

Overlap in the Functional Neural Systems Involved in Semantic and Episodic Memory Retrieval

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Abstract

■ Neuroimaging and neuropsychological data suggest that episodic and semantic memory may be mediated by distinct neural systems [Cabeza, R., & Nyberg, L. Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience*, 12, 1–47, 2000; Gabrieli, J. D. Disorders of memory in humans. *Current Opinion in Neurology and Neurosurgery*, 6, 93–97, 1993; Gabrieli, J. D. Cognitive neuroscience of human memory. *Annual Review of Psychology*, 49, 87–115, 1998; Squire, L. R. The organization and neural substrates of human memory. *International Journal of Neurology*, 21–22, 218–222, 1987; Squire, L. R., & Zola, S. M. Structure and function of declarative and nondeclarative memory systems. *Proceedings of the National Academy of Sciences, U.S.A.*, 93, 13515–13522, 1996; Tulving, E. Multiple memory systems and consciousness. *Human Neurobiology*, 6, 67–80, 1987]. However, an alternative perspective is that episodic and semantic memory represent different modes of processing within a single declarative memory system. To examine whether the multiple or the unitary system view better represents the data we conducted a network analysis using multivariate partial least squares (PLS) activation analysis followed by covariance structural equation modeling (SEM) of positron emission tomography data obtained while healthy adults performed episodic and semantic verbal retrieval tasks

[Duzel, E., Cabeza, R., Picton, T. W., Yonelinas, A. P., Heinze, H. J., Scheich, H., & Tulving, E. Task-related and item related processes in episodic and semantic retrieval: A combined PET and ERP study. *Proceedings of the National Academy of Sciences, U.S.A.*, 96, 1794–1799, 1999]. It is argued that if performance of episodic and semantic retrieval tasks are mediated by different memory systems, then there should be differences in both regional activations and interregional correlations related to each type of retrieval task, respectively. The PLS results identified brain regions that were differentially active during episodic retrieval versus semantic retrieval. Regions that showed maximal differences in regional activity between episodic retrieval tasks were used to construct separate functional models for episodic and semantic retrieval. Omnibus tests of these functional models failed to find a significant difference across tasks for both functional models. The pattern of path coefficients for the episodic retrieval model were not different across tasks, nor were the path coefficients for the semantic retrieval model. The SEM results suggest that the same memory network/system was engaged across tasks, given the similarities in path coefficients. Therefore, activation differences between episodic and semantic retrieval may reflect variation along a continuum of processing during task performance within the context of a single memory system. ■

INTRODUCTION

Neuropsychological data from medial temporal lobe amnesics, Korsakoff's amnesics, and patients with semantic dementia argues for the existence of separate episodic and semantic memory systems because these individuals typically exhibit poorer performance on tests examining one of the two memory systems, and spared functioning in the other (Cipolotti & Maguire, 2003; Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Rosen et al., 2002; Hodges & Graham, 2001; Garrard, Perry, & Hodges, 1997; Gabrieli, 1993, 1998; Squire, 1987; Warrington, 1979). These clinical data suggest that episodic memory retrieval is related to the intact functioning of the right anterior and dorsolateral prefrontal cortex (PFC) and the medial temporal lobes; whereas semantic memory retrieval is related to the intact functioning

of regions in neocortex that are involved in the processing of perceptual information and to left inferior PFC (Garrard et al., 1997).

Neuroimaging studies have also found functional dissociations in the activity of the inferotemporal cortex, medial temporal cortex, and PFC that roughly mirror the aforementioned neuropsychological findings (Cabeza & Nyberg, 2000; Nyberg & Cabeza, 2000; Nyberg, Cabeza, & Tulving, 1996; Vandenberghe, Price, Wise, Josephs, & Fracowiak, 1996; Martin, Wiggs, Ungerleider, & Haxby, 1995; Squire et al., 1992). In one positron emission tomography (PET) study, Vandenberghe et al. (1996) compared brain activity related to semantic retrieval for pictures and words and found a common neural network related to both verbal and nonverbal semantic retrieval. This network included the left inferior and middle temporal cortex and left inferior PFC (Vandenberghe et al., 1996). In contrast, episodic retrieval has

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been related to activity in both medial temporal cortex and PFC, particularly right PFC (Kohler, Moscovitch, Winocur, Houle, & McIntosh, 1998; Nyberg, Cabeza, et al., 1996; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Nyberg, Cabeza, et al. (1996) used PET to investigate the neural structures related to verbal episodic retrieval and found that left medial temporal activity was related to the level of retrieval success. In another PET study of recognition memory, right dorsolateral PFC activity was greater during the auditory presentation of previously encountered sentences ("old" sentences) versus novel sentences (Tulving, Kapur, Craik, et al., 1994). Right PFC activity has also consistently been found to be related to the episodic retrieval of visual verbal and nonverbal stimuli (Duzel et al., 1999; Cabeza, Kapur, et al., 1997; Haxby et al., 1996). Duzel et al. (1999) conducted a PET study investigating differences in brain activity related to episodic retrieval versus semantic retrieval of both previously studied words ("old" words) and novel words. They found right PFC activity related to episodic retrieval, left PFC activity related to semantic retrieval, and left medial temporal activity related to presentation of old versus novel words in the episodic retrieval condition. Thus, the results from neuroimaging studies of episodic memory support the results from neuropsychological studies and indicate that a functioning right PFC and medial temporal cortex are related to normal episodic retrieval.

