

Research Article

Distinguishing the Neural Correlates of Episodic Memory Encoding and Semantic Memory Retrieval

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ABSTRACT—*Episodic memory and semantic memory interact very closely. In particular, episodic memory encoding (EE) tends to elicit semantic memory retrieval (SR), and vice versa. Thus, similar activations for EE and SR in functional neuroimaging studies may reflect shared memory processes, or they may reflect the fact that EE and SR are usually confounded. To address this issue, we used a factorial functional magnetic resonance imaging approach to disentangle the neural correlates of EE and SR. Within the left temporal lobe, the hippocampus was associated with successful EE, whereas a posterior lateral region was associated with successful SR. Within the left inferior prefrontal cortex, a posterior region was involved in SR, a mid region was involved in both SR and EE, and an anterior region was involved in EE, but only when SR was also high. Thus, the neural correlates of EE and SR are dissociable but interact in specific brain regions.*

The term *episodic memory* refers to memory for personally experienced past events, and the term *semantic memory* refers to general knowledge of the world. Episodic and semantic memory are assumed to depend on memory systems that are different but interact very closely with each other (Tulving, 1983, 2002). In particular, the storage of new information into episodic memory (episodic memory encoding, or EE) is directly associated with the recovery of information from semantic memory (semantic

memory retrieval, or SR; Cabeza & Nyberg, 2000; Nyberg, Cabeza, & Tulving, 1996; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). In fact, SR and EE are so intimately related that it is almost impossible to isolate them by manipulating task instructions: When participants are asked to memorize a list of items (intentional EE), they tend to do so by processing the meaning of the information (incidental SR), and when they are instructed to retrieve semantic information (intentional SR), they typically also encode the retrieval event into episodic memory (incidental EE). This tendency of EE and SR to co-occur regardless of task instructions complicates the interpretation of functional neuroimaging evidence regarding the neural correlates of these two forms of memory. For example, the left prefrontal cortex is frequently activated during both EE and SR tasks (Cabeza & Nyberg, 2000; Habib, Nyberg, & Tulving, 2003; Nyberg et al., 1996; Tulving et al., 1994). Do these common regions reflect cognitive processes shared by EE and SR, or do they simply reflect the fact that EE tasks tend to also engage SR, and vice versa? To address this issue, it is critical to develop a functional neuroimaging method that can disentangle the neural correlates of EE and SR. This was the goal of the present study.

We employed a factorial event-related functional magnetic resonance imaging (fMRI) design that completely crossed levels of EE and SR (see Fig. 1). We measured neural activity not only when EE and SR were both high or both low, which is the typical situation, but also when one of them was high and the other low. Participants were scanned while performing an SR task in which they viewed word pairs and rated the association strength between the words in each pair. High ratings indicated that participants successfully retrieved semantic information linking the two words (high semantic retrieval, the *high-SR* condition),

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		Episodic Encoding	
		High EE	Low EE
Semantic Retrieval	High SR	High SR/High EE	High SR/Low EE
	Low SR	Low SR/High EE	Low SR/Low EE

Fig. 1. Factorial design disentangling episodic encoding (EE) and semantic retrieval (SR). We measured neural activity not only when EE and SR were both high or both low, which is the typical situation, but also when one of them was high and the other low.

whereas low ratings reflected a failure to retrieve such information (low semantic retrieval, the *low-SR* condition). After scanning, memory for the word pairs was tested with an associative recognition test, and performance on this test was used to distinguish between studied pairs that were subsequently remembered (high episodic encoding, the *high-EE* condition) and those that were subsequently forgotten (low episodic encoding, the *low-EE* condition). Although several fMRI studies have compared encoding activity for subsequently remembered versus forgotten trials (for a review, see Paller & Wagner, 2002), this is the first study to cross this manipulation with a manipulation of SR success.

The factorial method depicted in Figure 1 has two advantages over the standard method of comparing one episodic task with one semantic task (Nyberg et al., 2003; Rajah & McIntosh, 2005; Wiggs, Weisberg, & Martin, 1999). First, it addresses the problem that tasks are not “process pure” by allowing episodic and semantic memory processes to mix naturally during task performance and separating them off-line using performance measures. Second, because episodic and semantic memory are measured in the same task, our method controls for several factors that typically confound comparisons between episodic and semantic tasks, such as differences in task difficulty and age of the memories.

