

Magnetocephalography: A Non-Invasive Alternative to the Wada Procedure

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Objectives: This study evaluates the sensitivity and selectivity of a non-invasive language mapping procedure based on magnetoencephalography (MEG), for determining hemispheric dominance for language functions.

Methods: Brain magnetic activation profiles were obtained from 100 surgical candidates with medically intractable seizure disorder (aged 8-56 years) with a whole-head MEG system, in the context of a word recognition task. The degree of language-specific activity was indexed by 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 had Wada testing performed for determination of hemispheric dominance for language.

Results: Independent clinical judgments based on MEG and Wada data showed a high degree of concordance (87%). MEG 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 non-dominant hemisphere than predicted based on the Wada test. A number of objective criteria were derived based on this large patient series in order to ensure data quality and bolster the clinical utility of MEG for language mapping. *Conclusion:* MEG may be substituted for the Wada procedure in assessing hemispheric dominance for language in select cases.

KEY WORDS • Magnetoencephalography • temporal lobe • functional brain imaging • language laterality • Wada • epilepsy surgery

The Wada procedure, designed by Juhn Wada in 1949,³⁹ involves injection of barbiturates (typically sodium amobarbital) into the left and right internal carotid arteries, consecutively, resulting in temporary arrest of the function of each hemisphere. This renders functional assessment of the non-anesthetized hemisphere possible. Originally used for the purpose of determining hemispheric dominance for language, the procedure was subsequently modified to include assessment of the contribution of the non-injected hemisphere to memory.²⁴

While the Wada procedure is a well-established means for pre-operative evaluation of epilepsy surgery candidates,³⁰ there have been a number of concerns regarding its use^{7,16,23,30,34,37,42}. While non-invasive substitutes for the Wada procedure have been contemplated in the past, only with the recent emergence of functional

brain imaging techniques it has become possible realistically to consider such alternatives. The general approach to the estimation of hemispheric dominance for language, in most functional brain imaging studies, has been to consider the degree of activation of each hemisphere during performance of a language task as an index of the degree 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 non-invasive estimates has been assessed by comparison with the results of the Wada procedure in the same patients, although the need to consider the Wada procedure as the "gold standard" complicates the validation process in view of its above-mentioned limitations. For instance, Duncan et al.^{11,15} reported successful application of Positron Emission Tomography (PET) in obtaining lateralization estimates

during language processing tasks. Desmond et al.⁸ were the first to report concordance between functional Magnetic Resonance Imaging (fMRI) estimates of laterality, 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 epilepsy patients. Subsequent investigations, in which larger brain volumes were studied, also reported concordance between the laterality results derived from the brain imaging and the Wada procedures for adult and pediatric patients.^{1,14,41} However, Lehericy et al.²⁰ reported that such concordance was obtained only when frontal and not temporal lobe activation was considered, and only with one out of three language tasks they employed (i.e. verb generation, but not object naming and single word reading). While most of the studies that have been published on comparisons between brain imaging and Wada estimates of hemispheric dominance for language have generally shown concordance, discordance has also been reported in 5-10% of the cases.^{12,13,40}

At the same time language-mapping protocols were developed using Magnetoencephalography (MEG) to record event-related brain activity. Initial studies conducted by at least two research groups reported excellent concordance with the results of the Wada test in adults^{4,22} and children³, *on a patient-by-patient* basis. These promising results were further reinforced by the fact that the MEG-derived brain activation maps were shown to be valid and extremely accurate through comparisons with the results of intraoperative and extraoperative direct cortical stimulation mapping in individual patients.^{27,32,33} Based on our accumulated experience from the study of 200 epilepsy patients, 40 patients with temporal lobe brain tumors, and over 100 normal volunteers, these same MEG procedures were subsequently refined and a number of technical details have been implemented to further improve the robustness of the technique. The adapted protocol for patient testing and data analysis has been applied in the present investigation to the largest series of epilepsy patients reported to date who have undergone, preoperatively and independently, both functional brain imaging and the Wada procedure.

In this report we first detail the rationale and the specific procedures of MEG data analysis that we use for constructing maps of neuronal activation specific to receptive language functions. Second, we describe the method used for assessing hemispheric dominance for language on the basis of these maps. Third, we demonstrate that hemispheric dominance estimates for lan-

guage, derived from MEG maps, match the Wada estimates exceptionally well. Fourth, we demonstrate that even in cases where the two methods result in diverging laterality measurements, making clinical decisions on the basis of the 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.

