

# Localization of Semantic Processing Using Functional Magnetic Resonance Imaging

**Bennett A. Shaywitz, Kenneth R. Pugh, R. Todd Constable, Sally E. Shaywitz, Richard A. Bronen, Robert K. Fulbright, Donald P. Shankweiler, Leonard Katz, Jack M. Fletcher, Pawel Skudlarski, and John C. Gore**

*Departments of Pediatrics (B.A.S., S.E.S., K.R.P.), Neurology (B.A.S.), and Diagnostic Radiology (R.T.C., R.A.B., R.K.F., P.S., J.C.G.), Yale University School of Medicine, New Haven, Connecticut; Haskins Laboratories (K.R.P., D.P.S., L.K.); Department of Pediatrics, University of Texas-Houston, Houston, Texas (J.M.F.); and Department of Applied Physics, Yale University, New Haven, Connecticut (J.C.G.)*

---

**Abstract:** The relationship between the functional components of language and the anatomic foci of their neural systems represents a central issue in cognitive neuroscience. Conflicting results from a number of laboratories using positron emission tomography (PET) imaging techniques have led to a significant controversy over the specific neuroanatomic sites engaged by semantic processing. We report here results of an experiment designed to address this controversy, that is, whether semantic processing activates temporal and/or frontal brain regions. In this experiment we used cognitive tasks that emphasized either semantic or phonological information processing but that were similar on both memory search and response generation components, together with functional magnetic resonance imaging, to examine the neuroanatomic loci of lexical-semantic as opposed to phonological processing. We studied nine right-handed men performing two silent generation tasks: rhyme, and semantic category. The former focuses on word form (phonological information) while the latter focuses on word meaning (semantic information). By "phonological" we mean the process of apprehending the sound structures of language. By "semantic" we mean information about the word's contextually specified meanings. Semantic processing makes demands on, and activates widespread areas within, brain including the inferior frontal regions bilaterally and the left posterior temporal region. Phonological processing engages a more restricted neuroanatomic assembly involving primarily anterior left temporal lobe sites. © 1995 Wiley-Liss, Inc.

**Key words:** cognition, blood flow, language, phonology

---

## INTRODUCTION

The relationship between the functional components of language and the anatomic foci of their neural systems represents a central problem for cogni-

tive neuroscience. Current psycholinguistic models [Caplan, 1992; Gough, 1972; McClelland and Rumelhart, 1981; Shallice, 1988] assume that when an individual hears (or reads) a word, the recognition process involves information processing at several levels: an acoustic or visual feature analysis, and a phonological or orthographic analysis (i.e., one that represents phonemic information or letter information). Upon recognition of the word in lexical memory, both syntactic and semantic information about that word

---

Received for publication April 25, 1994; revision accepted August 26, 1994.

Address reprint requests to Dr. Bennett A. Shaywitz, P.O. Box 3333, New Haven, CT 06510-8064.

become available for higher level processing. Information relevant to the neuroanatomic loci of these language processes in normal individuals has been studied most recently by positron emission tomographic (PET) techniques that measure changes in regional cerebral blood flow or in the regional utilization of glucose or oxygen [Petersen and Fiez, 1993]. Conflicting results from a number of laboratories using PET have led to a significant controversy over the specific neuroanatomic sites engaged by semantic processing [Demonet et al., 1993; Petersen and Fiez, 1993; Wise et al., 1991].

### Frontal activation

One point of controversy concerns whether semantic processing activates left-lateralized inferior frontal regions, as suggested by the work of Petersen and his colleagues [1988, 1989]. Petersen et al. [1988] subtracted activations obtained on a word repetition control task (e.g., the subject repeats the word *bird*) from activations obtained in a verb generation experimental task (e.g., the subject is shown the noun *bird* and must generate and pronounce a relevant verb such as *flies*). Regions of activation unique to the experimental task included left dorsolateral prefrontal cortex, leading the authors to suggest that this region may play a critical role in semantic processing. However, while the experimental task does differ from the control task on the semantic dimension (i.e., it forces consideration of the meaning of the target noun), it also differs in other important respects, some of which are noted by the authors [Petersen et al., 1989]. First, the verb generation task involves crossing word class (noun to verb), while the control task does not. It has been suggested that verb naming deficits tend to be associated with frontal lesions [Damasio and Tranel, 1993]. Therefore it is possible that frontal activation in this task could be a function of the word class difference between the two conditions. Second, the verb generate task involves a search of lexical memory while the control task does not. A third related and potentially important difference between the two tasks is that responses in the experimental condition are self-generated (internally driven) while in the control condition they are externally driven. Wise et al. [1991] have hypothesized that frontal regions are critical in self-generated responding; therefore this constitutes another possibly relevant non-semantic difference between the two tasks.

Thus, differences with regard to word class, self-generated responding, or memory search could have been responsible for the frontal activation observed by

Petersen et al. [1988] and Frith et al. [1991] when examining the activations observed in generate-repeat subtractions. In short, the frontal activations observed in these studies cannot be unambiguously attributed to semantic aspects of processing. While frontal activation was also observed in a semantic monitoring task (a condition without self-generated responding), Petersen acknowledges that this result was statistically less robust [Petersen et al., 1989]. Furthermore, it seems unlikely that semantic knowledge systems would be located exclusively in that region. A more likely explanation is that activity at these frontal sites reflects the cognitive operations involved in particular components of semantic processing such as semantic memory search and/or response generation.

