

Activating the Medial Temporal Lobe during Oddity Judgment for Faces and Scenes

Andy C. H. Lee^{1,2}, Victoria L. Scahill² and Kim S. Graham^{2,3}

¹Department of Experimental Psychology, University of Oxford, Oxford OX1 3UD, UK, ²MRC Cognition and Brain Sciences Unit, Cambridge CB2 7EF, UK and ³Wales Institute of Cognitive Neuroscience, School of Psychology, Cardiff University, Cardiff CF10 3AT, UK

Impairments in visual discrimination beyond long-term declarative memory have been found in amnesic individuals, with hippocampal lesions resulting in deficits in scene discrimination and perirhinal cortex damage affecting object discrimination. To complement these findings, the present functional magnetic resonance imaging study found that in healthy participants oddity judgment for novel trial-unique scenes, compared with face or size oddity, was associated with increased posterior hippocampus and parahippocampal cortex activity. In contrast, perirhinal and anterior hippocampus activity was observed during unfamiliar trial-unique face oddity judgment, when contrasted with scene or size oddity tasks. Activity in all of these regions decreased as the stimuli were repeated across trials, reflecting the participants' increasing familiarity with the stimuli. This change was significant in all areas, with the exception of the perirhinal cortex, right anterior hippocampus, and to a lesser extent the left anterior hippocampus during face oddity judgment. One possibility is that the activity in these regions may not reflect entirely episodic memory encoding but, in part, processes beyond the mnemonic domain. Thus, the perirhinal cortex, and possibly anterior hippocampus, may play a more generic role in the discrimination and processing of objects.

Keywords: hippocampus, memory, perception, perirhinal cortex, visual discrimination

Introduction

Recent studies in nonhuman primates and humans have demonstrated significant deficits in visual discrimination following medial temporal lobe (MTL) damage, a pattern that cannot be explained easily by a primary deficit in long-term declarative memory. In the context of oddity judgment tests, in which the odd one out is selected from an array of images (e.g., a different color, shape, or face) and biconcurrent discrimination tasks, in which the rewarded item out of a pair of stimuli (e.g., black and white photographs) must be chosen, monkeys with selective perirhinal cortex lesions show impairments in the discrimination of complex objects but not relatively simple visual features such as color, shape, and size (Buckley et al. 2001; Bussey et al. 2002, 2003). Importantly, deficits in visual discrimination are not evident when other MTL structures are damaged. For instance, in a study by Saksida et al. (2006), a group of hippocampal lesioned monkeys were not impaired on a complex, visual configuration learning task, in contrast to animals with perirhinal damage that demonstrated a significant deficit.

Similar to monkeys with perirhinal lesions, damage to the human perirhinal cortex in the context of larger MTL lesions, most often after an anoxic episode, encephalitis, or due to the neurodegenerative condition semantic dementia (SD; Davies

et al. 2004), results in visual discrimination difficulties for complex objects and faces when participants are tested on modifications of the aforementioned oddity and biconcurrent discrimination tests (Barense et al. 2005; Lee, Bussey, et al. 2005; Lee, Buckley, et al. 2005, 2006). Extending the animal findings, human patients with predominant involvement of the hippocampus bilaterally (e.g., patients with Alzheimer's disease [AD] and cases with static hippocampal lesions) show selective discrimination deficits for spatial scenes, in the context of intact complex object discrimination (i.e., in oddity judgment and biconcurrent discrimination tasks; Lee, Bussey, et al. 2005; Lee, Buckley, et al. 2005, 2006). Critically, the impairments seen in human patients have been demonstrated on tasks that do not place an explicit demand on long-term memory, with no requirement to remember stimuli across trials (see, however, Levy et al. 2005; Shrager et al. 2006).

This convergence between findings from monkeys and humans provides strong support for the view that the primate MTL is not specialized for long-term declarative memory. Instead, this region seems to be involved in very short-term working memory (Ranganath and Blumenfeld 2005; Ranganath and D'Esposito 2005; Hannula et al. 2006; Hasselmo and Stern 2006; Olson et al. 2006; Hartley et al. 2007) or even higher order perception with the hippocampus and perirhinal cortex important for the processing of spatial scenes and objects, respectively (Murray and Bussey 1999; Gaffan 2001; Bussey and Saksida 2005; Lee, Barense, et al. 2005; Buckley and Gaffan 2006).

A plausible criticism of this account of MTL function in humans is its reliance upon positive evidence from studies in neuropsychological patients (Barense et al. 2005; Lee, Bussey, et al. 2005; Lee, Buckley, et al. 2005, 2006). Although such investigations are fundamentally important for understanding which brain regions are critical to a particular cognitive process, a serious limitation is the inability to conclusively reject involvement of other brain structures that may seem normal on structural scanning. For example, whereas qualitative structural analyses have suggested little or no damage to lateral temporal lobe regions in patients with reported scene and object discrimination deficits (Lee, Bussey, et al. 2005; Lee, Buckley, et al. 2005, 2006), concomitant involvement of higher order visual processing regions such as area TE/TEO has been suggested to underlie the observed discrimination deficits in patients with MTL damage (Buffalo 1999; Shrager et al. 2006; Squire et al. 2006). This alternative explanation is difficult to rule out completely given that it is not entirely certain where precisely area TE/TEO is located in the human brain. Nevertheless, one piece of evidence that hints against the possible involvement of this region is the finding that the aforementioned

amnesic patients often show intact discrimination of simple stimuli (i.e., oddity judgment for shape, color, and size)(Lee, Bussey, et al. 2005; Lee, Buckley, et al. 2005), a process that monkey electrophysiological studies have suggested is dependent upon area TE/TEO (Tanaka 1996). This logic rests, however, on the belief that area TE/TEO is indeed functionally homologous in monkey and human.

One means by which the contribution of the MTL to visual discrimination can be assessed further is the use of functional neuroimaging in healthy subjects. More specifically, the demonstration of significant MTL activity in healthy participants during spatial scene and object discrimination tasks would provide further evidence for the idea that the MTL mediates processes beyond long-term memory. The existing neuroimaging literature provides some convergent evidence in the domain of spatial and object memory, with the former often reporting activity in the hippocampus (particularly posterior regions; Burgess et al. 2001; Cansino et al. 2002; Düzel et al. 2003; Bohbot et al. 2004; Jordan et al. 2004; Parslow et al. 2004; Pihlajamäki et al. 2004; Voermans et al. 2004) and the latter demonstrating perirhinal cortex involvement (Pihlajamäki et al. 2004; Tyler et al. 2004; Köhler et al. 2005). To date, however, few studies have attempted to compare activations in different MTL regions using the types of stimuli that seem to be particularly sensitive in amnesic individuals and, moreover, in the context of tasks that do not require the participant to hold onto and utilize information obtained from prior trials.

The present study, therefore, used functional magnetic resonance imaging (fMRI) to scan healthy individuals during oddity judgment for various classes of stimuli. Two oddity judgment tasks were employed as experimental conditions, namely “face oddity,” in which 3 different views of the same face were presented alongside a different view of a different face, and “scene oddity,” in which 3 different views of the same computer generated scene (an indoor environment) were presented with a different view of a different scene (see Experimental Methods). For a baseline task, oddity judgment for squares of varying sizes was used. In keeping with our previous findings of scene oddity judgment difficulties in patients with hippocampal lesions and face oddity judgment deficits associated with perirhinal cortex damage, we predicted that the scene and face oddity tasks would be associated with significant activity in the hippocampus and perirhinal cortex, respectively.

Importantly, we attempted to disentangle activity related to processes beyond memory (i.e., perception) and that due to mnemonic processing (i.e., episodic memory encoding and working memory) by dividing the present task into 3 separate phases, with “novel” stimuli presented in phase 1 and the same stimuli repeated in phases 2 and 3. In the context of working and episodic memory tasks, greater activity in the MTL has been associated with the presentation of novel stimuli, with decreasing levels of activity as the stimuli become increasingly familiar (Ranganath and D’Esposito 2001; Düzel et al. 2003; Henson et al. 2003; Weis et al. 2004; Gonsalves et al. 2005; Köhler et al. 2005; Strange et al. 2005). Thus, we expected that any activity related predominantly to mnemonic processing would decrease significantly in magnitude as the subjects became familiar with the stimuli across the different sessions. In contrast, it was possible that activations reflecting to some extent processes beyond memory may not change significantly irrespective of the relative familiarity of the presented stimuli.

Experimental Methods

Subjects

Twenty-eight right-handed healthy subjects (10 males) were scanned. Only data for 15 subjects were used, however, as 13 subjects were excluded due to poor magnetic resonance imaging (MRI) signal in the anterior MTL (see Image Preprocessing). The ages of the subjects (4 males) included in the main analyses ranged from 19 to 35 years (mean = 24.27 years, standard deviation = 4.56). All subjects gave informed written consent after the nature of the study, and its possible consequences were explained to them. This work received ethical approval from the Cambridgeshire Local Research Ethics Committee.

