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Network analysis in episodic encoding and retrieval of word-pair associates: a PET study

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Abstract

The involvement of distributed brain regions in declarative memory has been hypothesized based on studies with verbal memory tasks. To characterize episodic declarative memory function further, 14 right-handed volunteers performed a visual verbal learning task using paired word associates. The volunteers underwent positron emission tomography. ^{15}O-butanol was used as a tracer of regional cerebral blood flow (rCBF). Inter-regional functional interactions were assessed based on within-task, across-subject inter-regional rCBF correlations. Anatomical connections between brain areas were based on known anatomy. Structural equation modelling was used to calculate the path coefficients representing the magnitudes of the functional influences of each area on the ones to which it is connected by anatomical pathways. The encoding and the retrieval network elicit similarities in a general manner but also differences. Strong functional linkages involving visual integration areas, parahippocampal regions, left precuneus and cingulate gyrus were found in both encoding and retrieval; the functional linkages between posterior regions and prefrontal regions were more closely linked during encoding, whereas functional linkages between the left parahippocampal region and posterior cingulate as well as extrastriate areas and posterior cingulate gyrus were stronger during retrieval. In conclusion, these findings support the idea of a global bihemispheric, asymmetric encoding/retrieval network subserving episodic declarative memory. Our results further underline the role of the precuneus in episodic memory, not only during retrieval but also during encoding.

Introduction

Memory has been the centre of attention for a considerable time, with good progress being made in understanding its nature. Schacter & Tulving (1994), for example, argue for a subdivision into declarative and procedural memory systems with a further division of the former into semantic and episodic memory. There are still many questions to answer about the brain networks involved in all of these memory systems, especially now that it is appreciated that memory function is distributed throughout the brain and not restricted to any particular region.

Increasing information has become available from brain imaging techniques about the networks of brain regions active while human subjects solve various cognitive tasks; a certain amount of overlap has been discovered between the networks involved in different tasks. A number of researchers have examined interactions between different brain regions using covariances of brain activity across space. The term ‘functional connectivity’ has been used to describe correlations of activity between neural elements and brain imaging (Friston *et al.*, 1993). A more refined progression from functional connectivity is ‘effective connectivity’ which represents the influence or effect which one neural element has on another (Friston *et al.*, 1993). It has been noticed, however, that one confound of effective connectivity is that inter-regional covariances may be influenced by direct influences, indirect interactions or common influences.

The application of structural equation modelling to brain imaging data has been proposed in order to differentiate between these influences (McIntosh & Gonzales-Lima, 1991, 1992; McIntosh *et al.*, 1994). Structural equation modelling, or path analysis, is a data-analysis technique allowing one to assess the numerical value or weight that each path in a given model should have for the model to account for the observed patterns of covariances. It is important to recognize that the use of structural equation modelling (McIntosh *et al.*, 1994) allows functional interactions between brain regions, and not just the levels of activity, to be ascertained during a task. Turning to the specific features of the present study, we examined a verbal episodic memory task during encoding or retrieval of visually presented semantically unrelated paired word associates. We aimed specifically to disentangle encoding and retrieval network representations in this memory task. Regional cerebral blood flow (rCBF) was measured using positron emisson tomography (PET) in 14 normal subjects with O-15-butanol during encoding and retrieval phases.

The subtraction analysis using statistical parametric mapping (Friston *et al.*, 1995a, b) of the data presented here (Halsband *et al.*,

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1998) supports the hypothesis of the presence of distributed brain structures subserving episodic encoding and retrieval of word pair associates. A left prefrontal activation during the encoding of visually-presented word pair associates was observed, whereas retrieval led to bilateral prefrontal activation as well as anterior cingulate activation. In addition, the results point to the important role of the precuneus in the retrieval of highly imaginable word-pair associates using visual imagery as a mnemonic strategy (Halsband *et al.*, 1998).

The aim of this study has already been specified in general; more specifically the data arising from the rCBF measurements were used firstly to obtain within-task across-subject correlations of the functional interactions between pairs of the involved brain regions, and secondly to determine the strength of the functional linkage between these regions by means of structural equation modelling during episodic encoding and retrieval. Thirdly, we investigated the resulting structural models to explore the differences in episodic encoding and retrieval.

Materials and methods

Subjects

Fourteen right-handed male volunteers (mean age 26.6 ± 3.4 years) with no history of neurological or psychiatric illness took part in the study. The study was approved by the ethical committee and federal authorities. Informed, written consent for participation in the study was obtained from each subject.

Positron emission computed tomography scanning

Six scans of regional cerebral blood flow (rCBF) were obtained for each subject using a GE PC4096 Plus scanner (Rota Kops *et al.*, 1990) which provides 15 transverse sections through the brain spaced 6.5 mm apart (centre to centre). Transmission scans performed with a ^{68}Ge/^{68}Ga rotating line source were used for measured attenuation correction. A laser positioning system was used to obtain images parallel to a line 27 mm above the canthomeatal line. Emission data were acquired in list mode for 3 min post-injection starting with the intravenous bolus administration of 1500 MBq ^{15}O-butanol. The list mode data was framed into a single frame of 40 s starting at the entry of the tracer into the brain comprising all 15 image planes (Herzog *et al.*, 1996). Using filtered backprojection, the reconstructed image resolution was ≈ 9 mm (full width half maximum). The activity images were regarded as estimates of rCBF. Standardization of rCBF was achieved by dividing each pixel value for a given scan by that subject's global CBF for that scan.

Paired word association learning

A visual verbal episodic memory task was used. Subjects were visually presented with word pairs. Study words were two-syllable German words that were between four and nine letters in length and of moderate frequency. The word pairs were semantically unrelated (hard associations) and therefore difficult to associate. Wechsler (1945) made a distinction between easy and hard word associations in his associative learning task of the Wechsler Memory Scale (Subtest VII). Word pairs (with the second word under the first to avoid lateralization effects) were presented on a 17-inch computer monitor placed at a distance of ≈ 70 cm from the eyes (font, Times New Roman; size, 72 points). The letters were white on a black screen and centred.

In a prestudy all subjects underwent testing of memory performance with the visual verbal memory task. Subjects were presented with 12 word pairs. Afterwards they were asked to retrieve the corresponding word pair associates after having been randomly presented with the first of the two words of each pair. The subject's individual performance was evaluated by repeating the storage and retrieval task for the number of times the volunteer needed to successfully retrieve ≈ 80% of the randomly-presented word pairs.

Using a new set of 12 word pairs, six PET measurements were performed for each volunteer. On each of the six trials the memory task began ≈ 30 s before the injection of a bolus of ^{15}O-butanol. During the first scan (storage), subjects were presented with 12 word pairs visually and had to read them aloud (presentation rate: 4 s word pair presentation, 1 s interval). Between scan 1 (first storage) and scan 2 (first retrieval) the same word-paired associates were presented in random order one to three times according to the number of encoding repetitions needed to retrieve an average accuracy of 80% of the word pair associates as evaluated by prestudy memory performance testing. During scan 2 the first words of the pair associates were visually presented (presentation rate: 4 s first word of a word pair, 1 s interval). The subjects had to read the first word of a word pair aloud and also to add the corresponding associated word aloud.

