

# “Pray or Prey?” Dissociation of Semantic Memory Retrieval from Episodic Memory Processes Using Positron Emission Tomography and a Novel Homophone Task

A. C. H. Lee,\*† T. W. Robbins,† K. S. Graham,\* and A. M. Owen\*

\*MRC Cognition & Brain Sciences Unit, 15 Chaucer Road, Cambridge; and †Department of Experimental Psychology, University of Cambridge, Cambridge, United Kingdom

Received July 10, 2001

**One problem in studying the neural basis of semantic memory using functional neuroimaging is that it is often difficult to disentangle activation associated with semantic memory retrieval from that associated with episodic memory encoding and retrieval. To address this issue, a novel homophone task was used in which subjects were PET scanned whilst learning a series of real words (e.g., prey). In a subsequent scan, the subjects were presented with homophone pairs (e.g., prey vs pray) and were required to choose the one that had been shown previously. In two corresponding baseline tasks, the subjects were scanned whilst learning and recognizing pronounceable non-words. Thus, while all of these tasks recruited either episodic memory encoding or retrieval processes, only the homophone tasks involved semantic memory retrieval. A conjunction analysis designed to isolate activation associated with semantic memory retrieval, revealed changes in several left lateral frontal regions (BA 9/10, 9/45), the left middle temporal cortex (BA 21), and in the left inferior temporoparietal cortex (BA 39). In contrast, a conjunction analysis designed to isolate activation associated with episodic memory encoding, revealed significant changes in the left hippocampus, as well as in the frontopolar cortex (BA 10) bilaterally, the left inferior parietal cortex (BA 40), and the left superior temporal gyrus (BA 22, 28). The present results clarify and extend recent attempts to understand the neural basis of semantic memory retrieval, by actively controlling for the confounding effects of episodic memory encoding and retrieval processes.** © 2002

Elsevier Science (USA)

## INTRODUCTION

The human declarative memory system is often assumed to comprise two distinct components, semantic and episodic memory. Semantic memory is our store of general knowledge of the world, facts, concepts, objects and the meanings of words. In contrast, episodic mem-

ory refers to the conscious recollection of personal experiences from the past which are specific in time and place (Tulving, 1972, 1983). The relationship between episodic and semantic memory is highly controversial, and in particular, there is a great interest in whether these two memory systems are cognitively and neurally dissociable (Graham *et al.*, 2000).

A number of recent functional imaging studies have attempted to investigate semantic memory directly using a variety of tasks, including word generation, (generating a verb in response to a presented noun, e.g., Petersen *et al.*, 1989; Wise *et al.*, 1991, verbal fluency, e.g., Frith *et al.*, 1991, and completion of word stems, e.g., Buckner *et al.*, 1995a), semantic judgement or categorisation tests, in which subjects are instructed to make judgements about the properties (e.g., positive versus negative words) of presented stimuli (Démonet *et al.*, 1994; Price *et al.*, 1997a; Jennings *et al.*, 1998) and, semantic association tests, in which subjects are instructed to learn relationships between stimuli (e.g., between a word category and an exemplar, Fletcher *et al.*, 1995). Other studies have investigated semantic memory less directly by using episodic memory encoding tasks that place a demand on semantic memory processes (Kapur *et al.*, 1994a). For example, Kapur *et al.* (1994a) scanned subjects while they remembered visually presented real words (episodic memory encoding) either by making a semantic decision (living/non-living; semantic memory retrieval) or a perceptual decision (the presence of the letter a) about each word.

Whether semantic memory has been investigated directly or indirectly, a network of regions, predominantly in the left hemisphere, has been typically activated (Petersen *et al.*, 1989; Wise *et al.*, 1991; Démonet *et al.*, 1992, 1994; Vandenberghe *et al.*, 1996; Mummery *et al.*, 1996; Wiggs *et al.*, 1999; for review see Price, 1998). The left temporal lobe has been identified as being important to semantic processing and two regions that have been consistently implicated are the anterior inferior temporal cortex and the posterior

temporoparietal cortex. For example, Vandenberghe *et al.* (1996) used positron emission tomography (PET) to scan healthy subjects while they carried out a semantic association task based on the Pyramid and Palm Trees Test (Howard and Patterson, 1992). Semantic processing was associated with an extensive region of significant regional cerebral blood flow (rCBF) change in the left hemisphere extending from the superior occipital gyrus through the middle and inferior temporal cortex to the inferior frontal gyrus.

Although many studies of semantic memory have focused on the role of the temporal lobe, regions in the left lateral frontal cortex have also been implicated in functional neuroimaging studies (Backman *et al.*, 1997; Binder *et al.*, 1999; Buckner *et al.*, 1995a, b; Dalla Barba *et al.*, 1998; Frith *et al.*, 1991; Kapur *et al.*, 1994a, b; Lepage *et al.*, 2000; Martin *et al.*, 1995, 1996; Mummery *et al.*, 1998; Petersen *et al.*, 1989, Poldrack, 1999; Ricci *et al.*, 1999; Thompson-Schill *et al.*, 1997, 1999; Vandenberghe *et al.*, 1996; Wagner *et al.*, 1997; Wiggs *et al.*, 1999; Wise *et al.*, 1991). For example, left inferior prefrontal cortex activation has been reported when a variety of semantic retrieval tasks have been compared to various control conditions, including rest (Wise *et al.*, 1991), orthographic decision (Demb *et al.*, 1995; Kapur *et al.*, 1994a), visual decision (Vandenberghe *et al.*, 1996), meaningless symbol viewing (Petersen *et al.*, 1989), and pseudoword viewing (Petersen *et al.*, 1990). While these results suggest that the left inferior frontal cortex is involved in the retrieval of semantic memory, there are two issues that complicate this interpretation. First, a small number of functional neuroimaging tasks have failed to activate the left inferior frontal cortex during tasks that undoubtedly involve semantic memory. For example, several studies have compared semantic decisions about real words (e.g., living vs nonliving) with phonological decisions about non-words (Binder *et al.*, 2000; Démonet *et al.*, 1992, 1994; Pugh *et al.*, 1996; Shaywitz *et al.*, 1995) and have not reported left prefrontal cortex activation. Second, neuropsychological studies have suggested that, whilst left prefrontal lesions patients may be impaired in their ability to generate semantically related words, this is not due to a deficit in semantic retrieval, but rather in other processes such as word selection that are required in word generation tasks (Swick and Knight, 1996; Thompson-Schill *et al.*, 1998). Moreover, left prefrontal lesion patients have normal language comprehension, with lesions to the temporal lobe being most often associated with impairments of semantic memory (Hodges *et al.*, 1992, 1995; Saffran and Schwartz, 1994).

The present study was designed to elucidate further the role of the left prefrontal cortex and different regions within the left temporal lobe in semantic memory using a novel homophone decision task. In many previous investigations of semantic memory it has been

difficult to differentiate activation associated with semantic memory retrieval from that associated with episodic memory encoding and retrieval. Although there is evidence to suggest that episodic and semantic memory are dissociable (Graham *et al.*, 2000; Parkin, 1982; Wood *et al.*, 1982), it has been suggested that the accessing of semantic memory is closely linked to the encoding of episodic memory ( Craik and Lockhart, 1972). This link between semantic memory retrieval and episodic memory encoding is evident in typical episodic memory tasks. For example, while learning a specific stimulus, a subject invariably retrieves information about the stimulus (e.g., semantic memory retrieval) as well as remembering the context in which the stimulus was presented (episodic memory encoding).

