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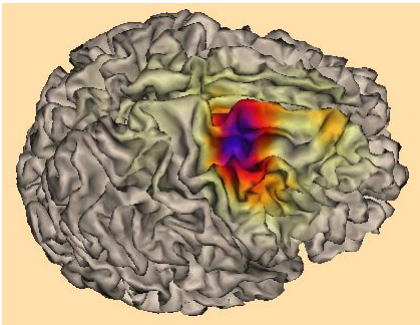
Electromagnetic source imaging in presurgical evaluation

Sándor Beniczky



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Outline

- Why do we need source imaging?
- How does it work:
  - *Basic principles*
  - *Methods - inverse solutions strategies*
- Clinical validation studies
- **Let´s read together voltage maps ☺**

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Localizing epileptiform discharges in EEG: traditionally

Location of the peak negativity on scalp:

- *Bipolar: phase reversal*
- *Referential: highest negative deflection*

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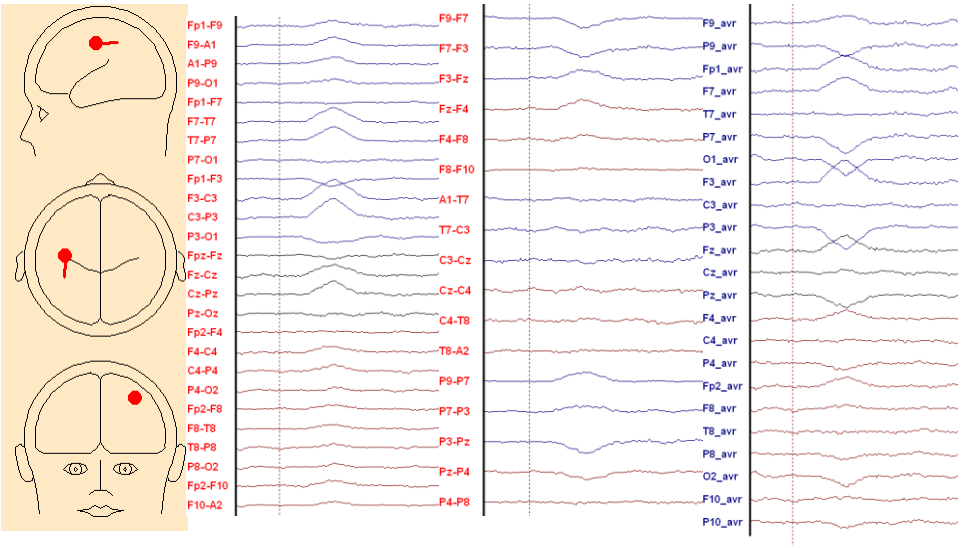

Source: in the postcentral gyrus

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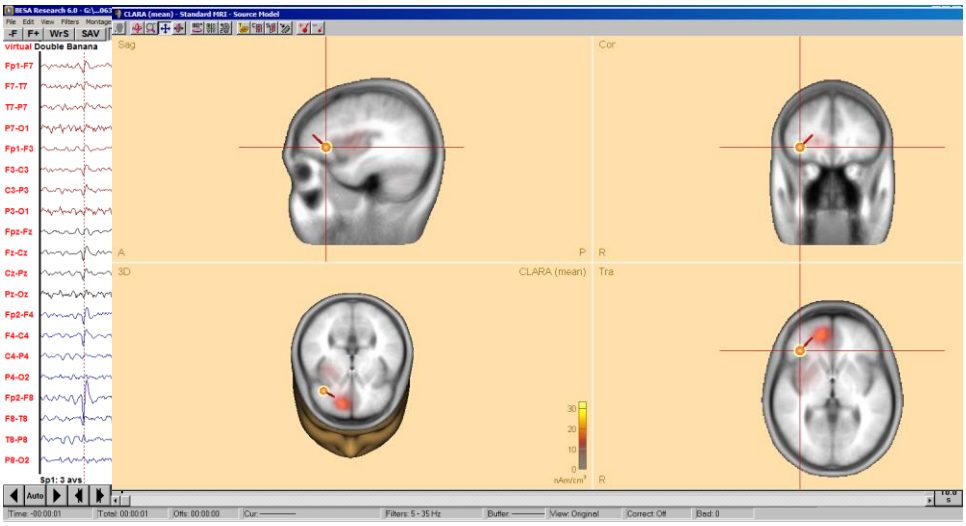

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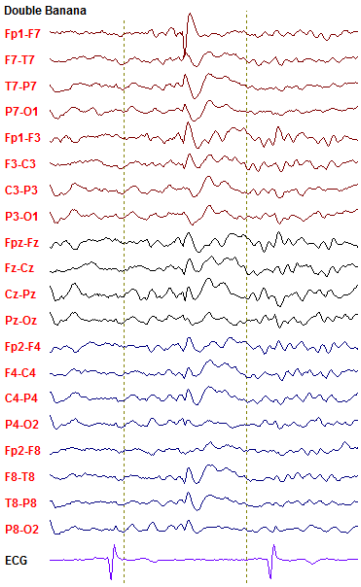

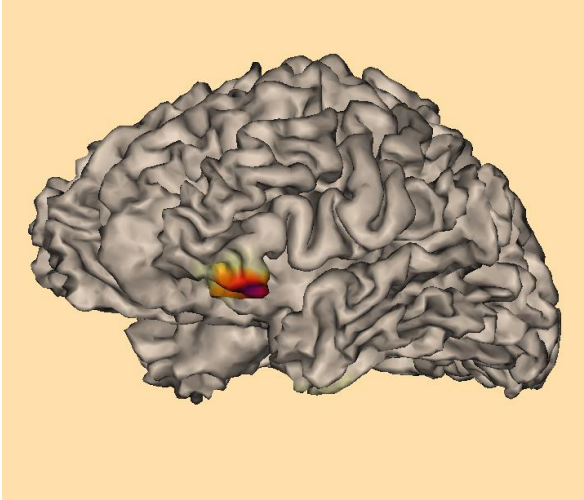

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- Why do we need source imaging?
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  - *Basic principles*
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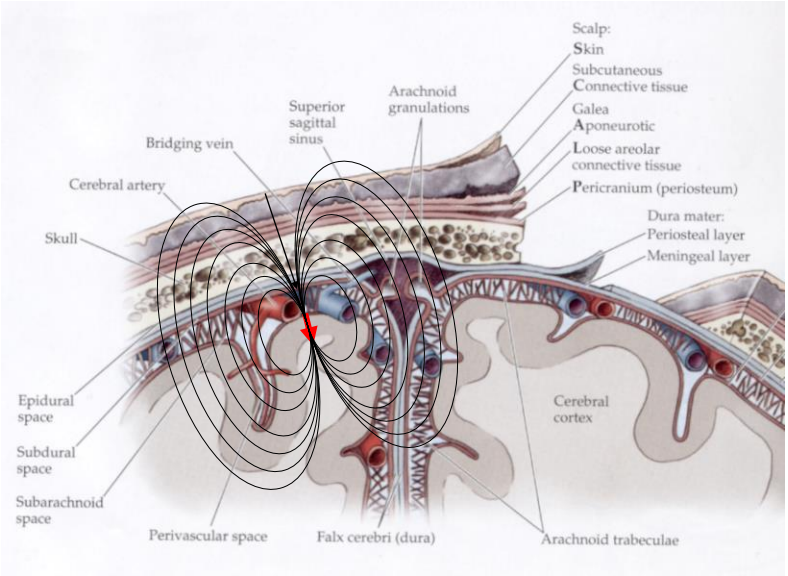

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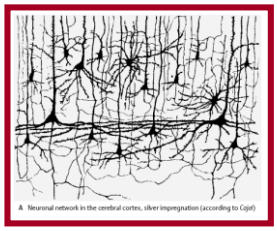

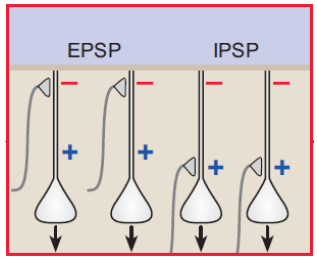

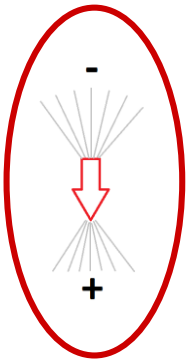

EDs – dipoles:

- Negative potential - at the cortical surface
- Positive potential – in the opposite direction

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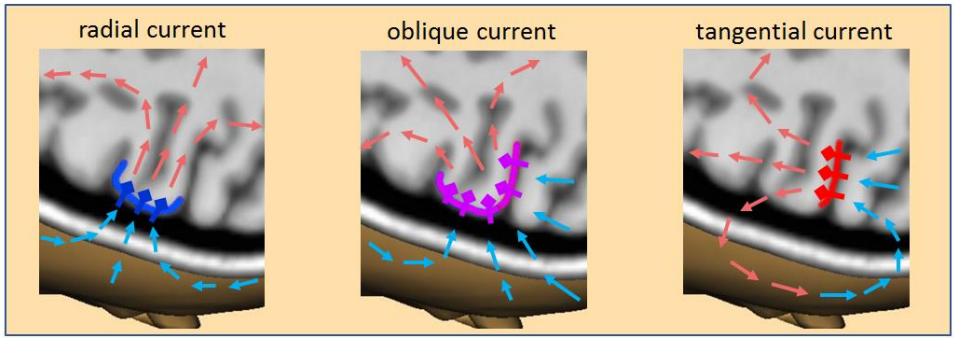

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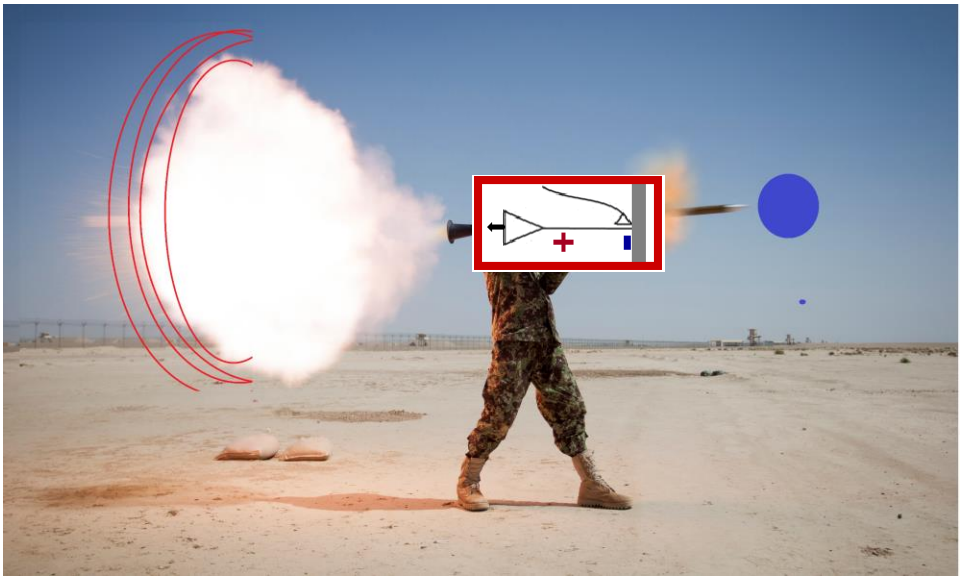

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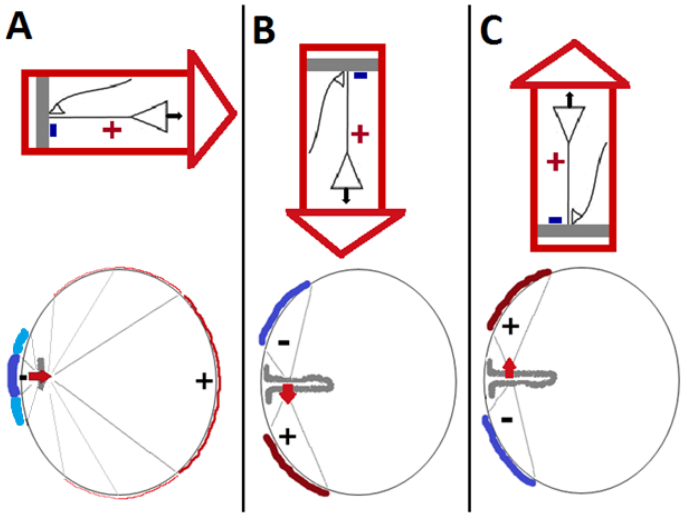

