What the Referring Physician Needs to Know About Magnetoencephalography (MEG)

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An American Clinical MEG Society Educational Webinar

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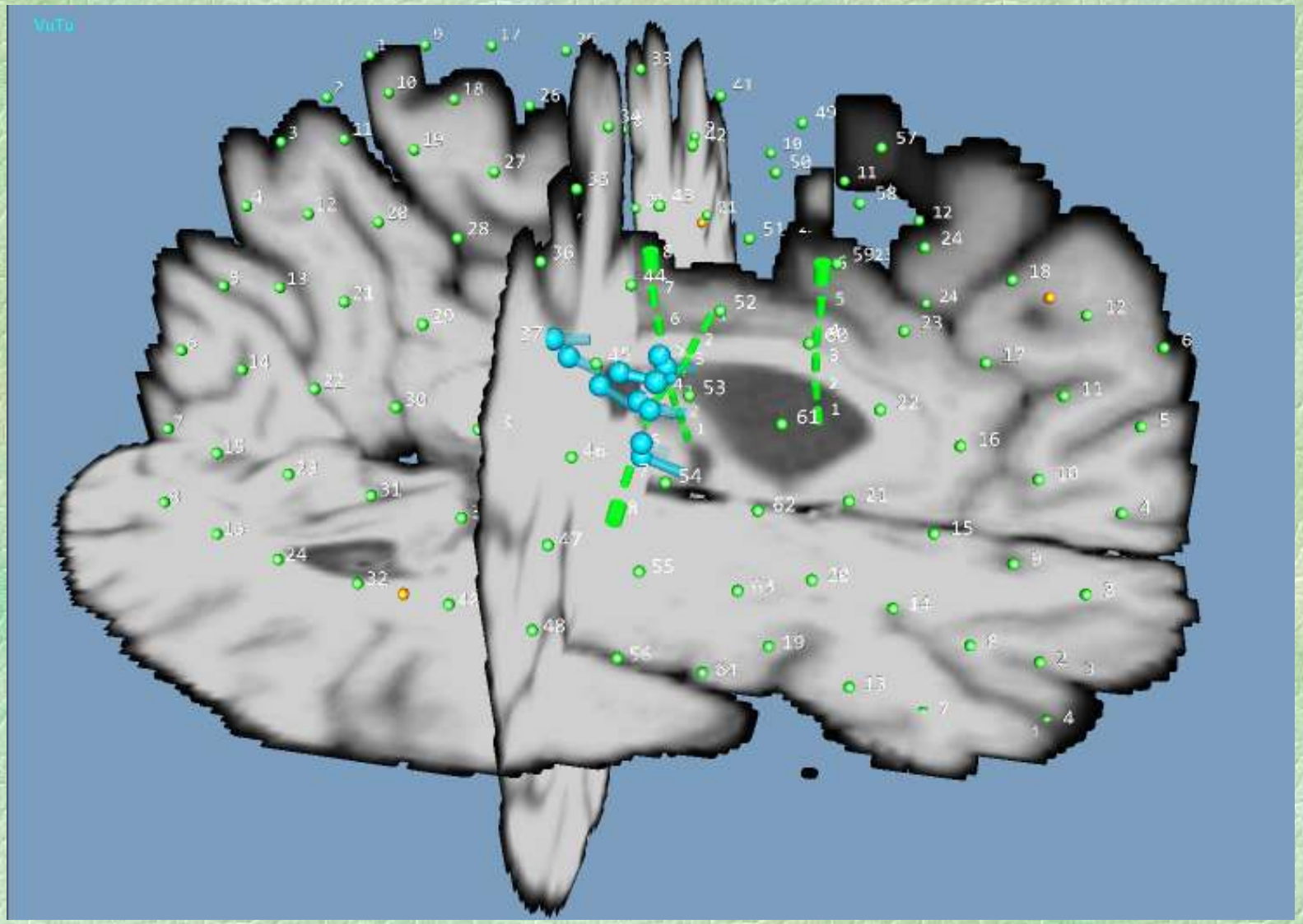
What is MEG?



Green dots = Subdural electrode positions.

Green cylinders = Depth electrode positions.

Blue lollipops = MEG dipoles, where sphere is locaton and stem is orientation.

Coregistration of MEG dipole sources and invasive electrodes

What is MEG?

Neurophysiological Principles

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

Easy acquisition of very high density (100-300channels), 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.

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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.

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What do we know about MEG?

MEG provides additional localizing information.

- (Wheless et al, 1999; Stefan et al, 2003; Pataraia 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)

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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

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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?

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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.

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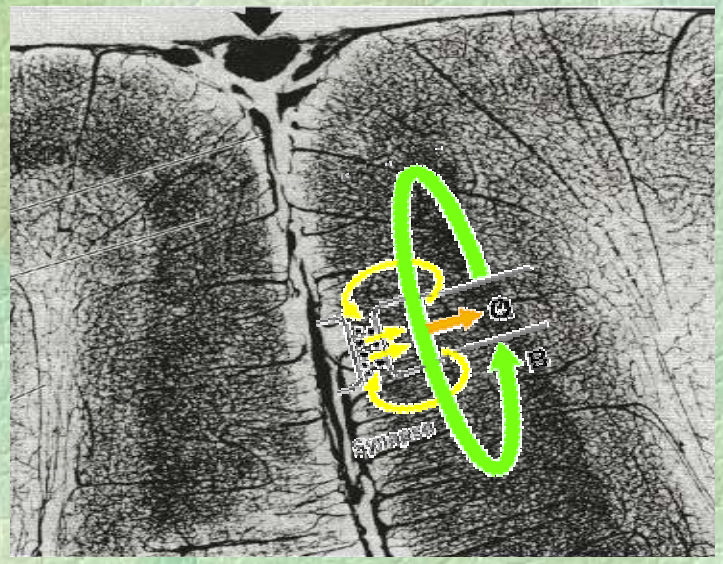
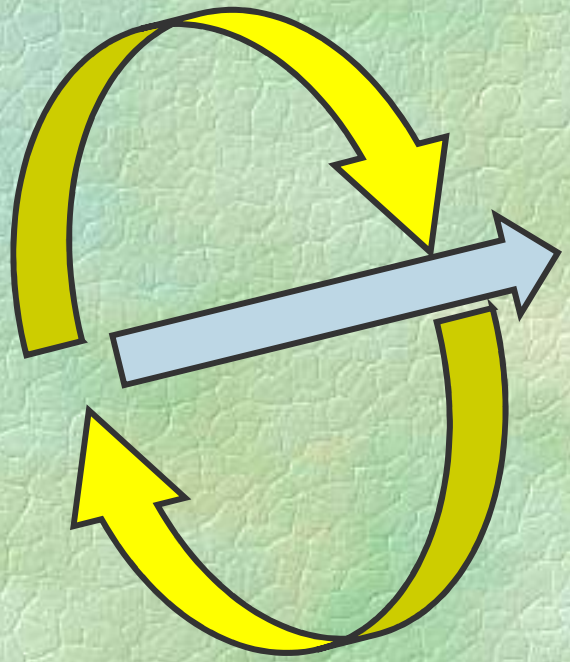
What is the MEG signal?

Genesis of EEG and MEG Signals:

A current dipole creates a magnetic field





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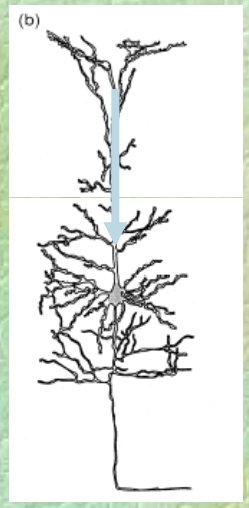
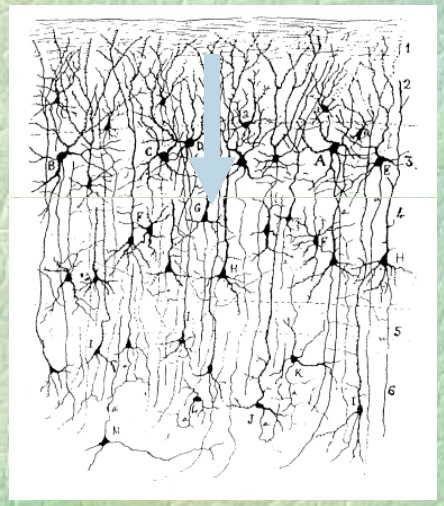
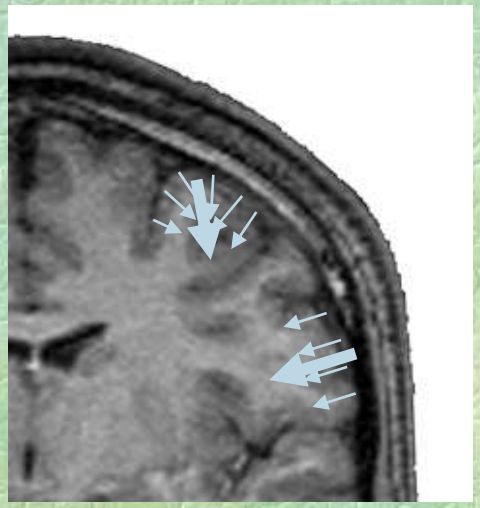
Dipolar representation of brain currents

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.

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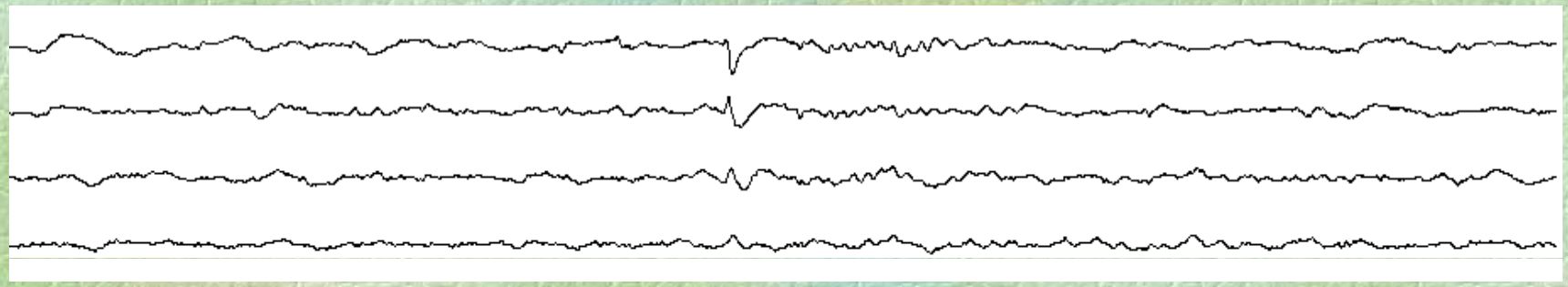
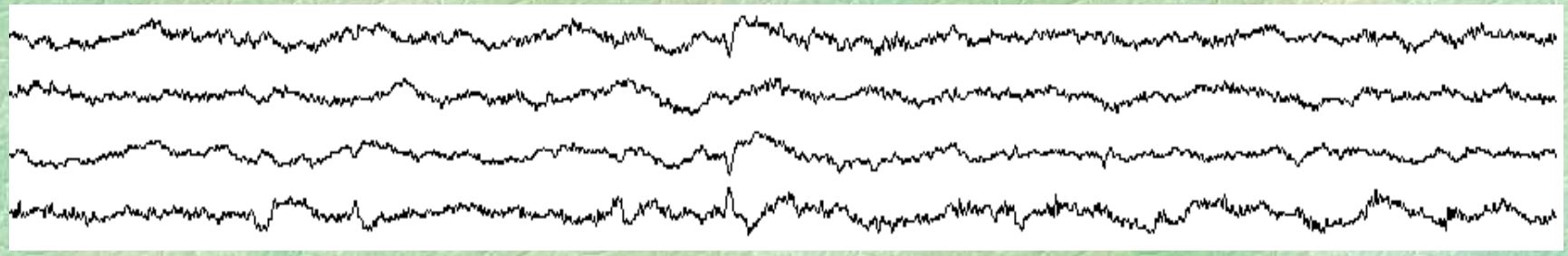
EEG and MEG Waveforms

EEG



MEG



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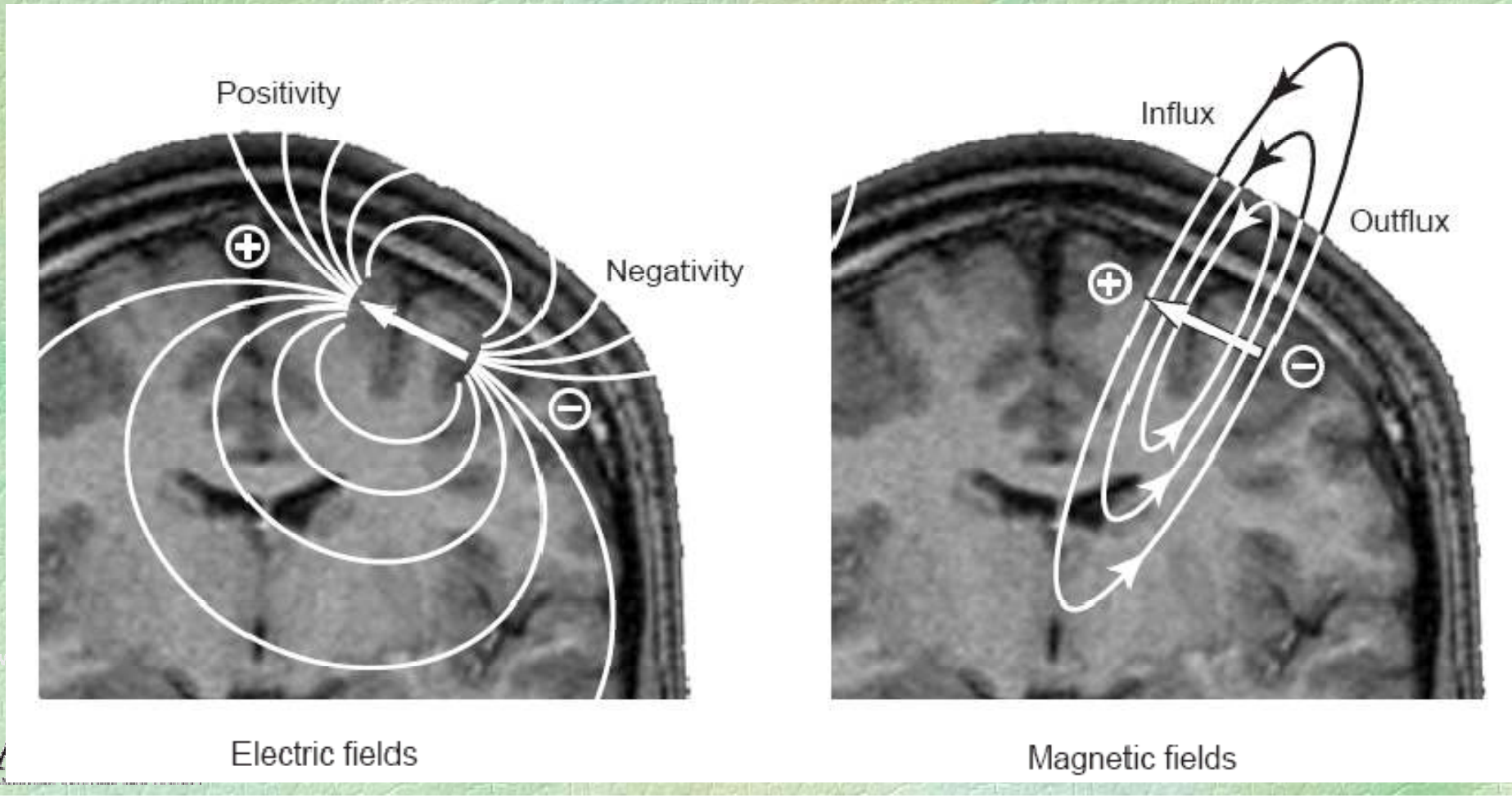
Electric fields and magnetic fields generated by a current dipole



How is MEG recorded?

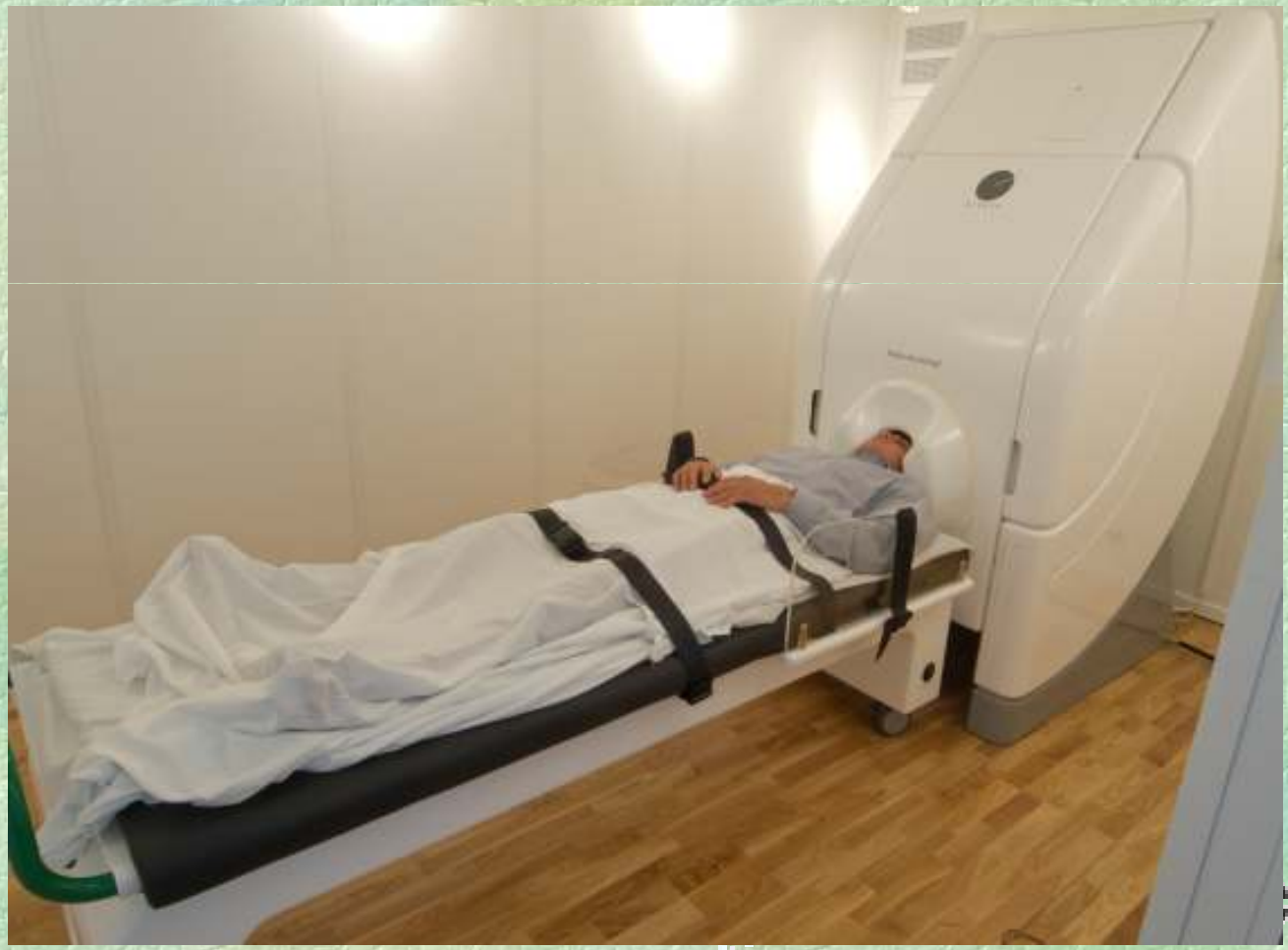
MEG Instrumentation

SQUID

Flux transformers

Shielded room

Head position indicator



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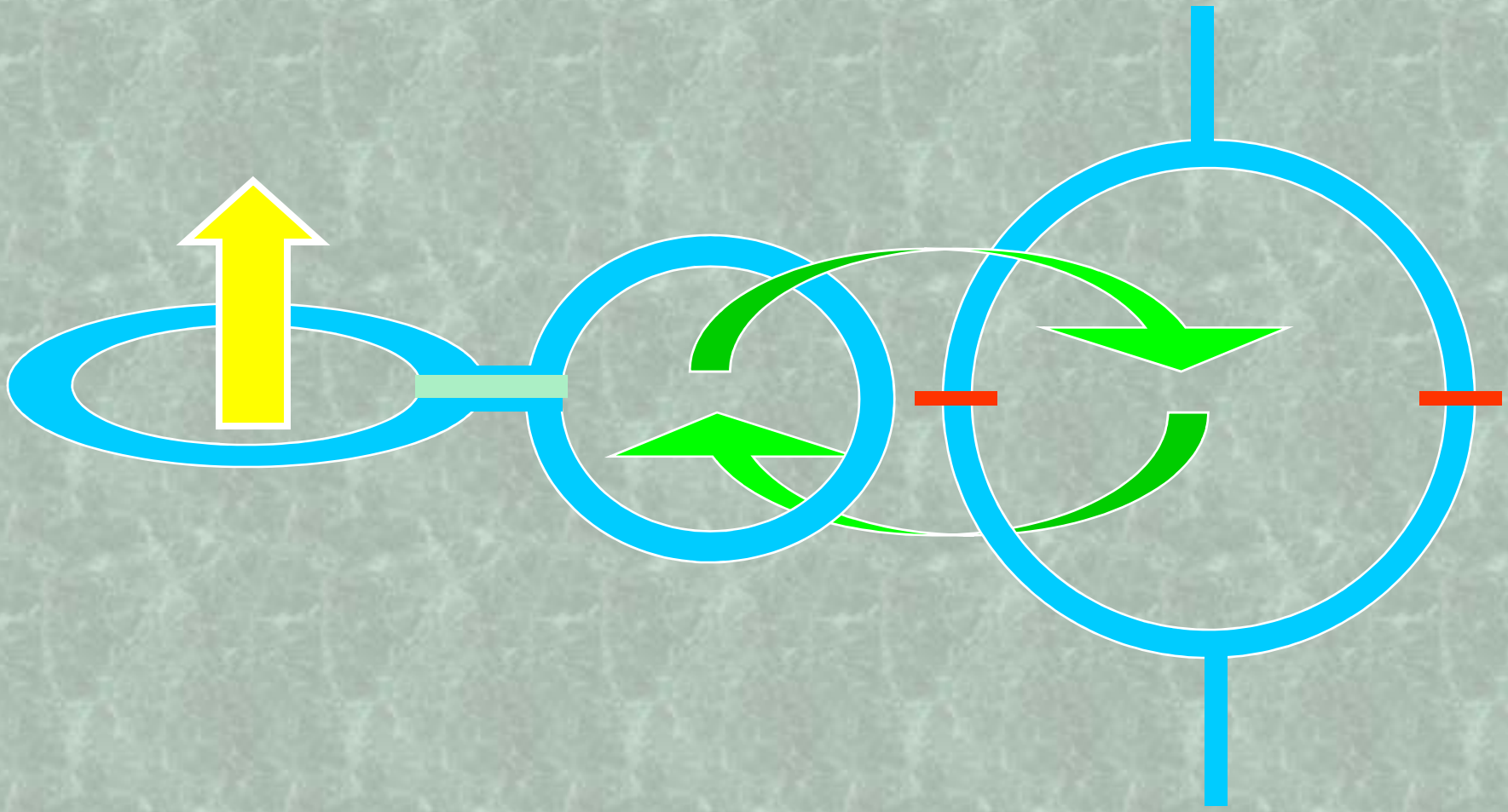
SQUID and Flux Transformer



How is MEG recorded?

MEG Procedures

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

- HPI measurement
- Fiducial measurement
- “Cloud” of scalp points

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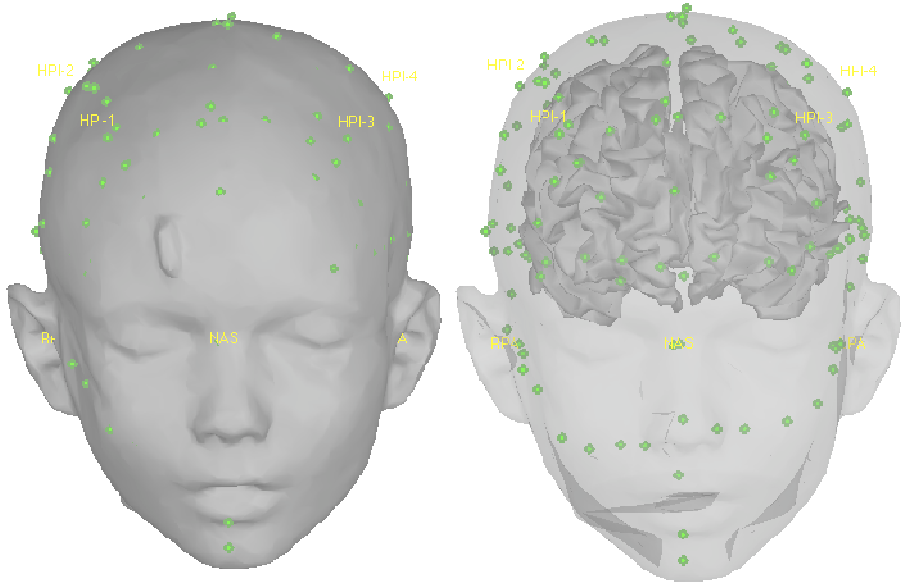
Careful Attention to Postion of Fiducials, Landmarks, HPI Coils

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, Naison)
- •Digitize 80-120 additional scalp points for coregistration with MRI



MEG Procedures

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

Simultaneous EEG and video monitoring with MEG

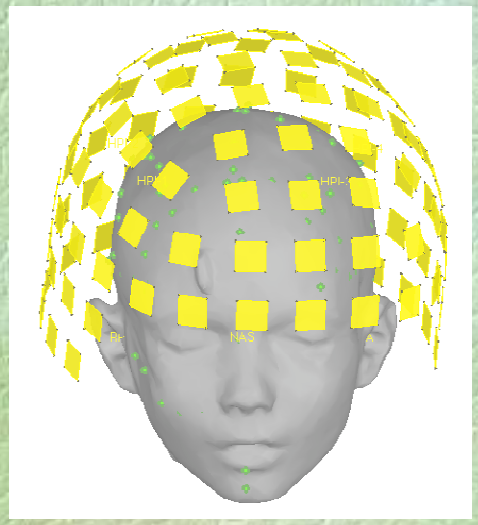
On-line marker entry

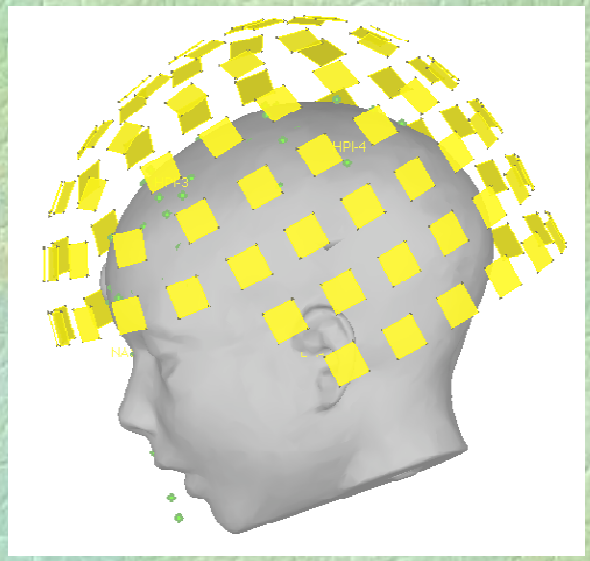
Feedback noise compensation

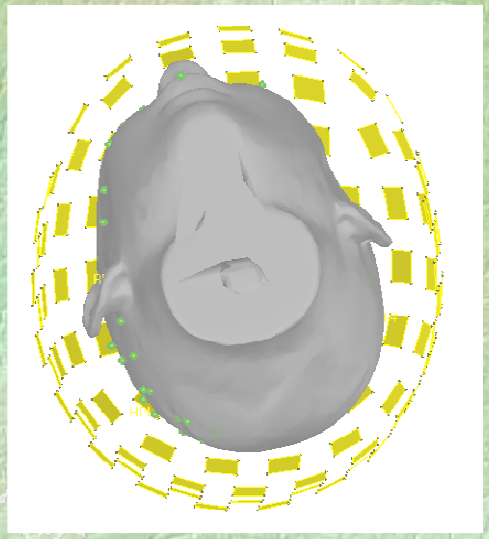
Continuous head-position monitoring

Alignment of Subject in MEG Array

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







Location of HPI coils monitored continuously.

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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.
3. Reference – free.
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.

