Biomedical Applications of Mathematics
Prof. P. Manganotti AA 2013-2014

High density EEG and Electrical Source Imaging

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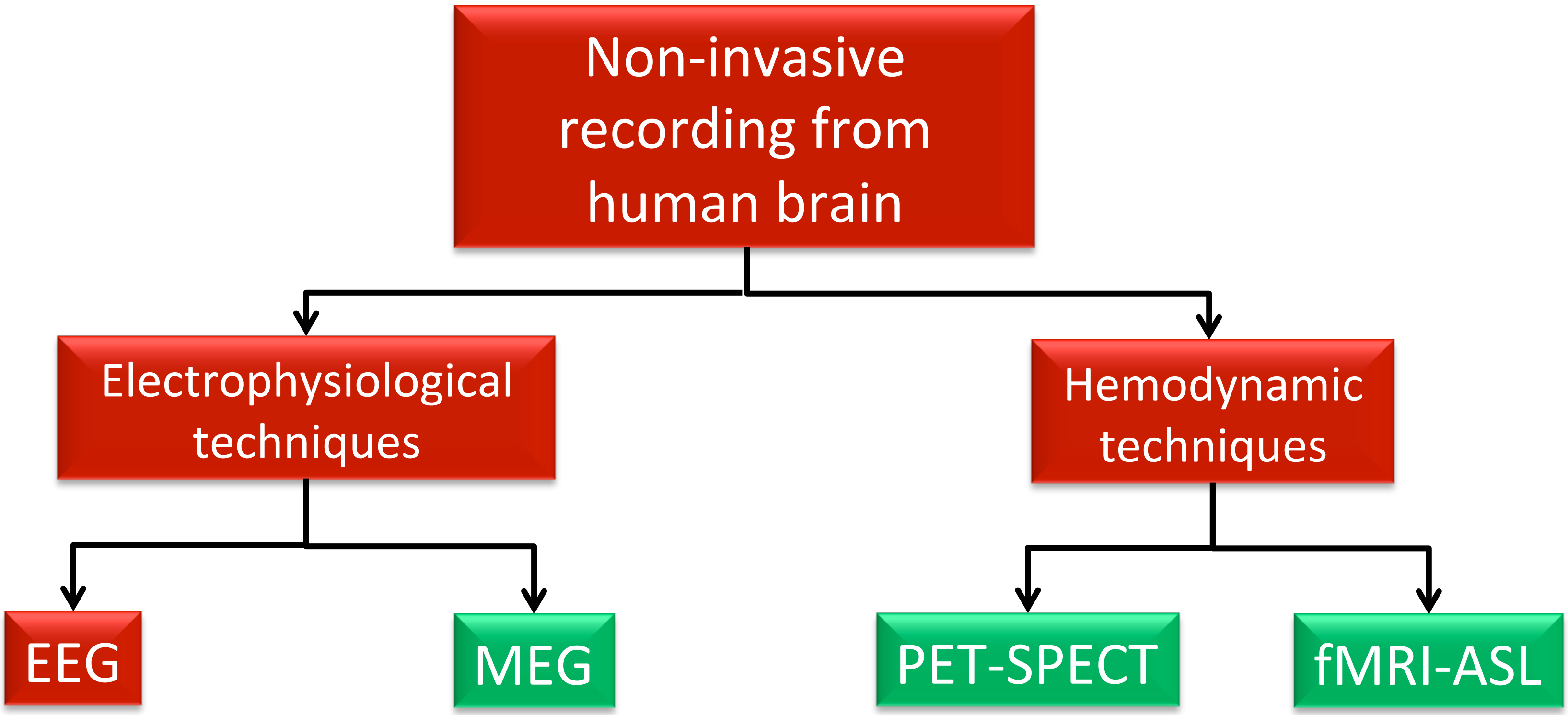
Measuring Neural Activity

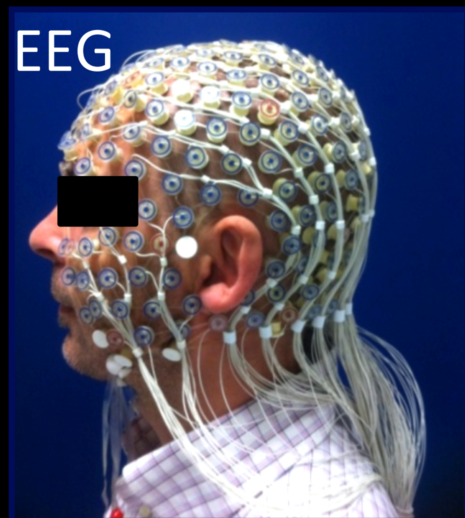


Poor spatial resolution
(about 1 cm)
Excellent temporal resolution
(< 1 ms)

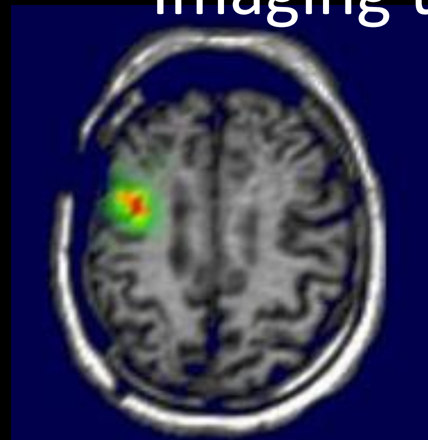
Excellent spatial resolution
(about 1-2 mm)
Poor temporal resolution
(about 1 s)

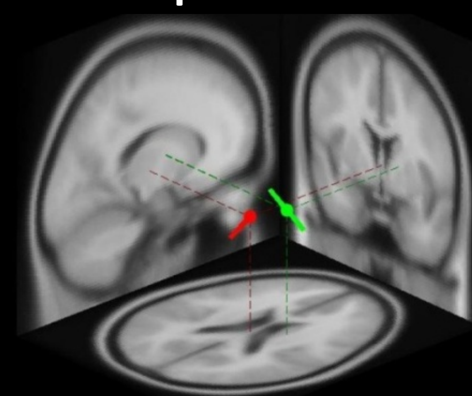
Non-invasive imaging tecniques

Measuring neural activity



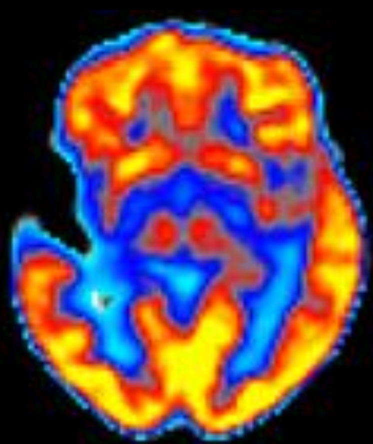
Imaging techiniques





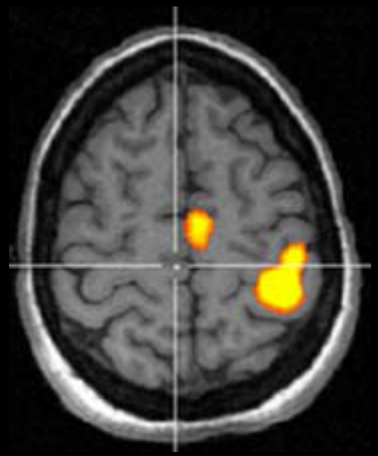
Non-invasive imaging tecniques

Measuring hemodynamic activity

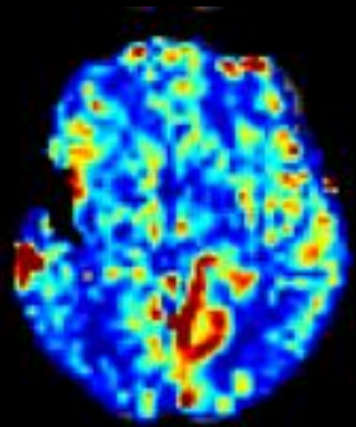


PET
(positron emission tomography)

SPECT
(single photon emission computed tomography)

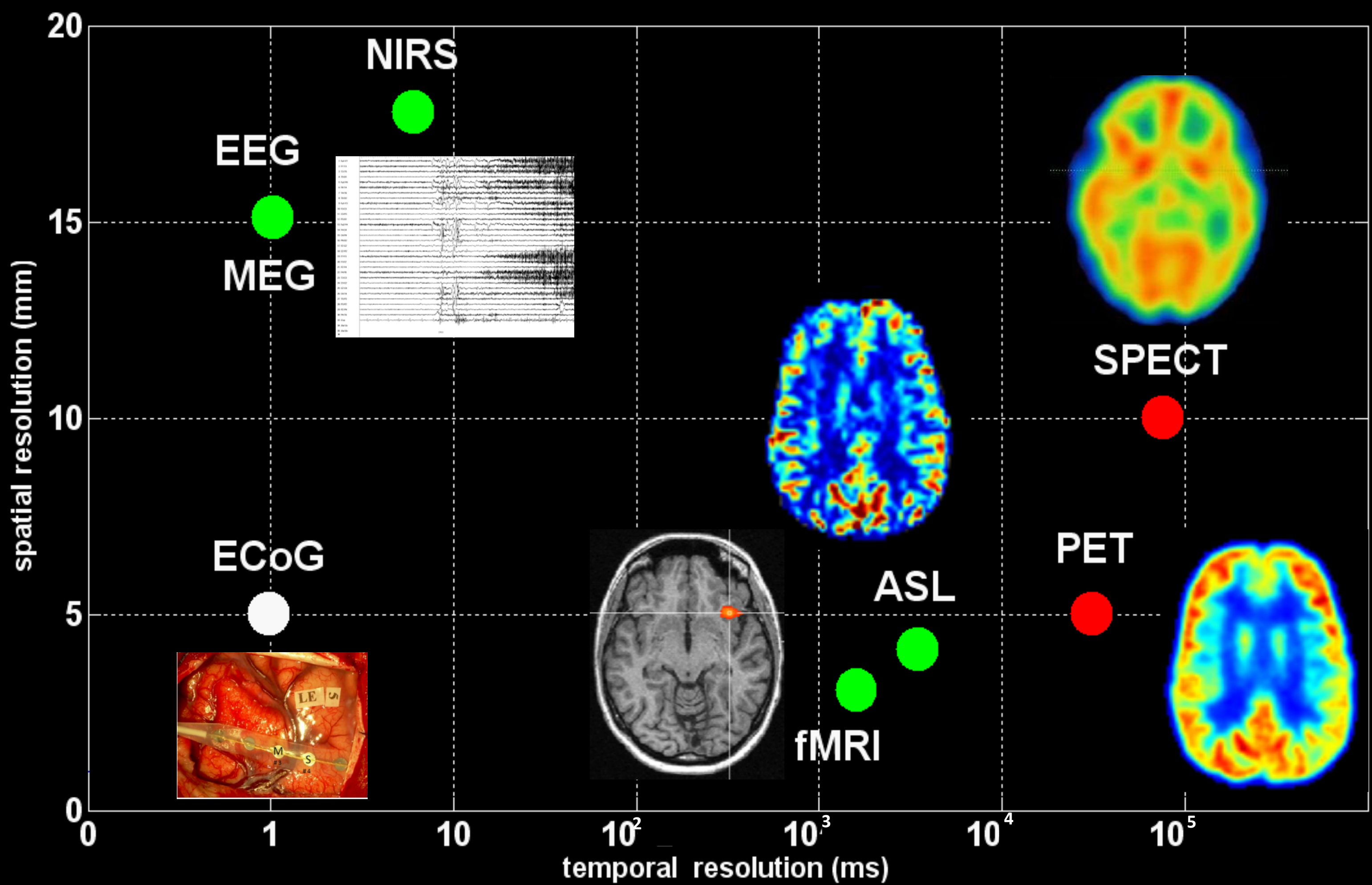


fMRI
(functional magnetic resonance imaging)



ASL
(arterial spin labellng)

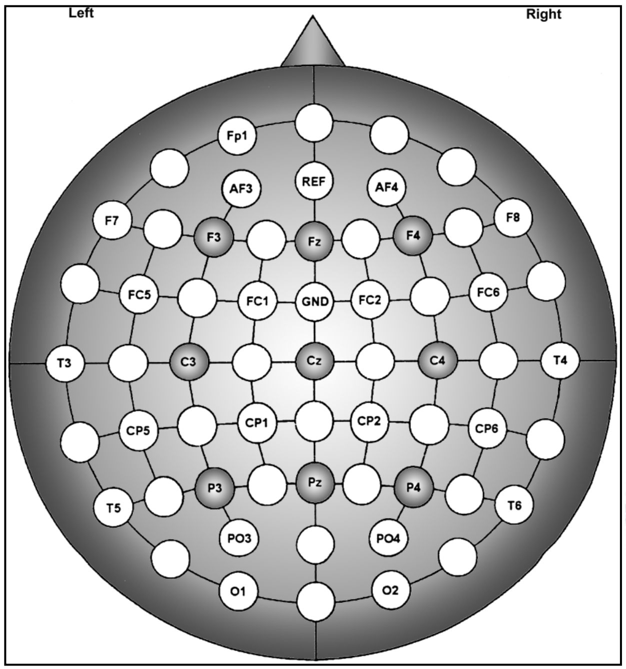
Temporal and Spatial resolution



Standard EEG and high-density EEG

Standard EEG

EEG is the recording of electrical activity along the scalp. EEG measures voltage fluctuations resulting from ionic current flows within the neurons of the brain.

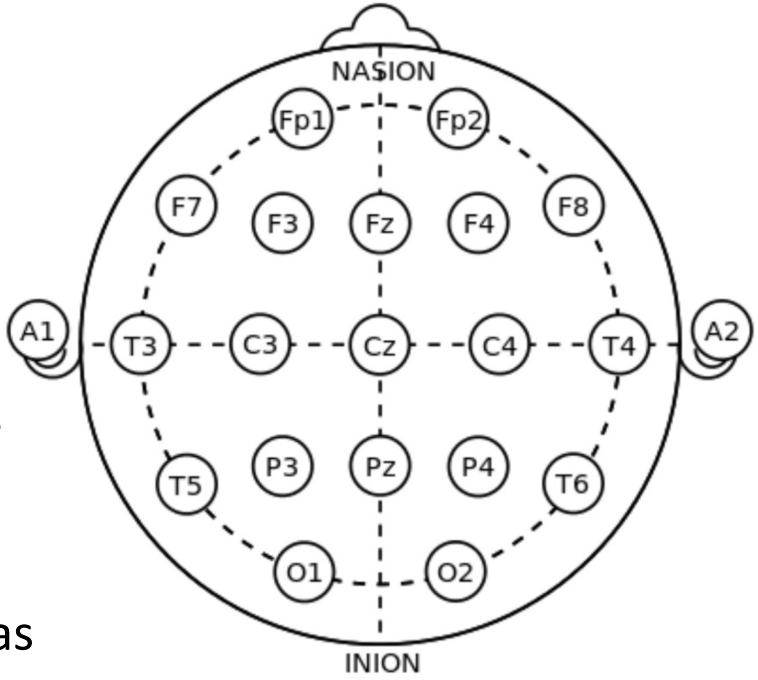


International 10-20 system

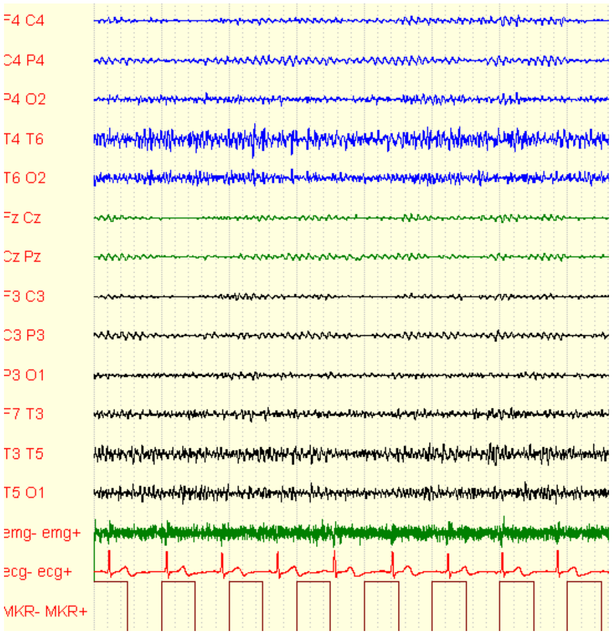
The "10" and "20" refer to the fact that the actual distances between adjacent electrodes are either 10% or 20% of the total front–back or right–left distance of the skull.

Standard EEG

- Each site has a letter to identify the lobe and a number to identify the hemisphere location.
- The letters F, T, C, P and O stand for frontal, temporal, central, parietal, and occipital lobes, respectively.
- A "z” refers to an electrode placed on the midline.
- Even numbers (2,4,6,8) refer to electrode positions on the right hemisphere, whereas odd numbers (1,3,5,7) refer to those on the left hemisphere.