We conducted two main analyses. First, we examined activity within the medial temporal lobes using a regions-of-interest (ROI) approach. According to one view, certain medial temporal regions, such as the hippocampus, are more involved in episodic than in semantic memory (Aggleton & Brown, 1999; Tulving & Markowitsch, 1998; Vargha-Khadem et al., 1997; Vargha-Khadem, Gadian, & Mishkin, 2001), whereas according to another view, medial temporal regions are similarly involved in these two forms of declarative memory (e.g., Squire & Zola, 1998). Second, we examined activity outside the medial temporal lobes using a whole-brain exploratory approach. We were particularly interested in regions in left lateral temporal cortex and left inferior prefrontal cortex (LIPC). Left lateral temporal activations tend to

be more frequent during SR than during EE tasks (Cabeza & Nyberg, 2000), but direct within-subjects contrasts are not available. As we noted earlier, left prefrontal activations are frequent during both EE and SR tasks, and this is particularly true for LIPC (Cabeza & Nyberg, 2000). However, it is unclear whether LIPC activations reflect EE, SR, or both, and whether different subregions of LIPC may be involved. In sum, using a factorial paradigm that disentangles EE- and SR-related activity, we investigated similarities and differences in neural activity, focusing in particular on medial temporal, left temporal, and LIPC regions.

METHOD

Participants

Fourteen Duke University undergraduate students (5 females; mean age = 19.8 years, $SD = 1.7$) were scanned and paid for their participation. They all consented to a protocol approved by Duke University’s institutional review board. Data from 2 subjects could not be used because of equipment malfunction, leaving 12 participants for the reported analyses.

Stimuli and Behavioral Procedures

The stimuli consisted of 368 words selected from the MRC Psycholinguistic Database (1997). The words were abstract, 4 to 11 letters long, and of moderate frequency. They were randomly combined into pairs with the only constraint being that the two words in each pair were of similar length (± 2 letters). Because of the random pairing, most pairs were unrelated (e.g., *donor-sequel*, *issue-spirit*, *fraud-matter*, *maker-health*), but, by chance, a few were moderately related (e.g., *safety-welfare*, *mutiny-justice*). A latent semantic pair-wise analysis (Latent Semantic Analysis, n.d.) yielded a mean association score of 0.09, which may be described as low.

Each fMRI run (four in total) consisted of one study block and one test block separated by a 30-s delay. Each block included 46 trials, each consisting of a word pair (3.4 s) followed by a fixation period (0.0–5.4 s jitter), which was used as baseline in fMRI analyses. Participants were instructed to respond while the pair was on the screen, and late responses were excluded from analyses. During each study trial, participants tried to retrieve a semantic link between the two words and made a four-choice SR decision (1 = *definitely there is a link*, 2 = *probably there is a link*, 3 = *probably there is no link*, 4 = *definitely there is no link*). In the fMRI analyses, responses of “1” and “2” were defined as high SR, and responses of “3” and “4” as low SR. The correlation of SR ratings across participants was low ($r = .20$), indicating that the high-SR/low-SR classification reflected the ability of a participant to retrieve a semantic link (e.g., *beauty-justice*: both words involve “harmony”), rather than a difference between related versus unrelated pairs, which should have been consistent across participants. Each test block consisted of 29 studied pairs (identical pairs) and 17 distractor pairs made of

words that had been studied in different pairs (recombined pairs). The distractors were created by randomly re-pairing the words with the constraint that the two words in each pair were of similar length. Because of the random re-pairing, the association score of recombined pairs in the latent semantic analysis (0.10) was similar to that of identical pairs (0.09). Only identical trials (29×4 runs = 116) were used in the fMRI analyses. During each test trial, participants made a four-choice episodic memory decision (1 = *definitely identical*, 2 = *probably identical*, 3 = *probably recombined*, 4 = *definitely recombined*). In the fMRI analyses, study items that subsequently elicited a response of “1” were classified as high EE, and the rest were classified as low EE.

fMRI Procedures

Images were collected using a 4-T GE scanner. Stimuli were presented with LCD goggles, and behavioral responses were recorded with a four-key response box. Anatomical and functional images consisted of 34 contiguous slices parallel to the anterior commissure–posterior commissure plane. The anatomical images were high-resolution T1-weighted images, acquired with a 450-ms repetition time, a 9-ms echo time, a 24-cm field of view, a 256^2 matrix, and a slice thickness of 1.9 mm. Functional images employed an inverse spiral sequence with a 1,700-ms repetition time, a 31-ms echo time, a 24-cm field of view, a 64^2 image matrix, and a 60° flip angle. Slice thickness was 3.75 mm, resulting in cubic 3.75-mm^3 isotropic voxels.

