Lateralized Human Brain Language Systems Demonstrated by Task Subtraction Functional Magnetic Resonance Imaging

Jeffrey R. Binder, MD; Stephen M. Rao, PhD; Thomas A. Hammeke, PhD; Julie A. Frost; Peter A. Bandettini; Andrzej Jesmanowicz, PhD; James S. Hyde, PhD

Objective: To develop a procedure for noninvasive measurement of language lateralization with functional magnetic resonance imaging (MRI).

Design: Functional neuroimaging using time-series echo-planar MRI.

Setting: University medical center research facility.

Subjects: Five healthy, right-handed, young adults.

Main Outcome Measures: Number of MRI voxels in left and right hemispheres showing task-related signal increases during two contrasting auditory processing tasks. The nonlinguistic task involved processing of pure tones, while the linguistic task involved processing of single words based on semantic content.

Results: The pure-tone processing task activated temporal lobe auditory areas and dorsolateral frontal regions bilaterally. Using this task as a control condition, the semantic processing task resulted in lateralized activity in distributed regions of the left hemisphere. A significant effect of task on intrahemispheric activity pattern was demonstrated in every subject. Results were reproduced in preliminary studies of test-retest reliability.

Conclusions: The results demonstrate the lateralized anatomy of semantic linguistic systems in contrast to nonlinguistic auditory sensory processors and introduce a task subtraction technique adapted for functional MRI as a noninvasive measure of language lateralization.

(Arch Neurol. 1995;52:593-601)

FUNCTIONAL neuroimaging using positron emission tomography (PET) has dramatically increased our understanding of language organization in the human brain. A major advance in this area followed the introduction and widespread use of a "subtraction" method for PET designed to identify brain structures specifically associated with particular cognitive processes.[1] The subtraction method compares blood flow maps generated under separate behavioral conditions that share some task requirements while differing in others. Subtraction of one map from another demonstrates those structures active during one task but not the other, reflecting differences in processing requirements between tasks. Using appropriate conditions, functional activity associated with early sensory processing and motor movement can be removed from the image, allowing the identification of regions associated with intermediate processing stages.[1-5]

Magnetic resonance imaging (MRI) during brain activation, herein referred to as functional magnetic resonance imaging (FMRI), is a new technique for measuring MRI signal changes associated with alterations in local cerebral blood oxygenation levels.[6-12] In explaining these changes, previous investigators have suggested that an increase in blood flow and oxygenation at the capillary venous level in metabolically active tissue[13] leads to decreased intravoxel dephasing, resulting in increased MRI signal in T_2- and T_2*-weighted images.[6,8-10,14] The FMRI method measures these event-related signal changes over time by acquiring a sequential series of images at the same tissue location. Although previous FMRI studies have examined only the signal changes occurring between active and resting states, it should be possible to measure

From the Departments of Neurology (Drs Binder, Rao, and Hammeke and Ms Frost) and Biophysics (Mr Bandettini and Drs Jesmanowicz and Hyde), Medical College of Wisconsin, Milwaukee.

See Subjects and Methods on next page

SUBJECTS AND METHODS

Subjects were three women and two men, aged 23 to 27 years, who had no neurologic symptoms, auditory symptoms, or known illness (**Table 1**). Edinburgh Handedness Inventory laterality quotients[20] ranged from 75 to 100, indicating strong right hand preferences. Subjects were recruited on a voluntary basis, gave written informed consent according to institutional guidelines, and were paid a small hourly stipend. All studies received prior approval by the institutional human research review committee.

APPARATUS AND SCANNING PROCEDURES

Imaging was performed at 1.5 T (General Electric Signa scanner) using three-axis head gradient and elliptical endcapped quadrature radiofrequency coils. A blipped gradient-echo, echo-planar sequence was used, with echo time of 40 milliseconds, repetition time of 3 seconds, field of view of 24 cm, matrix of 64×64, slice thickness of 10 mm, and voxel dimensions of 3.75×3.75×10 mm. At the time this study was conducted, scanner capabilities permitted simultaneous scanning of two brain slices. Symmetric sagittal slices of the left and right hemispheres were obtained, centered at positions 13 mm or 23 mm medial to the most lateral point of the temporal lobe on each side. Sequential images of each slice were collected concurrently by interleaving left- and right-sided acquisitions. Scanning also included acquisition of high-resolution anatomic images for localization purposes, located at the same plane and center position as the echo-planar images, using either a gradient recall at steady state or fast spin-echo sequence.

Each 138-image echo-planar series consisted of multiple periods of baseline, during which subjects rested or performed a "control" task, alternating with periods of activation, during which a contrasting "probe" task was performed (**Figure 1**). Subjects were scanned with eyes closed and room lights extinguished. Each series began with 10 images at rest (30 seconds) allowing MRI signal equilibrium to be reached, followed by 128 images during which activation alternated with baseline every 24 seconds (48 seconds per cycle, 16 images per cycle, eight cycles). Background scanner noise was constant through all baseline and activation periods. Stimuli were 16-bit digitally recorded pure tones and speech sounds that were presented at precise intervals using a computer playback system, amplified near the scanner using a magnetically shielded transducer system, and delivered to the subject via air conduction through a 180-cm length of paired plastic tubes. The tubes provided binaural stimulation through tightly fitting occlusive ear inserts that attenuated ambient scanner noise by 20 dB sound pressure level (SPL). Stimulus amplitude, which remained constant across all subjects, averaged 100 dB SPL for all tone and speech stimuli. Peak amplitude of the background scanner noise, which remained constant through all baseline and activation periods, was approximately 75 dB SPL after attenuation by the ear inserts. Subjects reported that the activation stimuli were subjectively louder than the background scanner noise.

