Recording and Interpretation of Cerebral Magnetic Fields

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Contemporary brain research progresses along two main lines: the microlevel approach explores single neurons and subcellular elements, while macrolevel studies focus on more complex cerebral functions, including behavior. This review presents results obtained mainly in our laboratory by means of an intermediate method, magnetoencephalography (MEG), which reflects cortical activity of neuronal populations at the level of cytoarchitectonic areas. Because it is completely noninvasive, MEG can be used to study brain functions that are characteristically human.

During the last 10 years several new methods have been introduced for studies of the human brain (*1*). Anatomical structures can now be precisely investigated by means of x-ray computer-assisted tomography (CT) and by magnetic resonance imaging (MRI). Functional information about the brain is obtained with regional cerebral blood flow measurements (RCBF) and, to an increasing extent, with positron emission tomography (PET). All of these methods allow studies of the human brain without opening the skull, but they are not totally noninvasive because the subject is exposed to x-rays, time-varying gradients of the magnetic field, or radioactive tracers.

The neuromagnetic technique (*2*), that is, the completely noninvasive recording of weak cerebral magnetic fields (typically 50 to 500 fT, which is one part in 10^9 or 10^8 of the earth's geomagnetic field) outside the head, was made practical by the invention of SQUID (superconducting quantum interference device) magnetometers (*3*). Developments toward multichannel systems (*4*) have greatly improved the speed and convenience of neuromagnetic recordings and have made it feasible to apply magnetoencephalography (MEG) for clinical purposes as well (*5*).

The probable sources of cerebral magnetic fields are electric currents in the synapses of synchronously activated pyramidal neurons (*2*). The apical dendrites of these cells are parallel to each other and perpendicular to the cortical surface, which is thus also the direction of the primary intracellular currents. Volume currents are generated in the surrounding tissue to complete the electrical circuit.

The human head can be approximated by a spherical conductor arranged in homogeneous layers. In this model, the external magnetic fields produced by radial (perpendicular to the skull) primary currents are canceled by the opposite fields generated by the ensuing volume currents (*2*). If the dipole is tangential (parallel to the skull), the radial component of the external magnetic field is caused by the primary current only, the volume currents being externally silent. Consequently, MEG on a real human head is mainly sensitive to activity in the fissural cortex, with gyri giving only weak signals. This is not a serious limitation because the major part of the cortex is in the fissures, including all primary sensory areas.

In a typical MEG experiment (Fig. 1), a sensory stimulus, such as an abrupt sound or a current pulse on the skin, is presented to the subject, and the evoked magnetic field is measured over the head. When the incoming impulse volley reaches the cortex, thousands of neurons are simultaneously activated and produce a rapidly changing magnetic field (Fig. 2). If the active cells occupy an area less than a few square centimeters, the current distribution can be approximated by a dipole.

Owing to external magnetic disturbances, SQUID noise, and spontaneous brain activity, tens or hundreds of successive MEG responses must be averaged to obtain an acceptable signal-to-noise ratio. In addition, for constructing the topographic field map from which the activated cortical region can be estimated, measurements must be made typically at 30 to 70 locations (Fig. 3). MEG experiments are thus time-consuming and easily cause fatigue in the subject. Multichannel instruments, with 100 to 200 SQUIDs sampling the whole head, are eagerly awaited.

Electroencephalography (EEG), that is, the measurement of electric scalp potentials, is a useful clinical tool (*6*) The primary source of EEG and MEG signals is the same. Electrical measurements require much less sophisticated equipment and give information about cortical activity, and also about deeper cerebral structures, including the brain stem. MEG is relatively insensitive to the deep sources, because the magnetic field diminishes rapidly as the source moves closer to the middle of the head; no field at all is expected from a dipole in the center of a sphere.