In summary, the majority of clinical and neuroimaging studies have provided support for the multiple memory systems view (Tulving, 1987). According to this view, there are separate memory systems that are specialized in processing specific types of information (e.g., semantic or world knowledge information and episodic or autobiographical information) and mediating different forms of behavior (e.g., making living/nonliving judgements, making recognition judgements; Schacter, 1994; Tulving, 1972). In addition, these systems are believed to be mediated by anatomically separate and functionally independent neural networks, which interact to some degree (Nyberg, McIntosh, & Tulving, 1998; Nyberg, Forkstam, Petersson, Cabeza, & Ingvar, 2002; Schacter, 1994; Tulving, 1972, 1992, 2002). However, the experiments that have provided evidence for separate episodic and semantic memory systems have focussed on activation *differences* between episodic and semantic memory and thus have looked for functional *dissociations*. Baddeley (1984) has pointed out one can make a list of perceptual differences of a single forest viewed from two different perspectives, such as from walking through it or viewing from above; however, this does not mean that there are two forests. There is just one forest that can be experienced differently. Similarly, just because there are definitional differences between the cognitive concepts of "episodic" and "semantic" memory this does not mean that at a physiological level there exist two separate and anatomically distinct mem-

ory systems. Moreover, just because different classes of memory can be dissociated does not mean that they are independent. Because all memory is acquired through experience it is possible that there is a single memory system in the brain. Memories acquired through this system may be either highly contextualized in time, space, and emotion or decontextualized along these dimensions. The cognitive constructs of episodic and semantic memory may reflect the two opposite ends of this contextual continuum of memory expression mediated by a unitary memory system in the brain (Baddeley, 1984; Kihlstrom, 1984; Roediger, 1984).

Although most neuropsychological and neuroimaging studies on episodic and semantic memory have looked for differences in the neural mechanisms underlying these two memory processes, there is evidence supporting the unitary memory system view as well. For example, Squire and Zola (1998) reviewed data obtained from children who acquired hippocampal damage early in life during their performance of episodic and semantic retrieval tasks and found that although their deficits in episodic retrieval outweighed their semantic retrieval deficits, these children still had some deficit in their semantic retrieval ability compared with normal controls. This suggests that the medial temporal cortex is important for both semantic and episodic retrieval. In addition, the hippocampus and associated structures have been found to be involved in nonepisodic declarative memory tasks, including trace conditioning and perceptual memory paradigms (Manns, Clark, & Squire, 2002; Clark, Manns, & Squire, 2001, 2002; Della-Maggiore et al., 2000; Clark & Squire, 1998; LaBar & Disterhoft, 1998; Deadwyler, Bunn, & Hampson, 1996; Squire et al., 1992). This suggests that the medial temporal cortex appears to have a more general learning and memory function that is not specific to episodic memory, although much debate exists surrounding this issue (Aggleton & Pearce, 2001; Nadel & Moscovitch, 2001; Moscovitch, 2000; Tulving, Habib, Nyberg, Lepage, & McIntosh, 1999; Vargha-Khadem et al., 1997; Squire & Zola, 1996, 1998; Squire, 1992; Squire et al., 1992). Similarly, evidence from frontal lobe patients indicate that the right dorsolateral PFC is not exclusively involved in episodic retrieval and the left PFC is not exclusively involved in semantic retrieval (Shimamura, 1995; Moscovitch, 1992; Petrides, 1989). In fact, the left PFC has been found to be important for the performance of episodic, source memory tasks (Rugg, Fletcher, Chua, & Dolan, 1999; Nolde, Johnson, & D'Esposito, 1998). Moreover, damage to left PFC impairs free recall and context memory task performance (Mangels, 1997; Stuss, Craik, Sayer, Franchi, & Alexander, 1996). This indicates that even though the left PFC is thought to be part of the semantic memory system, it is also involved during some types of episodic memory retrieval (Martin & Chao, 2001; Simons, Graham, Owen, Patterson, & Hodges, 2001; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001).

Neuroimaging studies have also found overlap in the brain regions involved in episodic and semantic memory (Nyberg et al., 2003; Nyberg et al., 2002; Duzel et al., 1999; Wiggs, Weisberg, & Martin, 1999). In one PET study, Wiggs et al. (1999) examined brain regions involved in the semantic retrieval of colors associated with objects and the episodic retrieval of previously studied pairings of uncommon colors associated with objects. In both retrieval tasks there was activity in left frontal cortex, bilateral posterior temporal cortex, and cerebellum when compared with a baseline perceptual task (Wiggs et al., 1999). Moreover, a comparison of the semantic retrieval scan versus an object-naming baseline scan indicated that semantic retrieval was related to activity in the right PFC, which has traditionally been associated with episodic retrieval (Wiggs et al., 1999). These findings indicate that temporal and frontal cortices are involved in both episodic and semantic retrieval and may be involved in mediating processes that are common to performing both tasks.

In a PET study conducted by Duzel et al. (1999), normal healthy subjects were scanned while performing episodic retrieval and semantic retrieval tasks consisting of (a) previously studied living and nonliving words (old words) and (b) novel living and nonliving words. Comparisons of scans obtained during presentation of living versus nonliving word stimuli, regardless of the type of memory retrieval being performed (episodic vs. semantic), found more activity in the left anterior cingulate and left PFC during the presentation of living words and more activity in the right cerebellum during the presentation of nonliving words. Comparisons of scans obtained during the presentation of old words versus novel words, regardless of type of word (living or nonliving) and type of retrieval task, found more activity in the right PFC during the presentation of old words. More activity in the right medial temporal cortex, left anterior temporal cortex, and left temporal cortex was observed during the presentation of new words relative to old words. These findings implicate roles for the medial temporal cortex, temporal cortex, PFC, and cerebellum in both episodic and semantic memory.