In order to disentangle semantic memory processes *per se* from those associated with episodic memory encoding and retrieval, in this study subjects were PET scanned whilst learning a series of real nonliving words with available homophone counterparts (*Homophone encoding*, e.g., prey). In a subsequent scan, the subjects were then presented with the remembered words paired with the corresponding homophone counterparts (*Homophone retrieval*, e.g., prey vs pray) and were required to choose the one that had been presented previously. In two corresponding baseline tasks, subjects were first scanned while learning a series of pronounceable nonwords (*Verbal encoding*, e.g., sligerit) and then while recognizing learned words from pairs of similar nonwords (*Verbal retrieval*, e.g., sligerit vs seigerit). Thus, while the homophone and verbal encoding and retrieval tasks differed in terms of their episodic memory demands (e.g., the encoding tasks recruited episodic memory encoding whilst the retrieval tasks recruited episodic memory retrieval), only the two homophone tasks involved the retrieval of semantic knowledge since the subjects were explicitly instructed to encode and retrieve the words on the basis of their meanings. However, neither of the homophone tasks involved semantic encoding processing in the sense that the subjects were not required to learn any new facts or word meanings. Accordingly, it was expected that the similarities between the two homophone tasks (when compared to their corresponding baseline tasks) would reveal those regions involved in semantic memory retrieval. In contrast, the similarities between the homophone encoding and verbal encoding tasks (when compared to their corresponding retrieval tasks) would reveal regions involved in episodic memory encoding whilst the similarities between the homophone retrieval and verbal retrieval tasks (when compared to their corresponding encoding tasks) would reveal regions involved in episodic memory retrieval.

## METHODS

### *Subjects*

Eight healthy subjects were scanned in total. However, one subject's scans could not be used in the data analysis due to irreversible corruption of the data set at acquisition. Of the seven subjects who were included in the analysis, five were right-handed males and two were right handed females. The age of the subjects varied between 21 and 61 years (mean age = 40.14 years). Although the age range was broad, an analysis of subgroups revealed no systematic differences, either behaviourally or in terms of rCBF, between the four youngest subjects and the three older subjects. In addition, in a related study using the same volunteers (scanned at the same time on related memory tasks), very similar patterns of activation were observed in young and old subjects (Lee *et al.*, 2000). Accordingly, age was not considered to be an important variable and the subject group was analysed as a whole throughout.

### *Image Acquisition and Data Analysis*

Two PET scans for each experimental condition were obtained for each subject using the General Electrics Advance system. This produces 35 simultaneous image slices per scan at an intrinsic resolution of approximately  $4.0 \times 5.0 \times 4.5$  mm. For each scan, rCBF was measured using the bolus  $\text{H}_2^{15}\text{O}$  methodology. Subjects received a 20-s intravenous bolus of  $\text{H}_2^{15}\text{O}$  through a forearm cannula at a concentration of  $300 \text{ Mbq ml}^{-1}$  and a flow rate of  $10 \text{ ml min}^{-1}$  just prior to PET data acquisition. With this method, each scan provides an image of rCBF integrated over a period of 90 s from when the tracer first enters the cerebral circulation.

Twelve PET scans were performed on each subject, although only 8 of these are relevant to the present study. The scans were pre-processed individually and then combined with the other subjects' scans for collective statistical analysis using the Statistical Parametric Mapping 99 (SPM 99) packages provided by the Wellcome Department of Cognitive Neurology (London, UK). For preprocessing, the scans were (1) realigned to the first scan and then post-hoc to a created mean, (2) normalized for global CBF value and also spatially normalised to conform to the standard brain described by Talairach and Tournoux (1988) and (3) spatially smoothed using an isotropic Gaussian kernel at 16 mm. For each subject, a 3-D MRI volume ( $256 \times 256 \times 128$  pixels, 3 mm thick) was also acquired using a 0.5T system, re-sliced and spatially normalized. This was coregistered with the PET data to allow direct anatomical localisation of regions with statistically significant change between conditions.

For the statistical analysis, the global CBF value was averaged across subjects for each activation state. Blood flow changes between each condition were then

estimated for each voxel according to the general linear model, as implemented by the method of SPM. An intensity threshold set at  $P \leq 0.001$  (uncorrected for multiple comparisons) was applied for activations occurring within the lateral frontal and temporal cortices (Worsley *et al.*, 1992, 1996). This uncorrected threshold was applied since many previous functional neuroimaging studies of semantic (see Introduction) and episodic memory (for review see Cabeza and Nyberg, 2000) have reported activation in these regions. Since no predictions were made with regard to regions outside the lateral frontal and temporal lobes, a corrected intensity threshold of  $P \leq 0.05$  was applied to the rest of the brain. This threshold, based on 3-D Gaussian random field theory, predicts the likelihood of obtaining a false positive in an extended 3-D field.

### *Procedure and Tasks*

Two experimental tasks and two baseline tasks were employed in this study and we refer to these as *Homophone Encoding*, *Homophone Retrieval*, *Verbal Encoding*, and *Verbal Retrieval*, respectively. Each of these was performed twice and different sets of stimuli were used each time a particular task was performed. Each scan lasted 90 s and the subjects were required to start each of the tasks approximately 10 s before the scan began.

An encoding task was always followed directly by its retrieval counterpart but in order to minimise any confusion between stimuli, a 4-scan gap was always imposed between two scans of the same task. Furthermore, in order to eliminate any possible effects of task order, the sequence in which the tasks were administered was systematically varied across subjects. The stimuli used in all the tasks were strings of large light blue letters in the middle of a black background and were presented on a touch-sensitive screen. The screen was suspended at a distance of approximately 0.50 m above the subject and was positioned such that the subject could see and comfortably touch the screen.

The subjects were given instructions for each task and a practice condition during the 8-minute interval between scans. In each of the encoding tasks, the subjects were required to remember 15 stimuli, presented three times each to give 45 stimulus presentations in all. The stimuli were presented in a pseudo-random order within each run of 15 and were organised across runs such that identical stimuli did not occur too closely together in time. The presentation was self-paced and the subjects were required to touch each stimulus on the screen in order to move from one stimulus to the next. Prior to scanning the subjects were trained to spend approximately 2 s looking at each stimulus. If the subjects failed to follow this instruction during the scan then the stimulus would automatically disappear from the screen after 2 s. After each encod-

ing task, the subjects were explicitly instructed not to rehearse the learnt stimuli during the delay that followed. Instead, an experimenter-paced reminder of all the learnt stimuli was presented just prior to the start of the corresponding retrieval task. In each of the retrieval tasks, the subjects were presented with the stimuli from the corresponding encoding task, each paired with a similar but unfamiliar stimulus. The order of presentation was again random and different from that in the encoding tasks. The subjects were required to touch the stimulus they had seen previously and this automatically led to the next trial. Reaction time and accuracy data were collected during each of the scans.

Each of the encoding and retrieval tasks was designed to encourage the subjects to learn and recall different aspects of the stimuli presented. Thus, the verbal tasks emphasized the verbal (i.e., phonological) nature of the stimuli whilst the homophone tasks emphasised the semantic (i.e., conceptual) nature of the stimuli.

### *Experimental Tasks*

*Homophone encoding (Fig. 1.1a).* The subjects were presented with a series of 15 common words (e.g., prey) with available homophone counterparts which were of the same letter length (e.g., pray) and which varied in spelling by only one or two letters. The words were presented in lower case letters and in an identical font. Since real words were used and the verbal and visual properties of the stimuli would be of minimal use in the retrieval task, this condition was designed to emphasize the use of semantic processing mechanisms and discourage the subjects from using visually or verbally mediated strategies to encode the stimuli.

*Homophone retrieval (Fig. 1.1b).* The subjects were presented with each stimulus from the homophone encoding condition paired with their homophone counterparts, which had identical phonological properties and were visually similar but with entirely different semantic meanings. To fully discourage retrieval based on encoded visual information, the stimuli were presented in upper case letters and in a font different to that used in the encoding task. Since the two-choice stimuli differed mainly in terms of their semantic properties, the emphasis on this task was on semantic access. Table 1.1 lists all the homophone pairs used in the semantic tasks.

