Negative BOLD response in the hippocampus during short-term spatial memory retrieval

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Abstract

A parieto-medial temporal pathway is thought to underlie spatial navigation in man. Functional magnetic resonance imaging was used to assess the role of this pathway, including the hippocampus, in the cognitive processes likely to underlie navigation based on environmental cues. Participants completed a short-term spatial memory task in virtual space, which required no navigation but involved the recognition of a target location from a foil location based on environmental landmarks. The results showed that spatial memory retrieval based on environmental landmarks was indeed associated with increased signal in regions of the parieto-medial temporal pathway, including the superior parietal cortex, the retrosplenial cortex and the lingual gyrus. However, the hippocampus demonstrated a signal decrease below the fixation baseline during landmark-based retrieval, whilst there was no signal change from baseline during retrieval based on viewer position. In a discussion of the origins of such negative blood-oxygen-level-dependent response in the hippocampus, we consider both a suppression of default activity and an increase in activity without a corresponding boost in cerebral blood flow as possible mechanisms.

Introduction

Efficient navigation requires a continuous coordination between the external environment as it is currently viewed and the internal representation of the same environment. Similarly, navigating from a new starting point or remembering a location following a viewpoint-shift requires coordination between the environment as seen from the current viewpoint and the internal representation of the space acquired previously. During virtual navigation, a dorsal neural pathway, which extends medially from the posterior parietal lobe to the medial temporal lobe via the retrosplenial cortex, is consistently shown to be active (Hartley et al., 2003; Maguire et al., 1998; Gron et al., 2000). A similar pathway has been implicated when participants are simply required to make a reference to an environmental landmark, either in order to make a distance judgement or to retrieve a remembered target location (Committeri et al., 2004; Galati et al., 2010; Schmidt et al., 2007), supporting a role for this pathway in the absence of actual navigation. Although the hippocampus is widely accepted to represent space in a world centred manner and thought to represent the ultimate endpoint of the navigation pathway (O'Keefe & Nadel, 1978; Burgess, 2008), its role in landmark-based retrieval of object locations has received mixed support in healthy individuals. The present study therefore aimed to investigate the role of the hippocampus, as part of the parieto-medial temporal pathway, in spatial memory retrieval based on environmental landmarks when no navigation is required.

There is little doubt that the hippocampus is important for spatial memory in humans. The discovery of place cells in the rodent and human hippocampus and demonstrations of severe spatial memory and learning deficits following hippocampal lesions in both species represents a fraction of the evidence supporting this conclusion

(O'Keefe & Nadel, 1978; Ekstrom et al., 2003; Morris, 1982; Bohbot et al., 1998; Maguire et al., 1996; Smith & Milner, 1981). Consistent with the idea that the hippocampus contributes to spatial memory by providing representations anchored in the external world, patients with hippocampal damage show a disproportionate impairment when a sudden shift to a different viewpoint forces the use of environmental landmarks to remember locations or spatial topographies (Abrahams et al., 1997; Holdstock, et al., 2000; King et al., 2002; Lee et al., 2005; Hartley et al., 2003). The rationale behind such paradigms relies on the assumption that a shift in viewpoint makes the viewer position unreliable as a cue to location, which in turn encourages the use of stable landmarks in the surrounding environment to remember locations. However, it has been shown that behavioural impairment following hippocampal damage tends to be detectable only at longer delays (Holdstock et al., 2000), greater memory loads (King et al., 2002; Abrahams et al., 1997; Axmacher et al., 2007) and higher environmental complexity (Hartley et al., 2003; Lee et al., 2005). Although this suggests that an otherwise intact parieto-medial temporal pathway is sufficient at lower task demands and that the hippocampus is only critical when task demands are high, we cannot rule out that the hippocampus of healthy individuals is involved whenever landmark-based memory is required.

Evidence derived from neuroimaging in healthy individuals has provided mixed support for such a landmark-based retrieval function of the hippocampus. In a visually rich room, Lambrey and colleagues (2012) asked participants to imagine movement of their own viewpoint around an array of four objects laid out on a table or a rotation of the table itself, after which memory for the object locations was tested in a change-detection

task. Only in the viewpoint rotation condition were the spatial relations between the array and the environmental features in the room undisrupted, although the predictable imagined rotation may have allowed for the use of viewer position as an additional cue. When the viewer rotation condition was contrasted with the array rotation condition at retrieval, activation was found in the left hippocampus, in addition to other regions in the parieto-medial temporal pathway, including the retrosplenial cortex and the parahippocampal gyrus. Antonova et al. (2009) similarly encouraged the use of the cues provided by abstract patterns on the walls of a circular virtual arena by asking participants to navigate to a single remembered target location from novel start positions. When contrasted with rest, small clusters of differential activation were demonstrated in the right hippocampus of young individuals, but not in old individuals. In an earlier study using the same task, however, no evidence for hippocampal activation could be demonstrated at retrieval (Parslow et al., 2004). Schmidt and colleagues (2007) also used a viewpoint-shift to encourage the use of landmarks in a virtual roof garden to solve a location change-detection task of a single object. Although several of the regions in the parieto-medial temporal pathway were implicated when such landmark-based memory retrieval was compared to a high-level control condition, no differential activation could be demonstrated in the hippocampus. Similarly, in a task without a memory component, Committeri and colleagues (2004) asked participants to make viewer-, object- and landmark-centred distance judgments in a virtual square arena in front of a building. Whilst the typical regions of the parieto-medial temporal pathway were active during the landmark-centred condition, including ventromedial occipito-temporal regions and the retrosplenial cortex, no differential activation was demonstrated in the hippocampus

proper. In summary, despite great variability in task requirements, support for the role of the parieto-medial temporal pathway in landmark-based referencing is surprisingly consistent, whilst the same cannot be said for the hippocampus. This indicates a general involvement of the parieto-medial temporal pathway in any attempt to reference a landmark whilst the role of the hippocampus appears more restricted.