By directly comparing episodic and semantic retrieval tasks, Duzel et al. (1999) also found activations specific to these memory tasks and thus emphasized the differences between episodic and semantic memory. Right prefrontal and posterior-cingulate activation was related to episodic retrieval and left prefrontal and temporal activation was related to semantic retrieval. However, one may argue that if these distinct activation patterns related to episodic and semantic memory, respectively, reflected the existence of two anatomically separate and functionally distinct memory systems, then the pattern of neural interactions within these separate networks should also be different. More specifically, the functional and/or effective connectivity among brain regions included in the episodic memory system should be greater

during episodic retrieval compared with semantic retrieval (Friston, 2002; Mechelli, Penny, Price, Gitelman, & Friston, 2002; Buchel & Friston, 2001; McIntosh, 1999; McIntosh, Cabeza, & Lobaugh, 1998; McIntosh & Gonzalez-Lima, 1994a). A parallel distinction should hold for the semantic memory system. If, instead, the pattern of functional and/or effective connectivity within each of the two memory networks is more similar than different during the performance of both episodic and semantic retrieval tasks, then this would imply that a similar neural system may be engaged during episodic and semantic retrieval processes (Friston, 2002; McIntosh, 1999; Friston et al., 1997; McIntosh et al., 1994). Such a finding would support the unitary memory system-multiple processes view of semantic and episodic memory (Baddley, 1984; Kihlstrom, 1984; Roediger, 1984). This would imply that a cognitive distinction between episodic and semantic retrieval does not necessitate a physiological distinction between two anatomically and functionally independent memory systems. Observed neuropsychological and neuroimaging dissociations between these two types of memory may then be interpreted as reflecting differences in the extent to which particular processes are involved in various tasks within a single system.

The focus of this article is to test the hypothesis that episodic and semantic retrieval are mediated by physiologically distinct memory systems, using the PET data obtained from the aforementioned study by Duzel et al. (1999). This hypothesis will be examined at the level of neural interactions by using anatomically based structural equation modeling (SEM; McIntosh, Grady, Haxby, Ungerleider, & Horwitz, 1996; McIntosh & Gonzalez-Lima, 1992b, 1994b). SEM is used in this study to assess whether within the same anatomical network, there exist differences in effective connections (path coefficients) that distinguish between episodic versus semantic systems. We are not assessing model appropriateness in the sense it is usually used in SEM. We are assuming the model is appropriate because it is based on the activation analysis, previous research findings, and known neuroanatomy (McIntosh, Grady et al., 1996; McIntosh & Gonzalez-Lima, 1992b, 1994b). In the current study we define a memory system as an anatomically and functionally distinct and integrated neural network that is specialized in processing a particular type of information (Buchel, Coull, & Friston, 1999; Nyberg et al., 1998, 2002; Nyberg, McIntosh, et al., 1996; McIntosh et al., 1994; Schacter, 1994; Tulving, 1972, 1992, 2002). Thus, support for a multiple memory systems view from the current neuroimaging study would be provided if (a) there were brain regions that were specifically activated during one memory task and not the other (anatomically and functionally distinct) *and* (b) these regions show a significantly different pattern of effective connections among themselves during the performance of this particular task, relative to

the other memory task, in the SEM analysis (functionally integrated) (Buchel et al., 1999; Nyberg, McIntosh, et al., 1996; McIntosh et al., 1994). For example, an SEM based on regions that were more active during episodic retrieval, should also have a significantly different pattern of effective connectivity between the performance of episodic retrieval versus the performance of semantic retrieval tasks. The nodes included in the current SEMs were selected objectively, from the PLS analysis results of the PET activation obtained by Duzel et al. (1999).

RESULTS

PLS Results

The first three latent variables (LVs) from the PLS analysis were significant according to the permutation test ($p < .05$). The second LV (LV2) represented the experimental effect of interest for the current article. This LV identified brain regions that were differentially related to the episodic versus semantic retrieval tasks. Figure 1 shows LV2. The bootstrapped singular image (s.i.) for LV2 is shown in Figure 1A. Only those voxels that had a bootstrap ratio greater than three are presented on this singular image. Significant voxels of positive and negative brain saliences are colored in white and black, respectively. Figure 1B shows a bar graph representing the design scores for each scan for LV2. The scan numbers on the x -axis correspond to the scans represented in Table 1. It is apparent from this plot that LV2 differentiates episodic and semantic retrieval tasks. The greatest difference appears to be between the episodic and the semantic retrieval of old living words.

Table 2 presents the local maxima of the positive and negative brain saliences. Regions of positive brain salience were more active in semantic retrieval relative to episodic retrieval. These regions included the left fusiform gyrus, left inferior and middle temporal gyri, left insula, left inferior frontal gyrus, right inferior temporal gyrus, right hippocampus, and bilateral superior frontal gyrus. Regions of negative brain salience were active during episodic memory retrieval relative to semantic memory retrieval. These regions were predominantly lateralized to the right hemisphere and included the middle occipital gyrus, middle temporal gyrus, cingulate gyrus, insula, and inferior and middle frontal gyri.

