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Regional activation of the human medial temporal lobe during intentional encoding of objects and positions

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ABSTRACT

The medial temporal lobe (MTL) consists of several regions thought to be involved in learning and memory. However, the degree of functional specialization among these regions remains unclear. Previous studies have demonstrated effects of both content and processing stage, but findings have been inconsistent. In particular, studies have suggested that the perirhinal cortex is more involved in object processing than spatial processing, while other regions such as the parahippocampal cortex have been implicated in spatial processing. In this study, functional magnetic resonance imaging (fMRI) optimized for the MTL region was used to probe MTL activation during intentional encoding of object identities or positions. A region of interest analysis showed that object encoding evoked stronger activation than position encoding in bilateral perirhinal cortex, temporopolar cortex, parahippocampal cortex, hippocampus and amygdala. Results also indicate an unexpected significant correlation in activation level between anterior and posterior portions in both the left parahippocampal cortex and left hippocampus. Exploratory analysis did not show any regional content effects during preparation and rehearsal stages. These results provide additional evidence for functional specialization within the MTL, but were less clear regarding the specific nature of content specificity in these regions.

Introduction

The medial temporal lobe (MTL) region, which consists of extensively and reciprocally connected structures such as the temporopolar cortex, perirhinal cortex, entorhinal cortex, amygdala, hippocampus, and the posterior parahippocampal cortex, is thought to be central in declarative memory formation, through its widespread functional connections throughout the neocortex. Some theories have stressed the importance of the MTL in the formation of long-term declarative memory and have suggested that lesions in any part of the MTL produce memory deficits (Squire and Zola-Morgan, 1991; Squire et al., 2004). Others have emphasized that different MTL structures play separate roles in declarative memory as well as in other cognitive functions such as higher-order visual perception (Murray et al., 2005; Graham and Gaffan, 2005), working memory (Axmacher et al., 2007; Piccioni et al., 2007; Olson et al., 2006a,b), and short-term memory (Piekema et al., 2006). It has been suggested that, during encoding, visual object features are processed in the perirhinal and lateral entorhinal cortex, while spatial context is processed in the adjacent medial entorhinal cortex and parahippocampal cortex (Eichenbaum et al., 2007). Indeed, lesions to the perirhinal cortex alone, or together with the entorhinal cortex, have been shown to cause significant deficits in the ability of humans (Barense et al., 2005), monkeys (Baxter and Murray, 2001) and rats (Prusky et al., 2004) to perform visual categorization and memory tasks, deficits not found when lesions are restricted to the hippocampus. It has also been suggested that the memory functions of MTL structures are dissociated according to stimulus content, where the perirhinal cortex contributes more heavily to processing of visual object information (Bussey et al., 2006), while the hippocampus and parahippocampal cortex contribute more in the processing of spatial information (Epstein et al., 1999; Burgess et al., 2002).

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Neuroimaging studies in humans have only partially supported the view of a regional specialization within the MTL related to memory content. For example, some have found the perirhinal cortex to be more strongly activated by novel visual items compared to novel spatial arrangements of familiar items (Pihlajamäki et al., 2004, 2005), while others have found that the perirhinal cortex was activated during both spatial and object memory encoding (Buffalo et al., 2006). Similar conflicting findings include the hippocampus and parahippocampal cortex, where Pihlajamäki et al. (2004) found an anterior–posterior gradient, in which the anterior hippocampus and anterior parahippocampal cortex were more involved in the processing of contextually novel objects, whereas the posterior hippocampus and posterior parahippocampal cortex were more involved in the processing of novel spatial arrangements. Conversely, Buffalo et al. (2006) found that the anterior parahippocampal cortex, but not the anterior hippocampus, was activated during spatial encoding. In this study, no significant effect of item or spatial processing was found in the posterior parts of the hippocampus or parahippocampal cortex. These diverging results show that the specific roles of the perirhinal cortex, parahippocampal cortex and hippocampus in object and spatial information processing are still unknown. While some of the differences between studies may reflect differences in paradigm design and task demands, differences in scanning parameters and statistical analysis may also contribute to the inconsistency of the results.

The present study aimed to elucidate the roles of the perirhinal cortex, parahippocampal cortex and hippocampus in the encoding of objects and positions. Based on previous findings, we proposed three structure-specific hypotheses. First, the perirhinal cortex was expected to be more involved in object encoding compared to position encoding. Second, the parahippocampal cortex was expected to show an anterior–posterior difference, in that the anterior portion was expected to be more involved in object encoding and the posterior portion was expected to be more involved in position encoding. Finally, a similar anterior–posterior difference was expected in the hippocampus, i.e., that the anterior portion would be more involved in object encoding and the posterior portion more involved in position encoding.

Finally, we were interested in exploring the role in encoding of objects and positions in adjacent MTL regions, including the temporopolar cortex, entorhinal cortex and amygdala (see Fig. 1). Thus, post-hoc testing of the difference between object and position encoding was performed in these regions. Our paradigm also allowed the study of the effects of content during preparation and rehearsal stages, for which we had no prior hypotheses (see Fig. 2).

To this end, fMRI was performed during an object and spatial encoding task, using an imaging sequence optimized to measure blood-oxygen-level-dependent (BOLD) signal changes in the MTL region. During the task, subjects were asked to either encode (and rehearse and retrieve) object identities or object positions. A region of interest (ROI) approach was used to analyze the data in each individual, so that conventional anatomical criteria for defining MTL subregions could be applied, and to avoid registration errors that might result from the application of spatial normalization methods.

Materials and methods

Subjects

Twenty-five subjects (11 female; mean age = 24.12, std. = 4.7, range 18–33, 20 right-handed, 5 left-handed, with normal or corrected to normal vision) were recruited through on-line advertisements (www.forsoegsperson.dk) from the region of Copenhagen, Denmark. All subjects first signed an informed consent, and were paid for their participation, then filled out a self-report questionnaire on medical history including neurological and psychiatric disorders. Subjects were also tested for estimated intelligence levels with DART (Danish Adult Reading Test) and WAIS vocabulary. For both tests a *z*-score was calculated based on Danish normative material. The study protocol was approved by the local ethics committee (KF 01 – 131/03). After careful examination of the self-report questionnaire and scanning results (structural and functional images), no subjects were excluded from the analysis.

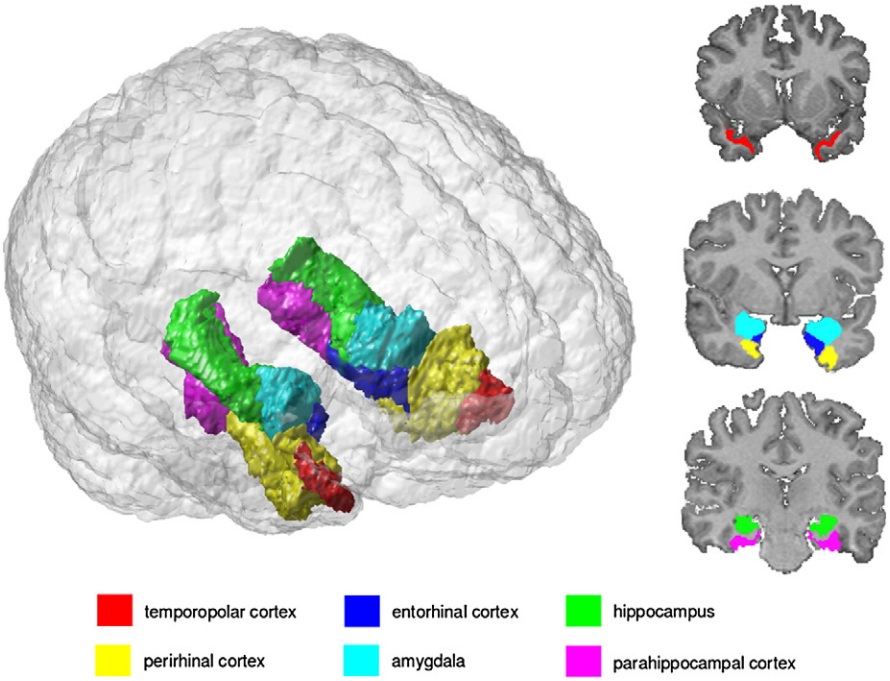

Fig. 1. The medial temporal lobe regions of interest studied. (Left) 3D reconstruction of ROIs drawn on one of the subjects in the study, and positioned within a transparent view of the native brain. (Right) three coronal slices showing the original ROI drawing in the same subject. See the Materials and methods section for further details.