Recent evidence derived from navigation-based spatial memory tasks has indicated that the hippocampus may be particularly important for the retrieval of environment-centred spatial representations that subsequently allow for goal-directed navigation. In a virtual Morris Water Maze, Shipman and Astur (2008) found evidence of hippocampal involvement only in the initial phase of navigation. Similarly, using a familiar large-scale virtual office environment, Xu et al. (2010) showed that the anterior hippocampus was more active during the initial phase of wayfinding. Furthermore, by linking the brain activity associated with virtual wayfinding with post-scan verbal accounts of the thought processes accompanying such wayfinding, Spiers and Maguire (2006) showed that the engagement of the hippocampus was brief and that it only occurred during planning of a route to a new destination and not during route execution. It can therefore be proposed that the implication of the hippocampus in navigation is a reflection of its role in environment-centred memory retrieval and not in navigational movement *per se*. Consequently, a task that encourages the use of an environment-centred memory representation should be associated with hippocampal recruitment, independent of navigational demands. As mentioned previously, whilst investigations of patients with hippocampal damage have provided general support for this prediction using viewpoint-shift tasks (e.g. King et al., 2002; Hartley, et al., 2003), neuroimaging

investigations in healthy volunteers have yet to reach a similar consensus (e.g. Schmidt et al., 2007; Antonova et al, 2009). The present study therefore aimed to further investigate the role of the hippocampus in non-navigational environment-centred spatial memory retrieval in a neuroimaging context.

The present study employed an encoding and recall paradigm where participants had to encode the location of a target within a circular arena in relation to landmarks provided on the walls of the arena. Following a delay period, they had to distinguish the target location from a foil location from a new viewpoint. This required participants to refer to the positions of the landmarks to identify the target location. In addition to this environment-centred condition (hereafter EC) the task employed two control conditions. In the viewer-centred condition (VC) the participants were instructed to imagine that the walls of the circular arena have moved, but that their own viewpoint and therefore the position of the target relative to themselves had not changed. The inclusion of this condition was crucial, as any processing of spatial information necessarily involves at least some form of body-centred spatial representation (e.g. location of the target stimulus and landmarks on the retina). Thus, the EC and the VC conditions were highly similar and should only differ in the need to rely on environmental landmarks to localize the target in the recall phase. While the environmental landmarks were crucial for retrieving the spatial representation in the EC condition, these same environmental landmarks were completely non-informative as spatial references in the VC condition. Previous studies have been inconsistent in this regard with some studies comparing tightly controlled conditions (e.g. Lambrey et al., 2012), whereas other studies compared conditions that differed in multiple aspects from one another. In the present study, participants were only

informed about whether the viewpoint *or* the walls had moved at the time of the delay, which ensured identical encoding processes in the two conditions. Consequently, any differential effects between the EC and the VC conditions in the recall phase should not be due to differences in preceding encoding strategies.

The second control condition in the present study was also highly similar to both the EC and VC conditions in terms of visual and motor processing, but differed from these two in that it did not require the encoding or retrieval of a target location, and will be referred to as the no-memory (NM) condition. Instead of memorizing a target location in the virtual arena, participants saw the empty arena during the presentation phase, and made a response selection based on a visual cue during the response phase (see below).

If the hippocampus is instrumental in providing a mental representation of a location relative to environmental landmarks, independently of navigational demands, subtracting any activation related to representations relative to the own body alone (VC condition) from activation related to environmental landmarks and the own body (EC condition) should maximize the specificity of the contrast in the present study. Since the EC condition was expected to involve translations between body-centred and environmental reference systems as well, it was hypothesized to also recruit the retrosplenial cortex to coordinate this translation. Contrasting the EC and VC conditions with the NM condition was expected to show activations related to both the encoding and the retrieval of spatial locations in large parts of the parieto-medial temporal pathway.

Materials and methods

Participants

Twenty young adults (10 female, 19-33 years, mean = 26.1 years) with no history of psychiatric or neurological illness were recruited. All participants were right-handed, as ascertained with the Edinburgh Handedness Inventory. The study was approved by the ethics committee at the Faculty of Medical Sciences at Newcastle University. Participants provided written informed consent prior to the study

Experimental task

The Northumberland Gallery Task (NGT) was developed to encourage encoding and retrieval of spatial locations in relation to environmental landmarks or the viewer. This task was developed over a series of experiments to ensure behavioural separation between conditions with above chance performance in all cases (Nilsson, 2010). A virtual circular arena, as viewed from the top of the boundary wall, with seven paintings (animal stimuli from Rossion and Pourtois, 2004) rendered at equidistance on the wall provided the context for the task. All trials exhibited the same temporal structure (Figure 1): a 250ms presentation of the virtual empty area followed by the presentation phase for 3000ms, during which the to-be-remembered location is marked with a pole somewhere inside the arena. This is followed by a delay phase (4750ms), another 250ms display of the empty arena and a response phase of 3500ms, in which the target location and a foil location are shown as two coloured markers on the floor of the arena. A full trial period therefore lasted exactly 11.75 seconds. Each trial was triggered by a scanner pulse. Thus, individual trials were separated by a short fixation cross of 1250ms duration (total trial-onset asynchrony of 13s=5*TR), or a longer baseline fixation period of 9050ms (total trial-onset asynchrony of 20.8s=8*TR; see below).

There were two conditions, which differed only in terms of the manipulation that occurred during the delay, out of view. The otherwise unfilled delay consisted of a scrambled image of the environment with a one-word instruction in the upper half of the screen, informing participants of the relevant manipulation for that particular trial. The instruction “You” indicated a manipulation of the viewer position along the top of the wall thereby encouraging the use of landmarks to locate the target (EC condition). The instruction “Walls” indicated the manipulation of landmark positions by a rotation of the walls, without any movement of the arena floor or of the observer position (VC condition). In the response phase, participants were required to distinguish the target location from the foil location, as quickly and as accurately as possible by identifying its colour and pressing the appropriate response button. To ensure identical task length for all participants, the scene of the response phase remained on the screen for the full 3.5 seconds independently of whether a response had been recorded within that time. In the NM condition no target location appeared during the presentation phase. The instruction “none” was shown during its delay phase, and in the response phase a pole was presented on top of one of the usual response options and participants were simply required to respond in accordance to the colour of that particular option. This NM condition was therefore identical in terms of the visual scene and the motor response required but involved no memory for location.