SEM Results

Model Construction

The peak voxels from LV2 that are presented in Table 2 were used to construct SEMs of episodic and semantic retrieval. These regions were chosen from the PLS results to represent the pattern of activations related to semantic and episodic retrieval. The eight peak regions of positive brain salience were used to construct the anatomical model for semantic retrieval, whereas the

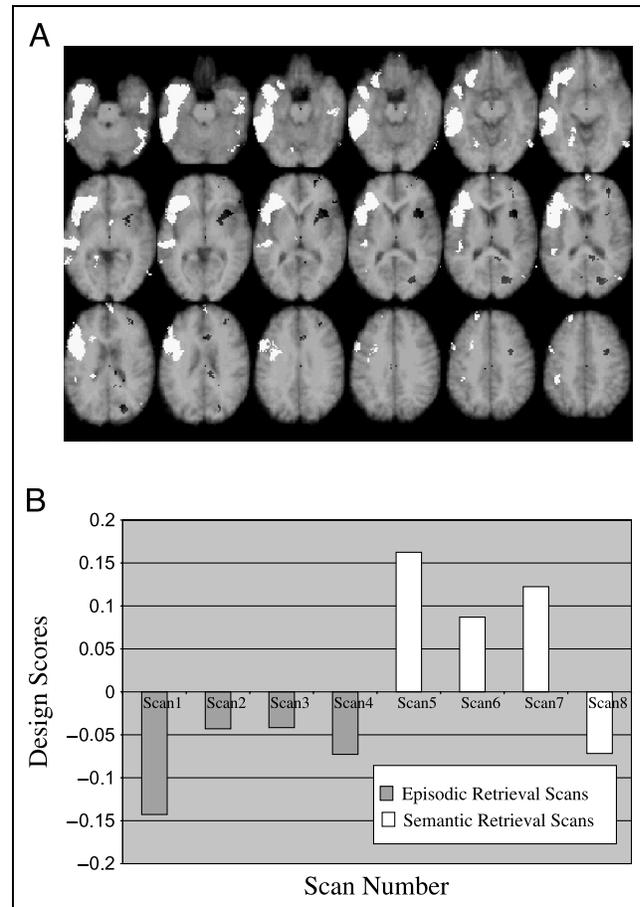


Figure 1. Latent variable 2 from PLS analysis. Part (A) shows the singular image (s.i.) for this latent variable. The white regions represent areas of positive brain salience and the black regions represent areas of negative brain salience. Part (B) consists of a bar graph depicting the design scores for each scan/task (Table 1 lists which tasks were being performed during each scan). This bar graph indicates the experimental effect for this LV. This LV differentiates scans 1 through 4 (episodic retrieval tasks) from scans 5 through 7 (semantic retrieval tasks). Scans 5 through 7 have positive design scores, indicating that semantic retrieval is related to increased activity in those regions of positive brain salience in the s.i., relative to regions of negative brain salience. Scans 1 through 4 have negative design scores, indicating that episodic retrieval is related to increased activity in those regions of negative brain salience in the s.i., relative to regions of positive brain salience.

seven peak regions of negative brain salience were used to construct the anatomical model for episodic retrieval. These models are presented in Figure 2. The anatomical models were constructed based on primate neuroanatomy (Maioli, Squatrito, Samolsky-Dekel, & Sanseverino, 1998; Bachevalier, Meunier, Lu, & Ungerleider, 1997; Miller, Erickson, & Desimone, 1996; Seltzer et al., 1996; Carmichael & Price, 1995a, 1995b; Goldman-Rakic, 1995; Webster, Bachevalier, & Ungerleider, 1994; Distler, Boussaoud, Desimone, & Ungerleider, 1993; Morecraft, Geula, & Mesulam, 1993; Goldman-Rakic, Funahashi, & Bruce, 1990; Leichnetz, 1990; Saint-Cyr, Ungerleider, & Desimone, 1990; Goldman-Rakic, Selemon, &

Table 1. Order of PET Scans

Scan Number	Type of Memory Retrieval Task	Old or New	Type of Words (Living or Nonliving)
1	Episodic	New	Living
2	Episodic	New	Nonliving
3	Episodic	Old	Living
4	Episodic	Old	Nonliving
5	Semantic	New	Living
6	Semantic	New	Nonliving
7	Semantic	Old	Living
8	Semantic	Old	Nonliving

“Old” or “New” refers to whether the word has been studied previously (“old”) or not (“new”).

Schwartz, 1984). In constructing the model it was assumed that Brodmann’s areas (BAs) 18, 37, and 21 in humans were homologous to areas V2, TEO, and TE in primates, respectively (Hof et al., 1997; Webster et al.,

1994; Distler et al., 1993; Ungerleider, Gaffan, & Pelak, 1989). In addition, frontal lobe connections were based on dorsal/ventral and anterior/posterior connections observed in monkeys (Petrides & Pandya, 1994; Pandya & Yeterian, 1990). The connections included in these models are tentative because they have not yet been confirmed experimentally in humans.

