

Dissociating patterns of anterior and posterior hippocampal activity and connectivity during distinct forms of category fluency

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A B S T R A C T

Recent work has suggested that there are functionally distinct contributions from hippocampal sub-regions to episodic memory retrieval. One view of this dissociation is that the anterior and posterior hippocampus support gist-based/conceptual and fine-grained/spatial memory representations, respectively. It is not clear if such distinctions hold for other cognitive domains. To test this possibility, we examined anterior and posterior hippocampal contributions to a standard semantic retrieval task, category fluency. During fMRI scanning, participants generated exemplars to categories that were based on conceptual (autobiographical categories – ‘movies that you have seen’) or spatio-perceptual (spatial categories – ‘items in a kitchen’) information. Our main finding was that the autobiographical categories preferentially recruited the anterior hippocampus whereas the spatial categories preferentially recruited the posterior hippocampus. Differences were also evident when we examined the patterns of task-based hippocampal connectivity associated with these two forms of fluency. Our findings provide evidence for a functional organization along the long axis of the hippocampus that is based on conceptual and perceptual relational retrieval and indicate that this manner of organization is apparent outside the domain of episodic memory.

Keywords:

Memory
Hippocampus
Functional dissociation
Connectivity

1. Introduction

There is considerable evidence that the hippocampus is a critical structure for episodic and spatial memory (Morris et al., 1982; Moscovitch, 2008; Nadel, 1991; Nadel and Moscovitch, 1997; Scoville and Milner, 1957; Squire, 1992). As the central hub of a network of brain regions, the hippocampus flexibly binds together concepts and details to form conscious and coherent mental representations of experiences or environments (Cipolotti and Moscovitch, 2005; Moscovitch, 1995; Nadel and Moscovitch, 1997). While earlier work characterized hippocampal support for forming these representations by viewing it as a homogenous structure, animal models and neuroimaging investigations have suggested that there is a division of labour along the longitudinal axis of the hippocampus, distinguishing functions between the anterior and posterior hippocampus (Bonnici et al., 2013; Fanselow and Dong, 2010; Gilboa et al., 2004; Maguire et al., 2006; Poppenk et al.,

2013; Strange et al., 2014; Viard et al., 2012).

A renewed interest in the functional organization of the hippocampus has triggered questions about the different types of mnemonic representations that are supported by the anterior and posterior hippocampus. One suggestion is that the anterior hippocampus is involved in semantic or conceptual-based representations, such as word meaning or object-feature integration (Davachi, 2006; Schacter and Wagner, 1999; Sheldon and Levine, 2015) whereas the posterior hippocampus is involved in smaller scale perceptually-based mnemonic representations, such as retrieving specific locations in space (Evensmoen et al., 2015, 2013; for another view, see Poppenk et al., 2013). Many of the studies that have examined functional differences within the hippocampus have used episodic memory measures, yet it is not clear how these distinctions are reflected in ostensibly non-episodic retrieval tasks (for some recent reports, see Nadel et al., 2013; Ryan et al., 2010). To address this issue, in the present study we chose to examine the neural mechanisms underlying category fluency, a semantic memory task in which previous research indicated some hippocampal involvement. We set out to determine the extent of involvement of the anterior and posterior hippocampus, and their functional connections, to the retrieval of

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different kinds of semantic information.

Our investigation is based on a large body of work that has indicated that the hippocampus contributes to and facilitates many forms of mental search (Addis and Schacter, 2011; Moscovitch et al., 2016; Olsen et al., 2012; Schiller et al., 2015), including search through one's semantic knowledge base (Race et al., 2013; Ryan et al., 2008; Sheldon and Moscovitch, 2012; Smith and Lah, 2011; Westmacott et al., 2004; Westmacott and Moscovitch, 2003). A host of studies have found medial temporal lobe (MTL), and more specifically hippocampal, involvement during category fluency, a task that is often considered to be in the domain of semantic memory (e.g., Catheline et al., 2015; Pihlajamaki et al., 2000; Ryan et al., 2008). For example, behavioral investigations have reported that generating items to some, but not all, categories benefit from recruiting hippocampally-mediated episodic processes, such as imagining walking through a zoo to produce items to the category of animal names (Vallee-Tourangeau et al., 1998). Neuropsychological investigations have reported that patients with MTL lesions are impaired at generating items for categories that are related to autobiographical or spatial information (e.g., 'names of friends', 'buildings along a main street in town'), but not for categories that are more weakly related to episodic representations (e.g., 'things that are red'; Greenberg et al., 2009).

In one of our past studies, we showed that the hippocampus and associated structures in the MTL were activated during tests of category fluency and this activation was dependent on the type of representations required by the given category (Sheldon and Moscovitch, 2012). Aligning with findings using patient populations from Greenberg et al. (2009), we found that hippocampal involvement was greater for categories in which item generation could benefit from hippocampally-mediated episodic processes, such as those that support constructing a scene (e.g., 'items in a kitchen') and those that support recalling personal information (e.g., 'names of friends'). Categories for which episodic representations or processes were less likely to benefit item generation (e.g., 'types of currency') were associated with less hippocampal involvement.

Here, we made use of the above-mentioned dataset to conduct additional analyses aimed at examining whether there are differential contributions of the anterior and posterior hippocampus, and their functional connections, to performance based on the nature of the category. Extending from findings from the episodic memory literature, we hypothesized that the anterior and posterior hippocampus will contribute to category fluency in different ways depending on the representations being recruited by the task. The anterior hippocampus will be preferentially engaged if category fluency benefits from recalling exemplars that are related via personally relevant event-like conceptual representations (e.g., 'names of friends'). This is because items for these categories are related to one another thematically, thereby providing a common conceptual thread among a set of exemplars or experiences (Nielson et al., 2015; Zeidman et al., 2015). We further hypothesized that if category fluency generation benefits from recalling items that are related together on a spatial dimension, such as a recalling a single perceptually-based mental construct (e.g., generating items to the category 'things in a park'), the posterior hippocampus will be preferentially recruited (Sheldon and Levine, 2016).

We were also interested in examining how the cortical connections of the hippocampal segments of interest differed in relation to the category fluency task. There is good evidence from established patterns of connectivity that the functional differences observed within the hippocampus are representative of larger scale cortical networks. In terms of structural connections, the anterior aspect of the hippocampus is preferentially connected to the prefrontal cortex (more specifically, the dorsal and medial

prefrontal cortex), amygdala and lateral temporal cortex, while the posterior hippocampus has projections mainly to the mammillary bodies, anterior thalamus and retrosplenial cortex and receives input from the posterior cingulate and the occipital and temporal cortex (for good reviews, see Poppenk et al., 2013; Strange et al., 2014). Functional connectivity analyses have suggested that the anterior and posterior hippocampi are part of broader anterior and posterior memory networks (Adnan et al., 2015; Ranganath and Ritchey, 2012). The anterior memory network, which includes the anterior MTLs and frontal regions, is involved in retrieving general constructs and concepts, and the posterior memory network, which includes the posterior MTLs and posterior cortical regions, is involved in retrieving perceptual details (Poppenk et al., 2013; Evensmoen et al., 2015). In support of this view, connectivity between the anterior hippocampus and prefrontal cortex was found to be more involved when constructing or accessing personal memories whereas connectivity between the posterior hippocampus and posterior cortical regions, namely the visual cortex, was more involved when elaborating on the details of those memories once they were retrieved (McCormick et al., 2015).