Each trial started from one of four start positions and manipulations in the experimental conditions occurred in clockwise and anticlockwise rotations at magnitudes of 45°, 90° and 135°. There were a total of 108 trials with 36 trials in each condition and 12 trials for each manipulation magnitude. In addition, there were 36 of the above

mentioned long fixation periods. The trial order was unique for each participant according to the following randomization scheme: Groups of three trials, one from each condition, along with a single long baseline period where first randomized internally and then strung together for the full experiment. Orders which put two long baseline periods next to each other were removed. These pseudorandom orders of trial types were then randomly filled with actual trial parameters (rotation angles/directions, target/foil locations). This procedure ensured that the conditions were equally distributed across time, and that each condition was approximately equally likely to be followed by any of the other conditions or a baseline period. It also ensured that the maximum temporal distance between two trials of the same or different condition was limited, thereby avoiding potential signal loss due to filtering of low-frequency noise.

Stimulus presentation and response recording were performed using the software Presentation® (version 14.9, Neurobehavioral Systems, Inc.). The NGT took 28.4 minutes to complete in the scanner. The trials were split into two separate scan runs lasting approximately 14.5 minutes each. After completing the NGT, a brief post-scan interview was implemented to ensure that the instructions had been understood and that an appropriate strategy had been used.

Insert Figure 1 here

Pre-scan training

Prior to the task, participants learned the landmark positions by studying a small-scale cardboard replica of the arena for two minutes. A second model, in which the frames were empty, was used at test. Based on a fixed order, the experimenter placed one out of seven landmark cards (animal drawings) in one of the empty frames and the

participant had to place a randomly drawn card in the correct frame relative to the first. This was repeated seven times and in the case of no errors, the NGT followed. If errors were made, the learning and testing procedure was repeated.

Participants were then given instruction about the NGT and watched an animation highlighting the manipulations of the task. Participants completed nine to eighteen demonstration trials before testing commenced in the scanner. These demonstration trials were designed to familiarize the participants with the trial structure and timing and with the three possible conditions. The experimenter made no strategy recommendations.

Image acquisition

MR scans were collected on a Philips Achieva 3T MR scanner using an 8-channel SENSE coil. A standard T1-weighted TFE scan sequence (voxel size $0.76x0.77x0.80mm^3$, 225 slices, TE=4.6ms) was used to acquire a structural scan for each participant. Two separate runs of functional scans were collected for the NGT using a single-shot EPI sequence (TE=30ms, TR=2600ms, voxel size $2.5x2.5x3.5mm^3$, 40 axial slices, tilted up approx. 20 degrees from the AC-PC line), with a total of 330 volumes per run. Three dummy volumes at the beginning of each run were immediately discarded. Stimulus presentation started after a further three volumes. Between both functional runs, a spoiled gradient echo (T1-FFE) field mapping sequence (voxel size $2x2x2mm^3$, TR=27ms, TE1=2.6ms, TE2=5.9ms,) was used to reconstruct magnetic field inhomogeneity.

fMRI pre-processing

The MR data analysis was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) in Matlab R2010b (The MathWorks, Inc.). Standard

pre-processing of functional images consisted of slice-time correction to the first slice, realignment and unwarping using the constructed fieldmap, normalization to standard anatomical space using normalization parameters previously estimated from the structural scans, and spatial smoothing with an 8 mm FWHM Gaussian smoothing kernel. The first-level model consisted of three separate events per trial and condition to model the three phases of a trial: presentation, delay and response. Since the presentation phases for EC and VC trials were indistinguishable for the participants (i.e. only during the delay were they told whether they or the walls will rotate), the onsets of the presentation phase for these two conditions were combined. The onsets were convolved with the canonical hemodynamic response function (HRF) of SPM. In addition, response times were added to the model as parametric modulators of BOLD amplitude of the response phase events. Trials in which no response was recorded (1.6% of trials) were included in the analysis as it is highly likely that participants were still engaged in the task during these trials, but simply did not respond in time. This is supported by the fact that the majority of these trials were in the EC condition, which had significantly higher response times than the other two conditions (see below). Non-response trials were allocated a fixed value of 3.5s for the parametric modulator, equivalent to the maximum possible RT in the response phase. Lastly, motion parameters for each session were added to the first-level model to serve as regressors of no interest.

Parameter estimates for the various predictors were then combined across both sessions and entered into second-level models. The main analysis included the contrasts for the response phase of the three conditions along with a subject factor. Family-wise

error correction was used to correct p-values for multiple comparisons to a Type-I error probability of 0.05 with an additional cluster extent threshold of 10 voxels.

BOLD signal time-courses for the entire trial were based on additional first-level models using a finite-impulse basis set of order 12 for the three conditions. Here, the beginning of the encoding phase was used to define the onset of each trial. In contrast to the canonical HRF analysis described above, EC and VC conditions were therefore modelled separately from encoding phase onwards (as part of the entire trial).

Results

Two participants were excluded from the analysis (one female, one male); one due to excessive motion during scanning, and one due to difficulties seeing the stimulus display, which the participant only reported after the scan.

