

Introduction to Source Analysis - ing Distributed Source Imaging using LORETA

BrainVision Analyzer 2 Webinar

Scientific Support Team Brain Products GmbH



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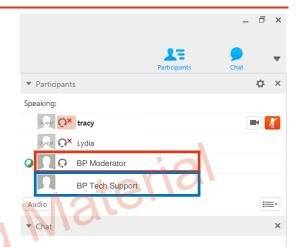


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- Questions related to <u>Webinar content</u> should be addressed to <u>BP Moderator</u>.
- Questions related to <u>technical issues</u> (video, sound) should be addressed to BP Tech Support.

Questions will either be answered directly or compiled for the open questions in the end.

Please ensure that your microphones are muted and that you do not start video streaming with your webcam.



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Goals

- Theoretical background of Source Analysis Ø
- Source Analysis using LORETA in Analyzer 2 V

Learning Outcomes

rall

- eaching Material Make use of LORETA's functionality in your processing pipeline V
- Data post-processing in the source domain Ø

Outline of the session



- 1. Theoretical background of Source Analysis
 - Why Source Analysis?
 - Principles of the Forward and Inverse problem
- 2. Theoretical basis of LORETA

Assumptions and constraints

- Implementation of LORETA in Analyzer 2
 - Ingredients of LORETA
 - Data post-processing in the source domain
 - Limitations of LORETA
 - DOs and DON'Ts of LORETA in Analyzer 2
 - Open Questions
- 5. Concluding Remarks



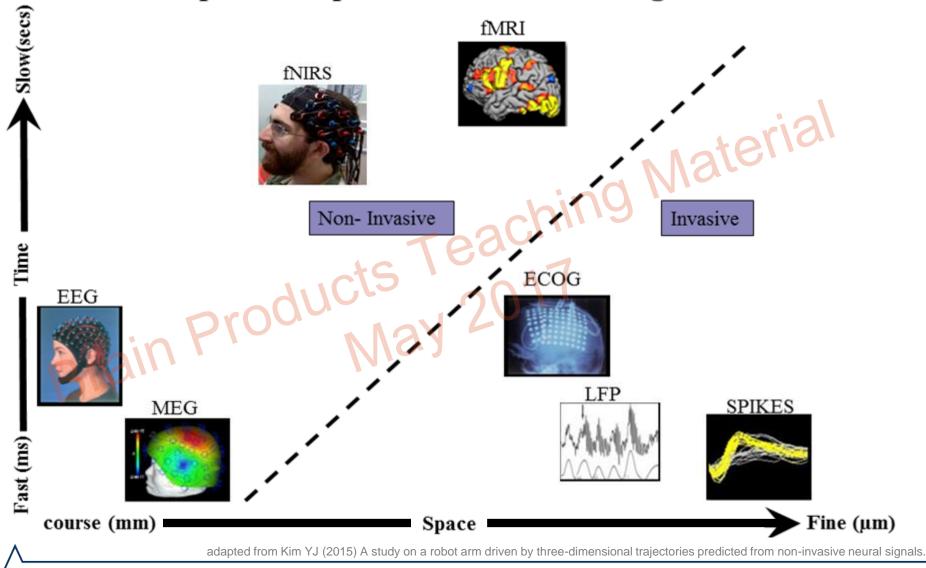




Multimodality \rightarrow Why EEG?



Spatio-temporal scale of Neural Signals





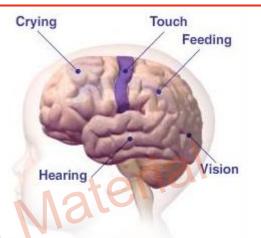
	EEG	fMRI
Temporal resolution	Excellent (milliseconds)	Poor (seconds)
Spatial resolution	Poor (cm)	G Excellent (mm)
What does it measure?	Electrical activity (direct)	Metabolic activity (non-direct)
Mobility	Portable	Non-portable
Price	Affordable	Expensive

EEG \rightarrow Superior temporal resolution with the cost of inferior spatial resolution!



Aim

To find the source of the brain activity by analyzing the electrical activity recorded from surface electrodes.



- Applications
 - Well-known experimental paradigms:
 - Resting state ongoing responses (1)
 - Auditory evoked potentials (2).
 - Somatosensory evoked potentials (3).
 - Cognitive event related potentials (4).
 - Spikes and/or Seizures (5).





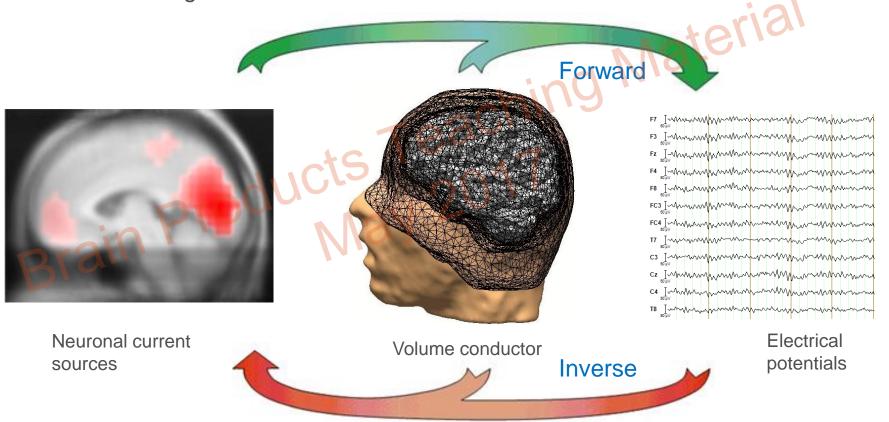
Why Source Analysis?



- EEG is a non-invasive measurement of macroscopic, reference-dependent observables of brain activity.
- EEG dynamics reflects the superposition of many neuronal systems distributed across the brain.
- Source Analysis is the approach to:
 - achieve a reference-free data representation.
 - decompose EEG patterns into its underlying neuronal sources.
 - Iocalize the sources of EEG activity within the brain.



- Forward modeling
- Inverse modeling

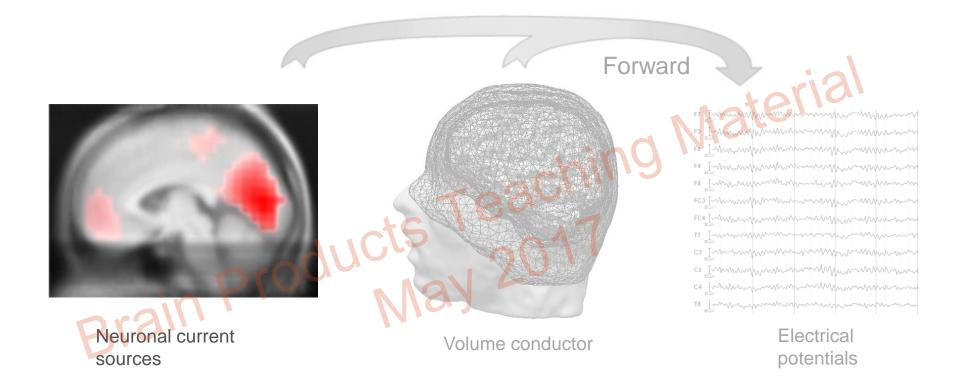




- (1) Source modeling
- (2) Anatomical modeling
- (3) Head modeling (volume conductor models) NO
- (4) Coordinate transformation (co-registration) Brain

