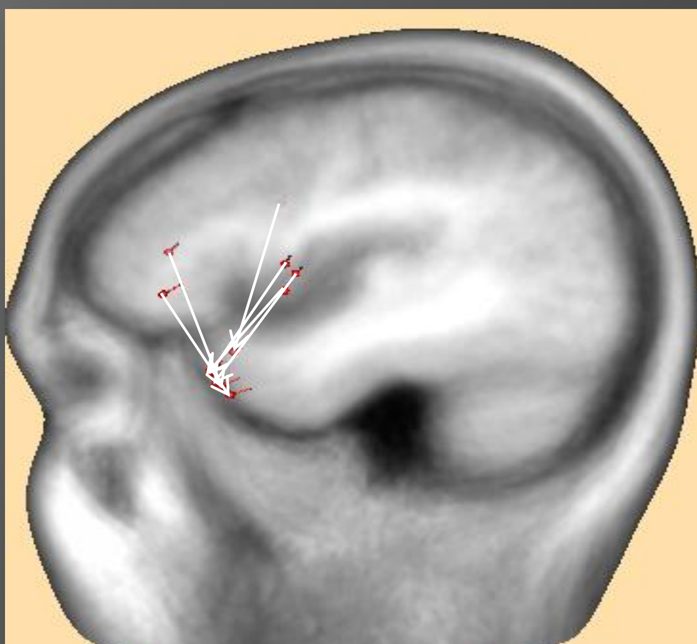
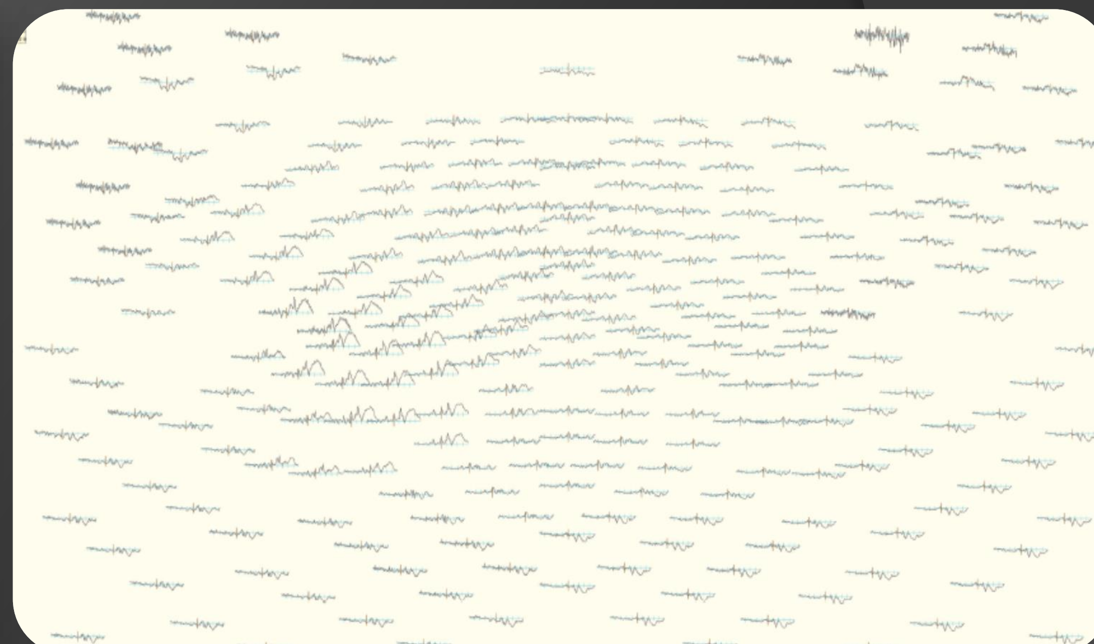
Chulalongkorn University
จุฬาลงกรณ์มหาวิทยาลัย
Pillar of the Kingdom

Chulalongkorn Comprehensive Epilepsy Centre

EEG source Localization (ESL): What do we know now ?





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JULY 24, 2014

Talk overview

- Theoretical background
- Fundamental of ESL (forward and inverse problems)
- Voltage topography of temporal spikes
- Improving source localization
- Dense array EEG (dEEG) and ESL

Introduction

- About 1/3 of patients are medically intractable

Kwan P and Brodie MJ; NEJM 2000

- Surgical resection of identifiable epileptic focus may be an option to help control seizure in some of these patients

Engel J Jr; NEJM 1996

- However, initial presurgical evaluation cannot disclose clear epileptic focus in some patients, particularly in MRI-negative focal epilepsy (MRN-E)

- Intracranial EEG recording (iEEG) as a gold standard is required to help delineate the potential epileptic focus
- However, considerable delay, expense, and possible morbidity are incurred if intracranial EEG monitoring becomes necessary
- Therefore, improving noninvasive investigations has thus become an area of increased interest

- Functional imaging techniques (PET, SPECT, fMRI) image *secondary phenomena*, such as blood flow or oxygen level, rather than measure epileptic brain activity directly

- None of these methods have sufficient temporal resolution to distinguish the origin of a spike or seizure from propagation

EEG source localization (ESL)

- The main advantage of *EEG and MEG* compared to other techniques for epileptic focus location is the *high temporal resolution*, which allows one to follow changes in the surface voltage distribution at a time scale of fractions of a second

- *Modern EEG interpretation* depends not only upon the identification of epileptiform potentials or rhythms but also upon their further analysis using *computer-based techniques*.

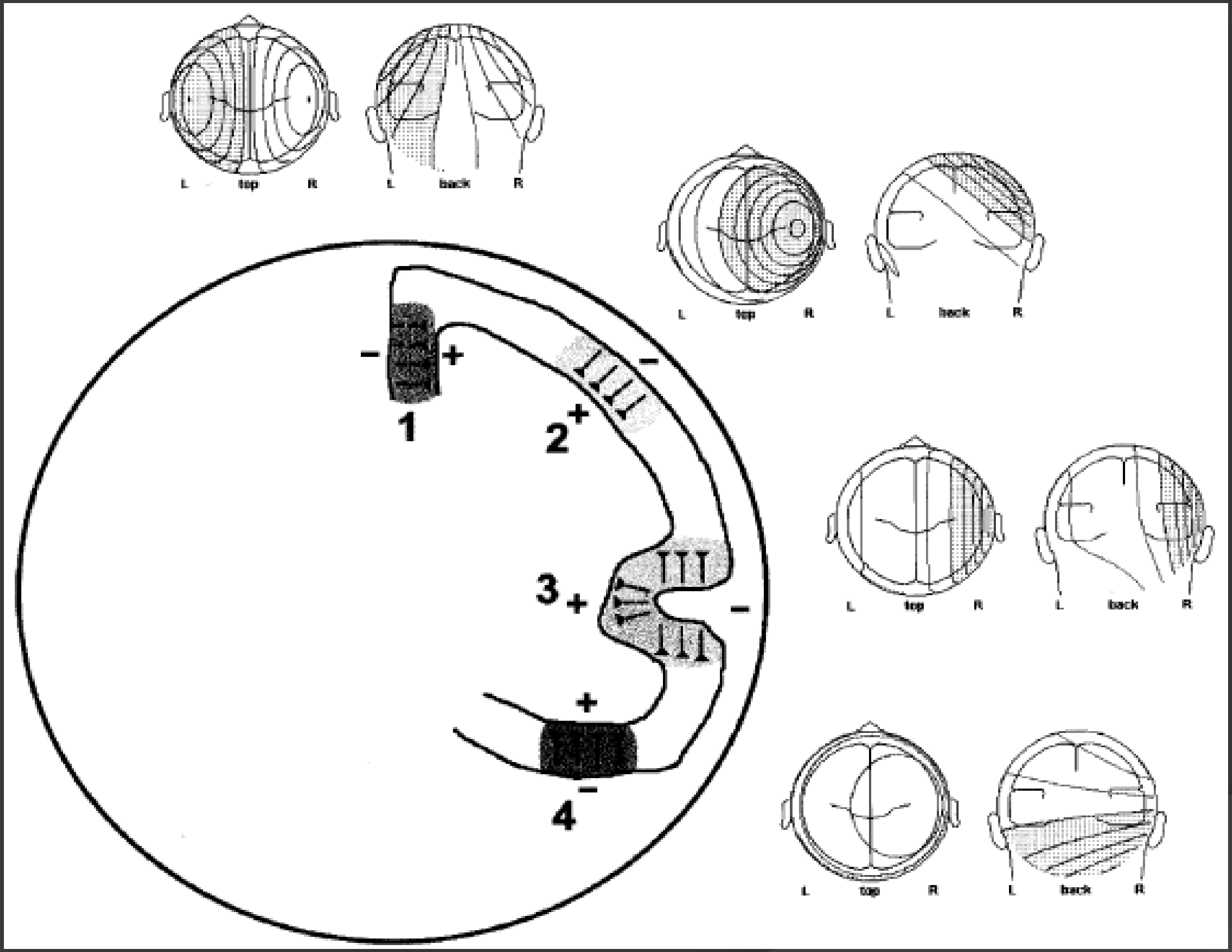
Theoretical background

- Epileptiform transients are usually negative when recorded from electrodes on or above the cortical surface.

- Electrodes on the other side of this active cortical layer, either in the underlying white matter or even the scalp opposite side of the head, record a positive potential

- Scalp EEG voltage fields therefore commonly have a *dipolar configuration*

Cortical EEG sources



Ebersole JS.; Epilepsia 2000

Cortical EEG sources

- Only *radial sources* produce a maximum directly above the generator
- Source *tangential* to the scalp produce little or no voltage directly above them
- In general, midline interhemispheric and basal cortical sources tend to be tangential; lateral convexity cortical sources tend to be radial

Ebersole JS.; Epilepsia 2000

Cortical EEG sources

- Sources on one bank of a sulcus in lateral cortex may be tangential; however, epileptiform sources are commonly so large that both banks of the sulcus are activated.

- These opposing fields cancel, leaving only the radial field from the sulcus bottom

Fundamental of ESL

Two fundamental problems exist in the practice of ESL

1) *Forward problem*

2) *Inverse problem*

Forward problem

- The forward problem is solved by specifying a set of conditions (compartments, surfaces, conductivities) for the head model, also referred as the volume conductor or forward model.

- Forward models range from *simple* (a single spherical shell models the brain surface) to *complex* (a four-layered realistic model, its compartments segmented from the patient’s MRI scan, models the brain, CSF, skull, and scalp surfaces)

- Two versions of forward modeling used in ESL today

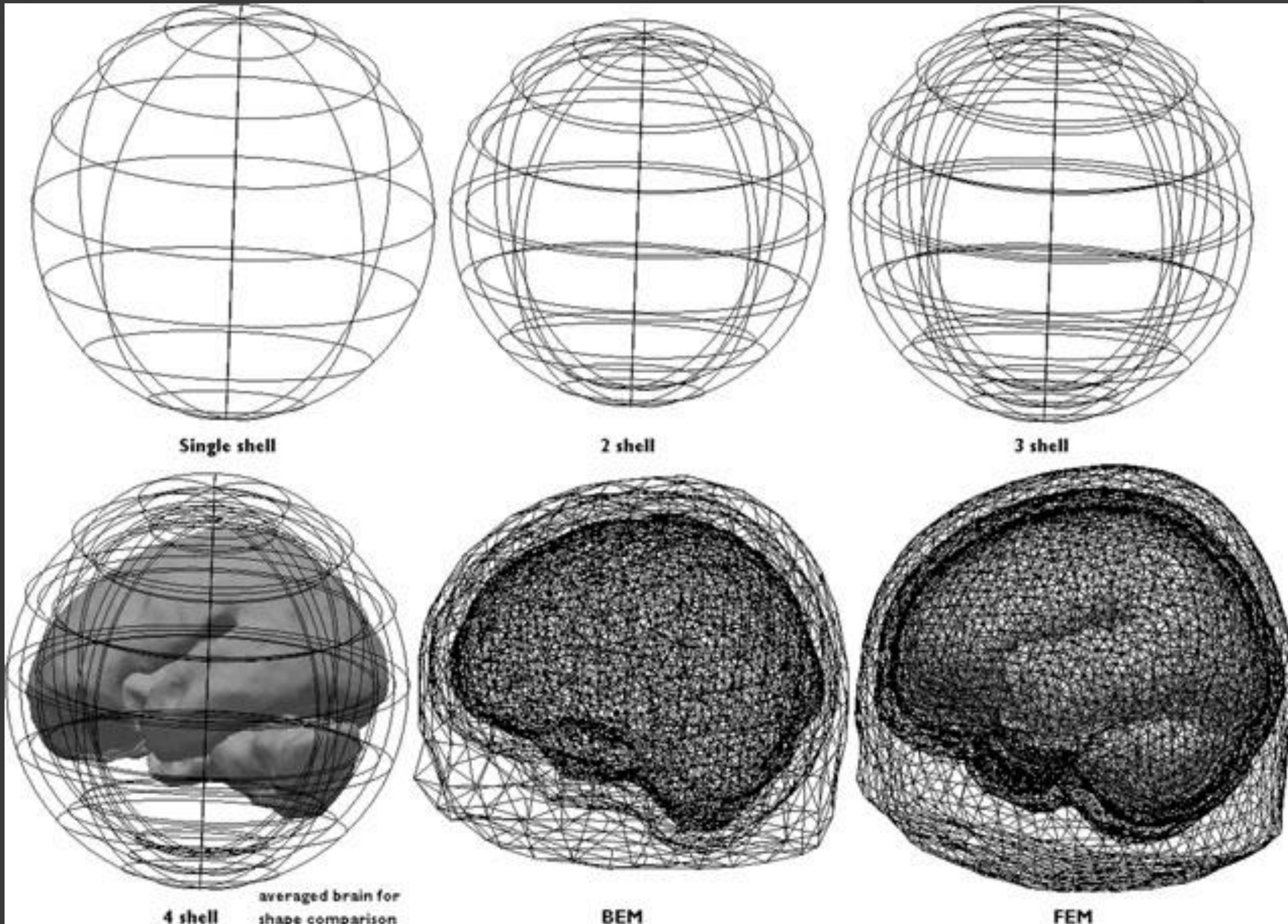
1) *Spherical shell models;*

range in complexity from one to four overlapping shell surfaces (Single shell, 2-shell, 3-shell, and 4-shell models)

2) *Realistic head models*; are subdivided into

Boundary element method (BEM)

Finite element method (FEM)


