THIS study was designed to test the various proposed explanations (semantic processing, willed action, production of a spoken response) for the unilateral activation of the left prefrontal cortex noted in PET studies of verbal processing. Twenty subjects underwent ^{15}O-water PET scans while undertaking a lexical task (detecting the letter 'a' in visually presented words) and a semantic task (categorizing nouns into living/non-living). The semantic task resulted in a significant unilateral left dorsolateral prefrontal activation. This finding suggests that the left inferior prefrontal cortex is the anatomical region involved in 'working with meaning', and that the activation does not reflect willed action, is not task-specific and is not attributable to the requirements of a spoken response.

The role of the left prefrontal cortex in verbal processing: semantic processing or willed action?

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Introduction

Positron emission tomography (PET), using ^{15}O-water as a tracer, has provided an important means of investigating the neural correlates of cognitive processes, especially the processing of verbal materials.[1] Most PET studies requiring a meaningful analysis of verbal material have shown a unilateral activation of the left dorsolateral prefrontal cortex (DLPFC).[1-5] Explanations for this finding fall into two broad categories. One, proposed by Petersen and colleagues,[1,4] holds that the DLPFC activity reflects a specific cognitive process, namely the use of the semantic information contained within the stimulus. The other, proposed by Frith and colleagues,[2,3] claims that the activation as observed in verbal processing tasks, is a specific instance of a more general strategy called 'willed action' (a task requires willed action when the response is 'not completely specified by the stimulus', regardless of the nature of the stimulus).[2,3] In addition to these two explanations it has been argued that the left DLPFC activation in verbal processing tasks may be related to the requirement of producing an overt spoken response[5,6] and may be unique to the verb-generation paradigm and not related to semantic processing per se.[6,7]

The present study was designed to compare the different explanations for the DLPFC activation. First, to distinguish between semantic processing[1,4] and willed action explanations,[2,3] we designed the tasks such that they differed in their semantic processing require-

ments, but did not differ along the willed-action dimension. Second, since most previous studies[1-3,5,8] required a spoken response, and it has been suggested that the left DLPFC activation seen in the semantic task may be a response-modality dependent activation,[5-7] we chose to use a hand-held mouse-click as a response mode. Third, to investigate whether the activation was unique to the specific task of verb-generation, and not to more general semantic processing per se,[6,7] the present study used word categorization. This requires semantic processing but is distinct from the verb-generation task. Fourth, in some of the previous studies the perceptual input was not identical across the comparison tasks,[2] or the rate of response generation varied across the two tasks.[3,9] In this study the semantic and the non-semantic tasks were identical in terms of input–output characteristics.

Material and Methods

Twenty right-handed healthy men (age range 21–45 years) participated in the study. The subjects provided informed consent and the experiment was conducted as approved by the Human Subject Use Committee of the University of Toronto. Twelve of these subjects also participated in a memory experiment after the PET scanning, the results of which have been presented elsewhere.[10] Subjects were screened to ensure that none suffered from a major medical, neurological or psychiatric disorder. Each subject undertook three tasks: a

non-verbal baseline task and two tasks with verbal stimuli. In both verbal tasks subjects were presented with words (3–7 letters long) on a computer screen (white lowercase letters on a black screen; 60 cm in front of the eyes, perpendicular to the line of sight). The words were centred on a central fixation point and appeared for 500 ms, one every 1.5 s with 80 in each task. The subjects were instructed to inspect each word and convey a decision via the click of a computer mouse held in their right hand. In the lexical task subjects decided if the word contained the letter 'a'; half of the words contained the letter 'a'. In the semantic task subjects decided if the referent of the word was living or non-living; equal number of words belonged to each category. In the baseline task arrows, instead of words, appeared at the fixation point at the same rate as the verbal tasks. The arrows pointed to the left or right in a random order and the subject had to click the appropriate mouse-button. This condition served as a non-verbal control for the attention and response requirements of the above semantic and lexical tasks and was included to discern those regions which were equally involved in both the lexical and semantic tasks. Each subject undertook one trial of the baseline task and two trials each of the semantic and lexical tasks.

