Electromagnetic Imaging of Brain Function

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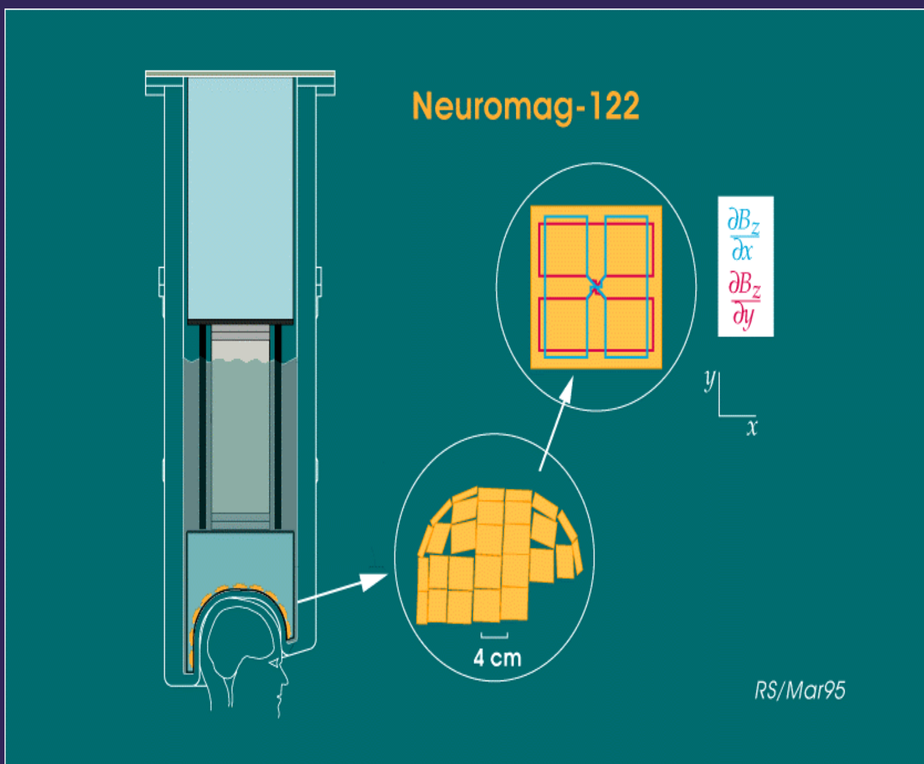
Thanks: Felix Darvas, Dimitrios Pantazis,Esen Kucukaltun-Yildirim, John Mosher, Sylvain Baillet, Tom Nichols

Magnetoencephalography

- MEG signals ~ 50-500fT (cf. Earth's magnetic field ~50mT)
- Detected using SQUID magnetometers

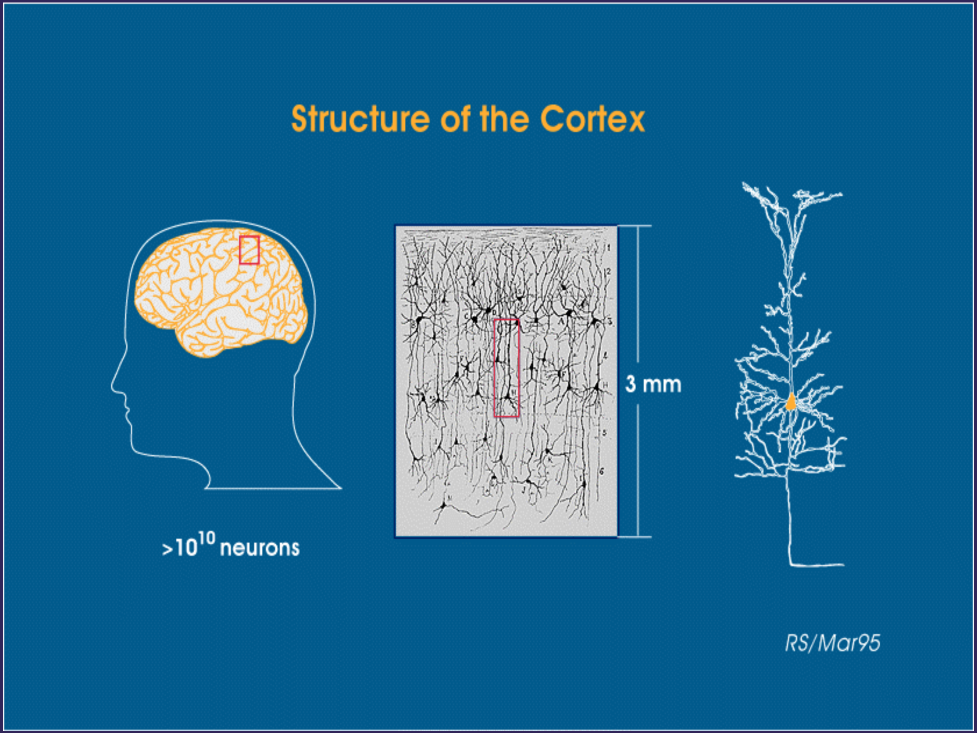


- Gradiometers and magnetic screening reduce interference
- Alternative to scalp potential recordings (EEG)


Multichannel MEG
ADC and amplifiers
Shielded room
MEG
Gantry
Liquid Helium
Sensors
Dewar
Data acquisition and processing

Neuromagnetic Fields

- Magnetic fields are produced by current flow in apical dendrites in cortical pyramidal neurons

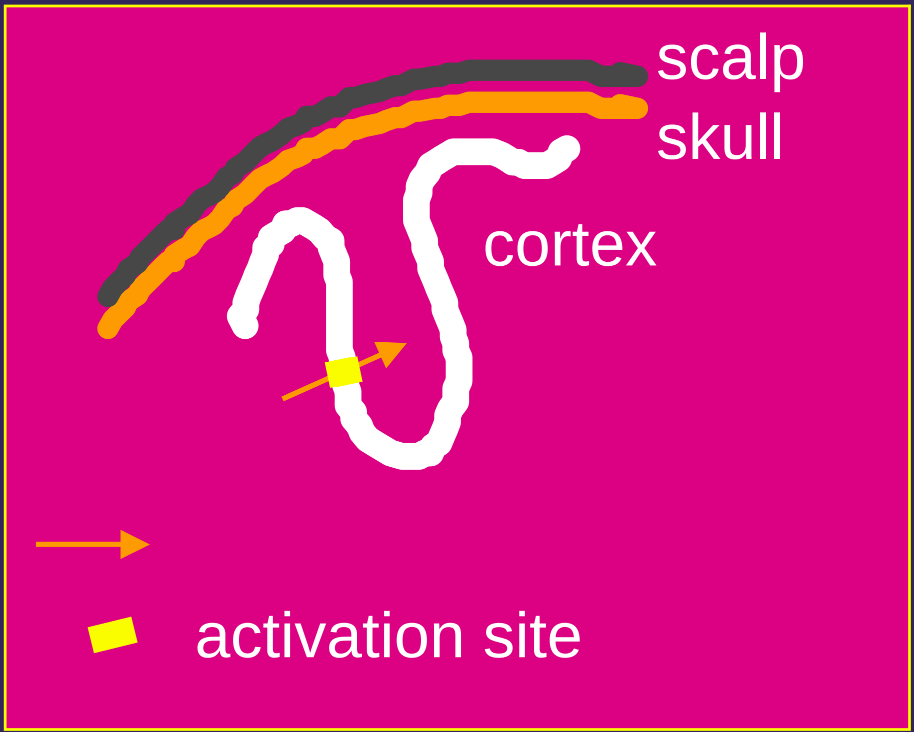


from Ritta Salmelin, low temperature lab, Helsinki university of Technology

- Interested in spontaneous and event related fields

- Event-locked averaging typically required for adequate SNR in ERPs/ERFs

Basic Source Model

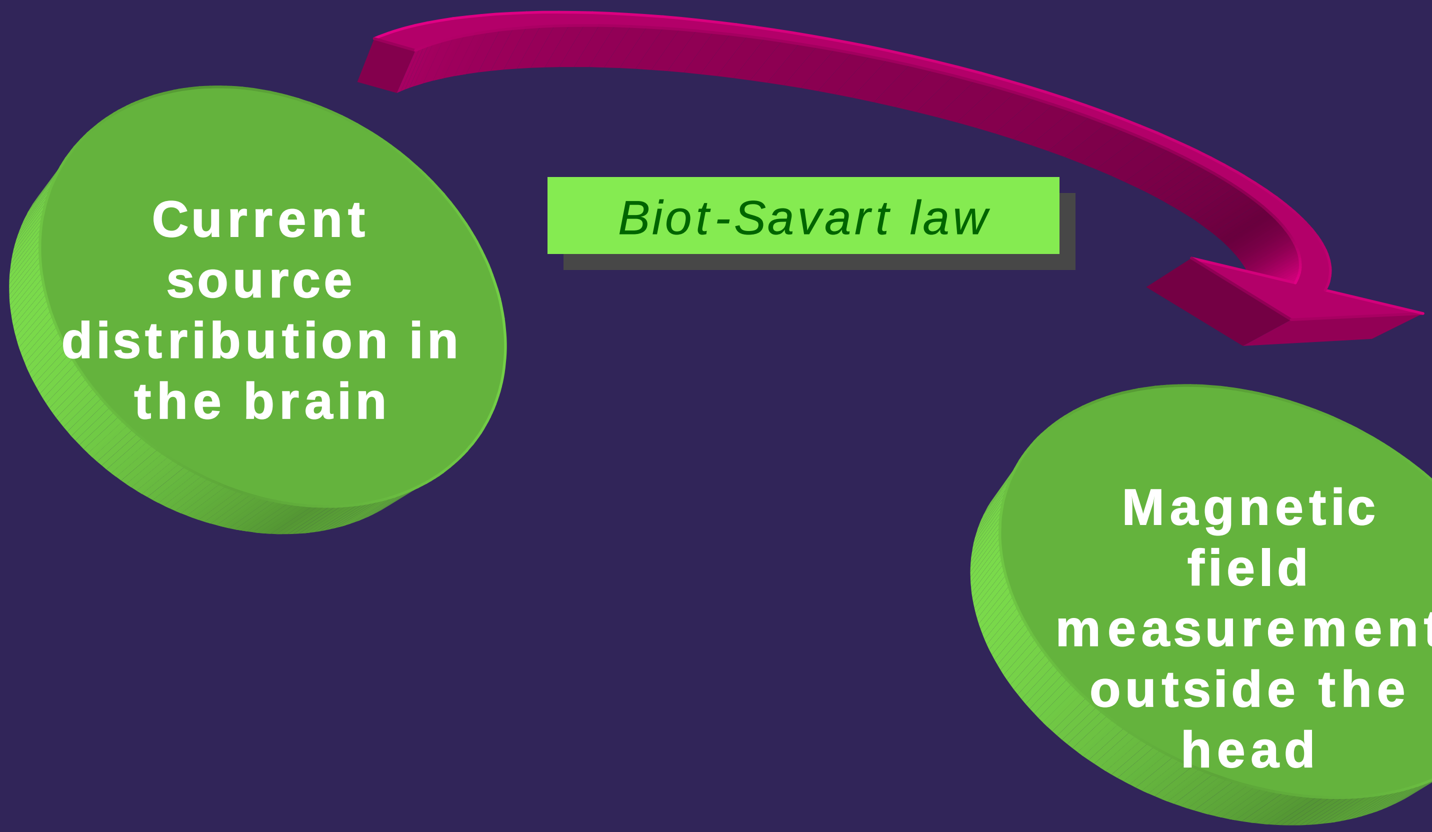


- Columnar organization of cortex and spatial functional specialization on cortical surface lead to ***current dipole* model** to represent focal regions of activation.

- **Source Estimation Problem**: find one or more current dipoles representing current sources in cortex (with orientation normal to the surface)

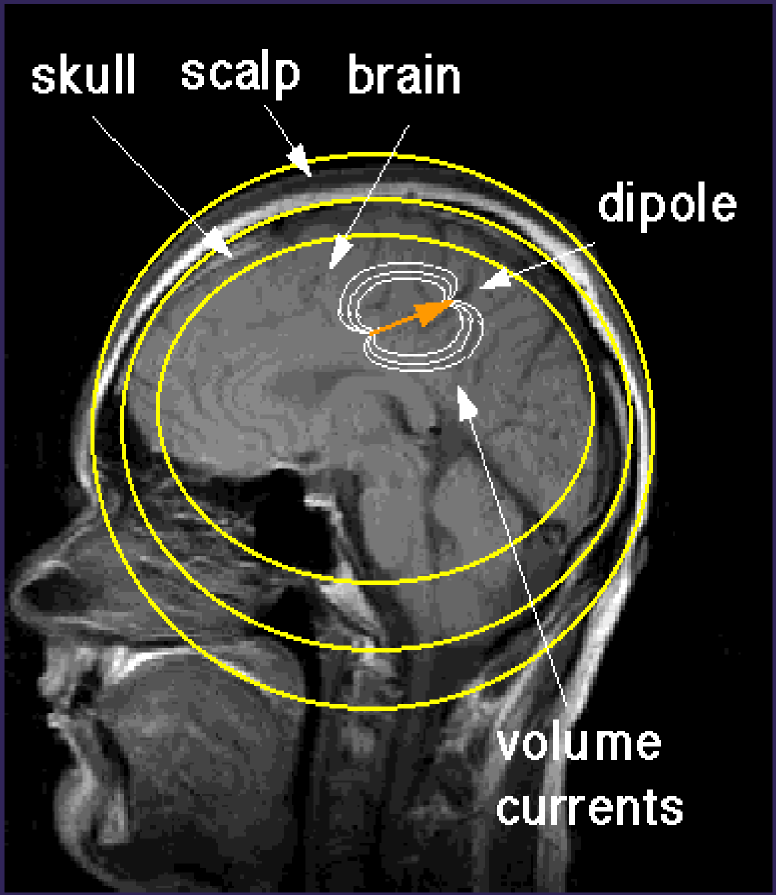
Forward Problem

Forward problem



Forward Models

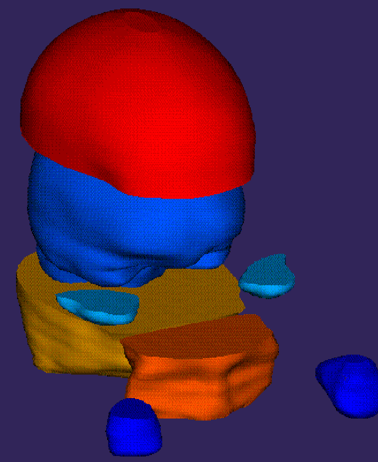
- Use quasistatic EM model to map from current source to measured fields
- Interested in “primary” rather than “volume” currents
- Spherical head: closed form
- Real head shape & cond-uctivity from MR: use BEM or FEM



Forward Model: BEM

- $$\boldsymbol{b}(\boldsymbol{r}) = \boldsymbol{b}_\infty(\boldsymbol{r}) - \frac{\mu_0}{4\pi}\sum_{i=1}^{m}(\sigma_i^- - \sigma_i^+)\left(\int_{S_i} v(\boldsymbol{r}')\boldsymbol{n}_i(\boldsymbol{r}') \times \boldsymbol{d}/d^3\right)da'$$

where: $$\boldsymbol{b}_\infty(\boldsymbol{r}) = \frac{\mu_0}{4\pi}\int_G \boldsymbol{j}^p(\boldsymbol{r}') \times \boldsymbol{d}/d^3\, d\boldsymbol{r}'$$

