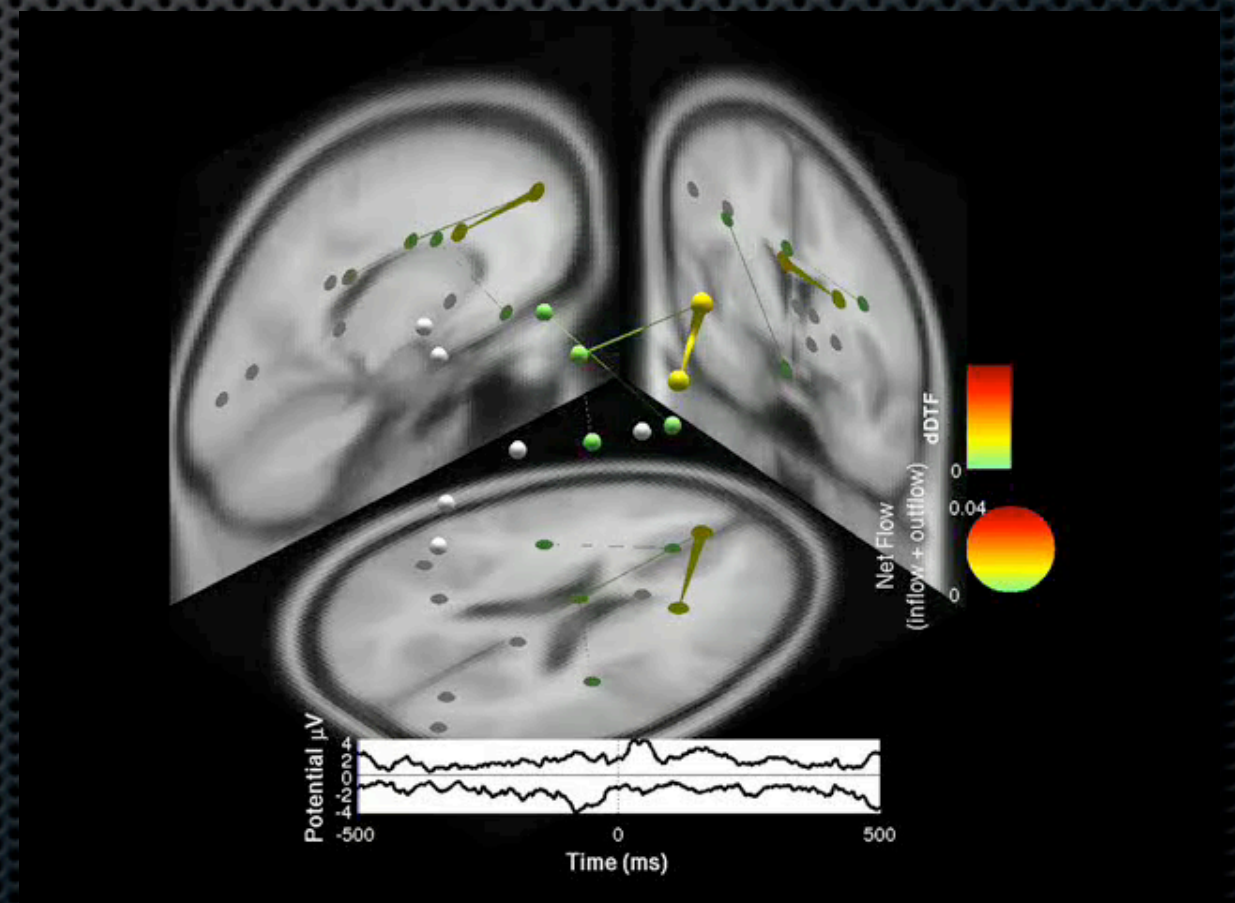


# Modeling Effective Connectivity and EEG Information Flow

Tim Mullen

10th EEGLAB Workshop  
Jyväskylä, Finland  
June 14 - June 17, 2010





# Introduction

- ✦ **The problem** -- Fundamental challenge in cognitive neuroscience: understand how information is represented and communicated in the brain. In particular, modeling the rapidly-changing dynamics of information flow in anatomical networks.
- ✦ **The goal** -- find ways to measure and visualize information flow and causality in human brains, and relate this to cognitive phenomena
- ✦ **Why?** -- “Knowledge of human brain connectivity will transform human neuroscience by providing not only a qualitatively novel class of data, but also by providing the basic framework necessary to synthesize diverse data and, ultimately, elucidate how our brains work in health, illness, youth, and old age.” (NIH FOA for Human Connectome Project).



# Different types of connectivity



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- **Structural Connectivity**

- anatomical





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DTI



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- ✦ symmetric, correlative





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# Many ways to model effective connectivity in EEG

- ✦ Coherence, Phase-locking value
- ✦ Cross-correlation
- ✦ Transfer Entropy
- ✦ Dynamic Causal Models
- ✦ Structural Equation Models
- ✦ Granger-Causal methods

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# Many ways to estimate coupling

Time-domain	Frequency-domain
Auto- and cross-covariance	Power Spectrum (auto- and cross-spectra)
Cross-correlation	Coherency and Partial Coherence (absCOH, imagCOH, pCOH)
Time-delay (e.g., $\operatorname{argmax}_{\tau} C(\tau)$ )	Phase slope, PLV
Mutual information, Transfer Entropy	
Granger Causality (Granger, 1969)	Granger Causality (Geweke, PDC, DTF, etc)
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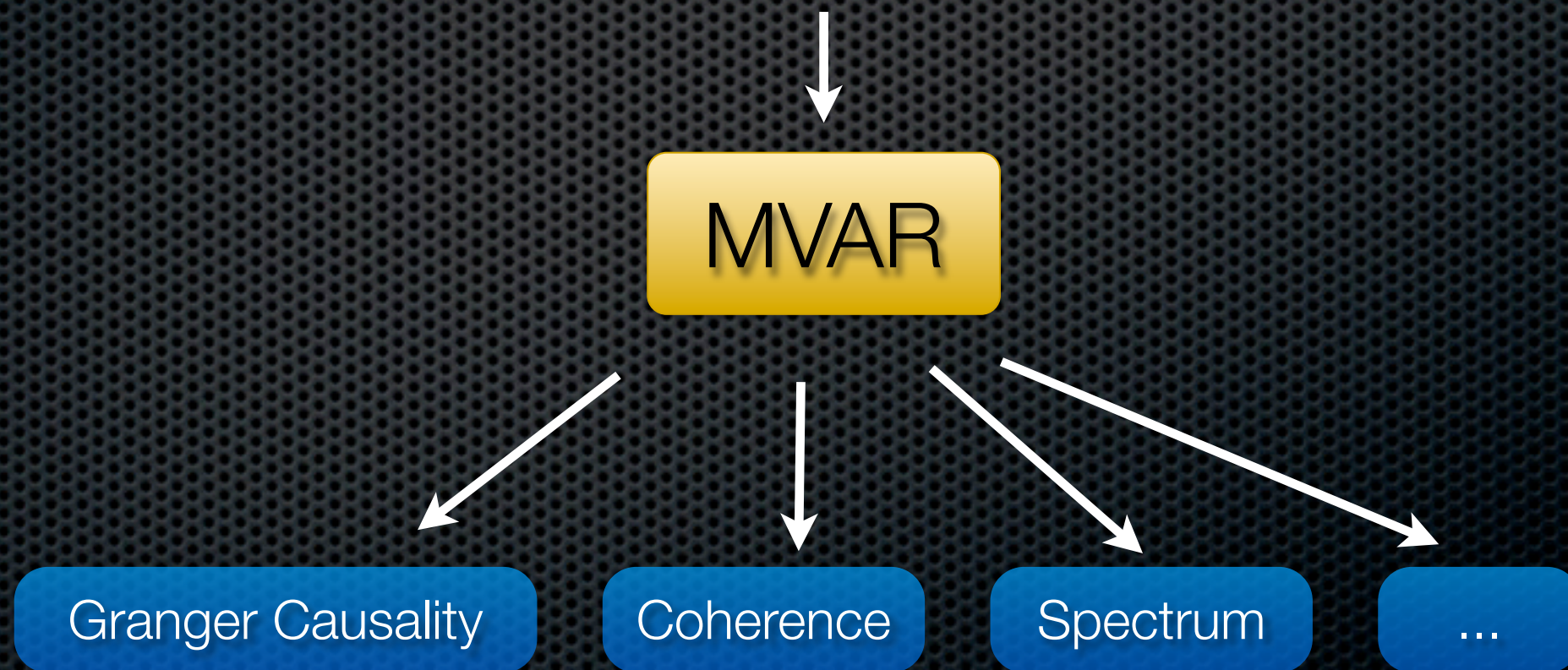
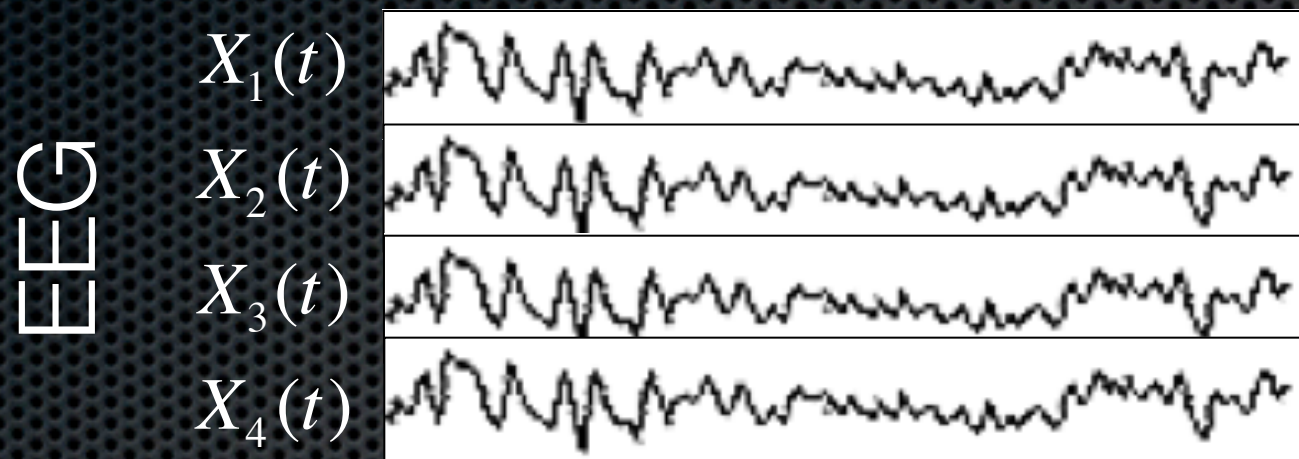


# Granger Causality

- First introduced by Wiener (1958). Later reformulated by Granger (1969) in the context of linear stochastic autoregressive models
- Relies on two assumptions:
  1. causes should precede their effects in time
  2. information in a cause's past should improve the prediction of the effect, above and beyond the information contained in the effect's own past.



# Multivariate Autoregressive (MVAR) Modeling





# Multivariate Autoregressive (MVAR) Modeling

- We have  $M$  variables (e.g., EEG channels or source activations):  
 $\mathbf{X}(t) = [\mathbf{X}_1(t), \mathbf{X}_2(t), \dots, \mathbf{X}_N(t)]^T$

MVAR  
model

$$\mathbf{X}(t) = \sum_{k=1}^p \mathbf{A}(k) \mathbf{X}(t-k) + \mathbf{E}(t)$$

model order

random noise process

multichannel data  
at current time  $t$

$M \times M$  matrix of model coefficients  
indicating variable dependencies at lag  $k$

multichannel data  $k$   
samples in the past

$$\mathbf{A}(k) = \begin{pmatrix} a_{11}(k) & \dots & a_{1M}(k) \\ \vdots & \ddots & \vdots \\ a_{M1}(k) & \dots & a_{MM}(k) \end{pmatrix}$$

$$\mathbf{E}(t) = N(0, \mathbf{V})$$



# Blackboard



# Multivariate Autoregressive (MVAR) Modeling

- Our Goal: Find least-squares estimate of **A**  
e.g., find **A** that minimizes the variance of the residuals **E**
- This is a convex problem with a unique solution, and thus **A** is completely determined by the data (and model order).
- Model order is typically determined by minimizing information criteria such as Akaike Information Criterion (AIC) for varying model order (p):

$$\text{AIC}(p) = 2\ln(\det(\mathbf{V})) + M^2p/N$$

Penalizes high model orders (parsimony)

entropy rate (amount of prediction error)



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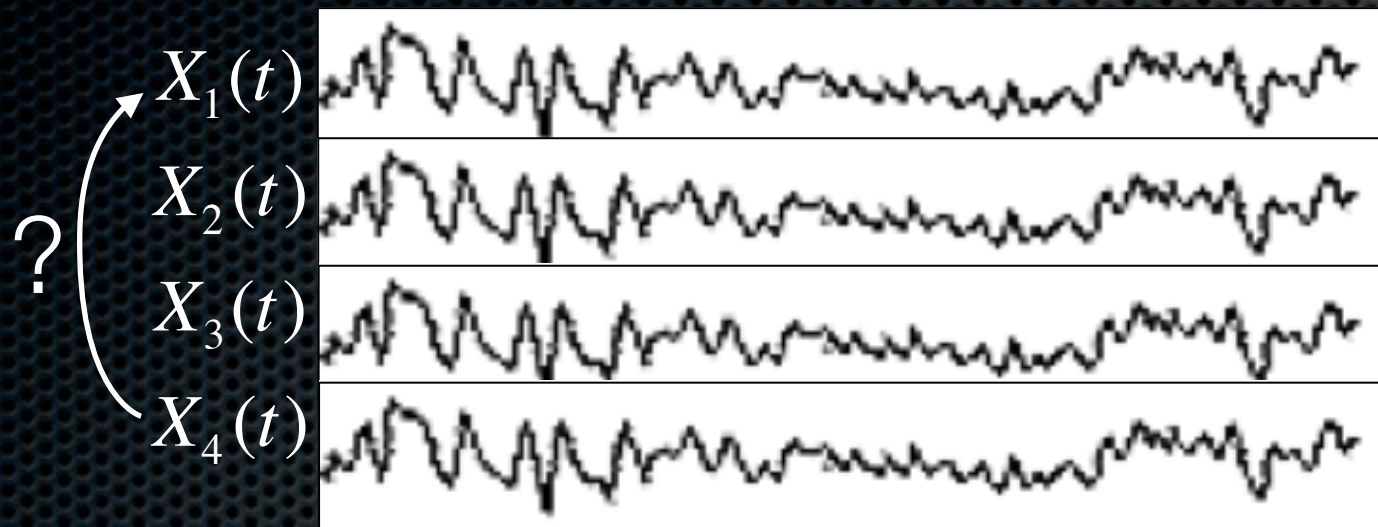
# Granger Causality

Test: Does  $\mathbf{X}_4$  granger-cause  $\mathbf{X}_1$  ?



# Granger Causality

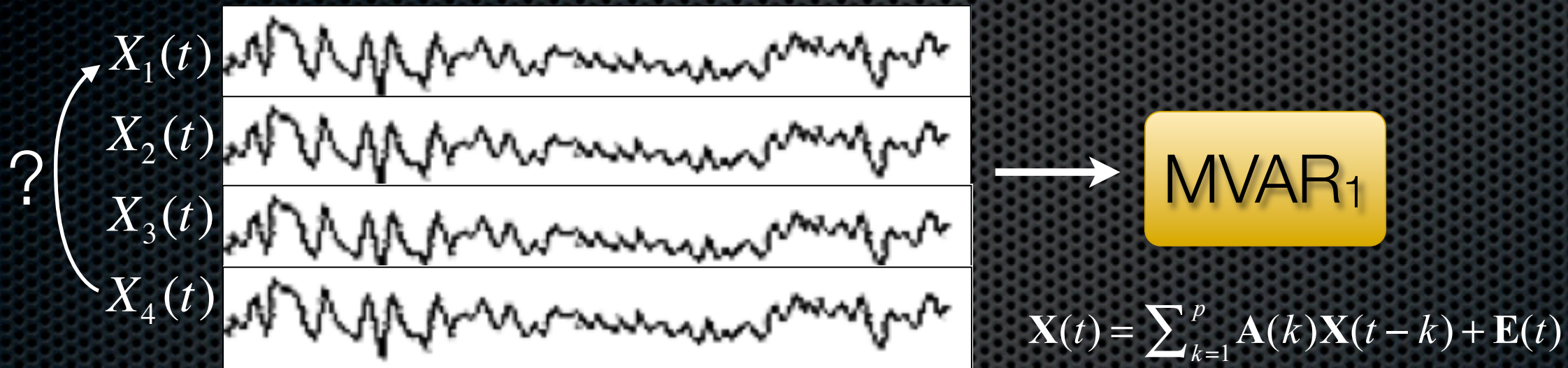
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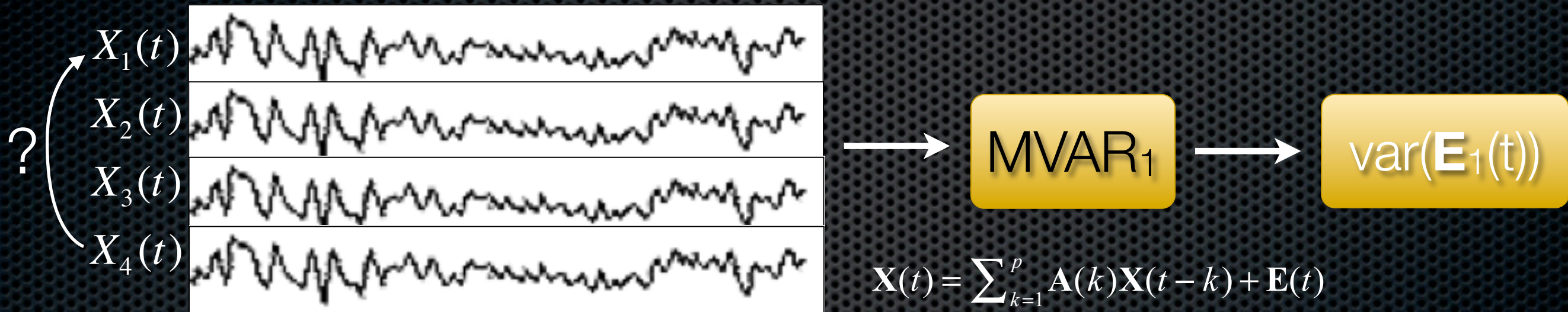
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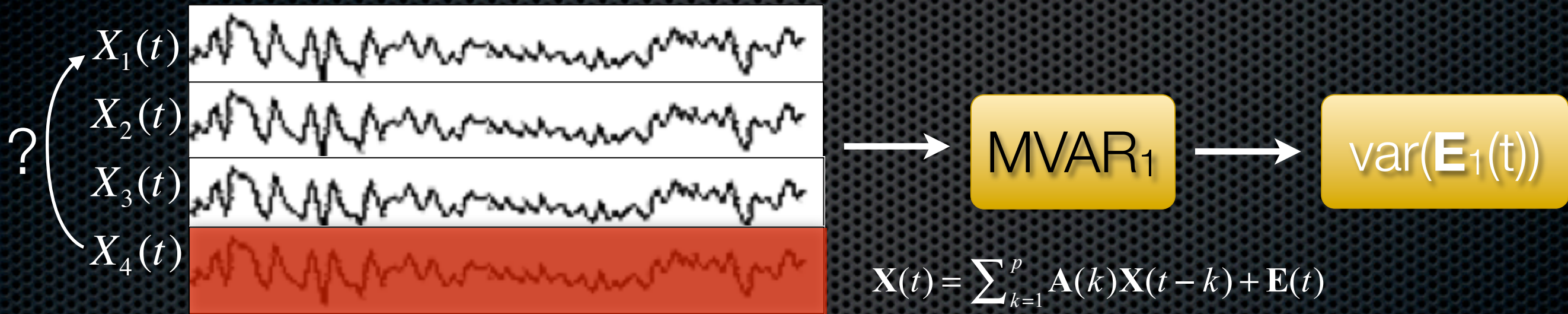
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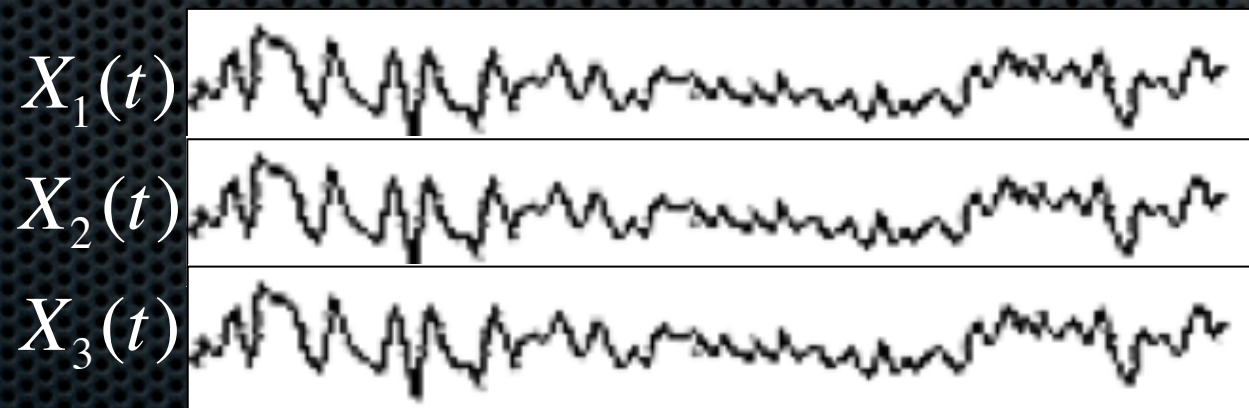
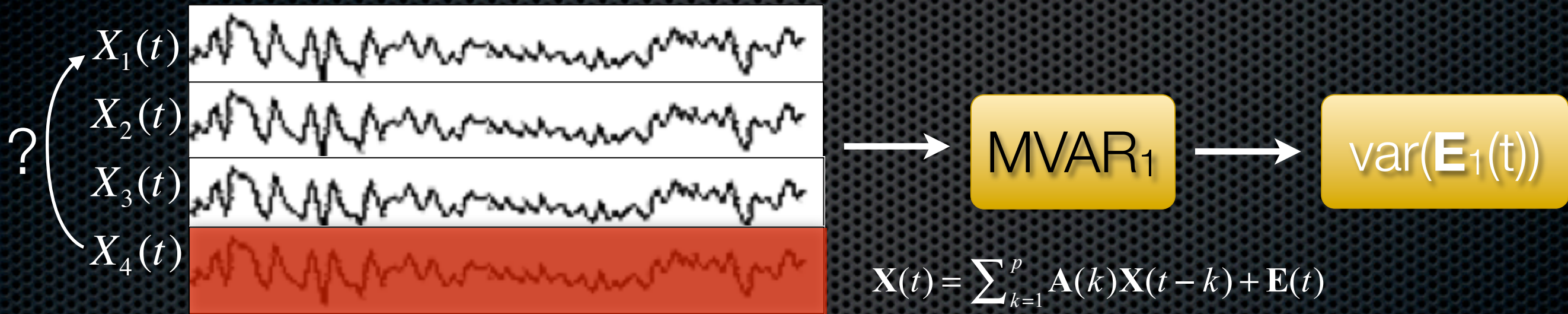
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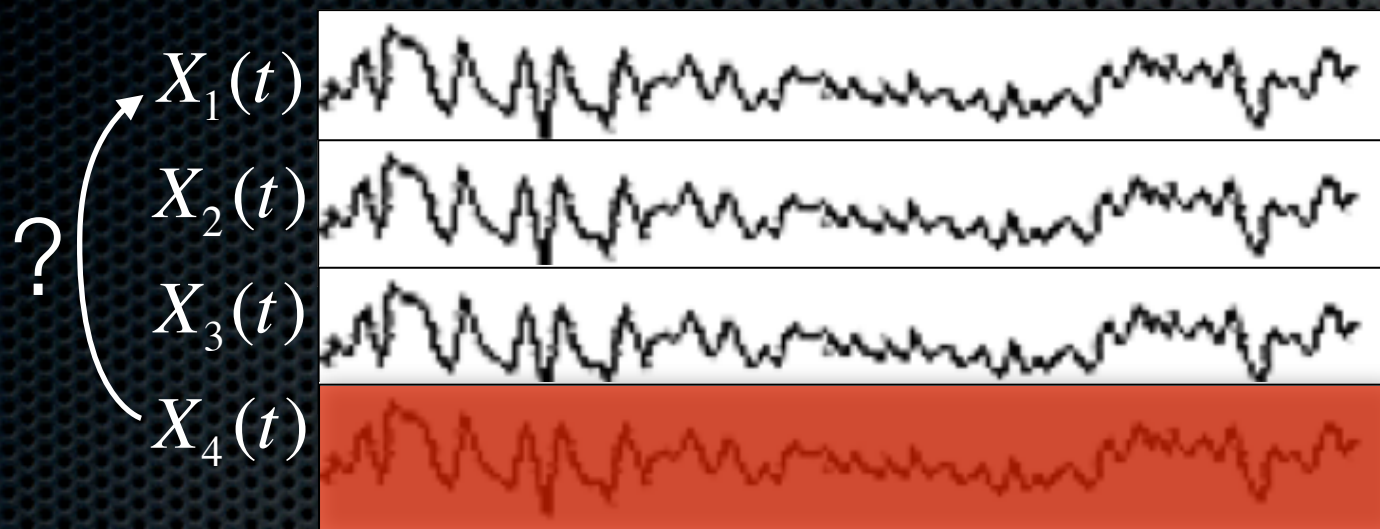
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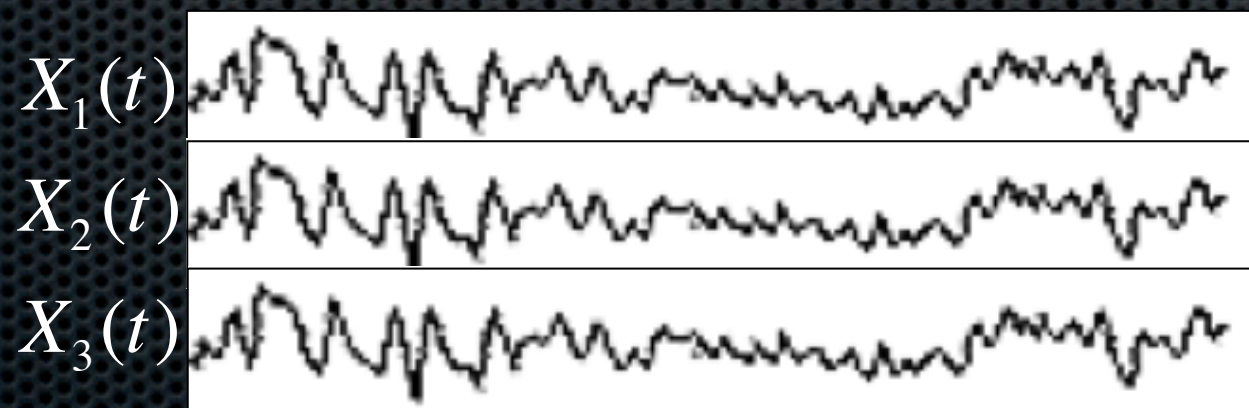


