

Right prefrontal cortex and episodic memory retrieval: a functional MRI test of the monitoring hypothesis

R. N. A. Henson,^{1,2} T. Shallice² and R. J. Dolan^{1,3}

¹Wellcome Department of Cognitive Neurology, Institute of Neurology and ²Institute of Cognitive Neuroscience, University College London and ³Royal Free Hospital School of Medicine, London, UK

Correspondence to: R. N. A. Henson, Wellcome Department of Cognitive Neurology, 12 Queen Square, London WC1N 3BG, UK
E-mail: r.henson@fil.ion.ucl.ac.uk

Summary

Though the right prefrontal cortex is often activated in neuroimaging studies of episodic memory retrieval, the functional significance of this activation remains unresolved. In this functional MRI study of 12 healthy volunteers, we tested the hypothesis that one role of the right prefrontal cortex is to monitor the information retrieved from episodic memory in order to make an appropriate response. The critical comparison was between two word recognition tasks that differed only in whether correct responses did or did not require

reference to the spatiotemporal context of words presented during a previous study episode. Activation in a dorsal midlateral region of the right prefrontal cortex was associated with increased contextual monitoring demands, whereas a more ventral region of the right prefrontal cortex showed retrieval-related activation that was independent of task instructions. This functional dissociation of dorsal and ventral right prefrontal regions is discussed in relation to a theoretical framework for the control of episodic memory retrieval.

Keywords: source memory; process dissociation; cueing; verifying

Abbreviations: BA = Brodmann area; BOLD = blood oxygenation level-dependent; fMRI = functional MRI

Introduction

The activation of the right prefrontal cortex is a consistent finding in neuroimaging studies of retrieval from episodic memory (for reviews, see Buckner and Peterson, 1996; Cabeza *et al.*, 1997a; Fletcher *et al.*, 1997; Nyberg *et al.*, 1996a). However, the functional interpretation of this activation remains unclear. The fact that damage to the prefrontal cortex does not cause dramatic impairments of episodic memory, in contrast with damage to the medial temporal and limbic regions (Scoville and Milner, 1957; Janowsky *et al.*, 1989), suggests that the prefrontal cortex is not necessary for the storage of, or access to, episodic memories. Rather, right prefrontal activation is likely to reflect strategic processes that pertain to the accuracy and completeness of information retrieved from episodic memory.

One proposal is that right prefrontal activation reflects the adoption of a retrieval mode: the state arising whenever one refers back in time to past experiences (Tulving, 1983; Kapur *et al.*, 1995; Nyberg *et al.*, 1995). According to one interpretation of this view, damage to the right prefrontal cortex does not impair retrieval *per se*, but rather the ability

to re-experience retrieved information as part of one's past (Levine *et al.*, 1998). An alternative proposal is that prefrontal activation reflects the degree of retrieval effort, the right (and left) prefrontal cortex being more active when retrieval is difficult (Schacter *et al.*, 1996a). Retrieval effort is distinct from retrieval success, in that retrieval can fail despite repeated retrieval attempts. A third proposal is that right prefrontal activation reflects processes operating subsequent to retrieval of information from episodic memory. Such post-retrieval processes might include the monitoring of whether the retrieved information is sufficient for the current task (Shallice *et al.*, 1994), and the utilization of that information to guide behaviour (Rugg *et al.*, 1996).

The debate between retrieval mode, retrieval effort and post-retrieval processing accounts is often framed in terms of retrieval attempt versus retrieval success. The retrieval mode and retrieval effort hypotheses predict that right prefrontal activity is independent of whether information is retrieved successfully. This prediction is consistent with several PET and functional MRI (fMRI) studies that have failed to find differential activation of the right prefrontal

cortex as a function of retrieval success (Kapur *et al.*, 1995; Nyberg *et al.*, 1995; Schacter *et al.*, 1996c, 1997; Buckner *et al.*, 1998a). However, other studies by Rugg and colleagues (Rugg *et al.*, 1996) and Buckner and colleagues (Buckner *et al.*, 1998b) have found greater activation of the right prefrontal cortex as the probability of retrieval success increased. The question of whether the right prefrontal cortex is sensitive to retrieval success therefore remains unresolved.

One reason for the confusion among previous neuroimaging experiments may be that the simple dichotomy of attempt versus success is not a fruitful approach for interpreting right prefrontal function during episodic retrieval. A more promising approach would appear to derive from detailed theoretical accounts of episodic retrieval. Burgess and Shallice (Burgess and Shallice, 1996), for example, developed a multistage model of retrieval to explain the patterns in protocols recorded as healthy volunteers recalled autobiographical memories. An important component of their model is an editor or monitoring process, which attempts to verify that the information retrieved via prior retrieval cues is appropriate for the current task. An example of such monitoring is illustrated by the question: 'When was your last trip abroad?'. It is likely that several memories will come to mind, in which case monitoring is required to select which of these memories relates specifically to the most recent trip. Similar monitoring processes were proposed within the retrieval frameworks developed by Norman and Bobrow (Norman and Bobrow, 1979) and Koriat and Goldsmith (Koriat and Goldsmith, 1996). Importantly, monitoring does not always correlate with retrieval success: the degree to which the right prefrontal cortex is activated as a function of retrieval success may depend on how closely one is monitoring the products of retrieval (for a similar suggestion, see Wagner *et al.*, 1998).

Another reason for the confusion among previous neuroimaging experiments may be a failure to distinguish activations within different regions of the right prefrontal cortex. At least three distinct regions of the right prefrontal cortex have been implicated in previous studies: an anterior region in Brodmann area (BA) 10 (e.g. Rugg *et al.*, 1996; Buckner *et al.*, 1998b), a dorsolateral region in BA 9/46 (e.g. Shallice *et al.*, 1994; Kapur *et al.*, 1995) and a ventral posterior region in BA 45/47 (e.g. Nyberg *et al.*, 1995; Schacter *et al.*, 1997). These regions may subservise distinct functions during episodic retrieval. In particular, the idea that dorsolateral regions of the prefrontal cortex are involved in monitoring was initially proposed by Petrides and colleagues (Petrides *et al.*, 1993) in the context of working memory tasks. Petrides (Petrides, 1994, 1995) later developed a more elaborate view in which '... ventrolateral frontal lobe regions are principally concerned with the active organization of sequences of responses based on conscious, explicit retrieval from posterior association systems. By contrast, dorsolateral frontal regions subservise a secondary level of executive processing and are recruited only when active manipulation

and monitoring of information within working memory are required.' (Owen, 1997, pp. 1329–30).