2

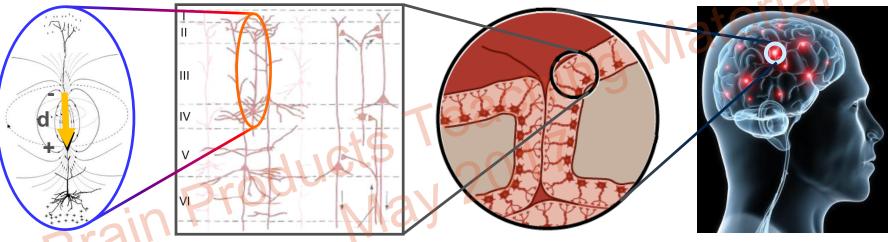




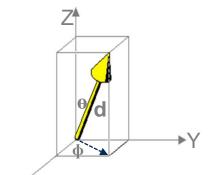
Forward Problem: Source Modeling



- Oscillations arise from the interplay of many neural ensembles through excitatory and inhibitory synapses.
- Primary current sources representing a focal area of synchronously active pyramidal cells can be modeled using equivalent current dipole.

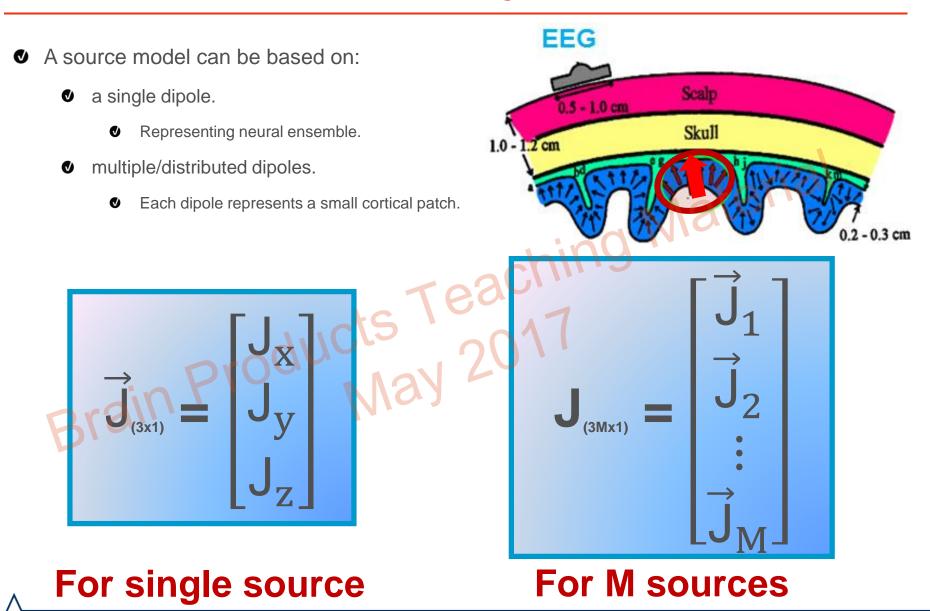


- Adipole is characterized by its 6 parameters:
 - 3 for its location,
 - 3 for its vectoral components in Cartesian coordinates:
 - 1 magnitude and 2 orientations expressed in spherical coordinates.

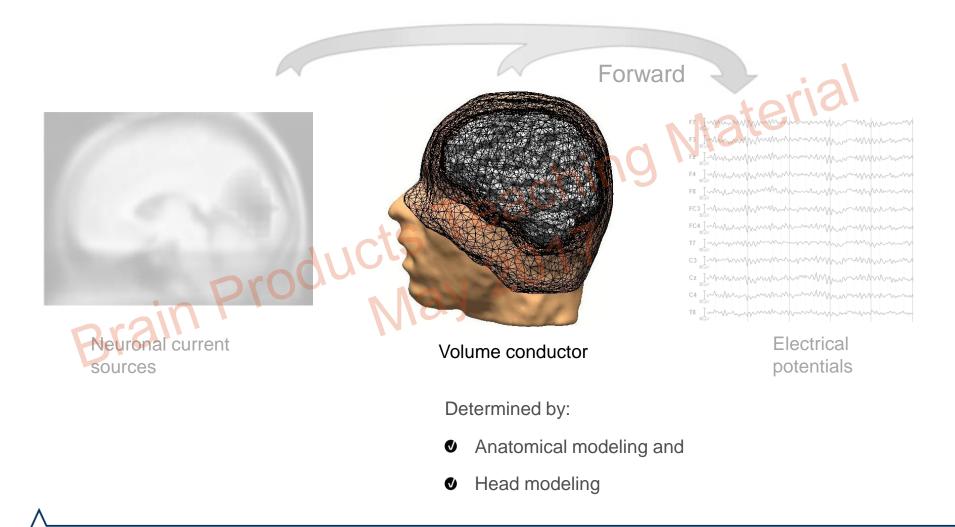


Forward Problem: Source Modeling









Forward Problem: Anatomical Modeling

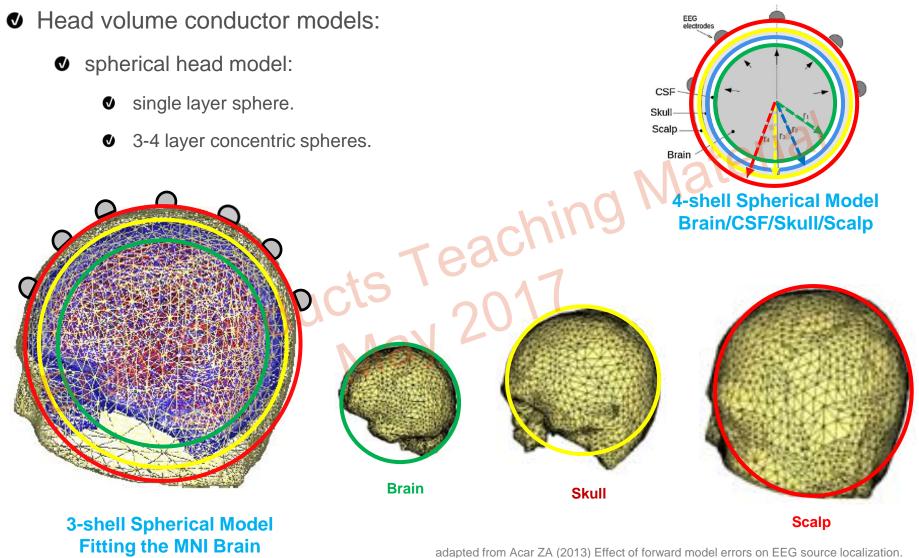


- Brain volume, shape and size vary across different people.
 - Standard brain template.
 - A brain template is an anatomical representation depicting finer anatomical details.
 - Generated either from:
 - a single representative subject or
 - multiple subjects → have higher signal-to-noise ratio and provide better contrast between grey and white matter.
 - Help in performing comparative analyses by transforming each of the individual's structural data to a well-established template → report results in standard coordinate system (e.g., MNI space or Talairach and Tournoux space).
 - Realistic (individual) brain.
 - Whole head T1 weighted MR of a particular subject.



