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Asymmetric frontal activation during episodic memory: the effects of stimulus type on encoding and retrieval

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Abstract

Recent functional neuroimaging studies have suggested that the left prefrontal cortex is preferentially involved in the encoding of episodic memory whilst the right prefrontal cortex is preferentially involved in the retrieval of episodic memory, irrespective of the type (e.g. modality) of information being remembered. In the present PET activation study, a 2×2 design was employed to investigate the relationship between encoding and retrieval of verbal and non-verbal material in episodic memory. Accordingly, seven healthy volunteers were scanned whilst encoding and then recalling stimuli which either emphasised visual or verbal processes. When encoding and retrieval tasks were compared directly, significantly greater prefrontal activation was observed in the encoding conditions, regardless of modality, although these changes were bilaterally distributed. In contrast when the verbal and visual memory tasks were compared directly, the former was associated with rCBF changes that were predominantly located in the left lateral frontal cortex whilst the latter was associated with rCBF changes that were predominantly located in the right lateral frontal cortex. These results suggest that encoding and retrieval may actually involve similar regions of the lateral prefrontal cortex when all factors relating to the type of stimulus material (i.e. modality), are appropriately controlled. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: PET; Episodic memory; Frontal lobes; Hemispheric asymmetry

1. Introduction

A common distinction made in the cognitive neuropsychology of memory [56,57] is that between semantic memory, which refers to people's general knowledge of the world [22] and episodic memory, which refers to the conscious recollection of personal experiences [57]. Although autobiographical memories (personally experienced episodes from one's past life) are most clearly synonymous with Tulving's original conception of episodic memory, most studies have used recall and recognition of recently studied material or 'new learning' as a vehicle for investigating episodic memory.

Over the past ten years, there has been a steady accumulation of experimental data to suggest that in humans there is an asymmetrical involvement of the left and right prefrontal cortices in the encoding and retrieval of episodic memory, respectively. For example, Kapur et al. [17] used positron emission tomography (PET) to examine 'deep' and 'shallow' episodic memory encoding by presenting healthy subjects with single nouns and instructing them to either decide whether they contained the letter 'a' (e.g. shallow processing) or decide whether the noun was 'living' (e.g. deep, semantic processing). On subtracting the blood flow associated with the shallow episodic memory encoding condition from that associated with the deep episodic memory encoding condition it was found that there was a significant activation of the left inferior prefrontal cortex. Since there was no significant differ-

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ence in activity in the right prefrontal cortex between the two encoding conditions, the data was taken to suggest that the left prefrontal cortex may be specialised for the encoding of episodic memory.

In a second PET study, Tulving et al. [58] examined episodic memory retrieval by instructing healthy subjects to learn auditory sentences in a pre-scan session and presenting them with new and old sentences mixed in varying proportions during subsequent PET scans. The subjects were required to keep track of new sentences, although, during the critical period of data acquisition in each scan, the sentences were either all new or all old. Subtraction of the activation associated with the *detection* of the new sentences from the activation associated with the *recognition* of old sentences showed significant right dorsolateral prefrontal cortex activation. On this basis, it was suggested that the right prefrontal cortex is more active than the left during episodic memory retrieval, or in this case, recognition.

A separate investigation by Shallice et al. [50] into episodic memory encoding and retrieval converged upon the same findings as Kapur et al. [17] and Tulving et al. [58]. For the encoding of episodic memory, subjects were PET scanned whilst being presented with rare word categories each paired with an exemplar from that category. For the retrieval of episodic memory, subjects were prompted with a category at a regular rate during scanning and had to recall the associated exemplar. It was found that, in comparison to a passive listening control condition, the episodic encoding condition activated the left anterior cingulate cortex extending to the left medial frontal gyrus (BA 9/10). In contrast, in comparison to a verbal repetition control task, the episodic memory retrieval task activated the right middle prefrontal cortex (BA 46/10) and the left anterior cingulate cortex (BA 32).

Since these initial investigations, many neuroimaging studies have provided evidence to support the asymmetrical involvement of the left and right prefrontal cortices in the encoding and retrieval of episodic memory, respectively. The majority of these studies have investigated episodic memory directly [e.g. 1,2,4,6,9–15,17,18,19,29,31–32,34,40,44–45,50,53,58], whilst others have investigated specific cognitive functions such as speech and language, which provide indirect information about the neural basis of episodic memory [e.g. 8,38,43]. In addition, most of these studies have used verbal material as stimuli [e.g. 2,4,6,7–12,17,19,31,32,38,40,43,45,50,53,58], although, non-verbal stimuli such as spatial patterns and faces have occasionally been used [e.g. 1,13–15,18,29,34,44]. A recent review of the literature has led Nyberg et al. [33] to conclude that there is convincing evidence to support an asymmetrical involvement of the left and right prefrontal cortices in the encoding and retrieval

of episodic memory, irrespective of whether verbal or non-verbal material is employed.

In spite of this evidence, there are a number of reasons to suggest that the hemispheric asymmetry model needs to be assessed further. First, a number of PET studies have provided data that are inconsistent with the predictions of the asymmetry model. For example, several studies have found that both the right and left prefrontal cortices are involved in both the encoding and retrieval of episodic memory [e.g. 2,5,18,40,49,59–60], while others have observed a complete absence of left or right prefrontal cortex activation during episodic memory retrieval [e.g. 16,21,48]. Second, according to the asymmetry model, patients with left sided prefrontal lesions should be disproportionately impaired at episodic memory encoding while patients with right sided prefrontal lesions should be disproportionately impaired at episodic memory retrieval. Although encoding has always proved difficult to assess in patients (since retrieval is invariably required to test the efficacy of encoding), there have been a number of neuropsychological studies to suggest that this is not the case. [e.g. 25,51,52,54]. Finally, the majority of studies supporting the asymmetry model have not systematically controlled for the possible disproportionate involvement of verbal processes in encoding or retrieval tasks, an important consideration given the known dominance of left hemisphere regions in language processes [26,27]. Recently, it has been suggested that subjects may preferentially use verbal strategies during the encoding of episodic information (whether that information is ostensibly verbal or not) and that these strategies may be less critical for efficient retrieval [34]. For example, memorisation of visual information is frequently accompanied by a sub-vocal verbal repetition of the material to be remembered. In contrast, if subjects are required to choose between two stimuli, one of which they have seen previously, verbalisation is not necessarily required for visual recognition to occur. Similarly, in studies where verbal material is employed, encoding often requires the subjects to repeat and/or learn a series of words, thereby emphasising sub-vocal or vocal articulation and rehearsal. In contrast, retrieval of those same words, particularly when tested through free recall, may be mediated by a combination of verbal, semantic or visual retrieval strategies.

