Localization of Auditory Response Sources Using Magnetoencephalography and Magnetic Resonance Imaging

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- Magnetoencephalography offers the possibility of localizing accurately and noninvasively the source of intracranial currents associated with normal and abnormal brain activity. The purpose of this study was to assess the validity and across-subject reliability of localization of cortical sources responding to ipsilateral and contralateral auditory stimulation. Magneto evoked fields to both stimulation conditions were measured in eight consecutive normal subjects, and the cortical sources of these fields were estimated on the basis of these measurements. Subsequent projection of the source location coordinates onto magnetic resonance images showed that in all subjects the sources were accurately estimated to fall in the vicinity of the auditory cortex and that two separate sources may account for the response to ipsilateral and contralateral stimulation. (Arch Neurol. 1990;47:33-37)

Although magnetoencephalography (MEG) and electroencephalography (EEG) are related methods for assessing brain activity, the measurement of magnetic fields about the head has several unique features that differ from those of electrical potentials. Magnetic fields are primarily due to intracellular dendritic currents and remain relatively undistorted as they emerge through tissue layers of inhomogeneous conductivity. Surface EEG recordings, in contrast, are products of volume currents that can be dramatically altered by the different types of tissue they encounter between their source and the surface recording site, thus rendering estimates of the location of their source very problematic.

An external magnetic field produced by a current source in a homogeneous sphere consists of two vector components, one radial and one tangential to the surface of the sphere. The design of the magnetic sensors used in this study allows for the measurement of the radial component of the magnetic field so that contributions from volume-conducted currents are negligible. Multiple measurements at different external locations over the scalp are used to estimate the location of the current source by fitting the data to a spherical model. Such an approach is quite accurate in identifying generators located a few centimeters away from the scalp surface.

Since MEG was first used in 1972 to record magnetic fields arising from intracranial currents, a considerable number of studies have been conducted attempting to localize sources of clinically significant events such as interictal spikes or of normal brain responses associated with sensory and motor activity. Precise localization of brain activity sources is, after all, the major putative advantage of MEG over traditional electrophysiologic procedures, ie, scalp-recorded EEG and evoked potentials (EPs). Up to the present time, however, attempts to substantiate the claim that MEG can provide valid localization for the sources of sensory responses in the brain may be questioned on pragmatic grounds. Namely, the location parameters of the sources, often reliably estimated from the recorded magnetic field over the scalp, are not routinely projected onto magnetic resonance images (MRIs) or computed tomograms of the individual subject's head that could allow one to verify whether the estimated source is actually localized in the appropriate anatomical structure. Rather, with the notable exception of a recent study in which calculated sources of the early positive peak of the auditory response were projected onto MRIs in a series of six subjects, most investigators project the calculated source location onto a generic model of the head. Moreover, in those rare occasions where tomographic images of the subjects' brain were used, this type of verification was performed on only one or two subjects.

Consequently, the present study was conducted to ascertain whether the source of a readily identifiable late component of the auditory evoked response known in the EP literature as N1 could be localized accurately (in the auditory projection area from which it purportedly arises) and reliably (ie,
in a series of eight different subjects). A secondary aim of the study was to determine whether responses to ipsilaterally and contralaterally presented acoustic stimuli are a common response or are generated at two different locations in the auditory cortex. It is clear that unless the sources of sensory activity, deduced from MEG measurements over the head surface, are shown to fall within the expected anatomical region in all subjects, future use of the MEG as an accurate, noninvasive localization procedure would remain doubtful.

SUBJECTS AND METHODS

Eight normal adult volunteers, five men and three women, ranging in age between 22 and 53 years, participated in the study. Each subject was tested individually in a magnetically shielded chamber (Vacuumschmelze GmbH). A 1-kHz tone generated by a stimulus generation module (Nicolet Compact Four), 50 milliseconds in duration (10-millisecond rise/fall and 30-millisecond plateau), with an intensity of 105 dB normal hearing level (nHL) at the source, was channeled to the subject’s ear through a 91.4-cm-long plastic tube of 0.18-cm inner diameter terminating in an insert earphone (Nicolet TIP-300). Similarly, white masking noise of 60 dB nHL at the source was channeled into the other ear. On the basis of the tube characteristics, we estimated that the intensity levels of the tone and the noise at the subject’s ears was about 96 dB and 50 dB nHL, respectively. The stimulus delivery rate was varied at random between 0.25/4 and 0.5/4 around a mean of 0.4/4. Fifty responses to the stimulus were averaged at each measurement point.

Measurements of the averaged evoked magnetic fields (MEFs) were made over the right hemisphere of each subject. A neuromagnetometer (BTI model 607) with seven, second-order gradiometers was used, allowing simultaneous measurement of EMFs at seven scalp positions about 1 cm apart and covering a circular area of about 6 cm in diameter. The seven gradiometers are superconducting and housed in a cryogenic container (Dewar), the tail end of which was placed successively at eight adjacent locations covering the recording area of interest over the scalp. These eight locations were sampled in a different random order for each subject. At each location, averaged EMFs to the tone delivered through the ipsilateral (right) and contralateral (left) ears were obtained from all seven channels before the Dewar was placed over the next location. The order of ear stimulation was counterbalanced over the eight locations for each subject. Consequently, a total of 56 averaged EMFs was obtained for each ear stimulation condition with each subject, constituting an adequate magnetic field map of the two responses.