Single shell
2 shell
3 shell
4 shell
averaged brain for
shape comparison
BEM
FEM

Forward problem

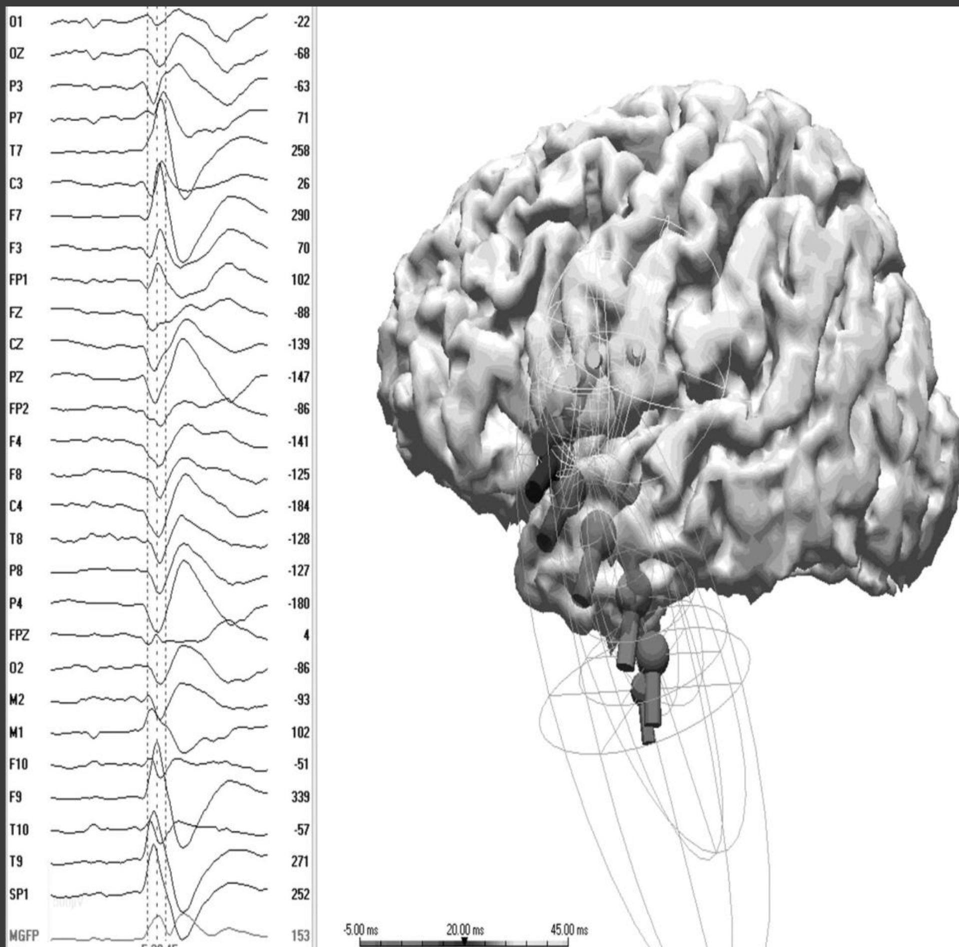
- There is little doubt that the modeling of basal source activity, as in temporal lobe epilepsy, is optimized with the use of *realistic head model* that more accurately delineate the nonspherical, *inferior aspects of the brain* compared to overlapping shell models

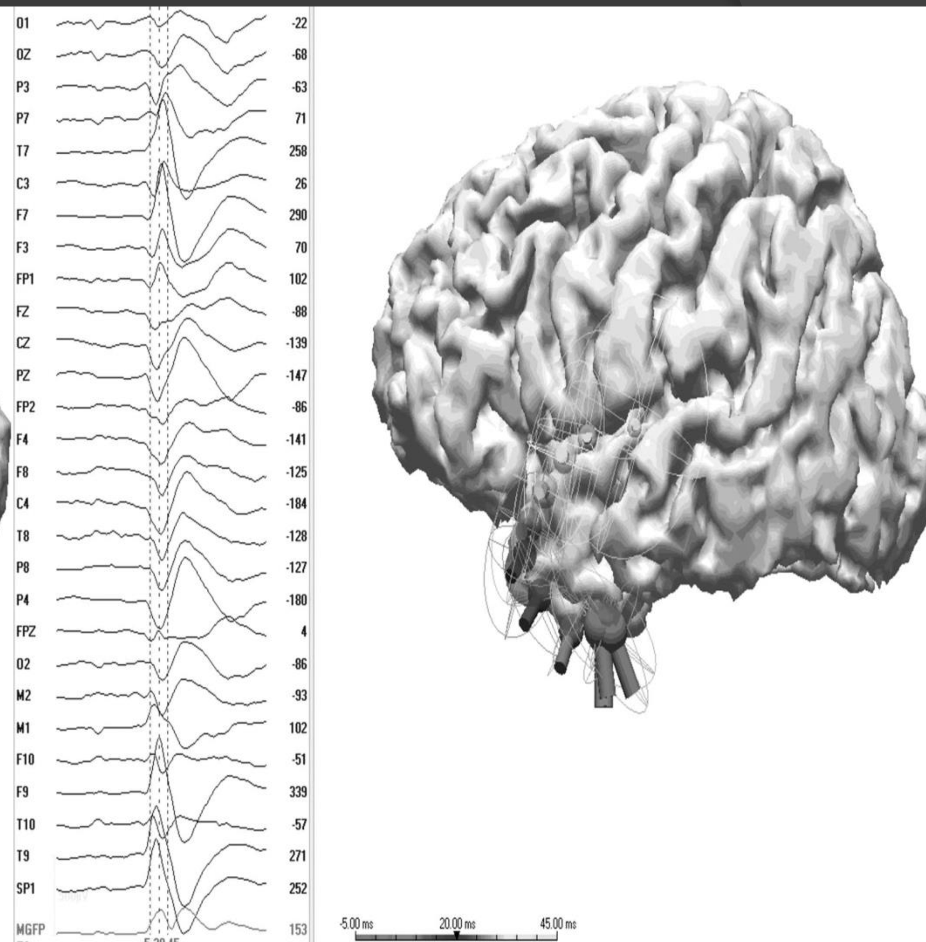
Ebersole JS.; J Clin Neuriphysiol 1997

- Spherical shell models commonly mislocalized known mesial temporal lobe source activity to frontal lobe

Cuffiin BN; IEEE Trans Biomed Eng 1996

Spherical model VS BEM Realistic head model in TLE



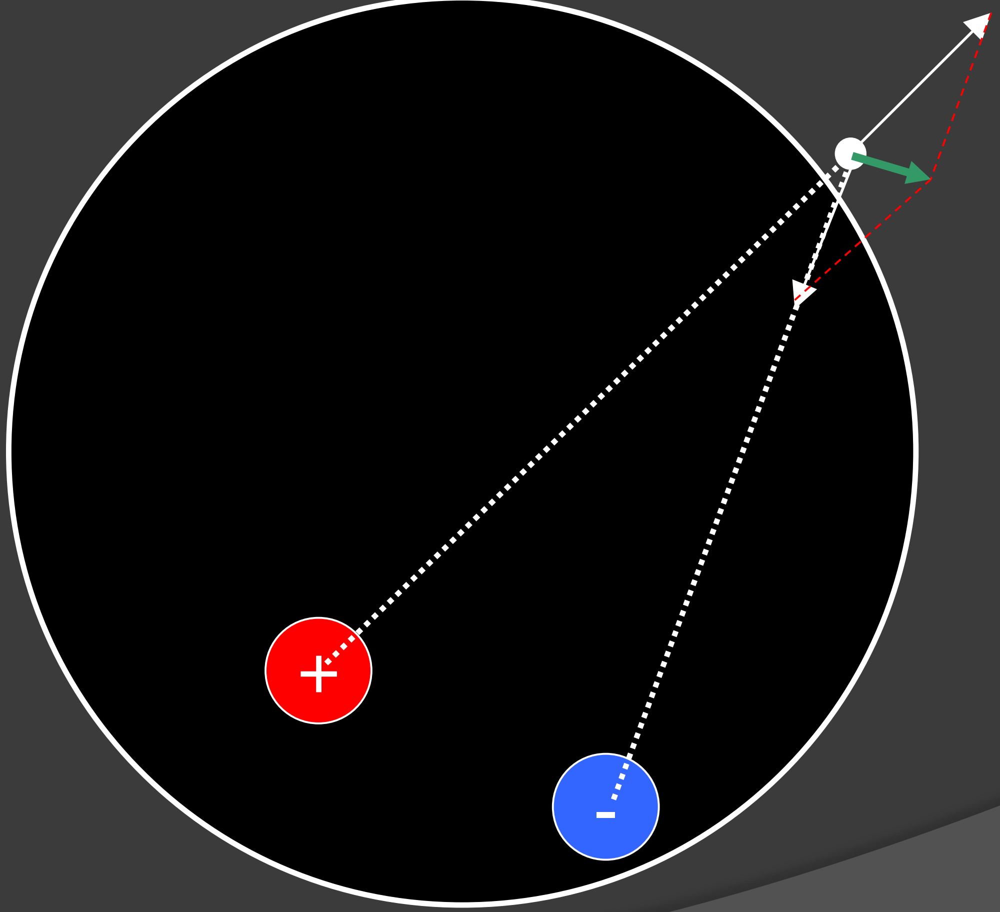


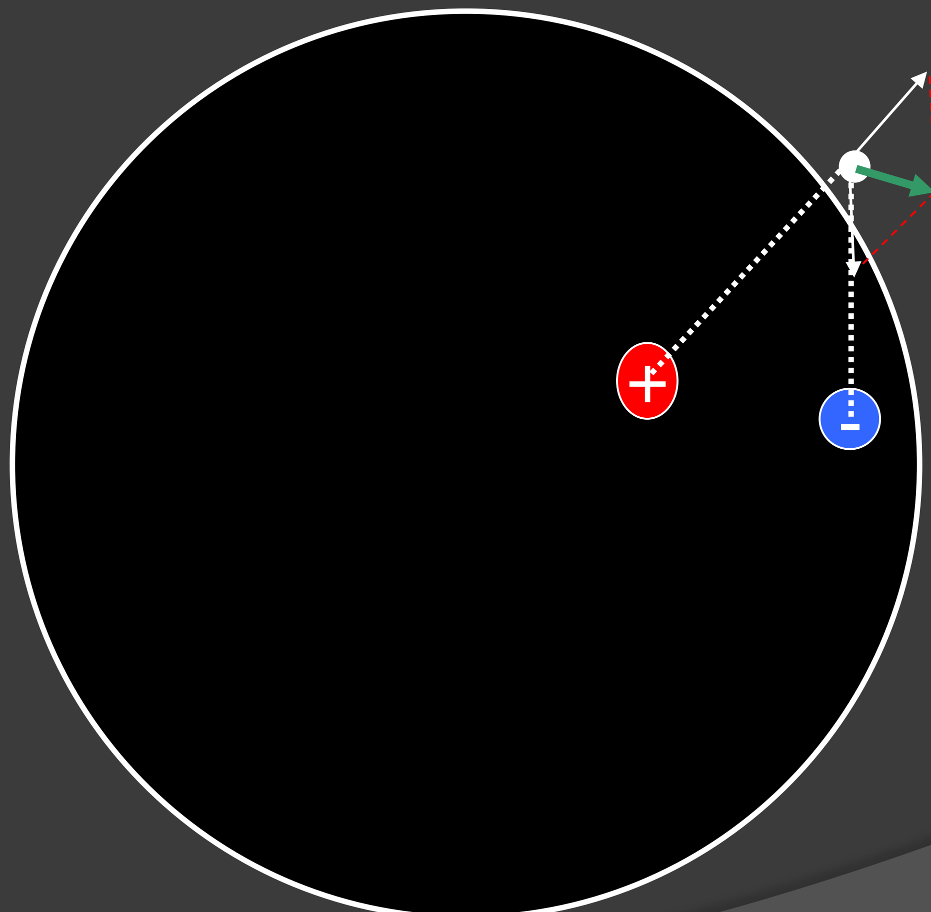
- *Spherical models* conform to *frontal and parietal brain convexities* reasonably well but are found wanting when it comes to the modeling of infero-occipital, infero- and mesial temporal, and orbitofrontal brain surfaces because brain cortex and skull departs most from a spherical shape

Ebersole JS.; *Current practice of clinical electroencephalography* 2003

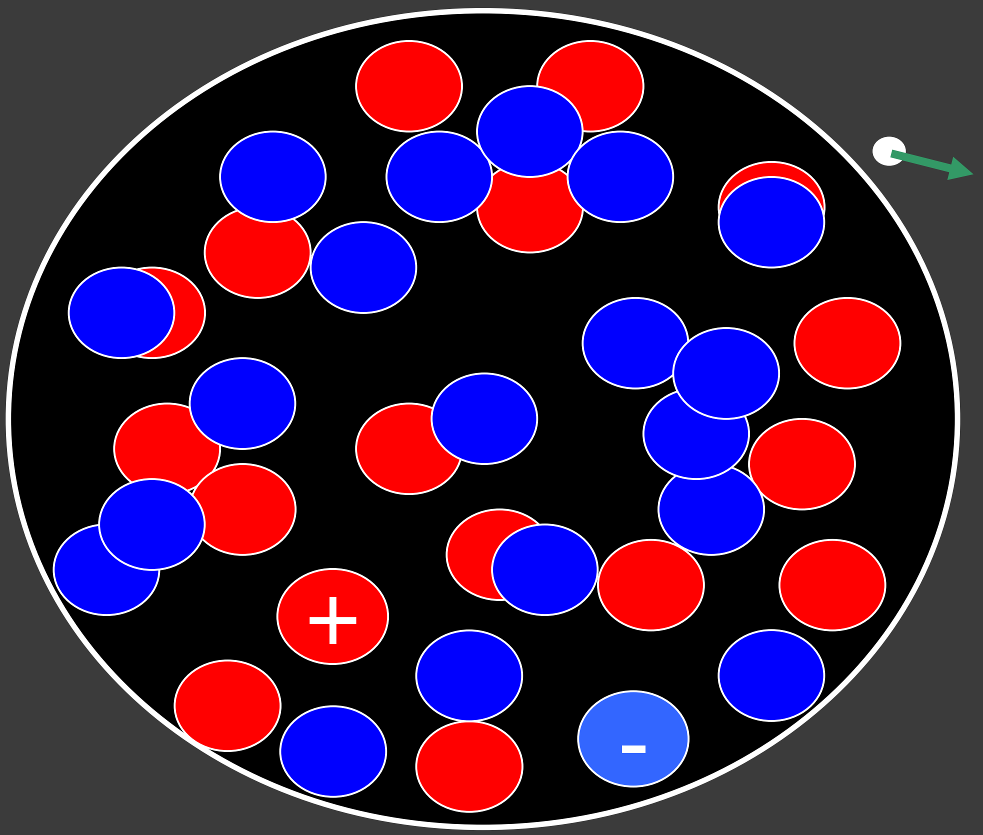
- Now the digital reconstruction of realistic forward models that predict the impact of volume conduction on the generation of scalp potentials remains a central theme in biophysics EEG research

Inverse problem

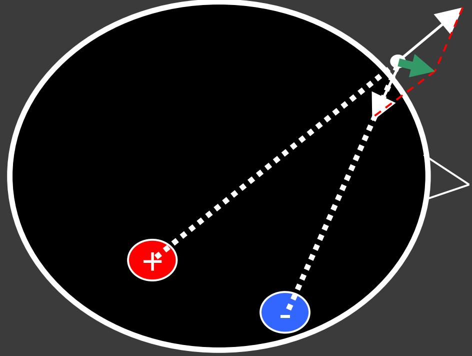


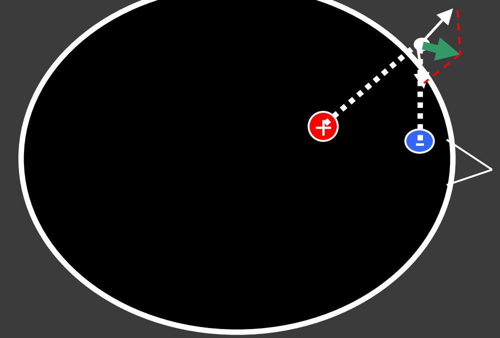


Any field potential vector could be consistent with an infinite number of possible dipoles



How do we know which one is <u>correct</u>?





We can't. There is no *correct* answer.

Source localization is an ILL-DEFINED PROBLEM

We can only see which one is ***better***

How can we get the best one (best-fit) ?