For cortical sources, however, MEG has much better spatial resolution than EEG, 1 to 2 mm under favorable conditions (*7*). Electrical potentials measured on the scalp are often badly distorted, because of various inhomogeneities in the head. It is then difficult to determine accurately the activated area in the brain. The magnetic field, in contrast, is produced by the less distorted currents that flow in the relatively homogeneous intracranial space. Because of the poor electrical conductivity of the skull, the irregular currents on the scalp and in the skull are weak and can be ignored as contributors to the external magnetic field (*8*).

The time resolution of MEG and EEG is better than a millisecond, which exceeds that of RCBF and PET by many orders of magnitude and makes it possible to follow spatiotemporal changes reflecting signal processing in the brain. This is important because the time span of electric activity in single neurons ranges from one to hundreds of milliseconds.

In studies of human neurophysiology, one of the most interesting applications of MEG is the investigation of the activity of the sensory projection areas (*9*). Here functional variations in the sites of the activity, rather than the absolute locations, are of primary

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interest. Monitoring the spatiotemporal changes gives information about the contributions of different brain areas during various types of tasks.

For example, an abrupt sound evokes a complex magnetic waveform (Fig. 2), which lasts several hundred milliseconds after the stimulus onset. During the various peaks of the response, the magnetic field patterns resemble those produced by current dipoles, located at the superior surface of the temporal lobe in the brain, within the Sylvian fissure; the dipole model is an idealization of currents densely packed into a small area. The sound activates auditory areas in both hemispheres, with slightly longer latencies to the ipsilateral than to the contralateral side. Often the locations of the equivalent dipoles are not the same during the different deflections of the response. One interpretation is that this is due to spatial changes, from one cytoarchitectonic area to another, in the focus of activity. Evoked responses may reflect either sequential or parallel signal processing in the auditory cortex.

Instrumentation

The magnetic field to be measured is coupled from the detection coil to the SQUID via a superconducting flux transformer. For operation, the present-day SQUIDs and flux transformers must be immersed in liquid helium at 4.2 K.

When an external field is imposed, a supercurrent is set up to keep the total flux through the transformer constant. The magnetic field produced by this current is then sensed by the SQUID. The detection coil is usually of gradiometric configuration, with the pick-up and compensation loops oppositely wound (Fig. 1). A first-order gradiometer is insensitive to homogeneous fields, because they impose the same but opposite flux on the pick-up and compensation coils. The device is effective, however, in measuring magnetic fields generated by nearby sources. If the pick-up coil is close to the head and if the distance to the compensation coil is more than 5 cm, the magnetic field produced by the brain is sensed essentially by the pick-up coil only.

A four-SQUID gradiometer was put to use in Helsinki in 1983 (*10*). Two years ago we commissioned a much improved device (*11*), consisting of seven dc-SQUIDs (*12*) in a hexagonal array; the diameter of the active measuring area is 9.3 cm (Figs. 1 and 4). The sensitivity of each channel in operation is 5 to 6 fT/$\sqrt{\text{Hz}}$; the intrinsic sensor noise, measured inside a superconducting shield, is 2 fT/$\sqrt{\text{Hz}}$. During experiments the noise is thus down to a level at which its main contribution is from the brain itself. In early 1989, a 24-channel instrument (*13*) will become ready for use in Helsinki.

A commercial seven-SQUID instrument is available (*14*); the sensitivity of each channel is 20 fT/$\sqrt{\text{Hz}}$ and the active measuring area has a diameter of 5.2 cm. In this device the sensitivity has been sacrificed by the use of second-order gradiometer detection coils

