J Neurosurg 106:90–98, 2007

Visualization of the frontotemporal language fibers by tractography combined with functional magnetic resonance imaging and magnetoencephalography

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Object. There is continuous interest in the monitoring of language function during tumor resection around the frontotemporal regions of the dominant hemisphere. The aim of this study was to visualize language-related subcortical connections, such as the arcuate fasciculus (AF) by diffusion tensor (DT) imaging–based tractography.

Methods. Twenty-two patients with brain lesions adjacent to the AF in the frontotemporal regions of the dominant hemisphere were studied. The AF tractography was accomplished by placing initiation and termination sites (seed and target points) in the frontal and temporal regions, which were functionally identified by using functional magnetic resonance (fMR) imaging in conjunction with a verb generation task and magnetoencephalography (MEG) in conjunction with a reading task. The combination of fMR imaging and MEG data clearly demonstrated the hemispheric dominance of language functions, which was confirmed by an intracranial amobarbital test (Wada procedure). In all 22 patients, the authors were able to consistently visualize the AF by DT imaging–based tractography, using the functionally identified seed and target points and a fractional anisotropy value of 0.16. In two of 22 cases investigated, the functional information, including the results of AF tractography, fMR imaging, and MEG, was imported to a neuronavigation system and was validated by bipolar electric stimulation of the cortical and subcortical areas during awake surgery. The cortical stimulation to the gyrus that included the area of activation identified in fMR imaging with the language task evoked speech arrest, while the subcortical stimulation close to the AF reproducibly caused paranomia without speech arrest. Postoperative AF tractography showed that the distances between the stimulus points and the AF were within 6 mm.

Conclusions. The combination of these techniques facilitated accurate identification of the location of the AF and verification of the language fibers.

KEY WORDS • arcuate fasciculus • subcortical stimulation • functional magnetic resonance imaging • language • magnetoencephalography • tractography

TUMOR resection in the frontotemporal regions of the dominant hemisphere entails a high risk of neurological consequences to language functions. It is essential to preserve the subcortical connections related to these language functions in addition to sparing eloquent cortices from injury. Several groups have proposed electrical subcortical stimulation during awake surgery as a reliable way to identify the eloquent subcortical connections.[6,7,11] However, there are several difficulties associated with this procedure, including the need to identify, for optimal stimulus points, the need for patients' cooperation and certain risks related to anesthesia. It is therefore desirable to quickly and accurately find the eloquent fibers of language functions within the limited operation time.

Recent progress in functional brain imaging has allowed the visualization of white matter connections in addition to the cortical distribution of language functions.[9,17,18] Fiber tracking processes (tractography) allow visualization of the major axonal fascicles of interest through calculation of the DT of each pixel.[1,14] Recently, several groups have succeeded in integrating DT imaging–based tractography of the corticospinal tract and the optic radiation into neuronavigation systems and have verified the integrated fibers by using electrophysiological techniques.[2,11]

The AF allows the connection between two essential epicenters of the language network—the IFG and the dorsolateral PFCs—and the posterior temporal region within the dominant hemisphere. It is very difficult to extract anisotropic components of the AF from DT imaging data because there are no anatomical landmarks for the initiation of tractography, and other subcortical fibers, such as the superior and inferior longitudinal fascicles and the corticospinal tract, were densely packed together with the AF in the frontotemporal region.

We recently reported the use of the combination of fMR

Abbreviations used in this paper: AF = arcuate fasciculus; DT = diffusion tensor; fMR = functional magnetic resonance; GBM = glioblastoma multiforme; IFG = inferior frontal gyrus; MEG = magnetoencephalography; MFG = middle frontal gyrus; MTG = middle temporal gyrus; PFC = prefrontal cortex; SMG = supramarginal gyrus; STG = superior temporal gyrus.

imaging and MEG to noninvasively detect the cortical areas of specific language functions.[9,10] In our study, we were able to clearly identify the expressive language area using fMR imaging in combination with a verb generation task, whereas MEG in combination with a reading task successfully depicted the receptive language function. By combining the advantages of the two approaches, we established a reliable method to identify the areas involved in global language functions. We have applied these noninvasive mapping techniques to identify the initiation and terminal sites (seed and target points) for AF tractography.

In the current study, we investigated 22 cases of brain lesions located in the dominant frontotemporal area and successfully visualized the spatial relationships between the AF and the lesions. In two of the 22 cases, the functional information, including the results of AF tractography, fMR imaging, and MEG, were imported to a neuronavigation system (functional neuronavigation), and the findings were validated using cortical and subcortical stimulation during awake surgery in these two patients. In this paper we describe the usefulness of DT imaging–based tractography for localizing language functions and demonstrate its reliability using subcortical mapping in two of the 22 cases studied.

Clinical Material and Methods

Patient Population

We studied 22 patients harboring an intraaxial tumor in the frontotemporal language area of the dominant hemisphere. All patients had little impairment of expressive or receptive language functions, except for dysarthria and hemiparesis, and underwent the intracranial amobarbital procedure (Wada test) to identify the language dominance. Because two of the patients had a lesion that partially involved the AF, we decided that they were candidates for awake surgery to spare the eloquent subcortical connections of language functions.

This study was approved by the institutional review board, and written informed consent was obtained from each subject before participation in the studies.

Visualization of the Language Networks

To place the seed and target points for AF tractography, we needed to localize the cortical language functions using fMR imaging and MEG. Details of the noninvasive cortical mapping have been reported elsewhere.[10]

Magnetic Resonance Imaging Protocols

All MR imaging was performed using a 1.5-tesla whole-body unit with echo planar capabilities and a standard whole-head transmitter–receiver coil (Vision, Siemens: Signa Echospeed, General Electric Medical Systems). During the experiments, foam cushions were used to immobilize the patient's head.

Functional MR Imaging With a Language Task

Functional MR imaging was performed with a T_2*-weighted echo planar imaging sequence (TE 62 msec; TR 114 msec; flip angle 90°; slice thickness 4 mm; slice gap 2 mm; field of view 260 mm; matrix 64 × 128; 14 slices). Each fMR imaging session consisted of three dummy image volumes, three activation periods, and four baseline (rest) periods. During each period, five echo planar imaging volumes were collected, yielding a total of 38 imaging volumes. Each patient was asked to silently generate a verb related to each acoustically presented noun. The interstimulus intervals ranged from 1600 to 2400 msec during the active periods. Reverse playback of the sound files was used to eliminate primary auditory activation for the rest period, using exactly the same interstimulus intervals as the active condition. The auditory stimuli were delivered binaurally via two 5-m-long plastic tubes terminating at headphones.

After acquiring the data, we used a motion detection program (MEDx, Medical Numerics) to identify and eliminate fMR imaging sessions containing motion artifact of more than 25% of the pixel size. After applying a gaussian spatial filter (7 mm in half width), we calculated functional activation maps by estimating the Z scores between the rest and activation periods, using Dr. View software (Asahi Kasei). Clusters with a Z score greater than 2.2 were accepted as indicating real activation. The result of each fMRI session was coregistered to 3D T_1-weighted MR images of each subject's head, maximizing the mutual information of the data sets with the affine transformation.[5]

Magnetoencephalography With a Language Task

The MEG signals were recorded with a 204-channel biomagnetometer (VectorView, Neuromag) in a magnetically shielded room. One hundred fifty words consisting of three Japanese letters were visually presented with a 300-msec exposure time and interstimulus intervals ranging from 2800 to 3200 msec during the MEG recording sessions, and the patients were asked to categorize the presented word as abstract or concrete. The averaged magnetic signals were digitally filtered between 0.1 and 30 Hz and obvious MEG deflections were visually identified on the basis of root mean squared fields of more than 10 sensors. Locations and moments of equivalent current dipoles were calculated every 2 msec from 250 to 600 msec after the stimulus onsets, using the single equivalent dipole model. Only dipoles with a correlation value of more than 0.85 were accepted. These dipoles were superimposed onto 3D MR images according to anatomical fiduciary landmarks.

Thus we obtained functional 3D MR images containing fMR imaging and MEG results and showing the cortical distribution of the language functions.

Diffusion Tensor Imaging–Based AF Tractography

Diffusion Tensor Imaging

All DT imaging was performed using a single-shot spin echo–echo planar sequence with an echo time of 66.4 msecs and a repetition time of 13000 msecs. Fifty-five interleaved, gapless, 3-mm-thick axial images were acquired in order to cover the entire brain. A field of view of 24 × 24 cm and a matrix of 128 × 128 interpolated to 256 × 256 were used. Diffusion gradients were applied in 15 noncollinear independent axes using a b value of 1000 seconds/mm^2 as the peak diffusion gradient. Non–diffusion-weighted images (T_2-weighted images) were also obtained with a b value of 0 seconds/mm^2. Realignment of these 15 DT imaging sets and compensation for eddy-current–induced morphing were performed on the basis of a T_2-weighted echo planar imaging set (b = 0) on an equipped workstation (Advantage Workstation 4.0, General Electric).[15]

Diffusion Tensor Calculation and DT Imaging–Based Tractography

The DT imaging data sets were analyzed by using freeware for diffusion tensor analysis and fiber tracking (Volume-One and dTV; URL: http://volume-one.org).[14] Interpolation along the z axis was also applied to obtain isotropic data (with a voxel size of 0.94 × 0.94 × 0.94 mm). The software determined six elements of the symmetric 3 × 3 matrix of the diffusion tensor at each voxel by least-square fitting, and the diffusion tensor was diagonalized to obtain three eigenvalues and three eigenvectors. The eigenvector ($e1$) associated with the largest eigenvalue ($\lambda 1$) was assumed to represent the local fiber direction. Anisotropy maps were obtained using orientation-independent fractional anisotropy. Coregistration between T_2-weighted echo planar images including the DT imaging–based tractography and functional 3D MR images was performed based on the maximization of mutual information by affine transformation.[5,15]

We determined the seed point for AF tractography on the functional 3D MR images of the frontal lobe so as to include most of the area of activation identified on fMR imaging using the language task. Similarly, the target was drawn on the ipsilataral superior temporal region, where the MEG language study dipoles were clustered. Diffusion tensor imaging–based tractography was initiated from the seed point from which lines were propagated in both anterograde and retrograde directions according to $e1$ at each pixel. Only the trajectories of the AF passing through both the seed and target points were retained for the analysis. When a pixel with an fractional anisotropy value lower than 0.16 was reached, the tracking process was terminated.

Two patients (Cases 21 and 22), who had lesions that partially involved the AF, underwent surgery with local anesthesia (awake surgery) so that functional cortical and subcortical mapping could be performed using electrical stimulation. For this procedure, we used additional processes as described in the following section.

Voxelization, Image Registration, Data Fusion, and Functional Neuronavigation

After AF fiber tracking, voxels containing tract fibers were marked with volume data, using the same matrix size is in DT imaging—in other words, voxelization of the tracking lines was performed. Because of the coregistration, the voxelized AF was in the same coordinate system of the T_2-weighted echo planar imaging data. Finally, the voxelized AF and the functional 3D MR images were simply fused and resliced using the DICOM (Digital Imaging and Communications in Medicine) format according to the original anatomical 3D MR imaging header information. After all these processes were completed, the results were visually evaluated by at least two radiologists and one neurosurgeon.

The resliced functional 3D MR imaging data, including the AF tractography data, was transferred to a neuronavigation system (Stealthstation; Medtronic Sofamor Danek). The neuronavigation system software was used to segment the functional information by setting the signal thresholds and color the areas identified by AF tractography, areas of fMR imaging activation, and MEG dipoles as yellow, red and blue, respectively. In this manner we performed functional neuronavigation.

