

RESEARCH ARTICLE

The medial temporal lobe functional connectivity patterns associated with forming different mental representations

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Abstract

The medial temporal lobes (MTL), and more specifically the hippocampus, are critical for forming mental representations of past experiences—autobiographical memories—and for forming other “nonexperienced” types of mental representations, such as imagined scenarios. How the MTL coordinate with other brain areas to create these different types of representations is not well understood. To address this issue, we performed a task-based functional connectivity analysis on a previously published dataset in which fMRI data were collected as participants created different types of mental representations under three conditions. One condition required forming and relating together details from a past event (autobiographical task), another required forming and relating together details of a spatial context (spatial task) and another condition required relating together conceptual/perceptual features of an object (conceptual task). We contrasted the connectivity patterns associated with a functionally defined region in the parahippocampal cortex (PHC) and anatomically defined anterior and posterior hippocampal segments across these tasks. Examining PHC connectivity patterns revealed that the PHC seed was distinctly connected to other MTL structures during the autobiographical task, to posterior parietal regions during the spatial task and to a distributed network of regions for the conceptual task. Examining hippocampal connectivity patterns revealed that the anterior hippocampus was preferentially connected to regions of default mode network during the autobiographical task and to areas implicated in semantic processing for the conceptual task whereas the posterior hippocampus was preferentially connected to medial-posterior regions of the brain during the spatial task. We interpret our findings as evidence that there are MTL-guided networks for forming distinct types of mental representations that align with functional distinctions within the hippocampus.

KEYWORDS

autobiographical memory, episodic memory, medial temporal lobes, relational retrieval

1 | INTRODUCTION

A traditional view of hippocampal and greater medial temporal lobes (MTL) functions is one that is exclusive to memory (Scoville & Milner, 1957), however it is now accepted that these structures are involved in a number of other cognitive tasks (Addis & Schacter, 2011; Moscovitch, Cabeza, Winocur, & Nadel, 2016; Olsen, Moses, Riggs, & Ryan, 2012; Schiller et al., 2015; Sheldon & Levine, 2016). Studies have reported that the MTL is actively involved in autobiographical memory retrieval (Ryan et al., 2001; Viard et al., 2007), scene construction (Maguire & Mullally, 2013), integrating perceptual features (Lee, Yeung, & Barense, 2012), and imagination tasks (Addis, Wong, & Schacter, 2008). One interpretation of the common involvement of the MTL in

these activities is that they all require forming relations among retrieved information to construct complex mental representations (Cohen et al., 1999; Eichenbaum, 2001). This leads to the question: How does the MTL coordinate brain activity for forming such diverse forms of mental representations? To address this question, we investigated whether the MTL interacts with neocortical areas as a function of relational demands of to-be-constructed mental representations.

This investigation stems from work showing that MTL processes will contribute to memory tasks as a function of the retrieval demands. For example, studies have found distinct MTL recruitment for forming and retrieving relations, retrieving novel versus familiar relations and for item versus associative memory retrieval (for some examples, see Davachi, Mitchell, & Wagner, 2003; Mayes, Montaldi, & Migo, 2007;

Saykin et al., 1999; Squire & Zola-Morgan, 1991; Staresina, Fell, Do Lam, Axmacher, & Henson, 2012; Wolk, Dunfee, Dickerson, Aizenstein, & DeKosky, 2011). In one of our recent studies, we found distinctions in the MTL (specifically in the hippocampus) across retrieval tasks that extended beyond the domain of remembering. In an fMRI study, participants completed three experimental tasks in which they retrieved autobiographical memories, spatial representations (i.e., forming between-item relations), or object-based representations (i.e., forming within-item relations with conceptual knowledge of the objects; Sheldon & Levine, 2015) in response to pictures of common objects. While all three tasks activated the MTL, the location of this activity was distributed along the longitudinal axis of the MTL. In line with other work (Collin, Milivojevic, & Doeller, 2015; Evensmoen et al., 2013; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013), anterior aspects of the MTL, including the hippocampus, were more strongly involved in forming object-based representations—retrieving within-item or global-conceptual relations—while posterior aspects were more strongly involved in forming spatial representations—retrieving fine-grained or contextual relations (for a recent review, see Sheldon & Levine, 2016). We took these results as evidence that the MTL, as a region, supports distinct forms of relational retrieval, even when a task is not necessarily mnemonic.

Expanding to greater functional neural networks, there is evidence for MTL connectivity patterns that dissociate based on task demands. In a recent study, Robin and colleagues (2015) reported that a real-world episodic memory retrieval task relied on the coupling of a MTL functional network with medial prefrontal and parietal regions more strongly than a similar spatial retrieval task, which recruited the same MTL network without coupling to prefrontal and parietal regions (for a related behavioral study, see Robin, Wynn, & Moscovitch, 2016). Additional evidence for task-based MTL-networks comes from a study that indicated that hippocampal connectivity patterns differ according to the phase of autobiographical memory retrieval. They found the anterior hippocampus was preferentially connected to the prefrontal cortex during initial phase of retrieval—when accessing information on a conceptual scale—whereas the posterior hippocampus was connected to posterior cortical regions during a later phase of retrieval—when one is elaborating on the specific contextual and perceptual details of a recalled event (McCormick, St-Laurent, Ty, Valiante, & McAndrews, 2015). In line with these results, a study from one of our laboratories found similar dissociable hippocampal/MTL networks between two forms of a category fluency task that had different relational retrieval demands (Sheldon & Chu, 2016).

