Cincinnati Children's Hospital Medical Center

Cincinnati, Ohio, USA

Medically Intractable Seizures in Pediatric Patients Evaluation and Surgical Treatment

Focus on Role of Magnetoencephalography (MEG) and dense array EEG (dEEG)

Douglas F. Rose MD
Professor Emeritus
Pediatrics and Neurology
Cincinnati Children's Hospital Medical Center
University of Cincinnati

Medication Resistant Seizures in Pediatrics

- Epilepsy occurs in 1–2% of the pediatric population (prevalence)
- 25-40% of children with epilepsy will not achieve seizure freedom with antiepileptic drugs (AEDs)
- Refractory epilepsy defined by the International League Against Epilepsy as failure to achieve sustained remission following trial of 2 or 3 appropriate AEDs
- Of the patients referred for epilepsy surgery in the USA, the average duration of their seizures prior to referral was 18 years, with a range from 2–58 years
- There is an interest in identifying epilepsy patients at an earlier age who are candidates for surgery to reduce morbidity and mortality from continued seizures.

McCoy, B. et al "Approach to refractory childhood seizures" Therapy (2010) 7(5), 497–506
Ramantani and Zentner "Epilepsy Surgery in Children and Adolescents" Neurology International Open 2017; 01(02)
Dlugos "The Early Identification of Candidates for Epilepsy Surgery" Arch Neurol. 2001;58(10):1543-1546.

General work-up for medication resistant seizures

1. Seizure history for each seizure type and response to medication
2. Birth history
3. Illnesses history
4. Family history
5. Neurology exam looking for focal deficits - looking for possible etiology

Focused History, Exam, and Tests

- Evaluating for focal onset of seizures
  - Simple or complex partial seizures that have not responded to several antiepileptic medications or
  - Focal interictal spikes or **ictal seizure onset** or **seizure semiology** that suggests a focal onset
- Intractability of seizures: several medications at good doses/blood levels with lack of response
- Routine EEGs that show unilateral interictal spikes or focal onset of seizures
- Genetic and metabolic screening if history suggestive

Presurgical Evaluation for Intractable Epilepsy

- Evaluation Goal: Determine intracranial location of onset of seizures and also the location of normally functioning brain regions, especially for language and hand motor
- VideoEEG Monday through Friday to capture at least one seizure, but preferably more. Medications tapered day of admission or night before (lamotrogine tapered prior week; benzodiazepines not tapered)
- MRI scan for anatomy; functional MRI for language hemispheric dominance
- PET scan + PET SPM (3D statistical comparison to nl PET scans in age matched cohort)
- Ictal SPECT scan if possible; Injections usually within 15 secs of seizure onset, but not always possible. Interictal SPECT scan also obtained for subtraction for SISCOM.
- Neuropsychological evaluation
- 3D noninvasive intracranial localization of spikes and seizures
  - Magnetoencephalography (MEG) with whole head 275 sensor array (CCHMC since January 2006)
  - Dense array EEG (dEEG) with 128 or 256 scalp electrodes, for some patients

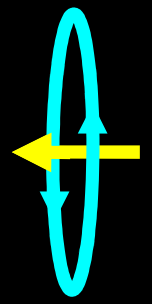
Good review of diagnostic tests: Ryvlin et al 2008 Dialogues Clin Neurosci. 10(1): 91–103

PET – positron emission tomography SPECT – single photon emission tomography

Fundamentals MEG/EEG

Similarities

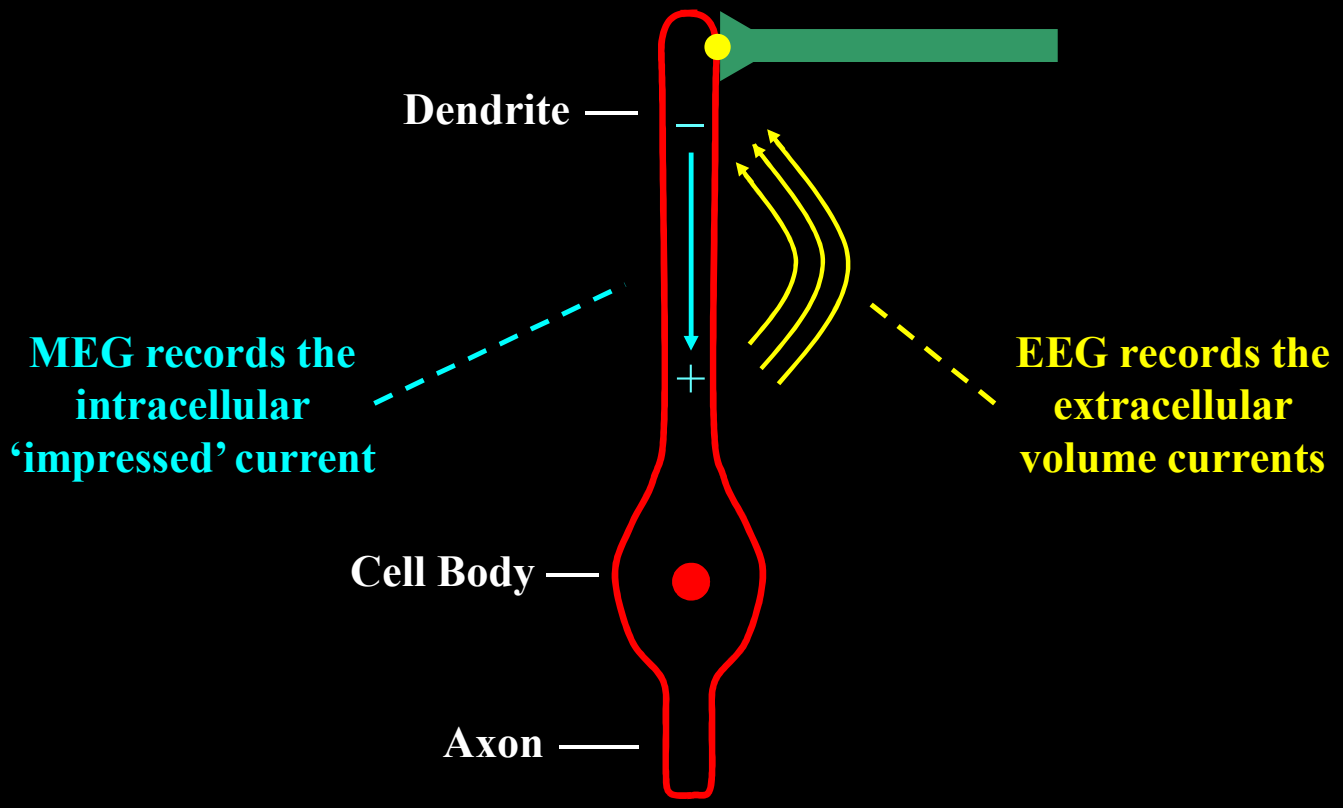
- Every electrical current has an associated magnetic field



Differences

- Currents Measured
  - MEG - intracellular currents
    - Can be configured to also record extracellular
  - EEG - extracellular
- Current Orientation
  - EEG – radial and tangential
  - MEG - tangential

Neuronal Membrane Depolarization

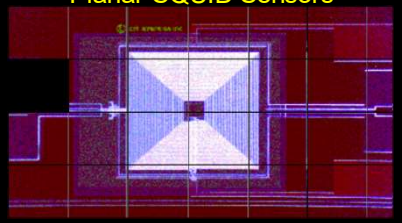


Magnetoencephalography (MEG)

- Whole head magnetometer with array of 275 fixed position sensors
- Record in magnetically shielded room for usually about 90 minutes, but occasionally under special circumstances up to 4 hours
- Determine location of sensor array relative to ‘fiduciary points’ on patient’s head (nasion, left and right preauricular points)
- Patient must remain essentially motionless (no more than 5 mm movement) during series of 2 min and 10 min sessions
- Most often epilepsy studies are recorded while the patient is asleep.

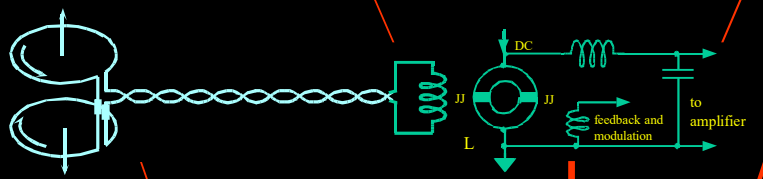
Whole head 275-channel Magnetometer

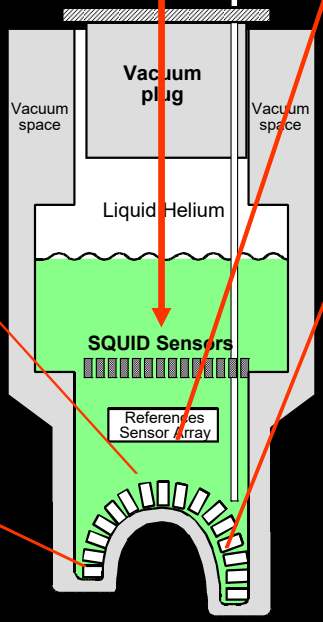
Planar SQUID Sensors



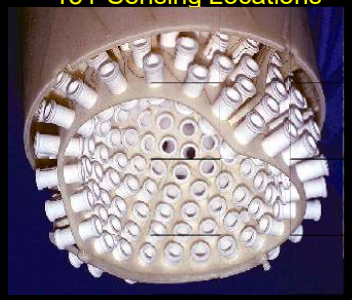
Whole-Cortex MEG System

FirstOrder Radial
Flux Transformers

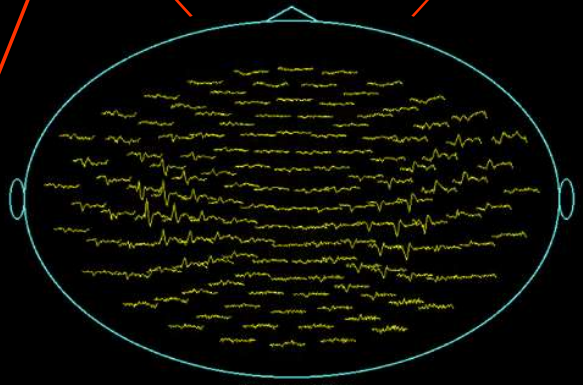




Sensing Coil Array
151-Sensing Locations



MEG Data



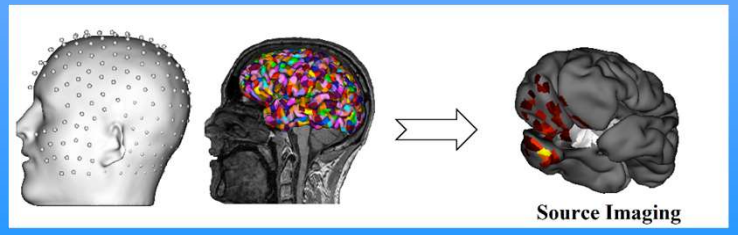
Processed Data
(3rd order gradient)

Courtesy of CTF

Dense Array EEG (dEEG)

