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The Influence of Explicit Instructions and Stimulus Material on Lateral Frontal Responses to an Encoding Task

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In this functional magnetic resonance imaging study, we explored the effects of both stimulus material and encoding task demands on activation in lateral prefrontal cortex (PFC). Two factors were manipulated: material type and task instructions. Subjects encoded words or abstract figures (factor 1: stimulus type) and were required to make either a meaning-based or a form-based (letter or shape) decision about each stimulus (factor 2: task instructions). Abstract figures engendered significantly higher levels of right PFC activity than did words. This effect was seen for meaning-based and form-based processing tasks and was significantly greater for the former. We did not observe a differential response of left lateral PFC to verbal and pictorial material. A double dissociation, however, was found within left PFC. A ventrolateral region (within left inferior frontal gyrus) showed the highest levels of activity when words were processed according to their meaning whereas activity in a more dorsolateral region (within left middle frontal gyrus) was greatest when words were processed according to their form (constituent letters). We have therefore observed a main effect of material type in producing lateralized activation of frontal lobes, although the strength of this effect is sensitive to the nature of the task that subjects are asked to perform. Left-side lateral PFC activity is also sensitive to task instructions but this effect was specific to verbal material. The complex patterns of frontal effect counsel against any simple dichotomy of frontal function at the level of either material or task type.

INTRODUCTION

Functional neuroimaging studies have provided consistent evidence for the involvement of lateral prefrontal cortex (PFC) in episodic memory encoding and retrieval (Fletcher and Henson, 2001). Early observations of a predominance of left PFC activation at encoding and right PFC activation at retrieval led to the Hemispheric Encoding Retrieval Asymmetry (HERA) model (Tulving *et al.*, 1994), which has been influential in framing functional neuroimaging studies of memory. More recent findings, however, have cast doubt upon whether the left–right dissociation in prefrontal function truly reflects an encoding–retrieval distinction. Nolde *et al.* have claimed that left PFC activation is crucial to "reflective processing" ("processes that . . . sustain, manipulate, revive and evaluate") and that a retrieval task that places demands on such processing will invoke left PFC activation (Nolde *et al.*, 1997). Others have suggested that the lateralization is determined by the nature of the presented material, with left-side activation reflecting verbal and right-side nonverbal material (Kelley *et al.*, 1998; Wagner *et al.*, 1998a; Kirchoff *et al.*, 2000). Such studies have been guided by the idea that right and left PFC subserve different processes, which are emphasized to differing extents with different materials. Thus, this view is distinct from the idea that left PFC deals with verbal and right PFC with nonverbal material per se. Views expressed by the authors of all of these studies (Nolde *et al.*, 1997; Kelley *et al.*, 1998; Wagner *et al.*, 1998a; Kirchoff *et al.*, 2000) are actually compatible with the original HERA formulation and Tulving *et al.*'s original suggestion included the caveat that left PFC activation subserved "the encoding of novel information into episodic memory, *at least for verbal or verbalisable materials*".[2] The current study too was set up with this position in mind: that the patterns of frontal lateralization depend upon both the material studied and the processes engaged.

Questions concerning the HERA model may be placed within a broader debate regarding the nature of

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[2] Our italics.

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functional parcellation in PFC. This debate has mainly addressed the question of whether PFC may be functionally subdivided in a *material-specific* (Goldman-Rakic 1987, 1998) or a *process-specific* (Petrides 1994, 1995) manner. The former view is that PFC supports working memory function and that subdivisions reflect the action of this function on different types of material. For example, VLPFC is concerned with object form and DLPFC with object location. This contrasts with the view that the difference between VLPFC and DLPFC lies not in the material maintained, but in the type of processes operating on that material, with the former important to maintenance of material (irrespective of type) in working memory and the latter to higher level processes such as manipulation and monitoring of studied material. While the nature of functional subdivisions within lateral PFC has been most fully explored with regard to object versus spatial processing in nonhuman primates, functional neuroimaging offers a way of establishing its relevance to human prefrontal function. Owen suggests that existing functional imaging studies of human working memory have produced little evidence in favor of the material-specific view (Owen, 1997). However, such reviews are by no means conclusive. One problem stems from the fact that experimental manipulations of the material type in humans may not be directly comparable to those in monkeys. It is possible that human subjects attempt to verbally recode nonverbal material, thus obfuscating differences associated with material type. Alternatively, it is possible that human subjects may attempt to chunk material in the most efficient way possible. Thus, a series of pieces of spatial information could, feasibly, be "objectified" into a shape. If this is so, it is no simple matter to interpret experimental manipulations in humans without exploring how task instructions affect the ways in which material is treated and vice versa.

The aim of the current study was to evaluate a further aspect of functional parcellation in human PFC. We were interested in whether differences occurring in brain activation in response to verbal and nonverbal material are dependent upon the nature of the task that subjects are required to perform. We therefore explored the influences of stimulus material and of task type (and of the interaction between them) on prefrontal activation using functional magnetic resonance imaging (fMRI). Stimulus type was varied (words versus abstract line drawings) together with the nature of the task that subjects were required to perform (subjects were required to think about either the connotations of the word/picture—"Does it look safe or dangerous?"—or their form). Abstract figures were used in order to minimize verbal recoding. Of course, the decision as to whether an abstract figure looks "safe" or "dangerous" is necessarily based upon highly subjective considerations. Criteria for the decision may include factors such as whether a picture comprised sharp or heavy-looking objects or objects that looked as though they might overbalance. In the setting of the current experiment, however, the final decision was unimportant. Manipulating the task demands for both figures and words enabled us to characterize the main effect of stimulus material, irrespective of task instructions, the effect of task instructions, irrespective of material type, and the interaction between these factors.

Note. The terms VLPFC and DLPFC are generally taken to refer to lateral PFC regions below the inferior frontal sulcus and above the inferior frontal sulcus, respectively. For clarity, we shall refer to activations in this study in terms of the frontal gyrus in which they are located.

MATERIAL AND METHODS

Twelve healthy volunteers (average age 28 years (range 20–36 years), 8 males) were recruited by advertisement. All were free from neurological or psychiatric illness and showed normal structural MRI scans. The local ethics committee approved the study and volunteers gave informed consent to the procedure. Due to subsequently discovered technical problems with stimulus presentation in 1 of the male subjects, data from this man were not usable. Data from 11 subjects were therefore used in the final analysis.