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$$\mathbf{X}(t) = \sum_{k=1}^p \mathbf{A}(k) \mathbf{X}(t-k) + \mathbf{E}(t)$$

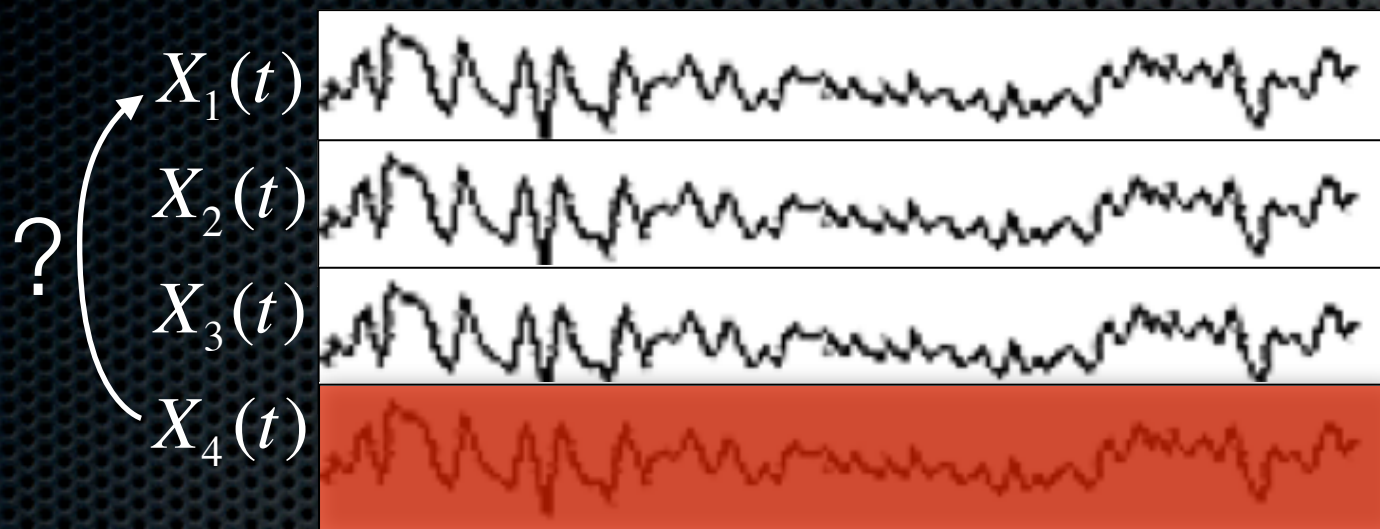


$$\mathbf{X}_{-4}(t) = \sum_{k=1}^p \tilde{\mathbf{A}}(k) \mathbf{X}_{-4}(t-k) + \tilde{\mathbf{E}}(t)$$

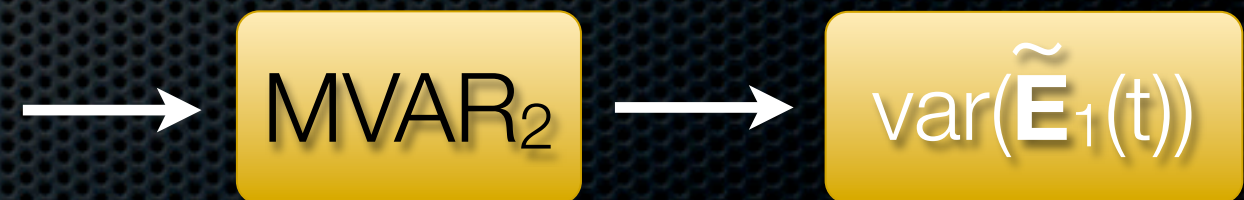
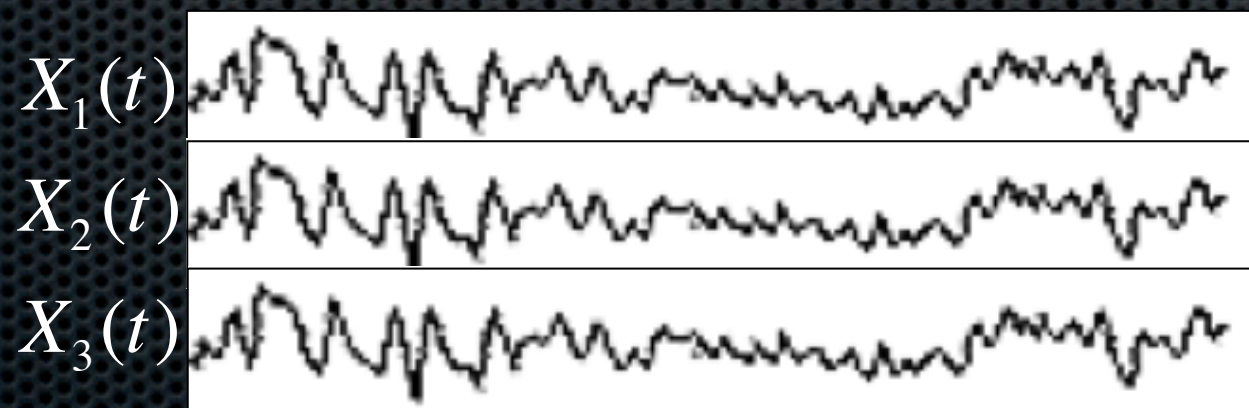


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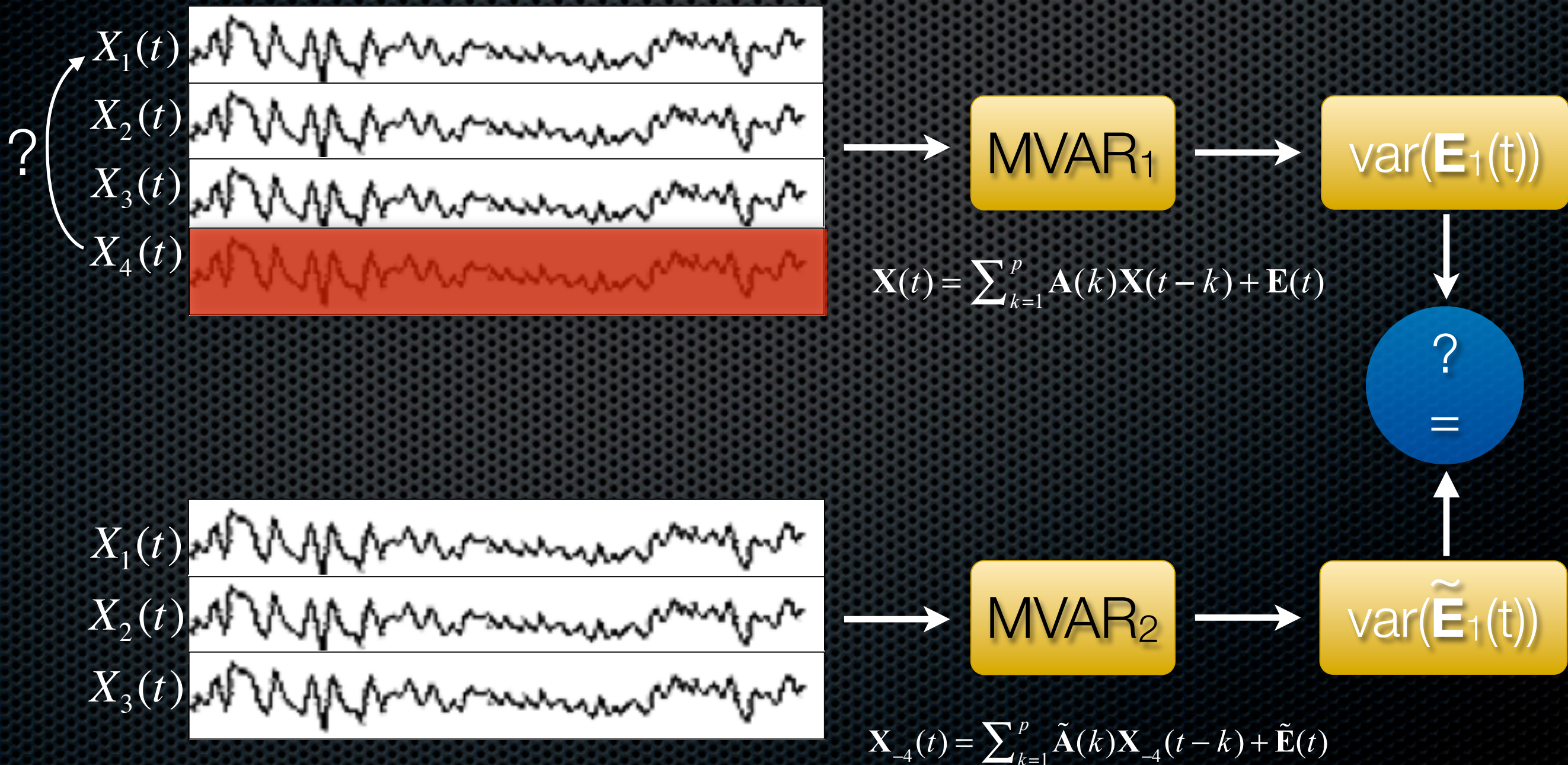


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# Granger Causality

Test: Does  $\mathbf{X}_4$  granger-cause  $\mathbf{X}_1$  ?





# Granger Causality - Time Domain

Let  $V$  represent the set of all variables in our model:  $V = \{1, 2, \dots, M\}$

$$\mathbf{X}_V(t) = \sum_{k=1}^p \mathbf{A}(k) \mathbf{X}_V(t-k) + \mathbf{E}(t)$$

Fit the full VAR model and obtain the mean-square prediction error when  $X_i$  is predicted from past values of  $\mathbf{X}_V$  :

$$\text{var}(X_i(t) | \mathbf{X}_V(\cdot)) = \text{var}(E_i(t)) = \sigma_{ii}$$

Where  $\mathbf{X}_V(\cdot) = \{\mathbf{X}_V(t-k), k \in \{1, \dots, p\}\}$

Now, suppose we exclude  $j$  from the set of variables and re-fit the model

$$\mathbf{X}_{-j}(t) = \sum_{k=1}^p \tilde{\mathbf{A}}(k) \mathbf{X}_{-j}(t-k) + \tilde{\mathbf{E}}(t)$$

$$\text{var}(X_i(t) | \mathbf{X}_{-j}(\cdot)) = \text{var}(\tilde{E}_i(t)) = \tilde{\sigma}_{ii}$$

In general,  $\sigma_{ii} \geq \tilde{\sigma}_{ii}$  and  $\sigma_{ii} = \tilde{\sigma}_{ii}$  if and only if the best linear predictor of  $X_i(t)$  based on the full past  $\mathbf{X}_V(t)$  does not depend on the past of  $X_j$



# Granger Causality – Time Domain

❖ This leads us to the following definition:

❖ Let  $I$  and  $J$  be two disjoint subsets of  $V$ . Then  $\mathbf{X}_J$  is granger *non-causal* with respect to  $\mathbf{X}_I$  conditioned on  $\mathbf{X}_V$  if the following two equivalent conditions hold:

1.  $|var(X_i(t) | \mathbf{X}_V(\cdot))| = |var(X_i(t) | \mathbf{X}_{-j}(\cdot))|$
2.  $\mathbf{A}_{IJ}(k) = 0$  for all  $k \in \{1, \dots, p\}$

❖ Equivalently,  $\mathbf{X}_J$  *granger-causes*  $\mathbf{X}_I$  if the RHS of (1) is significantly less than the LHS (including past of  $\mathbf{X}_J$  significantly reduces prediction error of  $\mathbf{X}_I$ ) or if any  $\mathbf{A}_{IJ}(k)$  is significantly greater than zero.

❖ Granger (1969) quantified this definition for bivariate processes in the form of an F-ratio:

$$F_{X_1 \leftarrow X_2} = \ln \left( \frac{var(\tilde{E}_1)}{var(E_1)} \right) = \ln \left( \frac{var(X_1(t) | X_1(\cdot))}{var(X_1(t) | X_1(\cdot), X_2(\cdot))} \right)$$



# Granger Causality Quiz

- Example: 2-channel VAR process of order 1

$$\begin{pmatrix} X_1(t) \\ X_2(t) \end{pmatrix} = \begin{pmatrix} 0.5 & 0 \\ 0.7 & 0.2 \end{pmatrix} \begin{pmatrix} X_1(t-1) \\ X_2(t-1) \end{pmatrix} + \begin{pmatrix} E_1(t) \\ E_2(t) \end{pmatrix}$$

$$X_1(t) = -0.5X_1(t-1) + 0X_2(t-1) + E_1(t)$$

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Which causal structure does this model correspond to?





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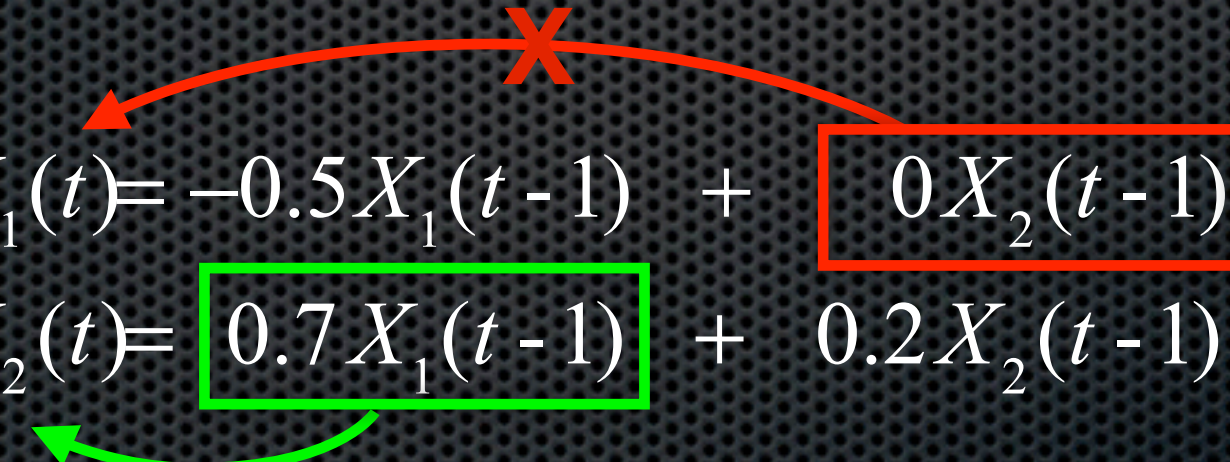




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Which causal structure does this model correspond to?

a) 1 → 2

b) 1 ← 2

c) 1 ↔ 2



# Granger Causality – Frequency Domain

- ✦ Granger-causal relationships can also be established in the frequency domain

$$\mathbf{X}(t) = \sum_{k=1}^p \mathbf{A}(k) \mathbf{X}(t-k) + \mathbf{E}(t)$$



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Rearranging terms we find that

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Fourier-transforming both sides yeilds

$$\mathbf{A}(f) \mathbf{X}(f) = \mathbf{E}(f) \quad \text{where } \mathbf{A}(f) = -\sum_{k=0}^p \mathbf{A}(k) e^{-i2\pi f k}$$

Likewise,  $\mathbf{X}(f)$  and  $\mathbf{E}(f)$  correspond to the fourier transforms of the data and residuals, respectively



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Multiplying on the left by  $\mathbf{A}(f)^{-1}$  yeilds

$$\mathbf{X}(f) = \mathbf{A}(f)^{-1} \mathbf{E}(f) = \mathbf{H}(f) \mathbf{E}(f)$$

Where  $\mathbf{H}(f)$  is the *transfer matrix* of the system.

