

Investigating the Interaction between Spatial Perception and Working Memory in the Human Medial Temporal Lobe

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Abstract

■ There has been considerable debate surrounding the functions of the medial temporal lobe (MTL). Although this region has been traditionally thought to subserve long-term declarative memory only, recent evidence suggests a role in short-term working memory and even higher order perception. To investigate this issue, functional neuroimaging was used to investigate the involvement of the MTL in spatial scene perception and working memory. Healthy participants were scanned during a working memory task incorporating two factors of working memory (high vs. low demand) and spatial processing (complex vs. simple). It was found that an increase in spatial processing demand produced significantly greater activity in the posterior hippocampus and parahippocampal cortex irrespective of whether working memory demand was high or low. In contrast, there was no region within

the MTL that increased significantly in activity during both the complex and the simple spatial processing conditions when working memory demand was increased. There was, however, a significant interaction effect between spatial processing and working memory in the right posterior hippocampus and parahippocampal cortex bilaterally: An increase in working memory demand produced a significant increase in activity in these areas during the complex, but not simple, spatial processing conditions. These findings suggest that although there may be a role for the MTL in both stimulus processing and working memory, increasing the latter does not necessarily increase posterior MTL involvement. We suggest that these structures may play a critical role in processing complex spatial representations, which, in turn, may form the basis of short- and long-term mnemonic processes. ■

INTRODUCTION

Contrary to traditional theory, there has been increasing evidence to suggest that the functions of the medial temporal lobe (MTL) structures may extend beyond long-term declarative memory. One recent theory postulates that the MTL is critical for higher order perception (i.e., the processing and formation of perceptual representations), with the hippocampus and parahippocampal cortex important for complex spatial scenes and the perirhinal cortex critical for complex object stimuli (Epstein, 2008; Murray, Bussey, & Saksida, 2007). Consistent with this, neuropsychological (Barens, Gaffan, & Graham, 2007; Lee, Buckley, et al., 2005, 2006; Lee, Bussey, et al., 2005) and functional neuroimaging (Barens, Henson, Lee, & Graham, 2009; O'Neil, Cate, & Kohler, 2009; Lee, Scahill, & Graham, 2008; Devlin & Price, 2007) studies have implicated the involvement of the MTL in simultaneous visual discrimination tests (see, however, Shrager, Gold, Hopkins, & Squire, 2006; Stark & Squire, 2000).

Although a few of these aforementioned studies have attempted to disentangle long-term memory from perceptual processes (O'Neil et al., 2009; Lee et al., 2008; Devlin & Price, 2007), the potential contribution of short-term

working memory processes has not been fully considered. This is highly important because there is a large body of evidence that has highlighted a role for the MTL in the short-term retention of information (Hannula & Ranganath, 2008; Hartley et al., 2007; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; Piekema, Kessels, Mars, Petersson, & Fernández, 2006; Ranganath & D'Esposito, 2001; Stern, Sherman, Kirshhoff, & Hasselmo, 2001; Holdstock, Gutnikov, Gaffan, & Mayes, 2000). It is possible, therefore, that the reported involvement of the MTL during visual discrimination tasks (in which comparisons are made across multiple simultaneously presented stimuli) may, in fact, reflect a general role of the MTL in working memory rather than an involvement in higher order perception. Thus, according to this interpretation, the functions of the MTL may not extend to the perceptual domain, with this region subserving processes within short- and long-term memory only.

The present study used fMRI to investigate the involvement of the MTL beyond long-term memory in the domains of working memory and perception, focusing on the spatial domain. A 2×2 factorial design was implemented incorporating two factors of spatial processing and working memory. Because increased working memory typically increases MTL activity (Schon, Quiroz, Hasselmo, & Stern, 2009; Axmacher et al., 2007; Stern et al., 2001),

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participants were presented with a stream of images and were required to detect two consecutive repetitions (low working memory) or repetitions separated by a single item (high working memory). Demands on spatial processing were manipulated by using two categories of stimuli. Given the involvement of the MTL in spatial navigation (Maguire, Nannery, & Spiers, 2006; Maguire, Frackowiak, & Frith, 1997) and discrimination tasks involving complex scene stimuli (Lee et al., 2008; Lee, Buckley, et al., 2005), spatial processing was emphasized by presenting images of three-dimensional virtual reality rooms. In contrast, because the MTL has not often been implicated in the visual discrimination and very short-term maintenance of egocentric spatial locations (van Asselen et al., 2006; Milner, Johnsrude, & Crane, 1997), lower spatial processing was achieved by presenting two-dimensional spatial arrays.

If the MTL plays a general role in the short-term maintenance of information, then an increase in working memory demand would result in significant increases in MTL activity, irrespective of spatial processing demands. In contrast, if the type of stimulus and thus degree of perception is critical to MTL involvement, then one would predict MTL activity to be modulated primarily by spatial processing requirements.

METHODS

Subjects

Eighteen right-handed healthy volunteers (7 women) were scanned, ranging from 21 to 34 years of age (mean age = 25.11 years; $SD = 3.85$). All participants gave informed written consent after the nature of the study and its possible consequences were explained to them. This work received ethical approval from the Oxfordshire Research Ethics Committee A (Ref: 07/H0604/115).

Scanning Procedure

The scanning was conducted at the Oxford Centre for Functional MRI of the Brain (FMRIB Centre), Oxford, UK, on a 3-T MRI system driven by a Varian Unity Inova console and equipped with an Oxford Magnet Technology magnet, a Tesla head gradient coil, and a Pulse Teq four-channel radiofrequency head coil. Four four-dimensional data sets were acquired for each participant using an EPI pulse sequence to acquire T2*-weighted image volumes with BOLD contrast. Axial-oblique slices angled away from the eye balls were obtained to prevent image ghosting (voxel resolution = $3 \times 3 \times 3$ mm, matrix size = $64 \times 64 \times 41$, repetition time [TR] = 3 sec, echo time [TE] = 30 msec, field of view [FOV] = 192×192 mm, flip angle = 90°). Each EPI run was 753 sec in duration, consisting of 247 scans and 4 dummy scans at the start to allow the MR signal to reach an equilibrium state (these were later discarded). A T1 structural scan and magnetic field maps were also obtained for each subject. The former was ac-

quired using a three-dimensional MP FLASH sequence (voxel resolution = $1 \times 1 \times 1$ mm; TR = 13 msec; TE = 5 msec; flip angle = 13° ; FOV = $512 \times 192 \times 200$ mm; matrix size = $512 \times 192 \times 200$), whereas the latter were acquired using a dual-echo two-dimensional flash sequence with echoes at 20 and 22.5 msec (TR = 4.1 s; TE = 20 msec; flip angle = $90/180^\circ$; FOV = 192×192 ; matrix size = $64 \times 64 \times 41$).