The fMRI analyses were performed using SPM2 (Wellcome Department of Imaging Neuroscience). Time series were corrected for differences in slice acquisition times and realigned. Anatomical images were co-registered with the functional images. Next, both anatomical and functional images were spatially normalized to a standard stereotactic space (Montreal Neurological Institute) and resliced to a resolution of $3 \times 3 \times 3$ mm. The coordinates were later converted to Talairach and Tournoux's (1988) space. Volumes were spatially smoothed (8 mm) and proportionally scaled to the whole-brain signal. For each subject, trial-related activity was assessed by convolving a vector of the onset times of the stimuli with a synthetic hemodynamic response function. The general linear model, as implemented in SPM2, was used to model the effects of interest and other confounding effects (e.g., head movement, magnetic field drift). Statistical parametric maps (SPMs) were identified for each participant by applying linear contrasts to the parameter estimates for the events of interest, resulting in a t statistic for every voxel. In addition to fixation, trials in four conditions (see Fig. 1) were coded: high-SR/high-EE, low-SR/low-EE, high-SR/low-EE, and low-SR/high-EE. There was an average of 28 ($SD = 11$) trials per condition.

Three types of analyses were conducted. First, to investigate EE-SR differences within the medial temporal lobes, we conducted hypothesis-driven analyses using an ROI approach. A

medial temporal lobe ROI including the hippocampus, as well as entorhinal, perirhinal, and parahippocampal cortices, was created on normalized images and applied as a mask to SPMs. The significance threshold for this ROI analysis was set at $p < .05$. Second, to investigate EE-SR similarities and differences in other brain regions, we conducted a standard whole-brain exploratory SPM analysis with a significance threshold of $p < .001$ and a minimum-extent threshold of three contiguous voxels. Finally, to determine whether activations reflected main effects of EE, SR, or both, or EE \times SR interactions, we submitted the betas (one per subject) for each activation identified in the first two analyses to a 2 (high EE vs. low EE) \times 2 (high SR vs. low SR) analysis of variance (ANOVA).

RESULTS

Behavioral Results

The percentage of trials in the four cells of the design was as follows (standard deviations in parentheses): high-EE/high-SR, 24 (10); high-EE/low-SR, 22 (9); low-EE/high-SR, 18 (10); and low-EE/low-SR, 36 (10). A 2 (EE: low vs. high) \times 2 (SR: low vs. high) ANOVA on these data yielded a significant main effect of SR (low SR > high SR, $p < .01$), qualified by a significant EE \times SR interaction ($p < .001$). This interaction reflected a greater percentage of trials in the low-EE/low-SR cell than in the other three cells. Given that the fMRI analyses identified greater activity for successful than for unsuccessful trials, the larger number of unsuccessful trials cannot account for the activations found. Mean reaction times (RTs) in milliseconds during the SR task were as follows (standard deviations in parentheses): high-EE/high-SR, 2,117 (304); high-EE/low-SR, 2,085 (300); low-EE/high-SR, 2,034 (368); and low-EE/low-SR, 2,105 (302). A 2 (EE: low vs. high) \times 2 (SR: low vs. high) ANOVA on these data yielded no significant effects. Thus, differences in activations cannot be attributed to time on task.

fMRI Results

Activated regions are listed in Table 1 and illustrated in Figure 2. The ROI analysis of the medial temporal lobes identified a hippocampal region showing greater activity for high than for low EE, but no reliable difference between high and low SR (see Fig. 2d). The ANOVA on the fMRI signal extracted from this activation confirmed a significant main effect of EE, but a nonsignificant main effect of SR and a nonsignificant EE \times SR interaction. No other medial temporal region showed activation differences as a function of EE or SR. Thus, the only activated region found within the medial temporal lobes was a hippocampal region that was associated with EE, but not with SR.

The whole-brain analysis yielded activation in several regions, including two areas in which we were particularly interested: the left lateral temporal cortex and the left prefrontal cortex. Within the left lateral temporal cortex, a posterior region

TABLE 1
Brain Regions Involved in Episodic Encoding (EE) and Semantic Retrieval (SR)

