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Perceptual deficits in amnesia: challenging the medial temporal lobe 'mnemonic' view

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Abstract

Recent animal studies suggest that the medial temporal lobe (MTL), which is thought to subserve memory exclusively, may support non-mnemonic perceptual processes, with the hippocampus and perirhinal cortex contributing to spatial and object perception, respectively. There is, however, no support for this view in humans, with human MTL lesions causing prominent memory deficits in the context of apparently normal perception. We assessed visual discrimination in amnesic cases to reveal that while selective hippocampal damaged patients could discriminate faces, objects, abstract art and colour, they were significantly poorer in discriminating spatial scenes. By contrast, patients with MTL damage, including perirhinal cortex, were significantly impaired in discriminating scenes, faces, and to a lesser extent objects, with relatively intact discrimination of art and colour. These novel observations imply that the human MTL subserves both perceptual and mnemonic functions, with the hippocampus and perirhinal cortex playing distinct roles in spatial and object discrimination, respectively.

Keywords: Hippocampus; Perirhinal cortex; Memory; Perception; Visual discrimination

1. Introduction

Multiple studies have demonstrated that activity of hippocampal neurons in rodents reflects aspects of spatial localisation and navigation (O'Keefe, 1976; O'Keefe & Burgess, 1996; O'Keefe, Burgess, Donnett, Jeffery, & Maguire, 1998; Wilson & McNaughton, 1993). Similarly, nonhuman primate data indicate that the hippocampus may only be crucial when spatial memory is critical for a task (Hampton, Hampstead, & Murray, in press; Murray, Davidson, Gaffan, Olton, & Suomi, 1989; Murray, Gaffan, & Mishkin, 1993; Murray & Mishkin, 1998). In contrast, lesion studies have revealed that perirhinal cortex ablations can impair a monkey's ability to make discriminations on the basis of visual feature conjunctions (e.g., object perception), while visual discrimination using single features such as size and colour remains intact (Buckley, Booth, Rolls, & Gaffan, 2001; Bussey, Saksida, & Murray, 2002, 2003). Although these findings from the animal literature suggest differential roles for the hippocampus and perirhinal cortex in spatial (Gaffan, 2001; O'Keefe, 1999) and object perception (Buckley, Booth, Rolls, & Gaffan, 2001; Bussey & Saksida, 2002; Bussey et al., 2002, 2003; Murray & Bussey, 1999), respectively, studies in humans indicate that the same conclusions may not extend to the human medial temporal lobe (MTL). First, while recent research demonstrates some functional homology between rat and human hippocampus, at least in terms of cells that might code for spatial location (Ekstrom et al., 2003), other evidence suggests that the human hippocampus is critical for spatial navigation and memory, rather than for basic spatial perception (Burgess

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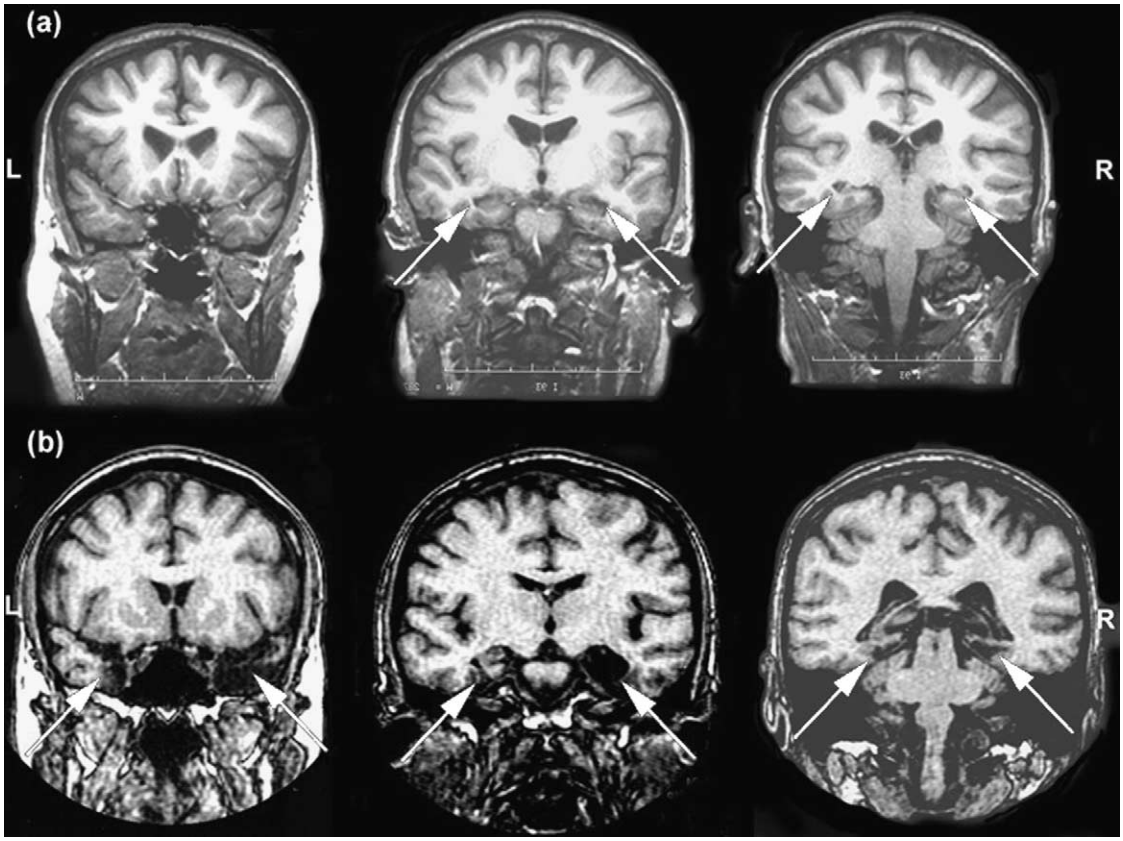

Fig. 1. Three coronal MRI scan slices for one representative patient from the (a) hippocampal and (b) MTL patient groups (arrows highlight regions of significant damage; L: left; R: right).