Cortical and Subcortical Mapping

A bipolar electrode with tips spaced 5 mm apart and delivering a biphasic current with a pulse frequency of 50 Hz and a single pulse phase duration of 1 msec (Ojemann Cortical Stimulator; Unique Medical) was applied to the brain of awake patients.

Cortical mapping was performed after the tumor and sulci/gyri had been identified using functional neuronavigation and ultrasonography. Motor mapping was performed first to find the appropriate stimulus intensity. The specific current intensity used for each patient was determined by progressively increasing the amplitude from a baseline of 4 mA, until a motor response (inhibition of voluntary hand movement by muscle contraction) was elicited, with 10 mA as the upper limit, and the goal of avoiding the generation of seizures. Once the motor mapping threshold was defined, the same intensity was used for both cortical and subcortical mapping of language functions. We systematically used simple language tasks, such as spontaneous speech, picture naming, and auditory comprehension, and stimulus points were determined by functional neuronavigation.

The patients were first asked to repeatedly speak the sentence, "The weather is good today," and the cortical regions in which cortical stimulation caused speech arrest or dysarthria were marked with sterilized tags. For the naming task, we showed the patients 20 different pictures, which were simple and easy to recognize during awake surgery, and observed the degree of speech arrest or paranomia caused by cortical and subcortical stimulation. During the auditory comprehension task, the patients were asked to follow simple verbal commands, such as requests to shake their hands, move their fingers, and open their mouths.

We removed the lesions, alternating resection and subcortical stimulation. The patients were asked to continue to speak a sentence or name an object when the resection approached the AF. We pursued resection in each case until we encountered eloquent pathways around the surgical cavity, as identified by functional neuronavigation and subcortical stimulation.

Results

Functional MR Imaging With a Verb Generation Task

The verb generation task was completed by and useful fMR imaging data was obtained from all 22 patients. Pixels activated during the verb generation task were clustered mainly in the IFG, MFG, dorsolateral PFC, and supplementary motor area. Activation in the IFG and MFG was significantly lateralized and therefore served as a good indicator for the dominant hemisphere in all patients (Fig. 1A). We found that the left hemisphere was dominant for expressive language function in 19 patients and the right in three patients (Figs. 1A and 2A). Functional MR imaging demonstrated activation in the suspected dominant hemisphere as

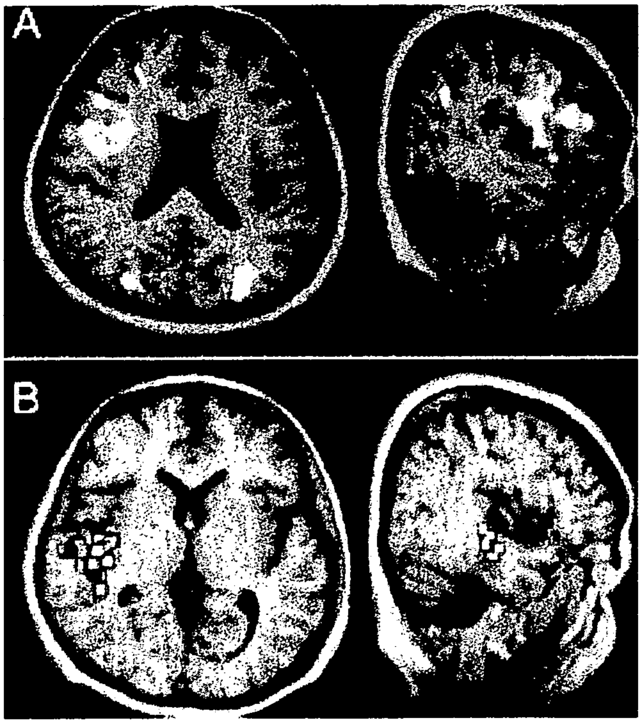

FIG. 1. Case 21. A right frontal lobe tumor in a 61-year-old, left-handed woman. A: Functional MR images obtained during a language task showing activation predominantly in the right IFG and the inferior part of the MFG. B: Magnetoencephalography source localizations obtained during a language task, superimposed on MR images, showing dipole clusters predominantly in the right STG and MTG. The left and right hemispheres contained 37 and 127 dipoles, respectively.

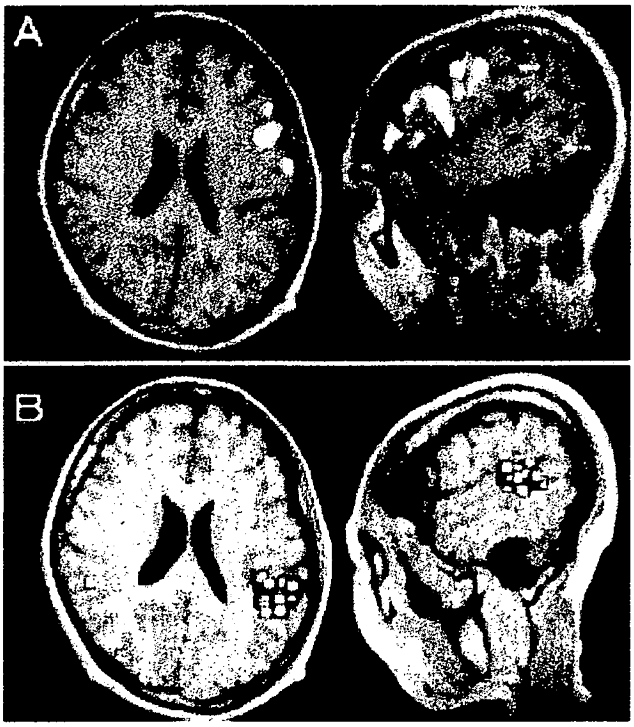

FIG. 2. Case 22. A left frontal lobe lesion in a 44-year-old, right-handed woman. A: Functional MR images obtained during a language task, showing activations mainly in the left MFG and dorsolateral PFC. B: Magnetoencephalography source localizations obtained during a language task, superimposed on MR images, showing dipole clusters in the left superior temporal region, including the SMG. The left and right hemispheres contained 93 and 19 dipoles, respectively.

follows: in the posterior part of the IFG (pars opecularis) and MFG in 12 patients, only in the MFG in six patients, and in the whole IFG in four patients. The dorsolateral PFC and supplementary motor area were bilaterally activated in 16 patients.

Magnetoencephalographic Profiles and Dipole Locations

All 22 patients were able to perform the MEG language task and demonstrated lexicosemantic responses peaking at approximately 400 msec after letter presentation (N400m). The N400m were predominantly observed in the MEG sensors covering the frontotemporal regions. Dipole clusters of the N400m were located in the superior temporal region, including the STG and MTG of the suspected dominant hemisphere in all 22 patients, in the SMG in 13 patients, and in the inferior temporal region (fusiform gyrus and ITG) in five patients (Fig. 1B and 2B). The results of the MEG language task showed that the left hemisphere was dominant for temporal lobe receptive-language function in 19 patients and the right hemisphere was dominant in three. The mean total numbers of dipoles in the suspected dominant and nondominant hemispheres (with SDs) were 92.0 ± 39.1 and 40.2 ± 25.8, respectively. The mean ratio (± SD) of the number of dipoles in the dominant hemisphere to the number in the nondominant hemisphere was 2.3 ± 1.8 (range 1.43–9.4).

The fMR imaging and MEG depicted the frontal expressive and temporal receptive language functions well and consistently identified the dominant hemisphere. The results of the noninvasive functional mapping were confirmed by results of the amobarbital test, that is, left-sided dominance in 19 patients and right-sided dominance in 3 patients. Demographic data on all the patients are shown in Table 1.

Arcuate Fasciculus Tractography

Although the AF is very difficult to locate on regular MR imaging sequences, the fractional anisotropy or color vector maps demonstrated the AF as a high-anisotropic or green (anterioposterior orientation) area in the frontotemporal white matter in all 22 patients (Fig. 3A and B). The tractography results were strongly supported by the results of the fMR imaging and MEG with language tasks (Fig. 3C and D). The area of activation on fMR imaging was usually greater than the size of the MEG dipole clusters in our previous studies.[9,10] We chose diameters of 25 and 30 mm for the seed and target spheres, respectively, thereby including more than 80% of the MEG dipoles and the pixels that were activated in the temporal and frontal language areas in the functional 3D images (Fig. 3E).

The AF was thus clearly distinguished from other subcortical connections, with little contamination (Fig. 3F).

TABLE 1

*Demographic data on 22 patients with lesions affecting the arcuate fascicles in the dominant hemisphere**

Case No.	Age (yrs), Sex	Handedness	Dominant Hemisphere			Lesion Location	Symptoms	Histological Findings
			fMRI	MEG	Wada Test			
1	38, M	rt	lt	lt	lt	lt temporal	gen seizure	astrocytoma (Gr I)
2	37, F	lt	rt	rt	rt	rt temporal	gen seizure	astrocytoma (Gr II)
3	28, M	rt	lt	lt	lt	lt frontotemporal	mild rt hemiparesis	astrocytoma (Gr III)
4	37, F	rt	lt	lt	lt	lt frontal	gen seizure	astrocytoma (Gr II)
5	54, M	rt	lt	lt	lt	lt temporal	none	GBM
6	28, F	rt	lt	lt	lt	lt temporal	gen seizure	astrocytoma (Gr II)
7	32, F	rt	lt	lt	lt	lt frontal	mild rt hemiparesis & dysarthria	astrocytoma (Gr III)
8	45, M	rt	lt	lt	lt	lt frontal	mild rt hemiparesis	astrocytoma (Gr III)
9	43, F	rt	lt	lt	lt	lt frontal	gen seizure	astrocytoma (Gr II)
10	32, M	rt	lt	lt	lt	lt frontal	none	astrocytoma (Gr II)
11	43, M	rt	lt	lt	lt	lt frontal	gen seizure	astrocytoma (Gr III)
12	32, F	rt	lt	lt	lt	lt frontotemporal	none	astrocytoma (Gr II)
13	18, F	rt	lt	lt	lt	lt frontal	gen seizure	astrocytoma (Gr II)
14	38, M	rt	lt	lt	lt	lt frontal	gen seizure	astrocytoma (Gr II)
15	50, F	rt	lt	lt	lt	lt frontal	none	astrocytoma (Gr III)
16	45, F	rt	lt	lt	lt	lt temporal	mild sensory aphasia	GBM
17	44, F	rt	lt	lt	lt	lt frontal	gen seizure	astrocytoma (Gr II)
18	71, M	rt	lt	lt	lt	lt frontal	rt hemiparasis & dysarthria	GBM
19	22, F	rt	lt	lt	lt	lt frontal	mild rt hemiparesis	GBM
20	49, M	lt	rt	rt	rt	rt frontotemporal	gen seizure	astrocytoma (Gr II)
21	61, F	lt	rt	rt	rt	rt frontal	dysarthria & numbness in lt face	GBM
22	44, F	rt	lt	lt	lt	lt frontal	transient amnesia	astrocytoma (Gr II)

* gen = generalized; Gr = grade.

