Functional MRI of Language Processing: Dependence on Input Modality and Temporal Lobe Epilepsy


Summary: Purpose: Functional magnetic resonance imaging (fMRI) using two language-comprehension tasks was evaluated to determine its ability to lateralize language processing and identify regions that must be spared in surgery. Methods: Two parallel cognitive language tasks, one using auditory input and the other visual input, were tested in a group of control subjects and in temporal lobe epilepsy patients who were candidates for surgical intervention. The patient studies provide an opportunity to compare functional MRI language localization with that obtained using Wada testing and electrocorticography. All of the patients in this study underwent all three procedures and a battery of neuropsychological testing. Such studies provide an opportunity not only to validate the fMRI findings but also, by comparing the patient results with those obtained in control subjects, to provide insight into the impact of a pathology such as epilepsy on cortical organization or functional patterns of activation. Results: The results reveal both modality-dependent and modality-independent language-processing patterns for visual versus auditory task presentation. The visual language task activated distinct sites in Broca’s area, BA (Brodmann area) 44 that were not activated in the auditory language task. The auditory language task strongly activated contralateral right BA22-21 area (homologous to Wernicke’s area on the left). Language lateralization scores were significantly stronger for visual than for auditory task presentation. The conjunction of activation from the two different input modalities (modality-independent areas) likely highlights regions that perform more abstract computations (e.g., syntactic or pragmatic processing) in language processing. Modality-specific areas (e.g., right Wernicke, left fusiform gyrus, Broca BA44, supramarginal gyrus), appear to cope with the computations relevant to making contact with these more abstract dimensions. Patients showed recruitment of contralateral homologous language areas (p < 0.005) that was significantly above that found in a normal control group. Extra- and intraoperative cortical stimulations were concordant with the fMRI data in eight of 10 cases. The fMRI lateralization scores were also consistent with the Wada testing in 8/10 patients.

ganization of these processes remains uncertain (1–3). The ability to develop a detailed map of language systems with a noninvasive technique may allow better prediction of clinical outcome after surgery in the language-dominant hemisphere.

Several studies of fMRI language activation have reported left hemisphere lateralization for language in control subjects and patients. However, only a very limited number of studies have validated their fMRI results with Wada testing in the same sample. Springer et al. (4) reported the largest sample of fMRI language lateralization to date. In this study, 100 normal controls and 50 patients with epilepsy were studied using a semantic decision task with auditory presentation of verbal stimuli. However, although they report that the epilepsy patients underwent the IAP (Wada test [5]), comparison of the laterality as determined by these two techniques is not reported. Nonetheless, they report fMRI-determined lateralization in normal subjects that is consistent with reported frequency of left and right hemisphere language dominance in other studies. In an earlier study, Desmond et al. (6) reported fMRI and Wada results in seven patients (3 right hemisphere dominant). Their fMRI task used visually presented words, and required a perceptual or semantic judgment about the subjects. The resulting activation of the inferior frontal gyrus and neighboring cortex (BA 45, 46 and 47) during fMRI was concordant with the Wada result in all 7 cases. Binder et al. (7) also reported a strong correlation between Wada test results and fMRI. In their sample of 22 consecutive epilepsy patients, the correlation between Wada results and a fMRI single-word activation task also suggested that language lateralization was a continuous, rather than a dichotomous, variable.

Determination of language lateralization is an important goal of both the Wada and fMRI. However, more-specific functional maps are often needed to assist with defining the boundaries of language for minimizing postoperative language morbidity. This is accomplished by using direct cortical stimulation of the cerebral cortex during surgery on an awake patient, or with implantation of subdural grids. To increase our understanding of fMRI activation patterns, direct clinical correlation of stimulation-derived functional maps with fMRI language maps is needed. Roux et al. (8) reported a series of 22 patients that underwent cortical stimulation and fMRI. Cortical stimulation for motor function (16 of the 22 patients) was consistent with the fMRI data. However, the remaining six patients had temporal lobe tumors and underwent stimulation for language mapping, for which concordance was poor and limited to anterior (precentral) language areas. Similar studies have been performed comparing positron emission tomography (PET) activation maps with cortical stimulation data (9,10) wherein increased blood flow was observed in PET imaging during both visual and auditory naming tasks, and these regions of increased flow corresponded to regions in which subdural electrodes disrupted language during electrical stimulation.

In general, fMRI language studies have shown promising results, but several issues limit interpretation and consequently the clinical applicability at present. First, the clinical correlations with the Wada test are good, but not perfect. This may be a methodologic issue with respect to the types of language tasks that are used, with fMRI more readily classifying language laterality along a continuum. Second, most of the studies that report Wada and fMRI results are small samples and use various methods, and consequently need replication. In addition, although it is clear that multiple methods can produce activation, the studies have been limited to single-method tasks and may not produce activation in a distributed language system. For example, studies have shown critical areas for word generation, semantic functions, and lexical processing, but only a limited number have established a pattern of whole-sentence processing, which requires both semantic and syntactic processing (11–17). The final difference between functional MRI mapping and Wada testing concerns the issue of which hemisphere is critical to a task (which is defined by Wada) versus regions that are involved in some aspect of a task (which are defined by fMRI, and which may or may not be critical). Comparing fMRI activation patterns with cortical stimulation and Wada results will improve our understanding of the patterns of activation observed in fMRI.

The present study was undertaken with several goals in mind. First, we examined cortical localization for sentence processing in both nonimpaired controls (n = 10) and a sample of epileptic patients (n = 10). The language tasks used were designed to engage broadly those neural circuits necessary for the lexical access, syntactic analysis, and comprehension of both spoken and printed language materials, thereby providing activation of a distributed language system. By examining activations coincident with both the auditory and visual input pathways, we separate perception effects from more direct language-processing effects. However, modality-specific areas are not less clinically important, as damage to such areas also can lead to cognitive deficits. Studies comparing visual and auditory input in language tasks have been demonstrated to be effective in PET imaging (9,10).

