Magnetoencephalography recording and analysis

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Abstract

Magnetoencephalography (MEG) non-invasively measures the magnetic field generated due to the excitatory postsynaptic electrical activity of the apical dendritic pyramidal cells. Such a tiny magnetic field is measured with the help of the biomagnetometer sensors coupled with the Super Conducting Quantum Interference Device (SQUID) inside the magnetically shielded room (MSR). The subjects are usually screened for the presence of ferromagnetic materials, and then the head position indicator coils, electroencephalography (EEG) electrodes (if measured simultaneously), and fiducials are digitized using a 3D digitizer, which aids in movement correction and also in transferring the MEG data from the head coordinates to the device and voxel coordinates, thereby enabling more accurate co-registration and localization. MEG data pre-processing involves filtering the data for environmental and subject interferences, artefact identification, and rejection. Magnetic resonance Imaging (MRI) is processed for correction and identifying fiducials. After choosing and computing for the appropriate head models (spherical or realistic; boundary/finite element model), the interictal/ictal epileptiform discharges are selected and modeled by an appropriate source modeling technique (clinically and commonly used — single equivalent current dipole — ECD model). The *equivalent current dipole* (ECD) source localization of the modeled *interictal epileptiform discharge* (IED) is considered physiologically valid or acceptable based on waveform morphology, isofield pattern, and dipole parameters (localization, dipole moment, confidence volume, goodness of fit). Thus, MEG source localization can aid clinicians in sublobar localization, lateralization, and grid placement, by evoking the irritative/seizure onset zone. It also accurately localizes the eloquent cortex-like visual, language areas. MEG also aids in diagnosing and delineating multiple novel findings in other neuropsychiatric disorders, including Alzheimer's disease, Parkinsonism, Traumatic brain injury, autistic disorders, and so oon.

Key Words

Epilepsy analysis, head and source model, Magnetoencephalography (MEG), MEG acquisition

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Introduction

Magnetoencephalography (MEG) is a non-invasive technique, which measures the magnetic fields associated with primary intracellular currents.[1] A majority of MEG signals are caused by excitatory postsynaptic potentials, due to the flow of ions into the postsynaptic dendritic membranes of the apical dendritic pyramidal cells. For a detectable MEG signal outside the scalp, approximately 1 million non-radially symmetric, spatially aligned neurons are synchronously activated, and they produce an externally observable magnetic field,[2,3] which generates about a 10-nAm electric field potential (EEG) and a 100-fT magnetic field (MEG) (1 femto Tesla = 10^{-15} Tesla).

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Although MEG mainly records the electrophysiological activities from the cerebral cortex, several studies suggest that signal generation occurs from the deeper subcortical structures like the cerebellum and thalamus. The magnetic field generated due to the volume current mostly does not contribute to MEG signals. The principal features of MEG are (a) Measure of direct neuronal activity; (b) Safe and non-invasive; (c) excellent temporal and reasonable spatial resolution; and (d) No impedance offered by intervening structures.

Instrumentation and general aspects of magnetoencephalography acquisition

Magnetically shielded room

Typically, the magnetic fields associated with evoked brain activity do not exceed a few hundred femto Tesla (1fT = 10^{-15} tesla) in amplitude and even the strongest magnetic signals associated with the epileptic discharges are Pico-Tesla (1pT = 10^{-12}Tesla) in amplitude, which is several orders of magnitude smaller than the earth's steady magnetic field, that is, 1 milli Tesla (= 10^{-3} Tesla) with the surrounding environment (e.g., power lines and traffic). To measure such a tiny signal from the brain, the MEG measurements have to be conducted in a magnetically shielded room (MSR), which acts as a shield to both low frequency and high frequency

signals, and is made of two or more layers of mu alloy and aluminum.

Magnetometers and gradiometers

Magnetic flux lines emanating from an intracranial source emerge on the scalp surface as concentric spheres, which are detected by magnetometers and gradiometers (either planar or axial). The entire assembly of the magnetometers and their corresponding SQUIDS[2] is encased in a dewar filled with liquid Helium at −296°Celsius. In recent times, the available MEG devices have 306 sensors — 102 magnetometers and 204 planar gradiometers (ELEKTA, Finland), in which one magnetometer is coupled to two split planar gradiometers in a single region, to cover the whole head.