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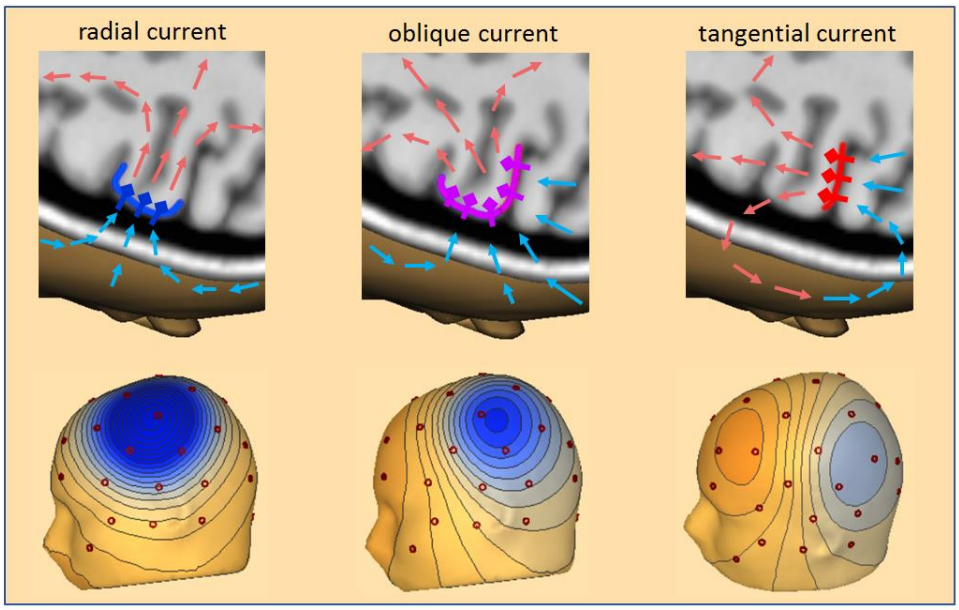
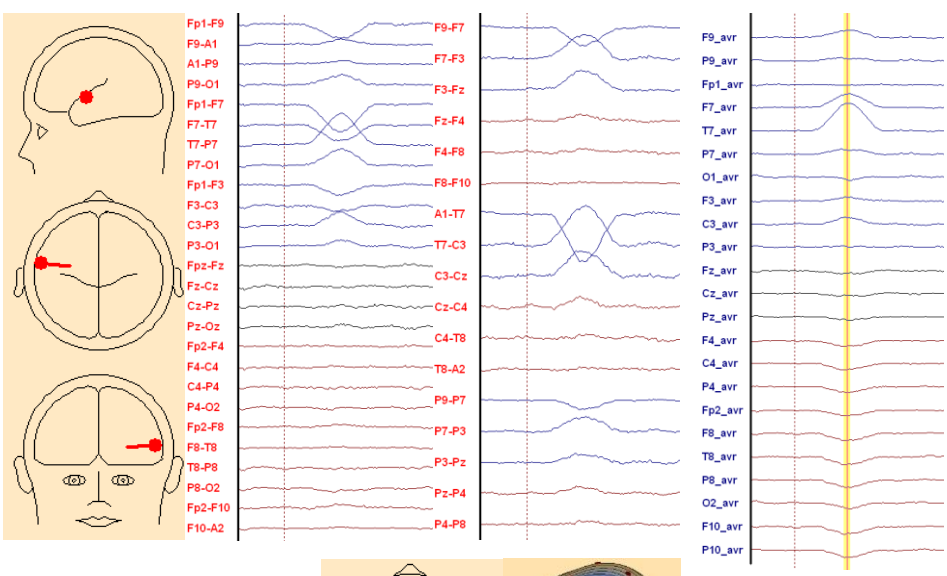
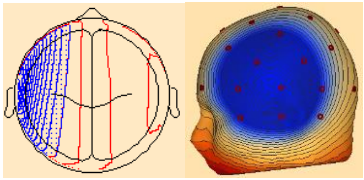
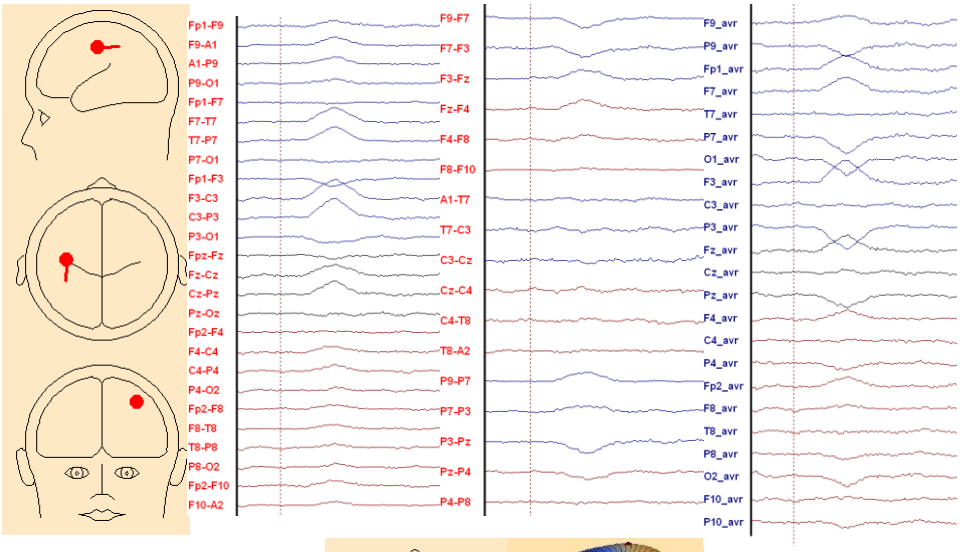


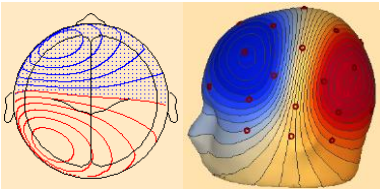


RADIAL DIPOLE
in the
anterior part of the
lateral temporal surface





TANGENTIAL DIPOLE
in the
postcentral gyrus



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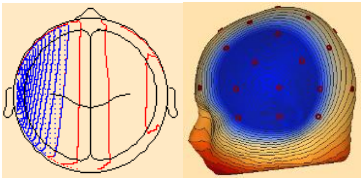

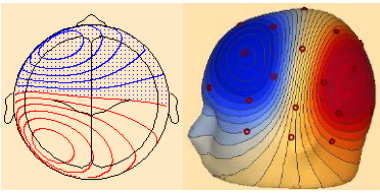

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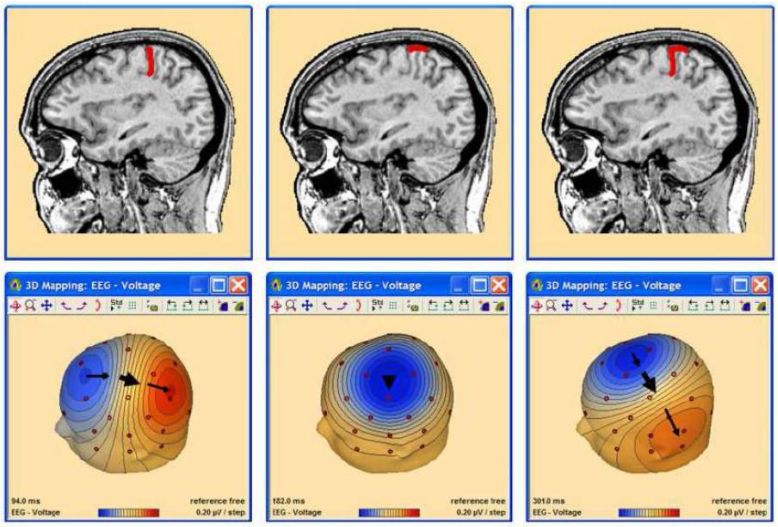

tangential - sulcus *radial - surface* *oblique - both*

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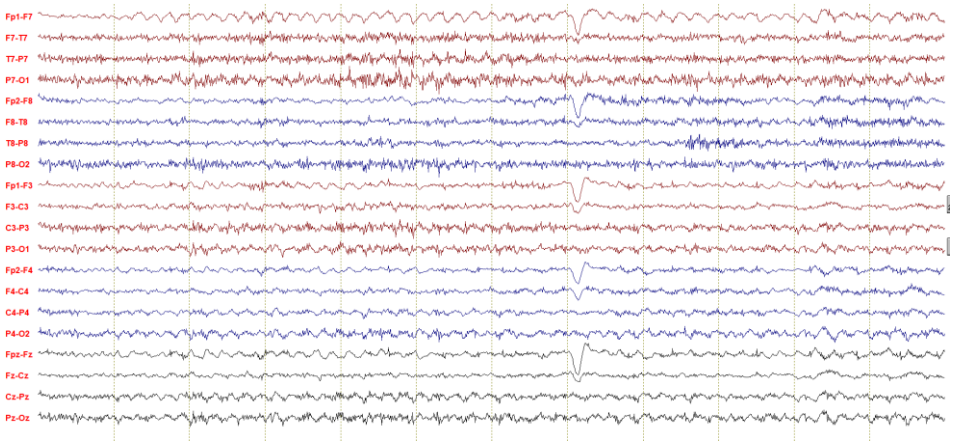

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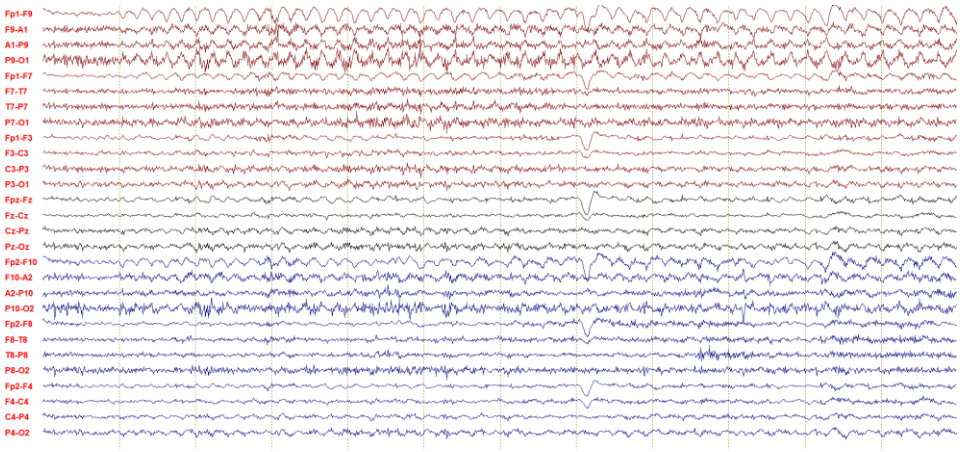

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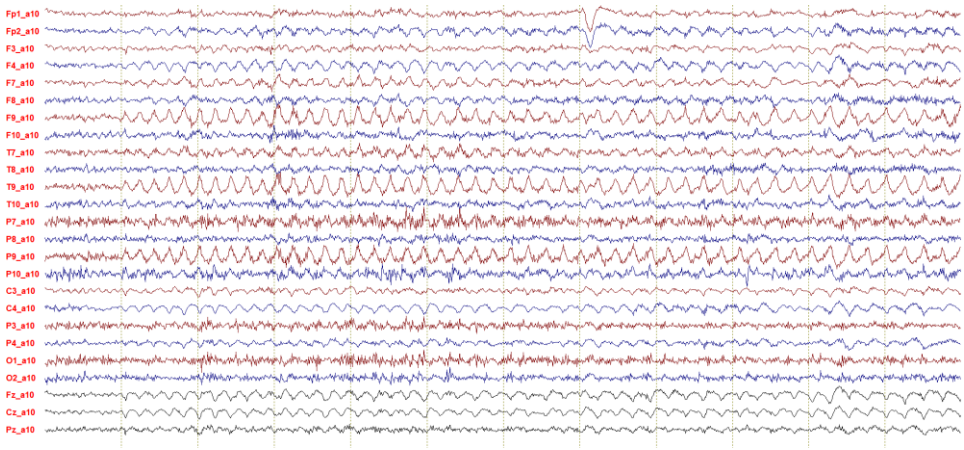

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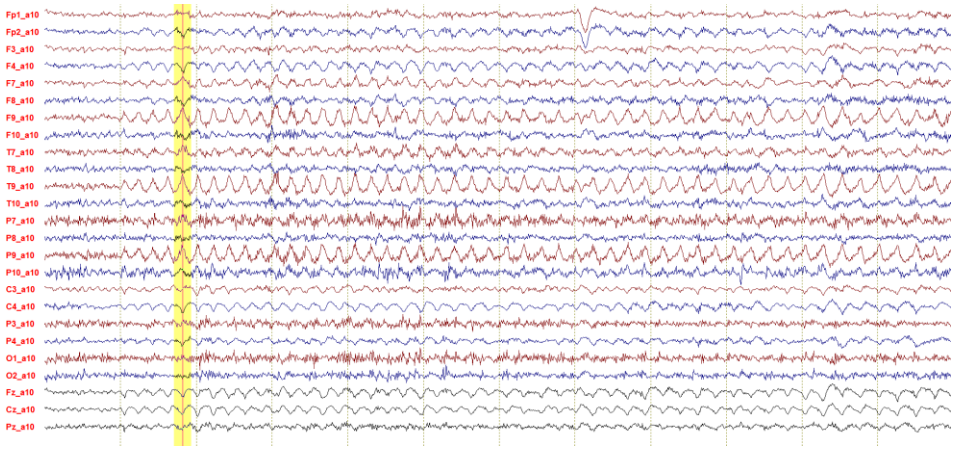

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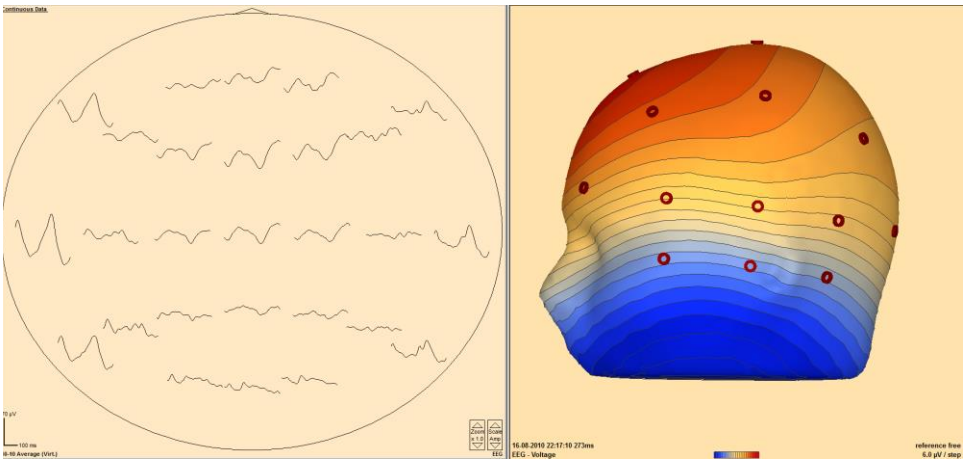

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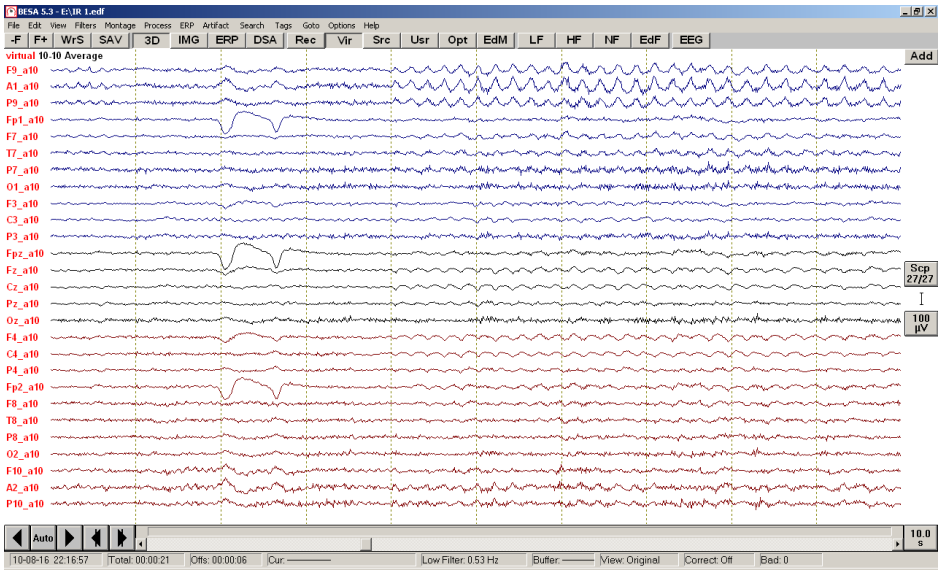
Ictal source imaging: several methods