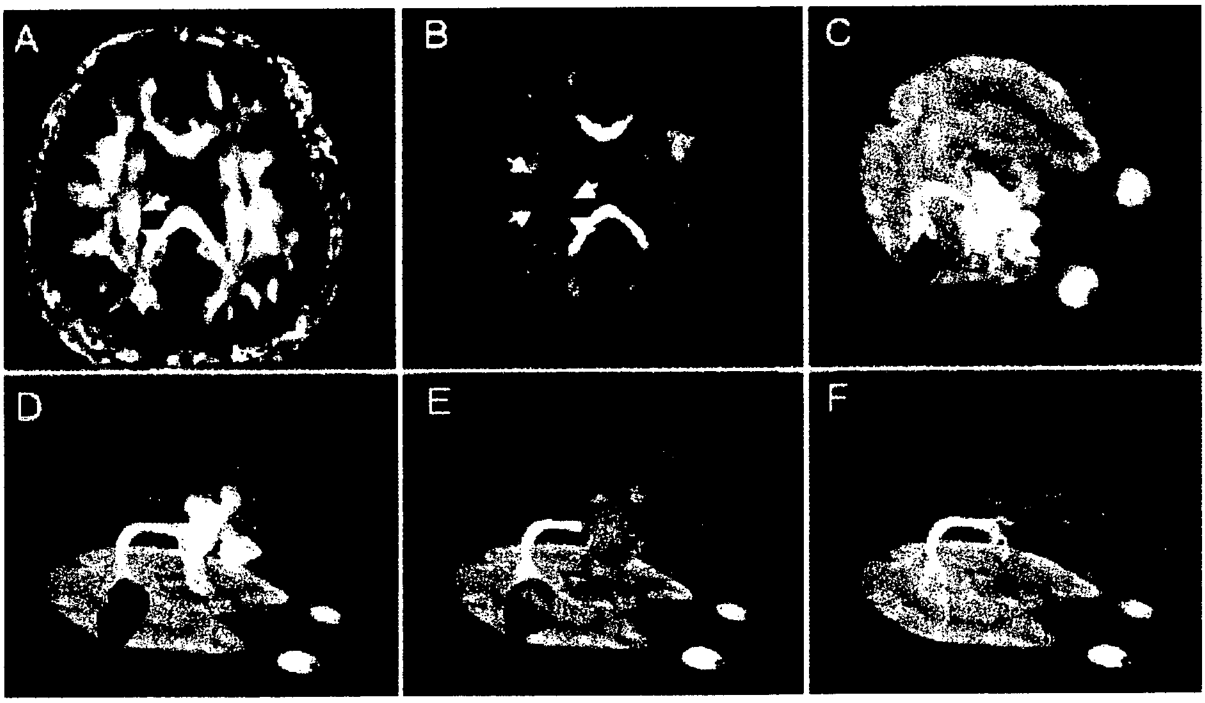

FIG. 3. Case 21. A: A fractional anisotropy map demonstrating higher anisotropic components, such as the AF *(red arrow)* and corticospinal tract *(white arrow)*, as white areas. B: A color vector map showing the fibers in the anteroposterior orientation, including the AF *(red arrow)* and corticospinal tract *(white arrow)*, which appear as green and blue areas, respectively. C and D: Three-dimensional reconstructions of functional information, including fMR imaging activation during a language task *(red)*, MEG dipoles from the MEG language task *(blue)* and results of AF tractography *(orange)*. E: Three-dimensional reconstruction of functional information showing the two regions of interest (seed and target points) for the AF tractography, which contain the frontal fMR imaging activation *(blue sphere)* and temporal MEG dipoles *(pink sphere)*. F: Results of AF tractography created by using the seed and target points and a threshold fractional anisotropy value of 0.16.

Regardless of whether the target was placed in the frontal-expressive or temporal-receptive language area, we obtained a reproducible AF profile. The mean fractional anisotropy value of all AF pixels was 0.17 ± 0.24. We, therefore, set a value of 0.16 as the appropriate threshold for extracting anisotropic components of the AF. The DT imaging–based tractography showed that the AF was medially compressed in five patients, inferiorly compressed in two, and partly involved by the lesions in two patients.

Cases of Awake Surgery

Awake surgery and subcortical stimulation were performed in two of the 22 cases. The symptom elicited by subcortical stimulation was consistent and highly reproducible in both cases.

Case 21

This 61-year-old, left-handed woman had suffered from dysarthria and numbness in her left lip for a month. Fluid-attenuated inversion-recovery MR imaging demonstrated a hyperintense 2-cm lesion mainly involving the right MFG (Fig. 4A). Functional MR imaging during verb generation demonstrated obvious activation in the posterior part of the right IFG and the inferior part of the MFG, which partly covered the tumor (Fig.1 A). On the MEG language task there were 127 dipoles in the right hemisphere and 37 in the left; the main dipole clusters were located in the right STG and MTG (Fig. 1B). The right hemispheric dominance, identified by the fMR image and MEG language tasks was confirmed by the Wada test. Because the tumor extended to the subcortical white matter in addition to involving parts of the MFG, it was important to clarify the spatial relationships between the eloquent structures and the lesion. The AF tractography was initiated from the seed point, including the area of activation on fMR imaging in the IFG, to the target point in the superior temporal region, and the U-shaped AF was visualized using an threshold fractional anisotropy value of 0.16 (Fig. 3).

During intraoperative cortical mapping, 10 mA of electrical current applied to the posterior part of the IFG and the inferior part of the MFG consistently caused speech arrest without oromotor seizure. Stimulation of the upper part of the MFG, however, elicited little dysarthria and no speech arrest (Fig. 5A and B). We therefore decided to perform a corticotomy in the upper part of the MFG, which covered the subcortical tumor. We removed the tumor carefully, observing whether subcortical stimulation caused language deficits. Although stimulation directly to the AF visualized on functional neuronavigation did not suppress spontaneous speech, it severely impaired naming acuity. During the subcortical stimulation, the patient could speak naturally, but failed to name all 15 pictures—that is, she experienced paranomia. The stimulus points related to paranomia were adjacent to the identified AF (Fig. 5). The resection was therefore stopped to preserve the language-related functions. We measured the minimum distance between the resection cavity and the identified AF by segmentation of signal intensity on isotropic postoperative DT images (Fig. 6A). Although the minimum distance was 1.2 mm and the AF seemed to be preserved on the DT imaging–based tractography, the patient suffered from transient but severe postoperative motor-dominant aphasia. The aphasia lasted for longer than 6 months and then gradually resolved. The histopathological diagnosis was GBM. One year after surgery, the patient's speech had deteriorated because of tumor recurrence and she was again experiencing motor-dominant aphasia.

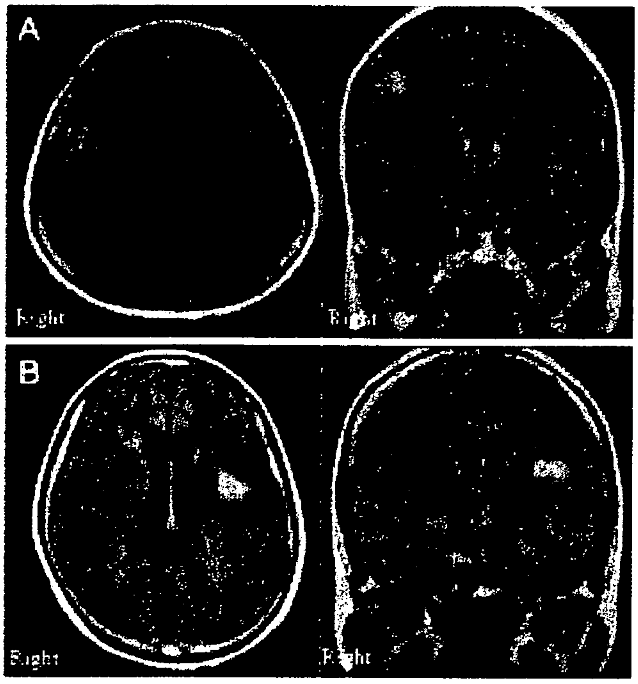

FIG. 4. Fluid-attenuated inversion-recovery MR images showing a hyperintense lesion in the right MFG of the patient in Case 21 (A) and in the left IFG and MFG of the patient in Case 22 (B). Hyperintense lesions suggest glial-origin tumors because of unclear tumor margins.

Case 22

This 44-year-old, right-handed woman with a suspected glial-origin lesion in the left frontal lobe (Fig. 4B) experienced transient amnesia. In the functional mapping studies, activation on fMR imaging was restricted to the left MFG and dorsolateral PFC, and MEG dipoles were concentrated in the left superior temporal region, including the SMG (Fig. 2A and B). We performed DT imaging–based tractography by using the functionally identified language centers, and we were able to visualize the AF and establish that it was partially involved by the tumor.

During awake surgery, speech arrest was elicited by cortical stimulation to the MFG, and we selected a transsulcal approach between the IFG and MFG. to reach the lesion. After partially removing the lesion, we found that subcortical stimulation to the AF at the bottom of the resection cavity caused paranomia without speech arrest. We stopped resection at this point on the basis of our experience in Case 21. The distance measured on the postoperative DT imaging was 5.4 mm. No neurological symptom was observed. The histopathological diagnosis was Grade II astrocytoma.

Discussion

There is continuous interest in the monitoring of lan-

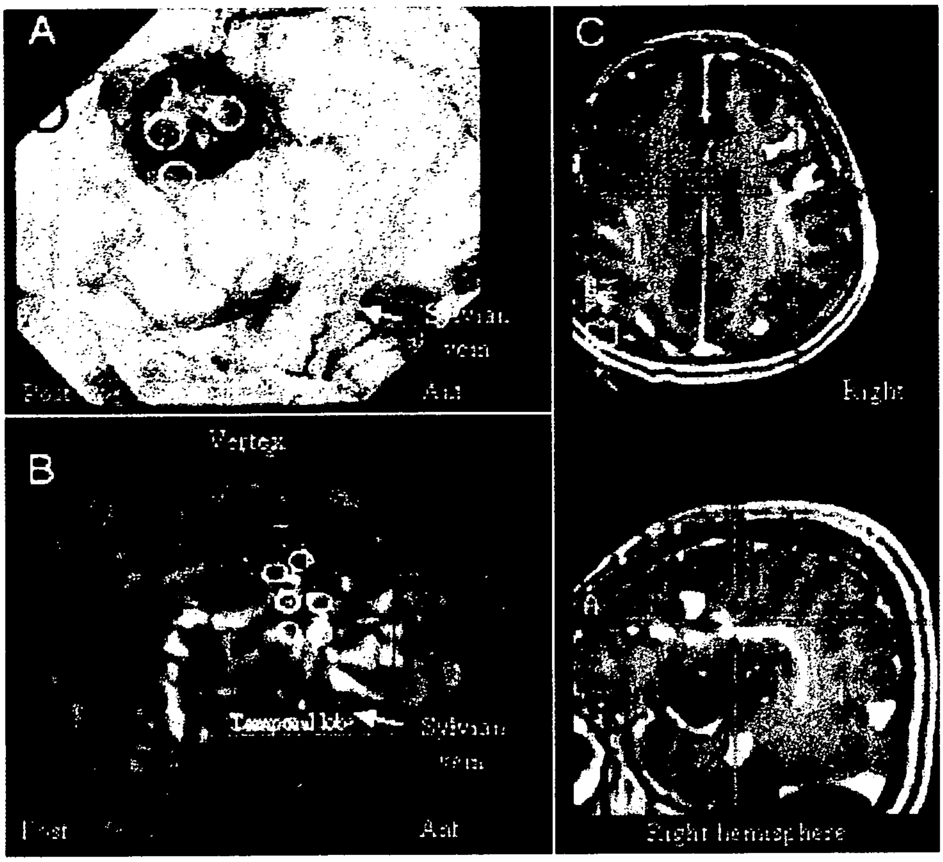

FIG. 5. Case 21. A: Photograph showing intraoperative findings. Cortical stimulation to the IFG and the inferior part of the MFG *(yellow circle)* and the primary motor cortex *(blue circle)* generated speech arrest and inhibition of voluntary hand movement, respectively. Subcortical stimulation to the bottom of the resection cavity *(red circle)* elicited paranomia without speech arrest. B: A 3D functional neuronavigation reconstruction of data from an MR image of the patient's entire head showing the activation on fMR imaging during the language task *(red)* as well as the AF *(yellow)* and MEG dipoles from the MEG language task *(blue)*. The *pink circle* and *blue square* indicate the corticotomy and the simulated operative window, respectively. Small *yellow, red, and blue circles* designate the stimulus points, which are the same as those in panel A. C: Two-dimensional MR images on the functional neuronavigation system demonstrating that resection reached the AF.

guage function during resection of tumors involving the frontotemporal regions. Awake surgery is the gold standard for direct monitoring of language functions, although this procedure entails certain risks related to anesthesia and requires that patients should be capable of cooperating during the operation. Electrical stimulation during awake surgery is also known to produce false-positive signs due to varying patient and stimulus conditions. In this study, DT imaging–based tractography with the seed and target points placed on functional 3D MR imaging, consistently visualized the AF in all 22 patients. In the two cases in which patients underwent awake surgery, stimulation to the gyri involving the areas identified on the fMR imaging language task evoked speech arrest, while subcortical stimulation to the AF consistently caused paranomia with no speech arrest. On the basis of the results of the subcortical mapping performed in Cases 21 and 22, we believe that the AF visualized on DT imaging–based tractography might be a real anatomical and functional structure.