& O'Keefe, 2003). Instead, the adjacent parahippocampal cortex has been highlighted as an important structure for encoding new perceptual information about the layout of spatial scenes (Epstein, Harris, Stanley, & Kanwisher, 1999). Second, patients with perirhinal cortex damage are able to match complex visual stimuli in tasks of minimal mnemonic demand, suggesting normal object perception (Buffalo, Reber, & Squire, 1998; Holdstock, Gutnikov, Gaffan, & Mayes, 2000; Stark & Squire, 2000). This discrepancy between the animal and human literature, however, may reflect the use of paradigms in humans that fail to tax perception of objects that share visual features.

To investigate this possibility, four amnesic patients with selective bilateral hippocampal damage and three amnesic patients with more extensive MTL lesions (Fig. 1; Table 1) were compared to healthy controls on different conditions of two simple computerised visual discrimination tasks. Given that the MTL-lesion patients were significantly older than the hippocampal group, two sets of age-matched controls were recruited. The two discrimination tasks were both based on the same experimental paradigm: On trials 1–3 of each condition, a pair of unfamiliar images from one of five stimulus categories (faces, objects, spatial scenes, abstract art, or colour) was presented on a touchscreen monitor and the subjects were instructed to identify the 'correct' picture by touching it. On selection, the correct stimulus produced a high tone, while the incorrect image was associated with a low tone. From trials 4–53, the same pictures were blended together to create 50 new trial unique pairs with five different levels of feature overlap: 0–9%, 10–19%, 20–29%, 30–39%, and 40–49% of shared features. There were 10 trials for each level of blending and these were pseudo-randomly ordered such that two trials from each level were presented during each block of 10 trials. The subjects were instructed to select the picture that they perceived to contain a greater proportion of the original correct stimulus and auditory feedback was provided for all trials. The administration of the different stimulus categories was pseudo-randomised and counterbalanced across all subjects.

The critical difference between the two tasks was that in the first task (Task 1, Fig. 2a) the subjects were required to remember the original target stimulus throughout each experimental condition. In contrast, in the second modified task (Task 2, Fig. 2b) this memory component was removed and the original target item was continually present on the computer screen.

2. Methods

2.1. Subjects

Seven amnesic patients with focal brain lesions participated in this study. All patients had structural MRI scans that

Table 1
Mean structural MRI scan ratings (with standard deviations) for various brain regions (ordered from anterior to posterior location in the brain), averaged across both hemispheres

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

Asterisk (*) represents significant difference in comparison to control mean. 0 indicates no visible damage, 3 (4 for anterior hippocampus) indicates complete absence of area. AntTemp: anterior temporal cortex; Amyg: Amygdala; PHG: parahippocampal gyrus; MBCS: medial bank of collateral sulcus; LBCS: lateral bank of collateral sulcus; MBOS: medial bank of occipital sulcus; AntHC: anterior hippocampus; LatTemp: lateral temporal cortex; PostHC: posterior hippocampus.

were rated by two independent, experienced neurologists and compared to the scans of a similar healthy control group (see Section 2.2). On the basis of these ratings (Tables 1 and 2), the patients were divided into those that had selective damage to the hippocampus bilaterally ('hippocampal group') and those that had larger MTL lesions ('MTL group'), including damage to the perirhinal cortex, as well as some injury to anterior and, in one case, lateral temporal lobe regions (Fig. 1). Of the four patients in the hippocampal group (age = 47.8 years; education = 15.3 years), two had suffered viral encephalitis, one had anoxia due to status epilepticus and one suffered carbon monoxide-induced hypoxia. Of the three patients in the MTL group (age = 67.7 years; education = 10.7 years), two were viral encephalitis patients and the third suffered traumatic intercerebral bleeding.

The patients were assessed with a series of standardised neuropsychological tests assessing memory and visual perception. These demonstrated that all patients had severe episodic memory problems but intact perceptual functions. For instance, both patient groups performed poorly on most episodic memory tests such as the Logical Memory (Story 1) immediate recall (Hippocampal (WMS-R): 37.0%; MTL (WMS-III): 22.7%), delayed recall (Hippocampal (WMS-R): 6.3%; MTL (WMS-III): 5.6%), and delayed recognition conditions (Hippocampal (WMS-R): 68.0%; MTL (WMS-III): 43.3%), the Rey Complex Figure delayed recall condition (Hippocampal: 19.7%; MTL: 10.6%), and the Warrington Recognition Memory Test faces condition (Hippocampal: 93.0%; MTL: 62.0%). In contrast, visuoperceptual performance as indicated by the Benton Face Test (Hippocampal: 90.7%; MTL: 80.2%), Rey Complex Figure copy (Hippocampal: 100%; MTL: 91.7%) and Visual Object Space Perception battery (both groups passed all object and space tests) was normal. While the hippocampal group exhibited intact semantic function, the MTL group was mildly impaired on semantic tests, including Word–Picture matching (Hippocampal: 100%; MTL: 88.6%), Naming (Hippocampal: 98.1%; MTL: 67.2%) and the Pyramids and Palm Trees picture condition (Hippocampal: 99.0%; MTL: 89.8%).