In summary, the goal of the current study was to characterize hippocampal anterior and posterior activity, and patterns of task-based connectivity, during two forms of a semantic retrieval task - category fluency - that tapped into autobiographical or spatial information. Both these forms of retrieval were equated across all task dimensions except for the nature of the information being retrieved. Aligning with models of hippocampal organization, we hypothesized that the anterior hippocampus would play a stronger role in autobiographical category fluency and the posterior hippocampus would play a stronger role in spatial category fluency because these tasks benefit from forming broad conceptual versus local perceptual representations, respectively (Moscovitch et al., 2016; Sheldon and Levine, 2016).

2. Materials and methods

A full description of the materials and experimental procedures are reported in a previous article (Sheldon and Moscovitch, 2012).

2.1. Participants

Sixteen participants (6 male; mean age 24.8 years, $SD=4.5$; mean education 17.0 years, $SD=2.3$; all right handed) with normal or corrected to normal vision participated in this study. All participants were free of psychiatric and neurological disorders, and contraindications for an MRI environment. Participants gave informed consent in accordance with the Rotman Research Institute/Baycrest Hospital ethical guidelines and received compensation for their participation. One participant was removed due to incomplete scanning session and excessive movement.

2.2. Stimuli

Fifteen categories that drew on autobiographical information (autobiographical categories, e.g., 'movies you've seen') and 15 categories that drew upon spatial contextual information (spatial categories, e.g., 'kitchen items') were analyzed with the 15 trials of a visual-motor baseline task (press a button when you see an 'X'; see Table 1 for example responses for the examined categories). In this study design, participants were also given 15 categories that relied upon semantic information (non-spatial semantic categories) and phonemic probes (think of words that begin with a particular letter), but these were not examined in this analysis as our original study did not demonstrate strong hippocampal involvement in these two tasks (Sheldon and Moscovitch, 2012).

Table 1
An example from each category condition and generated responses.

Category	Spatial	Autobiographical
Example Responses	Things in a bedroom Bed End-table Closet Chair Books Dresser	Cities you have visited Paris Moosejaw Edmonton Detroit Lima Dehli

2.3. Procedure

Prior to scanning, each participant received instructions and several examples to train them on the fluency task to be undertaken during scanning. They were told that the name of a category would appear on a screen and they were to generate (silently) as many items that belonged to that category as they could, pressing a button with their right index finger every time they generated an item. While in the scanner, participants were presented visually with each category in a pseudo-random order and were given 36 s to generate as many items as they could which belonged to that category. For the reported analyses, we included the first 24 s of the allotted 36 s generation period, limiting our analysis to this duration based on the average time that the participants spent generating items (i.e., the last response, on average, was made at 24 s). The name of the category remained on the screen for the entire generation time. Each category trial was separated by a twelve second inter-stimulus interval in which the participants were instructed to rest. Participants completed all 60 categories (and 15 baseline tasks) in five functional imaging runs. Each run lasted approximately twelve minutes. A post-scan interview asked participants about the items they generated to ensure they were performing the task as expected while in the scanner. All participants met this criterion.

2.4. Image acquisition

All imaging was performed on a 3 T Siemens full-body MRI machine with a standard 12-channel array head coil located at the Rotman Research Institute/Baycrest Hospital. Anatomical scans were acquired via T1-weighted volumetric MRI (TR=2000 ms, TE=2.63 ms, 160 axial slices, 1.0 mm isotropic thickness, FOV=256 mm). For the functional images, 30 axial slices with T2*- weighted EPI pulse sequence were obtained (TR=2000 ms, TE=30 ms, flip angle=70°, FOV=200 mm, voxel size=3.125 mm × 3.125 mm × 5 mm) with no spacing.

2.5. Image processing

The MRI data were reconstructed and pre-processed using SPM12 (University College London, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/software>). Functional preprocessing steps included slice-time correction, realignment, coregistration of the T1-weighted structural image to the functional images (resampled to 2 mm voxels), normalization to the MNI template and image smoothing (8 mm FWHM Gaussian kernel). For the structural MRI data, we performed an additional correction for magnetic field non-uniformities to recover image artifacts to prepare for hippocampal subregion segmentation (Sled et al., 1998). These images then underwent linear stereotaxic transformation (Collins et al., 1994) using the MNI template, and signal-intensity normalization prior to manual segmentation.

2.6. Whole brain analysis

We first confirmed the effects of the autobiographical and spatial category conditions on activity across the whole brain using the shortened retrieval trials analyzed in this study. A GLM included modeling all task trials with the onset of the cue and with the duration set to 24 s. In total, there were five task regressors (Autobiographical, Spatial, Semantic, Phonemic, Baseline) as well as six motion-related regressors. Given our specific experimental questions, we focused on contrasting the autobiographical and spatial category conditions. Second-level random effects analyses were run to determine the patterns of brain activity related to the autobiographical and spatial conditions against the baseline task (one-sample *t*-tests) and analyses were run that directly contrasted activity among these conditions (autobiographical > spatial and spatial > autobiographical). These results are reported at $p < 0.005$ with a cluster extent of 128. This cluster extent was established via 3dClustSim (Monte Carlo simulation technique using 10000 simulations) to meet a threshold equivalent to $p < 0.05$ while controlling for multiple voxel-wise comparisons across the whole brain.

2.7. Hippocampal segmentation and ROI analyses

We first segmented the hippocampus from the preprocessed MRI images using a previously described automated method (Collins and Pruessner, 2010), followed by manual quality control and correction according to a validated manual segmentation protocol (Pruessner et al., 2000). During the manual quality control, hippocampal labels were split into head, body and tail according to established anatomical landmarks (Pruessner et al., 2000). For estimating functional activity within the hippocampus, we first averaged the manually segmented left and right hippocampi from the anatomical scans of all participants and applied the GLM model described above. 3dClustSim was used to establish a cluster extent that was equivalent to $p < 0.05$ while controlling for multiple voxel-wise comparisons within this smaller hippocampal mask. Applying this correction, we set the resulting maps to a voxel-wise threshold of $p < 0.005$ and a cluster extent threshold of 65.

