Neurosurgical Focus™

Magnetoencephalographic mapping of the language-specific cortex

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Object. In this paper the authors introduce a novel use of magnetoencephalography (MEG) for noninvasive mapping of language-specific cortex in individual patients and in healthy volunteers.

Methods. The authors describe a series of six experiments in which normative MEG data were collected and the reliability, validity, and topographical accuracy of the data were assessed in patients who had also undergone the Wada procedure or language mapping through intraoperative cortical stimulation.

Conclusions. Findings include: 1) receptive language-specific areas can be reliably activated by simple language tasks and this activation can be readily recorded in short MEG sessions; 2) MEG-derived maps of each individual are reliable because they remain stable over time and are independent of whether auditory or visual stimuli are used to activate the brain; and 3) these maps are also valid because they concur with results of the Wada procedure in assessing hemispheric dominance for language and with the results of cortical stimulation in identifying the precise topography of receptive language regions within the dominant hemisphere.

Although the MEG mapping technique should be further refined, it has been shown to be efficacious by correctly identifying the language-dominant hemisphere and specific language-related regions within this hemisphere. Further development of the technique may render it a valuable adjunct for routine presurgical planning in many patients who harbor tumors or have epilepsy.

Key Words * magnetoencephalography * brain mapping * speech

In this paper, we outline the development of noninvasive procedures for mapping the receptive language cortex by using magnetoencephalography (MEG). Specifically, we describe a series of four experiments involving normal healthy volunteers and two additional studies involving neurosurgical patients, the purpose of which was to establish the reliability and validity of estimates of hemispheric dominance and of the locus and extent of language-specific cortex.

Magnetoencephalography is a completely noninvasive method of functional brain imaging that is akin to quantitative electroencephalography and complementary to other functional imaging methods such as functional magnetic resonance (MR) imaging or positron emission tomography scanning. Magnetoencephalography consists of: 1) recording, on the surface of the head, the magnetic flux associated with electrical currents in activated sets of neurons; 2) estimating the location of such sets (also referred to as "activity sources"); and 3) projecting them onto structural images of the brain (such as MR images), which allows for identification and visualization of the activated brain regions.[7,15]

Magnetoencephalography has undergone a rapid evolution during the past two decades and, especially when high temporal resolution is desired, has emerged as the method of choice for mapping the primary sensory cortex,[11,20,23,27,30] as well as the association cortex activated in the context of cognitive tasks.[14,21,24] Recently, the method has been approved by the United States Food and Drug Administration for clinical studies; it is used for identifying epileptogenic zones in the brain of patients with epilepsy[2,3] as well as for presurgical mapping of the somatosensory cortex.[4,5,9,17,26,29]

Among the issues that MEG could eventually address, identification of brain regions mediating language has always been most urgently sought because of its obvious practical implications. Advance knowledge of language-specific zones can facilitate surgical planning and reduce the risks of morbidity associated with resection of eloquent cortex, especially in cases of epilepsy surgery. Such knowledge is currently sought through invasive means such as the Wada procedure[8,28] and direct cortical stimulation, either intraoperatively or extraoperatively, via implanted electrodes or subdural electrode grids.[6,12]

As we will demonstrate in this paper, it now appears possible to acquire such information completely noninvasively and quite readily through MEG. Stimuli, verbal or otherwise, are known to evoke brain activity soon after they impinge on sensory receptors. One basic aspect of such activity is the intra- and extracellular flow of ions that generates electrical currents and magnetic fields. Repetitive application of the stimulus results in repeated evocation of the same currents and fields that, when recorded on the head surface and averaged, result in the well-known evoked potentials and their magnetic counterparts, the evoked fields (EFs). The distribution of EFs on the head surface lends itself, much more readily than the distribution of evoked potentials, to mathematical estimates of the location and extent of activation of the sets of brain cells that produce them.

Evoked fields, much like evoked potentials, are waveforms that represent variations in brain activity over time, following stimulus presentation. Some variations are consistent and specific to particular types of stimuli and are referred to as components. There are two basic types of components: early ones that have been shown to reflect activation of the primary sensory cortex[10,13,16,23,30] and late ones that reflect activation of the association cortex.[18,19,21,24] It is on the basis of these latter components that delineation of language-specific brain regions is accomplished.

CLINICAL MATERIAL AND METHODS

The protocols of all experiments outlined in this report were approved by the University of Texas Institutional Review Board. All volunteers and patients were asked to sign a consent form before participating in each study, after the nature of the procedures involved had been explained.

All MEG recordings were made using a multichannel neuromagnetometer consisting of 148 magnetometers arranged so that they cover the entire head. The instrument is housed in a magnetically shielded chamber designed for reducing environmental magnetic noise that interferes with the recordings of physiological signals. Healthy volunteers remain immobile while lying on a bed with their heads inside a helmetlike container of magnetometers. The recording session does not exceed 10 minutes and, thus, repeated measurements for the purpose of establishing the reliability of the results are feasible.

During the recording sessions, healthy volunteers or patients were exposed to a series of stimuli (verbal or nonverbal) delivered in the visual or auditory modality. The task of the volunteers and patients in all the studies described here was to attend to each stimulus in the series and indicate, by slightly moving their index finger, whether the stimulus (a word, tone, or picture of a face, depending on the particular experiment) had been presented earlier within the same series. Stimuli in a series were presented at a rate of one every 3 to 4 seconds. The duration of stimuli presentation varied according to the type and modality of the stimulation; orally presented words and auditory tones had an average duration of 460 msec, whereas visually presented words and faces were shown for 1000 msec. In all cases the duration was more than sufficient for the stimuli to be easily perceived even by patients with cognitive deficits.