Nine young (age = 47.2 years; education = 12.8 years) and eleven elderly (age = 67.0 years; education = 12.8 years) healthy subjects matched to the hippocampal group and the MTL group, respectively, were assessed on the first visual discrimination task. There were no significant differences in terms of age and education between each patient group and their matched controls (all $t < 0.2$, $P > 0.1$). The same control subjects were also recruited for the second visual discrimination task, although two young controls and one elderly control were not available. This, however, made no significant difference to the mean age and years of education of the two control groups (young age = 47.8 years; elderly age = 66.8 years; young education = 12.6 years; elderly education = 12.1 years).

Informed consent was obtained from all subjects. This study received ethical approval from the Cambridge and

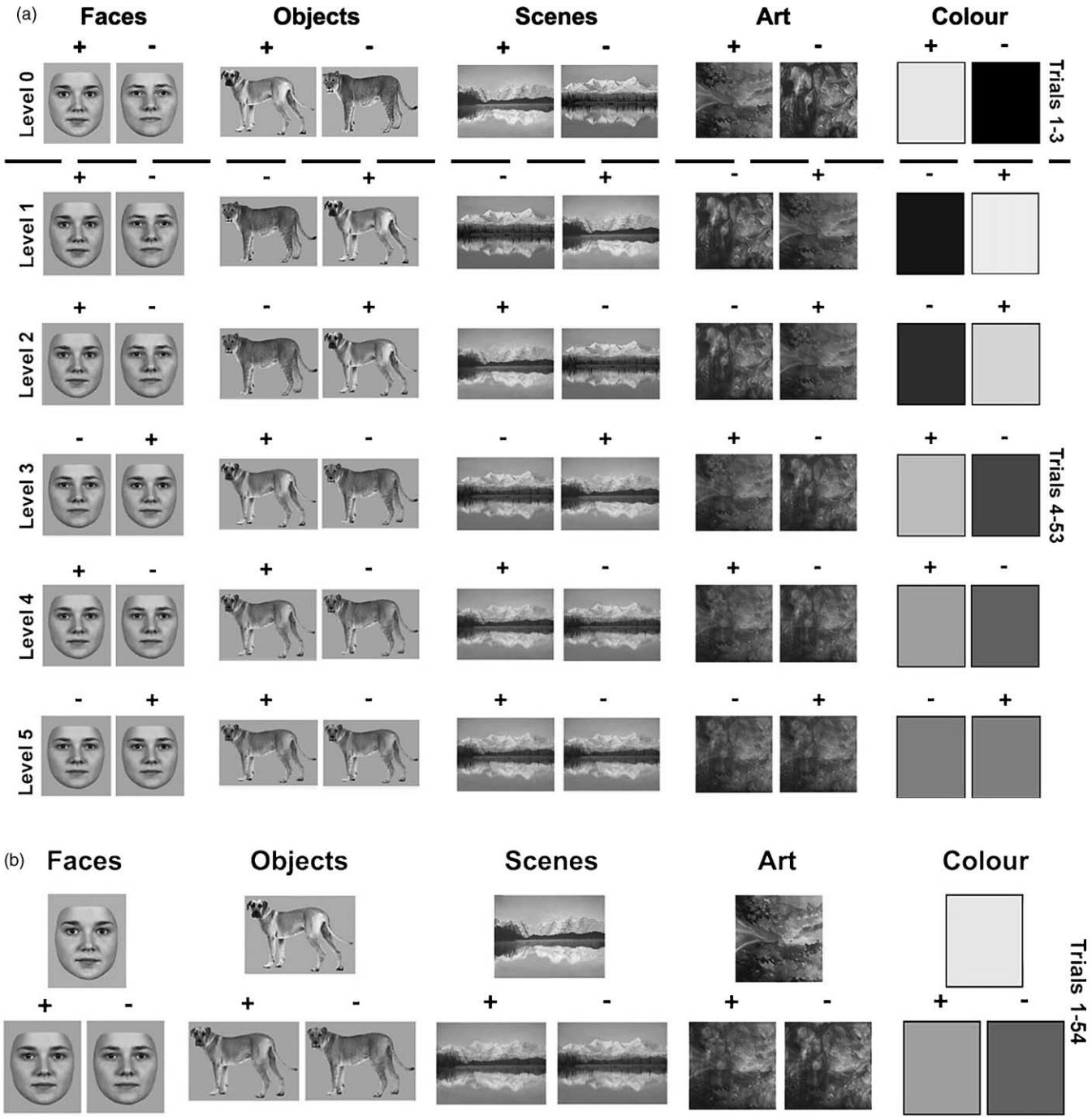

Fig. 2. (a) One trial from each level of feature overlap from the five conditions of the original task (Task 1); (b) one example from feature overlap level 4 from each condition of the modified task (Task 2); the original correct stimulus is displayed at the top. (+) indicates correct stimulus; (−) indicates incorrect stimulus.

Southampton Health Authority Local Research Ethics Committees (UK).

