Magnetoencephalography

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Introduction

The same fluctuating electrical sources in the brain that produce the scalp potentials of the electroencephalogram (EEG) also produce a magnetic field over the head. A measurement of this field is called a magnetoencephalogram (MEG). Because the MEG and EEG are produced by the same sources, MEG recordings can resemble those of EEG. For example, a single MEG trace (a recording of the fluctuating magnetic field vs. time at one location on the head) can resemble an EEG trace recorded at a related location. However, some MEG recordings look different from equivalent EEG recordings. Thus, an MEG spatial map over the head is quite different from the equivalent EEG map, where each map shows the magnetic field or scalp potential over a large region of the head, at one particular instant in time (sometimes called a snapshot). They are different because the MEG spatially samples the electrical sources differently. This allows the MEG map to provide some different information about the sources in the brain than does the EEG map. In that sense, the MEG is complementary to the EEG, and both are necessary to obtain the maximum amount of information about these electrical sources.

Among the noninvasive techniques for functional imaging of the human brain, the MEG and EEG are unique in that they are directly and instantaneously tied to neuronal currents, the brain's information-processing mechanism. In particular, the MEG and EEG signals are mostly produced by the postsynaptic currents in the pyramidal cells of layers III and V of the cortex. In contrast, functional magnetic resonance imaging (fMRI), positron emission tomography, and single-photon emission tomography have an indirect and delayed relationship to synaptic events through hemodynamics or metabolism. However, the spatial localization of MEG and EEG sources is uncertain, in contrast to definitive localization of the three tomographic methodologies. Other forms of brain imaging, such as MRI and computer assisted tomography, only look at anatomic structures, not functions. Use of the MEG is sometimes called magnetic source imaging.

The brain's fluctuating magnetic field is very weak, commensurate with the weak potentials measured by the EEG. MEG signal levels are typically below 10^{-12} T (tesla), or 10^{-8} G (gauss) in older units; this is much weaker than the urban fluctuating magnetic background of approximately 10^{-7} T or 10^{-3} G and weaker than the earth's steady field of approximately 0.5×10^{-4} T or 0.5 G. Therefore, the two main requirements for measuring the MEG are a magnetic detector of high sensitivity and the suppression of the fluctuating magnetic background (the steady background usually presents no problem).

The sensitive detector used is the SQUID (Superconducting Quantum Interference Device), which operates at 4 K and is therefore contained in a liquid helium dewar. Modern MEG dewars are helmet shaped and enclose most of the head. The dewar typically contains several hundred SQUIDs, where each SQUID is fed by a magnetic sensing coil, and most of these coils are arrayed on a spherical section over the head at grid points 2 or 3 cm apart. This spherical section is at an average distance of approximately 2 cm from the adult scalp, where some of the separation is due to the vacuum space in the dewar. The many sensing coils allow simultaneous magnetic field measurements at the many coil locations over the head, resulting in a continuous series of 'snapshot' maps over the head. The most fundamental choice of sensing coil is a simple wire loop, which measures the component of the magnetic field vector normal to the loop, B_z. One loop connected to its SQUID is called a magnetometer, and if all sensors in a dewar were chosen to be magnetometers, then each snapshot is a map of the magnetic component B_z over the head.