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High temporal and spatial resolution

Patient with parietal lobe seizures

Scalp video-EEG localization unclear

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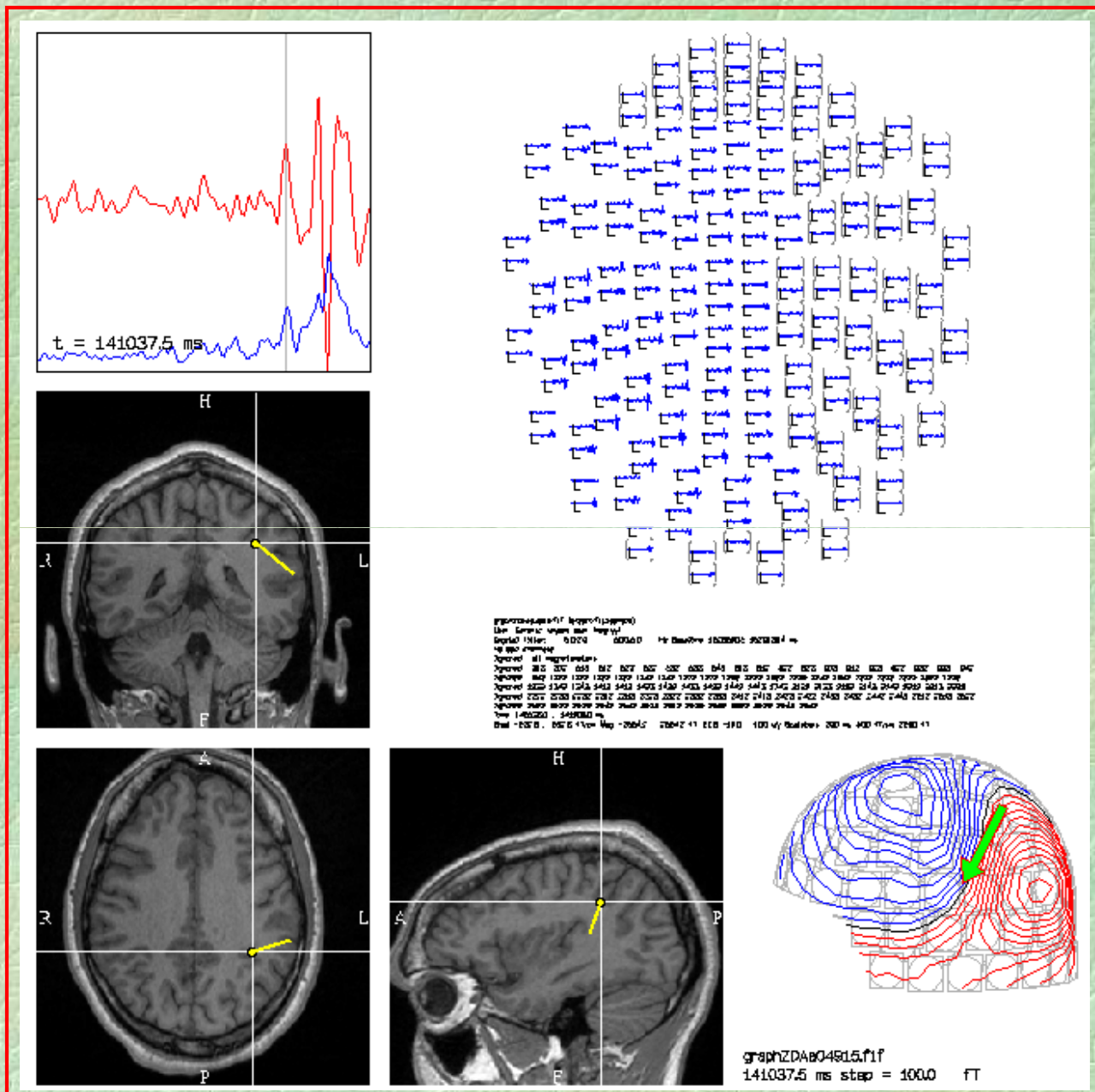
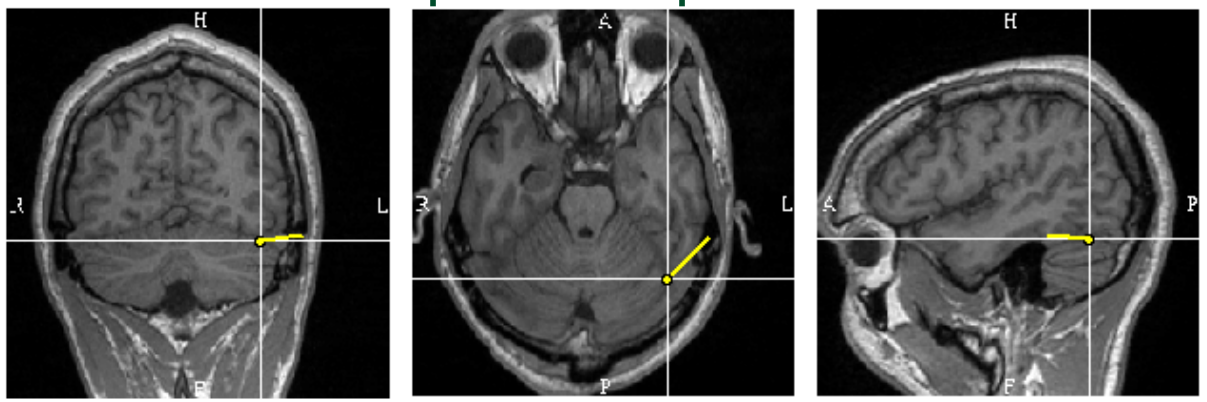
Polyspikes Originating from Left parietal



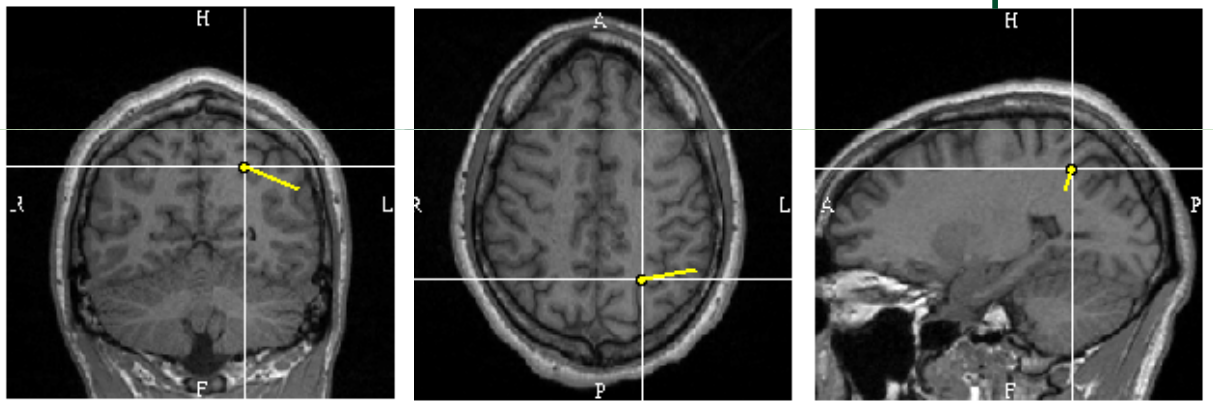
Propagation of Polyspike Activity to Left Parietal

Left basal temporo-occpital



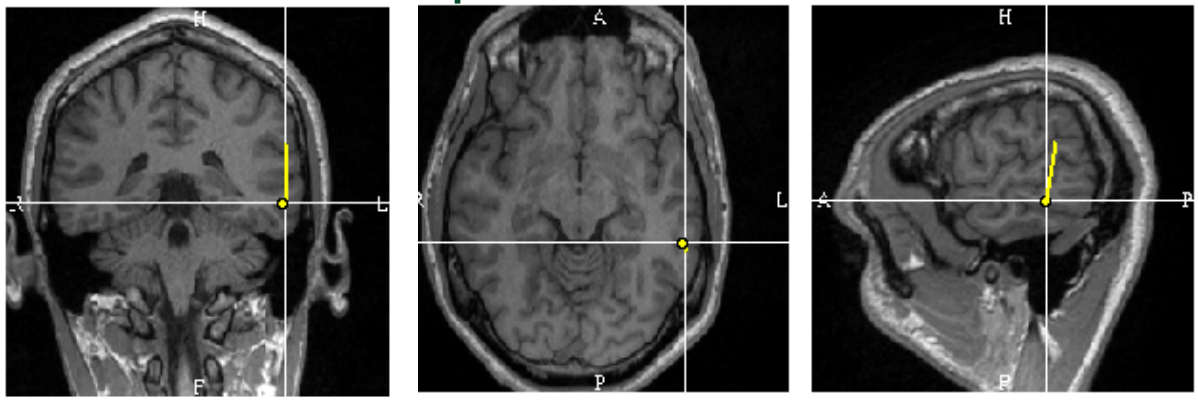
37 msec

Left inferior parietal



161 msec

Left middle temporal



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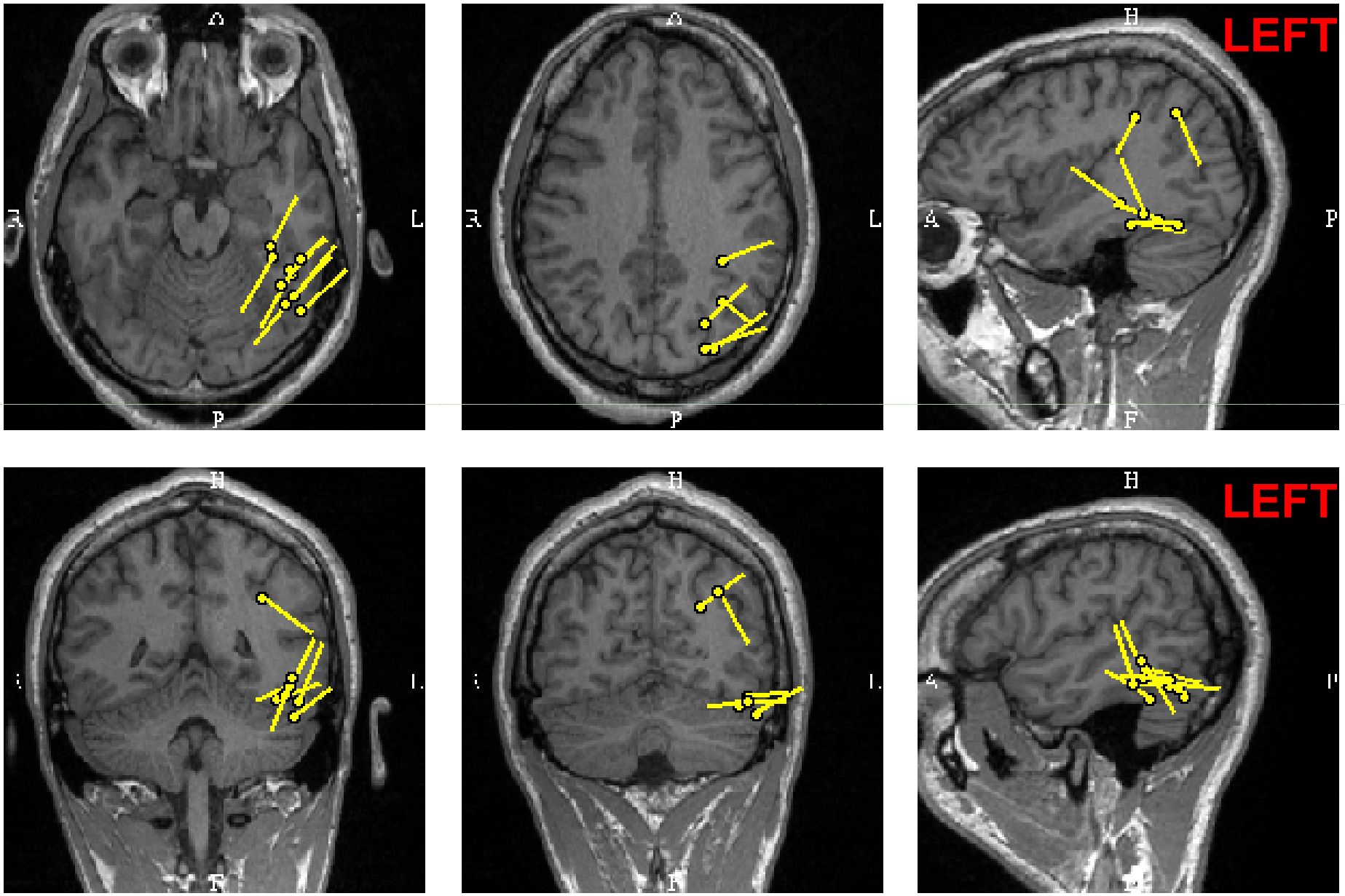
Representative interictal dipoles



High temporal and spatial resolution

Patient with non-localizable, non-lateralizable scalp video-EEG

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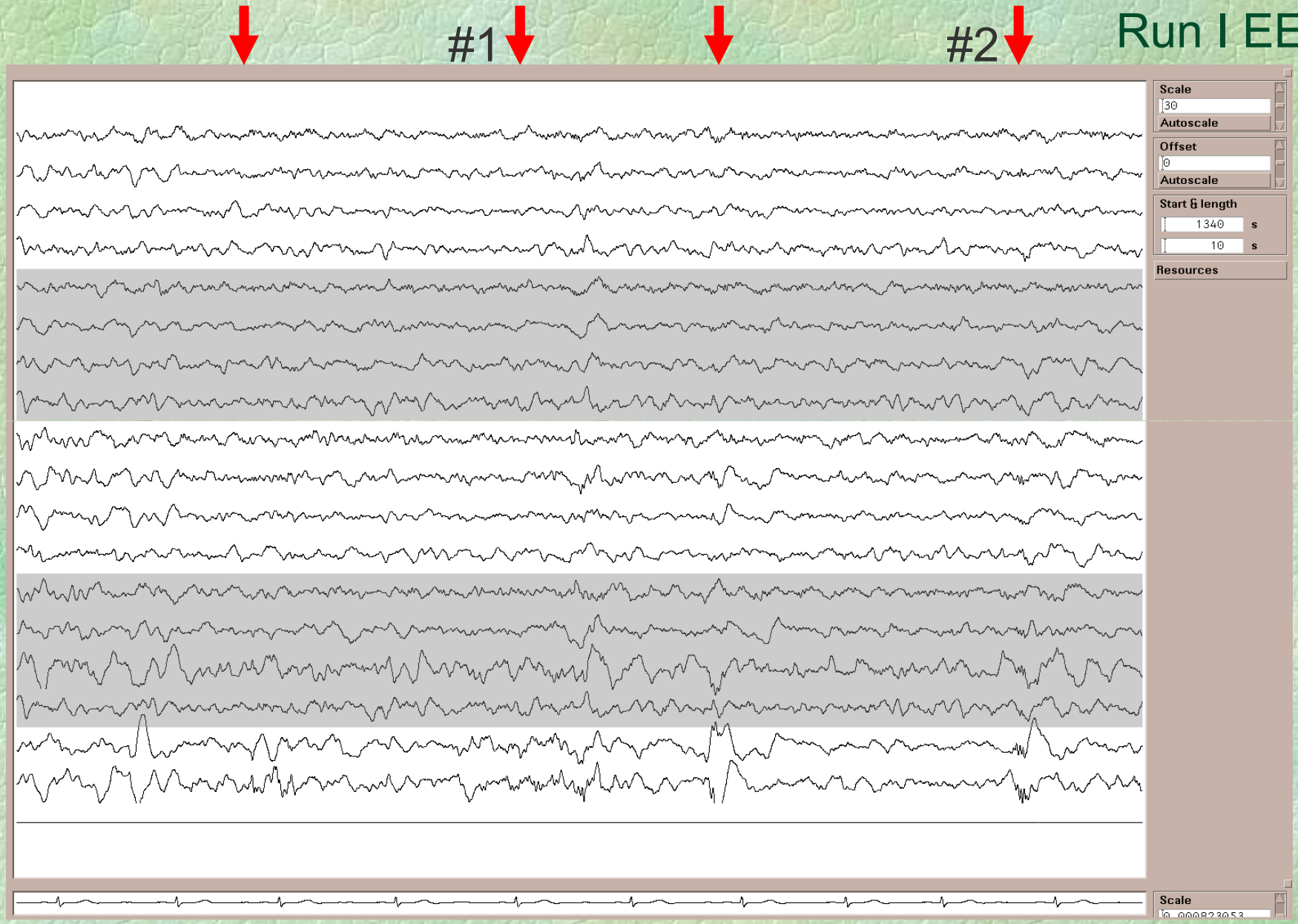
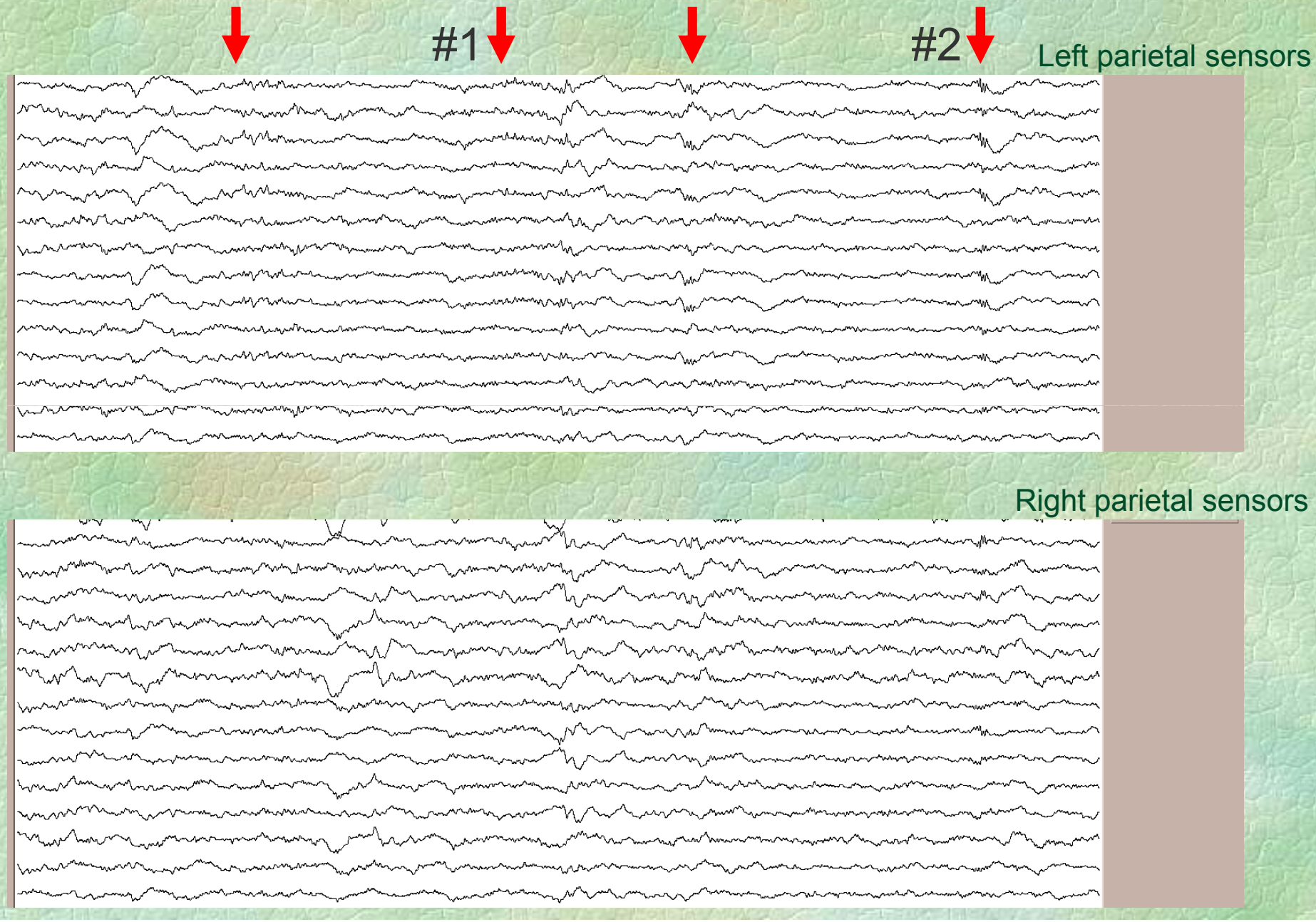
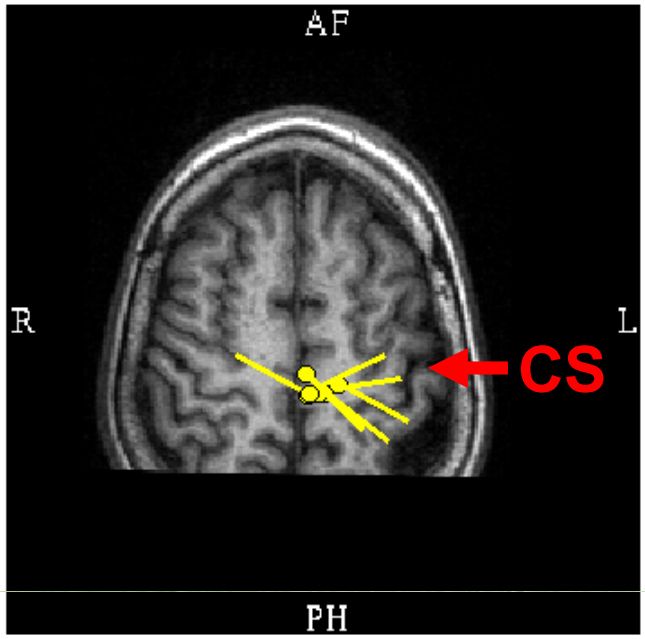
EEG: Polyspikes, Vertex

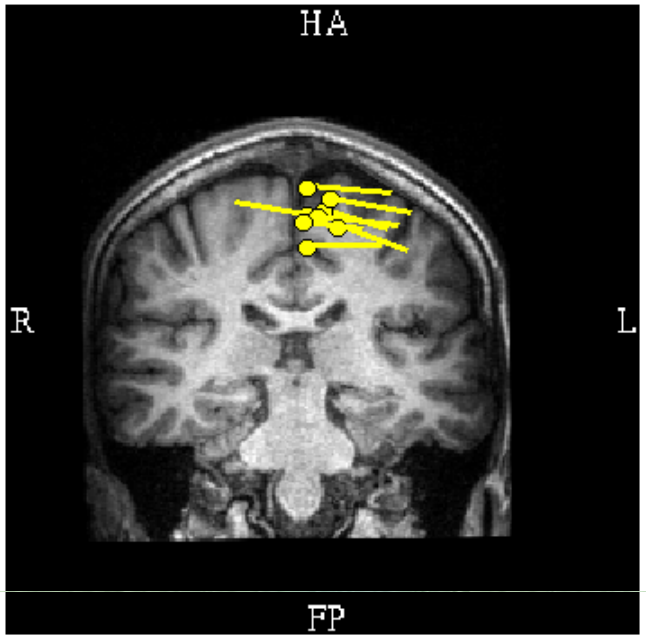


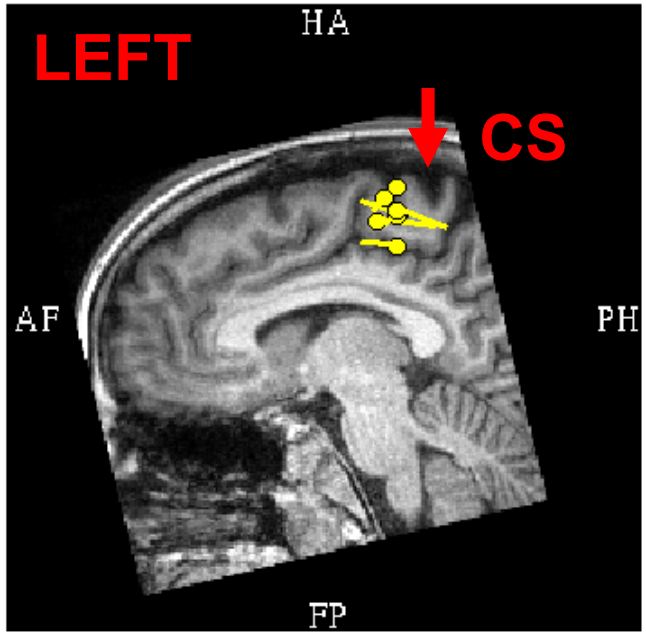
MEG: Polyspikes, Left > Right parietal sensors



All interictal dipoles: Left frontal







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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 cm^2 vs 6 cm^2 of synchronized discharging cortex.

(Oishi M, Otsubo H et al. Epileptic spikes: Magnetoencephalography vs simultaneous electrocorticography. Epilepsia 43: 1290-1295; 2002.)
(Agirre-Arrizubieta Z et al. Brain 132, 3060-07; 2009)

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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

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Differences and Similarities: EEG and MEG

Similarities

- Record the same phenomenon
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- 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

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Primary Clinical Applications

Sensory Mapping

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

Epileptic Spike Localization

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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

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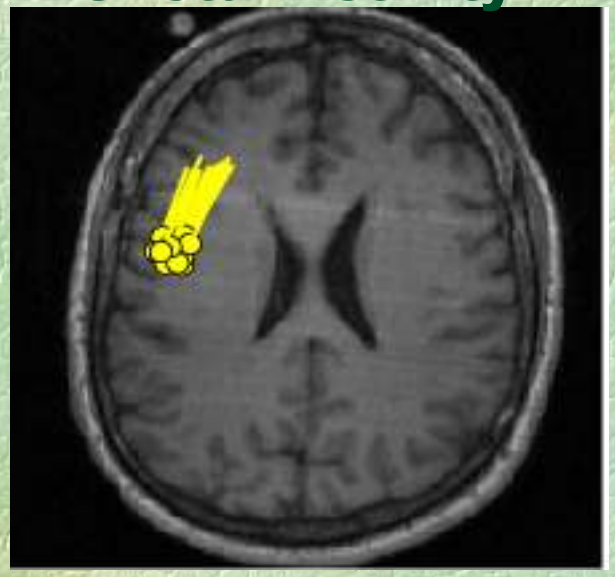
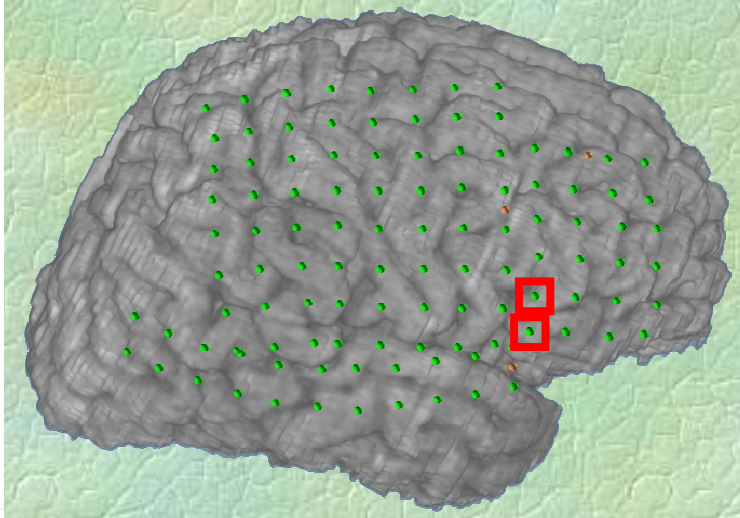
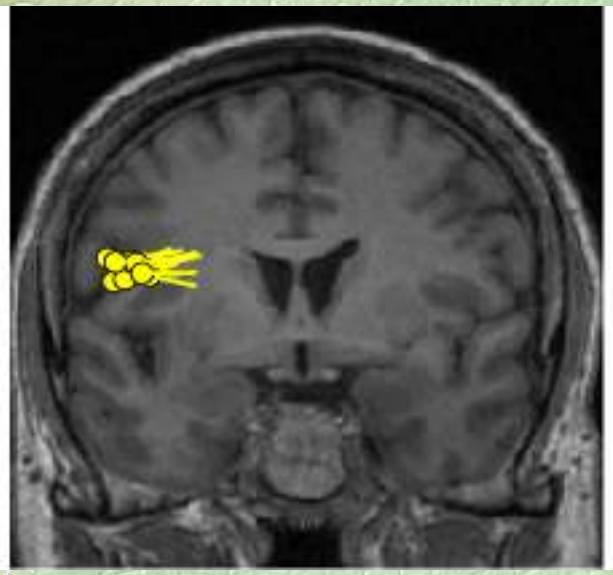
Correlation of MEG Localization of Interictal Discharges to ICEEEG Ictal Activity

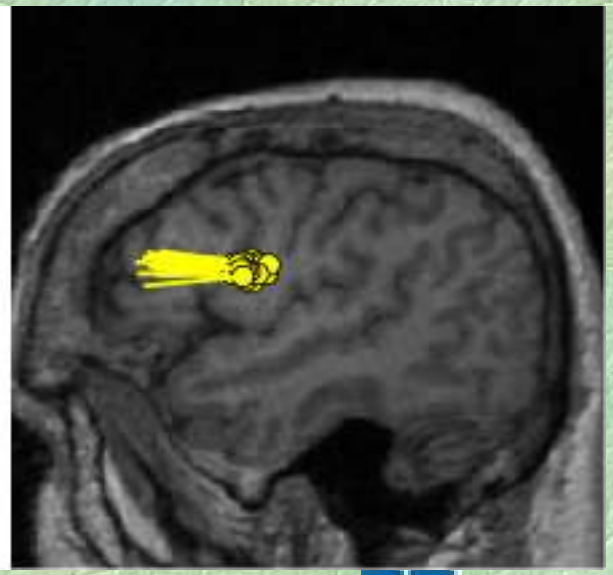




ICEEG: Seizure Onset

MEG: Interictal Dipoles





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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.

