CONRIBUTIONS OF THE ANTERIOR AND POSTERIOR HIPPOCAMPUS TO LONG-TERM MEMORY

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Distinct patterns of connectivity are thought to give rise to specialized functions within the anterior and posterior hippocampus. Consequently, there are several hypotheses regarding hippocampal long-axis specialization, including memory encoding versus retrieval, broad/gist-like representations versus detailed/fine-grained representations, and other cognitive processes versus spatial processing. This dissertation investigates the contributions of the anterior and posterior hippocampus to long-term memory. Chapter 1 investigates domain specificity in the hippocampus to determine how retrieval activity differs for two types of context information. Chapter 2 distinguishes between two prominent hypotheses of long-axis specialization to determine whether spatial memory encoding involves the anterior or posterior hippocampus. Chapter 3 investigates functional connectivity with the anterior and posterior hippocampus during spatial memory encoding and retrieval to test the predictions of the hippocampal encoding/retrieval and network (HERNET) model of memory (Kim, 2015). Together, the results presented in this dissertation provide insights into the roles of the anterior and posterior hippocampus and their interactions with the rest of the brain.

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GENERAL INTRODUCTION

The medial temporal lobe, including the hippocampus, parahippocampal cortex, and perirhinal cortex, is known to be critical for long-term memory. However, a large body of evidence indicates that there is functional specialization in the medial temporal lobe during episodic memory. One prominent model of medial temporal lobe function, the "binding of item and context" model, proposes that the perirhinal cortex processes item information, the parahippocampal cortex processes context information, and the hippocampus binds item and context details (Eichenbaum et al., 2007; Diana et al., 2007; Ranganath, 2010). As such, activity in the perirhinal cortex is often associated with item memory (memory for a particular item/object) and activity in the parahippocampal cortex and hippocampus is associated with source memory (memory for the context in which the item/object was encountered).

While the hippocampus as a whole is known to be involved in long-term memory, the anterior and posterior aspects of the hippocampus have little, if any, direct connectivity between them and largely non-overlapping patterns of connectivity with other brain regions (Kahn et al., 2008; Libby et al., 2012; Poppenk et al., 2013). Within the medial temporal lobe, the perirhinal cortex exhibits greater connectivity with the anterior hippocampus via the lateral entorhinal cortex, and the parahippocampal cortex exhibits greater connectivity with the posterior hippocampus via the medial entorhinal

cortex; therefore, functional specialization in other regions of the medial temporal lobe may lead to specialization across the long axis of the hippocampus (Libby et al., 2012; Poppenk et al., 2013; Knierim et al., 2014). Across the whole brain, the anterior hippocampus exhibits greater functional connectivity with the amygdala, ventromedial prefrontal cortex, and anterolateral temporal lobes, whereas the posterior hippocampus exhibits greater functional connectivity with the cuneus, precuneus, cingulate cortex, and parietal regions (Poppenk et al., 2013). Furthermore, the anterior hippocampus and posterior hippocampus also differ with respect to their cellular organization such that place cells, which selectively respond to particular spatial locations, are more numerous and have smaller receptive fields in the dorsal hippocampus of rodents (analogous to the human posterior hippocampus; Jung et al., 1994; Kjelstrup et al., 2008). These distinct patterns of connectivity and organization are thought to give rise to specialized functions in the anterior and posterior hippocampus.

Consequently, many hypotheses have been proposed with regard to differential processing along the longitudinal (anterior–posterior) axis of the hippocampus. For instance, it has been proposed that memory encoding is associated with the anterior hippocampus and memory retrieval is associated with the posterior hippocampus or that the anterior hippocampus is associated with broad/gist-like representations and the posterior hippocampus is associated with detailed/fine-grained representations (Poppenk et al., 2013). Other hypotheses indicate that the anterior hippocampus is specialized for motivational/emotional processing and that the posterior hippocampus is specialized for spatial processing (Poppenk et al., 2013).

The current dissertation explores the contributions of the anterior and posterior hippocampus to long-term memory. In Chapter 1, we investigate domain specificity of the hippocampus to better understand how spatial and non-spatial details of memory are represented in patterns of hippocampal activity. In Chapter 2, we distinguish between two prominent hypotheses of hippocampal long-axis specialization to determine whether anterior or posterior hippocampus is involved in spatial memory encoding. Finally, in Chapter 3, we investigate functional connectivity with the anterior and posterior hippocampus during a spatial memory task to investigate the predictions of the hippocampal encoding/retrieval and network (HERNET) model of memory (Kim, 2015).

1.0 CHAPTER 1

Distinct patterns of hippocampal activity associated with color and spatial source memory Haley A. Fritch, Preston P. Thakral, Scott D. Slotnick, and Robert S. Ross

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The hippocampus is known to be involved in source memory across a wide variety of stimuli and source types. Thus, source memory activity in the hippocampus is thought to be domain-general such that different types of source information are similarly processed in the hippocampus. However, there is some evidence of domain-specificity for spatial and temporal source information. The current fMRI study aimed to determine whether patterns of activity in the hippocampus differed for two types of visual source information: spatial location and background color. Participants completed three runs of a spatial memory task and three runs of a color memory task. During the study phase, 32 line drawings of common objects and animals were presented to either the left or right of fixation for the spatial memory task or on either a red or green background for the color memory task. During the test phase of both tasks, 48 object word labels were presented in the center of the screen and participants classified the corresponding item as old and previously on the "left"/on a "green" background, old and previously on the "right"/on a "red" background, or "new." Two analysis methods were employed to assess whether hippocampal activity differed between the two source types: a general linear model analysis and a classification-based searchlight multivoxel pattern analysis (MVPA). The searchlight MVPA revealed that activity associated with spatial memory and color memory could be classified with above-chance accuracy in a region of the right anterior hippocampus, and a follow-up analysis revealed that there was a significant effect of memory accuracy. These results indicate that different types of source memory are represented by distinct patterns of activity in the hippocampus.

The contributions of the hippocampus to source memory are often thought to be domain-general (Davachi, 2006; Staresina et al., 2011; Staresina et al., 2013; Rugg & Vilberg, 2013; Kim, 2010, 2011; Kafkas et al., 2017). Activity in the hippocampus has been linked to source memory across a wide range of domains including memory for spatial location (Cansino et al., 2002; Ross & Slotnick, 2008; Ekstrom et al., 2011; Jeye et al., 2018), background color (Weis et al., 2004; Tendolkar et al., 2008; Park et al., 2014), temporal context (Hayes et al., 2004; Ekstrom & Bookheimer, 2007; Ekstrom et al., 2011; Hseih et al., 2014), the task associated with an item during encoding (Davachi et al., 2003; Staresina & Davachi, 2008; Duarte et al., 2011; Diana, 2017), and the voice associated with a spoken word (Peters et al., 2007; Park et al., 2012). Additionally, studies that vary the type of item stimuli often find stimulus-invariant source memory effects in the hippocampus (Woodruff et al., 2004; Duarte et al., 2011; Kafkas et al., 2017). To further investigate domain-specific source memory effects, studies have directly compared activity associated with different types of source information. One study found that retrieval activity in the hippocampus scaled with response confidence for both visual and auditory source information, though activity associated with incorrect source judgements differed depending on modality (Thakral et al., 2015). Similarly, two subsequent memory analyses found domain-general encoding activity in the hippocampus for color and spatial source information (Uncapher et al., 2006) and for visual and auditory source information (Peters et al., 2007), providing further support for a domain-general role of the hippocampus.

Despite consistent involvement of the hippocampus across a wide array of source memory tasks, there is some evidence of domain-specificity in the hippocampus. For

instance, one study that varied the type of item stimuli found both stimulus-invariant source memory effects bilaterally and a region of the left posterior hippocampus that showed source memory effects only for pictorial stimuli, not word stimuli (Park et al., 2014), indicating that activity in certain regions of the hippocampus may be stimulusdependent. Additionally, while an early study found that hippocampal activity was similarly associated with spatial and temporal source retrieval (Hayes et al., 2004), a later study found both domain-general hippocampal activity and a region of the right hippocampus that produced greater activity associated with accurate retrieval of spatial information compared to temporal information (Ekstrom et al., 2011). Similarly, a representational similarity analysis (RSA) found that the spatial and temporal proximities of objects were coded in both distinct and overlapping voxels of the anterior hippocampus (Dueker et al., 2016). Thus, there is some evidence that spatial and temporal context information may be differentially coded in the hippocampus. However, only studies that investigated temporal source memory found domain-specific activity in the hippocampus. Therefore, it remains unclear whether source memory activity in the hippocampus is domain-general or if functional specialization in the anterior and posterior hippocampus would give rise to domain-specificity.

In addition to domain-specificity, there may be functional differences across the long-axis of the hippocampus in processing spatial and non-spatial information. The anterior hippocampus and posterior hippocampus have largely distinct patterns of connectivity with other regions of the medial temporal lobe. Specifically, the perirhinal cortex exhibits greater functional connectivity with the anterior hippocampus via the lateral entorhinal cortex, and the parahippocampal cortex exhibits greater connectivity

with the posterior hippocampus via the medial entorhinal cortex (Libby et al., 2012; Knierim et al., 2014). The connections to the parahippocampal cortex and medial entorhinal cortex are thought to give rise to spatial processing in the posterior hippocampus. Accordingly, one hypothesis of long-axis specialization proposes that the posterior hippocampus is involved in spatial processing and the anterior hippocampus is involved in other cognitive processes (Poppenk et al., 2013). In line with this hypothesis, place cells, which selectively respond to particular spatial locations, are more numerous and have smaller receptive fields in the dorsal hippocampus of rodents (analogous to the human posterior hippocampus; Jung et al., 1994; Kjelstrup et al., 2008). However, several studies have demonstrated that the anterior hippocampus (or ventral hippocampus in rodents) can also be involved in spatial memory (Cansino et al., 2002; Deuker et al., 2016; Contreras et al., 2018; Fritch et al., 2020). Nevertheless, the strong relationship between the posterior hippocampus and spatial processing leads to the hypothesis that the anterior hippocampus and posterior hippocampus may be preferentially associated with non-spatial and spatial memory, respectively. In fact, in rodents, lesions to the dorsal hippocampus impaired memory for a sequence of spatial locations, whereas lesions to the ventral hippocampus impaired memory for a sequence of odors (Hunsaker et al., 2008). Therefore, the differential inputs to the anterior and posterior hippocampus may result in specialized roles in memory.

In addition to hypotheses of long-axis specialization, there is evidence of hemispheric differences in hippocampal function. For instance, it has been shown that spatial memory preferentially engages the right hippocampus, whereas verbal memory preferentially engages the left hippocampus (e.g., Frings et al., 2006). Thus, different

types of source memory may result in differential activity between the left and right hippocampus.

The current study utilized two different source memory tasks to further investigate domain-specificity in the hippocampus by determining whether retrieval activity differed for two types of visual source information: spatial location and background color. Background color served as a non-spatial source detail to test hypotheses about differential processing of spatial and non-spatial information, and both of these tasks (i.e., remembering the spatial location of an item and remembering the color associated with an item) have been shown to activate the hippocampus in previous studies (spatial location: Cansino et al., 2002; Ross & Slotnick, 2008; color: Weis et al., 2004; Tendolkar et al., 2008; Park et al., 2014). As the anterior hippocampus and posterior hippocampus have different patterns of connectivity with other medial temporal lobe regions and there is evidence of hemispheric processing differences, it could be expected that each type of source information is preferentially processed by distinct regions of the hippocampus. Therefore, we first used a general linear model analysis to determine if any regions of the hippocampus were more strongly associated with one type of source memory than the other. We then used a classification-based searchlight MVPA to determine if patterns of activity in the hippocampus could be used to discriminate spatial and color source memory and investigate the location of these domain-specific patterns of activity (i.e., along the anterior-posterior extent of the hippocampus and across the left and right hippocampus).

Both univariate and multivariate analysis methods were employed to take advantage of their differential sensitivity to participant-level and voxel-level variability,

respectively (Davis et al., 2014), and their ability to detect clusters of differential activity and patterns of differential activity, respectively. If different types of source information are represented by magnitudes of activity in the hippocampus, the univariate analysis should produce significant differences in activity between spatial source memory and color source memory. If different types of source information are represented by patterns of hippocampal activity, MVPA should be able to classify the type of source information with above-chance accuracy. However, if source memory activity in the hippocampus is domain-general, MVPA should not be able to distinguish between color and spatial memory trials.

1.1 METHODS

1.1.1 Participants

Eighteen right-handed individuals (8 females, age range 20-32 years) with normal or corrected-to-normal vision from the Boston College community participated in the study. This sample size is comparable to prior studies investigating hippocampal pattern similarity and source memory (Hsieh et al., 2014; Fritch et al., 2020). Participants provided informed consent before the study and received monetary compensation for their participation. The protocol was approved by the Boston College Institutional Review Board. One participant was excluded from the analysis because they did not complete a sufficient number of runs of each memory task.