The group comparison (controls vs. patients) asks how patients with a history of neurologic impairment differ from controls when performing the same relatively simple language tasks. Most important, our goal is to validate the fMRI language findings in the patient sample by using established methods of determining language laterality (Wada test) and intrahemispheric localization (cortical stimulation). We contrast both in-
ferred lateralization and within-hemisphere localization from fMRI measures with standard measures including Wada testing and intra/extracortical stimulation.

**METHODS**

**Control subjects**

The control sample was composed of 10 healthy volunteers (numbers 1 to 10) without neurologic impairment: four women and six men. To match the patient population, we included two left-handed in addition to eight right-handed subjects. Ages ranged from 19 to 62 years (mean, 32.3; median, 33). Subjects were recruited on a voluntary basis, and gave informed consent according to institutional guidelines. Studies received prior approval by the institutional human research review committee.

**Patients**

The patient sample was composed of 10 consecutive epilepsy surgery candidates (numbers 11 to 20) with left hemisphere seizure foci in or proximal to cortical areas typically associated with language processing and production (Table 1). Patients were studied before they underwent a left hemisphere surgical procedure for seizure control. The population was composed of five women, and five men, aged from 24 to 51 years (mean, 37.9; median, 37). Two of the 10 patients were left-hand dominant (numbers 13, 14). Both of these patients had extensive structural abnormalities, in the left cerebral hemisphere, associated with perinatal injuries. A third patient (number 17) was ambidextrous, and had a congenital lesion and vascular malformation associated with Sturge–Weber syndrome. Pathologies included left parietal cortical migration disorder (number 11), left inferior frontal gyrus and precentral gyrus cortical dysplasia (number 12), left parietal porencephaly with left hippocampal atrophy (number 13), late childhood porencephaly in the left middle cerebral artery distribution with abnormal signal in the left hippocampus (number 14), left hippocampal atrophy (number 15), left inferior temporal gyrus 0.75-cm grade II astrocytoma (number 16), left temporoparietal Sturge–Weber (number 17), left temporal posttraumatic focus with normal MRI findings (number 18), left inferior temporal gyrus 0.5-cm dysembryoplastic neuroepithelial tumor (DNET) (number 19), left fusiform 0.75-cm cavernous malformation (number 20). Although this patient population represents a highly heterogeneous group, it allows a general examination of the effects of temporal lobe epilepsy on language function, and most important, it provides a population for validating the fMRI activation regions with cortical stimulation and Wada testing. These patients differed in the location of lesions and in the duration of epilepsy, and a much larger sample will be required to examine the effects of specific lesion types, lesion locations, and/or possible reorganization patterns as a function of epilepsy duration or onset.

**Tasks**

Language tasks were designed that required visual or auditory comprehension and processing of syntactic and semantic dimensions to judge sentence accuracy. Half of the sentences contained either syntactic or semantic er-

**TABLE 1. Patient description, and fMRI-Electro-Wada correlation results**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Handedness</th>
<th>Epileptic focus location and pathology</th>
<th>Duration of epilepsy (yr)</th>
<th>Grid mapping</th>
<th>Intraop mapping</th>
<th>Correlation fMRI–Electro</th>
<th>fMRI vs. Wada results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>F</td>
<td>RH</td>
<td>Left parietal cortical migration disorder</td>
<td>16</td>
<td>Yes</td>
<td>No</td>
<td>Good: 3/3</td>
<td>Similar</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>F</td>
<td>RH</td>
<td>Left frontal dysplasia</td>
<td>20</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td>Similar</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>F</td>
<td>RH</td>
<td>Left parietal porencephaly</td>
<td>23</td>
<td>Yes</td>
<td>Yes</td>
<td>Good: 0/0</td>
<td>Similar</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>M</td>
<td>LH</td>
<td>Left sylvian and hippocampal ischemia</td>
<td>41</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td>Similar</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>M</td>
<td>RH</td>
<td>Left hippocampal atrophy</td>
<td>21</td>
<td>Yes</td>
<td>No</td>
<td>Good: 0/0</td>
<td>Similar</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>M</td>
<td>RH</td>
<td>Left inferior temporal gyrus 0.75-cm lesion</td>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>Good: 3/3</td>
<td>Similar</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>M</td>
<td>Ambid</td>
<td>Left temporoparietal Sturge–Weber</td>
<td>35</td>
<td>Yes</td>
<td>No</td>
<td>Good: 3/3</td>
<td>Nonconcordant</td>
</tr>
<tr>
<td>8</td>
<td>51</td>
<td>M</td>
<td>RH</td>
<td>Left posttraumatic focus, normal MRI</td>
<td>17</td>
<td>Yes</td>
<td>Yes</td>
<td>Good: 2/2</td>
<td>Similar</td>
</tr>
<tr>
<td>9</td>
<td>42</td>
<td>F</td>
<td>RH</td>
<td>Left inferior temporal 0.5-cm DNET</td>
<td>13</td>
<td>Yes</td>
<td>No</td>
<td>Good: 4/4</td>
<td>Similar</td>
</tr>
<tr>
<td>10</td>
<td>49</td>
<td>F</td>
<td>RH</td>
<td>Left fusiform 0.75-cm cavernoma</td>
<td>1</td>
<td>No</td>
<td>No</td>
<td>Unknown 15/15</td>
<td>Similar 9/10</td>
</tr>
</tbody>
</table>

Patient population consisted of 10 consecutive epilepsy patients for whom an epileptic focus had been indicated to be in the temporal lobe near language functional cortex areas. The last two columns display the correlation between fMRI, electrophysiology, and Wada test results. The numbers refer to the number of sites activated with each modality (for example: 0/0 indicates no sites were activated in fMRI or electrocorticography) in the region covered by the electrodes. fMRI, functional magnetic resonance imaging; DNET, dysembryoplastic neuroepithelial tumor.
rors, such as nonsense noun or nonsense verb associations (babies can fly, baby can crying); half were good form sentences (for details on the stimuli, see refs. 16, 17). Subjects were required to respond via a button press if sentences (presented every 2.5 s) were fully correct, or either semantically–syntactically incorrect. One hundred sentences of three words (subject, verb, and complement) were presented orally or visually. Words were matched for length and number of syllables.

