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Evidence for asymmetric frontal-lobe involvement in episodic memory from functional magnetic resonance imaging and patients with unilateral frontal-lobe excisions

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Abstract

Recently, there has been considerable debate regarding the involvement of the left and right prefrontal cortices in the encoding and retrieval of episodic memory. In a previous PET study, we found that the use of easily verbalisable material may lead to activation predominantly in the left lateral frontal cortex whilst the use of non-easily verbalisable material may lead to activation predominantly in the right lateral frontal cortex, in both cases irrespective of encoding and retrieval processes. In order to replicate and extend these findings, the same task was modified for use with *f*MRI. Six healthy volunteers were scanned while encoding and then recalling stimuli that either emphasised visual or verbal processes. It was found that, in comparison to a baseline condition, the encoding of visual stimuli led to a bilateral activation of the prefrontal cortex whilst the encoding of verbal stimuli led to a preferential activation of the left prefrontal cortex. An effect of stimulus type was less evident during retrieval, with both visual and verbal stimuli leading to bilateral prefrontal cortex activation. Overall, encoding and retrieval activated similar regions of the prefrontal cortex suggesting that these areas mediate processes that are fundamental to both aspects of memory. To extend these findings further, the tasks used in the *f*MRI study were used to assess a group of patients with unilateral frontal lesions and a group of healthy control volunteers. The patients were significantly impaired compared to the healthy volunteers, although no significant differences were found in performance between the right- and left-sided lesioned patients. This result suggests that the memory-related asymmetries observed during functional neuroimaging studies may not be critical for task performance.

Keywords: Neuroimaging; Encoding; Retrieval; Lateralisation; Prefrontal cortex

1. Introduction

A common distinction made in the cognitive neuropsychology of memory is that between semantic memory, which refers to people's general knowledge of the world and episodic memory, which refers to the conscious recollection of personal experiences [58,59]. 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.

One model of episodic memory that has risen out of the human functional neuroimaging literature suggests that the left prefrontal cortex is predominantly involved in episodic memory encoding whilst the right prefrontal cortex is predominantly involved in episodic memory retrieval, irrespective of the type of information (e.g. verbal versus non-verbal) involved [20,38,50,60,61]. More recently, however, evidence has emerged to suggest that the left–right encoding–retrieval asymmetry model may not be an adequate framework for understanding the role of the human prefrontal cortex in episodic memory. In fact, given the known dominance of left hemisphere regions in language processes [28,31] a number of investigators have suggested that it is the involvement of verbally mediated mnemonic strategies, rather than encoding–retrieval processes, which determines the relative involvement of the left and right prefrontal cortices during episodic memory processes ([21,23,25,39,62]; for review, see [24]). For example, Owen et al. [42] suggested that subjects may preferentially use verbal strategies while encoding

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episodic information (whether that information is ostensibly verbal or not) and these strategies may be less critical for efficient retrieval. Thus, memorisation of *visual* information is frequently accompanied by subvocal verbal repetition of the to-be-remembered material. 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 emphasizing subvocal 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 and visual retrieval strategies.

In a previous study, we used Positron Emission Tomography (PET) to scan healthy volunteers while they encoded and then recalled stimuli that either emphasised visual or verbal processes (for full details, see [23]). Verbal stimuli led to activation predominantly in the left prefrontal cortex while visual stimuli led to activation predominantly in the right prefrontal cortex, in both cases, irrespective of encoding or retrieval processes. Whilst these results cast some doubt over the left–right encoding–retrieval asymmetry model of episodic memory, a number of methodological factors precluded more definite conclusions being drawn. First, a restriction on the number of PET scans allowed (imposed by radiation guidelines) precluded the use of a 'low-level' baseline condition in that study. Consequently, encoding conditions were always compared directly to retrieval conditions, and thus activation common to both of these processes would have been 'subtracted out' during the statistical analysis. Second, the use of a 90 s PET acquisition period required that each trial had to be repeated three times during the retrieval tasks. One consequence of this was that subjects' choices became increasingly automated during the course of each scan, irrespective of their accuracy. A reduction in activation observed during the retrieval tasks was one possible consequence of this (for further discussion, see [23]).

To extend the findings from the earlier PET study and to address these concerns, the same encoding and retrieval tasks were adapted for use with 3 T functional magnetic resonance imaging (*f*MRI), which also provides greater spatial and temporal resolution than PET. Two control conditions were designed to serve as baseline comparisons for the encoding and retrieval tasks. Given the results of the PET study, it was predicted that similar regions of the lateral frontal cortex would be involved in the encoding and retrieval tasks. In addition, it was hypothesised that the verbal tasks would lead to greater activation of the left prefrontal cortex whilst the visual tasks would lead to greater activation of the right prefrontal cortex, in both cases, irrespective of encoding or retrieval.

Although functional neuroimaging can identify which cortical and subcortical regions are involved in a particular process, it cannot reveal how *critical* any specific region is to that process. In a parallel study, therefore, the same tasks were adapted for testing patients with unilateral damage to the frontal cortex and comparisons were made with healthy control subjects. Given the predictions of the left–right encoding–retrieval asymmetry model, one might reasonably expect to observe a dissociation of encoding and retrieval deficits in patients with left or right unilateral prefrontal cortical excisions, respectively. This, however, does not appear to have been the case to date; past studies have suggested that unilateral prefrontal patients are not disproportionately impaired at either memory encoding or retrieval [27,51,52,55]. There is, however, some evidence to suggest that left- and right-sided frontal-lobe patients are differentially impaired at verbal and non-verbal memory tasks (e.g. [44]). On this basis and given the results of the previous PET study, it was predicted that left and right frontal patients would be disproportionately impaired at the verbal and non-verbal episodic memory tasks, respectively.

2. Study 1—*f*MRI study

2.1. Methods

2.1.1. Subjects

Six right-handed healthy subjects (three male, three female) were scanned. The age of the subjects varied between 23 and 50 years (mean age = 37 years). The study received ethical approval from the Central Oxford Research Ethics Committee.

2.1.2. Image acquisition and data analysis

Scanning was carried out at the Functional Magnetic Resonance Imaging of the Brain Centre (FMRIB), Oxford, UK on a 3 T MRI system driven by a Varian Unity Inova console and equipped with an Oxford Magnet Technology magnet, a Siemens body gradient coil and a bird-cage radio-frequency head coil. Two four-dimensional datasets were acquired for each subject, one for the visual tasks and one for the verbal tasks. Each dataset consisted of three experimental blocks of 160 s (480 s in total) and the onset of each experimental block was triggered using the FMRIB Stimulus Presentation Software version 1.2 (FSPS, FMRIB, Oxford, UK). Stimuli were presented via a projector on a white screen located at the foot end of the scanner bed, and the subjects could view this screen by wearing a pair of prism spectacles during scanning. Subjects' responses were made using two specified buttons ('left' and 'right') on a four-button response box held in the right hand and were recorded via FSPS. For functional data, an echo planar imaging (EPI) pulse sequence was implemented to acquire T2*-weighted image volumes with blood oxygen level dependent (BOLD) contrast. Each volume consisted of 17 mm × 7 mm slices with a TR of 2.5 s (TE = 28 ms). A T1 structural scan (32 mm × 7 mm slices) was also acquired for each subject. Foam padding was utilised to immobilise subjects within the MRI head coil.

All image pre-processing and statistical analyses were carried out using FMRIB's Easy Analysis Tool (FEAT) version 3.3, FMRIB, Oxford, UK [64], which is an extension of the MedX package (Sensor Systems, VA, USA). Pre-processing included: first, initial corrections to the data, for example to correct for slice-timing errors or slice drop-outs; second, motion correction, in which each volume was re-aligned to a pre-selected original volume in order to correct for subject movement; fluctuations in signal intensity due to motion were also corrected; third, spatial filtering, which convolves the data with a smoothing kernel (Gaussian filter); fourth, global intensity normalisation, resulting in all volumes ending up with the same mean intensity value; this was to account for the fact that the overall intensity of images may drift over time and furthermore, in order that a valid group statistical analysis could be conducted, all subjects' data must have the same mean signal intensity; and finally, temporal filtering, in which each data time series was convolved with a bandpass temporal filter to remove any unwanted low frequency drifts (e.g. scanner-related) and high frequency noise (e.g. from repetitive physiological signals such as breathing, the cardiac signal, etc.).

Statistical analyses were carried out on individual subjects' data as well as combined group data. To facilitate localisation of significant clusters of activation, *f*MRI data were registered to individual subjects' structural scans (in the case of individual subject data) or with a high resolution standard brain in Talairach space ([56], in the case of combined group data) using FMRIB's Linear Image Registration Tool (FLIRT) [18]. Group analyses were carried out using a fixed effects model since the number of subjects employed (six) did not make a random effects analysis feasible. However, it was found that between four and five of the six subjects' data corresponded closely to the group results indicating that changes were broadly consistent across subjects (see Section 2.2). For the group results, a threshold of $Z = 4$ was used to detect clusters of activation and those that survived a statistical threshold of $P = 0.05$ (corrected for multiple comparisons) are reported.