Berman and colleagues and our group have recently reported the use of DT imaging–based tractography and intraoperative neurophysiological monitoring for the preservation of the corticospinal tract.[2,11] Furthermore, we added an electrophysiological validation of the visualized corticospinal tract using direct subcortical stimulation. We used five-train monopolar electrical stimuli for the subcortical mapping and showed that the motor evoked potentials were consistently observed when distances between the stimulus point and the visualized corticospinal tract were within 5 mm on the functional neuronavigation.[11] The combination of subcortical stimulation and functional neuronavigation provided excellent identification of the anatomical profiles of the corticospinal tract.

Excellent illustrations of the AF and optic radiation in healthy volunteers were recently obtained using virtual fiber dissection with standardization of normal control data.[3,4] This technique, however, is not applicable in pathological brain conditions. In the investigations reported to date, this technology has only been used for anatomical studies; the studies did not involve the direct assessment of functional connectivity.

Duffau and colleagues have suggested that direct subcor-

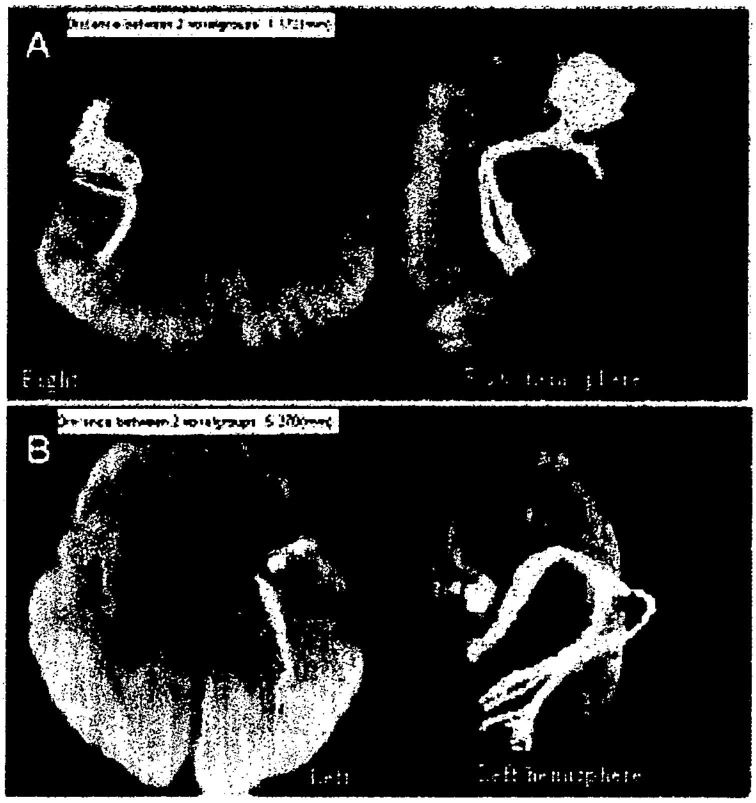

FIG. 6. Quantitative analysis of the distance between the resection cavity and the AF on isotropic images. A: The distance in Case 21 was 1.2 mm, and tumor resection caused transient but severe motor-dominant aphasia. B: The distance in Case 22 was 5.4 mm, and no neurological symptom was observed after resection.

tical stimulation offers the advantage of identifying the cortical and subcortical structures essential for language functions. In their studies, subcortical stimulation in the frontal lobe frequently caused semantic paraphasia.[7,8] Nevertheless, the subcortical stimulation procedure, including searching for optimal stimulus points and testing the several semantic tasks, requires the interruption of resection procedures, resulting in a longer operation time.

In the two cases in our study in which we performed intraoperative mapping, we found that speech arrest and paranomia were independently caused by the bipolar stimulation to the frontal cortex and AF, respectively. These dissociated impairments of expressive language functions were specifically produced by the alternate use of cortical and subcortical stimulations. The findings strongly suggested that suppression effects caused by subcortical stimulation to the AF spread over the whole language network, because there is probably little inhibitory system in the white matter. In addition, the distance between stimulus points and the visualized AF was 1.2 mm in Case 21 and 5.4 mm in 22. Because the patient in Case 22 did not experience postoperative neurological deterioration, we hypothesize that 6 mm might be a safe distance for resection, although we acknowledge that the small number of cases studied (two) limits the generalizability of our results.

We used two different modalities for noninvasive cortical mapping. Functional MR imaging has become popular for identifying hemispheric language dominance, and most investigators who have used this modality have found activations in the IFG and MFG during word generation and categorization tasks.[10,13,18]

Some researchers have focused on the correspondence between fMR imaging and cortical stimulation in the frontotemporal region and have reported speech arrest as a result of cortical stimulation to the frontal areas that showed activation during fMR imaging language tasks.[17,19] On the other hand, detection of the receptive language function by fMR imaging has been empirically more difficult than detection of expressive language function.[13,20]

Magnetoencephalography is another option that is highly complementary to fMR imaging. Cortical evoked potentials recorded by subdural electrodes have been reported to show responses at approximately 200 (early) and 400 (late) msec on the cortices of the left temporal base and the superior temporal gyrus after letter presentation.[16] The late potentials were observed mainly in the temporal region during experiments that required people to make decisions about visually presented words.[12] In our study, the late component sources in the periods between 250 and 600 msec were located mostly in the posterior parts of the temporal region. Using cortical stimulation, Simos and associates[21] have validated the locations of the MEG dipoles seen in the superior temporal region in association with language tasks, and they have shown excellent agreement between the mapping results of both techniques. Our method, using the results of fMR imaging and MEG, identified independent cortical centers of the frontal and temporal language functions and potential regions of interest for the AF tractography.

The fiber orientation depicted on DT imaging–based tractography reflects the average orientation of axonal fibers in each pixel and is susceptible to the extent of tissue heterogeneity. Within each pixel, a minor proportion of fibers always run in a different direction from the majority. Therefore, at present, DT imaging–based tractography can only provide gross anatomical information on major tracts in the white matter. For AF tractography, we acquired contiguous DT imaging slices with relatively thin slice thickness (3 mm) to increase the spatial resolution of the z axis to follow the curvature of the AF profile.

Conclusions

In the near future, several new techniques to improve DT imaging–based tractography should become available. These include high angular sampling of k-space, the interpolation or regularization of tensor fields, and global energy minimization for fiber tracking. The combination of these techniques should provide a powerful tool for preserving language-related functions in neurosurgery. Appropriate selections of the seed and target points determined by fMR imaging and MEG studies incorporating language tasks enable the elucidation of the real AF. Although the number of patients who underwent awake surgery in our study group is small, we did find that subcortical stimulation to the walls of the resection cavity consistently and efficiently caused semantic paranomia with no speech arrest. The electrophysiological validation in these patients supported the premise that DT imaging–based tractography can yield real functional information pertaining to the AF which can be valuable in neuroscience research as well as clinical practice. Studies of this kind will play an essential role in developing an understanding of the underlying semantic networks.

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Manuscript received February 23, 2006.

Accepted in final form August 7, 2006.

This work was supported in part by the Japan Epilepsy Research Foundation; the Takeda Promotion of Science Foundation; Grant-In-Aid No.17591502 for scientific research from MEXT (the Japanese Ministry of Education, Culture, Sports, and Technology); a Research Grant from the Princess Takamatsu Cancer Research Fund; the Terumo Promotion of Science Foundation; the Brain Science Foundation; and Grant-In-Aid No. 18020010 for scientific research on priority areas (integrative brain research) from MEXT.

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EXPRESSIVE AND RECEPTIVE LANGUAGE AREAS DETERMINED BY A NON-INVASIVE RELIABLE METHOD USING FUNCTIONAL MAGNETIC RESONANCE IMAGING AND MAGNETOENCEPHALOGRAPHY

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Received, March 23, 2006.
Accepted, October 13, 2006.

OBJECTIVE: It is known that functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) are sensitive to the frontal and temporal language function, respectively. Therefore, we established combined use of fMRI and MEG to make reliable identification of the global language dominance in pathological brain conditions.

METHODS: We investigated 117 patients with brain lesions whose language dominance was successfully confirmed by the Wada test. All patients were asked to generate verbs related to acoustically presented nouns (verb generation) for fMRI and to read three-letter words for fMRI and MEG.

RESULTS: fMRI typically showed prominent activations in the inferior and middle frontal gyri, whereas calculated dipoles on MEG typically clustered in the superior temporal region and the fusiform gyrus of the dominant hemisphere. A total of 87 patients were further analyzed using useful data from both the combined method and the Wada test. Remarkably, we observed a 100% match of the combined method results with the results of the Wada test, including two patients who showed expressive and receptive language areas dissociated into bilateral hemispheres.

CONCLUSION: The results demonstrate that this non-invasive and repeatable method is not only highly reliable in determining language dominance, but can also locate the expressive and receptive language areas separately. The method may be a potent alternative to invasive procedures of the Wada test and useful in treating patients with brain lesions.

KEY WORDS: Expressive language function, Functional magnetic resonance imaging, Language dominance, Magnetoencephalography, Receptive language function

Neurosurgery 60:296–306, 2007 DOI: 10.1227/01.NEU.0000249262.03451.0E www.neurosurgery-online.com

Brain asymmetries have been of considerable interest in neurology for more than a century. Based on clinicopathological studies, the "classical mode" of language organization consists of a frontal "expressive" area for planning and executing speech and writing, and a temporal "receptive" area for analysis and identification of linguistic sensory stimuli. This basic scheme of language functions has generally been accepted, with the assumption that both expressive and receptive functions dominantly exist in the same hemispheric side.

The Wada test has been considered the most reliable method to determine language dominance. According to one of the largest studies performed to date, 4 and 96% of right-handed subjects with chronic epilepsy have speech dominance in the right and left hemispheres, respectively (3). Furthermore, several studies suggested the possibility of atypical language representation in patients with chronic epilepsy (20–30%) (9, 28). However, the procedure of successive anesthetization of each hemisphere by intracarotid injections of sodium amobarbital requires catheterization and irradiation. Furthermore, the Wada test results can only demonstrate a relative distribution of language functions across the two hemispheres. More detailed information on localization of specified language functions within a hemisphere is important for understanding the language networks, as well as the treatment of brain lesions.

