MEG simulation studies related to epilepsy: What can MEG see and do?

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What is MEG?

- MEG – magnetoencephalography, measures small magnetic fields generated by neurons in the brain.
- EEG – electroencephalography, measures electric potential generated by neurons in the brain.
- MEG and EEG provide complimentary information, but different technical problems occur with MEG and EEG.

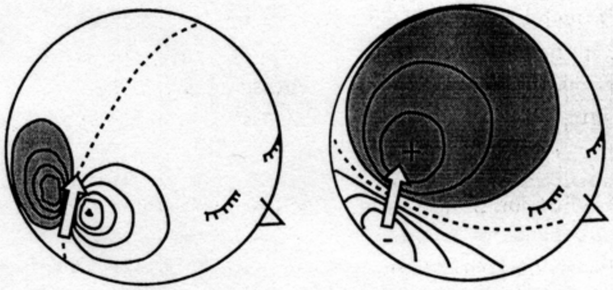


FIG. 5. Schematic illustration of idealized magnetic-field and electric-potential patterns produced by a tangential dipole (white arrow). The head was approximated with a four-compartment sphere consisting of the brain, the cerebrospinal fluid, the skull, and the scalp. From noninvasive measurements of the MEG or EEG field distributions, the active area in the brain can be determined by a least-squares fit to the data.

Hamalainen et al. Reviews of Modern Physics 65(2):413-497, 1993

What does MEG measure?

- Signal generated by the summation of graded potentials along the apical dendrites of pyramidal cells.
- >100,000 neurons are needed to generate a measurable signal.

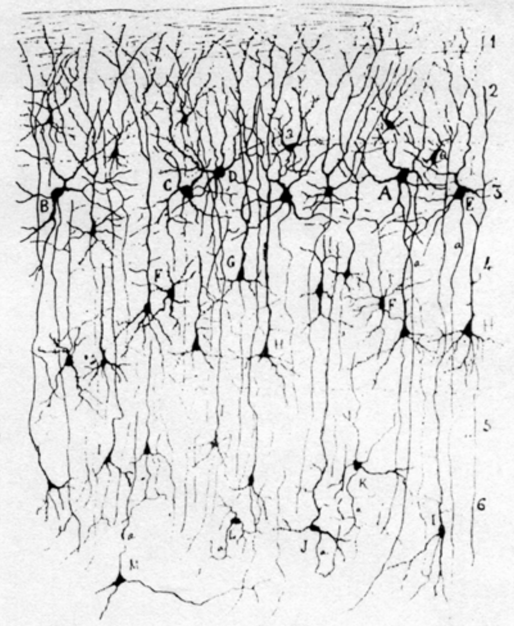


FIG. 14. Transverse section through the gray matter of rat cortex; the thickness of the sheet, from top to bottom, is in humans about 3 mm. A prominent pyramidal neuron (*H*) is illustrated in the middle and two stellate cells (*F*) nearby. The tissue was prepared by the Golgi method, which stains about 1% of the neurons. This picture was drawn by Ramón y Cajal in 1888.

Hamalainen et al. 1993

Magnetic field amplitudes due to other sources

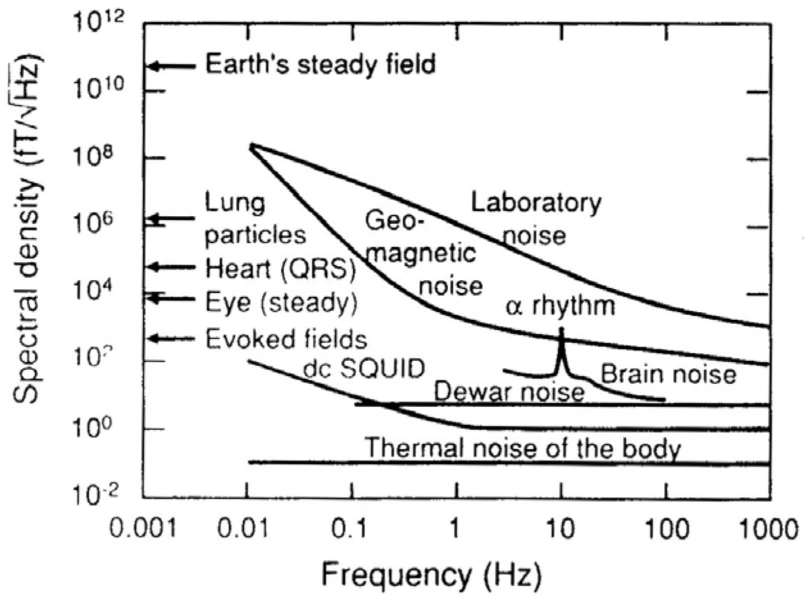


FIG. 8. Peak amplitudes (arrows) and spectral densities of fields due to typical biomagnetic and noise sources.

Hamalainen et al. 1993

How do we measure the small brain signals?

- Gradiometers are used to cancel distant magnetic fields and measure the local magnetic field gradients.

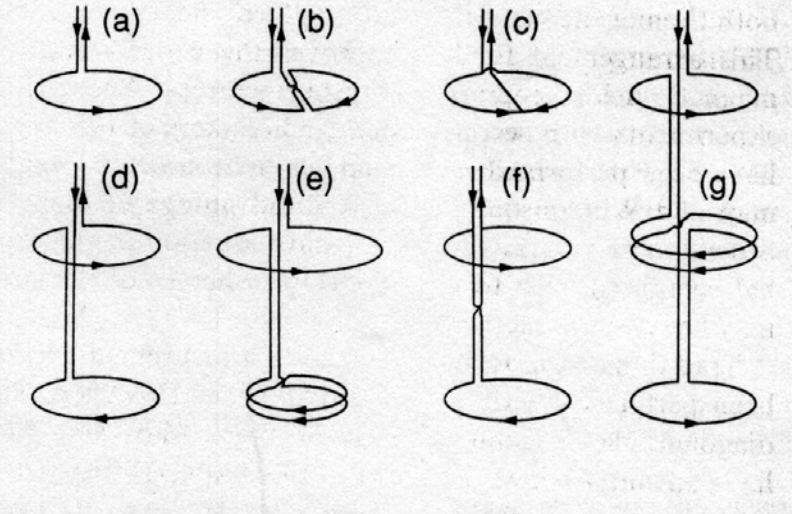


FIG. 26. Various types of flux transformers: (a) magnetometer; (b) series planar gradiometer; (c) parallel planar gradiometer; (d) symmetric series axial gradiometer; (e) asymmetric series axial gradiometer; (f) symmetric parallel axial gradiometer; and (g) second-order series axial gradiometer.