2.1.3. Procedure and tasks

Four different experimental tasks (*visual encoding*, *visual retrieval*, *verbal encoding* and *verbal retrieval*) and two control tasks (*encoding control* and *retrieval control*) were employed in this study. The visual and verbal tasks were divided into two separate experiments with an ABCDE–ABCDE–ABCDE design in which A refers to an encoding block, B refers to an encoding control block, C refers to a retrieval block, D refers to a retrieval control block and E refers to a rest period. Each ABCDE block was 160 s in length and was repeated three times to give a total run time of 480 s.

The stimuli used in all the tasks were strings of large light blue letters in the middle of a black background. Prior to scanning, the subjects were given instructions for each task and shown examples of the task stimuli. In each of the encoding blocks, the subjects were required to remember 10 novel stimuli presented once each at a fixed rate of one every 3 s. The subjects were instructed to press both buttons on the response box with the index and middle fingers of their right hand on the presentation of each stimulus. In each of the retrieval blocks, the subjects were presented with the stimuli from the corresponding encoding block (10 stimuli presented once each), each paired with a similar, but unfamiliar stimulus at a rate of one trial every 3 s. The order of presentation was random and differed from that in the encoding tasks. The subjects were required to press the appropriate response button corresponding to the position of the stimulus they had seen previously (e.g. pressing the left button with their right index finger to select the stimulus on the left of the screen and pressing the right button with their right middle finger to select the stimulus on the right of the screen). The subjects were instructed to make a response as soon as possible and to concentrate on the next trial if they were unable to make a response before the end of a trial (however, analysis of the behavioural data showed that this did not occur and that all subjects responded well within the trial interval of 3 s). Reaction time and accuracy data were collected during the course of scanning.

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. The control tasks were designed to place a similar demand on visual and motor processes but to minimise any demands placed on memory processes.

Fig. 1 illustrates each of the conditions.

1. *Visual encoding* (Fig. 1A(a)): 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. '  ' and 'ZXPQDF'). It is possible that this string of consonants had the capacity for verbal re-coding. However, since (a) the letter string was unpronounceable with no semantic meaning, (b) the fonts used were not easily processed verbally, and (c) the same letter string was presented in the visual retrieval condition (see later), this condition was designed to emphasise visual encoding mechanisms and to discourage subjects from using verbally mediated strategies for encoding.
2. *Visual retrieval* (Fig. 1A(b)): The subjects were presented with each stimulus from the visual encoding condition paired with the same letter string in an unfamiliar font (e.g. 'ZXPQDF' versus '  '). 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. 1B(a)): The subjects were presented with pronounceable non-words (e.g. 'sligerit'), 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

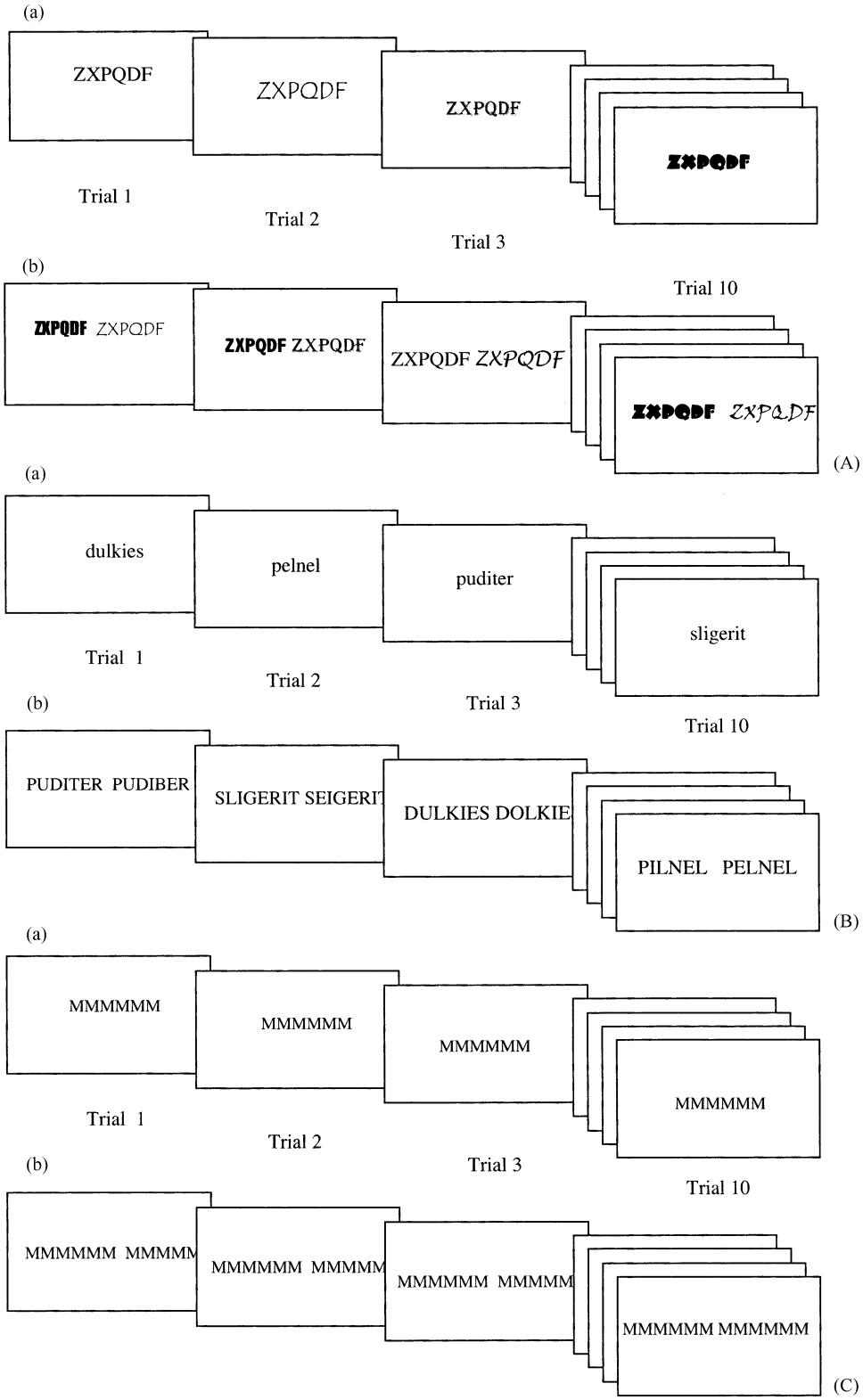

Fig. 1. (A) Schematic representation of: (a) visual encoding; (b) visual retrieval. (B) Schematic representation of: (a) verbal encoding; (b) verbal retrieval. (C) Schematic representation of: (a) control encoding; (b) retrieval encoding.

existing real words and yet, they possessed the phonemic structure characteristic of real words. Since the non-words had visual characteristics that 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(b)): 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' versus '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 of this task was on verbal retrieval.
5. *Encoding control* (Fig. 1C(a)): The subjects were presented with a string of six letters 'M' 10 times and, as in the encoding tasks, they were required to press both response buttons simultaneously on each presentation.
6. *Retrieval control* (Fig. 1C(b)): The subjects were simultaneously presented with two identical strings of six letters 'M' 10 times and were required to press the left and right response buttons alternatively on each presentation.
7. *Rest*: An additional rest condition was also included in which subjects were instructed to remain still whilst being presented with a blank black screen. A rest condition occurred for a short time (2.5 s) between the different encoding and retrieval conditions and also for a longer period (32.5 s) after each encoding–retrieval set. The former was a signal to the subjects that the task was about to change.

2.2. Results

2.2.1. Behavioural performance

On average, the subjects performed worse in the visual retrieval task (75.36%) compared to the verbal retrieval task (87.22%). However, a two-tailed paired *t*-test revealed that this difference was not significant ($t = -1.550$, $P = 0.182$). In addition to this, further analyses revealed that there was no correlation between performance and regional BOLD signal values. The mean reaction times for the visual and verbal retrieval tasks were 1.60 and 1.44 s, respectively. A two-tailed paired *t*-test showed that this difference was also not significant ($t = 1.899$, $P = 0.116$).

