**J Neurosurg 94**:445–453, 2001

# Magnetic source imaging of late evoked field responses to vowels: toward an assessment of hemispheric dominance for language

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*Object.* The goal of this study was to determine whether the late neuromagnetic field elicited by simple speech sounds, which is detected by magnetoencephalography, may be used to estimate hemispheric dominance for language and to guide or constrain the intraoperative search for essential language sites. If sufficiently robust, a noninvasive method for assessing hemispheric dominance for language could reduce the necessity for amobarbital testing and the extent of intraoperative cortical stimulation–based mapping, both of which carry the risk of morbidity.

*Methods.* Fifteen patients undergoing surgery for tumors during which intraoperative language mapping would be performed and two additional patients in whom intracarotid amobarbital testing confirmed right-hemisphere language dominance participated. Following a primary auditory response sources of late neuromagnetic fields elicited by vowel stimuli were modeled and coregistered using magnetic resonance images to form magnetic source (MS) images. A laterality index (LI) was calculated by summing the number of equivalent current dipolar sources in the late fields detected from each hemisphere. In 14 right-handed patients, 10 displayed left asymmetric LIs (0.37 ± 0.16, mean ± standard error of the mean in 14 patients). For both right-hemisphere dominant patients in whom an LI was obtainable, the LI was rightward. Stimulation-mapped essential language sites were found in 7 of 15 patients. For six of these seven patients, the MS image–derived LI was leftward.

*Conclusions.* Asymmetry in single equivalent dipole modeling of the late neuromagnetic field evoked by simple speech sounds correlates with hemispheric language dominance, although not to the degree necessary for individual clinical predictions. With further development, MS imaging of simple language tasks may be used preoperatively to predict language dominance and even to identify or constrain the intraoperative search for likely sites of essential language cortex.

**KEY WORDS • electrocortical activity • speech • magnetoencephalography • brain mapping • stimulation mapping**

ONE goal of functional neuroimaging is to identify the language cortex in neurosurgical patients to facilitate surgical planning and intraoperative guidance. In patients with neoplasms, medically intractable epilepsy, or arteriovenous malformations, for example, planned tissue resections might compromise essential language areas. Thus, the precise locations of these areas should be identified to avoid postoperative language deficits.[24] Intraoperative mapping of brain function by electrical stimulation of the cortex is the gold standard for locating cortical areas critical for language[20–22] and, in fact, the only definitive measure other than lesion analysis. Because resection of essential language areas can lead to persistent postoperative dysphasia, functional mapping is necessary to protect language functions while, at the same time, offering the possibility of more extensive resection by delineating functional centers. However, intraoperative electrical stimulation of the cortex carries significant risk of morbidity, cost, and time burden. If noninvasive presurgical mapping could effectively predict the location of critical language areas, preoperative decision making and approach planning could be improved. When intraoperative stimulation is nevertheless indicated, the preoperative data could be used to direct the electrical stimulation toward probable sites, thereby reducing procedural time and risk. In addition to preoperative identification of the language cortex, noninvasive functional neuroimaging offers a possible method for determination of the hemispheric dominance for language. The current standard clinical procedure for determining language dominance is the intracarotid amobarbital test (the Wada test),[32] which is

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*Abbreviations used in this paper:* ECD = equivalent current dipole; fMR = functional magnetic resonance; LI = laterality index; MEG = magnetoencephalography; MS = magnetic source; PET = positron emission tomography.

TABLE 1

*Characteristics of 17 neurological patients who underwent pre- and intraoperative language testing**

| Case No. | Age (yrs), Sex | Handedness | Location of Lesion | Type of Lesion | WHO Grade | Stimulation Mapping Result | Wada Test Result | MEG LI† |
|---|---|---|---|---|---|---|---|---|
| *awake craniotomies w/ language mapping* | | | | | | | | |
| 1 | 34, M | rt | lt posterior frontal | oligodendroglioma | II | anomia | NP | 1.00 |
| 2 | 32, M | rt | lt temporal | oligoastrocytoma | II | no sites | NP | 0.84 |
| 3 | 34, M | rt | lt insular | oligodendroglioma | II | speech arrest | NP | −0.44 |
| 4 | 56, F | rt | lt multicentric | glioblastoma multiforme | IV | anomia | NP | 0.76 |
| 5 | 37, M | rt | lt frontoparietal | oligodendroglioma | II | speech arrest | NP | 0.20 |
| 6 | 50, M | rt | lt anterior insular | oligodendroglioma | II | no sites | NP | −0.25 |
| 7 | 49, M | rt | lt insular | ganglioglioma‡ | U‡ | speech arrest | NP | 1.00 |
| 8 | 35, F | rt | lt frontotemporal & insular | anaplastic astrocytoma | II | speech arrest | NP | 0.14 |
| 9 | 33, M | rt | lt frontal | oligodendroglioma | II | no sites | NP | −0.32 |
| 10 | 42, M | rt | lt temporal | glioblastoma multiforme | IV | speech arrest | NP | 0.16 |
| 11 | 24, F | rt | lt temporoparietal | oligoastrocytoma | II | no sites | NP | 1.00 |
| 12 | 36, F | rt | lt insular | oligoastrocytoma | II | no sites | NP | −0.57 |
| 13 | 44, M | rt | lt anterior temporal | anaplastic astrocytoma | II | no sites | NP | 1.00 |
| 14 | 49, F | rt | lt posterior frontal | oligoastrocytoma | II | no sites | NP | 0.70 |
| 15 | 26, M | lt | rt posterior frontal | oligodendroglioma | II | no sites | rt side | ND |
| *surgeries w/o language mapping* | | | | | | | | |
| 16 | 44, F | lt | rt precentral | epilepsia partialis continua | — | NP | rt side | −0.13 |
| 17 | 14, F | lt | rt supplementary motor area | glioblastoma multiforme | IV | NP | rt side | −0.15 |

