Differentiable processing of objects, associations and scenes *within* the hippocampus

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Highlights

- Theories generally posit that the hippocampus (HC) executes one fundamental process
- We compared several of these processes in a rigorously matched manner using fMRI
- Dissociable processing of objects, associations and scenes was evident in the HC
- The HC is not uni-functional and extant theories may need to be revised

eTOC blurb

Dalton et al. show that there is dissociable processing of objects, associations and scenes within the hippocampus. This suggests that uni-functional accounts of its operation should be reconsidered, helping to reconcile opposing theories of hippocampal function.

Summary

There are numerous theories of hippocampal function, but each makes the inference that the hippocampus executes one fundamental process, such as associative binding or the mental construction of scenes. We devised a novel paradigm whereby different tasks were precisely matched for associative processing and mental construction, but either did or did not evoke scene representations. Combined with high resolution fMRI, we aimed to establish whether associative or scene processing preferentially engaged the hippocampus. The results were striking in showing that differentiable parts of the hippocampus, along with distinct cortical regions, were recruited for scene construction or non-scene evoking associative processing. We conclude that there may be multiple separable processing streams within the hippocampus that become engaged depending on task demands. Conceptual disagreements based on an 'either/or' view of the hippocampus should be eschewed in favour of a more nuanced understanding of its contributions to cognition.

Abbreviations

ENT	Entorhinal cortex
EVC	Early visual cortices
PCC	Posterior cingulate cortex
PHC	Posterior parahippocampal cortex
PRC	Perirhinal cortex
RSC	Retrosplenial cortex

Introduction

The last sixty years has seen significant developments in our understanding of the hippocampus. Its anatomy, cellular properties, electrophysiology and connectivity have been well characterised, particularly in non-humans (Scoville and Milner, 1957; Andersen et al., 2006; Ding and Van Hoesen, 2015). The function of the hippocampus has also been intensively scrutinised using electrophysiological recordings, lesion and neuropsychological studies, neuroimaging and computational modelling. From this work, there is long-standing agreement that the hippocampus is essential for supporting memory and, in humans, especially long-term episodic or autobiographical memory – the memory of personal past experiences (Scoville and Milner, 1957; Squire, 1992; Clark and Maguire, 2016). The hippocampus is also widely acknowledged to be necessary for facilitating spatial navigation (O'Keefe and Nadel, 1978). More recently, the hippocampus has been linked with other roles that include scene perception (Graham et al., 2010), short-term memory (Hartley et al., 2007; Hannula and Ranganath, 2008), constructing mental representations of scenes (Maguire and Mullally, 2013; Zeidman and Maguire, 2016), imagining the future (Schacter et al., 2012; Hassabis et al., 2007), decision-making (McCormick et al., 2016; Mullally and Maguire, 2014) and even mind-wandering (Karapanagiotidis et al., 2017). The question that has dominated the hippocampal field for decades is *how* does it support memory, navigation and these other functions? It is in attempting to provide an answer to this question that differing views have proliferated such that there is now a multitude of theories purporting to describe how the hippocampus works.

What these theories do in common is make the inference that the hippocampus is a unitary structure that executes one fundamental process or algorithm and this is what underpins the various cognitive functions. This view is understandable given that for many years the unidirectional trisynapic circuit of the hippocampus was regarded as the principal pathway for information processing through this structure (Andersen, 1975). However, we now know that there are multiple, parallel processing and feedback circuits which bypass the canonical trisynaptic pathway and directly

innervate specific hippocampal subregions (Kravitz et al., 2011, 2013; Insausti and Munoz, 2001), suggesting that different portions of the hippocampus may be differentially engaged by specific networks.

It is impossible to consider all the hippocampal theories here, and so we briefly summarise a selection that capture the essence of the major accounts, and which can broadly be thought of as emphasising space, associations or scenes. The cognitive map theory posits that the hippocampus specifically supports a flexible, allocentric representation of the spatial relationships present in an environment, and this fundamentally spatial scaffold also underpins episodic memory (O'Keefe and Nadel, 1978; Burgess et al., 2002). The relational theory proposes that the hippocampus is required for the binding of arbitrary relations among individual elements within an experience or associating items within a context regardless of whether or not these associations are couched within a spatial framework (Konkel and Cohen, 2009; Cohen and Eichenbaum, 1993). This view has much in common with other theories that place associative processing at the heart of hippocampal function, namely, the binding of item and context model (Ranganath, 2010; see also Ekstrom and Ranganath, 2017 for an extension to include time), the domain dichotomy model (Mayes et al., 2010), the configural theory (Rudy and Sutherland, 1995), the constructive episodic simulation hypothesis (Roberts et al., 2017) and the high resolution binding hypothesis (Yonelinas, 2013). Another perspective on the hippocampus, the emergent memory account, shares some features with the associational and cognitive map theories by stressing that the hippocampus represents complex conjunctions of information (in particular spatial and temporal) of which scenes are a prime example (Lee et al., 2012; Graham et al., 2010; Behrmann et al., 2016; see also Aggleton et al., 2007).

Finally, the scene construction theory posits that a prime function of the hippocampus is to construct models of the world in the form of spatially coherent scenes. This process is held to be vital for spatial navigation, autobiographical memory, simulating the future and aspects of

perception and decision-making (Maguire and Mullally, 2013). Maguire and Mullally (2013; see also Dalton and Maguire, 2017; Zeidman and Maguire 2016) define a scene as a three dimensional (3D) space which one could potentially step in to or operate within, viewed from a first person perspective and populated by objects or other features. Mullally and Maguire (2013) went further in operationalising scenes using tasks where participants were required to serially construct, and also deconstruct scenes, object-by-object, in their mind's eye. In order to subjectively achieve, or preserve, a sense of a coherent scene, participants required approximately three items. Summerfield et al. (2010) reported a similar finding. Participants therefore considered that a representation comprising at least three items in a 3D space was sufficient for them to experience a vivid and coherent scene in their mind's eye.

Scenes clearly encompass space, but scene construction theory differs from the cognitive map theory by linking the hippocampus with scenes that are viewed from a first-person egocentric perspective rather than allocentric spatial processing (see also Clark and Maguire, 2016). Moreover, scene construction theory does not consider scenes to be merely a collection of associations (objects with objects, objects with space) that are bound together to form a scene. Instead, it regards scenes as gestalts that exist as a whole that may be based on templates and linked with schema (Gilboa and Marlatte, 2017). Forming a scene out of multiple sets of associations does not seem to be a speedy or efficient way to process the continuous bombardment of stimulation that the brain experiences. In contrast, 'whole' scenes are a highly effective way of quickly encoding and retrieving information. Recently, scene construction has been linked with a specific part of the hippocampus – the anterior medial portion that encompasses the presubiculum and parasubiculum (pre/parasubiculum; Zeidman et al., 2015a; Zeidman et al., 2015b; Zeidman and Maguire, 2016; Hodgetts et al., 2016; Maas et al., 2014). Furthermore, Dalton and Maguire (2017) have outlined why the pre/parasubiculum might be neuroanatomically determined to preferentially process scenes, as it is

a primary target of the parieto-medial temporal visuospatial processing pathway (Kravitz et al., 2011).

The absence of a common theoretical framework means there is no consensus in the field about how the hippocampus works. This is compounded by a lack of clarity about definitions. For example, what does 'context' actually mean? What is a 'scene'? What is the precise definition of 'complexity' or 'high precision'?. There are also conflicting accounts of what aspects of cognition are impaired and preserved, for example in humans with hippocampal damage (Kim et al., 2015; Maguire et al., 2016). To help break through this impasse, we devised stimuli that were matched for content (objects and space), stimulus complexity, contextual relatedness, level of precision and the requirement for associative processing, mental imagery and mental construction, but which either did or did not evoke the mental experience of a scene representation. We deployed these matched stimuli during high resolution functional MRI (fMRI). It was then possible to examine hippocampal engagement during object, associative and scene processing in the most rigorous manner yet, and observe whether hippocampal recruitment was modulated by associative processing per se (as expounded by a number of hippocampal theories) or preferentially by scenes (as posited by the scene construction theory), thus potentially providing new evidence to inform key conceptual disagreements in the field.

Based on previous reports that three objects and a 3D space are sufficient to form the subjective experience of a scene during mental imagery (Summerfield et al., 2010; Mullally and Maguire, 2013), the two tasks of primary interest involved participants hearing three object descriptions and imagining them on either an imagined 2D or 3D space. With all else being equal in the stimuli, this simple manipulation of space gave rise to mental representations of non-scene 'arrays' (objects on the 2D space) and 'scenes' (on the 3D space) (Figure 1). We also included tasks that examined the representation of three objects without a spatial context where the objects were imagined one after

another in the same location on the centre of the screen, and the representation of either 2D or 3D space alone without objects. Overall, our novel paradigm allowed us to separately examine the neural correlates of mental construction of objects alone, two types of space (2D and 3D) and two different combinations of objects and space where only one gave rise to scene representations.

Given previous findings linking the anterior medial hippocampus – pre/parasubiculum – with scene processing (Zeidman et al., 2015a; Zeidman et al., 2015b; Zeidman and Maguire, 2016; Hodgetts et al., 2016; Maas et al., 2014), we predicted that this area would be activated by our scene construction task. Whether this engagement was preferential to scenes was now a question we could address given our closely matched non-scene relational/associative array task, or indeed whether our 3D space alone task would engage this region (although see Zeidman et al., 2012). We could also evaluate the recent prediction, based on anatomical considerations, that the objects task might preferentially activate prosubiculum/CA1 due to its strong direct link with the perirhinal cortex (PRC; Dalton and Maguire, 2017; Insausti and Munoz, 2001) even though, to the best of our knowledge, no such fMRI finding has been reported. More widely, we predicted that retrosplenial (RSC), posterior cingulate cortices (PCC) and posterior parahippocampal cortex (PHC) would be particularly active during the scene construction task given their known links with scene processing (Epstein, 2008), while the objects and array construction tasks would engage perirhinal cortex, given its acknowledged role in object processing (Nelson et al., 2016; Olarte-Sanchez et al., 2015; Buckley and Gaffan, 1998).