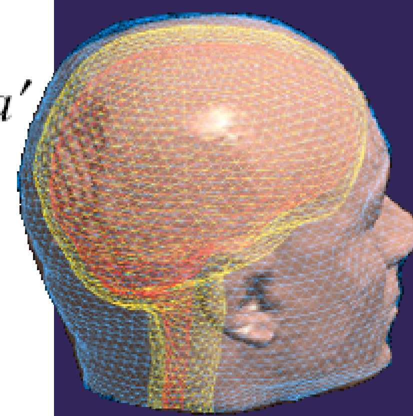


Homogenous compartments

- $$v_\infty(\boldsymbol{r}) = \frac{(\sigma_j^- + \sigma_j^+)}{2} v(\boldsymbol{r}) + \sum_{i=1}^{M}\frac{(\sigma_i^- - \sigma_i^+)}{4\pi}\int_{S_i} v(\boldsymbol{r}')\boldsymbol{n}_i(\boldsymbol{r}')\frac{\boldsymbol{d}}{d^3}da'$$

where

- $$v_\infty(\boldsymbol{r}) = \frac{1}{4\pi}\int_G \boldsymbol{j}^p(\boldsymbol{r}') \cdot \boldsymbol{d}/d^3\, d\boldsymbol{r}'$$



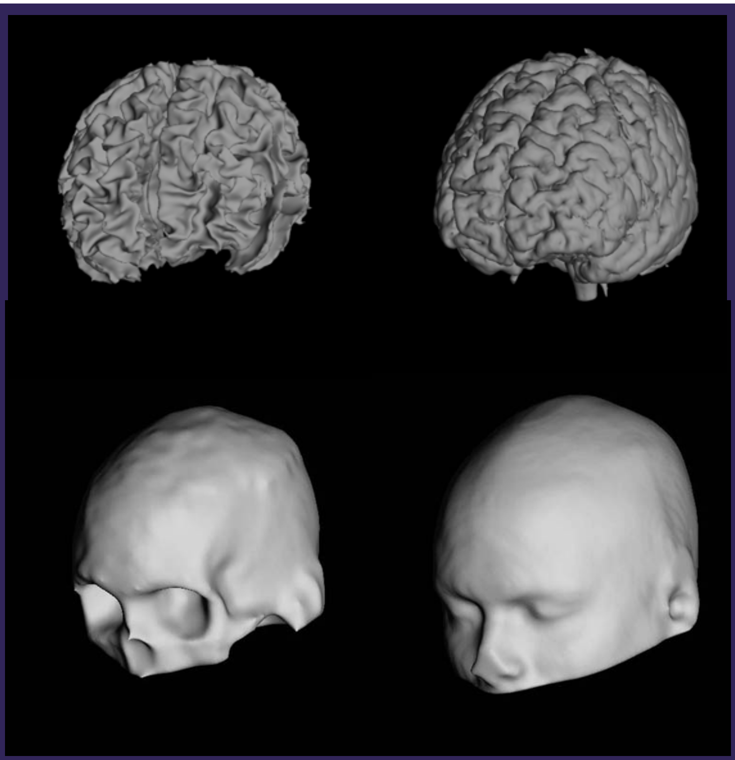
Realistic Head Model

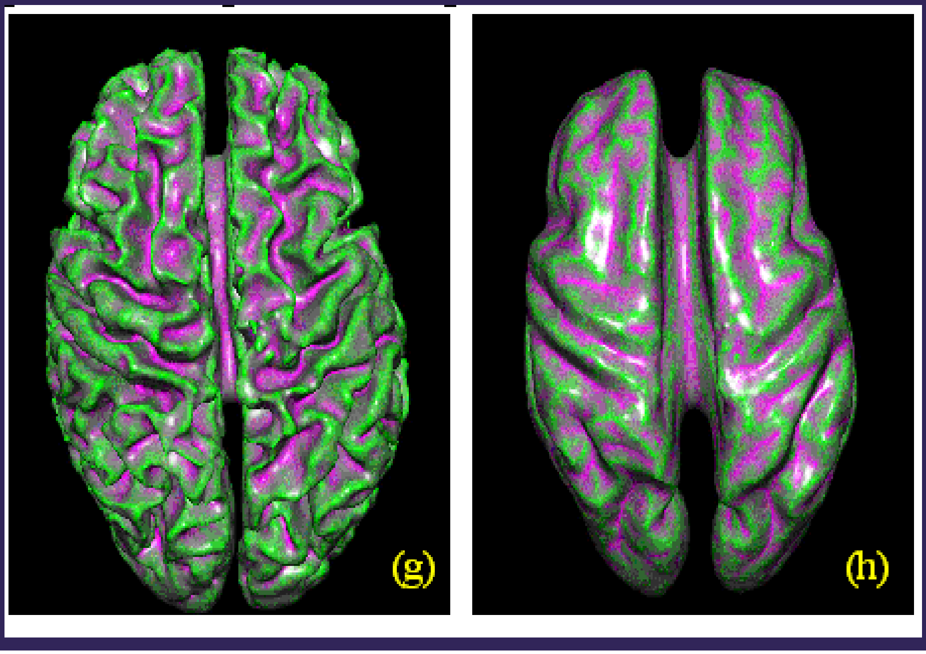
Tessellation

BEM - FEM

Tesselated Surfaces

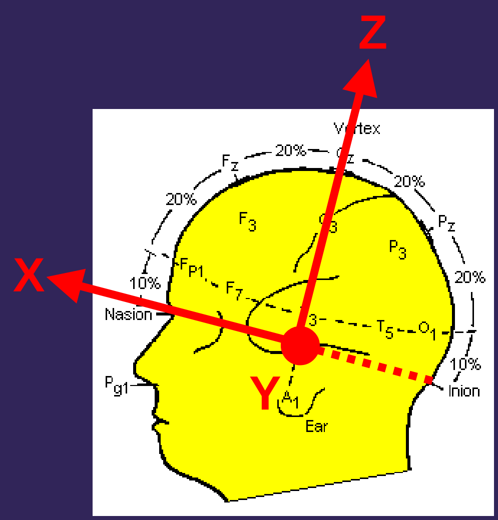
- Smoothed skull, scalp and brain surfaces for use in BEM forward computation
- High resolution cortical surface for use in cortically constrained imaging

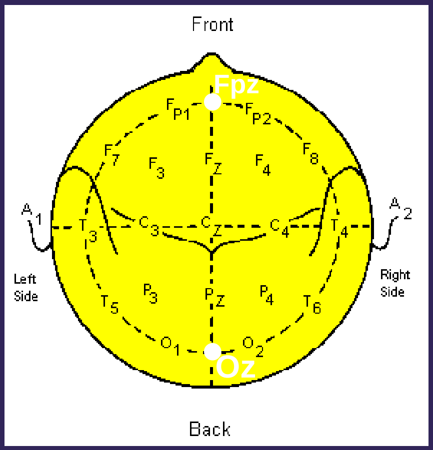




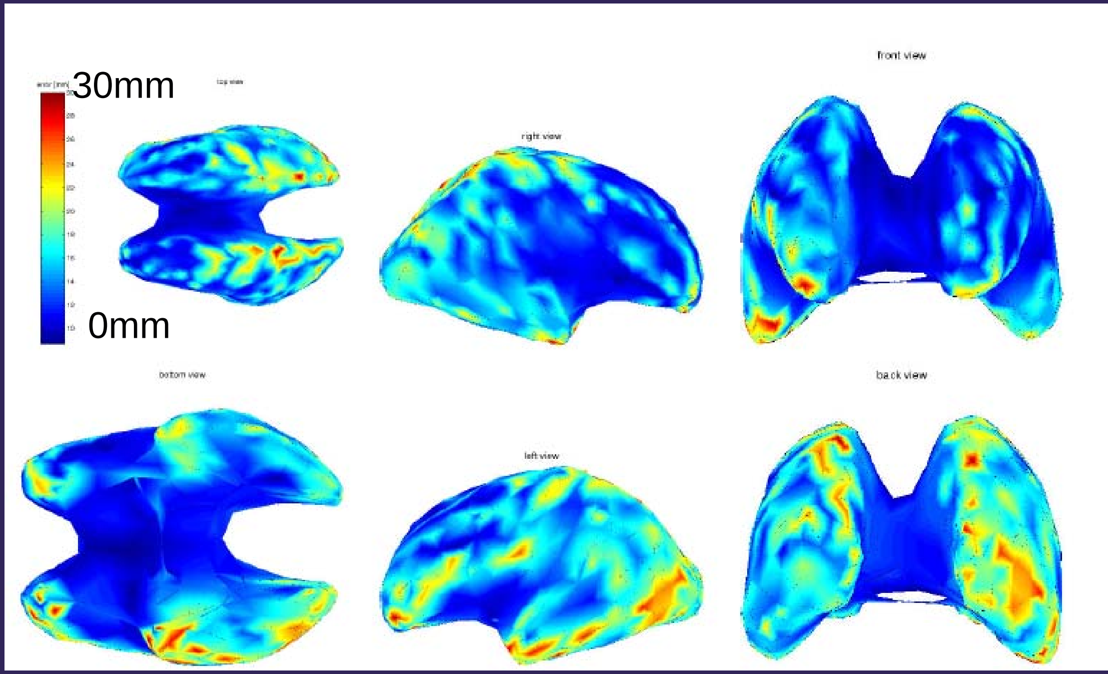
Forward Model: Generic Head

- In absence of MRI, use a standard brain/head atlas – warped to subject landmarks – for head modeling (rather than sphere).
- Use inverse warp to map sources back to stereotactic atlas space for inter-subject studies
- Warp based on thin-plate spline match of 25 cranial/scalp landmarks:

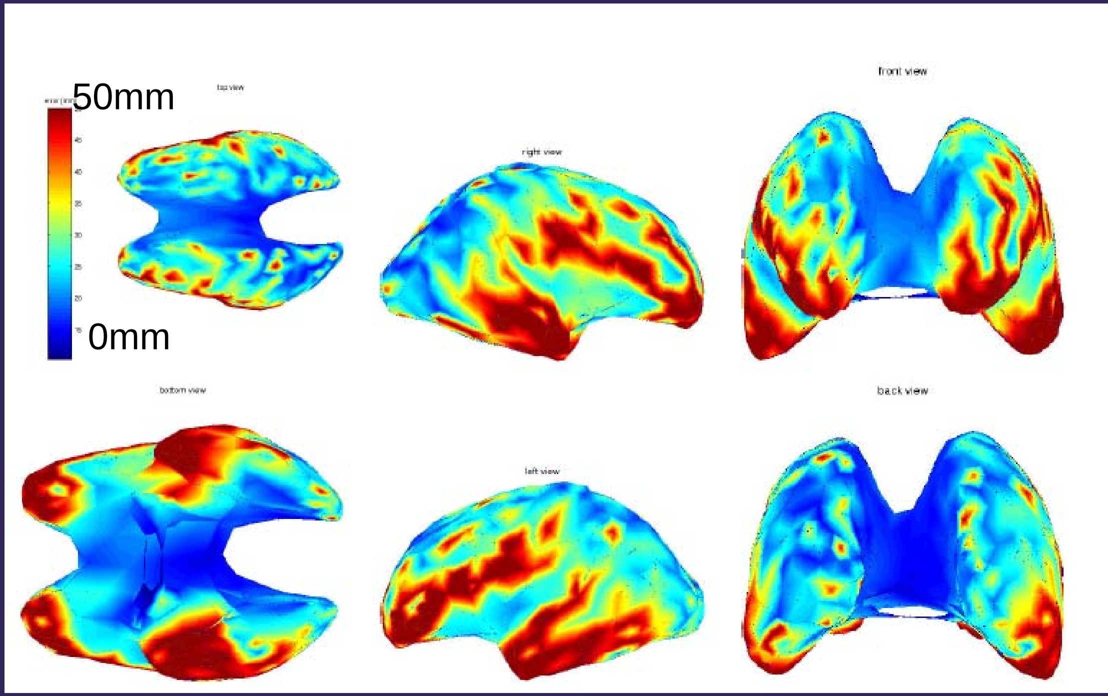




Mean dipole localization error (n=10 subjects) vs. true dipole location on cortex.



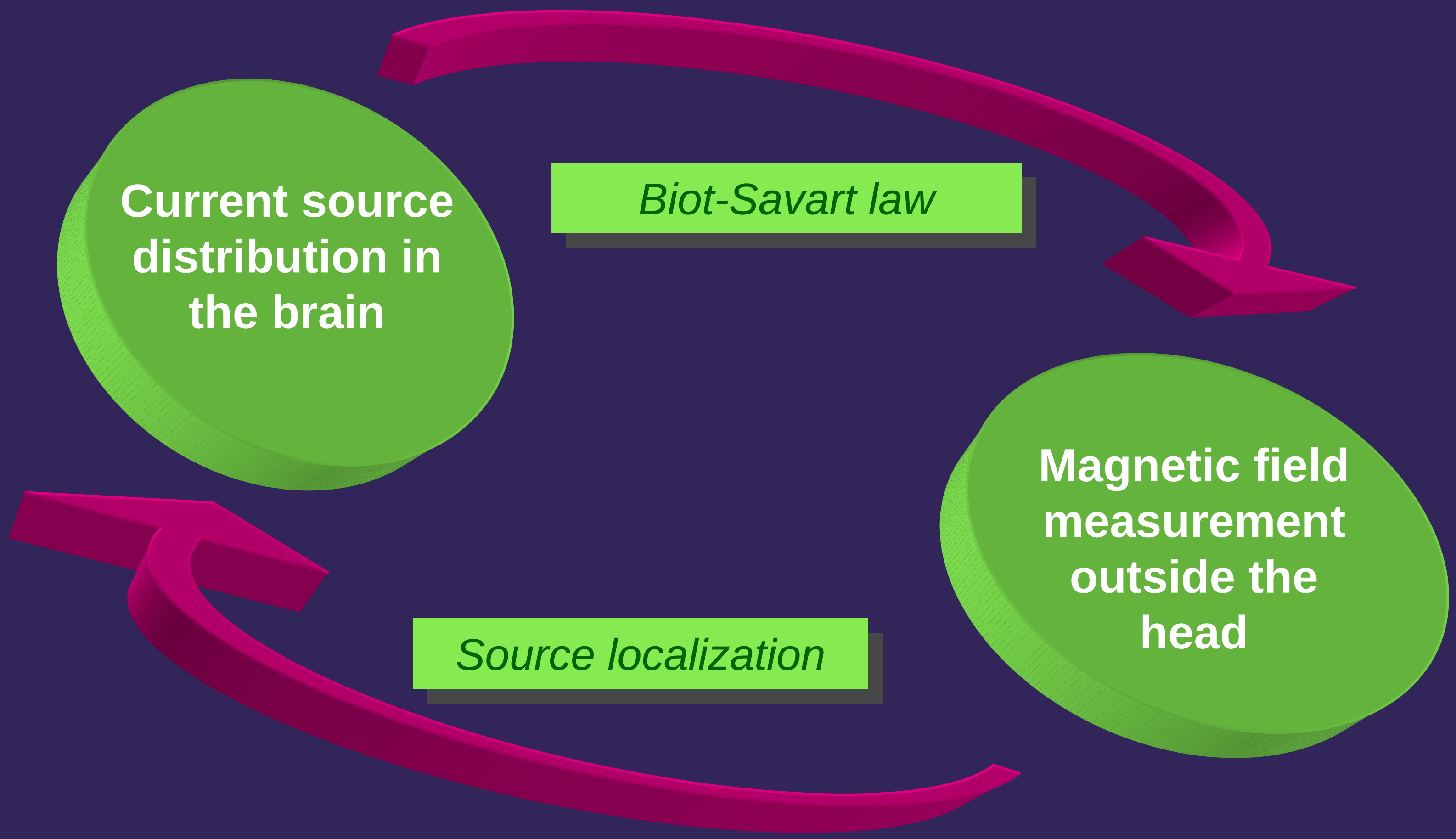
Localization using generic head model and TPS warp