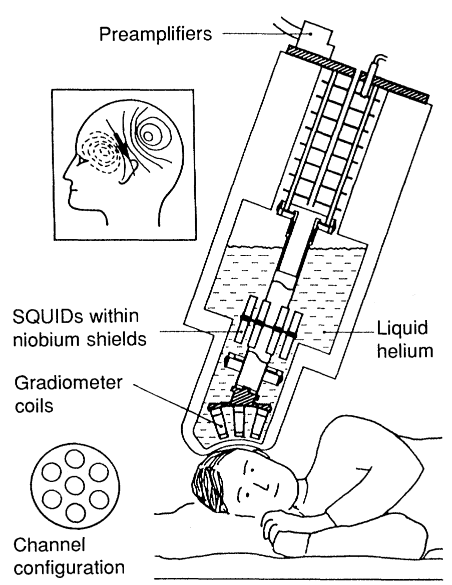

Fig. 1. Schematic illustration of a typical experimental situation for auditory measurements. The most important parts of the seven-SQUID instrument in Helsinki (*11*) are also shown; the midpoints of the different channels are separated by 36.5 mm. The dc-SQUIDs themselves were manufactured by the IBM Thomas J. Watson Research Center at Yorktown Heights, New York (*12*), and installed in collaboration with Dr. Claudia Tesche. The insert above depicts isocontours across the scalp for the radial component of the magnetic field, generated by an active area in the auditory cortex; the arrow illustrates the location of the equivalent current dipole.

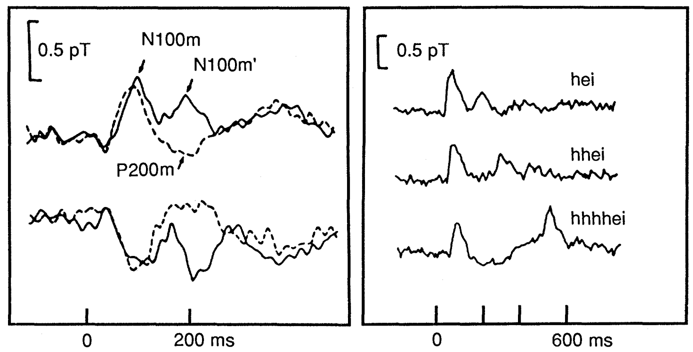

Fig. 2. (**Left**) Averaged magnetic responses (n = 120) to "hei" words (solid lines) and noise bursts (dashed lines) from the right hemisphere in one subject; the upper curves are from an anterior and the lower ones from a posterior measurement location near the ends of the Sylvian fissure. The passband was 0.05 to 70 Hz. (**Right**) Effect of increasing the duration of "h" in another subject. Further explanations in text. Modified from (*21*).

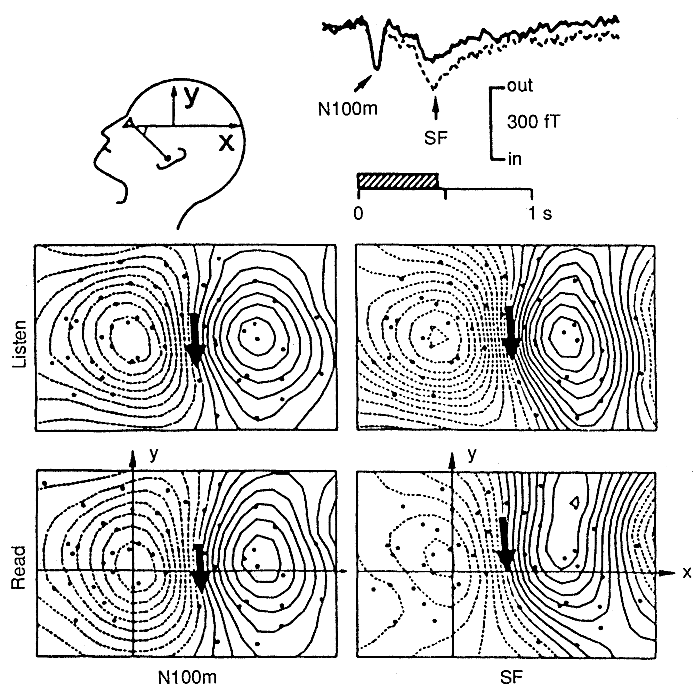

Fig. 3. Effects of attention on the auditory evoked signals in one subject. The tracing at the upper right shows responses to target words when the subject either ignored them (read, continuous line) or when he was involved in a word categorization task (listen, dashed line); the mean duration of the stimuli is given by the dashed bar on the time scale. Field maps over the left hemisphere are illustrated below during the N100m deflection and the sustained field (SF) for the "read" and "listen" situations; the measurement locations are indicated by dots. The isofield curves are separated by 20 fT. The coordinate system, shown on the schematic head, is printed on the lowest maps; the contours illustrate field strength 35 mm above the scalp. Modified from (*27*).

that provide improved rejection of field from environmental noise sources. This permits its use in a less expensive shielded room or even in an unshielded laboratory.