Control tasks were designed to direct subjects’ attention to the physical characteristics of nonlinguistic stimuli (tone or line decision). It is known that a variety of general-purpose nonlinguistic functional systems are activated during most language behaviors, and that an “automatic” processing of linguistic stimuli takes place at phonologic and semantic levels regardless of the behavioral situation (18). Activation from motor systems, visual systems, auditory systems, short-term memory systems, and attention–arousal networks are minimized in this study because our nonlinguistic control baselines were designed to engage these general-purpose nonlinguistic systems, and to accomplish this with minimal phonologic and semantic “automatic” processing.

The Auditory language task (ALTask) compared sentences (e.g., trees can eat) presented through an auditory headset, against a tone-decision baseline. The baseline periods contained pairs of two (identical or different) tones. Subjects had to respond depending on pitch similarity in each pair. Pairs were presented every 3 s. The task duration was 199 s with seven alternated cycles, 3Activation–4Baseline, 28 s each, and 10 trials each. TR was 1,500 ms.

The Visual language task (VLTask) compared visually presented language sentences against cross-match line decision (243 second task, nine alternated cycles, 4Activation–5Baseline, 25 s each, 10 trials each). TR was 1,848 ms. OFF-periods consisted of two (identical or different) rows of lines presented every 3 s. The ALTask and VLTask timing parameters were slightly different due to the ALTask involvement in another study. However, we have run these tasks with a range of timing parameters and found that small changes in paradigm timing produce little impact on the general activation patterns observed.

Logical AND combination: We also used a logical AND operation to determine the intersection of activated areas (common areas) between the ALTask and the VLTask, thus highlighting modality-input–independent areas. Individual t values in the ALTask and the VLTask must be above a t threshold of 1.5 to be taken into account in the logical AND operation. This analysis highlights cortical regions that are significantly activated in both the ALTask and VLTasks but not regions that are active in only one of the tasks. In this analysis, the regions highlighted are considered to be independent of input modality. This approach is analogous to the conjunction analysis approach of Bookheimer et al. (10) and Price et al. (19).

Imaging parameters
Scanning was conducted at 1.5 T on a General Electric (Milwaukee, WI) Signa scanner. Eight coronal oblique slices (8 mm thick, 1 mm gap) were acquired, orthogonal to the sylvian fissure. Functional imaging was performed using gradient-echo-EPI sequence (128 EPI images for each slice and for each run) with 50-ms echo time, 40 × 20-cm FOV, and 128 × 64 matrix. Additional higher-resolution T1-weighted anatomic reference images were performed in the same region to provide anatomic localization (conventional spin-echo imaging, FOV = 20 cm, matrix 256 × 256, two averages, TE/TR = 11/500 ms).

Data analysis and 3D alignment
Data were first checked for motion using a center-of-mass approach followed by a t test to detect activated voxels. All maps were thresholded at t > 1.5 [p uncorrected < 0.01 determined using the bootstrap method of Efron and Tibshirani (20)]. EPI data were analyzed with MatLab software using a Student’s t test on a voxel-by-voxel basis. Functional MRI data were then spatially combined in a two-step multimodality registration (21). First, the rigid alignment from each EPI series to the individual’s anatomic scan was determined. A 12-parameter warp was then estimated to bring each subject’s local anatomic scan into alignment with the Montreal Brain Atlas (22). These transformation estimates for the anatomic images were then applied to the functional maps for each subject, and activations from all subjects were transformed onto the atlas and averaged. Specific regions of interest were defined manually on axial slices in this 3D brain volume (~15 degrees from horizontal in Talairach space, parallel to BA 22). For all activated areas, quantitative assessments (mean intensities, surfaces, and standard deviations) were performed automatically on the MNI atlas using the registration software (21,23,24).

Data analysis for patient sample
Data analysis proceeded as for the Control subjects described earlier. For each patient, the activation maps were spatially registered to the patient’s high-resolution 3D SPGR T1-weighted anatomic preop MRI scan, using an automated 3D multimodality registration algorithm (21). Automatic extraction of implanted subdural electrode grids, from distorted postop MR scans, was then performed by an algorithm also developed at the Image Processing and Analysis Group of Yale University (25,26), and was automatically displayed in 3D together with the 3D fMRI reconstructed images (as shown in Fig. 3).
Language lateralization scoring

The laterality score \([100 \times (L - R)/(L + R)]\) measures the number of MRI voxels (with \(t\) value \(>1.5\)) in left (L) and right (R) hemispheres showing hemispheric-related signal predominance (7,27). Results range from \(-100\) (right speech) to \(+100\) (left speech). Laterality scores were calculated using all activations above a \(t > 1.5\) and also using only those activations above threshold in ROIs defining BA44/45 and posterior BA22. This latter approach was designed to exclude auditory cortical areas that contributed a high degree of bilateral activation in the auditory version of the language-comprehension task. Statistical analyses to compare language-laterality scores were performed using the Student’s \(t\) test.