ACTIVATION TASKS

Processing for simple acoustic information was tested using a pure-tone discrimination task ("tone monitoring"). In this task, subjects heard brief, clustered sequences of three to seven tones in which each constituent tone had either a low (500 Hz) or high (750 Hz) pitch. A response, consisting of briefly lifting the left index finger, was required for any sequence containing two tones of high pitch. Processing for semantic information was tested using a semantic decision task ("semantic monitoring"). In this task, subjects heard spoken English nouns designating animals (eg, "squirrel") and were required to respond with their left index finger according to specified semantic criteria. Criteria were that the animal named be both "native to the United States" and "commonly used by humans for food, clothing, or other purposes." The two tasks were matched for stimulus intensity (100 dB SPL), average stimulus duration per trial (0.75 seconds), average trial duration (3 seconds), and frequency of positive targets (one target per 8 seconds). Subjects received instructions and brief practice sessions with each task prior to entering the scanner.

Two task combinations were imaged. In the *tone monitoring–rest* subtraction, subjects performed the tone monitoring task eight times with eight intervening periods of rest. In the *semantic monitoring–tone monitoring* subtraction, subjects performed the semantic monitoring task eight times with eight intervening periods of tone monitoring. Brain areas that are equally active during both conditions were expected to show no signal change over time, whereas areas that are relatively more active during one of the con-

changes occurring between two active states that differ in a specific feature or set of features. Such changes would reflect brain activity specific to one of the tasks, and the regions showing such changes would be those participating more actively in one task than in the other. If feasible, this task subtraction technique could provide a powerful tool for the investigation of cognitive systems using FMRI.

We tested this method in a study of the anatomic organization of two distinct auditory processing stages with the aim of developing a noninvasive measure of language lateralization. We hypothesized that the processing of nonspeech sounds for elementary acoustic information (eg, pitch) would result in activity concentrated in unimodal auditory cortex bilaterally. In contrast, processing of speech sounds for semantic information was predicted to involve additional heteromodal areas in left frontal and posterior temporoparieto-occipital cortices.[1,5,15-19] Tasks were designed to control for nonlinguistic performance functions, including arousal, sustained attention, working memory, and motor response formation.

ditions should show signal enhancement that is temporally correlated with this condition (Figure 1). Areas activated by different conditions should show signal changes that are directly out of phase with one another.

Each subtraction was performed twice in each subject to obtain data from both lateral (13 mm from the temporal surface) and medial (23 mm from the temporal surface) slices. To test reproducibility of the response, subjects 1 and 3 had repeat testing of the *semantic monitoring–tone monitoring* condition for both sets of slices. Because of time limitations, subjects 1 and 3 did not have imaging of the medial slice during the *tone monitoring–rest* procedure. To test reproducibility across scanning sessions, subject 2 was tested again with the same tasks in a session 6 months later. The order of imaging for the slice combinations and tasks was varied randomly across subjects.

IMAGE ANALYSIS

Identification of voxels showing temporally correlated task activation was accomplished using the correlation technique described by Bandettini et al.[21] This method measures the correlation between a reference time series function and the time series data from each voxel. A previous analysis of the voxel data obtained in this study demonstrated considerable regional variation in temporal characteristics of the induced signal changes,[22] a situation that complicates the choice of a reference function for calculating the correlation. As shown in **Figure 2** (parts B and C), variability is present both in the latency preceding onset of signal change and in the rapidity with which signal changes are completed. To compensate for this variability, the correlation analysis was performed using two discontinuous square waves as reference functions (Figure 2, D). The discontinuity in the functions signifies that data points at these locations were not considered in the correlation computation.

These discontinuities were located at rise and fall points on the activation waves, thus minimizing variability in rise and fall rates as a factor influencing the correlation. To minimize the effects of variability in onset latency, the two reference functions were time shifted by one data point (3 seconds) relative to each other. For each voxel, the best correlation obtained with either reference function was used to determine significance. Only those voxels correlating at r of .45 or greater were considered significant. This cutoff corresponds to P of less than 10^{-5},[21] a value selected to reduce the likelihood of type I error owing to the large number of voxels (approximately 1000 per image) considered in each image analysis. This conservative threshold yields an average probability of less than .01 that *any voxel in the entire image* will exceed the threshold by chance alone. Images representing the magnitude of stimulus-locked signal change in these voxels were constructed by setting the brightness of each voxel to $K(r\varsigma)$, where ς is the SD of the voxel data (proportional to the magnitude of signal change), and K is a scale constant.[21] For anatomic localization, the brightness scale of the functional images was converted to a polychromatic scale, and functional images were superimposed on high-resolution anatomic images of the same brain slices after interpolating all images to 256×256.

In addition to the formation of functional images, quantitative counts were made of the area of activity (number of significantly active voxels) in each hemisphere and in specific regions during each subtraction procedure. Active voxels were defined as those showing significant positive correlations with periods of probe task performance. Intrahemispheric regions of interest included the following: (1) the frontal lobe, defined as all tissue rostral to the central sulcus and sylvian fissure; (2) the superior temporal gyrus, defined as all temporal lobe tissue within or superior to the superior temporal sulcus as far posterior as the termination of the sylvian fissure; and (3) temporo-parieto-occipital heteromodal cortex, defined as all temporal, temporo-occipital, or parietal tissue below the superior temporal sulcus, behind the sylvian fissure or behind the postcentral sulcus. Mean area measurements for the five subjects were compared for each hemisphere and for selected regions of interest using paired two-tailed t tests. The effect of task combination on the interhemispheric distribution of active voxels was tested individually for each subject using the χ^2 test.

PERFORMANCE ANALYSIS

Performance on the tone monitoring task was assessed by calculating overall accuracy on all trials of this task. Performance on the semantic monitoring task was assessed by correlating the pattern of responses produced by each subject with mean responses to the same stimuli produced by a group of 15 normal control subjects.

RESULTS

Overall performance accuracy exceeded 98% for the tone monitoring task, and correlations between individual and group mean responses on the semantic monitoring task were high ($r \geq .60$), indicating that the required tasks were performed and that subjects heard stimuli clearly despite the background scanner noise (see Table 1 for individual performance scores).