* ND = not defined; NP = not performed; U = undetermined; WHO = World Health Organization; — = not applicable.

† The MEG LI is derived by the equation: $LI = (N_L - N_R)/(N_L + N_R)$, where $N_L$ and $N_R$ represent the total number of late (approximately 150–400 msec) ECD fits per left and right hemisphere, respectively.

‡ The appearance of this lesion is most consistent with that of a ganglioglioma; however, the precise cause of the lesion remains undetermined without further biopsy, which is clinically unwarranted.

associated with levels of patient discomfort, cost, and morbidity that greatly exceed those of noninvasive imaging.

A variety of stimuli and task paradigms have been proposed for functional neuroimaging studies of language. Indices of language asymmetry have been derived from such studies by using the methods of fMR imaging,[1,4,8] PET, and MEG.[5,23,30,31,33] These LIs have been shown to be consistent with the results of intracarotid amobarbital testing and intraoperative stimulation mapping.[18,23,29]

In a previous study of healthy right-handed volunteers in our laboratory, we demonstrated leftward asymmetry in the late evoked neuromagnetic field elicited by simple speech sounds.[30] The number of time points in the late field (150–400 msec after stimulus onset) for which a single ECD model could adequately account for the magnetic field pattern observed on the magnetoencephalogram was approximately twofold greater in the left cerebral hemisphere than in the right hemisphere. Additionally, source localizations at these time points were observed to be more focal in the left hemisphere and more liberally distributed in the right hemisphere.

The hypotheses of the current study are the following: 1) similar asymmetry in the late neuromagnetic evoked field will be observed in neurosurgical patients; 2) these asymmetries will be consistent with hemispheric dominance as determined by intracarotid amobarbital testing, intraoperative electrical stimulation identification of essential language sites, or inference from handedness; and 3) source localizations of the late neuromagnetic evoked field when overlaid on MR images to form MS images will be anatomically consistent with sites of essential language determined intraoperatively by cortical stimulation.

## Clinical Material and Methods

### *Patient Population*

A consecutive series of 15 patients with supratentorial tumors (five women and 10 men) who underwent surgery as well as both preoperative MS imaging and intraoperative language stimulation mapping participated in this study. Fourteen patients were right handed and one was left handed. The left-handed patient also underwent intracarotid amobarbital testing to determine the hemispheric representation of language[32] and was determined to be right-hemisphere dominant. With the exception of this patient, all intraoperative stimulation mappings were performed in the left hemisphere. Two additional left-handed patients harboring cortical lesions underwent surgery after general anesthesia had been induced; these female patients underwent MS imaging without language mapping, but were also determined to be right-hemisphere dominant according to the results of intracarotid amobarbital tests. In the seventeen patients, ages ranged from 14 to 56 years, with a mean age of 38 years (Table 1).

### *Preoperative MS Imaging*

Neuromagnetic fields evoked by synthesized speech sounds were recorded. Two vowels were presented binaurally (/a/ and /u/, 300 msec duration) at two different pitches (for the male pitch the fundamental frequency was approximately 100 Hz; for the female pitch the fundamental frequency was approximately 200 Hz; see the article by Poeppel and colleagues[25] for complete stimuli parameters). The vowels were synthesized using a Klatt speech synthesizer (Sensyn software; Sensimetrics, Inc.,