Prerequisites for magnetoencephalography examination

All the volunteers must be screened before entering the MSR. Written informed consent should be obtained; in research studies, approval from the Institute Ethics Committee is a must.

Electromagnetic compatibility

An MEG recording may suffer from interference of several kinds: Ferromagnetic materials, electric currents, and radio-frequency signals. Commonly used nonmagnetic materials include aluminum, brass, copper, silver, gold, high-quality stainless steel, rubber, glass, wood, and many plastics (these materials should be tested for magnetic deflection). Few metals are MEG compatible, namely, aluminium, high quality steel, pure gold, and an MEG-compatible eye tracker device/surface EEG electrode.[4]

Workflow of magnetoencephalography acquisition [Figure 1]

Preparation of the system

After helium level monitoring and tuning of bad channels (if any), the acquisition parameters are set. All possible sources of magnetic artifacts/contamination must be removed from the MSR and one must ensure that there is adequate ventilation and oxygen level within the MSR.

Figure 1: MEG acquisition: (a) MEG (306 channel) dewar inside a magnetically shielded room (MSR), (b) Five-head positioning indicator (HPI) coils for head movement monitoring during acquisition, (c) 3D-digitization carried out using a wooden chair, goggles with transmitter, and a stylus with receiver, (d) patient MEG data acquisition with simultaneous EEG in erect posture

Empty room noise measurement and helium level check

The level of Helium within the MEG gantry should be checked. Ideally, MEG data acquisition should be carried out with a phantom at least once weekly, to ensure that the recording is accurate, with least error.[5] Empty room noise measurement should be carried out at the start of acquisition, and the average of noise across all sensors should be below 3fT/cm √Hz.

Acquisition parameters

a. **Sampling rate:** The sampling rate used is between 290 to 12 kHz, and for routine evoked stimulus studies it is used between 290 to 600 Hz; for epilepsy and related studies it is kept at 1 kHz to 2 kHz;
b. **Acquisition bandwidth:** The signal is filtered online with a band-pass between 0.1 and 330 Hz, and when ambient magnetic noise is very prominent, the high-pass filter may be set to 1 Hz.
c. **Duration of recording:** Approximately 15 minutes to a maximum of two hours, preferably with 10-15 minute block of each data, with measurement of head position before and after each block recording;
d. **Measurement with other bioelectric channels:** Recent MEG systems enable us to measure EEG — MEG simultaneously; both spontaneous and evoked brain responses can be measured. Monitoring of ocular, cardiac, and muscular activity is performed with Electro-oculogram (EOG), Electrocardiogram (EKG), and Electromyogram (EMG) electrodes, respectively, to eliminate contamination of those artifacts.

Preparation of the subject

Screening of subjects

a. **Implanted medical devices:** Implanted medical devices can be active, such as, pacemakers, defibrillators, neurostimulators, cochlear implants, and drug pumps, or passive, such as, hip/knee joint replacements, heart valves, aneurysm clips, coronary stents, and breast implants. Both types contain metallic components, although they hold no risk to the subject during an MEG recording, but may induce artifacts
b. **Metallic foreign bodies:** Metallic objects such as older fillings, braces, fixed dental wires, underwire bras, watches, keys, glasses, dentures, tattoos, makeup, dyes, spectacles, and hearing aids. All ferromagnetic items must be removed before volunteer enters the MSR. Routinely, it is better to change into a hospital dress and shift the subject to the preparation area, where all the vital parameters including head circumference — (maximum of 96 - 100 cm is accepted) — is measured. If simultaneous EEG recording is performed, the subject is prepared for EEG acquisition with surface electrode/cap. The HPI (Head position indicator) coils are placed onto the scalp or cap.

