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**Mini Review**

# Clinical utility of magnetoencephalography and its recent development

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**Abbreviations**

DC – direct current, ECD – equivalent current dipole, EEG – electroencephalography, IED – interictal epileptiform discharge, MEG – magnetoencephalography, MGH – Massachusetts General Hospital, MMVT -– multi-modal neuroimaging analysis and visualization tool, MRI – magnetic resonance imaging, OPM – optically pumped magnetometer, SQUID – superconducting quantum interference device

## Abstract

Magnetoencephalography (MEG) is an established functional brain imaging modality that was initially developed about 50 years ago and is currently used as a clinical tool for non-invasive assessment of human brain function. The temporal resolution of MEG and electroencephalography (EEG) are identical, although MEG offers many advantages over scalp EEG recordings in terms of localizing epileptic foci and eloquent cortex. Namely, MEG measurements are minimally distorted by cephalic tissue compared to EEG measurements. In this mini-review, we briefly examine the clinical utility of MEG in epilepsy and provide a demographic overview of MEG scans at our institution. The primary focus, however, is on recent developments in MEG technology that address the challenges faced by MEG systems.

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## Introduction

Magnetoencephalography (MEG) is a non-invasive recording of brain activity as reflected outside the skull in the form of magnetic fields generated by neuronal electrical currents [1]. The skull and the tissues surrounding the brain affect the magnetic fields measured by MEG much less than they affect the electrical impulses measured by electroencephalography (EEG). Thus, MEG is more accurate than EEG in source estimation, providing more reliable information about the locations of brain functions, whereas both modalities have identical temporal resolution. Additionally, MEG is more sensitive to tangential sources situated within sulci and cortical planes, compared to EEG which is less sensitive to source orientation. MEG can record 95% of cortical activity, significantly more than EEG, which is more attuned to radial sources [2].

One of the most distinctly utilized clinical applications of MEG is in patients with epilepsy, where MEG is employed regularly to help with epilepsy diagnosis, identification of interictal epileptiform discharges (IEDs), and functional mapping for presurgical evaluation in patients with brain tumor or vascular malformation. We focus on the clinical utility of MEG in epilepsy and present a demographic overview of MEG scans at our institution. Finally, we highlight recent developments in MEG technology that expand its application to many other fields.

## MEG Acquisition

MEG signals are recorded by coils inside the MEG helmet (the sensor space), which are coupled with superconducting quantum interference devices (SQUIDs) inside a dewar filled with liquid helium. The functioning of SQUID relies on the properties of superconductivity, where a small superconducting loop is utilized. Superconductivity necessitates cooling to very low temperatures using liquid helium to maintain the superconducting state. This cooling process is crucial because superconductivity allows SQUID to detect extremely weak magnetic fields generated by brain activity. The electromagnetic principles dictate that the magnetic field intensity decreases proportionate to the distance between the source and the coil; the distance of the coil from the subject's head should be as small as possible. Hence, the placement of sensors within a dewar could result in smaller MEG signals. Due to the limited helium capacity of the dewar, weekly refills are required. MEG systems are located inside magnetically shielded rooms to reduce environmental noise to a level compatible with brain signal measurements.

## The Dipole Model

The simplest and most widely applied source model in clinical MEG is the single equivalent current dipole (ECD), which assumes that at a given time instant, the salient brain activity is focal and restricted to a single brain region or multiple distant brain areas each of which can be modeled with an ECD. ECDs overlaid on individual structural magnetic resonance images (MRI) using thin-slice volumetric images serve to investigate the epileptic focus or functional mapping. This allows early identification of surgery candidates [3]. It facilitates planning of invasive recordings [4] and improves the results. MEG yields non-redundant information in up to about 30% of the cases and is confirmatory in an additional 50% [5]. Seizure-freedom rates after epilepsy surgery are higher when MEG findings are considered in the presurgical conference [5]. For functional mapping, MEG identifies eloquent areas using non-invasive stimuli: somatosensory and motor near the contralateral central sulcus, auditory around bilateral primary and associated auditory cortices, visual in the visual cortex, and language in the left language areas [6].

## Demographical Overview of Scans at Martinos Imaging Center

Martinos Center is equipped with a 306-channel whole-head MEG system (TRIUX neo, MEGIN Oy). The annual trend of clinical MEG scans at the

Center is shown in Fig. 1A. Approximately 100 patients have been scanned per year, referred by Massachusetts General Hospital (MGH) physicians, the pediatric epilepsy program at Boston Children's Hospital, or external referrals. There is a constant demand for pediatric scans where acquisition is challenging due to low motion tolerance (i.e., difficulty in keeping the head still inside the helmet) as well as difficulty in fully and tightly covering pediatric subjects' heads, because they are smaller in size and cannot be placed completely into the conventional adult helmet as their shoulders and relatively short necks limit the insertion depth. We address these challenges by using towels to fix their heads in the appropriate position and allowing family members to stay in the room to relax the patients. A total of 2302 cases were scanned from 2002 to 2023. The numbers of functional mappings are shown in Fig. 1B. An example of representative ECD results is shown in Fig. 2A–D for IED localization, and examples of functional mapping are depicted in Fig. 2E. The somatosensory-, motor-, auditory-, visual- and language-evoked fields are superimposed onto the individual MRIs.

