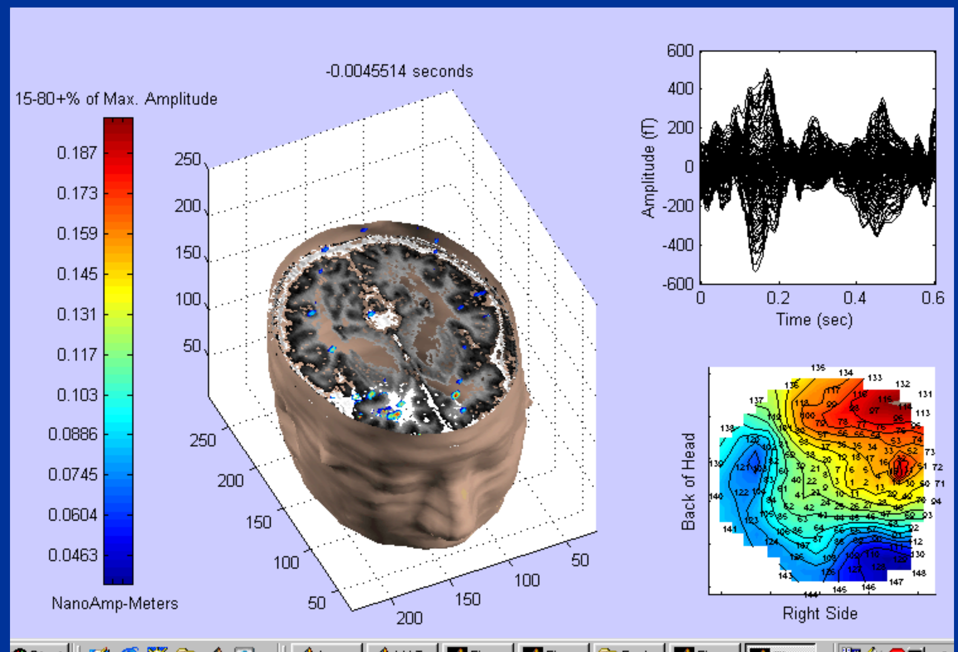
What can Epileptologists expect from MEG for

Assessment of Language
&
Resting State Coherence/Connectivity

Susan Bowyer Ph.D.
Scientist/Medical Physicist
Department of Neurology
Henry Ford Hospital



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30th International Epilepsy Congress Disclosure Form

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• None

2013 MONTREAL
23rd - 27th JUNE, 2013
30th INTERNATIONAL EPILEPSY CONGRESS

Understanding How Our Brain's Processes Language

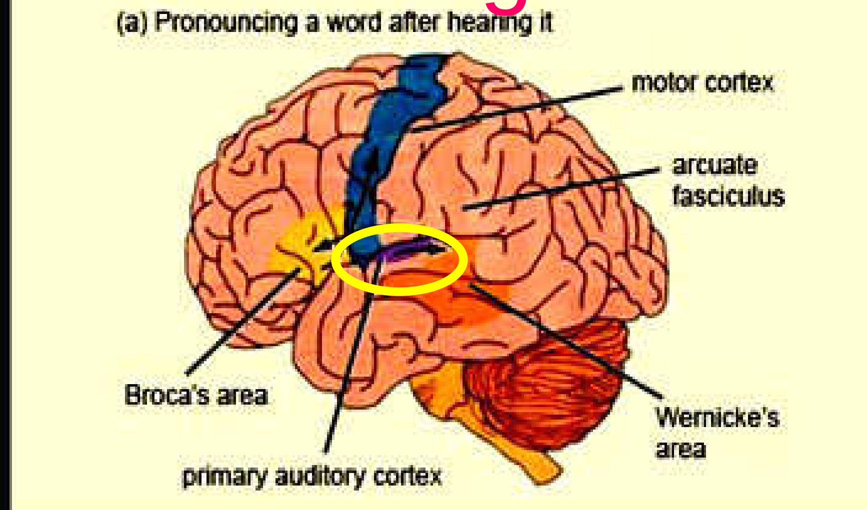
From
Cognition / Receptive
Wernicke's AREA

superior temporal gyrus (BA 22)
angular gyrus (BA 39)
supramarginal gyrus (BA 40)

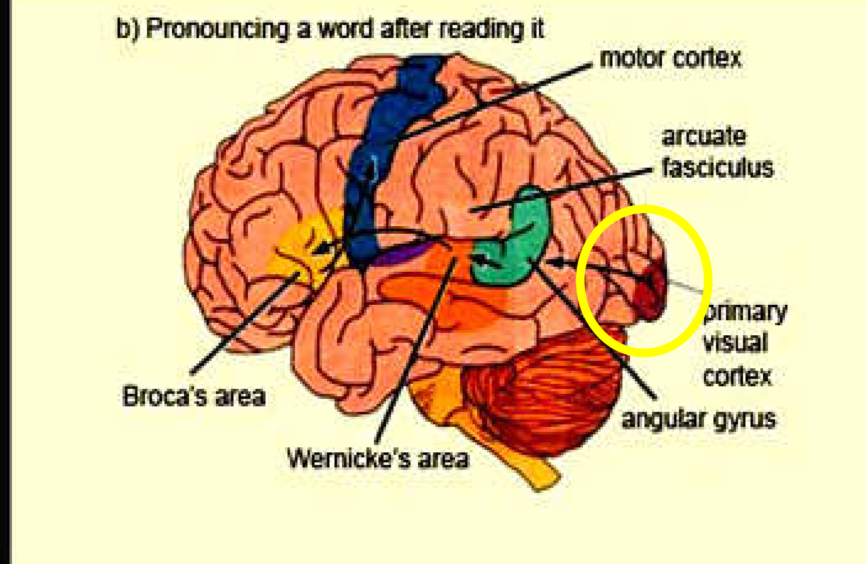
To
Production / Expressive
Broca's AREA

pars opercularis and pars triangularis
of the inferior frontal gyrus (BA 44 and 45)

Hearing



Reading



Website: The Brain from Top to Bottom

Language organization and reorganization in epilepsy

- Most healthy individuals are <u>left hemisphere dominant</u> for language
- Patients with Epilepsy in the left hemisphere epilepsy have a <u>higher likelihood of atypical language organization</u>
- The cerebral organization of language in epilepsy has been studied to explore the influence of unique clinical features inherent in epilepsy that might contribute to the reorganization of language, such as location of seizure onset, age of seizure onset, and extent of interictal epileptiform activity.
- Unlike the abrupt language changes that occur following acute brain injury with disruption of established language circuits, converging evidence suggests that the <u>chronic nature of epileptic activity can result in a developmental shift of language from the left to the right hemisphere or re-routing of language pathways from traditional to non-traditional areas within the dominant left hemisphere</u>.
- The use of imaging techniques are needed to reliably predict altered language networks in individual patients to provide definitive identification of language cortex for lateralization and localization necessary for clinical care.

Hamberger &, Cole Neuropsychol Rev. 2011

Language Guidelines

ACMEGS
AMERICAN CLINICAL MEG SOCIETY
ACMEGS.ORG

INVITED ARTICLE

American Clinical Magnetoencephalography Society Clinical Practice Guideline 2: Presurgical Functional Brain Mapping Using Magnetic Evoked Fields*

*Richard C. Burgess,† Michael E. Funke,‡ Susan M. Bowyer,§ Jeffrey D. Lewine,‖ Heidi E. Kirsch,¶ and Anto I. Bagić,#; for the ACMEGS Clinical Practice Guideline (CPG) Committee**,****

(*J Clin Neurophysiol* 2011;28: 355–361)

Like other laboratory tests, it is important that clinicians

Indications

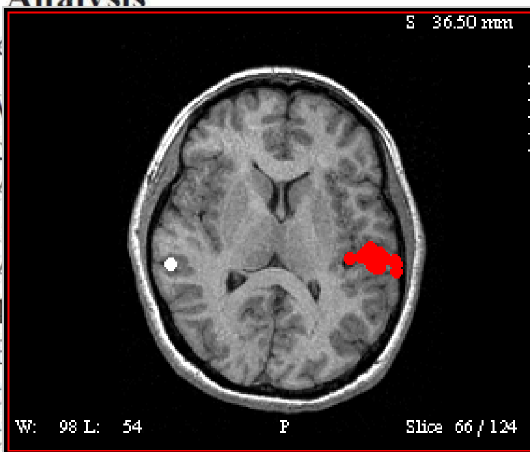
- Determining the **language-dominant hemisphere** in patients with either organic or functional brain diseases before surgical interventions, such as craniotomy, stereotactic or radiosurgical procedures: and/or
- Objective functional evaluation of language processing (i.e., identification of the **location and latencies**).

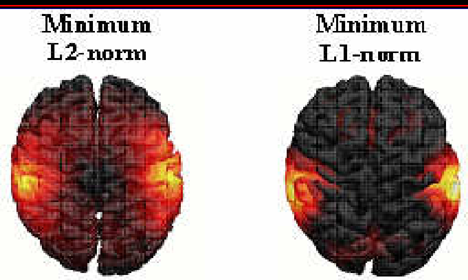
Guidelines for Language

Data Analysis

Av

- ...ntinuously recorded data ... the SNR.
- ...ochs is valid only when ... identical.
- ...ally achieved with 50 to ...
- ... quality control (latency, ... re presented acoustically, ... d be symmetrical in to- ... iseconds and with similar ...
- ... filtered 1 to 50 Hz.





Ini

- ... f long-latency language-related activity, it is important to evaluate the integrity of basic ... milliseconds.
- ... later... essing ... ual) ... promi... -laten...
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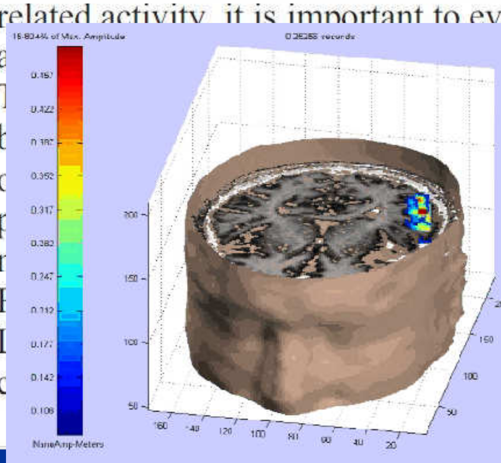
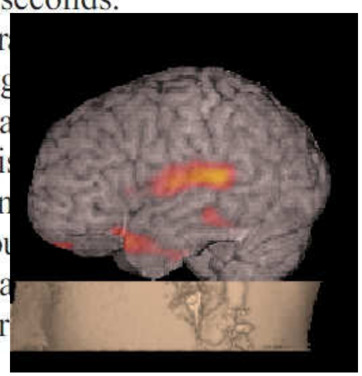




Hemispheric dominance for language

- The determination of hemispheric dominance for language is based on an assessment of how much language activity is evoked in each hemisphere, as assessed by the language evoked field.
- Several strategies are available for source assessment, including single and multiple dipole based strategies, and current reconstructions such as L1 norm, L2 norm, or MR-FOCUSS, and beamformers. Different laboratories have used different methods, but the most commonly used methods are based on dipoles and minimum norm estimates.
- One of the most commonly used methods is to use single moving dipoles to account for the activity beyond 150 milliseconds. In this method, at each time point, a restricted sensor array is identified encompassing the long-latency response(s). A single equivalent current dipole is calculated and if the goodness of fit exceeds a prespecified criteria (e.g., 90%), then the fits are considered valid and the dipole is retained. After all time points are fit (typically in 1-millisecond steps), a laterality index is calculated based on the number of valid dipole fits in each hemisphere. Here, laterality index is defined by $100 \times (R - L)/(R + L)$, where L and R are the number of accepted dipoles fit in the left and right hemispheres, respectively. Laterality index values from -100 to -20 indicate strong left hemisphere language dominance. Laterality index values from -19 to $+19$ indicate bilateral language activation. Laterality index values from $+20$ to $+100$ indicate right hemisphere language dominance.

Review article

Epileptic Disord 2010; 12 (2): 97-108

Language tasks used for the presurgical assessment of epileptic patients with MEG

Mona Pirmoradi[1,2], Renée Béland[1,2,3], Dang K. Nguyen[4], Benoit A. Bacon[5], Maryse Lassonde[1,2]

[1] Centre de Recherche en Neuropsychologie et Cognition, Université de Montréal
[2] Centre de Recherche, Centre Hospitalier Universitaire Sainte-Justine
[3] École d'orthophonie et d'audiologie, Université de Montréal
[4] Neurologie, Centre Hospitalier Universitaire de Montréal (Notre-Dame)
[5] Psychology, Bishop's University, Sherbrooke, Quebec

Received November 13, 2009; Accepted April 19, 2010

ABSTRACT – Determining the language dominant hemisphere and the intrahemispheric localization of this function are imperative in the planning of neurosurgical procedures in epileptic patients. New noninvasive diagnostic techniques are being developed to reduce the risks associated with more invasive techniques. The aim of this paper is to review the different protocols for lateralizing and/or localizing language functions using magnetoencephalography (MEG), a noninvasive technique. The reviewed studies include control and patient populations using various protocols which employ different expressive and receptive language tasks. The overall findings reveal high concordance between MEG and the intracarotid amobarbital test (IAT). Moreover, MEG allows intrahemispheric localization of receptive and expressive language functions. However, the different language tasks used with MEG, whether receptive or expressive, appear to activate the left temporal more than frontal areas. The best task to assess language comprehension in both adults and children appears to be a word recognition task. A verbal fluency task could be used to test language production in children and a verb generation task in adults.

Key words: epilepsy surgery, language, magnetoencephalography, localization, lateralization

Task Reference	Stimuli used	# of participants	Type of participants	Age	Concordance with IAT	Concordance with handedness
Passive listening Szymanski *et al.* 1999	Vowels, tones	7	Controls	m = 35	-	100%
Passive listening Szymanski *et al.* 2001	Vowels	15	Patients	14-56	71%	71%
Passive listening Kim and Chung 2008	Words	17	Patients	17-52	71%-94%	-
Categorization Simos *et al.* 1998	Words, tones	16	Controls	28-53	-	87.5%
Auditory recognition Breier *et al.* 1999b	Words, tones	15	Controls	26-44	-	87%
Auditory recognition Gootjes *et al.* 1999	Vowels, tones, notes	11	Controls	23-30	-	91%
Auditory recognition Kirveskari *et al.* 2006	Tones, vowels	27	Controls	21-54	-	70%-80%
Word recognition Breier *et al.* 1999a	Words (visual-auditory)	26	Patients	8-56	92%	-
Word recognition Breier *et al.* 2001	Words (visual-auditory)	19	Patients	8-18	87%	-
Word recognition Papanicolaou *et al.* 2004	Words (auditory)	100	Patients	8-56	87%	-
Word recognition Maestú *et al.* 2002	Words (auditory)	8	Patients	m = 25	87.5%	-
Word recognition Merrifield *et al.* 2007	Words (auditory)	16	Patients	m = 31.5	90%	-
Word recognition Doss *et al.* 2009	Words (auditory)	35	Patients	m = 29.6	86%	-
Semantic judgment McDonald *et al.* 2009	Words (visually)	8	Patients	25-53	75%-100%	-
Reading Hirata *et al.* 2009	Words	60	Patients	-	85%	-
Reading and picture naming Kober *et al.* 2001	Word	15	Controls & Patients	26-67	-	93%
Language production						
Task Reference	**Articulation**	**# of participants**	**Type of participants**	**Age**	**Concordance with IAT**	**Concordance with handedness**
Picture naming Bowyer *et al.* 2005b	Covert	27	Patients	10-59	78%	-
Picture naming Fisher *et al.* 2008	Covert and overt	9	Controls	24-48	-	44%
Verb generation Bowyer *et al.* 2005b	Covert	27	Patients	10-59	82%	-
Verb generation Breier and Papanicolaou 2008	Covert	8	Controls	18-75	-	100%
Verb generation Fisher *et al.* 2008	Covert and overt	9	Controls	24-48	-	100%
Letter fluency Fisher *et al.* 2008	Covert and overt	9	Controls	24-48	-	67%

Pirmoradi et al Epileptic Discord, 2010

Validated by IAT

Table 1. MEG studies investigating hemispheric language lateralization.

Language comprehension

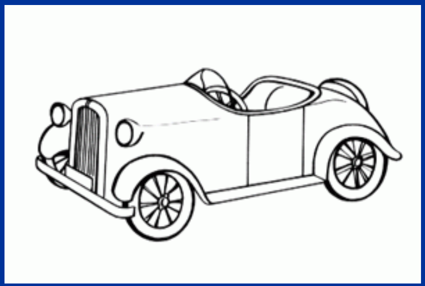
Task Reference	Stimuli used	# of participants	Type of participants	Age	Concordance with IAT	Concordance with handedness	
Passive listening Szymanski *et al.* 2001	Vowels	15	Patients	14-56	71%	71%	**Single Dipoles**
Passive listening Kim and Chung 2008	Words	17	Patients	17-52	71%-94%	-	**Current Distribution**
Word recognition Breier *et al.* 1999a	Words (visual-auditory)	26	Patients	8-56	92%	-	**Single Dipoles**
Word recognition Breier *et al.* 2001	Words (visual-auditory)	19	Patients	8-18	87%	-	**Single Dipoles**
Word recognition Papanicolaou *et al.* 2004	Words (auditory)	100	Patients	8-56	87%	-	**Single Dipoles**
Word recognition Maestú *et al.* 2002	Words (auditory)	8	Patients	m = 25	87.5%	-	**Single Dipoles**
Word recognition Merrifield *et al.* 2007	Words (auditory)	16	Patients	m = 31.5	90%	-	**Single Dipoles**
Word recognition Doss *et al.* 2009	Words (auditory)	35	Patients	m = 29.6	86%	-	**Single Dipoles**
Semantic judgment McDonald *et al.* 2009	Words (visually)	8	Patients	25-53	100%	-	**dSPM/ Current Distribution**
Reading Hirata *et al.* 2009	Words	60	Patients	-	95%	-	**SAM Beamformer**

Language production

Task Reference	Articulation	# of participants	Type of participants	Age	Concordance with IAT	Concordance with handedness	
Picture naming Bowyer *et al.* 2005b	Covert	27	Patients	10-59	96%	-	**Current distribution**
Verb generation Bowyer *et al.* 2005b	Covert	27	Patients	10-59	82%	-	**Current distribution**

Activation tasks to measure:

Receptive to Expressive
Cognition to Production

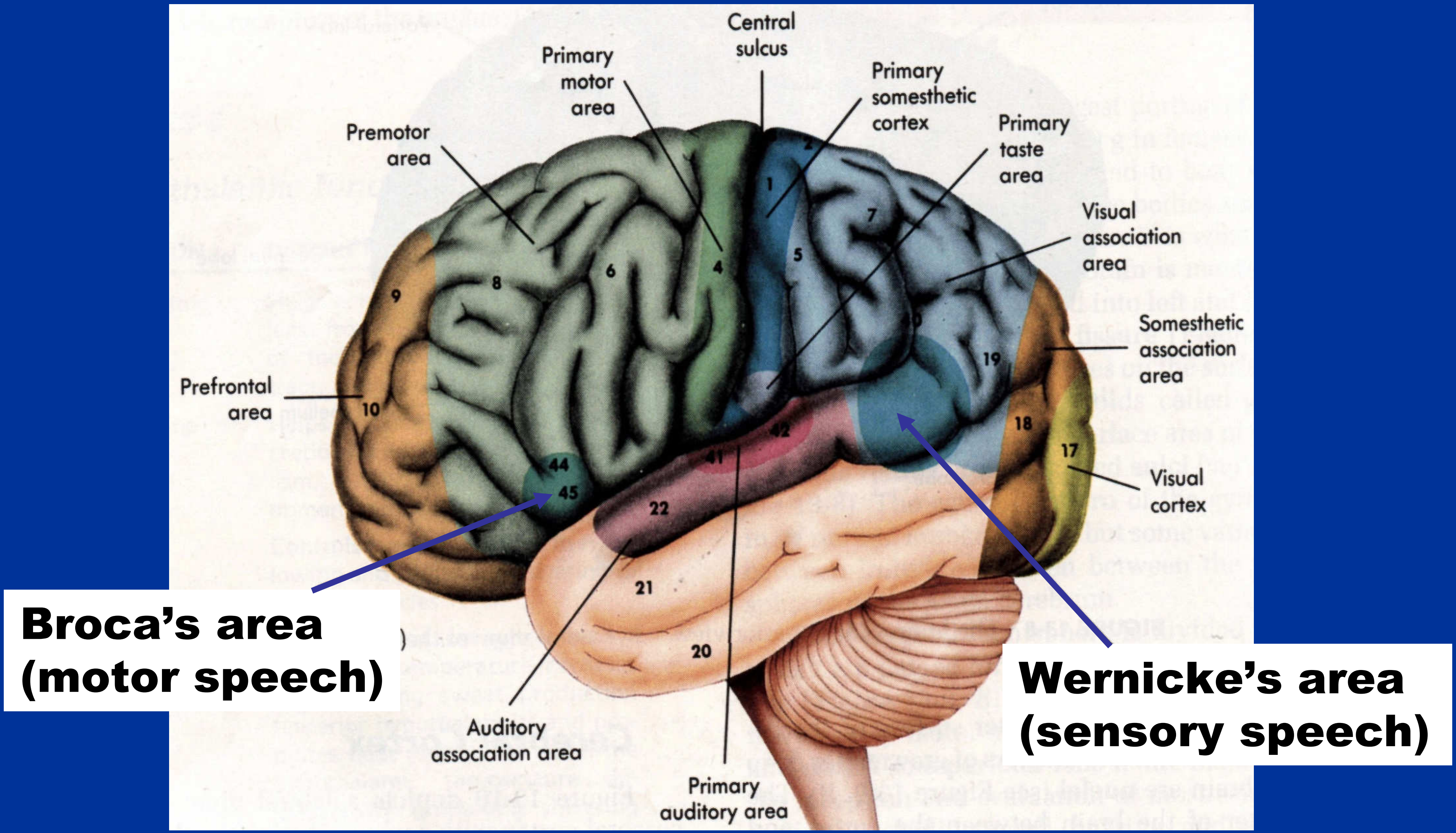


-Visual Picture naming
-Visual or Auditory Verb Generation

SPOON

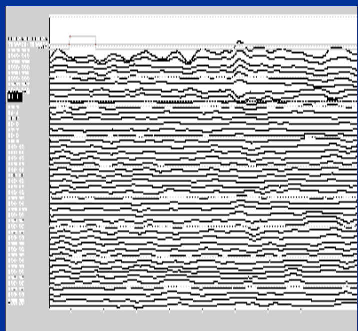
Receptive/Cognition ONLY
-Auditory Continuous recognition of Words
-Auditory listening to words

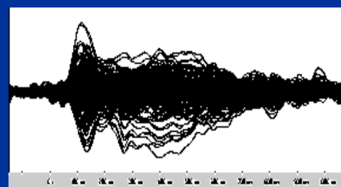
Localization of Language Areas



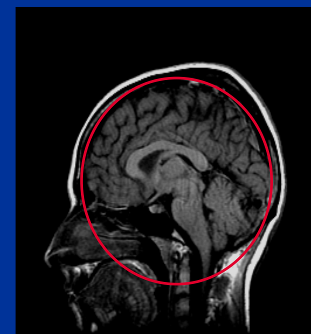
Activation task, modeling approach and ROIs...