Materials and Methods

Patients. 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 in Houston, Texas participated in this study. All experimental procedures were approved by the Institutional Review Board of the University of Texas – Houston Health Science Center and informed consent was obtained from all participants. This represented a consecutive series because essentially all focal resection epilepsy surgery candidates, regardless of the location of the suspected focus, were referred for language mapping using MEG as well as the Wada procedure at our center. Data for a subset of these patients have been previously reported in two preliminary studies, one focusing on adults ($n = 26$)⁴ the other on children ($n = 19$).³ In addition to both the Wada and MEG procedures, all patients underwent continuous video telemetry-EEG monitoring, brain MRI, and neuropsychological testing for the purpose of estimating the location of their epileptogenic zone. In selected cases intracranial electrodes were also used. The distribution of patients according to seizure onset, etiology and location of the epileptogenic zone is presented in Table 1. There

Table 1. Seizure etiology and focus

Table 1. Seizure etiology and focus	
Etiology	N
Cryptogenic	65
Symptomatic	35
Seizure Focus	
Left Mesial Temporal	54
Right Mesial Temporal	26
Left Frontal	10
Right Frontal	5
Left Hemisphere	2
Right Hemisphere	2
Non-localized	1

were 53 women and 47 men ranging in age from 8 to 56 years ($M = 27.3$, $SD = 12.1$). Eleven patients were determined to be left-handed using the Neurosensory Center Handedness Inventory.³⁸ All of the remaining patients were right-handed. In agreement with the findings of other previous larger scale studies,^{10,19} there was a preponderance of patients with left hemisphere seizure onset (67 vs. 33).

The Wada procedure. Several protocols for conducting the Wada procedure are available. In our center we have consistently used the one described by Loring and colleagues.²¹ In all cases the procedure was preceded by angiography, on which none of the patients exhibited evidence of cross-flow or anomalous vascularization that would affect interpretation of the results. Intracarotid injections of sodium amobarbital were administered by hand over a four to five second interval via a catheter following a transfemoral approach. Patients were generally given an initial bolus of sodium amytal that varied between 25 mg and 75 mg depending on their weight, and received incremental injections of 12.5 mg, as needed, to produce a contralateral hemiplegia. Mean dosages were $92.1 \text{ mg} \pm 18.8$ for injections in the right hemisphere and $93.1 \text{ mg} \pm 21.6$ for injections in the left. The hemisphere ipsilateral to the suspected seizure focus was always injected first. The patient's comprehension of simple instructions (e.g. "stick out your tongue") was tested first. After presentation of test items for subsequent recall and/or recognition, hemispheric dominance for language was determined in the following manner: First, through testing for comprehension of one and two-step commands (the most complex being commands involving inverted syntax). Second, through naming of objects or parts of objects presented as line drawings. Third, through a test of reading of sentences and fourth, through repetition of simple phrases. Performance on each of the tests was scored as either normal, or mildly, moderately or severely deficient. The identical procedure was repeated in the other hemisphere after approximately a 30-minute interval. A neuropsychologist (J.I.B.) blind to MEG results made a judgment as to hemispheric dominance for language using 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, paraphasic production during naming, repetition or reading) as well as receptive language (inability to produce accurate motor response to simple and complex commands) performance. In general, a hemisphere was deemed to support language

when its injection resulted in disruption of language in at least two of the above-named tests, with one test rated as having at least moderate disruption or when at least mild disruption was noted in at least 3 of the 4 tests.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 and in the absence of any evidence for anomalous vascularization.

MEG as a Functional Brain Imaging Method. In view of the fact that most neuroimaging studies involve either fMRI or PET and the fact that the use of MEG as a functional brain imaging method is not widespread as yet, it may be useful to provide a brief, general overview of the method and to specify the nature of the functional maps it provides. We believe that this description will make clear why MEG is well suited for the study of brain activation of patients, especially those with a compromised vascular system. A detailed description of whole-head MEG can be found in Papanicolaou et al.²⁷ Here the method will be described briefly, with special emphasis on those aspects that are most relevant to the present project.

