



Review

Hippocampal activation during retrieval of spatial context from episodic and semantic memory

Siobhan M. Hoscheidt^{a,*}, Lynn Nadel^a, Jessica Payne^b, Lee Ryan^a

^a Department of Psychology, University of Arizona, 1503 E. University Blvd., Building 86, Tucson, AZ 85721, United States

^b Department of Psychology, University of Notre Dame, Hagggar Hall, Room 122-B, Notre Dame, IN 46556, United States

ARTICLE INFO

Article history:

Received 25 March 2010

Accepted 3 April 2010

Available online 10 April 2010

Keywords:

Hippocampus

Medial temporal lobe

Spatial

Episodic

Semantic

ABSTRACT

The hippocampus, a region implicated in the processing of spatial information and episodic memory, is central to the debate concerning the relationship between episodic and semantic memory. Studies of medial temporal lobe amnesic patients provide evidence that the hippocampus is critical for the retrieval of episodic but not semantic memory. On the other hand, recent neuroimaging studies of intact individuals report hippocampal activation during retrieval of both autobiographical memories and semantic information that includes historical facts, famous faces, and categorical information, suggesting that episodic and semantic memory may engage the hippocampus during memory retrieval in similar ways. Few studies have matched episodic and semantic tasks for the degree to which they include spatial content, even though spatial content may be what drives hippocampal activation during semantic retrieval. To examine this issue, we conducted a functional magnetic resonance imaging (fMRI) study in which retrieval of spatial and nonspatial information was compared during an episodic and semantic recognition task. Results show that the hippocampus (1) participates preferentially in the retrieval of episodic memories; (2) is also engaged by retrieval of semantic memories, particularly those that include spatial information. These data suggest that sharp dissociations between episodic and semantic memory may be overly simplistic and that the hippocampus plays a role in the retrieval of spatial content whether drawn from a memory of one's own life experiences or real-world semantic knowledge.

Published by Elsevier B.V.

Contents

1. Introduction	122
2. Material and methods	123
2.1. Participants	123
2.2. Materials	123
2.3. Neuroimaging procedure	123
2.4. Image acquisition and analyses	123
3. Results	124
3.1. Experimental conditions versus control	124
3.2. ANOVA: memory type versus spatial content	124
3.3. ROI analyses for medial temporal lobe structures	124
3.4. Spatial content ROIs	126
3.5. Memory type ROIs	128
3.6. Overlapping ROIs	129
4. Discussion	129
4.1. The interaction between memory type and spatial content	129
4.2. The longitudinal axis of the hippocampus	130
4.3. The parahippocampal gyrus	130
4.4. The distribution of cortical activation	130
5. Summary	131
References	131

* Corresponding author. Tel.: +1 520 621 8792; fax: +1 520 621 9306.

E-mail address: smhosche@email.arizona.edu (S.M. Hoscheidt).

1. Introduction

A continuing debate in the cognitive neuroscience of memory concerns the retrieval of episodic memory and semantic knowledge: do these processes depend upon the same or distinct brain regions? In particular, does the hippocampus play an important role in episodic retrieval, semantic retrieval, or both? At least phenomenologically, it appears that episodic memory and semantic knowledge are dissociable. Remembering an episode from one's personal past involves the retrieval of the specific spatial-temporal context in which this event originally occurred. The rememberer experiences being mentally present in this context once again [1,2]—a context that serves to bind together the elements of the remembered event. By contrast, semantic memory is traditionally defined as the retrieval of facts, concepts and world knowledge; essentially information that is not bound to a unique spatial-temporal context and is not dependent on a sense of re-experiencing [3]. Most recent neuroimaging studies of hippocampus focus on episodic memory, and interest has turned to whether specific regions within the hippocampus play unique roles in two aspects of episode storage and retrieval—pattern separation and pattern completion (e.g., [4,5]).

However, the question of hippocampal involvement in semantic memory retrieval has resurfaced because of inconsistencies between patient and neuroimaging data (for review, see [6]). Generally, neuropsychological data derived from patients with extensive hippocampal damage have supported the view that episodic, but not semantic memory retrieval, is mediated by the hippocampus. Patients with medial temporal lobe amnesia are typically reported as normal on most semantic memory tasks (reviewed in [7]). For example, Schmolck et al. [8] found that amnesics were within normal limits on 25 classic semantic memory tasks compared to controls. Squire and others [9–11] emphasize that at least some amnesics show long-standing and significant deficits in semantic memory retrieval, even for well-established world knowledge. Semantic memory impairment tends to be more extensive if the damage extends outside the hippocampus into other medial temporal and lateral temporal lobe regions [8] and can reach the same level of severity as autobiographical memory loss, or even exceed it, in some patients [12,58].

Recent neuroimaging studies have shown quite consistently that hippocampal activation occurs in normal individuals during retrieval of various types of well-established semantic knowledge. These include tasks involving retrieval of category exemplars [13], spatial relations between objects [14], famous faces [15,16], historical events [17], and retrieval of semantic associations [18]. In addition, at least in normal individuals, retrieval of both episodic memory and semantic information appears to draw on brain networks that are more similar than dissimilar, and both networks include the hippocampus [19,20].

We have shown elsewhere that the inclusion of spatial information in particular leads to increases in activation of hippocampus, regardless of whether the source of the information is a single prior episode or well-established world knowledge. Ryan et al. [14] compared hippocampal activation during spatial and nonspatial relational judgments in semantic and episodic versions of the same task. Participants studied object arrays and then answered questions about the relationships between these objects. Each array contained four common objects (e.g., table, apple, telephone, flag), located in the four quadrants of the computer screen. Objects were depicted as photographs, cartoons, or line drawings. Participants were told to memorize the objects, the details of their appearance, and their location on the computer screen. In the test phase, one set of questions could only be answered by recalling the visual

characteristics of the array itself (episodic retrieval), while the other set of questions could only be answered with general knowledge about the real-world characteristics of the objects (semantic retrieval). Half of the questions in each category focused on spatial relational information, while the other half focused on nonspatial relations.

Several important findings emerged from this study. First, hippocampal activation was present in all the relational memory conditions, episodic and semantic. Second, spatial relational judgments elicited greater hippocampal activation compared to nonspatial judgments, and this preferential activation for spatial relations was observed equally for both semantic and episodic memory questions. The results suggest that the hippocampus is implicated in both episodic and semantic retrieval, and may preferentially contribute to retrieval when space and spatial relations are invoked.

Most neuroimaging studies to date have compared retrieval of well-established semantic information with very recently acquired episodic memories, such as living/nonliving judgments compared to old/new recognition for words on a list [21], common category exemplar generation compared to recalling a recently learned list of unusual category exemplars [13], or as described earlier, retrieval of real-world semantic relations between objects compared with relations between pictures of objects presented in a spatial array [14]. The only study to date that has utilized autobiographical event retrieval [17] assessed hippocampal activation while participants recognized autobiographical information or recognition of historical information, focusing on two factors—personal relevance (autobiographical versus historical), and temporal specificity (i.e., whether or not the information derived from a single event with a specific locus in time). The latter variable is important because this factor is often confounded in studies comparing episodic memories that derive from unique, single occurrence events with well-learned semantic knowledge that has been experienced on many occasions and in various contexts. Although hippocampal activation was greatest for memories that were personally relevant and had a specific locus in time (i.e., classic episodic events), all four memory conditions elicited significant hippocampal activation.

An additional defining feature of autobiographical events that may confound comparisons of episodic and semantic memory is spatial content. Recalling a unique autobiographical event most likely evokes recollection of the spatial context in which the event occurred. Recollection of a specific historical event may also elicit specific spatial information. For example, the cue “JFK’s assassination” almost universally brings to mind the familiar image of the motorcade driving along a street in Dallas. As described earlier, we found that semantic information about spatial relations among objects elicited hippocampal activation [14]. It may be the case that the retrieval of semantic information including spatial context will also activate the hippocampus. If, and how, this differs from the activation elicited by the spatial context of autobiographical memories remains to be determined.

In the current neuroimaging study we set out to investigate these issues. Our goal was to directly compare the activation in the hippocampus during the retrieval of spatial and nonspatial aspects of autobiographical memories and well-established semantic knowledge. To do this, we modified the Maguire and Mummery [17] true/false recognition task. We hypothesized that retrieval of spatial context would elicit hippocampal activation regardless of whether the retrieved information arose from episodic or semantic memory. We also hypothesized that hippocampal activation might increase during retrieval of any episodic information compared to semantic knowledge since spatial context plays such a key role in defining a unique autobiographical memory. The interaction of episodic memory and spatial context should elicit the most extensive hippocampal activation.

Table 1
Four experimental conditions used for “true or false” recognition task in scanner condition description and example.