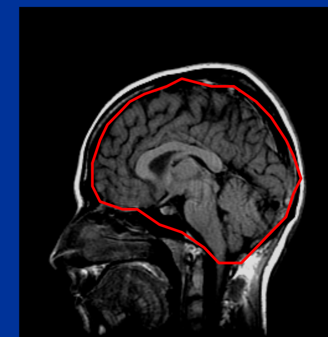
Data acquisition and preprocessing



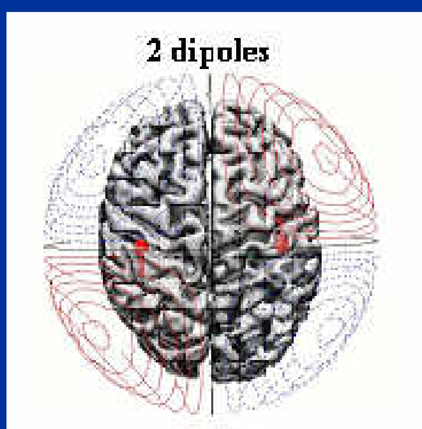


Head Modeling



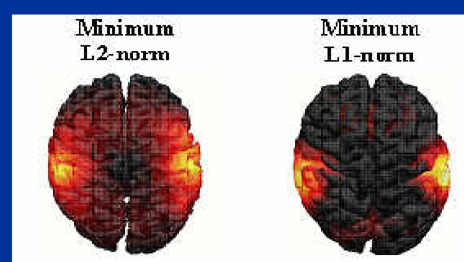


Least Squares Dipole fit

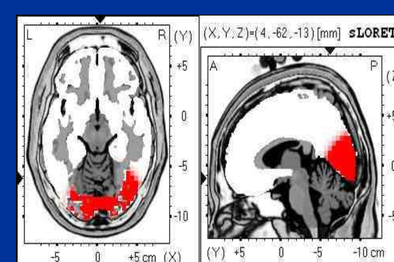


INVERSE SOLUTION

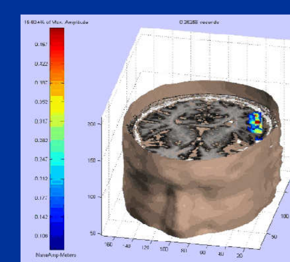
Current Density Reconstructions



Minimum Norm



sLORETA



MR-FOCUSS

In 2008 - 15 of the 21 USA MEG centers only use ECD analysis techniques

Bagic, J Clinical Neurophy 2011

Courtesy of Eduardo M Castillo, PhD

Initial Inspection of Early latency

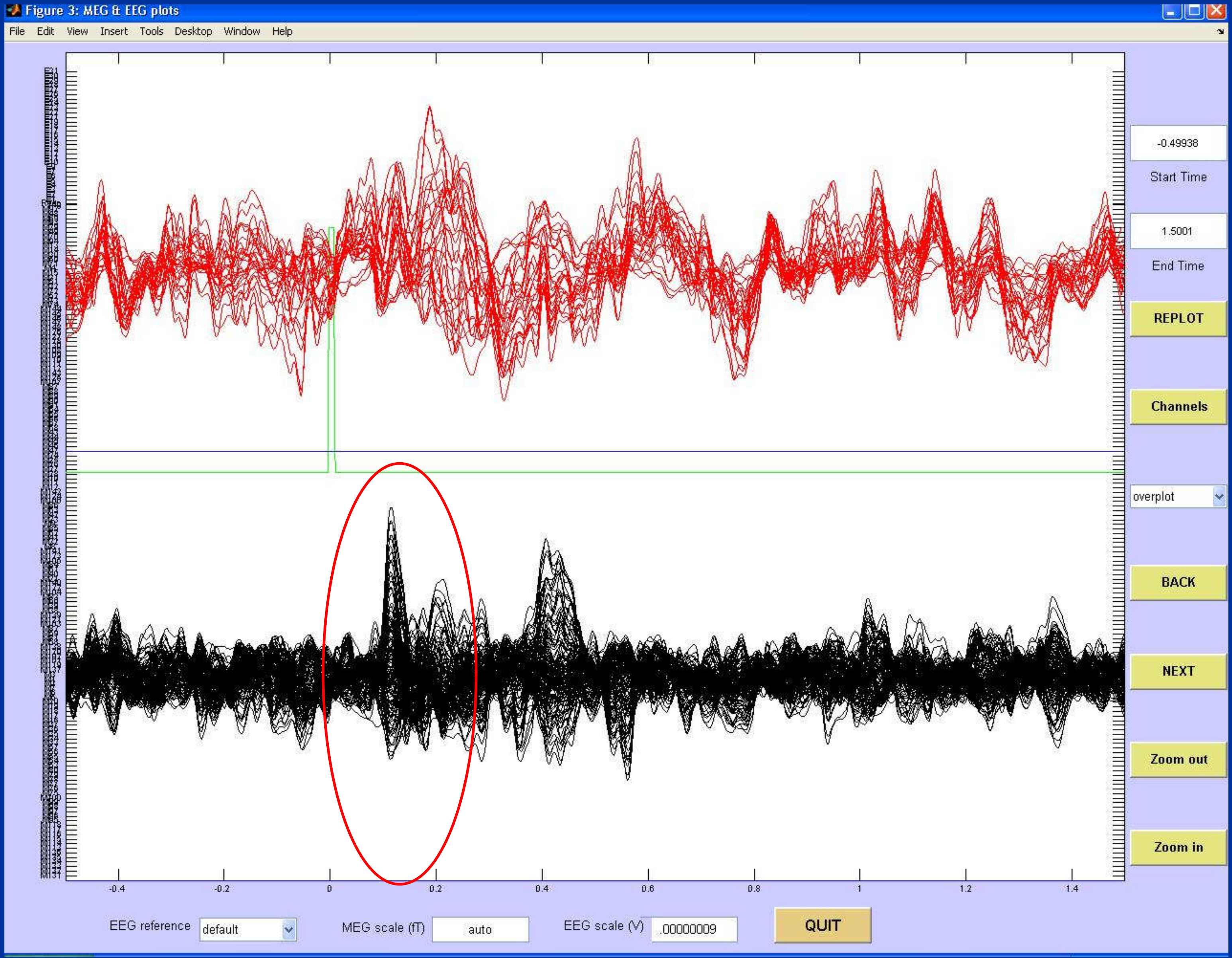
- Initial peaks (<150 ms) basic sensory processing
- It is important to evaluate the integrity of basic auditory/visual
- Early evoked fields can be used for quality control
  - Is the response clear (above the noise) and symmetrical
  - Is latency ~100 ms
  - Is location auditory cortex if stimuli are sounds
  - Is location visual cortex if stimuli are images

Verb Generation Task

31 EEG

Trigger

148 MEG



Patient with Epilepsy

Initial Inspection of Long latency

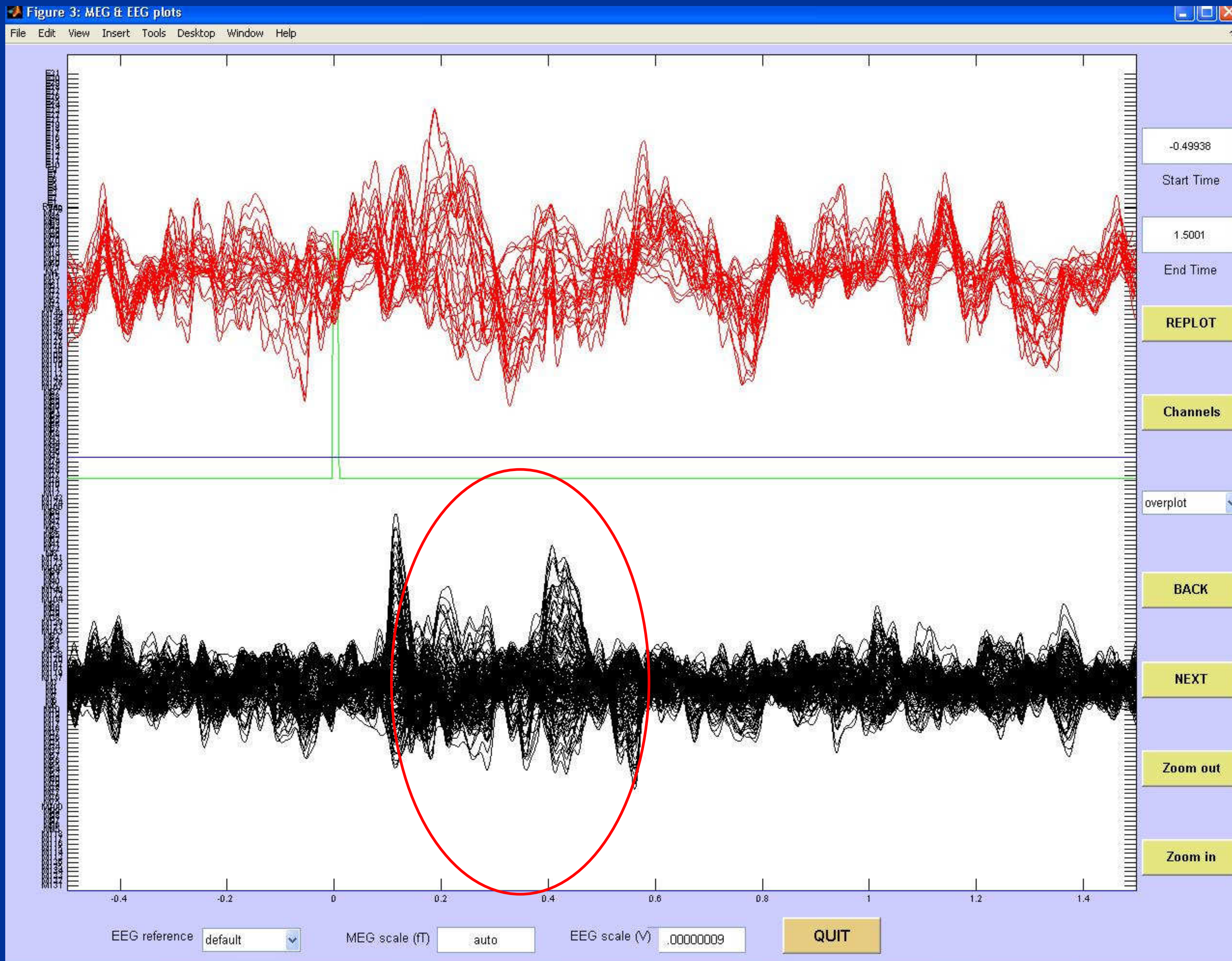
- Long latency responses (> 200 ms after stimuli onset) evoked by language stimulation
- Peaks will not be as clear or symmetrical as the early latencies as the Long latency contains activity arising from multiple language areas, independent of the method of stimulation, auditory or visual
- When subjects attend to the task the responses in the MEG waveform may become clearer (NOT sleep deprived)
- The signals reflect varying contributions from multiple language areas including:
  - Wernicke's language area (superior temporal gyrus Brodmann's area (BA 22), the angular gyrus (BA 39), the supramarginal gyrus (BA 40)
  - Broca's language area (pars opercularis and pars triangularis of the inferior frontal gyrus (BA 44 and 45).
- Different tasks change which regions dominate the evoked responses
- Regardless of the modality of stimulation and subtle details of the stimulation paradigms, linguistic stimuli evoke a response which normally has several peaks between 200-500 ms but may extend to 750 ms or beyond.

Verb Generation Task

31
EEG

Trigger

148
MEG



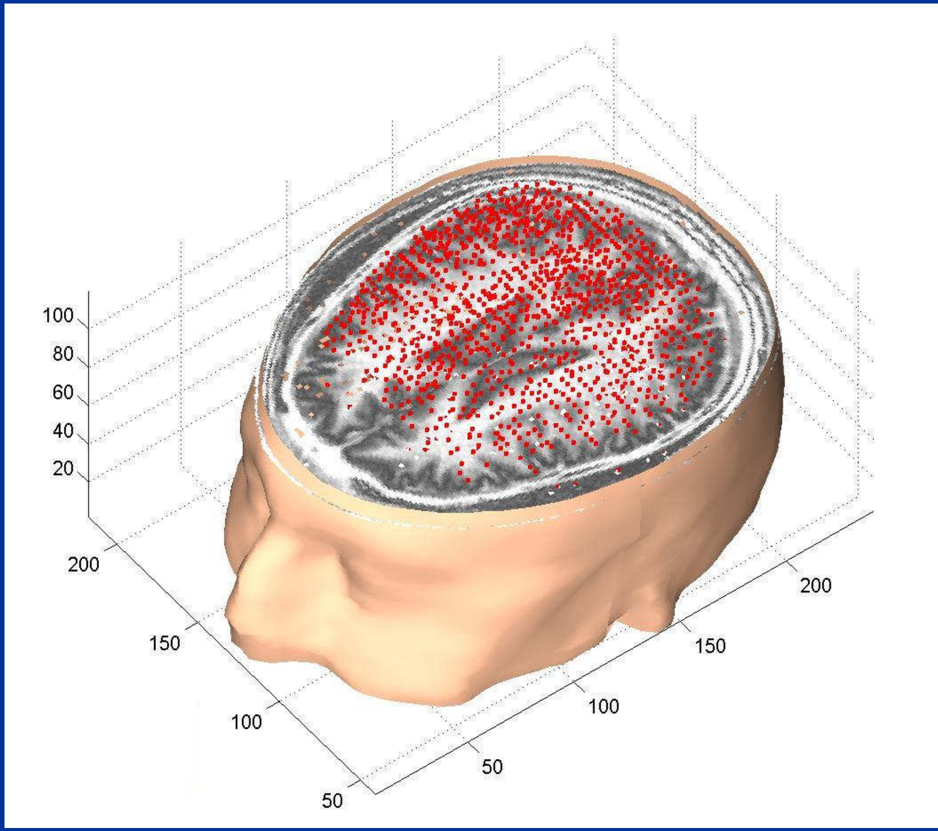
Patient with Epilepsy

MR-FOCUSS/Minimum Norm

- A non-linear current density imaging technique
- Images extended and compact sources of neuronal activity
- Incorporate a wavelet basis to obtain a multi-resolution description of the cortical source structure
- Performs focal changes of the source structure amplitudes for enhanced imaging of multiple simultaneously active compact sources
- For statistical robustness, ~20 solutions averaged to create images
- Relatively insensitive to noise
- Useful for studying the sequence of interhemispheric neuronal activity
- Can study time evolution of sources
- Available at: http://www.megimaging.com
- CTF and Neuromag imports are available

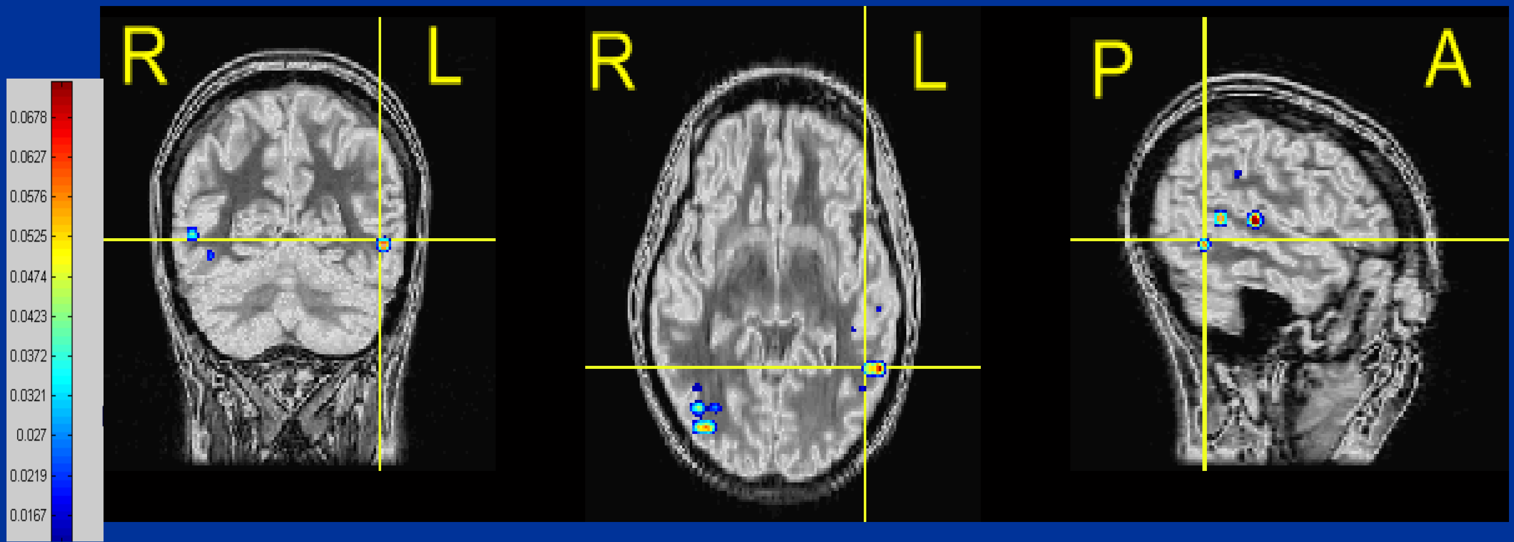
Moran et al, Brain Topography 2005

Cortical Model



- Created from Volumetric MRI Data
- 4000 cortical locations
- Distribution matches cortical gray matter

MEG during Verb Generation 239±31ms



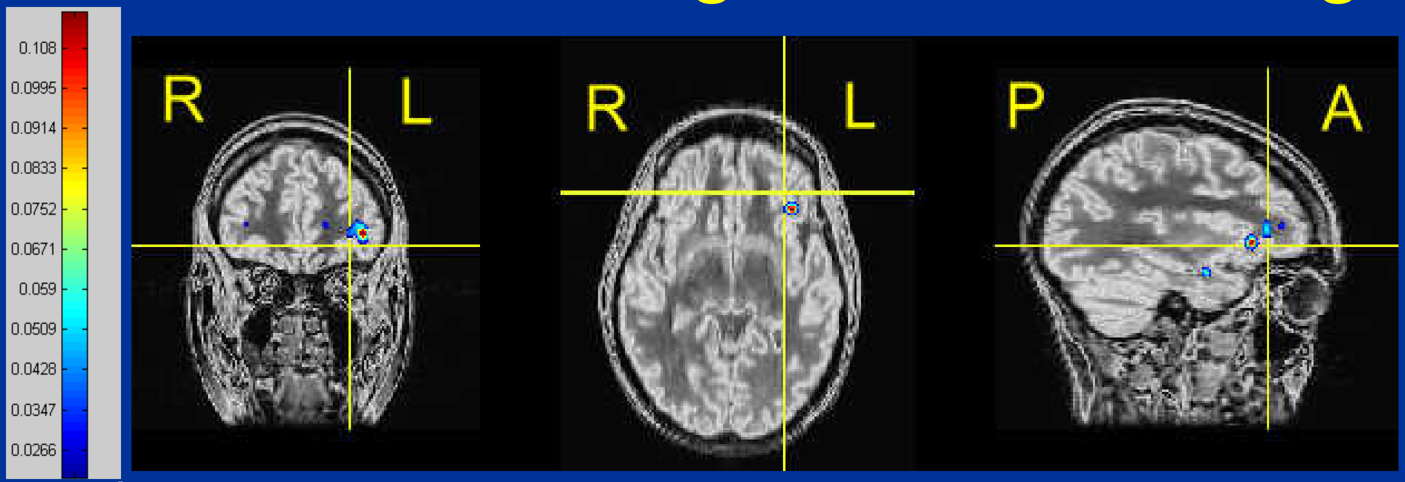
nanoAmp-meters

MEG localization at 255 ms after onset of Visual word. This is the point at which the brain is generating the verb. MR-FOCUSS results scale in nanoAmp-Meters

Wernicke's activation

Bowyer et al 2004

MEG during Picture Naming 436±40ms



nanoAmp-meters

MEG localization at 320 ms after onset of Visual picture. This is the point at which the brain is telling the mouth to say the word. MR-FOCUSS results scale in nanoAmp-Meters

VIDEO **MEG localization of language-specific cortex utilizing MR-FOCUSS**

S.M. Bowyer, PhD; J.E. Moran, PhD; K.M. Mason, REEGT; J.E. Constantinou, MD; B.J. Smith, MD; G.L. Barkley, MD; and N. Tepley, PhD

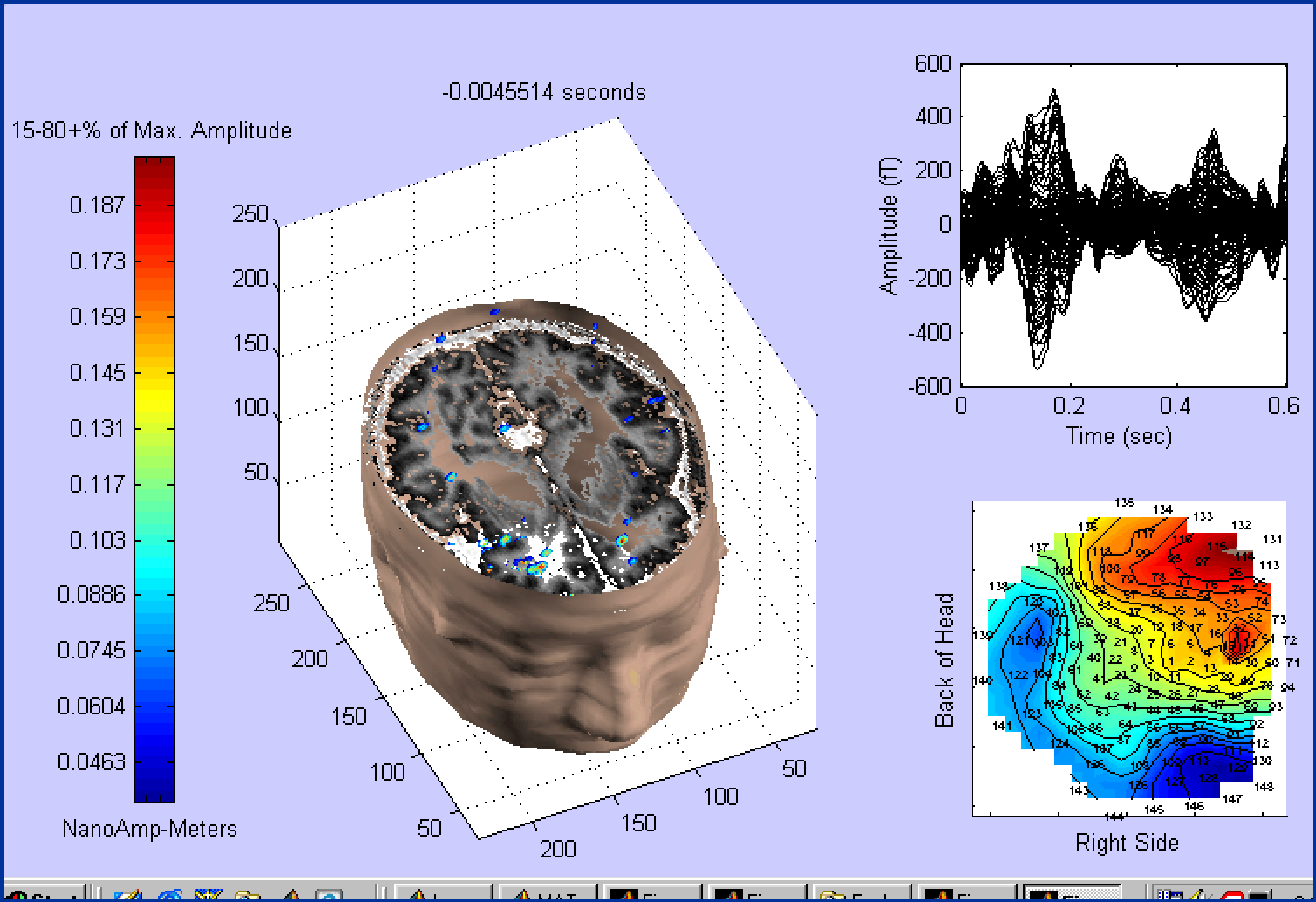
Abstract—Objective: To demonstrate noninvasive localization of cognitive cortical areas involved in language processing with magnetoencephalography (MEG) interpreted by multiresolution FOCUSS (MR-FOCUSS), a current density imaging technique. Method: MEG data were collected during verb-generation and picture-naming tasks from 18 right-handed control subjects and 24 right-handed patients with epilepsy. Results: The averaged epic data from the verb-generation task, analyzed by MR-FOCUSS, showed initial activation in the left supramarginal gyrus, superior temporal gyrus, and angular gyrus at 239 ± 31 ms in all subjects, consistent with other language mapping studies. Average amplitude of underlying cortical sources was ~452 pAm. The averaged epic data from the picture-naming task, analyzed by MR-FOCUSS, showed activation in the left inferior frontal gyrus (IFG) area starting at 436 ± 40 ms in all subjects. Average amplitudes of underlying cortical sources were ~380 pAm. Conclusion: The time course of neuronal language processing can be imaged noninvasively with millisecond resolution by magnetoencephalography using the multiresolution FOCUSS technique.

Broca's activation

NEUROLOGY 2004;62:2247–2255

Time Evolution of Language Processing

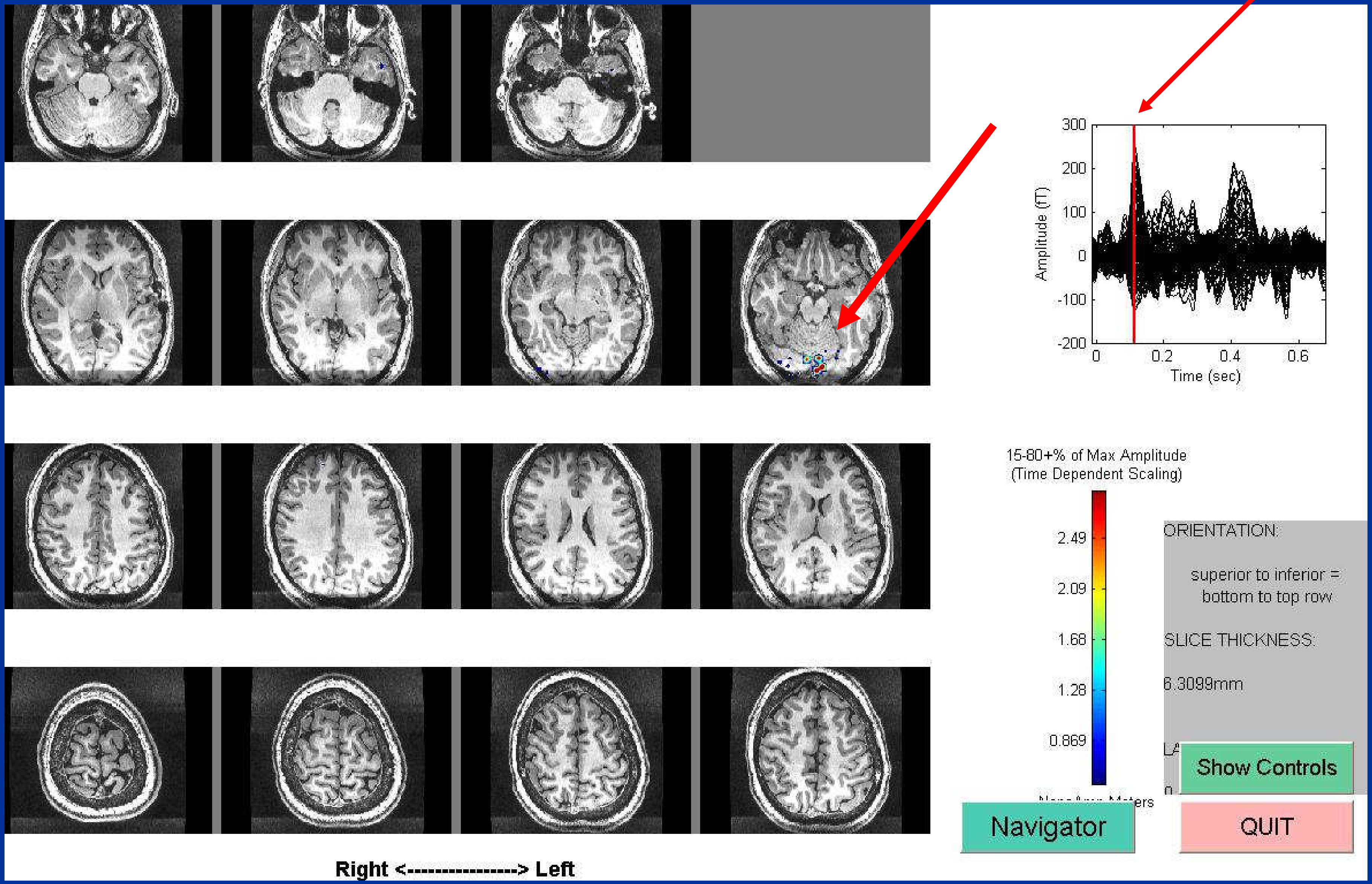
Normal Reading Subject during: Picture Naming