### *Baseline Tasks*

*Verbal encoding (Fig. 1.2a).* The subjects were presented with pronounceable nonwords (e.g., sligerit), each in lower case letters and in an identical font. Nonwords were selected which did not resemble, nor comprise, real words. Since the nonwords had visual characteristics that would be of minimal use in the

subsequent retrieval task, this condition was designed to emphasise the use of phonological mechanisms and discourage the subjects from using visually mediated strategies from encoding.

*Verbal retrieval (Fig. 1.2b).* The subjects were presented with each stimulus from the verbal encoding condition paired with unfamiliar nonwords, which were visually similar but nevertheless had distinct verbal properties (e.g., SLIGERIT vs SEIGERIT). In order to de-emphasise the visual properties of the stimuli further, the words were presented in upper case letters and in a different font to that used during the encoding condition. Since the two-choice stimuli differed mainly in terms of their verbal properties, the emphasis on this task was on verbal retrieval. Table 1.2 lists all the nonword pairs used in the control tasks.

## RESULTS

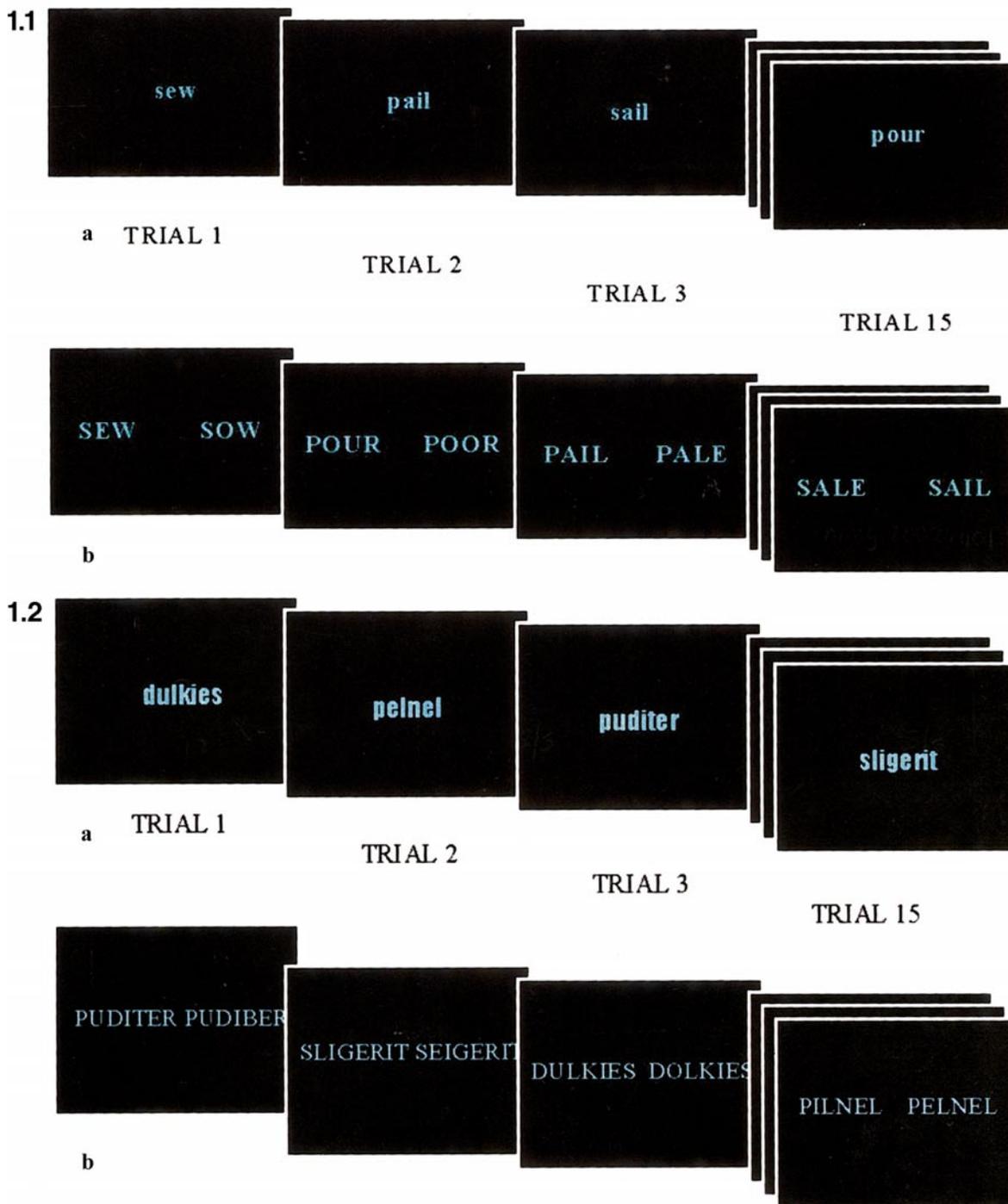
### *Performance*

The average performance on both of the retrieval tasks was above 90%, with scores on verbal retrieval being slightly more accurate (95.7% mean correct) than those for homophone retrieval (92.5% mean correct). The mean reaction times for the verbal retrieval tasks and homophone retrieval were 2.244 and 2.054 s, respectively. Two-tailed paired *t* tests indicated that the differences between the mean scores ( $t = 0.897$ ,  $P = 0.40$ ) and the mean reaction times ( $t = 1.613$ ,  $P = 0.158$ ) were not significant.

### *Blood-Flow Changes*

The statistical analysis of blood flow changes was designed to identify the cortical areas that are involved in semantic memory retrieval and episodic memory encoding and retrieval. Accordingly, a number of comparisons, defined *a priori*, were conducted between specific conditions. The results of these analyses, in terms of statistically significant differences in rCBF, are reported below and details are given in Tables 2–4, along with corresponding stereotaxic coordinates based on the brain atlas of Talairach and Tournoux (1988).

*Semantic memory retrieval.* A conjunction analysis was carried out on two direct comparisons between the two homophone tasks and their respective baselines (e.g., homophone encoding minus verbal encoding and homophone retrieval minus verbal retrieval). Conjunction analyses identify significant changes in blood flow across independent subtractions that are, in addition, not significantly different from each other (Price *et al.*, 1997b; Price and Friston, 1997). Thus, this global comparison was designed to identify significant changes in blood flow that were specific to semantic memory retrieval irrespective of episodic memory encoding or retrieval processes. Significant regions of rCBF were ob-