Subjects were scanned using a GEMS-Scanditronix PC-2048 head scanner (15 slices, 6.5 mm apart, inplane FWHM = 5–6 mm, bed position unchanged between scans in an individual) with a thermoplastic custom-fitted face-mask for head stabilization. Scans were done using 40 mCi of ^{15}O-water injected into a left forearm vein through an indwelling catheter. The task began 45 s prior to the 60 s PET data acquisition. The scans were 11 min apart. The images were attenuation-corrected and reconstructed using a Hanning filter. Integrated regional counts were used as an index of regional cerebral blood flow.[1] PET scans were analysed using statistical parametric mapping (SPM)[13] with ratio-transformation instead of the analysis of covariance to account for the variation in global blood flow. The steps involved were: stereotactic reorientation of the images along the bi-commissural (AC–PC) line;[14] plastic transformation of these images using a non-linear resampling technique to correct for anatomical variance across subject;[14] smoothing of the images using a 20 mm filter in the x and y dimensions and a 12 mm filter in the z dimension.[12] Global differences in integrated counts across scans were corrected using a ratio normalization.[13] The scans of different tasks were compared with each other on a pixel by pixel basis, and the statistical significance of any differences was assessed by comparing the magnitude of the difference at a pixel with the error variance at that particular pixel. The resulting map of the t-statistic at each pixel constitutes the SPM.[12] The SPM analysis extended from 20 mm below the bi-commissural line to 40 mm above. To minimize Type I errors the overall significance of a given comparison was assessed by comparing the total

number of pixels where the t-statistic was significant at $p < 0.005$, to the number of such pixels expected by chance, using a χ^2 distribution. The results of the comparison were reported only if the χ^2 statistic was significant at $p < 0.001$. The results are presented with reference to Talairach and Tournoux co-ordinates.[15] However, it should be pointed out that even though foci of activation are cited with millimetric resolution, due to the intersubject averaging and the smoothing filters applied to the images to increase the signal to noise ratio, the activity at any given point represents a weighted average of the activity in a sphere 20 mm in diameter centred around that pixel.

Results

Subjects performed all the tasks with high accuracy: baseline task, 99% correct; lexical tasks, 96.6% correct; semantic task, 94.6% correct ($F_{(2,36)} = 14$; all tasks significantly different at $p \leq 0.05$). Subjects' responses were fastest in the baseline task (mean response time = 526 ms); followed by the lexical task (mean response time = 918 ms); and the semantic task (mean response time = 965 ms) ($F_{(2,36)} = 203$; all tasks significantly different at $p \leq 0.05$).

Subtraction of the images of the lexical task from the semantic task showed a significant difference in the left dorsolateral prefrontal cortex (Fig. 1a; Table 1). This activation coincided mainly with the inferior frontal gyrus extending from Brodmann's areas 47 and 10 at its antero-inferior end to Brodmann's areas 45 and 46 at its postero-superior extremity. Subtraction of the semantic task from the lexical task revealed a significant difference posteriorly in the bilateral precuneus regions and bilateral inferior occipito-temporal region (Fig. 1b; Table 1). The baseline task was included to assess those regions which were activated in both the semantic and the lexical task, and hence would be missed in a direct comparison. Both the semantic as well as the lexical task, compared with the baseline task, activated the bilateral striate and extrastriate occipital cortex, the left inferior temporal cortex, bilateral inferior parietal cortex and the left motor strip. The activations in these regions were similar and therefore did not show any differences in the direct comparison of the semantic and the lexical task.