2.2. Scan rating method

Since electronic versions of the patients' scans were not available, it was not possible to obtain a volumetric measurement of the patients' lesions. Consequently, hard copies of the coronal MRI scans of the amnesic patients and 12 age-matched healthy controls (who did not participate in the experimental study) were assessed using a visual rating scale by two neurologists experienced at radiological evaluation. All scans were presented randomly with identifying information obscured. The rationale was to obtain temporal lobe volume data in an efficient and reliable manner and it was important that the method would not stipulate the

Table 2
Structural MRI scan ratings for various brain regions (ordered from anterior to posterior location in the brain) for each individual patient (averaged across hemispheres)

Subject	AntTemp	Amyg	PHG	MBCS	LBCS	MBOS	AntHC	LatTemp	PostHC
HC1	1*	1	0.75*	0.75	0.25	0	1.5*	1	0.75
HC2	0	0.5	0.25	0.5	0.25	0	2*	0	0.25
HC3	0	0	0.75*	0.75	0.5	0.25	1.25*	0.5	1*
HC4	0.5	0.25	0	0.75	0.25	0.25	1.5*	0.25	1*
MTL1	2*	2.25*	1.5*	1*	1.25*	2*	1.75*	1.75*	1.75*
MTL2	2*	3*	2.5*	2.75*	2.5*	2*	3*	1	2.75*
MTL3	1.75*	2.75*	2.75*	2.75*	2.5*	2.5*	2*	0.5	2*
Controls	0.313 (0.284)	0.375 (0.483)	0.188 (0.188)	0.521 (0.291)	0.271 (0.310)	0.333 (0.289)	0.458 (0.382)	0.458 (0.411)	0.271 (0.361)

As a comparison, the mean ratings for the control group (with standard deviations) are also shown. An asterisk (*) signifies that a patient's score is two standard deviations beyond the control mean (e.g., significant atrophy). 0 indicates no visible damage, 3 (4 for anterior hippocampus) indicates complete absence of area. HC: hippocampal-group patient; MTL: MTL-group patient: AntTemp: anterior temporal cortex; Amyg: Amygdala; PHG: parahippocampal gyrus; MBCS: medial bank of collateral sulcus; LBCS: lateral bank of collateral sulcus; MBOS: medial bank of occipital sulcus; AntHC: anterior hippocampus; LatTemp: lateral temporal cortex; PostHC: posterior hippocampus.

use of a single MRI machine or image acquisition protocol, but simply that the image quality was suitable for clinical reporting.

It is important to highlight that while MRI volumetry is the most rigorous method applicable in vivo, this technique is itself limited by marked baseline variation in the collateral sulcus, which is considered to be the critical anatomical landmark in the medial temporal lobe for delineating perirhinal cortex (Insausti et al., 1998). There is often major distortion of the collateral sulcus over and above any cortical volume loss in those cases where the antero-medial temporal lobe holds greatest interest. Given the difficulties in correcting such distortion by mathematical means, the use of a visual rating scale may often be the most appropriate methodology for use in the types of patient cases reported in this paper.

The adopted visual rating method was an expansion of a previously developed scale (Galton et al., 2001). This has been successively validated against volumetric measures and emphasizes medial temporal areas, namely the entorhinal and perirhinal cortices. A list of the rated regions and how they were assessed is given below. Other than the anterior hippocampus, which was rated on a 5-point scale (normal = 0, severe atrophy = 4) based on Scheltens et al. (1992), all regions were assessed using a 4-point scale (normal = 0, severe atrophy = 3). Each measure showed satisfactory inter-rater reliability (average kappa value = 0.5; Landis & Koch, 1997).

2.2.1. Anterior hippocampus

This was rated using the anterior-most pontine slice on a scale almost identical to that used by Galton et al. (2001). The widths of the choroidal fissure and temporal horn and the height of the hippocampal formation were visually assessed. This method is known to have good inter- and intrarater reliability and has been validated against both linear and volumetric measures obtained with different MRI sequences.

2.2.2. Anterior temporal lobe

Assessment of this region was on a 4-point scale and was based on the cerebral spinal fluid space between the back of the orbit and the temporal pole.

2.2.3. Amygdala

This was rated on the scan-slice anterior to the tip of the temporal horn, which corresponds to accepted MRI landmarks (Watson, Jack, & Cendes, 1997).

2.2.4. Lateral temporal lobe

Similar to the anterior hippocampus, this rating was based on the slice through the anterior pons and depended on the cortical thickness of the superior and middle temporal gyri.

2.2.5. Posterior hippocampus

This was rated on the anterior-most slice through the cerebral aqueduct, in parallel with the anterior measure, according to the width of the temporal horn and the height of the hippocampal formation.

2.2.6. Medial temporal lobe

Cortical thickness was rated at four points: the mid-point of the crown of the parahippocampal gyrus (corresponding to entorhinal cortex); the mid-point of the medial bank of the collateral sulcus (corresponding to transentorhinal cortex); the mid-point of the lateral bank of the collateral sulcus (corresponding to perirhinal cortex) and the medial bank of the occipitotemporal sulcus (Insausti et al., 1998). In each case, the ratings were performed on the slice showing the collateral sulcus at its longest. If the anatomic distortion was so severe that the gyral landmarks were unusable then a 'severe atrophy' rating was recorded.

Given that age was not found to be a significant factor in influencing the ratings for the healthy controls, all the 12 control subjects were considered as a single group. In addition to this, statistical analyses on the ratings for the two patient

groups and matched control group revealed that there were no significant differences between the left and right hemisphere scores for any of the measured brain regions (all $P > 0.1$). As a result, the ratings for each area were averaged across both hemispheres.