Electrophysiologic mapping

When a surgical procedure puts language areas at risk, language mapping using cortical stimulation is frequently performed either with direct cortical stimulation on the awake patient during surgery, or extraoperatively with subdural electrodes. Subdural electrodes also are often required for localizing the epileptogenic foci of patients with complex and drug-resistant epilepsy. Taking advantage of these subdural electrodes, cortical stimulation for brain mapping can be performed, providing useful information on highly functional brain areas: the inferior frontal (Broca’s area), posterior temporal (Wernicke’s area), and basal temporal language regions. Seven epilepsy patients of our study (patients 11, 13, 15–19) had subdural electrodes [Ad-Tech, 8 \(\times\) 8(64) contacts grid, \(1 \times 10\), \(1 \times 8\), \(1 \times 4\) contacts strip, \(1 \times 12\) contacts probe; \(1\) cm apart] implanted and then a post-implantation anatomic T1-weighted 3D SPGR MR sequence to define the placement of grids and strip contacts. Two patients (13 and 18) underwent direct bipolar cortical stimulation during an awake surgery. A Grass S12 Isolated Biphasic Stimulator was used to stimulate cortex through either a Grass Bipolar Stimulator Pen or an OMI Frameless Bipolar Stimulator Pen to allow registration in 3D frameless coordinates. Systematic bipolar stimulation was performed on all the contacts of the grids and strips. Language tasks performed during cortical stimulation were designed to assess the same abilities assessed during the Wada test (semantic processing, comprehension) and were the same for intraoperative and subdural grid stimulation. Language testing was performed continuously, with intermittent periods of stimulation. If the bipolar stimulation of two contacts led to a language task error or arrest, the site was determined to be essential for language.

Specifically, three types of tasks were used. The first task displayed a line drawing of a common object, which the patient was to name. Stimulation was applied before display of the line drawing, and continued until the patient named the drawing or until 5 s elapsed. The second stage of mapping presented printed sentences with a word missing at the end. The patient was to read the sentence aloud and supply the missing word, which was contextually related to the meaning of the sentence. Stimulation was applied before display of this sentence and continued until the patient read and supplied the missing stem or until 7 s had elapsed. Last, sentence repetition was assessed by presentation of a sentence, which the patient was required to repeat verbatim. Stimulation was applied just before the presentation of the sentence, and continued until the patient completed repetition of the sentence or until 7 s had elapsed. A positive response was considered any error in naming or repetition that coincided with the application of the stimulus.

Current levels during cortical stimulation were adjusted by raising the stimulation level from 2 mA to 10 mA in 2-mA increments until an effect on language appeared, up to a maximum of 10 mA at 50 Hz, with a 400-\(\mu\)s biphasic spike waveform. For intraoperative stimulation, patients were initially sedated with propofol. After skin, bone, and dura opening, sedation was reduced until the patient was awake. Cognitive examination and stimulation mapping were performed only when the patient was alert.

Wada tests and neuropsychological evaluation

Localization of cortex specialized for language processing and verbal production has important clinical value in planning surgery in the dominant hemisphere. Presurgical language assessment usually includes the intracarotid sodium amobarbital test [Wada Test (5)] to determine language laterality and hemispheric memory capacity. The Wada test at our institution involves infusion of 130 mg of sodium amobarbital into the internal carotid artery to produce transient unilateral anesthetization. During the period of maximal anesthetization, the patient’s language is assessed for verbal comprehension, repetition, and naming. Classification of language as left hemisphere dominant, right hemisphere dominant, or mixed language dominance is based on the patient’s responses during this period. The criteria for determining language dominance are interruption of speech after the injection, impaired comprehension, impaired sentence repetition, impaired naming, and production of paraphasic errors during the period of recovery. Assessment of verbal expression included adequacy of spontaneous verbal expression, naming (body part naming and confrontation naming), repetition of simple object names (e.g., body parts, simple objects such as a pen, keys) and sentences of increasing grammatic and phonemic complexity. Semantic processing was assessed through response to questions of increasing semantic complexity. Criteria for failure include loss of verbal expression (e.g., global aphasia after dominant hemisphere injection), impairment in quality of verbal expression as defined by pres-
ence of paraphasic errors during conversational speech and formal assessment of repetition or naming, and errors in responding to questions. Failure on any aspect of the language examination was used for determination of language laterality. Laterality was considered a categoric variable (left dominant, right dominant, or mixed/bilateral dominance). When making the classification of “mixed” dominance, we did not differentiate among patients that demonstrated different patterns of laterality based on different linguistic processes. None of the patients in the present sample were classified as having “mixed” or “bilateral” language dominance. Specific items for language assessment are derived from a variety of clinical language assessment instruments, including the Boston Diagnostic Aphasia Examination (BDAE), and items developed specifically for our version of the Wada test. All patients underwent the Wada test (see Table 1) and comprehensive neuropsychological examination that included assessment of IQ (WAIS-R Wechsler Adult Intelligence Scale–Revised), Boston Naming Test, controlled phonemic fluency, and measures of written language.

RESULTS FOR CONTROL GROUP

Consistent areas of activation were observed across subjects during both tasks. Figure 1 illustrates the average activity pattern for all the eight right-handed controls to a depth of 10 mm from the brain atlas surface using normal fusion software (28). Figure 2 shows a representative example of fMRI language mapping for a control subject (patient 6). fMRI laterization score results on the eight RH healthy volunteers (displayed for \( t \) threshold = 1.5 in Fig. 1) showed that the visual language task provided a statistically significant higher laterization score than the audio language task whether the whole brain or limited ROI laterality approach is used (Table 2). Total laterality scores between right-handed and left-handed normals showed a trend toward greater laterality in right-handed control subjects. Talairach coordinates were calculated for the center of each important region of activation (Table 3) (23).