Function and region	Brodmann's area	Talairach coordinates			<i>t</i> value (SPM analysis)	Analysis of variance results		
		<i>x</i>	<i>y</i>	<i>z</i>		SR	EE	EE × SR
Only EE								
Left hippocampus (Fig. 2d)		−30	−19	−11	2.68	n.s.	<i>p</i> < .05	n.s.
Thalamus		4	−22	1	5.07	n.s.	<i>p</i> < .001	n.s.
Only SR								
Left inferior frontal gyrus (Fig. 2a)	45	−56	19	9	5.52	<i>p</i> < .001	n.s.	n.s.
Left lateral temporal cortex (Fig. 2e)	22/39	−56	−59	13	5.55	<i>p</i> < .001	n.s.	n.s.
Right lateral temporal cortex	21	56	−37	−5	4.73	<i>p</i> < .001	n.s.	n.s.
Both EE and SR								
Left inferior frontal gyrus (Fig. 2b) ^a	45/47	−49	23	13	4.84	<i>p</i> < .005	<i>p</i> < .001	n.s.
	45/47	−49	33	−2	4.94	<i>p</i> < .09	<i>p</i> < .001	n.s.
EE × SR interaction								
Left inferior frontal gyrus (Fig. 2c)	47	−34	22	−8	5.55	<i>p</i> < .005	<i>p</i> < .001	<i>p</i> < .05

Note. SPM = statistical parametric mapping.

^aThe results shown in Figure 2b correspond to the first set of coordinates listed.

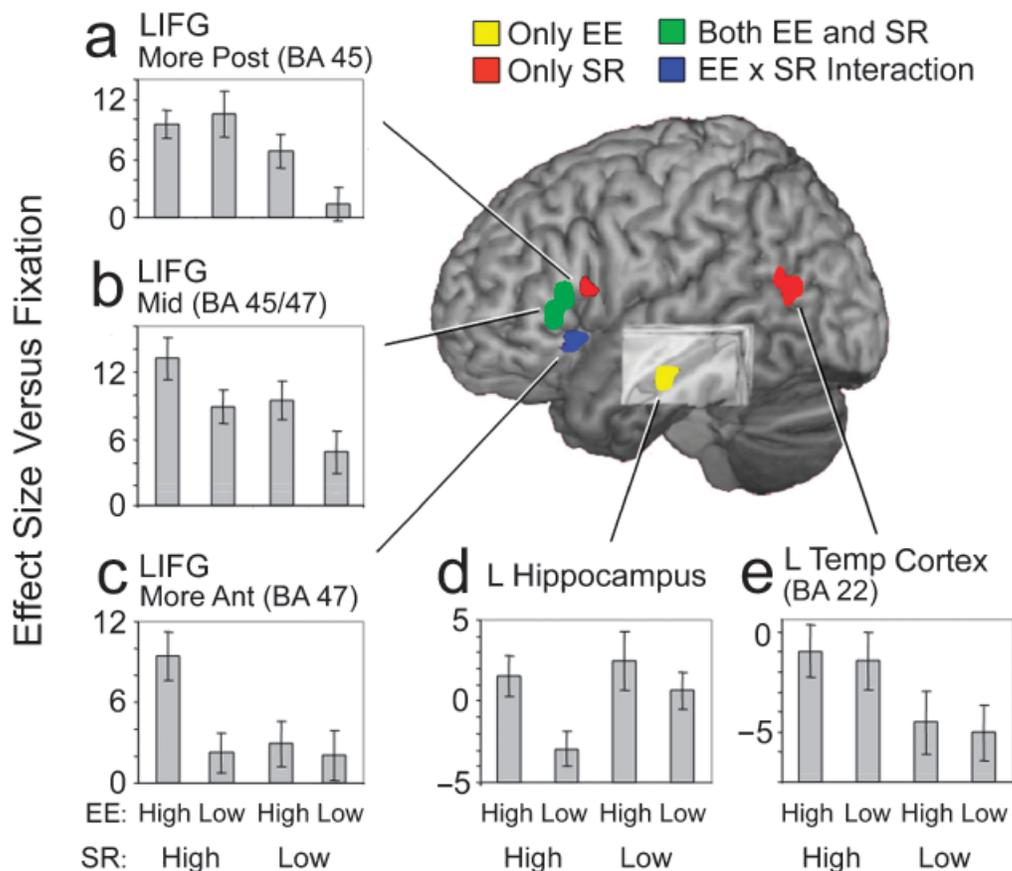


Fig. 2. Brain regions involved in episodic encoding (EE) and semantic retrieval (SR). In the surface rendering of the left hemisphere of a template brain, regions are color coded on the basis of results of analysis of variance. The cutout portion shows the hippocampus. In the graphs, the y-axis unit is the effect size (vs. fixation) of activation in the functional magnetic resonance imaging analyses. Effect size is graphed as a function of the success of EE (high vs. low) and the success of SR (high vs. low). Ant = anterior, BA = Brodmann's area, L = left, LIFG = left inferior frontal gyrus, Post = posterior, Temp = temporal.

of the superior temporal cortex showed greater activity for high than for low SR, but no difference between high and low EE (see Fig. 2e). Confirming this conclusion, the ANOVA on this region yielded a reliable main effect of SR, but a nonreliable main effect of EE and a nonreliable EE \times SR interaction. In other words, the left lateral temporal cortex was involved in SR, but not in EE.