Visual presentation of stimuli was accomplished using a projection system that was located outside the shielded chamber. The system projected the images through a small aperture onto a mirror inside the chamber, which, in turn, projected the images onto the chamber's ceiling, in the volunteers'/patients' direct line of vision at a distance of 1.5 m. The stimuli subtended a horizontal visual angle of 1 to 3š for word stimuli and 2š for the face stimuli on the retina. Corresponding vertical visual angle values were 0.5š and 3š, respectively. Thus, to view the entire stimulus, no scanning eye movements were necessary.

Auditory presentation of stimuli was controlled by a computer placed outside the chamber and delivered through 5-m-long plastic tubes, 5 mm in diameter, terminating in ear inserts. Stimulus amplitude was adjusted to an approximate 80-dB sound pressure level at the volunteers' or patients' ears.

Each individual stimulus in a particular series (visual, auditory, verbal, or nonverbal) produced an EF. Those EFs that were evoked by target stimuli (that is, stimuli identified as having occurred previously during the session) were averaged together after the end of the recording session. In all cases, the resulting average EFs consisted of early (30-150 msec poststimulus) and late (150-700 msec poststimulus) components. To identify the intracranial origin of the latter, we analyzed the magnetic field distribution, which had been recorded simultaneously over the entire head surface at successive points (4 msec apart) during the evolution of each component and which represented the amplitude of the component at each successive time point. The analysis consisted of application of a mathematical model in which intracranial activity sources (sets of active cells) are considered equivalent to physical current dipoles.[13,22] The mathematical model was intended to provide estimates of the location and strength of these sources, the activity of which produced the recorded magnetic fields at each point in time.

The location estimates of each "dipolar" source were specified with reference to a cartesian coordinate system anchored to 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 superimposition of the precise location of each dipolar source on the volunteers'/patients' MR images. Thus, the dipolar sources that accounted for a particular EF component identified the brain areas that were activated during that time interval in response to the stimulus. The degree of activation of a particular area (or the total duration of its activation) was estimated by the total number of successive dipoles that accounted for the EF components. The validity of this estimate was not based on any theoretical considerations, but was empirically derived. Namely, among all other possible indices of the degree of activation of an area (such as mean or median amperage of all dipolar sources), the number of sources was the one that resulted in the most consistent mapping results.

Successful mapping of language-specific cortex or, for that matter, cortex specialized for any cognitive function can be defined as the match between prior knowledge about the functional specialization of the brain and the MEG-derived maps. Specifically, in the case of receptive language, two aspects of functional specialization are beyond dispute: the overwhelming majority of people are left-hemisphere dominant; and the receptive language mechanism involves the posterior temporal and parietal cortex (Wernicke's area). Consequently, MEG mapping could only be considered successful if it showed clearly greater activation of the left hemisphere, concentrated in Wernicke's area, in virtually all healthy volunteers during verbal, but not nonverbal, tasks. For that to transpire, however, each of the several assumptions underlying the MEG procedure we used must be correct, namely: 1) the task of identifying which words in a list were previously presented can activate the receptive language-specific cortex; 2) language-specific activation is reflected in the late components of the EFs to the target words; 3) the mathematical model for estimating the sources of those components (that is, identifying the activated brain areas) is sufficiently valid; and 4) the number of sources thus identified is a valid index of the degree of activation of a particular brain area. If any of these four basic assumptions is invalid, the probability of deriving accurate and valid maps through MEG is incredibly slight. However, as it happened, reliable and valid maps were obtained in all six studies described below.

The first four experiments involved healthy volunteers. The experiments were conducted for the purpose of verifying the four aforementioned assumptions and, consequently, for developing the basic MEG mapping procedure and establishing its reliability. Following these four experiments, two studies were conducted in patients. The purpose of the first patient study was to assess the validity of MEG maps for individual patients insofar as they reveal hemispheric dominance for language, by comparing them with the results of the Wada procedure. The purpose of the second patient study was to assess the validity of precise localization of the MEG maps by comparing them with the results of intra- and extraoperative mapping using direct cortical stimulation. Although the same method (outlined earlier) was used in all six studies, there were procedural peculiarities specific to each. These, as well as the particular aims of each study, will be briefly described in Results.

Sources of Supplies and Equipment

We used the Magnes 2500 WH neuromagnetometer, which we purchased from Biomagnetic Technologies, Inc. (San Diego, CA), to make the MEG recordings. For auditory presentation of stimulation, we used Promold ear inserts, obtained from International Aquatic Trades, Inc. (Santa Cruz, CA) and controlled the stimulus presentation by using a Macintosh Powerbook 5300 computer from Apple Computers, Inc. (Cupertino, CA). Electrical stimulation was performed using a stimulator (model 13) provided by Grass Instruments (West Warwick, RI). The stereotactic Surgical Microscope Navigator system (model OPMI"ES), provided by Carl Zeiss, Inc. (Thornwood, NY), was used to locate the site of effective electrical stimulation on MR images.

RESULTS

Experiment 1

The specific aims of the first experiment were to verify that: 1) early components of EFs to visually presented words are due to activation of the primary visual cortex,[23] and those in response to the same words presented orally are due to activation of the primary auditory cortex;[10,13,30] and 2) the degree of activation resulting in the early EF components is bilaterally symmetrical, whereas late EF components associated with either orally or visually presented words reflect predominantly left hemisphere activation involving the posterior temporal and parietal cortex.