Data analysis

Image analysis was performed using modules of the Statistical Parametric Mapping (SPM) software package (Friston *et al.*, 1995a, b), programs written in MATLAB (Math works, Natick, MA, USA) for the correlation analysis (Horwitz *et al.*, 1995) and LISREL (Version 7.17, Scientific Software Inc.) for structural equation modelling. Image analysis was performed on a SPARC 20 workstation (Sun Microsystems).

Each reconstructed ^{15}O-butanol scan was realigned and reoriented along the bi-commissural line into a standard stereotactic space (Talairach & Tournoux, 1988) using a PET template. In the standard space, 1 voxel represents $2 \times 2 \times 4$ mm in the x, y and z dimensions, respectively (Friston *et al.*, 1995a; Friston *et al.*, 1995b). A Gaussian filter with a full width half maximum of 15 mm was applied.

Correlation coefficients were evaluated separately within task (encoding and retrieval task), across subjects between standardized rCBF in a reference voxel and standardized rCBF in all other brain voxels (Horwitz *et al.*, 1995). Because the rCBF data are heavily smoothed, the value of rCBF in a specific region can be represented by the value in one voxel.

Anatomical model

The anatomical model (regions and their anatomical interconnections) is presented in Fig. 1 and Table 1. The connections are mainly based on studies in nonhuman primates. For the frontal lobe connections we assumed they would correspond to the dorsal–ventral and anterior–posterior connections assessed in primates. The anatomical network comprises the visual cortical network, the limbic network and interhemispheric connections. A similar anatomical model has been used by McIntosh *et al.* (1996) employing a working memory task for faces.

This network of prefrontal, posterior cortical areas and limbic structures (Warrington & Weiskrantz, 1982; Goldman-Rakic, 1988) is heavily interconnected (Mesulam, 1990). The anterior cingulate cortex has substantial connections with the frontal, parietal and limbic structures and receives major inputs from various parts of the cerebral cortex (Pandya & Kuypers, 1969; Vogt *et al.*, 1979). The principal reciprocal connections of the dorsolateral prefrontal cortex are with the inferior parietal lobule, parahippocampus and cingulate gyrus (Jacobson & Trojanowski, 1977; Goldman-Rakic *et al.*, 1984; Goldman-Rakic, 1987; Pandya & Barnes, 1987). An important neural pathway connecting the prefrontal cortex with the hippocampus is by

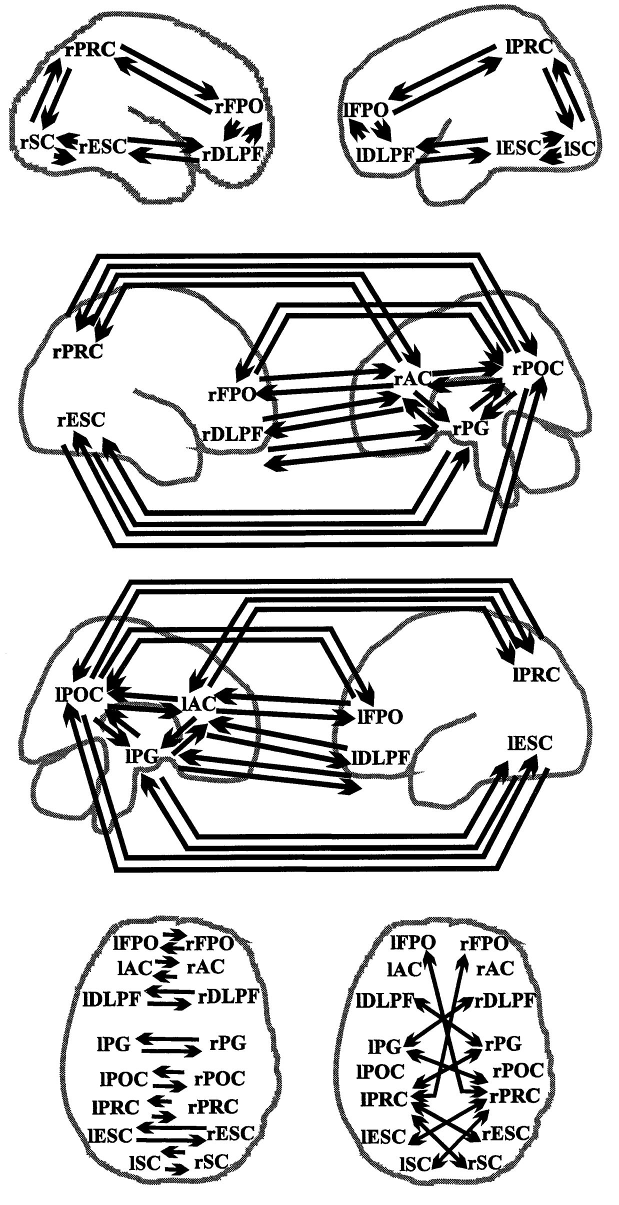

FIG. 1. Anatomical model for the network analysis. The connections are mainly based on studies in nonhuman primates (abbreviations in the figures are defined in Table 1 and in the Abbreviations list below).

TABLE 1. Location of representative voxels used in the network analysis

Structure	Abbreviation	*x*	y	z
Precuneus, left	lPRC	–8	–66	44
Precuneus, right	rPRC	8	–66	44
Frontopolar cortex, left	lFPO	–20	46	24
Frontopolar cortex, right	rFPO	22	62	20
Dorsolat. prefr. cortex, left	lDLPF	–44	22	4
Dorsolat. prefr. cortex, right	rDLPF	56	26	12
Posterior cingulate cortex, left	lPOC	–6	–58	28
Posterior cingulate cortex, right	rPOC	10	–56	20
Anterior cingulate cortex, left	lAC	–6	–8	44
Anterior cingulate cortex, right	rAC	6	–8	44
Striate cortex, left	lSC	–10	–82	0
Striate cortex, right	rSC	10	–82	0
Extrastriate cortex, left	lESC	–20	–62	–12
Extrastriate cortex, right	rESC	20	–64	–8
Parahippocampal gyrus, left	lPG	–22	–46	–8
Parahippocampal gyrus, right	rPG	24	–46	–8

The coordinates *x*, *y* and *z* (mm) are those of Talairach & Tournoux (1988).

way of a relay in the caudomedial lobule (Goldman-Rakic, 1984, 1988), an area presumed to represent the retrosplenial area of posterior cingulate cortex. The anatomical connections of the precuneus are widespread and include the prefrontal cortex (Petrides & Pandya, 1984; Goldman-Rakic, 1988) and the occipital cortices (Blum *et al.*, 1950).

The anatomical model consists of three subnetworks, (i) the visual network, (ii) the corticolimbic network and (iii) the interhemispheric network. We assumed only homologous left–right and right–left connections, apart from some heterologous contralateral influences between the left and the right hemispheres. Indications for nonhomologous connections were derived from modification indices (Jöreskog & Sörbom, 1989).

