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The influence of imagery and semantic cueing

P. C. Fletcher,[1] T. Shallice,[2] C. D. Frith,[1,2] R. S. J. Frackowiak[1] and R. J. Dolan[1]

[1]*The Wellcome Department of Cognitive Neurology, Institute of Neurology and* [2]*Department of Psychology, University College London, London, UK*

Correspondence to: P. C. Fletcher, The Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London WC1N 3BG, UK

Summary

The effects of imagery and semantic relatedness on cued retrieval of word pairs were examined in a functional imaging study of healthy volunteers. Subjects underwent 12 PET scans, preceded by the paced presentation of 12 paired associates. The associates were dichotomized into imageable and non-imageable groups. Within each group, the strength of semantic association between members of pairs was varied in an ordinal fashion. Subsequently, neural activity was measured while subjects were cued with the first item of each pair and required to recall the associated word. Recall of imageable words, when compared with non-imageable ones, was associated with activation of the precuneus, consistent with our hypothesis that this region is important in visual imagery at episodic retrieval. The reverse comparison, non-imageable versus imageable recall, was associated with activation of the left dorsolateral prefrontal cortex. Within

both imageable and non-imageable groups, decreasing semantic association showed a corresponding increase in frontal activity bilaterally. One possible explanation is that of a practice-related effect, weaker-linked pairs having a greater number of pre-scan presentations. However, this explanation is incomplete as the most semantically distant, and most rehearsed, pairs (randomly linked) were associated with a reversal of this effect. This finding can be explained if frontal activity is associated with the difficulty of eliminating inappropriate responses at retrieval. For both randomly linked pairs and closely related pairs it is more likely that erroneous responses will be generated and, therefore, the work done to eliminate them will be greater. Our findings indicate that patterns of neural activity during cued recall depend upon the nature of the material and on the degree of association between the cue and the response.

Keywords: episodic memory; retrieval; imagery; semantic relationship

Abbreviations: SPM = statistical parametric map; SPMt = SPM of the *t* statistic; SPMZ = SPMt transformed to the normal distribution

Introduction

Episodic memory, a form of long-term memory, refers to the memory for events where the associated experiences have a specific spatiotemporal reference (Tulving, 1983). Brain areas implicated in processes related to episodic memory include the medial temporal lobes (Scoville and Milner, 1957; Smith, 1989), diencephalic structures (Butters and Stuss, 1989), frontal lobes (Jetter *et al.*, 1986; Petrides, 1989; Incisa Della Rocchetta and Milner, 1993), the basal forebrain (Damasio *et al.*, 1985) and the retrosplenial area of the cingulate cortex (Valenstein *et al.*, 1987; Rudge and Warrington, 1991). Functional imaging studies in the intact brain have shown activation of most of these regions in association with memory tasks (Grasby *et al.*, 1993a; Petrides *et al.*, 1993; Squire *et al.*, 1992; Grasby *et al.*, 1993b) but it is true that there are also areas, implicated by lesion studies, in which

PET experiments have not shown consistent activation. This is true of the hippocampal and basal forebrain regions.

In the cued recall of auditorily presented word pairs, we previously identified two regions specific to episodic retrieval—the right prefrontal cortex and a medial parietal area, the precuneus (Shallice *et al.*, 1994). Both areas were also among those activated in studies that combined encoding and retrieval (Grasby *et al.*, 1993a; Grasby *et al.*, 1993b; Petrides *et al.*, 1993). Our finding that activation of these regions was specific to the retrieval stage is strengthened by similar findings from other groups using a different retrieval paradigm (sentence recognition) (Tulving *et al.*, 1994b) and a different presentation modality (Haxby *et al.*, 1993).

Our previous finding of right frontal and precuneus activation in paired associate retrieval provided the basis for

two hypotheses. First that activation of the precuneus is associated with the use of visual imagery as a mnemonic strategy at episodic retrieval. In the previous work (Grasby *et al.*, 1993*a*; Shallice *et al.*, 1994; Fletcher *et al.*, 1995*a*), we used easily imageable material and subjects commented on the degree to which they had used imagery as a mnemonic strategy. We speculated that the activation of the precuneus reflected this phenomenon. Secondly, we speculated that activation of the right frontal lobe at retrieval reflects cognitive processes which are involved in retrieval from episodic memory. These processes include monitoring and verification of responses. Thus, during the retrieval of a previously presented exemplar, given the category-cue, the task may demand that a subject internally generates a candidate response, assesses its suitability and responds accordingly. If a putative response is deemed incorrect, then further possibilities may need to be generated and assessed. We speculated that these cognitive operations are reflected in right frontal activation.

