NeuroImaging Training Program

mscohen@g.ucla.edu

Group ICA: Network Discovery with fMRI
Analytic Choices & Their Implications

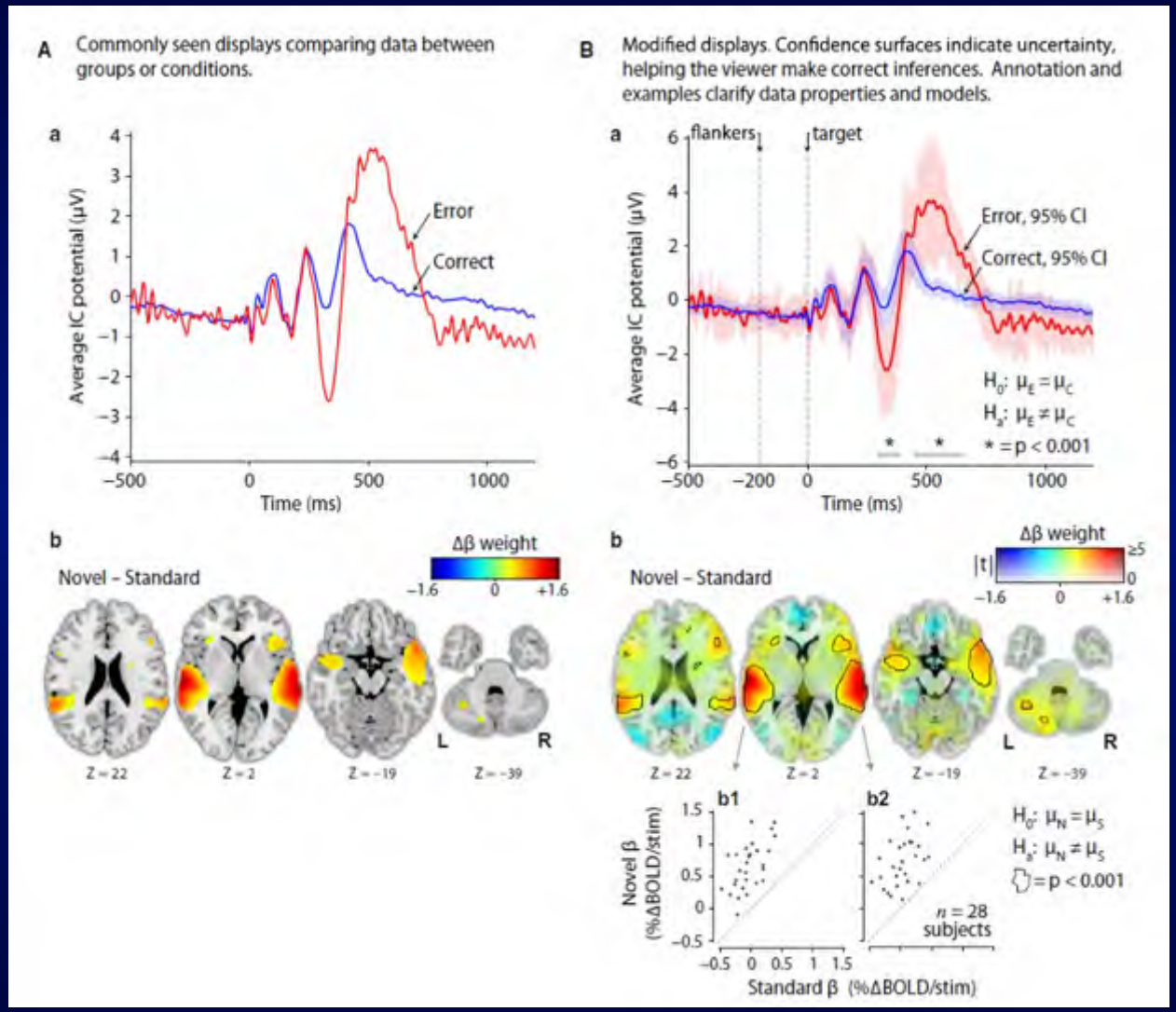
Vince D. Calhoun, Ph.D.
Executive Science Officer &
Director, Image Analysis & MR Research
The Mind Research Network

Distinguished Professor, Electrical and Computer Engineering
(primary), Biology, Computer Science, Psychiatry, & Neurosciences
The University of New Mexico

The Mind RESEARCH NETWORK
For Neurodiagnostic Discovery

The University of New Mexico

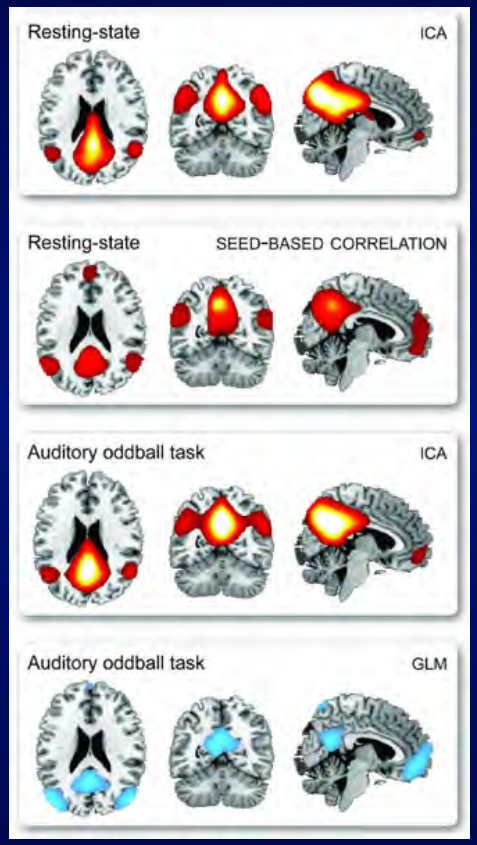
Brief comment on visualization



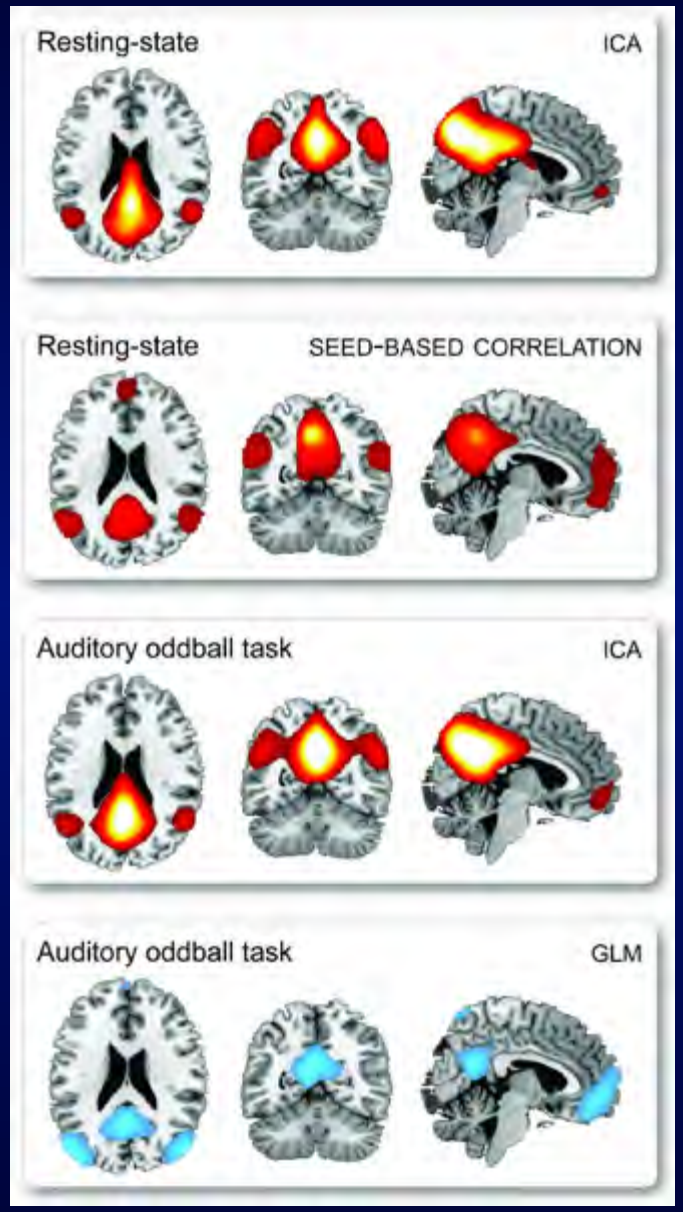
E. Allen, E. Erhardt, and V. D. Calhoun, "Data visualization in the neurosciences: overcoming the curse of dimensionality," *Neuron,* vol. 74, pp. 603-608, 2012

Outline of Talk

- Approaches
  - Seeds vs Components
  - Intro to ICA
  - Group ICA vs single subject
- Processing issues
  - Impact of (micro) motion
  - Autocorrelation
  - Band-pass filtering
- Other issues
  - Task vs Rest
  - Overlap of networks
- Applications
  - Diagnostic
  - Prediction
- Dynamic connectivity
- Summary



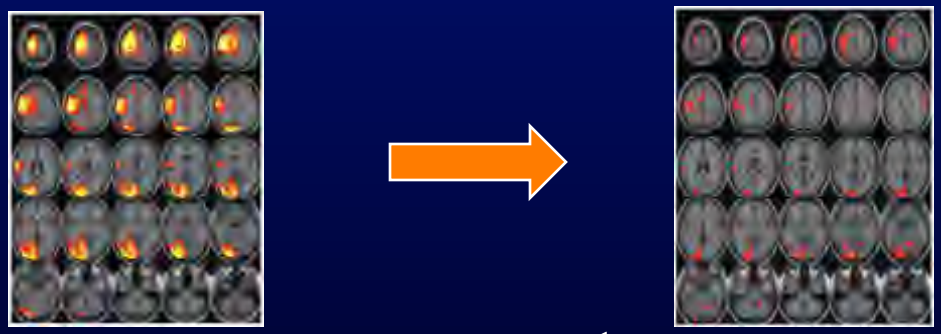
Convergence of Methods for Identifying Resting Networks



E. Erhardt, E. Allen, E. Damaraju, and V. D. Calhoun, "On network derivation, classification, and visualization: a response to Habeck and Moeller," Brain Connectivity, vol. 1, pp. 1-19, 2011.

Seeds vs Components

- Once fixed they are very similar
  - "Seed-based FC measures are shown to be the sum of independent component analysis-derived within network connectivities and between network connectivities" Joel SE, Caffo BS, van Zijl PC, Pekar JJ. On the relationship between seed-based and ICA-based measures of functional connectivity, Magn Reson Med. 2011 Sep;66(3):644-57
- ICA/seed hybrid (use ICA to derive seed regions or maps)
  - Kelly RE, Wang Z, Alexopoulos GS, Gunning FM, Murphy CF, Morimoto SS, Kanellopoulos D, Jia Z, Lim KO, Hoptman MJ. Hybrid ICA-Seed-Based Methods for fMRI Functional Connectivity Assessment: A Feasibility Study
- Spatially constrained approach
  - Q. Lin, J. Liu, Y. Zheng, H. Liang, and V. D. Calhoun, "Semi-blind Spatial ICA of fMRI Using Spatial Constraints", *Hum. Brain Map.*, vol. 31, 2010.
  - Y. Du and Y. Fan, "Group information guided ICA for fMRI data analysis," Neuroimage, vol. 69, pp. 157-197, Apr 1 2013.



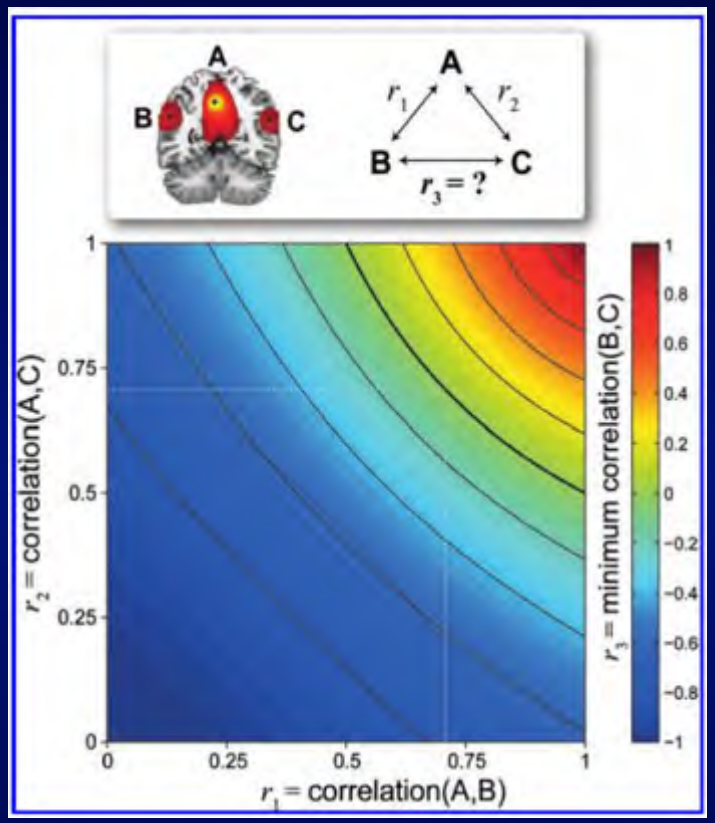
Great for artifact cleaning:

Y. Du, E. Allen, H. He, S. J., and V. D. Calhoun, "Brain functional networks extraction based on fMRI artifact removal: single subject and group approaches," in *EMBS*, Chicago, IL, 2014.

$$\langle \boldsymbol{\lambda} \rangle \mathbf{W} = \langle \boldsymbol{\rho} \rangle E\{G'_{\mathbf{y}}(\mathbf{W}\mathbf{x})\mathbf{x}^T\} - \frac{1}{2}\langle \boldsymbol{\mu} \rangle E\{g'_{\mathbf{y}}(\mathbf{y}:\mathbf{W})\mathbf{x}^T\}$$

Networks and Seeds

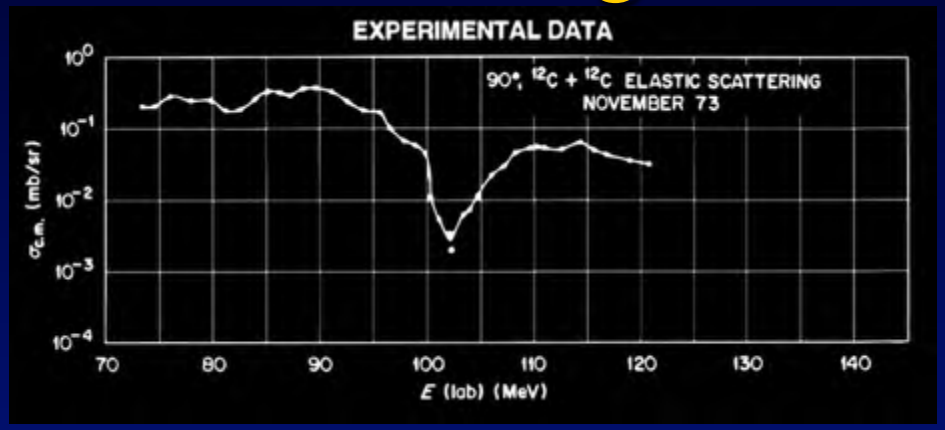
- Context determines the meaning and interpretation of the word "network" in brain imaging analysis.
  - GLM and seed-based methods define a network as a subset of voxels whose timeseries are significantly correlated with a reference signal.
  - ICA defines a network as a subset of voxels whose timeseries are significantly correlated with the estimated ICA timecourse
  - Using graph theory, a network may be defined as a connectivity matrix between nodes, which represent voxels, areas, or components.