Structural equation modelling

For the structural equation models, voxels that were identified through inter-regional correlation of rCBF estimates within each condition (Horwitz *et al.*, 1995) having a key relation to the experimental condition were selected. We used the stack model or multiple group approach in LISREL (Jöreskog & Sörbom, 1989; McIntosh & Gonzales-Lima, 1992; McIntosh *et al.*, 1994) to perform omnibus comparisons between conditions. We did not calculate a model for each of the conditions separately, but combined both in a single analysis (McIntosh *et al.*, 1996; Cabeza *et al.*, 1997). In the stacked model, functional models are compared as follows: all path coefficients are set to be equal between the two conditions (null hypothesis) and statistically probed with those where the path coefficients were allowed to differ (alternative hypothesis). To compare the two hypotheses, the χ^2-value for the alternative hypothesis is subtracted from the χ^2-value of the null model. This procedure allows the estimates to differ and thus allows estimation of the improvement in fit of the alternative model compared with the null model. A significant improvement in fit indicates a significant difference of functional interactions between conditions. Path coefficient values were normalized.

We calculated the functional model as follows: (i) the path coefficients for the feed-forward connections were tested within each hemisphere starting from the input node in visual striate cortex through the fusiform gyrus to the parahippocampal and to frontal regions; (ii) we fixed the estimates from analysis (i), and the path coefficients through the feed-back connections from frontal and limbic areas were compared between conditions within hemispheres; and (iii) the results from analysis (ii) were fixed and the interhemispheric connections were tested. In order to rule out the possibility that the solutions were influenced by the order of the analysis we reversed steps (i) and (ii).

Results

The main finding of this path analysis is a functional distinction of a network of brain regions subserving encoding and retrieval in episodic associative memory.

Network components

Locations of representative voxels used in the network analysis are depicted in Table 1 (coordinates are given in the coordinate system of Talairach & Tournoux, 1988). Correlation coefficients between brain regions in the encoding and retrieval tasks are displayed in Table 2 ($P < 0.05$).

TABLE 2. Pearson correlation coefficients between brain regions showing differential activity in encoding and retrieval ($P < 0.05$)

	lPRC	rPRC	lFPO	rFPO	lDLPF	rDLPF	lPOC	rPOC	lAC	rAC	lSC	rSC	lESC	rESC	lPG	rPG
lPRC	–						*0.54*	0.58								
rPRC	0.59	–					*0.57*									
lFPO	0.60		–	*0.80*												
rFPO	0.68	0.59		–		***0.66***										
lDLPF	0.53			0.60	–		*0.59*		–0.56							
rDLPF				**0.55**	0.74	–										
lPOC							–				*0.61*			0.63	0.58	
rPOC							0.82	–							*0.56*	
lAC	0.61	0.63		0.65	0.65				–							
rAC	0.61	0.56		0.80	0.77	0.59			0.84	–						
lSC											–	*0.79*		0.69	0.58	
rSC	0.78				0.64					0.54		–	***0.65***	***0.66***		
lESC					0.79							**0.67**	–	***0.74***	***0.78***	***0.69***
rESC	0.58			0.55	0.54							**0.78**	**0.71**	–	*0.77*	***0.64***
lPG					0.71								**0.72**		–	*0.58*
rPG	0.56			0.62	0.55					0.55		0.71	**0.63**	**0.90**		–

The upper right diagonal matrix (numbers in italics) is based on data from the retrieval condition and the lower left diagonal matrix on data from the encoding condition. The bold, underlined coefficients are of equivalent magnitude for encoding and retrieval (abbreviations are defined in Table 1 and in the Abbreviations list below).

During both encoding and retrieval, there were strong positive rCBF correlations between right and left striate cortex, as well as between right and left extrastriate cortex. Furthermore there were large positive rCBF correlations between right extrastriate cortex and right parahippocampal cortex as well as between left extrastriate cortex and left parahippocampal cortex. Strong positive correlations occurred to a greater extent during encoding vs. retrieval [i.e. $r_{(\mathrm{diff})} > 0.5$ between $r_{(\mathrm{encoding})}$ and $r_{(\mathrm{retrieval})}$] between the anterior cingulate cortex and the left precuneus as well as left dorsolateral prefrontal cortex. Large positive correlations were also observed between the right anterior cingulate cortex and the right dorsolateral prefrontal as well as right frontopolar cortex. Furthermore there were high correlations between the left precuneus and the anterior cingulate cortex. During retrival only [i.e. $r_{(\mathrm{diff})} > 0.5$ between $r_{(\mathrm{retrieval})}$ and $r_{(\mathrm{encoding})}$], large positive correlations were observed between the left parahippocampal gyrus and the posterior cingulate gyrus, where there was no correlation during encoding. There also exist positive correlations between the left precuneus and the left posterior cingulate cortex.

Structural equation modelling

There were significant task-related differences between the two networks as suggested by omnibus statistical comparisons. Statistical comparisons showed significant differences in functional linkages between the encoding vs. the retrieval network [$\chi^2_{\mathrm{diff}}(18) = 171$; $P < 0.001$]. This improvement in fit indicates a significant difference of functional interactions between the encoding and retrieval conditions. Figure 2 shows the structural models obtained for encoding (see Table 3a for path coefficients) and Fig. 3 shows the retrieval of word pair associates (see Table 3b for path coefficients).

Encoding network

Figure 2 presents the functional model for encoding. There are strong interactions between the primary visual cortex, extrastriate areas and the parahippocampal gyrus, all in the right hemisphere. A functional linkage also exists between primary visual cortex, extrastriate areas and the precuneus and the parahippocampal gyrus in the left hemisphere. Left and right parahippocampal gyrus are linked to the anterior cingulate gyrus. There is a functional interaction between extrastriate areas on the right and its companion in the left hemisphere. Right extrastriate areas are functionally linked to the right dorsolateral prefrontal area. The left dorsolateral prefrontal area is strongly linked with left extrastriate areas and vice versa. The left precuneus is strongly linked to left posterior and anterior cingulate, which itself interacts with the left dorsolateral prefrontal area. The right precuneus is strongly linked to the right anterior cingulate gyrus, which itself strongly interacts with the right dorsolateral prefrontal area and the frontopolar cortex. Corticolimbic interactions for the right hemisphere were dominated by the anterior cingulate to the dorsolateral prefrontal cortex and the frontopolar cortex and the functional interaction of extrastriate areas with the parahippocampal gyrus. Corticolimbic interactions for the left hemisphere were dominated by the paths from precuneus to anterior cingulate and dorsolateral prefrontal to extrastriate areas, and paths from precuneus to posterior cingulate. Interhemispheric interactions exist between right extrastriate cortex and its left sibling, of right anterior cingulate likewise, and of reciprocal influences between both parahippocampi and both posterior cingulates.