Hamalainen et al. 1993

122 channel Neuromag system

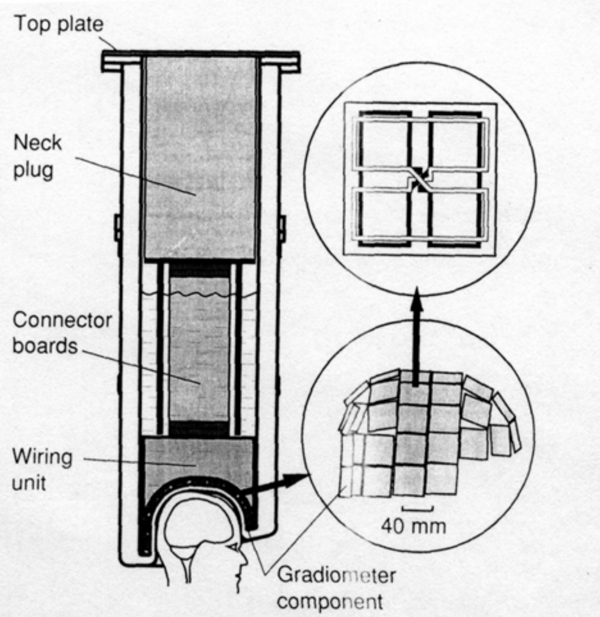
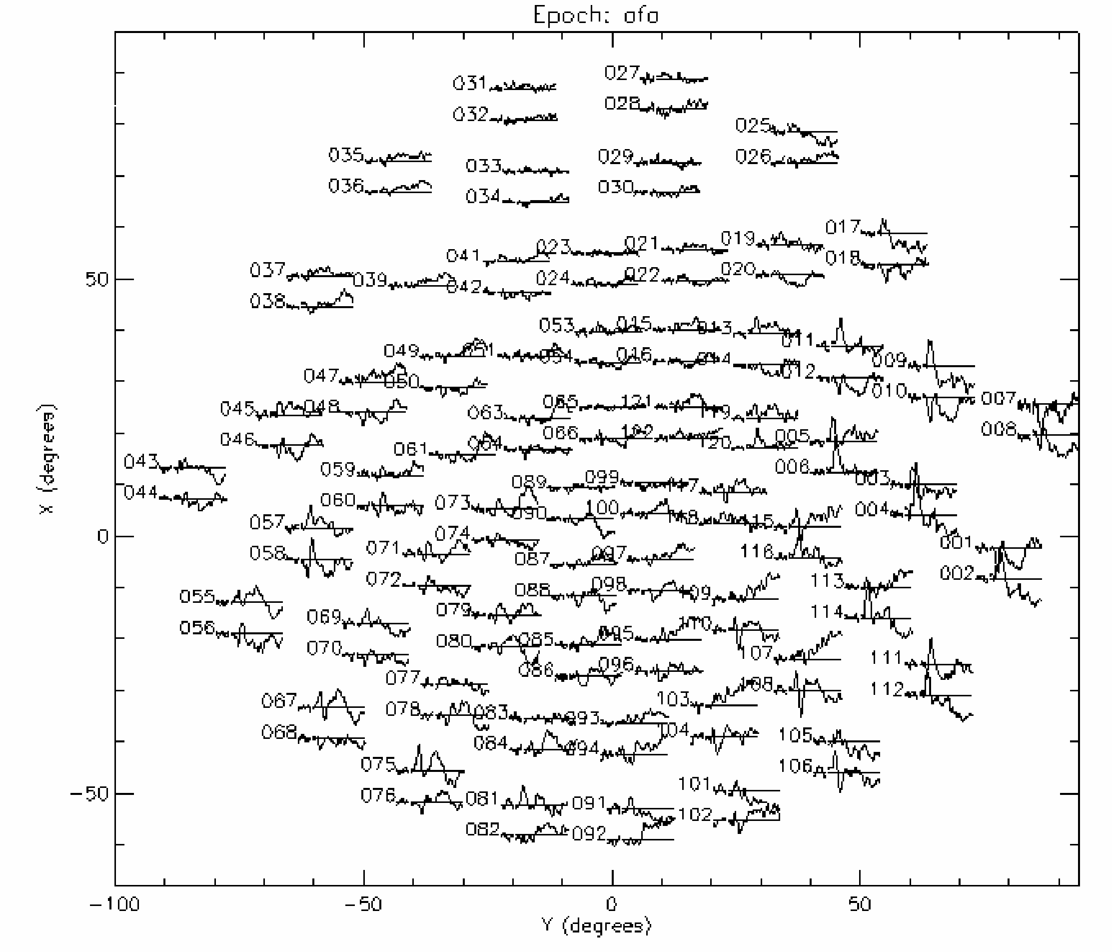


FIG. 41. The 122-channel gradiometer ("Neuromag-122") built in Helsinki. The main modules inside the Dewar are the top plate made of fiber glass and a printed circuit board, the neck plug of fiber-glass-coated foam plastic, the four connector boards, and the wiring unit with 61 two-channel plug-in gradiometer components. Multipair shielded cables are laminated into the surface layer of the neck plug and lead from the top plate to the connector boards where the components for the SQUID gain control are located. On the right, the distribution of the sensors (below) and the gradiometer chip (above) with the two orthogonal figure-of-eight coils are illustrated schematically.

Hamalainen et al. 1993

What we measure with MEG

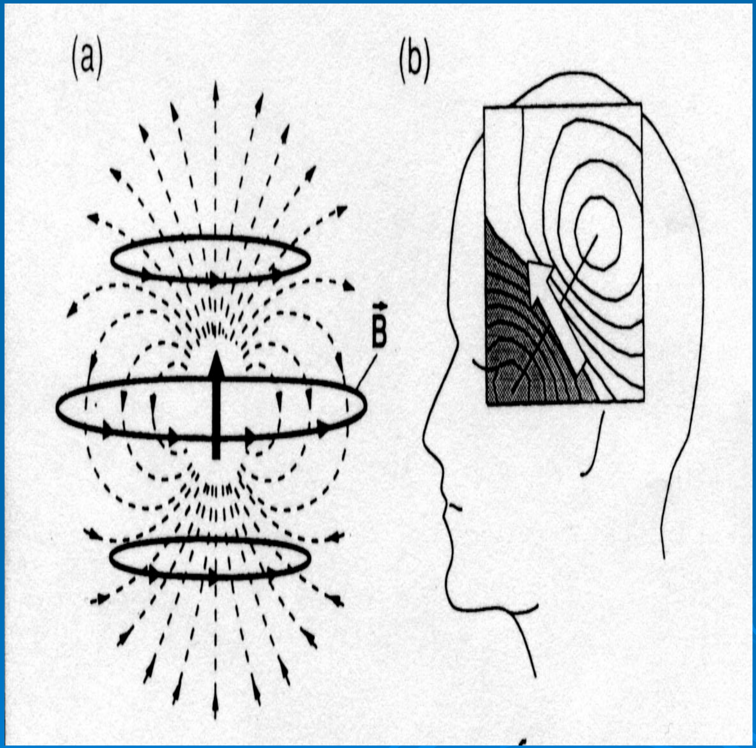


Non-uniqueness of the electromagnetic inverse problem

- Without knowing the number of sources active or the size of the source activation area, multiple configurations can generate the exact same signal at the sensors.
- Does this mean one can't determine the sources of the activity?
  - Kind of…but not really.