EEG rhytms

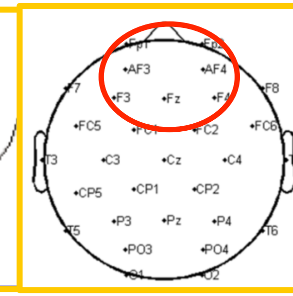


Rhithm	Frequency ranges (Hz)	Amplitude (mV)
Delta	0.5-4	20-200
Theta	4-8	5-100
Alpha	8-13	10-200
Beta	13-30	1-20

Locations

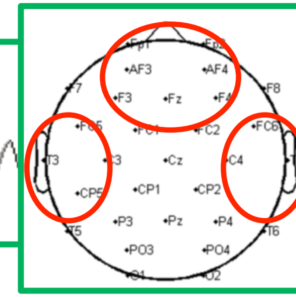
Delta

infants,
Deep sleep



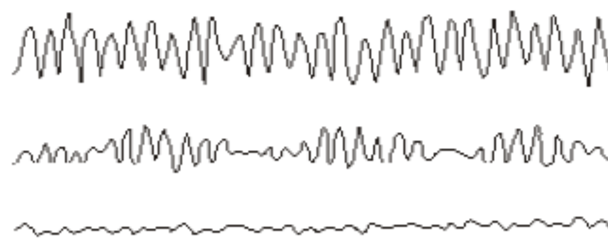
Theta

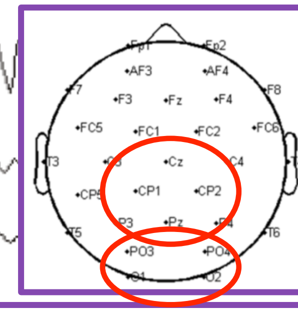
Childen,
Sleepiness



Alpha

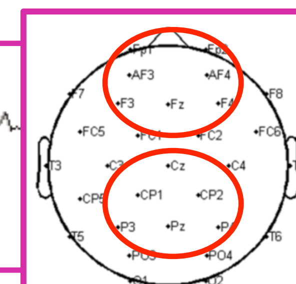
Occipitally and
parietally
Awake





Beta

Parietally and
frontally
Mental activity



Clinical Application of EEG

Diagnostic applications (Neurology) :

- **Epilepsy** (a condition that causes repeated brain seizures. Epileptic activity can create clear abnormalities on a standard EEG)
- **Dementia**
- **coma, encephalopathies, brain death**
- **sleep disorders** (one full night recordings)
- Brain tumors, stroke and other focal brain disorders but this use has decreased with the advent of anatomical imaging techniques

High density EEG system

EEG cap with 256 channels

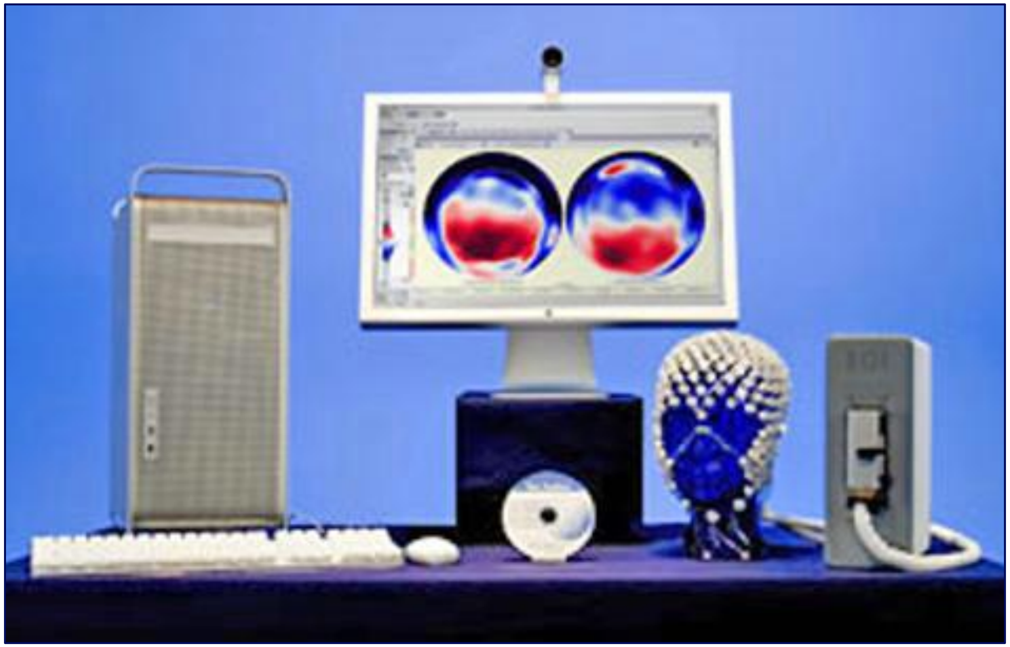
(Electrical Geodesics Inc. Eugene,OR, USA)

Elastic tension structure and electrolyte solution

Ag/AgCl electrodes

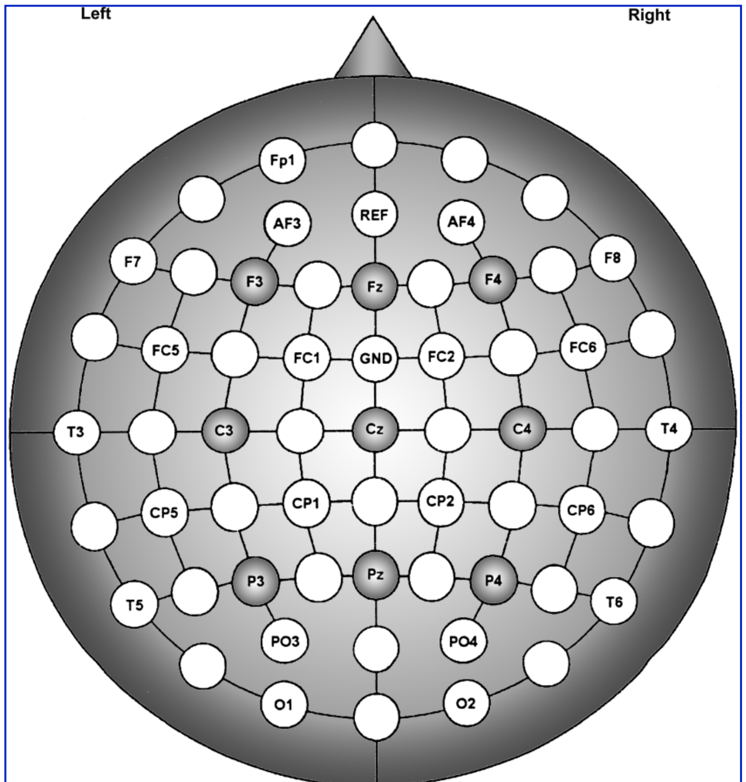
Application time of 10-15 minutes

Rate of acquisition (**until 20 kHz**)