Likewise,  $\mathbf{X}(f)$  and  $\mathbf{E}(f)$  correspond to the fourier transforms of the data and residuals, respectively



# Granger Causality – Frequency Domain

- ✧ The power spectral density matrix is given by  
 $\mathbf{S}(f) = \mathbf{X}(f)\mathbf{X}(f)^* = \mathbf{H}(f)\mathbf{V}\mathbf{H}^*(f)$  where  $\mathbf{V} = \text{cov}(\mathbf{E})$ .
- ✧ From  $\mathbf{S}(f)$ ,  $\mathbf{H}(f)$ , and  $\mathbf{A}(f) = \mathbf{H}(f)^{-1}$  we can obtain several useful estimates of coherence and causality/information flow.
- ✧ Definition:  $\mathbf{A}_{ij}(f) = 0$  for all frequencies  $f$  if and only if  $X_j$  is granger non-causal for  $X_i$ .
- ✧ In other words, if  $\mathbf{A}_{ij}(f)$  is significantly non-zero, then  $X_j$  granger-causes  $X_i$  (at frequency  $f$ )



# Granger Causality – Frequency Domain Estimators

## ✦ *Coherence measures*

$$C_{ij}(f) = \frac{S_{ij}(f)}{\sqrt{S_{ii}(f)S_{jj}(f)}}$$

Coherence

---

$$P_{ij}(f) = \frac{\hat{S}_{ij}(f)}{\sqrt{\hat{S}_{ii}(f)\hat{S}_{jj}(f)}}$$

$$\hat{\mathbf{S}} = \mathbf{S}^{-1}$$

Partial coherence

---

$$G_i(f) = \sqrt{1 - \frac{\det(\mathbf{S}(f))}{S_{ii}(f)\mathbf{M}_{ii}(f)}}$$

Multiple coherence



# Granger Causality – Frequency Domain Estimators

✱ (some) Causal measures

$$\theta_{ij}^2(f) = |H_{ij}(f)|^2$$

(non-normalized) Directed Transfer Function (DTF)

$$\gamma_{ij}^2(f) = \frac{|H_{ij}(f)|^2}{\sum_{k=1}^M |H_{ik}(f)|^2}$$

Normalized DTF

$$\delta_{ij}^2(f) = \eta_{ij}^2(f) P_{ij}^2(f) \quad \text{where} \quad \eta_{ij}^2(f) = \frac{|H_{ij}(f)|^2}{\sum_f \sum_{k=1}^M |H_{ik}(f)|^2}$$

ffDTF

partial coherence

Direct DTF

$$\pi_{ij}^2(f) = \frac{A_{ij}(f)^2}{\sum_{k=1}^M |A_{kj}(f)|^2}$$

Normalized Partial Directed Coherence (PDC)

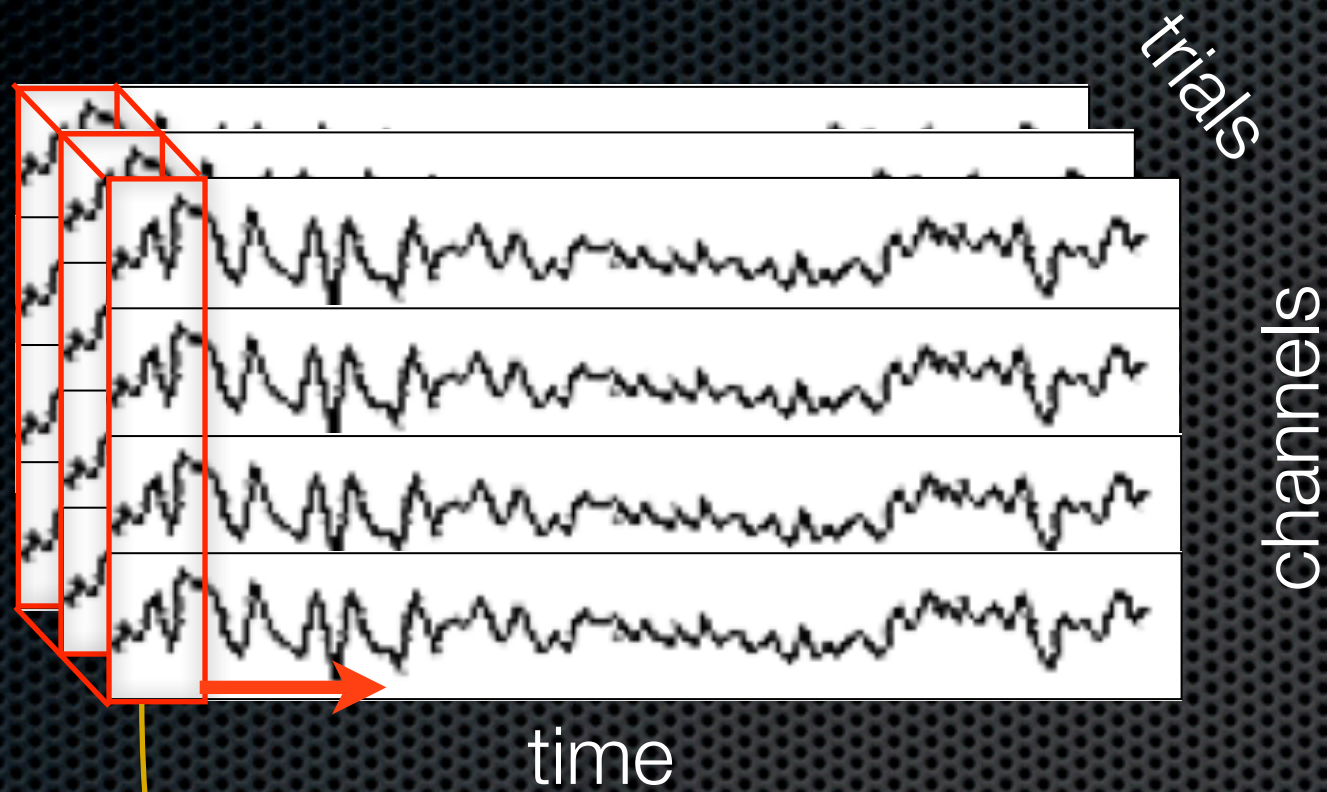


# Time-varying GC

- ✧ If we have multiple trials, we can make use of adaptive autoregressive models to allow time-varying estimates of granger-causality (useful for globally non-stationary processes exhibiting local stationarity)
- ✧ Each trial is treated as a realization of the same underlying stochastic process. We can average short-window estimates of the covariance matrices and model coefficients over multiple trials to reduce bias.
- ✧ We apply a (short) sliding window with high overlap and fit a separate model for each window.

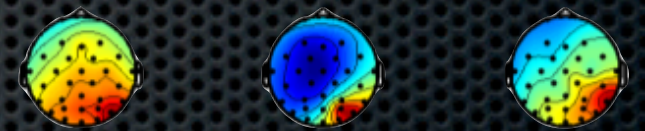


# Time-Varying GC

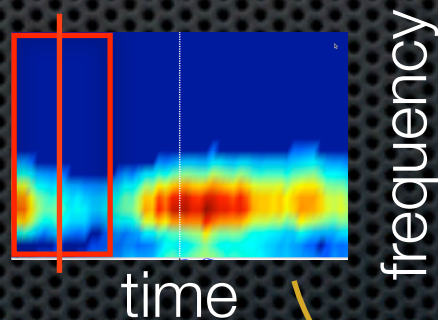


Analogous to short-time fourier transform

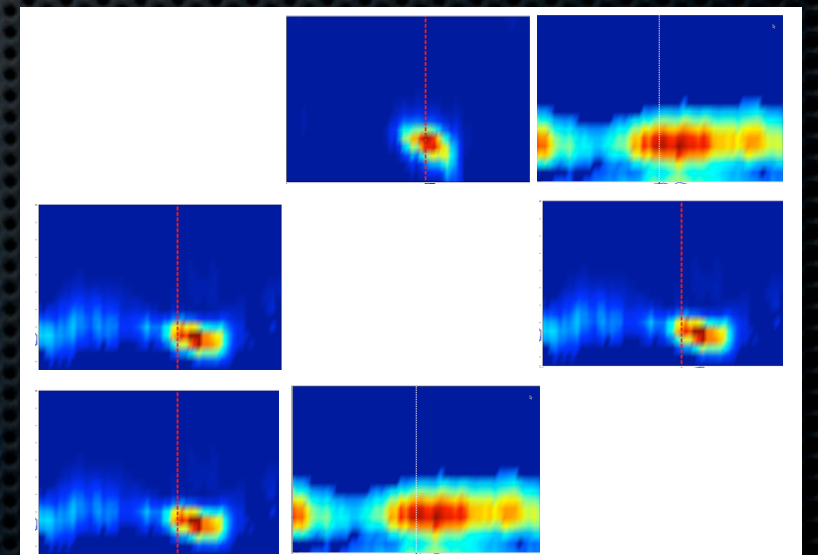
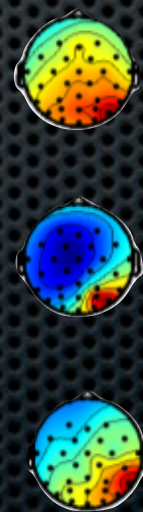
From



MVAR



To

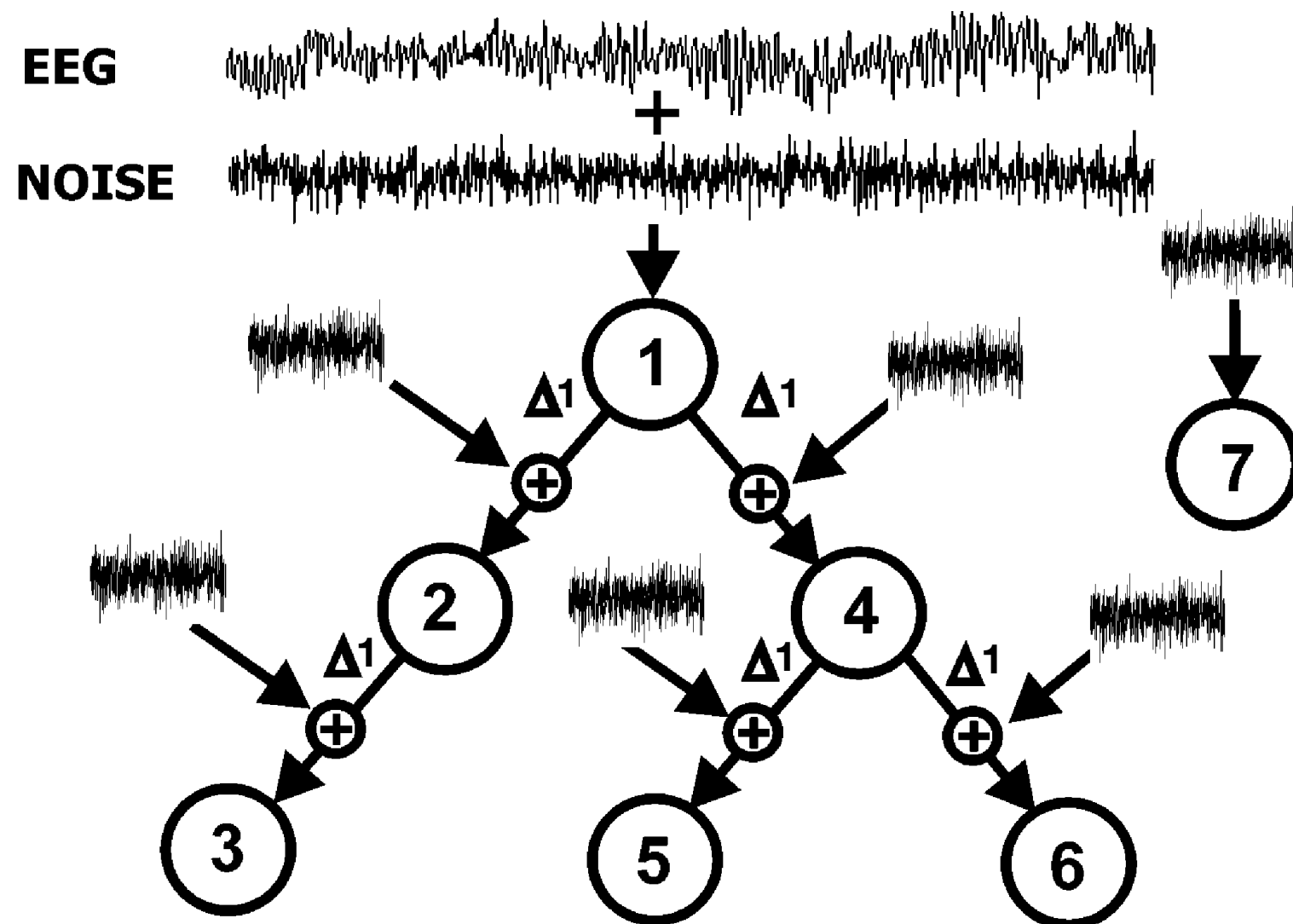


$$\mathbf{X}(t) = \sum_{k=1}^p \mathbf{A}(k) \mathbf{X}(t-k) + \mathbf{E}(t)$$

$$\mathbf{A}(f) \mathbf{X}(f) = \mathbf{E}(f)$$



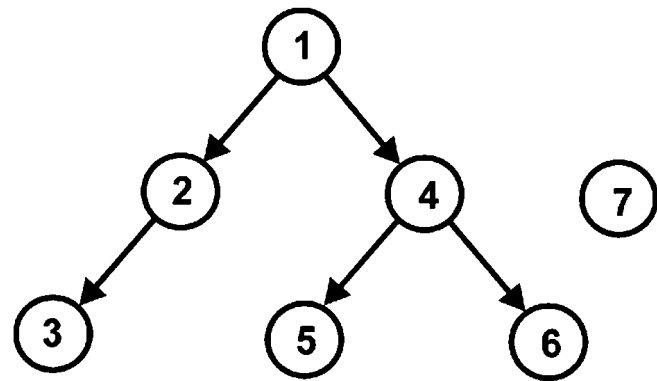
# Issue1: Which Measure to Use?