Episodic Memory	
Spatial	The location of, or a spatial relationship within, a past experienced event. e.g., “Your 21 st birthday party was held at the botanical gardens” or “During the wedding, Sally sat to your right”.
Nonspatial	A detail of a past experienced event that is not central to the context of the episode. e.g., “The color of your high school graduation gown was blue.”
Semantic Memory	
Spatial	Geographical knowledge of the locations of famous landmarks or the spatial relationships between states; e.g., “The Eiffel Tower is located in Paris” or “New Mexico is south of Colorado”.
Nonspatial	A nonspatial real-world fact, e.g., “The queen of England is Elizabeth.”

2. Material and methods

2.1. Participants

Seventeen healthy volunteers (nine females and eight males; mean age 22.2 years; range 18–30 years) were recruited from University of Arizona undergraduate courses. Volunteers were screened for prior head injury with sequelae, neurological and psychiatric disorders, past or present drug or alcohol abuse, and contraindications to MRI. All procedures in the study were approved by the University of Arizona Human Subject’s Committee. Participants gave informed consent and were given course credit for their participation in the study.

2.2. Materials

In order to obtain episodic material for the imaging session, participants first underwent an autobiographical interview which took approximately 2 h to complete. They were instructed to choose thirty events from a list of one hundred common life events (taken from [22]) that reminded them of a unique episode in their personal past they could recall in detail, for example, “your high school graduation” or “your first job”. Five events were selected from the list at a time, after which participants described the details of each event. Participants were then asked a set of semi-standardized questions designed to elicit spatial and nonspatial details, such as what they were wearing at the time, or where other people were standing/sitting in relation to them during the event. In addition, participants were asked when each event occurred and whether the event was positive, negative or neutral. Because all participants were young adults (mean age = 22 years), most memories reported were relatively recent, occurring within the past five years.

Four types of statements were created to be presented in a true/false recognition paradigm in the scanner: episodic-spatial, episodic-nonspatial, semantic-spatial, and semantic-nonspatial. Information from the autobiographical interview was the basis for participant-specific episodic statements that focused on specific nonspatial or spatial details from events. Examples of episodic nonspatial statements included “The color of your high school graduation gown was blue” and “In your bike accident you broke your wrist”. Example of episodic spatial statements included “During your wedding, Sally sat to your right” and “Your 21st birthday party was held at the botanical gardens”. Semantic statements were created that included well known spatial and nonspatial material. Nonspatial facts included world knowledge such as “The queen of England is Elizabeth” and “A gila monster is a type of lizard”. Spatial facts included spatial relational information such as “New Mexico is south of Colorado” and location information such as “The Eiffel tower is located in Paris” (see Table 1). Semantic statements were piloted in a behavioral study to ensure that accuracy and response times would be similar to episodic statements. For all statements, the critical information required for a true/false judgment was contained in the last word of the sentence, and sentence length was matched across conditions. Control items, designed to account for activation associated with reading, were ungrammatical sentences composed of prepositions and conjunctions, for example, “While yet therefore still about this” [17].

In total, participants were presented with 96 semantic statements that included 48 spatial (40 true, 8 false) and 48 nonspatial (40 true, 8 false), 68 episodic statements that included 34 spatial (30 true, 4 false) and 34 nonspatial (30 true, 4 false), and 60 control sentences. More semantic statements than episodic statements were included in the true/false task so that incorrect responses could be dropped while ensuring a similar number of correct response statements would be included in each of the four categories.

2.3. Neuroimaging procedure

One week after the interview participants returned for the scanning session. Prior to engaging in experimental procedures, participants performed a practice session to ensure that they understood the task. Statements were presented to participants on a computer outside the scanner. Participants were instructed to judge whether the statements were true or false and to respond accordingly by making a left or right mouse button press. For control sentences, participants were instructed to read the ungrammatical sentence carefully and to make a mouse button press when finished. True and false episodic statements presented during the practice session were based on hypothetical events created by the experimenters to avoid inadvertently cuing participants with events they would be tested on during the experimental session. Participants were instructed to choose a subset of hypothetical statements that they would respond to as true and a subset of statements that they would respond to as false, to practice responding with the appropriate button press. True and false semantic statements presented during the practice were not seen again during the experimental scanning session. Upon completion of the practice session, participants were oriented to fMRI procedures, placed supine on the MRI table, fitted with high-resolution goggles and earphones, and their heads were stabilized with cushions.

The scanning session consisted of four functional MRI scans (see Section 2.4). Stimuli were presented to participants during each of the four functional scans using DMDX (Version 3.1.4.1, [23]) via high-resolution goggles (Resonance Technologies, Inc., California). For the purpose of synchronizing stimulus onset and volume acquisition for event-related data analysis, DMDX was used to trigger the start of each functional scan and to record the onset of each stimulus, as well as recording button press responses and response times. Episodic and semantic statements were presented in separate scans, 2 episodic and 2 semantic. Spatial and nonspatial true/false statements and control sentences were presented in a pseudo-randomized fashion within each scan. The order of scans was counterbalanced across participants. Each episodic scan contained 49 statements—30 true (15 spatial, 15 nonspatial), 4 false (2 spatial, 2 nonspatial), and 15 control sentences. Each semantic scan contained 63 statements—40 true (20 spatial, 20 nonspatial), 8 false (4 spatial, 4 nonspatial), and 15 control sentences. All statements were preceded by a 3 s “True or False” or “Read” cue to alert participants to trial type that followed. True or false statements and control sentences were presented for 8 s and remained visible for the entire trial, regardless of when participants responded. Trials were separated by a 1 s inter-stimulus interval.

2.4. Image acquisition and analyses

Images were collected on a 3.0 Tesla Signa VH/i scanner whole body scanner (Signa Echo Speed; General Electric, Milwaukee, WI) using an 4-channel phased array head coil. A sagittal localizer was collected in three planes of section for image alignment, followed by a high resolution 3D SPGR anatomical scan (1.5 mm sagittal sections covering whole brain, matrix = 256 × 256, flip angle = 30, TR = 22 ms, TE = 3.0 ms, FOV = 25 cm). Functional scans were aligned axially parallel to the anterior commissure–posterior commissure plane, and acquired using a single-shot spiral in–out pulse sequence ([24]; matrix = 64, TR = 2040, TE = 30, sections = 30, FOV = 240 × 240 mm, 4 mm, no skip). Four functional scans were acquired (375 volumes × 2 scans; 293 volumes × 2 scans) each lasting approximately 12 min for a total scanning time of approximately 45 min.

fMRI data were analyzed using Statistical Parametric Mapping (SPM-5) software (Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/software/spm5>). Images were reconstructed offline and then realigned to the third volume for motion correction. Spatial normalization parameters were estimated by warping each participant’s mean functional image to the SPM5 MNI (Montreal Neurological Institute) EPI template [25]. The normalized images were resliced to 3 mm × 3 mm × 3 mm voxels and smoothed with an isotropic 7 mm FWHM gaussian kernel. Prior to spatial normalization a Fourier interpolation was applied across the whole brain to correct for differences in slice acquisition timing within a TR. A high-pass filter was applied to the data to exclude low-frequency components of the fMRI signal from analyses.

Statistical analyses were performed at the single-subject level using the general linear model implemented in SPM-5. Experimental and control task trials were modeled using an event-related design convolved with the canonical hemodynamic response function. Estimation of the onset time of the HDR was modeled to the onset time of experimental and control items with durations equal to zero. Statistical parametric maps were calculated to create contrast images comparing HDR estimates for experimental conditions to the control condition. Contrast images for each participant were submitted to a random effects group analysis, using a one-sample *t*-test [26]. A 2 × 2 full factorial ANOVA comparing memory type (episodic, semantic) and spatial content (spatial, nonspatial) was performed in SPM-5 to examine main effects and interactions. A false discovery rate (FDR) correction for multiple comparisons was applied to the simple contrasts and ANOVA group analyses [27]. Activation in all brain regions, including the medial temporal lobe region, were considered significant at $p < 0.05$, FDR corrected.

To better quantify differential activation in hippocampal and parahippocampal regions observed in the two-factor ANOVA, additional ROI analyses were performed using MarsBaR [28]. Effect sizes were extracted from ROIs for each participant and

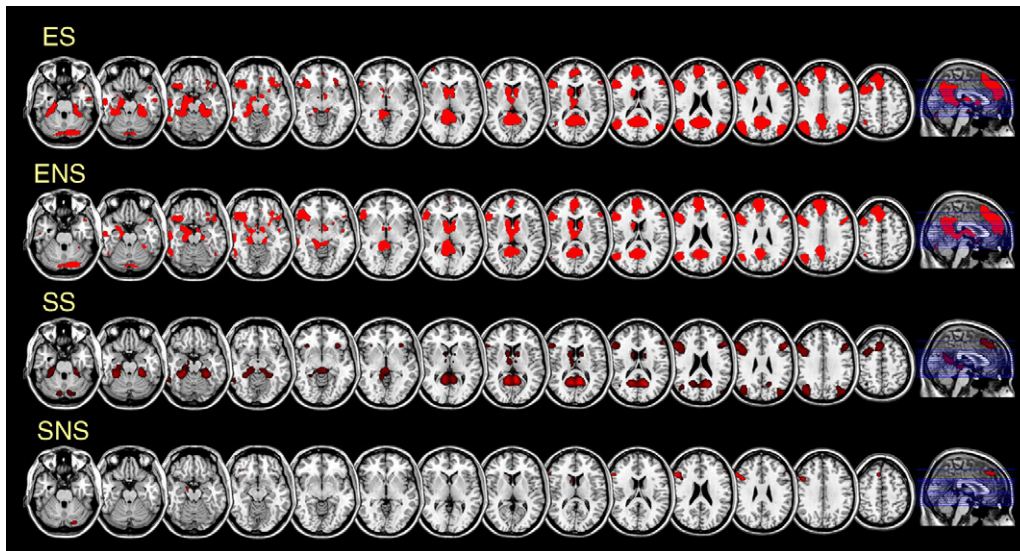


Fig. 1. Individual group effects comparing whole-brain activation for the retrieval of episodic spatial (ES), episodic nonspatial (ENS), semantic spatial (SS) and semantic nonspatial (SNS) conditions compared to the control task ($p < .05$, FDR corrected). Axial and sagittal slices were derived from a normalized T1 anatomical image. Images shown in radiological orientation.

analyzed in SPSS with a 2×2 repeated-measures ANOVA, comparing memory type (episodic, semantic) and spatial content (spatial, nonspatial).