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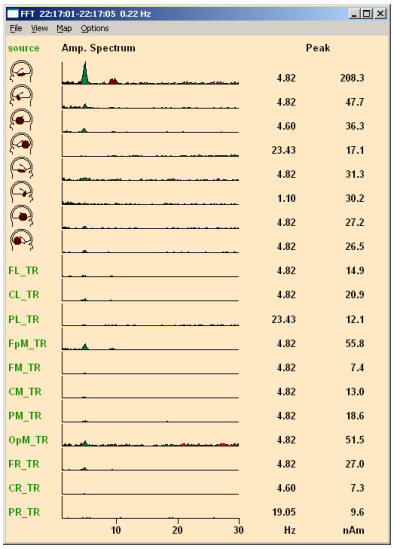
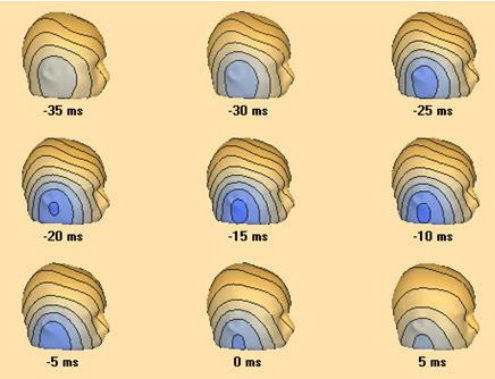
Phase-maps:

voltage-maps corresponding to the phases of the oscillatory signal





Rosenzweig et al., 2014

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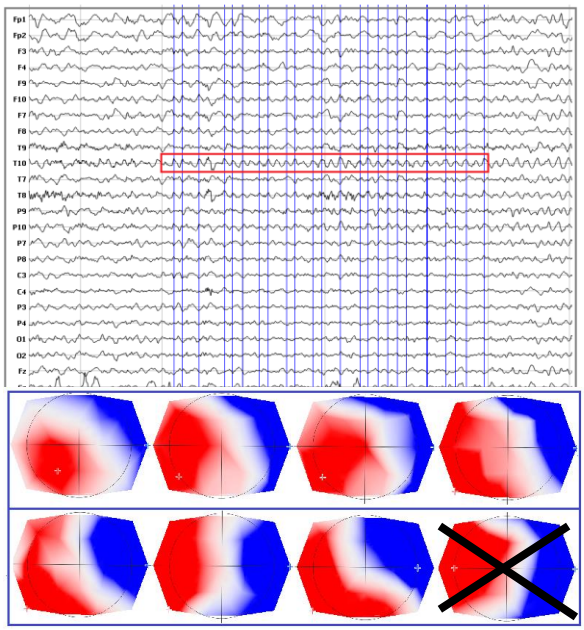

Beniczky et al., 2014

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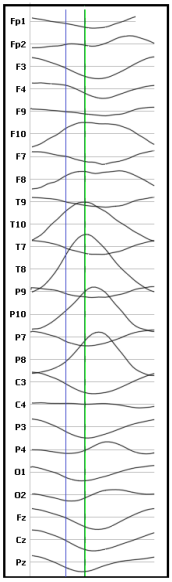

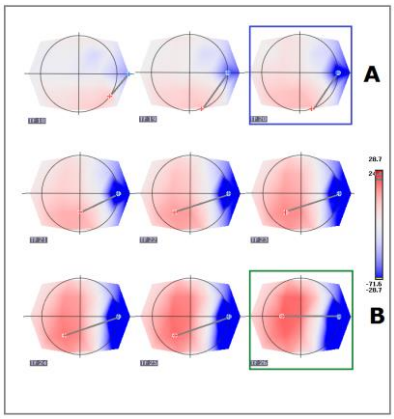

Beniczky et al., 2014

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MEG
MagnetoEncephaloGraphy

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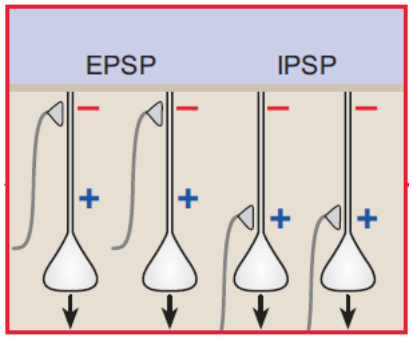
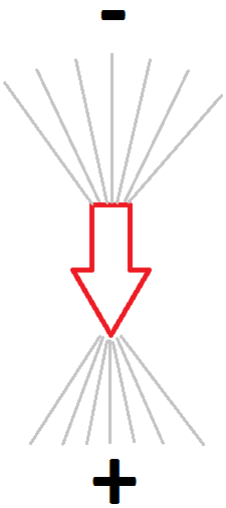
Current dipole





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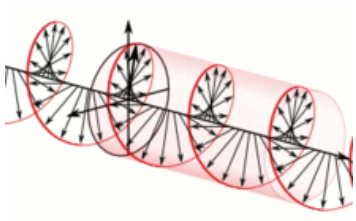

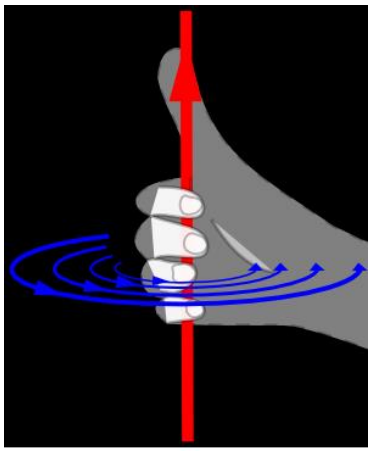

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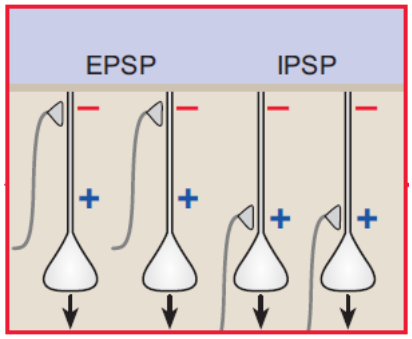

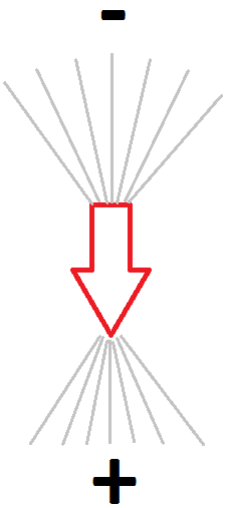

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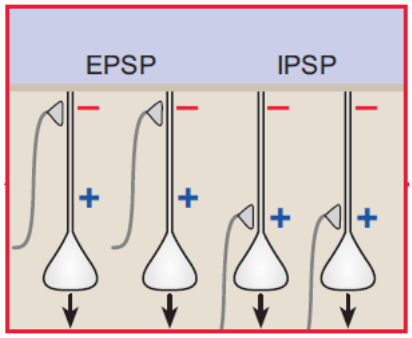
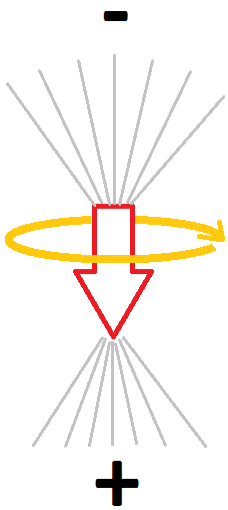
Current dipole





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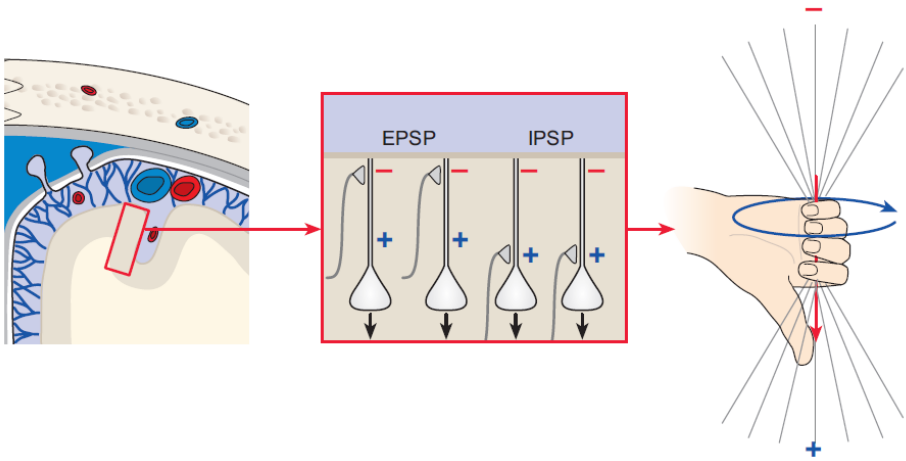
Current dipole



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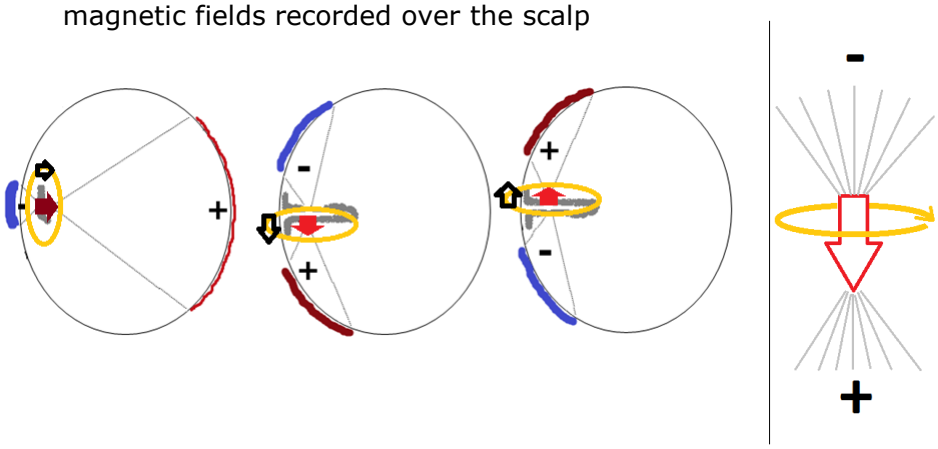
- The location & orientation of the source (current dipole) determines the distribution of the electric potentials and magnetic fields recorded over the scalp



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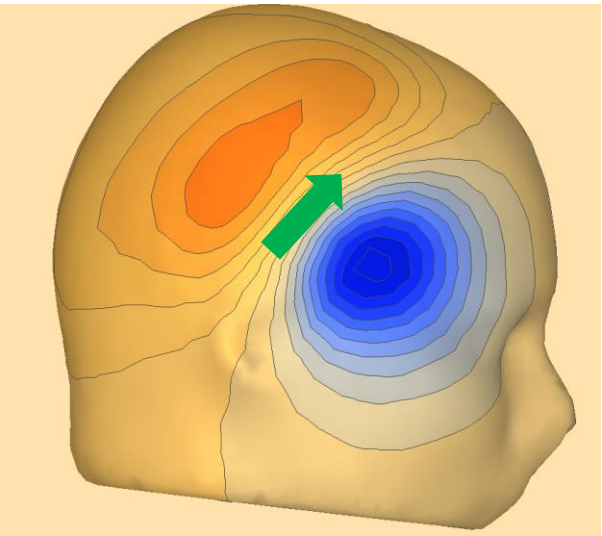
MEG

Magnetic field maps



The green arrow corresponds to the <u>intracellular flow</u> of a positive charge in the source.
As the flow is from the surface of the gray matter towards the white matter, this gross location, along with the direction of the flow suggests a source in the parietal operculum.

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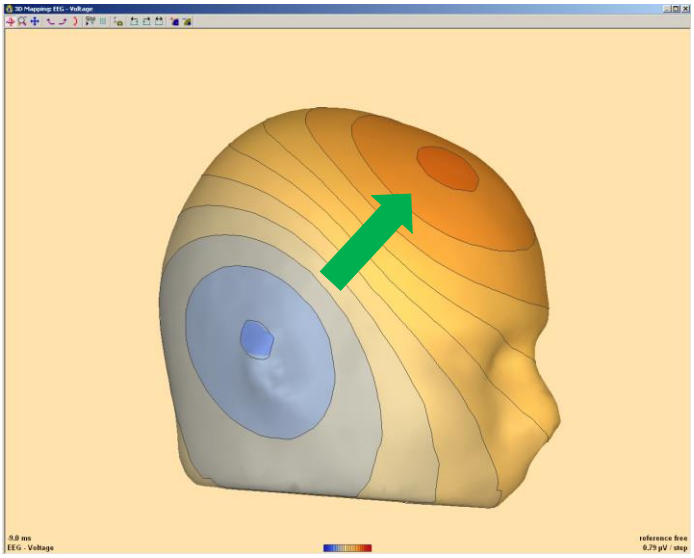
EEG

Voltage maps



Dipoles of EEG spikes are generated in the extracellular space: the surface of the gray matter is negative.
Thus both location and orientation of the EEG dipole fits with the MEG source.

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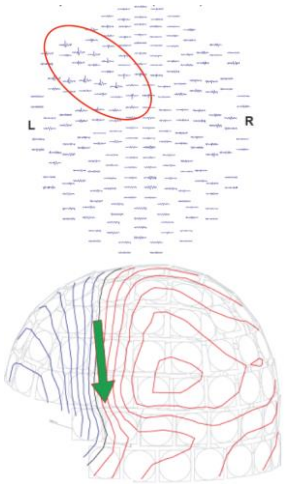
MEG is theoretically superior to EEG in source localization:

- Less attenuation (spreading) of the signals
- Homogenous signal propagation (electric signals: different conductivity in different tissues)
- Deeper sources/ sulci
- Higher spatial sampling



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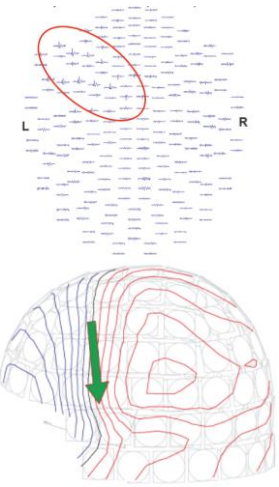

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HD-EEG

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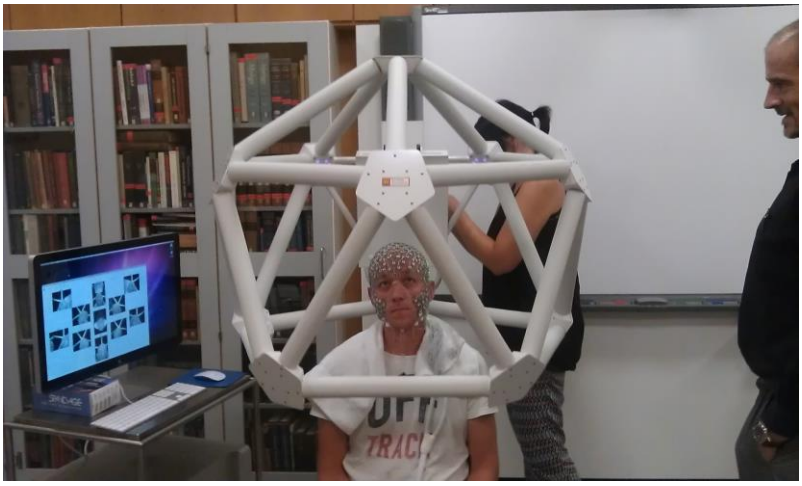

