Advances in Epilepsy Neurodiagnostics

The use of magnetoencephalography in epilepsy

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Disclosures

Consultant: UCB (speaker’s bureau); Lundbeck (speaker’s bureau)

Travel: NeuroPace
Objectives

Define magnetoencephalography (MEG) and review basic neurophysiology and what MEG measures

Briefly discuss basic MEG principles and techniques

Provide an overview of the clinical uses of MEG, primarily in drug resistant focal epilepsy

Review the utility and outcomes of MEG in people with epilepsy

Discuss advanced source imaging techniques and how they can be employed in a variety of epilepsy cases

Briefly look at the future of MEG and its role in different types of epilepsy, including generalized epilepsies
Case 1

26 y/or RH woman with a history of drug resistant focal epilepsy

Normal birth
Normal development

Concussion without clear LOC

First seizure at the age of 16 y/o
Experienced 6 seizures within 24 hours
Hospitalized for 6 days, no seizure medication trials initiated

Has another seizure (7th total) and placed on CBZ

CBZ not tolerated and transitioned LEV

Fails trials of OXC, TPM, LTG, ESL

Admitted to the epilepsy monitoring unit at Henry Ford Hospital
Case 1

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2005
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2015
- Admitted to the epilepsy monitoring unit at Henry Ford Hospital
- CBZ not tolerated and transitioned LEV
- Fails trial of CLB, placed on ZNS

Seizures continue, but improved on LTG, ESL, and ZNS
So what do we know and what have we learned from Case 1?

Seizures and epilepsy can be difficult to treat

The EEG is somewhat helpful (possibly right hemisphere lateralization)

MRI did not reveal an epileptic lesion

FDG-PET scan was consistent with right temporal lobe dysfunction

Is this drug resistant focal epilepsy?

Do we have enough information to proceed with an epilepsy surgical evaluation?

Are there other tests that may be helpful in localizing the epileptogenic zone?
Magnetoencephalography (MEG)

Magnetic fields

Function + Structure

MEG

MRI

MEG is a noninvasive method of recording from the head surface the magnetic flux associated with intracranial electrical currents.
Volume currents travel through the extracellular space
Encounter resistance via CSF, skull, etc. and these resistive elements are not uniformly resistive

**Magnetic flux is not subjected to this distortion**

Clinical magnetoencephalography and magnetic source imaging, 2009.
Magnetic fields and MEG

Dewar
Contains magnetometers and SQUID

Liquid He

SQUID
Ultra sensitive detector of magnetic flux, amplifies signal

Coil

Henry Ford Hospital MEG System
4D Neuroimaging Magnes 2500 WH
Magnetometers
Run with 32 channel simultaneous EEG
Brain source model - 6 spheres for forward model and constrain with 4000 dipole
Magnetic fields and MEG

Electrical current → Magnetic flux produces concentric spheres → Magnetometers (parallel to the head surface and placed at regular intervals)

Magnetic fields are small and epileptic discharges (fT)

Superconductors are used to pick up small magnetic fields

Lower resistance by lowering the temperature with helium (4 K)

Amplified by superconducting quantum interference device (SQUID) → Recorded MEG

Clinical magnetoencephalography and magnetic source imaging, 2009.
Magnetoencephalography (MEG)

Records magnetic flux associated with intracranial electrical currents.

Recorded MEG activity is through neuronal signaling and electroclinical process that is basic and direct.

- Other processes are indirect through other means
  - 1. Blood flow - fMRI, SPECT
  2. Metabolism - PET

Clinical magnetoencephalography and magnetic source imaging, 2009.
Dipoles and MSI

Abstraction that can be applied to electrical circumstances Measurement, which if existed, could produce the field distribution of the activity under study

In MEG/MSI the equivalent current dipole (ECD) is the most widely used MEG/MSI measurement (validated and reliable) - Most clinically useful and appropriate when there is a reason to believe that the measure field at a particular time point is generated by a single source

Clinical magnetoencephalography and magnetic source imaging, 2009.
The current clinical MEG indications
Epilepsy is a disease of the brain defined by any of the following conditions:

- 1. At least 2 unprovoked (or reflex) seizures occurring > 24 hours apart
- 2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
- 3. Diagnosis of an epilepsy syndrome

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome, but are now past the applicable age or those who have remained seizure-free for the last 10 years with no seizure medication for the last 5 years

Sometimes medications fail...

