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Perirhinal cortex activity during visual object discrimination: An event-related fMRI study

Andy C.H. Lee,* Stephan Bandelow, Christian Schwarzbauer, Richard N.A. Henson, and Kim S. Graham

MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 2EF, UK

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Previous fMRI studies have demonstrated preferential involvement of the perirhinal cortex and hippocampus in tasks of object and spatial memory, respectively. Here we investigated whether similar activity would also be present when object and spatial discrimination was assessed in the absence of explicit declarative memory demands. On each trial in the scanner, participants were presented simultaneously with two arrays of objects and were asked to indicate whether both arrays were identical, differed with respect to the identity of one object or differed with respect to the spatial arrangement of the objects. It was found that the detection of an object identity change was associated with significant right perirhinal cortex activity. We suggest that this perirhinal activity indicates a role of this structure in processes beyond declarative memory, for example, short-term visual working memory or higher order perception. Significantly greater hippocampal activity was not, however, observed during the spatial arrangement condition, perhaps due to the relatively low spatial processing demands of this task.

Introduction

The medial temporal lobe (MTL) is widely regarded as vital for long-term "declarative" memory (Cohen and Squire, 1980). One recent theoretical debate is whether the perirhinal cortex and other MTL structures function as a single unitary memory system (Squire and Zola-Morgan, 1991; Squire, 2004), or whether each area mediates a distinct process in long-term memory, for example, familiarity versus recollection (Aggleton and Brown, 1999; Brown and Aggleton, 2001). Although there is no overwhelming pattern of findings within the functional neuroimaging literature (for a review, see Henson, 2005), there appear to be two emerging trends that do imply functional segregation in the MTL. First, recent fMRI investigations have suggested that the perirhinal cortex may be critical to the encoding of item information in long-term memory, whereas the hippocampus and posterior parahippocampal cortex may be particularly important for encoding contextual information (Davachi et al., 2003; Ranganath et al., 2004). For instance, Davachi et al. (2003) found that encoding-related activity in the perirhinal cortex predicted subsequent recognition of previously seen words but not recollection of the context in which the words were first presented (i.e., source memory). In contrast, encoding-related activity in the hippocampus and posterior parahippocampal cortex predicted source but not item memory. Furthermore, a number of studies have found changes in perirhinal cortex activity associated with the recognition of previously learned items, including words, faces, abstract visual patterns and pictures of objects (e.g., De Zubicaray et al., 2001; Rombouts et al., 2001; Henson et al., 2003; Herron et al., 2004).

A second trend in the functional neuroimaging literature is that there is growing evidence to indicate that the perirhinal cortex may play a specific role in memory for objects (Pihlajamäki et al., 2004; Tyler et al., 2004). In comparison, the hippocampus (particularly posterior regions) may be preferentially involved in spatial memory. Hippocampal activity is typically associated with allocentric spatial paradigms (Burgess et al., 2001; Bohbot et al., 2004; Jordan et al., 2004; Parslow et al., 2004), although some studies have also reported significant activation of the hippocampus during tasks that assess spatial memory but do not explicitly require viewpoint independence (Cansino et al., 2002; Düzel et al., 2003; Pihlajamäki et al., 2004; Voermans et al., 2004). While a number of studies have investigated the involvement of the hippocampus and perirhinal cortex in spatial and object memory respectively (Düzel et al., 2003; Köhler et al., 2005), perhaps the most clear demonstration of this functional dichotomy comes from an fMRI study by Pihlajamäki et al. (2004) in which subjects were presented on each trial with 5 drawings of objects arranged within a 3 by 3 array of squares, and had to detect changes in this array across trials. Data analyses were restricted to a small temporal lobe volume encompassing the MTL and anterior temporal lobe, and it was found that when the identity of one object was changed across successive trials, with the arrangement of the objects held constant (i.e., when object memory was assessed), there was

* Corresponding author. Fax: +44 1223 359062.
E-mail address: andy.lee@mrc-cbu.cam.ac.uk (A.C.H. Lee).
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significant activity in the perirhinal cortex and anterior hippocampus. In contrast, when the arrangement of the images was altered across successive trials but the objects were identical (i.e., when egocentric spatial memory was assessed), the posterior hippocampus, but not the perirhinal cortex, was significantly activated.

A recent and more controversial extension to the notion that the perirhinal cortex and hippocampus are differentially involved in object and spatial memory is the suggestion that these two structures may, in fact, also subserve processes beyond long-term declarative memory, such as very short-term working memory (Ranganath and Blumenfeld, 2005; Ranganath and D'Esposito, 2005) or even the higher order perception of objects and spatial scenes (Murray and Bussey, 1999; Buckley et al., 2001; Gaffan, 2001; Bussey et al., 2002). Studies in nonhuman primates and amnesic human patients have demonstrated that lesions to the perirhinal cortex can impair the ability to discriminate objects (e.g., faces, novel objects), but not simple visual stimuli (e.g., color, size), in the context of tasks that do not possess an overt declarative memory demand (Buckley et al., 2001; Bussey et al., 2003; Lee et al., 2005a,b, 2006). Moreover, human amnesics with hippocampal damage exhibit difficulties discriminating spatial scenes when a high demand is placed on processing spatial information, for example, discriminating images of scenes that have been blended to create a high level of overlapping features or perceiving virtual reality rooms from multiple viewpoints (Lee et al., 2005a,b, 2006). Such findings have led to the view that the ventral "what" visual processing stream may culminate in the perirhinal cortex and that this area is critical to the processing of conjunctions of object features (Murray and Bussey, 1999). Similarly, it is possible that the hippocampus may be important for the representation of conjunctions of spatial information, binding together the different aspects that constitute a scene (Buckley et al., 2004; Lee et al., 2005b) and, which may contribute to the formation of a cognitive map (O'Keefe, 1976).

In disagreement with these recent ideas, however, there have been a few studies that have suggested that MTL damage does not, in fact, lead to visual discrimination difficulties (Stark and Squire, 2000; Levy et al., 2005; Shrager et al., 2006). It is unclear why this discrepancy in the literature exists although it is important to note that there are key experimental differences between these studies and those that have found discrimination deficits, which may explain some of the disparities in findings. In brief, these differences pertain to the types of stimuli used and the set sizes of these stimuli, whether trial-unique stimuli were employed, the performance levels of healthy controls and finally, the types of patients assessed and the location of their cortical damage (for further discussion, see Bussey et al., 2006; Buckley and Gaffan, 2006; Lee et al., 2005c; Squire et al., 2006).