## Advanced and Developing Technology

Recent advances in MEG strive to address the intrinsic limitations of MEG, together with the complexity of the spatiotemporal analysis of brain activities from MEG. A majority of these developments are available for clinical application.

(1) *Three-layer magnetically shielded room and helium recycler*: Martinos Center has a three-layer shielded room with two layers of high permeability materials and a thick layer of high-conductivity material, to exclude almost all fluctuating external fields. Additionally, closed-cycle cryocoolers have recently been introduced at the Center for helium recycling [7]. This system decreases helium costs and the environmental burden, enabling successful long-term MEG operation without helium refills.

(2) *"BabyMEG"*: An extra challenge with younger children, especially premature infants, is their

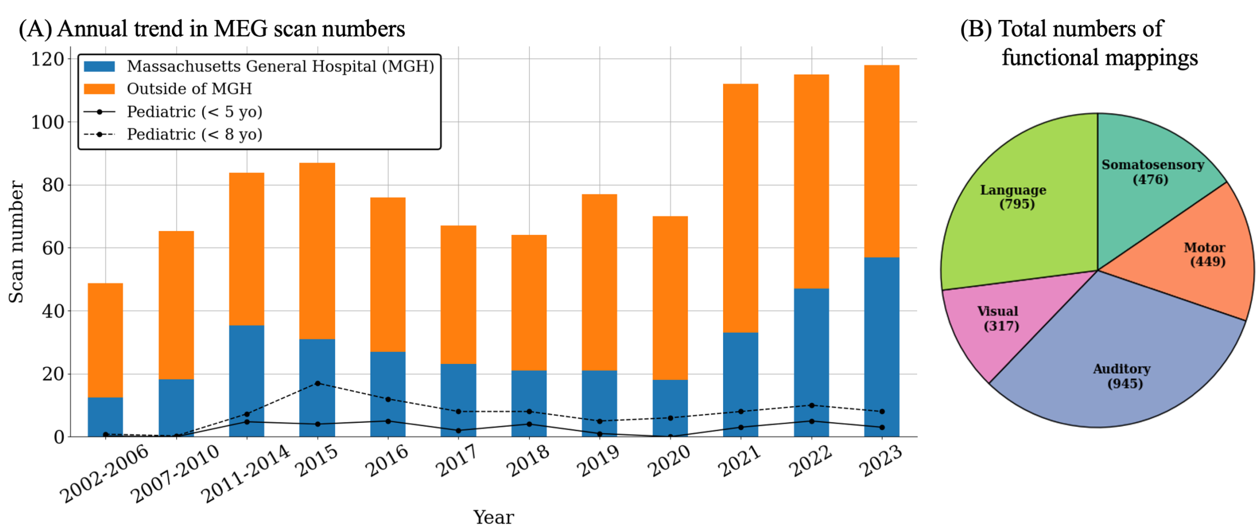


**Figure 1.** (A) Demographical overview of annual trend of clinical magnetoencephalography scan numbers at Martinos Center. The average scan numbers for the first several years during 2002–2014 are shown in ~ 4-year intervals. The overall scan number during 2002–2023 was 2302. The ongoing demand for pediatric populations (aged < 5 years and < 8 years; black lines), mainly referred from Boston Children's Hospital, is clearly illustrated by the black curves that show the pediatric population scan numbers. (B) Total number of functional mappings at Martinos Center. Multiple mappings may have been obtained from an individual patient.

