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Prefrontal regions supporting spontaneous and directed application of verbal learning strategies
Evidence from PET

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Summary

The prefrontal cortex has been implicated in strategic memory processes, including the ability to use semantic organizational strategies to facilitate episodic learning. An important feature of these strategies is the way they are applied in novel or ambiguous situations—failure to initiate effective strategies spontaneously in unstructured settings is a central cognitive deficit in patients with frontal lobe disorders. The current study examined strategic memory with PET and a verbal encoding paradigm that manipulated semantic organization in three encoding conditions: spontaneous, directed and unrelated. During the spontaneous condition, subjects heard 24 words that were related in four categories but presented in mixed order, and they were not informed of this structure beforehand. Any semantic reorganization was, therefore, initiated spontaneously by the subject. In the directed condition, subjects were given a different list of 24 related words and explicitly instructed to notice relationships and mentally group related words together to improve memory. The unrelated list consisted of 24 unrelated words. Behavioural measures included semantic clustering, which assessed active regrouping of words into semantic categories during free recall. In graded PET contrasts (directed > spontaneous > unrelated), two distinct activations were found in left inferior prefrontal cortex (inferior frontal gyrus) and left dorsolateral prefrontal cortex (middle frontal gyrus), corresponding to levels of semantic clustering observed in the behavioural data. Additional covariate analyses in the first spontaneous condition indicated that blood flow in orbitofrontal cortex (OFC) was strongly correlated with semantic clustering scores during immediate free recall. Thus, blood flow in OFC during encoding predicted which subjects would spontaneously initiate effective strategies during free recall. Our findings indicate that OFC performs an important, and previously unappreciated, role in strategic memory by supporting the early mobilization of effective behavioural strategies in novel or ambiguous situations. Once initiated, lateral regions of left prefrontal cortex control verbal semantic organization.

Keywords: positron emission tomography; episodic memory; semantic organization; prefrontal cortex; orbitofrontal cortex

Abbreviations: ANOVA = analysis of variance; BA = Brodmann area; CVLT = California Verbal Learning Test; DLPFC = dorsolateral prefrontal cortex; IPFC = inferior prefrontal cortex; OFC = orbitofrontal cortex; rCBF = regional cerebral blood flow; WMS-III = Wechsler Memory Scale-III

Introduction

Episodic memory refers to the process of encoding, storing and retrieving information associated with a distinct time and place (Tulving, 1983; Schacter and Tulving, 1994; Wheeler *et al.*, 1997). Numerous lines of evidence point to the importance of the prefrontal cortex for episodic memory, especially the strategic processes that are closely tied to executive functioning (e.g. Shimamura *et al.*, 1991). One example of strategic processing is semantic organization (Tulving, 1962; Mandler, 1967), whereby memory for lists of randomly ordered words from multiple semantic categories is improved when the relationships among items are processed and the words are mentally regrouped into categories. In comparison with healthy control subjects, patients with prefrontal lesions are less likely to apply semantic organizational strategies during encoding and retrieval (Gershberg and Shimamura, 1995).

Substantial evidence indicates that deficits associated with prefrontal dysfunction are most likely to emerge in novel situations that lack external structure (Shallice and Burgess, 1991, 1996; Goel *et al.*, 1997). In frontal lesion subjects, memory problems are most pronounced on measures of free recall, and improve disproportionately when cues or instructions to use specific strategies are provided (Incisa della Rocchetta and Milner, 1993; Gershberg and Shimamura, 1995; Hildebrandt *et al.*, 1998). Similar strategic memory impairments are also found in other neurological and psychiatric groups in which frontal lobe dysfunction is implicated (Pillon *et al.*, 1993, 1998; Savage, 1997; Iddon *et al.*, 1998; Savage *et al.*, 1999, 2000). Thus, one important function of the prefrontal cortex involves the ability to mobilize effective behavioural strategies in ambiguous unstructured situations (Shallice and Burgess, 1991). Many patients may be able to use semantic organizational strategies when given explicit guidance, yet fail to do so spontaneously.

For example, Knoke and colleagues found that patients with early-stage Parkinson's disease failed to use semantic clustering strategies during the standard administration of the California Verbal Learning Test (CVLT) (Knoke *et al.*, 1998). In the CVLT, subjects are presented with a list of 16 words containing an embedded semantic structure. The degree to which they actively impose semantic organizational strategies can be evaluated in relation to learning and memory performance by examining how items are semantically clustered during free recall. In the standard administration, words are presented so that no items from the same category occur together and subjects are not informed about the presence of semantic structure. Knoke and colleagues added two modified conditions to the standard protocol that provided increasingly explicit organizational cues. In the first condition, CVLT items were reorganized so that words were presented in category pairs but subjects were not informed of the semantic structure. In the second variation, words were presented in random order, and subjects were explicitly informed of the categorical nature of the lists (but not the category labels). They found that Parkinson's disease patients benefited progressively from the imposition of external structure. Subjects were most impaired in the standard administration, less in the paired presentation and normal in the explicitly informed condition (Knoke *et al.*, 1998).

Savage and colleagues recently used the CVLT to study strategic memory in patients with obsessive–compulsive disorder (Savage *et al.*, 2000). This disorder is characterized by intrusive thoughts and/or stereotyped behaviours and is believed to arise from dysfunction in frontal–striatal networks, especially those involving orbitofrontal cortex (OFC), anterior cingulate cortex and caudate nucleus (Rauch *et al.*, 1994, 1998; Saxena *et al.*, 1998). Savage found that obsessive–compulsive disorder patients failed to apply semantic organizational strategies spontaneously during encoding and that this impairment in strategy statistically mediated delayed free recall impairments. In addition, patients in the obsessive–compulsive disorder group improved disproportionately when they were provided with category cues at recall. These types of observations indicate that it is important to differentiate between failure to apply strategies and the incapacity to do so (Gershberg and Shimamura, 1995).

