What is MEG?

Coregistration of MEG dipole sources and invasive electrodes

- **Green dots** = Subdural electrode positions.
- **Green cylinders** = Depth electrode positions.
- **Blue lollipops** = MEG dipoles, where sphere is location and stem is orientation.
What is MEG?
Neurophysiological Principles

Based on recording of incredibly small magnetic fields (10^{-12} T).

Easy acquisition of very high density (100-300 channels), wideband (DC – 2000 Hz) recordings of currents within the brain.

Magnetic fields, as opposed to electrical currents, suffer minimum attenuation and distortion from the different tissues that they have to cross to reach the scalp surface.
What is MEG?

MEG is a localization tool.

Based on solid theoretical reasons, MEG has localization accuracy better than the scalp EEG.

- Greater number of sensors typically employed
- Simpler source modeling and calculation
- Anatomical co-registration with 3D-MRI

MEG is a neurophysiological technique, not an imaging method.
What do we know about MEG?

MEG provides **additional** localizing information.
- (Wheless et al, 1999; Stefan et al, 2003; Pataraya et al, 2004)

MEG results **change** the electrode coverage decisions for intracranial EEG.
- (Knowlton et al, 2009)

The yield of MEG is higher than scalp EEG.
- (Yoshinaga et al, 2002; Iwasaki et al, 2005)
MEG is a valuable component of the presurgical epilepsy evaluation

Evaluation goals in potential epilepsy surgery candidates:
- Locate the epileptogenic zone.
- Assess whether it can be resected to achieve seizure freedom.

Multi-modality investigative tools:
- Video-EEG monitoring +/- sphenoidals
- MRI
- PET/SPECT
- Neuropsychology
- Wada/fMRI
- MEG source localization
- Invasive Monitoring
What Are the Main Questions from Epileptologists?

1. What should the referring physician expect from a MEG study?
2. What are the basic MEG modalities, clinical indications, and capabilities?
3. For patients with epilepsy, how can MEG help?
4. What can epileptologists expect from MEG in the future?
Some polling questions for the audience

1) Where do you send patients for clinical diagnostic MEG studies?
   a) MEG lab in my own institution.
   b) MEG lab at another institution.
   c) I do not have convenient access to any MEG lab for my patients.
   d) I do not currently request MEG testing.

2) What clinical indications do you currently use MEG for, or would you like to use MEG for?
   a) Epileptogenic zone localization.
   b) Sensory and/or motor evoked fields.
   c) Language assessment.
   d) Both epilepsy localization and eloquent cortex mapping.

3) What has been the greatest limitation of MEG testing in your patients?
   a) Results have been negative or provide no new information.
   b) Results are discordant with the rest of the clinical picture.
   c) Contents of the reports are confusing or not clinically relevant.
   d) I have generally been satisfied with the results of clinical MEG testing and the reports that I receive.
What is the MEG signal?

Genesis of EEG and MEG Signals:
A current dipole creates a magnetic field
Dipolar representation of brain currents

The signals picked up by scalp electrodes or MEG sensors are generated by synchronized activity from many neurons:

- Postsynaptic potentials produce intracellular laminar currents
- Neocortical pyramidal neurons arranged in a palisade structure
- Typically seen as a current dipole perpendicular to the cortical surface

Dipolar models are based on the assumption that a small number of current sources (multiple dipoles) in the brain can adequately model surface measurements.
EEG and MEG Waveforms

EEG

MEG
Electric fields and magnetic fields generated by a current dipole
How is MEG recorded?

MEG Instrumentation

SQUID
Flux transformers
Shielded room
Head position indicator
SQUID and Flux Transformer
How is MEG recorded?

**MEG Procedures**

- Patient Preparation
  - System / Patient Setup
  - Data Recording
  - Data Analysis

**HPI measurement**

**Fiducial measurement**

**“Cloud” of scalp points**
Careful Attention to Position of Fiducials, Landmarks, HPI Coils

Use of HPI (head position indicator) coils:
- Number: 5
- Positions: Widely spaced over scalp but well inside array

Alignment of scalp with MRI and MEG array:
- Three fiducials (LPA, RPA, Nasion)
- Digitize 80-120 additional scalp points for coregistration with MRI
MEG Procedures

Simultaneous EEG and video monitoring with MEG

On-line marker entry

Feedback noise compensation

Continuous head-position monitoring
Alignment of Subject in MEG Array

Generation of alignment image in real-time to insure good position

Location of HPI coils monitored continuously.
MEG Procedures

Patient Preparation → System / Patient Setup → Data Recording → Data Analysis

- Review of markers
- Review of video
- Visual / manual analysis of every channel of MEG and EEG
- Montages
- Single ECD analysis at core
What are the Advantages of MEG?
Why use MEG in epilepsy patients?