Retrieval network

Figure 3 presents the functional model for retrieval. As for encoding, right primary visual cortex is functionally linked to the right extrastriate areas and thence to the right parahippocampal area; there is also an interaction of extrastriate areas on the right to its left hemisphere companion. However, there is now a bi-directional interaction of left and right primary visual cortex. Left primary visual cortex is also linked to left extrastriate areas, which itself is strongly linked to the left parahippocampal region. Instead of the interactions in the right hemisphere from primary visual cortex to the precuneus and thence to anterior cingulate and right frontopolar cortex and dorsolateral prefrontal cortex during encoding, for retrieval there are interactions between the extrastriate cortex and the posterior cingulate gyrus. There are important interactions between mainly left hemisphere parahippocampal, posterior cingulate and precuneus regions during retrieval as compared to encoding. Under retrieval conditions the right hemisphere strong and medium pathways are mainly feed-forward. There are also feed-back interactions from frontopolar cortex to precuneus (in both hemispheres) and from right dorsolateral prefrontal cortex to extrastriate areas on the right. There is a strong interaction between left dorsolateral prefrontal cortex and left frontopolar cortex (as for the right hemisphere) and at a medium level on the left from parahippocampal to extrastriate areas.

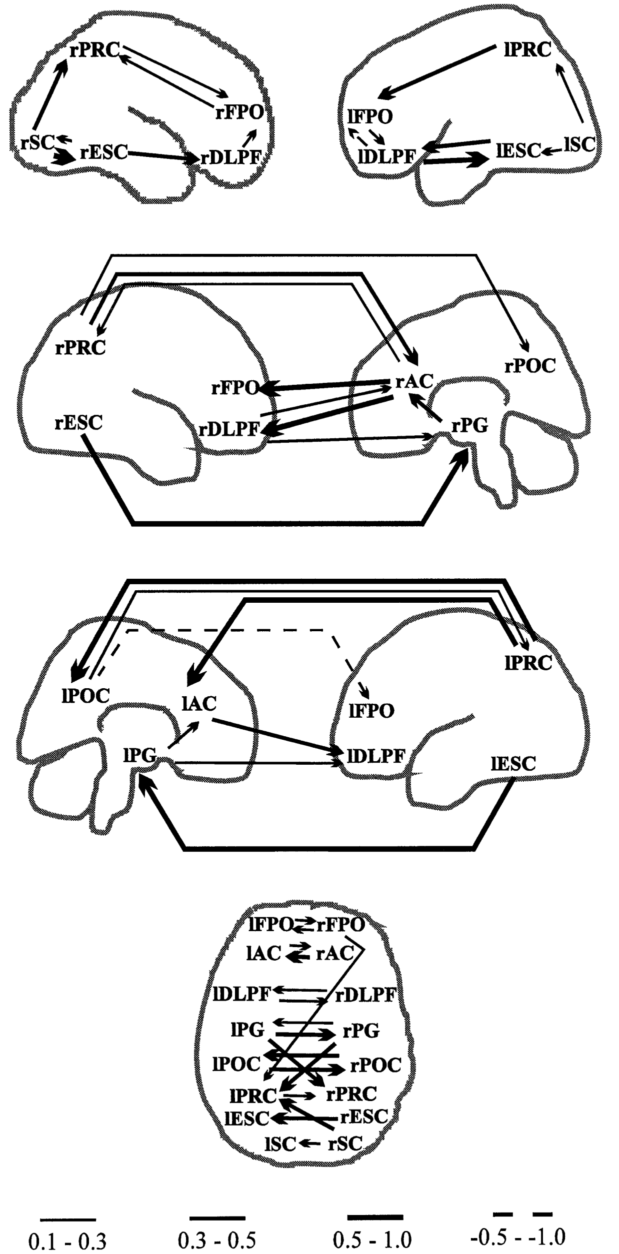

FIG. 2. Functional model for encoding. The magnitude of the functional influence is proportional to the width of the arrows. Positive path coefficients are shown as solid arrows whereas negative path coefficients are shown as segmented arrows (Path coefficients between –0.1 and +0.1 are not shown.)

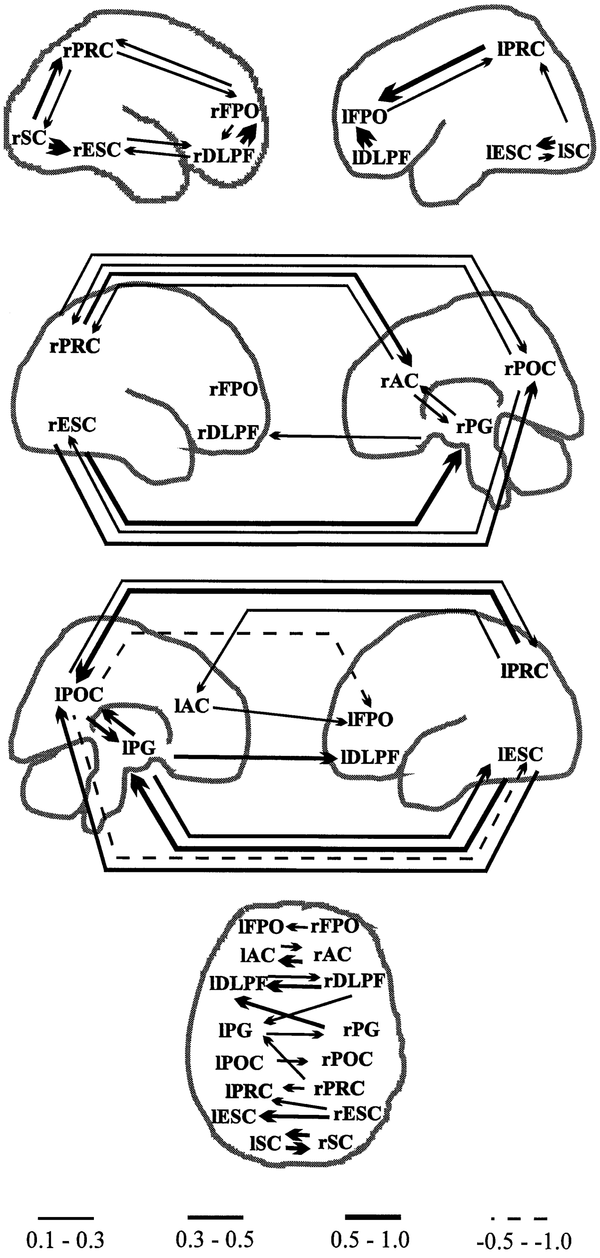

FIG. 3. Functional model for retrieval.

Discussion

Structural equation modelling of episodic encoding and retrieval revealed both similarities and differences in the interactions between brain regions.

There is a certain amount of overlap of the encoding network with that for retrieval in a general manner but also significant differences between the two networks. If looked at in terms of the strongest connecting paths between modules, say at or above a strength of 0.5, the common paths between the two conditions are from primary visual cortex to extrastriate areas and thence to the parahippocampal region on the right, from extrastriate areas to the parahippocampal region on the left, and from precuneus to posterior cingulate on the left. Figure 4 displays differences between the models where only those paths are displayed that differ by more than 0.4 between episodic encoding and retrieval. As a main finding our results show firstly that during encoding mostly anterior neocortical regions including the anterior cingulate cortex and prefrontal cortex strongly functionally interact where there is less interaction during retrieval. Secondly, during retrieval more posterior regions comprising parahippocampal cortex, posterior cingulate gyrus and extrastriate cortex are strongly interacting, where those interactions are less strong in episodic encoding.