To date, only two studies to our knowledge have investigated the significance of verbal strategies during memory encoding and retrieval. Using PET, Klingberg and Roland [21] found that stimuli which were difficult to encode using verbal processes (e.g. uncommon sounds) activated the right middle prefrontal cortex during memory encoding, whilst no prefrontal cortex activation was observed during memory retrieval. Similarly, Kelley et al. [20] used functional magnetic reson-

ance imaging (*fMRI*) to demonstrate that the left dorsal frontal cortex was predominantly activated during the encoding of words, whilst the right dorsal frontal cortex was predominantly activated during the encoding of stimuli which were more difficult to process verbally (e.g. faces). On the other hand, when line drawings of everyday objects, which could be easily processed visually and verbally, were encoded, bilateral dorsal frontal cortex activation was observed.

The present PET study was designed to investigate the neural basis of episodic memory further, by assessing directly the extent to which verbal processes may, or may not, affect the relative asymmetric involvement of left and right frontal regions in episodic memory encoding and retrieval. Accordingly, subjects were required to encode and then retrieve stimuli that varied in the extent to which they could be processed verbally. According to the encoding–retrieval asymmetry model, both the verbal and non-verbal *encoding* conditions should preferentially activate left prefrontal regions while the *retrieval* conditions should preferentially activate right prefrontal regions. Alternatively, if verbal processing is a significant factor then both encoding and retrieval of verbal material might be expected to preferentially involve left frontal regions, while the encoding and retrieval of non-verbal (e.g. visual) material might be expected to preferentially involve right frontal regions.

2. Methods

2.1. 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, 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 yr; see Table 7). Although the age range was broad, an analysis of sub-groups revealed no systematic differences, either behaviourally or in terms of rCBF, between the 4 youngest subjects and the three older subjects. Accordingly, age was not considered to be an important variable and the subject group was analysed as a whole throughout. Prior to scanning, all subjects were medically screened by a qualified clinician and gave written consent for participation in the study after its nature and possible consequences were explained to them. The study received ethical approval from the Cambridge Health Authority Local Research Ethics Committee (LREC).

2.2. 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, regional cerebral blood flow (rCBF) was measured using the bolus $H_2^{15}O$ methodology. Subjects received a 20 s intravenous bolus of $H_2^{15}O$ through a forearm cannula at a concentration of 300 Mbq ml^{-1} and a flow rate of $10 ml min^{-1}$ 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. Both processes were carried out using the Statistical Parametric Mapping 96 (SPM 96) package provided by the Wellcome Department of Cognitive Neurology, London, UK. For pre-processing, 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 normalized to conform to the standard brain described by Talairach and Tournoux [55] and (3) spatially smoothed using an isotropic Gaussian kernel at 16 mm. For each subject, a 3D MRI volume ($256 \times 256 \times 128$ pixels, 3 mm thick) was also acquired using a 0.5 T system, re-sliced and spatially normalized. This was co-registered with the PET data to allow direct anatomical localisation of regions with statistically significant rCBF 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 96. An intensity threshold set at $p \leq 0.001$ (uncorrected for multiple comparisons) was applied for activations occurring within the frontal cortex [61,62]. The uncorrected threshold was used on account of the predictions made, a priori, about activation occurring within the prefrontal cortex (see Introduction). Since no predictions were made with regard to regions outside the frontal lobe, 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.

2.3. Procedure and tasks

Four different tasks were employed in this study and

we refer to these as *Visual Encoding*, *Visual Retrieval*, *Verbal Encoding* and *Verbal Retrieval*. 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 blue letters in the middle of a black background and were presented on a touch-sensitive screen. This 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 during the 8-min interval between scans and were also given a practice condition, if necessary. 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 encoding 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 (15 stimuli presented three times), each paired with a similar but unfamiliar stimulus. In order to minimise encoding of new material during the retrieval tasks, the lures used in the repeated trials of the retrieval tasks were identical for each repetition. The order of presentation was again random and differed 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 after an inter-trial interval of 500 ms. 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 visual tasks emphasised the visual (i.e. orthographic) aspects of the stimuli, whilst the verbal tasks emphasised the verbal (i.e. phonological) nature of the stimuli.

Fig. 1 illustrates each of the conditions.

1. **Visual Encoding** (Fig. 1a—top): The subjects were presented with a fixed string of unpronounceable letters (e.g. 'ZXPQDF'), each time in a different, visually distinctive type of font (e.g. *ZXPQDF* and *ZXPQDF*). Since the letter string was unpronounceable with no semantic meaning and the fonts used were not easily processed verbally, this condition was designed to emphasise visual encoding mechanisms and to discourage subjects from using verbally mediated strategies for encoding.
2. **Visual Retrieval** (Fig. 1b—top): The subjects were presented with each stimulus from the visual encoding condition paired with the same letter string in an unfamiliar font. Since the two-choice stimuli differed only in terms of the font used, the emphasis on this task was on visual recognition.
3. **Verbal Encoding** (Fig. 1a—bottom): The subjects were presented with pronounceable non-words (e.g. 'slicerit'), each in lower case letters and in an identical font. The non-words were generated specifically for this study. They were constructed so as to not be similar to any existing real words and yet, they possessed the phonemic structure characteristic of real words. Since the non-words had visual characteristics which would be of minimal use in the subsequent retrieval task, this condition was designed to emphasise the use of verbal mechanisms and discourage the subjects from using visually mediated strategies for encoding.
4. **Verbal Retrieval** (Fig. 1b—bottom): The subjects were presented with each stimulus in the verbal encoding condition paired with unfamiliar non-words. The lures always differed from the targets by only one or two letters and thus, 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.

3. Results

3.1. Performance

The average performance on both of the retrieval tasks was above 90%, with performance on verbal retrieval being slightly more accurate (95.7% mean correct) than visual retrieval (94.0% mean correct). A two-tailed paired *t*-test indicated that the difference between these mean scores was not significant ($t = 0.474$; $p = 0.652$). The mean reaction times for the visual retrieval and verbal retrieval tasks were 2.458 s

and 2.244 s, respectively. A two-tailed paired *t*-test indicated that the difference between these mean times did reach significance ($t = 3.021$; $p = 0.008$).

3.2. Blood-flow changes

The statistical analysis of blood flow changes was designed to address two questions (1) whether encoding and retrieval conditions disproportionately recruited left and right hemisphere regions respectively, as would be predicted by the encoding–retrieval asymmetry model and (2) whether conditions that encour-