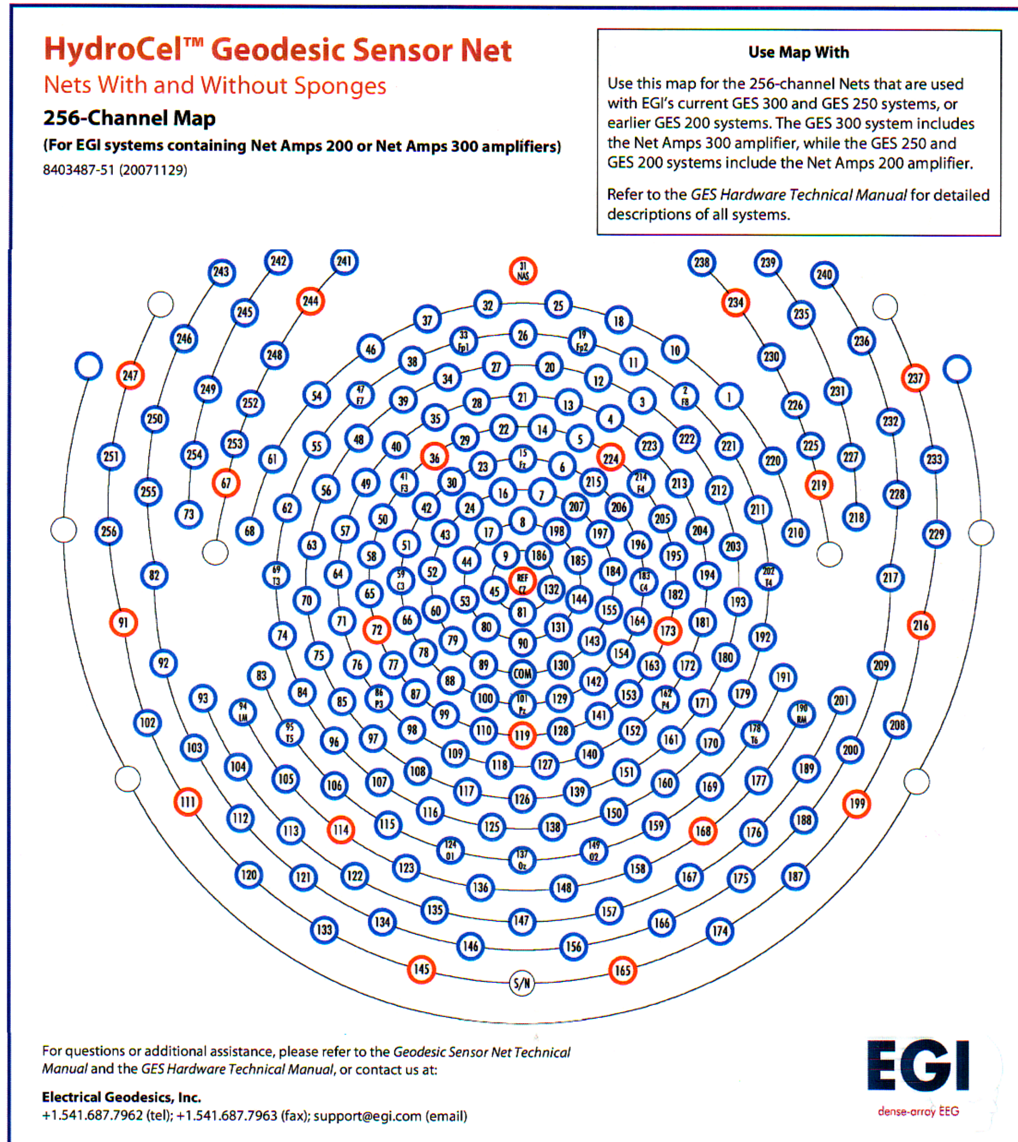


EEG channel configuration

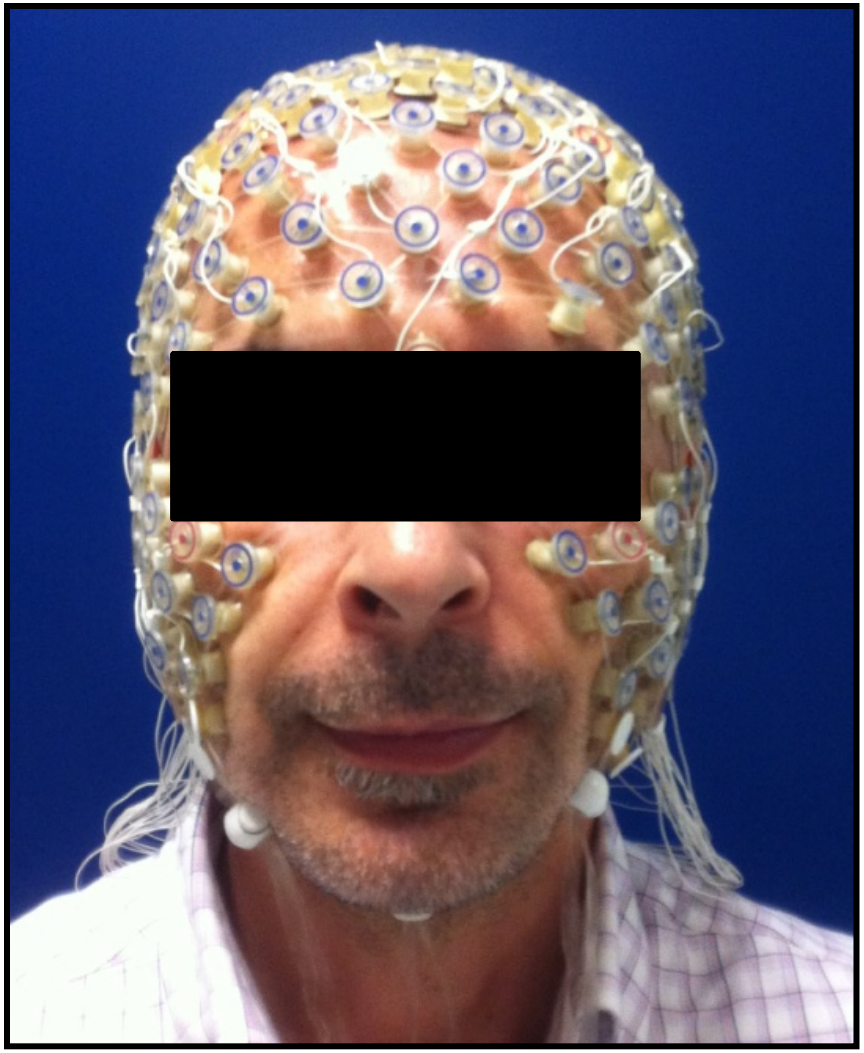
Standard EEG



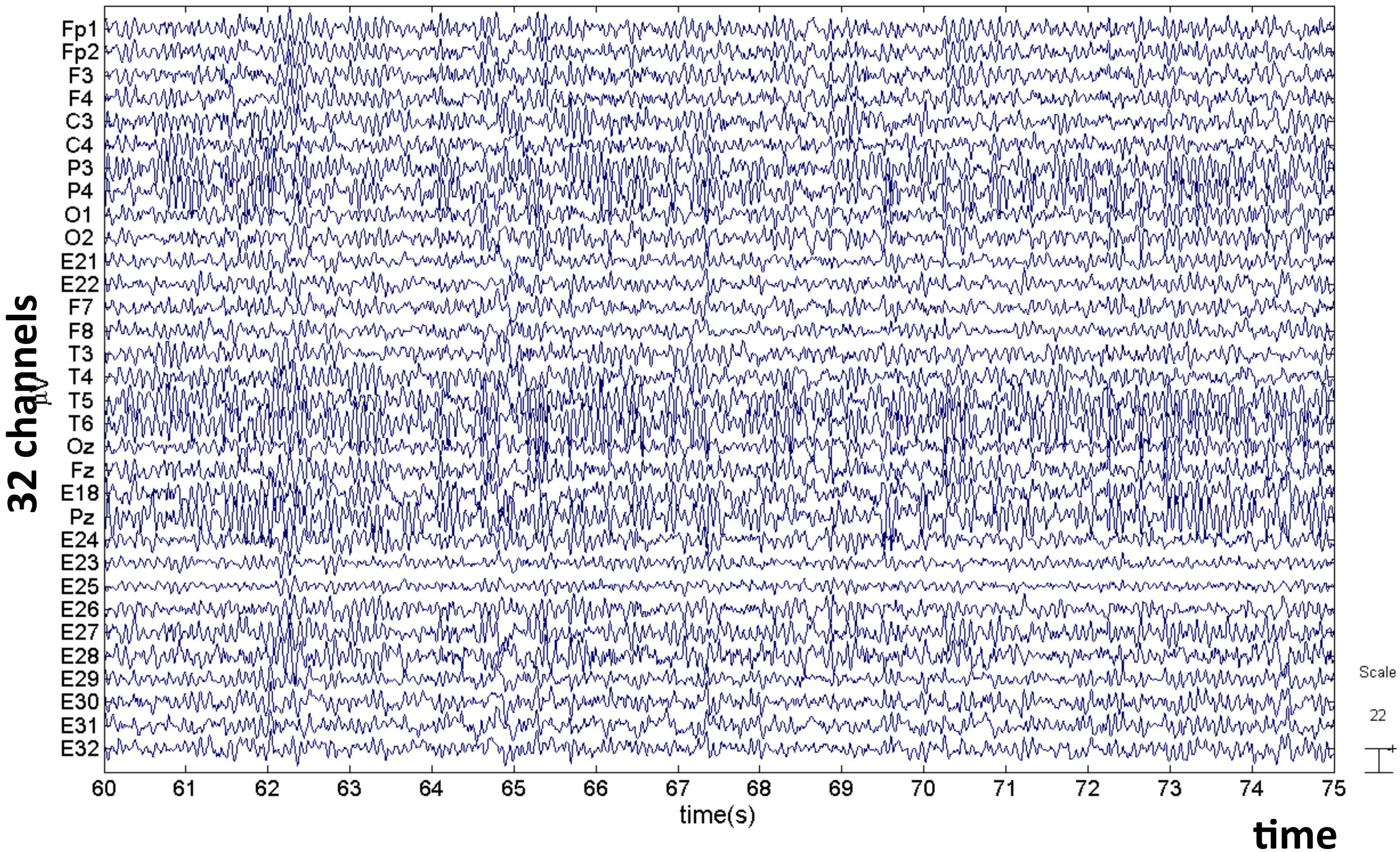
High-density EEG



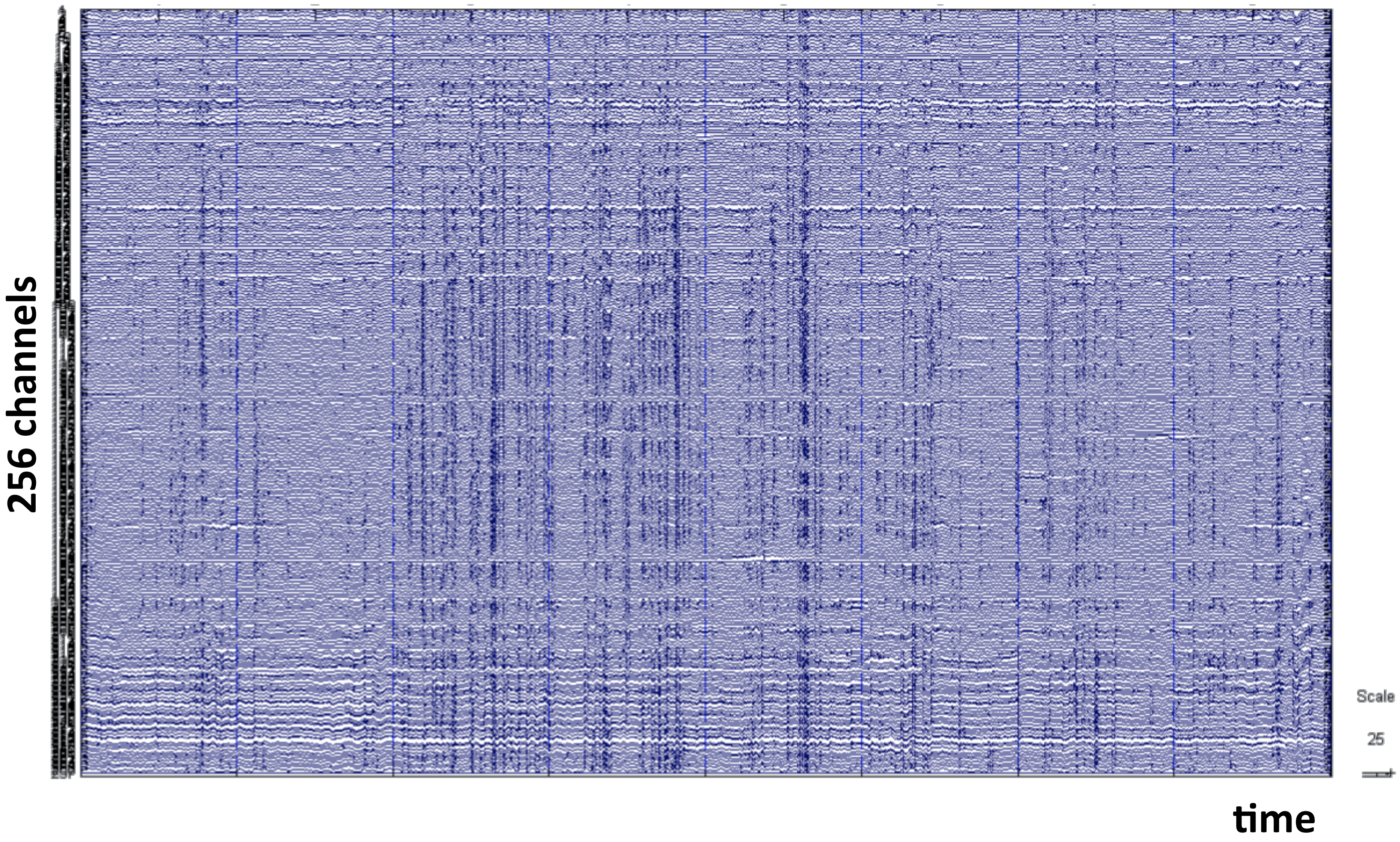
High density EEG cap – 256 channels



Standard EEG – 32 channels

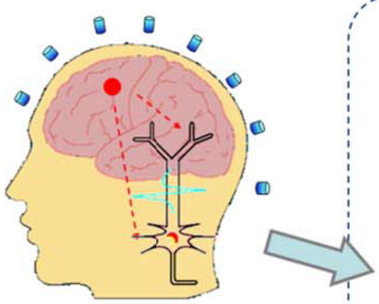


High density EEG – 256 channels

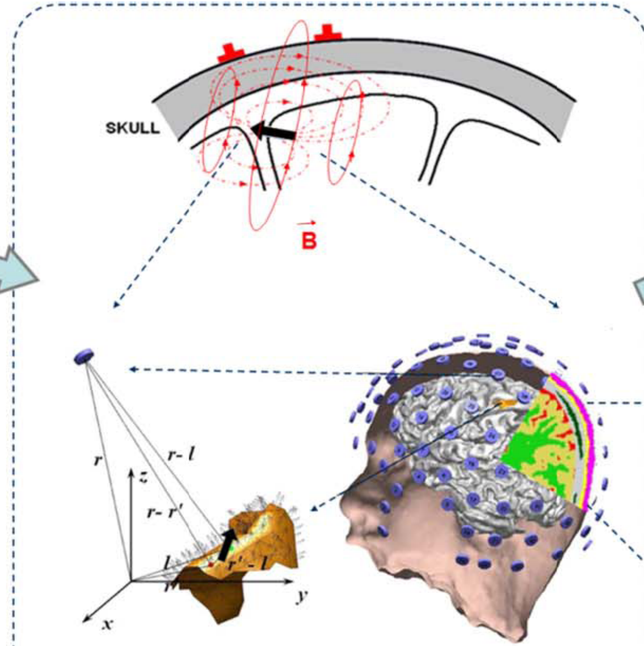


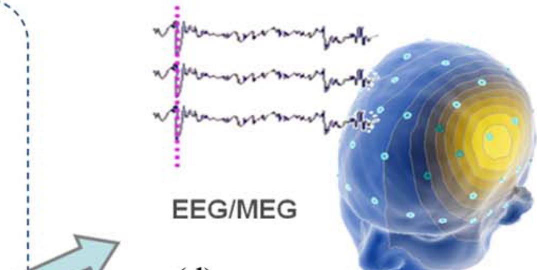
Electrical Source Imaging

Electrophysiological imaging of brain activity

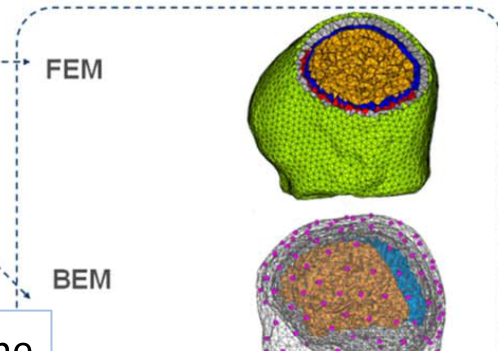


(a)





(d)



(c)

EEG/MEG signals are mainly generated from synchronized activation of cortical pyramidal neurons located within the cortical gray matter (a).

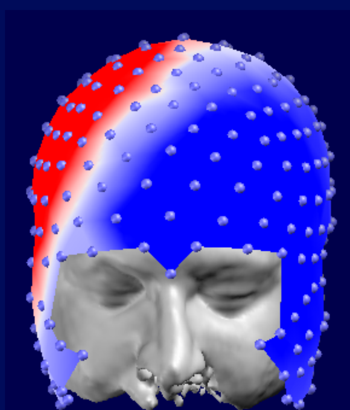
When pyramidal neurons are excited, the synaptic currents flowing across the cell membranes induce local excitatory postsynaptic potentials as well as magnetic fluxes, which collectively form the sources for EEG and MEG, respectively. When cortical neurons in columnar vicinity are in synchronized activation, the synaptic current flow, at a macroscopic level, approximates a **current dipole** located on cortical surface and oriented perpendicular to the local cortical surface (b).

The configuration (e.g. **location, magnitude, and orientation**) of such current dipole can be related with EEG or MEG signals through the modeling of head volume conduction (c).

[He et al., IEEE Transaction on Biomedical Engineering, 2011]

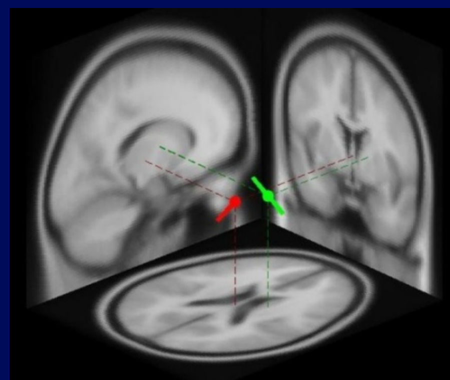
Electrical Source Imaging (ESI)

Scalp
electric field

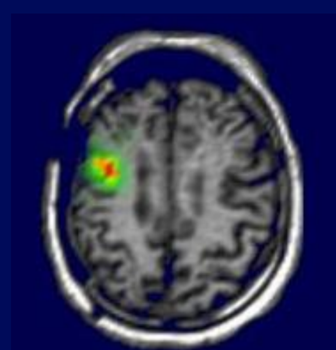


Source Model

Dipole

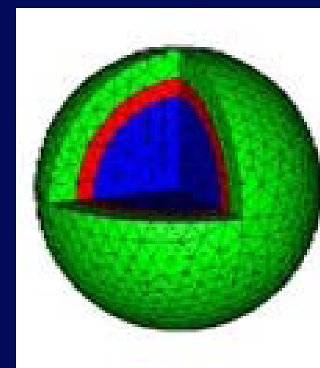


Distributed

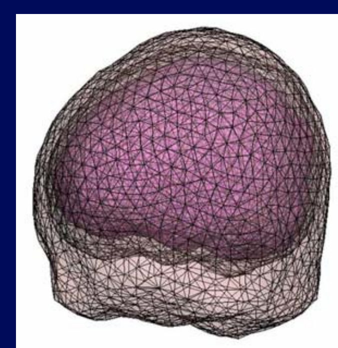


Head Model

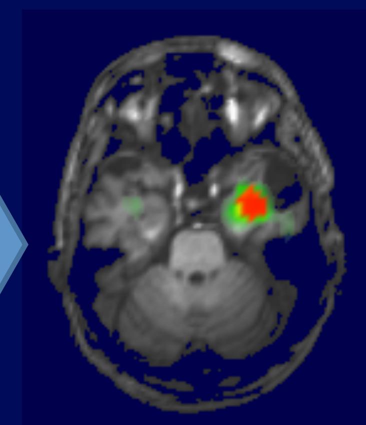
Spherical



Realistic



Sources
(current
density)



[Pascual-Marqui et al., 1994]
[Michel et al., 2004]

Electrical Source Imaging (ESI)

Electrophysiological source imaging (ESI) is a model-based approach for imaging electrical sources associated with brain activation from noninvasive EEG or MEG measurements.

ESI entails:

1) **forward modeling** of brain sources and head volume conduction to establish a linear source-to-measurement relationship.
2) **inverse imaging** of brain electrical sources from measured EEG, via various strategies, most commonly dipole localization and distributed source imaging.

Forward Problem

EEG forward problem describes the distribution of electric potentials for given source locations, orientations, and signals.
The relationship between EEG signals (Φ) and cortical current source dipoles (J) can be represented by a linear system:

?

$$\Phi = \mathbf{KJ} + c\mathbf{1}$$

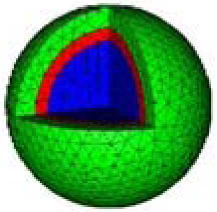
measured scalp potentials (EEG)

lead field matrix (describes how a unit dipole of a certain location and orientation is related to the EEG)

current density

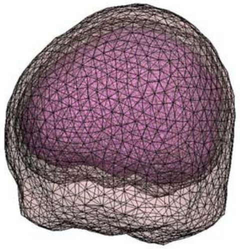
Head models

1. **Sphere-shaped head models**
   (uniform conductivity) → computationally efficient



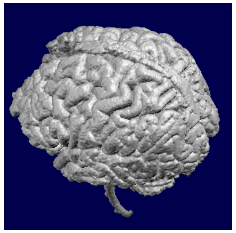
2. **Realistic Head Model:** these numerical models allow incorporating the realistic geometry of the head and brain after reconstruction of the anatomical structure from individual or standardized MRI data sets.

Boundary Element Method (BEM): gathers a more realistic shape of brain compartments of isotropic and homogeneous conductivities by using closed triangle meshes



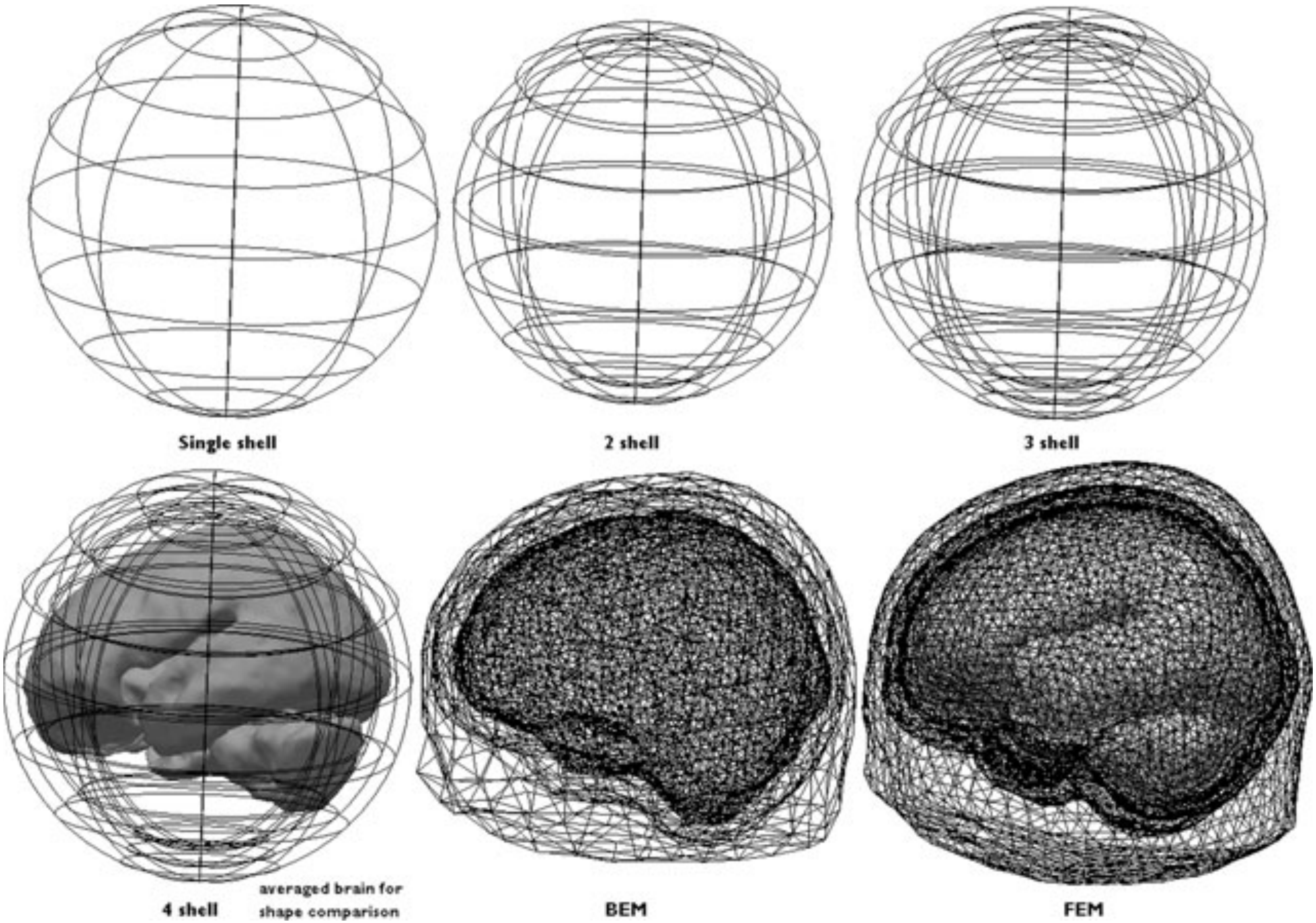
[Meijs et al., 1987]

Finite-Element Method (FEM): have better accuracy than the BEM because they allow a better representation of the cortical structures



[Bertrand et al., 1991, Awada et al., 1997]

Head Model



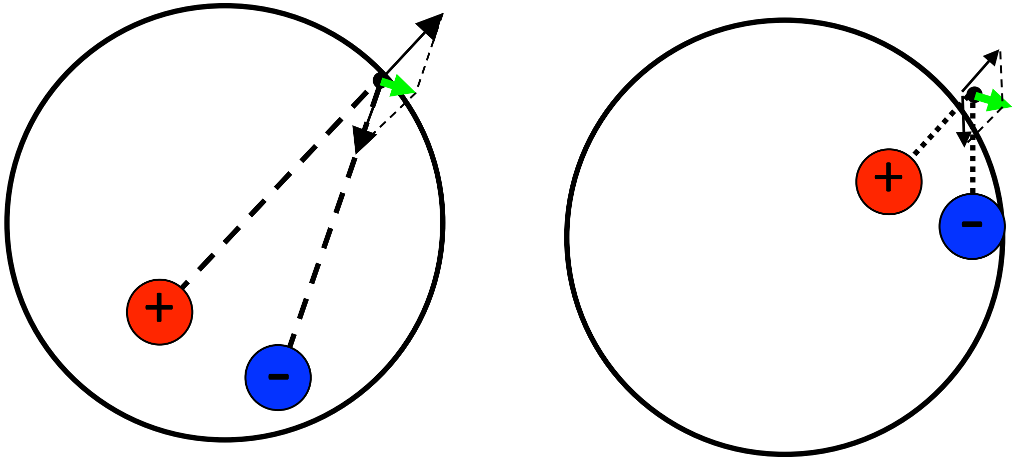
Realistic shape – (BEM isotropic, FEM anisotropic)

Plummer et al., Epilepsia, 2008

Inverse Problem

The inverse problem is used to convert measured electric potentials (EEG) into current densities of the sources.

The inverse problem is ill-posed because an infinity of different source configurations can produce the same EEG scalp distribution [Nurez and Srinivasan, 2006]

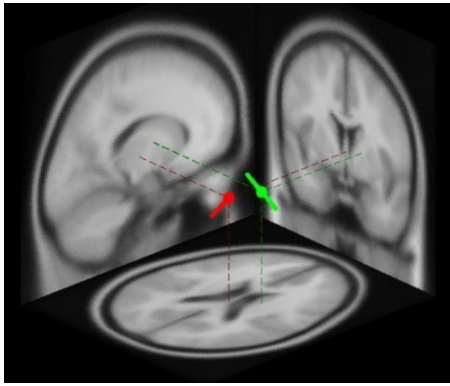


[Scherg and Von Cramon, 1985, Liu et al., 1998, Babiloni et al., 2003, Michel et al., 2004]

Inverse solutions

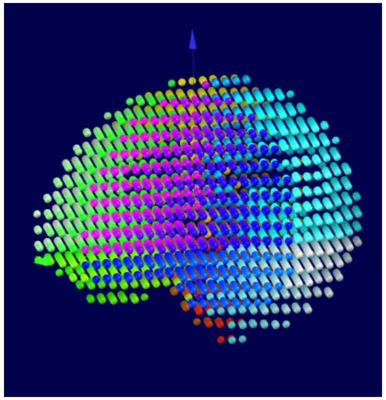
1. **DISCRETE**

   Equivalent current dipole (ECD) approach
   where the signals are assumed to be generated by few focal sources.



2. **DISTRIBUTED**

   Linear distributed (LD) approaches
   which consider that the dipoles are regularly distributed in cerebral volume according to a 3D grid and where all possible source locations are considered simultaneously.



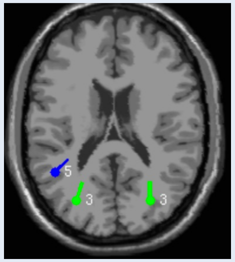
Equivalent current dipole approach

ECD assumes the underlying neuronal sources to be focal

Number of sources < number of sensors
OVERDETERMINED PROBLEM

The lead field matrix has more rows (number of sensors) than columns (number of sources)

Source model and source waveforms



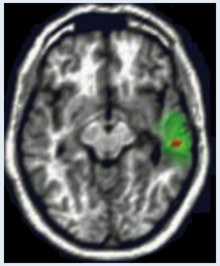
Linear distributed approches

The 3D grid of solution points is considered as a possible location of a brain activity source

Number of sources >> number of sensors
UNDERDETERMINED PROBLEM

The lead field matrix has more columns than rows

3D volume image for each time point



Equivalent current dipole

Parameter Estimate

To determine the best location of the sources, the squared error between the surface electric potential map generated by dipoles using a certain forward model and the actual measured potential map is calculated.

