

# “Sculpting the Response Space”—An Account of Left Prefrontal Activation at Encoding

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**Left lateral prefrontal cortex (PFC) is consistently activated in neuroimaging studies of memory encoding. Its role, however, remains unclear. We describe two functional magnetic resonance imaging (fMRI) studies addressing this question. In the first we used a blocked experimental design to explore the effect of repeated encoding of word paired associates. Initial presentation of word pairs was associated with left ventrolateral PFC activation that attenuated with subsequent presentations of the same lists. When well-learned lists were presented with word pairs rearranged, a left PFC activation, greater than that associated with the initial presentation, was observed. In a second experiment, the formation of these associative relationships was explored using an event-related design. Two types of word pairs were presented: closely related (e.g., King . . . Queen) and distantly related (e.g., Net . . . Ship). The same region of left PFC was differentially sensitive to these two event-types, showing a greater response for distantly related pairs. We suggest that left PFC activity, at memory encoding, reflects operations necessary to the formation of meaningful associations in the service of optimal learning. A crucial feature of such associative processing lies in selecting appropriate, and inhibiting inappropriate, semantic attributes of the study material.** © 2000

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## INTRODUCTION

Memory encoding has been associated with lateral PFC activation across a variety of experimental paradigms in functional neuroimaging (Haxby *et al.*, 1996; Kapur *et al.*, 1994; Shallice *et al.*, 1994; see Fletcher *et al.*, 1997, and Gabrieli *et al.*, 1998, for reviews). A number of characteristic features of this response are

noteworthy. First, left PFC activation is independent of the intention to memorise material (Kapur *et al.*, 1994). Second, left PFC is linked to efficient encoding since a simultaneous distracting task (which interferes with encoding) is associated with attenuation of activation (Shallice *et al.*, 1994). Moreover, event-related fMRI has shown evidence for a link between left PFC and encoding success (Wagner *et al.*, 1998). Third, the types of tasks associated with left PFC are those emphasizing the meaning rather than surface features of study items (Kapur *et al.*, 1994; Fletcher *et al.*, 1998) (i.e., “deep encoding tasks” ( Craik *et al.*, 1972)).

Questions remain, however, concerning the specific role of PFC at encoding. Both neuropsychological (Incassa Della Rochetta *et al.*, 1993; Gershberg *et al.*, 1995) and recent neuroimaging (Fletcher *et al.*, 1998) evidence suggests that PFC may be important for organization of study material known to be important for optimal learning (Segal *et al.*, 1967). In our previously reported neuroimaging study, left PFC activity was maximal when subjects were required to organize semantically related words, while simultaneous distraction attenuated this response (Fletcher *et al.*, 1998). In a further study, we showed that learning semantic linkages during encoding produced a maximal left PFC response when alternative links had already been formed and were no longer task-relevant (Dolan and Fletcher, 1997). These observations suggest that left PFC activation reflects both a requirement to emphasise relevant semantic attributes of study material and to suppress attributes that have become irrelevant. The more specific role of left PFC in the semantic processing associated with encoding tasks is unclear. Several possibilities have been suggested and these can be summarized as follows: first, it has been proposed that left PFC activation reflects the retrieval of semantic knowledge, (Tulving *et al.*, 1994). A second viewpoint is that left PFC's role lies in holding of semantic attributes of material in working memory (Gabrieli *et al.*, 1998). A third view is that left PFC activa-

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tion is associated with a higher level process concerned with the selection of semantic attributes that are relevant to the task at hand (Thompson-Schill *et al.*, 1997; Frith, in press). This view, that left PFC is concerned with selecting rather than retrieving or holding semantic attributes has been tested experimentally (Thompson-Schill *et al.*, 1997) and is implicit in proposals that left PFC activation in memory encoding reflects organization of encoded material according to its semantic attributes (Shallice *et al.*, 1994; Fletcher *et al.*, 1998). Alternatively, it has been suggested that the crucial feature of left PFC activation lies in the formation of associations even in the absence of any semantic evaluation (Passingham *et al.*, in press). A broader view is that left PFC activations are associated with "reflective activity" which comprises "detailed, deliberative analysis . . . maintenance of information while it is being evaluated, or the initiation of systematic self-cueing to retrieve additional information" (Nolde *et al.*, 1998). In fact, this latter view is sufficiently broadly formed to encompass all of the aforementioned accounts.

A major difficulty confronting attempts to distinguish between these possibilities is that it is difficult to manipulate the processes independently. Thus, for example, the frequently reported left PFC activation in semantic verbal fluency studies (Petersen *et al.*, 1988; Frith *et al.*, 1991) is compatible with any of the above accounts since these tasks are associated with retrieving, selecting, holding, and manipulating semantic information.

The current studies sought to address ambiguities in the interpretation of left PFC activation at encoding. The first experiment is closely related to our previous study of the influence of prior learning on word pair encoding (Dolan and Fletcher, 1997). In essence, it characterizes brain responses to the learning of new semantic relationships when different relationships to the same material have already been established. This can be compared directly with instances where semantic associations have been well learned and with cases where new semantic associations must be established in the absence of previously learned associations. In this way, selection processes may be dissociable from processes associated with retrieving and holding in mind semantic attributes since, we suggest, the critical feature of setting up new semantic associations to verbal material that has already been repeatedly presented lies in the selection of new attributes. There is no reason to suppose that the actual amount of semantic information will exceed that in the semantic processing of entirely novel material. Thus, a significantly greater left PFC activation in the former condition compared with the latter may be attributable to selecting rather than retrieving and holding in mind processes.

In a second fMRI experiment (experiment 2), we addressed the possibility that a task used to engage

semantically based organization might also place a greater working memory (WM) load on subjects and that this could account for an associated left PFC response. We therefore used an alternative approach, exploiting the capabilities of event-related fMRI (Buckner, 1998; Buckner *et al.*, 1998; Friston *et al.*, 1998) to explore responses to single items (paired associates) thus minimizing WM load. That is, we used the infrequent presentation of small amounts of material to enable us to minimize nonspecific WM effects. This is a possibility not afforded in our previous PET study that used a blocked design (Fletcher *et al.*, 1998).