The use of functional magnetic resonance imaging (fMRI) has recently been developed to identify the hemisphere with language dominance. Most language fMRI studies have observed activations in the inferior frontal gyrus (IFG) and middle frontal gyrus (MFG) using tasks such as word generation and categorization (16, 24, 29). Detection of the receptive language area by fMRI has been reported to be more difficult than that of the expressive language function, and the use of listening or sentence comprehension tasks has resulted in visualization of only a few pixels in the temporoparietal region (8, 16, 25, 26). In addition, a fundamental limitation of an fMRI-based brain mapping is the varying degrees of regional hemodynamic responses under pathological brain conditions (7, 10, 15). Therefore, a clinical interpretation of localized activations on fMRI remains complicated and controversial.

Magnetoencephalography (MEG) reflects intracellular electric current flow in the brain and allows accurate localization of the current dipole sources. Dipoles of MEG deflections that peaked at approximately 400 milliseconds after word presentation (late responses) have been observed to localize in the temporoparietal regions. These late responses have been considered to be related to the receptive language function (19, 20). We have also observed dense dipole clusters of the semantic late responses in the superior temporal gyrus (STG), supramarginal gyrus (SmG), and fusiform gyrus (FuG) of the suspected dominant hemisphere (11, 12). Therefore, we sought to use MEG not only as an additional diagnostic tool for identifying the language dominance, but also to localize the receptive language center.

In the present study, we describe a non-invasive method to locate the expressive and receptive language areas by co-utilizing fMRI and MEG. The language dominance determined by our method matched the results from the Wada test with 100% accuracy. The usefulness of the method was well demonstrated, especially in those patients who showed dissociated expressive and receptive language functions. The data show that this method is highly reliable and may be useful in the management of patients with brain lesions as well as in studying normal brain functions.

METHODS

Patients

The functional brain mapping using fMRI (with the verb generation task) and MEG was performed in 117 patients with brain lesions since August 1999 (>7 yr) after this project was approved by the Institutional Committee for Ethics (*Table 1*). fMRI studies with the abstract/concrete (A/C) categorization task were also performed in 106 patients. Ninety-seven patients also underwent the Wada test to confirm the dominant cerebral hemisphere for language functions. Six patients showed negative Wada test results owing to the steal effect of a large arteriovenous malformation (AVM) or an overdose. The final analyses were performed in 87 patients (48 men, 39 women), who underwent Wada test, fMRI, and MEG investigations. The mean age (± standard deviation) was 43.6 ± 14.1 years. The Edinburgh Handedness Inventory was used to estimate the patients' handedness (18). A written informed consent was obtained from the patient or his/her family before participation in the study.

Magnetic Resonance Protocols

Anatomic magnetic resonance imaging (MRI) and fMRI were performed during the same session with a 1.5-T whole-body magnetic resonance scanner with echo-planar capabilities and a standard whole-head transmit-receiver coil (Siemens Vision, Erlangen, Germany). During the procedures, foam cushions were used to immobilize the head.

Language fMRI

The patients were instructed to respond to all language tasks silently. fMRI data was acquired with a T2-weighted echo-planar imaging sequence (echo time, 62 ms; repetition time, 114 ms; flip angle, 90 degrees; slice thickness, 4 mm; slice gap, 2 mm; field of view, 260 mm; matrix, 64 × 128; 14 slices). Each fMRI session consisted of three dummy scan volumes followed by three activation and four baseline (rest) periods. During each period, five echo-planar imaging volumes were collected, yielding a total of 38 imaging volumes and 2 minutes 32 seconds in measurement time for each session. fMRI data of language-related semantic responses were acquired as follows. All subjects were examined with two different lexical semantic language paradigms; verb generation by listening to nouns and A/C categorization by reading words. All words for semantic tasks were selected from common Japanese words listed in the electronic dictionary of the National Institute for Japanese Language.

Verb Generation Task

For the auditory stimuli (duration ranges were between 400 and 600 ms), common concrete nouns spoken by a native Japanese speaker with a flat intonation were recorded and digitized with a sampling rate of 44,000 Hz. A backward playback of the sound files (reference sounds) was used to eliminate the primary auditory activation during the rest periods with the same inter-stimuli intervals (1600–2400 ms) as the active periods. The auditory stimuli were delivered binaurally via two 5-m-long plastic tubes terminating at a headphone. The sound intensity was approximately 95 dB sound pressure level at the subject's ear. Subjects were instructed to silently generate a verb related to each presented noun during the active periods and passively listen to the reference sounds during the rest periods.

A/C Categorization Task

Visual stimuli were presented on a liquid crystal display monitor with a mirror above the head coil allowing the patients to see the stimuli. Words consisting of three *Kana* letters (Japanese phonetic symbols) were presented in a 300-millisecond exposure time with interstimuli intervals ranging from 2800 to 3200 milliseconds. Patients were instructed to categorize the presented word silently into "abstract" or "concrete" based on the

TABLE 1. Summary of patients' brain lesions types[a]

	Glioma	Chronic Epilepsy	AVM	Meningioma	Cavernous malformation	Cerebral ischemia	Total
fMRI with VG + MEG	44	39	18	6	4	6	117
fMRI with A/C	41	34	15	6	4	6	106
Amytal test	42	29	16	6	4	0	97
Final analyses	39	26	12	6	4	0	87

[a] AVM, arteriovenous malformation; fMRI, functional magnetic resonance imaging; VG, verb generation task; MEG, magnetoencephalography; A/C, abstract/concrete categorization task.

nature of the word. During interval periods, patients passively viewed random dots of destructured *Kana* letters that were controlled to have the same luminance as the stimuli to eliminate primary visual responses.

Before scanning, all patients had a brief practice time, and the fMRI examinations were repeated for each task to confirm the reproducibility. After data acquisition, a motion detection program (MEDx; Medical Numerics, Sterling, VA) discarded fMRI sessions containing motion artifacts exceeding 25% of the pixel size. A Gaussian spatial filter (6 mm in half width) was applied, and functional activation maps were calculated by estimating the Z-scores between the rest and activation periods using Dr. View (Asahi Kasei, Tokyo, Japan). Pixels with Z-scores higher than 2.2 ($P < 0.05$) were considered to indicate real activation and were used for mapping. Image distortion of fMRI was corrected by maximizing the mutual information of the fMRI data sets and three-dimensional T1-weighted MRI (3D-MRI) scans of the patient's brain (morphing compensation). The result from each fMRI session was co-registered with the 3D-MRI by the Affine transformation (5). After total number of the activated pixels in the IFG and MEG were automatically counted, a patient was considered to have unilateral language dominance when hemispheric pixels of one hemisphere counted less than 70% of the other hemisphere. Otherwise, the language dominance was considered bilateral.

Language MEG

The MEG signals were recorded with a 204-channel biomagnetometer (VectorView; Neuromag, Helsinki, Finland) in a magnetically shielded room. To confirm the reproducibility, we acquired two data sets for each task by repeating the MEG recording on two different days. One hundred fifty nouns consisting of three *Kana* letters were visually presented with a 300-millisecond exposure time with interstimuli intervals ranging from 2800 to 3200 milliseconds. Patients were instructed to judge whether or not the presented word was "abstract" or "concrete" based on the nature of the word and to push a button with the index or middle finger (*Kana* reading task). Each epoch consisted of a 500-millisecond prestimulus baseline and a stimulus followed by a 1500-millisecond analysis period. Epochs with a reaction time exceeding 1200 milliseconds and MEG examinations with a successful task performance less than 70% were discarded.

One hundred fifty epochs of the magnetic signals were averaged and digitally filtered between 0.1 to 30 Hz. Significant MEG deflections were visually identified based on the square root mean fields of more than 10 sensors in the frontotemporal (FT) or temporo-occipital (TO) regions. Locations and dipole moments of equivalent current dipoles were calculated every 2 milliseconds from 250 to 600 milliseconds after the stimulus onsets using the single equivalent dipole and sphere head models. Only those dipoles of which the measured and the calculated field distributions showed a correlation value of more than 0.85 and confidence volumes less than 1000 mm^3 were used. To confirm the calculated results, the same MEG time sections were analyzed using a current density map (low-resolution tomography; LORETA, Curry, Neuroscan, and Compumedics USA, El Paso, TX). The coordinates of the MEG system were transformed into anatomic 3D-MRI scans by identifying external anatomic fiduciary markers (nasion, left/right preauricular points), and estimated dipoles were superimposed onto the 3D-MRI scans.

Dipoles located in the temporal region, including the STG, MTG, SmG, and FuG, were manually counted. A patient was considered to have unilateral language dominance when hemispheric dipoles of one hemisphere counted less than 70% of the other hemisphere. Otherwise, the language dominance was considered bilateral.

Determination of Language Dominance using fMRI and MEG

On the basis of the results of language fMRI and MEG, we determined language dominance for each patient. When the semantic activation in one side of the IFG and MFG was wider than that of the other side during the language fMRI tasks, a patient was considered to have unilateral dominance for the expressive language function. When one side of the temporal region included more MEG dipoles than the other during the language MEG task, we determined that a patient had laterality of the receptive language function.

The Wada Test

All patients received injections of amobarbital (100 mg in a 10% solution, Amytal; Eli Lilly and Co., Indianapolis, IN) through a catheter placed in the internal carotid artery. Language testing was performed during the observation period of maximal amobarbital action as indicated by contralateral brachial plegia. Patients were given the following tasks in the following order and up to four points were given, depending on the severity of the language disturbance: 0, no response; 1, meaningless utterance; 2, incorrect repetition or paraphasia; 3, self-correction; and 4, unimpaired.

The tasks were as follows:

1) Spontaneous counting. Patients were instructed to count, starting immediately before the amobarbital administration and continuously until the next task was given. If the patient could continue to count even after brachial plegia appeared, obvious speech arrest and no impairment indicate 0 and 4 points, respectively.
2) Letter reading. Patients were instructed to read aloud seven words consisting of three or four *Kana* letters. The maximum score was 28 points (seven items × four points).
3) Naming. Patients were asked to name aloud the five objects presented pictorially. The maximum score was 20 points (five items × four points).
4) Auditory comprehension. Patients were asked to carry out three simple tasks such as blinking eyes, opening the mouth, and raising the unparalyzed arm. The maximum score was 12 points (three items × four points).
5) Pointing objects. Patients were shown a picture with a set of four objects and were instructed to point to one chosen by the investigator (e.g., "Point to the cat."). The maximum score was 16 points (four items × four points).

Performance in Tasks 1 and 3 were considered to reflect the expressive language capabilities (maximum score, 24 points); performance in Tasks 2, 4, and 5 reflected receptive language functions (maximum score, 56 points).

RESULTS

Handedness and the Wada Test

Ninety-one patients (80 right-, eight left-, and three bilateral-handers) successfully underwent the Wada test. Language dominance was left, right, and bilateral hemispheres in 81, six, and four patients, respectively. The language dominance of the right-handed patients was left in 75 patients (93.8%), right in two patients (2.5%), and bilateral in three patients (including one patient with dissociated expression and receptive functions [3.8%]), respectively. For left-handed patients, four patients showed left and four showed right dominance. For both-handed patients, two showed left dominance and one bilateral (dissociated). These results were similar to those of previous reports on language dominance (3, 4).