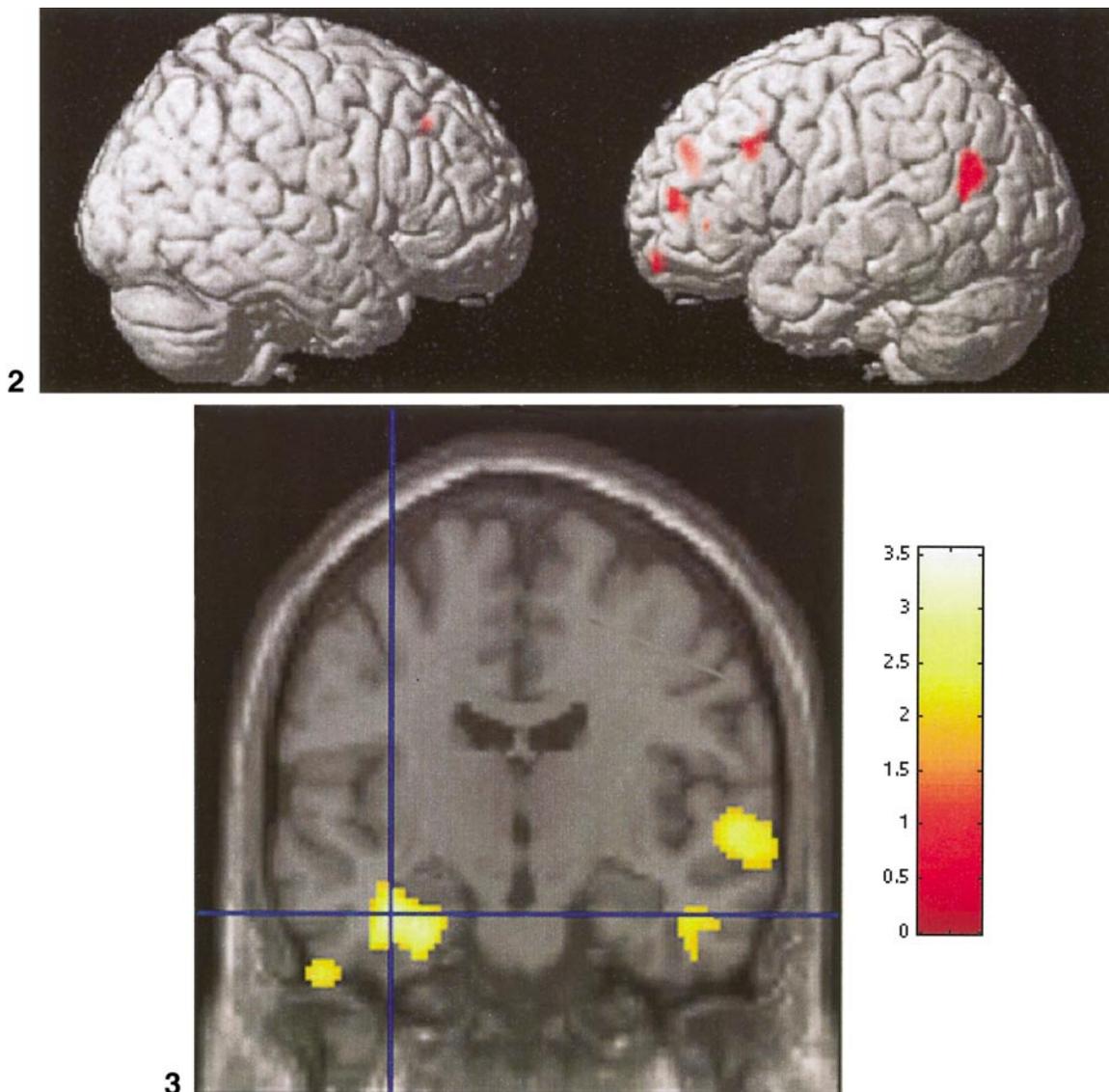
**FIG. 1.1.** Schematic representation of (a) Homophone encoding task; (b) Homophone retrieval task.

**FIG. 1.2.** Schematic representation of (a) Verbal encoding task; (b) Verbal retrieval task.

served only in the left hemisphere (see Fig. 2), in the left superior frontal cortex (BA 9/10), the left dorsolateral frontal cortex (BA 9/45), the left middle temporal cortex (BA 21), and the left inferior temporoparietal cortex (BA 37, 39).

*Episodic memory encoding.* A conjunction analysis of the subtractions Homophone Encoding minus Homo-

phone Retrieval and Verbal Encoding minus Verbal Retrieval was conducted to identify significant regions of rCBF associated with episodic memory encoding, irrespective of the type of task (e.g., homophone encoding or verbal encoding). In the left hemisphere, significant regions of rCBF change were observed in the frontopolar cortex (BA 10), the inferior parietal cortex



**FIG. 2.** Schematic diagram showing the regions of significant rCBF change associated with semantic memory retrieval.

**FIG. 3.** Schematic diagram showing the significant left hippocampal activation ( $P < 0.05$ , corrected for multiple comparisons) associated with episodic memory encoding.

(BA 40), the superior temporal cortex (BA 21, 38), and the hippocampus/parahippocampal gyrus (see Fig. 3). In the right hemisphere, significant regions of rCBF change were observed in the medial frontal cortex (BA 10), the frontopolar cortex and the superior temporal cortex (BA 22).

*Episodic memory retrieval.* A conjunction analysis of the subtractions Homophone Retrieval minus Homophone Encoding and Verbal Retrieval minus Verbal Encoding was conducted to identify significant regions of rCBF associated with episodic memory retrieval, irrespective of the type of task (e.g., homophone retrieval or verbal retrieval). Significant regions of rCBF change were observed in the left prestriate cortex (BA

18) and the right striate cortex (BA 17). No significant rCBF changes were observed more anteriorly.

## DISCUSSION

Given that semantic memory processes are invariably linked with episodic memory processes ( Craik and Lockhart, 1972), the current study adopted a novel experimental paradigm to isolate the neural correlates of semantic memory retrieval. By using two pairs of episodic memory encoding and retrieval tasks, one that did place a demand on semantic memory retrieval (homophone encoding and retrieval) and one that did not (verbal encoding and retrieval), it was possible to use a

**TABLE 1.1**

Homophone Pairs Used (15 Pairs for Each Homophone Encoding-Retrieval Set)

Homophone learnt during encoding	Distracter homophone during retrieval
Course	Coarse
Real	Reel
Soar	Sore
Beach	Beech
Stair	Stare
Cheap	Cheep
Stake	Steak
Peel	Peal
Ware	Wear
Pare	Pair
Bail	Bale
Pane	Pain
Prey	Pray
Peak	Peek
Steal	Steel
Leak	Leek
Bare	Bear
Hale	Hail
Mail	Male
Weak	Week
Sale	Sail
Hair	Hare
Fare	Fair
Dye	Die
Pail	Pale
Lone	Loan
Sow	Sew
Mane	Main
Brake	Break
Pour	Pore

series of conjunction analyses to dissociate regions of activation associated with semantic memory retrieval from that of episodic memory encoding and episodic memory retrieval.

### *Semantic Memory Retrieval*

Overall, the semantic memory retrieval condition was associated with significant activation in left hemisphere regions, including the left lateral frontal cortex (BA 9/10 and 9/45), the left middle temporal cortex (BA 21), and the left interior temporoparietal cortex (BA 39). Although significant left dorsolateral frontal activation has been observed previously when semantic tasks are compared with phonological tasks (e.g., Binder *et al.*, 1999; Poldrack *et al.*, 1999), this is certainly not always the case (e.g., Binder *et al.*, 2000; Démonet *et al.*, 1992, 1994; Pugh *et al.*, 1996; Shaywitz *et al.*, 1995). This broad literature, combined with the fact that the activation observed in the current study was relatively weak, suggests that the left dorsolateral frontal cortex is not involved in semantic memory *per se*. This issue has been discussed previously by Price *et al.* (1997a) who suggest that the left lateral prefrontal

cortex may play a rather more general role in memory; for example, in the initiation of strategic processes to facilitate task performance. Because such processes are likely to be equally relevant to semantic and non-semantic tasks, comparisons between phonological and semantic memory conditions may or may not lead to left lateral frontal activity, depending on the specific tasks used. In the current study, therefore, the internal search for the stored representations relating to the real words used in the homophone task may place a more significant load on strategic search processes than the corresponding search in the pseudo-words task, possibly due to increased interference generated by the use of familiar word pairs.