Since MEG signals are weak, rejection of external magnetic disturbances is of extreme importance. We perform our measurements inside a magnetically shielded enclosure of 2.4 by 2.4 by 2.4 m^3 inner dimensions (*15*). The room is made of three layers of aluminum, which effectively attenuate the high-frequency band of the external magnetic noise, and three layers of high-permeability mu-metal for shielding at low frequencies, which are particularly troublesome in MEG measurements. Above 1 Hz the shielding factor of our room is better than 10^5.

Interpretation of MEG Results

In the analysis of MEG data the underlying cortical source must be deduced from the externally measured magnetic field (Figs. 1 and 3). Although it is straightforward to calculate the electric and magnetic fields from given primary currents, the inverse is not true, even if complete knowledge of the field distribution outside the head were available (*16*). Additional assumptions are needed. Therefore, interpretation of MEG data must always rely on source and volume conductor models; additional anatomical and physiological information can be used to make the problem more tractable.

The most popular source model is a current dipole (typical strength 10 to 20 nA·m) within a conducting medium, the human head. In this case all field components can be directly calculated from the parameters of the diplole. The spherical model is, of course, a severe simplification. However, when it is compared with a realistically shaped multilayer head model (*17*), one finds that, in regions where deviations from sphericity are small, for example, in occipital areas, this model gives field values that are less than 2 to 3% in error, provided that the sphere is fitted to the local radius of curvature of the skull's inner surface. In frontotemporal sites, for example, the spherical model fails to reproduce the correct field pattern.

The realistically shaped multilayer head model (*17*) is computationally too tedious for routine use because explicit formulas for the magnetic field are not available. A good solution is to apply the homogeneous head approximation (*18*), in which the skull and the scalp are neglected and the head is replaced by a uniform conductor that has the shape of the skull's inner surface. This is justifiable since, as we have seen, only a small portion of the volume currents flow in the skull and on the scalp, thus giving a negligible contribution to the external magnetic field. The homogeneous head approximation performs substantially better than the sphere model in nonspherical areas; the required computing time is only slightly longer.

The dipolar assumption can be accepted if the field variance explained by the current dipole is reasonable and if the residual, that is, the difference between the measured and theoretical field patterns, can be accounted for by noise. Physiologically, the dipole is interpreted to represent the synchronous activation of tens or hundreds of square millimeters of cortical tissue.

When more and better MEG data become available, source modeling should be improved further. At present, a major drawback is the difficulty in discriminating between several simultaneously active dipoles; the use of information about temporal regularities of different sources might be helpful here (*19*). Methods have to be developed also for feeding other types of data into the analysis, for example, the simultaneously measured EEG recordings and the actual architecture of the subject's cerebral cortex as determined by MRI. Eventually, advanced signal analysis techniques must also be applied to reduce coherent brain noise (*20*).

Responses to Speech Sounds

Speech is a typically human function. In one of our series of auditory experiments (*21*), two 320-ms stimuli, a word and a noise burst, were alternately presented to the subject through a plastic tube and earpiece with a constant 1-s interval. The first stimulus was the Finnish word "hei" (pronounced "hay"), produced by a speech synthesizer; the fricative "h" lasted for 100 ms. Subjects were lying in our shielded room, with their eyes open, and counting the stimuli to maintain vigilance. The magnetic field perpendicular to the skull was measured over the temporal areas of both hemispheres, contralateral to the stimulated ear.

