Models of Functional Organization of the Lateral Prefrontal Cortex in Verbal Working Memory: Evidence in Favor of the Process Model

Laura H. F. Barde and Sharon L. Thompson-Schill

Abstract

■ Research on the functional organization of the lateral prefrontal cortex (PFC) in working memory continues to be fairly equivocal between two major frameworks: organization-by-process or organization-by-material. Although there is fairly strong evidence for organization-by-process models from event-related fMRI studies, some investigators argue that the nature of the stimulus material better defines the functional organization of the lateral PFC, particularly in more ventral regions (BA 47/45/44). Specifically, the anterior region of the ventrolateral PFC (BA 47/45) is hypothesized to subserve semantic processing while the posterior region (BA 44) may subserve phonological processing. In the current event-related fMRI study, we directly compared process-related versus material-related organizational principles in a verbal working memory task. Subjects performed a modified delayed response task in which they (1) retained a list of five words or five nonwords during the delay period (''maintenance''), or (2) performed a semantic (size reordering) or phonological (alphabetical reordering) task on the word or nonword lists, respectively (''manipulation''). We did not find evidence during the delay period of our task to support claims of anterior–posterior specializations in the ventrolateral PFC for semantic versus phonological processing. Subjects did, however, display greater neuronal activity during the delay period of manipulation trials than maintenance trials in both the dorsolateral PFC and posterior ventrolateral regions. These data are more consistent with the process model of the organization of lateral PFC in verbal working memory. ■

INTRODUCTION

Baddeley's (1986) multicomponent model of working memory explains how material is maintained on-line for the purposes of complex information processing by postulating the existence of two ''slave'' systems under the control of a ''central executive'' system. The mapping of these psychological constructs onto specific brain regions, in particular, the lateral prefrontal cortex (PFC), has been a somewhat controversial endeavor in the field of cognitive neuroscience. Thus far, two general models or characterizations have emerged from the debate: One approach has described variance in functional activity in the lateral PFC by the cognitive process that was being performed during a brief delay (e.g., maintenance or manipulation of information, selection between competing alternatives, or inhibition of irrelevant responses), whereas another approach has stated that the functional organization of the lateral PFC could be better defined by differences in stimulus content (e.g., spatial vs. object, semantic vs. phonological).

Interestingly, the investigations of the neural circuitry of the mid-dorsolateral PFC areas in the nonhuman primate brain (i.e., the sulcus principalis) have provided support for both models of human lateral PFC organization. On the one hand, the single-unit recordings of a delayed response task (addressing ''spatial'' working memory) and a delayed matching-to-sample task (addressing ''object'' working memory) found populations of neurons in dorsal regions of the lateral PFC whose responses did not differ according to the stimulus material (Quintana, Yajeya, & Fuster, 1988; Fuster, Bauer, & Jervey, 1982). The researchers interpreted these data as evidence against the ''functional parceling'' of stimulus features in a working memory task. On the other hand, Goldman-Rakic's electrophysiological and lesion studies of nonhuman primates (Wilson, Scalaidhe, & Goldman-Rakic, 1993; Funahashi, Bruce, & Goldman-Rakic, 1989; Goldman-Rakic, 1987) indicated the necessity of the dorsolateral PFC (area 46) in a spatial task and the ventrolateral PFC in an object task. This evidence was interpreted as a modular organizational scheme of the PFC that described anatomically discrete regions supporting separate types of materials during working memory. Specifically, they proposed that dorsal and ventral regions in the PFC subserved visuospatial and visual-object information, respectively.

Though not motivated by Goldman-Rakic's studies of nonhuman primates, conclusions made from human neuropsychological research are notable for the evidence

University of Pennsylvania

in favor of an organization-by-stimulus material model of the lateral PFC. Martin, Breedin, and Damian (1999) and Martin, Shelton, and Yaffee (1994) have described several patients with various lesions to the frontal operculum, the superior temporal, and/or the anterior parietal regions (all left hemisphere only) that demonstrated dissociable performances on numerous behavioral tasks. These tasks included speech perception (both syllable and word discrimination), syntactic processing, digit span (i.e., working memory), and recognition memory. Among their interpretations of these data was the hypothesis that there existed separate working memory systems for such cognitive processes as phonological and semantic capacities. Of course, defining a functional–anatomical homology in humans tended to be rather difficult, as human lesions to the PFC are rarely discrete. Instead, various neuroimaging techniques have been used to examine patterns of neural activity.

To test the organization-by-process model, D'Esposito, Postle, Ballard, and Lease (1999) used event-related fMRI and a modified delayed response task in which subjects were required to either retain a short sequence of letters over a delay (''maintenance'') or alphabetize the same letter sequence over the delay (''manipulation''). The event-related method additionally allowed these researchers to avoid potential failures of cognitive subtraction that can reduce the validity of empirical results determined through blocked designs. That is, rather than averaging relative signal changes over all components of the trial (i.e., stimulus, instruction, delay, probe, and response) as is done with blocked designs, the event-related method allowed them to analyze relative changes in neural activity that belonged only to the delay period (Postle & D'Esposito, 2000; Zarahn, Aguirre, & D'Esposito, 1997). In all subjects, neural activity associated with the delay period in the maintenance task was detected in both the ventro- and dorsolateral PFC regions, however, dorsolateral PFC activation increased during the delay period in the manipulation task. The authors suggested that the functional organization of the PFC in working memory could be described by cognitive processing demands in a dorsal versus ventral manner and possibly by stimulus features in a hemispheric fashion.