Behavioural performance

Sixteen of the 18 included participants made no errors during training; one person reached training criterion in the second cycle and one person in the third cycle. Non-response trials were excluded from the analysis of behavioural performance, which made up 1.6% of trials, of which 1.2% were EC, 0.3% were VC and 0.1% were NM trials. The percentage of trials in which participants successfully distinguished the target from the foil and reaction times referring to correct responses are presented in Table 1. A repeated measures ANOVA revealed significant differences between the three conditions in terms of accuracy ($F(2,34)=104.66$, $p<.001$) and reaction times ($F(2,34)=259.99$, $p<.001$). A pairwise multiple comparison (post hoc pairwise T test) showed that participants were less accurate in the EC condition compared to the VC ($p<.001$) and NM conditions ($p<.001$), and in the VC compared to the NM condition ($p<.05$). One-sample t-tests

confirmed that performance was above chance in all conditions (all $p<.001$). Similarly, reaction times were longer in the EC condition compared to the VC ($p<.001$) and NM condition ($p<.001$), whilst there was no difference between the VC and the NM condition ($p>.05$). In the EC condition, angle of rotation was found to have a significant effect on accuracy ($F(2,34)=12.76$, $p<.001$) and reaction time ($F(2,34)=30.49$; $p<.001$), by which a greater angle of rotation was associated with lower accuracy ($r=-.58$; $p<.001$) and longer response times ($r=.53$; $p<.001$). In contrast, angle of rotation had no effect on accuracy ($F(2,34)=.90$, $p=.42$) or on reaction times ($F(2,34)=.47$, $p=.63$) in the VC condition. This confirms that participants were taking the viewpoint shift into account when solving the EC trials, whilst they appropriately ignored and so were not affected by the shift of landmarks in the VC condition. In further support of this conclusion, all participants reported using an appropriate strategy in the post-scan interview.

Insert Table 1 here

fMRI results

Whole brain analysis

To investigate the brain regions involved in recognizing the target location based on environmental cues, independently of observer position, the signal acquired during the response phase in the EC condition was contrasted with the VC condition. A large network was observed, consisting of occipital, parietal, mediotemporal, as well as frontal regions (Figure 2). Local signal peaks were observed in regions of the parieto-medial temporal pathway, including the superior parietal lobe, the retrosplenial cortex and the lingual gyrus (Table 2). In all clusters, the EC condition was associated with greater signal above baseline than the VC condition (Table 2). For the reverse contrast, clusters

of differential signal were observed in frontal, parietal and temporal regions (Figure 2), with local signal peaks in the posterior cingulate cortex, the medial superior frontal gyrus and the hippocampus (Table 2). The contrast was generally characterized by the signal dropping below the baseline in the EC condition with a lesser drop or no change from baseline in the VC condition (Table 2). At encoding, the EC and VC conditions could not be differentiated and were therefore combined and contrasted with the NM condition. Clusters of differential signal associated with encoding were observed in occipital, parietal and frontal regions (see Table 3).

Insert Figure 2 here

Insert Table 2 here

Insert Table 3 here

Time course analyses

Time course analyses were performed in voxels of local peak activation in the superior parietal lobe, retrosplenial cortex, hippocampus and posterior cingulate cortex (Figure 3). Given the typical time course of the canonical HRF implemented in SPM, signal related to the encoding phase should peak around 5 seconds after trial onset, signal related to the delay phase should peak between 8 and 13 seconds after trial onset, and signal related to the recall phase should peak around 13 to 15 seconds after trial onset. In the early part of the time course (0-10s), BOLD signal changes in the EC condition and VC conditions appeared similar in all depicted regions, reflecting the necessarily identical encoding process for these two conditions. Later in the time series (13-16s), however, the change in BOLD signal in the EC condition was observed to be more substantial compared to the VC condition, which was reflected in the greater increase above the

fixation baseline in the superior parietal lobe and the retrosplenial cortex and a greater drop below the baseline in the posterior cingulate cortex and the hippocampus. In this part of the time course, as opposed to mirroring the BOLD signal change of the EC condition, the signal change associated with the VC condition was observed to converge towards that of the NM control condition. Across the time course, the NM control condition consistently produced a BOLD signal closer to baseline compared to the other two conditions.

Insert Figure 3 here

Discussion

The present study investigated whether the parieto-medial temporal pathway, with a particular focus on the hippocampus, is important for short-term memory retrieval of target locations based on environmental landmarks when no navigation is required. To this end, the Northumberland Gallery Task (NGT) was used to separate and contrast spatial memory based on environmental cues or viewer position. The environment-centred condition was found to be associated with a substantial cluster of activation extending medially from the superior part of the posterior parietal lobe to the medial temporal lobe, via the retrosplenial cortex, indicating that the full extent of the parieto-medial temporal pathway is important for the type of processing likely to precede spatial navigation based on environmental cues (Burgess, 2008; Kravitz et al., 2011; Shipman & Astur, 2008).

The posterior parietal involvement in the EC condition may appear contradictory to its predominantly viewer-centred role (Burgess, 2008). It is consistent, however, with studies linking this region to the coordination of body knowledge with sensory maps of

space (Committeri et al., 2004; Galati et al., 2010); whilst retinotopic and body-centred representations largely overlap in the VC condition, the shift in virtual position of the observer in the EC condition would have reduced this overlap, necessitating more substantial remapping between several viewer-centred coordinate systems in the EC condition. A posterior parietal involvement is also consistent with recent proposals extending the function of this region from solely involving transformations between different body-centred representations to also covering transformations between body-centred and environment-centred representations (Byrne et al., 2007; Calton & Taube, 2009; Save & Poucet, 2009). Independent of transformation type, a greater reliance on spatial transformations in the EC condition is likely to account for the posterior parietal involvement.

The strongest effect associated with the EC condition was observed in the retrosplenial cortex, which adds to existing evidence supporting its involvement in transformations between body-centred and environment-centred representations (Maguire 2001; Byrne et al., 2007; Burgess, 2008). It also supports a role for the retrosplenial cortex extending beyond navigation (Vann et al., 2009) to also include environmental referencing following an instantaneous shift in viewpoint (Galati et al., 2010). Furthermore, the time series analysis revealed an early and a late peak in BOLD signal change in the retrosplenial cortex, indicating that environmental referencing is likely to have taken place at encoding as well as at retrieval. The precuneus was also found to play a part in the EC condition, which may be linked to the imagery formed of the retrieved material (Fletcher et al., 1996; Burgess, et al., 2001). Specifically, following the viewpoint shift, the precuneus could have provided an updated image of the target

location and of obstructed parts of the scene. Furthermore, the EC condition was associated with activation in the lingual gyrus, which likely reflects the reliance on the orientation value of landmarks in this condition (Aguirre et al., 1998; Aguirre & D'Esposito, 1999). The absence of differential signal in the parahippocampal place area is likely to be accounted for by passive viewing of scenes, which took place in both conditions (Epstein & Kanwisher, 1998). From these results, it is evident that large parts of the parieto-medial temporal pathway feature when a reference to environmental landmarks is required, supporting its pre-navigational role.