Cortical activations of the left inferior frontal gyrus (IFG) in its opercular part (Broca’s area) were present in all subjects for both the VLTask and the ALTask. Acti-
Observations in BA44 were more frequent and stronger on the left for the VLTTask (n = 9/10) than for the ALTask (n = 2/10) whereas both tasks activated BA45 (n = 10/10). Quantitative comparison showed significant differences, p < 0.05 (Table 4) in BA 44. The left precentral sulcus (PrS) was activated in all subjects for the VLTTask and in half of the subjects for the ALTask. Left supplementary motor area (SMA) was activated mostly in the VLTTask in eight of 10 patients versus three of 10 for the ALTask.

A robust activation pattern emerged in the left BA22 [Wernicke’s area; superior temporal gyrus (STG)] in all subjects for both tasks (n = 10/10). Activation was observed in the higher-order auditory cortex in the auditory task, as would be expected, including BA42 (superior temporal planum) or BA41 (Heschel’s gyrus/primary auditory cortex) on either side during the ALTask, and the auditory task also preferentially activated posterior BA22 bilaterally, partly contributing to the more bilateral scores found with the auditory language task. Additional right posterior BA22 activation was far more frequent and stronger for the ALTask (n = 6/10) than for the VLTTask (n = 0/10). Quantitative comparison showed significant differences between these tasks in this region (Table 4). The left middle temporal gyrus (MTG, BA21), was activated by the VLTTask, whereas bilateral BA21 activations were present in all volunteers for the ALTask. Left fusiform gyrus (FuG, T4) activation was present in 70% of the subjects and only for the VLTTask. The left supramarginal gyrus (SMG, BA40) was activated only in the VLTTask. The angulate gyrus, known to play a role in reading, is not included in the scanning range of this study.

RESULTS FOR PATIENTS

fMRI activation results

In epilepsy patients with electrical and/or anatomic abnormalities in the dominant hemisphere, language-activation areas appeared less standardized than those of the normal volunteers. Functional MRI highlighted 71 areas involved in these tasks in the 10 patients. A strong
tendency for bilateral representation of language was not noticed, with total laterality scores between right-handed patients and right-handed normal volunteers showing a significant statistical difference ($t$ value 4.608, $p < 0.005$) (Table 2). This was true for both the visual and auditory language tasks, as well as for the conjunction analysis, and it was independent of whether the activations in all brain regions or in limited regions were used to determine laterality.

The opercular position of the left inferior frontal gyrus (Broca’s area), including parts of BA 6, 9, and 44 through 47, was the most consistently activated area across patients. It showed fMRI signal enhancement in all patients for the VLTask and for the ALTask. Inferior frontal gyrus activations among patients often tended to be bilateral: seven of 10 patients showed strong right IFG activation, whereas no such right-sided activation was detectable in normal subjects. BA 45 showed bilateral activations in both tasks. As we saw in the control subjects, left BA 44 on patients still showed stronger activity in the VLTask when compared with ALTask (10:3).

The superior temporal gyri (BA 22), middle temporal gyri (BA 21), and inferior temporal gyri (BA 20), were activated for both tasks equally in the right and the left hemispheres. In the left-handed patients, only the right superior temporal gyrus demonstrated consistent activation. The bilateral transverse temporal gyri and superior temporal planum did not show significant activation during the two tasks. The fusiform gyrus (T4) was activated on the left side in 60% of the patients and mostly by the VLTask. The right and left supramarginal gyri (BA 40) were activated in a few patients (four of 10), but

**TABLE 3. Talairach coordinates (x,y,z) of centers of activated regions**

<table>
<thead>
<tr>
<th>Areas</th>
<th>VLTask</th>
<th>ALTask</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supramarg gyr BA 40</td>
<td>$-48, -46, +35$</td>
<td>Poor activation</td>
<td>Poor activation</td>
</tr>
<tr>
<td>Wernicke’s area BA 22</td>
<td>$-52, -8.5, +8.5$</td>
<td>$+55, -7, +5$</td>
<td>$-59, -13, +9$</td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>$-42, -27, -20$</td>
<td>Poor activation</td>
<td>Poor activation</td>
</tr>
<tr>
<td>Inferior frontal G BA 45</td>
<td>$+49, +22.5, +12.5$</td>
<td>$+46, +25, +14$</td>
<td>$-51, +21, +12$</td>
</tr>
<tr>
<td>Inferior frontal G BA 44</td>
<td>$+49.5, +14, +22.5$</td>
<td>$+52, +13, +25$</td>
<td>$-54, +13, +23$</td>
</tr>
<tr>
<td>Precentral sulcus</td>
<td>$-46.5, -2, -42$</td>
<td>Poor activation</td>
<td>Poor activation</td>
</tr>
<tr>
<td>Supplementary motor area</td>
<td>$-5, +7, +58$</td>
<td>Poor activation</td>
<td>Poor activation</td>
</tr>
</tbody>
</table>

Talairach coordinates represent the center of mass of activated voxels. Coordinates listed with a plus–minus sign indicate that the ROI activated voxel measurements were performed exactly at the same coordinates in both hemispheres, to allow a direct voxel-based statistical comparison. ROI, region of interest.

Scores, displayed for $t$ threshold = 1.5, $p < 0.05$, showed that the visual language task provided a statistically significant higher lateralization score than the auditory language task ($t = 3.5$, $p < 0.005$) in control subjects, but this difference is not significant in the patient group, indicating possible nondominant hemisphere recruitment in epilepsy patients. Laterality score differences between patients and normal subjects are statistically significant for the VLTask ($p < 0.01$) and for the ALTask ($p < 0.01$). Total combined laterality scores for the intersection of the visual and auditory tasks were more lateralizing than either single score. Combined scores for the eight RH controls and the eight RH patients showed a significant statistical difference ($p < 0.02$).
Only during the VLT task. Thus in contrast to the control subjects, patients appeared to invoke a reliably greater right-hemisphere response for both the ALT and VLT tasks.