SEM Statistical Tests

Statistical tests comparing the episodic tasks versus the semantic tasks found no significant difference conditions using the episodic retrieval functional models, $\chi^2_{\text{diff}}(17) = 6.61$ $p = .98$ (Figure 2b). Tests comparing individual scans against one another failed to find any significant difference between any of the scans for the episodic retrieval functional model. The hierarchical analysis of individual connections within the episodic model, yielded a significant chi-square difference in the reciprocal connections between right anterior cingulate gyrus (BA 32) and right middle frontal gyrus (BA 9): $\chi^2_{\text{diff}}(3) = 11.7$, $p = .008$, for the connection from BA 9

Table 2. Local Maxima from LV2

Bootstrap Ratio	Talairach Coordinates			Gyral Location	Brodmann Area	Hemispheric Location	Corresponding Label in Network Models
	X	Y	Z				
<i>Local maxima regions of positive brain salience</i>							
4.53	-20	-60	-8	GF	19	Left	19
10.29	-46	-38	-16	GTI/GTM	21	Left	21
3.89	-24	-32	20	Insula		Left	INS
5.99	-30	34	4	GFI	45	Left	45
4.01	-24	48	40	GFS	8	Left	8
5.92	50	-62	-8	GTI	37	Right	37
3.36	12	-22	-16	RHPC		Right	HI
3.99	6	58	-12	GFS	11	Right	11
<i>Local minima regions of negative brain salience</i>							
5.87	20	-76	12	GOM	18	Right	18
2.80	44	-32	4	GTM	22	Right	22
6.80	28	14	8	Insula		Right	INS
3.95	10	-32	24	GC	23	Right	23
3.60	2	20	24	GC	32	Right	32
3.95	24	0	36	GFI	44	Right	44
3.48	28	40	24	GFM	9	Right	9

The bootstrap is the ratio of the parameter estimate from the PLS analysis for that voxel over its estimated standard error. Local maxima are those voxels positively related to the LV effect. The local maxima are more related to the semantic retrieval tasks in the experiment relative to episodic retrieval tasks. The local minima are those voxels negatively related to the LV effect. These voxels are more related to the episodic retrieval tasks relative to the semantic retrieval tasks. Gyral locations: GF = fusiform gyrus; GTI = inferior temporal gyrus; GTM = middle temporal gyrus; GFS = superior frontal gyrus; GOM = middle occipital gyrus; GC = cingulate gyrus; GFI = inferior frontal gyrus; GFM = middle frontal gyrus.

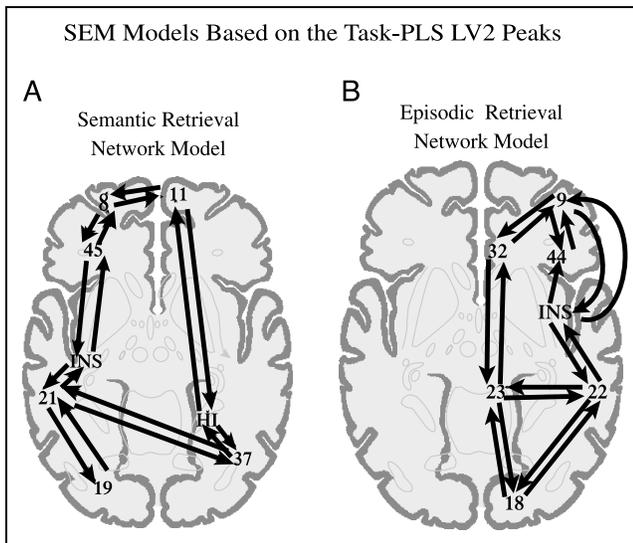


Figure 2. Anatomic model for the network analysis. The arrows represent the anatomic connections between brain regions that were determined from primate neuroanatomy studies. Part (A) represents the semantic retrieval anatomic model and part (B) represents the episodic retrieval anatomic model. The nodes of these models are represented by numbers or acronyms which refer to Brodmann areas (refer to Table 1).

to BA 32; $\chi^2_{\text{diff}}(3) = 9.43, p = .02$, for the connection from BA 32 to BA 9. During the episodic retrieval of old words there was a negative influence from BA 32 to BA 9 (path coefficient = -0.26). In contrast, during the episodic retrieval of new words, BA 32 had a positive influence (path coefficient = $+0.12$) on BA 9. In both conditions, the influence from BA 9 to BA 32 was near zero (path coefficient = ± 0.02). During semantic retrieval of old words there was a negative influence from BA 9 to BA 32 (path coefficient = -0.27). The influence from BA 32 to BA 9 was near zero (path coefficient = 0.03). In the semantic retrieval of new words there were negative reciprocal connections between BA 32 and BA 9 (path coefficient = -0.11 from BA 32 to BA 9; path coefficient = -0.50 from BA 9 to BA 32). However, because the omnibus test was insignificant, one must use caution in interpreting the individual stepwise analysis. Tests of the semantic retrieval model comparing the two episodic tasks versus the semantic tasks also found no significant difference, $\chi^2_{\text{diff}}(16) = 10.4, p = .84$. The hierarchical analysis of individual connections across all scans for the semantic model yielded a significant difference in the connection from right superior frontal gyrus (BA 11) to right hippocampus, $\chi^2_{\text{diff}}(3) = 10.1, p = .02$. During the semantic retrieval of old words there were negative reciprocal interactions between right BA 11 and right hippocampus (path coefficient = -0.18 from hippocampus to BA 11; path coefficient = -0.25 from BA 11 to hippocampus). Semantic retrieval of new words was related to very weak positive reciprocal interactions between these two

regions (path coefficients $< +0.05$). During the episodic retrieval of old words there were positive reciprocal interactions between BA 11 and hippocampus (path coefficient = $+0.19$ from hippocampus to BA 11; path coefficient = $+0.21$ from BA 11 to hippocampus). Episodic retrieval of new words was also associated with positive reciprocal interactions between BA 11 and hippocampus, but these interactions were weaker (path coefficient = $+0.12$ from hippocampus to BA 11; path coefficient $< +0.05$ from BA 11 to hippocampus). Again, caution must be exercised in interpreting the significant stepwise results because the overall omnibus test for the model was insignificant.