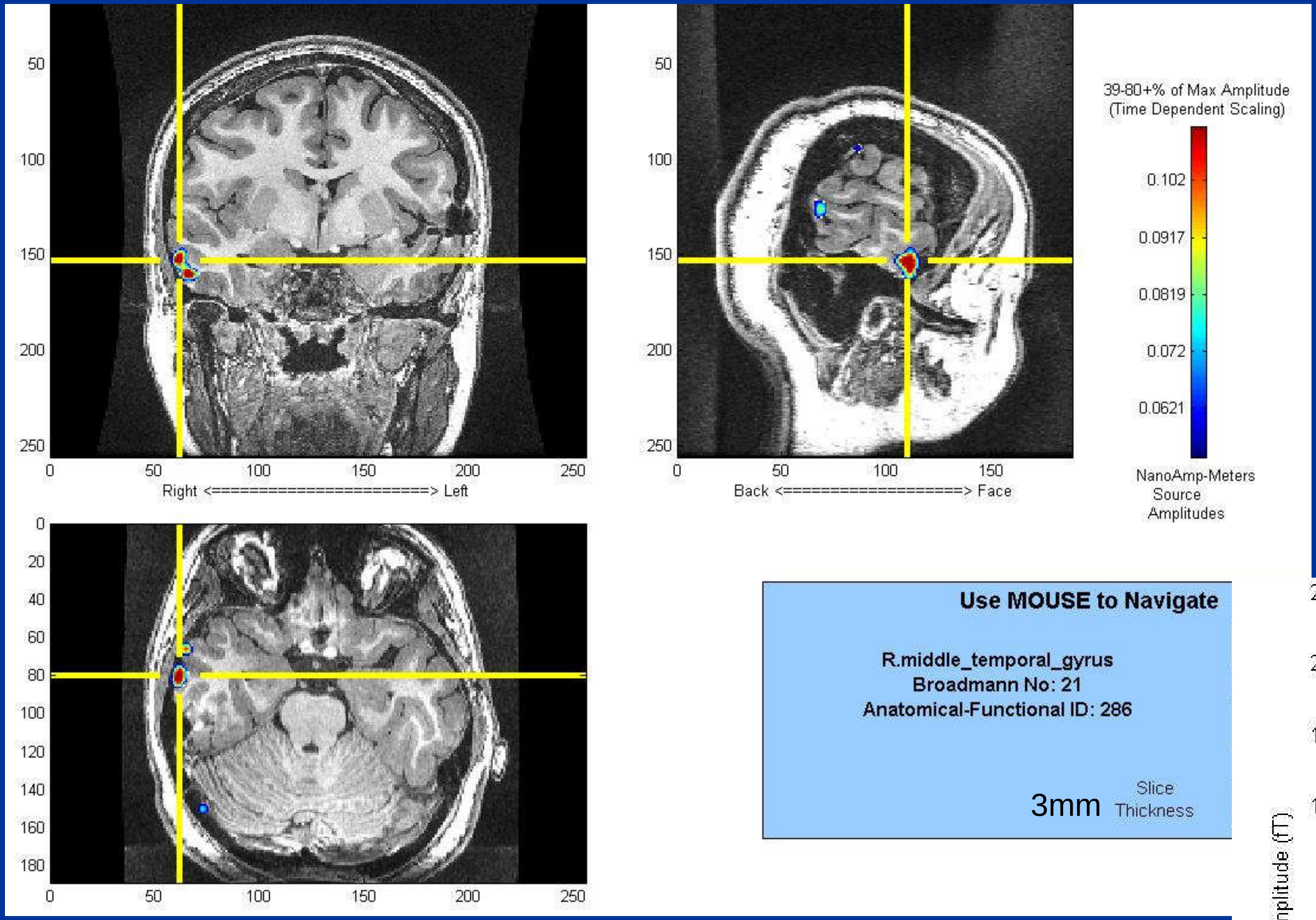
Bowyer et al 2004 Neurology

Visual peak

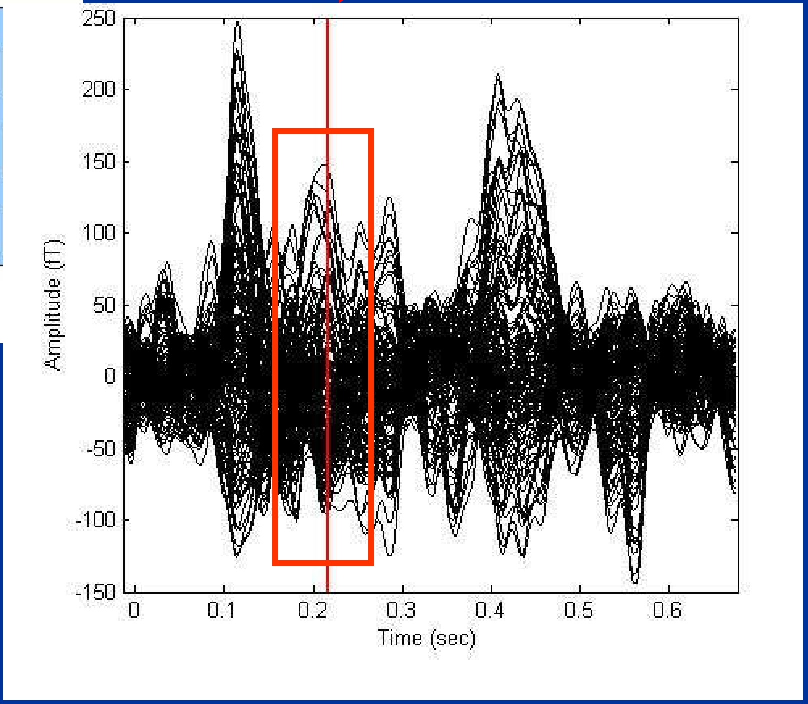
Latency 112ms



Wernicke's activation peak

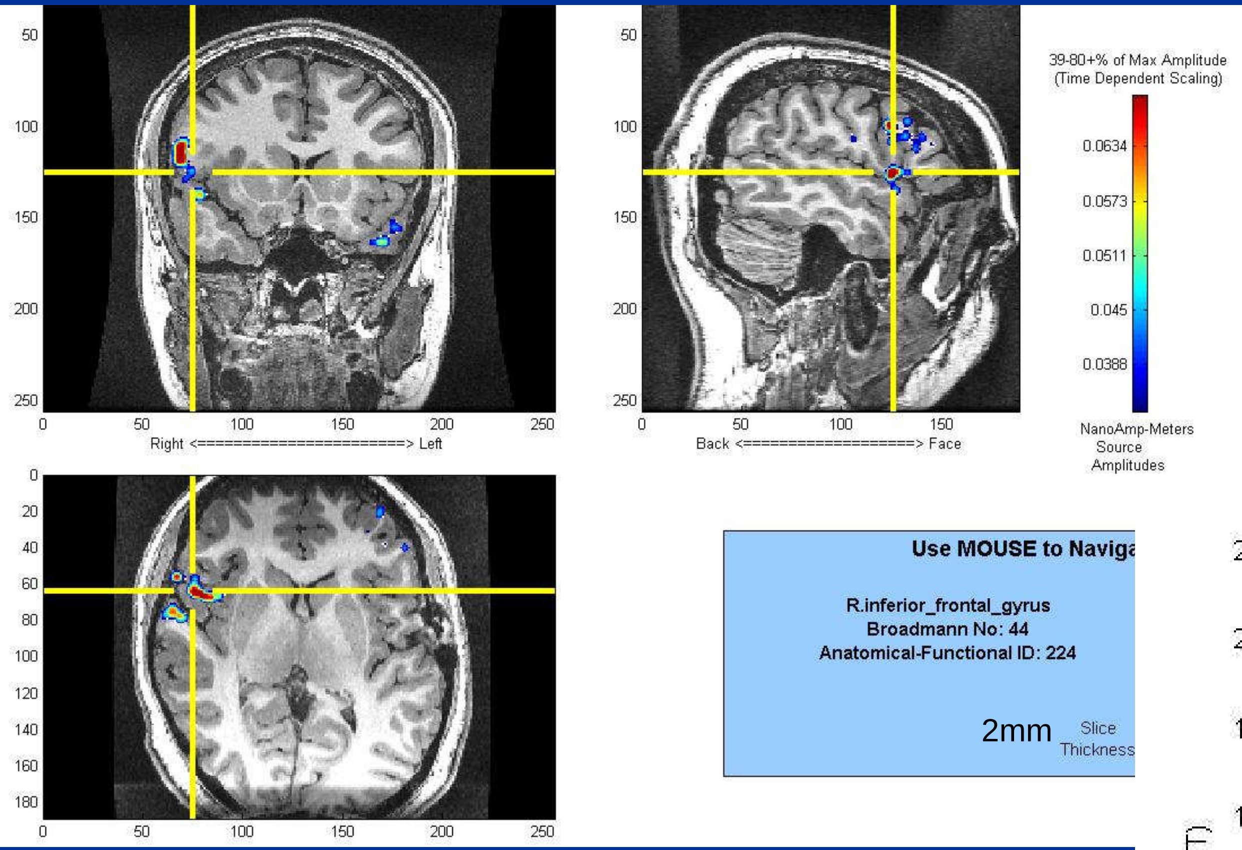


Latency 216ms

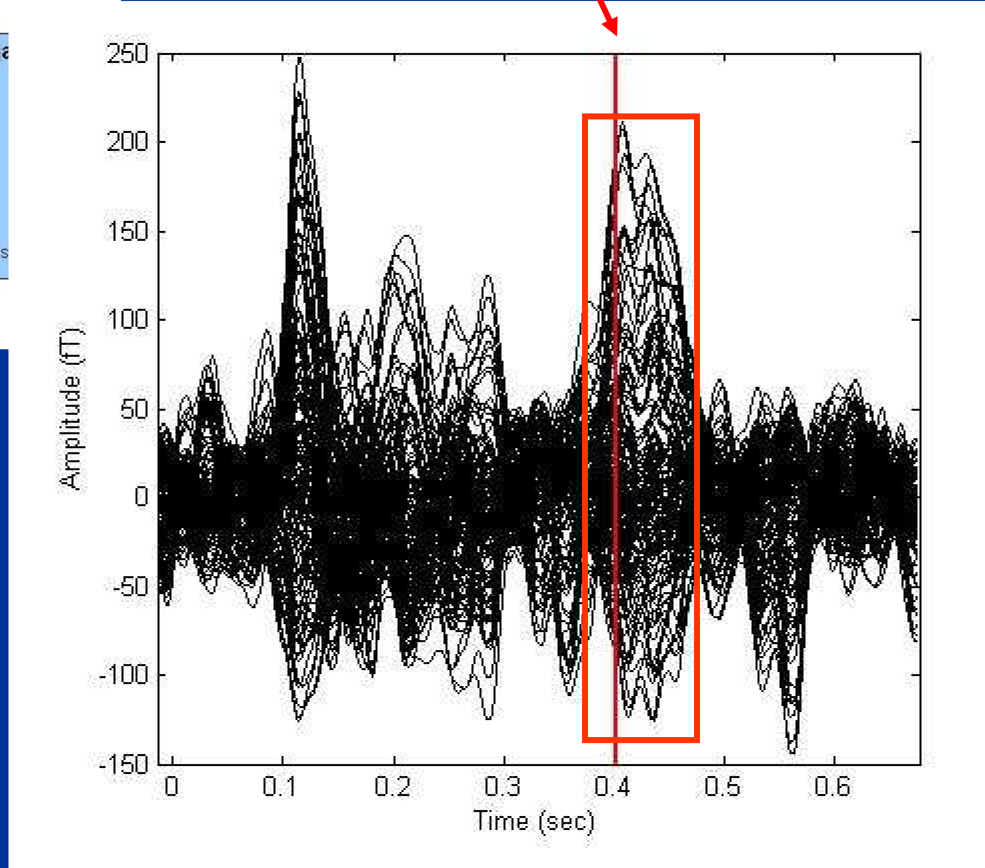


Laterality index = +17
Right lateralized

Broca's activation peak

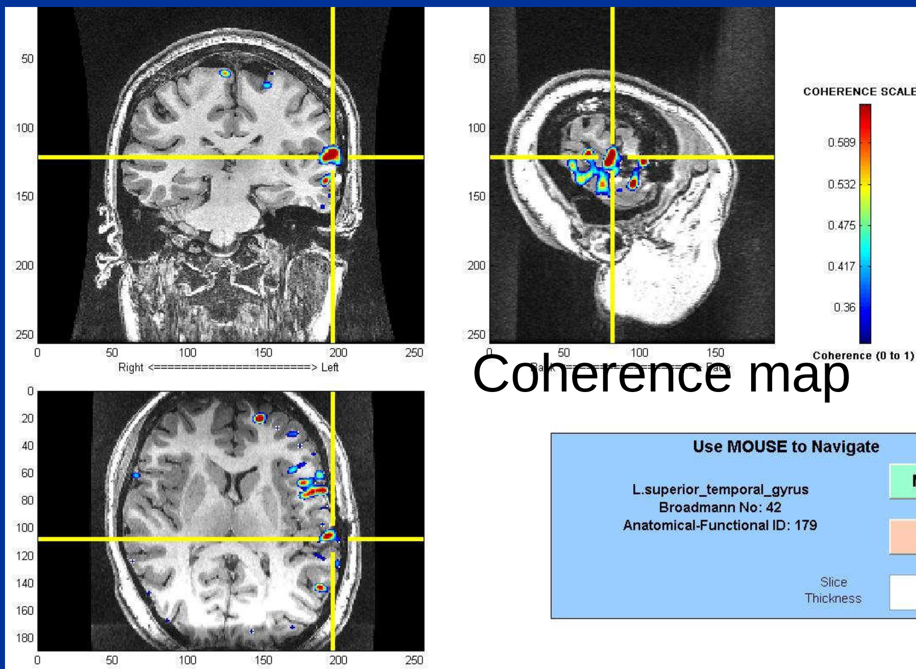


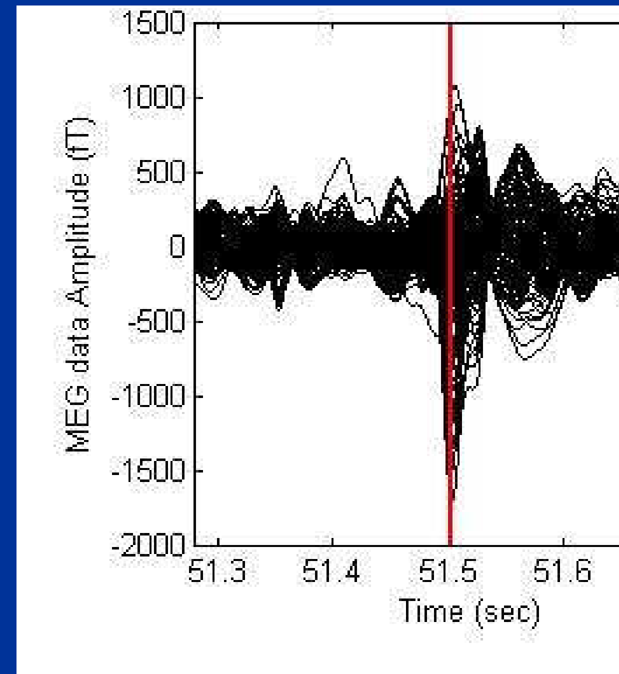
Latency 401ms

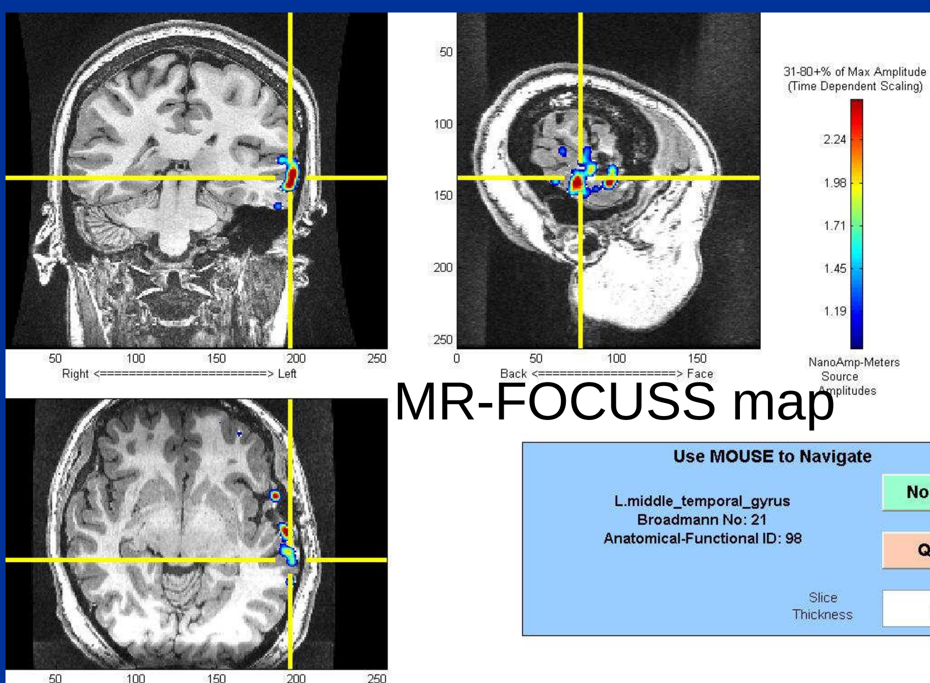


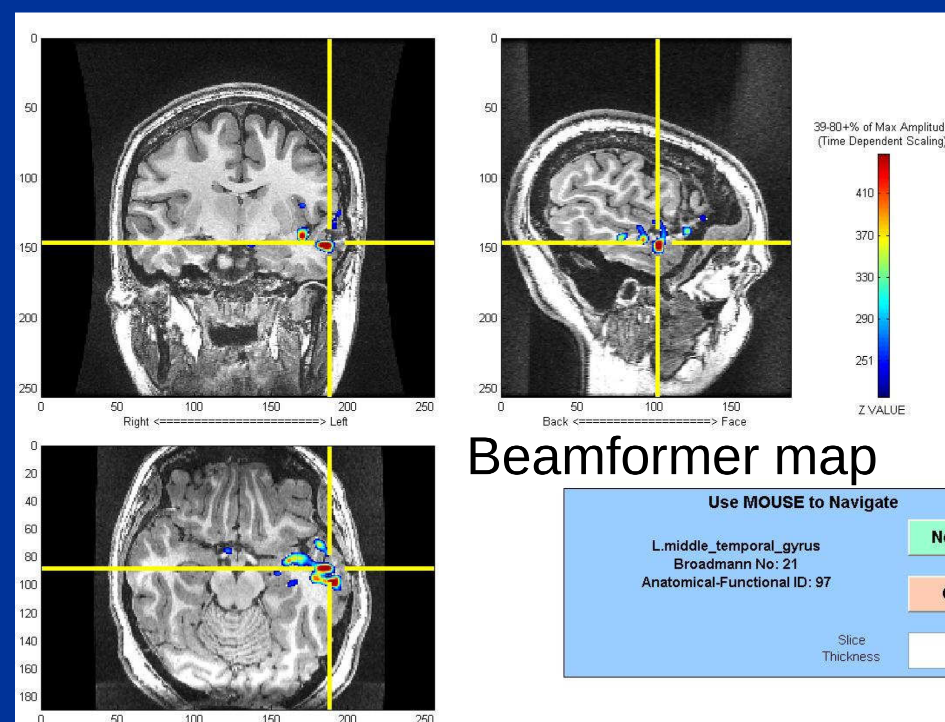
Laterality index = +32
Right lateralized

Epilepsy mapping





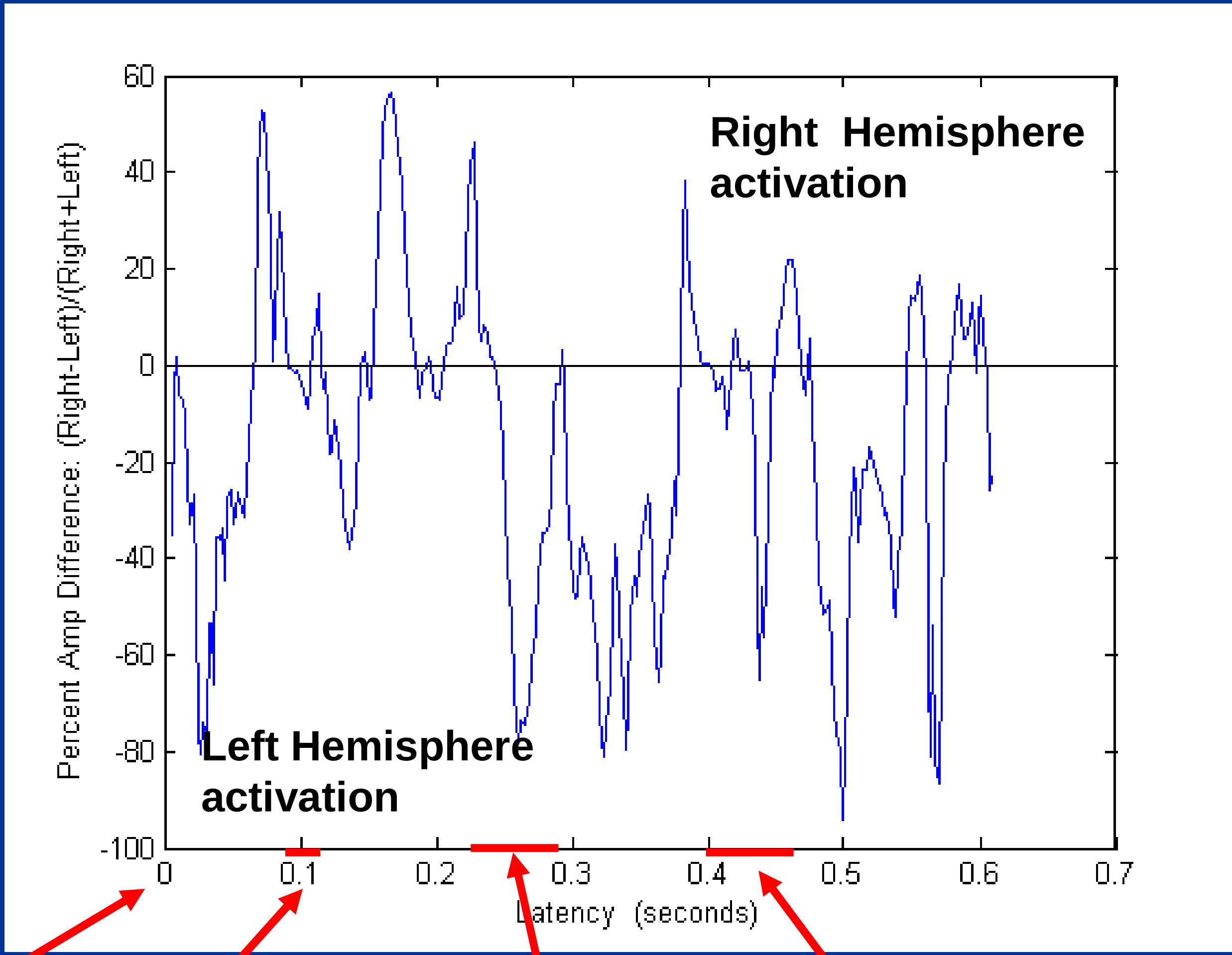




Language Laterality

Picture naming task found closest concurrence to WADA results (IAP) when compared to evoked brain activity seen between 396-460 ms

In 23 out of 24 epilepsy patients with a successful IAP, the Index for Broca's activation were in agreement with the results of the WADA (96% accuracy).



Stimuli onset

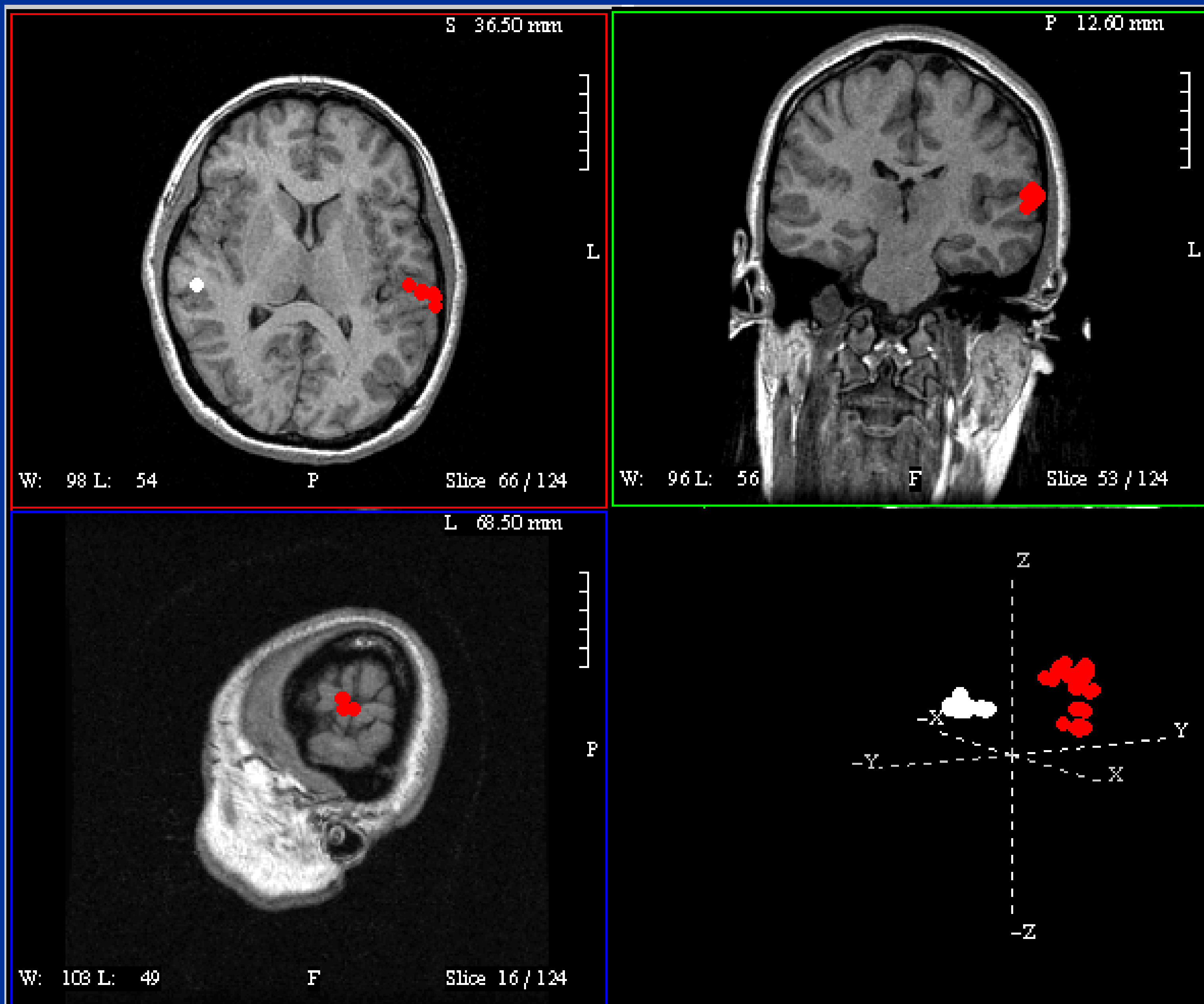
Visual processing

Comprehension (Wernick's) 230-290 ms

Motor speech (Broca's) 396-460ms

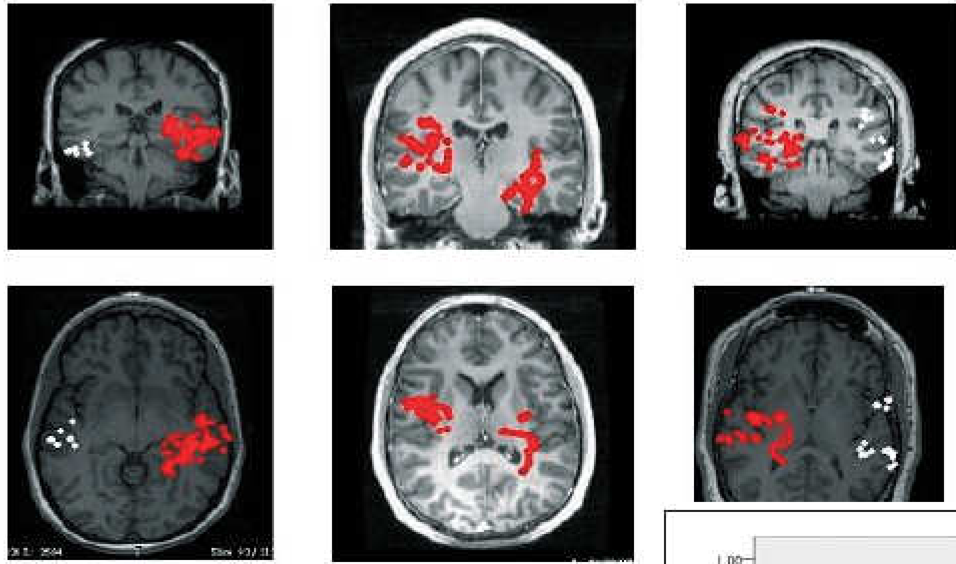
Bowyer et al 2005 Epilepsy & Behavior

Language Dipole Maps



Courtesy of Eduardo M Castillo, PhD

Figure 1.
Typical magnetoencephalography (MEG)-activation profiles *for three cases.* These figures represent composite MEG receptive language-activation sites using the word-recognition task and merged onto a central slice from 3Tesla magnetic resonance imaging (MRI). AI, asymmetry index.
Epilepsia © ILAE



The time windows for fitting the ECDs were typically 200–800 ms poststimulus. The word-recognition task consisted of 90 abstract English nouns. Some were presented to the patient prior to beginning the MEG acquisition, and they were instructed to try to remember as many of the words as possible. During each block, the patient was instructed to simply lift his/her index finger when they detected a target word.