We followed this analysis by specifying activity along the long axis of the hippocampus in the autobiographical and spatial condition in each participants' left and right hippocampal head, body and tail sections. The MarsBaR toolbox (<http://marsbar.sourceforge.net/>) was used to extract the mean signal (beta weights) from the first-level contrast images of each condition from each of these participant-specific anatomical segments. The extracted beta weights were entered into a repeated-measures ANOVA.

2.8. Task-based hippocampal connectivity analysis

2.8.1. ROI definitions

Driven by our theoretical interest in anterior and posterior hippocampal connectivity differences during task performance, we identified the peak area of activation overlap during the spatial and autobiographical conditions in the left and right hippocampal head and tail. We did this by running a conjunction analysis with the autobiographical and spatial condition activation maps and masked this analysis with four different images: the group averaged left and right hippocampal head and tail. Using a threshold of $p < 0.005$, 8 mm spherical ROIs were created that centered on the location of peak fMRI activity for each masked conjunction analysis. These ROIs were created using the MarsBaR toolbox. The coordinates of these peaks are reported in Section 3.4 of the results.

2.8.2. Task-based connectivity

We took a seed-to-voxel approach to connectivity by computing the temporal correlation between the mean BOLD time series in all four ROIs (i.e., left and right hippocampal head and tail, representing the anterior and posterior hippocampus, respectively) and all other areas of the brain. All analyses were done using the CONN toolbox (<https://www.nitrc.org/projects/conn/>).

Prior to assessing connectivity, extra processing steps were taken so that potential confounding effects were removed from the BOLD signal. This included removing the main activation effects of condition, done to avoid simply finding co-activation measures. Nuisance covariates (cerebrospinal fluid, white-matter signals and their derivatives, motion and their first order derivatives as well as outlier scans identified via the ART Artifact Detection Toolbox associated with CONN) were regressed out at the first level of analysis. Another processing step taken was to use a band-pass filter of 0.01 to eliminate the confounding effect of low-frequency fluctuations.

For each participant and each experimental condition (i.e., fluency task), correlation maps (Pearson r) were computed between the time series in the four ROIs and voxels in the rest of the brain and these were carried forward to a second level analysis. Here, paired comparisons (t -tests) were run with the total number of items generated for each participant used as covariate of non-interest for each of the four ROI-voxel maps. Group connectivity results are reported at $p < 0.005$ with clusters greater than 128 voxels as established with 3dClustSim.

3. Results

3.1. Confirmation of whole brain patterns of activity

As mentioned, we first tested whole brain activity associated with the autobiographical and spatial categories (Sheldon and Moscovitch, 2012). The autobiographical and spatial conditions were both associated with large swathes of voxel activity that centered upon the precuneus but also included the MTL regions as well as clusters of activity in the frontal, temporal and occipital lobes (Table 2). Directly comparing the two conditions revealed that the autobiographical condition was preferentially associated with activity in the angular gyrus, medial prefrontal cortex, right

Table 2

Peak regions (significant clusters that were > 8 mm apart) for the autobiographical and spatial category conditions compared to the visual-motor baseline task. The peaks of the clusters are reported in MNI coordinates (x, y, z).

Brain structure	x	y	z	Cluster size	Peak T value
Autobiographical					
Left precuneus	-6	-58	24	5461	12.65
Left angular gyrus	-48	-70	36	1254	11.75
Right angular gyrus	52	-64	30	737	9.61
Right cerebellum	6	-52	-50	325	9.61
Left middle frontal gyrus	-38	20	50	1974	9.51
Right superior frontal gyrus	24	36	48	1180	9.47
Left middle temporal gyrus	-58	-16	-18	332	9.33
Left anterior cingulate	-14	44	6	449	7.56
Right cerebellum	28	-28	-20	414	7.45
Left inferior occipital cortex	-18	-94	-10	357	6.7
Right cerebellum	42	-72	-40	171	5.99
Spatial					
Left fusiform gyrus	-30	-42	-12	1110	13.29
Right precuneus	18	-56	22	2493	13.21
Right fusiform gyrus	30	-40	-12	943	12.66
Left middle occipital cortex	-36	-78	38	1795	10.49
Right middle occipital cortex	46	-76	26	408	8.2
Left middle frontal cortex	-26	24	46	1208	7.96
Right middle frontal cortex	30	20	52	214	6.9

orbitofrontal cortex/temporal pole, left precuneus, bilateral angular gyrus, bilateral middle temporal lobe, and the right anterior hippocampus. The spatial condition was associated with more robust activity that centered on the right parahippocampal gyrus, bilateral superior parietal cortex, left inferior parietal lobe, right precuneus, bilateral insula, right middle occipital lobe, and left inferior frontal gyrus (Fig. 1).

3.2. Hippocampal activity

We next compared directly hippocampal activity between our conditions of interest to determine where along the long axis preferential hippocampal activity occurred. As noted in our methods, we used a hippocampal mask of the participants' bilateral anatomical hippocampi and extracted clusters within the hippocampus that were more active for the autobiographical or the spatial categories. This analysis revealed that the autobiographical category condition was preferentially associated with activity in the right anterior hippocampus (Fig. 2, cool colors) and the left anterior hippocampus at a more liberal threshold of $p < 0.05$ (MNI $x, y, z = -20, -14, -12$). The spatial category condition was preferentially associated with activity in posterior aspects of the left and right hippocampus (Fig. 2, warm colors).

3.3. Measuring hippocampal ROI responses

The above hippocampal analysis used an average hippocampal mask to determine how task demands influenced activity along the long axis. Using this mask may have included non-hippocampal activity in some of our participants due to individual differences in hippocampal shape and volume. Thus, to specify how each segment of the hippocampus contributed to our conditions of interest, we extracted the mean signal (beta weights) from each participants' first-level contrast images masked by their manually segmented left and right hippocampal head, body and tail (Fig. 3). In Fig. 3, we illustrate the beta weights for the hippocampal head, body and tail for completion, but for the following statistical analysis, we included activity within the head and tail as directed by our hypothesis. We entered the activity values associated with the head and tail into a repeated measures ANOVA with condition (spatial versus autobiographical), laterality (left versus right) and region (head versus tail) as factors. There was no main effect of category or region, but a main effect of laterality ($F(1,14) = 10.54$, $p = 0.006$). Critically, there were significant two way interactions between laterality and condition ($F(1,14) = 5.85$, $p = 0.03$) as well as between condition and region ($F(1,14) = 15.40$, $p = 0.002$), but no three-way interaction between laterality, condition and region.