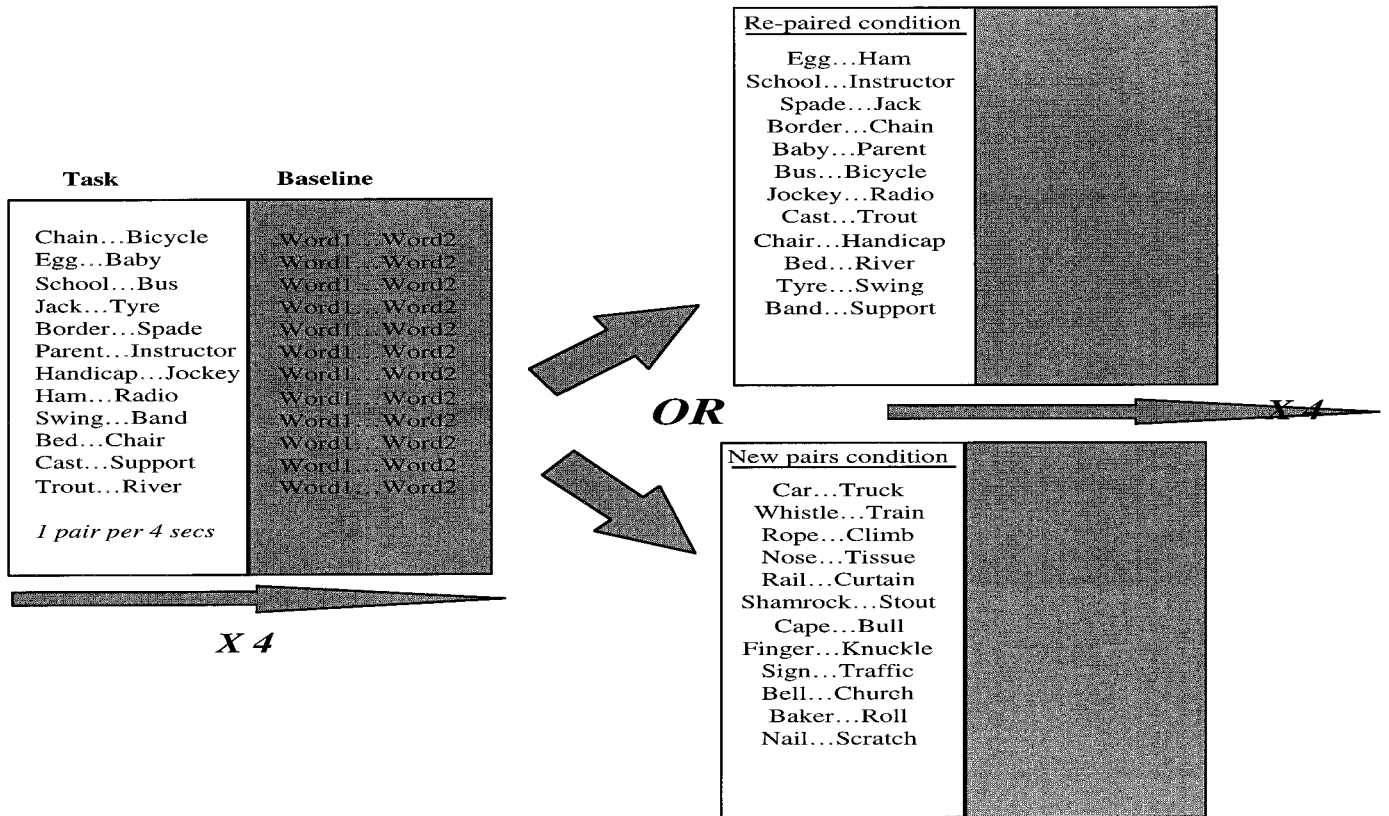
## MATERIALS AND METHODS—EXPERIMENT 1

### *Subjects*

MRI scanning was carried out on seven volunteer subjects (age range 23–36 years; mean age 28 years). All subjects were fit and healthy with no history of neurological or psychiatric illness or of drug/alcohol abuse. All subjects gave informed consent and the study was approved by the local hospital ethics committee.

### *Psychological Task*

Twelve word paired associates were presented visually, at a rate of one pair per 4 s, on a projection screen placed comfortably within subjects' field of view. Members of each pair were presented successively, each member being presented for 2 s. Thus subjects would see, for example, the stimulus "Bird. . ." for 2 s, followed by ". . .Note" for 2 s. When a list had been shown in its entirety, it was presented again (in a different order). An individual list was presented a total of four times, alternating with a baseline control task. Scanning occurred throughout. The baseline task consisted of the presentation of identically paced paired items which were shown repeatedly (that is only two items were seen throughout the block—simply the items: *word 1. . . word 2*). Subjects were instructed to read the pairs silently in the memory encoding task and to think about the word or concept that linked members of each pair. They were forewarned that, following scanning, a cued retrieval task would be administered. When the same list had been presented for the fourth time, the next baseline epoch was followed, without warning, by a second list. In this list, one of the following changes was implemented: Either 12 entirely new word pairs were presented or 12 pairs comprising the same words that had been learnt during the four initial presentations was presented but this time the pairings of individual words were rearranged. In both cases, the new word pairs were presented a total of four times alternating with the unchanging baseline task. The study design is summarized in Fig. 1.



**FIG. 1.** Study design for experiment 1. Sample lists are shown. Note: to prevent confounding effects produced by any systematic differences in strength of linkage between initially presented and re-paired items, in half of the subjects the order of presentation was reversed (that is, initially presented pairs in one half of the subjects were given as the re-paired items in the other half and vice versa).

### Scanning

A Siemens VISION system (Siemens, Erlangen), operating at 2 Tesla, was used to acquire both T1 anatomical and gradient-echo echo-planar T2\*-weighted image volumes with blood oxygenation level dependent (BOLD) contrast. For all subjects, data were acquired in four scanning sessions separated by a 5-min rest period. Aside from six “dummy” volumes, which were subsequently discarded to allow for T1 equilibration effects, a total of 384 functional volumes per subject (96 scans per session) were acquired. A TE of 40 ms was used and volumes were acquired continuously every 4800 ms. Each volume comprised 48 3-mm axial slices with in-plane resolution 3 × 3 mm positioned to cover the whole brain.

### Image Analysis

Data were analyzed using Statistical Parametric Mapping (SPM97, Wellcome Department of Cognitive Neurology, London, UK; Friston *et al.*, 1995). All volumes were realigned to the first volume and resliced using a sinc interpolation in space. Each volume was normalized to a standard EPI template volume (based on the MNI reference brain, (Cocosco *et al.*, 1997)) of 3 × 3 × 3-mm voxels in a standard space (Talairach