During the acquisition of EPI data, visual stimuli were presented with a computer program written using the Presentation software package (Neurobehavioral Systems, Inc.). This program was run on a desktop computer connected to an LCD projector (1024×768 pixel resolution) that projected onto a white screen situated at the foot of the MRI subject bed. 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 a specified button on a response box held in the right hand.

Experimental Paradigm

To investigate the involvement of the MTL in spatial processing and working memory, a 2×2 factorial design was implemented with one factor of working memory ("1-back" vs. "2-back") and one factor of spatial processing ("simple" vs. "complex"), therefore creating four separate experimental conditions (Figure 1): (A) "1-back simple"; (B) "1-back complex"; (C) "2-back simple"; and (D) "2-back complex." Similar to previous work (Barense et al., 2009; Lee et al., 2008), these conditions were organized in a blocked ABCD-ABCD-ABCD-ABCD-ABCD-ABCD-ABCD-ABCD design in each of the four EPI sessions to

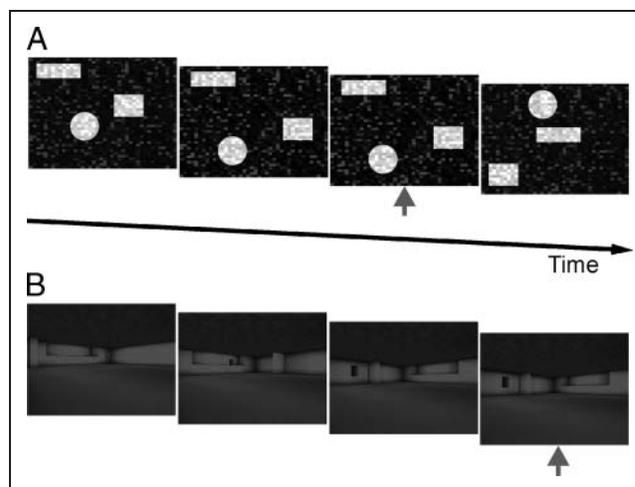


Figure 1. Four sample images from a block of the (A) 1-back simple and (B) 1-back complex conditions (typically eight color images/block in the experiment). In the former, the three moving features are common shapes, whereas in the latter the three moving features are a door cavity, a wide wall cavity, and a narrow wall protrusion. The arrows indicate a repetition target. The 2-back simple and complex tasks were similar except that the image repetitions were separated by a single stimulus to increase working memory demand.

maximize experimental power. Each condition lasted 20 sec per block, and in all task conditions, participants were presented with a succession of eight color images (24 bit, 800 × 600 pixels), each for 2.2 sec with a 0.3-sec interval between images. Before the start of each condition, the participants were presented with an instruction screen for 1.5 sec (i.e., “1-back” or “2-back”) followed by a 0.5-sec blank screen to inform them of the type of working memory task that they were to undertake. All participants received detailed instructions and three practice sessions with a different set of stimuli before data acquisition, two sessions before entering the scanner, and a third session in the scanner.

In the two 1-back tasks, the subjects were instructed to press the response button when a presented image was identical to the stimulus immediately preceding it, whereas in the 2-back conditions, the participants were required to indicate when a presented image was identical to the stimulus shown two images previously. Thus, the 2-back tasks were designed to place a greater demand on working memory by increasing memory load (subjects were required to hold two, as opposed to one, stimulus “on-line”) and maintenance duration (subjects were comparing information across three, as opposed to two, stimuli). To ensure that the subjects were consistently engaged throughout each block, there was either a single repetition target (i.e., a single image was repeated once in 50% of all blocks) or two repetition targets to be detected (i.e., two images were repeated once each in 50% of all blocks). The temporal occurrence of these repetitions in each sequence of eight images was pseudorandomized and counterbalanced across all conditions.

In the complex spatial processing conditions, the visual stimuli were snapshots of three-dimensional virtual reality rooms containing three distinct and moveable features (e.g., door, window, and floor cavity). These rooms were unfamiliar to the participants and, importantly, were specifically designed not to resemble real-world scenes or contain any objects that may trigger contextual processing or the retrieval of personal memories. The same room template was presented from an identical viewpoint in each block, and the locations of two or three of these moveable features were varied in a pseudorandom manner across the eight images in each block (the moveable features were not repeated across blocks).

In the simple spatial processing tasks, the participants were presented with scrambled images of the rooms shown in the complex conditions to create novel abstract patterns. The luminance in three subregions of these images was increased to create three common shapes (e.g., a rectangle, square, and circle) and the luminance of the remainder of the image was decreased proportionally to maintain the same overall luminance as the images presented in the complex conditions. The same scrambled abstract image template was presented in each block, and the locations of two or three of the shapes within the image were varied in a pseudorandom manner across the

eight images in each block (the moveable shapes changed in appearance across blocks). To avoid the impression of depth, the sizes of the moveable shapes were kept constant within a block.

In all conditions, the participants were encouraged to view each image as a single scene and to keep track of the locations of the three moveable features (two or three of the features were moved across images to prevent the subjects from solving the task by fixating on a single item). The number of moveable features (3) in each image was determined via behavioral piloting in an effort to match the difficulty of all conditions as closely as possible. Importantly, the simple and the complex spatial stimuli were designed to place a similar demand on contextual and relational processing. Both sets of stimuli required the tracking of three moveable features (common items such as shapes, doors, windows, etc.) within an unfamiliar spatial context (either a two-dimensional abstract array or a virtual reality room). Moreover, whereas the positions of the items in the complex spatial images could be remembered on the basis of the spatial relationships between the items and each item’s association with a particular component of the virtual reality room (i.e., wall, ceiling, or floor), the position of the shapes in the simple spatial stimuli could be remembered using the spatial relationships between the presented shapes as well as the position of each shape with respect to one or more features of the background abstract pattern. Importantly, the images for both the simple and the complex spatial conditions were equal in size, and the spatial distribution of the three moveable features in both types of stimuli was similar. Thus, we argue that the main difference between the simple stimuli and the complex rooms is that the latter placed a greater demand on spatial perception by requiring the processing of object-in-place information and geometrical features within a three-dimensional environment.

Finally, to minimize long-term memory processes, all stimuli besides the within-block image repetition targets were only used once across all four EPI sessions. In addition, no virtual reality room or scrambled image template was repeated across blocks.