The fluctuating background is suppressed mostly in two ways. First, the measurements are made in a magnetically shielded room, which can exclude almost all of the fluctuating external fields. An early example is shown in Figure 1. Second, the gradient of B_z can be measured instead of B_z itself, where the gradient is the difference in B_z at two locations over the head. These can be neighboring locations along the spherical surface, parallel to the skull, or they can be radially separated locations, perpendicular to the skull. The measurement in each case is said to be due, respectively, to a planar or a radial gradiometer. The planar gradiometer coil consists of two side-by-side loops magnetometer connected in opposition, whereas the radial gradiometer coil consists of two coaxial loops connected in opposition, separated radially. The background is suppressed because the gradient of the background is much reduced compared with that of the brain. In other words, a background source which is distant gives almost equal signals to the two gradiometer coils and hence is largely canceled,
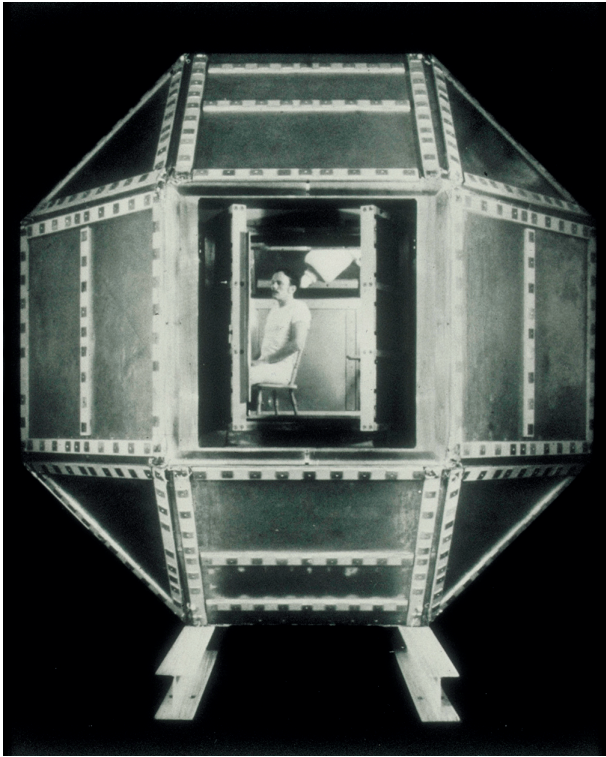
Figure 1 The magnetically shielded room at the Massachusetts Institute of Technology, where the first MEG measurements with the SQUID were made by one of the authors (Cohen) in 1972. This illustrates heavy, effective magnetic shielding. The walls contain five layers of shielding: three are of the expensive high-mu shielding material called moly permalloy, and two are of pure aluminum, for eddy current shielding. The room is roughly spherical because of the efficiency of this shape. This is an example of an effective room that removes almost all urban background, but it is expensive to build. Newer rooms are larger, to accommodate the large helmet dewars, but are box shaped and usually have fewer layers of moly permalloy and hence are basically less expensive. Also illustrated here is the basic setup for measuring the MEG. The subject is shown positioned for recording his MEG and wears clothes that contain no magnetic materials (no zippers or shoes), which could cause relatively large magnetic disturbances. The large white cylinder near the subject's head is the liquid helium dewar, and this early dewar contains only a single SQUID detector in the tail. At that time, before whole-head dewars were developed, maps were made by tedious sequential measurements over the head.

whereas the field from the nearby brain is different in each and hence is not canceled. A good, multilayer room can eliminate the background almost completely but adds expense, whereas the gradiometer method, although less expensive, cannot eliminate background as well. Each MEG system is a compromise among these various factors and can contain magnetometers, gradiometers, or a combination of these, housed in a particular choice of shielded room. The background can also be reduced in a third way – via software processing of the MEG signals, where the software is able to recognize signals from an outside source and reduce or eliminate them. The cost of an entire MEG system, including shielded room, SQUID system, hardware, and software, is approximately $3 million. For example, see **Figure 2**.

Using the MEG

MEG measurements are made in the following way. First, all magnetic material on the subject's body is removed or demagnetized, and the subject changes into magnetic-free clothes. Fiducial locations on the head are accurately noted; in one system, three small coils are attached, which will be continuously sensed by the MEG for accurate head location. If the EEG is to be recorded simultaneously with the MEG for complementary information, EEG electrodes are now applied to the scalp. Next, the subject, seated or in the supine position, is placed with his or her head in the helmet dewar, as shown in **Figure 2**. Next, the raw recordings are made, which consist of MEG traces on all channels, due either to evoked neural activity or to spontaneous activity, depending on the purpose of the session.