The experiment was designed to test the first of these hypotheses, namely that the precuneus subserves imagery-related retrieval, by varying the extent to which visual imagery could be used during retrieval. We employed two sets of lists, one consisting entirely of strongly imageable words and the other of weakly imageable words.

A technical problem in this type of investigation arises from the greater difficulty in recalling non-imageable words (Baddeley, 1990). Since scanning takes place at retrieval, differential levels of performance would confound interpretation of any differences in brain activity. To compensate for this difference, we gave subjects a greater number of pre-scan presentations of the non-imageable material. To ensure that this difference in number of presentations during the learning phase did not, of itself, influence our findings, we varied the strength of relationship between the elements of each pair. Thus, within each of the above two sets (imageable and non-imageable), lists were varied across six levels of semantic association, from a value of 5 (strongly associated) to 1 (weakly associated) with a final pair of sets being assigned a value of 0 (no semantic association), strength of association being judged on the basis of empirical norms (Keppel and Strand, 1970). For both imageable and non-imageable sets, strongly associated pairs required less training than weakly and randomly associated pairs. Therefore, there was a large variation in the number of pre-scan presentations within each of the two sets of lists (*see* Fig. 1) whilst performance was equalized during all 12 scans. The effect of this controlled variation in the novelty of material was covaried out in analysis of the effects of imagery in order to ensure that it did not influence the findings.

Methods
Subjects
Six right-handed (Oldfield, 1971) male subjects (age range 25–40 years) took part in the study. Medical
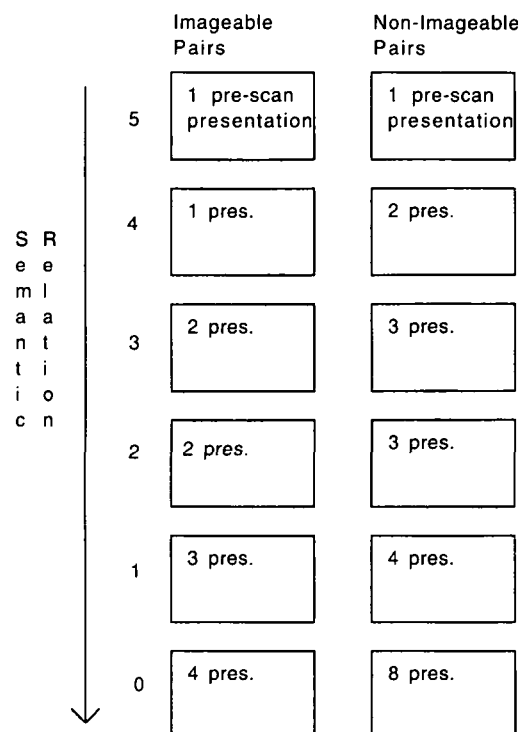
Fig. 1 Study design. Each box represents the retrieval paradigm during one PET scan. Material varied factorially (Imageable/Non-Imageable) and parametrically (semantic relationship). Thus, boxes on the left represent the six scans during which imageable material was retrieved, the boxes on the right represent the non-imageable scans. Going down, each set of scans varied in terms of the strength of semantic linkages between pairs (going down from '5' to '0', represented by numbers to the left of the boxes). The number of pre-scan presentations was varied according to both of these variations. The specific number for each condition is shown in the boxes.

histories taken from each subject showed them to be fit, healthy, on no medication and free from any history of neurological or psychiatric illness. The study was approved by the local hospital ethics committee and the Administration of Radioactive Substances Advisory Committee (UK) (ARSAC).

PET scanning
Each subject underwent 12 PET estimations of brain activity over a 2 h period. Scans were obtained using a CTI model 953B PET Scanner (CTI, Knoxville, Tenn., USA) with collimating septa retracted. Volunteers received a 20 s intravenous bolus of $H_2^{15}O$ at a concentration of 55 MBq ml^{-1} and a flow rate of 10 ml min^{-1} through a forearm cannula.

Psychological tasks
Subjects were scanned during cued paired associate retrieval. Each list, consisting of 12 pairs, was presented 5 min prior to the PET scan and the interval between presentation and recall was filled to prevent rehearsal. During each PET scan

subjects were cued with the first member of each pair and required to respond with the appropriate associate. The material was presented verbally to the subject by the experimenter at both acquisition and retrieval.

Each subject received six lists of imageable and six lists of non-imageable paired associates (one list was presented with each PET scan). Word pairs varied in terms of imageability according to the Quinlan Oxford Psycholinguistic database (Quinlan, 1992). Words with an imagery rating >450 were defined as imageable (e.g. 'Car–Truck). Words with an imagery rating <300 were defined as non-imageable (e.g. 'Come–Go'). A potential problem is that subjects may use some degree of visual imagery even in the retrieval of non-imageable material (since it can never be truly 'non'-imageable). Therefore, after each scan subjects were required to provide ratings (on a scale of 1–7) of the frequency and intensity of imagery which they had used in retrieval.