The precise location of each of the 56 measurement sites on the scalp was determined electronically with reference to a Cartesian coordinate system anchored on three landmarks (fiduciary points) on each subject’s head: two preauricular points and the nasion. The line passing through the two preauricular points served as the y-axis of the system. The line perpendicular to the y-axis passing through the nasion served as the x-axis, and the line perpendicular to the x-y plane passing through the x-y origin served as the z-axis.

Subsequently, three small, easily identifiable lipid markers (vitamin pills), placed over the three fiduciary points, served to define the coordinate system for MRIs. Following EMF recordings, MRIs were obtained from each subject using an imaging system (Technicare) with a 0.6-T magnet. Serial coronal MRI sections, 0.5 cm in thickness, were taken at right angles to the plane defined by the three fiduciary points (the x-y plane). Thus, the employment of a common coordinate system for the MEG and MRI data made it possible to visualize and define, for each subject, the anatomical structures onto which the calculated sources of the EMF responses were projected. The accuracy of this projection was limited by the following three factors: (1) the spatial resolution of the MRIs (ie, 0.625 cm); (2) the ambiguity associated with defining the center of each pill that served to mark each fiduciary point (±0.3 cm); and (3) small deviations in obtaining MRI sections perfectly perpendicular to the x-y plane. This latter source of error was corrected in each subject by adjusting trigonometrically for head tilt during MRI so as to restore reasonably accurate superimposition of the two Cartesian coordinate systems used for the MEG and the MRI scans.

RESULTS

The EMF waveforms were characterized by two major peaks very similar to those of the auditory EPs. The first peak, corresponding to the N1 of the EPs occurred with an average latency of 82.65 milliseconds for the contralateral stimulus and 105.03 milliseconds for the ipsilateral stimulus. The second peak corresponding to the P2 of the EPs was less well defined in the majority of the subjects and occurred with an average latency of 160 milliseconds. Subsequent analyses and discussion concern the first, most reliable and well-defined EMF peak.

The two magnetic field extremum for that peak (N1) were obtained in the same scalp locations as in previous studies.22 The positive (maximum) was anterior to the ear and the negative (minimum) was posterior and superior to the ear in all subjects. Moreover, the magnetic field strength was greater at the minimum extremum than at the maximum extremum as expected. Specifically, the peak amplitude at the minimum averaged -381.25 and -382.00 FT for contralateral and ipsilateral stimuli, respectively, and 347.75 and 233.25 FT at the maximum (Fig 1). Isofield contour maps for this peak, constructed on the basis of the 56 waveforms, were also similar to those reported in other studies23,24 for both stimulation conditions, suggesting that the response source could be treated as a single equivalent dipole (see Fig 1). The location of these sources was subsequently estimated on the basis of the recorded fields using a finite difference version of the Levenberg-Marquardt algorithm.25 The dipole localization solutions were made for the best-fitting sphere, the curvature of which was defined by the surface of the scalp within a circular area of approximately 5-cm radius over the auditory cortex in all but one subject who was unavailable for head curvature measurements. For this subject, the best-fitting sphere was defined as the one centered on the origin of the x-, y-, and z-axes. Estimation of the best-fitting sphere for the seven subjects was done through a least squares procedure.

In view of the fact that the EMF peak amplitude did not reach maximal values at exactly the same latency in all 56 waveforms, dipole solutions were performed for three to four adjacent peak latencies covering a latency range of 15 to 20 milliseconds. The dipole parameters (location, orientation, and strength) obtained at each latency point were essentially identical. Therefore, subsequent discussion will be centered on one such latency point. The dipole estimation algorithm represents an attempt to solve the inverse problem through a series of iterative, forward solutions whereby a set of dipole parameters (three of position in a Cartesian coordinate system, one of dipole strength, and one of orientation) are used to calculate a magnetic field on the surface of the best-fitting sphere. Then the calculated and the empirically obtained fields are compared using a least squares estimation procedure. If the degree of difference between the two fields is high, the dipole parameters are changed and a new field is calculated. This iterative procedure terminates when no further reduction in the differences between the two fields is obtained, and the dipole parameters of the last solution are considered as estimates of the actual location, orientation, and strength of the source that gave rise to the recorded magnetic field. Yet these estimates are not unique. An entirely different combination of values for the five dipole parameters could give rise to the same best-fitting field. This uncertainty is intrinsic to all inverse problem solutions and cannot be over-
come mathematically. No matter how reliably similar location parameters are obtained in all subjects, it is still possible that they are the wrong ones. This is precisely why independent confirmation of the validity of localization is necessary.