Methods

- Dipole fitting methods [Scherg, 1990]
- linear constrained minimum variance (LCMV) beamformers [Van Veen et al., 1997]
- the multiple signal classification (MUSIC) [Mosher and Leahy, 1998]
- ...

Limitations

- ECD models have some limits in estimating in advance the number of dipoles and localizing extended sources.

- The center of mass of the cortical activity is localized, but the distribution and the extension of the activity remain to be determined [He et al., 2011].

Linear distributed approches

The estimation of the dipole source configuration **J** is provided by the solution of the linear system:

?

$$\mathbf{\Phi} = \mathrm{K}\mathbf{J} + c\mathbf{1}$$

$\Phi \in R^{N_E \times 1}$ with $\Phi = (\Phi_1, \Phi_2, \ldots, \Phi_{N_E})^T$: is a $N_E \times 1$ known matrix of measurements of scalp electric potential differences

N_E: number of electrodes

$1 \in R^{N_E \times 1}$: is a vector of ones

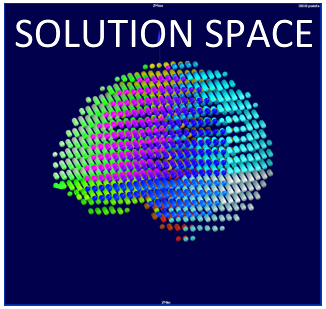
$\mathbf{J} \in R^{(3N_V \times 1)}$: matrix of current densities at N_V points within the brain volume

c : accounts for the physical nature of electric potential

$\mathrm{K} \in R^{N_E \times (3N_V)}$: transfer matrix or lead field matrix

$$\mathrm{K} = \begin{pmatrix} \mathbf{k}_{1,1}^T & \mathbf{k}_{1,2}^T & \cdots & \mathbf{k}_{1,N_V}^T \\ \mathbf{k}_{2,1}^T & \mathbf{k}_{2,2}^T & \cdots & \mathbf{k}_{2,N_V}^T \\ \cdots & & & \\ \mathbf{k}_{N_E,1}^T & \mathbf{k}_{N_E,2}^T & \cdots & \mathbf{k}_{N_E,N_V}^T \end{pmatrix}$$

$\mathbf{k}_{e,v} \in R^{3\times 1}$: are determined by all proprieties of the head, i.e. geometry and conductivity profile.



[Pascual-Marqui, Seikihara, Brandeis and Michel, Electrical Neuroimaging]

Particular inverse solutions

Minimum norm least square (MN) solution

$$\min_{\mathbf{J},c} \Psi \quad \text{with} \quad \Psi = \left\| \Phi - \mathbf{KJ} - c\mathbf{1} \right\|^2 + \lambda \mathbf{J}^T \mathbf{J}$$

[Hamalainen and Ilmoniemi, 1984]

Solution: $\hat{\mathbf{J}} = \mathbf{T}\Phi$ with $\mathbf{T} = \mathbf{K}^T \mathbf{H}(\mathbf{HKK}^T\mathbf{H} + \lambda \mathbf{H})^+$

$\mathbf{H} = \mathbf{I} - \frac{1}{N_E}\mathbf{1}\mathbf{1}^T$: denotes the N_ExN_E average reference operator

λ : Tikhonov regularization parameter

"+" denotes the Moore–Penrose generalized inverse

$\mathbf{I}$: N_ExN_E identity matrix

$\mathbf{1}$: Nx1 matrix comprised of ones

N_E : number of electrodes

Minimum norm solutions favors superficial sources and misplaces deep sources

Weighted minimum-norm least squares (WMN) solution

$$\min_{\mathbf{J},c} \Psi_D \quad \text{with} \quad \Psi_D = \left\| \Phi - \mathbf{KJ} - c\mathbf{1} \right\|^2 + \lambda \mathbf{J}^T \mathbf{DJ}$$

[Pascual-Marqui et al., 1994,
Gorodnitsky et al., 1995,
Grave de Peralta and Gonzalez, 1998]

Solution: $\hat{\mathbf{J}}_D = \mathbf{T}_D \Phi$ with $\mathbf{T}_D = \mathbf{D}^{-1}\mathbf{K}^T \mathbf{H}(\mathbf{HKD}^{-1}\mathbf{K}^T\mathbf{H} + \lambda \mathbf{H})^+$

D is used to "re-weight" the solution, i.e. to incorporate some prior knowledge about the spatial distribution of the source activity

Particular inverse solutions

Low-resolution electromagnetic tomography algorithm (LORETA)

$$\min_{\mathbf{J},c} \Psi_W \quad \text{with} \quad \Psi_W = \left\| \Phi - \mathbf{KJ} - c\mathbf{1} \right\|^2 + \lambda \mathbf{J}^T W \mathbf{J}$$

[Pascual-Marqui et al., 1994, 1999]

Solution: $\hat{\mathbf{J}}_W = \mathbf{T}_W \Phi$ with $\mathbf{T}_W = \mathbf{W}^{-1}\mathbf{K}^T\mathbf{H}(\mathbf{HKW}^{-1}\mathbf{K}^T\mathbf{H} + \lambda\mathbf{H})^+$

$$\mathbf{J}^T\mathbf{WJ} = \sum_v \left\| \mathbf{j}_v - AveNeighb(\mathbf{j}_v) \right\|^2$$

$AveNeighb$: average of current densities in the immediate neighborhood of point v, excluding point v

LORETA minimizes the squared norm of the Laplacian of the weighted 3D current-density vector field. It incorporates the ”smoothness assumption” selecting the inverse solution of the measured data with the smoothest distribution in space.

Local Autoregressive Average (LAURA)

$$\mathbf{J}^T\mathbf{W}_{Laura}\mathbf{J} = \sum_v \left\| \mathbf{j}_v - WeightedAveNeighb(\mathbf{j}_v) \right\|^2$$

[Grave de Peralta and Gonzalez, 2002]

The estimated activity at one point depends on the activity at neighboring points according to electromagnetic laws (i.e. the strength of the source declines with the inverse of the squared distance of the potential field).

Electrical Source Imaging: clinical applications

Electrical Source Imaging: clinical applications

Identification of spontaneous EEG activity:

- **Interictal activity** of epileptic patients
- **Alpha rhythm** (resting state)
- **Sleep waves** (spindle)

And evoked:

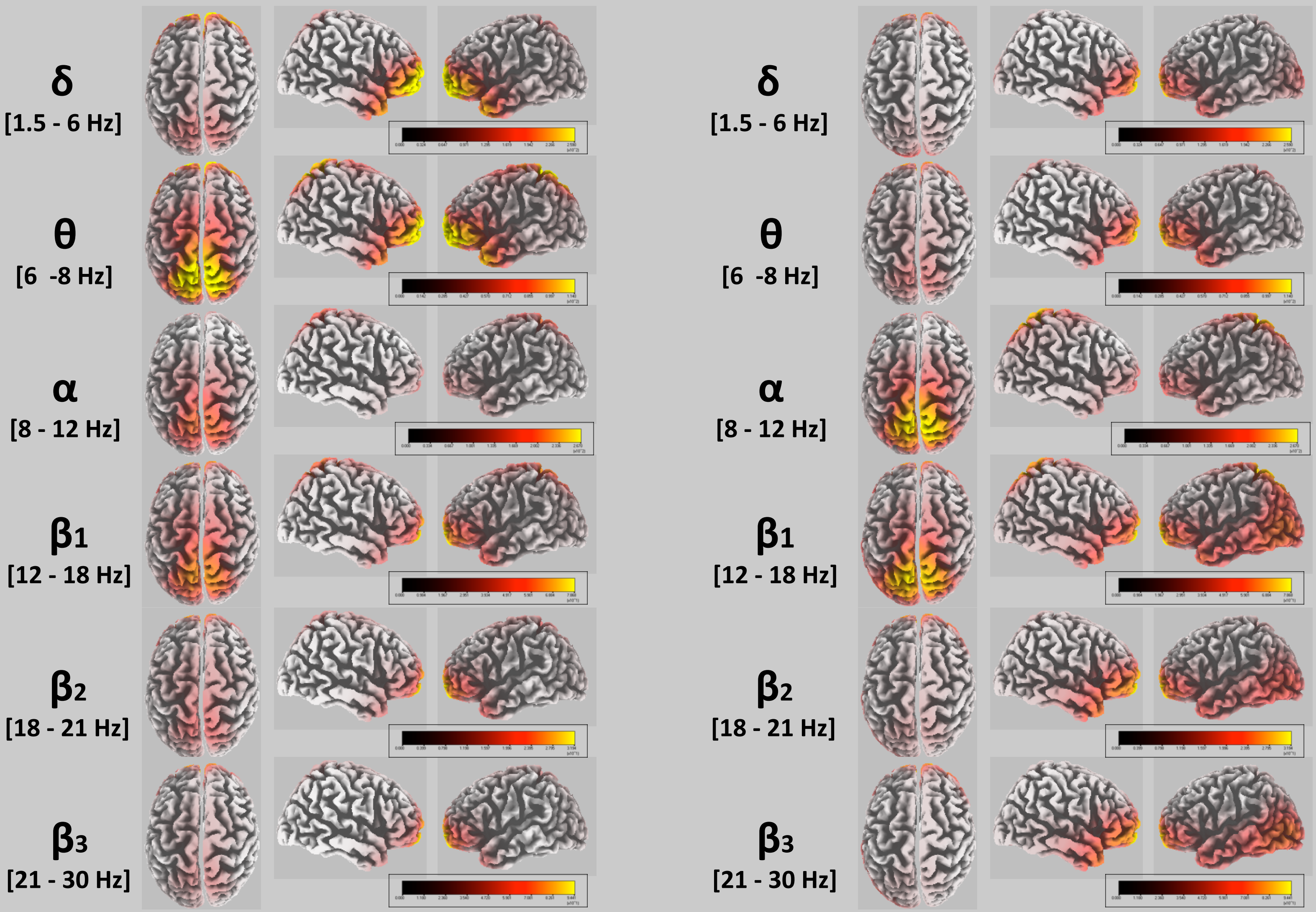
- **evoked potential**

Electrical Source Imaging of Alpha Rhythm

- Scalp EEG activity shows oscillations at a variety of frequencies.
- Several of these oscillations have characteristic frequency ranges, spatial distributions and are associated with different states of brain functioning (e.g. waking and the various sleep stages).

The localization of EEG rhythms in normal subjects, without any paradigm (attention, visual and auditory stimuli) or without CNS dysfunction are obtained from the EEG signal filtered for specific frequency bands.

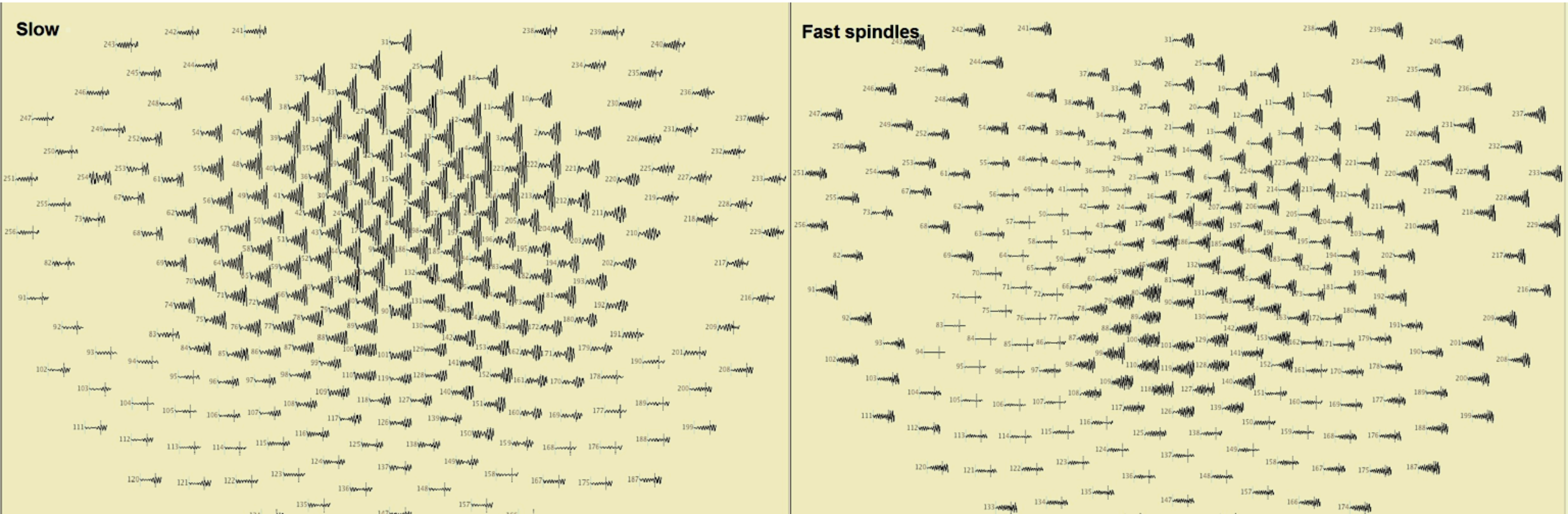
Electrical Source Imaging of Brain Rhythms



Sleep

Stage 1: a transition period between wakefulness → high amplitude **theta waves**
Stage 2: bursts of rapid, rhythmic brain wave activity known as **sleep spindles**
Stage 3: Deep, slow brain waves known as **delta waves**
Stage 4: **delta waves** occur during this time
Stage 5: **rapid eye movement (REM) sleep**

A sleep spindle is a burst of oscillatory brain activity visible on an EEG that occurs during stage 2 sleep. Sleep spindles are bursts of waxing and waning oscillations in the frequency of 10 to 15 Hz and last from 0.5 to 2 seconds.

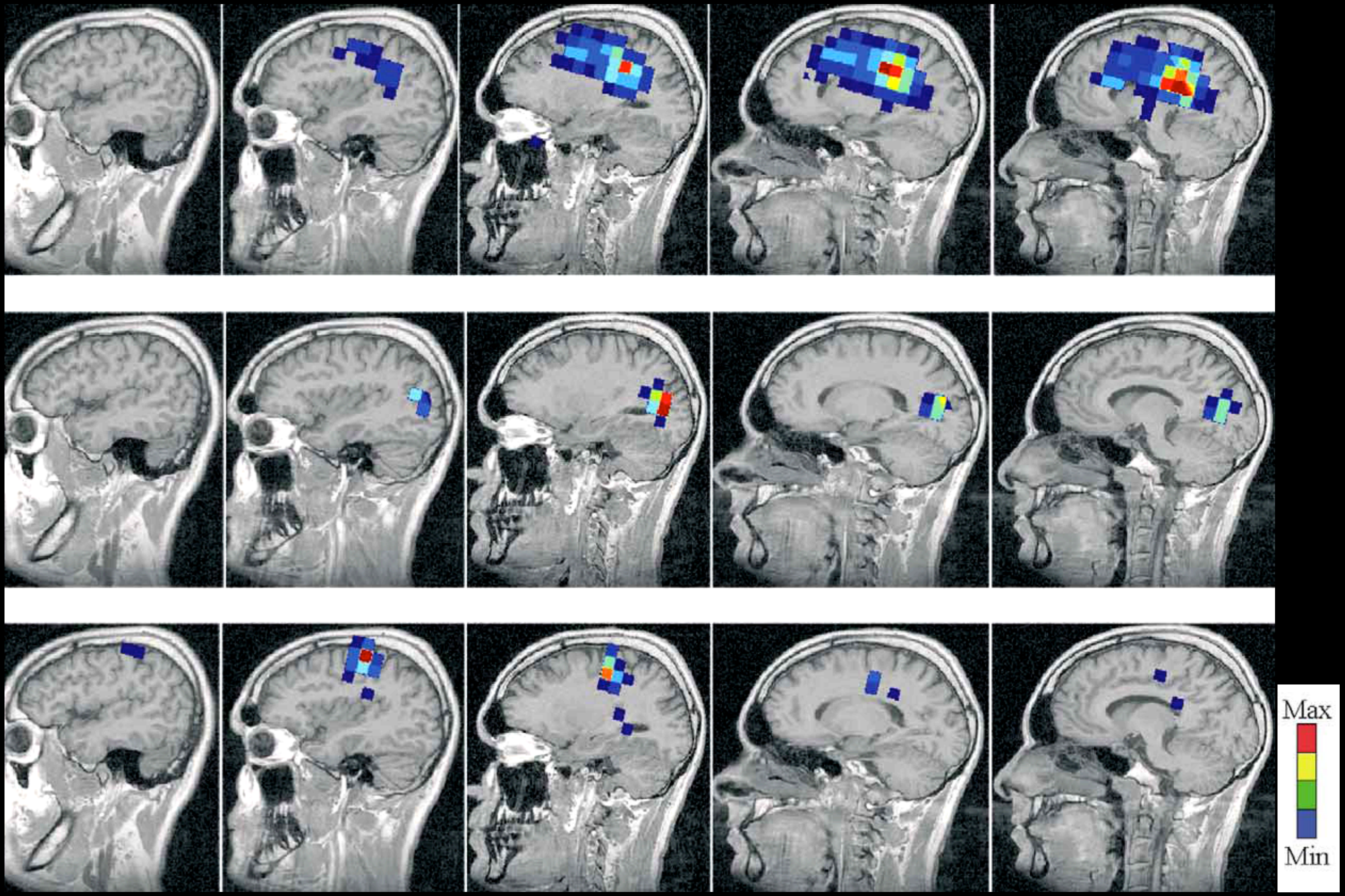


Electrical Source Imaging of Brain Rhythm

Spindle

Alpha rhythm

Mu rhythm



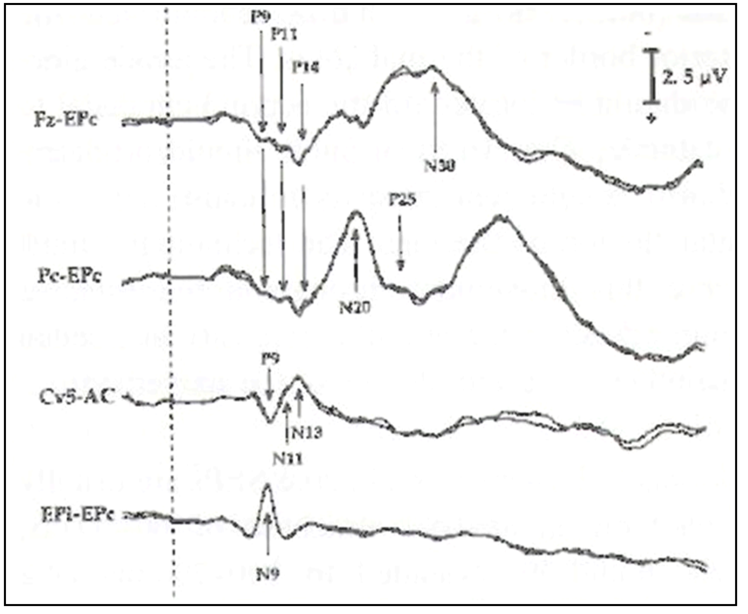
[Manshanden et al., Clin Neurophysiol 2002]

Evoked Potential (EP)

An evoked potential is an electrical potential recorded from the nervous system in response to stimulation of specific sensory nerve pathways.