E. Erhardt, E. Allen, E. Damaraju, and V. D. Calhoun, "On network derivation, classification, and visualization: a response to Habeck and Moeller," *Brain Connectivity,* vol. 1, pp. 1-19, 2011,

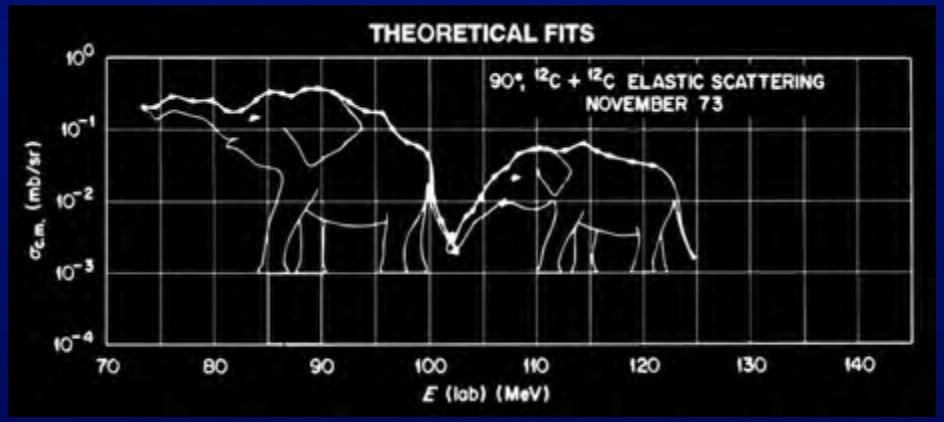
Modeling the Brain?

Results

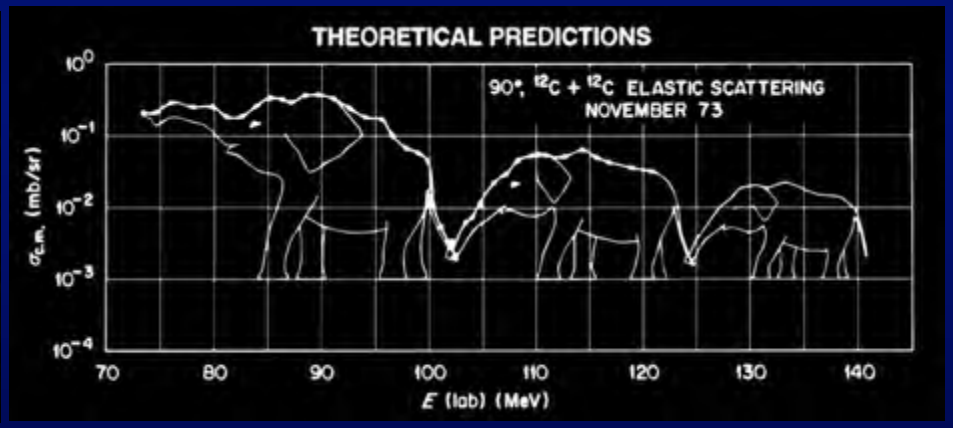


From "Science with a Smile" by Subramanian Raman

Modeling

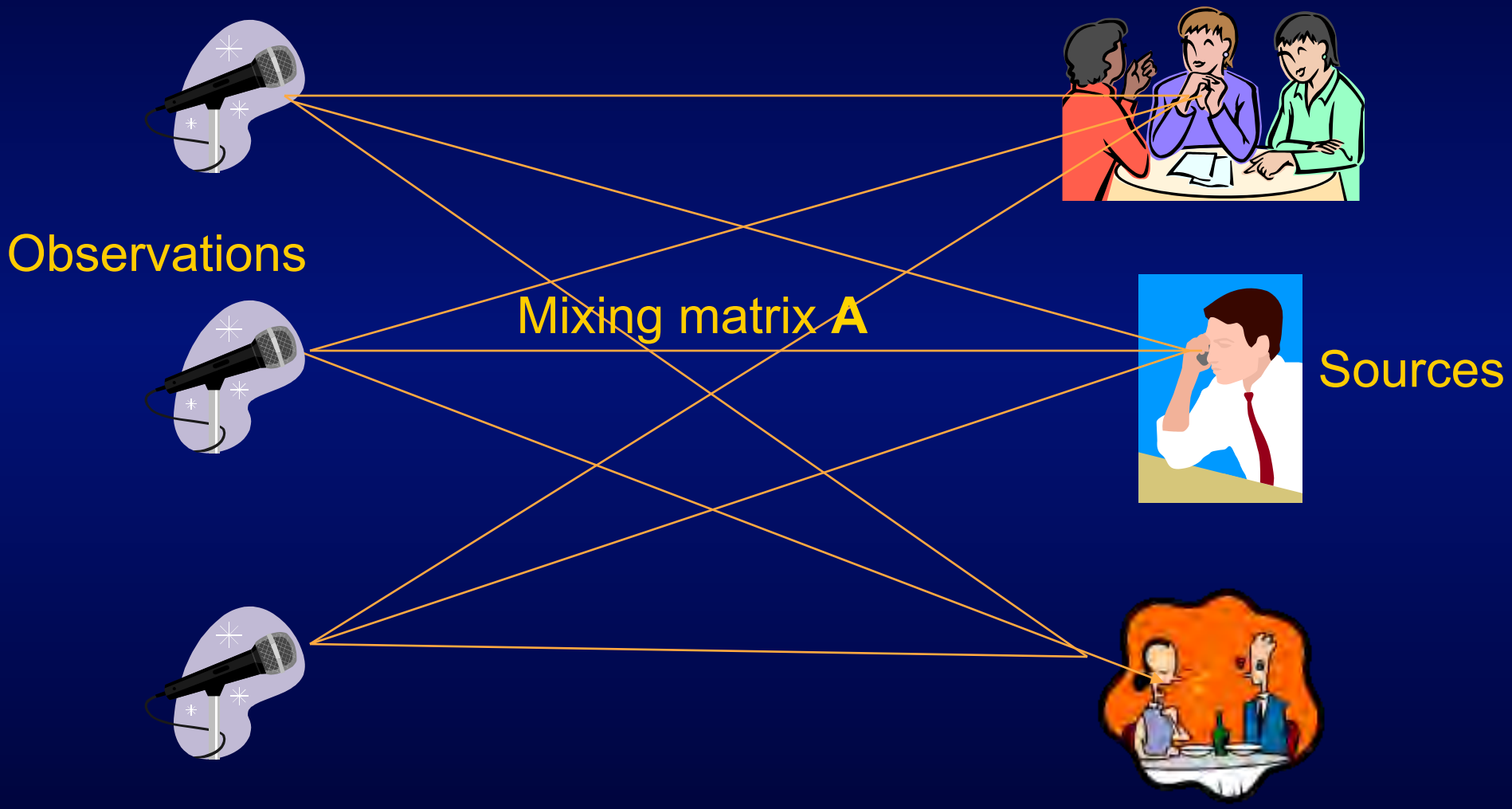


Discussion



- "All models are wrong, but some are useful!"
  - "All models are wrong." G.E. Box (1976) quoted by Marks Nester in, "An applied statistician's creed," Applied Statistics, 45(4):401-410, 1996.
- "I believe in ignorance-based methods because humans have a lot of ignorance and we should play to our strong suit."
  - Eric Lander, Whitehead Institute, M.I.T.

Blind Source Separation: The Cocktail Party Problem

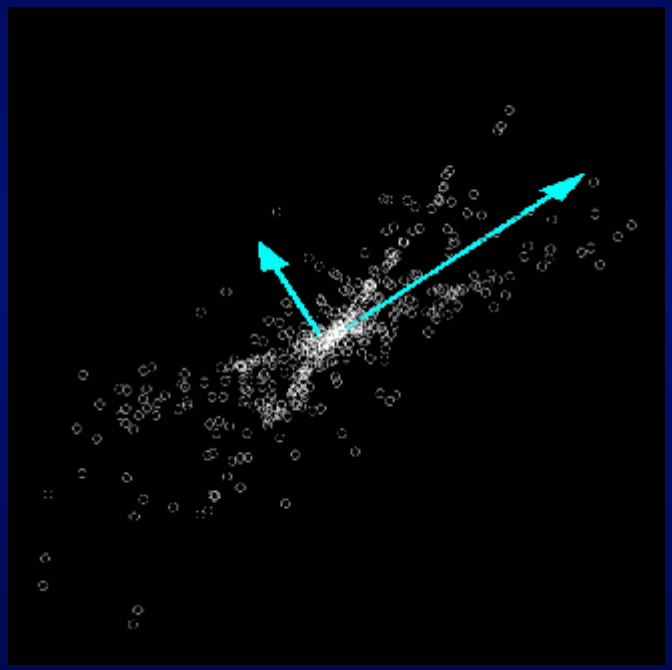


ICA vs PCA

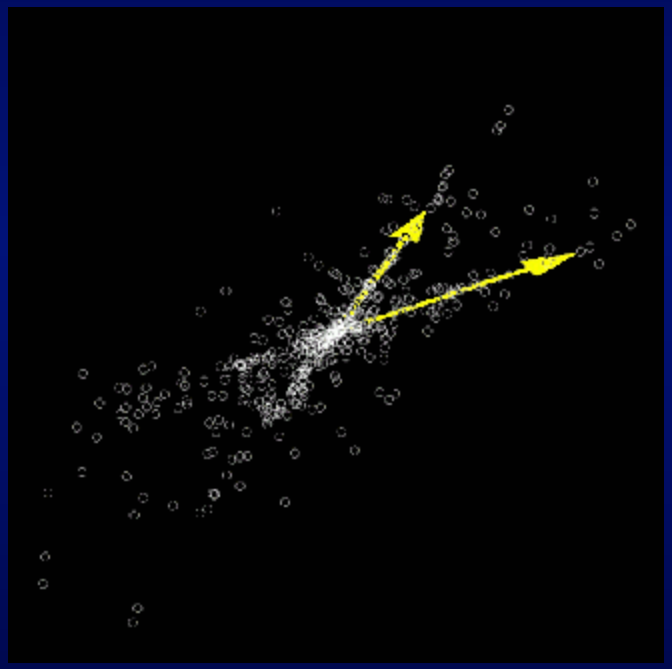
Uncorrelated: $E\{y_1 y_2\} = E\{y_1\}E\{y_2\}$

Independent: $p(y_1, y_2) = p(y_1)p(y_2)$

$$\Rightarrow E\{h(y_1)h(y_2)\} = E\{h(y_1)\}E\{h(y_2)\}$$



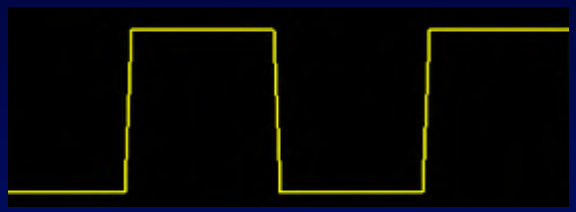
PCA finds directions of maximal variance (using second order statistics)



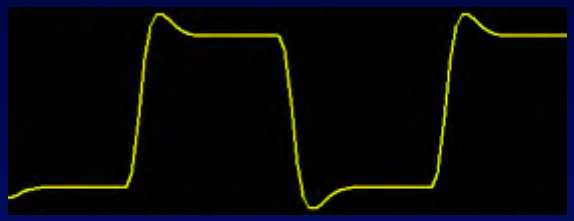
ICA finds directions which maximize independence (using higher order statistics)

General Linear Model

1. Model (1 or more Regressors)

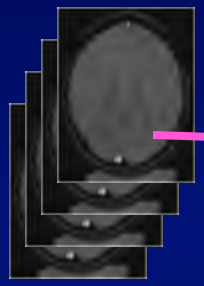


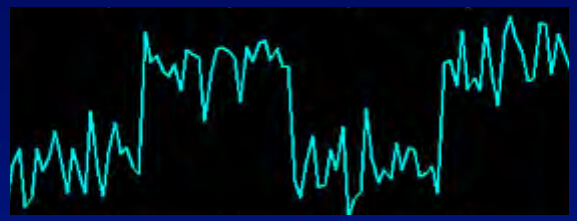
or



$x_i(j)$

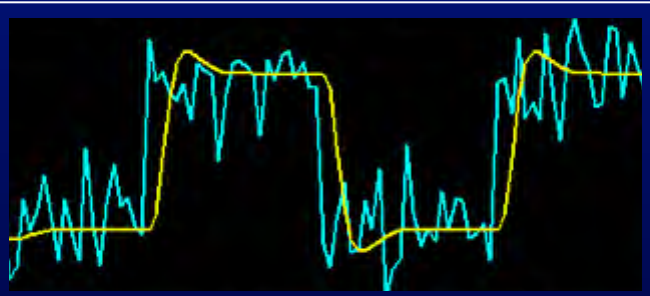
2. Data



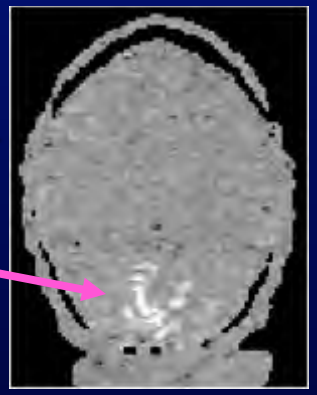


$y(j)$

3. Fitting the Model to the Data at each voxel

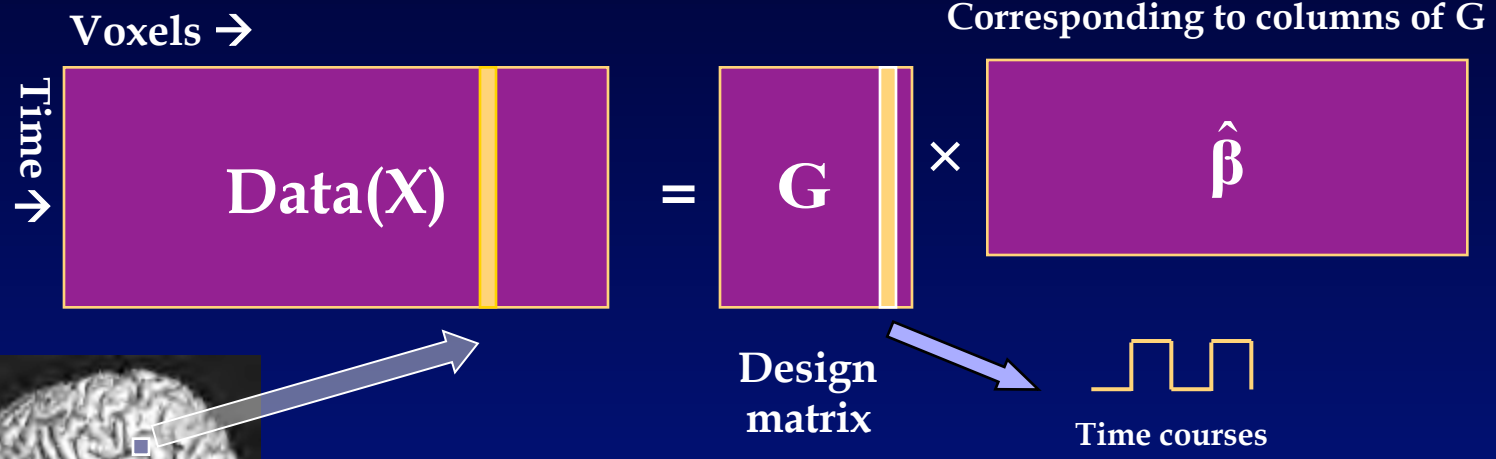


Regression Results

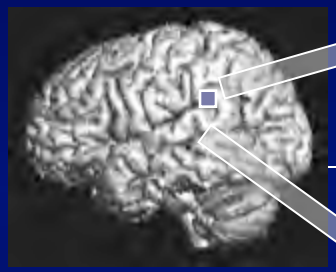


$$y(j) = \hat{\beta}_0 + \sum_{i=1}^{M} \hat{\beta}_i x_i(j) + e(j)$$

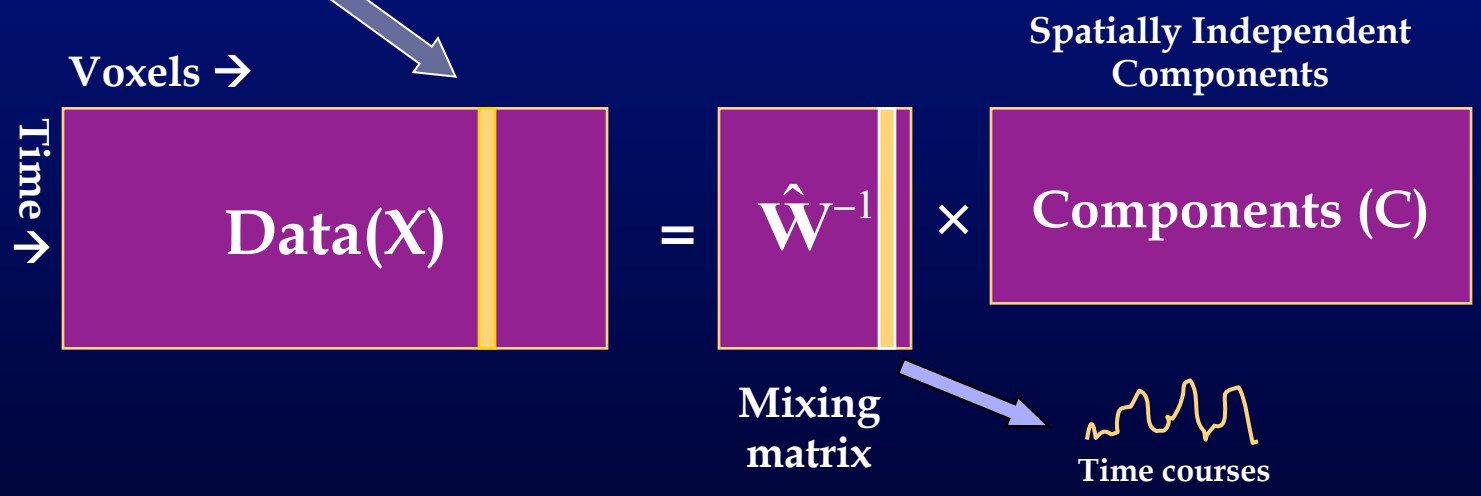
General Linear Model (GLM)



The GLM is by far the most common approach to analyzing fMRI data. To use this approach, one needs a model for the fMRI time course



Independent Component Analysis (ICA)



In spatial ICA, there is no model for the fMRI time course, this is estimated along with the hemodynamic source locations

ICA Halloween (Un)Mixer!