Image Acquisition

The scanning was carried out at the Wolfson Brain Imaging Centre (University of Cambridge, UK) using a 3T Bruker MRI scanner fitted with a head gradient insert and a birdcage resonator. Three 4-dimensional data sets were acquired for every subject. For each data set, an echo planar imaging (EPI) pulse sequence was implemented to acquire T_2^* -weighted image volumes with blood oxygen level-dependent (BOLD) contrast, and there were 21 axial oblique slices for each brain volume (slice thickness 4 mm, interslice distance 1 mm, matrix size 64×64 , in-plane resolution 3.9×3.9 mm, repetition time [TR] = 1.1 s, echo time [TE] = 27.5 ms, and flip angle = 65°). These slices were angled away from the eyeballs to prevent image ghosting. Each EPI session was 678 s in duration, consisting of 11 dummy scans at the start to allow the magnetic resonance signal to reach an equilibrium state (these were later discarded) and 606 subsequent data scans. A T_1 structural scan ($32 \text{ mm} \times 7 \text{ mm}$ slices) was acquired for each subject using a 3-dimensional spoiled gradient-echo sequence (TR = 19 ms, TE = 5 ms, flip angle = 25 degrees, field of view = $256 \times 220 \times 180$ mm, matrix size = $256 \times 220 \times 180$, and spatial resolution = $1 \times 1 \times 1$ mm). Magnetic field maps were also obtained for every subject using a multiecho FLASH sequence (for full details, see De Panfilis and Schwarzbauer 2005; Lee, Bandelow, et al. 2006). These field maps allowed BOLD signal levels to be determined in specified anatomical regions in each subject, thereby enabling the exclusion of participants from the final data analyses that did not have satisfactory BOLD signal in regions of interest (i.e., perirhinal cortex; see Image Preprocessing). In addition to this, the field maps were used to undistort the EPI data sets during image preprocessing (Jezzard and Balaban 1995; Cusack and Papadakis 2002; Cusack et al. 2003).

Visual stimuli were presented during scanning with a custom Microsoft Visual Basic 6.0 program (Microsoft Corporation, Redmond, WA) running on an IBM compatible desktop computer connected to an LCD projector (1024×768 pixels resolution). The latter projected onto a white screen situated behind the scanner subject bed, and this could be seen via an angled mirror placed directly above the subject’s eyes in the scanner. The responses for the experimental task were made using a 4-button response box held in the right hand, and response times and accuracy were automatically recorded by the computer.

Experimental Paradigm

Each EPI session (3 in total) consisted of 105 trials divided equally into a ABC-ABC-ABC-ABC-ABC-ABC-ABC blocked design where “A” refers to a face oddity condition, “B” refers to a scene oddity condition, and “C” refers to a size oddity condition (35 trials for each condition, split across 7 blocks of 5 trials). A blocked design was implemented in order to maximize experimental power. All stimuli were novel in the first EPI session (i.e., each stimulus was unfamiliar and only used in one trial). These stimuli were then repeated across sessions 2 and 3 in a different pseudorandomized presentation order.

In all 3 task conditions, a trial consisted of 4 images (faces, virtual reality scenes, or black squares) positioned in 2 rows of 2 on a white screen. Each trial lasted 6 s (5 s stimulus display time and 1 s intertrial interval), during which the participants were required to select the odd one out by pressing the corresponding button on a 4-button response box as quickly but as accurately as possible. The location of the odd stimulus was randomly determined in the 2×2 array. Figure 1 illustrates a single ABC block and a representative trial from each condition.

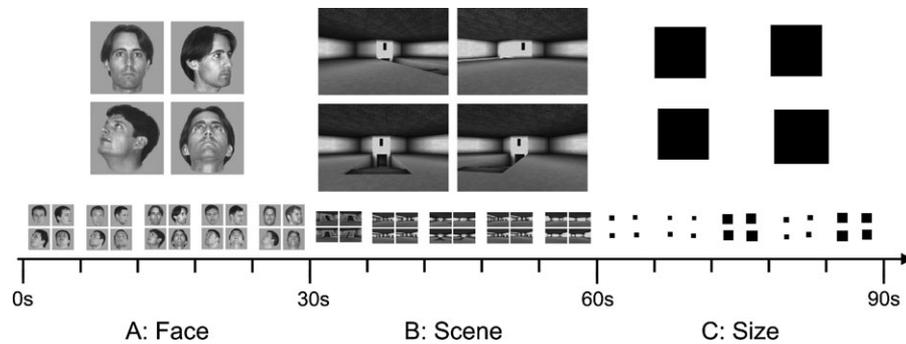


Figure 1. Schematic diagram of a single block of (a) face oddity, (b) scene oddity, and (c) size oddity trials.

- A) **Face Oddity:** On each trial, 4 grayscale images of human faces were presented on a gray background (256×256 pixels). Three of the images were of the same face taken from different viewpoints, whereas the fourth image was of a different face taken from another view. The same 4 viewpoints were used for each trial, with the top left image depicting a face looking directly ahead, the top right image depicting a face looking 45 degrees to the left, the bottom left image depicting a face looking 45 degrees to the right and tilted upward, and finally, the bottom right image depicting a face looking upwards. A set of 70 unfamiliar (nonfamous) male Caucasian faces (aged 20–40 years, with no spectacles) was used and 2 different faces were presented on each trial (i.e., no face was used more than once in each session).
- B) **Scene Oddity:** On each trial, 4 grayscale images of 3-dimensional virtual reality (computer generated) rooms were presented (460×370 pixels). Three of the images were of the same room taken from 3 different viewpoints, whereas the fourth image was of a different room taken from a fourth viewpoint. The 2 rooms in each trial were similar to each other but differed with respect to the size, orientation, and/or location of one or more features of the room (e.g., a window, staircase, and wall cavity). A set of 70 rooms were used, 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), with no room being used more than once in each session.
- C) **Size Oddity:** On each trial, 4 black squares of a randomly determined size were presented. Three squares were of the same dimension, whereas the fourth square was either larger or smaller in size. Each trial was unique within each EPI session, and the positions of the 4 squares in the 2×2 array were jittered such that the edges of the squares were not aligned. The latter allowed the difficulty of this condition to be closely matched to that of the face and scene oddity tasks.

Clear instructions and 2 short practice sessions involving a different set of stimuli (one outside and another inside the scanner) were administered prior to scanning.

Image Preprocessing

The fMRI data were preprocessed and analyzed using Statistical Parametric Mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London, UK). Preprocessing involved: 1) correcting all images for slice timing using the middle slice in each volume as a reference; 2) realigning all images with respect to the first image via sinc interpolation and creating a mean image; 3) undistorting the EPI data to correct for magnetic field distortions; 4) normalizing the undistorted images to $3 \times 3 \times 3$ -mm voxels in Montreal Neurological Institute (MNI) space, by using each subject's structural scan and a MNI T_1 -average brain template; and finally 5) spatially smoothing all normalized images with a 8-mm full-width, half-maximum Gaussian kernel.

It is well known that the anterior MTL regions (in particular the perirhinal cortex) often suffer from a low signal-to-noise ratio (Ojemann et al. 1997). Because the perirhinal cortex was one of the key regions of interest in this study, it was important, therefore, that any statistical

analyses did not include data sets in which there was a poor level of BOLD signal within this area. To achieve this, the BOLD sensitivity maps acquired for each participant were used to identify subjects that suffered from low signal in the perirhinal cortex. Given the anterior-posterior extent of the perirhinal cortex, a specific region of interest (ROI) within the perirhinal cortex was determined on the basis of previous work and was then used to investigate BOLD sensitivity. In an earlier study, a cluster of voxels within the perirhinal cortex was found to be significantly active when subjects successfully perceived a difference in object identity between 2 simultaneously presented groups of 3 object images (Lee, Bandelow, et al. 2006). An ROI sphere (10 mm diameter) centered on the most significant voxel from this finding ($36, -16, -24$) was defined for the current study. Because we had no prediction concerning the laterality of activity during the present oddity tasks, a similar ROI sphere was also created for the left hemisphere ($-36, -16, 24$). For every voxel in this bilateral ROI, the BOLD signal value was then extracted from the sensitivity maps for each subject. Any subjects' functional data were then excluded from statistical analysis if more than 40% of their voxels within this ROI in either hemisphere did not have a BOLD signal value of at least 0.8 (where 1 represents normal BOLD signal intensity). Using this criterion, 13 subjects were excluded from statistical analyses reported below. Critically, this methodological procedure, in which extent of BOLD signal dropout was estimated using BOLD sensitivity maps prior to any statistical analyses of the cognitive questions of interest is independent of any MTL lobe activity during the oddity tasks and consequently would not have influenced the pattern of results expected from the study, other than to increase the likelihood of obtaining reliable and robust signal in perirhinal cortex. The full analysis, including all 28 participants is reported in detail in the Supplementary material in order to allow readers to evaluate any differences across the different sized participant groups, and a discussion of these findings is included in the Discussion section.

Statistical Analysis: Effects of Stimulus Type

To assess the involvement of the MTL in oddity judgment for novel stimuli only, the data from the first EPI session were initially analyzed separately. For those subjects that remained following the aforementioned BOLD sensitivity assessment ($n = 15$), statistical analyses were first conducted at a single-subject level. The hemodynamic responses to each stimulus block (specified as time of stimulus onset of the first trial in a block until the subject's response time for the last trial in that block) were modeled using the standard canonical hemodynamic response function (HRF). To reduce the influence of extraexperimental subject error, blocks were only included if the behavioral performance was above chance (i.e., at least 2 out of 5 correct). Using this criteria, 5 face, 8 scene, and 2 size oddity blocks were removed from session one across all 15 subjects, leaving 100 face, 97 scene, and 103 size blocks. The resulting functions were then implemented in a general linear model (GLM), including a constant term. The data and model were high-pass filtered with a cut-off of $1/128$ s, to remove low-frequency noise. The parameter estimates relating to the height of the HRF response to each condition type (i.e., face, scene, and size oddity) were calculated on a voxel by voxel basis (Friston et al. 1995) to create one contrast image for each subject and event type.

