Magnetoencephalography: a noninvasive alternative to the Wada procedure

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Object. In this study the authors evaluated the sensitivity and selectivity of a noninvasive language mapping procedure based on magnetoencephalography (MEG), for determining hemispheric dominance for language functions.

Methods. Magnetic activation profiles of the brain were obtained from 100 surgical candidates (age range 8–56 years) with medically intractable seizure disorder by using a whole-head MEG system within the context of a word recognition task. The degree of language-specific activity was indexed according to the number of consecutive sources (modeled as single, moving current dipoles) in perisylvian brain areas. Only activity sources that were observed with a high degree of spatial and temporal overlap in two split-half data sets were used to compute the MEG laterality index. Independently, all patients underwent Wada testing for the determination of hemispheric dominance for language.

Independent clinical judgments based on MEG and Wada data showed a high degree of concordance (87%). Magnetoencephalography laterality judgments had an overall sensitivity of 98%, but a lower selectivity of 83%, which was due to the fact that MEG detected more activity in the nondominant hemisphere than was predicted based on the Wada test. A number of objective criteria were derived based on this large patient series to ensure data quality and bolster the clinical usefulness of MEG for language mapping.

Conclusions. Although the availability of MEG is still limited across epilepsy surgery centers, this study method may be substituted for the Wada procedure in assessing hemispheric dominance for language in select cases.

Key Words • magnetoencephalography • temporal lobe • functional magnetic resonance imaging • hemispheric dominance • language cortex • Wada test • epilepsy surgery

The Wada procedure, designed by Juhn Wada in 1949, involves the injection of barbiturate agents (typically sodium amobarbital) into the left and right internal carotid arteries, consecutively, resulting in the temporary arrest of function in each hemisphere. This permits functional assessment of the nonanesthetized hemisphere. Originally used to determine hemispheric dominance for language, the procedure was subsequently modified to include an assessment of the contribution of the noninjected hemisphere to memory. Although the Wada test is a well-established means of preoperative evaluation in epilepsy surgery candidates, there have been a number of concerns regarding its use. Noninvasive substitutes for the Wada procedure have been contemplated in the past, but only with the recent emergence of functional brain imaging techniques has it become possible realistically to consider such alternatives.

In most functional brain imaging studies, the general approach in estimating hemispheric dominance for language has involved an analysis of the degree of activation of each hemisphere during the performance of a language task as an index of its engagement. The difference in activation levels between the hemispheres has been used to derive an estimate of hemispheric dominance. The validity of these imaging-derived estimates has been assessed by comparing them with results obtained during a Wada procedure undertaken in the same patients. Note, however, that consideration of the Wada procedure as the gold standard complicates the validation process given its aforementioned limitations.

Some investigators have reported the successful use of positron emission tomography in obtaining lateralization estimates during language processing tasks. Desmond, et al., were the first to report a concordance between functional MR imaging estimates of laterality by using a semantic decision task, and laterality estimates derived from the Wada procedure. They found that a laterality index calculated from activity confined to a portion of the inferior frontal lobes was concordant with Wada results in a small sample of patients with epilepsy. Data from subsequent investigations in which larger brain volumes were studied al-

Abbreviations used in this paper: ERF = event-related field; MEG = magnetoencephalography; MR = magnetic resonance; RMS = root mean square.
so demonstrated concordance between laterality results derived from brain imaging and those from Wada procedures in adult and pediatric patients.\textsuperscript{1,14,21} Nonetheless, Lehericy, et al.,\textsuperscript{20} reported that such concordance was obtained only when frontal, not temporal, lobe activation was considered and only with one of three language tasks they used (that is, verb generation, but not object naming or single-word reading). Although most published studies on comparisons between brain imaging and Wada estimates of hemispheric dominance for language have generally shown concordance, discordance has been reported in 5 to 10\% of the cases.\textsuperscript{12,13,40}

Language-mapping protocols have been developed concurrently by using MEG to record event-related brain activity. Initial studies conducted by at least two research groups reported excellent concordance with results of the Wada test in adults\textsuperscript{4,22} and children,\textsuperscript{8} on a patient-by-patient basis. These promising findings were reinforced by the fact that the MEG-derived brain activation maps were shown to be valid and accurate through comparisons with results of intraoperative and extraoperative direct cortical stimulation mapping in individual patients.\textsuperscript{7,32,33} Based on our accumulated experience from a study of 200 patients with epilepsy, 40 patients with temporal lobe brain tumors, and more than 100 healthy volunteers, these same MEG procedures were subsequently refined and a number of technical details have been implemented to improve the robustness of the technique. The adapted protocol for patient testing and data analysis has been applied in the present study, which involves the largest series of patients with epilepsy reported to date who have preoperatively and independently undergone both functional brain imaging and the Wada procedure.