In the verbal episodic memory domain, Shallice and colleagues (Shallice *et al.*, 1994) argued that the right dorsal prefrontal activations in their study should also be attributed to monitoring. Petrides and colleagues (Petrides *et al.*, 1995) and Fletcher and colleagues (Fletcher *et al.*, 1998b) subsequently argued for a dorsal/ventral lateral distinction analogous to that made in the working memory domain. Though both compared free recall and paired associate recall, however, their arguments were based on a strikingly different pattern of results. Fletcher and colleagues (Fletcher *et al.*, 1998b) found right dorsolateral prefrontal activation when free recall was compared against paired associate recall, whereas Petrides and colleagues (Petrides *et al.*, 1995) found left ventrolateral prefrontal activation. Fletcher and colleagues (Fletcher *et al.*, 1998b) argued that free recall involves greater monitoring demands, whereas Petrides and colleagues (Petrides *et al.*, 1995) argued that the monitoring demands in their two tasks were comparable.

However, in neither of these studies (Petrides *et al.*, 1995; Fletcher *et al.*, 1998b) were the conditions directly set up to test the role of the prefrontal cortex in monitoring. In the present study, we made an explicit test of the hypothesis that the right dorsolateral prefrontal cortex is more active in conditions requiring greater monitoring of episodic retrieval. To test this prediction, we used fMRI to compare the brain activity of healthy volunteers while they studied visual words (our 'Encoding' conditions), retrieved memories of those words (our 'Recognition' conditions) or performed a simple visual-motor baseline task (our 'Control' condition). The Encoding conditions involved one of two instructions that oriented participants towards either a word's location in space (high or low on the screen) or its relative position in time (in the first or second of two lists). The Recognition conditions also involved one of two instructions, adapted from the process dissociation procedure of (Jacoby, 1996). One condition, the 'Inclusion' condition, involved the standard recognition instructions: to respond 'yes' whenever the participant saw a word that they remembered studying in the previous Encoding condition (an old word). The other Recognition condition, the 'Exclusion' condition, required participants to respond 'yes' only if they remembered studying an old word in one of the two spatial or temporal Encoding contexts. According to many theories (e.g. Jacoby, 1996; Mandler, 1980), recognition entails two processes: a non-specific, automatic feeling of familiarity, and a more explicit recollection of an item's prior occurrence. For old words in the Inclusion condition, either process can precipitate a 'yes' response. For old words in the Exclusion condition that were studied in the inappropriate context, however, the two processes are in opposition, in that successful recollection of the study context is necessary to overcome the sense of familiarity associated with old words. In other words, the Exclusion condition imposes

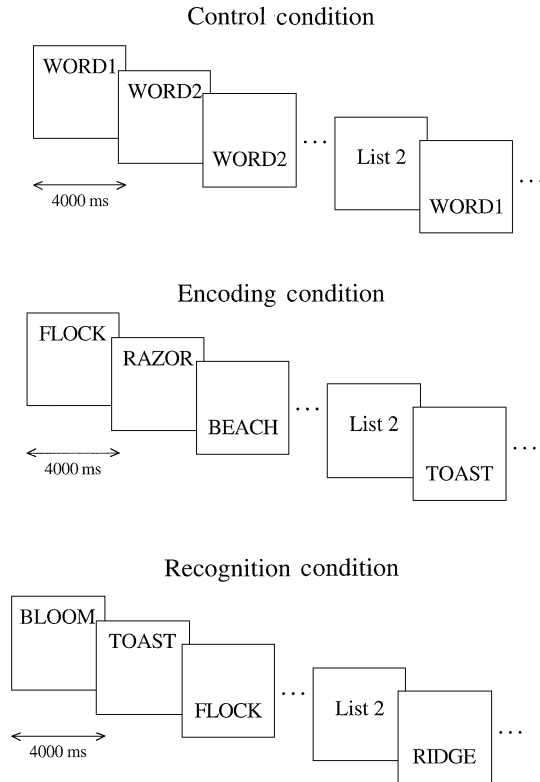


Fig. 1 Experimental procedure for a single trial of the Control, Encoding and Recognition conditions.

greater monitoring requirements. We therefore predicted greater activation in the right dorsolateral prefrontal cortex in the Exclusion condition than the Inclusion condition.

Methods

Participants

Informed consent was obtained from 12 right-handed volunteers (nine males), aged between 21 and 49 years (with a mean age of 28 years). The study was approved by the National Hospital for Neurology and Neurosurgery and Institute of Neurology Medical Ethics Committee.

Cognitive tasks

Participants were scanned during three basic conditions: the Encoding, Recognition and Control conditions. The procedure associated with one trial of each condition is shown in Fig. 1. All tasks involved sequential, visual presentation of 12 five-letter strings, each string prompting a 'yes' or 'no' finger response. The strings appeared randomly above or below the midline (with the constraint that a total of six strings appeared above and six below) and were split into two lists of six strings by a 'List 2' marker.

In the Control condition, the string 'WORD1' was presented for a random one-half of the trials, the string 'WORD2' for the other half, and the task was to respond 'yes' whenever the string was 'WORD1' (and 'no' otherwise).

In the Encoding condition, the strings were medium-frequency nouns, which participants were told to remember for the subsequent Recognition condition. The Encoding condition also involved one of two orienting tasks, in which participants responded 'yes' when a word was above the midline (the Space Encoding condition) or in the first list (the List Encoding condition), and 'no' otherwise.

In the Recognition condition, some of the words from the previous Encoding condition were redisplayed, intermixed with new words that had not been seen before. The Recognition condition also involved one of two instructions: an Inclusion condition, in which participants responded 'yes' when they recognized a word from the previous Encoding condition, regardless of its previous position on the screen or occurrence in List 1 or List 2, and an Exclusion condition, in which participants responded 'yes' only when they remembered a word appearing in a specific context in the previous Encoding condition. In the Space Exclusion condition, the relevant context was the word's previous height on the screen. For one-half of the blocks in this condition, participants responded 'yes' only if they remembered seeing the word above the midline; for the other half they responded 'yes' only if they remembered seeing the word below the midline. In the List Exclusion condition, the relevant context was the word's previous occurrence in List 1 or List 2: for one-half of the blocks in this condition participants responded 'yes' only if they remembered seeing the word in List 1; for the other half they responded 'yes' only if they remembered seeing the word in List 2. When they remembered the word appearing in a different context, or they did not remember seeing the word before, they responded 'no'. During an Encoding condition, participants did not know in advance whether the subsequent Recognition test would involve Inclusion or Exclusion instructions (though the nature of the Encoding instructions—whether they oriented participants towards space or list—would inform them as to the relevant dimension of any Exclusion task that might follow). Participants were told that the spatial and temporal position of the words during the Recognition conditions was irrelevant to the task, and unrelated to their position in the previous Encoding condition.

Experimental materials

Two hundred and forty nouns of five letters with a Kucera–Francis frequency between 10 and 100 were drawn from the MRC psycholinguistics database (http://www.psy.uwa.edu.au/uwa_mrc.htm) and were assigned randomly to the Encoding and Recognition conditions for each participant. One-half of the Recognition conditions involved six words from the previous Encoding condition and six new words (old : new ratio, 50%) and one-half included 10 words from the previous Encoding condition and two new words (old : new ratio, 83%). This manipulation was orthogonal to the type of Recognition instructions (i.e. Inclusion versus Exclusion conditions).

