Brain (1998), **121,** 1239–1248

The functional roles of prefrontal cortex in episodic memory
I. Encoding

P. C. Fletcher,[1] T. Shallice[2] and R. J. Dolan[1,3]

[1]*Wellcome Department of Cognitive Neurology, Institute of Neurology,* [2]*Institute of Cognitive Neuroscience and Department of Psychology, University College London,* [3]*Royal Free Hospital Medical School, London, UK*

Correspondence to: Paul Fletcher, Wellcome Department of Cognitive Neurology, Institute of Neurology, 12 Queen Square, London, WC1N 3BG, UK. E-mail: p.fletch@fil.ion.ucl.ac.uk

Summary
Functional neuroimaging studies of episodic memory consistently report an association between memory encoding operations and left prefrontal cortex (PFC) activation. Encoding-related activation has been described in dorsolateral, ventrolateral and anterior prefrontal regions. We tested the hypothesis that a specific component of this left PFC activation reflects organizational processes necessary for optimal memory encoding. Subjects underwent PET scans while learning auditorily presented word lists under dual task conditions. The degree to which they were required to organize word lists semantically was systematically varied across three experimental conditions. A task in which words were already organized produced the least degree of left PFC activity whereas a task requiring subjects to generate an organizational structure was associated with maximal activity in this region. This activation was localized to a region just above the inferior frontal sulcus. The functional specificity of this increased activity for organizational processes was tested using a concurrent distracting task known to disrupt these processes. Distraction resulted in a significant attenuation of this activation during the task emphasizing organizational processes but not other encoding tasks. In contrast, the distraction task resulted in reduced activity in a more ventral/anterior PFC region expressed equally for all memory tasks. The findings indicate that a key function of left dorsolateral PFC at encoding relates specifically to the use of executive processes necessary for the creation of an organizational structure. Activity in more ventral and anterior left PFC regions would appear to reflect a less specific component of episodic memory encoding.

Keywords: functional neuroimaging; memory; encoding; organization; prefrontal

Abbreviations: DLPFC = dorsolateral PFC; PFC = prefrontal cortex; SPM = statistical parametric mapping

Introduction
Neuropsychological and functional imaging data indicate that the frontal lobes have an important function in memory (Milner, 1971; Petrides, 1989; Squire *et al*., 1992; Grasby *et al*., 1993; Kapur *et al*., 1994; Shallice *et al*., 1994; Stuss *et al*., 1994; Tulving *et al*., 1994*b*; Gershberg and Shimamura, 1995; Dolan and Fletcher, 1997). In functional neuroimaging studies, an unpredicted, but highly consistent, lateralization of frontal lobe function has been observed with left prefrontal cortex (PFC) showing predominant activation in association with learning or encoding tasks and the right PFC in association with recall tasks (Tulving *et al*., 1994*a*; Fletcher *et al*., 1997). This lateralization is present irrespective of whether material is verbal (Kapur *et al*., 1994; Shallice *et al*., 1994; Tulving *et al*., 1994*b*) or nonverbal (Haxby *et al*., 1996). The functional significance of the left PFC activation at encoding is unclear although it appears that it is not necessarily associated with the intention to encode information, since an incidental encoding task (Kapur *et al*., 1994) activates the left PFC in association with high levels of subsequent performance. However, a critical link to encoding processes is indicated by the observation that, when encoding is performed with a concurrent distracting task, there is an impairment in subsequent recall and an attenuation of activation in the left PFC (Fletcher *et al*., 1995).

It has been suggested that activation of the left PFC in association with encoding may reflect the fact that the encoding is not independent of subjects' knowledge or semantic memory (Tulving, 1983). Thus, to learn a word within the context of an encoding experiment necessarily entails a knowledge of that word's meaning. The use of such knowledge has been suggested to underlie the left PFC activation seen in functional neuroimaging studies of memory encoding (Tulving *et al*., 1994*a*). This suggestion is consistent with the observation that tasks requiring subjects to make judgements about word meanings are associated with higher degrees of subsequent recall of those words than tasks emphasizing non-semantic aspects of the words, e.g. phonological or orthographic features (Craik and Lockhart, 1972). This observation, although criticized, has been highly influential and the close association between such tasks and optimal learning is reflected in the fact that tasks emphasizing meaning continue to be referred to as ‘deep’ encoding tasks.

A relevant observation, in this context, is that there are major advantages in subsequent recall when subjects are required to organize study material (Segal and Mandler, 1967). Neuropsychological studies indicate that an important aspect of the prefrontal contribution to memory function is in the organization of material (Incisa della Rocchetta and Milner, 1993; Gershberg and Shimamura, 1995). However, in these types of studies, it is difficult to separate out effects operating at encoding from those operating at retrieval since memory paradigms invariably involve both processes. Functional neuroimaging studies, on the other hand, are particularly suited to making such a separation. In the present study, we used this capability to examine the neural correlates of organizational processes specifically during encoding.

The term ‘organizing’, when applied to neuropsychological tasks, generally refers to the grouping of items on the basis of shared semantic attributes (Gershberg and Shimamura, 1995). Thus, a task requiring organization of material will overlap considerably with a ‘deep’ encoding task insofar as it will emphasize meaning. However, organizing has the additional requirement of manipulating material on the basis of its similarities to, or differences from, other material in the same study block.