1.1.2 Stimulus Protocol

Participants completed three runs of a spatial memory task and three runs of a color memory task (Fig. 1.1). For each participant, the runs alternated between the spatial memory task and color memory task and the order of runs was counterbalanced across participants. The stimuli used in both tasks were line drawings of common objects and animals from the International Picture Naming Project at the UCSD Center for Research in Language (Szekely et al., 2004). During the study phase of the spatial memory runs, 32 line drawings were presented to either the left or right of fixation. During the study phase of the color memory task, 32 line drawings were presented in the center of the screen on either a red or a green background. Each image was displayed for 2.5 seconds followed by a fixation period for 0.5 seconds. Participants were instructed to remember each line drawing and either its spatial location (during the spatial memory runs) or the background color (during the color memory runs). Distinct line drawings were presented on each run and the locations and background colors of each item were counterbalanced across participants using a Latin square design. Items were presented in pseudorandom order with the constraint that no more than three items could be presented in the same location or on the same background color consecutively. Each study phase was followed by a 30second retrieval instruction screen, a 30-second blank screen, and then the corresponding test phase. During the test phase of both tasks, 48 word labels (nouns, corresponding to the 32 items shown during encoding and 16 new items) were presented in the center of the screen for 3.0 seconds with a 1.0-7.0 second fixation period between labels. Participants classified each item as old and previously on the "left" or on a "green" background (depending on the task), old and previously on the "right" or on a "red"

background, or "new" by pressing a button with their left hand. Therefore, across the three runs of each memory task, 96 color trials and 96 spatial trials were utilized in the analyses.



Fig. 1.1. Stimulus and response protocol for the spatial memory task (A) and color memory task (B). During the study phase of the spatial memory runs, line drawings were presented to either the left or right of fixation. During the study phase of the color memory runs, line drawings were presented on either a red or green background. During the test phase of both tasks, nouns were presented in the center of the screen and participants identified the previous location or background color of each item. Example responses and corresponding response types are shown to the right of each test item.

1.1.3 Image Acquisition and Data Analysis

A Siemens 3 Tesla Trio Scanner with a 32-channel head coil was used to obtain imaging data. A magnetization-prepared rapid-gradient echo sequence was used to acquire anatomic images (TR = 30 ms, TE = 3.3 ms, 256×256 acquisition matrix, 128 slices, 1 mm slice thickness, $1.33 \times 1 \times 1$ mm resolution) and an echo-planar imaging sequence was used to acquire functional images (TR = 2,000 ms, TE = 30 ms, 64×64 acquisition matrix, 33 axial-oblique slices, interleaved bottom-to-top slice acquisition order, 4 mm slice thickness, 4 mm isotropic resolution).

fMRI data were processed and the general linear model analysis was conducted using SPM 12 (Wellcome Trust Centre for Neuroimaging, London, UK). Preprocessing of the data included slice-time correction, motion correction to the first image of each run, and spatial normalization to the Montreal Neurological Institute (MNI) template, which included resampling at 2 mm³. To maximize spatial resolution, spatial smoothing was not conducted. Anatomic images were also normalized to MNI space with 2 mm³ resolution. For each participant, a general linear model analysis was conducted that included the following event types: encoding of items in each spatial location, encoding of items on each background color, accurate retrieval of items presented in each spatial location (left-hits and right-hits), inaccurate retrieval of items in each spatial location (left-misses and right-misses), accurate retrieval of items presented on each background color (green-hits and red-hits), inaccurate retrieval of items on each background color (green-misses and red-misses), forgotten items, new items correctly identified as new (correct rejections), new items incorrectly identified as old (new-"left", new-"right", new-"green", and new-"red"), failures to respond, six motion realignment parameters (three translation and three rotation), and a constant. The contrast of color hits and spatial hits was conducted to reveal differential activity related to the type of source information retrieved. Although data was collected during the encoding phase, a subsequent memory analysis was not conducted due to the short inter-trial interval of 3 seconds, which precluded accurate estimation of the hemodynamic response during this phase. For each contrast, an individual voxel threshold of p < .001, cluster extent corrected to p < .05, was enforced. The applied cluster extent threshold of 24 voxels was calculated from 10,000 iterations of a Monte Carlo simulation using a spatial autocorrelation value of 3 mm (which was estimated using a null contrast image produced by contrasting even and odd hit trials from both tasks; see Slotnick, 2017a).

The hippocampal region of interest (ROI) was defined manually for each participant using known anatomical distinctions in the medial temporal lobe (Pruessner et al., 2000; Bernasconi et al., 2003; Devourney et al., 2013; Fig. 1.2). The anterior border was defined as the alveus of the hippocampus and the posterior border was defined as the point at which hippocampal gray matter could no long be seen inferomedially to the lateral ventricle. The hippocampal ROIs were then segmented into anterior and posterior regions at the slice in which the uncal apex disappeared.



Fig. 1.2. The hippocampus region of interest for one participant. The regions in red were included in the anterior hippocampus and the regions in blue were included in the posterior hippocampus.

The multivariate analyses were conducted using the Princeton MVPA Toolbox (https://pni.princeton.edu/pni-software-tools/mvpa-toolbox) and custom MATLAB scripts. Activity patterns within the hippocampal ROI were detrended to remove linear and quadratic trends and z-scored across time points within each run. Activity patterns associated with retrieval hits were then acquired by averaging activity levels three and four TRs after the onset of each item whose source was accurately remembered, corresponding to the peak of the canonical hemodynamic response (our preprocessing

and analysis pipeline follows other studies that employed a ROI-based approach to pattern similarity analysis e.g., Koen and Rugg 2016; Wang et al., 2016; Thakral, Wang, & Rugg 2017). Confounds related to individual trial reaction times were removed with linear regression and the residualized activity patterns were used in the multivariate analyses reported below.

A searchlight MVPA was employed to identify regions of the hippocampus where the patterns of activity differentially coded the two types of source. The searchlight used one-voxel radius spheres (i.e., 7 total voxels) centered on each voxel within the hippocampal ROIs. This sphere size (56 mm³) was chosen a priori because, using a similar paradigm, the hippocampal activations associated with spatial memory have been shown to be very small (average size 44.67 ± 5.45 mm³; Jeye et al., 2018). For each spherical set of voxels, a Gaussian Naïve Bayes classifier was trained to classify the type of source information (spatial or color) associated with retrieval-hit trials. Three-fold cross-validation was employed in which retrieval trials from two of the three runs for each task were used to train the classifier (i.e., the classifier was trained to distinguish color and spatial information using trials from two color runs and two spatial runs) and retrieval trials from the remaining run of each task were used to test classification accuracy. Classification accuracy was recorded as the proportion of correctly classified trials for the three cross-validation folds.

To ensure that the MVPA classifier was not biased toward the source memory condition with the greater number of hit trials (i.e., the task with greater memory accuracy), for each participant, a subset of trials from the memory task with greater accuracy was randomly sampled before the classification analysis to equate numbers with

the memory task containing the lower number of trials. This subsampling procedure was conducted 100 times to avoid possible sampling error. Classification accuracy was recorded as the average accuracy across the 100 iterations of subsampling and crossvalidation. Each sphere's accuracy was then z-scored by subtracting 50% (chance accuracy) and dividing by the standard deviation of accuracy across the 100 iterations. Therefore, the statistical tests used to assess above-chance accuracy compared these zscored accuracies versus zero.

To correct for multiple comparisons in the MVPA analysis, the identical randomeffect searchlight procedure was conducted 100 times with scrambled trial labels to produce a set of null volumes. An individual voxel threshold of p < .05 was employed, and across all null volumes, the cluster extent threshold was determined to ensure significant activity was corrected for multiple comparisons to p < .05 (see Slotnick, 2017a). This resulted in a minimum cluster extent threshold of 4 voxels, which was enforced for the MVPA searchlight analysis.

A representational similarity analysis (RSA) was used to assess whether the ability to classify patterns of activity was dependent on memory success. Given subjects' high memory accuracy (see the Results) and consequently, the low number of miss trials for many participants, this approach was used to probe for the effect of memory success because it is less sensitive to the effects of low trial numbers than the classification-based MVPA. For this follow-up analysis of memory success, participants with three or fewer miss trials for either of the tasks were excluded, resulting in a sample of 13 participants (for the participants included in this analysis, the number of miss trials for each task ranged from 4–24, mean = 12.6). Fisher z-transformed Pearson's correlations were

computed between pairs of retrieval-hit trials that shared the same source type (i.e., colorcolor and spatial-spatial source-matched similarity) and retrieval-miss trials that shared the same source type and then averaged to generate overall source-matched similarity values. To ensure similarity values were not inflated by within-run autocorrelation, correlations were only conducted on trials across separate runs (Mumford et al., 2014). For consistency with the primary searchlight MVPA analysis, we also tested for memorysuccess effects by evaluating MVPA classification accuracy with hits and misses (even though this method is more sensitive to low trial numbers, and thus was expected to produce null results).

For the behavioral analysis, item memory accuracy was defined as the percentage of old items correctly given an "old" response (old-hit rate) and new items correctly given a "new" response (new-correct rejection rate) regardless of source memory accuracy, weighted by the probability of each item type (i.e., (hit rate) x p(old item) + (correct rejection rate) x p(new item); Macmillan and Creelman, 2005). Source memory accuracy was defined as the percent of old items where source was correctly identified, contingent on correct item memory recognition. For both item memory accuracy and source memory accuracy, chance performance was 50% as there were two possible responses for each type of judgement (i.e., "old" and "new" for item memory, and "left" and "right" or "red" and "green" for source memory).

1.2 **RESULTS**

1.2.1 Behavioral Results

Item recognition accuracy was significantly greater than chance during both the spatial memory task ($84.5\% \pm 1.58\%$, mean ± 1 SE; t(16) = 21.88, p < .001) and the color memory task ($86.4\% \pm 1.54\%$; t(16) = 23.59, p < .001). For items correctly identified as old, spatial memory accuracy ($90.8\% \pm 1.3\%$) was significantly greater than color memory accuracy ($78.6\% \pm 1.8\%$; t(16) = 6.70, p < .001).

1.2.2 fMRI Results

Domain-specific memory activity was assessed using a general linear model analysis by contrasting accurate retrieval of spatial information and accurate retrieval of color information (spatial-hits > color-hits and color-hits > spatial-hits). These contrasts produced no significant hippocampal activity (even when no cluster extent threshold was enforced).

Searchlight MVPA was used to determine if any regions of the hippocampus contained patterns of activity that could be used to correctly classify the type of source information (i.e., spatial location or background color). This analysis revealed a region of the right anterior hippocampus in which classification accuracy for retrieval-hit trials was greater than chance (x = 26, y = -10, z = -28; Fig. 1.3).



Fig. 1.3 Region of above-chance classification accuracy from the searchlight multivoxel pattern analysis (MVPA) displayed on the group average anatomic image.

To verify that the above-chance classification accuracy was driven by source memory information, rather than some other difference between the two tasks, we next conducted an RSA within the cluster identified from the searchlight analysis using hits and misses in a subset of participants who had a sufficient number of miss trials. If the ability to classify the type of source information was influenced by memory success, the source-matched similarity values (i.e., the representational similarity between pairs of trials that share the same source information) for hit trials should be greater than the source-matched similarity for miss trials. This analysis revealed a significant decrease in source-matched similarity for misses compared to hits (t(12) = 2.89, p < .05), which suggests that the ability to classify patterns of activity in the primary analysis was driven by accurate source memory information. We also tested for memory-success effects by evaluating MVPA pattern similarity with both hits and misses in the same subset of participants who had a sufficient number of miss trials. This analysis revealed a

numerical, but nonsignificant, decrease in classification accuracy for hits and misses compared to only hits (z-scored accuracy with hits and misses = 2.89, z-scored accuracy with only hits = 2.95, t(12) < 1).

To determine if the results were primarily driven by color or spatial information we subtracted source-mismatched similarity values (i.e., the similarity computed from color-spatial hit trial pairs) from color source-matched similarity values (i.e., color-color similarity) and spatial source-matched similarity values (i.e., spatial-spatial similarity) and compared these two differences using a t-test. There was no significant difference between these values (t(16) < 1), suggesting that both types of source information contributed to the distinct patterns of activity.

1.3 DISCUSSION

The current results suggest that different types of source information are represented by distinct patterns of activity in the right anterior hippocampus. While the general linear model analysis did not reveal any hippocampal activations for the contrasts of spatial-hits and color-hits, the searchlight MVPA revealed that patterns of activity in the right anterior hippocampus could be used to correctly classify the type of source information.