How do we determine what generated the measured signals?

- Models are used to describe both the head geometry and the source(s).
- Head often modeled as a sphere
- Source is often modeled by a “current dipole”



Radial component of the magnetic field of a current dipole in a sphere

$$B_r = \frac{\mu_0}{4\pi} \frac{Q \times r_Q \cdot e_r}{\left| r - r_Q \right|^3}$$

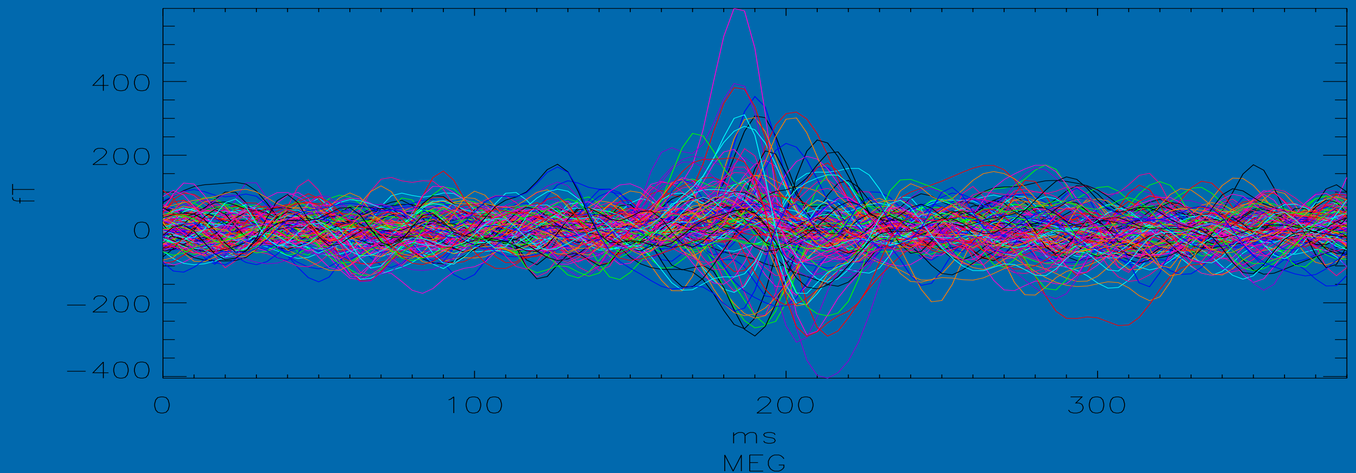
- Where, Q is the current dipole (strength and orientation), r_Q is the location of the current dipole, and r is the location of the measurement.

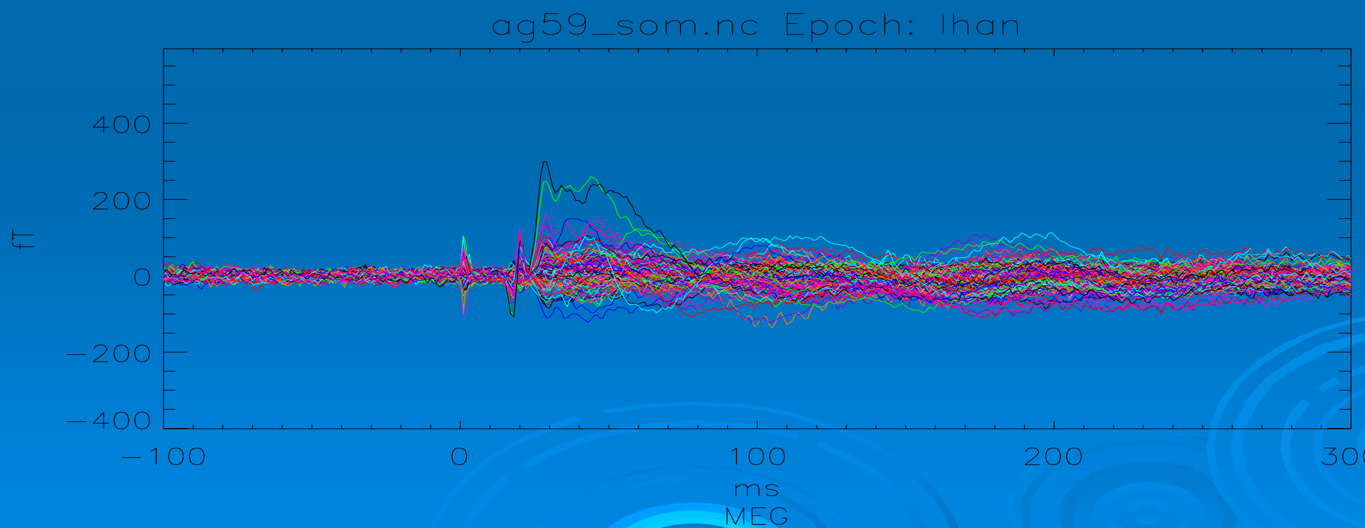
Goal of Frontal Lobe Study

- To determine the effect of real background brain activity on the localization of simulated frontal lobe interictal epileptic spikes using multi-dipole analysis.

Stephen et al. J Clin Neurophysiol. 20(1):1-16, 2003.