Seven right-handed adults (two men and five women with an age range of 26-40 years) participated in this experiment. All reached near-perfect performance in the task of identifying target words during both conditions. Moreover, in all seven, the sources of early (< 150 msec poststimulus) components of visual EFs were localized in the occipital cortex and those of the auditory EFs on the floor of the sylvian fissure, bilaterally. In addition, in all volunteers, the late components of EFs in response to both orally and visually presented words involved approximately twice as much activation in the left than in the right hemisphere (approximately twice as many dipolar sources, $p < 0.0001$), confirming the expectation of left hemisphere dominance for language. Moreover, in all volunteers, language-specific activation involved largely overlapping brain regions. These results are summarized in Fig. 1.

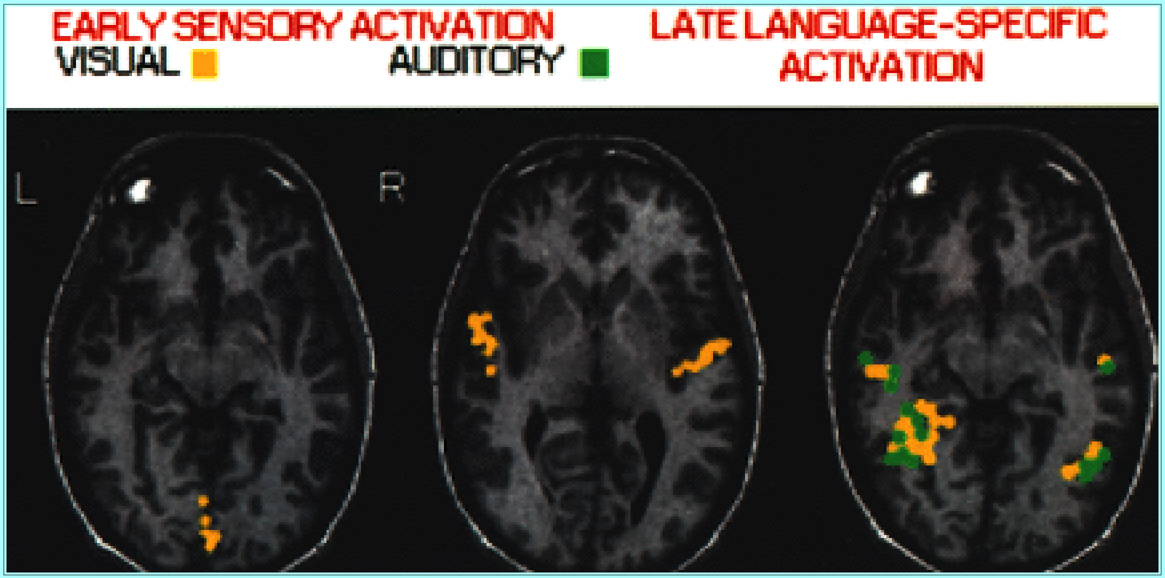

Fig. 1. Magnetoencephalography-derived maps obtained in a healthy volunteer. Activation sources extending over the width of 1 cm are projected onto the same transverse image. Left and Center: Cortical maps defined by the sources of the early EF components involving the visual (left) and auditory primary (center) projection areas. Right: Cortical map defined by the late or language-specific EF components involving the posterior temporal region. Note the clear overlap of maps derived from the auditory (green) and visual (yellow) presentation of the same words. Note also that, unlike the bilaterally symmetrical activation of the sensory cortex (left and center), the degree of activation in the left hemisphere is at least double that in the right, indicating left hemisphere dominance for language (right). With the exception of some topographic peculiarities specific to each individual, the same pattern of activation depicted here characterized the maps of all volunteers.

Experiments 2 and 3

The aim of the second and third experiments was to replicate Experiment 1 and to control for the possibility that hemispheric asymmetry in the degree of activation that accounts for the late EF components is not language specific but, instead, a peculiar feature of all late EF components.

Experiment 2 was performed with 15 right-handed normal volunteers (six men and nine women with an age range of 26-44 years). They performed the auditory word identification task and an identical tone identification task involving complex tone stimuli. All volunteers performed both tasks without difficulty. The results of this experiment are summarized in Fig. 2.