Significant activity in more anterior and superior regions of the frontal cortex (BA9/10) has been observed in some previous studies involving semantic memory processes (e.g., Buckner *et al.*, 1995b; Martin *et al.*, 1995; Wagner *et al.*, 1998a), although again this is not always the case (e.g., Binder *et al.*, 1999, 2000). Moreover, this region has also been activated in various types of ostensibly nonsemantic retrieval studies, including episodic memory retrieval (Kohler *et al.*,

**TABLE 1.2**

Nonword Pairs Used (15 Pairs for Each Verbal Encoding-Retrieval Set)

Nonword learned during encoding	Distracter nonword during retrieval
Fithering	Eithering
Dulkies	Dolkies
Sligerit	Seigerit
Pelnel	Pilnel
Puditer	Pudiber
Sladding	Slatting
Ballop	Bollop
Hedawakix	Hebawavix
Rubid	Pubid
Juperoly	Juseboly
Commerine	Connerine
Volderi	Volbeti
Nertez	Merdez
Hampent	Hempant
Rejooker	Retooker
Chark	Chirk
Tuncher	Tunkner
Tulmin	Tilmun
Tactioner	Tectioner
Atwol	Atwtol
Tilkey	Tilpey
Jayster	Joyster
Barrock	Borrack
Deeve	Deive
Silner	Selnir
Narken	Nerkan
Fennerizer	Femmerizer
Doster	Distor
Trinketine	Trinkeline
Glottering	Glottierung

TABLE 2

## Stereotaxic Coordinates of Activation Associated with Semantic Memory Retrieval

Conjunction analysis of (homophone encoding minus verbal encoding) and (homophone retrieval minus verbal retrieval)					
Region	BA	Stereotaxic coordinates			Z score
		x	y	z	
Left Hemisphere					
Superior frontal cortex	9/10	-20	46	20	4.70 <sup>a</sup>
Dorsolateral frontal cortex	9/45	-44	21	23	3.62
Middle temporal cortex	21	-59	1	-25	3.26
Middle temporal cortex	21	-57	-31	-7	3.27
Inferior temporoparietal cortex	39	-42	-65	25	4.84 <sup>a</sup>

<sup>a</sup> Survives threshold of  $P < 0.05$  corrected for multiple comparisons.

1998; Maguire *et al.*, 1998), and motor memory retrieval (Jenkins *et al.*, 1994). Again, therefore, it appears unlikely that the left superior frontal cortex is specifically concerned with word meaning, but rather, may play a more general role in memory retrieval that is applicable across several different cognitive domains.

Activation in the left middle temporal cortex (BA 21) has been associated with tasks involving pictures (Martin *et al.*, 1995, 1996; Vandenberghe *et al.*, 1996), words (e.g., Wise *et al.*, 1991; Démonet *et al.*, 1994), and faces (Gorno-Tempini *et al.*, 1998), suggesting that this area is involved in semantic processing across multiple domains. The fact that, in the current study, activation was observed in this area during semantic memory retrieval for words supports this general suggestion, although further neuroimaging studies will be required before more specific conclusions can be drawn.

Previous studies of semantic memory have suggested that the left posterior basal temporal lobe (BA 37) may be crucial for processes involved in the naming of visual (Moore and Price, 1997; Price and Friston, 1997), tactile (Büchel *et al.*, 1998), and auditory stimuli (Warburton *et al.*, 1996). For example, in one PET study, Moore and Price (1997) observed a region of common activity in the left posterior basal temporal lobe (BA 37) during two tasks that required naming visually presented words and naming pictures of everyday objects. The left posterior temporoparietal activation (BA 39) we observed here is located more dorsally to that identified by other studies. Furthermore, given that the homophone tasks utilised here were not designed to recruit naming processes, it is unlikely that this more dorsal BA 39 region subserves a similar name retrieval role to that of the left basal temporal lobe (BA 37). On the basis of this study alone, it is

TABLE 3

## Stereotaxic Coordinates of Activation Associated with Episodic Memory Encoding

Conjunction analysis of (homophone encoding minus homophone retrieval) and (verbal encoding minus verbal retrieval)					
Region	BA	Stereotaxic coordinates			Z score
		x	y	z	
Left hemisphere					
Frontopolar cortex	10	-12	64	12	5.08 <sup>a</sup>
Superior temporal cortex	38	-44	16	-24	3.76
Middle temporal cortex	21	-56	-6	-12	3.41
Hippocampus/Parahippocampal gyrus		-28	-7	-23	5.15 <sup>a</sup>
Hippocampus/Parahippocampal gyrus		-36	-13	-20	4.64 <sup>a</sup>
Middle temporal cortex	21	-51	-32	-10	3.61
Inferior parietal cortex	40	-57	-34	22	5.12 <sup>a</sup>
Right hemisphere					
Frontopolar cortex	10	8	68	-3	4.20
Medial frontal cortex	10	10	40	-10	5.13 <sup>a</sup>
Superior temporal cortex	22	67	-4	2	4.29

<sup>a</sup> Survives threshold of  $P < 0.05$  corrected for multiple comparisons.

TABLE 4

## Stereotaxic Coordinates of Activation Associated with Episodic Memory Retrieval

Conjunction analysis of (homophone retrieval minus homophone encoding) and (verbal retrieval minus verbal encoding)					
Region	BA	Stereotaxic coordinates			Z score
		x	y	z	
Left hemisphere					
Prestriate cortex	18	-18	-74	6	Infinite <sup>a</sup>
Right hemisphere					
Striate cortex	17	2	-87	6	Infinite <sup>a</sup>

<sup>a</sup> Survives threshold of  $P < 0.05$  corrected for multiple comparisons.

difficult to draw precise conclusions, although it seems likely that this area may mediate processes within semantic memory that are recruited during the retrieval of word meanings.

#### Episodic Memory Encoding

The medial temporal lobe structures have long been associated with various memory processes. In particular, the hippocampus and the parahippocampal gyrus have been implicated in long-term memory learning and recall, including spatial memory in rats (Morris *et al.*, 1982; Eichenbaum *et al.*, 1990), nonhuman primates (Parkinson *et al.*, 1988; Angeli *et al.*, 1993), and humans (Maguire *et al.*, 1996; Owen *et al.*, 1996; Aguirre and D'Esposito, 1997) as well as autobiographical memory in humans (Scoville and Milner, 1957; Zola-Morgan *et al.*, 1986; Vargha-Khadem *et al.*, 1997; Maguire and Mummery, 1999). The fact that the left hippocampus/parahippocampal gyri was activated during episodic memory encoding in the present study (see Fig. 3) is broadly consistent with this view and agrees more specifically with previous functional neuroimaging studies that have reported medial temporal lobe activation during new learning of word stimuli (Kelley *et al.*, 1998; Kopelman *et al.*, 1998; Fernandez *et al.*, 1998, Wagner *et al.*, 1998a).

More anteriorly, episodic memory encoding was found to be associated with significant regions of activation in the frontopolar cortex bilaterally (BA 10), and the right anterior medial frontal cortex (BA 10). While previous studies of episodic memory encoding have also activated these regions (Grady *et al.*, 1998; Wagner *et al.*, 1998b; McDermott *et al.*, 1999a; Lee *et al.*, 2000), their precise role is unclear. It has been suggested that the frontopolar cortex may subserve a monitoring process during episodic memory retrieval, during which information retrieved from memory is evaluated (Rugg *et al.*, 1998; Allan *et al.*, 2000). Extending this to the encoding process, it may be that the frontopolar cortex

is more generally involved in the monitoring of memoranda, including new, incoming information that is to be remembered.

The fact that we observed bilateral frontal cortex activation provides further evidence against the suggestion that the left prefrontal cortex is predominantly involved in episodic memory encoding whilst the right prefrontal cortex is predominantly involved in episodic memory retrieval (Tulving *et al.*, 1994; Nyberg *et al.*, 1996). Rather, current results lend further support to the alternative suggestion that similar regions of the prefrontal cortex are involved in episodic memory encoding and retrieval when all factors relating to the type of stimulus material (i.e., modality), are appropriately controlled (Kelley *et al.*, 1998; Wagner *et al.*, 1998b; McDermott *et al.*, 1999b; Lee *et al.*, 2000).