Behavioral Task

Eighty words and 80 line drawings were presented. Words were matched within a specified range for concreteness, familiarity, and frequency of usage. Abstract line drawings were created by two of the authors (PCF and NP-G) according to the criterion that they were not readily verbalizable. While this was verified, as far as possible, with pilot testing, we cannot rule out the possibility that some of the pictures at least would provoke subjects to verbally label them. We believe nevertheless that the results that follow are interpretable even in the face of this possibility. Examples of the material are shown in Fig. 1 together with a diagrammatic representation of the study design. Scanning was carried out in two sessions each consisting of eight 30-s blocks of study material alternating with eight 30-s blocks of fixation during which subjects were advised to relax in preparation for the next study block. The second session followed the first after approximately a 5-min gap, introduced for technical reasons. During each block, subjects were presented, visually, with 10 words or 10 pictures (each stimulus was visible for 3 s and was replaced, immediately, by the next stimulus). The presentation program used was MEL (MEL Professional, Version 2.0, Psychology Software Tools, Inc., Pittsburgh, PA) and a Polaroid Polarview

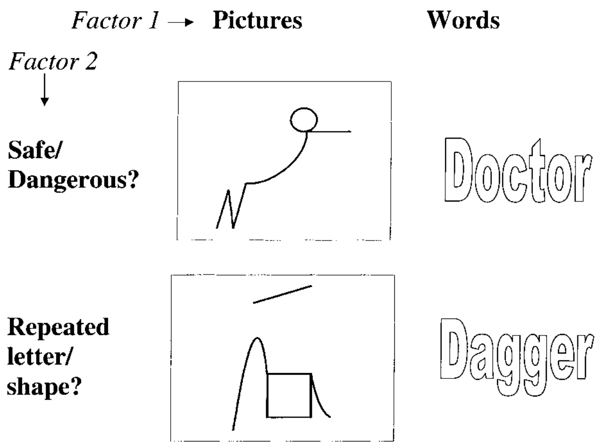


FIG. 1. Diagrammatic representation of experimental factors.

222 projector was used to deliver stimuli to a screen positioned comfortably in the subject's field of view.

Prior to scanning, subjects were shown sample stimuli and given instructions about the nature of the two tasks that they would be required to perform. They were also informed that recognition memory would be tested after scanning. In half of the blocks subjects were required to judge whether items seemed safe or dangerous to them. This will, henceforth, be referred to as the *meaning-based* processing condition. In the other half of the blocks, subjects were required to judge whether there was repetition of a letter (in the case of words) or of a shape (in the case of pictures). This will be referred to as the *form-based* processing condition. Unknown to the subjects, 50% of words and pictures had a repeated letter or shape. Additionally, the number of safe and dangerous words/pictures (as judged by two of the experimenters, PCF and N P-G) was balanced equally within blocks although, of course, the decision as to whether a given stimulus appeared dangerous or safe was subjective. Having been given these instructions and having established, prior to scanning, how to indicate their decision (safe/dangerous or repetition/no repetition) for each stimulus on a two-button keypad, scanning began. Each 30-s block of stimuli was preceded by a 30-s block during which subjects fixated on a central cross. This block had two purposes. First, it provided a window in which the instructions (repetition? or safe?) could be given in advance of the next block. These instructions were given for the last 6 s of each fixation block. Second, we hoped that, in providing a resting period, it would minimize the extent to which there would be carryover effects in which subjects tended automatically to process stimuli in one block according to instructions that had been given for the previous block. In view of the fact that this block is cognitively underspecified (comprising rest, fixation, and instructions) we did not intend it to be used as part of the subsequent analysis since we would be unhappy in trying to interpret regional activation differences among this condition and the experimental conditions.

There were thus four conditions: meaning-based processing of words, form-based processing of words, meaning-based processing of pictures, and form-based processing of pictures. Subjects experienced four blocks of each condition (two in each session) with the order of the four conditions reversed from the first to the second half of each session and the order of these was counterbalanced across subjects. Decisions and reaction times were recorded. In order to avoid systematic biases across conditions, the type of decision made on any given stimulus alternated from subject to subject.

After the scanning process, subjects underwent recognition memory tests in a quiet room. All items were presented on paper, intermixed with 40 unstudied items. Subjects were required to indicate whether they had seen an item before and the degree of confidence with which they made their decision ("definitely seen," "maybe seen," "maybe not seen," and "definitely not seen").

Scanning

Images were acquired using a Siemens Vision 1.5-T whole-body scanner with echo planar imaging (EPI) capability. A gradient echo EPI sequence was used (TE = 66 ms, TR = 5 s, flip angle = 90°). Thirty slices (each of 4-mm thickness, interslice gap 0.4 mm, FOV 200 mm, in-plane resolution 3.125 × 3.125 mm) were imaged. Using a midsagittal scout image, slices were oriented in the plane of the anterior–posterior commisure line. Additional high-resolution anatomical images were acquired for all subjects using the 3D magnetization-prepared, rapid acquisition gradient echo sequence with the following parameters: TE = 4.4 ms, TR = 11.4 ms, flip angle = 15°, inversion time = 300 ms, matrix = 200 × 256, FOV = 200 mm, 128 sagittal slices, slice thickness = 1.33 mm.

For each subject a total of 196 scans were acquired over the two sessions. The first 6 scans from each session were discarded to avoid $T2$ equilibration effects.

fMRI Analysis

Analysis was carried out with Statistical Parametric Mapping (Friston *et al.*, 1995a,b), version SPM99b (Wellcome Department of Cognitive Neurology, London, UK). Within each session, images were aligned to the first image acquired and then each was aligned to the first image of the first session. Resliced images were interpolated using a Sinc function. The mean EPI image was spatially normalized to an EPI template (Cocosco *et al.*, 1997) in standard space using nonlinear basis functions. Spatial smoothing was carried out with a Gaussian filter of 8 mm.

Blocks of stimuli were modeled using a boxcar function incorporating a delay appropriate to the hemody-

TABLE 1

Behavioral Data

Task	Reaction time (S.D.)	Percentage hit rate (SD)	Proportion confidently recognized (SD)
Meaning-based processing of pictures	1342 (456)	75 (20)	0.88 (0.1)
Meaning-based processing of words	1275 (410)	91 (12)	0.95 (0.1)
Form-based processing of pictures	1267 (452)	72 (25)	0.86 (0.2)
Form-based processing of words	1204 (433)	53 (17)	0.8 (0.3)

namic response. For each subject, the magnitude of effect (change in BOLD signal) for each condition, relative to the baseline condition, was computed together with residual variance. These parameter estimates were then compared across conditions to produced "contrast images" expressing contrasts of interest (main effects of material, main effects of processing task, and the interaction between the two). Each contrast image for each subject was taken to a second level in which group effects were explored using a simple *t* test, treating intersubject variability as a random effect. This final analysis produced group images showing the following effects:

1. simple main effects of stimulus material and processing requirements were obtained by comparing parameter estimates for pictures versus words (irrespective of processing) and meaning- versus form-based processing (irrespective of material), respectively;
2. the interaction of material type with the task instructions for that block.