One set of responses to noise bursts is shown in Fig. 2; the main deflections [N100m and P200m (*22*)] peak approximately 100 and 200 ms after the stimulus onset. Polarity reversal is obvious from the two curves, which are from measurement locations separated by about 6 cm (compare the dipolar field pattern of Fig. 1). The equivalent current dipole, which explains most of the field variance, is thus in the middle.

The 100-ms magnetic response to "hei," N100m, is followed by another deflection of the same polarity at about 200 ms, that is, 100 ms after the vowel onset. We denote this peak by N100m′; it is of opposite polarity to P200m, which is seen after responses to noise bursts (Fig. 2). N100m′ was observed after "hei" on both hemispheres for all our seven subjects. We thus found that 100 ms after the stimulus onset the responses to noise and "hei" are similar but that at 200 ms they are of opposite polarity. In 8 of the 14 hemispheres investigated, the equivalent dipole of the N100m′ peak for "hei" was statistically significantly anterior to the source of N100m, suggesting separate generators for these two deflections; the distance between the dipoles never exceeded 15 mm.

Several control experiments were performed to determine which features of the stimulus determine the occurrence of N100m′. For example, when the duration of the fricative was increased from 100 to 200 ms and then to 400 ms by replacing "hei" with "hhei" or "hhhhei," the N100m′ deflection appeared later, but peaked always about 100 ms after the vowel onset (Fig. 2). Only words beginning with voiceless fricatives, "f," "h," or "s," and followed by vowels resulted in a N100m′ deflection of similar magnitude and waveform as that observed for "hei." The type of the vowel was not critical for the occurrence of N100m′. The finding that only "ssseee," but not its mirror-word "eeesss," elicited N100m′ suggests that this response is not generated by the change per se, but is specific to the direction of the change.

In another measurement (*23*), closely related to the "hei" experiment, a 300-ms noise burst, imitating the fricative, was immediately followed by a 200-ms square-wave tone, simulating the vowel. An N100m′-type response was obtained 100 ms after the onset of the square-wave. For a sinusoidal tone after noise, the N100m′ deflection was either absent or it was smaller and of different waveform. In a square-wave stimulus, high-frequency transients are repeated at the basic frequency of the square-wave. The resulting sound pattern, therefore, acoustically resembles a vowel in which formant bursts are produced at the fundamental frequency of the speech.

It thus seems that, whereas N100m is evoked by the onset of every abrupt sound, N100m′ is specific to a particular acoustic pattern, present both in the transitions from fricative to vowel and noise to square-wave. The observed response thus appears to reflect feature-specific neural mechanisms, essential for further analysis of speech sounds.

The "hei" experiment (*21*) illustrates the first necessary step in revealing neural mechanisms of speech perception: one must identify responses evoked by the acoustic features of the stimulus in order to subtract these from the more complex responses associated with the analysis of a speech message. The next step is to compare the processing of the content of speech and nonspeech stimuli. Until now no significant evoked response differences have been observed.

Neural activity associated with language processing probably is not as synchronous as that occuring at the primary and secondary projection areas. This unfortunate situation, as far as MEG experiments are concerned, can be overcome by using more complex tasks and by recording long-latency responses, as has been done already in evoked potential studies (*24*).

It is possible to alter the ongoing activity of the auditory cortex by speech sounds and then to use "probe stimuli" to test the states of these cerebral areas. Studies made so far suggest that such modifications of auditory evoked fields are not specific to the speech per se but depend on the amount of frequency and amplitude transients within the modifying sounds (*25*).

Studies of Attention

Attention is one of the basic elements of cognitive functions. With MEG recordings, it is possible to study how the attentional state of the subject affects responses in cortical sensory-specific projection areas (*26*). Recently we have investigated (*27*) the effects of attentive listening on the evoked magnetic response in the human auditory cortex. The stimuli were five-letter Finnish words, all beginning with a "k" and ending with a vowel. Half of the stimuli were "targets," names of animals or plants, and the rest, other meaningful words. The stimuli were presented randomly with equal probability of targets and nontargets. The task of the subject was either to ignore all words by concentrating on reading a self-chosen novel or, in the attentive condition, to count the total number of targets.