Inverse problem

- The inverse problem is made soluble by the incooperation of mathematical constraints into inverse modeling algorithms.
- Traditional EEG analysis by visual inspection is based on the inaccurate assumption that the cortical generator must underlie the scalp EEG field maximum

Inverse problem

- These models are more correctly on the assumption that it is the relative location of both voltage maxima and the contours of the voltage fields between them that convey information concerning *source location, orientation, and propagation*

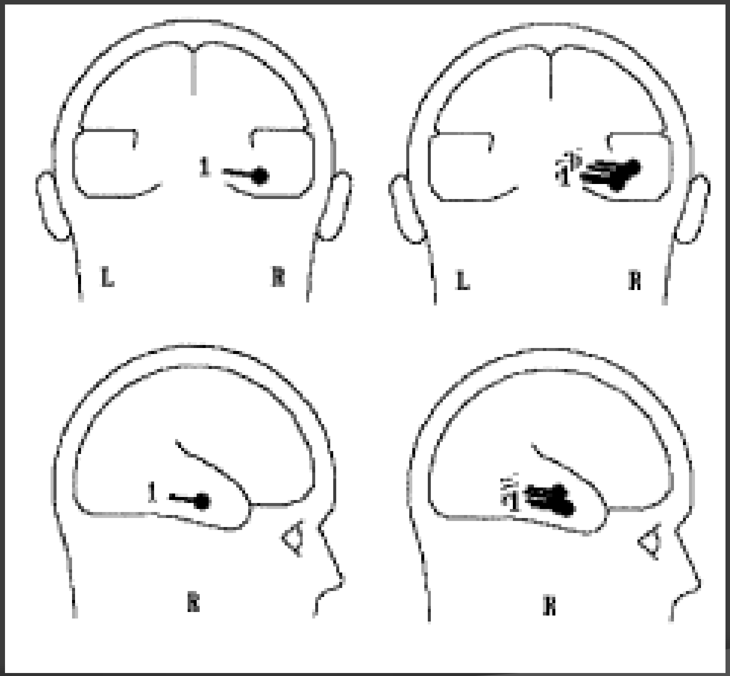
- The two major inverse modeling approaches are;

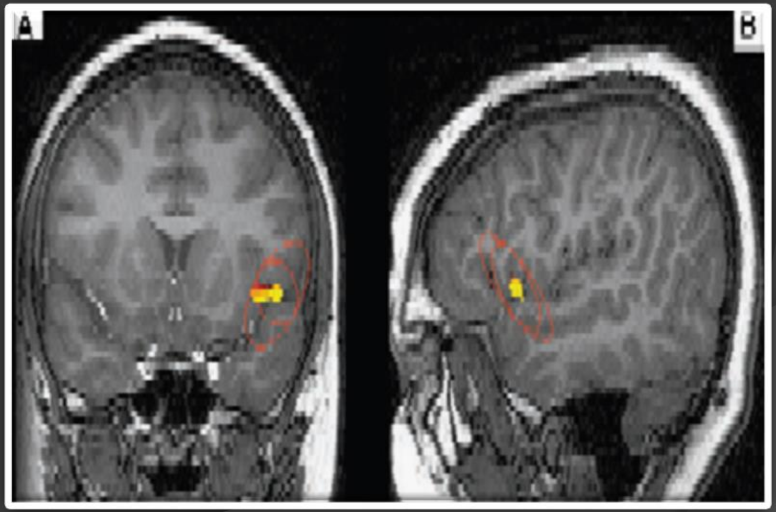
  1) *Dipolar modeling methods*

  2) *Distributed modeling methods*

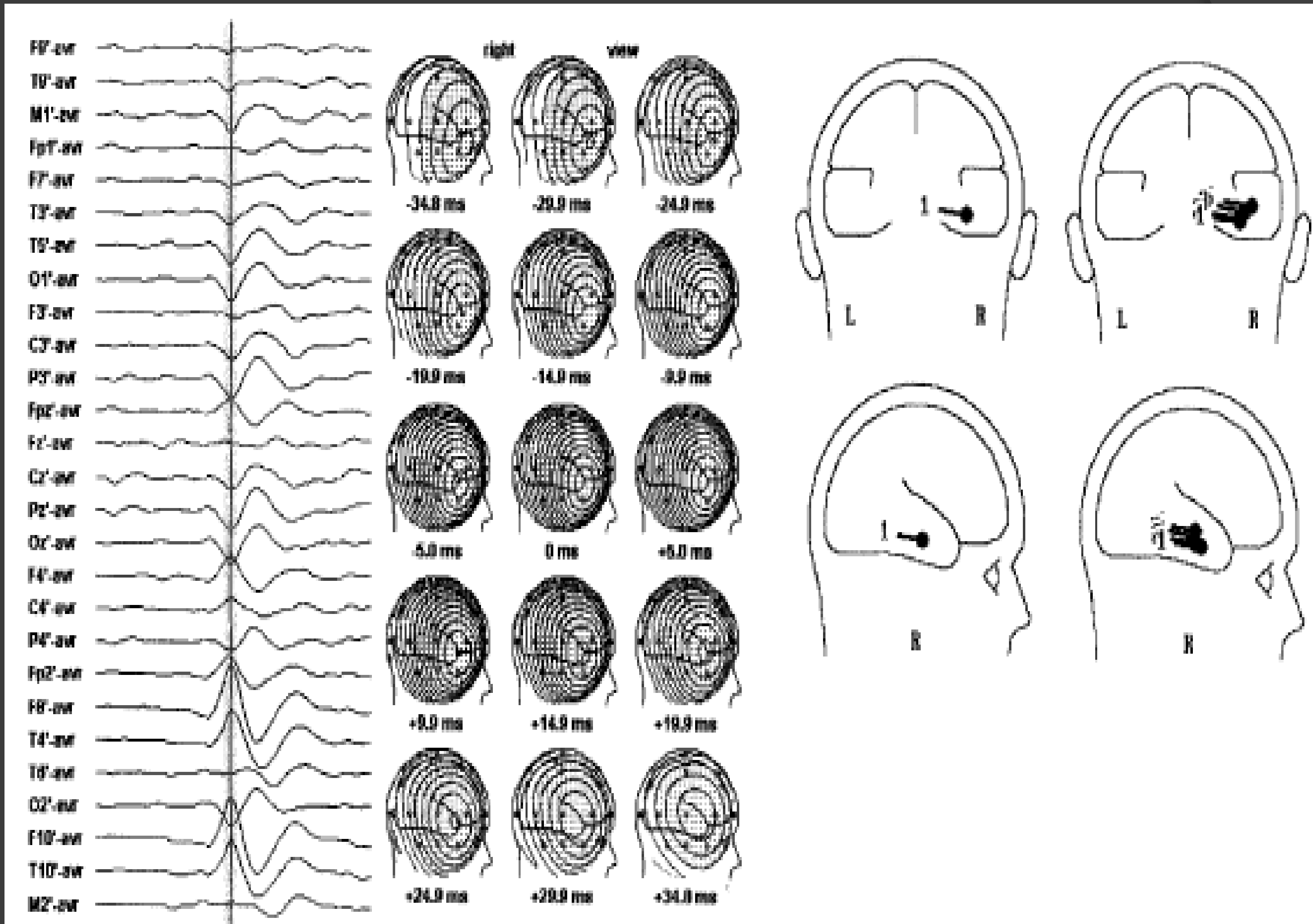
Dipolar modeling methods

- Dipole models provide point-like anatomical solutions for spike and seizure localization
- For spike or seizure voltage fields that are spatially stable over time, a *single instantaneous dipole model* is appropriate.





Ebersole JS.; J Clin Neurophysiol 2007



right
view
-34.8 ms
-29.9 ms
-24.9 ms
-19.9 ms
-14.9 ms
-9.9 ms
-5.0 ms
0 ms
+5.0 ms
+9.9 ms
+14.9 ms
+19.9 ms
+24.9 ms
+29.9 ms
+34.8 ms
L
R
L
R
R
R

Dipolar modeling methods

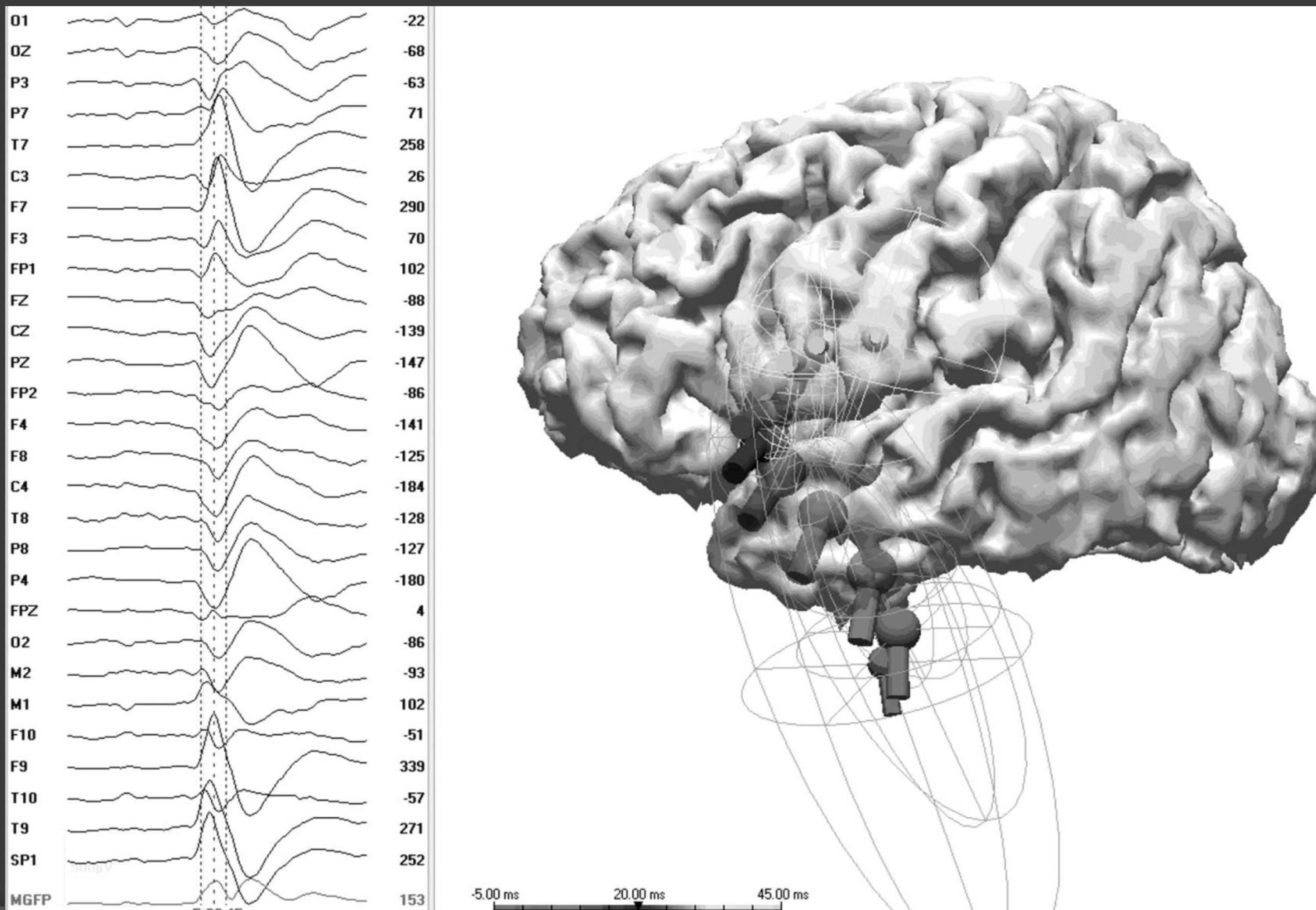
- In the case of spike or seizure fields with maxima that move in location or rotate, this model is inappropriate

- In dealing with more than a single equivalent dipole, there is no unique solution to the inverse problem

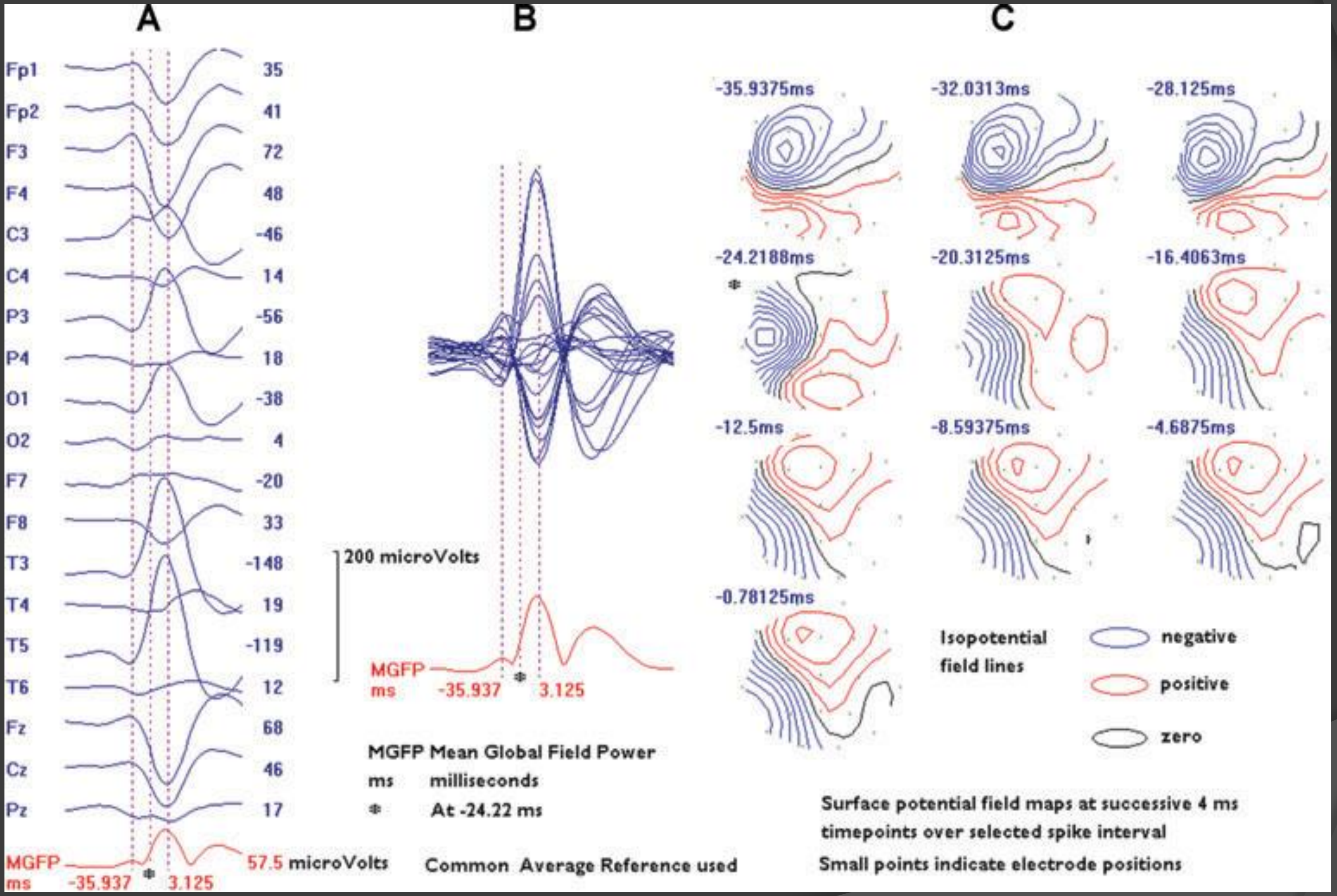
Dipolar modeling methods

- One of the solutions is *Moving dipole model*
- This moving dipole model may usefully reflect characteristics of spike or seizure propagation if the propagation is simple and unidirectional.