Cortical stimulation results vs. fMRI data

Cortical stimulation was performed in seven of 10 cases. The fMRI data were thresholded \((t > 1.5)\) to allow comparison with the stimulation results. The comparison was performed visually by identifying grid electrodes on the 3D surface rendered MRI volume (Fig. 3) and comparing the location of the grid activation with that from the combined visual/auditory fMRI results highlighted in the same 3D volume. The activation foci were considered to overlap if they were within 1 cm of each other (the difference between adjacent grid electrodes).

Cortical stimulation for the seven patients mapped five precentral areas, three supramarginal gyri, four Wernicke’s areas, two Broca’s areas, and one fusiform gyrus. All data from these extra- and intraoperative subdural cortical stimulations were fully concordant with the fMRI maps (Table 1); concordance index, 15/15 (100%). Cortical stimulation could not define all regions involved in language comprehension (as seen on fMRI) because of the limited region of the brain covered by the electrodes. Cortical stimulation for language mapping identified the location and extent of the inferior frontal (Broca’s area), posterior temporal (Wernicke’s area), and basal temporal language regions in 100% of the cases when grids were located on the suspected region. Cortical bipolar stimulation performed exactly on the Broca’s area as defined in the fMRI activation maps, clearly led to progressive deterioration of reading comprehension, and a progressive loss of tonality and speed of speech, leading to total speech arrest. Language deficits after stimulation of the posterior temporal regions involved naming and/or auditory comprehension (sentence-completion) deficits. The basal temporal language area (anterior fusiform gyrus) showed very sudden arrest of object-naming capacity when stimulated.

fMRI language laterality, Wada, and neuropsychological testing

Using the language criteria described earlier, eight of 10 patients in this sample were classified as left hemisphere language dominant, two of 10 were classified as right hemisphere language dominant, and none was classified as bilateral/mixed dominant (Table 2) using the Wada test. The fMRI laterality score was consistent with the Wada findings in eight of 10 cases when the whole brain was considered, and nine of 10 cases when BA 41/42 was excluded from the laterality scoring (Table 1). Visually presented language yielded a superior fMRI language-lateralization score and showed greater agreement with both Wada testing and neuropsychological findings (Table 2), although the best agreement was found with the laterality score calculated only using BA44/45 and posterior BA22 and the conjunction analysis of both tasks. The auditory language task tended to produce more bilateral activation primarily because of the higher-order auditory cortex activation bilaterally. The combined visual and auditory data highlighting modality input-independent areas provided the highest laterality scores. fMRI data were comparable to Wada tests on all but two patients. For instance, in patient 17, the functional MRI laterality score was −8/8/−22 (VLT/
ALT/ANDed) in the whole-brain analysis, indicating bi-
lateral speech, whereas the Wada test suggested left
speech. When a large region of the STG and parts of the
basal temporal language regions were excluded from this
analysis, however, the scores changed to 65/15/16, indi-
cating weak left lateralization. Figure 1 shows the 2D
coronal oblique activation maps for this patient. In Fig. 3,
3D fMRI maps of this patient are shown with the
cortical-stimulation data highlighted on the patient’s
subdural grid. This figure shows the excellent correspon-
dence obtained in the STG region and the depth of the
activation observed with fMRI compared with the
surface-limited surface coverage of the grid. Also note
that the fMRI provides many more activated regions and
covers most of the brain compared with the necessarily
very limited coverage of the implanted grid.

DISCUSSION

In the control subjects, our results showed several ar-
eas involved in auditory or visually presented language
exclusively. In addition, several areas were activated by
both tasks. Whereas it is obvious that primary auditory
areas will be different with these tasks, the baseline con-
ditions were designed to minimize these activations of
the primary auditory and visual cortex. The differential
activation patterns during the two language tasks repre-
sent basic differences in the processing of language in-
puts from these different modalities. Data showed that
auditory-presented language activates BA 45, whereas
the visually presented language task activates both BA 45
and 44. As suggested by the literature on this subject
(29–32), a possible function for the Broca area BA 44 is
to perform articulatory recoding of written language, es-
pecially a graphene-to-phoneme conversion. A possible
function for the Broca area BA 45 is to cope with the
demands of either working memory processing or syn-
tactic operations; a common requirement across modal-
ities (3). Both middle and superior left temporal gyri were
activated in the VLTTask, whereas for the ALTTask, bilat-
eral activation of both MTG and STG was observed. This
could imply that the inferior part of the STG is used for
processing only the auditory phonetic components of
language, and because written language also involves
phonology, the STG also is activated in the VLTTask but
only in the dominant STG (2,33–38). The superior tem-
poral gyrus appears to be directly concerned with audi-
tory language input. Converging data from a variety of
sources suggest that unimodal auditory systems of the
superior temporal gyrus decode the complex acoustic
features found in speech, presumably activating neural
representations of auditory speech at more-abstract lev-
els (1,39,40). When the higher-order auditory language
regions are eliminated from the lateralization calcula-
tions, the lateralization provided by the auditory task increases,
but it is still lower than that found with the visual lan-
guage task.