If the MTL does indeed subserve processes beyond long-term declarative memory then an alternative interpretation of the MTL activity typically seen in association with fMRI tasks of object and spatial memory (e.g., Pihlajamäki et al., 2004) is that this activity may, in fact, be indicative of a role for the perirhinal cortex and hippocampus in more generic object and spatial processing, including perception. In support of this possibility, a fMRI study by Tyler et al. (2004) reported significantly greater activity in the perirhinal cortex in participants during basic level naming of visually presented objects (i.e., naming the picture itself, for example, "cat", "dog") compared to naming at a domain level (i.e., classifying an object as living or nonliving). It was argued that basic level naming places a greater demand on fine-grained differentiation among objects and as a result, the perirhinal cortex is more heavily involved in basic level naming in its role as the apex of the ventral "what" visual processing stream (Tyler et al., 2004; Bright et al., 2005). It is important to note, however, that both Pihlajamäki et al. (2004) and Tyler et al. (2004) used experimental paradigms that placed a significant demand on declarative memory, with the former assessing (short-term) episodic memory processing, and the latter requiring the retrieval of semantic knowledge about objects. Consequently, it is difficult to ascertain whether the MTL activity observed in these studies reflects solely mnemonic processing, an interpretation in accordance with a traditional understanding of the MTL as subserving long-term memory exclusively (Stark and Squire, 2000; Levy et al., 2005; Shrager et al., 2006) or reflects to some extent underlying higher order perceptual processes as suggested by recent studies in nonhuman primates and humans (Buckley et al., 2001; Bussey et al., 2002; Lee et al., 2005a,b, 2006).

The current fMRI study, therefore, aimed to investigate whether perirhinal cortex and hippocampal activity would be present in a visual discrimination task that does not possess an explicit declarative memory demand. To achieve this, the paradigm of Pihlajamäki et al. (2004) was adapted by minimizing the need for subjects to encode and retrieve stimulus information across time. Within an event-related design, participants were presented simultaneously on each trial with two arrays of 6 squares (Fig. 1). Three of the squares in each array contained images of objects, whereas the remaining three squares were empty. The subjects were instructed to determine whether (1) both arrays were different with respect to the identity of one object (with spatial arrangement kept constant); (2) different with respect to the arrangement of the objects (with object identity kept constant); or (3) identical in terms of both object identity and arrangement. According to previous findings (Pihlajamäki et al., 2004; Tyler et al., 2004; Lee et al., 2005a,b), we predicted that the detection of an object difference between the two panels (i.e., successful visual object discrimination) would lead to significant perirhinal activity, and possibly anterior hippocampal activity. Likewise, it was possible that the detection of an arrangement change (i.e., successful spatial discrimination) would be associated with hippocampal activation, particularly in posterior regions.

Materials and Methods

Subjects

Twenty-two right-handed healthy subjects (4 male) were scanned in total. The data for 2 participants, however, had to be excluded prior to data analyses due to technical problems. For the subjects who were included, the ages ranged from 18 to 35 years (mean age = 25.09 years; stdev = 5.34). In the main neuroimaging data analyses of MTL structures only, a further 6 subjects were excluded (14 subjects remaining) due to significant MRI signal loss in regions of interest (see sections "Scanning procedure" and "Imaging data second-level statistical analysis—MTL only"). All subjects gave informed written consent after the nature of the study and its possible consequences were explained to them. This work

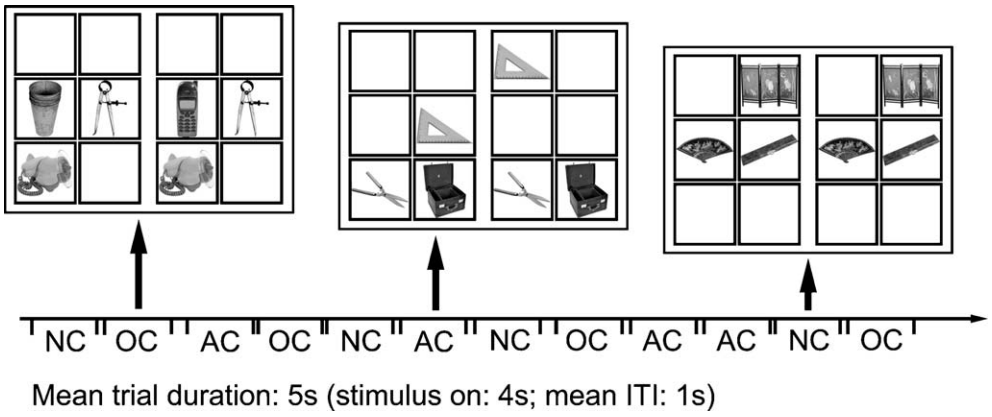

Fig. 1. Abbreviated time-line illustrating the three different trial types. Key: OC = *object change* condition; AC = *arrangement change* condition; NC = *no change* condition.

received ethical approval from the Cambridgeshire Local Research Ethics Committee.

Scanning procedure

The scanning was carried out at the Wolfson Brain Imaging Centre (Cambridge, UK) using a 3 T Bruker MRI scanner fitted with a head gradient insert and a birdcage resonator. Three four-dimensional datasets were acquired for every subject. For these, an echo planar imaging (EPI) pulse sequence was implemented to acquire *T*2*-weighted image volumes with blood oxygen level-dependent (BOLD) contrast. There were 21 axial-oblique slices for each brain volume angled away from the eye balls to prevent image ghosting (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, flip angle = 65°). The shortest possible TR was chosen in combination with the optimum flip angle (Ernst angle) in order to maximize the signal-to-noise ratio per unit time. Each EPI run was 650 s in duration, consisting of 580 scans and 11 dummy scans at the start to allow the MR signal to reach an equilibrium state (these were later discarded). A T1 structural scan (32 mm × 7 mm slices) and magnetic fieldmaps were also obtained for each subject. The former was acquired using a three-dimensional spoiled gradient echo (3D SPGR) sequence (TR = 19 ms; TE = 5 ms; flip angle = 25°; field of view = 256 × 220 × 180 mm; matrix size = 256 × 220 × 180 giving a spatial resolution of 1 × 1 × 1 mm).