We further examined condition and region effects, based on the significant interaction, in each hemisphere separately. For the left hemisphere, there was a main effect of condition ($F(1,14) = 4.84$, $p = 0.04$) with more activity during the spatial category condition compared to the autobiographical category condition, and an interaction between condition and region ($F(1,14) = 15.97$, $p < 0.001$). Pairwise comparisons revealed that this was mainly due to stronger activity in the hippocampal tail compared to the head for the spatial category condition ($p = 0.05$). For the right hemisphere, there was no main effect of condition, but an interaction between condition and region ($F(1,14) = 9.77$, $p = 0.007$). Pairwise comparisons revealed that this was mainly due to stronger activity in the hippocampal head compared to the tail for the autobiographical category condition ($p = 0.02$).

3.4. Hippocampal connectivity

Masking the conjunction analysis between the activation maps of the two category conditions with the group averaged

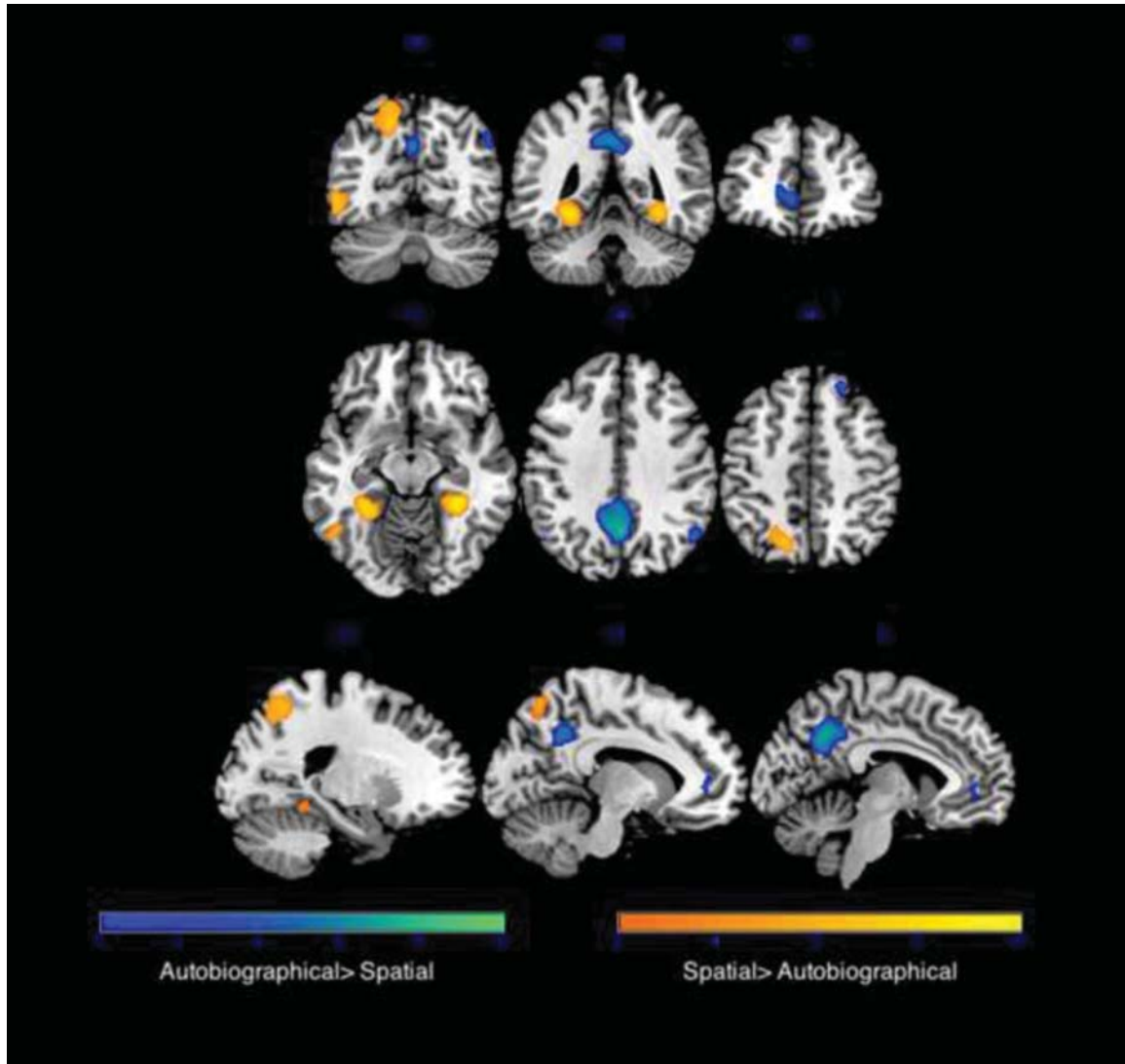


Fig. 1. The brain activation patterns selectively associated with the autobiographical category condition as compared to the spatial category condition (cool colors) and the brain regions that were selectively associated with the spatial category condition as compared to the autobiographical category condition (warm colors). The color bars indicate the t -statistic. The image was thresholded at $p < 0.005$ with a cluster extent > 128 .

hippocampal head and tail masks resulted in peaks of activity in anterior hippocampal regions that were in the very hind sections of the hippocampal head (MNI $x,y,z = -26, -26, -16$; $30, -26, -20$) and in posterior hippocampal regions (MNI $x,y,z = -28, -38, -12$; $28, -36, -12$). Spheres around these four peaks were entered in the hippocampal connectivity analysis as noted in our methods.

3.4.1. Anterior hippocampal connectivity (Table 3, Fig. 4)

Compared to the spatial categories, the autobiographical categories had stronger functional connections between the left anterior hippocampus and right superior temporal pole, left orbitofrontal cortex and the left inferior temporal cortex (at a reduced threshold). The spatial categories had stronger connections between the left anterior hippocampus and left occipital/fusiform gyrus and intra-connections with the hippocampus. Considering the right anterior hippocampus, the autobiographical categories had stronger functional connections to the left middle cingulate gyrus and the cerebellum as well as the right middle temporal cortex, but at a reduced threshold. The spatial categories had stronger connections between the right anterior hippocampus and the precuneus and left caudate (Table 3, Fig. 4).

3.4.2. Posterior hippocampal connectivity (Table 4, Fig. 5)

Compared to the spatial categories, the autobiographical categories had stronger functional connections between the left posterior hippocampus and the left and right supramarginal/angular gyrus and left inferior temporal gyrus. The spatial categories had stronger connections between the posterior hippocampus and a large cluster that encompassed the lingual gyrus, calcarine cortex and precuneus, as well as the frontal pole. Using the right posterior hippocampus as a seed demonstrated that the autobiographical categories had stronger functional connections to the anterior aspects of the left parahippocampal gyrus, which bled into the fusiform gyrus as well as the bilateral inferior parietal lobule and right middle temporal lobe (at a reduced threshold). The spatial categories had stronger connections between the right posterior hippocampus and the right calcarine/precuneus, temporal occipital fusiform gyri regions, and the frontal pole (Table 4, Fig. 5).