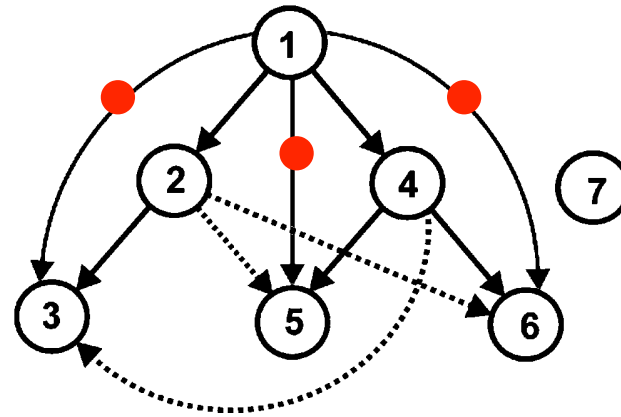
Kus et al, 2004



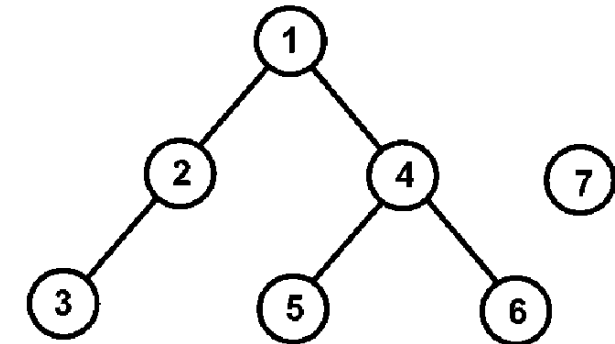
# Ground Truth



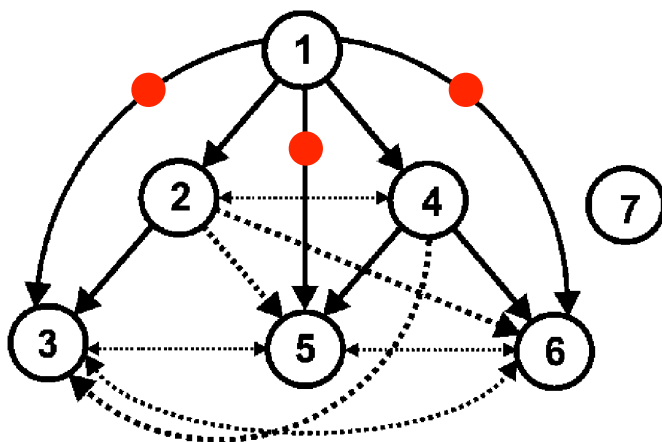
# Coherence



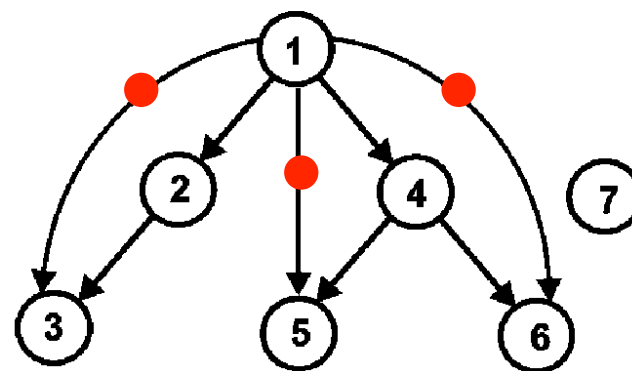
# Partial Coherence



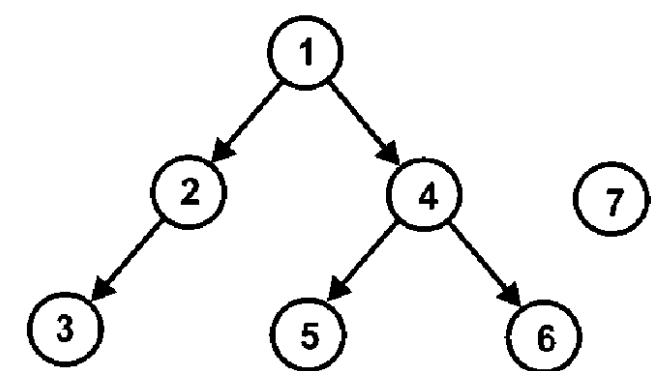
# Bivariate GC



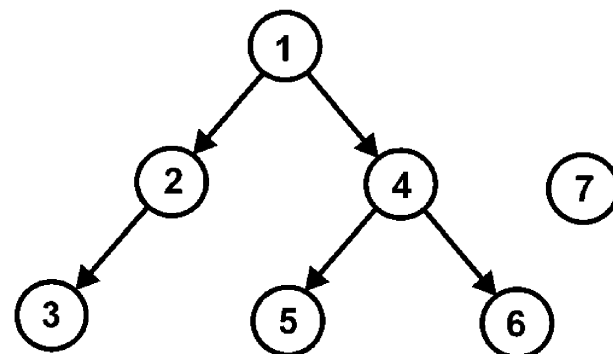
# DTF\*



# dDTF



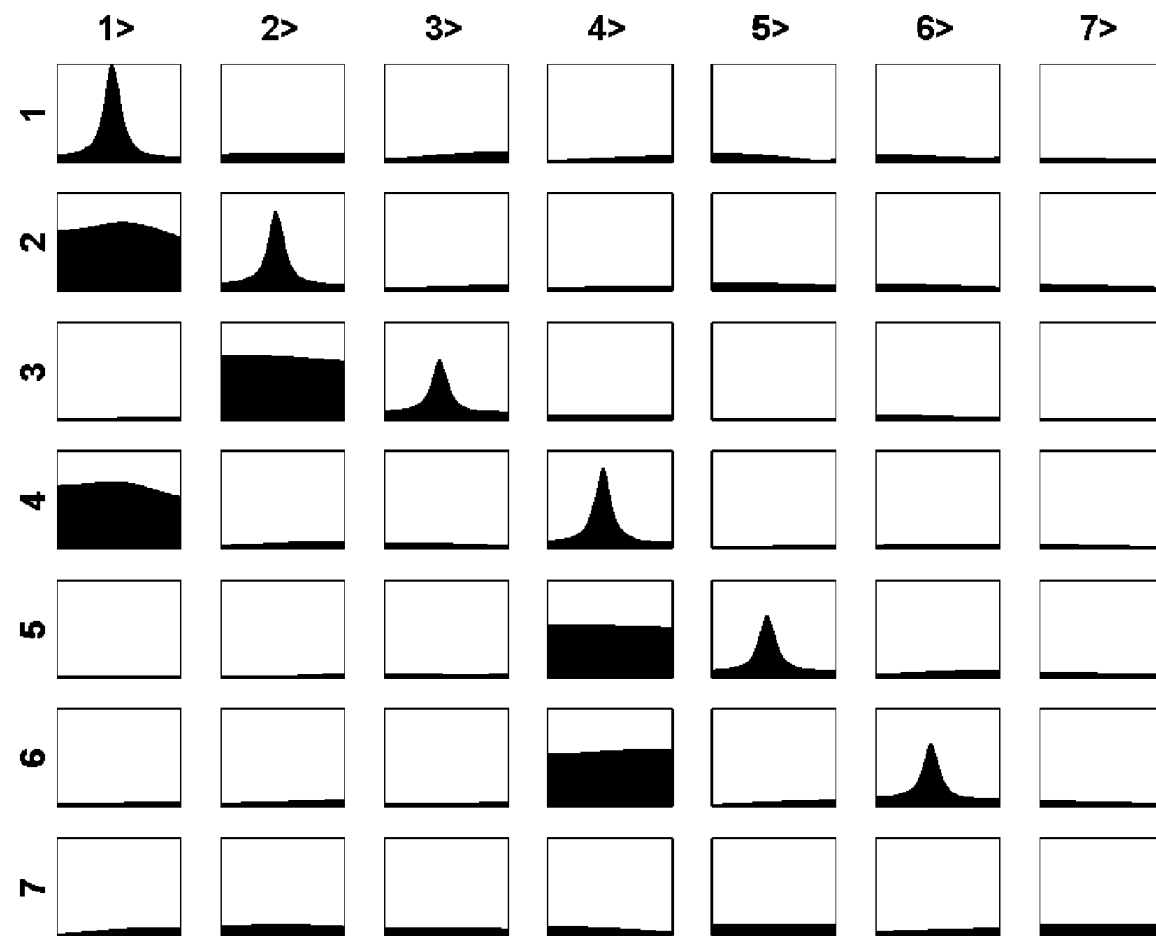
# PDC\*



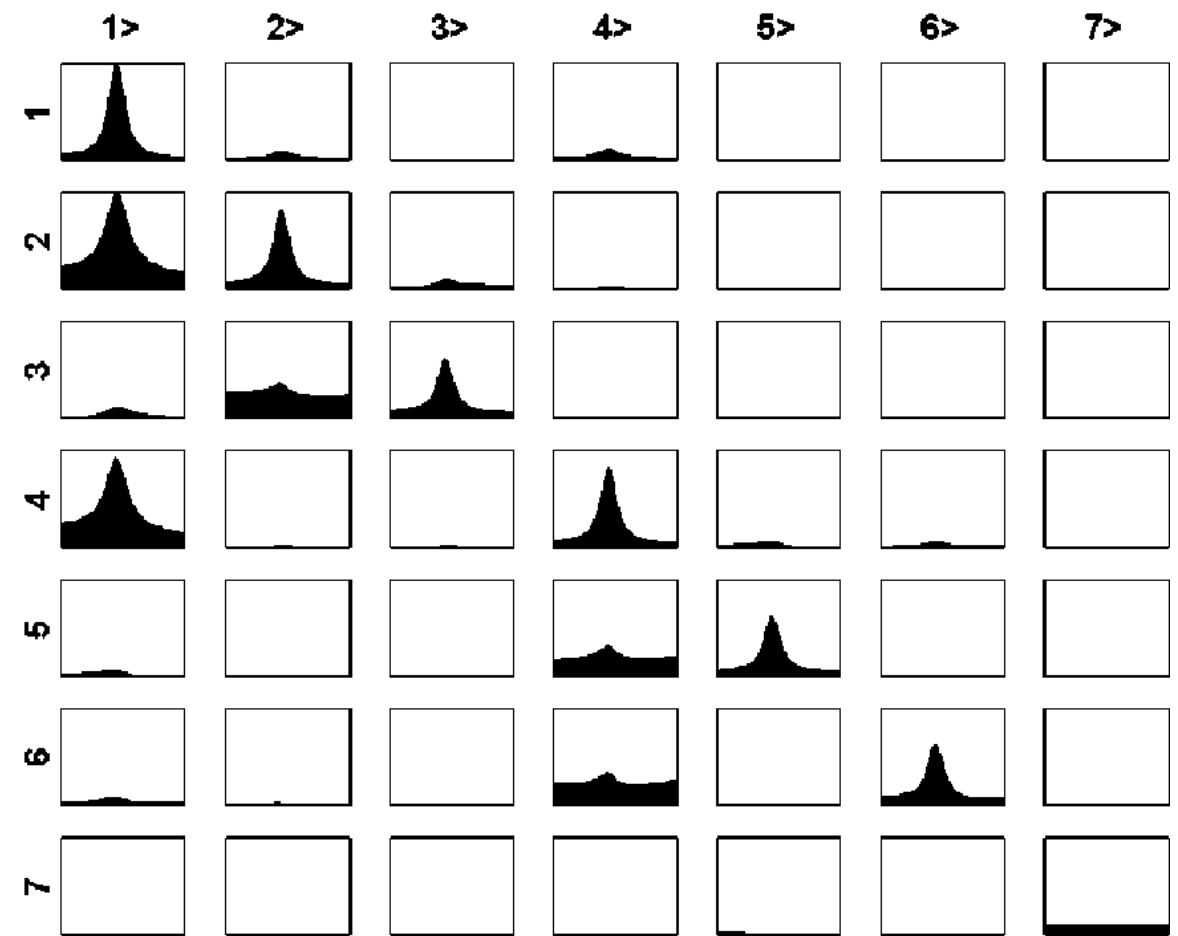
..... spurious  
 —●— indirect true flow  
 — direct true flow  
 \* non-normalized



# PDC versus DTF methods (spectral considerations)



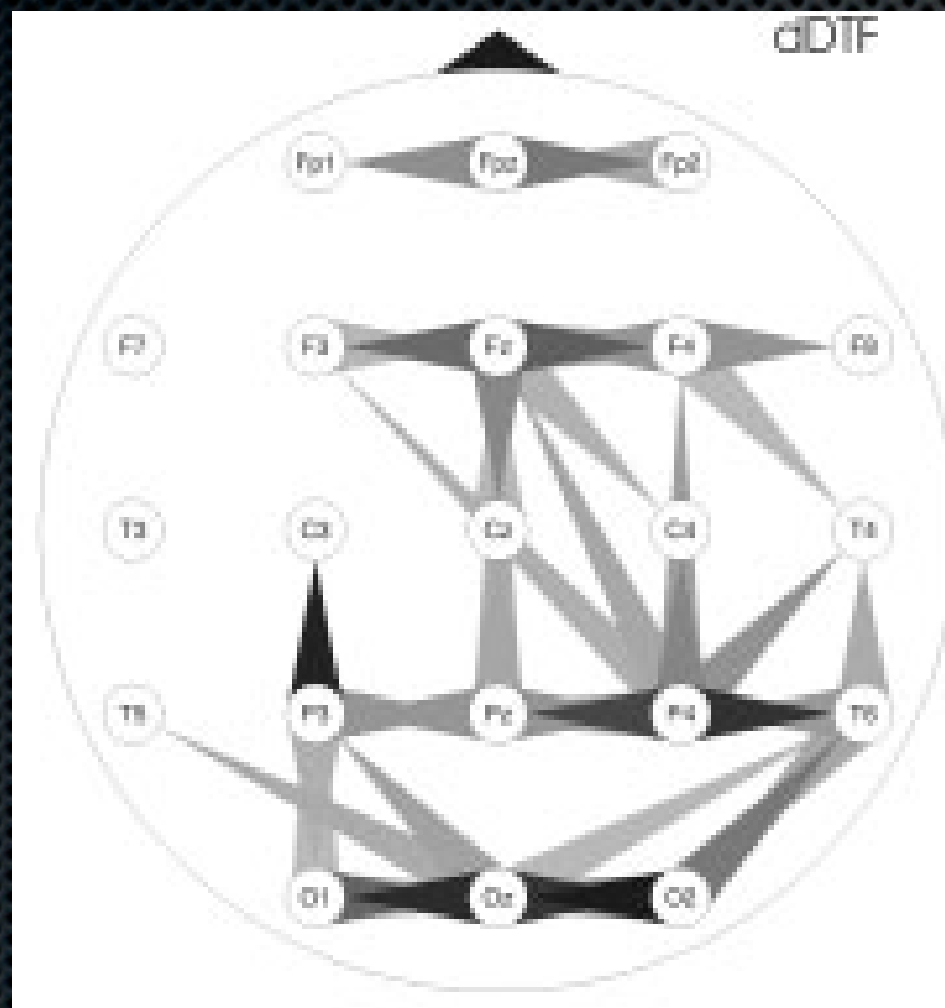
PDC



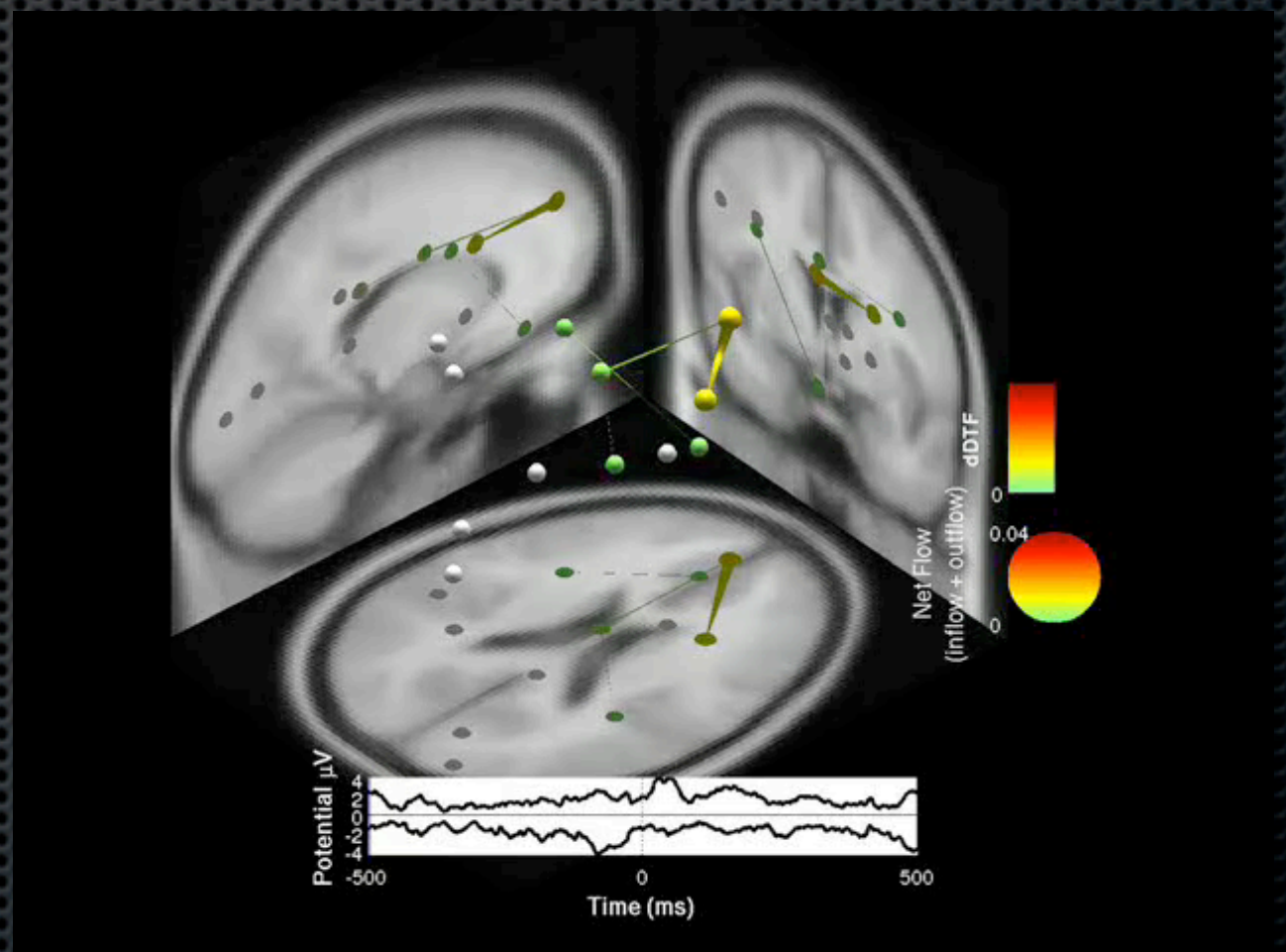
dDTF



# Issue 2: Scalp or Source?

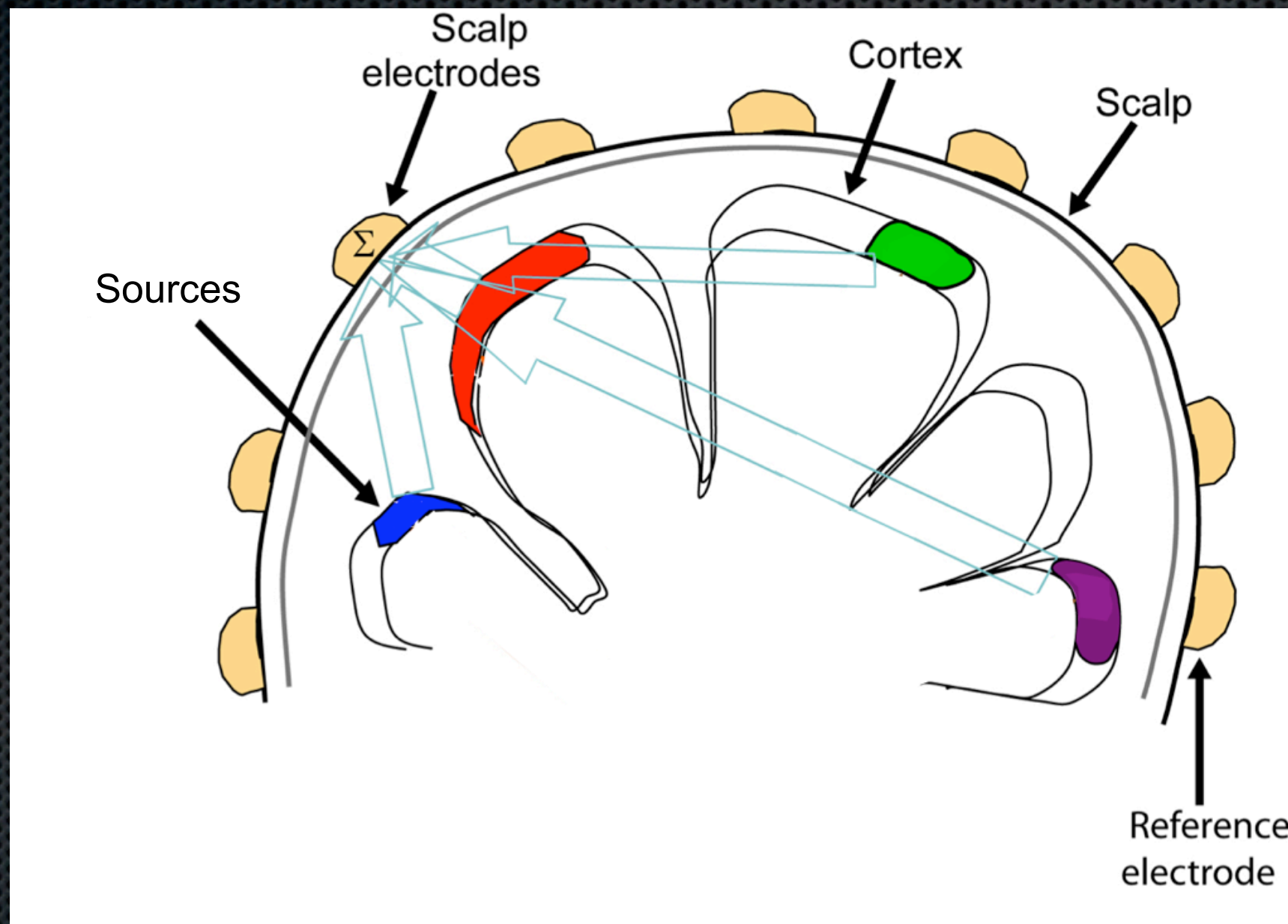


or





# Scalp or Source?



Volume Conduction

Makeig, 2007



# Volume Conduction (VC)

- ❖ Assumption: VC only affects instantaneous correlations and, since Granger Causality ignores instantaneous correlations, it should be immune to spurious correlations induced by VC. Therefore GC on channel data is sensible.
- ❖ False! VC affects *all* correlations

$$S(t) = \sum_{k=1}^p A(k)S(t-k) + E(t)$$

$$X(t) = MS(t)$$

$$X(t) = MS(t) = \sum_{k=1}^p MA(k)M^{-1}X(t-k) + ME(t)$$

$$\hat{V} = MVM^T$$

$$\hat{A}(k) = MA(k)M^{-1}$$

Noise covariance  
(instantaneous  
correlation) is  
transformed by M...

...but so is every  
coefficient matrix



# Volume Conduction (VC)

- ✧ Solutions?
- ✧ Apply BSS (e.g., ICA) to approximate mixing matrix,  $M$ , and recover sources,  $S$ . Then fit VAR models to source activations.
- ✧ Problem? It is not sufficient to identify just any mixing matrix. The “true” mixing matrix,  $M$ , must be identified to recover the “true” sources,  $S$ . This constitutes solving the inverse problem (provably intractable).
- ✧ ICA involves additional assumptions (global temporal independence of the sources)

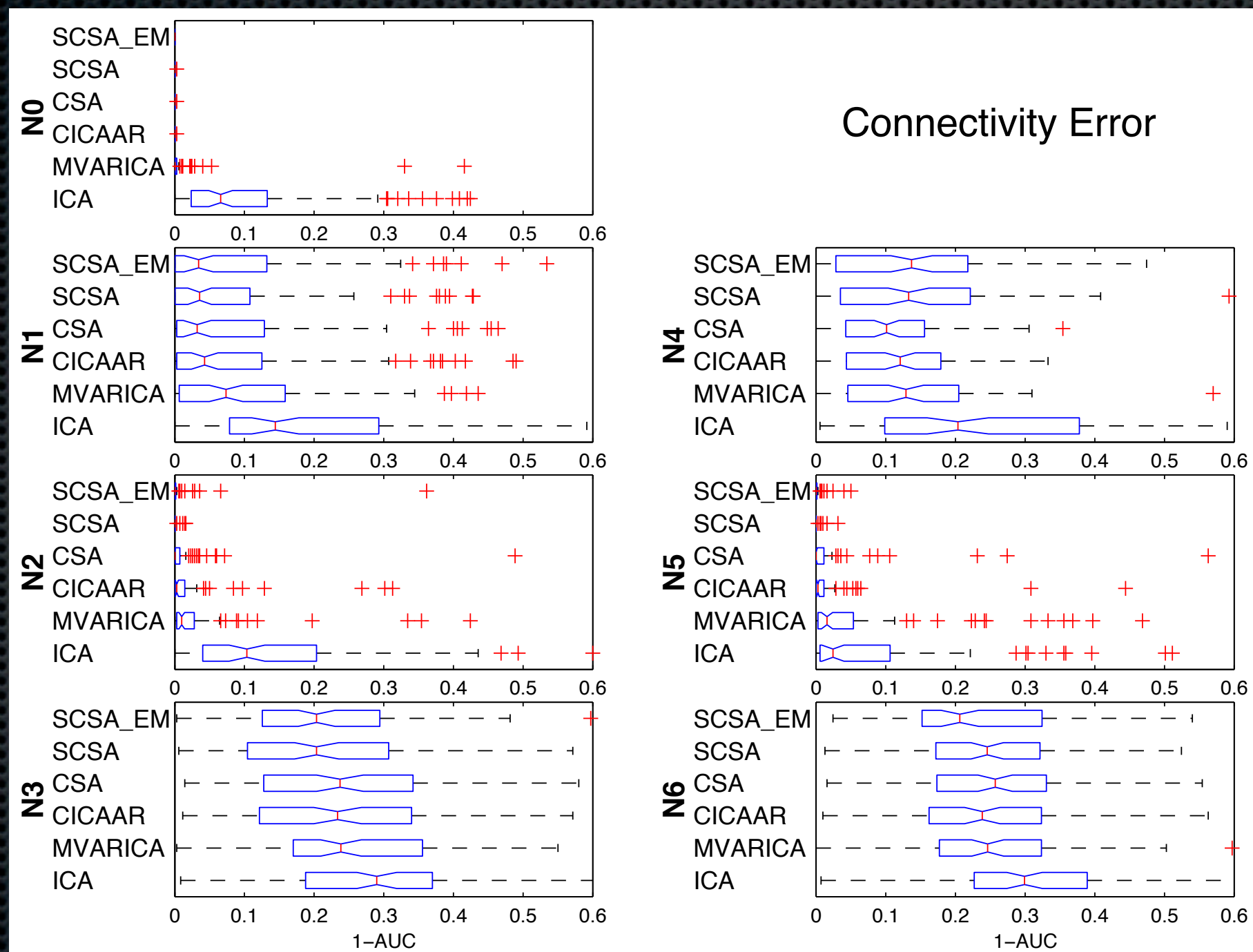


# Estimating Dependency of Independent Components?

- Isn't it a contradiction to examine dependence between Independent Components?
- Instantaneous (e.g., Infomax) ICA only explicitly enforces *instantaneous* independence. Time-delayed dependencies may be preserved (note this is *not* the case for temporal decorrelation methods like SOBI or complex ICA)
- ICA seeks to maximize *global* independence, transient dependencies are often preserved



# Estimating Dependency of Independent Components?



Haufe et al, 2008



# TUTORIAL



# Information Flow and Causality Toolbox (IFACT)

- A new (alpha) toolbox for source-space electrophysiological information flow and causality analysis (single-subject or group analysis) integrated into the EEGLAB software environment
- Modular architecture intended to support multiple modeling approaches
- Standardized data format and flexible access to sophisticated EEGLAB routines
- Emphasis on time-frequency domain approaches
- Novel interactive visualization methods for exploratory analysis of connectivity across time, frequency, and spatial location
- Group statistics via the EEGLAB STUDY routines (in development)



# Preprocessing



Preprocessing

Modeling



Preprocessing

Modeling

Statistics



Preprocessing

Modeling

Statistics

Visualization



Preprocessing

Modeling

Statistics

Visualization

- ✦ **Source-separation and localization**  
(performed externally using EEGLAB or other toolboxes)
- ✦ Filtering/Detrending
- ✦ Downsampling
- ✦ Differencing
- ✦ Normalization (temporal or ensemble)
- ✦ Trial balancing
- ✦ Tests for stationarity of the data (linear methods)

...