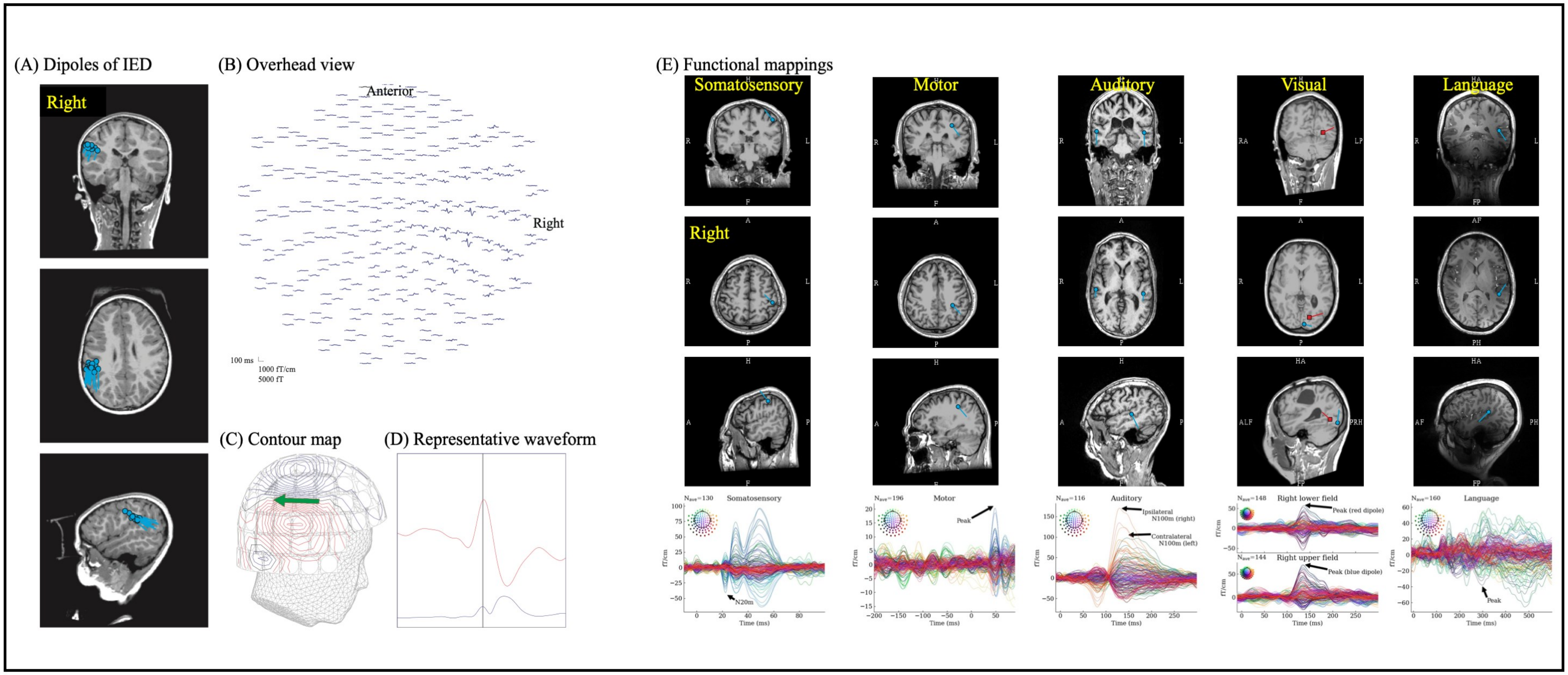


**Figure 2**. Representative equivalent current dipole (ECD) analysis of interictal epileptiform discharges (IED) obtained from a patient with a metabolic disorder (succinic semialdehyde dehydrogenase deficiency). (A) The three panels show coronal, axial, and sagittal sections with ECDs. Circle and bar indicate the location and orientation, respectively, of ECD. (B) Overhead view of a representative IED in 102 sensor triplets containing one magnetometer and two planar gradiometers. (C) Contour map at the onset of an IED suggesting a clear dipole pattern in the right parietal region. The arrow depicts the calculated ECD with orientation. (D) One representative sensor waveform from the parietal sensors (red) and root mean square of all the sensors (blue). The vertical line indicates the time for ECD calculation. (E) Representative equivalent ECD analysis from somatosensory-, motor-, auditory-, visual- and language-evoked fields, superimposed on each individual magnetic resonance image. The dipole of each evoked field corresponds to the following activities: somatosensory - N20m in response to right median nerve stimulation; motor - initial peak when pressing the button with the right index finger; auditory - ipsilateral (right hemisphere) and contralateral (left hemisphere) N100m in response to right ripple sounds; visual - initial peak in response to right lower field (upper panel) and right upper field (lower panel); language - the initial peak during 350–550 ms in the visual semantic decision task. The lower most panels show the butterfly plots of 204 gradiometers assigned with spatial color coding.

small head, which once placed in an adult MEG device is far away from the helmet walls, resulting in a distance from the neural currents to most MEG sensors several centimeters greater than a typical adult. This translates to weaker signals at MEG sensors. MEG instruments with optimized geometry for infants have been developed, which allow reliable detection of neural activity from pediatric patients younger than 5 years of age [7].