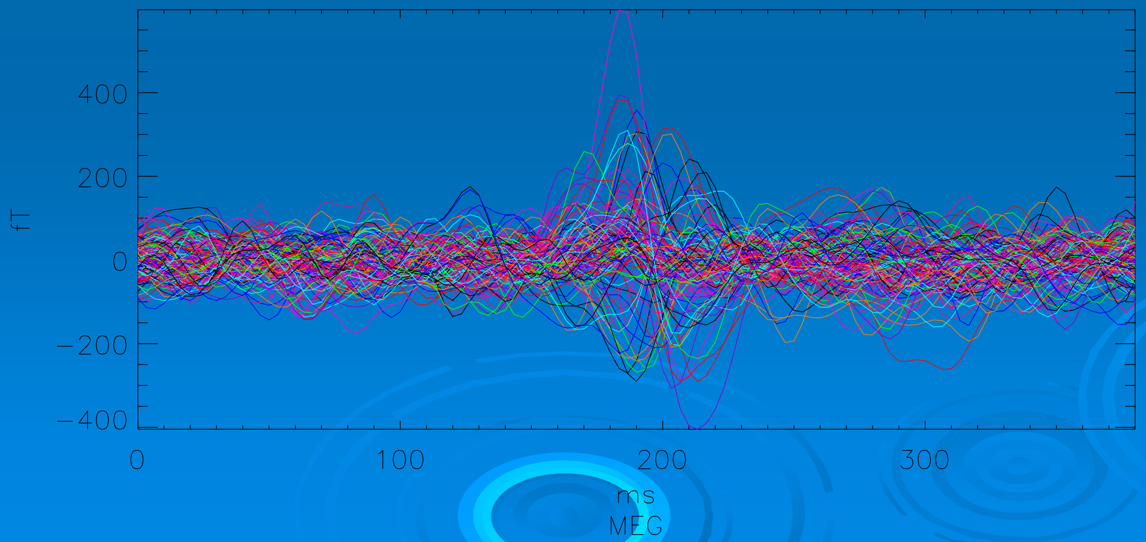
Interictal spikes versus Evoked Fields





Why MEG?

- Temporal resolution is the same as EEG (1 ms).
- One can follow the seizure and/or interictal spike activity in real time.
- MEG signal is not affected by changes in conductivity allowing one to model source locations.



Previous MEG Epilepsy Studies

- Most previous MEG studies were related to Temporal lobe epilepsy
- Most previous MEG studies in epilepsy applied a single dipole model at a single time point (initial peak of the interictal spike).
- Previous studies suggest that multi-dipole modeling could improve the results of epilepsy studies. (Ebersole 1997; van der Maij et al. 2001)

Motivation for Frontal Lobe Epilepsy Simulation Study

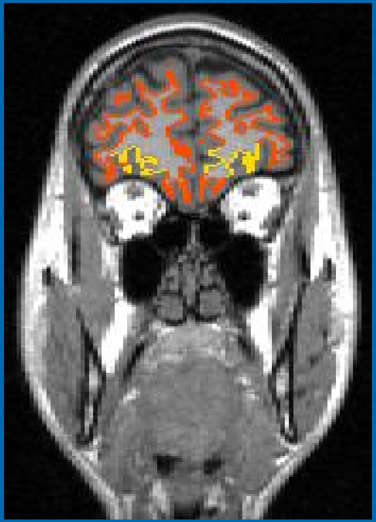
- Surgical success rate in frontal lobe epilepsy is 50-75% depending on presence of an identifiable lesion (e.g. Bautista et al. 1999, Girven et al. 2002; Jobst et al. 2000; Mosewich et al. 2001).
  - May be related to multi-focal seizure generators (Bautista 1999; Mosewich et al. 2000; Siegel et al. 2001; Wennberg et al. 1998)
  - Previous MEG studies have applied single time point and single dipole analysis
- Determine the effect of real background brain activity on source localization.

Previous MEG Simulation Studies

- Most previous simulation studies used computer generated Gaussian noise to determine theoretical limits of localization error, resolvability of sources, etc. (e.g. Supek and Aine, 1993; Leahy et al. 1998)
- Two studies used implanted electrodes in real human subjects to determine localization error -- but they signal averaged across ~100 stimulations (Cohen, et al. 1990; Balish, et al. 1991).

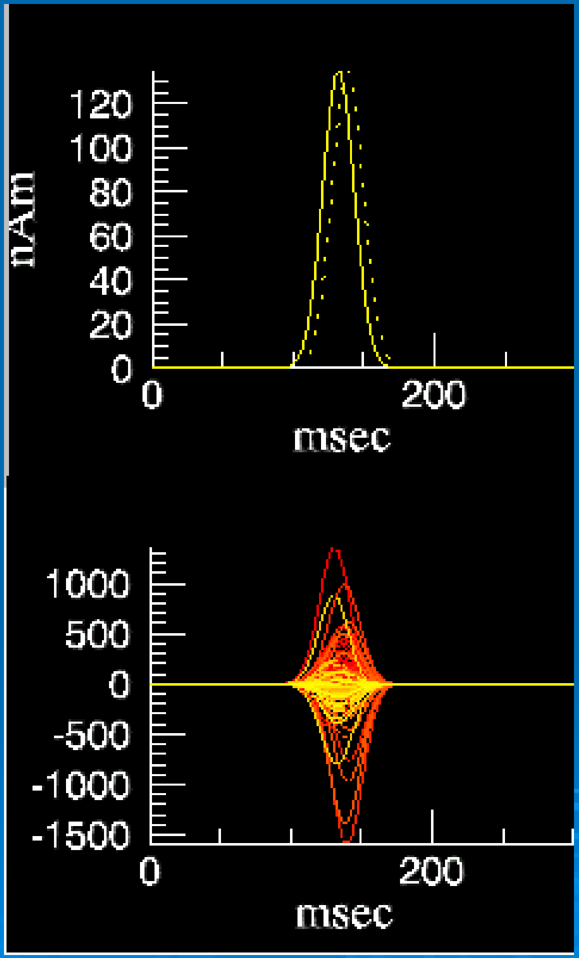
Example Simulations

Orbital Frontal (OF)



Premotor (PM)

PM Timecourses and Forward Fields



Simulation Details and Modeling Methods

- 1- and 2- source simulations for PM (135 nAm) and OF (180 nAm).
- 5 subjects, 5 epochs of background brain activity.
- The peak latencies were 133 and 143 ms.
- The simulated activity was added to 5 background brain activity files and modeled with 1-, 2-, 3-, and 4-dipole models.
- The time interval 100-170 ms was modeled.
- <u>Adequate models</u> were models that had localization error < 10 mm and latency error < 5 ms
- A "best" model was chosen for each simulation
- For over-modeled cases, closest source(s) were labeled "keep" and the additional source(s) were labeled "discard"

Example simulated interictal spikes with real background brain activity 2-source PM focal simulation