3.41 x 10²⁹ combinations

2012 - Kwan and Brodie: 25% no remission, 16% relapsing-remitting

2000 - Kwan and Brodie: 36% drug-resistant

1971 - Coatsworth: 33-38% pharmacoresistant

1880’s - Gowers: 36% medically intractable

DRE may be defined as the **failure of adequate trials of 2 tolerated and appropriately chosen** and used SM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.

**Important considerations regarding breakthrough seizures/relapse**
In general, breakthrough seizures that occur in temporal proximity to potentially seizure provoking external factors such as sleep deprivation, menstruation, intercurrent febrile illness, etc. should still be considered as evidence of inadequate seizure control and hence treatment failure, but seizure relapse due to poor treatment compliance should not.
The presurgical evaluation

Every patient

History

EEG
MRI

If DRE confirmed pursue presurgical evaluation

vEEG
EMU

Neuropsychological (NP) testing
Functional imaging (PET, SPECT, fMRI, MEG)
Language and memory localization (Wada procedure, NP, fMRI, MEG)
icEEG (Grids/strips or depths/sEEG)

Not sure?
Epilepsy CASES

Goal is to identify the epileptogenic zone

EPILEPSY SURGERY
MEG in drug resistant focal epilepsy

MEG provides evidence, and also distinguishes, between epileptogenic and nonepileptogenic foci.

MEG is primarily used as a noninvasive, pre-surgical test to identify:

- 1. Epileptogenic zone or irritative zone
- 2. Eloquent cortex near the epileptogenic zone or structural abnormality

MSI yields helpful information in approximately 5-35% of cases.

Epilepsy Behav. 2011;20:172-177.
MEG directed review of MRI

Funke et al. (2002) reviewed 29 patients with 44 epileptic MEG foci

- 12 (27%) of MEG spikes were concordant with MRI lesion, while 32 (73%) were discordant

- MEG-directed MRI review identified 4 occult gray matter migration lesions that were initially not seen

Later Funke and colleagues reviewed 40 patients with neocortical epilepsy

- 29 were sent to MRI for reevaluation and in 7 cases MEG led to specification of now clear, but previously unidentified lesions

Case 2

36 y/o RH woman with a history of brief (10-15 seconds) visual hallucinations of multicolored lights in the right upper quadrant that may progress to impaired awareness
Seizure
Case 2
Case 2
Transmantle sign
Tapering of abnormal white matter signal from the cortex to the ventricular surface

Case 2

MEG compared to icEEG

Knowlton et al. (2006) prospectively evaluated 49 patients who had MEG and then icEEG

Table 4
Magnetic source imaging vs. intracranial EEG

<table>
<thead>
<tr>
<th>Video/EEG</th>
<th>MSI Localized</th>
<th>MSI NL</th>
<th>MSI Negative</th>
<th>Intracranial EEG Localized</th>
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MEG localized the EZ at nearly the same proportion as icEEG (65.3% to 69.4%, respectively)

ExTLE, extra-temporal lobe epilepsy; MTLE, mesial temporal lobe epilepsy; LTLE, lateral temporal lobe epilepsy; NL, non-localized. (Modified from Knowlton et al., Ann Neurol 2006 with permission.)
19/36 (53%) had complete resection of the MEG focus and of these 19, 79% (15/19) were seizure free.

17/36 had MEG focus that was not resected and 13/17 (76.5%) had seizure recurrence.