Our hypothesis was that the widely seen activation of the left PFC in encoding tasks reflects, at least in part, a tendency or necessity to organize study material on the basis of semantic attributes. We required subjects to learn 16-item word lists and predicted that, in conditions where subjects were required to generate an organizational structure to facilitate encoding, we would observe a greater degree of left PFC activity than in conditions where material was already organized. We used two levels of organizational requirement and this aspect of the design enabled us to determine whether left PFC activation reflected the semantic abstraction process or more general demands of mentally manipulating the study material (which would involve, for example, the active maintenance of the list structure in working memory).

A further consideration is the possibility that activations are not directly associated with the experimental manipulation but reflect some associated, but incidental, features of the tasks. We addressed this issue using a dual task paradigm in which subjects are required to carry out a concurrent distracting procedure (Fletcher *et al*., 1995). Such a requirement can interfere specifically with the ability to encode material (Baddeley *et al*., 1984; Jacoby *et al*., 1993; Craik *et al*., 1996). If left PFC is associated with the organization of material at encoding, then a simultaneously performed distracting task, as well as producing subsequent impairments in retrieval, would reduce the level of left PFC activity. Furthermore, distraction-induced reductions in activation specific to some encoding conditions but not others, indicates process specificity for encoding-related PFC activations.

Material and methods

Subjects

Seven healthy, male, right-handed subjects (mean age 29.5 years, range 19–56 years) were scanned. Each subject underwent 12 separate scans. No subject had a history of past psychiatric or neurological illness and all gave informed consent. The studies were approved by the combined ethics committees of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology, London and the Administration of Radiation Safety Advisory Committee (UK). Scans of the distribution of $H_2{}^{15}O$ were obtained using a Siemens/CPS ECAT EXACT HR+ (model 962) PET scanner operated in high sensitivity 3D mode. Subjects received a total of 350 Mbq of $H_2{}^{15}O$ over 20 s through a forearm cannula. Data were acquired over 90 s for each scan. Attenuation-corrected data were reconstructed into 63 image planes with a resulting resolution of 6 mm at full-width half-maximum.

Encoding tasks

In the encoding experiment, study material consisted of three types of word list (all lists consisting of 16 words). The features of the three encoding tasks, together with a sample list from each, are summarized in Appendix 1. Lists were presented auditorily and varied according to the degree of organization that subjects were required to perform in order to facilitate encoding.

The Organize 1 condition

This was the least demanding condition with respect to the organizational requirements. Prior to the scan, subjects were informed that they would be presented with a list of 16 words and that this list would be structured, having an overall heading covering four categories, with four words representing each category. They were told what the heading and categories would be. They were further informed that presentation would be blocked. Subjects were instructed to try to learn all items and informed that bearing in mind this list structure in mind would be helpful. Five minutes after the scan, free recall was tested (see summary in Appendix 1).

The Organize 2 condition

This was more demanding than the Organize 1 condition with respect to organizational processes. Prior to the scan, subjects were informed that they would be presented with a list of 16 words and that this list would be structured, having an overall heading covering four categories, with four words representing each category. They were told what the heading and sub-headings would be. They were further informed that presentation would be unblocked. Subjects were instructed to try to learn all items and informed that bearing this list structure in mind would be helpful. Five minutes after the scan, free recall was tested (see summary in Appendix 1).

The Organize 3 condition

This was the most demanding condition with respect to organizational processes. Prior to the scan, subjects were informed that they would be presented with a list of 16 words and that this list would be structured, having an overall heading covering four categories, with four words representing each category. They were told what the overall heading would be, but that they would be required to work out what the sub-headings were. They were further informed that the presentation would be unblocked. Subjects were instructed to try to learn all items and informed that being able to work out the list structure (that is, the four categories) would be helpful to their subsequent recall. Five minutes after the scan, free recall was tested (see summary in Appendix 1).

As in our previous work (Shallice *et al*., 1994), we used a dual task approach involving both a more distracting and a less distracting motor task, as the former specifically affects episodic encoding by interfering with active organization processes. Here, subjects were required to watch a screen, suspended on a cradle ~45 cm away. On the screen was a photograph of a left hand. Sequentially, one of the four fingers was highlighted (once per second) and subjects were required to press the corresponding button on a key pad placed under their left hand. In the more distracting version of this task, stimuli (and therefore button presses) followed an unpredictable sequence. In the less distracting task, the sequence was predictable, moving from one finger to the next.

Thus this experiment constituted a 2×2 factorial design, with the first factor (organization of encoding material) having three levels (the Organize 1, Organize 2 and Organize 3 conditions) and the second factor (motor distracting task) having two levels (more distracting and less distracting). Consequently, there were six conditions with two scans per condition for each subject,.

Data analysis

Images were reconstructed into 63 planes, using a Hanning filter, resulting in a 6.4-mm transaxial and 5.7-mm axial resolution (full-width at half-maximum). The data were analysed with statistical parametric mapping (SPM) (Friston *et al*., 1995*a*, *b*) using SPM software from the Wellcome Department of Cognitive Neurology, London, UK (http://www.fil.ion.ucl.ac.uk) implemented in Matlab (Mathworks, Sherborn, Mass., USA). After initial realignment, the scans were transformed into standard stereotactic space (Talairach and Tournoux, 1988). The scans were smoothed using a Gaussian filter set at 12 mm full-width at half-maximum. The regional CBF-equivalent measurements were adjusted to a global CBF mean of 50 ml/dl/min. An ANCOVA (analysis of covariance) model (blocked by subject) was fitted to the data at each voxel, with a condition effect for each of the conditions, using global CBF as a confounding covariate. Predetermined contrasts of the condition effects of each voxel were assessed using the *t* statistic, giving a statistical image [$SPM_{\{t\}}$ transformed into an $SPM_{\{z\}}$] for each contrast. The chosen threshold of significance for main effects of conditions was $P < 0.001$ (uncorrected for multiple comparisons). An uncorrected threshold was chosen because of our *a priori* hypothesis with regard to the prefrontal cortex.