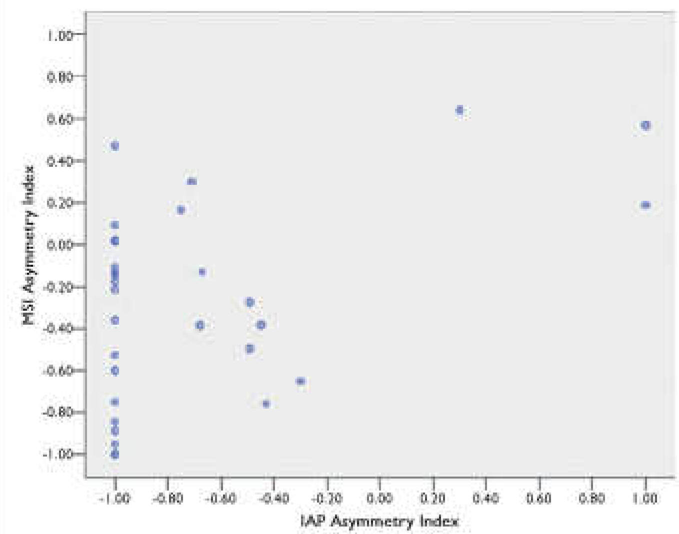


Figure 2.
Scatterplot of magnetic source imaging (MSI) and intracarotid amobarbital procedure (IAP) asymmetry indexes (AIs).
Epilepsia © ILAE

Doss et al 2009 Epilepsia

Classification of patients as bilaterally, left or right dominant for receptive language

MEG Laterality index as follows:

$$\frac{(\#\text{ of perisylvian ECDs in RH} - (\#\text{ of perisylvian ECDs in LH})}{(\#\text{ of perisylvian ECDs in RH}) + (\#\text{ of perisylvian ECDs in LH})}$$

Bilateral | Left | Right

Patient 1 (24 yrs) | Patient 2 (15 yrs): | Patient 3 (34 yrs):

Courtesy of Eduardo M Castillo, PhD

Beam Formers

- A beamformer is a set of spatial filter that linearly integrate information over multiple spatially distributed sensors.

- The basic principle of beamformer design is to allow the neuronal signal of interest to pass through in certain source locations and orientations, called pass-bands, while suppressing noise or unwanted signal in other source locations or orientations, called stop-bands.

- All existing beamformers in the EEG and MEG literature are narrow-passing-band beamformers, in which either the entire brain volume or just the cortical surface is divided into a grid of dipoles, and at each grid node, the beamformer allows signal from that node to pass and suppress signal/noise from other nodes.

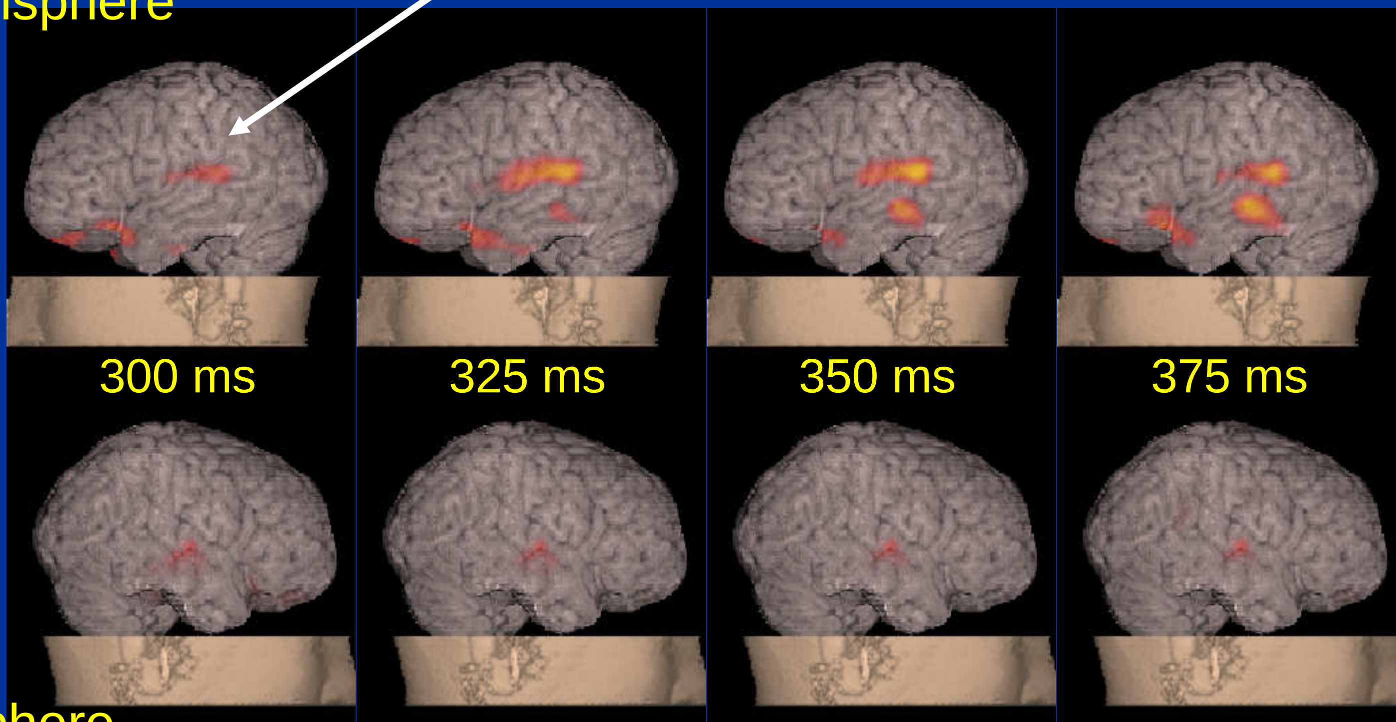
- Beamformers localizes <u>Uncorrelated</u> Brain activity.

- Two Types - Scalar and Vector beamformers

Robinson & Verba, Biomagnetism proceedings,1999

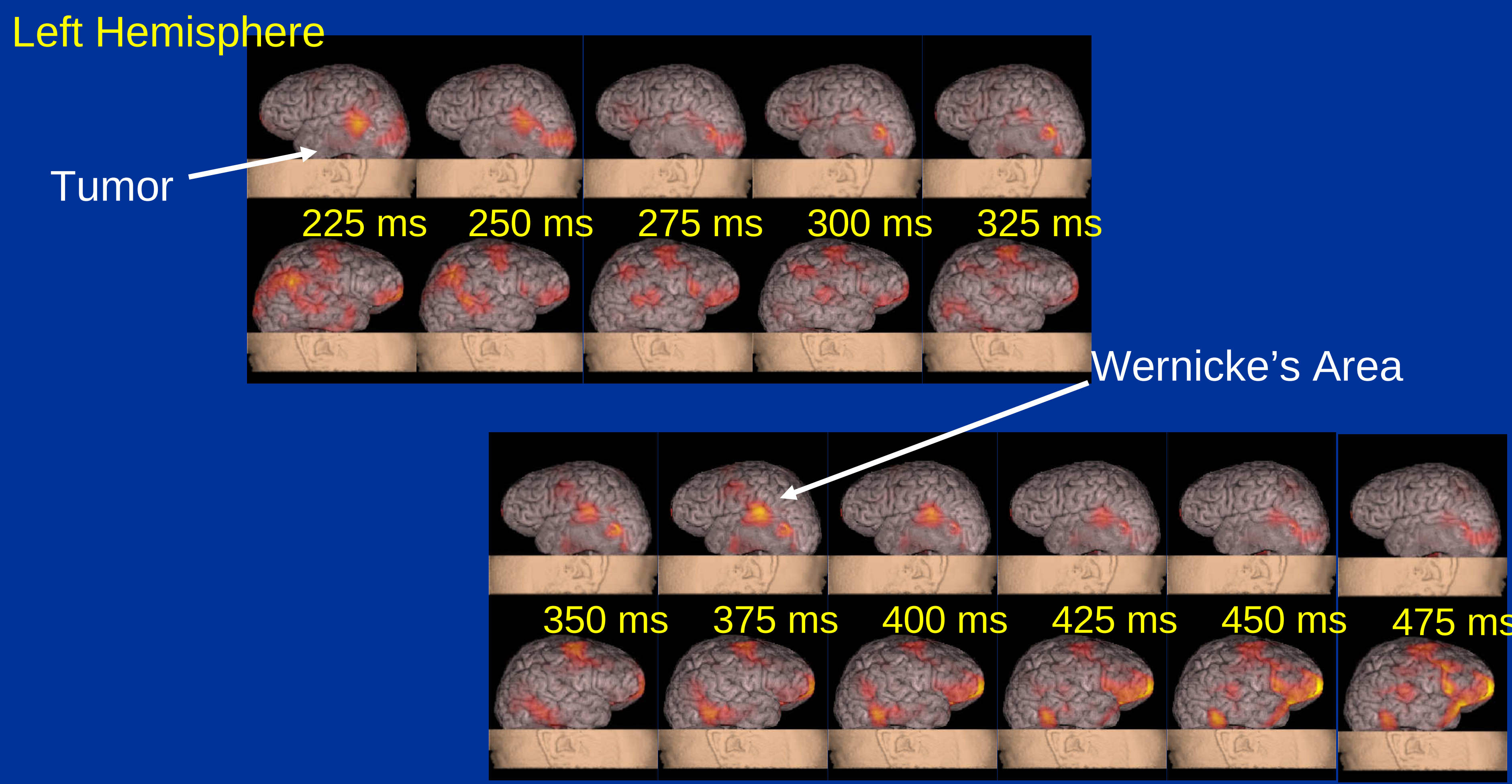
Huang et al, Brain Topography, 2004

Beamformer analysis of Language during passive reading



Passive listening to individual words. Each frame represents event-related activity integrated over a 50 ms time window. The time window was advanced in increments of 25 ms. In the passive listening task, activation can be seen in Wernicke's area, starting at about 300 ms. The language-related activations are seen mainly in the left hemisphere (Scale in pseudo Z-scores). Linearly constrained minimum variance (LCMV) Beamformer

Beamformer analysis of Language during picture naming



For a picture naming task, this tumor patient has a lesion occupying much of the left temporal lobe. Although activation appears in Wernicke’s area, starting at about 350 ms, there is considerable activity that persists in the right hemisphere (Scale in pseudo Z-scores). Linearly constrained minimum variance (LCMV) Beamformer

Coherence imaging in SOURCE space Extracting real-time FUNCTIONAL neural networks from MEG data

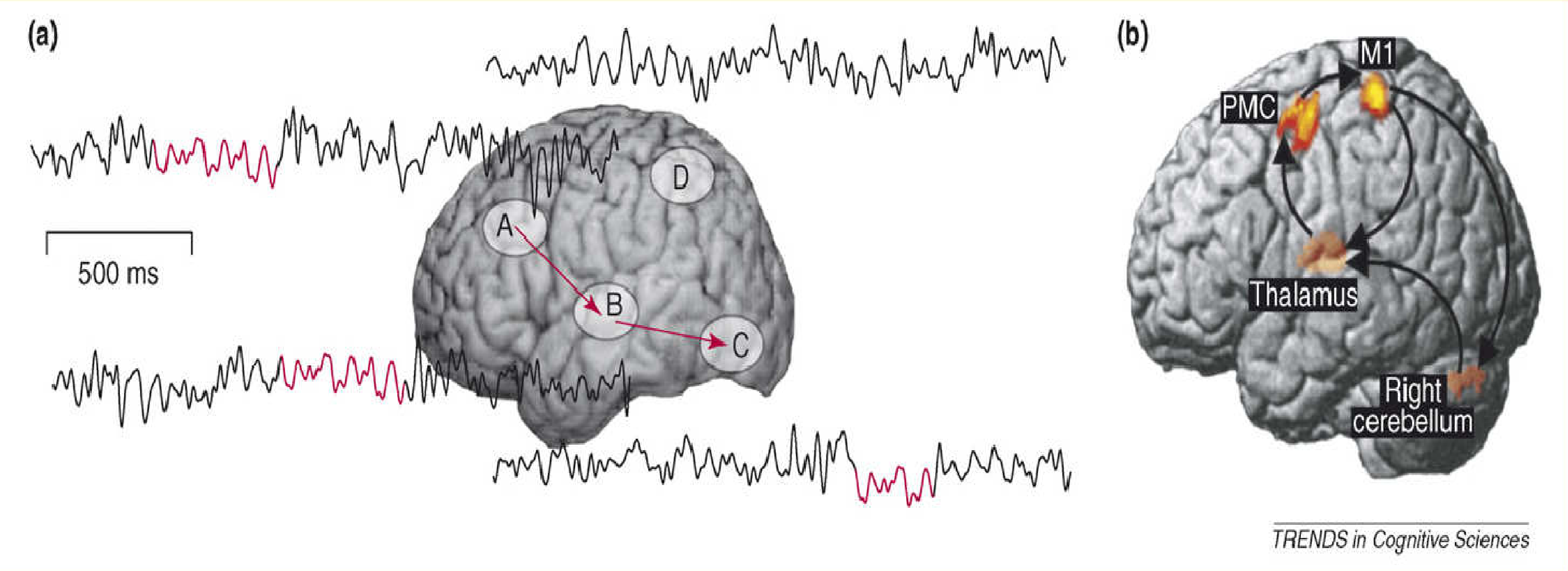
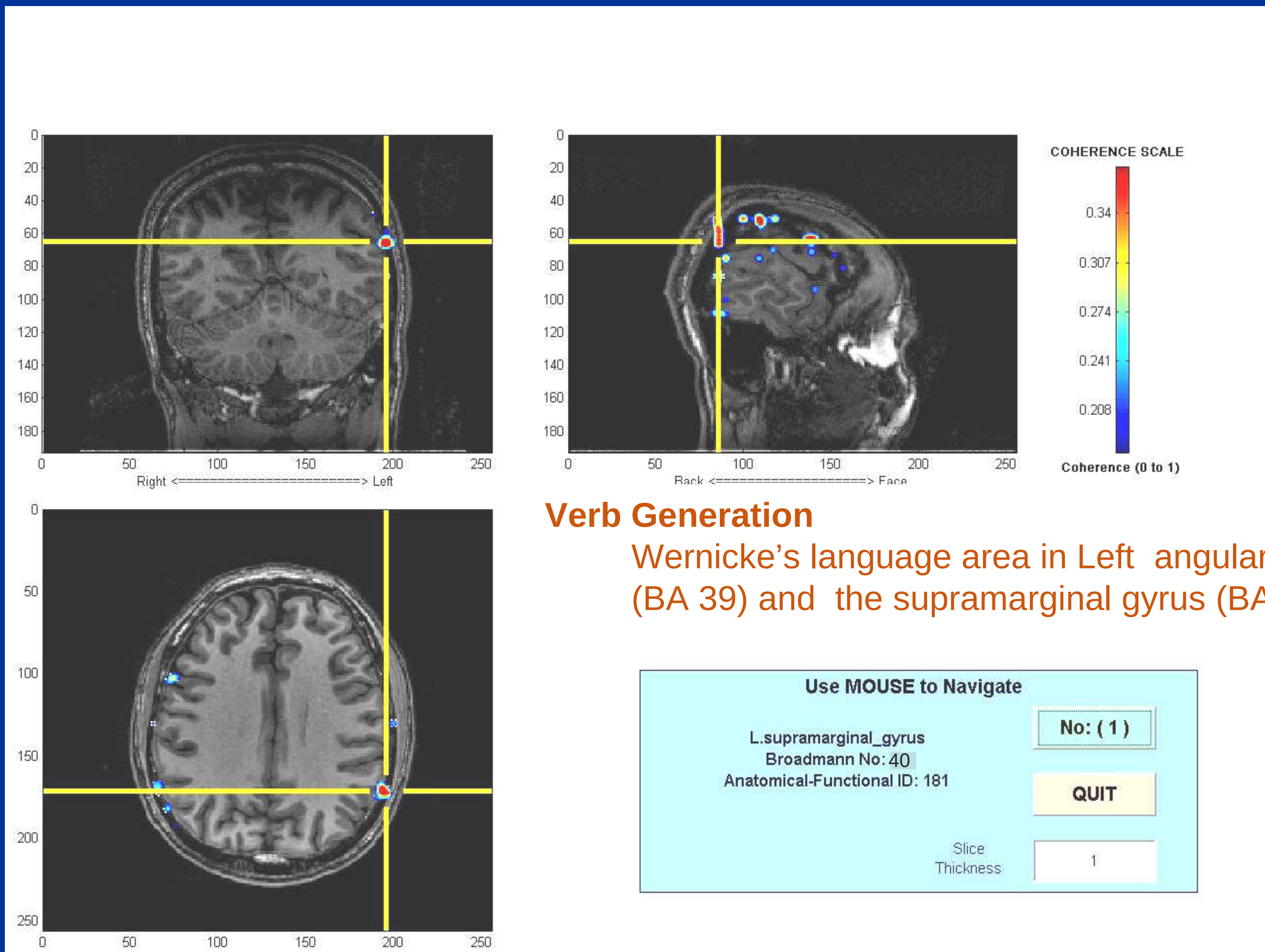


Figure I. Extracting long-range neural connectivity from MEG data. **(a)** Simplified presentation of the basic idea. Curves depict time courses of activity in four brain areas (gray ellipses). If neuronal populations in these areas are functionally connected, one would expect to detect similar time courses of activation in the different areas (red segments), at least occasionally. Time shifts between similar stretches of activity could be interpreted as flow of information. In this example, one could argue that there is a drive from area A to B and a weaker drive further to area C. Delays between the repeated segments are exaggerated. **(b)** Neural network during slow movements of the right index finger. Here, EMG from the moving finger provided a meaningful, nonbrain reference signal. EMG–MEG coherence led to the contralateral motor cortex, which served as a reference area for identification of the network within the brain. Abbreviations: M1, primary motor cortex; PMC, premotor cortex. Reproduced, with permission, from Ref. [48].

Gross J, et al Proc Natl, Acad Sci. 2002

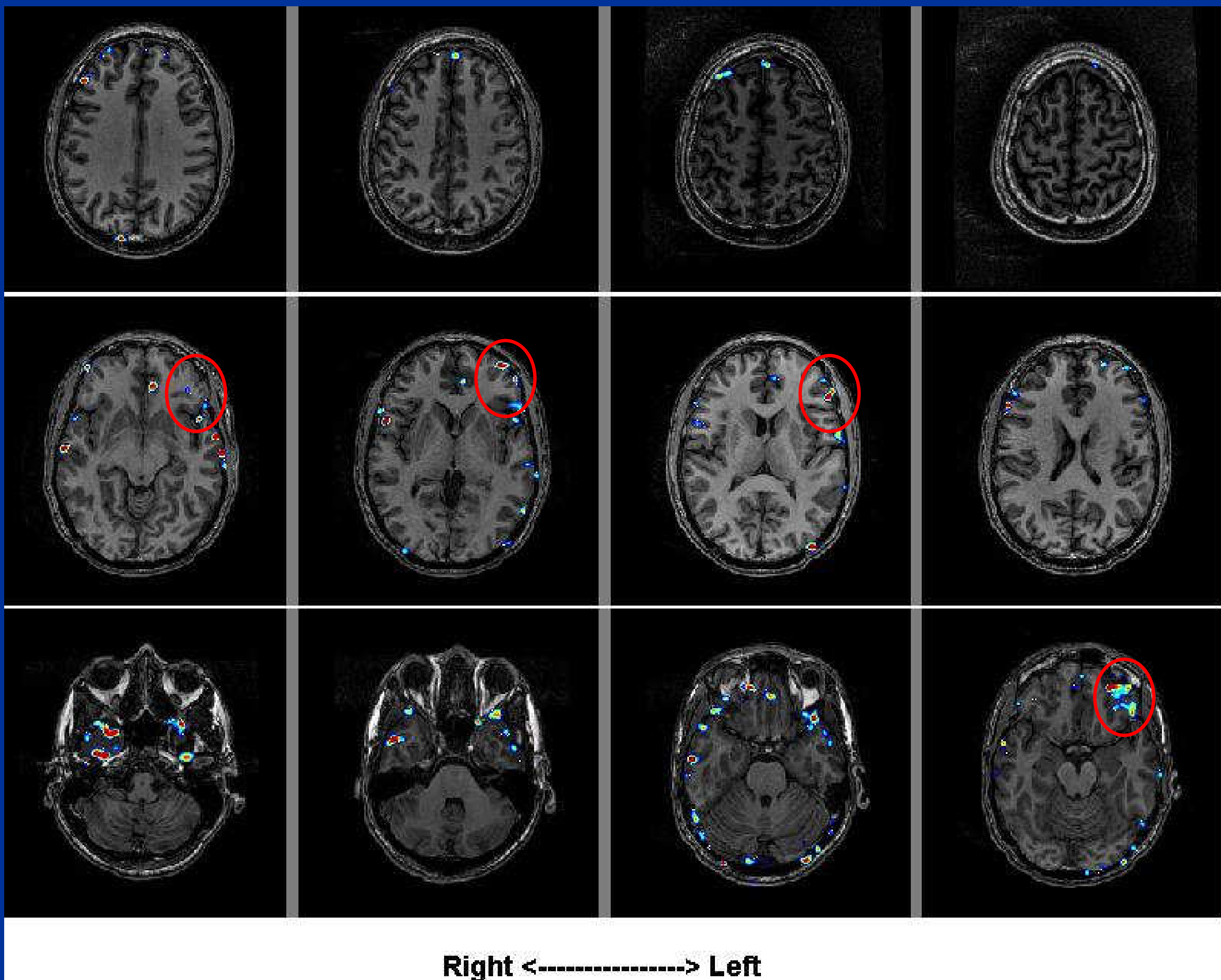
Coherence for language localization in Normal Readers



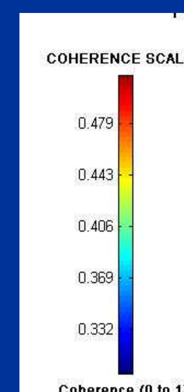
Verb Generation

Wernicke's language area in Left angular gyrus (BA 39) and the supramarginal gyrus (BA 40).