Results

Overview

Participants had extensive training before scanning to ensure task compliance. The fMRI experiment comprised six separate mental construction tasks (Figure 1). Our use of a mental imagery paradigm provided close contact with key functions linked with the hippocampus including autobiographical

memory retrieval, simulating the future and spatial navigation, to which mental imagery is inherent. Trials of each task were presented in a pseudo-randomised order across the experiment and participants engaged in mental construction with their eyes open while looking at a blank white screen. An 'Imagine Fixation' task (Figure 1A) required participants to imagine a black 'plus' sign in the centre of the white screen while hearing three nonsense phrases (see Figure 1G, left panel, for examples of the nonsense phrases), which compromised non-imageable abstract words, spoken one at a time, which were included in order to mirror the auditory input in the object tasks while precluding mental imagery. Participants were instructed to try not to interpret the nonsense phrases in any way. This 'Imagine Fixation' task was essentially a rest condition providing participants with some respite from the more challenging imagination tasks. In the 'Imagine Objects' task, participants heard simple descriptions of three objects, one at a time, and had to construct mental images of each object, one after the other, in the centre of the screen (Figure 1B; see Figure 1G, right panel, for examples of object descriptions). During 'Imagine 2D Grid' trials, participants constructed a mental image of a 2D grid covering the bottom 2/3 of the screen (Figure 1C). During 'Imagine 3D Grid' trials, participants constructed a mental image of a 3D grid covering the bottom 2/3 of the screen (Figure 1D). During trials of both grid tasks, participants heard three nonsense phrases (see Figure 1G, left panel, for examples of the nonsense phrases). During 'Construct Array' trials, participants first imagined a 2D grid on the bottom 2/3 of the screen and then constructed mental images of three auditorily presented objects, one at a time, in self-chosen arbitrary locations on the imagined 2D grid (Figure 1E). During 'Construct Scene' trials participants first imagined a 3D grid on the bottom 2/3 of the screen and then constructed mental images of three auditorily presented objects, one at a time, in self-chosen arbitrary locations on the imagined 3D grid (Figure 1F). The auditory stimuli for each task were carefully matched on a range of features. Of note also, the triplets of objects were never contextually related on any one trial, and specific object features were matched across tasks (see Experimental Procedures and Supplemental Experimental Procedures). It was emphasised to participants that the main focus of the experiment

was mental construction in the imagination. However, to ensure participants were attending throughout, we included catch trials where participants had to press a button if, during any trial, they heard a repeated phrase.

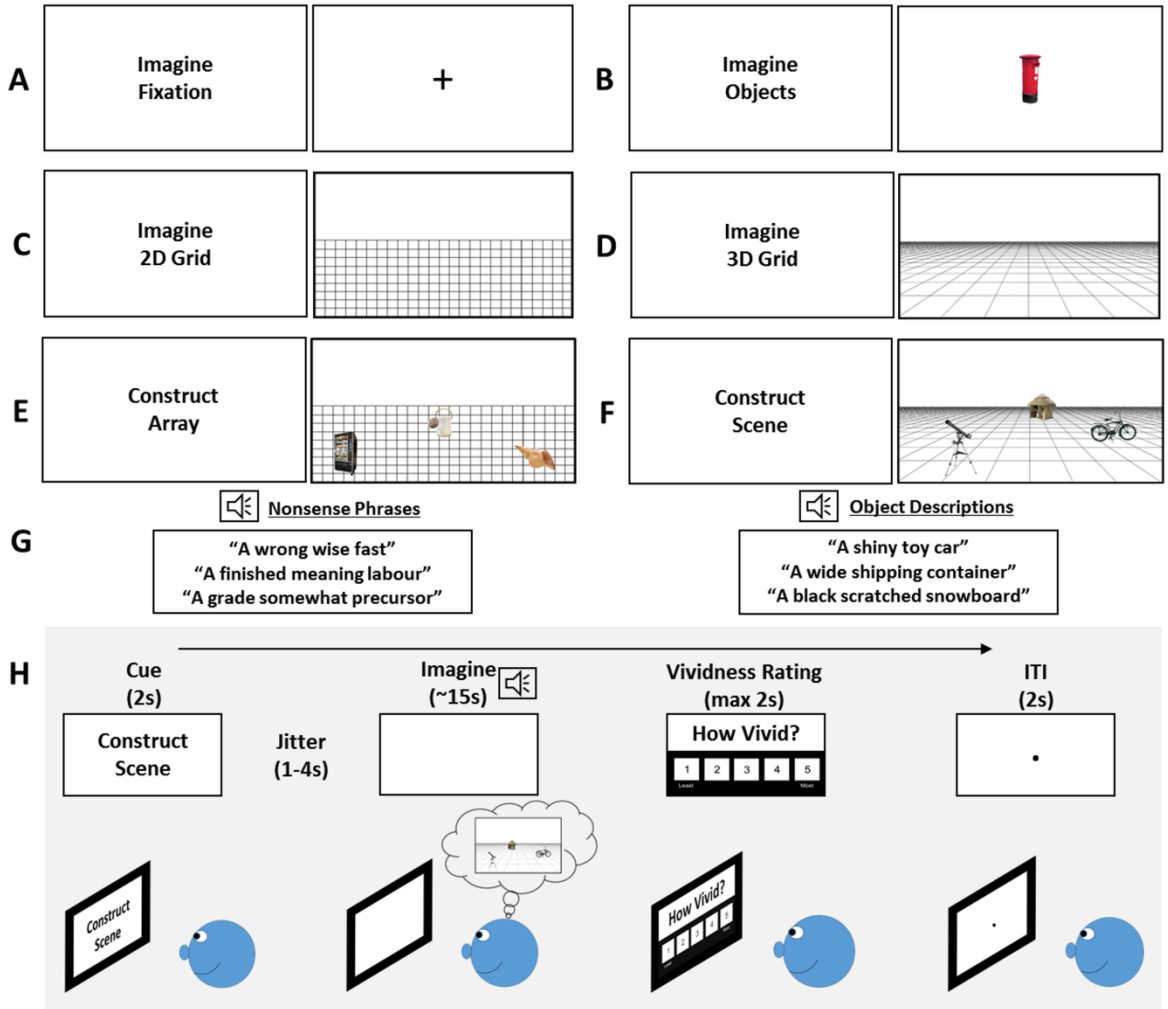

Figure 1. Experimental Design.
(A-F) Representations of how participants engaged in mental imagery during each task, with the text cues on the left of each panel. Note that participants looked a blank white screen during the imagination phases. The images depicted on the right of each panel are based on what participants said they imagined during the task. (G) Examples of object descriptions and nonsense phrases. (H) Example of the time line of a single trial.

Overall, this series of tasks allowed us to investigate the neural correlates of constructing mental representations of objects alone (with no spatial context), 2D and 3D spaces alone (with no objects) and objects associated with either a 2D or 3D space. Importantly, no visual stimuli were presented

during the imagination phase of any task (Figure 1H). Therefore, between-task differences in neural recruitment could not be influenced by differences in visual input.

Our primary tasks of interest were the Construct Array and Construct Scene tasks. They were very well matched, requiring mental construction and associative processing of objects in space. The only difference between them was the scene construction task required objects to be imagined on a 3D grid that gave rise to a scene-like representation (compare the panels in Figure 1E and F). Directly contrasting these tasks, therefore, allowed us to investigate brain regions that underpin scene construction while controlling completely for content, mental constructive and associative processes.

fMRI task comparisons

Our main focus here was on contrasts involving the Construct Scene task. The full results of all the task comparisons are provided in Table S1.

The contrast of primary interest was the Construct Scene task with the very closely matched Construct Array task. This comparison revealed that, in line with our prediction, when all other content, associative and constructive processes were accounted for, a circumscribed region of the anterior medial hippocampus (peak voxel at y = -24) encompassing the pre/parasubiculum was preferentially recruited, bilaterally, during scene construction along with the PHC, RSC and PCC (Figure 2B, Figure 3). Interestingly, the opposite contrast showed that array, more than scene, construction engaged bilateral entorhinal cortex (ENT), PRC, EVC and the left posterior hippocampus which was part of a larger cluster of activity which encompassed the anterior lingual gyrus and portions of the EVC. This contrast also revealed activation of the left ENT abutting the anterior medial hippocampus (peak voxel at y = -12) that was more anterior to the pre/parasubiculum engaged by scene construction (Figure 2B, Figure 3).