PET and functional MRI provide a means of studying the neural correlates of strategic processes in humans. Several investigators have proposed that prefrontal activations during episodic memory tasks reflect the use of executive control processes that support and enhance episodic learning and memory (e.g. Buckner *et al.*, 1999; Wagner, 1999). The specific patterns of prefrontal activation may be determined by the nature of these cognitive processes. Functional neuroimaging studies suggest that distinct prefrontal regions support different aspects of executive functioning, such as semantic processing (Demb *et al.*, 1995) and reorganization of items in working memory (D'Esposito *et al.*, 1998). Semantic processing appears to be supported by regions in the left inferior prefrontal cortex (IPFC), especially territories within the inferior frontal gyrus, whereas higher level control operations, such as updating and manipulating short-term representations, may be mediated by dorsolateral prefrontal cortex (DLPFC) (Owen *et al.*, 1996). Distinct regions of the prefrontal cortex may, therefore, control the various executive function operations that are necessary to implement semantic organizational strategies.

Fletcher and colleagues used PET to study semantic organizational processing. Their paradigm included three types of related word lists, designed to create three conditions of increasing organizational difficulty. Participants in this study were explicitly instructed to utilize semantic organizational strategies while they encoded the word lists. In the easiest condition, words were grouped into categories and subjects were informed of category names before scanning. In another condition, words in the lists were presented randomly and subjects were provided with category labels. In the most difficult condition, word lists were presented randomly and subjects were not given category headings. They found that one region of left DLPFC showed increased blood flow during the most difficult organization condition when compared with the two less demanding conditions (Fletcher *et al.*, 1998).

These findings point to the importance of left DLPFC in semantic organization. Interestingly, the study of Fletcher and colleagues did not find changes associated with semantic clustering manipulations in left IPFC—a region previously implicated in semantic processing (e.g. Gabrieli *et al.*, 1998). This is in some ways surprising, since semantic organization operations presumably involve processing of semantic relationships. One possible explanation for this is that all three encoding conditions in the Fletcher study (Fletcher *et al.*, 1998) involved related word lists; thus, subjects were encouraged to process semantic relationships across all conditions. The main manipulation of difficulty probably involved differences in monitoring and reorganization in working memory—functions for which DLPFC has been strongly implicated.

With these previous investigations in mind, the goal of the present study was to identify the neural basis of spontaneous and directed semantic organization using PET. We utilized a verbal encoding paradigm patterned very closely on the CVLT. The basic CVLT approach was modified to include three primary memory conditions that varied in the degree of externally provided structure (spontaneous and directed use of strategies) and semantic relatedness (related and unrelated lists). Behavioural data included a semantic clustering score, measuring active regrouping of words into semantic categories during recall. This design allowed us to manipulate semantic clustering levels over three encoding conditions, including an unrelated list condition. More critically, we could determine patterns of brain activity that predicted the spontaneous application of effective strategies in a novel and ambiguous learning situation.

Material and methods

Subjects

Participants were eight normal right-handed adults (four males, four females), with a mean age of 28 years (SD = 6.8) and mean education of 15.8 years (SD = 0.7). All were free of neurological and psychiatric illness (confirmed with a structured clinical interview; First *et al.*, 1995) and were not taking psychotropic or cardiovascular medication. Participants had no previous experience with semantic organizational tests, having never undergone formal memory testing. We imposed this criterion because we were interested in how strategies were selected and initiated in maximally novel learning situations. The Massachusetts General Hospital Subcommittee on Human Studies approved this study, and all subjects provided written informed consent.

Experimental paradigm

The general approach to manipulating semantic organization was modelled closely on the CVLT, which is a well-characterized clinical measure of strategic verbal memory (Delis *et al.*, 1987). Subjects in this study were scanned while they encoded related and unrelated word lists. The word lists were generated from 32 categories of words, with six words in each category. Sample word lists are provided in Table 1.

During each encoding condition, participants heard 24 words, with one word presented every 3.3 s. In the two related-list conditions, six words from each of four categories were presented so that no two words from the same category occurred consecutively; thus, any grouping by category during free recall was initiated by the subject. Words were matched across categories for length, concreteness and frequency.

Table 1 *Two sample word lists for the related conditions (fuzzy categories in parentheses)*

Categories	List	Categories	List
Metals	Titanium	Sporting equipment	Skates
(Electronics)	Headphones	(Desserts)	Doughnut
Plants/trees	Lilac	Parts of a house	Porch
(Furniture)	Lamp	(Staple foods)	Bread
	Television		Pudding
	Sofa		Cheese
	Magnolia		Fence
	Tin		Paddle
	Recliner		Pasta
	Computer		Brownie
	Cactus		Shingles
	Silver		Snorkel
	Nightstand		Rice
	Amplifier		Fudge
	Maple		Deck
	Lead		Skis
	Speakers		Cookie
	Futon		Eggs
	Spruce		Floor
	Copper		Baseball
	Radio		Cupcake
	Dresser		Butter
	Steel		Racket
	Birch		Chimney

Table 2 *The experimental procedure*

Condition	Scanning status	Behavioural measures
General instructions	Transmission scan	None
Practice trials		Free recall
Fixation baseline	PET scan 1	None
Spontaneous	PET scan 2 Digit span	Free recall
Spontaneous	PET scan 3	Free recall, cued recall, recognition
Directed	PET scan 4 Digit span	Free recall
Directed	PET scan 5	Free recall, cued recall, recognition
Unrelated	PET scan 6 Digit span	Free recall
Unrelated	PET scan 7	Free recall, recognition
Fixation baseline	PET scan 8	None

Participants underwent eight PET scans during a single session, with two scans for each of four conditions: three encoding conditions (spontaneous, directed, unrelated) and a low-level baseline condition (fixation). The procedures are outlined in Table 2.

At the start of the study, subjects were given general instructions regarding the task. Next, they heard a practice list, consisting of 16 unrelated words. They were told to listen carefully to the entire list and try to remember it. Subjects were instructed further that, after the list was presented, they should produce as many items as they could remember, in any order.

Scanning occurred during the memory encoding conditions, while subjects listened to 24 words presented by computer through external speakers. We also added a low-level fixation baseline condition. There were two encoding scans for each condition, with the same list repeated in the same order. The scanned conditions were as follows. (i) *Spontaneous*: words were related in four semantic categories (six words each), and subjects were not instructed about this organization beforehand or given any practice with related lists. (ii) *Directed*: words were related in four semantic categories (six words each), and subjects were explicitly instructed to notice the four categories and use them to improve their memory by mentally regrouping related items together (they were not told the category names). (iii) *Unrelated*: words in the list did not share any obvious semantic relationships. (iv) *Fixation baseline*: participants were instructed to look at the centre fixation cross (which was present in all conditions) and rest their mind. The instructions for the memory conditions were as follows:

Spontaneous: 'You will hear a list of words through the stereo speakers. You will also see a fixation cross in the centre of the screen. It is important that you keep your eyes open and focused on the fixation cross, but feel free to blink normally. Listen carefully to the entire word list and try to remember it. When the list is through, you will be instructed to say back as many of the items as you can remember. It doesn't matter what order you remember them in—just say as many as you can.'