Then, in most cases, steps are taken to extract the signal from the noise, where the noise is often unwanted MEG signal from areas of the head not being measured. Traditionally, this entails averaging the signal with respect to a repeated event (e.g., sensory stimulus onset) to produce an 'event-related field' completely analogous to the 'event-related potential' derived by averaging EEG. Increasingly, such 'time-domain' processing is supplemented by 'frequency domain' analyses in which the power in different frequency bands is estimated at different latencies after the stimulus and then averaged across trials. Such processing permits activity that is not strictly phase-locked to the stimulus to be studied. Finally, a sequence of spatial maps (snapshots) are extracted from the trace maps, each for a different instant in time, and used to estimate the neural sources in the brain that are generating the signals. This estimate is termed the 'inverse solution' and is usually the purpose of the measurements.

Unfortunately, inverse solution MEG (and EEG) maps have no unique solution and are handled as follows. All inverse solutions require, in addition to the MEG field map, two elements. First, they require a biophysical model for calculating how activity in any particular brain region would appear at the sensors. Such 'forward calculations' vary in regard to how accurately they model the shape of the head and the conductance in its various compartments. All inverse solutions also require *a priori* assumptions, allowing them to choose between the infinite

Figure 2 An example of a state-of-the-art MEG system. Although not apparent, this system is housed in a large shielded room. The entire structure at the subject's head is called a gantry, and it is set to perform an MEG scan of a subject in the supine position. The gantry can also be swung upward when needed to accommodate a subject in the sitting position. As in **Figure 1**, the subject wears no magnetic material. The subject's head is shown positioned in a helmet-shaped liquid helium dewar, as part of the gantry. This dewar contains 306 sensors surrounding the head, illustrated in the inset at left, oriented as if the patient was in the sitting position (head vertical). The sensors consist of 306 'pickup coils' centered at 102 locations over the head, with three different coils at each location. One coil is a simple outside square and hence a magnetometer; the other two are rectangular planar gradiometers, oriented at right angles to each other. Three SQUIDS are part of each square. Thus, the entire system consists of 102 magnetometers and 204 planar gradiometers for a total of 306 MEG channels. This MEG system, called Vector View 306, is made by Elekta AB (Finland). Other manufacturers supply similar systems, each with its own distinctive features.

number of current sources that can produce any given MEG (or EEG) map. The simplest inverse solutions assume that the field is generated by a single focal source, called a current dipole, that is defined by its position, orientation, and strength. Such assumptions are strictly accurate for only the first few milliseconds after the initial arrival of activity in sensory cortex – for example, prior to 20 ms in somatosensory cortex. However, in many cases the MEG field can be well approximated by an equivalent current dipole even when it is known to be generated in multiple locations of varying extent. Other *a priori* assumptions may concern how many brain areas are contributing to the solution, their focality, and/or their correlation with one another.

There exists extensive literature on MEG inverse methods. Some methods estimate the activity at all brain locations, whereas others restrict possible sources to dipoles that are in the cortex and perpendicular to its local surface, as determined from the MRI in the same subject. This assumption is reasonable because the MEG is mainly generated by currents within the apical dendrites of pyramidal neurons, which are oriented perpendicularly. These currents may be from ligand-gated channels at excitatory or inhibitory synapses or from voltage-gated active conductances. Action-potentials do not contribute significantly to the MEG due to the random (canceling) spatial arrangement of their generating currents and their lack of synchrony relative to their short duration; further, their 'ends' cancel internally. Note that although MEG and EEG are generated by current sources, most sources do not contribute to either one because of cancellation at many spatial levels within the same dendrite, cell, or cortical column

or between cortical areas. Thus, even if the inverse estimate were accurate, it would show only the uncanceled sources.

Inverse methods often use additional assumptions to localize activity, such as the assumption that the brain minimizes the total power across its surface or total current. Such assumptions have little, if any, biological justification. Consequently, it is important to seek validation of proposed solutions using more certain methods. The most direct validation can be obtained from intracranial EEG recordings during the same tasks as those recorded with MEG. Although certain localization can be obtained with intracranial EEG, such recordings are only obtained in the context of severe epilepsy, and only in clinically indicated locations, so issues of pathology and sampling limit their availability and interpretation. In healthy subjects, the reasonableness of MEG inverse estimates can be judged against fMRI results in the same task. However, there are many reasons why MEG and fMRI signals may be generated in different locations, so the lack of correspondence is not definitive. Conversely, the locations of fMRI activations may be used to bias MEG inverse estimates, provided that the method allows for mismatches between the underlying generators.