In this report we first detailed the rationale and specific procedures of MEG data analysis used for constructing maps of neuronal activation specific to receptive language function. Second, we described the method used for assessing hemispheric dominance for language on the basis of these maps. Third, we demonstrated that hemispheric dominance estimates for language, derived from MEG maps, match Wada estimates exceptionally well. Fourth, we demonstrated that, even in cases in which the two methods reveal divergent laterality measurements, basing clinical decisions on MEG estimates does not increase the chance of morbidity, thus justifying the conclusion that MEG mapping is a safe substitute for the Wada procedure in assessing hemispheric dominance for language.

### Clinical Material and Methods

#### Patient Population

One hundred patients with an intractable partial seizure disorder who were evaluated at the Texas Comprehensive Epilepsy Program of the University of Texas Medical School, Houston, Texas, participated in this study. All experimental procedures were approved by the Institutional Review Board of the University of Texas, Health Science Center at Houston, and informed consent was obtained from all participants. These patients represent a consecutive series because essentially all focal resection epilepsy surgery candidates at our center, regardless of the location of the suspected focus, are referred for language mapping with the aid of MEG and the Wada procedure. Data for a subset of these patients have been already reported in two preliminary studies, one focusing on 26 adults\textsuperscript{4} and the other on 19 children.\textsuperscript{8} In addition to both the Wada and MEG procedures, all patients underwent continuous video-electroencephalography telemetry monitoring, brain MR imaging, and neuropsychological testing for the purpose of estimating the location of the epileptogenic zone. In selected cases intracranial electrodes were also used. The distribution of patients according to seizure onset and origin as well as location of the epileptogenic zone is featured in Table 1. There were 53 women and 47 men, ranging in age from 8 to 56 years (mean \pm standard deviation, 27.3 \pm 12.1 years). Eleven patients were determined to be left-handed with the aid of the Neurosensory Center Handedness Inventory;\textsuperscript{40} the remaining patients were right-handed. In agreement with the findings of other previous larger-scale studies,\textsuperscript{10,19} there was a preponderance of patients with left hemisphere seizure onset (67 patients compared with 33 patients).

#### The Wada Procedure

Several protocols for conducting the Wada procedure are available. At our center we have consistently used the one described by Loring and colleagues.\textsuperscript{21} In all cases the Wada test was preceded by an angiography study, on which none of the patients exhibited evidence of cross-flow or anomalous vascularization that would affect interpretation of the results. Intracarotid artery injections of sodium amobarbital were administered by hand during a 4- to 5-second interval via a catheter, following a transfemoral approach. Patients were generally given an initial bolus of sodium amytal that varied between 25 and 75 mg, depending on their weight, and incremental injections of 12.5 mg, as needed, to produce a contralateral hemiplegia. Mean dosages were 92.1 \pm 18.8 mg for injections into the right hemisphere and 93.1 \pm 21.6 mg for injections into the left. The hemisphere ipsilateral to the suspected seizure focus was always injected first. The patient’s comprehension of simple instructions (for example, “stick out your tongue”) was tested first. After presenting test items for subsequent recall and/or recognition, hemispheric dominance for language was determined in the following manner: 1) testing for comprehension of one- and two-step commands (the most complex being commands involving inverted syntax); 2) naming of objects or parts of.
objects presented as line drawings; 3) reading of sentences; and 4) repetition of simple phrases. Performance on each of these tests was scored as either normal, or mildly, moderately, or severely deficient. The identical procedure was repeated in the other hemisphere after an approximately 30-minute interval. A neuropsychologist (J.I.B.), who was blinded to the MEG results, made a judgment as to hemispheric dominance for language based on each patient’s performance during the Wada procedure. Additional qualitative indications of dominance were derived from signs like the interruption of expressive language (speech arrest or paraphasic production during naming, repetition, or reading) as well as receptive language performance (inability to produce accurate motor response to simple and complex commands). In general, a hemisphere was deemed to support language when its injection resulted in the disruption of language in at least two of the aforementioned tests, with either one test being rated as having at least moderate disruption or at least three of the four tests being characterized with at least mild disruption.21 Unilateral language representation was inferred when only one hemisphere met these criteria. Bilateral language representation was inferred when criteria were met either during injection of both hemispheres, or when neither hemisphere met criteria despite adequate amounts of injected barbiturate agents and in the absence of any evidence for anomalous vascularization.