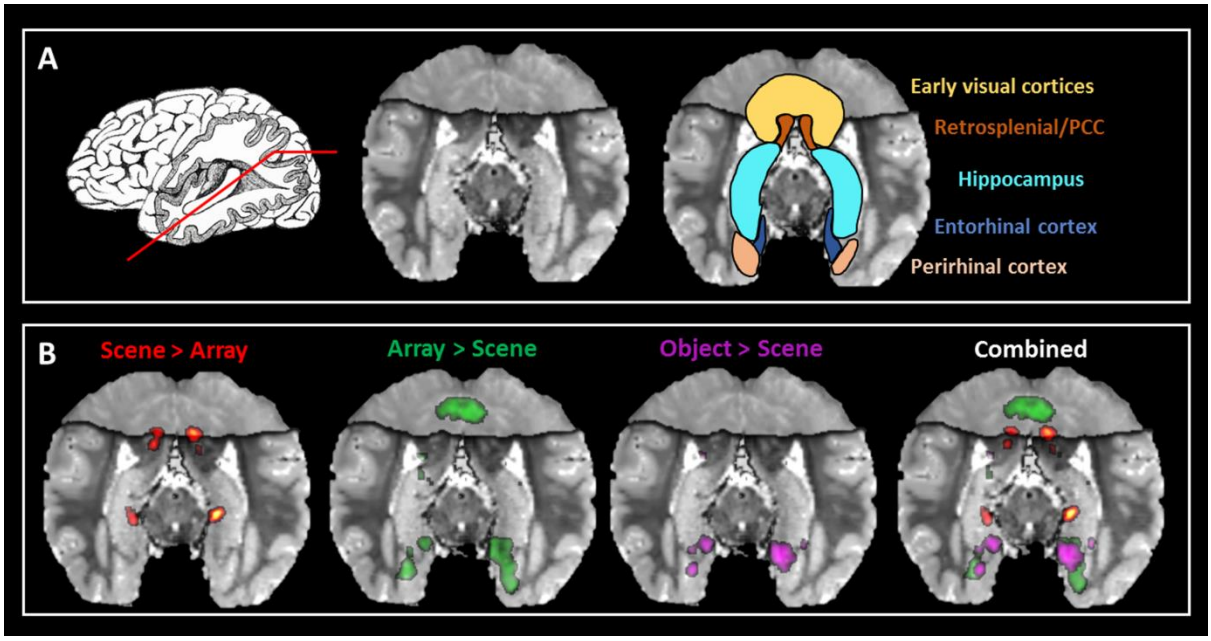

Figure 2. Results of the fMRI analysis.
(A) Left panel, a representation of the oblique angle cutting through the hippocampus used to present the results. Middle panel, shows the averaged structural MR image of the participants exposing the length of the hippocampus. Right panel, depicts the regions of particular interest. (B) From left to right, the results for the contrast of Construct Scene > Construct Array, Construct Array > Construct Scene, Imagine Object > Construct Scene and all of the results combined. PCC = posterior cingulate cortex; results are thresholded at $p < 0.05$.

The contrast of Construct Scene with Imagine Objects provided further support that bilateral pre/parasubiculum along with the PHC, RSC and PCC were specifically associated with scene construction (Figure 3, Table S1,). The reverse contrast showed that the mental construction of objects, more so than scenes, was associated with bilateral PRC and ENT. The right anterior lateral hippocampus, encompassing prosubiculum/CA1, and a left ENT activation that abutted the anterior medial hippocampus were also engaged. This area was more anterior (peak voxel at y = -10.5) to that associated with scene construction (Figure 2B, Figure 3).

The contrast of Construct Scenes with the Imagine 3D Grid revealed increased engagement of an anterior medial portion of the hippocampus in the approximate location of the uncus (peak voxel at y = -9) and bilateral PRC. The reverse contrast showed that the mental construction of 3D grids, more so than scenes, was associated with bilateral ENT and posterior portions of EVC. Imagine 3D

grid did not evoke increased hippocampal activation compared to Imagine 2D grid, suggesting that 3D space alone was insufficient to engage the hippocampus.

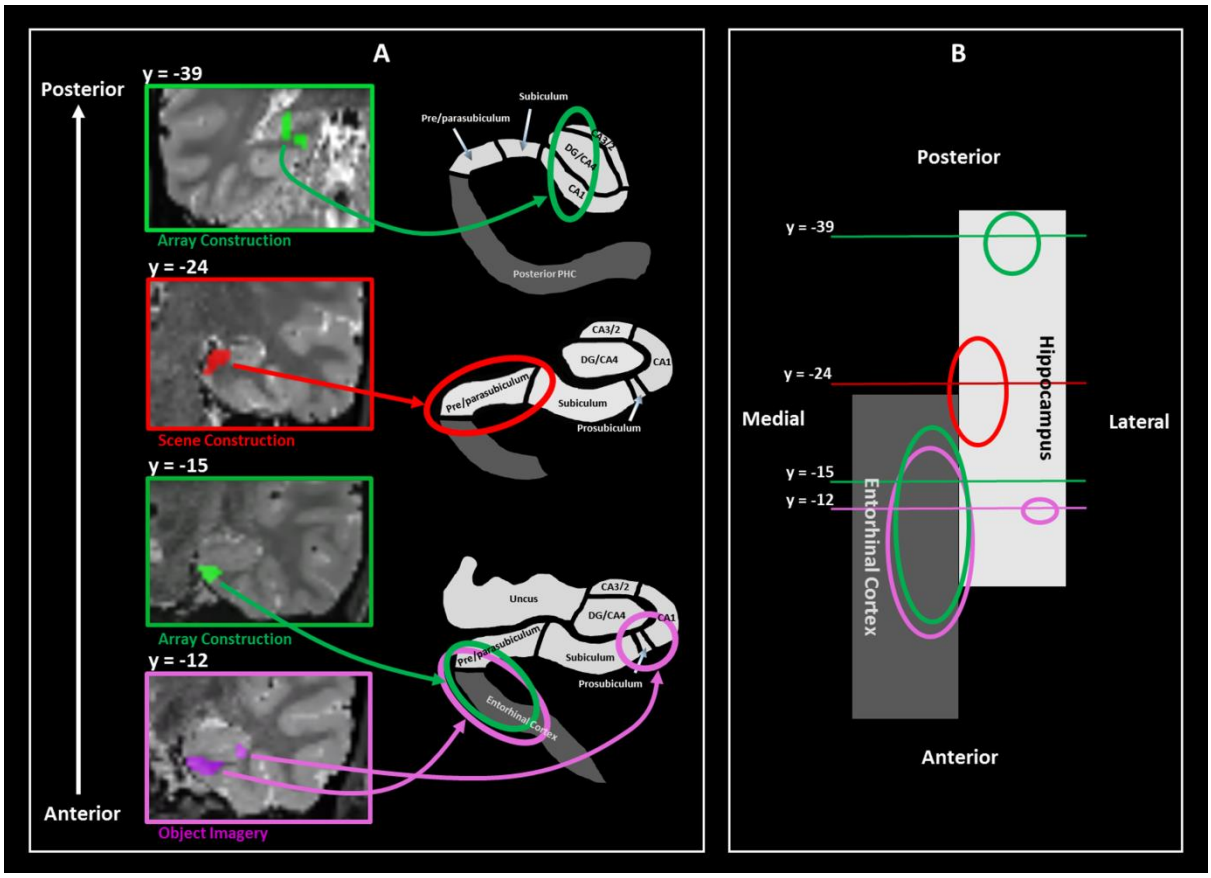

Figure 3. Summary of the main hippocampal activations.
(A) The location of the left posterior hippocampal activation for the Construct Array > Construct Scene contrast (left, top panel). The right anterior medial hippocampal activation – pre/parasubiculum – observed for the contrast of Construct Scene > Construct Array (left, second panel from top). The entorhinal region abutting the much more anterior pre/parasubiculum that was recruited for both Construct Array (left, third panel from top) and Imagine Objects (left, bottom panel) tasks more so than Construct Scenes. The right anterior lateral hippocampal activation – prosubiculum/CA1 – for the contrast of Imagine Objects > Construct Scene (left, bottom panel). The right panels show representative schematics of the locations of the hippocampal subregions. (B) Schematic representation of the hippocampus (white) and entorhinal cortex (grey) in the axial plane. The location of each of the coronal plane images presented in (A) are shown along with representations of the extent of each cluster.

To summarise (see Figure 3), our experimental design allowed us to parse the hippocampus and related areas dependent on the process that was being engaged. Circumscribed portions of the bilateral pre/parasubiculum (around y = -24) were specifically recruited during scene construction. By contrast, a more anterior portion of the ENT that abutted the anterior medial hippocampus was

engaged during both array and object construction. Of note, these activated regions were clearly distinct (explicit smoothing = 4mm; Euclidean distance between peak voxels of the Construct Scene versus Construct Array contrasts 11.89mm; Construct Array versus Imagine Object contrasts 13.64mm). The construction of mental images of arrays was also associated with increased activity in the posterior hippocampus as part of a larger cluster which encompassed the lingual gyrus and EVC. Object construction engaged anterior lateral hippocampus in the region of prosubiculum/CA1. Outside of the hippocampus, compared to array construction, the PHC, RSC and PCC were preferentially recruited during scene construction. In contrast, compared to scene construction, array construction was associated with more posterior portions of the EVC, while both array and object construction were more strongly associated with the ENT and PRC.

But could other factors have influenced the results? We conducted a range of further analyses to investigate.

Did participants truly engage with the tasks?

The construction of mental imagery cannot be directly measured. We therefore used a combination of methods to assess task attentiveness and compliance. First, we included catch trials where participants had to press a button if, during any trial, they heard a repeated phrase. On average, 94% (SD = 0.09) of catch trials were correctly identified indicating that participants remained attentive throughout the experiment.

Second, we utilised in-scan eye tracking to ensure participants were performing each task according to the instructions. For the Imagine Fixation and Imagine Objects tasks, participants were asked to focus their eyes on the centre of the screen where they imagined the plus sign or objects to be. When imagining the 2D and 3D grids, they were asked to move their eyes around where they imagined the grids to be on the screen. For the Construct Array and Construct Scene tasks,

participants were required to imagine each of three objects against the imagined 2D or 3D grid respectively. Visualisation of fixations confirmed that participants engaged in each task according to our instructions (see examples in Figure 4A).

To formally determine the extent of eye movements, we measured the variance of all fixations in the horizontal axis during the construction phase of each trial (Figure 4B). We predicted that if participants performed the mental imagery tasks as expected, there would be less variance in fixation location during the centre-focussed Imagine Fixation and Imagine Objects tasks and a more dispersed pattern of fixations across the other tasks. The results of a repeated measures ANOVA revealed a significant difference in the variance of fixations between tasks ($F_{2.58,64.58} = 24.51$, $p < 0.001$). In line with our prediction, post hoc analyses revealed significantly less variance during the Imagine Fixation task compared to the other tasks (compared to the Imagine 2D Grid $t_{25} = 6.047$, $p < 0.001$; Imagine 3D Grid $t_{25} = 5.295$, $p < 0.001$; Construct Array $t_{25} = 6.397$, $p = 0.001$; Construct Scene $t_{25} = 5.790$, $p < 0.001$). Significantly less variance was also observed in the Imagine Objects task compared to the other tasks (Imagine 2D Grid $t_{25} = 5.812$, $p < 0.001$; Imagine 3D Grid $t_{25} = 4.837$, $p < 0.001$; Construct Array $t_{25} = 6.401$, $p < 0.001$; Construct Scene $t_{25} = 5.151$, $p < 0.001$). There was no difference between the Imagine Fixation and Imagine Objects tasks ($t_{25} = 2.053$, $p = 0.542$). Variance during the Imagine 2D Grid task was significantly less than during the Imagine 3D Grid task ($t_{25} = 3.633$, $p = 0.019$). No other significant between-task differences were observed, including between the Construct Scene and Construct Array tasks ($t_{25} = 1.897$, $p = 0.660$).