Smith and Jonides' (1998, 1999a, 1999b) research using both PET and MRI technology generally supported the organization-by-stimulus content model by showing that each working memory system, namely, verbal, spatial, and object working memory, was separate and distinct from one another, and that each working memory system had three anatomically dissociable components: (1) a pure storage component, (2) a rehearsal component that refreshes information held in storage, and (3) an executive component that regulates the processing of the first two components. Other studies concurred with these findings, and further localized the neural representations of specific stimulus materials, namely, phonological and semantic capacities in the rehearsal process, to the left inferior PFC (Fiez, 1997; Shaywitz et al., 1995; Paulesu, Frith, & Frackowiack, 1993; Demonet et al., 1992).

Poldrack et al. (1999) recently examined the proposed functional specialization for phonological and semantic processing in human inferior PFC and argued that the nature of the stimulus material defined its functional organization. They used fMRI in a blocked design consisting of a semantic decision task (concrete/abstract judgments), a phonological task (syllable counting of real and nonwords), and a perceptual task (uppercase/lowercase decision). The anterior region of the ventrolateral PFC (BA 47/45) was found to subserve semantic processing while the posterior region (BA 44) subserved phonological processing. This process specificity in the PFC was further hypothesized to represent a semantic working memory system that could be partially dissociated from phonological capacities.

In sum, research on the functional organization of the lateral PFC in working memory has continued to be fairly equivocal between two major frameworks: organization-by-process or organization-by-material. We suggested two improvements that can be made on these studies. First, the conclusions reached by D'Esposito et al. (1999) regarding verbal working memory have been somewhat limited by their use of simple letters as stimuli. While it is certainly true that letters are elements of verbal information, one might argue that they could alternatively be viewed as abstract symbols. At the very least, this is more likely to happen with letters than with words or pronounceable nonwords. Therefore, a stronger test for the process model in verbal working memory would be to use words and nonwords, as there can be no doubt to their salience in language tasks.

Second, in regard to the validity of organization-by-stimulus material models, the type of stimuli used in defining semantic as opposed to phonological processes in verbal working memory could be improved. Specifically, due to the automaticity of accessing the meaning of a word during reading (MacLeod, 1991), it seems that Poldrack et al.'s (1999) use of word stimuli in a task meant to activate representations of ''phonological'' processes to the exclusion of representations of ''semantic'' processes is potentially invalid. The same activation in posterior ventrolateral areas attributed to phonological processing could alternatively be interpreted as processes related to the selection of task-relevant stimulus attributes (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). When word stimuli are used in a ''phonological'' task, it is likely that the word meaning will be accessed automatically, and therefore, the posterior ventrolateral activation could reflect a process of selection between the phonological and semantic information inherent in the word stimulus. In order to avoid this potential confound, it would be preferable to utilize word stimuli in a semantically based task (e.g., size judgment)

and nonword stimuli in a phonological task (e.g., alphabetizing) with the goal of reducing as much automatic semantic activation (i.e., word meaning) as possible.

The goal of this study was to directly compare process-related versus material-related organizational principles in a verbal working memory task using event-related fMRI. It is important to note at this juncture that by comparing these two models in the same study there is a unique opportunity to potentially demonstrate the coexistence of aspects of both models in the lateral PFC, an issue previously discussed in the literature (Postle & D'Esposito, 2000; Smith & Jonides, 1999a, 1999b). Subjects performed a modified delayed response task in which a set of five words (concrete nouns) or nonwords was presented simultaneously for 3 sec, followed by an instruction cue that was presented for 1 sec (FORWARD, ALPHABETIZE, or INCREASING SIZE), followed by an 8-sec delay, during which there was nothing presented onscreen, followed by a probe that was presented for 1 sec. Subjects were allowed up to 5 sec to respond to the probe "YES" or "NO" as indicated by bilateral button press. Following these events, there was a 17-sec inter-trial interval (ITI) that allowed the fMRI signal to return to baseline. The total time from trial onset to trial onset was 30 sec (see Figure 1).

Four distinct trial types were presented in randomized order. Subjects were asked to either (1) "maintain" a set of five words across a delay period, (2) "manipulate" (reorder them according to increasing size of the object/animal/person—a semantic judgment) this set of words, (3) "maintain" a set of five nonwords across a delay period, or (4) "manipulate" (alphabetize them—a phonological judgment) this set of nonwords (see Figure 2).