### Posterior temporal activation

Several studies have suggested a possible role for the left posterior temporal and parietal regions in semantic processing [Demonet et al., 1992; Hart and Gordon 1990; Wise et al., 1991]; however, Petersen and his colleagues failed to observe significant activation in those regions using the verb generate task [but see Raichle et al., 1994, for recent evidence of posterior temporal activation using this task]. A possible explanation for this discrepancy between the different laboratories lies within the nature of the cognitive tasks themselves. For example, it is probable that the baseline task (repeat noun) used in the study by Petersen et al. [1988] produces a certain degree of semantic processing in addition to phonological processing. Further, while the verb generate task should make semantic demands, word level associations between nouns and related verbs are quite strong, so that, for example, the word *bird* may generate *bird-flies* based on the strong word association rather than through classic semantic processing. Thus, under their task conditions the generate vs. repeat comparison might not have differed sufficiently on a semantic dimension and, as a result, activation in posterior temporal areas would not be consistently observed in the traditional subtraction strategy. In one PET study [Demonet et al., 1992] that involved monitoring adjective/noun pairs for two semantic attributes, inferior and posterior left temporal activation was observed. In that task the semantic demands would have been considerably stronger than in the generate task used by Petersen. Lesion studies have also suggested a semantic role for posterior temporal sites. For instance,

Hart and Gordon [1990] found strikingly consistent evidence that deficits in semantic comprehension were associated with lesions in left posterior temporal and inferior parietal sites.

### Issues in task design

The tasks used in the current investigation allow for a more precise test of the hypotheses regarding inferior frontal and posterior temporal involvement in semantic processing. Activation on a semantic category generate task (subjects are given a category label and generate several exemplars) is contrasted with that on a phonologically demanding rhyme generate task (subjects are given a target word and generate several rhyming items). The former is clearly semantic (operates on word meanings), involves extensive search of semantic memory, and requires self-generated responding. The latter task involves a search of phonological memory (presumably the phonological output lexicon) and self-generated responding as well, but for this task semantic information is not helpful; the task operates on word form (phonological information) and not on word meaning. Therefore, by including a control condition that also involves memory search and self-generated responding we can better determine whether *semantic* memory search and *semantic* generation make unique demands on areas within both frontal and temporal regions. It should be noted that while it is possible that some semantic information might be expected to be automatically activated during the rhyme generate task, we would anticipate that this activation would be minimal when contrasted with an explicitly semantic search task [see Raichle et al., 1994, for evidence that automated processing is associated with reduced activation relative to controlled and effortful processing].

The current experiment should help clarify whether Petersen's failure to observe activation within posterior temporal sites might have reflected the fact that in his experiment verb generation made relatively weak demands on semantic knowledge. Generating a set of exemplars from a given semantic category requires fairly extensive search of this knowledge system and therefore should strongly activate anatomical areas associated with the representations of these categories of knowledge. Even though the category and verb generate conditions differ in several ways, we assume that generating multiple exemplars is less likely to be confounded by strong word-level associations than would single verb generation.

Finally, while the semantic generate task makes greater semantic demands than the rhyme generate

task, the latter task should involve a more extensive search of the phonological lexicon. By subtracting the former task from the latter, information concerning anatomical sites associated with phonological processing might be obtained. However, the semantic generation task will also obviously engage a good deal of phonological processing and, as noted, our ability to detect relevant sites will be contingent on detecting differences in degree of activation.

### Functional MRI

The current experiment uses functional magnetic resonance imaging (fMRI) techniques to detect metabolic changes associated with performance of cognitive tasks. As first demonstrated *in vivo* by Ogawa et al. [1990a,b], the oxygenation state of hemoglobin influences the transverse magnetization decay time,  $T2^*$ , of brain tissue water, a property that offers the potential for detecting the effects of altered blood flow and oxygen balance in tissues. As the concentration of deoxyhemoglobin decreases, the intensity of the tissue MR signal increases because deoxyhemoglobin acts as an endogenous susceptibility contrast agent that shortens  $T2^*$ . Early studies [Blamire et al., 1992; Kwong et al., 1992; Ogawa et al., 1992] using this technology employed either ultra-fast (echo planar) MRI or high field strength to demonstrate brain activation under a number of different sensory stimuli, but standard MRI can be used as well. In a preliminary report limited to examining activations in the left frontal lobe, McCarthy et al. [1993] demonstrated the feasibility of MRI for studying cognitive processes [see also Constable et al., 1993; Schad et al., 1993].