Head 3D-digitization [Figure 1]

Information about the patient's head position, orientation, and shape is obtained by digitizing (3D digitizer) the standard fiducial points, HPI coils, EEG electrodes, and the required additional points creating Cartesian co-ordinates in a 3D space. Digitization of five HPI coils, EEG electrodes (surface electrode/cap), and landmarks, which include three bony fiducial points

(Nasion, left, and right pre-auricular points), and additional points, is performed

Reassurance, comfort, and positioning the subject

A suitably trained person should describe the procedure to the volunteer, explaining the sights, sounds, and experiences to be anticipated, as also the likely duration and communication process while recording, to avoid any discomfort. Adequate lighting and ventilation in the MSR is to be maintained. The head is positioned in such a way that it is with least distance from the helmet and standard practice is to adjust the patient's head position to optimize coverage with the region of interest. Recording can be carried out in a sitting/reclining/supine position.

Acquisition

The empty room measurement is done to ensure a good quality of recorded data. Then the patient is shifted into the MSR and placed in a comfortable position and brief screening is done. After a screen run and checking for EEG impedance (Ideally 100 ohms - 1 kiloohms), if the data is free of any contamination, a continuous recording is started for at least 30 minutes or more.

Head position tracking (cHPI)

Head positioning should be monitored either continuously throughout the acquisition or at the start and end of the recording. The MEG acquisition is done only with respect to the MEG device, instead of the anatomy of the subject. Therefore, MEG devices include a subsystem to determine the position of the head with respect to the MEG sensors. As MEG (unlike MRI) cannot directly measure the position of the head, small coils known as Head Position Indicator coils (HPI) placed at known locations on the scalp of the subject, when energized, will generate a magnetic field that helps us to localize the position of head in a three-dimensional space, with respect to the MEG sensor array. If continuous head position tracking is enabled, generally small movements are acceptable with a maximum error of 5 mm.

Pre-processing the data

Pre-processing of functional data (magnetoencephalography — electrocardiogram)

The recorded data is visually examined and then processed for head movement correction, and compensation (if any) is carried out using an inbuilt software ex., Max filter in the ELEKTA system[6] or a commercially available software [Table 1], and environmental interference and constant or periodic artifact correction is done by applying 'sss' or 'tsss'. Other biological artifacts (other than brain sources) are corrected manually or by a semi-automated method using ICA/template, matching each group of artifacts. Typically pre-processing involves the following steps:

a. Finding bad channels;
b. Head movement correction;
c. Software interference suppression:
    i. Signal-space projection (SSP)[7]
    ii. Signal-space separation (SSS);
    iii. t-Signal-space separation (t-SSS); and
d. Artifact identification and rejection —
    i. Environmental interferences;
    ii. Subject interference — cardiac artifact [Figure 2]; Ocular artifact; breathing artifacts and skeletal muscle activity [Figure 2], and from the non-biological sources like dental work, fillings and braces.

Pre-processing the image data (Magnetic Resonance Imaging/Positron Emission Tomography/Single-photon emission computed tomography)

Importing the image data

For accurate integration of MEG with MRI, fiducial markers (like vitamin E capsules) are placed during MRI acquisition. The MRI images are transferred from the PACS to the MEG workstation. Integration of MEG and MRI data necessitates the usage of either manufacturer provided or third-party software packages (both commercial - Table 1 and open source - Table 2) are used.

Co-registration

Three fiducial markers (Nasion, left, and right pre auricular points), placed during MRI acquisition help us to co-register the MEG data with the structural MRI. Subsequently, the rest of the digitized data points can be imported, following which the MEG functional data is embedded within the structural MRI data. Image co-registration involves identification of the fiducials in the MRI image, and the digitized 3D data are imported for accurate co-registration.[8] By measuring the HPI coil positions in the head coordinate system with a 3D digitizer and combining those co-ordinates with the sensor positions in the MEG device coordinate system, the MEG functional data can be transformed onto the MRI/voxel co-ordinate system. The MEG functional sources (dipoles) are transformed onto the anatomical MRI image of the subject, which is called Magnetic Source Imaging (MSI). It can also be mapped into a normalized brain space, such as Talairach, the Montreal Neurological Institute (MNI) standard brain, or other atlas brains[9-11]