When compared with rest, the tone monitoring task was associated with bilateral areas of significant signal enhancement, concentrated in the superior temporal gyri (STG) and lateral frontal lobes (Figure 1, top; **Figure 3**, left). These areas included primary auditory cortex of the transverse temporal (Heschl's) gyri and more distributed cortex on the dorsal STG and the superior temporal sulcus in Brodmann's area (BA) 22. Enhancement was observed in every subject in the dorsolateral frontal cortices bilaterally; this was concentrated on the precentral and inferior frontal sulci and was approximately symmetric in most sub-

Table 1. Subject Demographic and Performance Data*

Subject/ Sex/Age, y	LQ	TM Score, % Correct	SM Score, r
1/M/24	100	99.2	.82
2/F/27	100	99.2	.78
3/F/23	100	99.6	.83
4/M/25	75	99.6	.60
5/F/23	83	98.5	.73

**LQ indicates handedness laterality quotient[20]; TM, tone monitoring; and SM, semantic monitoring.*

jects. Small bilateral foci of activity were also observed in the inferior parietal lobes in subjects 1 and 3 through 5, and in the cerebellum in subjects 2, 4, and 5. Although the overall area of activity during the tone monitoring task was greater in the right hemisphere in subjects 2, 4, and 5, area measurements did not differ significantly between hemispheres for the group as a whole (**Table 2**). Restricting this comparison to regions of interest in the frontal or superior temporal lobe also produced no significant differences between left and right hemispheres on this task.

A different pattern emerged when semantic monitoring was alternated with tone monitoring (Figure 1, bottom; Figure 3, right). The bilateral STG activity observed during tone monitoring (Figure 3, subject 1, arrowhead) was almost entirely absent in the semantic-tone subtraction, suggesting that these auditory areas were equally active during both monitoring tasks. In contrast, large cortical regions of the left lateral frontal lobe, including parts of BA 6, 9, and 44 through 47 (Figure 3, subjects 1 and 2, long arrows), showed MRI signal enhancement that was specifically related to periods of semantic monitoring performance. These active areas were concentrated along the left inferior frontal and precentral sulci, spreading more inferiorly and anteriorly than the lateral frontal activity associated with tone monitoring. Other left hemisphere foci temporally correlated with semantic monitoring were observed in more posterior heteromodal areas, including the left middle temporal gyrus (BA 21; subjects 1, 4, and 5), the parietotemporal cortex of the angular gyrus (BA 39; subjects 1 and 3 through 5), and cortex at the lateral temporo-occipital junction (BA 37 and 19; subjects 1, 2, and 4). Although the precise location and extent of these activated regions varied from subject to subject, a general pattern of left lateral frontal and left temporo-parieto-occipital heteromodal activity was evident. Smaller and less intense foci were observed in similar frontal and temporal regions of the right hemisphere, particularly in subjects 3 through 5.

The total area of activity as measured by active voxel counts was significantly greater in the left hemisphere than in the right hemisphere during the *semantic monitoring–tone monitoring* procedure (Table 2). Significant regional lateralization to the left hemisphere was also demonstrated in comparisons of left and right frontal lobe activity (mean left=70.4; mean right=9.6; P=.018) and left and right temporo-parieto-occipital activity (mean left=36.4; mean right=3.2; P=.011). A χ^2 analysis of the left/right distribution of activity in the two task combinations showed in every subject highly significant task effects on interhemispheric distribution (Table 2).

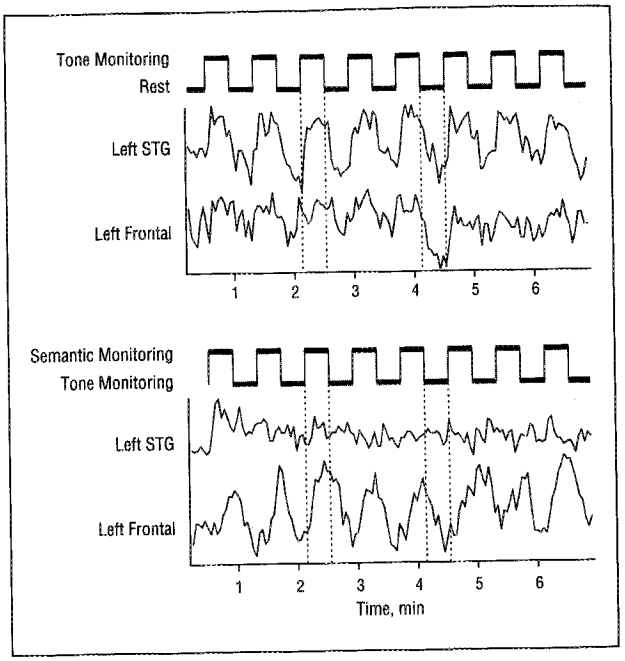

Figure 1. *Effects of task subtraction on activation-induced signal changes. Top, At the top are square wave deflections representing eight alternating cycles of "rest" and "tone monitoring" activity. Below this are averaged data from a sample of voxels in the left superior temporal gyrus (STG) and in the left lateral frontal lobe. The left STG shows signal changes that rise during tone monitoring activity and fall during rest periods. Smaller and less consistent changes are seen in the frontal lobe. Bottom, Alternation between semantic monitoring and tone monitoring eliminates signal fluctuations in the STG (same voxel sample as in top), presumably because the STG is equally activated by both tasks. In contrast, the frontal lobe shows signal changes that rise during semantic monitoring and fall during tone monitoring.*

Areas color-coded blue in Figure 3 were more active during the control condition of each procedure, which for the left side of Figure 3 consisted of a "resting" state, and for the right side of Figure 3 consisted of the tone monitoring task. These inversely correlated areas were typically small and of low intensity, and no consistent foci were observed across subjects during either task. Areas that were occasionally correlated with rest during the *tone monitoring–rest* procedure included the lateral frontal lobe (subject 2), the STG (subjects 3 and 5), and temporo-parieto-occipital regions (subjects 2, 3, and 5). The largest of these foci, in subjects 2 and 5 (Figure 3, arrowheads), were also areas that were activated by the semantic monitoring task (Figure 3, right), raising the possibility that these subjects may have been "rehearsing" the semantic monitoring task (ie, retrieving information about animals) during rest intervals of the tone monitoring procedure. Areas correlating with the tone monitoring task during the semantic–tone subtraction (blue, Figure 3, right) were located in the STG on either side (all subjects), the right postcentral sulcus (subjects 1 through 3 and 5), the right frontal lobe (subjects 1 and 2), and the right temporo-occipital junction (subject 5).