4. Discussion

In the current study, we investigated the patterns of hippocampal activity and connectivity that were associated with

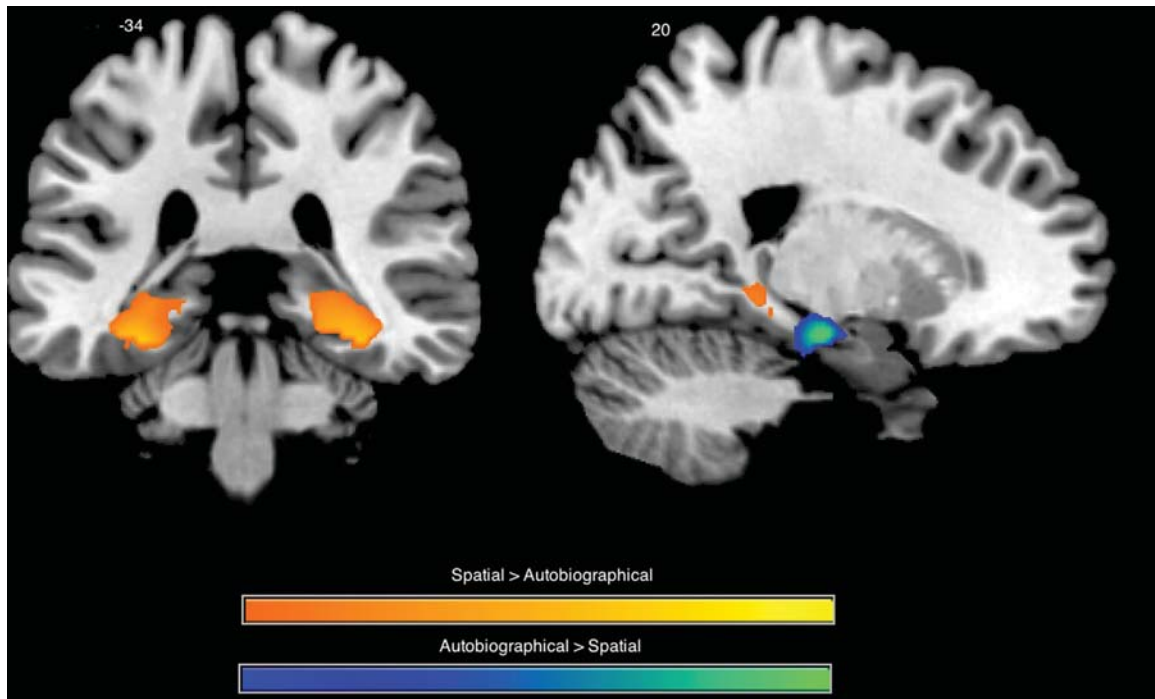


Fig. 2. A hippocampal ROI analysis. The contrasts of the autobiographical > spatial category conditions (cool colors) and the spatial > autobiographical category conditions (warm colors) were masked with an average of the participants bilateral hippocampi. The color bars indicate the t -statistic. The image was thresholded at $p < 0.005$ with a cluster extent > 65 .

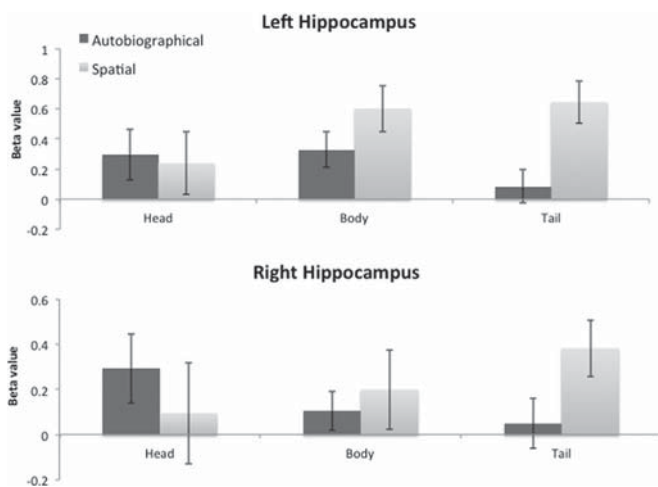


Fig. 3. The mean beta weights extracted from participant-specific left (top) and right (bottom) hippocampal head, body and tail ROIs for the autobiographical and spatial category conditions. Error bars indicate standard error across the participants.

retrieving distinct forms of categorical information. Consistent with our predictions, our main finding was that the anterior and posterior hippocampus were differentially involved in retrieving autobiographical versus spatial items during a category fluency task, an ostensibly semantic memory measure. We interpret our reported pattern as evidence for the theoretical view of hippocampal organization in which the anterior region is more involved in categorical/conceptual representations and the posterior region is associated with recovering fine-grain perceptual detail (Moscovitch et al., 2016; Poppenk et al., 2013; Sheldon and Levine, 2016). While previous studies have established this anterior/posterior distinction using episodic retrieval tasks, our study extends this view to semantic retrieval, providing indications for how the hippocampus functions outside the domain of episodic memory.

Table 3

Peak regions (significant clusters that were > 8 mm apart) for the autobiographical compared to spatial category condition as well as the spatial compared to the autobiographical category condition that were functionally connected to the left and right anterior hippocampus. The peaks of the clusters are reported in MNI coordinates (x, y, z).

Brain structure	x	y	z	Cluster size	Peak T value
Left					
Autobiographical > Spatial					
Right superior temporal pole	34	18	-16	231	7.29
Cerebellum	-52	-72	-42	172	5.60
Left medial orbital frontal cortex	-2	66	-16	139	5.60
Spatial > Autobiographical					
Left temporal/Occipital cortex	36	-56	-26	351	7.16
Left amygdala/hippocampus	-18	-10	-14	142	4.99
Right					
Autobiographical > Spatial					
Left middle cingulate gyrus	-16	-18	52	189	5.38
Cerebellum	-26	-18	-48	140	6.50
Spatial > Autobiographical					
Right precuneus	20	-66	16	465	7.92
Left caudate	-6	20	16	295	5.89

4.1. Task specific hippocampal activity

Prior reports have indicated that the hippocampus is involved in category fluency. For example, patients with MTL epilepsy and excisions have significant deficits on standard category fluency tasks (Gleissner and Elger, 2001). Neuroimaging studies have also reported hippocampal contributions to category fluency performance (Pihlajamaki et al., 2000; Shapira-Lichter et al., 2013; Sheldon and Moscovitch, 2012; Whitney et al., 2009). Here, we specify how these hippocampal contributions vary according to the nature of the given category. First, we found that generating