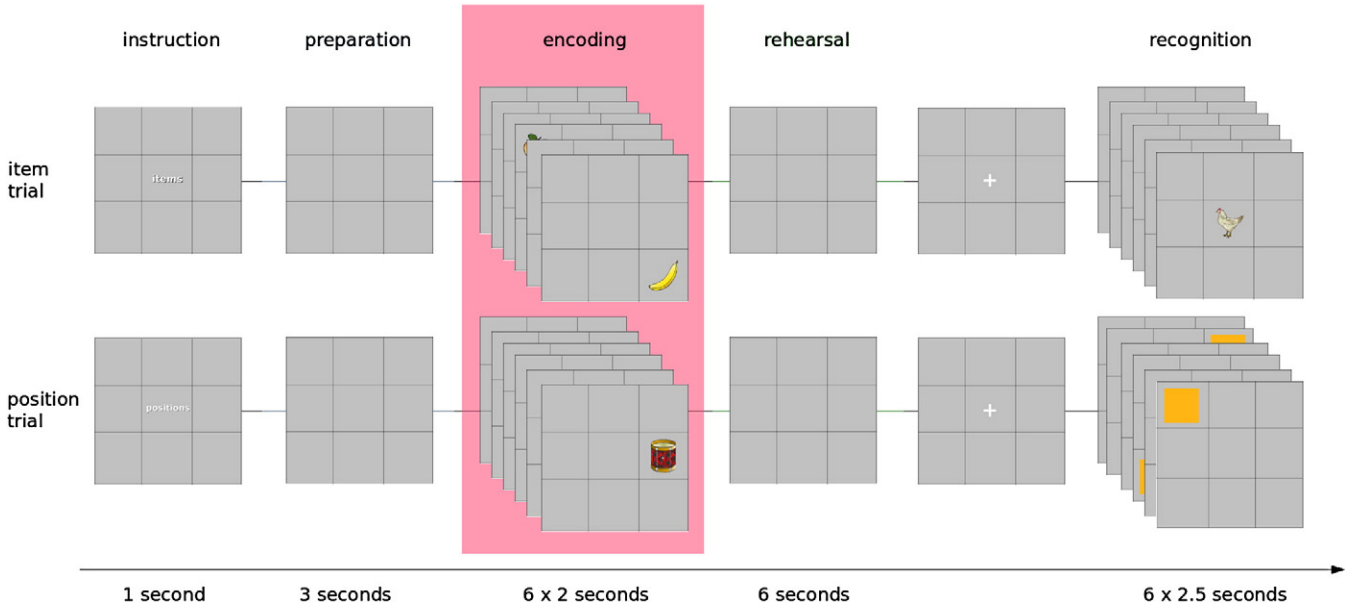

Fig. 2. The paradigm shown according to the two instruction versions. Both runs consisted of an instruction cue; a preparation phase; an encoding phase (marked with light red) with six trial-unique items and positions; a rehearsal phase; and a recognition phase with six old-new judgments. Only the instruction cue and recognition phases were visually different between the conditions. Numbers at the bottom indicate block duration in seconds. See the Materials and methods section for a more detailed explanation.

Structural imaging protocol

Structural images, used for the drawing of ROIs, were acquired using a Siemens Magnetom Trio 3 T MR scanner with an eight-channel head coil (Invivo, FL, USA) and included (1) a 3D whole-brain MPRAGE (magnetization prepared rapid acquisition gradient echo) scan with a voxel dimension of $1\times1\times1$ mm^3, field of view (FOV) 256 mm, matrix 256×256, repetition time (TR) / echo time (TE) / inversion time (TI) = 1540/3.93/800 ms, and a flip-angle of 9°; and (2) a 3D whole-head T2-weighted sequence with a voxel dimension of $1.1\times1.1\times1.1$ mm^3, FOV 282 mm, matrix 256×256, TR/TE = 3000/354 ms, and a flip-angle of 28.5°.

Structural image post-processing

The N3 program (Sled et al., 1998) was used to correct images for non-uniformity artifacts due to radio-frequency field inhomogeneities. Tissue classification was done using SPM2 (Wellcome Dept. of Imaging Neuroscience, London) on the N3 bias-corrected images (the SPM2 bias correction was turned off). Careful editing of the gray matter tissue images excluded voxels that were outside of the brain but adjacent to the MTL. Six ROIs (see Fig. 1) in each hemisphere were drawn on the native-space structural image using MNI Display (Montreal Neurological Institute, Montreal, Canada). An ROI drawing protocol for the temporopolar cortex, perirhinal cortex, entorhinal cortex, and parahippocampal cortex was adapted from the Insausti et al. (1998) and Pruessner et al. (2002) protocols; neuroanatomic guidelines for hippocampus and amygdala were adapted from those of Watson et al. (1992), and the atlas of Duvernoy (1991) was consulted. The border between the perirhinal cortex and entorhinal cortex was set, in the coronal plane, at the top of the parahippocampal gyrus, making the perirhinal ROI cover the entire inferior bank of the collateral sulcus until the posterior border to the parahippocampal cortex. This practice differs from that of others (Insausti et al., 1998) who have applied a more adaptive drawing protocol for the perirhinal–entorhinal border, based on the depth of the collateral sulcus. This deviation from previous criteria was made to reduce variability associated with subjective placement of the boundary within the collateral sulcus.

A test of ROI drawing reliability was performed on a different data set consisting of 13 healthy young subjects (9 female, age range 19–31). Here, all subject data including file headers were anonymized and an extra set for each subject was right-left flipped. Thus, ROIs in a total of 26 structural scans were drawn (by TZR) for intrarater comparison. An intraclass correlation test (Rousson et al., 2002) on each ROI volume showed a mean $r = 0.884$ for all regions (range 0.615 to 0.916). The lowest values were for the bilateral temporopolar cortex, all other correlations exceeded 0.8.

Functional imaging protocol

At higher field strengths such as 3T, EPI susceptibility artifacts, which especially occur in areas close to the nasal cavities, ear cavities, and perforated bones (Bellgowan et al., 2006), are especially pronounced in the MTL region. Recent developments in image acquisition have reduced these artifacts (Cho and Ro, 1992; Neufeld et al., 2005; Bellgowan et al., 2006), although in many neuroimaging studies of the MTL these methods have not been applied. For the functional scan we used a BOLD fMRI sequence optimized for the MTL structures based on the method suggested by Deichmann et al. (2003), adjusted to the MTL region.

We used EPI (Echo-Planar Imaging) with an 8-channel head coil, TR/TE = 2000/30 ms, 64×64 matrix. Initially, consistent placement and orientation of the participants' heads in the field of view was ensured by orienting subjects' heads to predefined orientation marks on the scanner head coil. The block of 33 slices was then oriented 20° oblique to the transverse plane so that the slices were roughly parallel to the long axis of the temporal lobe. The voxel size was $3\times3\times2$ mm with no interslice space. The 2 mm slice thickness was applied in order to further reduce susceptibility artifacts. The total scanning time was 702 s. Pulse and respiration were recorded, and sampled at 50 Hz, using an MR-compatible pulse oximeter and a respiration belt.

We also included a B_0 field measurement sequence after the EPI recording, with the 8-channel, TR/TE = 488/6.16 ms, 33 slices with inherited orientation from EPI scan ($3\times3\times2$ mm slices with no interslice gap, 20° oblique to the transverse plane).

Table 1
Statistical values content effects (object>position) during encoding.

Region	One-sample *t*-test	
	t	*p*
Temporopolar left	6.5	0.0000009**
Temporopolar right	5.4	0.00002*
Entorhinal left	4.1	0.0005
Entorhinal right	3.6	0.001
Perirhinal left	6.9	0.0000003**
Perirhinal right	5.4	0.00001*
Parahippocampal left	6.7	0.0000007**
Parahippocampal right	5.3	0.00002*
Hippocampus left	8.2	0.00000002**
Hippocampus right	6.7	0.0000007**
Amygdala left	8.6	0.000000008**
Amygdala right	7.4	0.0000001**

Significant results after Bonferroni correction are indicated with asterisk, where * = $p<0.00005$, and ** = $p<0.000005$ ($N=25$).