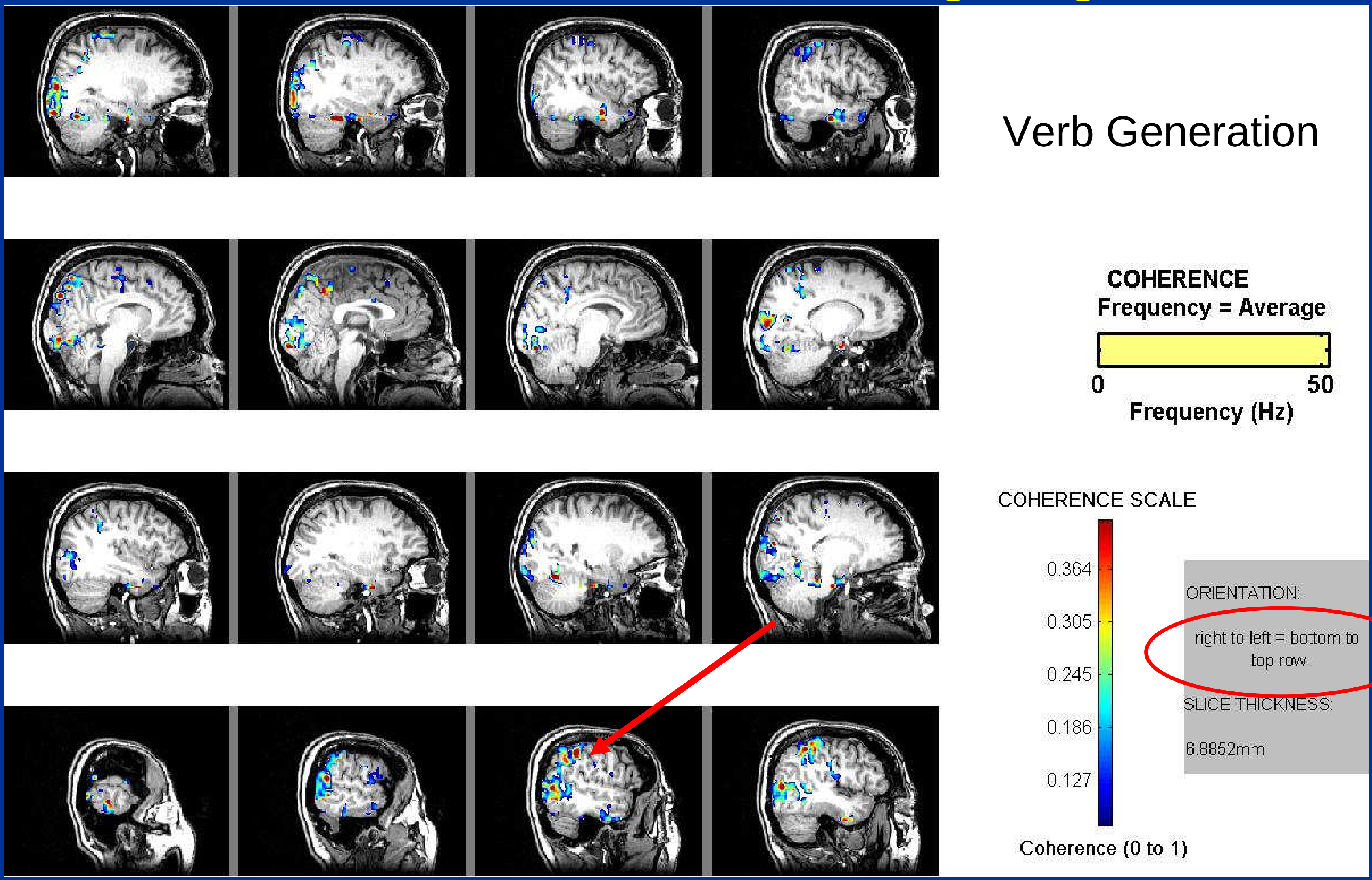
Coherence for language localization in Normal Readers



Picture Naming
Broca's language area
Left Inferior Frontal gyrus
BA 44 and 45

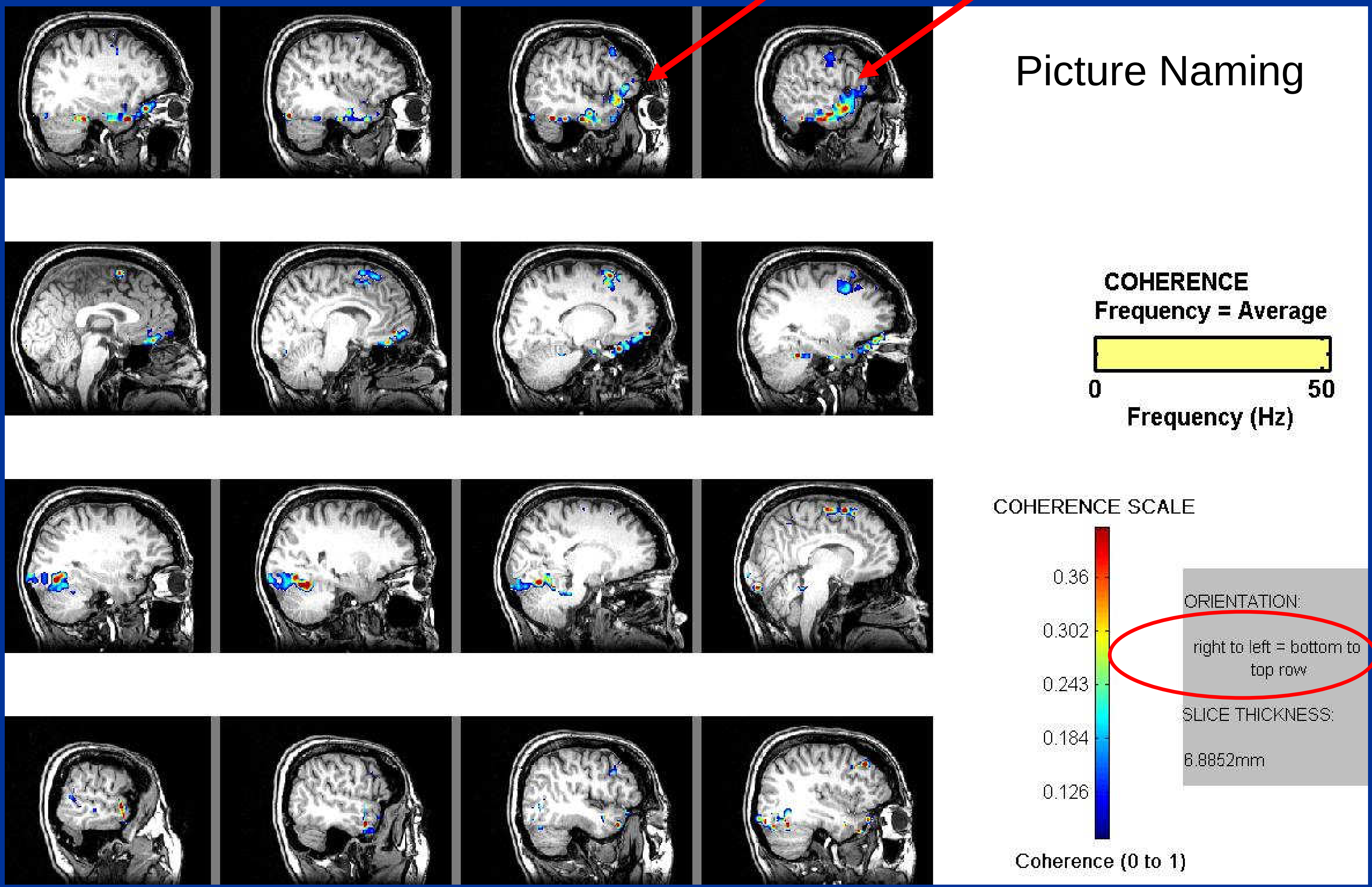


Wernicke's in Epilepsy patient Coherence imaging



Wernicke's language area is in the Right AG and SMG

Broca's in Epilepsy patient
Coherence imaging



Broca's language area is in the Left IFG and STG

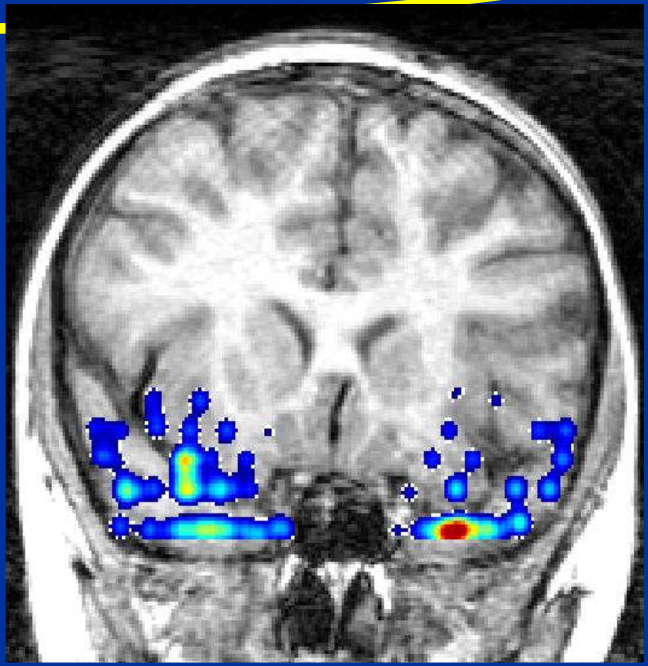
Henry Ford Hospital

MEG Language Summary

- MEG provides millimeter spatial resolution **PLUS** millisecond temporal resolution needed to understand language processing steps.
- MEG can provide information on the location, latency of cortical processing.
- **LOCATION** of Visual/Auditory, Wernicke's and Broca's areas activations.
- **LATERALITY index** of which hemisphere is most active.
- Utilizing Advance imaging techniques beyond ECD provides an expanded view of the regions of the brain that are **concurrently** involved in language processing.

What can Epileptologists expect from MEG for

Assessment of Language
&
Resting State Coherence/Connectivity

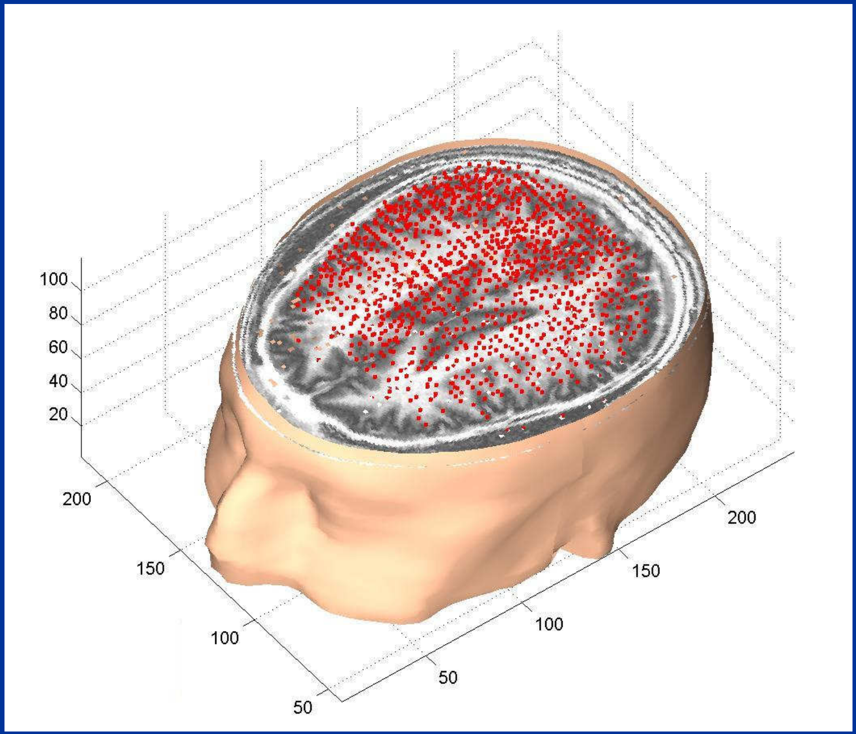


Susan Bowyer Ph.D.
Scientist/Medical Physicist
Department of Neurology
Henry Ford Hospital

www.megimaging.com
drsusan@umich.edu

Extracting real time FUNCTIONAL neural networks from MEG data

- Oscillations or rhythmic activity
- Synchronization of oscillatory activity



Cortical Model

- Created from Volumetric MRI Data
- ~4000 cortical locations
- Distribution matches cortical gray

Coherence

- The analysis of coherence between EEG electrode site and MEG sensors has been performed for many years. However, at best only regional inference of cortical connectivity can be estimated without **first imaging brain activity.**

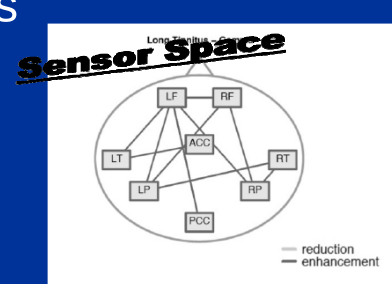
- Measures consistency of phase between cortical sites participating in a neuronal network

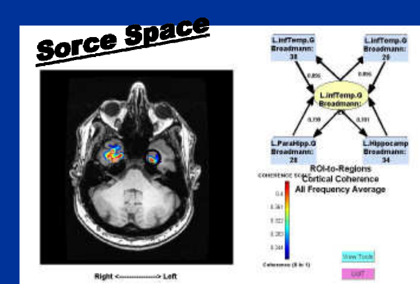
- Transients and oscillations of brain electric activity are found in MEG, EEG and ICEEG recordings of spontaneous brain activity. These transient waveforms and oscillations can be quantified by applying a time-frequency decomposition technique such as the short-time Fourier transform (sFFT).

- After transformation to a time frequency representation, the strength of network interactions can be estimated by calculation of coherence, which is a measure of synchrony between signals from different brain regions for each FFT frequency component.

- Coherence reflects the degree of information flow between groups of neurons.

- Advanced network evaluation techniques (Granger causality, narrow band filtering or Essential Mode Decomposition with Hilbert transforms, wavelets) can be applied to non-stationary data.
  - Determine the direction of network interactions
  - Quantify significance of network structures

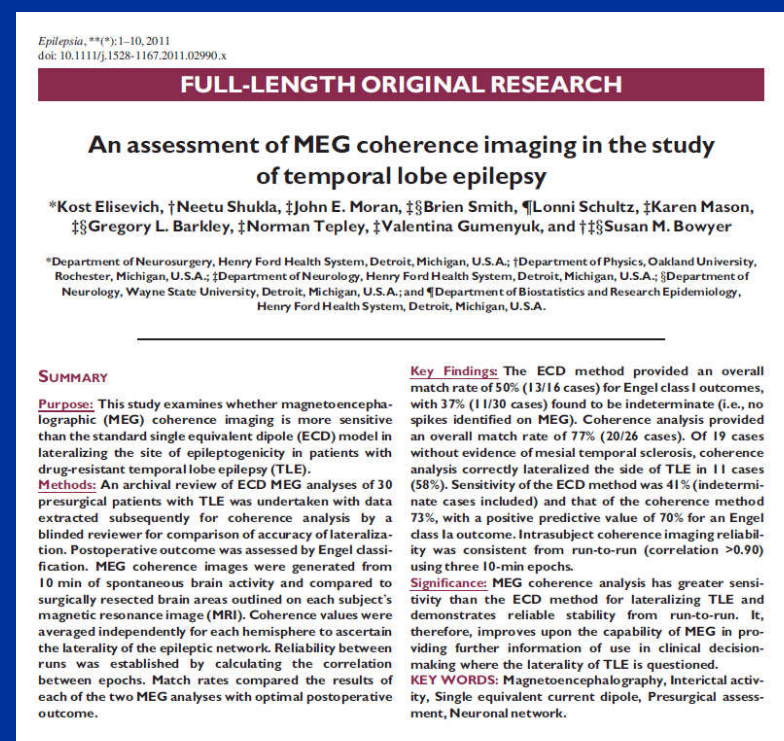




Purpose

This study examines the capability of magnetoencephalographic (MEG) coherence imaging to lateralize the site of epileptogenicity in patients with drug resistant temporal lobe epilepsy (TLE).

Specifically if no epileptic spikes are present.



Epilepsia, **(*):1–10, 2011
doi: 10.1111/j.1528-1167.2011.02990.x

FULL-LENGTH ORIGINAL RESEARCH

An assessment of MEG coherence imaging in the study of temporal lobe epilepsy

*Kost Elisevich, †Neetu Shukla, ‡John E. Moran, ‡§Brien Smith, ¶Lonni Schultz, ‡Karen Mason, ‡§Gregory L. Barkley, ‡Norman Tepley, ‡Valentina Gumenyuk, and †‡§Susan M. Bowyer

*Department of Neurosurgery, Henry Ford Health System, Detroit, Michigan, U.S.A.; †Department of Physics, Oakland University, Rochester, Michigan, U.S.A.; ‡Department of Neurology, Henry Ford Health System, Detroit, Michigan, U.S.A.; §Department of Neurology, Wayne State University, Detroit, Michigan, U.S.A.; and ¶Department of Biostatistics and Research Epidemiology, Henry Ford Health System, Detroit, Michigan, U.S.A.

SUMMARY

Purpose: This study examines whether magnetoencephalographic (MEG) coherence imaging is more sensitive than the standard single equivalent dipole (ECD) model in lateralizing the site of epileptogenicity in patients with drug-resistant temporal lobe epilepsy (TLE).

Methods: An archival review of ECD MEG analyses of 30 presurgical patients with TLE was undertaken with data extracted subsequently for coherence analysis by a blinded reviewer for comparison of accuracy of lateralization. Postoperative outcome was assessed by Engel classification. MEG coherence images were generated from 10 min of spontaneous brain activity and compared to surgically resected brain areas outlined on each subject's magnetic resonance image (MRI). Coherence values were averaged independently for each hemisphere to ascertain the laterality of the epileptic network. Reliability between runs was established by calculating the correlation between epochs. Match rates compared the results of each of the two MEG analyses with optimal postoperative outcome.

Key Findings: The ECD method provided an overall match rate of 50% (13/16 cases) for Engel class I outcomes, with 37% (11/30 cases) found to be indeterminate (i.e., no spikes identified on MEG). Coherence analysis provided an overall match rate of 77% (20/26 cases). Of 19 cases without evidence of mesial temporal sclerosis, coherence analysis correctly lateralized the side of TLE in 11 cases (58%). Sensitivity of the ECD method was 41% (indeterminate cases included) and that of the coherence method 73%, with a positive predictive value of 70% for an Engel class Ia outcome. Intrasubject coherence imaging reliability was consistent from run-to-run (correlation >0.90) using three 10-min epochs.

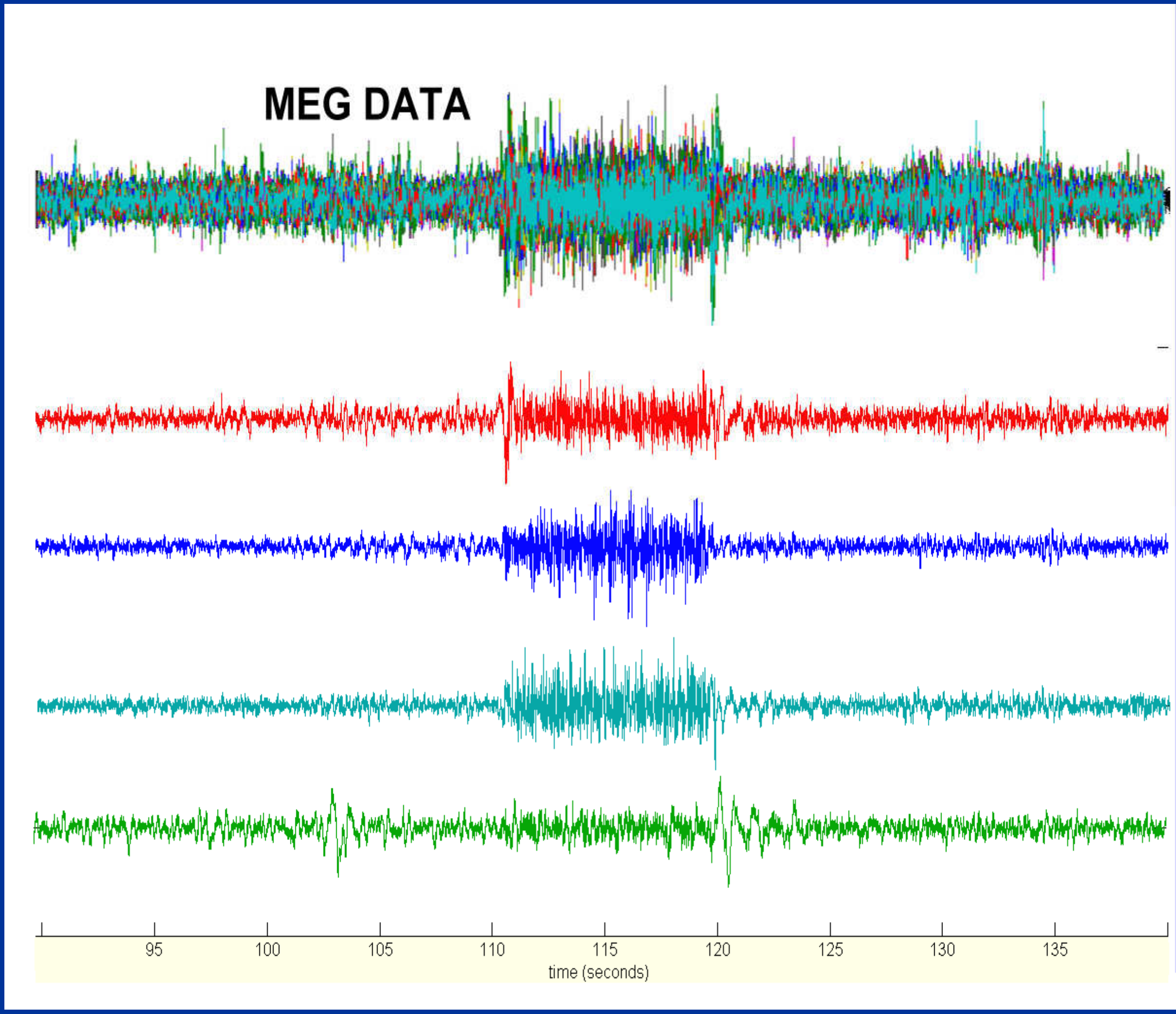
Significance: MEG coherence analysis has greater sensitivity than the ECD method for lateralizing TLE and demonstrates reliable stability from run-to-run. It, therefore, improves upon the capability of MEG in providing further information of use in clinical decision-making where the laterality of TLE is questioned.

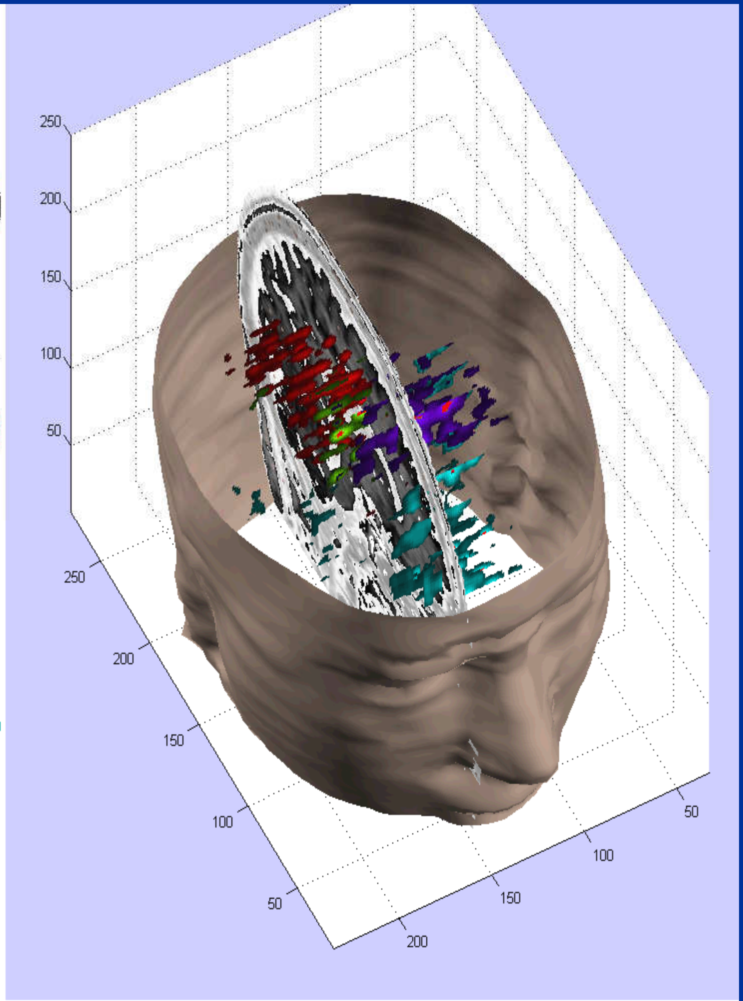
KEY WORDS: Magnetoencephalography, Interictal activity, Single equivalent current dipole, Presurgical assessment, Neuronal network.

Methods

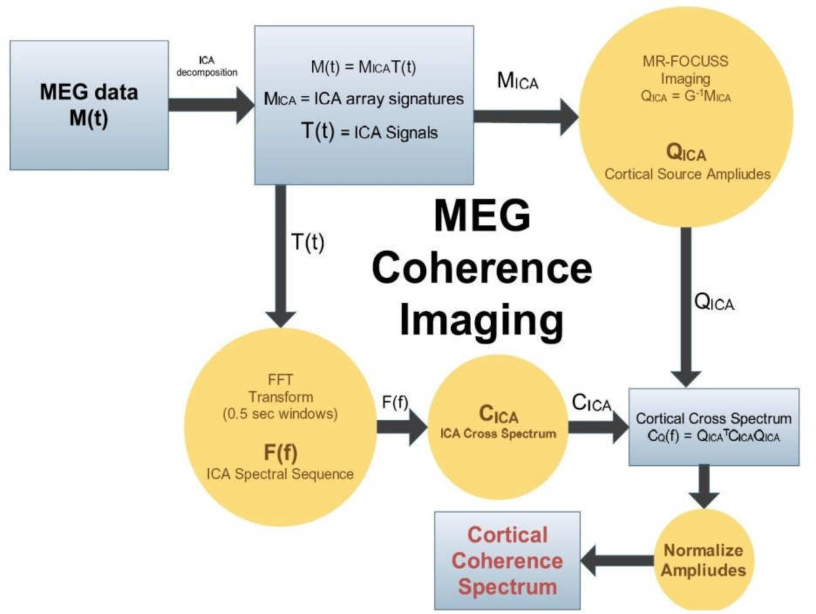
- An archival review of single equivalent current dipole (ECD) MEG analyses from
- 30 presurgical TLE patients
- Postoperative outcome was assessed by Engel class.
- MEG coherence images were generated from 10 minutes of spontaneous brain activity
- MEG coherence images were compared to surgically resected brain areas outlined on each subject’s MRI.
- Coherence values were averaged independently for each hemisphere to ascertain the laterality of the epileptic network.

ICA signal separation
MR-FOCUSS Imaging





Coherence Imaging: Calculation



1. Calculate time sequence of brain activity (divide data into 7.5 sec window)
   - ICA for extracting neuronal bursts of activity (epileptic signals)
   - MR-FOCUSS/Coherence imaging for determining the global extent of the epileptic network and the local spectrum of overall network coherence and connectivity. (Very, numerically efficient compared to other MEG methods)
2. Calculate FFT sequence (0.5 second windows)

   temporal sequences of sources are converted to temporal source FFT spectra
3. Calculate cross-spectral matrix between sources (ICA components) for each frequency
4. Calculate coherence between all network structures (1-Same 0-No similarity)
5. For each active cortical site the average coherence with all other sources is calculated for each frequency.
6. Both the Imaginary and Real components are incorporated in the coherence imaging results.