#### Episodic Memory Retrieval

In the present study, the episodic memory retrieval conditions produced significant regions of activation only in visual cortical areas (BA 17 and 18) in both hemispheres. This observation is in stark contrast to the plethora of neuroimaging studies that have consistently reported lateral frontal lobe activations during episodic memory retrieval (for review see Nyberg and Cabeza, 2000). A small number of studies have also failed to observe prefrontal cortical activation during episodic memory retrieval (Kapur *et al.*, 1995; Schacter *et al.*, 1996; Klingberg and Roland, 1998) and a likely explanation seems to be that relatively little activation is observed in this area when the retrieval task employed is relatively automatic. For example, Klingberg and Roland (1998) observed no prefrontal cortex activation while subjects were carrying out a pre-trained paired associate task at a high level of performance (98% accuracy). In contrast, in studies where prefrontal cortex activation has been observed during memory retrieval, performance levels have tended to be rather lower than this, possibly reflecting the less automated nature of the particular tasks employed. A similar explanation may account for the results of the present study since retrieval performance was high (i.e., over 92%), in both homophone and verbal retrieval tasks. Furthermore, since each retrieval task comprised 15 pairs of stimuli presented three times each, it is likely that the subjects' choices became increasingly automated during the course of each scan, regardless of whether they were accurate or not. Since rCBF during the retrieval conditions was assessed relative to the encoding conditions, which were undoubtedly less automated, it is likely that prefrontal activation was effectively subtracted out during the retrieval tasks.

The highly significant rCBF changes observed in the striate and prestriate cortices in association with episodic memory retrieval are likely due to the fact that during the retrieval tasks, the subjects were presented

with pairs of stimuli, whereas single stimuli were presented during the encoding tasks. In order to make a correct choice between these two options, the subjects presumably alternated their gaze between the two stimuli, producing more eye movements in the retrieval conditions than in the encoding conditions. Eye movements and associated increases in visual stimulation are known to increase rCBF in the visual cortex (Cheng *et al.*, 1995; Paus *et al.*, 1995). It is possible that some of the activation differences observed in this study may have arisen as a result difference in the visual properties of the stimuli used in the encoding and retrieval conditions. Although such an explanation seems very unlikely for activation peaks outside of visual areas, this possibility was addressed explicitly in a follow up study using fMRI (Lee *et al.*, in submission, 1999). In that study single stimuli with formally identical visual properties were presented during encoding and retrieval and a very similar pattern of results was found to that presented in the current study. However, any difference between the visual properties of the encoding and retrieval conditions is not relevant to the semantic memory analysis, which is the primary focus of this paper, since the two contrasts that comprised the conjunction analyses involved either two visually matched encoding conditions or two visually matched retrieval conditions (see Table 2). Thus, regions of activation associated with visual stimulation will have been effectively subtracted out leaving those regions corresponding to semantic memory retrieval.

### Conclusion

The present study used a novel homophone task to successfully dissociate semantic memory retrieval from episodic memory encoding and retrieval processes. In summary, semantic memory retrieval was associated with regions of activation in the left lateral frontal cortex and the left posterior temporoparietal cortex. In contrast, episodic memory encoding was associated with left hippocampal and bilateral frontopolar activation in line with previous studies.

### ACKNOWLEDGMENTS

We thank past and present staff of the Wolfson Brain Imaging Centre, in particular Steve Downey, Rebecca Lawrence, Iona Kendall, Emma Williams, Federico Turkheimer, Clare Galton, and Parwanjit Minhas, for their assistance with the present study. We thank Matthew Brett for statistical advice. We are also grateful to the volunteers who took part as well as the Wellcome Department of Cognitive Neurology, London, UK, for providing the SPM software. This work was supported by a BBSRC studentship to A.L. and Programme grant from the Wellcome Trust (T.W.R.) and completed within an MRC Co-operative Group in Brain, Behaviour and Neuropsychiatry.

### REFERENCES

- Aguirre, G. K., and D'Esposito, M. 1997. Environmental knowledge is subserved by separable dorsal/ventral neural areas. *J. Neurosci.* **17**: 2512–2518.
- Allan, K., Dolan, R. J., Fletcher, P. C., and Rugg, M. D. 2000. The role of the right anterior prefrontal cortex in episodic retrieval. *Neuroimage* **11**: 217–227.
- Angeli, S. J., Murray, E. A., and Mishkin, M. 1993. Hippocampotomized monkeys can remember one place but not two. *Neuropsychologia* **31**: 1021–1030.
- Backman, L., Almkvist, O., Andersson, J., Nordberg, A., Winblad, B., Reineck, R., and Langstrom, B. 1997. Brain activation in young and older adults during implicit and explicit retrieval. *J. Cogn. Neurosci.* **9**: 378–391.
- Binder, J. R., Frost, J. A., Hammeke, T. A., Bellgowan, P. S. F., Rao, S. M., and Cox, R. W. 1999. Conceptual processing during the conscious resting state: A functional MRI study. *J. Cogn. Neurosci.* **11**: 80–93.
- Binder, J. R., Frost, J. A., Hammeke, T. A., Bellgowan, P. S. F., Springer, J. A., Kaufman, J. N., and Possing, E. T. 2000. Human temporal lobe activation by speech and nonspeech sounds. *Cereb. Cortex* **10**: 512–528.
- Buckner, R. L., Petersen, S. E., Ojemann, J. G., Miezin, F. M., Squire, L. R., and Raichle, M. E. 1995a. Functional anatomical studies of explicit and implicit memory retrieval tasks. *J. Neurosci.* **15**: 12–29.
- Buckner, R. L., Raichle, M. E., Petersen, S. E. 1995b. Dissociation of human prefrontal cortical areas across different speech production tasks and gender groups. *J. Neurophysiol.* **74**: 2163–2173.
- Büchel, C., Price, C. J., and Friston, K. J. 1998. A multimodal language region in the ventral visual pathway. *Nature* **394**: 274–277.
- Cabeza, R., and Nyberg, L. 2000. Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J. Cogn. Neurosci.* **12**: 1–47.
- Cheng, K., Fujita, H., Kanno, I., Miura, S., and Tanaka, K. (1995). Human cortical regions activated by wide-field visual motion: an H2(15)O PET study. *J. Neurophysiol.* **74**: 413–427.
- Craik, F. I. M., and Lockhart, R. S. 1972. Levels of processing: A framework for memory research. *J. Verbal Learn. Verbal Behav.* **11**: 671–684.
- Dalla Barba, G., Parlato, V., Jobert, A., Samson, Y., and Pappata, S. 1998. Cortical networks implicated in semantic and episodic memory: Common or unique? *Cortex* **34**: 547–561.
- Demb, J. B., Desmond, J. E., Wagner, A. D., Vaidya, C. J., Glover, G. H., and Gabrieli, J. D. E. 1995. Semantic encoding and retrieval in the left inferior prefrontal cortex: A functional MRI study of task difficulty and process specificity. *J. Neurosci.* **15**: 5870–5878.
- Démonet, J. F., Chollet, F., Ramsay, S., Cardebat, D., Nespoulous, J. L., Wise, R., Rascol, A., and Frackowiak, R. 1992. The anatomy of phonological and semantic processing in normal subjects. *Brain* **115**: 1753–1768.
- Démonet, J. F., Price, C., Wise, R., and Frackowiak, R. S. 1994. A PET study of cognitive strategies in normal subjects during language tasks. Influence of phonetic ambiguity and sequence processing on phoneme monitoring. *Brain* **117**: 671–682.
- Eichenbaum, H., Stewart, C., Morris, R. G. 1990. Hippocampal representation in place learning. *J. Neurosci.* **10**: 3531–42.
- Fernandez, G., Weyerts, H., Schrader-Boische, M., Tendolkar, I., Smid, H. G., Tempelmann, C., Hinrichs, H., Scheich, H., Elger, C. E., Mangum, G. R., and Heinze, H.-J. 1998. Successful verbal encoding into episodic memory engages the posterior hippocampus: A parametrically analyzed functional magnetic resonance imaging study. *J. Neurosci.* **18**: 1841–1847.