The magnetic fieldmaps were acquired using a multi-echo FLASH sequence and they enabled BOLD signal levels to be determined in specified anatomical regions in each subject (De Panfilis and Schwarzbauer, 2005). 16 gradient echoes were acquired, the first echo was at 7.655 ms, and the interecho spacing was $\Delta t = 0.6336$ ms. Thirty-two axial slices were acquired (slice thickness 3 mm, interslice distance 1 mm, matrix size 64 × 64, in-plane resolution 3.7 × 3.7 mm). For these images, a thinner slice thickness (3 mm) was chosen compared to the EPI sequence in order to improve the accuracy of the calculation of the magnetic field gradient in the *z*-direction. The same slice thickness was not used for EPI acquisition since 32 slices would then have been required to cover the entire brain, resulting in a longer TR. Phase values φ_n were calculated from the real and imaginary components of the image intensity of the 16 gradient echo images, and the resulting ambiguity in the phase evolution was removed by phase unwrapping. Maps of the static magnetic field B_0 were then obtained by linear regression based on $\varphi_n = \varphi_0 - \gamma B_0.\mathrm{TE}_n$, where φ_0 is a constant phase offset, TE_n is the echo time of the *n*th echo image, and γ is the ^{1}H gyromagentic ratio. In order to eliminate the intrinsic phase difference between odd and even echoes, linear regression was performed separately for each echo type giving two values of B_0, which were subsequently averaged. From the resulting B_0 map, a BOLD sensitivity map was calculated for each subject based on a theoretical framework described in detail elsewhere (De Panfilis and Schwarzbauer, 2005). As a result of this procedure, it was then possible to exclude subjects from the final data analyses who did not have adequate BOLD signal in regions of interest that are known to be highly vulnerable to susceptibility artefacts (i.e. perirhinal cortex; see Results). In addition to this, the fieldmaps were used to undistort the EPI datasets during image preprocessing (Jezzard and Balaban, 1995; Cusack and Papadakis, 2002; Cusack et al., 2003).

During scanning, visual stimuli were presented with a custom program written using Microsoft Visual Basic 6.0 (Microsoft Corporation, Redmond, Washington, USA). This program was run on an IBM compatible desktop computer connected to a LCD projector (1024 × 768 pixel resolution) that projected onto a white screen situated behind the subject's head. The screen could be seen via an angled mirror placed above the subject's eyes in the scanner. The responses for the experimental task were made using three specified buttons on a four-button response box held in the right hand.

Experimental paradigm

Each EPI run (3 in total) consisted of 120 trials, divided equally into three types of events (40 each): *object change*; *arrangement change*; and *no change*. Within each run, these events were pseudo-randomized and there were three orders counterbalanced across the 3 EPI runs and the participants.

For all three event types, the subjects were presented with two simultaneous grids for 4 s (there was a randomly jittered intertrial interval, ITI, of mean 1 s, during which the screen was blank). The grids were 215 × 415 pixels in size and divided into 6 squares arranged in a 2 by 3 array (see Fig. 1). Three of the squares in each

grid contained greyscale digital photographs of everyday objects (taken from Photo Objects 50,000 Vol. 1–3, Hemara Technologies Inc, Quebec, Canada), whereas the remaining three squares were empty. The identity and positions of the objects were randomly determined and 400 items were used for each EPI run (total 1200), with each image *never* repeated across trials (i.e., every trial was unique). The subjects were instructed to compare the two grids on each trial and determine whether (1) the identity of one of the objects was different across the two grids (i.e., an *object change* event, indicated by a middle button box press); (2) the spatial position of one of the objects was different across the two grids (i.e., an *arrangement change* event, indicated by a right button box press); or (3) the two grids were identical both in terms of the objects and their arrangement (i.e., a *no change* event, indicated by a left button box press). The participants were encouraged to make their responses as quickly but as accurately as possible before the stimuli were removed from the screen and both performance accuracy and response times were recorded. To ensure that the subjects understood what they had to do in the task, a practice session involving a separate stimulus set was administered outside of the scanner prior to scanning.

Imaging data preprocessing

All fMRI data were preprocessed and analyzed using Statistical Parametric Mapping software (SPM2, Wellcome Department of Imaging Neuroscience, London). Data preprocessing consisted of (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 $3\times3\times3$ mm voxels in Montreal Neurological Institute (MNI) space, by using each subject's structural scan and a MNI T1 average brain template; and finally (5) spatially smoothing all normalized images with a 8 mm full width, half maximum (FWHM) Gaussian kernel.

Imaging data first-level statistical analysis

Following preprocessing, statistical analyses were first conducted at a single subject level. The hemodynamic responses to each trial type (specified as time of stimulus onset until the subject's response time) were modeled using the standard canonical hemodynamic response function (HRF). Only trials with a correct response were included in this analysis. The resulting functions were then implemented in a general linear model (GLM), including a constant term. The data and model were highpass filtered with a cut-off of 1/128 s, to remove low-frequency noise. The parameter estimates for each event type (i.e., *object change*, *arrangement change*, and *no change*) were calculated for each session on a voxel by voxel basis (Friston et al., 1995) and these were then averaged across sessions to create one contrast image for each subject and condition type.

Imaging data second-level statistical analysis—whole brain

For a second-level random effects group analysis, the parameter estimates for the three conditions (for all 20 subjects) were entered into a single GLM, and pairwise *t*-tests were conducted across the conditions using the pooled error from the model (Henson and Penny, 2003). These contrasts were between (1) *object change* and *no change* events; (2) *arrangement change* and *no change* events; and also, (3) *object change* and *arrangement change* events. To identify regions of significant BOLD signal change, a threshold of $p\leq0.05$ corrected for multiple comparisons via false detection rate (FDR) was applied at the whole brain level (Benjamini and Hochberg, 1995; Genovese et al., 2002). All coordinates were transformed from normalized MNI space to Talairach space (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) in order to determine the location of activation within the Talairach brain atlas (Talairach and Tournoux, 1988).

Imaging data second-level statistical analysis—MTL only

Given that the anterior MTL (particularly perirhinal cortex) can have low signal-to-noise ratio owing to susceptibility artifacts (Ojemann et al., 1997), it is possible that substantial BOLD signal loss in certain subjects in this region may undermine the significance of any activation at a group-level analysis. To account for this possibility, a BOLD signal analysis was conducted using the sensitivity maps acquired for each subject during scanning (see Scanning procedure). Given the anterior–posterior extent of the perirhinal cortex (Insausti et al., 1998), a region of interest (ROI) in the perirhinal cortex was first defined. This ROI was based on an area of activation that was observed in the perirhinal cortex at a low threshold of $p\leq0.05$ (uncorrected, whole brain level analysis) when activity for the *no change* condition was subtracted from activity associated with the *object change* condition. For every voxel in this ROI (35 in total, each $3\times3\times3$ mm), the BOLD signal value was then extracted from the sensitivity maps for each participant. Subjects' functional data were then excluded if more than 30% of their voxels within the ROI did not have a BOLD signal value of at least 0.8 (where 1 represents normal BOLD signal intensity). On this basis, 6 out of the 20 subjects' data were removed.