Head modeling

For accurate source localization (MSI), one needs to choose an appropriate head and source model. To localize the sources of the magnetic fields, it is essential to develop head models that incorporate the correct geometry and distribution of electrical conductivity within the actual heads. As both the primary current (major) and the secondary or volume currents (least) is responsible for the recorded magnetic field, *a priori* knowledge of the conductivity characteristics is essential for generating a solution to the forward problem. Various head

Table 1: Commercial (Third party) software

Name	URL
ASA	www.ant-neuro.com/products/asa/meg
BESA	www.besa.de/index home.htm
Curry	www.neuroscan.com/
EMSE	www.sourcesignal.com

Table 2: Open source software

Name	URL (mostly require MATLAB)
EEG lab	www.sccn.ucsd.edu/eeglab/
SPM	www.fil.ion.ucl.ac.uk/spm/
MEG tools	www.megimaging.com
Brainstorm	neuroimage.usc.edu/brainstorm/
MNE	www.nmr.mgh.harvard.edu/martinos/userInfo/data/sofMNE.php

models adopting different geometries and conductivities with different inherent errors, accuracy, computational efficiency, and ease of use are available. The following are some models commonly used:

a. Spherical head model;
b. Realistic Boundary Element Model; and
c. Realistic Finite element model.

Source modeling

Multiple source modeling algorithms had been developed over the years like, equivalent current dipole (ECD) modeling, distributed source imaging, current density distributions, beam former, and various spatial adaptive filtering techniques.

Discrete source model [Figure 3]

The ECD is a theoretical construct of activity over a considerable cortical area. We consider here that each equivalent current dipole represents an extended brain region. This approach assumes that fewer sources (unknown) are responsible for the generated field measurements (known), which are 'overdetermined,' or mathematically well-posed problems, that is, the number of sources < number of sensors. The discrete source models are used mostly in clinical MEG applications.[12]

a. **The single ECD model [Figure 1]:** Is most appropriate when we assume that the measured field at a discrete time point is generated by a single source that had been used in localizations of interictal spikes and in the presurgical mapping of an eloquent cortex after evoked stimulus;[13]
b. **Multiple ECD models:** To overcome the limitations in single dipole modeling, we can add more dipoles or more time points. Taken together, these comprise of the spatiotemporal dipole modeling approach,[14] where highly complex optimization algorithms like MUSIC, and recursive RAP-MUSIC methods[15] are used. After obtaining the dipole fit, the reliability of the location can be estimated by dipole confidence intervals (or confidence volumes).

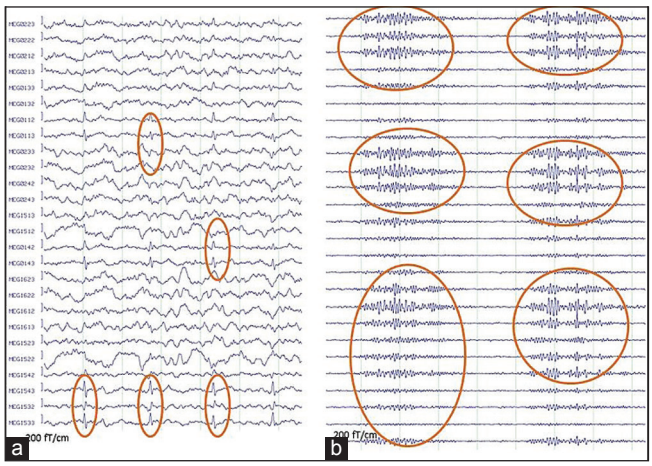

Figure 2: Various biological artifacts encountered during acquisition using low frequency = 3 Hz; high frequency = 70 Hz; Amplitude: MEG = 2 pT/cm: (a) periodically occurring artifacts in temporal sensors due to cardiac activity or arterial pulsation, (b) High frequency short burst activity in temporal sensors due to mastication

Distributed source models[16] [Figure 4]