Taken together, these measures provide quantitative evidence that participants paid attention during the experiment and engaged in mental imagery construction in accordance with task instructions.

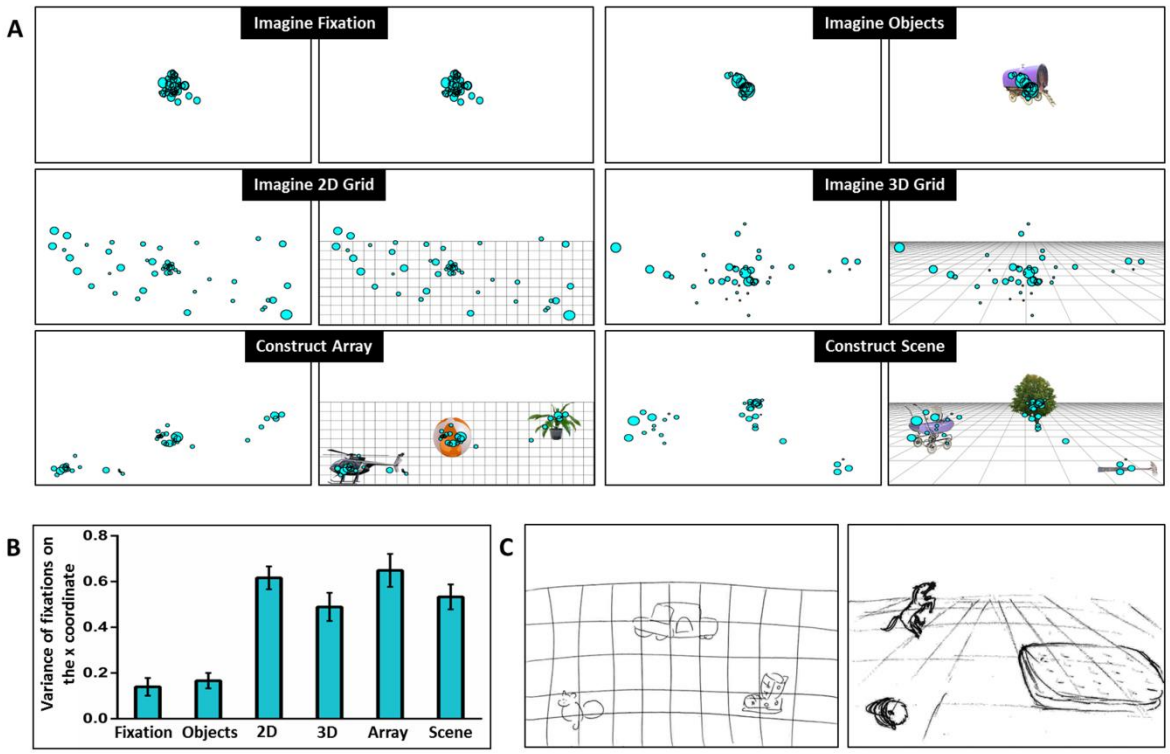

Figure 4. Eye movements and example of post-scan drawings.
(A) Representative examples of fixation locations (cyan circles) during the imagination phase of a single trial of each task are overlaid on a blank white screen on which participants focused their imagination (left panel). A visual representation of what participants were asked to imagine on the screen is shown to the right of each panel. Note the central focus of fixations for the Imagine Fixation and Imagine Objects tasks, the more dispersed pattern over the bottom 2/3 of the screen for the Imagine 2D Grid and Imagine 3D Grid tasks and the three clusters for both the Construct Array and Construct Scene tasks representing the locations of the imagined objects. (B) The mean variance (+/- 1 SEM) of fixations on the x coordinate during the imagination phase of each task is shown. (C) Representative examples of post-scan drawings for the Construct Array (left) and Construct Scene (right) tasks.

After scanning, we also asked participants to draw how they had imagined the arrays and scenes during the fMRI tasks. Examples are shown in Figure 4C and provide further evidence that participants complied with task requirements. The drawings also show that, despite both being composed of three objects related to a space, there was a clear representational difference between the arrays and the scenes. Further informative measures were obtained during a post-scan debriefing and these are described in following sections.

Was hippocampal recruitment related to mnemonic processing?

Once out of the scanner after completing the experiment, participants were given two surprise memory tests (see Experimental Procedures). Given the large number of stimuli, and the fact that there was no explicit instruction to encode information – rather the emphasis was on mental construction, and memory was never mentioned – our expectation was that performance would be poor, even at chance, on the memory tests. We felt it was necessary, however, to conduct these tests in case successful encoding differed across tasks, and this could have explained differences in the brain areas that were engaged. Scores (Means, SD) are shown in Table S2.

Participants first performed an item memory test, where they were auditorily presented with all 216 object descriptions heard during the Imagine Object, Construct Array and Construct Scene tasks (72 objects per task) and an additional 72 lure items which were not heard during the experiment. Object descriptions were randomised across tasks and were presented one at a time. For each object description participants were asked to respond 'yes' if they thought the object description was heard during the scanning experiment and 'no' if they thought it was not. Participants performed above chance at recalling stimuli that were from the Imagine Objects (t_{22} = 13.491, $p < 0.001$), Construct Array (t_{22} = 9.268, $p < 0.001$) and Construct Scene (t_{22} = 8.514, $p < 0.001$) tasks, and were above chance at identifying novel items (t_{22} = 13.710, $p < 0.001$). The good performance on this test (with task means between 70-83% correct – see Table S2) is another indication that the participants paid attention, encoded information and were engaged by the tasks.

A repeated measures ANOVA revealed a significant between-task effect on the item memory test ($F_{1.77, 38.98}$ = 9.524, $p < 0.001$). Post hoc analyses showed that participants were better at recognising object descriptions which were presented in the Imagine Objects task than objects presented in the Construct Array (t_{22} = 4.829, $p < 0.001$) and Construct Scene (t_{22} = 7.210, $p < 0.001$) tasks. Participants were also better at recognising novel items than objects presented in the Construct

Scene task (t_{22} = -3.382, p = 0.016). Notably, there was no significant difference between the Construct Array and Construct Scene tasks (t_{22} = 2.707, p = 0.075).

On the very challenging associative memory task, participants were auditorily presented with 72 sets of object triplets (24 sets from each of the Imagine Object, Construct Array and Construct Scene tasks). Forty eight of these object triplets (16 from each of the three tasks) had been presented together during the experiment (intact triplets). Twenty four of the object triplets (8 from each of the three tasks) contained object descriptions that were presented during the experiment, but not together in a triplet (recombined triplets). For each object triplet, participants were asked to respond 'yes' if they thought the objects were heard together during the fMRI experiment and 'no' if they were not (Table S2). As we expected, participants did not perform above chance on the recognition of intact triplets that were from the Imagine Objects (t_{22} = 0.368, p = 0.717), Construct Array (t_{22} = 1.177, p = 0.252) and Construct Scene (t_{22} = 0.682, p = 0.503) tasks. A repeated measures ANOVA showed that there were no significant differences between the tasks for either the recognition of intact object triplets ($F_{2,44}$ = 0.870, p = 0.426), or correct rejection of recombined object triplets ($F_{2,44}$ = 1.651, p = 0.204). This included no significant difference between Construct Array and Construct Scene tasks (intact triplets: t_{22} = 1.047, p = 0.667; recombined triplets: t_{22} = 1.124, p = 0.616).

Overall, these results revealed no significant differences in memory performance in particular between our two tasks of interest, Construct Array and Construct Scene. Therefore, the differences we observed in neural recruitment during fMRI cannot be accounted for by differences in encoding success.

Can imagery vividness account for hippocampal engagement?

During fMRI scanning, participants rated the vividness of mental imagery on each trial (see Experimental Procedures; Figure 1H; means (SDs) on Table S3). Results of the repeated measures ANOVA revealed a significant between-tasks difference in vividness ratings ($F_{2.70, 78.26} = 11.60$, $p < 0.001$). Post hoc analyses showed that mental imagery during the Imagine Objects task was rated as more vivid than during the Imagine Fixation ($t_{29} = 4.095$, $p = 0.005$), Imagine 2D Grid ($t_{29} = 5.586$, $p < 0.001$), Imagine 3D Grid ($t_{29} = 4.195$, $p = 0.004$), Construct Array ($t_{29} = 4.506$, $p < 0.001$) and Construct Scene ($t_{29} = 3.265$, $p = 0.041$) tasks. Imagery during the Construct Array task was rated significantly more vivid than during the Imagine 2D Grid task ($t_{29} = 3.398$, $p = 0.029$). Imagery during the Construct Scene task was rated significantly more vivid than during the Imagine 2D Grid ($t_{29} = 4.116$, $p = 0.004$) and Imagine 3D Grid ($t_{29} = 3.224$, $p = 0.046$) tasks. Importantly, no significant difference was observed between the Construct Array and Construct Scene tasks (t_{29} 2.116, $p = 0.483$).

Can perceived task difficulty or subjective differences in mental imagery account for hippocampal recruitment?