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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.

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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 Threee 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

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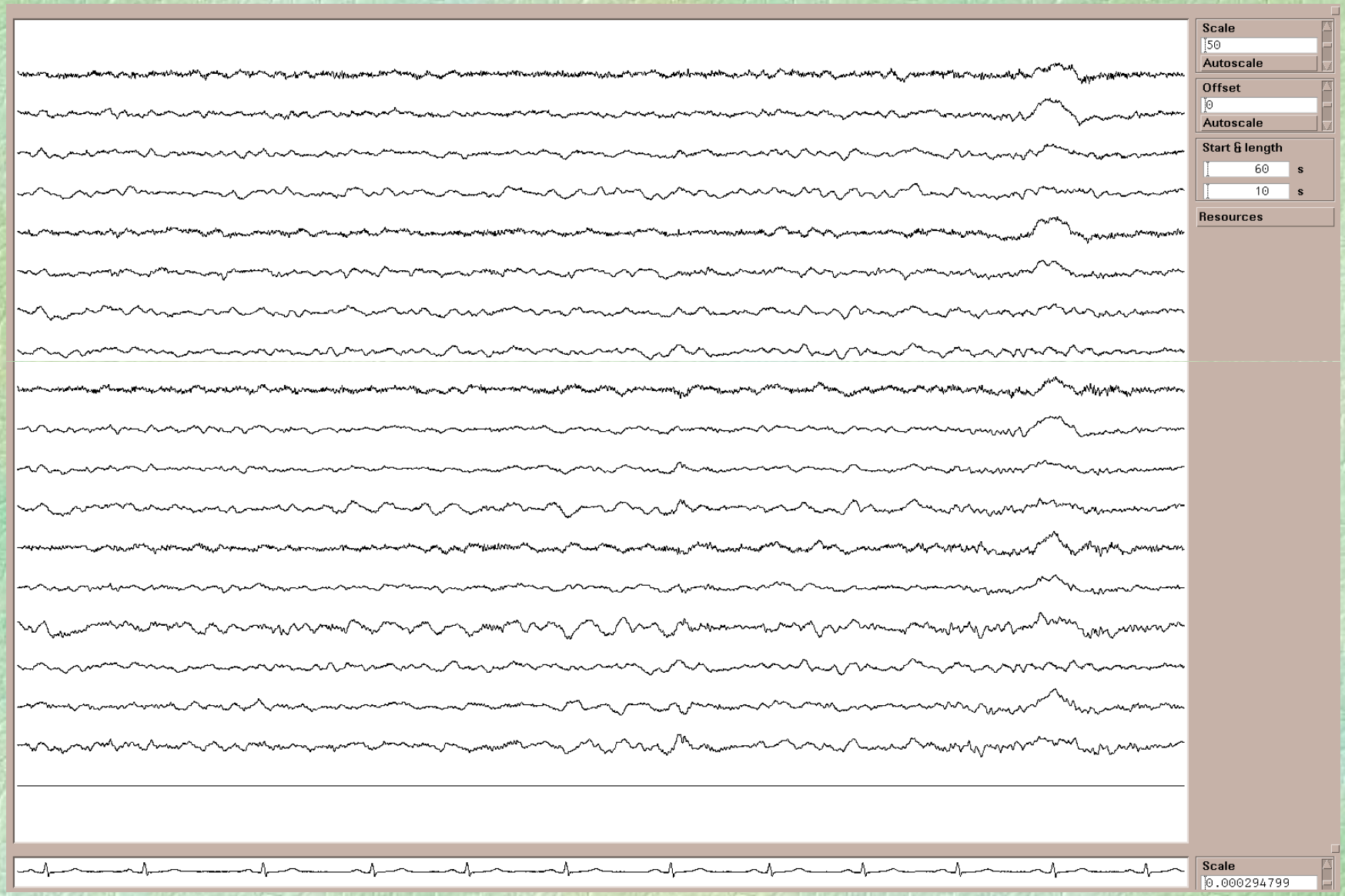
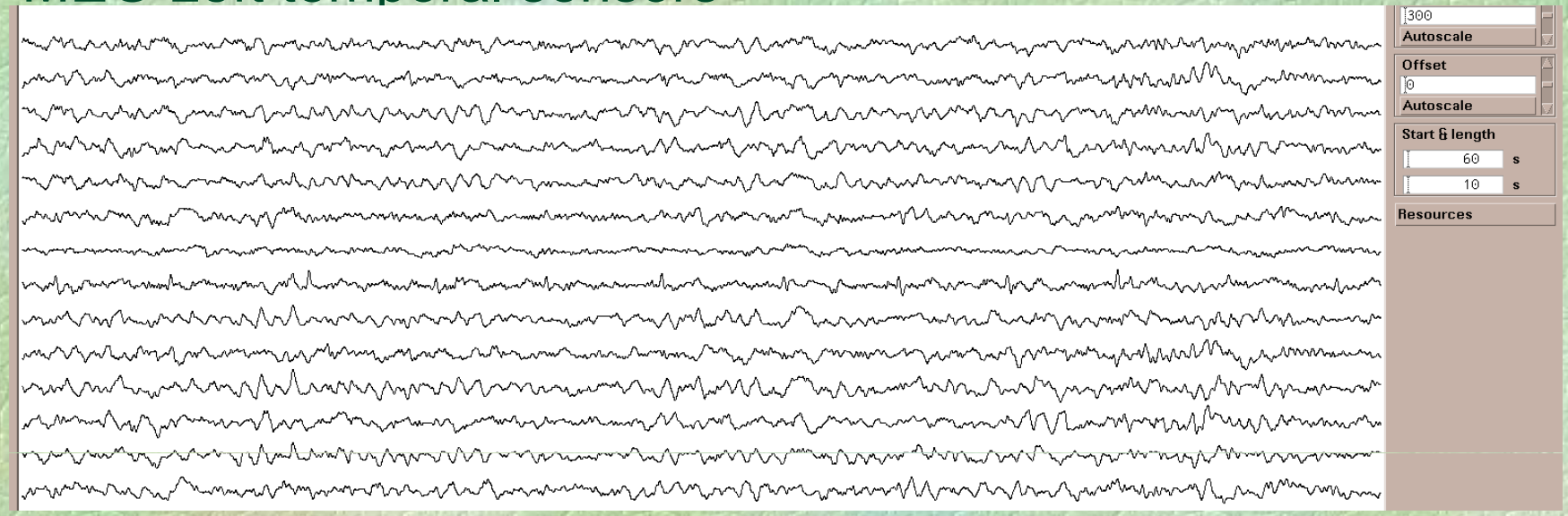
Spike, regional right temporal (Unique to MEG, not seen on EEG)

Run I: Double banana bipolar EEG

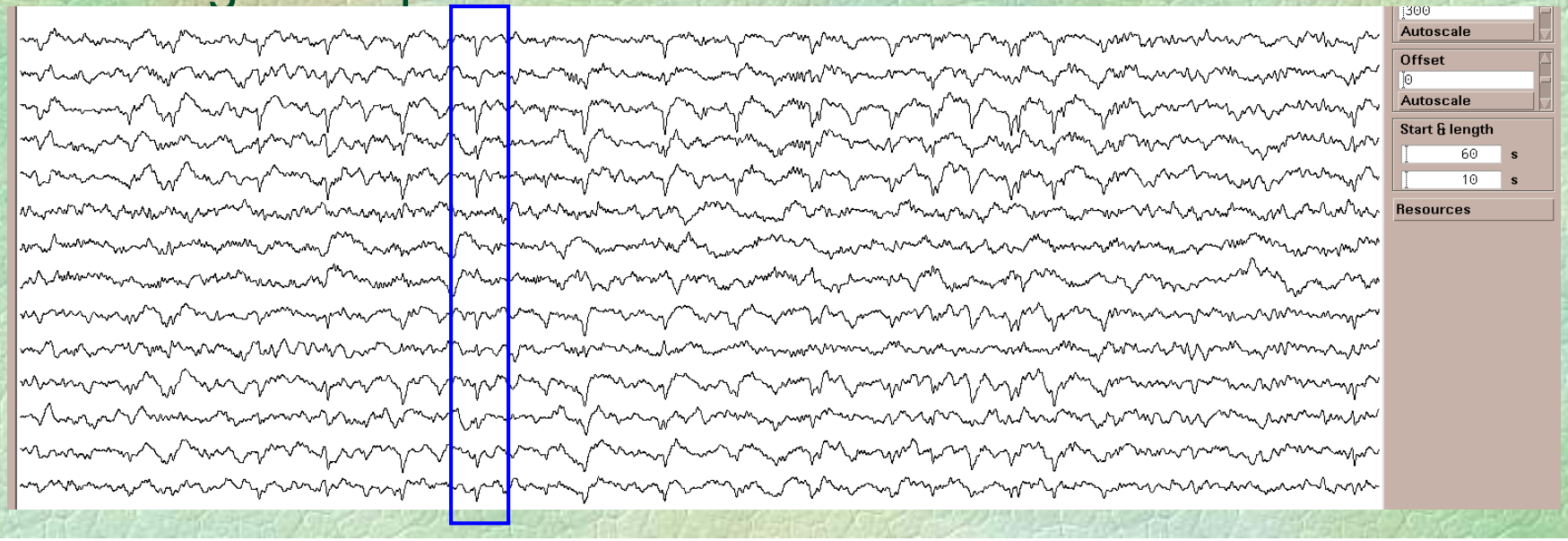


Spike, regional right temporal on MEG

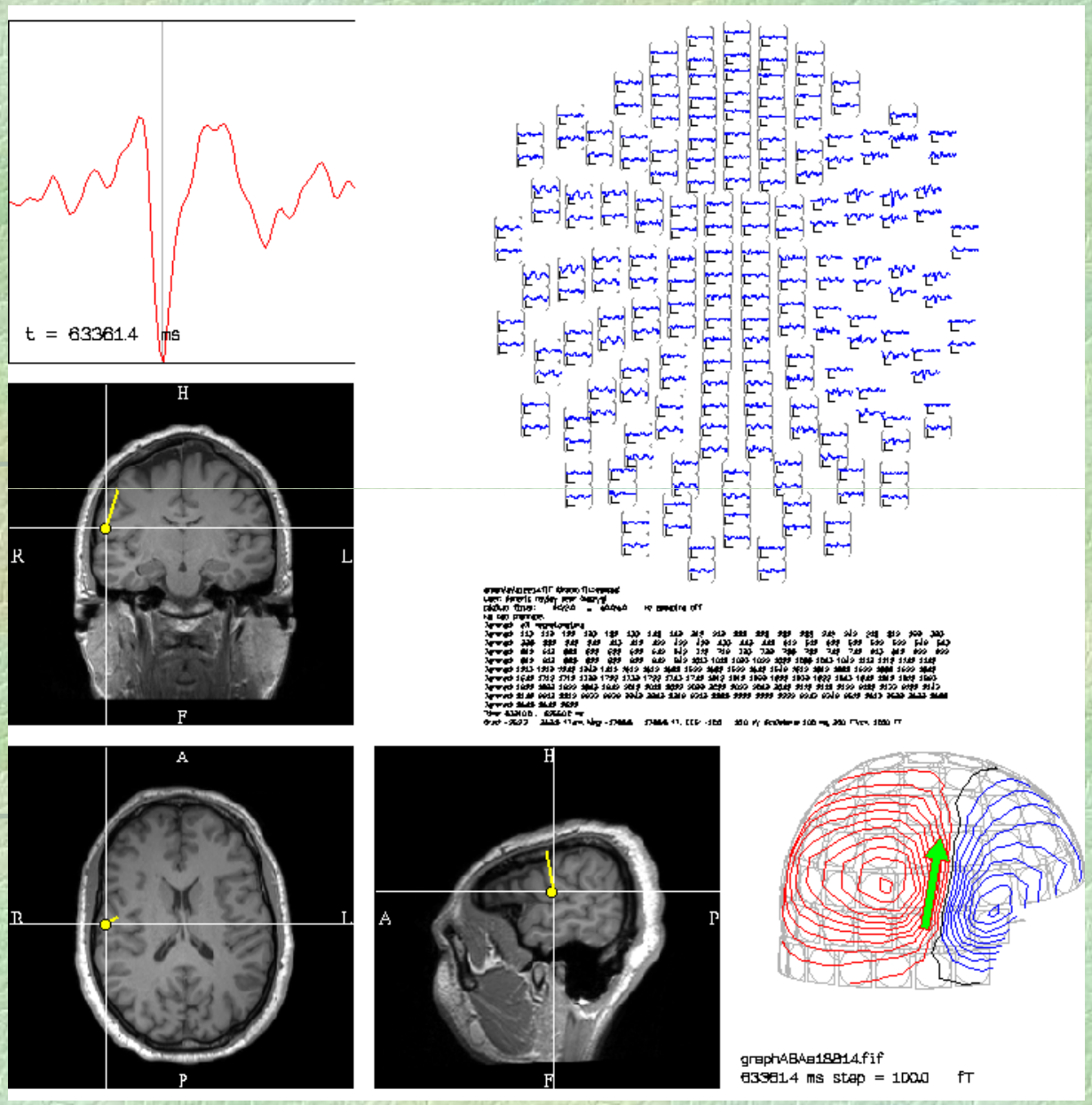
MEG Left temporal sensors



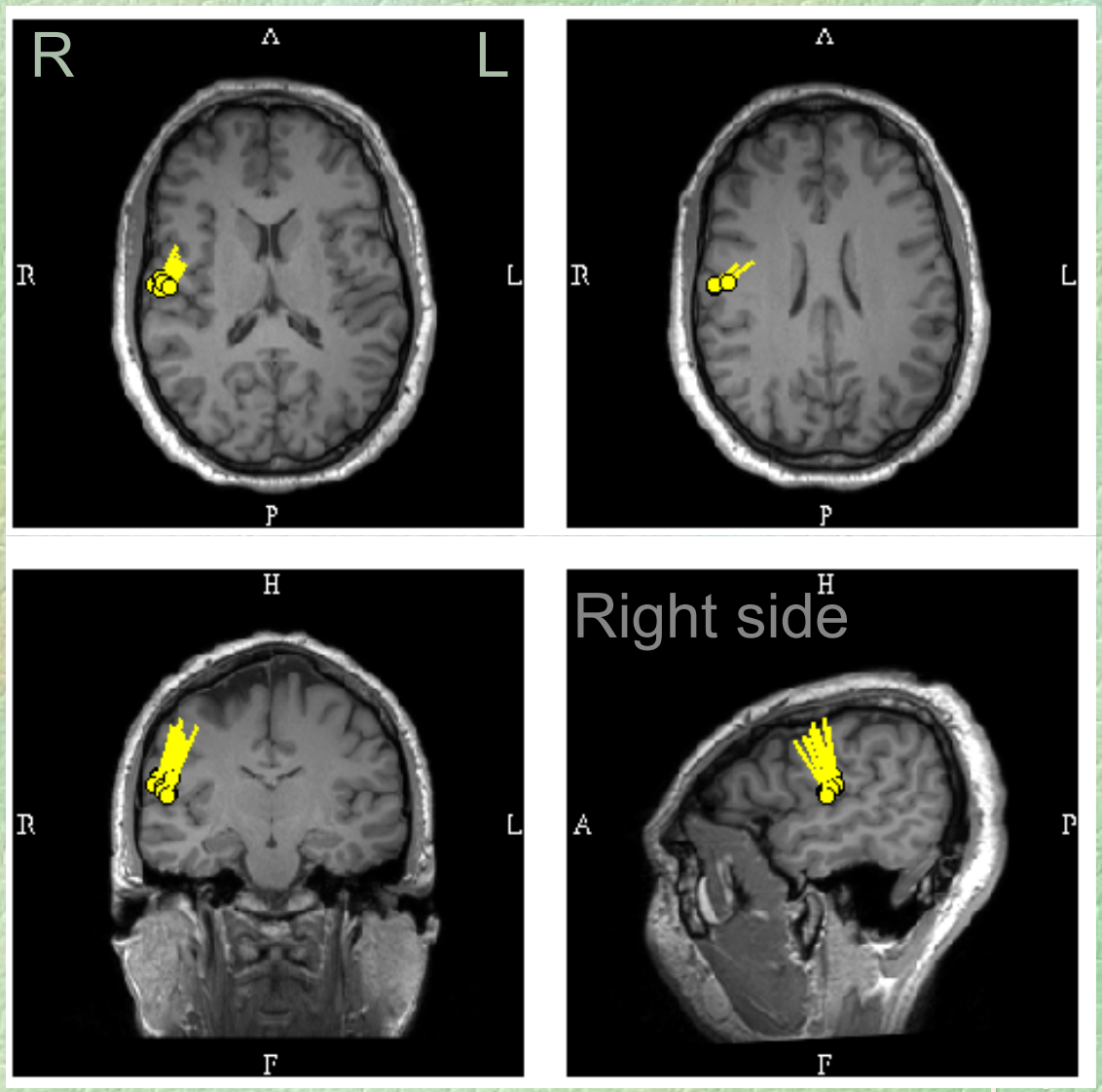
MEG Right temporal sensors



Right temporal spike dipole source localization



Representative spike dipoles



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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.

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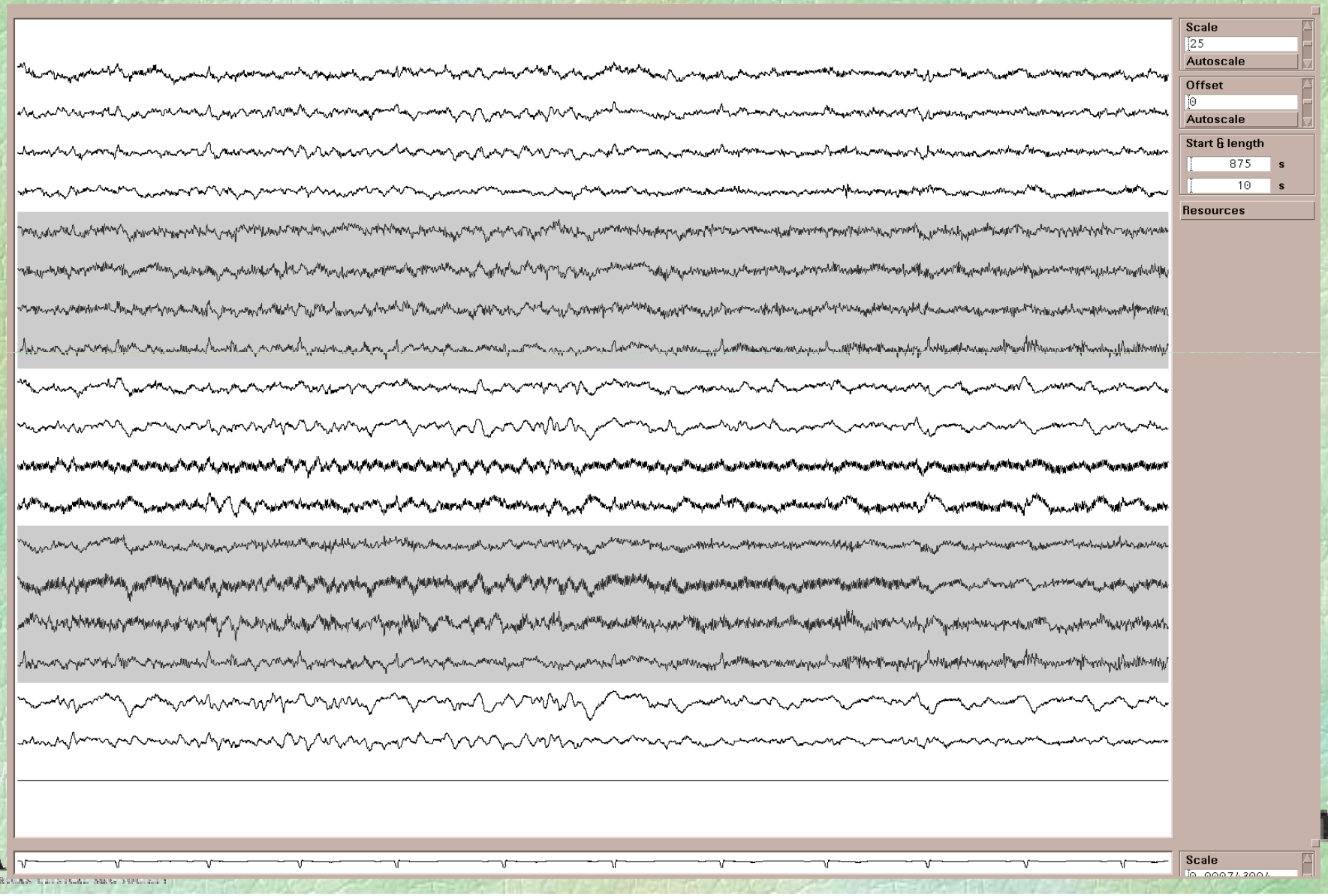
(MR# 57564962)

EEG: Intermittent slow, FP1/F3

1 sec | 100 uV

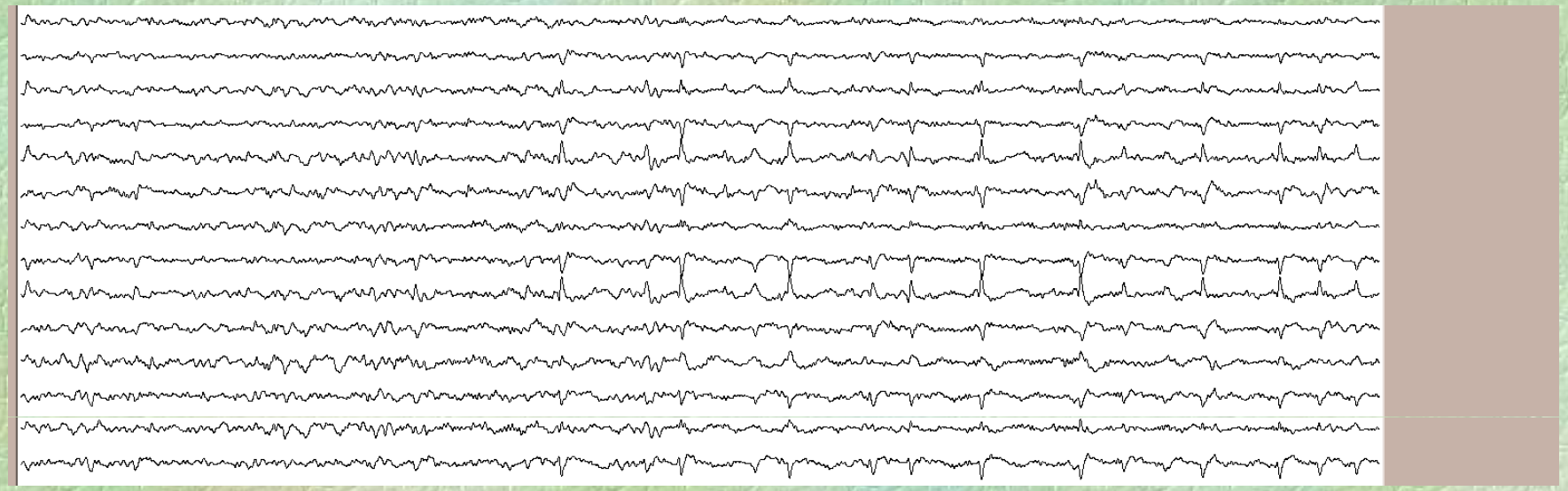
Run I EEG (Bipolar double bananna)



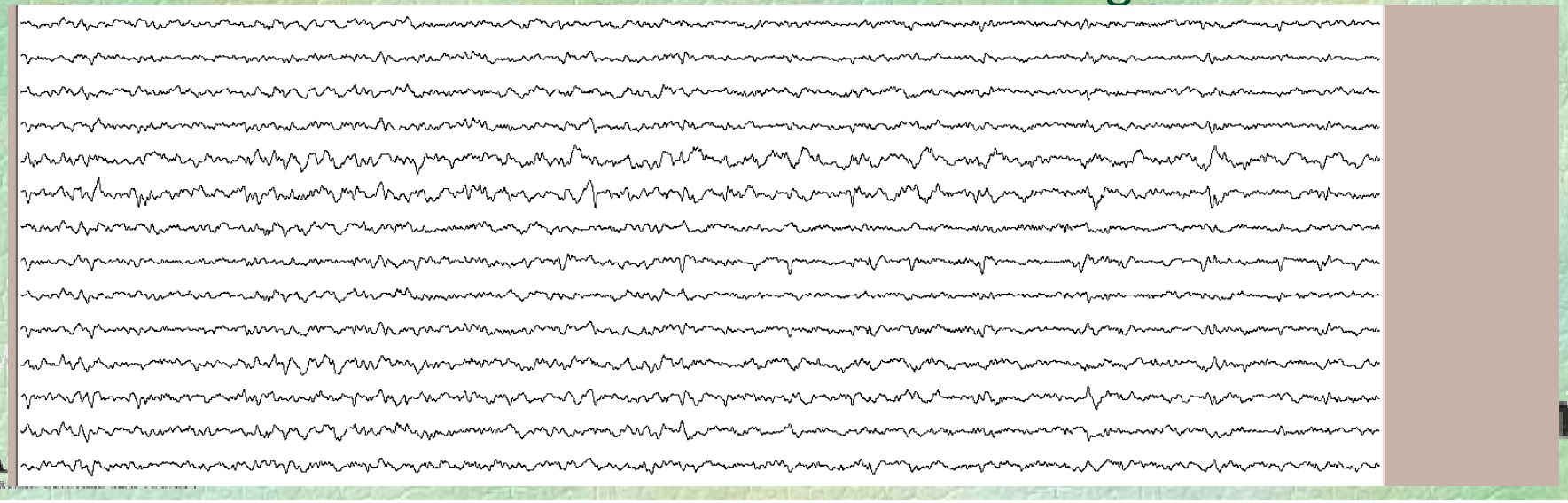
MEG: Run of sharp waves, Left frontal sensors (consistent localization)