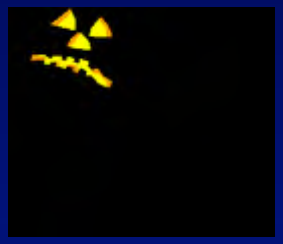
X = **A** × **S**

=

background

→ Time

candle 1



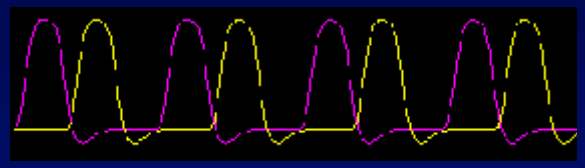
candle 2

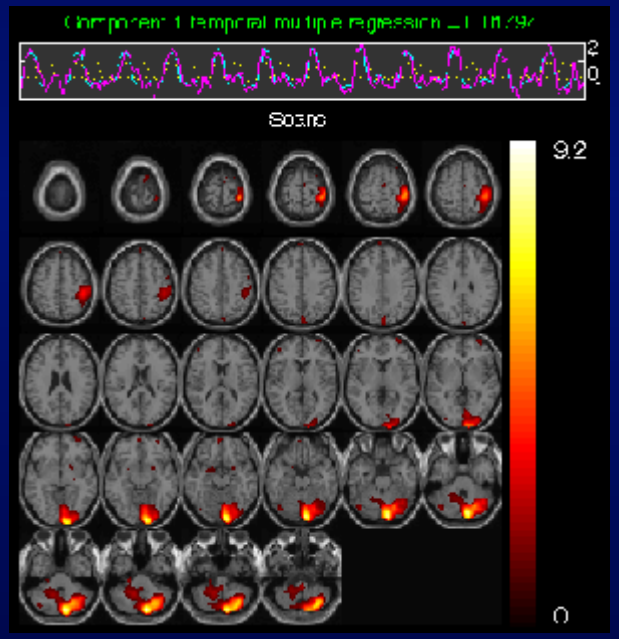
candle 3

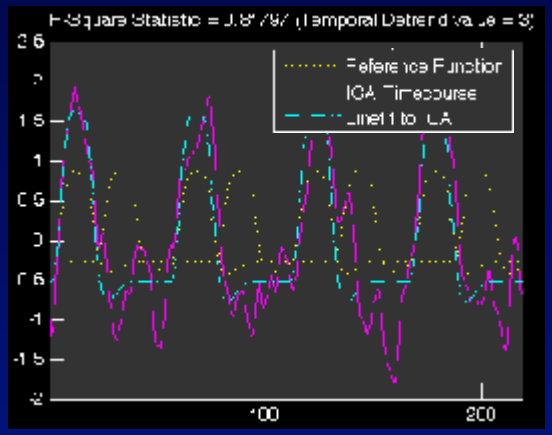
Candle out

Assessing Task Modulation of Components

- We can evaluate the component timecourses within a standard GLM approach.

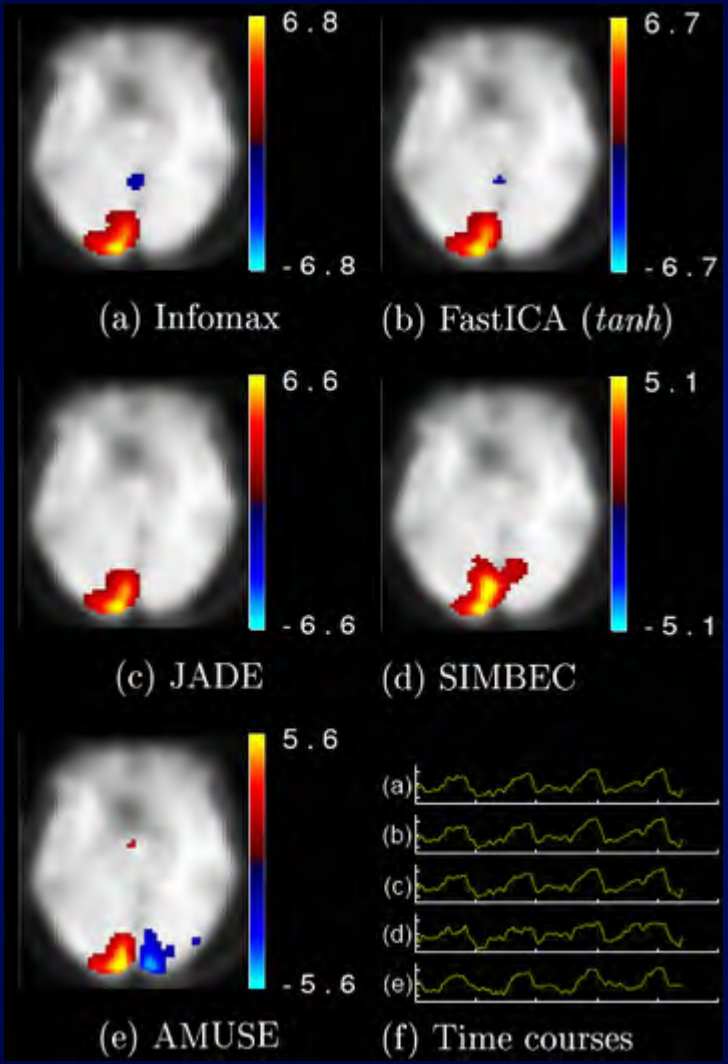


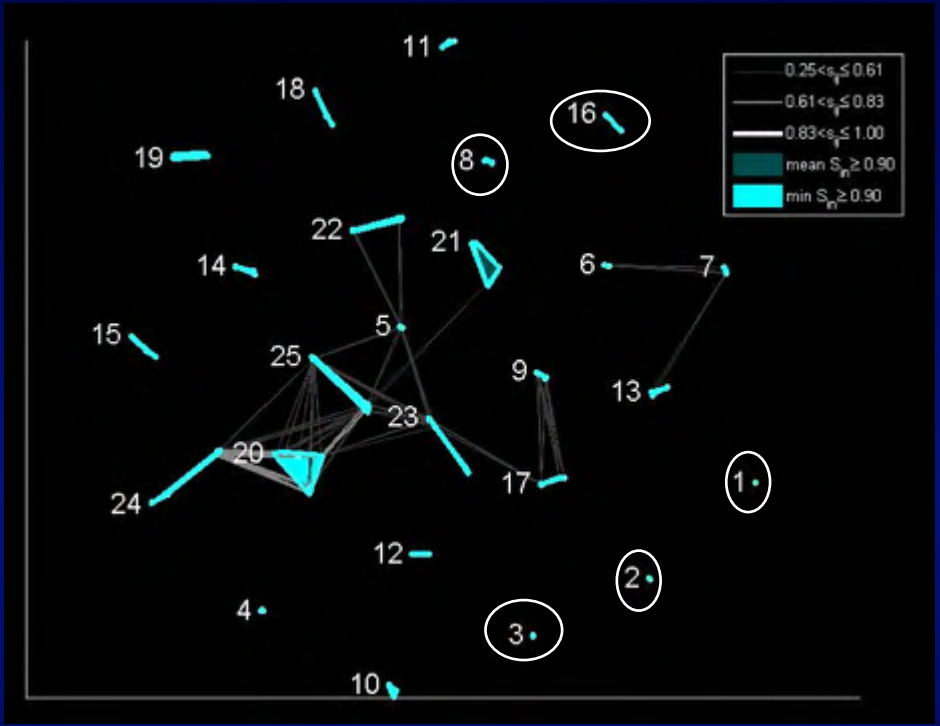




Comp#	R^2	Subject	Reg1	Reg2
3	0.81	1	1.89	0.02
		2	2.28	0.66
10	0.79	1	0.28	2.19
		2	0.65	2.03
4	0.017	1	-0.19	-0.40
		2	-0.10	0.08

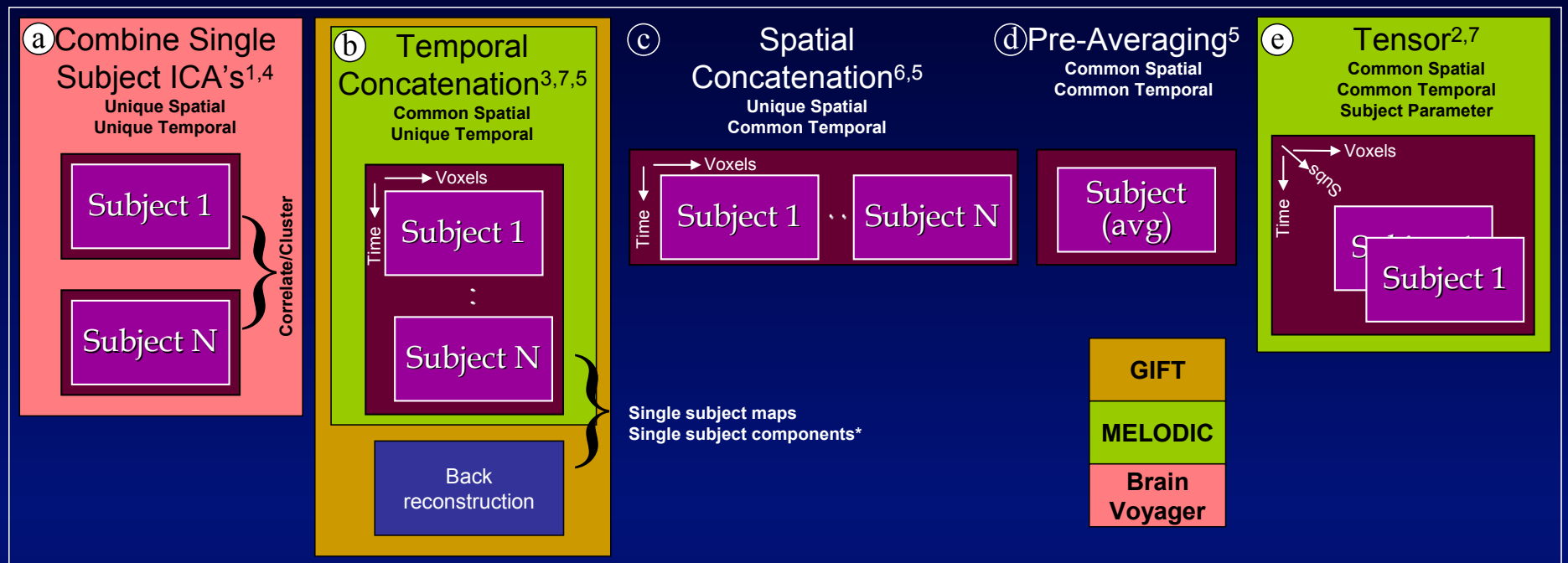
Consistency of ICA Algorithms





N. Correa, T. Adalı, and V. D. Calhoun, "Performance of Blind Source Separation Algorithms for fMRI Analysis," Mag.Res.Imag., vol. 25, p. 684, 2007

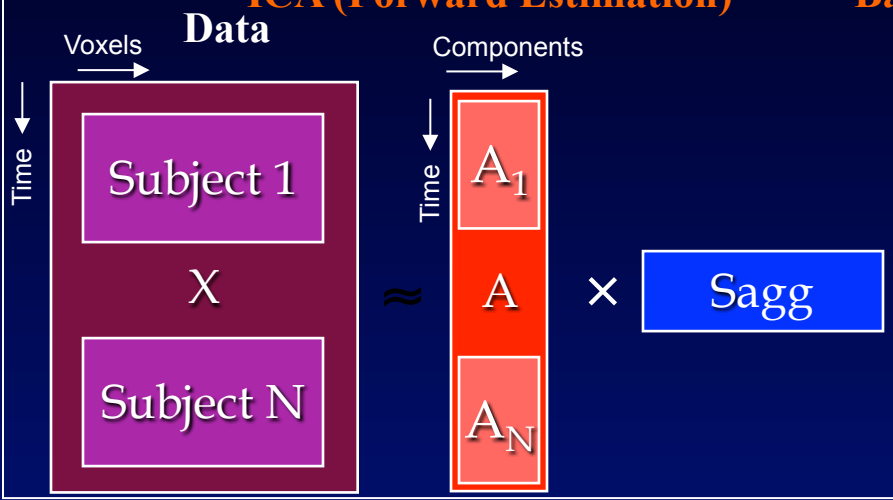
Group ICA



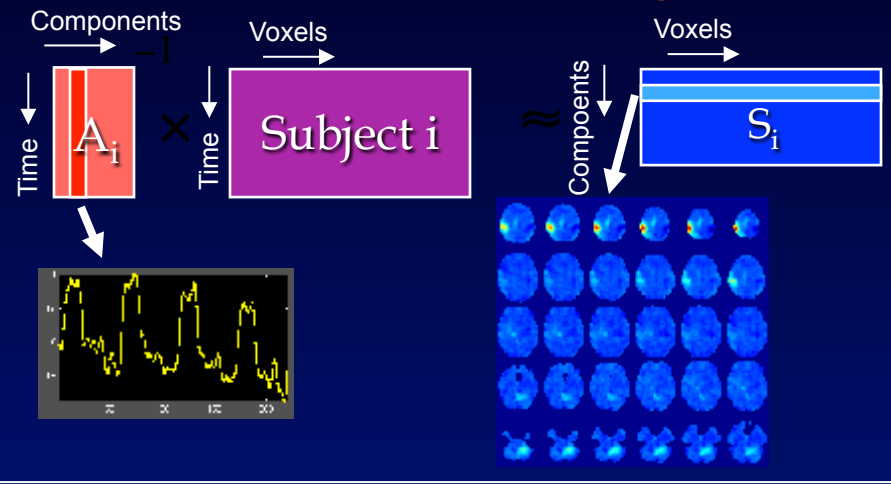
1) Calhoun VD, Adali T, McGinty V, Pekar JJ, Watson T, Pearlson GD. (2001): fMRI Activation In A Visual-Perception Task: Network Of Areas Detected Using The General Linear Model And Independent Component Analysis. NeuroImage 14(5):1080-1088.
2) Beckmann CF, Smith SM. (2005): Tensorial extensions of independent component analysis for multisubject FMRI analysis. NeuroImage 25(1):294-311.
3) Calhoun VD, Adali T, Pearlson GD, Pekar JJ. (2001): A Method for Making Group Inferences from Functional MRI Data Using Independent Component Analysis. Hum.Brain Map. 14(3):140-151.
4) Esposito F, Scarabino T, Hyvarinen A, Himberg J, Formisano E, Comani S, Tedeschi G, Goebel R, Seifritz E, Di SF. (2005): Independent component analysis of fMRI group studies by self-organizing clustering. Neuroimage. 25(1):193-205.
5) Schmithorst VJ, Holland SK. (2004): Comparison of three methods for generating group statistical inferences from independent component analysis of functional magnetic resonance imaging data. J.Magn Reson.Imaging 19(3):365-368.
6) Svensen M, Kruggel F, Benali H. (2002): ICA of fMRI Group Study Data. NeuroImage 16:551-563.
7) Guo Y, Giuseppe P. (In Press): A unified framework for group independent component analysis for multi-subject fMRI data. NeuroImage.