A second-level random-effects group analysis was subsequently carried out by entering the parameter estimates for the 3 conditions for each subject into a single GLM and then conducting pairwise *t*-tests across the conditions using the pooled error from the model (Henson and Penny 2003). These contrasts were between 1) face oddity and size oddity (i.e., face minus size oddity and size minus face oddity); 2) scene oddity and size oddity (i.e., scene minus size oddity and size minus scene oddity); and finally, 3) face oddity and scene oddity (i.e., face minus scene oddity and scene minus face oddity). Whereas the first 2 contrasts identified regions of activity that were significantly greater during the experimental tasks in comparison to size oddity judgment, only direct subtractions between the face and scene oddity tasks highlighted regions of activity that were specific to each experimental condition.

Given that activations within the temporal lobe were of primary interest, a small volume correction approach was carried out in the temporal lobes bilaterally. This volume was defined using MRICro (Rorden and Brett 2000) by an experienced neurologist and encompassed the lateral and medial surfaces of the temporal lobe from the tip of the temporal pole until a posterior limit of $y = -72$. Regions of activity which survived an intensity threshold of $P \leq 0.05$ corrected for multiple comparisons via false detection rate (FDR; Benjamini and Hochberg 1995; Genovese et al. 2002) are reported in Tables 1–3. All coordinates have been transformed from normalized MNI to Talairach space (see <http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>) in order to determine the location of activation within the Talairach and Tournoux (1988) brain atlas.

Table 1

Regions of significant BOLD signal change when the face oddity condition was contrasted with the size oddity condition in the first EPI session only

Region	Stereotaxic coordinates				<i>P</i> (FDR)	<i>Z</i> value
	Brodman area	<i>x</i>	<i>y</i>	<i>z</i>		
Increases for face oddity condition						
Right hemisphere						
Amygdala		18	-6	-12	<0.0001	5.40
Hippocampus		33	-18	-9	<0.0001	4.08
		24	-32	2	<0.0001	5.99
Superior temporal cortex	22	48	-43	12	0.004	3.32
Fusiform cortex	37	39	-50	-15	<0.0001	6.76
		42	-53	-10	<0.0001	6.73
	37	42	-62	-15	<0.0001	6.27
Middle temporal cortex	39	48	-67	6	<0.0001	4.87
Left hemisphere						
Amygdala		-18	-6	-12	<0.0001	5.35
Perirhinal cortex	36	-30	-7	-27	0.037	2.61
Hippocampus		-30	-12	-12	0.006	3.46
		-21	-32	-1	<0.0001	6.49
		-33	-32	-1	0.001	4.25
Fusiform cortex	37	-36	-47	-10	<0.0001	10.34
	37	-42	-59	-12	<0.0001	9.39
Middle temporal cortex	39	-42	-66	12	0.027	2.77
Increases for size oddity condition						
Right hemisphere						
Insula		42	2	-10	<0.0001	4.50
		42	-15	-2	0.001	3.96
Superior temporal cortex	22	56	-3	0	<0.0001	4.73
		48	-31	18	<0.0001	5.13
Inferior temporal cortex	20	48	-4	-23	0.004	3.44
Middle temporal cortex	21	45	-9	-10	<0.0001	4.50
		50	-29	-6	0.015	2.91
Transverse temporal cortex	41	39	-29	12	<0.0001	4.44
Lingual cortex	30/37	18	-47	-5	0.018	2.84
Fusiform cortex	19	18	-58	-2	0.01	3.06
Lingual cortex	18	21	-61	1	0.025	2.69
Left hemisphere						
Superior temporal cortex						
	22	-45	-3	0	<0.0001	5.15
		-59	-11	9	0.005	3.33
		-59	-31	18	<0.0001	4.75
	21	-59	-51	19	0.039	2.50
Insula		-42	-18	-4	<0.0001	5.17
Transverse temporal cortex	31	-39	-26	10	0.002	3.74
Middle temporal cortex	21	-62	-26	-4	0.011	3.04
Lingual cortex	19	-12	-55	0	0.009	3.11

Results: Effects of Stimulus Type

Behavioral Data

Figure 2 illustrates the behavioral performance for the subjects on the different conditions of the oddity task for session 1 only. Two 1-way analysis of variance (ANOVAs) conducted on all trials (i.e., including experimental blocks on which performance was at chance) revealed no significant difference between the 3 task conditions in terms of performance accuracy ($F_{2,42} = 0.519$, $P < 0.6$), but there was a significant difference with respect to response times for correct trials ($F_{2,42} = 30.844$, $P < 0.0001$). Further post hoc *t*-tests (Tukey's Honestly Significantly Different, HSD) to investigate the latter indicated that the response times for the face and scene oddity conditions were significantly slower than those for the size oddity condition (both $P < 0.0001$). In contrast, the response times for the face and scene oddity conditions were similarly matched ($P > 0.1$).

Imaging Data

Because this study was focused primarily on the MTL, only findings within this area are reported below. Regions of significant activation beyond the MTL are listed in Tables 1–3.

Table 2

Regions of significant BOLD signal change when the scene oddity condition was contrasted with the size oddity condition in the first EPI session only

Region	Stereotaxic coordinates				<i>P</i> (FDR)	<i>Z</i> value
	Brodman area	<i>x</i>	<i>y</i>	<i>z</i>		
Increases for scene oddity condition						
Right hemisphere						
Hippocampus		24	-32	2	<0.0001	6.53
Parahippocampal cortex	27	9	-32	-1	<0.0001	5.60
	36	33	-36	-13	<0.0001	6.39
	30	12	-41	2	<0.0001	4.98
		30	-47	-8	<0.0001	7.21
Inferior temporal cortex	37	53	-44	-8	<0.0001	4.99
Middle temporal cortex	39	45	-66	14	<0.0001	3.90
Left hemisphere						
Fusiform cortex	37	-33	-47	-10	<0.0001	7.03
	37	-48	-59	-15	<0.0001	5.19
	19	-33	-58	-2	<0.0001	6.35
Inferior temporal cortex	37	-50	-62	-10	<0.0001	5.19
Hippocampus		-24	-29	-4	<0.0001	6.22
		-21	-35	2	<0.0001	5.95
Parahippocampal cortex		-24	-52	0	<0.0001	6.10
Increases for size oddity condition						
Right hemisphere						
Middle temporal cortex	21	36	10	-28	0.004	3.60
		39	7	-31	0.007	3.38
		56	-13	-17	0.007	3.39
Insula		45	-9	-10	0.001	4.52
		42	-11	3	0.002	3.96
Superior temporal cortex	22	59	-6	6	0.001	4.33
Inferior temporal cortex	20	48	-7	-22	0.002	3.94
Transverse temporal cortex	41	50	-25	15	0.001	4.64
Left hemisphere						
Superior temporal cortex						
	38	-48	13	-23	0.031	2.66
	22	-56	-25	18	0.001	4.73
	22	-45	-37	18	0.003	3.78
	22	-56	-57	17	0.007	3.32
Insula		-45	-6	0	0.001	4.65
		-45	-9	-10	0.001	4.90
		-42	-18	-4	0.001	4.82
Perirhinal cortex	28/36	-24	-10	-25	0.014	3.03
Hippocampus		-9	-10	-17	0.007	3.34
		-21	-13	-17	0.009	3.24
		-30	-18	-17	0.007	3.32

Table 3

Regions of significant BOLD signal change when the face oddity condition was contrasted with the scene oddity condition in the first EPI session only

Region	Stereotaxic coordinates				P (FDR)	Z value
	Brodman area	x	y	z		
Increases for face oddity condition						
Right hemisphere						
Middle temporal cortex	21	36	10	-28	<0.0001	4.41
	37	53	-61	11	0.021	3.05
	39	48	-67	6	0.002	3.83
Amygdala	21	-7	-15		<0.0001	6.12
Perirhinal cortex	36	30	-7	-25	0.014	3.19
Fusiform cortex	37	42	-50	-18	<0.0001	4.88
Inferior temporal cortex	37	50	-70	3	0.001	4.15
Left hemisphere						
Amygdala		-18	-9	-15	<0.0001	5.60
		-30	-1	-18	<0.0001	5.08
Hippocampus		-30	-15	-17	0.001	4.03
Perirhinal cortex	36	-27	-7	-25	0.002	3.86
Fusiform cortex	37	-42	-50	-10	<0.0001	4.64
Increases for scene oddity condition						
Right hemisphere						
Superior temporal cortex	38	45	14	-11	0.022	2.68
	22	48	9	-3	0.012	2.88
		65	-17	4	0.024	2.64
Middle temporal cortex		53	-34	18	0.022	2.67
	21	59	-23	-1	0.02	2.70
	45	-29	-6		<0.0001	4.26
Thalamus		27	-32	10	0.004	3.28
Lingual cortex	30	12	-44	2	<0.0001	5.68
	19	12	-55	0	<0.0001	4.47
Parahippocampal cortex		30	-47	-8	<0.0001	7.51
Fusiform cortex	37	27	-58	3	<0.0001	6.36
Inferior temporal cortex	37	53	-59	-7	<0.0001	4.32
Left hemisphere						
Superior temporal cortex	38	-50	11	-3	0.01	2.96
	22	-53	5	-10	0.02	2.70
Middle temporal cortex	21	-62	-29	-1	0.027	2.59
	21	-53	-32	-6	0.009	2.98
Thalamus		-27	-32	4	0.006	3.10
Parahippocampal cortex		-30	-39	-13	<0.0001	5.86
		-24	-44	-8	<0.0001	6.46
		-21	-52	0	<0.0001	6.81
		-21	-52	0	<0.0001	6.81
Inferior temporal cortex	20	-53	-41	-8	0.027	2.59
	37	-53	-61	-4	0.003	3.31
Fusiform cortex	37	-27	-56	-5	<0.0001	6.75

