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Article abstract—We performed functional MRI (FMRI) in 22 consecutive epilepsy patients undergoing intracarotid amobarbital (Wada) testing and compared language lateralization measures obtained with the two procedures. FMRI used a single-word semantic decision task previously shown to activate lateralized language areas in normal adults. Correlation between the two tests was highly significant ($r = 0.96$; 95% CIs 0.90 to 0.98; $p < 0.0001$). These results validate the FMRI technique and suggest that "active" areas observed with this semantic processing task correspond to those underlying hemispheric dominance for language. The strong correlation observed supports the view that language lateralization is a continuous rather than a dichotomous variable. In addition to lateralization information, FMRI consistently demonstrated focal regions of activity in lateral frontal and temporo-parieto-occipital cortex. These functional maps may be helpful in defining the boundaries of surgical excisions.

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Localization of cortical functions in patients undergoing excisional brain surgery is useful in three ways: to predict the general level of risk should the planned excision proceed, to guide the surgeon in limiting the boundaries of the excision, and to help determine the location of abnormal brain areas (e.g., seizure foci) preoperatively. One commonly used localization technique is the intracarotid amobarbital, or Wada, test, which measures the relative lateralization of language and memory functions across the two hemispheres.[1,2] Preoperative determination of language lateralization is important in selecting patients for more invasive and specific localization procedures, such as intraoperative stimulation mapping.[3] Determination of language lateralization is particularly important in the preoperative evaluation of epilepsy patients, because this population may have a higher incidence of atypical language dominance than does the normal population.[4,5] Although there are several alternative methods for determining language dominance,[6,7] the Wada test remains the only method used routinely for this purpose.

The Wada test, although a proven measure of language lateralization, has several important limitations. First, the required angiographic procedure is invasive, with reported complication rates of up to 3%.[8] Second, the test measures only the relative distribution of language across the two hemispheres. More specific information about localization within a hemisphere, which might be useful for tailoring an excision, must be obtained by other means, such as intraoperative stimulation mapping. Third, validity of the test depends on demonstration of relatively separate and symmetric arterial supply routes for the two hemispheres. Thus, interpretation of the test may not be straightforward or possible in patients with azygous supply patterns or arterial crossflow.[9] Other methodologic drawbacks of the Wada test are limitations on the time available for testing distinct functions during the procedure, the occurrence of excessive sedation that limits the validity of language and memory tests, occasional difficulty obtaining adequate hemisphere anesthetization, and the unavailability of test-retest reliability data.[10-12]

Functional MRI (FMRI) may provide a noninvasive alternative to the Wada test. FMRI produces detailed brain images showing the location of MR signal changes associated with cerebral activity. Previous reports described applications of FMRI in mapping motor,[13-15] visual,[16-18] auditory,[19,20] and somatosensory[21] systems. Other investigators reported preliminary FMRI observations in neurologic patients.[22,23] Several groups observed lateralized FMRI responses during performance of linguistic tasks.[24-27] In previous reports, we described such responses during a single-word semantic decision task with appropriate controls for auditory processing and attentional activation.[28,29] What remains unclear from these studies is whether these lateralized regions

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observed in normal subjects actually correspond to systems underlying language dominance, as measured with the Wada test. A powerful argument in favor of such an interpretation would be the demonstration that Wada results can be predicted on the basis of FMRI lateralization patterns. In this article, we compare language lateralization data obtained with FMRI and with the Wada test in a series of epilepsy patients undergoing preoperative evaluation. Language laterality scores are calculated under the assumption that lateralization is a graded rather than a dichotomous or otherwise discrete phenomenon.[30] We test the hypothesis that a correlation exists between these laterality measures and describe the anatomic pattern of FMRI activation typically observed.