For further analysis, we subdivided the subjects into groups with chronic epilepsy and with non-epilepsy. In the epilepsy group (n = 29), left, right, and bilateral dominance was 24 (82.8%), three (10.3%), and two (6.9%), respectively. In the non-epilepsy group (n = 62), left, right, and bilateral dominance was 57 (91.6%), four (6.4%), and one (1.6%), respectively.

fMRI with the Verb Generation Task

The verb generation task was designed to locate the expressive language area by fMRI. Among 117 patients who underwent the verb generation task, 100 patients (84.6%) completed the task and provided useful fMRI data. The results showed that the dominant hemisphere for the expressive language function was left, right, and bilateral in 90, eight, and two patients, respectively. In the epilepsy group (n = 34), left, right, and bilateral dominance was 29 (85.2%), three (8.8%), and two (8.5%), respectively. In the non-epilepsy group (n = 66), left, right, and bilateral dominance was 61 (92.4%), five (7.6%), and zero (0%), respectively. The activated regions on fMRI mainly involved the IFG and MFG, the lateral precG, AG, and the supplementary motor area (SMA) (*Figs. 1* and 2).

In some patients, activations were observed in bilateral hemispheres. Except for two patients who showed bilateral dominance, the activations in the non-dominant hemisphere were restricted to MFG and precG and smaller in size, so the pixels did not reach a cluster significance (maximum values of Z-score, <2.2 or <10 pixels).

Compared with successful results of the Wada test, the successful rate of fMRI with the verb generation task was 90.1%. Seven patients with aphasia or dementia failed to complete the task. Three glioma patients with marked surrounding, four patients with brain ischemia and three patients with large arteriovenous malformations failed to exhibit significant activations in the frontal lobe (*Fig. 3*). These incomplete results are accounted for by the reported disadvantage of fMRI that data may be affected by the pathological changes of cerebral circulation (7, 10, 15).

fMRI with the A/C Categorization Task

The A/C categorization task was designed to locate the receptive language area by fMRI. Among 106 patients who performed the A/C categorization task, 71 (67.0%) completed the task and provided useful fMRI data. Compared with the verb generation task, the A/C categorization task more often activated wider areas in bilateral hemispheres (*Fig.* 2). Activations generally involved the bilateral frontal lobes, including the IFG, MFG, and precG, with laterality. The superior temporal regions, such as the STG and SmG, demonstrated activation spots in only 45% (n = 32) of the investigated patients, and the side predominance was not apparent in most cases. The fMRI data of the A/C categorization task were considered unsuitable to determine the receptive language areas and were not used for the final analyses.

Language MEG Profiles and Dipole Locations

The *Kana* reading task was designed to locate the receptive language area by MEG. The language MEG was performed in 117 patients, of whom 99 (85.4%) completed the task and provided useful data (*Figs. 1* and 2). Results showed that the dominant hemisphere for the receptive language function was left, right, and bilateral in 85, 11, and three patients, respectively. In the epilepsy group (n = 31), left, right, and bilateral dominance was 26 (83.9%), three (9.7%), and two (6.5%), respectively. In the non-epilepsy group (n = 68), left, right, and bilateral dominance was 59 (86.8%), eight (11.8%), and one (1.5%), respectively.

Dipole clusters of late deflections localized mainly in the superior temporal region (STG, MTG, and SmG), and 60% of investigated patients also showed dipoles in the inferior tempo-

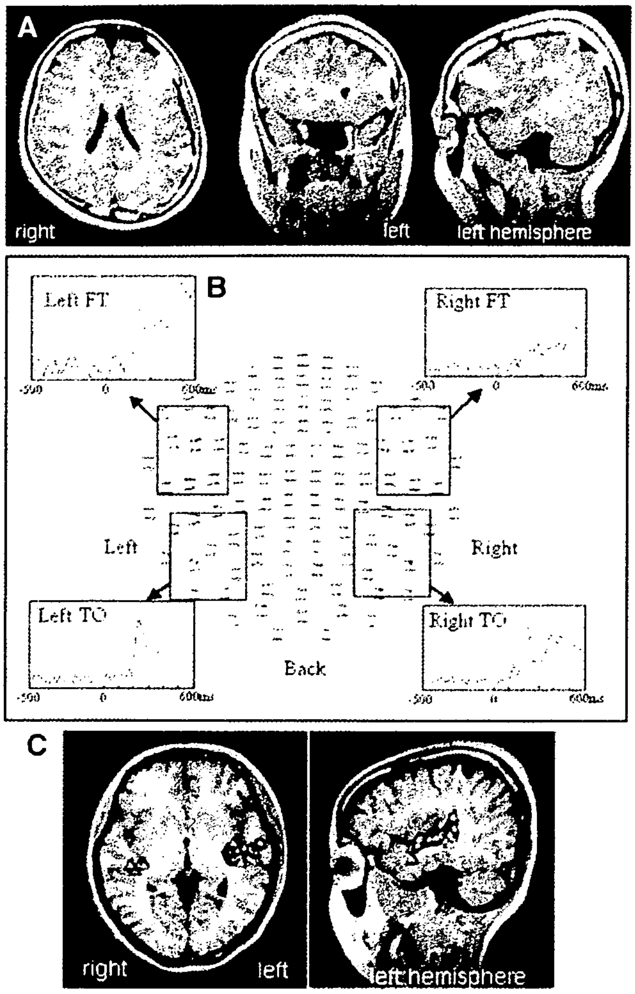

FIGURE 1. *A 24-year-old, right-handed man with epilepsy.* A, *fMRI with the verb generation task showing activations predominantly in the left IFG, MFG, PrecG, and parieto-occipital regions.* B, *square root mean field profiles of language MEG responses in the bilateral FT and TO regions. The left FT responses, peaking at 450 milliseconds, were markedly greater in amplitude than the right FT.* C, *source localization of the late deflections showing predominant dipole clusters* (arrowheads) *in the left superior temporal region. The left and right hemispheres contained 97 and 37 dipoles, respectively.*

ral region (FuG and inferior temporal gyrus). In 96 patients who showed unilateral language dominance, the total number of dipoles in the dominant versus non-dominant hemispheres was 124.1 ± 62.1 and 58 ± 30.9 (mean ± standard deviation), respectively. The ratio of the dipole number in the dominant hemisphere to the non-dominant hemisphere in each individual was 2.4 ± 1.7 (range, 1.43–14.4).

A typical result with all channels of MEG with the *Kana*-reading task is illustrated in *Figure 1*. Later deflections peaking at approximately 400 milliseconds were predominantly observed in the left FT. Bilateral TO regions demonstrated early deflections at approximately 200 milliseconds with short durations and little laterality. Estimated dipoles of the FT regions were densely accumulated in the left STG, MTG, and SmG (102 dipoles), whereas the right hemisphere showed fewer dipoles (54 dipoles) in the superior temporal region. This patient was thus determined to have receptive language dominance in the left temporal lobe.

The successful rate of language-MEG was 82.4%. Nine out of 39 epilepsy patients (23.1%) could not provide useful MEG data owing to artifacts from constant eye movements; the *Kana*-reading task was more difficult to complete than the verb generation task for patients with mental dysfunction. On the other hand, only one out of 18 AVM patients, owing to severe dyslexia, failed to provide useful MEG data, indicating that, in contrast to fMRI, MEG was not frequently affected by cerebral blood flow abnormalities (*Fig. 3*).

Combination of fMRI and MEG with Wada Test Verification

The verb generation task fMRI data depict expressive language areas well, but may be affected by cerebral blood flow abnormalities. The MEG results indicate receptive language areas well, but the task is rather complicated and may not be suited for patients with mental disorders. We sought to establish a non-invasive and reliable method to determine the laterality of language dominance by combining the advantages of these approaches. Furthermore, in terms of language functions, the results from fMRI and MEG can be integrated to locate expressive and receptive language areas and to provide reliable evidence whether or not there is dissociation. To verify the reliability of our method, 97 patients also underwent the Wada test.

Useful data from the method co-utilizing fMRI and MEG could be obtained from 87 out of 91 patients (95.6%). Remarkably, regarding language dominance, the results from the combination method matched the results of the Wada test in all 87 patients. Worth noting is that two patients (one with left temporal lobe epilepsy and the other with right insular astrocytoma) showed dissociated language areas using the combined method. The expressive language area was depicted in the left frontal lobe by fMRI, but the receptive language area was demonstrated in the right temporal lobe by MEG (*Fig. 4*). The Wada test results confirmed that both patients have language functions dissociated in the bilateral hemispheres. Among the 91 patients who underwent the Wada test, these were the only two patients in whom the Wada test detected dissociation of language functions.

In 12 epilepsy patients, the expressive and/or receptive language areas were electrophysiologically investigated via a subdural electrode implantation and the results were compared with those determined via the combined fMRI plus MEG method (*Fig. 5*). Out of eight patients who underwent cortical mapping for the expressive language area, all showed a speech arrest by electrical stimulation to the IFG and four to the MFG. All of the physiologically determined locations were confined within the areas depicted by the combined method. Out of six patients who received electrical stimuli to the temporal lobe, four showed responses interpretable as impaired speech comprehension. In all such cases, the electrophysiologically determined location matched the area depicted by the combined method, although MEG-depicted receptive language areas covered relatively broad areas of the temporal lobe. The regions determined by the combined method were always broader, but had the border within the adjacent gyri of those determined by electrophysiological mapping.

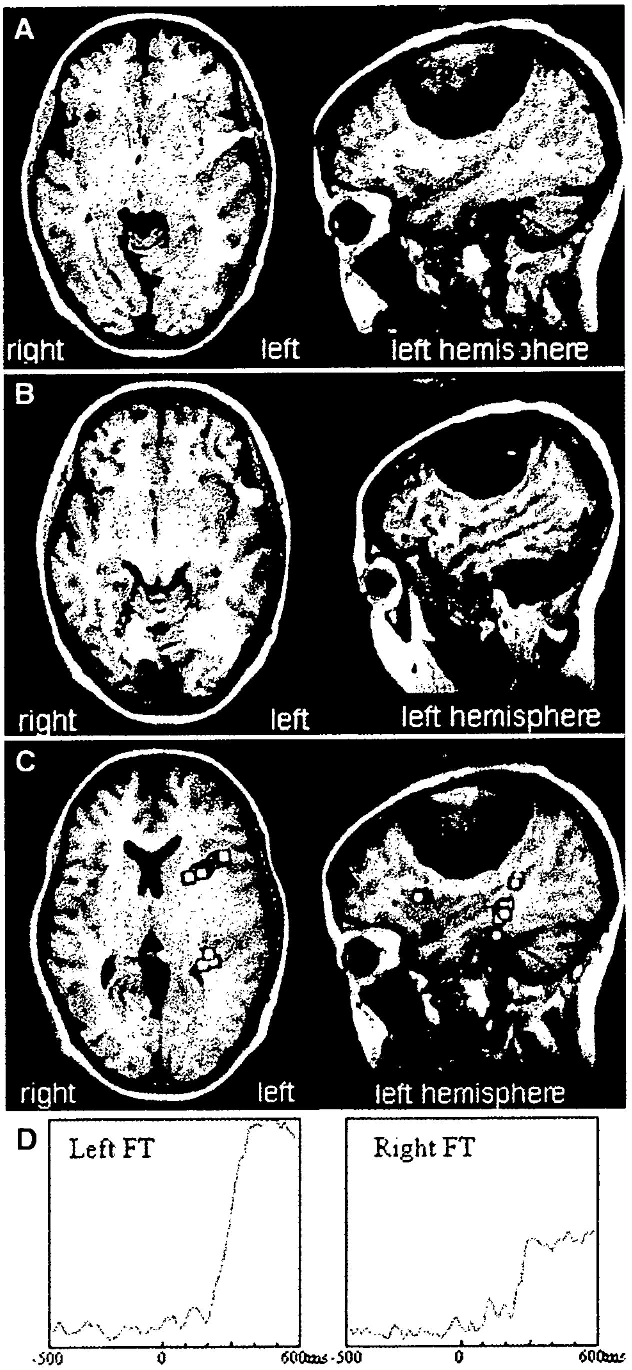

FIGURE 2. *A 16-year-old, right-handed female patient with a large meningioma in the left frontal region. The patient had no impairment of language or motor functions. A, fMRI with the verb generation task showed activations mainly in the left IFG and MFG that shifted inferiorly by the tumor. B, fMRI with the abstract/concrete categorization task demonstrated activations in the bilateral occipital regions in addition to small active spots in the left IFG. C, square root mean field profiles of language-MEG responses demonstrated that the left FT responses, peaking at 400 milliseconds, were markedly larger in amplitude than the right FT. D, source localization of the late deflections showed predominant dipole clusters in the left posterior temporal region. The left and right hemispheres contained 117 and 30 dipoles, respectively. The combined fMRI plus MEG method indicated left language dominance, which was confirmed by Wada test.*