Magnetoencephalography as a Functional Brain Imaging Method

Given that most neuroimaging studies involve either functional MR imaging or positron emission tomography and that the use of MEG as a functional brain imaging method is not yet widespread, we provided a brief, general overview of the method and specified the nature of the MEG-derived functional maps. A detailed description of whole-head MEG can be found in Panico & Kolou, et al.27 Here the method was described briefly, with special emphasis on those aspects that are most relevant to the present study.

Magnetoencephalography is substantially different from the functional brain imaging methods based on measures of blood flow, in which some patient populations may be inappropriate, difficult to interpret, or even misleading.20 With MEG, neurophysiological activity, in the form of magnetic flux generated by intracellular electrical currents in large neuronal aggregates, can be measured in a more direct fashion. Thus, it may provide a more direct index of sensory, motor, and cognitive task-specific activation compared with methods that rely on hemodynamic measures. Imaging of brain activation with the aid of MEG involves the following steps. Stimuli are known to evoke brain activity soon after they impinge on the sensory receptors. One basic aspect of such activity is the intracellular flow of ions, which generates electrical currents and magnetic fields. Repetitive application of a given stimulus results in repeated evocation of the same currents and fields which, when recorded on the head surface and averaged, result in the well-known evoked or event-related potentials and their magnetic counterparts, the ERFs. The distribution of the latter on the head surface lends itself, much more readily than the distribution of the former, to mathematical estimates of location and extent of activation of the sets of brain cells that produce them.

Event-related fields, much like event-related potentials, are waveform representations of brain activity over time following the onset of an external stimulus. Early portions of the ERF waveform (that is, up to 150–200 msec after stimulus onset) reflect neurophysiological activity in primary sensory cortices. Conversely, neurophysiological activity represented by later portions of the ERF waveform occurs primarily in association cortices. By estimating the regions that contribute to systematic variations in the late portions of the ERF waveform, one delineates the brain circuits responsible for cognitive and linguistic functions.

As part of the MEG language-mapping procedure in the present study, patients were exposed to a series of auditory stimuli in the form of words spoken in English. Each patient’s task involved attending to and recognizing each word and determining whether it had been presented earlier in the list. Each word produced an ERF record in the form of a time series of magnetic flux measurements from each of the 148 magnetometer sensors that covered the surface of the patient’s head. The ERF records associated with several consecutive word stimuli were then averaged. The resulting averaged ERFs consisted in all cases of an early (typically between 30 and 200 msec poststimulus onset) and a late portion (typically between 200 and 800 msec poststimulus onset, although task-relevant activity up to 1000 msec was occasionally observed). To identify the intracranial origin of ERFs, we analyzed the magnetic flux distribution that had been recorded simultaneously over the entire head surface at successive points (4 msec apart), thereby preserving the temporal information inherent in the MEG methodology. Analysis consisted of the application of a mathematical model that considered the intracranial activity sources (sets of active neurons) as equivalent to physical current dipoles31 and was intended to provide estimates of the location and strength of these sources, the activity of which had produced the recorded magnetic flux at each time point. The location estimates of each dipolar source were specified with reference to a cartesian coordinate system, anchored on three fiducial points on the head (the nasion and the external meatus of each ear). The same fiducial points were marked with vitamin pills, thus enabling precise registration of the location of each dipolar source on the participant’s MR image.

The dipolar source(s) that accounted for the average surface distribution of magnetic flux at each 4-msec time window indicated the brain areas activated at that time point. The derived activation maps consisted of clusters of temporally contiguous activity sources that were typically localized in the same anatomical region. In the context of word-recognition tasks, such as the one used in the present study, clusters spanned between 20 and 100 msec in duration, although it was not uncommon to observe successive sources in the same region (usually temporoparietal cortex in the dominant hemisphere) for 400 msec or longer. Variability in the number and temporal extent of source clusters can usually be accounted for by patient-specific factors and technical issues, such as neuromagnetometer sensitivity and overall signal-to-noise ratio data. The latter may vary depending on location, patient, and even the day and time of the recording. To ensure consistency across patients, laboratories, and over time, we have instituted a number of analysis procedures that are described in more detail later.

In addition to spatial coordinates, net electrical current
and the net magnetic flux associated with each activity source were computed. Note, however, that analysis of data from our previous studies indicates that the most reliable and valid measure of the degree of regional engagement in a particular cognitive or linguistic task is the total number of activity sources determined during the late portion of the ERF waveform. The validity of this estimate is not based on any theoretical considerations, but was empirically derived.14,22,32,33,35 The concurrent validity of each MEG-derived measure was reexamined in the present study by using a much larger patient series than in our previous studies.