- V. D. Calhoun, J. Liu, and T. Adali, "A Review of Group ICA for fMRI Data and ICA for Joint Inference of Imaging, Genetic, and ERP data," *NeuroImage, vol. 45, pp. 163-172, 2009.*
- E. Erhardt, S. Rachakonda, E. Bedrick, T. Adalı, and V. D. Calhoun, "Comparison of multi-subject ICA methods for analysis of fMRI data," *Human Brain Mapping*, vol. 12, pp. 2075-2095, 2011.
- V. D. Calhoun and T. Adalı, "Multi-subject Independent Component Analysis of fMRI: A Decade of Intrinsic Networks, Default Mode, and Neurodiagnostic Discovery," IEEE Reviews in Biomedical Engineering, vol. 5, pp. 60-73, 2012.

ICA (Forward Estimation)

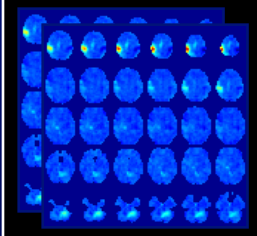


Back-reconstruction (PCA-based, Dual regression, etc)

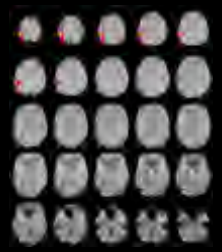


Component Images

Voxel-wise stats
(e.g. one-sample t-test, two-sample t-test, correlation, etc)



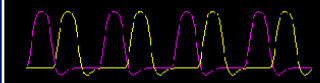
Component images (one per subject)



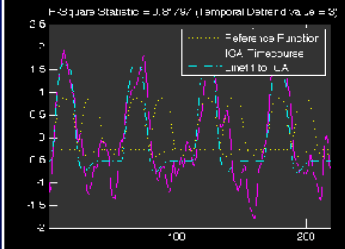
T-statistic

Component Timecourses

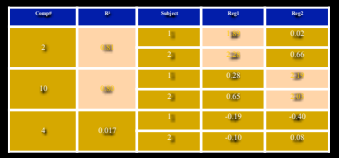
Task-modulation
(e.g. Fit timecourses to GLM model then test parameter)



Model timecourses

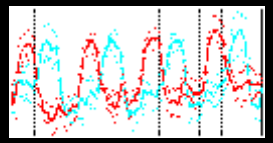


Multiple regression fit to ICA timecourses

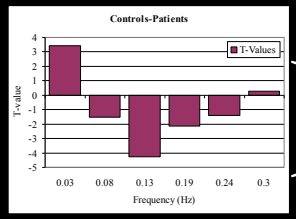


Beta-weights (second level model)

Spectra
(e.g. power spectra, fractal parameters, etc)

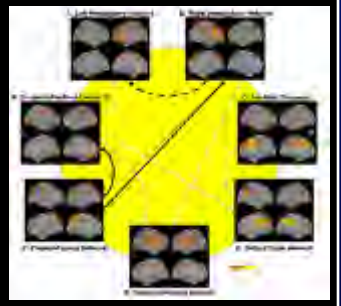


Component timecourses



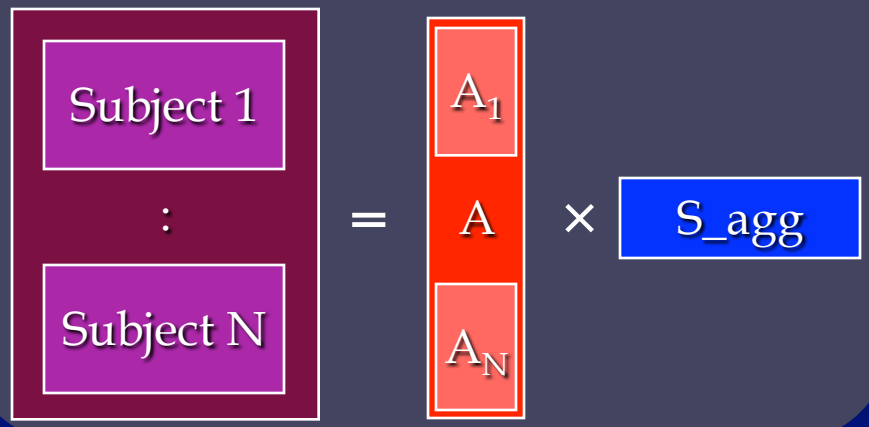
Power spectra group differences

Functional Network Connectivity
(e.g. inter-component correlation)

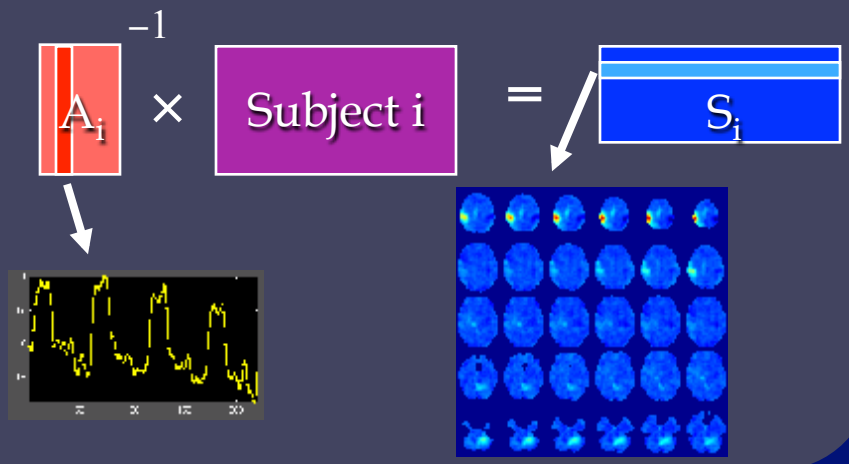


Group ICA

ICA (Forward Estimation)

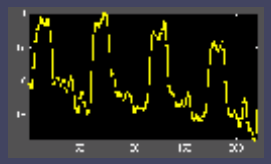


Back-reconstruction through inversion[1]

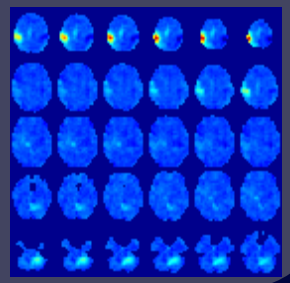


Back-reconstruction through Spatial-temporal (dual) regression[2,3]

1) Regress S_agg onto each timepoint of Subject i to generate A_i



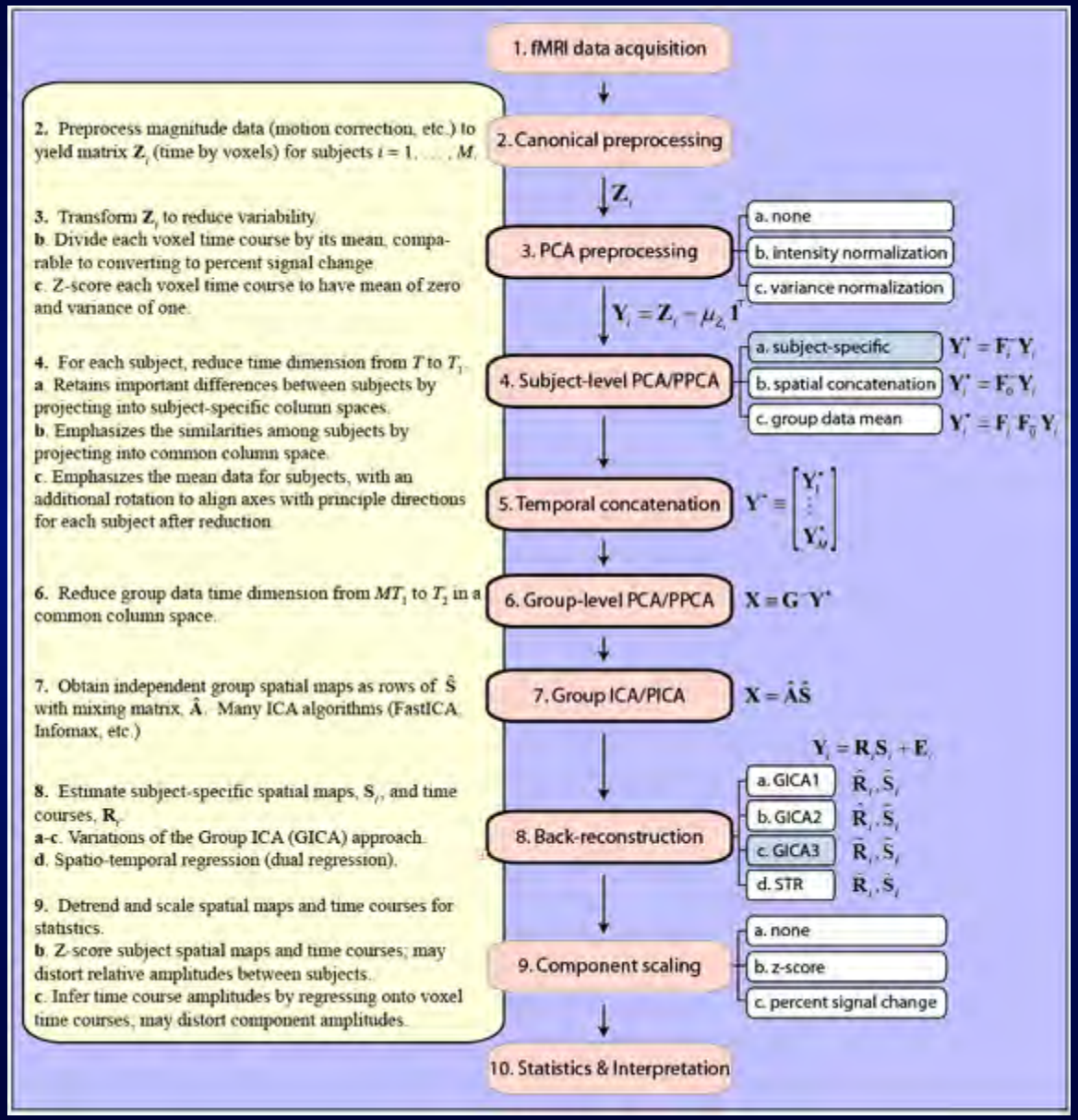
2) Regress A_i onto each image of Subject i to generate S_i

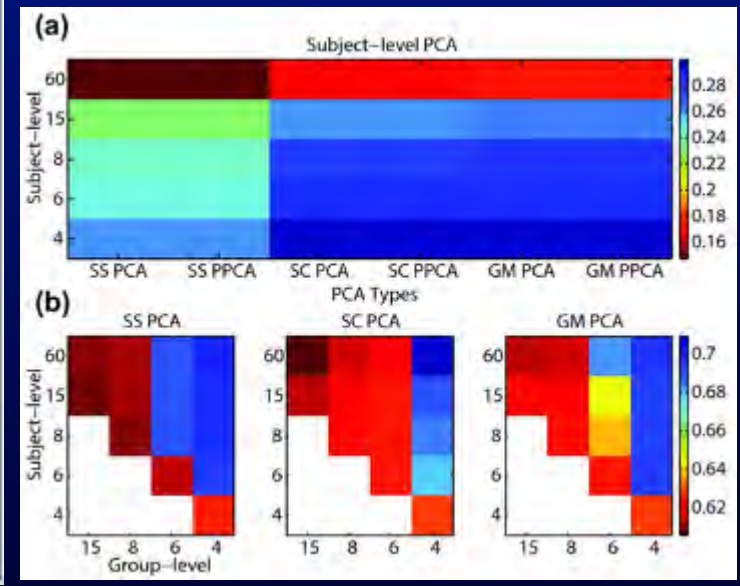


Iterate steps 1 & 2 until converged

E. Erhardt, S. Rachakonda, E. Bedrick, T. Adalı, and V. D. Calhoun, "Comparison of multi-subject ICA methods for analysis of fMRI data," Human Brain Mapping, vol. 12, pp. 2075-2095, 2011

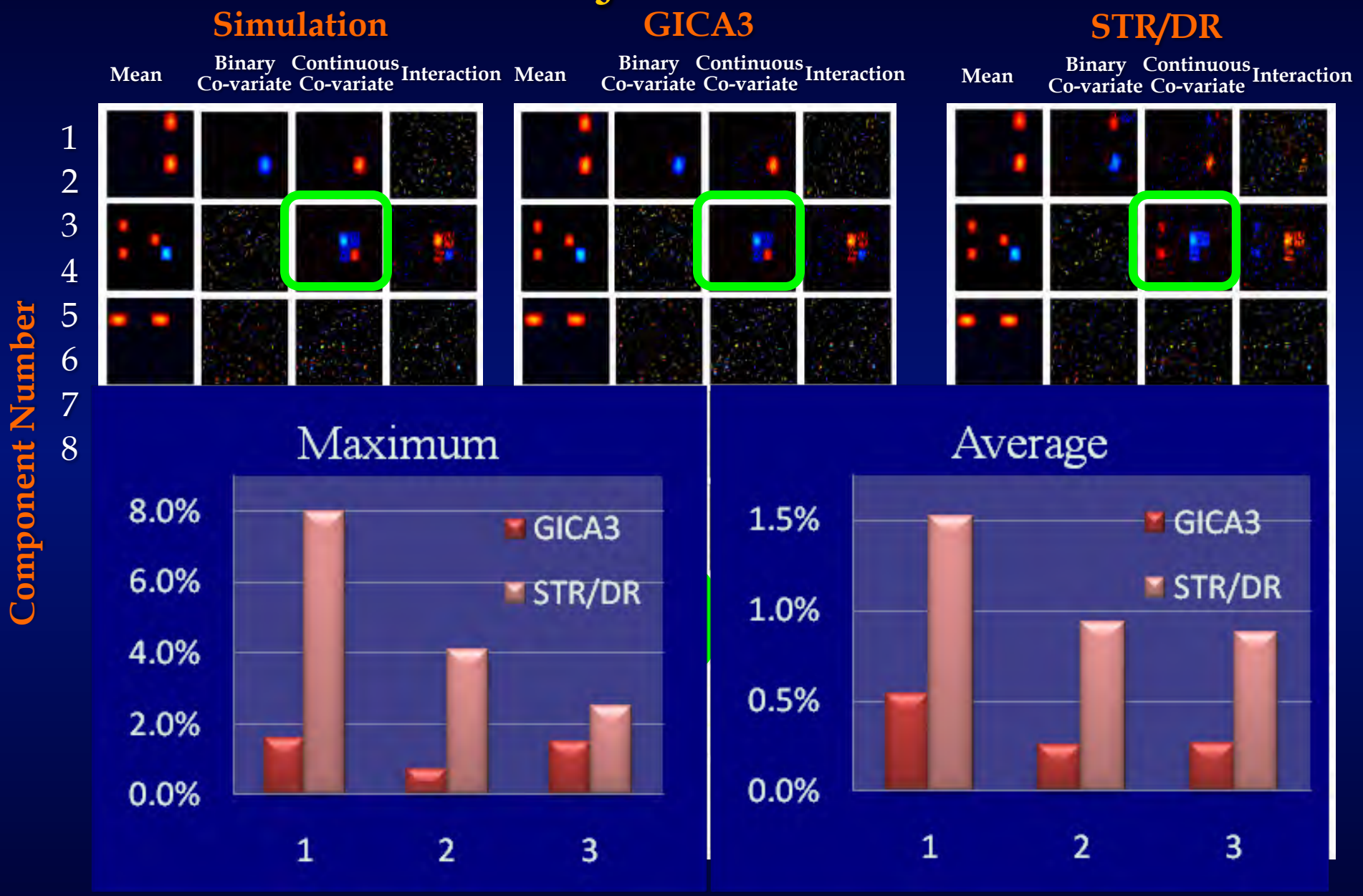
Evaluation of Group ICA Methods





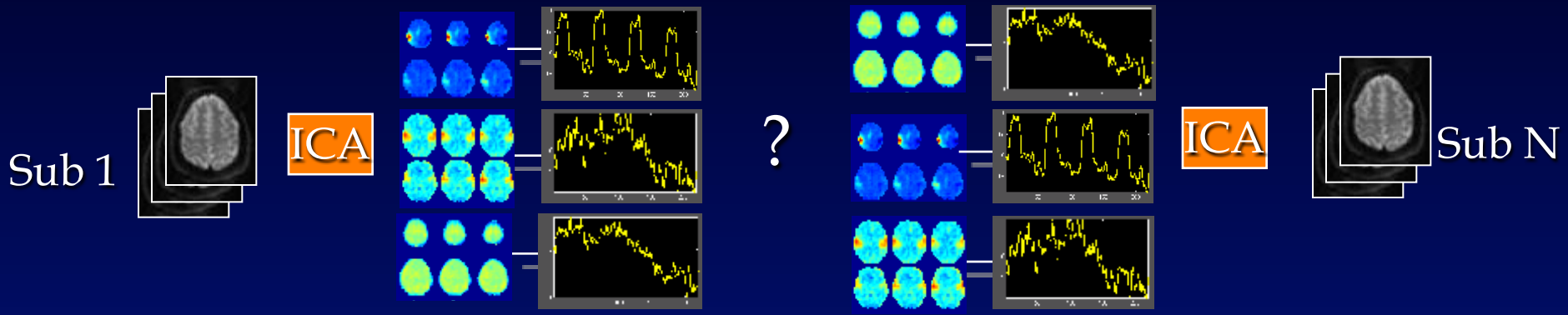
E. Erhardt, S. Rachakonda, E. Bedrick, T. Adali, and V. D. Calhoun, "Comparison of multi-subject ICA methods for analysis of fMRI data," Human Brain Mapping, vol. 12, pp. 2075-2095, 2011