Finally, within LIPC, three different activation patterns were identified. First, a more posterior LIPC region (Brodmann's area, BA, 45) showed high-low differences for SR, but not for EE (see Fig. 2a). Confirming this finding, the ANOVA yielded a reliable main effect of SR, but a nonreliable main effect of EE and a nonreliable SR \times EE interaction. Second, a mid LIPC region (BA 45/47) showed significant high-low differences for both SR and EE (see Fig. 2b). Consistent with this result, the ANOVA yielded reliable main effects of both SR and EE, but a nonsignificant SR \times EE interaction. Finally, a more anterior LIPC region (BA 47) showed greater activity for high than for low EE, but only in the high-SR condition (see Fig. 2c). Confirming this impression, the ANOVA yielded not only reliable main effects of EE and SR, but also a reliable EE \times SR interaction. In sum, within LIPC, a more posterior region was involved in SR but not EE, a mid region was involved in both SR and EE, and a more anterior region showed an SR \times EE interaction because it was involved in EE only when SR was high.

DISCUSSION

The present study yielded two main findings. First, within the left temporal lobe, there was a double dissociation between the left hippocampus, which was associated with EE but not SR, and the lateral temporal cortex, which was associated with SR but not EE. Second, within LIPC, a more posterior region was involved in SR, a mid region was involved in both SR and EE, and a more anterior region was involved in EE, but only when SR was high. We discuss these two findings in separate sections.

Left Temporal Lobe

As illustrated by Figure 2d, the hippocampus was more activated for items that were subsequently remembered (high EE) than for those that were subsequently forgotten (low EE), regardless of whether SR for these items was high or low. This result is consistent with the hypothesis that the hippocampus is more involved in episodic than in semantic memory (e.g., Aggleton & Brown, 1999; Tulving & Markowitsch, 1998; Vargha-Khadem et al., 1997, 2001). To date, this idea has been supported primarily by lesion data. For example, Vargha-Khadem and her collaborators reported several cases of developmental amnesic patients who have selective hippocampal lesions and who are severely impaired in episodic memory but show relatively preserved semantic memory (Vargha-Khadem et al., 1997, 2001). However, proponents of the idea that the hippocampus

is similarly involved in semantic and episodic memory have argued that the episodic memory of these patients is not completely disrupted and that their semantic memory is not perfectly intact (Squire & Zola, 1998). This debate illustrates the difficulty of comparing episodic and semantic memory using different tasks; it is always questionable whether episodic and semantic tasks were properly matched in terms of scales, task difficulty, age of memories, and other relevant variables. The present approach attenuates these problems by comparing episodic and semantic memory within the same task. The differences in hippocampal activity depicted in Figure 2d occurred during the same task and for the same kind of stimuli, with the only difference being whether trials were sorted according to SR success or EE success. Thus, using a novel factorial approach to disentangle SR- and EE-related activity, the present study has provided direct evidence that some hippocampal regions are more involved in episodic than in semantic memory.

Whereas the left hippocampus was associated with EE but not SR, the left temporal cortex showed the opposite pattern. As illustrated by Figure 2d, activity in left posterior temporal cortex (BA 22/39) was greater for high SR than for low SR, but did not differ as a function of whether items were subsequently remembered (high EE) or forgotten (low EE). This region partly overlaps with Wernicke's area, which has been strongly associated with processing the meaning of words (for a review, see Wise & Price, 2006). Given that the stimuli were abstract words, this finding is also consistent with functional neuroimaging evidence that the left posterior temporal cortex is involved in accessing the meaning of abstract nouns (e.g., Grossman et al., 2002). Whereas it has been suggested that the left posterior temporal cortex is involved in SR for nonunique entities (Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004), functional neuroimaging studies (for a review, see Thompson-Schill, Kan, & Oliver, 2006) and lesion studies (Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; for a review, see Graham, Patterson, & Hodges, 1999) often indicate that a left anterior temporal region is associated with SR for unique information (e.g., proper names; Tsukiura et al., 2002).

The finding of a significant SR effect in regions previously associated with semantic processes demonstrates the efficacy and validity of the SR manipulation. This finding has implications for cognitive theories of memory encoding. In general, the process of integrating incoming information with preexistent knowledge, or elaboration, tends to be associated with improved encoding and subsequent memory (e.g., Craik & Tulving, 1975). The present results show an exception to this general trend: Greater activity in left temporal cortex was associated with elaboration, but it was not associated with successful episodic encoding. Taken together with the results for the hippocampus, this finding also demonstrates the power of our factorial design to dissociate regions differentially involved in EE versus SR. More generally, the double dissociation between the hippocampus

being more involved in EE than SR and the left lateral temporal cortex being more involved in SR than EE adds to evidence that episodic and semantic memory depend on different memory systems (Nyberg & Tulving, 1996; Tulving, 2002).