Methods. *Subjects.* Subjects were consecutive patients with full-scale Wechsler Adult Intelligence Scale-Revised IQ scores ≥80 who were undergoing comprehensive evaluation at the Medical College of Wisconsin for surgical treatment of epilepsy. Patients selected for surgical evaluation met the following criteria: medically intractable epilepsy, restricted lifestyle because of recurrent seizures, and probable focal onset of seizures. All patients had neurologic examinations, continuous 16-channel inpatient video-EEG monitoring, preoperative neuropsychological testing, interictal and postictal single-photon emission CT, a standardized Wada test, and routine brain MRI. Subjects gave written informed consent for FMRI. All completed the Edinburgh Handedness Inventory (EHI).[31]

Wada methods. Baseline language and memory tests were administered 2 hours before the Wada test, using alternate forms of the same tests used in the Wada. The Wada procedure was similar to that described by Loring et al.[32] With the patient in the supine position with arms elevated and outstretched, 125 mg of sodium amytal was injected by hand over a 4- to 5-second interval into the internal carotid artery while the patient counted aloud by ones. The side of suspected seizure focus was injected first. Simultaneous EEG was conducted during the procedure to monitor the onset and cessation of slowing in both hemispheres. If contralateral flaccid hemiplegia was not present, an additional 25- or 50-mg bolus of sodium amytal was injected. Counting disruption was numerically rated, as well as ability to follow two simple midline commands just after injection. Between 30 and 60 seconds postinjection, objects and line drawings were presented for later memory testing. Numerical ratings were then made on four language tasks: (1) comprehension of three one- and two-step commands of increasing difficulty (the most difficult including inverted syntax), (2) naming objects or parts of objects depicted in line drawings, (3) phrase repetition, and (4) sentence reading. All ratings used a 0 to 3 scale, with lower scores reflecting poorer performance. Language tasks were repeated until the patient performed at baseline levels. Only the first two presentations of the four language tasks were scored. Also included in the scoring was a rating of paraphasic errors, based on the total number of errors during each series of language tests (0, >5 errors; 1, 3 to 5 errors; 2, 1 to 2 errors; and 3, no errors). Only trials conducted before return of motor functioning were included in final language calculations. A total score of 33 on the language measures was possible unless there was early return of motor function.

Approximately 30 minutes after the first injection, the identical procedure was repeated with 100 mg injected into the contralateral hemisphere. A Wada laterality index (Wada LI) was calculated for each patient as the difference $[P_L - P_R]$, where P_L and P_R are the percentage scores (of the total possible) from the language tasks for the right (test left) injection and the left (test right) injection. This approach yields LIs ranging between +100 (strong left hemisphere dominance) and −100 (strong right hemisphere dominance). Wada calculations were performed by a neuropsychologist blind to the FMRI results.

FMRI image acquisition. MRI studies were conducted on a 1.5-T GE Signa scanner (General Electric, Milwaukee, WI) equipped with custom gradient and rf coils designed for whole-brain echoplanar imaging. FMRI used a blipped gradient-echo echoplanar sequence (TE 40 ms, TR 4 sec, matrix 64 × 64, slice thickness 8 mm, and field of view 24 cm). Ten sagittal slices were acquired, with 5 contiguous slices in the left hemisphere and 5 in the right hemisphere. Slices were positioned to cover the central two-thirds (40 mm) of each hemisphere, excluding the most medial and most lateral 10 to 20 mm. Care was taken to place slices symmetrically in the left and right hemisphere in each case. Series of 100 consecutive images were acquired simultaneously at each slice location during eight cycles of task activation. High-resolution anatomic reference images were obtained through the entire brain using either a T_2-weighted fast spin-echo or T_1-weighted spoiled gradient-echo sequence.

FMRI activation tasks. Subjects were scanned with eyes closed and room lights dimmed. Stimuli were digitally recorded as pure tones and speech sounds presented at precise intervals using a computer playback system. Characteristics of the sound delivery apparatus have been described elsewhere.[29] Each 100-image echoplanar series consisted of multiple periods of baseline, during which subjects performed a tone discrimination control task, alternating with periods of activation, during which a contrasting semantic decision task was performed.[28,29] Each series began with four resting images (16 seconds) during which MR signal equilibrium was reached, followed by 96 images during which the semantic task alternated with the tone task every 24 seconds (48 s/cycle, 12 images per cycle, eight cycles). In the tone task, subjects heard brief sequences of three to seven tones. Each constituent tone had either a low (500 Hz) or high (750 Hz) pitch. A button press response (using the nondominant hand) was required for any sequence containing two high-pitch tones. In the semantic task, subjects heard spoken English nouns designating animals (e.g., "squirrel") and responded according to specified semantic criteria. Target words were animals that are both "native to the United States" and "commonly used by humans." The two tasks were matched for stimulus intensity, 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 before entering the scanner. The tone discrimination task has been shown to control for activation of superior temporal auditory processors as well as nonlinguistic lateral frontal lobe attentional systems.[28] The se-

mantic decision-tone discrimination combination has been demonstrated to produce strongly lateralized activation in lateral frontal and temporoparietal heteromodal cortex of the dominant hemisphere in normal subjects.[29,33]