Preprocessing

Modeling

Statistics

Visualization

Model Fitting

Validation

Connectivity



Preprocessing

Modeling

Statistics

Visualization

Model Fitting

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Connectivity



Preprocessing

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Connectivity

	Linear	Nonlinear
Parametric	<div>MVAR Modeling</div> <div>Sparse MVAR</div> <div>Bayesian MVAR</div>	Dual Extended Kalman Filtering
Nonparametric	<div>Nonparametric MVAR (spectral factorization)</div> <div>Multivariate phase-distribution</div>	Transfer Entropy



fully implemented



partially-developed



coming soon



Preprocessing

Modeling

Statistics

Visualization

Model Fitting

Validation

Connectivity

- ✦ Whiteness of Residuals

- ✦ Portmanteau tests

- ✦ Autocorrelation function

- ✦ Durbin-Watson test

- ✦ Model Consistency

- ✦ Model Stability



fully implemented



partially-developed



coming soon



Preprocessing

Modeling

Statistics

Visualization

Model Fitting

Validation

Connectivity

MVAR

- Power spectrum (ERSP)
- Coherence (Coh), Partial Coherence (pCoh), Multiple Coherence (mCoh)
- Partial Directed Coherence (PDC)
- Generalized PDC (GPDC)
- Partial Directed Coherence Factor (PDCF)
- Renormalized PDC (rPDC) \*
- Directed Transfer Function (DTF)
- Direct Directed Transfer Function (dDTF)
- Granger-Geweke Causality (GGC)
- Conditional GGC
- Blockwise GGC \*

Other

- Transfer Entropy \*
- Multivariate phase-locking value (mPLV) \*



fully implemented



partially-developed



coming soon



Preprocessing

Modeling

Statistics

Visualization



Preprocessing

Modeling

Statistics

Visualization

## Parametric

Asymptotic analytic estimates of confidence intervals

Applies to: PDC, nPDC, DTF, nDTF, rPDC

Tests:  $H_{\text{null}}$ ,  $H_{\text{base}}$ ,  $H_{\text{AB}}$

Confidence intervals using thin-plate smoothing splines

Applies to: dDTF

Tests:  $H_{\text{base}}$ ,  $H_{\text{AB}}$

$$H_{\text{null}} : \mathbf{C}_{ij} \leq \mathbf{C}_{\text{null}}$$

$$H_{\text{base}} : \mathbf{C}_{ij} \leq \mathbf{C}_{\text{baseline}}$$

$$H_{\text{AB}} : \mathbf{C}_{ij}^{\text{A}} = \mathbf{C}_{ij}^{\text{B}}$$



fully implemented



partially-developed



coming soon



Preprocessing

Modeling

Statistics

Visualization

## Parametric

Asymptotic analytic estimates of confidence intervals

Applies to: PDC, nPDC, DTF, nDTF, rPDC

Tests:  $H_{\text{null}}$ ,  $H_{\text{base}}$ ,  $H_{\text{AB}}$

Confidence intervals using thin-plate smoothing splines

Applies to: dDTF

Tests:  $H_{\text{base}}$ ,  $H_{\text{AB}}$

## Non-parametric

Phase-randomization

Applies to: all

Tests:  $H_{\text{null}}$

Permutation Tests

Applies to: all

Tests:  $H_{\text{AB}}$ ,  $H_{\text{base}}$

Bootstrap and Jackknife

Applies to: all

Tests:  $H_{\text{AB}}$ ,  $H_{\text{base}}$

$$H_{\text{null}} : \mathbf{C}_{ij} \leq \mathbf{C}_{\text{null}}$$

$$H_{\text{base}} : \mathbf{C}_{ij} \leq \mathbf{C}_{\text{baseline}}$$

$$H_{\text{AB}} : \mathbf{C}_{ij}^{\text{A}} = \mathbf{C}_{ij}^{\text{B}}$$



fully implemented



partially-developed



coming soon



Preprocessing

Modeling

Statistics

Visualization

Interactive Time-Frequency Grid

Interactive Brainmovie3D

Interactive Causal Projection

Directed Graphs on anatomicals (ECoG)

and more...

All of these currently support single-subject or (beta) group analysis  
ROI connectivity analysis can currently be performed using dipole clustering



fully implemented



partially-developed

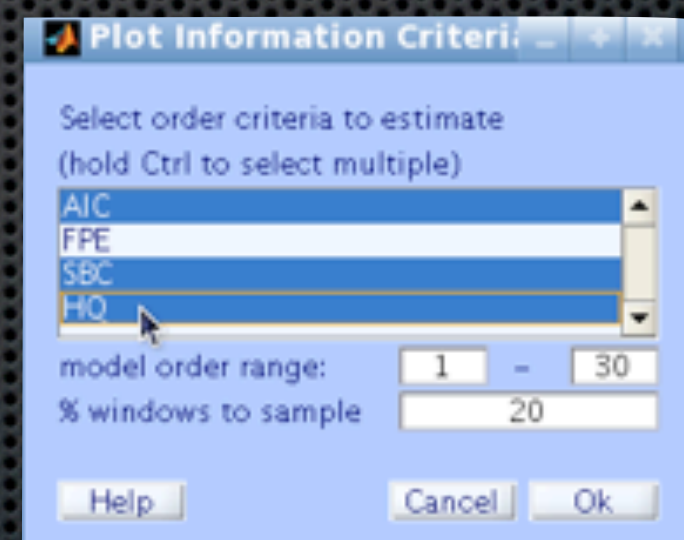
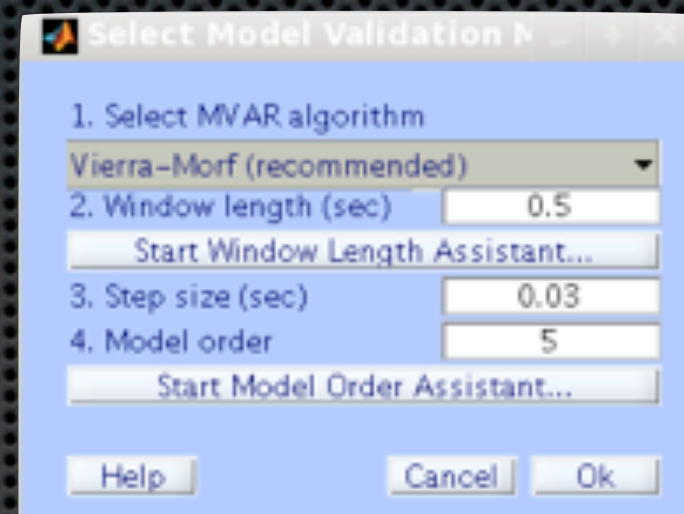
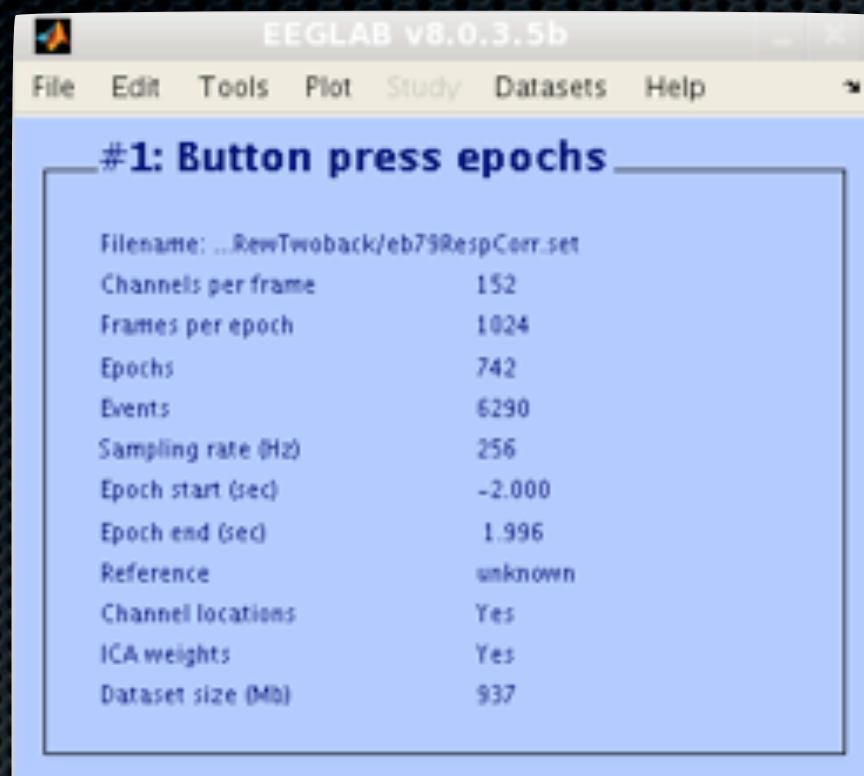


coming soon

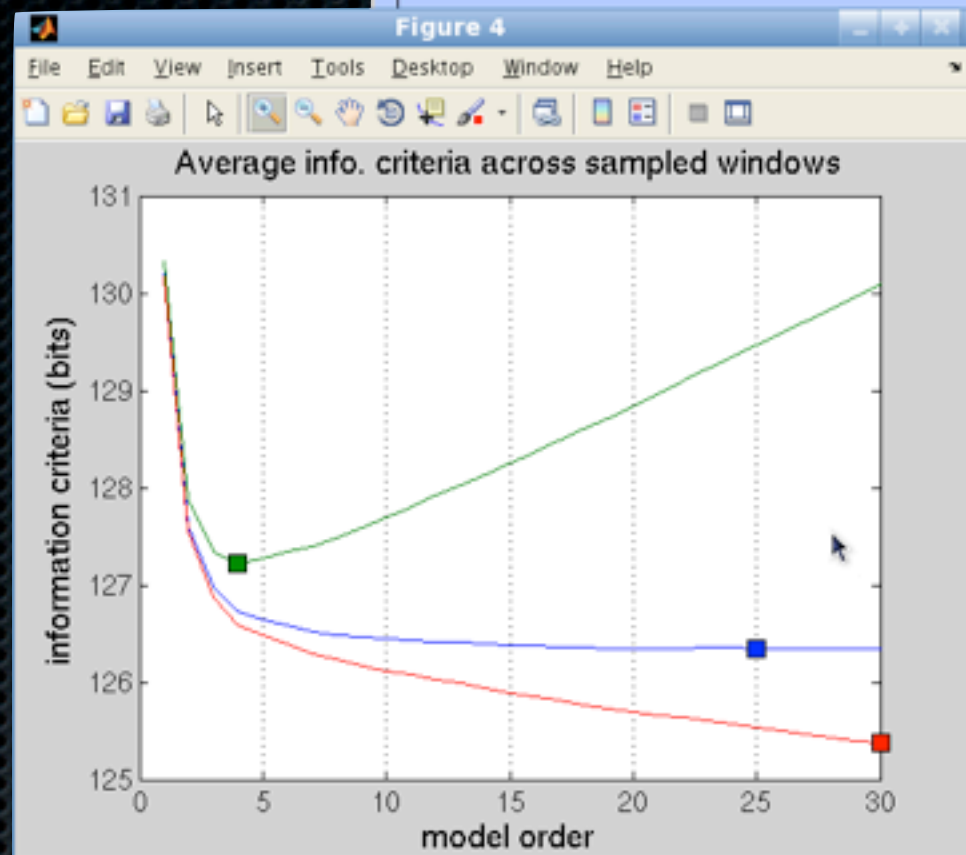
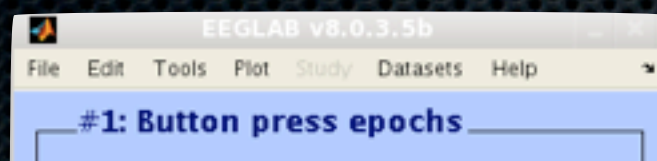


# Demonstration of (basic) data processing pipeline









Select Model Validation

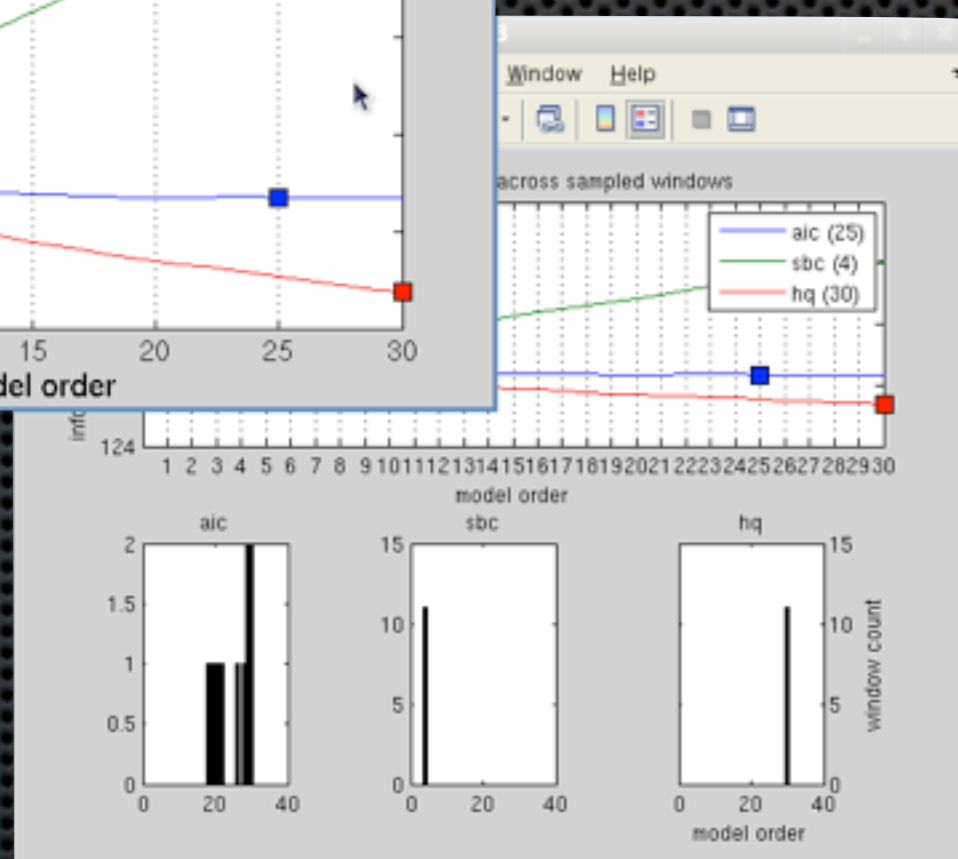
1. Select MVAR algorithm  
Vierra-Morf (recommended)

2. Window length (sec) 0.5  
Start Window Length Assistant...

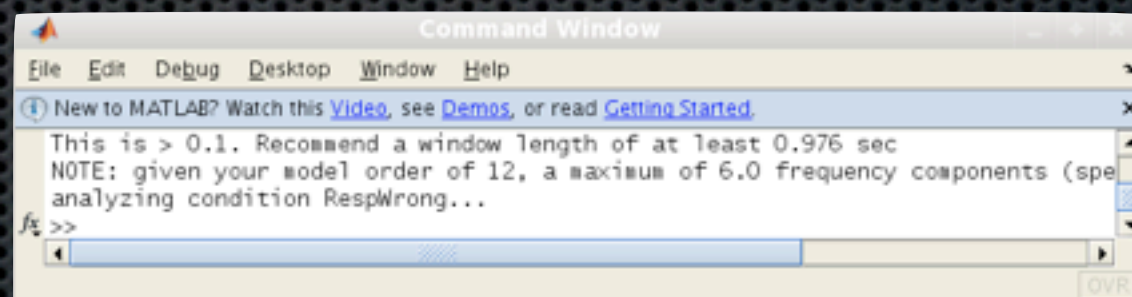
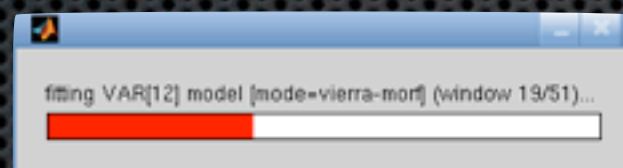
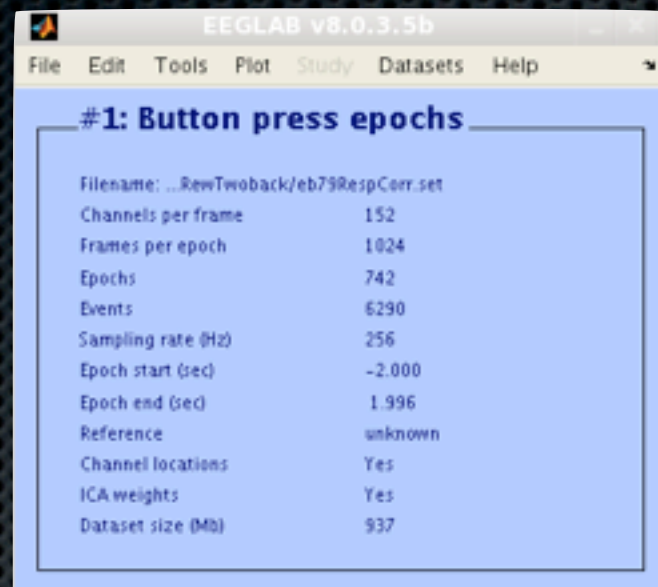
3. Step size (sec) 0.03

4. Model order 5  
Start Model Order Assistant...

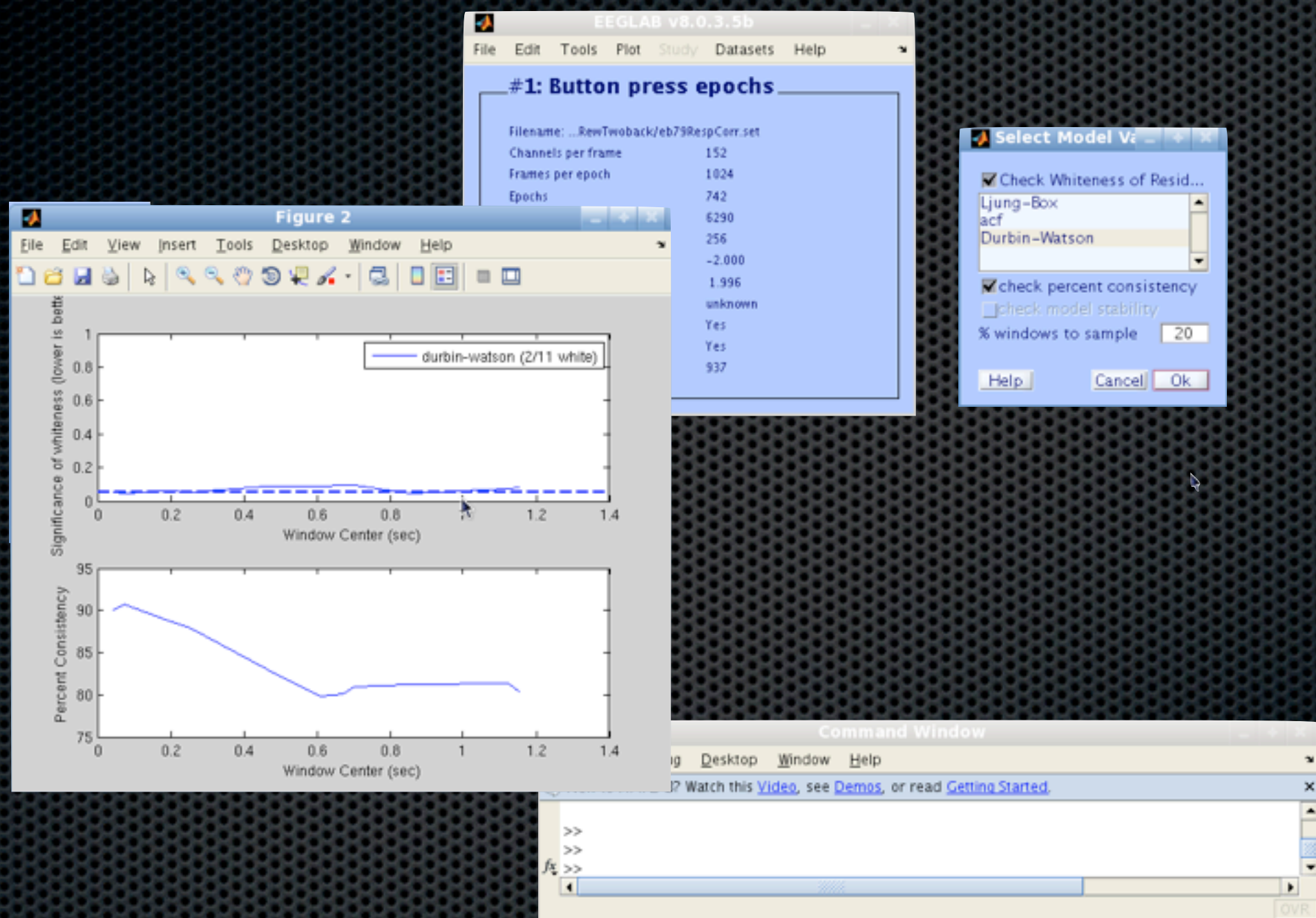
Help Cancel Ok



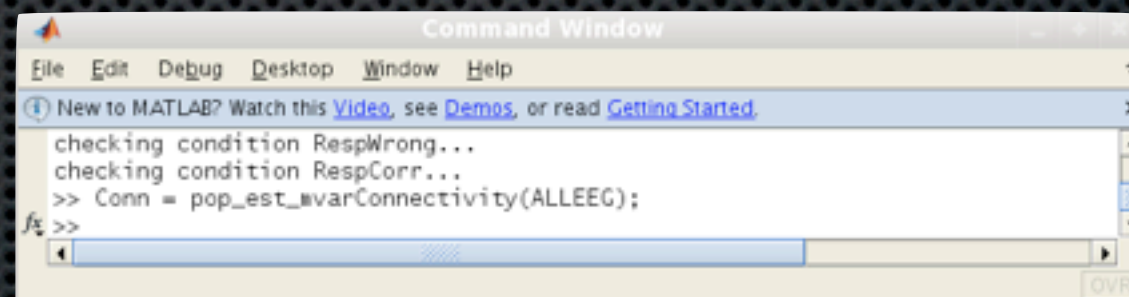
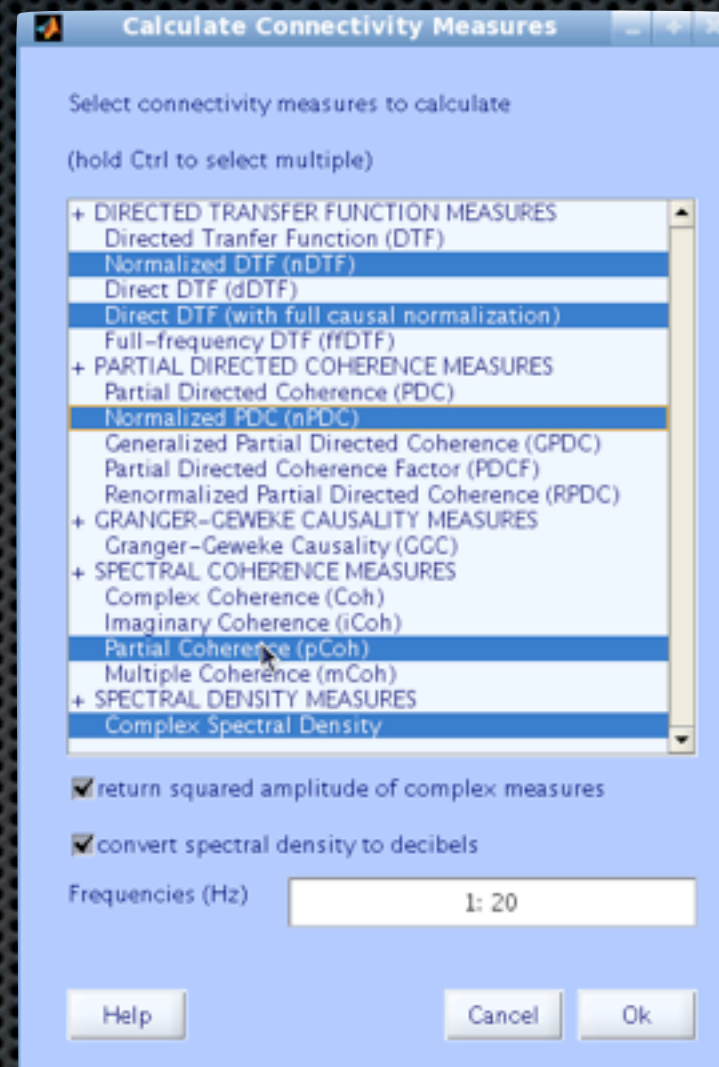