- dEEG sometimes referred to as ‘high density’ scalp EEG
- Number of electrodes: usually 64 or greater, e.g., 128, 256
- Cap or net with equally spaced scalp electrodes - no gluing
- Record at bedside daytime and overnight usually 24 -72 hours
- Patient may move throughout recording session
  - Best recordings for seizure onset are when patient is initially motionless - usually that means asleep
  - Our best recordings for seizures have been overnight and following morning
- Determine location of electrodes relative to ‘fiduciary points’ (nasion, left and right preauricular)

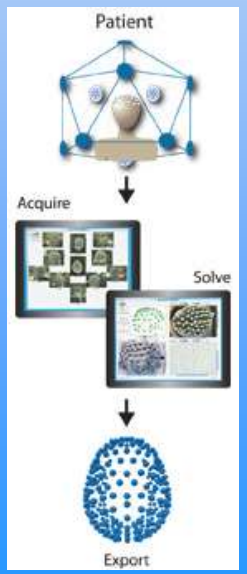
Dense Array EEG (dEEG)



Localization of Scalp Electrodes relative to Head

Digitizing Pen localizing each separate electrode

11 simultaneous cameras



Wand waved over head

Recording results

- MEG
  - Typically capture interictal spikes
  - For 1 in 20 patients (5%) capture seizures
- dEEG
  - Typically capture both interictal spikes and seizures (though selected patients with frequent seizures)

Analysis of results: Quantitative MEG and dEEG

A. Total number of interictal spikes and seizures per unit time (awake and asleep)

B. Apparent surface location (topography) of each: frontal, central, temporal, parietal, occipital - grouping into spike types by morphology and apparent surface location - and tabulate number of spikes (or seizures) in each group

C. **Time-frequency analysis** (TFA) to determine the electromagnetic frequency that is becoming active first

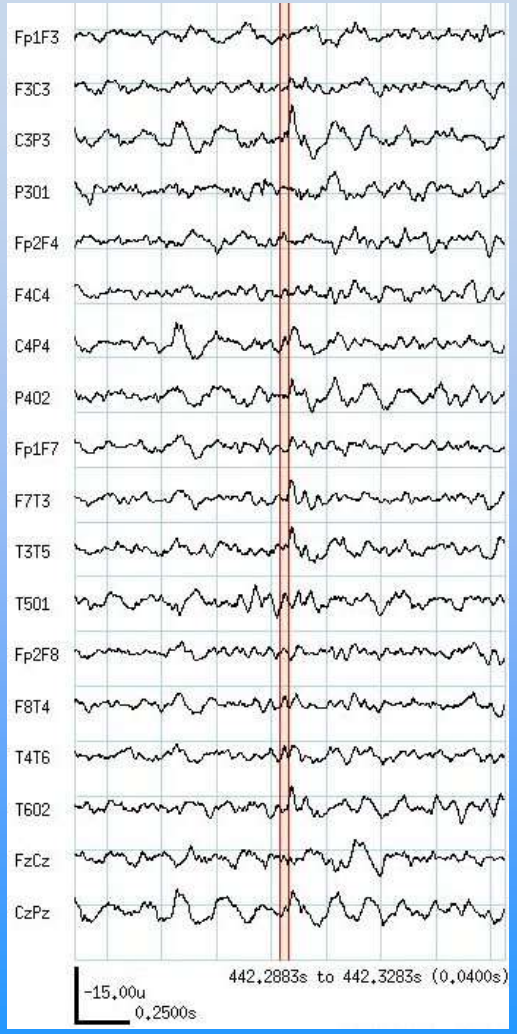
D. **3D intracranial source localization** of individual interictal spike in each grouping and each recorded seizure

Time-frequency Analysis (TFA) of epileptiform discharge

- TFA - the time domain waveform is transformed to the frequency domain over time with the Short Time Fast Fourier transform or Wavelets
  - Evaluate the change of power (neuronal activity) at each frequency over time
  - Determine the frequency that shows the first increase in activity at the beginning of a spike or seizure.
- The TFA plot shows the ‘frequency content’ of an interictal discharge or seizure onset
- The earliest change in frequency power can occur earlier than apparent by just looking at the interictal spike or seizure onset in the time domain.

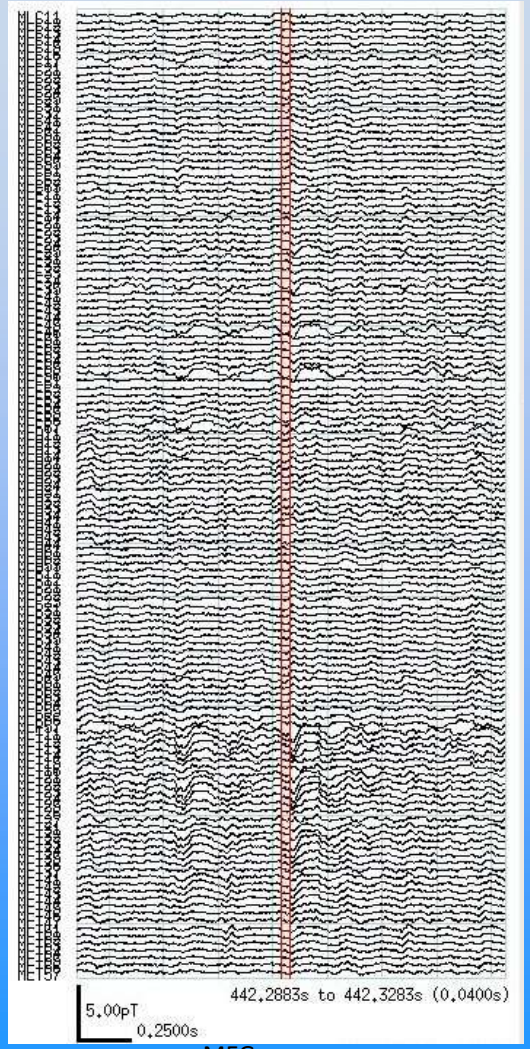
13 ½ y/o female

Left parietal



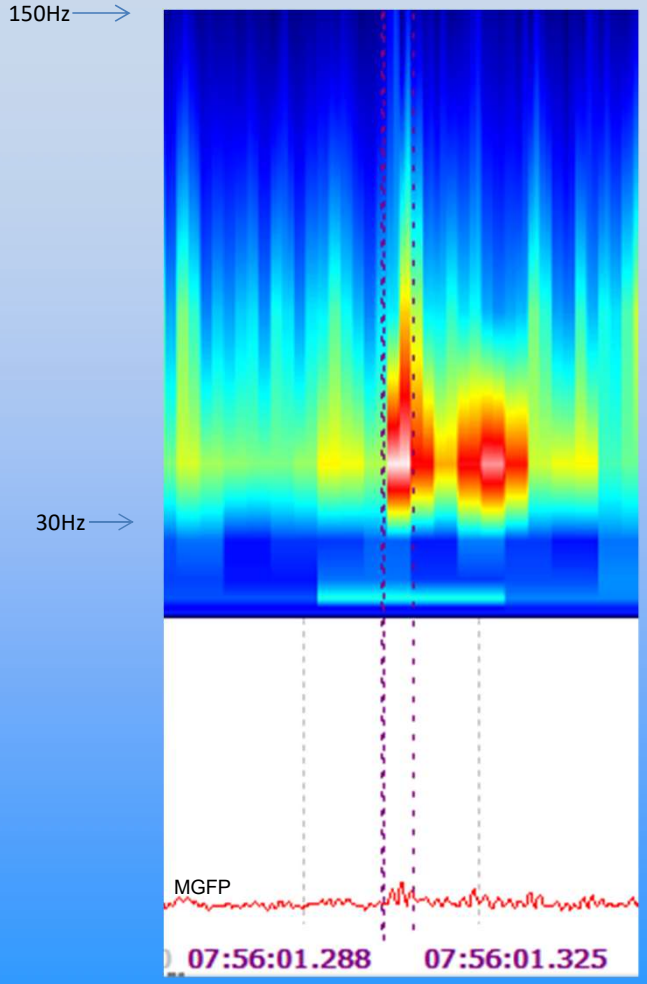
EEG

(3 - 70Hz, 0. 2500 sec/div)



MEG

(3-70Hz, 0.2500sec/div)

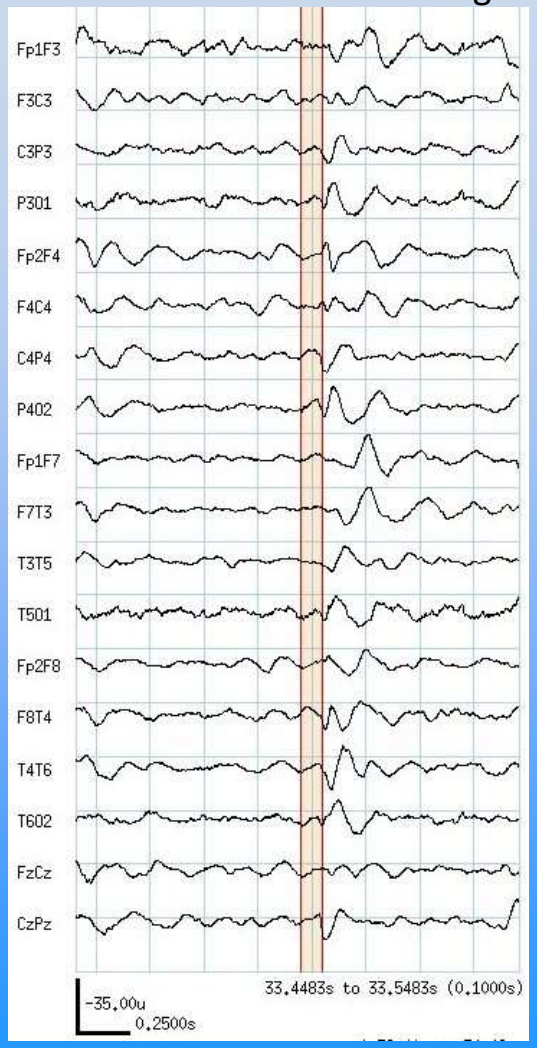


MEG spectrum

(30-70Hz)