Face Oddity versus Size Oddity

When activity associated with the size oddity condition was subtracted from that associated with the face oddity task, significant regions of BOLD signal change were observed in the left perirhinal cortex (Fig. 3a), the posterior hippocampus bilaterally, and also the anterior hippocampus extending into the amygdala in both hemispheres. A plot of the contrast estimates across the 3 task conditions at the local maxima of the perirhinal cortex activation revealed that the BOLD signal change was greatest in this region for the face oddity task, followed by the size and scene oddity conditions (Fig. 3b). The reverse contrast (face oddity subtracted from size oddity) did not yield any significant regions of activity anywhere within the MTL.

Scene Oddity versus Size Oddity

The subtraction "scene oddity minus size oddity" produced significant regions of BOLD signal change in the posterior hippocampus (Fig. 3c) and parahippocampal cortex bilaterally. Figure 3d illustrates the contrast estimates in the left posterior hippocampus across the 3 task conditions and reveals that activity in this area was greatest for the scene oddity task, followed by the face and size conditions. When activity associated with scene oddity judgment was subtracted from that

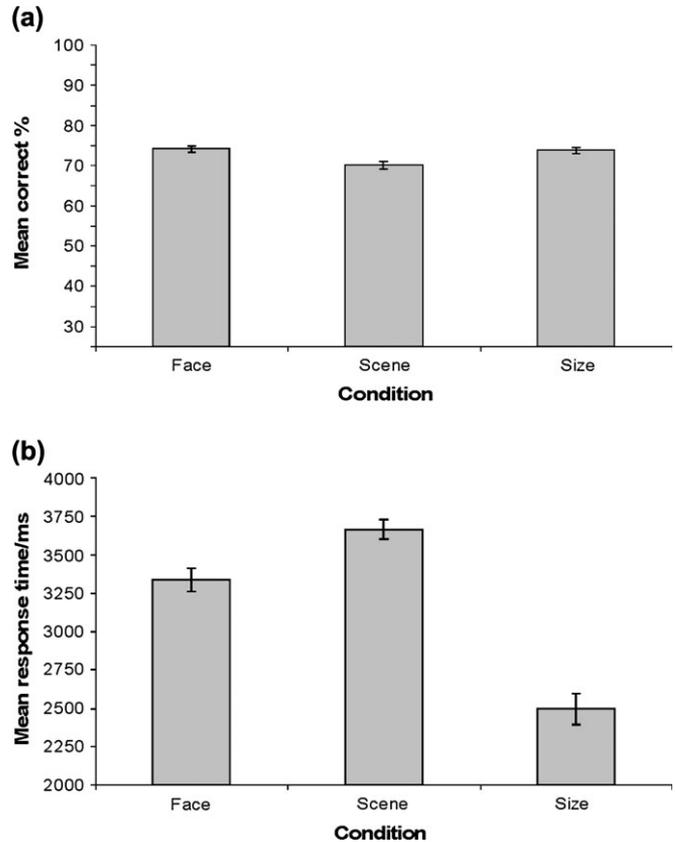


Figure 2. Mean (a) response accuracy and (b) response times (\pm standard error [SE]) for the 3 task conditions in the first scanning session only (includes all behavioral data, including experimental blocks on which performance was below chance).

associated with size oddity (size oddity - scene oddity), significant regions of activity were observed in the left perirhinal cortex and the left anterior hippocampus.

Face Oddity versus Scene Oddity

When the face and scene oddity tasks were contrasted with each other, regions of significant activity were observed in the MTL (Fig. 4). The face oddity condition was associated with significant bilateral perirhinal cortex activity, as well as significant BOLD signal change in the left anterior hippocampus and the amygdala bilaterally. From Figure 4a, it can be seen that a significant cluster of activity was found encompassing the anterior hippocampus and perirhinal cortex. It is possible that the perirhinal cortex activity was simply a result of activity "spilling over" from the anterior hippocampus. This is, however, unlikely because the observed left perirhinal cortex activation (-27, -7, -25) was almost identical to that found for the face minus size oddity subtraction (-30, -7, -27), in which 2 distinct clusters of activity were clearly evident in the left anterior hippocampus and perirhinal cortex (Fig. 3).

In contrast to the face oddity condition, scene oddity produced significant activity in a network of posterior regions encompassing the posterior hippocampus and parahippocampal cortex (local maxima in the left parahippocampal cortex).

Statistical Analysis: Effects of Stimulus Repetition

The first statistical analysis revealed significant regions of activity within the MTL. In particular, greater perirhinal cortex

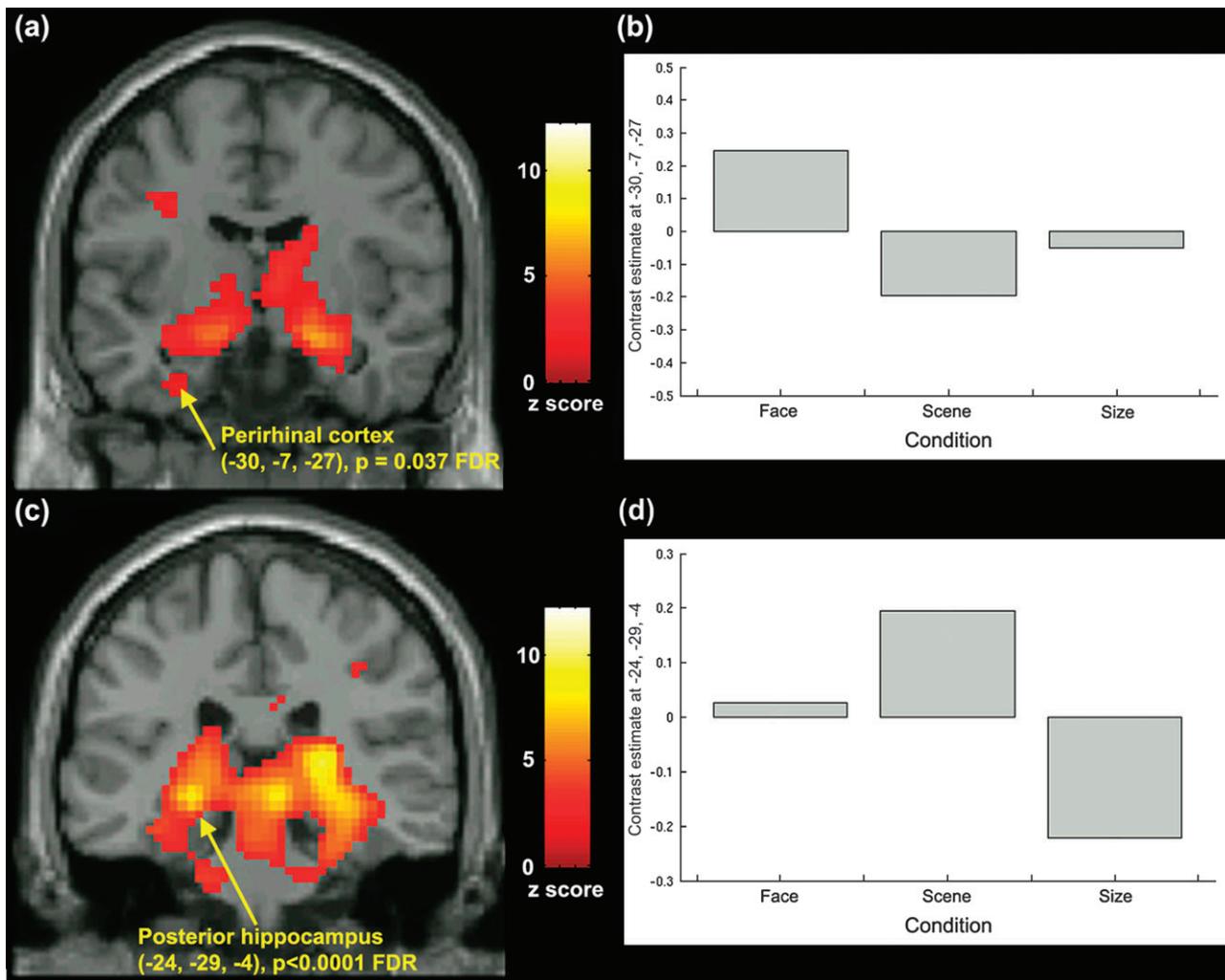


Figure 3. (a) Significant regions of activity when the size oddity condition was subtracted from the face oddity task, superimposed on a coronal slice of a standard MNI brain template. (b) The contrast estimates for the left perirhinal cortex activation across the 3 task conditions. Part (c) shows the significant regions of activity when the size oddity condition was subtracted from the scene oddity task, superimposed on a coronal slice of a standard brain template. (d) The contrast estimates for the left posterior hippocampus activation across the 3 task conditions. For both contrast estimate graphs, $\gamma = 0$ corresponds to the mean level of activity across all 3 conditions.