MEG is substantially different from the functional brain imaging methods that are based on measures of blood flow, which, for some patient populations may be inappropriate, difficult to interpret, or even misleading.²⁹ 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, than methods that rely on hemodynamic measures. Imaging of brain activation with MEG involves the following steps. Stimuli, whether somatosensory, visual, auditory, or linguistic, 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 event-related fields (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 the lo-

cation and extent of activation of the sets of brain cells that produce them.

ERFs, much like event-related potentials, are waveforms representing variations of brain activity over time, following the onset of an external stimulus. Early portions of the ERF waveform (i.e., up to 150-200 ms 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. It is by estimation of the regions that contribute to systematic variations in late portions of the ERF waveform that delineation of the outline of the brain circuits responsible for cognitive and linguistic functions may be accomplished.

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 spoken English words. The patient's task was to attend to and recognize each word, and determine 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 together. The resulting average ERFs, in all cases, consisted of an early (typically between 30 and 200 ms post-stimulus onset) and a late portion (typically between 200 and 800 ms post-stimulus onset, although task-relevant activity up to 1000 ms 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 ms apart), thereby preserving the temporal information that is inherent in the MEG methodology. The analysis consisted of the application of a mathematical model which considered the intracranial activity sources (sets of active neurons) as equivalent to physical current dipoles embedded in a spherical conductor approximating the local skull curvature³¹ 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 MRI.

The dipolar source(s) that accounted for the average surface distribution of magnetic flux at each 4-ms time window identified the brain areas activated at that time point. The derived activation maps consisted of *clusters* of temporally contiguous activity sources which were typically localized in the same anatomical region. In the context of word recognition tasks, like the one used in the present study, clusters spanned between 20 and 100 ms in duration, although it was not uncommon to observe successive sources in the same region (usually temporo-parietal cortex in the dominant hemisphere) for 400 ms or more. Variability in the number and temporal extent of source clusters can usually be accounted for by (a) patient-specific factors and (b) by technical issues, such as neuromagnetometer sensitivity and overall data signal-to-noise ratio. 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 will be described in more detail in subsequent paragraphs.

In addition to spatial coordinates, the net electrical current, as well as the net magnetic flux, associated with each activity source are computed. However, data from our previous studies indicate 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 computed during the late portion of the ERF waveform. The validity of this estimate is not based on any theoretical considerations, but was empirically derived.^{3,4,22,32,33,35} The concurrent validity of each MEG-derived measure was re-examined in the present study using a much larger patient series than our previous studies.

Stimuli and Tasks. Patients were given a recognition memory task for spoken words and ERFs were recorded to each word stimulus. The word list consisted of 90 abstract English nouns with scores of 3.0 or lower on the Paivio Concreteness scale.²⁵ Word frequency ranged from "very frequent" (AA) to 9 occurrences per million for some words.³⁶ A native speaker of English with a flat intonation produced the stimuli (duration between 300 and 750 ms, mean: 450 ms), which were digitized with a sampling rate of 22,000 Hz and 16-bit resolution, edited (to remove artifacts and ensure a uniform sound envelop) and stored on a portable computer that was also used for stimulus presentation. The stimuli were delivered binaurally via two 5 m-long plastic tubes terminating in ear inserts. Intensity was 80 dB SPL at the patient's outer ear.

Thirty words from each list were used as targets and the remaining 60 as distractors forming six blocks of trials. There were no significant differences between the target and distractor lists in either word concreteness or frequency. The target stimuli were repeated in every block (in a different random order each time), mixed with 10 new distractors. The target stimuli were presented for study once or twice (depending upon the patient's overall verbal memory capacity) immediately prior to the MEG scan. 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 sec). A printed word version of this task was used, in addition to the auditory, in some of the first patients in the series. Use of this task was discontinued early in the course of the study, based on concerns regarding (1) the increased complexity of implementing a second, similar task, in a different modality, (2) the added complexity of data analysis procedures, and (3) problems in the interpretation of results in patients who experience developmental reading disability. Accordingly, only data from the auditory version of this task are 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 4-6 (Session 2).

Patients were asked to lift their index finger whenever they detected a repeated word. The responding hand was counterbalanced across sessions. During the scan the patient was asked to keep his/her eyes open, fixating on a dark dot placed on the ceiling at eye level, in order to reduce eye movements or blinks and prevent ERF contamination by rhythmic activity (typically in the alpha band) which can seriously interfere with the accurate detection of task-related brain activity.