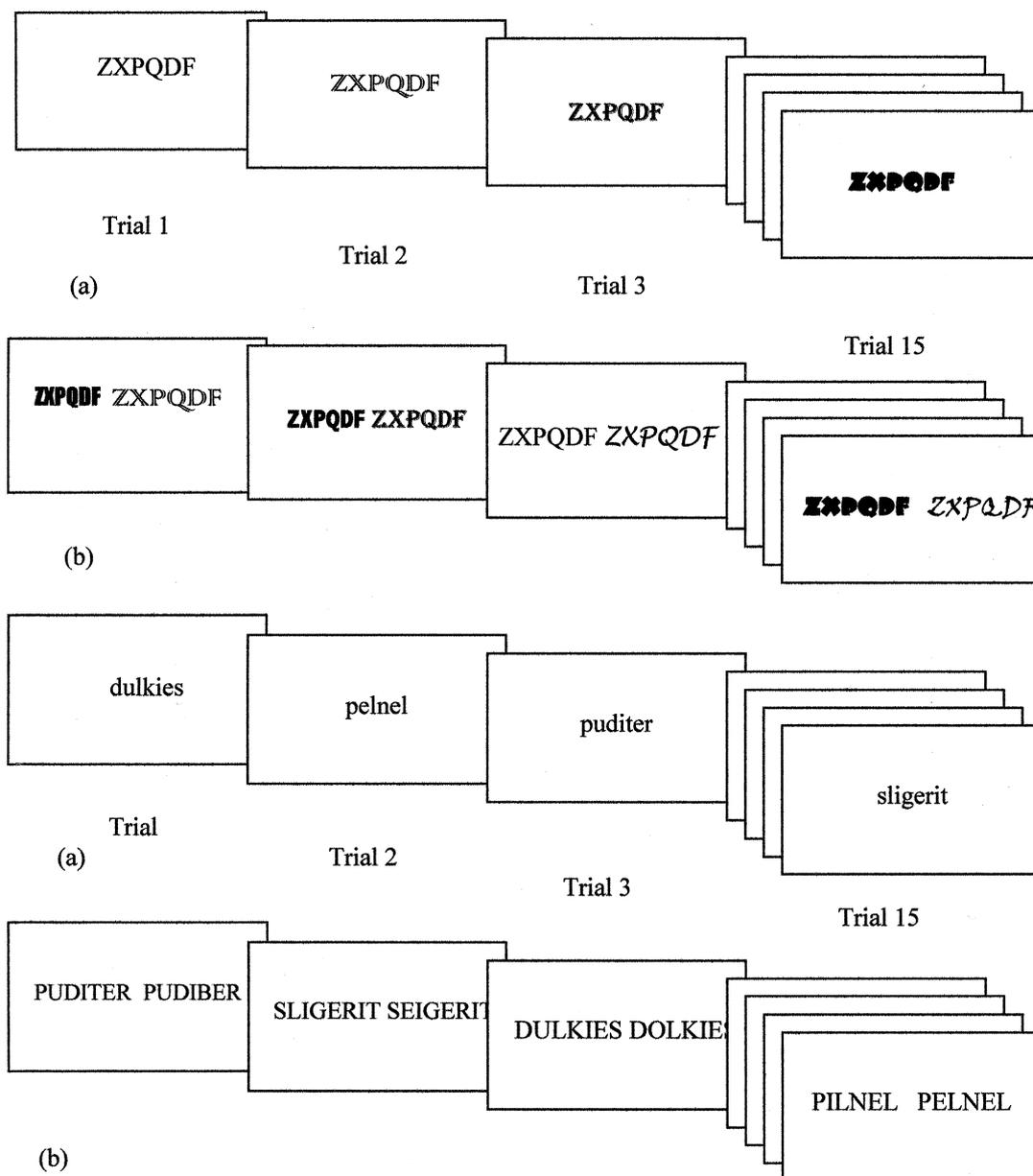


Fig. 1. (a—top) Schematic representation of the visual encoding task and (b—top) the visual retrieval task. (a—bottom) Schematic representation of the verbal encoding task and (b—bottom) verbal retrieval task.

Table 1

Stereotaxic coordinates of activation when all the encoding conditions were compared to all the retrieval conditions^a

Region	BA	Stereotaxic coordinates			Z score
		x	y	z	
<i>Conjunction analysis of visual encoding–visual retrieval and verbal encoding–verbal retrieval</i>					
Left hemisphere					
Frontal polar cortex	10	–10	64	8	3.48
Amygdala		–22	–4	–24	5.23
Right hemisphere					
Frontal polar cortex	10	18	62	16	3.73
Ventromedial frontal cortex	10	4	46	–12	3.72
Anterior temporal pole	38	36	10	–28	4.76
<i>Conjunction analysis of visual retrieval–visual encoding and verbal retrieval–verbal encoding</i>					
Left hemisphere					
Visual cortex	17/18	–16	–78	–4	8.55
Right hemisphere					
Visual cortex	17/18	10	–78	–4	8.76

^a The activation foci in this and subsequent Tables 2–6 represent statistically significant changes in normalized rCBF. The stereotaxic coordinates were generated by SPM96. *x* = medial-to-lateral distance relative to the midline (positive = right hemisphere); *y* = anterior-to-posterior distance relative to the anterior commissure (positive = anterior); *z* = superior-to-inferior distance relative to the anterior commissure line (positive = superior).

aged the use of verbal strategies disproportionately recruited left hemisphere regions irrespective of whether the subject was encoding or retrieving the learnt information. Accordingly, a number of subtractions, 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 1–6, along with corresponding stereotaxic coordinates based on the brain atlas of Talairach and Tournoux [55].

3.2.1. Encoding vs retrieval

A conjunction analysis was carried out on the two direct comparisons between the encoding and retrieval tasks (e.g. visual encoding minus visual retrieval and verbal encoding minus verbal retrieval). Conjunction

analyses identify significant changes in blood flow across independent subtractions that are, in addition, not significantly different from each other [41,42]. Thus, this global comparison was designed to identify significant changes in blood flow, which were specific to memory encoding *irrespective* of stimulus modality. In the prefrontal cortex, significant changes in rCBF were observed bilaterally in the frontal polar cortex (BA 10) and the right ventromedial frontal cortex (BA 10). Other significant rCBF changes were observed in the right anterior temporal pole (BA 38) and the left amygdala (see Fig. 2a). In the present study, the statistical threshold adopted for all conjunction analyses (that is, the threshold set to test the hypothesis that changes in blood flow across independent subtractions are non-significantly different in magnitude) was $p \leq 0.001$ (uncorrected) for changes within the frontal lobe and $p \leq 0.05$ (corrected) for changes outside the frontal lobe.

A second conjunction analysis (visual retrieval minus visual encoding and verbal retrieval minus verbal encoding) was designed to identify significant changes in rCBF that were specific to memory retrieval irrespective of stimulus modality. No significant rCBF changes were observed in the prefrontal cortex. When the significance threshold was dropped to explore the data further, non-significant bilateral prefrontal rCBF changes were observed, in the left ($Z = 2.03$) and right ($Z = 2.58$) dorsolateral frontal cortex (BA 9/46). Significant rCBF changes were also observed bilaterally in the striate cortex (BA 17).