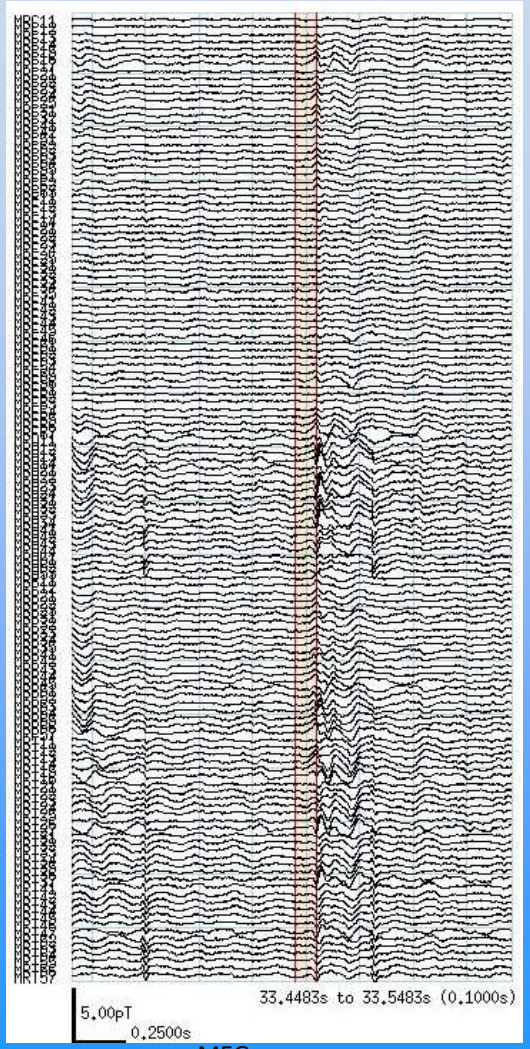
2 year 10 month old female

Right parietal



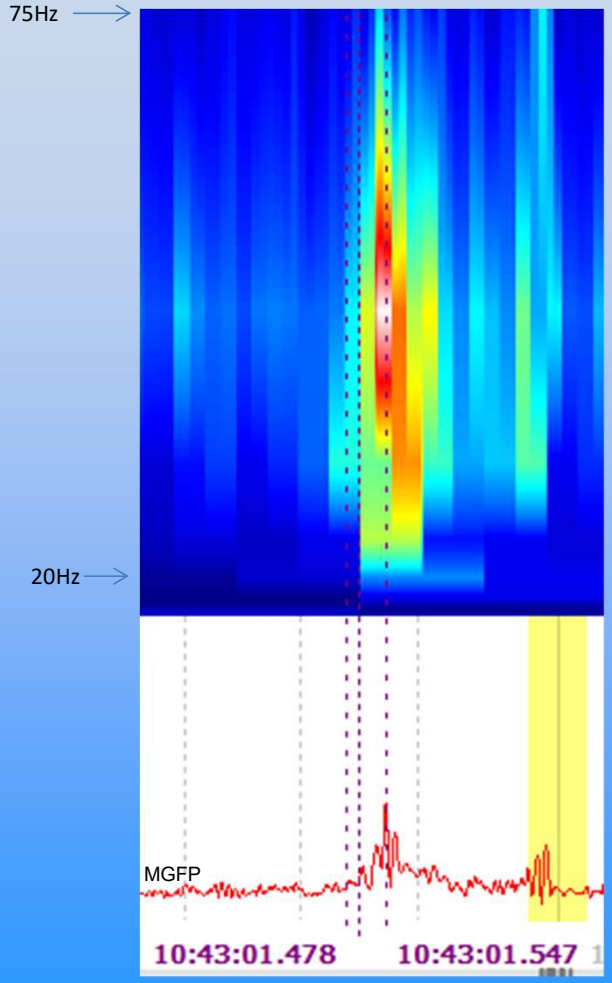
EEG

(3 - 70Hz, 0. 2500 sec/div)



MEG

(3-70Hz, 0.2500sec/div)



MEG spectrum

(20-70Hz)

Analysis of results: Quantitative MEG and dEEG

3D intracranial source localization of individual spike in each spike type in each topographic grouping

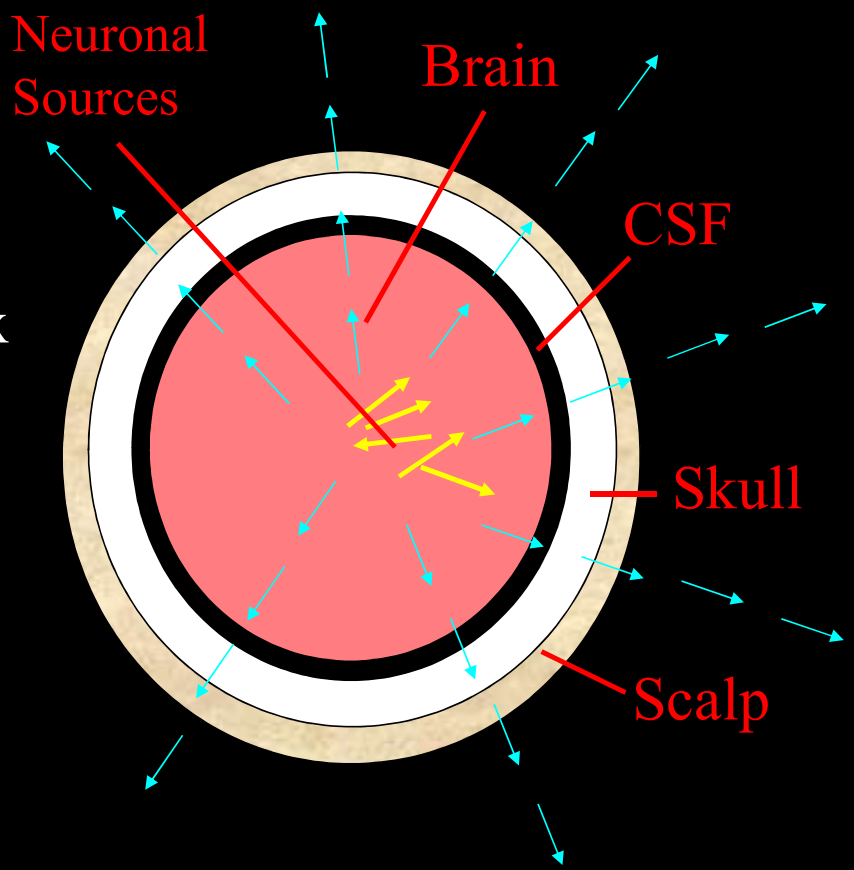
- From the MEG or dEEG signals recorded noninvasively outside the head, use mathematical models to estimate the intracranial location of the interictal spikes or onset of a seizure

- Need two mathematical models:
  - **Source model** generating the electromagnetic signal (neurons)
  - **Head model** determining how the intracranial signals get to the recording sensors outside the head
- Here's why and how:

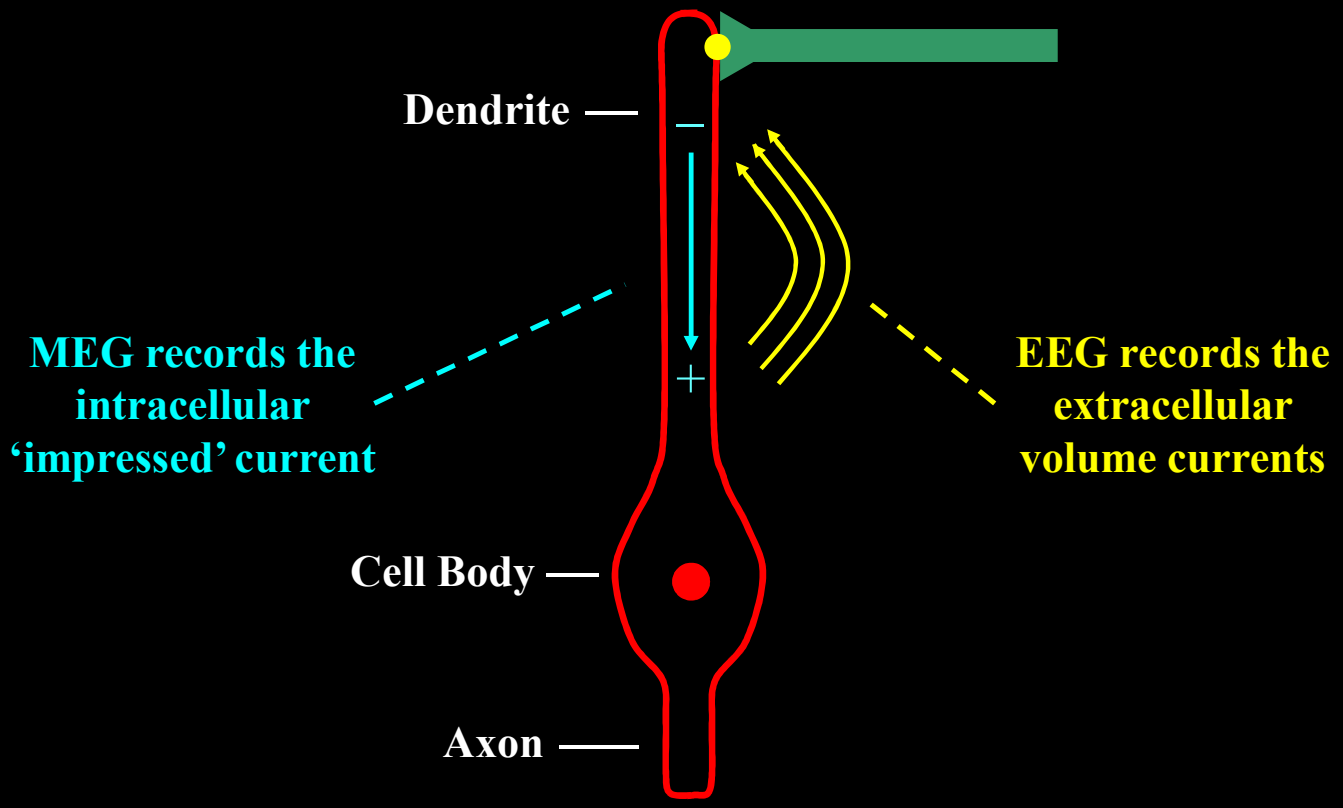
Fundamentals MEG/EEG

Source Localization

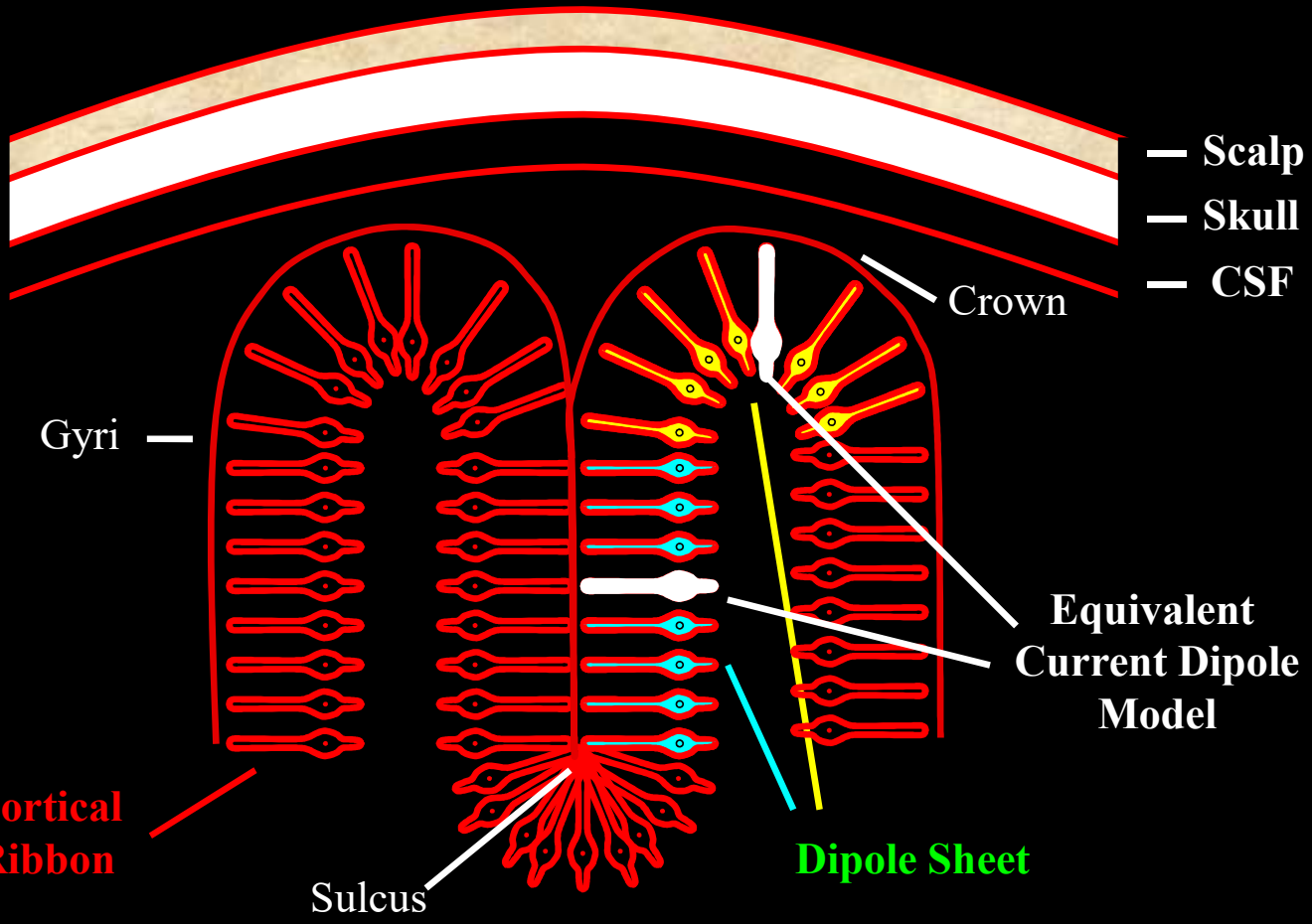
- Source model
  - EEG/MEG - Complex
- Head model
  - EEG - Complex
    - Need conductivities
  - MEG - Simple
    - Conductivities not needed



Neuronal Membrane Depolarization



Current Dipole Sheet



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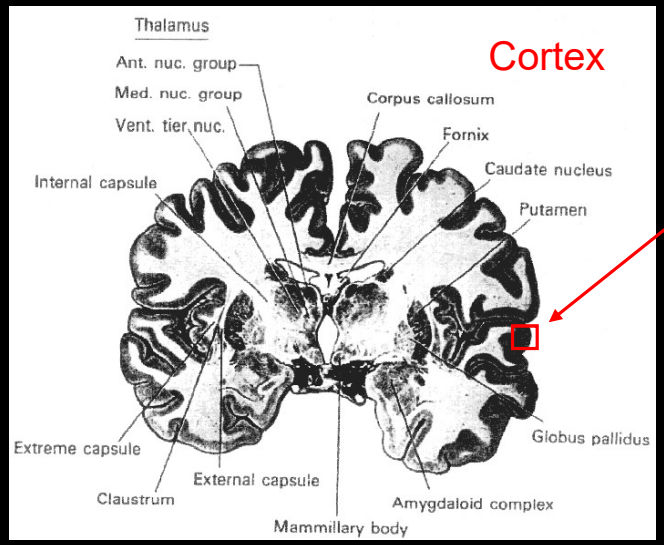
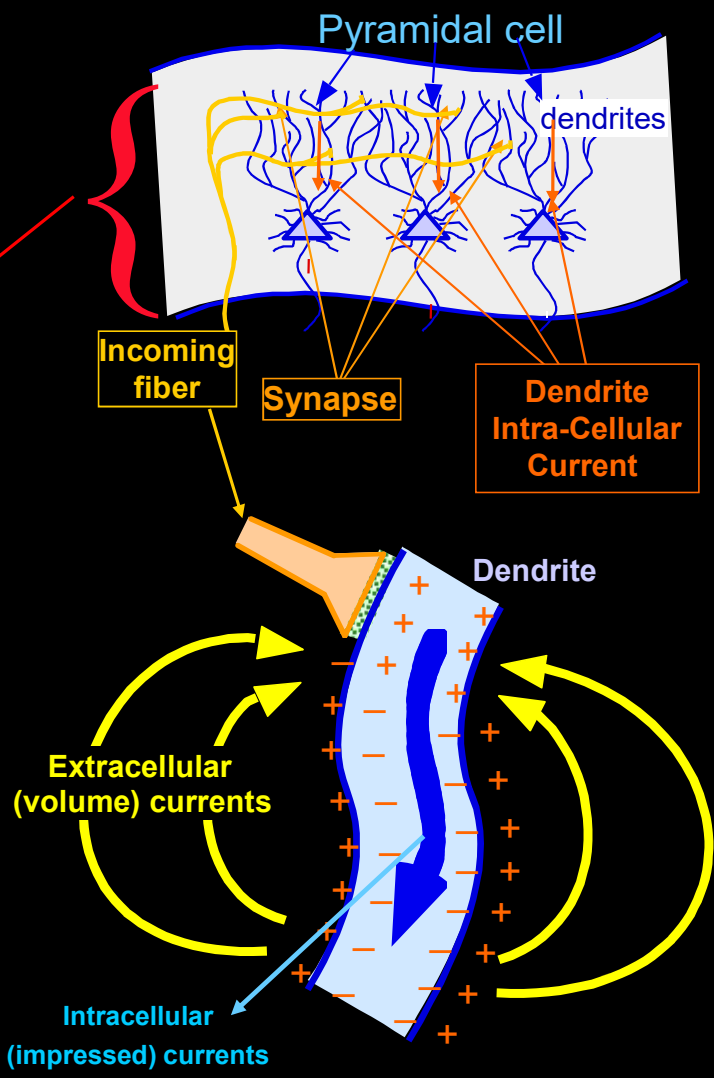
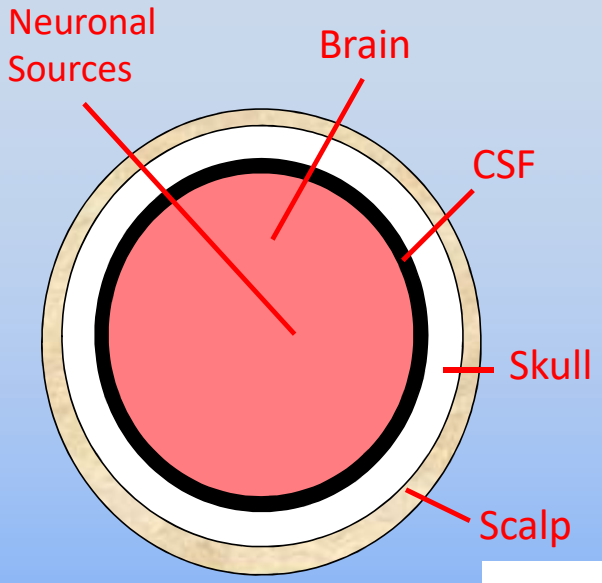
Source of MEG Signal



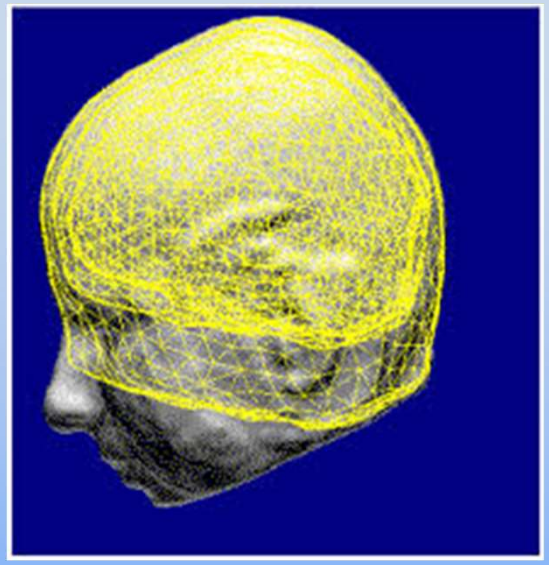


It is Estimated that for a Detectable MEG Signal Approximately 10^5 to 10^6 Cells Must Collectively Fire