Evoked potential amplitudes ranging from less than a µV to several µV (compared to tens of µV for EEG).

To resolve these low-amplitude potentials against the background of ongoing EEG and external noise, **signal averaging** is usually required.
The signal is time-locked to the stimulus and most of the noise occurs randomly, allowing the noise to be averaged out with averaging of repeated responses.



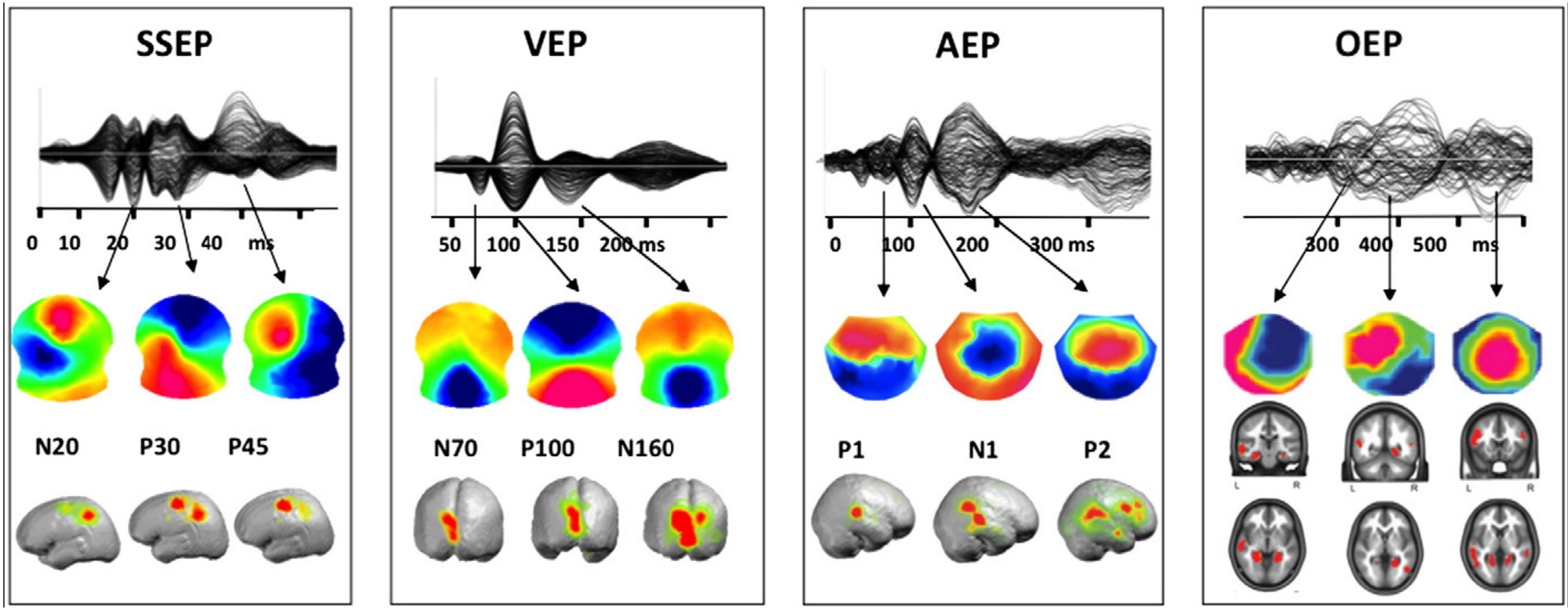
Electrical Source Imaging of EP

256-channel somatosensory evoked potential (SSEP) after right median nerve stimulation

256-channel visual evoked potential (VEP) after full-field checkerboard reversal

192-channel auditory evoked potential (AEP) after short tones

64-channel olfactory evoked potential after unilateral nostril stimulation with hydrogen sulfide



[Lascano et al., J. Clin. Neurophysiol 2009]

Drug resistant focal epilepsy

The feature of partial seizures is the presence of abnormal electrical activity that originates from an epileptic foci.

Seizures prevent healthy development and may cause brain damage.

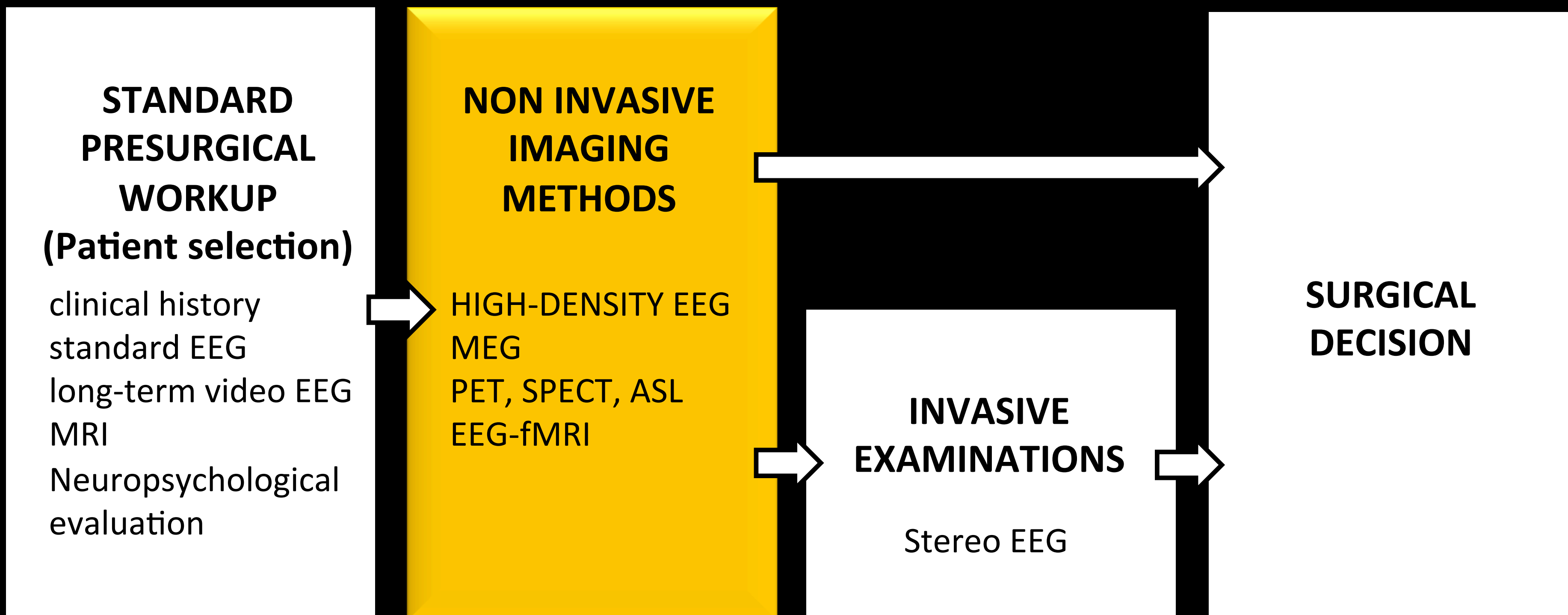
Treatment

35% of focal epilepsy patients do not respond to medication, and must undergo surgical resection of the epileptic focal points.

Surgery requires accurate localization of the foci.

Candidate for epilepsy surgery

- Persistent seizures despite appropriate pharmacological treatment
- Impairment of quality of life due to ongoing seizures



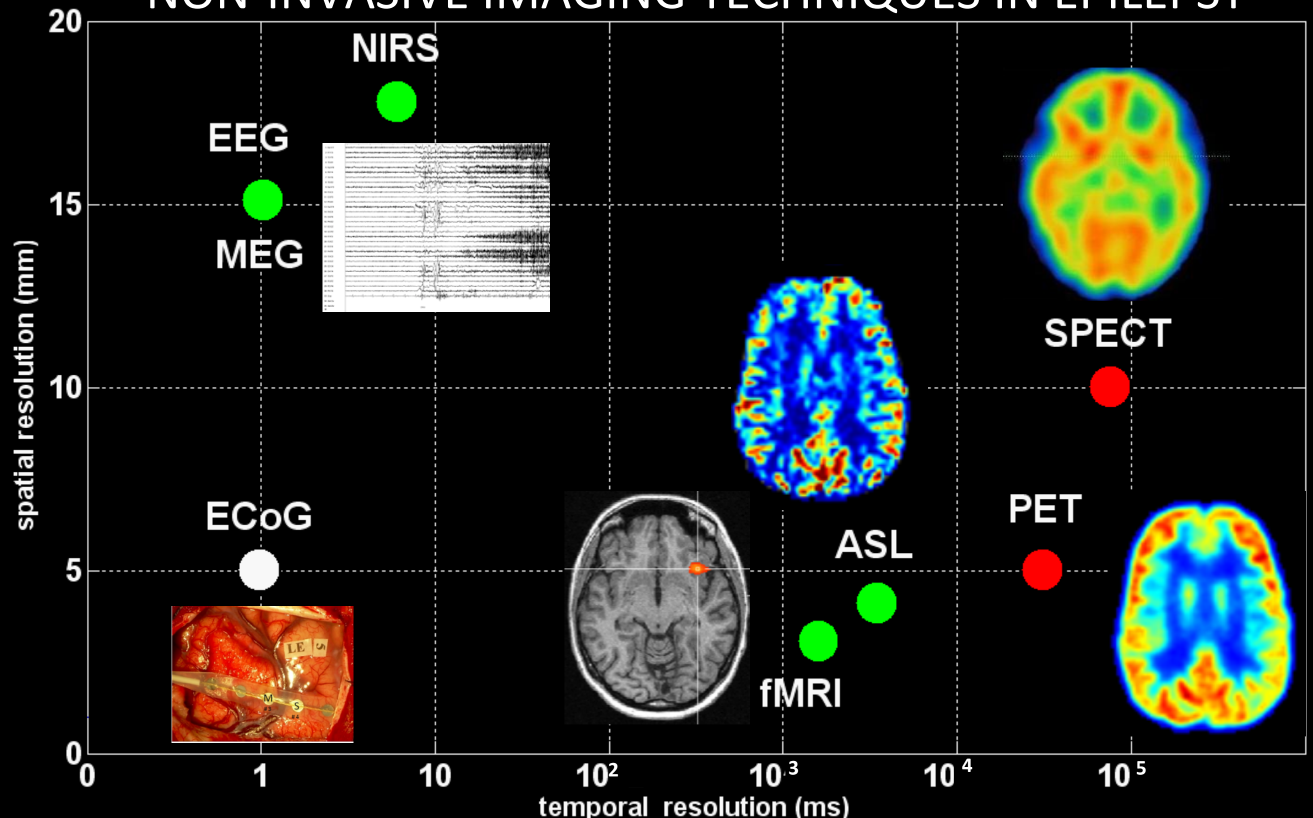
They do not always provide the localizing accuracy required for surgical planning

Candidate for epilepsy surgery

- Standard presurgical workup does not always provide the localizing accuracy required for surgical planning

- Non-invasive imaging methods are useful to correctly identify the activity before the surgery treatment

NON-INVASIVE IMAGING TECHNIQUES IN EPILEPSY



Each bears limitations that can be partly overcome by combining their results!

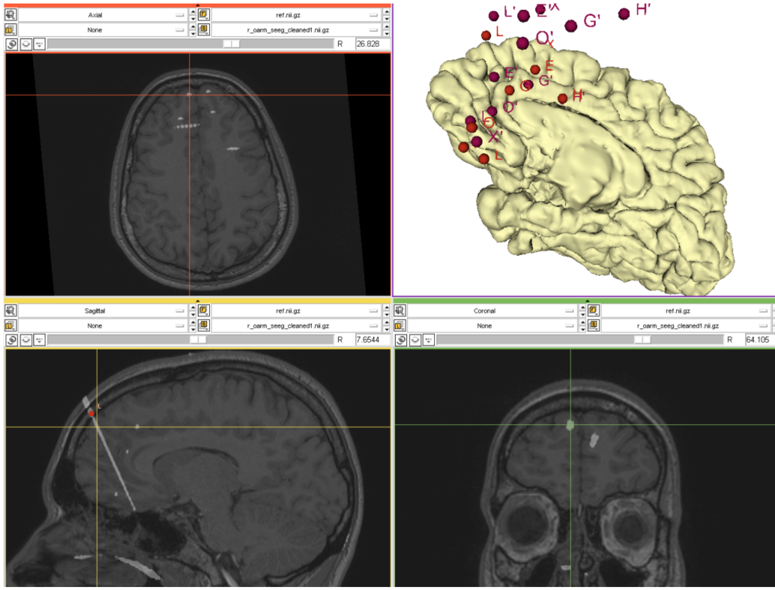
(Bagshaw et al., 2006; Brodbeck et al., 2010; Groening et al., 2009; Storti et al., 2012; Vulliemoz et al., 2010ab)

Invasive examinations

Stereo EEG

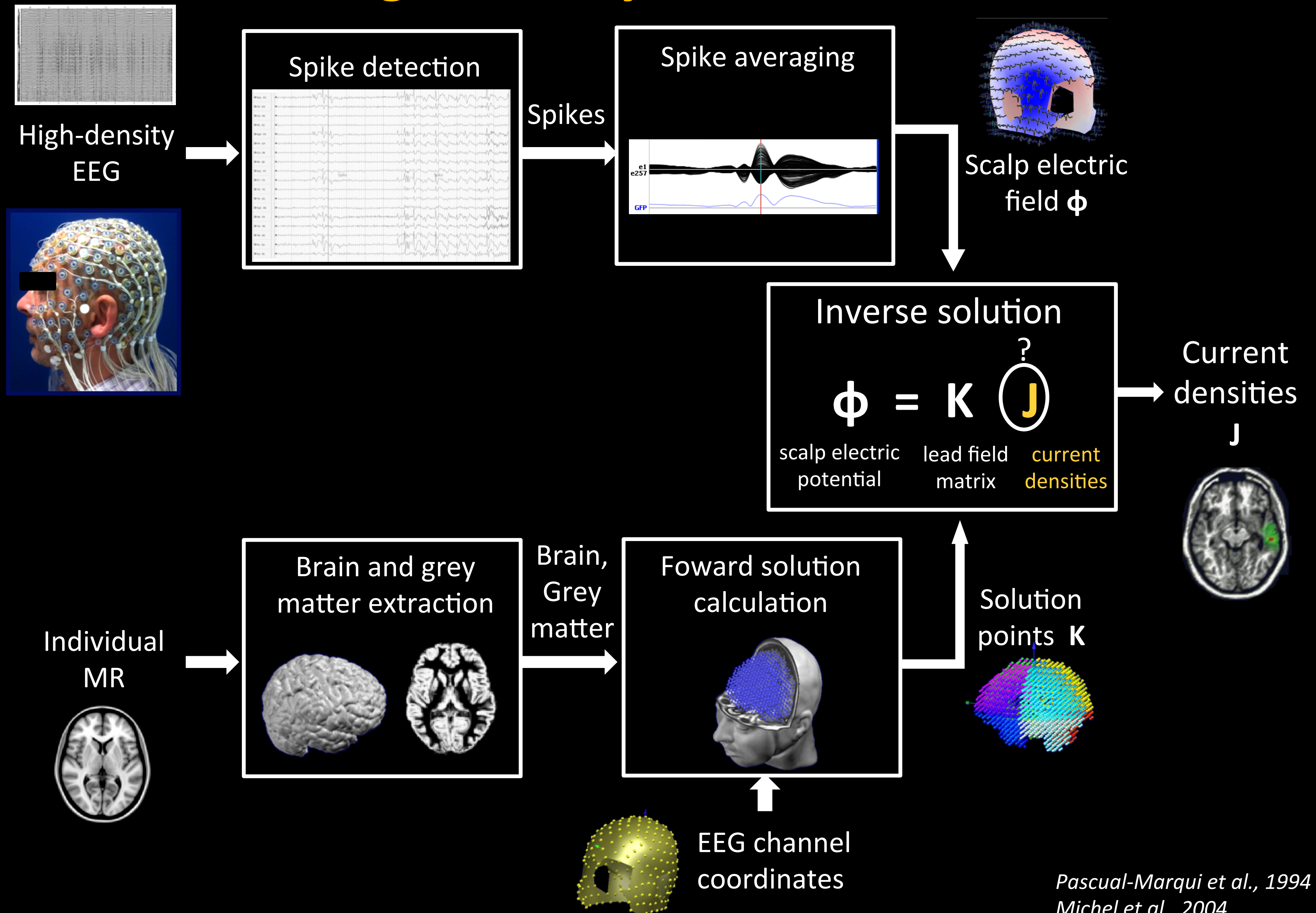
Intracerebral electrodes:

- are implanted into the selected brain area to record the electrical activity during epileptic seizures.
- define with accuracy the boundaries of the epileptogenic zone, i.e. the area of brain generating the seizures.
- The implantation of intracerebral electrodes is carried out on the basis of non-invasive examinations.
- It is used in patients with epilepsy not responding to drug treatment, and who are potential candidates to receive brain surgery.