2.2.2. BOLD response changes

The statistical analyses (defined a priori) were designed primarily to investigate which regions of the frontal-lobes are recruited during the encoding and retrieval of visual and verbal stimuli. The results of these analyses, in terms of statistically significant group differences in BOLD response, are reported below and details are given in Tables 1–6, along with corresponding stereotaxic co-ordinates based on the brain atlas of Talairach and Tournoux [56]. For each

Table 1
Stereotaxic co-ordinates of activation when the visual encoding condition was compared to the encoding control task

Region	BA	Stereotaxic co-ordinates			*P*-value
		x	*y*	*z*	
Visual encoding – encoding control					
Left hemisphere					
Inferior frontal cortex	44	−40	7	25	0.01
Superior parietal cortex	7	−23	−69	35	0.001
Right hemisphere					
Ventrolateral frontal cortex	45	44	25	12	0.001
Anterior cingulate cortex	32	4	16	42	0.001
Motor cortex	1	26	−31	74	0.001
Cerebellum	–	13	−55	−46	0.001
Prestriate cortex	19	35	−70	6	0.001

Table 2
Stereotaxic co-ordinates of activation when the visual retrieval condition was compared to the retrieval control task

Region	BA	Stereotaxic co-ordinates			*P*-value
		x	*y*	*z*	
Visual retrieval – retrieval control					
Left hemisphere					
Inferior frontal cortex	45/44	−38	18	16	0.001
Superior frontal cortex	6	−24	−5	48	0.04
Right hemisphere					
Ventrolateral prefrontal cortex	45	40	35	8	0.001
Anterior cingulate cortex	32	16	14	37	0.001
Striate cortex	17	1	−67	10	0.001

Table 3
Stereotaxic co-ordinates of activation when the visual encoding condition was compared to the visual retrieval condition

Region	BA	Stereotaxic co-ordinates			*P*-value
		x	*y*	*z*	
Visual encoding – visual retrieval					
Left hemisphere					
Middle temporal cortex	37	−44	−61	26	0.01
Visual retrieval – visual encoding					
Left hemisphere					
Ventrolateral prefrontal cortex	47	−32	22	−3	0.001
Precuneus	7	−1	−57	60	0.01
Superior parietal cortex	7	−19	−63	48	0.001
Cerebellum	–	0	−70	−9	0.001
Right hemisphere					
Dorsolateral prefrontal cortex	46	42	45	5	0.001
Ventrolateral prefrontal cortex	47	41	27	−4	0.01
Superior parietal cortex	7	12	−77	53	0.02

Table 4
Stereotaxic co-ordinates of activation when the verbal encoding condition was compared to the encoding control task

Region	BA	Stereotaxic co-ordinates			*P*-value
		x	*y*	*z*	
Verbal encoding – encoding control					
Left hemisphere					
Inferior frontal cortex	44	−43	8	20	0.001
Inferior temporal cortex	37	−43	−66	−15	0.001
Superior parietal cortex	7	−24	−66	38	0.02
Right hemisphere					
Cerebellum	–	44	−63	−24	0.04

Table 5
Stereotaxic co-ordinates of activation when the verbal retrieval condition was compared to the retrieval control task

Region	BA	Stereotaxic co-ordinates			*P*-value
		x	*y*	*z*	
Verbal retrieval – retrieval control					
Left hemisphere					
Ventrolateral prefrontal cortex	45	−41	18	18	0.001
Cerebellum	–	−28	−61	−16	0.001
Inferior parietal cortex	40	−41	−61	37	0.001
Right hemisphere					
Ventrolateral prefrontal cortex	45	41	32	15	0.001
Ventrolateral prefrontal cortex	45/47	41	22	−7	0.001
Anterior cingulate cortex	32	3	18	38	0.001
Striate cortex	17	7	−73	6	0.001

comparison, four or five of the six subjects' datasets corresponded closely to the group results indicating that the changes were broadly consistent across subjects. Since the verbal and visual tasks were compared directly in the previous PET study (see [23]) and comparing scans between two separate *f*MRI data acquisition runs is susceptible to methodological problems (e.g. drift effects), comparisons were not made between visual and verbal scans.

Table 6
Stereotaxic co-ordinates of activation when the verbal retrieval condition was compared to the verbal encoding task

Region	BA	Stereotaxic co-ordinates			*P*-value
		x	*y*	*z*	
Verbal retrieval – verbal encoding					
Left hemisphere					
Cerebellum	–	−12	−53	−7	0.02
Striate cortex	17	−4	−72	12	0.00
Right hemisphere					
Ventrolateral prefrontal cortex	45	40	32	18	0.01
Anterior cingulate cortex	32	3	17	41	0.01
Precuneus	7	1	−57	58	0.04
Inferior parietal lobe	7	32	−57	38	0.01
Cerebellum	–	30	−70	−21	0.00

2.2.3. Visual encoding

When activation during the encoding control task was subtracted from that during the visual encoding condition, significant regions of activation were observed in the left inferior frontal cortex (BA 44), left superior parietal cortex (7), right ventrolateral frontal cortex (BA 45), right anterior cingulate cortex (BA 32), right motor cortex (BA 1), right cerebellum and right prestriate cortex (BA 19; see Table 1 and Fig. 2).

2.2.4. Visual retrieval

When activation during the retrieval control task was subtracted from that during the visual retrieval condition, significant regions of activation were observed in the left inferior frontal cortex (BA 45/44), the left superior frontal cortex (BA 6), the right ventrolateral prefrontal cortex (BA 45), the right anterior cingulate cortex (BA 32) and the right striate cortex (BA 17; see Table 2 and Fig. 2).

2.2.5. Visual encoding versus visual retrieval

When activation during the visual retrieval condition was subtracted from that during the visual encoding condition, a significant region of activation was observed in the left middle temporal cortex (BA 37). The reverse comparison revealed significant activation in the left precuneus (BA 7), the left cerebellum, the ventrolateral prefrontal cortex (BA 47) bilaterally, the superior parietal cortex (BA 7) bilaterally and the right dorsolateral prefrontal cortex (BA 46; see Table 3).

2.2.6. ROI analysis for visual conditions

The BOLD signal intensity values were extracted for each subject for the cluster of significant activation (660 voxels) in the right ventrolateral frontal cortex (BA 45) identified by the visual encoding minus encoding control comparison. From Fig. 3, it can be seen that the BOLD signal was greatest in this cluster during the visual retrieval task, followed by the visual encoding task and the control and rest conditions, a pattern that was consistent across all six subjects. A univariate ANOVA, with 'BOLD signal' as the dependent variable, 'condition' as a fixed factor and 'subject' as a random factor, revealed a significant main effect of condition. Post-hoc analyses (Tukey's HSD) showed that there was a significant difference between the visual retrieval and visual encoding tasks ($P = 0.03$) as well as between each of these tasks and the control and rest conditions ($P < 0.0001$). There was no significant difference between any of the control and rest conditions ($P > 0.4$).

2.2.7. Verbal encoding

When the activation during the encoding control task was subtracted from that during the verbal encoding condition, significant regions of activation were observed in the left inferior frontal cortex (BA 44), the left inferior temporal cortex (BA 37), the left superior parietal cortex (BA 7) and finally, the right cerebellum (see Table 4 and Fig. 4).