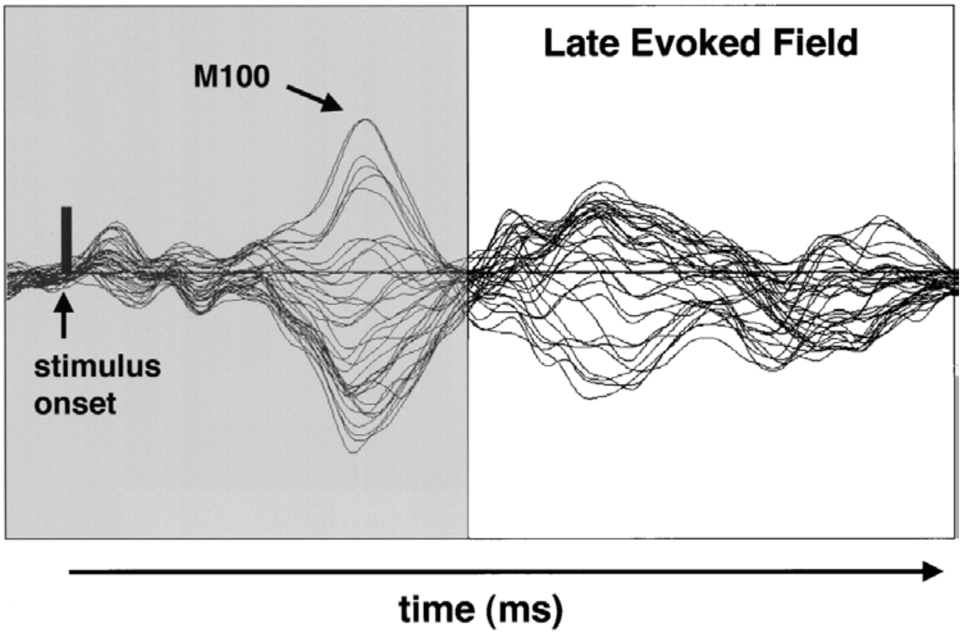

FIG. 1. Example of the magnetic field evoked by a one-vowel stimulus in a representative patient. Each of 37 individual sensor traces has been overlaid onto a common time axis, with the y-axis indicating field strength in femtoteslas. The primary evoked response, designated M100 or the peak in the root mean square evoked field amplitude across the sensor array in the latency window, lasting 80 to 150 msec following stimulus onset, is indicated by the *arrow*. The late field commences when the root mean square magnetic field reaches its first minimum level in amplitude following the M100 peak, as indicated by the vertical line.

Cambridge, MA) and presented at a 40-dB sensation level using transducers (EarTone 3A; Etymotic Research, Elk Grove Village, IL) through air tubes ending in foam-insert earphones. Each vowel stimulus was presented 100 times in a pseudorandom interleaved sequence, with randomized interstimulus intervals of 1000 ± 100 msec by using PsyScope software.[6] The patients were instructed to listen passively to the speech sounds.

The MEG signal was recorded in a magnetically shielded room with a twin 37-channel biomagnetometer system (Magnes II; Biomagnetic Technologies, Inc., San Diego, CA). Each sensor contained 37 axially oriented first-order gradiometers arranged concentrically over a concave spherical surface (diameter 14.4 cm). One sensor array was placed over the temporal lobe of the right hemisphere, and the other over the temporal lobe of the left hemisphere. Each sensor array was manually repositioned to capture the M100 response to a 1-kHz reference tone optimally such that an antisymmetric field distribution passed through the center of the concentric array (for further details, see the article by Roberts[27]). External fiducial markers (located over the left and right preauricular points and the nasion) were recorded with a transceiver-based system in reference to the sensor array. By locating these same landmarks in the MR image volume, MEG source localizations were later transposed to the anatomical MR image, within an estimated 4-mm error of measurement.[13] A high-resolution MR image was obtained the day before surgery by using a 1.5-tesla scanner (Signa; General Electric Medical Systems, Milwaukee, WI) with a spoiled gradient pulse sequence (TR 35 msec, TE 5 msec, flip angle 30°, matrix 256 × 256 × 124, and field of view 24 × 24 × 18.6 cm), resulting in image voxels that were approximately 1 × 1 × 1.5 $mm^3$.

Epochs of MEG data 600 msec in length were collected beginning 100 msec before stimulation by using a 1-Hz cut-off high-pass filter at a sampling rate of 1041 Hz/channel, thus yielding approximately 1 msec temporal resolution. Time-locked MEG epochs for each of the four types of stimulus were separately averaged to improve the signal-to-noise ratio and then digitally filtered using a passband of 1 to 40 Hz to eliminate high-frequency noise.