## MATERIALS AND METHODS

### Tasks

Two silent generation tasks were employed: rhyme (phonological) and semantic category. In the rhyme generation task the subject was presented with a target word and instructed to generate rhyming words silently until the next target word was presented. Words from several different classes were included, as were a large number of different word bodies (rimes) in the set. In the semantic category generation task the subject was presented with a category label (e.g., mammals, car parts, etc.) and asked to generate exemplars silently until the next category was given. Auditory presentation of targets was used. A new target (word or category) was presented every 8 seconds with the first target presented 6 seconds before the

onset of the scan (each scan took 26 seconds to complete). No words or category labels were repeated during the experiment. We chose an 8 second trial interval because pilot work suggested that subjects could always generate enough responses on both tasks to fill this interval. The tasks were presented sequentially, interleaving rhyme and category tasks, until 16 scans had been completed for each task. The activations (i.e., significant increases in signal) analyzed here are based on two subtraction conditions: semantic (category generate)-phonological (rhyme generate) and phonological-semantic, hereafter labeled as semantic and phonological, respectively. Thus each task served both as an activation and control condition in this design.

### Imaging methods and analyses

Nine right-handed men, ages 22–46 were studied. Subjects were placed supine in a 1.5 Tesla GE MR unit and were then fitted with ear plugs connected to plastic tubes, which in turn were connected to a mouthpiece through which tasks were presented by one of us. Once the ear plugs were in place, the subject's head was secured by foam padding. The intercommissural line was localized in a series of standard spin echo T1-weighted sagittal images with the following parameters: TE = 13 ms, TR = 500 ms, field of view = 24 cm, 11 slices 5 mm thick skip 5 mm, 256 × 128 matrix with 1 acquisition. A conventional flow-compensated gradient echo imaging sequence was used for the activation studies. The imaging plane was axial oblique and prescribed from the sagittal scout scan. The imaging parameters were as follows: flip angle = 40°, TE = 40 ms, TR = 100 ms, field of view = 40 cm, 8 mm thick slices with an 8 mm slice gap centered along the intercommissural line, an imaging matrix of 256 × 128 with 2 acquisitions.

Motion effects from different sources may cause ghost artifacts and pixel misregistrations over the course of each experiment. Thus, simple subtraction of consecutive images in order to demonstrate the activated region is unsatisfactory. Instead, each pixel in each set of control and activation images generated a number of paired data sets that were subjected to a comparison by Student's *t*-test. The data pairs from the 16 activation and 16 control images were divided into two sets of 8 and a map of the *t*-statistic was calculated for each pixel and for each of the two sets of pairs. The resulting two images of the *t*-statistic distribution were then thresholded such that any pixel with a *t*-value greater than a set threshold was assigned a value of 1, while any pixel with a *t*-value of less than

the threshold was assigned a value of zero. The two *t*-maps were then logically ANDed together such that only those pixels that had a value of 1 in both *t*-maps were assigned a bright intensity (and hence satisfied our criteria for significant signal increases) on a high resolution T1-weighted image. The threshold was defined as the *t* value such that there was 0.1 chance that the difference between the activation and control images occurred purely by chance ( $P < 0.1$ ). Thus the resultant clusters of pixels depict only those regions for which the stimulation produced a significant difference signal at the  $P < 0.01$  level. A split *t*-test was used because motion artifacts and misregistrations may cause a large signal change in one or more images, thereby producing an unfair bias in the standard *t*-test. It is unlikely that such a large shift would occur in both halves of the image acquisition interval and thus only one of the two *t*-tests would become biased by the shift. Therefore, the probability of retaining spurious activations is reduced when the two *t*-maps are logically ANDed together.

The split *t*-statistic does not eliminate all of the spurious noise signals, however. To eliminate further chance activations, a 3 × 3 median filter was applied to the *t*-maps prior to the logical ANDing step. The effect of this median filter is to remove isolated pixel clusters containing 4 pixels or less with minimal impact on activation resolution. Isolated pixel clusters are considerably more likely than larger clusters to arise by chance (Type I error) alone. By forcing the clusters to contain more than 4 significant pixels, we remove many of those pixels that appear to activate by chance. It is possible that by adopting this requirement we might not detect some true activation that is highly localized. However, accepting only relatively large clusters is very conservative and yet still provides us with higher in-plane resolution than previous studies. Other checks for gross motion were made by tracking the image center of mass, but in the studies reported here these were not significant.

The initial analysis identified those clusters of pixels that significantly differed in these subtractions for each subject. The localization of the areas of activation was determined by three observers all "blind" to the experimental condition, and any differences between observers were reconciled by consensus. Regions of activation were localized [Duvernoy, 1991] into the following regions: superior, middle, and inferior frontal; superior, middle, and inferior temporal, insula, subcortical gray matter (including basal ganglia, thalamus, geniculate body), occipital lobe, and limbic structures (includes subcallosal region, cingulate gyrus, parahippocampal regions, hippocampus, and fornix).

For statistical purposes, apparent activations in the subcortical white matter were classified together with those in the adjacent cortex. While there is no clear explanation for the observed white matter clusters, at this early stage it is essential that all activations be reported and considered, in order to determine across investigations whether these activations are indeed reliable.