Localization using spherical head model and TPS warp

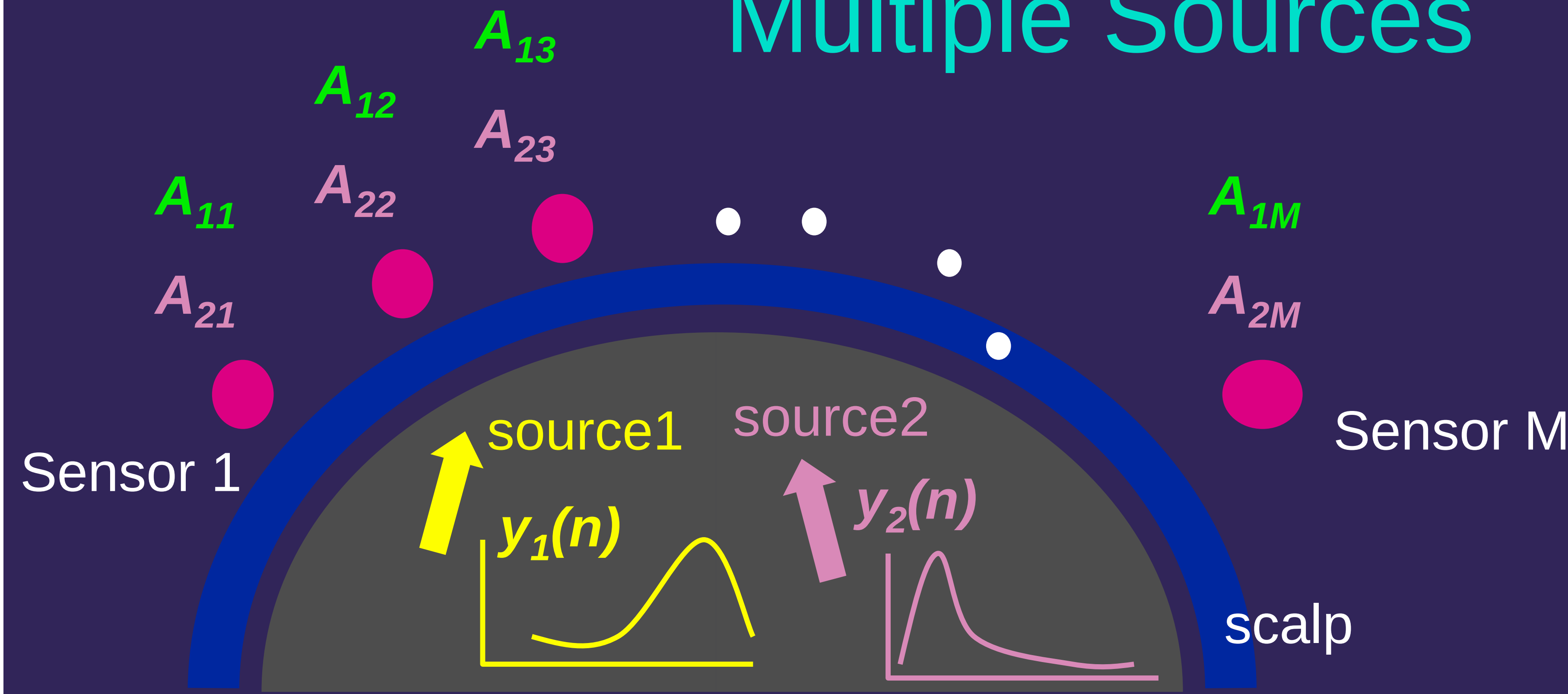
Forward and Inverse Problems

Forward problem



Inverse problem

Multiple Sources



$$\begin{bmatrix} b_1(n) \\ \vdots \\ b_M(n) \end{bmatrix} = \begin{bmatrix} A_{11} & A_{21} \\ \vdots & \vdots \\ A_{1M} & A_{2M} \end{bmatrix} \begin{bmatrix} y_1(n) \\ y_2(n) \end{bmatrix} \qquad n = 1, \ldots N$$

General Form of Forward Problem

- Magnetic fields are *linear function* of the dipole amplitudes or moments
- Magnetic fields are *nonlinear function* of the dipole locations and head model
- All inverse methods reduce to (approximately) solving

$$\boldsymbol{b} = \boldsymbol{A}\boldsymbol{y} + \boldsymbol{n}$$

Inverse Methods

- Competing requirements
  - » Representation of complex spatio-temporal sources
  - » Deal with relatively small number of spatial measurements
- Approaches
  - » Cortically constrained imaging
  - » Parametric source estimation
  - » Scanning beamformers (“virtual depth electrode”)

Imaging

- Place current dipole at each element in cortical surface tesselation
- Constrain dipole orientation using cortical surface normals
- Solve resulting set of linear equations for dipole amplitudes
- Equations highly underdetermined (~300 measurements, 100,000 unknowns?)
- Use regularization or Bayesian approach

Minimum Norm Imaging

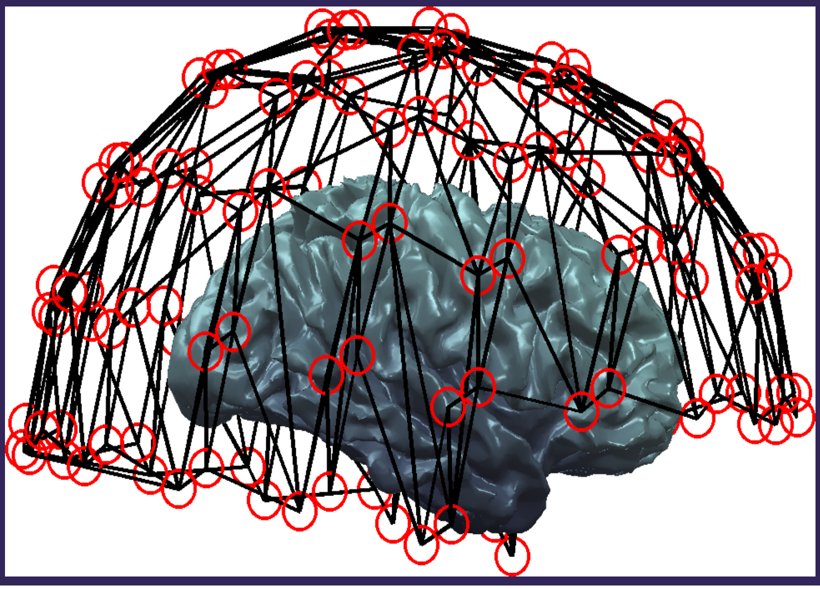
- Solve:

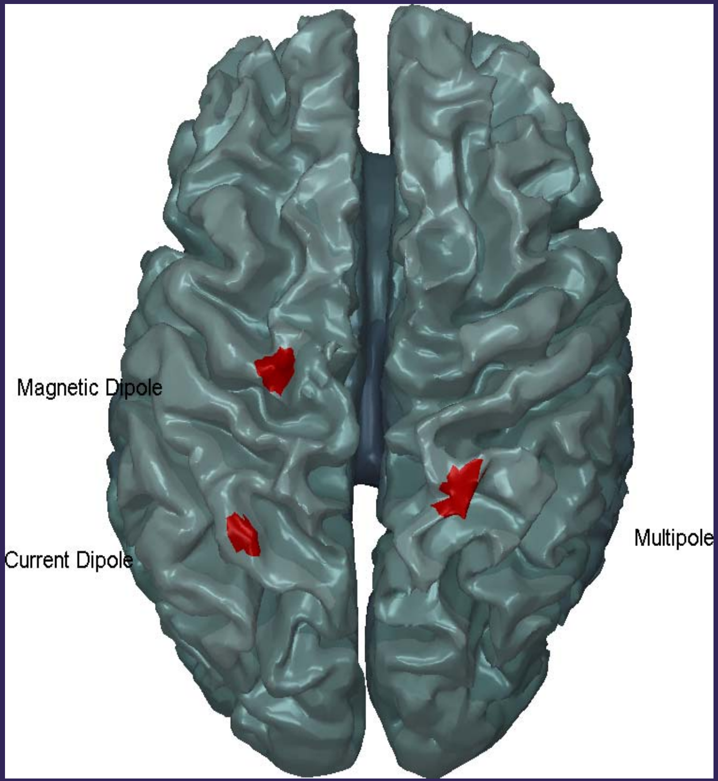
$$\min \left\| \mathbf{b} - \mathbf{A}\mathbf{y} \right\|_2^2 + \lambda \left\| \mathbf{W}\mathbf{y} \right\|_2^2$$

- Choice of weight function:
  - » $W = I$: minimum energy solution
  - » $W = W_{norm} = diag\left[1/\|a_1\|, \dots, 1/\|a_N\|\right]$:column-weighted min-norm
  - » $W = W_{norm} B$ where B is the Laplacian operator: LORETA (Pascual-Marqui et al 94)

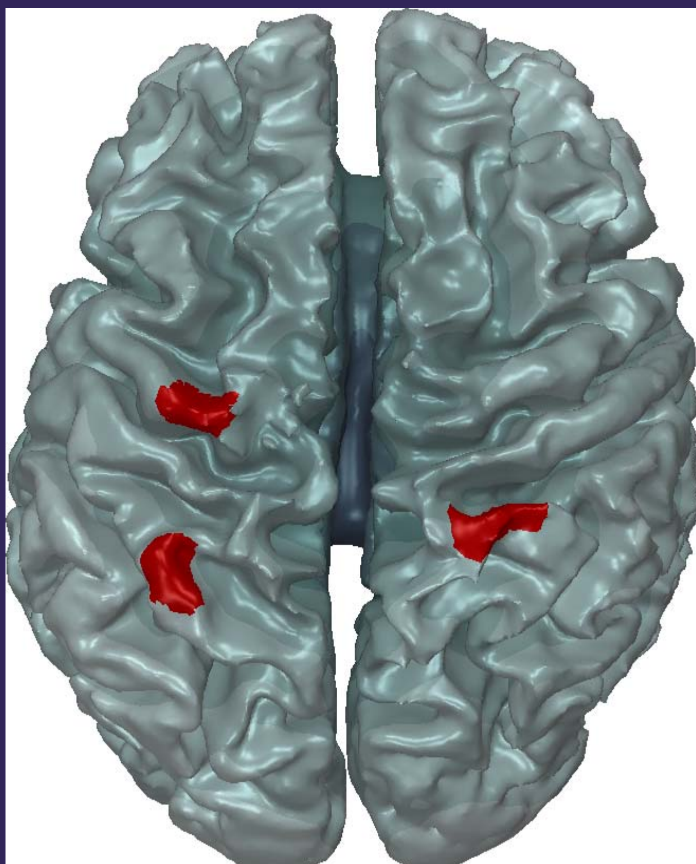
Simulation Study

- 122 planar gradiometers (Neuromag-122)
- 100k cortical triangles
- 3 distributed sources

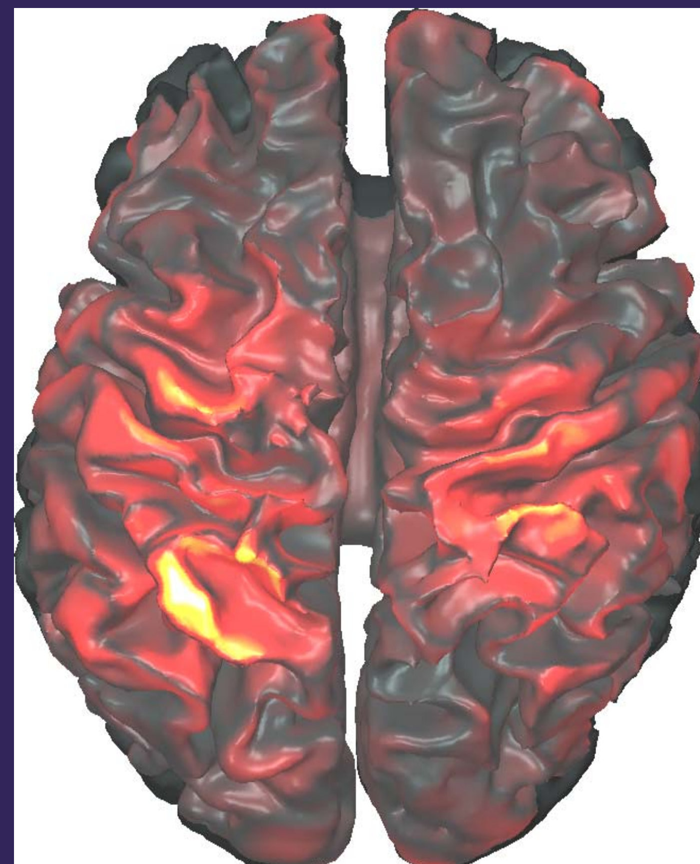




Minimum-Norm Solutions

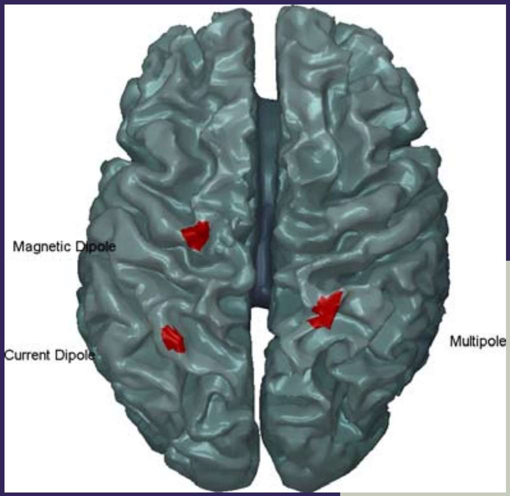


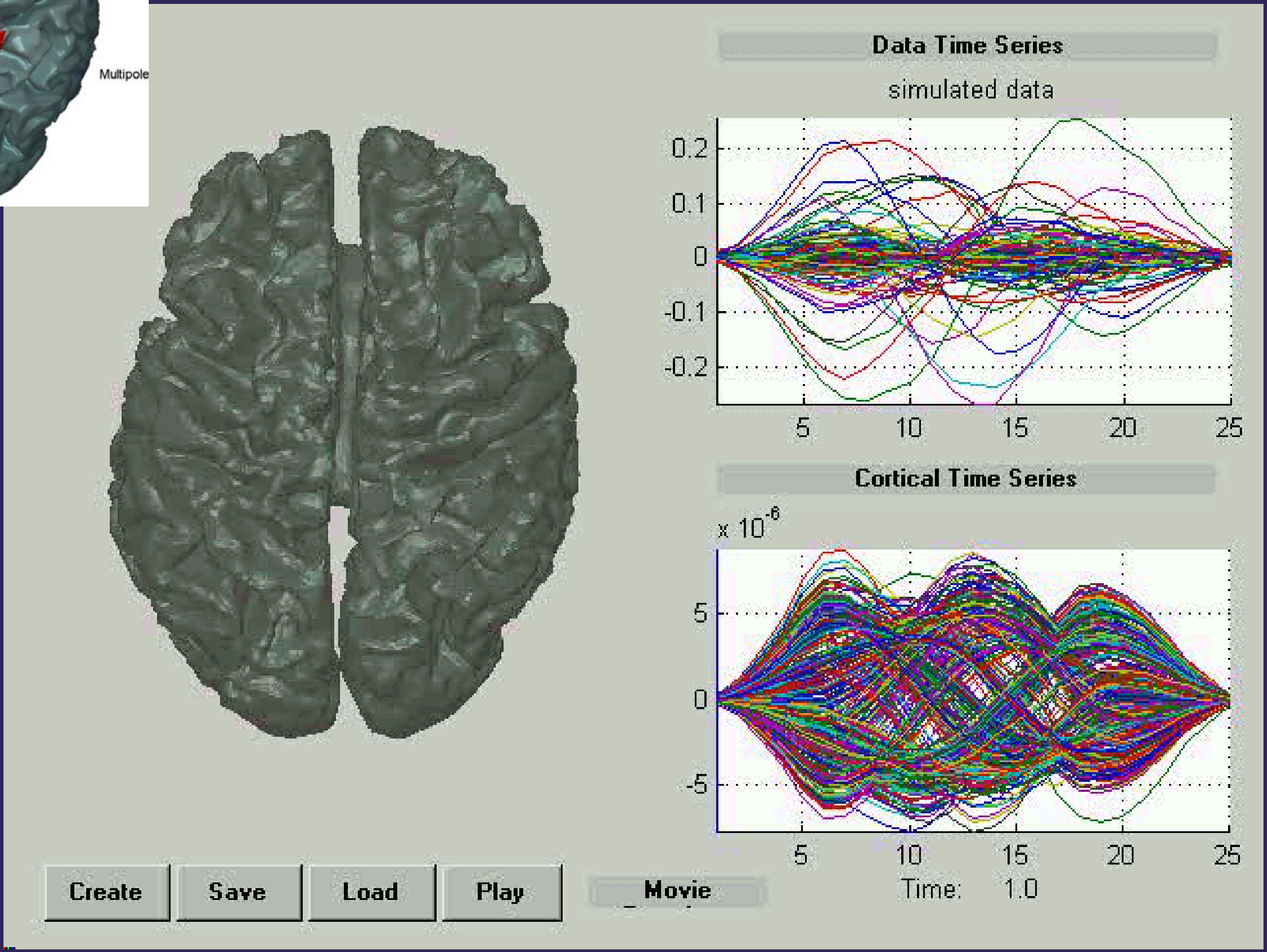
Simulated



Estimated

Dynamic Solutions





Improving Image Resolution

- Introduce prior information (fMRI) in weighting function [Dale&Sereno 93, Liu, Belliveau, Dale 98]
- Non-quadratic penalty function, e.g.