Differences between MEG and EEG

There are three differences between MEG and EEG instantaneous spatial maps that allow the MEG to give different information from the EEG. These differences are calculated when the head is idealized as a system of concentric spherical shells representing the scalp and skull, etc. Also, the current source generating the MEG and EEG is idealized to be a dipole, the simplest source possible (a more complex neural source can always be synthesized as a sum of dipoles). In the following, we discuss the calculated MEG and EEG maps and compare them with regard to their ability to determine the location and angle of the dipole which generated them – that is, to localize the originating dipole.

The first difference is due only to the orientation of the dipole. For a dipole oriented radially to the spherical surface (skull), it can be shown, surprisingly, that the external magnetic field is everywhere zero; hence, there is no MEG signal. This is due to the symmetry cancellations in perfectly spherical conductors. Therefore, there is only an MEG signal for a dipole oriented tangentially, where there is no perfect symmetry cancellation. Because the MEG/EEG sources are mostly pyramidal cells in the cortex, and these have a net direction perpendicular to the cortical surface, it follows that sources radial to the skull are mostly located on the gyri and tangential sources mostly in
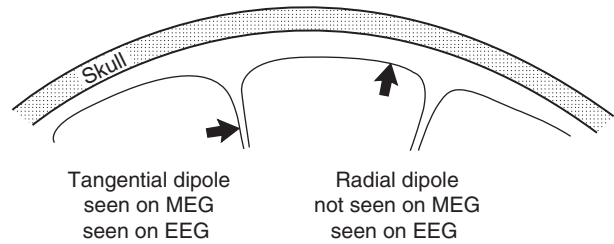

Figure 3 Two electrical sources in the cortex; one is oriented tangentially to the spherical skull and the other radially. Each is represented as a current dipole (arrows). Because sources in the cortex are oriented perpendicularly to the cortical surface, tangential sources are located in the sulci and radial sources are in the gyri. Although the EEG sees both sources, it is dominated by the radial sources in the gyri. If the radial dipole were shifted, for example, to the right, slightly into the bend, it would then have a small tangential component and hence would now be visible on the MEG. Thus, the gyral area of invisibility is less than is apparent. Also, in cases in which the lower ends of sulci bend around, there are radial–tangential complications.

the sulci, as shown in Figure 3. Thus, the MEG is largely due to the sources in the sulci; the EEG is due to both. Therefore, one consequence of this difference is that the MEG should see those tangential sources that on the EEG may be dominated or masked by strong radial sources. Indeed, radial sources tend to dominate the EEG because on the gyri they are closer to the electrodes on the scalp. The fact that radial sources produce zero external field has an important consequence for sources deep in the head. Because a dipole at the center of a sphere is always a radial source and hence produces zero external field, it follows that the MEG due to deep sources is suppressed compared to the EEG; the deeper the source, the more the suppression. Because of this radial–dipole difference, the MEG map is due to a subgroup of the sources seen on the EEG. That is, the MEG sees less than does the EEG.