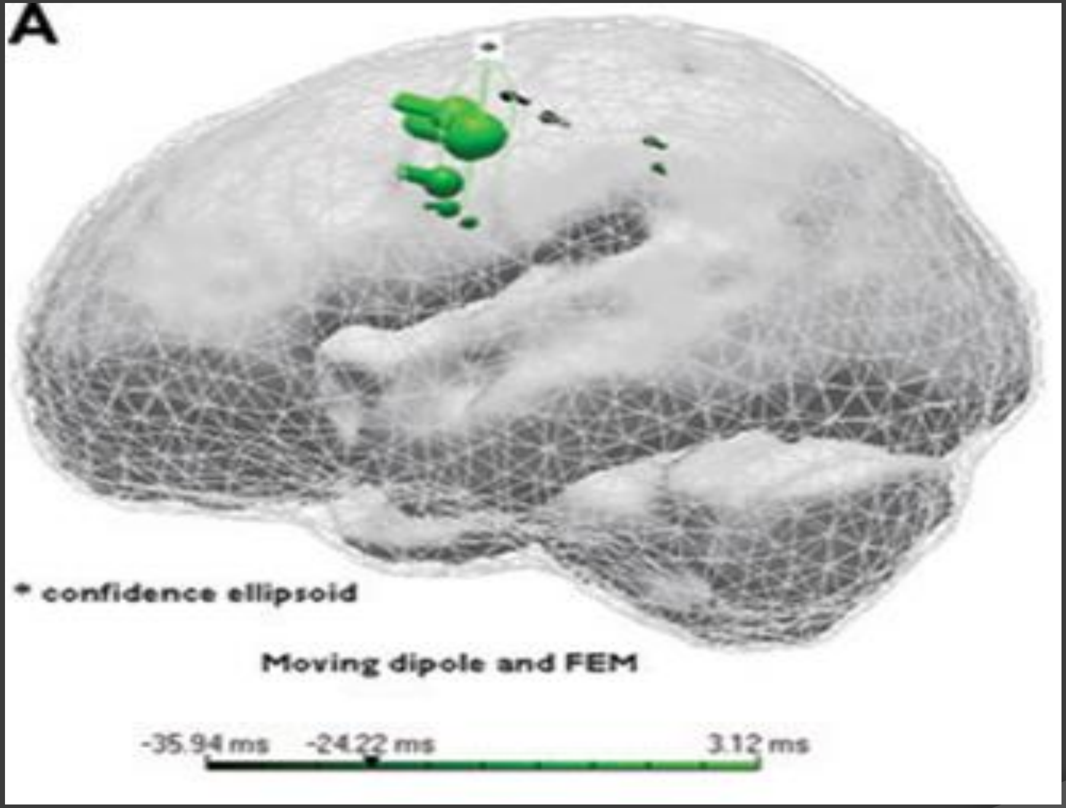
Moving dipole model



Benign focal epilepsy of childhood



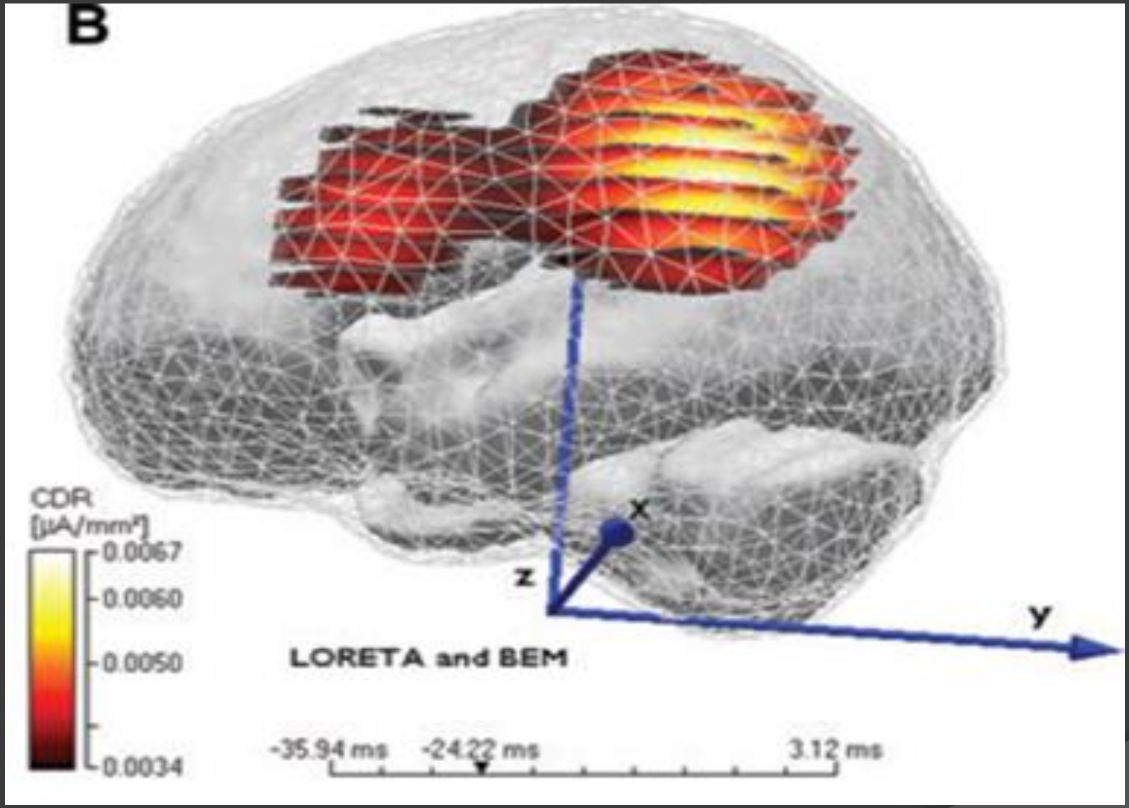
Benign focal epilepsy of childhood; Moving dipole inverse model



Distributed modeling methods

- For this method, no assumption is made on the number of dipoles used to solve the inverse problem.
- The working premise is that multiple sources may be simultaneously active across multiple locations at a given instant in time

Benign focal epilepsy of childhood; Distributed inverse model



Distributed inverse model

- Tends to generate broad, smoothed ESL solutions as neighborhood sources are model term conditioned to assume similar strenghts.
- Therefore, it is difficult to appreciate the relative timing of overlapping source components contributing to the modeled cortical activity across the early spike interval

Voltage topography of temporal spikes

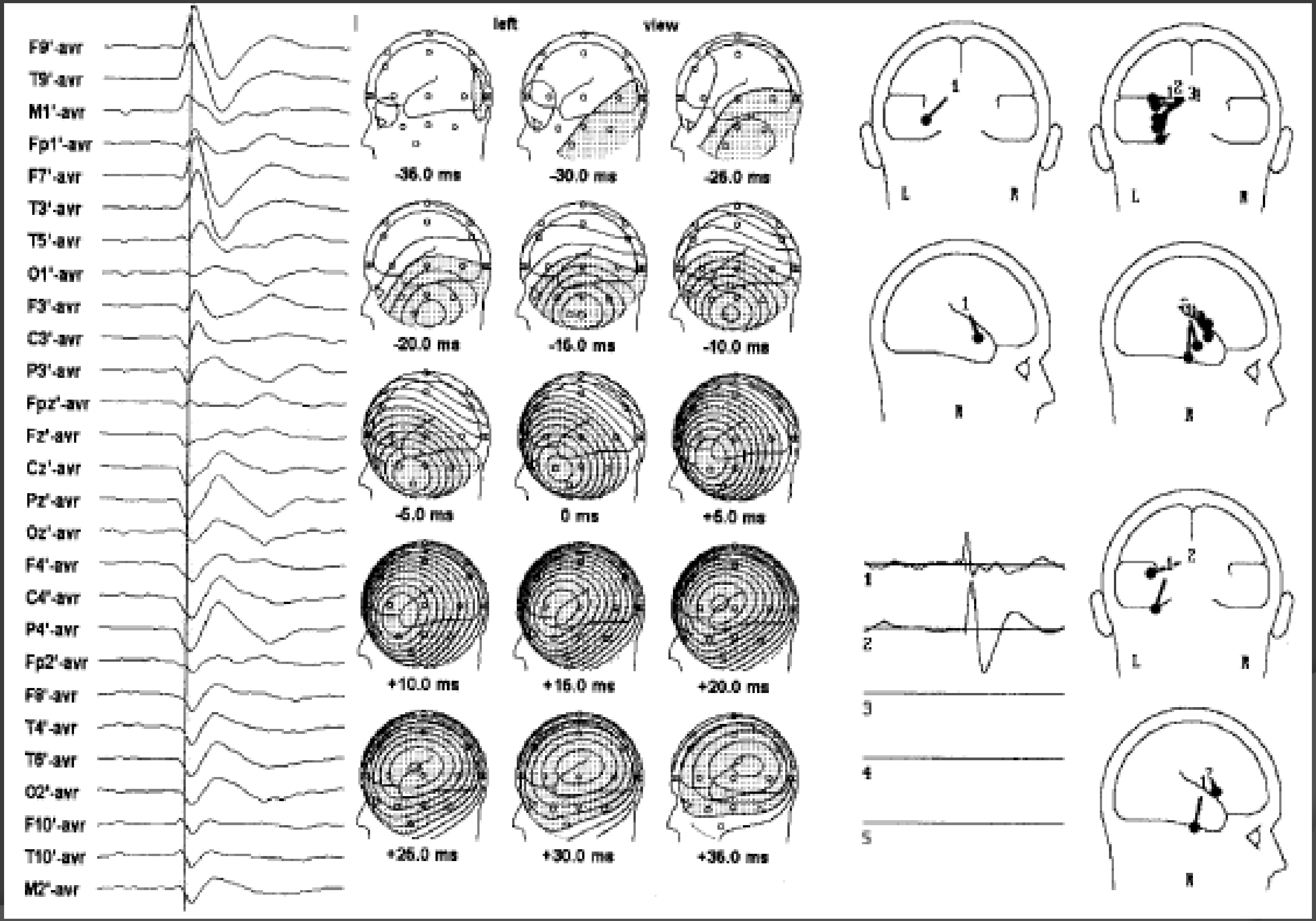
Voltage topography

- Ebersole JS et al. divided temporal spikes in 2 types

  Type 1 spike field
  : associated positive field maximum near the vertex
  : tended to have unilateral hippocampal atrophy
  : intracranial EEG seizures began in *mesial temporal structures*
  : increased likelihood of seizure elimination following standard anteromedial temporal resection

Ebersole JS and Wade PB; Neurology 1991

Type 1 spike field



Voltage topography

Type 2 spike field

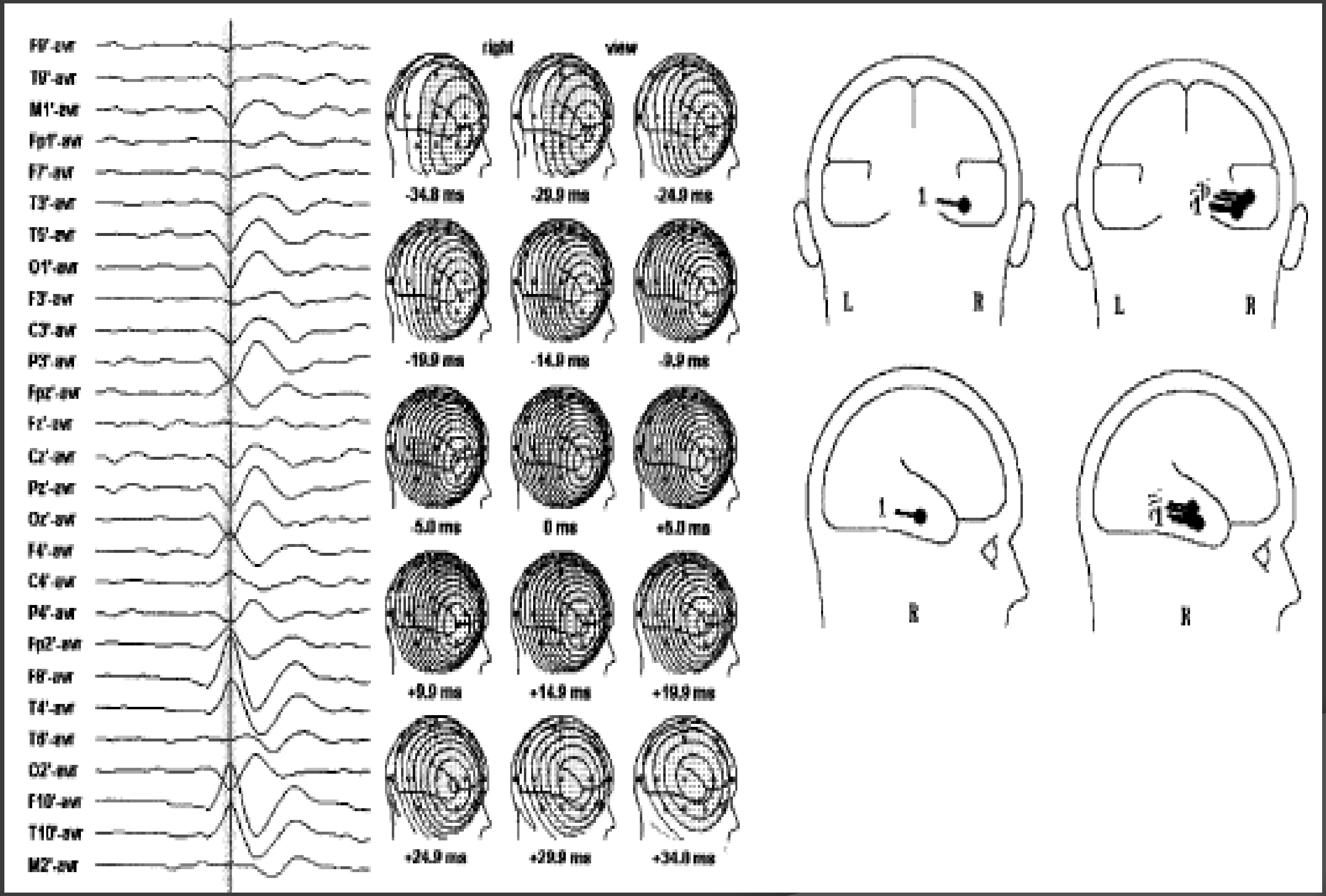
: associated positive field maximum at contralateral temporal area

: less like to have hippocampal atrophy

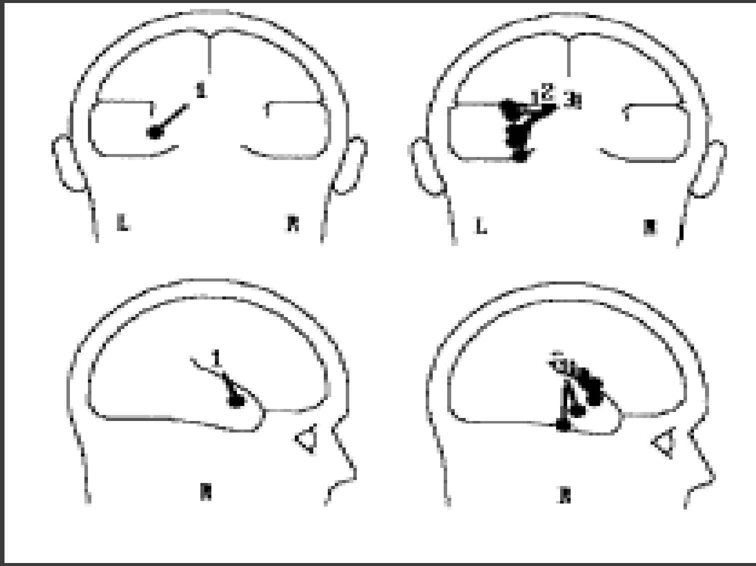
: intracranial EEG seizures originating from *nonmesial temporal structures*

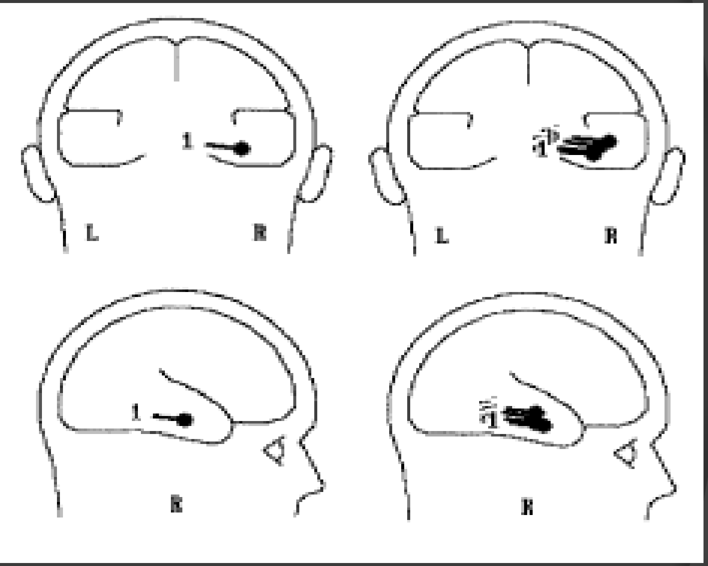
: less likely to be surgical successes

Type 2 spike field



Type 1 versus Type 2 spike





Type 1 spike

Type 2 spike

Mean dipole elevation 42º
(SD 5.0)