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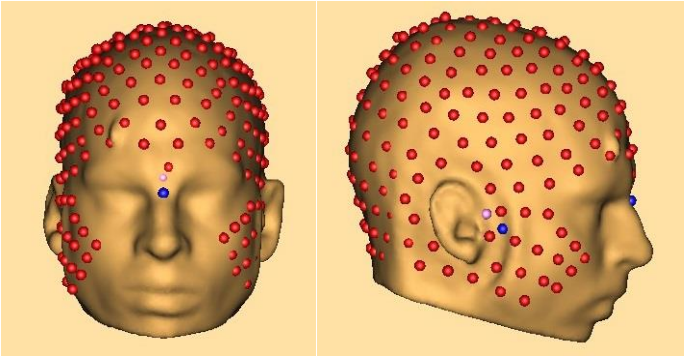

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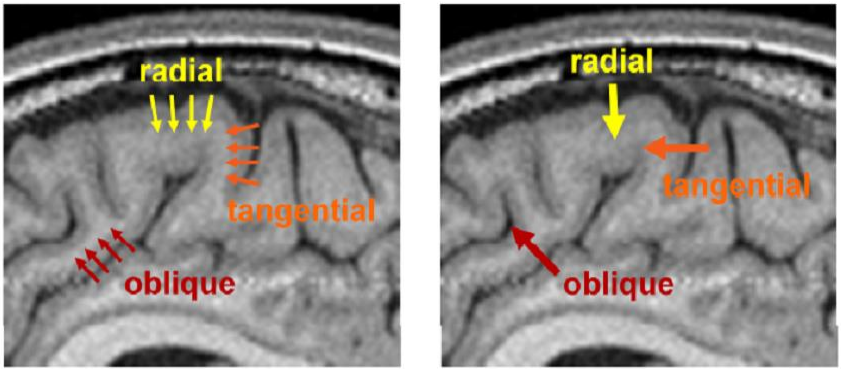
MEG & EEG are complementary:

- Radial dipole: EEG
- Tangential dipole: MEG (best) + EEG



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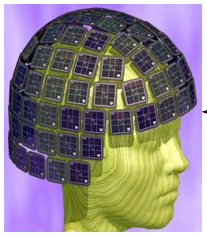
MEG



EEG

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Simultaneous recording of MEG & EEG

MEEG:

- 306 MEG sensors in 102 locations
  - 102 mangnetometers
  - 204 gradiometers
- 80 EEG electrodes

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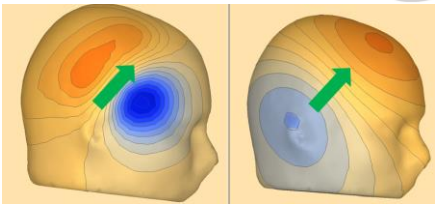
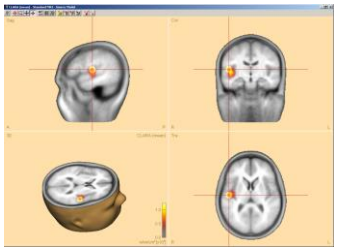
- Voltage maps / field maps are the starting points for all source analysis methods



- How to get from the maps to the imaging of the source in the brain?



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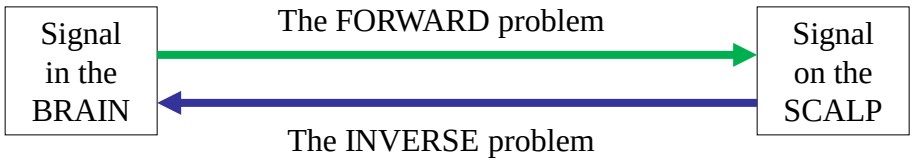
SOURCE ANALYSIS / LOCALIZATION / IMAGING



- The forward problem: well-defined solution
- The inverse problem: **unknowns>>measured data** THUS:
  - no single definite solution but multiple possible solutions
  - additional **constraints** are needed

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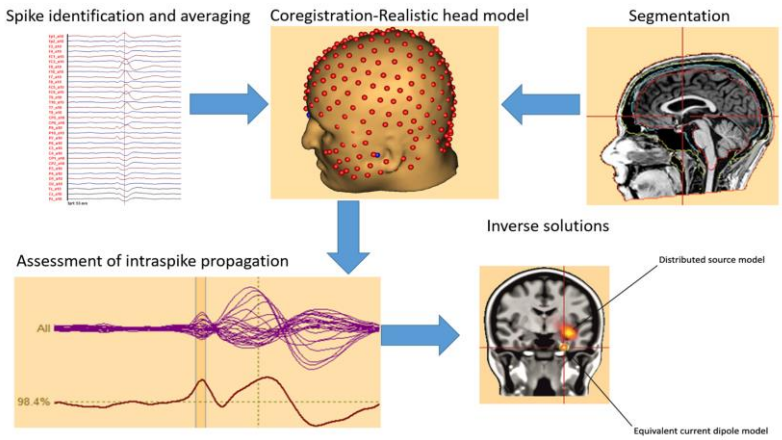
Source imaging:
Estimating the localization of the source in the brain



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Mathematical modeling: inverse solutions
Several types of approaches – all based on dipoles

- **Classical dipole fitting**
- **Scanning for dipoles**
  - MUSIC / RAP-MUSIC
  - Beamfomer
- **Distributed source models**
  - Minimum Norm / Weighted MN
  - LORETA
  - LAURA

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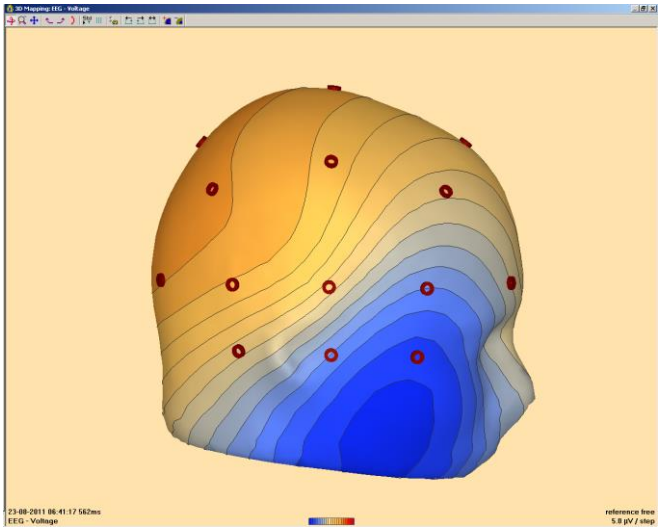

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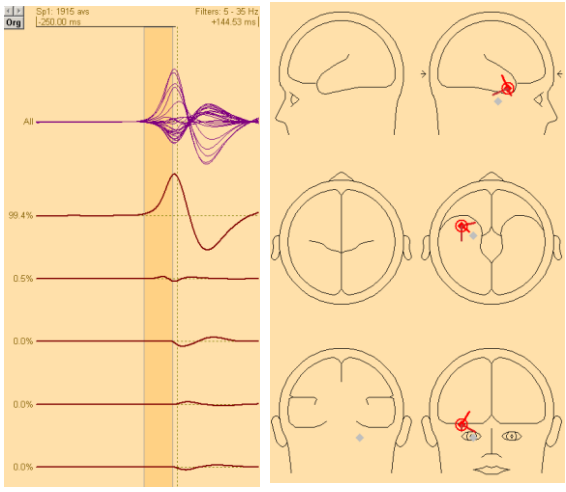
Dipole fit



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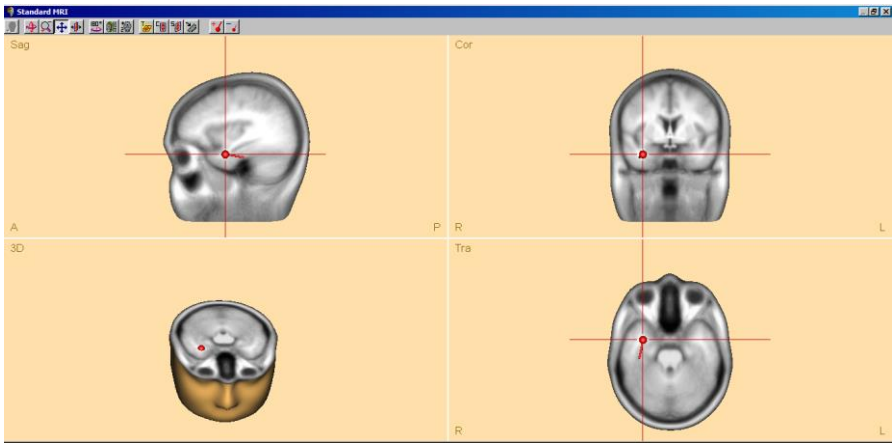

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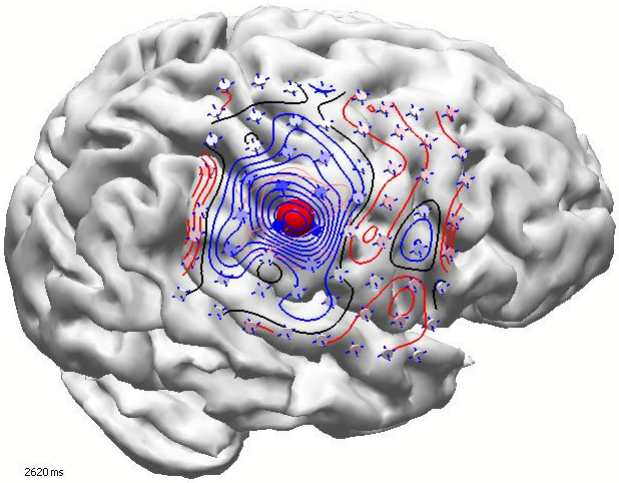

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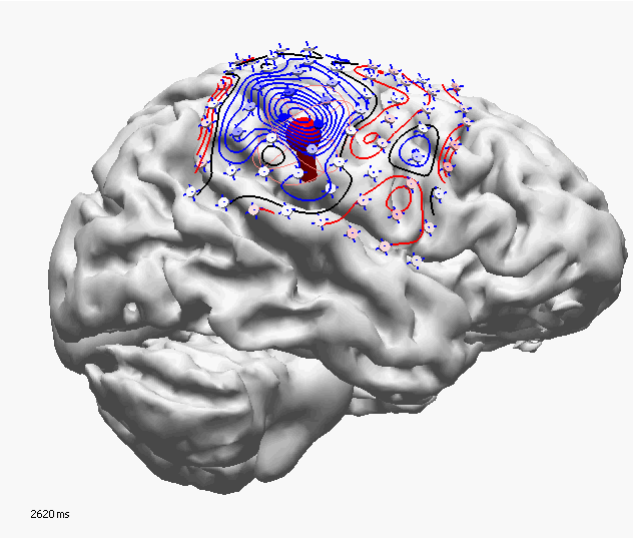

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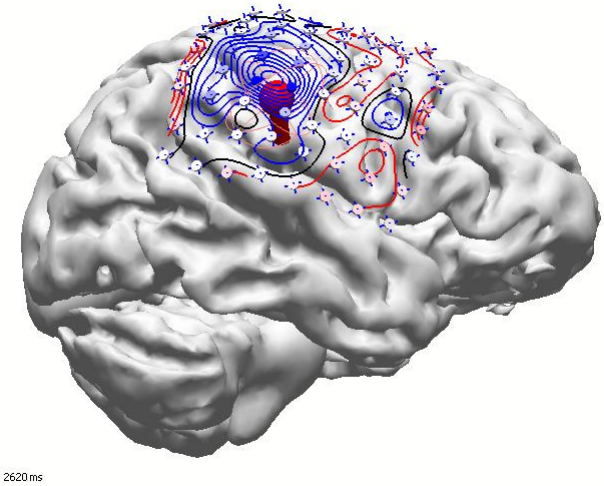

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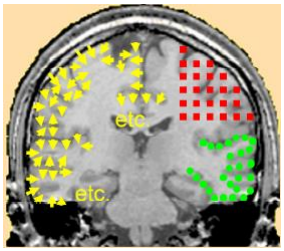
Distributed Source models:

- Aims at: reconstructing the cortical electric activity
- Cortex: many small dipoles; each point linearly relates to measured data (only strength varies).



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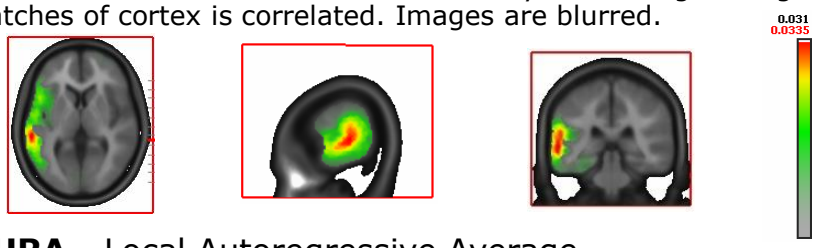
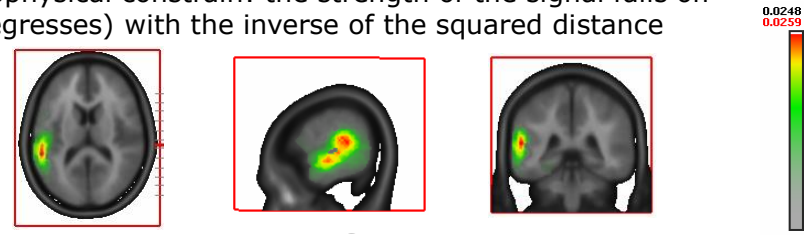
LORETA - Low Resolution Electromagnetic Tomography

- Aims at a smooth distribution: the activity of the neighboring patches of cortex is correlated. Images are blurred.



LAURA - Local Autoregressive Average

- Biophysical constrain: the strength of the signal falls off (regresses) with the inverse of the squared distance



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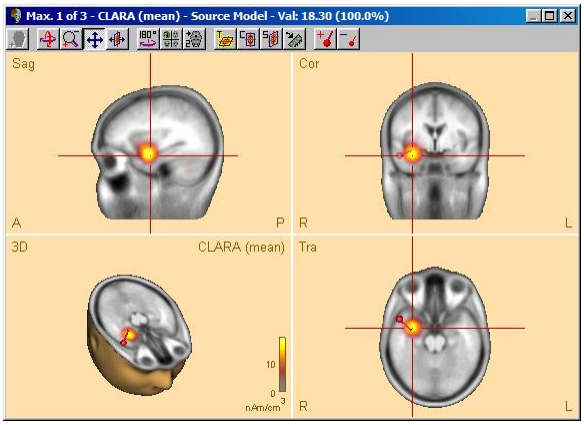

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Outline

- Why do we need source imaging?
- How does it work:
  - *Basic principles*
  - *Methods / inverse solutions strategies*
- **Validation studies**
- **Let´s read together voltage maps ☺**

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Validation studies

How reliable / accurate are these methods?