Experimental procedure

The words were presented in 24-point Helvetica font using a Macintosh computer, and were projected onto a screen ~300 mm above the participant in the MRI scanner. The resulting visual angle for single items was ~2°. Words were presented every 4 s (3500 ms on; 500 ms off), during which time participants used the index finger of their right hand to make a 'yes' response on a keypad or the middle finger of their right hand to make a 'no' response. The two lists of six words were demarcated by a List 2 marker presented for 4 s between the sixth and seventh words. Each block was preceded by a brief reminder of the instructions for the following block, which was displayed for 8.2 s, resulting in a total of 60.2 s per block.

The tasks were performed in four sessions of 12 blocks, each 12-min session consisting of four Control–Encoding–Recognition triplets. Sessions were separated by a 2-min rest period. The order of Space/List Encoding conditions and Inclusion/Exclusion Recognition conditions within this structure was counterbalanced across participants.

fMRI scanning technique

A 2 T Siemens VISION system (Siemens, Erlangen, Germany) was used to acquire both T₁ anatomical volume images (1 × 1 × 1.5 mm voxels) and T₂*-weighted echoplanar images (64 × 64 × 3 mm pixels, TE = 40 ms) with blood oxygenation level-dependent (BOLD) contrast. Each echoplanar image comprised 48 1.8 mm axial slices taken every 3 mm, positioned to cover the whole brain. Thin slices reduce susceptibility artefacts at frontal polar regions (Young *et al.*, 1988), regions that have previously been associated with episodic retrieval (Rugg *et al.*, 1996; Buckner *et al.*, 1998b). A total of 692 volume images were taken continuously with an effective repetition time (TR) of 4.3 s/volume, the first five dummy volumes in each session being discarded to allow for T₁ equilibration effects.

The scanner was synchronized with the presentation of the instructions of each block, and the ratio of interscan to interstimulus interval ensured that voxels were sampled at different phases relative to stimulus onset (with a total of 14 scans per block). There were 16 repetitions of the Control condition, eight repetitions of each type of Encoding condition (Space versus List) and four repetitions of each type of Recognition condition (Space versus List and Inclusion versus Exclusion).

Data analysis

Data were analysed using statistical parametric mapping (SPM97d, Wellcome Department of Cognitive Neurology, London, UK; Friston *et al.*, 1995). All volumes were realigned to the first volume (actual head movement was <3 mm in all cases) and resliced using a sinc interpolation, adjusting for residual motion-related signal changes. A mean image

created from the realigned volumes was coregistered with the structural T₁ volume and the structural volumes were spatially normalized to a standard template (the MNI brain of Cocosco *et al.*, 1997) of 3 × 3 × 3 mm voxels in the space of Talairach and Tournoux (1988) using non-linear basis functions. The derived spatial transformation was applied to the realigned T₂* volumes, which were then spatially smoothed with a 10 mm full width at half maximum isotropic Gaussian kernel (in order to make comparisons across participants and to permit application of random field theory for corrected statistical inference; Friston *et al.*, 1994). A mean image was created for each condition in each session, allowing for the haemodynamic lag between conditions, high-pass filtering across each session using low-frequency cosine functions with a cut-off of 360 s (to remove low-frequency drifts in the BOLD signal; Holmes *et al.*, 1997), and globally scaling image intensity to a grand mean of 100. The resulting mean images for each condition were averaged across the four sessions, producing seven condition images for each participant (Control, Encoding Space, Encoding List, Inclusion Space, Inclusion List, Exclusion Space and Exclusion List).

Condition effects at each voxel were estimated according to the general linear model and regionally specific effects were compared using linear contrasts. Each contrast produced a statistical parametric map of the *t* statistic for each voxel, which was subsequently transformed to the unit normal *Z* distribution. Unless stated otherwise, the activated areas reported below consisted of voxels that survived a voxel-wise multiple-comparison correction of $P < 0.05$ ($Z > 4.60$) using a random effect model. The maxima of these areas were localized on the T₁ template brain and labelled using the nomenclature of Talairach and Tournoux (1988) and Brodmann (1909) for consistency with previous studies.

Results

Behavioural data

Performance was almost perfect in the Control and Encoding conditions, and over 85% correct on average in the Inclusion and Exclusion conditions (Table 1). A 2 × 2 repeated-measures analysis of variance (ANOVA) revealed a significant effect of Inclusion versus Exclusion instructions [$F(1,11) = 5.45$, $P < 0.05$], but any effect of study context or interaction between recognition instructions and study context failed to reach significance [$F(1,11) < 4.36$]. The mean correct reaction times were longer for Encoding than Control conditions, and longer for Exclusion than Inclusion conditions. The latter was confirmed by a second 2 × 2 ANOVA, which showed a significant effect of recognition instructions [$F(1,11) = 31.84$, $P < 0.001$]. There was also a significant effect of study context [$F(1,11) = 12.40$, $P < 0.01$], which was apparent in the longer reaction times in the Space Exclusion condition than List Exclusion condition, though any interaction failed to reach significance [$F(1,11) = 3.72$]. The reduced performance

Table 1 Proportion of correct responses and mean correct reaction time in each condition

		Control	Encoding		Recognition inclusion		Exclusion	
			Space	List	Space	List	Space	List
Correct	Mean	0.98	0.98	0.99	0.94	0.88	0.86	0.86
	SD	0.03	0.04	0.01	0.05	0.08	0.09	0.07
Reaction time	Mean	731	1057	1107	1045	1044	1417	1265
	SD	139	387	408	185	187	241	240

levels and longer reactions in the Exclusion condition relative to the Inclusion condition are consistent with greater monitoring demands. The reaction time difference between List and Space recognition conditions was not predicted, and we offer no explanation for this difference.

The false alarm rate to new words was 0.04 in both Inclusion and Exclusion conditions, giving a hit–false alarm index of $0.88 - 0.04 = 0.84$ in the Inclusion condition. The probability of incorrect ‘yes’ responses to old words in the Exclusion condition was 0.17, reflecting situations where monitoring had failed (giving an effective hit–false alarm rate of $0.79 - 0.17 - 0.04 = 0.58$). Application of the process dissociation equations of Jacoby (1996) estimated the familiarity component as 0.72 (SD = 0.16) and the recollective component also as 0.72 (SD = 0.29). The high level of overall performance (given that there were only 12 words per recognition condition) explains why these values are greater than usually found.