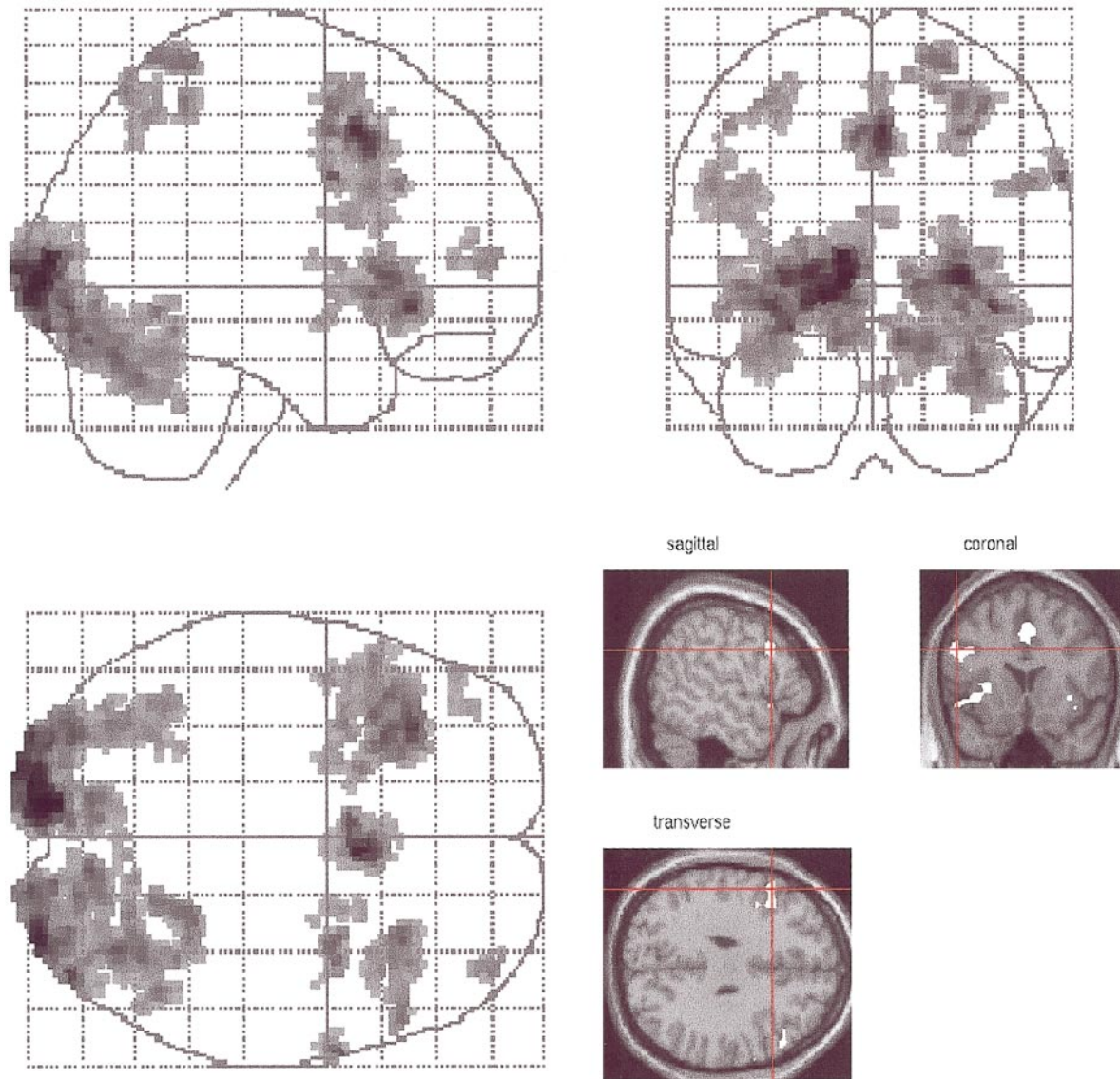
and Tournoux, 1988), using nonlinear basis functions. The T1 structural volume was coregistered with the mean realigned EPI volume and normalized with the same deformation parameters. Finally, the EPI volumes were smoothed with a 8-mm FWHM isotropic Gaussian kernel to accommodate further anatomical differences across participants and proportionally scaled to a global mean of 100.

**TABLE 1**

Experiment 1: Regions Showing Differential Responses to Word Paired Associate Encoding Compared to Baseline Task

Region	Coordinates	Z score
Left inferior	-32, 30, -6	6.8
Frontal gyrus	-52, 16, 30	4.8
Right inferior	30, 24, 2	5.7
Frontal gyrus	54, 24, 32	5.1
Left occipital cortex	-10, -96, 2	7.6
Right occipital cortex	30, -96, 4	7.3
Medial frontal	4, 12, 46	7.2
Cortex/anterior cingulate cortex	-4, 8, 46	6.0
Right parietal cortex	24, -46, 66	5.5
Left parietal cortex	-28, -50, 40	4.0

*Note.* Coordinates refer to Talairach and Tournoux (1988).



**FIG. 2.** Statistical parametric map (SPM) of regions showing a significantly greater BOLD response ( $P < 0.001$ ) for the encoding than the baseline task (irrespective of time-related changes) in experiment 1. Results are presented as a maximum intensity projection or “Glass brain,” showing views from the right (top left panel), from behind (top right panel) and from above (bottom left panel). The regions activated are listed in Table 1. In the bottom right panel are orthogonal sections of a T1-weighted anatomical image with sections chosen at the left prefrontal voxel of maximum intensity ( $x, y, z = -44, 26, 18$ ) onto which the SPM has been rendered to show in more detail the prefrontal activations.

As well as a simple subtraction of baseline from activation tasks, enabling a definition of the non-time-dependent system associated with word pair encoding, we characterized changes in activation as a function of increasing familiarity with study material. Furthermore, we explored regions responding to a change in well-learned word lists depending upon whether that change was in the items themselves or in the way in which items (individual words) were paired with each other. In order to do this, we compared the activations (compared to the baseline) associated with the first presentation of rearranged pairs with average activa-

tions (compared to baseline) for the initial presentation of these pairs prior to their rearrangement combined with activations associated with initial presentation of all other pairs. That is, in brief, we compared activations produced by re-pairing with activations associated with novel items. In view of the fact that lists were not counter-balanced across subjects, we performed a further comparison limited to those lists occurring in the re-pairing condition. This was identical to the re-paired versus novel comparison but used only those lists associated with the re-pairing condition. That is, we compared activations, relative to baseline, after

pair rearrangement to activations on initial presentation of this material. This was carried out to establish that activations were not merely the result of a systematic bias in the nature of the word lists across conditions.<sup>2</sup>

In order to minimize a risk of false positives, and to ascertain that the regions reported all show an activation relative to the baseline condition, we used the first analysis (that is, all task versus all baseline scans) to define a subset of voxels. The analysis of the interaction effects was applied only to this "mask" subset of voxels. In using this approach, we can be more confident that changes reported were changes in absolute activation (relative to baseline). Further, this use of a constrained subset of voxels constitutes a stricter approach with respect to the prevention of false positive results as it means that fewer voxel-wise comparisons are carried out. In the third analysis—the one addressing regions sensitive to a change in the pairing of already-learned words—we also used this mask. In view of our strong and spatially precise a priori hypothesis with respect to left PFC, we set an uncorrected threshold for this region ( $P < 0.05$ ). For all other regions effects surviving a threshold of  $P < 0.001$  are reported. The use of the mask rendered the standard SPM correction for multiple comparisons inappropriate.

For all effects, subjects' data were modelled separately and group results are presented as the conjunction of activations across all seven subjects (Price *et al.*, 1997). In essence, this means that we examined the data only for changes common to all subjects. The conjunction analysis indicates effects that do not differ significantly between subjects in terms of magnitude and location.

## MATERIALS AND METHODS—EXPERIMENT 2

### *Subjects*

MRI scanning was carried out on six volunteer subjects (age range 24–32 years; mean age 27 years). All subjects were fit and healthy with no history of neurological or psychiatric illness or of drug/alcohol abuse. All subjects gave informed consent and the study was approved by the local hospital ethics committee.

### *Psychological Tasks*

During scanning, subjects were presented with word pairs. Pairs were presented visually, at a rate of one pair per 12 s, projected onto a screen comfortably within subjects' field of view. Each word stayed on the screen for 1 s. Thus, there was an interstimulus interval of 10 s. When the second word in a pair had been

presented, it was replaced with a fixation cross. Subjects were instructed to read each pair and to consider the concept or word that linked the two members of each pair. They were warned that, following scanning, cued retrieval would be tested. Sixty pairs were presented during each scanning session. Thirty were designated as closely related (e.g., king . . . queen) and 30 were designated distantly linked (e.g., prince . . . skull). Pairs were generated according to simple criteria. They were designated as closely related when members of a pair showed an immediate and obvious link, such as belonging clearly to the same category. When the shared semantic attributes were accessible only through the use of indirect semantic mediation, they were designated as distantly related. Thus, we used an informal, but clear, categorization of pairs. Words used in the study did not differ systematically in concreteness, frequency, or familiarity. Unfortunately, it is unavoidable that some pairs that had been deemed distantly related would be found, by subjects, to be closely related (or vice versa). However, this would generate type II error in our imaging data. This does not, therefore, affect the reliability of our reported activations.