- >100 clinical studies on EMSI

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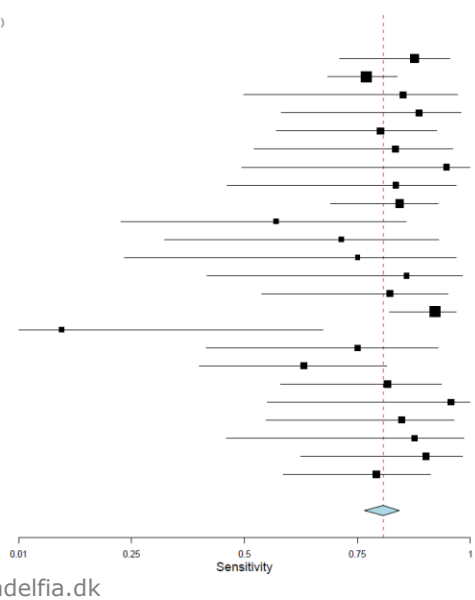
II-ESI

Sensitivity

Studies	Estimate (95% C.I.)	TP/(TP + FN)
Abdallah 2017	0.875 (0.711, 0.952)	28/32
Brodbeck−1 2011	0.769 (0.684, 0.837)	90/117
Brodbeck−2 2010	0.850 (0.500, 0.970)	8/9
Brodbeck−3 2009	0.885 (0.583, 0.977)	11/12
Birot 2014	0.800 (0.572, 0.923)	16/20
Centeno 2017	0.833 (0.523, 0.958)	10/12
Elshof 2012	0.944 (0.495, 0.997)	8/8
Feng −1 2018	0.833 (0.464, 0.967)	7/8
Feng−2 2016	0.842 (0.690, 0.927)	32/38
Gavaret−1 2008	0.571 (0.230, 0.856)	4/7
Gavaret−2 2004	0.714 (0.327, 0.928)	5/7
Heers 2014	0.750 (0.238, 0.966)	3/4
Kargiotis 2014	0.857 (0.419, 0.980)	6/7
Lantz 2003	0.821 (0.540, 0.948)	11/13
Lascano 2016	0.919 (0.820, 0.966)	57/62
Leitzen 2003	0.100 (0.006, 0.674)	0/4
Mazerio 2015	0.750 (0.418, 0.926)	7/9
Megevand 2014	0.632 (0.403, 0.813)	12/19
Michel 2004	0.816 (0.581, 0.934)	15/18
Park 2015	0.955 (0.552, 0.997)	10/10
Rikir 2014	0.846 (0.549, 0.961)	11/13
Russo 2016	0.875 (0.463, 0.983)	7/8
Sperli 2006	0.900 (0.625, 0.980)	13/14
vanMilero 2017	0.792 (0.587, 0.911)	19/24
Overall (I^2=1.95 %, P=0.434)	**0.806 (0.765, 0.841)**	**390/475**



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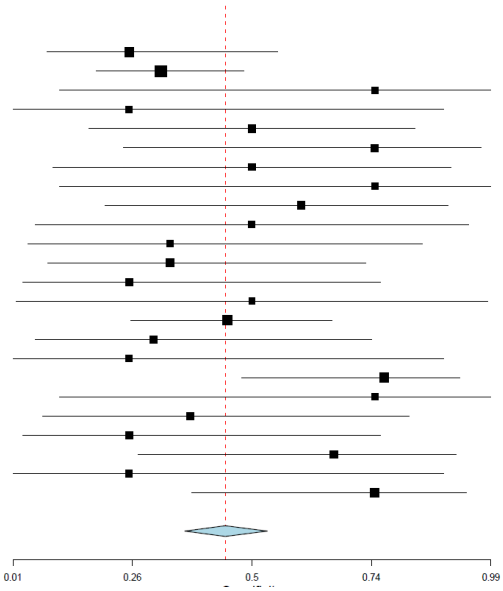
II-ESI

Specificity

Studies	Estimate (95% C.I.)	TN/(FP + TN)
Abdallah 2017	0.250 (0.083, 0.552)	3/12
Brodbeck−1 2011	0.314 (0.183, 0.483)	11/35
Brodbeck−2 2010	0.750 (0.109, 0.987)	1/1
Brodbeck−3 2009	0.250 (0.013, 0.891)	0/1
Birot 2014	0.500 (0.168, 0.832)	3/6
Centeno 2017	0.750 (0.238, 0.966)	3/4
Elshof 2012	0.500 (0.094, 0.906)	1/2
Feng −1 2018	0.750 (0.109, 0.987)	1/1
Feng−2 2016	0.600 (0.200, 0.900)	3/5
Gavaret−1 2008	0.500 (0.059, 0.941)	1/2
Gavaret−2 2004	0.333 (0.043, 0.846)	1/3
Heers 2014	0.333 (0.084, 0.732)	2/6
Kargiotis 2014	0.250 (0.034, 0.762)	1/4
Lantz 2003	0.500 (0.019, 0.981)	0/0
Lascano 2016	0.450 (0.253, 0.664)	9/20
Leitzen 2003	0.300 (0.060, 0.744)	1/4
Mazerio 2015	0.250 (0.013, 0.891)	0/1
Megevand 2014	0.769 (0.478, 0.924)	10/13
Michel 2004	0.750 (0.109, 0.987)	1/1
Park 2015	0.375 (0.073, 0.820)	1/3
Rikir 2014	0.250 (0.034, 0.762)	1/4
Russo 2016	0.667 (0.268, 0.916)	4/6
Sperli 2006	0.250 (0.013, 0.891)	0/1
vanMilero 2017	0.750 (0.377, 0.937)	6/8
Overall (I^2=0 % , P=0.681)	**0.446 (0.363, 0.531)**	**64/143**



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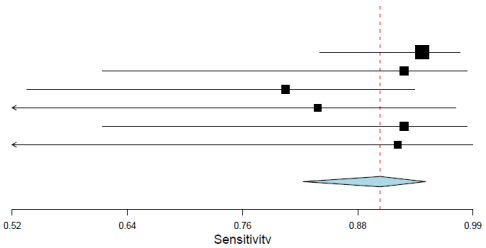
IC-ESI

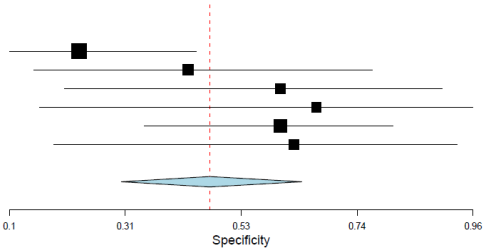
Sensitivity

Studies	Estimate (95% C.I.)	TP/(TP + FN)
Assaf et al 1999	0.942 (0.836, 0.981)	49/52
Benizcky et a1 (1) 2013	0.923 (0.609, 0.989)	12/13
Benizcky et al (2) 2016	0.800 (0.530, 0.934)	12/15
Chunsheng et al 2016	0.833 (0.369, 0.977)	5/6
Koren et al 2018	0.923 (0.609, 0.989)	12/13
Nemtsas 2017	0.917 (0.378, 0.995)	5/5
Overall (I^2=0 % , P=0.694)	**0.899 (0.818, 0.946)**	**95/104**



Specificity

Studies	Estimate (95% C.I.)	TN/(FP + TN)
Assaf et al 1999	0.227 (0.098, 0.444)	5/22
Benizcky et a1 (1) 2013	0.429 (0.144, 0.770)	3/7
Benizcky et al (2) 2016	0.600 (0.200, 0.900)	3/5
Chunsheng et al 2016	0.667 (0.154, 0.957)	2/3
Koren et al 2018	0.600 (0.348, 0.808)	9/15
Nemtsas 2017	0.625 (0.180, 0.927)	2/3
Overall (I^2=26.77 % , P=0.234)	**0.469 (0.305, 0.639)**	**24/55**



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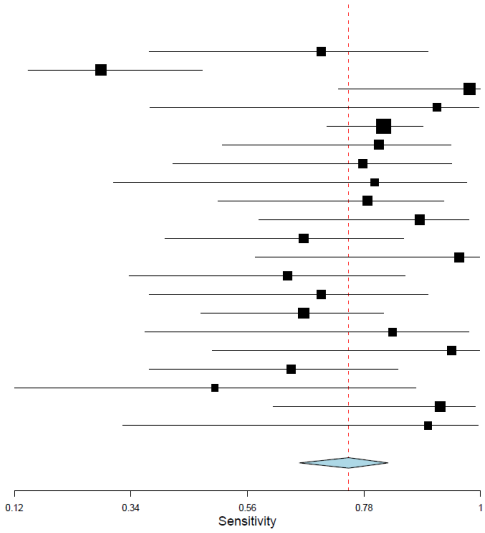
Sensitivity

Studies	Estimate (95% C.I.)	TP/(TP + FN)
Almubarak et al 2014	0.700 (0.376, 0.900)	7/10
Agirre- Arrizubieta et al 2009	0.286 (0.150, 0.476)	8/28
Assaf et al 2004	0.978 (0.732, 0.999)	22/22
Chang et al 2009	0.917 (0.378, 0.995)	5/5
Englot et al 2015	0.817 (0.710, 0.891)	58/71
Holowka et al 2004	0.808 (0.514, 0.943)	10/12
Kim H et al 2012	0.778 (0.421, 0.944)	7/9
Jeong et al 2012	0.800 (0.309, 0.973)	4/5
Kaiboriboon et al 2010	0.786 (0.506, 0.929)	11/14
Kasper et al 2018	0.885 (0.583, 0.977)	11/12
Kim et al 2013	0.667 (0.406, 0.854)	10/15
Knowlton et al 1997	0.958 (0.575, 0.997)	11/11
Mamelak et al 2002	0.636 (0.339, 0.857)	7/11
Schneider et al 2012	0.700 (0.376, 0.900)	7/10
Smith et al 2003	0.667 (0.473, 0.817)	18/27
Sutherling et al 2008	0.833 (0.369, 0.977)	5/6
Koptelova et al 2013	0.944 (0.495, 0.997)	8/8
Wang et al (1) 2014	0.643 (0.376, 0.843)	9/14
Wang et al (2) 2015	0.500 (0.123, 0.877)	2/4
Wu XT et al (1) 2012	0.923 (0.609, 0.989)	12/13
Wu XT et al (2) 2012	0.900 (0.326, 0.994)	4/4
Overall (I^2=50.26 % , P=0.005)	**0.751 (0.659, 0.825)**	**236/311**



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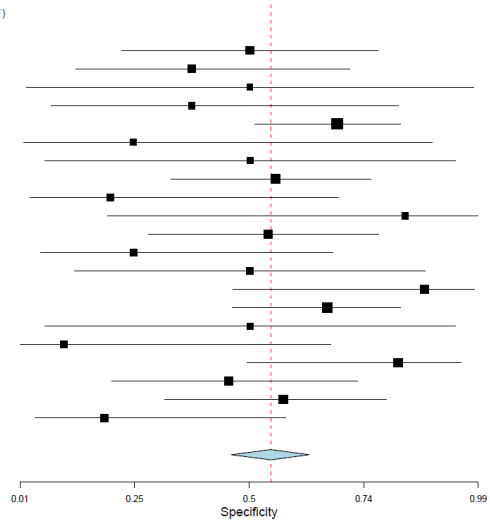
Specificity

Studies	Estimate (95% C.I.)	TN/(FP + TN)
Almubarak et al 2014	0.500 (0.225, 0.775)	5/10
Agirre- Arrizubieta et al 2009	0.375 (0.125, 0.715)	3/8
Assaf et al 2004	0.500 (0.019, 0.981)	0/0
Chang et al 2009	0.375 (0.073, 0.820)	1/3
Englot et al 2015	0.688 (0.510, 0.823)	22/32
Holowka et al 2004	0.250 (0.013, 0.891)	0/1
Kim H et al 2012	0.500 (0.059, 0.941)	1/2
Jeong et al 2012	0.556 (0.330, 0.760)	10/18
Kaiboriboon et al 2010	0.200 (0.027, 0.691)	1/5
Kasper et al 2018	0.833 (0.194, 0.990)	2/2
Kim et al 2013	0.538 (0.282, 0.776)	7/13
Knowlton et al 1997	0.250 (0.050, 0.679)	1/5
Mamelak et al 2002	0.500 (0.123, 0.877)	2/4
Schneider et al 2012	0.875 (0.463, 0.983)	7/8
Smith et al 2003	0.667 (0.461, 0.824)	16/24
Sutherling et al 2008	0.500 (0.059, 0.941)	1/2
Koptelova et al 2013	0.100 (0.006, 0.674)	0/4
Wang et al (1) 2014	0.818 (0.493, 0.954)	9/11
Wang et al (2) 2015	0.455 (0.203, 0.732)	5/11
Wu XT et al (1) 2012	0.571 (0.316, 0.794)	8/14
Wu XT et al (2) 2012	0.188 (0.038, 0.577)	1/7
Overall (I^2=11.09 % , P=0.314)	**0.545 (0.460, 0.627)**	**102/184**



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Interictal - ESI

doi:10.1093/brain/awr243 Brain 2011: 134; 2887–2897 | 2887
BRAIN
A JOURNAL OF NEUROLOGY

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

Verena Brodbeck,[1] Laurent Spinelli,[2] Agustina M. Lascano,[1] Michael Wissmeier,[3] Maria-Isabel Vargas,[3] Serge Vulliemoz,[2] Claudio Pollo,[4] Karl Schaller,[5] Christoph M. Michel[1] and Margitta Seeck[2]

- Prospective, blinded
- Gold standard: surgical outcome

- Sensitivity: 84% Specificity of 88%
- PPV: 97% NPV: 50%

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Ictal - ESI

FULL-LENGTH ORIGINAL RESEARCH

Source localization of rhythmic ictal EEG activity: A study of diagnostic accuracy following STARD criteria

*†Sándor Beniczky, ‡§Göran Lantz, *¶Ivana Rosenzweig, **Per Åkeson, ††Birthe Pedersen, ‡‡§§Lars H. Pinborg, ‡‡¶¶Morten Ziebell, ¶¶Bo Jespersen, and †Anders Fuglsang-Frederiksen

Epilepsia, 54(10):1743–1752, 2013
doi: 10.1111/epi.12339

- Prospective, blinded, STARD criteria
- 42 patients

- Sensitivity: 70% Specificity: 76%
- PPV: 92% NPV: 43%.

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Interictal - MSI

DOI: 10.1093/brain/awg239 Advanced Access publication July 22, 2003 *Brain* (2003), **126**, 2396–2405

Magnetic brain source imaging of focal epileptic activity: a synopsis of 455 cases

H. Stefan, C. Hummel, G. Scheler, A. Genow, K. Druschky, C. Tilz, M. Kaltenhäuser, R. Hopfengärtner, M. Buchfelder[1] and J. Romstöck[1]

- Retrospectively evaluated
- Sensitivity: 70%

- Clinical utility: it supplied
  - additional information in 35%
  - information crucial to final decision making in 10%.