Imaging data

Initial analyses failed to find any significant differences in BOLD signal between the Space versus List conditions at either encoding or retrieval. This is unlike the PET study of Nyberg and colleagues (Nyberg *et al.*, 1996b), which found differential activation during encoding and retrieval of spatial versus temporal information. One possible reason for this discrepancy is that participants in our study were semantically elaborating the words at encoding, regardless of whether they were oriented towards the words’ location in space or position in the first or second list. For example, the presentation of the word FLOCK high on the screen might prompt participants to imagine a flock of sheep on top of a mountain. Similarly, presentation of the word FLOCK in the first list might prompt participants to invent a story that began with a flock of sheep. Indeed, all participants reported attempting such elaboration during the two Encoding conditions. Given that the resulting memory traces were likely to be mental images and/or ordered stories in both cases, the content of the memories retrieved during the Recognition conditions would also be comparable. In view of the absence of any differential activation, subsequent analyses were therefore collapsed across the Space/List manipulation.

Comparison of Encoding and Control conditions

Contrasting the Encoding conditions against the Control condition revealed a number of different activations, predominantly left-lateralized (Table 2 and Fig. 2A). These included a large region of the left prefrontal cortex (BA 6/9/44/45/46), smaller regions of the right middle (BA 46) and superior (BA 8) frontal gyri, and the anterior cingulate cortex (BA 32). Activations were also present in the left superior parietal gyrus (BA 7), left fusiform gyrus (BA 37) and right cerebellum. These regions are often associated with deep encoding of verbal material (Shallice *et al.*, 1994; Tulving *et al.*, 1994b; Kapur *et al.*, 1994; Fletcher *et al.*, 1998a).

The opposite contrast revealed deactivations in the Encoding condition relative to the Control condition in anterior medial frontal gyri (BA 10/11), bilateral insula (BA 13/22), bilateral superior temporal gyri (BA 22), extending into the postcentral (BA 40) and middle temporal gyrus (BA 21) on the right, the right middle occipital gyrus (BA 37), and bilateral middle and posterior cingulate cortex (BA 24/30). The bilateral deactivations of temporal gyri are often associated with semantic retrieval and left prefrontal activation (Frith *et al.*, 1991).

Comparison of Inclusion and Control conditions

Contrasting the Inclusion Recognition condition against the Control condition (Table 3 and Fig. 2B) revealed several activation foci in the right prefrontal cortex and in smaller regions of the left middle and inferior prefrontal gyri (BA 9/45), the rostral and dorsal anterior cingulate gyri (BA 32/24) and the left cerebellum. This right-lateralized pattern of activation, in contrast with the left-lateralized pattern associated with the Encoding condition (above), is consistent with the HERA (Hemispheric Encoding Retrieval Asymmetry) generalization (Tulving *et al.*, 1994a; Nyberg *et al.*, 1996a).

The right prefrontal activations comprised a posterior region of superior frontal gyrus (BA 8), a dorsolateral region of the middle frontal gyrus (BA 9/46) and a ventrolateral/anterior insula region of the inferior frontal gyrus (BA 47).

Table 2 Maxima within regions showing significant ($P < 0.05$ corrected) BOLD signal changes in comparison of Encoding and Control conditions

Region of activation	Left/right	Brodmann area	Number of voxels	Talairach coordinates			Z value
				x	y	z	
Increases during Encoding							
Middle frontal gyrus	L	9	1038	-45	15	18	7.38
	L	6		-39	12	51	6.71
	L	46		-51	27	18	7.01
Middle frontal gyrus	R	46	103	42	39	21	5.74
Superior frontal gyrus	R	8	20	33	21	51	5.49
Anterior cingulate	B	32	135	-3	21	42	6.10
Superior parietal gyrus	L	7	35	-30	-66	45	5.25
Fusiform gyrus	L	37	52	-48	-60	-18	5.66
Cerebellum	R	-	33	36	-60	-27	5.52
Increases during Control							
Medial frontal gyrus	B	10	525	3	51	0	6.86
	B	11		-9	45	-60	6.72
Insula	L	22	28	-45	-9	-3	5.49
	R	13	49	42	-9	-6	6.40
Superior temporal gyrus	L	22	98	-63	-15	6	5.69
	R	22	230	63	-9	0	5.60
Middle temporal gyrus	R	21	14	66	-6	-18	5.47
Cingulate	B	24	44	3	-12	42	5.70
Posterior cingulate	B	30	211	-6	-48	27	6.26
Middle occipital gyrus	R	37	35	54	-66	3	5.69

L = left; R = right; B = bilateral.

One or more of these activations has been found in almost every study of episodic retrieval (see Discussion). Though the activation of more anterior regions of the right prefrontal cortex (BA 10/11) that has been observed in previous studies was not significant at the corrected threshold, activation clearly extended into such regions when the threshold was lowered to an uncorrected $P < 0.001$.

The opposite contrast revealed a large region of deactivation in the anterior medial prefrontal gyri (BA 10/11), together with smaller regions in the left (BA 37) and right (BA 39) middle occipital gyri, in the Inclusion condition relative to the Control condition.

Comparison of Exclusion and Control conditions

Contrasting the Exclusion Recognition condition against the Control condition (Table 4 and Fig. 2C) revealed activations of large regions of both left and right lateral prefrontal cortex, and both left and right superior parietal cortex. This more symmetrical pattern of activation is less consistent with the HERA generalization of Tulving *et al.* (1994a). The bilateral prefrontal activations comprised posterior regions of the superior frontal gyri (BA 6/8), a dorsolateral region of the middle frontal gyri (BA 9/46), ventrolateral/anterior insula regions of the inferior frontal gyri (BA 47) and anterior regions of the inferior frontal gyri (BA 10/11). Other activations included bilateral anterior cingulate gyri (BA 32), bilateral middle temporal gyri (BA 21), bilateral medial

precuneus (BA 7), the left cerebellum and the cerebellar vermis.

The opposite contrast revealed a large region of deactivation in the anterior medial prefrontal gyri (BA 10/11) in the Exclusion condition relative to the Control condition, as in previous contrasts. Deactivations were also seen in the right anterior temporal pole (BA 38), the left and right superior temporal gyri (BA 22), including the posterior regions of the insula, bilateral middle cingulate gyrus (BA 24), right hippocampus, right postcentral gyrus (BA 40), and left (BA 37) and right (BA 39) middle occipital gyri.

Comparison of Exclusion and Inclusion conditions

Contrasting the Exclusion condition against the Inclusion condition (Table 5 and Fig. 2D) revealed activation in the left and right dorsolateral regions of the middle frontal gyri (BA 46) and the left posterior superior parietal cortex (BA 19). Thus, direct comparison of the two recognition conditions revealed that our Exclusion instructions produced greater activation in the dorsolateral prefrontal region identified in the previous Inclusion versus Control and Exclusion versus Control contrasts. The instructional manipulation also produced greater activation in the homologous region of the left prefrontal cortex and in a region close to the left superior parietal region identified in the previous Encoding versus Control and Exclusion versus Control contrasts.