1 sec | 500 fT/cm

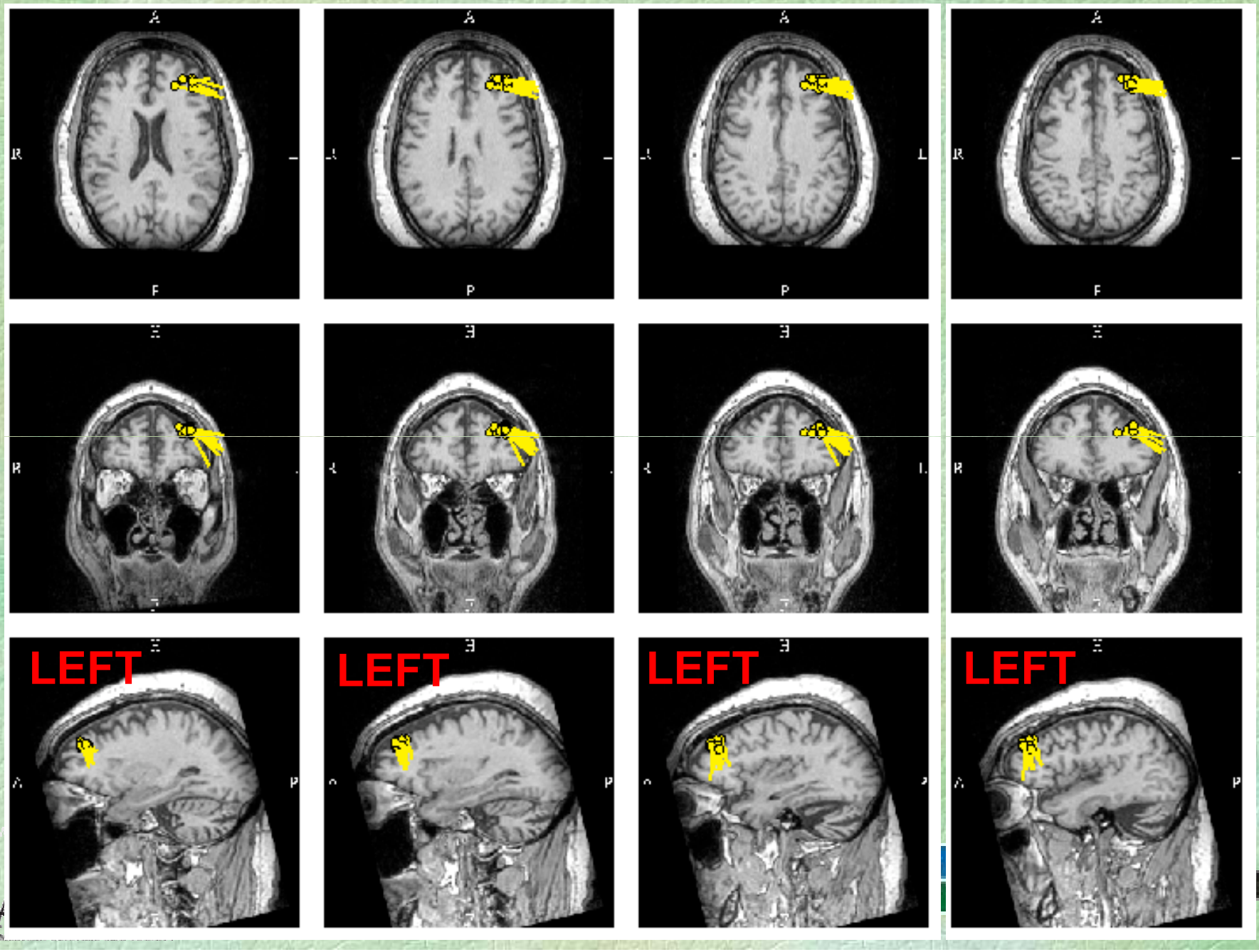
Left frontal sensors



Right frontal sensors

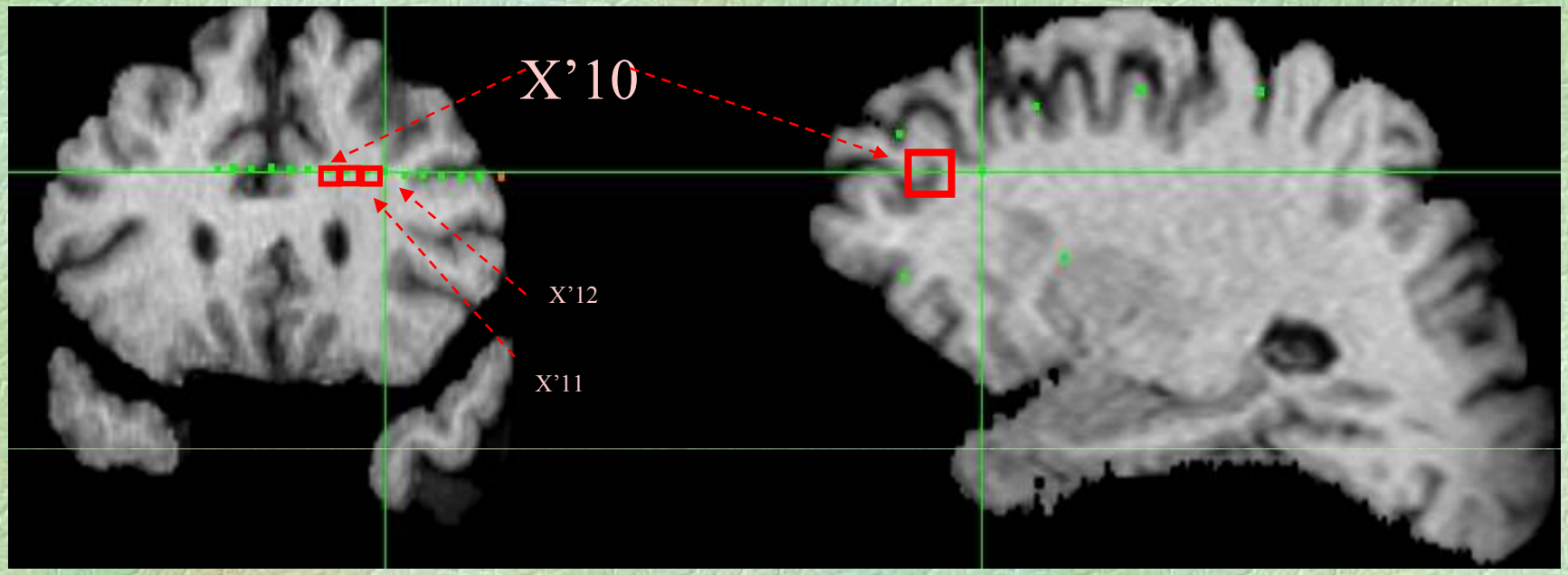


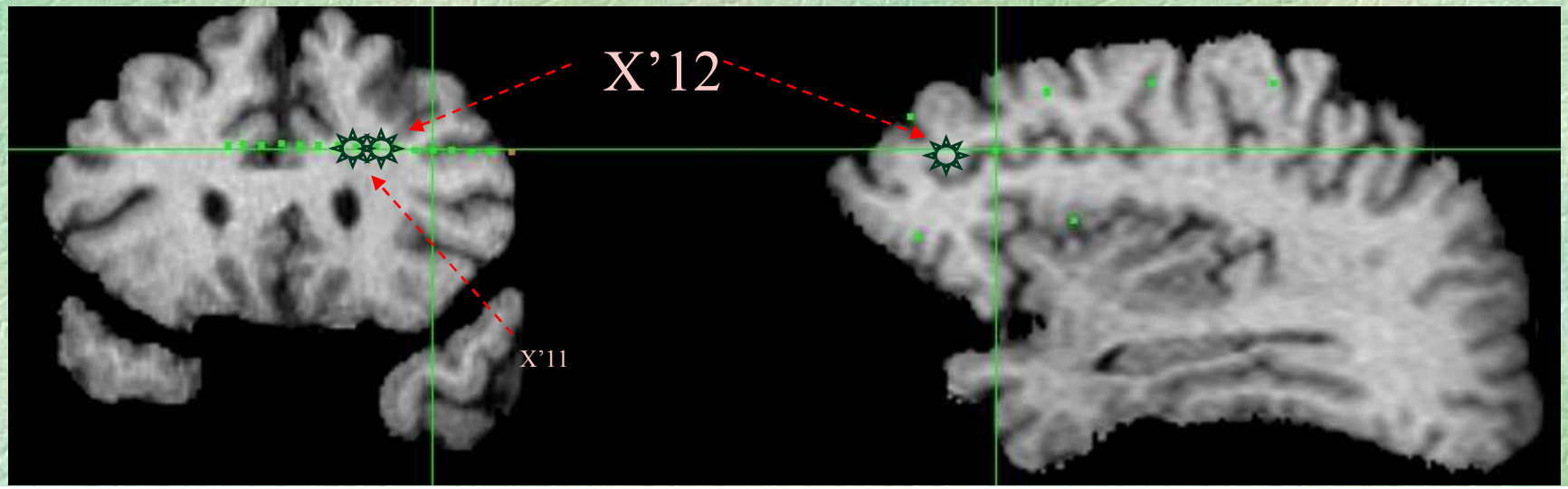
MEG Sources: Left middle frontal gyrus and superior frontal sulcus



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)

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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)

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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

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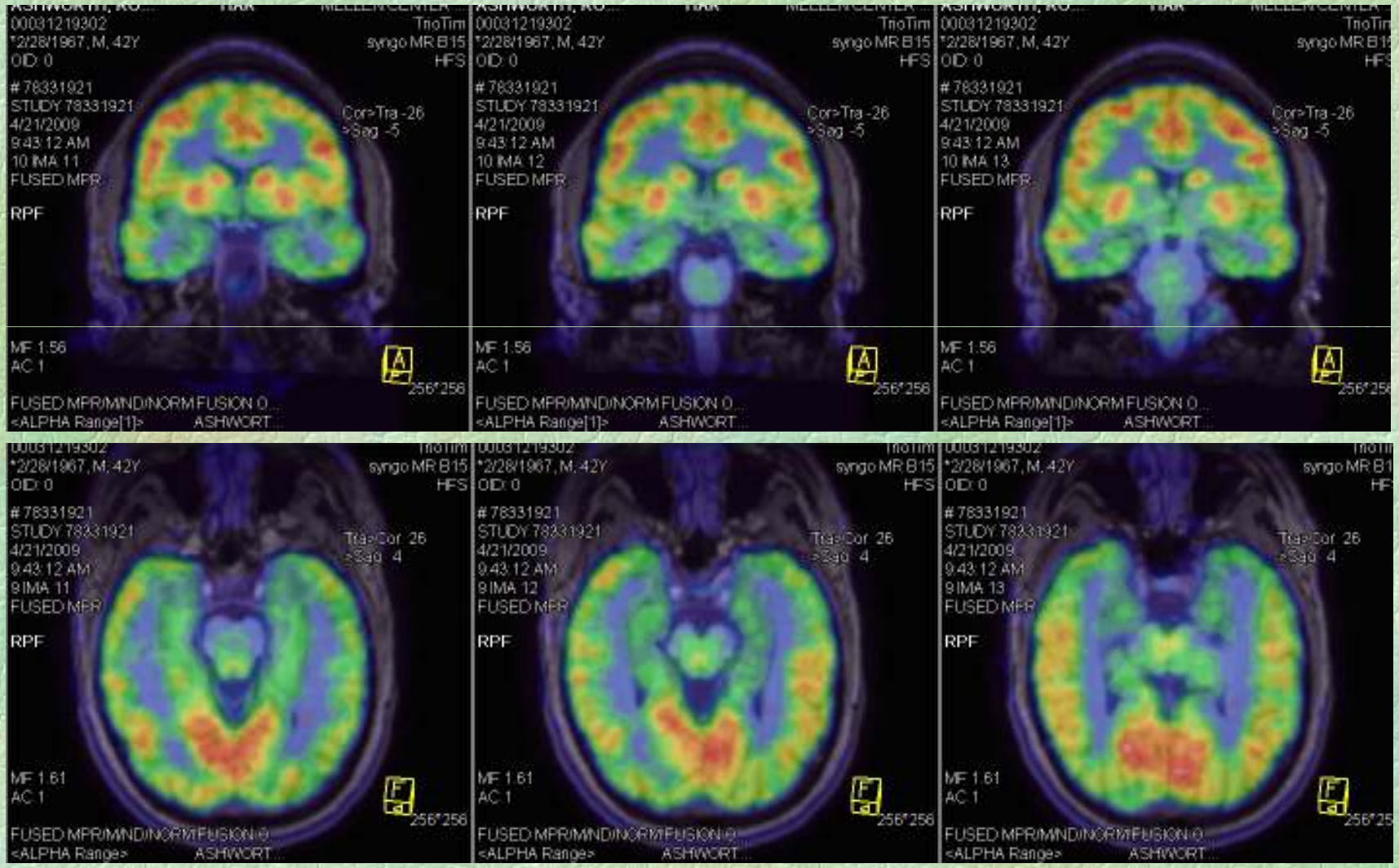
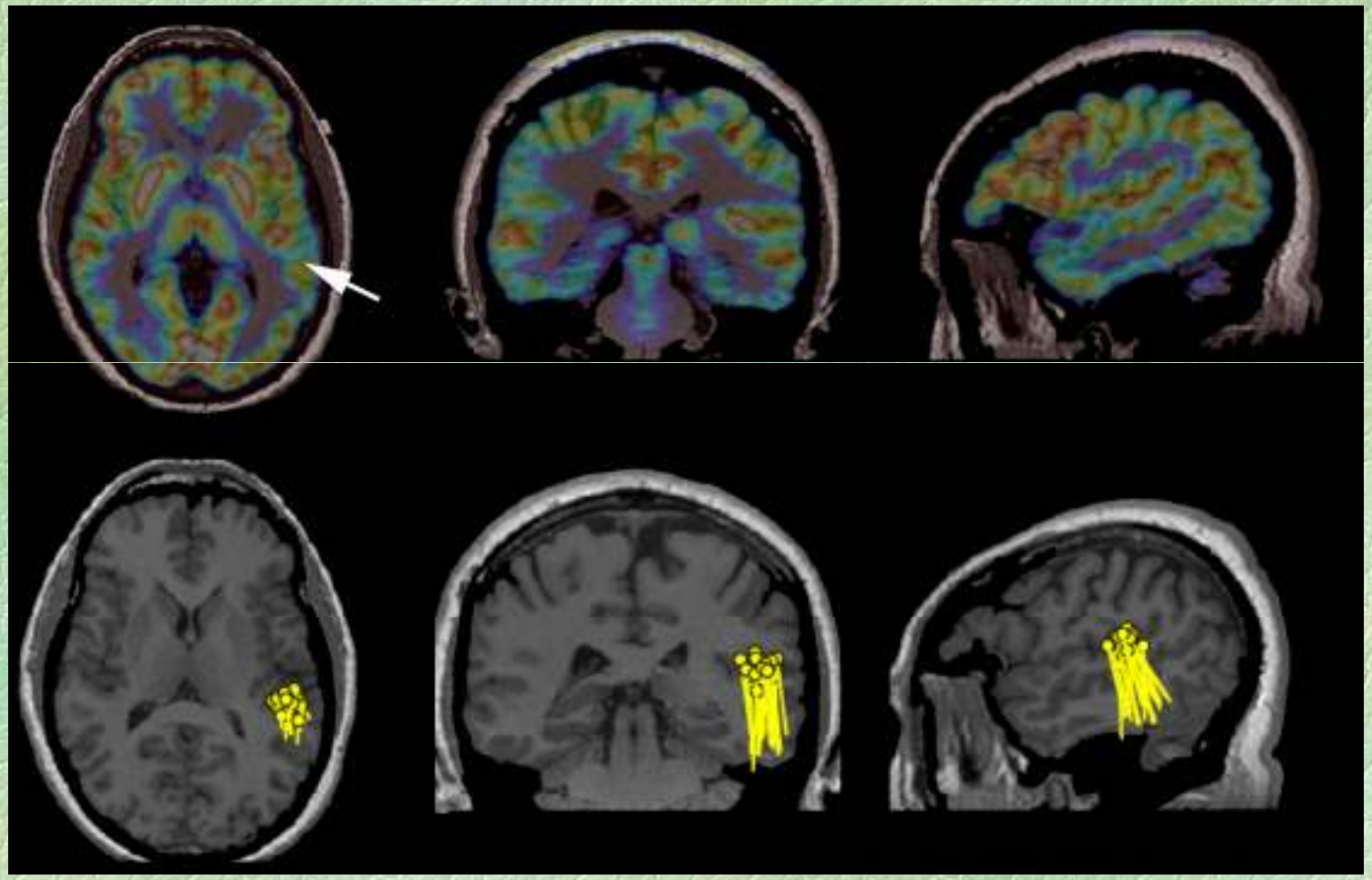
PET: Nonspecific

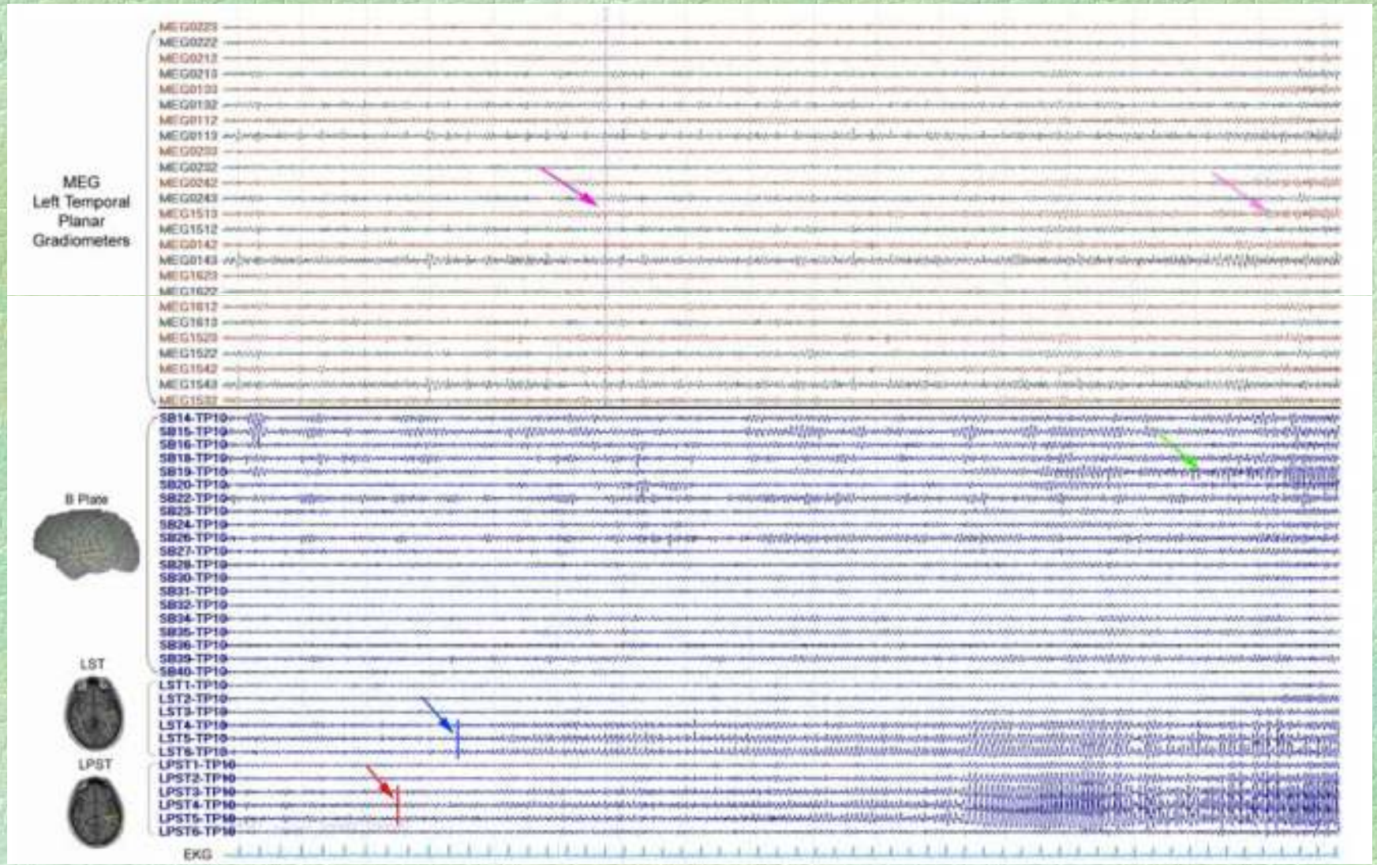


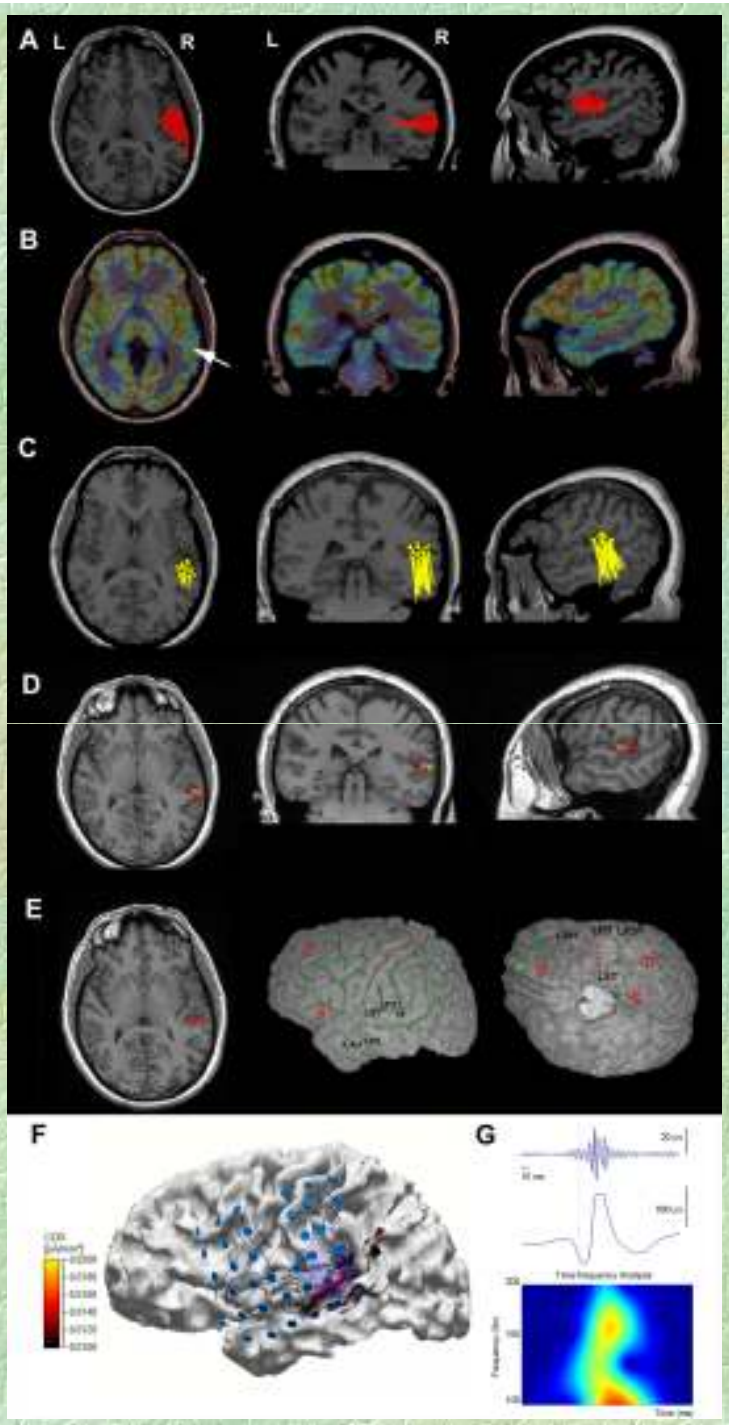
Simultaneous Multi-Modality Review: PET and MEG



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)

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Some Myths and Realities about MEG

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

Myth #2: MEG only records interictal activity

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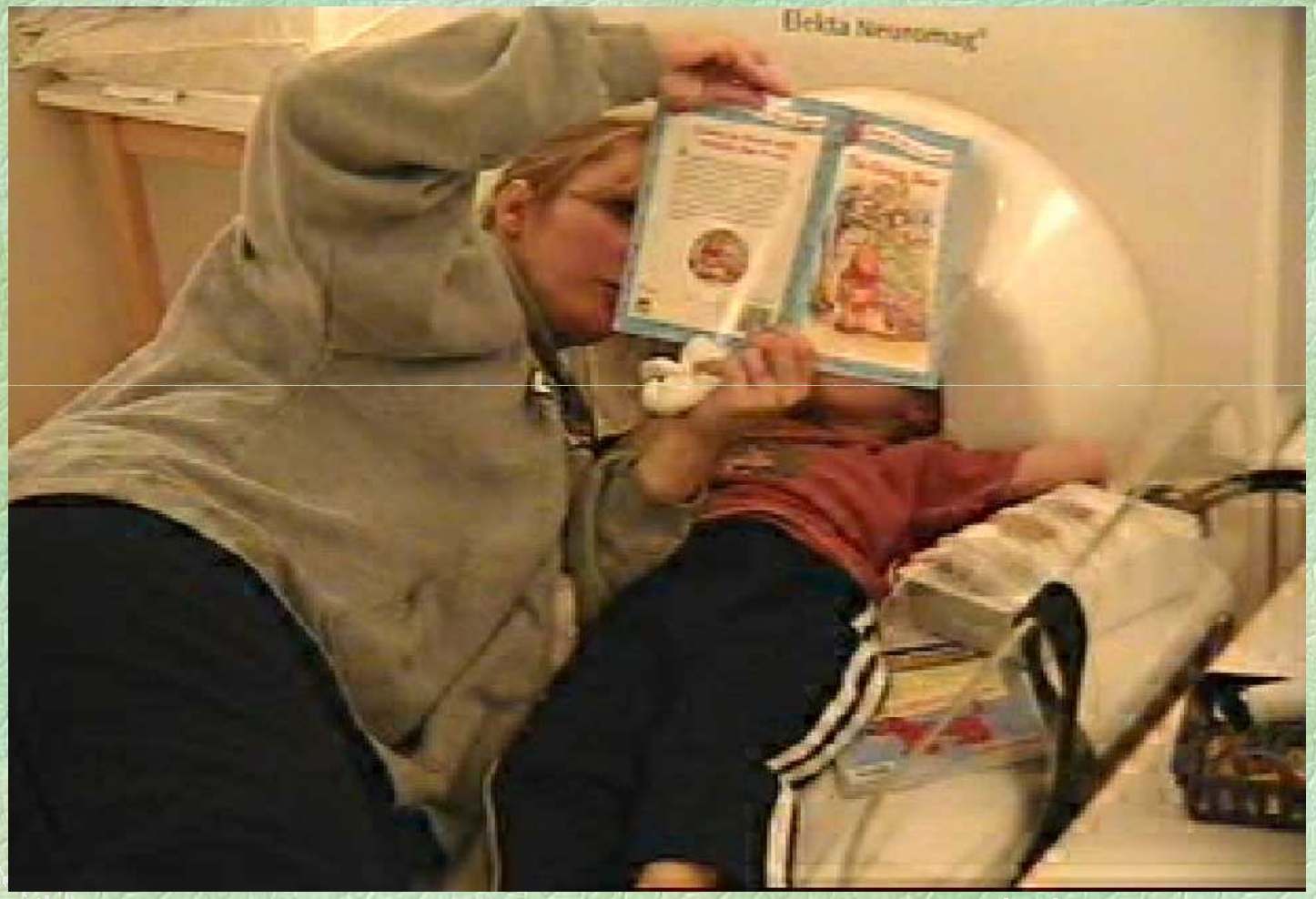
Myth #1: MEG is too sensitive to noise and artifact.