ILLUSTRATIVE CASES

Patient 1

A 16-year-old, right-handed female patient had experienced transient numbness in her left upper extremity with a 2-month history. T1-weighted MRI scans demonstrated an extra-axial cystic lesion in the left frontal region. Although the lesion markedly compressed the frontal lobe, she had no impairment of language and motor functions. fMRI with the verb generation task demonstrated obvious activation in the left IFG and MFG shifted inferiorly by the lesion (*Fig. 2A*). The A/C categorization task activated a small area of the left IFG, but mainly the bilateral occipital lobes. Concerning MEG with the *Kana* reading task, RMS of the left FT was much higher than that of the right, and numbers of semantic dipoles were 117 and 30 in left and right hemispheres, respectively. The main dipole clusters were located in the left IFG and STG. The tumor was totally removed and histopathological diagnosis was meningioma.

Patient 2

A 24-year-old, right-handed male patient had a large AVM in the left frontal lobe. fMRI detected little activation in the IFG or MFG, although a part of the left angular gyrus was activated by the verb generation task (*Fig. 3A*). MEG, however, disclosed numerous dipole accumulations in the left superior temporal region. In the MEG examination, the left and right hemispheres contained 130 and 45 dipoles, respectively, suggesting left language dominance (*Fig. 3B*). Auditory comprehension and letter-reading were suppressed by administration of amobarbital into the left carotid artery, although motor language function was preserved. These findings suggested that the steal effect caused by the AVM partly interfered with functional brain mapping of fMRI and the Wada test. In this case, MEG was helpful to decide language dominance (*Fig. 3*).

Patient 3

A 32-year-old, right-handed man experienced amnesia for several minutes. T1-weighted MRI scans and brain computed tomographic scans disclosed a hypointense and hypodense mass in the right insular cortex involving the surrounding white matter. Computed tomographic scans performed 6 years earlier, however, revealed no abnormality. These findings suggested that a low-grade astrocytoma might

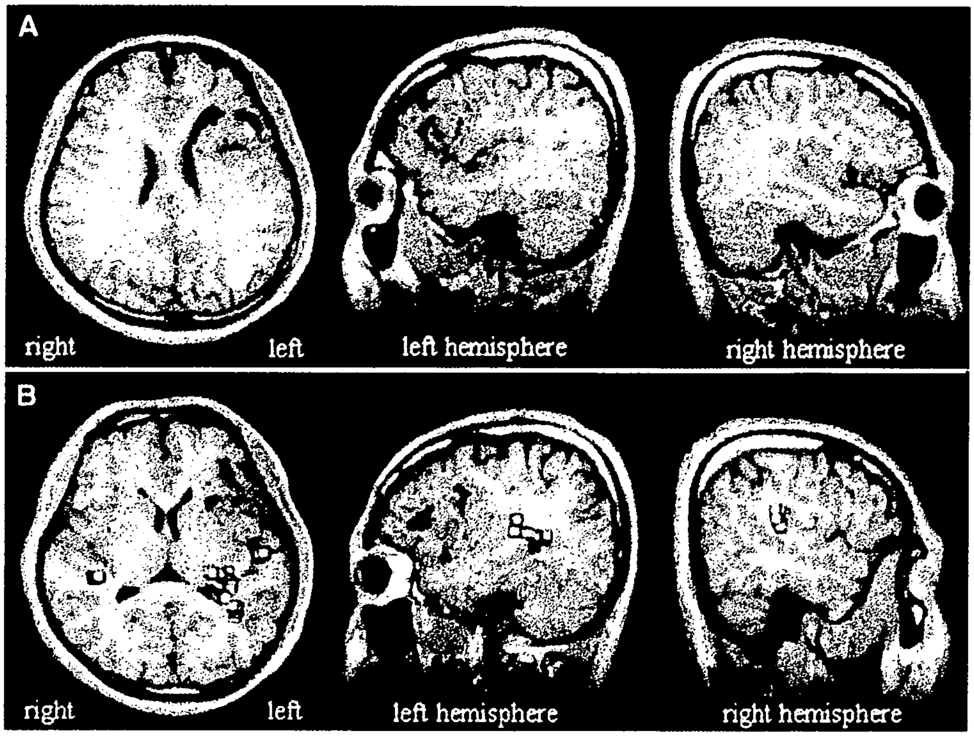

FIGURE 3. *A 24-year-old, right-handed man with a large AVM in the left frontal lobe.* A, *fMRI with the verb generation task showed little activation in the left frontal lobe where the AVM was located.* B, *source localization of the late FT and TO deflections on MEG showed predominant dipole clusters in the left posterior STG. The left and right hemispheres contained 123 and 51 dipoles, respectively.*

have slowly developed during the past 6 years. In the results of the verb generation task, the left hemisphere had obvious activations in the IFG, MFG, precG, and the angular gyrus, indicating that this patient had left dominance of motor-language functions (*Fig. 4A*). In contrast, estimated dipoles of the FT responses were concentrated in the posterior part of the right STG and MTG (138 dipoles) and another dipole cluster (64 dipoles) of the TO region was localized in the right FuG. The total dipole number of the left hemisphere (48 dipoles) did not reach even a quarter of that of the right hemisphere, suggesting right-sided dominance of temporal language functions (*Fig. 4*).

During the Wada test, he stopped counting (0 out of 4 points; 0%) and failed to name objects (6 out of 20 points; 30%) after left intracarotid injection, whereas letter-reading (21 out of 28 points; 75%), auditory comprehension (12 out of 12 points, 100%), and pointing objects tasks (16 out of 16 points; 100%) were well preserved. In contrast, after right intracarotid injection, letter reading (13 out of 28 points; 45%), auditory comprehension (3 out of 12 point; 25%), and pointing objects (4 out of 16 points; 25%) tasks were markedly suppressed, although he continued to count correctly without speech blockade (4 out of 4 points; 100%) and could perform naming (17 out of 20 points; 85%). These findings suggested that language functions were distributed separately over the bilateral hemispheres, and the expressive and receptive language functions were dissociated in the left frontal and right temporal lobes, respectively. A striking fact was that the combination of fMRI and MEG predicted the special profiles of language functions noninvasively.

DISCUSSION

We demonstrated that our method using both fMRI with the verb generation task and MEG with the *Kana* reading task is highly reliable in determining the language dominance in patients with brain lesions. The accuracy of the dominance laterality was confirmed by a 100% match with the results from the Wada test. fMRI and MEG compensated each other's disadvantages. The tasks of fMRI were rather simple and could be accomplished even by patients with mental dysfunctions, whereas MEG results were seldom affected by cerebral blood flow abnormalities. Reliable data on language functions were also obtained by combining the advantageous features of fMRI and MEG. fMRI with the verb generation task well depicted the expressive language area as activations in the frontal lobe, most commonly in the IFG. MEG, on the other hand, showed dipole clusters predominantly in the superior temporal regions representing the receptive language area. In the epilepsy group, left and bilateral dominance were approximately 85% and more than 6%, respectively, whereas, in the non-epilepsy group, left and bilateral dominance were more than 90% and less than 2%, respectively. The combined method, including the Wada test, fMRI, and MEG, clearly demonstrated bilateral dominance is more often observed in the epilepsy group than in the non-epilepsy group.

In our study, two out of 87 patients analyzed (2.3%) were found to have dissociation of the expressive and receptive language functions by co-utilization of fMRI and MEG, verified by the Wada test, which best described the usefulness of our method in identifying the areas of the two language functions separately. In both cases, neither modality alone demonstrated the dissociation. Although several cases have been reported that dissociated language functions were found by fMRI, none of those was proven by the Wada test (2, 8, 21, 23). Our results show that neither fMRI nor MEG alone is sufficient to accurately locate the expressive and receptive language areas, and the combined use is the key to obtaining high reliability.

The results from electrophysiological investigation via a subdural electrode implantation in 12 patients further confirmed the accuracy of the present method. Pouratian et al. (22) reported that the sensitivity and specificity of language-fMRI

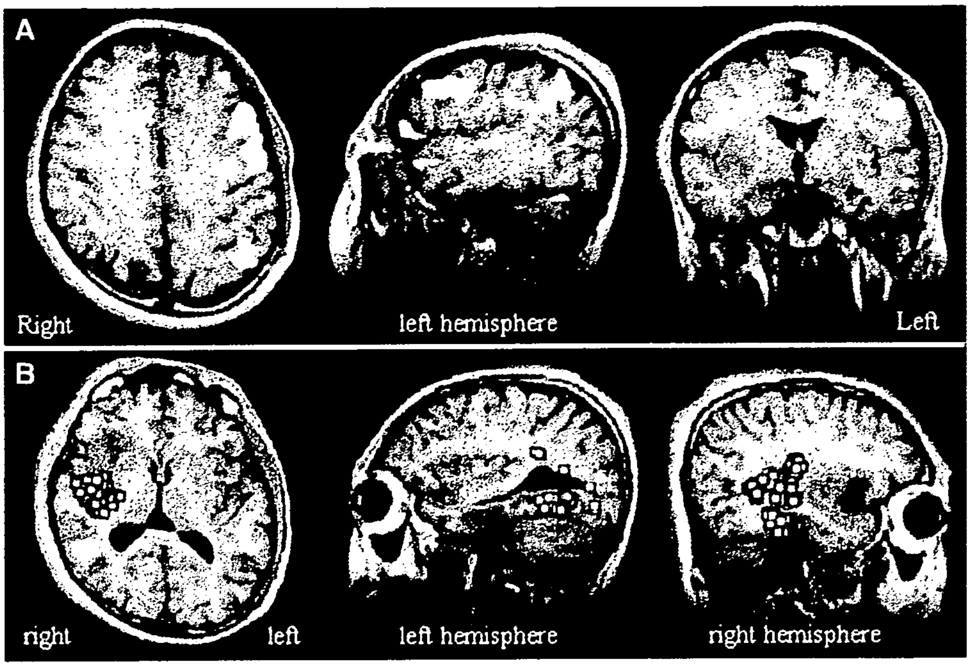

FIGURE 4. *A 32-year-old, right-handed man with astrocytoma in the right insular cortex and the surrounding white matter.* A, *fMRI with the verb generation task showed main activations in the IFG, MFG, precG, and AG, indicating left dominance of the expressive language function.* B, *in contrast to the fMRI results, source localization of the late FT deflections on MEG showed predominant dipole clusters in the right temporal lobe. The left and right hemispheres contained 48 and 202 dipoles, respectively. The combined fMRI plus MEG method thus indicated dissociated frontal motor and temporal receptive language functions. This result was confirmed by the Wada test. The patient showed impaired counting and object naming after amobarbitol injection into the left carotid artery. In contrast, letter reading, auditory comprehension and object pointing tasks were markedly suppressed, without counting impairment and speech blockade, after amobarbitol injection into the right carotid artery.*