3. Results

3.1. Experimental conditions versus control

Fig. 1 and Table 2 show the results of random effects analyses comparing each of the four memory conditions to the control task. The episodic memory conditions showed nearly identical patterns of whole-brain activation consistent with previous studies of autobiographical memory retrieval, including bilateral hippocampus and parahippocampal gyrus, bilateral superior, middle, and inferior frontal regions, medial prefrontal cortex, middle and inferior temporal gyrus, precuneus and posterior cingulate, bilateral parietal cortex, basal ganglia, and bilateral thalamic regions. The one region that appeared to differentiate between episodic conditions was the fusiform gyrus, showing extensive bilateral activation for the episodic spatial condition but not the episodic nonspatial condition.

The semantic spatial retrieval condition elicited posterior cortical activations that were similar to the episodic spatial condition, including posterior cingulate, posterior parietal cortex bilaterally, and bilateral fusiform gyrus activation. In contrast, the semantic nonspatial condition showed no significant activation in posterior regions. Episodic and semantic conditions also elicited activation in different frontal regions, with episodic memory conditions showing activation in superior and medial frontal gyri, while semantic memory conditions showed activation primarily in the inferior frontal gyrus bilaterally.

3.2. ANOVA: memory type versus spatial content

The two-factor ANOVA yielded two main effects; a main effect of spatial content (spatial > nonspatial) and a main effect of mem-

ory type (episodic > semantic). No regions showed the opposite main effects, and no region showed a significant interaction at $p < .05$, FDR corrected. Fig. 2 and Table 3 depict these results, indicating that some regions specifically differentiated memory type, others differentiated spatial from nonspatial retrieval, while some regions showed overlapping main effects. The main effect of memory type indicated greater activation for episodic compared to semantic retrieval in the medial frontal lobe and anterior cingulate, posterior parietal cortex bilaterally including supramarginal gyrus, precuneus, retrosplenial cortex, hippocampus, and parahippocampal gyrus. The main effect of spatial content indicated greater activation for spatial compared to nonspatial retrieval in bilateral inferior and middle prefrontal cortex, bilateral fusiform gyrus, left cerebellum, and the right thalamus. Regions in which the two main effects overlapped included the precuneus, bilateral posterior parietal cortex, and bilateral hippocampus and parahippocampal gyrus.

The main effects observed in medial temporal lobe structures are shown in detail in Fig. 3. Greater activation for episodic compared to semantic retrieval was observed in the middle and anterior portions of the hippocampus bilaterally, as well as a small medial section of the parahippocampal/entorhinal cortex. Greater activation for retrieval of spatial compared to nonspatial information was evident in bilateral posterior sections of the hippocampus (although the extent was somewhat smaller on the left) and the entire extent of the parahippocampal cortex bilaterally.

3.3. ROI analyses for medial temporal lobe structures

Although the whole-brain ANOVA did not reveal any regions showing a significant interaction between memory type and spatial content, several regions of the medial temporal lobe, precuneus, and lateral parietal regions showed two main effects, suggesting increasing activation for episodic retrieval and additional increases in activation during spatial retrieval. It is possible, however, that

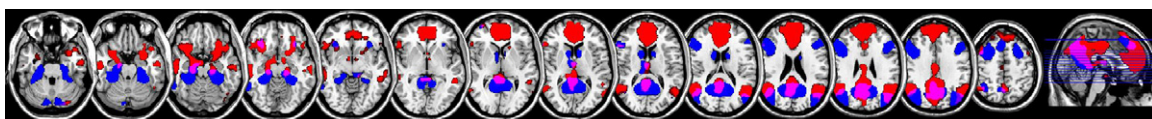


Fig. 2. Group effects for SPM-5 ANOVA analysis ($p < 0.05$; FDR corrected) main effect of memory type (red), main effect of space (blue) and regions of overlap (purple).

interactions were not observed because of the relatively stringent statistical criterion employed, particularly in the medial temporal lobe which typically yields lower amplitude hemodynamic responses, leading researchers to employ a less stringent statistical criterion (for example, [13,29,30]) or additional ROI analyses

(for example, [14], Hippocampus) in these regions. To further elucidate the activation in medial temporal lobe regions, an ROI analysis was performed using anatomical templates from MarsBAR [28]. The templates for hippocampus and parahippocampal cortex were crossed with the ANOVA results to obtain three ROIs for hippocam-

Table 2
Activations for experimental conditions compared to control task.

Contrast—Episodic Spatial > Control						
Region	<i>k</i>	<i>p</i> (<i>uncorr</i>)	<i>x</i>	<i>y</i>	<i>z</i>	Z-score
R Angulargyrus	974	0.000	42	-74	40	4.87
L Angulargyrus	411	0.000	-46	-78	30	5.08
R Ant. Cingulate	275	0.000	10	46	28	4.26
R Amygdala	159	0.000	18	-2	-16	4.48
L Amygdala	32	0.006	-22	-2	-18	2.50
R Cerebellum	15	0.000	8	-44	0	3.94
L Cerebellum	326	0.000	-22	-84	-28	4.55
R Caudate	398	0.000	12	8	18	4.35
L Caudate	279	0.000	-6	6	6	3.37
L Cuneus	340	0.000	-12	-58	20	5.04
R Inf. Frontal gyrus	1016	0.000	58	24	30	4.58
L Inf. Frontal gyrus	541	0.000	-54	30	18	4.30
R Sup. Med. Frontal gyrus	3233	0.000	2	40	44	4.73
R Mid. Frontal gyrus	824	0.000	56	26	32	3.93
L Mid. Frontal gyrus	113	0.000	-40	12	34	3.60
R Sup. Frontal gyrus	334	0.000	14	52	46	4.09
R Fusiformgyrus	429	0.000	22	-36	-16	4.73
L Fusiformgyrus	414	0.000	-32	-36	-20	4.06
R Hippocampus	139	0.000	20	-22	-14	4.91
L Hippocampus	32	0.000	-16	-28	-12	3.51
R Insula	87	0.000	28	24	-12	4.07
R Lingualgyrus	322	0.000	10	-46	4	5.88
L Lingual gyrus	39	0.000	-6	-48	2	4.05
R Post. Cingulate	380	0.000	4	-58	30	5.07
R Mid. Occipital lobe	539	0.000	44	-66	24	4.40
L Mid. Occipital lobe	490	0.000	-44	-78	32	4.97
L Inf. Parietal	23	0.000	-34	-72	40	3.99
R Parahippocampalgyrus	385	0.000	20	-22	-16	5.37
L Parahippocampalgyrus	311	0.000	-26	-28	-24	3.72
R Precuneus	2080	0.000	10	-46	6	5.72
L Precuneus	2080	0.000	-8	-54	12	5.86
R Sup. Motor	276	0.000	8	24	52	4.24
R Mid Temporal	263	0.000	44	-66	22	4.37
L Mid Temporal	121	0.000	-48	-72	22	3.73
R Thalamus	92	0.000	8	-8	10	3.63
R Vermis	129	0.000	8	-46	2	5.14
Contrast—Episodic Nonspatial > Control						
Region	<i>k</i>	<i>p</i> (<i>uncorr</i>)	<i>x</i>	<i>y</i>	<i>z</i>	Z-score
R Angular gyrus	868	0.000	36	-64	40	4.35
L Angular gyrus	96	0.001	-48	-76	26	3.18
R Cingulate	351	0.000	8	-50	28	4.57
R Cuneus	31	0.000	4	-62	20	4.81
L Cuneus	45	0.000	-2	-64	22	3.96
R Inf. Frontal Orb	631	0.000	46	24	-12	4.39
L Inf. Frontal Orb	329	0.000	-30	32	-14	3.78
R Inf. Frontal gyrus	1185	0.000	56	24	26	4.75
R Mid. Frontal gyrus	341	0.000	38	10	58	3.91
L Mid Frontal gyrus	12	0.001	-42	12	34	3.11
R Sup Frontal gyrus	560	0.000	14	48	34	4.89
R Sup Med Frontal	3642	0.000	12	46	36	5.60
R Hippocampus	120	0.000	16	-4	-16	4.31
L Hippocampus	15	0.001	-18	-20	-16	3.24
R Insula	124	0.000	28	22	-14	4.25
L Insula	8	0.001	-30	18	-14	3.19
R Lingualgyrus	338	0.000	10	-42	2	4.50
L Lingualgyrus	28	0.000	-6	-46	2	3.79
R Parahippocampalgyrus	150	0.000	18	-2	-18	4.55
L Parahippocampalgyrus	28	0.000	-14	-30	-12	3.31
R Precuneus	1548	0.000	4	-60	20	4.92
L Precuneus	1548	0.000	-4	-56	18	4.81
R Thalamus	356	0.000	4	-12	10	4.12
L Thalamus	356	0.000	-8	-6	8	3.59
L Vermis	149	0.000	-2	-42	0	4.03

Table 2 (Continued.)

