Magnetoencephalography and Magnetic Source Modeling

23

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Introduction

The generators of neuromagnetic signals are essentially the same as those of EEG signals. Summation of synchronous postsynaptic potentials occurs to a greater degree when there are regular arrays of similarly oriented cells, as for instance in the pyramidal cell layer in the cortex. Magnetic fields generated by electrical currents in the cortex are oriented perpendicular to the direction of neuronal currents. This, together with the folded geometry of the cortex, results in some differences in the cortical surfaces that contribute to EEG and magnetoencephalography (MEG) signals. MEG sensors are sensitive to magnetic fields that are orthogonal to the head surface. This corresponds to electrical fields that are parallel to the scalp surface, such as those generated by cortical surfaces in the sulcal banks. EEG, on the other hand, is preferentially sensitive to radially oriented electrical fields generated at the crests of gyri.

Magnetic fields generated by the brain are of the order of 100 femtotesla ($\sim 10^{-13}$ T). For comparison, the electrical activity of the heart generates magnetic fields that are greater by many orders of magnitude. The ambient electromagnetic noise in an urban environment is even greater. The detection of weak magnetic fields generated by the brain, therefore, requires not only highly sensitive instruments, but also a magnetically quiet environment that is usually provided by a magnetically shielded room (MSR).

MEG History

The key enabling technology that allows the recording of very weak magnetic fields is the superconducting quantum interference device (SQUID). This device is based on a quantum phenomenon called the Josephson effect which describes the current flow through a very thin insulator that separates two superconductors. Before the era of SQUIDs, David Cohen at MIT had demonstrated in 1968 that it is possible to record cortically generated magnetic fields in a magnetically shielded environment. The recordings used coils wound around ferrite cores and employed signal averaging based on simultaneous recorded EEG signals. The earliest commercially available SQUIDs were used by David Cohen and others at MIT to record the first magnetocardiogram—a signal that is several orders of magnitude larger than magnetic fields generated by the brain. By 1971, the first MEG records of the alpha rhythm were demonstrated [1].

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MEG Equipment and Recording

From early devices with a single magnetometer, MEG recording technology has evolved over the years to multichannel systems with several hundred sensors.

MEG recording systems are housed in a magnetically shielded room, which isolates the recording system from ambient magnetic interference from various sources in the environment. In order to achieve sufficient attenuation of ambient magnetic interference, the walls of the MSR may have several layers of different types of metal that attenuate magnetic interference in different frequency bands. In addition to passive shielding, some MSRs may also have active coils in the walls which generate their own magnetic fields to cancel ambient fields.

Magnetic fields generated by the brain are picked up by *flux transformers* which are inductively coupled to the SQUIDs. The flux transformers can be configured as *magnetometers* or *gradiometers*. Magnetometers—a simple example being a conducting loop—produce output currents with magnitudes that are determined by the magnetic flux through the loop. Gradiometers, on the other hand, are configured by coupling two conducting loops either side by side (in the same plane), or along an axis, in such a fashion that the net output is proportional to the difference in magnetic fluxes through the two loops. These planar or axial gradiometers detect magnetic field gradients rather than absolute magnetic flux at a location. In typical MEG recording systems, an array of flux transformers are arranged in the shape of a helmet at the bottom of a container called a *dewar*. The *dewar* also houses the SQUIDs and is filled with liquid helium to maintain the temperatures low enough to permit superconductivity. The outputs of these sensors are amplified, then digitized, and recorded using digital recording systems.

In addition to localizing spontaneous epileptic activity, MEG studies are often performed to localize functional cortices. Localization of primary sensory areas is performed by source modeling of evoked responses to simple stimuli (visual, auditory, or somatosensory). For the lateralization of language functions, a language task such as a word listening task or word reading task may be employed. Localization of motor areas requires the patient to perform simple motor tasks such as tapping a finger. For evoked responses to be sufficiently well defined and stand out above the resting background oscillations, many trials of the task (typically >100) are usually repeated. The responses recorded at each sensor are averaged across trials in order to obtain satisfactory signal-to-noise ratios prior to modeling the sources of these evoked responses.

Magnetic Source Modeling

In tandem with the development of the recording hardware, the rapid evolution of computing technology has made it possible to take the recorded activity from the MEG sensors and model the cortical generators of the activity. This step is referred to as magnetic source modeling or magnetic source imaging (MSI).