Prefrontal cortex

Neuropsychological studies suggest that the prefrontal cortex is involved in strategic processing (Moscovitch, 1992; Moscovitch *et al.*, 1995), temporal ordering (Petrides, 1989) and the organization of search (Shallice, 1988). In humans, frontal lobe lesions, though not generally recognized as causing deficits on recognition

TABLE 3. Path coefficients: each coefficient corresponds to the path going from the region in the column heading to the region in the row heading. The bold, underlined coefficients differ by >0.4 between the models.

TABLE 3A Encoding path coefficients

	lPRC	rPRC	lFPO	rFPO	lDLPF	rDLPF	lPOC	rPOC	lAC	rAC	lSC	rSC	lESC	rESC	lPG	rPG
lPRC	–			0.21			0.13		0.25		0.22	**0.45**		–0.28		0.26
rPRC	0.14	–	0.18	0.16				–0.10		0.13		0.40			0.17	
lFPO	0.49	–0.16	–	0.28	–0.52		–0.53									
rFPO		0.23	0.15	–		0.18				**0.50**						
lDLPF			0.25		–	0.28			**0.40**				**0.39**		0.29	
rDLPF				–0.12	0.11	–				**0.52**				0.44		–0.24
lPOC	0.53		–0.21				–	**0.40**					–0.23			
rPOC		0.22					0.47	–								
lAC	0.52								–	0.39					0.11	
rAC		0.35				0.14			0.24	–						0.42
lSC											–	0.14	–0.10			
rSC		–0.19										–		0.25		
lESC		–0.23			**0.55**						0.20		–	0.46	–0.16	
rESC	0.16							–0.23				0.76	–0.20	–		–0.15
lPG		–0.10							–0.11				0.73		–	0.10
rPG					–0.29	0.18		–0.19						0.84	0.35	–

TABLE 3B. Retrieval path coefficients

	lPRC	rPRC	lFPO	rFPO	lDLPF	rDLPF	lPOC	rPOC	lAC	rAC	lSC	rSC	lESC	rESC	lPG	rPG
lPRC	–	0.17	0.18	0.27			0.29				0.18	–0.23		0.13		–0.25
rPRC		–		0.15				0.21		0.19	0.10	0.35	–0.17			
lFPO	0.69	–0.17	–	0.42	**0.50**		–0.67		0.24							
rFPO	–0.17	0.24	0.16	–		0.54										
lDLPF			–0.12		–	0.12			–0.15				–0.41		0.48	0.35
rDLPF				0.21	0.27	–								0.23	–0.39	0.16
lPOC	0.51		–0.26				–	–0.13					**0.30**		**0.42**	
rPOC		0.13					0.25	–						0.39		
lAC	0.28						–0.30		–	0.40					–0.15	
rAC		0.45						–0.14	0.24	–						0.10
lSC	–0.15	0.17									–	0.53	0.18			
rSC		–0.12										–				
lESC							–0.75				0.43		–	0.40	**0.49**	
rESC						0.16		**0.27**				0.64		–		
lPG		0.25			–0.37	0.12	0.40		–0.11				0.68		–	
rPG								0.20		0.20				0.68	0.22	–

Abbreviations are defined in Table 1 and in the Abbreviations list below.

and recall tasks (Ghent *et al.*, 1962; Stuss *et al.*, 1982; Smith & Milner, 1984; Squire, 1987), are reported to impair the free recall of word lists.

Left frontal lobe activation relates to word meaning retrieval (Buckner, 1996), external order monitoring (Petrides, 1996), short- and long-term recognition of words (Andreasen *et al.*, 1995), visual working memory (Salmon *et al.*, 1996) and effortful retrieval, maintainance and/or long-term control of semantic information (Fiez, 1997), strategic control of semantic retrieval (Randolph *et al.*, 1996), active encoding and retrieval of information held in posterior cortical association areas (Petrides *et al.*, 1995), encoding of object features (Owen *et al.*, 1996) and word and picture associative and visual semantic tasks (Vandenberghe *et al.*, 1996). Right frontal lobe involvement has been shown in episodic memory retrieval for words and faces (Buckner, 1996) and working memory updating of syllables (Salmon *et al.*, 1996).

Our results are indicative of strong feed-forward and feed-back interactions between the left dorsolateral prefrontal cortex and extrastriate cortex during encoding, which do not occur for retrieval. In a path analysis of a face-matching paradigm over various delay times, McIntosh *et al.* (1996) also found a strong functional interaction between the dorsolateral prefrontal cortex and extrastriate visual cortex. During retrieval only, we show that the left dorsolateral prefrontal cortex interacts strongly with the left frontopolar cortex. In a path analysis by Cabeza *et al.* (1997) on a paired word association task in young and old subjects there were positive interactions between right inferior frontal cortex and frontopolar cortex during encoding which is in line with our findings. In young normal volunteers there was a dissociation between the functional interactions of left and right inferior frontal cortex between episodic encoding and retrieval (Cabeza *et al.*, 1997). Our path analysis reveals an asymmetry of interhemispheric interactions between the prefrontal areas, but there is clearly bilateral prefrontal involvement in encoding and retrieval with an asymmetry in the strength of functional interactions between conditions.

Cingulate cortex

Clinical evidence supports the importance of the cingulate cortex in memory function (Valenstein *et al.*, 1987; Rudge & Warrington, 1991). It has been suggested that the caudomedial lobule forms an important link in the hippocampal connections to the neocortex that is highly developed in primates (Goldman-Rakic, 1988). The cingulate cortex shows an important role in the maintenance of goal-directed behaviours, i.e. in auditory-verbal graded response memory tasks (Grasby *et al.*, 1993), in verbal memory tasks (Petrides *et al.*, 1993; Fink *et al.*, 1996; Halsband *et al.*, 1998), in decision-making responses (Corbetta *et al.*, 1991) and in verification of temporal order (Nyberg *et al.*, 1996). Shallice *et al.* (1994)