FMRI data analysis. Identification of event-related MR signal changes used the correlation approach of Bandettini et al.[34] In brief, this method correlates the time-series MRI signal data (excluding signal equilibration images at the beginning of the series) with a reference vector on a voxel-by-voxel basis. A threshold value for the correlation coefficient is chosen to eliminate those voxels not significantly correlated with the activation procedure. The final functional image is created by superimposing significantly activated voxels on corresponding anatomic images of the same brain tissue.

Reference vectors were derived directly from each data set using a two-step method that selects voxels strongly correlated ($r \geq 0.70$) with a simple mathematical model of the activation procedure (the model used for this study was a discontinuous square wave function; see reference 29), and then computes a data set-specific reference vector as the mean vector of this selected group of voxels. The eight activation cycles comprising this mean vector are then averaged across time to produce a mean activation waveform, which is repeated eight times to obtain the final reference vector. The correlation test was then performed again for each voxel using this empirically derived reference vector, with a correlation threshold of $r \geq 0.40$. The probability that any given voxel will exceed this threshold by chance is approximately $p < 0.0001$[34] or $p < 0.05$ for a set of 500 voxels. As a check on the validity of this threshold, thresholds were also determined empirically for each patient by correlating each data set with an aperiodic reference vector (a random number series). The distribution of resulting r values describes the range of correlations that occur by chance at a given probability level. When the desired probability is $p < 0.05$ that any brain voxel in a slice will exceed the threshold by chance, empiric thresholds derived by this method ranged from $r \geq 0.35$ to $r \geq 0.43$, with a mean of 0.39 for the entire group of patients. Thus, the average probability of a false-positive voxel is less than 0.05 per slice using a threshold of 0.40, or approximately one false-positive voxel for each 20 brain slices. Because the average number of active voxels per slice was 14.6, the statistically estimated proportion of false-positive voxels was approximately 1 in 292, or less than 0.4%.

Activation volumes were determined in each patient by counting the significantly activated voxels in each hemisphere. An FMRI LI was calculated for each patient as the ratio $([V_L - V_R]/[V_L + V_R]) \times 100$, where V_L and V_R are activation volumes for the left and right hemispheres. This approach yields LIs ranging between +100 (strong left hemisphere dominance) and −100 (strong right hemisphere dominance). Despite differences in appearance, the formulae for Wada and FMRI LIs are hypothesized to be equivalent, because the percentage correct scores for the Wada test are thought to reflect the ratio of unanesthetized to total "language tissue," that is, P_L is hypothesized to reflect $V_L/[V_L + V_R]$ and P_R is hypothesized to reflect $V_R/[V_L + V_R]$. Thus, the Wada LI, $[P_L - P_R]$, is hypothetically equivalent to $[V_L - V_R]/[V_L + V_R]$, which is the formula for the FMRI LI. FMRI analysis was automated and was performed by a research technician blind to the Wada results.

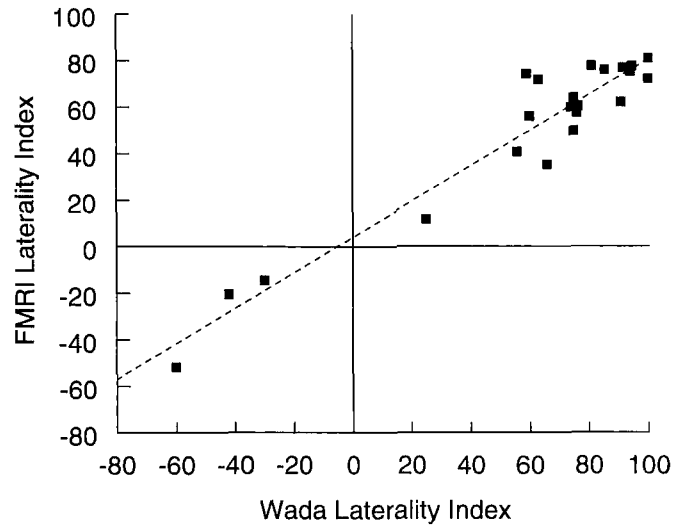

Figure 1. FMRI laterality index plotted against Wada laterality index for 22 epilepsy patients. The regression function, $y = 0.764x + 4.3$, is shown as a dashed line. The correlation coefficient is 0.96.