Forward Problem: Head Modeling



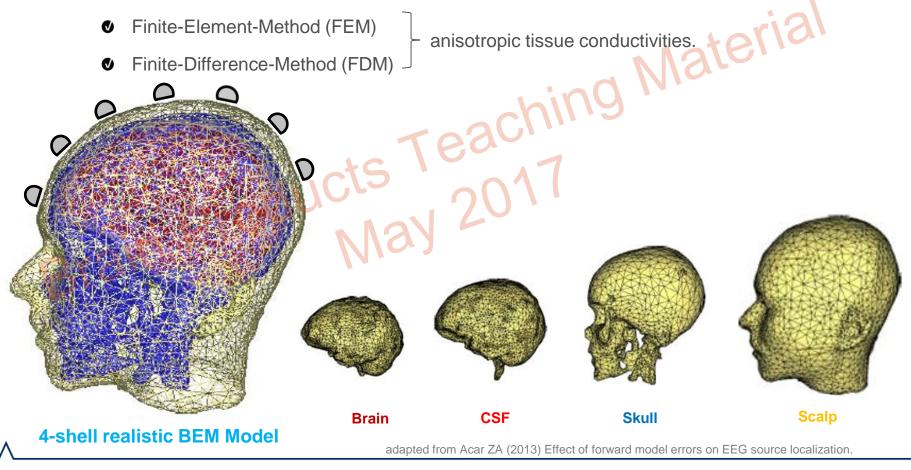


adapted from Nunez PL, Srinivasan R. (2006) Electric fields of the brain.

Forward Problem: Head Modeling



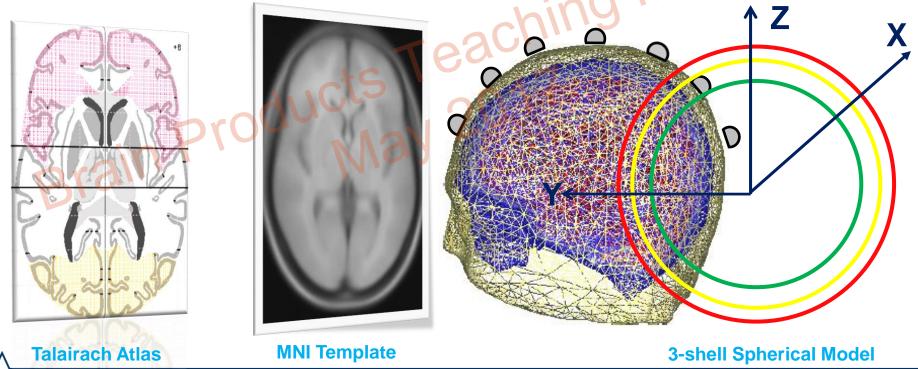
- Head volume conductor models:
 - ✓ realistic head model:
 - Boundary-Element-Method (BEM): assumes isotropic tissue conductivities.



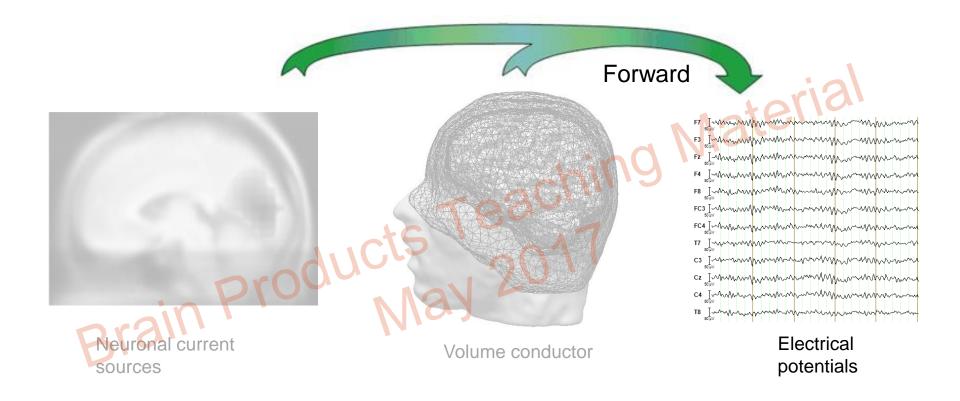
(4) Forward Problem: Co-registration



- ✓ To compute the electrical signals produced by dipole(s),
 - the anatomy,
 - the head model and
- must be expressed in the same coordinate system.
- \bullet the electrode positions \Box
- Often the pre-auricular and nasion points are used as anatomical landmarks.



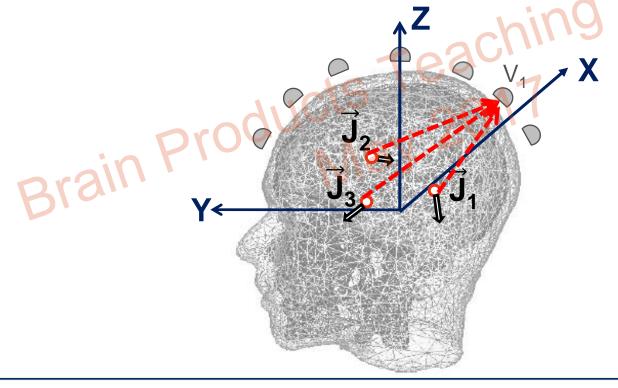






Given:

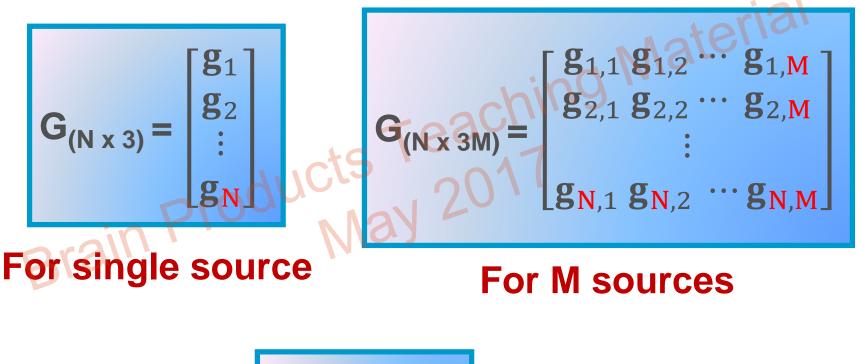
- position, orientation, magnitude of any neuronal current sources (\vec{J}) .
- volume conductor geometry of the brain, skull, and scalp.
- ✓ Wanted: voltage distribution over the scalp (V).
 - Leadfield maps the neuronal current values to the voltage measurements at a specific position.