Thus, there is evidence that the processes evoked during a memory task drive MTL activity and connectivity patterns, particularly between anterior and posterior MTL subregions. This evidence aligns well with a proposal put forward by Ranganath and Ritchey (2012), which states that the MTL interacts with cortical areas based on the specific demands of a memory task. Drawing upon evidence of separate MTL networks for relating together item-item details and item-context details (Eichenbaum, Yonelinas, & Ranganath, 2007), they proposed an anterior and a posterior MTL memory system. The anterior MTL system connects the perirhinal cortex to the ventral temporopolar

cortex, amygdala and lateral orbitofrontal cortex and is involved in relating and retrieving conceptual information associated with a memory. The posterior MTL system connects the parahippocampal cortex (PHC) to the posterior cingulate, angular gyrus and other regions of the default mode network (DMN), which is often active during autobiographical memory and related mental representation tasks (e.g., Rugg & Vilberg, 2013), and is critical for creating links between recalled item information and the context details of a remembered event. This proposed anterior and posterior MTL network dissociation is reminiscent of the functional distinctions along the longitudinal axis of the hippocampus (Poppenk et al., 2013; Strange, Witter, Lein, & Moser, 2014). More specifically, there is a growing body of work showing that the anterior hippocampus is involved in retrieving information on a global/broader (i.e., conceptual) scale whereas the posterior hippocampus is involved in retrieving information with more fine-grained details, particularly when information has to be retrieved within a specific spatial context (Collin et al., 2015; Evensmoen et al., 2015, 2013; Sheldon, McAndrews, Pruessner, & Moscovitch, 2016). These differences have also been associated with specific hippocampal-cortical networks (McCormick et al., 2015; Persson, Stening, Nordin, & Soderlund, 2017; Sheldon et al., 2016).

In this study, we asked whether these discussed functional distinctions hold for broader retrieval tasks. We reanalyzed a previously published dataset to assess differences in MTL and hippocampal task-based functional connectivity across three retrieval tasks that preferentially recruited forming either autobiographical, spatial or conceptually-based mental representations (Sheldon & Levine, 2015). We first focused on task-based differences between the connections of a functionally-defined MTL seed region and the rest of the brain by examining connections of the region that was similarly active in all three retrieval conditions, which happened to be in the well-connected PHC (Furtak, Wei, Agster, & Burwell, 2007; Ward et al., 2014; Witter et al., 2000). We then focused on activity and connectivity of the structurally-defined anterior and posterior hippocampus to determine how these relational tasks are supported by different cortical networks emerging along the long axis of the hippocampus (Collins & Pruessner, 2010; Davachi et al., 2003; Sheldon & Chu, 2016). Using both the functionally-defined MTL and anatomical hippocampal subdivisions as seed regions for connectivity analyses, we tested the following predictions. If autobiographical retrieval requires MTL structures—particularly in the anterior hippocampus—to act in concert with cortical regions involved in conceptual and self-referential processing, we expect stronger connections between the MTL and regions such as the medial frontal and posterior cingulate cortex for the autobiographical condition. If spatial retrieval, as noted by Ranganath and Ritchey's (2012) model, recruits more posterior aspects of the MTL—including the hippocampus—and cortex, we expect that the spatial condition will recruit posterior MTL connections to such brain regions and that this condition will recruit more robust posterior than anterior hippocampal connectivity patterns. Finally, if retrieving conceptual information requires the MTL to connect with more lateral temporal regions implicated in accessing semantic information, then the conceptual task should recruit MTL—most specifically anterior hippocampal—connections to these areas.

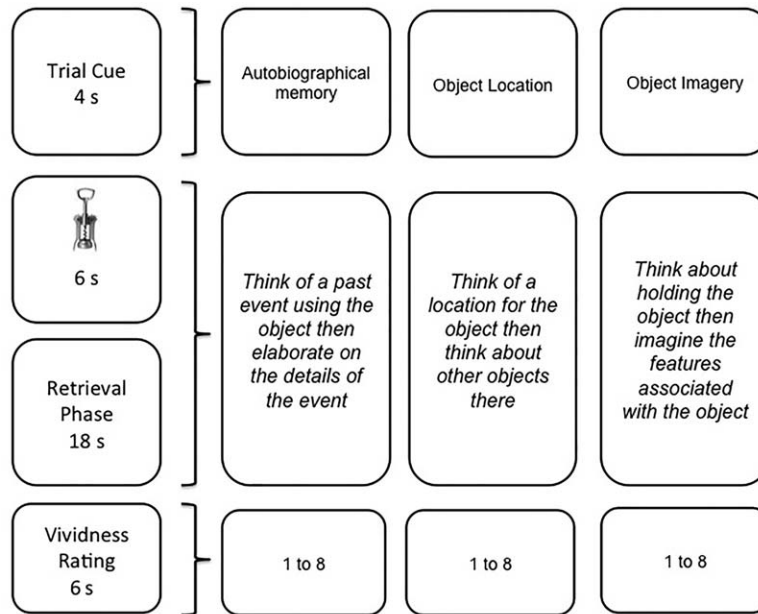


FIGURE 1 A schematic of the experimental design. For each trial, a cue was presented for 4 seconds that was followed by a randomly selected visual object. Participants were to use this object to retrieve the required information associated with the trial (as indicated by the cue). This object was presented for 6 seconds, but participants were given another 18 seconds to generate the information. Each trial concluded with a vividness rating of the formed mental representation that was made on a likert scale that ranged from 1 to 8. Participants were given 6 seconds to make this rating

2 | MATERIALS AND METHODS

2.1 | Participants

Twenty-eight healthy young adults participated in this study. The participants all gave informed consent and received compensation for their participation in accord with the Baycrest Health Sciences Centre ethical guidelines. One participant's data were not included in the following analyses due to a failure to appropriately follow task instructions, and one participant's data were not included due to noise in the fMRI signal, thus the analyzed sample was 26 participants (16 female; average age = 26 years, average years of education = 17 years).