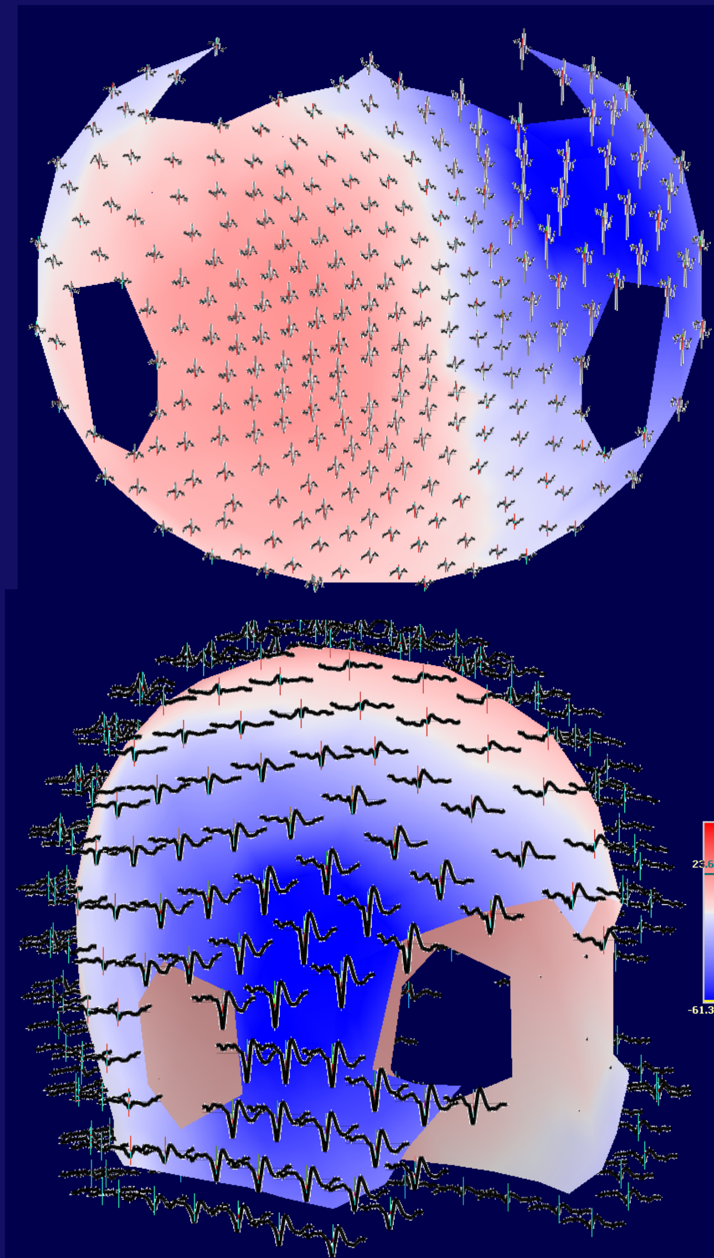


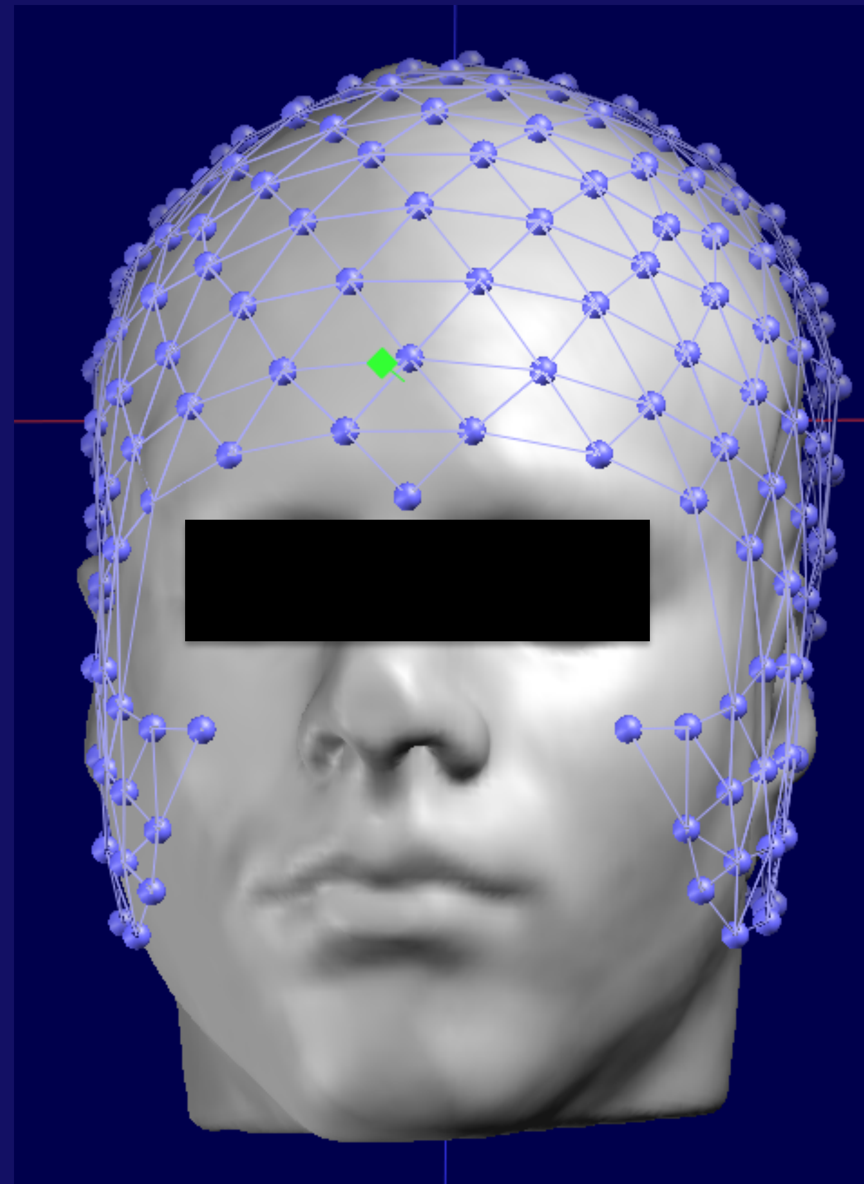
Niguarda Hospital

High-density EEG and ESI



Electrodes registration

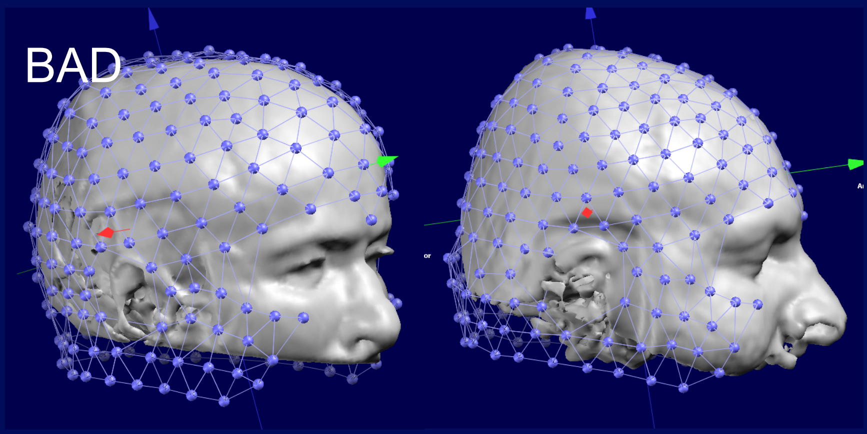


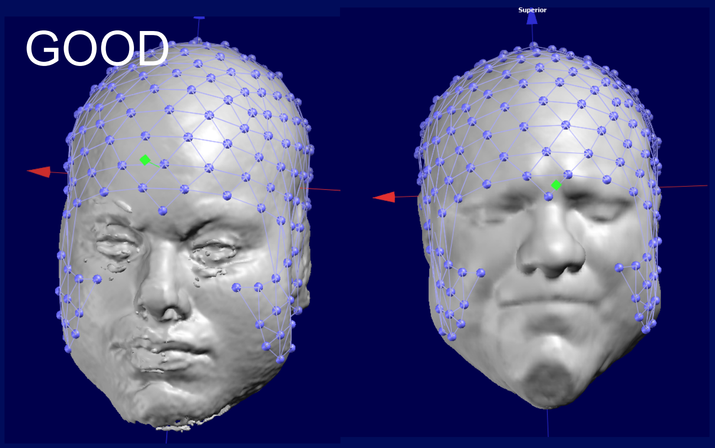


Cartool software

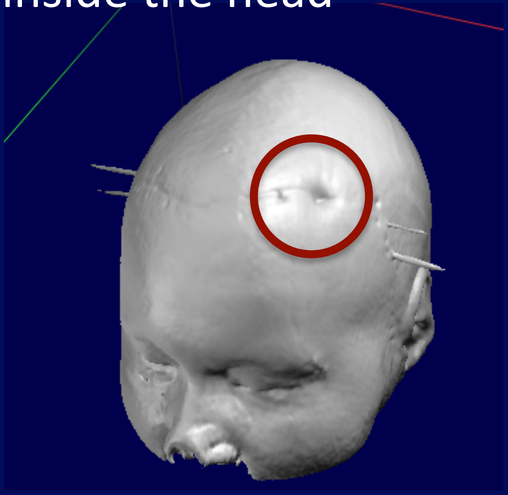
Electrodes registration : practical issues

1. Electrodes floating in the air below the MRI cut



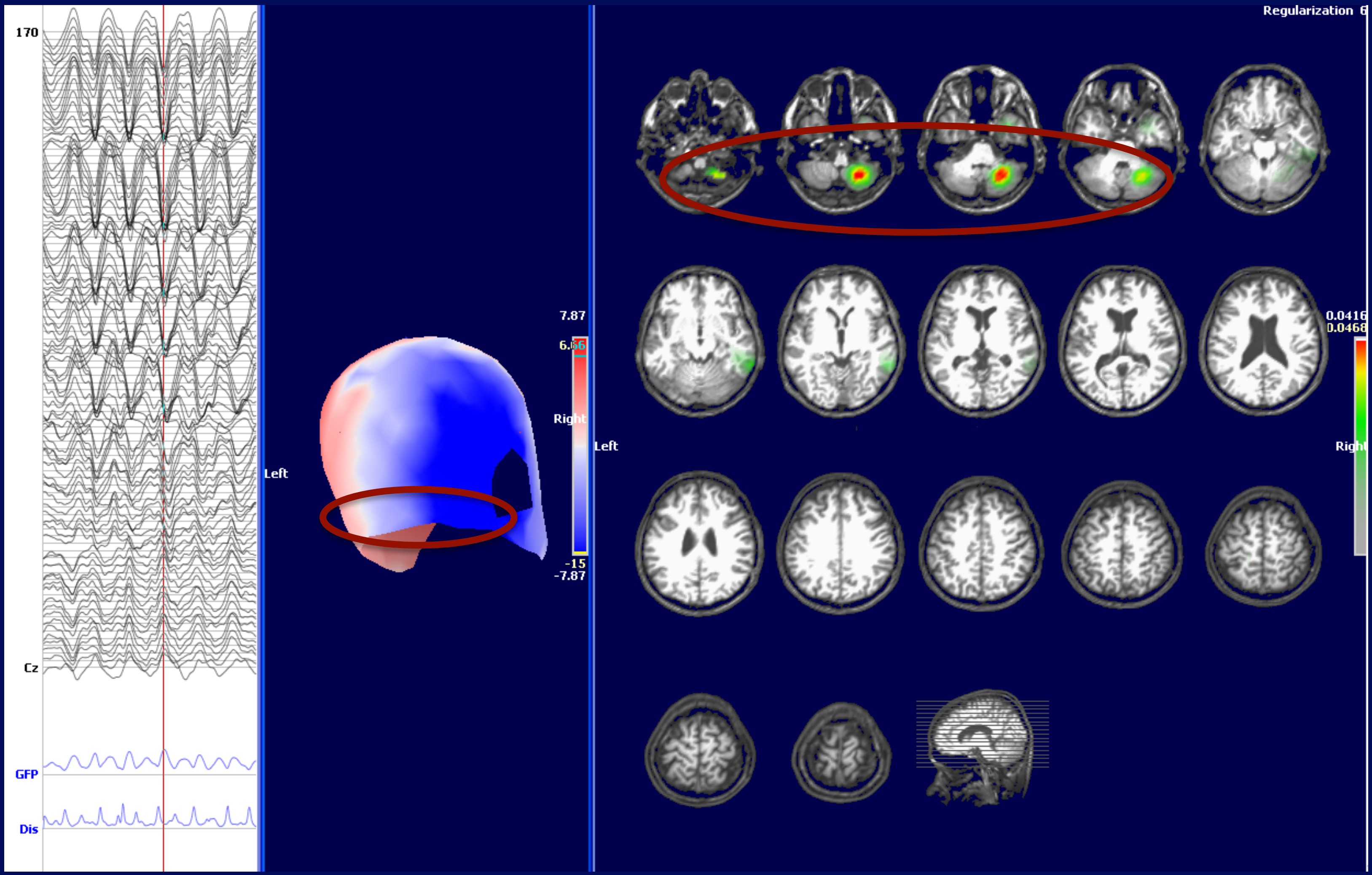


2. Registering electrodes to a corrupted MRI (irregular surface) → some electrodes could land inside the head



MRI (brain and grey matter extraction): issues

3. Skull-stripped brain should contain grey and white matters and void of cerebellum



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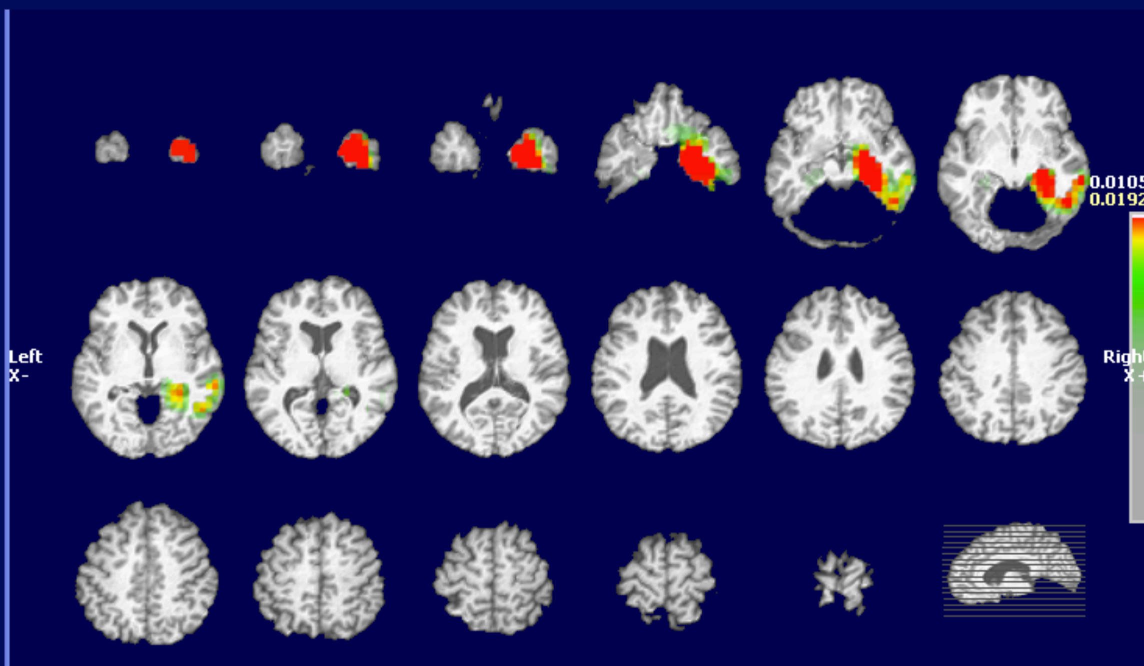
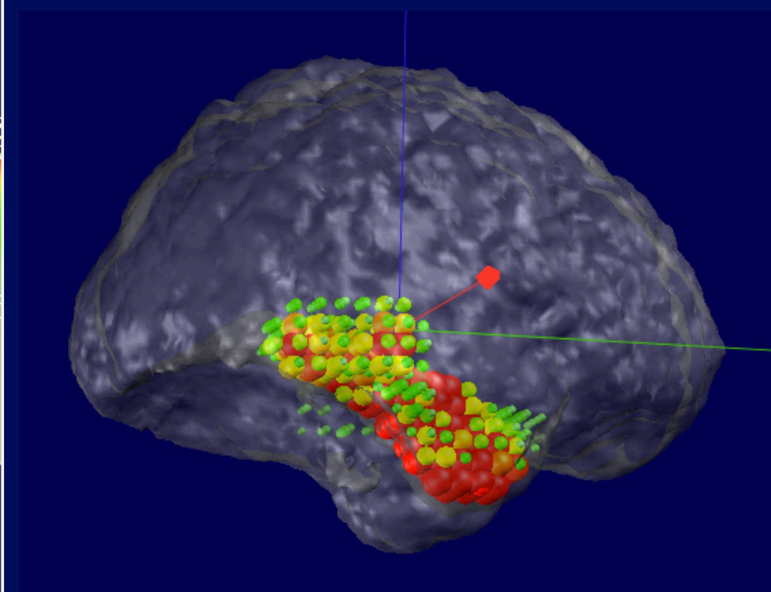
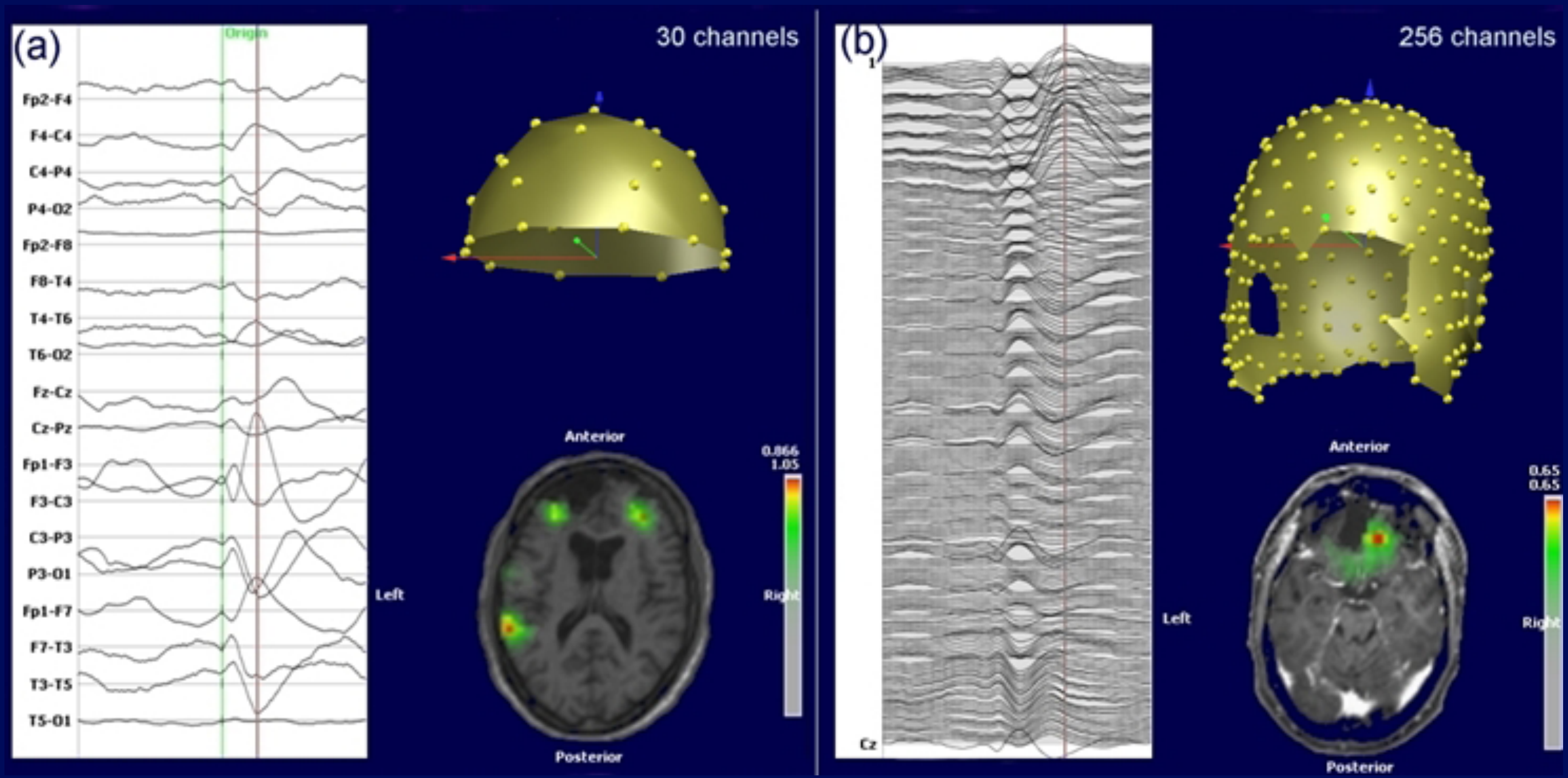