Forward Problem: Leadfield Matrix



For N number of channels, the leadfield matrix, G, representing the solution to the forward problem given one single dipole or M multiple dipoles in the x-, y-, and z- directions is given as:

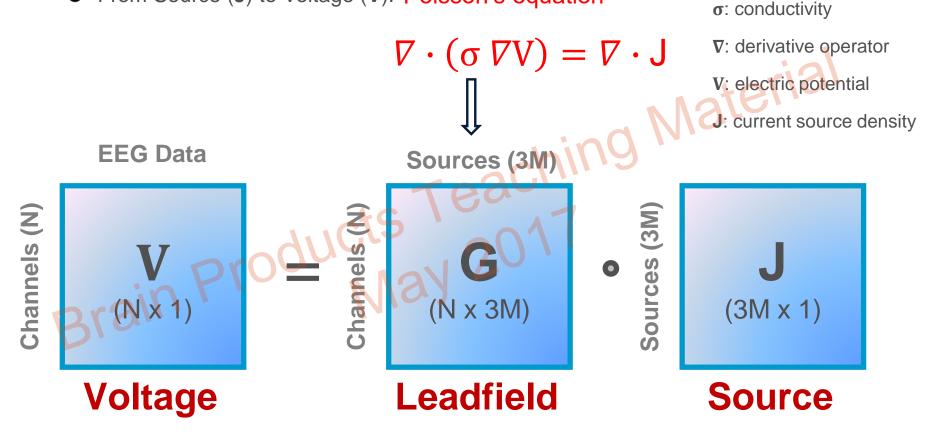


$$\mathbf{g}_{(3 \times 1)} = \left[g_{\mathrm{x}} g_{\mathrm{y}} g_{\mathrm{z}} \right]$$

Forward Solution: from Dipoles to Scalp Topography



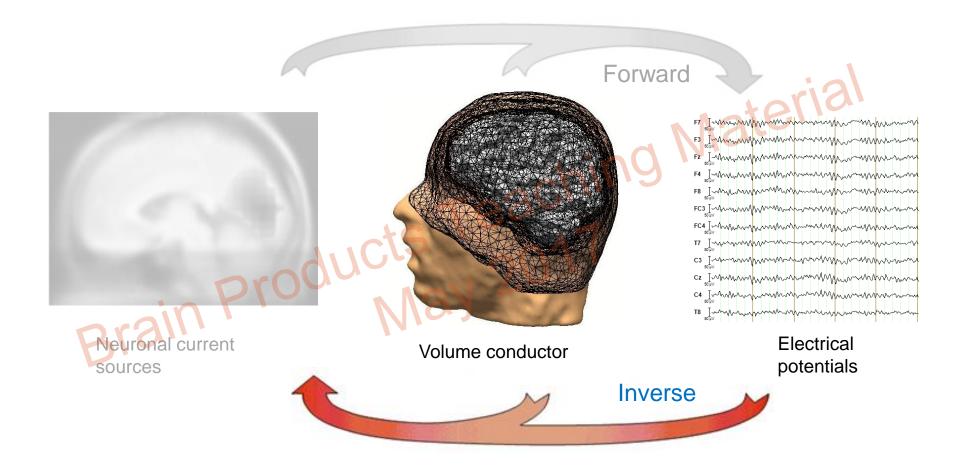
- Modeling of the potentials produced by the dipoles.
 - ✓ From Source (J) to Voltage (V): Poisson's equation





- EEG signal is generated by neuronal current sources.
 - Current sources are distributed assemblies modeled using equivalent current dipoles located in source space.
- The relation between source matrix and voltage matrix is mediated by the Leadfield comprising:
 - the physics of how currents and electric fields behave inside the conductive medium (head).
 - a volume conduction model (providing geometric and resistive properties).
- Solving the forward problem enables us to determine the electrical potentials created by the primary current sources.
 - An accurate forward solution is a necessary pre-requisite for solving the inverse problem.

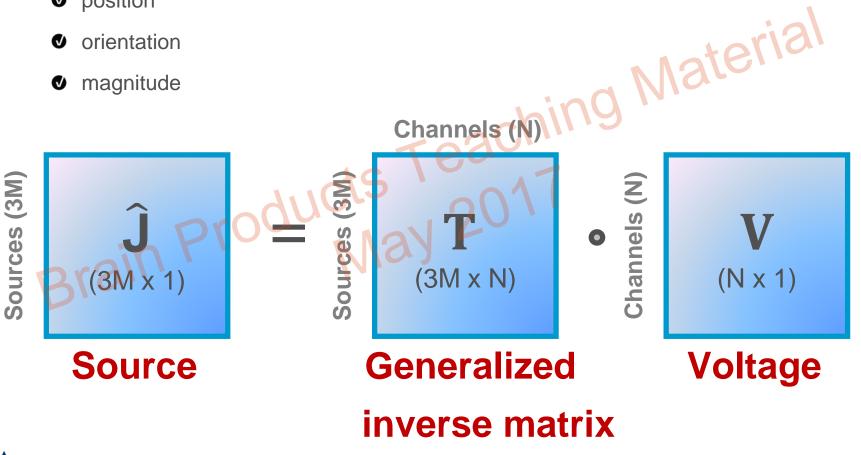




Inverse Problem

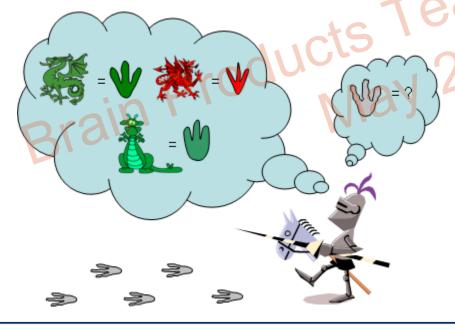


- **Given**: voltage measurements obtained from the forward problem. V
- Wanted: equivalent source (current dipole) described by its: V
 - position





- Estimation of the currents that produced the measured data \rightarrow ill-posed problem!
- What is a well-posed problem? (as defined by the Mathematician Jacques Hadamard)
 - The problem must have a solution.
 - V The solution must be unique.
 - Material The solution must be stable under small changes to the data. V



- Different current distributions can explain the measured data \rightarrow nonunique solutions (M >> N).
- Estimated sources can be sensitive to noise \rightarrow unstable.

Inverse Problem



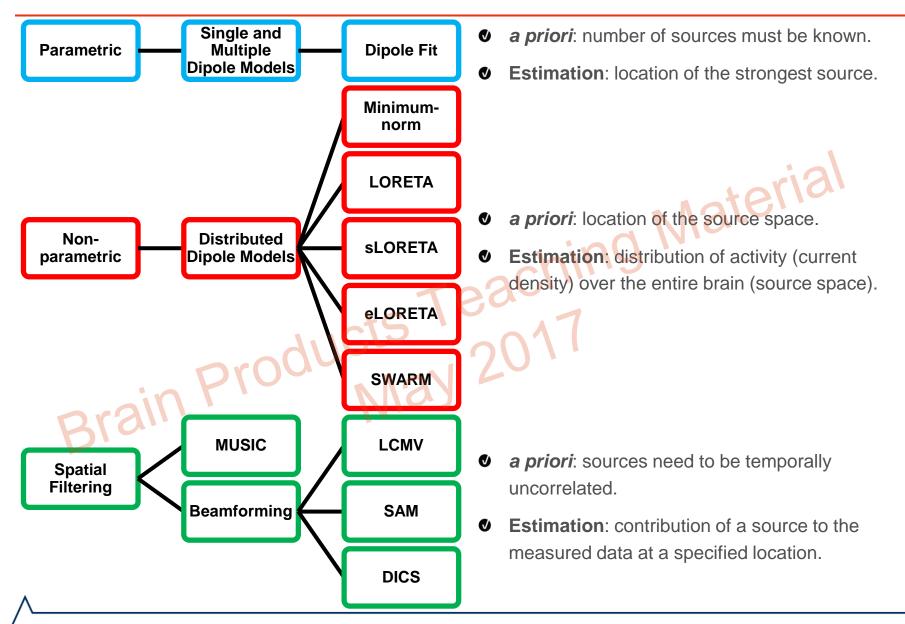
- How do we tackle the ill-posed nature of the inverse problem?
 - By setting certain assumptions/constraints.
 - Functional constraints:
 - *a priori* information about the number of sources/dipoles.
 - dipole location and/or orientation can be fixed which reduces the number of parameters.