Here, we consider that each equivalent current dipole represents one small brain segment. This approach assumes that a larger number of unknown sources (few thousand) generate the external field compared to the assumption that less number of known sensors (few hundred) is an underdetermined or mathematically ill-posed problem, that is, number of sources >> number of sensors. All distributed source images suffer from 'smearing' (when a data generated by focal brain activity, on reconstructing 3D image it is blurred and non-focal) and crosstalk (reconstructed activity at any location is contaminated by activity from other brain sources). It is mainly used in research studies: (a) Minimum-norm models, (b) LORET (c) LORETA/sw LORETA), (d) LAURA, and (e) CLARA.

Statistical analysis

Magnetoencephalography patterns of normal and abnormal brain activity [Figure 5]

Although the human brain produces activity in a wide range of frequencies (0.5 to 500 Hz), the most clinically relevant activities lie below 70 Hz (normal physiological or spontaneous waves) and the frequency bands are alpha (8 to 13 Hz), beta (13 Hz), theta (4 to 8 Hz), and delta (1 to 4 Hz).

Abnormal brain activities could either be due to focal structural lesions (e.g., tumors, vascular malformations) or lesional epilepsy or diffuse encephalopathy (e.g., viral encephalitis, traumatic brain injury, and coma). Abnormal brain wave patterns include Spikes (20 - 70 milliseconds), spike-and-wave complexes, polyspikes, sharp waves (70 - 200 milliseconds), and slow waves.[17,18] In practice the MEG spikes are identified visually in MEG recordings with the knowledge of EEG waveforms, by looking at the EEG and MEG simultaneously, based on its amplitude, duration, sharpness, and emergence from the background.[17,18] The probability of increased spikes detection rate is superior in MEG than in EEG, because of a better signal-to-noise ratio.[19] Ultimately, one modality may improve the spike identification rate in the other, thus a combined approach is always better than a single one.

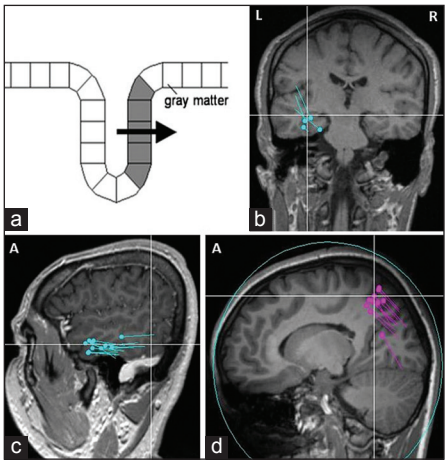

Figure 3: Discrete source imaging: (a) Showing the overdetermined problem adapted from Hoechstetter *et al.* 2010[16]. Equivalent Current Dipole (ECD) modeling of IED revealing dipole cluster, (b) Left basal-medial temporal lobe (c) Left lateral temporal lobe, and (d) Right parietal lobe

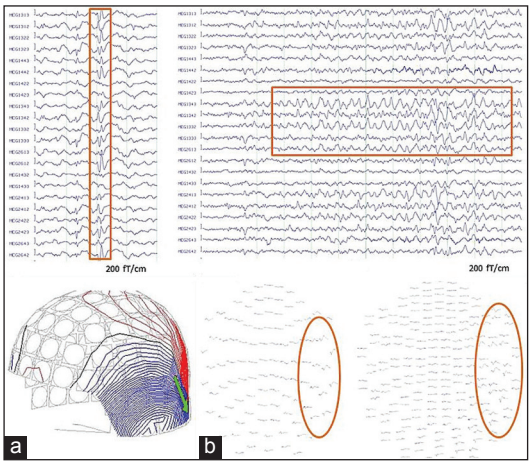

Figure 4: Distributed source imaging: (a) Showing the underdetermined problem adapted from (Hoechstetter *et al.* 2010)[16]; (b) Spatiotemporal minimum norm estimate of cortical activity (widespread, smeared); (c) Focal volume of activity involved during IED modeling (with CLARA) comparable with dipole modeling (with MUSIC)