Behavioral Data Analyses

For all tasks, the proportion of hits (H, correct identification of repetition stimuli) and false alarms (FA, incorrect identification of a new stimulus as a repetition) were calculated. Signal detection theory as applied to logistic distributions was then used to derive two behavioral measures of (1) sensitivity, $d_L = \ln([H(1 - FA)] / [(1 - H)FA])$, and (2) bias, $C_L = 0.5[\ln([(1 - FA)(1 - H)] / [(H)(FA)])]$, where \ln = natural log (Snodgrass & Corwin, 1988), and a more positive bias score reflects a more conservative approach to the task (i.e., a bias to classify an image as new rather than a repetition). All false alarm rates or hits equal to 0 or 1 were adjusted by 0.01 (Kane, Conway, Miura, & Colflesh, 2007). Four 2 × 2 repeated measures ANOVAs

were then conducted with working memory (1-back vs. 2-back) and spatial processing (simple vs. complex) as the independent variables and H, FA, d_L , and C_L as the dependent variables in each analysis.

Imaging Data Preprocessing

Imaging data preprocessing and analyses were conducted using the fMRI Expert Analysis Tool (FEAT version 5.98) part of the FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). Single subject data were first preprocessed using a number of steps: (1) realigning all images using rigid body registration to the central volume (Jenkinson, Bannister, Brady, & Smith, 2002); (2) unwarping the EPI data using the acquired field maps to correct for distortions due to magnetic field inhomogeneities (Jenkinson et al., 2002); (3) segmenting brain matter from nonbrain matter using a mesh deformation approach; (4) applying spatial smoothing using a Gaussian kernel of FWHM 8.0 mm; (5) implementing grand mean intensity normalization of the data set by a single multiplicative factor; (6) carrying out high-pass temporal filtering using Gaussian-weighted least-squares straight line fitting with $\sigma = 50$ s; (7) using independent component analysis-based exploratory data analysis to identify and remove unexpected artifacts (Beckmann & Smith, 2004); and finally (8) registering each data set to standard Montreal Neurological Institute (MNI) space using the MNI152 template and affine registration (Jenkinson et al., 2002; Jenkinson & Smith, 2001).

Imaging Data Statistical Analyses

For each EPI session for each subject, a general linear model was fit in prewhitened data space with four explanatory variables (corresponding to the onsets and durations of the four experimental conditions) and their temporal derivatives (Woolrich, Ripley, Brady, & Smith, 2001). Each explanatory variable was convolved with a double-gamma function to model the human hemodynamic response function and temporally filtered with the same high-pass filter as the data. To minimize the influence of extra-experimental subject error, blocks were only included if no false alarms were made and at least one repetition target was accurately detected. Accordingly, on average, one block was removed for each participant for the two 1-back tasks, whereas three blocks were removed, on average, per participant for the two 2-back conditions (note, however, that analyses using this criteria or including all blocks produced similar activation findings—the overall patterns and locations of activity were comparable but with a decrease in statistical significance when blocks were excluded because of reduced power). Thus, a parameter estimate image was created for each explanatory variable as well as a number of planned contrasts to examine differential activity across experimental conditions: (1) the main effect of spatial processing: (1-back complex + 2-back

complex) versus (1-back simple + 2-back simple); (2) the main effect of working memory: (2-back simple + 2-back complex) versus (1-back simple + 1-back complex); and (3) the interaction between spatial processing and working memory (2-back complex – 1-back complex) versus (2-back simple – 1-back simple). A second-level statistical analysis was then conducted across the four EPI sessions for each subject using a standard weighted fixed effects model, and with each EPI session as a higher level regressor. Finally, a third higher level group analysis was carried out on all 18 subjects' data, with a mixed effects model (taking into account fixed effects variance [within session] and random effects variance [between subjects/session]) using Bayesian modeling and estimation (for details of this approach, see Woolrich et al., 2009).

To identify regions of significant activation within the MTL, a random field-based voxel-wise intensity threshold of $p < .05$ family-wise error corrected for multiple comparisons (Worsley et al., 1995) was applied with a small volume correction (*svc*) using an anatomical mask of ROIs in the MTL. This mask was created using the Harvard–Oxford Cortical and Subcortical Structural Atlases and incorporated the hippocampus, entorhinal cortex, perirhinal cortex, and parahippocampal cortex, bilaterally. For regions beyond the MTL, a random field-based voxelwise intensity threshold of $p < .05$ family-wise error corrected for multiple comparisons at the whole brain level was used. The pattern of activity in significant regions of MTL activity was explored further post hoc by creating an ROI sphere (4 mm in diameter) centered on the voxel of maximum significance (as identified by the three planned contrasts detailed in the previous paragraph) and extracting the mean percent signal change across the four experimental conditions. These values were then submitted to a series of *a priori* defined *t* tests using standard statistical software (1) 1-back simple versus 1-back complex; (2) 2-back simple versus 2-back complex; (3) 1-back simple versus 2-back simple; and (4) 1-back complex versus 2-back complex. All coordinates (x, y, z) are reported in MNI space.

RESULTS

Behavioral Data

Figure 2 illustrates the mean values for H, FA, d_L , and C_L for the different experimental conditions. Overall task performance was very high as indicated by the high proportion of hits and very low proportion of false alarms across all tasks. Statistical analyses showed that the two 1-back conditions were matched on all behavioral measures and thus equal in difficulty. In comparison, the two 2-back conditions were generally more difficult, with significant differences between these two conditions on all behavioral indices other than hits. The statistical results for d_L and C_L are shown below (additional analyses for hits and false alarms in accompanying Supplementary material).