- Fletcher, P., Frith, C., Grasby, P., Shallice, T., Frackowiak, R. S. J., and Dolan, R. J. 1995. Brain systems for encoding and retrieval of auditory-verbal memory: An *in vivo* study in humans. *Brain* **118**: 401–416.
- Frith, C. D., Friston, K. J., Liddle, P. F., and Frackowiak, R. S. 1991. A PET study of word finding. *Neuropsychologia* **29**: 1137–1148.
- Gorno-Tempini, M. L., Price, C. J., Josephs, O., Vandenberghe, R., Cappa, S. F., Kapur, N., and Frackowiak, R. S. 1998. The neural systems sustaining face and proper-name processing. *Brain* **121**: 2103–2118.
- Grady, C. L., McIntosh, A. R., Rajah, M. N., and Craik, F. I. M. 1998. Neural correlates of the episodic encoding of pictures and words. *Proc. Nat. Acad. Sci. USA* **95**: 2703–2708.
- Graham, K. S., Simons, J. S., Pratt, K. H., Patterson, K., & Hodges, J. R. 2000. Insights from semantic dementia on the relationship between episodic and semantic memory. *Neuropsychologia* **38**: 313–324.
- Hodges, J. R., Patterson, K., Oxbury, S., and Funnell, E. 1992. Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. *Brain* **115**: 1783–1806.
- Hodges, J. R., Graham, N., and Patterson, K. 1995. Charting the progression in semantic dementia: Implications for the organisation of semantic memory. *Memory* **3**: 463–495.
- Howard, D., and Patterson, K. 1992. *Pyramids and Palmtree: A Test of Semantic Access from Words and Pictures*. Thames Valley Test Co., Bury St. Edmunds, Suffolk, UK.
- Jenkins, I. H., Brooks, D. J., Nixon, P. D., and Frackowiak, R. S. J. 1994. Motor sequence learning: A study with positron emission tomography. *J. Neurosci.* **14**: 3775–3790.
- Jennings, J. M., McIntosh, A. R., and Kapur, S. 1998. Mapping neural interactivity onto regional activity: An analysis of semantic processing and response mode interactions. *Neuroimage* **7**: 244–254.
- Kapur, S., Craik, F. I. M., Tulving, E., Wilson, A. A., Houle, S., and Brown, G. M. 1994a. Neuroanatomical correlates of encoding in episodic memory: Levels of processing effect. *Proc. Nat. Acad. Sci. USA* **91**: 2008–2011.
- Kapur, S., Rose, R., Liddle, P. F., Zipursky, R. B., Brown, G. M., Stuss, D., Houle, S., and Tulving, E. 1994b. The role of left prefrontal cortex in verbal processing: Semantic processing or willed action? *Neuroreport* **5**: 2193–2196.
- Kapur, N., Craik, F. I. M., Jones, C., Brown, G. M., Houle, S., and Tulving, E. 1995. Activation of human hippocampal formation during memory for faces: A PET study. *Neuroreport* **6**: 1880–1884.
- Kelley, W. M., Miezin, F. M., McDermott, K. B., Buckner, R. L., Raichle, M. E., Cohen, N. J., Ollinger, J. M., Akbudak, E., Conturo, T. E., Snyder, A. Z., and Petersen, S. E. 1998. Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and non-verbal memory encoding. *Neuron* **20**: 927–936.
- Klingberg, T., and Roland, P. 1998. Right prefrontal activation during encoding, but not during retrieval, in a non-verbal paired-associates task. *Cereb. Cortex* **8**: 73–79.
- Kohler, S., Moscovitch, M., Wincour, G., Houle, S., & McIntosh, A. R. 1998. Networks of domain-specific and general regions involved in episodic memory for spatial location and object identity. *Neuropsychologia* **36**: 129–142.
- Kopelman, M. D., Stevens, T. G., Foli, S., and Grasby, P. 1998. PET activation of the medial temporal lobe in learning. *Brain* **121**: 875–887.
- Lee, A. C. H., Robbins, T. W., Pickard, J. D., and Owen, A. M. 1999. Episodic memory encoding and retrieval: A combined PET and fMRI study. *Soc. Neurosci. Abstracts* **25**: 647.
- Lee, A. C. H., Robbins, T. W., Pickard, J. D., and Owen, A. M. 2000. Asymmetric frontal activation during episodic memory: The effects of stimulus type on encoding and retrieval. *Neuropsychologia* **38**: 677–692.
- Lee, A. C. H., Robbins, T. W., Smith, S., Calvert, G. A., Tracey, I., Matthews, P., and Owen, A. M. Evidence for asymmetric frontal lobe involvement in episodic memory from functional magnetic resonance imaging and patients with unilateral frontal lobe excisions. *Neuropsychologia*, submitted.
- Lepage, M., Habib, R., Cormier, H., Houle, S., and McIntosh, A. R. 2000a. Neural correlates of semantic associative encoding in episodic memory. *Cogn. Brain Res.* **9**: 271–280.
- Maguire, E. A., Frackowiak, R. S., and Frith, C. D. 1996. Learning to find your way: A role for the human hippocampal formation. *Proc. R. Soc. Lond.* **B263**: 1745–1750.
- Maguire, E. A., Burgess, N., Donnett, J. G., Frackowiak, R. S., Frith, C. D., and O'Keefe, J. 1998. Knowing where and getting there: a human navigation network. *Science* **280**: 921–924.
- Maguire, E. A., and Mummery, C. J. 1999. Differential modulation of a common memory retrieval network revealed by positron emission tomography. *Hippocampus* **9**: 54–61.
- Martin, A., Haxby, J. V., Lalonde, F. M., Wiggs, C. L., and Ungerleider, L. G. 1995. Discrete cortical regions associated with knowledge of color and knowledge of action. *Science* **270**: 102–105.
- Martin, A., Wiggs, C. L., Ungerleider, L. G., and Haxby, J. V. 1996. Neural correlates of category-specific knowledge. *Nature* **379**: 649–652.
- McDermott, K. B., Ojemann, J. G., Petersen, S. E., Ollinger, J. M., Snyder, A. Z., Akbudak, E., Conturo, T. E., and Raichle, M. E. 1999a. Direct comparison of episodic encoding and retrieval of words: An event-related fMRI study. *Memory* **7**: 661–678.
- McDermott, K. B., Buckner, R. L., Petersen, S. E., Kelley, W. M., and Sanders, A. L. 1999b. Set- and code-specific activation in the frontal cortex: An fMRI study of encoding and retrieval of faces and words. *J. Cogn. Neurosci.* **11**: 631–640.
- Moore, C. J., and Price, C. J. 1999. Three distinct ventral occipito-temporal regions for reading and object naming. *Neuroimage* **10**: 181–192.
- Morris, R. G., Garrud, P., Rawlins, J. N., and O'Keefe, J. 1982. Place navigation impaired in rats with hippocampal lesions. *Nature* **297**: 681–3.
- Mummery, C. J., Patterson, K., Hodges, J. R., and Wise, R. J. 1996. Generating 'tiger' as an animal name or a word beginning with T: Differences in brain activation. *Proc. R. Soc. Lond. Series B* **263**: 989–995.
- Mummery, C. J., Patterson, K., Hodges, J. R., and Price, C. J. 1998. Functional neuroanatomy of the semantic system: Divisible by what? *J. Cogn. Neurosci.* **10**: 766–777.
- Nyberg, L., Cabeza, R., and Tulving, E. 1996. PET studies of encoding and retrieval: The HERA model. *Psychonomic Bull. Rev.* **3**: 135–148.
- Owen, A. M., Evans, A. C., and Petrides, M. 1996. A specific role for the right-parahippocampal gyrus in the retrieval of object location. *J. Cogn. Neurosci.* **8**: 588–602.
- Parkin, A. J. 1982. Residual learning capability in organic amnesia. *Cortex* **18**: 417–440.
- Parkinson, J. K., Murray, E. A., and Mishkin, M. 1988. A selective mnemonic role for the hippocampus in monkeys: Memory for the location of objects. *J. Neurosci.* **8**: 4159–4167.
- Paus, T., Marrett S., Worsley, K. J., and Evans, A. C. 1995. Extraretinal modulation of cerebral blood flow in the human visual cortex: Implications for saccadic suppression. *J. Neurophysiol.* **74**: 2179–2183.
- Petersen, S. E., Fox, P. T., Posner, M. L., Mintun, M., and Raichle, M. E. 1989. Positron emission tomographic studies of the processing of single words. *J. Cogn. Neurosci.* **1**: 153–170.