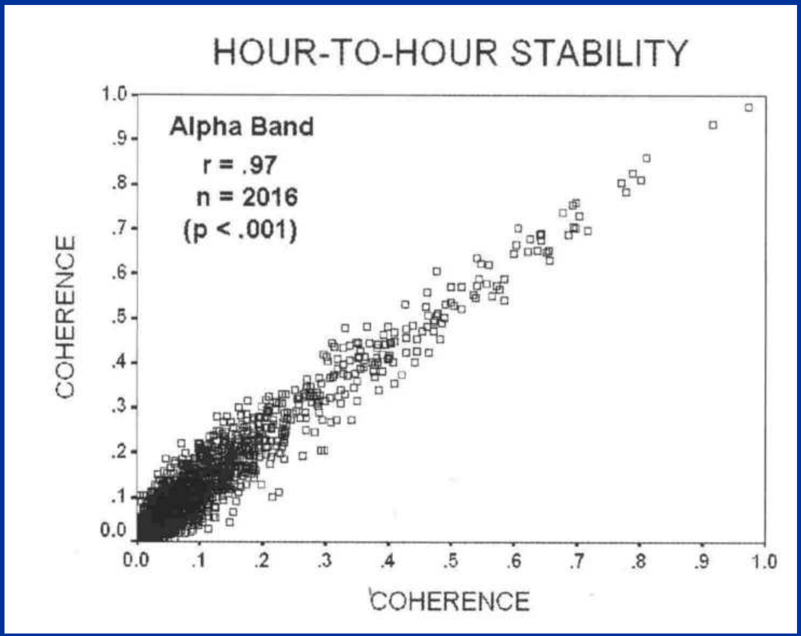
Moran, Biomag, 2006

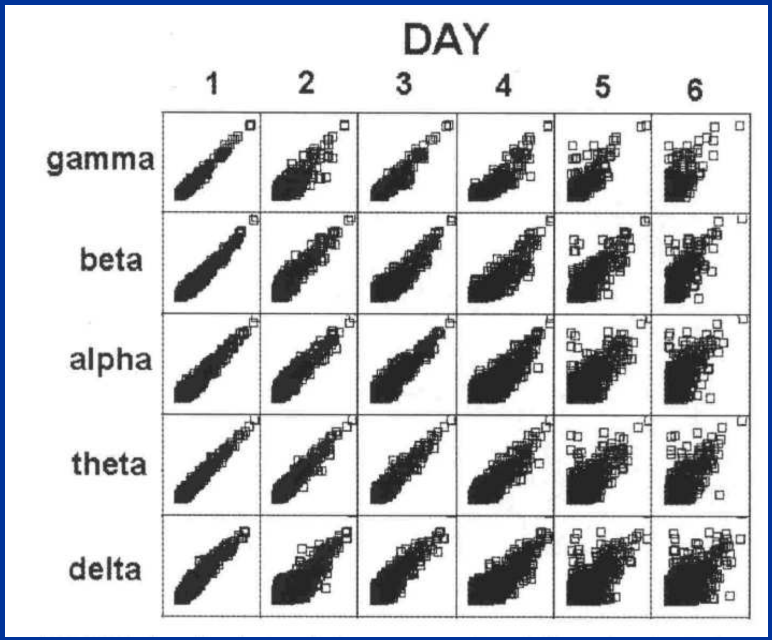
Coherence and Epilepsy

ECoG studies:

Coherence is very stable over time

V.L Towle, et.al., Frequency Domain Analysis of Human Subdural Recordings. J. Clin. Neurophysiology, Vol. 34 No. 2, pp 205 – 213, 2007





MEG Imaged Coherence Mapping Compared to Electrocortical Recordings

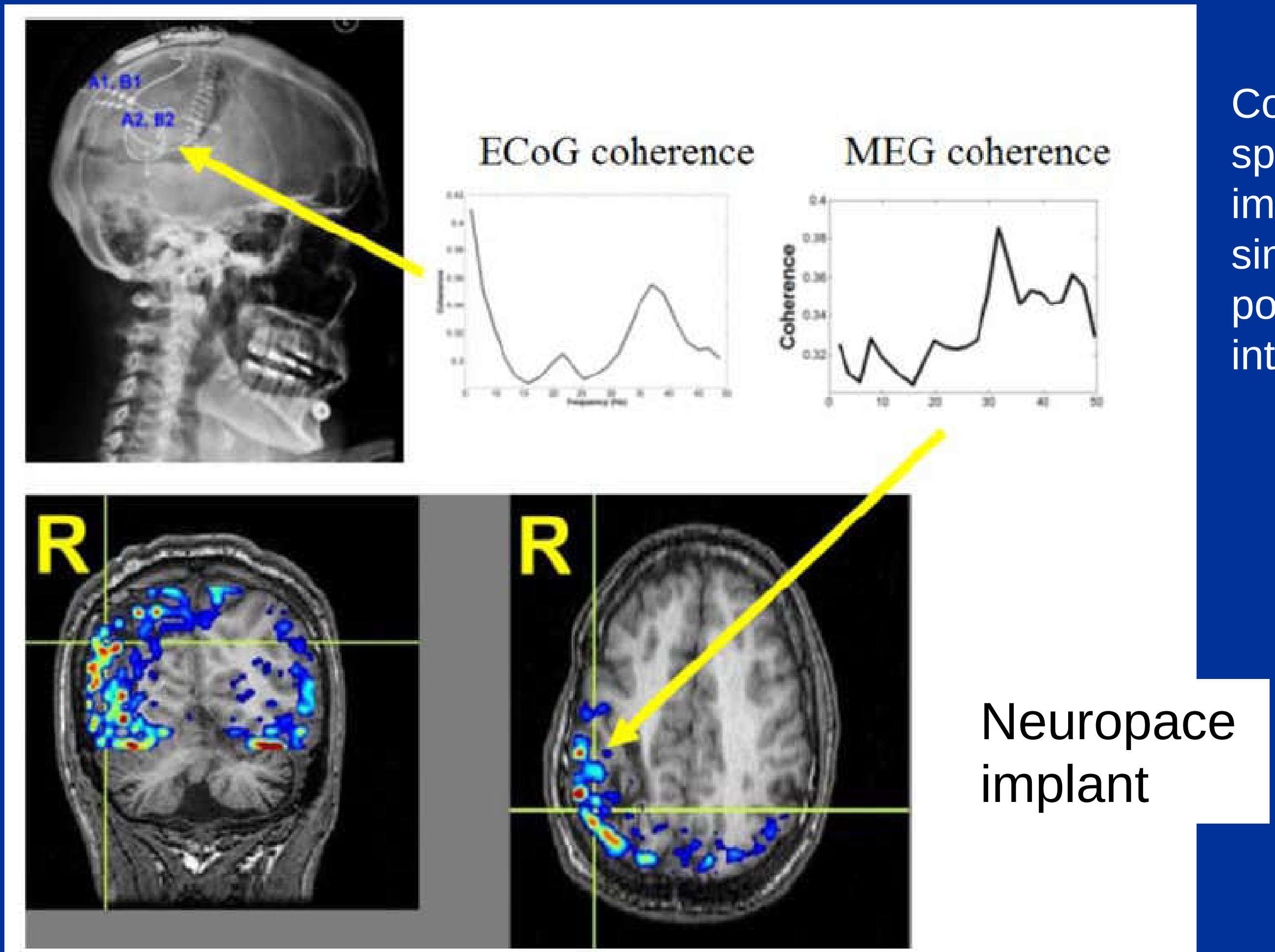


Fig 1. MEG imaged coherence and corresponding interictal ECOG coherence are similar, especially in the 30-40 Hz coherence band.

Coherence and power spectra of the MEG imaged data were very similar to coherence and power spectra from intracranial electrodes

Moran J. et al. *2006, MEG Coherence Imaging Compared to Electrocortical Recordings from NeuroPace Implants to Determine the Location of Ictal Onset in Epilepsy Patients,* in *15th International Conference on Biomagnetism*.

Table 3

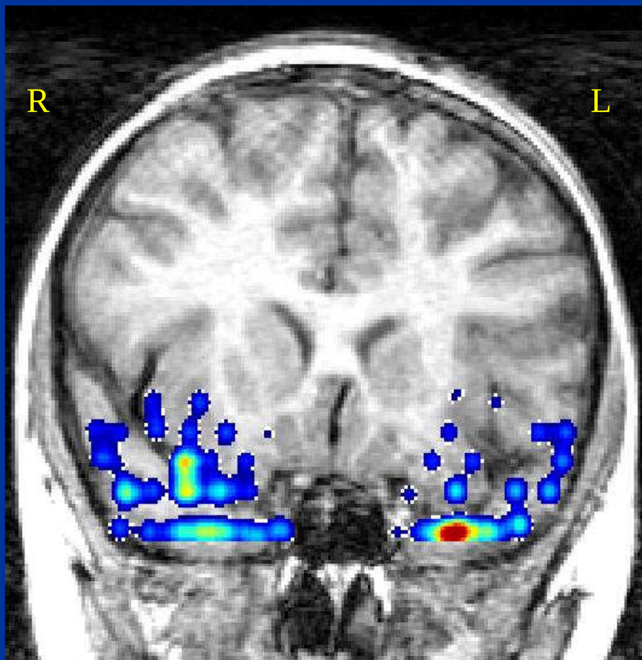
Table 3: Summary of Engel classes with ECD and MEG analyses

Engel Class	EC D		Coherence analysis	
	Match*	No Match	Match*	No Match
Ia	9	13	16	6
Ib	1	0	1	0
Ic	1	0	1	0
Id	2	0	2	0
IIa	0	1	1	0
IIb	1	0	1	0
IIIa	2	0	1	1
Total	**16**	**14**	**23**	**7**

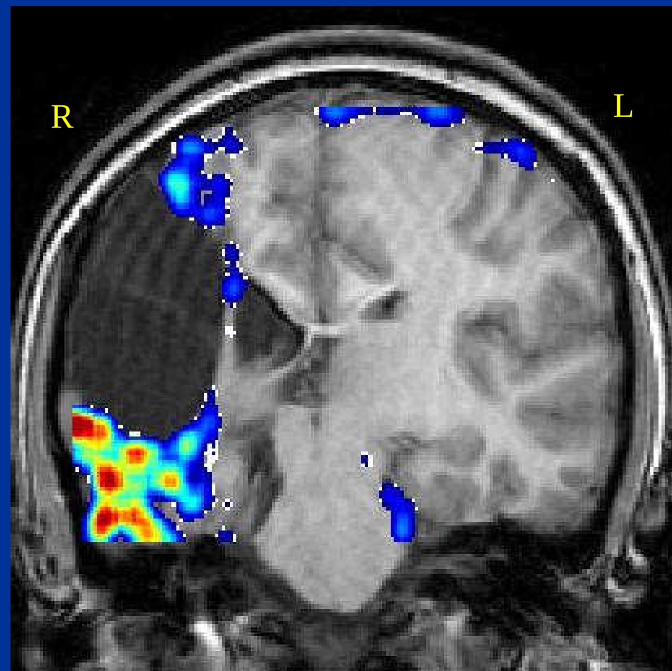
*A match indicates agreement of MEG analysis with the surgical resection.
Coherence 77% (20/26) ; ECD 50%(13/26)

Elisevich et al, Epilepsia 2011

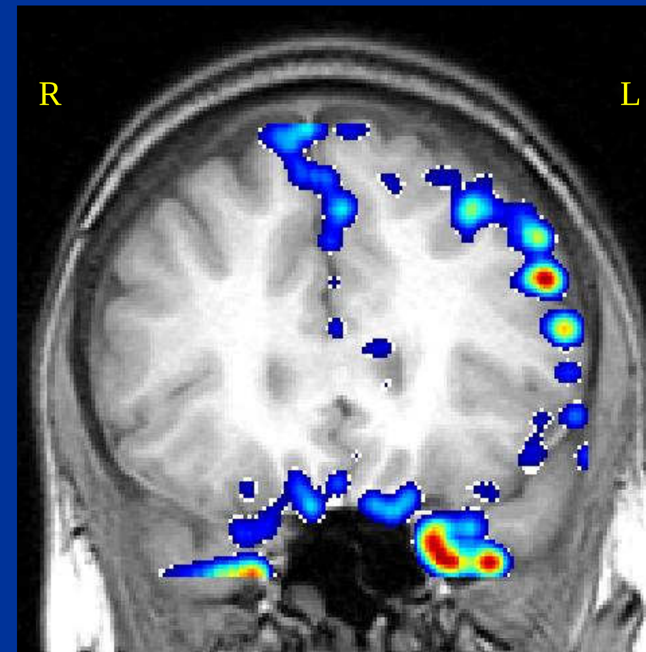
Epilepsy Patients



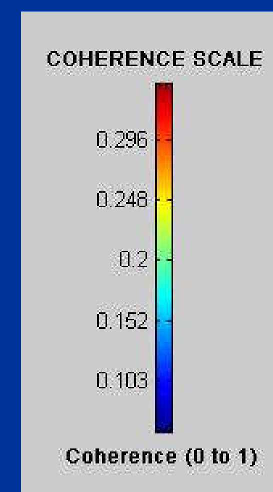
Subject #1: Left temporal resection



Subject #11: Right temporal resection



Subject #7 Left temporal resection



- Increased coherence (presurgical) was localized to the concordant area of resection in 77% (20/26) temporal lobe epilepsy cases.
- 5/6 cases with a **normal** presurgical MRI were correctly localized by coherence measures.
- **11/30 patients had no epileptiform activity, of these 8 were still able to be analyzed and localized effectively using coherence analysis to achieve a class Ia outcome.**

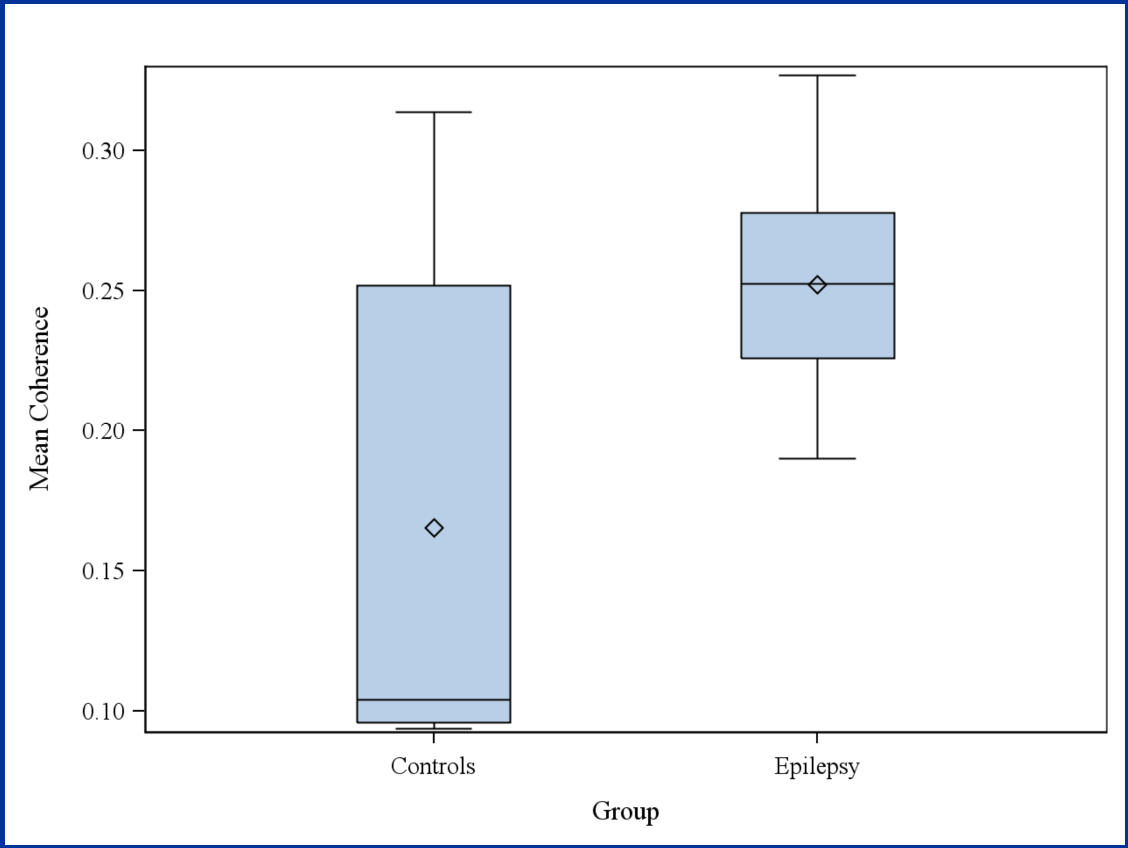
Elisevich et al, Epilepsia, 2011

Coherence levels

Using only the class I outcome results (i.e., absence of disabling seizures) as a measure of success, the mean coherence value was found to be 0.26 ± 0.03 in patients with epilepsy.

Control subjects demonstrated no area of high coherence, as expected, and a lower mean coherence value (0.17 ± 0.09).

Box plots showing mean (◇), median, interquartile range and minimum and maximum values of coherence for the Controls and Patients. The difference between the two groups was significant.



Results

- Sensitivity of the ECD method was 41% (9/22) (indeterminate cases included) with a positive predictive value of 56% (9/16) for an Engel class Ia outcome
- Sensitivity of the Imaged Coherence method was 73% (16/22) with a positive predictive value of 70% (16/23) for an Engel class Ia outcome
- Specificity for both methods was 13% (1/8) there were 7 false postives

Sensitivity and Specificity

of ECD and Coherence analysis methods.

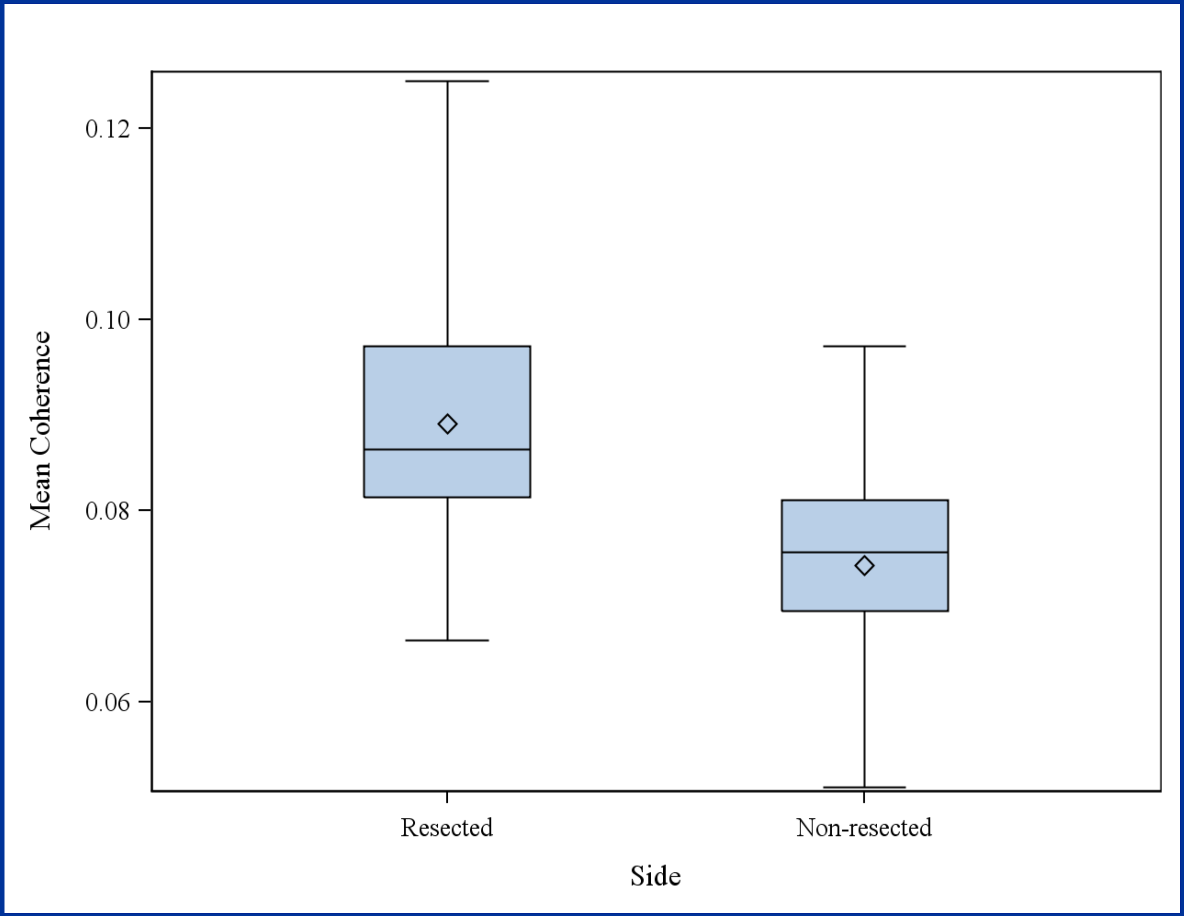
ECD and Engel class outcome			
	Ia	Not Ia	Total
Match*	9	7	16
Not Match	13	1	14
Total	22	8	30
Sensitivity of Engel class Ia		41	
Specificity of Engel class Ia		13	

Coherence and Engel class outcome			
	Ia	Not Ia	Total
Match*	16	7	23
Not Match	6	1	7
Total	22	8	30
Sensitivity of Engel class Ia		73	
Specificity of Engel class Ia		13	

*A match indicates agreement of MEG analysis with the laterality of the surgical resection and, therefore, the result of standard investigation.

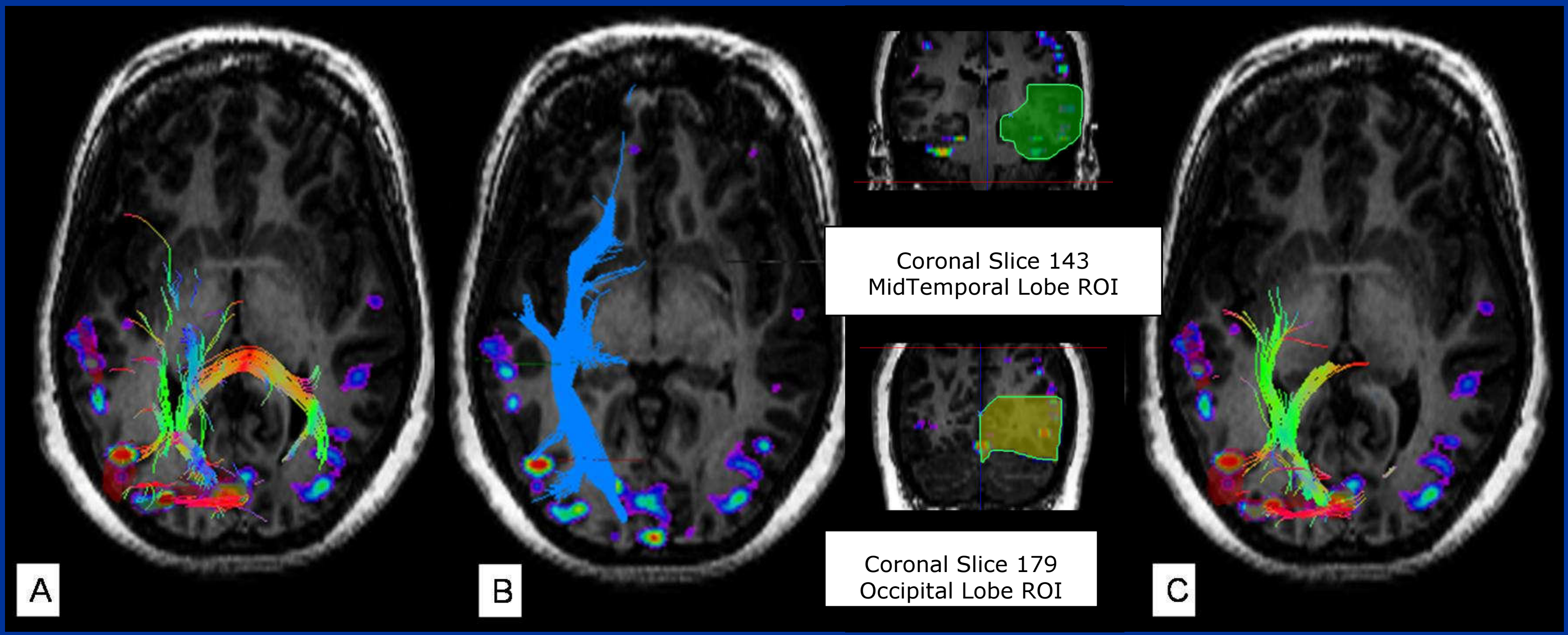
Elisevich et al, Epilepsia 2011

Hemispheric Coherence Levels



Box plots showing mean (◇), median, interquartile range and minimum and maximum values of coherence for the resected and nonresected hemispheres. The difference between the two sides was significant ($p<0.001$).

Epileptic Networks
DTI Fiber Tracts (anatomical) connect
MEG Imaged Coherence (functional)



MEG imaged coherence of spontaneous cortical activity overlaid on the volumetric MRI of Patient with Epilepsy. Coherence scaling shown as low to high on blue to red color scale.

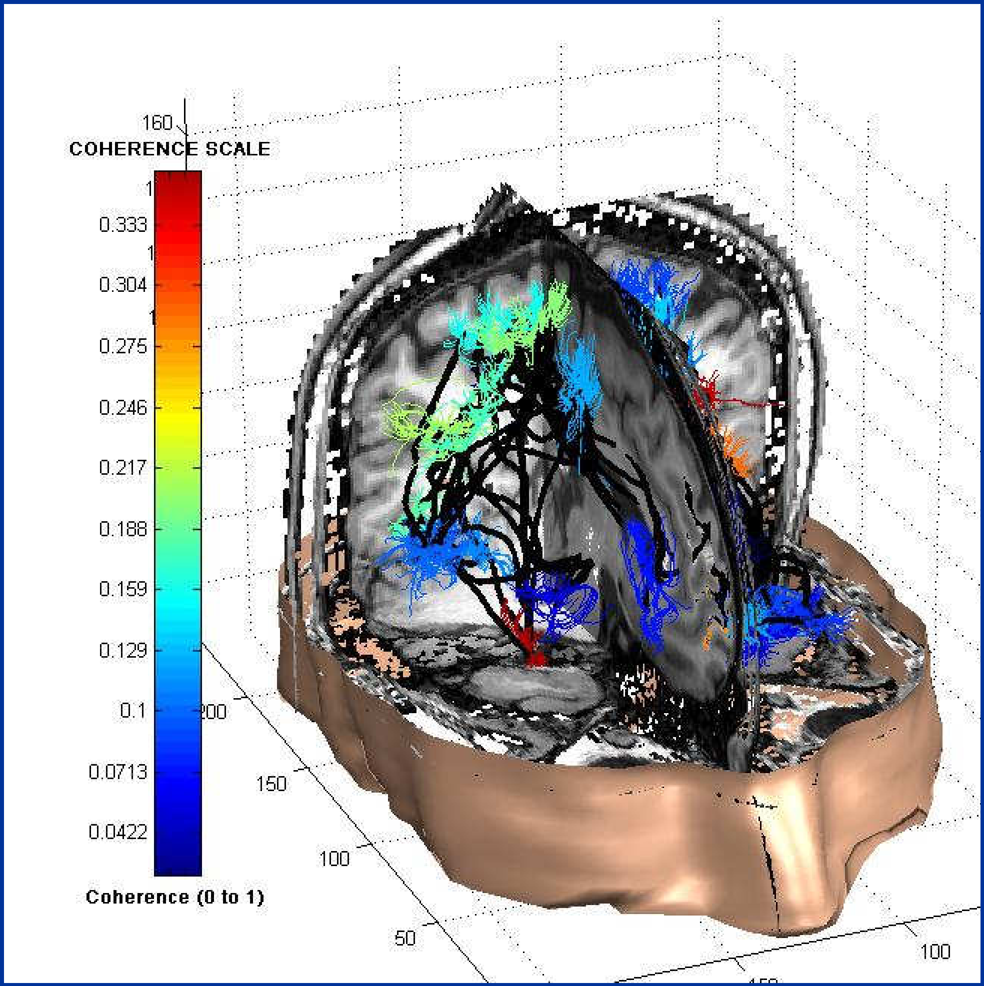
A. Superior view of fibers tracked from ROI bounding high coherence in right parietal lobe.