Table 1 summarises the mean ratings for those patients who had selective hippocampal damage (and thus grouped in the 'hippocampal group'), those that had larger MTL lesions (and thus categorised in the 'MTL group'), and the healthy control subjects, while Table 2 gives the rating scores for each individual subject. A repeated-measures ANOVA with a within-group factor of 'rating' and a between-groups factor of 'subject group' indicated that there was significant variability across the nine ratings that were used ($F(8,128) > 5$, $P < 0.0001$), as well as a significant overall difference between the three subject groups ($F(2,16) > 80$, $P < 0.0001$). There was also a significant 'rating' by 'subject group' interaction ($F(2,16) > 4$, $P < 0.0001$) and one-way ANOVAs to investigate this further revealed that there was a significant group difference on all ratings (all $F(2,16) > 17$, $P < 0.0001$) other than the lateral temporal lobe measure ($F(2,16) < 3$, $P > 0.1$), suggesting that both patient groups did not have significant damage to this region. Posthoc analyses on the measures in which there was a significant group difference showed that the hippocampal group had significantly greater atrophy of the anterior hippocampus compared to the control group ($P < 0.001$) but did not differ significantly on any other anatomical measure (all $P > 0.1$). In contrast, the MTL group received significantly greater rating scores compared to the control group on all measures (all $P < 0.0001$).

2.3. Task

An average period of 6 months separated the administration of the two visual discrimination tasks. All testing was conducted using a 15" SVGA LCD touchscreen (1024 × 768 resolution) attached to a computer. Subjects were given instructions and a practice task prior to each testing session. All stimuli were presented in greyscale (average size: 250 × 250 pixels) and all subjects saw the same stimuli. For each task condition there were multiple stimulus pairs—Faces: four pairs (two of female faces, two of male faces); Objects: two pairs (one of animals and one of musical instruments); Scenes: three pairs (all of outdoor scenes); Art: three pairs (all of abstract artwork); Colour: three pairs (Red and blue, black and white, green and orange). Different levels of feature overlap were created by blending user-specified ratios of the images within each stimulus pair using commercially available computer software (Morpheus Photo Animator, ACD Systems Ltd, Saanichton, Canada). Images were chosen such that the pictures within each stimulus pair could not be discriminated on the basis of one conspicuous feature at any level of feature overlap. Statistical analyses were carried out on data subsequent to trials 1–3, during which all subjects were able to successfully identify the correct stimulus on both versions of the visual discrimination task. The administration of the different stimulus categories was pseudo-randomised and counterbalanced across all subjects.

2.4. Statistics

A repeated-measures analysis of variance (ANOVA) was conducted on the performance accuracy data. A single within-subject factor of 'Task' was incorporated with five levels corresponding to the five test conditions. Given the structure of the subject groups (i.e., each patient group was matched with its own control group), two between-subject factors 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 hippocampal group and their matched controls) and MTL (incorporating the MTL group and their matched controls). A significant interaction between these three factors ('Task' × 'Health' × 'Lesion Type') indicated that the difference between the MTL group and their matched controls was significantly different from that between the hippocampal patients and their respective controls, and that this difference varied significantly across the five task conditions. To investigate this interaction, the results from each condition were analysed separately with univariate ANOVAs, incorporating the same two between-subject factors of 'Health' and 'Lesion Type' and a dependent variable of performance. Significant 'Health' by 'Lesion Type' interactions were examined further using posthoc independent-sample *t*-tests between each patient group and their matched control group. Since the patients were predicted to be significantly impaired on the scenes (hippocampal and MTL), faces (MTL) and object (MTL) conditions, a one-tailed significance threshold ($P < 0.05$) was adopted for all *t*-tests.

3. Results

3.1. Task 1

Statistical analyses on the performance data from Task 1 (Fig. 3a) indicated that the two patient groups, when compared to their respective controls, did not perform similarly across the different task conditions (e.g., a significant 'Task' by 'Health' by 'Lesion Type' interaction: $F(4, 92) > 7$, $P < 0.001$). In particular, the disparity between the MTL patients and their controls was significantly greater than that between the hippocampal group and their controls (e.g., a significant 'Health' by 'Lesion Type' interaction) only on the face, object and scene conditions (all $F(1, 23) > 4$, $P < 0.05$). Further posthoc *t*-tests to investigate this revealed that there was a significant difference between the hippocampal group and their matched controls in discriminating scenes ($t(11) > 2$, $P = 0.01$), but not faces or objects (both $t(11) \leq 1$, $P > 0.1$). The MTL-group patients however performed at a significantly poorer level compared to their matched controls on the face ($t(12) > 3$, $P = 0.004$), object ($t(12) > 2$, $P = 0.03$) and scene

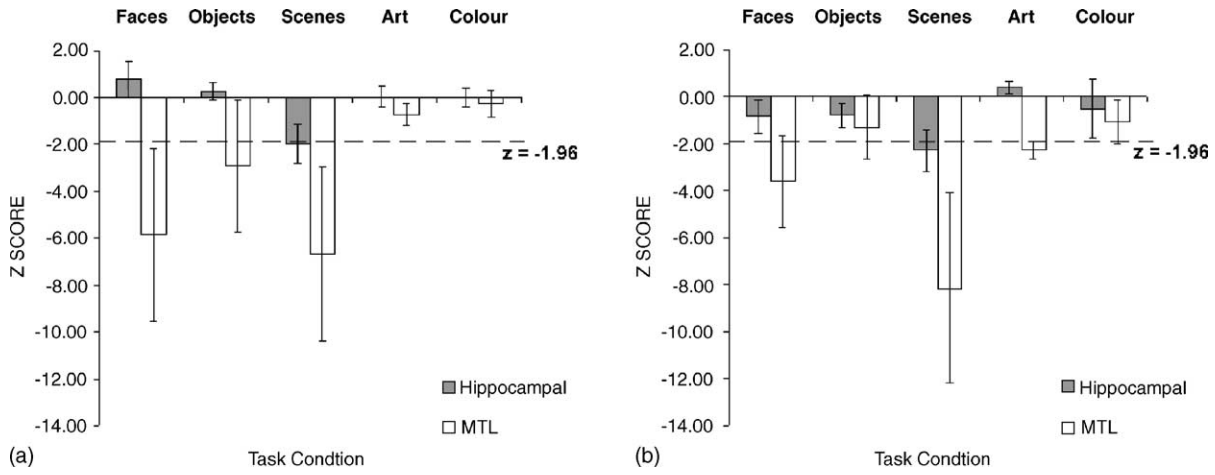

Fig. 3. Z score plots for the two patient groups when compared to their matched controls on (a) the five original; and (b) the five modified task conditions (scores beyond z = −1.96 indicate significant impairment).