Results

Memory performance data

Recall performance was tested in each subject after every scan, and is given in Table 1A. With the less distracting motor task, performance was similar across all word lists. Non-parametric testing showed that the effect of distraction differed significantly across conditions (Friedman two-way analysis of variance by ranks: [$\chi^2(6) = 39.7$, $P < 0.001$]. In the presence of the more distracting task performance in the Organize 3 condition was impaired (Wilcoxon $t = 0$, $P < 0.02$).

In the Organize 3 condition, where category sub-headings were unknown prior to list presentation, subjects were, in almost every case, able to report the appropriate list structure when debriefed after each scan. A measure of the extent to which subjects used the organizational structure to aid retrieval was provided by counting the number of times they shifted category unnecessarily during free recall. Since there were four categories, at least three shifts were necessary to cover them all. Table 1B shows the number of unforced category shifts following each of the encoding conditions. It can be seen that there were more unforced shifts following the Organize 3 condition, in the presence of the more distracting task than with the distracting task or in either of the other encoding conditions.

Functional imaging results

Effects of requirement to organize study material

We examined regions specifically responsive to the need to organize study material, i.e. activations occurring to a significantly greater extent in the Organize 3 condition when compared, in separate contrasts, with the Organize 2 and

Organize 1 conditions. That is, it was found that the only region surviving the pre-set threshold ($P < 0.001$) was a region of the left PFC (roughly corresponding to Brodmann area 9/46). The focus of activation was mapped onto a series of structural magnetic resonance images from eight separate subjects (images which had been stereotactically normalized into the same space). In every case, it lay just above the inferior frontal sulcus and may, thus, be termed dorsolateral. For this reason we shall refer to this region as dorsolateral PFC (DLPFC) but its proximity to the inferior frontal sulcus should be borne in mind (see Table 2 and Fig. 1A).

Effects of distraction

The effects of the more distracting task were analysed in two ways. In one analysis, examining the attenuating effects of distraction, the search volume was confined to voxels that were significantly more active in the condition making the greatest organizational demands on the subjects. This analysis thus addressed the question of whether regions activated in association with organizational requirements would show a relative attenuation of activation in the presence of the more distracting task (which impairs such organizational processing). A distraction-associated attenuation was observed in left DLPFC. Crucially, with regard to memory performance, the distracting task had no effect on the Organize 1 or Organize 2 performance but produced a significant impairment with Organize 3 (see Table 1 and Fig. 1B). The parallel profiles of the neurophysiological reduction and the impaired behavioural performance allow us to infer that, in the Organize 3 condition, a critical function, whose instantiation involves the left DLPFC, relates to organizing study material. These data are shown graphically in Fig. 2.

In a further exploration of the data, we performed a conjunction analysis (Price and Friston, 1997) in order to identify regions where activity was reduced in the presence of the distraction task irrespective of the type of encoding task (i.e. Across the Organize 1, Organize 2 and Organize 3 conditions). This analysis was carried out by making 3 comparisons: [Organize 1 (less distracting task)] minus [Organize 1 (more distracting task)], [Organize 2 (less distracting task)] minus [Organize 2 (more distracting task)], [Organize 3 (less distracting task)] minus [Organize 3 (more distracting task)].

These analyses were examined conjointly to show regions where the more distracting sensorimotor task produced a reduction of activity that was statistically indistinguishable across the three encoding types, i.e. it revealed regions where the more distracting task produced an effect that was independent of the experimentally manipulated encoding demands. It identified regions in mediodorsal and antero-ventral regions of left PFC. The mediodorsal activation extended ventrally into anterior cingulate cortex (see Table 3 and Figs 3 and 4).

Table 1 *Performance measures*

	Organize 1	Organize 2	Organize 3
(A) Performance (± SD)			
More distraction at encoding	12.6 ± 2.9	11.8 ± 1.4	10.3 ± 1.8
Less distraction at encoding	12.7 ± 2.1	12.1 ± 2.1	12.2 ± 2.1
(B) Unforced category changes at retrieval (± SD)			
More distraction at encoding	0.5 ± 0.7	0.8 ± 0.9	2.1 ± 1.1
Less distraction at encoding	0.4 ± 0.4	0.9 ± 0.9	0.9 ± 0.5

(A) Post-scan recall performance (number of words from a maximum of 16), shown for the three types of encoding task under high and low distracting conditions. (B) The number of unforced category changes at recall for each condition.

Table 2 *Encoding coordinates (left DLPFC)*

	Memory (in presence of less distracting task)		Attenuating effect of distraction	
	x, *y*, *z*,	*Z*-score	*x*, *y*, *z*,	*Z*-score
Organize 3 minus Organize 2	–36, 22, 30	2.3	–36, 24, 28	2.1
Organize 3 minus Organize 2	–36, 22, 30	2.3	–36, 24, 28	2.1
Organize 2 minus Organize 1	–34, 14, 22	3.2	–	

Brain regions activated in association with the encoding conditions. Coordinates (Talairach and Tournoux, 1988) of voxels of maximal activation are given. Coordinates are given for the range of condition comparisons for the left DLPFC alone as this was the sole region that differentiated between the memory tasks at the chosen threshold ($P < 0.001$, $Z = 3.09$). Although other regions were shown to be affected by the presence of the more distracting task, only activation in the left DLPFC was conjointly associated with the requirement to organize study material and an attenuation by distraction.

