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Functional MR of Frontal Lobe Activation: Comparison with Wada Language Results

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PURPOSE: **Our purpose was to determine the utility of functional MR imaging in conjunction with a word-generation paradigm in the assessment of language lateralization.**

METHODS: **Functional MR imaging and Wada testing for language lateralization was performed in patients with complex partial seizures during the performance of word-generation tasks. A language lateralization quotient was calculated from the number of activated pixels in the right and left hemispheres. A language laterality score was derived from the Wada results as the percentage of correct responses during right internal carotid artery injection minus the percentage of correct responses during left internal carotid injection. A correlation coefficient between the functional MR imaging results and the Wada language laterality scores was calculated.**

RESULTS: **In 13 patients, hemispheric dominance based on Wada testing was confirmed by functional MR imaging during silent word generation. The Wada laterality scores varied from 100 to −100 and the functional MR imaging scores varied from 100 to −10. The language lateralization scores determined by functional MR imaging correlated significantly with the language lateralization scores derived from Wada testing.**

CONCLUSION: **Functional MR imaging performed during word generation is an accurate method for lateralizing language function in patients with complex partial epilepsy.**

A noninvasive method for lateralizing language function would have practical benefit for the estimated 150,000 patients who are candidates for surgical management of epilepsy (1). Less invasive and cheaper methods of mapping cerebral functions and identifying epileptogenic foci have been the target of research (NIH Consensus Panel on Epilepsy). The Wada test currently used to determine the cerebral representation of language requires catheterization of the carotid arteries and successive anesthetization of each hemisphere (2). Despite its cost and risk, the Wada test is used routinely at institutions with epilepsy treatment programs to evaluate the organization of language and memory in patients being examined for tailored temporal lobectomy to control seizures (3–6). Functional MR imaging techniques for mapping language function may ultimately provide greater accuracy and less risk than the Wada test for the assessment of language.

Language functions have been mapped noninvasively with functional MR imaging in healthy volunteers and patients, lateralization has been assessed with the use of semantic monitoring tasks (7, 8), and word-generation tasks have been used in clinical studies of patients with cerebral space-occupying lesions (9). The purpose of this study was to compare the word-generation task with the Wada test in the evaluation of language lateralization.

Methods

Patients scheduled for a Wada test between January and October 1996 for the preoperative evaluation of medically intractable epilepsy were asked to participate in the study. Exclusion criteria included a history of substance abuse, brain injury, other neurologic or psychiatric disorders, cardiopulmonary insufficiency, psychosis, or contraindications to MR imaging or angiography, and an inability to perform the task paradigms or to speak English. Thirteen consecutive patients were enrolled and none excluded. The nine women and four men with partial complex seizures ranged in age from 22 to 43 years. Informed consent was obtained from all participants.

As part of the preoperative assessment, all patients underwent comprehensive neuropsychological testing and neurologic

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examination. Age of seizure onset, frequency and type(s) of seizures, and duration of epilepsy were recorded. Inpatient long-term simultaneous video/EEG monitoring, postictal and interictal single-photon emission CT, and MR imaging were performed in the localization of epileptogenic focus. Handedness was assessed by means of the Edinburgh inventory (10). Onset of seizures ranged from 9 months to 23 years of age; one patient was left handed and 12 were right handed.

For the word-generation task, patients were instructed to think of words that begin with a specific letter until cued to stop. The letters and the cues to start and stop were provided from a recorded tape. Functional MR imaging data were acquired while the subjects responded to the instructions.

The functional MR images were obtained on a commercial 1.5-T imager equipped with a bird cage–type head coil and a three-axis gradient coil (11, 12). A series of localizer images was obtained in axial, coronal, and/or sagittal planes. Anatomic 1-cm-thick reference images that encompassed the brain were acquired with spin-echo acquisitions and parameters of 600/20/2 (TR/TE/excitations), a 24-cm field of view, and a 128 × 256 matrix. For each anatomic image, a series of single-shot blipped echo-planar gradient images was acquired at intervals of 2 seconds. During the acquisition, there were three periods of task performance (each 20 seconds in length) interspersed with four periods of rest (20 seconds in length). Technical parameters for the functional images were 1000,2000/40, a 64 × 64 matrix, a 24-cm field of view, 1-cm-thick sections, and an acquisition time of 40 milliseconds (12). The time course of the signal intensity in each pixel over 140 seconds was plotted and compared by means of a cross-correlation program to a reference function representing an idealized response to the task. The reference function was a modified square wave with a period of 40 seconds, and the first 5 seconds of the time course and the first 5 seconds of each rest and task period were excluded in the co-correlation calculation. Pixels with a significant correlation ($P < .0001$) to the reference function were displayed as activated pixels. The activated pixels on the functional images were then overlaid on the exactly corresponding anatomic reference images by means of an image-processing program (12). The number of activated pixels in the language activation regions (inferior frontal gyrus, precentral gyrus, and subcentral gyrus) in each hemisphere were counted by an investigator blinded to the Wada results. The language laterality quotient was calculated by $(100)(L - R)/(L + R)$.