Dipole Models	Number of parameters to be estimated	
Moving	6 (free location (x, y, and z), free orientation (θ and ϕ), and magnitude)	
Rotating	3 (free orientation (Θ and ϕ) and magnitude)	
Fixed Provide America	1 (magnitude of x-, y-, or z-components)	

- e.g., minimum-norm, maximum smoothness.
- Anatomical constraints:
 - sources lie on a 3D cortical space (grid) and each grid consists of 3 dipole components i.e., in the x, y, and z-directions.

Inverse Methods







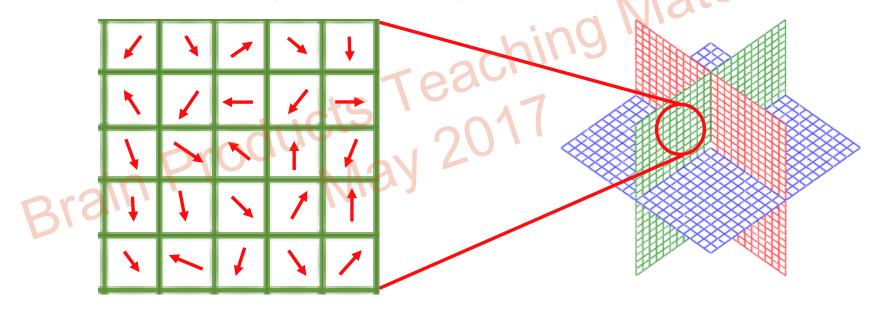
Low Resolution Brain Electromagnetic Tomography ateria Brain Products Teaching May 2017



What is LORETA?



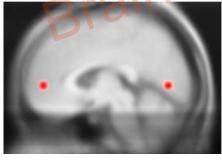
- LORETA is one of the most established distributed-source imaging or current density reconstruction methods.
 - The distributed activity throughout the brain volume is computed.
 - The volume is discretized as a dense 3D grid where a single dipole is located on each grid point confined in a given source space (e.g., the cortex).



• Goal: Estimate the magnitude of the dipole at each grid point (voxel).

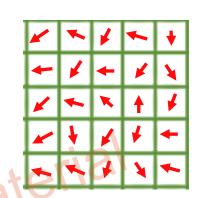
Theoretical basis of LORETA

- Assumption: neighboring sources tend to be synchronized i.e., they have similar orientation and magnitudes.
- Mathematical constraint: maximal smoothness of source intensity values.
 - Introduce a source model term based on the Laplacian operator (second spatial derivative).
 - Smoothest possible (unique) inverse solution!
- ✓ LORETA's localization properties:
 - Low spatial resolution preserving the location of maximal activity.



2 distinct sources

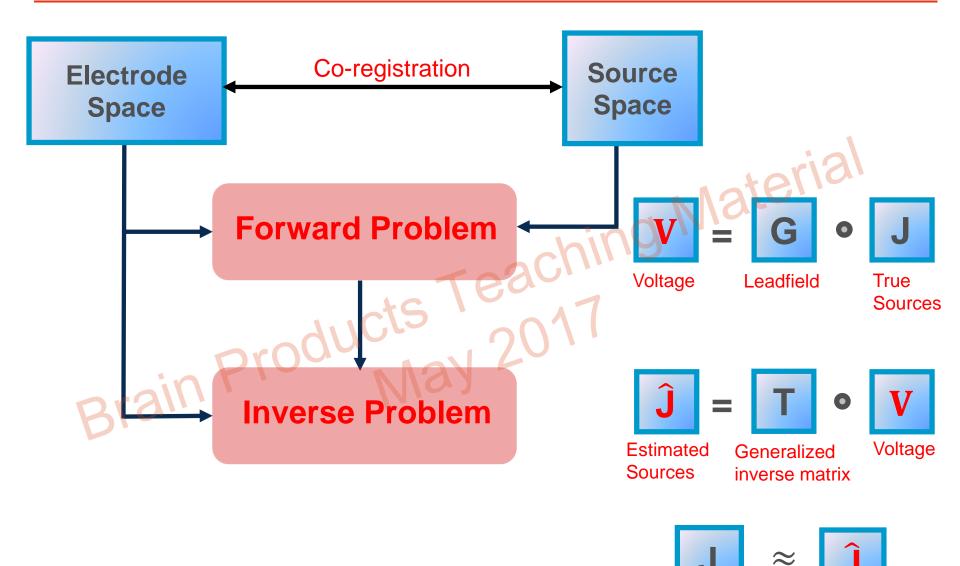
The corresponding smoothed activation map



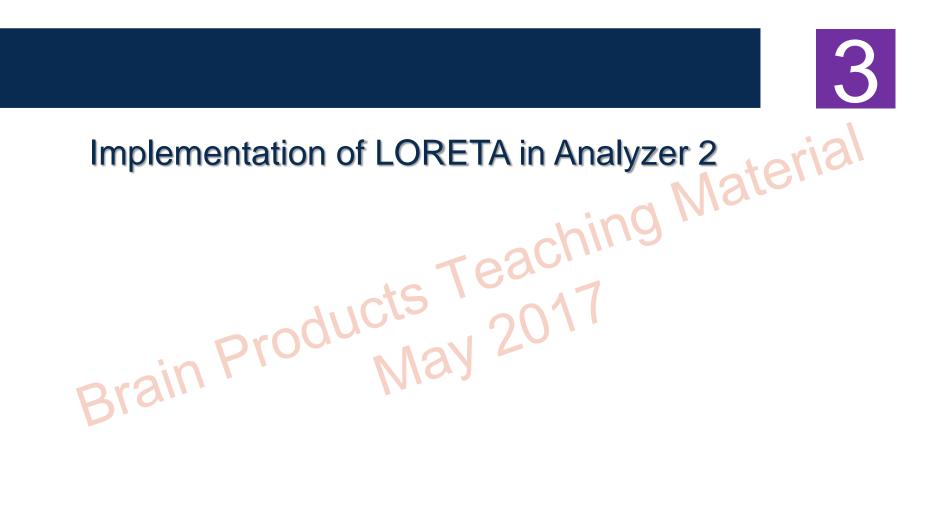
- W: source-depth weighting matrix
- λ : regularization parameter
- B: Laplacian operator





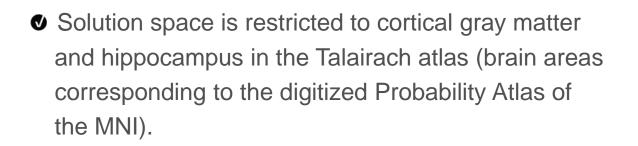




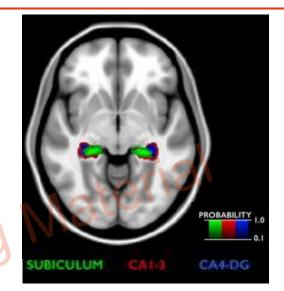




LORETA Ingredients: Source Model



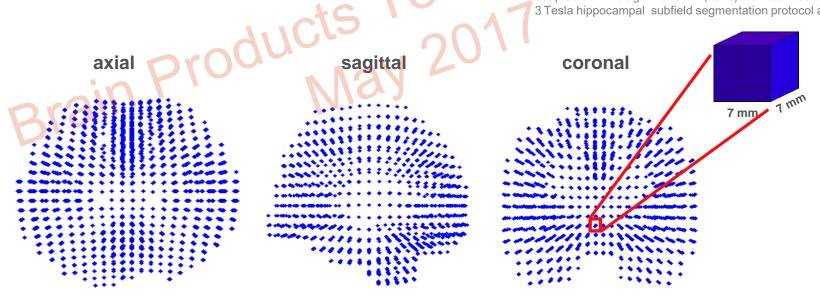
The source space grid comprises 2394 voxels at 7 mm spatial resolution.