Our a priori interest lay solely in lateral PFC. For this reason, the level of type I error control was set at $P < 0.001$ uncorrected for multiple comparisons. For all other regions, a corrected level of significance ($P < 0.05$) was set. These thresholds define the regions upon which we will focus our discussion. However, because of the nature of such a functional neuroimaging study, which must be considered, at present, a partly exploratory enterprise, we believe that results should also be reported that do not achieve these levels of significance. Thus, our tables include regions that are not part of lateral PFC and do not reach the predefined threshold for significance. We report this information but refrain from discussing or drawing conclusions about it.

RESULTS

Behavioral Results

Reaction time data and postscanning retrieval levels for each of the tasks are presented in Table 1. Repeated-measures ANOVA was carried out on reaction time data and showed no significant effect of material ($F(1,10) = 1.64$, $P = 0.23$), process ($F(1,10) = 2.9$, $P = 0.12$), or interaction between them ($F(1,10) = 0.49$, $P = 0.5$).

Postscan recognition memory performance is also shown in Table 1. No main effect of material type was seen ($F(1,10) = 0.01$, $P = 0.95$), but task instructions produced a significant effect ($F(1,10) = 61.2$, $P < 0.001$). The process-by-material interaction was significant ($F(1,10) = 49.4$, $P < 0.001$). In brief, maximal levels of postscan recognition occurred for words that had been encoded according to their meaning and minimal levels for words encoded according to their form. Encoding of pictures produced intermediate levels of subsequent recognition. The proportion of hits that were made with complete confidence following each condition is also shown in Table 1 and mirrored the pattern of overall number of hits.

Imaging results

1. Main Effects of Stimulus Material

a. Regions showing greater activation for words than pictures. This analysis was carried out by contrasting the combination of the form-based and meaning-based encoding of words with the same combination for abstract figures. The sole region within PFC showing this main effect was left medial PFC. No lateral prefrontal areas were identified by this contrast. See Table 2a.

b. Regions showing greater activation for pictures than words. Right MFG and IFG showed relatively greater activity in the combined abstract figures condition; see Table 2b.

TABLE 2

Region	Coordinates {88}	Z score
a. Words greater than pictures		
Ventral anteromedial PFC (left)	−10, 54, −8	4.4
Dorsal anteromedial PFC (left)	−8, 46, 44	4.1
	−8, 54, 32	4.1
White matter (left)	−22, 0, 30	4.8
Inferior occipital gyrus (left)	−30, −86, −4	4.2
Inferior occipital gyrus (right)	18, −88, −2	3.7
Middle temporal gyrus (left)	−50, −20, −14	4.2
Superior temporal gyrus (left)	−64, −32, 8	3.9
b. Pictures greater than words		
Inferior/middle frontal gyrus (right)	46, 16, 16	4.3
	56, 24, 24	3.9
Inferior frontal gyrus (right)	52, 36, 10	4.1
	44, 36, 6	3.6
Hippocampal/lingual gyrus (left and right)	−22, −50, −6	5
	28, −58, −6	3.7
Superior lobe (left and right)	22, −62, 50	4.6
	−22, −62, 62	4.2

TABLE 3

Region	Coordinates	Z score
a. Meaning-based greater than form-based processing		
Dorsal anteromedial PFC (left)	−4, 54, 42	4.1
b. Form-based greater than meaning-based		
Middle frontal gyrus (right)	42, 36, 28	3.7
Lingual gyrus (right)	26, −52, 2	3.7

2. Main Effects of Task Instructions

a. Regions showing greater activity when subjects are instructed to process items according to "meaning." The combined words plus figures (meaning-based encoding) was contrasted with combined words plus figures (form-based encoding) conditions (see Table 3a). No lateral PFC region was identified by this contrast.

b. Regions showing greater activity when subjects are instructed to process items according to "form." This was the reverse of comparison 2a. The sole lateral prefrontal effect lay in right MFG (see Table 3b).

3. Interactions between Task Instructions and Material Type

a. Words (meaning versus form) versus abstract figures (meaning versus form). To evaluate this interaction, parameter estimates for meaning-based word processing, form-based word processing, meaning-based figure processing, and form-based figure processing were weighted as 1, −1, −1, and 1, respectively. Left IFG was the sole lateral prefrontal region showing this interaction (see Table 4a and Figs. 2a, 3, and 4).

b. Words (form versus meaning) versus abstract figures (form versus meaning). To explore this interaction, parameter estimates for meaning-based word processing, form-based word processing, meaning-based figure processing, and form-based figure processing were weighted −1, 1, 1, and −1, respectively. This contrast identified right and left MFG (see Table 4b and Figs. 2b, 3, and 4).

The results from such interaction analyses are necessarily ambiguous. We have therefore plotted, for each of the identified areas of left and right lateral PFC, the parameter estimates. These are plotted relative to the condition showing the lowest level of activity (see Figs. 3 and 4). The plots provide a qualitative description of the relative levels of activity across all four conditions for each of the identified brain regions. However, since we are ultimately interested in direct tests of differences between the conditions, plots are shown (Figs. 5 and 6) of direct comparisons of parameter estimates between words and pictures (for each task type) and between meaning and form tasks (for each material type). The plots shown in Figs. 5 and 6 include the error bars appropriate to the contrasts that generated them.