In stark contrast to the regions discussed above, the hippocampus showed a greater signal in the VC condition compared to the EC condition. Relative to the fixation baseline, however, this effect was characterized by a large drop in signal below baseline in the EC condition and little change from baseline in the VC condition. This effect also appeared to be relatively exclusive to the retrieval phase of the task, as indicated by the time series analysis. Although contradictory to the predictions, a negative BOLD response in the hippocampus is not an uncommon finding. Such a response has been associated with virtual versions of traditional spatial memory tasks, including the Morris Water Maze (Shipman & Astur, 2008) and the Radial Arm Maze (Astur et al., 2005), as well as with increasing goal distance in a route-planning task (Viard et al., 2011), autobiographical spatial judgments of long-term memories (Rekkas et al., 2005) and detection of location changes following an imagined shift in viewpoint (Lambrey et al., 2012). Such reports of negative hippocampal BOLD responses in spatially demanding and arguably hippocampus-relevant task conditions not only indicate the reliability of the finding but also highlight the need for interpretation.

Whilst the positive BOLD response has been related to increased neuronal activity (Logothetis et al. 2001), the mechanisms underlying the negative BOLD response are much less clear (Hayes & Huxtable, 2012). Three theoretical accounts are generally offered; a) the negative deflection could be the result of vascular steal by which oxygenated blood is diverted away from less active areas to more active areas, b) of an active neuronal suppression in the region, or c) of a contradictory *increase* in neuronal activity without a corresponding boost in blood flow (Wade, 2002). Whilst vascular steal is unlikely due to the small changes in cerebral blood flow accompanying cognition and the substantial hemodynamic reserve of the brain (Gusnard & Raichle, 2001), the two latter accounts are relevant in the present context.

It is possible that the EC condition, contrary to the prediction, requires a functional suppression of the hippocampus. Such an interpretation was favoured by Reas et al. (2011), who demonstrated a negative BOLD response in the hippocampus during elaborate associative recall, which was greater for poorly remembered than for strongly remembered items. It was argued that the longer memory search accompanying poorly remembered items required a greater suppression of encoding-related activity in the hippocampus, in favour of retrieval-related processes taking place elsewhere. Compared to the VC condition, the EC condition indeed required a longer memory search, in addition to potential retrieval of obscured relevant landmarks. However, no evidence was found of an increased BOLD response in the anterior hippocampus at encoding, contradicting the idea that signal in this region is reflective of encoding processes in the task. In addition, in the case of a functional suppression, one would expect greater suppression to be associated with better performance. Contrary to this, the generally

poorer performance in the EC condition relative to the VC condition supports an inverse relationship between the level of negative BOLD signal and performance, similarly to the results of Reas et al. (2011).

As opposed to a task-specific effect, the link between negative BOLD signal and poor performance may instead indicate a general effect of task difficulty. In support of such an interpretation, at rest, the hippocampus demonstrates functional correlations with the default network, which consistently shows deactivations during active compared to passive baseline conditions (Shulman et al., 1997) and during difficult compared to easy task conditions (McKiernan et al., 2003; Gimbel & Brewer, 2011). Furthermore, it is noteworthy that several of the studies demonstrating hippocampal deactivations in arguably hippocampus-relevant conditions reported worse behavioural performance in that particular condition (Rekkas et al., 2005; Shipman & Astur, 2008; Rodriguez, 2010; Lambrey et al., 2012). However, the coupling of the hippocampus with other default regions during memory retrieval appears to vary according to task condition (Gimbel & Brewer, 2011; Huijbers et al., 2011; Reas et al., 2011), which indicates that the areas deactivated during memory retrieval may only partially overlap with those deactivated during non-memory tasks (Israel et al., 2010). In relation to this, although the more difficult EC condition was associated with deactivations in default regions such as the medial prefrontal cortex, the posterior cingulate cortex and the inferior parietal lobule, it was associated with strong activations in another default region, the retrosplenial cortex (Buckner et al., 2008). More importantly, when BOLD signal is not used as the measure of neuronal activity, previous studies tend to contradict a suppression of hippocampal activity during spatial memory tasks. For example, when contrasted to a visuomotor

control condition, goal-directed navigation has been found to be associated with increased cerebral blood flow to the hippocampus, as measured by positron emission tomography (Maguire et al., 1997), and with increased theta activity in the hippocampus, as measured by magnetoencephalography (Cornwell et al., 2008). Furthermore, contrary to the characteristics of the default network, neurons in the hippocampus have been found to show no or very low activity during baseline conditions whilst firing selectively in response to different categories of visual stimuli (Quiroga et al., 2005; Kraskov et al., 2007). Thus, although a task-independent effect of difficulty cannot be excluded in the present study, a general suppression of the default network may not fully account for the negative BOLD response in the hippocampus.

The negative BOLD response in the EC condition may not be a reflection of suppression of neuronal activity but of an *increase* of neuronal activity. This is possible because of the relative nature of the BOLD signal, which depends on a complex interplay between changes in cerebral blood flow (CBF), cerebral blood volume (CBV) and oxygen metabolism (cerebral metabolic rate of oxygen, $CMRO_2$) that results from neuronal activity (Buxton et al., 2004; Logothetis & Wandell 2004; Buxton, 2012). In fact, measurable increases in BOLD signal rely on a relatively greater increase in CBF compared to $CMRO_2$ (Ogawa et al., 1990). Consequently, if neuronal activity causes a greater increase in $CMRO_2$ relative to the increase in CBF, a decreased BOLD signal could theoretically result (Buxton, 2012).