conditions ($t(12) > 3$, $P = 0.002$). In contrast, neither patient group was significantly different from their control group in the discrimination of art and colour (both $t \leq 1$, $P > 0.2$), suggesting intact performance on these two stimulus categories. As adjudged by the accuracy of both healthy control subject groups, only the face condition was significantly more difficult than all other conditions, (face versus rest: all $P < 0.05$), while the colour task was significantly easier than the rest (colour versus rest: all $P < 0.0001$). It seems highly unlikely, therefore, that the observed patient impairments in the face, object and scene conditions are attributable to task difficulty.

The performance of the two patient groups and their respective controls did not vary significantly from the start to the finish of each condition on which there was a significant group impairment (all $P > 0.07$), indicating that any perceptual deficit was not modulated by the delay between presentation of the original stimuli and subsequent test. This analysis confirms that (a) the patients did not forget the target stimulus before the end of the test condition and (b) that the controls did not show a subtle learning effect across trials that was not present in patients.

3.2. Task 2

Given that the two patient groups were impaired in Task 1 on the specific stimulus categories predicted from the animal literature only (i.e., spatial scenes following hippocampal dysfunction (Gaffan, 1994, 2001) and objects, including faces, following perirhinal cortex damage (Buckley et al., 2001; Bussey et al., 2002, 2003; Murray & Bussey, 1999) and that performance in all groups was not influenced in a delay-dependent manner, one may conclude that a general mnemonic problem is unlikely to explain the observed deficits. To categorically rule out, however, the possibility of domain-specific memory impairments in the two patient groups (i.e., a scene memory deficit in both patient groups and additional face and object memory deficits in the MTL patient group), we repeated Task 1 with one significant change: the addition of the original 'correct' stimulus above every picture pair presented during the 54 trials of each task condition (Fig. 2b). Thus, this modified task did not require the subjects to learn the original correct stimulus and they were simply instructed to select the picture that looked most similar to the displayed original correct image.

It was found that across all five stimulus categories, the performance of the two patient groups and their matched controls on the modified version of the visual discrimination task did not differ significantly from that on the original task (all $P > 0.07$). This suggests that memory was not critical to performance in the original test and emphasises the perceptual nature of the patients' discrimination deficits. In keeping with this conclusion, and similar to Expt. 1, there was a significant interaction effect between the factors of 'Task', 'Health' and 'Lesion Type' ($F(4,76) > 3$, $P = 0.009$). Univariate ANOVAs to investigate this interaction further revealed that there was a significant 'Health' by 'Lesion Type' interaction on the face, scene and art conditions (all $F(1,19) > 5$, $P \leq 0.03$), but not on the object or colour tasks (both $F(1,19) < 0.5$, $P > 0.5$). Posthoc t-tests showed that the hippocampal patients were selectively impaired in the discrimination of spatial scenes in the new version of the task ($t(9) > 2$, $P = 0.01$; Fig. 3b). Similarly, the MTL group demonstrated a significant impairment in the discrimination of both faces ($t(10) > 3$, $P = 0.01$) and scenes ($t(10) > 3$, $P = 0.008$), but not colour ($t(10) < 2$, $P > 0.1$). In contrast to the original task, there was no significant MTL group deficit in the discrimination of objects ($t(10) < 2$, $P > 0.1$), while there was an impairment in the art condition ($t(10) > 3$, $P = 0.01$). In both these cases, the effects were driven by the performance of a single patient, with two out of the three MTL patients showing significant impairment in the discrimination of objects ($t(9) > 3$, $P = 0.003$) and only one MTL patient demonstrating any significant difficulties with abstract art.