The parameter estimates for the remaining 14 data sets (one for each experimental condition) were then entered into a single GLM and pairwise contrasts were conducted between each of the task conditions (as in whole brain analysis, above). To identify regions of significant BOLD signal change within the MTL, a threshold of $p\leq0.05$, FDR-corrected was used. A small volume correction (SVC) was applied using a mask encompassing the middle temporal pole, fusiform gyrus, parahippocampal gyrus and hippocampus bilaterally. These cortical regions were selected in order to cover the entirety of our regions of interest (i.e., the perirhinal cortex and hippocampus). The mask was created using the Anatomical Automatic Labeling (AAL) brain atlas (Tzourio-Mazoyer et al., 2002) and the Wake Forest University Pick Atlas Tool.

Results

Behavioral data

All the subjects performed at a high level across all three task conditions (performance accuracy above 90%) and were able to respond well within the period for which the stimuli were presented (4 s; see Fig. 2). One-way analyses of variance (ANOVA) with one within-subject factor of event type revealed that the participants performed significantly differently across the

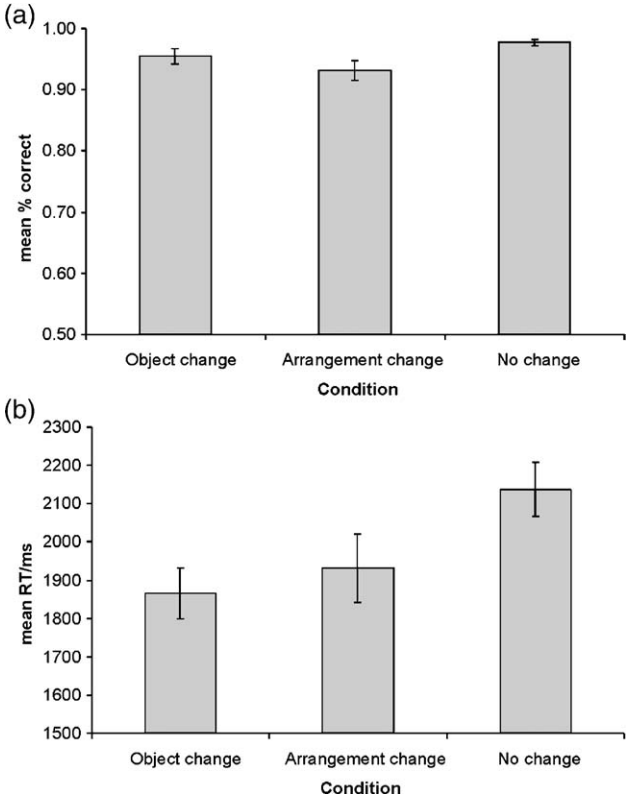

Fig. 2. Graphs showing (a) the mean percentage correct; and (b) the mean response times (correct trials only) for the three task conditions.

different task conditions in terms of accuracy ($F(2,57)=3.50$, $p=0.037$) and response times ($F(2,57)=3.61$, $p=0.034$). Post hoc analyses (Tukey's HSD) were conducted to investigate these differences further and these indicated that the subjects were significantly more accurate on the *no change* trials compared to the *arrangement change* events ($p=0.038$). There were, however, no significant differences in terms of performance accuracy between the *arrangement change* and *object change* trials, nor between the *object change* and *no change* trials (both $p>0.3$). With respect to response times, the subjects were significantly slower on the *no change* events compared to the *object change* trials ($p=0.038$), with the response times being similar between the *no change* and *arrangement change* trials, and also the *object change* and *arrangement change* trials (both $p>0.1$).

Neuroimaging data

Regions of significant activity at a whole brain level (beyond the MTL) using all 20 subjects are listed in Tables 1–3. Since this study is focused primarily on the MTL, however, only the findings from the second group statistical analysis following BOLD signal examination (14 subjects, MTL only) are reported in depth below. Beyond the MTL, the pattern of cortical activity for these 14 subjects was highly similar to that observed for the larger group of 20 participants, albeit less statistically significant due to a reduction in subjects. It is important to note that, as is the case with all functional neuroimaging studies, the localization of significant regions of activation is only approximate due to the smoothing employed during data preprocessing (8 mm FWHM) and the image voxel size (normalized data: $3\times3\times3$ mm). This is particularly true of relatively smaller brain structures such as those within the MTL.

Table 1
Regions of significant BOLD signal change beyond the MTL (all 20 subjects) when the *object change* condition was contrasted with the *no change* condition (key: L=left, R=right, pfc=prefrontal cortex)

Region	BA	Stereotaxic coordinates			*P* (FDR)	*Z* value
		x	*y*	*z*		
Increases for *object change* condition						
Frontal lobe						
L anterior cingulate	8	−9	42	34	0.009	3.67
L ventrolateral pfc	45/47	−53	27	12	<0.0001	5.50
R dorsolateral pfc	9	48	22	32	0.005	3.86
L dorsolateral pfc	9/44	−45	16	30	<0.0001	6.04
L precentral cortex	6	−53	−4	14	0.046	2.98
Temporal lobe						
R inferior temporal cortex	37	62	−44	−3	0.001	4.55
L inferior temporal cortex	37	−53	−53	−7	<0.0001	4.65
L superior temporal cortex	39	−53	−60	28	0.006	3.78
R superior temporal cortex	39	53	−63	28	0.025	3.24
Subcortical structures						
L caudate nucleus		−12	7	13	0.009	3.67
R thalamus		21	−5	17	0.039	3.05
L putamen		−27	−12	−2	0.002	4.21
R cerebellum		33	−53	−20	0.003	4.05
		27	−63	−30	0.047	2.97
		24	−71	−22	0.009	3.65
Increases for *no change* condition						
Frontal lobe						
R dorsolateral pfc	46	33	44	9	0.004	4.15
R ventrolateral pfc	47	24	38	−4	0.024	3.31
		33	26	−1	0.005	4.10
R anterior cingulate cortex	32	9	19	35	0.003	4.30
R inferior frontal cortex	6	48	2	30	0.015	3.54
R middle frontal cortex	6	27	−1	41	0.005	4.03
L superior frontal cortex	6/4	−27	−7	39	0.014	3.60
Temporal lobe						
R middle temporal cortex	21	50	8	−23	0.043	3.03
L middle temporal cortex	21	−56	−3	−7	0.045	3.01
L fusiform cortex	37	−42	−38	7	0.047	2.99
R posterior cingulate cortex	30	12	−46	11	0.01	3.77
Subcortical structures						
R globus pallidus		21	−12	1	0.037	3.10
L corpus callosum		−27	−40	16	0.024	3.33
Parietal lobe						
R inferior parietal cortex	40	45	−36	29	0.018	3.45
R inferior parietal cortex	7	24	−53	41	0.002	4.76
Occipital lobe						
R visual cortex	19	30	−77	26	0.001	4.80
	18/19	18	−89	21	<0.0001	6.10
L visual cortex	19	−36	−78	12	0.003	4.31
	18	−6	−88	−6	0.003	4.31
	18	−18	−92	16	0.001	4.96