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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: 10^8 fT

(fT = femto Tesla or 10^{-15} Tesla)

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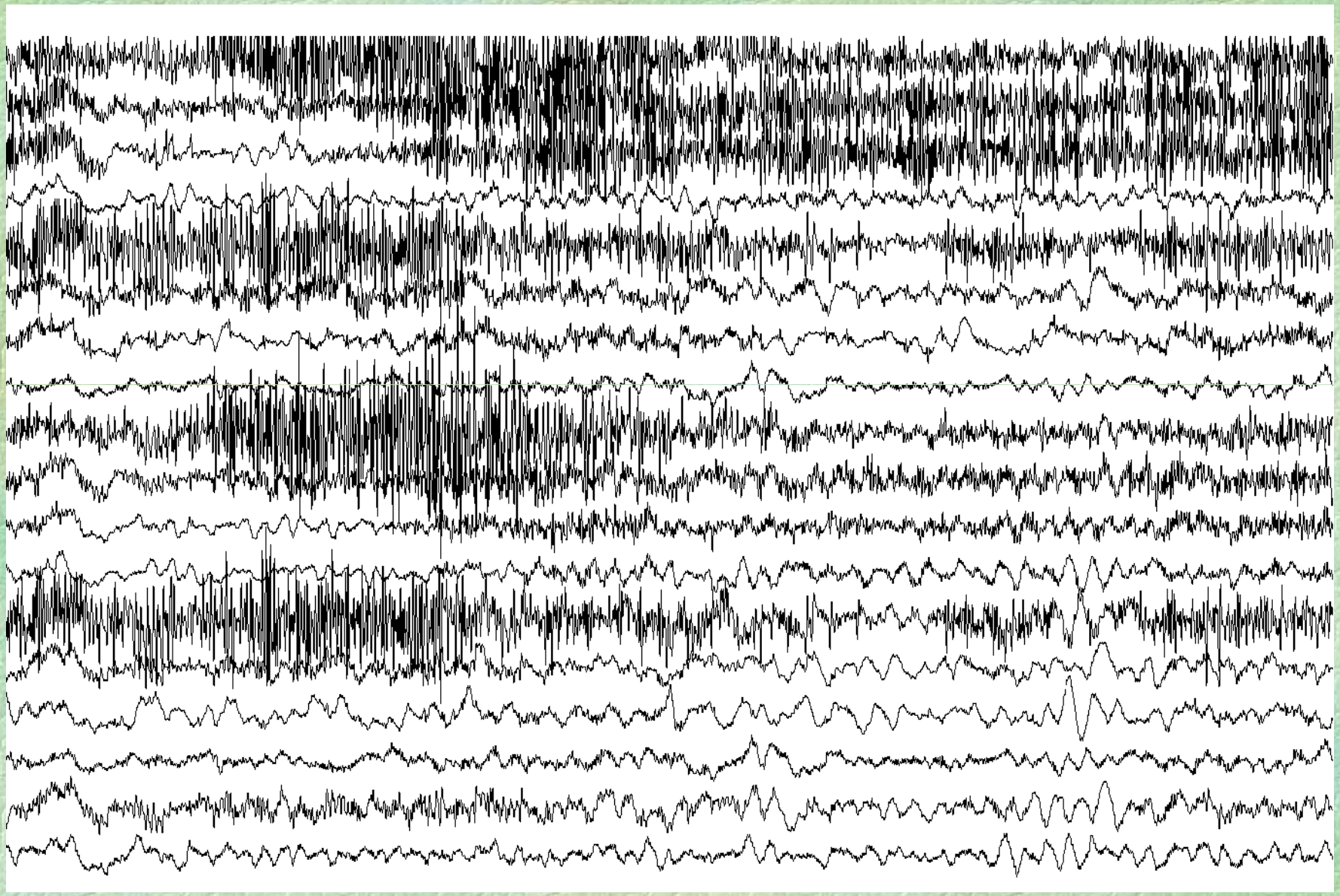
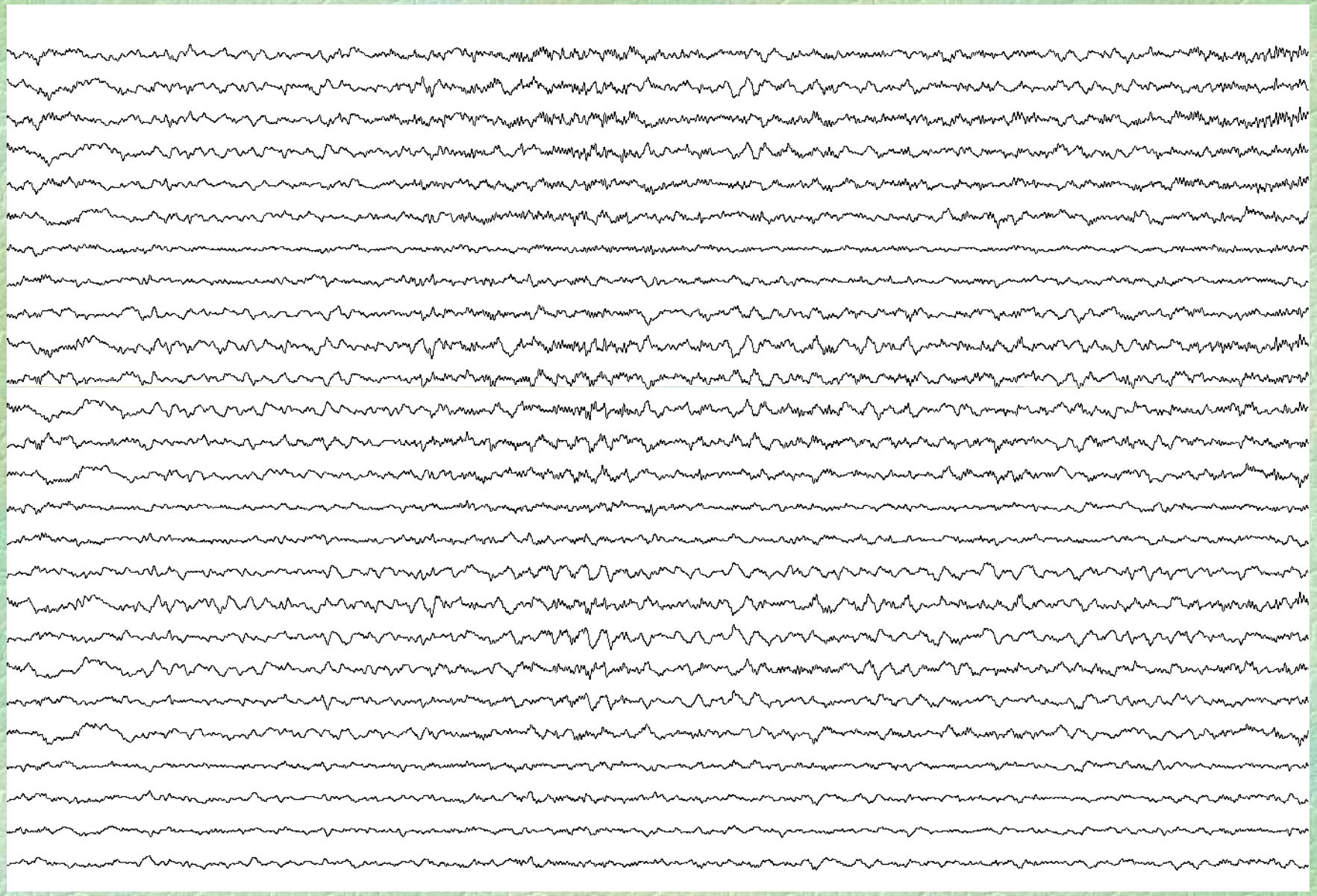
MEG's Immunity to EMG Artifact

EEG



Same Time Epoch as EEG on Previous Slide

MEG



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)

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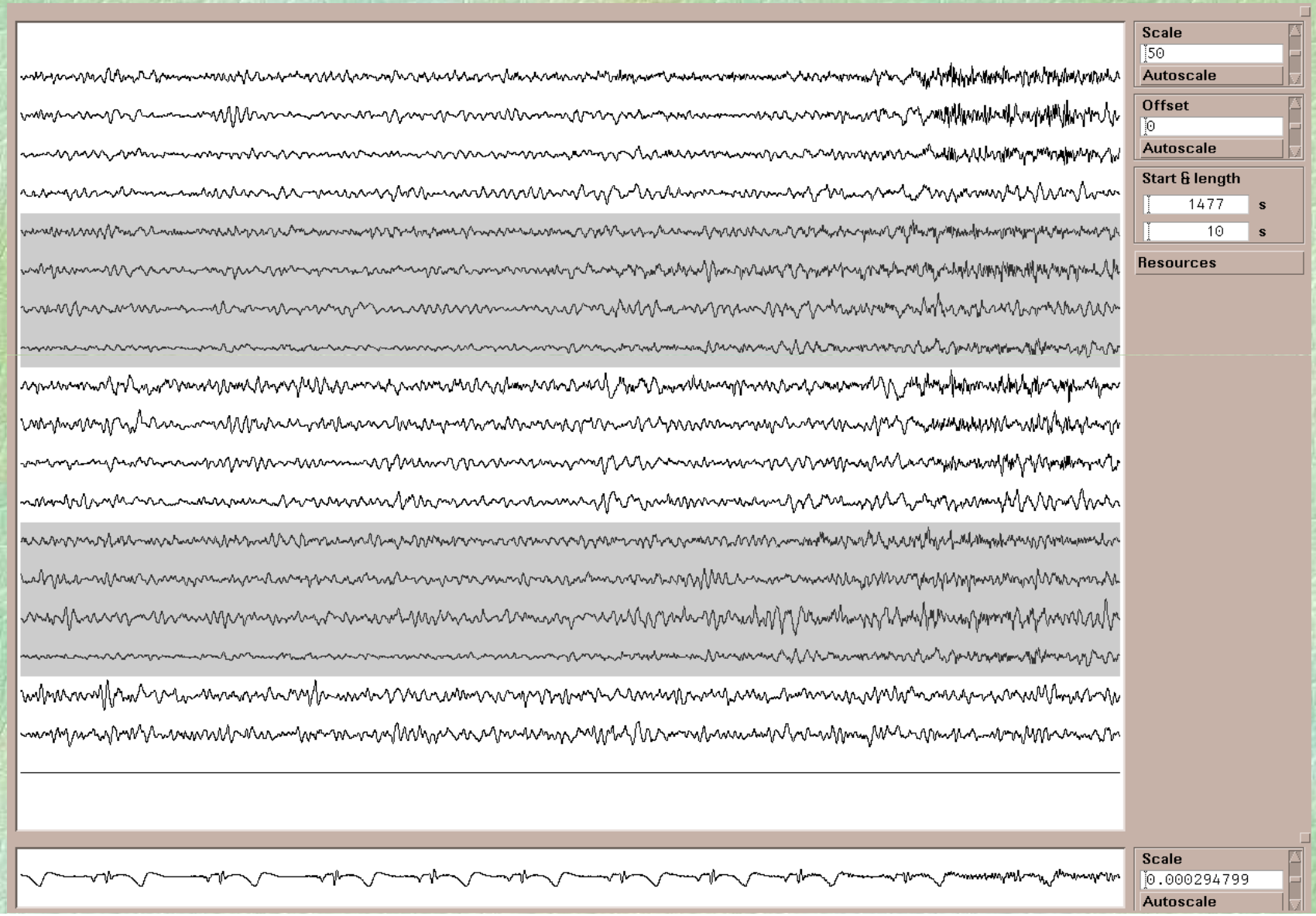
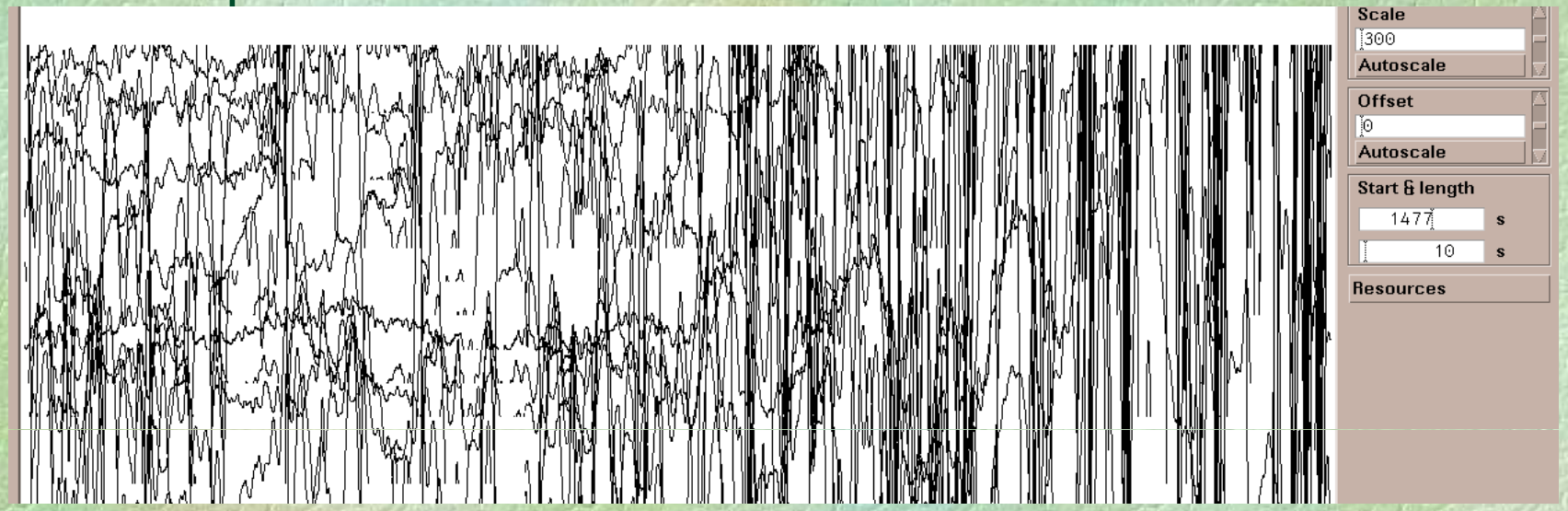
EEG:

Run I: Double banana bipolar EEG

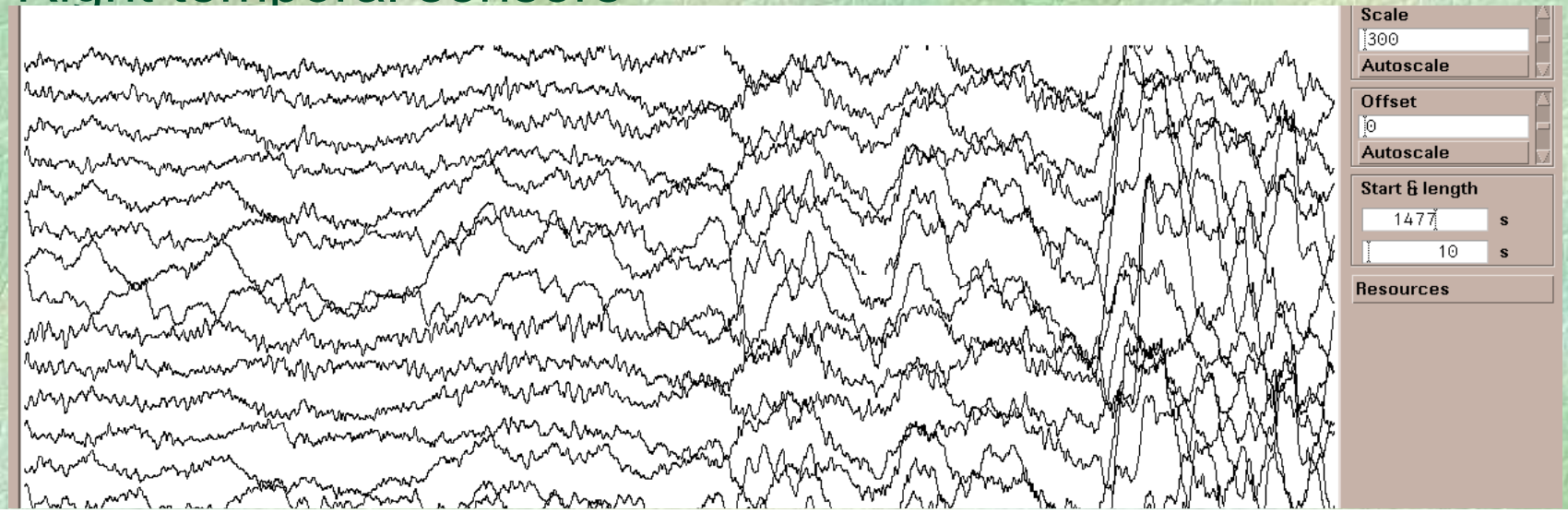


MEG without tSSS (temporal signal space separation)

Left temporal sensors

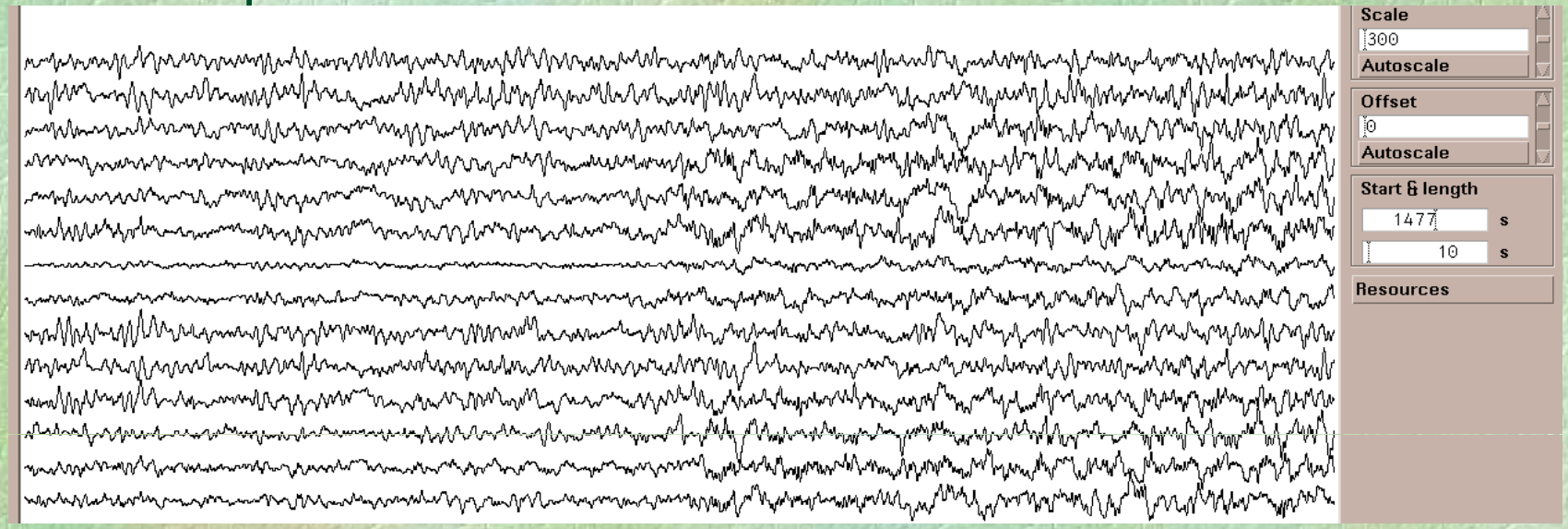


Right temporal sensors

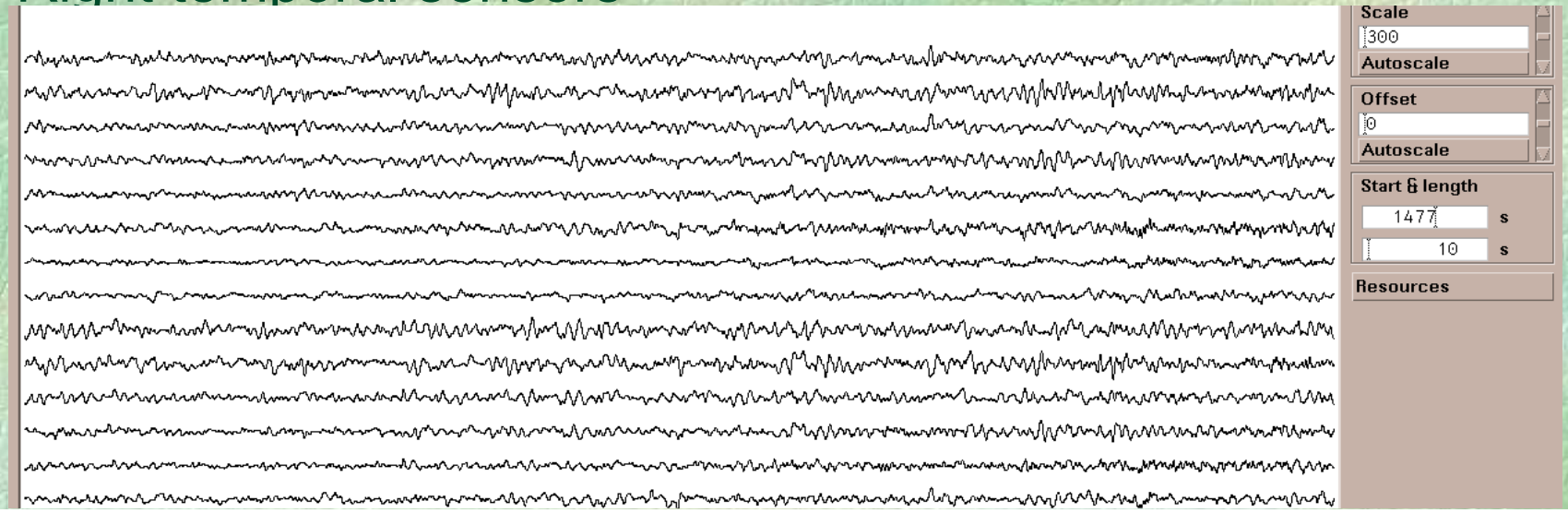


MEG with tSSS (same time segment with same amplitude scale)

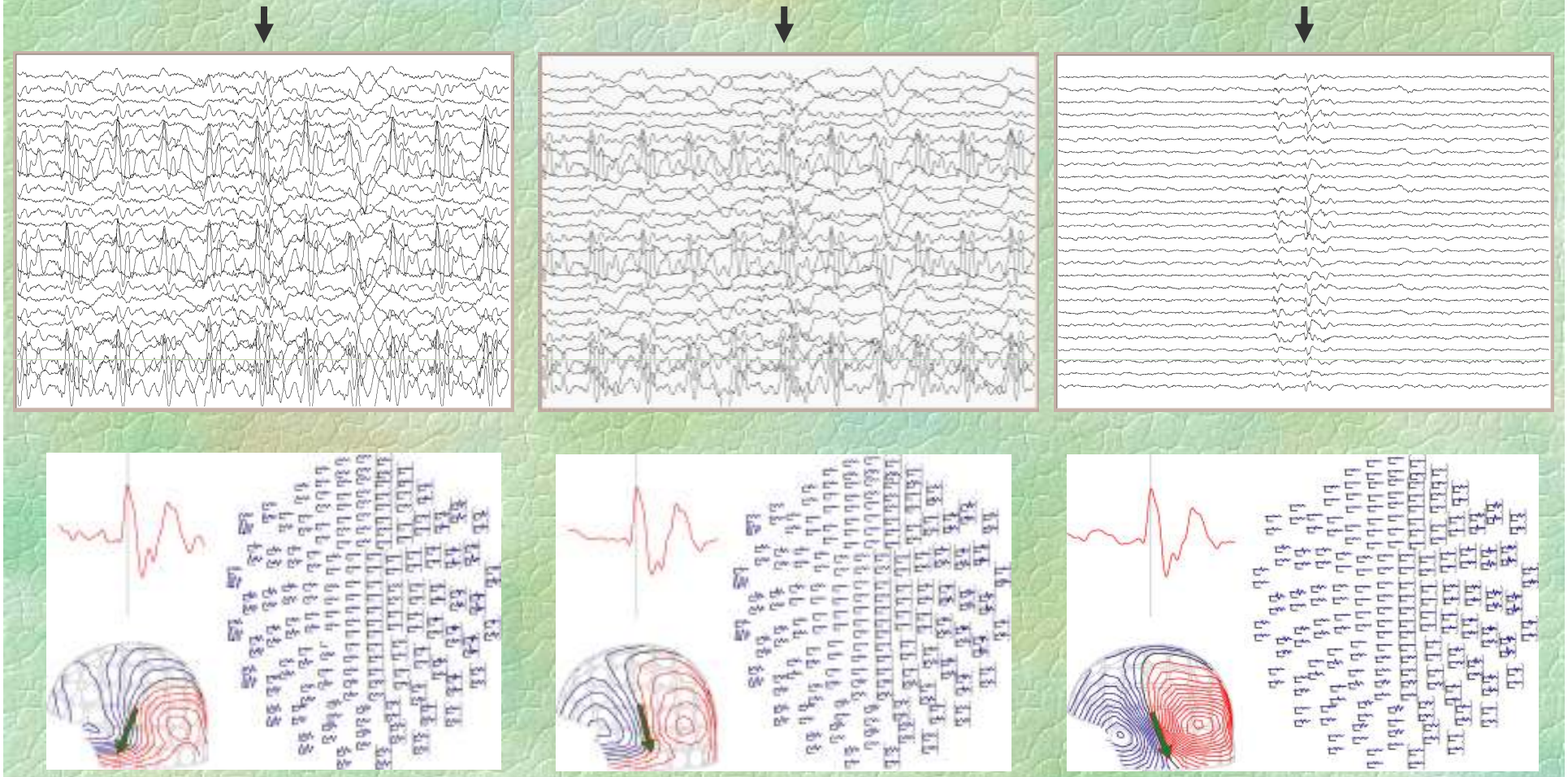
Left temporal sensors



Right temporal sensors



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



no SSS SSS tSSS

(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.

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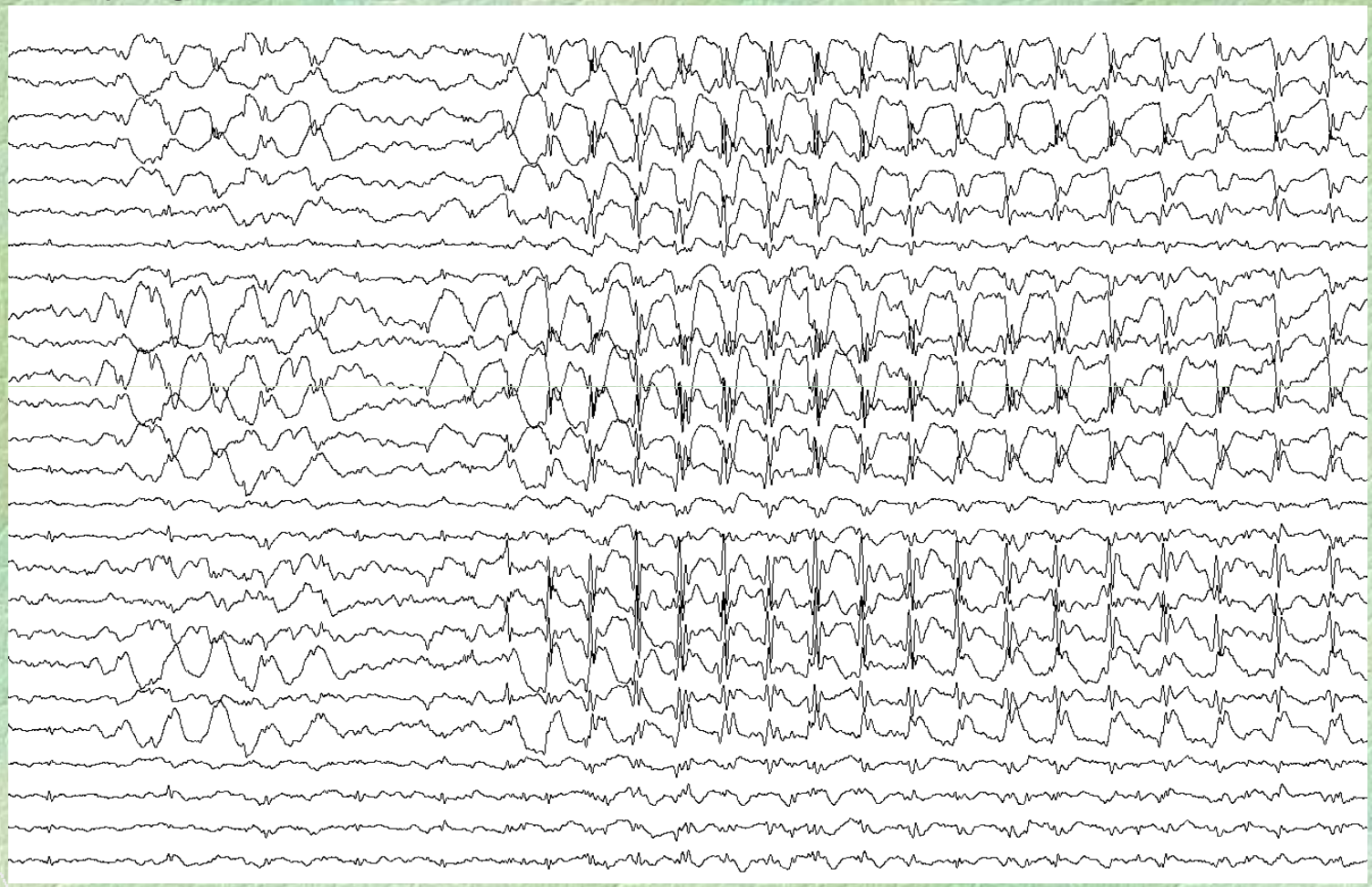
Ictal MEG Recording

Left temporal gradiometers



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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)

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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.

*Bagic, Knowlton, Rose, Ebersole. CPG #1. J Clin Neurophysiol, 2011.
Burgess, Funke, Bowyer, Lewine, Kirsch, Bagic. CPG #2. J Clin Neurophysiol, 2011.
Bagic, Knowlton, Rose, Ebersole. CPG #3. J Clin Neurophysiol, 2011.
Bagic, Barkley, Rose, Ebersole. CPG #4. J Clin Neurophysiol, 2011.

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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

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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

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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.

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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

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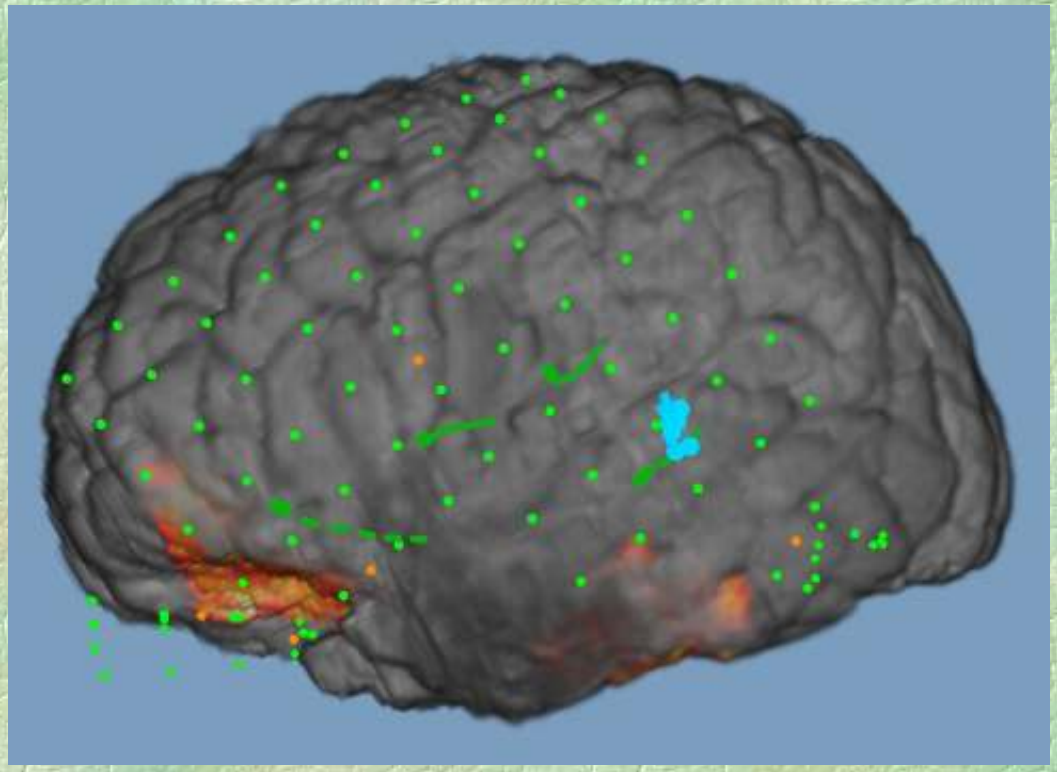
Dipole Sources Coregistered with Surface-Reconstructed MRI



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

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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

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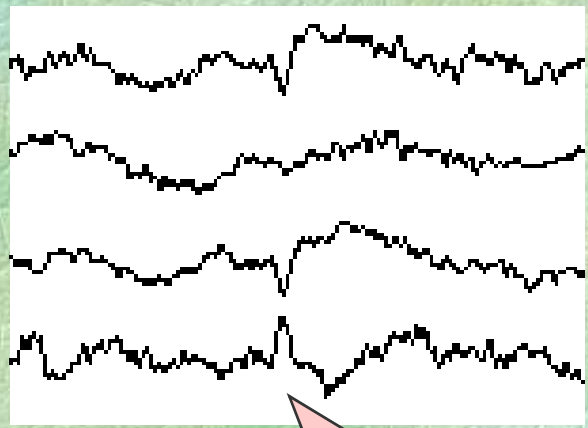
Additional slides for Q & A period

How is MEG analyzed and interpreted (1)

First identify important waveforms (e.g. spikes)

- By time correlation with EEG ?
- Blindly ?
- From spike detector ?