Stimuli and Tasks

Patients were given a recognition memory task for spoken words, and ERFS were recorded for each word stimulus. The word list consisted of 90 abstract English nouns with scores of 3 or lower on the Paivio Concreteness Scale.32 Word frequency ranged from very frequent (scored AA) to nine occurrences per million for some words.32 A native speaker of English with a flat intonation produced the stimuli (mean duration 450 msec, range 300–750 msec), which were digitized using a sampling rate of 22,000 Hz and 16-bit resolution, edited (to remove artifacts and ensure a uniform sound envelope), and stored on a portable computer that was also used for stimulus presentation. The stimuli were delivered binaurally with an intensity of an 80-dB sound pressure level at the patient’s outer ear through two 5-m-long plastic tubes terminating in ear inserts.

Thirty words from each list were used as targets and the remaining 60 as distractors, which made for six blocks of trials. There was no significant difference between target and distractor word lists in terms of either word concreteness or frequency. The target stimuli were repeated in every block (in a different random order each time) and were mixed with 10 new distractors. The target stimuli were presented for study once or twice (depending on the patient’s overall verbal memory capacity) immediately prior to MEG. Stimulus presentation parameters were identical during the actual recording and the study session. Stimuli were presented with a variable interstimulus interval (2.5–3.5 seconds). In addition to the auditory version a visual version of this task was used in some of the patients in the series. Use of the printed-word task was discontinued early in the course of the study, based on the following concerns: 1) the increased complexity of implementing a second similar task in a different modality; 2) the added complexity of data analysis procedures; and 3) the problems involved in the interpretation of results in patients who experience reading difficulty. Accordingly, only data from the auditory version of this task were included in the current data set. To ensure the test–retest reliability of the results, data from the first three blocks of trials (henceforth referred to as “Session 1”) were averaged separately from ERF data collected during Blocks 4 to 6 (Session 2).

Patients were asked to lift their index finger whenever they recognized a repeated word. The responding hand was counterbalanced across sessions. During MEG patients were asked to keep their eyes open, fixating on a dark dot placed on the ceiling in their direct line of vision, to reduce eye movements or blinks and prevent ERF contamination by rhythmic activity (typically in the alpha band), which can interfere with the accurate detection of task-related brain activity.

Magnetoecephalography Data Acquisition and Analysis

All patients were tested using a whole-head neuromagnetometer (4D Neuroimaging, San Diego, CA) equipped with 148 magnetometer sensors and housed in a magnetically shielded room designed to reduce environmental magnetic noise that might interfere with biological signals. The typical recording session required the patient to lie motionless on a bed with his or her head inside the helmetlike device for approximately 15 minutes. The signal was filtered online with a bandpass filter between 0.1 and 20 Hz, digitized for 950 msec (254-Hz sampling rate) including a 150-msec prestimulus period, and subjected to an adaptive filtering procedure that is part of the 4D Neuroimaging signal analysis package. These steps are necessary to minimize the amount of low-frequency magnetic noise typically present in MEG recordings. The next step involved visual inspection of single-trial ERF segments to identify those contaminated by eye- or head-movement–related magnetic artifacts or by epileptogenic activity. Movement artifacts were defined as magnetic flux deflections in excess of 3 picotesla (peak-to-peak amplitude) in the recordings obtained from magnetometer sensors located over the eyes. Given that it is possible to mistake small blinks or lateral eye movements for magnetic deflections caused by brain activity, the surface distribution of magnetic flux associated with these deflections was frequently taken into account. Event-related field epochs that contained more than two interictal epileptiform events (spikes or sharp waves) were similarly excluded from further analyses.

A minimum of 140 artifact-free ERF epochs were used to calculate two averaged waveforms (70 from the first three and 70 from the last three blocks of the word-recognition task). Averaged ERF data were then inspected visually to verify that they were of a quality sufficient to support a clinical judgment of laterality. The following criteria were used: 1) a mean prestimulus RMS (that is, an estimate of noise or task-independent magnetic flux in the recordings) less than 25 femtotesla; 2) an RMS ratio of signal (that is, magnetic flux associated with a given computed source) to noise (that is, mean magnetic flux during the prestimulus time interval) greater than 2:1; 3) an asymmetry in the peak field strength of the N1m response less than 25% of the total (that is, summed across hemispheres) N1m field strength (N1m is the first major component of the auditory ERF that peaks between 80–120 msec poststimulus; it is the magnetic counterpart of the electrical N100 or the first prominent negative wave in the recording of volume currents from auditory cortex); and 4) an absence of sharp epileptiform activity in the single-epoch data or, if present, an incidence of no more than one epileptiform event in less than 20% of the ERF data segments. Data from 15 patients were excluded from further analyses because they did not meet one or more of the criteria listed previously (Fig. 1).