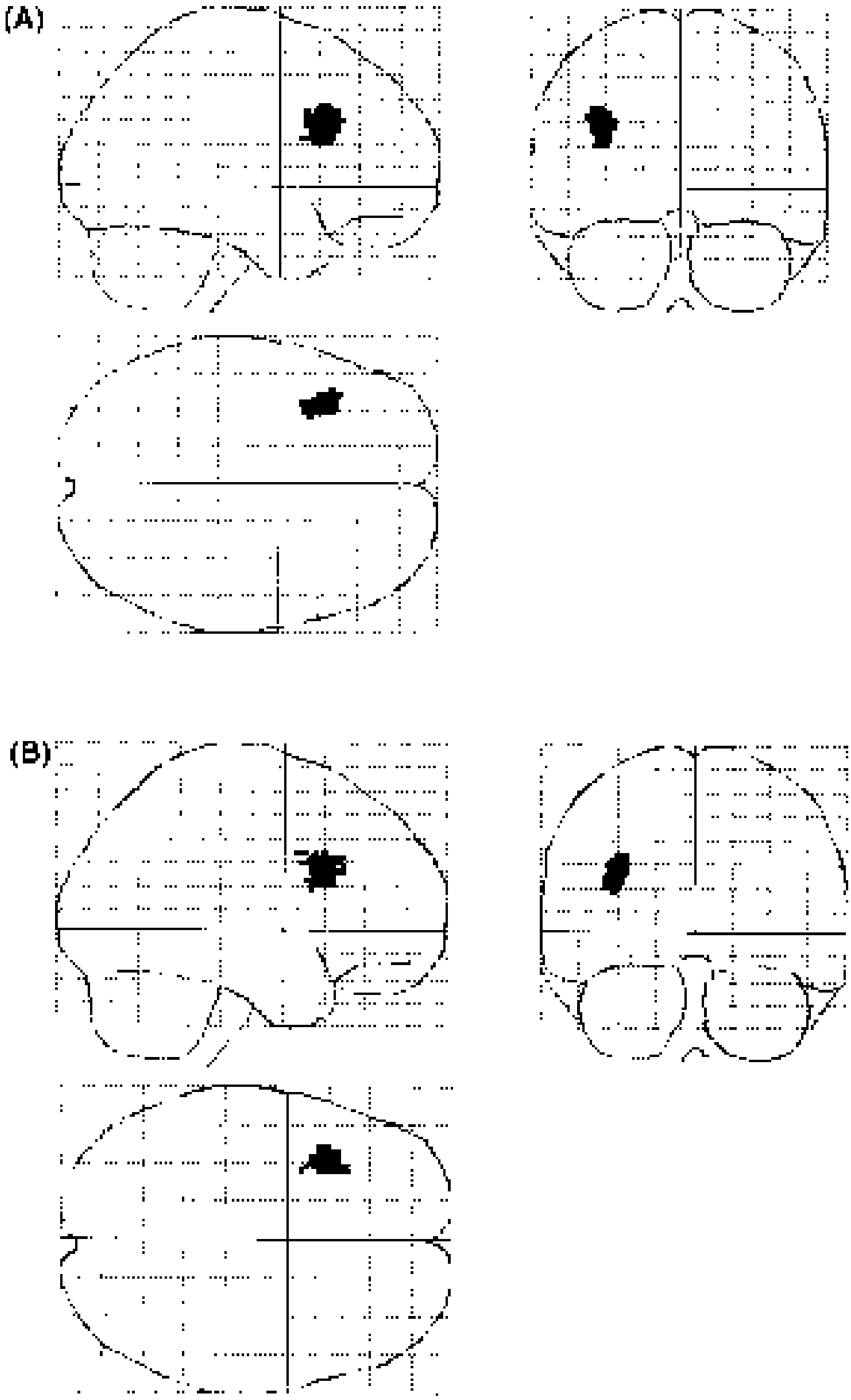

Fig. 1 Encoding-related activations. SPMs of (**A**) the main effects of the requirement to organize study material and (**B**) the memory–distraction interaction are shown. The SPM of the brain regions associated with the requirement to generate and use an organizational structure (**A**) was produced by contrasting scans obtained during the Organize 3 condition with the combination of those obtained during the Organize 1 and the Organize 2 conditions. The activations are seen as orthogonally viewed 'glass brains', from the right (*top left*), from behind (*top right*) and from above (*bottom left*). The statistical threshold was set at $P < 0.001$. Relative activation in left DLPFC is shown. (**B**) Regions in which these organization-related activations are attenuated by simultaneous performance of the more distracting task. This analysis of the effects of distraction was constrained to areas showing an effect of the requirement to organize material by constraining it to the sub-set of voxels identified by the comparison shown in **A**. This use of 'masking' enabled us to limit our consideration of distraction effects to the relevant organizational system (Fletcher *et al*., 1995).