BRAIN

Solutions for neurophysiological re

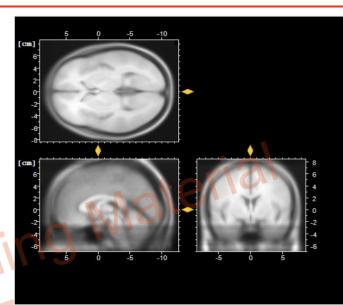
adapted from Kulaga-Y.J. et al. (2015) Multi-contrast submillimetric 3 Tesla hippocampal subfield segmentation protocol and dataset.





LORETA Ingredients: Anatomical and Head Model

- Anatomies
 - Based on MNI templates:
 - MNI-305 (Collins, 1994):
 - average of the 3D brain T1 weighted MR images of 305 representative subjects.
 - MNI-Colin (scans of MNI lab member Colin Holmes):
 - Colin-PD weighted images.
 - Colin-T2 weighted images.
 - Colin-T1 weighted images.
 - Co-registered to Talairach atlas (Talairach & Tournoux, 1988).
 - Brain structures (defined in the Talairach atlas).
- Head Model
 - 3-shell spherical head model registered to the Talairach human brain atlas based on the MNI brain.



Anatomy:	Average305 \checkmark
	MNI-Colin-PD
	MNI-Average305-T1
	MNI-Colin-T2
	MNI-Colin-T1
	Average 305

LORETA Ingredients: Co-registration



- Expressing electrode co-ordinates and the head anatomy in the same coordinate system.
- Spherical coordinates are used to specify a point on the surface of the head.

+ X Right

- Consisting of the variables r, θ , ϕ .
- The origin is the intersection of the lines passing:
 - through **T7** and **T8** (x-axis).
 - through Oz and Fpz (y-axis)
 - through **Cz** (z-axis).
- Radius for:
 - non-scalp electrodes (e.g., ECG), **r** = **0**.
 - scalp electrodes, $\mathbf{r} = \mathbf{1}$.

Front

Left

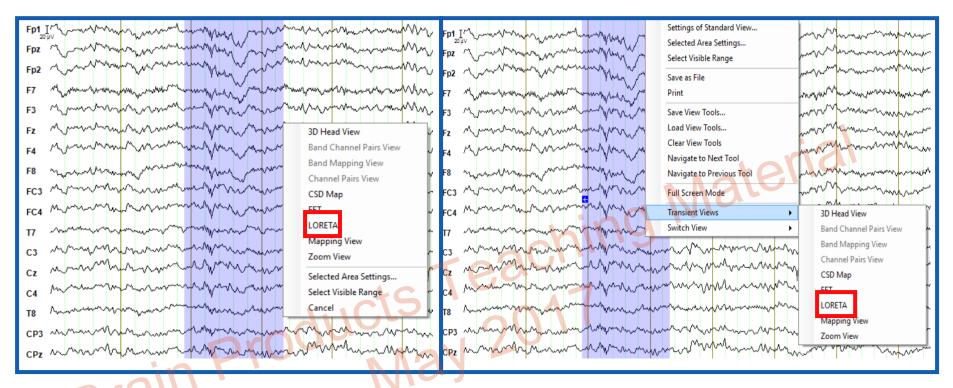


- ✓ LORETA transformation is accessible as a:
 - Transient transformation
 - For temporary display and inspection of the EEG data.
 - Exploratory analysis which provides a first impression about the location of areas of activation (clusters) → to infer the Region-of-Interests (ROIs).
 - Computation is done only for data points selected by the user.
 - Output is generated in a dockable window in the main window display.
 - Primary transformation
 - Allows to specify ROIs.
 - Generates a new history node which contains the average current density within each ROI (provided as a LORETA channel).

	🧌 🍄 –	•		_														
V	File	Display	Transformations	Add Ins	Export	Macros	Solutions	History Template	Help									
Channe	l Preprocessin	ıg 🗸 🔅 Cha	nge Sampling Rate 🧃	🔅 Linear Deriva	tion	Data Filtering	g ~	🔯 Ocular Correction ICA	🔅 FFT	Ő	Inverse ICA	Result Evaluation ~	i Segmentation	Statistical Analysis 🗸	ö Data Comparison	🔅 LORETA	🔯 Data Cache	ö Import Markers
Data Pr	eprocessing ~	🔹 🤯 Edit	Channels 🙀	🐉 Topographic I	Interpolation	Artifact	Rejection			iverse 👸	Wavelet Extraction 👸 PCA	Baseline Correction		Cross Correlation			🔯 Edit Markers	
🔯 Ada	d Channels	🤯 Lev	el Trigger 🛛	🔅 Formula Evalu	uator	🔯 Raw Dat	ta Inspection	🔯 Ocular Correction	🄯 ICA	- 4	Wavelets	🔯 DC Detrend	Not Average	Coherence	Covariance	🔯 CB Correction	🔯 Edit User Properties	🔯 Matlab
Dataset Preprocessing					Artifact Rejection/Reduction			Fre	Frequency and Component Analysis		Segment Analysis Functions		Comparison and Statistics		Special Signal Pro	Others		

LORETA: as a Transient Transformation





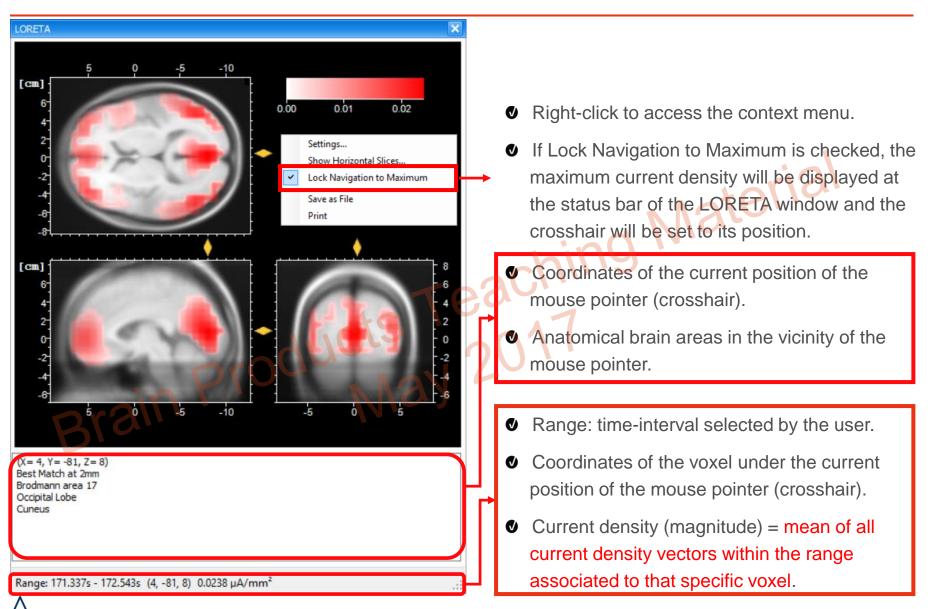
- Option 1
 - Use the mouse to select an interval.
 - Release the mouse button.
 - Contex menu appears in which you can select LORETA.