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Sensitivity

- Depends on the location of the source
- *Simultaneous MEG and intracranial recordings*:
  - interhemispheric and orbito-frontal: 90%
  - superior frontal, central, lateral temporal: 75%
  - mesial temporal: 25%

Agirre-Arrizubieta et al 2009

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Clinical Utility:
Change in the decision on epilepsy surgery

Paper	Inclusion criteria	Nr. PATIENTS	CHANGE
Sutherling et al. 2008	all consecutive surgical candidates with neocortical epilepsy	69	23 (33%)
Knowlton et al. 2009	all patients planned for intracranial work-up	77	18 (23%) (additional electrode coverage)
De Tiège et al. 2012	all consecutive surgical candidates	70	15 (21%) (44% of eTL-cases)
Ito et al 2014	pt studied for clinical diagnosis and preoperative evaluation	73	17 (23%)

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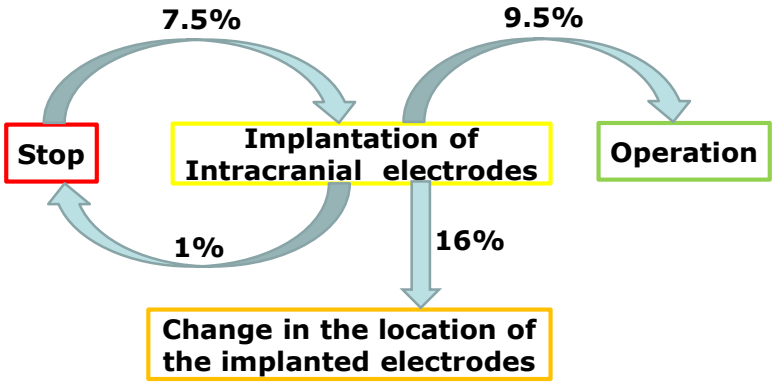
Clinical Utility

Change in clinical decision: 34% (29/85)



Changes were useful in 82% (14/17)

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How is **source imaging** compared to **visual analysis by experts?**

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How is **source imaging** compared to **visual analysis by experts?**

(*J Clin Neurophysiol* 2014;31: 1–9) ORIGINAL RESEARCH

Beyond the Double Banana: Improved Recognition of Temporal Lobe Seizures in Long-Term EEG

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TABLE 1. Sensitivity, Specificity, and Weighted Measurement of Agreement With the Reference Standard for the Various Montages and Electrode Arrays in Decreasing Order of Sensitivity

Montage (Number of Electrodes)	Sensitivity (%)	Specificity (%)	Weighted Kappa Coefficient (95% CI)
Phase maps	**83**	100	0.792 (0.56–1.00)
RF (25)	**63**	100	0.673 (0.45–0.90)
Voltage maps	**60**	100	0.653 (0.43–0.87)
CA (25)	**60**	100	0.653 (0.43–0.87)
SD (25)	**57**	100	0.553 (0.34–0.76)
LB (25)	**53**	100	0.571 (0.36–0.78)
SM	50	100	0.573 (0.36–0.78)
CSD (25)	37	100	0.555 (0.35–0.76)
SD (19)	33	80	0.340 (0.17–0.51)
CA (19)	30	80	0.377 (0.17–0.58)
LB (19)	27	100	0.229 (0.08–0.38)
TB (25)	23	90	0.415 (0.22–0.61)
TB (19)	17	80	0.248 (0.10–0.40)

Significant increase in sensitivity as compared with double banana is marked in bold; (19) and (25) denote the number of electrodes in the array.
CA, common average; CI, confidence interval; CSD, current source density; LB, longitudinal bipolar; RF, reference free; SD, source derivation; SM, source montage; TB, transversal bipolar.

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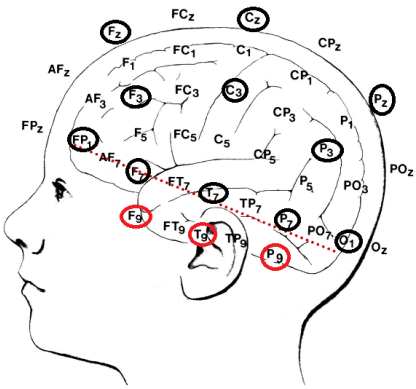

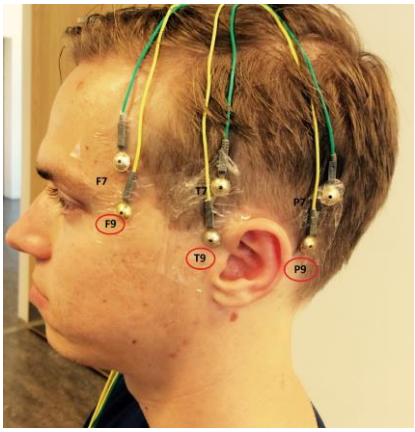

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Let´s read voltage maps!

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Prerequisites for constructing correct voltage maps:

- Common average montage (”Reference free” montage in BESA)
  NB: do not exclude electrodes for calculating the avg.
- Even coverage of the scalp:
  - Minimum: 10-20 electrodes + 6 electrodes in the inferior temporal chain
- Software for interpolation

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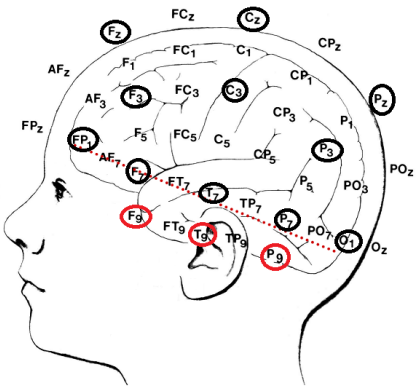

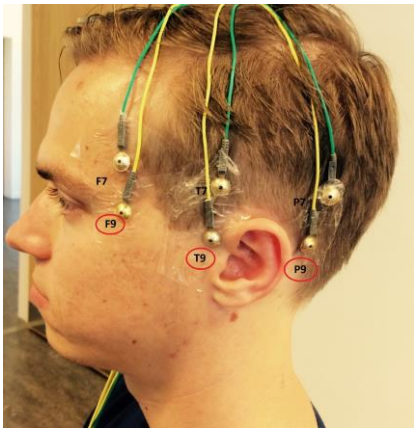

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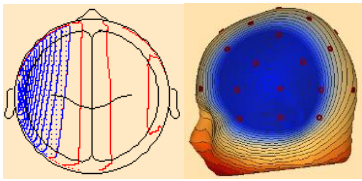
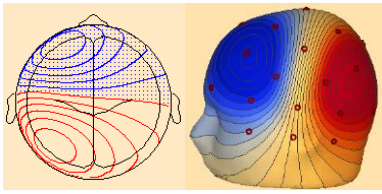
Rules for interpreting voltage maps:

- *Voltage maps suggesting **radial** orientation*



- *Voltage maps suggesting **tangential** orientation*



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- **Propagation of the epileptiform activity from one area to another area**
- **Reflected by changes in time of the voltage-maps.**

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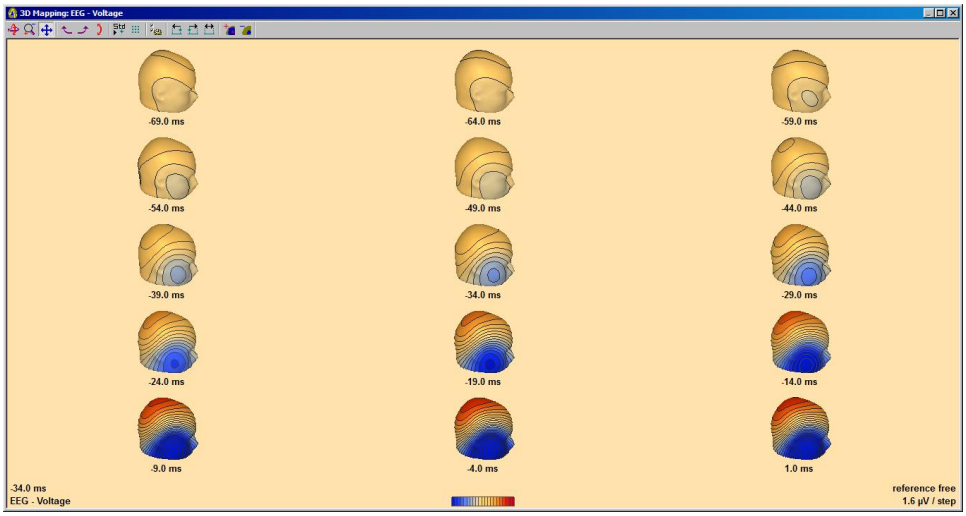
Voltage map stable in time: no propagation



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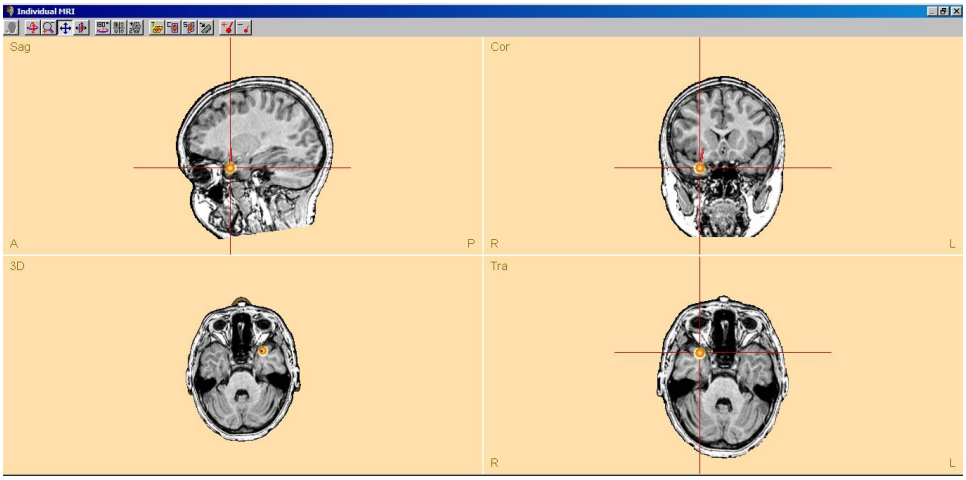

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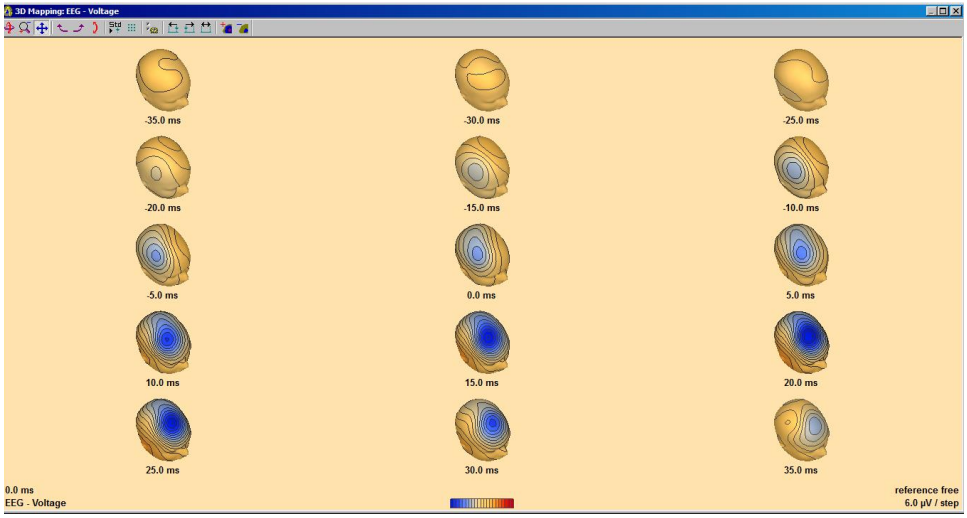
Voltage map changes in time: propagation



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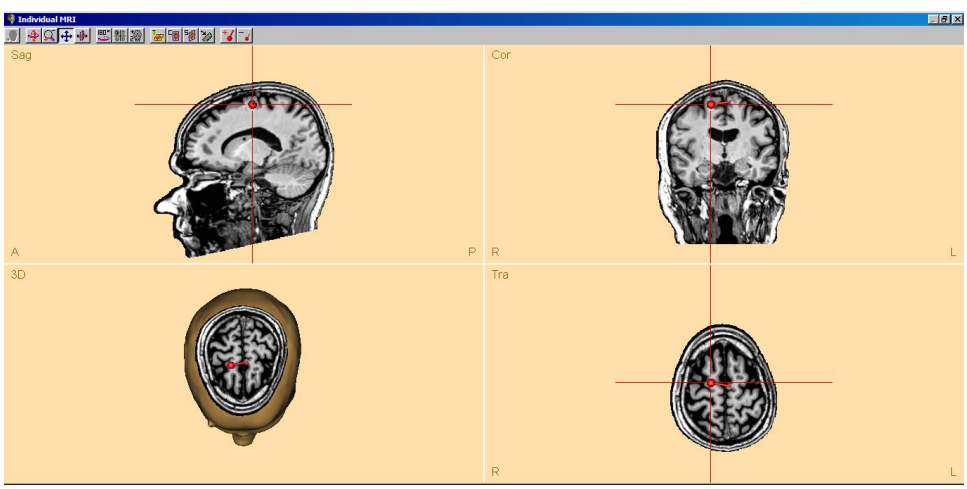

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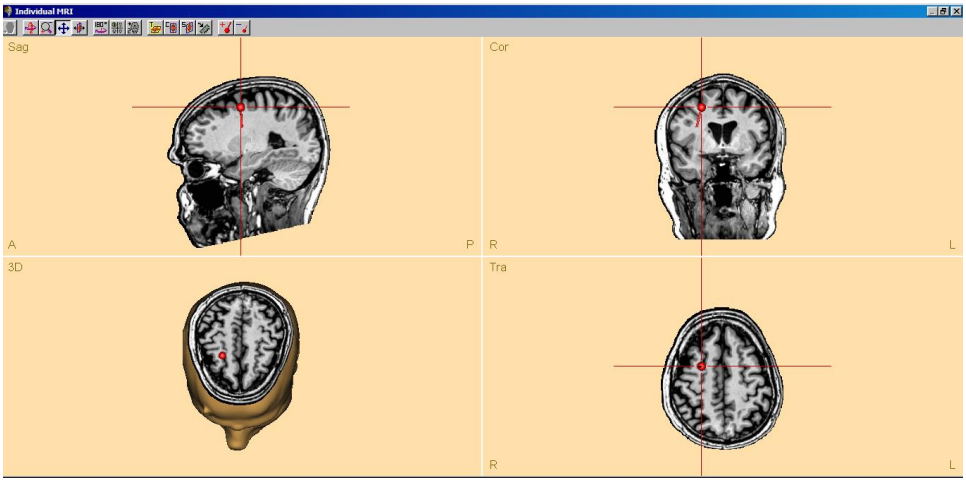

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Where to analyse spikes: at onset or at peak?

- Onset:
  - Closer to the real spike-generator
  - Lower s/n; jitter during averaging
- Peak:
  - Better s/n; no jitter (avg. Aligned to peak)
  - More likely to come from a propagated source

Analyze both onset and peak!

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Why do we need averaging at all?