The intracranial generators of the observed ERFS (activity sources) in acceptable data sets were modeled as single equivalent current dipoles and fitted at successive 4-msec intervals by using the nonlinear Levenberg–Marquardt algorithm.33 For a given point in time, the source-fitting algorithm was applied to the magnetic flux measurements obtained from a group of 34 to 38 sensors, always including both magnetic flux extremes. Source computation was restricted to latency periods during which a single pair of
magnetic flux extremes dominated the left and/or the right half of the head surface. The algorithm used in this study searched for the source that was most likely to have produced the observed magnetic field distribution at a given point in time. Source solutions were considered to be satisfactory if they were associated with a correlation coefficient of at least 0.9 between the observed and the best predicted magnetic field distribution. After dipole fitting, the estimated activity sources from the two recording sessions were merged and ranked by the degree of latency overlap and the spatial proximity by using an automated algorithm developed by 4D Neuroimaging. This program, which is outlined in detail in the Appendix, minimizes subjective judgments and substantially reduces analysis time.

To determine the anatomical regions corresponding to each activity source, the source locations, which were initially computed in reference to the MEG cartesian coordinate system mentioned previously, were coregistered on T1-weighted MR images (TR 13.6 msec, TE 4.8 msec, recording matrix 256 × 256 pixels, excitation 1, field of view 240 mm, slice thickness 1.4 mm) obtained in each participant. Transformation of the MEG coordinate system into MR imaging–defined space was achieved with the aid of three lipid capsules inserted into the patient’s ear canals and attached to the nasion, which could be easily visualized on the MR images by using the overlay tool that is part of the 4D Neuroimaging software. A standard MR imaging atlas of the human brain served as a reference for the identification of the cerebral structures at which sources were localized. As in previous studies featuring the English and Spanish versions of this task, activity sources were situated in frontal and temporal lobe (both mesial and lateral) areas. Although all patients presented with activity sources in the posterior portion of the superior temporal gyrus (often extending ventrally into the superior temporal sulcus and caudally into the supramarginal gyrus), fewer patients had sources in the middle temporal gyrus (71%), mesial temporal (79%), and inferior frontal areas (45%). Here we will use the term “perisylvian” to refer to activation anywhere in this broader region, which includes the Wernicke area. It is important to note that MEG activity sources were often found bilaterally in these areas, even in individuals who, according to both the Wada and MEG findings, were left-hemisphere dominant for language. Occasionally, activity sources were situated in perisylvian and not included in the derivation of estimates of hemispheric dominance for receptive language function.

Satisfactory source solutions can be described on the basis of four complementary measures: 1) location (that is, spatial coordinates on the MEG cartesian coordinate system defined by the ear canals and the nasion); 2) estimated current moment of the net neuronal population response (in nanoAmperemeters); 3) global field power (RMS) of the measured magnetic flux used to calculate each activity source (in femtoTeslas); and 4) latency or delay after stimulus onset at which point a given source is estimated (in milliseconds). In our previous studies with healthy volunteers and patients, the method that produced the most conclusive results as an index of the degree of regional activation was the total number of successive activity sources in a particular area or group of areas. Nonetheless, the potential usefulness of information regarding the strength of each activity source (with respect to both the intracranial electrical current and the ensuing magnetic flux recorded at the head surface) was also considered in the present study when appropriate.

**Laterality Judgments**

A neurophysiologist who was blinded to the Wada results made a judgment as to cerebral dominance for language based on the MEG-derived maps. This procedure consisted of the following: 1) selecting activity sources computed during the late portion of the ERF waveform for each hemisphere and testing session (that is, > 200 msec); 2) determining the number of automatically clustered activity sources in perisylvian regions for each hemisphere and each testing session separately (see earlier text for the method of cluster derivation); and 3) creating a laterality index according to the formula (R – L)/(R + L), where R represents the number of acceptable late activity sources observed in the right hemisphere and L represents the number of acceptable late activity sources observed in the left hemisphere.
right hemisphere and L the corresponding number on the left. Index values between −0.1 and 0.1 were considered to be indicative of bilaterally symmetric activation, whereas values greater than 0.1 or less than −0.1 indicated right- or left-hemisphere dominance, respectively.