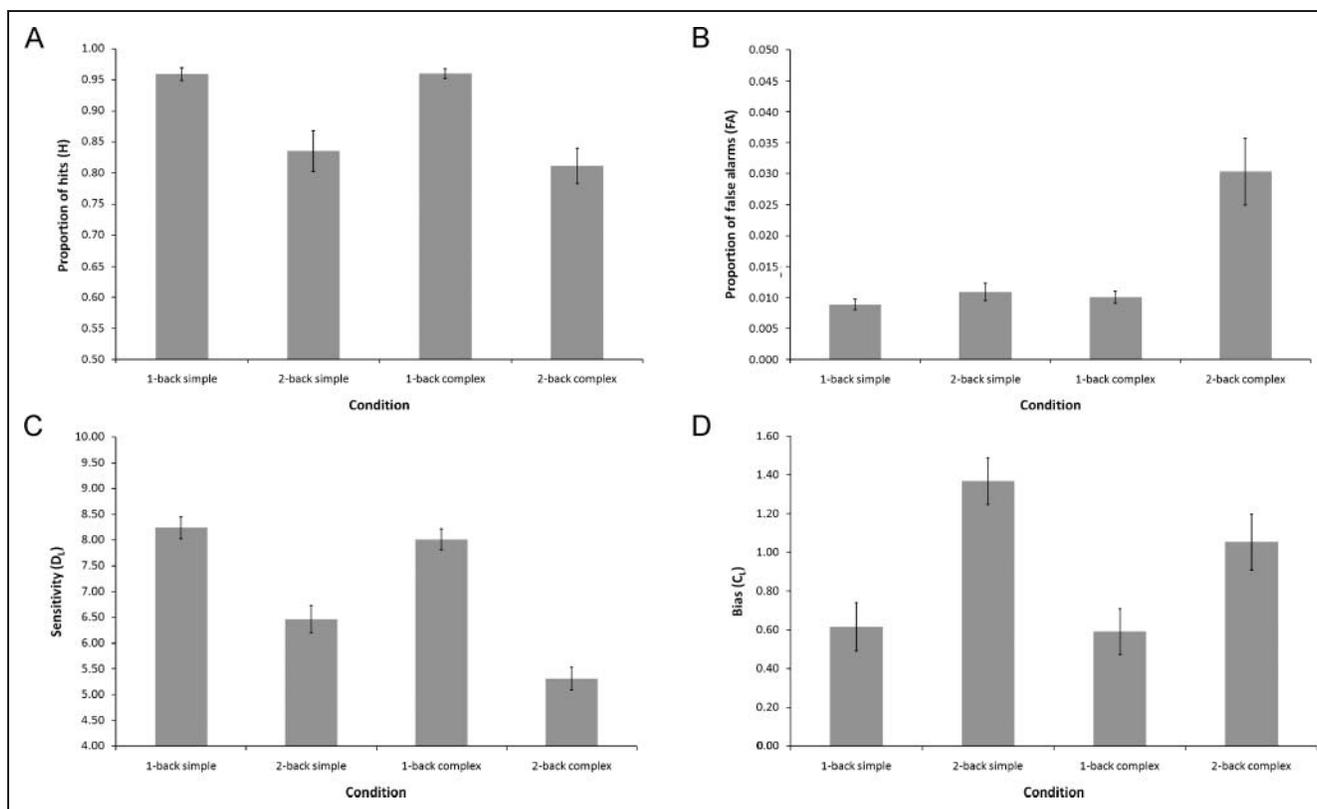


Figure 2. Mean behavioral measures across the four task conditions including (A) proportion of hits; (B) proportion of false alarms; (C) sensitivity, and (D) bias.

d_L

A repeated measures ANOVA revealed a significant main effect of working memory, $F(1, 17) = 165.11, p \leq .0001$, spatial processing, $F(1, 17) = 8.40, p \leq .0001$, as well as a significant interaction between these two factors, $F(1, 17) = 7.50, p = .01$. Paired samples t tests revealed no significant differences between the two 1-back tasks, $t(17) = 0.87, p = .4$. In contrast, the subjects demonstrated significantly greater sensitivity during the 1-back simple task versus the 2-back simple task, $t(17) = 6.58, p \leq .0001$; the 1-back complex task versus the 2-back complex task, $t(17) = 12.65, p \leq .0001$; and the 2-back simple task versus the 2-back complex task, $t(17) = 4.86, p \leq .0001$.

C_L

A repeated measures ANOVA revealed a significant main effect of working memory, $F(1, 17) = 43.96, p \leq .0001$, but not spatial processing, $F(1, 17) = 2.70, p = .1$. There was, however, a significant interaction between these two factors, $F(1, 17) = 4.37, p = .05$. In keeping with all other behavioral measures, there was no significant difference between the two 1-back tasks, $t(17) = 0.20, p = .8$. In contrast, the subjects demonstrated significantly greater bias during the 2-back simple task versus the 1-back simple task, $t(17) = 7.65, p \leq .0001$; the 2-back complex task versus the 1-back complex task, $t(17) = 3.58, p = .002$; and

the 2-back complex task versus the 2-back simple task, $t(17) = 2.60, p = .02$.

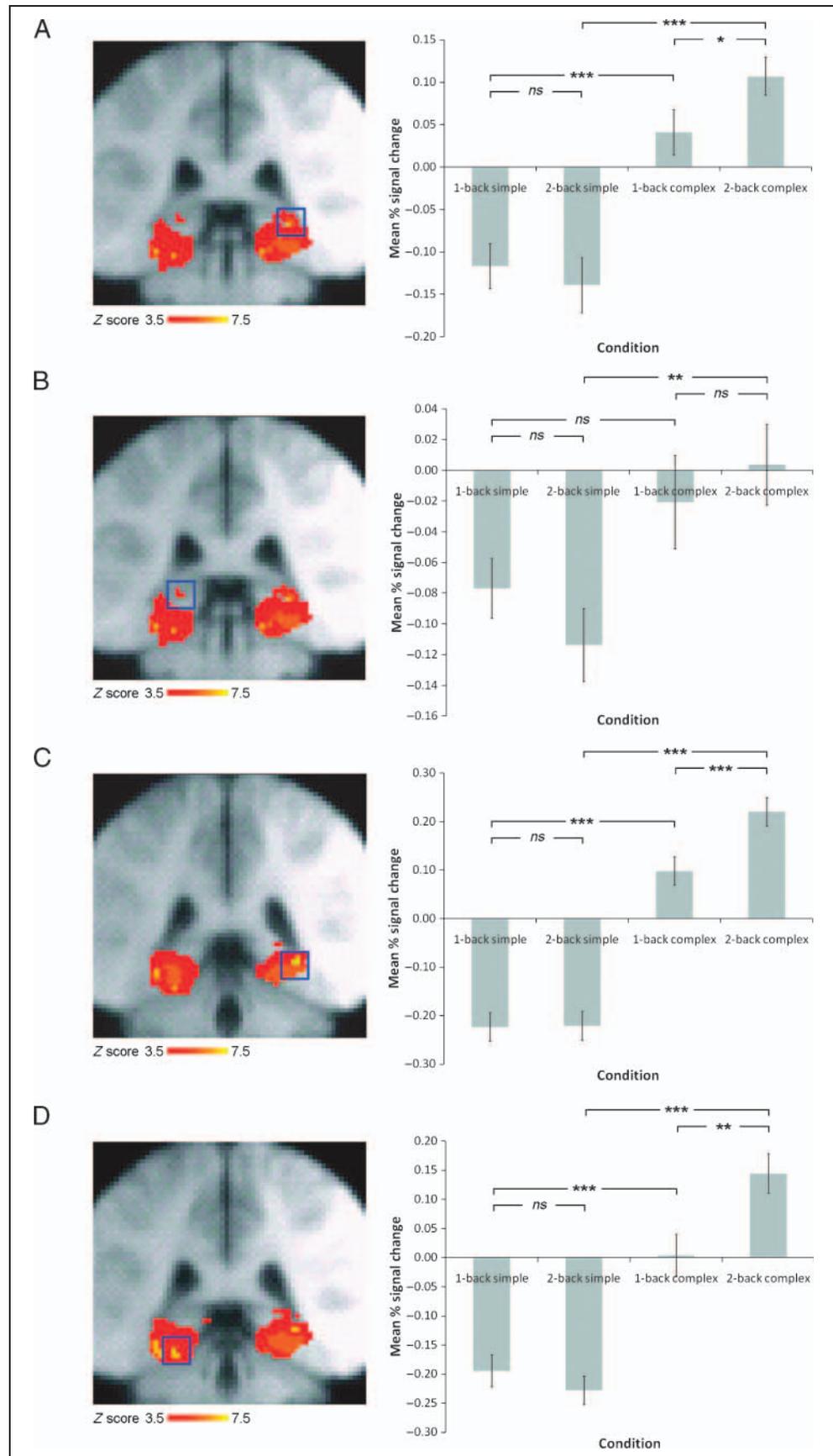
Neuroimaging Data

Because this study is focused on the MTL, only significant findings from this region will be discussed in depth below. Regions of significant activity beyond the MTL are listed in Supplementary Tables 1–3.