Figure 4 illustrates the locations of positively

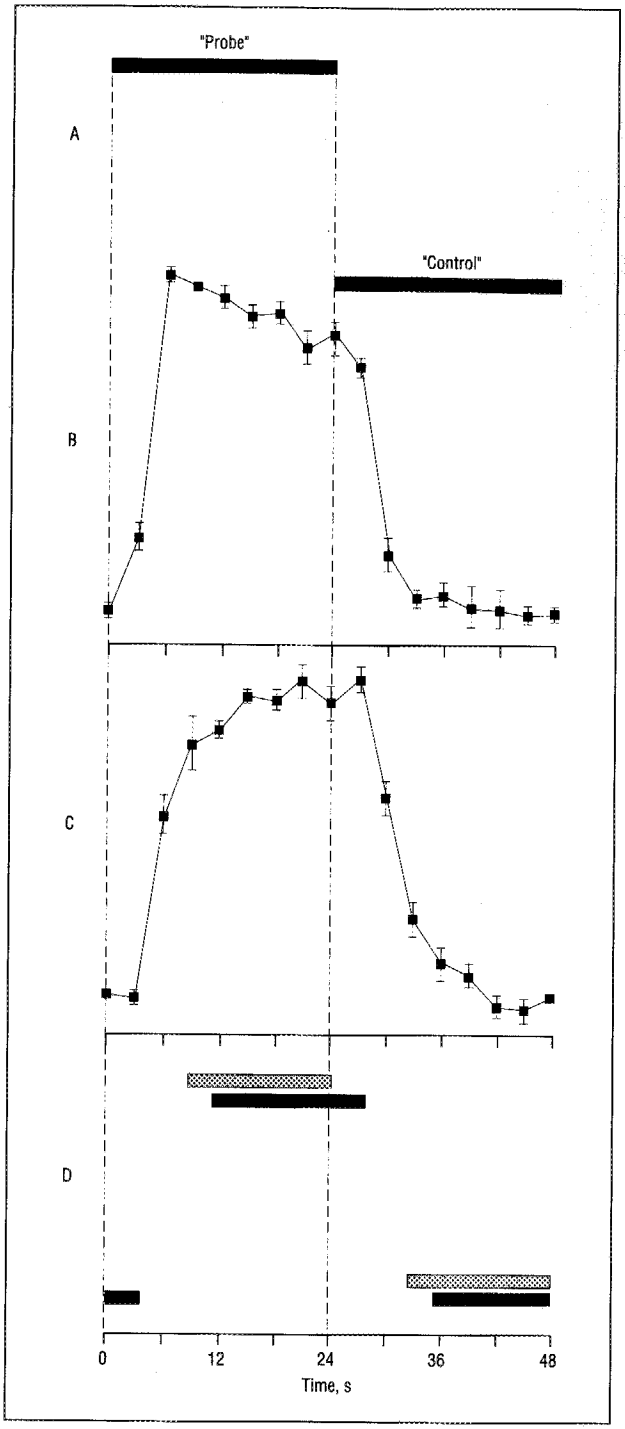

Figure 2. *Averaged signal changes and reference functions. A, Square wave deflection indicating one cycle of probe and control task activity. B, Average normalized signal changes (three subjects) in the left superior temporal gyrus during the* tone monitoring–rest *subtraction. Error bars indicate 95% confidence intervals. C, Average normalized signal changes in the left lateral frontal lobe during the* semantic monitoring–tone monitoring *subtraction. The latency to rise onset is longer, rise to maximum slower, latency to fall onset longer, and return to baseline slower than in B. D, Two discontinuous square wave reference functions (black and gray) used in the correlation analysis to identify active voxels.*