DISCUSSION

In the current study we constructed SEMs for episodic retrieval and semantic retrieval tasks. The nodes included in these models were those regions that maximally differentiated episodic and semantic retrieval tasks based on activity changes across tasks. We argue that if these two distinct patterns of activity for episodic and semantic retrieval tasks reflected the existence of distinct episodic and semantic memory systems, then the pattern of interactions (effective connectivity) within the SEMs for these two tasks should also be distinguishable. Thus, significant χ^2_{diff} for the episodic retrieval model and the semantic retrieval model would strongly support the multiple memory systems view by showing that both activation and connectivity differences exist within distinct neural networks during the performance of episodic retrieval versus semantic retrieval, respectively. Such an interpretation is supported by previous network analyses of neuroimaging data (Buchel et al., 1999; Nyberg, McIntosh et al., 1996; McIntosh et al., 1994). For example, McIntosh et al. (1994) performed a network analysis on PET data obtained while subjects performed an object vision and a spatial vision task. Based on activation differences, a single SEM was constructed that included regions involved in both object (ventral visual stream) and spatial vision (dorsal visual stream) for the right hemisphere. An equivalent SEM was constructed for the left hemisphere. Omnibus tests of the two SEMs found that there were significant differences in the path coefficients between the object versus spatial vision tasks. There were stronger (larger) path coefficients among regions in the SEM that were from the ventral visual stream during object vision. During spatial vision there were stronger path coefficients among regions from dorsal visual stream. These results were taken to support the view that the object and spatial vision tasks reflected the functioning of two separate visual systems (the ventral and dorsal visual systems, respectively) because regions that were more active for one task relative to the other were also more functionally integrated (effectively connected) during one task versus the other.

The results from the current analysis indicate that even though the SEMs were constructed by using nodes that showed maximal differences in regional activity during episodic versus semantic retrieval tasks, the pattern of neural interactions within each of these models was not significantly different between these two retrieval tasks. The pattern of path coefficients for the episodic retrieval model were not different across tasks, nor were the path coefficients for the semantic retrieval model. As mentioned in the Introduction, if the SEM for episodic memory retrieval did reflect the functioning of a distinct memory system, then one may expect there to be significant differences in the path coefficients (effect connectivity) when subjects performed this task, relative to the semantic retrieval task, and vice versa.

Generally, failure to reject the null hypothesis (that the pattern of coefficients is similar across conditions) does not mean the null hypothesis is correct because it may reflect Type II error. Given the sample size, it is possible that we lacked statistical power to distinguish covariance patterns in these data. However, given the striking similarity of the majority of the paths in the present model (the observed value for the χ^2_{diff} and degrees and freedom were very close), we suggest that the failure to reject the null hypothesis in the current experiment may reflect an actual overlap in the pattern of interactions among brain regions across episodic and semantic retrieval. Taken together, the results from the current study suggest that the regions involved in both episodic and semantic retrieval interact similarly regardless of the type of memory retrieval engaged. Therefore, if a memory system is defined as a neural system that shows a unique memory-type-specific activation pattern *and* a functional interaction pattern, then the similarities in network interactions across episodic and semantic retrieval that were observed in the current study argue against the existence of separate episodic and semantic memory systems in the brain. Instead, these results imply that episodic and semantic retrieval were mediated by a single network. During episodic retrieval tasks, those nodes that were related to physiological processes that were more important for episodic retrieval increased their activity level during these tasks compared with the semantic retrieval tasks. Similarly, during semantic retrieval tasks, those nodes related to physiological processes that were more important for semantic retrieval increased their activity during these tasks relative to the episodic retrieval tasks. The SEM results suggest that the same memory network/system was engaged across tasks, given the similarities in path coefficients, and activity modulation within and between nodes signals the physiological variation in episodic and semantic memory.

It is interesting to note that there were some differences in the path coefficients across scan conditions in the hierarchical analysis of the within-retrieval models.

One may argue that these differences explain why episodic and semantic memory have traditionally been discussed as separate cognitive systems. Interestingly, the main regions that showed differences in interactions in the within model stepwise analysis included the right PFC and the hippocampus. As mentioned previously, the majority of neuropsychological and neuroimaging studies have highlighted how hippocampal and PFC function differentiate episodic and semantic memory performance (Nadel & Moscovitch, 2001; Tulving et al., 1999; Squire & Zola, 1996; Tulving, Kapur, Craik et al., 1994; Tulving, Kapur, Markowitsch et al., 1994; Squire et al., 1992). The current SEM analysis indicates that it may be the pattern of neural interaction among these regions that may be crucial for understanding the difference between episodic and semantic memory on a cognitive level. However, one should not assume that this finding supports a multiple memory systems framework because the overall omnibus tests failed to find a difference across tasks. Instead, this physiological interaction may reflect a process within a single neural system that differentiates these tasks. It is unclear at this time what this process may be on a cognitive level. Using techniques measuring effective connectivity, one can relate physiological interactions to behavioral measures. Unfortunately, it is not possible to do this analysis with these data due to the small number of PET scans per subject. However, fMRI studies using SEM have shown promising results in this regard (Glabus et al., 2003; Buchel et al., 1999).