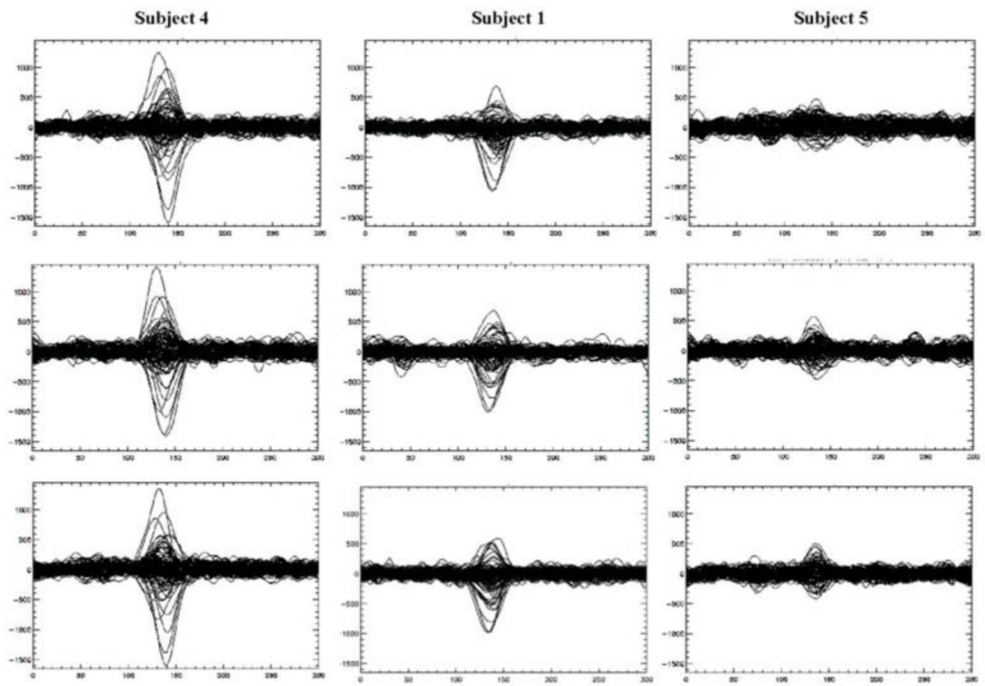
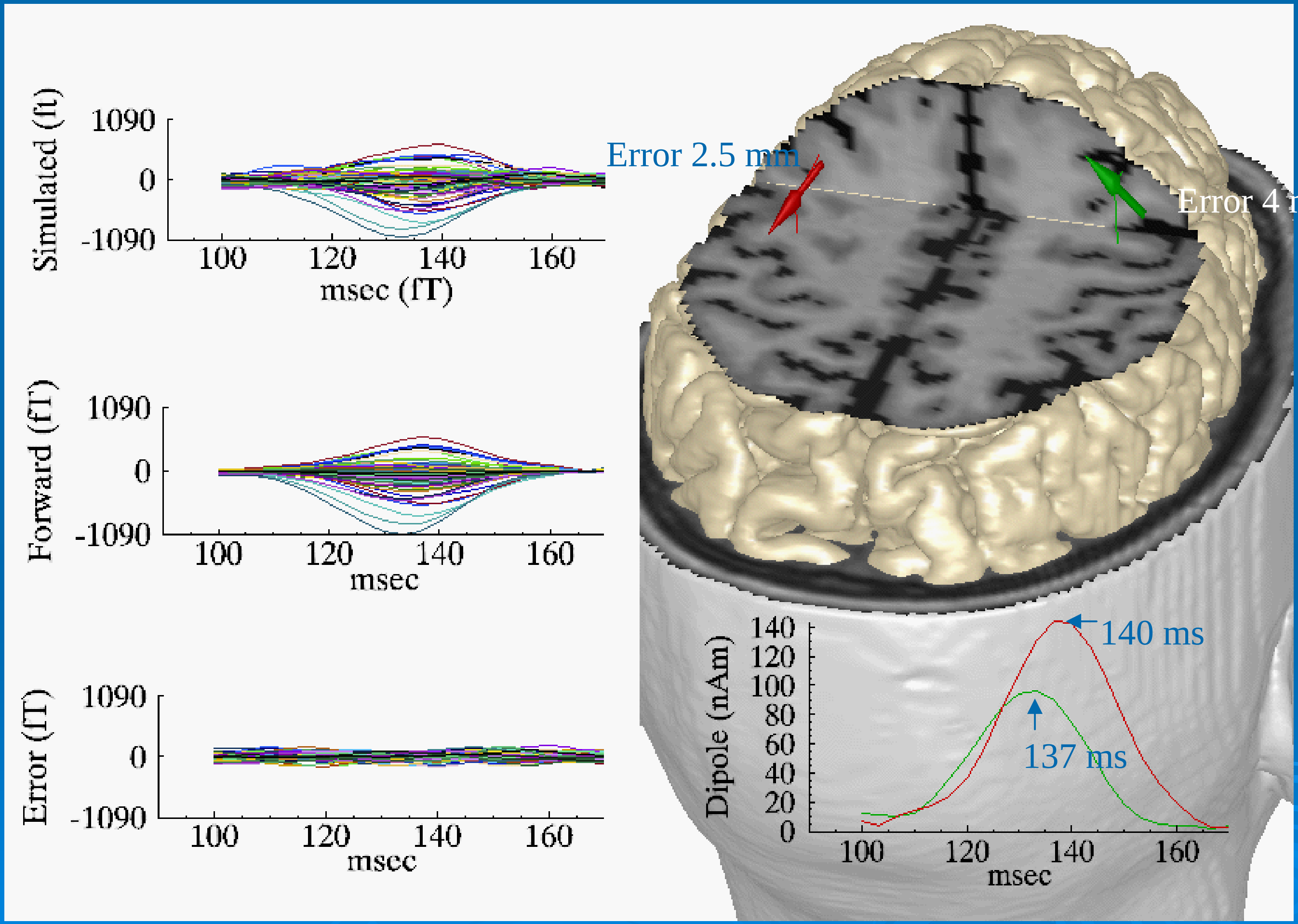