Table 2
Regions of significant BOLD signal change beyond the MTL (all 20 subjects) when the *arrangement change* condition was contrasted with the *no change* condition (key: L=left, R=right, pfc=prefrontal cortex)

Increases for *arrangement change* condition						
Region	BA	Stereotaxic coordinates			*P* (FDR)	*Z* value
		x	*y*	*z*		
Frontal lobe						
L dorsolateral pfc	46	−39	47	3	<0.0001	5.10
		−45	27	24	<0.0001	6.12
	9/44	−45	16	30	<0.0001	6.55
R dorsolateral pfc	46	45	44	3	<0.0001	4.78
	9/46	48	33	23	<0.0001	4.63
	9	48	22	32	<0.0001	4.85
L inferior frontal cortex	10	−45	43	−5	<0.0001	5.11
L anterior cingulate cortex	32	−3	20	40	<0.0001	5.71
		−6	−1	47	<0.0001	5.27
	24	−12	13	27	<0.0001	5.21
R middle frontal cortex	6	18	17	49	0.002	3.56
		24	11	41	<0.0001	4.94
L ventrolateral pfc	47	−33	17	−18	0.045	2.31
L middle frontal cortex	6	−21	5	46	<0.0001	5.32
R motor cortex	4	59	−13	28	0.001	3.77
Temporal lobe						
L insular	43	−53	−11	14	0.046	2.30
L middle temporal cortex	21	−59	−29	−6	0.037	2.40
R inferior temporal cortex	37	59	−47	−8	<0.0001	5.23
L inferior temporal cortex	37	−56	−53	−5	<0.0001	4.80
		−50	−69	12	0.022	2.66
R superior temporal cortex	22/21	−42	−55	17	<0.0001	4.27
Subcortical structures						
L caudate nucleus		−15	10	22	<0.0001	4.94
		−12	1	11	<0.0001	5.51
R putamen		27	−1	−10	0.005	3.29
L putamen		−27	−6	−2	<0.0001	5.07
		−27	−14	6	<0.0001	5.47
R thalamus		18	−5	14	<0.0001	4.89
L thalamus		−18	−17	12	<0.0001	4.69
		−9	−23	9	<0.0001	5.84
R cerebellum		21	−51	−20	<0.0001	5.97
		24	−71	−22	<0.0001	4.66
L cerebellum		−18	−65	−19	<0.0001	4.68
Parietal lobe						
L inferior parietal cortex	40	−48	−28	21	0.005	3.29
		−42	−30	42	<0.0001	4.89
		−36	−51	38	<0.0001	5.42
R inferior parietal cortex	40	50	−33	49	<0.0001	5.95
		39	−50	44	<0.0001	4.77
	39	42	−71	34	<0.0001	4.78
L precuneus	7	9	−56	41	0.04	2.37
Occipital lobe						
L visual cortex	18	−3	−96	10	0.012	2.90

No suprathreshold changes for *no change* condition.

Object change versus no change

When activity associated with the *no change* condition was subtracted from that during the *object change* trials, significant changes in BOLD signal were observed in the right perirhinal cortex (as defined by Insausti et al., 1998) (x=36, y=−16, z=−24, Z=4.05, p=0.03 FDR SVC) and the right posterior hippocampus (x=30, y=−38, z=−3, Z=3.75, p=0.05 FDR SVC) (Fig. 3). As seen from a plot of the contrast estimates, activity in both these regions was greatest in the *object change* condition, followed by the *arrangement change* and *no change* conditions (Fig. 3). There were no significant BOLD signal changes anywhere in the MTL when the *object change* task was subtracted from the *no change* condition.

Arrangement change versus no change

Contrary to prediction, the subtraction "*arrangement change* minus *no change*" did not produce a significant region of BOLD signal change in the hippocampus or elsewhere in the MTL (i.e., entorhinal cortex, parahippocampal cortex), even when a more

Table 3
Regions of significant BOLD signal change beyond the MTL (all 20 subjects) when the *object change* condition was contrasted with the *arrangement change* condition (key: L=left, R=right, pfc=prefrontal cortex)

Increases for *arrangement change* condition						
Region	BA	Stereotaxic coordinates			*P* (FDR)	*Z* value
		x	*y*	*z*		
Frontal lobe						
L orbitofrontal cortex	11	−24	52	−8	0.01	3.07
R ventrolateral pfc	47	33	23	−6	<0.0001	4.62
R anterior cingulate cortex	32	6	19	35	<0.0001	5.74
L anterior cingulate cortex	32	−12	16	35	<0.0001	5.09
		−6	−1	47	<0.0001	4.59
R inferior frontal cortex	44	53	10	22	<0.0001	5.35
R superior frontal cortex	6	24	5	44	<0.0001	5.24
L middle frontal cortex	6	−24	−1	47	<0.0001	5.29
Temporal lobe						
L superior temporal cortex	22	−56	20	1	0.01	3.04
		−56	3	0	0.001	4.10
		−56	−49	11	0.002	3.81
L insula		−39	14	−3	0.001	4.11
R middle temporal cortex	21	53	−52	3	<0.0001	5.64
	39	45	−69	20	0.001	4.27
L middle temporal cortex	39	−48	−69	12	<0.0001	5.30
Subcortical structures						
R corpus callosum		15	7	27	<0.0001	4.93
		6	−28	21	<0.0001	4.38
R ventrolateral nucleus		15	−11	12	<0.0001	4.78
L pulvinar		−9	−23	9	<0.0001	4.80
L cerebellum		−3	−25	23	0.001	4.14
		−27	−68	−19	<0.0001	4.43
R pulvinar		21	−29	10	<0.0001	4.79
Parietal lobe						
R inferior parietal cortex	40	50	−33	49	<0.0001	6.41
	7/39	36	−71	34	<0.0001	5.48
L inferior parietal cortex	40	−36	−36	43	<0.0001	4.70
Occipital lobe						
R visual cortex	18	18	−89	21	<0.0001	5.65
	18	12	−95	13	0.001	4.10
L visual cortex	18	−6	−96	10	0.001	4.17

No suprathreshold changes for *object change* condition.