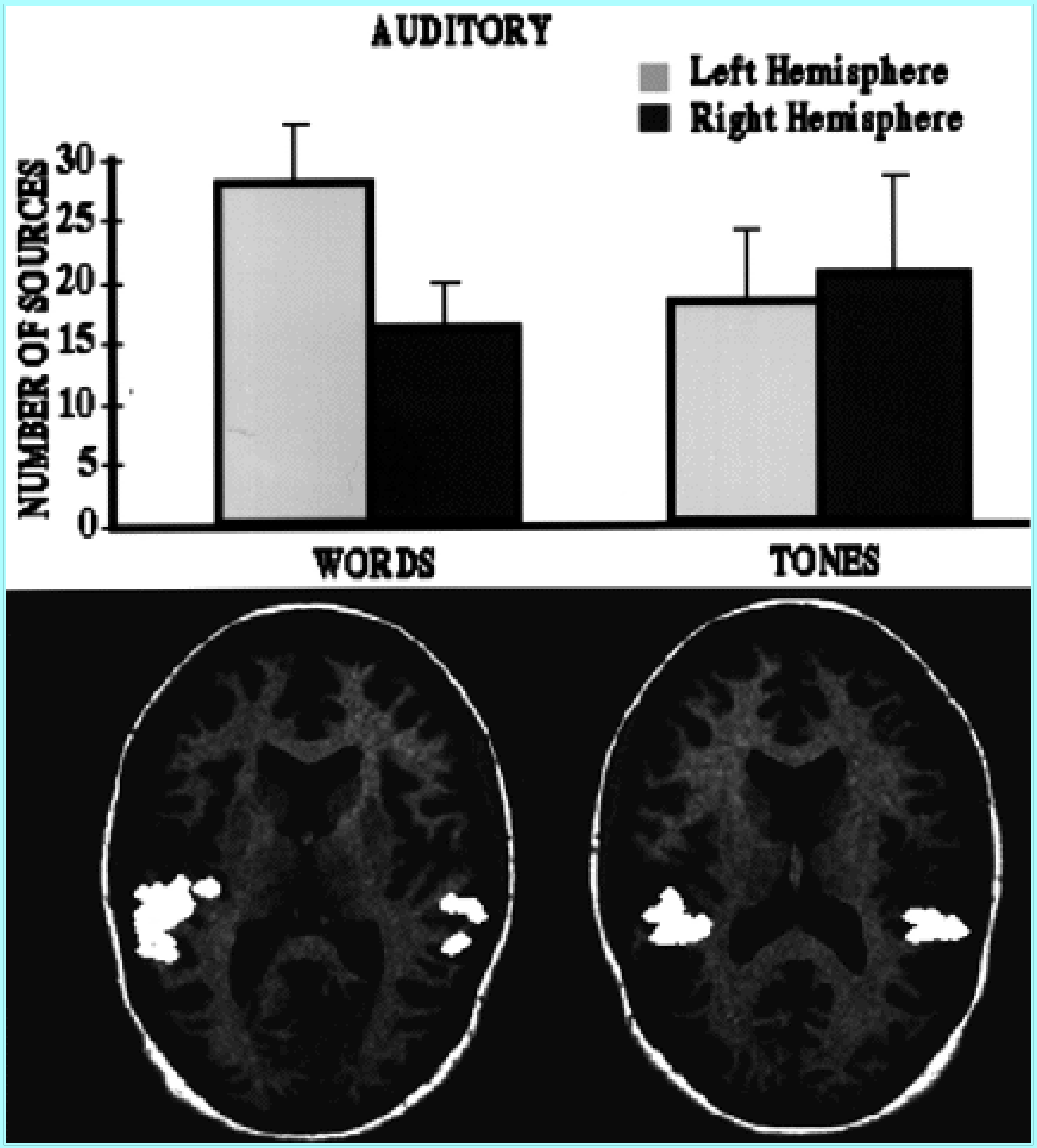

Fig. 2. Upper: Bar graph depicting the mean number of sources of the late EF components in response to words and tones for all volunteers (bars represent standard error of the mean). A clear hemispheric asymmetry in the degree of activation during the linguistic task was found, as expected, whereas no such asymmetries were found during the control tone-identification task. Lower: Magnetoencephalography-derived maps obtained in a healthy volunteer showing asymmetry of activation during the language task (left) and symmetry of activation during the nonlinguistic tone task (right), characteristic of the activation patterns of the entire group of volunteers.

Once again, approximately twice as many sources of late EFs were found in the left hemisphere compared with the right during the word identification task ($p < 0.001$) and equal numbers of sources (on the average) in both hemispheres during the tone identification task ($p > 0.05$). Clearly, the hemispheric asymmetries in activation appear to be language specific. In this experiment, 13 of the 15 volunteers showed this effect.

The areas activated during the language task were identical to those in Experiment 1. Activity sources were invariably found in the posterior lateral aspect of the temporal lobe, accompanied in most cases by sources in the supramarginal gyrus. Frequently, activity was observed in medial temporal regions and, occasionally, in the angular gyrus as well. The areas activated during the tone identification task were typically restricted to the superior lateral aspect of both temporal lobes. The early EF components in response to both tones and words were, once again, accounted for by sources on the floor of the sylvian fissure, thus replicating, in that respect, the first experiment. These results were also in agreement with previous findings from our laboratory in which an auditory semantic matching task for words was used.[25]

The third experiment involved a subset of 11 volunteers (five men and six women with an age range of 25-40 years) who performed the visual word identification task and a control task of identifying pictures of human faces. The sources of the early components of EFs in response to words and faces were indistinguishable, both involving the visual cortex as in Experiment 1. In contrast, the sources of the late EF components clearly differentiated between tasks. The results of that experiment are summarized in Fig. 3.