In addition to providing an estimate of hemispheric dominance for receptive language functions, activity-source maps were used to determine the location and extent of the temporal lobe region that consistently showed language-specific activity. This region was defined by the location of spatially and temporally overlapping activity sources across the two split halves of the activation task. In previous studies this region was found to overlap closely with the Wernicke area, defined as the cortical area linked to receptive language deficits when electrically stimulated (in the context of extra- or intraoperative mapping).32,33

**Results**

Figure 2 contains MEG–MR imaging coregistered scans for three representative cases, demonstrating predominantly left-hemisphere activity, bilateral activity, and predominantly right-hemisphere activity during word-recognition tasks. The patients in these cases showed similar interhemispheric asymmetries in language function during the Wada procedure, which were judged to be left-, bilateral-, and right-hemisphere lateralized for language, respectively, on the basis of both procedures. Similar coregistered scans were obtained in all patients in this study and judgments were made about hemispheric dominance for language as described earlier.

**Concordance Between MEG and Wada Findings on Hemispheric Dominance**

The relationship between clinical judgments made using the MEG and Wada procedures is presented in Table 2. There is strong concordance between the independent clinical judgments made with each test. Results of both the MEG and Wada procedures exhibited complete agreement in 74 (87%) of 85 cases (Fisher exact test, p < 0.0001). There were 11 discordant cases. In the majority of these patients (seven patients) MEG studies demonstrated considerable activity in both hemispheres, although the Wada results exhibited left-hemisphere dominance. In four of seven of these patients the epileptogenic zone was located in the right hemisphere, and it is possible that the degree of neurophysiological activity detected and successfully modeled from that hemisphere was inflated by the presence of focal epileptiform activity not initially detected and therefore not rejected at the single-epoch level.

Further analyses indicated no significant relationship between the probability of a discordant judgment and the hemisphere (binomial test, p > 0.17), location of seizure onset (temporal compared with extratemporal region; binomial test, p < 0.75), seizure origin (lesional compared with cryptogenic origin; binomial test, p > 0.3), handedness (binomial test, p > 0.4), or left- (p > 0.4) or right-hemisphere (p > 0.7) amobarbital dosage during the Wada procedure.
Magnetoecephalography as a noninvasive alternative to the Wada test

Clinical Usefulness of Language Judgments Based on the MEG Procedure

One can use the Wada procedure to determine whether invasive mapping and/or a tailored surgical approach will be required to avoid impinging on suspected eloquent cortex. Therefore, the test of the clinical usefulness of the MEG procedure is the extent to which it is able to detect the presence of language function in the hemisphere in which surgery will be performed. The concordance between results of the MEG and Wada procedures regarding the potential presence of eloquent cortex in the hemisphere of seizure onset is featured in Table 3. As demonstrated, results of the MEG and Wada procedures disagree regarding the potential presence of eloquent cortex in the hemisphere of operation in only six cases. In five of these cases MEG findings indicated the presence of language representation, whereas Wada results revealed none; in one case the reverse was true. Indices of sensitivity (probability of detection of eloquent cortex when it is present), specificity (probability of detection of the absence of eloquent cortex when it is absent), positive predictive value (probability that when MEG results indicates that eloquent cortex is present it actually is), and negative predictive value (probability that when MEG findings indicate that eloquent cortex is absent it actually is absent) are presented later. These statistics are all relative to the Wada procedure, considered here as the gold standard. The MEG judgments show excellent sensitivity (98%), positive (91%) and negative (96%) predictive value, and very good specificity (83%).

Clinical Use of Alternative Measures of Language-Specific Activity

In a separate set of analyses we examined the relationship between language dominance determined using the Wada test, and hemispheric asymmetries in the degree of neurophysiological activity in posterior language areas, indexed using two complementary measures (the peak global field power [RMS] and the peak current moment [Q]). Both RMS and Q values were extracted from the set of sources that had been selected in the automatic clustering program described earlier. The derived cluster of sources included those that had occurred in the same anatomical region (with a 1-cm tolerance radius) in close temporal proximity (<100 msec) in both MEG recording sessions. A third measure, onset latency of each cluster after stimulus onset, was also examined. In addition, hemispheric asymmetries in the onset latency of activity in this region were assessed. An analysis of variance with hemisphere as a repeated measures factor and hemisphere dominance group (either left or bihemispheric representation—given the small number of patients with right-hemisphere dominance in the sample) as a between-subjects factor was performed on each of the three measures. The main effects of hemisphere were found for onset latency (F(1,80) = 4.03, p < 0.048) and peak RMS (F(1,80) = 6.2, p < 0.015), indicating that, regardless of hemispheric dominance, reliable activity in the vicinity of the Wernicke area occurred earlier and was associated with greater magnetic flux than that in the homotopic right-hemisphere region. A nonsignificant trend in the same direction was found for Q (p > 0.15).

Similar analyses of variance were performed on the RMS of the magnetic flux sampled at the peak of the N1m response, the latency of that peak (after stimulus onset), and the current dipole moment (Q) associated with the activity source accounting for the N1m peak. There was no main effect or interaction, corroborating previous results in healthy volunteers that hemispheric asymmetries occurring during the processing of each word stimulus were not caused by systematic asymmetries in the initial response of the auditory cortex to the stimulus.