were dependent on the task, lobe, and matching criterion. The sensitivity and specificity of fMRI activations during expressive linguistic tasks in the frontal lobe were found to be up to 100 and 66.7%, respectively, in the frontal lobe. FitzGerald et al. (6) reported that sensitivity and specificity for all multiple language tasks ranged from 81 to 53% (6). On the other hand, several groups have reported that the language map obtained from fMRI poorly matched the intraoperative electrical stimulation mapping (6, 25). In our study of language-fMRI, every electrical stimuli to the IFG, where the fMRI-activation was observed, caused speech arrest. However, the stimulation to MFG caused language-related symptoms in only half of patients. Although the sensitivity of fMRI might be high, there are still several issues of individual variability of fMRI activation and semantic tasks. The discrepancy can be partly accounted for by the fundamental differences in methodology such that the electrical stimulation directly blocks the specific language functions, whereas fMRI picks up all activated areas involved in the language tasks. Therefore, fMRI-based mapping largely depends on the design of the performing task. We tested two different tasks for fMRI and found the verb generation task better suited for language mapping than the A/C categorization task. The significance of activations depicted on fMRI is still under debate. Language-fMRI activations may be related to various semantic components of the task, including the will to retrieve verbal materials and the memory related to articulations. Despite that the A/C categorization task was designed to detect the receptive language area, activations in the temporoparietal region was less frequently observed than in the frontal region. Neural activities in the temporoparietal area are considered relatively scarce (25), and the discrepant activities of the frontal and temporoparietal regions may be owing to physiological variations of brain regions. Alternatively, the frontal and temporal lobes may have different oscillations (brain rhythms) of brain activity in response to verbal tasks, which are reflected in changes in neuronal currents and cerebral blood flow.

Our study demonstrated that dominance of the receptive language function could be accurately determined by MEG. For that purpose, we originally designed the task of three-letter word reading and silent categorization and used the dipoles calculated from late deflections to process the MEG results. It has been reported that cortical evoked potentials recorded by subdural electrodes showed responses at approximately 200 (early) and 400 (late) milliseconds in the left temporal lobe cortex after letter presentation (1, 17). The late potentials have been noted especially in tasks involving decisions based on visually presented words (13, 14). In this study, the sources of late responses (250–600 ms) were located mostly in the posterior temporal region, and the laterality of dipole clusters accurately reflected the receptive language dominance. It has been reported that dipoles in the superior temporal region showed an excellent agreement with an intraoperative electrical mapping (27). We also included dipoles in the FuG for language dominance determination based on our experience with a case in which an injury of FuG resulted in pure dyslexia (12). These contrivances in our method may have led to improvement in accuracy on language dominance determination over previous reports (20). Basic technical issues of the MEG investigation still remain. Eye movement artifacts were strong enough to distort the baseline of the MEG data. In our study, we asked patients to keep gazing at the center of the screen during the semantic decision without blinking. As a result, artifacts were observed at later than 600 milliseconds after letter presentation and usually did not affect the early and late semantic responses. It is, however, important to prevent artifacts by monitoring eye movements and using rejection thresholds.

In conclusion, by co-utilizing fMRI and MEG, we established a method to determine language dominance with a high reliability. The fMRI activations with the verb generation task identified the expressive language area, whereas the language MEG dipoles located the receptive language areas. Our institution is now routinely using the combined technique to identify the language dominance. If it does not produce data on cerebral dominance, we additionally perform the Wada test before surgery. This non-invasive and repeatable method may be an effective alternative to the Wada test and may be useful in the management of patients with brain lesions.

Disclosure

This work was supported in part by the Japan Epilepsy Research Foundation, Takeda Promotion of Science Foundation, a grant-in-aid No.17591502 for scientific research from MEXT, a Research Grant of the Princess Takamatsu Cancer Research Fund, Terumo Promotion of Science Foundation, Brain Science foundation, and Grant-in-Aid No. 18020010 for Scientific Research on Priority Areas Integrative Brain Research from MEXT.

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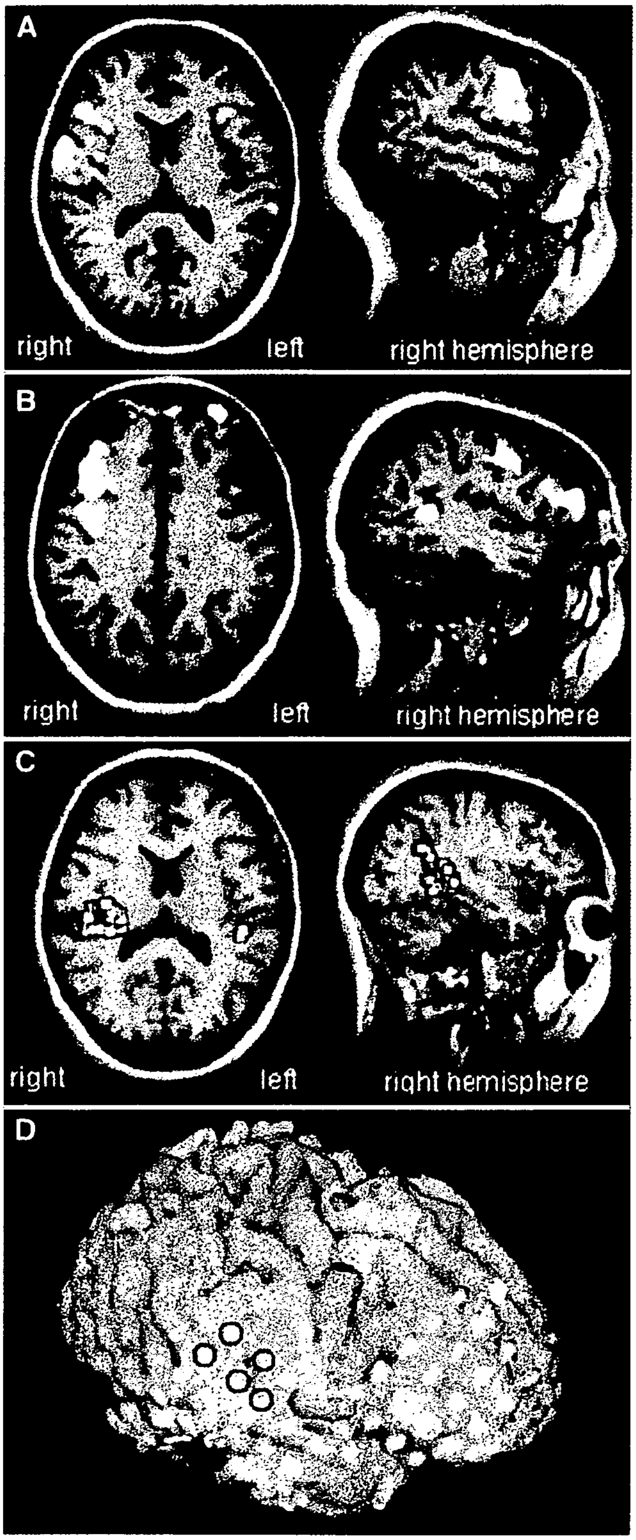

FIGURE 5. *A 40-year-old, left-handed woman with epilepsy.* A, *fMRI with the verb generation task showed activations predominantly in the right IFG and MFG.* B, *fMRI with the A/C categorization task demonstrated activations in the right MFG and the posterior STG.* C, *source localization of the late deflections on MEG showed predominant dipole clusters* (white squares) *in the right posterior temporal region. The left and right hemispheres showed 44 and 144 dipoles, respectively.* D, *three-dimensionally reconstructed MRI scans fused with activation of the verb generation-fMRI* (orange) *and dipoles of language-MEG* (blue). *After implantation of subdural electrodes* (gold), *cortical mapping was performed with 50Hz bipolar electrical stimulation. Stimulation with intensity of 7mA to the right IFG caused speech arrest* (white circles), *whereas stimulation to the posterior STG caused impairment of auditory comprehension and reading capability* (black circles).

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COMMENTS

This is an interesting article evaluating the complementary features of functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) to assess language lateralization in 87 patients. Whereas any test of language lateralization is suspect if 100% correlation is found, the authors have carefully described their techniques and the analysis of results. It is quite apparent that fMRI with verb generation tasks is best at activating anterior language areas, whereas abstract versus concrete naming tasks can be less robust. This is a good article and a large experience worthy of publication.

G. Rees Cosgrove
Burlington, Massachusetts

The authors have applied fMRI and MEG techniques to localize speech function in a large number of patients with different brain lesions. They were able to supplement the two noninvasive tests with the Wada test in 80% of the patients. They were able to obtain useful data with the co-utilization of fMRI and MEG in 95.6% of the patients and found a somewhat surprisingly good match with the results of the Wada test in 100% of those. In the results section, the authors discuss a few differences to the localization of language areas by electrophysiological means. They point out the fact that atypical language dominance or bilateral language representation is more frequent in patients with chronic epilepsy than in those without epilepsy. This is an important fact not known to many neurosurgeons who are not ordinarily involved with epilepsy cases. The results of this study make it more likely that, in the future, the invasive Wada test procedure might be abolished in those institutions at which MEG is available. This constitutes a notable limitation of this noninvasive technique. If fMRI is used alone, the success rate for obtaining useful data is 84.6% for word generation tasks and only 67% for the abstract/concrete categorization task. This is quite an interesting study and the results are very promising; however, the limitations are not economical. A number of patients cannot complete all the tasks necessary for fMRI study, and MEG studies can be disturbed by eye movement artifacts. We look forward to other reports confirming these promising results.

Johannes Schramm
Bonn, Germany

The authors present some very interesting data in the realm of functional imaging to determine cerebral dominance for language. Currently, the standard modality for determining cerebral dominance is the venerable Wada test. In this study, the authors use both MEG and fMRI to determine language dominance based on activation in the inferior frontal gyrus and middle frontal gyrus using fMRI and dipole moments reflecting or indicating receptive language fields in the temporal lobe. As expected, they had some difficulty with the fMRI data owing to the underlying deficit in the patient, which suggests that fMRI is not always as good as one might expect in terms of determining cerebral dominance using a verb generation silent language task. We know that fMRI is not a good choice for defining receptive language fields that correspond to intraoperative stimulation mapping. However, when fMRI was used together with MEG, the authors were able to demonstrate 100% concordance with data from the Wada test. Thus, this is a very important study indicating that, in the near future, it may be possible to bypass the Wada test with these two powerful functional imaging modalities. That being said, not every institution is going to be able to obtain both of these functional tests. Therefore, it is unlikely that this strategy is going to replace Wada tests completely. Yet, this is a very important line of investigation and a novel observation that points out the frailties of functional imaging for cerebral dominance localization and the potential power when the different functional tests are combined.

Mitchel S. Berger
San Francisco, California

Portrait of James Figg (1695–1734), by William Hogarth, (1697–1764). Acknowledged in Britain as the "Father of Boxing," Figg popularized the sport with teaching and exhibitions and, following victories over all the other British contenders, declared himself "heavyweight champion of England" in 1719.