LIPC

The second main finding of the study is the gradient in LIPC from a more dorsal-posterior region (BA 45; Fig. 2a), which was more involved in SR than EE; to a mid region (BA 45/47; Fig. 2b), which was involved in both SR and EE; to a more ventral-anterior region (BA 47; Fig. 2c), which was involved in EE, but only when SR was high. This gradient overlaps with distinctions among LIPC subregions found in research on language function (for a review, see Hagoot, 2005). The posterior LIPC region associated with SR overlaps with Broca's area. Thus, areas in the vicinity of Broca's and Wernicke's language areas (see the preceding discussion on the left temporal lobe) may be involved in recovering meaning without necessarily leading to successful EE. Some authors have associated posterior LIPC with phonological processing (e.g., Poldrack et al., 1999), whereas others have emphasized the role of this region in executive operations, such as selection (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997) and inhibitory control (Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998). The notion that this region plays a role in selection accounts well for the involvement of posterior LIPC in successful SR trials, as these trials involved the retrieval of numerous semantic links. This notion can also explain why posterior LIPC did not contribute to successful EE, because selection operates on the output of SR rather than on semantic processing per se.

The finding that a mid LIPC region was associated with both successful SR and successful EE is consistent with the hypothesis that the left prefrontal cortex contributes to both EE and SR (Tulving et al., 1994) and with meta-analyses of functional neuroimaging data showing left prefrontal activations during EE and SR tasks, particularly in LIPC (Habib et al., 2003; Nyberg et al., 1996; Tulving et al., 1994). Given the use of word pairs in this experiment, this finding is also consistent with functional neuroimaging evidence linking LIPC to relational memory encoding (e.g., Fletcher, Shallice, & Dolan, 2000; Henson, Shallice, Josephs, & Dolan, 2002; Lepage, Habib, Cormier, Houle, & McIntosh, 2000). Although consistent with available evidence, our finding adds to the existing data in two important ways: First, we have demonstrated overlapping EE-SR activity in LIPC using a task that disentangles the contributions of each process. Thus, unlike previous findings, the present result cannot simply be attributed to the fact that EE and SR tend to co-occur. Second, the present finding adds anatomical specificity by associating shared EE-SR activity with a specific area of LIPC, that is, mid LIPC. The association of more posterior LIPC with successful SR and the association of this mid area with both successful SR and successful EE suggest that

specific regions of LIPC can support aspects of both EE and SR tasks, whereas others can be more involved in SR than in EE.

Finally, the finding of an anterior LIPC area that supported EE, but only when SR was high, is consistent with the idea that episodic and semantic memory interact very closely (Tulving, 1983). This finding is also in agreement with the notion that elaboration leads to successful encoding (Craik & Tulving, 1975), and with functional neuroimaging evidence that activity associated with these processes may overlap (Otten, Henson, & Rugg, 2001). Functional neuroimaging studies have associated anterior LIPC with controlled semantic retrieval (Gold & Buckner, 2002; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001), and the present finding indicates that this process enhances EE as predicted by the notion of elaboration (Craik & Tulving, 1975). At the same time, the present results suggest a refinement of this notion. Although the activation pattern in anterior LIPC fits perfectly with the idea that successful SR leads to successful EE, in other brain regions, SR and EE were dissociated. As noted before, the hippocampus was associated with successful EE, but not with successful SR, whereas posterior LIPC and left posterior temporal regions were associated with successful SR, but not with successful EE. In other words, successful SR activity was neither necessary nor sufficient for successful EE activity.

The finding that successful EE depended on successful SR in the case of anterior LIPC but not in the case of the hippocampus may be also interpreted in terms of the controlled-automatic distinction. According to Moscovitch's (1992) memory model, for example, the prefrontal cortex contributes to EE because of its role in strategic control processes (*working-with-memory*), whereas the hippocampus contributes to EE because it automatically binds consciously apprehended information. Consistent with this idea, an fMRI study by Reber et al. (2002) found that LIPC activity was modulated by instructions to remember versus forget presented information, but subsequent memory effects in left hippocampal and parahippocampal regions were not altered. Given that the attempt to remember (intentional EE) leads to greater semantic processing (incidental SR), the findings of Reber et al. are consistent with the results of the present study. Also, using a modified version of the Deese-Roediger-McDermott false memory paradigm, we recently found that LIPC activity during encoding predicted subsequent true memory as well as subsequent false memory, whereas hippocampal activity predicted subsequent true but not subsequent false memory (Kim & Cabeza, in press). In all these studies, LIPC was associated with controlled encoding processes, whereas hippocampal activity was associated with automatic encoding operations.