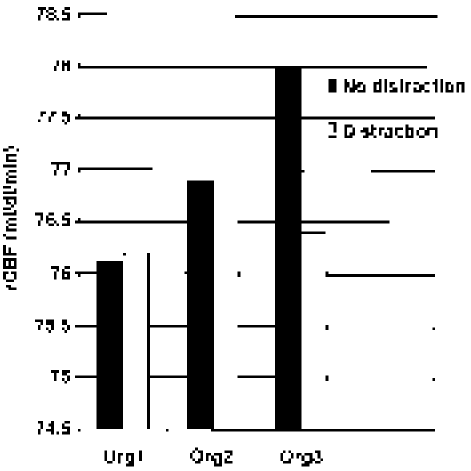

Fig. 2 A graphic representation of left DLPFC (coordinates –36, 22, 28) cerebral blood flow equivalents across the memory tasks: the Organize 1 (Org 1), Organize 2 (Org 2) and Organize 3 (Org 3) conditions, both in the presence and the absence of a more distracting task.

Discussion

The primary findings support our hypothesis that the left PFC activation observed during memory encoding tasks reflects a specific component of the encoding process. Specifically, the data suggest that this component relates to deriving commonalities of meaning among the words presented in order to create an organizational structure. Furthermore, they localize this function to a discrete area of a more dorsolateral region of the left PFC.

The type of abstraction necessary in the critical condition in this study has been shown to enhance encoding (Segal and Mandler, 1967; Craik and Lockhart, 1972). Such abstraction processes are known to be impaired in association with prefrontal lesions (Benton, 1968; Bornstein and Leason, 1985). The interpretation that the left DLPFC activation reflects the creation of an organizational structure gains support from the other key finding in our study—that activation in this region was attenuated by distraction. It is noteworthy that the more distracting task, as well as leading to an attenuation in regional brain activation, produced a large increase in the number of unforced category shifts during subsequent retrieval in the Organize 3 condition. These subsequent (post-scan) behavioural effects enable us to link this activity to the organizational sub-processes engaged by our task.

A key aspect of the abstraction/organizational processes required in our study is the requirement to assess study material with respect to semantic properties. This demand was maximized in the Organize 3 condition where subjects were required to use the presented material to create the structure *de novo*. Thus, in this condition, subjects were required to consider a broader range of semantic attributes than in the other two conditions where the list structure was already known. With respect to this observation, it is noteworthy that previous studies emphasizing semantic

Table 3 *Brain regions showing greater activity in the less distracting motor task, irrespective of the encoding task*

Region (Brodmann area)	*x, y, z,*	*Z*-score
Superior/middle frontal gyrus (10)	–20, 52, –8	4.3
Middle frontal gyrus (10/46)	–32, 50, 16	3.6
Superior frontal gyrus (8)	–2, 40, 56	3.9
Anterior cingulate/superior frontal gyrus (8/32)	–2, 30, 36	3.7

Coordinates are shown with the same convention as Table 2.

processing during encoding have shown left prefrontal activations (Cabeza *et al*., 1997). Further, this activation has been found in studies which require semantic processing in the absence of any explicit memory encoding demands (Kapur *et al*., 1994). It is also consistent with the well known finding that frontally damaged patients have difficulties in abstracting the meanings of proverbs (McCarthy and Warrington, 1990). More recent functional neuroimaging findings provide further support for the contention that the encoding-related left PFC activation relates to semantic processes required at encoding (Dolan and Fletcher, 1997). In this study, involving the encoding of paired associates, maximal left DLPFC activation was elicited by a manipulation in which previously learnt category–exemplar pairings were changed and new linkages had to be formed. Therefore, taken in conjunction with the current study, there is good evidence that left PFC activation in memory encoding reflects a requirement for processing study material with respect to meaning.

Why should the more distracting task selectively affect the Organize 3 condition? It has been shown that performance of a variety of tasks which require PFC is impaired when a demanding sensorimotor task, which itself does not appear to make great demands on executive or working memory resources, has to be carried out at the same time (Moscovitch, 1994). It was argued that carrying out such a sensorimotor task produces the analogue of a frontal lobe syndrome in the normal subject. The results obtained in this study are in accordance with this perspective. In the less distracting condition, Organize 3 is associated with greater activation of the left DLPFC than the Organize 1 and 2 conditions and it is the condition where distraction significantly affects performance both quantitatively (in terms of the number of items subsequently recalled) and qualitatively (in terms of the degree of organization at recall) and where activation is reduced in the more distracting condition.

What processes are involved in this interference effect? Since carrying out the more distracting task leads to a reduction in left DLPFC activation (in association with the Organize 3 condition) it is implausible that the interference occurs because the distracting task requires the same resources as the primary task. Instead, we suggest that the constraint on processing is in the use of attentional resources. In brief, we suggest that the supervisory and working memory functions of the PFC cannot be adequately utilized unless