Ekstrom (2010) proposed that the negative BOLD response in the hippocampus during memory encoding and retrieval tasks could be explained by such a neurovascular account. In support of this account, the coupling between CBF and $CMRO_2$ in the

hippocampus appears more complex than that traditionally observed in the cortex (Restom et al., 2008; Leontiev et al., 2007), possibly as a result of a more limited vascular capacity in the hippocampus compared to cortex (Borowsky & Collins, 1989). For example, whilst BOLD changes in the parahippocampus were found to be positively correlated with local field potential (LFP) power changes in a sample of epilepsy patients during a spatial navigation task, BOLD changes in the hippocampus showed a weak or no correlation with LFP power changes (Ekstrom et al., 2009). Furthermore, Schridde et al. (2008) found that induced seizures in the rat resulted in marked increases in LFP activity across the entire brain but that such increases were associated with negative BOLD responses in the hippocampus and with positive BOLD responses in the cortex. Importantly, the coupling between $CMRO_2$ and CBF was found to account for the negative BOLD response; the increase in $CRMO_2$ nearly matched the increase in CBF in the hippocampus whilst the normal $CBF/CMRO_2$ overshoot was observed in the cortex. Based on such results, Ekstrom (2010) proposed that demanding memory tasks may be associated with an increase in $CMRO_2$ that is just matched or even undershot by the increase in CBF, which, when contrasted with a resting baseline condition, results in a negative BOLD signal. Considering the lack of signal change relative to the baseline in the VC condition, such a scenario could account for the present findings: the demand of the EC condition could have caused the oxygen consumption in the hippocampus to exceed its supply, resulting in a negative BOLD signal in the face of increased neuronal activity.

The discussion above has highlighted two valid but mutually exclusive accounts of the negative BOLD signal demonstrated in the hippocampus, which is the direct

consequence of the indirect relationship between BOLD signal and neuronal activity. Although an independent baseline allowed a more comprehensive interpretation of the unpredicted pattern of BOLD signal in the present study, a more direct measure of neuronal activity will be required to characterise the precise relationship between BOLD signal and neuronal activity in the human hippocampus. We argue, in agreement with previous recommendations (Ekstrom, 2010; Hayes & Huxtable, 2012), that techniques such as calibrated fMRI and multimodal imaging have the potential of disambiguating the mechanisms underlying the BOLD response in the hippocampus, which will be critical for experimental interpretations in both basic and applied research settings.

Conclusion

In line with the predictions, the present study has demonstrated the importance of the parieto-medial temporal pathway in short-term spatial memory that relies on environmental landmarks, even when no navigation is required. The hippocampus was found to play a differential role in the environment-centred condition, but in contrast to the prediction, this role was characterized by a substantial negative BOLD response. As such, the present study builds on previous demonstrations of a negative BOLD response in the hippocampus in spatially demanding task conditions. Although a suppression of default activity is a valid account, this would be in stark contrast to a long and robust tradition of linking the hippocampus to spatial memory, both at an electrophysiological (e.g. O'Keefe & Nadel, 1978) and at a pathophysiological level (e.g. King et al., 2002). We therefore suggest that the alternative account, by which the negative BOLD response is a reflection of *increased* neuronal activity without a corresponding boost in cerebral blood flow, is explored in future investigations.

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Figure 1. Trial structure and example stimuli. In the Environment-centred (EC) (a) and Viewer-centred (VC) (b) conditions, the target location (green pole) was presented. During the delay phase, participants were informed of the upcoming manipulation via an instruction, which was overlaid on a scrambled image of the virtual scene. In the response phase, participants had to select the target location over a foil location after a shift in viewpoint (a) or a rotation of the walls (b). In the No-Memory (NM) condition (c), no target location was presented, and in the response phase participants simply had to identify the colour of the marker on which the pole was standing.

Figure 2. Activation maps for the Environment-centred (EC) vs. Viewer-centred (VC) contrast at retrieval. Activations maps are shown in axial sections on the average normalised structural image computed from our sample data. Regions shown in yellow exhibited greater signal in the EC condition whilst regions shown in red exhibited greater signal in the VC condition (p<.05, FWE, k≥10). Numbers represent Z coordinates in MNI space.

Figure 3. Plots of BOLD signal time course changes in the superior parietal lobe (a), retrosplenial cortex (b), hippocampus (c) and the posterior cingulate cortex (d). Time course changes are shown in sagittal sections on the average normalised structural image computed from our sample data (activation maps: p<.05, FWE, k≥10). The voxels selected for analysis were the ones with peak differences in the Environment-centred (EC) vs. Viewer-centred (VC) contrasts in each of the regions. Signal changes in the EC (blue, solid), VC (green, dashed) and No-Memory (NM) conditions (red, dotted) were modelled from the onset of the trial.

Table 1
Behavioral data from the Northumberland Gallery Task (mean±standard deviation).

Condition	Rotation angle (degrees)	Accuracy (% correct)	Reaction time (ms)
No-Memory	-	98%±3	1136±236ms
Environment centred	average	77%±7	2280±270ms
	45°	86%±8	2075±315ms
	90°	77%±10	2300±292ms
	135°	67%±15	2529±287ms
Viewer-centred	average	96%±4	1225±207ms
	45°	95%±6	1220±210ms
	90°	96%±7	1206±288ms
	135°	97%±4	1252±219ms

Table 2

Peak activations for the whole brain analyses when contrasting the Environment-centred (EC) and Viewer-centred (VC) conditions (p<.05, FWE, k≥10). Differences from baseline for the two conditions are marked as + when positive, as - when negative and as 0 when not significant.