Conclusion

The present study used the well-known subsequent-memory procedure in an associative recognition paradigm that allowed the factors of EE and SR to be teased apart. Previous imaging

studies and meta-analyses have suggested a strong influence of SR on EE and have found many overlapping regions of activation. However, we were able to isolate both those regions and task-specific regions within the same participants and using the same stimuli, within a single study. There were two main findings: First, within the left temporal lobe, there was a double dissociation whereby the left hippocampus selectively supported EE, regardless of the level of SR, and a posterior lateral temporal region supported SR, regardless of the level of EE. Second, within LIPC, we found a gradient in which a more dorsal-posterior region was involved in SR, a mid region was involved in both SR and EE, and a more ventral-anterior region was involved in EE, but only when SR was high. These results suggest the need to refine existing ideas regarding the role of the hippocampus in EE and the complexity of LIPC contributions to SR and EE. More generally, they support the notion that episodic and semantic memory depend on different but closely interacting memory systems.

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REFERENCES

- Aggleton, J.P., & Brown, M.W. (1999). Episodic memory, amnesia, and the hippocampal-anterior thalamic axis [Target article and commentaries]. *Behavioral and Brain Sciences*, *22*, 425–489.
- Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience*, *12*, 1–47.
- Craik, F.I.M., & Tulving, E. (1975). Depth of processing and the retention of words in episodic memory. *Journal of Experimental Psychology: General*, *104*, 268–294.
- Damasio, H., Grabowski, T.J., Tranel, D., Hichwa, R.D., & Damasio, A.R. (1996). A neural basis for lexical retrieval. *Nature*, *380*, 499–505.
- Damasio, H., Tranel, D., Grabowski, T., Adolphs, R., & Damasio, A. (2004). Neural systems behind word and concept retrieval. *Cognition*, *92*, 179–229.
- Fletcher, P.C., Shallice, T., & Dolan, R.J. (2000). “Sculpting the response space”—an account of left prefrontal activation at encoding. *NeuroImage*, *12*, 404–417.
- Gold, B.T., & Buckner, R.L. (2002). Common prefrontal regions co-activate with dissociable posterior regions during controlled semantic and phonological tasks. *Neuron*, *35*, 803–812.
- Graham, K.S., Patterson, K., & Hodges, J.R. (1999). Episodic memory: New insights from the study of semantic dementia. *Current Opinion in Neurobiology*, *9*, 245–250.
- Grossman, M., Koenig, P., DeVita, C., Glosser, G., Alsop, D., Detre, J., & Gee, J. (2002). The neural basis for category-specific knowledge: An fMRI study. *NeuroImage*, *15*, 936–948.
- Habib, R., Nyberg, L., & Tulving, E. (2003). Hemispheric asymmetries of memory: The HERA model revisited. *Trends in Cognitive Sciences*, *7*, 241–245.
- Hagoort, P. (2005). On Broca, brain, and binding: A new framework. *Trends in Cognitive Sciences*, *9*, 416–423.
- Henson, R.N., Shallice, T., Josephs, O., & Dolan, R.J. (2002). Functional magnetic resonance imaging of proactive interference during spoken cued recall. *NeuroImage*, *17*, 543–558.
- Jonides, J., Smith, E.E., Marshuetz, C., Koeppe, R.A., & Reuter-Lorenz, P.A. (1998). Inhibition in verbal working memory revealed by brain activation. *Proceedings of the National Academy of Sciences, USA*, *95*, 8410–8413.
- Kim, H., & Cabeza, R. (in press). Differential contributions of prefrontal, medial temporal, and sensory-perceptual regions to true and false memory formation. *Cerebral Cortex*.
- Latent Semantic Analysis [Computer software]. (n.d.). Retrieved from <http://lsa.colorado.edu/>
- Lepage, M., Habib, R., Cormier, H., Houle, S., & McIntosh, A.R. (2000). Neural correlates of semantic associative encoding in episodic memory. *Cognitive Brain Research*, *9*, 271–280.
- Moscovitch, M. (1992). Memory and working-with-memory: A component process model based on modules and central systems. *Journal of Cognitive Neuroscience*, *4*, 257–267.
- MRC Psycholinguistic Database [Computer software]. (1997). Retrieved from <http://www.psy.uwa.edu.au/MRCDataBase/mrc2/html>
- Nyberg, L., Cabeza, R., & Tulving, E. (1996). PET studies of encoding and retrieval: The HERA model. *Psychonomic Bulletin & Review*, *3*, 135–148.
- Nyberg, L., Marklund, P., Persson, J., Cabeza, R., Forkstam, C., Pettersson, K.M., & Ingvar, M. (2003). Common prefrontal activations during working memory, episodic memory, and semantic memory. *Neuropsychologia*, *41*, 371–377.
- Nyberg, L., & Tulving, E. (1996). Classifying human long-term memory: Evidence from converging dissociations. *European Journal of Cognitive Psychology*, *8*, 163–183.
- Otten, L.J., Henson, R.N., & Rugg, M.D. (2001). Depth of processing effects on neural correlates of memory encoding: Relationship between findings from across- and within-task comparisons. *Brain*, *124*, 399–412.
- Paller, K.A., & Wagner, A.D. (2002). Observing the transformation of experience into memory. *Trends in Cognitive Sciences*, *6*, 93–102.
- Poldrack, R.A., Wagner, A.D., Prull, M.W., Desmond, J.E., Glover, G.H., & Gabrieli, J.D.E. (1999). Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *NeuroImage*, *10*, 15–35.
- Rajah, M.N., & McIntosh, A.R. (2005). Overlap in the functional neural systems involved in semantic and episodic memory retrieval. *Journal of Cognitive Neuroscience*, *17*, 470–482.
- Reber, P.J., Siwieg, R.M., Gitelman, D.R., Parrish, T.B., Mesulam, M.M., & Paller, K.A. (2002). Neural correlates of successful encoding identified using functional magnetic resonance imaging. *Journal of Neuroscience*, *22*, 9541–9548.
- Squire, L.R., & Zola, S. (1998). Episodic memory, semantic memory, and amnesia. *Hippocampus*, *8*, 205–211.
- Talairach, J., & Tournoux, P. (1988). *A co-planar stereotaxic atlas of the human brain*. Stuttgart, Germany: Thieme.
- Thompson-Schill, S.L., D’Esposito, M., Aguirre, G.K., & Farah, M.J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. *Proceedings of the National Academy of Sciences, USA*, *94*, 14792–14797.
- Thompson-Schill, S.L., Kan, I.P., & Oliver, R.T. (2006). Functional neuroimaging of semantic memory. In R. Cabeza & A. Kingstone (Eds.), *Handbook of functional neuroimaging of cognition* (2nd ed., pp. 149–190). Cambridge, MA: MIT Press.