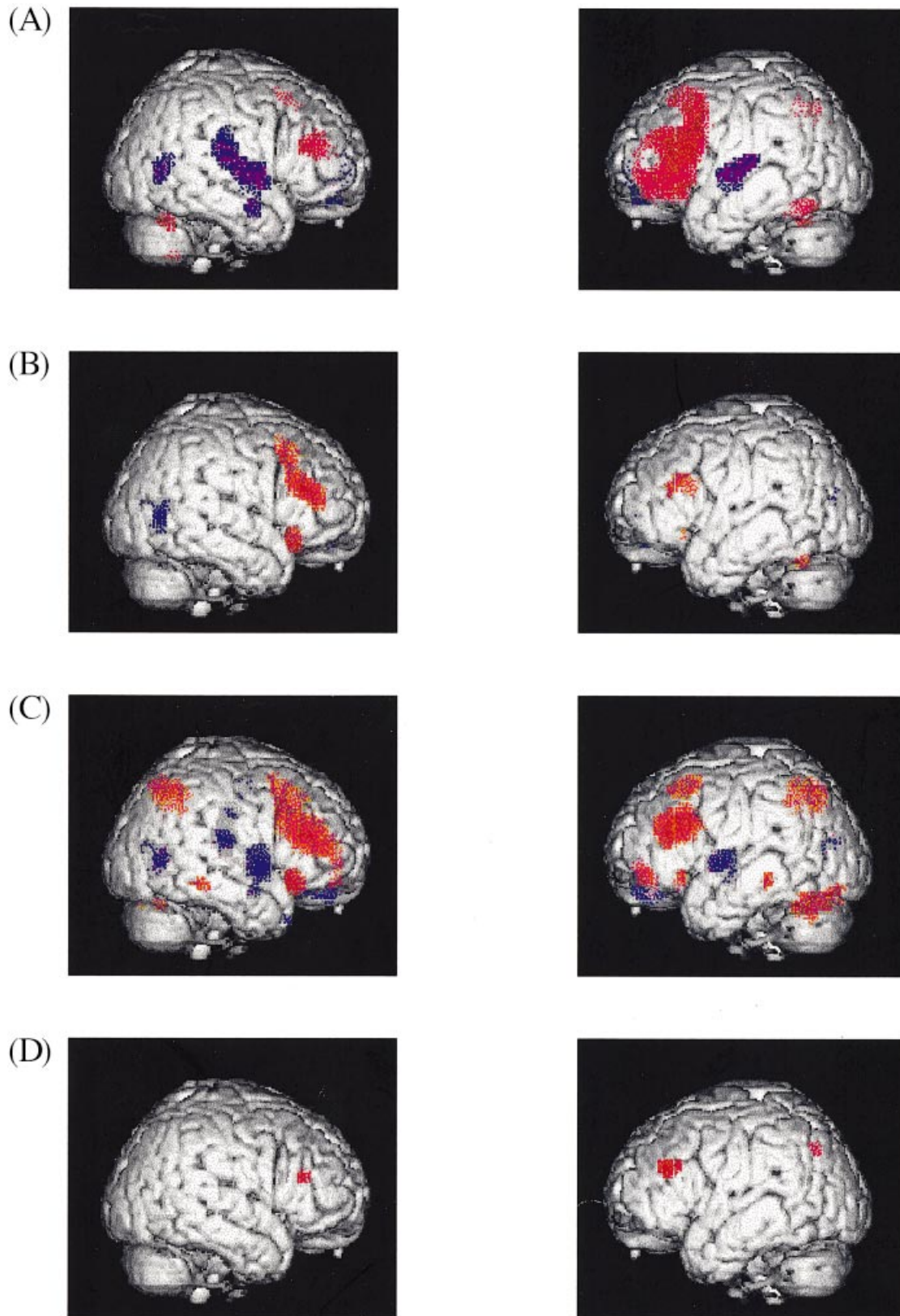


Fig. 2 Lateral areas showing BOLD signal increases (red) and decreases (blue) in comparisons of (A) the Encoding condition relative to the Control condition, (B) the Inclusion condition relative to the Control condition, (C) the Exclusion condition relative to the Control condition and (D) the Exclusion condition relative to the Inclusion condition. For the purpose of illustration the threshold is slightly lower ($P < 0.0001$ uncorrected) than in Tables 2–5.

Table 3 Maxima of regions showing significant ($P < 0.05$ corrected) BOLD signal changes in comparison of Inclusion and Control conditions

Region of activation	Left/right	Brodmann area	Number of voxels	Talairach coordinates			Z value
				x	y	z	
Increases during Inclusion							
Superior frontal gyrus	R	8	33	45	18	45	5.23
Middle frontal gyrus	R	46	124	48	27	24	6.62
	L	9	1	-51	24	30	4.60
Inferior frontal gyrus	R	47	48	36	24	-12	6.24
	L	45	10	-42	15	21	4.92
Anterior cingulate	R	32	31	6	36	27	5.42
Cingulate	R	24	1	1	-21	27	4.63
Cerebellum	L	-	3	-39	-57	-24	4.73
Increases during Control							
Medial frontal gyrus	B	10	263	-12	45	-6	6.15
	B	11		3	33	-8	5.65
Middle occipital gyrus	R	37	47	54	-66	0	5.40
	L	39	2	-45	-78	15	4.63

L = left; R = right; B = bilateral.

Table 4 Maxima of regions showing significant ($P < 0.05$ corrected) BOLD signal changes in comparison of Exclusion and Control conditions

Region of activation	Left/right	Brodmann area	Number of voxels	Talairach coordinates			Z value
				x	y	z	
Increases during Exclusion							
Middle frontal gyrus	R	46	580	48	30	21	7.74
Superior frontal gyrus	R	8		33	24	48	6.85
Middle frontal gyrus	L	46	337	-48	27	27	7.17
Superior frontal gyrus	L	8	72	-30	27	51	5.96
Inferior frontal gyrus	R	47	111	36	24	-9	7.13
	L	47	27	-30	24	-6	5.50
	R	11	3	36	51	-12	4.63
	L	11	46	-42	45	-6	5.85
Anterior cingulate	B	32	154	6	36	27	6.47
Middle temporal gyrus	R	21	11	66	-39	-12	5.02
	L	21	3	-66	-33	-9	4.75
Superior parietal gyrus	L	7	196	-30	-66	45	6.46
	R	7	206	39	-63	45	5.85
Precuneus	B	7	51	9	-69	39	5.21
Cerebellum	L	-	88	-42	-60	-27	5.58
	B	-	34	-6	-78	-24	4.81
Increases during Control							
Medial frontal gyrus	B	10	803	-9	45	-6	7.11
	B	11		3	27	-12	6.85
Temporal pole	R	38	14	45	21	-36	5.54
Superior temporal gyrus	R	22	153	60	3	-3	5.75
Insula	R	22		45	-6	-6	5.67
Superior temporal gyrus	L	22	76	-63	-3	6	5.08
Insula	L	22		-48	-9	-3	5.42
Hippocampus	R	-	4	33	-12	-21	4.85
Cingulate gyrus	B	24	45	3	-9	42	5.52
Postcentral gyrus	R	40	173	57	-24	21	6.14
Middle occipital gyrus	R	37	72	54	-66	3	6.34
	L	39	11	-42	-69	12	4.97

L = left; R = right; B = bilateral.