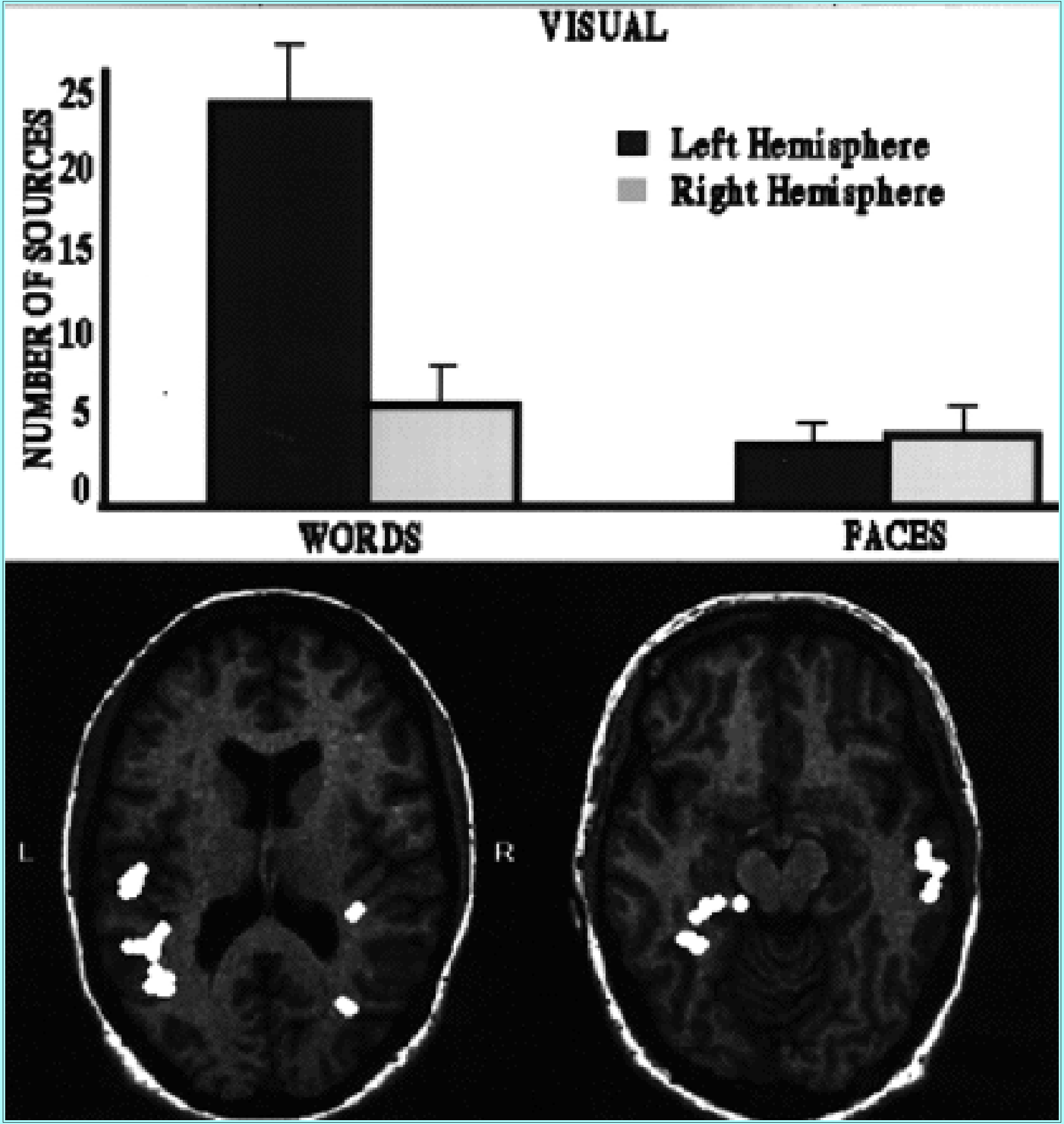

Fig. 3. Upper: Bar graph depicting the mean number of language-specific and face recognition-specific activity sources (bars represent standard error of the mean). Note the

expected left hemisphere dominance for the former and bilaterally symmetrical activation for the latter. Lower: Magnetoencephalography-derived maps obtained in a healthy volunteer representing the typical activation pattern for the word- and face-identification tasks.

As in Experiment 1, approximately twice as many sources were found in the left hemisphere compared with the right in 10 of the 11 volunteers ($p < 0.001$) during the word identification task, whereas the face identification task was characterized by bilaterally symmetrical hemispheric activation ($p > 0.05$). Moreover, the areas activated during the verbal task matched those found in the previous two experiments, whereas the pattern of activation during the face identification task involved areas located in the posterior ventral aspect of the temporal lobe and in the occipital lobe. Thus, it appears that: 1) hemispheric asymmetries in activation revealed by MEG are language specific; 2) such asymmetries are in the predicted direction (left hemisphere dominance); 3) to a great extent, the language-specific areas overlap independently of stimulus modality; and 4) these areas involve those known to subserve receptive language.

The three experiments considered together demonstrate the reliability and validity of the MEG maps (and the mapping procedures) for groups of healthy volunteers. A fourth experiment was undertaken to establish the reliability of the MEG maps at the level of individual volunteers in the sense of their stability over time.

Experiment 4

The visual word identification task was given to 16 volunteers (five men and 11 women with an age range of 23-42 years) on two occasions, separated by a 1-hour interval. The stability of the maps both in degree of relative hemispheric activation and locus of activation is shown in Fig. 4.