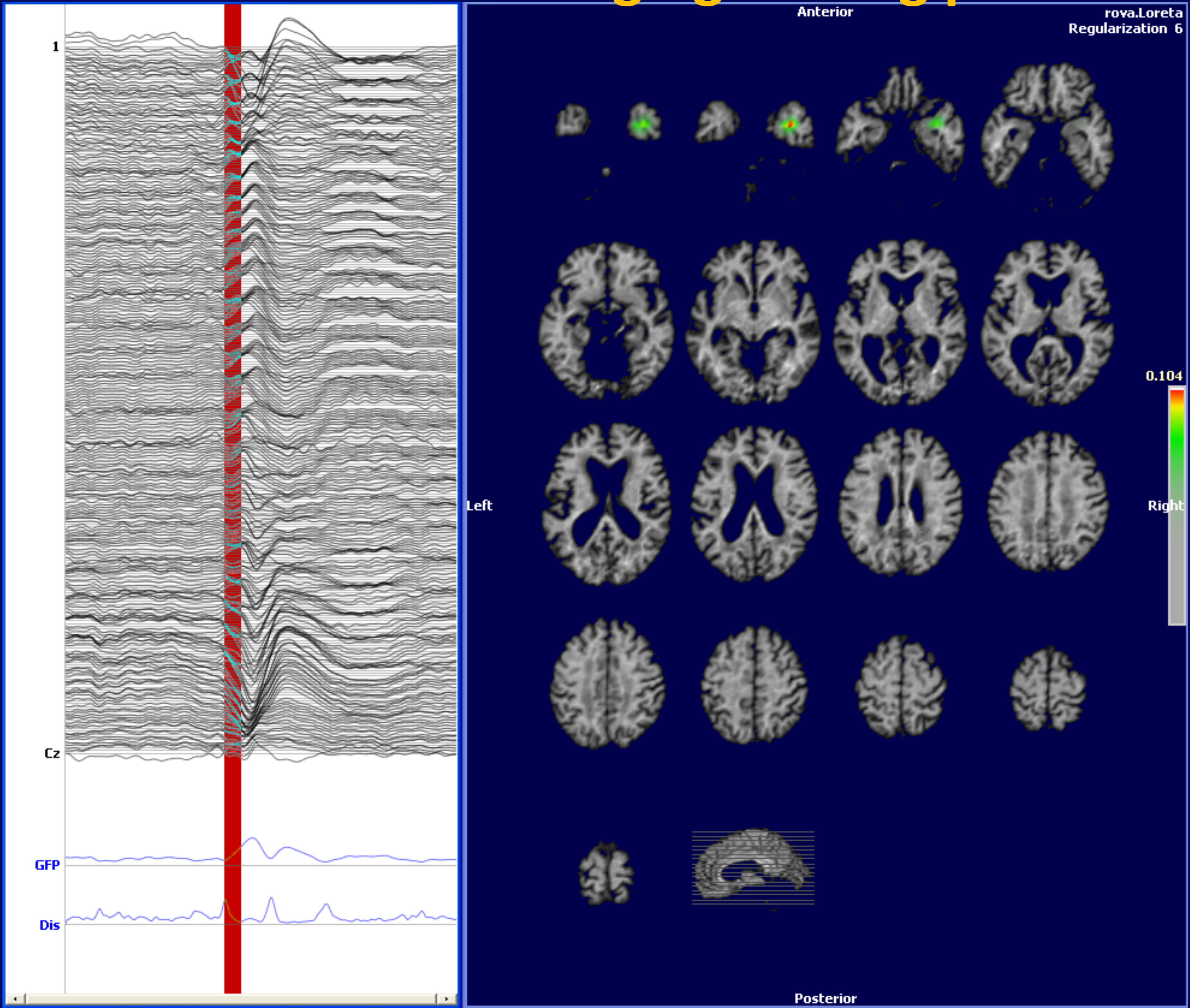


Effect of the number of electrodes on the estimation of the source

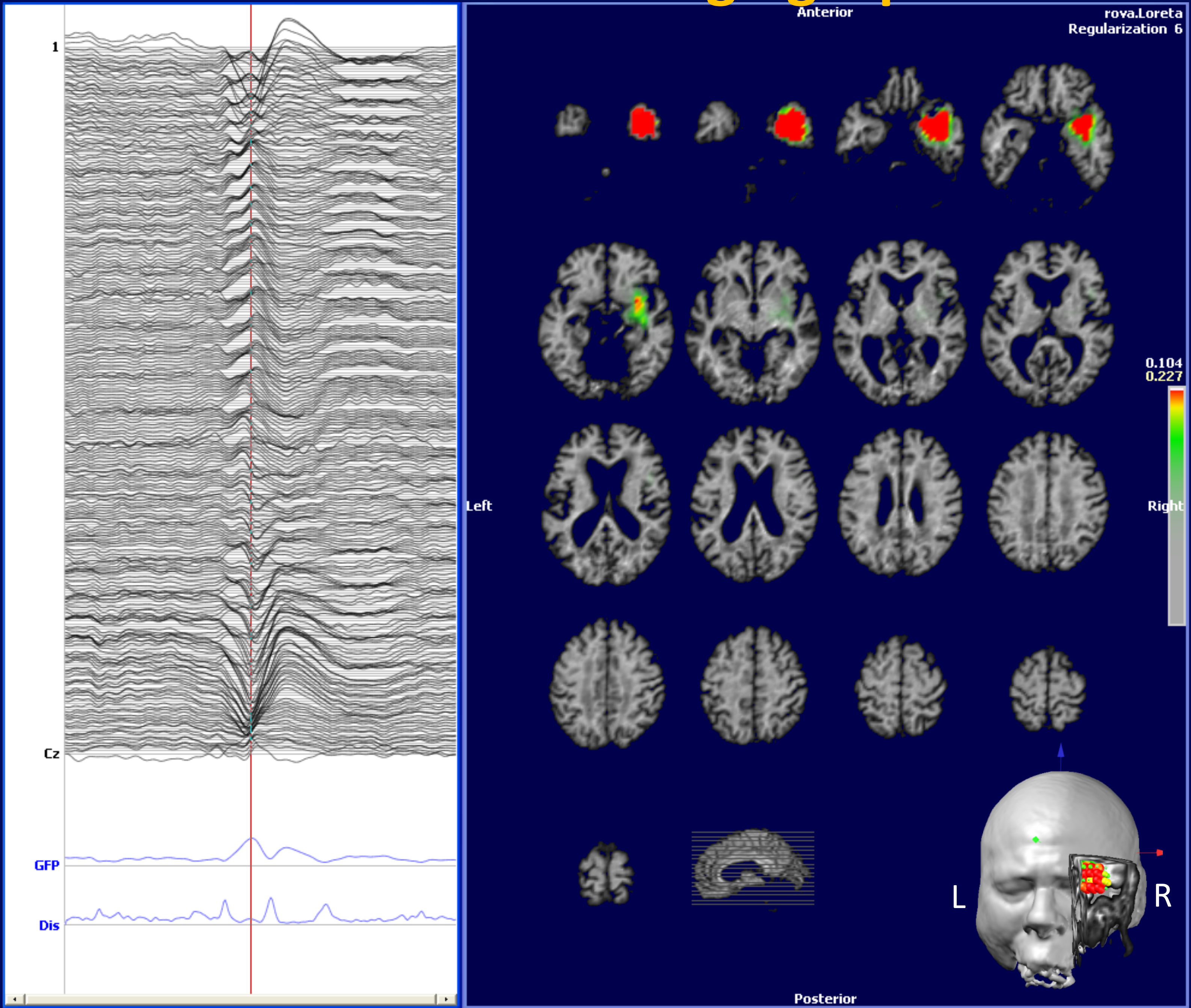


The source localization can be biased by a low number of electrodes [Michel et al., 2004] → increasing the number of electrodes the localization can be improved.

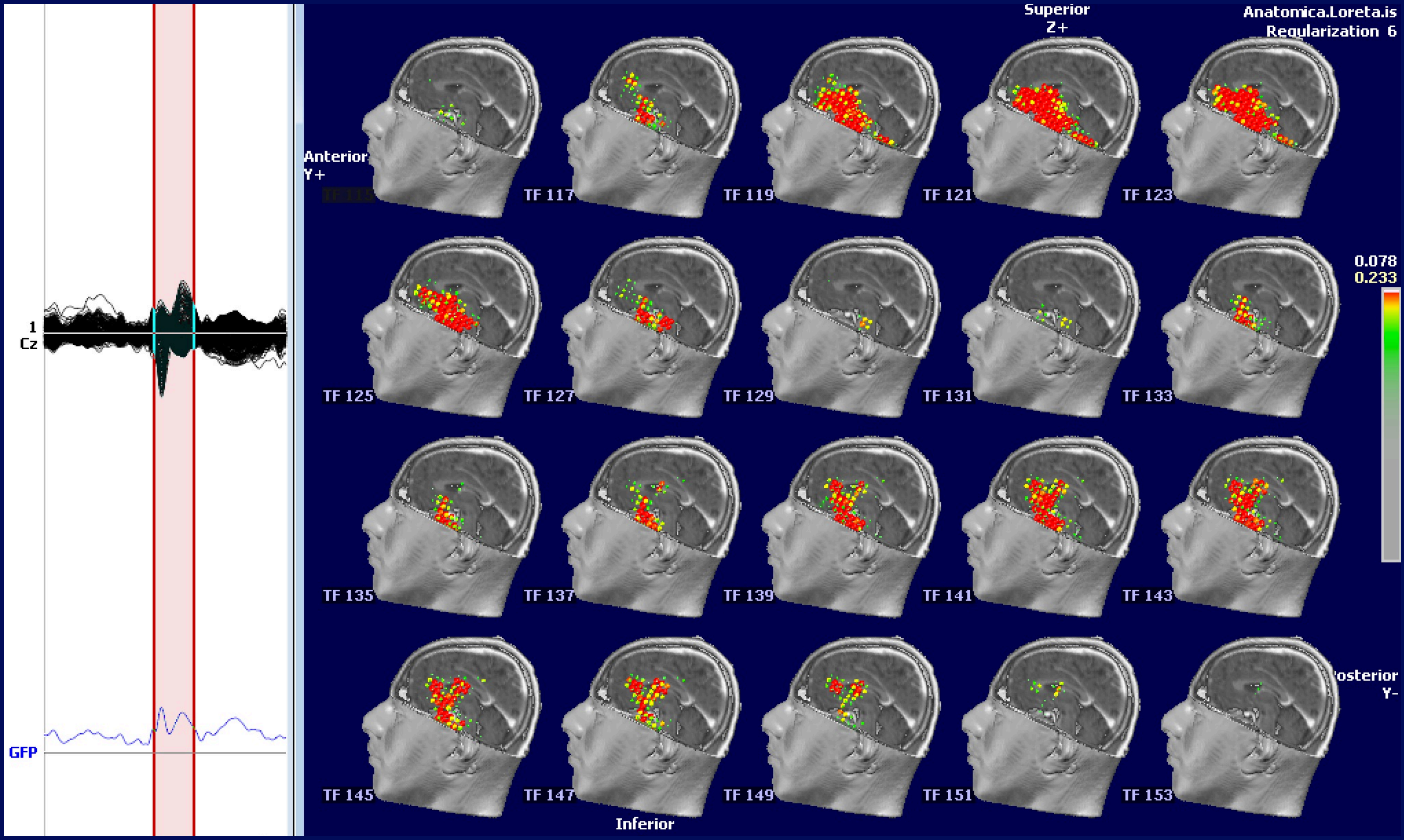
Electrical source imaging – rising phase