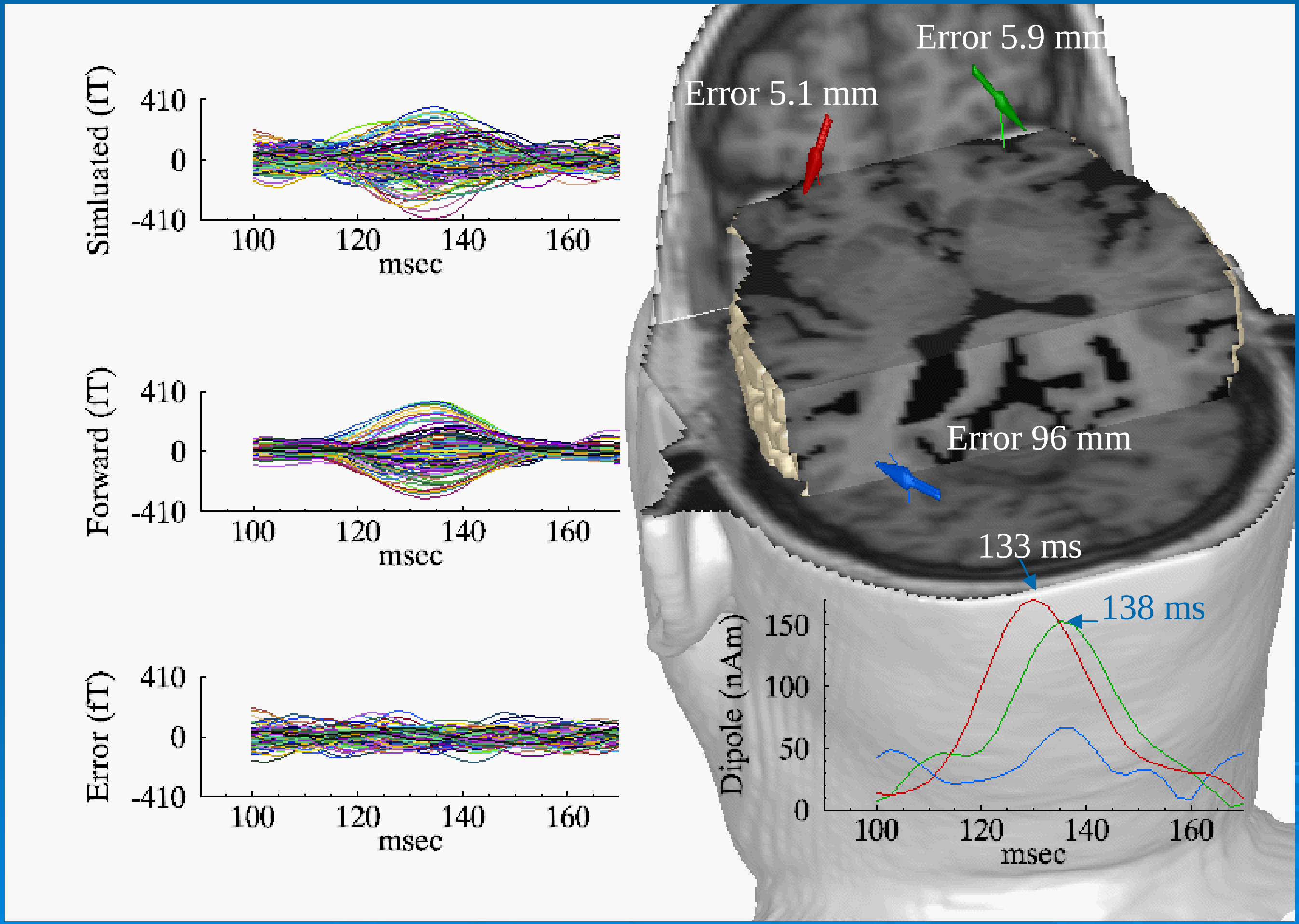
Figure 2

2-dipole model for 2-source PM simulation Subject 1

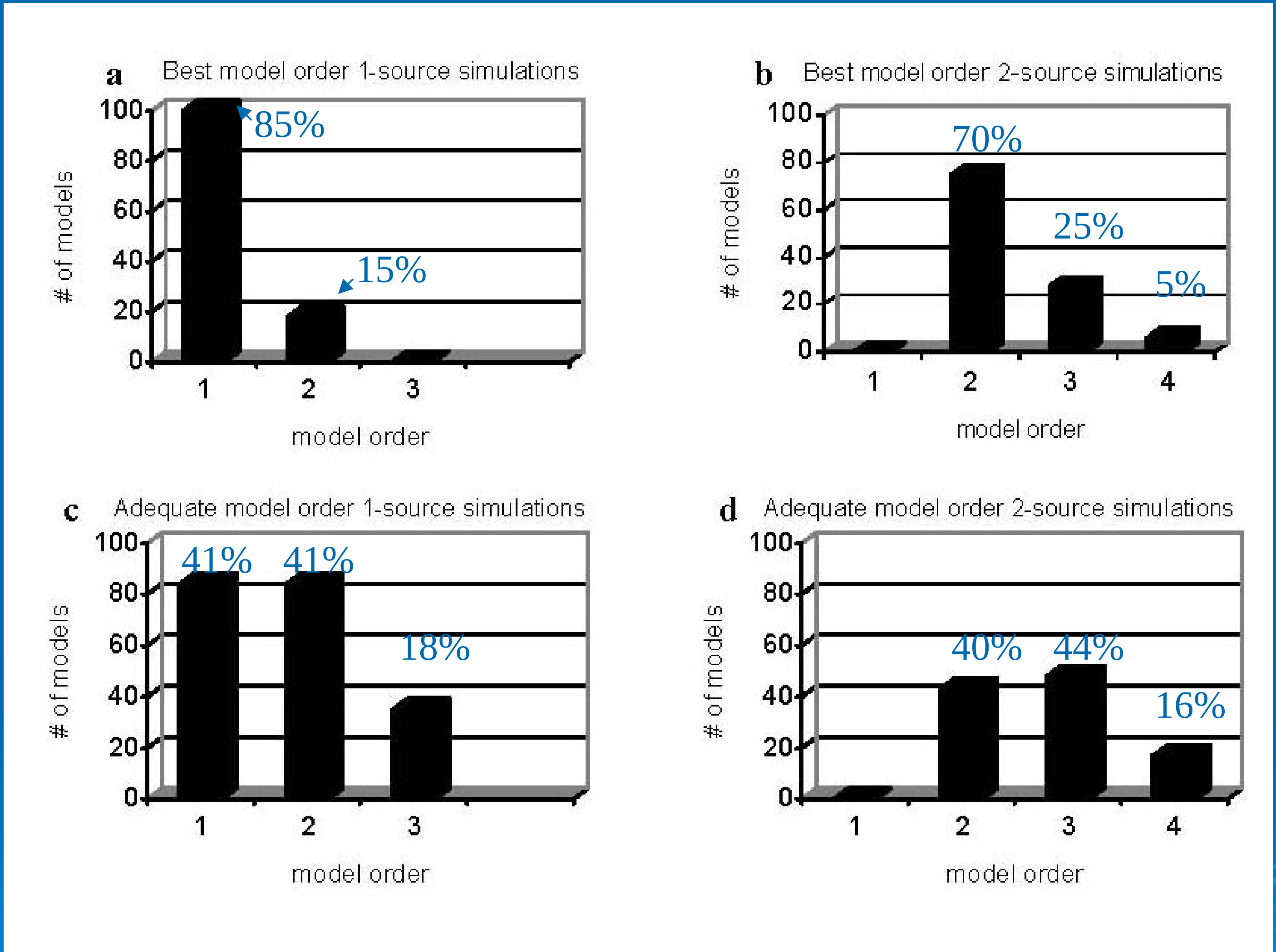


Correct amplitude 135 nAm

3-dipole model for 2-source OF simulation Subject 2

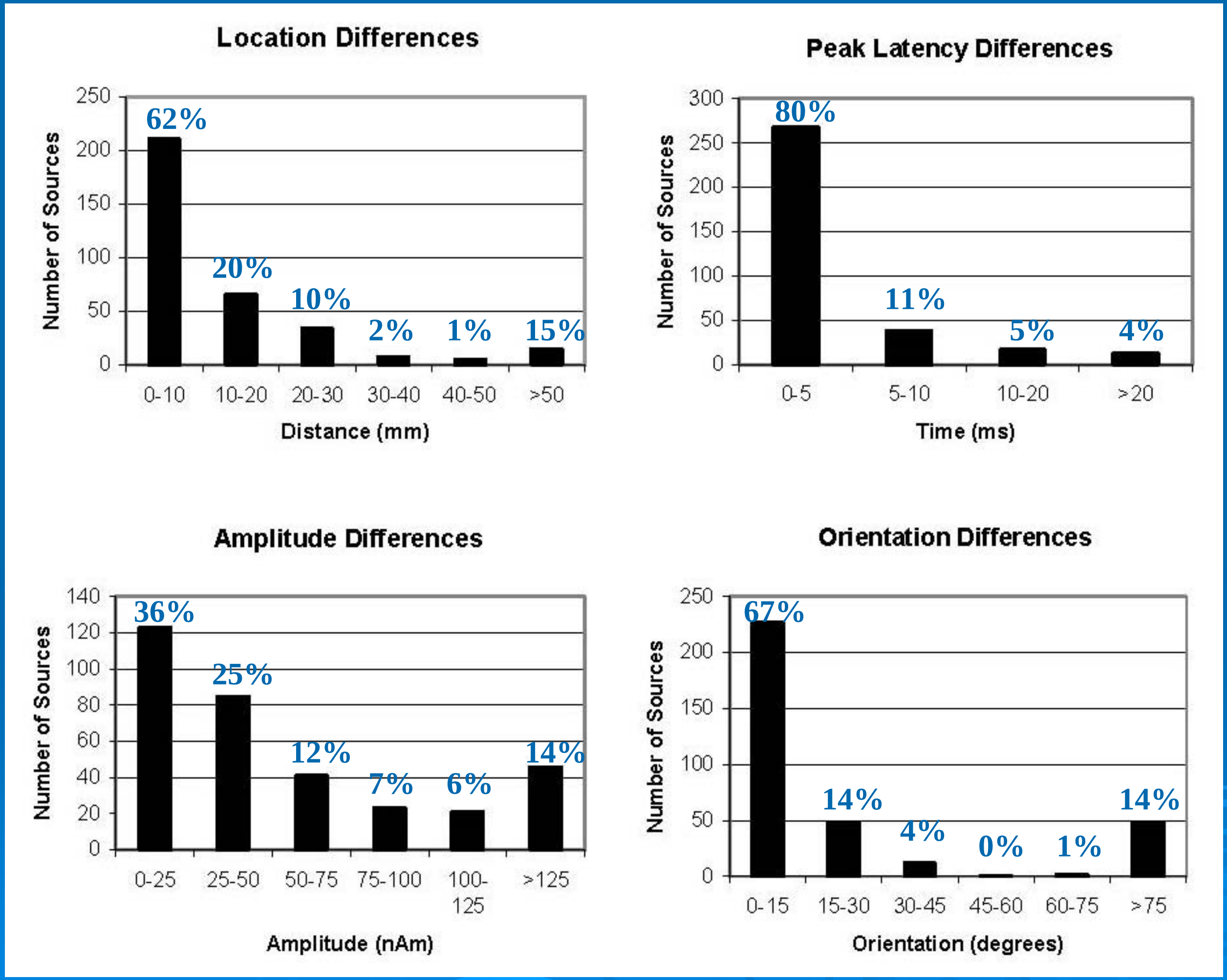


Correct Amplitude 180 nAm



a
Best model order 1-source simulations
# of models
100
80
60
40
20
0
1
2
3
model order
85%
15%
b
Best model order 2-source simulations
# of models
100
80
60
40
20
0
1
2
3
4
model order
70%
25%
5%
c
Adequate model order 1-source simulations
# of models
100
80
60
40
20
0
1
2
3
model order
41%
41%
18%
d
Adequate model order 2-source simulations
# of models
100
80
60
40
20
0
1
2
3
4
model order
40%
44%
16%