To access the validity of the source localization solutions obtained for each subject during ipsilateral and contralateral ear stimulation, the source location values (given in millimeters along the x-, y-, and z-axes of the coordinate system) were projected onto the appropriate coronal sections of the MRI, since, as mentioned above, the same fiduciary points defined the same coordinate system in both the EEG and MRI spaces. The results of this procedure are shown in Fig 2.

The dipolelike sources of both responses (to ipsilateral and contralateral stimuli) were in the vicinity of the auditory cortex in all eight subjects. To obtain an estimate of between-subject variability in source localization, a central point on the floor of the sylvian fissure, midway between the lateral and medial edges of the temporal lobe of each subject's MRI section, was defined (Fig 2), and the distance of each of the two sources (to contralateral and ipsilateral stimuli) was measured from that central point. Subsequently, the average location of each source over the eight subjects was computed. The mean locus of the response to the contralateral stimulus was 3.75 mm medial to the central point (SD = 5.77 mm), 2.50 mm below the floor of the sylvian fissure (SD = 4.53 mm), and 2.63 mm posterior to the central point (SD = 3.81 mm). The corresponding values of the response source to the ipsilateral stimulus were 2.88 mm (SD = 7.39 mm) medial, 5.00 mm (SD = 5.48 mm) below the fissure floor, and 0.38 mm (SD = 4.93 mm) anterior to the central point. Figure 2 shows the relative mean position of the two dipoles on the coronal plane. Thus, the response source to the contralateral stimulus appears to be medial, superior, and posterior to that of the ipsilateral stimulus. Although neither the distance nor the strength (in amperes) of the two sources is statistically different, their relative orientation does differ by 54.62° (t = 2.46; df = 7; P < .007), indicating that the two responses may be generated by adjacent yet differently oriented cortical columns in the auditory cortex.

**COMMENT**

In this study we systematically explored the feasibility of identifying the brain structure that contains the source of the auditory response known in the EP literature as N1, using an unselected group of normal subjects. We demonstrated first that the equivalent dipole locations as calculated on the basis of the externally recorded magnetic fields do fall within the vicinity of the auditory projection area in each of the eight subjects. This indicates that, in spite of violations of the assumptions underlying the source localization algorithm used (such as varying degrees of deviations from sphericity of different heads), and in spite of measurement errors and spatial resolution limitations of the MRI alluded to previously, one can achieve acceptable localization accuracy for brain events that are substantially more feeble than clinically significant ones such as interictal spikes.

Of course, the precise degree of localization accuracy is quite difficult to ascertain in this type of study for the following reasons: (1) it is difficult to define on MRI the precise borders of the auditory cortex; (2) there is no independent confirmation for the assumption that a particular peak of the sensory response must arise within a particular small region of the auditory projection area; and (3) the degree of actual variation of the functional anatomy of different subjects is unknown. Nevertheless, even within the above-mentioned limits of certainty, it is possible to improve the accuracy of localization and to identify obvious errors. For example, small deviations of the auditory response sources along the vertical axis, i.e., either above or below the floor of the sylvian fissure, are most likely due to measurement errors. Specifically, they may be due to the fact that measurements of the lower part of the magnetic field (over the cheek bone) result in lower field strength values due to greater deviations of these points in distance and angle from the ideal sphere defined by the cranial cavity, and systematically bias localization of the source along the vertical direction. Such errors could, in principle, be minimized, and we are in the process of developing methods to account for them.

The secondary aim of this study was to examine whether responses to ipsilateral and contralateral stimulation under identical conditions are generated by different sources as previous
Fig 2.—Coronal magnetic resonance imaging sections containing the N1 source for the contralateral stimulus (large cross) and the ipsilateral stimulus (small cross) for each subject and the mean location of each source over all the subjects, along with the SD on the vertical and horizontal directions, projected on the MRI of one subject.
studies have shown,24-27-29 and to determine the spatial relation of the two sources. In addition, in view of the known asymmetry in the auditory pathways, and the fact that we used masking noise, we expected to find that the response to the ipsilateral stimulus would be weaker and of longer latency.

With respect to the former issue, our data tend to support the contention that separate adjacent regions in the right auditory cortex respond to contralateral and ipsilateral stimulation, yet further investigations are necessary to confirm it.

With respect to relative response strength in the two stimulation conditions, our expectations based on previous results28,29 were disconfirmed by the data. Both, the measured external field strengths (in femtotesla) and the calculated source strength (in amperes), were comparable in the two conditions. Nevertheless, the ipsilateral response was of significantly slower latency than the contralateral response by 22.38 milliseconds, as previously reported.28,29 The physiologic mechanisms of this reliable latency difference are currently being investigated in the context of another study in our laboratory.

In conclusion, this study represents an initial systematic and successful attempt to assess the validity and between-subjects variability of source localization using MEG and MRI. The results obtained demonstrate the feasibility of employing these two imaging modalities to identify, noninvasively and quite accurately, sources of normal brain activity, thus rendering MEG a viable adjunct to positron emission tomography or to depth EEG recording procedures30 in localizing sources of pathologic activity such as interictal spikes.

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References


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