- Petersen, S. E., Fox, P. T., Snyder, A. Z., and Raichle, M. E. 1990. Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli. *Science* **249**: 1041–1044.
- Poldrack, R. A., Wagner, A. D., Prull, M. W., Desmond, J. E., Glover, G. H., and Gabrieli, J. D. E. 1999. Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage* **10**: 15–35.
- Price, C. J., and Friston, K. J. 1997. Cognitive conjunction: A new approach to brain activation experiments. *Neuroimage* **5**: 261–270.
- Price, C. J., Moore, C. J., Humphreys, G. W., and Wise, R. J. S. 1997a. Segregating semantic from phonological processes during reading. *J. Cogn. Neurosci.* **9**: 727–733.
- Price, C. J., Moore, C. J. and Friston K. J. 1997b. Subtractions, conjunctions and interactions in experimental design of activation studies. *Hum. Brain Mapp.* **5**: 264–272.
- Price, C. J. 1998. The functional anatomy of word comprehension and production. *Trends Cogn. Sci.* **2**: 281–288.
- Pugh, K. R., Shaywitz, B. A., Shaywitz, S. E., Constable, R. T., Skudlarski, P., Fulbright, R. K., Bronen, R. A., Shankweiler, D. P., Katz, L., Fletcher, J. M., and Gore, J. C. 1996. Cerebral organization of component processes in reading. *Brain* **119**: 1221–1238.
- Ricci, P. T., Zekowicz, B. J., Nebes, R. D., Meltzer, C. C., Mintun, M. A., and Becker, J. T. 1999. Functional neuroanatomy of semantic memory: Recognition of semantic associations. *Neuroimage* **9**: 88–96.
- Rugg, M. D., Fletcher, P. C., Allan, K., Frith, C. D., Frackowiak, R. S. J., and Dolan, R. J. 1998. Neural correlates of memory retrieval during recognition memory and cued recall. *Neuroimage* **8**: 262–273.
- Saffran, E. M., and Schwartz, M. F. 1994. Of cabbages and things: Semantic memory from a neuropsychological perspective: A tutorial review. In *Attention and Performance Vol. XV: Conscious and Nonconscious Information Processing* (C. Umiltà and M. Moscovitch, Eds.), pp. 507–534. MIT Press, Cambridge, MA.
- Schacter, D. L., Reiman, E., Uecker, A., Polster, M. R., Yung, L. S., and Cooper, L. A. 1995. Brain regions associated with retrieval of structurally coherent visual information. *Nature* **376**: 587–590.
- Scoville, W. B., and Milner, B. 1957. Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psych.* **20**: 11–21.
- Shaywitz, B. A., Shaywitz, S. E., Pugh, K. R., Constable, R. T., Skudlarski, P., Fulbright, R. K., Bronen R. A., Fletcher, J. M., Shankweiler D. P., Katz L., *et al.* 1995. Sex differences in the functional organization of the brain for language. *Nature* **373**: 607–609.
- Swick, R., and Knight, R. T. 1996. Is prefrontal cortex involved in cued recall? A neuropsychological test of PET findings. *Neuropsychologia* **34**: 1937–1841.
- Talairach, J., and Tournoux, P. 1988. *Co-planar Stereotaxic Atlas of the Human Brain*. Thieme Medical Publishers, New York.
- Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., and Farah, M. J. 1997. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. *Proc. Nat. Acad. Sci. USA* **94**: 14792–19797.
- Thompson-Schill, S. L., Swick, D., Farah, M. J., D'Esposito, M., Kan, I. P., and Knight, R. T. 1998. Verb generation in patients with focal frontal lesions: A neuropsychological test of neuroimaging findings. *Proc. Nat. Acad. Sci. USA* **95**: 15855–15860.
- Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., and Farah, M. J. 1999. Effects of repetition and competition on the activity in left prefrontal cortex during word generation. *Neuron* **23**: 513–522.
- Tulving, E. (1972). Episodic and semantic memory. In *Organisation of Memory* (E. T. W. Donaldson, Ed), pp. 381–403. Academic Press, New York.
- Tulving, E. 1983. *Elements of Episodic Memory*. Oxford Univ. Press, New York.
- Tulving, E., Kapur, S., Craik, F. I. M., Moscovitch, M., and Houle, S. 1994. Hemispheric encoding/retrieval asymmetry in episodic memory: Positron emission tomography findings. *Proc. Nat. Acad. Sci. USA* **91**: 2016–2020.
- Vargha-Khadem, F., Gadian, D. G., Watkins, K. E., Connelly, A., van Paesschen, W., and Mishkin, M. 1997. Differential effects of early hippocampal pathology on episodic and semantic memory. *Science* **277**: 376–380.
- Vandenberghe, R., Price, C., Wise, R., Josephs, O., and Frackowiak, R. S. 1996. Functional anatomy of a common semantic system for words and pictures. *Nature* **383**: 254–256.
- Warburton, E., Wise, R. J. S., Price, C. J., Weiller, C., Hadar, U., Ramsay, S., and Frackowiak, R. S. J. 1996. Studies with positron emission tomography of noun and verb retrieval by normal subjects. *Brain* **119**: 159–179.
- Wagner, A. D., Desmond, J. E., Demb, J. B., Glover, G. H., and Gabrieli, J. D. E. 1997. Semantic repetition priming for verbal and pictorial knowledge: A functional MRI study of left inferior prefrontal cortex. *J. Cogn. Neurosci.* **9**: 714–726.
- Wagner, A. D., Poldrack, R. A., Eldridge, L. L., Desmond, J. E., Glover, G. H., and Gabrieli, J. D. 1998a. Material-specific lateralization of prefrontal activation during episodic encoding and retrieval. *Neuroreport* **1219**: 3711–3717.
- Wagner, A. D., Schacter, D. L., Rotte, M., Koustaal, W., Maril, A., Dale, A. M., Rosen, B. R., and Buckner, R. L. 1998b. Building memories: Remembering and forgetting of verbal experiences as predicted by brain activity. *Science* **281**: 1188–1191.
- Wiggs, C. L., Weisberg, J., and Martin, A. 1999. Neural correlates of semantic and episodic memory retrieval. *Neuropsychologia* **37**: 103–118.
- Wise, R., Chollet, F., Hadar, U., Friston, K., Hoffner, E., and Frackowiak, R. 1991. Distribution of cortical neural networks involved in word comprehension and word retrieval. *Brain* **114**: 1803–1817.
- Wood, F., Ebert, V., and Kinsbourne, M. 1982. The episodic-semantic memory distinction in memory and amnesia: Clinical and experimental observations. In *Human Memory and Amnesia* (L. S. Cermak, Ed.), pp. 167–194. Erlbaum, Hillsdale, NJ.
- Worsley, K. J., Evans, A. C., Marrett, S., and Neelin, P. 1992. Determining the number of statistically significant areas of activation in subtracted activation studies from PET. *J. Cereb. Blood Flow Metab.* **12**: 900–918.
- Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Friston, K. J., and Evans, A. C. 1996. A unified statistical approach for determining significant signals in images of cerebral activation. *Hum. Brain Mapp.* **4**: 58–73.
- Zola-Morgan, S., Squire, L. R., & Amaral, D. G. 1986. Human amnesia and the medial temporal region: Enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *J. Neurosci.* **6**: 2950–2967.