Contrast—Semantic Spatial > Control						
Region	<i>k</i>	<i>p</i> (<i>uncorr</i>)	<i>x</i>	<i>y</i>	<i>z</i>	Z-score
R Angulargyrus	328	0.000	38	−74	40	4.40
L Angulargyrus	92	0.000	−34	−66	42	4.19
L Calcarine	749	0.000	−12	−56	12	5.34
R Caudate	230	0.000	12	6	14	3.55
L Caudate	160	0.001	−14	2	18	3.22
R Cerebellum	94	0.000	26	−40	−20	4.43
L Cerebellum	36	0.000	−24	−36	−24	4.16
R Cuneus	45	0.000	18	−60	20	4.29
L Cuneus	179	0.000	−16	−62	20	5.46
R Inf. Frontal gyrus	779	0.000	56	24	26	4.42
L Inf. Frontal gyrus	379	0.000	.54	30	22	4.75
R Sup. Med. Frontal gyrus	740	0.000	2	38	42	4.08
R Mid. Frontal gyrus	189	0.000	34	8	58	4.24
L Mid. Frontal gyrus	25	0.000	−50	24	32	3.85
L Fusiform	35	0.000	−34	−68	40	4.33
R Lingualgyrus	294	0.000	12	−52	6	4.93
L Lingualgyrus	42	0.000	−8	−52	2	3.64
R Mid. Occipital	487	0.000	40	−74	38	4.38
L Mid. Occipital	408	0.000	−34	−66	40	4.28
L Inf. Parietal	35	0.000	−34	−68	40	4.33
R. Parahippocampalgyrus	286	0.000	20	−32	−16	4.17
L Parahippocampalgyrus	199	0.000	−24	−30	−20	4.17
R Precuneus	777	0.000	12	−48	6	4.96
L Precuneus	777	0.000	−8	−48	10	5.50
R Supp. Motor	223	0.000	8	18	52	4.09
R Vermis	84	0.000	6	−54	6	4.19
Semantic Nonspatial > Control						
Region	<i>k</i>	<i>p</i> (<i>uncorr</i>)	<i>x</i>	<i>y</i>	<i>z</i>	Z-score
R Inf. Frontal gyrus	896	0.000	56	24	24	4.38
L Inf. Frontal gyrus	257	0.000	−48	26	28	3.66
R Sup. Med. Frontal gyrus	1337	0.000	12	50	44	4.43
R Hippocampus	6	0.000	16	−6	−16	4.04
R Supp. Motor	83	0.000	8	24	50	3.88

Only clusters with an extent of at least 5 voxels were listed. For all Z-scores, p 's < 0.001, FDR corrected. *x*, *y*, and *z* coordinates in Talairach space; L = left; R = right; mid = middle; temp. = temporal; sup. = superior; inf. = inferior; med. = medial; ant. = anterior; post. = posterior.

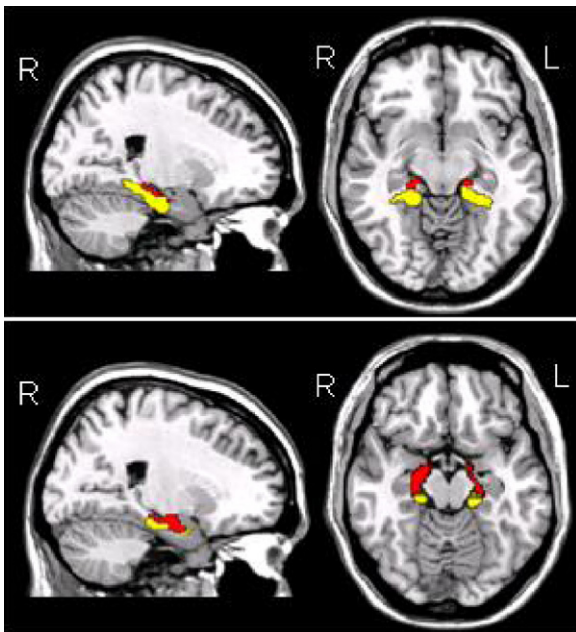


Fig. 3. Group effects MarsBAR ROI analysis for SPM-5 ANOVA ($p < 0.05$; FDR corrected; whole-brain). Main effect of space (spatial > nonspatial) in hippocampus (red) and parahippocampalgyrus (yellow) (top panel). Main effect of memory type (episodic > semantic) in hippocampus (red) and parahippocampalgyrus (yellow) (bottom panel).

pus (see Fig. 4) and three ROIs for parahippocampal cortex (see Fig. 5), corresponding to regions showing only a main effect of memory type (episodic > semantic), regions showing only a main effect of spatial content (spatial > nonspatial), and regions showing overlapping main effects of memory type and spatial content. Effect sizes within each of the six ROIs were extracted for individual participants from the SPM analyses comparing the four experimental conditions to the control condition (described earlier). These effect sizes were entered into a three-factor repeated-measures ANOVA comparing memory type (episodic, semantic), spatial content (spatial, nonspatial), and hemisphere (left, right). Because none of the analyses described below demonstrated an interaction with hemisphere, the effect sizes for corresponding ROIs were averaged across left and right hemispheres, and hemisphere was dropped from the analyses. The results are depicted in Figs. 4 and 5.

3.4. Spatial content ROIs

When the effect sizes were compared directly, the ROIs associated with the spatial > nonspatial contrast actually demonstrated two additive main effects, with no interaction. The hippocampus showed both a main effect of memory type ($F_{[1,16]} = 6.67$, $p < .02$) with greater overall activation for episodic compared to semantic retrieval, and a main effect of spatial content ($F_{[1,16]} = 14.95$, $p < .001$), with greater overall activation for spatial retrieval compared to nonspatial retrieval. The parahippocampal cortex showed the same two additive effects with no interaction, a main effect of memory type ($F_{[1,16]} = 7.98$, $p < .012$) and a main effect of spatial content ($F_{[1,16]} = 45.34$, $p < .0001$).