Results. *Patients.* Twenty-seven patients met entry criteria and underwent successful Wada testing. Of these, 24 patients were available for FMRI before surgery and agreed to participate in the FMRI procedure. One became claustrophobic soon after entering the scanner and was unable to complete the test. In one other case, the data were unusable because of a scanner malfunction. The remaining 22 patients included 14 women and 8 men, ranging in age from 17 to 64 years. Age at seizure onset ranged from birth to 32 years, with seizures beginning before age 10 years in 9 of 22 patients. Two patients were left-handed, 1 ambidextrous, and the others right-handed. Thirteen patients had normal routine MRIs, whereas the others had left temporal lobe atrophic or sclerotic changes (4 patients), temporal lobe cavernous angiomas (2 patients), or left hemisphere encephalomalacia (3 patients). For detailed information regarding the patients, including side of seizure focus and EHI scores, please see the Note at the end of this article.

Language dominance. The Wada and FMRI tests were concordant in all cases in determining the hemisphere with greater language representation. Eighteen patients (16 right-handed, 1 ambidextrous, and 1 left-handed) had strong left hemisphere dominance for language as judged by the Wada test, with LIs ranging from +56 to +100. These same 18 patients also showed clear left hemisphere dominance by FMRI, with LIs ranging from +35 to +81. The four remaining patients (three right-handed and one left-handed) had atypical language distributions as judged by both Wada and FMRI. Wada LIs in these patients ranged from −60 to +25, and corresponding FMRI LIs ranged from −52 to +12.

Correlation between the two tests (figure 1) was very high ($r = 0.96$; 95% CIs 0.90 to 0.98; $p < 0.0001$). This correlation also held for the 18 patients with strong left hemisphere dominance ($r = 0.61$; $p < 0.007$), indicating a