MEG data acquisition and analysis. All patients were tested with 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 helmet-like device for approximately 15 minutes. The signal was filtered online with a band pass between 0.1 and 20 Hz, digitized for 950 ms (254 Hz sampling rate), including a 150 ms pre-stimulus period, and subjected to an adaptive filtering procedure that is part of the 4-D Neuroimaging signal analysis package. These steps are

necessary to minimize the amount of low frequency magnetic noise that is typically present in MEG recordings. The next step involved visual inspection of single-trial ERF segments in order to identify those contaminated by (a) eye- or head-movement related magnetic artifacts, or (b) epileptogenic activity. Movement artifacts were defined as magnetic flux deflections in excess of 3 picoTesla (pT) peak-to-peak in the recordings from magnetometer sensors located over the eyes. As it is possible to mistake small blinks or lateral eye movements with magnetic deflections caused by brain activity, the surface distribution of magnetic flux associated with these deflections was frequently taken into account. ERF 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 sufficient quality to support a clinical judgement of laterality. The following criteria were employed: (1) mean prestimulus Root Mean Square (RMS; an estimate of "noise" or task-independent magnetic flux in the recordings) < 25 femto Tesla (fT), (2) RMS ratio of "signal" (ie., magnetic flux associated with a given computed source) to "noise" (ie., mean magnetic flux during the prestimulus time interval) $> 2:1$, (3) asymmetry in the peak field strength of the N1m (ie., the first major component of the auditory ERF that peaks between 80-120 ms post-stimulus) response $< 25\%$ of the total (i.e. summed across hemispheres) N1m field strength, (4) absence of sharp epileptiform activity in the single epoch data or, if present, incidence of no more than one epileptiform event in $< 20\%$ of the ERF data segments. Data from 15 patients were excluded from further analyses for not meeting one or more of the criteria listed above. Figure 1 presents two examples from that group of patients.

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 ms intervals by using the nonlinear Levenberg-Marquardt algorithm.³¹ For a given point in time, the source fitting algorithm was applied to the magnetic flux measurements obtained from a group of 34-38 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 sur-

face. The algorithm used in this study searched for the source

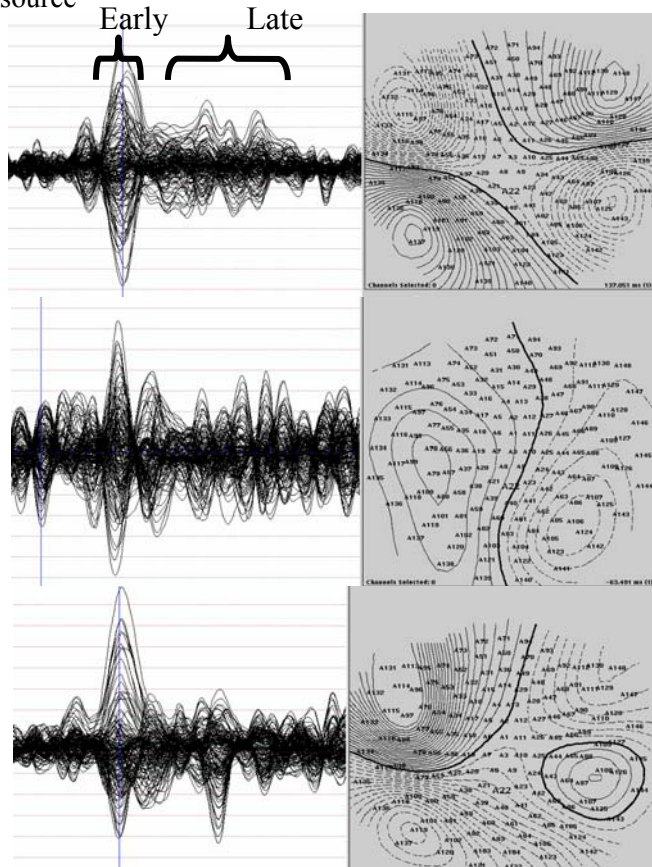


Figure 1. *Upper panel:* Averaged ERF waveforms recorded from the entire set of 148 magnetometer sensors during a typical MEG recording session. The inset displays the isofield contour map of magnetic flux recorded at the peak of the auditory N1m response. Notice the symmetry between the left and right hemisphere maps. *Middle panel:* An example of unacceptable MEG data due to excessive contamination by large amplitude rhythmic background activity (in this case primarily in the alpha band, originating from occipital cortices as the inset indicates). *Lower panel:* An example of data sets not used for clinical judgment due to the presence of a significant lateral asymmetry in the amplitude of the N1m response ($[\text{left N1m RMS} - \text{right N1m RMS}] / \text{Sum}(\text{left, right N1m RMS}) > .3$).

that was most likely to have produced the observed magnetic field distribution at a given point in time. Source solutions were considered 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 (i) the degree of latency overlap and (ii) spatial proximity 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.