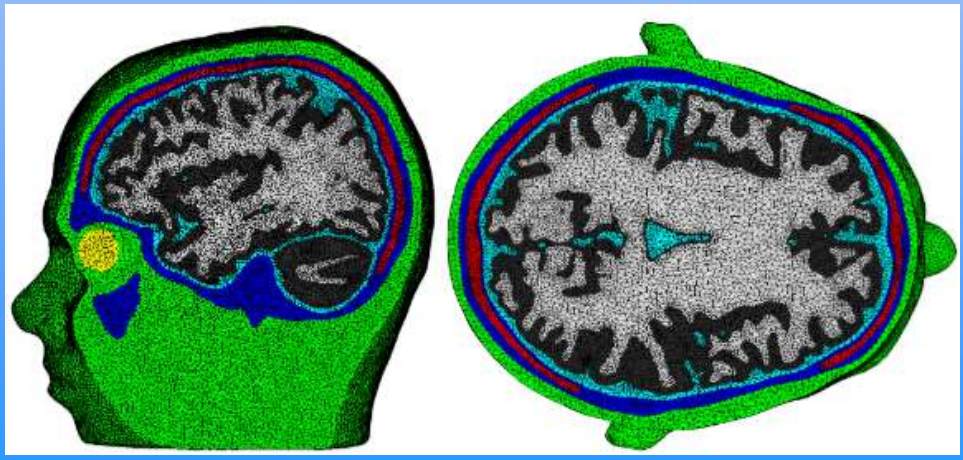
Mathematical Head Models



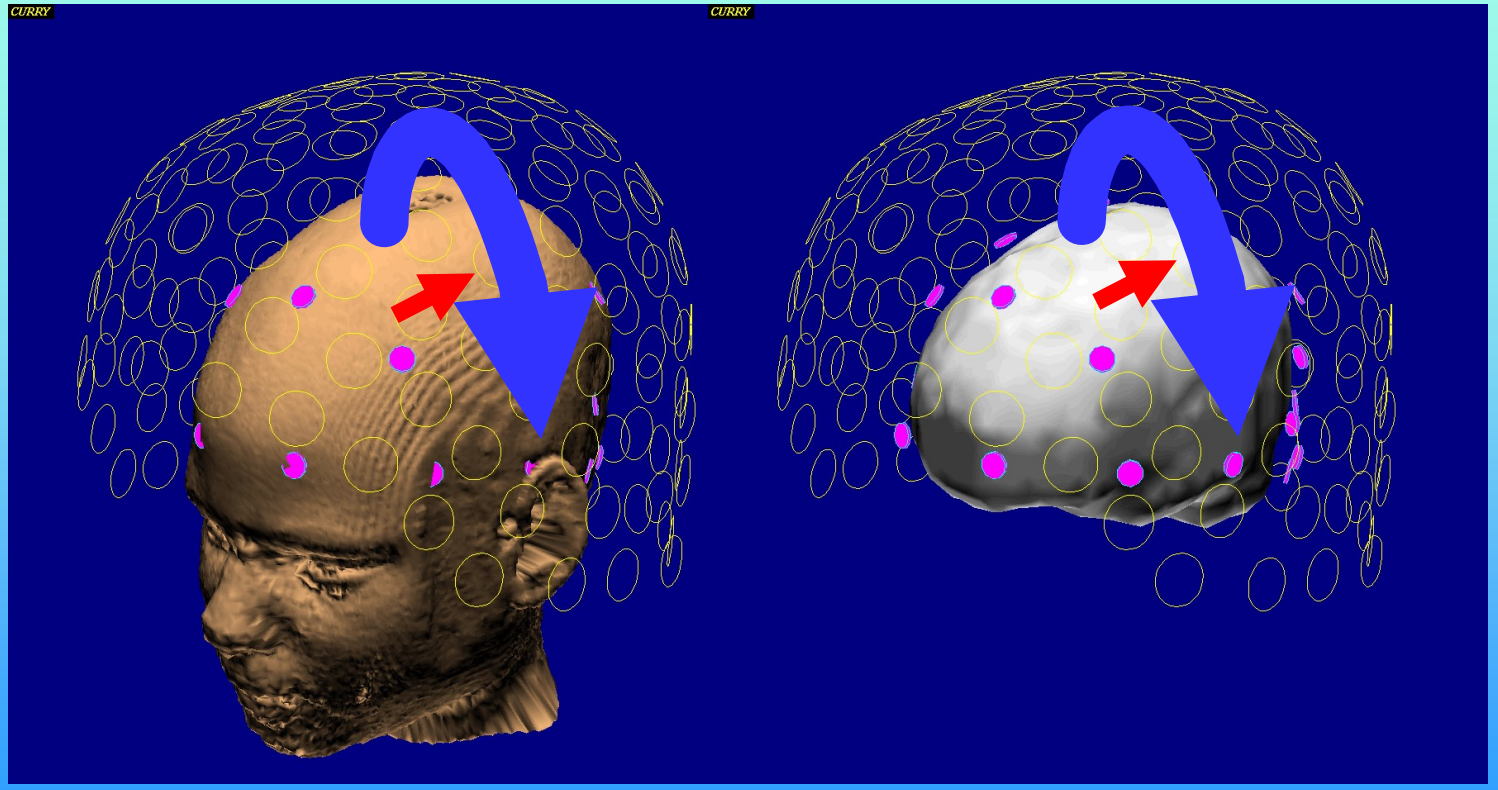
Spherical head model
Concentric spherical surfaces nested within each other.



Realistic head model: Boundary element model (BEM) (Consecutive triangulated surfaces nested within each other and constructed from patient's own MRI scan)



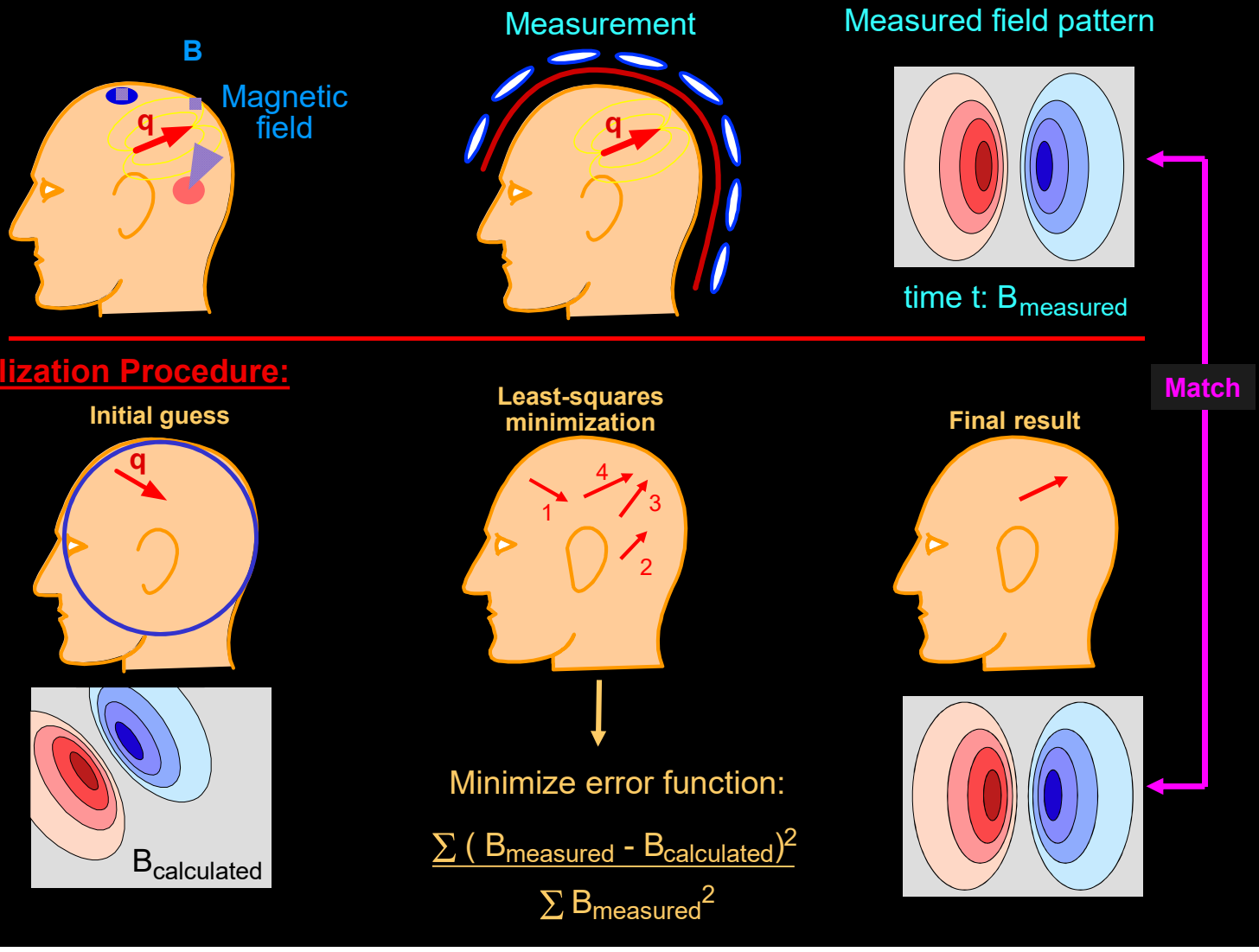
Realistic head model: Finite element model (FEM)
(Consecutive regions of cubes nested within each other and constructed from patient's own MRI scan)


CURRY
CURRY

Intracranial Source Localization

- **Inverse Solution** – would use the EEG and MEG signals recorded outside the head to directly calculate the location of the source inside the head.
  - Possible for a single intracranial source
  - Not possible if there two or more intracranial sources active at the same time
  - Most patients with epilepsy may have two or more sources active simultaneously
  - "Inverse problem" – not solvable
- **Forward Solution** – we choose a "putative source" at a location within the head. Then we can calculate what signals would be recorded at each EEG or MEG sensor outside the head.
  - All of the source localization models use this approach
  - Can start with a single putative dipole source at a single location as the **"Equivalent Current Dipole (ECD) Method"** and stepwise move the source location to improve the fit to the recorded data.
  - Can also use variations on the above method
    - Start with fixed number of putative dipoles (ie Multiple ECD method with 2-8 putative source dipoles)
    - Sequentially evaluate all source locations throughout the head and then assess for best fit
      - Multiple Signal Classification (MUSIC)
      - Dipole Scan/Deviation Scan
    - Simultaneously evaluate all source locations throughout the head for the best fit
      - Minimum Norm Estimation (MNE); LAURA, sLORETA,, SWARM, eLORETA, L1 Norm, Lp Norm
      - Low resolution electromagnetic topography (LORETA)

ECD Localization Procedure



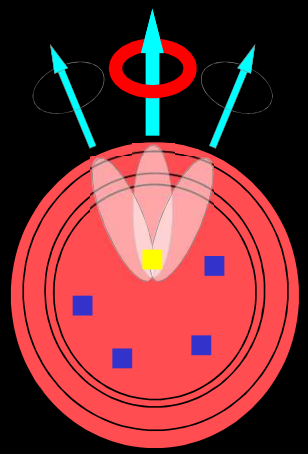
Beamformer Method of Source Localization

- MEG head model so simple that can mathematically ‘tune’ the sensor array to see signals in a small region of the brain and then can scan the brain by sequentially ‘tuning’ the array to adjacent locations.
- In our center we scan 330,000 locations 2.5 mm apart. Beamformer has been attempted with EEG but the accuracy of the head models for the forward solution need to be improved.
- When we detect statistical bursts of activity (excess ‘kurtosis’) at a location, we can look at the continuous activity (waveform) to look for spike or seizure activity. We can compare multiple intracranial locations to find the earliest onset of activity.

Magnetometer Sensitivity Profile

Directional sensitivity
of magnetometer

Mathematically
simple head model



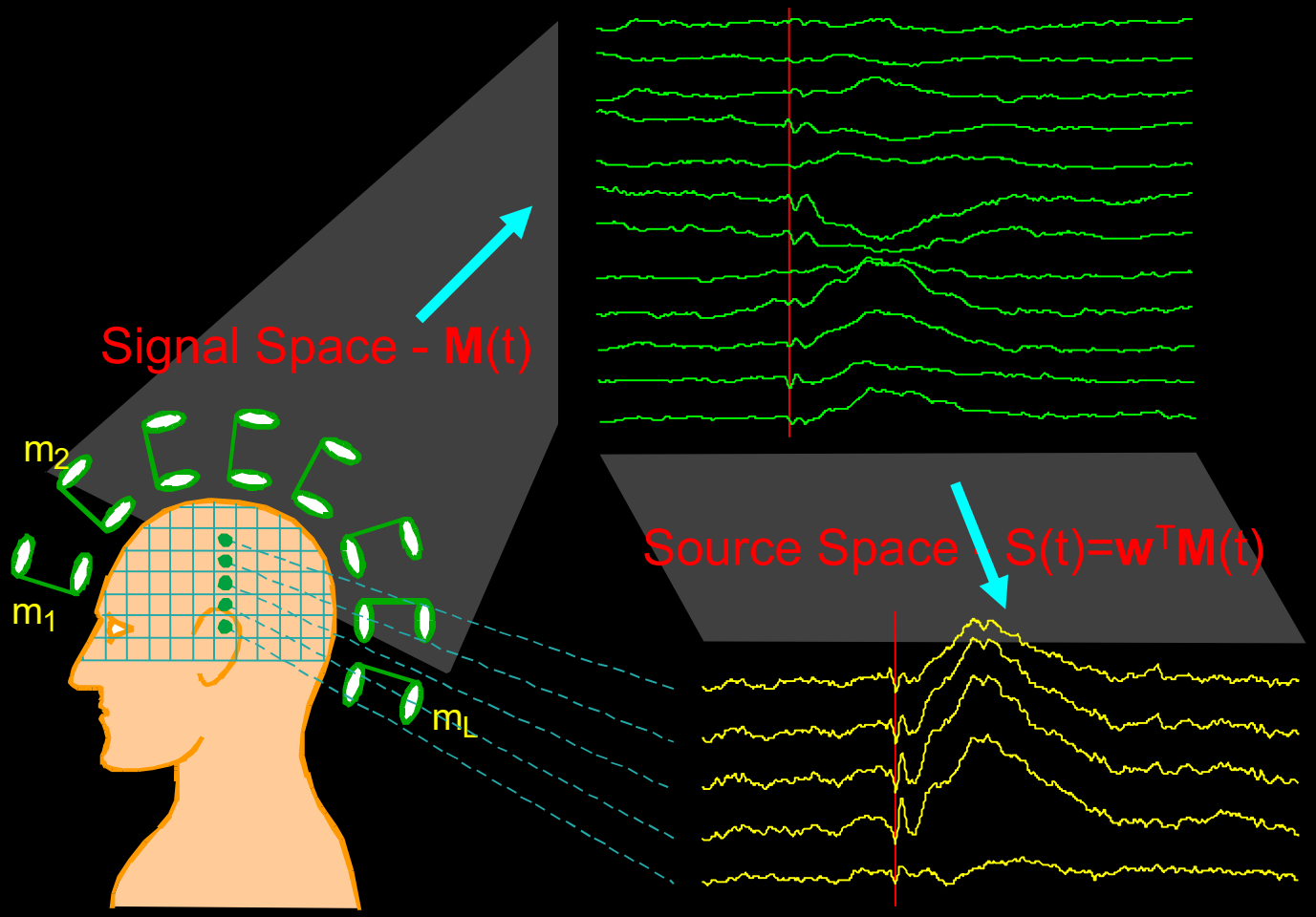
Principle 1: Large array can be 'tuned' to be most sensitive to a particular region (voxel) of the head.