Mean dipole elevation 2º
(SD 10.0)

Type 1 versus Type 2 spike

Type 1 spike

- *vertical or oblique orientation*
- subtemporal negative field, vertex positive field maximum
- generated by *basal* and *inferolateral cortex*
- was not thought to reflect hippocampal or amygdalar activity directly. Rather, it was the common and preferred propagation of mesial structure epileptiform activity

Type 2 spike

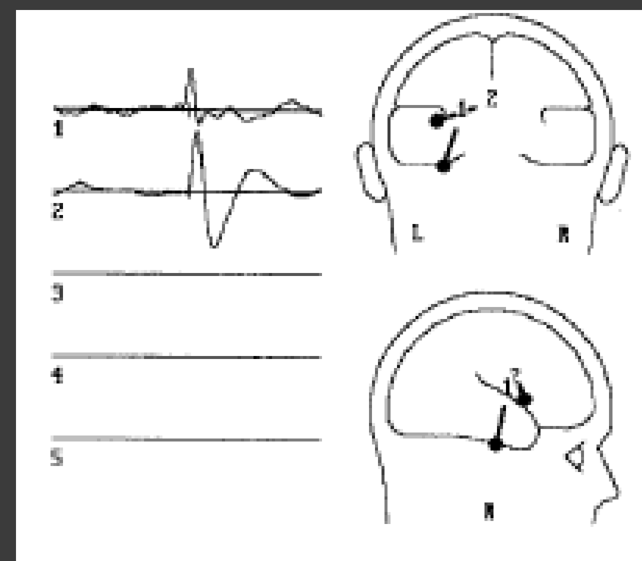
- *radial to the lateral skull convexity*
- lateral negative maximum, positive maximum over the contralateral temporal area
- generated by *lateral temporal cortex*

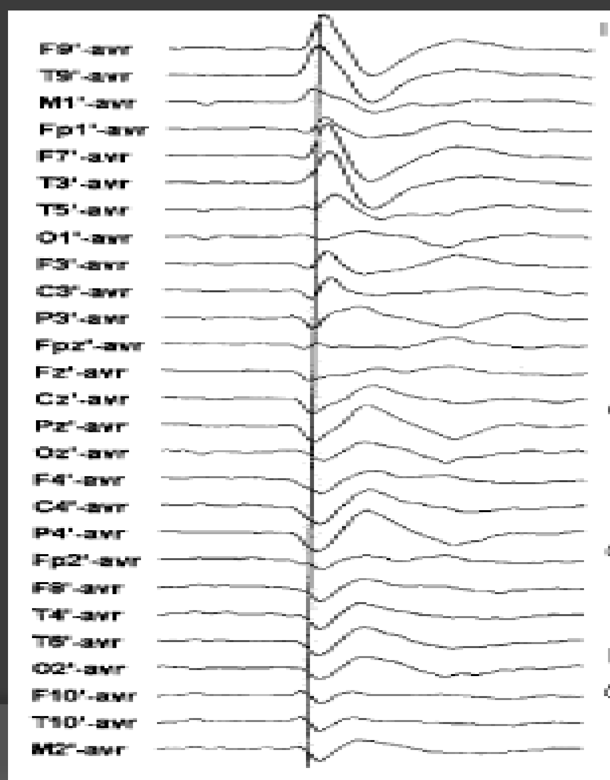
Modeling spike propagation

- Type 1 spike topography is the result of the superposition of fields from both sources when their activity overlaps in time

  1st dipole : vertical and tangential to the lateral skull convexity

  2nd dipole : horizontal and radial

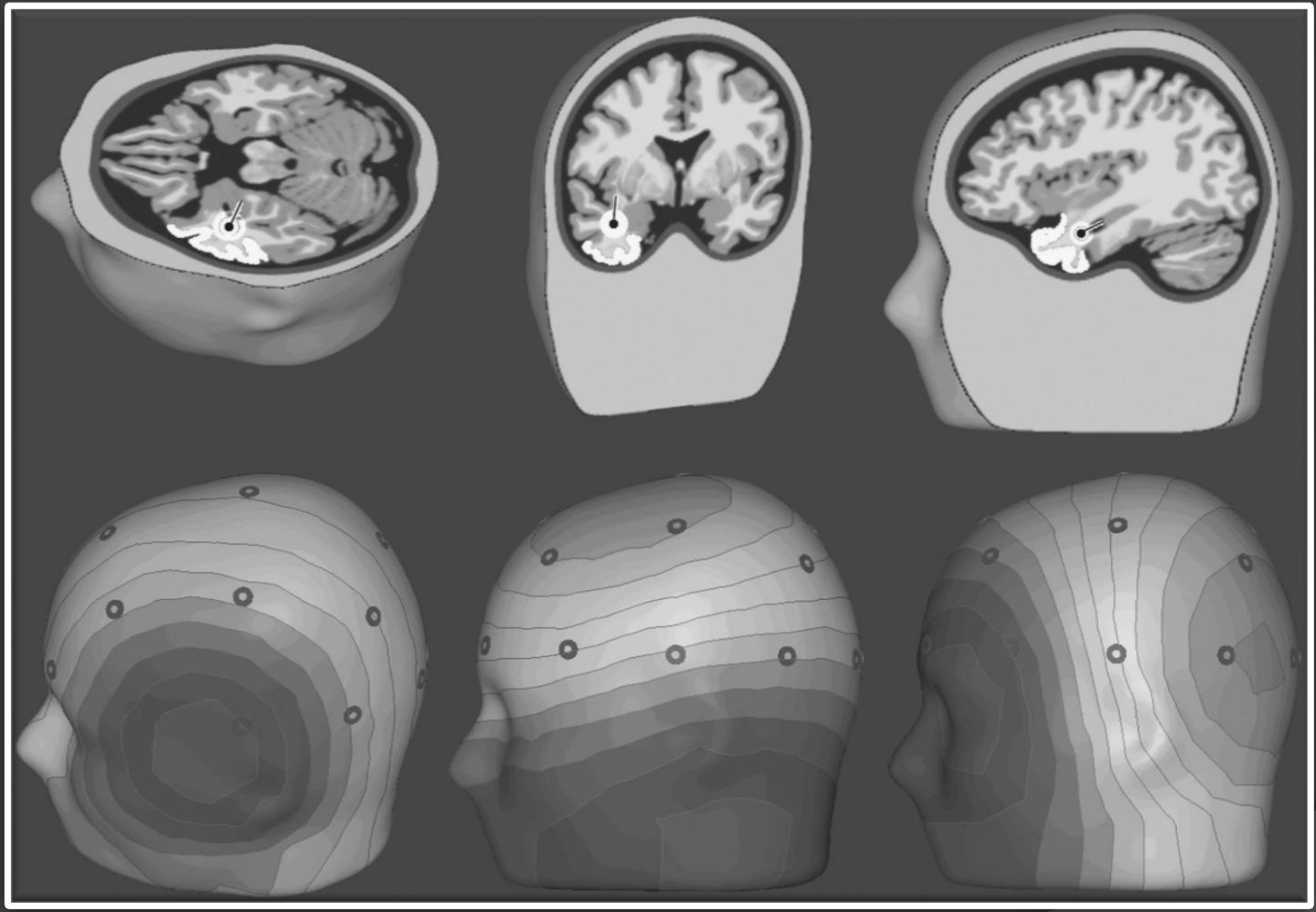




Basal → lateral cortex propagation

Modeling spike propagation

- Spikes that originate in *basal temporal cortex* may produce a similar voltage field. Alternatively, these spikes frequently propagate into *temporal tip cortex*.
- Temporal tip spike source result in a voltage field with *frontotemporal to frontopolar negative maximum* and *posterior positive maximum*



Signal-to-noise problem

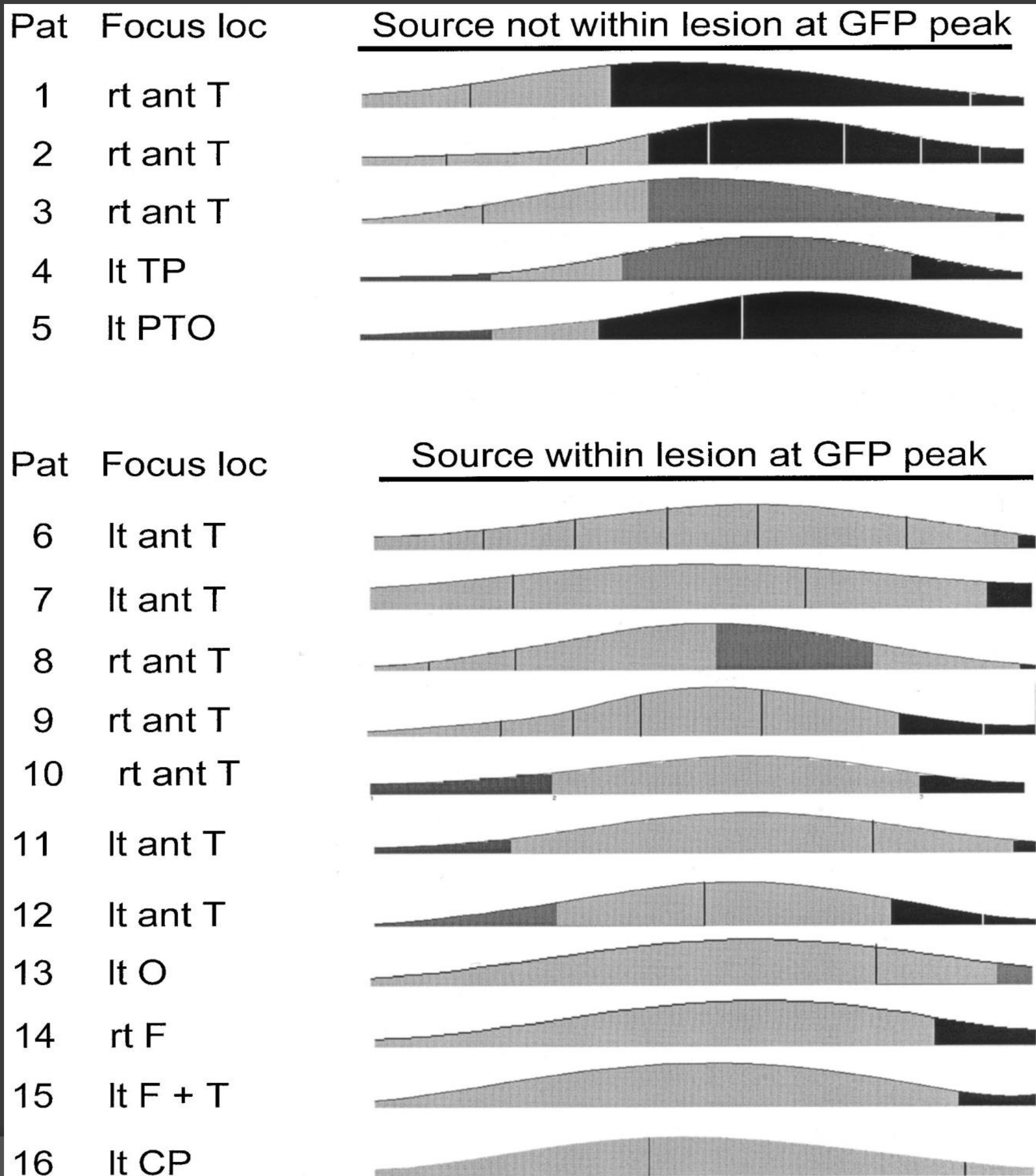
- Overlapping activities during the onset phase may remain high enough to result in substantial mislocalization of the initial source activity even when averages of 10-20 spikes are analyzed

- *Appropriate filtering of the spike* is vital to enhance the fast initial spike activity relative to the overlapping slower onset activities of the propagated spikes and background EEG.

- Therefore, *HPF at frequencies of at least 3 Hz or higher* helps to enhance the initial relative to the propagated spike activity and to reduces the slow background EEG activity

Which part of the spike should be modeled ?

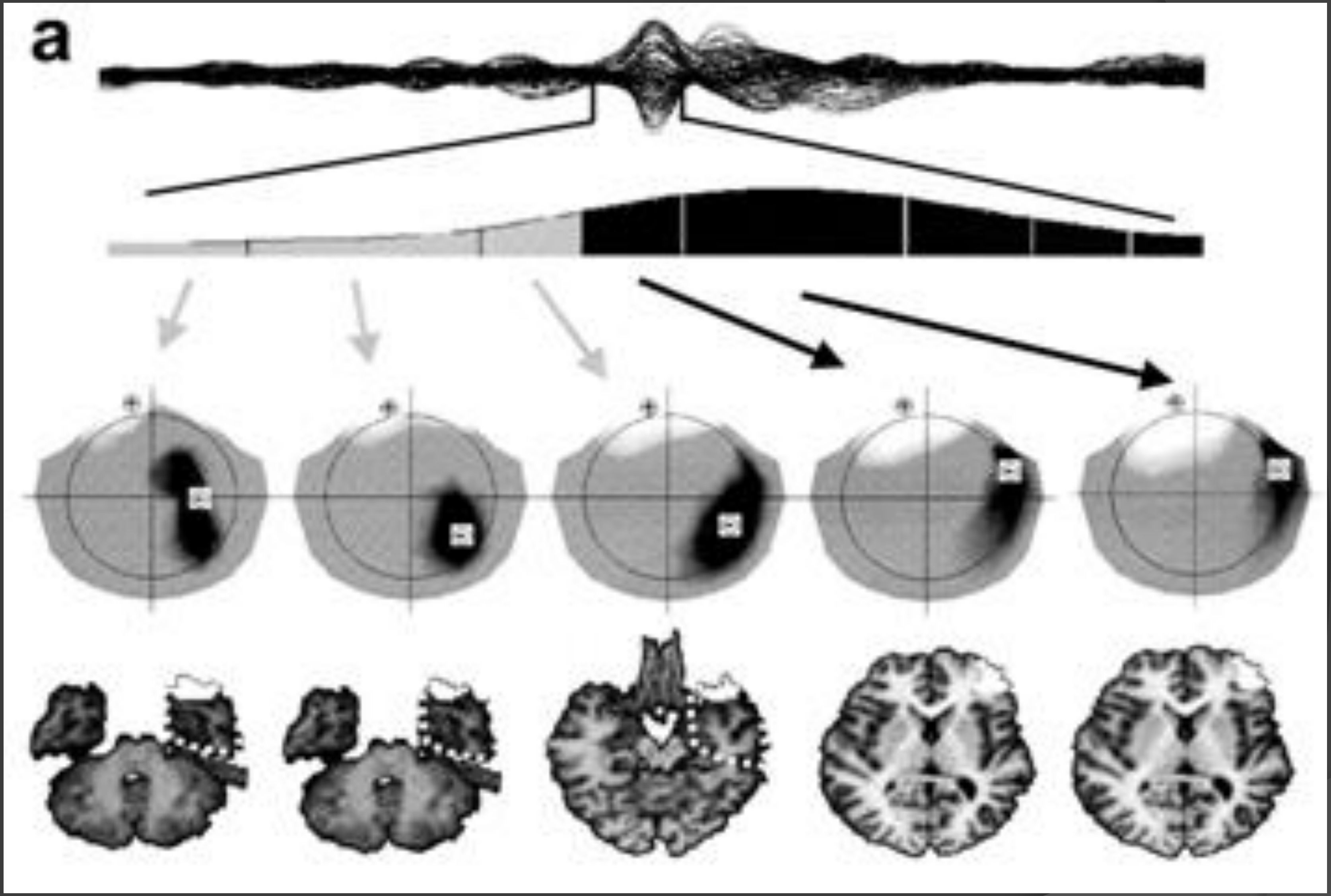
- Lantz G. et.al (2003) analyzed spikes from 16 patients suffering from pharmaco-resistant partial epilepsy, who had been recorded with 125-electrode protocol.
- All of the patients have a clear MRI lesion and be seizure-free after epilepsy surgery.
- They did source reconstruction in different segmentations of the spike/sharp waves



Light gray: source location is within the lesion

Dark gray: source locations are at the border of the lesion (< 10 mm distance)

Black: source locations at more than 10 mm distance from the lesion



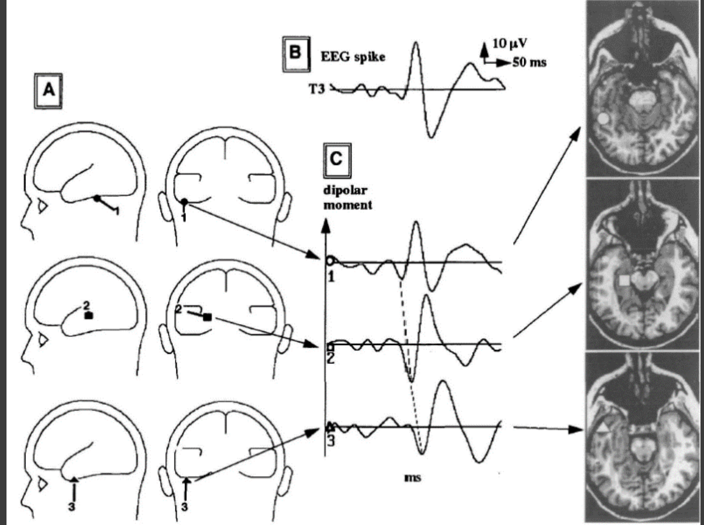
MRI shows a right mesial temporal tumor (DNET);
White dotted line delineates the defined lesion

Which part of the spike should be modeled ?