Activation paradigm

The task involved 18 blocks in an equal number of object and position tasks. The data were taken from a full run of 19 blocks, in which the last block was excluded from the analysis in order to obtain an equal number of fMRI acquisitions per stimulus type. Each block included a 1 s instruction cue; a 3 s preparation epoch; 6 stimuli presented serially 2 s each for encoding; a 6 s rehearsal epoch; and 6 stimuli presented serially 2.5 s each for old/new recognition judgments (see Fig. 2). Each encoding stimulus was a unique, colored Snodgrass and Vanderwart-like object (Rossion and Pourtois, 2004) presented in a trial-unique location among 9 locations in a 3×3 spatial grid. During preparation and rehearsal, an empty grid was displayed. Just prior to the instruction cue and recognition phase a white cross appeared at the middle of the grid for 1 s, signaling the onset of the encoding or recognition phase. In the object memory blocks, recognition stimuli were 3 old and 3 novel stimuli in a fixed pseudorandom order. In the position memory blocks, recognition stimuli were grids in which an orange square appeared in 3 old and 3 novel positions in the grids, again in a pseudorandom order. The instruction cue indicated whether the subjects were to encode (and rehearse and recognize) the objects or the grid locations in the subsequent series of stimuli. Subjects were explicitly instructed to ignore positions if their task was to focus on objects, and, conversely, to ignore objects during the position task. During the rehearsal epoch, subjects were asked to try to keep the object identities or grid locations in mind. Nine blocks of each task were presented in a fixed pseudorandom order. All subjects were trained outside the scanner for approximately 10 min using a different set of objects.

All stimuli were presented using IFIS and E-Prime software (http://www.pstnet.com/products/e-prime/) using a Canon LV 7545 LCD projector equipped with a Buhl optics lens with a refresh rate of 60 Hz (full brightness = 3700 ANSI lumens, setting = 10; Contrast = 800:1, setting = 32). The stimuli were back projected onto a screen and viewed via mirrors placed on the head coil above the subject's head. The full screen size corresponded to 24°×18° visual angle and was presented in 800×600 pixel resolution.

Behavioral analysis for performance during the fMRI session was performed in SPSS 15.0; accuracy scores and reaction times during the recognition condition were computed for each subject applying a 2-tailed paired-samples *t*-test for studying the effects of content on recognition accuracy and reaction times.

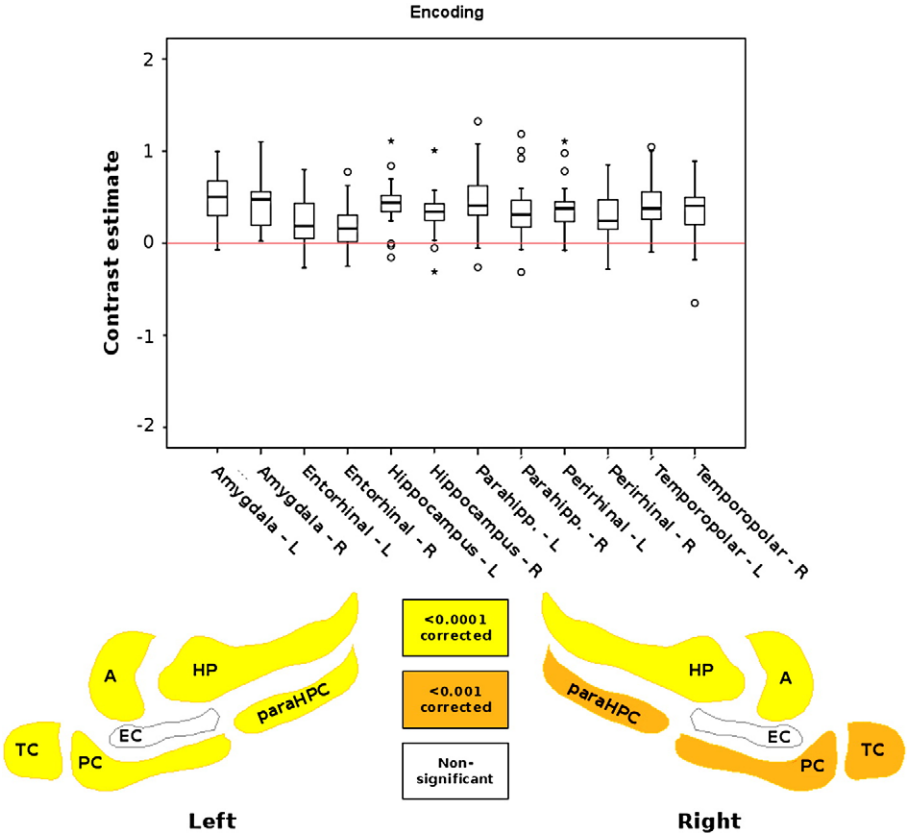

Fig. 3. Regional contrast effects during encoding. (Top) Boxplot showing activation differences for object and position encoding in all MTL regions of interest. Each plot shows the differential value of each contrast for each MTL region. Each box indicates upper, median and lower quartiles, whiskers indicate smallest and largest non-outlier observation, circles indicate outliers, stars indicate extreme scores. Red line indicates null effect. (Bottom) Color scaled model of regional differences (at $p<0.001$) during encoding, where bottom lines and numbers indicate (one-tailed) *p*-values for the comparison between perirhinal and parahippocampal cortex in each hemisphere. Abbreviations are: TC = temporopolar cortex, EC = entorhinal cortex, PC = perirhinal cortex, paraHPC = parahippocampal cortex, HP = hippocampus, and AM = amygdala.

BOLD analysis

The EPI data analysis was performed in native space using SPM5. Realignment with no smoothing was used. Each individual's EPI image series was coregistered to his/her AC–PC aligned structural image. For each content condition (object and position) preparation, encoding, rehearsal, and recognition were entered as separate regressors in the design matrix, leading to a total of 8 regressors of interest. The recognition stage was included as a regressor in the analysis, but since this stage used different visual stimuli, any difference or lack thereof in BOLD signal during this stage may be explained by the use of different visual stimuli, rather than differences in processing of content. The