- **Increase signal-to-noise ratio**
  - Noise cancels out (not consistent across the discharges)
  - The ”real” spike-signal is always there (reinforced)
  - Just like EP, ERP, S-NCS

- **Evidence both for EEG and MEG** (Wennberg; Bast)
  - Individual-spikes: clusters; it is the noise that makes them scatter
  - Accuracy significantly improved after averaging a minimum of 5 spikes!

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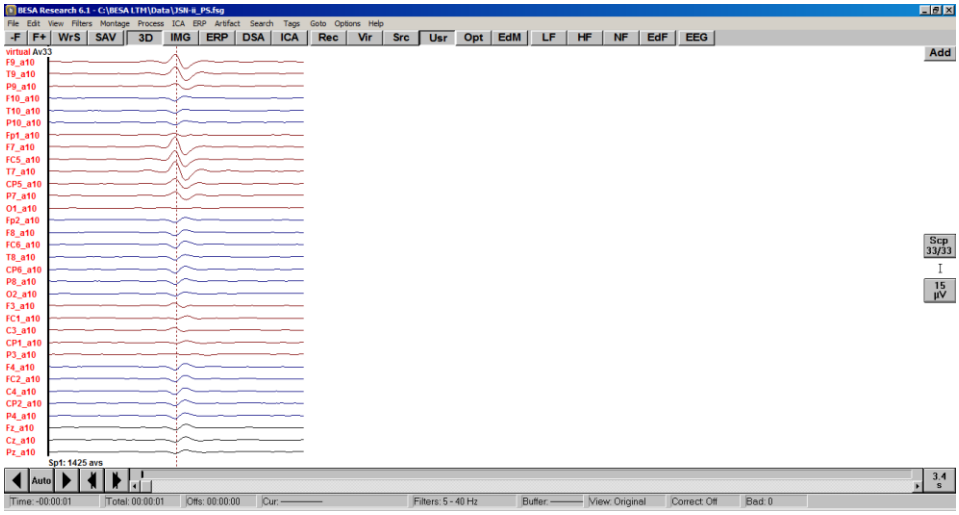

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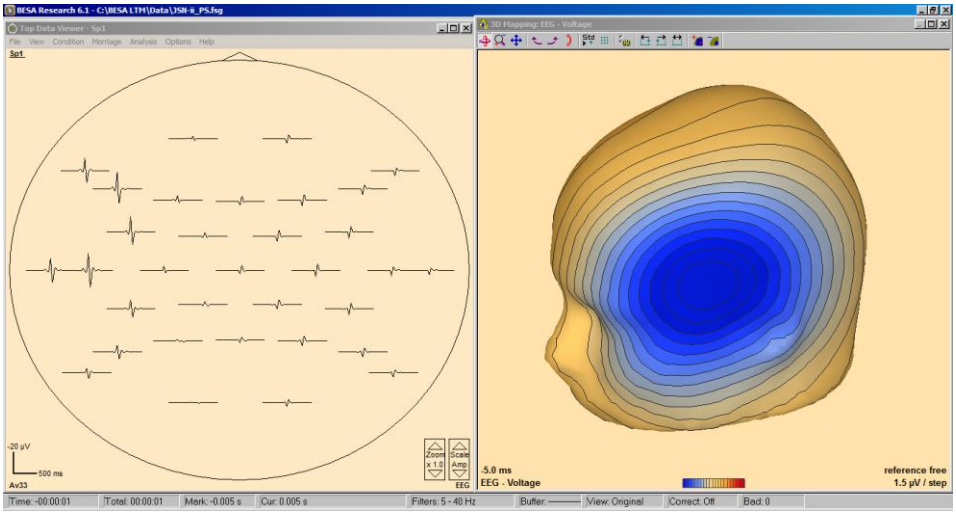

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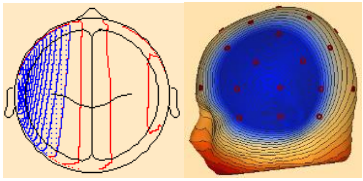

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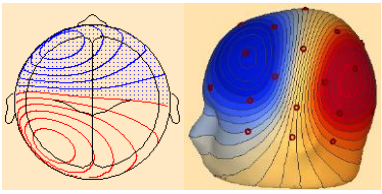

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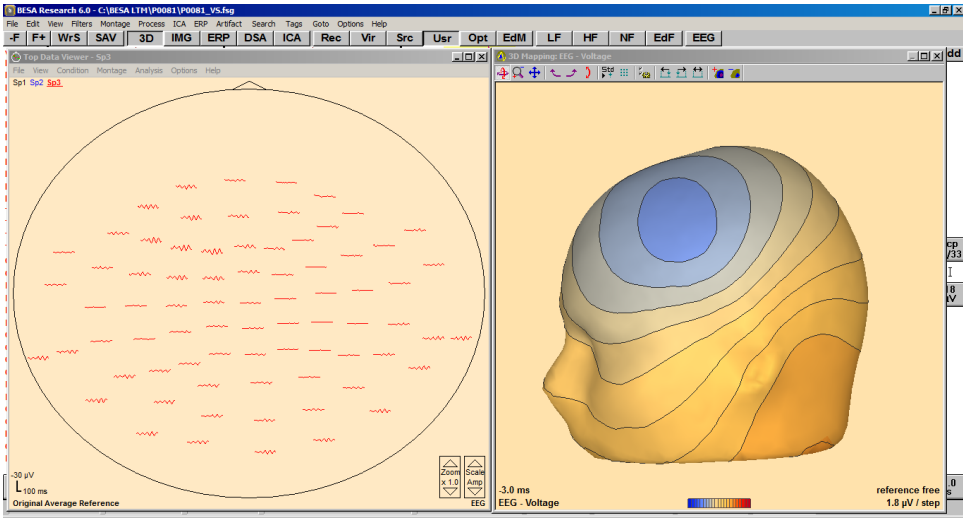

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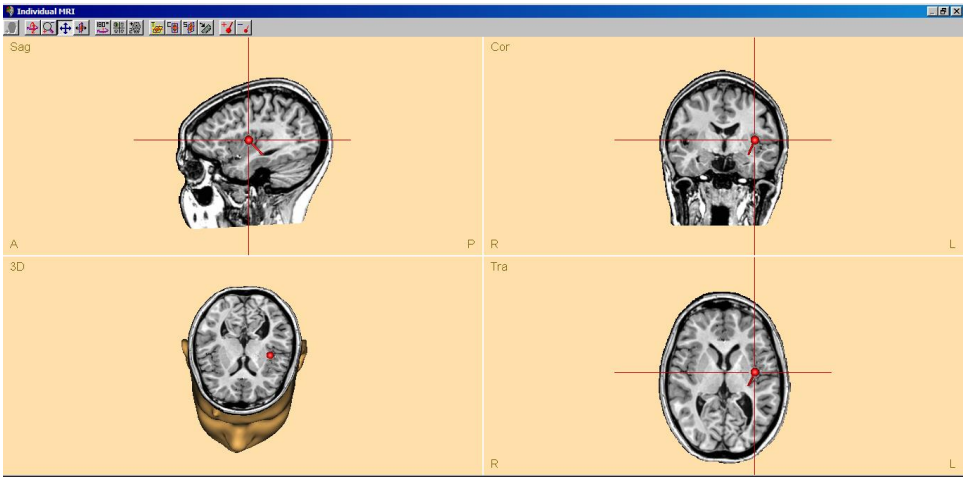

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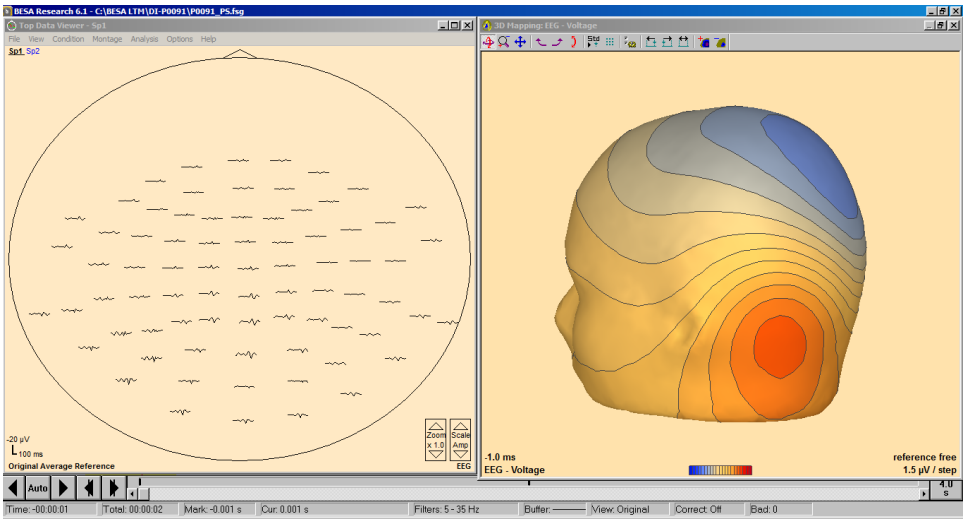

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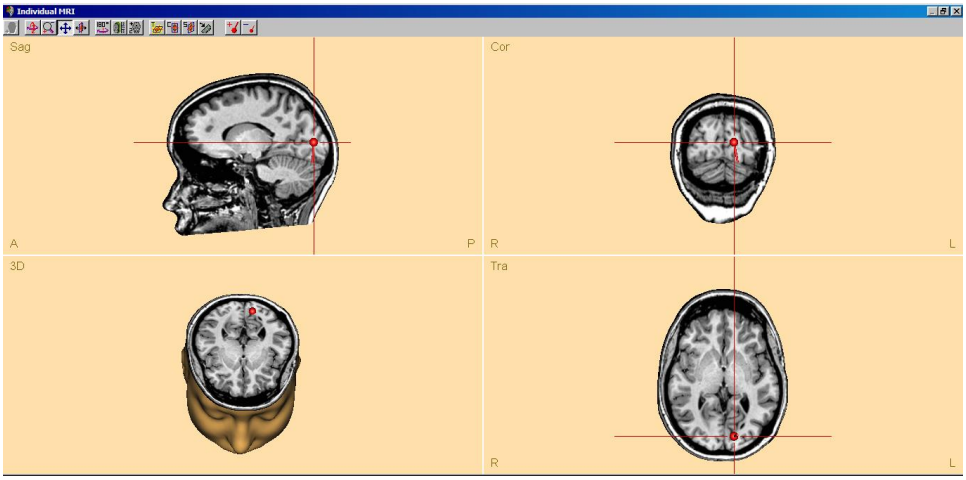

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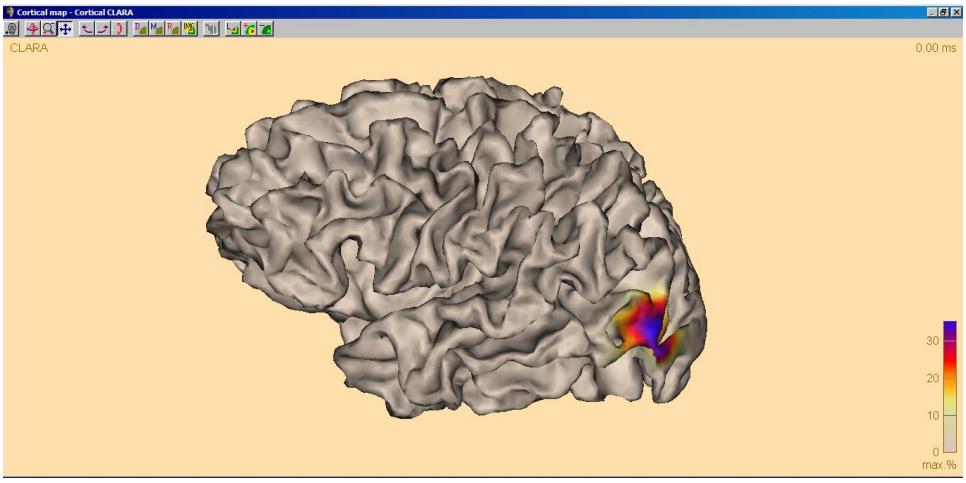

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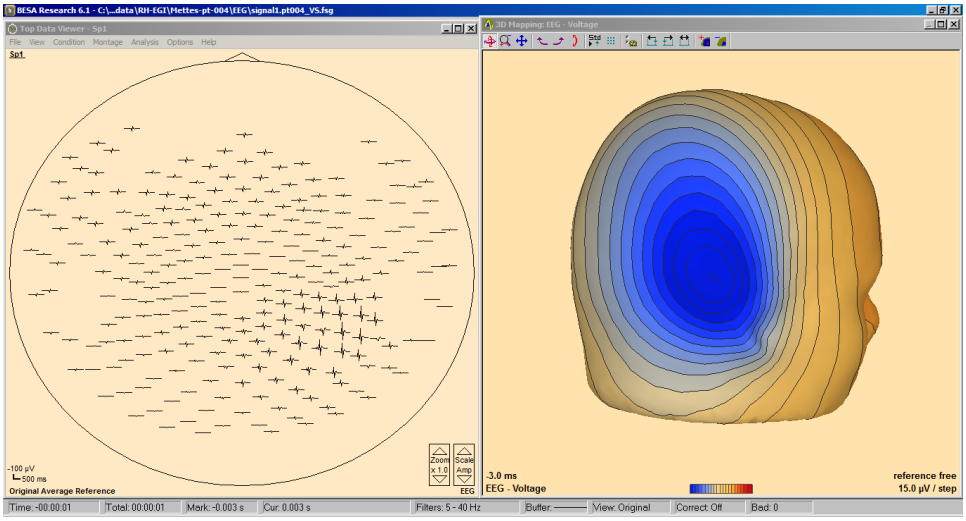

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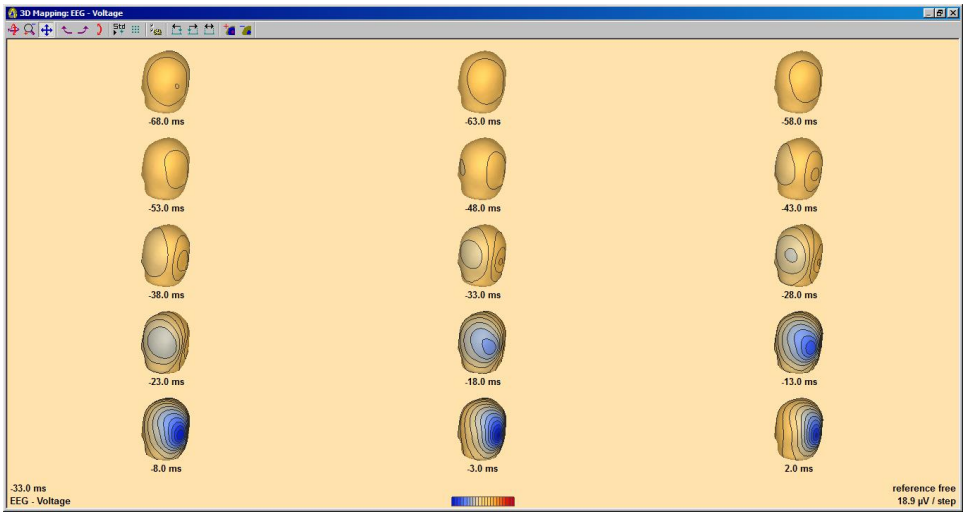