Summary of Task and Modality Effects in PFC

a. Left PFC (see Fig. 3). Left IFG is the site of an interaction between material and task. The nature of this interaction is shown in Fig. 5. There is a meaning

TABLE 4

Interaction

Region	Coordinates	Z score
a. Words$_{(meaning\ vs\ form)}$ vs pictures$_{(meaning\ vs\ form)}$		
Inferior frontal gyrus (left)	−52, 28, −6	3.2
Inferior parietal lobe (left)	−48, −62, 34	4.3
Middle temporal gyrus (left)	−60, −8, −10	3.8
Superior temporal gyrus (left)	−62, −16, 2	3.4
	−56, −32, 16	3.4
Precuneus/posterior cingulate gyrus (left)	−10, −52, 32	3.6
b. Words$_{(form\ vs\ meanning)}$ vs pictures$_{(form\ vs\ meaning)}$		
Middle frontal gyrus (left)	−40, 28, 28	3.9
Middle frontal gyrus (right)	42, 30, 32	3.8
Inferior frontal gyrus (left)	−40, 6, 30	3.3
White matter (depth of right inferior frontal sulcus?)	30, 10, 28	3.9
Precuneus (left)	−28, −74, 36	3.7
	−8, −62, 58	3.3
Precuneus (right)	20, −80, 26	3.5
Inferior parietal lobe (left)	−38, −40, 36	3.2
Inferior parietal lobe (right)	32, −50, 44	3.6
White matter	28, −18, 26	3.7

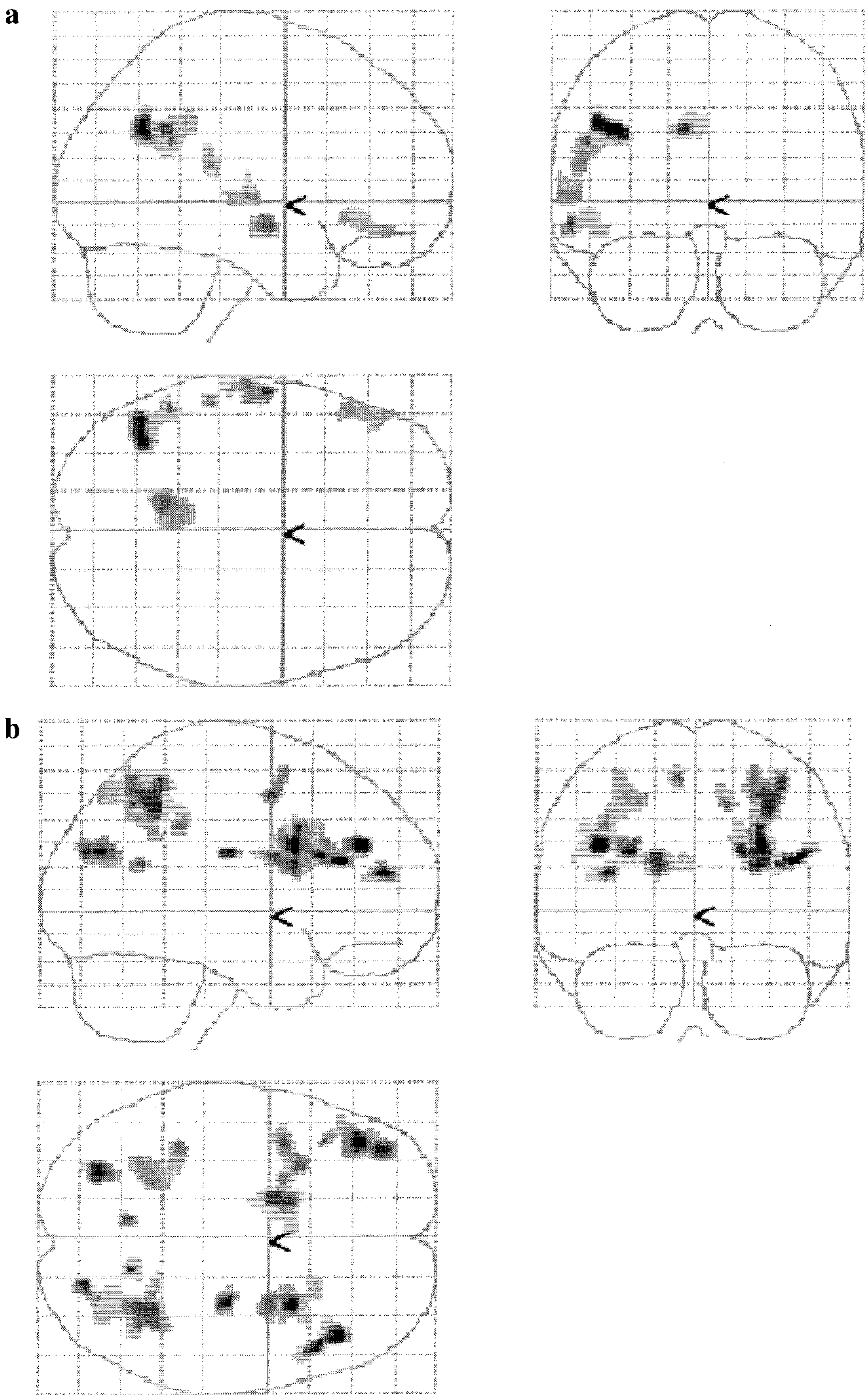
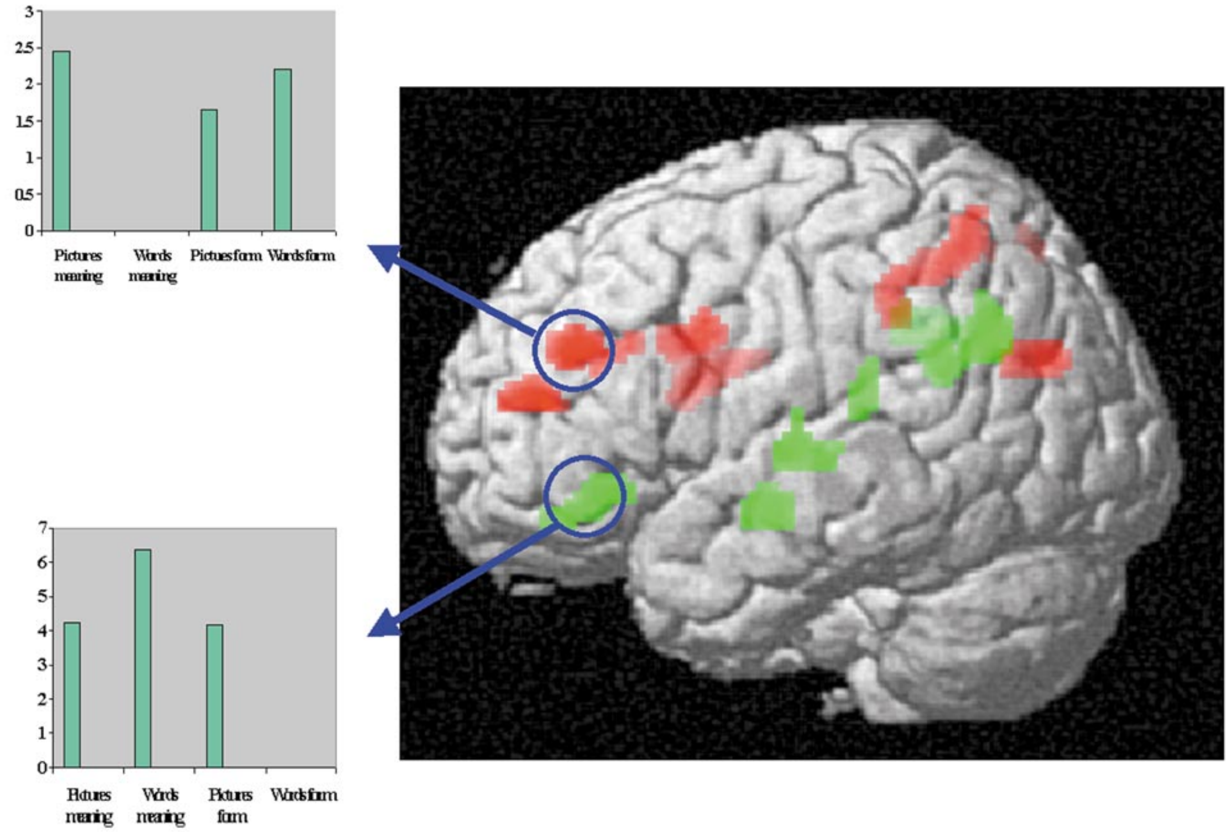