As well as the variation of the imagery rating for each list of words, the nature of the bonds within each pair was also varied. Pair associations were rated on a scale of 5 (close relationship) to 1 (distant relationship) to 0 (no relationship) (Keppel and Strand, 1970). Imageable and non-imageable lists were presented in counterbalanced order with pseudo-randomization of the order of strength of semantic association.

In brief, the paired associates changed across two dimensions, ranging from semantically close, imageable pairs (e.g. 'King–Queen') and semantically close, non-imageable pairs (e.g. 'Near–Close') to semantically distant, imageable pairs (e.g. 'Arm–Muscle') and semantically distant, non-imageable pairs (e.g. 'Happiness–Love') and to semantically unrelated, imageable pairs (e.g. 'Puppy–Hurricane') and semantically unrelated, non-imageable pairs (e.g. 'Secure–Irony'). Highly imageable items should be more easily recalled (Paivio, 1969; Baddeley, 1991) as should closely semantically related pairs thus providing a control for the potential pitfall of differential performance. On the basis of a pilot study using a different but comparable group of subjects, we used different numbers of pre-scan presentations across the 12 conditions in order that the performance during scans was equated. This pre-scan variability was limited to the number of presentations of lists, and subjects were not tested on performance prior to the scans. The overall study design is summarized in Fig. 1.

Data analysis

The data were analysed with statistical parametric mapping (using SPM95 software from the Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks Inc., Sherborn, Mass., USA). Our statistical parametric maps (SPM) combine a general linear model and the theory of Gaussian fields to make statistical inferences about regional effects (Friston *et al.*, 1991, 1994; Worsley *et al.*, 1992).

The scans from each subject were realigned using the first as reference. The six parameters of this rigid body

Table 1

Strength of semantic association	Memory performance, score out of 12 (SD)	
	Low imageability	High imageability
5	11.3 (0.8)	10.7 (1)
4	8.7 (1.4)	10 (1.8)
3	9.2 (1.9)	9.2 (1.9)
2	9.3 (0.8)	10.2 (1.8)
1	9.2 (1)	8.8 (2.1)
0	9.5 (2.1)	8.8 (1.2)

transformation were estimated using a least squares approach (Friston *et al.*, 1995a). Following realignment, all images were transformed into a standard space (Talairach and Tournoux, 1988). This normalizing spatial transformation matches each scan to a reference template image that already conforms to the standard space (Friston *et al.*, 1995a). As a final preprocessing step, the images were smoothed using an isotropic Gaussian kernel. The condition, subject and covariate effects were estimated according to the general linear model at each voxel (Friston *et al.*, 1995b). To test hypotheses about regionally specific condition effects, the estimates were compared using linear compounds or contrasts. The resulting set of voxel values for each contrast constitute an SPM of the t statistic, (SPMt). The SPMt were transformed to the unit normal distribution (SPMZ) and thresholded at $P = 0.001$ uncorrected for multiple comparisons.

Results
Psychological performance
No significant difference in performance across the two groups of scans (imageable and non-imageable lists) was seen nor was there any difference in performance associated with semantic distance. Performance is summarized in Table 1. Subjective ratings of imagery differed significantly across the two types of list with subjects consistently using a greater degree of imagery for the lists designated as imageable.

PET results
The PET activations were examined with respect to two main comparisons. First, we determined areas where increased brain activity occurred in association with recall of imageable word pairs (contrasting with scans acquired during recall of non-imageable pairs). Secondly, we carried out the opposite contrast to determine areas of increased brain activity occurring in association with recall of non-imageable word pairs (contrasting with scans acquired during recall of imageable pairs).

Variation in semantic distance between pair members provided the basis for a third comparison, namely to determine areas where brain activity altered with changing strength of semantic relationship. This correlation was performed

Table 2 *Effects of imageability on retrieval*

Region	Coordinates			Z score
	x	y	z	
Imageable versus non-imageable retrieval				
Precuneus	6	−46	36	3.5
	2	−58	32	3.3
	−2	−54	32	3.2
Right superior temporal gyrus	42	−48	16	3.4
Left anterior cingulate	−12	38	0	3.7
Right fusiform gyrus	42	−26	16	3.7
Non-imageable versus imageable retrieval				
Left PFC	−54 .	20	12	5.5

PFC = prefrontal cortex.

separately across each of the sets of imageable and of non-imageable pairs and also for both groups combined.