Contrast	Region	Local peak	Left				Right			
			Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (EC/VC)	Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (EC/VC)
EC>VC	Parieto-occipital-temporal		10830							
		Retrosplenial cortex		13.48	-16, -70, 10	+ / +	-	12.20	18, -62, 16	+ / +
		Lingual gyrus		10.48	-12, -61, 0	+ / +	-	8.15	26, -86, -10	+ / +
		Fusiform gyrus		6.55	-38, -44, -20	+ / +	-	6.74	38, -42, -22	+ / +
		Inf. occipital gyrus		7.90	-38, -76, -12	+ / +	-	7.16	38, -76, -12	+ / +
		Precuneus		8.88	-4, -64, 52	+ / +	-	9.93	12, -66, 52	+ / +
		Sup. parietal lobe		8.84	-16, -70, 54	+ / +	-	13.24	20, -72, 48	+ / +
		Mid. temporal gyrus		-	-	+ / +	41	6.49	46, -70, 14	+ / +
	Frontal									
		Insula	197	8.93	-28, 24, -2	+ / +	119	6.69	32, 26, -4	+ / +
		Medial frontal gyrus	671	8.33	-6, 10, 50	+ / +	-	7.83	2, 14, 50	+ / +
		Mid. frontal gyrus	442	9.39	-24, 0, 52	+ / +	319	7.74	34, 0, 50	+ / +
		Inf. frontal gyrus	64	6.85	50, 32, 24	+ / +	-	-	-	+ / +
		Precentral gyrus	402	8.74	-38, 8, 30	+ / +	18	6.02	46, 12, 30	+ / +
	Other									
		Brain stem	302	7.91	-4, -28, -4	+ / +	-	-	-	
		Basal ganglia	48	7.28	-12, 0, -2,	+ / +	-	-	-	
		Cerebellum	-	-	-		34	6.65	8, -72, -26	+ / +
VC>EC	Parietal									
		Posterior cingulate cortex	217	7.76	-10, -50, 26	- / -	18	6.39	6, -50, 24	- / -
	Frontal									
		Insula	1624	9.34	-38, -10, 14	0 / +	35	7.02	38, 6, 10	0 / +
		Angular gyrus	11	6.86	-42, -64, 28	- / -	14	6.28	52, -58, 28	- / -
		Sup. medial frontal gyrus	143	6.70	-8, 54, 0	- / -	24	6.34	8, 58, 18	- / -
		Sup. frontal gyrus	88	7.68	-14, 54, 24	- / -	-	-	-	
		Precentral gyrus	-	-	-		31	7.01	44, -20, 52	- / 0
		Supramarginal gyrus	51	6.42	58, -24, 22	0 / 0	-	-	-	
	Temporal									
		Temporal pole	-	-	-		96	7.98	42, 10, -34	- / -
		Mid. temporal gyrus	-	-	-		275	7.08	54, -38, 0	- / 0
			-	-	-		21	6.55	52, 2, -20	- / -
		Hippocampus	11	6.31	-28, -14, -22	- / 0	86	7.07	30, -16, -18	- / 0

Table 3. Peak activations for the whole brain analyses when contrasting encoding (Environment-centred and Viewer-centred conditions combined) with the No-Memory (NM) condition (p<.05, FWE, k≥10). Differences from baseline for the two conditions are marked as + when positive, as - when negative and as 0 when not significant.

Contrast	Region	Local peak	Left				Right			
			Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (Enc/NM)	Cluster (voxels)	t-value	x,y,z (MNI)	Diff. baseline (Enc/NM)
Encod > NoMem	Parietal									
		Sup. parietal lobe	1635	13.94	-30, -46, 42	+ / 0	169	9.72	42, -40, 48	+ / 0
			-	-	-		534	10.91	18, -66, 54	+ / +
		Angular gyrus	-	-	-		65	8.64	32, -54, 42	+ / +
	Occipital									
		Mid. occipital gyrus	-	-	-		1727	12.94	24, -88, 8	+ / +
		Inf. occipital gyrus	1904	14.71	-38, -78, -4	+ / +	-	-	-	
		Cuneus	27	8.75	-10, -94, 16	+ / +	-	-	-	
	Frontal									
		Inf. frontal gyrus	385	11.42	-38, 6, 26	+/ 0	-	-	-	
		Mid. fontal gyrus	127	9.57	-22, 4, 48	+ / 0	-	-	-	
			55	9.22	-46, 2, 48	+ / +	-	-	-	
			-	-	-		48	9.61	28, 8, 56	+ / 0
		Medial frontal gyrus	199	9.88	-5, 10, 50	+ / 0	-	-	-	
	Other									
		Putamen	75	9.06	-14, 10, 4	+ / 0	-	-	-	
NoMem > Encod	Frontal									
		Medial frontal gyrus	47	8.30	0, 62, 16	- / 0	-	-	-	
	Other									
		Sub-gyral temporal	32	8.95	-30, -54, 2	- / 0				