Discussion

Excellent concordance between MEG language profiles and Wada procedure results was observed in this study. Judgments regarding the relative degree of language representation in each hemisphere were completely concordant in 87% of the cases, and there was no case in which MEG and Wada-based judgments regarding hemispheric dominance for language were diametrically opposed. In addition, in only one case did Wada results indicate that the potential presence of eloquent cortex in the hemisphere to be operated on would have been ignored using MEG. Consistent with these observations, the clinical use of MEG for the detection of language-specific cortex in the hemisphere of seizure onset—using the Wada procedure results as the gold standard—demonstrated excellent sensitivity, positive predictive value, and negative predictive value.

Although the specificity of the MEG procedure was very good, when MEG and Wada results were discordant, the MEG findings, for the most part, tended to indicate the possibility of bilateral representation and the Wada procedure revealed unilateral representation. Therefore, the MEG procedure was more likely to produce a positive result than the Wada test. This finding is not completely unexpected, because functional brain imaging studies performed using a variety of methods consistently demonstrate bilateral activation in neurologically intact control volunteers individually during the performance of language tasks, even when the activity is predominant in one of the two hemispheres. In contrast, a large number of patients (43 patients) in the current study showed no behavioral effect on injection of an anesthetic agent into the right internal carotid artery during the Wada procedure, a finding that was not explained by abnormal vascularization or amobarbital dosage. Another relevant issue in a comparison of the results of the Wada procedure and those of the MEG protocol described in this report is that although the former incorporated tests of both expressive and receptive language functions, the latter assessed neurophysiological activation elicited in the context of a receptive language task. With recent improvements in the sampling density of magnetic sensors, it is now possible reliably to record and model brain activity associated with

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the engagement of anterior language areas in the performance of expressive tasks (such as word-fluency and picture-naming tasks). Brain activation protocols that target these regions have been successfully used in the context of hemodynamic imaging methods\textsuperscript{11,12,17} and are expected to complement existing protocols to further increase the selectivity of MEG-derived estimates of hemispheric dominance for language function.

Accumulated experience with the study of more than 240 patients and 100 healthy control volunteers who had undergone presurgical language mapping by using identical procedures prompted a number of revisions in the MEG data analysis procedures to ensure data integrity. It became evident that an index of hemispheric asymmetry based on the total number of activity sources observed during two MEG recording sessions is not as selective for determining hemispheric dominance as is a hemispheric asymmetry index based only on activity sources in perisylvian language areas that occur with a high degree of spatial and temporal consistency during two consecutive MEG sessions. In our studies we have repeatedly observed that only a subset of the activity sources localized in the perisylvian areas appear consistently in a given patient, that is, in consecutive repetitions of the same activation task or across split-half replications. In the course of combined MEG and electrocortical stimulation studies we have ascertained that these consistently observed activity sources most accurately indicate the location of receptive language–specific cortex.\textsuperscript{33} In other words, the region that is producing neurophysiological activity (in the context of an aural word-recognition task) reflected in those activity sources coincides with the region that when stimulated electrically causes severe disruption in a patient’s ability to perceive and understand spoken utterances.

Although MEG appears to be an acceptable substitute for the Wada test in determining whether language is present in the hemisphere in which surgery is to occur, the latter can also be used to provide data regarding the relative importance of each hemisphere for memory function. If the hemisphere contralateral to the epileptogenic side is unable to support memory function, individuals who undergo anterior temporal lobectomy, including resection of portions of the hippocampus, may be at an increased risk of developing an amnesic disorder\textsuperscript{15} postoperatively. These individuals may therefore be refused surgery. In addition, despite the inconsistent effects of the anesthetic agent on mesial temporal structures during the Wada procedure and the consequent difficulties in interpreting memory testing, Wada performance has been shown to correlate with outcome\textsuperscript{18} and has been used as an adjunct to electrophysiological and imaging modalities in determining the side of seizure onset at a number of centers.\textsuperscript{30} Thus, in cases in which memory is not an issue (for example, extratemporal surgery) MEG may be substituted for the Wada procedure. Preliminary MEG studies have been successfully used to map neurophysiological activity in temporal lobe structures known to be critical for memory function in healthy volunteers.\textsuperscript{28} The usefulness of such information for determining hemispheric dominance for memory function in candidates for epilepsy surgery has been difficult to establish. Thus, at present, if information regarding memory status in either hemisphere is required, the Wada procedure, even with its limitations, may need to be considered.