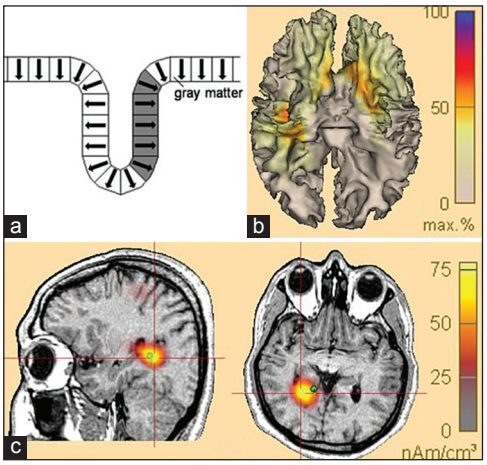

Figure 5: Interictal epileptiform activity (IED) observed as (a) Focal spike and wave pattern in temporal lobe epilepsy; (b) Generalized intermittent spike and wave discharge with rhythmic buildup seen in atypical absence seizure; (c) Topographical isofield contour map at the peak of the spike showing a tight sink-and-source dipolar pattern, with direction of dipole vectors; (d) Activity observed in the overall magnetometer (left) and all the gradiometer (right) channels where data is analyzed at low frequency = 3 Hz, high frequency = 70 Hz, and Amplitude: MEG = 2 pT/cm

Selection of magnetoencephalography spikes, head model, and source model

After choosing the appropriate head model (spherical head model-for clinical epilepsy studies, and more realistic head models-for research purposes), the origin of sphere approximation with x, y, z coordinate correction is performed, with the subject's digitized head coordinates, by using the voxel coordinate system.

Interictal epileptiform discharges are identified visually, based on the morphology, temporal characteristics, localization, and dominant/standing against the background activity. Each epoch is defined as a selected event of interest (IED) with 50 to 100 milliseconds pre and post event. MEG spikes with or without simultaneous EEG spikes; occurring at least > 1 second from the previous spikes, when there are continuous discharges, are considered, but MEG spikes along with the ECG wave and slow wave modeling may be avoided. Subsequently, each epoch is transferred for source modeling. The commonly used and clinically validated source modeling is single ECD modeling.

Selection of dipole sources[20]

During source modeling, we need to identify the following:

a. Ideally the cursor is placed at the onset of the IED and every millisecond of the event is examined, till the peak, for reasonable magnetic field topography, by visualizing the isofield contour map.
b. The topography must be of a tight 'sink and source' pattern, with minimal background noise.
c. At consecutive time points, the locations of the dipole must stay within 1 cm in the x, y, z axes, and the sequential field map must be stable, with no rotation. If field rotation occurs, identify the earlier points before the peak.
d. It is better to analyze the spikes individually rather than averaging them, as it may result in loss of spatial and temporal information.[1]
e. The seizure onset zone corresponds to the zone of the earliest spike. Hence, selection of the earliest spike peak with reasonable magnetic field topography is used for dipole source analysis.

Source localization[21]

At the earliest spike peak, the dipole is fitted using a single or multiple ECDs. After the fit, the following dipole parameters are noted:

a. Residual error between the calculated and magnetic field topography must be less than 30%.
b. Goodness of fit must be > 70% (frequently used, may be kept flexible).
c. If the magnetic isofield contour map shows a single, distinctive, dipolar pattern, a single ECD can be used to estimate the generator source. If multipolar pattern/complex fields are observed multiple ECD analyses may be considered.
d. Dipole strength/moment must be of 100 - 500 nAm. Dipole sources outside this range are not physiological and are disregarded.
e. Confidence volume must be < 0.3 cm^3. Usually on either side of the peak, the confidence volume is more, so SNR is lesser.

Averaging

Similar spikes identify the center of activity of a cluster of dipoles by improving the SNR and decreasing the confidence volume; but spatial and temporal information may be diminished. If the fitted dipoles accept one or more of the above criteria, they can be regarded as valid dipoles for further analysis. Dipole location and orientation are noted in the voxel coordinate system, using commercially available or open software. None of these parameters can increase the accuracy of our model unless we have a strong understanding of the merits and demerits of the MEG dipole model and appreciation of the cortical sources.