Two supplementary analyses were then conducted to investigate the rCBF changes that were associated with memory encoding and retrieval *within* each modality:

Table 2

Stereotaxic coordinates of activation when visual encoding was compared to visual retrieval

Region	BA	Stereotaxic coordinates			Z score
		x	y	z	
<i>Visual encoding minus visual retrieval</i>					
Right hemisphere					
Dorsolateral frontal cortex	9/10	24	56	20	3.01
Anterior temporal pole		36	8	–28	4.13
<i>Visual retrieval minus visual encoding</i>					
Left hemisphere					
Visual cortex	18	–16	–76	–4	5.69
Right hemisphere					
Visual cortex	18	14	–76	0	6.09

Table 3
Stereotaxic coordinates of activation when verbal encoding was compared to verbal retrieval

Region	BA	Stereotaxic coordinates			Z score
		x	y	z	
<i>Verbal encoding minus verbal retrieval</i>					
Left hemisphere					
Medial frontal cortex	8	– 14	32	36	3.06
Frontal polar cortex	10	– 8	68	8	3.51
Anterior temporal pole	39	– 24	6	– 28	4.73
Right hemisphere					
Ventromedial frontal cortex	10	1	46	– 8	4.15
Superior temporal cortex	38	46	– 18	4	4.51
<i>Verbal retrieval minus verbal encoding</i>					
Left hemisphere					
Prestriate cortex	18/19	14	– 80	– 4	6.70
Right hemisphere					
Prestriate cortex	18	– 14	– 94	4	7.06

3.2.1.1. *Visual encoding vs visual retrieval.* When visual retrieval was subtracted from visual encoding, significant changes in rCBF were observed only in the right dorsolateral frontal cortex (BA 9/10) and in the right anterior temporal pole. In contrast, when visual encoding was subtracted from visual retrieval significant rCBF changes were observed in the left and right prestriate cortices (BA 18) only. No significant rCBF changes were observed in the prefrontal cortex.

3.2.1.2. *Verbal encoding vs verbal retrieval.* When verbal retrieval was subtracted from verbal encoding, significant rCBF changes were observed bilaterally, in the right ventromedial frontal cortex (BA 10), left anterior frontal pole (BA 10) and the left medial frontal cortex (BA 8). More posteriorly, significant rCBF changes were observed in the left anterior temporal pole (BA 39) and the right superior temporal sulcus (BA 38).

When the verbal encoding condition was subtracted from the verbal retrieval condition significant rCBF changes were observed in the visual cortex (BA 18/19) bilaterally, with no significant rCBF changes in the prefrontal cortex.

The analyses described above were designed to test whether encoding and retrieval conditions disproportionately recruit left and right hemispheric regions respectively, across a number of different stimulus types. No evidence was found to support this position. Thus, in both the visual and verbal conditions, encoding was associated with significant bilateral frontal lobe rCBF changes whilst retrieval was associated with no frontal lobe rCBF changes at all.

3.2.2. *Verbal vs visual processing*

A conjunction analysis was conducted (visual encoding minus verbal encoding and visual retrieval minus

Table 4
Stereotaxic coordinates of activation when visual conditions were compared to verbal conditions

Region	BA	Stereotaxic coordinates			Z score
		x	y	z	
<i>Conjunction analysis of visual encoding–verbal encoding and visual retrieval–verbal retrieval</i>					
Left hemisphere					
Dorsolateral frontal cortex	9	– 36	42	40	3.33
Right hemisphere					
Dorsolateral frontal cortex	46	56	42	12	3.27
Dorsolateral frontal cortex	9	58	22	32	3.92
Dorsolateral frontal cortex	9	18	38	32	4.44
Inferior temporal gyrus	37	54	– 48	– 24	6.54
Visual cortex	17/18	36	– 88	4	4.99
<i>Conjunction analysis of verbal encoding–visual encoding and verbal retrieval–visual retrieval</i>					
Left hemisphere					
Inferior frontal cortex	44	– 56	10	8	3.15
Inferior frontal cortex	44	– 56	6	18	3.78
Middle temporal gyrus	22/21	– 46	– 40	4	4.68

Table 5
Stereotaxic coordinates of activation when visual encoding was compared to verbal encoding

Region	Stereotaxic coordinates				Z score
	BA	x	y	z	
<i>Visual encoding minus verbal encoding</i>					
Left hemisphere					
Frontal polar cortex	10	-44	51	-8	3.2
Right hemisphere					
Dorsolateral frontal cortex	9/46	40	50	28	3.08
Anterior cingulate cortex		14	34	16	3.61

verbal retrieval), in order to identify those significant changes in rCBF that were specific to visual episodic memory, irrespective of encoding or retrieval processes. Significant regions of rCBF change were observed predominantly in the right hemisphere (see Fig. 2b). Thus, 3 regions of significant rCBF change were observed in the right dorsolateral frontal cortex (BA 9, BA 46), whilst one region of significant rCBF change was observed in the left dorsolateral frontal

Table 6
Stereotaxic coordinates of activation when visual retrieval was compared to verbal retrieval

Region	Stereotaxic coordinates				Z score
	BA	x	y	z	
<i>Visual retrieval minus verbal retrieval</i>					
Left hemisphere					
Orbitofrontal cortex	11	-26	22	-8	3.03
Right hemisphere					
Orbitofrontal cortex		18	54	-12	3.03
Dorsolateral frontal cortex	9	60	24	28	3.41
Dorsolateral frontal cortex	9	18	40	36	3.52
<i>Verbal retrieval minus visual retrieval</i>					
Left hemisphere					
Ventrolateral frontal cortex	47	-54	20	0	4.10
Inferior frontal cortex	44	-56	8	16	4.19

cortex (BA 9). Significant changes in rCBF were also observed more posteriorly, in the right striate and pre-striate cortices (17/18) and the right inferior temporal gyrus (BA 37).

A second conjunction analysis (verbal encoding

Table 7
Adjusted blood counts for each subject for two representative voxels in the contrast visual retrieval vs verbal retrieval^a

Subject	Sex	Age	Condition	Average adjusted blood count (ml/100 g/60 s)
(i) Adjusted blood counts for $x = 60, y = 24, z = 28$				
1	M	22	Visual retrieval	57.62
			Verbal retrieval	53.66
2	M	61	Visual retrieval	55.83
			Verbal retrieval	53.08
3	M	44	Visual retrieval	57.05
			Verbal retrieval	49.79
4	F	56	Visual retrieval	55.00
			Verbal retrieval	54.26
5	F	51	Visual retrieval	55.66
			Verbal retrieval	53.04
6	M	21	Visual retrieval	54.03
			Verbal retrieval	52.38
7	M	25	Visual retrieval	53.45
			Verbal retrieval	54.28
(ii) Adjusted blood counts for $x = -54, y = 20, z = 0$				
1	M	22	Visual retrieval	76.14
			Verbal retrieval	78.15
2	M	61	Visual retrieval	76.00
			Verbal retrieval	75.48
3	M	44	Visual retrieval	71.93
			Verbal retrieval	78.72
4	F	56	Visual retrieval	69.58
			Verbal retrieval	80.27
5	F	51	Visual retrieval	74.68
			Verbal retrieval	77.03
6	M	21	Visual retrieval	73.63
			Verbal retrieval	78.34
7	M	25	Visual retrieval	76.41
			Verbal retrieval	8.00

^a Adjusted blood flow counts for each subject at (i) $x = 60, y = 24, z = 28$ and (ii) $x = -54, y = 20, z = 0$ for the contrast visual retrieval vs verbal retrieval.