Directed: same as in spontaneous, plus, 'This time, notice that the words can be grouped into four different categories. By grouping the words together into these related categories, you will remember more words. For example, in the first scanned list, you could have grouped the words into —, —, — and —. The words from this new list can be grouped also, but you will hear different words and different categories than the first time. The words can be grouped into four categories. Be sure and group the words together into categories this time as you learn them.'

Unrelated: same as in spontaneous, plus, 'This time, you will not notice any obvious relationships among the words. These words will not fit neatly into category groups. You can remember these words in any order.'

The paradigm was developed and tested extensively in pilot studies in order to develop word lists that promoted significant differences in semantic clustering between the spontaneous and directed conditions. Specifically, we generated word lists in 32 categories for which normal subjects showed some clustering in the spontaneous condition but significantly less than in the directed condition. We adapted an approach implemented in the CVLT (Delis *et al.*, 1987). Of the four categories in each related list, two were unrelated to the others and two shared 'fuzzy' semantic relationships (e.g. precious stones and jewellery). This manipulation made the task more challenging and minimized ceiling effects for clustering in normal subjects (Delis *et al.*, 1987). The unrelated list for each subject was constructed by taking one word from each of the remaining 24 categories. Words were counterbalanced across subjects such that each word appeared once in each condition.

The order of the directed and unrelated conditions was counterbalanced across subjects, and the fixation baseline was always the first and last scan. The spontaneous condition always occurred following the first fixation baseline in order to ensure that the strategies imposed by subjects were as 'spontaneous' as possible—specifically that subjects were not anticipating the presence of semantic structure in the word lists. Detailed behavioural data were collected immediately after each scan, without intervening distraction (see Table 2). Free recall was measured immediately after each encoding scan; category-cued recall was measured, following free recall, after the second scan for the two related-list conditions (spontaneous, directed). Finally, recognition (yes–no; 24 targets, 24 distractors) was measured after the second scan for each of the three memory conditions. The Digit Span subtest of the Wechsler Memory Scale-III (WMS-III) (Psychological Corporation, 1997) was administered between the first and second scan of each encoding condition in order to prevent rehearsal.

PET scanning

The PET facilities and general procedures are similar to those described previously (e.g. Rauch *et al.*, 1995). Briefly, an individually moulded thermoplastic face mask (True Scan, Annapolis, Md., USA) was used to minimize head motion and subjects were fitted with a nasal cannula and overlying face mask, which were attached to radiolabelled gas inflow and a vacuum, respectively. Participants were given general instructions and completed the practice test. PET data were acquired subsequently in eight 60 s scans while subjects performed the cognitive tasks and inhaled ^{15}O-labelled CO_2 gas. A Scanditronix PC4096 15 slice whole-body PET camera was used in the stationary mode (General Electric, Milwaukee, Wis., USA). The slice geometry consists of contiguous slices with a centre-to-centre distance of 6.5 mm (axial field = 97.5 mm) and in-plane resolution of 6.0 mm FWHM (full width at half maximum). The axial field of view of the PET camera precluded total brain coverage, but head positioning was designed to ensure complete coverage from the inferior temporal lobes through the prefrontal cortex. Small portions of the superior sensory and motor cortices, superior parietal cortex, the inferior cerebellum and the brainstem were outside the field of view.

During scanning, participants listened to words presented through computer speakers, while looking ahead at a computer monitor with a central fixation cross (+), ~35 cm from their eyes. Each scan was followed by a 10 min washout period, during which subjects underwent memory testing (free recall, cued recall, recognition), completed distraction tasks (WMS-III Digit Span) and/or rested. PET images were reconstructed using a conventional convolution–backprojection algorithm, correcting for photon absorption, scatter and dead time

Table 3 *Summary of behavioural performance data (standard deviations in parentheses)*

	Spontaneous	Directed	Unrelated	Results
Strategy measures				
Semantic clustering	0.71 (0.25)	0.87 (0.16)	N/A	D > S
Serial clustering	0.06 (0.06)	0.02 (0.05)	0.27 (0.15)	U > S, U > D
Free recall	16.31 (3.32)	17.81 (2.75)	14.00 (6.16)	D > U
Cued recall	20.25 (2.25)	20.00 (3.07)	N/A	n.s.
Recognition (discriminability)	0.98 (0.03)	0.98 (0.02)	0.97 (0.03)	n.s.

N/A = not applicable; n.s. = non significant.

effects. The Hanning-weighted reconstruction filter was set to yield 8.0 mm in-plane spatial resolution FWHM.

Behavioural measures of strategy and memory

There were five primary behavioural measures in this study, all patterned closely after the CVLT (Delis *et al.*, 1987): (i) *semantic clustering* for the two related-list conditions (spontaneous, directed); (ii) *serial clustering* for all three encoding conditions (spontaneous, directed, unrelated); (iii) *free recall* for all three encoding conditions; (iv) *cued recall* (i.e. category-cued) for the two related-list conditions; and (v) *recognition discriminability* for all three encoding conditions.

Our two measures of strategy were the semantic and serial clustering scores. In the case of semantic clustering, a 'cluster' was defined as consecutive recall of two words from the same category. For serial clustering, a 'cluster' was defined as consecutive recall of two words, in the same order, as they were presented during encoding. Semantic clustering, therefore, measured the subjects' tendencies to group words together actively according to their shared semantic features, while serial clustering measured tendencies to remember items in the same order as they were presented. Clustering scores were calculated to reflect the proportion of clustered responses out of the total possible clusters for that condition. Thus, the semantic clustering score was defined as: [clusters/(words recalled – categories recalled)] and the serial clustering score was defined as: [clusters/(words recalled – 1)].