Table 5 Maxima of regions showing significant ($P < 0.05$ corrected) BOLD signal changes in comparison of Exclusion and Inclusion Recognition conditions

Region of activation	Left/right	Brodmann area	Number of voxels	Talairach coordinates			Z value
				x	y	z	
Increases during Exclusion							
Middle frontal gyrus	L	46	26	-48	30	27	5.39
	R	46	3	48	30	21	4.85
Superior parietal gyrus	L	19	3	-36	-66	39	4.72

L = left; R = right; B = bilateral.

Possible confounds

One possible confound in our comparison of Inclusion and Exclusion conditions is that there are necessarily fewer correct 'yes' responses in our Exclusion condition than in our Inclusion condition. To address this problem, we performed an orthogonal contrast of recognition conditions with a high old : new word ratio (83%) against recognition conditions with a low old : new ratio (50%; see Methods). The higher old : new ratio entailed a greater number of 'yes' responses. Only one area showed greater activation in the high-ratio condition that survived our corrected threshold, in the right cuneus ($x = 12$, $y = -81$, $z = 33$, BA 19), and no area showed greater activation in the low-ratio condition. We can speculate that the cuneus activation reflected greater visual processing or imagery associated with old words than new. The more important finding was that no brain area activated in our Exclusion versus Inclusion condition contrast showed differential activation as a function of old : new ratio, even when the threshold was lowered to an uncorrected $P < 0.001$. The differential activations in our Inclusion and Exclusion conditions are therefore unlikely to reflect simply different frequencies of 'yes' responses.

A second possible confound correlated with our Inclusion versus Exclusion contrasts is the difference in performance levels, given that performance was significantly worse in our Exclusion condition (though only by 5% on average). This problem was addressed by repeating the above contrast of Exclusion versus Inclusion conditions, but introducing the percentage of correct responses of individual participants as a confounding covariate in an SPM ANCOVA (Friston *et al.*, 1995). Removing the variance potentially attributable to performance in this manner did reduce the significance of the activations in the prefrontal and left parietal areas. Nonetheless, the pattern of brain activation in the bilateral, dorsal prefrontal and left posterior parietal regions remained evident at a lower threshold of $P < 0.001$ uncorrected. A similar pattern resulted when mean correct reaction times were entered as a confounding covariate. These analyses suggest that considerable variance remained accountable for by our instructional change between Exclusion and Inclusion conditions.

Summary of contrasts

Four regions revealed by the above comparisons that were of particular interest were the left dorsolateral prefrontal

cortex (BA 46), the left superior parietal cortex (BA 7/19), the right dorsolateral prefrontal cortex (BA 46) and the right ventral prefrontal cortex (BA 47). The mean percentage BOLD signal change in the maxima of these regions is plotted for each condition in Fig. 3. The left prefrontal region (Fig. 3A) was activated in all experimental conditions relative to the control condition, but was particularly active for the Encoding condition and, to a lesser extent, the Exclusion condition. This is consistent with the proposed role of the left prefrontal cortex in the semantic processing necessary for deep encoding (Kapur *et al.*, 1994; Fletcher *et al.*, 1998a) and the suggestion that similar semantic processing and re-encoding can occur during episodic retrieval (Nyberg *et al.*, 1996a; see Discussion below). A similar but attenuated pattern was seen for the left ventrolateral prefrontal region identified in Table 4, which is close to that found by Petrides and colleagues (Petrides *et al.*, 1995). Given that any differential activation of this region did not reach significance in our direct comparison of the Exclusion versus Inclusion conditions, however, we do not offer a functional interpretation for this region.

The left parietal region (Fig. 3B) was also activated across all the experimental conditions, but was particularly active in the Exclusion condition. According to the nomenclature of Talairach and Tournoux, this region is the lateral border of the precuneus, an area often implicated in episodic retrieval and which has been associated with imagery (Fletcher *et al.*, 1995, 1996; but see Buckner *et al.*, 1996). Neural activity in such a region may explain the electrophysiological differences recorded by left parietal electrodes during episodic retrieval (Rugg, 1995), particularly during retrieval of contextual (source) information (Wilding and Rugg, 1996, 1997).

Most interesting are the different activation profiles for the dorsal and ventral regions of the right prefrontal cortex. The ventral region (Fig. 3D), lying on the boundary between the posterior prefrontal and anterior insula cortex, is activated only during episodic retrieval, showing increases in BOLD signal of similar magnitudes in the Inclusion and Exclusion conditions relative to the Control and Encoding conditions. The dorsal region, however (Fig. 3C), shows a larger increase in the Exclusion condition than in the Inclusion condition. We have therefore observed a single dissociation between activation in two regions of the right prefrontal cortex across our two recognition conditions: the ventral region is

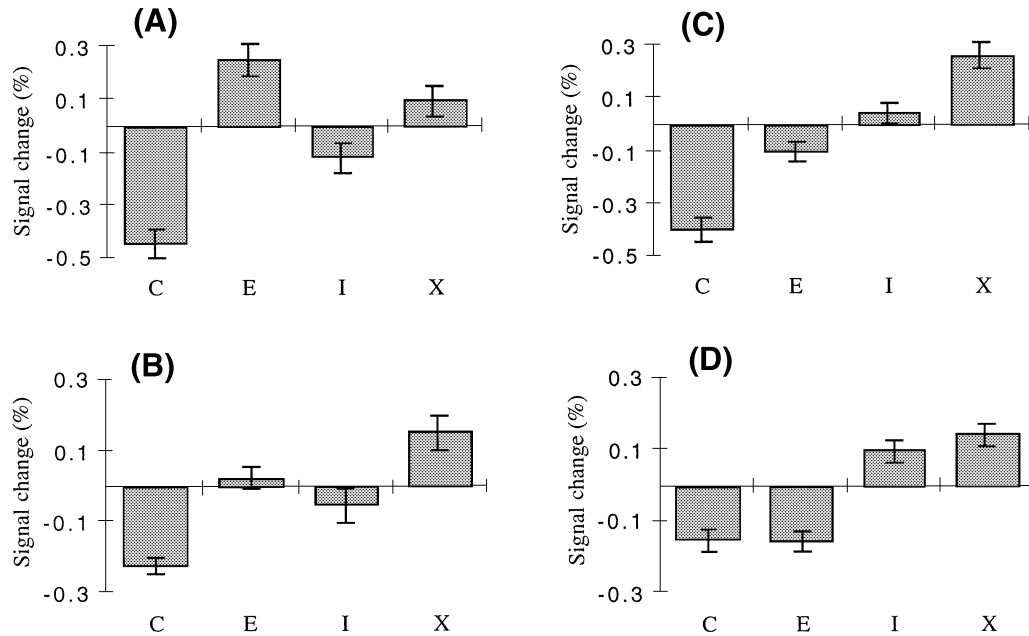


Fig. 3 Percentage BOLD signal change in each condition relative to the mean across all voxels and conditions, for maxima identified in Tables 4 and 5 in (A) the left dorsolateral prefrontal cortex ($-48, 30, 27$), (B) left posterior parietal cortex ($-36, -66, 39$), (C) right dorsolateral prefrontal cortex ($48, 30, 21$) and (D) right ventral posterior prefrontal cortex ($36, 21, -15$). C = Control; E = Encoding; I = Inclusion; X = Exclusion. Error bars show standard error of the mean.

insensitive to our recognition instructions, consistent perhaps with the concept of a retrieval mode (Kapur *et al.*, 1995), whereas the dorsal region is sensitive to our Exclusion condition, consistent with our monitoring hypothesis.