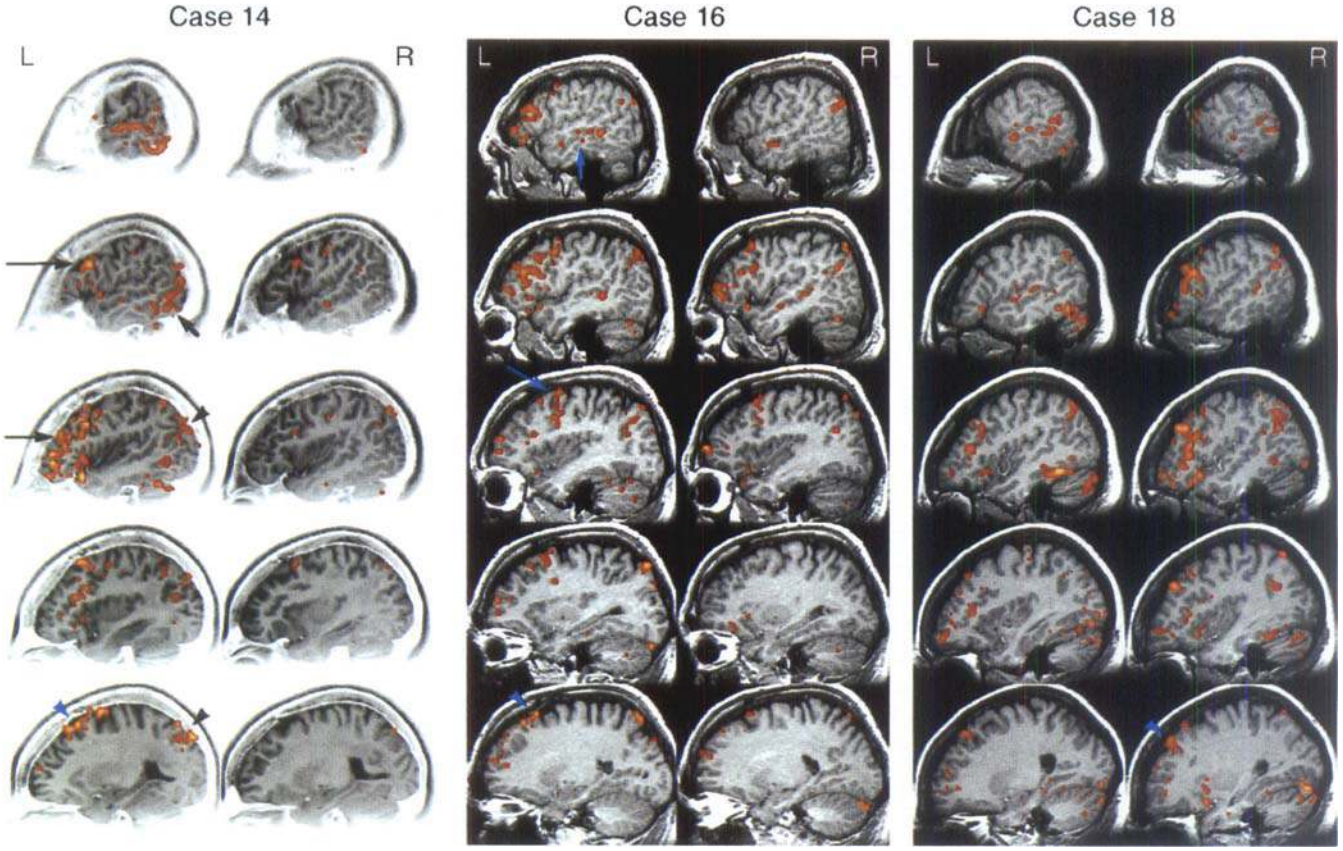

Figure 2. FMRI activation maps from three representative patients, illustrating the continuum of language lateralization across individuals. Areas demonstrating significant signal increase during the semantic decision task are highlighted using a qualitative red-yellow scale, with red indicating smaller absolute signal changes and yellow larger changes. Left and right slices are symmetrically placed in each patient; slices differ across patients because of differences in brain size and shape. Patient 14 had strong left hemisphere lateralization by FMRI (LI = 72), whereas patient 16 had more symmetric language distribution with left dominance (LI = 35) and patient 18 had relative right dominance (LI = −20). Areas prominently activated include the inferior frontal sulcus, middle frontal gyrus, and lateral orbital sulcus (long black arrows); the angular gyrus (black arrowheads); the superior precentral sulcus (long blue arrow); the superior frontal sulcus and gyrus (blue arrowheads); the posterior ventrolateral temporal lobe (short black arrow); and the superior temporal sulcus (short blue arrow). Small foci are demonstrated in the cerebellum bilaterally and in the dorsal temporal pole.

continuum of language lateralization even within this narrower range of values. There was no significant correlation in this sample of patients between a laterality index derived from the EHI and the Wada test LI ($r = 0.29$; $p = 0.194$) nor between the EHI and FMRI LIs ($r = 0.30$; $p = 0.178$). Although average LIs were more positive (indicating relatively stronger left dominance) in the group of patients with right hemisphere seizure foci than in patients with left hemisphere foci on all three lateralization measures, a one-factor ANOVA revealed that these group mean differences were not statistically significant.

Regional language localization by FMRI. Figure 2 illustrates the location of active pixels in three representative subjects, one with strong left hemisphere dominance (patient 14), one with mixed primarily left language dominance (patient 16), and one with mixed primarily right language dominance (patient 18). "Active" voxels are those demonstrating relatively increased levels of MRI signal during the semantic decision task compared with the control task (tone discrimination). The main foci of activity were in the lateral frontal lobe and temporal-parietal-occipital junction in all subjects. Specific active structures included, in roughly descending order of frequency, the inferior and middle frontal gyri (Brodmann areas [BA] 9 and 44 to 46), the superior precentral sulcus (BA 6), the superior frontal gyrus and sulcus (BA 8 and 9), the angular gyrus (BA 39), the posterior inferior temporal gyrus and fusiform gyrus (BA 37), and the posterior superior temporal sulcus and middle temporal gyrus (BA 21/22). Although the supramarginal gyrus (BA 40) is usually considered to be a language area, there was relatively little activation in this region.