The free recall score was the total number of recalled words, minus intrusions and perseverations, in response to free recall instructions (i.e. 'Tell me all the words you can remember'), while the cued recall score was the number of correctly recalled items following category cues (e.g. 'Tell me all the words you can remember that were *metals*.'). Recognition was evaluated following free recall and cued recall in a 48-item (24 targets, 24 distractors) yes–no test (e.g. 'Did *titanium* appear in the list?'). The recognition score of interest was a discriminability index designed to correct for guessing; it was calculated as: [1 – {(false positives + false negatives)/48}] × 100.

PET data analysis

Images were realigned to correct for motion and transformed into the standard stereotactic space of Talairach (Talairach and Tournoux, 1988) using previously described procedures (Alpert *et al.*, 1993, 1996). Images were smoothed with a two-dimensional Gaussian filter of width 20 mm FWHM. All statistical analyses were performed using SPM95 (Statistical Parametric Mapping 95—Wellcome Department of Cognitive Neurology, London, UK), except for the direct contrasts, which utilized SPM96 in order to implement the masking option. Images were scaled to 50 ml/min per 100 g to yield normalized images of regional cerebral blood flow (rCBF).

For the graded and direct subtraction analyses, PET data were analysed using analysis of variance (ANOVA) and the general linear model, with condition as an explanatory variable and the two scans for each condition entered as replicates. For each linear contrast, t statistics were calculated and then transformed to Z scores, representing differences in blood flow between conditions. For the covariate analyses, the primary dependent behavioural measure (semantic clustering) was regressed onto PET blood flow data for that condition in order to generate statistical parametric maps representing correlations between rCBF and organization. This was done using the Covariates Only module from SPM95. Results of the covariate analyses were also converted to Z scores. All statistical parametric maps were thresholded at an uncorrected $P < 0.001$ (i.e. $Z > 3.09$), with the added requirement that at least three contiguous voxels exceeded this statistical level (i.e. $k \geqslant 3$). This was the threshold used to determine statistical significance for *a priori* hypotheses. These regions were selected based on previous literature (e.g. Fletcher *et al.*, 1998; Buckner *et al.*, 1999; Wagner, 1999) and were strictly limited to left lateral prefrontal cortex. Other observed activations were considered to be statistically significant if at least three contiguous voxels exceeded $Z > 4.20$, corresponding to an uncorrected $P < 1 \times 10^{-5}$.

Results

Behavioural data

Analyses of the behavioural data revealed that levels of semantic clustering varied in a progressive manner across the different encoding conditions (see Table 3).

Semantic clustering

Scores were evaluated with two-factor (trial × condition) repeated-measures ANOVA. Results indicated a significant effect for condition, $F(1,7) = 7.81$, $P = 0.01$, but no effects for trial, $F(1,7) = 0.51$, $P = 0.49$, nor was there an interaction, $F(1,7) = 1.22$, $P = 0.17$. Repeated-measures ANOVA of the serial clustering scores indicated a significant main effect for condition, $F(2,14) = 24.41$, $P < 0.0001$, but not for trial, $F(1,7) = 0.33$, $P = 0.57$, or the interaction, $F(2,14) = 0.61$, $P = 0.55$. Follow-up analyses of the condition effect found that serial clustering scores were higher in the unrelated condition than in both of the other two conditions (all $P < 0.0001$). Additional analyses of the semantic and serial clustering data indicated that there was a significant negative correlation between semantic clustering and serial clustering in the spontaneous condition, $r(6) = -0.76$, $P = 0.03$. For instance, the two subjects who obtained semantic clustering scores of <50% in the spontaneous condition showed the highest serial clustering scores. This indicates that subjects who failed to use semantic strategies in the spontaneous condition tended to use serial order strategies (as opposed to some other idiosyncratic approach). Thus, overall results from the strategy data indicate that subjects used semantic strategies more in the directed condition than in the spontaneous condition, and they used serial order strategies more in the unrelated condition than in both related-list conditions. Also, note that the absence of an effect for trial in both strategy analyses indicates that the same strategies were used consistently in both trials of each condition. Subjects initiated a definite strategy during the first free recall trial and persisted with it in the second.

Free recall

Scores were also evaluated via two-factor repeated-measures ANOVA. Analyses indicated significant main effects for trial, $F(1,7) = 9.09$, $P = 0.009$, and condition, $F(2,14) = 4.46$, $P = 0.02$, with no interaction, $F(2,14) = 0.04$, $P = 0.96$. Thus, subjects recalled more words in trial 2 than in trial 1 across all conditions (although their strategies did not change). Follow-up comparisons of the condition effect indicated that subjects recalled more words in the directed condition than in the unrelated condition ($P = 0.04$). Overall, results indicated that subjects semantically clustered more in the directed condition than in the spontaneous condition, and that they obtained higher free recall scores in the directed condition than in the unrelated condition. Across the two trials of the same condition, subjects recalled more words, although they tended to use the same strategy initiated in the first trial. There were no differences in cued recall or recognition across the conditions (all $P > 0.90$).

PET data

To investigate brain systems underlying semantic organization during verbal learning, we performed three sets of analyses on the PET data sets. Primary results from these analyses are summarized in Table 4.

Graded contrast

First, we conducted a graded contrast, comparing rCBF across the three encoding conditions based on *a priori* predictions in left lateral prefrontal cortex. The experiment was designed such that semantic clustering levels would be highest in the directed condition, less in the spontaneous condition and lowest (by definition 0) in the unrelated condition. These expectations were supported by analyses of the behavioural data. The graded contrast of the PET data was defined (weighted) such that regions of activation represented voxels where rCBF increased in a graded fashion, with directed > spontaneous > unrelated. This analysis identified two (and only two) regions of significant activation (see Table 4): (i) left DLPFC [~Brodmann area (BA) 9] and (ii) left IPFC (~BA 45/46).

To illustrate further how these regions were activated, we inspected the maps for differences between each encoding condition and the fixation baseline condition. The directed versus baseline contrast identified activations in left IPFC (Z score = 5.62; $x, y, z = -36, 36, 12$) and left DLPFC (Z score = 5.52; $x, y, z = -38, 22, 24$). The spontaneous versus baseline contrast found regions of significant change in left IPFC (Z score = 3.92; $x, y, z = -34, 34, 12$) and left DLPFC (Z score = 4.28; $x, y, z = -36, 18, 24$). The unrelated versus baseline contrast identified activations in left DLPFC (Z score = 3.78; $x, y, z = -40, 20, 24$) and IPFC; however, this was actually in a different location from the others (Z score = 3.86; $x, y, z = -34, 44, 8$). Results from the graded contrast are illustrated in Fig. 1.