FIG. 2. SPM showing task-by-material interactions. Orthogonal "glass brain" views are shown sagitally from the right (upper left of each figure), coronally from behind (right), and transversely from above (lower left). These images were thresholded at $P < 0.001$. a. [(Words meaning vs words form) vs (pictures meaning vs pictures form)]. b. [(Words form vs words meaning) vs (pictures form vs pictures meaning)].

versus form effect present for words but not pictures. Left MFG shows the opposite pattern, that is a form vs meaning effect for words but not pictures.

b. Right PFC (see Fig. 4). In both right MFG and IFG greater levels of activity are observed in association with abstract figures (see Fig. 6). As can be seen, in



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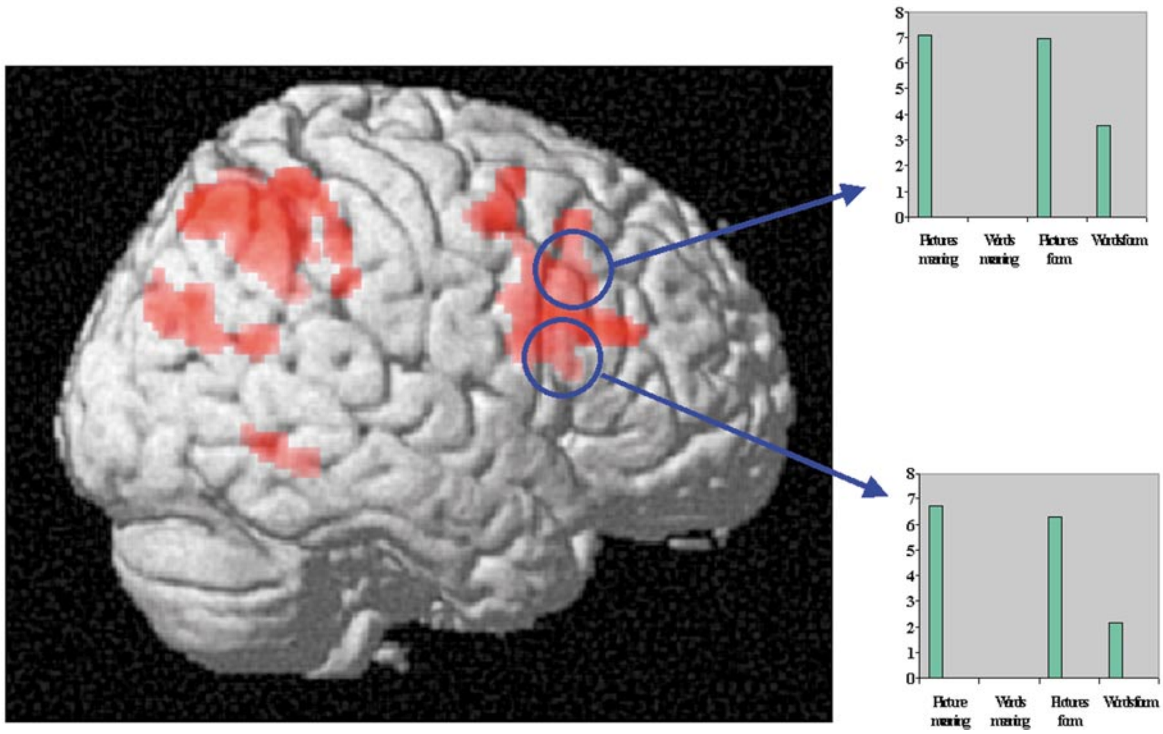

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FIG. 3. Cortical rendering of left-side task-by-material interactions. Images were thresholded at $P < 0.001$ and rendered onto the surface of a single structural MRI scan spatially normalized into a standard stereotactic space {88}. Activations (thresholded at $P < 0.001$) associated with [(words meaning vs words form) vs (pictures meaning vs pictures form)] are shown in green and those associated with [(words form vs words meaning) vs (pictures form vs pictures meaning)] are shown in red. The graphs show plots of parameter estimates for the dorsolateral and ventrolateral regions of PFC identified by the two interactions. These are intended to show relative levels of signal across the four