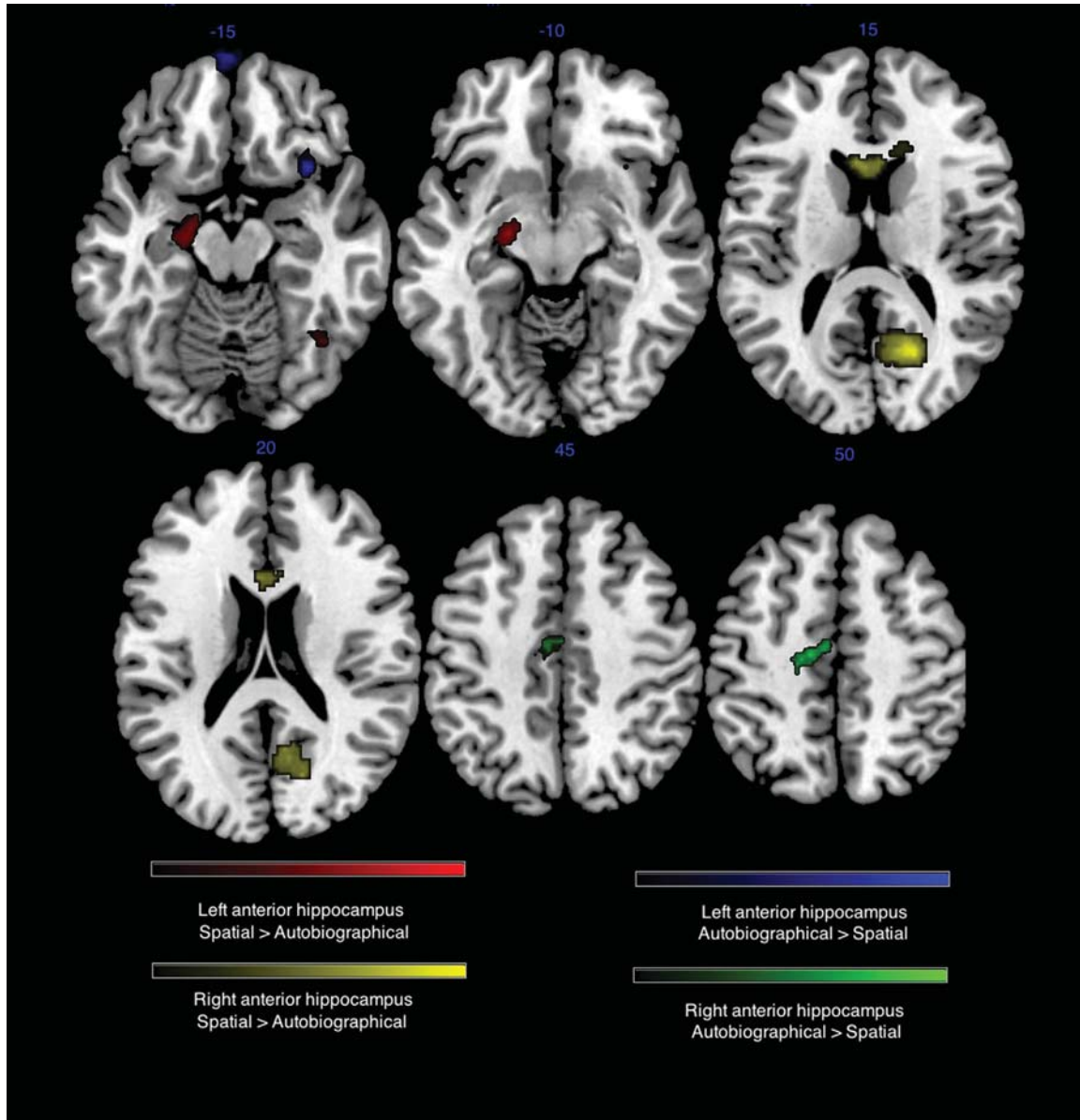


Fig. 4. A functional connectivity analysis that reported the brain regions that were more strongly connected to the anterior hippocampus during the autobiographical category condition as compared to the spatial category condition (blue and green for the left and right anterior hippocampus) and the brain regions that were more strongly connected to the anterior hippocampus during the spatial as compared to the autobiographical category condition (red and yellow for the left and right anterior hippocampus). The image was thresholded at $p < 0.005$ with a cluster extent > 128 (see Table 4). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

items to autobiographical categories preferentially recruited the anterior hippocampus. For these categories, participants were asked to recall personally-relevant semantic or conceptual information. We distinguished these categories from the spatial categories used in our study based on an a-priori notion that autobiographical categorical retrieval requires one to generate multiple exemplars based on similar underlying personally-relevant conceptual themes (e.g., thinking of 'people from work' and 'childhood friends' for the category 'names of friends'). Our finding accords well with the view and other reports that the anterior hippocampus is recruited for establishing links between conceptual information by combining multiple forms of information, such as semantic, spatial and emotional information (Zeidman et al., 2015) or integrating distinct experiences on a conceptual or global scale (Nielson et al., 2015; Zeidman et al., 2015). Anterior aspects of the hippocampus are also well connected with brain regions that support more global concept retrieval (Fairhall and Caramazza,

2013a, 2013b) and schema processing (van Kesteren et al., 2012; Preston and Eichenbaum, 2013; Ghosh and Gilboa, 2014; Moscovitch et al., 2016), such as the (ventromedial) prefrontal and lateral (anterior) temporal cortex.

While there was more robust involvement of the anterior hippocampus when generating items to the autobiographical categories, we found greater activity within the posterior hippocampus for the spatial category condition. We suggest that generating items to those categories benefited from thinking about specific spatial-perceptual relations within a mentally constructed environment. For example, to generate items to the category 'things in a kitchen', a useful strategy is to bring to a mind an image of a kitchen and list items in close spatial proximity (e.g., oven, sink, coffee maker), though we note that we did not systematically question our participants to ascertain whether they used this strategy. We speculate from our findings, however, that retrieving these small-scale spatial relations is best supported by

Table 4

Peak regions (significant clusters that were > 8 mm apart) for the autobiographical compared to spatial category condition as well as the spatial compared to the autobiographical category condition that were functionally connected to the left and right posterior hippocampus. The peaks of the clusters are reported in MNI coordinates (x, y, z).