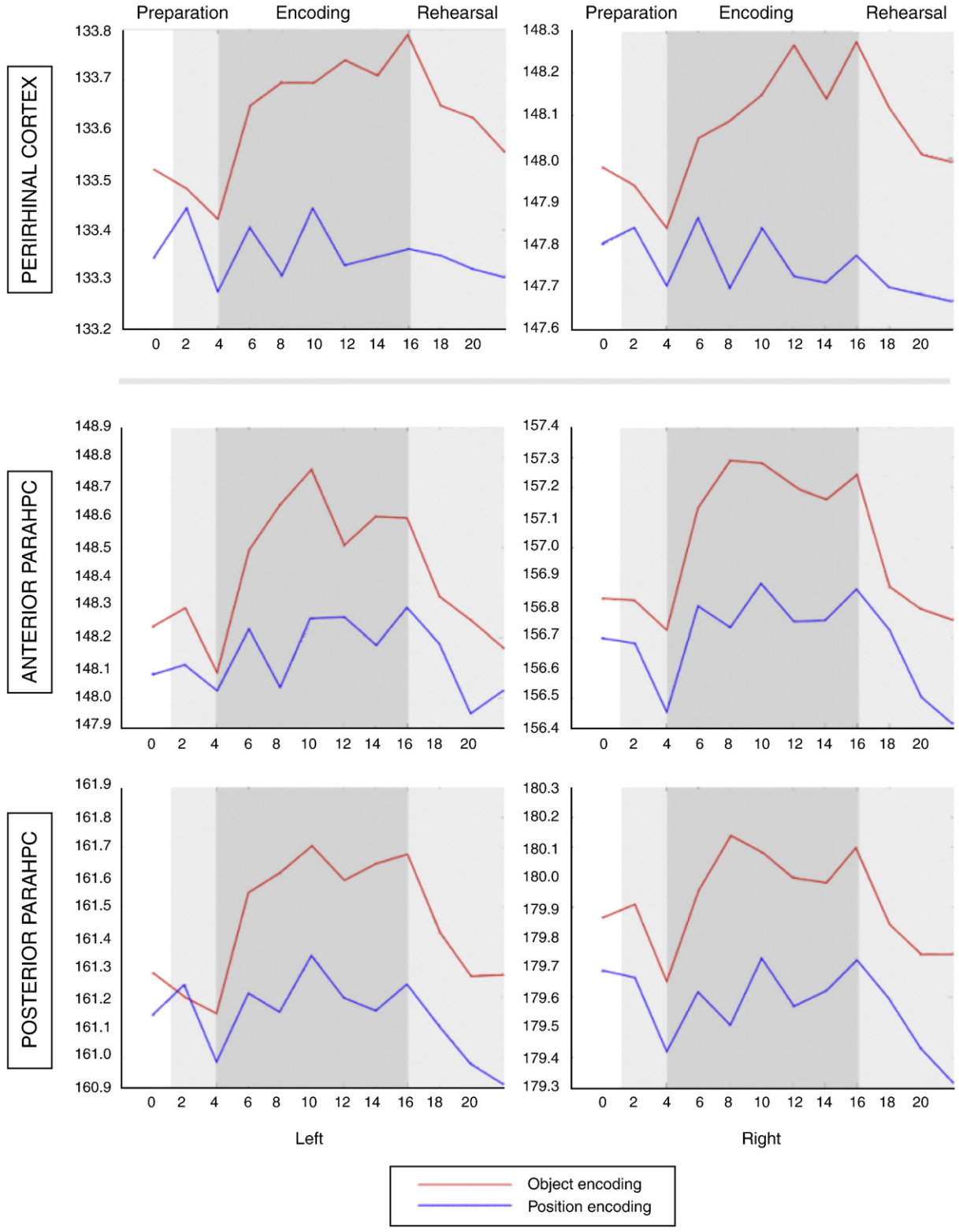

Fig. 4. Averaged time-series for object (red) and position (blue) encoding runs in the perirhinal cortex (top) and separate anterior and posterior subdivisions of the parahippocampal cortex (bottom). Dark gray area indicates encoding stage, light gray indicates preparation and rehearsal stages. Numbers on *x*-axis indicates seconds. See Results section for a detailed explanation.

regressors were convolved with a canonical haemodynamic response function. Nuisance regressors for respiration, heartbeat and motion were included in the analysis (Lund et al., 2006). Within every ROI, EPI data from all voxels were averaged in the calculation of the ROI specific regressor. For each ROI the average value for the contrasts of interest (object vs. position comparisons for preparation, encoding and rehearsal) were fed into a second level analysis, where a one-sample *t*-test was made. All statistical tests were made in SPSS 15.

Our analysis first tested the hypothesized effect in the perirhinal cortex, where we applied a one-sample *t*-test. We then tested our hypotheses on the difference between anterior and posterior regions of the parahippocampal cortex and hippocampus. For this analysis, anterior and posterior subregions of each individual's parahippocampal cortices and hippocampi were distinguished by projecting the respective coordinate sets (with origin in each regions centre of mass) onto the principal axis. Each region was subdivided into three subregions with equal masses, and only the anterior and posterior regions of each structure were used for analysis. The average values for the contrast of interest (object encoding vs. position encoding) of each anterior and posterior subregion were fed into a second level analysis, where a paired-sample *t*-test was made for direct comparison of anterior and posterior regions within each ROI.

We further analyzed the effects of content in regions for which we had no prior hypotheses (i.e., temporopolar cortex, entorhinal cortex, and amygdala). For the analysis of the encoding stage, we made a total of 20 tests (all whole ROIs, $n=12$, plus anterior and posterior subregions, $n=8$), for which we applied a correction for multiple comparisons by multiplying *p*-values with the number of tests (Bonferroni correction, $n=20$), unless otherwise stated.

Finally, we tested the difference between object and position processing during preparation and rehearsal stages. As with the encoding stage, in each stage analysis, we corrected for multiple comparisons (Bonferroni, $n=20$).

As MTL regions are situated in regions suffering from image artifacts when using EPI, we wanted to test whether there were any significant regional differences in signal values in this region. We therefore computed the gradient of the B_0 field in each region and examined the relationship of these values to BOLD contrast values.

Results

Based on a brief assessment (see Materials and methods), subjects' *z*-scores for DART (mean = 0.85, std. = 1.17) and WAIS vocabulary (mean = 0.40, std. = 1.28) were all within the normal range. Comparing reaction times and accuracy for object and position tasks, we found lower mean reaction time for object recognition (*objects*: mean/std. = 1000/102 ms, *positions*: 1049/84; $p=0.050$) but no difference in mean accuracy levels (*objects*: mean/std. = 5.18/0.40, *positions*: 5.30/0.33 of six possible correct responses; $p=0.193$).

During encoding, both perirhinal cortices were significantly more active during object encoding than position encoding (see Table 1 and Fig. 3). In both the left and right perirhinal cortex 22 subjects (88%) showed the object>position encoding effect, while 3 subjects (12%) did not display any such (or opposite) difference.

To investigate the nature of the response within the left and right perirhinal cortex and parahippocampal cortex during the different paradigms, we looked at the averaged responses of those voxels within the native-space perirhinal ROIs that surpassed the relevant threshold ($p=0.05$, uncorrected). A block-length for encoding of 12 s and TR of 2 s afforded a temporal resolution of 6 samples per activation block. Averaging was also performed over the repeats of each of the preparation and rehearsal blocks. Fig. 4 illustrates the greater response found during the object-encoding block (red line) compared with that during the position-encoding one (blue line) in both the perirhinal cortex and the anterior and posterior parts of the parahippocampal cortex.

At the whole-structure level, both the parahippocampal cortex and hippocampus were significantly more active bilaterally during object encoding than position encoding (See Table 1). To test for regional differences within each ROI, we performed a paired-samples *t*-test of the contrast score in the anterior and posterior parts of each of the hippocampal and parahippocampal ROIs. The analysis did not show any

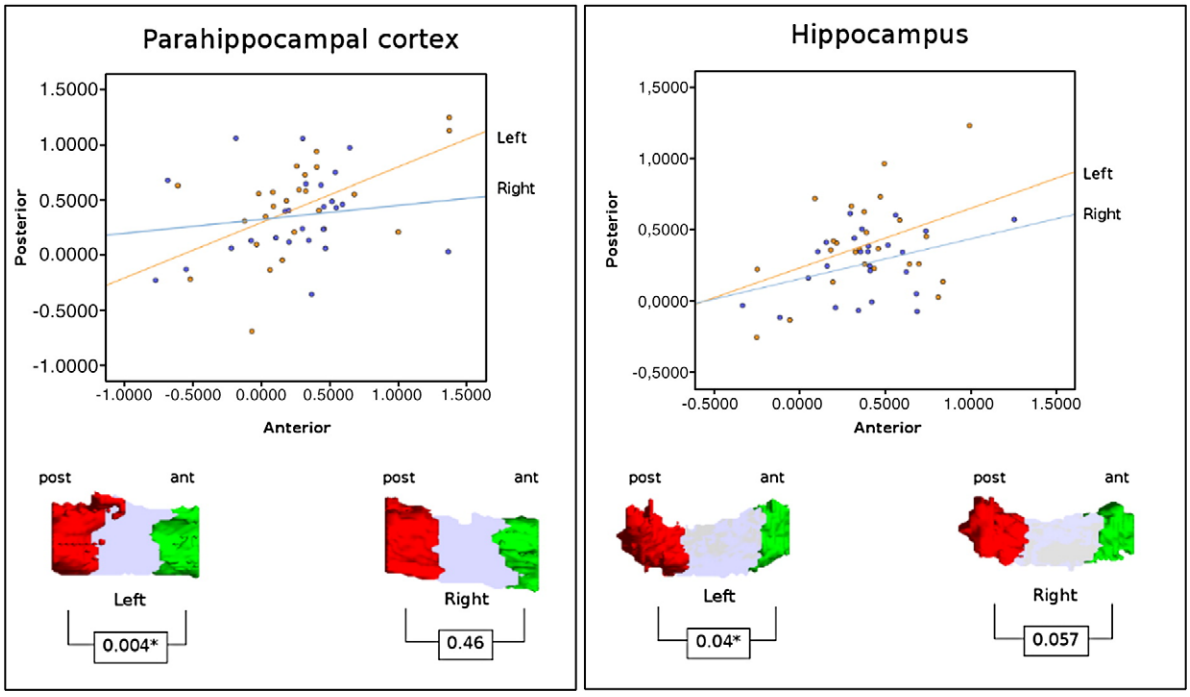

Fig. 5. Comparing anterior and posterior subregions of the parahippocampal cortex (left box) and the hippocampus (right box). The top graph shows the relationship between anterior (*x*-axis) and posterior (*y*-axis) contrast values (object encoding>position encoding) for right and left hemisphere. Bottom figures show anterior (green) and posterior (red) parts of each structure, illustrated from one individual. Bottom numbers display uncorrected *p*-values for each anterior–posterior test, asterisk indicates significant *p*-value ($p<0.05$, uncorrected).

significant anterior–posterior differences in either hemisphere. We then performed a post-hoc correlation analysis of the contrast values in the anterior and posterior portions of the hippocampus and parahippocampal cortex in each hemisphere. Here, we observed a correlation trend between anterior–posterior pairs, in particular in the left parahippocampal cortex ($r=0.55$, $p=0.004$ uncorrected) and the left hippocampus ($r=0.41$, $p=0.04$, uncorrected), but not in the right parahippocampal cortex ($r=0.154$, $p=0.46$, uncorrected) or the right hippocampus ($r=0.386$, $p=0.057$, uncorrected). This is illustrated in Fig. 5.

