhinal cortex resolves feature ambiguity in complex visual discriminations. Eur J Neurosci 15:365–374.

Bussey TJ, Saksida LM, Murray EA. 2003. Impairments in visual discrimination after perirhinal cortex lesions: testing "declarative" vs. "perceptual-mnemonic" views of perirhinal cortex function. Eur J Neurosci 17:649–660.

Cave CB, Squire LR. 1992. Intact verbal and nonverbal short-term memory following damage to the human hippocampus. Hippocampus 2:151–163.

Cohen NJ, Ryan J, Hunt C, Romine L, Wszalek T, Nash C. 1999. Hippocampal system and declarative (relational) memory: summarizing the data from functional neuroimaging studies. Hippocampus 9:83–98.

Davies RR, Graham KS, Xuereb JH, Williams GB, Hodges JR. 2004. The human perirhinal cortex and semantic memory. Eur J Neurosci 20:2441–2446.

Duzel E, Habib R, Rotte M, Guderian S, Tulving E, Heinze HJ. 2003. Human hippocampal and parahippocampal activity during visual associative recognition memory for spatial and nonspatial stimulus configurations. J Neurosci 23:9439–9444.

Eacott MJ, Gaffan D, Murray EA. 1994. Preserved recognition memory for small sets, and impaired stimulus identification for large sets, following rhinal cortex ablations in monkeys. Eur J Neurosci 6:1466–1478.

Eichenbaum H, Cohen NJ. 2002. From Conditioning to Conscious Recollection: Memory Systems of the Brain. Oxford, UK: Oxford University Press.

Eichenbaum H, Otto T, Cohen NJ. 1992. The hippocampus–what does it do? Behav Neural Biol 57:2–36.

Eichenbaum H, Otto T, Cohen NJ. 1994. Two functional components of the hippocampal memory system. Behav Brain Sci 17:449–518.

Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham EA, Newman EL, Fried I. 2003. Cellular networks underlying human spatial navigation. Nature 425:184–188.

Epstein R, Kanwisher N. 1998. A cortical representation of the local visual environment. Nature 392:598–601.

Epstein R, Harris A, Stanley D, Kanwisher N. 1999. The parahippocampal place area: recognition, navigation, or encoding? Neuron 23:115–125.

Feigenbaum JD, Morris RG. 2004. Allocentric versus egocentric spatial memory after unilateral temporal lobectomy in humans. Neuropsychology 18:462–472.