The objective of magnetic source modeling is to account for the topography of the magnetic fields measured at a given point in time in the MEG sensors using a hypothetical generator within the brain. The problem of determining brain sources from a set of measurements at the sensors is an example of an *inverse problem*. In this case, the inverse problem is highly underdetermined; i.e., there are far too many unknown variables and not enough constraints for there to be a unique solution to the problem. Such inverse problems are often referred to as "ill-posed" inverse problems. There are an infinite number of configurations of model sources within the brain which could all produce the same observed sensor level recordings. In order to make this problem tractable, we first need to model how magnetic fields associated with any given electrical generator within the head propagate to the sensors. This is called the

forward model. The forward model requires an anatomical model of the head and the structures from which the electrical activity arises. This is referred to as the *head model*. Once a forward model is defined, it is possible to generate many hypotheses about possible generators of the observed sensor measurements and identify the hypothesis that best explains the measurements. Different source modeling techniques differ in the nature of the forward modeling and the types of generators permitted.

Of the various source modeling methods that have been developed over the years, *equivalent current dipole* (ECD) modeling has found wide use in clinical applications. ECD modeling assumes that the electrical generators of activity measured at MEG sensors are point dipoles: a source and sink (positive and negative ends) separated by an infinitesimally small distance. Although real generators of electrical activity in the brain are not point sources, ECD modeling has proven to be clinically useful in localizing the sources of epileptic spike activity and evoked potentials. Dipolar models are defined by their locations (x-, y-, and z-coordinates in a frame of reference to which the patients' head model has been co-registered) and orientation (defined by 2 parameters). Additional "goodness-of-fit" parameters quantify how well a model dipole accounts for the observed neuromagnetic fields.

Several alternative techniques for source modeling currently exist, for instance techniques that model the generators as a distributed field of point dipolar sources. These distributed source modeling approaches have predominantly been used in research applications thus far. Source modeling methods can also be applied to the electrical signals recorded by EEG. However, because magnetic fields are not affected by CSF, meninges, skull and scalp, or skull breaches, the head modeling requirements for magnetic source modeling are much simpler. This translates into higher spatial resolution for an equivalent number of recording locations around the head for magnetic source modeling compared to electrical source modeling [2].

Source Modeling of Epileptic Activity and Evoked Responses

When modeling the sources of epileptic activity, the recorded MEG data are first reviewed visually by an experienced electroencephalographer to identify epileptic spike events or ictal activity which can then be subjected to source modeling.

Epileptic spikes seen in MEG may not always be seen in the simultaneous EEG recording, and likewise, not all EEG spikes are represented in MEG. Since MEG sees the magnetic component of an electrical event in the cortex, it is in theory more sensitive to electrical currents that are tangential to the head surface—as for instance from the banks of sulci. EEG, on the other hand, is more sensitive to radial sources, such as those generated at the crests of gyri. In most instances, however, epileptic spikes have generators that are several square centimeters in area and have both radial and tangential components. However, the spike may lead in one or the other modality depending on whether the tangential or radial sources dominate at the onset of the spike.

Once epileptic spikes are identified in the MEG sensors, dipolar models are typically employed to localize the sources in clinical applications. Figure 23.1 shows an example of interictal epileptic spike events whose sources localize to the right medial temporal regions. Due to the relatively short duration of MEG recordings compared to long-term EEG monitoring studies, ictal events during MEG are uncommon. However, when ictal activity is recorded, early ictal rhythms that precede any head movements can be subjected to source modeling to localize seizure onset zones. An example of dipolar source modeling applied to ictal rhythms is shown in Fig. 23.2.

There is ample evidence that magnetic source modeling of evoked responses can reliably localize primary sensory cortices (visual, auditory, and somatosensory). Figure 23.3 shows an example of source modeling of somatosensory evoked response to median nerve stimulation using dipolar modeling and dSPM [3]. Localization of primary motor cortex using dipolar