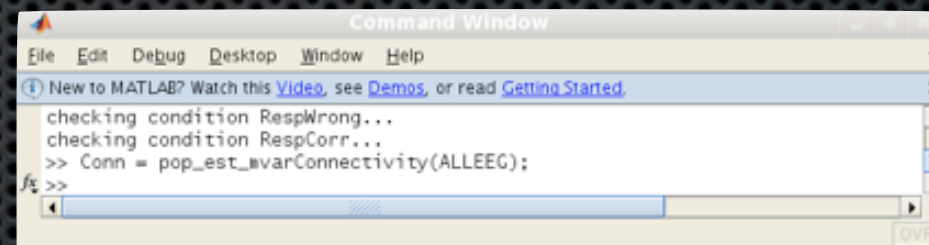
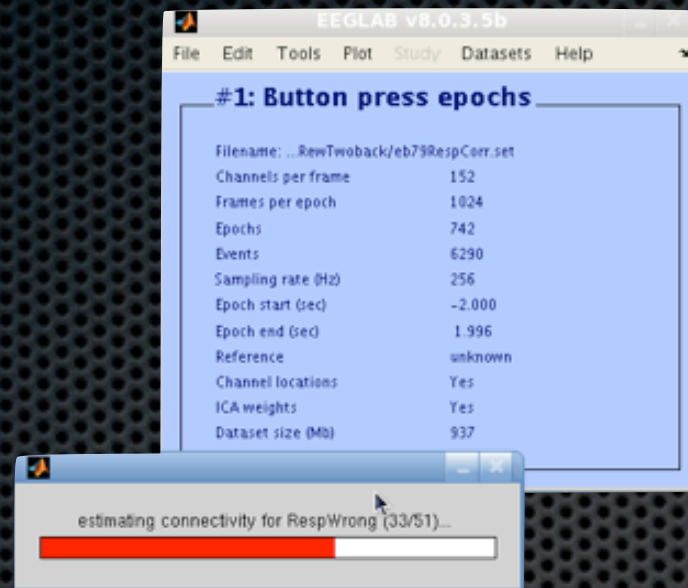