Gaffan D. 2001. What is a memory system? Horel's critique revisited. Behav Brain Res 127:5–11.
Galton CJ, Gomez-Anson B, Antoun N, Scheltens P, Patterson K, Graves M, Sahakian BJ, Hodges JR. 2001. Temporal lobe rating scale: application to Alzheimer's disease and frontotemporal dementia. J Neurol Neurosurg Psychiatry 70:165–173.
Hampton RR. Monkey perirhinal cortex is critical for visual memory, but not for visual perception: reexamination of the behavioural evidence from monkeys. Q J Exp Psychol B, in press.
Hampton RR, Hampstead BM, Murray EA. 2004. Selective hippocampal damage in rhesus monkeys impairs spatial memory in an open-field test. Hippocampus 14:808–818.
Henson RN. A mini-review of fMRI studies of human medial temporal lobe activity associated with recognition memory. Q J Exp Psychol B, in press.
Henson RN, Cansino S, Herron JE, Robb WG, Rugg MD. 2003. A familiarity signal in human anterior medial temporal cortex? Hippocampus 13:301–304.
Hodges JR, Patterson K, Oxbury S, Funnell E. 1992. Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. Brain 115(Part 6):1783–1806.
Holdstock JS, Gutnikov SA, Gaffan D, Mayes AR. 2000a. Perceptual and mnemonic matching-to-sample in humans: contributions of the hippocampus, perirhinal and other medial temporal lobe cortices. Cortex 36:301–322.
Holdstock JS, Mayes AR, Cezayirli E, Isaac CL, Aggleton JP, Roberts N. 2000b. A comparison of egocentric and allocentric spatial memory in a patient with selective hippocampal damage. Neuropsychologia 38:410–425.
Horel JA. 1978. The neuroanatomy of amnesia. A critique of the hippocampal memory hypothesis. Brain 101:403–445.
Hori E, Tabuchi E, Matsumura N, Tamura R, Eifuku S, Endo S, Nishijo H, Ono T. 2003. Representation of place by monkey hippocampal neurons in real and virtual translocation. Hippocampus 13:190–196.
Hovius M, Kellenbach ML, Graham KS, Hodges JR, Patterson K. 2003. What does the object decision task measure? Reflections on the basis of evidence from semantic dementia. Neuropsychology 17:100–107.
Insausti R, Juottonen K, Soininen H, Insausti AM, Partanen K, Vainio P, Laakso MP, Pitkanen A. 1998. MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. Am J Neuroradiol 19:659–671.
Kanwisher N, McDermott J, Chun MM. 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. J Neurosci 17:4302–4311.
King JA, Burgess N, Hartley T, Vargha-Khadem F, O'Keefe J. 2002. Human hippocampus and viewpoint dependence in spatial memory. Hippocampus 12:811–820.
King JA, Trinkler I, Hartley T, Vargha-Khadem F, Burgess N. 2004. The hippocampal role in spatial memory and the familiarity–recollection distinction: a case study. Neuropsychology 18:405–417.
Lee AC, Bussey TJ, Murray EA, Saksida LM, Epstein RA, Kapur N, Hodges JR, Graham KS. 2005. Perceptual deficits in amnesia: challenging the medial temporal lobe "mnemonic" view. Neuropsychologia 43:1–11.
Lee ACH, Barense MD, Graham KS. The contribution of the human medial temporal lobe to perception: bridging the gap between animal and human studies. Q J Exp Psychol B, in press.
Levy DA, Shrager Y, Squire LR. 2005. Intact visual discrimination of complex and feature-ambiguous stimuli in the absence of perirhinal cortex. Learn Mem 12:61–66.
Li L, Miller EK, Desimone R. 1993. The representation of stimulus familiarity in anterior inferior temporal cortex. J Neurophysiol 69:1918–1929.
Maguire EA, Frackowiak RS, Frith CD. 1997. Recalling routes around London: activation of the right hippocampus in taxi drivers. J Neurosci 17:7103–7110.
Meunier M, Bachevalier J, Mishkin M, Murray EA. 1993. Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. J Neurosci 13:5418–5432.
Moores E, Laiti L, Chelazzi L. 2003. Associative knowledge controls deployment of visual selective attention. Nat Neurosci 6:182–189.
Morris RG, Garrud P, Rawlins JN, O'Keefe J. 1982. Place navigation impaired in rats with hippocampal lesions. Nature 297:681–683.
Murray EA, Bussey TJ. 1999. Perceptual-mnemonic functions of the perirhinal cortex. Trends Cogn Sci 3:142–151.
Murray EA, Davidson M, Gaffan D, Olton DS, Suomi S. 1989. Effects of fornix transection and cingulate cortical ablation on spatial memory in rhesus monkeys. Exp Brain Res 74:173–186.
Murray EA, Gaffan D, Mishkin M. 1993. Neural substrates of visual stimulus-stimulus association in rhesus monkeys. J Neurosci 13:4549–4561.
O'Keefe J. 1976. Place units in the hippocampus of the freely moving rat. Exp Neurol 51:78–109.
O'Keefe J. 1999. Do hippocampal pyramidal cells signal non-spatial as well as spatial information? Hippocampus 9:352–364.
O'Keefe J, Burgess N. 1996. Geometric determinants of the place fields of hippocampal neurons. Nature 381:425–428.
O'Keefe J, Burgess N, Donnett JG, Jeffery KJ, Maguire EA. 1998. Place cells, navigational accuracy, and the human hippocampus. Philos Trans Roy Soc Lond B Biol Sci 353:1333–1340.
Ono T, Nakamura K, Fukuda M, Tamura R. 1991. Place recognition responses of neurons in monkey hippocampus. Neurosci Lett 121:194–198.
Ono T, Nakamura K, Nishijo H, Eifuku S. 1993. Monkey hippocampal neurons related to spatial and nonspatial functions. J Neurophysiol 70:1516–1529.
Pihlajamaki M, Tanila H, Kononen M, Hanninen T, Hamalainen A, Soininen H, Aronen HJ. 2004. Visual presentation of novel objects and new spatial arrangements of objects differentially activates the medial temporal lobe subareas in humans. Eur J Neurosci 19:1939–1949.
Ranganath C, D'Esposito M. 2001. Medial temporal lobe activity associated with active maintenance of novel information. Neuron 31:865–873.
Ranganath C, Blumenfeld RS. Doubts about double dissociations between short-term and long-term memory. Trends Cogn Neurosci, in press.
Rempel-Clower NL, Zola SM, Squire LR, Amaral DG. 1996. Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. J Neurosci 16:5233–5255.
Robertson RG, Rolls ET, Georges-François P. 1998. Spatial view cells in the primate hippocampus: effects of removal of view details. J Neurophysiol 79:1145–1156.
Seltzer B, Pandya DN. 1978. Afferent cortical connections and architectonics of the superior temporal sulcus and surrounding cortex in the rhesus monkey. Brain Res 149:1–24.
Snowden J, Goulding P, Neary D. 1989. Semantic dementia: a form of circumscribed cerebral atrophy. Behav Neurol 2:167–182.
Sobotka S, Ringo JL. 1993. Investigation of long-term recognition and association memory in unit responses from inferotemporal cortex. Exp Brain Res 96:28–38.
Sobotka S, Ringo JL. 1996. Mnemonic responses of single units recorded from monkey inferotemporal cortex, accessed via transcommissural versus direct pathways: a dissociation between unit activity and behavior. J Neurosci 16:4222–4230.
Spiers HJ, Maguire EA, Burgess N. 2001. Hippocampal amnesia. Neurocase 7:357–382.
Squire LR, Zola-Morgan S. 1991. The medial temporal lobe memory system. Science 253:1380–1386.
Stark CE, Squire LR. 2000. Intact visual perceptual discrimination in humans in the absence of perirhinal cortex. Learn Mem 7:273–278.
Tanaka K. 1996. Inferotemporal cortex and object vision. Annu Rev Neurosci 19:109–139.
Tanaka K. 2003. Columns for complex visual object features in the inferotemporal cortex: clustering of cells with similar but slightly different stimulus selectivities. Cereb Cortex 13:90–99.