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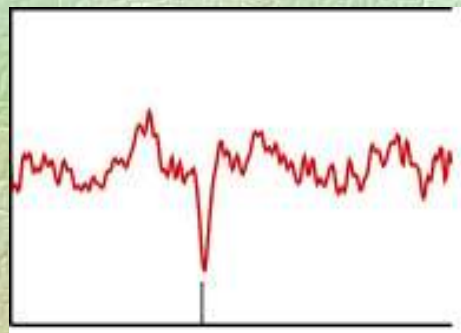
Analysis of MEG Signals (2)

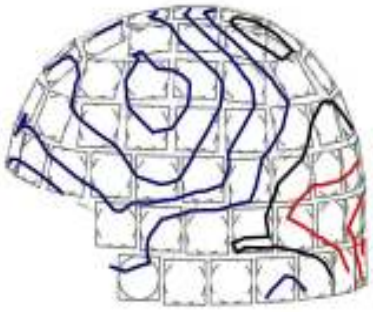
Field determination requires computerized calculation



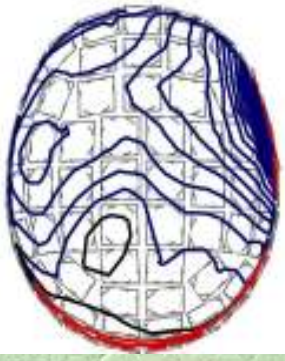
Iso-magnetic field map

200fT/step

Top view



Lt lateral view



Rt lateral view

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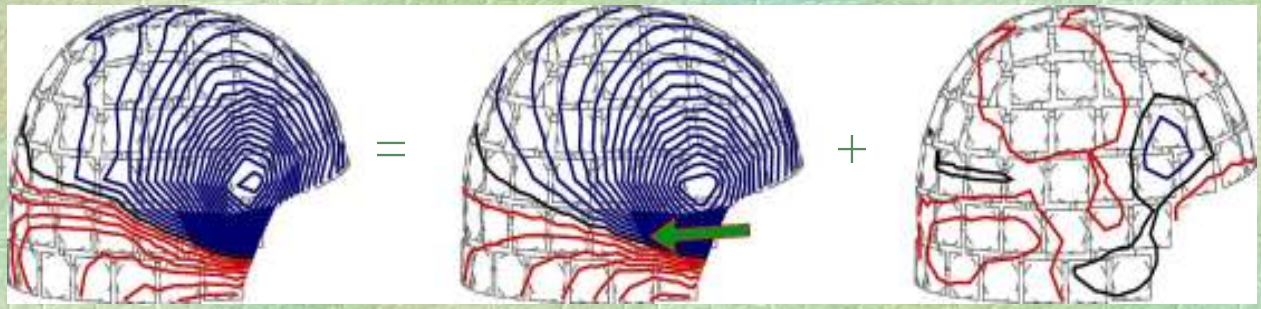
Analysis of MEG Signals (3)

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 mm
(Q)= 373 nAm
Goodness of fit = 84.5%

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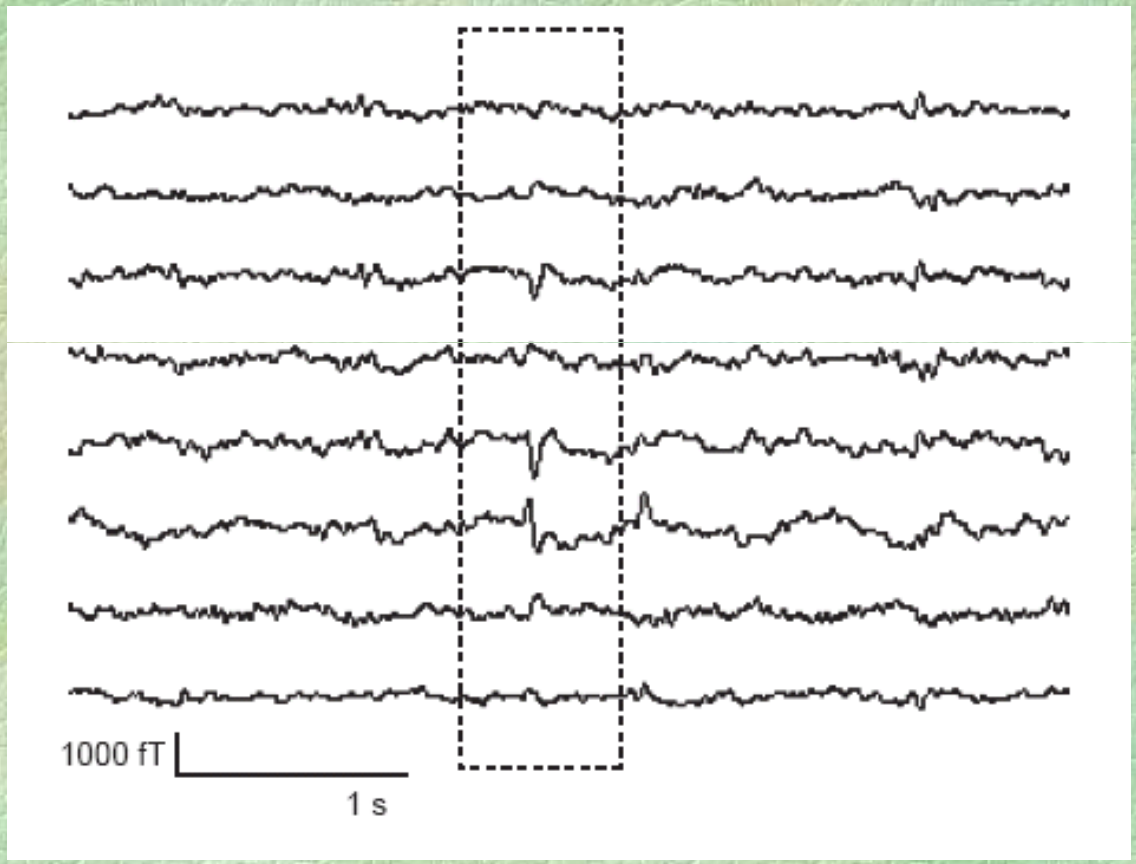
Spike Source Estimation (4) --- Solving the Inverse Problem

Recording spontaneous MEG activity --- trace mode



Typical MEG waveforms from sensors overlying the right central region; an epileptiform spike is outlined.

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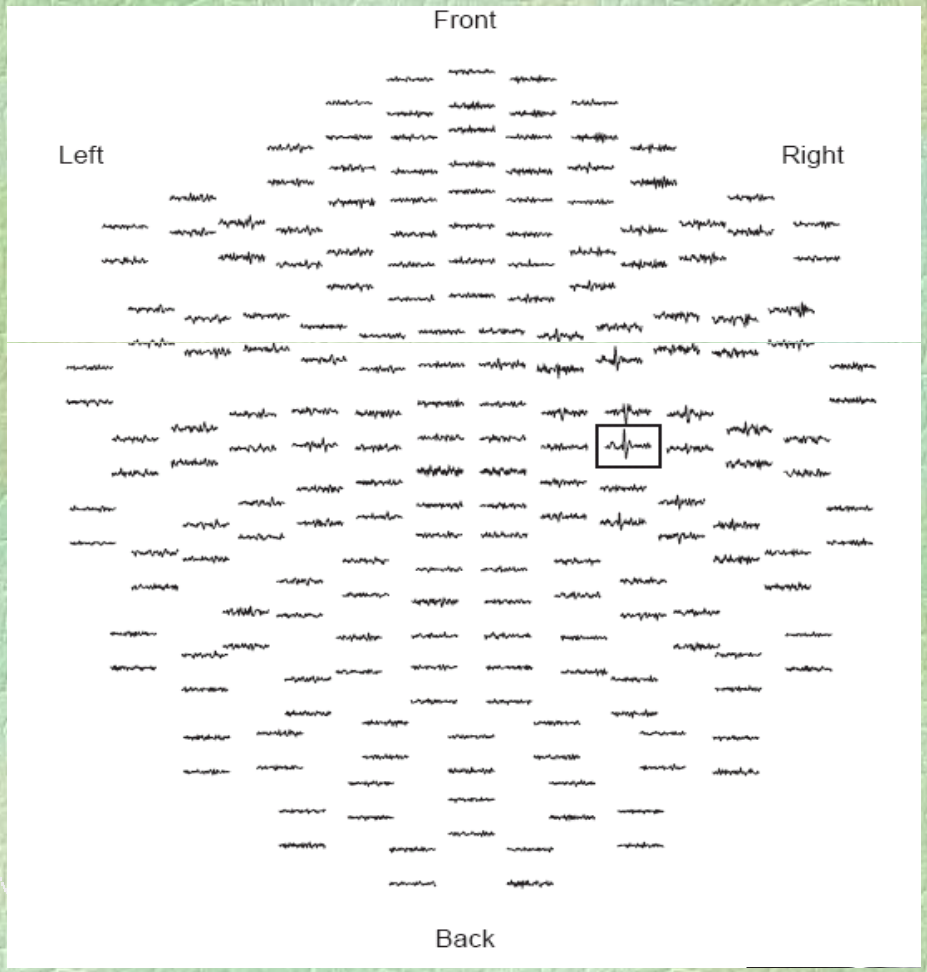
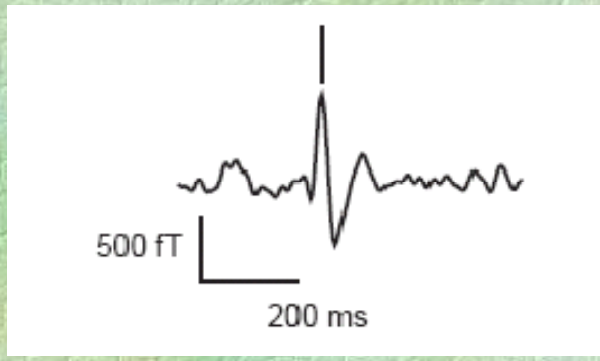
Spike Source Estimation (4) --- Solving the Inverse Problem

Topographic view of MEG activity during the bracketed epoch



Expanded view of MEG activity at maximally active sensor



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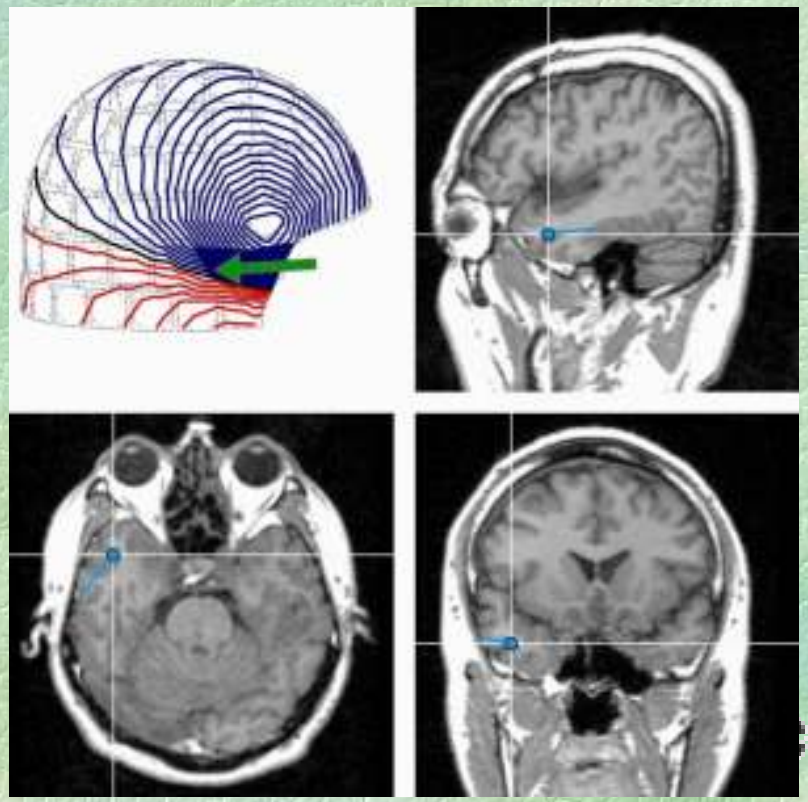
Analysis of MEG Signals (5)

Co-registration to Anatomy

- Requires 3-dimensional coordinate digitization of surface landmarks
- Import 3-D MRI

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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).

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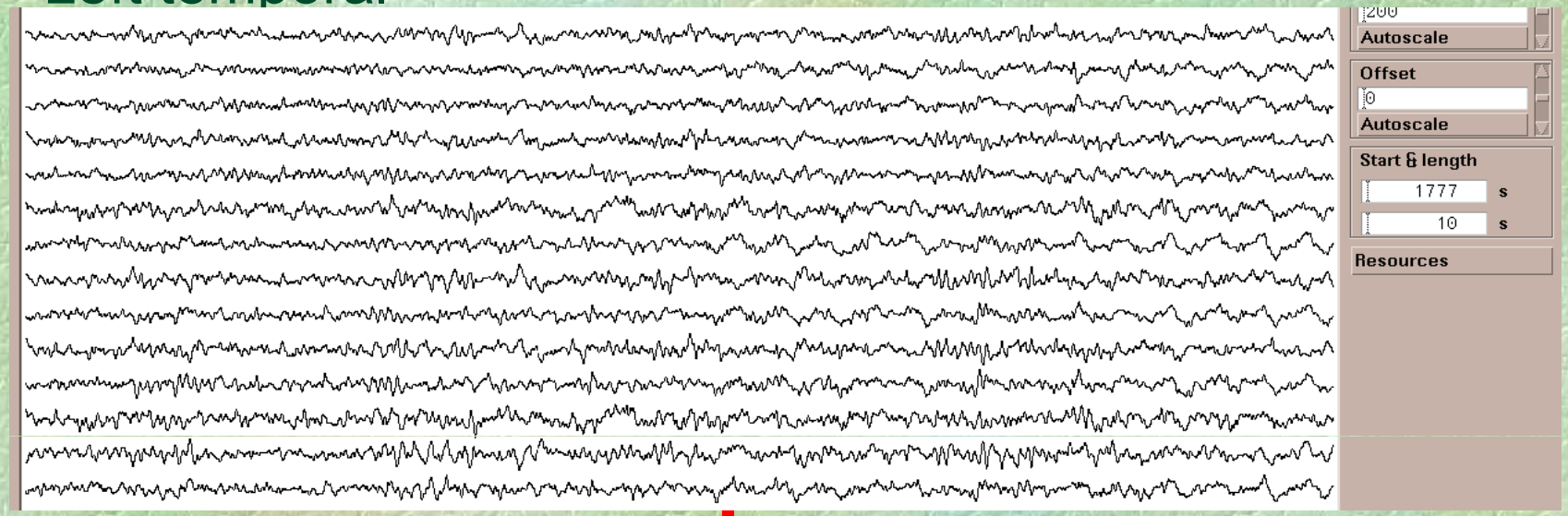
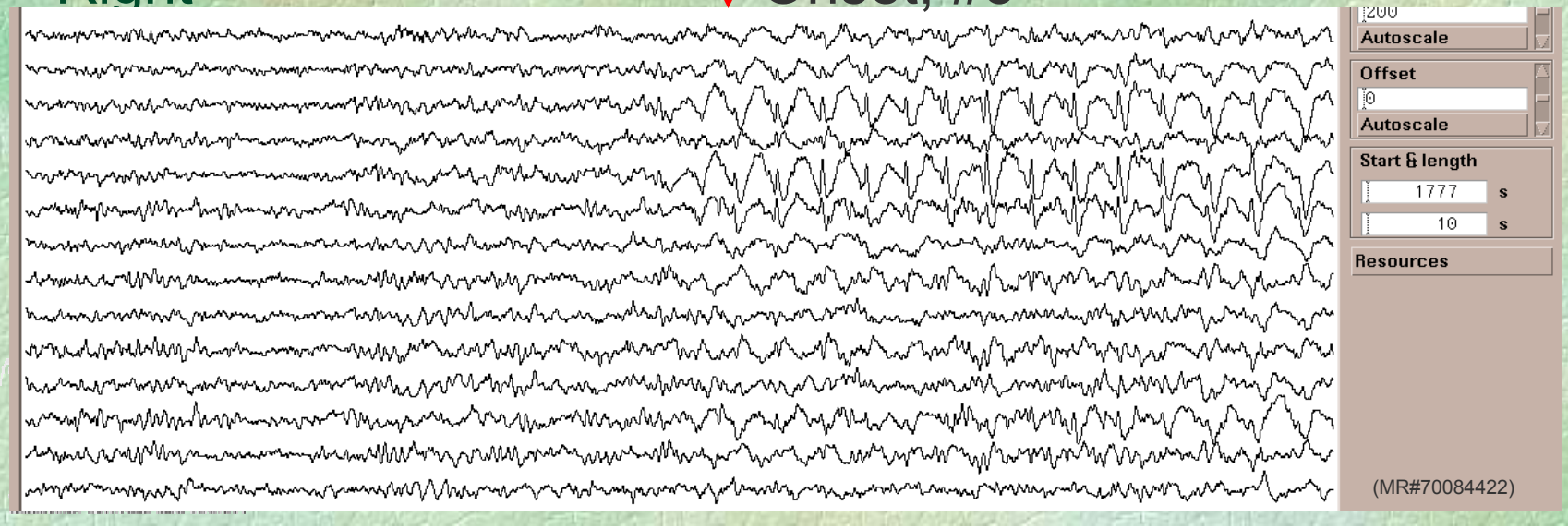
NCS Seizure. MEG: Spike and wave complex, Right parietal sensors

Left temporal



Right

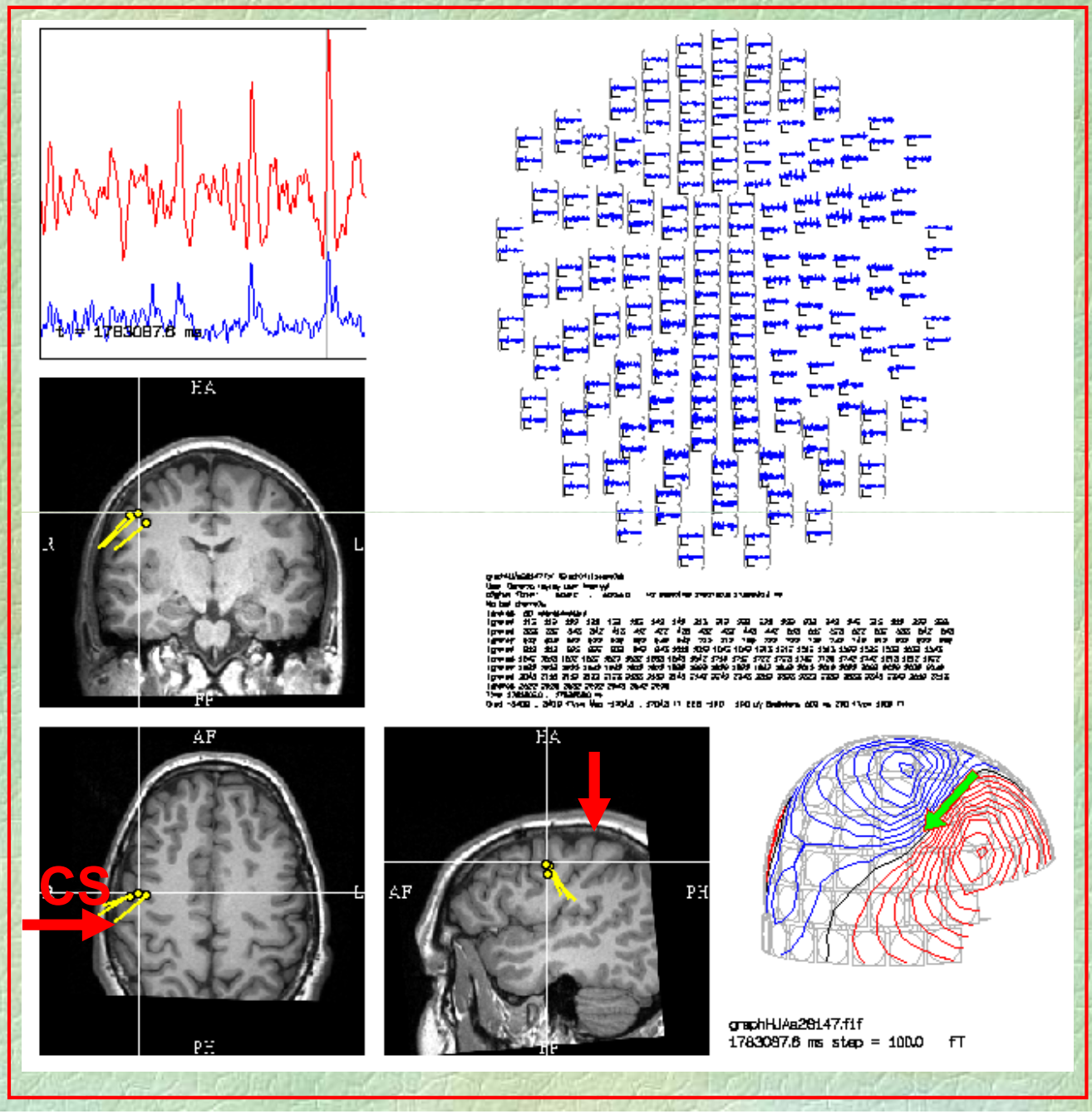
Onset, #5



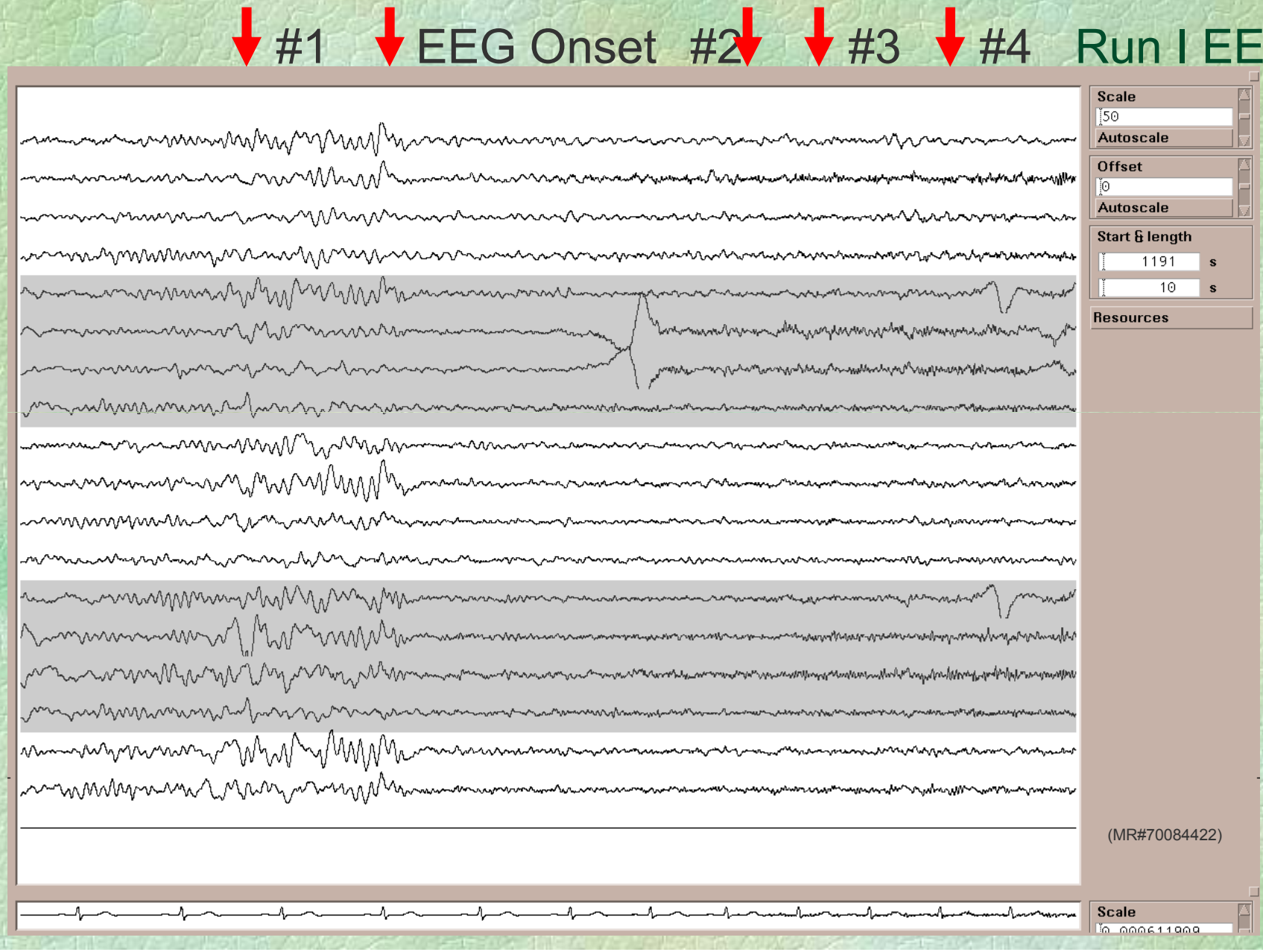
Clinic

(MR#70084422)

Dipole of #5 (Onset): Right posterior middle frontal gyrus (stable)