In all four conditions, the probe at the end of the delay period consisted of a word or nonword and a number. Subjects were required to determine if the word or nonword would be in the ordinal position represented by the number if the items in the original memory set

were either maintained or manipulated according to the instruction. We defined three regions of interest (ROIs) for each subject; one in the dorsolateral PFC, one in the anterior ventrolateral PFC, and a final one in the posterior ventrolateral PFC. A prediction of the organization-by-stimulus content model would be increased neural activity during word trials ("semantic processing") relative to nonword trials ("phonological processing") in the anterior ventrolateral ROI, and the reverse in the posterior ventrolateral ROI. However, we predicted that neural activity in the PFC during the delay period would be consistent with the process model such that increases would be detected during manipulation trials relative to maintenance trials in the dorsolateral ROI.

RESULTS

Behavioral Data

There was no main effect for process on accuracy of performance (manipulation vs. maintenance), $t(5) = 0.31$, $p > .05$, and no interaction between process and stimulus material, $t(5) = 1.03$, $p > .05$. There was a main effect for stimulus material (nonword trials more difficult than word trials), $t(5) = 2.85$, $p < .05$. This result raises a potential confound between stimulus material and difficulty. In this case, nonwords were harder to "maintain" or "manipulate" over the delay, thus conceivably requiring greater neural activity; however, that prediction was disconfirmed upon analysis of the imaging data shown below. Further, there were no main effects of process, $t(5) = 2.51$, $p > .05$, or stimulus Material, $t(5) = 2.38$, $p > .05$ on reaction times, and no interaction, $t(5) = 2.07$, $p > .05$ (see Table 1).

Imaging Data

Voxels that exceeded threshold and evidenced a main effect comprising of the sum of coefficients of the delay

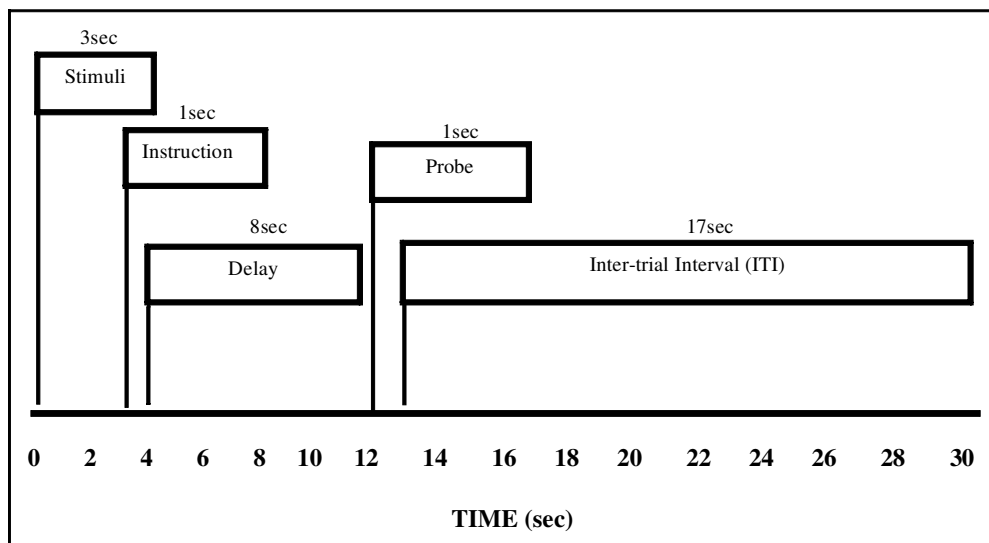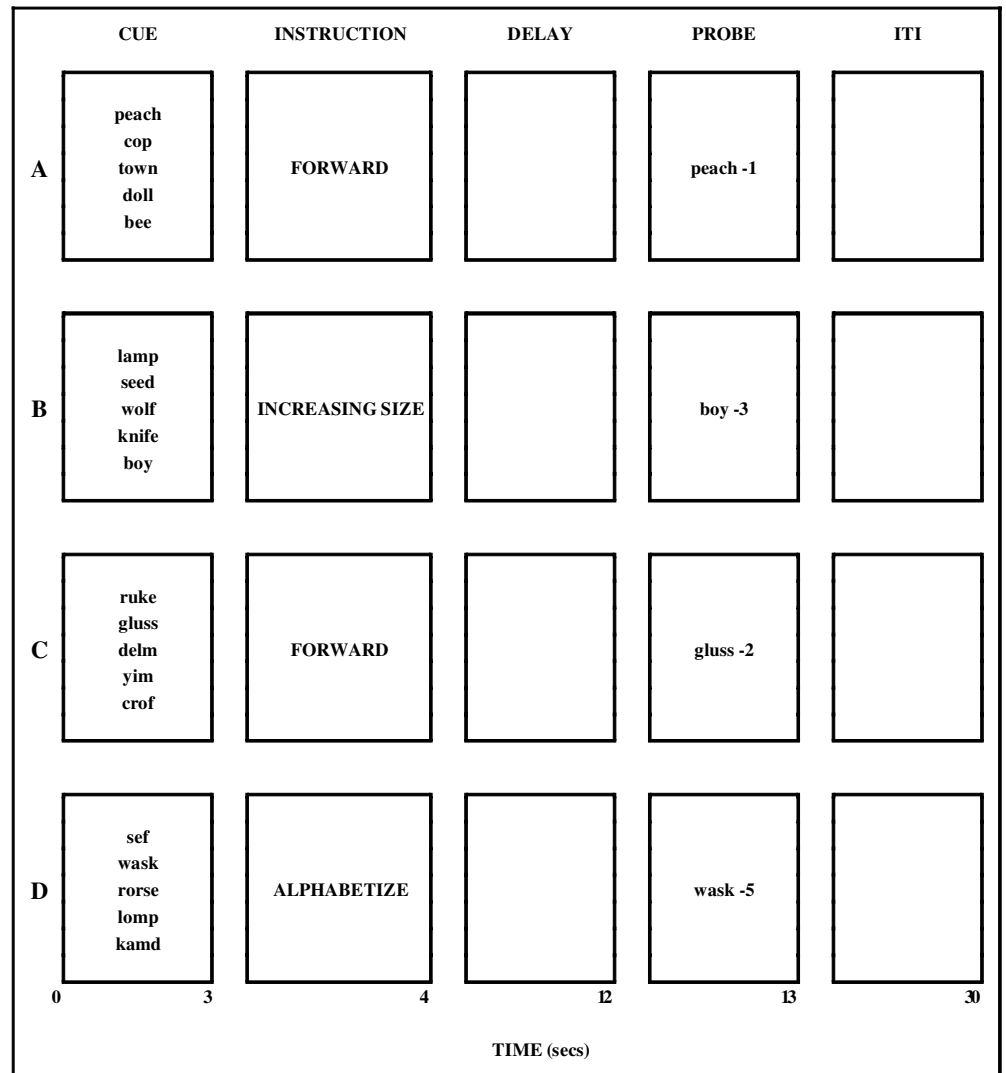**Figure 1.** The event-related task design.