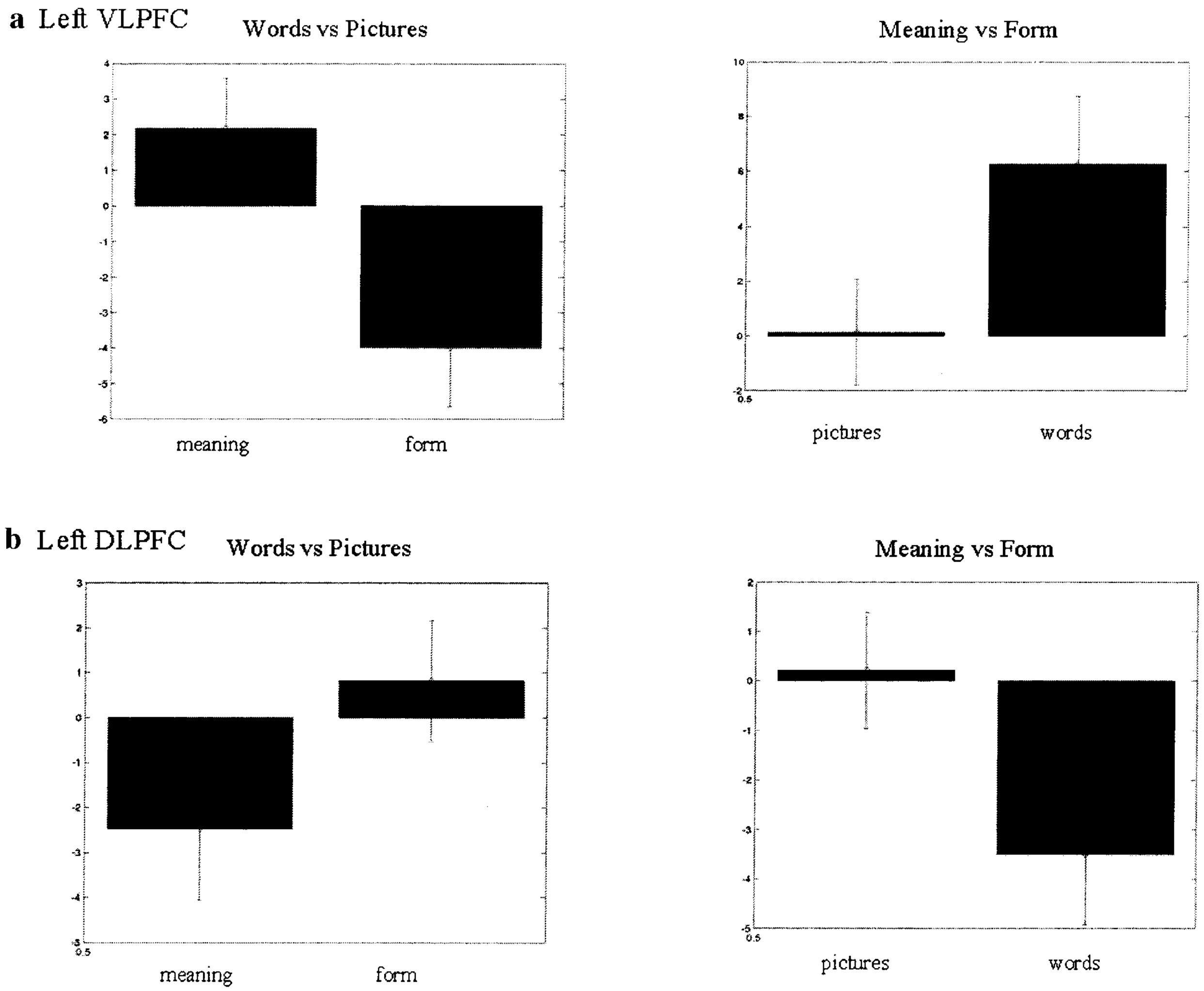

FIG. 5. (a) Parameter estimates from left IFG. Note that these data come from those presented in the graphs in Figs. 3 and 4. The same data are presented as shown in Fig. 3 but these plots show the results of direct subtractions. Thus, the zero mark indicates no difference between the two conditions compared and a negative-going bar indicates that there is relatively greater activity in the condition being subtracted. The left side of the figure shows the words minus pictures for meaning and form tasks (as labeled). Error bars relevant to each of the separate contrasts are shown. (b) Parameter estimates from left MFG. Arranged as above.

both regions, this effect is weaker in the case of form-based than meaning-based processing. This attenuation was statistically significant in MFG but not in IFG although a trend was noted ($P < 0.01$, uncorrected) in the latter.

DISCUSSION

Our experiment has produced three noteworthy findings. First, lateralization of prefrontal activation is material-dependent, with right PFC showing signifi-

conditions. In each case, the condition associated with the lowest level has been deemed as a “baseline” and its value set to zero. Parameter estimates associated with the other conditions are plotted relative to this baseline. These graphs are intended only to orient the reader with respect to relative levels of activity across the four experimental conditions. Error bars would be inappropriate here since the statistical tests used involved a direct comparison between conditions. We have provided graphs of the contrasts between conditions, together with appropriate error bars, in Figs. 5 and 6.

FIG. 4. Cortical rendering of right-side task by material interactions. Images prepared as described in Fig. 3. Activations associated with the [(words form vs words meaning) vs (pictures form vs pictures meaning)] interaction are shown. No activations in the right hemisphere were identified by the opposite contrast. The graphs (prepared as in Fig. 3) show plots from dorsolateral and ventrolateral foci.