Our post-hoc analysis of the encoding stage demonstrated that a large portion of the MTL was more strongly activated during object encoding compared to position encoding. As Table 1 shows, this included bilateral temporopolar cortex and amygdala, though the effect was not significant in the entorhinal cortex.

In order to demonstrate that the paradigm lead to general activation differences in the brain, we conducted a native space analysis of regions showing larger activation during object encoding than position encoding, and the opposite contrast (larger activation during position encoding than object encoding). In all 25 subjects we found a clear dissociation in spatial localization and extent of brain activation for the two contrasts. The first contrast (object encoding>position encoding) generally showed activation differences in the primary visual cortex, ventral occipital and temporal regions and in MTL structures. The second contrast (position encoding>object encoding) demonstrated dorsal occipital and ventral parietal activation differences. This suggests that the paradigm as such taxed different neural mechanisms, and was suggestive of a ventral–dorsal processing difference for object and position encoding, respectively (see Supplementary materials). However, due to our limited field of view, we could not assess further differences in neural activation levels at the whole-brain level.

For the preparation and rehearsal stages, we found no significant difference in the processing of objects and locations.

Our test for any significant regional differences in signal values in the MTL, computed as regional differences in the B_0 as well as the relationship of these values to BOLD contrast values, did not show any dependence between gradients in the B_0 field and BOLD contrast values. Consistent with this, residualizing the ROI contrast values for local B_0 gradients did not change these results.

Discussion

By studying the effects of intentional encoding of objects and positions, we found task-related differences in the MTL region. Our first analysis focused on the hypothesized effects of content during encoding in the perirhinal cortex. Here, we found that the perirhinal cortex was bilaterally more engaged by object encoding compared to position encoding. This supports our hypothesis that the perirhinal cortex is involved in object-specific encoding; and the finding corroborates similar results from both the human and non-human primate literature (Aggleton and Brown, 2005; Wan et al., 1999; Bussey et al., 2002, 2005). Converging evidence from lesion studies of monkeys (Baxter and Murray, 2001), rats (Prusky et al., 2004) and humans (Barense et al., 2005), as well as from neuroimaging studies (Pihlajamäki et al., 2005) have implicated the perirhinal cortex in object processing. Furthermore, studies using immediate early gene imaging in rats indicate that the perirhinal cortex, but not the hippocampus, is involved in processing novel, as opposed to familiar, visual objects. (Aggleton and Brown, 2005; Wan et al., 1999; Zhu et al., 1995, 1996). Further support for this functional dissociation comes from anatomical studies showing that the perirhinal cortex receives the majority of its afferents from what has been termed the "ventral visual stream", a system involved in the identification and recognition of visual objects.

Previous studies have shown that the parahippocampal cortex receives the majority of its input from areas that make up the "dorsal visual stream" that is thought to process location and spatial context of objects (Burwell and Amaral, 1998; Witter et al., 1989). Furthermore, the posterior parahippocampal cortex has previously been reported to be strongly activated by spatial stimuli, in particular pictures of scenes, compared to pictures of objects (Epstein and Kanwisher, 1998; Epstein et al., 1999; Downing et al., 2006) Contrary to this notion, we found that the parahippocampal cortex was significantly more engaged in object encoding than position encoding. To rule out that this result could be driven by a difference between anterior and posterior subregions of the parahippocampal cortex, we compared the content effect in anterior and posterior parahippocampal cortex. However, we found that there was no difference between anterior and posterior subregions in their relative engagement in object and position encoding. On the contrary, the results suggested that there was a correlation between the subregions, in particular in the left hemisphere. Furthermore, our time-series analysis of the anterior and posterior parts of the parahippocampal cortex demonstrated that the object encoding stage, but not the position encoding stage, was accompanied by a large increase in BOLD signal. One may argue that the anterior parahippocampal cortex did show some responsiveness to position encoding (see Fig. 4, middle time-series), but this does not agree with the expected effect in the posterior parahippocampal cortex.

Our findings are inconsistent with previous studies that have demonstrated a role for the parahippocampal cortex in spatial processing (Pihlajamäki et al., 2005; Epstein et al., 1999; Burgess et al., 2002). For example, Pihlajamäki et al. (2005) found increased activation in the perirhinal cortex during novel item processing, and increased activation in the parahippocampal cortex during processing of novel spatial arrangements. Buffalo et al. (2006) found that the perirhinal cortex was activated both during item and spatial processing and there was only a trend toward greater object processing activation in this structure. Conversely, the anterior parahippocampal cortex showed increased activation for spatial processing only. The results reported here suggest that there may be different kinds of spatial processing, and that the spatial advantage reported in other studies may be explained by the saliency of spatial information. Future studies should be conducted in order to directly address the role of the parahippocampal cortex in spatial processing at different levels of complexity.

It should be noted that demands for position processing may have failed to activate the parahippocampal cortex. Using a paradigm very similar to the present study, Mitchell et al. (2000) found that while object processing evoked more activity than position processing in limited parts of the MTL, no MTL regions exhibited greater activity during position processing. Indeed, this is very similar to our own findings, in which the entire MTL seems to be more engaged by object encoding than position encoding, although the position encoding condition did seem to engage other brain structures related to spatial processing (see Supplementary materials).

There are several factors that may have contributed to discrepancies in results of these studies of object and position encoding. First, the object and position encoding tasks may have differed with respect to how much they taxed the encoding apparatus. In several studies, including the present study, the objects presented represented members of a virtually limitless set of possibilities, while the positions to be encoded represented a small set of possibilities; for example, in the present study only nine positions were possible. Thus, in one sense, objects were "low frequency" stimuli, while positions were "high frequency" stimuli. Low frequency stimuli are known to be more difficult to process at study phase, although they may be more easily recognized at the test phase (Glanzer and Adams, 1985; Ostergaard, 1998; Diana and Reder, 2006). This may have resulted in the presence of object but not position effects in the present study and in the study by Mitchell et al. (2000). Interestingly, in the Buffalo et al. (2006) study, in which position effects in MTL structures were more

prominent than object effects, the objects were drawn from a more restricted set of similar objects, and thus may have, from an encoding perspective, been more similar to higher frequency items.

Alternatively, the lack of position effects may relate to the low spatial complexity of the position stimuli. Recent studies suggest a role for the parahippocampal cortex region in more complex spatial processing, such as scenes (Buffalo et al., 2006; Henderson et al., in press; Epstein et al., 2007) and other contextual stimuli (Aminoff et al., 2007). Thus, although the current spatial task may be regarded as depending on a spatial processing system per se, it may not have involved sufficiently complex visual stimuli to engage the posterior MTL region. It has been suggested that the parahippocampal cortex is functionally divided into an anterior and posterior region, where the anterior parts are involved in object-specific processing while the posterior parts are involved in position and place processing (Pihlajamäki et al., 2005). Our results did not confirm this expected anterior–posterior functional dissociation, but rather demonstrated a correlation trend between anterior and posterior subregions of the parahippocampal cortex, especially in the left hemisphere. This may be attributable to the use of a relatively simple spatial task. Consequently, comparing visual object encoding and encoding of complex spatial stimuli (e.g., scenes) may cause an anterior–posterior processing difference in the parahippocampal cortex (as well as in the hippocampus). Indeed, this may be the main reason for diverging findings between studies using a simple spatial task (Buffalo et al., 2006; Mitchell et al., 2000, and the present study), and studies using more complex spatial stimuli (Pihlajamäki et al., 2005; Epstein et al., 1999; Burgess et al., 2002).