Figure 2. Depiction of the four conditions in our modified delayed response task. A represents a trial in the word-maintain condition; B represents a trial in the word-manipulate condition; C represents a trial in the nonword-maintain condition; D represents a trial in the nonword-manipulate condition.

period covariates of all four conditions were detected in all three ROIs in all subjects (see Figure 3 for representative subject).

Direct contrasts of delay period neural activity on spatially averaged voxels within the ROIs in the manipulation versus maintenance conditions and the word versus nonword conditions were then performed, yielding individual t values. These values were subsequently used as the dependent variable in a group random effects analysis as an indicator of statistical effect size (i.e., magnitude of BOLD signal change relative to noise).
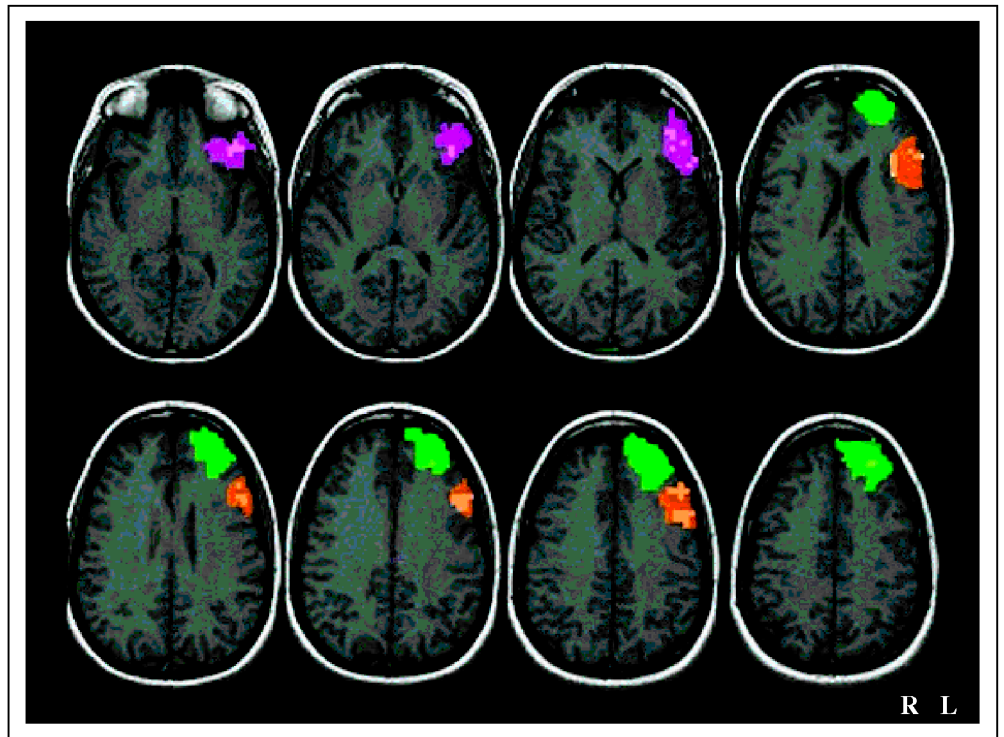
Five out of the six subjects displayed significantly greater neuronal activity during the delay period of manipulation trials than maintenance trials in both the dorsolateral PFC and posterior ventrolateral regions (group random effects analysis of process main effect in the dorsolateral PFC, $t = 4.37$, $df = 5$, $p < .05$, and the

Table 1. Average Accuracy (% Correct) and Reaction Time Measures (msec) in the Four Experimental Conditions

	Stimulus Material			
Process	Word		Nonword	
Manipulation	82.7% (5.5)	2293 msec (526)	80.8% (5.5)	2236 msec (410)
Maintenance	87.3% (9.02)	1817 msec (280)	78.0% (10.3)	2265 msec (502)

Standard deviations are in parentheses. There was a main effect of stimulus material on accuracy of performance, but no interaction. There were no main effects of process or stimulus material on reaction times and no interaction.