Tulving E, Markowitsch HJ. 1998. Episodic and declarative memory: role of the hippocampus. Hippocampus 8:198–204.

Ungerleider L, Mishkin M. 1982. Two cortical visual systems. In: Ingle D, Goodale M, Mansfield R, editors. Analysis of visual behavior. Cambridge, MA: MIT Press. p 549–586.

Von Bonin G, Bailey P. 1947. The neocortex of Macaca mulatta. Urbana, IL: University of Illinois.

Warrington EK. 1975. The selective impairment of semantic memory. Q J Exp Psychol 27:635–657.

Wilson MA, McNaughton BL. 1993. Dynamics of the hippocampal ensemble code for space. Science 261:1055–1058.

Winters BD, Forwood SE, Cowell RA, Saksida LM, Bussey TJ. 2004. Double dissociation between the effects of peri-postrhinal cortex and hippocampal lesions on tests of object recognition and spatial memory: heterogeneity of function within the temporal lobe. J Neurosci 24:5901–5908.

Xiang JZ, Brown MW. 1998. Differential neuronal encoding of novelty, familiarity and recency in regions of the anterior temporal lobe. Neuropharmacology 37:657–676.

Zola-Morgan S, Squire LR, Ramus SJ. 1994. Severity of memory impairment in monkeys as a function of locus and extent of damage within the medial temporal lobe memory system. Hippocampus 5:232–239.