Discussion

Consistent with previous reports[1,2,5–8] we also found activation in the left dorsolateral prefrontal cortex. Our comparison tasks do not differ in their willed action requirements as in both tasks the response was completely and unambiguously specified by the stimulus. Therefore, the observed activation of the left DLPFC in the semantic task is not readily attributable to willed action.[2] Furthermore, the observed left
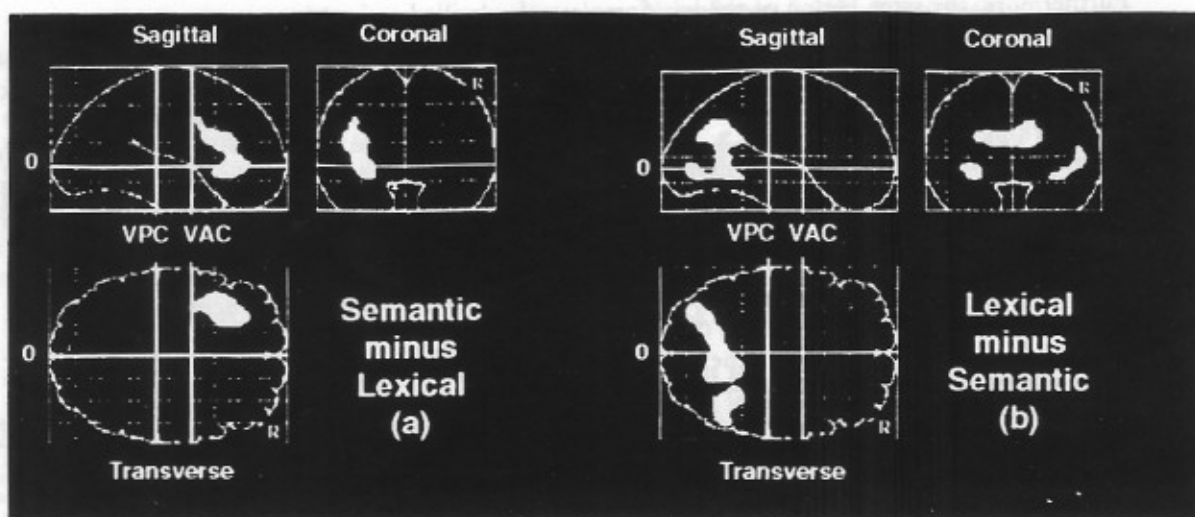
FIG. 1. Brain regions which showed an increased rCBF in the semantic minus lexical (a) and lexical minus semantic task (b) at $p < 0.005$. The results are projected in three two-dimensional planes as seen from above (transverse projection, 'R' signifies right side, VAC is a vertical line through the anterior commissure, VPC is a vertical line through the posterior commissure); as seen from the side (sagittal projection, frontal regions to the right, occipital to the left); and as seen from behind (coronal projection, 'R' signifies right side). The superimposed dotted grid represents Talairach and Tournoux coordinate space. A solid vertical line through the anterior commissure (VAC); a solid vertical line through the posterior commissure (VPC) and a solid line through the anterior commissure and the posterior commissure (marked by a '0' in the margin) is provided for orientation.

DLPFC activation is not specific to the verb-generation paradigm and a spoken response is not a necessary condition for the activation.

How then, should one best understand the observed left DLPFC actions? Our present report, as well as other recent studies which have activated the left DLPFC without any willed action requirements,[16,17] refute a general strategic explanation like willed action. Because categorization judgments in our semantic task required access to and utilization of the meaning of the word in a way that the 'a'-detection task did not, our findings agree with the suggestions of Petersen and colleagues that the left DLPFC is involved in the processing of semantic information. Based on work

with primates, Goldman-Rakic[18] has suggested that a central role of the dorsolateral prefrontal cortex is to manipulate representational knowledge to achieve a certain goal. Different anatomical regions of the prefrontal cortex carry out similar processes, but are specialized to work with different domains of information.[18] In keeping with this view of prefrontal functioning, and consistent with the left lateralization of linguistic function in humans, we think of the left DLPFC as a region of the brain specialized for manipulating semantic representations or 'working with meaning', to reach a goal within an instructional context.