The two regions of left prefrontal cortex identified in this study were the two regions predicted to change in relation to levels of semantic clustering. The left DLPFC activation ($x, y, z = -36, 22, 28$) corresponds to BA 9, and is precisely the same territory as that identified by Fletcher and colleagues (Fletcher *et al.*, 1998). The left IPFC activation ($x, y, z = -36, 34, 12$) corresponds to BA 45/46 and is within a region of inferior frontal gyrus identified in numerous other investigations of verbal semantic processing (e.g. see Gabrieli *et al.*, 1998). It is important to note that IPFC is used here to describe this activation in the inferior frontal gyrus, consistent with the nomenclature of previously published imaging studies; in fact, the activation is anatomically located in lateral prefrontal cortex.

Covariate analyses

The second set of analyses involved covariate analyses between PET rCBF measures during encoding and the semantic clustering scores measured during immediate free recall (see Table 4). Activations identified in this way can be conceptualized as defining regions in which rCBF levels measured during encoding predicted subsequent strategic behaviour during recall. It is noteworthy that we observed a range of clustering in the spontaneous condition, with some subjects clustering at high levels from the very beginning,

Table 4 *PET results: areas of signal change meeting our statistical criteria for significance (i.e.* $Z > 3.09$ *for* a priori *hypotheses and* $Z > 4.2$ *for other regions; three or more contiguous voxels)*

	Z score	Coordinates			Region (Brodmann area)
		x	*y*	*z*	
Graded contrast by clustering:					
$D > S > U$	3.36	–36	22	28	L Middle frontal gyrus (9)
	3.20	–36	34	12	L Inferior frontal gyrus (45/46)
Covariate analyses with clustering:					
Spontaneous (scan 1)	4.38	14	54	–12	R Orbitofrontal (11)
	4.31	2	54	–4	R Ventromedial prefrontal (10)
Directed:					
Directed versus unrelated	3.29	–36	32	12	L Inferior frontal gyrus (45/46)
Directed versus spontaneous	3.20	–38	38	8	L Inferior frontal gyrus (45/46)
	3.19	–38	24	28	L Middle frontal gyrus (9)
Spontaneous:					
Spontaneous versus directed	4.31	0	46	8	Anterior cingulate (32)
Unrelated:					
Unrelated versus directed	4.20	–54	2	–16	L Inferior temporal (20/21)

Coordinates refer to the maximum voxel locations in Talairach space. D = directed; S = spontaneous; U = unrelated; L = left; R = right.

and others showing very little spontaneous clustering. Thus, behavioural data in the spontaneous condition were ideally suited for a covariance analysis. rCBF covariates for clustering in the first spontaneous scan identified a large and highly significant expanse of activation in right ventromedial prefrontal cortex that included three distinct statistical peaks ranging on the *z*-axis from –4 to –24 mm. The greatest spatial extent of significant activation occurred throughout the OFC. Two of these regions are listed in Table 4. The third peak (*Z* score = 4.01; *x*, *y*, *z* = 12, 30, –24), did not meet strict criteria for significance. None of the other covariate contrasts revealed activations that approached our criteria for statistical significance ($Z > 4.2$).

The most striking finding from the covariate analyses was the strong positive correlation between rCBF in the OFC and initial spontaneous semantic organization. Subjects with higher rCBF in the OFC were the ones who later clustered, indicating a role for this region in supporting the mobilization of effective strategic memory processes. To characterize this finding further, we performed a region of interest-based analysis from the territory of maximal correlation in the spontaneous 1 condition (*x*, *y*, *z* = 14, 54, –12) and compared it with the same region for spontaneous 2. Mean rCBF values were calculated from nine contiguous voxels centred at the pixel of maximal statistical significance. The Pearson *r* value between mean rCBF and semantic clustering in spontaneous 1 was 0.96 ($P < 0.0001$, uncorrected), while it was 0.64 ($P = 0.09$, uncorrected) in spontaneous 2. The corresponding *Z* scores were 4.46 and 1.70, respectively. These two correlations were compared directly and the difference expressed as a *Z* score (Glass and Hopkins, 1984). This direct comparison yielded a Z_{diff} of 1.90, $P < 0.03$, indicating that the correlation between blood flow and clustering in this region was significantly greater in the spontaneous 1 condition than in spontaneous 2. Figure 2 illustrates the area of correlation in the region of maximal covariation in spontaneous 1, anatomically located in the OFC (*x*, *y*, *z* = 14, 54, –12).

Direct contrasts

The third set of analyses involved direct contrasts between the three encoding conditions (see Table 4). In addition to showing significant change (*Z* score > 3.09 in at least three contiguous voxels for *a priori* hypotheses or $Z > 4.2$ for non-specified regions), we imposed an additional constraint in these direct contrasts: in order to be considered a region of significant *increase*, the voxels identified in the direct contrast also had to be significantly activated in contrasts with the low-level fixation baseline. This procedure does not change the actual *P* values and should not be interpreted as making our tests more statistically conservative. It is used only to verify that a particular activation represents an increase from resting baseline, rather than a decrease in the condition with which it is compared. Masking was performed using the masking procedure of SPM96, with the low-level baseline contrast as the image mask. Contrasts involving the directed condition (Table 4) were consistent with the findings from the graded analysis. The directed versus unrelated contrast identified one region of significant activation in the left IPFC territory. Although the left DLPFC territory did not reach our formal threshold for significance and is not listed in Table 4, it did show subthreshold change with the centre of activation in exactly the same location as in the graded contrast (*Z* score = 2.66; *x*, *y*, *z* = –36, 22, 28). The directed versus spontaneous contrasts identified both regions in the left IPFC and left DLPFC.

In the direct contrasts for the spontaneous condition, only one area met our significance criteria for non-specified activations, located in the anterior cingulate (~BA 32) for the spontaneous versus directed contrast. Contrasts involving the unrelated condition identified one territory of significant change in the left inferior temporal cortex (~BA 20/21), for the unrelated versus directed contrast.