Table 3

Main Effect of Memory Type (Episodic)							
Region	<i>k</i>	<i>p</i> (<i>uncorr</i>)	<i>x</i>	<i>y</i>	<i>z</i>	Z-score	
R Amygdala	149	0.000	24	0	−20	4.35	
L Amygdala	125	0.000	−30	2	−20	4.09	
R Angulargyrus	1280	0.000	52	−54	24	4.98	
L Angulargyrus	824	0.000	−52	−62	24	5.75	
L Ant. Cingulate	2266	0.000	−6	42	4	5.72	
R Mid. Cingulate	1611	0.000	0	−48	34	7.31	
R Post. Cingulate	685	0.000	0	−48	32	7.54	
R Cuneus	734	0.000	0	−72	34	4.63	
R Inf. Orbital Frontal gyrus	466	0.000	36	20	−18	4.83	
L Inf. Orbital Frontal gyrus	396	0.000	−30	20	−16	5.46	
R Mid. Orbital Frontal gyrus	318	0.000	2	50	−2	5.56	
R Sup. Frontal gyrus	892	0.000	22	52	36	4.97	
L Sup. Frontal gyrus	799	0.000	−18	54	38	4.17	
R Sup. Med Frontal gyrus	4105	0.000	2	60	8	5.97	
R Hippocampus	156	0.000	20	−22	−14	4.45	
L Hippocampus	59	0.000	−16	−26	−12	4.45	
R Insula	182	0.000	28	20	−16	5.22	
L Insula	135	0.000	−30	18	−16	5.51	
R Inf. Sup. Parietal	122	0.000	56	−62	38	4.61	
R Parahippocampalgyrus	125	0.000	20	−24	−16	4.77	
L Parahippocampalgyrus	65	0.000	−16	−24	−16	4.19	
R Precuneus	3077	0.000	0	−50	34	7.19	
L Supramarginalgyrus	30	0.000	−58	−56	28	4.35	
R Mid. Temporal	1845	0.000	60	−60	20	4.78	
L Mid. Temporal	1609	0.000	−52	−62	22	6.12	
R Sup. Temp Pole	67	0.000	30	4	−22	4.51	
L Sup. Temp Pole	266	0.000	−28	6	−20	4.67	
Main Effect of Spatial Content (Space)							
Region	<i>k</i>	<i>p</i> (<i>uncorr</i>)	<i>x</i>	<i>y</i>	<i>z</i>	Z-score	
R Angulargyrus	752	0.000	40	−76	40	6.98	
L Angulargyrus	309	0.000	−44	−78	30	7.39	
R Caudate	272	0.000	12	6	16	4.37	
L Caudate	243	0.000	−14	2	20	3.30	
R Cerebellum	260	0.000	24	−38	−20	6.03	
L Cerebellum	162	0.000	−20	−36	−20	5.70	
R Post. Cingulate	82	0.000	4	−46	10	6.24	
L Post. Cingulate	253	0.000	−6	−44	8	6.82	
R Cuneus	678	0.000	18	−60	20	7.76	
R Inf. Frontal gyrus	770	0.000	58	24	30	5.14	
L Inf. Frontal gyrus	491	0.000	−48	26	28	5.17	
R Mid. Frontal gyrus	1080	0.000	32	6	60	5.97	
L Mid. Frontal gyrus	660	0.000	−26	12	54	5.08	
R Sup. Frontal gyrus	568	0.000	32	6	62	5.70	
L Sup. Frontal gyrus	87	0.000	−24	16	54	4.81	
R Sup. Med. Frontal gyrus	858	0.000	10	26	50	4.37	
R Fusiformgyrus	527	0.000	22	−36	−16	7.01	
L Fusiformgyrus	503	0.000	−26	−38	−18	6.49	
R Hippocampus	10	0.000	24	−22	−16	3.65	
L Hippocampus	8	0.000	−16	−28	−12	3.93	
R Lingualgyrus	459	0.000	12	−56	8	7.65	
L Lingualgyrus	109	0.000	−8	−50	2	6.01	
R Mid. Occipital	722	0.000	36	−82	34	6.97	
L Mid. Occipital	739	0.000	−44	−78	32	7.47	
R Inf. Parietal	222	0.000	38	−50	46	4.16	
L Inf. Parietal	76	0.000	−36	−74	40	6.75	
R Parahippocampalgyrus	508	0.000	22	−36	−14	6.41	
L Parahippocampalgyrus	454	0.000	−24	−32	−18	5.70	
R Precuneus	2622	0.000	16	−58	14	7.65	
L Precuneus	2622	0.000	−10	−56	12	7.14	
R Supp. Motor	176	0.000	10	24	50	4.56	
R Mid. Temporal	128	0.000	44	−68	22	5.00	
L Mid Temporal	52	0.000	−48	−76	20	4.66	
R Thalamus	188	0.000	8	−10	10	3.78	
R Vermis	183	0.000	6	−50	6	6.92	

Activation table for the main effect of memory type (episodic) and the main effect of spatial content (space). Only clusters with an extent of at least 5 voxels were listed. For all Z-scores, *p*'s < 0.001, FDR corrected. *x*, *y*, and *z* coordinates in Talairach space; L = left; R = right; B = bilateral; mid = middle; sup. = superior; inf. = inferior; med. = medial; ant. = anterior; post. = posterior.

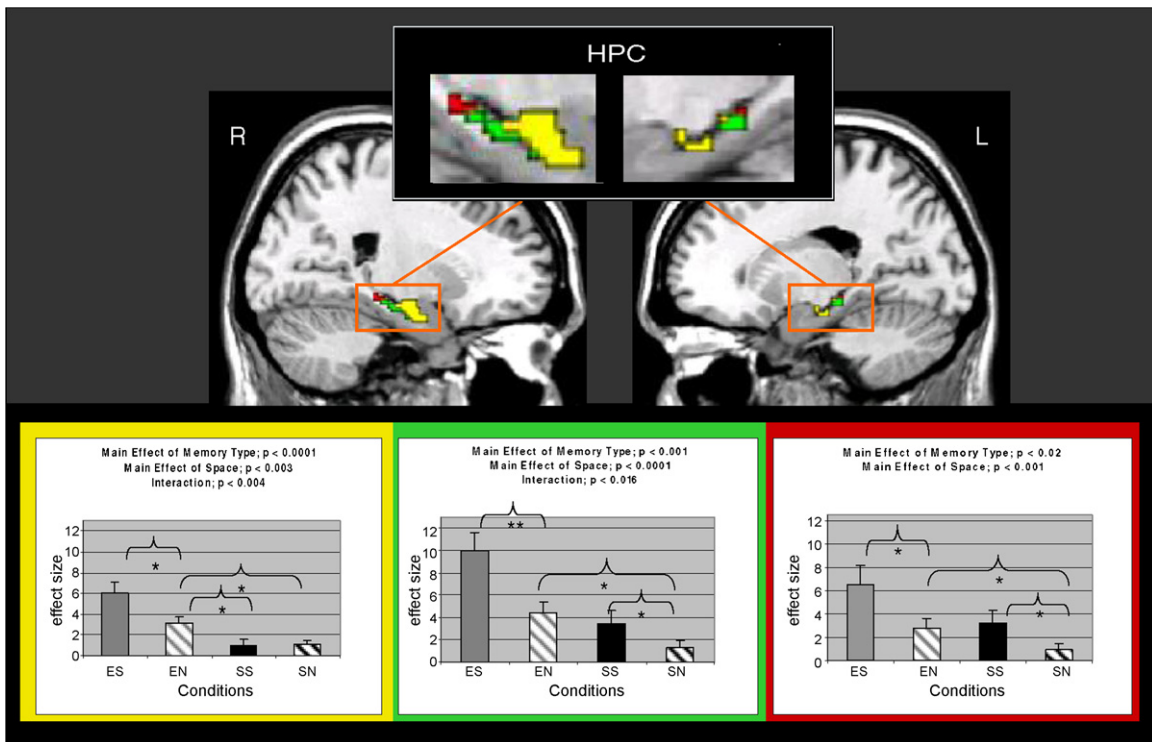


Fig. 4. Group effects for SPM-5 ANOVA MarsBAR ROI analysis in the hippocampus ($p < 0.05$; FDR corrected; whole-brain). ROIs show activation for the main effect of memory type (yellow), the main effect of space (red) and regions of overlap (green).

3.5. Memory type ROIs

Comparing the effect sizes from the ROIs associated with the episodic > semantic contrast demonstrated a significant interaction between memory type and spatial content in both the

hippocampus ($F_{[1,16]} = 11.38, p < .004$) and parahippocampal cortex ($F_{[1,16]} = 15.65, p < .001$). Follow-up paired t -tests in the hippocampus indicated significant differences between all conditions ($t(16)$'s $> 4.07, p$'s $< .001$) with the exception of the comparison between the semantic spatial and semantic nonspatial condi-

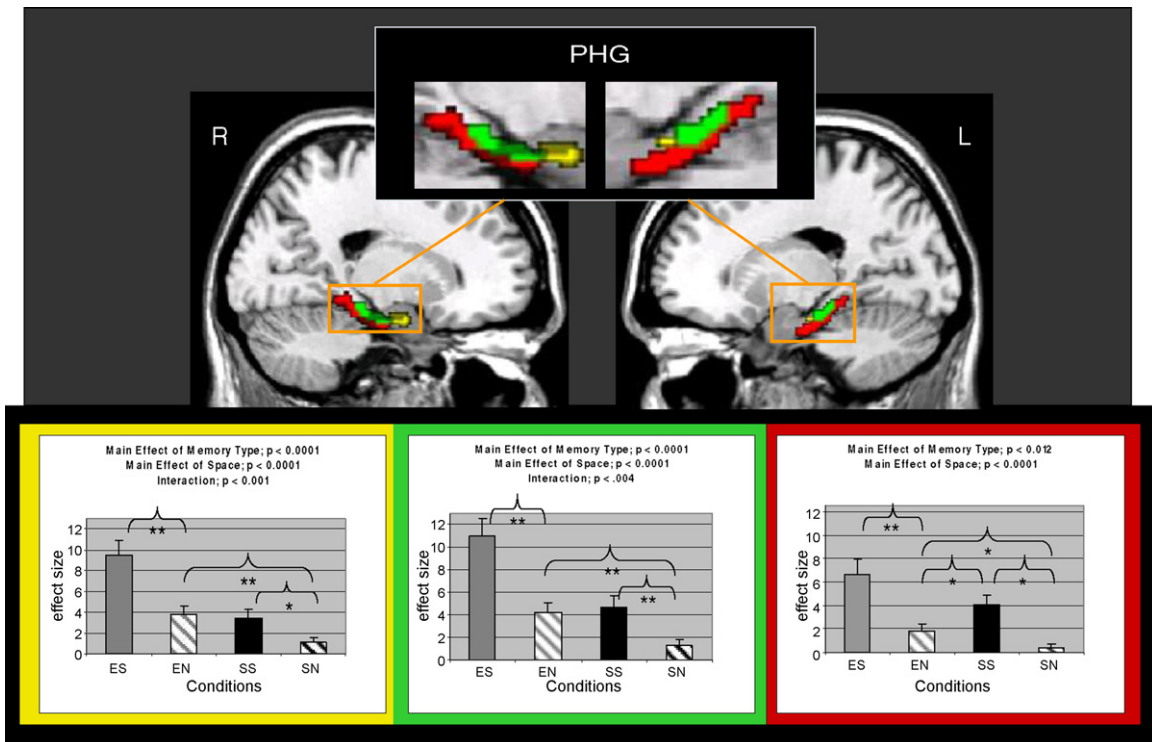


Fig. 5. Group effects for SPM-5 ANOVA MarsBAR ROI analysis in the parahippocampal gyrus ($p < 0.05$; FDR corrected; whole-brain). ROIs show activation for the main effect of memory type (yellow), the main effect of space (red) and regions of overlap (green).

tions ($t < 1$, ns). Follow-up paired t -tests in the parahippocampal cortex showed significant differences between all conditions ($t(16)$'s > 5.15 , p 's $< .0001$) with the exception of the episodic non-spatial and semantic spatial conditions that showed similar levels of activation ($t < 1$, ns).