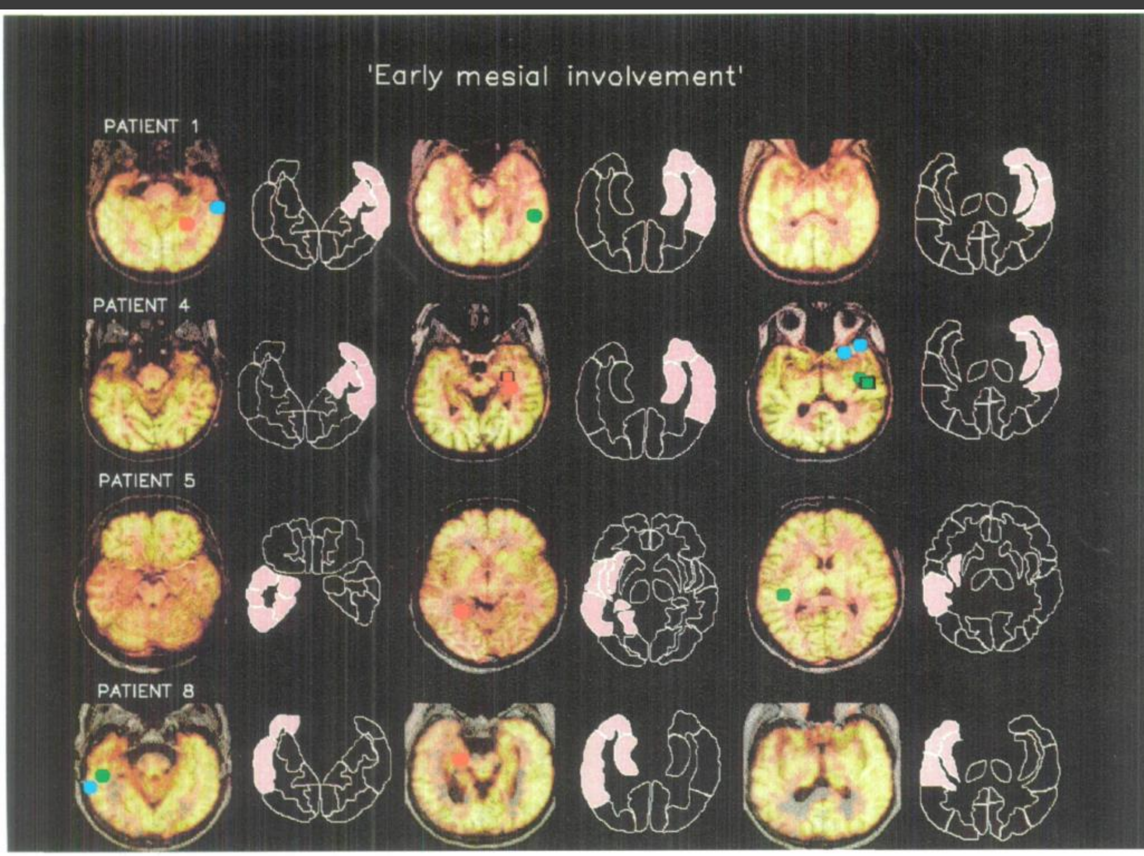
- They concluded that the time period **halfway** *(around 50% of the rising time, the source was within the lesion in all patients)* from spike onset to spike peak seems to be the most reliable for source localization purposes.

Correlations between spike dipole modelling and FDG-PET data

- Marlet I et.al (1996) studied the spatial relationships between the intracranial generators of interictal paroxysm assessed by dipole modelling of EEG spikes, and the metabolic abnormalities demonstrated by PET-scan
- They found that the dipolar sources of these 8 studied patients were always included within the hypometabolic area.
- They concluded that the ***spatio-temporal spread of neuronal hyperactivity underlying interictal spiking suggests the presence of preferential epileptogenic networks inside the hypometabolic temporal lobe***.



Circles : early source
Squares: main source
Triangles: late source



Pink area: decrease in glucose uptake
Red circle: early source
Green circle: main source
Blue circles: late source

Improving source localization

Improving source localization

- Supplementary electrodes and the number of electrodes recorded
- Coregistering EEG data with MRI
- Realistic head models

Supplementary electrodes

- The standard International 10-20 temporal electrode chain passes across the superior aspect of the temporal lobe.
- Supplementary *inferior temporal electrodes* are necessary for properly recording the negative field of basal frontal, temporal, and occipital spikes/seizures.
- Sphenoidal or the so-called anterior temporal electrodes, T1 and T2, are useful in this regard.

Combined use of sphenoid electrodes and dipole localization method for the identification of the mesial temporal focus

- Yoshinaga H et.al (2001) studied 4 patients suffering from drug-resistant epilepsy

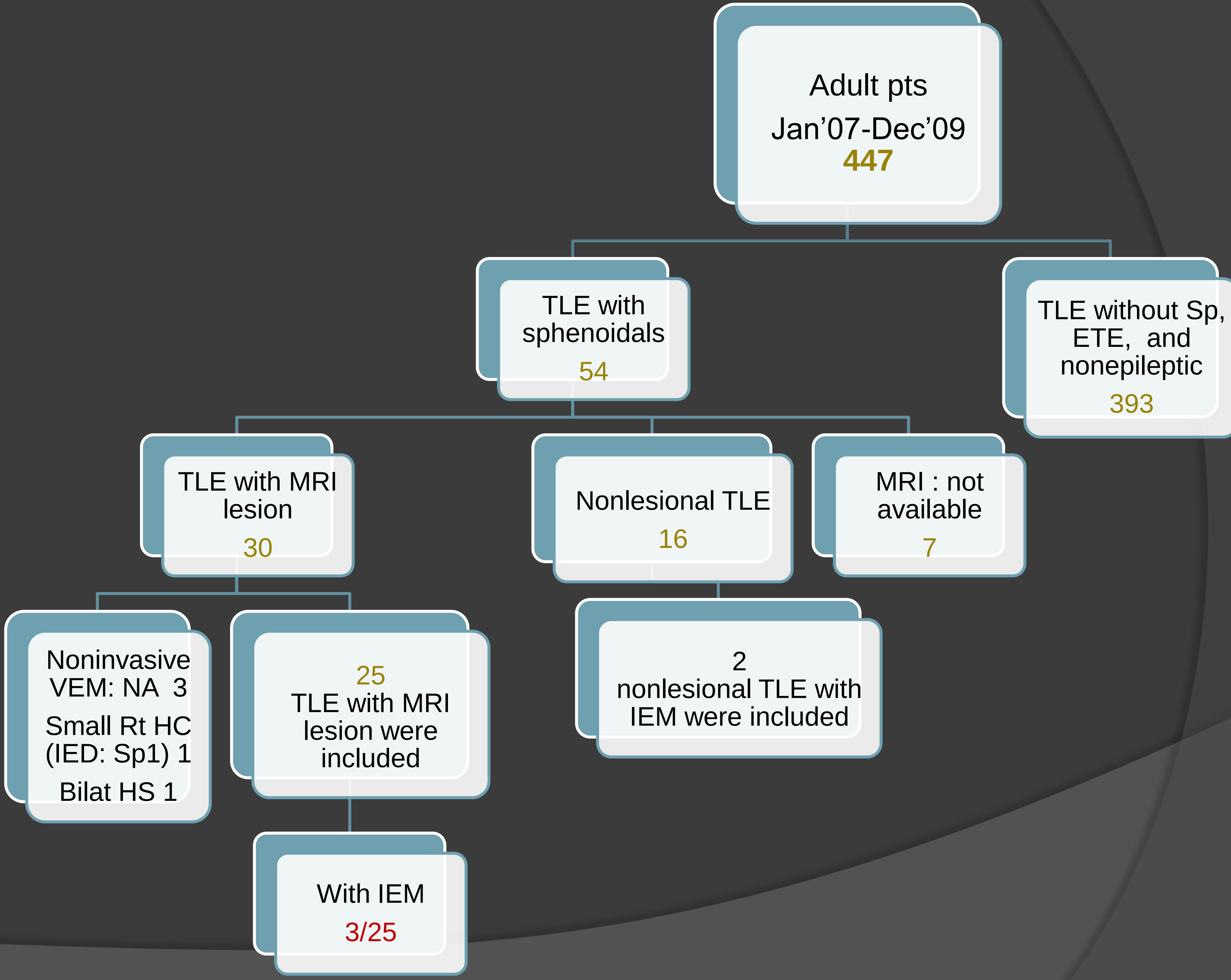
- Dipole localization analysis of spikes recorded by sphenoid electrodes was performed.

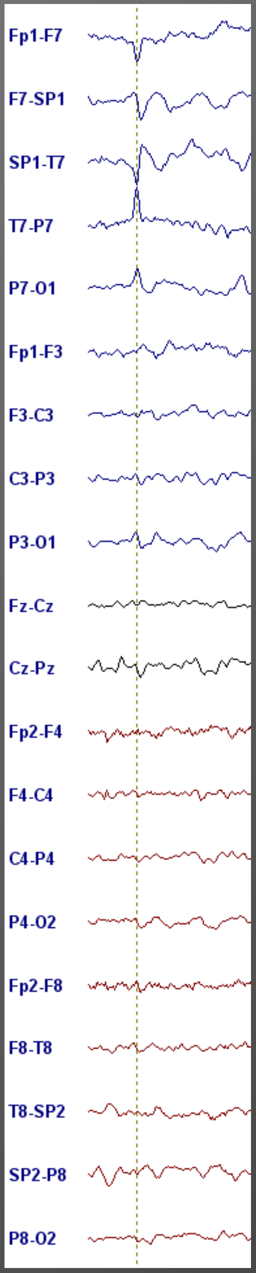
- Spikes which show phase reversal in sphenoid electrodes can be differentiated as to whether they are mesial temporal spikes or frontal basal spikes, according to the dipole locations

SPHENOIDAL ELECTRODES SIGNIFICANTLY CHANGE THE RESULTS OF SOURCE LOCALIZATION OF INTERICTAL SPIKES FOR A LARGE PERCENTAGE OF PATIENTS WITH TEMPORAL LOBE EPILEPSY

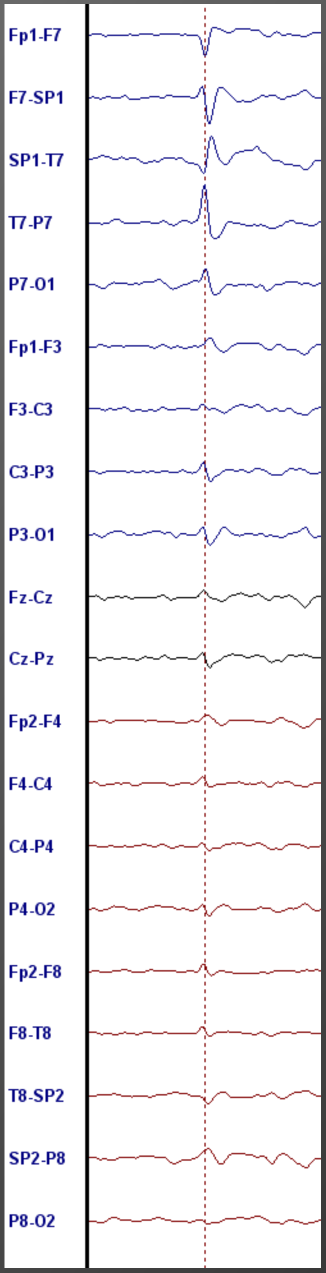
M B Hamaneh, C Limotai, H Luders

J Clin Neurophysiol 2011

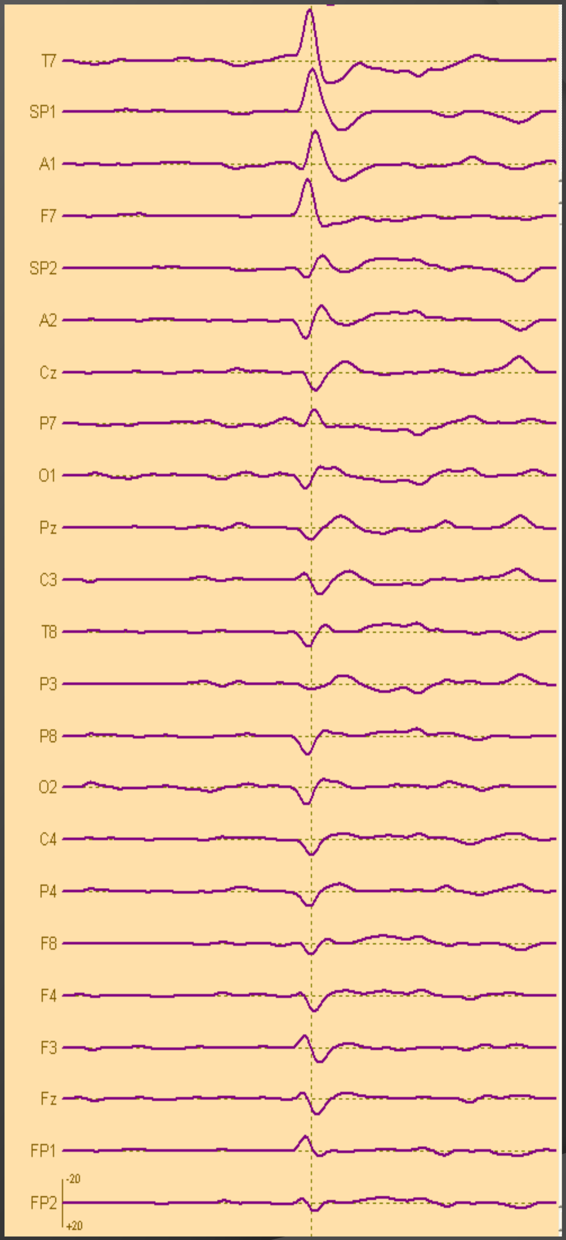

Adult pts
Jan'07-Dec'09
447
TLE with sphenoidals
54
TLE without Sp, ETE, and nonepileptic
393
TLE with MRI lesion
30
Nonlesional TLE
16
MRI : not available
7
Noninvasive VEM: NA 3
Small Rt HC (IED: Sp1) 1
Bilat HS 1
25
TLE with MRI lesion were included
2
nonlesional TLE with IEM were included
With IEM
3/25