The current findings are consistent with the specula-
tion that aspects of IFG, particularly pars triangularis
(BA 45), are involved in modality-independent linguistic
processing of the auditory and visual sentences, in for
example, syntax or working-memory roles. In a recent
examination of syntactic/semantic dissociations in sen-
tence processing Dapretto and Bookheimer (3) presented
pairs of spoken sentences, and listeners judged whether
the two tokens had the same or a different meaning. To
isolate syntactic regions, some pairs varied with respect
either to form (e.g., active/passive voice) or word order.
For the semantic manipulation, tokens differed with re-
spect to lexical–semantic features (e.g., words with same
or different meanings in the sentence pairs). Within IFG,
although BA 45 (pars triangularis) showed similar activ-
ation across conditions, unique foci in BA 44 were ob-
tained in the syntactic condition along with unique foci
in BA 47 for the semantic condition. The authors con-
cluded that parts of pars opercularis (BA 44) are impli-
cated when syntactic processing is taxed. These results
clearly implicate a unique response in BA 44 to the voice
and order (syntactic) manipulations. However, it should
be noted that because syntactic analysis is required for all
sentences, irrespective of condition, the consistent acti-
vation of BA 45 (but not BA 44) might be taken to imply,
as suggested by the current findings, that aspects of BA 45
serve a functional role in sentence parsing. Recently
Caplan et al. in two experiments (11,41) observed maxi-
mal response in pars triangularis (BA 45) to manipu-
lations of syntactic complexity. The current results, also
implicating a more anterior locus for modality-indepen-
dent activation, lend support to the argument that BA 45
contains neural systems critical for sentence analysis.
Clearly, further studies are required to characterize more
precisely the functional differences between these re-
gions in sentence processing and to distinguish syntactic
operations from working memory.

The left fusiform gyrus (FuG), which is often referred
to as a component of the basal temporal language area
(42), was activated in 60% of the subjects, but primarily
for the VLTTask. This modality dependence is consistent
with earlier data implicating the region in visual word-
recognition studies (42) and likely reflects this modality-
specific processing. Nobre et al. (43) has shown that the
anterior FuG is involved in word/nonword tasks and se-
matic priming effects. Posterior right FuG activation
also was activated in our study, probably because of
visual shape recognition and letter-string processing
(44). We also obtained weak activation in this region in
the auditory language task, possibly related to visualiza-
tion of the auditory input, a phenomenon that has been
observed previously in PET studies (9,45).

The patient results are notable in several respects.
First, we observed good concordance between fMRI language activation and both Wada language lateralization and intrahemispheric language localization as determined by electrocortical stimulation. This indicates that fMRI activation can provide a useful adjunct to established methods of language mapping in epilepsy patients with dominant hemisphere foci. However, there were some disparities between the techniques that require further discussion, and indicate the need for further refinement of the technique before fMRI can be used more confidently for language mapping in surgical planning.

Second, our results indicated more regions that correlated with the language tasks in the patients as compared with normal controls. This was true for visual language, auditory language, and the modality-independent areas. This has important implications for the understanding of language function in epilepsy patients, and may provide insight into the substrate of language recovery after surgery in the dominant hemisphere. All of the patients had intractable temporal lobe epilepsy, but the group was quite diverse in terms of the exact location of the lesions and the onset of the first epileptic event. The impact of these factors on the patterns of activation for language comprehension requires a much larger sample size and is the subject of ongoing investigation at our institution. Nonetheless, the right-hemisphere shift seems a general characteristic of this group.

One of the important clinical applications of fMRI is the ability to provide noninvasive language lateralization and localization information (46). For the 10 patients that underwent the Wada test, our results showed good concordance with the fMRI in eight of 10 cases. The discordant patients (16 and 17) showed bilateral activation (or weak left lateralization depending on the regions used to calculate laterality) during the fMRI language tasks, but were classified as “left hemisphere dominant” by Wada testing. Although cortical stimulation in these patients identified language areas in the left hemisphere, this does not necessarily preclude the presence of language in the right hemisphere, because the right hemisphere was not stimulated. This apparently discordant finding highlights several important questions with respect to use of fMRI language localization in surgical planning. First, the fMRI and Wada test differ in a fundamental way. Functional MRI is an imaging approach that elucidates the cortex that is differentially active during, and presumably involved in cognitive processing of, the language tasks, but that may not necessarily be critical for language production. In contrast, the Wada test involves pharmacologic deactivation of the language cortex, providing a reversible simulation of the effects of surgery and allowing identification of areas critical for language by producing aphasia during the period of deactivation. The Wada test also typically provides information on the laterality of mnemonic processing that to date has not been easily obtained with fMRI.

The information provided by functional MRI is distinct from the Wada test and cortical stimulation in several respects. The Wada test, although the current gold standard because of its specificity, lacks spatial/anatomic resolution and does not provide the localizing information within a hemisphere that potentially can be obtained using fMRI. In contrast, fMRI has the ability to provide a more detailed intrahemispheric map of language localization with greater functional and anatomic specificity (47). Furthermore, fMRI has the potential to provide information from a single source that is now available only through multiple sources (i.e., Wada testing, cortical mapping). Functional MRI is also noninvasive, and can be more easily repeated than the Wada test and cortical mapping studies with little or no risk to the patient. Thus, its continued development is desirable, and it remains to be seen whether fMRI will serve as an adjunct test procedure to the Wada and cortical stimulation or if, over time, it may partially replace these invasive methods.

The fMRI concordance with intrahemispheric language mapping via cortical stimulation was good, providing both positive (i.e., impairment with stimulation in areas activated for fMRI) and negative (i.e., absence of stimulation-induced impairment in fMRI “silent” areas) concordance in all patients that underwent mapping. Although there are many technical issues to consider when comparing fMRI and cortical stimulation (48), we observed a strong correlation between data from the intra–extraoperative stimulation mapping studies and the functional MRI maps (15 of 15). As expected, cortical stimulation indicated only the strictly sufficient basic language areas for language production (e.g., Broca’s area), whereas fMRI highlighted many more areas (71) than did cortical stimulation (15). fMRI showed additional activation in regions such as the SMA, ITG, and deep sulcal regions not only related to productive language areas, but also indicative or more complex language-comprehension processes. The primary limitation of cortical stimulation is lack of brain coverage, which is responsible for the large differences in the number of activation sites observed. In addition, high-intensity cortical stimulation can induce an efficient cortical inhibition or excitation at depth or laterally from the stimulation site, leading to localization problems. Conversely, an insufficient cortical bipolar stimulation intensity (<10 mA–50 Hz) may not provide sufficient stimulation to affect some functional areas. Our experience indicates that fMRI is far more descriptive (in the sense that many more regions of the brain can be explored) and that its sensitivity is higher than that of cortical stimulation. But cortical stimulation is more specific in terms of defining which areas are critical. Functional MRI highlights all regions involved in a specific task, but
it does not distinguish between areas involved and areas that are critical to the task. Cortical stimulation conversely (10,42,49) is highly specific for critical productive language areas.