3.6. Overlapping ROIs

The effect sizes from the ROIs associated with two main effects showed an interaction between memory type and spatial content in both the hippocampus ($F_{[1,16]} = 7.27$, $p < .016$) and the parahippocampal cortex ($F_{[1,16]} = 11.29$, $p < .004$). Follow-up paired t -tests in the hippocampus showed significant differences between all conditions ($t(16)$'s > 3.6 , p 's $< .002$) with the exception of the episodic nonspatial and semantic spatial conditions ($t(16) = 1.05$, ns). In the parahippocampal cortex, a similar pattern of results was observed, with all paired comparisons significantly different ($t(16)$'s > 4.38 , p 's $< .001$) excepting the comparison between the episodic nonspatial and semantic spatial conditions ($t < 1$, ns).

4. Discussion

4.1. The interaction between memory type and spatial content

The primary goal of the current study was to compare hippocampal activation while varying spatial content within episodic and semantic memory. Although all four retrieval conditions activated the hippocampus, retrieval of episodic memory elicited more activation than did retrieval of semantic memory. As in previous studies, we observed differences in the distribution of activation along the longitudinal axis of the hippocampus: spatial retrieval (both within episodic and semantic memory) elicited more posterior activation, while nonspatial retrieval elicited more anterior activation (discussed in more detail below). There appears to be an overall interaction between the kind of memory (episodic or semantic) and the presence or absence of spatial content in eliciting activation within the medial temporal lobes. The largest, most consistent, activations were observed in the episodic-spatial condition, followed by semantic-spatial, and then the two nonspatial conditions. These results suggest that the hippocampus is critically involved in processing information about spatial context and spatial relations, regardless of whether the source of the spatial information is a prior single event or well-established world knowledge.

Our results suggest that the nature of retrieved information (spatial versus nonspatial) determines which brain regions are recruited during memory retrieval to a greater extent than the source of the memory (episodic or semantic). Episodic memory and semantic spatial, but critically not semantic nonspatial, conditions elicited activation in similar brain regions, particularly in posterior regions typically activated during the visuospatial processing associated with spatial localization, maze learning and mental navigation (e.g., the precuneus, inferior parietal lobes, fusiform gyrus and the parahippocampal cortex) ([31–34]; for review, see [35]). This perspective is at odds with the recent argument [36] that hippocampal function is best defined in terms of the kinds of representations it supports – relational in their view – rather than the nature of information it processes. In our view it is the spatial nature of the information that determines hippocampal involvement, not its relational character.

Prior discussions of the relation between episodic and semantic memory have tended to conflate two rather different questions: (1) where is episodic and semantic information actually stored, and (2) what neural systems are involved in the process of retrieving episodic and semantic information? The answers to these ques-

tions need not be the same. The study of patients with focal lesions sheds light primarily on the first question, while neuroimaging studies tend to address the second. We believe these two types of memory can be independent of one another structurally, but not functionally, particularly in individuals with normal intact brains. Such considerations lead away from thinking about the neural correlates of memory in terms of fixed memory systems, such as the medial temporal lobe declarative memory system [11]. In line with recent discussions of the boundaries between memory and perceptual systems (e.g., [37]), we are inclined to the view that structures in the temporal lobe are best thought of as both processing and representing specific forms of information that are called into play as a function of task demands. The defining features of episodic memory tasks ensure that they always involve the retrieval of spatial context, and that is why these tasks necessarily engage hippocampus, amongst other structures. Semantic memory tasks may or may not elicit spatial processing, depending upon the specific requirements of the task, and hippocampal engagement could depend upon whether or not spatial context is relevant. The present results suggest that such is the case when spatial context varies in a semantic task.

Category production, another semantic memory task, can also elicit substantial hippocampal activation, even when one tries to remove the spatial component. This task requires participants to retrieve as many examples as possible from a common category such as *fruits and vegetables*. Such knowledge is clearly semantic, and it has been assumed that individuals with damage in the medial temporal lobe can produce category exemplars at a near normal levels, at least when the damage does not extend beyond medial temporal structures ([8]; but see [38]). However, when this task is performed by cognitively normal individuals, considerable fMRI activation is observed in the hippocampus and neighboring medial temporal lobe structures [13]. In this situation, we and others (e.g., [39]) have suggested that participants rely on episodic memory to help retrieve semantic information. For example, when seeking members of a category such as *kitchen utensils*, many individuals will imagine themselves standing in a kitchen, typically their own, and use that as a basis for generating the required items. Though Ryan et al. [13] found activation within the hippocampus for all categories, whether or not participants relied on spatial strategies to generate exemplars, the activation was greater for strategies that relied on spatial location and navigation through space.

Barsalou [39] emphasizes an integrated view of episodic and semantic memory in which semantic knowledge is embedded within the framework of episodic knowledge, both generic and unique. Instead of focusing on abstracted concepts, Barsalou emphasizes the critical role of instances for generating semantic knowledge. This integrated view of episodic and semantic memory has received recent support not only from cognitive psychology [40,41] but also from recent neuroimaging studies emphasizing the singularity of the neural networks that underlie these various tasks [19,20,42]. This leads to the notion that the hippocampus is not merely “involved but not necessary” for semantic retrieval. Rather, the presentation of a cue generates an automatic response from the hippocampus that leads to the retrieval of any information that is relevant and accessible to the person, including prior episodes, semantically related material, and so on. Therefore, multiple interactive knowledge systems are engaged cooperatively via the hippocampus, depending upon the requirements of the task, providing complementary routes for retrieval. By this view, the hippocampus becomes not the structure that differentiates memory systems, but the structure that mediates the interactions between many memory systems. To the degree that regions are required for the task, they will be engaged. Episodic and semantic systems are interactive, and in the normal case, a cue will conjure up what-

ever is required in service of the task demands, be it episodic and semantic.

Understanding the interaction of these systems will probably require the integration of data from studies of both normal and brain-injured individuals. For example, as described earlier, intact individuals will often use personally relevant contexts (their kitchen, their garage, etc.) in order to generate categorical exemplars to very familiar categories. But does this strategy actually impart any benefit? Recently, Greenberg et al. [43] compared the performance of medial temporal lobe amnesics to matched controls during category production. Compared to controls, amnesics produced significantly fewer exemplars for categories that were highly likely to elicit personally relevant spatial contexts in control participants. The two groups were similar, however, when the category did not elicit such personally relevant retrieval strategies. The results are consistent with our argument that episodic activation is not merely a by-product of cueing in semantic tasks, but may in fact play an important role in increasing the efficiency of retrieval, even in retrieval tasks that have been traditionally viewed as classically semantic, such as category production.

4.2. The longitudinal axis of the hippocampus

Region of interest analyses performed on hippocampus and parahippocampal gyrus along the anterior–posterior axis of the medial temporal lobe revealed intriguing differences in localization of activation associated with the two main effects that we observed—memory type (episodic > semantic), and spatial content (spatial > nonspatial). The main effect of memory type demonstrated greater activation during episodic retrieval than semantic retrieval that was localized anteriorly in the hippocampus and parahippocampal gyrus. In contrast, increased activation for spatial compared to nonspatial content was localized more posteriorly in both these regions. Interestingly, the overlap between these two main effects showed a region of activation that was localized in the middle of each structure. These results are consistent with a recent study from our laboratory [14] also showing a more posterior distribution for hippocampal activation associated with retrieval of spatial content, regardless of whether the source of the information retrieved was episodic or semantic.