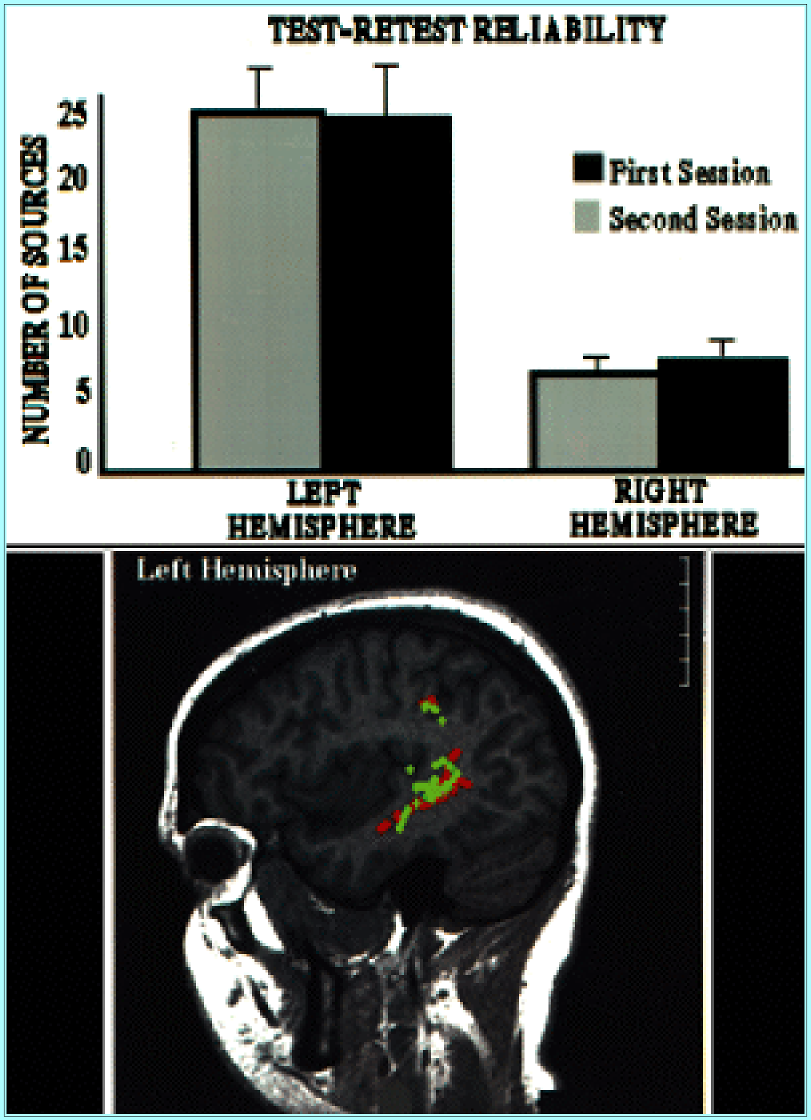

Fig. 4. Upper: Bar graph showing the mean number of sources that remained essentially identical in each hemisphere during the two mapping sessions. This demonstrates the reliability of cortical language-specific maps. Lower: Sagittal image obtained in one representative volunteer showing the replicability of the topographic detail of the language-specific maps from the first session (green) to the second (red).

On average, the number of late EF sources in the left hemisphere was nearly identical for the two replications (25.7 and 25.6, respectively, $p < 0.05$); this was also true, albeit to a lesser extent, in the right hemisphere. In all 16 volunteers there was a clear asymmetry in the degree of activation favoring the left hemisphere. The direction of hemispheric asymmetries in activation was replicated in the second session in all 16 cases. Moreover, the distribution of activation was essentially identical, with minor variations, between the first and second replication in 15 of the 16 volunteers.

This experiment concluded our series of normative studies undertaken to establish the reliability of the procedure and its validity (the latter defined as the degree of concordance between the MEG-derived maps and expectations based on prior knowledge of the functional brain organization for language). However, for this procedure to be used confidently for presurgical mapping of the language-specific cortex, it was necessary to demonstrate first that its predictions of hemispheric dominance and the specific locus of the language-specific cortex accord with those made by standard procedures that are currently used with confidence and are considered as "gold standards," namely, the Wada procedure and direct cortical stimulation. A fifth experiment was performed to ascertain the degree of concordance between MEG and Wada testing with respect to assessment of the hemispheric dominance of language in individual patients A sixth experiment was performed to ascertain the degree of concordance between MEG and direct cortical stimulation procedures.

Experiment 5

Twelve consecutive candidates for epilepsy surgery (eight men and four women with an age range of 24-41 years) who had undergone Wada testing were evaluated. For three patients who were dyslexic we used the auditory version of the word identification task and for the rest of the patients we used the visual version. On the basis of the number of cortical sources that accounted for the late EF components, two patients were identified as right-hemisphere dominant for language (approximately twice as many sources in the right hemisphere than in the left), nine patients were identified as left-hemisphere dominant (approximately twice as many sources in the left hemisphere than in the right), and one patient was identified as having bilateral language representation (essentially equal numbers of sources in both hemispheres). With the exception of one of the two right hemisphere-dominant patients who was left handed, all others were right handed.

Hemispheric dominance for language in the same patients was determined independently during the Wada procedure. To assess laterality for language during this procedure, patients were given tests of reading, naming, repetition, and comprehension (in the form of a modified token test) after intracarotid amobarbital injection.[1] Performance on each of these tests was rated on a four-point scale (unimpaired, mildly impaired, moderately impaired, and severely impaired). Language representation in the hemisphere ipsilateral to the side of injection was inferred if performance was at least mildly impaired on two tests with performance on another at least moderately impaired. Language representation in the hemisphere contralateral to the side of the injection was inferred if performance was no worse than mildly impaired on at least three of the four tests.

The degree of concordance between MEG and Wada testing for this patient sample was perfect, as is shown in Table 1.

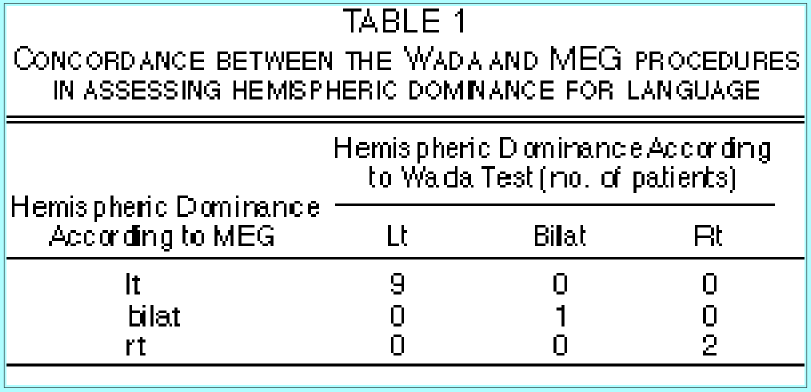

TABLE 1

Concordance between the Wada and MEG procedures in assessing hemispheric dominance for language

Hemispheric Dominance According to MEG	Hemispheric Dominance According to Wada Test (no. of patients)		
	Lt	Bilat	Rt
lt	9	0	0
bilat	0	1	0
rt	0	0	2