For the Wada test, a standard protocol was used (13). In this procedure, baseline testing of memory, language, and motor strength is conducted before angiography is performed. The patient is brought to the radiology department with scalp electrodes in place. The internal carotid arteries are catheterized in the conventional manner. Angiograms are obtained by digital recording for 10 seconds after the injection of contrast medium selectively into the internal carotid artery. The images are inspected before Wada testing, and any vascular abnormalities are recorded. Patients with significant anomalies of the cerebral circulation are excluded from the statistical analyses. Starting usually with the side of the epileptogenic focus, amobarbital sodium (100 mg) is injected by hand over a 4-second interval into the internal carotid artery with EEG monitoring and with patients instructed to maintain their arms in an elevated position. The technical sufficiency of the intracarotid injection is demonstrated by EEG slowing and loss of arm control. Counting, comprehension, naming, repetition, and reading are rated. After a 30-minute delay, the test is repeated in the contralateral hemisphere. The expressive language score (0 to 4) is based on disruption of counting ability at the initiation of the Wada test (4 = normal or slowed; 3 = counting perseveration with normal sequencing; 2 = sequencing errors; 1 = single number or word perseveration; 0 = arrest for greater than 20 seconds). Comprehension is assessed formally by a modified token test, which consists of four geometric shapes of different colors that are presented vertically in the subject's ipsilateral visual field. Commands of increasing complexity are issued. A score of 3 is awarded for completion of the complex two-stage command with inverted syntax, a score of 2 is given for successful completion of the simple two-stage command, a score of 1 is awarded for the one-stage commands, and a 0 is assigned if the subject could not execute any commands. Two line drawings of common objects (ie, a watch and a jacket) are then presented, and the subject is asked to name them and their various parts. After the object-naming task, the patient is asked to repeat phrases (eg, "No if's, and's, or but's"), and the repetition is graded on a scale of 0 to 3. Finally, the subject is asked to read two sentences, during which paraphasic responses are recorded. The total score for each hemisphere is the percentage of correct language responses occurring before the return of motor function in the hemiplegic limb. The language laterality score is derived by ascertaining the percentage of correct responses during injection of the right hemisphere minus the percentage of correct responses during injection of the left side times 100. Ratios for the laterality scores derived from functional MR imaging and from Wada testing are correlated, and the Pearson correlation coefficient and the P value are calculated.

Results

Activation from the motor (control) task was judged to be technically adequate in each patient. In 13 patients, activation during silent word generation was identified in the language regions of the frontal lobe. In two patients, activation was exclusively in the left hemisphere (score 100); in the one left-handed patient, it was more prominent in the right hemisphere (score, −10); and in all others it was distributed between the two hemispheres, with a majority of activity in the left hemisphere. The activated pixels were anatomically related predominantly to the inferior frontal gyrus and the precentral gyrus. In addition to the inferior frontal lobe, activation was noted in most cases around the central sulcus or in the midline near the supplementary motor area and anterior cingulate, but these regions of activation were not included in the tabulation.

In the Wada procedure, the injections were judged to produce adequate hemispheric anesthesia in all 13 patients. No significant angiographic abnormalities were detected. During the Wada test, seven patients had left hemispheric language (score, 100); one had right hemispheric language (score, −100), and five had a distribution of language between the hemispheres (scores, 50 to 95). The left-handed patient had predominantly right hemispheric activation on functional MR imaging and right hemispheric lateralization on Wada testing.

The Wada and functional MR imaging scores had a correlation coefficient of .93. Functional MR imaging identified the patients who had left-dominant, right-dominant, and bilateral language distributions by Wada testing. Thus, lateralization of hemispheric dominance was concordant in 13 cases (Fig 1). The Wada and functional MR imaging scores for each patient are shown in the Table and in Figure 2. Correlation was significant at $P = .0001$. When the one strongly right-dominant case was excluded, the correlation coefficient became .80 ($P = .0015$).

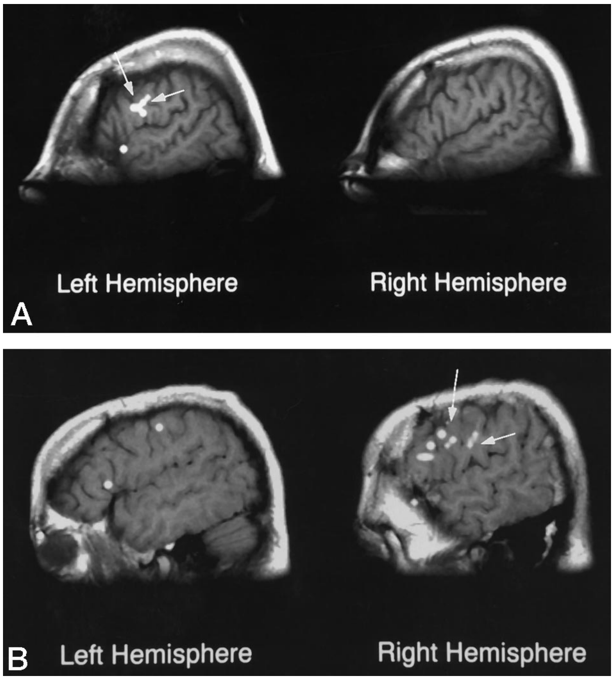

FIG 1. *A*, Sagittal functional MR images during activation related to silent word-generation task in patient 4. The patient has epilepsy and left hemispheric dominance, as determined by Wada testing. Activation is seen around inferior frontal gyrus in left hemisphere (*arrows*), with no activation in the right hemisphere.