Two further problems with the current paradigm may have influenced our results. First, the lack of significant position effects may be explained by repetition suppression effects. While the objects in the object task were not repeated, the spatial layout of the position task remained the same across trials. This repetition difference between the tasks may decrease the responsiveness in the parahippocampal cortex for the spatial task relative to the object task. A further confound with the current position task is that it may be influenced by encoding strategy. That is, the task of encoding and remembering the use of trial-unique grid locations may be solved by memorizing the three of nine grid locations that were not used. This as opposed to the task of the harder task of remembering six out of nine grid locations. Consequently, the observed greater activation in the object task may in part be driven by the greater processing demand in the object task.

In a post-hoc analysis we explored the difference in activation in other MTL regions, including the temporopolar cortex, entorhinal cortex, and amygdala, during object and position encoding. Some of these activations were unexpected, including the bilateral involvement of the temporopolar cortex and amygdala in object encoding compared to position encoding. However, previous studies have suggested a role for the temporopolar cortex in visual recognition (Nakamura and Kubota, 1995), semantic memory (Davies et al., 2004), and recognition awareness (Sewards and Sewards, 2002); and for the amygdala in emotional learning (e.g., Leppanen and Nelson, 2006; Rosen and Donley, 2006), and novelty processing (Fried et al., 2002; Moses et al., 2002). The present results suggest that these structures may be more strongly engaged by object encoding that position encoding.

The object encoding task appeared to evoke stronger activations than positions in a number of regions, though there was evidence that the strength of these effects differed both by region and by hemisphere. In addition, the left hemisphere seemed to differ more strongly between object and position encoding than the right hemisphere. Thus, although the present paradigm was unable to produce truly dissociated effects of object vs. position encoding in the MTL region, the results are still consistent with regional differences in this content effect.

The paradigm allowed exploratory analysis of the effects of content during preparation and rehearsal. In addition, we modeled but did not report effects of content during the recognition stage, as significant differences in regional content effects may be greatly influenced by visually different stimuli. The present paradigm explicitly used a task involving the maintenance of object or spatial information for brief periods of time (~6 s), a task that is related to working memory. However, no significant effect of content was found during preparation or rehearsal stages. These results are inconsistent with previous studies that have implicated distinct roles for MTL regions object and spatial working memory (Stern et al., 2001; Petersson et al., 2006; Olson et al., 2006a,b; Nichols et al., 2006; Axmacher et al., 2007, 2008). Such studies have demonstrated a role of the MTL and inferior temporal cortex in active maintenance of novel information. In particular, using a task of encoding, maintenance and recognition of novel faces, Ranganath and D'Esposito (2001) demonstrated a double dissociation between the response properties of the anterior hippocampal and parahippocampal regions. It was found that the hippocampus was more engaged during maintenance of novel faces, but not during encoding or recognition stages. Conversely, the parahippocampal cortex demonstrated increased activation during encoding and recognition of novel faces but not during the maintenance stage. In a similar study (Ranganath et al., 2004), it was found that subregions of the inferior temporal cortex were differentially engaged during short-time maintenance of such content specific information (faces and houses). Furthermore, Piekema et al. (2006) demonstrated MTL engagement during working memory for features that are processed in different cortical regions. In particular, the hippocampus may be crucial to working memory binding of divergent features. This offers a suggestion for the results presented here. The task used in the present study stressed the maintenance of either objects of positions. Following the findings made by Piekema et al. it is possible that a working memory engagement of the MTL region may require the encoding and maintenance of object–location associations, rather than separate processing of objects and positions. Indeed, in a very similar setup Mitchell et al. (2000) demonstrated a higher engagement of the left anterior hippocampus during object–position associative maintenance. This suggests that MTL regions such as the hippocampus may be involved in the maintenance of object–location associations, but not in object or location processing alone.

ROI analysis

In the present study, an optimized MRI sequence was used to test whether specific regions of the MTL are differentially activated during mnemonic processing of objects and positions. One caveat in the functional neuroimaging of MTL structures is the use of whole-brain image acquisition that may lead to significant loss of signal in this region due to susceptibility artifacts, especially at high-field fMRI scanners at and above 3 T (Bellgowan et al., 2006). A second potential problem is the regular use of spatial normalization and smoothing of functional images (Ashburner and Friston, 1999). Studies of such methods have shown that MTL regions are poorly registered across individuals with standard methods (Salmond et al., 2002), and systematically different in subjects with memory impairments (Krishnan et al., 2006). Thus, spatial normalization procedures may spatially displace MTL activations when moving brains from native space into a standard frame of reference. In previous work, we have demonstrated that MTL structures are spatially displaced following spatial normalization with the use of standard methods (Ramsøy et al., 2005, Liptrot et al. 2006). In this paper we have tried to accommodate these difficulties by 1) using an image acquisition sequence that is optimized for the MTL region, and 2) analyzing regional brain activation in each subject's non-normalized brain by comparing the activation levels in anatomically predefined structures.

A few caveats should be considered for the present study. First, the perirhinal cortex and entorhinal cortex were defined using the collateral sulcus in its entire depth. The perirhinal ROI might therefore have partly included the lateral most part of the entorhinal cortex. This part of the entorhinal cortex has been shown to receive inputs from the perirhinal cortex as part of the ventral stream projections (Eichenbaum et al., 2007; Guarnieri et al., 2006). Distinctions observed here between perirhinal cortex and entorhinal cortex may have been mediated to some extent by this imprecision in boundary delineation.

Second, in order to maximize the signal to noise ratio in the MTL region the BOLD signal was not recorded at the whole-brain level. It is likely that at least some of the effects for content and processing steps that we have found in the MTL apply to other areas of the brain as well, such as the dorsolateral prefrontal cortex. This area is known to be involved in different functions that relate to the present paradigm, including preparation (Rowe et al., 2002) and both object and spatial working memory (Deco et al., 2004). Furthermore, one could expect that the parietal cortex may be involved in the attentional modulation produced by object or position instructions (Aso et al., 2007). Indeed, our exploratory analysis did reveal that the dorsal occipital cortex and ventral parietal cortex were more engaged during position encoding than object encoding. However, our limited field of view did not allow the assessment of these effects at the whole-brain level. Consequently, a combination of local (MTL) and global brain activation neuroimaging is needed to explore the complex interactions between the MTL regions and the regions with which they are connected.

Finally, the present analysis included considerations of the effect of regional B_0 inhomogeneities, and their relationship to differences in BOLD contrasts. B_0 in the MTL region is known to be heterogeneous, especially along the anterior–posterior axis, though B_0 values are more bilaterally symmetrical. Thus, regional differences in the size of activation effects, particularly along the anterior–posterior axis, can result from poor sensitivity in anterior regions with low B_0. Our analysis revealed no evidence of a dependence of the object–position contrast values on B_0 inhomogeneities and when regional B_0 gradient values were used as covariates, the results of the analyses were unchanged. Thus it seems unlikely that the observed pattern of content effects across the regions we examined is strongly influenced by B_0 inhomogeneity.

There may be other factors that make direct comparison of BOLD effects within MTL regions difficult. For example, it has been argued that systematic differences in the microvascular structure and especially the relative alignment of draining veins to B_0 may have an impact on the BOLD signal (Sheth et al., 2004; Roberts et al., 2007; Prinster et al., 1997; Hall et al., 2002). In the MTL, regions such as the hippocampus, amygdala and the parahippocampal region have significantly different microvasculature, and it may be possible that this has an impact on regional differences in the BOLD signal. Other factors include regional differences in partial volume effects (due to different ROI sizes), coil sensitivity, and physiological noise (e.g., the proximity to large arteries). Many of these factors can be accounted for, at least partially, as we have done with the use of cardiac and respiratory recordings as nuisance regressors in the model. The collective effect of these factors on regional differences in BOLD signal, as well as methods to control for these factors, requires more attention.

Conclusion

The present study provides further evidence for a significant role of several MTL regions in the encoding of objects and positions. As predicted, there was evidence that object encoding more strongly engaged the perirhinal cortex than did position encoding. In general, the object encoding task seemed to engage large portions of the MTL bilaterally, and no MTL region displayed preferential activation during position encoding. Contrary to our expectations, direct comparisons of the anterior and posterior parts of the parahippocampal cortex or hippocampus did not yield any significant difference in their differential involvement in object and position encoding. On the contrary, our results suggested that the content effects in the anterior and posterior subregions were correlated, especially in the left hemisphere. Unfortunately, perhaps because the encoding demands in the position condition were lower, the results are less conclusive regarding the relative roles of the MTL structures in encoding of spatial information. These unexpected observations warrant further examination for confirmation in prospective studies.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2009.03.082.