Experiment 6

A smaller series of four patients, all of whom were surgical candidates, have thus far participated in this study. Three of the patients underwent electrical stimulation of the cortex intraoperatively and one extraoperatively through implanted electrode grids. Patients in the former group included two men aged 68 and 21 years, respectively, and one woman aged 28 years. Magnetic resonance imaging performed in the first patient had indicated a probable glioma in the left posterior temporal region; MR imaging performed in the second patient had shown a large cystic mass in the left temporal lobe. The MR imaging findings in the third patient suggested the presence of a cavernous angioma in the left temporoparietal junction near the posterior horn of the lateral ventricle. The MEG-derived receptive language maps for these patients were coregistered with their structural MR images. Intraoperative language mapping was performed by applying cortical stimulation during the presentation of a short phrase or question. Interruption of receptive language was inferred when the patient experienced difficulty with repeating phrases or correctly responding to questions (for example, Do ponies shave?) after cessation of stimulation. Results were verified by repetition and presentation of material without stimulation to rule out after discharge or obtundation. Cortical stimulation was applied using a four-contact subdural strip that consisted of platinum disk electrodes which were 1 cm in diameter,and embedded in a silastic sheath. Of the set of four, a pair of adjacent electrodes were connected to the output terminals of a stimulator and placed on the exposed cortical surface at locations selected in sequence to evaluate the regions around the lesion. The stimulation current was varied at each stimulation site from 8.5 to 17.5 mA in a stepwise fashion. Disruption of language occurred at specific cortical regions, as shown in Fig. 5.

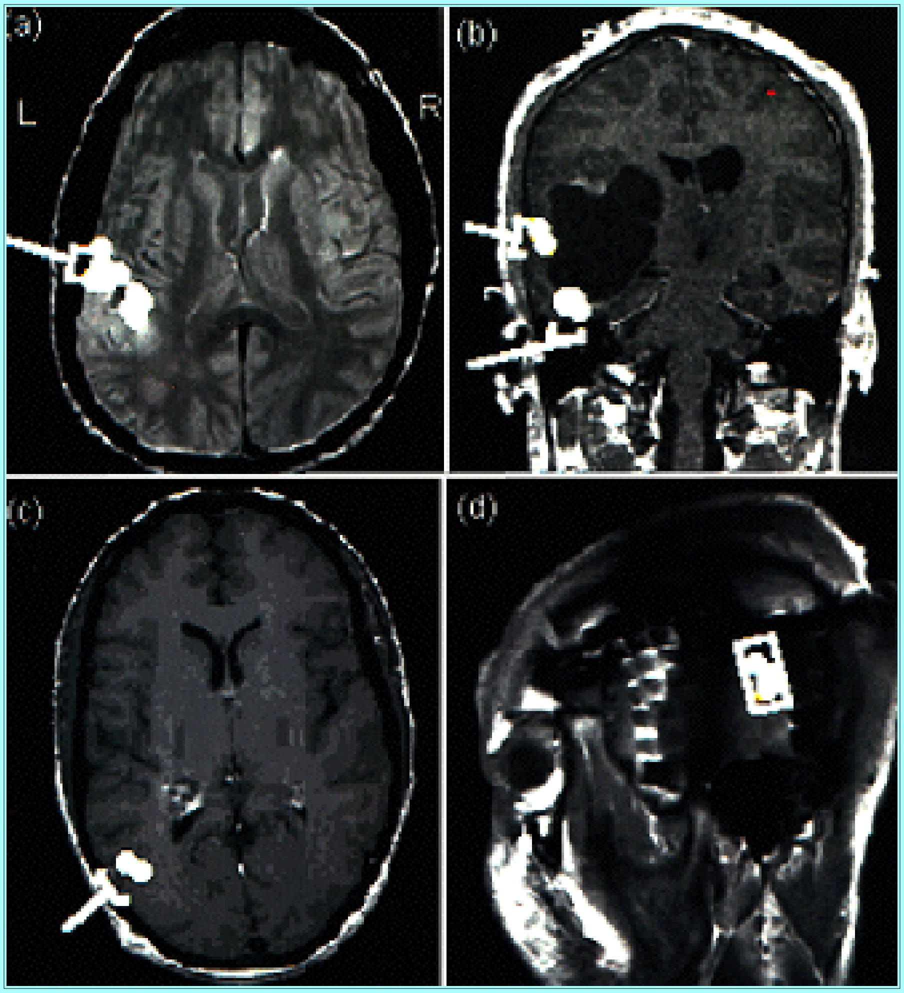

Fig. 5. Presurgical images obtained in four patients showing the locus of the most dense activation during the language task and the sites (indicated by brackets for the patients shown in a-c and by the white square for the patient shown in d) where cortical stimulation resulted in the arrest of the speech-comprehension process. Note the perfect overlap in the MEG-derived and cortical stimulation-derived language-specific sites. The patient shown in b is especially interesting because intraoperative mapping revealed two spatially distinct

regions which, when stimulated, produced transient language deficits. Stimulation of areas between those sites did not produce any deficits. The MEG-derived clusters of activity sources were found in both sites.

The site of effective electrical stimulation was noted by the surgeon on the appropriate MR image with the aid of a frameless stereotactic system. The images containing the MEG-derived map and the marked site(s) of successful electrical stimulation were compared. As shown in Fig. 5 (a-c), there was a perfect match between the areas of densest concentration of MEG-derived language-specific activity sources and the sites of effective stimulation in each patient.

The same concordance was observed in the fourth case (extraoperative stimulation) shown in Fig. 5d. This patient had a long-term 64-contact parietotemporal grid. Speech mapping was conducted over the superior and posterior portions of the grid. The electrical stimulus consisted of a 50-Hz, 5-second-long train of square wave pulses, each lasting 500 μsec, delivered at intensities of up to 11.5 mA. A modified token test was used to test language during grid stimulation. This test involved presentation of a row of five different-colored circles above a second row of five different-colored squares with instructions to the patient to point to particular combinations of circles and squares. Electrical stimulation coincided with the presentation of each particular instruction. Any form of error or significant increase in response time was considered evidence of speech interruption. Stimulation and nonstimulation trials were randomly intermixed and at least five or more errors were required to consider a site language specific. All identified language and surrounding nonlanguage sites were thoroughly tested at least twice to confirm the findings. The overlap between the cluster of MEG-derived language-specific sources with the site associated with language deficits during cortical stimulation mapping is apparent in Fig. 5d.