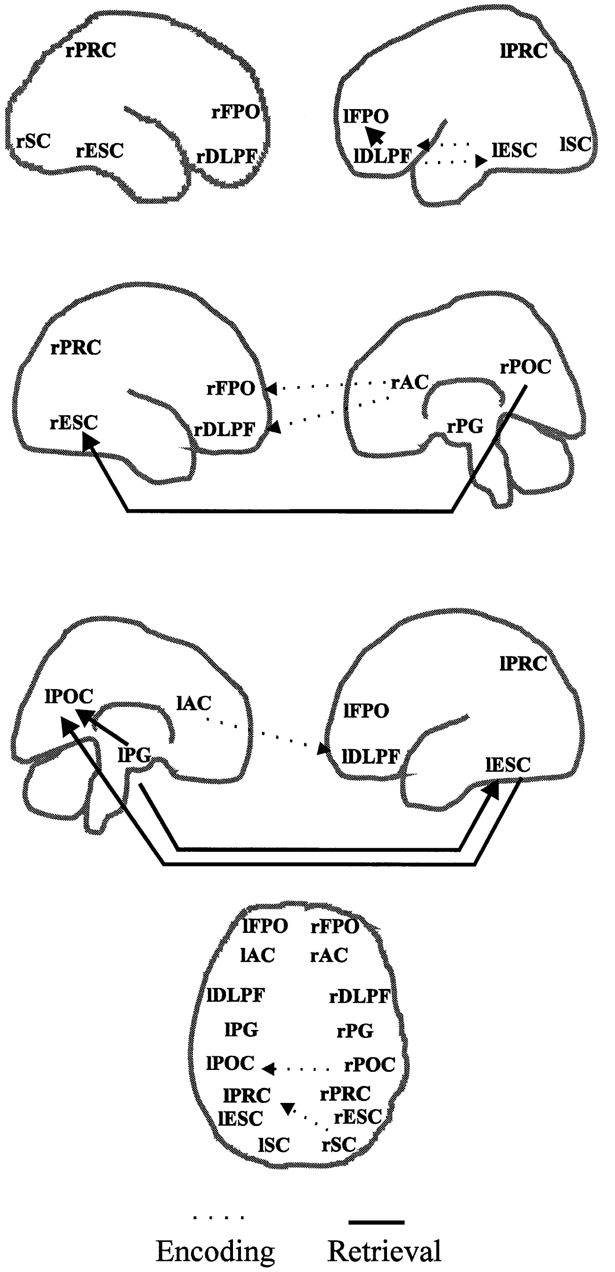

FIG. 4. Main differences in the functional models for encoding and retrieval. Only paths that differ by more than 0.4 between the models are displayed. Dotted line, encoding; solid line, retrieval.

found a double dissociation between anterior cingulate cortex and prefrontal cortex: the former was preferentially activated in response selection and maintenance of goal-directed behaviours, whereas the latter was involved in the organization of supervisory thought processes.

As a main finding our results show that during encoding the left and right anterior cingulate strongly interact with the left and right dorsolateral prefrontal cortex, and the right anterior cingulate interacts with the frontopolar cortex where there is no interaction during retrieval. McIntosh *et al.* (1996) found a strong functional interaction between the cingulate cortex and frontal areas. Furthermore, our results indicate that during retrieval the posterior cingulate cortex is more strongly functionally linked to extrastriate cortex and parahippocampal gyrus.

Parahippocampal gyrus

The parahippocampal gyrus plays an important role in active mnemonic processing (Petrides, 1996), in encoding of novel pictures (Stern *et al.*, 1996), word and picture associative and visual semantic tasks (Vandenberghe *et al.*, 1996), episodic compared to semantic retrieval of episodic memory (Fink *et al.*, 1996) and encoding of novel pictures (Stern *et al.*, 1996).

Our results point to an involvement of the parahippocampal gyrus which is strongly interconnected with the posterior cingulate cortex during retrieval, whereas there is less interaction apparent during encoding. In both encoding and retrieval, the left and right parahippocampal gyri interact with the corresponding extrastriate cortex. This is in line with findings of McIntosh *et al.* (1996) who found that throughout all the delays in the face-matching case the parahippocampal gyrus was functionally linked to extrastriate visual cortex. Rajah *et al.* (1997) also showed similarities to our model interactions. Their structural model for encoding showed strong interactions among hippocampus, extrastriate cortex and cingulate cortex. Köhler *et al.* (1998) assessed right hemispheric mesial temporal lobe interactions with the posterior neocortex by means of path analysis for spatial and object retrieval. During object retrieval there were interactions between right extrastriate cortex and parahippocampal gyrus. The authors provide evidence that mesial temporal lobe interactions depend on the domain of information to be recovered and show positive interactions involving ventral posterior regions for object retrieval which is in line with our findings with involvement of ventral posterior regions for verbal memory items employing a high degree of imagery.

Precuneus

The precuneus clearly plays a pivotal role in our paired word association task. There exist extensive connections between the precuneus, prefrontal and cingulate regions (Mesulam, 1990). Anatomical evidence indicates prefrontal (Petrides & Pandya, 1984; Goldman-Rakic, 1988), temporal, occipital and thalamic connections (Blum *et al.*, 1950; Pribram & Barry, 1956). Involvement of the precuneus has been shown in episodic as compared to semantic memory retrieval (Tulving *et al.*, 1994; Grady *et al.*, 1995; Schacter *et al.*, 1995; N. Kapur *et al.*, 1995; S. Kapur *et al.*, 1995; Fletcher *et al.*, 1995b, 1996; Moscovitch *et al.*, 1995; Fink *et al.*, 1996; Halsband *et al.*, 1998; Mottaghy *et al.*, 1999). It was shown in a recent study by our group that the precuneus is not only significantly activated during the recall of highly imaginable words but also during the recall of abstract words, and plays a major role in a network of distributed brain regions in episodic retrieval irrespective of the presentation modality (visual–verbal/auditory–verbal) (Krause *et al.*, 1999). The results of the path analysis underline the role of the precuneus in episodic retrieval. Our findings additionally demonstrate its involvement during encoding as evident from its strong functional interactions (i.e. connections with primary visual cortex, extrastriate areas, parahippocampus, anterior and posterior cingulate and prefrontal cortex).

Conclusion

Our findings provide evidence for a global bihemispheric, asymmetric encoding/retrieval network subserving episodic declarative memory. For the interhemispheric interactions the functional models reveal an encoding/retrieval asymmetry. During encoding the left hemispheric functional influences were greater in number and strength of path coefficients than the right hemispheric ones.

During retrieval, the right hemispheric functional influences dominated as compared to the left hemispheric ones. Our findings provide evidence that distinct prefrontal areas (dorsolateral prefrontal and frontopolar cortex) are differentially involved in episodic memory and support the hypothesis of functionally specialized regions in prefrontal cortex. Our results underline the role of the precuneus in episodic retrieval, but additionally demonstrate its involvement during encoding as evident from its strong functional interactions.

Abbreviations

lAC, anterior cingulate cortex, left; lDLPF, dorsolateral prefrontal cortex, left; lESC, extrastriate cortex, left; lFPO, frontopolar cortex, left; lPG, parahippocampal gyrus, left; lPOC, posterior cingulate cortex, left; lPRC, precuneus, left; lSC, striate cortex, left; PET, positron emission tomography; rAC, anterior cingulate cortex, right; rCBF, regional cerebral blood flow; rDLPF, dorsolateral prefrontal cortex, right; rESC, extrastriate cortex, right; rFPO, frontopolar cortex, right; rPG, parahippocampal gyrus, right; rPOC, posterior cingulate cortex, right; rPRC, precuneus, right; rSC, striate cortex, right; SPM, statistical parametric mapping.

References

Andreasen, N.C., O'Leary, D.S., Arndt, S., Cizaldo, T., Hurtig, R., Rezai, K., Watkins, G., Boles Ponto, L.L. & Hichwa, R.D. (1995) Short-term and long-term verbal memory: a positron emission tomography study. *Proc. Natl Acad. Sci. USA*, **92**, 5111–5115.

Blum, J.S., Chow, K.L. & Pribram, K.H. (1950) A behavioural analysis of the organization of the parieto-temporo-preoccipital cortex. *J. Comp. Neurol.*, **93**, 53–100.