In order to determine the anatomical regions corresponding to each activity source, source locations, which were initially computed in reference to the MEG Cartesian coordinate system mentioned above, were co-registered on T1-weighted, magnetic resonance (MR) images (TR 13.6 ms; TE 4.8 ms; recording matrix 256 x 256 pixels, 1 excitation, 240 mm field of view, and 1.4 mm slice thickness) obtained from each participant. Transformation of the MEG coordinate system into MRI-defined space was achieved with the aid of three lipid capsules inserted into the ear canals and attached to the nasion which could be easily visualized on the MRIs, using the MR Overlay tool which is part of the 4-D Neuroimaging software. A standard MRI atlas of the human brain⁶ served as a reference for the identification of the cerebral structures where sources were localized. As in previous studies using the English and Spanish versions of this task,^{3,4,22,27} activity sources were found in frontal and temporal lobe (both mesial and lateral) areas. While all patients presented 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 Wernicke's 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 procedures were left hemisphere dominant for language. Occasionally, activity sources were found in perirolandic areas and were 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: (a) location (i.e., spatial coordinates on the MEG Cartesian coordinate system defined by the ear canals and the nasion), (b) estimated current moment of the net neuronal population response (in nanoAmpere-meters - nA.m), (c) global field power (RMS) of the measured magnetic flux used to calculate each activity source (in femtoTesla - fT), and (d) latency or delay after stimulus onset at which point a given source is estimated (in milliseconds - ms). In our previous studies with healthy volunteers and patients, the method that produced the most conclusive re-

sults 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. However, the potential utility of information regarding the strength of *each* activity source (both with respect to 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 blind to the Wada results made a judgment as to cerebral dominance for language based on the MEG 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 (i.e., $> \sim 200$ ms),

(2) Determining the number of automatically clustered activity sources in "perisylvian" regions for each hemisphere and testing session separately (see above 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 the corresponding number on the left. Index values between -0.1 and 0.1 were considered as indicative of bilaterally symmetric activation, whereas values >0.1 or <-0.1 as indicative of 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 Wernicke's area, defined as the cortical area which, when electrically stimulated (in the context of extra- or intra-operative mapping) results in receptive language deficits.^{32,33}

Results

Figure 2 contains MEG - MRI co-registered scans for three representative patients showing: (a) predominantly left hemisphere activity, (b) bilateral activity and, (c) predominantly right hemisphere activity during the word recognition tasks. These patients showed similar interhemispheric asymmetries in language function during the Wada procedure, and were judged to be left, bilateral, and right hemisphere lateralized for language, respectively, on the basis of both procedures. Similar

co-registered scans were obtained for all patients in this study and judgments were made as to hemispheric dominance for language as described above. The estimated location of receptive-language specific cortex in the same patients is shown in Figure 2 as well.

Concordance between MEG and Wada hemisphere dominance judgments. 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 using each test. The MEG and Wada procedures exhibited complete agreement in 74 out of 85 (87%) of the cases (Fisher's exact test, $p < .0001$). There were 11 discordant cases. In the majority of these patients ($n=7$) MEG detected considerable activity in both hemispheres, although the Wada suggested left hemisphere dominance. In 4/7 of these patients the epileptogenic zone was in the right hemisphere, and it is possible that the degree of neurophysiological activity detected and successfully modelled from that hemisphere was inflated by the presence of focal epileptiform activity that was not initially detected and therefore not rejected at the single-epoch level.

Table 2. Comparison of judgments of hemispheric dominance for language by the Wada and MEG procedures.