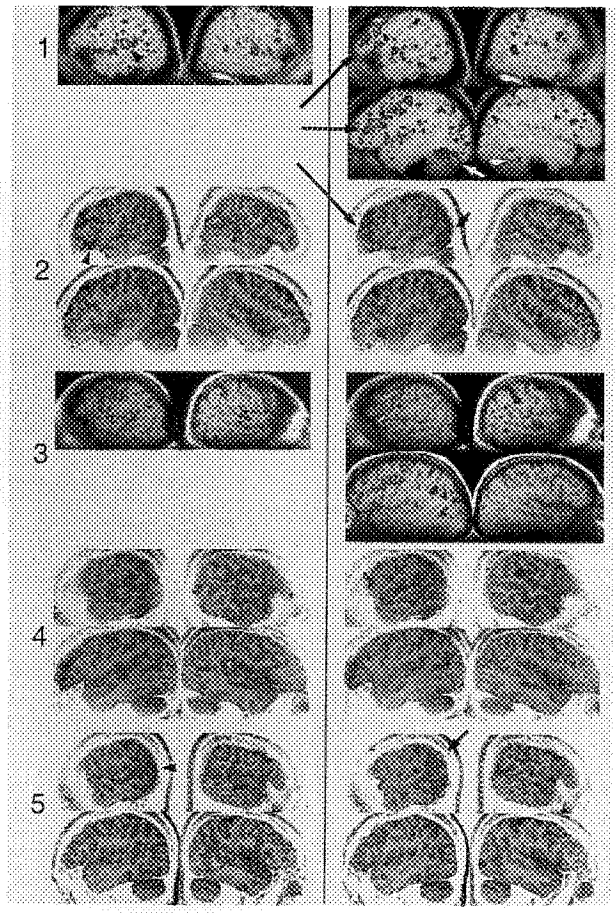

Figure 3. *Brain activation images in five subjects. For each subject, lateral brain slices are placed above medial slices, and left and right slices face in opposite directions. Activation during the* tone monitoring–rest *subtraction is shown on the left half of the figure; activation during the* semantic monitoring–tone monitoring *subtraction is shown on the right. Signal increases during the "probe" task (tone monitoring on left, semantic monitoring on right) are coded in red-yellow; signal increases during the "control" task ("rest" on left, tone monitoring on right) are coded in blue-cyan. Cortical tissue is darker than white matter on the anatomic images. Activation in superior temporal gyri bilaterally during tone monitoring (arrowhead, subject 1) is eliminated in the semantic-tone subtraction. Areas prominently activated during semantic monitoring include the left lateral frontal lobe (long arrows, subjects 1 and 2), left ventrolateral temporo-occipital junction (short arrows, subjects 1 and 2), and left angular gyrus region (arrow, subject 5). Several foci active during the rest state were also active during semantic monitoring (arrowheads, subjects 2 and 5).*

correlated voxels from the test-retest comparisons in subjects 1 through 3. The within-session comparisons (top half of Figure 4) show reproducibility of the lateralized frontal and posterior responses characterizing the *semantic monitoring–tone monitoring* subtraction, although small variations are present. The across-session comparisons in subject 2 (lower half of Figure 4) also suggest reproducibility of the response patterns, both in the *tone monitoring–rest* procedure and in the *semantic monitoring–tone monitoring* procedure. Although an effort was made to replicate exact slice locations across the two sessions with subject 2, slices were not identical. Despite these small discrepancies, laterality quotients were very similar across sessions for both the *tone monitoring–rest* procedure (laterality quotient for trial 1=−15; trial 2=−24) and for the *semantic monitoring–tone monitoring* procedure (trial 1=94; trial 2=89). The χ^2 test again showed highly significant effects of task condition on interhemispheric activity distribution (χ^2=55; $P<.001$).

Table 2. Area Measurements (Number of Positively Correlated Voxels), Laterality Quotients, and Comparisons for Two Task Subtraction Procedures

Subject	Tone Monitoring–Rest			Semantic–Tone Monitoring			$P(\chi^2)$
	Left	Right	LQ*	Left	Right	LQ*	
1	64	25	44	186	15	85	<.001 (22.1)
2	52	71	−15	105	3	94	<.001 (79.7)
3	33	13	43	106	12	80	<.01 (8.4)
4	51	113	−38	105	37	48	<.001 (55.9)
5	67	129	−32	79	30	45	<.001 (41.2)
Mean	53.4	70.2		116.2	19.4		
P(L vs R)		NS†			.0096		

*LQ indicates laterality quotient, computed as 100×(left−right)/(left+right).
†NS indicates not significant.

COMMENT

These preliminary observations suggest that FMRI could provide a noninvasive means of determining language lateralization. Although the precise location of signal enhancement associated with semantic processing varied from subject to subject, a general pattern of left frontal and left posterior heteromodal activity was observed. Patterns of lateralization seemed to be reproducible within and across testing sessions, despite small variations in slice positioning. Other investigators have also found FMRI response patterns to be reproducible across sessions.[23]

The test devised for this study examined two distinct anatomic systems important to human language function. Converging data from a variety of sources suggest that unimodal auditory systems of the superior temporal lobe decode the complex acoustic features found in speech, presumably activating neural representations of auditory speech at more abstract levels.[1,2,12,24-29] In addition to unimodal auditory processors, there likely exist supramodal language systems responsible for processes that link input from diverse brain regions and perform behaviorally relevant transformations and computations between auditory and other codes.[30] One example important to language function is the learned association of speech stimuli with various symbols, concepts, mental images, and motor responses; these associations and the processes by which they are activated by sensory representations may be described as a "semantic system."[30-33] While both auditory sensory processors and linguistic cognitive systems have been investigated using PET, the anatomic organization of the semantic system underlying many complex language functions remains uncertain.[1,2,5]

The preliminary results reported herein agree with previous studies suggesting qualitative differences between the anatomic structures subserving these two levels of auditory processing. Both of the tasks used were complex, attention-requiring tasks that could be expected to activate a distributed network of cortical regions. Our tone monitoring task required subjects to discriminate high and low pitches, to store complex instructions in verbal working memory, to monitor occurrences of a target tone, to mentally group sequences of tones into discrete clusters, and to perform a motor response according to learned verbal criteria. There were also demands on global executive systems governing sustained attention. The semantic monitoring task made similar demands on working memory, on the ability to group acoustic stimuli into relevant sequences, on performance of a simple motor act, and on sustained attention. Unlike the tone task, however, the semantic task directed attention not to the auditory stimulus itself, but to the stored semantic information (eg, verbal concepts, mental images) associated with the stimulus through previous experience. The cognitive subtraction MRI method eliminated areas used in common for both of these tasks, permitting brain areas to be identified that were specifically associated with this semantic processing component.

Our results agree with previous PET studies by Petersen et al[1] suggesting participation of the left lateral frontal lobe in semantic processing. The control task used for subtraction in these PET studies was significantly different from ours and consisted of spoken repetition of the same word stimuli used for the semantic task. This control provides an ideal means of subtracting any activity due to early auditory processing, since the same acoustic stimuli are used for both tasks. Lesion cases have shown, however, that repetition may occur as an involuntary, automatic response to speech input[15,34,35]; this task, therefore, may not provide an adequate control for various cognitive functions not specifically related to semantic processing, including verbal working memory and sustained attention. We sought to control for these task requirements by using a relatively complex, attention-requiring task for the control condition. The use of meaningful word stimuli for the control task in previous studies also could have adversely affected the results, since some processing of semantic information occurs automatically in the presence of meaningful stimuli even without a subject's conscious awareness of the stimulus content.[36-39] We therefore chose for our control condition simple auditory stimuli (pure tones) lacking a verbal semantic context.