The first and second comparisons represent examples of a cognitive subtraction design in which one group of scans is compared directly with another. The third comparison represents a correlation of brain activity with a variable systematically manipulated across scans.

Comparison 1: brain activity associated with retrieval of visually imageable word pairs

This analysis showed activation of the precuneus, the left anterior cingulate cortex, the right superior temporal gyrus and the right fusiform gyrus (*see* Table 2 and Fig. 2A).

Comparison 2: brain activity associated with retrieval of non-imageable word pairs

This constitutes the complement of the above comparison and showed activation of the left dorsolateral prefrontal cortex (*see* Table 2 and Fig. 2B). One potential confounding factor in comparisons is that of differing numbers of pre-scan presentations used in the two sets of paired associate lists with the non-imageable lists having, overall, a large number (*see* Fig. 1) as they were more difficult to learn. Thus, any overall difference in activation between the two sets might, potentially, be accounted for by differences in novelty of the test material. In order to exclude this possibility, the data were reanalysed with the number of prior presentations as a covariate. Covarying out numbers of pre-scan presentations had no effect on the size or locus of the activations.
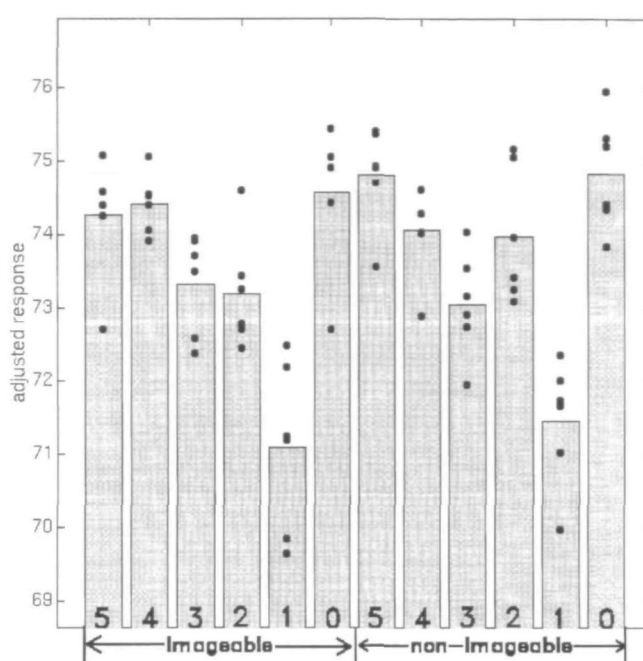
Comparison 3: the effects of the strength of the semantic relationship between pairs

A significant decrease in brain activity in the right medial and dorsolateral prefrontal cortex, was observed in association with decreasing semantic relationship (from 5 to 0).
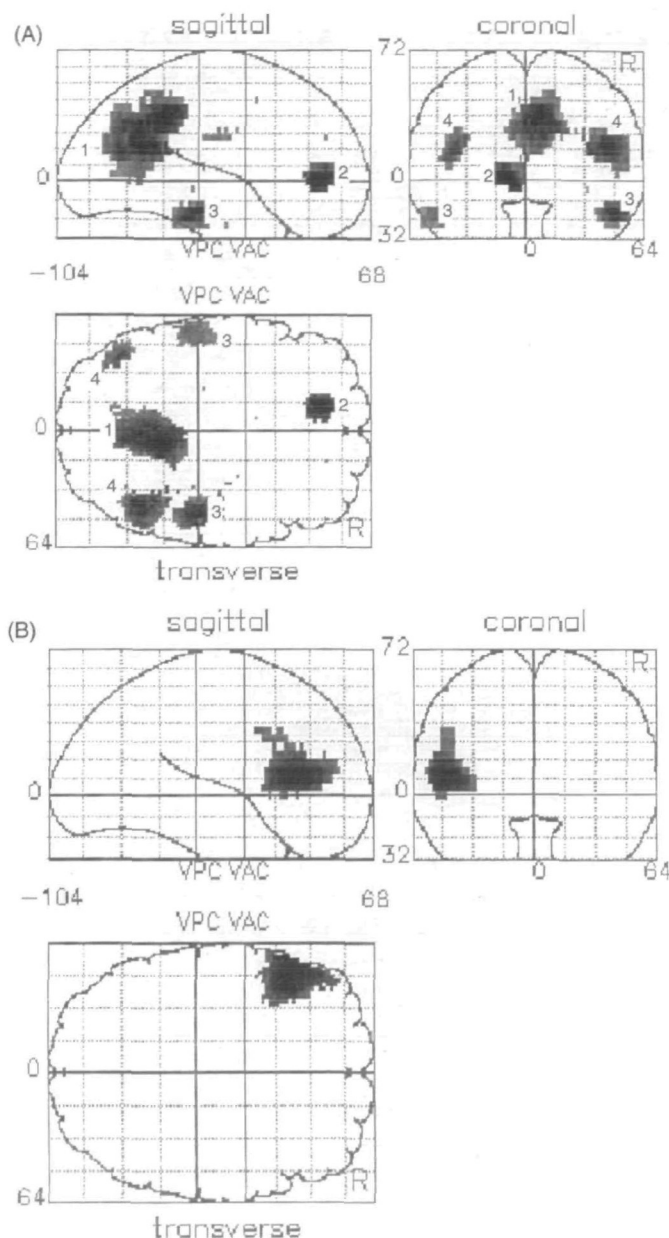
Fig. 2 Statistical parametric maps (SPMs) prepared as described in text. (**A**) Areas of increased activity associated with recall of imageable paired associates. Regions shown are: 1 = precuneus; 2 = left anterior cingulate cortex; 3 = fusiform gyri; 4 = superior temporal gyri. The SPM is shown at a low threshold to show the trend towards bilateral and largely symmetrical activations. The areas which survive an appropriately stringent threshold ($P < 0.001$) are those detailed in Table 2. (**B**) Increased activity associated with recall of non-imageable paired associates—this comparison shows activation solely of the left dorsolateral prefrontal cortex.