Brain structure	x	y	z	Cluster size	Peak T value
Left					
Autobiographical > Spatial					
Left angular gyrus	-52	-50	40	314	6.72
Left middle cingulate gyrus	-4	-20	44	171	4.56
Right inferior parietal lobule	54	-34	44	145	4.59
Right angular gyrus	54	-50	28	133	4.48
Left inferior temporal gyrus	-36	-8	-26	131	4.63
Spatial > Autobiographical					
Left calcarine gyrus/lingual gyrus	-14	-72	4	1051	6.72
Cerebellum	20	-68	-40	186	5.01
Left frontal pole	-30	48	-18	173	6.20
Left occipital/ fusiform gyrus	-36	-74	-18	138	4.25
Right					
Autobiographical > Spatial					
Left fusiform gyrus	-14	-24	-44	385	6.26
Right inferior parietal lobule	42	-36	44	215	4.93
Left inferior parietal lobule	-50	-40	38	209	5.35
Spatial > Autobiographical					
Right precuneus	16	-8	60	273	5.92
Left calcarine cortex	-12	-66	8	258	4.69
Right precuneus	6	-66	14	197	4.43
Right frontal pole	28	48	-14	134	5.80
Right temporal occipital cortex	44	-50	-32	129	5.72

the posterior hippocampus. This interpretation fits well with other results that have shown that the posterior hippocampus is more active for making specific directional judgments when navigating or recalling spatial environments (Evensmoen et al., 2015, 2013; Kumaran and Maguire, 2005; Maguire et al., 2006) and when thinking about an appropriate spatial environment in which one would encounter an object (e.g., a broom; Sheldon and Levine, 2015). The greater involvement of the posterior hippocampus in processing detailed, relational spatial information is reflected also at the structural level, with enlarged posterior relative to anterior hippocampal volumes in London taxi drivers (Maguire et al., 2006), and in people who perform well on tests of recollection (Poppenk and Moscovitch, 2012), which are related to perceptually detailed memory (Moscovitch et al., 2016).

4.2. Task specific hippocampal connectivity

Our connectivity analyses indicated that both hippocampal regions had distinct pattern of functional connectivity for each task. Prior research on resting state connectivity has revealed functionally distinct sub-networks related to memory that includes the hippocampus (Campbell et al., 2013; Fox et al., 2005; Spreng et al., 2013) and there has been interest in how these networks are involved in task-based performance. For instance, Robin et al. (2015) found evidence that underlying differences in hippocampal connectivity related to these sub-networks was sensitive to memory task demands. Robin and colleagues (2015) reported that episodic, as compared to spatial, memory retrieval was preferentially associated with stronger connections between the hippocampus and prefrontal cortical regions, which fits with some of our reported connectivity dissociations between autobiographical and spatial category fluency. Specifically, we found greater task-related connectivity between the anterior

hippocampus and loci in the prefrontal cortex and the temporal pole and between the posterior hippocampus and bilateral angular gyri/inferior parietal lobule for the autobiographical categories. When retrieving autobiographical information, the hippocampus interacts preferentially with regions that have been implicated in cognitive control and semantic/schematic processing (Preston and Eichenbaum, 2013; van Kesteren et al., 2012). The spatial categories showed enhanced connectivity between the posterior hippocampus and regions of the brain in the ventral visual stream (calcarine, lingual gyrus, precuneus) which are implicated in visual imagery and perceptual processing (Ranganath and Ritchey, 2012; Sheldon et al., 2016; Zeidman et al., 2015), but also enhanced anterior hippocampal connections with other regions of the MTL and the lateral occipital cortex that are not typically connected to this subregion. This combination of both posterior and anterior hippocampal connectivity could be driven by increased intra-hippocampal connectivity during the spatial category task with the posterior hippocampal activity driving the reported cortical connections (see Robin et al., 2015, for a similar proposal).

With respect to the study by Robin et al., (2015), our category fluency task should not be equated with retrieval of detailed autobiographical or even spatial memories, which likely involves both the anterior and posterior hippocampus. In thinking about this difference, the results of a recent study by McCormick et al. (2015) may be instructive. They found that during the initial, constructive phase of autobiographical event recall, activation was more prominent in the anterior hippocampus and its connectivity pattern resembled that reported in this study. At later, elaboration stages, activation shifted towards the posterior hippocampus, and its connectivity now resembled that reported in our study for the spatial condition. McCormick et al. (2015) interpreted their findings as supporting Conway and Pleydell-Pierce's (2000) model in which the initial stages of remembering draw on thematic information represented in anterior cortical structures, which then serves as a framework or scaffold, for generating detailed representations associated with an event.

4.3. Implications for theories of hippocampal processing specificity

One of the main theoretical implications of our study is that classical distinctions, such as between episodic and semantic memory, and tasks used to measure them, do not fully capture hippocampal function. Instead, we propose that to conceptualize processing-specificity within the hippocampus requires a framework that identifies the component processes and representations implicated during retrieval (Moscovitch, 1992; Moscovitch et al., 2016). In particular, functional specialization along the long axis of the hippocampus seems to depend in part on the extent to which a given task can benefit from constructing conceptual versus perceptual relational representations (Sheldon and Levine, 2016). Under this view, anterior hippocampal processes are useful for integrating distinct informational elements around a central conceptual node, relating a common theme among a set of ideas or experiences, as seen in the autobiographical condition (also see, Nielson et al., 2015; Zeidman et al., 2015). This is accomplished by the anterior hippocampus operating in conjunction with regions that support broader conceptions, such as schemas (ventromedial prefrontal cortex), semantics (e.g. anterior temporal lobe) and emotion (e.g. amygdala and orbitofrontal cortex) (Moscovitch et al., 2016). Conversely, the posterior hippocampus is recruited for retrieving information on a smaller scale that is derived from or retrieved around a spatial-based representation, which is mostly prominently showcased by the spatial category condition in the current study. As illustrated by our connectivity results, the posterior hippocampus can work in concert with regions involved in imagery and perceptual processing to form such mental