Principle 2: For a particular recording segment, large array can simultaneously be 'tuned' to be less sensitive to concurrent noise sources.

Synthetic Aperture Magnetometry (SAM)

- Magnetic signal recorded by large array magnetometer for brief period of time: 2 minutes.
- Tune magnetometer to a particular voxel in the head, decreasing sensitivity to noise sources, and examine the signal in the voxel during recording.
- Retune the magnetometer to an adjacent voxel; examine the 2 minute signal at that voxel.
- Sequentially scan all the voxels in the head. Reconstruct the 3-D sources over the time course of the recording.

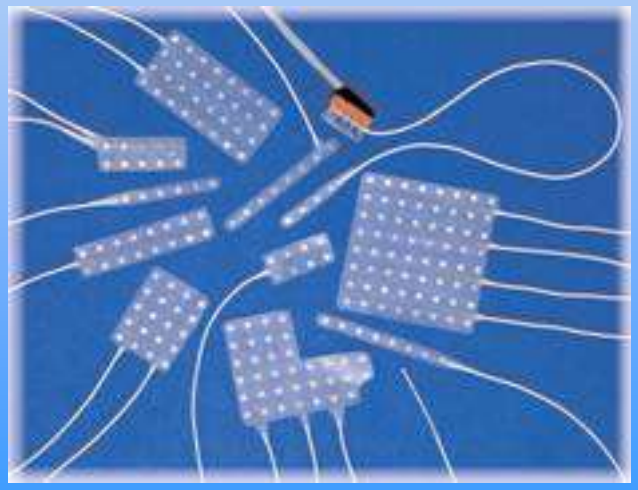
Decomposition of Signal Space Into Source Waveforms

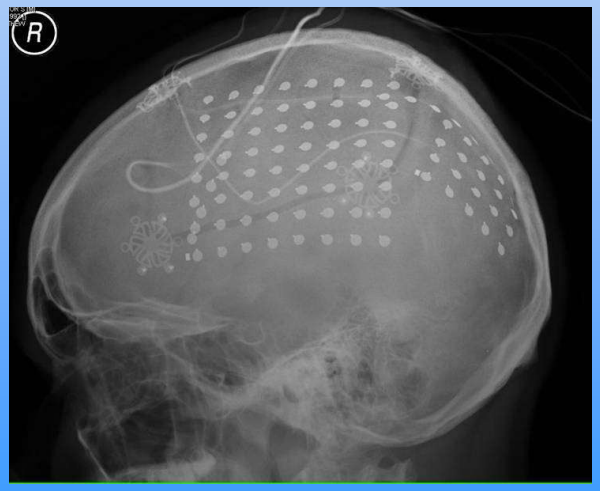


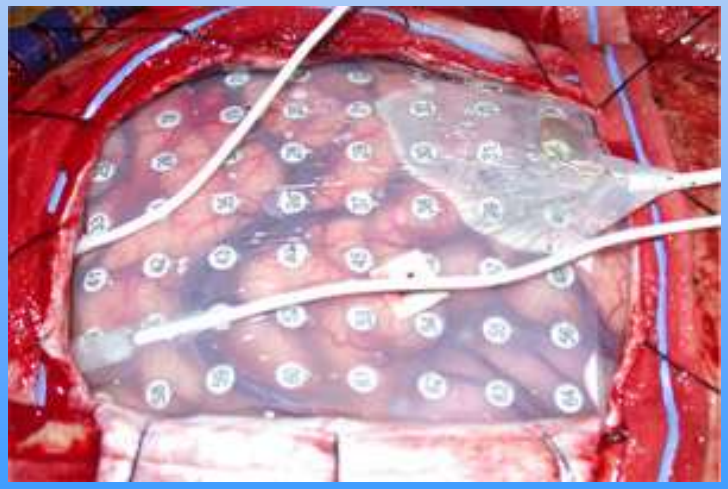
Intracranial monitoring

- In pediatrics, usually need to follow noninvasive source localization with direct brain recording
  - **Subdural electrodes** - thin disc electrodes embedded in thin pliable silastic in a row of several electrodes (subdural strip electrode) or in an array of rows and columns (subdural grid electrodes)
  - **Depth/stereotactic electrodes** – long, small-diameter, somewhat stiff wires with multiple recording contacts along the depth of the wire

Subdural Electrodes



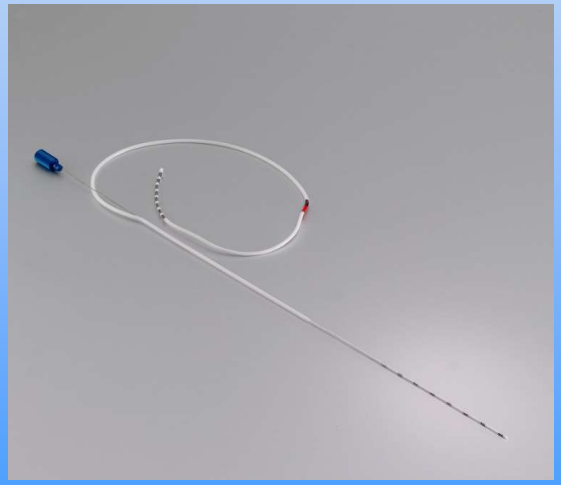


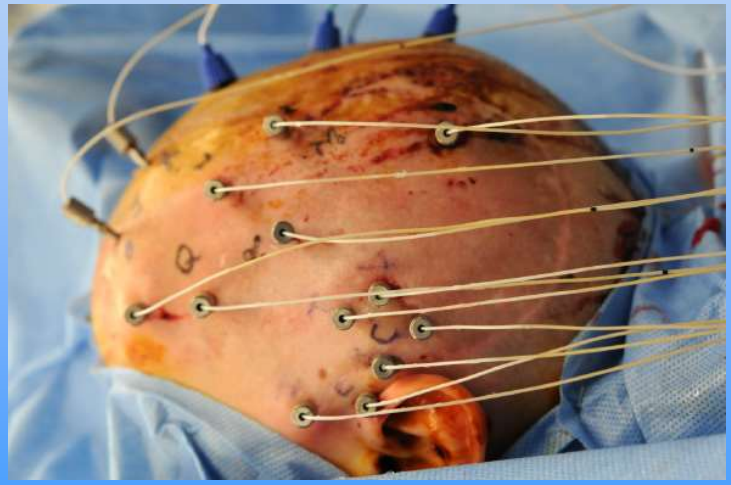


Subdural electrodes

- **Pros:** Can localize language and hand function in addition to recording location of seizure onset
- Does not penetrate the brain
- Plan craniotomy to match future probable seizure focus resection
- **Cons:** Craniotomy required - significant patient discomfort and postoperative dural scarring.
- Recording just from the surface of the brain, albeit both lateral and mesial surfaces
- Difficult to record from both sides of the brain during one surgical admission, as would require bilateral craniotomies.
- Usually have to do resection at the time of removing subdural electrodes

Stereotactic Electrodes





Depth electrodes – Stereotactic EEG (SEEG)

Pros:

- Small skull perforations; no or minimal dural scarring
- Can record from both sides of the brain during one surgical admission if side of ictal (seizure) onset not clear
- Shorter recovery time after recording procedure than for subdurals
- Can spend more time reviewing recording findings before surgical treatment

Cons:

- Since needles penetrate brain, need to place electrodes stereotactically. Best is planning trajectories with a 3D MRI vascular map; and stereotactic instrument like ROSA (Robotic Stereotactic Assistance)
- Difficult to do functional mapping for hand and language critical regions

Robotic targeting for stereoEEG depth electrodes

Surgical Treatment

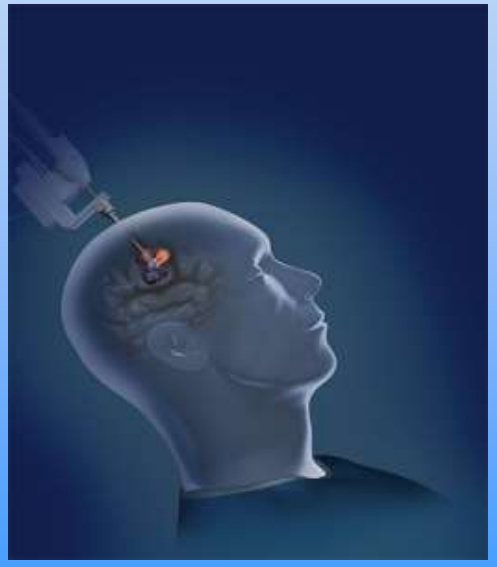
Resection

- Craniotomy size and resection size based on size of ictal onset region and its immediate spread
- Pros: Direct visual and surgical access to resection site
- Cons: Dural scarring: makes any subsequent resection difficult