The similarity in left lateral frontal activation in our and previous studies, despite differences in control conditions, confirms a major role for this area in semantic processing. This frontal localization is at odds, however, with classic concepts of fluent aphasia[40] and with

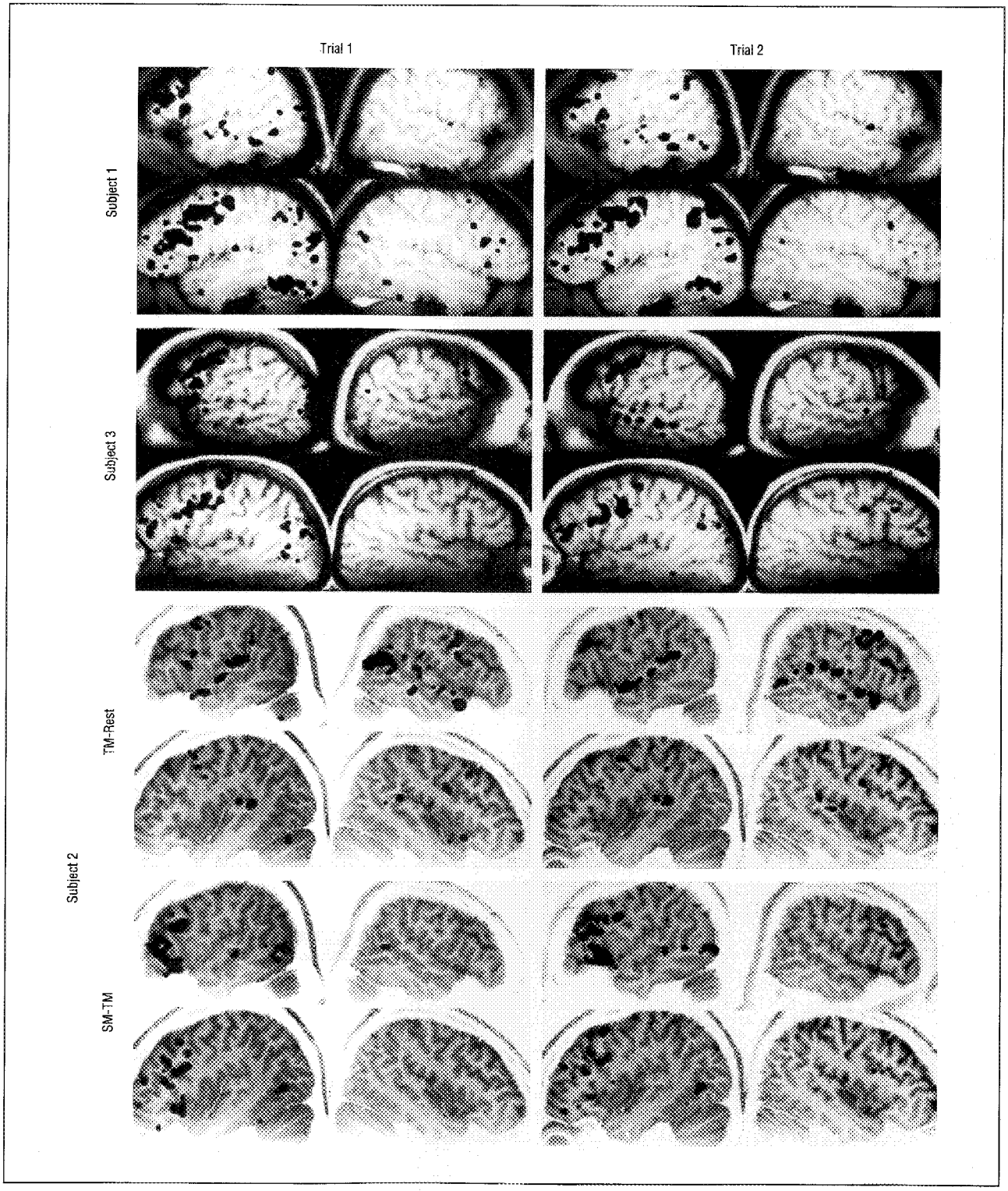

Figure 4. *Results of reproducibility studies in subjects 1 through 3. Activated areas are shown in black on the brain images. Observations in subjects 1 and 3 (top half of figure) were within-session comparisons, in which the* semantic monitoring–tone monitoring *procedure was repeated without subject repositioning. Observations in subject 2 (bottom half of figure) were made across scanning sessions, with similar but not identical positioning of slices. Repeated tests included both the* tone monitoring–rest *(TM-rest) and the* semantic monitoring–tone monitoring *(SM-TM) procedures.*

numerous modern lesion studies suggesting semantic knowledge deficits after posterior dominant temporal or temporoparietal lesions.[16-19,41] Our semantic task also showed significant activation in these more posterior areas, suggesting the importance of both left frontal and left posterior polymodal areas in semantic processing. Similar results have recently been reported in a PET study by Démonet and colleagues[5] using slightly different semantic and control tasks. One explanation for this widespread activity is that the frontal and posterior regions

may provide complementary functions in a distributed network controlling semantic processing. Lesion studies suggest that the left posterior components of this network constitute sites of storage for highly structured forms of semantic information.[41-43] The left frontal component, in contrast, may contain mechanisms facilitating access to this posterior information store.[44,45]

OUR RESULTS suggest that processing of nonspeech stimuli for pitch and simple sequence information (tone monitoring task) activates bilateral auditory and dorsolateral frontal cortices. We hypothesize that the bilateral frontal activity observed in this case is related to attentional and working memory components of the task. The greater area of activity in the right hemisphere in three of the subjects supports similar observations made using PET.[4] The specific component of the tone monitoring task responsible for right lateralization is uncertain from these data. Storage of pitch information in nonverbal working memory may depend primarily on right frontotemporal regions.[4,46]

Our findings differ from those obtained by McCarthy et al[11] from subjects performing a semantically mediated fluency task. This task reportedly produced bilateral, symmetric inferior frontal activation (other brain regions were not imaged), although activation occurred only when responses were spoken aloud and not when the task was "performed covertly." Explanations for the differences between this study and ours are tentative at best. As noted by McCarthy et al, the dependence of signal enhancement on orofacial movement production suggests a closer association with motor response systems than with semantic processing. This could also explain the lack of hemispheric lateralization observed by McCarthy et al that conflicts with PET studies using similar activation procedures.[1-3] The axial slice selected by McCarthy et al was located 8 mm below the anteroposterior commissural line, which would have been below the major frontal foci of activity observed in our subjects.