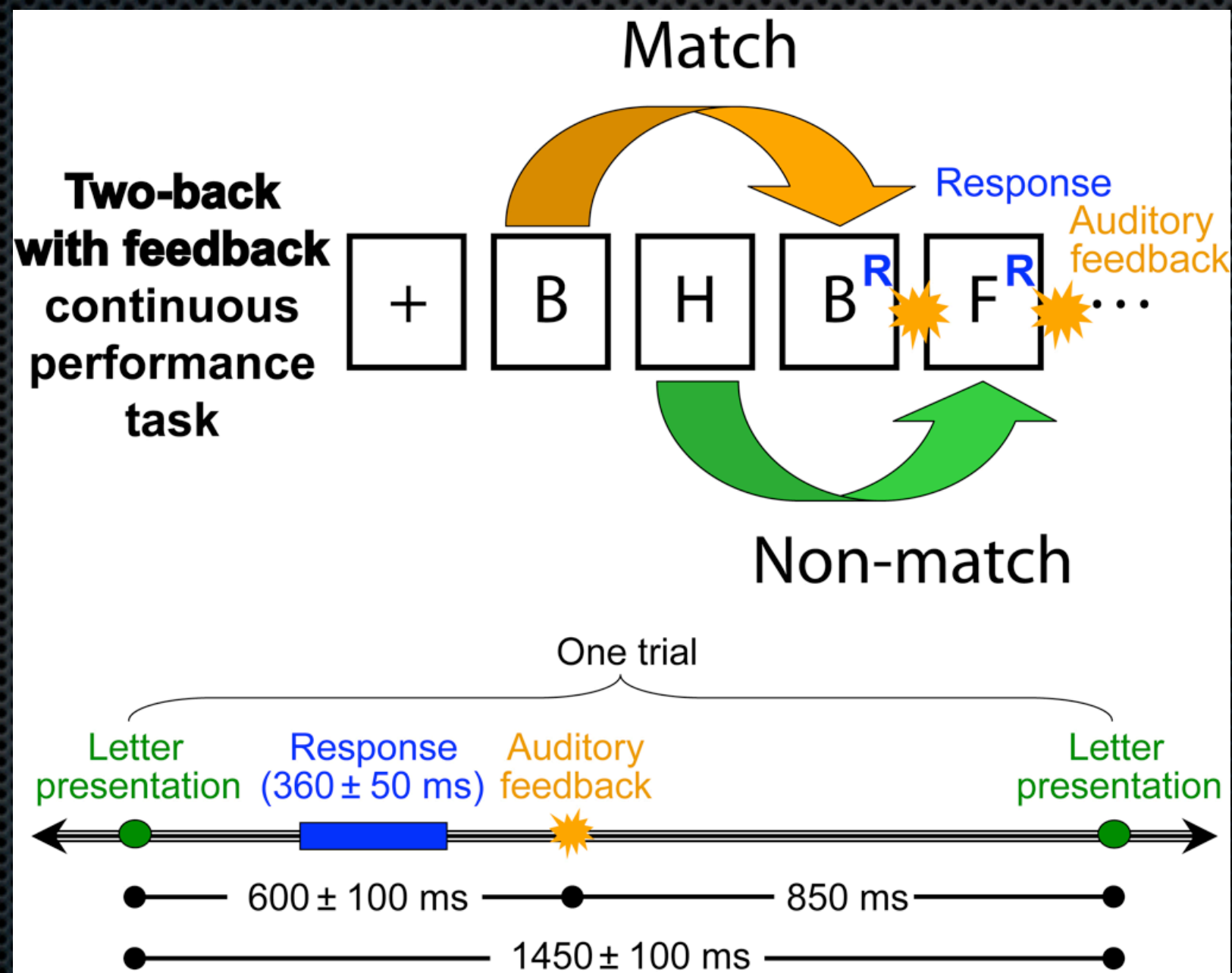








# Two-back task with feedback

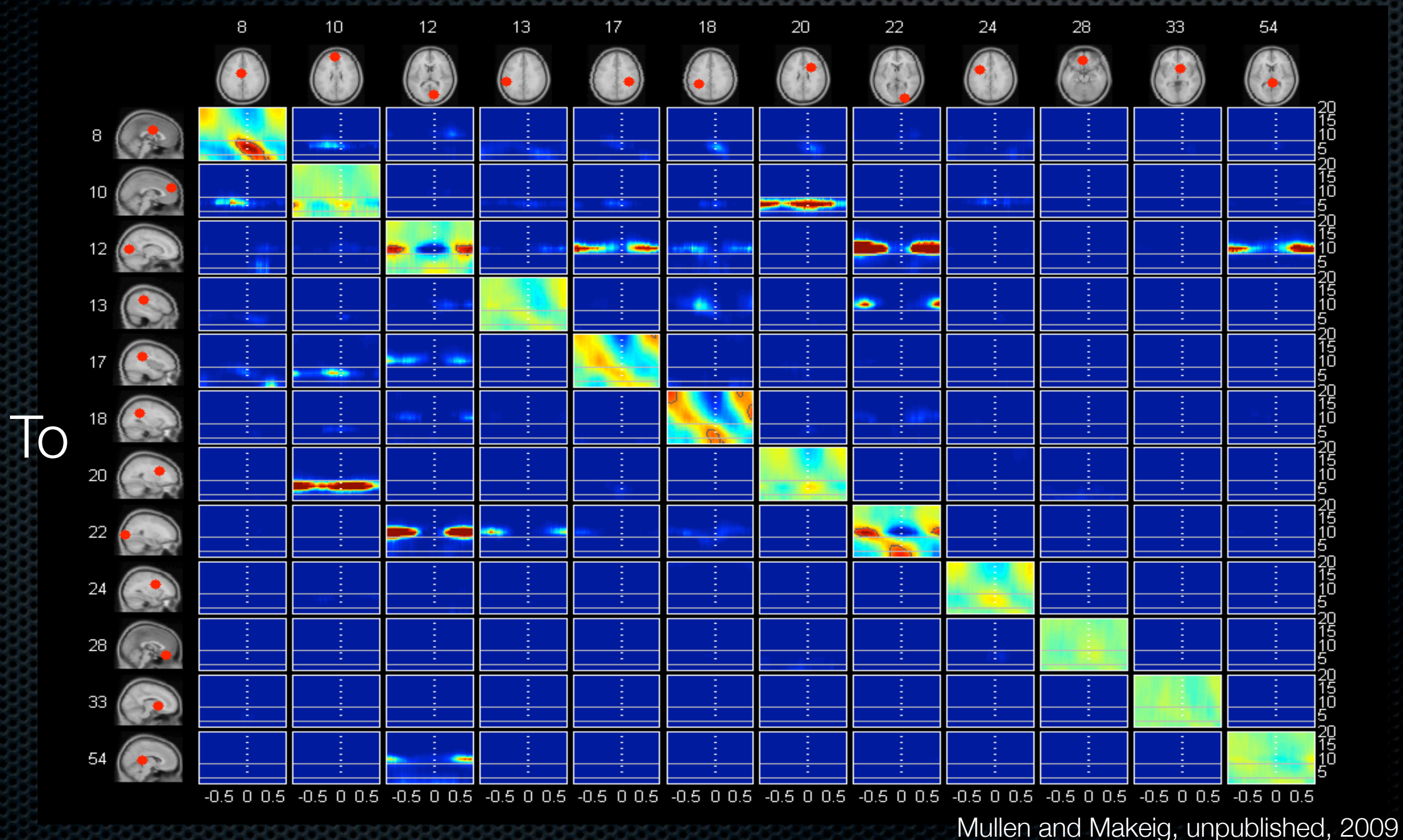


Onton and Makeig,  
2007



# Interactive Time-Frequency Grid

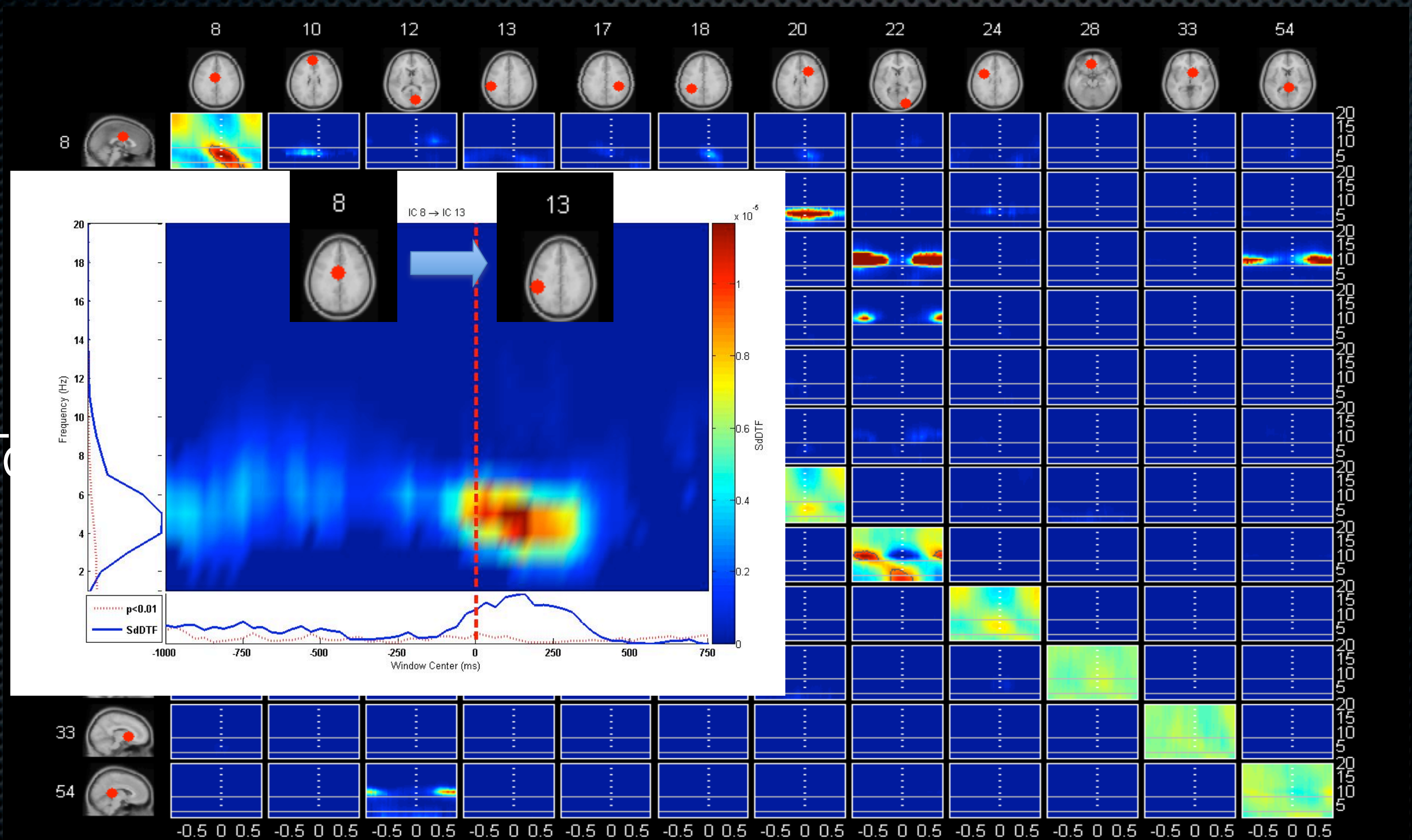
From





# Interactive Time-Frequency Grid

## From

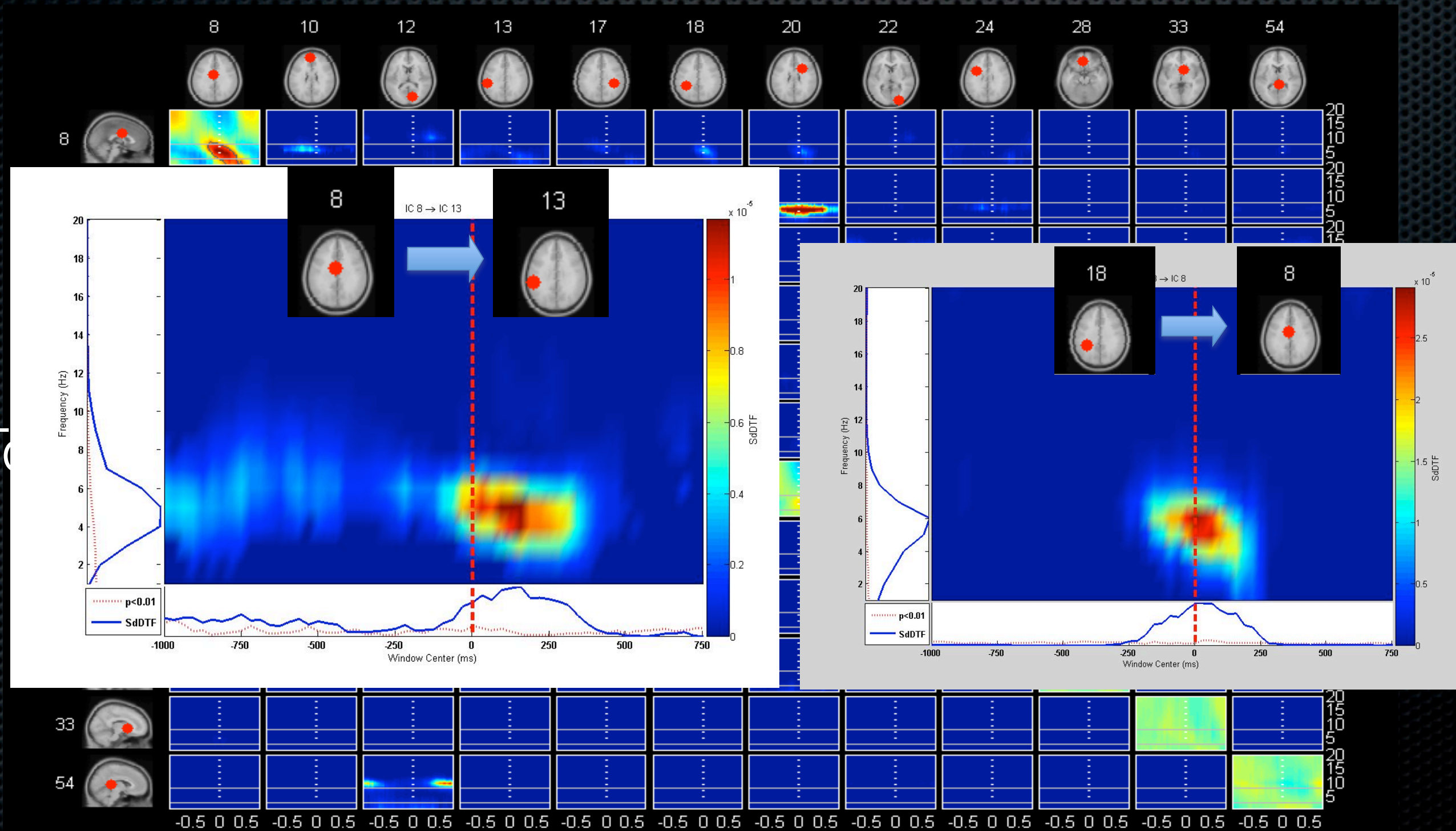


Mullen and Makeig, unpublished, 2009



# Interactive Time-Frequency Grid

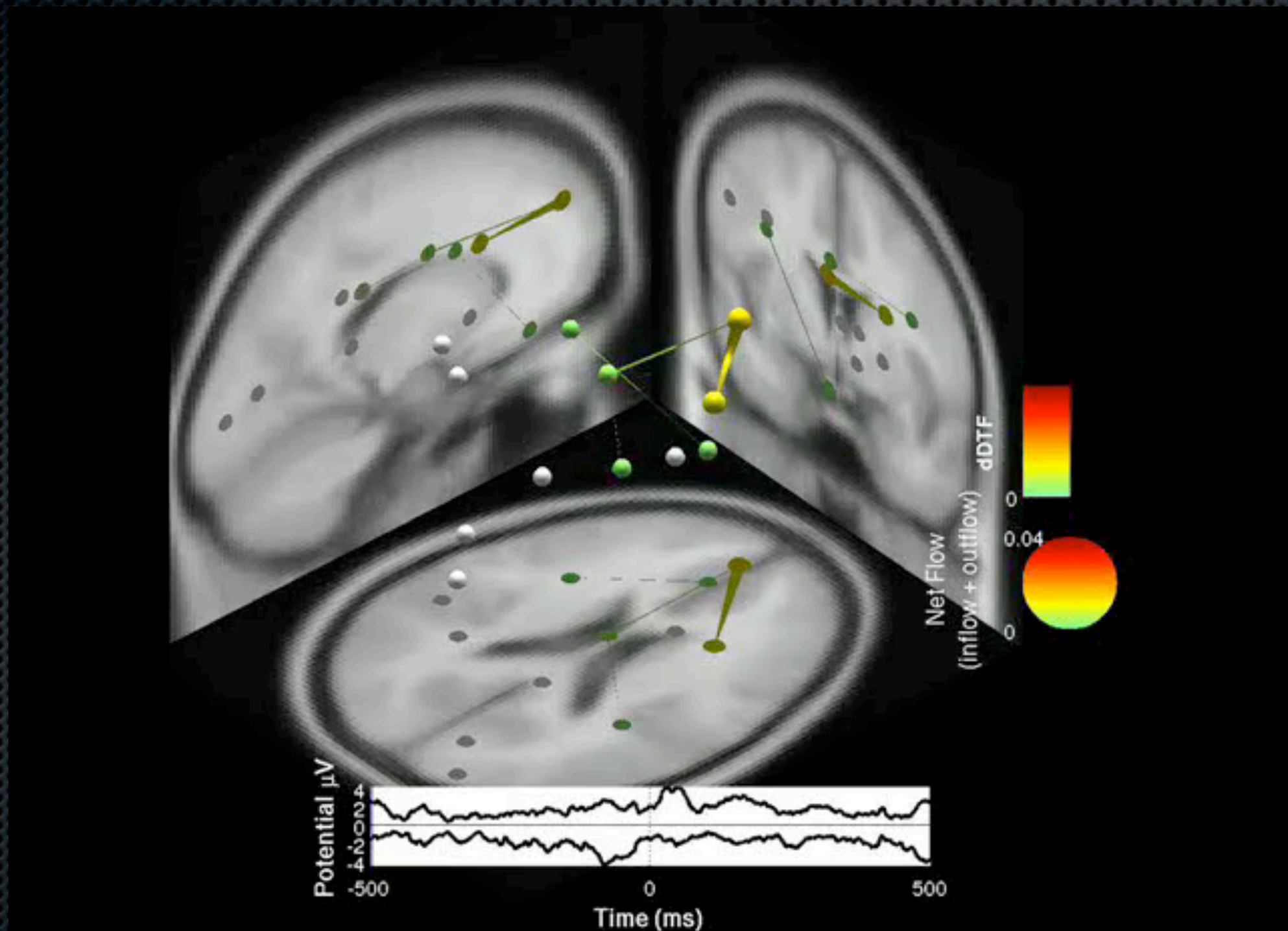
## From



Mullen and Makeig, unpublished, 2009

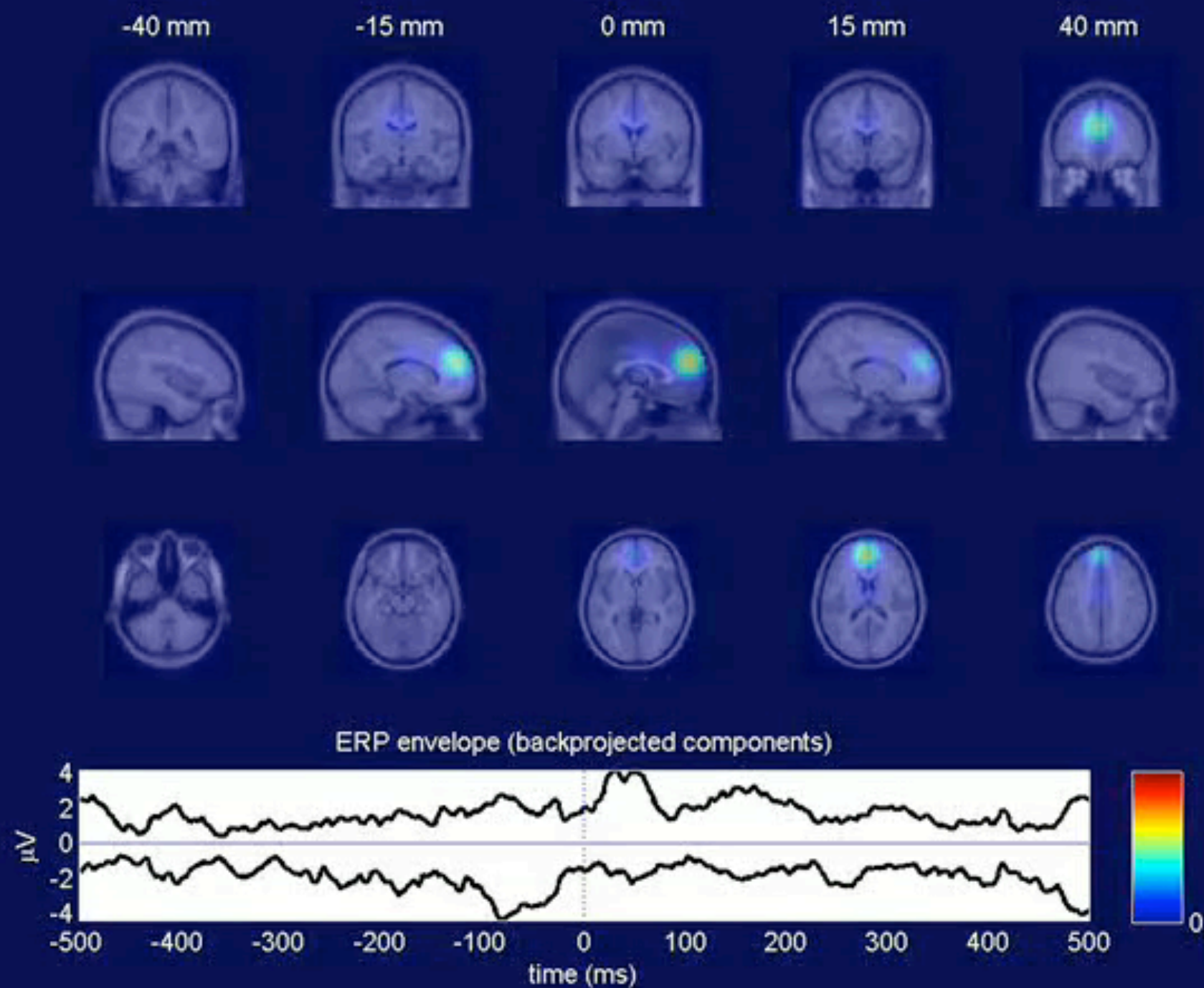


# Causal Interactive Brainmovie





# Causal Density Movie

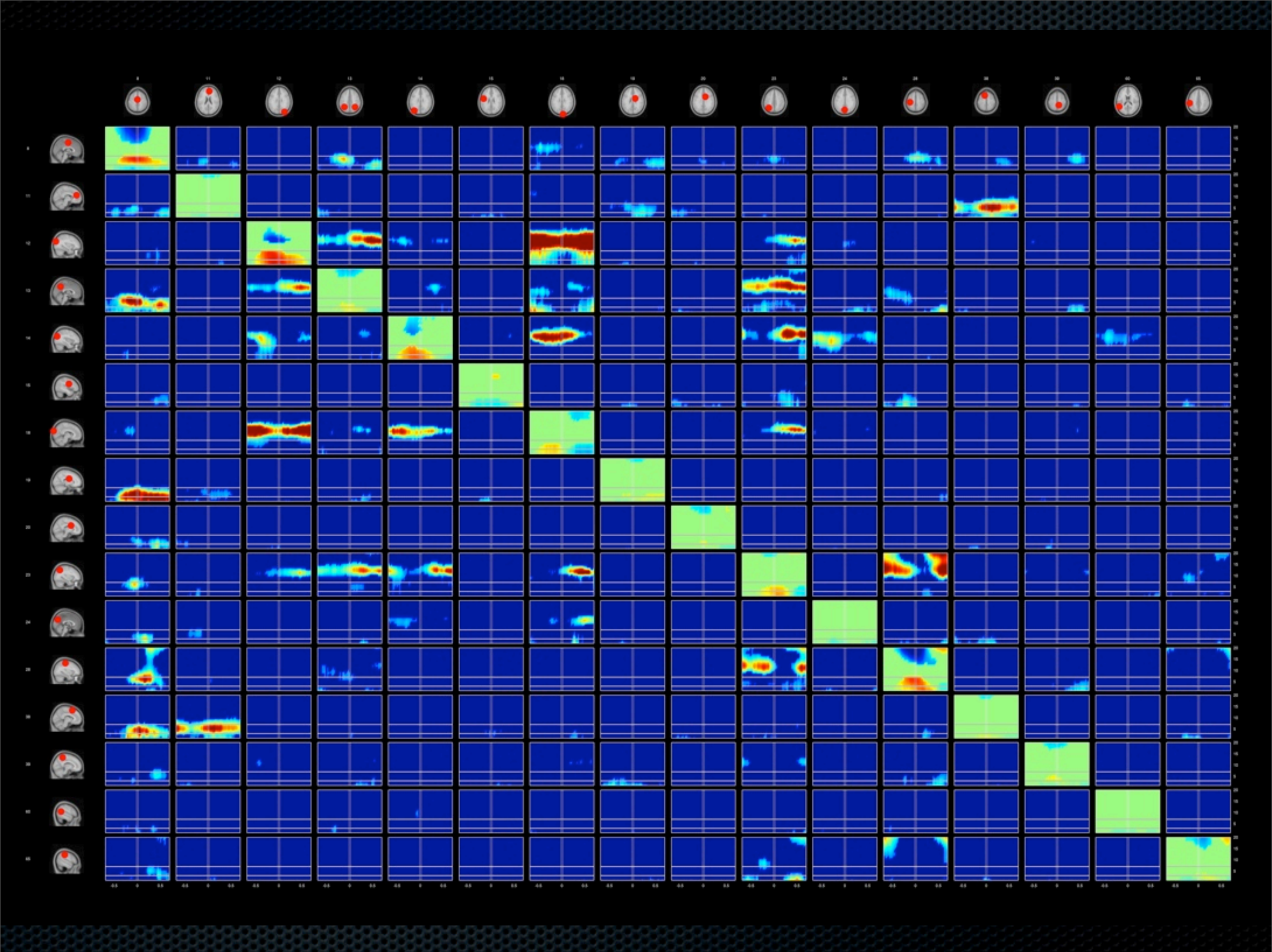




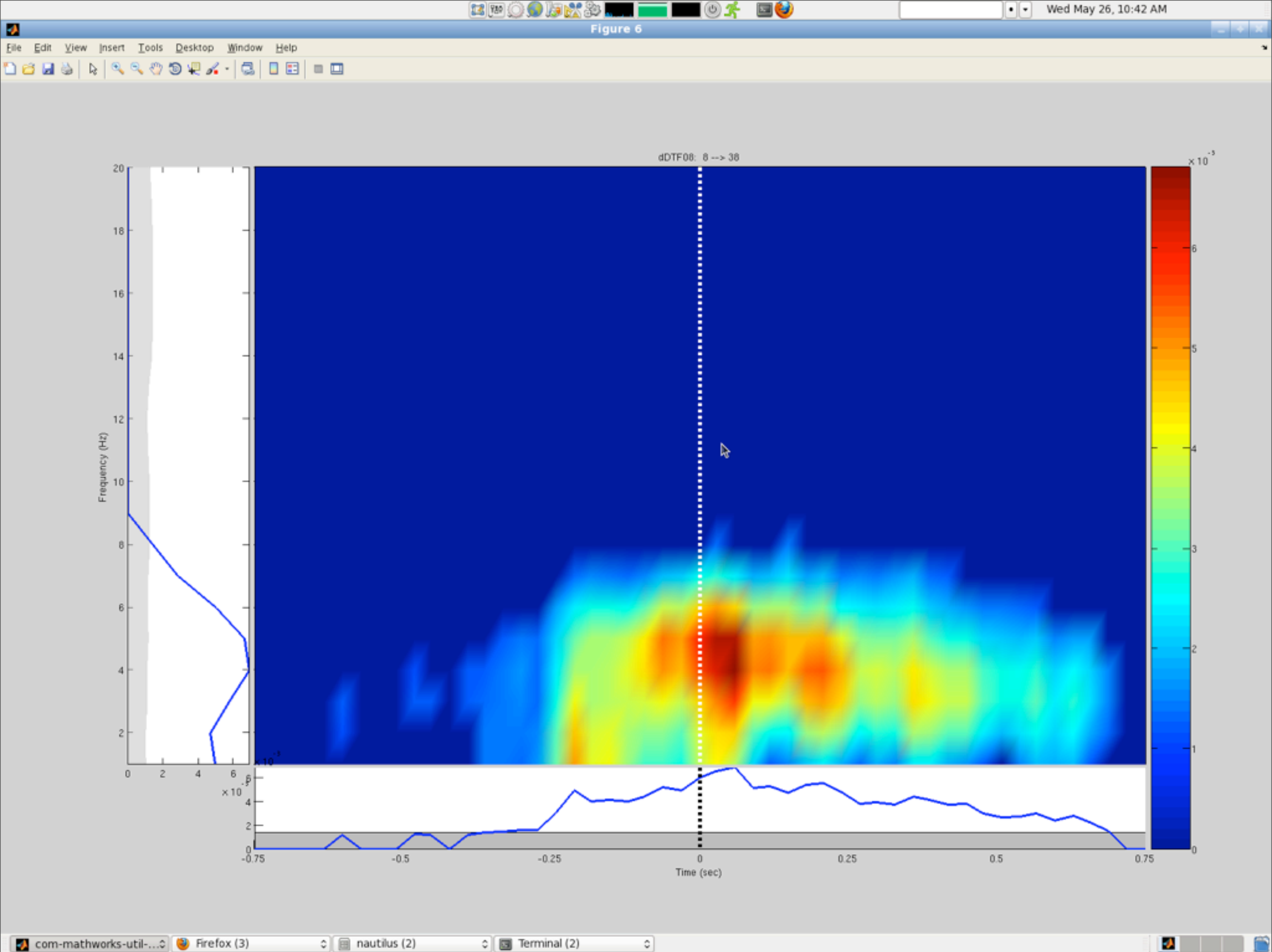
# Future Work

- ✦ Improvement of architecture, GUI, and EEGLAB integration (in collaboration with EEGLAB developer Arnaud Delorme)
- ✦ Ongoing implementation/incorporation of state-of-the-art methods for causal analysis
- ✦ Improved development of group statistics (in collaboration with Dr. Wesley Thompson)
- ✦ Further validation of effective connectivity measures using ECoG, CCEP, and DTI (in collaboration with Dr. Nitin Tandon, UT Houston)