In the debriefing after scanning, and once the surprise memory tests were completed, participants were asked about their experience of performing each task (see Experimental Procedures and means (SDs) on Table S3). Participants reported that they could perform the tasks with ease with no between-task differences for perceived task difficulty ($F_{3.37,97.85} = 2.396$, $p = 0.066$; including no difference between the Construct Array and Construct Scene tasks, $t_{29} = 0.524$, $p = 1.00$). Significant between-task differences were observed for the rating of mind-wandering ($F_{3.46,100.39} = 3.638$, $p = 0.011$). Post hoc analyses showed that compared to the Imagine Objects task, participants were more prone to engage in mind-wandering during the Imagine Fixation ($t_{29} = 3.465$, $p = 0.025$) task. This makes sense considering the fixation task was included as a rest condition for participants. There was no significant difference between Construct Array and Construct Scene tasks ($t_{29} = 0.436$,

p = 1.00). Significant differences were also observed on the rating of detail of mental imagery ($F_{3.47, 100.70}$ = 3.510, p = 0.014). Post hoc analyses showed that mental imagery during the Construct Scene task was significantly more detailed than during the '2D Grid' task (t_{29} = 3.093, p = 0.043). No other significant between-task differences were observed, including between Construct Array and Construct Scene tasks (t_{29} = 1.884, p = 0.514).

Participants further confirmed that mental imagery during the Construct Scene task induced the subjective experience of 'seeing' a scene and the average success of participants ability to create a scene in their minds eye was rated 3.8 (SD = 0.84) on a 1-5 scale (5 = always successful). In contrast, participants reported a clear sense of imagining objects on a 2D grid during the Construct Array task and stated that they rarely felt a need to repress mental imagery of scenes during this task, rating an average of 1.3 (SD = 0.69) on a 1-5 scale (1 = never repressed). Direct comparison showed that, as expected, the Construct Scene task was rated as subjectively more 3D than the Construct Array task which was rated more 2D (t_{29} = 11.988, p < 0.001). There were no significant differences between the tasks (including between Construct Array and Construct Scenes tasks) on several other subjective measures: the creation of narratives about the stimuli ($F_{2.15,62.43}$ = 0.597, p = 0.565; Construct Array versus Construct Scene t_{29} = 1.00, p = 0.981), the fixedness of the viewpoint ($F_{1.96,56.75}$ = 0.139, p = 0.867; Construct Array versus Construct Scene t_{29} = 0.441, p = 0.999) and the inclusion of extraneous objects or other details ($F_{2,58}$ = 0.957, p = 0.390; Construct Array versus Construct Scene t_{29} = 1.055, p = 0.657).

In summary, subjective measures indicated that the participants performed the task with ease, and adhered to the instructions. As might be expected, there were some minor differences, for example increased mind-wandering during the Imagine Fixation task but, importantly, no significant differences between the Construct Array and Construct Scene tasks.

Results summary

The results of the fMRI analyses revealed that when other associative and mental constructive processes were taken into account, a specific region of the anterior medial hippocampus – corresponding to the location of the pre/parasubiculum – was engaged during scene construction along with other regions which have previously been linked to scene processing including the PHC, RSC and PCC. In contrast, array construction was more strongly associated with the ENT, PRC, posterior portions of EVC and activation within the left posterior and left ENT abutting the anterior medial hippocampus. Importantly, this latter activation was in a location more anterior to the cluster observed during scene construction. Interestingly, the Imagine Objects task resulted in activation of the anterior lateral hippocampus. The differing patterns of neural recruitment between the very tightly matched Construct Array and Construct Scene tasks could not be accounted for by differences in eye movements, mnemonic processing or the phenomenology of mental imagery.

Discussion

The aim of this study was to compare accounts that place associative processes at the heart of hippocampal function with the theory that proposes scene construction as its key role. Using closely matched tasks during high resolution fMRI we found that, as predicted, the pre/parasubiculum in the anterior medial hippocampus was preferentially engaged by the construction of scenes – consisting of three objects and a 3D space. However, it was also evident that different regions *within* the hippocampus were engaged by the construction of arrays that were comprised of three objects and 2D space that did not evoke scenes. In this case, the posterior hippocampus and an ENT region that abutted the anterior hippocampus were recruited. Even the imagination of object triplets that had no spatial context activated this latter region along with an anterior portion of the prosubiculum/CA1. Overall, these results show that one reason for the widescale disagreement about how the hippocampus operates may be because it does not only do 'space' or 'associations' or 'scenes'. Instead, there may be multiple processing circuits within the hippocampus that become

engaged depending on task demands. As such, there is evidence for each theory, and by recasting our view of the hippocampus from uni-functional to multi-functional, these disparate accounts of the hippocampus could be reconciled.

Our primary contrast of interest was scene construction compared with array construction. These tasks were very closely matched in terms of stimulus content and the mental constructive and associative processes required to perform the tasks. Attention, eye movements, encoding success and perceived difficulty also did not differ between them. Phenomenologically, the vividness and detail of their imagery was also matched. Nevertheless, in line with our prediction and previous reports, a circumscribed portion of the pre/parasubiculum in the anterior medial hippocampus was preferentially involved in scene construction (Zeidman and Maguire, 2016; Zeidman et al., 2015a; Zeidman et al., 2015b; Hodgetts et al., 2016; Maas et al., 2014). Importantly, our findings reveal for the first time that this region is preferentially recruited, not for mental construction per se, not for imagining a 3D space alone (see also Zeidman et al., 2012), but specifically for mental construction of scenes that are couched within a naturalistic 3D spatial framework. Drawing on the latest anatomical findings, Dalton and Maguire (2017) recently noted that the pre/parasubiculum is a primary target of the parieto-medial temporal processing pathway and may receive integrated information from foveal and peripheral visual inputs (Kravitz et al., 2011). Thus, it has privileged access to holistic representations of the environment and so could be neuroanatomically determined to preferentially process scenes. Indeed, Dalton and Maguire (2017) suggest the pre/parasubiculum is the hippocampal 'hub' for scene-based cognition. The PHC, RSC and PCC are also implicated in the anatomical scene processing network connecting with the pre/parasubiculum. Aligning with this evidence and their known links with scene processing (Epstein, 2008), these brain areas were more engaged during scene compared to array construction.

By contrast, array construction engaged a different set of brain areas, namely, the ENT, PRC and posterior portions of EVC with the left ENT/PRC cluster extending to abut the anterior medial hippocampus and the EVC cluster extending anteriorly along the lingual gyrus and into the left posterior hippocampus. Unlike the very circumscribed hippocampal engagement observed for scene construction, hippocampal activity elicited by array construction was not confined to the hippocampus. In the anterior, where the activity involved the ENT and abutted the hippocampus, the location bordered the pre/parasubiculum much more anteriorly than that for scene construction. Therefore, naturalistic 3D scene representations may engage a circumscribed portion of the anterior pre/parasubiculum in unison with the PHC and RSC/PCC. By contrast, more general or abstracted forms of spatial imagery, such as objects in a 2D space (see also Constantinescu et al., 2016), might recruit an anterior portion of the ENT abutting the very anterior pre/parasubiculum closely linked with the PRC. The different parts of the hippocampus and distinct cortical regions engaged by scenes and arrays (and also the object triplets), despite the close matching of the tasks, precludes the view that scenes are merely being enabled by processing sets of associations similar to those underpinning array construction. What we document here are separable mental construction processes giving rise to distinct types of representation in and around the hippocampus.

Considering the posterior hippocampal activation during array construction, this area has been implicated in a broad range of cognitive processes (Strange et al., 2014; Poppenk et al., 2013; Zeidman and Maguire, 2016), including spatial memory (Maguire et al., 2006; Moser and Moser, 1998) and paired associates learning using an object-location paradigm that required mnemonic processing of objects in a 2D space (de Rover et al., 2011). While our results reflect involvement of the posterior hippocampus in mental imagery of objects in a 2D rather than 3D space, it is unlikely that the posterior hippocampus is only involved in this form of mental imagery. The activation associated with array construction was located in the posterior most tip of the left hippocampus which, as noted by Dalton et al. (2017) may be predominantly composed of posterior portions of

CA1. However, the anatomy of the most posterior portion of hippocampus in humans is complex, with much still to learn. Ultra-high resolution MRI investigations at the level of subfields are required to further inform our understanding of posterior hippocampal contributions to specific cognitive processes.

On each trial in the Construct Objects task, participants had to imagine three objects, one at a time, in the centre of the screen. This task was not designed to be a close match for the array and scene tasks, but rather was included to inform about the brain areas engaged during object only associations and object construction, where spatial context was irrelevant. Of note, memory for the objects in this task was significantly better than those in the array and scene construction tasks, as was the vividness of the imagery. Therefore, any fMRI results should be interpreted with this is mind. PRC recruitment during the construction of object imagery would be predicted, and indeed was found, considering the strong association between the PRC and object-centred cognition (Murray et al., 2007). Overall, the objects task engaged very similar areas to those recruited for array construction, namely, the PRC, ENT abutting the very anterior medial left hippocampus. This may reflect a generic area for non-scene based associative processing. Where object construction differed from both array and scene tasks was in the activation of the right anterior lateral hippocampus in the region that aligns with the location of the prosubiculum/CA1. This finding is concordant with the prediction of Dalton and Maguire (2017), based on the known neuroanatomy, where PRC, ENT and prosubiculum/CA1 are heavily interconnected (Li et al., 2017; Insausti and Munoz, 2001). Therefore, as with the array and scene construction tasks, the mental construction of isolated objects engaged a differentiable portion of the hippocampus.

Our results show that for associations between objects, between objects and 2D space or objects and 3D space, the hippocampus does not seem to favour one type of representation over another; it is not a story of exclusivity. Rather, there may be different circuits within the hippocampus, each

associated with different cortical inputs, which become engaged depending on the nature of the stimuli and the task at hand. This may explain why it has been so difficult to reconcile hippocampal theories that have focused on one type of process or representation to the exclusion of others. Our results may also explain why disparate patterns of preservation and impairment are reported in patients with bilateral hippocampal lesions. For any individual, damage may affect particular subregions within the hippocampus moreso than others. These subtle case-by-case differences in the microscopic topography of damage and sparing may impact on cognition in different ways yet remain undetectable by current MRI technology.