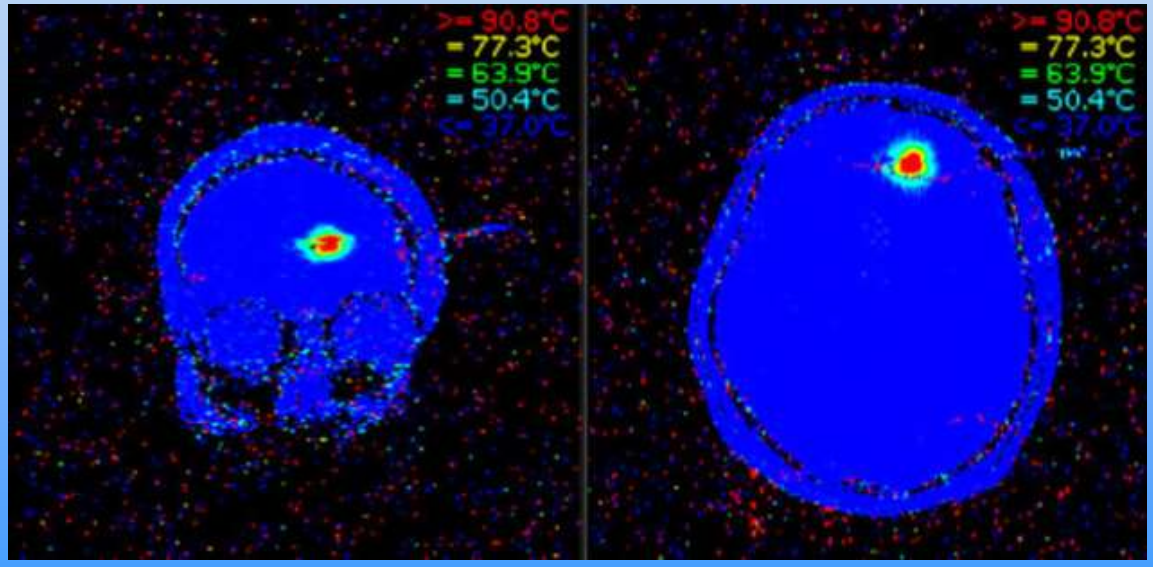
Laser ablation

- Heating of tissue surrounding laser tip
- Best for localized lesions
- Can be best for small deep lesions
- Use same ROSA system as was used to place recording electrodes
- Tissue heat changes monitored with simultaneous MRI

MRI-Guided Laser Ablation Technology for Minimally Invasive Neurosurgery



Visualase Thermal Laser Ablation

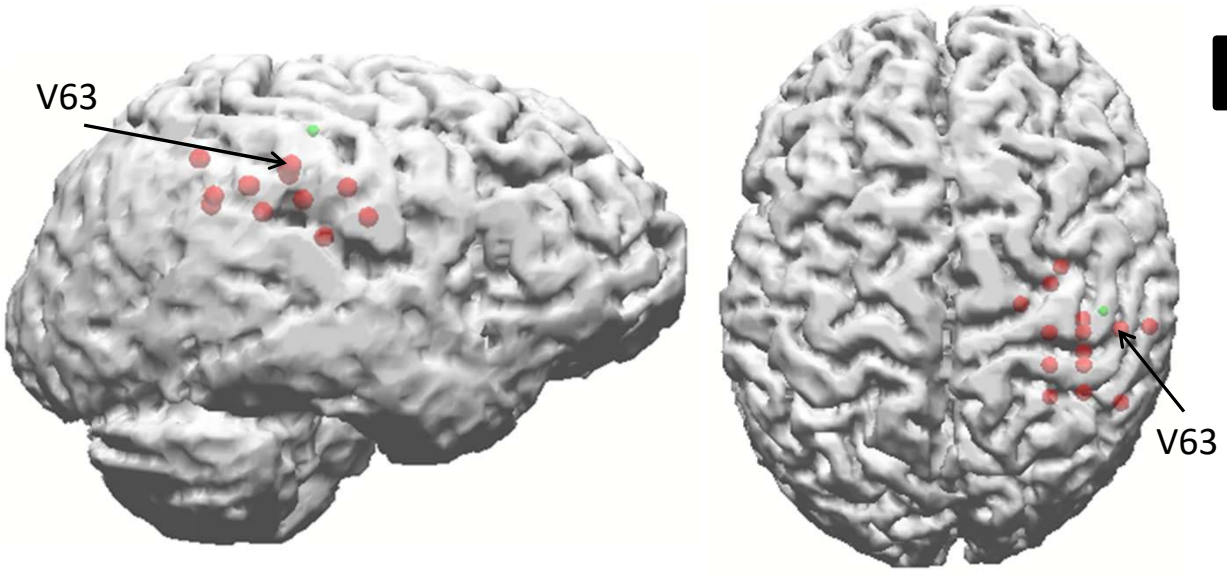


Intraoperative coronal and axial thermograms during MRI-guided laser ablation of the left mesial frontal area.(Cleveland Clinic)

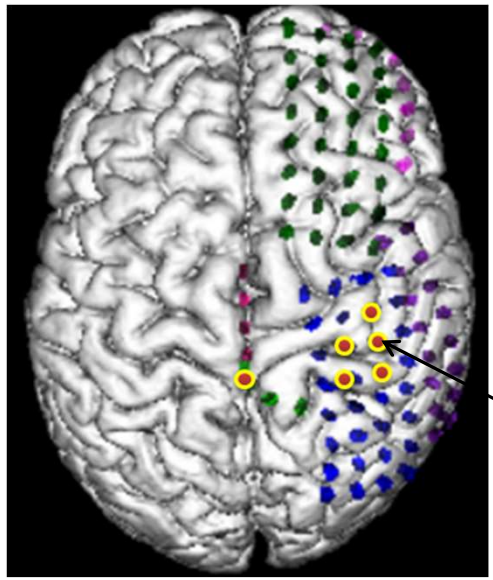
Two Brief Case Studies

MEG

A



B



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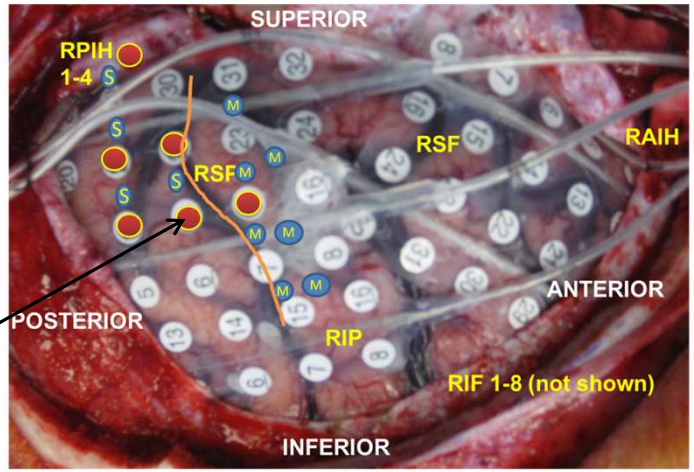
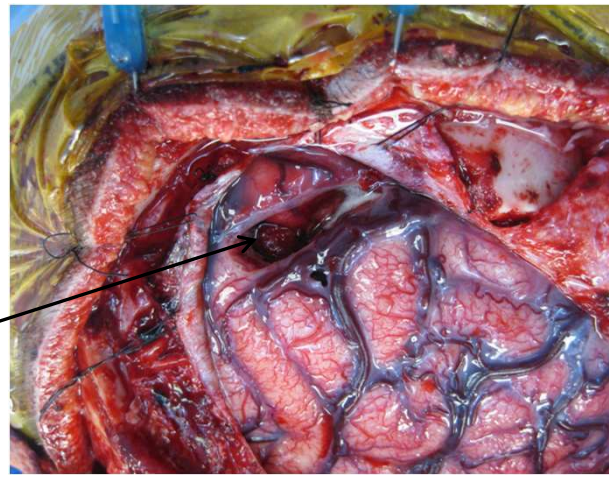


RSF14

D



Resection

dEEG

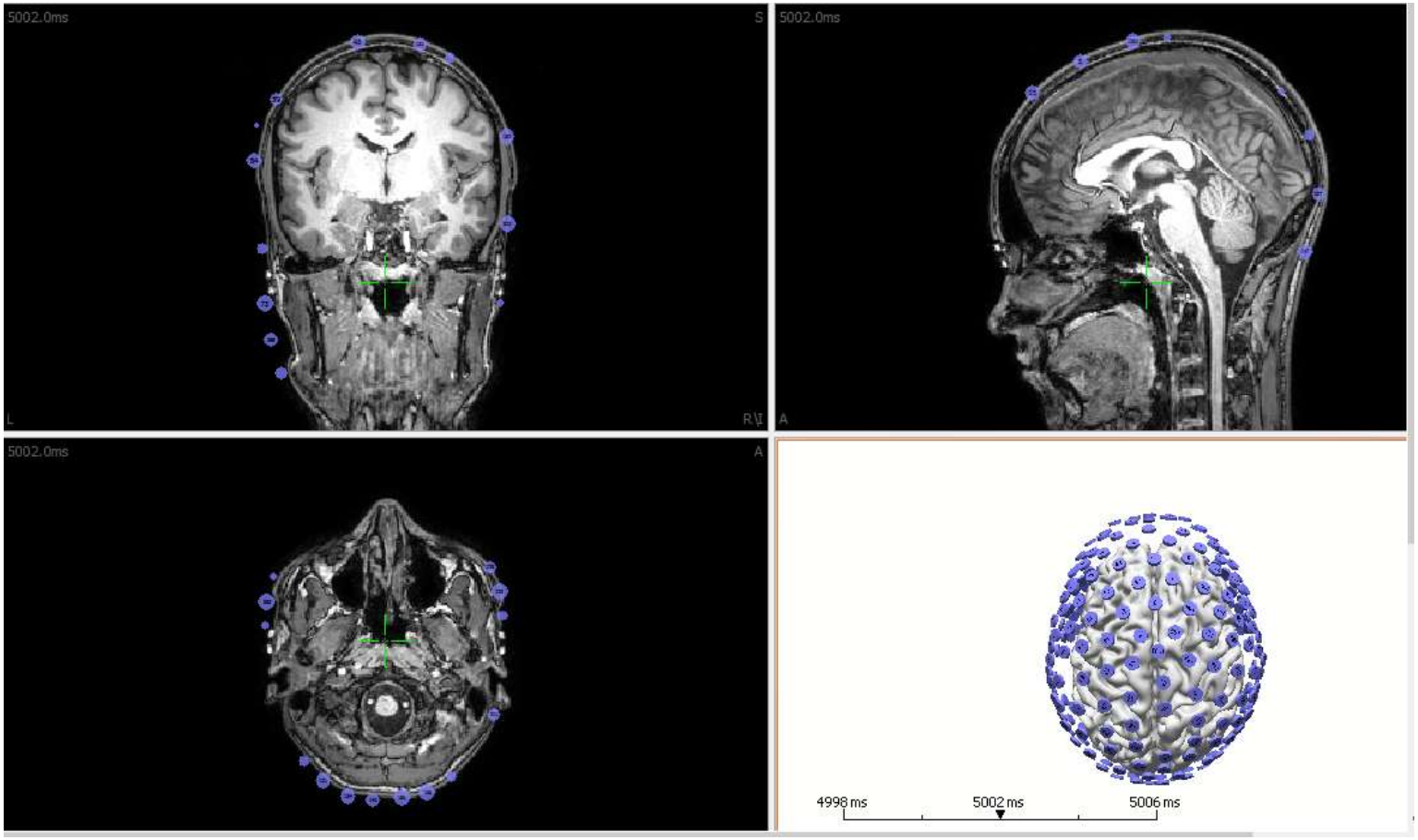


Figure 1: dEEG array fused to MRI scan and relationship to segmented cortical brain