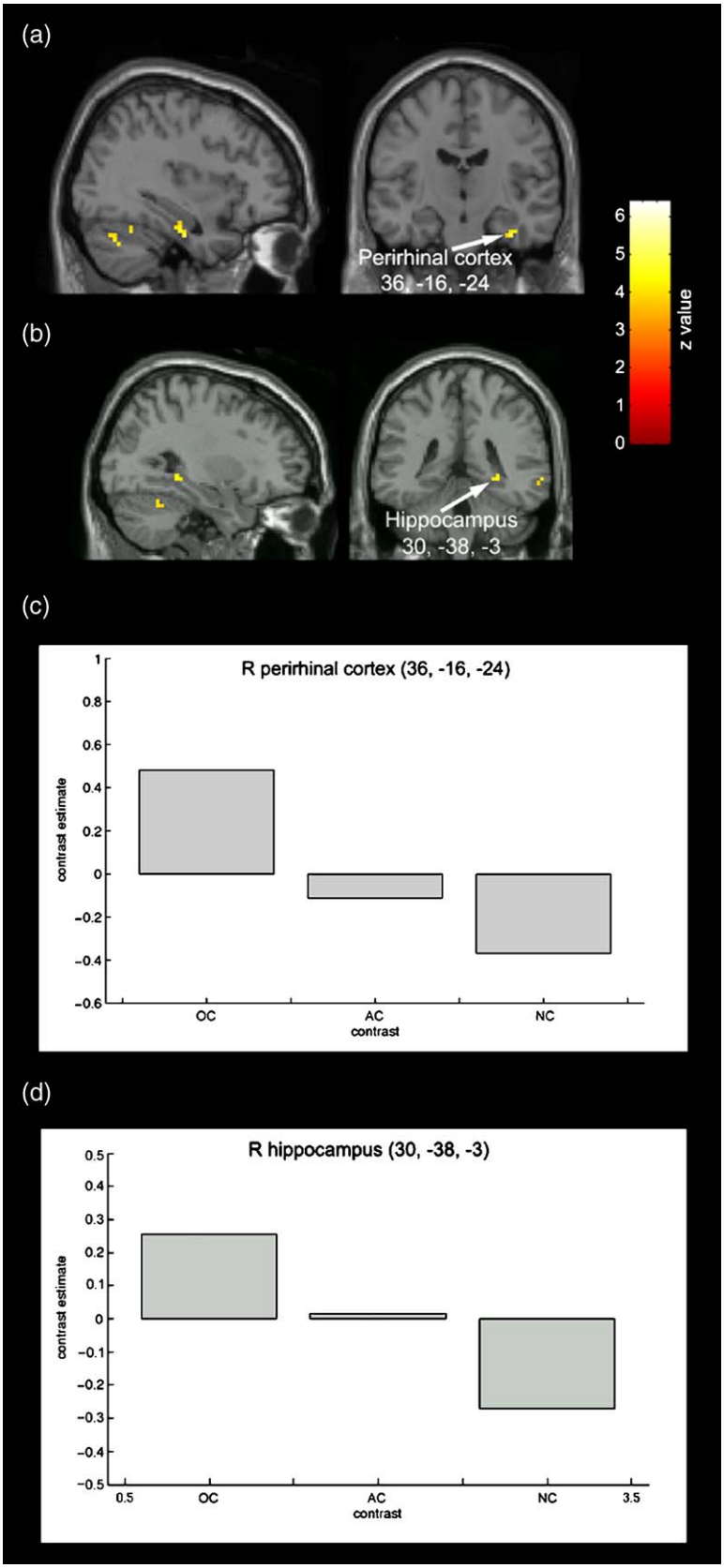

Fig. 3. Significant (a) perirhinal cortex; and (b) hippocampal activity ($p \leq 0.05$ FDR) during the *object change* condition (for the 14 subjects following BOLD sensitivity analysis, correct trials only), shown on a single coronal and sagittal MNI brain template slice. The contrast estimates for these two regions of activity at $x=36$, $y=-16$, $z=-24$ and $x=30$, $y=-38$, $z=-3$ across the three trial types are represented in panels (c–d), respectively.

liberal statistical threshold ($p<0.005$ uncorrected) was adopted to investigate the data further. Similarly, no suprathreshold clusters of activity were observed in the MTL for the *no change* trials in comparison to the *arrangement change* condition.

Object change versus arrangement change

When contrasted with each other, neither the *object change* nor the *arrangement change* conditions were associated with significantly greater BOLD activity in the MTL at $p\leq0.05$ (FDR SVC). To investigate the possibility that subthreshold activity may be present, a lower significance level ($p<0.005$ uncorrected) was adopted to explore the SPMs further. This revealed that the *object change* task was associated with a bilateral region of BOLD signal change that extended from the hippocampus into the collateral sulcus (i.e., perirhinal cortex). Local maxima were observed at $x=27$, $y=-15$, $z=-17$ ($Z=3.33$) and $x=-27$, $y=-18$, $z=-17$ ($Z=3.13$). No regions of activity were observed in other MTL structures including the entorhinal cortex and parahippocampal cortex.

Discussion

The current fMRI study demonstrated that it is possible to observe medial temporal lobe (MTL) activity in the context of a visual discrimination task that did not place an explicit demand on declarative memory processing. When the subjects successfully detected a difference in object identity between two simultaneously presented arrays of images, greater activity was found in the right perirhinal cortex and right posterior hippocampus (Fig. 3). No consistent MTL activity was observed, however, when the participants detected a difference in spatial arrangement between the two object arrays.

The observed perirhinal cortex activation during the *object change* condition is in a similar region to that demonstrated by Pihlajamäki et al. (2004) in a related experimental paradigm (see Introduction). Crucially, however, whereas Pihlajamäki et al. (2004) found bilateral perirhinal cortex activity in association with the detection of an object identity change between two image arrays presented *across* trials (i.e., successful object memory retrieval over time), the present study observed right perirhinal cortex activity when subjects detected a change in object identity between two image arrays presented *within* a *single* trial (i.e., successful simultaneous object discrimination). Unlike the findings of Pihlajamäki et al. (2004), therefore, the current observation of perirhinal cortex activity during the *object change* trials cannot be attributed to memory retrieval since the subjects were not required to remember stimuli across trials and furthermore, each image was only presented once.

It is possible that the perirhinal cortex activation reflected incidental episodic memory encoding of the objects during the visual discrimination task. This would be consistent with a number of previous fMRI studies that have observed activity close to perirhinal cortex during the incidental encoding of subsequently remembered words in tasks such as reading, visual imagery, and semantic and/or orthographic decision (Otten et al., 2002; Davachi et al., 2003; Morcom et al., 2003; Ranganath et al., 2004). This incidental encoding may be related to the relative novelty of stimuli, since novelty has also been associated with MTL activity (Kirchhoff et al., 2000; Köhler et al., 2005; Strange et al., 2005). Critically, the present study attempted to minimize activation associated with incidental encoding or novelty by contrasting conditions that were closely matched. Each object was only presented in one trial in the experiment, so the objects themselves were matched in terms of novelty. It is important to note, however, that the *object change* condition differed from the other two conditions with respect to one of multiple simultaneously presented objects. Thus, one could argue that the perirhinal activity reflected the additional encoding/novelty of a fourth unique object in the *object change* condition (relative to the encoding/novelty of the three unique objects in the other two conditions; see Fig. 1).