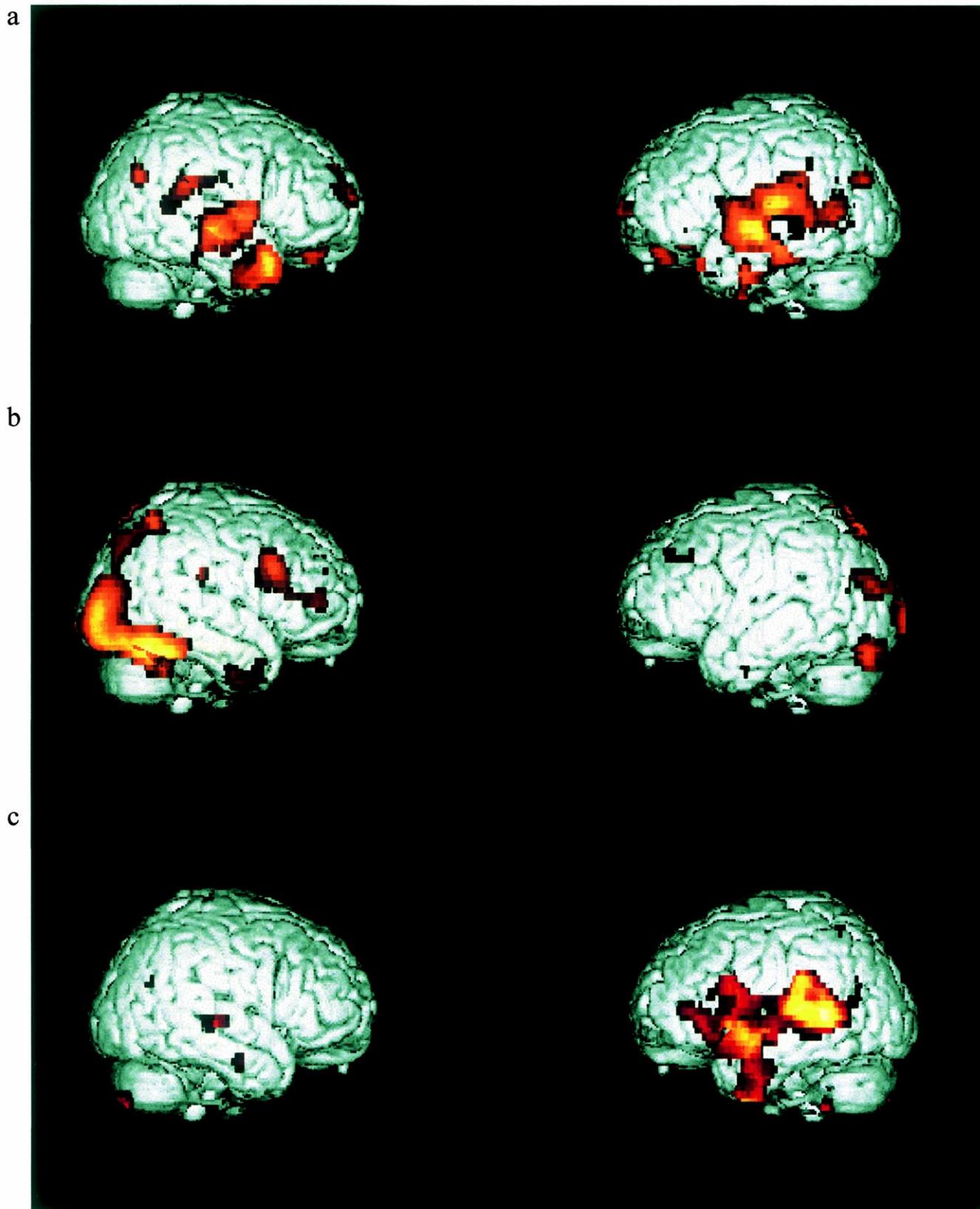


Fig. 2. (a) Schematic diagram showing the regions of significant rCBF change from the conjunction analysis (visual encoding — visual retrieval and verbal encoding — verbal retrieval) superimposed on an average 3D rendered MRI scan. In the prefrontal cortex, bilateral activation was observed in frontopolar area 10. (b) Schematic diagram showing the regions of significant rCBF change from the conjunction analysis of (visual encoding — verbal encoding and visual retrieval — verbal retrieval) superimposed on an average 3D rendered MRI scan. In the prefrontal cortex, significant rCBF changes were observed predominantly in the right hemisphere. (c) Schematic diagram showing the regions of significant rCBF change from the conjunction analysis of (verbal encoding — visual encoding and verbal retrieval — visual retrieval) superimposed on an average 3D rendered MRI scan. Two significant regions of rCBF change were observed in the left inferior frontal gyrus (area 44).

minus visual encoding and verbal retrieval minus visual retrieval) was designed to identify those significant changes in rCBF that were specific to verbal episodic memory, irrespective of encoding or retrieval processes (Fig. 2c). Two significant regions of rCBF change were observed in the left inferior frontal gyrus (BA 44). More posteriorly, there was a significant change in rCBF in the left middle temporal gyrus (BA 22/21).

Supplementary analyses were then conducted to investigate the rCBF changes that were associated with verbal and visual processing during encoding and retrieval:

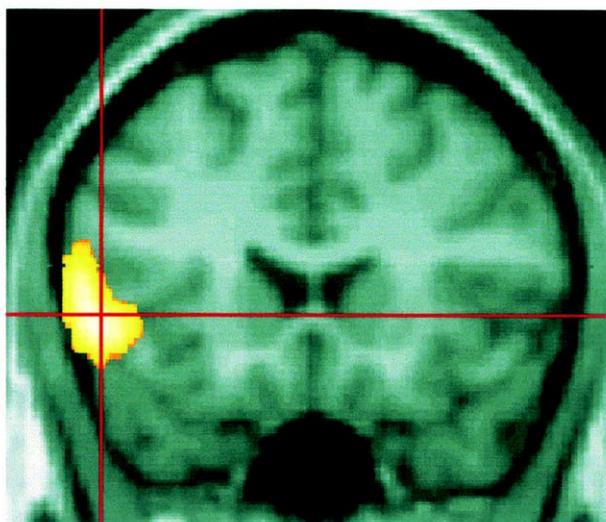
3.2.2.1. Visual encoding vs verbal encoding. When the verbal encoding condition was subtracted from the visual encoding condition significant regions of rCBF change were observed in the left frontal polar cortex, the right dorsolateral frontal cortex and the right anterior cingulate cortex. In contrast, when the visual encoding condition was subtracted from the verbal encoding condition, there were no significant regions of rCBF change. When the significance threshold was dropped to explore the data further, non-significant rCBF changes were observed in the left inferior frontal gyrus (BA 9; $Z = 2.48$), the left orbitofrontal cortex (BA 11, $Z = 2.47$, $Z = 2.38$) and the left frontopolar cortex (BA = 10; $Z = 2.46$).