Figure 3. All delay period suprathreshold activity in the dorsolateral and ventrolateral ROIs in a representative subject. Voxels are shown underneath transparent ROI masks (pink: anterior VLPFC; green: DLPFC; orange: posterior VLPFC).

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posterior ventrolateral PFC, $t = 4.84$, $df = 5$, $p < .05$, see Figure 4). No PFC voxels demonstrated significantly greater activity in the maintenance versus manipulation delay periods. There was no main effect of stimulus material in either the anterior ventrolateral ROI ($t = .18$, $df = 5$, $p > .05$), or the posterior ventrolateral ROI ($t = 2.26$, $df = 5$, $p > .05$, see Figure 4).

Only one subject out of five displayed significantly greater neuronal activity during the delay period of word trials than nonword trials in the anterior ventrolateral ROI only (Subject TP, $t = 1.99$, $df = 1252$, $p < .05$), and two subjects demonstrated significantly greater neuronal

activity during the delay period of word trials than nonword trials in the posterior ventrolateral ROI (Subject HM, $t = 4.82$, $df = 1252$, $p < .05$; and Subject JN, $t = 1.66$, $df = 1252$, $p < .05$). Note that this last result was the opposite of what would be predicted by the organization-by-stimulus content model proposed by Poldrack et al. (1999).

The trial-averaged signal across all subjects from suprathreshold voxels exhibiting the main effect of delay period activity in a conjunction area encompassing the three ROIs is shown in Figure 5. The x-axis represents time (sec), yielding 30 sec from trial onset to

Figure 4. Group random effects analysis of process and stimulus material main effects in the dorsolateral, anterior ventrolateral, and posterior ventrolateral PFC regions of interest. Dashed line represents threshold value ($t = 2.57$).
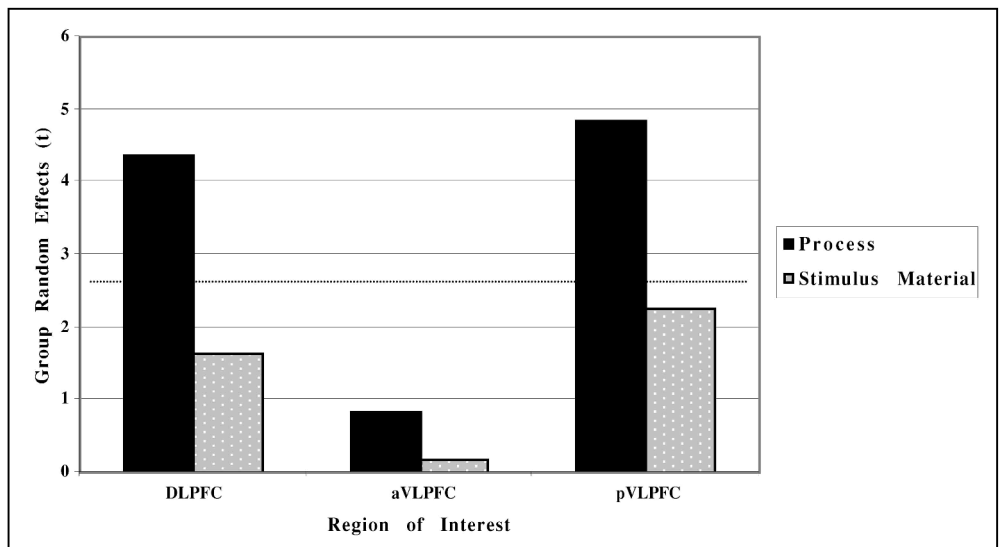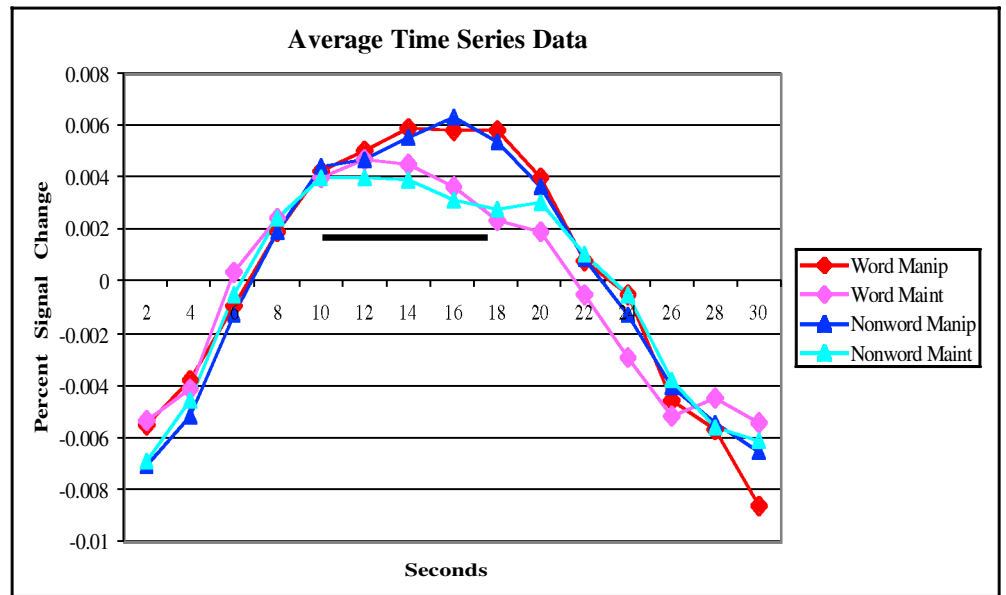
Average Time Series Data