While some theoretical accounts have posited that distinct areas within the medial temporal lobe may preferentially process specific types of representation (Graham et al., 2010; Barense et al., 2005), perhaps surprisingly, such representational differences have not typically been extended to processing *within* the hippocampus. Of course the hippocampus has long been known to have different subfields, and in recent years possible functional differentiation down the long axis of the hippocampus has received increasing attention (reviewed in Poppenk et al., 2013; Nadel et al., 2013; Strange et al., 2014; Zeidman and Maguire, 2016) as have subfield specific hypotheses relating to proposed theories of pattern separation and completion (Guzman et al., 2016; Berron et al., 2017). In addition, non-human primate tract tracing studies have shown clear differences in how different cortical and subcortical brain regions send direct innervations not only to specific hippocampal subfields (Ding et al., 2000; Rockland and Van Hoesen, 1999; DeVito, 1980) but also disproportionately interact with specific portions of subfields along the longitudinal (anterior–posterior) and transverse (distal–proximal) axes of the hippocampus (Insausti and Munoz, 2001). Despite this, however, at a conceptual level, the neuroimaging and neuropsychological literatures are still dominated and influenced by a mono-functional perception of the hippocampus which, in light of the results reported here, may be inaccurate and could continue to impede the field's progress.

Future work is needed to precisely characterise the different information processing streams within the human hippocampus, both anatomically and functionally. Presumably these circuits are linked, but how and to what extent will also be important questions to address. In humans, little is known about intrahippocampal functional connectivity or even connectivity between hippocampal subfields and the rest of the brain. Here we used high resolution (f)MRI which allowed us to identify specific subregions within the hippocampus. However, to progress further, the use of ultra-high resolution (f)MRI is clearly warranted to help move us beyond an 'either/or' view of the hippocampus to a more nuanced understanding of its multifaceted contributions to cognition.

Experimental Procedures

Participants

Thirty healthy, right handed participants took part in the study (20 females, mean age 24 years, SD 4.12). All had normal or corrected to normal vision and gave written informed consent to participate in accordance with the University College London research ethics committee.

Tasks and Procedure

Each participant visited on two separate days. Visit 1 consisted of acquisition of structural brain images (see Supplemental Experimental Procedures). Visit 2 comprised the fMRI experiment. On arrival for visit 2, participants engaged in a pre-scan training and practice period which lasted approximately two hours, where each task were explained in detail (see Supplemental Experimental Procedures) and visual examples of how to imagine during each task, similar to those illustrated in Figure 1A-F, were presented.

Each trial of the experiment (Figure 1H) was comprised of a visual cue (2 seconds) which informed of the task, followed by jitter (1 - 4 seconds) and then the imagination phase of ~15 seconds. During the imagination phase, participants engaged in the mental imagery pertinent to a task while hearing three auditory phrases (either objects or nonsense, depending on the task, Figure 1G) delivered via MR compatible headphones (Sensimetrics model S14). The length of each auditory phrase was approximately 2s followed by a 1s gap between the presentation of each phrase. After hearing the third auditory phrase, participants had approximately 7s to finalise and maintain the mental image they had created. They were required to do this with their eyes open while looking at a blank white screen. They then rated the vividness of their mental image on a 1 (not vivid at all) - 5 (extremely vivid) scale (max 2 seconds). Finally, an inter-trial interval of 2 seconds preceded the cue for the next trial. Twenty four trials were presented for each task (144 trials in total) in a pseudo-randomised order across 4 separate blocks. Each block lasted approximately 15 minutes and blocks were separated by a brief rest period. It was emphasised that the main objective of the experiment was to create vivid mental images. However, to ensure participant attentiveness, they had to press a button if an auditorily presented phrase was repeated - an additional 12 such catch trials (2 per task) were included across the experiment.

Stimuli

All object descriptions and nonsense phrases were three words in length and matched across tasks for syllable number and utterance length. The number of space defining (SD) and space ambiguous (SA) objects (Mullally and Maguire, 2013) were matched across the Imagine Objects, Construct Array and Construct Scene tasks, and the order of presentation of SD/SA items was balanced across all trials. The permanence of objects (whether it is likely to be fixed in location or not; Auger et al., 2012) was also matched across tasks. In addition, object triplets were arranged so that objects within each triplet had no obvious semantic or contextual associations. See the Supplemental Experimental Procedures for further details about the stimuli.

In-scan eyetracking

Eyetracking data were acquired using an Eyelink 1000 Plus (SR Research) eyetracker. The right eye was used for calibration, recording and analyses. During the imagination phase the x and y coordinate of all fixations were recorded. We calculated the variance of all fixation locations in the horizontal axis. Visualisation of fixation locations was performed with Eyelink Data Viewer (SR Research). Eyetracking data from 4 participants were unavailable due to technical issues.

Post-scan surprise memory tests

After leaving the scanner, participants were taken to a testing room and given surprise item and associative yes/no recognition memory tasks, as described above in the main text. Participants also gave a confidence rating on a 1-5 scale for each decision. For both memory tasks timing was self-paced (up to a maximum of 5 seconds) for both the choices and confidence ratings. Note that we do not include the data from the confidence ratings from the associative memory test as they were, perhaps unsurprisingly, dominated by 'guessing' ratings. Memory test data from 7 participants were unavailable due to technical issues.

Post-scan debriefing

Following the memory tests, participants were probed on how they approached each task, and performed a number of ratings as described in the Results section and Table S3.

Behavioural data analyses

Data from eyetracking, in-scan vividness ratings, post-scan memory tests and debrief ratings were analysed using repeated measures ANOVAs (SPSS 17.0, Chicago: SPSS inc.) with a significance threshold of $p < 0.05$ and Sidak corrected post hoc analyses. Where Mauchly's test indicated that the

assumption of sphericity had been violated, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity.

fMRI data acquisition and analyses

Structural and functional MRI data acquisition, preprocessing and analyses are described in the Supplemental Information. fMRI data were analysed using multivariate task Partial Least Squares (PLS) analyses (Krishnan et al., 2011; McIntosh & Lobaugh, 2004).

Supplemental Information

Includes 3 tables and Supplemental Experimental Procedures.

Author contributions

M.A.D., P.Z. and E.A.M. designed the study; M.A.D. conducted the experiment; M.A.D. analysed the data with input from P.Z., C.M. and E.A.M.; E.A.M. and M.A.D. wrote the paper with input from P.Z. and C.M. All authors approved the submission of the final manuscript.

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Supplemental Data

Table S1. Results of the fMRI task comparisons, related to Figure 2 and Figure 3

	Contrast	*Brain Regions*	*Hemisphere (L/R)*	*MNI peak coordinate*			*BSR*	*Number of voxels*
Construct scene	***Construct Scene* > *Construct Array* (p = 0.004)**	Anterior medial hippocampus – pre/parasubiculum	R	22.5	-24	-16.5	3.7655	56
		Anterior calcarine sulcus (encompassing anterior lingual gyrus / posterior cingulate cortex / retrosplenial cortex / inferior precuneus)	L	-10.5	-51	6	3.3724	81
		Anterior calcarine sulcus (encompassing anterior lingual gyrus / posterior cingulate cortex / retrosplenial cortex / inferior precuneus)	R	9.0	-55.5	12.0	3.2213	102
		Posterior PHC	R	28.5	-43.5	-10.5	2.8698	36
		Anterior medial hippocampus – pre/parasubiculum	L	-21.0	-21.0	-19.5	2.8138	45
		Posterior fusiform cortex	R	28.5	-33.0	-18.0	2.4450	20
	***Construct Scene* > *Imagine Objects* (p = 0.015)**	Anterior lingual gyrus (encompassing inferior precuneus / posterior cingulate cortex / retrosplenial cortex and extending posteriorly to encompass posterior lingual gyrus / posterior calcarine sulcus)	R / L	10.5	-55.5	7.5	4.8465	3041
		Posterior PHC	L	-30.0	-42.0	-10.5	4.0339	249
		Posterior hippocampus	R	18.0	-37.5	1.5	3.9468	55
		Posterior PHC (extending anteriorly to encompassing anterior medial hippocampus – pre/parasubiculum)	R	28.5	-42.0	-12.0	3.7299	360
		Anterior PHC (perirhinal cortex)	L	-33.0	-24.0	-34.5	3.6459	29
		Retrosplenial cortex / posterior cingulate cortex	L	-7.5	-39.0	6.0	3.0623	16
		Anterior medial hippocampus – pre/parasubiculum	L	-25.5	-24.0	-16.5	2.9320	52
		Posterior fusiform cortex	R	21.0	-60.0	-12.0	2.2978	14
	***Construct Scene* > *Imagine 3D Grid* (p = 0.005)**	Anterior lingual gyrus (encompassing anterior calcarine sulcus / inferior precuneus / posterior cingulate cortex / retrosplenial cortex)	R	9	-54	9	6.0388	341
		Inferior precuneus (encompassing posterior cingulate cortex / retrosplenial cortex / anterior calcarine sulcus / anterior lingual gyrus)	L	-4.5	-55.5	10.5	5.7412	314