Although this patient series is small, the chances that the concordance between MEG-derived and cortical stimulation-derived language maps occurred at random are even smaller. It appears, therefore, that MEG-derived maps provide valid information regarding the location of the language-specific cortex within the dominant hemisphere.

DISCUSSION

The normative and patient data presented in this paper indicate that accurate mapping of the language-specific cortex by using the noninvasive, repeatable, and relatively brief MEG procedure is possible. In addition, they support the validity of the measure we used to assess hemispheric asymmetries, namely counting the number of sources that account for late EF components in each hemisphere. As mentioned earlier, this measure was empirically derived. It represents the number of identifiable dipolar sources in each hemisphere that are active during the time period following presentation of stimuli. This number obviously depends on the relative frequency of discharge of neuronal aggregates (dipolar sources) within the time period following the stimulus, but it may also depend on the intensity of the discharges, which is a function of the number of simultaneously active cells within an aggregate. In other words, the greater the number of sufficiently intense sources within a hemisphere during a given time interval, the greater the chance that such sources will be detected and identified. At present, it is unclear which of these possible aspects of brain activation is most reflected by the measure used. However, no matter whether the number of identified sources reflects the frequency or intensity of the responses of neuronal aggregates, it does provide a reliable and useful estimate of regional brain involvement in language.

Our results also indicate that routine use of MEG for presurgical language mapping may also become possible provided that some remaining issues are resolved by additional studies in the near future. The most important of these issues are summarized here.

First, indications of the validity of MEG-derived maps emerging from the two patient studies must be multiplied by increasing the number of comparisons between MEG and the Wada testing results and between MEG and cortical stimulation results. We are currently pursuing this task by continuing to perform MEG mapping with additional patients who have undergone, or will undergo, the Wada procedure as well as patients who will undergo intraoperative speech mapping.

Second, the relative number or the proportion of language-related activity sources in each hemisphere that is required for claiming right, left, or bilateral hemisphere language representation must be empirically specified. At present, we have identified as left- or right-hemisphere dominant those individuals who have more than twice as many sources on one hemisphere compared with the other hemisphere and as bilateral the patient who happened to have almost the same number of sources on both hemispheres. However, a situation is likely to arise in which the numbers of sources active in the two hemispheres are not nearly equal or clearly unequal and a decision must be made as to how much hemispheric difference in activation is sufficient for correctly identifying a patient as having unilateral or bilateral hemisphere language representation. As we increase the series of patients in whom MEG and Wada data are obtained, we will be able to characterize quantitatively the relationship between the behaviorally established criteria for language laterality on the Wada test and the degree of MEG-derived hemispheric asymmetries. In this manner, the optimum cutoff number of sources and the corresponding confidence intervals for determining language lateralization by using the MEG procedure will be established.

Third, bearing in mind that a great variety of tasks can be considered linguistic and different tasks are used for activating language-specific cortex in the context of MEG, Wada testing, and cortical stimulation, it is possible that slightly different maps may appear in the future as a result of discrepancies among these procedures. To address this issue we are developing alternative tasks for use with MEG mapping that closely resemble those used during the Wada and intraoperative mapping procedures.

Fourth, in view of the fact that no task can be purely linguistic, but all involve to a greater or lesser degree other cognitive operations, it is likely that the cortical maps we are currently constructing are not exclusively language specific. For example, the word identification task we used for MEG mapping may result in activity sources that are memory specific in addition to those that are language specific because the task does involve recognition memory. We are attempting to address this issue and to separate, to the degree possible, activation specific to language from activation specific to other cognitive functions in the context of developing alternative tasks for MEG mapping mentioned earlier.

Fifth, given that language-specific maps differ across patients not only in topographic detail but also in extent, it is often difficult to identify a single contiguous language-related area. For instance, although evidence for activation (high concentration of sources) in the superior temporal gyrus shows impressive consistency both between and within individuals, the same is not always true for the supramarginal and angular gyrus. There the concentration of activity sources is often quite low. At present, we have been using the highest spatial concentration of sources to identify such contiguous areas; however, we cannot be certain what the functional significance of areas with lower concentration of sources might be. To address this issue, we plan to devise a scale for grading the degree of language interference produced by focal cortical stimulation in different regions and to correlate this measure with the density of the

MEG-derived sources in these regions.

Sixth, given that presurgical mapping of the expressive language cortex is often desirable, expressive language tasks must be devised for mapping the frontal cortex. We have devised such a task involving covert articulation of nonsense syllables. We have collected preliminary evidence that we can activate the expressive language cortex in addition to Wernicke's area and we are now in the process of assessing the validity and reliability of this MEG mapping task, as we have done for the word identification task.

CONCLUSIONS

It appears that language mapping in healthy volunteers or patients can now be performed readily and completely noninvasively by using MEG. It is also apparent that MEG-derived maps, although slightly different across individuals (as it would be expected) do reveal the expected incidence of left hemisphere dominance and the expected topographic pattern. Moreover, MEG maps are reliable and valid because they are in agreement with the results of the two current gold standards, the Wada procedure and direct cortical stimulation, at the level of individual patients. Although the MEG mapping technique should be further refined, it already has been shown to be efficacious by correctly identifying the language-dominant hemisphere as well as specific language-related regions within it. Further development of the technique may render it a valuable adjunct for routine presurgical planning in many patients who harbor tumors or have epilepsy.

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