Our preferred explanation for the greater perirhinal cortex activation during the *object change* condition is that this activity reflects a role for the perirhinal cortex in object processing in a domain beyond long-term declarative memory, for example, very short-term visual working memory or perception. With respect to the former, previous studies have demonstrated activity in the perirhinal cortex of nonhuman primates and humans during working memory tasks involving visual stimuli (Davachi and Goldman-Rakic, 2001; Ranganath and D'Esposito, 2001; Stern et al., 2001). It is possible, therefore, that the perirhinal cortex activity found in the current study reflects the greater working memory demand of detecting a novel object in the *object change* condition. Alternatively, the observed perirhinal activation may be indicative of a role in object perception as proposed by recent nonhuman primate studies (Buckley et al., 2001; Bussey et al., 2002, 2003). As mentioned in the Introduction, it has been suggested that the perirhinal cortex may process conjunctions of object features (i.e., the perception of whole objects) as the apex of the ventral visual processing stream (Ungerleider and Mishkin, 1982). Previous studies have demonstrated that perirhinal cortex damage can impair the ability to discriminate simultaneously presented objects when there is a high level of feature overlap between the stimuli (Buckley et al., 2001; Bussey et al., 2002; Lee et al., 2005a,b) (although see Levy et al., 2005; Shrager et al., 2006). Our opinion is that the presence of high feature overlap forces discriminations to be made on the basis of perceiving whole objects, which patients with perirhinal cortex damage have difficulties with. In a similar way, the present fMRI study used black and white stimuli to encourage subjects to detect a difference in object identity via object perception, rather than the discrimination of single features. Subsequently, even though the objects were unique from each other, greater perirhinal activation was observed during the *object change* trials. It is possible that even greater perirhinal cortex activity could be elicited by increasing the level of feature overlap between the objects on each trial via the presentation of images that are specifically designed to share a large number of features. Interestingly, we have recently administered the present experimental task to an amnesic patient with perirhinal cortex damage and in agreement with our interpretation of the observed perirhinal activity, this patient performed worse on the *object change* condition in comparison to the *no change* condition, in terms of significantly longer response times and poorer response accuracy (Lee and Graham, unpublished data).

Another possible interpretation of the perirhinal cortex activity observed in association with the *object change* condition is that this activation may reflect incidental semantic memory retrieval, for instance, the implicit naming of the objects that were different between the two image arrays in this condition. In agreement with this idea, Tyler et al. (2004) observed perirhinal cortex

activity in the context of a basic level naming task and moreover, recent work in semantic dementia, a disease associated with the progressive cross-modal loss of semantic memory (Snowden et al., 1989; Hodges et al., 1992), has highlighted a crucial role for the perirhinal cortex in conceptual knowledge (Davies et al., 2004) (although see Moss et al., 2005). Importantly, this interpretation is not necessarily contradictory to the view that the perirhinal cortex may play a critical role in the processing of feature conjunctions. Murray and Bussey (1999) argue that the involvement of the perirhinal cortex in object processing may be akin to semantic memory (see, however, Simons et al., 1999). Moreover, Tyler and colleagues have suggested that the involvement of the perirhinal cortex in fine-grained discriminations among objects is indicative of a role in a larger network of conceptual representation in the brain (Tyler and Moss, 2001; Tyler et al., 2004; Bright et al., 2005).

In contrast to a wide-range of existing studies that have observed hippocampal activity during tasks of spatial memory (e.g., Bohbot et al., 2004; Burgess et al., 2001; Cansino et al., 2002; Düzel et al., 2003; Köhler et al., 2005; Pihlajamäki et al., 2004; Voermans et al., 2004), the present *arrangement change* condition was not associated with significantly greater activity in the hippocampus in comparison to the other conditions. In fact, a region of activation in the posterior hippocampus was observed when the *object change* trials were contrasted with the *no change* trials. Only anterior hippocampal activity was observed, however, when activity associated with the *arrangement change* condition was subtracted from that during the *object change* task, in line with previous studies that have observed anterior hippocampus activation during object recognition tasks (e.g., Pihlajamäki et al., 2004; Köhler et al., 2005).

It is possible that the absence of significantly greater hippocampal activity during the *arrangement change* trials can be explained by considering the cognitive demands of this task condition. In our previous patient studies, a high demand on spatial processing was necessary for patients with selective hippocampal damage to exhibit difficulties in visual discrimination tasks that placed a minimal demand on declarative memory. For instance, hippocampal lesion patients were found to be able to discriminate images of three-dimensional virtual reality rooms that were presented from the same view-point but struggled when these rooms were shown from multiple vantage points (Lee et al., 2005b). Similarly, the same patients exhibited difficulties differentiating two-dimensional scene images when these were blended to create a high level of overlapping features (Lee et al., 2005a). The present *arrangement change* condition simply required the subjects to detect the relocation of a single object within a two-dimensional plane and thus, it is plausible that this task did not place a sufficient demand on spatial processing to produce significant hippocampal activity in comparison to the *object* and *no change* conditions.

Activity in the parahippocampal cortex has often been observed during spatial memory tasks, particularly tests that involve object–location associations (Düzel et al., 2003; Johnsrude et al., 1999). It is surprising, therefore, that similar activity was not observed in the current study, particularly during the *arrangement change* condition. One possible explanation is that since the stimuli for the three task conditions were highly similar and the different trials types were intermixed pseudo-randomly, the participants were forced to process object, spatial, and spatial–object bindings on every trial. Thus, there may have been an insufficient difference in object-in-place processing between the *arrangement change* trials and the other two conditions to observe significantly greater parahippocampal cortex activity in the former. A similar interpretation may also apply to the lack of hippocampal activity during the *arrangement change* condition, with the need for more varying demands on spatial processing across the different conditions to produce greater hippocampal activity in association with the detection of an arrangement change.

The finding of hippocampal activity during the *object change* condition is not inconsistent with a relational memory theory of the hippocampus, which postulates that the hippocampus is critical for the long-term representation of flexible associations between distinct items (Eichenbaum et al., 1994; Eichenbaum and Cohen, 2002). In particular, the observed hippocampal activity may reflect the processing of new associations (between the displayed objects) that are created as a result of the presentation of a different image in one of the two visual arrays in each *object change* trial (Fig. 1). This possibility may also explain why hippocampal activity was observed in the *object*, but not *arrangement*, *change* condition.

It is important to note that the MTL activity observed during the *object change* trials is unlikely to reflect the possibility that this condition was more cognitively demanding overall. While greater MTL activity was observed during the *object change* task compared to the *arrangement change* condition, activation throughout the brain was higher in the latter. Moreover, performance in the *object change* condition was not significantly different from that during the *arrangement change* condition in terms of response accuracy or response time.