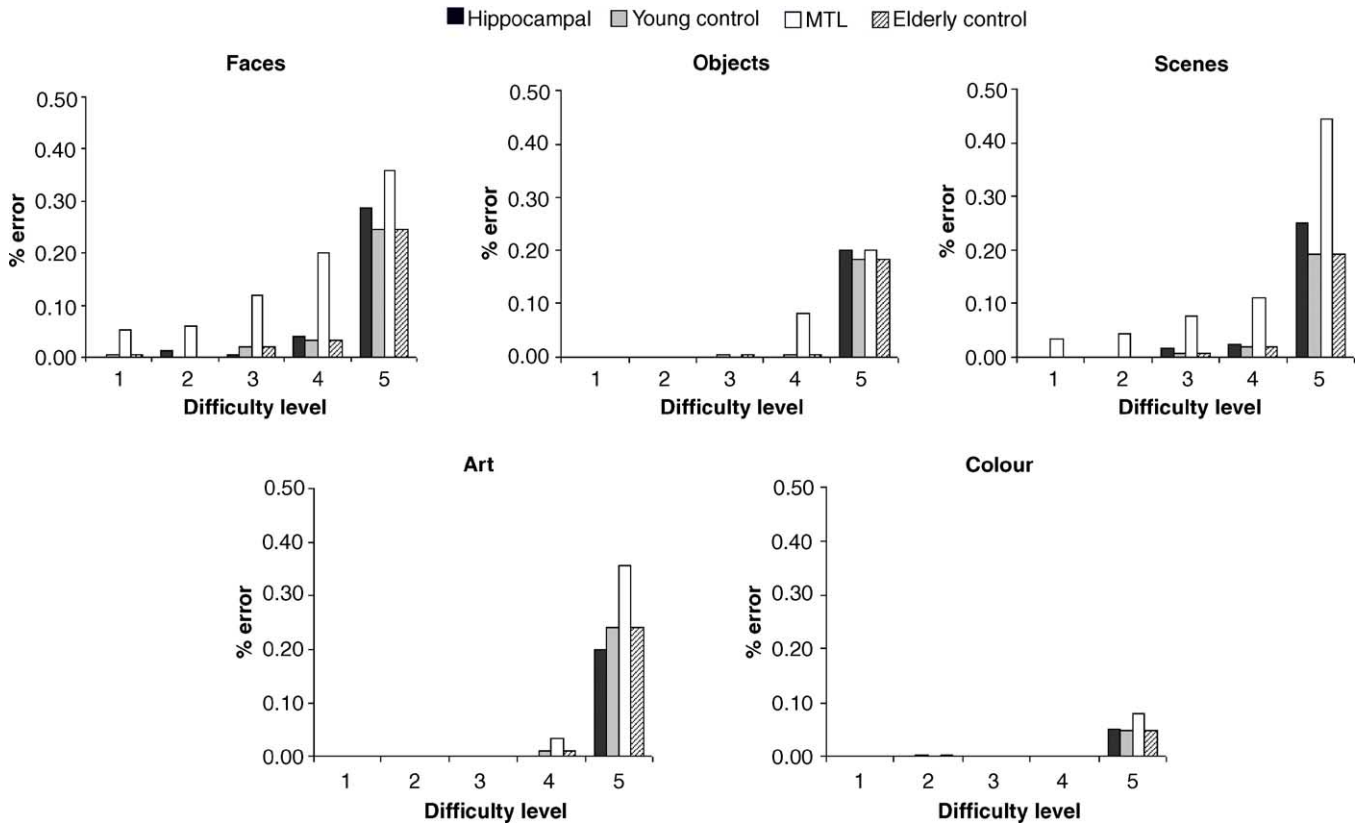

Fig. 4. Mean percent error for each subject group for the 5 levels of feature overlap (1 = 0–9%, 2 = 10–19%, 3 = 20–29%, 4 = 30–39%, and 5 = 40–49%) on each condition of the modified task. A similar pattern was seen for the original task.

Similar to Task 1, it is important to note that none of the groups demonstrated a significant learning effect across the five 10-trial blocks of each condition in the modified test. If anything, the young control group performed significantly poorer across time in the scenes condition ($P < 0.001$), while the elderly control group's performance deteriorated across the blocks in the scenes and faces conditions (both $P < 0.03$). This underlines the fact that the differences in performance between our patient and control groups was not due to a learning effect seen only in the controls.

3.3. *Effect of feature overlap*

One critical feature of both versions of the visual discrimination paradigm was that the stimuli were blended to create different degrees of feature overlap. As predicted, this factor was found to influence the patients' performance in a similar manner across both tests. In the scenes condition, both patient groups made an increasing number of errors as the level of blending increased. A similar pattern was observed for the MTL group in the objects condition, suggesting that the patients failed perceptually to differentiate stimuli that were blended to a significant degree. On the faces condition, however, the MTL group made a significant number of errors even at a low level of blending, a finding attributable to the inherently high degree of feature overlap between faces even when not blended (Fig. 4).

4. Discussion

Using two versions of a fine visual discrimination paradigm, we have demonstrated that lesions to the hippocampus and perirhinal cortex can lead to difficulties in the discrimination of spatial scenes and objects, respectively. Importantly, our data challenge the current belief that the human MTL subserves mnemonic processes exclusively (Schacter & Tulving, 1994; Spiers, Maguire, & Burgess, 2001; Squire & Zola-Morgan, 1991; Tulving & Markowitsch, 1998; Zola-Morgan, Squire, & Ramus, 1994) and suggests that the human MTL, like its animal counterpart, may also subserve non-mnemonic perceptual processes.

The striking similarity between our two tasks—one in which the subjects were required to remember the target stimuli and another in which the target stimuli was constantly visible—clearly rules out the possibility that the problems seen in our patients can be attributed to mnemonic processing, and instead highlight the difficulties faced by these cases in visual perception. The only area of significant common damage in the two patient groups was the hippocampus, predominantly to the anterior region, and notably, the only cognitive

deficit exhibited by both groups was for spatial scene discrimination. Furthermore, the MTL group, which possessed greater damage to the hippocampus in comparison to the hippocampal group (Table 1), had the larger impairment in scene discrimination, suggesting a direct relationship between the extent of damage to this region and the severity of impairment on this task.

Beyond the hippocampus, the MTL group also had damage that extended into other MTL areas, in particular perirhinal cortex. Consistent with the proposal that this region processes feature conjunctions (Bussey et al., 2002, 2003; Murray & Bussey, 1999), the MTL group exhibited additional difficulties on the face and, to a lesser extent, the object conditions. The damage seen in the MTL patients also affected, to varying degrees, anterior and lateral temporal lobe areas. It is unlikely, however, that the perceptual deficits reported here were due to concomitant involvement of inferolateral temporal regions, including the fusiform gyrus, as two of the three MTL patients did not possess significant damage to this region. The relatively intact performance of the MTL patients on the colour condition reinforces this notion, as the discrimination of colour has been shown to be dependent on these lateral temporal lobe regions (Buckley, Gaffan, & Murray, 1997; Tanaka, 2003). It is possible, however, that anterior temporal areas are critical to face and object perception since the human perirhinal cortex extends into the temporal pole (Insausti et al., 1998). Thus, it remains unclear how these two regions may contribute to the perceptual processes assessed by our tasks.