The other two differences in MEG and EEG maps involve actual map patterns due to a tangential dipole. These are illustrated in Figure 4. First, the MEG pattern is seen to be oriented perpendicularly to the EEG pattern due to a basic orthogonality between magnetic and electrical fields. Consequently, MEG localizes a source better in the y direction, whereas the EEG localizes better in the x direction. Second, the MEG pattern is somewhat tighter, largely due to the smearing by the high-resistivity skull of the surface potentials measured by the EEG. In contrast, for perfectly spherical surfaces, the MEG is unaffected by the resistivities of the different layers. The consequence of this size difference is that the MEG localizes a tangential dipole somewhat better in its best direction (y), in comparison to the EEG in its best direction (x), if all other factors are equal, such as
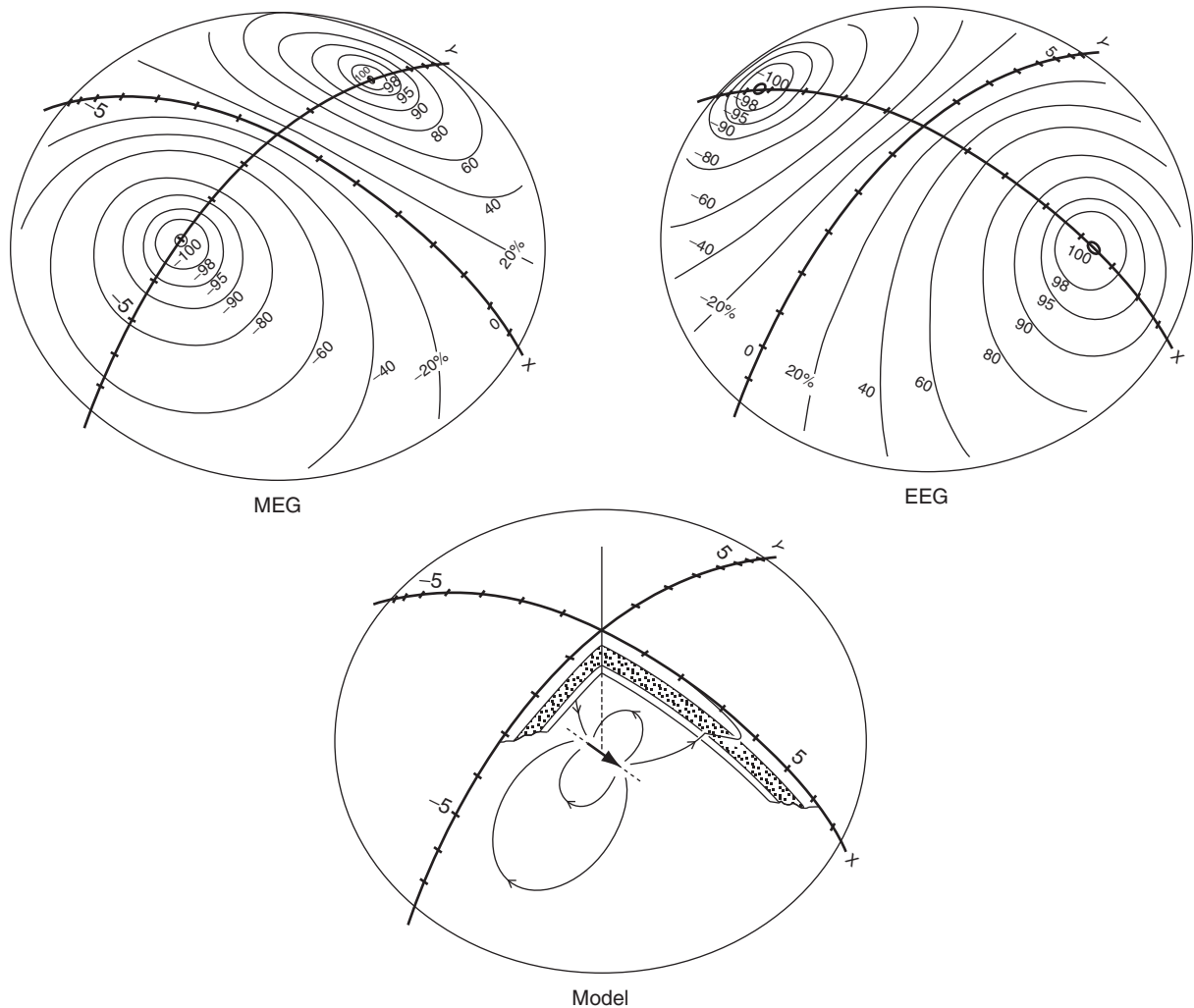
Figure 4 Difference between the MEG and EEG maps, computed by using an ideal spherical model of the head containing a tangential dipole source (arrow) at a depth of 2.7 cm. The model cutaway shows four spherical boundaries representing scalp, skull, cerebrospinal fluid, and brain. The continuous spreading currents generated by the dipole are seen as thin lines. The maps are shown on a spherical 'cap,' which has x and y coordinates with ticks at each centimeter, with contour lines every 20%. The MEG map is of the component of magnetic field vector normal to the surface (B_z), whereas the EEG map is of the surface potential V. The MEG map is different from the EEG map in that it is oriented by 90° and is tighter by approximately 30%. It can therefore localize somewhat better in its 'best' direction (y) compared with the best direction (x) in the EEG, according to this ideal model.