Effect of Spatial Processing

In comparison with the simple spatial tasks ($p < .05$ corrected MTL *svc*), the two complex spatial conditions were associated with significantly greater activity predominantly in the posterior MTL, in particular the posterior hippocampus bilaterally (right: 28, $-38, -6, Z = 6.40$; left: $-22, -38, -4, Z = 4.69$; Figure 3A and B), the parahippocampal cortex bilaterally (right: 30, $-42, -8, Z = 7.56$; 26, $-30, -20, Z = 5.51$; left: $-24, -40, -18, Z = 6.82$; $-34, -36, -18, Z = 5.18$; Figure 3C and D), and also a more anterior region in the left hippocampus ($-34, -22, -16, Z = 4.76$). In contrast, the simple spatial tasks were not associated with any significant regions of MTL activity in comparison to the complex conditions, even when a liberal significance threshold was applied ($p < .05$ uncorrected for multiple comparisons).

Figure 3. Significant increase in activity associated with an increase in spatial processing demands in (A) right hippocampus (28, -38, -6); (B) left hippocampus (-22, -38, -4); (C) right parahippocampal cortex (30, -42, -8); and (D) left parahippocampal cortex (-24, -40, -18). A significant interaction effect was observed in the right hippocampus and bilateral parahippocampal cortex. Activity rendered on the MNI152 template at $p < .05$ corrected (MTL *svc*), with the ROIs highlighted by a blue square. When a more stringent threshold of $p < .05$ (whole brain corrected) was applied, the activity in the right hippocampus and parahippocampal cortex was observed as two distinct clusters (see Supplementary material). *ns* = not significant; * $p < .05$; ** $p < .001$; *** $p < .0001$.



Examining the mean percent signal change from the significant clusters associated with the complex spatial conditions (see Methods) revealed identical patterns of activity in the right posterior hippocampus and parahippocampal cortex bilaterally. Activity in these three regions was significantly greater in the 2-back complex spatial task compared with the 2-back simple task, all $t(17) > 5.0$, $p < .0001$, and likewise in the 1-back complex spatial task compared with the 1-back simple task, all $t(17) > 4.6$, $p < .0001$, reflecting a main effect of spatial processing. Critically, however, examining the effect of an increase in working memory demand in these areas revealed a significant interaction effect: there was a significant difference between the 1-back and the 2-back complex spatial tasks, all $t(17) > 2.9$, $p < .01$, with a higher level of activity in the latter, but not between the 1-back and the 2-back simple spatial tasks, all $t(17) < 1.3$, $p > .2$. To confirm this, almost identical right posterior hippocampus and bilateral parahippocampal cortex clusters were identified in the planned comparison examining the interaction between the two factors of interest (see Interaction between Spatial Processing and Working Memory section).

Extracting mean percent signal change in the left posterior hippocampus cluster revealed a slightly different pattern of activity. Activity associated with the two-back complex task was significantly greater than that during the 2-back simple task, $t(17) = 3.26$, $p = .005$. There were, however, no significant differences in any of the other *a priori* comparisons (all $t < 1.8$, $p > .08$), although there was a trend toward activity in the 1-back complex task being significantly greater than that in the 1-back simple task, $t(17) = 1.80$, $p = .09$, supporting a main effect of spatial processing demand in this region.

Planned ROI comparisons in the more anterior left hippocampal cluster revealed that this region was not associated with an increase in spatial processing demand. Although there was greater activity here during the 2-back complex spatial task versus the 2-back simple spatial task, $t(17) = 3.25$, $p = .005$, there was no significant difference between the 1-back complex and the 1-back simple tasks, $t(17) = 1.24$, $p = .2$. Moreover, although there was greater activity during the 1-back simple spatial task compared with the 2-back simple spatial condition, $t(17) = 3.03$, $p = .008$, there was no significant difference in activity in this region between the two complex spatial conditions, $t(17) = 0.40$, $p = .7$. Thus, it appears that the significant main effect in this left hippocampal region was driven by the fact that the 2-back simple spatial condition was associated with little signal change.

Effect of Working Memory

In comparison with the 1-back tasks ($p < .05$ corrected MTL *svc*), the two 2-back conditions were associated with a single region of significant signal change in the right parahippocampal cortex (28, -42, -14, $Z = 3.71$). This cluster of activity was highly similar to that observed for a main

effect of spatial processing and, as evident from the pattern of activity here (Figure 3C), was driven by the significant change in activity between the two complex spatial conditions and not between the two simple tasks. When the data were explored further with a more liberal significance threshold ($p < .05$ uncorrected), a similar region of activity was observed in the left hemisphere (-28, -42, -22, $Z = 3.65$), again reflecting the increase in activity in the left parahippocampal cortex when working memory was increased in the complex spatial tasks but not the simple conditions (Figure 3D). Indeed, as highlighted earlier, these two parahippocampal cortex clusters were identified in the planned interaction analysis (see Interaction between Spatial Processing and Working Memory section).

Surprisingly, the two 1-back tasks were associated with greater MTL activity, predominantly in the anterior portion. Significantly greater activity was observed in the hippocampus bilaterally (right: 30, -8, -26, $Z = 5.64$; 24, -18, -12, $Z = 6.05$; left: -20, -4, -28, $Z = 5.65$; -28, -12, -24, $Z = 4.95$) and the right posterior entorhinal cortex (right: 18, -14, -30, $Z = 5.05$). Extracting the mean signal change in the right anterior hippocampus cluster (Figure 4A) revealed no significant difference in activity between the two 1-back tasks, $t(17) = 0.60$, $p = .6$, or between the two complex spatial conditions, $t(17) = 1.76$, $p = .1$. There was, however, significantly greater activity in the 1-back simple spatial task compared with the 2-back simple spatial task, $t(17) = 6.06$, $p \leq .0001$, as well as greater activity in the 2-back complex spatial task versus the 2-back simple spatial condition, $t(17) = 2.40$, $p = .03$. In contrast, ROI analyses in the left anterior hippocampus cluster (Figure 4B) revealed no significant differences between the two 1-back tasks, $t(17) = 1.93$, $p = .07$, or between the two 2-back tasks, $t(17) = 0.18$, $p = .9$, but significantly greater activity in each 1-back task compared with its 2-back equivalent, both $t(17) > 4.1$, $p < .001$. In the right entorhinal cortex (Figure 4C), there was a significant difference between the two simple spatial conditions, with greater activity in the 1-back version, $t(17) = 4.79$, $p \leq .0001$, but not between the two 1-back tasks, the two complex spatial conditions, or the two 2-back tasks, all $t(17) < 1.9$, $p > .07$.