Neuromagnetic evoked fields elicited by the vowel stimuli were modeled in single ECD sources at 1-msec intervals from 0 to 400 msec after stimulus onset. Instantaneous source modeling solutions were assessed using standard criteria of model–data correlation ($r > 0.97$) and current dipole moment (current dipole strength $< 50$ nanoampere meters). The major component of the auditory evoked neuromagnetic field (M100) was determined to be the peak in the root mean square evoked field amplitude across the sensor array during the latency window that lasted 80 to 150 msec after stimulus onset. The late field was then defined as that magnetic field activity occurring in a 250-msec latency range beginning immediately after the major component, that is, commencing at a latency at which the root mean square magnetic field reaches its first minimum level of amplitude after the M100 peak (Fig. 1). From the 250 time points of the late evoked field of each hemisphere, candidate dipole sources were counted only if the instantaneous model–data correlation exceeded 0.97. This yielded a certain number of qualifying time points in the left and right ($N_L$ and $N_R$, respectively) hemispheres. An LI was then computed for

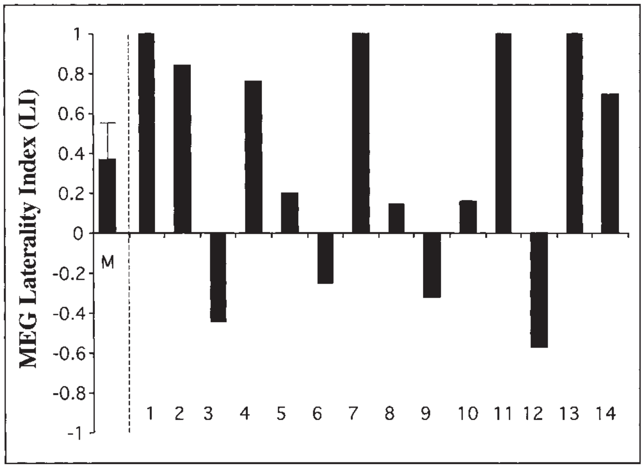

FIG. 2. Bar graph demonstrating average MEG LIs for all right-handed patients (Cases 1–14). M = mean LI with standard error of the mean; numerals = LIs for individual patients.

each patient based on the total number of qualifying ECDs in each hemisphere by using the following equation: $LI = (N_L - N_R)/(N_L + N_R)$. All LI values by definition lay between $-1$ and $+1$. Positive values of the LI thus indicate leftward asymmetry and negative values indicate rightward asymmetry.

*Intracarotid Amobarbital Test*

Language dominance was tested using sequential unilateral hemisphere anesthetization only in the three left-handed patients. After a catheter had been placed into the femoral artery and threaded up into one internal carotid artery, 125 mg of amobarbital was injected to anesthetize the cerebral hemisphere. Continuous electroencephalographic monitoring was performed. During the time of maximum anesthetic effect, the patient was challenged with both expressive (for example, naming objects, describing pictures of actions, reading words, repeating sentences, creating sentences) and receptive (for example, pointing to common objects on command, performing the Modified Token Test, hearing sentences) language tasks. Both hemispheres were injected with amobarbital on the same day. Performance was classified by hemisphere as right only, left only, right equivalent to left, right greater than left, or left greater than right, based on whether the injection had any effect on language functioning and, if so, whether the effects were greater after the right or left hemisphere had been anesthetized. All three patients included in this study were classified as right hemisphere only.

*Intraoperative Stimulation Mapping Procedure*

Intraoperative stimulation mapping was performed to identify essential language cortex before undertaking tumor resection.[2,3] Previous research has determined that excisions maintaining the functional integrity of cortex within a 1-cm radius of essential language sites result in significantly fewer permanent postoperative linguistic deficits. After applying a local anesthetic agent of a mixture of lidocaine and marcaine to the scalp and dura mater, intravenous propofol (Diprivan) administration was initiated to induce a deep, albeit nonanalgesic, hypnotic state. A craniotomy tailored to the location of the tumor by using image guidance was performed to expose the surface of the dura mater. Before the dura was incised, administration of propofol was discontinued. After 8 to 15 minutes, the patient became coherent and the dura was incised to expose the cortical surface. Direct, low-voltage electrical stimulation was delivered across a 5-mm bipolar electrode that was placed on the moist cortical surface parallel to the sulcus by using a constant-current generator that produces a train of biphasic square-wave 60-Hz pulses with 1.25 msec/phase. The maximum train duration used was 4 seconds. The largest current that evoked no afterdischarges was selected for stimulation mapping; in this study it ranged from 2 to 6 mA. After mapping sensory and motor cortex, stimulation was used to elicit the following responses: 1) speech arrest during counting; 2) anomic or dysnomic responses during picture naming; and 3) alexic or dyslexic responses during reading. Electrical stimulation was applied quasirandomly at 20 to 30 sites, 1 cm apart, covering the portion of the exposed cortical surface in the area of proposed resection. All sites were labeled with sterile numbered tickets, which were later photographed.