1. Inherently higher source resolution.
2. Direct connection to patient (i.e. pasting electrodes on) is not required.
4. Signals not attenuated or distorted by bone and scalp, or other inhomogeneities that exist between brain and surface.
5. Therefore for source analysis, the head modelling problem is significantly simpler.
6. Easy to obtain multichannel, whole-head, high spatial-density recordings.
7. No exposure to radiation, magnetic field, or other active device.
High temporal and spatial resolution

Patient with parietal lobe seizures
Scalp video-EEG localization unclear
Polyspikes Originating from Left parietal
Propagating Polyspike Activity to Left Parietal

Left basal temporo-occipital

Left inferior parietal

37 msec

Left middle temporal

161 msec
Representative interictal dipoles
High temporal and spatial resolution

Patient with non-localizable, non-lateralizable scalp video-EEG
EEG: Polyspikes, Vertex

Run I EEG

#1

#2
MEG: Polyspikes, Left > Right parietal sensors
All interictal dipoles: Left frontal
Why does MEG have a higher yield than EEG?

EEG and MEG are complementary. MEG not only sees some different source, but sees more sources.

Geography:
• MEG is more sensitive to tangential sources, while EEG is more sensitive to radial sources.
• Approximately 2/3 of cortex lies in sulci, i.e. more tangential sources.

Resolution:
• MEG has an inherently higher resolution.
• Requires only ~4 cm² vs 6 cm² of synchronized discharging cortex.
  (Agirre-Arrizubieta Z et al. Brain 132, 3060-07; 2009)
Differences and Similarities: EEG and MEG

Similarities
- Record the same phenomenon
  - Same time-resolution
  - Spontaneous activities (epileptic spikes, non-epileptiform physiological), evoked responses (SEP, VEP, AEP)
- Sensitivity to brain volume and depth
Differences and Similarities: EEG and MEG

Similarities
- Record the same phenomenon
  - Same time-resolution
  - Spontaneous activities (epileptic spikes, non-epileptiform physiological), evoked responses (SEP, VEP, AEP)
- Sensitivity to brain volume and depth

Differences
- Sensitivity to the current dipole orientation
  - Tangential or vertical to the scalp surface
- Complexity of the forward model
  - Feasibility of the computerized source estimation
- Analysis
- MEG is reference-free
- Number of sensors
- Duration of the recording
- Different sensitivity to external noises
- Cost
- Established knowledge
Primary Clinical Applications

Sensory Mapping
- Usually in relation to a lesion
- Mapping often done prior to resection

Epileptic Spike Localization
What are the Indications for MEG in Epilepsy?

- Localization tool for interictal spikes
- Planning of intracranial investigations: grid placement, sEEG, etc.
- Normal MRI or discordance between other non-invasive studies
- Pre-existing cranial defects (reoperations)
- Extensive lesions
- Multiple lesions
- Functional mapping
- Bilateral synchrony
- Normal EEG
Correlation of MEG Localization of Interictal Discharges to ICEEG Ictal Activity

MEG: Interictal Dipoles

ICEEG: Seizure Onset
Patient Examples

MEG localization is especially useful in patients with previous neurosurgery or other skull defects.