### *Scanning*

A Siemens VISION system (Siemens, Erlangen), operating at 2 Tesla, was used to acquire both T1 anatomical and gradient-echo echoplanar T2\*-weighted image volumes with blood oxygenation level dependent (BOLD) contrast. For all subjects, data were acquired in one scanning session lasting approximately 20 min. Aside from six "dummy" volumes, which were subsequently discarded to allow for T1 equilibration effects, a total of 196 functional volumes per subject were acquired. A TE of 40 ms was used. Volumes were acquired continuously every 4800 ms. Each volume comprised 48 3-mm axial slices with in-plane resolution of  $3 \times 3$  mm positioned to cover the whole brain.

### *Image Analysis*

Data were analyzed using Statistical Parametric Mapping (SPM97, Wellcome Department of Cognitive Neurology, London, UK; Friston *et al.*, 1995). All volumes were realigned to the first volume and resliced using a sinc interpolation in space. Each volume was normalized to a standard EPI template volume (based on the MNI reference brain (Cocosco *et al.*, 1997)) of  $3 \times 3 \times 3$ -mm voxels in a standard space (Talairach and Tournoux, 1988), using nonlinear basis functions. The T1 structural volume was coregistered with the mean realigned EPI volume and normalized with the same deformation parameters. Finally, the EPI volumes were smoothed with a 8-mm FWHM isotropic Gaussian kernel to accommodate further anatomical differences across participants and proportionally scaled to a global mean of 100.

<sup>2</sup> We are grateful to an anonymous referee for drawing our attention to this point.

Stimuli were classified according to three event-types: pairs with a close semantic relationship, those with a distant semantic relationship and finally those that were not associated, subsequently with successful cued retrieval. The latter items were ignored in the analysis of the fMRI data.

Treating the acquired volumes as a time series, the hemodynamic responses (to the onset or presentation of the second word in the pair) for each event-type were modelled with a canonical, synthetic haemodynamic response function and its first-order derivative with respect to time (Josephs *et al.*, 1997). The inclusion of the derivative caters for small deviations in the onset of the haemodynamic response (Friston *et al.*, 1998). These functions were used as covariates in a general linear model, together with a constant term and a basis set of cosine functions with a cut-off period of 90 s to remove low frequency drifts in the BOLD signal (Friston *et al.*, 1998). The parameter estimates for the height of the canonical response for each event-type covariate resulting from the mean least squares fit of the model to the data were obtained. Pair-wise contrasts between the height parameter estimate for event-types were tested by voxel-specific, repeated measures *t* tests across participants. These were subsequently transformed to the unit normal *Z* distribution to create a statistical parametric map (SPM) for each contrast. Given that differential activity in left PFC was predicted on the basis of previous studies of paired associate encoding and was the subject of our *a priori* hypothesis, an uncorrected threshold, as for experiment 1, was set ( $P < 0.05$ ). In fact, the left PFC effect survived correction for multiple comparisons.

Having carried out the group analysis we plotted event-related responses for all six individual subjects in order to ascertain that any reported findings were common to all subjects and not produced by an especially strong response in only a subgroup.

## RESULTS—EXPERIMENT 1

### *Behavioral*

Cued retrieval was tested after the scanning session. Subjects were cued with the first item in each pair and required to respond with the second. In some cases a given cue was associated with two responses (when pairings had been rearranged). In these cases, subjects were required to name both items with which the cue had been paired. The cue was chosen as the one that had been presented first during the initial presentation of items. This means that cued retrieval following pair rearrangement occurred in a different setting from retrieval where no such rearrangement occurred. While this is not ideal with regard to the behavioral measurement, it had no bearing upon the neuroimaging results that we present. The mean scores were near ceiling:

**TABLE 2**

Experiment 1: Regions Showing Decreasing Activation with Repeated Presentation of a Word Pair List

Region	Coordinates	<i>Z</i> score
Left inferior Frontal gyrus	−46, 18, 28 −44, 18, 18 −52, 12, 16	5.1 4.3 4.3
Left occipital cortex	−24, −92, −10	3.9
Right occipital cortex	24, −82, −22	5.2
Cerebellum	−40, −52, −14 38, −62, −24	4.6 4.7

initially presented pairs 99.2% (range 91.7–100%); entirely novel pairs 98.3% (range 91.7–100%); old words rearranged 96.7% (range 83.3–100%). This ceiling effect occurred because every pair had been presented a total of four times. No significant differences were noted between new and rearranged pairs. In effect, the influence of proactive interference on postscan retrieval is likely to be submerged by the greater effect of repeated learning.

### *Functional Neuroimaging*

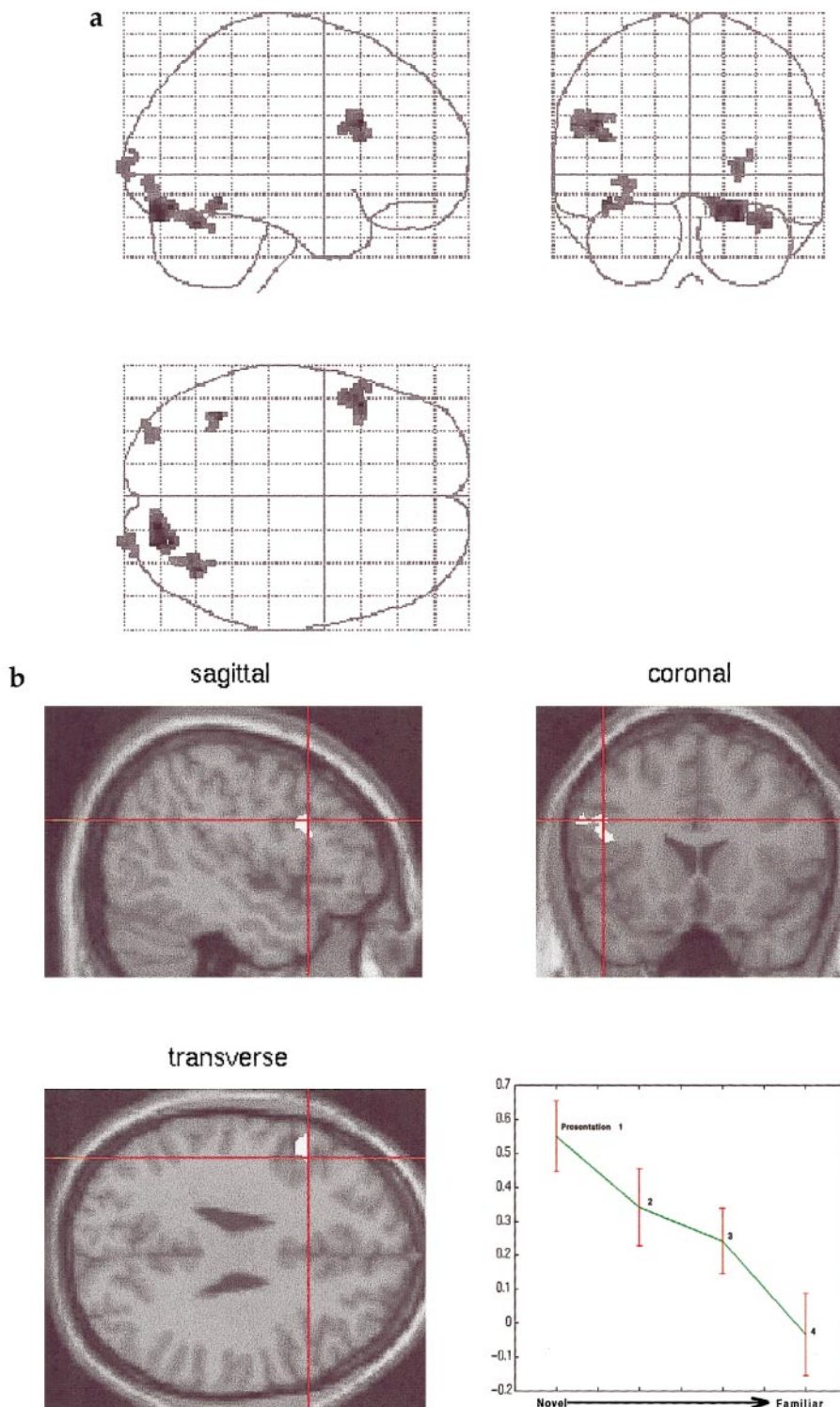
Comparison of encoding with baseline tasks produced evidence of activation in a number of areas including, as predicted, left PFC (ventrolaterally). The results from this analysis are summarized in Table 1 and Fig. 2. The regions showing a decrease in activation, relative to the baseline task, as pairs become more familiar (from presentation 1 to 4) are shown in Table 2 and Fig. 3. Left VLPFC showed a significant time-dependent effect.