Buckner, R.L. (1996) Beyond HERA: Contributions of specific prefrontal brain areas to long-term memory retrieval. *Psychonomic Bull. Rev.*, **3**, 149–158.

Cabeza, R., McIntosh, A.R., Tulving, E., Nyberg, L. & Grady, C.L. (1997) Age-related differences in effective neural connectivity during encoding and recall. *Neuroreport*, **8**, 3479–3483.

Corbetta, M., Miezin, F.M., Dobmeyer, S., Shulman, G.L. & Petersen, S.E. (1991) Selective and devided attention during visual discriminations of shape, color and speed: Functional anatomy by positron emission tomography. *J. Neurosci.*, **11**, 2383–2402.

Fiez, J.A. (1997) Phonology, semantics and the role of the left inferior prefrontal cortex. *Human Brain Mapp.*, **5**, 79–83.

Fink, G.R., Markowitsch, H.J., Reinckemeier, M., Bruckbauer, T., Kessler, J. & Heiss, W.D. (1996) Cerebral representation of one's own past: Neural networks involved in autobiographical memory. *J. Neurosci.*, **16**, 4275–4282.

Fletcher, P.C., Frith, C.D., Grasby, P.M., Shallice, T., Frackowiak, R.S.J. & Dolan, R.J. (1995b) Brain systems for encoding and retrieval of auditory verbal memory: an in vivo study in humans. *Brain*, **118**, 401–416.

Fletcher, P.C., Shallice, T., Frith, C.D., Frackowiak, R.S.J. & Dolan, R.J. (1996) Brain activity during memory retrieval: The influence of imagery and semantic cueing. *Brain*, **119**, 1587–1596.

Friston, K.J., Ashburner, J., Frith, C.D., Poline, J.-B., Heather, J.D. & Frackowiak, R.S.J. (1995a) Spatial registration and normalization of images. *Human Brain Mapp.*, **2**, 165–189.

Friston, K.J., Frith, C.D., Liddle, P.F. & Frackowiak, R.S.J. (1993) Functional connectivity: The principal-component analysis of large (PET) data sets. *J. Cereb. Blood Flow Metab.*, **13**, 5–14.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.-B., Frith, C.D. & Frackowiak, R.S.J. (1995b) Statistical parametric mapping in functional imaging: a general linear approach. *Human Brain Mapp.*, **2**, 189–210.

Ghent, L., Mishkin, M. & Teuber, H.L. (1962) Short-term memory after frontal-lobe injury in man. *J. Comp. Physiol. Psychol.*, **55**, 705–709.

Goldman-Rakic, P.S. (1987) Circuitry of primate prefrontal cortex and regulation of behaviour by representational memory. In Mountcastle, V.B. (ed.), *Handbook of Physiology,* Section I, Vol. 5, Part 1. American Physiological Society, Bethesda, pp. 373–417. MD.

Goldman-Rakic, P.S. (1988) Topography of cognition: Parallel distributed networks in primate association cortex. *Annu. Rev. Neurosci.*, **11**, 137–156.

Goldman-Rakic, P.S., Selemon, L.D. & Schartz, M.L. (1984) Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. *J. Neurosci.*, **12**, 719–743.

Grady, C.L., McIntosh, A.R., Horwitz, B., Maisog, J.M., Ungerleider, L.G., Mentis, M.J., Pietrini, P., Scharpiro, M.B. & Haxby, J.V. (1995) Age-related reductions in human recognition memory due to impaired encoding. *Science*, **269**, 218–221.

Grasby, P.M., Frith, C.D., Friston, K.J., Bench, C., Frackowiak, R.S.J. & Dolan, R.J. (1993) Functional Mapping of Brain areas implicated in auditory-verbal memory function. *Brain*, **116**, 1–20.

Halsband, U., Krause, B.J., Schmidt, D., Herzog, H., Tellmann, L. & Müller-Gärtner, H.-W. (1998) Encoding and retrieval in declarative learning: a positron emission tomography study. *Behav. Brain Res.*, **97**, 69–78.

Herzog, H., Seitz, R.J., Tellmann, L., Rota Kops, E., Jülicher, F., Schlaug, G., Kleinschmidt, A. & Müller-Gärtner, H.-W. (1996) Quantification of regional cerebral blood flow with O-15-butanol and positron emission tomography in humans. *J. Cereb. Blood Flow Metab.*, **16**, 645–649.

Horwitz, B., McIntosh, A.R., Haxby, J.V. & Grady, C.L. (1995) Network analysis of brain cognitive function using metabolic and blood flow data. *Behav. Brain Res.*, **66**, 187–193.

Jacobson, S. & Trojanowski, J.Q. (1977) Prefrontal granular cortex of the rhesus monkey. I. Intrahemispheric cortical afferents. *Brain Res.*, **132**, 209–233.

Jöreskog, K.G. & Sörbom, D. (1989) *LISREL 7 User's Reference Guide*. Scientific Software, Inc., Mooresville, IN.

Kapur, S., Craik, F.I.M., Jones, C., Brown, G.M., Houle, S. & Tulving, E. (1995) Functional role of the prefrontal cortex in retrieval of memories: a PET study. *Neuroreport*, **6**, 1880–1884.

Kapur, N., Friston, K.J., Young, A., Frith, C.D. & Frackowiak, R.S.J. (1995) Activation of human hippocampal formation during memory for faces: a PET Study. *Cortex*, **31**, 99–108.

Köhler, S., McIntosh, A.R., Moscovitch, M. & Winocur, G. (1998) Functional Interactions between the medial temporal lobes and posterior neocortex related to episodic memory retrieval. *Cereb. Cortex*, **8**, 451–461.

Krause, B.J., Schmidt, D., Mottaghy, F.M., Taylor, J., Halsband, U., Herzog, H., Tellmann, L. & Müller-Gärtner, H.-W. (1999a) Episodic retrieval activates the precuneus irrespective of the imagery content of word pair associates: a positron emission tomography study. *Brain*, **122**, 255–263.

Krause, B.J., Schmidt, D., Mottaghy, F.M., Taylor, J., Halsband, U., Herzog, H., Tellmann, L. & Müller-Gärtner, H.-W. (1999b) Episodic retrieval activates the precuneus irrespective of the imagery content of word pair associates: a positron emission tomography study. *Brain*, **122**, 255–263.

McIntosh, A.R. & Gonzales-Lima, F. (1991) Structural modeling of functional neural pathways mapped with 2-deoxyglucose: Effects of acousic startle habituation on the auditory system. *Brain Res.*, **547**, 295–302.

McIntosh, A.R. & Gonzales-Lima, F. (1992) Structural modeling of functional visual pathways mapped with 2-deoxyglucose: Effects of patterned light and footshock. *Brain Res.*, **578**, 75–86.

McIntosh, A.R., Grady, C.L., Haxby, J.V., Ungerleider, L.G. & Horwitz, B. (1996) Changes in limbic and prefrontal interactions in a working memory task for faces. *Cereb. Cortex*, **6**, 571–584.

McIntosh, A.R., Grady, C.L., Ungerleider, L.G., Haxby, J.V., Rapoport, S.I. & Horwitz, B. (1994) Network analysis of cortical visual pathways mapped with PET. *J. Neurosci.*, **14**, 655–666.