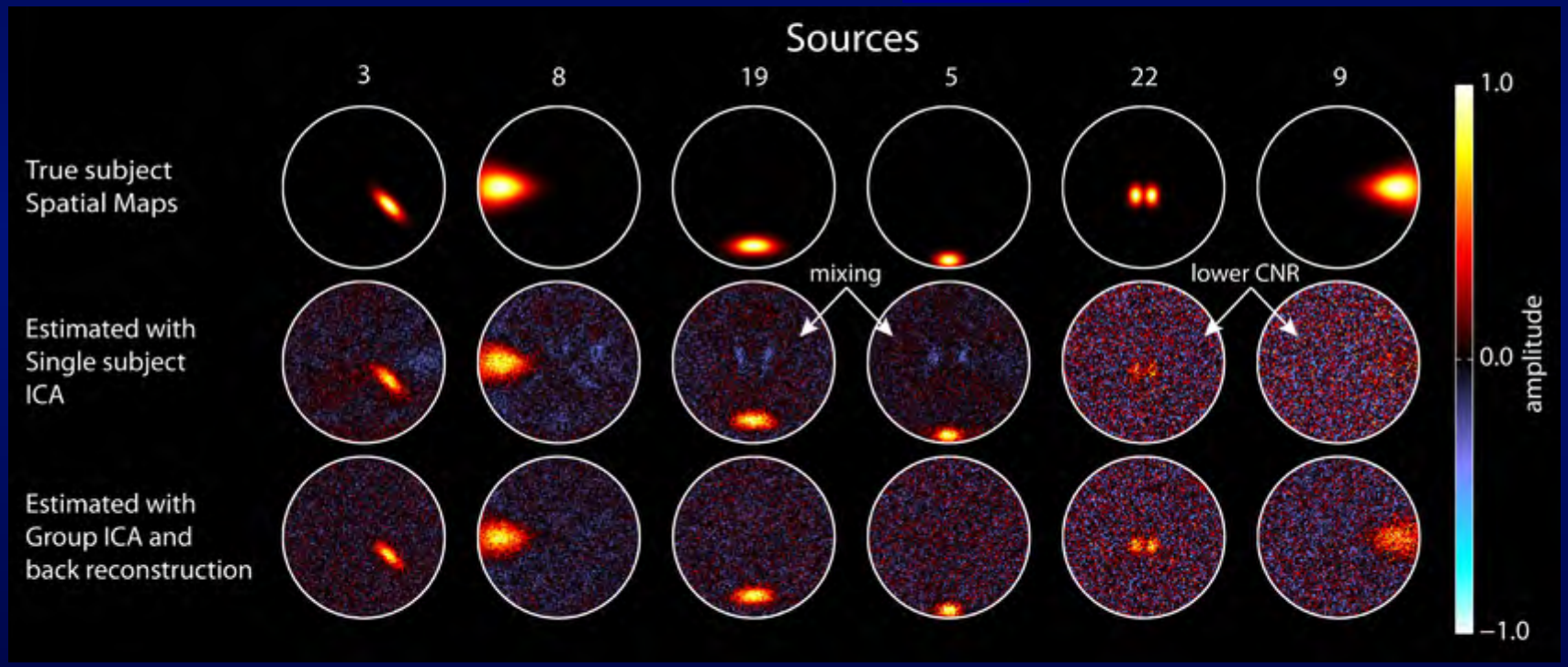
Inter-subject Covariation



E. Erhardt, S. Rachakonda, E. Bedrick, T. Adali, and V. D. Calhoun, "Comparison of multi-subject ICA methods for analysis of fMRI data," Human Brain Mapping, vol. 12, pp. 2075-2095, 2011

Single Subject ICA vs Group ICA

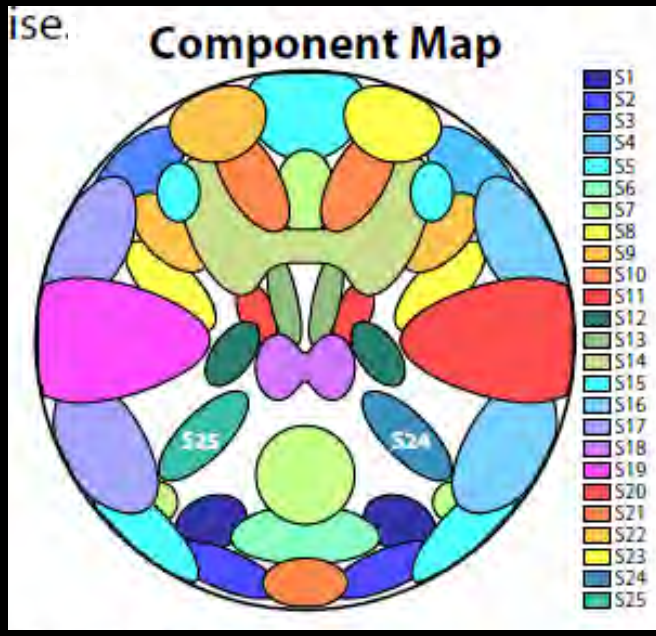




E. Erhardt, E. Allen, Y. Wei, T. Eichele, and V. D. Calhoun, "SimTB, a simulation toolbox for fMRI data under a model of spatiotemporal separability," NeuroImage, vol. 59, pp. 4160-4167, 2012.

E. A. Allen, E. Erhardt, Y. Wei, T. Eichele, and V. D. Calhoun, "Capturing inter-subject variability with group independent component analysis of fMRI data: a simulation study," NeuroImage, vol. 59, pp. 4141-4159, 2012.

Pushing the Limits of Group ICA (simTB)



Parameter	Notation	Value
number of subjects	M	30
number of components	C	25
number of voxels	V	148 x 148
number of timepoints	T	150
repetition time	TR	2
percent signal change	g	3
contrast-to-noise ratio	CNR	1

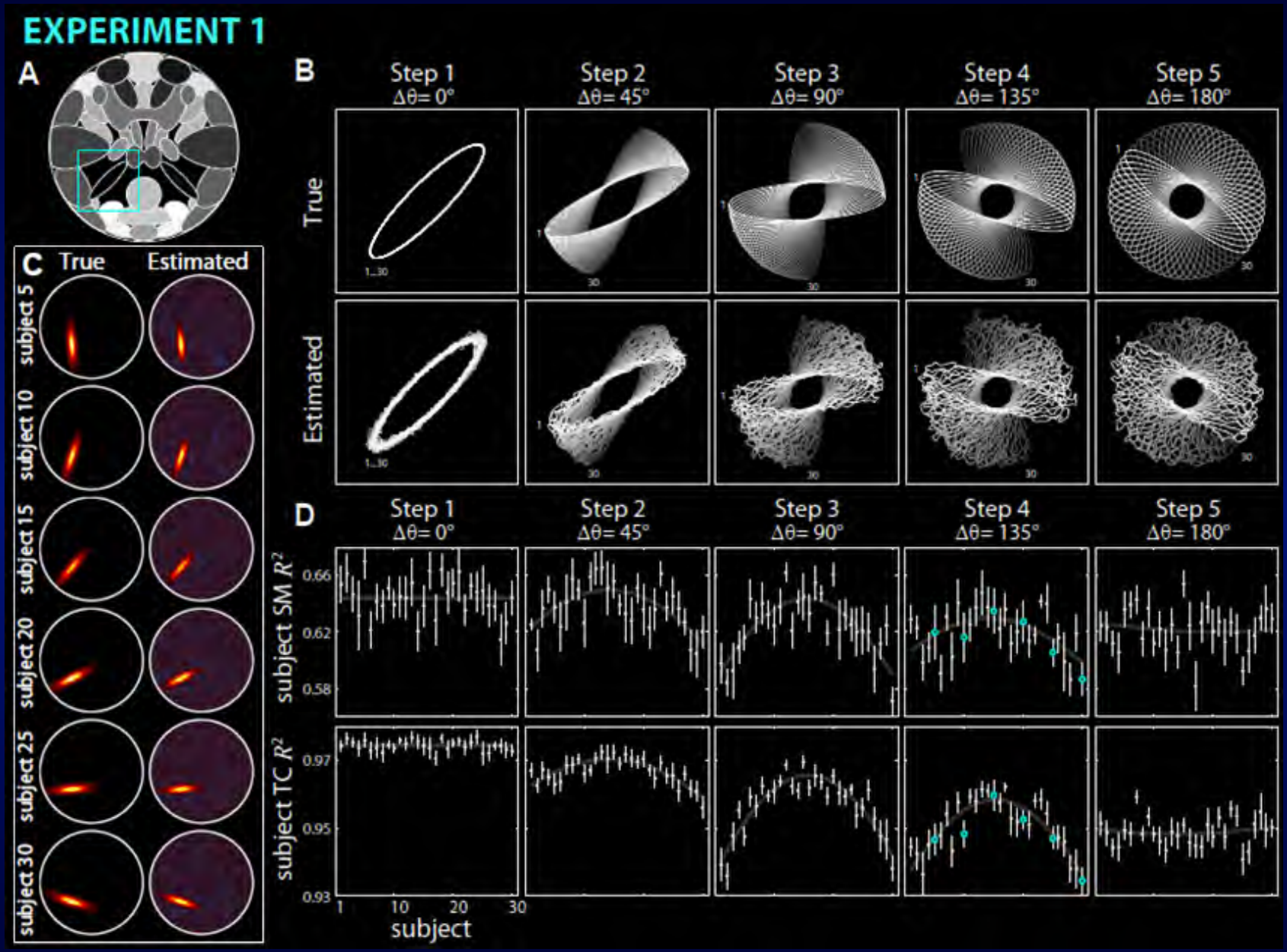
- Roughly 30 SMs can be selected through the graphical user interface by clicking on components, or by component number in the batch script
- For each subject, each selected component can be included or not, be translated and rotated in space, and the spatial spread of the component can be increased or decreased
- Each SM is normalized to have a peak-to-peak amplitude range of one

E. Erhardt, E. Allen, Y. Wei, T. Eichele, and V. D. Calhoun, "SimTB, a simulation toolbox for fMRI data under a model of spatiotemporal separability," NeuroImage, vol. 59, pp. 4160-4167, 2012.

E. A. Allen, E. Erhardt, Y. Wei, T. Eichele, and V. D. Calhoun, "Capturing inter-subject variability with group independent component analysis of fMRI data: a simulation study," NeuroImage, vol. 59, pp. 4141-4159, 2012.

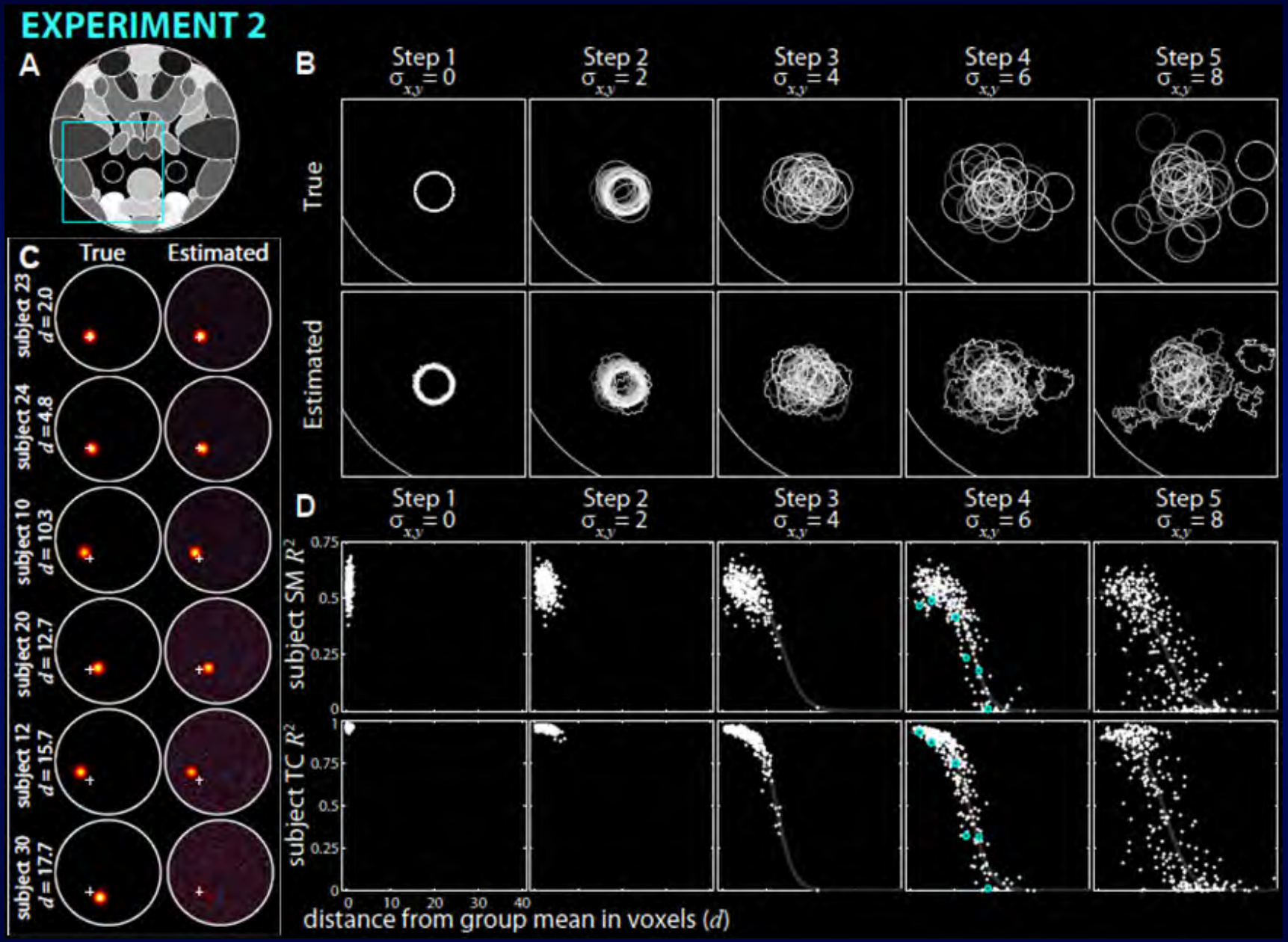
http://mialab.mrn.org/software/simtb

Rotation



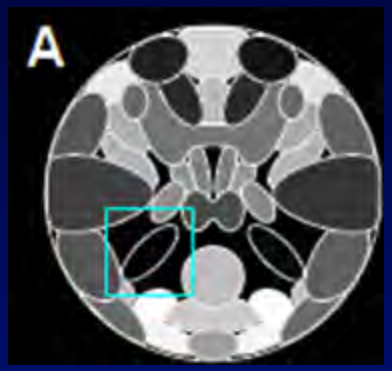
E. A. Allen, E. Erhardt, Y. Wei, T. Eichele, and V. D. Calhoun, "Capturing inter-subject variability with group independent component analysis of fMRI data: a simulation study," NeuroImage, vol. 59, pp. 4141-4159, 2012.