The comparison exploring for regions showing a significantly greater response to pair rearrangement than pair novelty is shown in Table 3 and Fig. 4. The effect in left VLPFC was significant at  $P < 0.01$ , although the effect of using the orthogonally specified mask (at  $P < 0.001$ ) is to reduce our volume of interest thus making false positive results less likely. A more constrained analysis, comparing re-paired items with initial presentation of those same items in their original pairings showed an effect in the same region of left PFC. This was seen at a reduced threshold ( $P < 0.01$ ). A contributory factor to its failure to survive the more stringent threshold is probably the reduction in the number of observations contributing to this comparison. Nevertheless its presence and location makes us confident that the left PFC effect is not a result of a bias due to failure to counterbalance lists across subjects.

## RESULTS—EXPERIMENT 2

### *Behavioral*

In experiment 2, we examined cued retrieval postscanning and directly compared the number of cor-



**FIG. 3.** (a) Statistical parametric map (SPM) of regions showing a significant ( $P < 0.001$ ) decrease in activations relative to the baseline task with repeated presentations of the same lists in experiment 1. This comparison was “masked” with the contrast between activation and baseline tasks, shown in Fig. 2 (see text). The regions activated are listed in Table 2. Results are presented as a maximum intensity projection or “Glass brain,” showing views from the right (top left panel), from behind (top right panel), and from above (bottom left panel). (b) Orthogonal sections of a T1-weighted anatomical image that conforms to standard stereotactic space. Superimposed on these sections is the SPM ( $P < 0.001$ ) shown in Fig. 5a above. The section has been chosen at the voxel which showed maximal effect with the contrast ( $x, y, z = -46, 18, 28$ ). In the bottom right panel, we have plotted the activations in this voxel, relative to the baseline task, for the repetitions of each word list.

**TABLE 3**

Experiment 1: Regions Showing Significantly Greater Activation when Previously Learned Pairs Are Rearranged Compared to when Novel Pairs Are Presented

Region	Coordinates	Z score
Left inferior Frontal gyrus	-36, 20, 24	2.3
	-46, 14, 28	1.7
	-52, 12, 30	1.7
Right occipital cortex	14, -80, -20	5.2

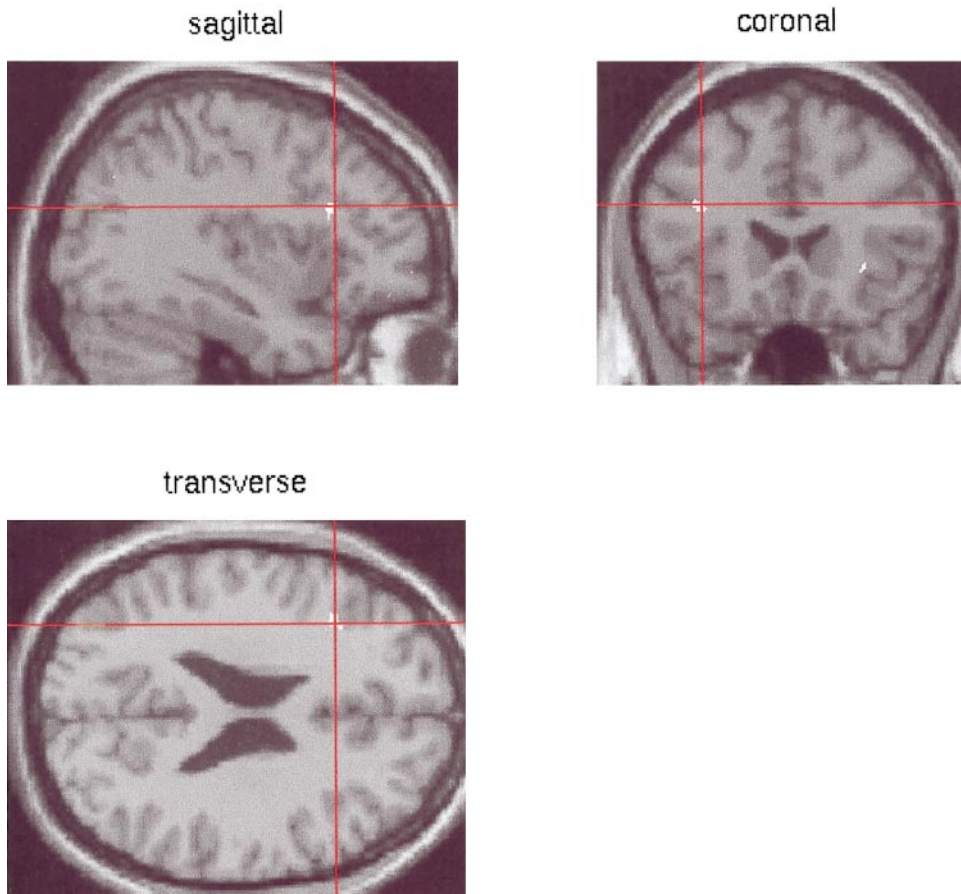
rect responses for the two types of pair: closely and distantly semantically related. The mean performance for subsequent cued retrieval of closely linked pairs was 28/30 (range 24–30). The mean performance for subsequent cued retrieval of distantly linked pairs was 27.4/30 (range 25–30). These performance measures did not differ significantly. We also debriefed subjects with respect to their ability to generate semantic mediators in order to link pair members. In virtually all cases, subjects were able to recall a concept or word,

which they had generated in order to do so. There was no evidence that their success at doing so differed across the two conditions but all reported that the distantly related pairs required a less clear and obvious mediation in order to produce a link.

### Functional Neuroimaging

In a number of regions, distantly linked pairs were associated with significantly greater activity than closely linked pairs (see Table 4 and Fig. 5). The only region to survive correction for multiple comparisons was left VLPFC (unlike experiment 1, masking was not used in the analysis and therefore the correction for multiple comparisons becomes appropriate). The left prefrontal region is shown in more detail in Fig. 5 together with the individual BOLD responses for each event type for each of the six subjects. It can be seen that, across all of the subjects, the BOLD response was greater for the distantly than the closely linked pairs.