Interaction between Spatial Processing and Working Memory

To investigate the interaction between working memory load and spatial processing demands, the contrast (2-back complex minus 1-back complex) minus (2-back simple minus 1-back simple) was conducted. This revealed significant clusters in the right (26, -42, -14, $Z = 5.23$; 28, -32, -20, $Z = 4.96$) and left parahippocampal cortex (-22, -46, -12, $Z = 4.73$), almost identical to that observed during increased spatial processing (see Effect of Spatial Processing section) and increased working memory (see Effect of Working Memory section). As evident from the pattern of activity in these two regions (Figure 3C and D),

Figure 4. Significant increase in activity associated with a decrease in working memory demands in (A) right hippocampus (24, -18, -12); (B) left hippocampus (-20, -4, -28); and (C) right entorhinal cortex (18, -14, -30). Activity rendered on the MNI152 template at $p < .05$ corrected (MTL *svc*), with the ROIs highlighted by a blue square. *ns* = not significant; $*p < .05$; $**p < .001$; $***p < .0001$.

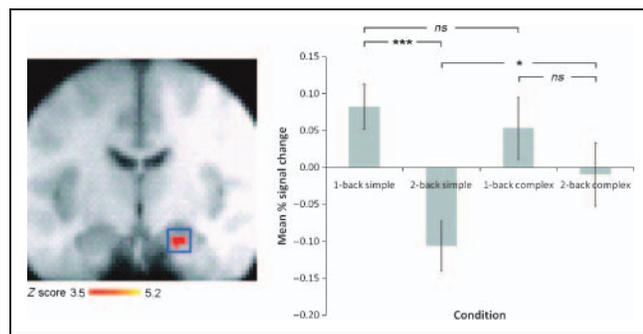
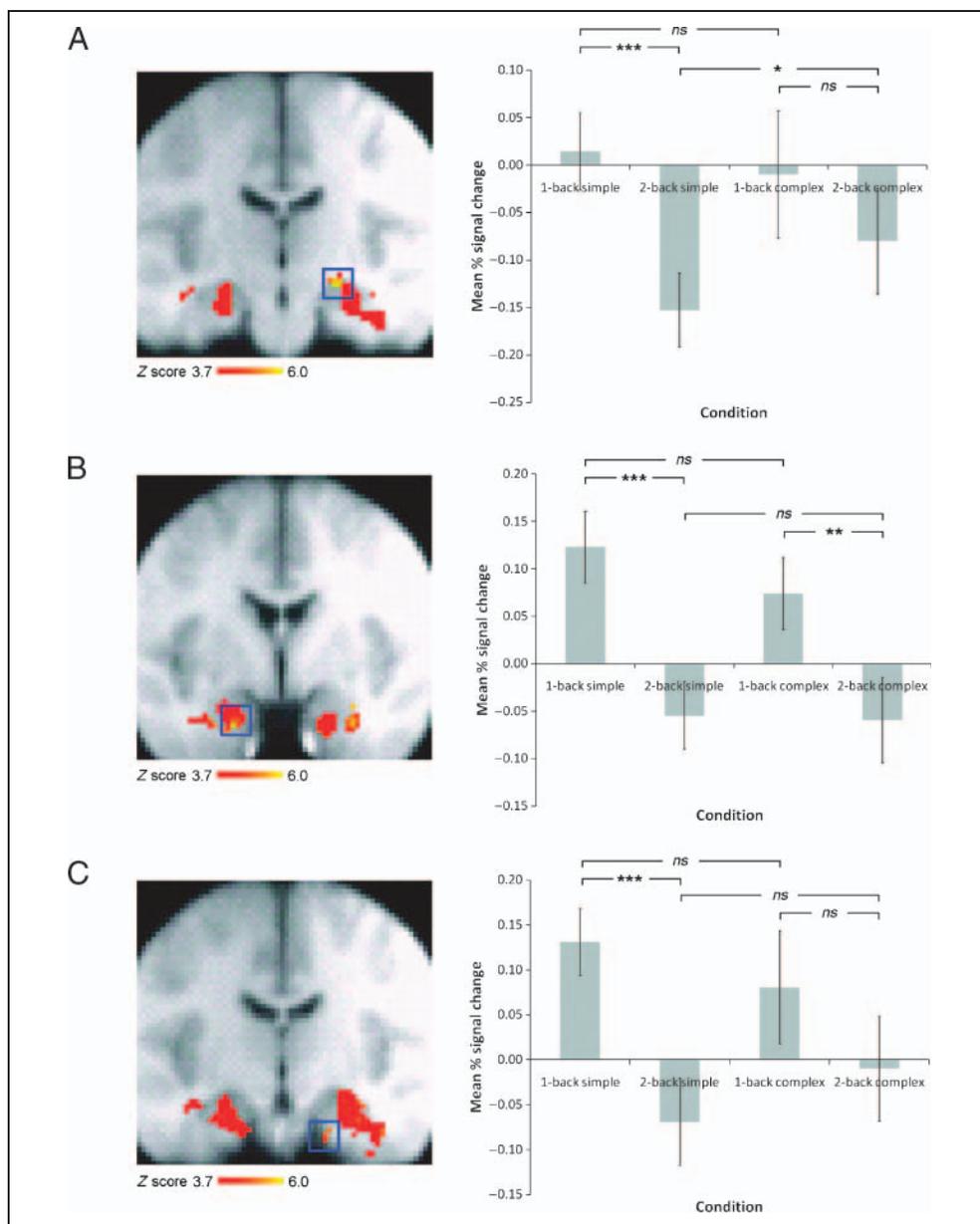


Figure 5. Significant interaction effect in the right hippocampus (20, -12, -22). Activity rendered on the MNI152 template at $p < .05$ corrected (MTL *svc*), with the ROI highlighted by a blue square. *ns* = not significant; $*p < .05$; $**p < .001$; $***p < .0001$.