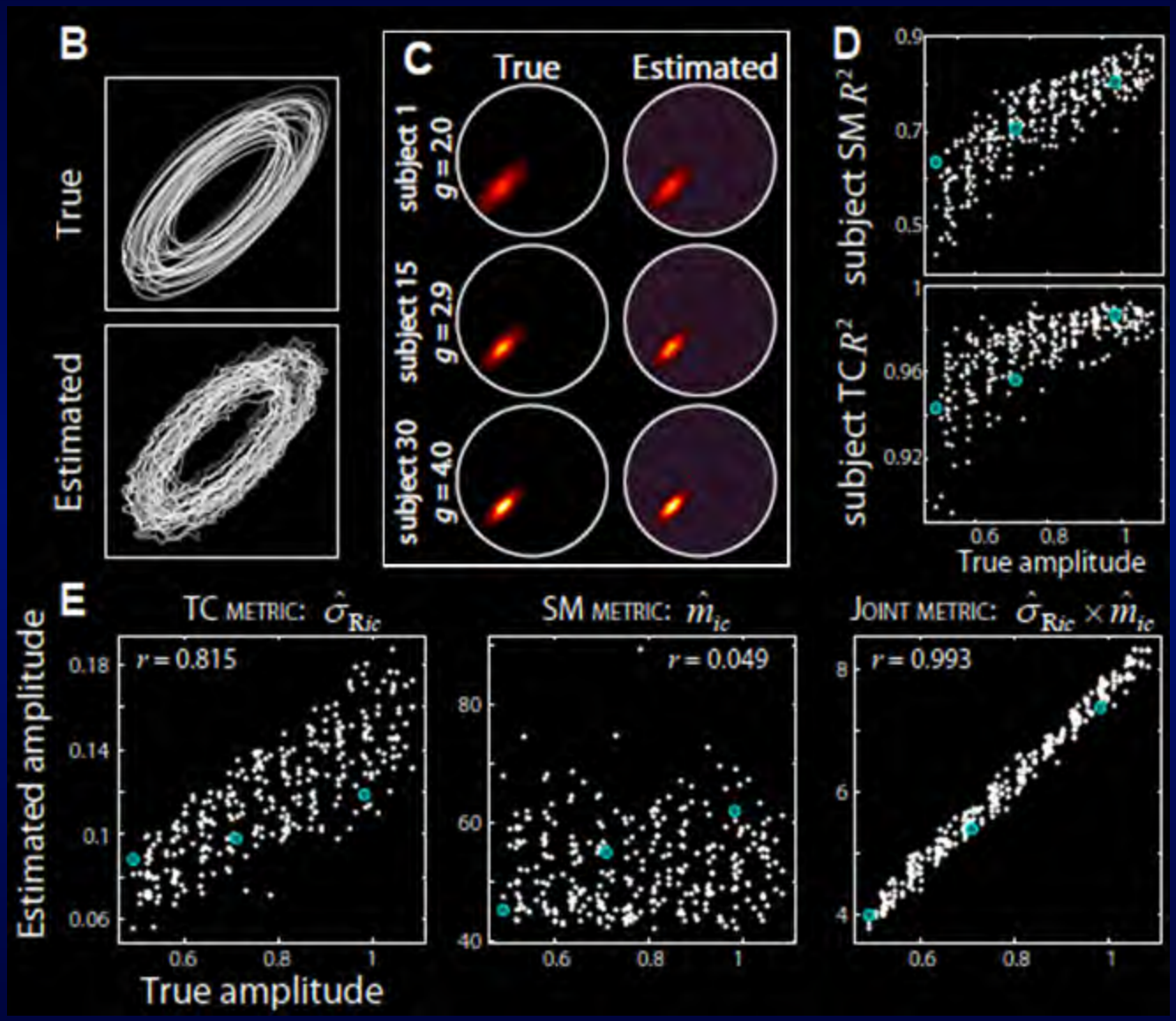
Position



E. A. Allen, E. Erhardt, Y. Wei, T. Eichele, and V. D. Calhoun, "Capturing inter-subject variability with group independent component analysis of fMRI data: a simulation study," NeuroImage, vol. 59, pp. 4141-4159, 2012.

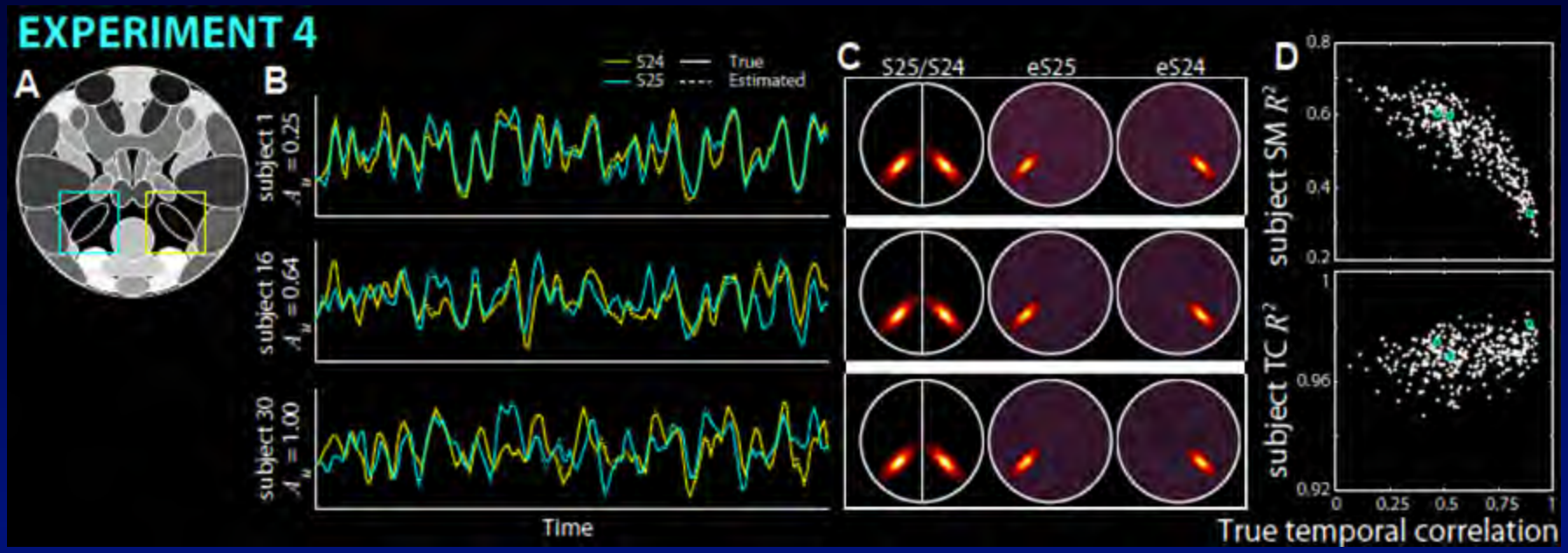
Amplitude

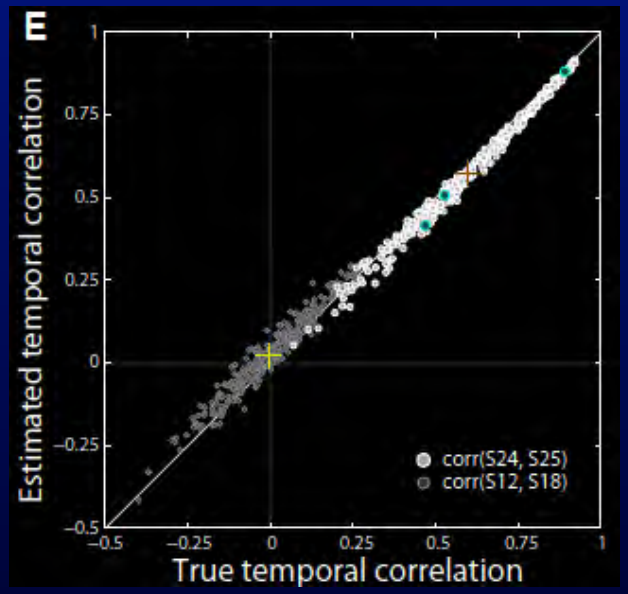




E. A. Allen, E. Erhardt, Y. Wei, T. Eichele, and V. D. Calhoun, "Capturing inter-subject variability with group independent component analysis of fMRI data: a simulation study," NeuroImage, vol. 59, pp. 4141-4159, 2012.

Temporal Correlation Among Components (FNC)





E. A. Allen, E. Erhardt, Y. Wei, T. Eichele, and V. D. Calhoun, "Capturing inter-subject variability with group independent component analysis of fMRI data: a simulation study," NeuroImage, vol. 59, pp. 4141-4159, 2012.

Collaborative Informatics & Neuroimaging Suite (COINS)

http://coins.mrn.org

http://coins.mrn.org/dx

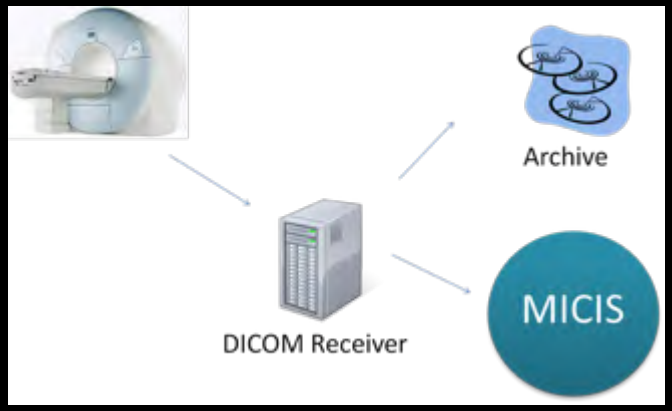
COINS Tools

MICIS
DICOM Receiver
Assessment Manager
Self Assessment
Tablet
Query Builder
Portals
CAS
My Security
Data Exchange

Fully Open Source stack (LAPP)

Current counts of important artifacts

- PIs 110
- Studies 509
- Subjects ~ 24,000
- Scan Sessions ~ 34,000
- Clinical Assessments ~ 355,000

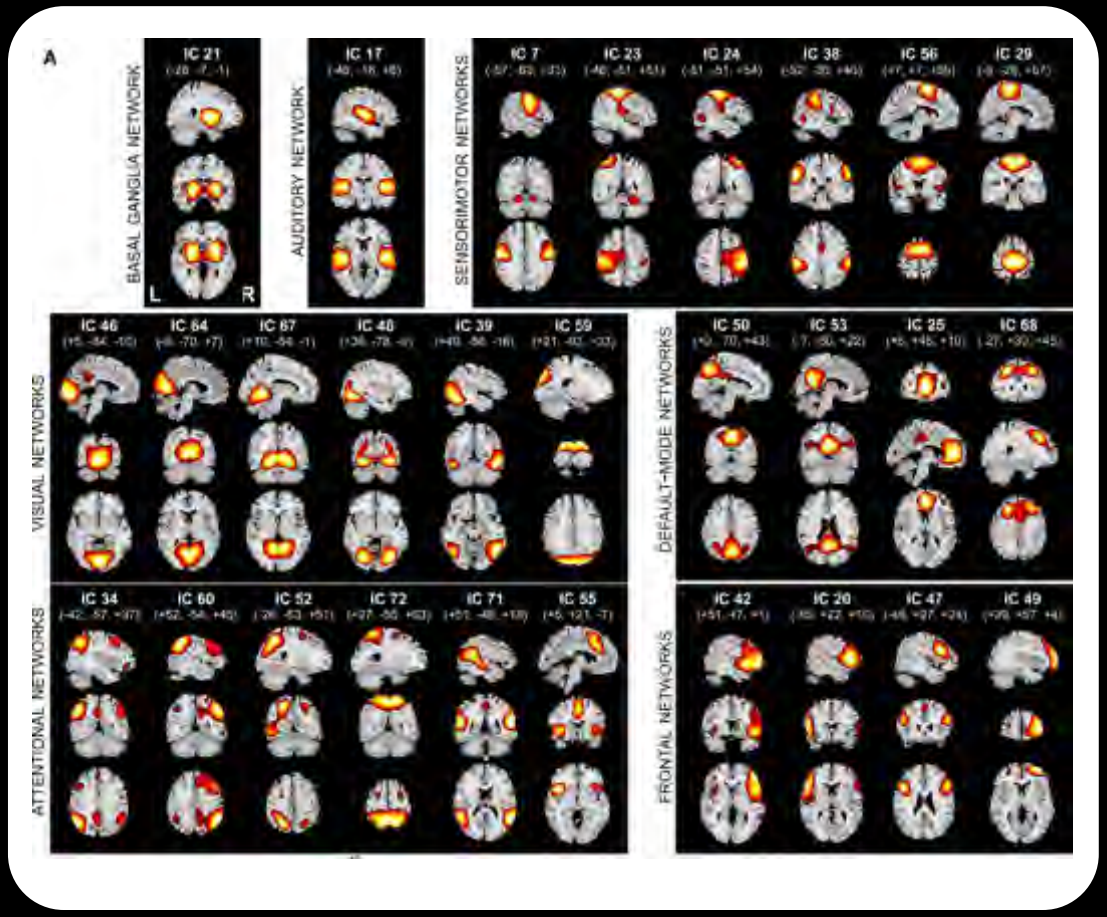


M. King, D. Wood, B. Miller, R. Kelly, W. Courtney, D. Landis, R. Wang, J. Turner, and V. D. Calhoun, "Automated collection of imaging and phenotypic data to centralized and distributed data repositories," Frontiers in Neuroinformatics, in press, PMC Journal - In Process.

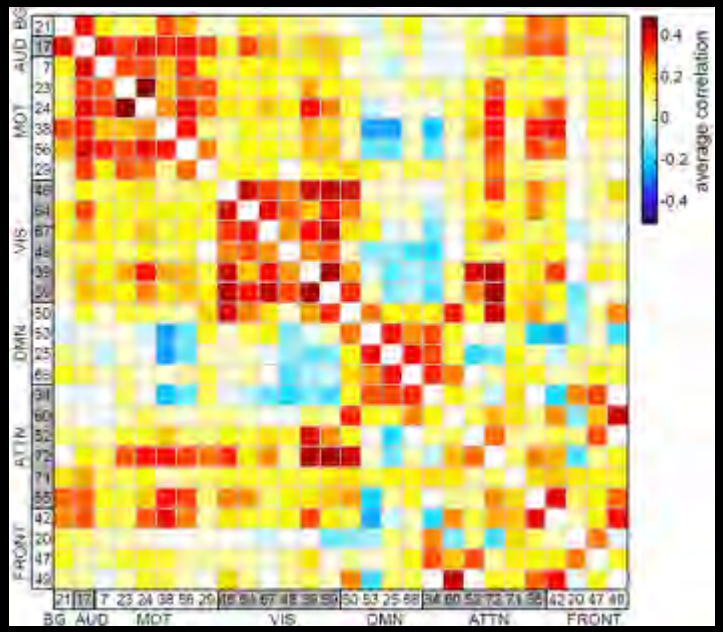
D. Wood, M. King, D. Landis, W. Courtney, R. Wang, R. Kelly, J. Turner, and V. D. Calhoun, "Harnessing modern web application technology to create intuitive and efficient data visualization and sharing tools," Frontiers in Neuroinformatics, in press, PMC Journal - In Process.