FIGURE 1

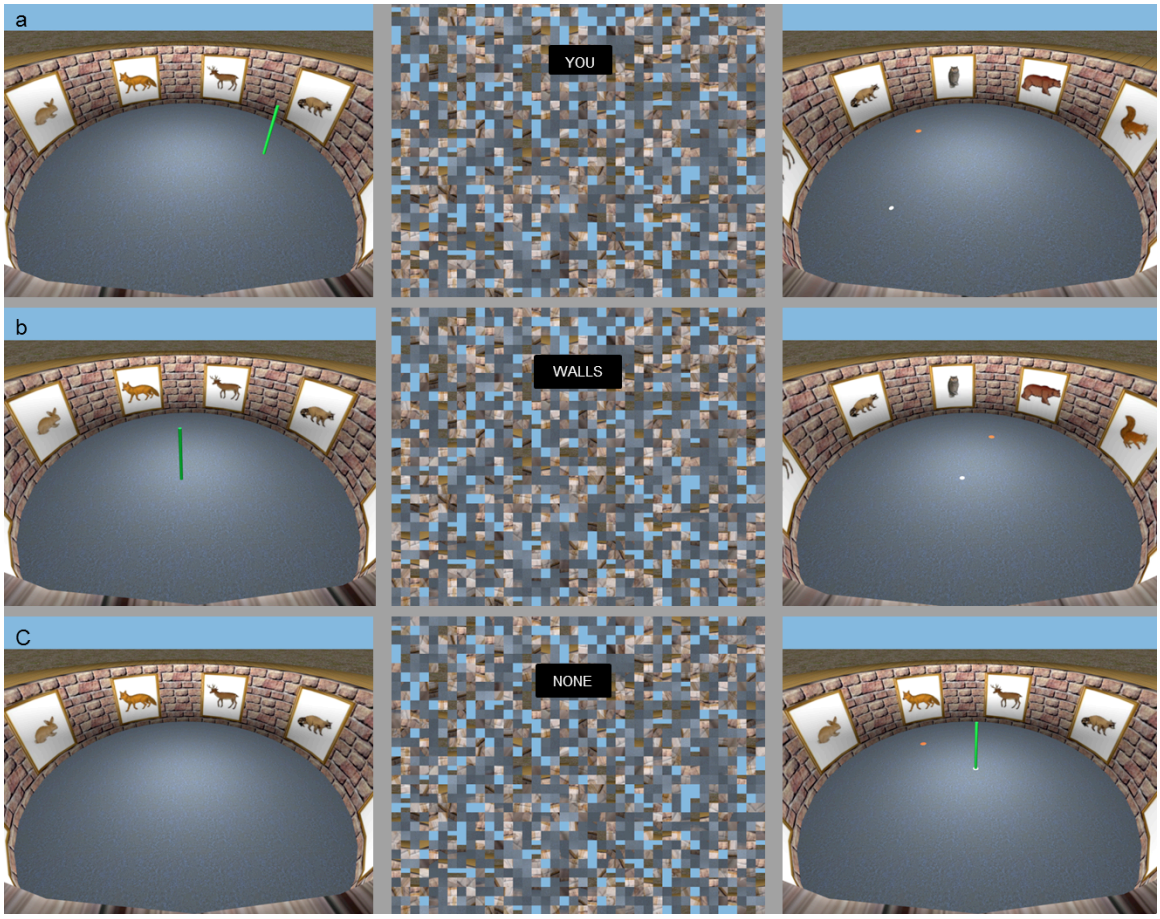

Figure 2

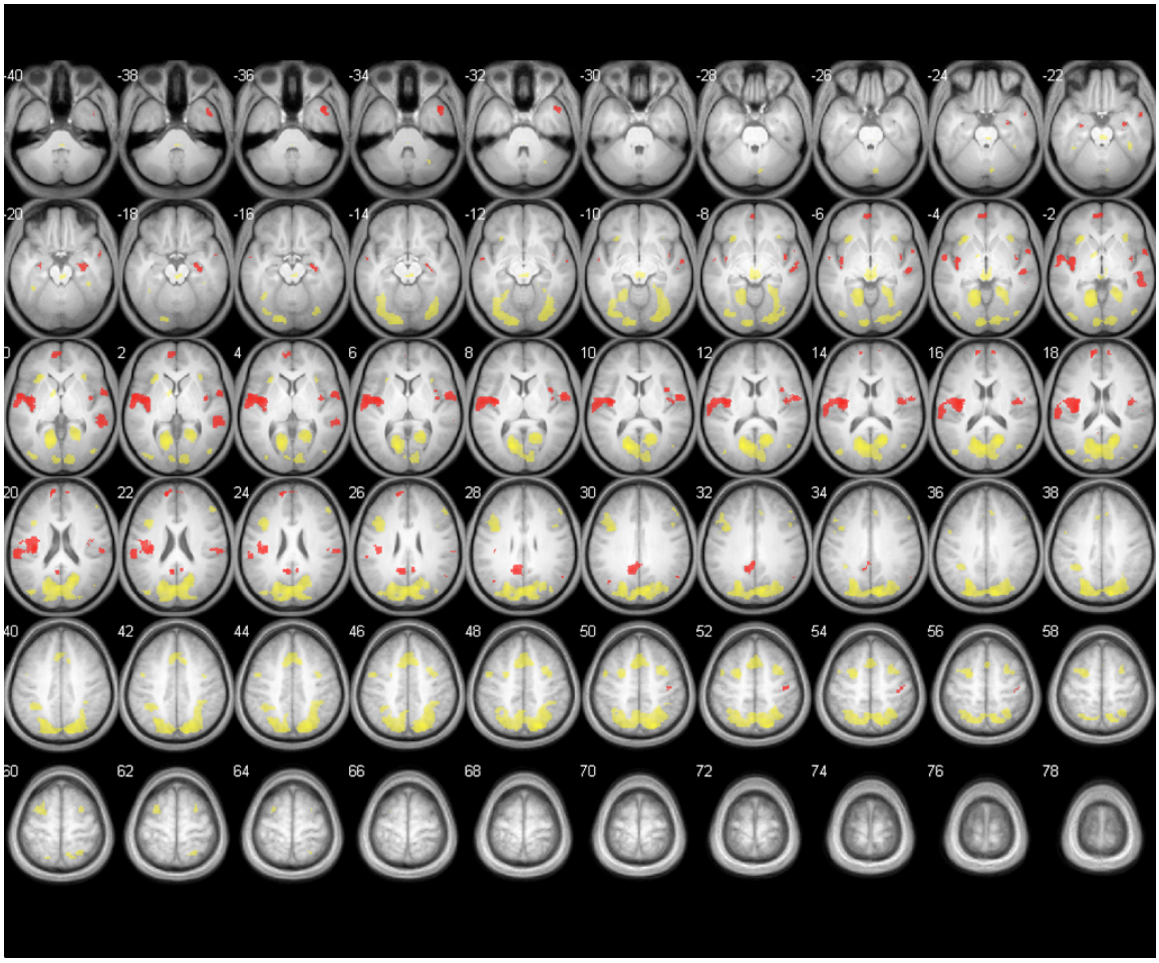
-40 -38 -36 -34 -32 -30 -28 -26 -24 -22
-20 -18 -16 -14 -12 -10 -8 -6 -4 -2
0 2 4 6 8 10 12 14 16 18
20 22 24 26 28 30 32 34 36 38
40 42 44 46 48 50 52 54 56 58
60 62 64 66 68 70 72 74 76 78

FIGURE 3