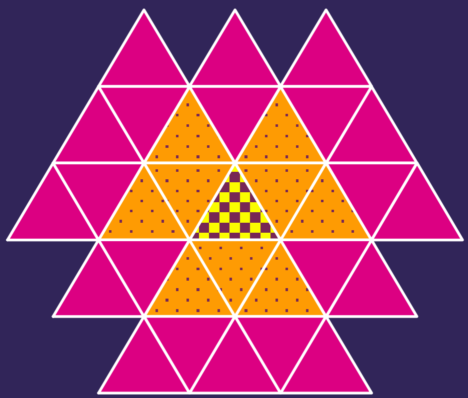
$$\min \|\boldsymbol{y}\|_p = \left|\sum_i \boldsymbol{y}_i^p\right|^{\frac{1}{p}} \quad \text{subject to } |\boldsymbol{b} - \boldsymbol{A}\boldsymbol{y}| \leq \boldsymbol{\varepsilon}$$

[Jeffs&Leahy 87 (p <1), Matsuura&Okabe 95 (p=1)]

- Nonlinear Bayesian imaging methods [Baillet et al ‘98, Phillips et al ‘98, Shmidt et al ‘01….]

Sparse Focal Source Prior

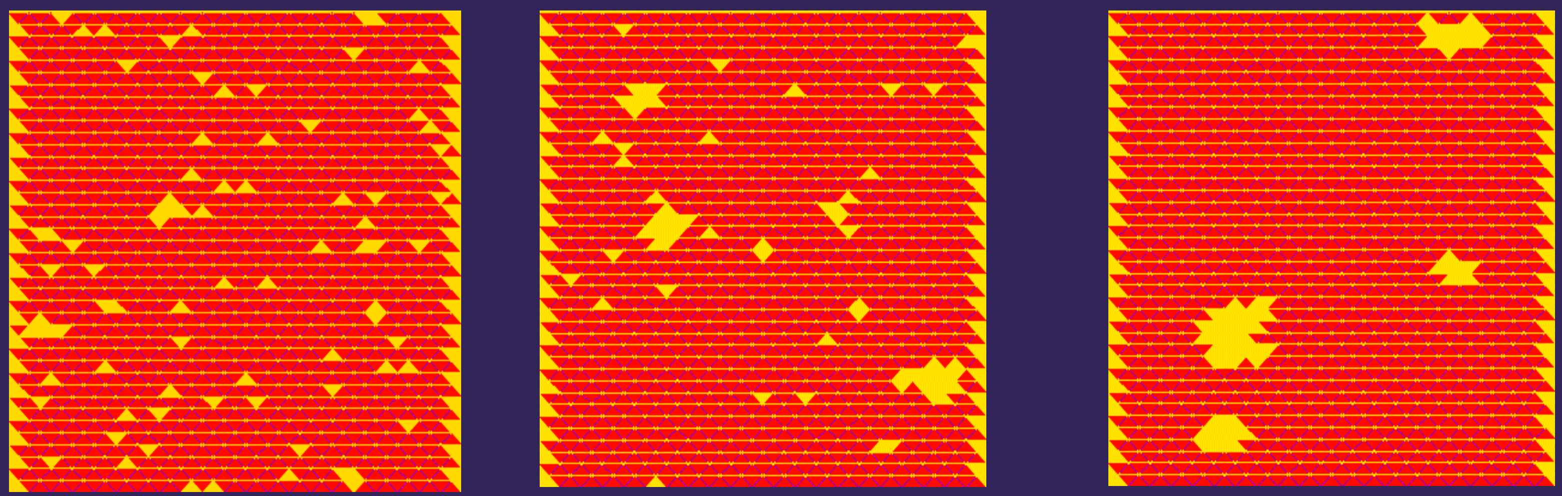
Triangular Tessellation



Pixel of interest

Nine nearest pixels

\+ Complete neighborhood



Q=1, α=0.2,β=0.20 Q=2, α=0.2,β=0.06 Q=3, α=0.2,β=0.017

Parametric Methods

- Current dipole fitting
  - » Assume few current dipoles, unknown locations and moments (Brenner,Williamson,Kaufman 78)
  - » Nonlinear least squares estimation problem with five parameters per dipole (Wood 82)

$$\min_{y,\theta} \left\| b - A(\theta) y \right\|_2^2$$

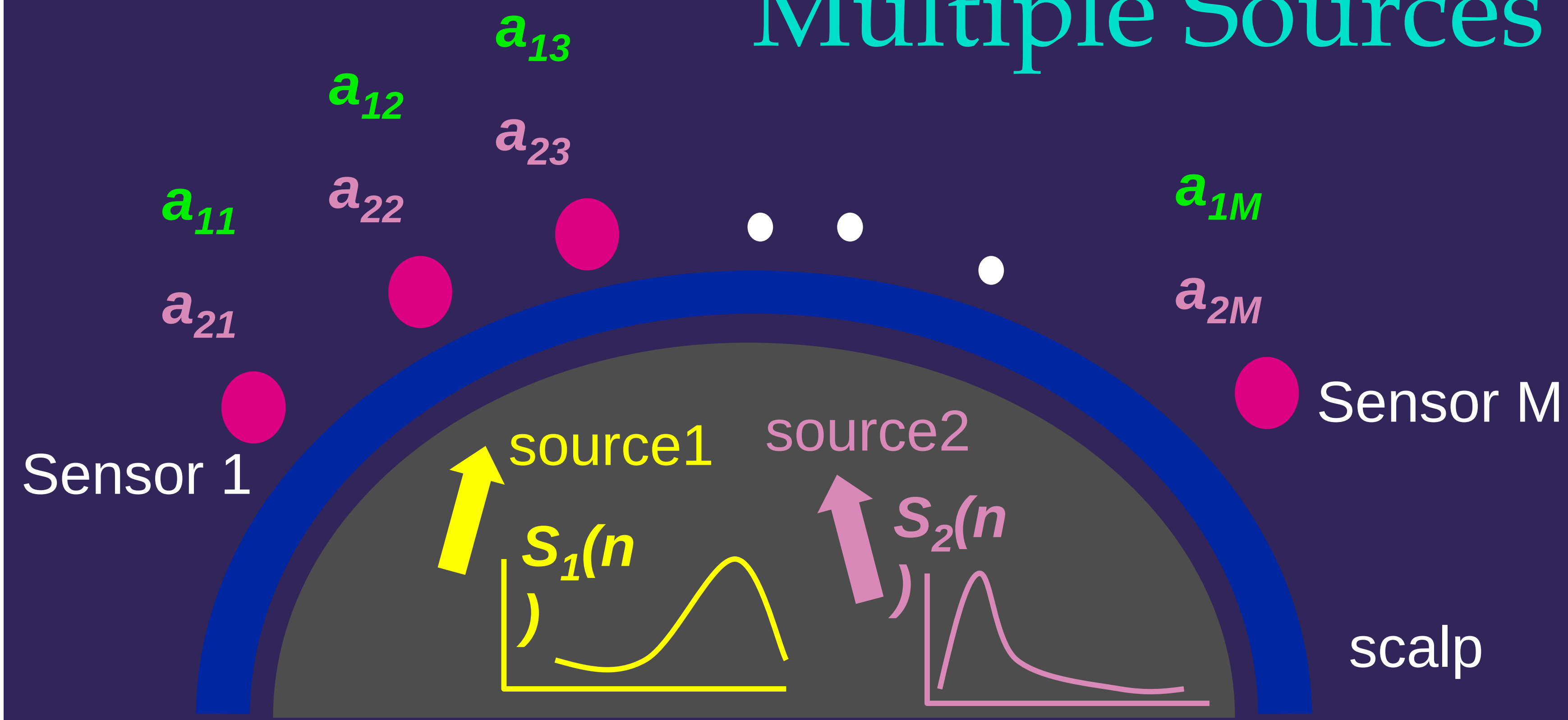
  - » For dynamic data (Scherg Von Cramon 85):

$$\min_{Y,\theta} \left\| B - A(\theta) Y \right\|_2^2$$

Limitations of Dipole Modeling

- Current dipoles may not adequately represent more distributed activation → Use multipolar models
- Non-convex numerical problem → Use subspace scanning methods
- Can be difficult to intepret if sources not in cortex → Use cortical remapping

Multiple Sources



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$$n = 1, \ldots N$$

$$F = AS^T$$

MUSIC Source Localization

- Column space of F contains linear combinations of “gain vectors” for each source
- Span of column space can be found from SVD of data:

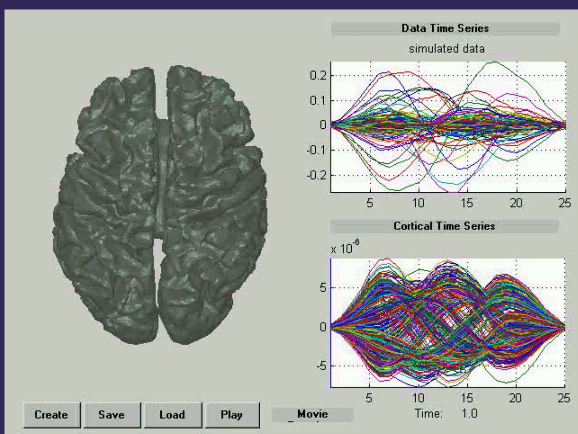
$$U = \begin{bmatrix} \underline{u}_1 & \underline{u}_2 \end{bmatrix} \qquad F = U\Sigma V^T$$

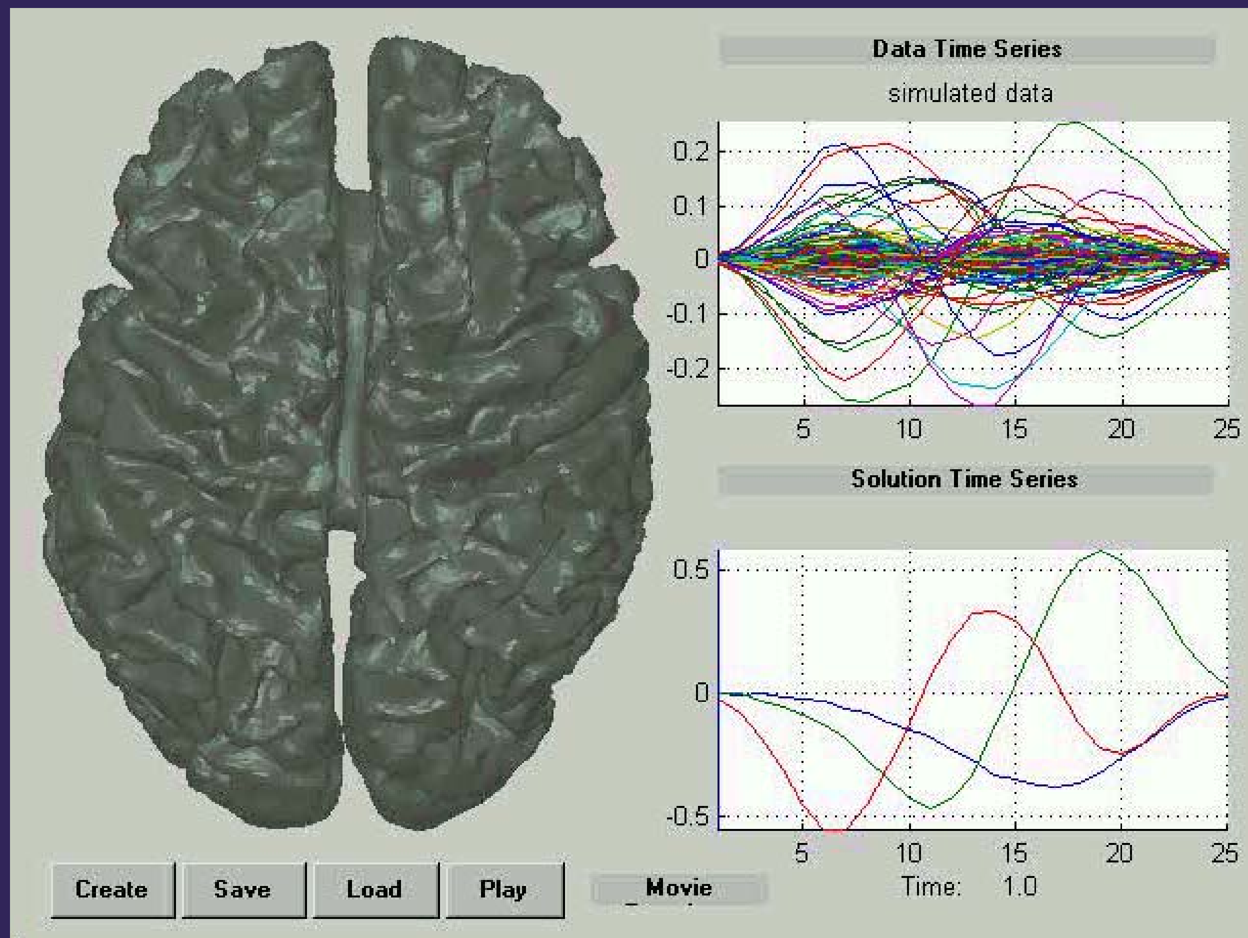
- MUSIC:
  - » compute gain vectors for each potential source location and project onto signal subspace:

$$\frac{\left\| U^T \underline{a} \right\|}{\left\| \underline{a} \right\|} \le 1$$