### Conclusions

In view of our results, we conclude that MEG, used in the manner detailed in the Clinical Material and Methods section of this report, can serve as a substitute for the Wada procedure preoperatively to determine when surgery may potentially impinge on language-specific cortex. Although the functional significance of bilateral activation on MEG is as yet unclear, the practical consequences of the discordant judgments would have been limited to invasive mapping and/or tailoring of surgery in four patients (4% of the cohort), and no language mapping in one patient in whom it might have been necessary. Thus MEG may provide a more conservatively conservative test for the presence of language function in the hemisphere subject to surgery, compared with the Wada procedure.

In addition to being completely noninvasive and relatively fast (~30 minutes of testing) with no physical risk and minimal discomfort, the MEG procedure has the distinct advantage of providing accurate data regarding the location of receptive and expressive language cortex.\textsuperscript{52,33} Note that MEG is not yet widely available, even in countries with well-established epilepsy surgery programs (including the US), which limits the generalizability of MEG-based presurgical mapping. On the other hand, when available, the MEG study can be repeated easily to ensure optimal patient cooperation. In cases in which resection is to occur near areas that may putatively support language function, invasive procedures such as electrocortical stimulation mapping may be greatly shortened by using MEG-derived maps as a guide or even avoided altogether when there is a great enough distance between the MEG maps and the areas to be affected by surgery. Given that MEG is quite sensitive to atypical topographic representation of language function,\textsuperscript{28,33} in the event that unusual or multiple locations are detected, invasive mapping and/or surgery can be appropriately tailored to avoid postoperative functional deficits.

### Appendix

#### Activity Source Clustering Program

1) Bounding Box. A pair of boxes are created outside of which activity sources are rejected. The two boxes are defined by seven variables: $x_{\text{min}}$, the minimum acceptable value for $x$, typically 6 cm; $x_{\text{max}}$, the maximum acceptable value for $x$, typically 6 cm; $y_{\text{min}}$, the minimum acceptable value for $y$, typically 9 cm; $y_{\text{max}}$, the maximum acceptable value for $y$, typically 9 cm; $z_{\text{min}}$, the minimum acceptable value for $z$, typically 2 cm; $z_{\text{max}}$, the maximum acceptable value for $z$, typically 2 cm; and $y_{\text{exclude}}$, the distance from $y=0$ plane to exclude, typically 2 cm.

2) A minimum acceptable correlation, $\text{mincorr}$, is defined, typically as 90%. All activity sources with correlations less than mincorr are rejected.

3) The remaining activity sources are ranked based on three criteria: a) the number of activity sources nearby in space; b) the number of activity sources nearby in time; and c) whether the activity source location is repeated in the test/retest data sets. d) Only the highest ranked activity sources are kept.

a) Ranking for the number of activity sources nearby in space is performed using a gaussian weighting factor, which is calculated as follows:

$$S_{ij} = e^{-\left(\frac{x^2}{2\sigma_x^2}\right) - \left(\frac{y^2}{2\sigma_y^2}\right)}$$
Magnetoencephalography as a noninvasive alternative to the Wada test

where $d$ is the distance between activity sources $i$ and $j$, and $\sigma_i$ is input and sets the scale for the falloff of the ranking value. $\sigma_i$ is input as dist and is typically 1 cm.

- Ranking for the number of activity sources nearby in time is performed using a gaussian weighting factor, which is calculated as follows:

$$T_{ij} = \frac{1}{\sqrt{2\pi\sigma_i^2}}$$

where $t$ is the time difference between activity sources $i$ and $j$, and $\sigma_i$ is input and sets the scale for the falloff of the ranking value. $\sigma_i$ is input as time and typically is 50 msec.

- The ranking factor for each activity source is determined by combining the three aforementioned ranking factors for each other activity source and by summing the results. This leads to

$$R_i = \sum_{j\neq i} S_{ij} \cdot T_{ij} \cdot [1 - W \cdot \delta_{ij}^{\text{same}} + 1],$$

where $R_i$ is the ranking factor for the $i$th activity source; $S_{ij}$ is the spatial factor as defined below; $T_{ij}$ is the temporal factor as defined below; $\delta_{ij}^{\text{same}}$ is 1 when the activity sources are from the same data set, and 0 when they are from different data sets; and $[1 - W \cdot \delta_{ij}^{\text{same}} + 1]$ is the test/retest weighting factor and is equal to $W$ when the activity sources are from the same data set, and equal to 1 when the activity sources are from different data sets. $W$ is input as relweight and is typically 20%.

- Once the ranking values are calculated, the top $n\%$ are output to the final file. $n$ is input as keep and is typically 60 to 70%.

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