Transfer to a neuronavigation system

Finally, these composite DICOM images are loaded onto the neuronavigation system that may be used in the Operating Room for stereotactic surgery, which guides the surgeon in reaching the intracranial source (i.e., epileptogenic foci) needed to be resected and also helps us to preserve the eloquent cortex.

Report generation[22]

The general recommendations for an MEG report are that it should include at least the following:

General aspects

(a) Patient's demographical profile, clinical and seizure history (b) Explaining the findings of other investigations performed — like scalp EEG, video EEG, MRI, and other imaging. (c) Status of the patient during acquisition (conscious/alert/awake/drowsy or asleep) and handedness of the patient.

Magnetoencephalography/Electroencephalography technical aspects

This should contain at least:

i. The name of the system and number of sensors (MEG) or number of channels (EEG) used for acquisition.
ii. Duration of the recording and status of the patient during recording (Log book can be maintained).
iii. If any activation procedures (hyperventilation, photic stimulation) performed should be mentioned.
iv. Software used for filtering out the raw data and artifact correction performed.
v. Category of head model and source model used to perform the analysis.

Describing significant magnetoencephalography — electroencephalography finding

This includes description of all the normal and abnormal MEG-EEG features objectively on the basis of morphology, background activity, slowing (if any), sleep, and interictal and ictal epileptiform activity.

Magnetoencephalography—electroencephalography source localization

This should at least include the approximate number of IEDs observed, the number of IEDs accepted, and source model, based on goodness of fit, dipole moment, and other criteria. Channels showing maximum amplitude of electric potential/magnetic field, number of clusters, major clusters of sources in lobar or sublobar lateralization, and localization and its orientation should be described.

Impression and clinical correlation

If MEG is performed as part of a presurgical evaluation, then clinically relevant information must be provided, which can guide the clinicians for the intracranial placement of electrodes, to help take a decision to resect the epileptogenic cortex and preserve the eloquent cortex, and provide information on a subtle lesion (if any). In addition it must state whether the MEG — EEG source localization is consistent with semiology, EEG focus/MRI/other functional imaging. If not consistent, the possible reasons and other recommendations can be described. The American Clinical MEG Society Guideline states that a report in minimum must contain abnormal raw MEG — EEG traces, topographic field maps, and magnetic source images, with dipole source localizations co-registered with the patient's brain MRI.

Applications of magnetoencephalography

Clinical applications

To enhance localization of epileptic seizure foci[12] and presurgical planning by non-invasively localizing the eloquent areas within the brain.

Research applications

(a) To study distributions of brain activity related to cognitive function; (b) Parkinsonism: The earliest studies using MEG had been to investigate the Parkinsonian tremor.[23] The clinical utility of MEG in the diagnosis and treatment of Parkinson's disease is to quantify the effects of the cortical stimulation technique such as *transcranial magnetic stimulation* (TMS),[24] which decreases the patient's symptoms. (c) In psychiatric disorders like schizophrenia, low frequency oscillatory activity is found to be more predominant than in normal individuals,[25-27] and multiple studies done on Alzheimer's disease, bipolar affective disorders, major depressive disorders, and obsessive compulsive disorders makes us understand the pathophysiology behind it. (d) Recent studies and approaches have reached a wide variety of diseases including patients with multiple sclerosis, Sjogren's syndrome, alcoholism, and facial pain.

Recent advances and future directions

Major exploration occurs in real-time monitoring (rt-MEG) and/or when combining Brain Computer Interface (BCI) devices, fetal MEG, to distinguish between physiological and pathological aging, in differentiating schizoaffective disorder and schizophrenia, and using the differences between the auditory steady-state responses of patients. More promising findings in the next arena of MEG, in clinical settings, could be in Autistic Spectrum Disorder (ASD) children and in studying the functional connectivity of the so called 'resting-state network,'[(1)28] using MEG.

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