Modeled versus Correct Parameters of Keep sources for the Best Models



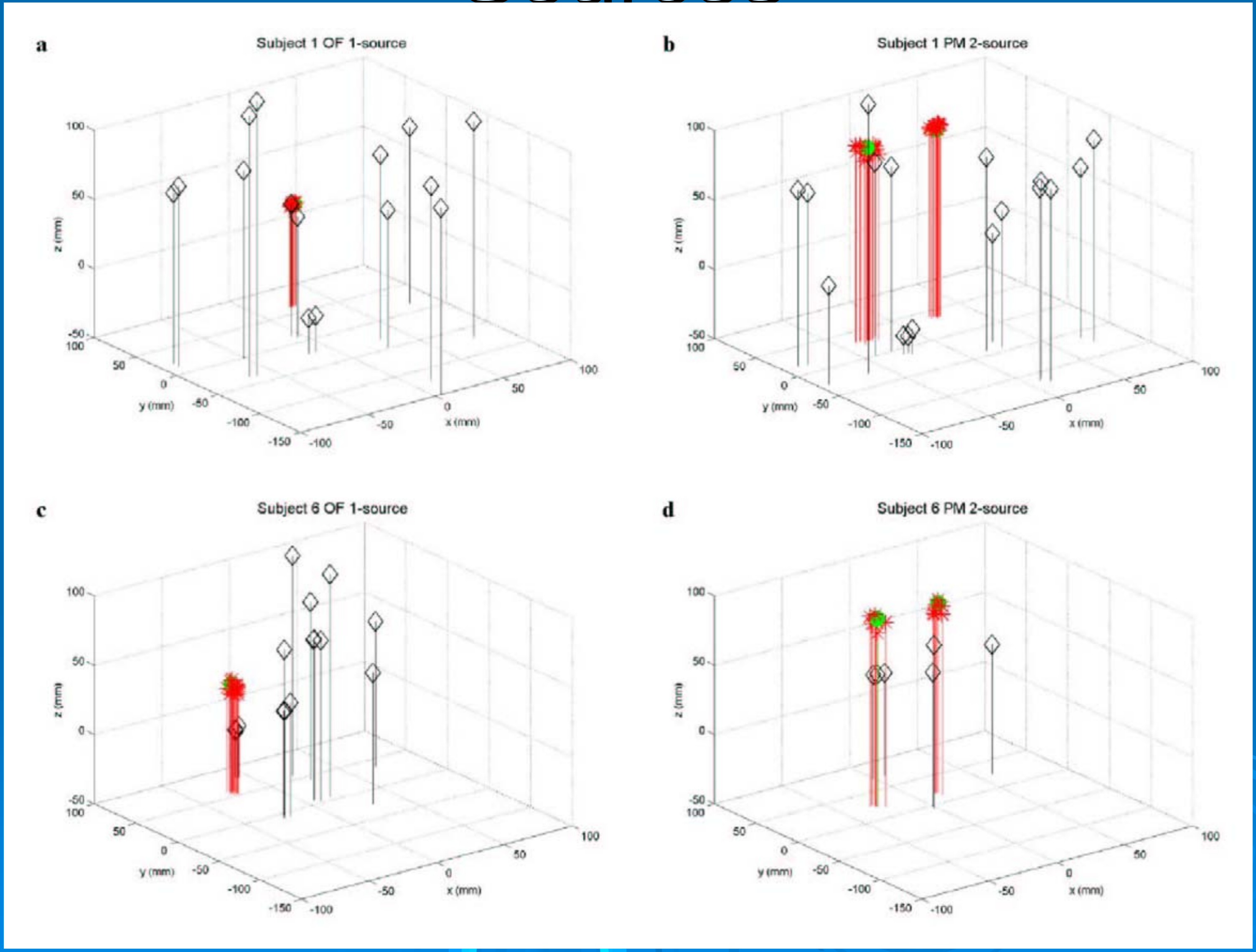
Summary of adequate model results

Table 2. Summary of Adequate model results, Errors - μ (σ)

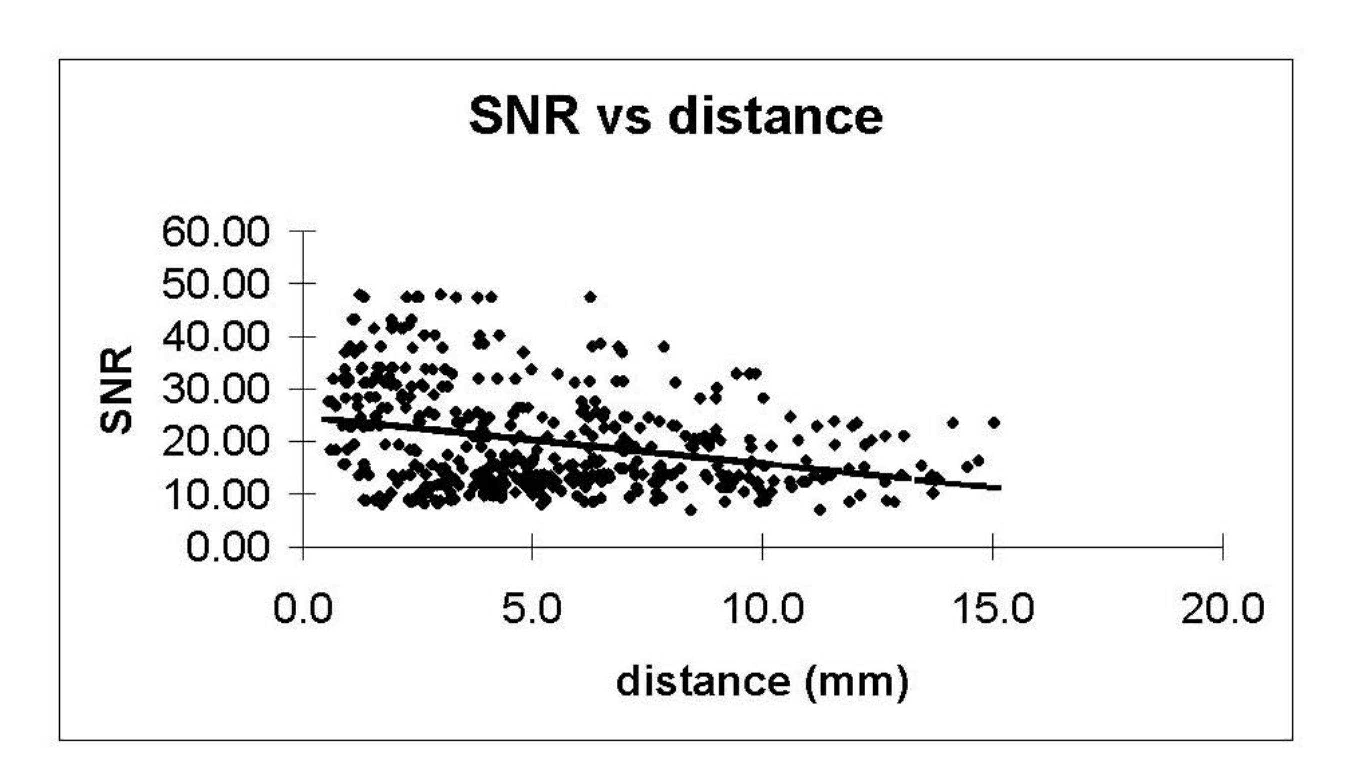
Source	Distance (mm)	Latency (ms)	Amplitude (nAm)	Orientation (°)
Keep (N = 423)	4.6 (2.6)	2.2 (2.2)	33 (41)	9 (7)
Discard (N = 233)	97 (35)	18.5 (11)	168 (202)	92 (62)

- Cohen et al. 1990 reported error of 8 mm
- Sutherling et al. 1988 reported error of 12 mm
- Diekmann et al. 1998 reported error of 18 mm
- Nakasato et al. 1994, Stefan et al. 1992, and Wheless et al. 1999 only reported qualitative comparisons

Example Keep and Discard Sources



Correlation of localization error with SNR of original spike



r = -0.31, p < 0.001

Summary of Results and Conclusions of Frontal Lobe Study

- Real background brain activity influences the ability to properly model simulated activity.
- Multi-dipole modeling should be used to determine the accurate location and timing of spike activity.
- The consistency of spike related activity and the random location of unrelated brain activity should allow one to properly localize spike related activity.
- The variability of appearance of same spike based on differences in background brain activity cautions against spike averaging.

Collaborators

- Jerry Shih, MD, Neurology (PI)
- Cheryl Aine, PhD, Radiology
- Steve Peterson, PhD, Pharmacy
- Doug Ranken, Biophysics Group, LANL
- David Hudson, BRINM, VAMC
- Michael Weisend, PhD, VAMC

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