Psychophysiological interactions

Given the hypothesis that the right dorsolateral prefrontal cortex is involved in monitoring retrieval from episodic memory, we performed a final analysis in which the signal measured in this area was used as a regressor for the signal measured in all other brain areas. More specifically, we identified areas in which the slope of the regression showed a significant increase in our Exclusion condition relative to our Inclusion condition (a psychophysiological interaction; Friston *et al.*, 1997). Assuming that the dorsal prefrontal cortex modulates retrieval-related activity in the ventral prefrontal cortex during monitoring, we predicted that the right ventral prefrontal region identified in previous subtractions would be one such area. This prediction was confirmed, with a right ventral area ($x = 39, y = 12, z = -18$) evincing the psychophysiological interaction at $P < 0.001$ uncorrected. Interestingly, when a similar analysis was performed using the signal measured in the ventral region as the regressor, no voxel within the dorsal prefrontal region showed a psychophysiological interaction at $P < 0.001$. This suggests that the dorsal region is exerting a unidirectional influence on the ventral region across the Inclusion and Exclusion conditions.

Discussion

In support of our monitoring hypothesis, we identified a dorsolateral region in the right prefrontal cortex that was significantly more active in our Exclusion condition than in our Inclusion condition. These recognition conditions involved equivalent stimuli and identical presentation parameters, differing only in the instructions for the appropriate response: correct responses in the Inclusion condition were independent of the study context, whereas correct responses in the Exclusion condition required careful monitoring of the study context. Furthermore, we identified a more ventral region of the right prefrontal cortex, bordering on the anterior insula cortex, which was activated in both our recognition conditions but was insensitive to the recognition instructions. The failure to distinguish these dorsal and ventral regions in most previous neuroimaging studies may explain some of the confusion regarding the role of the right prefrontal cortex during episodic retrieval. Below we discuss the function of both regions within a single theoretical framework for episodic retrieval.

According to the model of episodic retrieval proposed by Burgess and Shallice (Burgess and Shallice, 1996; Shallice and Burgess, 1996), retrieval is an iterative, reconstructive process (for similar views, see Bartlett, 1932; Moscovitch, 1989; Schacter *et al.*, 1998). Two key stages in this model are (i) specification of retrieval cues ('descriptor processes') and (ii) monitoring of the information retrieved via those cues ('memory editor processes'). If the monitoring process reveals that the information retrieved is inappropriate or

incomplete, further retrieval cues are specified and the processes repeated. We propose that the cue specification process is subserved by the ventral region of the right prefrontal cortex and that the monitoring process is subserved by the dorsal region of the right prefrontal cortex. The greater monitoring demands of our Exclusion condition can then explain the greater activation of the dorsal region relative to our Inclusion condition. The lack of any such difference in the ventral region can be explained if the retrieval cues are equivalent for the two conditions. This equivalence holds if we assume that the dominant retrieval cue in both recognition tasks is the 'copy cue' of the word itself.

Our ventral/dorsal prefrontal distinction is related to that developed by Petrides (Petrides, 1994, 1995) from studies of working memory, and which he has also applied to verbal long-term memory (Petrides *et al.*, 1995). According to both hypotheses, the processes subserved by the dorsal region modulate those subserved by the ventral region. Such modulation might explain the unidirectional influence of dorsal activity on ventral activity identified in the present study, an influence that was particularly strong in our Exclusion condition. More generally, because retrieval of episodic information from long-term memory is likely to entail temporary maintenance and manipulation of that information in working memory, it is perhaps not surprising that similar prefrontal activations are observed in studies of episodic retrieval and working memory. Indeed, a process-based distinction, rather than a time-based or content-based distinction, would seem more appropriate for the functional anatomical study of the prefrontal cortex.

Relation to previous neuroimaging studies

Our hypothesis is supported by the double dissociation between activation of the ventral and dorsal right prefrontal regions observed by Fletcher and colleagues (Fletcher *et al.*, 1998b), in which the ventral region was more active in a category-cued recall task, whereas the dorsal region was more active in a free recall task. The ventral activation would reflect the larger number of (externally provided) retrieval cues in the cued recall task, whereas the dorsal activation would reflect the greater monitoring demands of the free recall task. Increased monitoring would also be implicated when intentional retrieval tasks are compared with incidental retrieval tasks (Rugg *et al.*, 1997) and when a task that requires discrimination of the temporal order of two old words is compared with a task that requires discrimination of an old word from a new word (Cabeza *et al.*, 1997b), consistent with the right dorsal prefrontal activations observed in both studies. Though there was little apparent monitoring requirement in the passive listening task of Tulving and colleagues (Tulving *et al.*, 1994b), the right dorsolateral prefrontal activation observed when participants heard sentences they had studied previously versus sentences they had not is likely to reflect the high semantic content of the stimuli. Such sentences are likely to prompt participants to

reconstruct and discriminate between elaborate memory traces, a process involving considerable monitoring (Shallice and Burgess, 1996).

How can our hypothesis explain the failure to find any significant difference in right prefrontal activation during recognition of old versus new words (Kapur *et al.*, 1995; Nyberg *et al.*, 1995), veridical versus false recognition judgements (Schacter *et al.*, 1997) or cued recall versus recognition (Cabeza *et al.*, 1997a)? The lack of any differential activation in the ventral prefrontal region might be expected, given that the external retrieval cues were comparable in all cases. The lack of any differential activation in the dorsal prefrontal region would be attributed to the plausible assumption that these tasks differ little in their monitoring demands. The failure to find a significant difference in right prefrontal activation for old and new words in the event-related fMRI studies of Buckner and colleagues (Buckner *et al.*, 1998a) and Schacter and colleagues (Schacter *et al.*, 1997) may also reflect equivalent cueing and monitoring demands for the two types of word. The differences in right prefrontal activation associated with old and new word discriminations found by Buckner and colleagues (Buckner *et al.*, 1998b) and Rugg and colleagues (Rugg *et al.*, 1996) resulted from blocked designs. These are conditions under which differences in monitoring processes are more likely, given that people tend to alter their response criterion as a function of the response tendencies they perceive in different blocks (e.g. people may monitor retrieval more closely when most words seem old; for a related argument, see Johnson *et al.*, 1997). In an explicit test of such a hypothesis, Wagner and colleagues (Wagner *et al.*, 1998) found that the right dorsolateral prefrontal cortex was more active for high than for low densities of old words only when the instructions informed participants of these densities, which was likely to encourage more monitoring in the high-density condition.