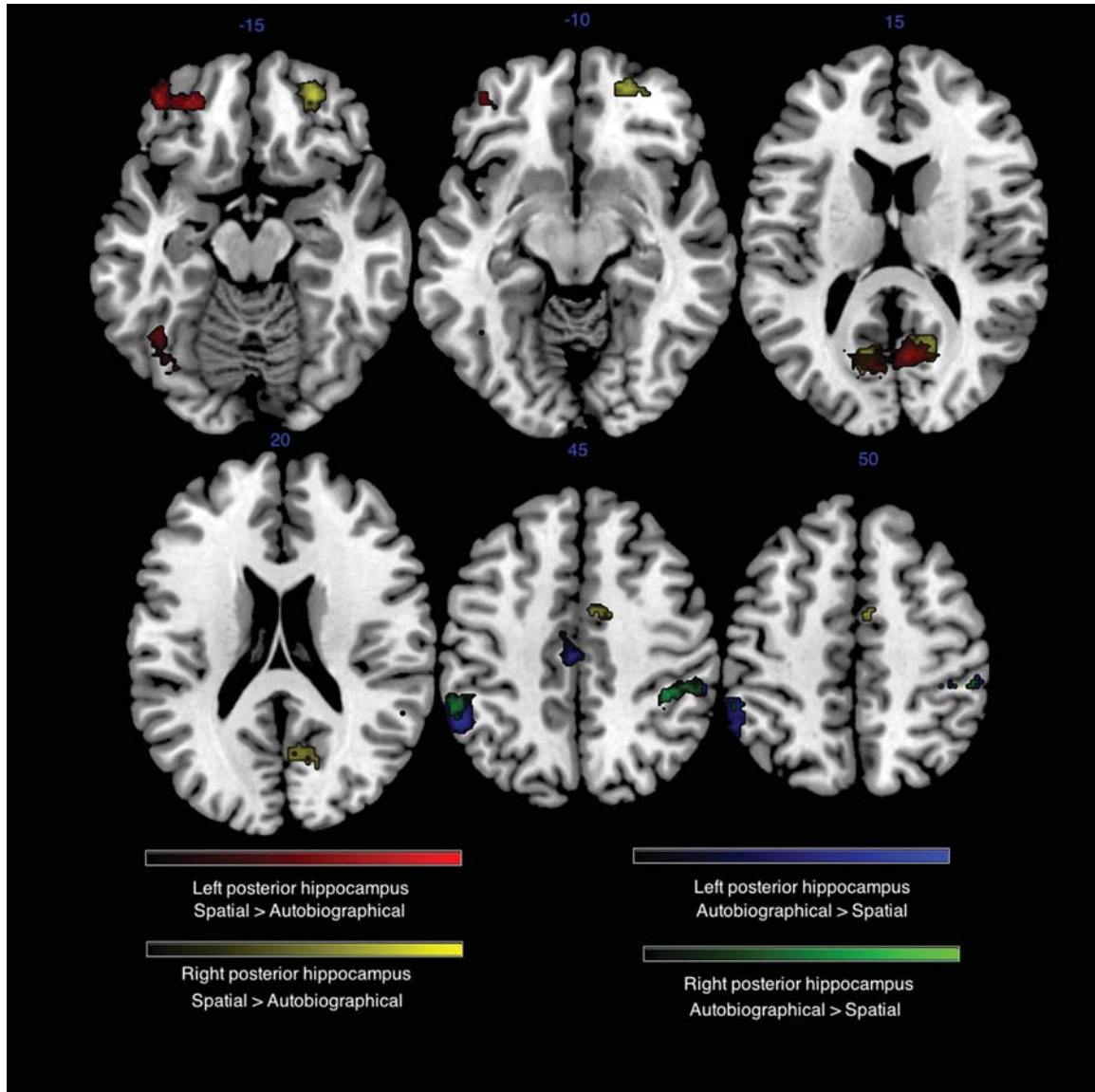


Fig. 5. A functional connectivity analysis that reported the brain regions that were more strongly connected to the posterior hippocampus during the autobiographical category condition as compared to the spatial category condition (blue and green for the left and right posterior hippocampus) and the brain regions that were more strongly connected to the posterior hippocampus during the spatial as compared to the autobiographical category condition (red and yellow for the left and right posterior hippocampus). The image was thresholded at $p < 0.005$ with a cluster extent > 128 (see Table 4). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

constructions via relational processing (Sheldon and Levine, 2016).

Although the above framework guided our interpretation of the presented results, we considered other possible views. Proponents of the scene construction hypothesis (Maguire and Mullally, 2013; Zeidman and Maguire, 2016) would predict greater anterior hippocampal activation during the spatial category task, which on the surface requires constructing a spatial scene that is then examined for exemplars. The autobiographical fluency task, on the other hand, is not based on constructing scenes, but rather evoking life-themes (Conway, 2009) to generate exemplars related to them. Although our findings would seem contrary to the scene construction hypothesis, more careful analyses could reveal that generating autobiographical exemplars depends on creating scenes in which these individuals were encountered, such as school buildings and classrooms, when thinking of friends. By contrast, the spatial category task may be more heavily weighted towards fine-grained perceptual detail in generating the items rather the construction of the scene itself. Our functional

connectivity analysis, which indicates that both anterior and posterior regions are implicated in both tasks, but with differential connectivity, is not inconsistent with the scene construction hypothesis.

Another possible way to interpret our findings draws on pattern separation and completion computations of the hippocampus (for a similar discussion, see Addis and Schacter, 2011; Kesner and Rolls, 2015; Rolls, 1991). With respect to the current study, generating items for the autobiographical categories involves retrieving items that aren't often represented as a complete concept or pattern (e.g., listing names of friends from different times in our lives, places, etc.). Thus, this category may more strongly rely on hippocampal pattern separation mechanisms. Retrieving items for the spatial categories likely requires hippocampal pattern completion mechanisms because these categories can benefit from re-activating a scene in one's mind to recall multiple items, thereby using the category as a code to construct a mental scene or event. Although speculative, this interpretation operates at a lower level

than the previously discussed views and attempts to explain how intrinsic hippocampal circuitry may be used to implement higher-level functions. However, one would have to assume that patterns separation and pattern completion mechanisms are distributed differentially along the long axis of the hippocampus in a way that would conform to our results.

There are still other conceptualizations of hippocampal processing that may be compatible with our data. For example, one could argue that autobiographical categories are more novel than the spatial categories (i.e., we are less likely to try to recall all the books we have read than to think about the organization of our kitchen). Under this view, autobiographical categories would pose an unusual demand on associative relational processing because they are ad-hoc in nature, whereas spatial categories would require generating items from well-learned semantic categories that are potentially more familiar with respect to everyday experiences (Poppenk et al., 2010). Another potential conceptualization of our findings is that the spatial categories primarily promote the recall of objects (e.g., kitchen utensils) that may or may not be perceptually detailed whereas the autobiographical categories primarily promote the recall of proper nouns (e.g., names of movies, friends, etc.). Such a conceptualization is particularly well-equipped to describe the connections between the anterior hippocampus and the temporal pole for the autobiographical categories, which is a critical region for proper name and person representations (Drane et al., 2008; Liu et al., 2016). Although we set out to test specific hypotheses extending from our framework of hippocampal processing specificity, we mention these plausible interpretations to raise the question about how best to define the contributions of the hippocampus.

5. Conclusions

Even though participants were ostensibly engaging semantic memory during autobiographical and spatial category fluency, different regions of the hippocampus were recruited when performing each of the tasks. Our findings of anterior/posterior hippocampal dissociations, both with respect to overall activation and with respect to functional connectivity, are similar to those reported in the episodic memory literature. Our findings provide evidence for a functional organization along the long axis of the hippocampus that is based on conceptual and perceptual relational retrieval and indicate that this manner of organization is apparent outside the domain of episodic memory.

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