2.2 | Stimuli

Sixty images of familiar objects were selected from a standardized bank of visual stimuli (<http://boss.smugmug.com/>). All the chosen objects had similar ratings of familiarity (between 3 and 4.5 out of 5) and visual complexity (a minimum score of 2 out of 5). All images featured objects that could be held and had multiple associated sensory details such that all of the pictured objects could act as appropriate cues for all the experimental tasks.

2.3 | Experimental task and procedure

Before scanning, participants were trained on the experimental tasks and given several practice trials in a mock scanner. In the scanner, each trial began with a cue phase that indicated the task the participant was to perform in response to the upcoming image. These cues were “autobiographical memory”, “object location”, “object imagery,” and “odd/

even” to indicate the autobiographical, spatial, conceptual and baseline task, respectively. After the cue, the participants were then presented with a pictured object and asked to think about a past personal memory (autobiographical), a location the object would be present in (spatial), or imagine holding the object and think of it's many features (conceptual; n.b., in our previous paper, the conceptual condition was referred to as “within-item” and the spatial condition was referred to as “item-context”). They were told to press a button when they had this thought in mind and spend the remainder of the trial period (24 s) thinking about the associated details of the mental image. Each trial ended with a six second vividness rating made on a scale of 1 to 8 and then a six second rest period. Participants completed five functional runs that each contained randomly presented trials of each experimental condition (four of each) and two baseline trials. Figure 1 illustrates a schematic of the experimental design. After the in-scan session, participants completed a post-scan interview in which they were shown each object cue they saw in the scanner and they described the details of the recalled memory if it was presented in the autobiographical condition, the generated location if it was presented in the spatial condition and the features/concepts of the object if it was presented in the conceptual condition and then made additional ratings. This postscan interview session confirmed that the participants were completing the in-scanner task appropriately (see Sheldon & Levine, 2015 for a full report).

2.4 | Imaging acquisition

MRI data were collected on a 3 Tesla Siemens full-body MRI machine with a standard 12-channel array head coil located at the Rotman Research Institute at the Baycrest Health Sciences Centre. Anatomical

scans were first acquired via T1-weighted volumetric MRI (TR = 2,000 ms, TE = 2.63 ms, 160 axial slices, 1.0-mm thickness, FOV = 256 mm). Functional scans were acquired with 32 4.5-mm thick axial slices with T2*-weighted EPI pulse sequence (64 × 64 acquisition matrix; TR/TE = 2,000/30 ms, flip angle = 70, FOV = 200 mm, 3.1 × 3.1 × 4.5 mm³ voxels) with no spacing.

2.5 | Image processing and analysis

2.5.1 | Task activity

We ran a univariate analysis to establish the task-based region of interest (ROI) for the functional connectivity analysis. For all participants, task trials were modeled with the onset of the object cue (i.e., image). Each trial (24 s) was time-binned according to when the participant started accessing the required representation (initial) and when they had accessed and started elaborating on the representation (retrieval; indicated via a button press) to distinguish between activity associated with information access (initial) and forming relational representation (retrieval). Time-binning the trials also introduced pseudo-jitter into our design by including the variance in response time (button press). Six trial regressors (autobiographical initial, spatial initial, conceptual initial, autobiographical retrieval, spatial retrieval, conceptual retrieval) and regressors associated with cue phase, the baseline task and in-scanner rating phase were entered into a first-level general linear model and convolved with a canonical HRF. A second level random effects analysis determined the patterns of brain activity associated with the three experimental conditions of interest (autobiographical retrieval, spatial retrieval, conceptual retrieval).

2.6 | ROI definitions

2.6.1 | Task-based MTL source

One way to establish functional connectivity is to use sources defined by task-based activity (Smith et al., 2011). Following methods used by researchers that investigated a similar research question as the one asked in the current study (Zeidman, Mullally, & Maguire, 2015), we defined a task-based source (i.e., seed) as the region within the MTL that had the greatest neural overlap between the three experimental tasks. We ran a conjunction analysis in SPM12 with the autobiographical retrieval, spatial retrieval, conceptual retrieval contrast images ($p < .005$ uncorrected) and restricted the resulting map with an MTL anatomical mask in MNI space. One cluster was commonly recruited for these three tasks that peaked in the left parahippocampal cortex, PHC (MNI coordinates at $-32, -32, -24$; $k = 267$). This entire cluster was used to create the task-based ROI for the connectivity analysis.

2.6.2 | Anatomically-defined hippocampal segments sources

Another way to establish functional connectivity is to use anatomical sources. We created anatomical hippocampal ROIs based on the average anatomical images (in MNI space) of five participants that were scanned for another experiment. We defined the anterior and posterior hippocampus based on the rostral and caudal slices of the hippocampus, respectively, approximately at MNI coordinates of $y = 0$ to $y = -6$

for the anterior hippocampus and $y = -33$ to $y = -40$ for the posterior hippocampus (Olsen et al., 2009, 2013; Yushkevich et al., 2015). Separate left and right anatomical hippocampal ROIs were created and connectivity analyses were preceded by extracting activity in these segments with the MarsBaR toolbox (<http://marsbar.sourceforge.net/>) for each condition as an aid in interpreting the connectivity results.