The lack of significant findings from the general linear model analysis is in line with previous studies that have found domain-general source memory effects in the hippocampus (e.g., Uncapher et al., 2006; Staresina et al., 2011; for reviews, see Rugg & Vilberg, 2013; Kim, 2010, 2011). These results indicate that activity levels in the hippocampus were similar across both source memory tasks. However, null univariate results may alternatively be a consequence of insufficient sensitivity with this type of analysis. Indeed, the significant MVPA results indicate that the right anterior hippocampus does contain differential representations for different types of source information. As mentioned in the introduction, the null general linear model findings in contrast to the significant MVPA findings could reflect the differential sensitivity of these analyses to participant-level and voxel-level variability, respectively (Davis et al. 2014; see also Thakral, Wang, & Rugg 2017). Additionally, null findings from the general linear model analysis and significant findings from the MVPA suggest that different types of source information may be differentially represented in patterns of hippocampal activity rather than preferentially processed by distinct regions of the hippocampus.

Above-chance classification accuracy in the right anterior hippocampus was likely driven by source information. Conducting the RSA on miss trials resulted in a significant decrease in source-matched similarity compared to hit trials and conducting the MVPA with both hit and miss trials, as compared to only hit trials, resulted in a numerical decrease in classification accuracy. If there were some other factor driving differential activity in the two tasks, such as differences in subjects' motivation or memory strategies, analyzing miss trials should not have lowered source-matched similarity values and classification accuracy. As such, this decrease suggests that the source-specific activity observed in the primary analysis (of hits) was driven by accurate source memory, rather than other differences between the two tasks. However, it is also possible that similarity differences were driven by distinct cognitive processes engaged

during the retrieval of spatial and nonspatial information, rather than the content of the retrieved memories (Rugg et al., 2008).

As mentioned in the introduction, previous studies have found activity in the hippocampus that differs for spatial and temporal source memory (Ekstrom et al., 2011; Dueker et al., 2016). It is possible that spatial and temporal source information are processed differently than non-spatial source information (e.g., color) as the hippocampus is often thought to be specialized for spatial and temporal information due to the existence of hippocampal place cells and time cells (MacDonald et al., 2011; Howard & Eichenbaum, 2015; Ekstrom & Ranganath, 2017; Umbach et al., 2020). Because the current study also utilized a spatial memory task, the finding of source-specific patterns of activity may reflect that hippocampal activity associated with spatial information is distinct from activity associated with non-spatial source information. Specifically, the patterns of activity associated with spatial source information may have reflected activity in cell populations specialized for spatial processing (e.g., place cells), whereas patterns of activity associated with color source information may have reflected activity in cells not specialized for spatial processing, but not necessarily specialized for color processing. Indeed, previous studies have also found patterns of hippocampal activity that differed depending on spatial location (e.g., Hassabis et al., 2009; Sulpizio et al., 2014; Kim et al., 2017; Fritch et al., 2020). However, it has been argued that activity associated with place cells cannot be detected with fMRI and findings of location-specific hippocampal activity patterns are instead driven by visual/perceptual confounds or analysis issues (Nolan et al., 2018). Importantly, there were no perceptual differences between the retrieval phases of the two memory tasks employed in the current study. Nevertheless, it is possible that the

current results were driven by differences other than activity in distributed patterns of hippocampal cells selective for spatial and non-spatial information. Whether differential hippocampal activity would be found for different types of non-spatial source memory is a topic of future research.

The current results, along with previous evidence, indicate that distinct patterns of hippocampal activity may represent the spatial, temporal, and non-spatial details of an event. Two previous MVPA studies attempted to classify object categories (e.g., objects, scenes, and faces) in medial temporal lobe regions and found that classification accuracy in the hippocampus was at chance levels (Diana et al., 2008; Huffman & Stark, 2014). The inability to classify item information, in contrast to the current finding that context information can be distinguished, may indicate that when item and context information are bound by the hippocampus, representations of the item information are specific to the current context. This idea is in line with the results of Hsieh et al. (2014) which found that hippocampal activity patterns contained information about objects in their temporal context, but not about objects alone (i.e., there was little similarity between activity patterns associated with encounters with the same object in different temporal contexts). Hsieh et al. proposed that this coding of object-context associations may allow the hippocampus to distinguish between multiple encounters with the same object in different contexts. Similarly, it has been shown that conjunctive hippocampal representations of events have a hierarchical organization in which context information is superordinate to object identity (i.e., there is a higher degree of similarity between representations that share context information than between representations that share object information; McKenzie et al., 2016). Therefore, distinct representations of spatial, temporal, and non-

spatial context information may serve as an organizing principle to link memories with shared context details.

Neither region of the hippocampus was preferentially associated with one type of source information; however, distinct patterns of color and spatial source memory were found in the right anterior hippocampus from the searchlight MVPA. Although null findings in the posterior hippocampus could be due to many factors (e.g., a lack of an effect, a method with insufficient sensitivity, or a high level of noise), the specific stimuli and task demands may have led to stronger involvement of the anterior hippocampus due to differential inputs along the long axis of the hippocampus. As mentioned previously, the anterior and posterior hippocampus preferentially receive input from the perirhinal cortex via the lateral entorhinal cortex and parahippocampal cortex via the medial entorhinal cortex, respectively. A recent meta-analysis found that memory studies using object stimuli tend to find subsequent memory and retrieval effects in more anterior regions of the hippocampus compared to studies that use scene or face stimuli (Grady, 2019), which is likely related to the stimulus preferences of the perirhinal cortex and parahippocampal cortex. Additionally, the finding of above-chance classification accuracy in the right hippocampus may be due to preferential processing of visual-spatial information in this region (Frings et al., 2006; Slotnick, 2017b).

The behavioral results indicate that participants could more accurately remember the previous location of an item than the color associated with an item. This finding is consistent with the behavioral results of a previous study in which spatial memory accuracy was greater than color memory accuracy (Uncapher et al., 2006). Additionally, Cooper and Ritchey (2019) recently found that participants' spatial memory judgements

were more precise than color memory judgements. Superior memory for spatial location over background color may be a result of the increased biological relevance of spatial memory or the fact that spatial memory is used on a more regular basis in everyday life.

One limitation of the current study is the relatively low sample size, particularly in the RSA of hits and misses in which only a subset of subjects' data could be included due to low numbers of miss trials. Additionally, having separate runs for color memory and spatial memory could have introduced unexpected differences between the tasks such as context-selective pre-retrieval processing (Polyn et al., 2005). However, the decrease in source-matched similarity for miss trials provides evidence against this possibility and suggests that classification accuracy was driven by source memory success.

While source memory activity in the hippocampus is often thought to be domaingeneral, the current results indicate that domain-specific patterns of hippocampal activity are associated with spatial source memory and color source memory. These results suggest that different types of source information are differentially processed by the hippocampus and coded in domain-specific patterns of activity.

2.0 CHAPTER 2

The anterior hippocampus is associated with spatial memory encoding Haley A Fritch, Sean P MacEvoy, Preston P Thakral, Brittany M Jeye, Robert S Ross, and Scott D Slotnick

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There are many hypotheses regarding specialization of the anterior versus posterior hippocampus including memory encoding versus retrieval and other cognitive processes versus spatial memory. In the present functional magnetic resonance imaging study, we distinguished between the hypothesis linking encoding to the anterior hippocampus and the hypothesis linking spatial memory to the posterior hippocampus by evaluating whether spatial memory encoding involved the anterior hippocampus or the posterior hippocampus. During encoding, participants viewed abstract shapes in each of four visual field quadrants while instructed to maintain central fixation. During retrieval, old shapes were presented at fixation and participants identified the previous quadrant of each shape. A general linear model analysis did not reveal encoding activations in the anterior or posterior hippocampus. These results motivated a multi-voxel pattern analysis to assess whether there were distinct patterns of activity associated with encoding shapes in each quadrant within the anterior or posterior hippocampus. For each participant, patterns of activity associated with each quadrant were split by run (i.e., odd runs versus even runs) and the patterns in half the data were used to classify patterns in the other half of the data. Classification accuracy for items at encoding, collapsed over subsequent accuracy, was significantly above chance in the anterior but not posterior hippocampus. The present findings indicate that spatial memory encoding is associated with patterns of activity in the anterior hippocampus.

The medial temporal lobe consists of the hippocampus and surrounding cortical regions including the perirhinal cortex (within the anterior medial temporal lobe) and the parahippocampal cortex (within the posterior medial temporal lobe). A large body of evidence indicates that the perirhinal cortex and the parahippocampal cortex are involved in item processing and context processing, respectively, and the hippocampus binds item and context information during long-term memory (Diana et al., 2007; Eichenbaum et al., 2007; Ranganath, 2010). Specifically, item memory, which is typically isolated by comparing old item hits and misses, has been associated with activity in the perirhinal cortex, while context memory (e.g., memory for item color or spatial location) has been associated with activity in the parahippocampal cortex and the hippocampus. Although it has been argued that differential activity in these regions reflects a memory strength confound (Squire et al., 2007), the same pattern of activity has been observed when item memory strength is greater than context memory or vice versa (Slotnick, 2013).

Within the hippocampus, many hypotheses have been proposed with regard to differential processing along its longitudinal (anterior–posterior) axis including long-term memory encoding versus retrieval, global versus local spatial representations, and other cognitive processes versus spatial memory (Poppenk et al., 2013). Of importance, these hypotheses are not mutually exclusive because they involve related and overlapping cognitive processes. An early meta-analysis of 52 positron emission tomography (PET) studies reported that encoding activations were largely restricted to the anterior hippocampus and retrieval activations were largely restricted to the posterior hippocampus, which was referred to as the hippocampus encoding–retrieval (HIPER) model (Lepage et al., 1998). However, shortly thereafter, another meta-analysis of PET

and functional magnetic resonance imaging (fMRI) studies claimed that there was little evidence for this anterior-posterior distinction (Schacter & Wagner, 1999), although only the PET results included a sufficient number of studies to be meaningful. An important difference between the two studies is that Lepage et al. (1998) largely restricted their analysis to activations within the hippocampus, whereas Schacter and Wagner (1999) analyzed activations in the MTL more broadly (i.e., the hippocampus and surrounding cortical regions). Consequently, Schacter and Wagner (1999) reported a number of PET encoding activations located in the posterior MTL (i.e., the parahippocampal cortex), which was interpreted as contradictory to the HIPER model. However, based on our current-day understanding of the functional roles of the MTL sub-regions, the encoding activations in the parahippocampal cortex observed by Schacter and Wagner (1999) likely reflected context processing during encoding and did not contradict the existence of an encoding-retrieval distinction within the hippocampus per se. Indeed, when encoding and retrieval activations are considered only within the hippocampus proper, the HIPER model is supported by the PET results of both Lepage et al. (Fig. 2.1A, p < p.001, Fisher exact test) and Schacter and Wagner (Fig. 2.1B, p < .05, chi-square test).



Fig. 2.1 Right, hippocampal encoding and retrieval activations included in the metaanalyses conducted by (A) Lepage et al. (Reprinted from Hippocampus, Volume 8, Martin Lepage, Reza Habib, and Endel Tulving, Hippocampal PET activations of memory encoding and retrieval: The HIPER model, Pages 313–322, Copyright (1998), with permission from John Wiley & Sons, Inc.) and (B) Schacter and Wagner (Reprinted from Hippocampus, Volume 9, Daniel L. Schacter and Anthony D. Wagner, Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval, Pages 7–24, Copyright (1999), with permission from John Wiley & Sons, Inc.). (C) Regions that demonstrated greater encoding than retrieval activity (yellow) or greater retrieval than encoding activity (blue) in the meta-analysis conducted by Kim et al. (Reprinted from Hippocampus, Volume 25, Hongkeun Kim, Encoding and retrieval along the long axis of the hippocampus and their relationships with dorsal attention and default mode networks: The HERNET model, Pages 500–510, Copyright (2015), with permission from John Wiley & Sons, Inc.).

In the last two decades, many fMRI studies have investigated the long-term memory encoding-retrieval distinction along the long axis of the hippocampus. Although an earlier qualitative fMRI review did not observe such a distinction (Henson, 2005; see also, Schacter & Wagner, 1999), a few years later, an activation likelihood estimation meta-analysis provided evidence that the anterior hippocampus is associated with longterm memory encoding (Spaniol et al., 2009). Recently, another activation likelihood estimation meta-analysis provided compelling evidence that long-term memory encoding was associated with the anterior hippocampus and long-term memory retrieval was associated with the posterior hippocampus (Fig. 2.1C; Kim et al., 2015; Langnes et al., 2018, reported similar results). The fMRI findings and the PET findings reviewed above provide convergent support for the HIPER model.