In conclusion, neuropsychological and neuroimaging dissociations may be interpreted as reflecting different but interacting systems or as reflecting different modes of functioning with a single system. The multiple memory systems view assumes that qualitatively different forms of memory represent separate psychological and biological memory systems (Rolls, 2000; Schacter, Wagner, & Buckner, 2000; Tulving, 1985). Accordingly, a memory system is thought to consist of a distributed neural network that is anatomically connected and functionally integrated. Each memory system is believed to process a different type of information, use unique operations, and be neurologically discrete and independent in its function (Tulving, 1985). The results from the current SEM analysis do not support this particular version of the multiple memory systems view. However, there were small differences in neural interactions across conditions. It is possible that the particular tasks employed by Duzel et al. (1999) promoted a high degree of similarity in the interregional correlations between tasks because all the words employed in both the episodic and semantic retrieval tasks were initially studied using a semantic judgement of pleasantness. This may have resulted in tasks not being systems pure: There may have been incidental episodic retrieval during the semantic retrieval tasks and incidental semantic retrieval during

the episodic retrieval tasks. Thus, in the future it would be beneficial to examine effective connectivity patterns between more systems pure semantic memory (SM) and episodic memory (EM) tasks to validate our current findings. Nevertheless, it is interesting that despite these similarities in processes engaged, the PLS analysis still identified strong activation differences between retrieval tasks. Only by examining interregional correlations with SEM were the similarities across tasks identified.

To summarize, if a memory system should exhibit *both* a significant and *unique pattern of activation* and a significant and *unique pattern of neural interaction* during the performance of a task that specifically requires its participation (Rolls, 2000; Schacter et al., 2000; Tulving, 1985), then the current SEM analysis argues for the unitary memory system view (Menon, Boyett-Anderson, Schatzberg, & Reiss, 2002; Nyberg et al., 2002; Dalla Barba, Parlato, Jobert, Samson, & Pappata, 1998; Mesulam, 1994; Eysenck, 1988; Roediger, 1984; Craik & Lockhart, 1972). Episodic and semantic memory retrieval may be viewed as different modes of activation within a single neurobiological system. In the course of normal operation, episodic and semantic memory operations may be too entwined to be considered as different neural systems. For example, the performance of any episodic memory task draws on one's semantic memory to some degree (Menon et al., 2002; Nyberg et al., 2002; Squire & Zola, 1998; Craik & Jennings, 1992). Although one can cite behavioral or clinical circumstances that dissociate memory systems, it is not a logical conclusion that, under normal circumstances, the systems act independently (Menon et al., 2002; Nyberg et al., 2002; Poldrack et al., 2001; Haxby, Petit, Ungerleider, & Courtney, 2000; McIntosh, 2000; Moscovitch, 2000; Nyberg et al., 2000; Schacter et al., 2000; Stuss & Alexander, 2000; Wiggs et al., 1999; Dalla Barba et al., 1998; Squire & Zola, 1998; Gluck & Myers, 1997; Vargha-Khadem et al., 1997; Mesulam, 1994, 1998; Roediger, 1984). Indeed, given the interactive nature of brain function, it is highly unlikely that such independence represents standard operations (Nyberg et al., 2002; Poldrack et al., 2001; Poldrack & Packard, 2003; McIntosh, 1998, 1999; Mesulam, 1998).

METHODS

PET Methods

The behavioral and PET scanning methods of this study have been reported elsewhere and are summarized below (Duzel et al., 1999). Eight PET scans were obtained from 11 young adults (6 women, 5 men) while they performed either an episodic retrieval task ("old/new" recognition task) or a semantic retrieval task ("living/nonliving" semantic judgement). Before each of the retrieval tasks, subjects performed an encoding task in which they were required to make pleasant/

unpleasant judgements for 20 words. After the encoding phase, subjects performed either episodic or semantic retrieval task. During the retrieval tasks, subjects were presented with 40 words and 20 random letter strings. During the 60-sec PET image acquisition interval for the retrieval tasks, subjects were presented with one of the following four stimulus types: (1) previously seen (old) living words, (2) old nonliving words, (3) novel living words, or (4) novel nonliving words. These four stimulus types were presented while subjects performed episodic retrieval tasks (resulting in four episodic retrieval PET conditions) and while subjects performed semantic retrieval tasks (resulting in four semantic retrieval PET conditions). Thus, the stimulus type and retrieval task type was completely crossed. These scans were counterbalanced across subjects; Table 1 shows the order in which these eight scans were placed before statistical analysis.

Image Normalization and Activation Analysis

Each subject's PET images were registered using the statistical parametric mapping software (SPM95; Wellcome Department of Cognitive Neurology, London, UK). First, each subject's images were realigned to their first PET image, by using a rigid body transformation, to correct for head movement. The realigned images were spatially transformed by matching each subject's image to a regional cerebral blood flow (rCBF) template that conformed to Talairach and Tournoux stereotaxic space (1988). Images were then smoothed, with the use of a 15-mm isotropic Gaussian filter, to minimize individual anatomic variability. To control for individual differences in whole-brain rCBF, each subject's transformed image was adjusted to their own global blood flow using a ratio adjustment in which each pixel value was divided by the average whole-brain flow value within a scan.