Discussion. Measures of language lateralization obtained by the Wada test and by FMRI were highly correlated in this series of patients with epilepsy. As expected, most patients (18/22) were strongly left hemisphere dominant, whereas the remainder had more symmetric language or right hemisphere dominance. Lateralization indexes varied continuously over a range from strong left to strong right dominance on both tests. A common approach in previous Wada test research has been to divide this continuum into categories such as "exclusive left dominance," "bilateral language," and "exclusive right

dominance." Even studies using quantitative language ratings like those used here have incorporated thresholds for abnormal performance to exclude deficits resulting from nonspecific effects of sedation, thereby defining most subjects as "exclusively" left dominant.[30] The present results demonstrate that even within a range that would typically be defined as exclusive left dominance, there is variation among subjects on the Wada test that is correlated with similar variation in FMRI activation maps. These data emphasize that language lateralization occurs along a graded continuum, even though most individuals have relatively strong left lateralization. Two anatomic mechanisms could explain this gradation in language lateralization. It may be that the phonologic, semantic, working memory, attentional, motor, and other component functions used in language are each located in one or the other hemisphere, with the number of these functional "modules" in each hemisphere varying from person to person. Alternatively, each linguistic component might be represented to some extent in both hemispheres, with the distribution varying across individuals. These two proposals are not mutually exclusive. Although our data do not test these models directly, the continuous variation we observed in language lateralization across individuals could be taken as indirect evidence for the latter model.

This is the first FMRI study to demonstrate validation of this technique through intrasubject comparisons with another functional localization method. (See "Note added in proofs" on page 983.) The close similarity between Wada and FMRI results suggests that the areas of activation observed using this FMRI procedure are, or at least largely include, those underlying language dominance. This correspondence may seem surprising at first, given the differences between the semantic decision task used for FMRI and the naming and auditory comprehension tasks emphasized in the Wada test. We propose that the semantic processing network activated in the FMRI procedure is also crucial for comprehension of spoken speech and for linguistic identification of visual stimuli. Although these latter tasks also place demands on auditory and visual perceptual systems and on motor response systems, it is the semantic component that is lateralized and forms the basis of hemispheric language dominance on both FMRI and Wada tests.

These results therefore support FMRI as a promising alternative to the Wada test for the determination of language lateralization. In contrast to the Wada test, FMRI is entirely noninvasive and without significant health risks. FMRI is not affected by underlying arterial supply patterns, can be easily repeated if necessary without additional risk, and affords the examiner sufficient time to test a range of cortical functions. Because the entire brain is assayed simultaneously, results are not confounded by difficulties in reproducing test conditions separately for each hemisphere as in the Wada test. For example, the Wada test may occasionally overestimate language symmetry because of inadequate anesthetization of the dominant hemisphere or because of arterial crossflow after nondominant hemisphere injection.[9,11,35] Unlike the Wada test, FMRI provides detailed information about the spatial localization of functions within each hemisphere, potentially offering the neurosurgeon useful data for minimizing the adverse effects of an excision.

Several factors could limit the general applicability of FMRI. We observed claustrophobic reactions in one patient and in a small percentage of normal volunteers. A small proportion of patients are unsuitable for MRI scanning because of cardiac pacemakers, metallic substances in the skull, or extreme obesity. Movement during scanning is a potential problem that introduces large artifacts in the time-series data. Methods of dealing with this problem include head restraints, discarding portions of the time-series contaminated by movement, and spatial registration of data during postprocessing. Although we did not note extensive movement artifacts in this series of patients, the problem is likely to be worse in patients with more compromised cognitive abilities, particularly in those with attentional deficits. Automated image registration methods may be capable of correcting some or all of these motion problems.[36,37] Finally, the specific FMRI tasks used in this study are unsuitable for neurologic patients with moderate cognitive deficits. To achieve the broadest application of FMRI, it will be necessary to develop a standardized collection of qualitatively similar tasks covering a range of difficulty levels and to assign patients to suitable test forms based on results of standardized pre-scan screening tests.