Examination of regional cerebral blood flow (rCBF) equivalents indicated that the pattern of activity within this region did not show a linear change across all the variations in semantic association. Across associations 5 to 1 (i.e. strong to weak linkage) there was a decrease in activity (*see* Fig. 3 and Table 3), but assessment of frontal rCBF

Fig. 3 Activation with decreasing semantic distance. This SPM excludes randomly linked pair recall. It combines imageable and non-imageable material, both of which show a strikingly similar pattern when analysed separately. The SPM indicates a predominantly frontal deactivation progressing from semantic distance '5' to '1'. Areas activated are shown in Table 2.

Table 3 *Decreases in activity associated with decreasing strength of semantic relationship*

Region	Coordinates			Z score
	x	*y*	*z*	
Imageable pairs				
Medial frontal gyrus	8	38	40	6.1
Right PGC	34	38	16	5.7
Right superior/middletemporal gyrus	42	–30	4	4.1
Posterior cingulate gyrus	8	–28	12	3.7
Non-imageable pairs				
Medial frontal gyrus	2	32	40	5.9
Right PFC	30	48	0	5.3
	28	42	8	5.2
Right superior/middle temporal gyrus	32	0	– 16	3.2
Left superior temporal gyrus	–40	–14	8	3.1

PFC = prefrontal cortex.

Table 4 *Random versus linked paired associate recall*

Region	Coordinates			Z score
	x	*y*	*z*	
Medial frontal gyrus	4	30	44	6
	–4	52	28	4.3
Right PFC	14	50	12	4.3
	20	44	16	4.2
Left PFC	–26	48	20	3.3

PFC = prefrontal cortex.

Fig. 4 rCBF equivalent values from a medial frontal pixel (coordinates *x, y, z* = –2, 50, 32) showing that the frontal decrease in activity associated with weakening semantic linkage (values shown at the base of rCBF bars) is relatively linear across the linked pairs (5 to 1) but that this is reversed for the unlinked pairs (0).

equivalents showed that this linear pattern was completely reversed in association with the randomly associated pairs (*see* Fig. 4). A direct comparison between the semantically and the randomly linked pairs was therefore made. This compared the set of random-linked pairs with the five sets of (varyingly) semantically linked pairs. We constrained the analysis to an appropriate subset of voxels. This voxel subset was defined by the analysis showing those brain areas in which activity decreased across semantic distances 5 to 1 (i.e. the comparison shown in Fig. 3) and thus it ensured that any significant change in activity could not be a result of increased number of pre-scan presentations in the random pairs. In the masked region were the areas where extrapolation of the linear trend with semantic distance would predict decreased activation for the non-associated pairs. The results, however, showed significantly increased frontal activity in the recall of random associates in certain areas (*see* Fig. 5).