As noted previously, spatial memory has often been linked to the posterior hippocampus (Moser & Moser, 1998; Poppenk et al., 2013); however, there is also evidence that the anterior hippocampus is associated with spatial memory. fMRI evidence indicates that spatial navigation preferentially activates the posterior hippocampus (Kuhn & Gallinat, 2014; Duarte et al., 2014; Grady, 2019) and a longitudinal study of London taxi drivers found that the size of the posterior hippocampus increased as they learned the layout of the city (Woolet & Maguire, 2011). Although a study that lesioned the ventral hippocampus in rats (analogous to the anterior hippocampus in humans) also observed spatial memory impairments (Broadbent et al., 2004), spatial memory studies in rodents have historically targeted the dorsal hippocampus (analogous to the posterior hippocampus in humans) because the ventral hippocampus is more difficult to reach (cf., Nadel et al., 2013). Nevertheless, there are place cells in the ventral hippocampus of rats (analogous to the human anterior hippocampus), which indicates that spatial processing may be distributed along its long axis (Kjelstrup et al., 2008). Furthermore, an fMRI study found that accurate retrieval of spatial location information activated the anterior hippocampus (Cansino et al., 2002), a representational similarity analysis found that
patterns of activity in the anterior hippocampus represent the spatial and temporal proximities of objects previously experienced during a navigation task (Deuker et al., 2016), and a recent rat study showed that navigation of relatively complex environments can activate the ventral hippocampus (Contreras et al., 2018). Therefore, the anterior hippocampus does appear to be involved in spatial processing during some tasks.

Critically, spatial navigation involves multiple cognitive processes including path integration, spatial updating, and wayfinding (cf., Jeye et al., 2018); thus, previous associations between spatial navigation and the posterior hippocampus may have reflected one of these processes rather than spatial memory. In the current study, we distinguished between the hypothesis linking encoding to the anterior hippocampus and the hypothesis linking spatial memory to the posterior hippocampus using a long-term memory task that isolated spatial memory for items presented in each of the four quadrants of the visual field (Fig. 2.2). In particular, activity in the anterior hippocampus during spatial memory encoding can be used to distinguish between these two hypotheses. If encoding, regardless of memory type (including spatial memory), is associated with the anterior hippocampus, encoding should involve the anterior hippocampus. However, if spatial memory, regardless of memory phase (encoding or

retrieval), is associated with the posterior hippocampus, encoding should not involve the anterior hippocampus (and should only involve the posterior hippocampus).



Fig. 2.2 During the study phase (left), participants viewed abstract shapes presented in the upper-right, upper-left, lower-right, or lower-left quadrant of the visual field. During the test phase (right), participants viewed the same shapes presented at fixation and identified in which quadrant the shape had previously appeared. Example responses and corresponding response types are shown to the right.

We first conducted a general linear model analysis to confirm there were subsequent memory effects in regions that have been associated with spatial memory by contrasting correct spatial memory (hits) and incorrect spatial memory (misses) in addition to considering hits alone. As there were no significant activations in the hippocampus (see below), we then collapsed over memory accuracy (i.e., hits and misses) to maximize power, which was motivated by the PET studies described above that employed blocked designs and produced a robust anterior–posterior/encoding–retrieval distinction in the hippocampus. A general linear model analysis with these collapsed data again produced no significant activations in the hippocampus. Therefore, a multi-voxel pattern analysis (MVPA) was employed to assess whether the encoding patterns associated with memory for information in each visual field quadrant was unique within the anterior hippocampus or posterior hippocampus. To anticipate the results, we found that patterns of activity in the anterior but not posterior hippocampus classified encoding quadrants at above chance levels.

2.1 METHODS

2.1.1 Participants

Sixteen right-handed individuals (13 females, age range 20-29 years old) with normal or corrected-to-normal vision from the Boston College community participated in the study. Participants received \$10 for the training session and \$25 per hour for the fMRI scanning session. All participants provided informed consent before each session and the Boston College Institutional Review Board approved the procedure.

2.1.2 Stimulus Protocol

Participants completed a training session, consisting of one quarter-length and one full-length run, and then an fMRI scanning session, consisting of an anatomic scan and seven or eight full-length runs (fourteen participants completed eight runs and two participants completed seven runs). Before each run, participants were instructed to maintain central fixation and remember the spatial location of each shape. A prior study

using a similar task found that participants maintained fixation to within 1° of visual angle (Slotnick & Thakral, 2011). All runs consisted of a study phase followed by a test phase (Fig. 2.2). Stimuli for the task were computer-generated abstract shapes (for information on shape construction, see Slotnick & Schacter, 2004). Different shapes were used for each run and shape locations were counterbalanced across participants using a Latin Square design. During the study phase, 32 abstract shapes were presented in one of four spatial locations: the upper left, upper right, lower left, or lower right quadrant of the visual field. The same number of shapes appeared in each of the four quadrants. Shapes spanned 3.8° of visual angle and their nearest edge was 2.1° of visual angle away from the central fixation point. Each shape appeared for 2.5 seconds with a 0.5 second fixation period. Shapes were displayed three times and presentation order was randomized with the constraint that no more than three items appeared consecutively in the same location. During the test phase, shapes from the study phase were presented for 3.0 seconds at fixation followed by a 2.5-second reminder screen to provide a confidence rating and a 0.5 to 4.5 second fixation period. Participants responded by pressing a button with the fingers of their left hand to classify each shape as previously presented in the "upper left", "upper right", "lower left" or "lower right" (while the shape was on the screen) and then provided an "unsure", "sure" or "very sure" rating (during the confidence rating reminder period).

2.1.3 Image Acquisition and Data Analysis

A Siemens 3 Tesla Trio Scanner with a 32-channel head coil was used to obtain imaging data. A magnetization-prepared rapid-gradient echo sequence was used to

acquire anatomic images (TR = 30 ms, TE = 3.3 ms, 256×256 acquisition matrix, 128 slices, 1 mm slice thickness, $1.33 \times 1 \times 1$ mm resolution) and an echo-planar imaging sequence was used to acquire functional images (TR = 2,000 ms, TE = 30 ms, 64×64 acquisition matrix, 34 axial-oblique slices parallel to the anterior-posterior commissure plane, interleaved bottom-to-top slice acquisition order, 4 mm slice thickness, 4 mm isotropic resolution).

fMRI data were processed and the general linear model and ANOVA analyses were conducted using SPM 12 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom). Preprocessing of the data included slice-time correction, motion correction to the first image of each run, and spatial normalization to the Montreal Neurological Institute (MNI) template, which included resampling at 2 mm³. To maximize spatial resolution, spatial smoothing was not conducted. Anatomic images were also normalized to MNI space with 2 mm³ resolution and averaged across participants. For each participant, a general linear model analysis was conducted that included the following event types: encoding of items in each visual field quadrant that were later accurately retrieved (i.e. upper-left, lower-left, upper-right, and lower-right subsequent hits), encoding of items in each visual field quadrant that were later inaccurately retrieved (i.e. upper-left, lower-left, upper-right, and lower-right subsequent misses), accurate retrieval of items in each visual field quadrant (i.e. upper-left, lowerleft, upper-right, and lower-right hits), inaccurate retrieval of items in each visual field quadrant (upper-left, lower-left, upper-right, and lower-right misses), failures to respond, and a constant. A high-pass filter of .0078 Hertz (1/128 seconds) was employed, which was well below the fundamental frequency of our design (e.g., the four encoding event

protocols differed only at frequencies above approximately 2 Hertz). A 2 (memory accuracy) x 4 (visual field quadrant) within-subject ANOVA was used to test for effects and interactions at encoding. For all comparisons, an individual voxel threshold of p < .001 was enforced, cluster-extent corrected to p < .05. A cluster extent threshold of 24 resampled voxels was determined from a Monte Carlo simulation with 10,000 iterations using a spatial autocorrelation value of 3.56 mm (which was estimated using a null contrast image obtained by contrasting retrieval hits in the upper left quadrant versus all other retrieval hits; see Slotnick, 2017a).

MVPA was conducted using custom scripts written in MATLAB (MathWorks, Natick, Massachusetts). Voxels in the hippocampus were identified manually using the group anatomic image based on anatomical distinctions within the medial temporal lobe (Insausti et al., 1998; Pruessner et al., 2000; Bernasconi et al., 2003; Malykhin et al., 2007). The anterior-posterior span of the hippocampal region analyzed was first determined from a prior general linear model analysis conducted in Jeye et al. (2018) such that hippocampal voxels between the most posterior (y = -34) and the most anterior (y = -8) activations were selected (note, all coordinates are provided in MNI space). To ensure that no voxels in the hippocampal tail were excluded, the posterior border was then extended to y = -40. The hippocampal voxels were then segmented based on the coordinate guidelines recommended by Poppenk et al. (2013), which proposed the anterior hippocampus, analogous to the hippocampal head, is at and anterior to y = -21. We included slices at this location and more anterior in the anterior hippocampus and included slices more posterior to this location in the posterior hippocampus. To ensure that this coordinate accurately segmented the hippocampus, the division between the

anterior and posterior hippocampus (defined as the disappearance of the uncal apex) was located in each participant's anatomic image. The average coordinate was y = -21.3(standard deviation = 0.7).

To conduct the MVPA, each of the following steps was repeated for each participant. The same procedure was employed for encoding within each quadrant, collapsed over subsequent memory, and encoding hits. For each run of each participant, a general linear model analysis was conducted using the event types listed above. Encoding activity associated with shapes in each of the four quadrants was isolated with a weighted contrast of the shapes in a particular quadrant versus shapes in the other three quadrants (where each of the other three quadrants received a relative weight of one third compared to the quadrant of interest). Voxels with a value of zero for all runs and quadrants were removed to eliminate voxels with signal dropout. The classification procedure employed a method similar to that used in Haxby et al. (2001). The hippocampal activity patterns for encoding in each quadrant were then split in half by run (i.e., even runs versus odd runs). Each voxel's response magnitudes in odd runs were averaged together to create a template pattern and voxel magnitudes of the even runs were averaged to create a test pattern, yielding four template patterns and four test patterns, one for each encoding quadrant. Each template pattern was then separately correlated with each of the four test patterns to assess similarity across the same voxels in the template and test patterns. If a test pattern was most highly correlated with (most similar to) the template pattern in the same quadrant, the classification for that test pattern was recorded as "correct". If a test pattern was most highly correlated with the template pattern for encoding in one of the other three quadrants, the classification for that test pattern was recorded as "incorrect".

Each participant's accuracy rate was the rate of correct classification across all four test patterns. As each test pattern was compared to four template patterns, chance accuracy was 25%. If patterns of encoding or retrieval activity in a region of the hippocampus contain information about spatial location, classification accuracy for voxels in that region should be greater than chance. Thus, a one-tailed t-test was used to assess whether classification accuracy for the anterior or posterior hippocampus was greater than chance, and a two-tailed t-test was used to assess whether classification accuracy differed between the anterior and posterior hippocampus. Although there were a sufficient number of runs for each participant to analyze hits separately (i.e., all participants had at least 6 out of 8 runs with hits in each quadrant), there were not a sufficient number of runs for each participant to analyze misses separately (i.e., only 12 participants had at least 6 of 8 runs with misses in each quadrant).

2.2 RESULTS

2.2.1 Behavioral Results

A repeated-measures ANOVA revealed that spatial memory accuracy differed for shapes presented in the upper left (58.0%, chance = 25%), lower left (64.9%), upper right (66.2%), and lower right (57.8%) quadrants of the visual field (F(3,45) = 3.38, p < .05). Follow-up comparisons indicated that accuracy differed for shapes presented in the upper left and lower left quadrants (t(15) = 2.67, p < .05) and for shapes presented in the upper right and lower right quadrants (t(15) = 2.44, p < .05). A second repeated-measures

ANOVA revealed that reaction times at retrieval also differed for shapes presented in the upper left (1748 ms), lower left (1803 ms), upper right (1830 ms), and lower right (1795 ms) quadrants of the visual field (F(3,45) = 3.69, p < .05). Follow-up comparisons indicated that reaction times differed for shapes presented in the upper left and lower left quadrants (t(15) = 2.55, p < .05) and for shapes presented in the upper left and upper right quadrants (t(15) = 2.69, p < .05). Although there were significant differences in accuracy and reaction time between quadrants, the range of quadrant accuracy (58-66%, chance = 25%) and reaction time (1748-1830) was relatively consistent across quadrants.