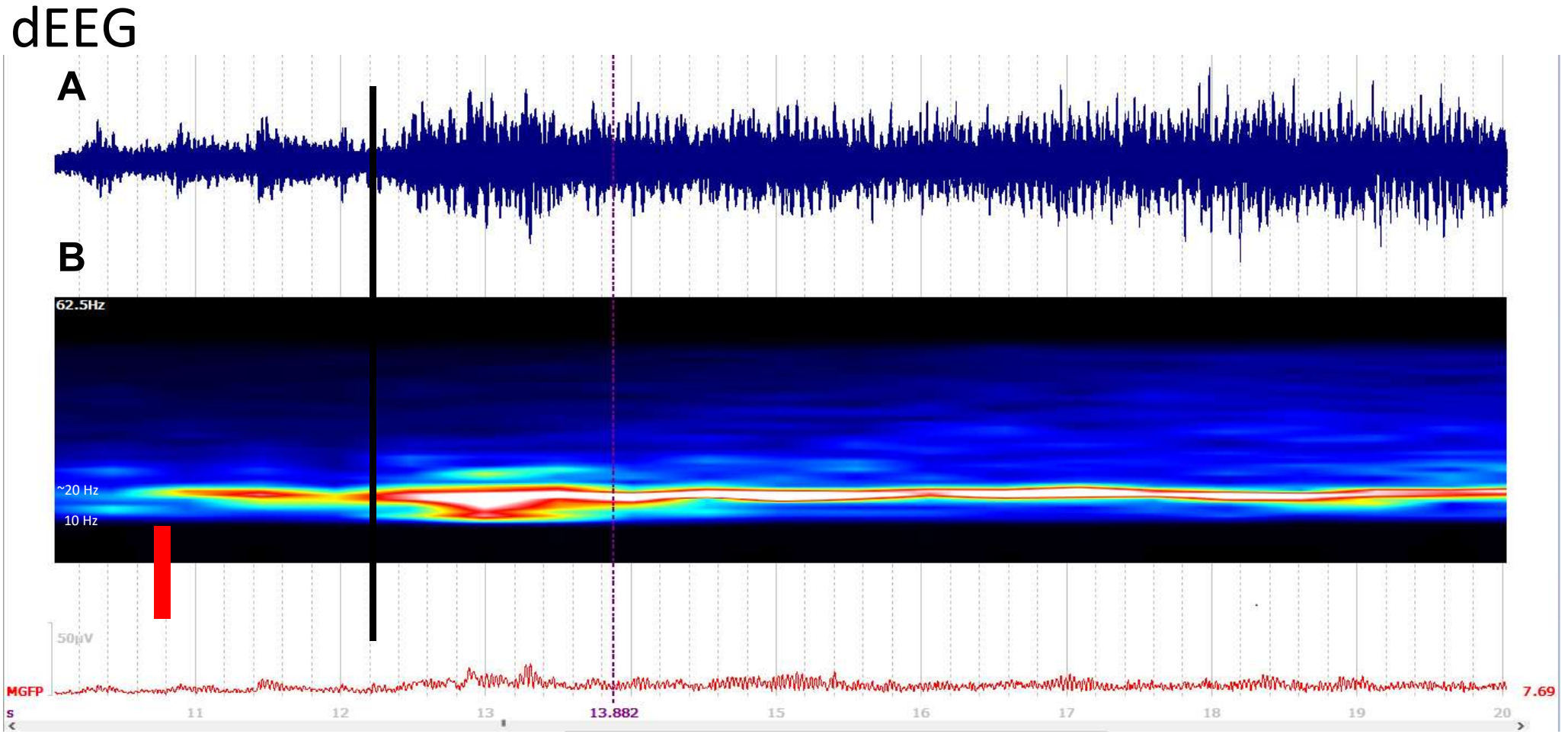


Figure 2: A. Butterfly plot of 256 channel EEG. Vertical black line at approximate clinical onset.10 -70 Hz. B. Short Time Fast Fourier Transform (STFT) of 256 channels, 10-62.5 Hz. Vertical red line at time window for source estimation / localization. C. Mean global field power (MGFP) evolution during ictal onset.

dEEG

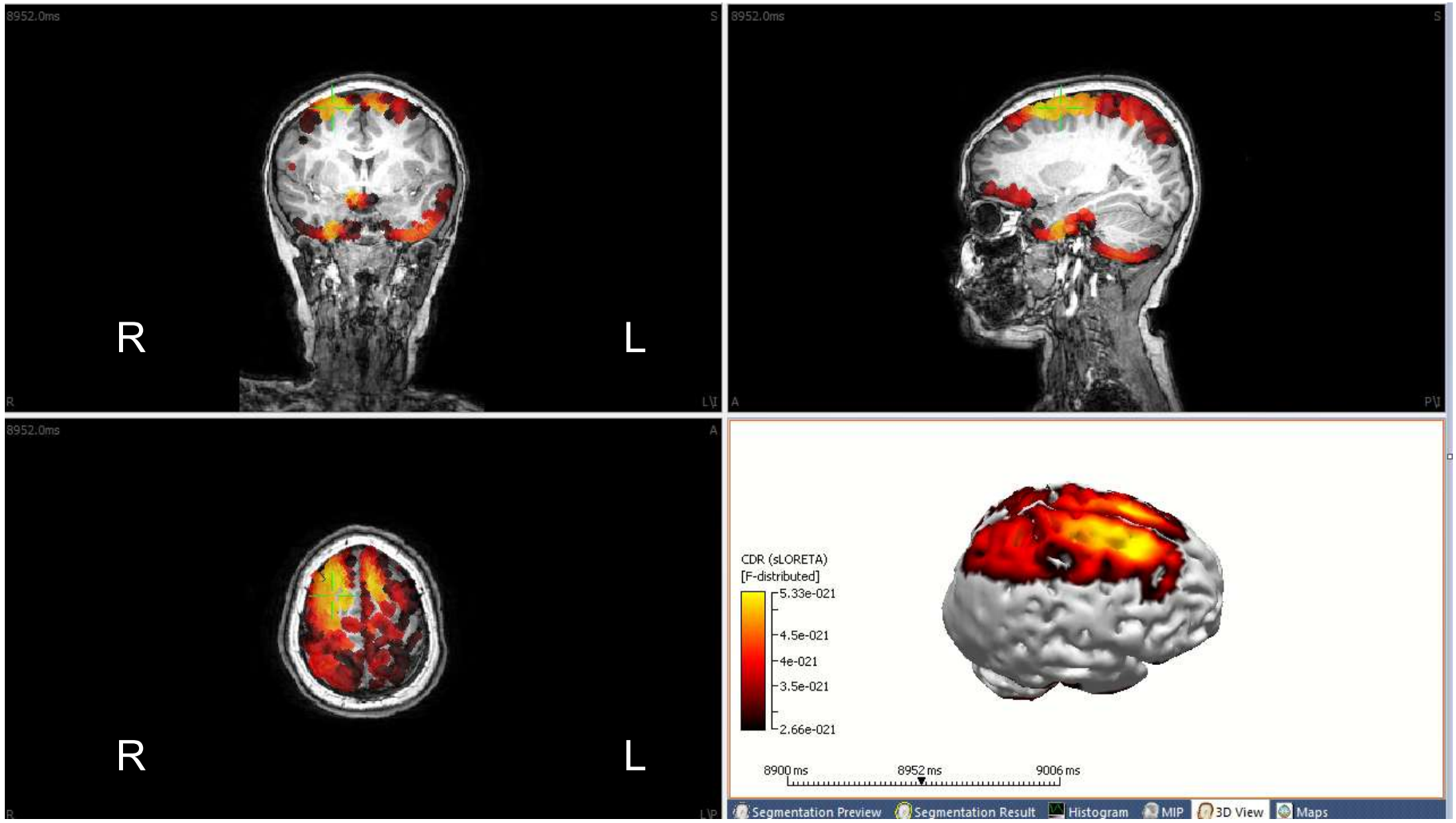


Figure 3: Source localization of ictal onset with sLORETA


Thank you for your attention

Other surgical treatments at CCHMC

- Functional Hemispherectomy
- Corpus Callosotomy
- Vagal Nerve Stimulators

	Age Yrs	Sz	BF Grid	BF LOC	SubD Loc	Resection	OutCome	TBC0
1	7.3	1 EC	5x5x5	R S P	ND	R S P	Sz-free 3 yrs	81/43
2	15.5	2 EC	5x5x5	R S P	RSP	R S P	Sz-free 2 yrs	6
3	10.5	1 EC	5x5x5	L Fp	ND	Awaiting Surgery	-	0.2
4	34	1 EC	5x8x5	L I T	ND	Awaiting SISCOM	-	5
5	44	1 EC	$3x4x5x2^3$	R M T	ND	Awaiting responsive stimulation	-	17

EC=electroclinical, Fp=frontopolar, I=inferior, L=left, M=mesial, ND = Not Done, P=parietal, R=right, S=superior, TBCO= time before clinical onset in seconds

	Age yrs	dEEG array	Szs	10-20 Head Region Location	dEEG Source Location	iEEG Source Location	SurgicalSite	Outcome
1	17	256	4	NonLoc; L Hmsph	L sup F	L sup F	L sup F	sz free 15 m, then SPS
2	6	128	2	R P	no electrode file	no iEEG	R P lesionectomy	sz free at 6 month
3	7	256	1	R T sharp waves	R inf TO jnct	no iEEG	R T lesionectomy	sz free at 18 month
4	12	256	3	NonLoc, L Hmsph; L T; multifocal	NonLoc	Done at other institution	L Tp	sz continue
5	12	256	1	R O	R O	no iEEG	R O lesionectomy	sz free-2 years, off meds 1 year
6	7	256	2	R F	R F	R F	R F	no sz at 3 month
7	17	256	2	R F	R F	ND-Y	ND-Y	sz stopped after med change
8	7	256	8	L F; L T	L post F	ND-Y	ND-Y	sz stopped after med change
9	5	128	3	D; Midfrontal; R F	R T, L FT	R sup & inf F	R F lobectomy	sz continue; VNS placed
10	4	128	0	L F; R F	-	no iEEG	hemispherectomy	sz continue
11	7	256	4	R T	R sup post F, sup ant P	R midparietal	R P lesionectomy	sz continue
12	13	256	1	R T, L F	R P + F + T; L Fp	R F+T+P,	R F, R T	no sz at 1 year
13	15	256	3	R central	R parietal	R parietal	R parietal	no sz at 6 month
14	6	128	1	NonLoc	R parietal	R&L Hmsph	CC	sz -free 3 years, off meds

Table: Ant=anterior, CC=corpus callosotomy, D=diffuse, Hmsph=hemisphere, F=frontal, Fp=frontal pole, FT=frontotemporal, inf=inferior, jnct=junction, L=left, NonLoc= nonlocalizing, R=right, P=parietal, post=posterior, sup=superior, sz=seizure, SPS=simple partial seizure, T=temporal, TO= temporo-occipital, Tp=temporal pole