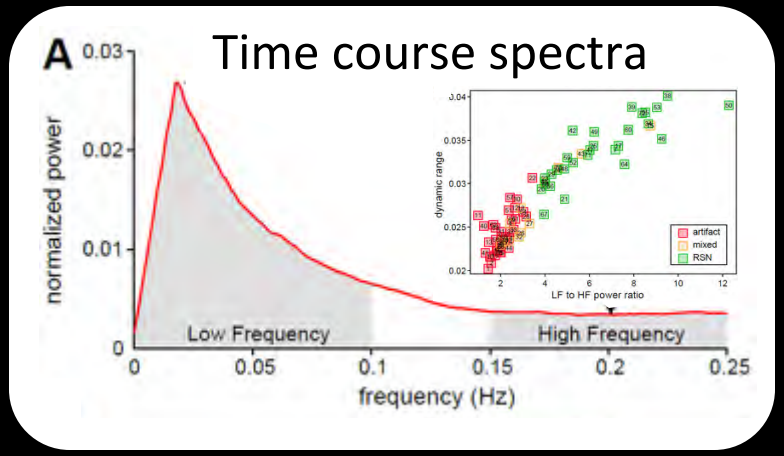
Group ICA of Rest fMRI Data: N=603

Component spatial maps



Functional network connectivity (FNC)





28 labeled components
& superset of 75 components
N=603 subjects
http://mialab.mrn.org/data

E. Allen, et al, "A baseline for the multivariate comparison of resting state networks," *Frontiers in Systems Neuroscience,* vol. 5, p. 12, 2011.

Multivariate Testing Framework

univariate models

(1) H_0: $\beta_1 = 0$

:

(v) H_0: $\beta_v = 0$

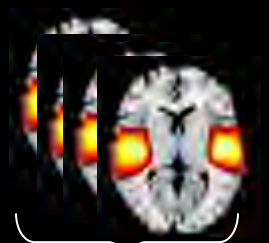
Is voxel *i* affected by age?

multivariate models

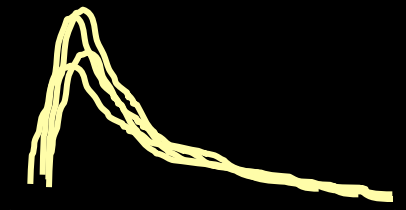
H_0: $\beta_1 = \beta_2 = \ldots \beta_v = 0$

Are any of these voxels affected by age?