		Wada		
		Left	Bilateral	Right
MEG	Left	57	2	0
	Bilateral	7	15	1
	Right	0	1	2

Further analyses indicated no significant relationship between the probability of discordant judgment and the hemisphere (binomial test $p > .17$) or location of seizure onset (temporal vs. extratemporal; binomial test, $p < .75$), seizure etiology (lesional vs. cryptogenic; binomial test, $p > .3$), handedness (binomial test, $p > .4$), and left ($p > .4$) or right ($p > .7$) hemisphere amobarbital dosage during the Wada procedure.

Clinical utility of language judgments made using the MEG procedure. One aspect of the Wada procedure is its use to determine whether invasive mapping and/or a

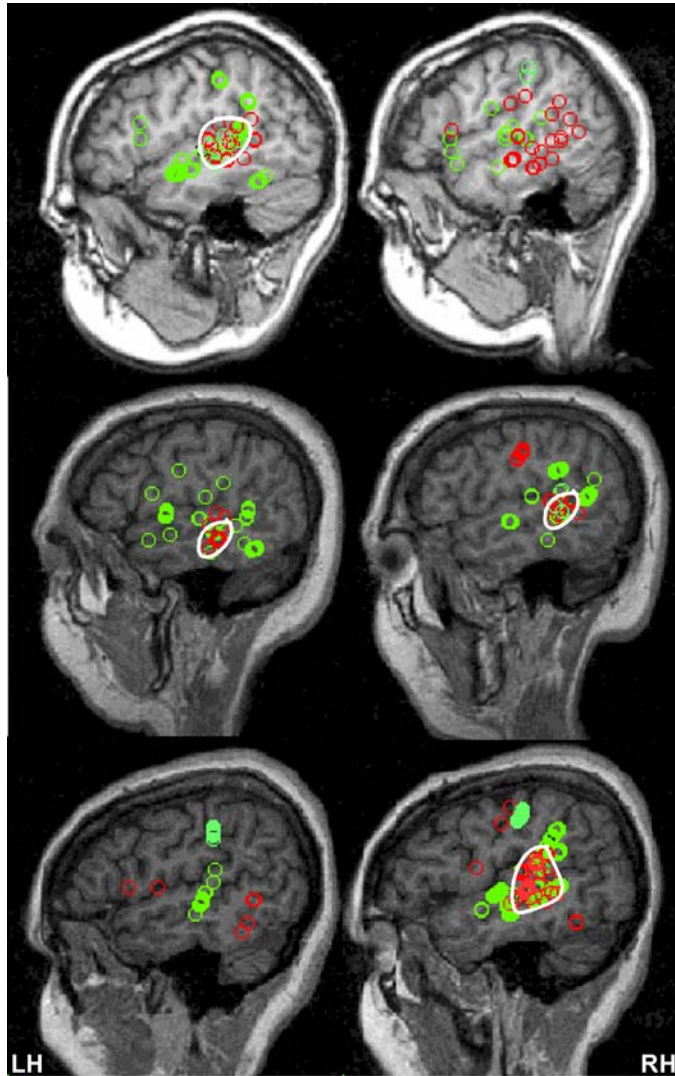


Figure 2. Typical activation profiles from a patient with left (upper panel) or right hemisphere dominance (lower panel), or bihemispheric representation of language function (middle panel). Activity sources found in the left hemisphere are shown on the left and those computed in the right hemisphere are shown on the right hand side of the figure. Each activation profile represents sources computed after the initial sensory activation (> 200 ms post-stimulus onset) and were actually localized within 1.5 cm from the sagittal slice selected for display. Activity sources obtained during the first half of the activation trials are shown as green circles, whereas corresponding sources obtained during the second half are shown as red circles. The region of spatial overlap between the two maps within a given hemisphere (lateral projection) is marked by a white circle. This region has been shown in previous studies to correspond with the receptive language-specific cortex in patients who, in addition to the Wada procedure, underwent electrocortical stimulation mapping within the dominant hemisphere.³²⁻³³

tailored surgical approach are required in order to avoid impinging on suspected eloquent cortex. Therefore, the test of the clinical utility of the MEG procedure is the extent to which it is able to detect the presence of language function in the hemisphere where the operation is to take place. The concordance of the MEG and Wada procedures regarding the potential presence of eloquent cortex in the hemisphere of seizure onset is presented in Table 3. As can be seen, the MEG and Wada procedures disagree regarding the potential presence of eloquent cortex in the hemisphere of operation in only six cases. In 5 of these cases MEG indicated the presence of language representation while Wada suggested 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 indicates eloquent cortex is present it actually is) and negative predictive value (probability that when MEG indicates eloquent cortex is absent it actually is absent) are also presented in Table 3. These statistics are all relative to the Wada procedure, considered here as the “gold standard”. As can be seen, the MEG judgments show excellent sensitivity, positive and negative predictive value, and very good specificity.