Cortically Remapped Sources

- Use patch-growing for cortical remapping



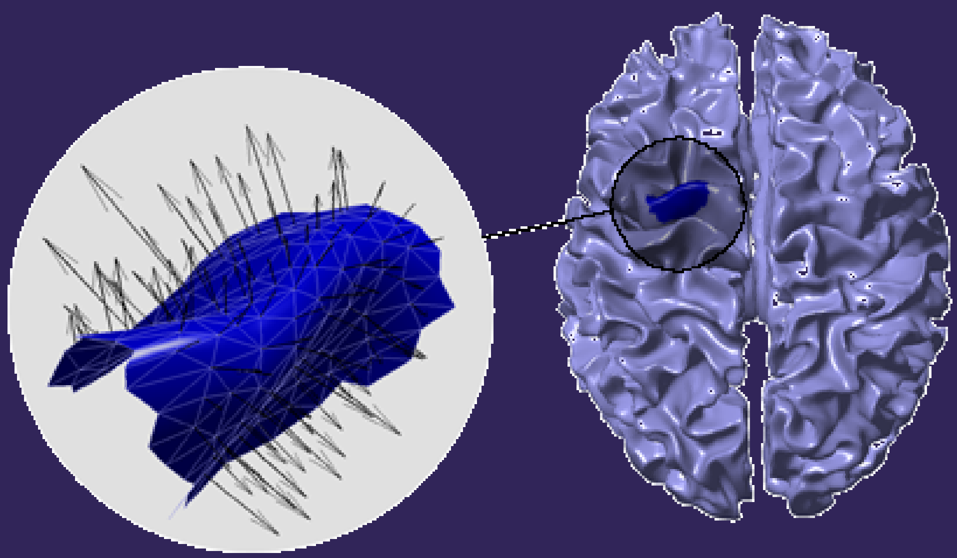


Multipolar Models

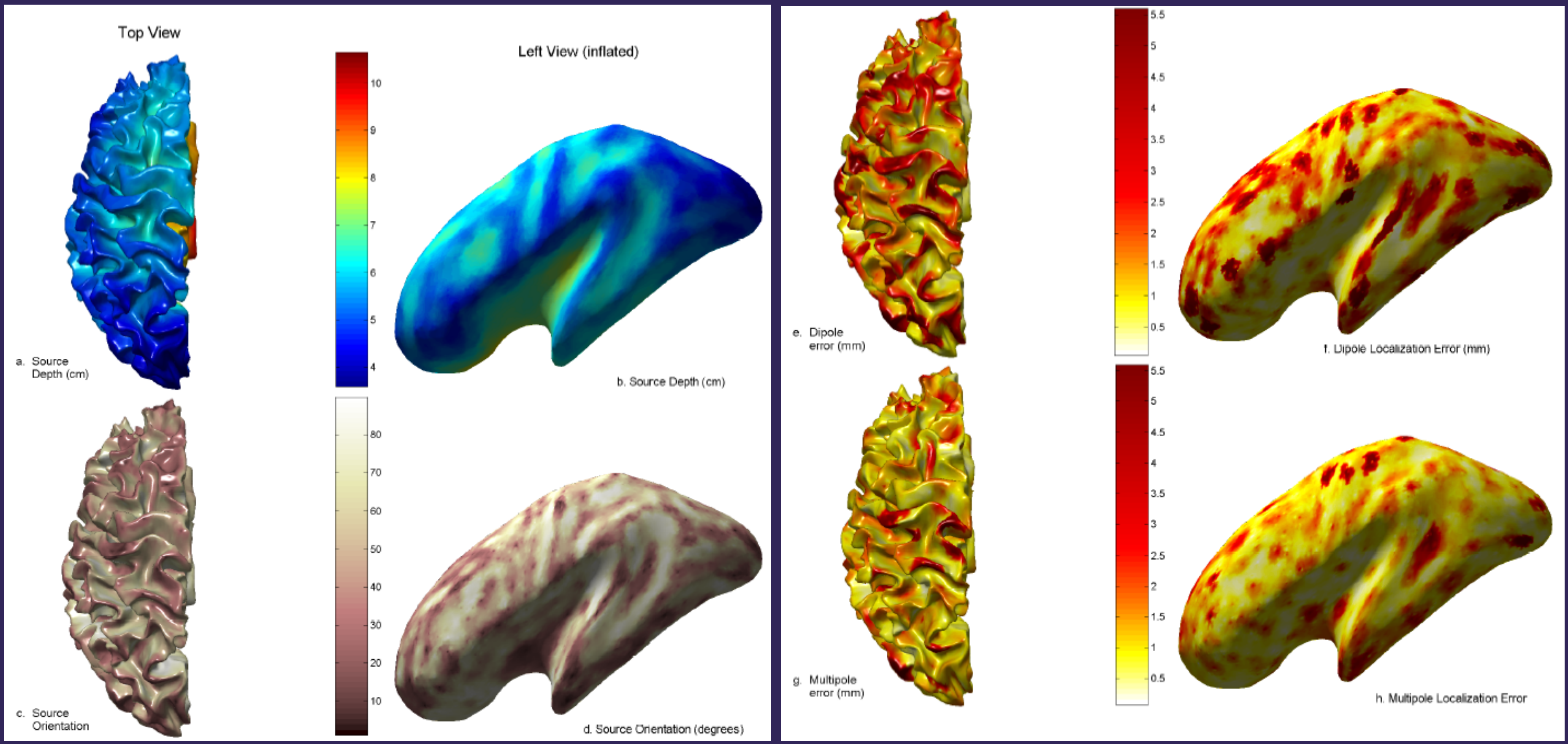
ECD

1st Order Multipole

Increasing Source Size/Complexity



Use of multipolar models in cortical source localization



Virtual Depth Electrodes

- Adaptive beamforming or spatial filtering

$$y = W(x_0)^T F = W(x_0)^T AS^T$$

  - » Design weights with constraint:

$$W(x_0)^T G(x) = \boldsymbol{I}$$

  - » Control degrees of freedom by minimimzing output power:

$$\min \; E[y^T y] = tr[W^T C_F W]$$

Solution

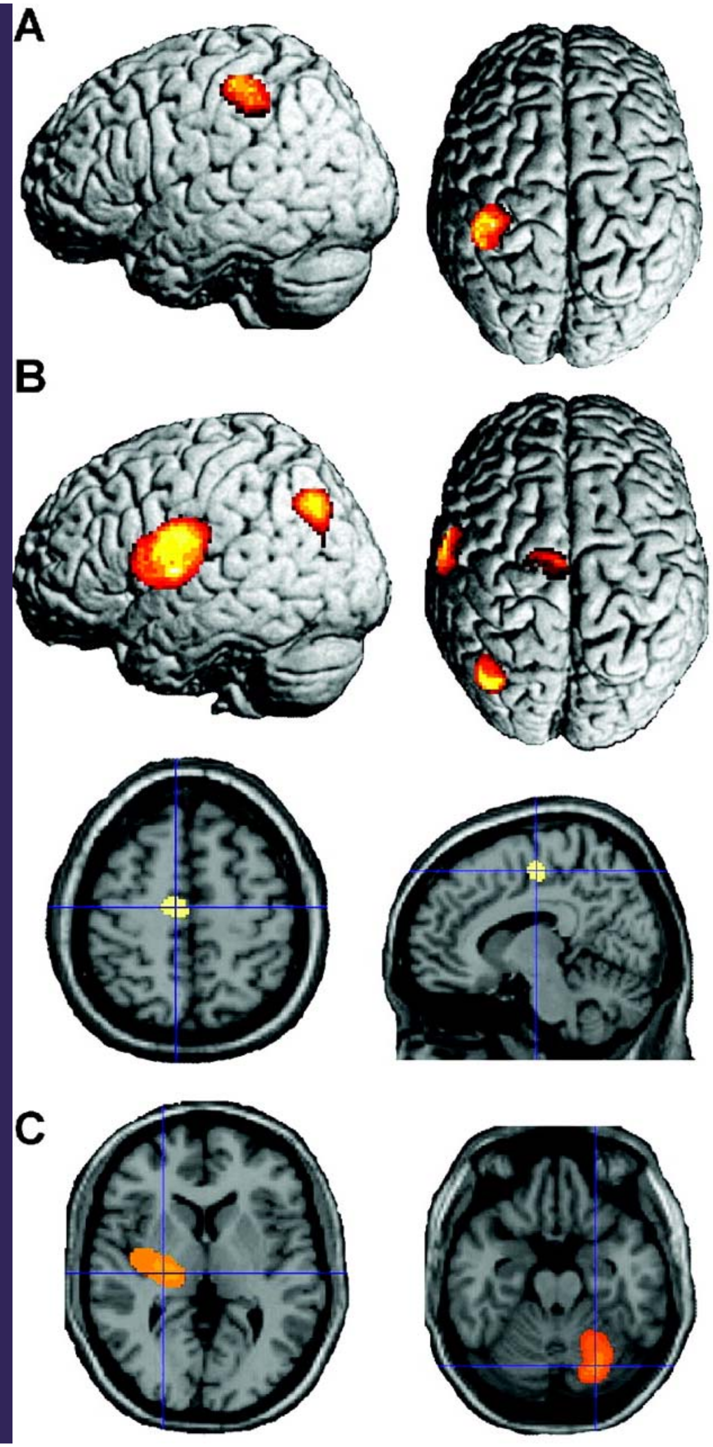
$$W^T = [G^T R_F^{-1} G]^{-1} G^T R_F^{-1}$$

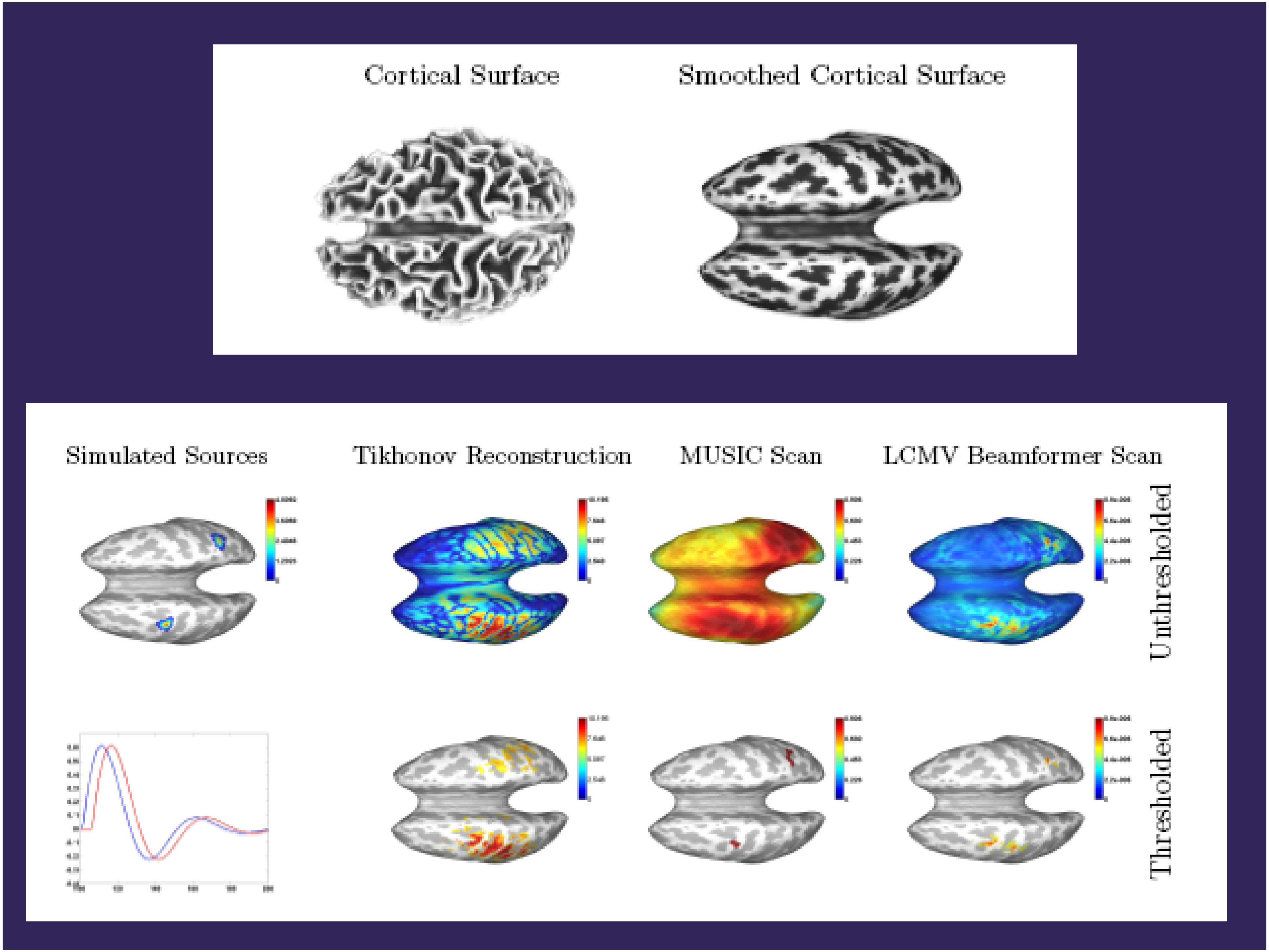
- Scan over cortical surface

- weight by noise-only response: “Neural Activity Index”

“The cerebral oscillatory network of parkinsonian resting tremor”

Timmermann et al., Brain, 2002





Cortical Surface
Smoothed Cortical Surface
Simulated Sources
Tikhonov Reconstruction
MUSIC Scan
LCMV Beamformer Scan
Unthresholded
Thresholded

Performance Analysis

And

Validation

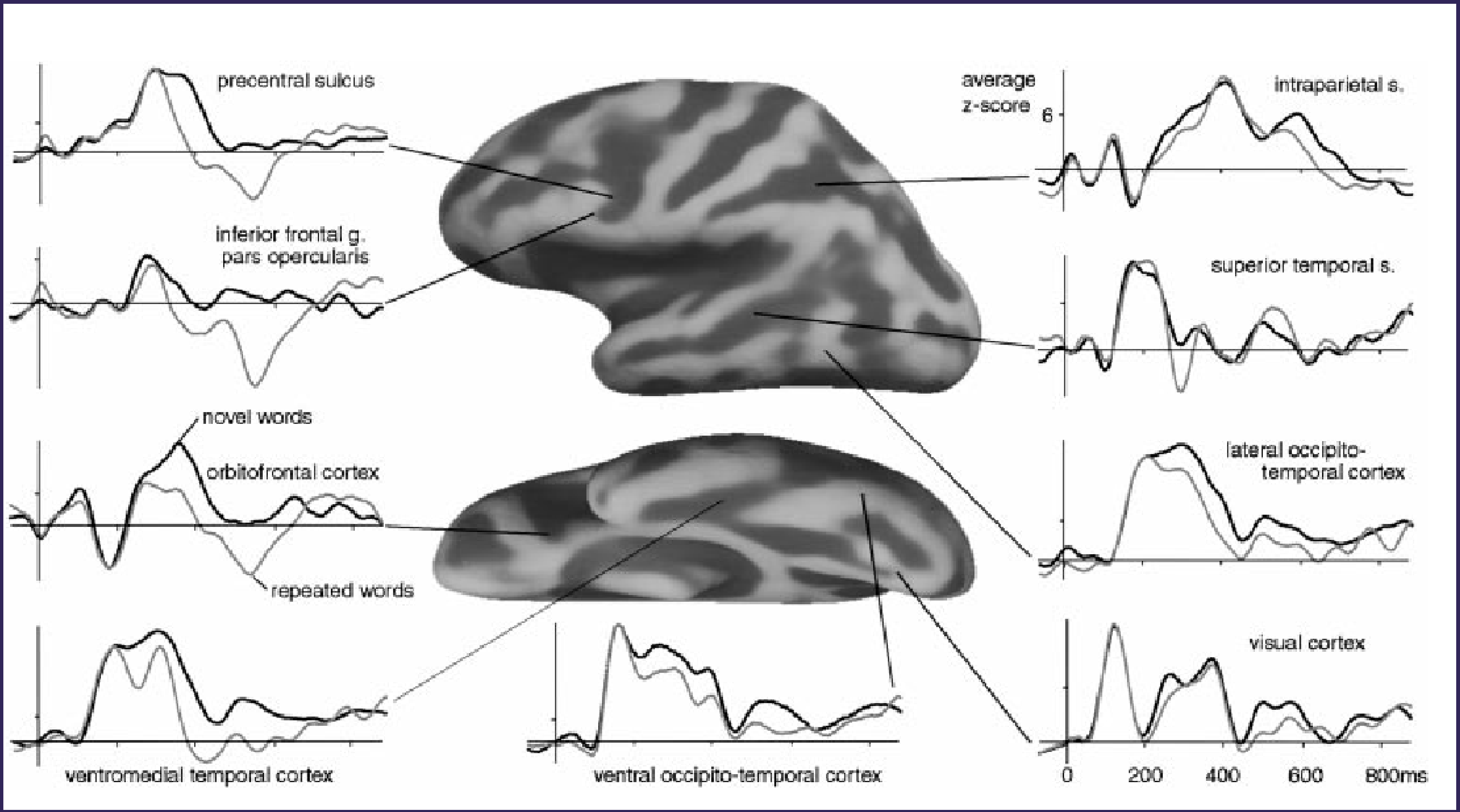
Sources of Variability and Error

- Background environmental and physiological noise
- Intrinsic trial-to-trial variability in brain response
- Registration: MEG vs. anatomy
- Head models
- Data acquisition system model

Quantifying Performance

- Simulation/theory:
  - » Theoretical: e.g. CR bounds
  - » Monte Carlo simulations
  - » Simulation-based ROC analysis
- Phantom studies
  - » Localization accuracy
- Real data
  - » bootstrap analysis
  - » Permutation and RF based activation detection
  - » Cross-modality (MEG vs. fMRI, depth electrodes….