The LIs calculated for both Wada and FMRI tests will depend on a number of procedural variables and on the adequacy of experimental controls. One important factor is the choice of a control task for FMRI. It must be assumed, for example, that some of the component functions activated during a complex language task are bilaterally represented or represented in the "nondominant" hemisphere. Examples of such functions are the processing of auditory information in speech sounds, which occurs bilaterally in the superior temporal gyri,[19,38] and the systems specialized for maintenance and distribution of attention, which are located primarily in the right hemisphere.[39,40] If activation of these functions is not "subtracted" using a suitable control task, then task-induced activity that is unrelated to the linguistic functions of interest will occur in the nondominant hemisphere, resulting in LIs that are closer to symmetry than they should be. A similar error would result from using a control task with linguistic features (e.g., repetition of words), which could have the effect of nullifying some of the language-associated activity in the dominant hemisphere.

The FMRI LI is dependent on the correlation threshold used to identify active voxels. At low correlation thresholds (i.e., $r < 0.30$ in this study), the

occurrence of false-positive correlations in both hemispheres moves the LI toward zero. At high thresholds (i.e., $r > 0.50$), the number of active voxels becomes small—potentially affecting reliability—and many "truly" activated voxels are excluded. In plotting the LI as a function of correlation threshold, we observed, in most cases, a deviation away from zero as the r threshold is increased from 0 to 0.30, with the LI reaching a plateau by $r = 0.40$. Above $r = 0.50$, there is usually instability and erratic fluctuation of the LI due to the small number of voxels passing the threshold. These ranges of r are, of course, specific to the present study, because the statistical power of r depends on the number of data points (i.e., the number of images) considered in each correlation[34] and, to a lesser extent, on the interscan interval, or TR, that affects the degree of autocorrelation present in the data.[41]

The main areas of activation observed during our semantic processing task included the lateral and superior frontal lobe, the angular gyrus, and the posterior ventrolateral temporal lobe. Our imaging methods omitted lateral portions of gyri in the perisylvian region as well as entire gyri on the medial brain surface. We thus cannot comment on possible activation in these areas. The observed pattern of frontal and posterior heteromodal activation replicates our previous findings using the same procedure in normals[29] and is in accordance with PET data obtained using a similar task.[42] We interpreted this pattern as indicating a distributed neural network for linguistic comprehension, governing access and retrieval from semantic memory.[29] Although the activation maps produced by FMRI may prove useful in tailoring the boundaries of surgical resections—and may eventually supplant intraoperative stimulation mapping for this purpose—the validity of this application will require formal demonstration. Specifically, it will be necessary to test whether removal of areas "active" on FMRI is correlated with postoperative changes in neuropsychological test performance and whether such correlations are as good as or better than those obtained using intraoperative mapping techniques.[43-45]

In addition to its application in language testing, the Wada test is often used to determine lateralization of memory functions.[46] Memory lateralization data may assist in determining the hemisphere of seizure origin and appear to be important in predicting seizure control after surgery.[47,48] If FMRI is to replace the Wada test in clinical use, it will be necessary to develop and validate FMRI procedures for localizing verbal memory systems. The language task used in this study can be viewed as an index of long-term semantic memory, which is likely to be one of the component systems activated during typical declarative verbal memory tasks such as those used in the Wada test. Several investigators emphasized involvement of the lateral temporal neocortex in such tasks;[49,50] these areas are similar in location to the posterior ventrolateral temporal areas (BA 37 and 21/22) activated in the present study. It may also be possible to use FMRI to map medial temporal structures (parahippocampus and hippocampus) that are believed to play a dominant role in the consolidation of long-term declarative memories, although this possibility remains at present an open question.

Note. Readers can obtain 1 page of supplementary material from the National Auxiliary Publications Service, c/o Microfiche Publications, PO Box 3513, Grand Central Station, New York, NY 10163-3513. Request document no. 05261. Remit with your order (not under separate cover), in US funds only, $7.75 for photocopies or $4.00 for microfiche. Outside the United States and Canada, add postage of $4.50 for the first 20 pages and $1.00 for each 10 pages of material thereafter, or $1.75 for the first microfiche and $.50 for each fiche thereafter. There is a $15.00 invoicing charge on all orders filled before payment.

Note added in proofs. We recently learned of a similar study by Desmond et al. (Brain, in press) that reports close agreement between FMRI and Wada language results in 7 patients.

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