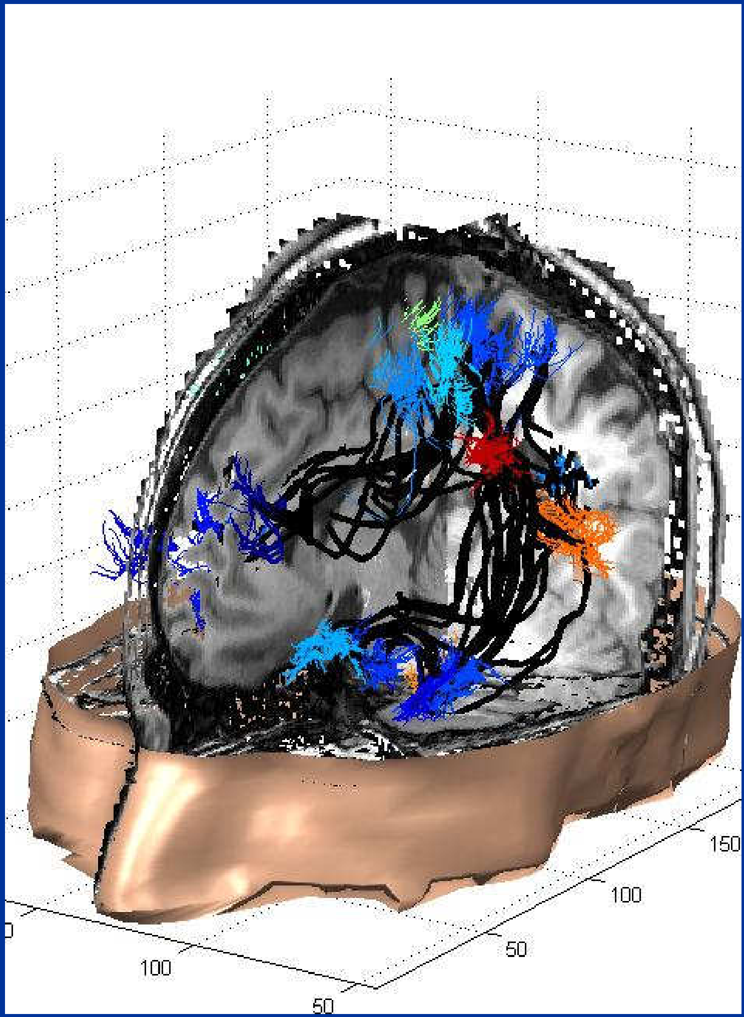
B. Inferior Longitudinal Fasciculus (ILF) tracked with the standard two ROI method between the Mid Temporal and Occipital lobes shown inset.

C. Inferior view of same fibers from view **A**. Areas of high coherence are linked with fibers from the ILF as well as occipital projections of the callosal fibers.

Weiland et al, In Preparation

MEG Imaged Coherence of Resting State overlaid with active DTI Fibers





Discussion:

- MEG coherence analysis has greater sensitivity than the ECD method for lateralizing TLE.
- Is useful even when epileptic spikes are absent.
- Provides unique functional information for clinical decision-making where the laterality of TLE is questioned.
- Can overlay with DTI Fiber Tracts to view both the functional (MEG) and anatomical (DTI) Network

Future Direction

The Clinical Questions

Where is the best location for intervention?

Where does a patient’s epilepsy start?

Epileptic Activity is not Focal

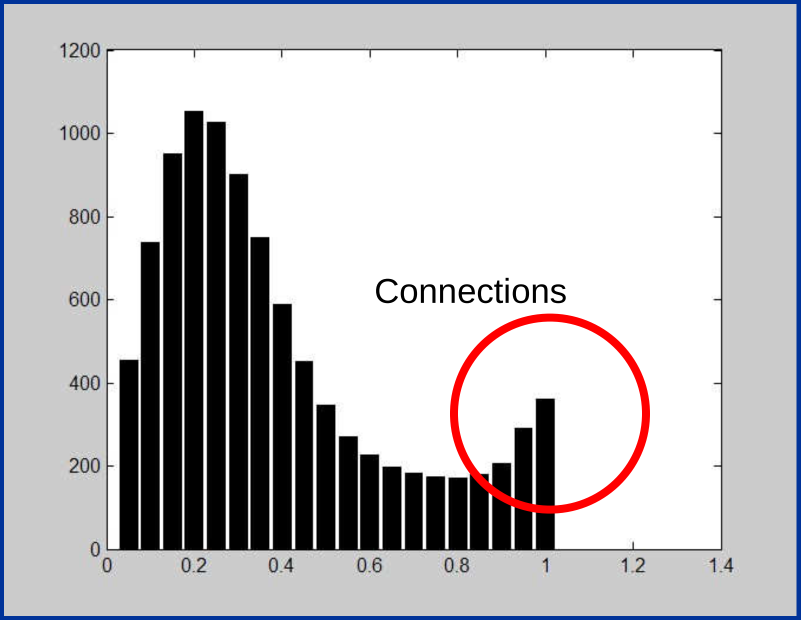
- Rapid spread throughout a well established, well connected, often global network
- Amplitude and frequency depends on connectivity
- Large rapid fluctuations in brain activity
- Amplitude of activity and network behavior is distinctly different from normal brain network behavior
- Generators of abnormal brain activity have different behaviors than other network components
- Components of the epileptic network have different ictal and interictal activities.

Next Step

- Coherence imaged results
- Discriminant analysis is well suited for utilizing differences in coherence and connectivity to create discriminant functions that can be used to identify active generator sites when applied to new patient data.
- Further, discriminant analysis can provide predictors of surgical outcome.
- Discriminant analysis performed to train and to predict
  - Multiple discriminant functions applied and results averaged in predict mode (use the training MEG data samples to estimate the values of the parameters)
  - Data base of discriminant functions constructed in train mode such that individual variations are well accommodated (the MEG data samples to estimate a classifier based on the values of parameters)

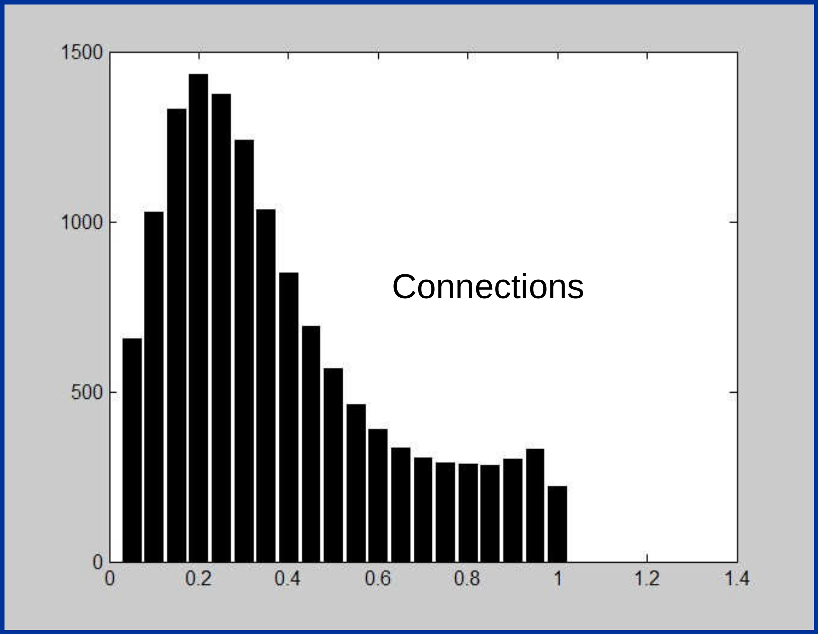
Coherence-Connectivity distribution

- The coherence distribution: one site with all other sites
- It is distinctly different for sources that have different connectivity.



coherence

Within Epileptic Zone

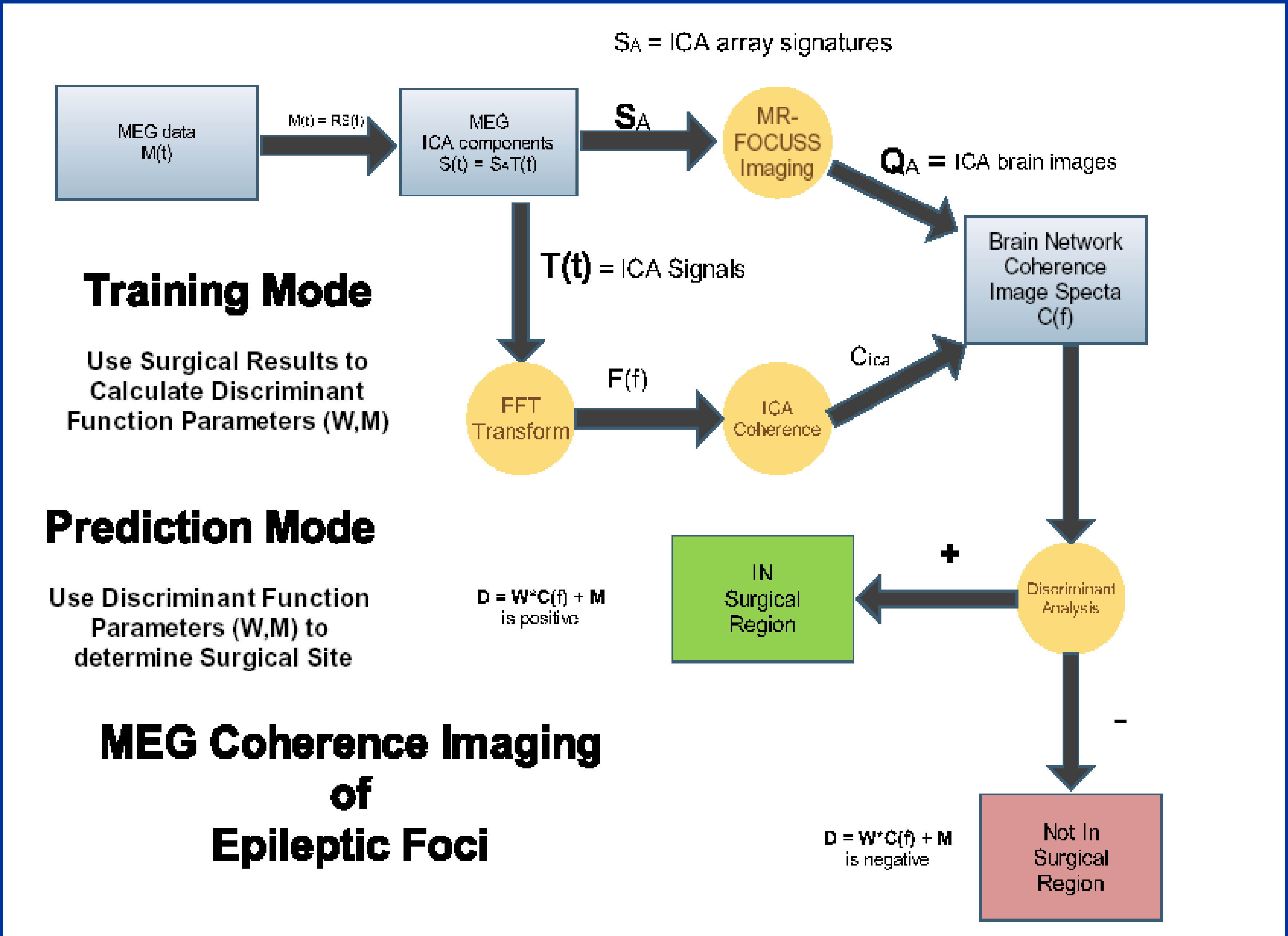


coherence

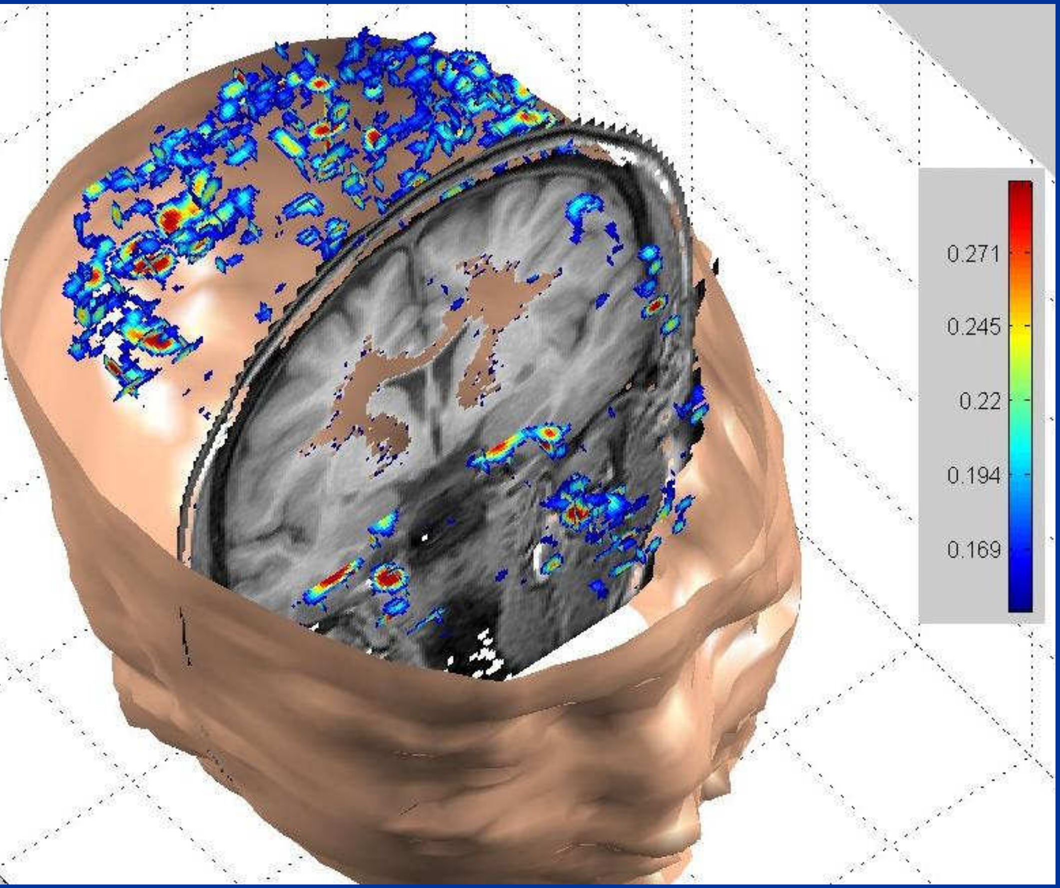
Outside Epileptic Zone

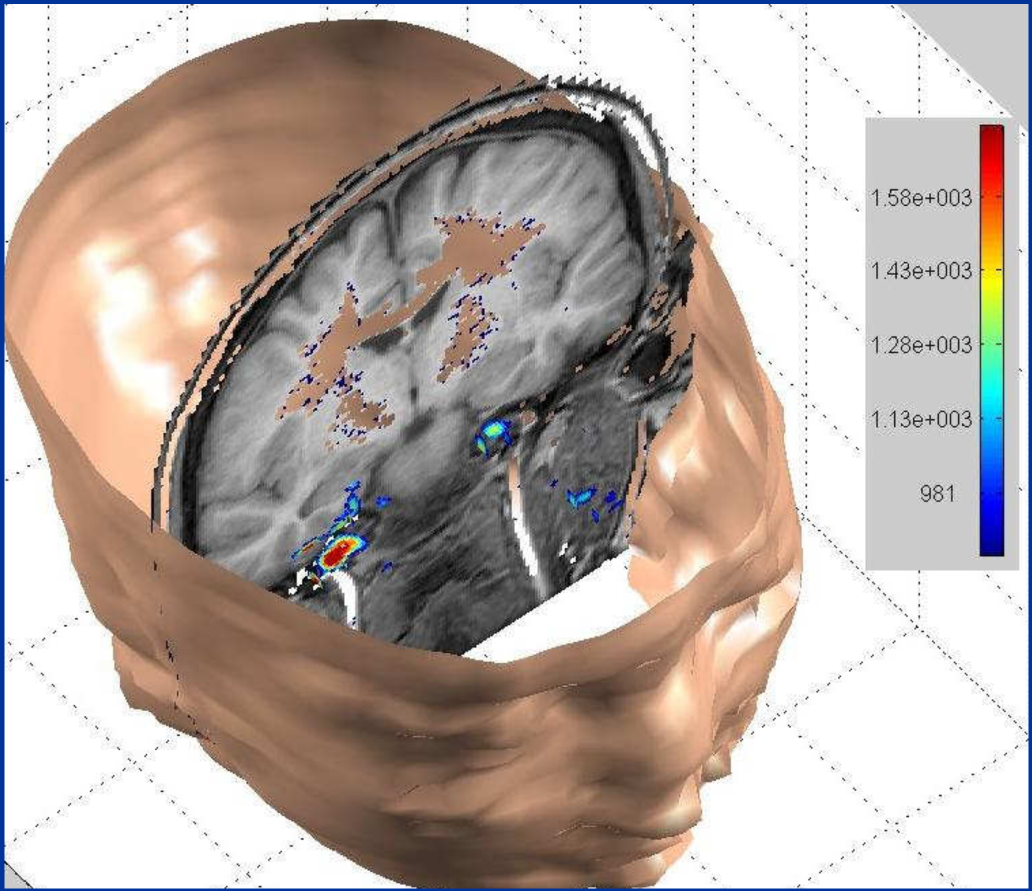
These are coherent sites that are well connected

Coherence Imaging and Discriminant Analysis



Discriminant Image Results

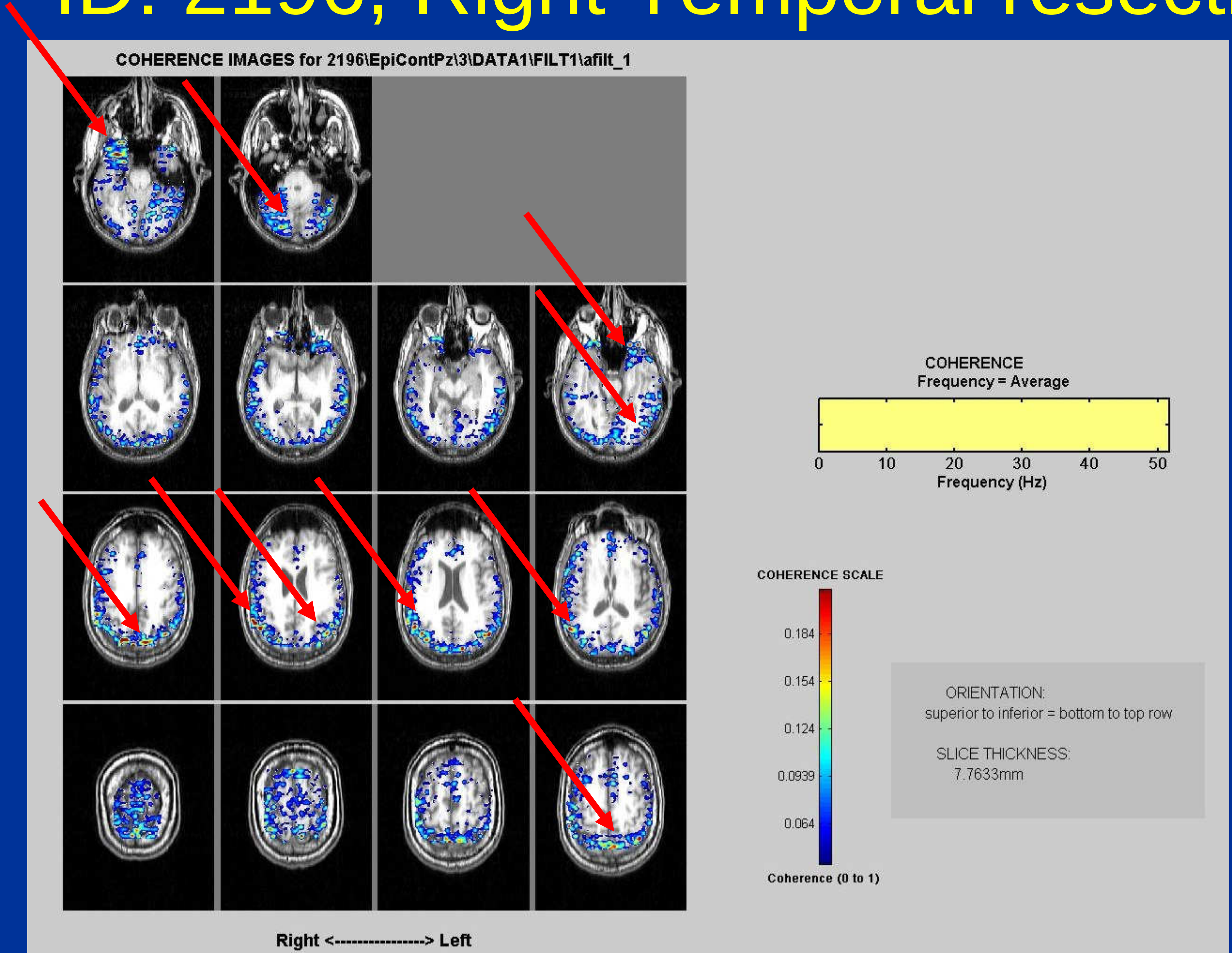




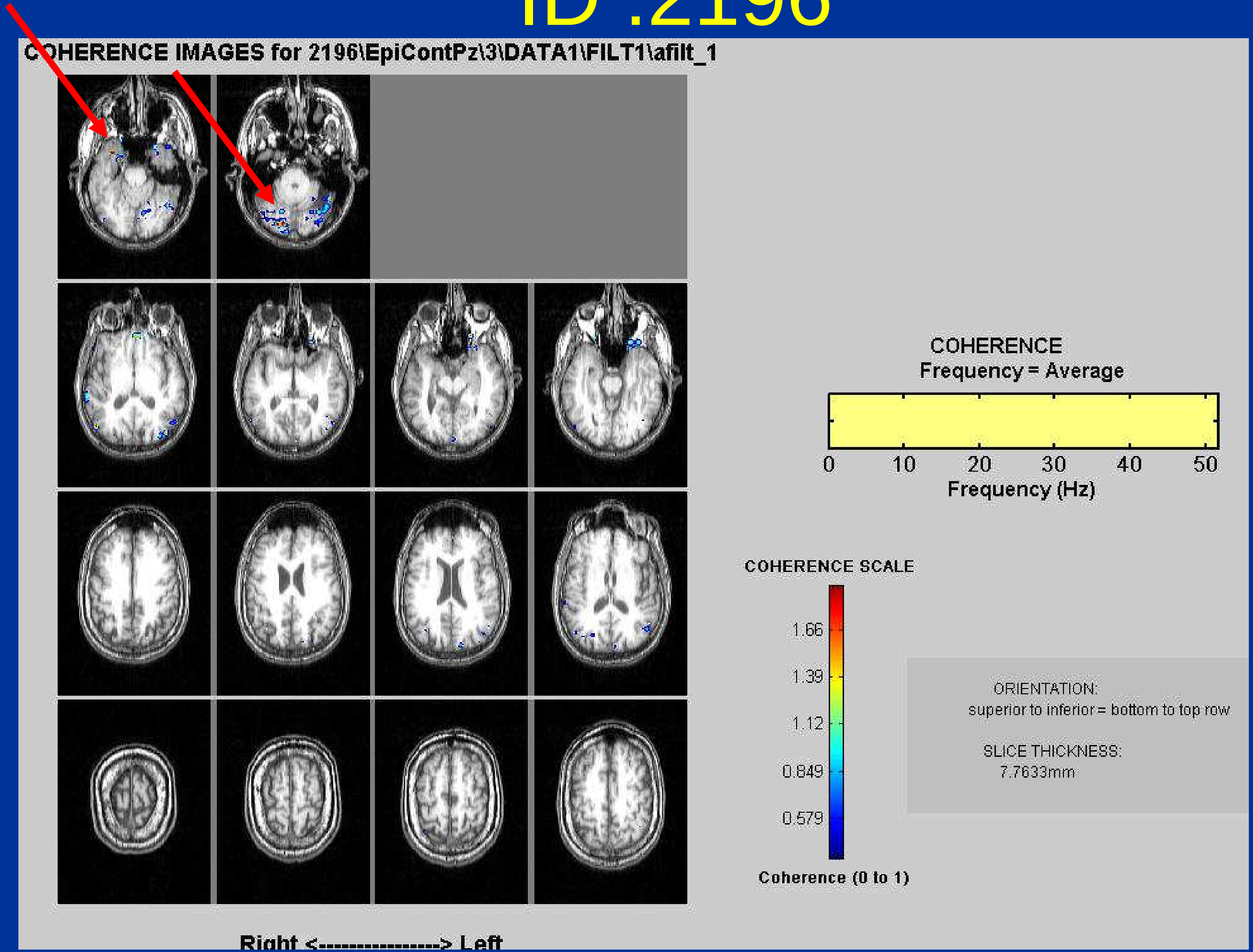
Coherence results

Discriminant Score

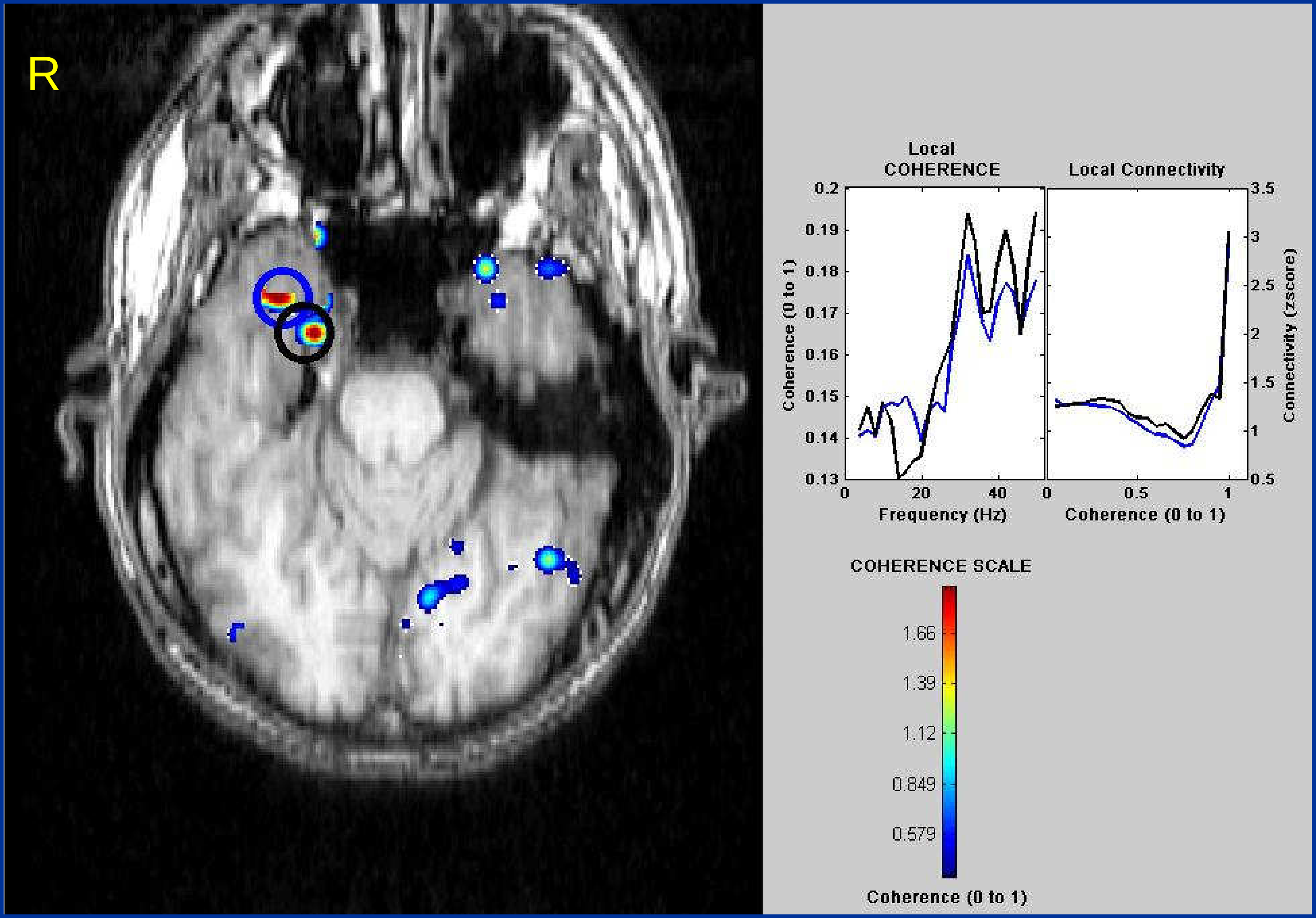
Coherence all:
ID: 2196, Right Temporal resection