The findings of the current study are important because they address an apparent discrepancy in the cognitive neuropsychology literature. On the one hand, there is mounting evidence that the perirhinal cortex is involved in perception in animals (Buckley et al., 2001; Bussey & Saksida, 2002; Bussey et al., 2002, 2003), a suggestion that has also been extended to the hippocampus (Gaffan, 2001). In contrast, studies in humans have, to date, pointed towards an exclusive role of the MTL in memory formation. Our data challenge this traditional view by demonstrating that patients with selective hippocampal damage can show a perceptual deficit specifically related to the discrimination of real-world spatial scenes, while patients with larger MTL lesions encompassing the hippocampus and perirhinal cortex, show similar, albeit greater, impairment for spatial scenes, as well as deficits that extend to face and object stimuli. Crucially, all of the amnesic patients performed within the normal range on existing standard tests of perception, such as the Visual Object Space Perception Battery (see Section 2). This highlights the fact that well-defined tasks that place a significant demand on the relevant perceptual processes, such as processing of conjunctions of spatial and object information, are required to reveal the patients' underlying perceptual deficits.

Two potential caveats with the present study are: (1) the deficits observed in our patients may have been due to a learning effect that was only present in the controls and (2) the scene discrimination impairment in the hippocampal group was, while highly significant, relatively small in magnitude (see Fig. 4). The fact that none of the subject groups showed a significant effect of learning in the two versions of our discrimination paradigm and, moreover that the control groups made an increasing number of errors across trial blocks for certain stimuli argues strongly against the first caveat. The possibility of learning, however, cannot be ruled out entirely unless a trial-unique perceptual task is administered (while no stimuli were repeated in the paradigm used in the present study, the same two images were used to generate the 50 different image pairs for each task condition). In keeping with this line of thought, we recently tested the same patients on a novel trial-unique visual discrimination task, in which they were required to select the odd stimulus from a visual array (Lee et al., submitted). Consistent with the findings of the current study, the hippocampal group patients had difficulties discriminating images of virtual reality scenes while the MTL-group patients exhibited an additional deficit in discriminating faces. In addition to this, the hippocampal group demonstrated a much greater deficit in scene discrimination in comparison to that observed in the current study (the hippocampal group performed on average 20% worse than their control group: HC mean: 65%, HC S.D.: 14%; Control mean: 86%, Control S.D.: 6%).

If true, our findings highlight three intriguing issues for further investigation. First, our proposal that the hippocampal damage in our patients results in poor spatial discrimination cannot explain why these cases exhibit mnemonic impairments on tests that do not, at least overtly, possess a spatial component (e.g., delayed story recall). It has been suggested in the animal literature, perhaps rather controversially, that the perceptual deficits documented after MTL damage may underlie the significant memory impairments seen after such injury (Gaffan, 2001; Horel, 1978; O'Keefe, 1999). Further studies would need to consider how difficulties in spatial perception could contribute to such neuropsychological deficits, but for now it seems more plausible that the human hippocampus is not uniquely specialised for spatial perception. Instead, this structure may play a more generalised role in associative or relational memory (Eichenbaum, Otto, & Cohen, 1992) beyond the object level, of which spatial perception may be an example. For instance, while the hippocampus may be involved in processing conjunctions of spatial relationships between the objects that constitute a scene, the perirhinal cortex may play an important role in processing conjunctions of single visual features that constitute an object.

Second, as mentioned earlier it has been proposed that the human parahippocampus plays a particular role in encoding new perceptual information about the layout of scenes (Epstein et al., 1999), while the hippocampus itself is critical for spatial navigation and related tasks (Burgess & O'Keefe, 2003). Notably, however, while two of the hippocampal patients did have mild atrophy to the parahippocampal gyrus (Table 2), their performance in the current study did not differ significantly from that of the other two patients, suggesting that damage to this region was not a critical factor in the spa-

tial scene deficits documented here. In addition to this, we have recently found that the same patients do not possess a general impairment in scene perception: instead deficits only emerge when the patients need to process conjunctions of spatial features, for instance within a virtual reality scene (Lee et al., submitted). Our findings are therefore inconsistent with the strict division of labour described in the literature and suggest instead that the hippocampus and parahippocampus may both play a critical role in spatial perception.

Third, the MTL-group patients reported here showed greater difficulties with face, compared to object, discrimination, a finding that could lead one to conclude that these patients suffer a relatively selective impairment in face processing. This assumption seems unlikely given that all three patients have been found to show normal processing of faces in circumstances in which they could utilise single facial features (Lee et al., submitted). Furthermore, two of the patients showed a clear and replicable deficit in object discrimination in the current study, suggesting that their impairment goes beyond the face domain. Complementary evidence comes from a recent functional imaging experiment in neurologically healthy controls, in which the perirhinal cortex was activated during changes in object identity (Pihlajamäki, Tanila, Könönen, Hänninen, Hämäläinen, Soininen, & Aronen, 2004). These findings are consistent with the view that perirhinal cortex is involved in object perception, especially when discrimination stresses conjunctions of object features.

In conclusion, our findings are a significant first demonstration that the human MTL, like its nonhuman primate counterpart, is not exclusively specialised for mnemonic processing, and that intact hippocampus and perirhinal cortex may be essential for processes underlying successful scene and object perception, respectively.

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