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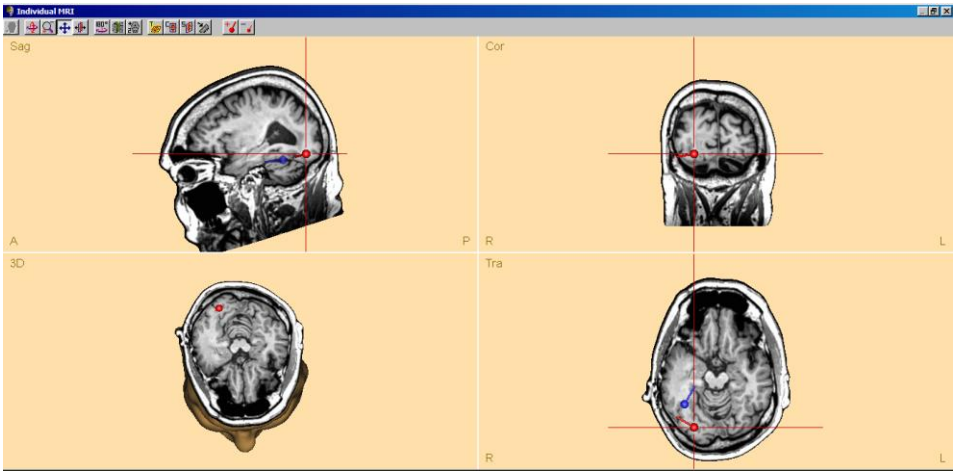

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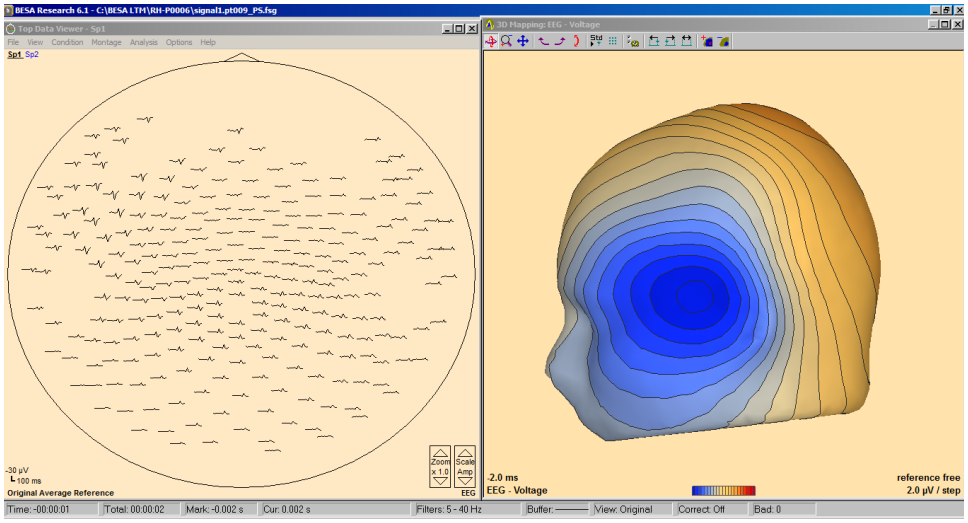

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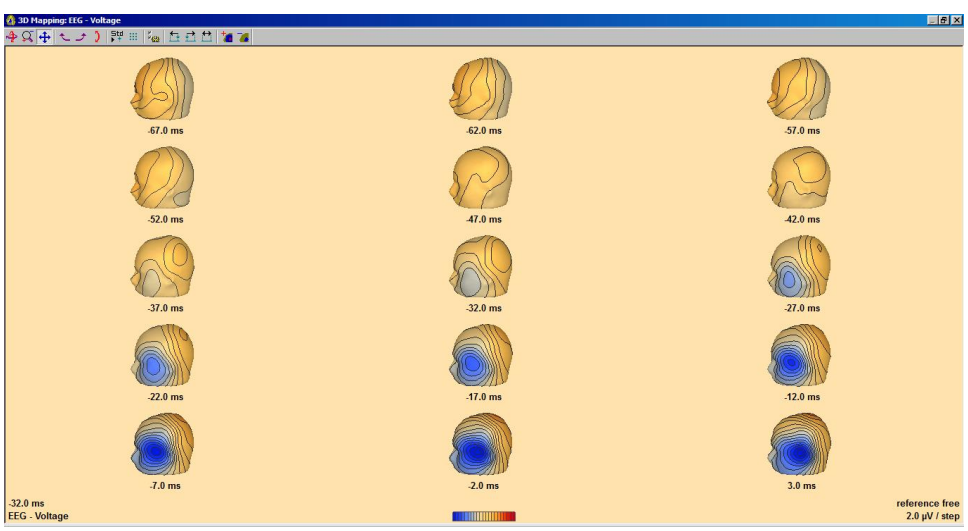

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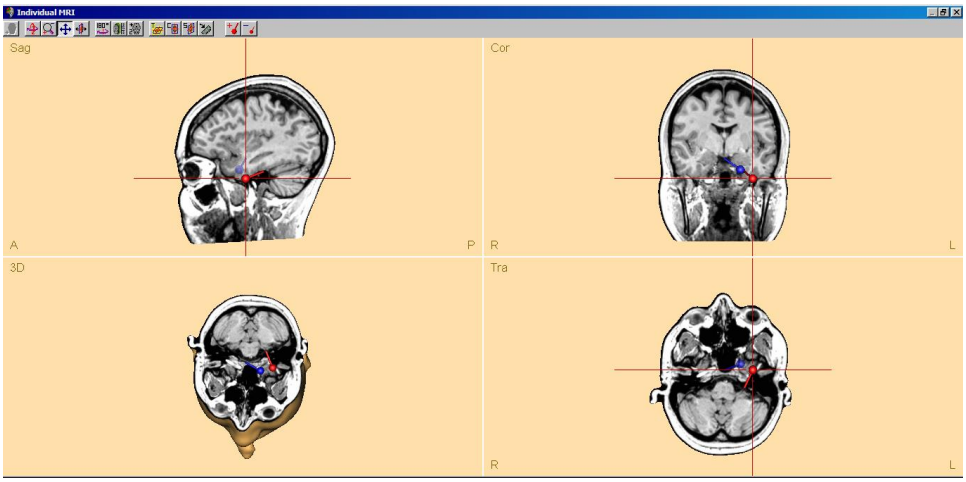

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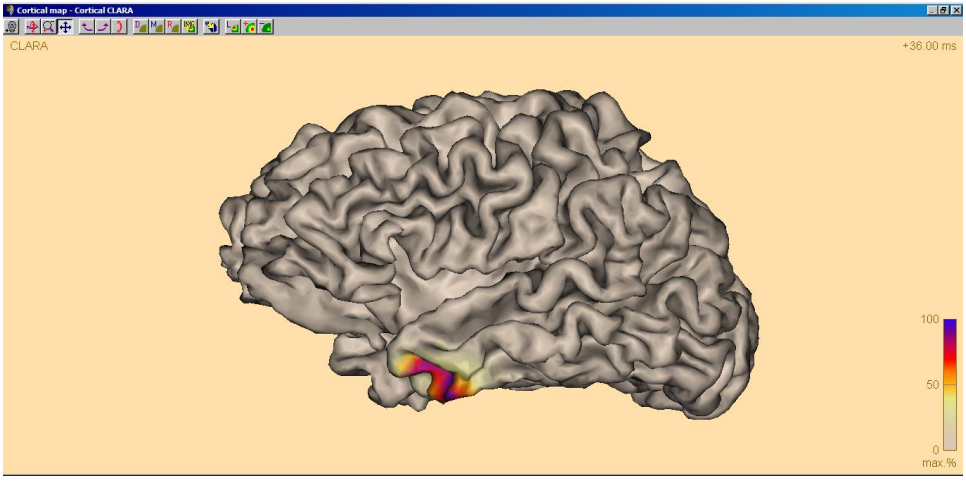

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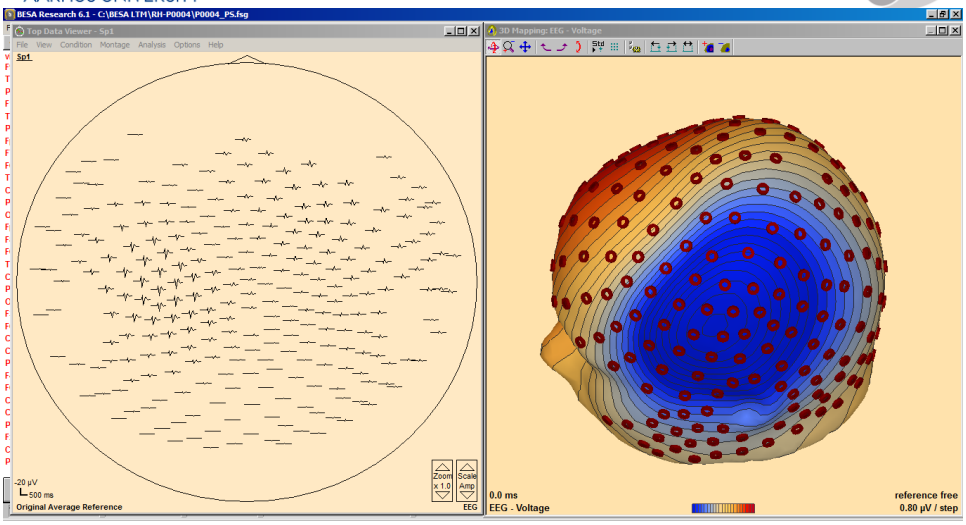

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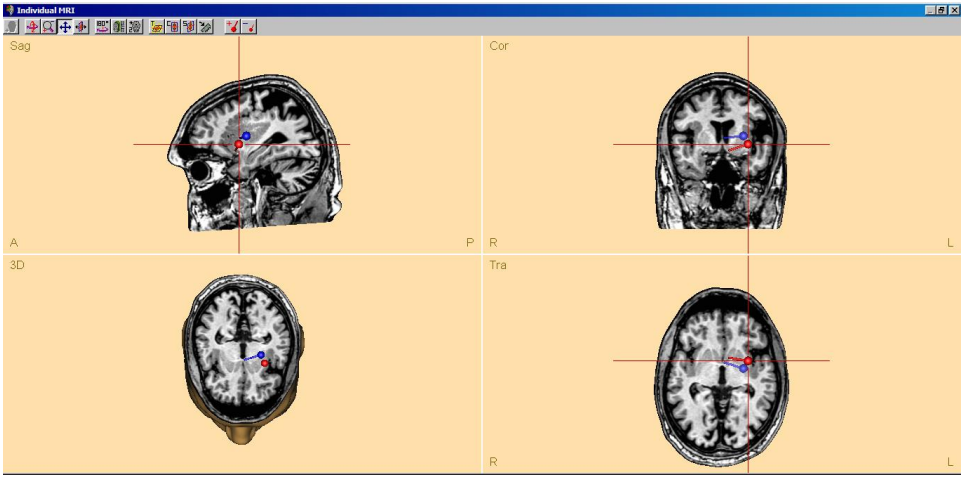

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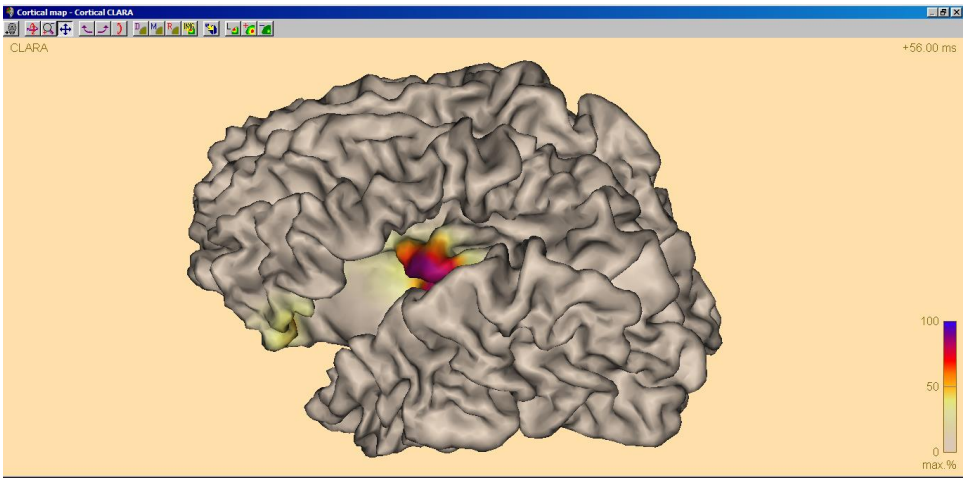

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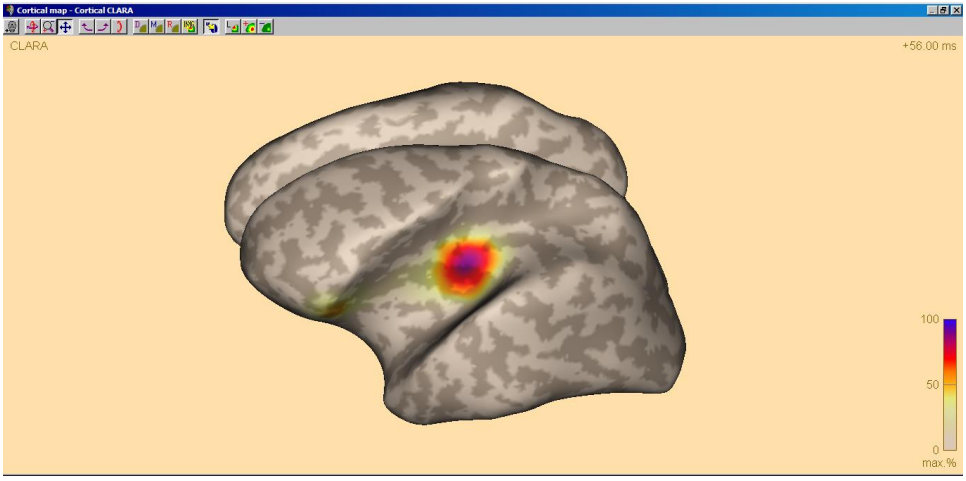

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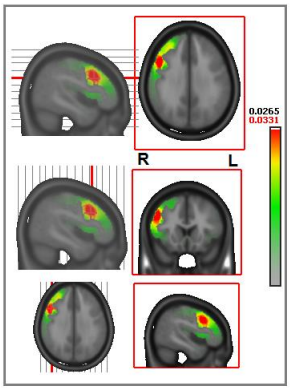
Take home message

EMSI

- Has a dg. accuracy similar / superior to other functional imaging methods
- Yields clinically relevant, new information
- Important tool in the presurgical evaluation of patients with epilepsy



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