3.2.2.2. Visual retrieval vs verbal retrieval. When the verbal retrieval condition was subtracted from the visual retrieval condition significant regions of rCBF change were observed in the right dorsolateral prefrontal cortex (BA 9), the right superior frontal gyrus (BA 8) and the orbitofrontal cortex bilaterally (BA 11; see Fig. 3a). In contrast, when the visual retrieval condition was subtracted from the verbal retrieval condition, significant regions of rCBF change were observed in the left inferior frontal gyrus (BA 44) and in the left ventrolateral frontal cortex (BA 47; see Fig. 3b).

In order to investigate whether changes in blood flow were similar across all subjects across conditions, we examined the adjusted blood flow counts for each subject for the key contrasts (Table 7). In general, the results were highly consistent across subjects. For example, Tables 7(i) and 7(ii) show the adjusted blood flow counts for each subject for the two contrasts between visual retrieval and verbal retrieval (visual retrieval minus verbal retrieval and verbal retrieval minus visual retrieval) for the significant voxels at $x = 60$, $y = 24$, $z = 28$ and $x = -54$, $y = 20$, $z = 0$. These data are represented graphically in Fig. 4. As illustrated, blood flow was found to change similarly across the seven subjects included in this study.

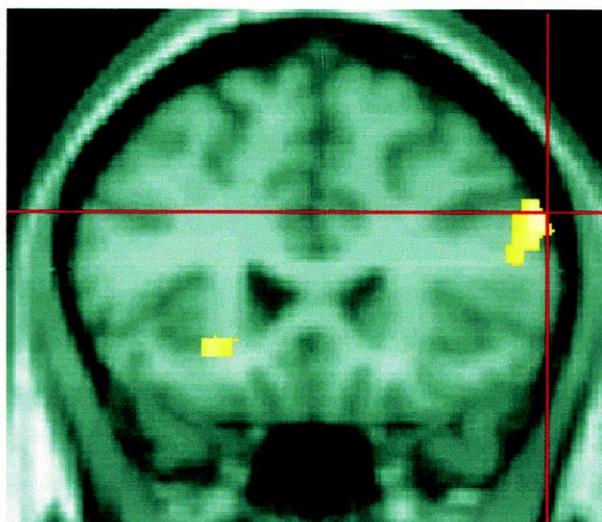
Finally, since the primary aim of this study was to explore two separate factors in memory (i.e. encoding/

$y = 20$



(a)

$y = 24$



(b)

Fig. 3. Schematic diagram showing the regions of significant rCBF change from (a) verbal retrieval minus visual retrieval and (b) visual retrieval minus verbal retrieval superimposed on two separate coronal sections of an average MRI scan ($y = 20$; $y = 24$).

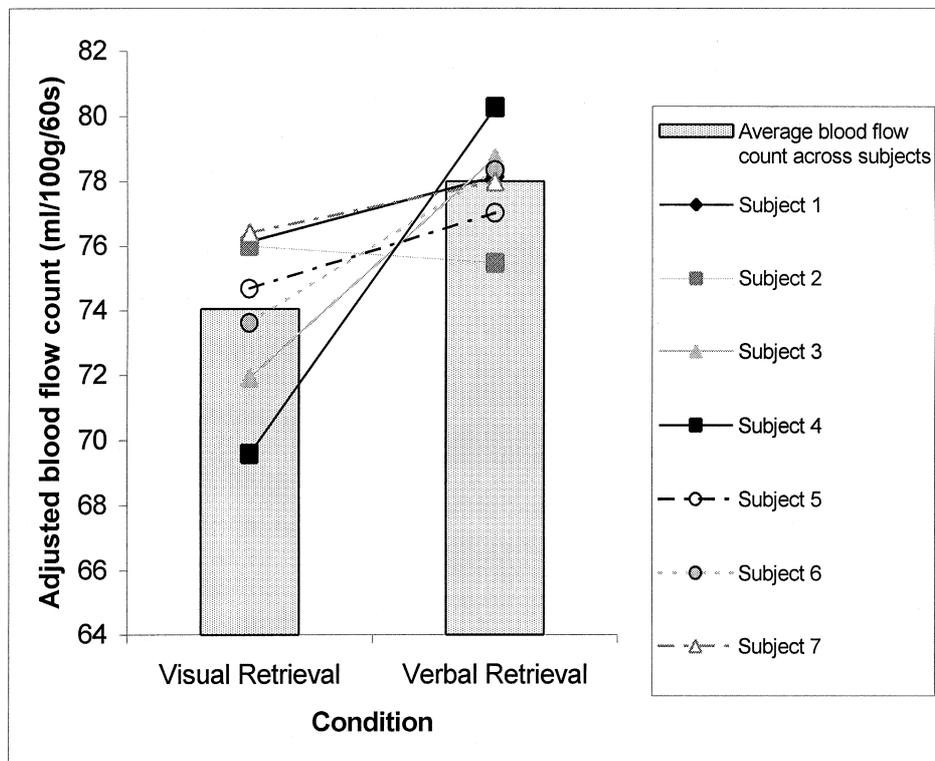
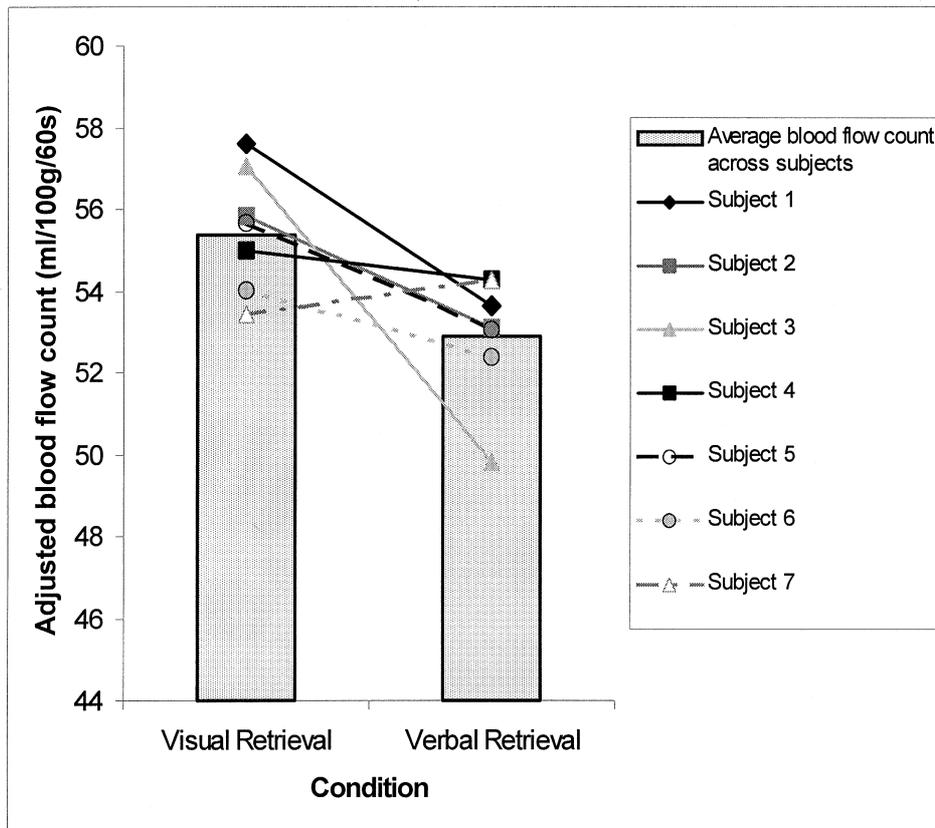


Fig. 4. Graph to illustrate the adjusted blood flow counts for each subject at (i) $x = 60, y = 24, z = 28$ and (ii) $x = -54, y = 20, z = 0$ for the contrast visual retrieval vs verbal retrieval.

retrieval and modality), the interactions between these two variables, e.g. (verbal encoding — verbal retrieval) — (visual encoding — visual retrieval) and (verbal retrieval — verbal encoding) — (visual retrieval — visual encoding), were examined. No significant differences were observed.