Several research groups have begun to focus on understanding anterior–posterior hippocampus differences. In work with rats, two ideas have emerged: single-cell recordings have shown that as one moves from the dorsal to the ventral hippocampus (equivalent to the posterior to anterior gradient in humans) the size of “place” fields increases (cf., [44]). These authors conclude that the hippocampus is concerned with space throughout its length, but at different spatial scales. A somewhat different idea emerged from work with lesioned animals: that the ventral hippocampus is integral to fear and anxiety (e.g., [45]). One way to bring these ideas together would be to assume that the ventral hippocampus, whose cells have very large place fields, is critical in coding for contexts as a whole rather than precise locations within them. Much of the work relating ventral hippocampus to fear utilizes context fear or open field procedures, which share the common element of large-scale context. In work with humans, Bunzeck et al. [46] argued that anterior–posterior differences in fMRI activation in the MTL reflect distinct cognitive processes. They suggested that anterior MTL regions are related to novelty detection or encoding of novel information, while posterior MTL regions are associated with the retrieval process. This notion cannot account for the present results, since all the conditions in the study required retrieval of familiar and well-established information. Alternatively, if we assume relative homogeneity of structure along the anterior–posterior axis of the hippocampus, then anterior–posterior dissociations may reflect differences in inputs from various neocortical regions that are also

involved in the retrieval task, rather than a qualitative difference in cognitive processing. Recent anatomical work with macaque monkeys [47] shows a complex pattern of topographically organized input to the hippocampus via the entorhinal and perirhinal cortex. Some projections terminate throughout the entorhinal cortex while others project in limited fashion rostrally (orbitofrontal cortex, insular cortex, anterior cingulate cortex, perirhinal cortex), intermediately (upper bank of the superior temporal sulcus, unimodal auditory association cortex), or caudally (parietal and retrosplenial cortices). Entorhinal cortex, in turn, converges with other sources of input to project primarily to posterior hippocampus, while rostral perirhinal, insular, and olfactory cortex project to the anterior portion of the hippocampus. The anterior–posterior distribution suggests that the hippocampus may mediate a single process that is carried out on different types of information whose inputs are differentially placed along the long axis of the hippocampus.

Our results suggest that posterior hippocampus is predominantly activated by spatial content, whereas anterior hippocampus is preferentially activated by episodic rather than semantic memory retrievals. Chadwick et al. [48] report the same distinction: spatial content in posterior hippocampus, and episodic (autobiographical) memory in anterior hippocampus. On the assumption that it is the spatial contextual content in episodic memory that interests the hippocampus, this line of thinking is consistent with the work in rats linking dorsal hippocampus to precise representations of space and navigation, and the ventral hippocampus to large-scale representations of space, and contextual fear and anxiety. This approach to understanding differentiation of function along the longitudinal axis of the hippocampus warrants further investigation.

4.3. The parahippocampal gyrus

Traditionally, the functional contribution of the parahippocampal gyrus has been examined directly in spatial navigation tasks and passively observed in episodic memory studies. These findings provide support for the notion that the parahippocampal gyrus is involved in memory retrieval, beyond its role in encoding spatial scenes [49], and is preferentially involved in retrieval of spatial, compared to nonspatial, episodic information [50,51]. The current study provides additional evidence that the parahippocampal gyrus is also involved in retrieval of spatial representations from semantic knowledge, consistent with our previous work [14]. However, as depicted in Fig. 5, the interaction between memory type and spatial content is evident throughout the parahippocampal gyrus. The greatest activation along the entire axis of the region is elicited by the combination of episodic and spatial information.

4.4. The distribution of cortical activation

The regions that differentiated semantic and episodic tasks were not medial temporal, but rather other cortical regions that have been previously implicated in episodic retrieval, including medial and lateral prefrontal cortex bilaterally, parietal cortex, and the precuneus. Given the clear differences between semantic and episodic retrieval in these regions, how can we account for the similarity of activation networks reported in several recent studies of episodic and semantic memory retrieval? For example, Rajah and McIntosh [19] compared the networks mediating episodic and semantic retrieval tasks. They found that separate models failed to differentiate one task from the other, suggesting that the same memory network was engaged across tasks. A similar outcome was recently reported by Burianova [20,42], showing overlapping networks of activation during semantic and episodic retrieval that included regions of left medial temporal lobe. These authors suggest that differences between episodic and semantic retrieval likely reflected

variation along a continuum of processing during task performance, rather than the output of two completely independent memory systems.

Elsewhere [6] we have argued that recruitment of cortical areas depends upon the specifics of the task—the more similar the type of information required for episodic and semantic tasks, the more likely that the same regions will be recruited during retrieval. Thus, the appropriate contrast may not be episodic versus semantic, but rather such things as spatial versus nonspatial, personally relevant versus not, and other things not considered here, such as perspective, verbal encoding of content, and so on. Nevertheless, there may indeed be aspects of experience that will always be integral to episodic memory tasks. Episodic memory, by definition, requires the retrieval of contextual information about time and place—the individual determines not only whether something has been experienced before, but whether the experience occurred during a particular event and not others. Episodic memory also requires a determination of the degree to which the self was present in relation to the retrieved material. The precuneus, for example, has been implicated in various types of tasks self-processing operations including first-person perspective taking and the experience of agency (for review, see [52]). It has been proposed that precuneus may be a critical component of the brain network mediating self-consciousness and self-related mental representations. If this is correct, it would be difficult to devise an episodic memory task that did not engage precuneus, at least to some extent.

5. Summary

In summary, the current data provide evidence that the hippocampus is engaged during the retrieval of episodic memory and spatial context. Our results demonstrated that the hippocampus participates preferentially in the retrieval of episodic memories but is also engaged to a significant degree by the retrieval of semantic memories, particularly those that include spatial information. Recent statements of Multiple Trace Theory (MTT) [53,54] emphasize a distinction between detailed perceptual-spatial representations that make rich re-experiencing possible and schematic representations that allow for coarse memory retrievals. Richly detailed spatial representations (or cognitive maps) are assumed to depend on the hippocampus while coarse (semantic) representations are not. Within MTT, the hippocampal spatial representations “index” the semantic representations of actors, actions and objects that comprise an episode. Retrieving an episodic memory requires the activation of critical hippocampal circuits, which then call up the largely neocortical circuits representing the elements of that episode. On the assumption that storing, retrieving and processing spatial cognitive maps necessitates hippocampal involvement, it is not surprising that spatial context and spatial relations preferentially activate the hippocampus.

The present findings support the view that the hippocampus plays a critical role in the storage and retrieval of episodic memory and spatial information [55–57], and extend this view to retrieval of spatial context within semantic memory [6]. Patterns of whole-brain activation observed during retrieval of episodic memory and spatial semantic memory did not markedly differ, which is inconsistent with the notion that retrieval of episodic memory and semantic knowledge always engage functionally separate systems [3]. The results suggest that sharp dissociations between episodic and semantic memory may be overly simplistic and that the hippocampus plays a role in the retrieval of spatial content whether drawn from a memory of one’s own life experiences or real-world semantic knowledge.

Finally, differences in the location of activation along the anterior–posterior axis of the hippocampus and parahippocam-

pal gyrus, observed for main effects, may suggest that activation in the medial temporal lobe, and accompanying brain regions that provide input to the medial temporal lobe, is driven by the type of information being processed (i.e., spatial versus nonspatial), rather than the type of memory (episodic or semantic) being retrieved. Future research will be needed to better understand anterior–posterior differences observed within the hippocampus and the complex interaction between traditionally defined episodic and semantic memory systems within the domain of space.