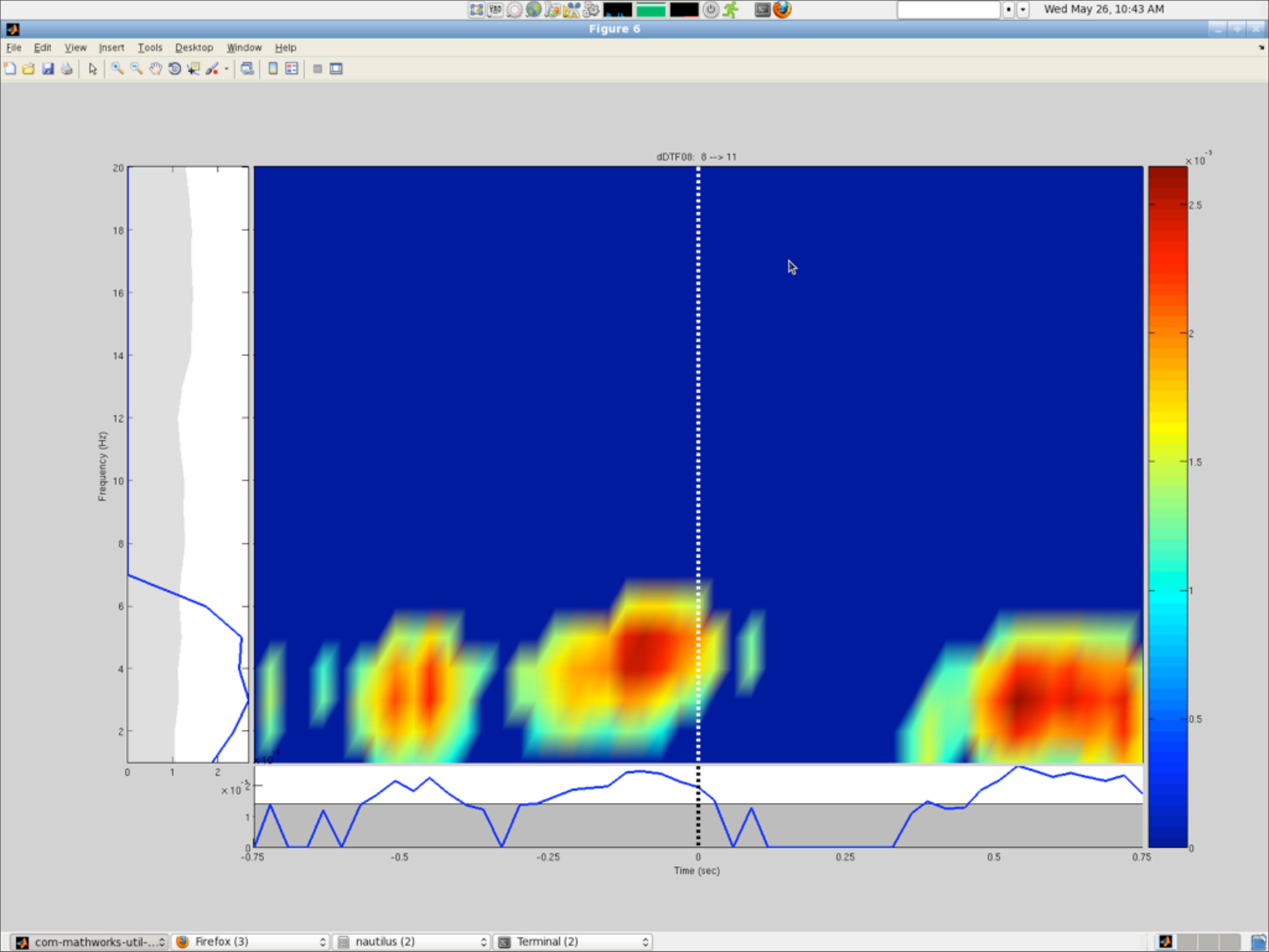




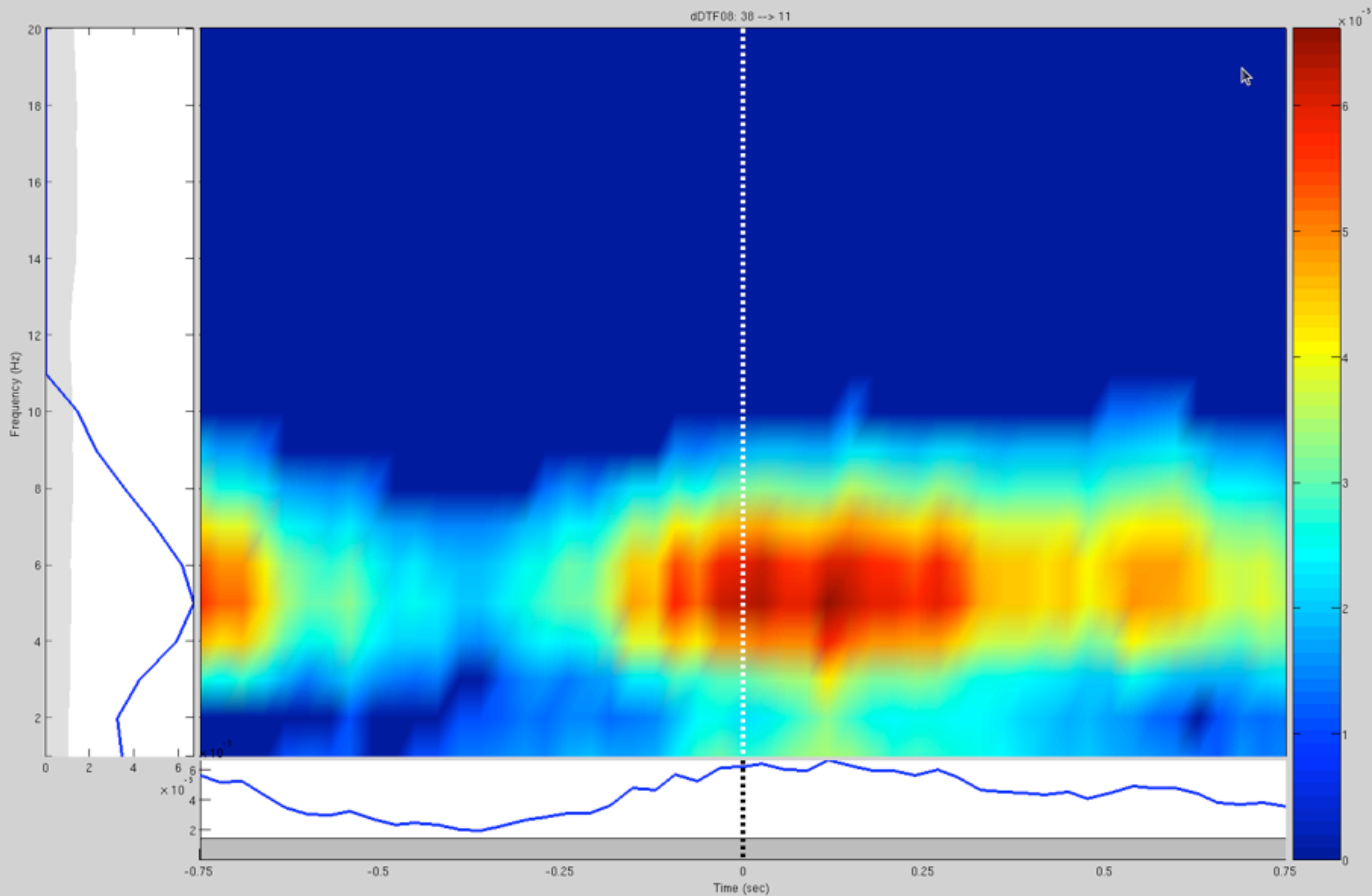






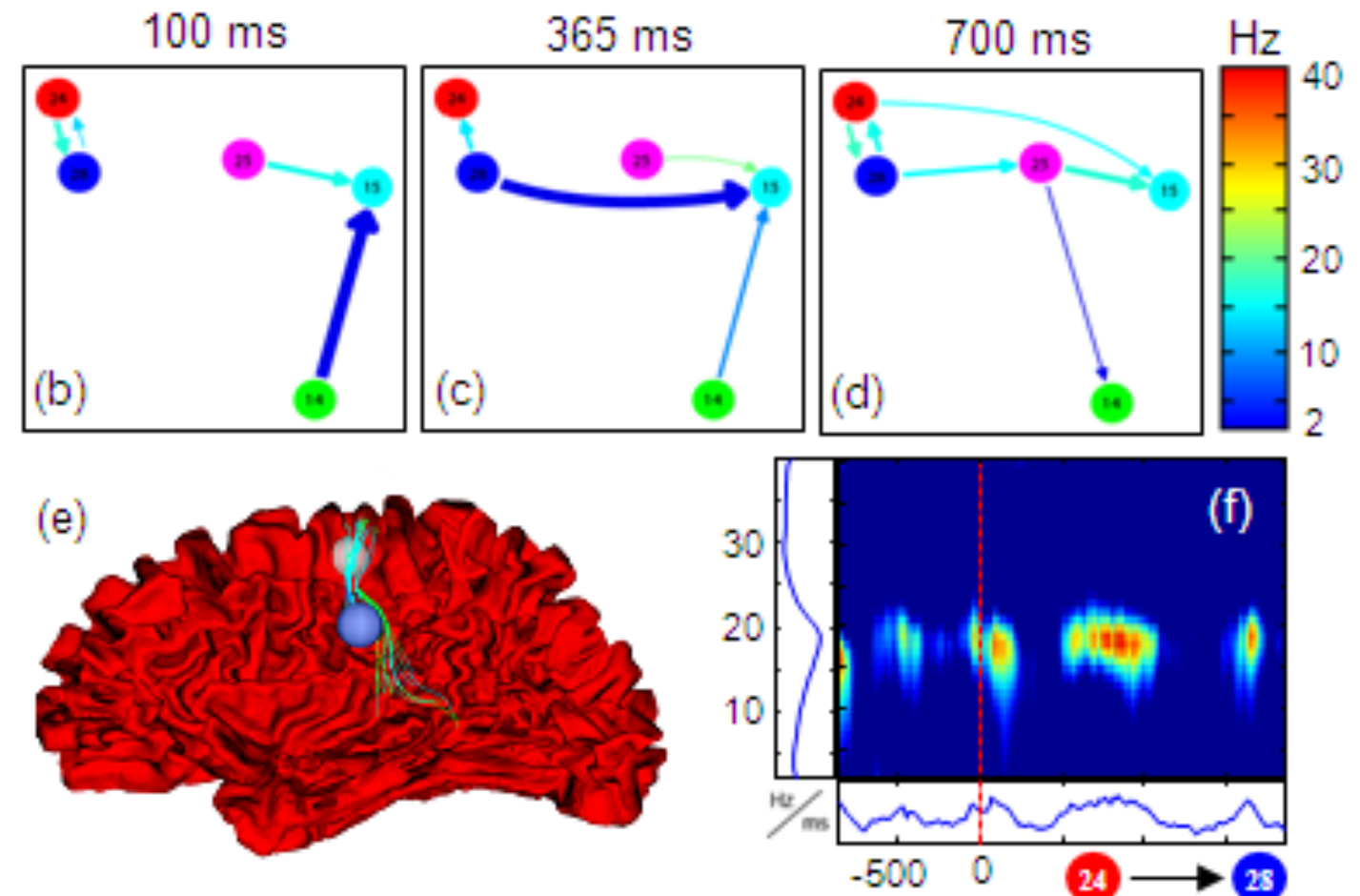
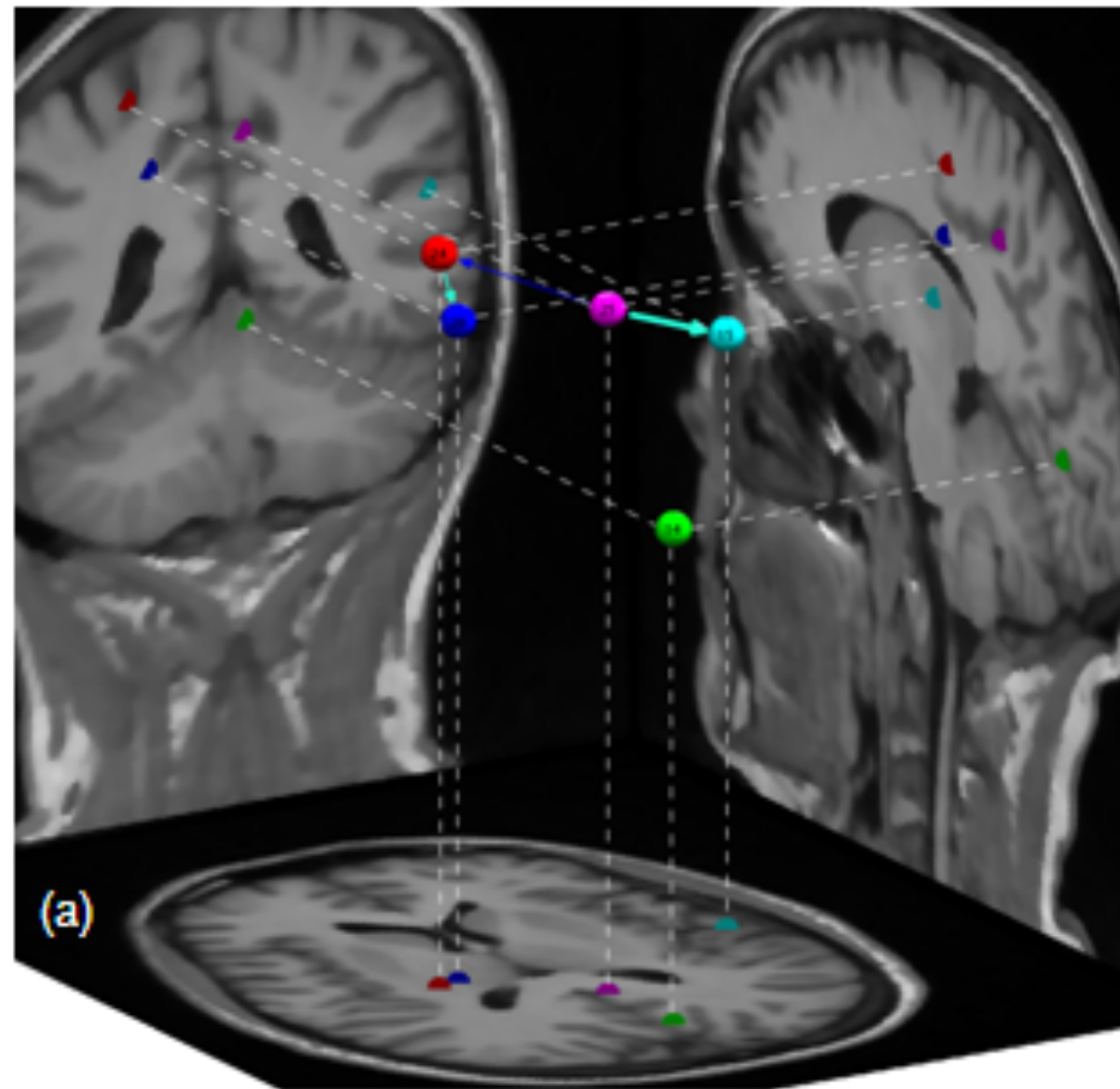








- 200 ms



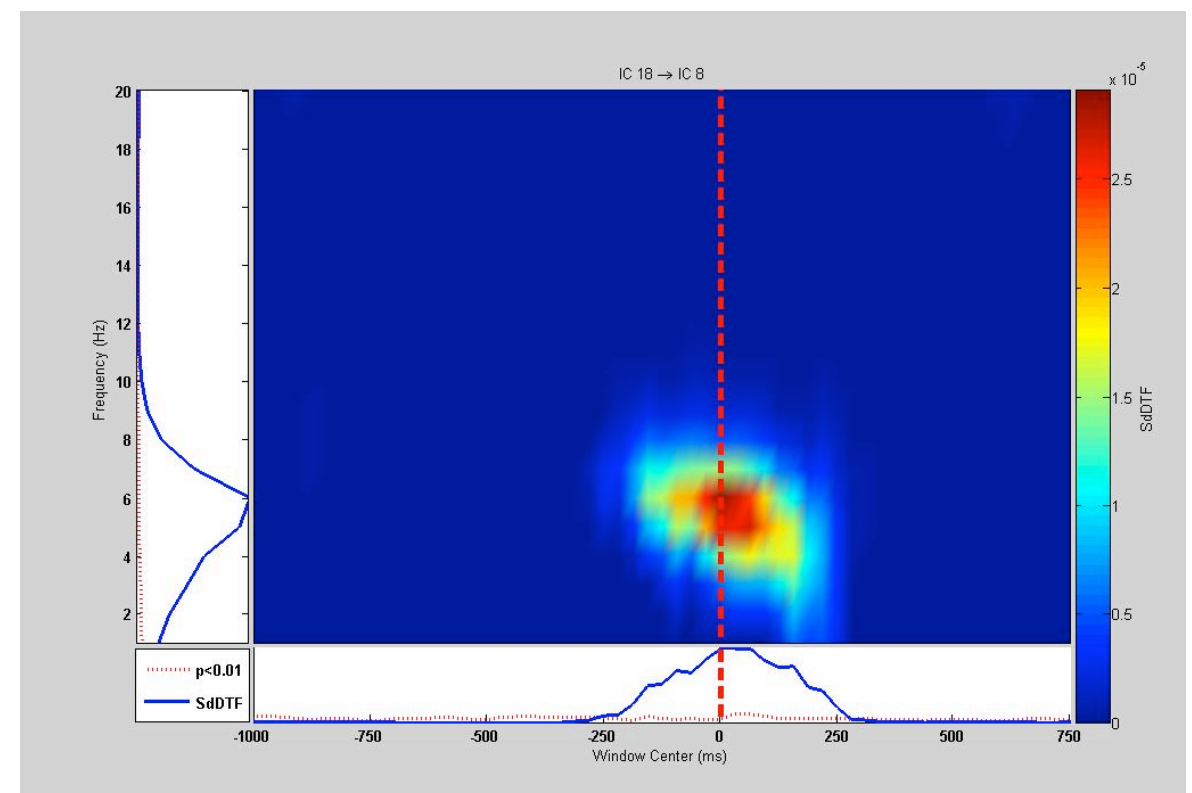
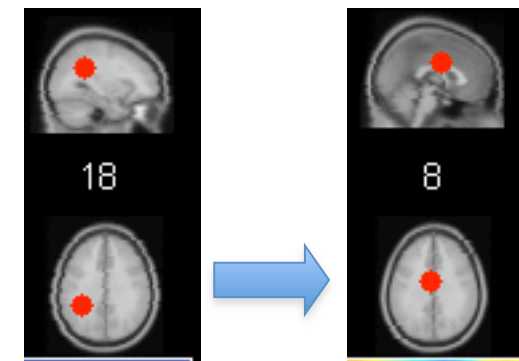
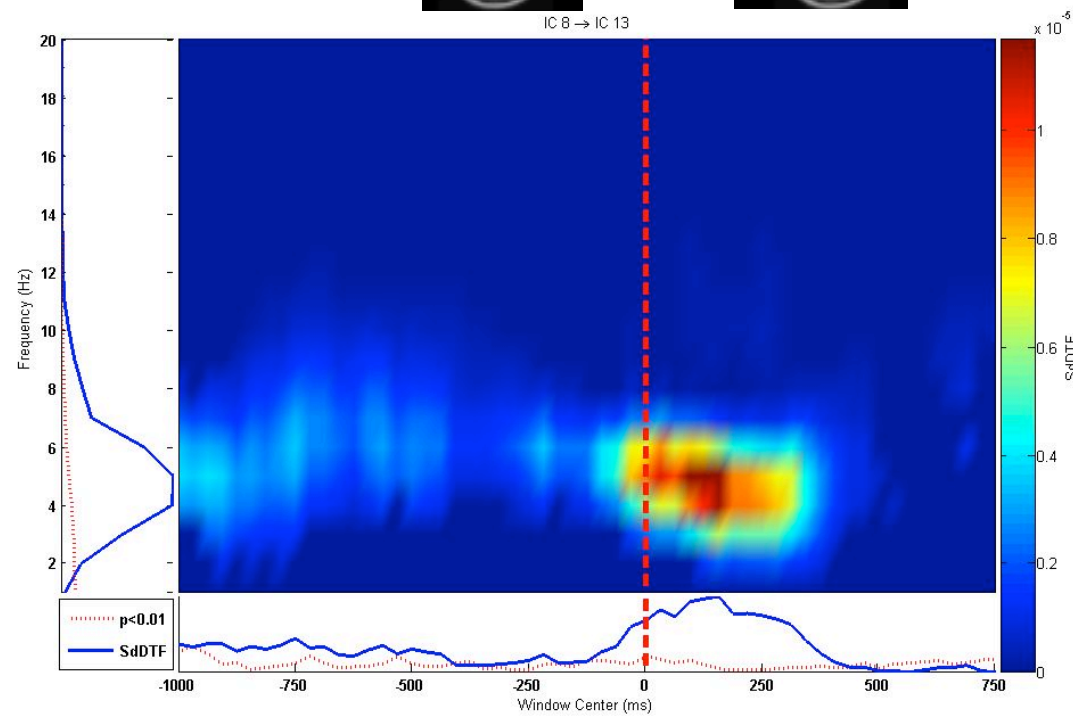
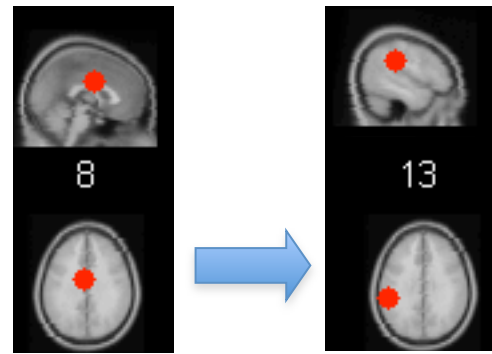
**Figure 4.** Structural and effective connectivity between five localized ICs during oddball task of one subject. Panels (a)-(d) show significant ( $p < 0.01$ ) dynamic Granger-causal influences between source-localized ICs

Arrow colors denote frequency; thickness, strength of connectivity. Features include (b) early post-stimulus visual cortex (green node) outflow, (c) inter-hemispheric parietal  $\rightarrow$  temporal theta band info flow, (d) emergence of inter-hemispheric beta band flows near 700 ms. Closely spaced dorsocentral ICs 24 (red) and 28 (blue) show a consistent pattern of mostly bi-directional connectivity throughout the trial; (e) DWI-derived fibers connecting locations of these two ICs (using DST fiber tracking seeded at 6-mm ROIs centered on IC equiv. dipoles). (f) SDTF time-frequency display shows transient beta-frequency information flows from (superior) IC24 (red) to IC28 (blue), with a 10-or-more cycle peak 500-1000 ms following target onset (dashed red line). Marginal traces show marginal maxima.



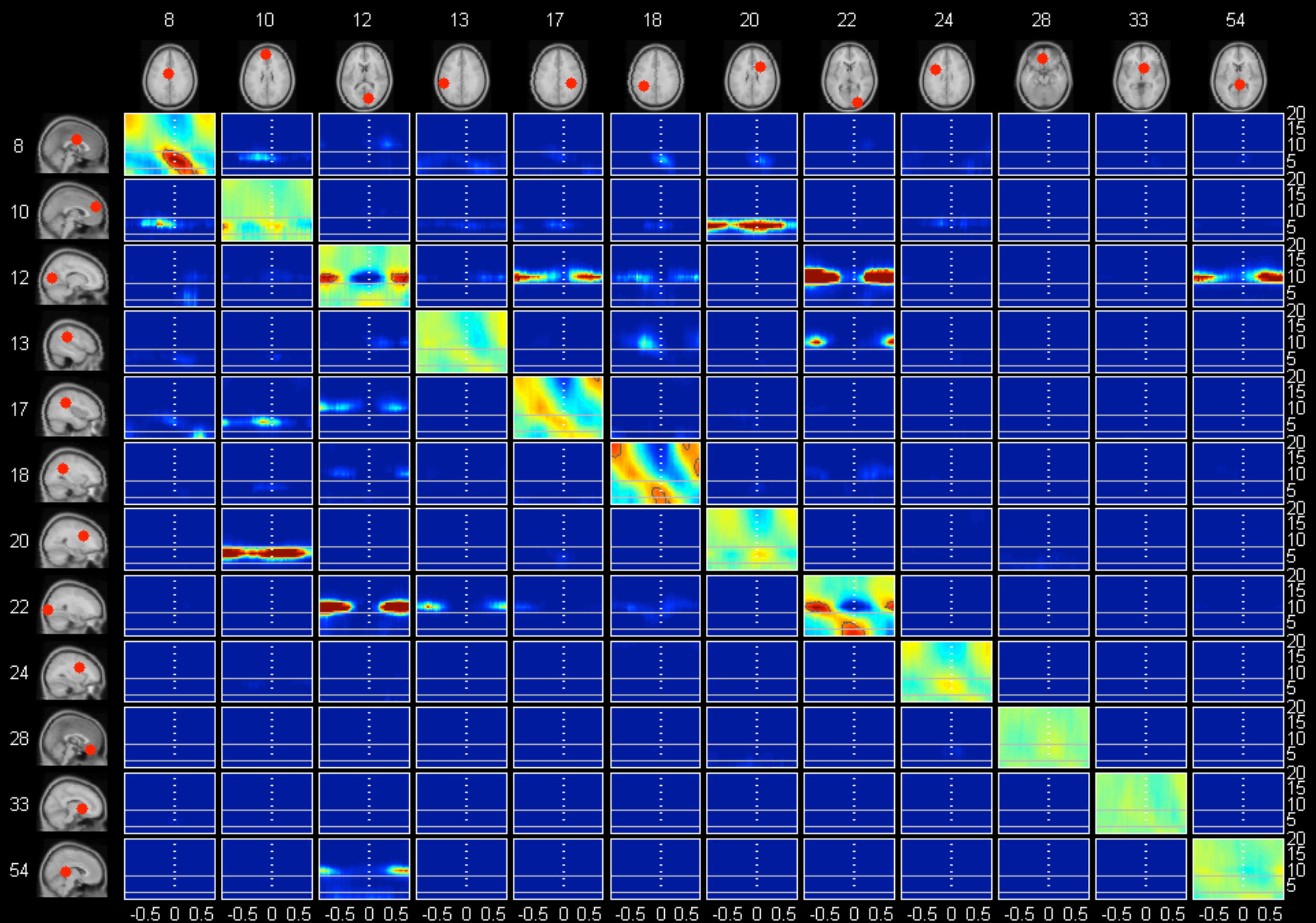
# Transient Theta Coherence Event

## Two-back with Feedback Task



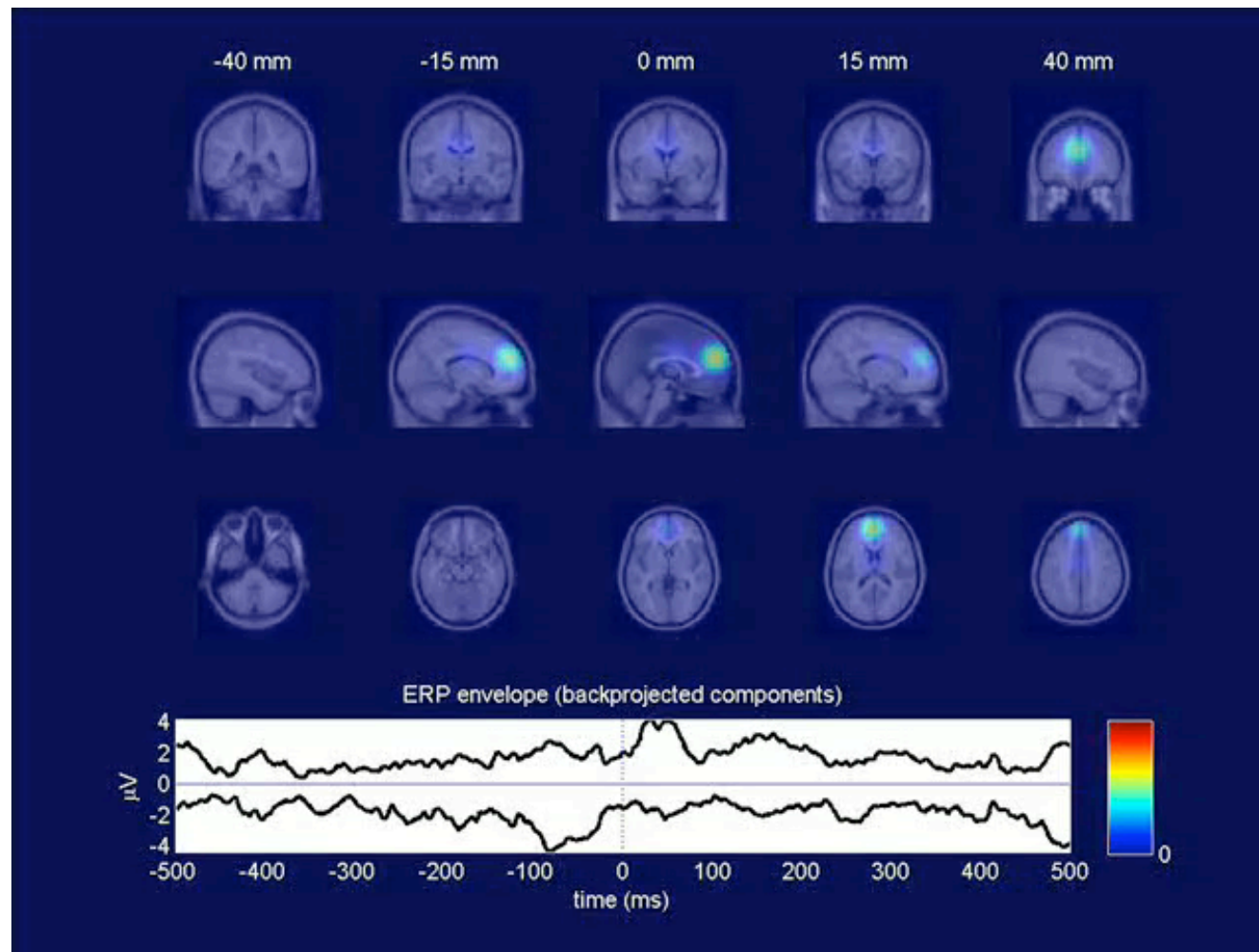


# SdDTF representation of a Two-back Task Theta Event





# SdDTF representation of a Two-back Task Theta Event





# SdDTF representation of a Two-back Task Theta Event