Option 2

- An interval has already been selected.
- Right-click to access the contex menu.
- Click on Transient Views to acess the visualization options and select LORETA.

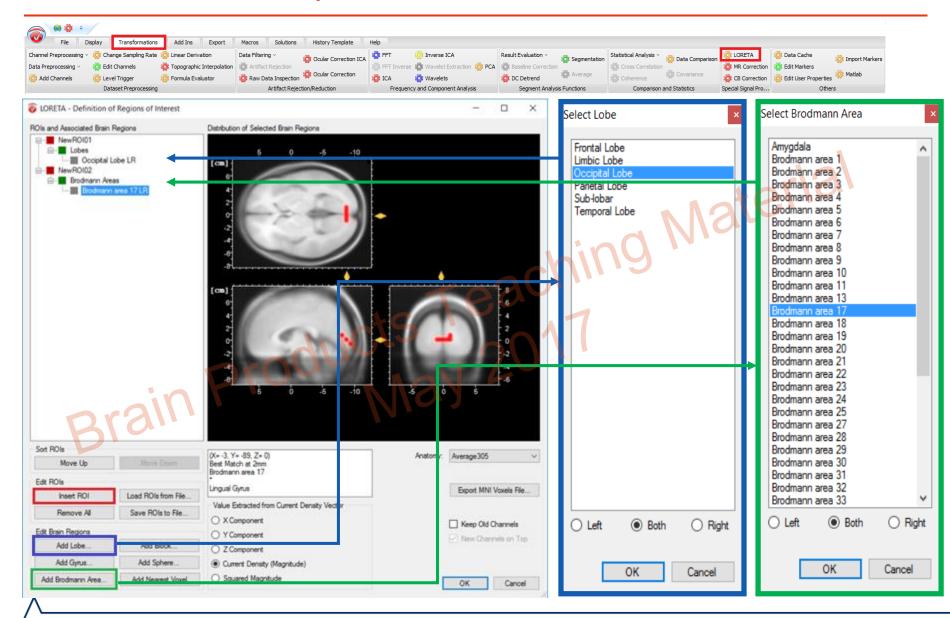
LORETA: as a Transient Transformation





LORETA: as a Primary Transformation





Outputs of LORETA



- LORETA computations can be specified for:
 - mean of the current density vectors across the:
 - ♦ X Component
 - \checkmark Y Component \vdash within a ROI.
 - Z Component
 - mean of all current density vectors within a ROL
 - Current Density (Magnitude)
 - opwer of the mean current density vectors within a ROI.

L

Squared Magnitude

Value Extracted from Current Density Vector
○ X Component
O Y Component
O Z Component
 Current Density (Magnitude)
O Squared Magnitude

Loading ROIs





- Export the predefined ROI template to a *.csv file using the option "Export MNI Voxels File..."
- The *.csv file contains the x-, y-, and z- MNI coordinates as well as the associated anatomical data of the brain areas consisting of 2394 voxels in the source space.

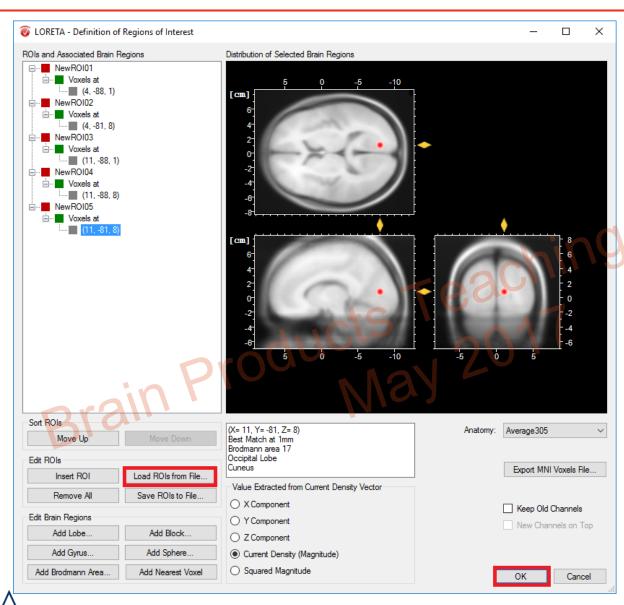


A B C	D)		E	F	G
2394 = number of voxels						
5 = number of ROIs						
X-MNI	Y-MNI Z	-MNI	Lobe	Structure	Brodmann area	ROI-number [10] (if zero then not included in any ROI)
-52	-11	-41	Temporal Lobe	Inferior Temporal Gyrus	Brodmann area 2	0
-45	-11	-41	Temporal Lobe	Inferior Temporal Gyrus	Brodmann area 2	0
-38	-11	-41	Limbic Lobe	Uncus	Brodmann area 2	0
-31	-11	-41	Limbic Lobe	Uncus	Brodmann area 2	0
32	-11	-41	Limbic Lobe	Uncus	Brodmann area 2	0
39	-11	-41	Temporal Lobe	Inferior Temporal Gyrus	Brodmann area 2	0
				0		-
-31	-88	_	*	Middle Occipital Gyrus	Brodmann area 1	
-10	-88		*	Lingual Gyrus	Brodmann area 1	
-3	-88		*	Lingual Gyrus	Brodmann area 1	
4	-88		*	Lingual Gyrus	Brodmann area 1	7
11	-88	1	*	Lingual Gyrus	Brodmann area 1	7
32	-88	1	*	Middle Occipital Gyrus	Brodmann area 1	8
39	-88	1	*	Middle Occipital Gyrus	Brodmann area 1	8
-31	-88		Occipital Lobe	Middle Occipital Gyrus	Brodmann area 1	
-3	-88		Occipital Lobe	Cuneus	Brodmann area 1	
4	-88	8	Occipital Lobe	Cuneus	Brodmann area 1	8
11	-88	8	Occipital Lobe	Cuneus	Brodmann area 1	7
32	-88	8	Occipital Lobe	Middle Occipital Gyrus	Brodmann area 1	9
39	-88	8	Occipital Lobe	Middle Occipital Gyrus	Brodmann area 1	8
-45	-81	8	Occipital Lobe	Middle Occipital Gyrus	Brodmann area 1	9
-10	-81	8	Occipital Lobe	Cuneus	Brodmann area 1	7
-3	-81	8	Occipital Lobe	Cuneus	Brodmann area 1	7
4	-81	8	Occipital Lobe	Cuneus	Brodmann area 1	7
11	-81	8	Occipital Lobe	Cuneus	Brodmann area 1	7
39	-81	8	Occipital Lobe	Middle Occipital Gyrus	Brodmann area 1	9
46	-81	8		Middle Occipital Gyrus	Brodmann area 1	9
-52	-74			Middle Temporal Gyrus	Brodmann area 3	9
-45	-74			Middle Temporal Gyrus	Brodmann area 3	9

- Open the file in Excel/notepad and search for the desired ROI and number the identified voxels by changing the ROInumber (as shown in column G) from 0 to 1, 2, 3, 4,....
- Save the *.csv file containing all the 2394 voxels after marking the desired voxels within a ROI.

Loading ROIs





Load the modified *.csv file using the button "Load ROIs from File..."

After pressing OK a node named LORETA will be generated in the history tree containing the source signals corresponding to the desired voxels within a ROI.