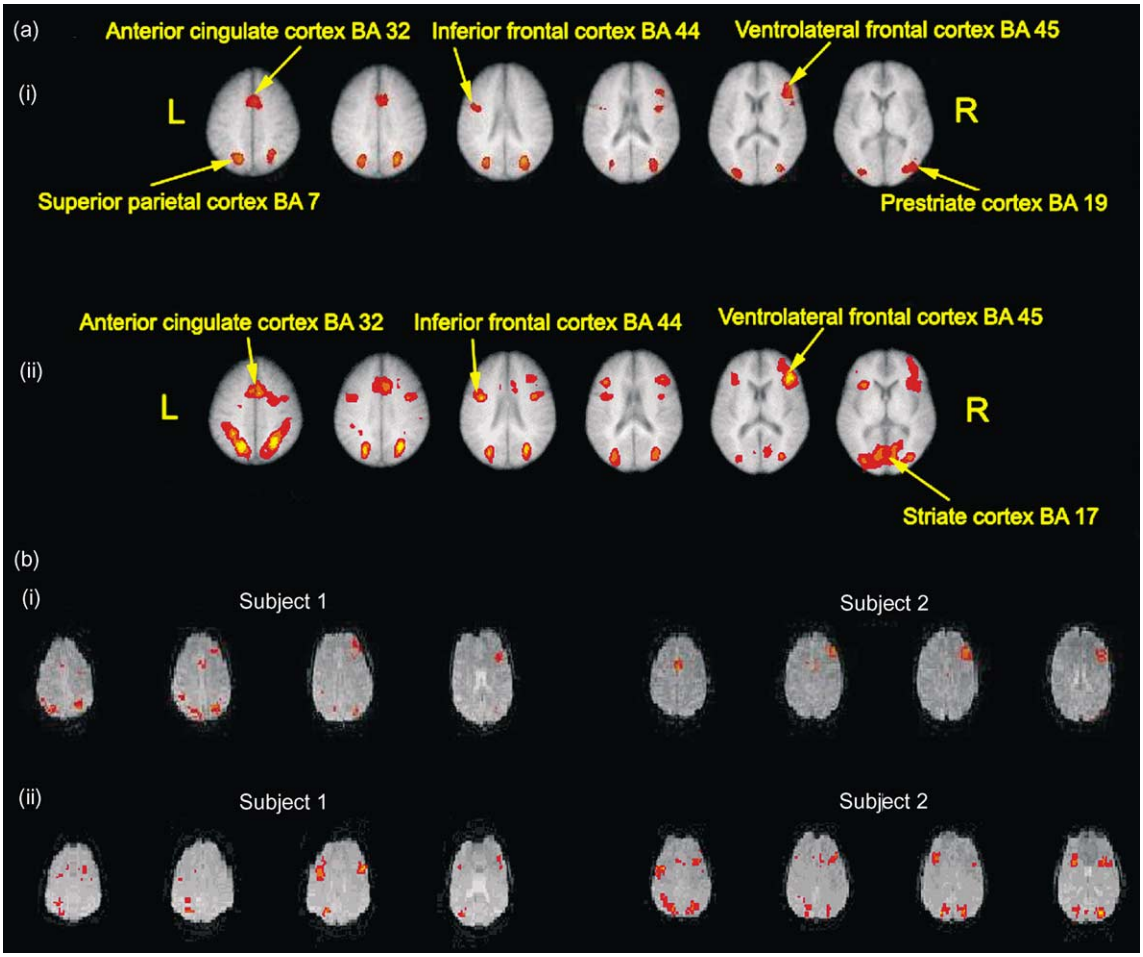

Fig. 2. (a) Schematic diagram showing the regions of significant group BOLD signal change when (i) the encoding control task was subtracted from the visual encoding condition and (ii) the retrieval control task was subtracted from the visual retrieval condition (registered to standard Talairach brain volume). (b) Schematic diagram showing the regions of significant BOLD signal change for two selected individual subjects (registered to individual subjects' structural MRI) when (i) the encoding control task was subtracted from the visual encoding condition and (ii) the retrieval control task was subtracted from the visual retrieval condition.

2.2.8. Verbal retrieval

When the activation during the retrieval control task was subtracted from that during the verbal retrieval condition, significant regions of activation were observed in the left ventrolateral prefrontal cortex (BA 45), the left cerebellum, the left inferior parietal cortex (BA 40), the right ventrolateral prefrontal cortex (BA 45, 47), the right anterior cingulate cortex (BA 32) and the right striate cortex (BA 17; see Table 5 and Fig. 4).

2.2.9. Verbal encoding versus verbal retrieval

When the activation during the verbal retrieval condition was subtracted from that during the verbal encoding condition, no significant regions of activation were observed. However, the reverse comparison revealed significant regions of rCBF change in the left striate cortex (BA 17), the right ventrolateral prefrontal cortex (BA 45), the right anterior cingulate cortex (BA 32), the right precuneus (BA 7), the right inferior parietal lobe (BA 7) and finally, the cerebellum bilaterally (see Table 6).

2.2.10. ROI analysis for verbal conditions

The BOLD signal intensity values were extracted for each subject for the cluster of significant activation (160 voxels) in the left inferior frontal cortex (BA 44) extending into the ventrolateral frontal cortex (BA 45) identified by the verbal encoding minus encoding control comparison. From Fig. 5, it can be seen that the BOLD signal was greatest in this cluster during the verbal retrieval task, followed by the verbal encoding task and the control and rest conditions, a pattern that was identical in all but one subject. A univariate ANOVA, with 'BOLD signal' as the dependent variable, 'condition' as a fixed factor and 'subject' as a random factor revealed a significant main effect of condition. Post-hoc analyses (Tukey's HSD) showed that there was no significant difference between the verbal retrieval and

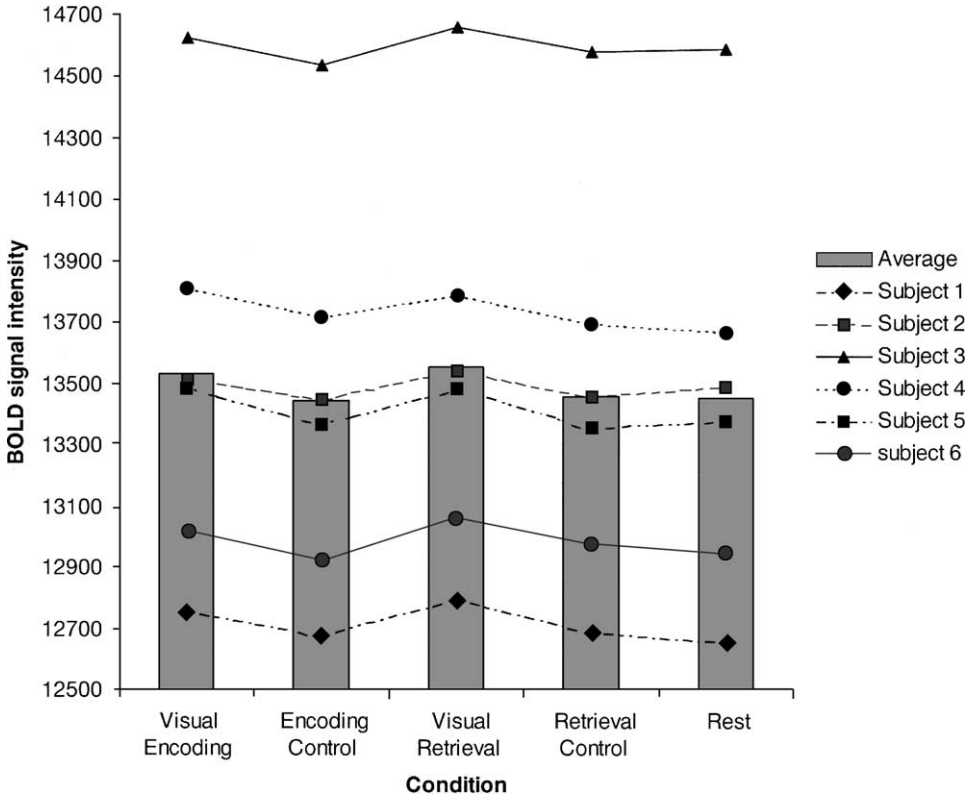

Fig. 3. Graph to illustrate the mean BOLD signal intensity for each subject in the right ventrolateral frontal cortex (BA 45) activation cluster during the different conditions.

verbal encoding tasks ($P = 0.48$), although there was a significant difference between each of these tasks and the control and rest conditions ($P < 0.0001$). There was no significant difference between any of the control and rest conditions ($P > 0.8$).

2.2.11. Summary of results

In summary, the encoding and retrieval tasks both activated left and right frontal-lobe regions. During encoding, the visual stimuli produced activation in both left and right lateral frontal regions whilst the verbal stimuli produced activation predominantly in the left lateral frontal cortex. During retrieval, there was bilateral activation of the lateral frontal cortex, irrespective of the type of material involved.

2.3. Discussion

In a previous PET study, a novel episodic memory task was used to show that stimuli which are easily verbalised tend to activate the left prefrontal cortex whilst stimuli which are not easily verbalised tend to activate the right prefrontal cortex, in both cases, irrespective of episodic memory encoding or retrieval processes [23]. In this study, the same task was adapted for use with 3 T *f*MRI and the results both support and extend these previous findings.

When activation during the encoding control task was compared to that during the visual encoding condition, significant regions of activation were observed in left and right frontal-lobe regions. In contrast, when activation during the encoding control task was compared to that during the verbal encoding condition, significant frontal activation was observed in the left hemisphere only (BA 44). These results confirm that the type of information being processed (e.g. visual versus verbal) can influence the extent to which the left and right prefrontal cortices are recruited during memory encoding.

To date, only a small number of neuroimaging studies have compared encoding of non-verbal stimuli (e.g. faces, abstract patterns) with a baseline condition [14,21,22,46] and the results have been rather mixed. Whilst Haxby et al. [14] reported unilateral left prefrontal cortex activation during the encoding of faces, Kelley et al. [21] and Klingberg and Roland [22] reported unilateral right prefrontal cortex activation during the encoding of faces and the learning of a non-verbal paired associates task, respectively. In contrast, as in the current study, Roland and Gulyas [46] reported bilateral prefrontal cortex activation during the encoding of complex visual geometrical patterns. Given these previous findings, it is unclear whether activation in the left prefrontal cortex during encoding of non-verbal material reflects the recruitment of phonological processes that may facilitate