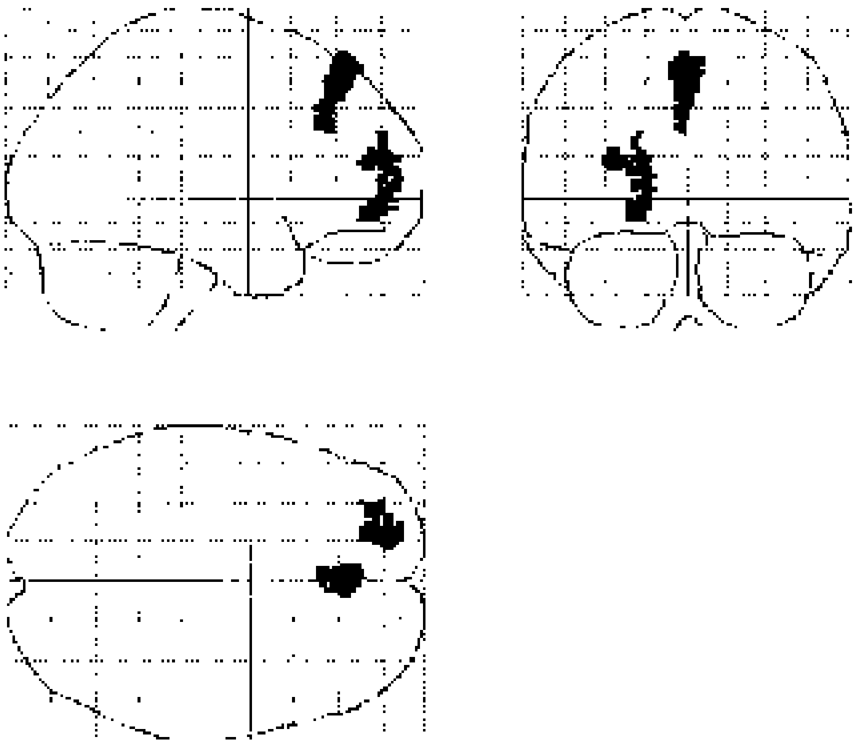

Fig. 3 Regions showing reduction in brain activity associated with the less distracting task. SPMs are shown as for Fig. 1.

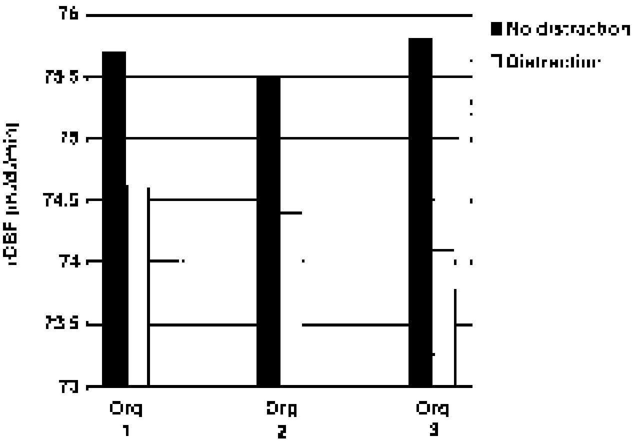

Fig. 4 A graphic representation of left ventral anterior PFC (coordinates –20, 52, –8) cerebral blood flow equivalents across the memory tasks: the Organize 1 (Org 1), Organize 2 (Org 2) and Organize 3 (Org 3) condition, in the presence both of the more distracting and the less distracting task.

the subject is able to attend to the memory task and that the distracting task prevents full attendance.

All of the memory tasks used in the study make demands on working memory processes required for active maintenance of list structure in order to perform the necessary manipulations of presented material. However, an explanation of our results in terms of working memory processes is difficult to sustain. The study design enabled us to dissociate activations associated with the semantic abstraction necessary in the generation and use of an organizational structure from activations associated with the mental manipulation or grouping of semantically similar study items. The latter, we suggest, would be prominent in both the Organize 3 and Organize 2 conditions. In the former, subjects were not informed as to the skeleton of the list structure while in the latter, they were. The former condition, therefore, required subjects to assess each consecutive item on the basis of its meaning and how this related to other presented items, building up an organizational structure which they deemed appropriate and allotting items to appropriate parts of this structure. During the Organize 2 condition, they were already aware of the organizational structure and were required simply to assess each item on the basis of where it would fit into that structure. The observation that the activity in the left PFC is significantly greater in the Organize 3 than the Organize 2 condition enables us to infer a function that is more than just the active maintenance of study material. Further, left DLPFC activation associated with the Organize 3 condition cannot merely be ascribed to non-specific 'effort' since, as expected, subjects reported that the Organize 3 condition in the presence of the concurrent distracting task required more effort, yet this condition was associated with attenuated activity in this region.

Why, then, is there no apparent effect of distraction in the Organize 2 condition? We suggest that the observed specificity of the effect of distraction fits with a distinction made between the processing and storage aspects of working memory tasks under dual task conditions (Craik *et al*., 1990).

This is in accord with our finding that the Organize 3 condition, which emphasizes processing demands, was significantly affected by distraction whereas the Organize 2 condition, which has equivalent storage but lesser processing requirements, was not. The lack of a distracting effect on the Organize 2 condition compared with the Organize 1 condition condition perhaps reflects that the former condition places a relative emphasis on storage rather than processing demands.