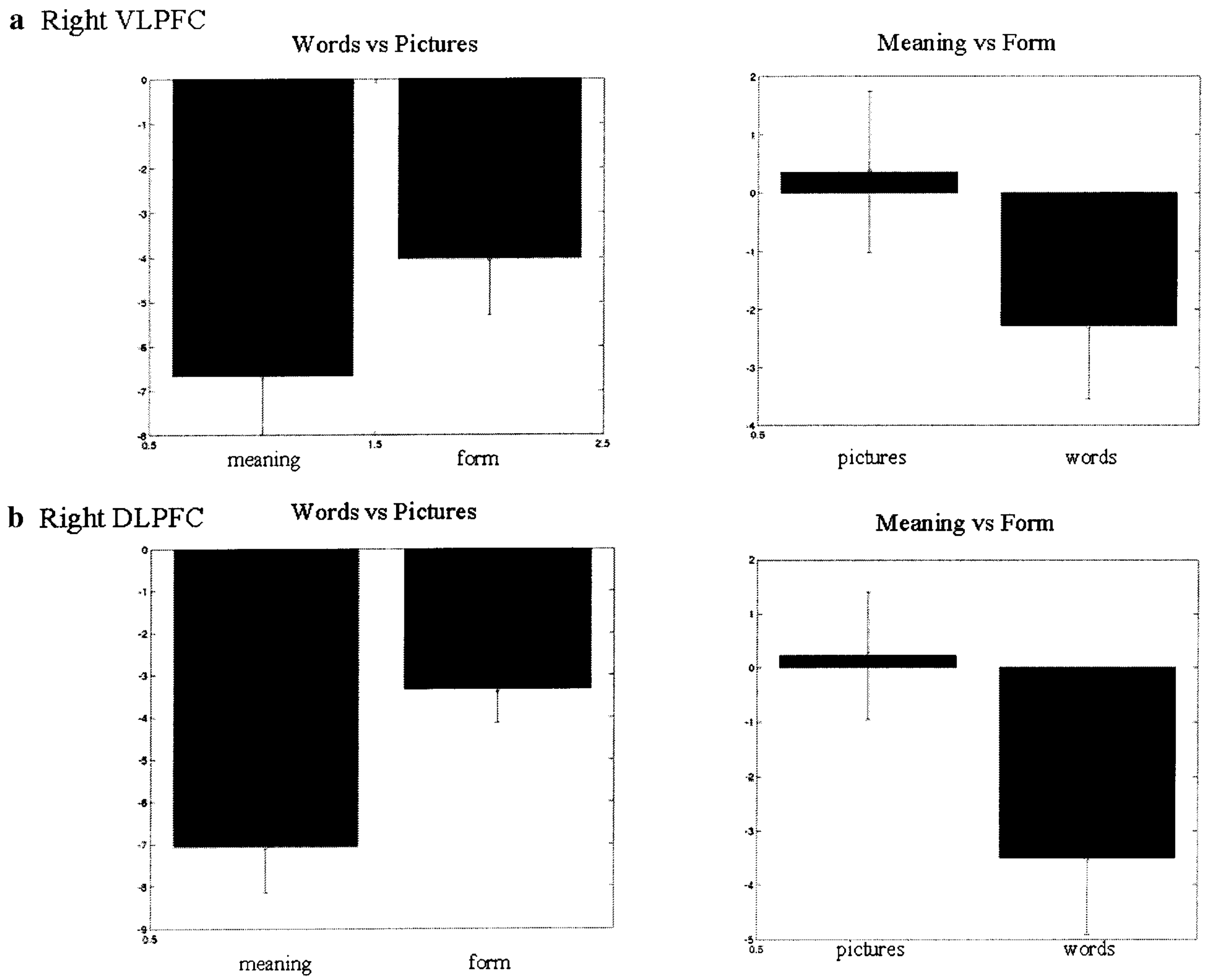

FIG. 6. (a) Parameter estimates from right IFG arranged as for Fig. 5. The same data are presented as shown in Fig. 4 but these plots show the results of direct subtractions. (b) Parameter estimates from right MFG arranged as for Fig. 5.

cantly greater levels of activity for abstract figures than words. Second, right PFC is the site of an interaction between the two experimental factors. While it is differentially sensitive to abstract figures, this effect is significantly attenuated when words are processed in a way that emphasizes the constituent letters rather than the overall meaning. Third, although left PFC shows no main effect of material, a double dissociation between ventrolateral (IFG) and dorsolateral (MFG) regions is seen: these regions are differentially sensitive to processing demands for words only. We consider the possible functional significance of these observations below.

Material-Related Lateralization of PFC Function

For both meaning-based and form-based encoding, activation in right MFG and right IFG is significantly greater for pictures than words. An interaction, however, is seen in right MFG: the picture versus word effect is significantly attenuated when subjects are instructed to process items according to form. This attenuation was also noted as a trend ($P < 0.01$, uncorrected) in right IFG. As seen in Figs. 4 and 6, the two right frontal foci probably form part of the same overall region of activation. Moreover, they show very similar patterns of activity. We do not, therefore, argue that we have here observed any sign of dissociation between patterns of activation in right MFG and IFG.

The strong lateralization of the observed word–picture difference is consistent with other recent fMRI studies of encoding (Kelley *et al.*, 1998; Wagner *et al.*, 1998a; Kirchoff *et al.*, 2000) and with working memory studies suggesting a predominance of left PFC activation for verbal material (Paulesu *et al.*, 1993; Awh and Jonides, 1996; Smith and Jonides, 1997) and right PFC for nonverbal material (Smith and Jonides, 1994, 1995; Baker *et al.*, 1996; Smith *et al.*, 1996). This series of findings suggests that Tulving *et al.* were wise to be cautious in framing their original formulation of the HERA model as relevant to verbal but not necessarily nonverbal material (Tulving *et al.*, 1994). The existing evidence strongly favors material specificity as a major basis for memory-related dissociations between left and right PFC. However, it is unlikely to be material per se since the encoding instructions had a clear effect on the degree to which words were associated with right PFC activation: when a word is treated according to its form (that is, as an array of letters rather than a single meaningful entity), right MFG (and possibly, IFG) activity is greater than when it is treated as a meaningful word. This observation is in keeping with that of Kelley *et al.*, who explored frontal activity during intentional encoding and passive viewing, establishing that the lateralization produced by material type was greatly attenuated in the latter condition (Kelley *et al.*, 1998). The view that has emerged from these and other data (Haxby *et al.*, 1996; Wagner *et al.*, 1998a) is that in a task emphasising visuospatial, "icon-like" representations of material, right PFC is emphasized, whereas when verbal representation is emphasized, left PFC activation predominates. It might be argued that the form-based processing of words, in the current experiments, is highly verbal insofar as subjects must use a verbal maintenance strategy to hold a given letter on line while searching a word for a match. However, in addition, this may be treated as a highly visual task with subjects holding a visual representation of the letter and exploring the word for a matching visual representation. Such processing is minimized when subjects are processing words according to meaning.

Any consideration of these, and other, patterns of findings with respect to frontal lateralization should, however, take into account the possibility that, merely because activation in right PFC is significantly stronger for pictorial material, we cannot conclude that it does not occur for verbal material. More specifically, we are not suggesting that right PFC is inactive when words are encoded, even when those words are processed according to their meaning. Rather, this was the experimental condition under which measured activity was lowest. The lateralization that we have seen here, like all observations in functional neuroimaging, is relative rather than absolute. It indicates a predominance of right-side activation for pictures but not, necessarily, an absence for words. Kirchoff *et al.* have provided trial-specific fMRI data suggesting, for example, that right IFG is sensitive to words as well as pictures although activation is significantly greater in the latter (Kirchoff *et al.*, 2000).