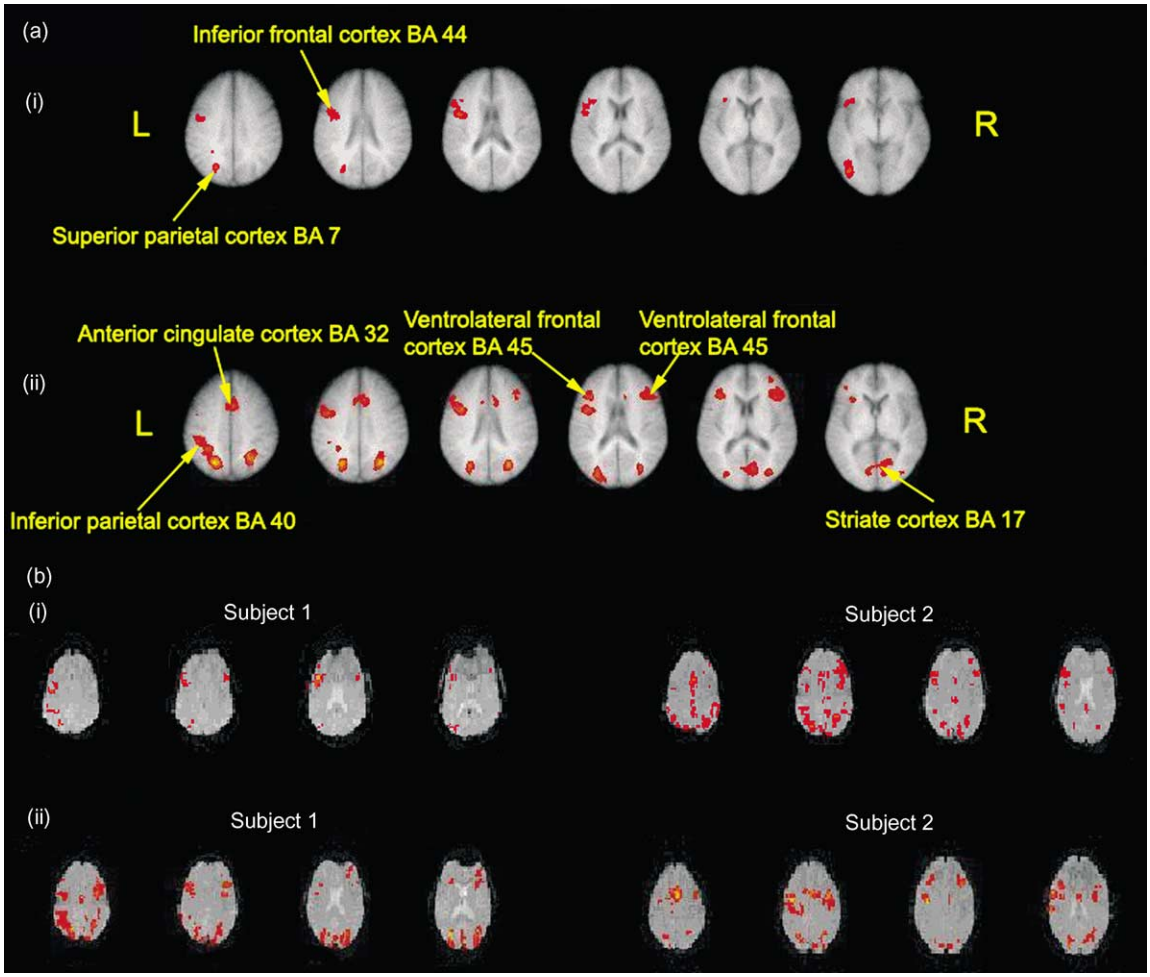

Fig. 4. (a) Schematic diagram showing the regions of significant group BOLD signal change when (i) the encoding control task was subtracted from the verbal encoding condition and (ii) the retrieval control task was subtracted from the verbal retrieval condition (registered to standard Talairach brain volume). (b) Schematic diagram for two selected individual subjects (registered to individual subjects' structural MRI) showing the regions of significant BOLD signal change when (i) the encoding control task was subtracted from the verbal encoding condition and (ii) the retrieval control task was subtracted from the verbal retrieval condition.

encoding processes, the processes of memory encoding per se, or a combination of the two.

A number of previous studies have compared the encoding of verbal stimuli with a baseline condition and again, the results have been mixed. For example, whilst some studies have reported left prefrontal cortex activation [20,21,45,50], others have reported bilateral prefrontal cortex activation [15,32] whilst at least one has reported only right prefrontal activation [5]. This variation may reflect differences in the tasks used, leading to changes in the specific demands that are placed on encoding processes. For example, in the current study the stimuli were explicitly designed to encourage verbal encoding processes and discourage any visual or semantic processing. Accordingly, activation was observed predominantly in the left frontal-lobe. In other studies, however, even though ostensibly verbal stimuli have been used (e.g. [32,12]), the visuo-spatial or semantic characteristics of those stimuli may still have lead to a wider recruitment of neural regions reflecting the involvement of non-verbal processes.

Unexpectedly, stimulus type did not effect the lateralisation of prefrontal cortex activation during the retrieval tasks. When the retrieval control condition was compared with the visual retrieval condition, significant regions of rCBF change were observed in the frontal-lobes bilaterally; specifically, in the left inferior frontal cortex (BA 45/44), the left superior frontal cortex (BA 6), the right ventrolateral prefrontal cortex (BA 45) and the right anterior cingulate cortex (BA 32). When the retrieval control condition was compared with the verbal retrieval condition, similar regions of activity were observed in the left ventrolateral prefrontal cortex (BA 45), the right ventrolateral prefrontal cortex (BA 45/47) and the right anterior cingulate cortex (BA 32). These results suggest that, whilst stimulus type may have some effects on the overall lateralisation of prefrontal cortex activation during memory retrieval [23,25,39,62], by and large, prefrontal

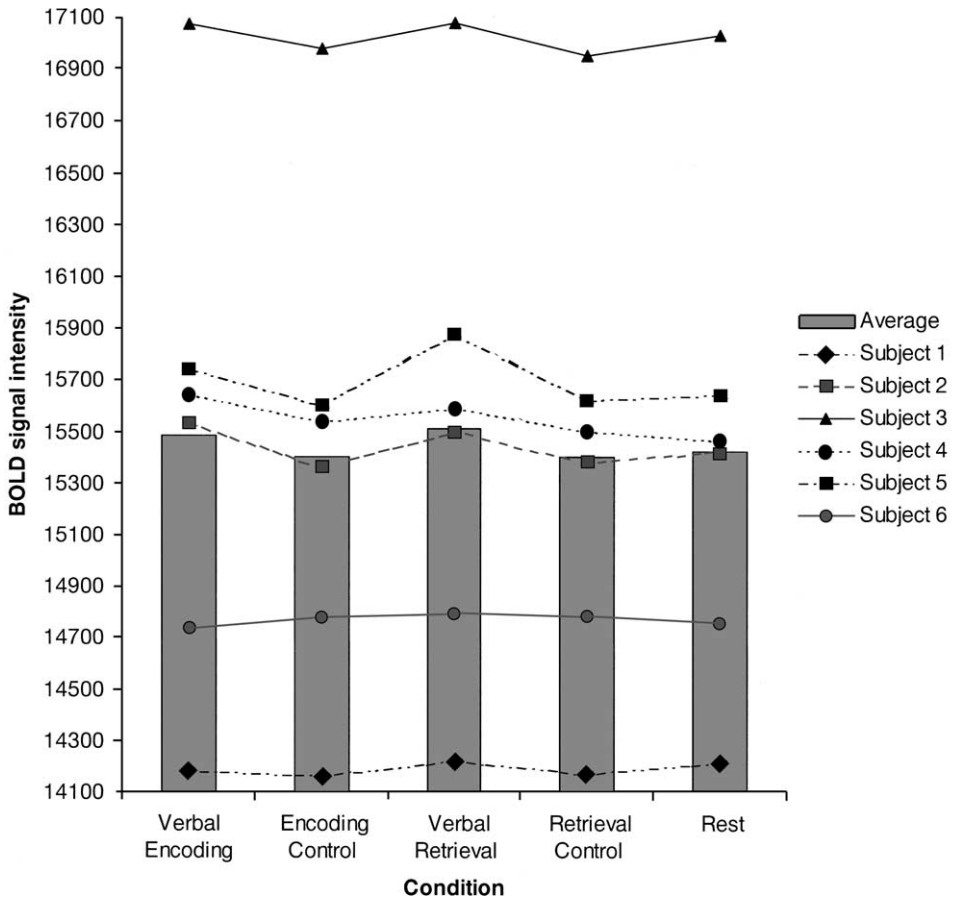

Fig. 5. Graph to illustrate the mean BOLD signal intensity for each subject in the left inferior frontal cortex (BA 44/45) activation cluster during the different conditions.

cortical regions are recruited bilaterally (for review, see [24]).

It is worth noting that some of the inconsistencies in studies in this area are undoubtedly due to differences in the types of statistical comparison performed and its effect on the overall pattern of activation observed. For example, several of the studies that have reported an effect of stimulus type on the lateralisation of prefrontal cortex activation during episodic memory processes [23,25,62] have directly compared similar experimental tasks of differing stimulus modality with each another (e.g. a visual encoding task versus a verbal encoding task and a visual retrieval task versus a verbal retrieval task), rather than with a low-level baseline condition. By comparing two tasks that are similar in all respects expect for stimulus type, any common regions of activation between them are likely to be subtracted out (including certain processes that may be essential components of performance, but equally relevant to both tasks), leaving regions of activation that are specific to the stimuli of the tasks.