B, Sagittal functional MR images during activation related to silent word-generation task in patient 1, in whom the Wada test identified right hemispheric dominance. Activation is more predominant in the inferior frontal region of the right hemisphere (*arrows*).

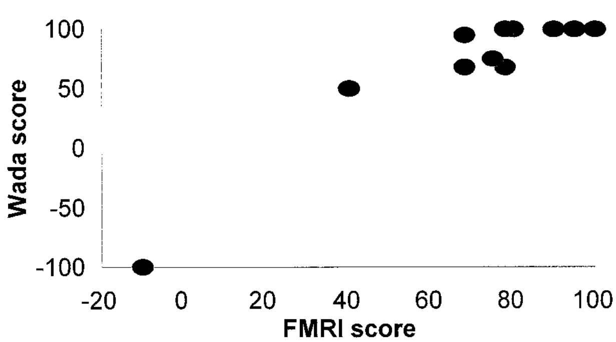

FIG 2. Degree of hemispheric lateralization, as determined by functional MR imaging score, is plotted against Wada test score showing the degree of hemispheric dominance (r = .91).

Discussion

Consistent with previous research (7, 8), our study shows that Wada testing and functional MR imaging provide similar results. Previous comparisons have been based on different language task paradigms. Since the language task may involve other cognitive systems, such as short-term memory or attention, it may produce some activation in either hemisphere that is not specific for language function. Functional MR imaging may show left hemispheric activation in patients in whom predominantly right-sided language

TABLE: Scores for language lateralization for functional MR and Wada testing

Patient	Laterality Scores	
	Functional MR	Wada Test
1	−10	−100
2	90	100
3	80	100
4	100	100
5	40	50
6	78	68
7	78	100
8	100	100
9	95	100
11	68	68
12	75	75
13	68	95
	95	100

dominance by the Wada test is uncertain. In some cases in which the Wada test shows right hemispheric dominance, intraoperative cortical stimulation shows some left hemisphere language functions (14). The Wada test is limited by the brief time during which the hemisphere is anesthetized, by somnolence, and by vascular abnormalities that permit some anesthetic to reach the opposite hemisphere. The Wada test yields a number of false-positive findings in the lateralization of memory (15).

While the left hemisphere is dominant for language in most healthy subjects, a recent functional MR imaging study showed differences in language lateralization in healthy right-handed control subjects and epilepsy patients (16). The nondominant hemisphere plays a larger role in language function in patients with epilepsy than it does in neurologically intact subjects. In one study, 10% of patients undergoing injection of barbiturate in the right carotid artery during the Wada test (17) had aphasia. In another study of epileptic patients, speech representation was bilateral or exclusively in the right hemisphere in 72% (18). In the epileptic patients with bilateral speech representation, speech was often not arrested by the amobarbital injections into either carotid artery, but responses to the language tasks were dysphasic from both injections. In some of these cases, the dysphasic patterns from the injections on each side were different, suggesting that different language functions were located in each hemisphere (19). Injection into one hemisphere produced errors in naming but little or no disturbance in serial repetition tasks, such as counting; injection into the other hemisphere produced errors and hesitation in verbal serial ordering tasks with little or no disturbance in naming (18). By comparison, aphasia from an acquired lesion in the right hemisphere in nonepileptic right handers is rare (20). While the Wada test is not a perfect standard of reference, an initial comparison of functional MR imaging and Wada testing is justified because "Wada is the least ambiguous technique available . . . against which noninvasive cerebral dominance techniques have been evaluated" (13).

In addition to the limitations of the Wada test itself, our study has other limitations. Although statistical significance was shown, the number of cases was small. The optimal language task for determining hemispheric dominance has not been determined; with some tasks, such as rhyming, investigators have shown that both right and left hemispheres are normally active, at least in women (21). Subtraction of auditory tasks from language tasks, as done in some investigations (7), may improve lateralization, but the tasks, because of their complexity and duration, are not well suited to many patients. A good artifact-reduction system or reregistration of images was not used; instead, the study relied on the patients' ability to cooperate with the instruction not to move. Movement generates artifacts that are likely to be randomly distributed between the two hemispheres (22).

Conclusion

Our findings suggest that the Wada test performed with a word-generation paradigm reliably identifies the hemispheric dominance for language. When functional MR imaging techniques are developed to evaluate the memory functions as reliably as the Wada procedure does, functional MR imaging may replace the Wada test. Studies investigating the concurrent and predictive value of functional MR imaging are also needed.

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