		Posterior PHC	L	-24	-37.5	-19.5	5.5618	723
		Posterior PHC	R	25.5	-34.5	-21	4.6426	488
		Anterior PHC (perirhinal cortex)	L	-31.5	-6	-36	3.6334	89
		Anterior medial hippocampus – uncus	L	-12	-9	-25.5	3.3703	10
		Anterior PHC (perirhinal cortex)	R	30	-3	-40.5	3.3075	110
		Anterior medial hippocampus – uncus	R	22.5	-7.5	-25.5	2.6372	26
Construct array	***Construct Array* > *Construct Scene* (p = 0.004)**	Anterior lingual gyrus (extending anteriorly to encompass posterior hippocampus and extending posteriorly to encompass posterior lingual gyrus / posterior calcarine sulcus)	L / R	-16.5	-51.0	-4.5	4.9728	3479
		Anterior PHC (perirhinal cortex / entorhinal cortex)	L	-28.5	-1.5	-39.0	3.8068	181
		Anterior PHC (perirhinal cortex / entorhinal cortex)	R	28.5	3.0	-43.5	3.6093	440
		Anterior PHC (Entorhinal cortex / abutting the anterior medial hippocampus)	L	-19.5	-12.0	-27.0	3.1719	119
		Anterior PHC (Entorhinal cortex)	L	-19.5	4.5	-36.0	2.7904	27
		Anterior lingual gyrus	R	4.5	-63.0	4.5	2.5501	10
	***Construct Array* > *Imagine Objects* (p = 0.005)**	Posterior calcarine sulcus (encompassing posterior lingual gyrus extending anteriorly to encompass anterior lingual gyrus / posterior PHC / posterior hippocampus)	R / L	10.5	-81.0	4.5	6.4355	6992
		Anterior PHC (perirhinal cortex)	R	24.0	1.5	-39.0	3.6467	47
		Posterior PHC	R	34.5	-36.0	-13.5	2.4383	10
		Anterior PHC (entorhinal cortex)	L	-21.0	-16.5	-30.0	2.3777	16
		Anterior PHC (perirhinal cortex)	L	-28.5	-4.5	-37.5	2.3342	17
		Middle lateral hippocampus – CA1	L	-34.5	-25.5	-16.5	2.3212	15
	***Construct Array* > *Imagine 2D Grid* (p < 0.001)**	Posterior PHC (extending anteriorly to encompass entorhinal cortex / perirhinal cortex)	L	-30	-27	-24	5.3247	1014
		Posterior PHC (extending anteriorly to encompass entorhinal cortex / perirhinal cortex)	R	31.5	-24	-22.5	4.5307	522
		Inferior precuneus (encompassing anterior calcarine sulcus / posterior cingulate cortex / retrosplenial cortex / posterior hippocampus)	L	-6	-52.5	12	4.1098	488
		Posterior hippocampus (encompassing inferior precuneus / posterior cingulate cortex / retrosplenial cortex)	R	15	-39	3	4.0605	279
		Anterior PHC (perirhinal cortex)	R	22.5	0	-49.5	3.3109	73
		Anterior lingual gyrus	L	-24	-54	-3	2.7134	21
Imagine objects	***Imagine Objects* > *Construct Scene* (p = 0.015)**	Anterior PHC (entorhinal cortex / perirhinal cortex)	R	21.0	-9.0	-33.0	3.4047	241
		Anterior lateral hippocampus – CA1	R	33.0	-10.5	-27.0	3.3312	11
		Anterior PHC (perirhinal cortex)	L	-25.5	-3.0	-39.0	3.2742	34
		Anterior PHC (entorhinal cortex / abutting the anterior	L	-18.0	-10.5	-27.0	3.2310	126

		medial hippocampus)						
	***Imagine Objects* > *Construct Array* (p = 0.005)**	Anterior lateral hippocampus – CA1	R	30.0	-13.5	-21.0	3.0863	42
Imagine 3D grid	***Imagine 3D Grid* > *Construct Scene* (p = 0.005)**	Posterior lingual gyrus (encompassing posterior calcarine sulcus extending anteriorly to anterior lingual gyrus)	L / R	-10.5	-78	-10.5	5.2507	3088
		Posterior fusiform cortex	R	27	-55.5	-18	3.4263	33
		Anterior calcarine sulcus	L	-22.5	-66	9	3.3149	24
		Anterior lingual gyrus	R	27	-52.5	-6	3.1481	134
		Anterior lingual gyrus	L	-22.5	-45	-1.5	3.102	14
		Anterior lingual gyrus	L	-33	-54	-6	3.0345	13
		Anterior PHC (entorhinal cortex)	R	15	-6	-31.5	2.8463	73
		Anterior PHC (entorhinal cortex)	L	-18	-4.5	-31.5	2.4347	27
	***Imagine 3D Grid* > *Imagine 2D Grid* (p = 0.191)**	**No significant between-task differences**	-	-	-	-	-	-
Imagine 2D grid	***Imagine 2D Grid* > *Construct Array* (p < 0.001)**	Posterior lingual gyrus (encompassing posterior calcarine sulcus extending anteriorly to anterior lingual gyrus / anterior calcarine sulcus)	L / R	-16.5	-72	-10.5	5.38	2134
		Anterior calcarine sulcus	R	22.5	-61.5	10.5	3.9023	45
		Posterior calcarine sulcus		0	-90	-4.5	3.4177	20
		Anterior hippocampus	R	28.5	-19.5	-15	2.6862	36
		Anterior lingual gyrus	R	24	-46.5	-10.5	2.6018	27
		Anterior calcarine sulcus	L	-21	-66	6	2.3526	22
	***Imagine 2D Grid* > *Imagine 3D grid* (p = 0.191)**	**No significant between-task differences**	-	-	-	-	-	-

PHC = parahippocampal cortex; L = Left; R = Right; BSR = Boot Strap Ratio (reliability of voxel saliences); BSR > 1.96 = $p < 0.05$; > 2.58 = $p < 0.01$; > 3.29 = $p < 0.001$. Note that *p* values in the 'Contrast' column relate to condition differences following permutation testing of the latent variables.

Table S2. Item and associative memory test performance (% correct), related to the Results section.

Task	Mean ± standard deviation
Item memory	
Imagine Object	82.85 ± 11.68
Construct Array	76.03 ± 13.47
Construct Scene	71.07 ± 11.87
Identifying Novel Items	81.94 ± 11.17
Associative memory intact triplets	
Imagine Object	51.09 ± 14.18
Construct Array	55.16 ± 21.04
Construct Scene	51.90 ± 13.38
Associative memory recombined triplets	
Imagine Object	46.20 ± 17.45
Construct Array	54.35 ± 19.44
Construct Scene	48.91 ± 19.91

Table S3. Subjective measures, related to the Results section.

Question	Rating (Yes/No or 1-5 Likert scale)		Task	Mean ± SD
How vivid was your imagination of the xxxx?	1 = not vivid at all …	…5 = extremely vivid	Imagine Fixation Imagine Object Imagine 2D grid Imagine 3D grid Construct Array Construct Scene	3.77 ± 0.65 4.16 ± 0.53 3.69 ± 0.62 3.84 ± 0.57 3.96 ± 0.52 4.03 ± 0.53
How difficult was it to imagine the xxxx?	1 = very easy…	…5 = very difficult	Imagine Fixation Imagine Object Imagine 2D grid Imagine 3D grid Construct Array Construct Scene	2.58 ± 1.22 2.01 ± 0.75 2.65 ± 1.09 2.13 ± 0.88 2.35 ± 0.76 2.43 ± 0.85
How often did you engage in off-task thoughts (mind-wander) during this task?	1 = never…	…5 = always	Imagine Fixation Imagine Object Imagine 2D grid Imagine 3D grid Construct Array Construct Scene	2.22 ± 0.80 1.77 ± 0.57 2.30 ± 0.99 1.87 ± 0.67 1.88 ± 0.65 1.95 ± 0.83
In general, how detailed do you think your images of the xxxx were?	1 = Hardly any details at all…	…5 = Extremely richly detailed	Imagine Object Imagine 2D grid Imagine 3D grid Construct Array Construct Scene	3.27 ± 0.45 2.97 ± 0.81 3.22 ± 0.67 3.27 ± 0.69 3.45 ± 0.62
In general, did you feel that you successfully imagined the objects in a scene?	1 = never successful. . .	. . .5 = always successful	Construct Scene	3.77 ± 0.84
Did you feel that you imagined the objects in a scene at all and try to repress this?	1 = never repressed. . .	. . .5 = always repressed	Construct Array	1.28 ± 0.69
On a scale of 1-5, how 2D/3D was your mental imagery during this task?	1 = completely 2D. . .	. . .5 = completely 3D	Construct Array Construct Scene	1.90 ± 0.84 4.10 ± 0.82

Did you make up any stories or scenarios related to the xxxx?	0 = No 1 = Yes		Imagine Object Imagine 2D grid Imagine 3D grid Construct Array Construct Scene	0.02 ± 0.09 0.07 ± 0.25 0.02 ± 0.09 0.03 ± 0.18 0.07 ± 0.25
Did you keep your viewpoint fixed?	0 = No 1 = Yes		Imagine 2D grid Imagine 3D grid Construct Array Construct Scene	0.98 ± 0.09 0.97 ± 0.18 0.97 ± 0.18 0.98 ± 0.09
To what extent did you imagine other objects or details in addition to the given objects? Did you. . . ?	1 = think of objects with other details the entire time. . .	. . . 5 = not think of other objects or details at all	Imagine Object Construct Array Construct Scene	4.07 ± 0.83 4.23 ± 0.73 4.08 ± 0.77

Supplemental Experimental Procedures

Participants engaged in four practice trials of each task while sitting at a desktop computer in a darkened room. They rated the vividness of mental imagery for each trial on a scale of 1-5. If they gave a rating of 3 or below on any practice trial, they repeated the practice session. When participants rated 4 or above on all practice trials and indicated that they could vividly engage in the mental imagery relevant to each task, they were transferred to the scanner for the experiment.

Imagine Fixation

Participants were asked to create a mental image of a black 'plus' sign in the centre of the blank white screen (Figure 1A). While imagining the plus sign, participants were auditorily presented with three nonsense phrases, spoken one at a time (see Figure 1G for examples). This task was included as a 'rest' task to give participants respite from the more challenging imagery tasks described below.

Imagine Objects

Participants were instructed, when hearing the first object description, to imagine the object alone in the centre of the blank white screen (Figure 1B). When hearing the second object description, they were asked to imagine the second object in place of the first in the centre of the screen and when hearing the third object description, to imagine it in place of the second object. During pre-scan training, participants were instructed and trained to imagine each object in complete isolation.

Imagine 2D Grid and Imagine 3D Grid

Participants were asked to create a mental image of a regular, flat 2D grid covering roughly the bottom 2/3 of the blank screen (Figure 1C). For the Imagine 3D Grid task, participants were asked to create a mental image of a 3D grid covering roughly the bottom 2/3 of the blank screen (see Figure 1D). The important difference between these tasks is that the 3D grid induces a sense of depth and 3D space. While imagining the grids, participants were auditorily presented with three nonsense phrases, spoken one at a time (Figure 1G for examples).