A recent review of all functional neuroimaging literature by Cabeza and Nyberg [6] suggested that the right prefrontal cortex may be preferentially involved in episodic memory retrieval irrespective of the type of information involved (e.g. visual versus verbal). In the current study, there was little evidence to support this possibility: subtracting activation during the verbal encoding condition from that during the verbal retrieval condition did produce a significant region of activation in the right lateral frontal cortex (BA 45), although subtracting activation during the visual encoding condition from that during the visual retrieval condition produced activation bilaterally in both right and left lateral frontal regions (BA 46, 47).

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’ [19,26,37,47–49], ‘monitoring’ [40,43], organisational strategies [9,10] and reflective processing [35,36]. The current study was not designed to investigate these processes in any detail but rather, to focus on the general role of the left and right frontal-lobes in episodic memory encoding and retrieval in the context of the proposed left–right encoding–retrieval model [38,60]).

In the present study, there was considerable overlap between those frontal regions that were activated during the encoding and retrieval conditions. For example, the left inferior frontal cortex (BA 44/45) and the right ventrolateral

prefrontal cortex (BA 45) were significantly activated during both the visual encoding and visual retrieval conditions. This pattern is all the more obvious from the ROI analyses (see Figs. 3 and 5), which show that voxels which were significantly active during the encoding tasks were also significantly active during the corresponding the retrieval tasks. Again, these data suggest that similar regions of the frontal-lobe may be involved in episodic memory encoding and retrieval processes when factors related to stimulus type are appropriately controlled.

It must be noted that, overall, activation in the frontal-lobes was significantly greater during the retrieval tasks than during the corresponding encoding tasks, as shown by the direct comparison between these conditions. It is unclear why this effect was observed, although one obvious interpretation is that the retrieval tasks placed a greater demand on mnemonic processes mediated by lateral frontal-lobe regions. For example, during the encoding tasks, the subjects were required to encode successively presented stimuli in terms of their phonological or visual properties. In contrast, during the retrieval tasks, the subjects were presented with pairs of stimuli, from which they had to choose the exemplars they had been previously presented. Interference at this stage, from the competing stimulus, may have contributed significantly to the overall cognitive load as well as evoking additional control processes, possibly dependant on lateral frontal regions, to deal with this competition.

3. Study 2—neuropsychological study

As discussed earlier, several functional neuroimaging studies have provided evidence to suggest that material type (e.g. visual versus verbal) can influence the lateralisation of frontal-lobe activity during episodic memory encoding and retrieval tasks [21,23,25,62]. Broadly speaking, the results of the *f*MRI study described previously lend some support to this suggestion.

According to these observations, it might be predicted that left frontal lesions would disproportionately impair episodic memory when verbal stimuli are employed whilst right frontal lesions would disproportionately impair episodic memory when visual stimuli are employed. In a follow-up investigation, this hypothesis was tested directly by comparing groups of patients with left or right frontal-lobe lesions and healthy matched controls on the same episodic memory task.

3.1. Methods

3.1.1. Subjects

Table 7 gives a summary of the mean characteristics of the subject groups included in this study. A number of general neuropsychological test scores are provided for all three groups, including the National Adult Reading Test (NART) [34], which provides an estimate of pre-morbid verbal IQ, Form A of the Cattell Culture Fair Test [57], which provides a measure of fluid intelligence, and a version of the Matching to Sample (MTS) test from the Cambridge Neuropsychological Automated Test Battery (CANTAB, Cambridge Cognition, UK), which assesses visual recognition memory for abstract patterns at a simultaneous condition and delays of 0 and 4 s. Performance on the Wisconsin Card Sorting Task (WCST) [4,13,33], which assesses set shift, and the Controlled Oral Word Association Test (COWAT) [2,3], which assesses verbal fluency are also provided for the frontal patients groups only.

3.1.2. Frontal lesion patients

Twenty unilateral frontal-lobe lesion patients from the Cambridge Cognitive Neuroscience Research Panel (CCRNP) were included in this study. The CCNRP has the approval for such studies from the Cambridge Health Authority Local Research Ethics Committee. Of the patients tested, 10 had sustained a right frontal lesion, including one haemorrhage, one aneurysm of the anterior communicating artery, three infarcts, three meningioma resections and two frontal-lobectomies. The average period between surgery and time of testing was 30.88 months (range: 18–68 months). Ten left unilateral frontal patients were tested, including four aneurysms of the anterior communicating artery, three subarachnoid haemorrhages, two meningioma resections and one case of encephalmalacia due to an haemorrhage. The average period of time between surgery and testing was 34.22 months (range: 8–73 months). Figs. 6 and 7 illustrate the location and size of the lesions for all of the frontal lesion patients that were tested and for whom structural MRI scans were available ($N = 13$). For the patients who did not have available MRI scans, the official hospital computer tomography lesion descriptions were: one with a small lateral frontal cortex lesion, one with a left inferior frontal cortex lesions, one with a left frontal cortex/subinsula lesion, three with a left frontal cortex lesion and one with a right ventromedial frontal cortex lesion. Two of the right frontal lesion patients were found to have additional damage to regions outside of the frontal-lobe. However, data from these subjects were not discarded for reasons discussed in the results section. The majority of the patients had English as their first language although one had English as his second language. However, this patient had resided in the UK for an extended period and was fluent in English. Apart from one left frontal patient, all the patients were right hand dominant.

3.1.3. Control subjects

The frontal lesion patients were compared with right-handed healthy volunteers from the MRC Cognition Brain Sciences Unit volunteer panel (20 in total). This panel is an accumulating database of volunteers who have been screened for past and present mental illnesses and brain injury. The subjects all had English as their first language and were matched for sex, age and IQ with the frontal lesion

Table 7
Summary of characteristics of the unilateral left frontal patients, the unilateral right frontal patients and the healthy controls

Group	*N*	M/F[a]	Age (years)	Duration[b] (months)	NART[c] verbal IQ	Cattell	DMTS[d] (%correct)			WCST[e]			COWT[f] (words)
							Sim	0 s	4 s	Cat[g]	General Err[h]	Persev Err[i]	
Left frontal	10	5/5	53.20	34.22	118 (2.06)	102 (12.93)	1 (0.00)	0.90 (0.045)	0.86 (0.052)	4.75 (1.25)	14.00 (9.06)	9.25 (8.92)	40.20 (7.76)
Right frontal	10	3/7	56.8	30.88	116 (1.95)	87 (5.08)	0.98 (0.018)	0.91 (0.076)	0.85 (0.047)	4.40 (0.71)	17.80 (4.63)	8.90 (4.93)	34.78 (4.04)
Control	20	8/12	55.65	–	117 (1.04)	105 (3.55)	0.99 (0.013)	0.98 (0.018)	0.95 (0.026)	–	–	–	–

[a] Male/female numbers.
[b] Average time between surgery and testing.
[c] National Adult Reading Test.
[d] Delayed Matching to Sample (scores are given at each delay).
[e] Wisconsin Card Sorting Task.
[f] Controlled Oral Word Association Test.
[g] Category sorted.
[h] General errors.
[i] Perseveration errors.

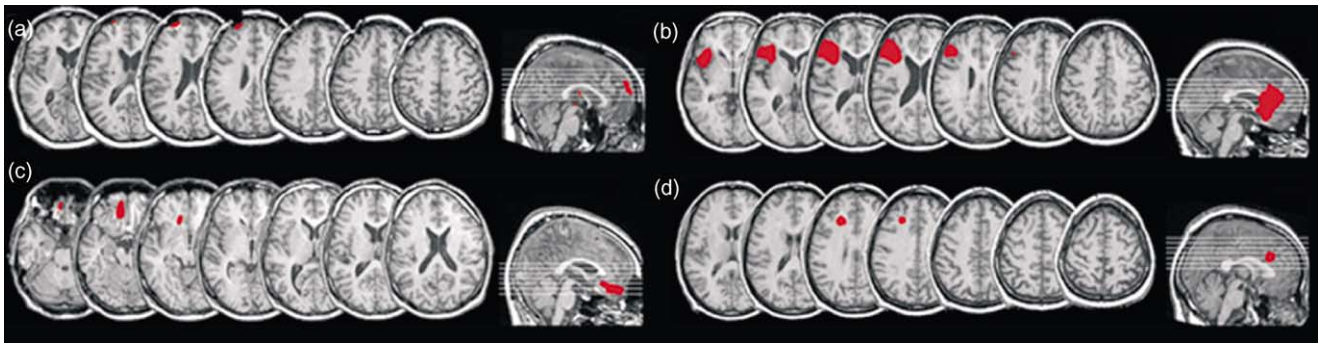

Fig. 6. (a–d) Structural MRI scans of unilateral left frontal-lobe patients (where available). Red shading highlights lesion.

patients (Table 7). All of the control subjects were tested at the MRC Cognition and Brain Sciences Unit, Cambridge, UK.