Electrical source imaging – peak

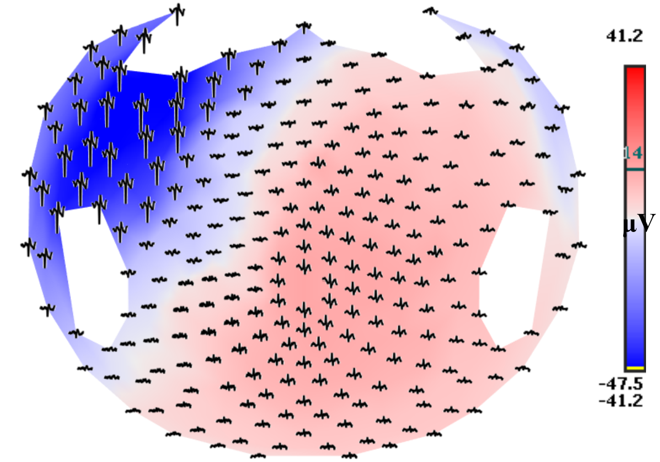


Time Course – example



Patient 1 - temporal epilepsy

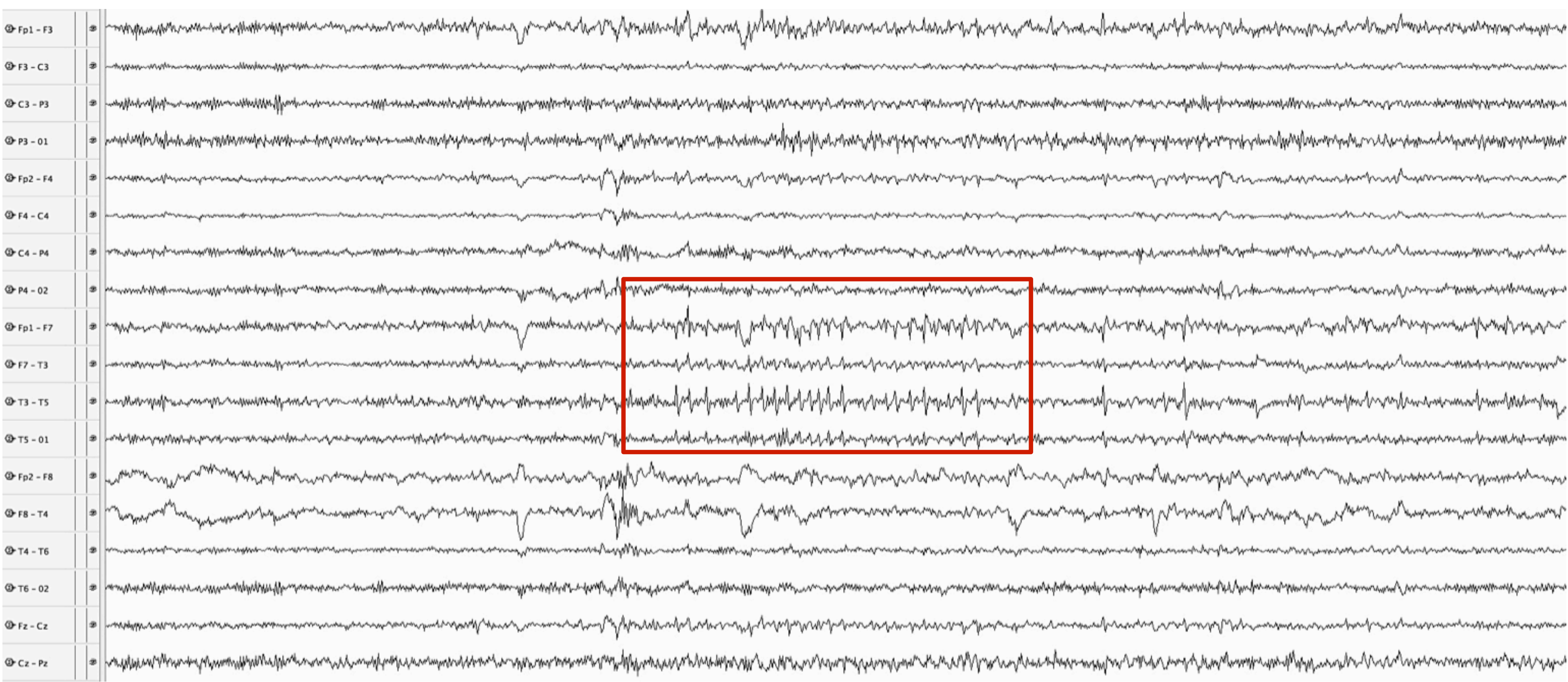
36-year-old woman



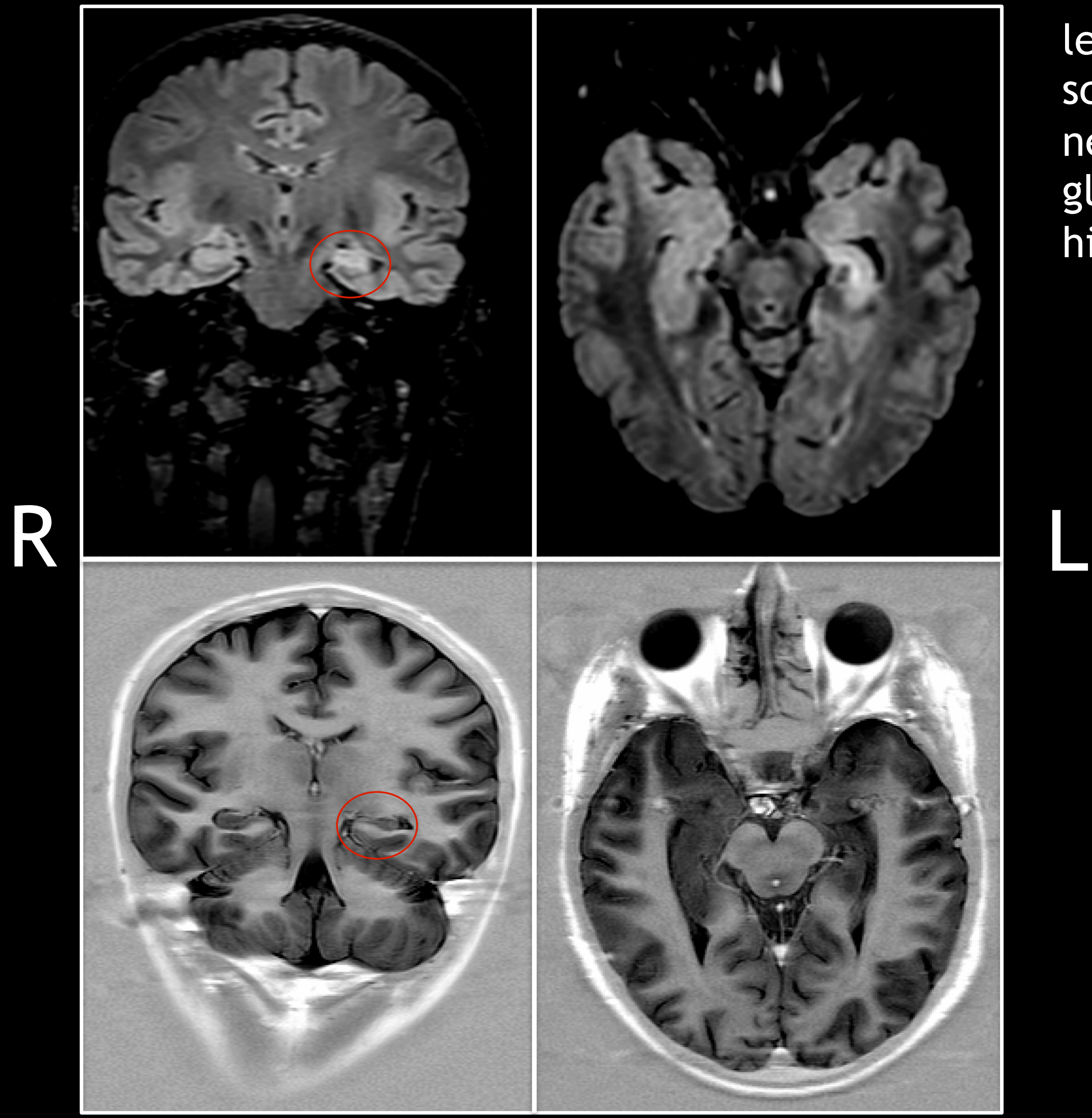
Seizure Events. Repeated episodes of febrile convulsions (9-12 months). Frequent episodes (17 years) characterized by oral automatism, tachycardia, nausea, gastralgia and then right head version, right arm hyperextension and intra-rotation, and left-hand fiddling, tonic-clonic movements.

Anatomy. The MRI scan revealed left hippocampal sclerosis.

High-density EEG. Epileptiform discharges such as pseudorhythmic runs of spikes over the left anterior temporal lobe that, on the 2D visualization, localized on the anterior zygomatic derivations.

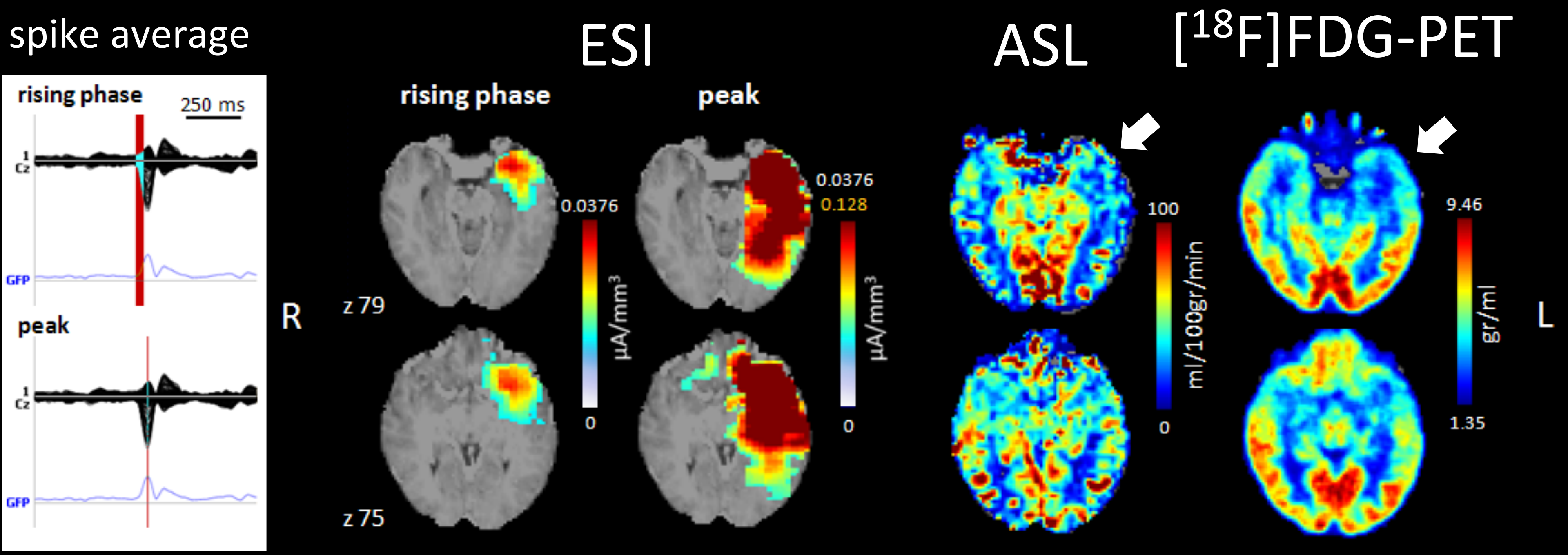


Patient 1 - temporal epilepsy



left hippocampal sclerosis: severe neuronal cell loss and gliosis in the hippocampus

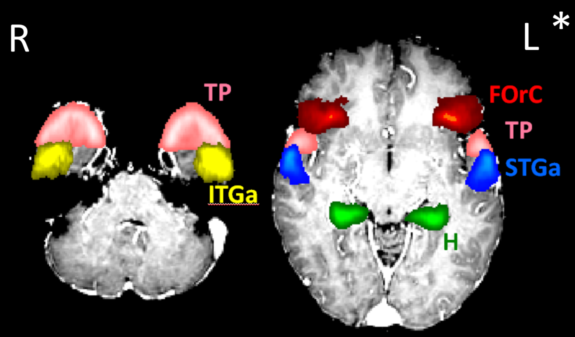
Patient 1 - temporal epilepsy



This patient was evaluated with hdEEG, ASL, and PET during the interictal phase.

Patient 1 - Quantification results

ROI ANALYSIS



	r-H	l-H	r- ITGa	l- ITGa	r-TP	l-TP	r-STGa	l-STGa	r-FOrC	l-FOrC
CD	0.006	0.010	0.006	0.015	0.005	0.021	0.006	0.012	0.006	0.019
CBF	64.83	50.58	22.81	24.42	44.50	29.42	42.78	40.39	46.62	45.05
SUV	4.74	3.98	3.94	4.04	4.06	3.62	5.44	4.77	5.61	4.61

CD: [μA/mm^3] CBF: [ml/100g/min] SUV: [g/ml]

SURGERY

Surgical resection of the left hippocampus.

During the postoperative follow-up, patient no. 1 (1 year) reported no seizure occurrence.

Patient 2 - temporal epilepsy

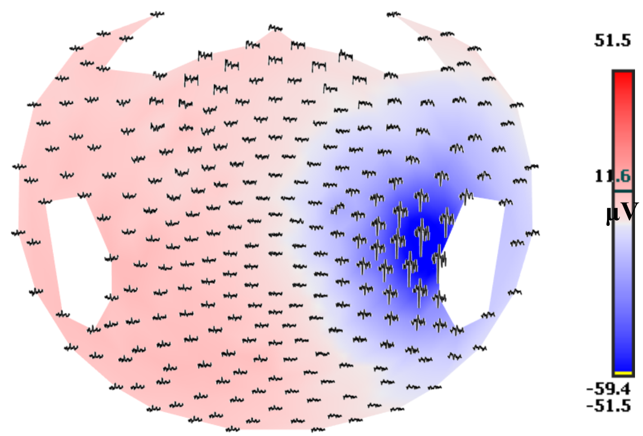
36-year-old man

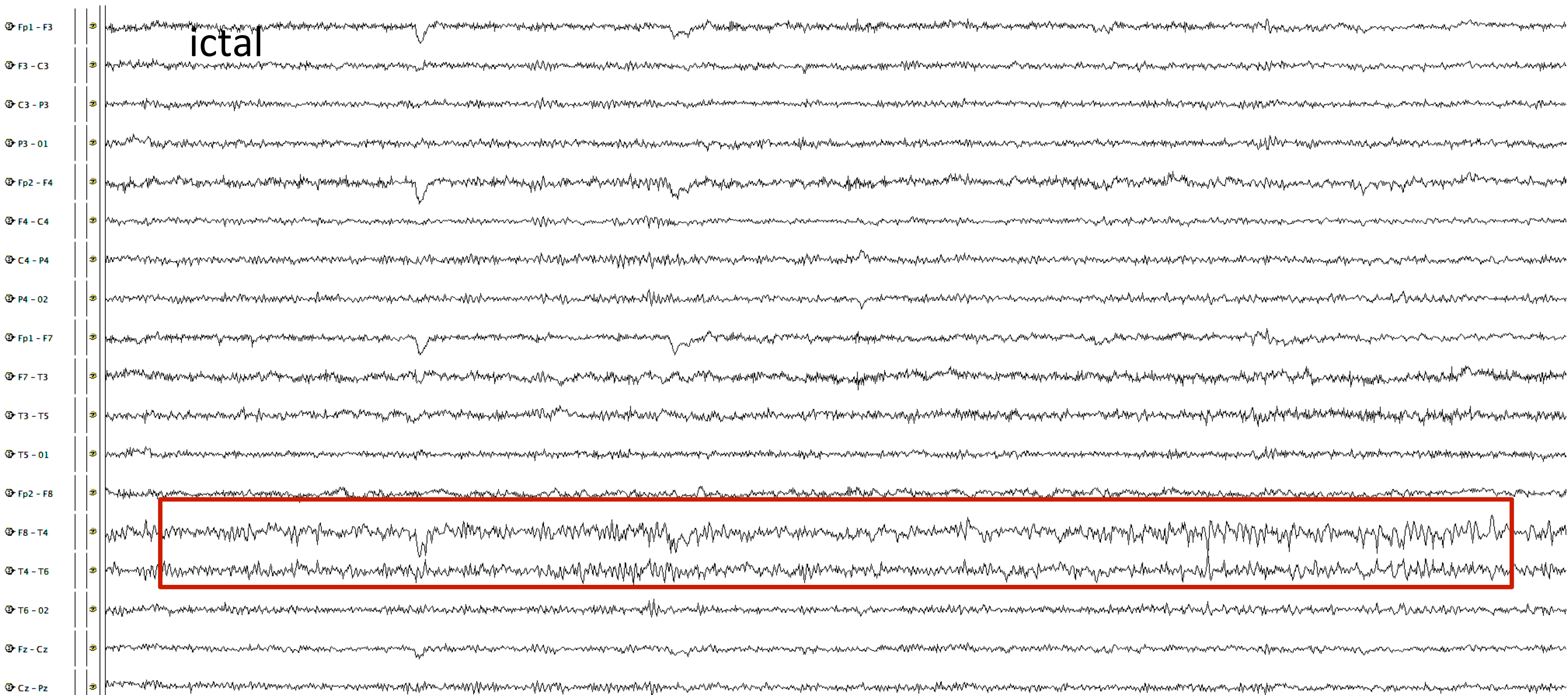
Seizure events. Partial seizures (19 years) characterized by noise in the left ear, flushing, eye redness, and left-arm gesturing.

Anatomy. MRI scans were always normal.

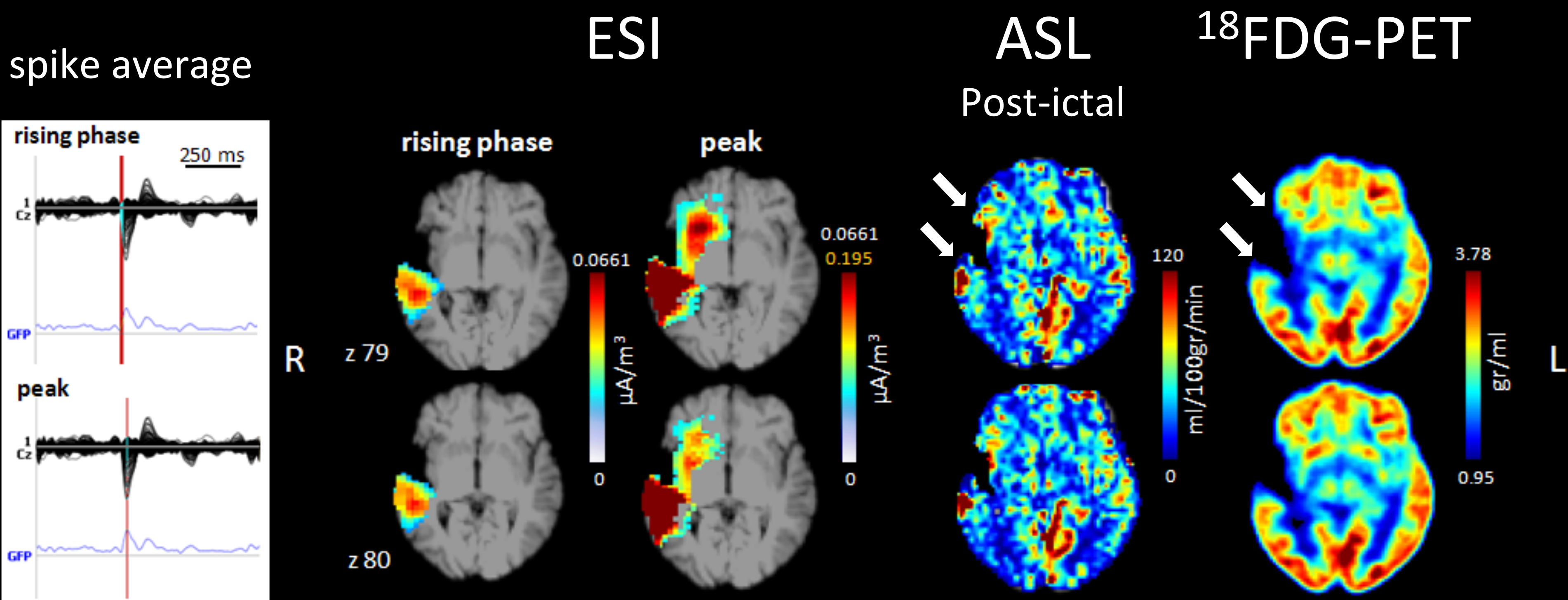
Stereo EEG and surgery. A stereo EEG investigation pointed to an epileptogenic zone over the first temporal gyrus that was surgically resected. Despite surgery, the seizures persisted.

High-density EEG. (Seizures) a burst of spikes (10 Hz) at the right temporal derivations, followed by sharp-waves with intermixed brief lapses (0.5 s) of rapid spikes sometimes spreading to the contralateral leads.





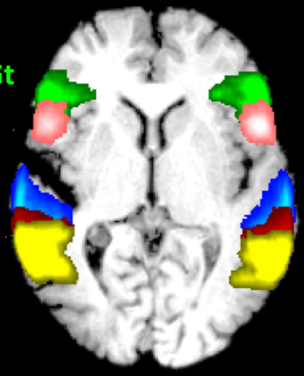
Patient 2 - temporal epilepsy



PET was performed during the interictal phase, while ASL was performed during the post-ictal phase, 15 minutes after a seizure recorded with hdEEG.

Patient 2 - Quantification results

ROI ANALYSIS



	r-MTGp	l-MTGp	r-STGp	l-STGp	r-IFGo	l-IFGo	r-IFGt	l-IFGt	r-MTGto	l-MTGto
CD	0.044	0.005	0.038	0.004	0.014	0.005	0.008	0.008	0.024	0.006
CBF	76.08	52.11	75.89	55.01	70.58	33.59	47.06	24.63	47.80	44.40
SUV	1.88	2.65	2.11	3.00	3.23	3.14	2.83	2.92	2.65	3.02

CD: [µA/mm³] CBF: [ml/100g/min] SUV: [g/ml]

SURGERY

On the basis of our findings patient no. 2 was excluded as surgery candidate.

- Non-invasive imaging methods as ESI can be very useful to correctly identify the activity before the surgery treatment or to reduce intracranial recordings before the surgery treatment.

- Multiple imaging modalities in the same patient allow for a more accurate identification of the epileptogenic zone, providing better surgical outcomes.