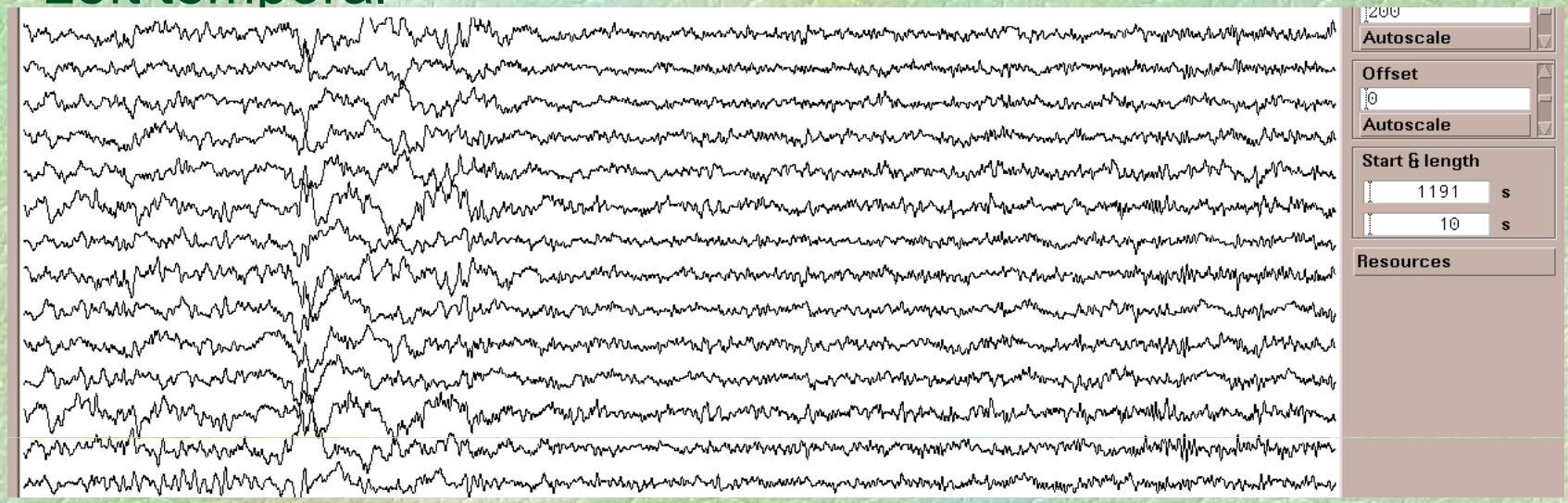


Clinical Seizure. EEG: Onset, Right centro-parietal, Somatosensory Aura

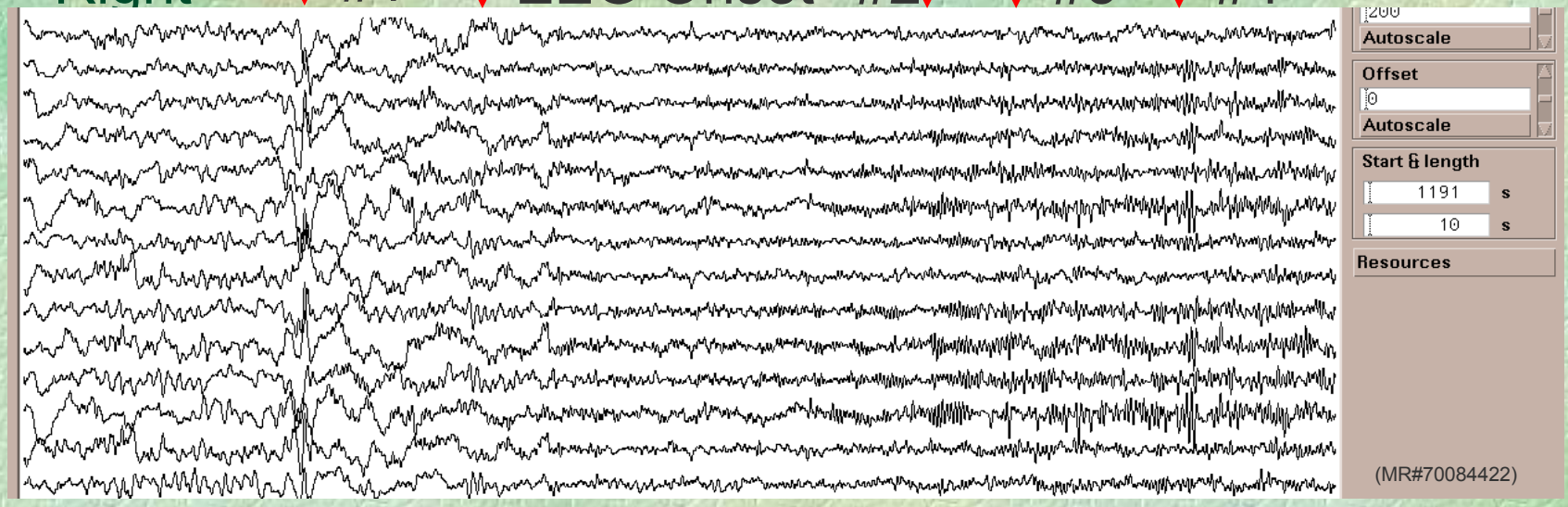


Clinical Seizure. MEG: Attenuation -> beta, polyspikes, Right parietal sensors

Left temporal

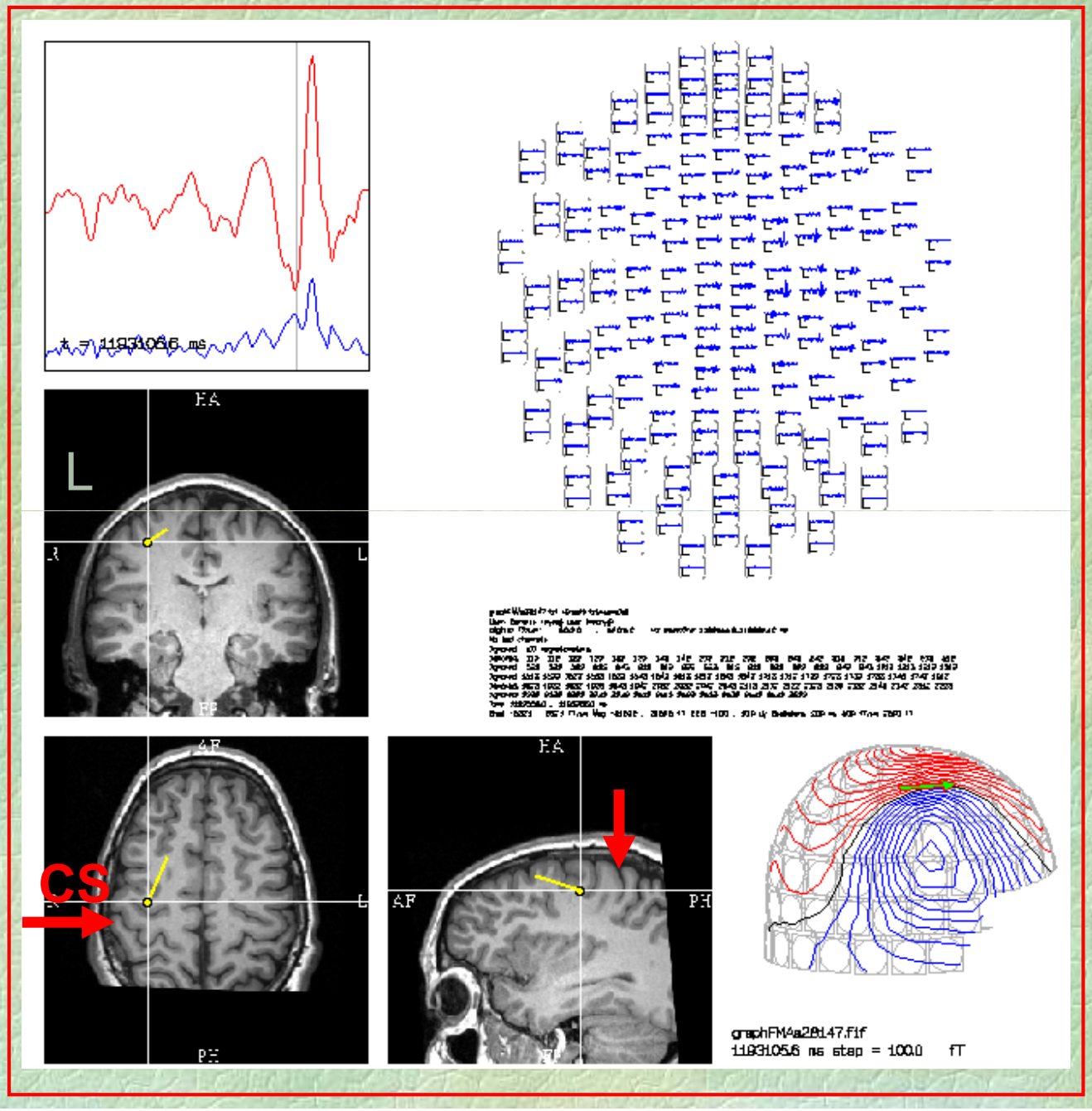


Right #1 EEG Onset #2 #3 #4

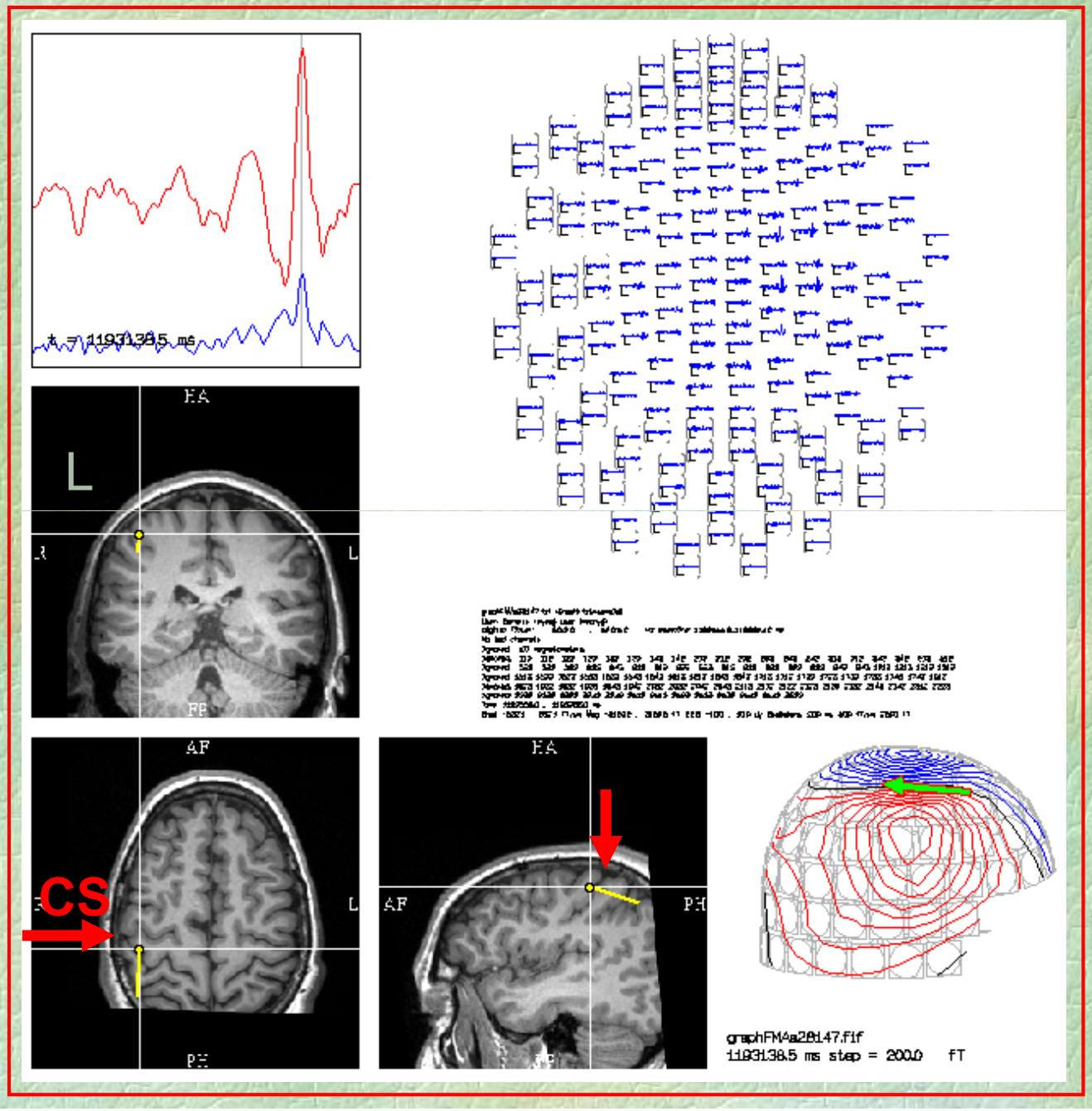


(MR#70084422)

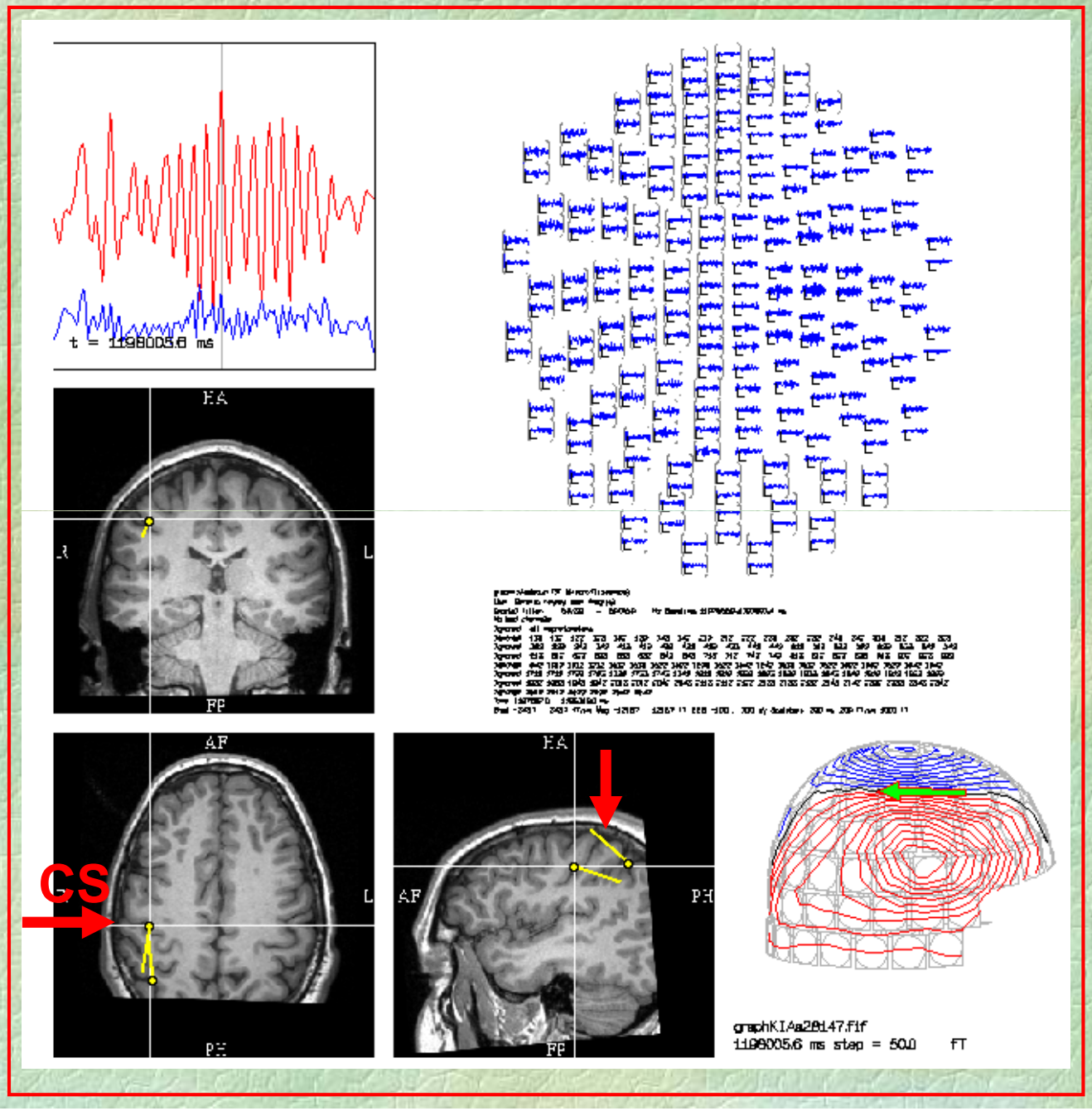
Dipole of #1-1 (early component): Right posterior middle frontal gyrus



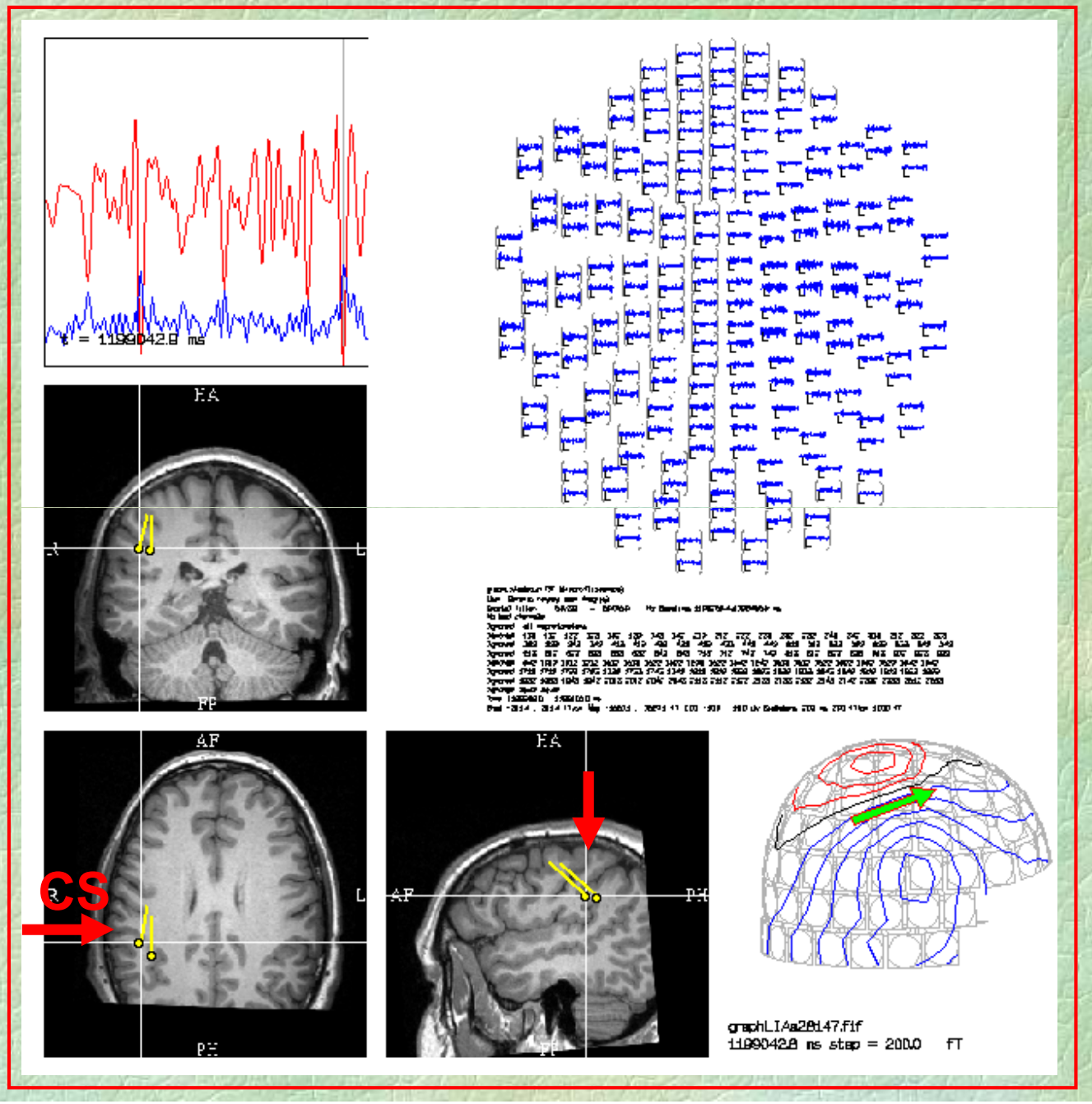
Dipole of #1-2 (late component): Right precentral gyrus



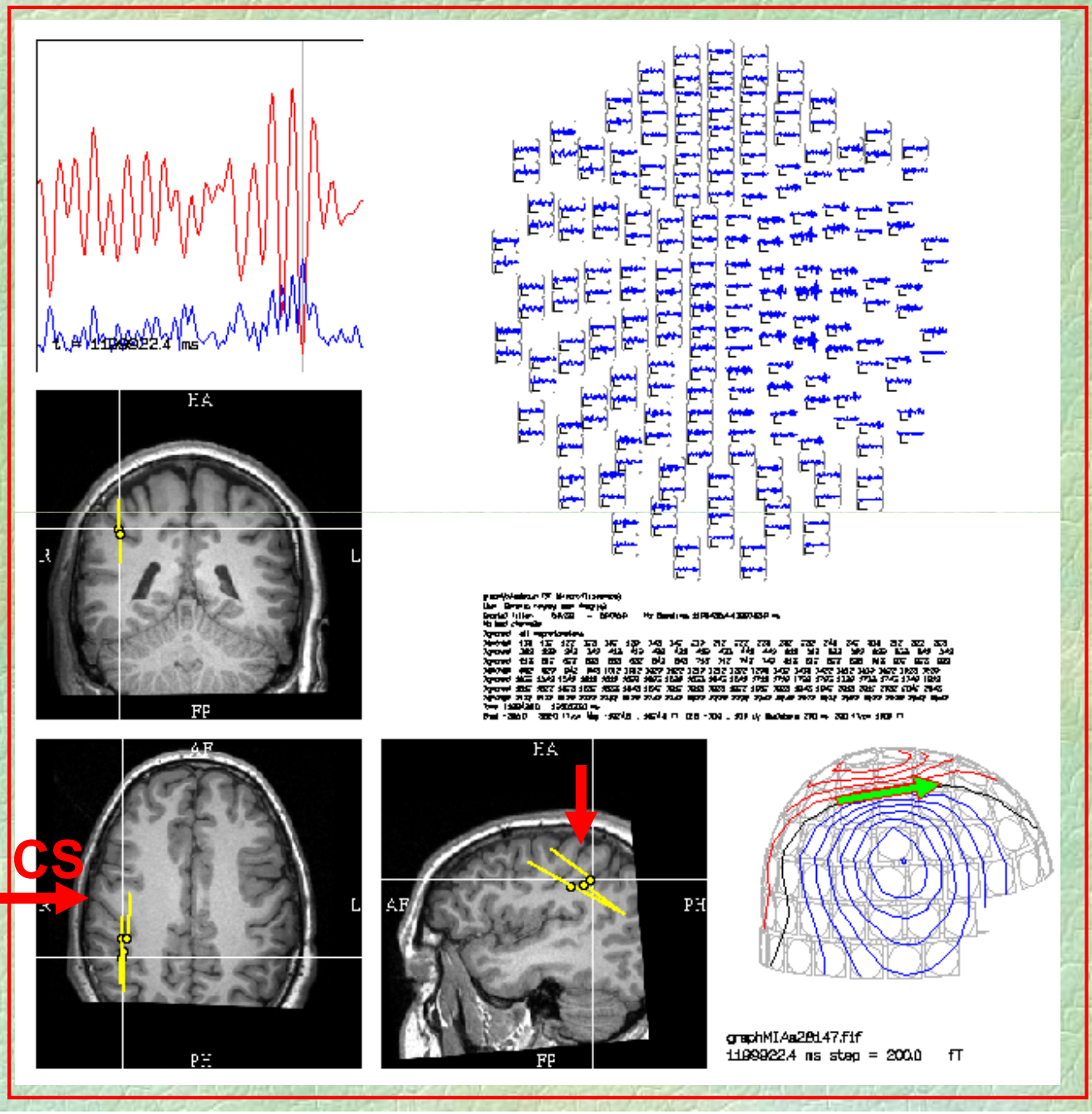
Dipole of #2 (3.3 sec after onset): Right precentral & parietal (unstable)



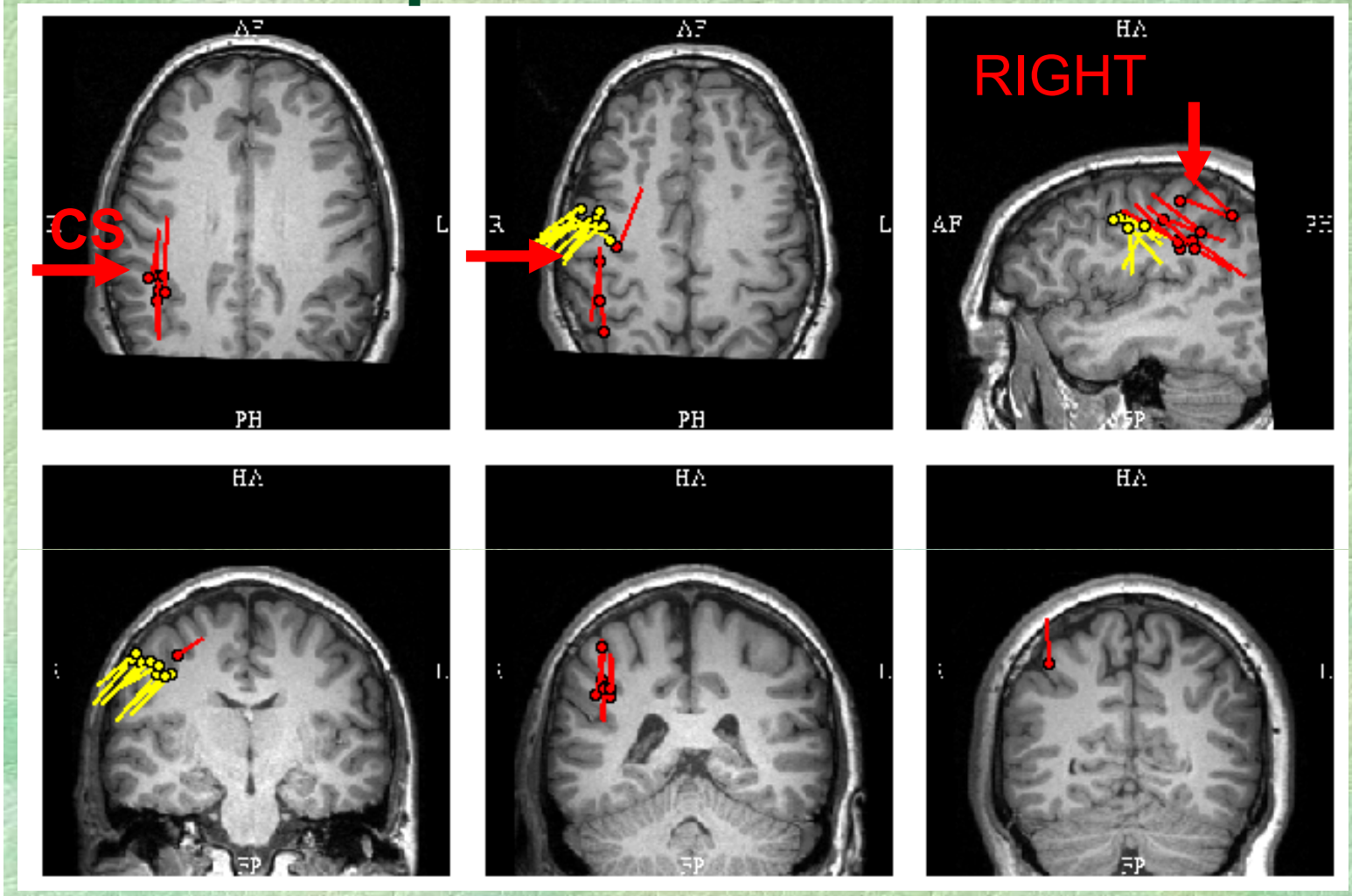
Dipole of #3 (3.9 sec after): Right postcentral (hand and face) (stable)



Dipole of #4 (5.2 sec after): Right postcentral (hand and face) (stable)