and anterior hippocampus activity was observed during the face oddity condition, whereas the scene oddity task was associated with greater BOLD signal change in the posterior hippocampus and parahippocampal cortex. Given that these findings were from the first EPI session only, in which all stimuli were presented for the first time, it is possible that the observed MTL activity reflected stimulus novelty (i.e., incidental encoding). To investigate this possibility a second statistical analysis was conducted to assess whether activity within the MTL was modulated by repetition of the stimuli across the 3 EPI sessions. More specifically, if the MTL activity observed during the first session was due, in part, to incidental encoding, then one would expect this activity to decrease significantly as the stimuli became increasingly familiar to the subjects (termed the old-new effect, Henson et al. 2003).

At the single-subject level, the hemodynamic responses to each stimulus block within each EPI session were first modeled using the standard canonical HRF. Across all 3 EPI sessions, a total of 7 face, 11 scene, and 6 size oddity blocks were excluded due to poor behavioral performance (i.e., below chance), leaving 308 face, 304 scene, and 309 size blocks across all 15

subjects. The resulting functions were then implemented in a GLM with a constant term, and the data and model were high-pass filtered with a cut-off of 1/128 s. The parameter estimates relating to the height of the HRF response to each condition type within each EPI session were calculated on a voxel by voxel basis (Friston et al. 1995). For each subject and session, the following pairwise contrasts were then conducted 1) face oddity minus size oddity; and 2) scene oddity minus size oddity. These contrasts were chosen in order to take into account the baseline condition, and as seen in the previous analysis, they yielded clear MTL activations that were similar to those seen for the face versus scene oddity comparisons. In total 6 contrast images were created per participant (i.e., face minus size oddity for sessions 1, 2, and 3; and scene minus size oddity for sessions 1, 2, and 3).

Second-level random-effects group analyses were then conducted by performing 2 separate 1-way ANOVAs across all subjects, one between the parameter estimates for the face minus size subtraction for every session and a second between the parameter estimates for the scene minus size subtraction for every session. For each ANOVA, F -tests were then performed

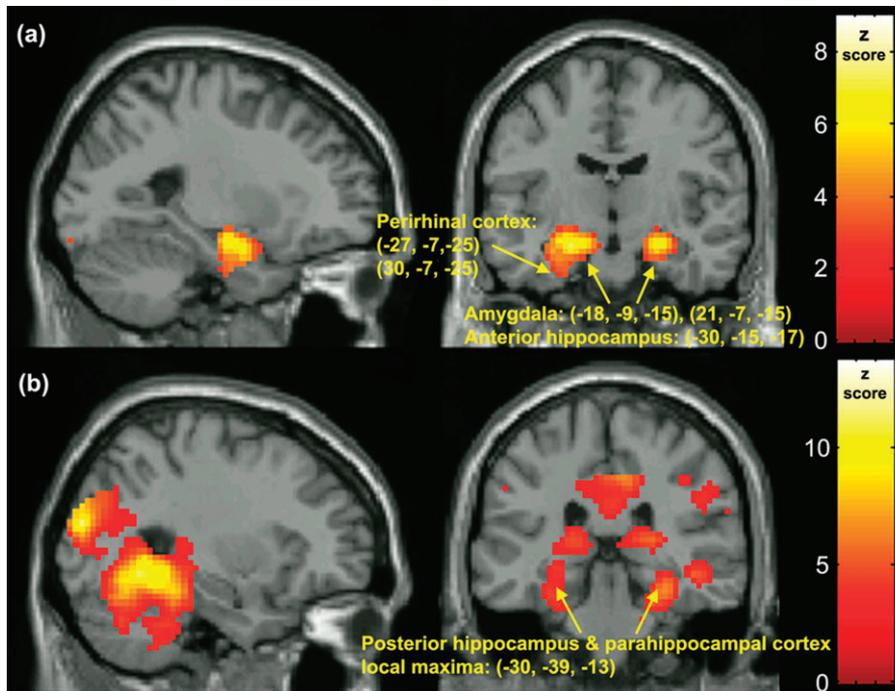


Figure 4. Significant regions of activity associated with (a) face oddity judgment and (b) scene oddity judgment when these 2 conditions were contrasted with each other, superimposed on a coronal slice of a standard MNI brain template.

using the MarsBar tool (Brett et al. 2002) to assess the effect of stimulus repetition on MTL activity observed during the first EPI session. For the face minus size comparison, 3 ROIs were used, which were created by defining 5 mm spheres centered on the left perirhinal cortex (-30, -7, -27) and left (-30, -12, -12) and right (33, -18, -9) anterior hippocampal activations that were observed for the face minus size subtraction at the group level for the first EPI session only. In contrast, four 5 mm ROI spheres were used for the space minus size comparison, including the most posterior foci in the hippocampus (left: -21, -35, 2; right: 24, -32, 2) and the left (-24, -52, 0) and right (30, -47, -8) parahippocampal cortex. The center of these regions were established on the basis of the MTL activity that was seen when the size condition was subtracted from the space oddity task at the group level for the first EPI session only (see Results: Effects of Stimulus Type).

Results: Effects of Stimulus Repetition

Behavioral Data

As expected, the subjects' behavioral performance in terms of response accuracy and response times improved across the 3 EPI sessions (Fig. 5). A repeated-measures ANOVA was conducted on the accuracy data for all trials (i.e., including experimental blocks on which performance was at chance), and this revealed a significant effect of session ($F_{2,28} = 29.65$, $P < 0.0001$), but not condition type ($F_{2,28} = 0.45$, $P = 0.6$). Three 1-way ANOVAs were then conducted for each condition, and these indicated that there was a significant improvement in accuracy across sessions for the face ($F_{2,42} = 3.93$, $P = 0.03$) and scene oddity ($F_{2,42} = 3.49$, $P = 0.04$) tasks, but not for the size oddity task ($F_{2,42} = 0.53$, $P = 0.6$). The lack of significant improvement in the size condition is not surprising because it would have been difficult for the subjects to remember a large

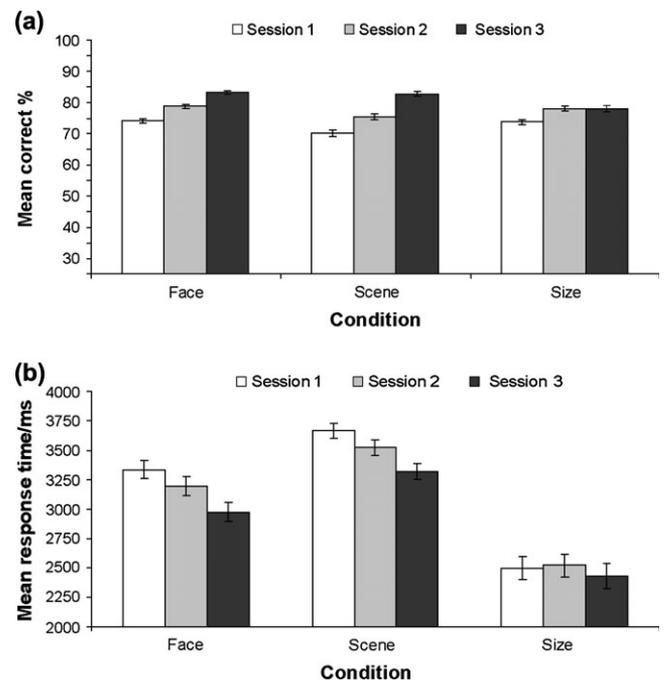


Figure 5. Mean (a) response accuracy and (b) response times (\pm SE) for the 3 task conditions in each of the 3 scanning sessions (includes all behavioral data, including experimental blocks on which performance was below chance).

number of individual black squares across trials, which differed only with respect to size. Further post hoc tests (Tukey's HSD) for the face and scene conditions showed that in both cases, there was no statistically significant improvement between sessions 1 and 2 (both $P > 0.3$) or between sessions 2 and 3 (both $P > 0.3$). There was, however, a significant difference between the first and last sessions (both $P \leq 0.03$).

Similar statistical analyses were also conducted for the response time data, again including all trials. In contrast to the above, a repeated-measures ANOVA revealed significant effects of session ($F_{2,28} = 75.75, P < 0.0001$), condition type ($F_{2,28} = 16.28, P < 0.0001$) and also, a significant interaction between these 2 factors ($F_{4,56} = 4.07, P = 0.006$). Further, 1-way ANOVAs showed that there was a significant effect of session on response times for the scene oddity task ($F_{2,42} = 3.90, P = 0.03$), whereas there was only a trend toward a significant effect for the face oddity condition ($F_{2,42} = 2.96, P = 0.06$) and no significant difference across sessions for size oddity judgment ($F_{2,42} = 0.12, P = 0.9$). Post hoc tests (Tukey's HSD) for the scene condition revealed that there was a significant difference in response times between the first and third sessions ($P = 0.02$), but not between any of the other sessions (all $P > 0.2$).