Analyses of variance were conducted with subjects as a random factor. The dependent measure was a size-weighted count of the number of activated clusters (by size weighting we reduce the possibility that errors in measurement will inadvertently bias our analyses). Repeated measure variables included: task (phonological vs. semantic), area (e.g., superior, middle, inferior frontal), and hemisphere (left vs. right). By using only significant activations as the dependent measure, we can assess whether the differences observed within regions are reliable across subjects. This test of reliability across subjects has the merits of being a fairly conservative analysis, representing essentially a statistical analysis on an already conservative statistical analysis of pixel clusters. Separate analyses were conducted on the following regions: frontal, temporal, insula, limbic, and occipital. Significant effects and interactions are reported below.

## RESULTS

Activations in regions of interest are summarized in Figure 1. In the frontal region, the mean number of activations were 0.97, 0.40, and 1.36 for the superior, middle, and inferior areas respectively [ $F(2,16) = 25.63$ ,  $P < 0.001$ ]. Task was marginally significant [ $F(1,8) = 3.84$ ,  $P = 0.09$ ], with 1.11 and 0.704 the mean number of activations for the semantic and phonological tasks, respectively. The only other term that approached significance was the task by area interaction [ $F(2,16) = 2.70$ ,  $P = 0.12$ ]. Inspection of the data showed fewer activations in the middle area than in the other two areas. Moreover, there was a concomitant disparity in cell variances (cell standard deviations ranged from 0 and 0.330 to 1.054 and 1.453). However, when the data were separated by area of origin, cell variances within each area were more nearly homogeneous. Given the heterogeneity of variance, and our declared interest in the inferior frontal area, we conducted separate analyses for each area. For the inferior area there was a main effect of task [ $F(1,8) = 5.64$ ,  $P < 0.05$ ]. The means for the semantic and phonological conditions were 1.89 and 0.83, respectively. Further, this increased activation in the semantic task was apparently bilateral; the interaction with hemisphere

was not significant ( $F < 1.0$ ). The means for inferior frontal areas were semantic left = 1.56, semantic right = 2.22, phonological left = 0.67, and phonological right = 1.00; thus, there was no asymmetry.<sup>1</sup>

A main effect of area was observed in the temporal region analysis [ $F(2,16) = 4.03$ ,  $P < 0.05$ ]. The means were 0.78, 0.58, and 0.07 for the superior, middle, and inferior areas, respectively. However, there were no task effects or interactions in this initial analysis of the temporal region. While both the semantic and phonological tasks produced equivalent numbers of clusters ( $F < 1.0$ ), as noted above, some evidence [Demonet et al., 1992; Hart and Gordon, 1990; Raichle, et al., 1994] suggests that the semantic task should produce more left hemisphere *posterior* temporal activation. To investigate this possibility, activations were classified as occurring at either posterior or anterior temporal sites based on their position relative to a mid-commissural line. An analysis of variance performed on these data from the temporal region revealed a three-way interaction among task, site (anterior/posterior), and hemisphere [ $F(1,8) = 15.077$ ,  $P < 0.01$ ]. As expected, greater semantic activation was observed at posterior (mean = 0.59) than at anterior (mean = 0.11) left hemisphere sites. Right hemisphere activations in this task were 0.19 and 0.26 for the posterior and anterior sites, respectively. The means for the phonological task were 0.19, 0.15, 0.37, and 0.11 for the left posterior, left anterior, right posterior, and right anterior sites, respectively.

No reliable effects of task were observed in any of the other regions analyzed. However, in the occipital region both task and task by hemisphere interactions approached significance ( $P < 0.20$  for both). The means were 0.56, 2.11, 0.68, and 0.22 for semantic left, seman-

<sup>1</sup>It might be argued that frontal regions are likely to be more artifact-prone than others, due, for example, to the proximity of nasal sinuses, and further, that random activations might be more likely in one task than the other. While the statistical significance (across subjects) of the differences between the semantic and phonological tasks in inferior frontal regions addresses this concern directly, an additional control analysis was conducted as well. We subtracted the images from the first half of semantic trials from the second half of these trials, and the same was done for the rhyme task. It is predicted that the number and the location of activations observed in these pseudo-subtractions should not differ reliably across either regions or tasks. The results were consistent with this hypothesis; there were not reliably more activations observed in the inferior, middle, or superior frontal areas than in the corresponding temporal areas ( $F < 1$ ), nor did the interaction between this factor and area approach significance ( $F < 1$ ). This reinforces the conclusion that the observed differences in the frontal region in the primary analyses were genuine reflections of task-specific processing demands.