next trial onset. The *y*-axis represents percentage signal change in hemodynamic response function. The solid bar represents approximate location in time of the delay period. In all conditions, the fMRI signal was greater than baseline throughout the period of time corresponding to the delay period, taking into account the delay and dispersion of the fMRI signal (Aguirre, Zarahn, & D'Esposito, 1998). Lastly, during both word and nonword trials, the trial-averaged signal for the manipulation condition was greater than the maintenance condition.

DISCUSSION

Although there is fairly strong evidence in favor of an organization-by-process model for the functional organization of the lateral PFC in working memory (D'Esposito, Postle, & Rypma, 2000; D'Esposito et al., 1999), some investigators continue to argue that the nature of the stimulus material better defines the functional organization of the lateral PFC, particularly in more ventral regions (BA 47/45/44). Specifically, the anterior region has been hypothesized to subserve semantic processing while the posterior region (BA 44) may subserve phonological processing (Poldrack et al., 1999). The present study sought to directly test these two major frameworks of the functional organization of the lateral PFC in verbal working memory with an event-related fMRI method in which subjects either maintained or manipulated word and nonword stimuli (in semantic and phonological tasks, respectively) in a modified delayed response task. This design yielded four trial types: manipulation of word material, manipulation of nonword material, maintenance of word material, and maintenance of nonword material. Group random effects analyses performed on the behavioral and imaging results of the current

experiment were found to be consistent with the processing model.

The behavioral results determined by the current experimental design were more favorable compared to the most recent study of the processing model in verbal working memory (D'Esposito et al., 1999). In their study, D'Esposito and colleagues found accuracy and reaction time differences between maintenance and manipulation conditions, potentially implying that increases in dorsolateral PFC activity that were observed during manipulation trials may have reflected only increases in difficulty of the task rather than a functionally specific change related to the processing demands of the task. However, our results allow us to interpret the relative changes in neural activity detected during the delay period to the cognitive processes in question, rather than a potential confound. Behaviorally, there were no accuracy or reaction time differences found between the tasks performed in this study, with the exception of reduced accuracy for trials in which nonword information was manipulated or maintained compared to word stimuli. From this behavioral result, one might have predicted increased neural activity according to stimulus material and thus consistent with the organization-by-content model, but this was not found in the analysis of our imaging data. We attribute the behavioral result to simply the subjects' greater familiarity with performing cognitive computations on word stimuli.

The imaging results were highly consistent with previous neuroimaging findings in support of the process model, and indicated that five out of the six subjects displayed significantly greater neuronal activity during the delay period of manipulation trials than maintenance trials in both the dorsolateral PFC and posterior ventrolateral regions. Also consistent with the literature, no PFC voxels demonstrated significantly greater activity

in the maintenance versus manipulation delay periods. Though it was not empirically tested, casual review of the remaining subject's imaging data revealed what appeared to be greater activation of dorsolateral PFC areas in the right hemisphere rather than in the left hemisphere as expected. A similar result was reported by D'Esposito et al. (1999) and does not preclude the existing evidence in support of the process model. Two subjects (HM and JN) showed a main effect of stimulus material in the posterior ventrolateral ROI, the reverse of what the organization-by-stimulus model would predict, and only one subject (TP) demonstrated significantly greater neuronal activity during the delay period of word trials when compared to nonword trials in the anterior region of the ventrolateral PFC, evidence that may be interpreted to be consistent with the organization-by-stimulus model. However, all three subjects demonstrated the manipulation effect in both the dorsolateral and posterior ventrolateral regions of PFC, evidence that again does not preclude support for the process model in verbal working memory.

Our results were not consistent, therefore, with previous neuroimaging studies of the effect of stimulus material on the functional organization of the PFC in verbal working memory. That is, we did not find significant evidence to support the idea that semantic processing preferentially activates anterior ventrolateral regions of the lateral PFC when compared to phonological processing (Poldrack et al., 1999). As the method of image analysis utilized in this experiment differed from that study, let the reader be assured that our posterior ventrolateral ROI encompassed the cited LIPC cluster maxima in both their phonological > case and psuedoword phonological > case conditions. Additionally, our anterior ventrolateral ROI included the peak activations noted in their semantic > case condition. One goal of Poldrack and colleagues' recent study was to use fMRI to "[determine] the degree to which semantic and phonological processing results in distinct patterns of neural activation" (p. 17). From the point of view of task decomposition, potential problems appear to exist in the execution of the cognitive tasks on two counts. First, when word stimuli are used in a "phonological" task, it is likely that the word meaning will be accessed automatically (MacLeod, 1991), and therefore the posterior ventrolateral activation could reflect a process of selection (Thompson-Schill et al., 1997) between the phonological and semantic information inherent in the word stimulus (or simply inhibition of that semantic information).