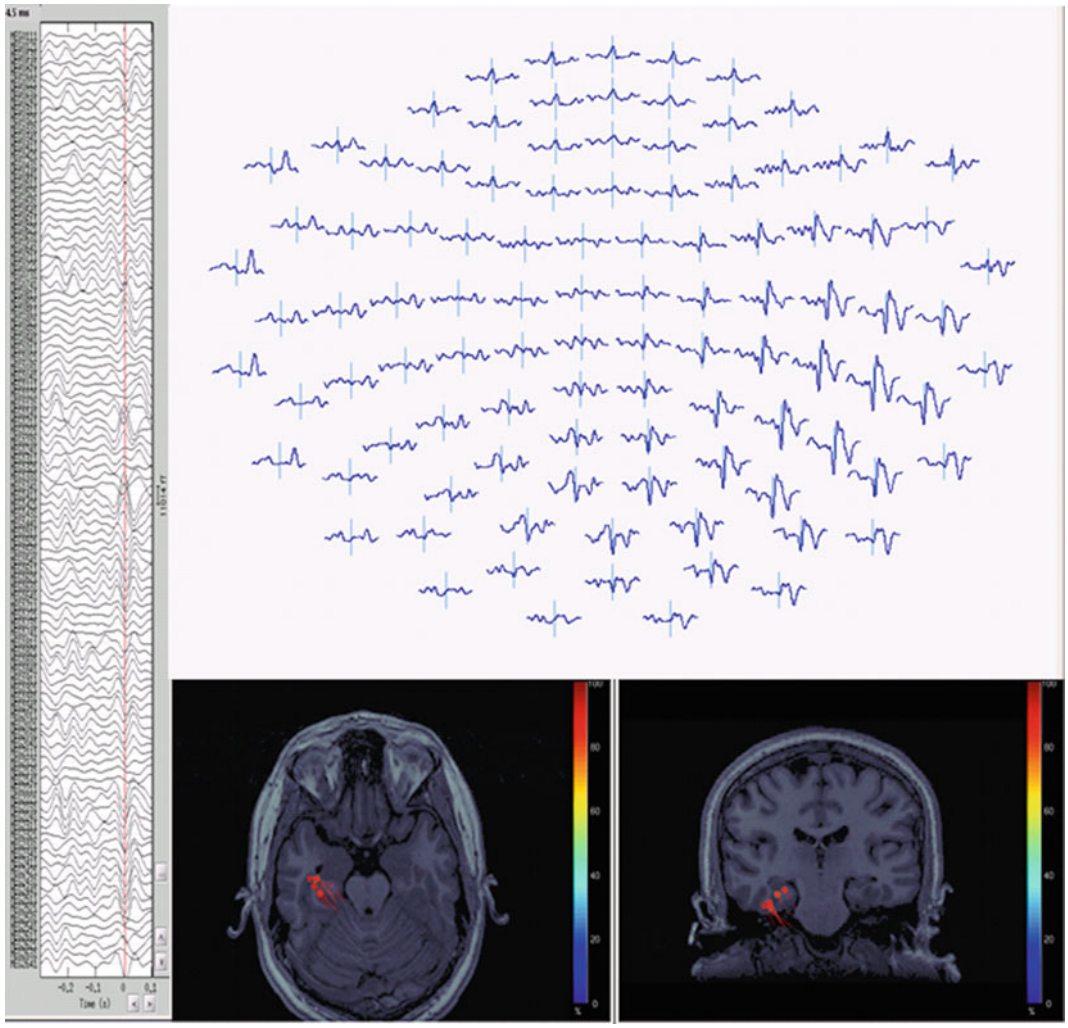

Fig. 23.1 Dipolar sources of epileptic spikes. The panels above show an example of dipolar source models of epileptic spike activity. The panel on the *far left* shows MEG traces from a subset of magnetometers with the cursor marking an epileptic spike event. A sensor level topographic representation of the event is shown in the *top right panel*, along with dipolar sources of a collection of such events on axial and coronal planes through the dipole cluster in the *bottom right panel*

modeling of motor preparation potentials is, however, less reliable [4]. Alternative methods to localize changes in beta band oscillatory activity in the motor cortex have been explored with greater success [5], although yet to be widely adopted.

For lateralizing language, neuromagnetic responses to auditory language stimuli have been found to be concordant with the Wada test in 87% of patients [6]. Using the same methods, Doss et al. [7] found language representation in the hemisphere to be treated with a concordance rate of 86% with the Wada test in 35 patients, with a sensitivity of 80% and specificity of 100%. Several smaller studies have reported MEG–Wada concordance rates between 69 and 100% using a variety of paradigms and analysis methods.