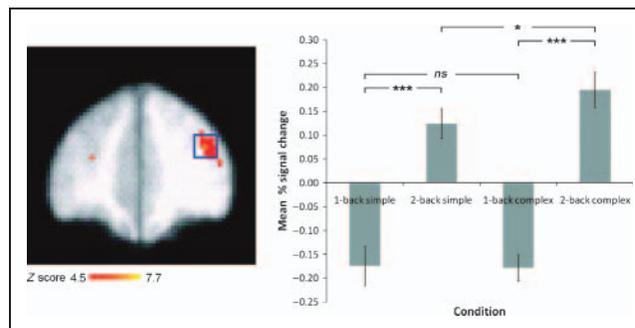


Figure 6. Significant increase in activity in the right lateral pFC (36, 46, 22) associated with an increase in working memory demand. Activity rendered on the MNI152 template at $p < .05$ (whole brain corrected), with the ROI highlighted by a blue square. *ns* = not significant; $*p < .05$; $**p < .001$; $***p < .0001$.

the interaction here was due to a significant increase in activity between the 2-back and the 1-back complex spatial tasks, but not between the two simple spatial tasks.

A significant region of signal change was also observed in the right anterior hippocampus (20, -12, -22, $Z = 3.84$; Figure 5). The pattern of activity here was similar to that observed in the right anterior hippocampus associated with a decrease in working memory demand (see Effect of Working Memory section). There was no significant difference between the two 1-back tasks, $t(17) = 1.07$, $p = .3$, during which activity was greatest or between the two complex spatial tasks, $t(17) = 1.78$, $p = .09$. There was, however, significantly greater activity during the 1-back simple spatial task compared with the 2-back simple spatial task, $t(17) = 6.12$, $p \leq .0001$, as well as greater activity during the 2-back complex spatial task versus the 2-back simple spatial task, $t(17) = 3.01$, $p = .008$.

Finally, using a more liberal threshold of significance ($p < .05$ uncorrected) to explore the data further revealed activity in the right posterior hippocampus (30, -38, -8, $Z = 3.37$), similar to that observed for a main effect of spatial processing. The presence of this cluster of activity, which was just below the corrected significance threshold adopted in this study, is not surprising given that an increase in working memory demand during complex, but not simple, spatial processing was found to increase activity in this region (see Effect of Spatial Processing section; Figure 3A).

The reverse contrast of (2-back simple minus 1-back simple) minus (2-back complex minus 1-back complex) did not yield any significant regions of signal change in the MTL, even at a liberal significance threshold ($p < .05$ uncorrected for multiple comparisons).

DISCUSSION

This study is, to our knowledge, the first to use functional neuroimaging to investigate MTL involvement beyond the long-term memory domain by focusing on working memory and spatial perception and how these two processes may interact. Using a factorial design to manipulate working memory and spatial processing demands, significant bilateral posterior hippocampus and parahippocampal cortex activity was observed in association with increased spatial processing demand, irrespective of working memory load. Importantly, there was an interaction effect in the right posterior hippocampus and parahippocampal cortex bilaterally, with increasing working memory demand associated with greater activity in these areas for the complex but not simple spatial conditions. No significant regions of MTL activity were found in association with an increase in working memory demand across both simple and complex spatial conditions, although there was greater bilateral anterior hippocampus and right entorhinal cortex activity associated with a lower working memory demand.

Despite behavioral piloting, performance levels during scanning were not matched across all experimental conditions. It is unlikely, however, that all the observed changes in activity were due to differences in task difficulty. There was no significant difference in performance between the two 1-back tasks, although right posterior hippocampus and bilateral parahippocampal cortex were differentially activated across these two conditions. Moreover, no significant increases in MTL activity were observed following an increase in difficulty due to a greater working memory demand.

To minimize and match mnemonic demands between the simple and the complex spatial tasks, images were not repeated across task blocks, and the number of stimulus repetitions within each block was equal across conditions. Furthermore, unfamiliar stimuli were used to reduce contextual processing (Bar & Aminoff, 2003). It is possible, however, that differing levels of incidental encoding may account for the observed MTL findings. To investigate this, a behavioral study was conducted (see Supplementary material) in which participants performed a modified version of the fMRI paradigm followed by a surprise “yes/no” recognition test. Recognition was low across all task conditions, indicating limited incidental encoding. Importantly, items from the two complex tasks and the 2-back simple condition were remembered similarly, with significantly greater subsequent recognition for each of these conditions compared with the 1-back simple task. This profile of recognition does not match the fMRI findings and indicates that the increased posterior hippocampal and parahippocampal cortex activity during the complex spatial conditions cannot be explained entirely by differences in incidental encoding between the complex and the simple spatial images. Instead, we suggest that these increases in activity reflect differences in spatial processing between the two types of stimuli.

The decision to manipulate spatial processing demands by asking participants to track the locations of three features within a virtual reality room or spatial array was based on work that has investigated the role of the MTL in various spatial tasks. Patients with MTL damage are typically not impaired at simultaneous object-in-place discriminations or the encoding and retrieval of spatial locations within a two-dimensional egocentric spatial array after very short delays of a few seconds (van Asselen et al., 2006; Milner et al., 1997). Moreover, neuroimaging studies have not consistently observed MTL activity during the discrimination and short-term maintenance of two-dimensional locations alone (Bor, Duncan, Lee, Parr, & Owen, 2006; Lee, Bandelow, Schwarzbauer, Henson, & Graham, 2006). In contrast, tasks using real-world-like stimuli have repeatedly implicated a role for the hippocampus and parahippocampal cortex, whether in the context of simultaneous discrimination, passive viewing, working memory, or long-term memory processing (Hannula & Ranganath, 2008; Lee et al., 2008; Lee, Buckley, et al., 2005; Burgess, Maguire, Spiers, & O’Keefe, 2001; Aguirre & D’Esposito, 1999; Epstein &

Kanwisher, 1998; Maguire et al., 1997). There are obvious differences between the two types of spatial stimuli used here, most notably that the virtual reality rooms were three-dimensional, whereas the spatial arrays only possessed two dimensions. The parahippocampal cortex has been shown to be sensitive to three-dimensional geometric structure (Henderson, Larson, & Zhu, 2008), and this property may (although not necessarily) emphasize other spatial processes such as allocentric spatial processing, which the hippocampus is critical for (Burgess, 2008; although see Shrager, Bayley, Bontempi, Hopkins, & Squire, 2007). A systematic study manipulating viewpoint processing (allocentric vs. egocentric) and dimensionality of spatial stimuli (two-dimensional vs. three-dimensional) in the context of an n -back task would provide direct insight into the processes underlying the increased involvement of the parahippocampal cortex and hippocampus during the complex spatial conditions used here.