Two limitations of the current study require comment. The first of these is the restriction of image acquisition to relatively lateral brain areas. Although our methods have recently been updated to allow whole-brain data acquisition, this preliminary study was limited to four slices imaged during two scanning sequences. As a result, we have no information regarding more medial brain structures, such as the cingulate, paracingulate, and supplementary motor areas, which may have been activated symmetrically or asymmetrically during these tasks. Such activation would not in principle alter the lateralization findings of this study, which apply only to lateral convexity structures.

A second limitation is the relatively low spatial resolution of the functional images obtained in this study. The voxel size was large enough that small (eg, diameter <1 mm) regions of activity could have been missed because of intravoxel signal averaging with inactive tissue. Another consequence of this limitation is that the size of venous structures responsible for signal enhancement remains uncertain. It is possible that some voxels appeared "active" because they contained large veins that drained active regions located some distance away, rather than small intraparenchymal venous structures.[47]

Despite these limitations, our FMRI semantic monitoring subtraction may prove useful as a noninvasive indicator of language lateralization, potentially replacing the intracarotid amobarbital (Wada) test[48] for this purpose. The FMRI procedure would be easier to administer and repeat, and would offer considerably lower risk to patients than the Wada test. In addition to hemispheric lateralization information, the FMRI procedure provides intrahemispheric localization information that the Wada test does not furnish. Test-retest reliability of the Wada test is not known or easily obtainable, whereas such measures could be obtained for the FMRI test. We currently are testing the procedure in a large number of right- and left-handed normal subjects to assess reliability and normal variability, and in an abnormal population undergoing Wada tests to assess the degree of correlation between these measures. The Wada test is also used in many centers to measure laterality of memory functions. To date and to our knowledge, there has been no investigation of long-term verbal memory systems with FMRI, although procedures for activating this brain system will be required before FMRI can completely supplant the Wada test for clinical use.

Accepted for publication May 17, 1994.

This investigation was supported in part by a grant from the McDonnell-Pew Program in Cognitive Neuroscience, St Louis, Mo, and by grant CA41464 from the National Institutes of Health, Bethesda, Md.

Reprint requests to Department of Neurology, Medical College of Wisconsin, 9200 W Wisconsin Ave, Milwaukee, WI 53226 (Dr Binder).

REFERENCES

1. Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME. Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature.* 1988;331:585-589.
2. Wise R, Chollet F, Hadar U, Friston K, Hoffner E, Frackowiak R. Distribution of cortical neural networks involved in word comprehension and word retrieval. *Brain.* 1991;114:1803-1817.
3. Frith CD, Friston KJ, Liddle PF, Frackowiak RSJ. A PET study of word finding. *Neuropsychologia.* 1991;29:1137-1148.
4. Zatorre RJ, Evans AC, Meyer E, Gjedde A. Lateralization of phonetic and pitch discrimination in speech processing. *Science.* 1992;256:846-849.
5. Démonet J-F, Chollet F, Ramsay S, et al. The anatomy of phonological and semantic processing in normal subjects. *Brain.* 1992;115:1753-1768.
6. Bandettini PA, Wong EC, Hinks RS, Tikofsky RS, Hyde JS. Time course EPI of human brain function during task activation. *Magn Reson Med.* 1992;25:390-397.
7. Rao SM, Binder JR, Bandettini PA, et al. Functional magnetic resonance imaging of complex human movements. *Neurology.* 1993;43:2311-2318.
8. Kwong KK, Belliveau JW, Chesler DA, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci U S A.* 1992;89:5675-5679.
9. Ogawa S, Tank DW, Menon R, et al. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping using MRI. *Proc Natl Acad Sci U S A.* 1992;89:5951-5955.