A region of right PFC also showed a difference between the two event types (see Table 4 and Figs. 5 and



**FIG. 4.** Orthogonal sections of a T1-weighted anatomical image that conforms to a standard stereotactic space. Superimposed on these sections is the SPM ( $P < 0.05$ ) resulting from the comparison of rearranged pairs to novel pairs in experiment 1 (see Table 3). The section has been chosen at the voxel in left PFC, which showed maximal effect with this contrast ( $x, y, z = -36, 20, 24$ ). This comparison was “masked” with the contrast between activation and baseline tasks, shown in Fig. 2 (see text).



TABLE 4

Experiment 2: Regions Showing Differential Responses for Closely and Distantly Related Pairs

Region	Distant versus Close		Z score
	Coordinates		
Left inferior Frontal gyrus	-44, 26, 18		5.0
	-50, 32, 16		4.2
	-40, 8, 28		3.7
Right inferior Frontal gyrus	54, 30, 22		4.3
Right cerebellum	32, -78, -32		4.8
Right occipital cortex	6, -72, 8		3.9

6), but the plots for individual subjects showed that this effect was only present in three of the six. In view of this, and the fact that the activation did not survive the correction for multiple comparisons, we shall not discuss this area further.

The reverse comparison (that is, closely linked pairs versus distantly linked pairs) showed no regions surviving correction for multiple comparisons.

## DISCUSSION

These results extend findings from earlier studies implicating left PFC in the formation of meaningful

associations between items of study material (Dolan and Fletcher, 1997; Fletcher *et al.*, 1998). When the need for such processing is increased (in experiment 1 through rearrangement of semantic linkages, in experiment 2 through presentation of word pairs that were not obviously semantically related) left PFC activation is correspondingly greater. Moreover, the studies give us grounds for relating left PFC activity more specifically to this semantic associative processing rather than to item novelty or to WM and to be more specific about the role of the region in this semantic associative process. These results are consistent with functional neuroimaging studies of verbal encoding in which the emphasis has been on items' meaning (Kapur *et al.*, 1994) and, in the case of word pair encoding, on the semantic attributes shared by paired study items (Shallice *et al.*, 1994).

In considering the functional significance of our observed pattern of results in left PFC, it is important to address an issue surrounding the use of encoding tasks in functional neuroimaging. A distinction can be made between intentional and incidental encoding tasks. The former are accompanied by task instructions that there will be a later memory test whereas, in the latter, the memory test phase is administered without prior expectation. Our observations were made in the context of an intentional encoding task but we suggest

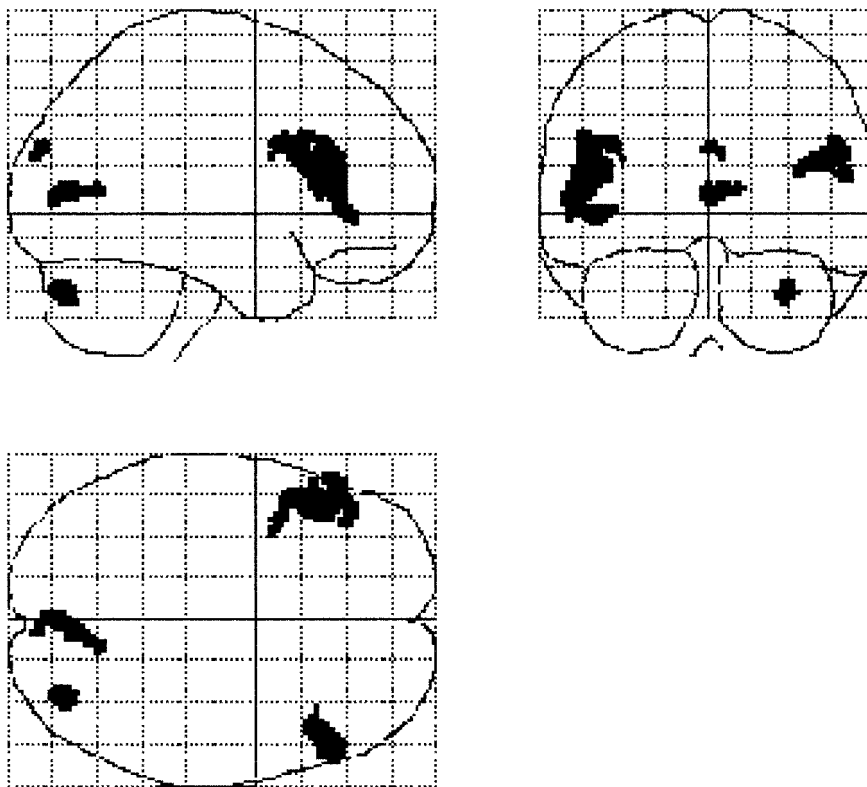


FIG. 5. Statistical parametric map (SPM) of regions showing a significantly greater BOLD response ( $P < 0.001$ ) for Distantly linked than for Closely linked pairs in experiment 2. Results are presented as a maximum intensity projection or "Glass brain," showing views from the right (top left panel), from behind (top right panel), and from above (bottom left panel). The regions activated are shown in Table 4.

that similar PFC activity would be evident in incidental tasks where subjects attend to semantic attributes but are not given explicit encoding instructions. For example, in a PET study of incidental encoding, attending to the meaning of items was associated with higher left PFC activity than attending to orthography (Kapur *et al.*, 1994).