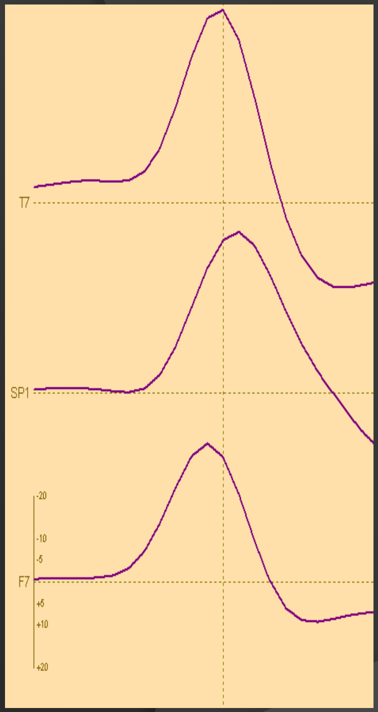
Prototype



Averaged



Averaged in referential montage



The first three channels

Pattern search and averaging

- Pattern search
  - A two-step approach was taken.
  - In the first step all spikes with at least 75% correlation to the template were identified and automatically averaged.
  - The averaged activity was then used as a new template for the second step.
  - In the second step all spikes with more than 85% similarity to the template were identified.
  - The selected patterns were visually inspected to exclude the noisy spikes.
  - spike clusters with less than 10 members were also excluded.
  - Filters: 3-30 Hz
- Averaging

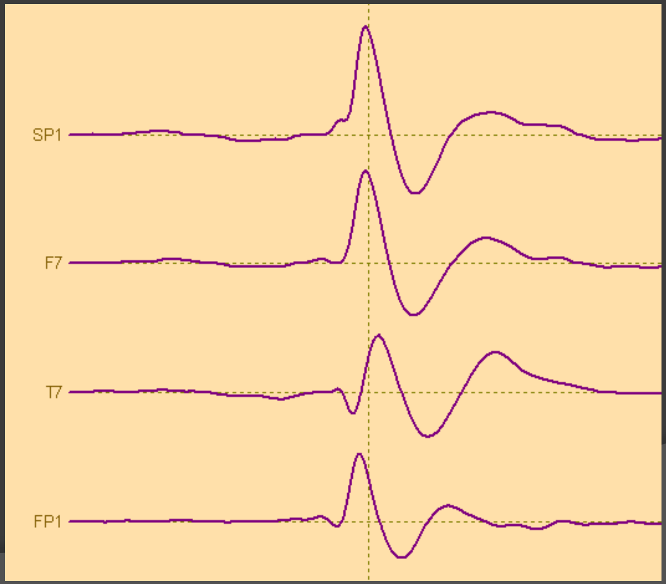
A 1s epoch (500 ms before and after the trigger) was used

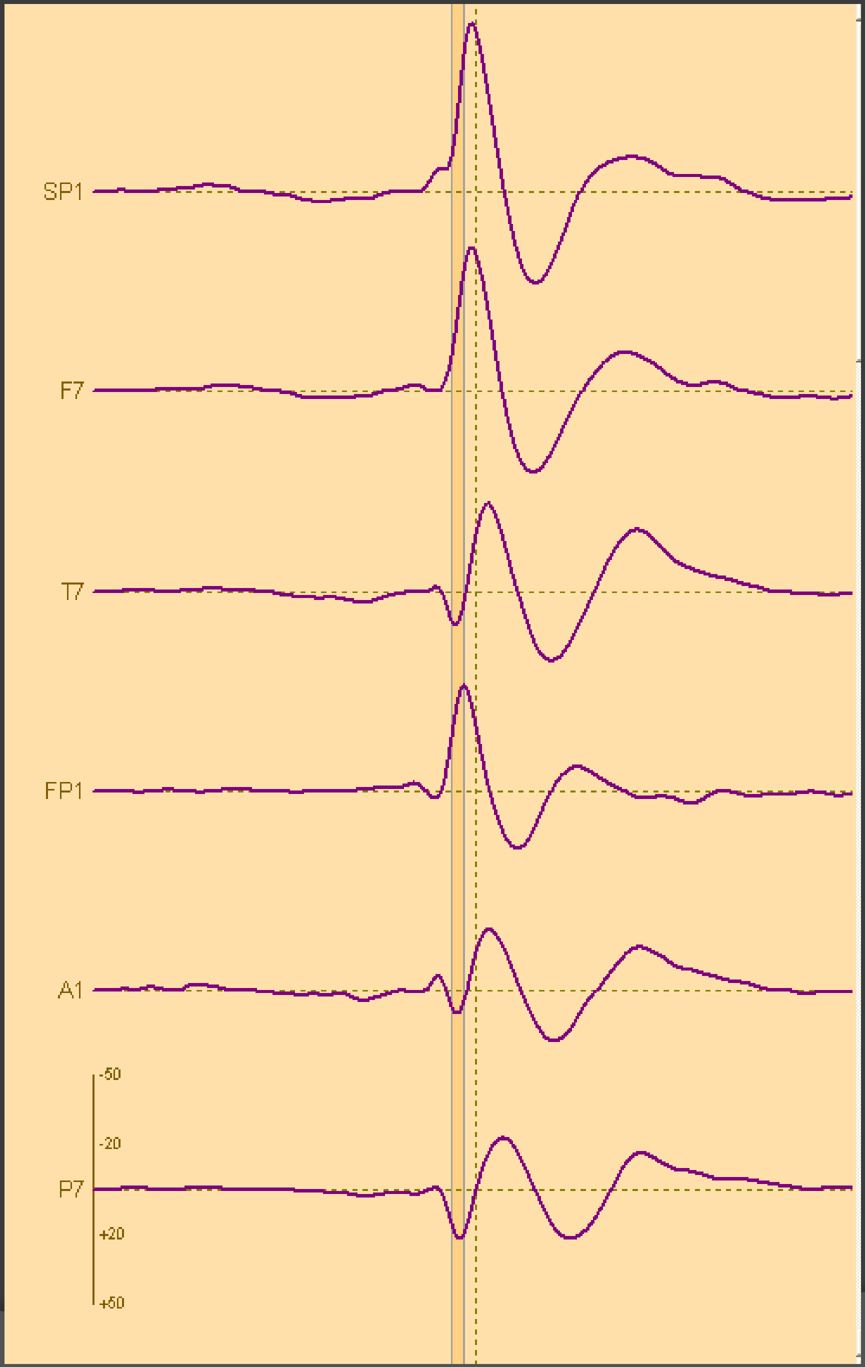
No filter was applied

Source localization

- To avoid spikes with low SNR, the selected peaks had to satisfy the following criteria:
  - The peak must appear later than the time at which the global field power (GFP) equals 10 times the maximum GFP of the background (-500 ms to -100 ms)
  - **At the peak, the channel with largest deflection must account for at least 10% of the GFP**.

GFP = Sum of squared amplitudes of all channels



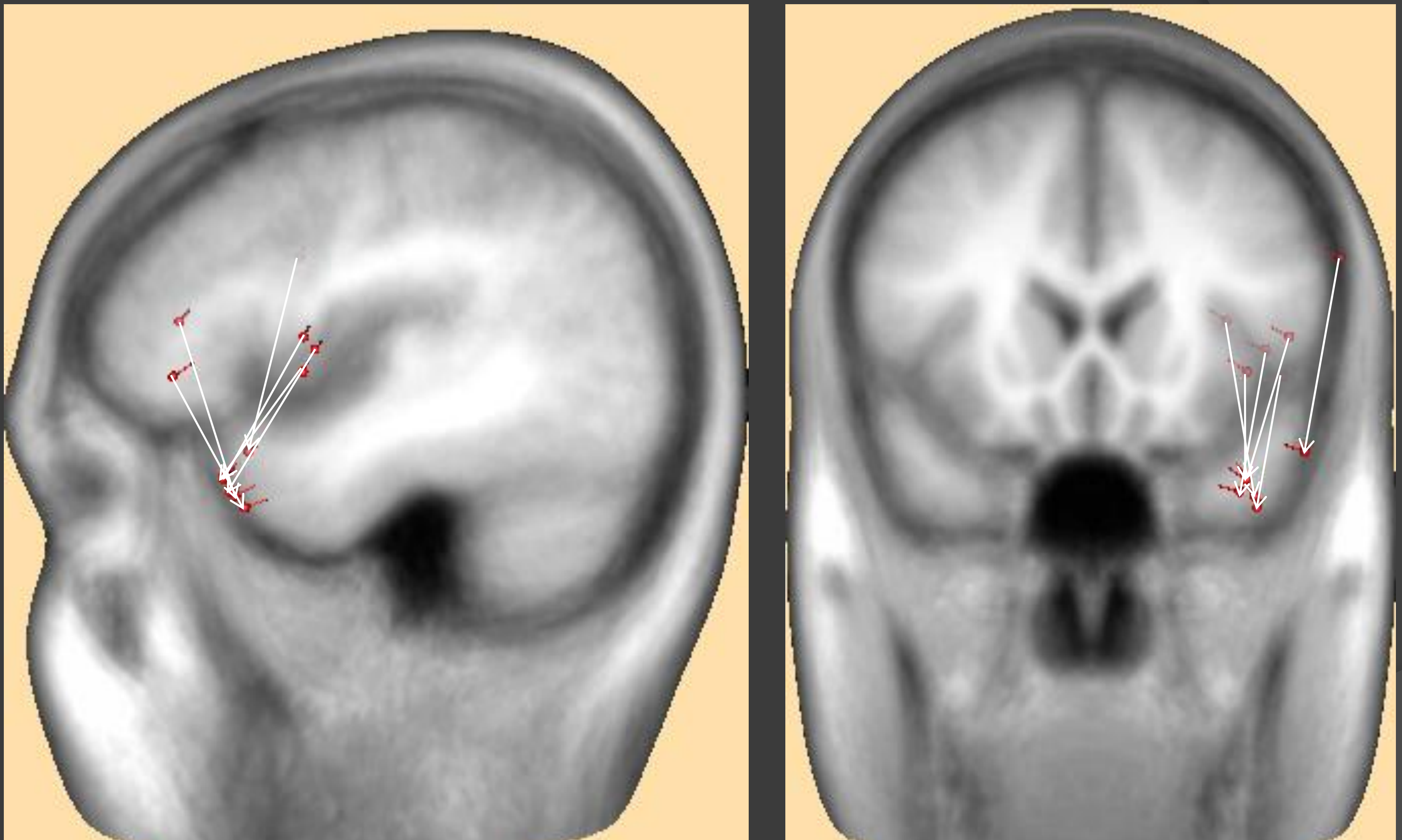


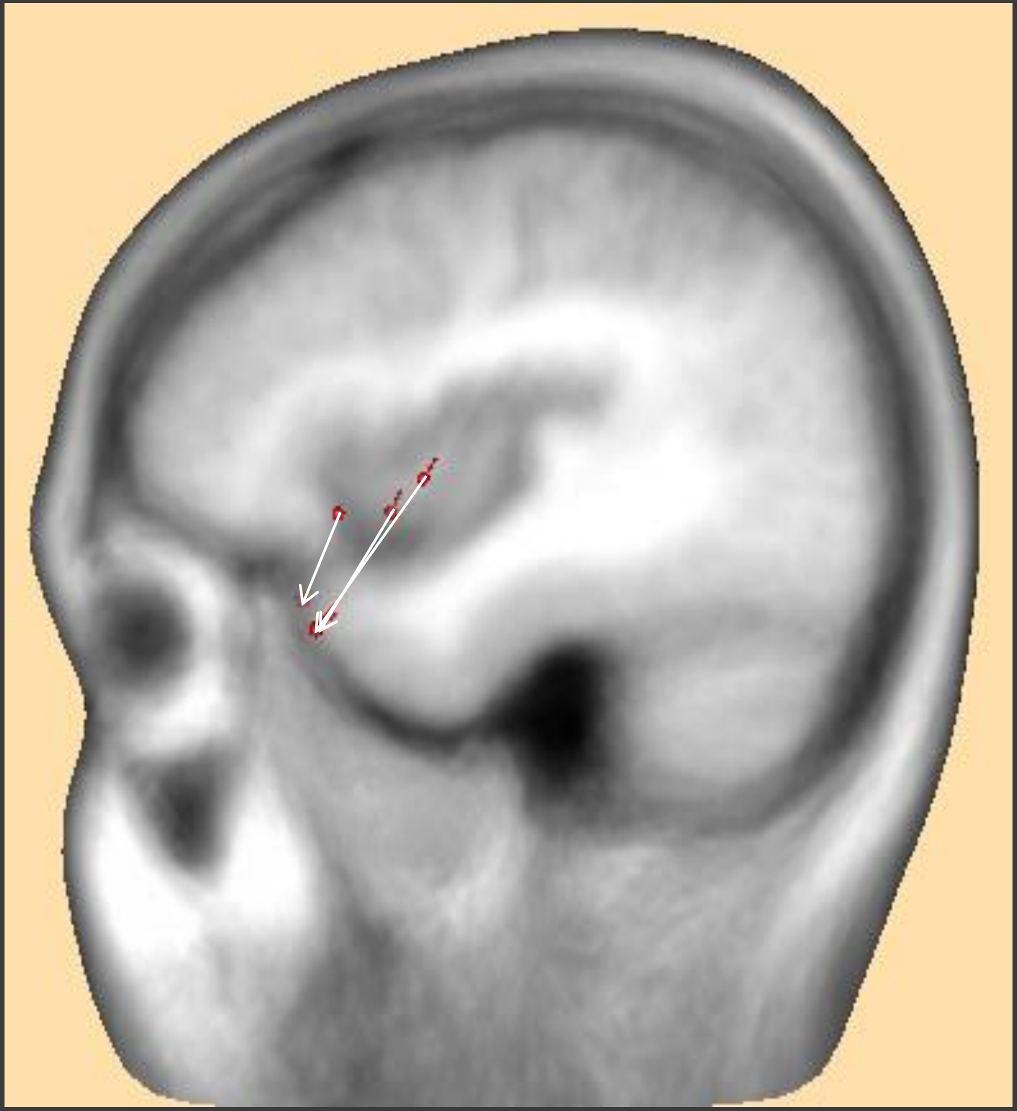
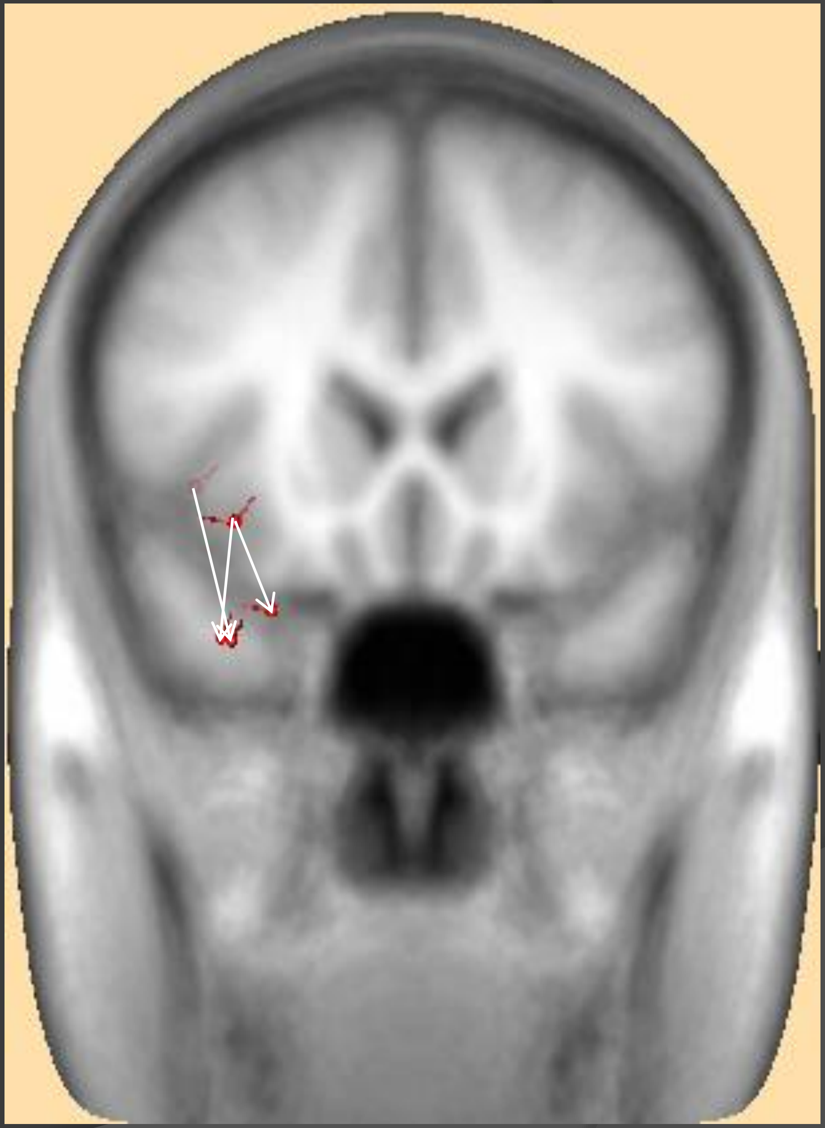
A single fixed dipole was fitted to the data at the time interval beginning at the halfway point between the onset and the peak, and ending at the spike peak.