MEG vs. Depth electrode data

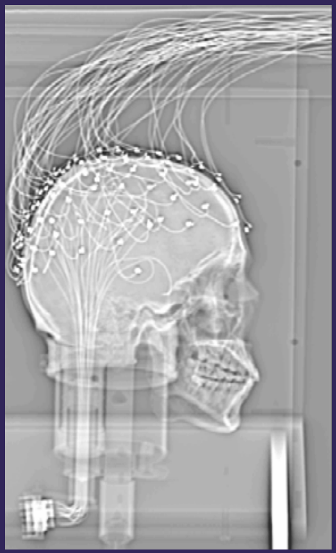


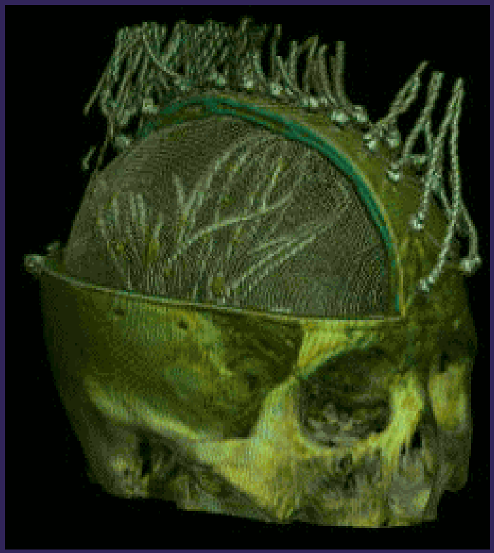
Dale et al., 2000

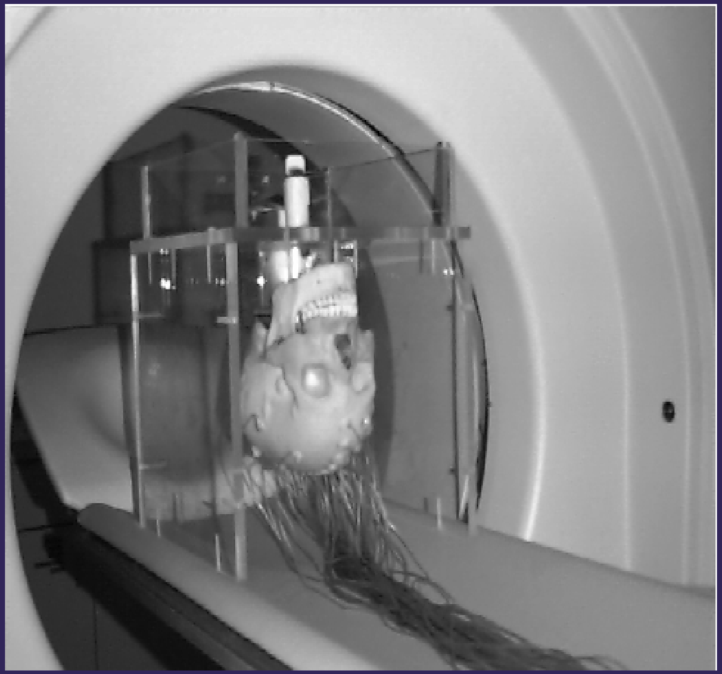
Dale et al., Neuron, 2000

Phantom Study

- 32 current dipoles in human skull phantom
- Ground truth from CT scan
- MEG data from Neuromag-22
- Sources fit using R-MUSIC, spherical and realistic BEM forward models

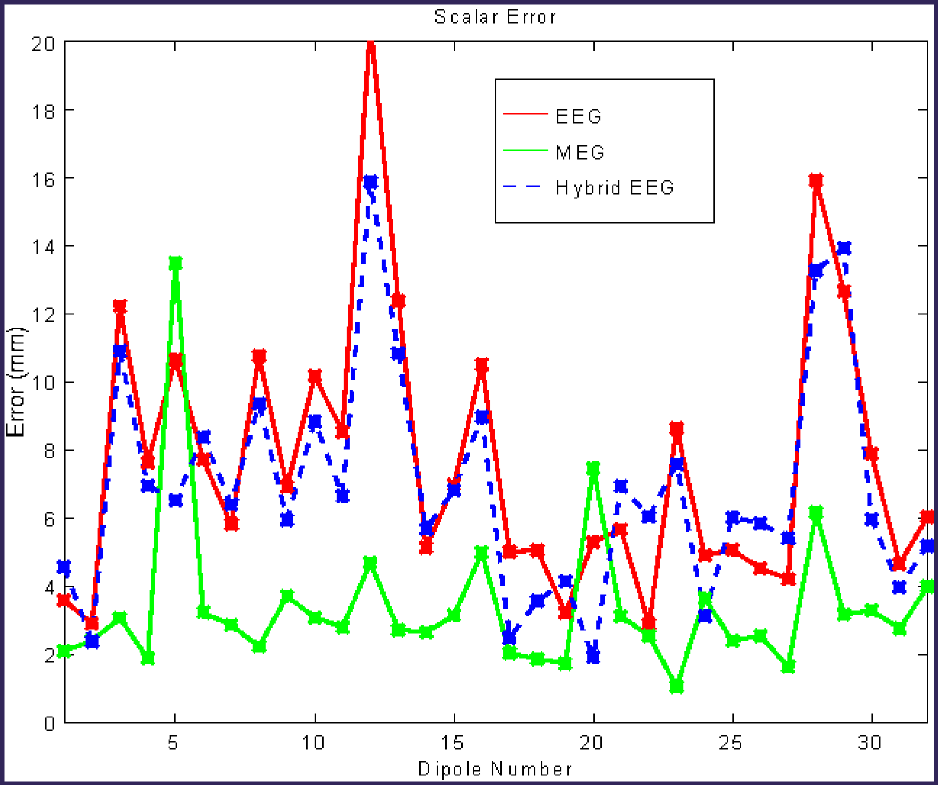


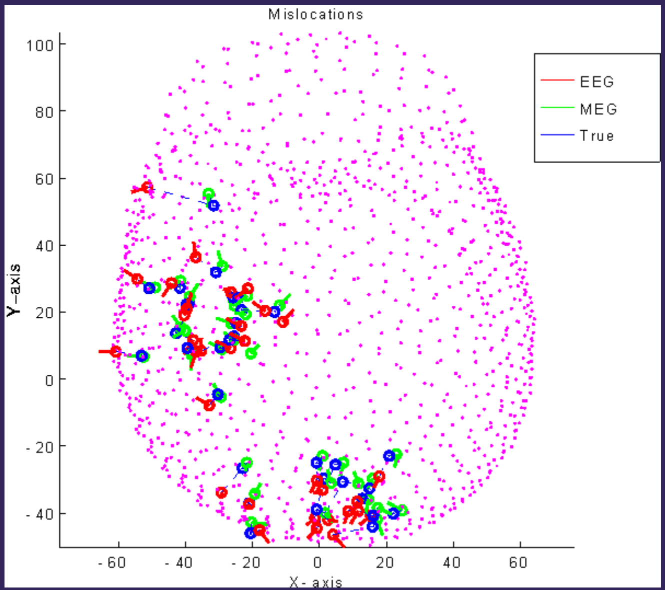




Phantom Localization Errors

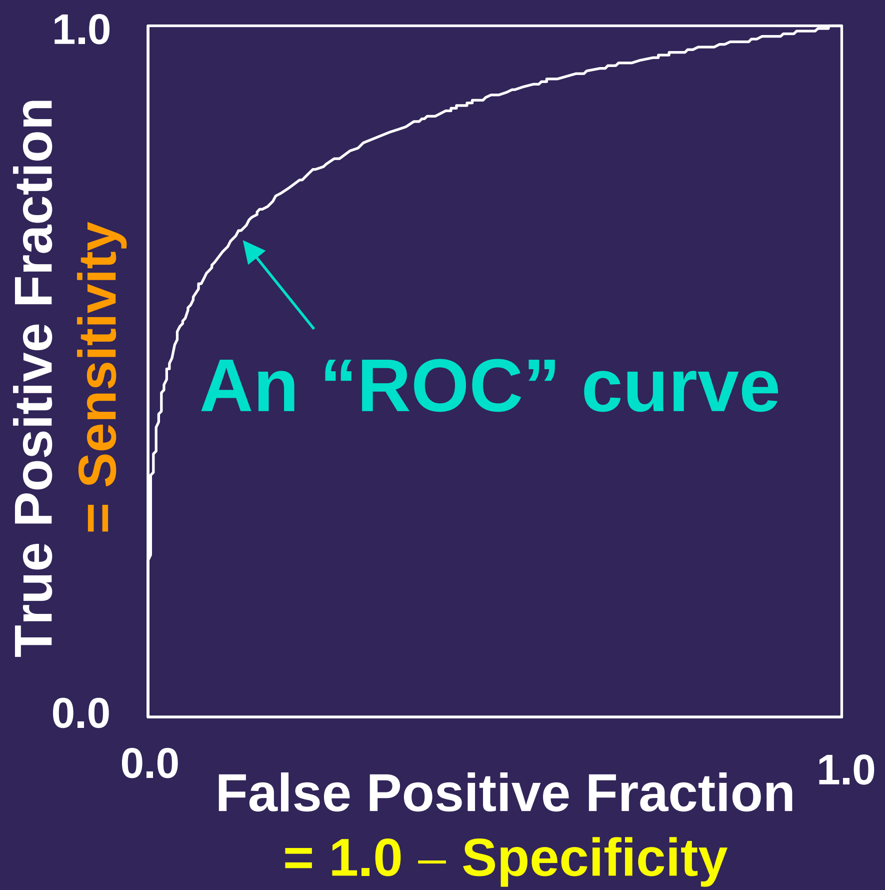
- Average error for 32 dipoles using spherical head model: 4.1mm
- Average error for 32 dipoles using BEM head model: 3.4mm





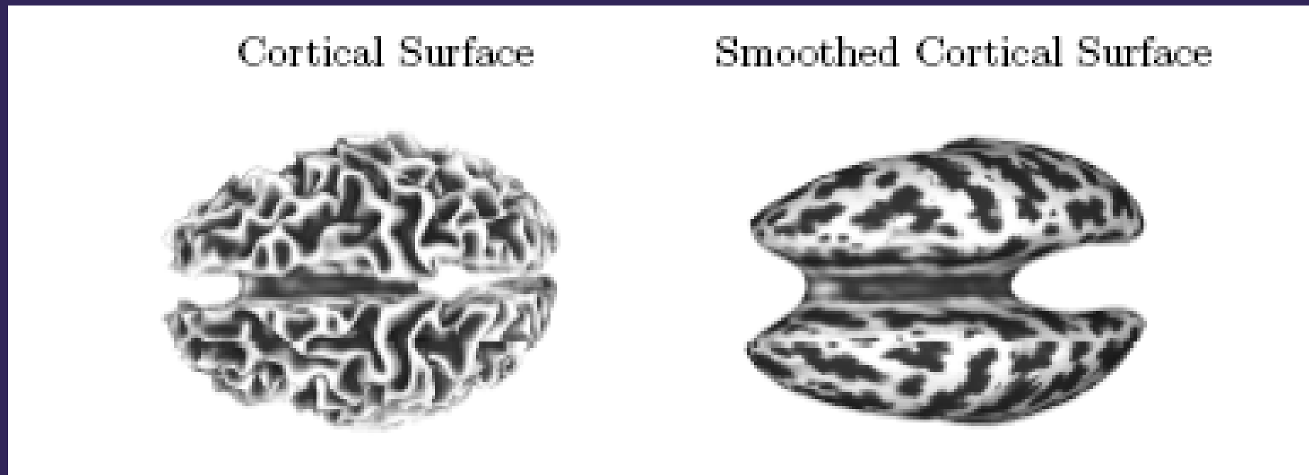
Objective Task-Based Evaluation: ROC analysis

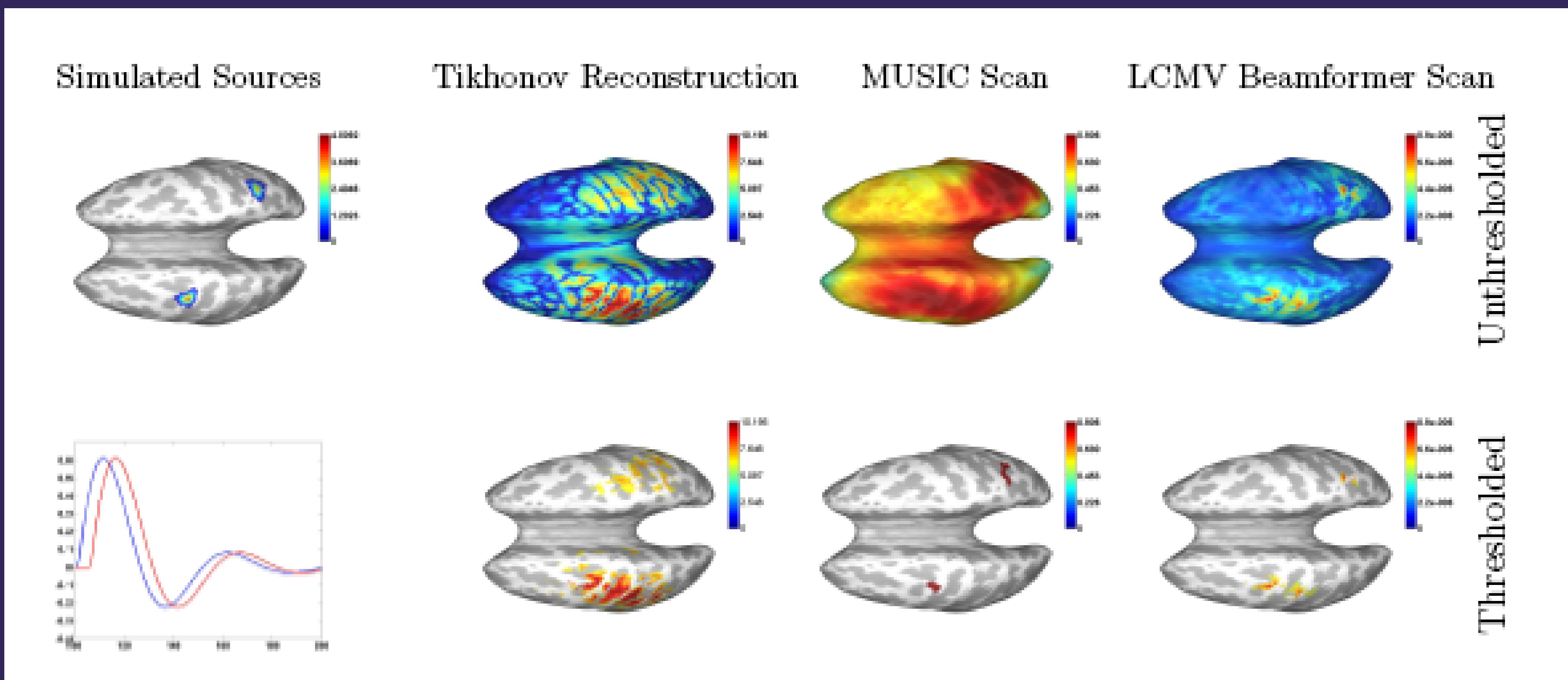
- Sensitivity: Probability of calling an actually-positive case "Positive"
- TPF = TP / (TP + FN)
- Specificity: Probability of calling an actually-negative case "Negative"
- TNF = TN / (TN + FP)