Head shape, deformities, or position in the sensor array do not interfere.
Patient #1: MRI and EEG negative

History
• 34 year old male
• Right-handed
• One febrile seizure at age 2.5
• Onset: 10 years old
• Current seizures, up to 30/day, consist of a spasm in the neck and throat, sometimes accompanied by head turning to left, eye closure and facial grimacing
• Most recent GTC seizure was 15 years ago.
Patient #1 EEG and VEEG evaluations

- 1987 VEEG monitoring: 16 episodes recorded, none with any EEG change
- 1988 VEEG monitoring: 1 seizure lateralized to right
- 1989 Three multihour EEG: No epileptiform abnormalities
- 1993 Routine EEG: Normal
- 1995 Routine EEG: Normal
- 2002 Routine EEG: Normal
- 2011 Routine EEG: Normal
- 2011 (February) 6 day VEEG monitoring: Many seizures with no EEG change, Two seizures with EEG patterns at the vertex, slightly higher on left
- 2011 (March) MEG
Spike, regional right temporal (Unique to MEG, not seen on EEG)

Run I: Double banana bipolar EEG
Spike, regional right temporal on MEG

MEG Left temporal sensors

MEG Right temporal sensors
Right temporal spike dipole source localization
Representative spike dipoles

Right side
Patient #2: Scalp EEG Negative Case Example

History:

55 year old, right handed male with onset of epilepsy at age 25.

Mostly nocturnal seizures, sometimes in clusters, consisting of asymmetrical tonic posturing.

Previous EEGs have been negative.

MRI negative.

Ictal SPECT showed bilateral frontal activation.

VEEG monitoring showed extremely rare bifrontal spikes and non-localizable seizures.
EEG: Intermittent slow, FP1/F3

Run I EEG (Bipolar double banana)

1 sec  100 uV
MEG: Run of sharp waves, Left frontal sensors (consistent localization)

1 sec  500 fT/cm

Left frontal sensors

Right frontal sensors
MEG Sources: Left middle frontal gyrus and superior frontal sulcus
Ictal Onset (☐) & CS seizure (☀)

11 Spontaneous seizures captured with onset at X’10,11,12
MEG in EEG-Negative Patients

Routine MEGs:
- 358 Patients, 375 Studies
- Feb 2008 – Jan 2012

Previous Routine EEG: 145 Patients (40.5%)
- No Epileptic Activity: 58 Patients (40%)

MEG Results:
- Localizable dipoles: 38 Patients (65.5%)
- MEG-Unique Information: 12 Pt (31.6%)

( Ito et al. American Epilepsy Society Meeting, 2012 )
MEG in Non-Focal VEEG Patients

Routine MEG 358 Patients, 375 Studies
Previous EMU Evaluation 336 Patients (93.4%)
- Only generalized, no regional Activity:
  83 Patients (24.7%)

MEG Results:
- Localizable dipoles: 48 Patients (57.8%)
- MEG-Unique Information: 5 Pt (10.4%)

( Ito et al. American Epilepsy Society Meeting, 2012 )
Patient #3: MEG prompts re-review of a previously negative PET, identifying a subtle hypometabolism

History:
42 yo right handed male
Sz triggered by music with lyrics (or just thinking about the lyrics) that he knows
Sz Classification: Auditory aura → Dialeptic → Right versive → GTC
PET: Nonspecific
Simultaneous Multi-Modality Review: PET and MEG

MEG highlights a subtle hypometabolism on a previously negative PET
Simultaneous MEG and Subdural Grid Recording
Multi-modality integration

(Wang et al 2012, J of Neurology)
Some Myths and Realities about MEG

Myth #1: MEG is too sensitive to artifacts and noise

Myth #2: MEG only records interictal activity
Myth #1: MEG is too sensitive to noise and artifact.
Relative Field Strength

Brain sources:
Evoked cortical fields: 10 fT
Alpha rhythm: 1000 fT

Noise sources:
Earth’s magnetic field: ~50 µT
Field from home appliances and wiring: <10 µT
Urban environmental noise: 10⁸ fT

(fT = femto Tesla or 10⁻¹⁵ Tesla)
MEG’s Immunity to EMG Artifact

EEG
Patient with multiple implants

20 y.o. RH female with seizure onset age 13

Three seizure types:
- Dialeptic → right version → right arm tonic → GTC
- Bilateral limb myoclonus
- Generalized myoclonic with eye blinking and shoulder shrugging

S / P VNS implantation 2 yrs ago with no benefit

Scalp VEEG: Interictal and ictal discharges generalized

Multiple body piercings, three of which were unremoveable (one in left ear)
EEG:
Run I: Double banana bipolar EEG
MEG without tSSS (temporal signal space separation)

Left temporal sensors

Right temporal sensors
MEG with tSSS (same time segment with same amplitude scale)

Left temporal sensors

Right temporal sensors
Effect of tSSS Noise Cancellation in a Patient with a Left Temporal Spike and a VNS

(Taulu and Simola 2006: Jin, Burgess et al 2012)
Myth #2: MEG only records interictal epileptic activity

While MEG has been found most suitable for evaluation of interictal activity, as noted above, ictal MEG recordings have been made --- frequently serendipitously.