Although this study is predominantly concerned with activation within the MTL, two particular observations beyond this region merit brief discussion. Firstly, one could predict that on comparison with each other the *object change* condition would be associated with activation of the ventral 'what' visual processing stream whereas the *arrangement change* condition would activate the dorsal 'where' visual processing stream. This, however, was not the case (see Table 3). At a whole brain level, no suprathreshold regions of activity were observed during the *object change* condition in comparison to the *arrangement change* trials. Furthermore, although greater parietal cortex activity was found during the *arrangement change* condition, this was in the context of greater neural activity throughout the brain, including the frontal and temporal lobes. The lack of activity during the *object change* condition may reflect the fact that subjects were required to process object information on all trial types (see earlier comment). On the other hand, it appears that the *arrangement change* condition was more cognitively demanding overall leading to a greater network of activity in multiple cortical areas.

A second interesting finding is that a subcortical network of activity, including the caudate nucleus, putamen and thalamic nuclei, was observed in association with the *arrangement change* condition (see Table 2). The caudate nucleus, in particular, was found to be most active during the *arrangement change* trials, followed by the *object change* and *no change* conditions (see Fig. 4). Activity in the caudate nucleus has been previously observed across a variety of studies, including those investigating spatial memory (Maguire et al., 1998; Hartley et al., 2003; Bohbot et al., 2004; Voermans et al., 2004), working memory (e.g., Gazzaley et al., 2004), stimulus–response learning (e.g., Toni and Passingham, 1999; O'Doherty et al., 2002; O'Doherty et al., 2004), probabilistic classification (e.g., Poldrack et al., 1999; Poldrack et al., 2001; Seger and Cincotta, 2005), and set shifting (e.g., Cools et al., 2002, 2004).

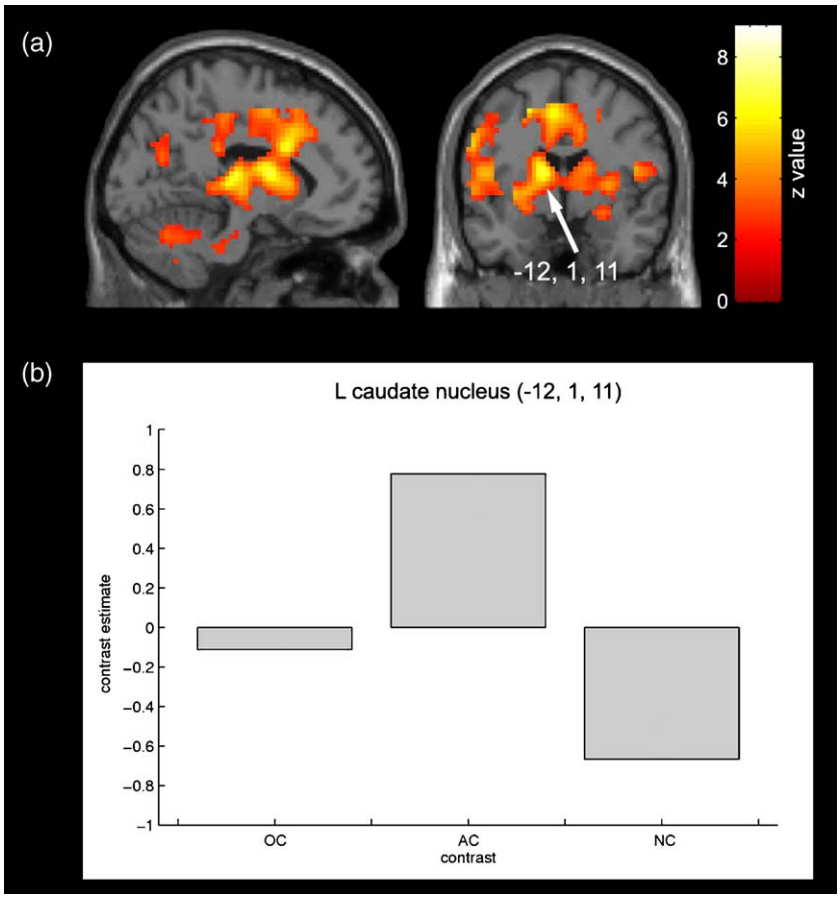

Fig. 4. (a) Significant caudate nucleus activity ($p \leq 0.05$ FDR) during the *arrangement change* condition, shown on a sagittal and coronal brain template slice (for all 20 subjects prior to BOLD sensitivity analysis, correct trials only). The contrast estimates for this region of activity at $x = -12$, $y = 1$, $z = 11$ across the three trial types are shown in panel (b).

With respect to spatial memory, activation of the caudate nucleus has been found in the context of navigation tasks involving virtual reality environments and typically has been observed when spatial processing has been kept to a minimum. For example, Hartley et al. (2003) observed caudate activity when subjects were asked to follow a specified path and were not required to forge their own route within a virtual town. Similarly, Bohbot et al. (2004) reported activity of the caudate nucleus when participants did not use surrounding landmarks to remember the location of objects in a virtual radial maze but rather, used nonspatial strategies such as counting the arms of the maze from a single starting point and remembering the object locations according to their number. One suggestion, therefore, is that the caudate activity seen during these tasks may reflect the role of this structure in habitual stimulus–response association (Packard and Knowlton, 2002; White and McDonald, 2002), for example, during repeated responding (e.g., turning left or right) to directional cues.

In the present study, it is difficult to comprehend how this interpretation can account for the greater caudate activity that was found during the *arrangement change* condition given that this task was not designed to assess specifically habit formation. In addition to this, it has been demonstrated that Huntington's disease patients, who have significant caudate nucleus dysfunction, suffer from poor spatial recognition and object location memory (Lawrence et al., 2000; Brandt et al., 2005). The possibility remains, therefore, that the caudate nucleus may play a role in spatial memory. Additional studies will be necessary to investigate this issue further.

To summarize, the current study has demonstrated perirhinal cortex activity during an object discrimination task that did not explicitly demand long-term declarative memory. It is possible that this finding may reflect incidental declarative memory processes, for example, episodic memory encoding or semantic knowledge retrieval. An alternative interpretation, however, is that the observed perirhinal cortex activation may support a role for this MTL area in processes beyond declarative memory, such as short-term working memory or even the higher order perception of objects. Significantly greater hippocampal activity was not observed when participants carried out the *arrangement change* condition. Given our previous findings of spatial discrimination deficits in hippocampal lesion patients, this absence of significant hippocampal activity is surprising and may be explained by the relatively low spatial processing demands of the spatial discrimination task employed.

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