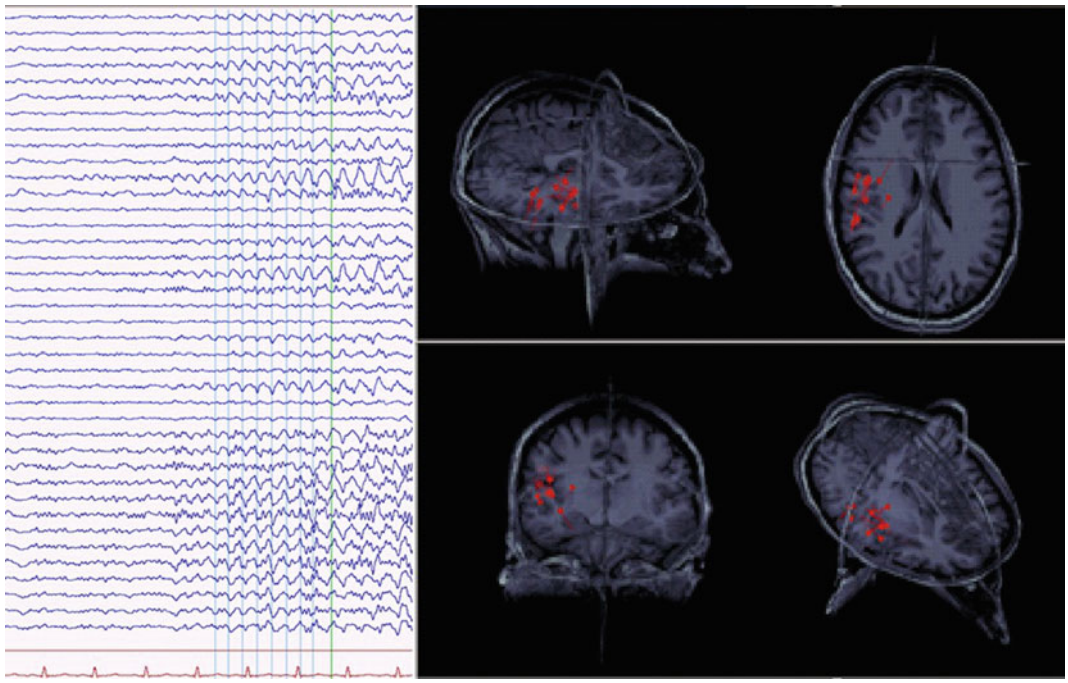

Fig. 23.2 Dipolar sources of ictal sharp rhythms. The *panels above* show an example of ictal source modeling using MEG. The traces on the *left panel* show seizure onset as recorded in a subset of MEG sensors. Dipolar sources of successive peaks of the ictal waveform are shown on planar views in the panels on the *right*

The Role of MEG in Presurgical Evaluations

Unlike EEG, MEG is not indicated for the initial evaluation of new-onset seizures but can provide valuable localization of epileptic pathology in patients with medically refractory epilepsy who are undergoing evaluations for epilepsy surgery. MEG primarily localizes interictal epileptic abnormalities which help identify "irritative zones" in the brain. Source modeling of interictal spikes using MEG may be particularly useful in patients with normal MR imaging, large or cystic lesions, lesions of indeterminate significance to the patient's epilepsy, or with multifocal or rapidly propagated spikes.

MEG is also clinically indicated for localizing primary motor or sensory cortices (somatosensory, visual, or auditory) to guide surgical planning for epilepsy, tumors, or vascular lesions, and can also be used to determine hemispheric language dominance.

The spatial accuracy of MEG and magnetic source modeling for localizing "irritative zones" is second only to invasive EEG [8]. MEG-guided review of MRI data has also been reported to identify subtle abnormalities that were previously missed, especially focal cortical dysplasia [9–11]. However, MEG should not be viewed as a tool that replaces invasive EEG or other noninvasive tests such as PET or SPECT. There is now sufficient evidence that MEG can provide significant non-duplicative information to improve surgical outcomes or preempt expensive invasive intracranial EEG studies [12–15]. While MEG may not eliminate the need for intracranial EEG studies, it can help generate better hypotheses about seizure onset zones, and thereby guide electrode placement for invasive EEG studies [16, 17].