2.6.3 | Functional connectivity analysis

The MRI data were preprocessed with specification required for connectivity analysis and analyzed using the Conn toolbox (www.nitrc.org/projects/conn/). After the initial preprocessing steps noted above (slice-time correction, realignment, coregistration of the T1-weighted structural image to the functional images, normalization, and smoothing), additional measures were taken to remove potential confounding effects from the BOLD signal known to affect connectivity analyses. Specifically, nuisance covariates (cerebrospinal fluid, white-matter signals and their derivatives, motion and their first order derivatives) were regressed out at the first level of analysis. We also identified outlier scans with ART (Artifact Detection Toolbox) associated with Conn. Outliers were defined as those in which the global signal was greater than three standard deviations of the mean and those with head movement greater than 0.9 mm of scan-to-scan deviation, which is a critical processing step to take given that head motion strongly affects connectivity measures (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). We also filtered the data with a band-pass filter of 0.008.

2.6.4 | ROI-voxel connectivity

We conducted a series of seed-to-voxel context-dependent gPPI (generalized psychophysiological interactions) analyses. We focused our task differences by examining the conditions for the time bin that occurred after the button response was made (retrieval), ensuring that we were measuring connectivity differences driven by the type of mental representation formed and not differences in accessing information. For each experimental condition, the average BOLD time-series (i.e., the average time-course across all voxels) from the ROIs (the PHC or the anatomical hippocampal segments) was extracted and the interaction between the conditions of interest (task) and the ROI time-series was regressed against all brain voxels. This GLM approach includes the main effect of the task and seed so that the interaction effects of interest are independent of these main effects. The resulting fisher-z transformed correlation maps were carried forward into a second level ANOVA analyses and all the results are reported with cluster corrected at FDR .05 significance level. Clusters were identified via AAL atlas (www.alivelearn.net/xjview).

3 | RESULTS

3.1 | Behavioral results

There was a difference between the three experimental conditions for the in-scanner vividness ratings ($F(2,52) = 3.86, p = .03$) such that the autobiographical condition was rated as less vivid compared to the conceptual condition (mean = 5.5, $SD = 1.0$ and mean = 5.9, $SD = 1.1$, respectively; $t(26) = 2.40, p = .02$) and no differences emerged between these two conditions and the spatial condition (mean = 5.8,

TABLE 1 Brain regions that were preferentially connected to the parahippocampal cortex (PHC) for each experimental retrieval condition

Brain structure	BA	x	y	z	Cluster size	T value
Autobiographical retrieval						
Right parahippocampal gyrus and hippocampus	24	26	-18	-20	114	6.00
Spatial retrieval						
Left middle and superior lateral occipital cortex	19	-30	-74	38	101	4.92
Left superior and middle frontal gyrus	32	-8	18	50	56	5.08
Conceptual retrieval						
Left inferior parietal lobe/supramarginal gyrus	40	-56	-28	22	297	5.16
Left superior/middle frontal gyrus	10	-24	42	22	123	5.10
Right superior frontal/postcentral gyrus	6	20	4	68	78	5.24
Right inferior parietal lobule	40	36	-46	46	72	4.15
Right inferior frontal gyrus/temporal lobe	44	58	4	12	179	6.58
Right middle/anterior cingulate gyrus	24	-42	2	46	440	5.59
Right middle frontal gyrus	10	26	54	26	123	5.96
Right inferior parietal lobe/supramarginal gyrus	40	62	-28	30	596	6.22
Right insula/temporal pole	13	42	2	0	57	4.85
Left insula/temporal pole	13	-42	-6	-4	105	4.98

The x, y, z coordinates are in MNI space and represent the peak of the significant cluster. The data were thresholded at $p < .001$ with a cluster FDR-corrected threshold set to $p < .05$.

$SD = 1.1$). For a more complete description of the behavioral results, see our previously published report (Sheldon & Levine, 2015).

3.2 | Task-based MTL connectivity patterns

The only PHC connection that was associated more strongly with the autobiographical condition compared to the other two conditions was a region within the right MTL, which included the hippocampus (Table 1, top). The PHC connections that were more strongly associated with the spatial condition included two clusters that peaked in superior parietal lobule/middle lateral occipital cortex and the left middle and superior frontal gyrus (Table 1, middle). The PHC connections more strongly associated with the conceptual condition and included a much more distributed network, with anterior and lateral brain regions (e.g., bilateral superior temporal gyri left middle temporal gyrus, the postcentral

gyrus, the supramarginal gyrus). Notably, these are regions not typically associated with the PHC connectivity patterns (Table 1, bottom).

3.3 | Hippocampal segment activity

We extracted the mean signal (beta weights) from each participant's first-level contrast images associated with the conditions of interest (the retrieval time bin for each experimental task) for the four hippocampal ROIs (left and right anterior and posterior segments). These values are plotted in Figure 2 and indicate that these regions were active to some degree across conditions. To examine recruitment differences within the conditions along the hippocampal longitudinal axis, we compared anterior and posterior recruitment for each hemisphere for each task using Wilcoxon signed-ranks tests, as the values were not normally distributed. For the autobiographical condition, there was a greater