Finally, because there was a main effect of condition for the response times, three 1-way ANOVAs were conducted for each session across the 3 condition types. These revealed that there was a significant effect of condition type in sessions 1, 2, and 3 (all $F_{2,42} > 15, P < 0.0001$), and post hoc tests showed that in each case, this was due to the response times for the size oddity task being significantly slower in comparison to those for the face and scene oddity conditions (all $P \leq 0.005$). There were no significant differences between the response times

for face and scene oddity judgment in any of the 3 EPI sessions (all $P < 0.09$).

Imaging Data

Face Oddity Minus Size Oddity

Using ANOVAs across all 3 scanning runs, none of the MTL ROIs defined from the analysis of the first EPI session were associated with a significant effect of stimulus repetition (left perirhinal cortex: $P = 0.4$, left anterior hippocampus: $P = 0.2$; right anterior hippocampus: $P = 0.2$). It is important to note, however, that there was a nonsignificant decrease in activity in all of these regions (Fig. 6).

Behavioral data analyses indicated that there was only a significant improvement in performance accuracy between sessions 1 and 3, and not between session 1 and 2 or between sessions 2 and 3. Thus, to investigate further the findings from the imaging analysis ANOVAs, *t*-tests were conducted using the MarsBar tool between sessions 1 and 3 only in order to assess any differences in activation in the left perirhinal cortex, left and right anterior hippocampus ROIs. These tests revealed that there was still no significant effect of stimulus repetition in the left perirhinal cortex ($P = 0.2$) and right anterior hippocampus ($P = 0.2$) despite a significant improvement in task performance,

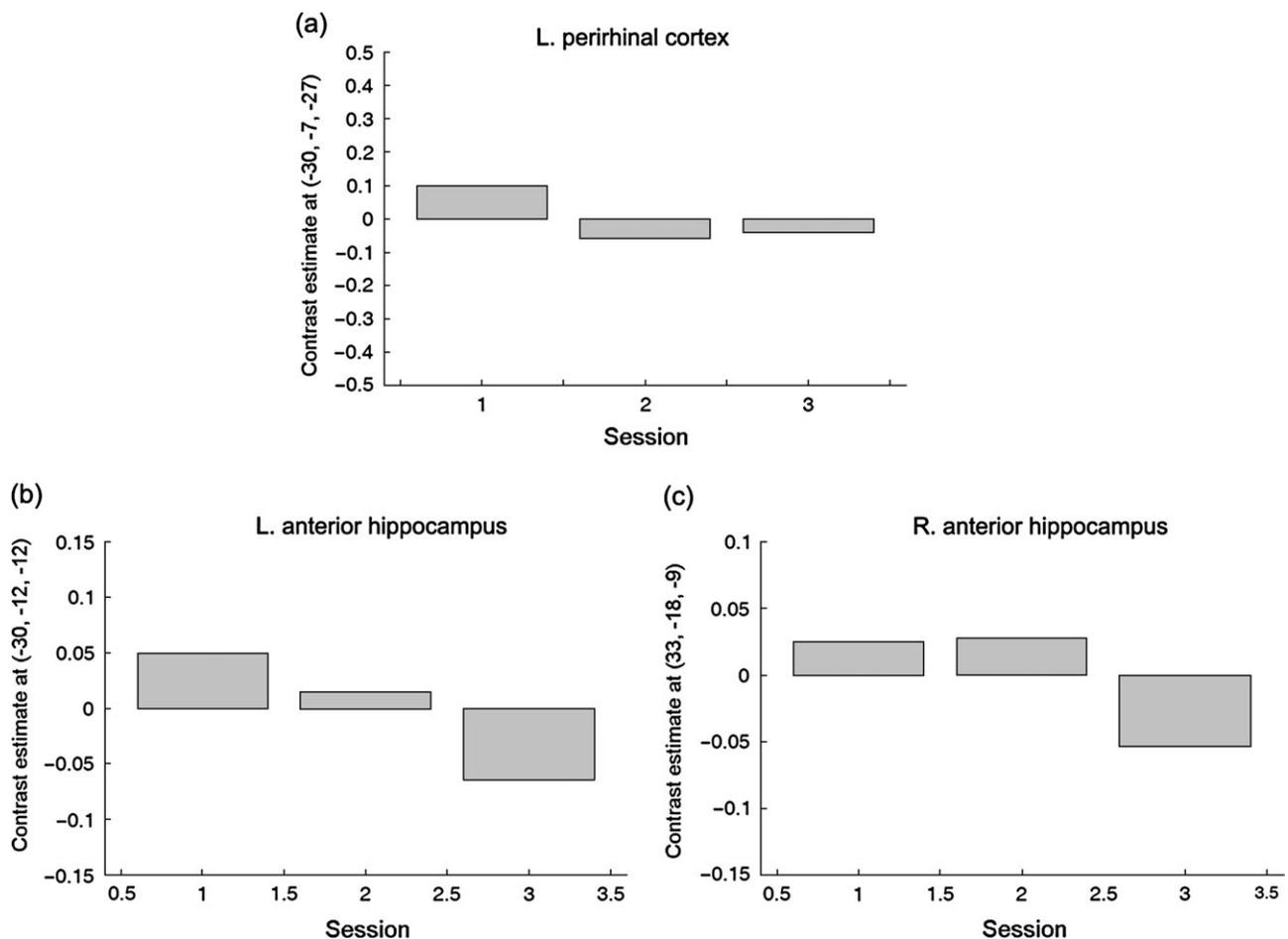


Figure 6. Contrast estimates for the most significant voxel in ROI in the (a) left perirhinal cortex and (b) left and (c) right anterior hippocampus, across each of the scanning sessions. These ROIs were identified from the subtraction “face oddity minus size oddity” for the first scanning session only. On the y axis, 0 reflects the mean level of activity across all 3 sessions.

although there was a trend toward significance in the left anterior hippocampus ($P = 0.07$).

Scene Oddity Minus Size Oddity

ANOVAs revealed that activity in the right posterior hippocampus ($P = 0.04$) and parahippocampal cortex ($P = 0.004$) ROIs (definition based on the first analysis) were found to be modulated significantly as the stimuli were repeated across the 3 EPI sessions. In the right posterior hippocampus, there was a slight decrease in activity across the first 2 sessions, followed by a larger decrease in activation in the last session. Similarly, in the right parahippocampal cortex there were successive decreases in activity in the second and third EPI sessions (see Fig. 7). In contrast, there was no effect of session in the left parahippocampal cortex ($P = 0.1$), nor the left posterior hippocampus ROI ($P = 0.2$).

Further investigation of this null finding using the MarsBar tool to conduct t -tests across sessions 1 and 3 only revealed, however, that both of these ROIs were associated with a significant decrease in activation when session 2 was not considered (left parahippocampal cortex, $P = 0.02$; left posterior hippocampus, $P = 0.05$; Fig. 7).

Discussion

Nonhuman primates and humans with perirhinal cortex damage have significant difficulties with oddity judgments for faces and

other objects presented from different views (Buckley et al. 2001; Lee, Buckley, et al. 2005, 2006), whereas humans with hippocampal lesions have deficits in making oddity judgments for spatial scenes presented from different views (Lee, Buckley, et al. 2005, 2006). To provide convergent evidence regarding the neural correlates of these tasks, the present study used fMRI to scan healthy subjects during oddity judgment for various types of stimuli. Consistent with the published lesion studies, face oddity judgment was associated with greater activity in the perirhinal cortex and anterior hippocampus when contrasted with scene oddity judgment, whereas a scene oddity condition led to greater activation of the posterior hippocampus and parahippocampal cortex when compared with face oddity.

Stimulus Effects in the MTL

Previous neuroimaging and neuropsychological studies have suggested functional differences between MTL regions in the processing of objects and scenes in the context of mnemonic and visual discrimination tasks, with the perirhinal cortex implicated in processing objects, including faces, and the hippocampus important for spatial scenes (Murray et al. 1989; Zhu et al. 1996; Bohbot et al. 1998, 2004; Holdstock et al. 2000; Vann et al. 2000; Buckley et al. 2001; Spiers et al. 2001; King et al. 2002; Hartley et al. 2003; Hampton et al. 2004; Jordan et al. 2004; Voermans et al. 2004; Winters et al. 2004; Lee, Buckley, et al.