Partial Least Squares

PLS, a multivariate technique, was used to examine how changes in rCBF across all eight PET scans were related to the experimental design. This was done to identify candidate voxels that would later be used in the SEM analysis. The details for conducting the PLS analysis have been explained elsewhere and the reader is encouraged to refer to these sources to supplement the summary (Duzel et al., 2003; Nyberg et al., 2002; Della-Maggiore et al., 2000; Grady, McIntosh, Rajah, Beig, & Craik, 1999; Cabeza, Grady, et al., 1997; McIntosh, Bookstein, Haxby, & Grady, 1996). To apply PLS we first constructed a matrix of orthogonal Helmert contrasts, representing the experimental design (design matrix) and a matrix of all the PET data for all subjects across all eight scans (data matrix). These design and data matrices were then cross-correlated. This cross-correlation matrix was then

decomposed by using the singular value decomposition algorithm into a set of seven mutually orthogonal paired LVs that identified cohesive patterns of brain activity that were related to the experimental design. An LV pair consists of design saliences and brain saliences. The design saliences are weights for the design contrasts that indicate which effect is represented by the brain activity in a particular LV. Design scores were calculated by multiplying the design salience with the corresponding contrasts and summing all the cross-products (dot product). The design scores represent how all eight scans differ for a given LV. The brain saliences are a matrix of weights that index the relation of each brain voxel to the experimental effect. Brain saliences can be either negative or positive. Positive brain saliences identify areas positively correlated to the experimental effect, and negative saliences identify regions that are negatively correlated with the experimental effect. Each LV pair is displayed as a singular image to show the spatial pattern of image covariance with each experimental effect (Jennings et al., 1997; McIntosh, Bookstein, et al., 1996). We plotted the design scores for the scans to determine how rCBF in brain areas associated with a particular LV were related to the overall experimental design.

The statistical strength of each LV was assessed by conducting a permutation test (McIntosh, Lobaugh, Cabeza, Bookstein, & Houle, 1998; McIntosh, Rajah, & Lobaugh, 1999). To identify dominant and stable voxels within a singular image, a bootstrap analysis of standard errors was conducted (Efron & Tibshirani, 1986). Peak voxels with singular image weights greater than twice the estimated standard error were considered reliable. Local maxima were selected from the bootstrap results. The Talairach and Tournoux (1988) atlas was used to localize these maxima. The bootstrap method allowed us to identify voxels that consistently contributed to the experimental effect within each LV.

Structural Equation Modeling

Specifying Retrieval Models

Brain regions of interest were chosen based on the PLS analysis. Separate models were constructed to represent the two retrieval or memory types: episodic and semantic. The aim was to assess whether there were any differences across scans for either a model aimed at exclusively representing episodic memory retrieval or a model aimed at exclusively representing semantic memory retrieval. The two within retrieval type models will be referred to as the episodic retrieval model and the semantic retrieval model. The models were constructed for the four retrieval scans consisting of living word stimuli: episodic retrieval of old living words, episodic retrieval of new living words, semantic retrieval of old living words, and semantic retrieval of living new words. Only these scan conditions were compared because they

showed the greatest difference between episodic and semantic retrieval tasks according to the PLS analysis results. The anatomic connections were derived from the known primate neuroanatomy (Barbas & Blatt, 1995; Carmichael & Price, 1995a, 1995b; Petrides & Pandya, 1994; Distler et al., 1993; Goldman-Rakic et al., 1984; Pandya, Dye, et al., 1971). Complete methodological details, principles, and limitations of the applications of SEM to functional neuroimaging data have been discussed previously (McIntosh, Bookstein, et al., 1996; McIntosh & Gonzalez-Lima, 1991).

Statistical Assessment of SEMs

Omnibus tests were conducted between the four scan conditions using the stacked model in LISREL (version 8, Scientific Software Inc., Mooresville, IN) to assess the episodic retrieval model and the semantic retrieval model, respectively (McIntosh & Gonzalez-Lima, 1992a; Joreskog & Sorbom, 1984). This procedure has been validated and applied to both PET and fMRI data in previous studies (Buchel et al., 1999; Rajah, McIntosh & Grady, 1999; Cabeza, McIntosh, Tulving, Nyberg, & Grady, 1997; Nyberg, McIntosh et al., 1996; Horwitz, McIntosh, Haxby, & Grady, 1995; Grafton, Sutton, Couldwell, Lew, & Waterm, 1994; McIntosh et al., 1994; Horwitz & McIntosh, 1993; McIntosh & Gonzalez-Lima, 1992a, 1994a). A null functional model, where the path coefficients were set to be equal between conditions was compared to an alternative functional model, in which the coefficients were allowed to vary across conditions. The two models were evaluated by comparing their respective goodness-of-fit χ^2 values and calculating a χ^2_{diff} . The significance of the χ^2_{diff} was assessed by using the difference degrees of freedom between the null and alternative models. If the alternative model had a significantly lower χ^2 than the null model, then the path coefficients that were allowed to vary in the alternative model were significantly different between conditions. Therefore, comparisons of models in which the path coefficients were either constrained or unconstrained across conditions served as an omnibus test for changes in functional interactions (McIntosh, Bookstein, et al., 1996). In addition to the omnibus test, each individual scan condition was tested against the null model to determine whether any single scan condition differed within the episodic and semantic models. A significant χ^2_{diff} would reflect differences in the effective connectivity between conditions for a given functional model and support a multiple memory systems view.

The significance of individual connections within the episodic and semantic retrieval models was assessed by conducting a hierarchical model analysis in LISREL (McIntosh & Gonzalez-Lima, 1992a; Joreskog & Sorbom, 1984). In the null model, the connections for each retrieval model were set to be equal between the new and old conditions within each memory task type. In the alternate

models, each reciprocal connection was allowed to vary in a stepwise manner. Those connections that were significantly different between conditions (as assessed by χ^2_{diff} between null and alternate models) were set to vary as the analysis progressed to the next connections. Those connections that were not significantly different between conditions were set to be equal across conditions as the analysis progressed to the next connections.

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