2.2.2 Whole-Brain General Linear Model Results

The effect of memory accuracy was assessed for encoding by contrasting subsequent spatial memory hits versus subsequent spatial memory misses. This contrast produced activations in a number of regions associated with visual long-term memory including the left prefrontal cortex (left inferior frontal sulcus), bilateral intraparietal sulcus, bilateral temporal cortex (bilateral inferior temporal sulcus), and bilateral visual processing regions (BA19; Fig. 2.3 and Table 2.1, top). The effect of quadrant for encoding hits resulted in one activation in visual processing regions (BA 17/18; Table 2.1, middle), reflecting the perceptual differences associated with encoding shapes in different quadrants of the visual field. The interaction between quadrant and accuracy for encoding did not yield any significant activations. In an effort to increase power and reveal sub-threshold hippocampal activity, we also tested the effect of quadrant at encoding collapsed over subsequent accuracy. This produced activity in early visual processing regions (including BA 17/18/19; Table 2.1, bottom), which can be attributed

to perceptual processing differences, but no significant activations within the hippocampus.



Fig. 2.3 Whole-brain activity associated with accurate spatial memory encountered	oding
identified using the contrast of hits > misses.	

Table 2.1. Effects of accuracy and quadrant for cheoding.

Region	BA	х	V	Z
Effect of accuracy at encoding (hits $>$ misses)			·	
Left Inferior Frontal Sulcus	9/44	-34	6	34
Left Intraparietal Sulcus	7/19/37/40	-28	-58	40
Right Intraparietal Sulcus	7/19/37/40	30	-60	46
Left Inferior Temporal Sulcus	19/37	-44	-60	-8
Right Inferior Temporal Sulcus	19/37	44	-64	-10
Left Middle Occipital Gyrus/Inferior Occipital Gyrus	19	-32	-84	0
Right Inferior Occipital Gyrus	19	34	-78	-6
Main effect of quadrant for encoding hits				
Left Calcarine Sulcus/Cuneus	17/18	-10	-94	12
Effect of quadrant at encoding (collapsed over subsequent a	(ccuracy)			
Right Superior Parietal Lobule	7	10	-60	56
Right Precuneus	7	8	-50	52
Left Lingual Gyrus	18/19	-16	-82	-12
Left Cuneus	17/18	-12	-94	8
Left Calcarine Sulcus/Lingual Gyrus	17/18	-6	-82	-4
Right Cuneus	17/18	12	-74	12
Right Calcarine Sulcus/Cuneus	17	2	-74	10

BA refers to Brodmann area and MNI coordinate (x, y, z) refers to the center of each activation.

2.2.3 Hippocampal MVPA Results

As the whole-brain general linear model analysis did not produce any hippocampal activations, MVPA was used to determine if patterns of activity associated with encoding, collapsed over subsequent accuracy, in the anterior hippocampus or posterior hippocampus contained information about the encoding quadrant. This was done by measuring how well activity patterns evoked by shapes in each quadrant in half of the study runs could classify the positions of shapes in the other half of the study runs. In the anterior hippocampus, the average classification accuracy was greater than chance (35.9%, chance = 25%, t(15) = 1.96, p = .034; Fig. 2.4, left), and there was no significant correlation between the behavioral accuracy and classification accuracy of each quadrant (r = -0.67, p = .33; i.e., quadrants with higher behavioral accuracy did not have higherclassification accuracy). By contrast with the anterior hippocampus results, in the posterior hippocampus, classification accuracy did not significantly differ from chance (28.1%, t(15) < 1; Fig. 2.4, right). However, classification accuracy in the anterior hippocampus was not significantly greater than that of the posterior hippocampus (t(15) =1.00). The same MVPA procedure was employed for encoding trials in which the shape's location was later accurately retrieved (i.e., subsequent hits). For subsequent hits, the average classification accuracy across participants and quadrants was not significantly

greater than chance in the anterior hippocampus (26.6%, t(15) < 1) or the posterior hippocampus (31.3%, t(15) = 1.46, p = 0.082).



Fig. 2.4 MVPA classification accuracies of encoding activity patterns in the anterior and posterior hippocampus (mean ± 1 standard error; *p < .05).

2.3 DISCUSSION

The present results indicate that the anterior hippocampus is preferentially involved in spatial memory encoding of items in different visual field quadrants. Patterns of encoding activity in the anterior, but not posterior, hippocampus correctly classified stimulus quadrants at above-chance levels (Fig. 2.3). These differential hippocampal patterns can be attributed to spatial memory encoding rather than spatial perception, as spatial perception alone (e.g., retinotopic mapping) does not activate the hippocampus. Although there was no significant difference between classification accuracy for the anterior and posterior hippocampus, the critical finding of above-chance classification accuracy in the anterior hippocampus can be used to distinguish between the two

hypotheses set out in the introduction, which differ with respect to involvement of the anterior hippocampus during spatial memory encoding.

The general linear model analysis did not reveal any significant hippocampal activations even though other fMRI studies have reported hippocampal activity during spatial navigation (Kuhn & Gallinat, 2014; Duarte et al., 2014; Grady, 2019), which can be assumed to reflect spatial encoding. Moreover, the data used in the present study to investigate spatial memory encoding were previously used in a general linear model analysis to investigate spatial memory retrieval (Jeye et al., 2018), although the cluster extent threshold enforced in that study was smaller than in the present study. As significant effects versus null effects can be due to a variety of reasons, including task, analysis, or power differences, the fact that we observed null general linear model results and significant MVPA results indicates that patterns of activity were more sensitive in revealing hippocampal involvement during spatial memory encoding.

Collapsing over subsequent hits and misses resulted in a classification accuracy of 35.9% in the anterior hippocampus, whereas subsequent hits alone resulted in a classification accuracy of 26.6%. This implies that there is some information in the activity patterns of misses. It should be underscored that successful encoding is not the only factor that determines whether a spatial location is retrieved. There are shared cognitive processes involved in successful and unsuccessful encoding, and some of the successfully encoded items may have been forgotten between the study phase and the test phase. Our finding that collapsing over hits and misses is more sensitive than analyzing hits alone suggests that subsequent hits and misses share some meaningful pattern of activity during encoding. Considering all trials, rather than only subsequent hits, also

increases power, which may explain why significant results were observed for the collapsed analysis but not the analysis of hits alone. The present MVPA results are also aligned with previous PET studies (Lepage et al., 1998; Schacter & Wagner, 1999), which effectively collapsed over hits and misses because this method lacks the temporal resolution to implement event-related designs. On the other hand, subsequent memory effects have been observed in the anterior hippocampus with fMRI (e.g. Kim et al., 2015), which suggests that the encoding patterns of hits and misses are also somewhat distinct. The degree to which the activity patterns of hits and misses are overlapping and distinct is a topic of future research.

As mentioned in the introduction, place cells are present along the extent of the hippocampal long axis with the size of their receptive fields decreasing from anterior to posterior (Kjelstrup et al., 2008), suggesting that both the anterior hippocampus and posterior hippocampus can represent spatial memory. Similarly, fMRI studies have found a relationship between the scale of the spatial information being remembered and the position of activity along the hippocampus, where fine-grained spatial representations involved the posterior hippocampus and coarse-grained spatial representations involved the anterior hippocampus (Evensmoen et al., 2015; Nielson et al., 2015). It has also been shown that place cells in the primate hippocampus respond to eye movements and gaze location (Meister & Buffalo, 2016), so it is possible that in the current study, cells may have responded to the attended location on the screen during encoding. The size of place cell receptive fields in the anterior hippocampus may be well suited for representing large scale spatial information, such as visual field quadrants. This would explain why the spatial memory paradigm used in the current study revealed involvement of the anterior

hippocampus, whereas other studies of spatial memory and navigation in which information was likely represented on smaller spatial scales found greater involvement of the posterior hippocampus. However, null results across the entire posterior hippocampus do not necessarily mean that the posterior hippocampus was not involved in spatial memory encoding. Involvement of the posterior hippocampus in spatial memory encoding is a topic of future research.

Our finding that the anterior hippocampus is preferentially involved with spatial memory encoding is in line with the encoding-retrieval/anterior-posterior distinction. Further support for this distinction in the hippocampus stems from evidence that novelty and familiarity preferentially activate the anterior and posterior hippocampus, respectively (Dolan & Fletch, 1999; Strange et al., 1999; Daselaar et al., 2006; Poppenk et al., 2010). This novelty-familiarity distinction maps onto the encoding-retrieval distinction as novel information is encoded to a greater degree than familiar information and retrieval involves assessment of previously encoded/familiar information (cf., Tulving & Kroll, 1995). Thus, activity in the anterior hippocampus during encounters with novel stimuli can be assumed to reflect encoding of the new information, and activity in the posterior hippocampus during encounters with familiar stimuli, which are less likely to prompt encoding, can be assumed to reflect retrieval of the previously encoded information. Additional support for the encoding-retrieval distinction comes from a recent episodic memory simulation study that found a subsequent memory effect (i.e., details of the simulations that were later remembered versus forgotten) in the anterior hippocampus and transient activity in the posterior hippocampus that may have

reflected retrieval of details used to generate the simulations (Thakral, Benoit, & Schacter 2017).

Anatomy also supports the encoding–retrieval distinction along the long axis of the hippocampus. The hippocampal encoding/retrieval and network (HERNET) model proposed by Kim et al. (2015) builds upon Lepage et al.'s (1998) HIPER model by incorporating information about anatomical and functional connectivity with the hippocampus. The HERNET model proposes that encoding, which is inherently related to external attention, relies on the anterior hippocampus and the dorsal attention network, whereas retrieval, which is tied to internal attention, relies on the posterior hippocampus and the default network.

Some studies have failed to find an anterior–posterior/encoding–retrieval distinction in the hippocampus. Null findings, particularly in light of many significant findings, are always questionable and may be due to insensitive methods of analysis or protocols that did not isolate these cognitive processes. For instance, a blocked fMRI study conducted by Greicius et al. (2003) found greater encoding activity and retrieval activity in the posterior hippocampus than the anterior hippocampus. However, an uncorrected voxel threshold of p < .05 was employed that resulted in a very large number of "active" voxels (i.e., type I error) and the analysis was restricted to the hippocampal region of interest (masking out the widespread type I error that would have been apparent on a whole brain map). In fact, there was activity associated with encoding and retrieval in both the anterior and posterior hippocampus because of the high rate of type I error, and the apparent posterior activity actually reflected that the mask was larger in the posterior hippocampus. A hippocampal depth electrode study with temporal lobe epilepsy

patients used a verbal memory task and also failed to find encoding activity or retrieval activity in the anterior hippocampus (Ludowig et al., 2008). However, the memory paradigm employed involved continuous old–new word recognition, which involves both encoding and retrieval, making it hard to separate the effects of these two processes.

A recent hippocampal depth electrode study with epilepsy patients, where electrodes were in the anterior and posterior hippocampus, found subsequent memory effects in the posterior hippocampus in the theta frequency band (Lin et al., 2017). However, an even more recent study with additional subjects (from the same research group) found that the posterior hippocampus is more strongly involved in retrieval than encoding and the anterior hippocampus is more strongly involved in encoding than retrieval in the gamma frequency band (Lin et al., 2018). These findings suggest that PET and fMRI anterior–posterior hippocampus specialization results reflect gamma frequency band activity (the association between fMRI activity and gamma band activity has long been known; Logothetis et al., 2001). This should be investigated further in future depth electrode studies.

Long-axis specialization of the hippocampus during encoding and retrieval seems inconsistent with the results of single-unit recording studies that show retrieval involves the reactivation of the same neurons as encoding (Strange et al., 2014). However, these models of hippocampal function are not inconsistent with one another. During encoding, novel information is related to previous memories that share overlapping details (and it is presumably broad, gist-like details that are shared across events), whereas during retrieval, it is necessary to retrieve the particular fine-grain details of one specific memory, but not the overlapping information. Because the anterior and posterior

hippocampus have been linked to gist/coarse-grain and detailed/fine-grain representations, respectively (Poppenk et al., 2013), it is possible that the anterior hippocampus is more strongly engaged during encoding and the posterior hippocampus during retrieval, even though neurons across the whole hippocampus are active during both processes.

Our results provide evidence that the anterior hippocampus is preferentially involved in spatial memory encoding, which is in line with the hypothesis that there is an encoding–retrieval distinction along the long axis of the hippocampus. Furthermore, the current results indicate that, during encoding, this distinction extends to spatial memory, which demonstrates that spatial processing is not restricted to the posterior hippocampus.