Construct Array

Participants were instructed to first imagine the 2D grid on the bottom 2/3 of the screen. While doing this, participants were auditorily presented with three object descriptions one after another which they imagined on the 2D grid. More specifically, participants were asked, when hearing the first object description, to imagine the object in an arbitrary location on the 2D grid. When hearing the second object description, participants were asked to imagine it on another arbitrarily chosen location on the 2D grid while maintaining the image of the first object in its original location. When hearing the third object description, participants were asked to imagine it on another part of the 2D grid while maintaining the image of the first two objects in their original positions. We explicitly told participants that the final product of their mental imagery was to be three objects in random locations on a flat 2D grid (Figure 1E).

Construct Scene

Participants were instructed to first imagine a 3D grid on the bottom 2/3 of the screen. While doing this, they were auditorily presented with three object descriptions one at a time which they were asked to imagine on the imagined 3D grid. Specifically, participants were asked, when hearing the first object description, to imagine the object in any location on the 3D grid. When hearing the second object description, participants were asked to imagine it on another location on the 3D grid while maintaining the image of the first object in its original position. When hearing the third object description, participants were asked to imagine it on another part of the 3D grid while maintaining the image of the first two objects in their original locations. The final product of their mental imagery was to be 3 objects in a simple scene (Figure 1F).

Additional task instructions

For all tasks which required object imagery, we emphasised the importance of engaging imagination rather than memory for each object. We asked participants to imagine a unique version of each object based on the descriptions alone and, as far as possible, not to recall specific objects that they are familiar with, any personal memories involving the objects or any places that they might associate with the described objects. We also asked participants not to imagine any movement, even if objects had movable parts, but to create static images of each object in their mind's eye.

For the Imagine 2D Grid and Imagine 3D Grid tasks, participants were instructed to keep their 'viewpoint' of the grid fixed and static and not to imagine either the grid moving or themselves moving along the grid. In

contrast to the 2D grid, mental imagery of the 3D grid induces a sense of depth and participants were additionally asked not to imagine moving 'into' the 3D space in anyway.

For the Construct Array and Construct Scene tasks, participants were asked that for each trial, they keep the objects completely separate from each other so that no objects physically touched and no objects interacted. We asked participants not to add any additional elements but to create the arrays and scenes using only the objects presented to them. Participants were asked to utilise the full extent of the grids to place the objects and to continue imagining the objects on the grids for the duration of the imagination period. Also, having imagined all three objects on the grid, participants were asked not to mentally 'rearrange' the objects. Rather, they were asked to leave them where they were initially placed in their mind's eye. We asked participants to keep their viewpoint fixed and central and not to imagine themselves or any objects moving in any way. For the Construct Array task, we emphasised the importance of not linking the objects together into some sort of a scene but to arbitrarily place the objects in random locations.

Additional information about the object descriptions

Previous research suggests that during mental imagery of scenes, three objects appear to be the minimum required to illicit both the subjective feeling of a scene and the point at which the hippocampus is recruited when mentally constructing scenes (Mullally and Maguire, 2013; Summerfield et al., 2010). We therefore presented three objects per trial. We recorded separate audio files for each object description and nonsense phrase. These were recorded in a sound proof room and spoken by a male voice in an even tone.

We kept specific qualities of the object descriptions and nonsense phrases consistent across tasks. Prior to the experiment, a separate group of participants (n = 10) rated each object description on whether it was space defining (SD) or space ambiguous (SA) (see Mullally and Maguire, 2013) and also for ratings of object permanence (Auger et al., 2012; Mullally and Maguire, 2011). A subset of 50 object descriptions and 50 nonsense phrases were further rated for imageability.

In relation to the object descriptions, the Imagine Objects, Construct Array and Construct Scene tasks were matched according to the number of SD and SA objects ($F_{2,215} = 0.128$, $p = 0.880$), ratings of object permanence ($F_{2,215} = 0.106$, $p = 0.899$), syllable number ($F_{2,215} = 0.234$, $p = 0.792$) and utterance length ($F_{2,215} = 0.014$, $p = 0.986$). In addition, the order of presentation of SD/SA items was balanced across all trials. For each object triplet, we grouped objects together that had no obvious semantic associations.

In relation to nonsense phrases, syllable number ($F_{2,215} = 1.953$, $p = 0.144$) and utterance length ($F_{2,215} = 0.591$, $p = 0.555$) were matched across the Imagine Fixation, Imagine 2D Grid and Imagine 3D Grid tasks. In addition, syllable number ($F_{5,431} = 0.925$, $p = 0.464$) and utterance length ($F_{5,431} = 0.658$, $p = 0.656$) were matched across all tasks, and the nonsense phrases were rated as significantly less imageable than the object descriptions ($t_{1,49} = 81.261$, $p < 0.001$).

MRI

Data acquisition and preprocessing

Structural and functional MRI data were acquired using a 3T Siemens Trio scanner (Siemens, Erlangen, Germany) with a 32-channel head coil within a partial volume centred on the temporal lobe and included the entire extent of the temporal lobe and all of our other regions of interest.

Structural images were collected using a single-slab 3D T2-weighted turbo spin echo sequence with variable flip angles (SPACE) (Mugler 3rd et al., 2000) in combination with parallel imaging, to simultaneously achieve a high image resolution of ~500 μm, high sampling efficiency and short scan time while maintaining a sufficient signal-to-noise ratio (SNR). After excitation of a single axial slab the image was read out with the following parameters: resolution = 0.52 x 0.52 x 0.5 mm^3, matrix = 384 x 328, partitions = 104, partition thickness = 0.5 mm, partition oversampling = 15.4%, field of view = 200 x 171 mm 2, TE = 353 ms, TR = 3200 ms, GRAPPA x 2 in phase-encoding (PE) direction, bandwidth = 434 Hz/pixel, echo spacing = 4.98 ms, turbo factor in PE direction = 177, echo train duration = 881, averages = 1.9. For reduction of signal bias due to, for example, spatial variation in coil sensitivity profiles, the images were normalized using a prescan, and a weak intensity filter was applied as implemented by the scanner's manufacturer. To improve the SNR of the anatomical image, three scans were acquired for each participant, coregistered and averaged. Additionally, a whole brain 3D FLASH structural scan was acquired with a resolution of 1 x 1 x 1 mm.

Functional data were acquired using a 3D echo planar imaging (EPI) sequence which has been demonstrated to yield improved BOLD sensitivity compared to 2D EPI acquisitions (Lutti et al., 2013). Image resolution was 1.5mm^3 isotropic and the field-of-view was 192mm in-plane. Forty slices were acquired with 20% oversampling to avoid wrap-around artefacts due to imperfect slab excitation profile. The echo time (TE) was 37.30 ms and the volume repetition time (TR) was 3.65s. Parallel imaging with GRAPPA image reconstruction (Griswold et al., 2002) acceleration factor 2 along the phase-encoding direction was used to minimise image distortions and yield optimal BOLD sensitivity. The dummy volumes necessary to reach steady state and the GRAPPA reconstruction kernel were acquired prior to the acquisition of the image data as described in Lutti et al. (2013). Correction of the distortions in the EPI images was implemented using B0-field maps obtained from double-echo FLASH acquisitions (matrix size 64x64; 64 slices; spatial resolution 3mm^3; short TE=10 ms; long TE=12.46 ms; TR=1020 ms) and processed using the FieldMap toolbox in SPM (Hutton et al., 2002).

Preprocessing of structural and fMRI data was conducted using SPM12 (www.fil.ion.ac.uk/spm). All images were first bias corrected, to compensate for image inhomogeneity associated with the 32 channel head coil (Van Leemput et al., 1999). Fieldmaps were collected and used to generate voxel displacement maps. EPIs for each session were then realigned to the first image and unwarped using the voxel displacement maps calculated above. The three high-resolution structural images were averaged to reduce noise, and co-registered to the whole brain structural FLASH scan. EPIs were also co-registered to the whole brain structural scan and spatially smoothed using a Gaussian smoothing kernel of 4 x 4 x 4 mm full-width at half maximum.

Data analysis

We used a large region of interest that included the whole medial temporal lobe – hippocampus, PRC, ENT, as well as PHC, RSC and PCC which have been implicated in scene processing. The mask also extended posteriorly to encompass regions of the early visual cortices (EVC) including the precuneus (only inferior portions due to the partial volume), the calcarine sulcus, the lingual gyrus and portions of the posterior fusiform cortex, given these regions have previously been implicated in different elements of mental imagery (de Gelder et al., 2016; Lambert et al., 2002; Klein et al., 2000).

We used non-rotated task Partial Least Squares (PLS) for data analysis which is a multivariate method for extracting distributed signal changes related to varying task demands. Data for each of our tasks were included in a block design analysis and we conducted separate analyses for each of our contrasts of interest. Significance for each contrast was independently determined using a permutation test with 1000 permutations. We considered latent variables under $p = 0.05$ as significant. The reliability of voxel saliences was assessed by means of a bootstrap estimation of the standard error (McIntosh and Lobaugh, 2004). Bootstrapping is a sampling technique in which subjects are randomly selected into the analysis with replacement from the entire group of subjects. For each new sample, the entire PLS analysis is re-calculated. In the present study, this sampling and analysis procedure was carried out 500 times, resulting in estimates of the standard error of the salience at each voxel. No corrections for multiple comparisons are necessary because the voxel saliences are calculated in a single mathematical step on the whole volume. We considered clusters of 10 or more voxels in which the bootstrap ratio was greater than 1.96 (approximately equivalent to $p < 0.05$) to represent reliable voxels. In the current analyses, we specified a 14.6 second temporal window for each event (i.e. 4 TRs) to include the active phase of mental construction. Importantly, for each significant contrast reported in the main text, confidence intervals did not cross the 0 line suggesting that each condition contributed to the pattern.

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