Discussion

This study used PET to examine brain regions underlying semantic organizational strategies during verbal learning. The most unique aspect of our paradigm was the ability to separate regions supporting semantic organization from those supporting strategy mobilization. The primary contrasts identified three prefrontal regions, which appear to make distinct contributions to strategic verbal memory. The findings implicate two territories in left lateral prefrontal cortex in cognitive operations underlying semantic organization, while ventromedial prefrontal cortex, especially the OFC, is implicated in strategy mobilization.

Lateral prefrontal cortex

Two regions in the left lateral prefrontal cortex varied in the graded analyses that were defined to parallel levels of actual semantic organization (directed > spontaneous > unrelated). These were left DLPFC, corresponding to BA 9, and left IPFC, extending across the border of BA 45 and 46 in the inferior frontal gyrus (see Fig. 1).

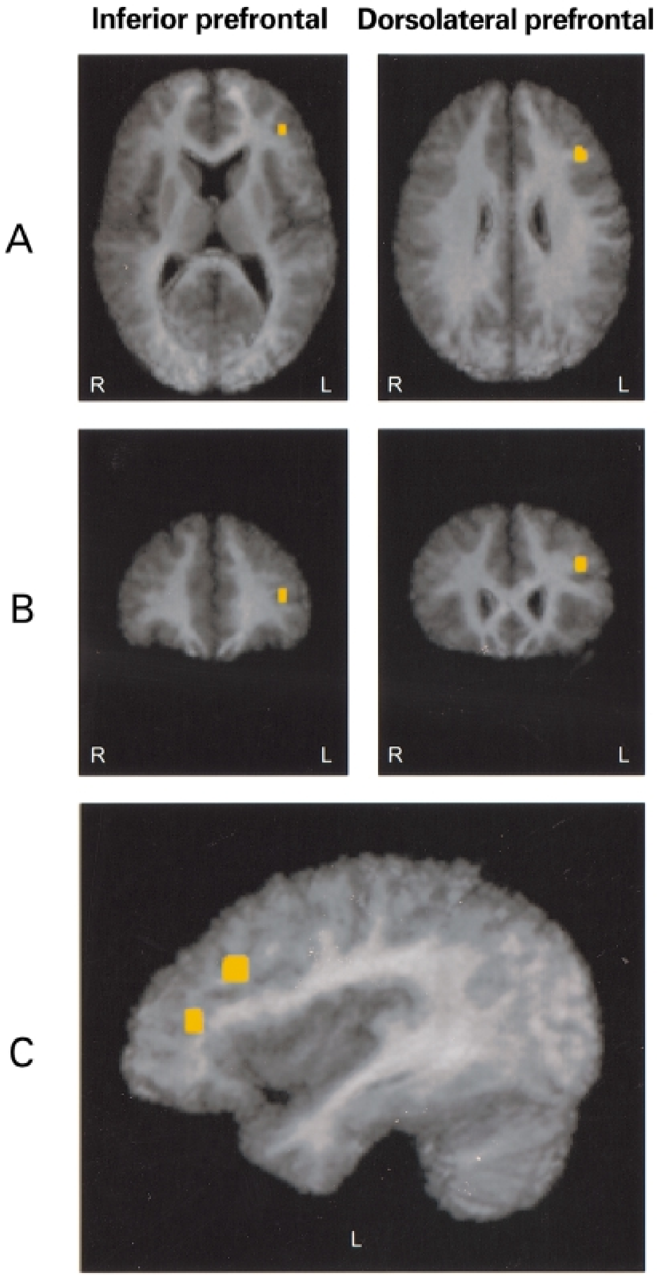

Fig. 1 PET statistical maps from the graded contrast presented co-registered with averaged MRIs. The graded contrast was weighted such that regions of activation represent voxels where rCBF increased in a graded fashion—directed > spontaneous > unrelated—and thereby mirrored observed levels of semantic clustering. Activations were thresholded to a Z score >3.09, $P < 0.001$. These activations are presented in axial (**A**), coronal (**B**) and sagittal (**C**) views. Significant regions of rCBF change, corresponding to levels of semantic clustering, were found in two regions of lateral PFC: left IPFC (x, y, z = –36, 34, 12) and left DLPFC (x, y, z = –36, 22, 28).

Dorsolateral prefrontal cortex

The increased response in DLPFC across our three encoding conditions suggests that demands on executive control processes increased in parallel with participants' increased use of semantic organization strategies. Evidence regarding the nature of these control processes comes from prior neuroimaging studies of working memory. Specifically, recent data suggest that DLPFC activation is associated with conditions that require participants to monitor, manipulate and/or update the contents of working memory (Owen *et al.*, 1996; D'Esposito *et al.*, 1998; Smith and Jonides, 1999). These control processes may support semantic organization because they allow participants to monitor the mixed list of study words and update or manipulate the representations in working memory as they mentally regroup related words together.

A similar association between left DLPFC and semantic organization was described by Fletcher and colleagues (Fletcher *et al.*, 1998). In that PET study, participants were scanned while they encoded related word lists that varied in the degree of semantic organization required. The investigators found that a region in the left DLPFC—identical to the coordinates reported here—was activated with increasing organizational demands. This region was maximally active in their most difficult organization condition, which was very similar to our directed condition. Current results provide strong support for Fletcher and