3.0 CHAPTER 3

Functional connectivity with the anterior and posterior hippocampus during spatial memory Haley A. Fritch, Dylan S. Spets, and Scott D. Slotnick

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Evidence of differential connectivity and activity patterns across the long-axis of the hippocampus has led to many hypotheses about functional specialization of the anterior and posterior hippocampus, including a hypothesis linking the anterior hippocampus to memory encoding and the posterior hippocampus to memory retrieval. The hippocampal encoding/retrieval and network (HERNET) model of memory predicts that encoding should engage the anterior hippocampus and the attention network, whereas retrieval should engage the posterior hippocampus and the default network. In a previous fMRI study that employed multivoxel pattern analysis, we found that the patterns of activity in the anterior hippocampus predicted the quadrant of spatial memory encoding. In the current fMRI study, we investigated whether the spatial memory encoding activity in the anterior hippocampus and retrieval activity in the posterior hippocampus had a higher degree of connectivity to the attention network or the default network. During the study phase, abstract shapes were presented in each quadrant of the visual field and participants were instructed to remember each shape's location while maintaining central fixation. During the test phase, the same shapes were presented in the center of the screen and participants identified the previous location of each shape. Generalized psychophysiological interaction analyses were conducted between the anatomically defined anterior and posterior hippocampus and the rest of the brain. This revealed preferential connectivity between the anterior hippocampus and regions of the attention network during encoding and between the posterior hippocampus and regions of the default network during retrieval. In addition, there were location-specific patterns of connectivity with the anterior hippocampus and posterior hippocampus during encoding and retrieval of right visual field items. These results suggest that the anterior and posterior hippocampus interact with regions of the attention network and default network during spatial memory encoding and retrieval, respectively, and support the HERNET model of memory.

Interactions between the hippocampus and other cortical regions are thought to play an important role in the formation and retrieval of memories. However, the anterior hippocampus and posterior hippocampus have largely non-overlapping patterns of connectivity with other brain regions. The anterior hippocampus has greater connectivity with the perirhinal cortex and prefrontal cortex, whereas the posterior hippocampus has greater connectivity with the parahippocampal cortex and parietal regions (Kahn et al., 2008; Libby et al., 2012; Grady; 2019). These distinct patterns of connectivity are thought to give rise to functional specialization along the long axis of the hippocampus. Consequently, several hypotheses of specialized functions between the anterior and posterior hippocampus have been proposed, including broad/gist-like versus detailed representations, other cognitive processes versus spatial memory, and episodic memory encoding versus retrieval (Poppenk et al., 2013).

A meta-analysis of PET studies provided evidence for a hippocampal encoding– retrieval (HIPER) distinction, in which the anterior hippocampus is associated with memory encoding and the posterior hippocampus is associated with memory retrieval (Lepage et al., 1998). Though some studies have not observed evidence of an encoding versus retrieval distinction (Schacter & Wagner, 1999; Henson, 2005; but see Fritch et al., 2020), two activation likelihood estimation meta analyses provided support for the HIPER model (Spaniol et al., 2009; Kim, 2015). The hippocampal encoding–retrieval and network (HERNET) model proposed by Kim (2015) expanded upon the HIPER model to incorporate anatomic and functional connectivity patterns with the anterior and posterior hippocampus. The HERNET model proposes that encoding, which relies on external attention, should engage the anterior hippocampus and the attention network,

whereas retrieval, which is more closely related to internal attention because it relies on the reactivation and modulation of internal memory representations, should engage the default network. A meta-analysis of subsequent memory, recollection, and autobiographical retrieval effects provided support for this predicted dissociation (Kim, 2015). The activation likelihood estimation analysis of subsequent memory effects (identified with the contrast of remembered > forgotten) revealed involvement of the anterior hippocampus and several attention network regions, including the inferior frontal junction, intraparietal sulcus, motion-processing region MT+, and inferior temporal cortex. Analysis of retrieval effects (recollection > familiarity and autobiographical retrieval > control) revealed involvement of the posterior hippocampus and default network regions, including anteromedial prefrontal cortex, posterior cingulate, retrosplenial cortex, and inferior parietal lobule.

In a previous study, we sought to distinguish between the encoding versus retrieval hypothesis of long-axis specialization and the hypothesis linking the posterior hippocampus to spatial processing using a spatial memory task (Fritch et al., 2020). Specifically, the study addressed the question of whether spatial memory encoding involved the anterior hippocampus, which would provide support for an encoding– retrieval distinction, or the posterior hippocampus, which would support the spatial processing hypothesis. A general linear model analysis did not reveal any encoding activations in the hippocampus. However, using multi-voxel pattern analysis, it was determined that patterns of encoding activity, regardless of subsequent memory accuracy, in the anterior (but not posterior) hippocampus, could be used to classify encoding locations with above-chance accuracy. This above-chance classification accuracy

indicates that the locations of items were represented in patterns of encoding activity in the anterior hippocampus. These results indicate that the anterior hippocampus is associated with spatial memory encoding of visual field quadrants, providing support for the encoding–retrieval hypothesis.

The current study sought to investigate functional connectivity with the anterior hippocampus during spatial memory encoding. Although Fritch et al. (2020) only found spatial memory encoding effects in the anterior hippocampus, it is possible that differences between the anterior and posterior hippocampus do exist, but the previous multi-voxel pattern analysis was not sensitive enough to detect posterior hippocampus involvement. Therefore, the current study also investigated functional connectivity with the posterior hippocampus during retrieval to test both predictions of the HERNET model. The HERNET model predicts functional connectivity between the anterior hippocampus and regions of the attention network during encoding and functional connectivity between the posterior hippocampus and regions of the default network during retrieval. There is also evidence that functional connectivity with the default network is stronger in the anterior hippocampus than the posterior hippocampus (c.f., Grady, 2019), which would predict functional connectivity between the anterior hippocampus and the default network during encoding. If the HENET model is correct, 1) the majority of regions functionally connected with the anterior hippocampus during encoding should lie within the attention network, rather than the default network, and 2) the majority of regions functionally connected with the posterior hippocampus during retrieval should lie within the default network, rather than the attention network. As previous studies have provided evidence of hemispheric processing differences during

spatial memory (e.g., Slotnick & Moo, 2006), a secondary goal of the current study was to investigate differential connectivity associated with memory for shapes in the right visual field versus left visual field. If differential processing of items in the left and right hemifields is observed, it would support previous hemispheric processing asymmetry findings and provide a direction for future research. To anticipate the results, we found greater connectivity between the anterior hippocampus and the attention network than the default network during spatial memory encoding and greater connectivity between the posterior hippocampus and the default network than the attention network during retrieval. We also found greater functional connectivity between the hippocampus and other cortical regions during encoding and retrieval of items in the right versus left visual field.

3.1 METHODS

3.1.1 Participants

Sixteen right-handed individuals (13 females, age range 20-29 years old) with normal or corrected-to-normal vision from the Boston College community participated in the study. This sample size is similar to other studies investigating spatial memory activity in the hippocampus and functional connectivity with the medial temporal lobe (e.g., Libby et al., 2012; Duarte et al., 2014) and was expected to provide sufficient power to capture spatial memory effects as several previous fMRI studies have observed spatial memory effects in the hippocampus with similar sample sizes (e.g., Cansino et al., 2002; Ross & Slotnick, 2008; Duarte et al., 2014). All participants provided informed consent and the procedure was approved by the Boston College Institutional Review Board.

3.1.2 Stimulus Protocol

Each participant completed a training session, consisting of one quarter-length and one full-length run, and a scanning session, consisting of an anatomic scan and seven or eight full-length runs. Before each run, participants were instructed to maintain central fixation and remember the location of each shape to be presented (Fig. 3.1). During the study phase, 32 abstract shapes were presented in one of the four quadrants of the visual field for 2.5 seconds followed by a 0.5 second fixation period (for details on shape construction, see Slotnick & Schacter, 2004). An equal number of shapes were presented in each quadrant and each shape was shown in its respective location three times. Shapes were not repeated across runs and the presentation order of the shapes was pseudorandomized with the constraint that no more than three shapes could be presented in the same location consecutively. During the test phase, the same shapes from the study phase were presented at fixation for 3.0 seconds, followed by a 2.5 second reminder to provide a confidence rating and a 0.5-4.5 second fixation period. Participants used their left hand to classify the previous quadrant of each shape (i.e., "upper-left", "lower-left", "upper-right", or "lower-right") and provide an "unsure"-"sure" -"very sure" confidence rating.



Fig. 3.1. Stimulus and response protocol. Left, during the study phase, abstract shapes were presented in each quadrant of the visual field. Right, during the test phase, shapes were presented in the center of the screen and participants identified the previous location of each item (example responses and corresponding event types are shown to the right).

3.1.3 Image Acquisition and Data Analysis

Images were acquired using a Siemens 3 Tesla Trio Scanner with a 32-channel head coil. A magnetization-prepared rapid-gradient echo sequence was used to acquire anatomic images (TR = 30 ms, TE = 3.3 ms, 256×256 acquisition matrix, 128 slices, 1 mm slice thickness, $1.33 \times 1 \times 1$ mm resolution) and an echo-planar imaging sequence was used to acquire functional images (TR = 2000 ms, TE = 30 ms, 64 × 64 acquisition matrix, 34 slices, interleaved bottom-to-top slice acquisition order, 4 mm slice thickness, 4 mm isotropic resolution).

Data preprocessing and the general linear model analysis were conducted using SPM 12 (Wellcome Trust Centre for Neuroimaging, London, UK). Preprocessing consisted of slice-time correction, motion correction to the first image of each run, and normalization to the Montreal Neurological Institute (MNI) template, which included resampling voxels at 2 mm³. Spatial smoothing was not conducted to maximize spatial resolution. Anatomic images were also normalized to MNI space with 2 mm isotropic resolution and averaged across participants. For the subsequent memory and retrieval hits versus misses analyses (see below), runs were concatenated following motion correction using a custom script written in MATLAB (MathWorks, Natick, MA), which included a temporal high-pass filter to remove linear, quadratic, cubic and quartic trends within each run before concatenation. For each participant, a general linear model was created that included the following event types: encoding of items in each visual field quadrant, accurate retrieval of items in each quadrant (i.e. upper-left, lower-left, upper-right, and lower-right misses), failures to respond, and a constant (we collapsed over confidence rating to maximize power). A second general linear model was created based on subsequent memory analysis in which encoding events were separated based on subsequent accuracy at retrieval (i.e. upper-left, lower-left, upper-right, and lower-right misses).

The anterior and posterior hippocampus anatomic regions of interest (ROIs) were defined using the group average anatomic image and established anatomic distinctions within the medial temporal lobe (Fig. 3.2; Pruessner et al., 2000; Bernasconi et al., 2003). The border between the anterior and posterior hippocampus was placed according to the coordinate guidelines recommended by Poppenk et al. (2013), which proposed the anterior hippocampus is at and anterior to y = -21 (in MNI space). Therefore, slices at this location and more anterior were included in the anterior hippocampus ROI and slices posterior to this location were included in the posterior hippocampus ROI.



Fig. 3.2. Anterior and posterior hippocampus ROIs. The anatomically-defined anterior and posterior hippocampus ROIs were used as seed regions for the gPPI analyses (in cyan and yellow, respectively, displayed on the group anatomic image).

Functional connectivity with the anterior and posterior hippocampus was assessed using a generalized psychophysiological interaction (gPPI) analysis (McLaren et al., 2012) with each participant's first-level general linear model. The seed regions were defined as the intersection between the anterior and posterior hippocampus ROIs and each participant's functional images created during first-level modeling, which excluded voxels with a constant value across all scans or with a mean value less than 80% of the global signal. Anterior hippocampal functional connectivity associated with spatial memory encoding was assessed using a contrast of all encoding events > baseline (with coefficients of 1 for each encoding event and 0 for all other event types), a contrast of subsequent hits > subsequent misses (across all encoding quadrants), and an analysis of (encoding > baseline) – (retrieval > baseline). Location-specific functional connectivity

was assessed using contrasts of encoding shapes in the right visual field versus left visual field. Posterior hippocampal functional connectivity during retrieval was assessed using parallel analyses: a contrast of all retrieval events > baseline, a contrast of retrieval hits > misses, an analysis of (retrieval > baseline) – (encoding > baseline), and contrasts of retrieving shapes previously presented in the right visual field versus left visual field. The contrasts of encoding and retrieval versus baseline were thresholded at p < .000001, cluster extent corrected to p < .05. All other contrasts were thresholded at p < .01, cluster extent corrected to p < .05, except for the contrast of retrieval hits > misses, which was thresholded at p < .001, cluster extent corrected to p < .05, to avoid type I error that was evident from activations in white matter at p < .01 (which is likely related to the greater variability at retrieval; see the Functional Connectivity Results). A stricter threshold was chosen for the encoding and retrieval versus baseline analyses to account for the increased activity that would be expected during periods of task compared to no task; similar thresholds have been used in previous studies (e.g., Kanwisher et al., 1997; Avidan et al., 2002).