modeling errors – for example, errors in knowing the conductivities of all the layers. However, such modeling errors are considered worse for the EEG, which thus favors the MEG.

Thus, all in all, MEG advantage in localizing a dipole is in the range of about 30% better (dipole shown here) to perhaps a factor of 2 better, depending for example, on resistivity errors in the EEG modeling. Also, in the actual nonspherical head, the difference between radical and tangential dipoles becomes diffused. Although there have been recurrent claims that the MEG can localize a dipole source far better than can the EEG – for example, to within 2 mm (because of reduced sensitivity to conductivity errors) – there is no experimental evidence for this claim in the human

head. The one reported experiment under these conditions, using implanted current sources in the brain, has shown only a minor advantage, yielding 8 mm accuracy for the MEG versus 10 mm for the EEG. Also, several advanced computer modeling studies have shown no significant MEG localization advantage. Finally, because MEG calculated sources are laid onto MRIs of the subjects, there is a co-registration error from MRI to MEG of approximately 3 mm. In brief, the 2 mm claim is unproven and unreasonable. However, the MEG has contributed to EEG source localization in an unexpected way. Because the MEG was developed in physics labs, advanced techniques were used for inverse solutions on the maps to find the sources. EEG data had usually been interpreted

by visual inspection, occasionally with large errors. However, EEG manufacturers began duplicating the MEG inverse solutions, and now include such software in EEG systems, so that EEG localization is now more accurate.

Based on the three differences discussed above, it can simply be stated as "the MEG usually sees less than the EEG sees, but sees it somewhat more clearly".

There are other MEG–EEG differences that are of a more practical nature. One difference, favorable to the EEG, is the MEG nuisance of embedded magnetic material in the subject, such as magnetic dental work, which creates large interfering magnetic signals. This material can often be demagnetized with a handheld magnetic eraser. However, there are differences that are favorable to the MEG. One is that the MEG does not require electrodes to be pasted on the head, as does the EEG. Perhaps a more important difference concerns DC; galvanic skin (scalp) potentials severely hamper EEG DC measurements, but the MEG does not see these obstacles. In this regard, the MEG has a distinct advantage that has yet to be fully exploited.

Current Status and Future Prospects

There are approximately 120 whole-head MEG systems in use or on order throughout the world, some with more than 300 SQUIDs per helmet. Many of these systems are located in Germany, Japan, the United States, Finland, and Canada. Thus, an increasing number of MEG maps are being recorded, often in combination with EEG maps, due both to spontaneous signals and to event-related signals. The overall purpose is to determine if the selectivity of the MEG can clarify the sources of the signals. The efforts are divided into two broad areas: research on the workings of the normal brain and the search for clinical applications of the MEG.

In research on the normal brain, MEGs are being studied for responses evoked by stimulation of each of the five senses. To date, MEG has produced evidence supporting locations of sources in the primary sensory cortices. One early example is the well-studied 20 ms somatosensory signal from the human brain in response to peripheral nerve (wrist) stimulation. From the EEG alone, the source of this signal had been ambiguous, with a choice between two radial or one tangential sources. However, the combination of MEG and EEG maps showed the source to be mostly a tangential dipole. In another example involving somatosensory cortex, MEG and EEG were combined to study the finger representation in the cortex. It was found that MEG and EEG combined gave more localization accuracy than each separately. Some of

the studies used MEG without EEG; one such study reported increased strength of cortical sources of left fingers of string players. Without EEG maps, however, there can be doubt that the useful information obtained was indeed due to MEG selectivity.