Based on each patient's preoperative performance, line drawings that could be readily and consistently named by each patient were selected from a set of 60 drawings for use during intraoperative stimulation mapping. The drawings were presented in random order by using a slide projector at a rate of one picture every 5.4 seconds. Stimulation was initiated just before the picture was presented and was continued for up to 3 seconds or until the patient responded. A site essential for speech or naming was identified only if stimulation did not also evoke gross motor movements of the face, lips, throat, or tongue. Clinically significant language sites, at which the probability of an error was significant at less than 0.05 (usually $\geq$ two errors in three attempts),[11] were recorded directly on the same high-resolution preoperative MR image selected for MS imaging by using an infrared-based stereotactically coregistered frameless three-dimensional image guidance system equipped with a Stealth probe (Stealth Station; Sofamor Danek, Memphis, TN). Essential language sites were saved as coordinates and displayed as points on axial, coronal, and sagittal views of the preoperative MR images. The exact position of the Stealth probe was indicated by superimposed cross hairs.

Source localizations modeled from the MEG data were displayed on the same preoperative MR image, forming MS images so that the locations of ECD sources and essential language sites could be directly compared. This was accomplished by selecting the axial view on MR imaging of a slice that contained an essential language site identified intraoperatively and the equivalent axial slice from the MS imaging volume that contained the ECD source localizations. If that slice contained no ECD sources, the adjacent superior and inferior slices were examined. The intraoperatively defined essential language site and an ECD source were determined to be in agreement if their separation was less than or equal to 3 mm in both the superoinferior and anteroposterior axes. Because electrical stimulation mapping is restricted to the cortical surface, whereas MS imaging is sensitive to deeper sources in the sulcal banks, an apparent mediolateral discordance was tolerated.

## Results

Pathological studies of specimens obtained during the 16 operations for brain tumors confirmed the diagnosis of one ganglioma, six oligodendrogliomas, four oligoastrocytomas, two anaplastic astrocytomas, and three glioblastomas multiforme. The 17th patient underwent resection of epileptic foci from the motor strip. Fourteen of the 17 lesions were present in the left hemisphere and three in the right hemisphere. Of the 15 cases in which intraoperative language mapping was performed, five involved tumors primarily occupying the temporal lobe (one multicentric), five the frontal or frontoparietal regions, four the insular region, and one the frontotemporal and insular regions.

### *Stimulation Mapping*

Essential language sites were located using intraoperative electrical stimulation in seven of 15 patients. In two of these patients localization was determined by disruption of visual confrontation naming (anomia), and in five patients by speech arrest without induction of motor movements (that is, Broca area). All essential language sites were found in the left hemisphere. One anomia site was located in the frontal lobe and the other in the temporal lobe. All speech arrest sites were located in the inferior frontal gyrus.

### *Lateralization Indices of MEG*

The major early component of the vowel-elicited neuromagnetic response, M100, displayed no significant amplitude bias between hemispheres (73 ± 9 femtotesla in the left hemisphere compared with 66 ± 6 femtotesla in the right hemisphere, $p = 0.39$). However, in 10 (71%) of the 14 right-handed patients, the MEG LIs derived from the late field dipole–enumerating analysis were indeed positive (that is, demonstrating leftward bias). Although there was a slight (approximately 10%), nonsignificant tendency for left hemisphere M100 amplitudes to exceed the corresponding right hemisphere M100 amplitudes, LIs based on relative M100 amplitudes did not correlate with the LIs derived from the late-field dipole enumerating analysis and, therefore, could not account for the discrepant four right-handed patients in whom late field dipole–enumerating LIs were rightward. Overall, in 14 patients the value of the late field dipole–enumerating LI was 0.37 ± 0.16 (mean ± standard error of the mean; Fig. 2).

In six (86%) of the seven cases in which stimulation mapping demonstrated left-hemisphere essential language sites, MEG LIs were leftward. Of the remaining seven right-handed patients who underwent left-hemisphere intraoperative language mapping and in whom no essential language sites were found in the region mapped, MEG laterality was leftward in four and rightward in three.

For the two left-handed patients in whom surgery was performed after induction of general anesthesia and in whom amobarbital test results indicated clear-cut right-hemisphere predominance, MEG LIs were rightward (that is, negative numbers). Low evoked field amplitudes precluded dipole source modeling (and thus lateralization assessment) for the third left-handed patient, who underwent intraoperative language mapping.

### *Dipole Source–Stimulation-Mapped Language Site Colocalization Using MEG*

The neuromagnetic sources of the late evoked field primarily clustered on the superior temporal gyrus and the posterior inferior frontal lobe. Five of seven intraoperative language sites were recorded stereotactically by using the Stealth station. All were sites of stimulation-mapped nonmotor speech arrest in the posterior portion of the inferior frontal lobe, which was consistent with the classic descriptions of the Broca area (Fig. 3). In all five cases, multiple, sequential, time-resolved neuromagnetic sources colocalized with the stimulation-mapped sites (Fig. 3). In only one case (Case 10) did these modeled dipoles meet the stringent criterion ($r > 0.97$) set for computing the LI. However, in three cases they met a less stringent, but well-accepted criterion for data–model fit (that is, $r > 0.95$); in only one case (Case 5) was the criterion lower ($r > 0.91$). These spatially colocalizing dipoles were also clustered in the time domain, with an overall latency range across patients of 261 to 327 msec after stimulus onset (Fig. 3).