3.1.4. Procedure

All testing was carried out on a portable Advantech PPC-120 RT computer with a touch sensitive screen. In each testing session, the subjects were positioned to see the screen clearly and were instructed to make responses during the tasks by touching the screen with the index finger of their dominant hand. Prior to the start of each test, clear instructions were given to the subjects. Short practice tasks, one for each test, were also administered in order to ensure that the subjects had understood the instructions.

Adapted versions of the visual and verbal tasks described in the *f*MRI study above were administered to the subjects (see Section 2.1 for details). For the encoding phase of each task, subjects were presented with 15 stimuli repeated three times each in a pseudo-random order. A fixed interval of 30 s was then inserted between the end of the encoding phase and the start of the retrieval phase. Subjects were then presented with 15 forced choice recognition trials and were

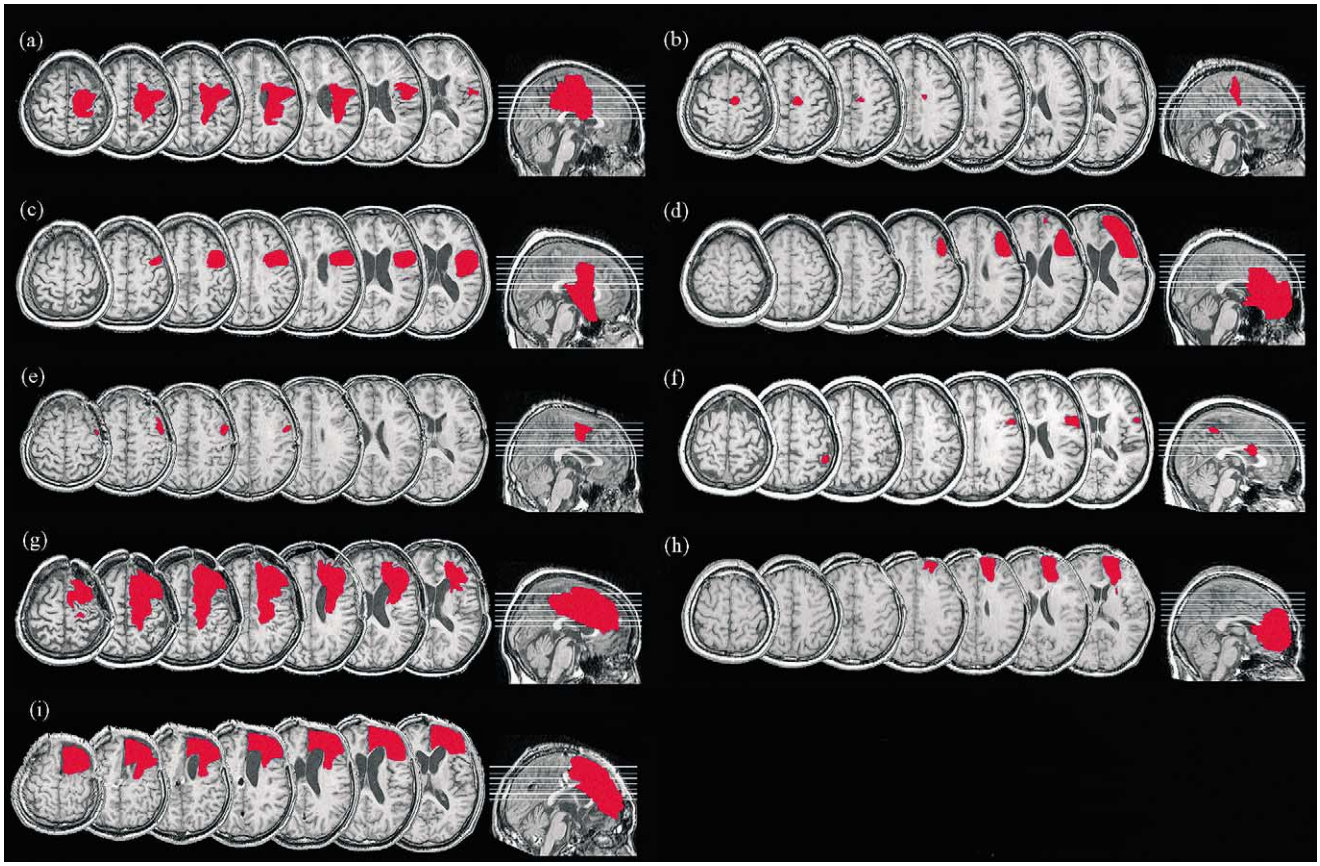

Fig. 7. (a–i) Structural MRI scans of unilateral right frontal-lobe patients (where available). Red shading highlights lesion.

instructed to select the stimuli that they had seen previously. The order in which the visual and verbal tasks were administered was counterbalanced across all subjects. The subjects' responses and response times were recorded by the test computer.

3.2. Results

3.2.1. Background neuropsychology

Age: An independent sample *t*-test revealed that the age of the frontal patients (right and left groups combined) was not significantly different compared to that of the control group ($t = 0.083$, $P > 0.9$).

NART: An independent sample *t*-test showed that there were no significant differences between the frontal patients combined and the control group in terms of verbal IQ as measured by the NART ($t = 0.036$, $P > 0.9$).

Cattell: In line with previous studies (e.g. [8]) there was a significant difference between the frontal patients combined and the control group in terms of IQ as measured by the Cattell intelligence test ($t = 2.442$, $P = 0.021$). However, there was no significant difference between the two frontal patient groups ($t = 1.112$, $P > 0.2$).

MTS: An independent sample *t*-test revealed that the frontal patients (right and left groups combined) were not significantly impaired compared to the control group on the simultaneous condition of the MTS task ($t = 0.035$, $t > 0.9$). A repeated measures ANOVA was used to analyse the delay conditions and this revealed a significant main effect of delay ($F = 4.823$, $P = 0.034$) and a trend towards a significant effect of group ($F = 3.899$, $P = 0.056$). However, there was no significant interaction between delay and group.

WCST: Planned independent sample *t*-tests revealed that the two frontal groups did not differ from each other in terms of categories sorted ($t = 0.254$, $P > 0.50$), general errors made ($t = 0.412$, $P > 0.50$) or perseverative errors made ($t = 0.037$, $P > 0.50$). Furthermore, the scores on these measures were comparable to the performance of frontal lesion patients reported in other studies (e.g. [33]).

COWT: Both frontal groups were found to perform within the normal range (scores between 31 and 44) of the COWT [3]. An independent sample *t*-test revealed that there was no significant difference between the two groups ($t = 0.690$, $P > 0.50$).

In summary, the patients included in this study presented with typical frontal lesion characteristics. The frontal patients were significantly impaired on standard neuropsychological tests that recruit frontal-lobe dependent cognitive processes, including the WCST and Cattell Culture Fair Test. However, the frontal patients exhibited intact performance on the NART, COWT and MTS task, suggesting that there was no general cognitive decline. Lastly, there was no significant difference between the left and right frontal groups on any of the measures used.

3.2.2. Patient lesions

Analysis of the structural MRI scans revealed that two of the right frontal patients' lesions extended beyond the frontal-lobe, including the post-central sulcus in one case and the parietal operculum in the other. Given the difficulties in recruiting frontal-lobe patients, the data from these subjects were not discarded for a number of reasons. First, box plots revealed that their behavioural data were within two standard deviations of the group mean values, and thus, were not outliers. Second, the results of the statistical analyses of the group data were not altered by the inclusion or exclusion of these subjects' data. Third, to our knowledge, the damaged parietal regions have not been implicated previously in impaired episodic memory processes, which are most often associated with damage to frontal-lobe regions (for review, see [63]) or to medial temporal lobe and diencephalic structures (for review, see [53]).

It is possible that the heterogeneous nature of the aetiologies of the patients could have confounded the findings in the current study. In particular, almost half of the left frontal patient group had aneurysms of the anterior communicating artery (ACoA), a condition which has been reported to be associated with serious memory impairment (e.g. [1,7]). However, an analysis of subgroups revealed that the left frontal patients with aneurysms of the ACoA were not significantly impaired in comparison to the other left frontal patients on the tasks used in the current study. Thus, it is unlikely that the inclusion of ACoA aneurysm patients could have confounded the present results.

3.2.3. Task accuracy

Fig. 8 illustrates the mean performance scores of each group on the retrieval tasks. Since the scores of each group did not satisfy the criterion of homogeneity of variance, an arcsine transformation was employed prior to statistical analysis. To assess the performance of the patients overall, a two-way ANOVA was conducted with one within-subjects factor for stimulus type (visual versus verbal) and one between-subjects factor for subject group (control versus left and right patients combined). This revealed significant effects of stimulus type ($F(1, 38) = 15.663$, $P = 0.0001$) and subject group ($F(1, 38) = 9.022$, $P = 0.005$), although there was no significant interaction between these two factors ($F(1, 38) = 0.160$, $P = 0.692$).

A second planned two-way ANOVA was conducted to compare the two patient groups directly. This revealed a significant effect of stimulus type ($F(1, 18) = 13.521$, $P = 0.002$), but no significant difference between the two patient groups ($F(1, 18) = 0.014$, $P = 0.906$). There was no significant interaction of stimulus type × patient group ($F(1, 18) = 0.275$, $P = 0.607$).