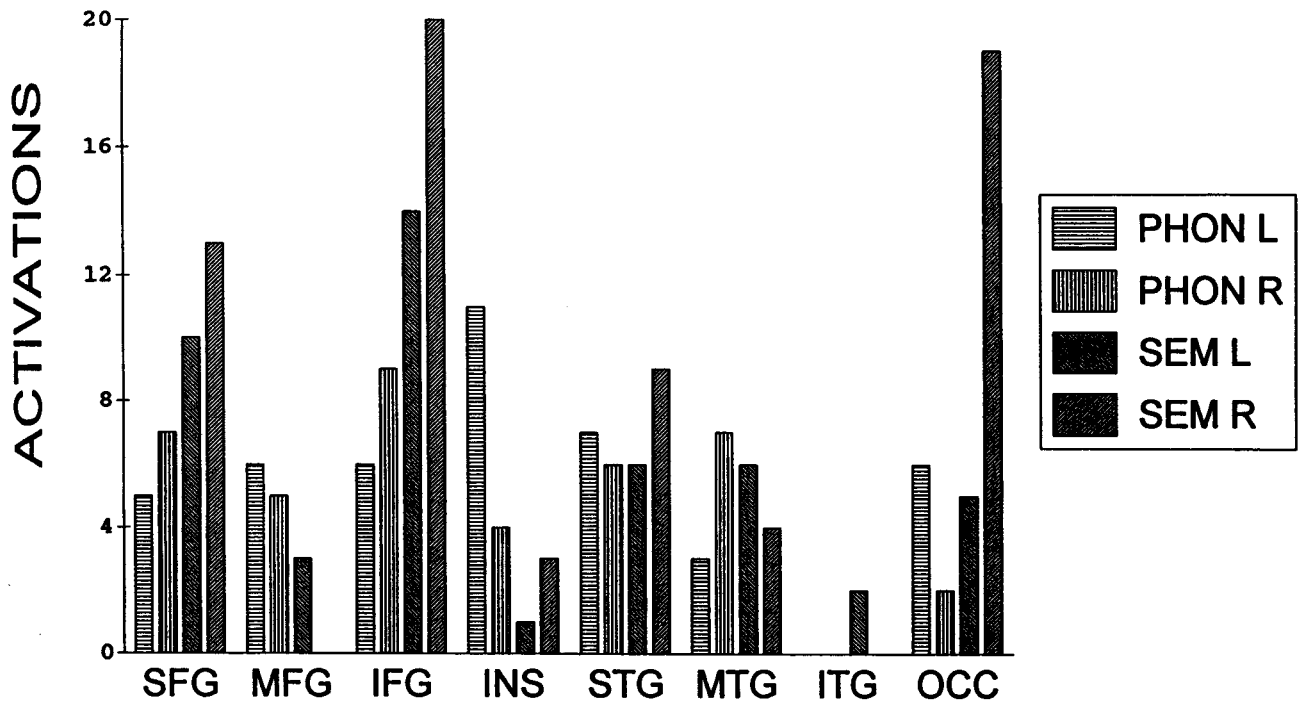


Figure 1.

Brain activations in regions of interest. Total number of activations over all subjects are shown along the ordinate for eight regions: superior frontal gyrus (SFG), middle frontal gyrus (MFG), inferior frontal gyrus (IFG), insula (INS), superior temporal gyrus (STG),

middle temporal gyrus (MTG), inferior temporal gyrus (ITG), and occipital cortex (OCC). Results are shown for left and right hemispheres (R, L) resulting from phonologic (PHON) and semantic (SEM) activations.

tic right, phonological left, and phonological right, respectively.

### Composite analysis

For all regions it is desirable to determine whether the activations produced by a given task tended to occur at common sites, and whether these sites differed between tasks. In order to make this determination, the images were linearly scaled along orthogonal directions so that the major axes of each slice were co-registered. The individual scaled activation maps were then superimposed, so that the clusters that had been identified on each subject and that formed the basis of the analysis of variance described above could now be visualized for the group as a whole. As indicated in Figure 2, semantic processing is associated with activation in frontal regions bilaterally, and in posterior portions of the left temporal lobe. A right occipital site is seen in this analysis as well. In contrast, phonological processing activates sites in the anterior portion of the left temporal lobe as well as sites within the left insular cortex.

### Correlational analysis

Exploratory correlational analyses were conducted on the plausible assumption that several anatomically distinct regions would most likely contribute to a given cognitive operation [Friston et al., 1993]. The goal was to identify those areas that tended to co-vary within a given task among our subjects. Correlations among the following regions and areas were measured: inferior, middle, and superior frontal, inferior, middle, and superior temporal, insula, limbic, and occipital. Table I presents significant correlations (with significance levels noted) for both the semantic and phonological subtractions. In the semantic task most of the correlations were within hemisphere. In the phonological task, however, a tendency toward bilateral correlations is evident. Several strong right hemisphere correlations were observed in the semantic task.