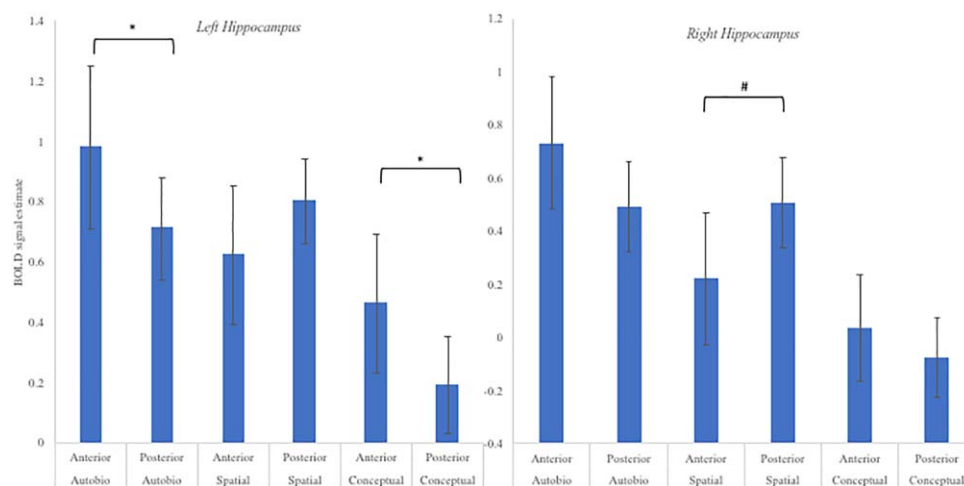


FIGURE 2 The average beta weights extracted from the right and left hippocampal anterior and posterior segments for each retrieval task condition. Error bars indicate standard error across the participants [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Brain regions that were preferentially connected to anterior and posterior hippocampal anatomical ROIs for each experimental retrieval condition

Autobiographical retrieval						
Connected brain structures	BA	x	y	z	Cluster	T
Left anterior						
Right precuneus	31	8	-52	16	1129	6.47
Right angular gyrus/supramarginal gyrus	39	42	-54	26	272	5.13
Left cerebellum/fusiform gyrus		-20	-36	-24	78	5.01
Left posterior cingulate/precuneus	29	-10	-52	6	73	6.43
Right medial frontal gyrus	10	14	46	-12	69	5.15
Right anterior						
Left precuneus	31	4	-56	34	1608	7.29
Left cerebellum		4	-56	-42	316	5.86
Right superior temporal lobe/angular gyrus	22	46	-56	22	232	4.86
Left posterior parahippocampal cortex		-22	-36	-24	121	4.91
Left anterior cingulate/medial frontal	32	-10	32	0	92	6.68
Left orbital frontal cortex (medial)	10	10	46	-10	67	4.54
Left superior temporal lobe/angular gyrus	39	-42	-56	22	56	5.39
Left middle temporal gyrus	21	-56	-18	-14	53	5.51
Left medial frontal gyrus	11	-8	32	-20	48	4.68
Right superior and medial frontal lobe	8	22	32	40	46	5.23
Left angular gyrus	39	-50	-66	30	45	4.41
Right posterior cingulate	29	8	-44	6	36	4.59
Left posterior						
Right angular gyrus	39	36	-54	30	76	4.28
Right posterior NA						
Spatial Retrieval						
Connected brain structures	BA	x	y	z	Cluster	T
Left anterior NA						
Right anterior						
Right inferior frontal gyrus	46	42	40	16	113	4.63
Right middle frontal gyrus	10	42	54	0	75	4.76
Left superior/medial frontal gyrus	6	-10	26	44	53	4.9
Left superior frontal gyrus	6	-22	18	58	47	4.13
Left posterior						
Left superior parietal lobule/precuneus		8	-70	54	267	5.34
Left inferior parietal lobule	3	-34	-32	50	185	4.64
Right superior frontal gyrus		24	-6	56	148	5.32
Left parietal lobe/precuneus	4	0	-34	70	83	4.93
Right posterior NA						
Conceptual Retrieval						
Connected brain structures	BA	x	y	z	Cluster	T
Left anterior						
Right superior temporal gyrus/temporal pole	22/6	52	6	10	644	6.58
Left posterior supramarginal gyrus	2	-58	-46	26	289	6.44
Left temporal pole	22/6	-46	-6	8	183	5.62
Right postcentral gyrus	6	50	4	32	63	5
Right anterior						
Right superior temporal gyrus/temporal pole	22	58	-2	0	295	5.54
Left superior temporal gyrus/temporal pole	41/22	-60	-1	6	77	4.76
Left posterior						
Left posterior supramarginal gyrus	40	-56	-48	36	77	4.76
Right posterior NA						

The x, y, z coordinates are in MNI space and represent the peak of the significant cluster. The data were thresholded at $p < .001$ with a cluster FDR-corrected threshold set to $p < .05$.