Responses of one subject from one measurement location are illustrated in Fig. 3. The most prominent deflection (N100m) peaks 110 to 130 ms after the onset of the word, and it is followed by a sustained field (SF), which outlasts the stimulus. During attentive listening, SF increases considerably: the responses to attended and ignored stimuli start to deviate after N100m. The signals recorded for targets and nontargets, however, did not differ in any systematic way. Similar results were obtained in a task during which the subject had to classify two tones on the basis of their durations. Attentional mechanisms, therefore, process word and nonword stimuli in a very similar manner in this type of measurement. In a dichotic experiment, with tones presented randomly to either the left or right ear, the evoked response change associated with attention paid to the stimuli of one ear was significantly stronger and longer for relevant than irrelevant tones (*27*).

The field maps to word stimuli (Fig. 3) are dipolar, both during N100m and the sustained field, with equivalent source locations in the supratemporal auditory cortex. These experiments show that there is a significant difference in the activity of the human brain, depending on whether the subject pays attention to the sound stimulus or not. It thus seems that neuromagnetic studies can be used for investigating the neural basis of cognitive processes. Further, MEG recordings might be helpful for investigations of lateralization of basic neural mechanisms underlying different cerebral functions. Hemispheric asymmetry has been observed in several studies (*21, 27, 28*): the equivalent dipoles of auditory evoked responses are, in right-handed subjects, typically 1 to 2 cm posterior in the left to their location in the right hemisphere.

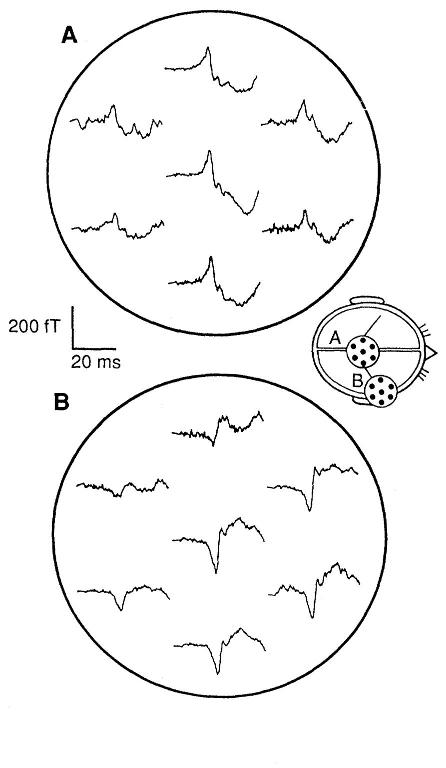

Fig. 4. Somatically evoked magnetic fields at the upper (**A**) and lower (**B**) ends of the right central sulcus, measured from one subject. The responses were recorded using our seven-SQUID instrument (Fig. 1). The interstimulus interval is 200 to 220 ms, the traces are averages of about 1000 responses, passband is 0.05 to 2000 Hz, and the sampling frequency is 8 kHz. The most prominent peak occurs at 19 ms [upward in (A) and downward in (B)]. Modified from (*29*).

Somatosensory Studies

Clear magnetic responses are elicited by stimulation of various mixed and sensory peripheral nerves (*9*). Figure 4 shows that the first response after electric stimulation of the median nerve at the wrist peaks 19 ms after the stimulus. The polarities of the responses are opposite at the upper and lower ends of the central sulcus, and the equivalent source is in the somatosensory hand area, probably at Brodmann area 3b. The dipole is oriented toward superficial parts of the cortex, in agreement with source currents that are associated with neural excitation of deep cortical layers, caused by the first input to the cortex. This interpretation is supported by the insensitivity of the 19-ms deflection to the stimulus repetition rate (*29*). The next deflection, at about 30 ms, increases clearly in amplitude when the repetition rate is decreased from 5 to 2 Hz; evidently polysynaptic pathways are involved.