All ICTAL dipoles

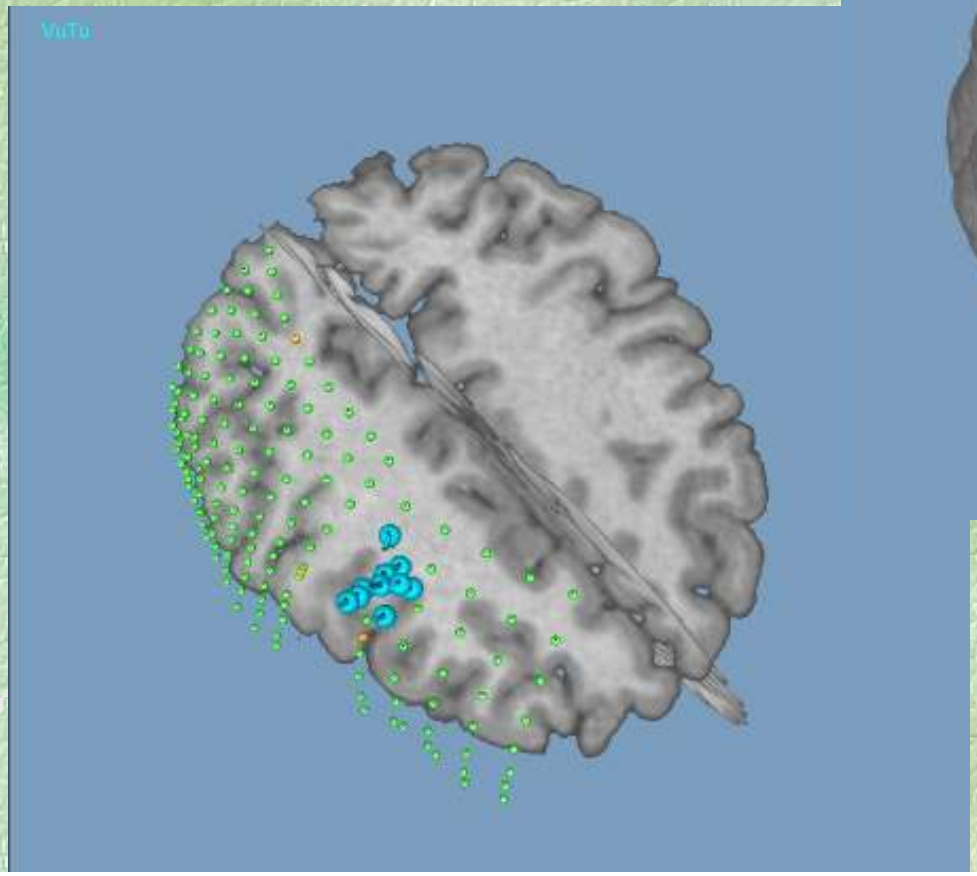


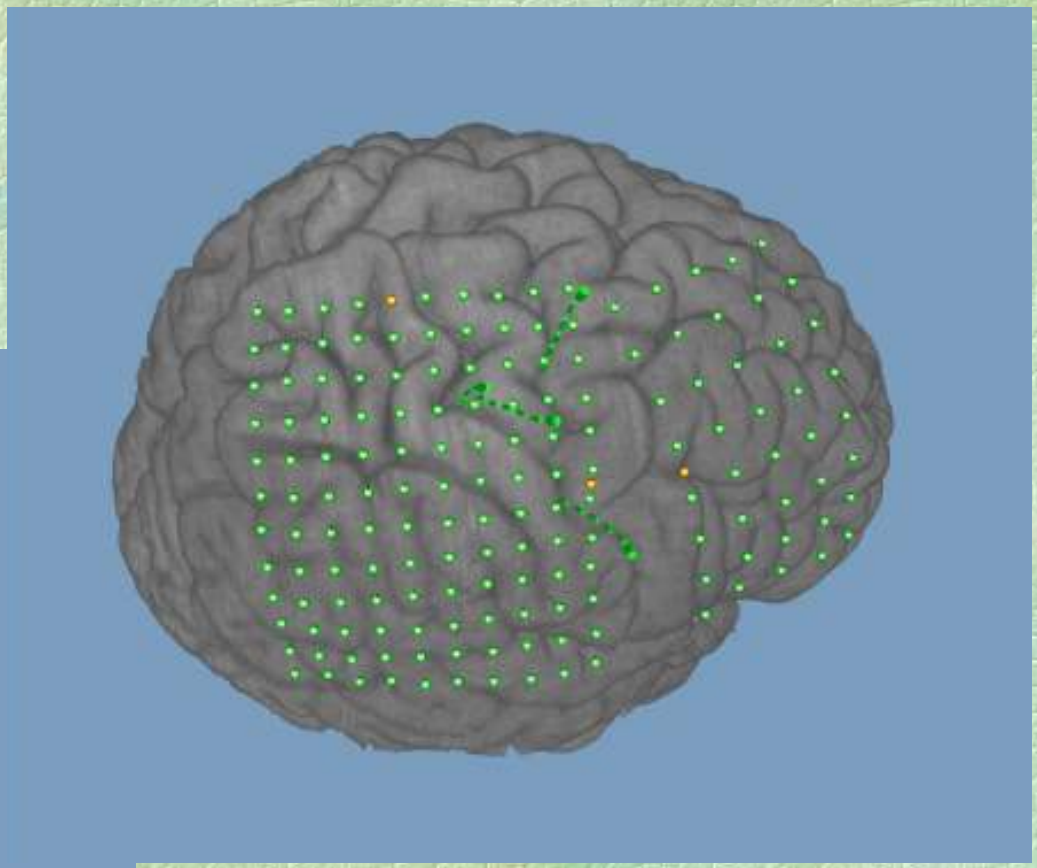
Clinical Sz
1 recorded

NCS Sz
Awake
10-50 sec
5 recorded
(2 dipoles ea

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





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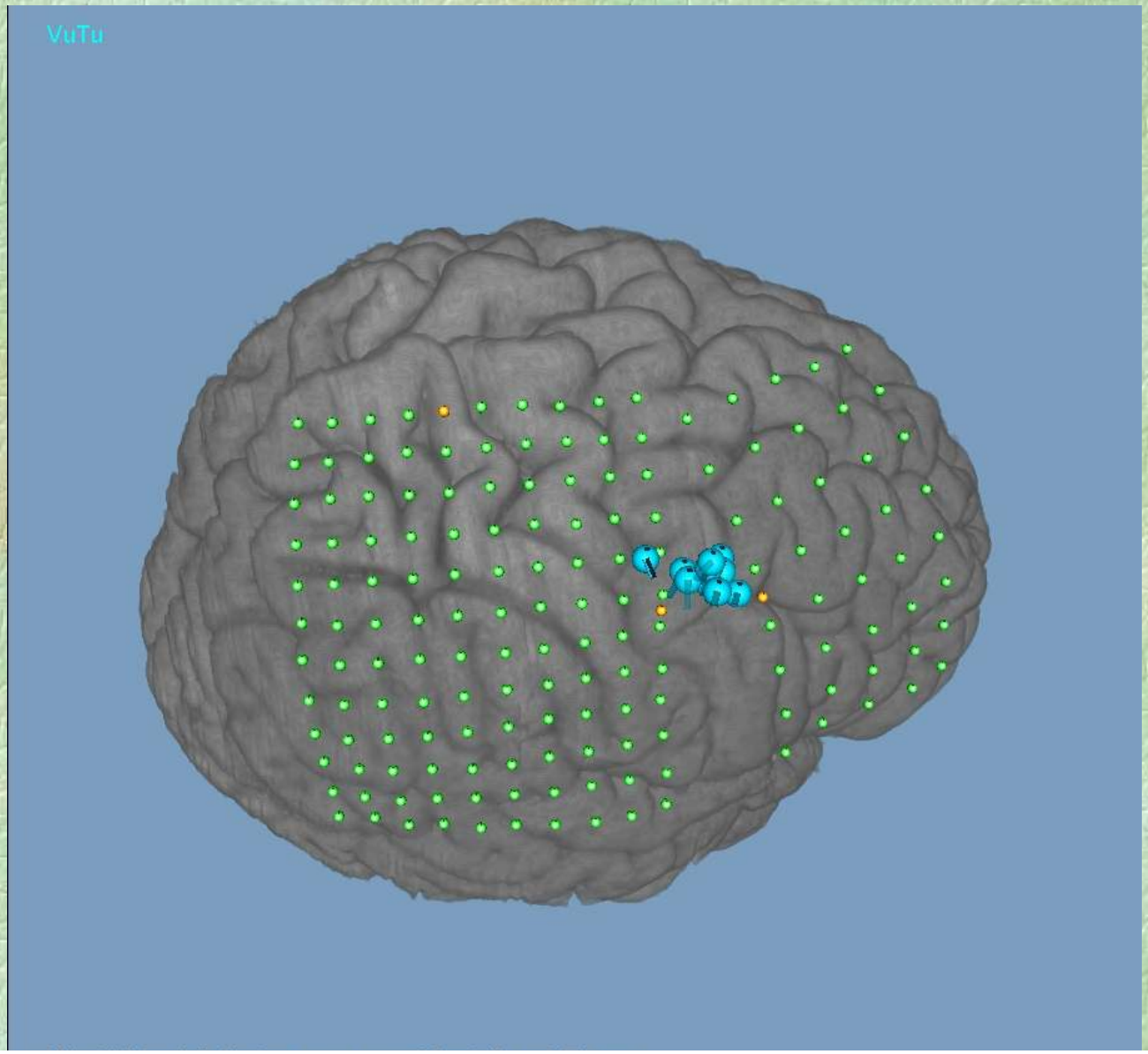
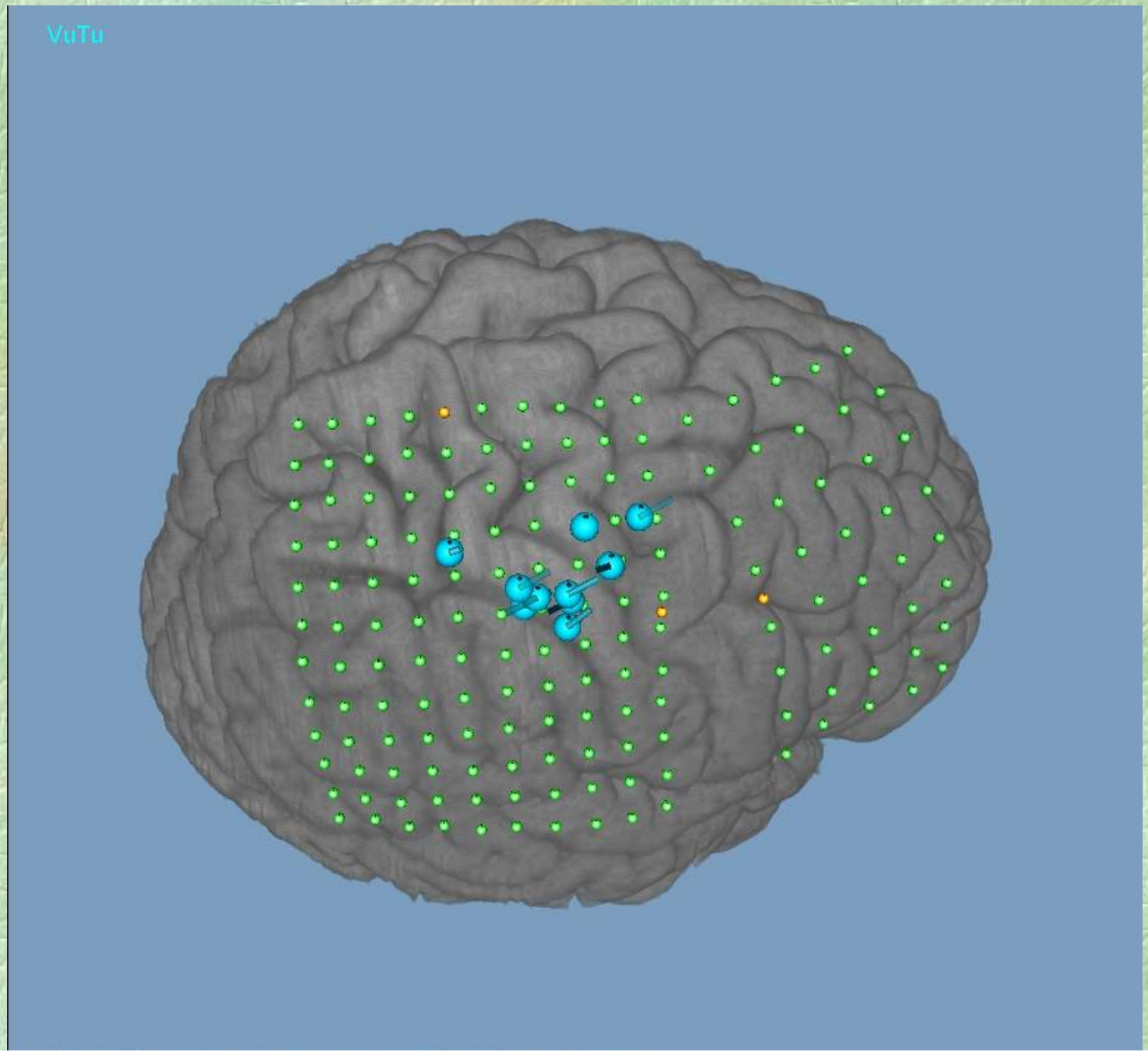
Dipoles of NCS Seizures



Dipoles of Clinical Seizures

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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

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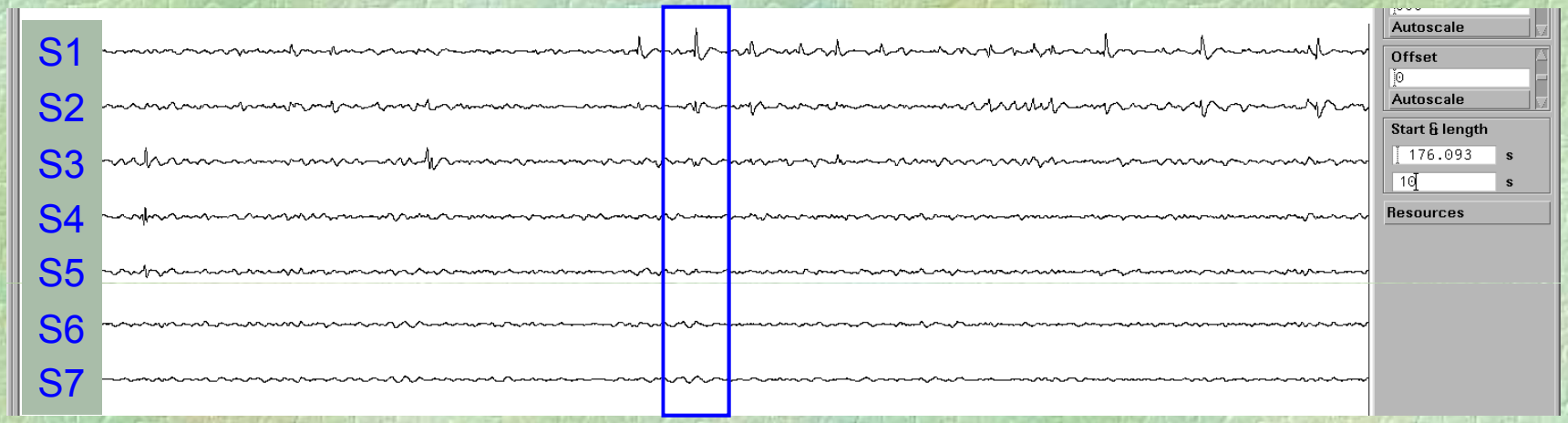
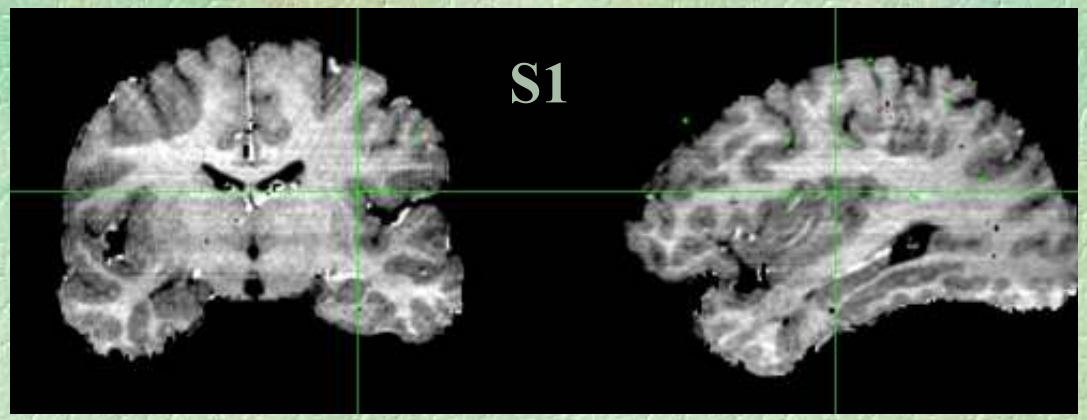
Simultaneous MEG and SEEG (Case 1)

SEEG





Depth of contact: Approx. **39** mm

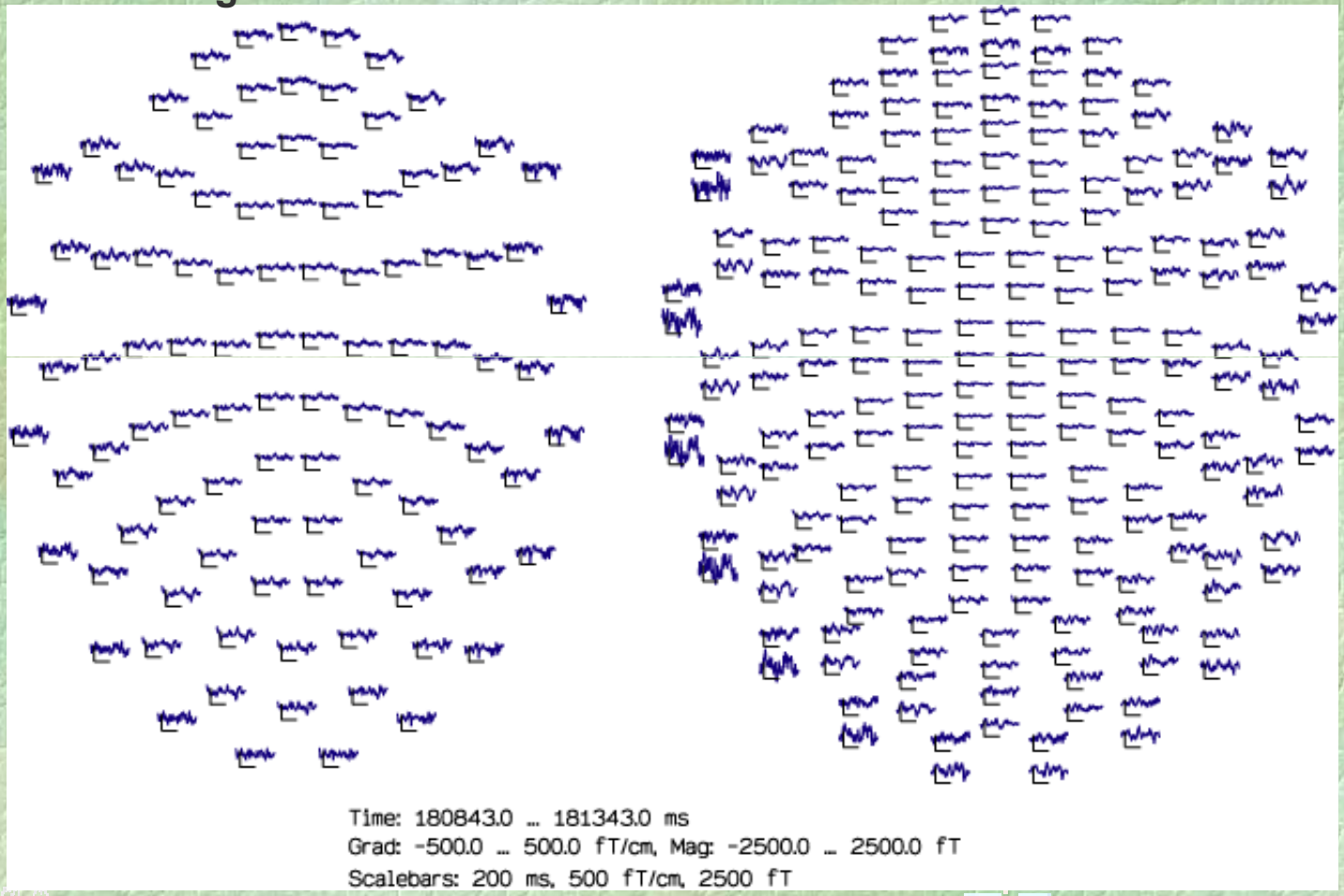
Max. Amplitude:
304.5 ± 137.0 uV (202.6 – 878.6)

Number of Contacts >200 uV:
1 contact (30 SPKs)
2 contacts (7 SPKs)

Simultaneous MEG and SEEG (Case 1)

Magnetometer

Gradiometer



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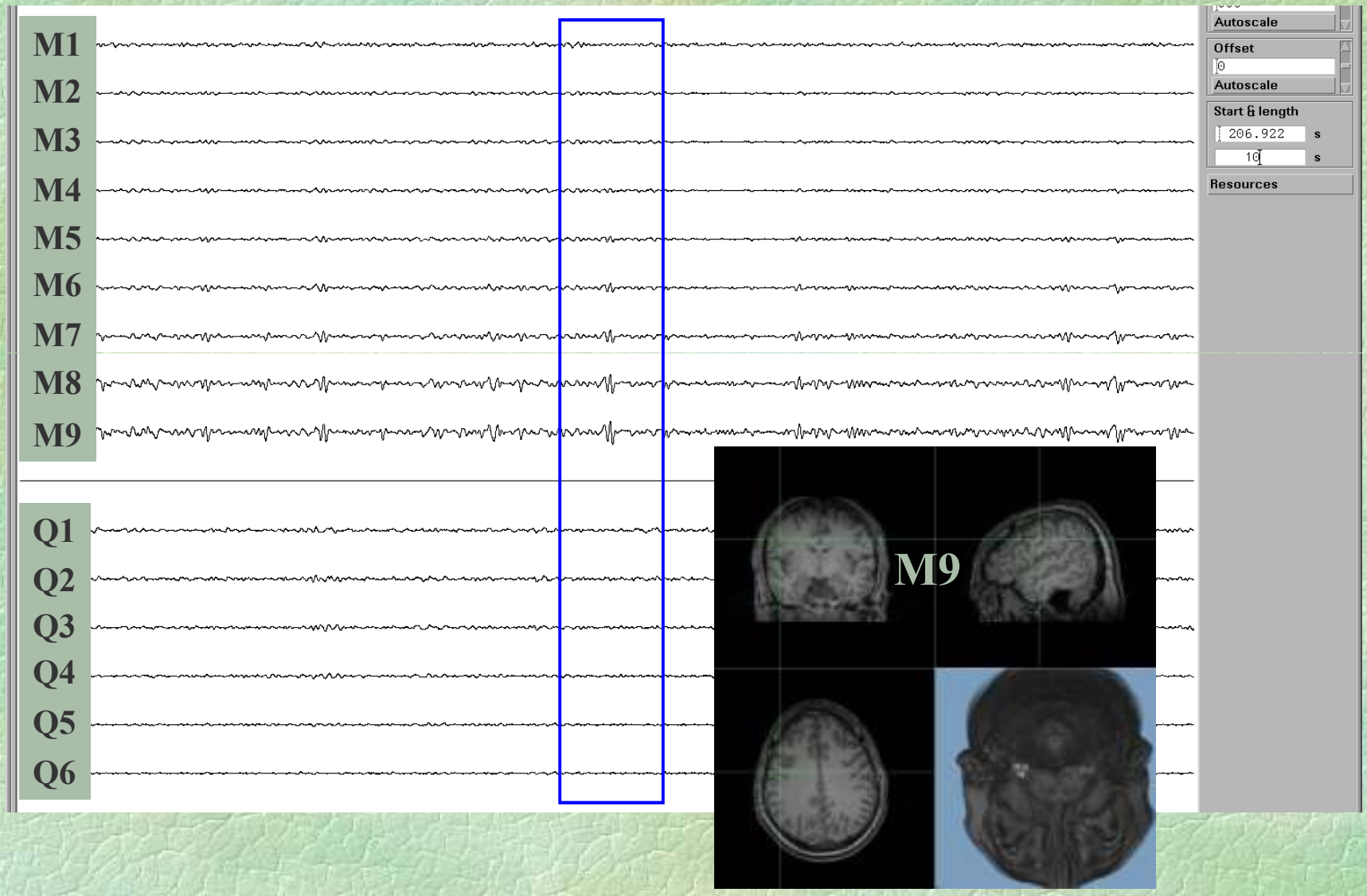
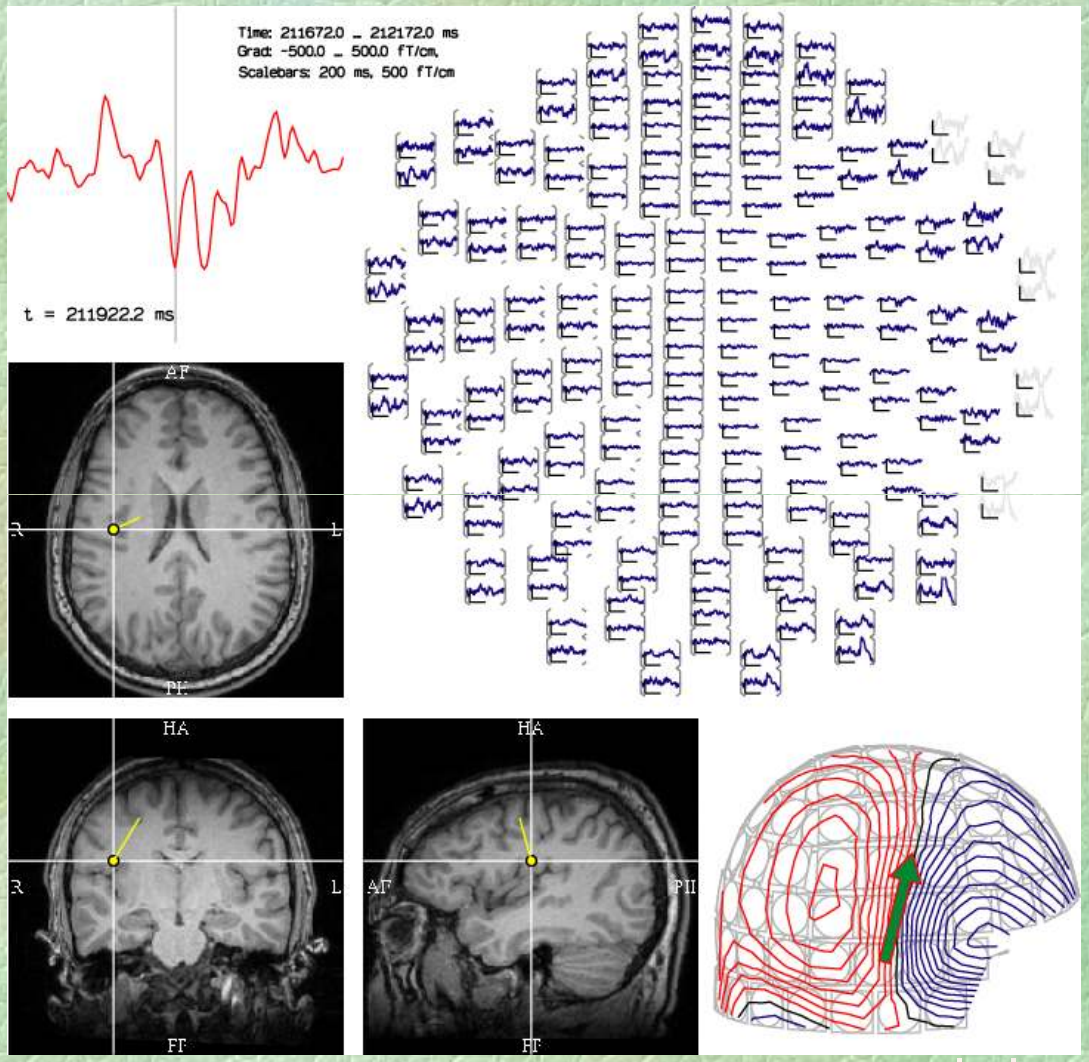
Simultaneous MEG and SEEG (Case 3)



Simultaneous MEG and SEEG (Case 3)



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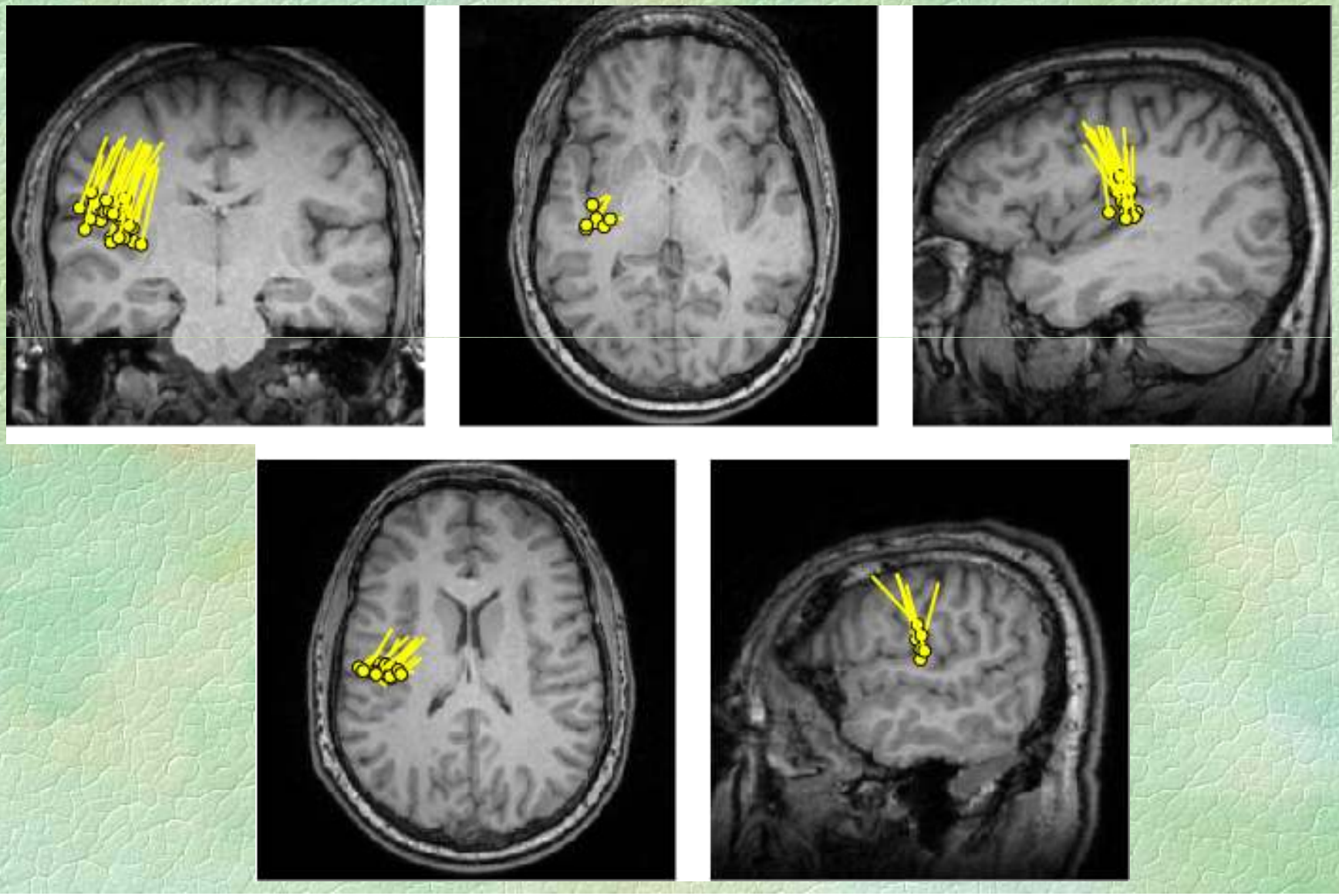
Simultaneous MEG and SEEG (Case 3)



Summary of 3 Cases

CASE	1	2	3
Depth of Contact (mm)	39	21	20
Average of Max. Amplitude (uV)	304.5	250.6	468.0
Number of Contacts >200 uV	1-2	1-2	1-4
Detectability (%)	0	0	66.0

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