Overall, MEG has demonstrated internal organization in some of the primary areas of the human brain – organization that was previously seen only in the animal brain. MEG has also shown the separation of activity between primary and secondary areas, for example, in the somatosensory cortex and in the auditory cortex. Interactions between successive cortical areas are increasingly being inferred from the phase-locking, coherence, or Granger causality, calculated on individual trials between waveforms recorded at different locations.

MEGs are being studied with regard to the later components as well. After processing in these initial sensory areas of the brain, there are further processors that decode certain classes of stimuli, such as faces. MEG has been able to localize the face area to the same location identified with fMRI and intracranial EEG and has been used to characterize its cognitive responses to a range of face-like stimuli (Figure 5). The situation becomes more complicated when moving further downstream to neural activity underlying higher cognitive functions, such as understanding sentences. The fact that neural activity can spread to distant cortical areas in approximately 20 ms suggests that multiple widespread cortical areas may be involved in the response to words, which peaks at approximately 400 ms. Modeling in such situations with a distributed source instead of a dipole (Figure 6) localizes MEG activity to the same locations that have been found with hemodynamic measures and with direct intracranial EEG recordings in epileptic patients. Data suggest that in situations such as these, efforts to localize distributed generators appear to have been more successful with MEG than with EEG. If true, this may be due to the fact that, as previously mentioned, the MEG sees fewer sources with a somewhat tighter field than EEG and thus is better able to disentangle multiple distributed sources. However, it is also possible that with better forward models and inverse methods, EEG will be equally successful in localizing complex distributed generators. In any case, modeling studies and some experiments clearly suggest that the best localization will only be obtained by combining MEG and EEG.

Concerning clinical application of MEG, efforts are being made to evaluate MEG usefulness in various areas, including presurgical functional mapping, head injury, and epileptic spike localization. The purpose of presurgical mapping is to locate the regions of the sensorimotor strip using evoked response in order to
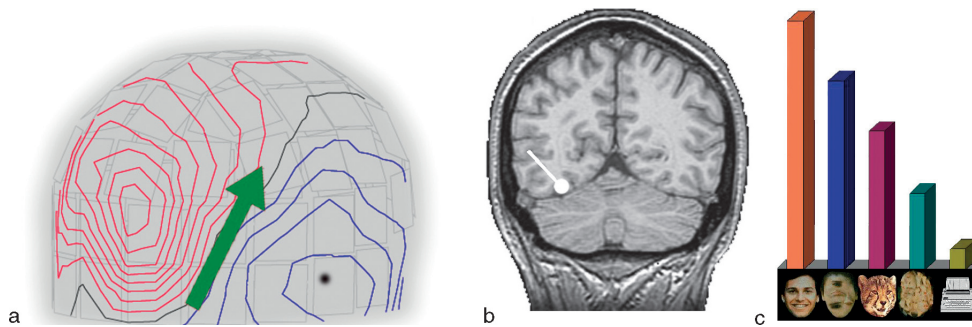
Figure 5 Use of MEG in face recognition research. (a) MEG contour map (50 fT step/line) drawn on the head of the subject and sampled at 165 ms after a photo has been viewed. The head is viewed from the right rear; the dark spot marks the right ear. The pattern is seen to be roughly dipolar; hence, a single dipole was assumed for the source. An inverse solution located the dipole(green arrow), where the depth is not seen here. (b) The same dipole source superimposed on the subject's MRI, seen from the front. Here, the dipole is shown as a white dot, for accurate location, in the right fusiform gyrus. The attached rod gives the dipole direction and amplitude. (c) The dipole amplitudes after viewing any of five face photographs and controls, averaged over ten subjects. The normal human face evokes the largest response. The MEG can thus be used to estimate the location, timing, and strength of a neural process associated with face encoding (Halgren et al.).
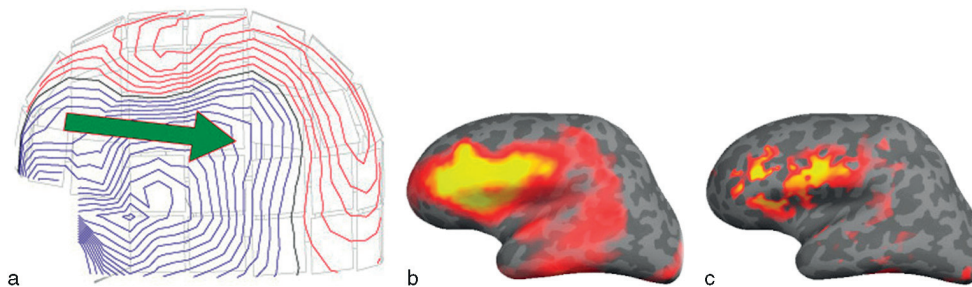