Interpretation of the other observed effect of distraction on neural activity, expressed in the ventral, anterior PFC and the dorsomedial/anterior cingulate cortex, common to all encoding conditions, must be speculative. Because we did not scan the subjects during the performance of the motor task alone, we cannot conclude that the mediodorsal and anterior ventral reductions in left PFC activity are necessarily the result of an interaction between the encoding and the more distracting tasks. The observed effects might, for example, reflect a fundamental difference in the ways in which the distracting and non-distracting motor tasks are carried out, irrespective of whether they are performed in the presence of an encoding task. Thus, it could be the case that the highly predictable, less distracting motor task can be performed in a fundamentally different way to the unpredictable, more distracting task insofar as subjects can only plan their next response on the basis of their previous one in the former task. Such planning, it might be argued, underlies the relatively greater left mediodorsal/cingulate and anterior PFC activation. However, we suggest that this interpretation is unlikely to be correct in view of our previous findings in a study of paired associate encoding (Fletcher *et al*., 1995) where we also observed that a distracting task (similar to the one used in the current experiment) was associated with a reduction in left PFC activity. This reduction only occurred in the presence of episodic memory encoding, but not during a simple passive listening task. The area of the left PFC showing a distraction–memory interaction in that study included an anterior ventral region overlapping with that seen in the current experiment. The previous encoding condition did not include any requirement to organize study material, and thus was similar to the simplest encoding task in the current experiment (i.e. the Organize 1 condition). The more ventral and anterior regions of the left PFC may, therefore, be concerned with aspects of encoding which are common to all of the encoding tasks used in this study. As subsequent retrieval performance in the Organize 1 and Organize 2 conditions was not significantly impaired, this indicates that these aspects were not crucial to performance of the memory tasks used in this experiment. This may appear puzzling in the light of our previous finding (Fletcher *et al*., 1995) that decreases in this region were associated with sub-optimal paired associate encoding. However, there are a number of factors which may have made the memory paradigm used in this study somewhat less sensitive to encoding efficiency unrelated to organization. The motor tasks in the current experiment were slightly easier, the study material was presented less rapidly (one word every 4 s as opposed to a pair of words every 3 s) and retrieving a set of individual, unrelated items (as was the case in our previous study) may well be a more sensitive measure of encoding efficiency than retrieving clusters of linked items. If this is so, it makes the differential behavioural effect of distraction in the Organize 3 condition, and its relation to left DLPFC activity more striking.

Thus, our study has provided evidence for differential functions within the left PFC: a more dorsolateral region showing sensitivity to the task requiring a high degree of semantic abstraction and more ventral, anterior and medial regions showing indistinguishable patterns of response irrespective of the encoding task demands. Previous functional neuroimaging studies of memory, while there are exceptions (Stern *et al*., 1996), have shown a consistent involvement of the left PFC at encoding. They have not, however, shown an easily identifiable pattern with respect to localization within the frontal lobe. The majority of previous studies (Kapur *et al*., 1994; Shallice *et al*., 1994; Haxby *et al*., 1996; Stern *et al*., 1996) have shown encoding-related activations which are ventral relative to the regions specifically associated with the Organize 3 condition. An exception is a study referred to above (Dolan and Fletcher, 1997) which was associated with a dorsolateral activation in conditions emphasizing word meanings.

In summary, our study addresses a highly consistent functional imaging finding, namely that of an encoding-related left PFC activation. We provide evidence that a dorsolateral component of this activation forms part of the brain system mediating the formation of an organizational structure and, more specifically, with abstraction of relevant semantic attributes of study material. This abstraction enables an assessment of the commonalities and differences which is the basis for segregating and grouping material to optimize encoding. Our observations further suggest that there is functional specialization within the PFC making it desirable that functional neuroimaging studies of encoding employ increasingly specific tasks in order to evaluate encoding-related brain activity more fruitfully.

Acknowledgements

We wish to thank Andrew Holmes for statistical advice. P.C.F. and R.J.D. are supported by the Wellcome Trust.

References

Baddeley A, Lewis V, Eldridge M, Thomson N. Attention and retrieval from long-term memory. J Exp Psychol 1984; 113: 518–40.

Benton AL. Differential behavioral effects in frontal lobe disease. Neuropsychologia 1968; 6: 53–60.

Bornstein RA, Leason ML. Effects of localized lesions on the verbal concept attainment test. J Clin Exp Neuropsychol 1985; 7: 421–9.

Cabeza R, Grady CL, Nyberg L, McIntosh AR, Tulving E, Kapur S, et al. Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. J Neurosci 1997; 17: 391–400.

Craik FI, Lockhart RS. Levels of processing: a framework for memory research. J Verb Learn Verb Behav 1972; 11: 671–84.

Craik FI, Morris RG, Gick ML. Adult age differences in working memory. In: Vallar G, Shallice T, editors. Neuropsychological impairments of short-term memory. Cambridge: Cambridge University Press; 1990. p. 247–67.

Craik FI, Govoni R, Naveh-Benjamin M, Anderson ND. The effects of divided attention on encoding and retrieval processes in human memory. J Exp Psychol Gen 1996; 125: 159–80.

Dolan RJ, Fletcher PC. Dissociating prefrontal and hippocampal function in episodic memory encoding. Nature 1997; 388: 582–5.

Fletcher PC, Frith CD, Grasby PM, Shallice T, Frackowiak RS, Dolan RJ. Brain systems for encoding and retrieval of auditory-verbal memory: an in vivo study in humans. Brain 1995; 118: 401–16.

Fletcher PC, Frith CD, Rugg MD. The functional neuroanatomy of episodic memory. Trends Neurosci 1997; 20: 213–8.

Friston KJ, Ashburner J, Frith CD, Poline J-B, Heather JD, Frackowiak RS. Spatial registration and normalization of images. Hum Brain Mapp 1995a; 3: 165–89.

Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RS. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 1995b; 2: 189–210.

Gershberg FB, Shimamura AP. Impaired use of organizational strategies in free recall following frontal lobe damage. Neuropsychologia 1995; 33: 1305–33.

Grasby PM, Frith CD, Friston KJ, Bench C, Frackowiak RS, Dolan RJ. Functional mapping of brain areas implicated in auditory–verbal memory function. Brain 1993; 116: 1–20.

Haxby JV, Ungerleider LG, Horwitz B, Maisog JM, Rapoport SI, Grady CL. Face encoding and recognition in the human brain. Proc Natl Acad Sci USA 1996; 93: 922–7.