References

- [1] Tulving E. Episodic memory and autoeosis: uniquely human? In: Terrace HS, Metcalfe J, editors. *The missing link in cognition: origins of self-reflective consciousness*. Oxford University Press; 2005. p. 3–56.
- [2] Tulving E. Episodic memory: from mind to brain. *Annu Rev Psychol* 2002;53:1–25.
- [3] Tulving E. *Elements of episodic memory*. Oxford: Clarendon Press; 1983.
- [4] Bakker A, Stark C, Kirwan C, Miller M. Pattern separation in the human hippocampal CA3 and dentate gyrus. *Science* 2008;319(5870):1640–2.
- [5] Carr V, Rissman J, Wagner A. Imaging the human medial temporal lobe with high-resolution fMRI. *Neuron* 2010;65(3):298–308.
- [6] Ryan L, Hoscheidt S, Nadel L. Perspectives on episodic and semantic memory retrieval. In: Dere E, Easton A, Nadel L, Huston JP, editors. *Handbook of behavioral neuroscience series, vol. 18, handbook of episodic memory*. Netherlands: Elsevier Sciences; 2008. p. 5–18.
- [7] Moscovitch M, Nadel L, Winocur G, Gilboa A, Rosenbaum S. The cognitive neuroscience of remote episodic, semantic and spatial memory. *Curr Opin Neurobiol* 2006;16(2):179–90.
- [8] Schmolck H, Kensinger E, Corkin S, Squire L. Semantic knowledge in patient H.M. and other patients with bilateral medial and lateral temporal lobe lesions. *Hippocampus* 2002;12:520–33.
- [9] Manns J, Hopkins R, Squire L. Semantic memory and the human hippocampus. *Neuron* 2003;38(1):127–33.
- [10] Luo J, Niki K. Role of medial temporal lobe in extensive retrieval of task related knowledge. *Hippocampus* 2002;12(4):487–94.
- [11] Squire L, Stark C, Clark R. The medial temporal lobe. *Annu Rev Neurosci* 2004;27:279–306.
- [12] Bayley P, Hopkins R, Squire L. Successful recollection of remote autobiographical memories by amnesic patients with medial temporal lobe lesions. *Neuron* 2003;38(1):135–44.
- [13] Ryan L, Cox C, Hayes S, Nadel L. Hippocampal activation during episodic and semantic memory retrieval: comparing category production and category cued recall. *Neuropsychologia* 2008;46(8):2109–21.
- [14] Ryan L, Lin C-Y, Ketcham K, Nadel L. The role of medial temporal lobe in retrieving spatial and nonspatial relations from episodic and semantic memory. *Hippocampus* 2010;139(1):11–8.
- [15] Bernard F, Bullmore E, Graham K, Thompson S, Hodges J, Fletcher P. The hippocampal region involved in successful recognition of both remote and recent famous faces. *Neuroimage* 2004;22(4):1704–14.
- [16] Leveroni C, Seidenberg M, Mayer A, Mead L, Binder J, Rao S. Neural systems underlying the recognition of familiar and newly learned faces. *J Neurosci* 2000;20(2):878–86.
- [17] Maguire E, Mummery C. Differential modulation of a common memory retrieval network revealed by positron emission tomography. *Hippocampus* 1999;9(1):54–61.
- [18] Henke K, Mondadori C, Treyer V, Nitsch R, Buck A, Hock C. Nonconscious formation and reactivation of semantic associations by way of the medial temporal lobe. *Neuropsychologia* 2003;41:863–76.
- [19] Rajah M, McIntosh A. Overlap in the functional neural systems involved in semantic and episodic memory retrieval. *J Cogn Neurosci* 2005;17(3):470–82.
- [20] Burianova H, Grady C. Common and unique neural activations in autobiographical, episodic, and semantic retrieval. *J Cogn Neurosci* 2007;19(9):1520–34.
- [21] Duzel E, Cabeza R, Picton T, Yonelinas A, Scheich H, Heinze H, et al. Task-related and item-related brain processes of memory retrieval. *Proc Natl Acad Sci USA* 1999;96:1794–9.
- [22] Ryan L, Nadel L, Keil K, Putnam K, Schnyer D, Trouard T, et al. Hippocampal complex and retrieval of recent and very remote autobiographical memories: evidence from functional magnetic resonance imaging in neurologically intact people. *Hippocampus* 2001;11(16):707–14.
- [23] Forster K, Forster J. DMDX: a windows display program with millisecond accuracy. *Behav Res Methods Instrum Comput* 2003;35:116–24.
- [24] Glover G, Law C. Spiral-in/out BOLD fMRI for increased SNR and reduced susceptibility artifacts. *Magn Reson Med* 2001;46(3):515–22.
- [25] Ashburner J, Friston K. Nonlinear spatial normalization using basis functions. *Hum Brain Mapp* 1999;7(4):254–66.
- [26] Friston K, Holmes A, Price C, Buchel C, Worsley K. Multisubject fMRI studies and conjunction analyses. *Neuroimage* 1999;10:385–96.
- [27] Genovese C, Lazar N, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 2002;15:870–8.

- [28] Brett M, Anton J, Valabregue R, Poline J. Region of interest analysis using an SPM toolbox [abstract]. Presented at the eighth international conference on functional mapping of the human brain. *Neuroimage* 2002;16.
- [29] Dobbins I, Rice H, Wagner A, Schacter D. Memory orientation and success: separable neurocognitive components underlying episodic recognition. *Neuropsychologia* 2003;41(3):318–33.
- [30] Addis D, Wong A, Schacter D. Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. *Neuropsychologia* 2007;45(7):1363–77.
- [31] Van Horn J, Gold J, Esposito G. Changing patterns of brain activation during maze learning. *Brain Res* 1998;793(1–2):29–38.
- [32] Ghaem O, Mellet E, Crivello F, Tzourio N, Mazoyer B, Berthoz A, et al. Mental navigation along memorized routes activates the hippocampus, precuneus, and insula. *NeuroReport* 1997;8(3):739–44.
- [33] Hartley T, Maguire E, Spiers H, Burgess N. The well-worn route and the path less traveled: distinct neural bases for route following and wayfinding in humans. *Neuron* 2003;37(5):877–88.
- [34] Maguire E, Burgess N, Donnett J, Frackowiak R, Frith C, O'Keefe J. Knowing where and getting there: a human navigation network. *Science* 1998;280:921–3.
- [35] Bird C, Burgess N. The hippocampus and memory: insights from spatial processing. *Nat Rev Neurosci* 2008;9(3):182–94.
- [36] Konkel A, Cohen N. Relational memory and the hippocampus: representations and methods. *Front Neurosci* 2009;3(2):166–74.
- [37] Graham K, Barense M, Lee A. Going beyond LTM in the MTL: a synthesis of neuropsychological and neuroimaging findings on the role of the medial temporal lobe in memory and perception. *Neuropsychologia* 2010;48(4):831–53.
- [38] Gleissner U, Elger C. The hippocampal contribution to verbal fluency in patients with temporal lobe epilepsy. *Cortex* 2001;37(1):55–63.
- [39] Barsalou LW. The content and organization of autobiographical memories. In: Neisser U, Winograd E, editors. *Remembering reconsidered: ecological and traditional approaches to the study of memory*. Cambridge University Press; 1988. p. 193–243.
- [40] Vallee-Tourangeau F, Anthonys S, Austin N. Strategies for generating multiple instances of common and ad hoc categories. *Memory* 1998;6(5):555–92.
- [41] Westmacott R, Moscovitch M. The contribution of autobiographical significance to semantic memory. *Mem Cogn* 2003;31(5):761–74.
- [42] Burianova H, McIntosh A, Grady C. A common functional brain network for autobiographical, episodic, and semantic memory retrieval. *Neuroimage* 2010;49(1):865–74.
- [43] Greenberg D, Keane M, Ryan L, Verfaellie M. Impaired category fluency in medial temporal lobe amnesia: the role of episodic memory. *J Neurosci* 2009;29(35):10900–8.
- [44] Kjelstrup KB, Solstad T, Brun VH, Hafting T, Leutgeb S, Witter MP, et al. Finite scale of spatial representation in the hippocampus. *Science* 2008;321:140–3.
- [45] Bannerman DM, Yee BK, Good MA, Heupel MJ, Iversen SD, Rawlins JN. Double dissociation of function within the hippocampus: a comparison of dorsal, ventral, and complete hippocampus cytotoxic lesions. *Behav Neurosci* 1999;113:1170–88.
- [46] Bunzeck N, Schutze H, Duzel E. Category-specific organization of prefrontal response-facilitation during priming. *Neuropsychologia* 2006;44(10):1765–76.
- [47] Mohedano-Moriano A, Pro-Sistiaga P, Arroyo-Jimenez M, Artacho-Perula E, Insausti A, Marcos P, et al. Topographical and laminar distribution of cortical input to the monkey entorhinal cortex. *J Anat* 2007;211(2):250–60.
- [48] Chadwick MJ, Hassabis D, Weiskopf N, Maguire EA. Decoding individual episodic memory traces in the human hippocampus. *Curr Biol* 2010;20:1–4.
- [49] Kohler S, Crane J, Milner B. Differential contributions of the parahippocampal place area and the anterior hippocampus to human memory for scenes. *Hippocampus* 2002;12(6):718–23.
- [50] Hayes S, Ryan L, Schnyer D, Nadel L. An fMRI study of episodic memory: retrieval of object, spatial, and temporal information. *Behav Neurosci* 2004;118(5):885–96.
- [51] Hayes S, Nadel L, Ryan L. The effect of scene context on episodic object recognition: parahippocampal cortex mediates memory encoding and retrieval success. *Hippocampus* 2007;17(9):873–89.
- [52] Cavanna A, Trimble M. The precuneus: a review of its functional anatomy and behavioral correlate. *Brain* 2006;129(3):564–83.
- [53] Moscovitch M, Rosenbaum R, Giboa A, Addis D, Westmacott R, Grady C, et al. Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. *J Anat* 2005;207:35–66.
- [54] Nadel L, Winocur G, Ryan L, Moscovitch M. Systems consolidation and hippocampus: two views. *Debates Neurosci* 2007;1(2–4):55–66.
- [55] Nadel L, Moscovitch M. Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr Opin Neurobiol* 1997;7(2):217–27.
- [56] Nadel L, Moscovitch M. Hippocampal contributions to cortical plasticity. *Neuropharmacology* 1998;37(4–5):431–9.
- [57] O'Keefe J, Nadel L. *The hippocampus as a cognitive map*. Oxford: Clarendon Press; 1978.
- [58] Bayley P, Squire L. Failure to acquire new semantic knowledge in patients with large medial temporal lobe lesions. *Hippocampus* 2005;15(2):273–80.