To determine the cluster extent thresholds, 10,000 Monte Carlo simulations were conducted using the acquisition volume parameters, a spatial autocorrelation value of 3.56, and the desired individual voxel and familywise p-values (Slotnick, 2017a). This spatial autocorrelation value was computed by contrasting retrieval hits in the upper left quadrant versus all other retrieval hits in an effort to estimate a null contrast image (all encoding contrasts were evaluated and the smallest spatial autocorrelation value was selected, as it can be assumed higher values were due to spatial correlation associated the true activations rather than noise). This simulation produced a cluster extent threshold of

8 voxels for an individual voxel threshold of p < .000001, corresponding to the task versus baseline contrasts, 24 voxels for an individual voxel threshold of p < .001, corresponding to the retrieval hits versus misses contrast, and 40 voxels for an individual voxel threshold of p < .01, corresponding to all other contrasts.

For the comparison of PPI beta weights associated with encoding and retrieval, beta weights associated with encoding and retrieval trials were extracted for each participant from 2 mm spheres centered around the peak voxel of each activation identified from the encoding > baseline gPPI analysis using custom MATLAB scripts. To determine the variability of PPI beta weights at encoding and retrieval, the betweenparticipant standard error of beta weight magnitudes was calculated for each functionally connected region and a paired samples t-test was used to compare the standard errors of each region across encoding and retrieval.

3.1.4 Neurosynth Meta-Analysis

Regions within the default network and attention network were identified from a Neurosynth meta-analysis using the search terms "visual attention"(124 studies)/"spatial attention"(149 studies) and "default network"(96 studies)/"default mode"(777 studies), respectively (neurosynth.org; for each pair of related search terms, a conjunction was used to produce activations from either map). Neurosynth identifies studies to include in each term-based meta-analysis by searching for articles in its database that use the search term within the abstract/full text at a high frequency (>1 in 1000 words). Activation coordinates extracted from these articles are then included in the meta analysis to identify regions consistently associated with the search term (for a detailed description of the

methods, see Yarkoni et al., 2011). This method of network identification was chosen because the Neurosynth database is updated regularly to include new studies and thus, provides an up-to-date analysis of these networks.

3.2 RESULTS

3.2.1 Behavioral Results

Memory accuracy was significantly greater than chance for shapes presented in all four quadrants of the visual field: the upper left (58.0%, chance = 25%, t(15) = 6.24, p < .001), lower left (64.9%, t(15) = 8.19, p < .001), upper right (66.2%, t(15) = 10.23, p < .001), and lower right (57.8%, t(15) = 6.59, p < .001). A repeated-measures ANOVA revealed that spatial memory accuracy differed for shapes presented in the four quadrants of the visual field (F(3,45) = 3.38, p < .05); however, the range of accuracy (57.8–66.2%) was relatively consistent across quadrants. Collapsing across the upper and lower visual fields, there was no significant difference in memory accuracy between shapes presented in the left and right visual fields (t(15) < 1).

3.2.2 Neurosynth Meta-Analysis Results

Fig. 3.3 illustrates the attention network and the default network identified from the Neurosynth meta-analysis. Regions of the attention network include the posterior superior frontal sulcus and precentral sulcus (frontal eye fields), intraparietal sulcus, posterior superior temporal sulcus (temporoparietal junction), ascending limb of the inferior temporal sulcus (MT+), superior and middle occipital gyri, and calcarine sulcus/V1. Regions of the default network include the anterior superior frontal sulcus, anterior/inferior medial prefrontal cortex, inferior parietal lobule, posterior cingulate, retrosplenial cortex, temporal pole, middle temporal gyrus, inferior temporal sulcus, inferior temporal gyrus, parahippocampal cortex, the hippocampus, and cerebellum. There are also several common regions between the two networks including the posterior medial frontal cortex, anterior cingulate, precuneus, and cuneus.



Fig. 3.3. Attention network and default network. Results of the Neurosynth meta-analysis conducted to identify the attention network (in red) and default network (in blue; overlap between the two networks is shown in magenta).

3.2.3 Functional Connectivity Results

The gPPI analysis of all encoding events revealed functional connectivity between the anterior hippocampus and several regions of the attention network, including the posterior superior frontal sulcus (frontal eye fields), intraparietal sulcus, superior occipital gyrus, and calcarine sulcus/V1 (Fig. 3.4; Table 3.1, top). There was functional connectivity between the anterior hippocampus and two regions of the default network– the posterior hippocampus and posterior cingulate (Fig. 3.4). There was also functional connectivity between the anterior hippocampus and the posterior/superior medial frontal cortex, anterior cingulate, and precuneus; however, these regions were common to both networks and thus were not diagnostic of either network. Functional connectivity with the anterior hippocampus was also found for regions not associated with either network, including sensorimotor cortex, paracentral lobule, insula, and the putamen. A subsequent memory analysis was conducted to assess differential functional connectivity between subsequent hits and misses; however, there were no significant differences between these event types. The comparison of functional connectivity during encoding versus retrieval revealed significant differential connectivity in only two regions of the left lateral temporal lobe (Table 3.1, middle). However, there were no regions that exhibited significant functional connectivity with the anterior hippocampus during retrieval. A follow-up analysis of PPI beta weights in each of the significant clusters identified from the encoding analysis revealed that there was significantly larger variability in beta weights for retrieval compared to encoding (average standard error across regions at encoding = 0.06, average standard error at retrieval = 0.14, t(36) = 12.35, p < .001), indicating that there was inconsistent functional connectivity with the anterior hippocampus during retrieval across participants.



Fig. 3.4. Functional connectivity results for all encoding events. Functional connectivity between the anterior hippocampus and the rest of the brain during encoding. Activations within regions uniquely associated with the attention network or the default network are circled (in red and blue, respectively).

Table 3.1. Functional connectivity with the anterior hippocampus during encoding.

Region	BA	х	У	Z
All encoding events			-	
Left Superior Frontal Sulcus	6	-20	-8	54
Right Superior Frontal Sulcus	6	26	-2	50
Left Medial Frontal Cortex	6	-2	0	62
Right Medial Frontal Cortex	6	4	-6	62
Left Medial Frontal Cortex	4	-2	-6	46
Right Medial Frontal Cortex/Posterior Cingulate Sulcus	4/6/31	6	-10	44
Left Central Sulcus	3	-54	-8	26
Right Central Sulcus	3/4	34	-22	48
Left Central Sulcus	3/4	-34	-24	44
Left Paracentral Lobule	5	-2	-36	56
Right Paracentral Lobule	5	4	-28	60
Right Postcentral Gyrus	1/3	58	-8	32
Right Postcentral Sulcus	2/5	50	-20	40
Right Postcentral Sulcus	2/5/7	38	-32	50
Left Postcentral Sulcus	2/5	-36	-36	54
Left Intraparietal Sulcus/Postcentral Sulcus	2/7/40	-42	-32	40
Left Intraparietal Sulcus/Postcentral Sulcus	2/7/40	-30	-34	46
Right Posterior Cingulate Gyrus/Precuneus	7/31	12	-48	52
Left Posterior Cingulate Gyrus/Precuneus	7/31	-2	-48	44
Right Posterior Cingulate Gyrus/Precuneus	7/31	4	-60	30
Left Precuneus	7	-4	-44	54
Superior Occipital Gyrus	19	-24	-78	28

Left Calcarine Sulcus/Parietooccipital Sulcus	17	-12	-58	10
Left Calcarine Sulcus	17	-14	-72	6
Right Calcarine Sulcus	17	14	-72	0
Left Anterior Cingulate Sulcus	24	-8	12	34
Right Anterior Cingulate Sulcus	24	10	10	36
Left Posterior Cingulate Gyrus	31	-4	-16	46
Right Posterior Cingulate Sulcus	4/31	12	-28	46
Right Posterior Cingulate Sulcus	4/31	16	-30	38
Right Posterior Cingulate Sulcus	5/31	8	-42	34
Left Posterior Cingulate Gyrus	31	-8	-44	30
Left Posterior Cingulate Gyrus	31	-8	-42	48
Right Posterior Cingulate Gyrus	23/31	4	-52	32
Left Posterior Cingulate Gyrus	31	-4	-60	26
Left Posterior Hippocampus	-	-26	-36	-6
Left Insula	-	-36	6	4
Left Insula	-	-34	-20	6
Right Insula	-	38	-12	16
Right Insula	-	36	-20	16
Left Putamen	-	-30	-14	8
Right Putamen	-	32	-18	4
Encoding > Retrieval				
Left Superior Temporal Gyrus	22/42	-56	-40	10
Left Middle Temporal Gyrus/Superior Temporal Gyrus/Sulcus	21/22	-56	-16	-6
Right > Left				
Right Inferior Frontal Gyrus	45/46	44	34	8
Left Inferior Frontal Gyrus	45	-42	26	8
Right Inferior Frontal Sulcus	9/44	52	14	26
Left Middle Frontal Gyrus	9/46	-30	24	30
Right Superior Frontal Sulcus	6/8/9	24	4	50
Right Anterior Cingulate Gyrus/Sulcus	24/32	10	20	36
Left Occipitotemporal Sulcus	37	-50	-58	-10
Right Insula	-	36	2	0
Right Insula	-	34	-8	-6
Left Putamen/Caudate	-	-16	12	0
Right Putamen	-	26	4	0

Left > *Right* No activations

BA refers to Brodmann area and MNI coordinate (x, y, z) refers to the center of each activation.

We next assessed differential connectivity with the anterior hippocampus associated with encoding items in different visual field locations. The contrast of encoding items in the right visual field versus left visual field revealed hemifield-specific functional connectivity between the anterior hippocampus and the lateral prefrontal cortex, anterior cingulate gyrus, occipitotemporal sulcus, insula, and putamen/caudate (Fig. 3.5; Table 3.1, middle). The reverse contrast did not produce any significant activations (Table 3.1, bottom).



Fig. 3.5. Differential functional connectivity with the anterior hippocampus between items in each hemifield (encoding right > encoding left in blue; there were no significant activations for encoding left > encoding right).

The gPPI analysis of all retrieval events revealed functional connectivity between the posterior hippocampus and one region of the default network – the posterior cingulate (Fig. 3.6A; Table 3.2, top). Functional connectivity was also found between the posterior hippocampus and postcentral sulcus, which is not associated with either network. A contrast of hits and misses was used to assess differential functional connectivity with the posterior hippocampus during accurate and inaccurate retrieval; however, there were no significant differences between these event types. The analysis of differential connectivity associated with retrieval versus encoding revealed greater connectivity with two regions of the default network: the anterior superior frontal sulcus and medial prefrontal cortex (Fig. 3.6B; Table 3.2, middle). This analysis also revealed greater functional connectivity with the anterior prefrontal cortex, lateral prefrontal cortex, and caudate, which are not associated with either network.



Fig. 3.6. Functional connectivity with the posterior hippocampus during retrieval. (A) Functional connectivity for all retrieval events. (B) Differential connectivity associated with retrieval > encoding. Activations within regions uniquely associated with the default network are circled in blue.

Table 3.2. Functional connectivity with the posterior hippocampus during retrieval.

Table 5.2. Functional connectivity with the posterior inppocan	ipus during retreva	.1.		
Region	BA	Х	у	Z
All retrieval events				
Right Postcentral Sulcus	2	36	-34	52
Right Posterior Cingulate Gyrus	23/31	2	-32	38
Left Posterior Cingulate Gyrus	23	-10	-42	30
Left Posterior Cingulate Gyrus	23/31	-4	-48	30
<i>Retrieval</i> > <i>Encoding</i>				
Right Anterior Prefrontal Cortex	10/46	26	50	28
Left Superior Frontal Sulcus/Middle Frontal Gyrus	9/46	-30	24	44
Left Middle Frontal Gyrus/Inferior Frontal Sulcus	45/46	-46	26	24
Left Medial Prefrontal Cortex	6	-2	32	42
Right Medial Prefrontal Cortex	6	2	34	42
Left Caudate	-	-12	-4	16
Right > Left				
Right Anterior Prefrontal Cortex/Superior Frontal Sulcus/ Middle Frontal Gyrus/Inferior Frontal Sulcus	9/10/46	26	38	24
Right Anterior Prefrontal Cortex/Superior Frontal Sulcus/ Middle Frontal Gyrus/Inferior Frontal Sulcus	9/10/46	-28	38	32
Left Anterior Cingulate Gyrus	24/32/33	-2	36	8
Right Anterior Cingulate Gyrus	24/32/33	2	36	10
Left Anterior Cingulate Gyrus/Sulcus	24/32	-6	50	16
Left Posterior Cingulate Sulcus	5/31	-2	-28	46
Right Posterior Cingulate Sulcus	5/31	2	-30	48
Right Insula	-	38	24	4
Right Caudate	-	8	8	4

Left > *Right* <u>No activations</u>

BA refers to Brodmann area and MNI coordinate (x, y, z) refers to the center of each activation.
The contrast of items previously presented in the right visual field compared to the left visual field revealed hemifield-specific functional connectivity between the posterior hippocampus and the anterior prefrontal cortex, anterior cingulate, posterior cingulate, caudate, and insula (Fig. 3.7; Table 3.2, middle). The reverse contrast did not produce any significant activations (Table 3.2, bottom).