- Pre-requisites of source analysis (LORETA):
 - spatial arrangement of the scalp electrodes (electrode positions: standard or realistic).
 - ♥ time-domain EEG data.
- Recommended conditions for the quality of source analysis: ateria
 number of electrodes

 - \blacksquare uniform distribution of electrodes across the head \rightarrow Equidistant electrode positioning.
 - \blacksquare low electrode positioning error \rightarrow use high-precision electrode localizer, for e.g., CapTrak.
 - \checkmark high signal-to-noise ratio (SNR) of input data \rightarrow good data pre-processing.

Interim Summary



- Modes of LORETA operation in Analyzer 2:
 - as a Transient transformation.
 - For temporary display and inspection purpose.
 - Computation is done only for data points selected by the user.
 - Outputs the average current density (magnitude) within the range associated to a specific voxel.
 - as a Primary transformation.
 - Allows defining and/or loading region of interest (ROIs) from a file.
 - Outputs for a single time point the:
 - current density (magnitude) for each specified component (x-,y-,z-) or,
 - average current density (magnitude) for the selected ROI or
 - power of the average current density for the selected ROI.

Data Post-processing in the Source Domain



- Measure extraction and export for statistical analysis.
 - Export Current Density from LORETA.
 - Generic Data Export (via *Export* > *Node Export* > *Generic Data*).
 - Area Information Export (*via Export > Multiple Export > Area Information*).
 - Peak Detection (via Transformations > Segment Analysis Functions > Result Evaluation > Peak Detection).
 - Peak Information Export (via Export > Multiple Export > Peak Information).







- LORETA has a low spatial resolution and assumes that neighboring sources are correlated.
 - However, functionally very distinct areas can be anatomically very close. Therefore, the argument of correlation as a physiological justification for the LORETA algorithm should be taken with caution.
 - Moreover, far-distance correlations result in over-smoothed, blurred solutions. For instance, homologous areas in both hemispheres or two distinct areas along a sulcus.

Frequency-domain and time-frequency domain source analyses are not supported (in Analyzer)!

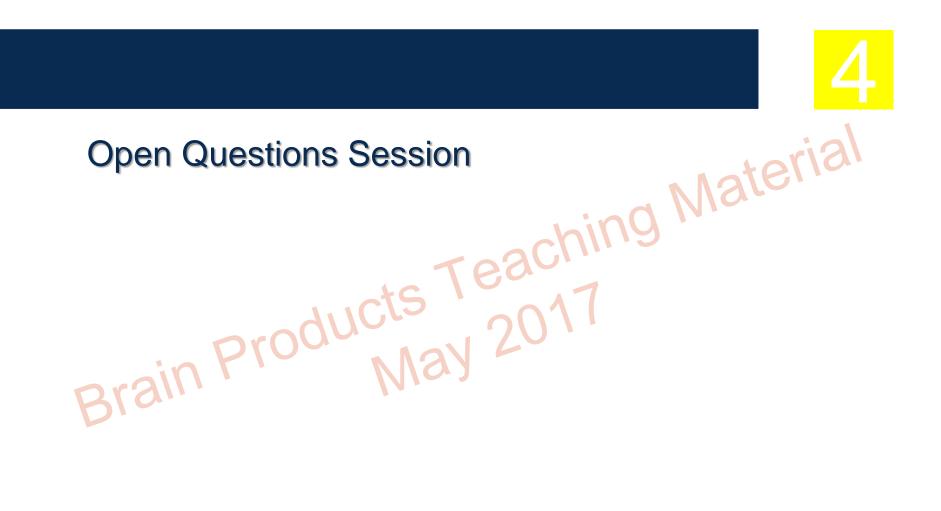
Dos and DON'Ts of LORETA in Analyzer 2



- The only valid input to LORETA is voltage (time-domain).
- ✓ LORETA transform <u>shall not</u> be applied to:
 - CSD
 FFT and Coherence spectra
 Wavelets
 Complex Demodulation
 Z-transformed data
 P-values
 T-test values
 Bipolar recordings

more details: http://www.uzh.ch/keyinst/NewLORETA/Misuse/Misuse.htm









5 Brain Products Teaching Material May 2017





- Spatiotemporal EEG dynamics partially encode the information about the underlying neural V dynamics.
- LORETA leads to reasonable source configurations but has its own limitations. V Materia
- Be aware of the requisites and misuses of the LORETA transform. V
- ROIs for LORETA analysis should be defined at best on the basis of previous scientific reports. Ø

Exploratory analysis using LORETA Transient View can help you to identify areas of activation, V which then can be potentially used as ROIs.

Source analysis is great, is needed, but is a difficult problem. There is no "gold standard" method V available yet. Be cautious in drawing inferences related to the location and magnitude of the sources.

References – Journal articles



- Pascual-Marqui RD, Michel CM, Lehmann D (1994). Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. *International Journal of Psychophysiology*, 18:49-65.
- Pascual-Marqui RD, Lehmann D, Koenig T, Kochi K, Merlo MCG, et al. (1999). Low resolution brain electromagnetic tomography (LORETA) functional imaging in acute, neuroleptic-naive, firstepisode, productive schizophrenia. *Psychiatry Res.*, 90: 169–179.
- Pascual-Marqui, RD (1999). Review of methods for solving the EEG inverse problem. International Journal of Bioelectromagnetism, 1(1), 75-86.
- Pascual-Marqui RD, Esslen M, Kochi K, Lehmann D (2002). Functional imaging with low resolution brain electromagnetic tomography (LORETA): a review. *Methods & Findings in Experimental & Clinical Pharmacology*, 24C:91-95.
- Michel CM, Murray MM, Lantz G, Gonzalez S, Spinelli L, et al. (2004). EEG source imaging. *Clinical Neurophysiology*, 115(10), 2195-2222.

References – Brain Products materials



- Analyzer User Manual (current version 2.1.1)
 - http://www.brainproducts.com/downloads.php?kid=5&tab=2#dlukat_52

7.6 Transforms in the Special Signal Processing group							
		8.5 LORETA					
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Source a	nalysis aims at solvin	The transient LORETA transform is used for source localization based on the Low Resolution					
current s	ources in the brain fr	Electromagnetic Tomography procedure described by R. D. Pascual-Marqui.					

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Beyond surface EEG: An invitation to source analysis with LORETA

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This article presents the improved version of the LORETA transform in the new version of Analyzer 2.1.0 (to be released in the course of October 2014). The main features of the new LORETA dialog are explained and the virtues of LORETA analysis of EEG data are discussed. Hopefully this brief introduction will encourage you to use the new LORETA transform and push your research questions beyond the head surface into the neural source domain.

Introduction

The fundamental discovery of the human electroencephalogram (EEG) by Hans Berger gave a new twist to the history of human neuroscience. After many decades of research and applications, EEG continues to be a very active and stimulating field of research. One of the main reasons is that EEG reflects the underlying dynamic symphony of neural activity at the millisecond scale, which offers a privileged window into brain function and the neural underpinnings of cognition. However, non-invasive human EEG recordings meet a natural frontier at the head surface, which prohibits direct access to the neural source domain. Therefore, true neural activity can only be inferred from the electrical potentials measured at each electrode site on the scale. Source analysis techniques aim to estimate the location and dynamics of the underlying neural generators of EEG, i.e., to provide a solution to the EEG inverse problem (Grech et al., 2008). Although there is theoretically no unique



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