Table 3. Comparison of determinations of whether language is present in the hemisphere to be operated on by the Wada and MEG procedures

		Wada		
		Language Present	Language Absent	
MEG	Language Present	54	5	Positive Predictive Value = .91
	Language Absent	1	25	Negative Predictive Value = .96
		Sensitivity = Specificity =		
		.98 .83		

Clinical utility of alternative measures of language-specific activity. In a separate set of analyses we examined the relationship between language dominance determined with the Wada test and hemispheric asymmetries in the degree of neurophysiological activity in pos-

terior language areas, indexed by two complementary measures: the peak global field power (RMS) and the peak current moment (Q). RMS and Q values were extracted from the set of sources that were selected by the automatic clustering program, described above. The derived cluster of sources included those that occurred in the same anatomical region (with a 1-cm tolerance radius) in close temporal proximity (<100 ms) in both MEG recording sessions. A third measure, onset latency of each cluster after stimulus onset, was also examined. Hemispheric asymmetries in the onset latency of activity in this region were also assessed. An ANOVA with Hemisphere as a repeated measures factor and Hemisphere Dominance Group (left or bihemispheric representation--given the small number of patients with right hemisphere dominance in the present sample) was performed on each of the three measures. Main effects of Hemisphere were found for onset latency, $F(1,80) = 4.03$, $p < .048$, and peak RMS, $F(1,80) = 6.20$, $p < .015$, indicating that regardless of hemispheric dominance, reliable activity in the vicinity of Wernicke's area occurred earlier, and was associated with greater magnetic flux, than in the homotopic right hemisphere region. A non-significant trend in the same direction was found for Q ($p > .15$).

Similar ANOVAs were performed on the RMS of 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 were no main effects or interactions, corroborating previous results from healthy volunteers that hemispheric asymmetries observed 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 the Wada procedure were 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 were no cases where MEG and Wada judgments regarding hemispheric dominance for language were diametrically opposed. In addition, in only one case did Wada results suggest that the potential presence of eloquent cortex in the hemisphere to be operated upon would have been ignored using MEG. Consistent with these observations, measures of the clinical utility of MEG for detection of language-specific cortex in the hemisphere of seizure

onset, using the Wada procedure results as the gold standard, indicated excellent sensitivity, positive predictive value and negative predictive value.

While specificity of the MEG procedure was very good, when the MEG and Wada judgments were discordant, the MEG procedure, for the most part, tended to indicate the possibility of bilateral representation where the Wada procedure suggested unilateral representation. Therefore, the MEG procedure was more likely to produce a positive result than the Wada procedure. This finding is not completely unexpected, as functional brain imaging studies using a variety of imaging methods consistently detect bilateral activation in neurologically intact control subjects on an individual basis during the performance of language tasks, even when the activity is predominant in one of the two hemispheres.² In contrast, a large number ($n=43$) of patients in the current study showed no behavioral effect of injection of anesthetic into the right internal carotid artery during the Wada procedure, a finding that was not explained by abnormal vascularization or amobarbital dosage. Another issue that is relevant to the comparison of the results of the Wada procedure with the results of the MEG protocol described in this report, is that while the former incorporated tests of both expressive and receptive language function, 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 to reliably record and model brain activity associated with 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,^{1,12,17} and are expected to complement existing protocols to further increase the selectivity of MEG-derived estimates of hemispheric dominance for language function.

Accumulating experience from over 240 patients and 100 normal control subjects who have undergone pre-surgical language mapping 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 a hemispheric asymmetry index based only on activity sources in perisylvian language areas that occur with a high degree of spatial and temporal consistency over two consecutive MEG sessions. In our studies we have repeatedly observed that

only a subset of the activity sources that are localized in 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.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 results in severe disruption of the patient's ability to perceive and understand spoken utterances.