Connectivity -total discriminant ID :2196

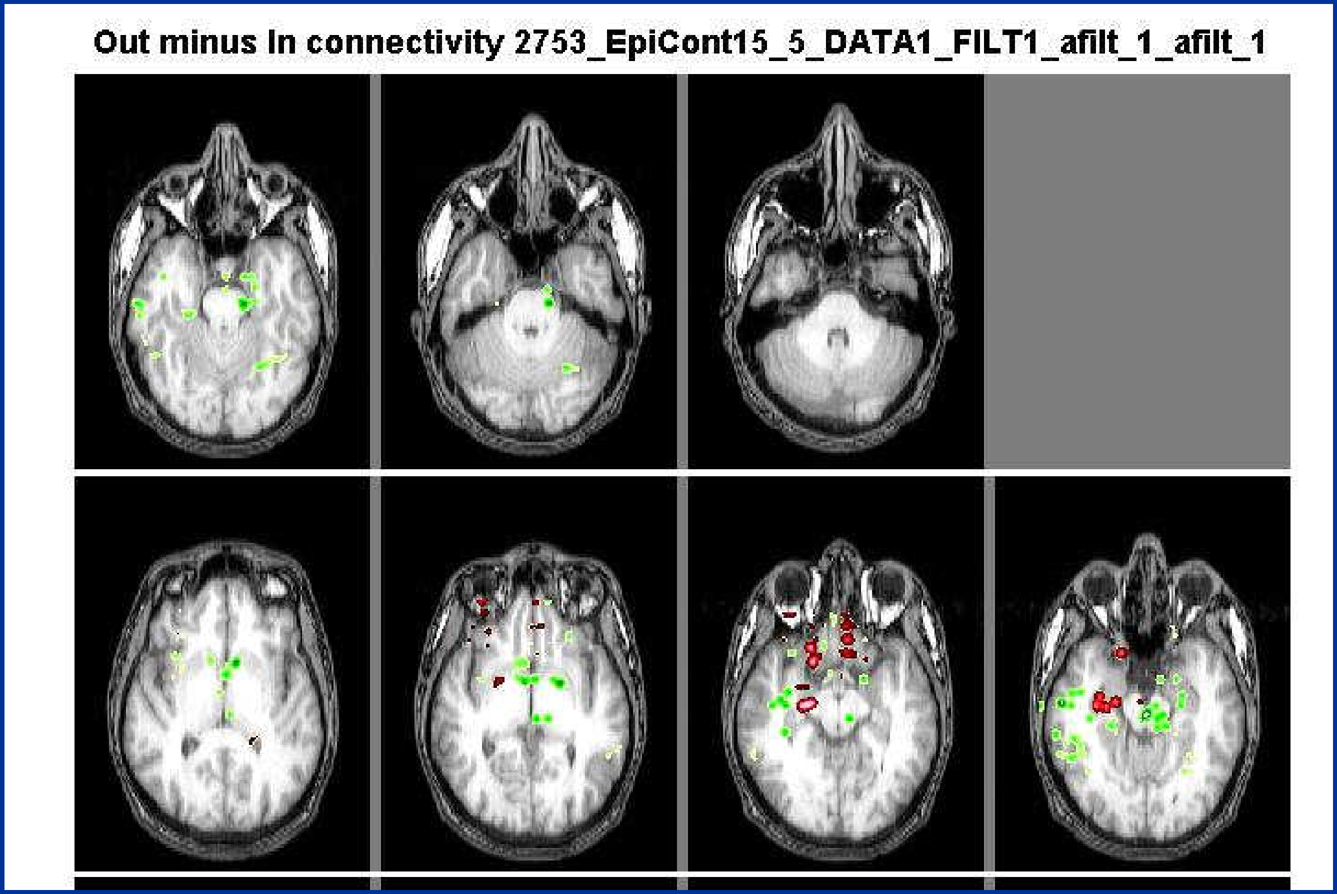


Connectivity total discriminant ID 2196 Right temporal resection

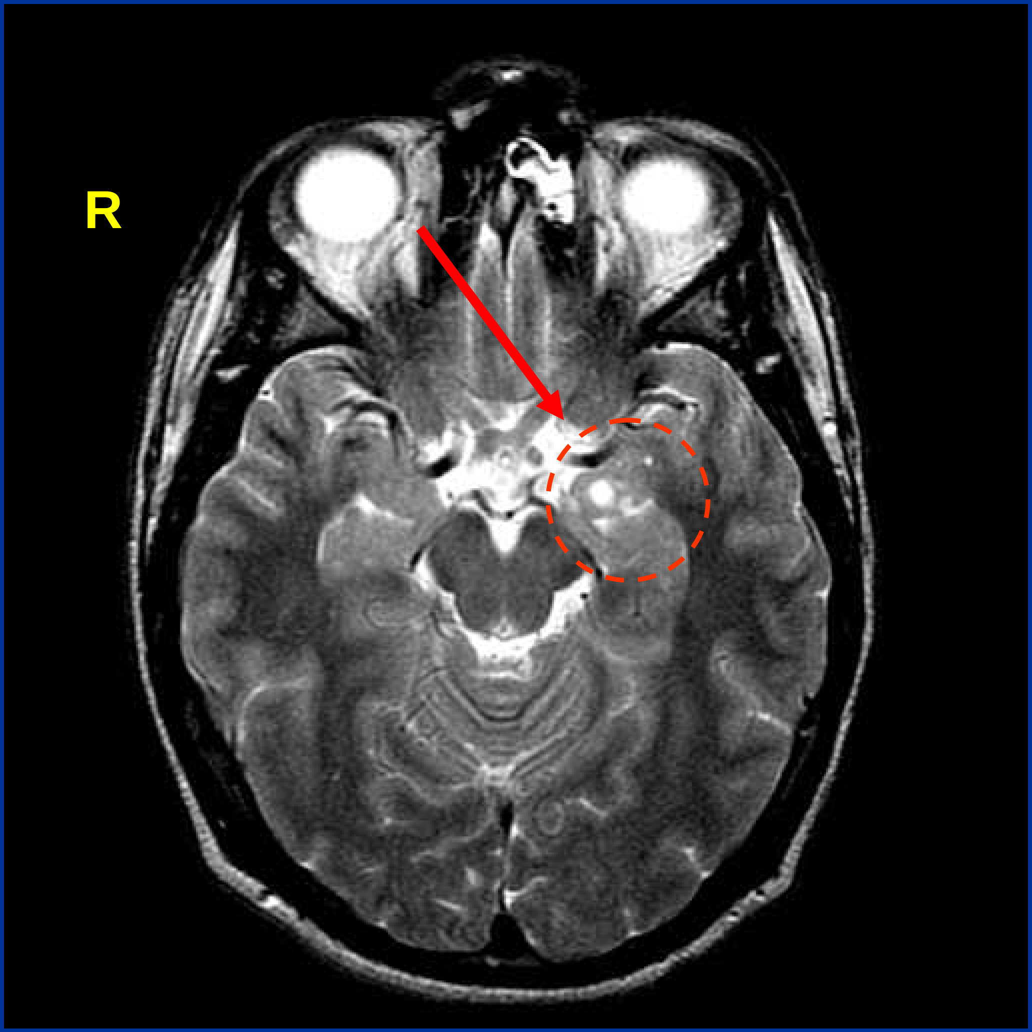


These are the sites that are well connected in this Patient's epileptic network.

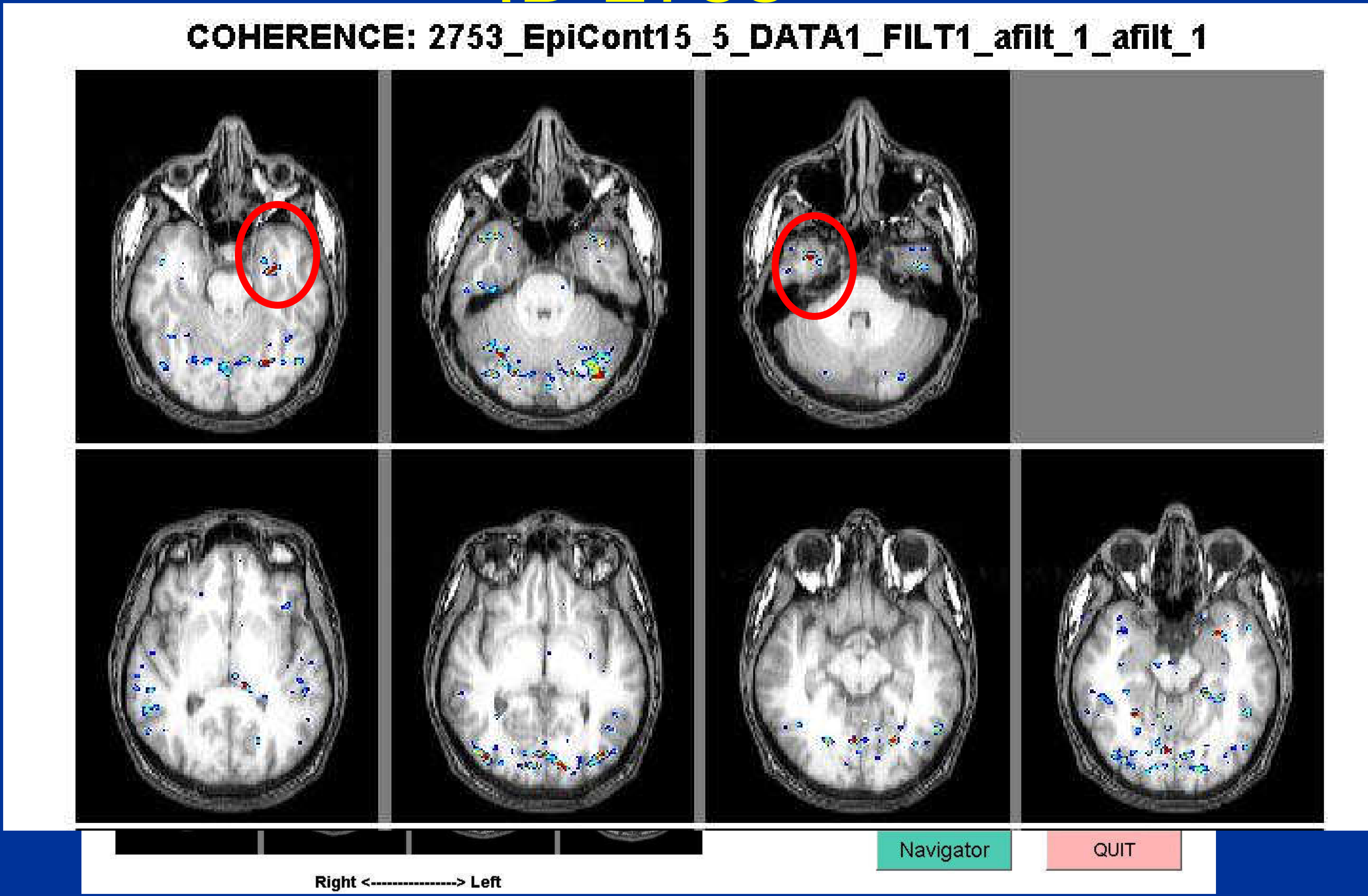
Where does it start!!
IN OUT Coupling
Grainger Causality
is used to determine how information is flowing in the imaged network



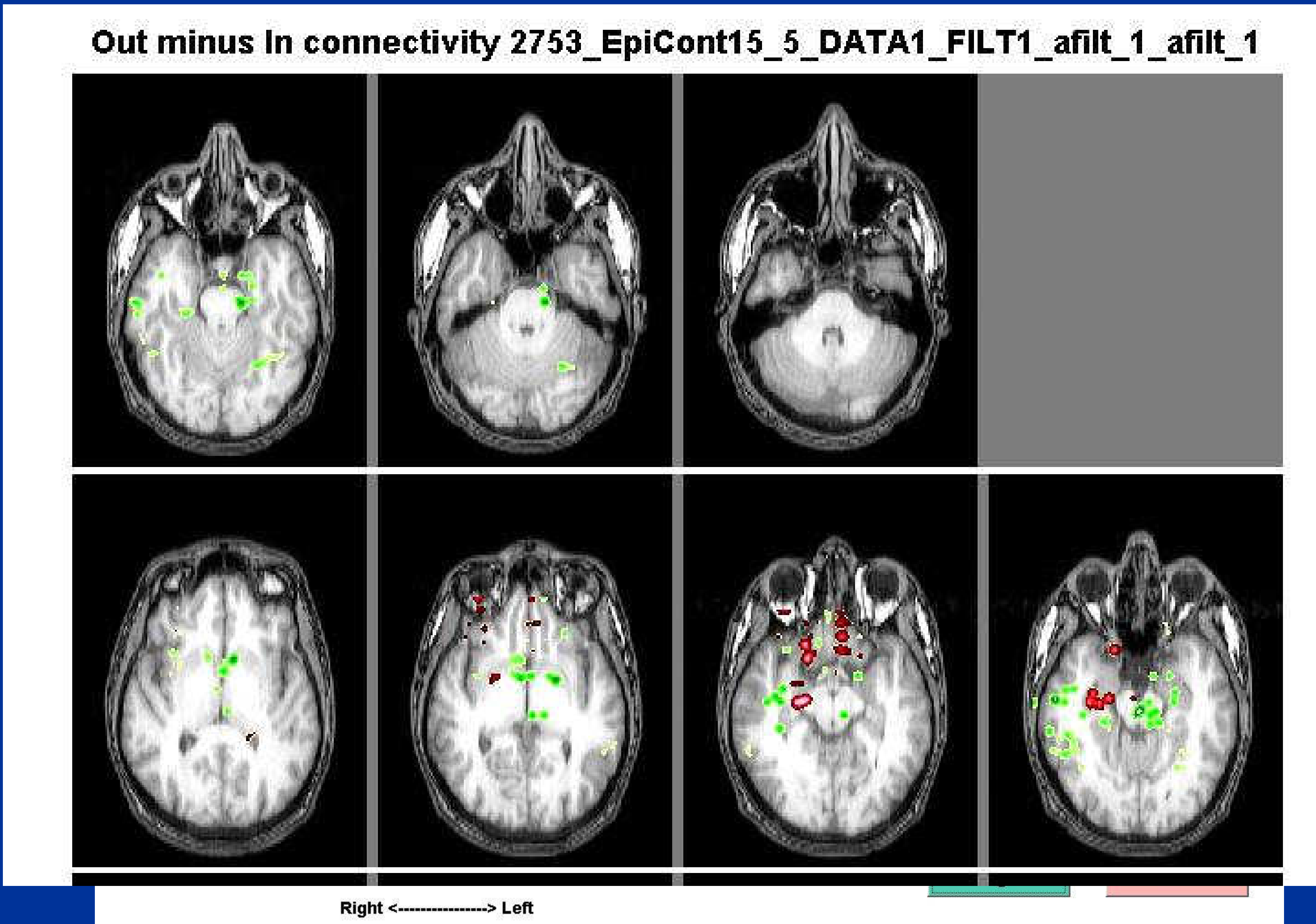
Lesions in Left Temporal
ID 2753



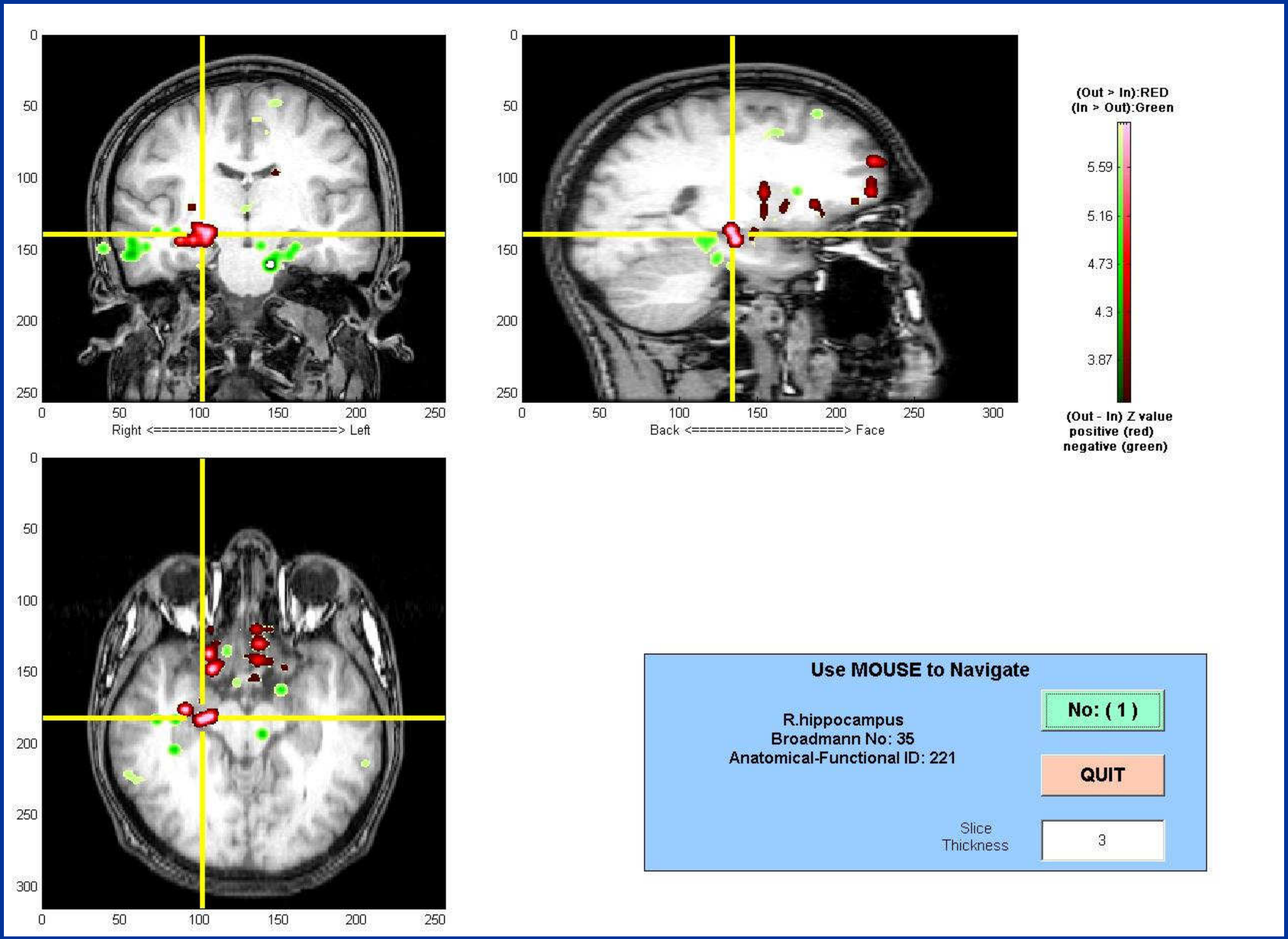
Mean Regional Coherence ID 2753



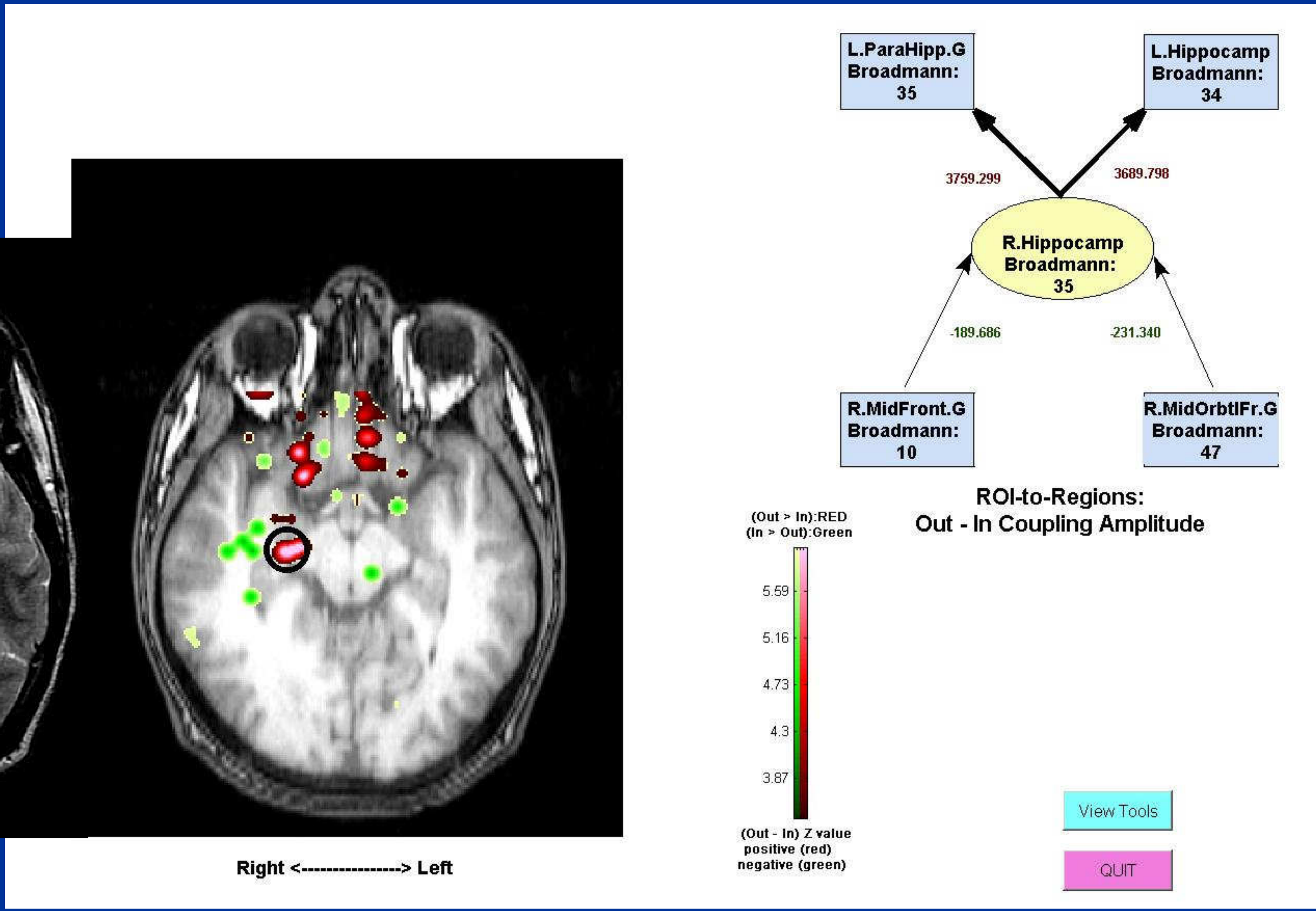
IN OUT Coupling
Grainger Causality



Top location

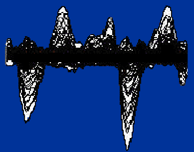


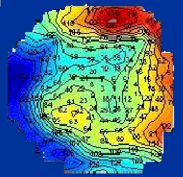
Locations that are communicating



In Summary

- MEG non-invasively detects electrical brain activity from cortical neurons
- MEG builds sophisticated 3-D and 4-D road maps of functional brain activity
- Imaged Coherence detects the functional brain network
- DTI uses MRI to image the fiber tracks (anatomical brain network) that connect MEG imaged functional networks
- Combining MEG and DTI can lead to better understanding of epileptic networks and their connectivity.
- MEG can localize eloquent cortex for Auditory, Visual, Sensory, Motor and Language functioning
- MEG can localize abnormal brain activity in patients
- MEG can be used to detect where disease disrupts brain function and how therapy can improve outcome
- MEG can guide surgical interventions for brain tumors, arteriole vascular malformation (AVM) and Epilepsy.
- In the future MEG can be used to predict the probability of success
- Many new areas of research are rapidly emerging





Thank you for your attention!

My Collaborators:

Gregory L Barkley, MD
Andrew Zillgitt, MD
Mariana Spanaki-Varelas, MD
Jason Schwalb, MD
Vibhangini Wasada, MD
Basel Assaad MD
Lori Schuh, MD
Kost Elisevich, MD, PhD
Brien Smith, MD
David Burdette, MD

Karen M Mason, REEG/MEG

Norman Tepley, PhD
John E Moran, PhD
Stephen Robinson, PhD
Quan Jiang, PhD
Barbara Weiland, PhD
Valentina Gumenyuk, PhD
Jinsheng Zhang, PhD

Renee Lajiness-O’Neill, PhD
Jennifer Peacock, PhD
Margaret Greenwald, PhD
Li Hsieh, PhD

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Neural Connectivity

- Correlation is a measure of similarity between amplitudes of 2 time series (i.e. 2 channels of MEG data).
- Cross-correlation further includes information on systematic timed shifts between the 2 time series.
- Cross-spectral density can be calculated by multiplying the Fourier-transformed signals (frequency space) of the time series.
- Coherence is obtained by normalizing the cross spectral density with the power spectral density of both time series. Its values ranges from :

  0 (no similarity) to

  1 (identical time series).