Mesulam, M.M. (1990) Large-scale neurocognitive networks and distributed processing for attention, language and memory. *Ann. Neurol.*, **28**, 597–613.

Moscovitch, M. (1992) Memory and working-with-memory: a component process model based on modules and central systems. *J. Cognit. Neurosci.*, **4**, 257–267.

Moscovitch, M., Kapur, S., Köhler, S. & Houle, S. (1995) Distinct neural correlates of visual long-term memory for spatial location and object identity: a positron emission tomography (PET) study in humans. *Proc. Natl Acad. Sci. USA*, **92**, 3721–3725.

Mottaghy, F.M., Shah, N.J., Krause, B.J., Schmidt, D., Halsband, U., Jäncke, L. & Müller-Gärtner, H.-W. (1999) Neuronal correlates of encoding and retrieval in episodic memory during a paired word association task: a functional magnetic resonance imaging study. *Exp. Brain Res.*, (in press).

Nyberg, L., Cabeza, R. & Tulving, E. (1996) PET studies of encoding and retrieval: The HERA model. *Psychonom. Bull. Rev.*, **3**, 135–148.

Owen, A.M., Milner, B., Petrides, M. & Evans, A.C. (1996) Memory for object features versus memory for object location: a positron-emission tomography study of encoding and retrieval processes. *Proc. Natl Acad. Sci. USA*, **93**, 9212–9217.

Pandya, D.N. & Barnes, C.L. (1987) Architecture and connections of the frontal lobes. In Perecman, E. (ed.), *The Frontal Lobes Revisited.* IRBN Press, New York, pp. 41–71.

Pandya, D.N. & Kuypers, H.G.J.M. (1969) Cortico-cortical connections in the rhesus-monkey. *Brain Res.*, **13**, 13–36.

Petrides, M. (1989) Frontal lobes and memory. In *Handbook of Neuropsychology* (eds F. Bollar & J. Grafman), pp. 75–90. Elsevier, Amsterdam.

Petrides, M. (1996) Specialized systems for the processing of mnemonic information. *Philos. Trans. R Soc. Lond. B Biol. Sci.*, **1346**, 1455–1461.

Petrides, M., Alivisatos, B. & Evans, A.C. (1995) Functional activation of the human ventrolateral frontal cortex during mnemonic retrieval of verbal information. *Proc. Natl Acad. Sci. USA*, **92**, 5803–5807.

Petrides, M., Alivisatos, B., Meyer, E. & Evans, A.C. (1993) Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proc. Natl Acad. Sci. USA*, **90**, 878–882.

Petrides, M. & Pandya, D.N. (1984) Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. *J. Comp. Neurol.*, **228**, 105–116.

Pribram, H.B. & Barry, J. (1956) Further behavioural analysis of parieto-temporo-preoccipital cortex. *J. Neurophysiol.*, **19**, 99–106.

Rajah, M.N., McIntosh, A.R., Stuss, D.T. & Grady, C.L. (1997) Mediation of encoding and recognition of faces by cross-hemispheric and prefrontal interactions. *Soc. Neurosci. Abstr.*, **23**, 191.3.

Randolph, C., Braun, A.R., Goldberg, T.E. & Chase, T.N. (1996) Semantic fluency in Alzheimer's, Parkinson's and Huntington's disease: Dissociation of storage and retrieval failures. *Neuropsychology*, **7**, 82–88.

Rota Kops, E., Herzog, H., Schmid, A., Holte, S. & Feinendegen, L. (1990) Performance characteristics of an eight-ring whole body PET scanner. *J. Comp. Ass. Tomogr.*, **14**, 437–445.

Rudge, P. & Warrington, E.K. (1991) Selective impairment of memory and visual perception in splenial tumours. *Brain*, **114**, 349–360.

Salmon. E., Van der Linden, M., Collette, F., Delfiore, G., Maquet, P., Degueldre, C., Luxen, A. & Franck, G. (1996) Regional brain activity during working memory tasks. *Brain*, **119**, 1617–1625.

Schacter, D.L., Reiman, E., Uecker, A., Polster, M.R., Yung, L.S. & Cooper, L.A. (1995) Brain regions associated with retrieval of structurally coherent visual information. *Nature*, **368**, 633–635.

Schacter, D.L. & Tulving, E. (eds) (1994) *Memory Systems*. MIT press, Cambridge, MA.

Shallice, T. (ed.) (1988) *From Neuropsychology to Mental Structure.* Cambridge University Press, Cambridge, UK.

Shallice, T., Fletcher, P., Frith, C.D., Grasby, P., Frackowiak, R.S.J. & Dolan, R.J. (1994) Brain regions associated with acquisition and retrieval of verbal episodic memory. *Nature*, **368**, 633–635.

Smith, M.L. & Milner, B. (1984) Differential effects of frontal lobe lesions on cognitive estimation and spatial memory. *Neuropsychologia*, **22**, 697–705.

Squire, L.R. (1987) *Memory and Brain*. Oxford University Press, New York.

Stern, C.E., Corkin, S., Gonzales, R.G., Guimares, A.R., Baker, J.R., Jennings, P.J., Carr, C.A., Sugiura, R.M., Vedantham, V. & Rosen, B.R. (1996) The hippocampal formation participates in novel picture encoding: Evidence from functional magnetic resonance imaging. *Proc. Natl Acad. Sci. USA*, **93**, 8660–8665.

Stuss, D.T., Kaplan, E.F., Benson, D.F., Weir, W.S., Chiulli, S. & Sarazin, F.F. (1982) Evidence for the involvement of orbitofrontal cortex in memory functions: an interference effect. *J. Comp. Physiol. Psychol.*, **96**, 913–925.

Talairach, J. & Tournoux, P. (1988) *Co-Planar Stereotactic Atlas of the Human Brain: 3-Dimensional Proportional System: an Approach to Cerebral Imaging.* Thieme, Stuttgart.

Tulving, E., Kapur, S., Markowitsch, H.J., Craik, F.I.M., Habib, R. & Houle, S. (1994) Neuroanatomical correlates of retrieval in episodic memory: auditory sentence recognition. *Proc. Natl Acad. Sci. USA*, **91,** 2012–2015.

Valenstein, E., Bowers, D., Verfaellie, M., Heilman, K.M., Day, A. & Watson, R.T. (1987) Retrosplenial amnesia. *Brain*, **110**, 1631–1646.

Vandenberghe, R., Price, C., Wise, R., Josephs, O. & Frackowiak, R.S.J. (1996) Functional anatomy of a common semantic system for words and pictures. *Nature*, **383**, 254–256.

Vogt, B.A., Rosene, D.L. & Pandya, D.N. (1979) Thalamic and cortical afferents differentiate anterior from posterior cingulate cortex in the monkey. *Science*, **204**, 205–207.

Warrington, E.K. & Weiskrantz, L. (1982) Amnesia: a disconnection syndrome? *Neuropsychologia*, **20**, 233–249.

Wechsler, D. (1945) A standardized memory scale for clinical use. *J. Psychol.*, **19**, 87–95.