Despite the obliteration of the MEG signal by movement artifact during an ictus, a sizable proportion of focal seizures are manifest by EEG/MEG activity for many seconds (typically 5-20) prior to any clinical movements, or even without any movements (patients with frequent auras).

These recordings of ictal onset by MEG can yield precise localization of the epileptogenic zone.
Ictal MEG Recording

Left temporal gradiometers
Ictal MEG studies at Cleveland Clinic

All epilepsy patients -
  - Between February 2008 – January 2012
  - Who underwent VEEG and
  - Who also had MEG studies within 6 months

309 total MEGs, 139 inpatients (45%), 170 outpatients
228 positive interictal MEGs
  - 106/139 (76%) inpatients, 122/170 (72%) outpatients
  - I.e. Similar proportion (p = n.s.)

39 ictal MEGs (12.6%)
  - 26 (67%) inpatients and (33%) in outpatients
  - Significantly higher in inpatients 26/139 (19%) than in outpatients 13/170 (8%) p <0.01

Of the 39 ictal MEGs, 25 (64%) localized using SECD
  - Approximately half of which (14 or 56%) were not localizable by VEEG.

( Ito et al. 30th International Epilepsy Congress, 2013 )
What should the referring physician expect from a MEG study?

The publication of Clinical Practice Guidelines* has helped to establish referring physicians’ expectations for a high level of quality in the interpretation and for practical utility from the results. Centers with MEGs are striving to practice according to these guidelines.

What Can Epileptologists Expect From MEG?

A routine and standardized procedure.

ACMEGS Clinical Practice Guidelines CPG # 1:
Recording and Analysis of Spontaneous Cerebral Activity

ACMEGS Clinical Practice Guidelines CPG # 2:
Presurgical Functional Brain Mapping Using Magnetic Evoked Fields
What Can Epileptologists Expect From MEG?

A clear and helpful report.
An answer to the clinical question posed.

ACMEGS Clinical Practice Guidelines CPG # 3:
MEG-EEG Reporting
How does MEG help to fill in the gaps in our clinical understanding?

MEG is a “complementary” technique with different sensitivity, i.e. it adds new and unique information.

MEG prompts focused re-review of other structural and functional tests.

MEG’s whole-head coverage fills in the gaps left by other techniques.

MEG helps to explain results of other tests when they are surprising and to understand discordant results.
Beyond the basics: What might we expect in the future?

- Noise cancellation
- Movement compensation
- Streamlined software
- Multimodality integration and neuronavigation
- Analysis of connectivity and other quantitative assessments
- Replacement for intracranial VEEG monitoring
Dipole Sources Coregistered with Surface-Reconstructed MRI

MEG dipole sources (blue)
Subdural grids (green)
Stereotactic EEG electrodes (green)
Previous Resection (orange)
For Further Information

Regarding:
MEG Clinical Practice Guidelines
Conferences, Courses & Symposia
Scientific Information

American Clinical MEG Society
Phone: 414 918-9804
Email: mkelley@acmegs.org
Web: http://ACMEGS.org

Regarding:
Evaluation of Epilepsy
Clinical Consultation
MEG Testing

Cleveland Clinic Epilepsy Center
Phone: 216 444-0601
Email: epilepsy@ccf.org
Web: http://my.clevelandclinic.org/neurological_institute/epilepsy
Additional slides for Q & A period
How is MEG analyzed and interpreted (1)

First identify important waveforms (e.g. spikes)
- By time correlation with EEG?
- Blindly?
- From spike detector?