## Discussion

### *Hemispheric Language Dominance*

The MEG language LI, based on enumerating the number of single ECD sources modeled in the late auditory magnetic field evoked by vowel stimuli, was consistent with language dominance, as expected by handedness (left hemisphere asymmetry for 10 (71%) of the 14 right-handed patients tested) or confirmed by the results of the amobarbital test (two of two left-handed patients with confirmed right-hemisphere dominance). This agreement was found in spite of the simplicity of the stimuli (synthesized vowels), and accords well with findings of recent studies in which a similar method of analysis was used, albeit with a much more complex task of word recognition.[23]

Although the agreement with the results of the amobarbital tests in both left-handed right-hemisphere dominant cases is striking, the percentage of right-handed patients in whom left-hemisphere predominant MEG lateralization could be determined was somewhat lower (71%) than that for language dominance as measured using the intracarotid amobarbital test (92–99%).[32] There are several possible explanations for the lower-than-expected incidence of the leftward LI, determined by MEG: vowels are much simpler linguistically than words and, thus, asymmetry in the response evoked by them may be inherently different from, even though related to, language dominance as determined by other means. It is, in fact, somewhat remarkable that the responses to such rudimentary phonological stimuli demonstrate any degree of left-hemisphere lateralization. Alternatively, the current measure of MEG lateralization may not be sufficiently sensitive, even if vowel processing were indeed representative of language as a whole. Finally, the displacement and dysfunction of neural tissue caused by tumor encroachment into the language-dominant hemisphere may alter the hemispheric