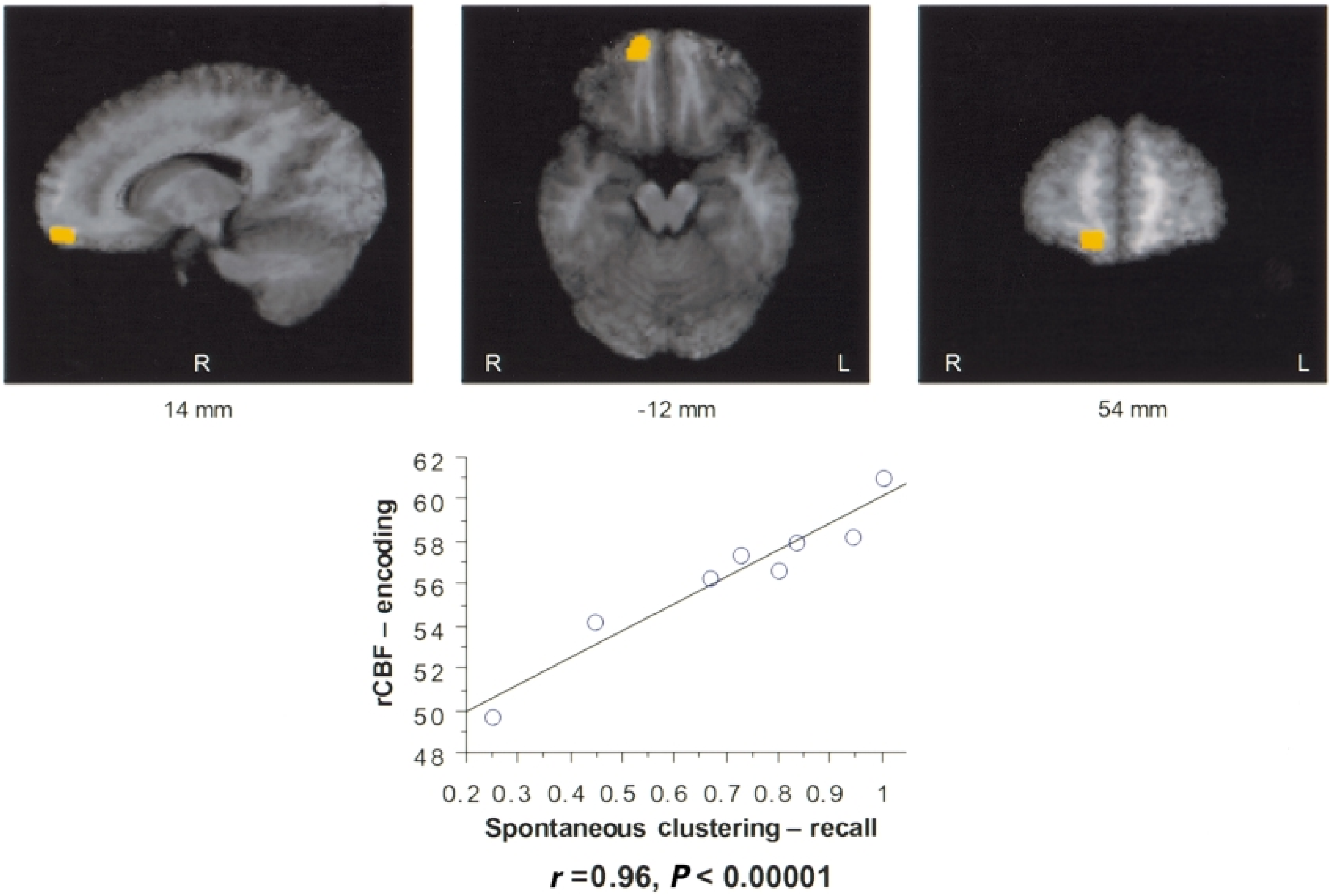

Fig. 2 PET statistical maps from the covariate analyses showing the orbitofrontal region (x, y, z = 14, 54, –12) corresponding to the territory of maximal covariation, co-registered with averaged MRIs along sagittal, axial and coronal planes of view. Also depicted is a graphical representation of this significant correlation between rCBF during the first spontaneous encoding condition and semantic clustering scores during immediate free recall. Mean rCBF values were calculated from nine contiguous voxels centred at the pixel of maximal statistical significance for each activation and correlated (Pearson) with semantic organization scores measured during immediate recall, $r(6) = 0.96$, $P < 0.00001$. The other two statistical peaks included: left ventromedial PFC (x, y, z = 2, 54, –4), $r(6) = 0.95$, $P < 0.00001$; and left OFC (x, y, z = 12, 30, –24), $r(6) = 0.94$, $P < 0.0001$. rCBF in these regions during encoding predicted which subjects would spontaneously initiate semantic organizational strategies at recall.

colleagues' conclusion that the left DLPFC is involved in creating an organizational structure during encoding.

Inferior prefrontal cortex

The present study also identified a region of left IPFC that varied with semantic organization demands. The location of this activation in the inferior frontal gyrus was very similar to findings from previous functional imaging studies of semantic processing and episodic encoding (Gabrieli *et al.*, 1998; Wagner *et al.*, 1999). The left IPFC has been identified in memory encoding studies when subjects are required to process semantic features of items (Kapur *et al.*, 1994; Demb *et al.*, 1995; Fletcher *et al.*, 1995), with greater activation in left IPFC during encoding associated with more confident and accurate subsequent verbal recognition (Wagner *et al.*, 1998). The observation of a graded response in this region across the directed–spontaneous–unrelated manipulation suggests that executive control processes mediating the evaluation and/or retrieval of semantic knowledge were differentially recruited during encoding.

The study of semantic organization by Fletcher and colleagues (Fletcher *et al.*, 1998) did not find that the left IPFC was associated specifically with increasing organizational demands. One possible reason for this discrepancy is that in their study, the difficult organization condition was compared with two other conditions—both using related word lists—that also required considerable semantic processing. Thus, all conditions involved semantic retrieval and evaluation of words, and thereby placed considerable demands on left IPFC. In contrast, in the present study, participants engaged in semantic analysis and organization to a lesser extent in the spontaneous trials because they were not told that such a strategy would be effective, and also in the unrelated trials because semantic organization strategies were not possible.

Our findings in left prefrontal cortex during encoding are consistent with the hemispheric encoding and retrieval asymmetry model (HERA; Tulving *et al.*, 1994), which proposes that left prefrontal cortex is involved preferentially in encoding while right prefrontal cortex is most active during retrieval. However, recent tests of this model (Kelley *et al.*, 1998; Lee *et al.*, 2000) indicate that lateralization may also be affected by the content or nature of the material (e.g. verbal, visual), especially with respect to IPFC. Our results and those of others indicate that left lateral prefrontal activations are especially prominent when verbal semantic organizational strategies are stressed.

Orbitofrontal cortex

The covariate analysis revealed significant positive correlations (r = 0.94–0.96) between rCBF in the right OFC during the first spontaneous encoding trial and organizational strategies during immediate recall (see Fig. 2). Thus, rCBF predicted which subjects would later spontaneously exhibit effective semantic strategies. Consideration of previous animal and human studies may shed further light on the significance of this novel finding.