The analyses described above were designed to test the extent to which the apparent left–right encoding–retrieval asymmetry within episodic memory may be disrupted by controlling for the effects of verbal and non-verbal processing mechanisms. Preliminary evidence was observed to support this position. Thus, verbal memory processes were associated with significant rCBF changes that were located predominantly in the left frontal lobe, whilst visual memory processes were associated with significant rCBF changes that were located predominantly in the right frontal lobe.

4. Discussion

4.1. Functional lateralisation of episodic memory encoding and retrieval

Models of episodic memory have suggested a disproportionate involvement of the left and right prefrontal cortices in the encoding and retrieval of episodic memory, respectively. According to these models, the left prefrontal cortex should be preferentially involved in the encoding of episodic memory whilst the right prefrontal cortex should be preferentially involved in the retrieval of episodic memory, irrespective of the modality of the material involved [17,50,58]. The results of the current study provide no evidence to support these predictions and furthermore, suggest that apparent asymmetries in frontal lobe involvement may, in part, reflect the use of verbal strategies during memory encoding, which are less evident during memory retrieval [20–21,34].

When a conjunction analysis was performed on the two comparisons; (1) visual encoding minus visual retrieval; and (2) verbal encoding minus verbal retrieval, significant regions of rCBF change were observed bilaterally in the frontal polar cortex and in the right ventromedial frontal cortex. Bilateral rCBF changes in the dorsolateral frontal cortex were also observed in a conjunction analysis of the reverse subtractions (e.g. retrieval minus encoding), although these did not reach statistical significance according to our conservative criteria. Clearly, neither of these analyses provides any evidence to suggest that there are common regions of activation within the left prefrontal cortex during episodic memory encoding and common regions of activation within the right prefrontal cortex during episodic memory retrieval.

Examining the data within stimulus type also pro-

vided no evidence to support the predictions of the hemispheric asymmetry model. Thus, within the prefrontal cortex, verbal encoding minus verbal retrieval yielded significant regions of rCBF change in the right ventromedial frontal cortex, the left frontal polar cortex and the left medial frontal cortex. Moreover, visual encoding minus visual retrieval only yielded one significant region of rCBF change in the right dorsolateral frontal cortex. The fact that the latter subtraction failed to identify any significant regions of rCBF change in the left prefrontal cortex, whilst the former subtraction did, provides preliminary evidence that the left prefrontal cortex may be preferentially involved during memory encoding only when the material involved is verbal in nature. This supports the findings of recent studies by Klingberg and Roland [21] and Kelley et al. [20]. Klingberg and Roland [21] PET scanned subjects whilst they learned a paired associate task involving sounds and visual patterns which were difficult to verbalise and reported significant activation in the right prefrontal cortex only. Similarly, Kelley et al. [20] used *f*MRI to demonstrate that, whilst the encoding of words activated the left prefrontal cortex, the encoding of faces, which are relatively more difficult to process verbally, activated the right prefrontal cortex. In contrast, the encoding of line drawings of everyday objects, which are easily processed either visually or verbally, produced bilateral activation of the prefrontal cortex.

In the present study, both verbal retrieval minus verbal encoding and visual retrieval minus visual encoding failed to identify any significant regions of rCBF change within the prefrontal cortex. The conjunction analysis (visual retrieval minus visual encoding and verbal retrieval minus verbal encoding) yielded similar findings. Similar results have been reported previously by Kapur et al. [16], Schacter et al. [48] and Klingberg and Roland [21] all of whom observed no prefrontal cortical activation during episodic memory retrieval. It has been suggested that such results reflect the relatively automated nature of the episodic retrieval tasks. For example, Klingberg and Roland [21] 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 studies where prefrontal cortex activation has been observed during memory retrieval, performance levels have been generally lower than this, possibly reflecting the less automated nature of the particular tasks employed [e.g. 13,15]. A similar explanation may account for the results of the present study since retrieval performance was very high (i.e. over 94%), in both conditions. 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 the 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 is effectively ‘subtracted out’ during the retrieval tasks. This explanation seems even more likely given that prefrontal activation foci *were* observed when the two retrieval conditions were compared directly.

4.2. Lateralisation of episodic memory according to information type

In the present study, preliminary evidence emerged to suggest that the apparent lateralisation of episodic memory seen in previous work may reflect, in part, the effect of verbal vs non-verbal processing mechanisms. Thus, a conjunction analysis combining the comparisons between visual encoding minus verbal encoding and visual retrieval minus verbal retrieval identified multiple significant rCBF changes in the right dorso-lateral frontal lobe, although one smaller change was also observed in the left dorsolateral prefrontal cortex. These regions, therefore, appear to be involved in visual episodic memory, irrespective of whether the subject is encoding or retrieving information. To explore this issue further, rCBF during the verbal retrieval task was subtracted from that during the visual retrieval task. Again, the most pronounced changes were located in the right dorsolateral frontal cortex.

A similar analysis designed to identify those regions preferentially involved in verbal episodic memory (verbal encoding minus visual encoding and verbal retrieval minus visual retrieval) identified two significant rCBF changes in the left inferior frontal cortex (area 44). Subsequent comparisons revealed that, compared to the visual retrieval task, verbal retrieval yielded significant rCBF changes in the same region and also in the left mid-ventrolateral frontal cortex (BA 47). Similarly, subtracting the visual encoding condition from the verbal encoding condition yielded regions of rCBF change in the left prefrontal cortex only, although, these failed to reach statistical significance according to our conservative criteria. These observations concur fully with the fact that the left hemisphere is dominant for language processes in over 90% of the normal population [e.g. 26,27]. More specifically, human neuropsychological and imaging studies suggest that Broca’s area is centrally involved in language processes, and particularly in the generation of phonetics for the production of speech.