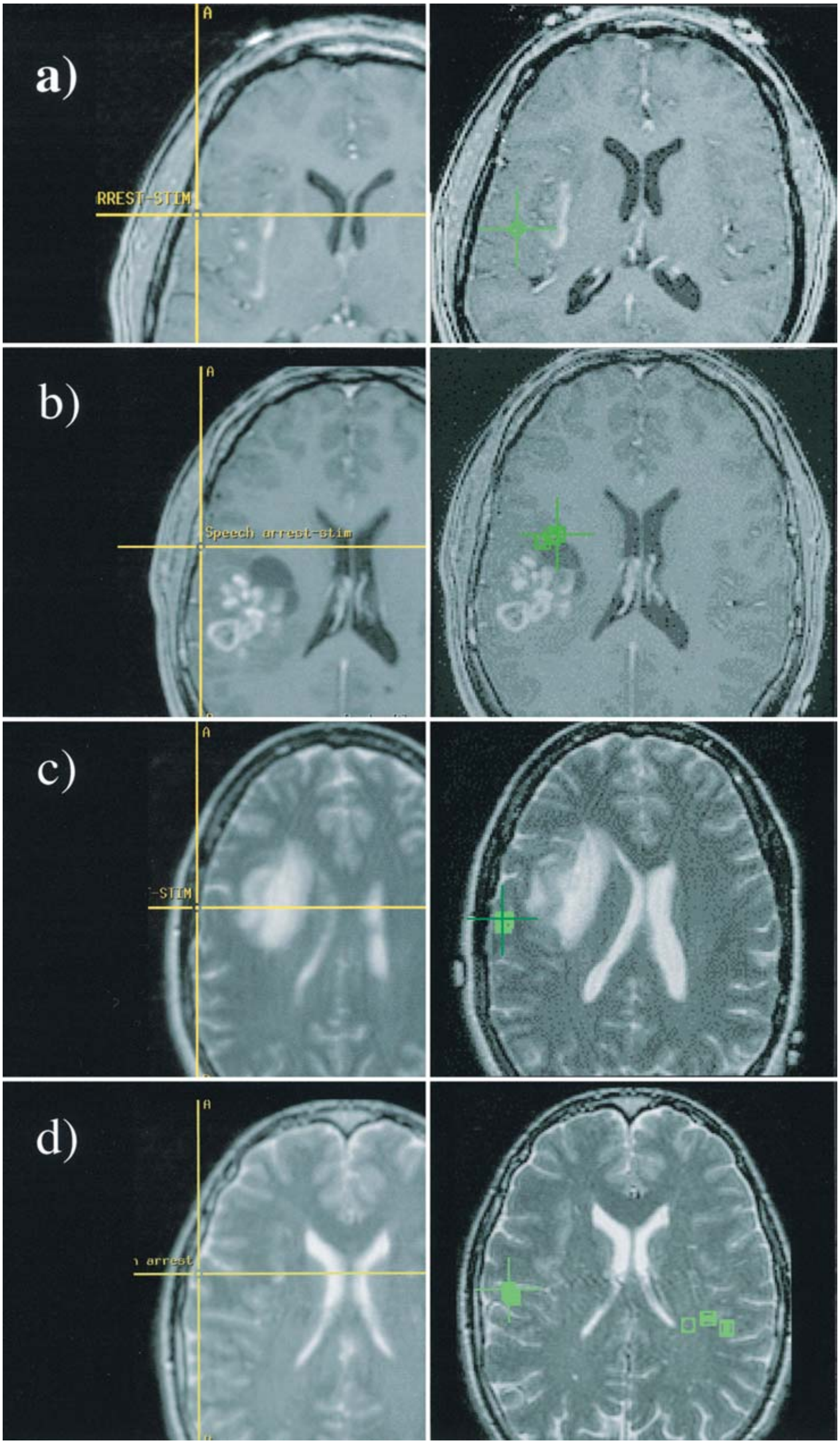

FIG. 3. Axial MR images. *Left:* Preoperative MR slices on which the stimulation-mapped sites of speech arrest *(yellow crosshairs)* were recorded intraoperatively. *Right:* Corresponding slices with late MEG modeled current dipole sources *(green)* superimposed. The *green crosshairs* indicate the source closest to the intraoperative essential language site. Rows indicate data obtained in separate patients. a: Case 10. A cluster

FIG. 3 *(continued)*→

balance of phonological processing, because of the compensatory plasticity of the opposite hemisphere, or may result in artifactual disturbance in the size, synchrony, and tangential orientation of the neural ensembles whose firing underlies the MEG response.

When we consider only those right-handed cases for which left hemisphere language lateralization was confirmed by the results of intraoperative stimulation mapping, six (86%) of seven demonstrated concordant MEG asymmetries. The single case of discordant MEG/intraoperative results, with stimulation-induced speech arrest, could be related to opposite lateralizations for receptive and expressive language functions, a rare, though not impossible, functional organization that is usually attributed to reorganization following early brain damage.[15] In seven of 14 cases in which left hemisphere electrical stimulation mapping was performed, no sites were found that met the criteria to be considered essential for language, despite the right handedness of the patients. In three of those cases, MEG asymmetry was rightward, and in four it was leftward. In such cases in which intraoperative cortical stimulation fails to identify essential language sites, the following are possible: 1) the limited craniotomy exposed no essential language regions; 2) the stimulation mapping failed to locate regions that were exposed, perhaps as a result of insufficient current; or 3) the MEG laterality (when rightward) was correct and language, in fact, was predominantly represented in the nonsurgically treated right hemisphere.

### *Colocalization Within the Broca Area*

When essential language sites were recorded using intraoperative stereotactic navigation, it was possible to compare their locations with sites of single ECD sources from the late evoked field superimposed onto the same MR image volume. Dipole sources close to essential language sites were found in all cases, agreeing closely in both the anteroposterior and the inferosuperior dimensions, but lying more medially in most cases. The intrinsic sensitivity of MS imaging to the tangential orientation of neurons lying in the banks of sulci, as opposed to the surface constraint of sites found with electrical stimulation mapping, largely accounts for mediolateral discrepancies.[26]

It is interesting to note that colocalization was demonstrated for late field sources evoked in response to speech sound reception in an anatomical area associated with speech production. Colocalization has previously been reported between receptive speech MEG sources and stimulation-mapped sites of receptive speech disruption.[23,29] However, it is less expected that sources modeled from fields evoked by vowel reception, previously reported to be the most concentrated in the superior temporal plane,[30] would colocalize with inferior frontal speech disruption sites. However, the finding that receptive speech-evoked late neuromagnetic field sources colocalized with stimulation-mapped speech arrest sites may be consistent with the motor model of speech perception.[12,16,17]

### *General Discussion*

The primary finding of this study is that indices of hemispheric lateralization can be derived from the later latency window of the auditory evoked neuromagnetic field, which is elicited in response to simple vowel stimuli. In the majority of cases, such estimations of hemispheric lateralization of language dominance were consistent with the results of amobarbital testing and/or intraoperative findings of essential language sites attained using electrical stimulation. The analysis method that we used (enumerating qualifying ECD fits for the evoked field of each hemisphere) has previously been shown to be efficacious for estimation of hemispheric dominance, in conjunction with more complex language/memory task paradigms. In this study, we show that estimates of lateralization may, in fact, be derived in a similar fashion from somewhat simpler language stimuli, even without explicit task demands.