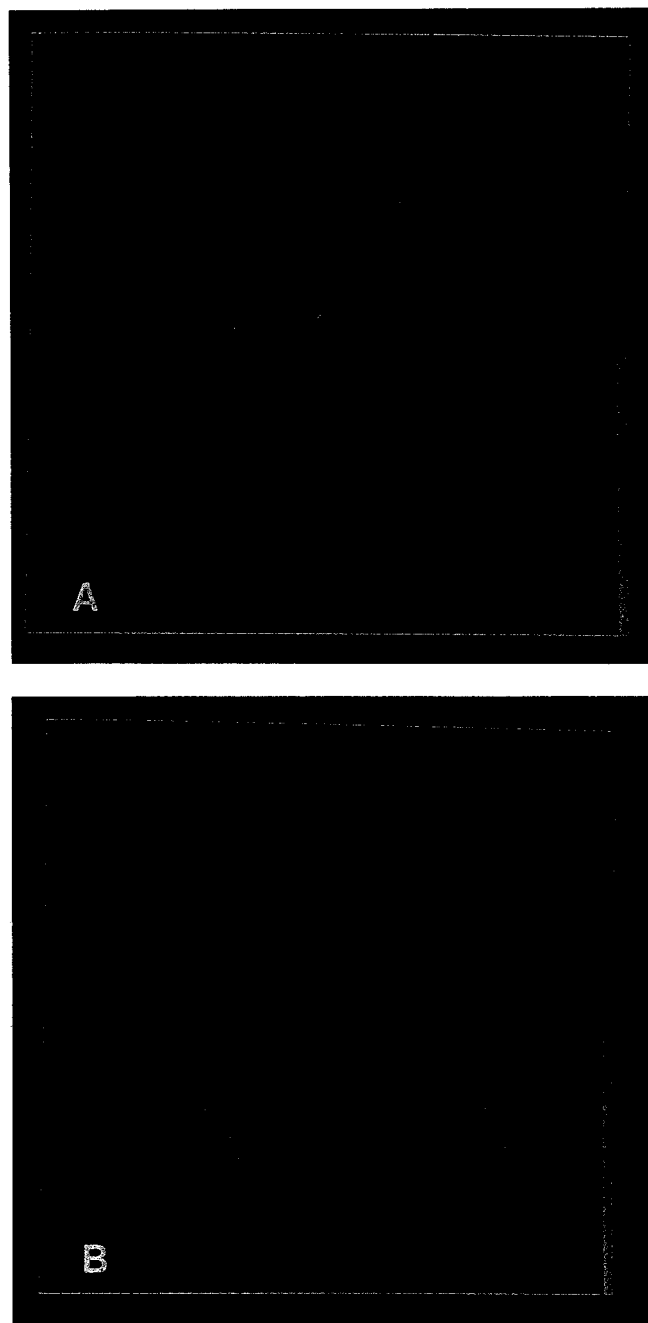
A cluster analysis was performed on these data and revealed two prominent semantic task groupings. The first was right hemispheric and included right superior temporal, occipital, insular, and limbic areas. A

second cluster was bi-hemispheric and consisted exclusively of temporal areas: right middle, left inferior, left middle, and left superior temporal areas. In the corresponding phonological task analysis, two prominent clusters were again observed. The first included the left and right superior temporal region along with the left occipital region. The second included both left and right superior frontal and left and right middle temporal regions. Clearly, in the phonological task both the

simple correlations and the cluster analysis reveal a tendency for analogous regions within the left and right hemispheres to be strongly associated. This pattern, however, is not prevalent in the semantic analysis.

## DISCUSSION

Taken together, the functional methods and the tasks used in these studies address a major controversy relating to the neuroanatomic foci of semantic processing; our findings indicate that semantic processing makes demands on and activates widespread areas within brain, including the inferior frontal regions bilaterally and the left posterior temporal region. Phonological processing, on the other hand,



**Figure 2.**

Summation of color-coded activation data superimposed on axial T1-weighted MR images at 8 mm above the bicommissural plane (A) and at the bicommissural plane (B). Orange/yellow areas represent activations based on the semantic minus phonological condition. Blue areas are the result of the phonological minus semantic condition. The areas included in this figure are those in which the summed *t* value was greater than 4 and the median *t* value greater than 0.6. By convention, images are oriented so that the left-hand side of the figure shows the right side of the brain. The following numbers in parentheses represent the geometric center of activation location (*x*, transverse with left hemisphere negative; *y*, anterior-posterior; *z*, cranio-caudal) in millimeters according to the CA-CP proportional grid system based on the atlas of Talairach and Tournoux [1988]. **A:** Semantic activation is seen in the left superior frontal gyrus (-20, 65, 8), subcortical white matter (-22, 40, 8), insula (-35, 15, 8), thalamus (-8, -10, 8), splenium of corpus callosum (-5, -27, 8), isthmus of cingulate gyrus (-7, -41, 8), and forceps major (-22, -50, 8). On the right side, the superior frontal gyrus/cingulate gyrus/corpus callosum genu region (15, 45, 8), inferior frontal gyrus (46, 27, 8), and corpus callosum were activated. Phonological activation occurred in the left precentral/superior temporal gyri (-60, 2, 8) and right middle frontal gyrus (31, 53, 8). **B:** Note semantic activation involving the left superior/middle temporal (-55, -35, 0) and occipital gyri (-5, -82, 0) and the right superior frontal (12, 53, 0) inferior frontal gyri (46, 32, 0), middle temporal/inferior temporal/middle occipital gyri and adjacent white matter (35, 60, 0), and in region of superior sagittal sinus (8, -88, 0). Phonological activation is seen involving the left insula/external capsule region (-31, 10, 0), insula/superior temporal gyrus (-40, -8, 0), and middle temporal (-38, 54, 0) and occipital gyri (-25, -74, 0). The right middle frontal (31, 61, 0), cingulate (6, 31, 0), insula (28, 10, 0), and middle temporal gyri (47, -46, 0) as well as the right anterior limb of the internal capsule (9, 0, 0) are activated.