Second, there are potential issues with the pairing of the abstract/concrete judgment task (i.e., a "semantic" process) with the syllable counting task (i.e., a "phonological" process) in that semantic and phonological processes are not unitary operations; rather, they are sets of subroutines. Thus, it is critically important that task decomposition between these two measures of cognitive processes be more suitably controlled in order to minimize the differences between them and thereby improve the specificity of the interpretation of neural differences between the two conditions. These two tasks—syllable counting and abstract/concrete judgment—differ along more than one cognitive (sub)process and it is therefore not clear what "semantic" or "phonemic" processes are eliciting the neural activity described. Furthermore, it is unlikely that subjects sounded out the words (i.e., used a phonological process) in order to count syllables—the longest words used in the experiment were only three syllables. It is more likely that subjects used their familiarity (i.e., semantic knowledge) with the words to make the syllable judgment.

We propose that our design, which chose to pair a size-reordering task (i.e., our "semantic" process) with an alphabetical-reordering task (i.e., our "phonological" process), is a significant improvement upon previous studies of this nature. For the purposes of simplification, we have described the nonword working memory task as a pure measure of phonological processing; of course, it is possible that other processes (i.e., orthographic) may contribute to performance on this task. However, our conclusions regarding organization-by-material (or lack thereof) still hold as long as one assumes that the nonword task differs from the word task with regard to semantic processing. Thus, given the assumption that verbal working memory for words and nonwords differs in the extent of semantic processing, our failure to detect a difference in neural activity between these two conditions is inconsistent with an organization-by-material model. Future research will be necessary to tease apart the orthographic and phonological contributions to the nonword memory tasks.

One issue in the fMRI studies of ventral frontal regions is whether there was enough fMRI signal detected from the anterior region of subjects' ventrolateral PFC, as the possibility of BOLD fMRI signal dropout increases closer to the orbitofrontal cortex. The anterior ventrolateral PFC mask was drawn for each subject and encompassed only the lateral orbital gyri and sulci, the pars orbitalis, and the pars triangularis up to approximately 10 mm above the subject's anterior–posterior commissure, giving an average of 135 voxels in this ROI. An average of 20% of these voxels were suprathreshold for all delay period activity, which is consistent with the literature and thus provided us with adequate reassurance that we obtained sufficient data upon which to base our conclusions regarding the organization of the lateral PFC and verbal working memory. Furthermore, the percentage of voxels activated above threshold per mask was consistent across the other two ROIs utilized in this study (see Table 2).

Finally, we agree that the experimental conditions utilized in the current study could be improved by further refinement of their component processes. It has

Table 2. Percent Significant Activity in Lateral PFC Voxels Representing All Delay Period Conditions, Shown as Number of Suprathreshold Voxels (Numerator) over Total Number of Voxels in Each ROI Mask (Denominator)

Subject	aVLPFC		pVLPFC		DLPFC	
	ROI Mask					
HM	45/145	31%	47/152	31%	49/164	30%
KM	9/157	6%	22/125	18%	20/242	8%
JN	16/77	20%	20/129	16%	35/175	19%
TP	36/162	22%	19/158	12%	39/206	19%
SS	31/114	27%	54/172	31%	67/284	24%
MW	23/157	15%	31/143	22%	39/263	15%
Average size of ROI in voxels	135		147		222	

been suggested elsewhere (Kimberg, D'Esposito, & Farah, 1998) that ''manipulation'' processes may be further deconstructed or simply bear resemblance to other executive processes inherent in working memory, and as such, the relative changes in neural activity in the dorsolateral and ventrolateral PFC that we have ascribed to ''manipulation'' or ''maintenance'' may not be highly precise. For instance, reordering a set of words according to increasing size of the object/animal/person may consist of subroutines such as: (1) reading the visual stimulus, (2) retrieving the word meaning from long-term memory, (3) maintaining the words and word meanings over the delay, (4) switching attention among the items held in memory, (5) strategic reorganization of the currently active representations, (6) inhibition of the original order of the stimulus set, (7) evaluation of the newly selected order, and (8) response preparation. Future research will be necessary to provide control tasks that selectively manipulate these component processes to determine if the organization-by-process model is upheld in working memory.

In sum, our data are more consistent with the process model of the organization of the lateral PFC in verbal working memory. Our use of an event-related fMRI method is notable for its unique ability to avoid inferential constraints, instead allowing us to analyze neural activity during the delay period of the task uncontaminated by other parts of the task. Additionally, the use of words and nonwords provided a stronger test of segregation of semantic and phonological processes, respectively, in ventrolateral PFC regions than has been recently tested. While it was clear that ventrolateral PFC regions are involved in the maintenance of linguistic information in our task, our evidence was not congruent with the organization-by-stimulus material hypothesis as it has been described previously.