Discussion

Our experimental design enabled us to examine the patterns of activation when two features of paired associate recall were varied. These features were the nature of the material (imageable versus non-imageable) and the degree of semantic association between pair members. The findings clearly demonstrate that these variables have a profound influence on the pattern of brain activation.
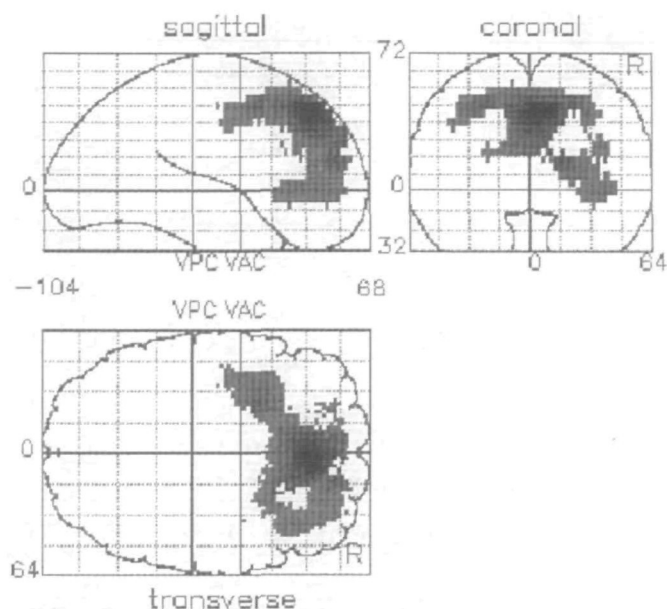
Fig. 5 Comparison of random pair with linked pair recall. This SPM shows only those voxels that were significant using two orthogonal or independent contrasts. The first reflects the regions deactivated in association with increasing semantic distance for the linked pairs only (i.e. The contrast shown in Fig. 3). The second reflect where this deactivation is reversed in moving from linked to unlinked pair recall. The first contrast, in effect, masks the second to a specific subset of voxels. This subset indicates those areas where there is a decrease in activity associated with increasing pre-scan practice. The use of this mask, therefore, ensures that the random versus linked contrast is not confounded by the increasing number of pre-scan practice associated with the former condition since it shows there is an increase in these areas when pairs are not semantically linked. Areas activated are the medial frontal gyrus, and the dorsolateral prefrontal cortex bilaterally, with a predominance on the right.

Visual imagery in memory retrieval

Our previous experiment, comparing an episodic retrieval task with a semantic memory control, showed activation of the right prefrontal cortex and the precuneus (Shallice *et al.*, 1994; Fletcher *et al.*, 1995a). In the present study, which examined episodic retrieval in all conditions, the recall of two types of material was compared in order to test the hypothesis that precuneus activation arises from the use of visual imagery to aid memory retrieval. Whilst it is certainly possible that subjects could have used some degree of imagery in the retrieval of the abstract pairs, the success of this differentiation of study material in producing different retrieval procedures was confirmed by the subjective ratings of the strength of imagery used during the scanning phase (with the recall of imageable pairs producing a significantly greater subjective rating of imagery used). Moreover, the possibility that the activations found to be associated with recall of imageable material are confounded either by differential performance or a practise/novelty effect is ruled out for the following reasons. First, performance did not vary across conditions. Secondly, covarying for the amount of practice/degree of novelty led to no change in the pattern

of activation. The activation of the precuneus was the sole finding in the comparison which was restricted to the previously defined episodic retrieval system. This finding is discussed elsewhere (Fletcher *et al.*, 1995b). The precuneus activation was also evident in an unconstrained comparison in addition to other activations detailed in Table 2 and shown in Fig. 2A.

It is noteworthy that in our previous episodic memory retrieval experiment (Shallice *et al.*, 1994), apart from the precuneus, we did not see activation of any of the other three areas (the left anterior cingulate gyrus, the fusiform gyrus and the superior temporal gyrus). The imagery used by subjects in this study required them to pay little attention to any detailed analysis of the items being imaged; there were minimal requirements to generate elaborate images. Image inspection, however, was crucial and it was perhaps this which was reflected in the activation of the precuneus. Our previous study employed concrete/imageable material in both activation and control conditions (Shallice *et al.*, 1994) making it seem likely that, across all conditions, there would be a degree of activation associated with the automatic generation of images. These images would only need to be inspected in the episodic memory condition. We suggested that this phenomenon was reflected in precuneus activation. In the current experiment, however, concrete/imageable material was only presented in six of the scans, therefore we would expect comparison of imageable with non-imageable recall to reflect processes in image generation as well as image inspection. A particularly interesting finding in relation to this possibility is that of activation of the fusiform gyrus. This suggests that extra-striate visual areas have a role in visual imagery. Indeed, in a recent study involving intracranial electrical recording (Nobre and McCarthy, 1995), the anterior fusiform gyrus was identified as the neural generator of field potentials in response to words. Of particular interest in relation to our findings was the observation that maximal responses were elicited by highly imageable, concrete words. Results from our previous study of episodic memory retrieval did not show activation of fusiform or parietotemporal regions, despite subjects' reports that they utilized imagery as a recall strategy in the retrieval condition. This lends support to our contention that these regions are automatically activated by imageable words, while the precuneus is required for conscious visual imagery (in this case, in the context of retrieval) functioning as 'the mind's eye'.