Objective Task-Based Evaluation: ROC analysis

- Standard ROC analysis
  - » Binary decision for the presence of a target; location known
- Location-Response ROC (LROC)
  - » Specify the location of a target
  - » Only one target allowed
- Free-Response ROC (FROC)
  - » Presentation and detection of multiple targets per image
  - » Suitable for neuroimaging studies; we expect many simultaneously activated brain areas


Cortical Surface
Smoothed Cortical Surface


Simulated Sources
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LCMV Beamformer Scan
Unthresholded
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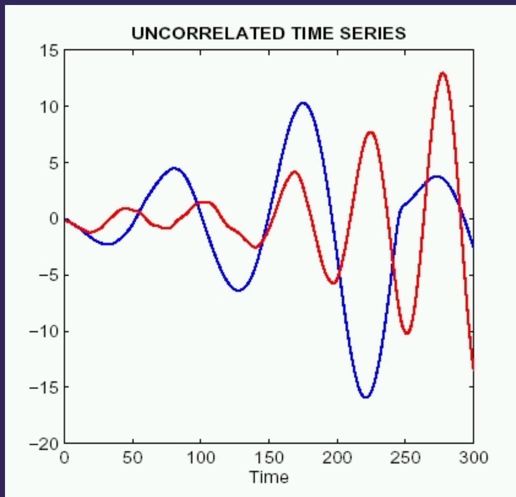
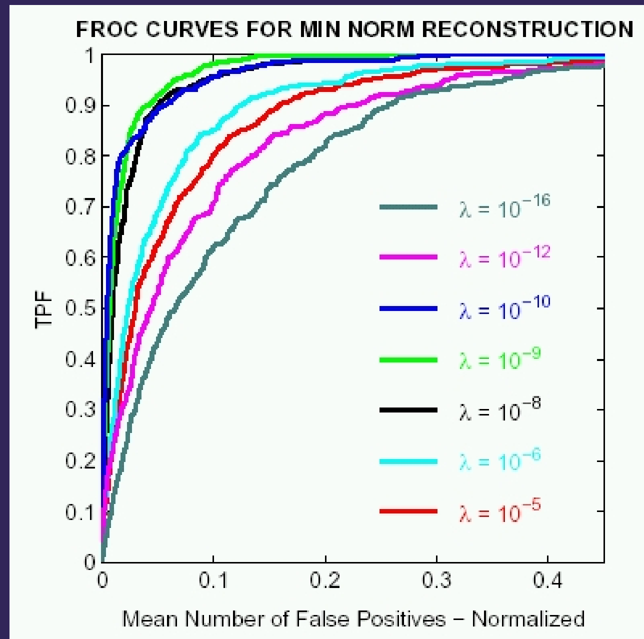
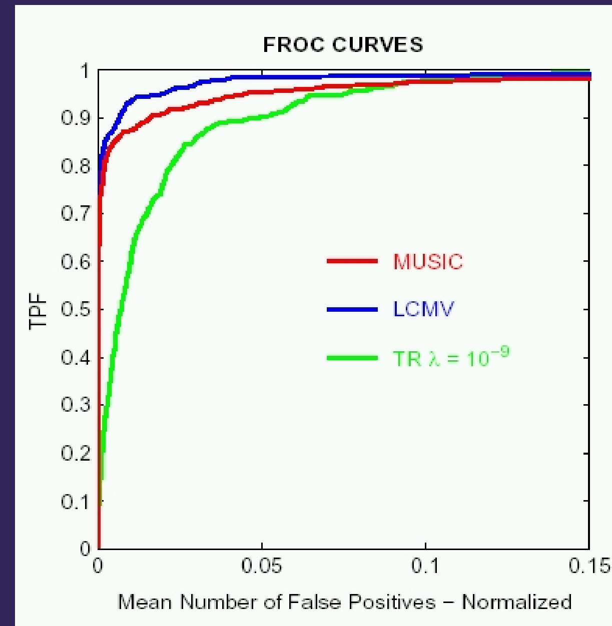






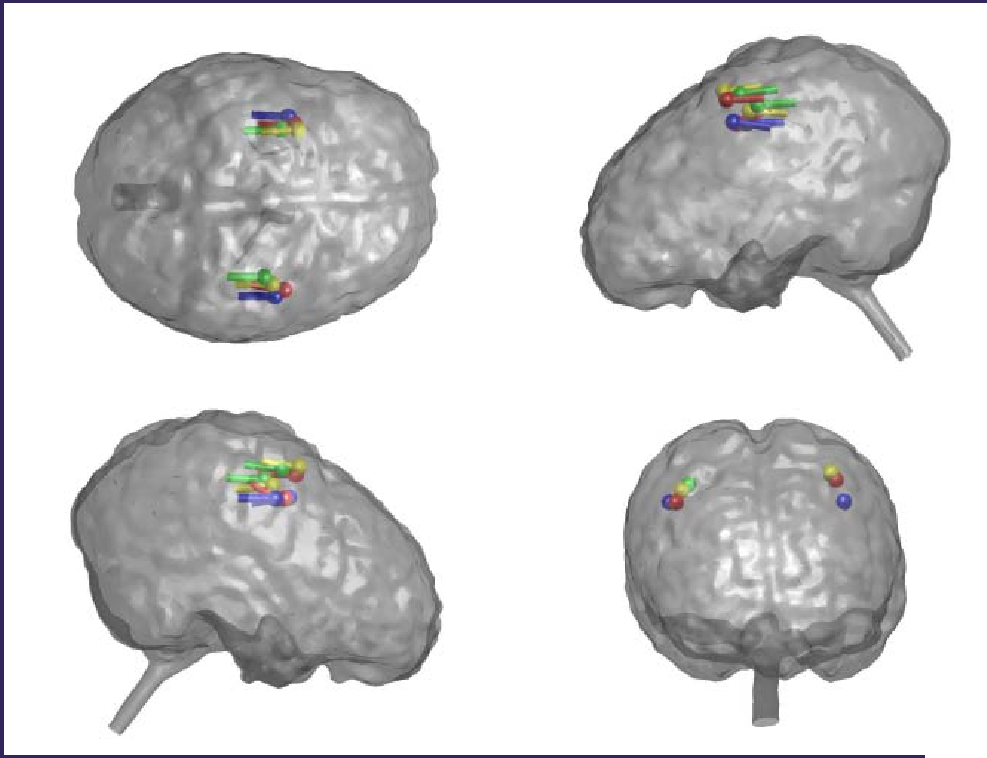
Timeseries of two uncorrelated patches randomly positioned on the cortical surface

FROC curves for different regularization parameters (Tiknonov-Regularized Min-Norm reconstruction)

FROC curves for MUSIC, LCMV Beamformer, and Min-Norm reconstruction

Experimental data: Bootstrap of Dipole Localization

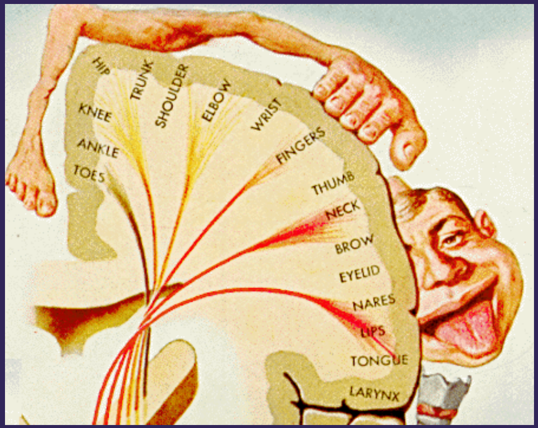
- Approach:
  - Epochs can be viewed as a set of independent realizations of the brain's response
  - Sample with replacement from epochs and average to produce "new" data sets
  - Apply inverse procedure to each bootstrap data set
  - Cluster resulting dipoles (GMM)
  - Estimate statistics (mean and standard deviation) from the bootstrap resamples
- Applied to somatosensory stimulation data sets for 4 left and right hand digits, 30-60ms post stimulus; 500 trials per digit, 5000 bootstrap resamples



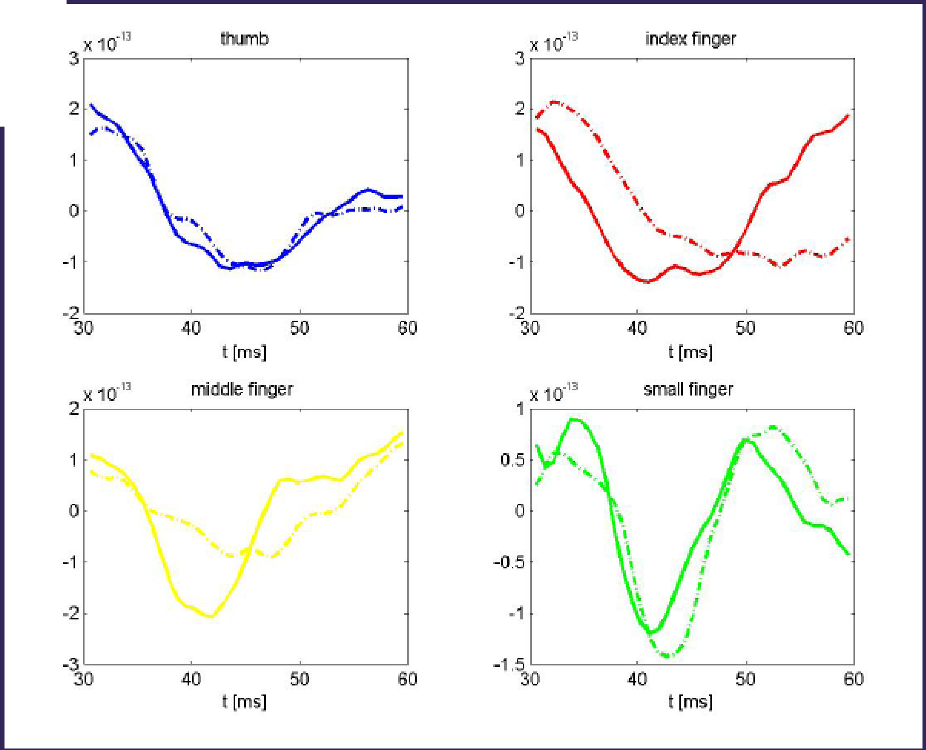
Somatosensory data

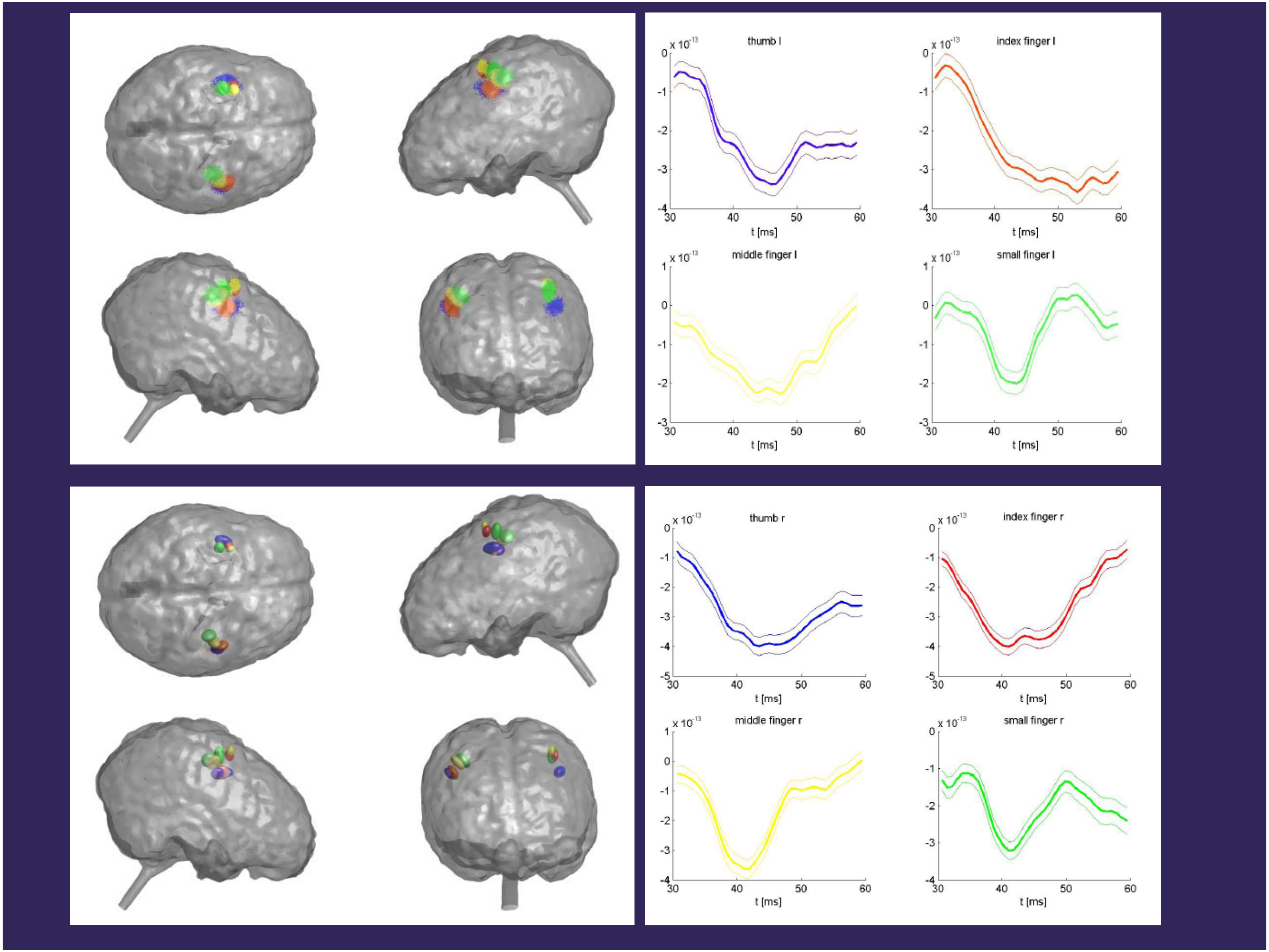
Electric stimulation of 4 digits of left and right hand