References

Aggleton, J.P., Brown, M.W., 2005. Contrasting hippocampal and perirhinal cortex function using immediate early gene imaging. Q. J. Exp. Psychol. B 58 (3–4), 218–233.
Aminoff, E., Gronau, N., Bar, M., 2007. The parahippocampal cortex mediates spatial and nonspatial associations. Cereb. Cortex 17 (7), 1493–1503.
Ashburner, J., Friston, K.J., 1999. Nonlinear spatial normalization using basis functions. Hum. Brain Mapp. 7 (4), 254–266.
Aso, T., Hanakawa, T., Matsuo, K., Toma, K., Shibasaki, H., Fukuyama, H., Nakai, T., 2007. Subregions of human parietal cortex selectively encoding object orientation. Neurosci. Lett. 415 (3), 225–230.
Axmacher, N., Mormann, F., Fernández, G., Cohen, M.X., Elger, C.E., Fell, J., 2007. Sustained neural activity patterns during working memory in the human medial temporal lobe. J. Neurosci. 27 (29), 7807–7816.
Axmacher, N., Schmitz, D.P., Weinreich, I., Elger, C.E., Fell, J., 2008. Interaction of working memory and long-term memory in the medial temporal lobe. Cerebral. Cortex.
Barense, M.D., Bussey, T.J., Lee, A.C., Rogers, T.T., Davies, R.R., Saksida, L.M., Murray, E.A., Graham, K.S., 2005. Functional specialization in the human medial temporal lobe. J. Neurosci. 25 (44), 10239–10246.
Baxter, M.G., Murray, E.A., 2001. Opposite relationship of hippocampal and rhinal cortex damage to delayed nonmatching-to-sample deficits in monkeys. Hippocampus 11 (1), 61–71.
Bellgowan, P.S., Bandettini, P.A., van Gelderen, P., Martin, A., Bodurka, J., 2006. Improved BOLD detection in the medial temporal region using parallel imaging and voxel volume reduction. NeuroImage 29 (4), 1244–1251.
Buffalo E.A., Bellgowan P.S., Martin A. (2006) Distinct roles for medial temporal lobe structures in memory for objects and their locations. Learn Mem. Sep–Oct;13(5): 638–43. [Electronic publication 2006 Sep 15].
Burgess, N., Maguire, E.A., O'Keefe, J., 2002. The human hippocampus and spatial and episodic memory. Neuron 35 (4), 625–641 [Aug 15].
Burwell, R.D., Amaral, D.G., 1998. Cortical afferents of the perirhinal, postrhinal, and entorhinal cortices of the rat. J. Comp. Neurol. 398 (2), 179–205 [Aug 24].
Bussey, T.J., Saksida, L.M., Murray, E.A., 2002. Perirhinal cortex resolves feature ambiguity in complex visual discriminations. Eur. J. Neurosci. 15 (2), 365–374 [Jan].
Bussey, T.J., Saksida, L.M., Murray, E.A., 2005. The perceptual-mnemonic/feature conjunction model of perirhinal cortex function. Q. J. Exp. Psychol. B 58 (3–4), 269–282 [Jul–Oct].
Bussey, T.J., Saksida, L.M., Murray, E.A., 2006. Perirhinal cortex and feature-ambiguous discriminations. Learn. Mem. 13 (2), 103–105 [Mar–Apr].
Cho, Z.H., Ro, Y.M., 1992. Reduction of susceptibility artifact in gradient-echo imaging. Magn. Reson. Med. 23 (1), 193–200 [Jan].
Davies, R.R., Graham, K.S., Xuereb, J.H., Williams, G.B., Hodges, J.R., 2004. The human perirhinal cortex and semantic memory. Eur. J. Neurosci. 20 (9), 2441–2446 [Nov].
Deco, G., Rolls, E.T., Horwitz, B., 2004. “What” and “where” in visual working memory: a computational neurodynamical perspective for integrating FMRI and single-neuron data. J. Cogn. Neurosci. 16 (4), 683–701 [May].
Deichmann, R., Gottfried, J.A., Hutton, C., Turner, R., 2003. Optimized EPI for fMRI studies of the orbitofrontal cortex. NeuroImage 19 (2 Pt. 1), 430–441.
Diana, R.A., Reder, L.M., 2006. The low-frequency encoding disadvantage: word frequency affects processing demands. J. Exp. Psychol. Learn. Mem. Cogn. 32 (4), 805–815.
Downing, P.E., Chan, A.W., Peelen, M.V., Dodds, C.M., Kanwisher, N., 2006. Domain specificity in visual cortex. Cereb. Cortex 16 (10), 1453–1461.
Duvernoy, H.M., 1991. The Human Brain: Surface, Three-dimensional Sectional Anatomy with MRI, and Blood Supply2nd edition. Springer-Verlag, Wien.