Our understanding of a role for the posterior hippocampus and parahippocampal cortex in “spatial perception” is not dissimilar to the notion that these structures are involved in the formation and long-term encoding of spatial representations as suggested by others (Epstein, 2008; O’Keefe & Nadel, 1978). Indeed, the observed parahippocampal cortex activity is comparable in location to the parahippocampal place area (Epstein & Kanwisher, 1998), a region implicated in representing scenes. Because similar activity profiles were observed here for the right posterior hippocampus and bilateral parahippocampal cortex (but not left posterior hippocampus), the current data do not elucidate the differential contributions of these two regions to scene processing. Nevertheless, the presence of an interaction effect in both regions (increasing working memory demand associated with an increase in activity during the complex but not simple spatial conditions) supports the idea that complex spatial representations formed in these areas may form the basis for mnemonic processing in short-term memory as demonstrated here, long-term declarative memory (Bird, Vargha-Khadem, & Burgess, 2008; Taylor, Henson, & Graham, 2007), and even nondeclarative memory (Graham et al., 2006). This idea is not highly dissimilar to the recent proposal that working memory may be an emergent property of functions pertaining to sensation, action, or stimulus representation (Postle, 2006). Critically, however, our suggestion extends this account to the domains of long-term and nondeclarative memory and argues specifically that different forms of memory for complex spatial stimuli may be, at least in part, an emergent property of the complex spatial representations that are processed by the posterior MTL.

Previous work has demonstrated that an increase in working memory load is associated with greater MTL activity (Schon et al., 2009; Axmacher et al., 2007; Stern et al., 2001). To an extent, our data are consistent with this given the increased posterior MTL activity during the 2-back complex spatial condition compared with the 1-back com-

plex task. Where our findings differ is that this increase in posterior MTL activity was not observed when two-dimensional spatial arrays were presented, suggesting that greater working memory demand does not necessarily increase MTL involvement; hence, the MTL does not play a general role in working memory. Earlier research has implicated stimulus novelty (Ranganath & D’Esposito, 2001; Stern et al., 2001) as a critical factor in determining MTL involvement during working memory tasks, although the use of novel stimuli in both simple and complex spatial conditions here rules out this explanation. Our explanation for the inconsistent increase in MTL activity following greater working memory demand pertains to the different types of spatial stimuli used and the greater degree of spatial processing required by the complex spatial images. This contrasts to regions beyond the MTL, which are known to play a more general role in working memory. For example, we observed an increase in lateral pFC activity when working memory demand was increased, irrespective of stimulus type (Figure 6).

It is important to note that our study examined the role of the MTL in working memory and perception by focusing on the spatial domain and does not directly address the issue of stimulus specialization within the MTL. We observed predominant posterior MTL activity in association with an increase in spatial processing demand, which although supports a greater involvement of the posterior, compared with anterior, hippocampus in processing spatial stimuli (Furtak, Wei, Agster, & Burwell, 2007; Pihlajamäki et al., 2004; Maguire et al., 2003; Colombo, Fernandez, Nakamura, & Gross, 1998; Moser, Moser, & Andersen, 1993) does not rule out a role for this region in processing other stimuli.

Beyond the posterior MTL, we found that lower working memory demand resulted in greater anterior MTL activity. The observation of decreased MTL activity during highly demanding cognitive tasks (and vice versa) is not new (Vincent et al., 2006; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Stark & Squire, 2001) and may reflect changes in incidental mnemonic processing. To undermine this explanation here, greater posterior MTL activity was observed when working memory demand was increased for the complex spatial stimuli. Furthermore, our supplemental behavioral findings indicate that greater incidental encoding is likely to have occurred during the 2-back tasks than the 1-back simple condition during which anterior MTL activity was greatest. One interesting possibility is that because participants were required to detect successive image repetitions that were not separated by an intervening stimulus in the 1-back task, the increase in MTL activity during this condition may reflect an attentional shift in focus toward novelty detection. This explanation, however, cannot explain a previous report of increased MTL activity following reduced working memory demand in the same context of an n -back paradigm (Meyer-Lindenberg et al., 2001). In this study, participants were presented with the same four digits on

each trial (1–4) and performed a 0-back task (in which they selected a digit highlighted in red) or a 2-back task (in which they selected the digit highlighted in red two trials previously), with greater MTL activity in the former. Thus, the basis of our observed increase in MTL activity in association with reduced WM demand is not entirely clear and necessitates further investigation.

One prominent theory of MTL function suggests that the hippocampus is critical for the processing of flexible, relational memories regardless of stimulus type (Eichenbaum, Otto, & Cohen, 1994). It has been suggested that relational memories contribute to not only long-term memory but also working memory and even perceptual decisions (Hannula, Tranel, & Cohen, 2006; Ryan & Cohen, 2004a, 2004b). One key difference, however, between this suggestion and a perceptual view of the MTL (Murray et al., 2007) is that the former does not propose a role for the MTL in higher order perception (i.e., the processing and formation of perceptual representations) and argues that any reported perceptual deficits following MTL damage (Barens et al., 2007; Lee, Buckley, et al., 2005; Lee, Bussey, et al., 2005) may be explained by a primary impairment in relational memory. Although it is impossible to rule out entirely, there are a number of reasons why we believe relational memory theory cannot provide a full explanation for the present findings. First, as demonstrated by our supplemental behavioral study, the observed patterns of MTL activity cannot be accounted for by memory encoding processes (for similar findings in the perirhinal cortex, see also O’Neil et al., 2009; Devlin & Price, 2007). Second, novel stimuli were used for both the complex and the simple stimuli such that neither were likely to trigger substantial incidental retrieval of personal relational memories (although virtual reality rooms were used for the complex stimuli they were specifically designed to be dissimilar to scenes that one would encounter in the real world and did not contain any real-world objects). Third, relational memory theory would predict an increase in MTL activity following increased working memory demand irrespective of the type of spatial stimuli: compared with the 1-back version, the 2-back paradigm required double the number of items (and the relationships between them) to be processed for both the simple and the complex spatial stimuli and yet increased posterior hippocampal activity was only observed for the complex stimuli. Needless to say, opinion remains divided as to whether the MTL subserves perception or its functions are restricted to the mnemonic domain (Baxter, 2009; Suzuki, 2009). Here, we are arguing for the former, although considerably more research is necessary to understand precisely how the MTL may contribute to perception and the undoubtedly complex relationship between perceptual and mnemonic processes.

In conclusion, this study demonstrates that both perception and working memory are highly interactive and can influence MTL activity. Although we found that an increase in spatial processing recruits posterior MTL struc-

tures, an increase in WM demand does not necessarily do so, underlying the importance of the former to posterior MTL involvement. These structures may play a role in processing representations of complex spatial scenes, which may underlie working memory and long-term memory processes.

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