3.2.4. Response times

Fig. 9 illustrates the mean response times of each group on the retrieval tasks. Since the response times of each group did not satisfy the criterion of homogeneity of variance,

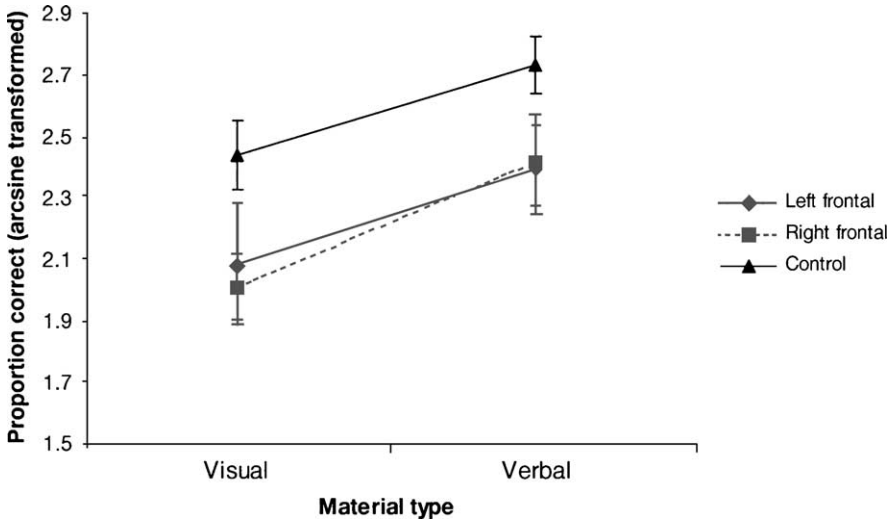

Fig. 8. Mean proportion correct (arcsine transformed) for the visual retrieval and verbal retrieval tasks.

a $\log_{10}$ transformation was carried out on the data prior to statistical analysis. To assess the response times of the patients overall, a two-way ANOVA was conducted with one within-subjects factor for stimulus type (visual versus verbal) and one between-subjects factor for subject group (control versus left and right patients combined). This revealed significant effects of stimulus type ($F(1, 38) = 8.186$, $P = 0.007$) and subject group ($F(1, 38) = 6.221$, $P = 0.017$), but no significant interaction between these two factors ($F(1, 38) = 1.309$, $P = 0.260$).

In order to compare the left and right frontal patients, a second two-way ANOVA was conducted. This revealed that there was no significant difference between stimulus type ($F(1, 18) = 1.838$, $P = 0.192$) or the two patient groups ($F(1, 18) = 0.0001$, $P = 0.988$). There was also no significant interaction of stimulus type × patient group ($F(1, 18) = 2.712$, $P = 0.117$).

3.3. Discussion

Previous studies have shown that right frontal-lobe patients are not significantly worse than left frontal-lobe patients on episodic memory retrieval tasks [27,51,52,55]. However, to date, no study has explicitly compared stimuli that are difficult to verbalise with those that are highly verbalisable, an important consideration given the recent neuroimaging evidence which has suggested that material type can determine the relative involvement of the right and left frontal-lobes during episodic memory processes [21,25,62].

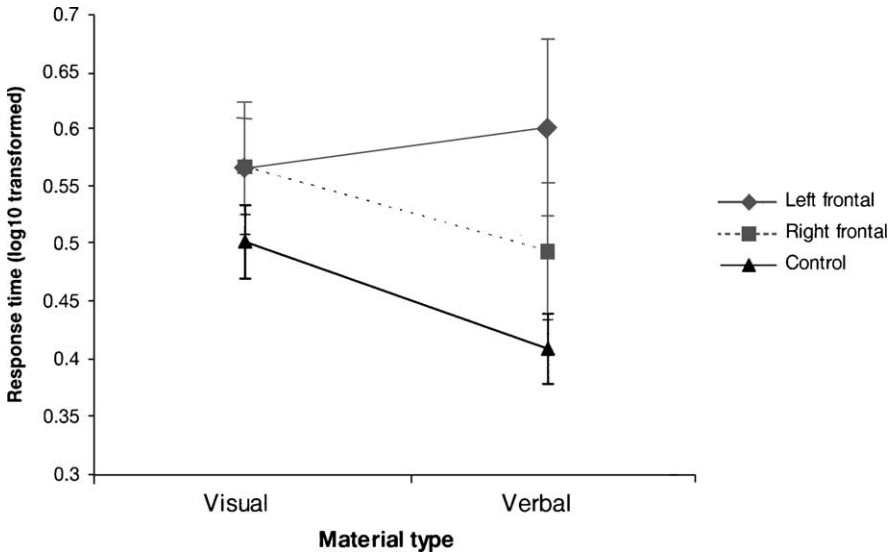

Fig. 9. Mean response times ($\log_{10}$ transformed) for the visual retrieval and verbal retrieval tasks.

The present results revealed that the frontal-lobe patients (left and right patients combined) were significantly impaired on the visual and verbal tasks compared to the controls. In line with previous studies, the frontal patients in the current study were impaired on tasks of frontal function, including the WCST (e.g. [29,33]) and the Cattell Culture Fair Test (e.g. [8]). However, given that the patients did not possess significantly lower NART scores and were not significantly impaired on verbal fluency or single item visual recognition memory as measured by the COWT and MTS tasks, respectively, their impairment on the current visual and verbal tasks is unlikely to be the result of a generalised cognitive decline. The majority of past studies that have investigated episodic memory using *recognition* memory tasks have shown that frontal lesion patients are not significantly impaired compared to healthy control subjects [17,30,51]. Why an impairment in recognition was found in the present study is not clear although one obvious difference between the current investigation and past studies is that semantically 'empty' stimuli (e.g. non-words and unique type fonts) were employed. In contrast, previous studies have often used semantically rich stimuli such as real words and pictures of everyday objects (e.g. [30,51,54]). It is likely that the use of semantically 'empty' stimuli in this study increased the difficulty of the recognition tasks significantly since the subjects were required to learn and recall stimuli for which they had no previous experience.

An alternative explanation for the discrepancy between this and past studies of episodic recognition memory is that the target (or learned) and distractor items used in the current study were designed to be very similar. For example, in the verbal retrieval task, the target and distracter items differed by only one or two letters (e.g. 'dulkies' versus 'dolkies') and in the visual retrieval task, distracter fonts were chosen that were similar to the target fonts (e.g. '  ' and ''). In contrast to this, past studies have often used target and distracter items that are highly dissimilar, for example, contrasting real words or objects that differ in terms of their semantic, verbal and visual properties [30,51,54]). One possible effect of using highly similar target and distractor items is that this may place a greater demand on 'strategic' or 'organisational' processes that are necessary to maintain performance on episodic memory tasks where interference from competing items is high. In fact, a number of recent neuropsychological [11,16] and functional neuroimaging studies [9,10] have demonstrated that such processes are often recruited during episodic memory tasks and are similar to those strategic processes that are assumed to be essential for various forms of working memory [24,41]. Moreover, such processes are likely to be mediated by the prefrontal cortex, providing a plausible explanation for the fact that the frontal lesion patients in this study were significantly impaired on the recognition memory tasks.

In the present study, there were no significant differences between the left and right frontal-lobe patients' performance and response times on either the visual or verbal tasks. This result runs contrary to the predictions from a previous PET study [23] and other functional neuroimaging studies [21,25,62] that have found that the left prefrontal cortex is more active during verbal memory tasks, whilst the right prefrontal cortex is more active during visual memory tasks. One potential explanation for this discrepancy is the possibility that some of the patients had sustained bilateral damage although close inspection of the patients' structural MRI and CT scans did not suggest that this was the case. Recovery of cognitive function due to neural reorganisation following trauma may also underlie the apparent lack of difference between the left and right frontal patients. However, a qualitative analysis of the behavioural data indicated that this explanation is unlikely, with time since surgery not appearing to be a significant factor in determining performance. It may be argued that a lack of an interaction between material type and side of lesion is consistent with a left–right asymmetry model of episodic memory [21,25,62], with the left-sided patients suffering from an encoding deficit and the right-sided patients suffering from a retrieval deficit. This is unlikely, however, given the number of functional neuroimaging studies that have undermined such a model by demonstrating that it is the stimulus modality (e.g. visual versus verbal) that is the main factor in determining the hemispheric lateralisation of activity during both memory encoding and retrieval processes [21,25,62]. A more likely explanation is that whilst the type of material involved may result in asymmetrical prefrontal cortical activity (as evident from functional neuroimaging studies), this asymmetry is not *critical* for task performance. Rather, it appears that both hemispheres of the frontal-lobe are required for successful performance on the tasks used in this study and that damage to either causes significant impairment. Such findings indicate the importance of parallel neuropsychological and functional imaging studies when assessing their relevance for understanding normal memory processes.

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