Eichenbaum, H., Yonelinas, A.R., Ranganath, C., 2007. The medial temporal lobe and recognition memory. Annu. Rev. Neurosci. 30, 123–152 [February].
Epstein, R., Kanwisher, N., 1998. A cortical representation of the local visual environment. Nature 392 (6676), 598–601.
Epstein, R., Harris, A., Stanley, D., Kanwisher, N., 1999. The parahippocampal place area: recognition, navigation, or encoding? Neuron 23 (1), 115–125 [May].
Epstein, R.A., Parker, W.E., Feiler, A.M., 2007. Where am I now? Distinct roles for parahippocampal and retrosplenial cortices in place recognition. J. Neurosci. 27 (23), 6141–6149.
Fried, I., Cameron, K.A., Yashar, S., Fong, R., Morrow, J.W., 2002. Inhibitory and excitatory responses of single neurons in the human medial temporal lobe during recognition of faces and objects. Cereb. Cortex 12 (6), 575–584 [Jun].
Glanzer, M., Adams, J.K., 1985. The mirror effect in recognition memory. Mem. Cogn. 13 (1), 8–20.
Graham, K.S., Gaffan, D., 2005. The role of the medial temporal lobe in memory and perception: evidence from rats, nonhuman primates and humans. Q. J. Exp. Psychol. B 58 (3–4), 193–201 [Jul–Oct].
Hall, D.A., Gonçalves, M.S., Smith, S., Jezzard, P., Haggard, M.P., Kornak, J., 2002. A method for determining venous contribution to BOLD contrast sensory activation. Magn. Reson. Imaging 20 (10), 695–706 [Dec].
Henderson J.M., Larson C.L., Zhu D.C. (in press). Full Scenes produce more activation than Close-up Scenes and Scene-Diagnostic Objects in parahippocampal and retrosplenial cortex: an fMRI study. Brain Cogn.
Insausti, R., Juottonen, K., Soininen, H., Insausti, A.M., Partanen, K., Vainio, P., Laakso, M.P., Pitkänen, A., 1998. MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. AJNR Am. J. Neuroradiol. 19 (4), 659–671 [Apr].
Krishnan, S., Slavin, M.J., Tran, T.T., Doraiswamy, P.M., Petrella, J.R., 2006. Accuracy of spatial normalization of the hippocampus: implications for fMRI research in memory disorders. NeuroImage 31 (2), 560–571 [Jun].
Leppanen, J.M., Nelson, C.A., 2006. The development and neural bases of facial emotion recognition. Adv. Child. Dev. Behav. 34, 207–246.
Liptrot, M.G., Ramsøy, T.Z., Lund, T.E., Sidaros, K., Christensen, M.S., Nielsen, F.Å., Baaré, W., Jernigan, T.L., 2006. The downside of spatial normalisation in fmri of medial temporal lobe structures. Proc. Intl. Soc. Magn. Reson. Med. 3270.
Lund, T.E., Madsen, K.H., Sidaros, K., Luo, W.L., Nichols, T.E., 2006. Non-white noise in fMRI: does modelling have an impact? NeuroImage 29 (1), 54–66 [Jan 1].
Mitchell, K.J., Johnson, M.K., Raye, C.L., D'Esposito, M., 2000. fMRI evidence of age-related hippocampal dysfunction in feature binding in working memory. Brain Res. Cogn. Brain Res. 10 (1–2), 197–206 [Sep].
Moses, S.N., Sutherland, R.J., McDonald, R.J., 2002. Differential involvement of amygdala and hippocampus in responding to novel objects and contexts. Brain Res. Bull. 58 (5), 517–527 [Sep 15].
Murray, E.A., Graham, K.S., Gaffan, D., 2005. Perirhinal cortex and its neighbours in the medial temporal lobe: contributions to memory and perception. Q. J. Exp. Psychol. B 58 (3–4), 378–396 [Jul–Oct Review].
Nakamura, K., Kubota, K., 1995. Mnemonic firing of neurons in the monkey temporal pole during a visual recognition memory task. J. Neurophysiol. 74 (1), 162–178 [Jul].
Neufeld, A., Assaf, Y., Graif, M., Hendler, T., Navon, G., 2005. Susceptibility-matched envelope for the correction of EPI artifacts. Magn. Reson. Imaging 23 (9), 947–951 [Nov].
Nichols, E.A., Kao, Y., Verfaellie, M., Gabrieli, J.D.E., 2006. Working memory and long-term memory for faces: evidence from fMRI and global amnesia for involvement of the medial temporal lobes. Hippocampus 16 (7), 604–616.
Olson, I.R., Page, K., Moore, K.S., Chatterjee, A., Verfaellie, M., 2006a. Working memory for conjunctions relies on the medial temporal lobe. J. Neurosci. 26 (17), 4596–4601.
Olson, I.R., Moore, K.S., Stark, M., Chatterjee, A., 2006b. Visual working memory is impaired when the medial temporal lobe is damaged. J. Cogn. Neurosci. 18 (7), 1087–1097.
Ostergaard, A.L., 1998. The effects on priming of word frequency, number of repetitions, and delay depend on the magnitude of priming. Mem. Cogn. 26 (1), 40–60.
Petersson, K.M., Gisselgård, J., Gretzer, M., Ingvar, M., 2006. Interaction between a verbal working memory network and the medial temporal lobe. NeuroImage 33 (4), 1207–1217.
Piekema, C., Kessels, R.P., Mars, R.B., Petersson, K.M., Fernández, G., 2006. The right hippocampus participates in short-term memory maintenance of object–location associations. NeuroImage 33 (1), 374–382.
Pihlajamäki, M., Tanila, H., Könönen, M., Hänninen, T., Hämäläinen, A., Soininen, H., Aronen, H.J., 2004. Visual presentation of novel objects and new spatial arrangements of objects differentially activates the medial temporal lobe subareas in humans. Eur. J. Neurosci. 19 (7), 1939–1949 [Apr].
Pihlajamäki, M., Tanila, H., Könönen, M., Hänninen, T., Aronen, H.J., Soininen, H., 2005. Distinct and overlapping fMRI activation networks for processing of novel identities and locations of objects. Eur. J. Neurosci. 22 (8), 2095–2105 [Oct].
Prinster, A., Pierpaoli, C., Turner, R., Jezzard, P., 1997. Simultaneous measurement of DeltaR2 and DeltaR2* in cat brain during hypoxia and hypercapnia. NeuroImage 6 (3), 191–200 [Oct].
Pruessner, J.C., Köhler, S., Crane, J., Pruessner, M., Lord, C., Byrne, A., Kabani, N., Collins, D.L., Evans, A.C., 2002. Volumetry of temporopolar, perirhinal, entorhinal and parahippocampal cortex from high-resolution MR images: considering the variability of the collateral sulcus. Cereb. Cortex 12 (12), 1342–1353 [Dec].
Prusky, G.T., Douglas, R.M., Nelson, L., Shabanpoor, A., Sutherland, R.J., 2004. Visual memory task for rats reveals an essential role for hippocampus and perirhinal cortex. Proc. Natl. Acad. Sci. U. S. A. 101 (14), 5064–5068.
Ramsøy, T.Z., Lund, T.E., Liptrot, M.G., Sidaros, K., Christensen, M.S., Nielsen, F.Å., Jernigan, T.L., 2005. Effects of Spatial Normalization on Detection of Perirhinal Cortex Activation in Individual Subjects Using fMRI. Proceedings of the Alzheimer's Assocation International Conference on Prevention of Dementia, 2005 June 18–21. Washington, D.C.
Ranganath, C., D'Esposito, M., 2001. Medial temporal lobe activity associated with active maintenance of novel information. Neuron 31, 865–873.
Ranganath, C., Cohen, M.X., Dam, C., D'Esposito, M., 2004. Inferior temporal, prefrontal, and hippocampal contributions to visual working memory maintenance and associative memory retrieval. J. Neurosci. 24 (16), 3917–3925.
Roberts, K.C., Tran, T.T., Song, A.W., Woldorff, M.G., 2007. Component structure of event-related fMRI responses in the different neurovascular compartments. Magn. Reson. Imaging 25 (3), 328–334 [Apr].
Rosen, J.B., Donley, M.P., 2006. Animal studies of amygdala function in fear and uncertainty: relevance to human research. Biol. Psychol. 73 (1), 49–60 [Jul].
Rossion, B., Pourtois, G., 2004. Revisiting Snodgrass and Vanderwart's object set: the role of surface detail in basic-level object recognition. Perception 33, 217–236.
Rousson, V., Gasser, T., Seifert, B., 2002. Assessing intrarater, interrater and test–retest reliability of continuous measurements. Stat. Med. 21 (22), 3431–3446 [Nov 30].
Rowe, J.B., Toni, I., Josephs, O., Frackowiak, R.S., Passingham, R.E., 2002. The prefrontal cortex: response selection or maintenance within working memory? Science 288 (5471), 1656–1660 [2000 Jun 2].
Salmond, C.H., Ashburner, J., Vargha-Khadem, F., Connelly, A., Gadian, D.G., Friston, K.J., 2002. The precision of anatomical normalization in the medial temporal lobe using spatial basis functions. NeuroImage 17 (1), 507–512 [Sep].
Sewards, T.V., Sewards, M.A., 2002. On the neural correlates of object recognition awareness: relationship to computational activities and activities mediating perceptual awareness. Conscious. Cogn. 11 (1), 51–77 [Mar].
Sheth, S.A., Nemoto, M., Guiou, M., Walker, M., Pouratian, N., Hageman, N., Toga, A.W., 2004. Columnar specificity of microvascular oxygenation and volume responses: implications for functional brain mapping. J. Neurosci. 24 (3), 634–641 [Jan 21].
Sled, J.G., Zijdenbos, A.P., Evans, A.C., 1998. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans. Med. Imag. 17 (1), 87–97 [Feb].
Squire, L.R., Zola-Morgan, S., 1991. The medial temporal lobe memory system. Science 253 (5026), 1380–1386 [Sep 20].
Squire, L.R., Stark, C.E., Clark, R.E., 2004. The medial temporal lobe. Annu. Rev. Neurosci. 27, 279–306.
Stern, C.E., Sherman, S.J., Kirchhoff, B.A., Hasselmo, M.E., 2001. Medial temporal and prefrontal contributions to working memory tasks with novel and familiar stimuli. Hippocampus 11 (4), 337–346.
Wan, H., Aggleton, J.P., Brown, M.W., 1999. Different contributions of the hippocampus and perirhinal cortex to recognition memory. J. Neurosci. 19 (3), 1142–1148 [Feb 1].
Watson, C., Andermann, F., Gloor, P., Jones-Gotman, M., Peters, T., Evans, A., Oliviera, A., Melanson, D., Leroux, G., 1992. Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. Neurology 42, 1743–1750.
Witter, M.P., Groenewegen, H.J., Lopes da Silva, F.H., Lohman, A.H., 1989. Functional organization of the extrinsic and intrinsic circuitry of the parahippocampal region. Prog. Neurobiol. 33 (3), 161–253.
Zhu, X.O., Brown, M.W., McCabe, B.J., Aggleton, J.P., 1995. Effects of the novelty or familiarity of visual stimuli on the expression of the immediate early gene c-fos in rat brain. Neuroscience 69 (3), 821–829 [Dec].
Zhu, X.O., McCabe, B.J., Aggleton, J.P., Brown, M.W., 1996. Mapping visual recognition memory through expression of the immediate early gene c-fos. NeuroReport 7 (11), 1871–1875 [Jul 29].