While MEG appears to be an acceptable substitute for the Wada for the purposes of determining whether language is present in the hemisphere where an operation is to occur, the Wada procedure is also 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 increased risk for developing an amnesic disorder³⁴ post-operatively. These individuals may therefore be refused operation. In addition, despite the inconsistent effects of the anesthetic on mesial temporal structures during the Wada procedure, Wada performance has been shown to correlate with outcome¹⁸ and is used as an adjunct to electrophysiological and imaging modalities in determining the side of seizure onset in a number of centers.³⁰ Thus, in cases where memory is not an issue (e.g. extratemporal surgery) MEG may substitute for the Wada procedure. Preliminary MEG studies have been successful in mapping neurophysiological activity in temporal lobe structures known to be critical for memory function in normal volunteers.²⁸ The utility of such information for determining hemispheric dominance for memory function in epilepsy surgery candidates 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.

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Conclusion

In view of the results, the conclusion appears inescapable that MEG, used in the manner detailed in the methods section of this report, could serve as a substitute for the Wada procedure for the purposes of preoperative surgical planning when surgery may potentially impinge language-specific cortex. While the functional significance of bilateral MEG activation is as yet not clear, the practical consequences of the discordant judgments would have been limited to invasive mapping and/or tailoring of surgery for four patients, representing 4% of the cohort, and no language mapping for one patient where it might have been necessary. Thus MEG may provide a modestly more conservative test for the presence of language function in the hemisphere of operation, as compared with the Wada procedure.

In addition to being completely non-invasive with no physical risk and minimal discomfort, as well as relatively fast (approximately ½ hour of testing), the MEG procedure has the distinct advantage of providing accurate data regarding the location of receptive and expressive language cortex.^{5,32,33} It should be noted that the availability of MEG is still quite limited, even in countries with well-organized epilepsy surgery programs (including the United States), posing some questions regarding the generalizability of MEG-based presurgical mapping. On the other hand, the MEG test can easily be repeated to ensure optimal patient cooperation. In cases where surgical 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 maps as a guide, or even avoided altogether when there is deemed to be a large enough distance between MEG maps and the areas to be affected by surgery. Since MEG is quite sensitive to atypical topographic representation of language function,^{26,33} in the event that unusual or multiple locations are detected, invasive mapping and/or surgery can be appropriately tailored to avoid post-operative functional deficits.

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Appendix: Activity Source Clustering Program

Bounding Box

A pair of boxes is created outside of which activity sources are rejected. The two boxes are defined by 7 variables

xmin: the minimum acceptable value for x, typically -6 cm

xmax: the maximum acceptable value for x, typically 6 cm

ymin: the minimum acceptable value for y, typically -9 cm

ymax: the maximum acceptable value for y, typically 9 cm

zmin: the minimum acceptable value for z, typically 2 cm

zmax: the maximum acceptable value for z, typically 8 cm

yexclude: the distance from y=0 plane to exclude, typically 2 cm

A minimum acceptable correlation, **mincor**, is defined, typically 90%. All activity sources with correlations less than **mincor** are rejected.

Keeping only the best activity sources.

The remaining activity sources are then ranked based on three criteria: i) the number of activity sources nearby in space, ii) the number of activity sources nearby in time, iii) whether the activity source location is repeated in the test/re-test data sets. Finally, only the highest ranked activity sources are kept.

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

$$R_i = \sum_{j, j \neq i} S_{ij} * T_{ij} * [(W - 1)\delta_{ij}^{dataset} + 1],$$

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, $\delta_{ij}^{dataset}$ is 1 when the activity sources are from the same data set and 0 when they are from different data sets, and $[(W - 1)\delta_{ij}^{dataset} + 1]$ 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%.

Ranking for number of activity sources nearby in space.

This is done using a Gaussian weighting factor calculated as follows.

$S_{ij} = e^{-\left(\frac{d^2}{2\sigma_d^2}\right)}$ where d is the distance between activity sources i and j , and σ_d is input and sets the scale for the falloff of the ranking value. σ_d is input as '**dist**' and is typically 1 cm.

Ranking for number of activity sources nearby in time.

This is done using a Gaussian weighting factor calculated as follows.

$T_{ij} = e^{-\left(\frac{t^2}{2\sigma_t^2}\right)}$ where t is the time difference between activity sources i and j , and σ_t is input and sets the scale for the falloff of the ranking value. σ_t is input as '**time**' and is typically is 50 msec.

Portion of activity sources to keep.

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