Stimulation of various parts of the body evokes activity at different areas of the brain; the sites of the equivalent dipoles correspond to the well-known somatotopic organization of the primary somatosensory cortex SI (*30*): the projection of thumb is about 1 cm lateral to that of the little finger, and stimulation of the ankle activates the inner surface of the contralateral hemisphere, with the first cortical response at 40 ms (*31*). In addition to activity at SI, it is also possible to record MEG responses from the secondary somatosensory area SII (*32*), which has remained out of reach of scalp EEG measurements. SII is activated bilaterally, with slightly longer latencies to the ipsilateral than to the contralateral side.

Selective activation of pain afferents evokes strong magnetic signals (*33*). For example, a response is observed about 3 cm anterior to SII, about 90 ms after a current pulse to the tooth pulp. Painful carbon dioxide pulses, embedded within a continuous airflow and led to the nasal cavity, activate the secondary somatosensory cortex with the peak at about 350 ms after the stimulus onset.

Clinical Perspectives

The good spatial accuracy of MEG has led to the first serious clinical application of the method, preoperative localization of epileptic foci in patients suffering from partial seizures (*5*). This type of work was reviewed recently in *Science* (*34*).

Recording electric potentials and magnetic fields simultaneously, under identical conditions, gives more complete information about neuronal activation patterns than either method alone (*35*). Tangential components of the current dipoles can be estimated first, on the basis of magnetic data. The equivalent sources thereby found may then be used in forward calculations to obtain the electrical potential on the scalp. Comparison of the predicted and measured potential distributions gives information about radial or deep sources that are not visible in the magnetic data.

Combined electrical and magnetic recordings have supported specific hypotheses regarding the cortical localization of the generators of some somatosensory and auditory responses. Electrical evoked potentials, if their sources are known, are important indicators of the integrity of sensory pathways from the periphery to the cortex and have applications in clinical diagnostics of neurological disorders (*36*).

Interesting and clinically useful data can also be obtained from patients suffering from disorders of the peripheral sensory receptors or sensory pathways or from lesions in the cortical projection areas. For example, the activity of the auditory cortex of three deaf persons who use a cochlear prosthesis has been investigated (*37*). Such patients receive artificial input to their auditory pathways by direct electrical stimulation of the auditory nerve, on which they base their often surprisingly good perception of speech. In aphasic patients, both increased and decreased auditory responses have been observed on the lesioned side (*38*), which suggests that neuromagnetic recordings may be used to classify the functional disorder in more detail than what is possible by other clinical or by anatomical evidence.

The ability of MEG measurements to give selective information about the functions of sensory projection areas of both hemispheres also opens the possibility of following cerebral maturation of healthy and diseased children.

Conclusions

It seems that for a long time MEG and EEG will remain the only noninvasive methods for monitoring brain activity on a millisecond scale. Multichannel MEG systems are presently expensive, on the order of $1 to $2 million, but developments in SQUID technology, magnetic shielding, electronics, and computers will probably lower the cost in the future. If practical high-T_c SQUIDs (*39*) and magnetic shields can be made, the cost of an installation may drop significantly.

Because synchrony of cortical events largely determines the measurable magnetic fields, MEG data obtained so far usually reflect the activity of the most synchronous, modality-specific areas, comprising 20% of the total cortical surface. One future goal is to detect signals from other regions as well and to be able to differentiate better between simultaneous responses from several cytoarchitectonic areas.

By investigating the spatiotemporal course of MEG recordings it should be possible to study several aspects of signal processing in the brain. Basic research of this type may, in the future, be one of the most important applications of magnetoencephalography.

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22. The deflections are denoted according to their electric counterparts. N100m thus means that the peak appears at 100-ms mean latency after the stimulus onset and that the simultaneous electric signal, N100, is negative at the vertex; m refers to magnetic. Peaks designated with a P would show vertex positivity in EEG measurements.
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