TABLE I. Correlations between region by task

	Correlation
Semantic task	
R. superior temporal × R. limbic	0.67*
R. insula × R. limbic	0.75*
R. occipital × R. superior temporal	0.76*
R. insula × R. superior frontal	0.67*
L. inferior temporal × L. middle temporal	0.76*
L. occipital × L. superior frontal	0.69*
L. middle temporal × R. middle temporal	0.76*
Phonological task	
R. middle frontal × L. middle frontal	0.68*
R. middle temporal × L. superior frontal	0.69*
L. superior frontal × R. superior frontal	0.70*
L. middle temporal × L. superior frontal	0.74*
L. superior temporal × R. superior temporal	0.84**

\* $P < 0.05$ .\*\* $P < 0.01$ .

engages a more restricted neuroanatomic assembly, involving primarily anterior left temporal lobe sites.

A reliable increase in the number of activations observed at both left and right hemisphere inferior frontal regions was obtained in the semantic category generation task. As noted, in the Petersen study [Peterson et al., 1988] frontal activation was left lateralized. Whether the tendency to observe right as well as left hemisphere activation in the current study is a function of some difference between the semantic tasks used (e.g., it is possible that generating multiple exemplars is in some sense more cognitively demanding than generating single responses in the verb task), or instead reflects greater sensitivity to signal changes with fMRI remains to be determined. However, it should be noted that in the McCarthy et al. [1993] fMRI study, which used the verb generate task, wherein left hemisphere inferior frontal activation was observed for most subjects, for the two subjects who had right hemisphere scans, significant changes in signal were also observed in the right inferior frontal area. While the results from only two subjects

must be viewed as tentative, this observation would seem to be consistent with the possibility that differences between fMRI and PET sensitivity could account for this discrepancy.

It is important to note that in the current study some frontal activations were observed in both tasks both within and across subjects; we interpret the fact that more than twice as many activations were observed in the semantic task as reflecting a relatively greater demand placed on this region when search and generate processes focus on semantic as opposed to phonological knowledge structures. The exact locations of some of these frontal sites differed somewhat across subjects and hence would not be apparent in the composite image. Our ability, nonetheless, to detect reliable differences in activity within this region in the subject by subject analysis attests to the utility of individual analyses.

The hypothesis that semantic processing activates posterior temporal areas was confirmed in this experiment both in the individual analyses and by the composite analysis. Our analysis of the temporal region revealed a reliable task by hemisphere by anterior/posterior interaction. Within the left hemisphere most of the semantic activations were observed at posterior sites. Further, in the composite analysis a clear anterior to posterior distinction between the phonological and semantic activations is apparent. It seems reasonable to assert that the activations within the temporal lobe sites were more homogeneous across subjects given that the pattern is also revealed in the composite analysis. This result conforms with observations by Demonet and colleagues [1992] and Wise and his colleagues [Wise et al., 1991] as well as with clinical observations [Hart and Gordon, 1990]. The failure to observe this pattern of activation in Petersen's verb generate task [Petersen et al., 1988] may indeed have been due to the relatively weak demands placed on semantic processing by that task.

Exploratory correlational analyses for the semantic task revealed a right hemisphere clustering that included occipital, limbic, insular, and superior temporal regions. It should be noted that strong right hemisphere occipital activation was observed in the composite analysis, and a marginally significant interaction between task and hemisphere in this region was observed in the initial analyses as well. It might be hypothesized that these four regions form a distributed and functionally related system relevant to some aspect(s) of semantic processing. For example, the strong activation observed within the occipital lobe bilaterally and within the optic radiation white matter areas could be related to an imagery component of the



semantic processing task. Anecdotally, many of our subjects reported that the semantic generate task engaged imagery while the rhyme generate task did not. The pattern of correlations, in general, simply indicate that activation in one of these regions tends to co-occur with activation in these other regions as well. The fact that several of these regions were not reliably related to performance in the overall analyses (e.g., not reliable across subjects) may reveal something about the consequences of individual differences in processing strategies. For instance, some but not all of our subjects may activate a given area. However, for those who do so, other areas tend to be activated as well. In the current experiment, with a relatively small sample, this type of analysis must be treated as exploratory. However, we believe that by examining patterns of co-variation across regions for different subjects a better understanding of the neuroanatomy of individual differences might be obtained in future investigations.

The primary sites of unique activation in the rhyme task were observed at left anterior temporal and left insular regions (Fig. 2). Obviously, the phonological overlap between the two generate tasks may limit our ability to detect all sites relevant to phonological processing. For example, posterior temporal phonological sites have been reported in other studies [Demonet et al., 1992]. Subsequent studies will involve contrasting phonological tasks with specifically nonphonological control tasks.