METHODS

Subjects

Six right-handed subjects (4 women, 2 men, mean age 23.3 years, range 18–27) from the undergraduate and graduate campuses of the University of Pennsylvania participated in this study. Subjects were excluded if they had any medical, neurological, or psychiatric illness or if they were nonnative English speakers. All subjects gave informed consent and were treated in accordance with institutional and APA guidelines.

Design and Materials

Each experimental block consisted of 12 trials, three of each condition, presented in randomized order. Each subject performed eight blocks for a total of 96 trials in the entire experiment. A total of 180 gradient-echo echo-planar images in time were obtained per slice in each 360-sec run. Thus, a total of 1440 observations were obtained per voxel per subject.

The stimuli consisted of 240 single-syllable English words (nouns) between three and six letters in length (average Kucera–Frances frequency approximately 55) and 240 single-syllable pronounceable nonwords. Nonwords were either one- to two-letter permutations of the word stimuli used in this experiment or were obtained from previously published papers, also matched for length to the word stimuli. All verbal stimuli were presented in white font on a black background.

Image Acquisition

Imaging was performed on a 1.5-T SIGNA scanner (GE Medical Systems) equipped with a fast gradient system for echo-planar imaging. A standard radio-frequency (RF) head coil was used with foam padding to comfortably restrict head motion. High-resolution sagittal and axial T1-weighted images were obtained in every subject prior to the collection of experimental data. We used a gradient-echo, echo-planar sequence (TR = 2000 msec, TE = 50 msec) to acquire data sensitive to the BOLD signal (Kwong et al., 1992; Ogawa et al., 1992). Resolution was 3.75 by 3.75 mm in-plane and 5 mm between planes for a total of 21 axial slices acquired per subject. Twenty seconds of gradient and RF pulses preceded the actual data acquisition to allow tissue to reach steady-state magnetization. Subjects viewed the stimuli via the Avotec Silent Vision stimulus display system, which consisted of a pair of lightweight fiber-optic glasses mounted on the head coil and a color LCD projector located outside the MRI bore. Subjects viewed computer-generated (Psyscope 1.2.5 on a Macintosh) stimulus material transmitted to the glasses by fiber-optic image guides. The entire testing session, including signing of informed consent, training, testing, and debriefing, lasted 90 min.

Subjects were paid US$20 as compensation for their participation.

Image Analysis

Off-line data processing was performed on SUN Ultra workstations using programs written in Interactive Data Language (Research Systems, Boulder, CO, USA) and VoxBo software (www.voxbo.org). Data were sinc interpolated in time after image reconstruction and before motion correction. A six-parameter (three translational and three rotational), rigid-body, least squares realignment routine was performed for motion correction. There was no normalization or spatial smoothing performed on the imaging data.

The principles of the event-related fMRI analysis used in this experiment have been published elsewhere (Zarahn et al., 1997). Briefly, we modeled the fMRI signal changes that occurred during a given behavioral trial by creating covariates of interest consisting of shifted BOLD impulse response functions (IRFs) that were placed at specific time points in the trial (i.e., corresponding to the stimulus presentation, the instruction, the delay period, the response, and the intertrial interval). We used a standard IRF in our analyses, which is essentially the putative fMRI response resulting from a pulse of neural activity. This method increases the statistical and functional specificity of our empirical tests of the relationship between BOLD fMRI signal and unique neural activity elicited by a discrete component of our behavioral task (i.e., the delay period) because we can discriminate between neural activity associated with the trial component of interest and that of other components.

We used a modified general linear model for serially correlated error terms (Worsley & Friston, 1995) that incorporated a filter to remove frequencies above 0.25 Hz and below 0.02 Hz to remove artifacts in the data. Relationships in the delay period between conditions were tested by contrasts that yielded t statistics with 1252 degrees of freedom. The false-positive rate was controlled at $\alpha = 0.05$ by Bonferroni correction for the number of voxels per ROI per subject. We created three ROIs for each subject according to anatomical landmarks (Rajkowska & Goldman-Rakic, 1995). First, each subject's anterior and posterior commissures were located on anatomical T1 axial images. The anterior ventrolateral PFC mask (Brodmann's areas 47 and anterior area 45) was delimited by the lateral orbital gyrus and sulcus, the pars orbitalis, and the pars triangularis up to approximately 10 mm above the subject's AC–PC line. The posterior ventrolateral PFC mask (posterior Brodmann's area 45 and all of area 44) was bounded ventrally at 10 mm above the subject's AC–PC line and included the remaining area of the pars triangularis as well as the pars opercularis up to approximately 35 mm above the AC–PC line. Finally, the dorsolateral PFC

mask (Brodmann's areas 9 and 46) was drawn for each subject beginning at approximately 15 mm above the AC–PC line and included the middle and superior frontal gyri according to anatomical landmarks (Rajkowska & Goldman-Rakic, 1995). All hypothesis testing was restricted to these ROIs.

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