Incisa della Rocchetta I, Milner B. Strategic search and retrieval inhibition: the role of the frontal lobes. Neuropsychologia 1993; 31: 503–24.

Jacoby LJ, Ste-Marie D, Toth JP. Redefining automaticity: unconscious influences, awareness, and control. In: Baddeley A, Weizkrantz L, editors. Attention: selection, awareness, and control. Oxford: Clarendon Press; 1993. p. 261–82.

Kapur S, Craik FI, Tulving E, Wilson AA, Houle S, Brown GM. Neuroanatomical correlates of encoding in episodic memory: levels of processing effect [see comments]. Proc Natl Acad Sci USA 1994; 91: 2008–11. Comment in: Proc Natl Acad Sci USA 1994; 91: 1989–91.

McCarthy RA, Warrington EK. Cognitive neuropsychology. A clinical introduction. San Diego: Academic Press; 1990.

Milner B. Interhemispheric differences in the localization of psychological processes in man. Br Med Bull 1971; 27: 272–7.

Moscovitch M. Cognitive resources and dual-task interference effects at retrieval in normal people: the role of the frontal lobes and medial temporal cortex. Neuropsychology 1994; 8: 524–34.

Petrides M. Frontal lobes and memory. In: Boller F, Grafman J, editors. Handbook of Neuropsychology, Vol. 3. Amsterdam: Elsevier; 1989: 75–90.

Price CJ, Friston KJ. Cognitive conjunction: a new approach to brain activation experiments. Neuroimage 1997; 5: 261–70.

Segal MA, Mandler G. Directionality and organizational processes in paired-associate learning. J Exp Psychol 1967; 74: 305–12.

Shallice T, Fletcher P, Frith CD, Grasby P, Frackowiak RS, Dolan RJ. Brain regions associated with acquisition and retrieval of verbal episodic memory. Nature 1994; 368: 633–5.

Squire LR, Ojemann JG, Miezin FM, Petersen SE, Videen TO, Raichle ME. Activation of the hippocampus in normal humans: a functional anatomical study of memory. Proc Natl Acad Sci USA 1992; 89: 1837–41.

Stern CE, Corkin S, González RG, Guimaraes AR, Baker JR, Jennings PJ, et al. The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. Proc Natl Acad Sci USA 1996; 93: 8660–5.

Stuss DT, Alexander MP, Palumbo CL, Buckle L, Sayer L, Pogue J. Organizational strategies of patients with unilateral or bilateral frontal lobe injury in word list learning tasks. Neuropsychology 1994; 8: 355–73.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme; 1988.

Tulving E. Elements of episodic memory. Oxford: Clarendon Press; 1983.

Tulving E, Kapur S, Craik FI, Moscovitch M, Houle S. Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings [see comments]. Proc Natl Acad Sci, USA 1994a; 91: 2016–20. Comment in: Proc Natl Acad Sci USA 1994; 91: 1989–91.

Tulving E, Kapur S, Markowitsch HJ, Craik FI, Habib R, Houle S. Neuroanatomical correlates of retrieval in episodic memory: auditory sentence recognition [see comments]. Proc Natl Acad Sci USA 1994b; 91: 2012–5. Comment in: Proc Natl Acad Sci USA 1994; 91: 1989–91.

Received December 16, 1997. Accepted February 9, 1998

Appendix 1

The Organize 1 condition

Pre-scan instructions

You will be read a list of 16 words at the rate of one word every three seconds. Listen to these words and try to remember them. The list will cover four categories each represented by four words. The overall list heading is Animals and the four categories will be: Birds, Mammals, Invertebrates and Fish. The words will be read out in the groups to which they belong.

Scan

Kestrel
Osprey
Chaffinch
Quail
Pig
Gerbil
Gorilla
Hedgehog
Snail
Octopus
Worm
Jellyfish
Pike
Trout
Carp
Salmon

Post-scan testing instructions

Tell me as many words as you can remember. Using the list structure will aid your recall.

The Organize 2 condition

Pre-scan instructions

You will be read a list of 16 words at the rate of one word every three seconds. Listen to these words and try to remember them. The list will cover four categories each represented by four words. The overall list heading is Drinks and the four categories will be: Wines, Juices, Beers and Hot drinks. The words will be read out in a randomized order and you should try to allocate each successive word into the appropriate category.

Scan

Hock
Carrot
Stout
Espresso
Bovril
Ale
Grapefruit
Burgundy
Mango
Chianti
Mild
Darjeeling
Cocoa
Apple
Sauterne
Lager

Post-scan testing instructions

Tell me as many words as you can remember. Using the list structure will aid your recall.

The Organize 3 condition

Pre-scan instructions

You will be read a list of 16 words at the rate of one word every three seconds. Listen to these words and try to remember them. The list will cover four categories each represented by four words. The overall list heading is Foods. As you listen to the words, try to work out what the four categories might be and to allocate each word into the appropriate one.

Scan

Grape
Sausage
Herring
Turbot
Croissant
Mango
Kipper
Ham
Raspberry
Venison
Bream
Nan
Pitta
Veal
Banana
Rye

Post-scan testing instructions

Tell me what you think the four categories were (actual categories were: Fruit, Meat, Fish and Bread). Tell me as many words as you can remember.

Note: the lists used for the Organize 1, 2 and 3 conditions were varied from subject to subject in order to prevent material specific effects.