Double Dissociation of Activation within Left Lateral PFC

The meaning versus form effect for words, observed in left IFG, is consistent with previous functional imaging observations (Petersen *et al.*, 1988; Frith *et al.*, 1991; Kapur *et al.*, 1994; Raichle *et al.*, 1994) as is the observation of higher levels of postscan recognition following conditions associated with higher levels of activation in IFG (Wagner *et al.*, 1998b; Otten *et al.*, 2001). Recent findings by Otten *et al.* suggest that the left IFG region, which is sensitive to a semantic decision task, overlaps the region predicting subsequent successful retrieval (Otten *et al.*, 2001). It has been suggested that left IFG activation reflects retrieval (Kapur *et al.*, 1994; Tulving *et al.*, 1994) or maintenance (Gabrieli *et al.*, 1998) of semantic material or the selection processes (Thompson-Schill *et al.*, 1997; Thompson-Schill *et al.*, 1999; Fletcher *et al.*, 2000) that are intrinsic to semantic tasks. Passingham *et al.* described a role for IFG in the representation of associations among cues, responses, and outcomes (Passingham *et al.*, 2000).

In a review of the functional imaging studies on working memory and long-term memory encoding and retrieval, Fletcher and Henson suggest that a key feature linking tasks that are associated with IFG activation lies in the requirement to update the contents of working memory, in some cases from semantic memory, a suggestion that fits with the observations of left IFG activity made here and elsewhere. This distinguishes its role from that of MFG, which is sensitive to the requirement to monitor and manipulate the contents of working memory (Fletcher and Henson, 2001). This position is based upon that of Petrides described earlier (Petrides, 1994, 1995, 1998). Moreover, it is compatible with the other aspect of our left PFC dissociation. In our form-based task, the search for repetitions required subjects to select and reselect letters or shapes as temporary targets in order to look for a match within the rest of the word or figure. Such a process would presumably necessitate a constant monitoring and manipulation of the contents of working memory and, on the basis of these views, would invoke left MFG activation. There are a number of studies that have shown tasks emphasizing manipulation of the contents of working memory to be associated with dorsolateral PFC activation (Smith *et al.*, 1996; D'Esposito *et al.*, 1999; Jahanshahi *et al.*, 2000).

The observed dissociation in patterns of activation across left IFG and MFG, for the verbal material, is therefore noteworthy and plausible in light of existing imaging findings and theoretical positions. In distinction, there was no evidence of either VLPFC or DLPFC sensitivity to task type for the pictorial material. However, we are reluctant to interpret this lack of effect because postscan recognition scores indicate the absence of a "levels of processing" effect for pictures (an absence that is consistent with previous behavioral and imaging findings (Baddeley, 1978; Grady *et al.*, 1998)). This must alert us to the likelihood that form- and meaning-based task instructions had no effect on the ways in which subjects actually processed the pictures. This lack of imaging effect could therefore be considered the physiological reflection of the lack of a behavioral (levels of processing) effect. As Fig. 3 shows, the level of activity associated with left IFG reflects the levels of subsequent recognition (for both words and pictures) seen in Table 1. For both left IFG and MFG, activity associated with pictures is not at a "baseline" level (see Figs. 3 and 5). This, and other studies (Kelley *et al.*, 1998; Kirchoff *et al.*, 2000), suggest that it is wrong, therefore, to state that left PFC regions are insensitive to picture processing. Rather, they appear to be insensitive to task instructions (with this insensitivity reflected in the absence of the levels of processing effect).

At first sight, these findings appear to contradict to a previous PET study (Vandenberghe *et al.*, 1996) in which left VLPFC showed an effect of meaning- versus form-based processing for both words and pictures and was therefore suggested to form part of a "common semantic system." However, in Vandenberghe *et al.*'s study, nameable rather than abstract line drawings were used and this may explain the differential effects of meaning- versus form-based processing. In another comparable PET study, Grady *et al.* explored the effects of three different encoding processes upon brain activity associated with both words and line drawings of familiar objects (Grady *et al.*, 1998). Under two conditions, incidental encoding was explored at deep (meaning-based) and shallow (form-based) levels. Under a third condition, subjects were instructed that subsequent memory would be tested and that they should attempt to memorize the words. As with our study, they found that the encoding task had an effect on postscan recognition for words but not pictures. In a dorsal focus of left lateral PFC, they observed a complex interaction, compatible with the effect seen in the current study. The combination of form-based and intentional (but unspecified) encoding versus semantically based encoding was associated with activation of MFG for words compared to pictures. The locus of this activation (x, y, z = −32, −32, 36) was close to that seen in the comparable contrast in our study (−40, 28, 28). In this study, there was another focus of activation near this region (−40, 16, 28) that showed a word-specific increase for intentional learning versus nonsemantic processing. This second locus of activation may be incompatible with the observation in our study although we suggest that this is difficult to assess fully without a clearer idea of how, precisely, subjects were approaching the intentional encoding condition.

In a pair of fMRI studies relevant to the current one, Belger *et al.* explored the effects of stimulus material (object versus spatial) and task (working memory versus perceptual control) (Belger *et al.*, 1998). They observed that working memory for shapes was associated with left middle frontal gyrus activation. Right MFG, however, did not differentiate between shape and location working memory. These findings are compatible with a previous study by the same group (McCarthy *et al.*, 1996). Belger *et al.* also showed that, when shape and location working memory tasks are compared with relevant perceptual control tasks, right MFG activation is seen to be common to both whereas left IFG and MFG activation appears specific to shape working memory (although the authors do acknowledge that the shape was more difficult than the location task). Our findings are compatible with these and extend upon them in the observation of a left IFG/MFG double dissociation. We too found that processing shapes (pictorial stimuli) was associated with widespread frontal activation of both right and left MFG and IFG. Moreover, when encoding task demands were such that processing of words emphasized individual letters rather than overall meaning, there were greater levels of left MFG and right MFG/IFG activation, whereas a task emphasizing meaning over component parts preferentially activated left IFG.

In brief, therefore, our findings indicate a clear sensitivity of right lateral PFC to the type of material that is presented but further suggest that picture versus word effect is sensitive to what subjects are actually asked to do. The functional subdivisions within left PFC reflect task instructions for verbal material only. Against the background of the debate over whether subdivisions within PFC reflect material or process, our results suggest that they are sensitive to both. It is plausible that a change in the nature of material may produce a different type of processing and that a change in task demands will change the nature of the material (thus, when certain instructions are given, a word loses its cohesion and becomes merely an array of letters). If this is correct, and our results suggest that it holds true at the level of neuronal activation, it points to the requirement for a closer evaluation of what the terms "process" and "material" are referring to when applied to tasks used in humans.

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