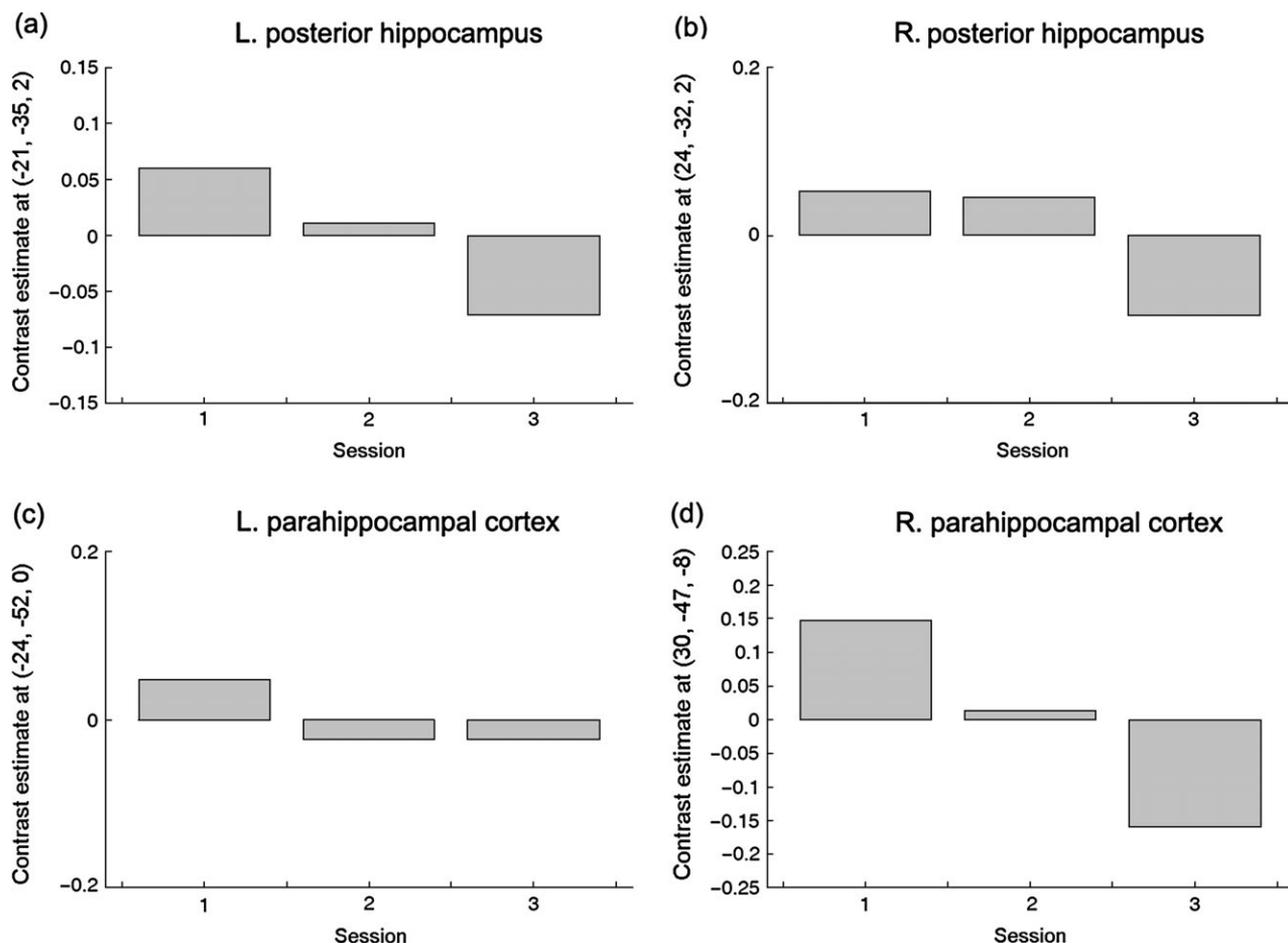


Figure 7. Contrast estimates for the most significant voxel in ROI in the (a) left and (b) right posterior hippocampus and (c) left and (d) right parahippocampal cortex across each of the scanning sessions. These ROIs were identified from the subtraction scene oddity minus size oddity for the first scanning session only. On the y axis, 0 reflects the mean level of activity across all 3 sessions.

2006). Our current data clearly support this division of labor within the MTL but also raise the possibility of further specialization within the hippocampus, with the anterior hippocampus playing a general role in object processing and the posterior hippocampus in spatial scene processing. This anterior-posterior dichotomy is supported by several lines of evidence in the literature. First, anatomical studies in animals suggest that different regions of the hippocampus receive unique afferents from the entorhinal cortex (Witter et al. 1989; Dolorfo and Amaral 1998). Second, there appears to be a greater concentration of neurons that are active during tasks of spatial memory in posterior, compared with anterior, regions of the monkey hippocampus (Colombo et al. 1998). Third, human anterior hippocampal activity has been observed during memory and discrimination tasks involving objects (Pihlajamäki et al. 2004; Köhler et al. 2005; Lee, Bandelow, et al. 2006), whereas tasks involving spatial stimuli, such as navigation and memory for spatial locations, have been associated with activity more posteriorly in the hippocampus (Maguire et al. 1997; Burgess et al. 2001; Parslow et al. 2004; Pihlajamäki et al. 2004).

Further evidence for a functional distinction between the anterior and posterior hippocampus comes from a neuropsychological study that assessed visual discrimination in SD and AD patients (Lee, Buckley, et al. 2006). Both diseases are characterized by damage throughout the MTL, although SD is associated with disproportionate perirhinal cortex and anterior hippocampus damage and AD patients have greater damage to the posterior hippocampus (Laakso et al. 2000; Chan et al. 2001). Consistent with the idea that the anterior and posterior hippocampus may be functionally distinct, the SD patients were impaired in oddity judgment for faces but not scenes, whereas the AD cases exhibited the reverse performance profile.

Although the amygdala is not a focus of this study, it is important to highlight that activity of this structure was seen during face oddity. This observation supports a role for the amygdala in face processing and emotion perception (Adolphs et al. 1994; Haxby et al. 2000; Gorno-Tempini et al. 2001). It is unlikely that amygdala dysfunction, by itself, can explain the face oddity judgment impairments seen in previous patient studies (Lee, Buckley, et al. 2005, 2006) as damage to this structure was not present in all patients and the deficits shown by these individuals were only present on different view, but not same view, face discrimination.

The MTL and Processes beyond Memory

A novel aspect of the current study was the use of an experimental paradigm that did not place an explicit demand on long-term memory; there was no explicit requirement to remember stimuli across trials because the subjects were instructed to select the odd one out from an array of simultaneously presented images. The observed MTL activity during face and scene oddity judgment may, therefore, reflect one or more cognitive processes required to perform this type of discrimination, including complex object/scene perception (O'Keefe and Nadel 1978; Murray and Bussey 1999; Buckley and Gaffan 2006; Graham et al. 2006), short-term working memory (Ranganath and Blumenfeld 2005; Ranganath and D'Esposito 2005), or alternatively, incidental episodic encoding. In an effort to dissociate MTL activity related to these different processes, the participants were presented with previously unseen stimuli during the first EPI session, followed by repetitions of the same stimuli in the ensuing second and third sessions. Thus, whereas

perceptual demands are likely to have remained similar across the EPI sessions, memory processing may have varied as the stimuli were repeated, for instance, with greater incidental memory encoding during the first session when the stimuli were novel. Consistent with this hypothesis, the subjects' behavioral performance on face and scene oddity improved significantly across the 3 runs as measured by improved accuracy and shorter response times, suggesting item learning as the same images were presented across sessions.

As mentioned in the Introduction, increasing familiarity with presented stimuli has been associated with decreasing levels of MTL activity in the context of episodic memory (Düzel et al. 2003; Henson et al. 2003; Weis et al. 2004; Gonsalves et al. 2005; Köhler et al. 2005; Strange et al. 2005) and working memory tasks (Ranganath and D'Esposito 2001). In the present study, the different MTL activations all decreased in magnitude as the stimuli were repeated from sessions 1 to 3 (Figs. 6 and 7). Not all of these changes were statistically significant, however: neither the activity in the left perirhinal cortex nor bilateral anterior hippocampus during face oddity reduced significantly from sessions 1 to 3, even as the stimuli became more familiar to the subjects. This observation was true irrespective of whether ANOVAs were used to analyze activity across sessions 1, 2, and 3 or *t*-tests were conducted across sessions 1 and 3 only, between which there was the greatest improvement in task performance (although the latter produced a trend toward significance in the left anterior hippocampus).

The lack of a significant decrease in activity in left perirhinal cortex and right anterior hippocampus (and to a lesser extent the left anterior hippocampus) during the repetition of face stimuli contradicts previous studies that have demonstrated significant novelty signals in the anterior MTL and deserves careful consideration. One viable possibility is that the current experimental design was not conducive for the detection of encoding related activity in the anterior MTL (although significant encoding effects were seen more posteriorly—see later comment). In contrast to previous investigations, a blocked design was used here and participants' memory for individual stimuli was not assessed, for example, via a "yes/no" recognition test. Thus, it was not possible to exclude trials for which participants had failed to successfully learn the presented stimuli and to conduct systematic analyses of the cortical regions involved in successful encoding (or familiarity detection).

Furthermore, the lack of a postscanning recognition test meant that it was unknown whether the improvement in task performance across scanning sessions was explicit or implicit in nature. The MTL is traditionally thought to be critical to explicit, but not implicit, memory (Cohen and Squire 1980), and thus, a failure to observe novelty signals in the anterior MTL may reflect the absence of explicit learning. Recent research has, however, questioned this psychological distinction, demonstrating MTL involvement in implicit memory tasks (Chun and Phelps 1999; Turk-Browne et al. 2006) and deficits in implicit memory for scenes, but not faces, in amnesic individuals (Graham et al. 2006). The latter study is further evidence that the type of presented stimulus (i.e., objects vs. scenes) may be a more critical determinant of MTL involvement than the nature of the memory taxed.