Our two other findings in this comparison, i.e. activation of the right superior temporal gyrus and the left anterior cingulate gyrus have been reported by another group examining episodic memory retrieval (Tulving *et al.*, 1994b). In this experiment in which subjects were required to recognize previously presented, easily imageable sentences, activations were seen at very similar coordinates.

Some, but not all, previous functional imaging studies of complex, multi-component tasks which involve imagery report activation of parieto-occipital and temporo-occipital cortex but not of primary visual areas (Roland and Gulyás,

1994). Activation of early visual processing areas has been reported particularly in studies where a feature of the experimental paradigms is selective attention to components of the generated images (Roland and Friberg, 1985; Kosslyn *et al.*, 1993). The unconstrained analysis did reveal the involvement of extra-striate visual areas in association with imageable material. However, it is noteworthy that no early visual processing regions were activated. This provides evidence that, in memory based imagery at least, it is higher visual processing areas which are involved.

Left prefrontal activation in non-imageable recall

The left lateral prefrontal cortex was the only area activated in association with the cued recall of non-imageable words. Its activation was unaffected by the greater degree of pre-scan rehearsal of the material. Activation of this region occurs frequently in PET studies of memory (Grasby *et al.*, 1993*a*; Petrides *et al.*, 1993). Specifically, it has been activated in association with episodic memory encoding (Kapur *et al.*, 1994; Shallice *et al.*, 1994). One suggestion is that the observed activation of this region in association with a number of other tasks (verb generation and other verbal fluency tasks) reflects the obligatory episodic encoding processes which occur with the retrieval of semantic information (Tulving *et al.*, 1994*a*). It is not immediately apparent how such an explanation would be relevant to our current findings given that this area is active during retrieval of non-imageable material. A greater degree of concurrent encoding in the recall of non-imageable material seems unlikely. One possible, but highly speculative, explanation might be that non-imageable retrieval is more effortful and requires greater processing, being analogous to a deep encoding task, and that is known to activate the left prefrontal cortex (Kapur *et al.*, 1994). This, however, is at odds with the fact that the non-imageable material was presented more frequently during the pre-scan period which, presumably, renders the words less novel and thus less likely to become the subject of new encoding during the scan.

The presence of left prefrontal cortex activity in this condition does, however, strongly suggest that the pattern of prefrontal activation during episodic recall is affected by the nature of the material to be recalled. When it is not easy to link the words by forming a composite image which can be regenerated at retrieval, the cue prompts reactivation of a phonological or semantic link between the elements of the word pair. In this case, the subject can no longer generate a response by inspecting a previously formed image but is required to make alternative links between the cue and the response.

This explanation, that the differential left prefrontal activation may be attributable to separable access of imageable and non-imageable representations to language output systems, is again highly speculative. However, there is evidence from the neuropsychological literature of a dissociation between the ability to produce normally ('internally') generated speech and the ability to name, read and repeat (Costello and Warrington, 1989). Patients with dynamic aphasia (in which the lesion has been suggested to lie in the left prefrontal cortex; *see* McCarthy and Warrington, 1990) show very little spontaneous speech but performance is unimpaired in highly constrained conditions such as naming, repetition and yes/no responding. In addition, the ability to complete a sentence is spared if a single word is required but not when the task demands a phrase (Costello and Warrington, 1989; Breen and Warrington, 1994). Moreover, the effect is not necessarily related to processes involved in producing syntax but appears, instead, to be linked to the production of words. Thus the patient could produce a sentence describing a concrete action (the reporter test) but was extremely poor at generating words beginning with a specific letter (word fluency).

One possibility is that, for the concrete pairs in our study, the use of imagery allows the output phonological word-form to be accessed through a relatively automatic naming procedure. For abstract pairs, however, this procedure cannot be used and an abstract semantic link must be employed, requiring that the processes impaired in dynamic aphasia be utilized for reaching the phonological word form.

A right prefrontal activation, evident in our previous study of episodic recall (Shallice *et al.*, 1994), was not present in any of the comparisons of imageable and non-imageable pair recall. This confirms that our experimental design achieved equal engagement of episodic retrieval processes mediated by this region for both the imageable and non-imageable items. Our previous hypothesis was that activation of this region reflects processes carried out on retrieved information (Shallice *et al.*, 1994) (processes such as monitoring and verification referred to below) and it would predict that different modes of accessing material, whether imagery-based or semantic-based, would not be reflected in differential activation of this region.