Frequency band: 3-30 HZ

Head model: Finite element model, based on an averaged standard MRI and not the actual MRI.

At first the dipole was fitted to the whole data set. Then the sphenoidals were turned off and the dipole was fitted to the same exact time interval.



Results

- The results suggest that sphenoidals can significantly affect the position of the fitted dipoles.

- It should be noted that in **9/17 patients (53%), without sphenoidal recording, the fitted dipole location shifted outside the temporal lobes**. These could be insular or frontal lobes.

- This large shift is perhaps due to the fact that basal temporal activities are not, at least to some extent, detected by the 10/20 scalp EEG electrodes.

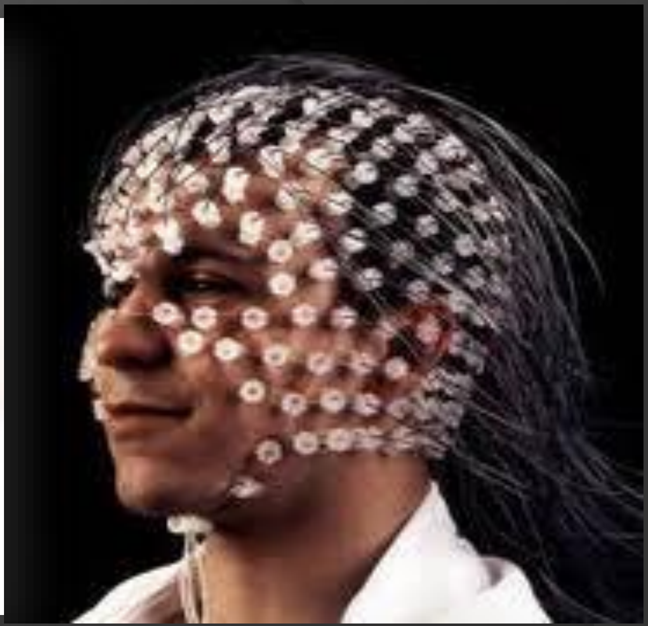
In summary

- Our results suggest that ***including the sphenoidal electrodes in source localization of patients with temporal lobe epilepsy can help better localize the epileptogenic zone in a large percentage of patients*****.**

- The inclusion of these electrodes appears to be especially important when they show ***Sp1 or Sp2 maximum amplitude activity***, which is usually the case in patients with ***mesial temporal lobe epilepsy.***

How many electrodes are needed ?

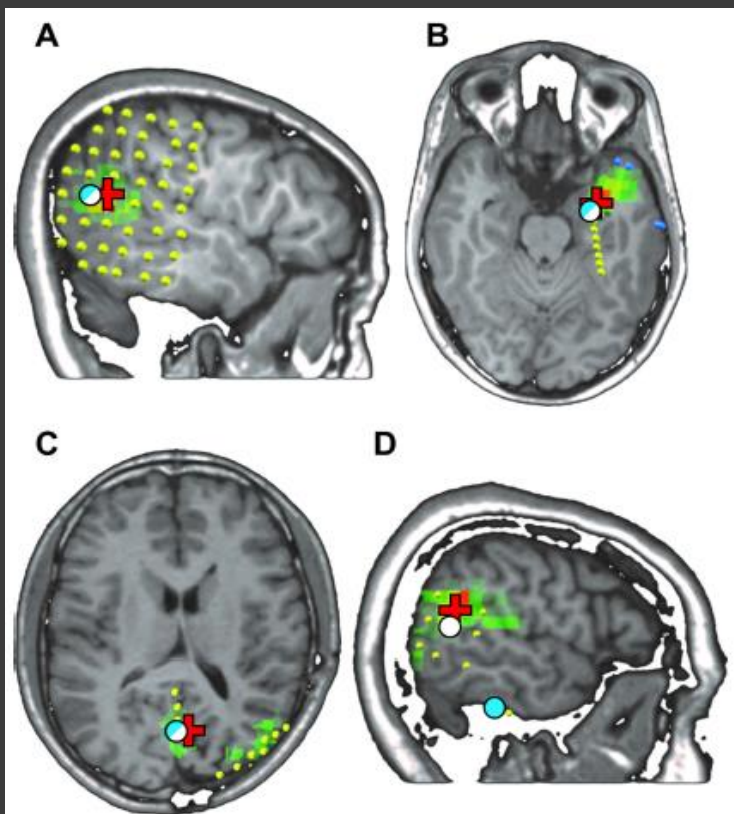
- Lantz G et.al (2003) studied the accuracy of epileptic source localization with high electrode density in 14 epileptic patients undergoing presurgical evaluation
- 13 of the 14 patients had cortical resections and all are seizure free (Engel class I)
- The ESL accuracy, indexed by the distance from the nearest surgical margin to the location of a single fit inverse model, *improved by around 2 cm from a 31 to a 63 electrode set-up*, with *little change from a 63 to a 123 electrode set-up*.



Dense array EEG (dEEG) and ESL

Electric source imaging of interictal activity accurately localises the seizure onset zone

Pierre Mégevand,[1] Laurent Spinelli,[1,2] Mélanie Genetti,[3] Verena Brodbeck,[2,4] Shahan Momjian,[5] Karl Schaller,[5] Christoph M Michel,[2,3] Serge Vulliemoz,[1,2] Margitta Seeck[1,2]

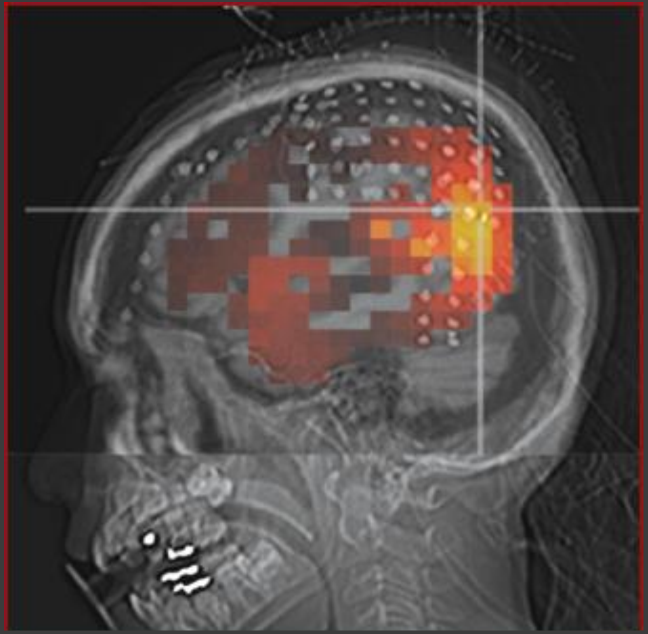


- 38 pts with focal epilepsy who underwent iEEG
- 128-256 channels EEG
- Distance between ESI maximum and intracranial SOZ and IZ

- Localization of interictal spikes provides an excellent estimate of the SOZ in the majority of the patients

Megevand P et al; JNNP 2014

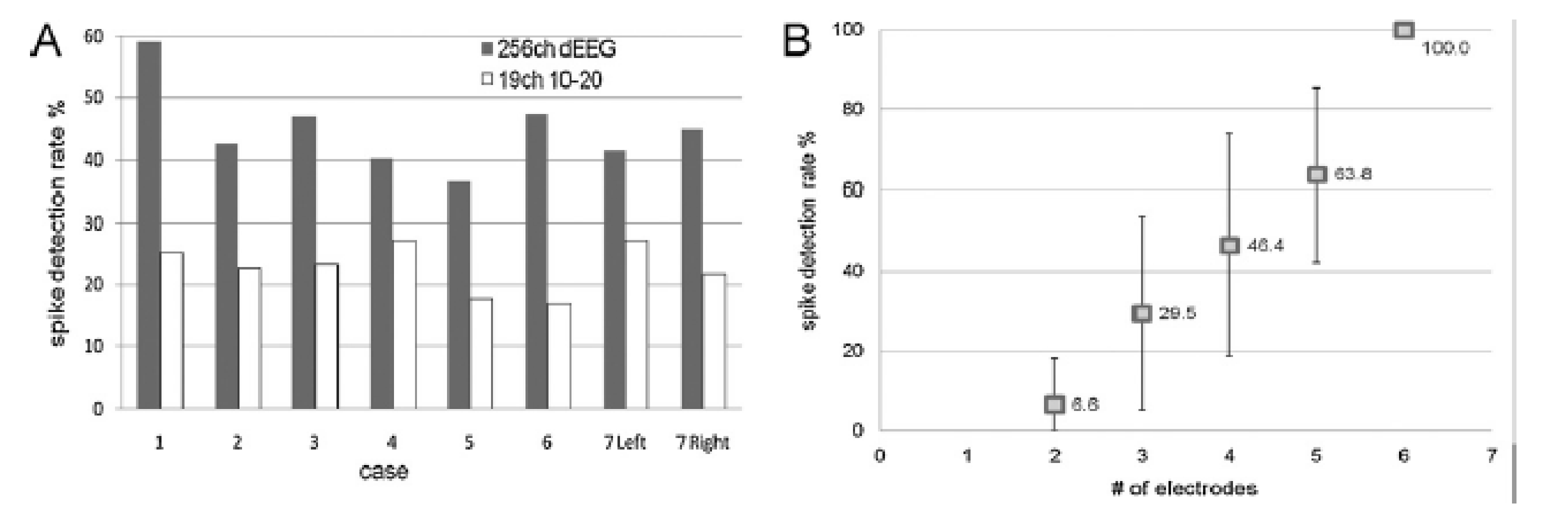
Comparing Noninvasive Dense Array and Intracranial Electroencephalography for Localization of Seizures



- 8/10 pts: dEEG localized ictal onsets to the same regions as iEEG

Holmes M et al; Neurosurgery 2010

Comparison of dense array EEG with simultaneous intracranial EEG for Interictal spike detection and localization

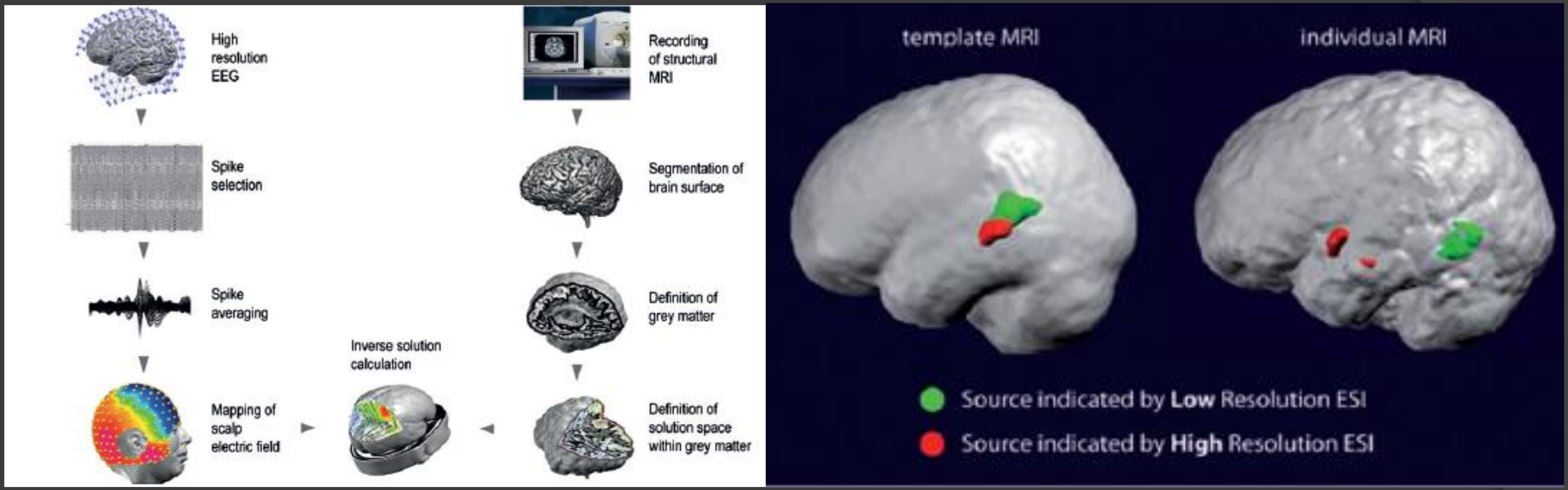


- 7 pts with mesial temporal lobe epilepsy
- 256-channel dEEG
- dEEG: 45% of iEEG spikes were detected

  19-channel: 22%
- 256-channel dEEG required *at least 5 cm^2* of synchronized cortical activity for the spike to be detected with visual inspection of surface dEEG ***(scalp EEG: Cooper et al >6 cm^2 Tao et al at least 10 cm^2, MEG at least 4 cm^2)***

Yamazaki M et al; Epilepsy Res 2012

Electroencephalographic source imaging: a prospective study of 152 operated epileptic patients



Brodbeck V et al; Brain 2011

Impact of low/high resolution EEG and template and individual MRI on ESL accuracy

Measure	LR-ESI/t-MRI (%)		LR-ESI/i-MRI		HR-ESI/t-MRI		HR-ESI/i-MRI
	n = 152	n = 52	n = 98	n = 52	n = 55	n = 52	n = 52
Sensitivity	55.6	59.1	65.9	72.7	76.1	75.0	84.1
Specificity	58.8	62.5	53.8	75.0	55.6	62.5	87.5
PPV	92.6	89.7	91.8	94.1	89.7	91.7	97.4
NPV	15.5	21.7	28.1	33.3	31.3	31.3	50.0

Comparison of the accuracy of epileptic localization between MRI, PET, SPECT and HR-ESI/i-MRI

Measure	MRI (%)		PET (%)		SPECT (%)		HR-ESI/i-MRI (%)
	n = 152	n = 52	n = 147	n = 51	n = 119	n = 43	n = 52
Sensitivity	76.3	72.7	68.7	65.1	57.7	54.3	84.1
Specificity	52.9	50.0	43.8	37.5	46.7	62.5	87.5
PPV	94.5	94.1	93.8	93.3	88.2	86.4	97.4
NPV	25.6	33.3	19.6	28.6	13.7	23.8	50.0

Brodbeck V et al; Brain 2011

Conclusion

- ESL is a noninvasively promising tool to help localize the epileptic focus
- Even though, at present it cannot be used to replace the iEEG, ESL may be helpful to guide the placement of intracranial electrodes
- Realistic head model, dEEG along with ESL coregistration on the patient’s MRI instead of template MRI improve the accuracy of ESL

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