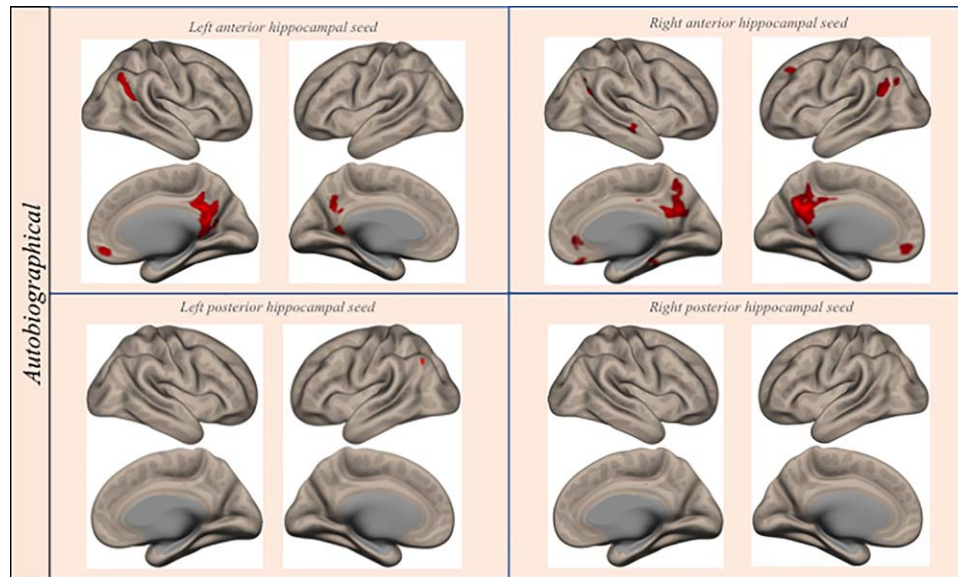


FIGURE 3 Brain regions that were more strongly connected to the hippocampal anatomical subregions during the autobiographical retrieval condition as compared to the spatial or conceptual condition ($p < .001$ with a cluster threshold FDR corrected to $p < .05$) [Color figure can be viewed at wileyonlinelibrary.com]

activity in the right anterior than posterior hippocampus ($Z = 2.56$, $p = .03$), but no difference between the left anterior and posterior hippocampal activity ($Z = .98$, $p = .17$). For the spatial condition, there was a trend toward more posterior than anterior activity in the right hippocampus ($Z = 1.77$, $p = .07$) and no difference between the left anterior and posterior hippocampal activity ($Z = .59$, $p = .56$). For the conceptual condition, there was more anterior than posterior activity in the right hippocampus ($Z = 2.16$, $p = .03$) and no difference between left anterior and posterior hippocampal activity ($Z = 1.37$, $p = .17$).

3.4 | Hippocampal connectivity patterns

3.4.1 | Autobiographical retrieval

Compared to the spatial and conceptual conditions, the autobiographical condition was associated with stronger connections between the anterior hippocampus (left and right) and the posterior cingulate cortex, angular gyrus, and medial prefrontal cortex. The left posterior hippocampus was more strongly associated with one cluster in the left superior parietal lobule, but there were no preferential connections to the right posterior hippocampus that exceeded the statistical threshold (Table 2, Figure 3).

3.4.2 | Spatial retrieval

Compared to the autobiographical and conceptual conditions, the spatial condition was associated with stronger connections between the right anterior hippocampus and clusters in the right frontal pole (superior aspects), the middle frontal gyrus, and the left superior frontal gyrus. The left posterior hippocampus was more strongly connected with clusters in the left superior parietal lobule, the superior aspects of the lateral occipital cortex, and the superior frontal gyrus. The left anterior hippocampus and the right posterior hippocampus did not show

any preferential connections for this condition that exceeded the significance threshold (Table 2, Figure 4).

3.4.3 | Conceptual retrieval

Compared to the autobiographical and spatial conditions, the conceptual condition was associated with stronger connections between the right anterior hippocampus and the right insula/inferior frontal gyrus as well as the left lateral, superior temporal pole (planum temporale) and the left anterior hippocampus was more strongly associated with the right and left temporal pole/insular regions (larger cluster for the right) and the left supramarginal gyrus (posterior). No areas were preferentially connected with the right posterior hippocampus, but the left posterior hippocampus was associated with a similar posterior left aspect of the superior marginal gyrus (Table 2, Figure 5).

4 | DISCUSSION

We reanalyzed a previously published dataset (Sheldon & Levine, 2015) to provide new evidence that the MTLs, including the hippocampus, are connected to different cortical regions, as a function of task demands—whether a task requires forming relations to create an autobiographical, a spatial or a conceptual mental representation. We ran a functional connectivity analysis that used an area of the MTL commonly active in the three tested conditions, located in the PHC, and found evidence that an active MTL region can dynamically interact with the cortex depending on what relations must be formed within a mental representation, which speaks to the flexibility of MTL involvement in cognition (Andrews-Hanna, Saxe, & Yarkoni, 2014; Andrews-Hanna, Smallwood, & Spreng, 2014). We also ran a series of hippocampal connectivity analyses that used anatomically defined anterior and posterior segments as seed regions. The resulting data indicated that there are heterogeneous

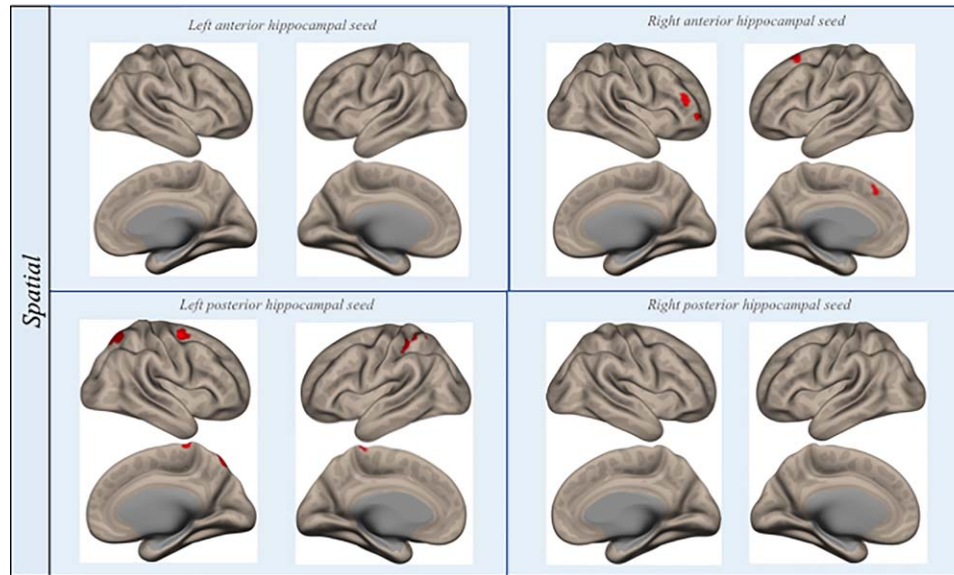


FIGURE 4 Brain regions that were more strongly connected to the hippocampal anatomical subregions during the spatial retrieval condition as compared to the autobiographical or conceptual condition ($p < .001$ with a cluster threshold FDR corrected to $p < .05$) [Color figure can be viewed at wileyonlinelibrary.com]