An alternative explanation for our failure to observe a significant decrease in the left perirhinal cortex and anterior hippocampus (particularly in the right hemisphere) activity across EPI sessions is that these activations may not be due

entirely to episodic memory encoding or active working memory maintenance of novel face stimuli. Instead, it is possible that the observed activity reflects, in part, a role for these regions in processing object information beyond the mnemonic domain. To investigate this further, it would be necessary to repeat the current study in the context of an event-related paradigm with intermixed oddity judgment trials for faces, scenes, and size, to allow for more detailed analyses of the effects of stimulus learning on MTL activity.

Concerning scene oddity, activity in the right posterior hippocampus and parahippocampal cortex did decrease significantly when activity across all sessions was considered. Significant changes were also observed in these regions in the left hemisphere but only when activity in sessions 1 and 3 were analyzed separately from that in session 2. This significant decrease in activity provides clear evidence that the MTL signal observed during the scene oddity task in session 1 reflects the encoding of the novel stimuli. This does not necessarily rule out the involvement of the posterior hippocampus in scene perception but strongly indicates that this region does not mediate scene perception exclusively and plays an important role in memory for spatial information.

It is important to highlight that there is some uncertainty surrounding the interpretation of decreases or even increases in BOLD signal within MTL regions, typically associated with the subsequent recognition of previously seen stimuli (see Henson 2005). For instance, it is possible that a decrease in BOLD signal within MTL structures would be predicted by both a perceptual and a mnemonic account. In the former, this could reflect a strengthening of novel perceptual representations resulting in faster and more efficient activation of these items (a form of perceptual learning and/or priming; Graham et al. 2006). In the latter, the decreases would reflect episodic encoding of the presented stimuli. It is difficult, therefore, to conclusively interpret the present MTL findings as reflecting perceptual and/or mnemonic processing. Indeed, the distinction between perception and memory can be unclear because any representations that are created following the perception of a stimulus may form the basis of all memories, whether in the episodic or working memory domain.

Theories of Scene and Object Processing

Besides hippocampal and perirhinal activity, scene and face oddity judgment were also associated with activity in the parahippocampal place area (PPA; Epstein and Kanwisher 1998) and the fusiform face area (FFA; Kanwisher et al. 1997; McCarthy et al. 1997), respectively. It is unclear how the contribution of the PPA and FFA to scene and face processing may differ from that of the hippocampus and perirhinal cortex. A mnemonic account of the MTL suggests that the hippocampus and perirhinal cortex are only critical to the rehearsal of episodic details of spatial/object memories and that the actual spatial/object schema are stored and processed in other regions, such as the PPA and FFA. Thus, the hippocampus, for example, may not be important for all remote spatial memories and complex spatial processing can be conducted in the absence of this structure following brain injury (Teng and Squire 1999; Rosenbaum et al. 2000; Moscovitch et al. 2005).

In contrast, a perceptual account of the hippocampus and perirhinal cortex suggests that representations of scenes/objects are stored in these 2 regions. Consequently, these structures are recruited irrespective of the age of a spatial/

object memory or the relative familiarity of a presented spatial/object stimulus. One prominent theory is that the hippocampus, particularly the posterior extent, may process allocentric representations of spatial scenes to form a cognitive map (O'Keefe and Nadel 1978; Burgess et al. 2002). In contrast, the PPA may coordinate the information that is necessary for the construction of these allocentric maps, for instance, egocentric representations or topographical information (Aguirre and D'Esposito 1999; Burgess et al. 2002; Epstein et al. 2003). A similar idea may also extend to object processing with the FFA being critical to the viewpoint-dependent representation of faces and the perirhinal cortex having a broader role of processing viewpoint-independent representations of objects (including faces). Although the present data do not speak to this issue, it is possible that this interpretation is oversimplistic. First, it has been debated whether the FFA and PPA are indeed specialized for the processing of faces and spatial scenes only or whether both of these areas are part of a larger network of cortical regions that are involved in the processing of objects in general (Haxby et al. 2001; Hanson et al. 2004). Second, our previous patient work has demonstrated that visual discrimination deficits can be elicited in patients with MTL damage even when the processing of viewpoint-independent representations is not required. For instance, cases with hippocampal damage are impaired at discriminating images of spatial scenes, which have been blended to create a high level of overlapping features, whereas patients with perirhinal damage have difficulties discriminating objects that share many features (Barene et al. 2005; Lee, Bussey, et al. 2005).

An alternative theory is that the posterior hippocampus may process conjunctions of spatial features (i.e., the spatial relationships between the items that constitute a scene; Buckley et al. 2004), whereas the perirhinal cortex, and perhaps the anterior hippocampus, may process conjunctions of object features (i.e., the relationships between the features that constitute an object; Murray and Bussey 1999). This idea is not dissimilar to the relational memory theory (Eichenbaum et al. 1994; Eichenbaum and Cohen 2002), which suggests that the hippocampus is critical for the formation of memories for relationships among distinct items. One crucial difference, however, is that this alternative view proposes that the cognitive function of the MTL may not be restricted to long-term declarative memory. Thus, the hippocampus and perirhinal cortex may store representations of spatial scenes and objects, which are activated during tasks involving scenes and objects irrespective of the demands placed on mnemonic processing (i.e., tests of perception, short-term working memory, long-term declarative memory, or even nondeclarative memory; Graham et al. 2006).

Interestingly, this study found significant perirhinal cortex activity during size oddity judgment when compared with the scene oddity task. This finding perhaps emphasizes the specialization of the perirhinal cortex for the processing of objects and not spatial scenes but is seemingly at odds with the idea that the perirhinal cortex processes complex objects. Further research is necessary to understand this issue further, but one possible explanation is that even the perception of some less complex objects places a need for processing feature conjunctions (i.e., the sides, color and size of the shape). This demand, however, is relatively low compared with that during different views face oddity judgment as evidenced by the greater perirhinal activity during the face task. Moreover, processing feature conjunctions is unlikely to be critical to successful performance on size

oddy judgment because patients with perirhinal damage are intact on this task (Lee, Buckley, et al. 2005).

The Use of BOLD Sensitivity Maps

A defining characteristic of the present study is that BOLD sensitivity maps were acquired for all participants in order to assess the signal in the anterior MTL. An ROI in the perirhinal cortex was defined on the basis of a previous study (Lee, Bandelow, et al. 2006) and those subjects with poor MRI signal in this area on the basis of a predetermined threshold were excluded from the imaging analyses. Critically, this procedure was based on a factor (extent of BOLD signal dropout) that was independent from the experimental effects of interest (MTL activity during oddity judgment). Moreover, it appears unlikely that the use of BOLD sensitivity maps affected experimental findings beyond the anterior MTL. The accompanying Supplementary material details the findings when the same neuroimaging analyses were conducted on all 28 subjects' data, including those with poor anterior MTL BOLD signal. Beyond the anterior MTL, the patterns of activity associated with the experimental conditions for all 28 subjects were extremely similar to those seen for the preselected 15 participants, albeit more significant due to a greater number of subjects and thus more statistical power (Supplementary Tables 1–3; Supplementary Fig. 1). Significant perirhinal cortex activity was not, however, observed for all 28 participants in association with face oddity judgment, presumably due to the inclusion of a large number of subjects in whom there was substantial BOLD signal dropout in the region of the perirhinal cortex. Statistical analysis on all 28 participants also failed to reproduce the local maxima within the left and right anterior hippocampus during face oddity, although there was a significant cluster of activity encompassing the amygdala and spreading posteriorly into the anterior hippocampus. Finally, stimulus repetition analyses on all 28 subjects for regions beyond the perirhinal cortex yielded results similar to those for the smaller group of preselected subjects. For the scene minus size oddity comparison, there were significant changes in BOLD signal across the 3 EPI sessions in ROIs in the posterior hippocampus and parahippocampal cortex bilaterally (defined from the 28 subject analyses). There was no significant decrease in BOLD signal, however, in the left or right anterior hippocampus for the face minus size oddity subtraction, using ROIs defined from the 15 subject analyses (because the 28 subject analyses produced no local maxima in this region; Supplementary Material Part 2, Supplementary Figs 2 and 3).

Summary

This study clearly demonstrates differential involvement of distinct MTL structures in the processing of different classes of stimuli in the context of a visual discrimination task. Face oddity judgment was associated with amygdala, perirhinal cortex, and anterior hippocampus activity, whereas scene oddity judgment resulted in significant posterior hippocampus and parahippocampal cortex activity. It is uncertain whether these perirhinal and hippocampus activations reflect perceptual processes, mnemonic processing, or a combination of the two. Nevertheless, considering previous work in nonhuman primates and human patients with MTL damage, it is possible that the current findings support a role for the perirhinal cortex (and possibly anterior hippocampus) in processing object feature

conjunctions and the posterior hippocampus in processing complex spatial scenes.

Supplementary Material

Supplementary materials can be found at: <http://www.cercor.oxfordjournals.org/>.

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Notes

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Address correspondence to email: andy.lee@psy.ox.ac.uk.

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