In conclusion, the current study incorporates two important features designed specifically to eliminate the ambiguities noted in previous studies. The first involves the particular cognitive tasks. The tasks used here were specifically designed to equate memory search and response generation components, allowing semantic processes to be more clearly differentiated from other components of language processing, specifically phonological processes. A second feature relates to the use of fMRI, a methodology that offers significant advantages. Thus, this methodology allows us to examine the neuroanatomic foci of specific linguistic processes both by analysis of individual images on a case-by-case basis and by examination of a composite image; previous reports have all relied on the findings present in a composite derived from a group of subjects. Such composites can be misleading since they may be biased by the activity of just a few subjects. In contrast, in fMRI it is possible to determine brain activation patterns on an individual subject-by-subject basis, as was done in arriving at the data shown in Figure 1. The similarity of localization of language processes provided by the individual subject-

by-subject analysis compared with that seen on the composite in Figure 2 suggests that these findings are not artifactually weighted by a few nonrepresentative cases and reinforces our belief that the activation patterns reported are reliable and generalizable.

## ACKNOWLEDGMENTS

This research was supported by grants from the National Institute of Child Health and Human Development (PO1 HD21888, P50 HD25802, and HD01994).

## REFERENCES

- Blamire AM, Ogawa S, Ugurbil K, Rothman D, McCarthy G, et al. (1992): Dynamic mapping of human visual cortex by high-speed MRI. *Proc Natl Acad Sci USA* 89:11069-11073.
- Caplan D (1992): *Language: Structure, Processing, and Disorders*. Cambridge, MA: MIT Press.
- Constable RT, McCarthy G, Allison T, Anderson AW, Gore JC (1993): Functional brain imaging at 1.5T using conventional gradient echo MR imaging techniques. *Magn Reson Imaging* 11:451-459.
- Damasio AR, Tranel D (1993): Nouns and verbs are retrieved with differently distributed neural systems. *Proc Natl Acad Sci USA* 90:4957-4960.
- Demonet JF, Chollet F, Ramsey S, Cardebat D, Nespoulous JL, Wise R, Rascol A, Frackowiak R (1992): The anatomy of phonological and semantic processing in normal subjects. *Brain* 115:1753-1768.
- Demonet JF, Wise R, Frackowiak RSJ (1993): Language functions explored in normal subjects by positron emission tomography: A critical review. *Hum Brain Mapp* 1:39-47.
- Duvernoy HM (1991): *The Human Brain*. Vienna: Springer-Verlag.
- Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ (1993): Functional connectivity: The principal-component analysis of large (PET) data sets. *J Cereb Blood Flow Metab* 13:5-14.
- Frith CD, Friston KJ, Liddle PF, Frackowiak RSJ (1991): A PET study of word finding. *Neuropsychologia* 29:1137-1148.
- Gough PE (1972): One second of reading. In: Kavanagh JF, Mattingly IG (eds): *Language by Ear and Eye: The Relationship Between Speech and Reading*. Cambridge, MA: MIT Press, pp
- Hart J, Gordon B (1990): Delineation of single-word semantic comprehension deficits in aphasia, with anatomical correlation. *Ann Neurol* 27:226-231.
- Kwong KK, Belliveau JW, Chester DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R, Cheng H.-M., Brady TJ, Rosen BR (1992): Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci USA* 89:5675-5679.
- McCarthy G, Blamire AM, Rothman DL, Gruetter R, Shulman RG (1993): Echo-planar magnetic resonance imaging studies of frontal cortex activation during word generation in humans. *Proc Natl Acad Sci USA* 90:4952-4956.
- McClelland JL, Rumelhart DE (1981): An interactive activation model of context effects in letter perception: Part 1. An account of basic findings. *Psychol Rev* 88:375-407.
- Ogawa S, Lee TM, Nayak AS, Glynn P (1990a): Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn Reson Medicine* 14:68-78.

- Ogawa S, Lee TM, Kay AR, Tank DW (1990b): Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci USA* 87:9868-9872.
- Ogawa S, Tank DW, Menon R, Ellerman JM, Kim SG, Merkle H, Ugurbil K (1992): Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci USA* 89:5951-5955.
- Petersen SE, Fiez JA (1993): The processing of single words studied with positron emission tomography. *Annu Rev Neurosci* 1:509-530.
- Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME (1988): Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* 331:585-589.
- Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME (1989): Positron emission tomographic studies of the processing of single words. *J Cogn Neurosci* 1:153-170.
- Raichle ME, Fiez JA, Videen TO, MacLeod AK, Pardo JV, Fox PT, Petersen SE (1994): Practice-related changes in human brain functional anatomy during nonmotor learning. *Cereb Cortex* 4:8-26.
- Schad LR, Trost U, Knopp MV, Muller E, Lorenz WJ (1993): Motor cortex stimulation measured by magnetic resonance imaging on a standard 1.5T clinical scanner. *Magn Reson Imaging* 11:461-464.
- Shallice T (1988): *From neuropsychology to mental structure*. Cambridge: Cambridge University Press.
- Talairach J, Tournoux P (1988): *Co-planar Stereotaxic Atlas of the Human Brain. 3-Dimensional Proportional System: An Approach to Cerebral Imaging*. New York: Thieme Medical Publishers, Inc.
- Wise R, Chollet F, Hadar U, Friston K, Hoffner E, Frackowiak R (1991): Distribution of cortical neural networks involved in word comprehension and word retrieval. *Brain* 11:1803-1817.
- Zatorre RJ, Evans AC, Meyer E, Gjedde A (1992): Lateralization of phonetic and pitch discrimination in speech processing. *Science* 256:846-849.