10. Frahm J, Merboldt K-D, Hänicke W. Functional MRI of human brain at high spatial resolution. *Magn Reson Med.* 1993;29:139-144.
11. McCarthy G, Blamire AM, Rothman DL, Gruetter R, Shulman RG. Echo-planar magnetic resonance imaging studies of frontal cortex activation during word generation in humans. *Proc Natl Acad Sci U S A.* 1993;90:4952-4956.
12. Binder JR, Rao SM, Hammeke TA, et al. Functional magnetic resonance imaging of human auditory cortex. *Ann Neurol.* 1994;35:662-672.
13. Fox PT, Raichle ME. Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects. *Proc Natl Acad Sci U S A.* 1986;83:1140-1144.
14. Ogawa S, Lee TM, Nayak AS, Glynn P. Oxygenation-sensitive contrast in magnetic resonance image of rodent brain at high magnetic fields. *Magn Reson Med.* 1990;14:68-78.
15. Geschwind N, Quadfasel FA, Segarra JM. Isolation of the speech area. *Neuropsychologia.* 1968;6:327-340.
16. Coughlan AK, Warrington EK. Word-comprehension and word-retrieval in patients with localized cerebral lesions. *Brain.* 1978;101:163-185.
17. Warrington EK, Shallice T. Category specific semantic impairments. *Brain.* 1984; 107:829-854.
18. Bub DN, Black S, Hampson E, Kertesz A. Semantic encoding of pictures and words: some neuropsychological observations. *Cogn Neuropsychol.* 1988;5: 27-66.
19. Alexander MP, Hiltbrunner B, Fischer RS. Distributed anatomy of transcortical sensory aphasia. *Arch Neurol.* 1989;46:885-892.
20. Oldfield RC. The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia.* 1971;9:97-113.
21. Bandettini PA, Jesmanowicz A, Wong EC, Hyde JS. Processing strategies for time-course data sets in functional MRI of the human brain. *Magn Reson Med.* 1993;30:161-173.
22. Binder JR, Rao SM, Hammeke TA, et al. Temporal characteristics of functional magnetic resonance signal change in lateral frontal and auditory cortex. *Proc Soc Magn Reson Med.* 1993;3:5. Abstract.
23. Cohen NJ, Banich MT, Kramer AF, et al. Assessing test-retest reliability of functional MRI data. *Proc Soc Magn Reson Med.* 1993;3:1410. Abstract.
24. Whitfield IC, Evans EF. Responses of auditory cortical neurons to stimuli of changing frequency. *J Neurophysiol.* 1965;28:655-672.
25. Winter P, Funkenstein HH. The effect of species-specific vocalization on the discharge of auditory cortical cells in the awake squirrel monkey *(Saimiri sciureus). Exp Brain Res.* 1973;18:489-504.
26. Mendelson JR, Cynader MS. Sensitivity of cat primary auditory cortex (AI) to the direction and rate of frequency modulation. *Brain Res.* 1985;327:331-335.
27. Liberman AM, Cooper FS, Shankweiler DP, Studdert-Kennedy M. Perception of the speech code. *Psychol Rev.* 1967;74:431-461.
28. Auerbach SH, Allard T, Naeser M, Alexander MP, Albert ML. Pure word deafness: analysis of a case with bilateral lesions and a defect at the prephonemic level. *Brain.* 1982;105:271-300.
29. Tanaka Y, Yamadori A, Mori E. Pure word deafness following bilateral lesions: a psychophysical analysis. *Brain.* 1987;110:381-403.
30. Damasio AR. Time-locked multiregional retroactivation: a systems-level proposal for the neural substrates of recall and recognition. *Cognition.* 1989;33: 25-62.
31. Tulving E. Episodic and semantic memory. In: Tulving E, Donaldson W, eds. *Organization of Memory.* Orlando, Fla: Academic Press Inc; 1972:381-403.
32. Warrington EK. Neuropsychological studies of verbal semantic systems. *Philos Trans R Soc Lond.* 1981;295(series B):411-423.
33. Shallice T. Specialisation within the semantic system. *Cogn Neuropsychol.* 1988; 5:133-142.
34. Liepmann H. Ein Fall von Echolalie. *Neurol Zentralbl.* 1900;19:389-399.
35. Brown JW. The problem of repetition: a study of 'conduction' aphasia and the 'isolation' syndrome. *Cortex.* 1975;11:37-52.
36. LaBerge D, Samuels J. Toward a theory of automatic information processing in reading. *Cogn Psychol.* 1974;6:293-323.
37. Carr TH, McCauley C, Sperber RD, Parmalee CM. Words, pictures, and priming: on semantic activation, conscious identification, and the automaticity of information processing. *J Exp Psychol Hum Percept Perform.* 1982;8:757-777.
38. Marcel AJ. Conscious and unconscious perception: experiments on visual masking and word recognition. *Cogn Psychol.* 1983;15:197-237.
39. Bajo MT. Semantic facilitation with pictures and words. *J Exp Psychol Learn Mem Cogn.* 1988;14:579-589.
40. Wernicke C. *Der aphasische Symptomenkomplex.* Breslau, Poland: Cohn & Weigert; 1874.
41. Warrington EK, McCarthy RA. Categories of knowledge: further fractionations and an attempted integration. *Brain.* 1987;110:1273-1296.
42. Hart J, Gordon B. Delineation of single-word semantic comprehension deficits in aphasia, with anatomic correlation. *Ann Neurol.* 1990;27:226-231.
43. Hillis AE, Caramazza A. Category-specific naming and comprehension impairment: a double dissociation. *Brain.* 1991;114:2081-2094.
44. Milberg W, Blumstein SE, Dworetzky B. Processing of lexical ambiguities in aphasia. *Brain Lang.* 1987;31:138-150.
45. Swinney D, Zurif E, Nicol J. The effects of focal brain damage on sentence processing: an examination of the neurological organization of a mental module. *J Cogn Neurosci.* 1989;1:25-37.
46. Zatorre RJ, Samson S. Role of the right temporal neocortex in retention of pitch in auditory short-term memory. *Brain.* 1991;114:2403-2417.
47. Menon RS, Ogawa S, Merkle H, Tank DW, Ugurbil K. Sub-millimeter functional MRI studies of photic stimulation: spatial separation of the tissue and vessel BOLD response using FLASH at 4 Tesla. *Proc Soc Magn Reson Med.* 1993;3:165. Abstract.
48. Loring DW, Meador KJ, Lee GP, King DW. *Amobarbital Effects and Lateralized Brain Function: The Wada Test.* New York, NY: Springer-Verlag NY Inc; 1992.

ARCHIVES Circulation

The ARCHIVES is available by request to nonfederal physicians in the United States (50 states and Washington, DC) whose official American Medical Association masterfile record shows a primary specialty of neurology or child neurology in an office- or hospital-based practice as a staff physician, resident in training beyond the first year, or clinical fellow.

If you meet the above qualification criteria and are not currently receiving the ARCHIVES and would like to receive it each month, you must complete a free subscription request card. To receive a request card, please write to Kathryn Osten, American Medical Association, Circulation Processing Department, 515 N State St, Chicago, IL 60610 (FAX 312-464-5831). A subscription request card wil be sent to you in response. If you are a resident or fellow, please include verification of your training program and a complete mailing address.