Decreases of frontal activity with decreasing novelty

Our initial examination of the correlation between cerebral activity and increasing semantic distance (from 5 to 0) showed substantial areas of decreased activity (predominantly frontally) for both imageable and non-imageable sets of material. This finding was unexpected since greater semantic distance is associated with more difficulty in acquisition of the material. We therefore examined, in detail, the profile of rCBF change in frontal regions. The pattern which emerged showed a linear decrease in activity across semantic distances 5 to 1 with a significant reversal of this pattern for the two sets of randomly associated pairs (semantic distance 0). We therefore provisionally excluded the last two scans from the correlation analysis, restricting our analysis

to the five sets of pairs where a semantic link (of varying strength) existed. The results, shown in Fig. 3, indicated a predominantly frontal decrease in activation with increasing semantic distance.

As two different factors (semantic distance and number of training trials) necessarily vary across these conditions, one must be cautious in interpreting this result. However, a natural explanation is to view the decreases in activity as an effect of increased practice. Such an effect has been described before in relation to a verbal fluency task (Raichle *et al.*, 1994). In addition, Tulving *et al.* (1994*c*) have found that there is a greater degree of activation of a number of brain regions (including medial prefrontal cortex) during presentation of novel material, when compared with old material. Thus, the fact that we see a decrease in frontal activity with decreasing strength of semantic relationship could be explicable in terms of the decrease in material novelty across these lists.

However, a second aspect of our findings shows that relative novelty of the retrieved material *per se* is an insufficient explanation of the whole pattern. The graph of rCBF equivalents across increasing semantic distance (Fig. 4) indicates clearly the non-linearity of the pattern. If the activation in the two excluded scans (the random pairs) are compared with the weighted mean of the related pairs, a significantly greater activation is obtained in the former (*see* Fig. 5), in a very similar region to that where an increase in semantic distance leads to reduced activation in the related pairs. It is clear that any explanation of decreased activity in terms of reducing novelty, that is, an increase in the number of training trials, cannot account for the full pattern of results since the random pairs have the greatest number of training trials and are therefore the least novel.

Retrieval of random versus semantically linked pairs

The analysis of randomly linked versus semantically linked pairs was constrained to those areas which showed reduced activation in association with increasing training for the semantically linked pairs alone. In this way, we could be certain that the increased activation in the areas seen in the former comparison could not be explained by the increasing practice associated with the unlinked pairs. Areas showing increased activity with the unlinked pair recall by comparison with semantically cued pair recall were the frontal regions including the dorsomedial and dorsolateral prefrontal cortex bilaterally.

Neuropsychologically, when one considers the random pairs, two effects might be anticipated. First, at encoding, mediators would be expected to be used to encode the unrelated pairs. It has been shown that two patients with left frontal lesions were unable to learn unrelated paired associates, but they could do so if a possible way of organizing the links between the pairs was provided (Signoret and

Lhermitte, 1976). Given that the use of mediators at retrieval also require frontal activation, then this would account for the activity observed.

Secondly, at retrieval *per se* random pairs would differ from other pairs in a rather subtle way. A frequent error type in retrieving one of a set of unrelated paired associates is a response which was appropriate for one of the other stimuli. The learning of the response set can, in effect, precede the learning of the appropriate pairs. By contrast, when responses are semantically related to the stimuli, a correct putative response would not be related semantically to any other stimuli in the list and so the possibility of this type of error can be easily excluded. Thus, random pairs need much more careful monitoring and verification of the appropriateness of putative responses than do semantically related paired associates. At first sight it seems paradoxical that the most frontal activity should be observed both when retrieving strongly related pairs and when pairs were unrelated. However, the paradox can be resolved if this activity is associated with processes concerned with distinguishing between possible responses (i.e. monitoring and verification). The presentation of a cue word is likely to elicit a number of possible response words. One of these may be the actual word paired with the cue. Other words likely to be elicited in error are those closely associated with the cue word (error a) and response words associated with other cue words in the original list (error b). We propose that frontal activity is greater when it is more difficult to eliminate these alternative responses. In the case of semantically linked pairs, response words from other parts of the list (error b) can easily be eliminated because they are not semantically related to the current cue word. This strategy is not available for the unrelated pairs and therefore more effort is required to eliminate these inappropriate responses. Words closely associated with the cue word (error a) are most difficult to eliminate in the lists in which the correct response word is also closely related. For the pairs in which the semantic relation is low, closely associated words can be eliminated precisely because they are too closely associated to the cue word. This admittedly ad hoc account shows how a single mechanism can result in both close semantic pairings and semantically unrelated pairings being more difficult to retrieve than pairs with an intermediate degree of relatedness. If this account is correct, it relates frontal activity to the difficulty in eliminating incorrect responses and, presumably, it would be possible to observe increased reaction time and reduced confidence for the closely related and the unrelated pairs.

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