(3) *Optically pumped magnetometer (OPM)*: OPMs that utilize optical devices are newly developed helium-free MEG sensors [8, 9]. They can be placed directly on the scalp thereby improving signal-to-noise ratios at room temperature, by effectively reducing the distance between sources and sensors. The transmission of laser light through a gas cell containing a vapor of spin-polarized rubidium atoms decreases in the presence of an external magnetic field, thus providing a highly sensitive measure of the local magnetic field. This new technology has been applied to epilepsy in pediatric as well as adult patients [10]. It is expected that wearable OPM-based MEG may be used more widely than current MEG systems and may become an affordable alternative to scalp EEG, with the potential benefits of increasing spatial accuracy and increasing sensitivity to deep sources.

(4) *Direct current (DC) measurement*: Fluctuating (AC) magnetic fields produced by neurons are well known. However, ultra-low-frequency or DC magnetic fields of biological origin have been known to be measurable from 102 planar gradiometers (SQUIDs) [11]. In the head, DC signals emitted from ferromagnetic materials, i.e., magnetites, are measured with MEG, which can potentially lead to disease diagnostic capabilities in neurological disorders such as Alzheimer's disease.

(5) *Multi-modal Neuroimaging Analysis and Visualization Tool (MMVT; Fig. 3)*: MMVT is a 4D (3D and time) neuroimaging tool that can simultaneously visualize desired combinations of MRI, EEG, MEG, functional MRI, nuclear imaging, and intracranial EEG [12]. This tool allows researchers and clinicians to interact with their neuroimaging functional and anatomical data through simultaneous interactive visualization of these existing imaging modalities.

(6) *Cerebellar source*: Due to the extremely intricate folding, it is difficult to obtain detailed and topologically correct reconstructions of the geometry of the cerebellar cortical surface from standard MRI (~ 1 mm resolution). A new algorithm has been developed to reconstruct the cerebellar cortex from standard MRI by a diffeomorphic technique, where another reconstruction of high-resolution MRI is registered to a subject [13]. Based on this algorithm, cerebel-

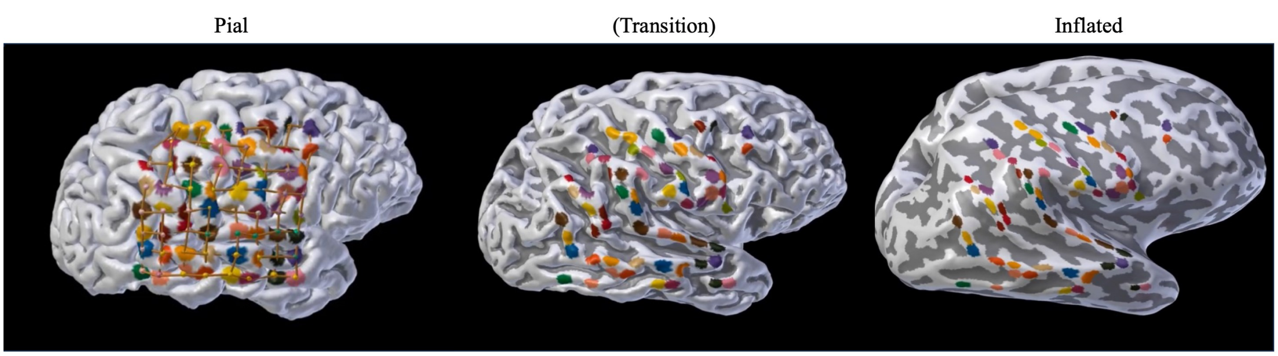


**Figure 3.** Example of brain reconstruction presented by multimodality visualization tool (MMVT). Surface electrodes are depicted within the pial brain model (left) and the inflated model (right). These images are easily switched in a user-friendly interactive graphical user interface (not shown), enabling seamless transition between them (middle). While the electrode grids appear to be placed in adjacent areas on the brain surface, the inflated model in which the brain sulci are expanded (gray) reveals that the electrode placement is not anatomically close.

lar signals that potentially play a role in seizure networks can be detected [14].

(7) *$BSS_{T/k}$ (fractional type of blind source separation) for automatic detection of IEDs*: Increasing the number of MEG sensors increases the time required for the evaluation process, because the current analysis is based mostly on visual inspection. Our proposed method [15], $BSS_{T/k}$, based on a stochastic process represented by independent component analysis or blind source separation, uses the time-delayed correlation and grasps non-stationary waveforms of IEDs. It may, therefore, be used for automatic detection of IEDs.

## Conclusion

More than 200 whole-head MEG devices have been in operation worldwide, whereas the main clinical application of MEG is in epilepsy for localizing brain areas that contain sources of IEDs, and functionally mapping areas of brain networks essential for motor and sensory function, as well as language production/comprehension, an essential part of planning brain surgery in many epilepsy and tumor surgeries. MEG studies and analyses have the potential to extend to more applications such as evaluation of neurological and psychiatric syndromes as well as developmental disorders, and examination of the integrity of cortical brain networks.

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## Conflict of interest

None to declare.

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