- Tsukiura, T., Fujii, T., Fukatsu, R., Otsuki, T., Okuda, J., Umetsu, A., et al. (2002). Neural basis of the retrieval of people's names: Evidence from brain-damaged patients and fMRI. *Journal of Cognitive Neuroscience*, *14*, 922–937.
- Tulving, E. (1983). *Elements of episodic memory*. Oxford, England: Oxford University Press.
- Tulving, E. (2002). Episodic memory: From mind to brain. *Annual Review of Psychology*, *53*, 1–25.
- Tulving, E., Kapur, S., Craik, F.I.M., Moscovitch, M., & Houle, S. (1994). Hemispheric encoding/retrieval asymmetry in episodic memory: Positron emission tomography findings. *Proceedings of the National Academy of Sciences, USA*, *91*, 2016–2020.
- Tulving, E., & Markowitsch, H.J. (1998). Episodic and declarative memory: Role of the hippocampus. *Hippocampus*, *8*, 198–204.
- Vargha-Khadem, F., Gadian, D.G., & Mishkin, M. (2001). Dissociations in cognitive memory: The syndrome of developmental amnesia. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, *356*, 1435–1440.
- Vargha-Khadem, F., Gadian, D.G., Watkins, K.E., Connelly, A., Van Paesschen, W., & Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. *Science*, *277*, 376–380.
- Wagner, A.D., Pare-Blagoev, E.J., Clark, J., & Poldrack, R.A. (2001). Recovering meaning: Left prefrontal cortex guides controlled semantic retrieval. *Neuron*, *31*, 329–338.
- Wiggs, C.L., Weisberg, J., & Martin, A. (1999). Neural correlates of semantic and episodic memory retrieval. *Neuropsychologia*, *37*, 103–118.
- Wise, R.J.S., & Price, C.J. (2006). Functional imaging of language. In R. Cabeza & A. Kingstone (Eds.), *Handbook of functional neuroimaging of cognition* (2nd ed., pp. 191–228). Cambridge, MA: MIT Press.

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