Fig. 7. Differential functional connectivity with the posterior hippocampus at retrieval between items in each hemifield (right > left in magenta; there were no significant activations for left > right).

3.3 DISCUSSION

The current analysis revealed preferential functional connectivity between the anterior hippocampus and regions of the attention network during spatial memory encoding and between the posterior hippocampus and some regions of the default network during retrieval. These results are in line with the HERNET model of memory and suggest that the anterior hippocampus and attention network interact during encoding, whereas the posterior hippocampus and default network interact during retrieval. Anterior and posterior hippocampal functional connectivity was also found with a number of non-diagnostic regions that are either common to both networks or not included in either network, which does not provide support for or contradict the HERNET model. Importantly, activations outside of these two networks would be expected considering that the current study utilized a spatial memory task that engaged cognitive processes apart from encoding and retrieval. For instance, activations in regions associated with sensorimotor processing, such as the central sulcus, postcentral gyrus, paracentral lobule, and putamen, would be expected from the comparison of task versus baseline.

The only regions uniquely associated with the default network that exhibited functional connectivity with the anterior hippocampus during encoding were the posterior hippocampus and posterior cingulate. Though there is little direct connectivity between the anterior hippocampus and posterior hippocampus in rodents and non-human primates, there is some evidence for longitudinal connections in humans (Parekh et al., 2015) and these regions are thought to communicate indirectly through other medial temporal lobe regions (Fanselow & Dong, 2010). Additionally, the posterior hippocampus receives input from the parahippocampal cortex and the dorsal visual processing stream and is known to be involved in spatial processing, including spatial navigation and spatial memory (Woolet & Maguire, 2011; Kuhn & Gallinat, 2014; Duarte et al., 2014; Grady, 2019). Likewise, the posterior cingulate is known to be involved in spatial processing and episodic memory (Epstein, 2008; Burles et al., 2018; Natu et al., 2019). Therefore, anterior hippocampus functional connectivity with the posterior cingulate and posterior hippocampus during spatial memory encoding likely indicates spatial processing in these regions rather than engagement of the default network. If spatial memory encoding

engaged the anterior hippocampus and the default network, functional connectivity with other regions of the default network that are not involved in spatial processing would be expected. Therefore, connectivity with the posterior hippocampus and posterior cingulate does not necessarily contradict the HERNET model.

The HERNET model also predicts functional connectivity between the posterior hippocampus and the default network during memory retrieval. The current results provided some support for this prediction by demonstrating functional connectivity between the posterior hippocampus and the posterior cingulate, medial prefrontal cortex, and anterior superior frontal gyrus. Furthermore, the current analyses did not reveal functional connectivity between the posterior hippocampus and any regions of the attention network.

The contrast of subsequent hits and misses did not reveal differential connectivity patterns. This suggests that hippocampal-cortical functional connectivity was similar during encoding of items later remembered and forgotten. Though some fMRI studies have reported differential activity associated with subsequent hits and misses (e.g., Kim, 2015), this result is in line with Fritch et al. (2020) that found collapsing over subsequent hits and misses was more sensitive than analyzing subsequent hits alone, and PET studies (Lepage et al., 1998), which effectively collapsed over hits and misses because they lacked the temporal resolution to analyze these event types separately. Importantly, successful encoding is not the only factor that affects later retrieval accuracy. There are likely shared cognitive processes and activity patterns associated with subsequent hits and misses (cf., Fritch et al., 2020).

As mentioned in the introduction, in addition to the HERNET model, which was the focus of the present investigation, there have been many hypotheses regarding functional specialization along the long axis of the hippocampus (Poppenk et al., 2013). One hypothesis is that the anterior hippocampus is preferentially associated with memory encoding, while the posterior hippocampus is preferentially associated with memory retrieval (for a review, see Fritch et al., 2020). The present finding that the anterior hippocampus is functionally connected to the posterior hippocampus (Table 3.1) would appear to contradict the hypothesis of an encoding-retrieval distinction. Interestingly, this posterior hippocampus involvement during encoding was not previously revealed by a general linear model analysis or multi-voxel pattern analysis (Fritch et al., 2020), indicating that the current gPPI analysis may have been more sensitive for identifying activity in the posterior hippocampus during encoding. However, it is important to note that items were presented three times during the encoding phase, such that posterior hippocampus activity during this period may have reflected cued retrieval of the previous presentation(s). Thus, the present results do not contradict the encoding-retrieval anterior-posterior hypothesis of hippocampal function. By contrast, the current results do contradict the hypothesis that links the posterior, but not anterior, hippocampus to spatial processing by demonstrating that the anterior hippocampus interacts with various cortical regions during spatial memory encoding. Another hypothesis of long-axis specialization proposes that the scale of information representation decreases from broad/gist-like representations in the anterior hippocampus to fine-grained/detailed representations in the posterior hippocampus. We found more regions of functional connectivity with the anterior hippocampus than the posterior hippocampus, which may be a result of greater

activation of the anterior hippocampus in the current spatial memory task. Likewise, Fritch et al. (2020) provided MPVA evidence that the anterior hippocampus, but not posterior hippocampus, was involved in the current task. Therefore, the relatively few regions of functional connectivity with the posterior hippocampus, along with the lack of significant posterior hippocampus results discussed in Fritch et al. (2020), may indicate that the anterior hippocampus is preferentially involved with spatial memory for visual field quadrants because it is well suited for representing this scale of information.

One limitation of the current study is the relatively small sample size, which may have affected the ability to detect small to medium effects, including those related to memory accuracy. Future studies should investigate these connectivity differences further with a larger sample size.

Contrasts of spatial memory encoding and retrieval of different locations revealed greater functional connectivity between the hippocampus and other cortical regions during encoding and retrieval of items presented in the right visual field than the left visual field. As stimuli in the right visual field are initially processed in the left hemisphere, which is thought to be responsible for conscious processing (Gazzaniga, 2000), this finding may indicate greater conscious processing of items in the right visual field. There is also evidence that the left hemisphere is associated with categorical processing of spatial relationships and the right hemisphere is associated with coordinate processing of spatial relationships (Slotnick & Moo, 2006). As categorical processing is more closely related to verbal memory strategies (e.g., using the verbal label "upper-left" to remember the location of an item), this may explain the observed functional connectivity with language processing regions (e.g., the left inferior frontal gyrus/Broca's

area) during encoding. Therefore, greater functional connectivity during encoding and retrieval of items presented in the right visual field may reflect greater categorical or verbal processing of shapes in the right visual field.

The current results provide no evidence of functional connectivity between the anterior hippocampus and default network during spatial memory encoding or between the posterior hippocampus and attention network during spatial memory retrieval. Rather, the present findings suggest that spatial memory encoding is associated with interactions between the anterior hippocampus and the attention network and spatial memory retrieval is associated with interactions between the posterior hippocampus and the posterior hippocampus and default network, which is consistent with the HERNET model of memory.

GENERAL DISCUSSION

In Chapter 1, we investigated domain specificity in the hippocampus to determine whether retrieval activity differed for spatial and color context memory. Although a general linear model analysis did not result in any hippocampal activations for the contrast of accurate spatial memory and accurate color memory, a searchlight MVPA revealed a region of the right anterior hippocampus in which the type of source information could be classified with above-chance accuracy. These results indicate that different types of context information are represented by distinct patterns of activity in the hippocampus.

In Chapter 2, we distinguished between two hypotheses of hippocampal long-axis specialization (i.e., the encoding-retrieval/anterior-posterior distinction and the hypothesis linking the posterior hippocampus to spatial processing) to determine whether spatial memory encoding involved the anterior hippocampus or posterior hippocampus. While a general linear model analysis did not reveal any significant activations in the hippocampus for the effect of visual field quadrant, patterns of encoding activity in the anterior, but not posterior, hippocampus correctly classified stimulus quadrants at above-chance levels. These results suggest that the anterior hippocampus is involved in spatial memory encoding of items in different visual field quadrants, which is in line with the hypothesis of an encoding-retrieval/anterior-posterior distinction and contradicts the hypothesis linking the posterior, but not anterior, hippocampus to spatial processing.

In both Chapter 1 and Chapter 2, general linear model analyses did not produce any significant activations within the hippocampus associated with different contexts

(i.e., spatial versus color or visual field quadrant); however, MVPA revealed abovechance classification accuracies. Null general linear model findings in contrast to significant MVPA findings could reflect the differential sensitivity of these analyses to participant-level and voxel-level variability, respectively (Davis et al. 2014; see also Thakral et al., 2017). Furthermore, null general linear model results and significant MVPA results suggest that information about an item's context is represented in distributed patterns of hippocampal activity. The idea that context processing is distributed in the hippocampus is supported by evidence that both the lateral entorhinal cortex and medial entorhinal cortex provide spatial/contextual input to the anterior and posterior hippocampus, respectively (Knierim et al., 2014), and place cells, which selectively respond to spatial locations, are present along the entire extent of the hippocampal long axis (Kjelstrup et al., 2008).

Furthermore, in both Chapter 1 and Chapter 2, above-chance classification accuracy was found in the anterior hippocampus. While null results in the posterior hippocampus do not necessarily mean that the posterior hippocampus was not involved (as null results could be due to many factors), involvement of the anterior hippocampus in both of these tasks may be the result of the differential inputs and cell properties in this region. For instance, cells in the anterior hippocampus are known to have broader receptive fields and fire less selectively than cells in the posterior hippocampus, and most of the connections between the hippocampus and prefrontal cortex arise in the anterior hippocampus, which is thought to be important for the schematic organization of memories (Eichenbaum, 2017). Consequently, one hypothesis of hippocampal long-axis specialization links the anterior hippocampus to broad/gist-like information and the

posterior hippocampus to more detailed information (Poppenk et al., 2013). Therefore, anterior hippocampal involvement in these studies may reflect that left/right or red/green and visual field quadrant judgements did not require very detailed memories. Furthermore, as mentioned previously, the anterior and posterior hippocampus preferentially receive input from the perirhinal cortex via the lateral entorhinal cortex and parahippocampal cortex via the medial entorhinal cortex, respectively. Although both regions of the entorhinal cortex provide spatial/contextual information to the hippocampus, it has been proposed that the lateral entorhinal cortex processes the context of objects, whereas the medial entorhinal cortex processes the context of the animal/individual (Knierim et al., 2014). Therefore, the current finding that activity in the anterior hippocampus contained information about the context associated with objects/shapes may indicate that this distinction extends to the hippocampus such that the anterior hippocampus preferentially processes the context of items and the posterior hippocampus processes the context of the individual (which may explain why the posterior hippocampus is often associated with spatial navigation; Woolet & Maguire, 2011; Kuhn & Gallinat, 2014; Duarte et al., 2014; Grady, 2019).

Finally, in Chapter 3, we investigated functional connectivity with the anterior and posterior hippocampus during spatial memory encoding and retrieval to test the predictions of the HERNET model of memory (Kim 2015). The gPPI analysis revealed preferential functional connectivity between the anterior hippocampus and regions of the attention network during spatial memory encoding and between the posterior hippocampus and some regions of the default network during retrieval. These findings suggest that spatial memory encoding is associated with interactions between the anterior

hippocampus and the attention network and spatial memory retrieval is associated with interactions between the posterior hippocampus and default network.

At first glance, the encoding-retrieval/anterior-posterior distinction that is supported by Chapter 2 and Chapter 3 seems inconsistent with the results of Chapter 1, which showed that patterns of retrieval activity in the anterior hippocampus contained context information. Importantly, evidence that memory encoding and retrieval are preferentially associated with the anterior and posterior hippocampus, respectively, does not mean that these processes are exclusively carried out by these regions. In fact, such a dichotomy would contradict the results of single-unit recording studies that show retrieval involves the reactivation of the same neurons as encoding (Strange et al., 2014). Instead, it is likely that, due to differences in the scale of their representations and interactions with other brain regions, the anterior hippocampus is more strongly engaged during encoding and the posterior hippocampus is more strongly engaged during retrieval, even though neurons across the whole hippocampus are active during both processes. Indeed, functional connectivity between the anterior and posterior hippocampus was reported in Chapter 3, indicating that these regions likely both contribute to spatial memory encoding. Furthermore, the various stimulus properties and cognitive demands of memory tasks likely affect the patterns of activity in the hippocampus, leading to differential involvement of the anterior and posterior hippocampus during different tasks.

Together, the results presented in this dissertation provide insights into the contributions of the anterior and posterior hippocampus and their interactions with the rest of the brain during long-term memory.

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