Spike!
Analysis of MEG Signals (2)

Field determination requires computerized calculation.
Analysis of MEG Signals (3)

Source localization – dipole modeling

- Single or multiple dipole modeling – most common
- Iteratively search dipole parameters (location, orientation, current strength) for best fit to the actual field distribution
- Requires a starting point (initial guess) for search

Measurement = Model + Residual

Modeled dipole parameters

\[(x, y, z) = 45.2, 31.7, 8.8 \text{ mm} \]

\[(Q) = 373 \text{ nAm} \]

Goodness of fit = 84.5%
Spike Source Estimation (4) --- Solving the Inverse Problem

Recording spontaneous MEG activity --- trace mode

Typical MEG waveforms from sensors overlying the right central region; an epileptiform spike is outlined.
Spike Source Estimation (4) --- Solving the Inverse Problem

Topographic view of MEG activity during the bracketed epoch

Expanded view of MEG activity at maximally active sensor
Analysis of MEG Signals (5)

Co-registration to Anatomy
- Requires 3-dimensional coordinate digitization of surface landmarks
- Import 3-D MRI
Ictal MEG Analysis

MEG’s strength: Time dimension!

Example case:
Six seizures during MEG recording,
1 clinical seizure and
5 with no clinical signs (NCS).
NCS Seizure. MEG: Spike and wave complex, Right parietal sensors

Left temporal

Right parietal sensors

Onset, #5

(MR#70084422)
Dipole of #5 (Onset): Right posterior middle frontal gyrus (stable)
Clinical Seizure. EEG: Onset, Right centro-parietal, Somatosensory Aura

#1 EEG Onset #2 #3 #4 Run I EEG

(MRI#70084422)
Clinical Seizure. MEG: Attenuation -> beta, polyspikes, Right parietal sensors

Left temporal

Right

#1  EEG Onset  #2  #3  #4
Dipole of #1-1 (early component): Right posterior middle frontal gyrus
Dipole of #1-2 (late component): Right precentral gyrus
Dipole of #2 (3.3 sec after onset): Right precentral & parietal (unstable)
Dipole of #3 (3.9 sec after): Right postcentral (hand and face) (stable)
Dipole of #4 (5.2 sec after): Right postcentral (hand and face) (stable)
The likely reason that one out of the six seizures had clinical manifestations is because of propagation of that seizure from the posterior middle frontal gyrus to the post central gyrus.
Subdural Grids and Depth Electrodes
Dipoles of NCS Seizures
Dipoles of Clinical Seizures
Does MEG See It All?

Study of MEG ability to detect and localize spikes recorded on SEEG

- 3 simultaneous MEG / SEEG recordings
  - Both TLE and ETLE
- 30 MEG patients who underwent intracranial recordings after MEG
  - All extratemporal
- To assess factors which determine concordance between MEG and ICEEG
- Depth of contacts / sources
- Amplitude of spikes on intracranial electrodes
- “Tightness of clusters” on MEG
- Dipole orientation

Jin, Burgess et al., JES 2010
Simultaneous MEG and SEEG (Case 1)

**SEEG**

<table>
<thead>
<tr>
<th>S1</th>
<th>S2</th>
<th>S3</th>
<th>S4</th>
<th>S5</th>
<th>S6</th>
<th>S7</th>
</tr>
</thead>
</table>

- **Depth of contact**: Approx. 39 mm
- **Max. Amplitude**: \(304.5 \pm 137.0\) uV (202.6 – 878.6)
- **Number of Contacts >200 uV**:
  - 1 contact (30 SPKs)
  - 2 contacts (7 SPKs)
Simultaneous MEG and SEEG (Case 1)

Magnetometer

Gradiometer

Time: 1808430 ... 1813430 ms
Grad: -500.0 ... 500.0 ft/cm, Mag: -2500.0 ... 2500.0 ft
Scalebars: 200 ms, 500 ft/cm, 2500 ft
Simultaneous MEG and SEEG (Case 3)

SEEG

M1
M2
M3
M4
M5
M6
M7
M8
M9

Q1
Q2
Q3
Q4
Q5
Q6

M9
Simultaneous MEG and SEEG (Case 3)
Simultaneous MEG and SEEG (Case 3)
## Summary of 3 Cases

<table>
<thead>
<tr>
<th>CASE</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depth of Contact (mm)</td>
<td>39</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Average of Max. Amplitude (uV)</td>
<td>304.5</td>
<td>250.6</td>
<td>468.0</td>
</tr>
<tr>
<td>Number of Contacts &gt;200 uV</td>
<td>1-2</td>
<td>1-2</td>
<td>1-4</td>
</tr>
<tr>
<td>Detectability (%)</td>
<td>0</td>
<td>0</td>
<td>66.0</td>
</tr>
</tbody>
</table>