Animal studies

The animal literature has implicated the OFC in operations underlying the motivational control of goal-directed behaviour (Rolls, 1996, 1999; Gallagher *et al.*, 1999). Tremblay and Schultz found that OFC neurones in monkeys responded differentially based on the animals' preference among reinforcers, as reflected in their ultimate behavioural choice, rather than physical properties of the reinforcers (e.g. food or liquid) (Tremblay and Schultz, 1999). Activity in the OFC, therefore, predicted future behavioural choice. The role of the OFC may be especially important early in learning. For instance, Dias and colleagues reported that OFC lesions in monkeys impaired stimulus–reward reversals, but only during the first reversal trial (Dias *et al.*, 1997). Studies of odour discrimination learning in rats also show that OFC neurones fire in anticipation of rewarding and aversive outcomes, early in the course of training, before reliable behavioural discriminations have developed (Schoenbaum *et al.*, 1998; Lipton *et al.*, 1999). These and other animal studies implicate the OFC in early motivational processes guiding behaviour based on anticipation of future reward (Schoenbaum *et al.*, 1998).

Human lesion studies

Humans subjects with lesion in OFC often perform normally on standard measures of neuropsychological functioning, yet have profound problems in 'real life' situations (Eslinger and Damasio, 1985; Rolls *et al.*, 1994). For example, within the context of a card-playing gambling paradigm (Bechara *et al.*, 1996, 1997, 1998, 1999), OFC patients have been observed consistently to make choices associated with immediate gain but long-term loss. This problem has been described by Damasio as difficulty using anticipated future consequences to guide ongoing behaviour in unstructured situations (Damasio, 1996). Our verbal learning paradigm shares this characteristic lack of structure with the gambling task. In both paradigms, the tests have been designed so that the most effective strategy is deliberately obscured. Subjects must, therefore, derive and implement the optimal strategy in the absence of external cueing and concrete feedback. Further evidence for the role of OFC in strategy mobilization comes from Levine and colleagues (Levine *et al.*, 1998), who evaluated patients with various prefronal lesions using a strategy application task described previously (Shallice and Burgess, 1991). They found that patients with lesions involving ventromedial prefrontal cortex, including OFC, had the most difficulty on this test.

Functional imaging studies of OFC

Functional imaging studies specifically targeting OFC are also beginning to appear in the imaging literature. A PET study found that OFC activation was associated with inhibition of previously learned stimulus–response associations on a test of visuospatial orientation (Nobre *et al.*, 1999). OFC has also been implicated in a card-playing task in which subjects were instructed to make their best educated 'guess' regarding upcoming card suit or colour (Elliott *et al.*, 1999). OFC activation was associated specifically with more difficult guessing demands, as subjects had to deal with increasing uncertainty while weighing past instances of success and failure over a number of trials. Rogers and colleagues reported results of a PET study using a computerized 'risk-taking' task, patterned very closely after the Bechara/Damasio gambling paradigm. During scanning, subjects had to choose small, high probability rewards over large, low probability rewards. The authors found activations in right orbital and inferior prefrontal cortex as subjects resolved conflicts between these competing choices (Rogers *et al.*, 1999).

The role of OFC in strategic behaviour

Taken together, previous studies indicate that OFC mediates the early inhibition of automatic behaviour in favour of developing a plan for future action based on expected consequences, especially in novel or ambiguous situations. Results from the current study suggest that these operations play an important role in directing strategic memory processes. We observed that subjects in this study immediately initiated a definitive approach—either semantic or serial order—and persisted with it through the second spontaneous trial. Subjects who did not initiate semantic strategies spontaneously were able to do so once given external guidance in the directed condition. Animal and human studies reviewed here indicate that OFC is especially important during the early stages of learning. Our data are consistent with this: correlations between the right OFC and clustering occurred only during the first run of the spontaneous condition. This makes sense since subjects are engaging in strategy selection only in the first spontaneous condition

Anatomically, posterior OFC has reciprocal connections with limbic structures such as the amygdala, while anterior regions of OFC are connected predominantly with association cortex, such as DLPFC and anterior cingulate (Zald and Kim, 1996). OFC is, therefore, anatomically positioned as a convergence zone for emotional (limbic) and cognitive (prefrontal) information. It is connected in such a way as to use limbic information to determine the motivational significance of stimuli (Rolls, 1999) and then initiate executive processes mediated in other regions of prefrontal cortex. These abilities are most critical in novel or unstructured situations in which individuals must resolve conflicts between competing choices on the basis of ambiguous or competing information (e.g. Bechara et *al.*, 1998). Some caution is warranted, however, in interpreting the current finding in OFC—additional studies are needed to confirm that this result is not dependent on specific characteristics of our approach.

This paradigm was patterned very closely on a widely used clinical measure of verbal memory—the CVLT. Results from this study indicate that it is important to differentiate between failure to mobilize strategies and the incapacity to do so (Gershberg and Shimamura, 1995). In the case of strategic memory, prefrontal territories important for strategy mobilization can be distinguished from those that actually support the strategies. It may, therefore, be clinically useful to evaluate strategic memory with both undirected and directed instructions. The role of OFC in memory may have been unappreciated previously in imaging studies for the same reasons that it was missed in clinical neuropsychological investigations: the paradigms used in these studies tend to be highly structured and participants are given very specific instructions. Continued use of more 'open-ended' (Shallice and Burgess, 1991) cognitive activation paradigms might help to clarify further the role of OFC in cognition.

Prefrontal activations during encoding reflect the recruitment of specific executive processes that ultimately enhance encoding and retrieval of new episodic memories (Buckner *et al.*, 1999; Wagner, 1999). The specific pattern of prefrontal activation in a given study is probably dependent on the nature of the processes engaged by the memory paradigm and the participants' strategic approach. Our findings indicate that OFC plays a role in mobilizing strategies during a novel and ambiguous verbal learning task. Once initiated, regions in left lateral prefrontal cortex mediate strategic semantic reorganization, which involves processing word meaning, and monitoring and reorganizing items in working memory. These data fit well with an emerging perspective of prefrontal cortex, in which specialized regions support functionally distinct but complementary executive control operations.

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