Locations



Time series



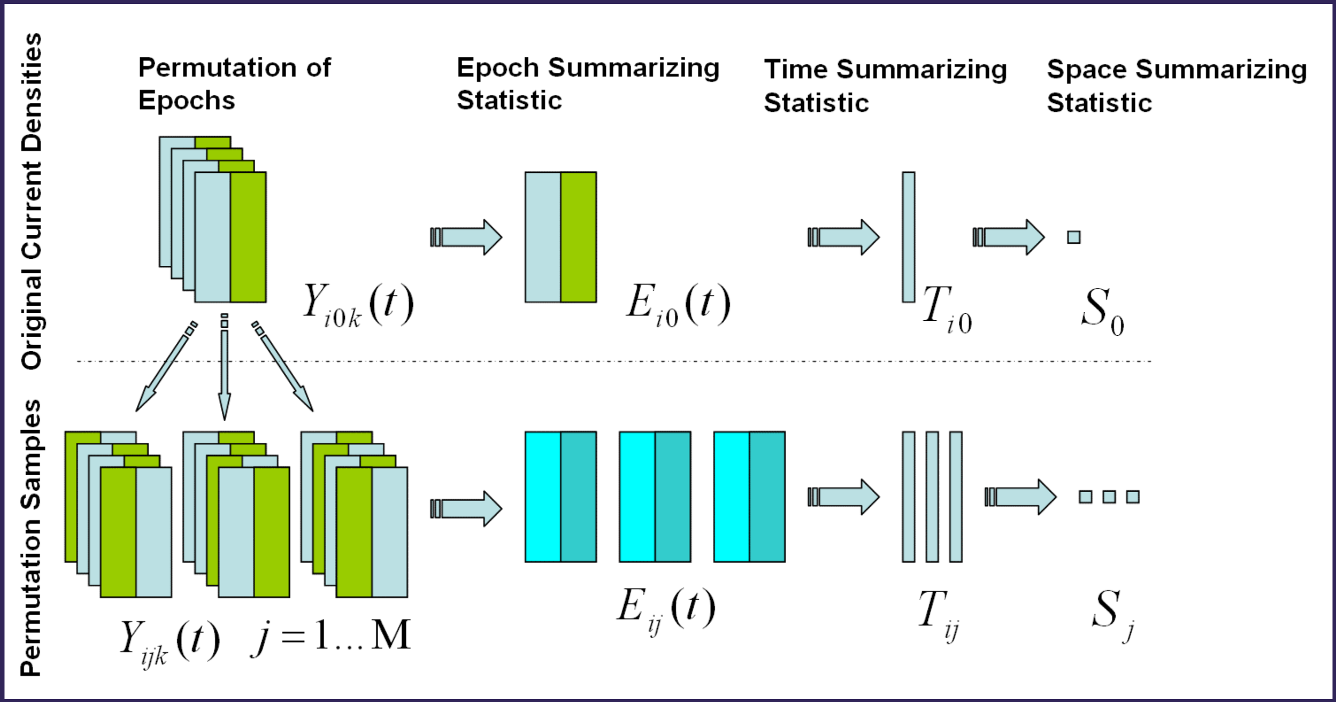


thumb l
index finger l
middle finger l
small finger l
thumb r
index finger r
middle finger r
small finger r
x 10^-13
t [ms]

Activation Detection: Control of FWER in Cortical Imaging

- Imaging methods result in low resolution reconstruction maps
- Noise exhibits highly nonuniform spatial correlation
- We need a principled way of identifying true activation versus noise artifacts
- How: threshold voxel-wise statistic on the image to control FWER.

Permutation Test



t: Time index

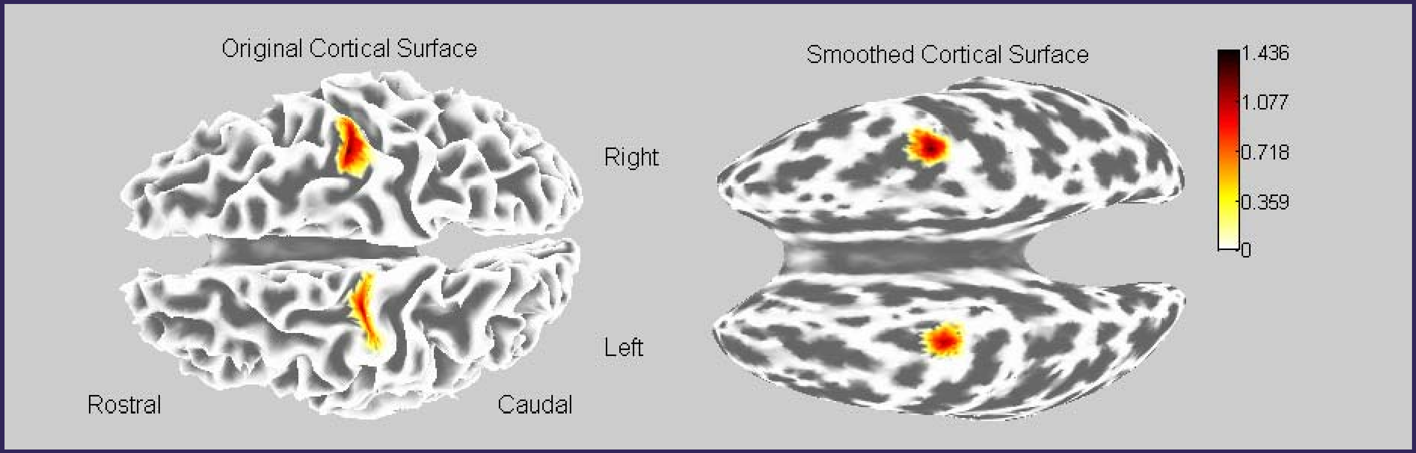
i: Spatial index

j: Permutation index

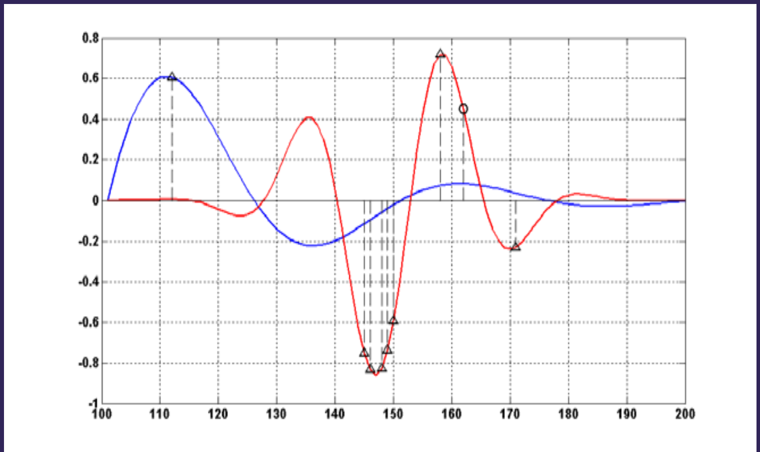
k: Epoch index

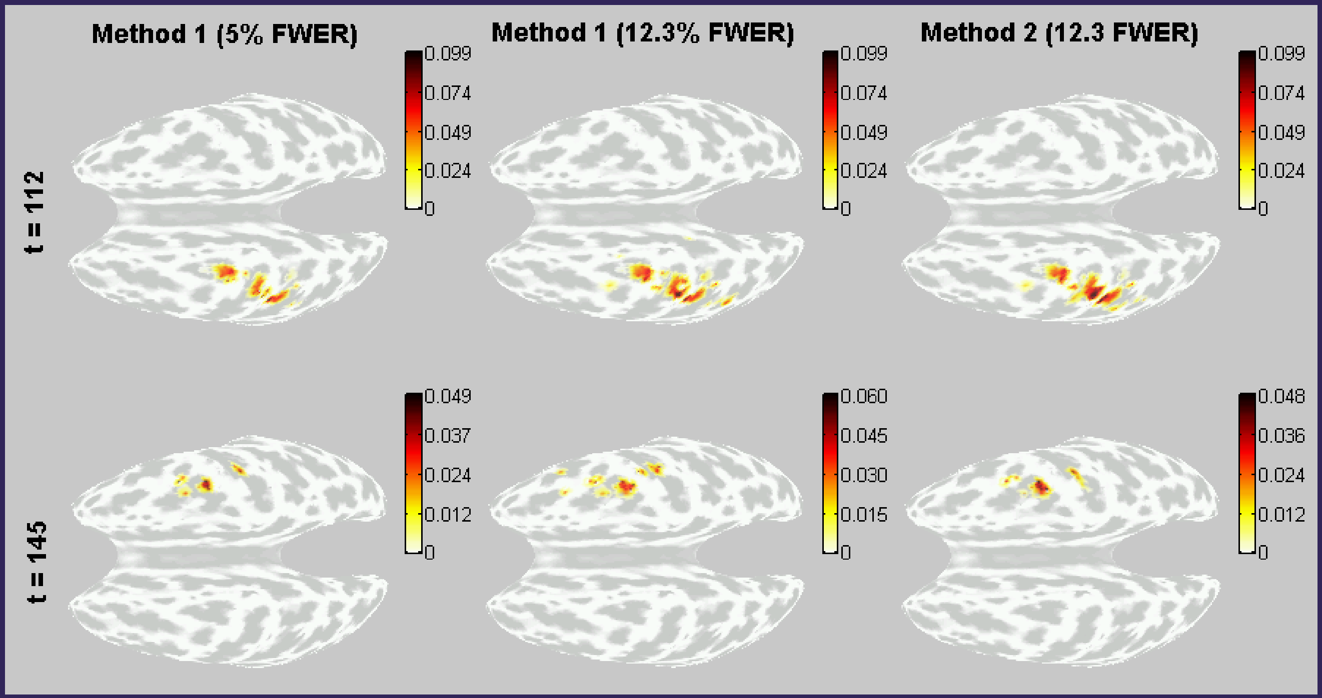
	Epoch-Summarizing $E_{ij}(t)$	$E_{ij}(t)$ Normalized $E_{ij}^n(t)$	Time-Summarizing T_{ij}	T_{ij} Normalized T_{ij}^n	Space-Summarizing S_j
Method 1	$mean_k\{Y_{ijk}(t)\}$	$E_{ij}(t)/s_{ij}$	$\max_t\{\lvert E_{ij}^n(t)\rvert\}$	T_{ij}	$\max_i\{T_{ij}^n\}$
Method 2	$mean_k\{Y_{ijk}(t)\}$	$E_{ij}(t)/s_{ij}$	$\max_t\{\lvert E_{ij}^n(t)\rvert\}$	$p_i(T_{ij})$	$\min_i\{T_{ij}^n\}$

Simulation study



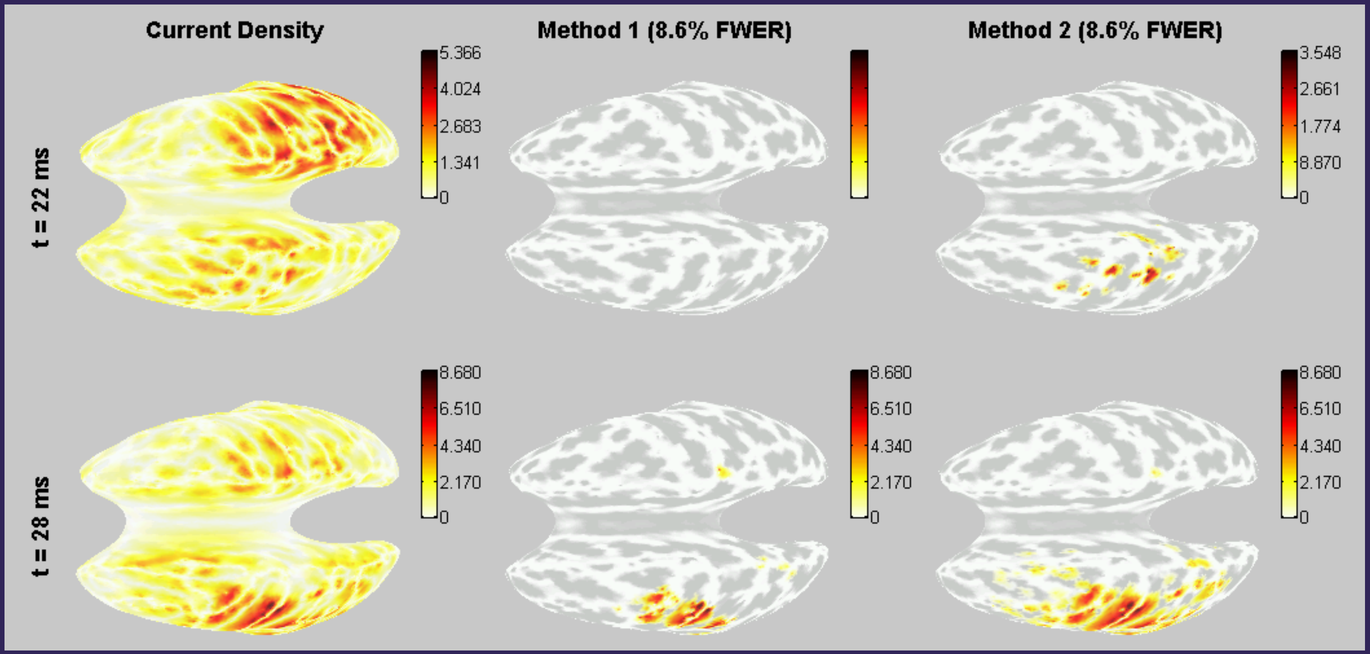
- Two sources where simulated. Source 1 (left) and source 2 (right) are shown on the original and smoothed version of a cortical surface.
- Timecourse of simulated sources and points of source identification at α=0.123. Triangles for both methods, circles for only method 1



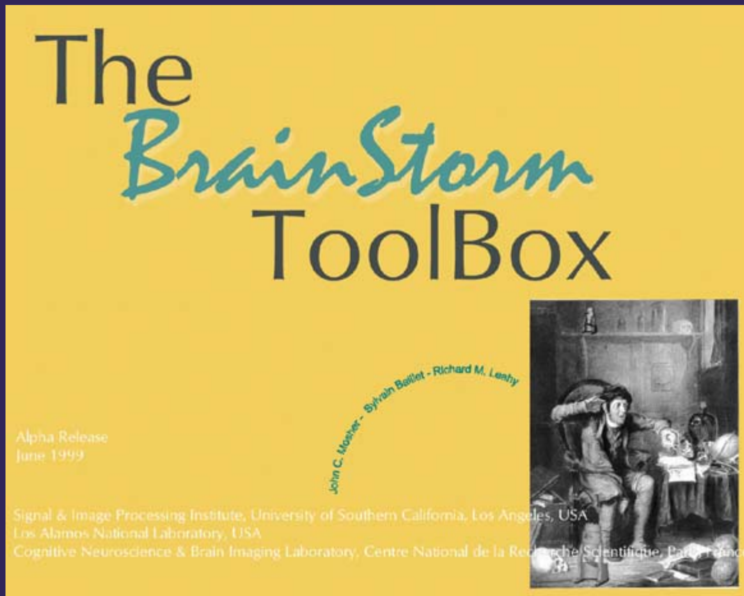


- Examples of significant activation maps for method 1 and 2 for two time instances. Reconstruction appears spread on the smooth cortical surface, but active sources are in neighboring sulci in the original cortical surface. The lowest achieved FWER for method 2 is α=0.123

Somatosensory study (right thumb)



- The data acquisition was done using a CTF Systems Inc. Omega 151 system. The somatosensory stimulation was an electrical square-wave pulse delivered to the right thumb of a healthy right-handed subject.
- Method 2 appear to be more sensitive. At t = 22 ms it appears to correct the current density map, which shows the main activity in the ipsilateral hemisphere.



BrainStorm

Software:

http://neuroimage.usc.edu

BrainSuite