There are some differences in sensitivity in our approach compared with other approaches previously described. Several factors may account for these variations: 1) differences in MEG systems (a whole-head[23] array rather than the 74-channel twin-sensor array used in the current study; 2) different stimuli (visual and auditory words[23] compared with the passively heard vowels used in the present study); 3) differences in the stringency of source data–model correlation criteria ($r > 0.93$[23] compared with $r > 0.97$, used in our study); and 4) different tasks (memory recognition[23] compared with passive perception selected for the present study). Vowels are simpler acoustically and linguistically than words—the latter would be more likely to evoke a greater portion of the hierarchical, linguistic neural pathways involved in lexical and semantic processing. Although potentially reducing noise from spurious dipole fits, the more stringent criteria for acceptable dipole modeling may, in some instances, have resulted in too few acceptable source localizations and, hence, a floor effect. The paradigm espoused by Papanicolaou, et al.,[23] included continuous word-recognition task performance, both a mnemonic and a higher-level linguistic task, potentially resulting in measurement of activity related to phonological, lexical, and semantic processing. This broader activation of asymmetric processing modules might result in a more robust and reliable indicator of language dominance. Finally, the laterality measure specified by Papanicolaou, et al., was based on selective averaging of trials during which word recognition occurred, thus emphasizing any responses evoked by verbal recognition and, possibly, emphasizing the linguistic specificity of the evoked response.

These differences point to specific considerations for the design of MS imaging language tasks that may meet the goals of preoperative determination of hemispheric language dominance and essential language site locations.

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of sequential sources between latencies of 307 and 319 msec matched the speech arrest site, with the closest site evident at 317 msec ($r > 0.97$). b: Case 5. A cluster of five sequential sources between latencies of 323 and 327 msec matched the speech arrest site, with the closest site evident at 326 msec ($r > 0.91$). c: Case 8. A series of four sequential sources between latencies of 261 and 273 msec colocalized with the speech arrest site, with the closest site evident at 261 msec ($r > 0.96$). d: Case 7. Three sources colocalized with the speech arrest site between latencies of 322 and 324 msec, with the closest site evident at 324 msec ($r > 0.95$).

Unlike less temporally precise far-field methods for imaging neural activity, such as fMR imaging or PET, which sum activity over many seconds, simpler paradigms that emphasize relatively early ($<$ 500 msec) and time-locked poststimulus processing are more robust and interpretable using MS imaging. Thus, in the time scale of blood flow indices of neural activity (for example, fMR and PET imaging), even the late evoked fields studied here occur very close to stimulus presentation.

The present MS imaging results confirm our previous findings in a healthy right-handed population[30] and are consistent with the findings of Zouridakis, et al.,[33] further suggesting that MEG may be useful as an adjunctive procedure for identifying hemispheric language dominance. A recent MEG study found a reliable leftward asymmetry in response to a vowel perception task, by first subtracting the magnitude of the evoked response to tones from that to vowels within each hemisphere.[10] Thus, it appears that improvements in several aspects of the MS imaging procedure may make it more reliable on an individual basis. These improvements include the following: 1) adjustments in the criteria for data inclusion to avoid floor effects; 2) use of a higher-level language task (although no more complex than necessary to avoid uninterpretable magnetic field interactions); and 3) selective averaging of trials that meet specific linguistic behavioral criteria. Using a task that at least meets the latter criterion, some researchers have reported a correspondence between MEG asymmetry and amobarbital test–measured language dominance, which was concordant for all but two borderline left-asymmetric cases not classified as bilateral in a total of 26 cases.[5]

The validity of source modeling is problematic in general because of the ill-posed inverse problem. It is well known that multiple sources may contribute to evoked field measurements and that interference effects can influence the apparent neuromagnetic fields and any attempt to source model. Despite the fact that single ECD modeling provides an oversimplification of the brain's activity, a sequential analysis reveals that the method is useful for identifying hemispheric language dominance. Furthermore, MS imaging of late evoked fields may indeed be useful for indicating areas of potential language involvement, which should be mapped in detail intraoperatively. Another extension of this work would be to model the late evoked field by using alternative modeling methods such as multiple dipole models,[19] MEG multiple signal classification,[28] time-frequency analysis, or modeling using constraints from other imaging modalities.[7,9,14]

## Conclusions

The late neuromagnetic field evoked in response to vowels demonstrated an overall leftward asymmetry in the number of modeled dipoles among right-handed neurosurgical patients and a rightward asymmetry in two patients with amobarbital test–confirmed right-hemisphere language dominance. This consonance between MS imaging asymmetry and language dominance was observed despite the simplicity of the stimuli and the lack of task imposition. Modeled sources occurring 260 to 330 msec after stimulus onset also colocalized with stimulation-mapped sites of speech arrest in the inferior frontal gyrus. Although MS imaging holds promise as a measurement tool for predicting hemispheric language dominance and the sites of essential language cortex, further investigations and validation studies are needed in which more complex linguistic stimuli and tasks are used, and in which methods for quantifying the late evoked field asymmetry and sources are addressed.

## Acknowledgments

The authors thank Susanne Homna, R.T., Jeff Walker, R.T., and Anthony Leong for excellent technical assistance, and Paul Ferrari, B.S., and Hagen Schiffbauer, M.D., Ph.D. for helpful discussions.

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Manuscript received May 24, 2000.

Accepted in final form October 17, 2000.

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