The results of this study cannot be easily reconciled with a number of related observations which have found support for hemispheric asymmetry in episodic memory encoding and retrieval. For example, a number of PET studies, using verbal stimuli, have observed

right prefrontal cortex activation during memory retrieval [e.g. 8,10,31,38,43,50,58] whilst a number of studies using non-verbal material have observed left prefrontal cortex activation during memory encoding [e.g. 13,15,29,34]. It is important to emphasise, however, that the use of verbal or non-verbal material does not ensure that the subjects encode and retrieve the material entirely on the basis of verbal or non-verbal processes, respectively. The encoding of visual material may often involve sub-vocal verbal descriptions of the material to be remembered, whilst successful recognition of this material may require only visual recognition processes. In contrast, whilst the encoding of words clearly emphasises sub-vocal or vocal verbal articulation and rehearsal, the retrieval of these words may be facilitated by a combination of verbal, semantic or visual strategies.

It may be argued that the failure to find evidence in support of a left–right asymmetry in episodic memory encoding and retrieval in this study was related to the fact that semantically ‘empty’ test material were used. It is certainly true that the majority of evidence cited in favour of the left–right frontal asymmetry model comes from studies in which semantically rich stimuli were employed [e.g. 17,58, etc.]. However, we do not believe that this issue is relevant to the current debate. For example, several previous studies have also used semantically empty material and yet, have yielded evidence cited in favour of a left–right frontal asymmetry model [e.g. 15]. Similarly, several studies have actively controlled for level of semantic processing and have still found evidence cited in favour of a left–right asymmetry model [e.g. 50]. On the other hand, several previous investigations have used stimuli which are semantic ‘rich’ and yet, as in the present study, have still failed to find evidence in support of a left–right frontal asymmetry model [e.g. 20]. Finally, the subjects in the present study were also scanned during two conditions that involved semantically rich material. While the results are not reported here, no evidence for a left–right encoding–retrieval asymmetry was found (A.C.H. Lee, T.W. Robbins, J.D. Pickard and A.M. Owen, 1999, unpublished).

It is important to point out that the left-sided activations associated with the verbal conditions (e.g. as reported in Tables 4, 5 and 6) may reflect general phonological processes that are not specifically related to memory per se. This point, however, does not detract from the main implication of the present findings, that is, that the left–right hemispheric asymmetry reported in previous studies of encoding and retrieval may be a reflection not of discrete mnemonic processes as widely assumed, but of the greater recruitment of verbally based rehearsal processes during encoding in comparison to retrieval. The majority of previous studies that have investigated episodic memory encoding and

retrieval have not adequately controlled for this factor. Consequently, in many cases, left sided activation observed during an encoding task may, in fact, reflect the disproportionate involvement of verbal and phonological processes recruited to facilitate normal memory function.

Recently, numerous functional imaging studies have sought to relate specific cognitive processes to the frontal activation foci observed during memory encoding and/or retrieval tasks. Such processes include 'retrieval attempt and success' [e.g. 18,31,45–47,24], 'monitoring' [e.g. 35,39], organisational strategies [e.g. 11,12] and reflective processing [e.g. 30]. Although the present study was not explicitly designed to address any of these issues, but rather, the general relationship between encoding, retrieval and frontal asymmetry, it is possible to relate the main results to some of these theoretical concepts. In particular, verbal retrieval minus visual retrieval yielded a significant activation focus in the left ventrolateral prefrontal cortex (BA 47) while the reverse subtraction yielded a significant activation focus in the right dorsolateral prefrontal cortex (BA 46/9). A general theoretical framework for understanding the relationship between the dorsal and ventral regions of the prefrontal cortex has recently been proposed [39]. According to that model, the ventrolateral frontal cortex constitutes a first level of interaction between the more posterior temporal and parietal cortices, which have been suggested to mediate basic memory functions such as the long-term storage and further processing of incoming and recalled information [39]. In this capacity, the ventrolateral frontal cortex is assumed to be critical for various executive or 'organisational' processes, such as comparisons between, or judgements about, remembered stimuli and the active organisation of responses based on conscious, explicit retrieval of information from long term memory. In contrast, the mid-dorsolateral frontal cortex is assumed to provide a second level of processing within memory and is recruited when active manipulation or 'monitoring' of remembered information is required. Several recent functional neuroimaging studies designed specifically to address this issue have demonstrated that either or both the ventrolateral and dorsolateral regions of the frontal cortex may be activated during various working memory tasks depending upon the specific processes required [35,36]. In the context of this process-specific model, it is not entirely clear why the verbal retrieval task used in the current study should produce activation that is more ventral in the left hemisphere to that produced in the right hemisphere during the visual retrieval task. One intriguing possibility is that the verbal tasks in the present study rely more heavily on mechanisms of rehearsal and repetition (corresponding perhaps to the articulatory loop component of Baddeley's working memory model, [3])

that are assumed to depend on the ventrolateral frontal cortex [39], while the more difficult visual memory task may require strategies that depend to a greater extent on dorsal regions.

This discussion has focused on the pattern of activation foci observed within the prefrontal cortices since it is these regions that are central to current models of episodic memory encoding and retrieval. However, several other aspects of the results are worthy of note. For example, compared to the verbal encoding and retrieval conditions, the visual encoding and retrieval conditions yielded an extensive region of significant rCBF change in the right hemisphere, spreading from lateral striate cortex into the right ventral occipitotemporal and inferotemporal regions. In contrast, when the visual encoding and retrieval conditions were subtracted from the verbal encoding and retrieval conditions, a posterior region of significant rCBF change was observed in the left middle temporal lobe region. These observations concur fully with human neuropsychological [e.g. 26–28] and neuroimaging studies [e.g. 20,23] demonstrating that verbal and visual declarative memory processes are mediated disproportionately by left and right posterior association cortices, respectively.

It is also notable that, relative to the two encoding conditions, the memory retrieval tasks were frequently associated with rCBF changes in the striate and prestriate cortices. 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 [e.g. 7,37].

Previous studies of episodic memory retrieval have reported significant activations in the medial and lateral parietal areas during episodic memory retrieval. rCBF changes were not observed in these regions in the current study. The most parsimonious explanation for this is that the present study was unusual in that no non-memory 'control' condition was employed. It is possible that in comparing the encoding and retrieval conditions directly, any activation in the parietal areas was effectively 'subtracted out', being equally present in both conditions. While the design of the current study does not allow us to confirm that this is indeed the case, future studies will seek to investigate this issue more directly.

In summary, the present study has found no evidence to support the hypothesis that the left prefrontal cortex is preferentially involved in the encoding of episodic memory whilst the right prefrontal cortex is pre-

ferentially involved in the retrieval of episodic memory [17,50,58]. In contrast, in both visual and verbal memory conditions, encoding was associated predominantly with bilateral frontal lobe rCBF changes whilst retrieval was associated with no frontal rCBF changes at all. Furthermore, the results provide preliminary support for an alternative hypothesis; that is, that the apparent asymmetry within episodic memory may reflect the differential involvement of verbal and non-verbal processing mechanisms during encoding and retrieval. Thus, verbal memory tasks were most clearly associated with significant rCBF changes in the left lateral prefrontal cortex, whilst visual memory tasks were most clearly associated with changes in the right lateral prefrontal cortex.

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