functions supported by these sub-regions and extend models of specialization along the long-axis of the hippocampus (e.g., Collin et al., 2015; Evensmoen et al., 2013; Poppenk et al., 2013; Sheldon & Levine, 2016) to models of MTL-guided cortical networks (Ranganath & Ritchey, 2012). Interpretations of the specific patterns that emerged from these two sets of analyses are discussed below.

The functionally-defined MTL seed region was defined as the area that was commonly recruited by all three experimental conditions, which was located the PHC. This region is strongly connected to the DMN and has been implicated as a core component of the DMN's

memory sub-network that supports the processing needed for recollection-based memory (Ranganath & Ritchey, 2012) as well as simulating scenes and hypothetical scenarios (e.g., Ritchey, Libby, & Ranganath, 2015; Spreng, Mar, & Kim, 2009; Szpunar, Chan, & McDermott, 2009). Thus, it makes sense that the autobiographical and spatial task in our study recruited this PHC region, but it is interesting that this region was also involved in the conceptual task—a task that was not concerned with simulating scenarios or event recollection, but about gathering within-item relations to form a (conceptual) representation of an object. We interpret this result as evidence that PHC function is

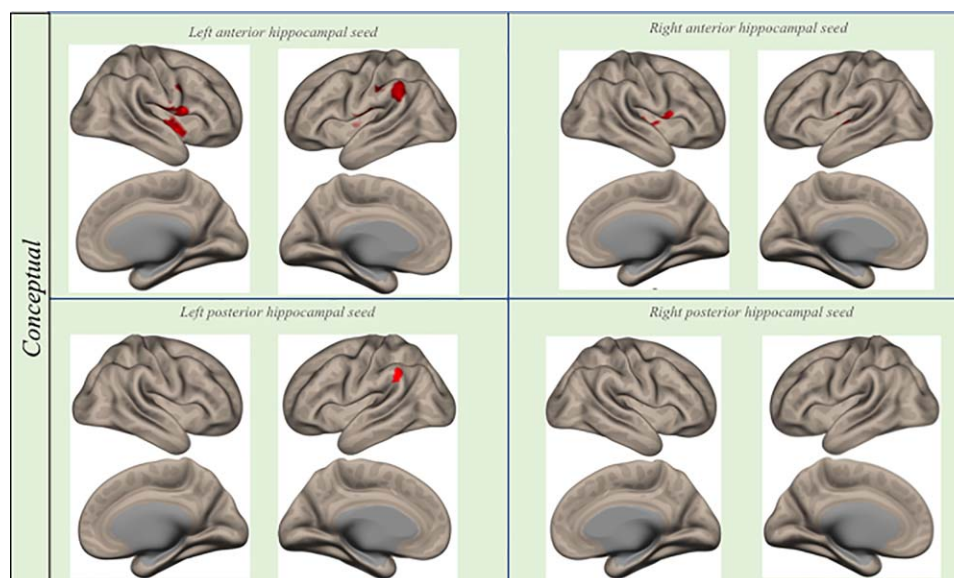


FIGURE 5 Brain regions that were more strongly connected to the hippocampal anatomical subregions during the conceptual retrieval condition as compared to the spatial or autobiographical condition ($p < .001$ with a cluster threshold FDR corrected to $p < .05$) [Color figure can be viewed at wileyonlinelibrary.com]

determined by the relational demands required for forming a mental representation and not than the precise representation that needs to be built.

In addition to this evidence that the PHC, as a region, is commonly involved in a range of mental representation tasks, our data also suggest that the nature of the representation will determine how the PHC is connected to the rest of the brain. We found that for autobiographical retrieval—thinking about past personal experiences—the PHC only had preferential interconnections to hippocampal regions, which we interpret as requiring the integration of different types of relations, like spatial and conceptual relations (e.g., remembering where you were and what happened), that are predominately processed by different regions of the MTL. The PHC connectivity pattern distinctly associated with the spatial task involved regions associated with low level visual processing (cuneus, middle occipital cortex) and regions implicated in integration of spatial relations (Sack, 2009; Seghier, 2013), which suggests that forming a predominately spatial mental representation has a selective reliance on basic visuo-spatial processes than forming other representations. Such a result fits with research that has indicated that connections between the MTL and visuo-spatial cortical areas serve several goal-directed spatial navigation functions. Some of this work has provided evidence that cross-talk between these regions is needed to code for visual cues (e.g., optic flow) present in the external world in service of forming a spatial map (Brown, Hasselmo, & Stern, 2014; Chrastil, Sherrill, Hasselmo, & Stern, 2015; Sherrill et al., 2015). Our results suggest that this relationship is present even when forming mental simulations of spatial representations.