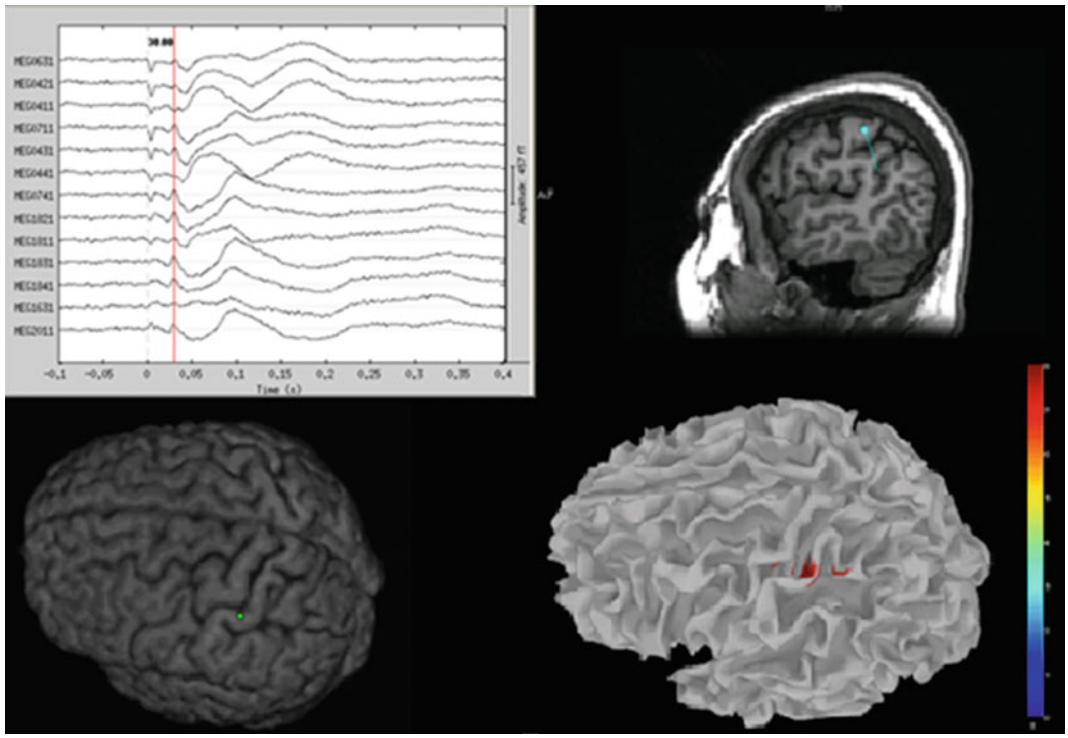

Fig. 23.3 Dipolar and distributed source models (dSPM) for somatosensory evoked responses. The *left upper panel* shows the evoked responses to somatosensory stimulation of the right median nerve in a subset of MEG sensors in the left central region. Dipolar sources at the peak of the response are shown in the *top right* and *bottom left panels*. A distributed source model for the same point in time is shown in the *bottom right panel* (dSPM with a threshold of $p < 0.001$). Both the dipole model and maxima of the dSPM activation localize to the post-central gyrus in an area consistent with anatomically predicted hand somatosensory representation

Some Limitations of Current Clinical MEG Methodologies

Localizing "irritative zones" is often insufficient to predict seizure onset zones, especially when they are multifocal. Unfortunately, ictal MEG studies are not the norm since it is impractical to monitor patients in a MEG scanner for an extended period of time in order to capture seizures. In about 20% of MEG studies, no epileptic spikes may be observed during the recording. In these cases, MEG is unable to provide useful localizing information about epileptic pathology. Alternative interictal biomarkers of epilepsy such as focal slow waves or pathological high-frequency oscillations are therefore of interest.

While most clinical applications of MEG employ dipolar source modeling techniques, dipolar models are unsuitable for studying network phenomena such as functional connectivity, causal interactions, or network dynamics which may have relevance to localizing and modeling epileptic networks.

For localizing function, although source modeling of evoked responses provides good localization of primary sensory cortices, these techniques remain to be validated for mapping language networks in the anterior temporal or frontal neocortices to guide surgical resection boundaries.

Summary

MEG and magnetic source modeling provide a noninvasive technique for localizing spontaneous and evoked brain activity with high spatiotemporal resolution. Single *equivalent current dipoles* remain the most widely used source modeling method in clinical applications, although imaging methods are increasingly being explored. MEG and source modeling of epileptic activity can provide significant non-redundant information to help improve outcomes of epilepsy surgeries or preempt expensive invasive EEG studies. MEG also provides an alternative to fMRI for noninvasively localizing eloquent cortices for neurosurgical planning.

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