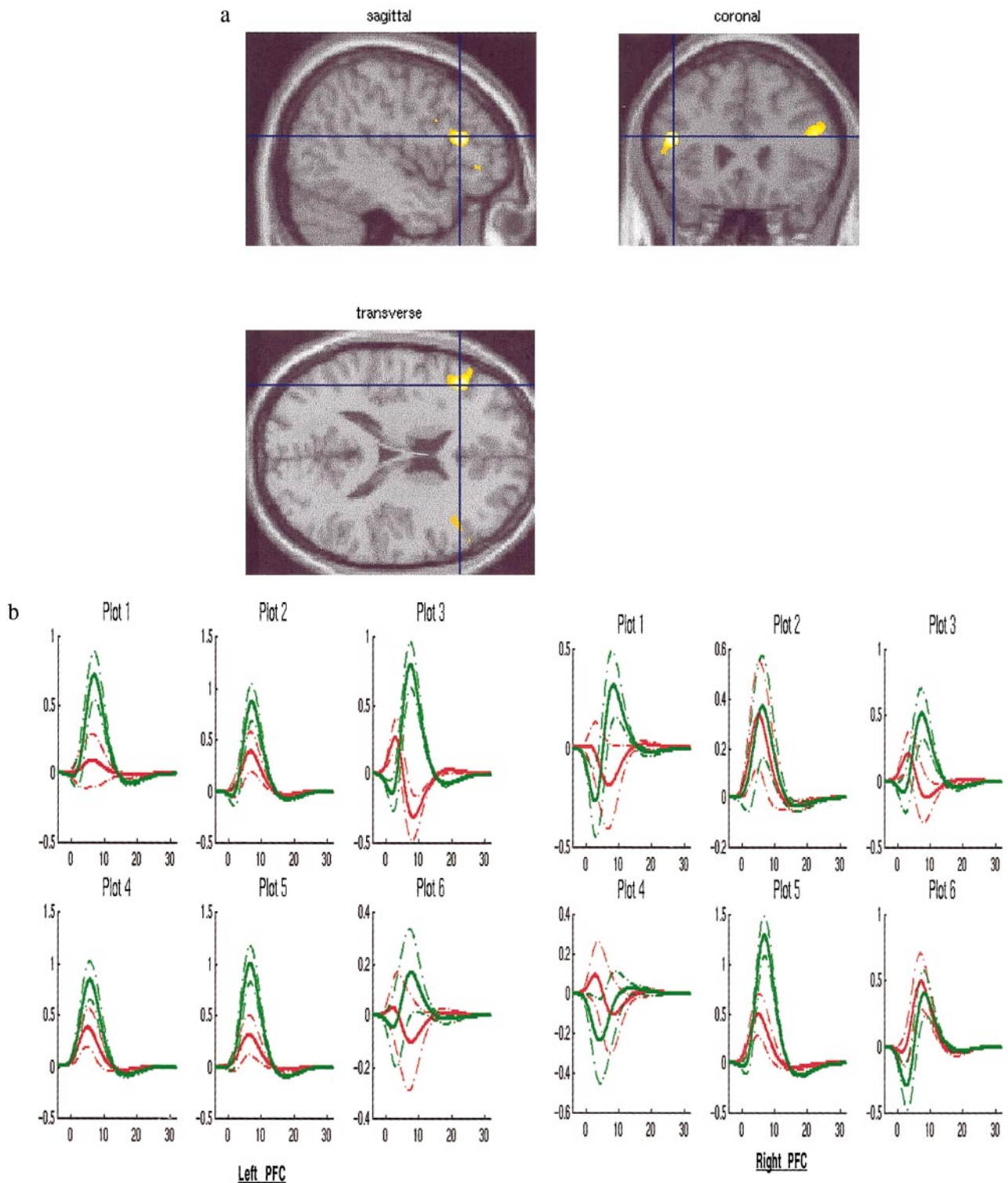
Can we be more specific about the localization of the observed left PFC activations and the processes that they subserve? Anatomically, there is considerable consistency across the two experiments with effects of interest occurring, in all cases, in left inferior frontal gyrus (see Tables 1–4), a region that is referred to as ventrolateral prefrontal cortex. In fact, there has been a strong degree of consistency of localization of prefrontal activation across a number of tasks engaging intentional and incidental memory encoding (Kapur *et al.*, 1995; Shallice *et al.*, 1994; Dolan and Fletcher, 1997; Kopelman *et al.*, 1998). Common to these tasks has been an emphasis on the semantic attributes of material and the finding of left ventrolateral PFC activation is compatible with other functional neuroimaging tasks engaging semantic processing both explicitly (Petersen *et al.*, 1988; Nathaniel James *et al.*, 1997; Ricci *et al.*, 1999) and implicitly (Petersen *et al.*, 1990). Further, it has been shown that this region of left PFC is increasingly responsive to presentation of consonant strings as they acquire meaning within the context of an artificial grammar system (Fletcher *et al.*, 1999). The region also appears to be sensitive to semantic processing irrespective of whether material is verbal or pictorial (Vandenberghe *et al.*, 1996). However, we are cautious in interpreting the lateralization of function observed in these two experiments. While the encoding-retrieval lateralization of activations has been discussed in detail (Tulving *et al.*, 1994), more recent evidence has suggested that it relates to modality of studied material rather than memory stage (Kelley *et al.*, 1998). The current studies used solely verbal material and we must concede that the lateralization of our finding may reflect this.

Experiment 1 used a study design that was similar to our previous PET study (Dolan and Fletcher, 1997). Here, left PFC activation was maximal when new associations were made to familiar items (that is, when A–B; C–D, etc. had been learned and during scanning subjects were presented with A–E; B–F, etc.). The foci of left PFC activation (–46, 16, 32 and –46, 26, 24) are close to those reported in the current experiments. This previous study described the focus of activation as “left dorsolateral PFC,” but its spread into ventral regions was commented upon. However, a potential problem in interpreting the results was that changing semantic associations occurred in the presence of novel material (that is, when A–E and B–F were presented, items E and F were novel). Thus, the results might be interpretable in terms of an interaction between item nov-

elty and semantic processing. Experiment 1 of the current study addressed this issue by ensuring that a changing semantic linkage was not associated with item novelty (that is, A–B, C–D, etc. were learned and then presented as A–D, B–C, etc.).

An additional advantage of the current study lay in the use of fMRI, enabling repeated measurements. This allowed us to characterize the profile of change across time as associations were learned and then broken. Two notable findings emerge from these data. First, an initial left PFC response to word paired associates is attenuated with repeated presentations of those pairs (Fig. 3b). This is consistent with the finding that more practised tasks do not require frontal mediation (Raichle *et al.*, 1994). It also suggests at least two possibilities. On one hand, it is conceivable that left PFC is responsive purely to the novelty of the study material (within the context of the experiment). By the fourth presentation they had, of course, become familiar. An alternative possibility is that the reduction in left PFC activation reflects a decrease in processing demands for these word pairs after repeated presentations. This experiment has enabled us to distinguish between these two possibilities. Since re-pairing of familiar words evoked a response in left PFC that was significantly greater than when pairs were presented for the first time we can argue against an explanation of left PFC activity purely in terms of item novelty.

It might be argued that the re-pairing condition is associated with the need to consider novel semantic attributes of the previously presented pairs. Thus, with reference to Fig. 1, an initial presentation of, for example, “Ham. . .” when paired with “. . .Radio” emphasizes a set of attributes that changes when, following rearrangement, “. . .Ham” is paired with “Egg. . .”. Likewise for “. . .Radio,” which is subsequently paired with “Jockey. . .”. Nevertheless, we do not believe our findings to be explicable purely in terms of novel semantic attributes per se. We conclude this firstly because processing of a new set of such attributes was necessarily a feature of processing novel as well as rearranged pairs. A second piece of evidence lies in our previous finding that left PFC (Dolan and Fletcher, 1997) activity increases for both an “old category–new exemplar” condition (in which the nature of semantic linkage does not qualitatively change from the comparison “old category–old exemplar” condition) and a “new category–old exemplar” condition (in which there is a qualitative change in the nature of the link e.g., “Sportsman. . .Boxer” changes to “Dog. . .Boxer”). This finding that left PFC does not distinguish between these two conditions, but does distinguish between either of these conditions and a “new category–new exemplar” condition, seems to indicate that the crucial area of sensitivity lies in the requirement to create a new linkage in the face of an existing one, that is, in reselecting the semantic attributes of relevance.



**FIG. 6.** (a) Orthogonal sections of a T1-weighted anatomical image that conforms to a standard stereotactic space. Superimposed on these sections is the SPM ( $P < 0.001$ ) shown in Fig. 5, indicating regions showing a significantly greater BOLD response for Distantly linked than for Closely linked pairs. Sections have been chosen at the voxel of maximal difference (coordinates  $x, y, z = -44, 26, 18$ —see table 4) to show the left PFC region. (b) Plots of the individual BOLD responses from left and right PFC (chosen from voxel of maximal difference [ $-44, 26, 18$  and  $54, 20, 32$ ]—see Table 4) for each of the six subjects. The average within-subject BOLD response for a Distantly linked pair is shown in green with the standard error (broken green line). The average within-subject BOLD response for a Closely linked pair is shown in red with the standard error (broken red line). It can be seen that the left PFC response is consistently greater for the former across all six subjects. The right PFC difference, although it survives a statistical threshold of  $P < 0.001$ , is found in only half of the subjects.