Given such a role, lesions in the activated regions would not affect the comprehension of verbal material but would impair the ability to use verbal information in a goal-related context. Deficits in categorial verbal fluency and symptoms of transcortical motor aphasia seen in patients with lesions of these areas are compatible with such a role.[19,20] More recently, Stuss and colleagues,[21] in a study of memory performance in patients with focal frontal lesion, have demonstrated a specific role for the left dorsolateral frontal regions in the organization of and access to semantic material.

While 'working with meaning' characterizes the role of the left dorsolateral prefrontal cortex in verbal processing, this function can be further fractionated into component cognitive processes reflecting semantic access, manipulation of the representation in context of the instructions and mapping the response on to an output system. At this stage it is unclear if these are the correct component processes, and if so, which processes best reflects the prefrontal contribution.[1]

Table 1 The regions which showed significant difference in the semantic task minus the lexical task, and lexical task minus the semantic task

Region (Brodmann's area)	Representative voxel			Z-score
Semantic minus lexical task				
Left dorsolateral prefrontal cortex	-30	-30	-4	4.2
(45, 46, 47, 10)	-32	-34	4	3.9
	-38	26	12	3.6
	-38	22	20	4.9
Lexical minus semantic task				
Bilateral precuneus region (23, 31)	10	-54	20	3.9
	-20	-68	24	3.3
Bilat. Lat. occipito-temporal region				
(18, 19, 37)	34	-50	-4	3.6
	-30	-78	-4	3.4

For each comparison the activated regions are given an anatomical name and Broadmann's areas based on the Talairach atlas. The Talairach co-ordinates (x, y, z in mm, left is negative) of representative voxels along with the Z-score of the standardized t-statistic at the point are provided for reference. Since the activations were volumetric, the complete extent of the activations is best appreciated with reference to Figure 1.

Furthermore, the same region of the left dorsolateral prefrontal cortex that seems to be involved in verbal processing has also been activated in non-verbal motor tasks suggesting that this region subserves more than just 'working with meaning'.[2]

Other important observations need to be highlighted. First, we observed a small, yet significant activation of the left prefrontal cortex in the lexical task, compared with the lexical baseline, in Brodmann's areas 45 and 46. This activation was restricted to a small region in the postero-superior extent of the activation observed in the semantic task over the baseline task. A similar activation has also been observed by Petersen[22] in silent viewing of words when there were no explicit instructions to utilize the meaning of the word. It is speculated that this activation represents an involuntary engagement of the prefrontal cortex.[22] Second, when compared with the semantic task, the lexical task shows a significant increase in the bilateral precuneus regions and bilaterally in the inferior lateral occipito-temporal region. The precuneus region has been implicated in spatial imagery[23] and the infero-lateral occipito-temporal region is considered important in object recognition.[24] The observed increase in these regions in the lexical task (compared with the semantic task) may be related to the search for letter 'a' undertaken in the lexical task. Third, there were robust decreases in the semantic task, compared with the baseline task, bilaterally in the posterior aspects of the superior and middle temporal gyrus. This is similar to the decreases observed by other groups.[21] The significance and correct interpretation of these decreases is not clear. It has been suggested that these decreases may reflect a shift in attention away from the unattended modalities.[21]

Conclusion

The left DLPFC activation in tasks requiring meaningful analysis of words is a reliable observation. We have shown that a general strategic explanation like 'willed action' is not necessary to explain these activations. The left DLPFC activation can be observed using paradigms other than verb-generation and the activations are not dependent on the response modality. In keeping with the overall view of the prefrontal cortex as involved in working with representational knowledge, we propose that the left dorsolateral region of the prefrontal cortex is a region involved in 'working with meaning' of a stimulus to reach a goal in an instructional context.

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