With that said, another way to interpret these preferential connections for the spatial task is that they do not represent generating spatial representations per se, but reflect coordinating concepts together at a fine-grain level that is simply a characteristic of or best exemplified by spatial representations (Parkinson, Liu, & Wheatley, 2014; Yamakawa, Kanai, Matsumura, & Naito, 2009). Our current study is limited in providing evidence for or against this interpretation, but a future study could directly compare MTL connections to the parietal cortex for different forms of relational retrieval at different scales (e.g., recruiting fine-grained or global details from a mental representation) to gather such data.

Unlike the autobiographical or spatial task, the PHC connectivity pattern associated with the “conceptual” task—the task that asked participants to retrieve and relate diverse sensory and conceptual details of an item - included several regions outside of the DMN. In fact, this condition was associated with the most extensive connectivity pattern among the three conditions even though it had the least MTL activation (also see, Sheldon & Levine, 2015). This could be because representing the related features and concepts of the object required both high and low level perceptual processes (e.g., thinking about how an object looks and functions), thus demanding integrating a greater diversity of details than the other tasks. This diversity of required details could have also made the task demands of the conceptual condition more ambiguous than the autobiographical or spatial conditions, for which the task demands were more clear-cut—and more common (e.g., past experiences or common spaces). This interpretation follows some

of our previous work, which has shown that the MTL is involved differently in tasks that are more ambiguous in nature compared to those that are more well-defined (Sheldon & Moscovitch, 2012). Extending from this idea, this would mean the extended PHC (i.e., MTL) network involved in the conceptual condition represents a difference in the subjective experience of mental representation compared to the other tasks. This loosely fits with the behavioral finding that the conceptual condition was associated with higher vividness ratings than the other conditions (but only significantly so when compared to the autobiographical condition). Since we do not know if vividness was interpreted similarly across the three conditions, we are hesitant to include these behavioral ratings into our analyses, but bring this idea forward as an intriguing avenue for future research.

Following efforts to better understand the functional specialization along the hippocampal long-axis and how this specialization extends to greater cortical networks, our second analysis examined activity and connectivity of the anterior and posterior sub-regions of the hippocampus. Fitting with our prior report and other work (Even-smoen et al., 2013, 2015; Kumaran & Maguire, 2005; Maguire, Woollett, & Spiers, 2006), we found greater anterior than posterior hippocampal activations for the conceptual representations, whereas spatial representations were associated with greater posterior than anterior hippocampal activation. This suggests that the anterior hippocampus is critical for forming boarder representations from a diverse or integrated knowledge base and the posterior hippocampus for forming mental representations that are localized to a specific experience or context (for a good review of hippocampal functional specialization, see Strange et al., 2014).

Our focus, however, was on the task-related patterns of connectivity associated with these hippocampal subregions and how they shifted according to task demands. Overall, the distinctions we report align with the proposed MTL memory guided networks by Ranganath and Ritchey (2012; also see Ritchey et al., 2015) and further suggest that this network difference may reflect a functional division of labor within the hippocampus—one that distinguishes between conceptual and contextual processing. This is based on our findings that, first, the autobiographical condition was associated with anterior hippocampal connections to the posterior cingulate cortex and the medial prefrontal cortex (ventral), a pattern previously implicated in higher-level self-referential processing tasks (Davey, Pujol, & Harrison, 2016; Harrison et al., 2008; Qin & Northoff, 2011; Whitfield-Gabrieli et al., 2011). Second, the conceptual condition was associated with specific anterior hippocampal connections to areas implicated in semantic and schematic processing, suggesting that recruiting conceptual knowledge may be done flexibly by this hippocampal subregion (Mack et al., 2017). Finally, unlike the other two conditions, the spatial condition yielded stronger posterior hippocampal connections to regions involved in visuo-spatial processing (e.g., superior parietal lobule and the precuneus) that have been observed during similar spatial tasks (Baldassano, Beck, & Fei-Fei, 2017; Baldassano, Esteva, Fei-Fei, & Beck, 2016).

Another noteworthy result from this analysis was that all three retrieval tasks were each associated with some distinct right anterior hippocampal connectivity pattern, which suggests a basic underlying

role of this region in forming mental representations. This dovetails with recent findings that the anterior hippocampus is preferentially connected to cortical regions implicated in mental simulation tasks (Baldassano et al., 2017) and is necessary for initiating the construction of complex mental scenarios (Ito & Lee, 2016; Mack, Love, & Preston, 2017), which would implicate the anterior hippocampus in a wide variety of functions that require mental representations to guide behavior. Uncovering the nature of this common role of the anterior hippocampus in orchestrating mental representations is a topic worthy of further research, and one that is receiving attention by memory researchers (Schacter, Benoit, & Szpunar, 2017; Zeidman & Maguire, 2016).

In conclusion, we suggest that there are specific MTL- and hippocampally-guided neural networks recruited as a function of the relational retrieval demands of to-be-formed mental representation. Here, autobiographical retrieval required hippocampal networks that include medial frontal and posterior cingulate connections common to the DMN as well as intra-MTL connections to form complex representations by relating together information at both broad and specific levels. Spatial retrieval required MTL connections to the precuneus and occipital cortex as well as a specific posterior hippocampal network to posterior parietal regions to form fine-grained contextual representations. Finally, diffuse MTL- and anterior hippocampal-cortical connections were required for the retrieval tasks that specifically taxed conceptual or within-item relations to form more global mental representations. These patterns provide strong evidence that regional MTL and hippocampal specialization is evident in broader neural networks. Moreover, our findings raise new questions about the precise computations that are being performed by these different MTL networks, particularly those that are driven by distinct regions along the longitudinal axis of the hippocampus.

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