One caveat that should be considered with regard to experiment 1 is that the rearrangement of pairs in the re-pairing condition was associated with an unavoidable reordering of the words. Thus, a word that appeared as the first member of a pair during the initial presentation may be second during the subsequent presentation (e.g., "Ham" in Fig. 1). It is therefore possible that the left PFC effect might reflect this change in order rather than a change in the semantic processing contingent upon the re-pairing. This possibility cannot be fully excluded but the previous experiment (Dolan and Fletcher, 1997) suggests that it is unlikely since, in that experiment, a left PFC effect was seen in a re-pairing condition that did not require a reordering of stimuli.

The critical question concerns the nature of the semantic processes that engender left PFC activation. As outlined, the main theoretical accounts are concerned with the role of left PFC in retrieval, holding on-line or selection of semantic attributes. Attempts to distinguish between these possibilities have met with difficulties in that the greater selection demands are invariably associated with greater retrieval and holding demands. One study attempting to address this used "high" and "low" selection tasks in three different types of semantic decision making task: generation, classification, and comparison (Thompson-Schill *et al.*, 1997). They found that, in the different tasks, broad areas of left PFC showed a preferential sensitivity to the high rather than the low selection condition and, further, suggested that these results could not be due to greater amounts of semantic information being retrieved and held on-line. Although it is difficult to be entirely confident that we can separate amount of semantic attributes from degree to which selection processes are engaged, their results are compatible, in this respect, with ours. In a further study (Thompson-Schill *et al.*, 1999), analogous to our previous encoding study (Dolan and Fletcher, 1997) the effect of "competition" on a semantic generation task was explored. Having already learned to generate one type of response (e.g., color) to a word, subjects were then required to generate another (e.g., action). It was found that left inferior PFC was particularly sensitive to this task demand. This finding may be interpretable in a similar way as the effect of pair rearrangement in the current experiment.

We suggest that our re-pairing condition enables us to engage selection processes without increasing the retrieval or holding processes. Thus, consider the greater left prefrontal activation in the re-paired compared to the novel condition. There is no reason to suggest that the former task requires the subject to retrieve and hold on-line a greater number of semantic attributes than the latter. Indeed, we would suggest that, in this task, the semantic field has been narrowed. What is required is the suppression of previously learned associations and the selection of different

attributes. It is this feature which is critically different in the two conditions. Of course, one consideration is that retrieval demands are greater in the re-pairing condition since subjects necessarily retrieve old as well as establishing new associations. However, by the fourth presentation, the familiar associations no longer engender a measurable left PFC response relative to baseline (Fig. 3a).

Experiment 2 used an event-related design to explore further this type of processing of study material. Our previous PET study characterising changes associated with semantically based organisation (Fletcher *et al.*, 1998) is open to the criticism that blocking of study material engages working memory processes intensively. Consequently, the differential involvement of such processes across conditions might explain the varying pattern of frontal activations. We suggest that the increased magnitude of left PFC BOLD signal in response to "distantly-related" word pairs is unlikely to reflect simple working memory because the amount of material presented to subjects was minimised and was equal for both closely and distantly-related pairs.

Additionally, it is worth remarking that there are further advantages to the use of an event-related experimental design. First, the observed activations associated with a blocked design may simply reflect the experimental blocking of a particular stimulus and a particular response type. In the current study the two types of stimuli (closely and distantly related word pairs) were intermixed. Thus, the differential left PFC effect is not an artefact of blocked presentation. Event-related designs have been used increasingly in fMRI studies and have produced critical observations with respect to the degree of memory encoding success (Wagner *et al.*, 1998; Brewer *et al.*, 1998). Note that we excluded from analysis all instances where the study presentation was not followed, postscan, by successful cued retrieval. Thus, we were able to interpret the event-related differences without reference to subsequent performance measures.

Reviewing the functional neuroimaging literature, Gabrieli and colleagues have suggested that the left inferior frontal activations observed in studies of language and memory serve a form of domain-specific working memory (Gabrieli *et al.*, 1998) in that they are associated with tasks requiring the maintenance of semantic information "on-line." This position is not consistent with the current data since the activation tasks in experiments 1 and 2 do not require that different amounts of semantic information must be retained but rather that the semantic attributes of study items must be attended to more selectively. Thus, in experiment 1, the condition in which semantically rearranged material must be encoded requires subjects to ignore or inhibit semantic attributes which they had previously found relevant. Nevertheless, it is possible that the event-related left PFC signal in experiment 2

does reflect an increase in the amount of semantic attributes, which must be retrieved and held on-line for the distantly related pairs since it is feasible that subjects must explore a greater semantic field in order to establish the highly specific link between such items. However, one might equally well argue that, while weakly related word pairs may require the generation of mediating semantic concepts, this occurs within a narrow semantic field since they share very few semantic attributes. The closely linked items, however, share a number of semantic features, all of which would be relevant to the study task. At present, it is not possible to distinguish between these two possibilities solely on the basis of experiment 2, but, viewed in conjunction with experiment 1, we favor the interpretation that the left VLPFC activation reflects the requirement to select appropriate semantic attributes.

A crucial feature of our tasks lies in the need to select and use appropriate semantic attributes. With this in mind, our data support the position (Thompson-Schill *et al.*, 1997; Frith, in press) that left PFC is concerned with the selection of semantic attributes. This is related to the idea that left PFC supports a supervisory system modulating routine processing in novel situations (Norman and Shallice, 1986). Frith suggests that left PFC is specifically associated with the selection of an appropriate set of nonautomatic responses and, moreover, that a sine qua non for this is the creation of an arbitrary category of appropriate responses and the suppression of responses which lie outside this ad hoc and temporary category. He refers to this as "sculpting of the response space." Thus in Thompson-Schill *et al.* (1997), in particular, in the Classification and Comparison High Selection conditions that they used, the subject is given a clue as to which dimension of the relation between a pair of words is relevant as the pair is presented. This may be seen as directly relating to Frith's "sculpting" operation. It is these two conditions of Thompson-Schill *et al.* where the activation maxima more closely resemble those of our study. In our tasks, although no overt response was required, subjects were carrying out an internal semantic operation: specifically, the generation of a semantic link between words. Thus, this operation was required to produce the internal "response." Common to the activation tasks associated with left PFC activation, in both experiments, was the novel/nonroutine nature of the semantic association that had to be produced.

We suggest that a crucial component of the activation tasks in experiments 1 and 2 lies in Frith's "sculpting" requirement. Thus, the rearrangement of study material in experiment 1 requires that, for each word, a previous "response space" becomes inappropriate and a new one is required. In experiment 2, a highly specific response space must be created *de novo* for each distantly related word pair, while, as words in closely related pairs have multiple overlapping semantic at-

tributes, this becomes unnecessary for these items. This sculpting, a combination of inhibiting the inappropriate and identifying the appropriate semantic features is, Frith argues, a vital function of left PFC. Processing of material in this way may be the key to optimal memory encoding.

In brief, we propose that an effective episodic memory trace is created if, and only if, this sculpting of the response space occurs, and that this occurs even when the task does not explicitly have a memory component. This follows suggestions by Sussman (1975) and Shallice (1988) that encoding in episodic memory occurs specifically in nonroutine situations. This type of processing is, we suggest, the crucial feature of a deep encoding task ( Craik *et al.*, 1972) and our results suggest that it is supported by left PFC.

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