Figure 6 Use of the MEG with multimodal integration in reading research. Subjects read words and made a semantic judgment (pressing a key if the word referred to an object or animal more than 1 foot in length). MEG maps were produced by subtracting the signals evoked by novel words from those evoked by words that had been read previously in the same task. (a) MEG contour map, viewed from the subject's left, at 540 ms after stimulus onset. Again, the pattern is roughly dipolar, and the green arrow shows the computed source dipole. It appears 'off-center' in this case because of the angle of view. (b) A determination of the sources, from the same contour map, using a nondipolar advanced inverse method allowing a continuous distribution, but sources are now constrained to be on the cortical surface (Dale et al.). The 'inflated' left cortical surface is shown in the same view as in (a). (c) The same data as b, except the source has been further biased by the fMRI location of activation in the same subject and task. Note the increased spatial detail revealed by the integration of the fMRI information in the same task. The MEG data thus reflect the repetition priming effect on semantic processing.

minimize neurological deficit due to surgery. MEG localizes well in this task, as does fMRI. In some cases, the hemodynamic response near a tumor or arteriovenous malformation may be abnormal, and MEG may thus be preferable. In head injury, MEG appears to show focal slow-wave abnormalities more reliably than does EEG; hence, it shows more promise of providing localizing information. In the measurement of epileptic spikes, MEG, when used with EEG, is able to clarify or localize some epileptic foci better than can EEG alone. MEG has also shown spikes that appear to be masked on EEG by other spontaneous brain activity, seen less on MEG. Definitive localization of seizure foci, adequate to guide their surgical removal, often requires the placement of intracerebral electrodes.

The hope is that the noninvasive combination of MEG and EEG may allow such electrodes to be more successfully targeted or, in some cases, to be avoided altogether. MEG also appears useful when a skull defect from a prior operation severely distorts the propagation of EEG to the scalp. In this regard, MEG of neonates, which have begun to be measured with smaller helmets, has an advantage in source localization because the fontanelles in the infant skull cause larger errors in EEG. Also, MEG research studies on neuropsychiatric disorders such as schizophrenia, autism, and pain often show promise because of MEG's greater specificity compared with EEG. These studies can provide insight into the neural bases of severe dysfunction in the absence of any structural abnormality.

Expansion of clinical MEG use from regional referral centers to community hospitals will require further evaluation.

Concerning future possibilities, work measuring low-field MRIs using SQUID detectors shows promise for simultaneous measurement of MEG and MRI, eliminating the coregistration error (~ 3 mm). The future possibilities of MEG depend on how well its advantages will balance against its practical problems and high cost. The practical problems include not only the reduction of magnetic background but also the effort in maintaining a cryogenic system that needs refilling with liquid helium once or twice per week. A cost reduction would make MEG more attractive for clinical diagnosis. In any case, MEG will be used well into the future, both because the large MEG systems now in use or coming online will generate many years of investigations and because there is a general, long-term need for noninvasive measurements of the brain.

See also: Cognition: An Overview of Neuroimaging Techniques; Electroencephalography (EEG); Electrophysiology: EEG and ERP Analysis; Event-Related Potentials (ERPs) and Cognitive Processing; Evoked Potentials: Recording Methods; Human Depth Electrodes; Neuroimaging.

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