Right frontal activity has also been implicated in electrophysiological studies of episodic retrieval. Using recognition instructions similar to those employed here, Wilding and Rugg (Wilding and Rugg, 1997) showed that the magnitude of the right frontal event-related potential was greater for correct 'yes' responses to old words studied in the appropriate context than for correct 'no' responses to old words studied in the inappropriate context. Moreover, this difference appeared late in the recording epoch, supporting the authors' hypothesis that it reflected processes operating subsequent to retrieval. Monitoring is clearly one such process. Greater monitoring demands for correct 'yes' responses than for correct 'no' responses in Wilding and Rugg's Exclusion condition may reflect a stricter criterion adopted by participants for 'yes' responses. The monitoring hypothesis can also explain why Uhl and colleagues (Uhl *et al.*, 1994) reported a right frontal negative DC (direct current) shift under conditions of high proactive interference, *viz.* situations where monitoring is required to select one of multiple competing responses.

Relation to neuropsychological studies

Though the episodic memory deficits of patients with frontal lobe damage are generally mild compared with those of patients with medial temporal or limbic damage, their recall is marked by poorer organization (Stuss *et al.*, 1994; Gershberg and Shimamura, 1995), increased susceptibility to interference (Incisa della Rocchetta and Milner, 1993; Shimamura *et al.*, 1995) and impoverished recall of spatial and temporal context (Janowsky *et al.*, 1989; Shimamura *et al.*, 1990). However, these deficits are more pronounced with left rather than right frontal lesions, at least for verbal information (Incisa della Rocchetta and Milner, 1993; Stuss *et al.*, 1994; Swick and Knight, 1996). This may reflect the fact that deficits in retrieval are difficult to isolate from deficits in encoding with patient studies, given that the left prefrontal cortex is thought to be particularly important for effective encoding (Tulving *et al.*, 1994a; Nyberg *et al.*, 1996a). Nonetheless, there are some neuropsychological findings following right prefrontal damage that are easier to attribute specifically to retrieval problems, and that are consistent with our monitoring hypothesis. Stuss and colleagues (Stuss *et al.*, 1994), for example, reported excessive repetitions during recall in a group of right frontal patients, the majority of whom had damage to dorsolateral regions of the prefrontal cortex, and Schacter and colleagues (Schacter *et al.*, 1996b) described a patient (BG) with an extensive lesion in the right posterior frontal cortex who made unusual numbers of false alarms in recognition tests. Both patterns of deficit may be attributed to a failure of monitoring. More generally, we note that the disinhibition hypothesis proposed by Shimamura (Shimamura, 1995) to explain episodic memory deficits in frontal patients is similar to the monitoring hypothesis proposed here.

Activations of other areas in the present study

In addition to the dorsal region of the right prefrontal cortex, greater activation in the Exclusion than in the Inclusion condition was observed in the left dorsolateral prefrontal cortex and the left superior parietal cortex. The left parietal activation may be associated with greater visuospatial attentional demands (Corbetta *et al.*, 1993; Coull and Nobre, 1998) in our Exclusion condition. Though we cannot discount this possibility, we note that similar regions have been activated in studies of episodic retrieval in which spatial position was not manipulated (Cabeza *et al.*, 1997a; Rugg *et al.*, 1996, 1997; Tulving *et al.*, 1994b). Moreover, we have recently observed differential event-related activation of this region during discrimination of old and new words intermixed within the same session, which is difficult to attribute to differential attentional demands. An alternative proposal is that the left parietal activation reflects retrieval of source information, which may underlie the differences in event-related potential at left parietal electrodes associated with successful source retrieval (for a review, see Allan *et al.*,

1998). This proposal is consistent with the greater emphasis on retrieval of contextual information in our Exclusion task than in our Inclusion task.

A similar source-retrieval explanation might be applied to our left dorsolateral prefrontal activation. This would be consistent with the greater left prefrontal activation observed during intentional retrieval of words previously studied under deep versus shallow encoding (Rugg *et al.*, 1997), given that the source information in our study was likely to involve deep, verbal elaborations of the words on the basis of their spatiotemporal position (see Results). Indeed, a greater amount of semantic processing accompanying retrieval of elaborate verbal episodic memories may result in further episodic encoding (Nyberg *et al.*, 1996a; for a counter-argument, see Nolde *et al.*, 1998), which is consistent with the clear left lateralization of dorsolateral prefrontal activation during our Encoding condition (Fig. 3). Other studies (Schacter *et al.*, 1996a; Buckner *et al.*, 1998b), however, have found the opposite result, with greater left prefrontal activation during retrieval of words studied shallowly, which the authors attributed to greater 'retrieval effort'. An alternative possibility is that the left prefrontal cortex, like its right homologue, subserves the monitoring of episodic retrieval. This possibility is more consistent with the neuropsychological evidence reviewed above and with a recent meta-analysis by Nolde and colleagues (Nolde *et al.*, 1998), who suggested that left prefrontal activation during episodic retrieval varies as a function of the engagement of reflective processes, such as monitoring.

The functional interpretation of activation in the anterior right prefrontal cortex, the third region associated with episodic retrieval by previous studies (see Introduction), is not immediately apparent from our results. We note that a monitoring hypothesis similar to that tested here was used by Fletcher and colleagues (Fletcher *et al.*, 1996) to explain their finding that the anterior right prefrontal activity measured by PET was a U-shaped function of the degree of semantic relatedness between paired associates during cued recall: relative to weakly related pairs, strongly related pairs were seen to require verification that the information retrieved was not a consequence of free (semantic) associations to the cue, whereas randomly related pairs were seen to require verification that the information retrieved was not the associate of a different word presented in the study phase. A similar region was activated in the Exclusion versus Control contrast of the present study, but not in the Inclusion versus Control contrast (except at a lower threshold) or in the direct contrast between Exclusion and Inclusion conditions (even at a lower threshold). For these reasons, coupled with the fact that the anterior regions of the prefrontal cortex are prone to susceptibility artefacts with fMRI, we do not offer a functional interpretation of retrieval-related activation in this region on the basis of the present results.

Conclusion

The present study provides support for the hypothesis that a dorsal midlateral region of the right prefrontal cortex is

involved in monitoring information retrieved from episodic memory. In contrast, a cue specification hypothesis was proposed to explain the finding that a ventral posterior region of the right prefrontal cortex showed retrieval-related activation that appeared insensitive to a change in monitoring requirements. The failure to attribute different functions to these distinct regions may explain some of the previous confusion regarding the role of the right prefrontal cortex during episodic retrieval.

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