There were several interesting findings in the comparison between the control subjects and patients in this study. First, the strength of the activation was lower in patients. This may be due to drug effects on cerebral activation or blood-flow changes, or possibly due to the effects of the disease itself. Furthermore, patients demonstrated significantly lower lateralization scores compared with normal controls. Total laterality scores between right-handed patients and right-handed controls showed a significant statistical difference ($t = 3, p < 0.02$). Both the VLTTask and the ALTTask showed bilateral activation of the STG, MTG, ITG, and IFG in the patients. These differences may provide evidence for area recruitment in epilepsy, but a much larger sample is needed to investigate this issue in detail. These results agree with those of Springer et al. (4), who found higher variability in language dominance for epilepsy patients compared with control subjects when using a simple single-word semantic decision task. Studies of developmental dyslexia have shown reduced laterality in reading disabled children and adults (50,51). An increased role for the nondominant hemisphere in language tasks may also reflect to some degree a compensatory response to impoverished LH language function (52). Behavioral analysis on these patients (Table 5) illustrates they were impaired on various aspects of language tasks. It is possible that the impaired performance on neuropsychological measures of language in these patients also is somehow related to the strength of activation. Correlation of level of impairment with strength of activation will require a much larger sample of patients, as well as broader sampling of language function to address this question adequately.

**Table 5. Neuropsychological data**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Hand side</th>
<th>Wada test</th>
<th>Raw score</th>
<th>z score</th>
<th>IQ scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Verbal</td>
</tr>
<tr>
<td>11</td>
<td>RH</td>
<td>L</td>
<td>46</td>
<td>–2.44</td>
<td>*</td>
</tr>
<tr>
<td>12</td>
<td>RH</td>
<td>L</td>
<td>23</td>
<td>–11.75</td>
<td>100</td>
</tr>
<tr>
<td>13</td>
<td>LH</td>
<td>R</td>
<td>*</td>
<td>–</td>
<td>*</td>
</tr>
<tr>
<td>14</td>
<td>LH</td>
<td>R</td>
<td>28</td>
<td>–6.54</td>
<td>70</td>
</tr>
<tr>
<td>15</td>
<td>RH</td>
<td>L</td>
<td>44</td>
<td>–2.95</td>
<td>88</td>
</tr>
<tr>
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<td>L</td>
<td>46</td>
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<td>79</td>
</tr>
<tr>
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<td>91</td>
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<tr>
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<td>90</td>
</tr>
<tr>
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<td>43</td>
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<tr>
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<td>RH</td>
<td>L</td>
<td>52</td>
<td>–0.68</td>
<td>87</td>
</tr>
</tbody>
</table>

Patient neuropsychological behavior scores on language tests demonstrate a range of impairments across these subjects. There was no significant correlation, however, between these behavior scores and the fMRI activation amplitude.

Thulborn et al. (53) recently showed that, in two adult patients recovering from stroke-induced aphasia, fMRI demonstrated modification of the language-activation pattern, at 6 months, from a left to a homologous right hemispheric pattern. An earlier study examining the effects of early unilateral lesions on language laterality found that early left lesions were associated with increased participation of the right hemisphere (54). Comparing left lesion and right lesion subjects, they found no differences in full-scale and verbal IQs and no correlation between either FSIQ or VIQ with rCBF or distractivity measures for listening to sentences (data shown in Table 5). Similarly we also found no relationship between these gross receptive language scores and lateralization, although this is a topic we are currently investigating in more detail.

All of these studies suggest that there may be recruitment of contralateral homologous areas, and hence the development of a contralateral homologous language pattern. In our patients, the etiology of bilateral language is unclear. Patients could have developed either a spontaneous initial bilateral representation of language during childhood or had secondary language bilateralization after becoming left speech dominant with normal language organization during childhood. If patients tend to have more “bilateral” activation as the norm, it will be necessary to determine the extent to which areas in or near activated areas produce impairments if resected. Although one is not likely to resect an area that both the Wada and fMRI studies suggest is involved in language, what is the meaning of resecting and activated area in the “nondominant” hemisphere? Again, further studies are needed to investigate this issue.

**Conclusions**

In this study, we have identified input modality–dependent and input modality–independent cortical regions involved in a language-comprehension task for both normal controls and epilepsy patients. The combined results from parallel auditory and visual input tasks allow the identification of input modality–independent language areas. The separate modality-specific activation maps also are of interest. Both modality-specific and modality-independent areas are important areas to consider when planning a neurosurgical intervention. Comparing a normal control group with a consecutive group of intractable temporal lobe epilepsy patients revealed that, relative to the control group, all patients in the study showed recruitment of contralateral homologous areas in the right hemisphere. This strong bilateralization of language in patients, compared with a group of control subjects, may provide evidence of language plasticity in epilepsy.

It was also demonstrated that fMRI provides a sensi-
tive measure of many of the disparate regions in the brain that contribute to language comprehension. We have shown good agreement between fMRI language processing for sentence comprehension with Wada and cortical stimulation. Validation of the fMRI mapping approach through studies similar to this with cortical stimulation superimposed on the subject’s 3D MRI and fMRI volume will eventually pave the way for fMRI to become an important clinical tool in neurological planning.

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