MEG predicts seizure freedom following surgery

Seizure freedom in 85% of 68 patients with concordant and specific MEG results

Concordant and specific MEG findings predicted seizure freedom with an odds ratio of 5.11
Moving from signals to dynamic networks
Neural synchrony
With 16 true positive results, CSI had a **sensitivity of 73%**

CSI provided a **positive predictive value for Engel class Ia outcome was 70% (16/23)**
Decreases in functional connectivity in people with LRE may have poorer outcomes

“Enhanced regional functional connectivity at the area of resection may help predict seizure outcome and aid surgical planning.”
Measuring connectivity with CSI
Subtle left fronto-central sharp waves on EEG
Left fronto-central sharp waves more prominent on MEG
Case 3

CSI localized to left post-central gyrus with restricted network

Right <-> Left
Case 3

The areas of the most seizure activity (contact 11) and initial spread (5, 6, 12, 17 and 18) were marked with a cut number. The perirolandic grid was removed. A new 4 contact strip was placed over the cortex perpendicular to the central sulcus. SSEPs were used to localize the central sulcus with N20-P20 phase reversal. The postcentral gyrus was localized anteriorly, with its posterior portion under the anterior portion of contacts 5 and 6, indicating that the epileptogenic zone was safe to resect.

Consistently reproducible somatosensory evoked responses were obtained and the N20-P20 phase reversal was easily identified. The N20-P20 phase reversal consistently took place between contacts 3 and 4, localizing the postcentral gyrus anterior to the site of the primary seizure focus (contact #5 of the subdural grid), with its posterior portion under the anterior portion of contacts #5 and 6 of the subdural grid.
Case 3 postoperative seizures

Onset plus 20 seconds
CONCLUSIONS

• We used MEG to determine the network properties in patients with epilepsy to identify the flow of information in the epileptic network.

• The MEG results from coherence source imaging (CSI) can provide information on the location of brain regions that are dominant and the direction and level of communication between brain regions.

• Our study found that resection of high coherent areas that were receivers as opposed to a sender appeared to result in a worse outcome.

• This may be due to the nature of a receiving area in the brain being the regions where the epilepsy propagated to, as opposed to the location where the epilepsy initiated.

• We hypothesize that the epileptic network is very dynamic and highly plastic and therefore may be able to change the direction of information flow.
Can combining MEG with other imaging techniques provide more information?

Multimodal imaging
MEG and absence seizures

At frequency bands of 1-20 Hz there was activation in the parietal region and at 20-70 Hz in the lateral frontal region.
Patient 7 - JME (Myoclonic and absence seizures)

The “Frontal-insular-thalamic network”

Multiple dipole analyses showed activity in the bilateral homologous central and temporal regions.
Focal networks in GGE

Patient 1

Patient 3

Zillgitt, AES 2014.
Mapping eloquent cortex with MEG
Language-related brain magnetic fields (LRFs)

MEG localization of language-specific cortex utilizing MR-FOCUSS

S.M. Bowyer, PhD; J.E. Moran, PhD; K.M. Mason, REEGT; J.E. Constantinou, MD; B.J. Smith, MD; G.L. Barkley, MD; and N. Tepley, PhD

Language laterality determined by MEG mapping with MR-FOCUSS

Susan M. Bowyer, John E. Moran, Barbara J. Weiland, Karen M. Mason, Margaret L. Greenwald, Brien J. Smith, Gregory L. Barkley, Norman Tepley

Available online at www.sciencedirect.com

Epilepsy & Behavior 6 (2005) 235-241


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<th>Picture verb generation MEG</th>
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6.75% of US adult population has a brain disorder Translates to 1/7 households in the US
So where does that leave us with Case 1?
Case 1

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Case 1

2 Spike populations with loosely formed clusters in the right frontal and posterior temporal/parietal region

All left hemisphere dipoles are propagated spikes that originated over the right hemisphere
Conclusions

MEG measures magnetic fields produced from electrical currents

MEG is not a new technology; it has a well established role and indication in evaluating the irritative (and possibly epileptogenic) zone in drug resistant localization-related epilepsy

Localization of the epileptogenic zone with MEG may predict seizure freedom following epilepsy surgery

With the ability to directly measure dynamic neuronal networks through advanced source modeling, MEG may allow for precise delineation of epileptic networks

Additionally, MEG can aid in localization of eloquent cortex including higher cortical functions, e.g., language
Noninvasive Brain Imaging
High temporal (ms) and spatial (mm) resolution

Magnetoencephalography (MEG)

MEG can be used to localize areas involved in:
- Epilepsy (Interictal spikes, Seizures, Networks)
- Auditory, Visual, Somatosensory, Motor and Language (Receptive & Expressive) processing

Call for more information 313-916-1075 or email sbowyer1@hfhs.org  www.MEGimaging.com