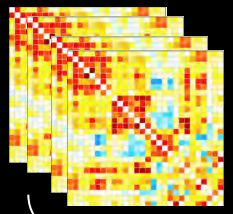
Y =

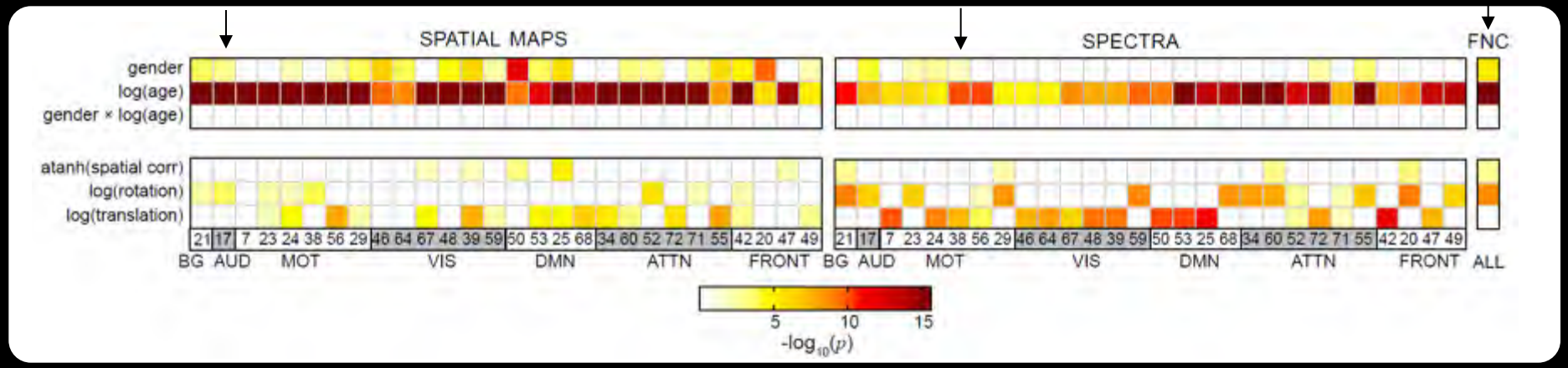


Y =

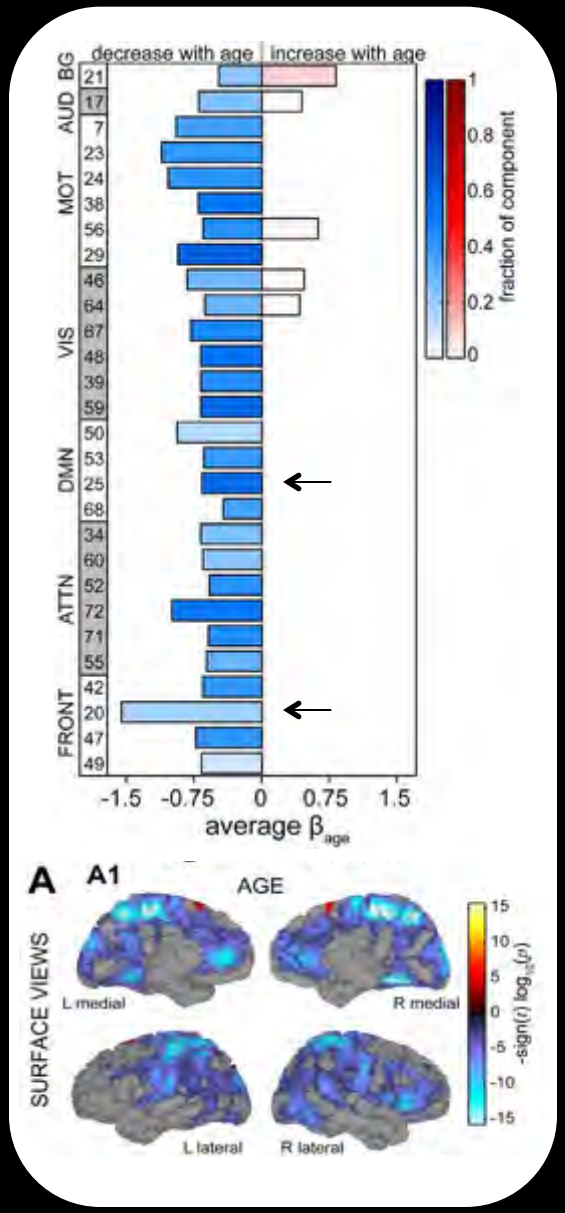


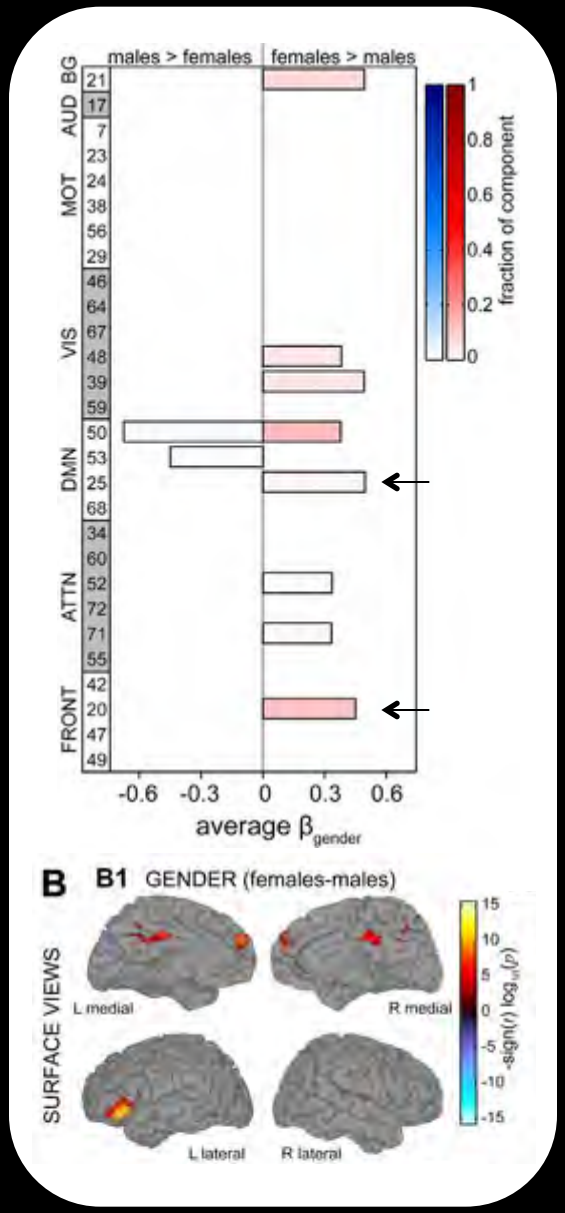
Y =



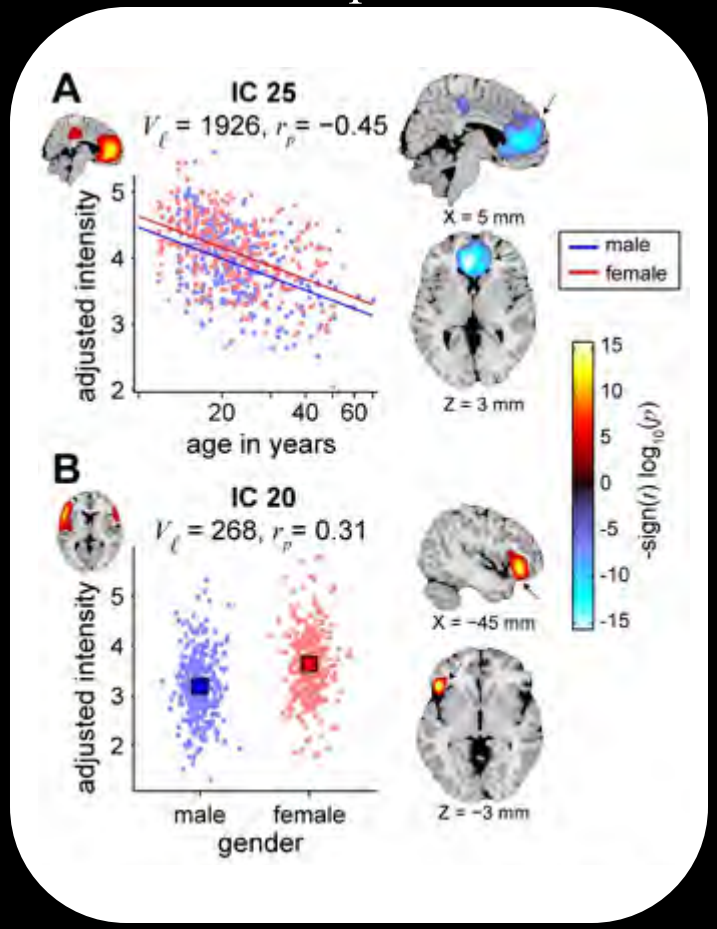


Univariate Followup



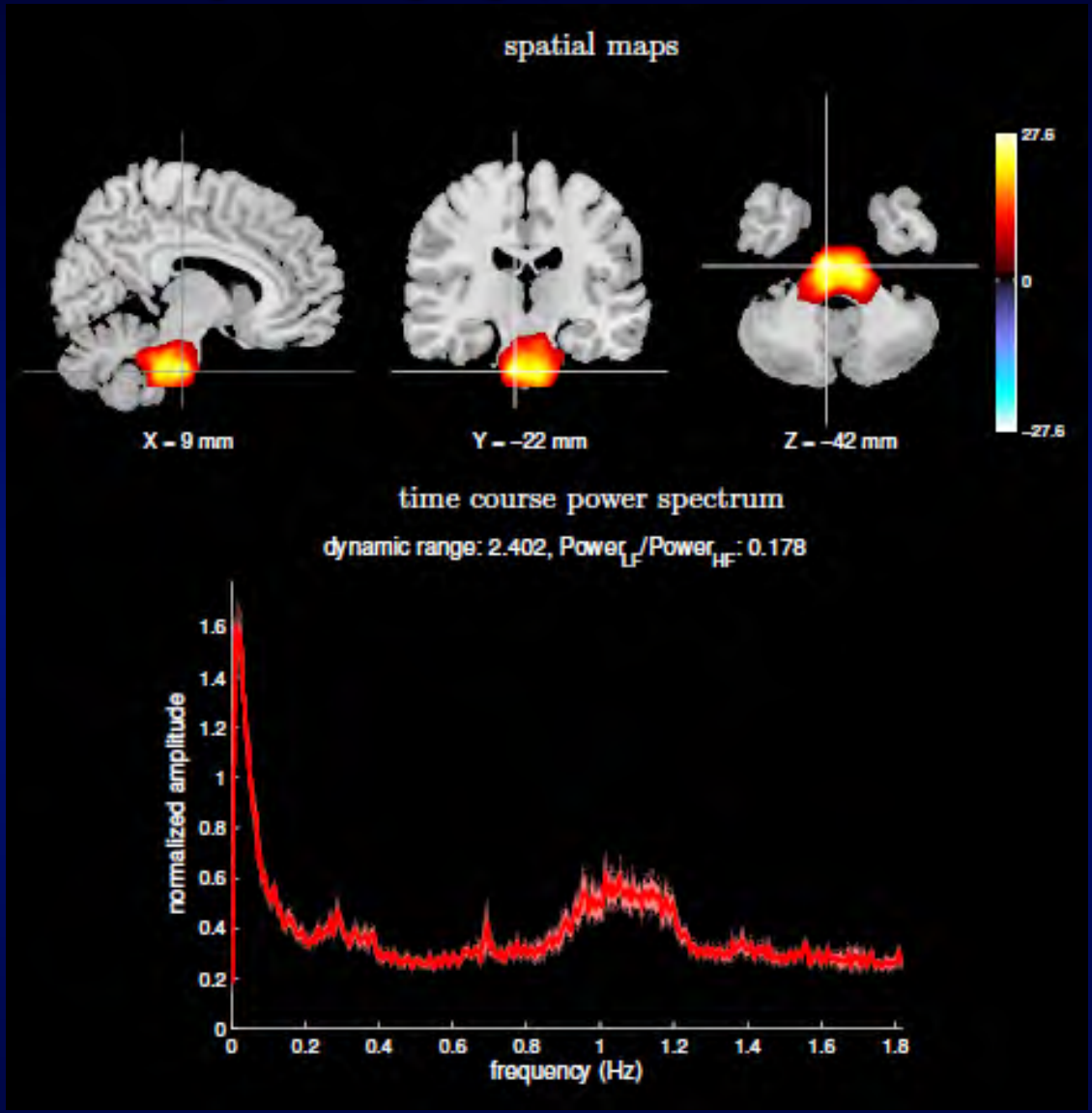


examples



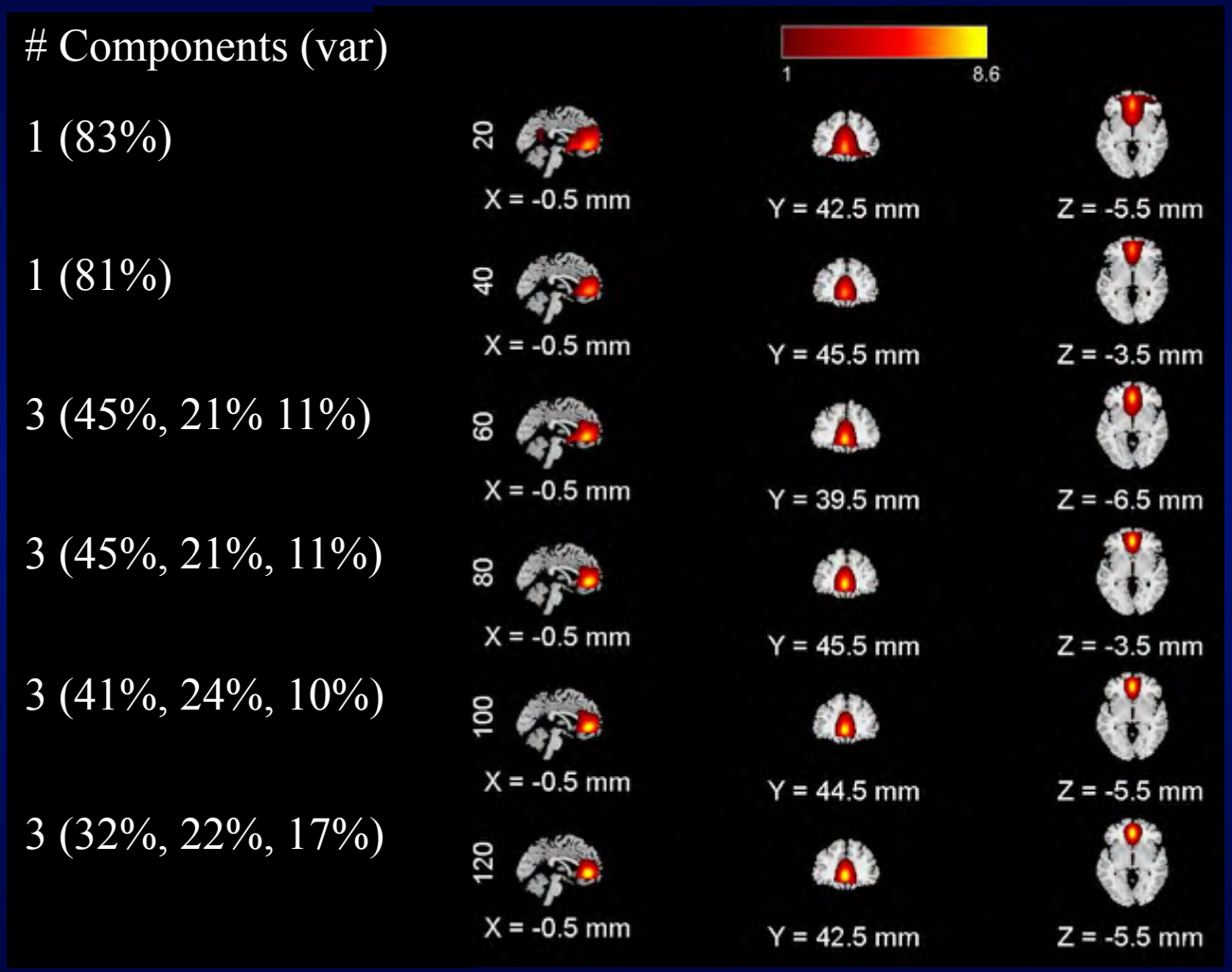
E. Allen, et al, "A baseline for the multivariate comparison of resting state networks," *Frontiers in Systems Neuroscience,* vol. 5:2, 2011.

Rapid Imaging (multiband EPI)



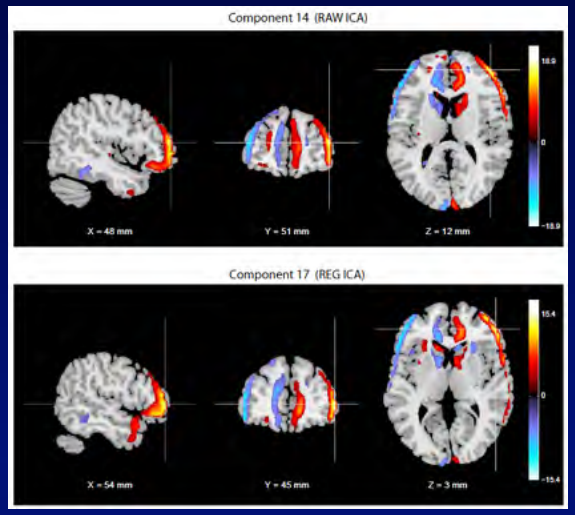
TR=275ms, 39 subjects

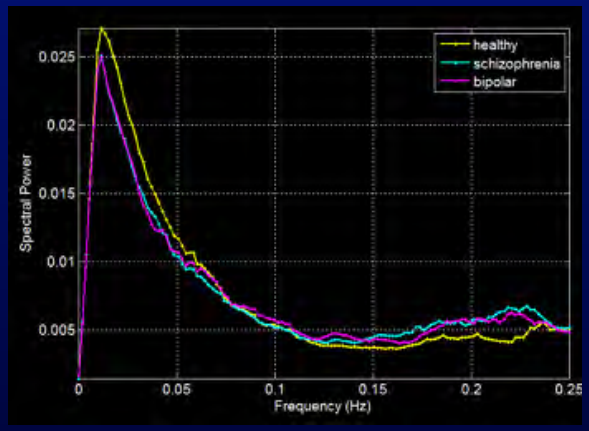
On ICA Model Order: Reconstruction of low model order from high model order



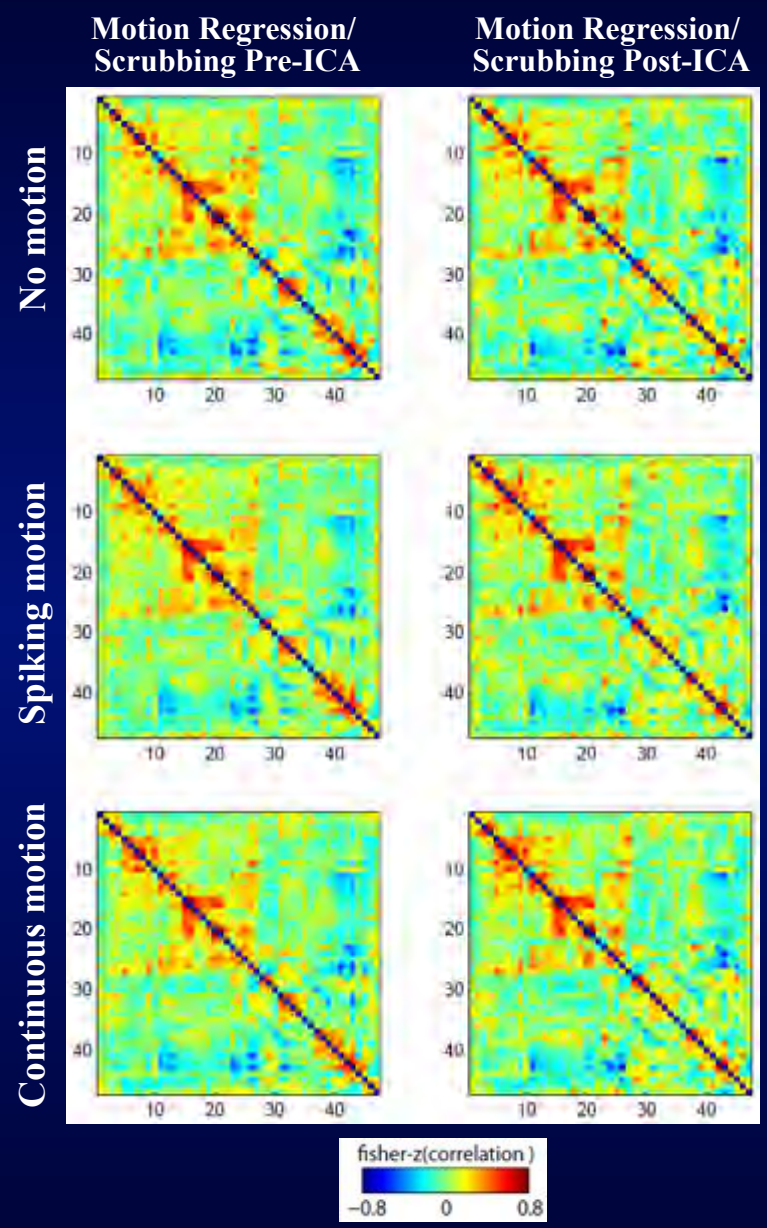
Outline of Talk

- Approaches
  - Seeds vs Components
  - Intro to ICA
  - Group ICA vs single subject
- Processing issues
  - Impact of (micro) motion
  - Autocorrelation
  - Band-pass filtering
- Other issues
  - Task vs Rest
  - Overlap of networks
- Applications
  - Diagnostic
  - Prediction
- Dynamic connectivity
- Summary

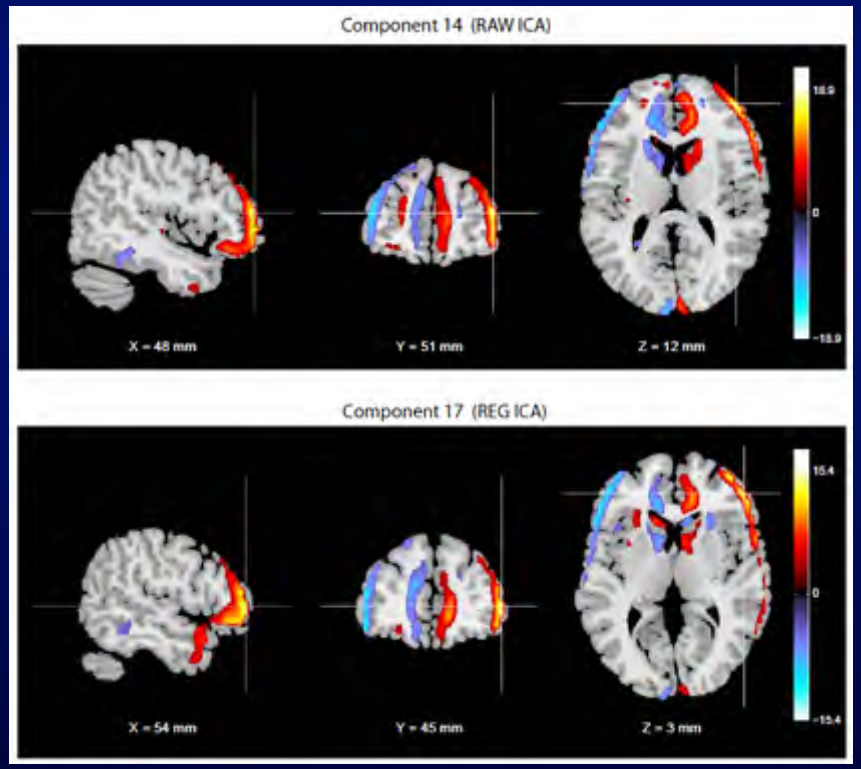




Impact of motion on FNC

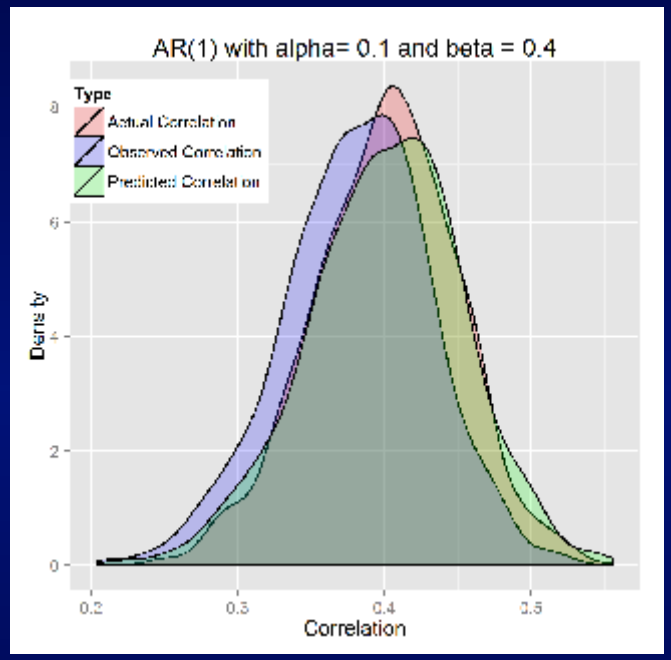


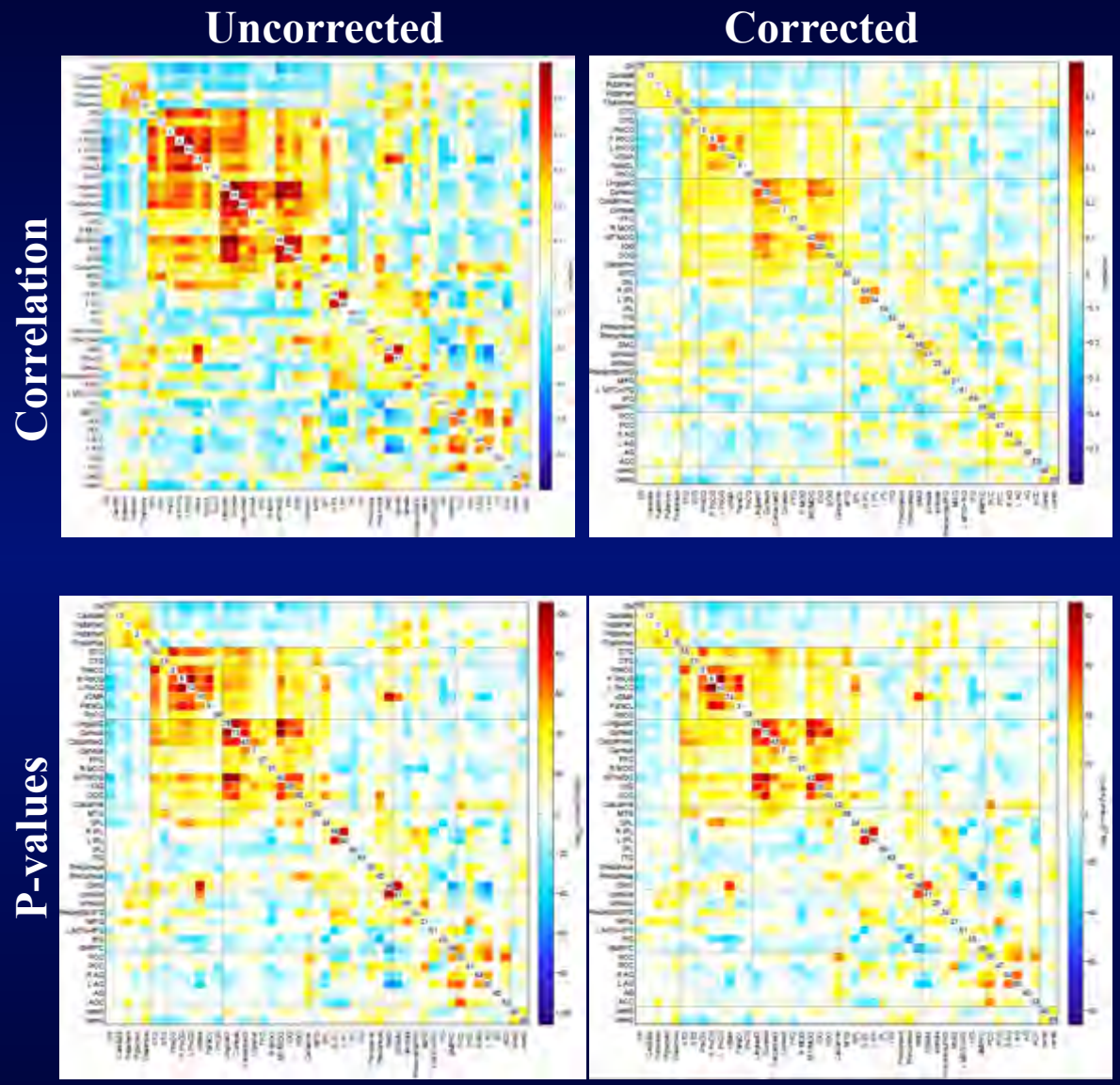
- We selected 3 sets of subjects (total N = 199).
- Non Movers (NM) :Subject group who had very small framewise micromovements (FD_rms < 0.2 mm in general) (N1 = 68)
- Continuous Movers (CM): Subject group who had continuous framewise micromovements of 0.2 mm or higher (more micromovements) (N2 = 66)
- Spikey Movers (SM): Subject group who had reasonable framewise micromovements but with occasional big jerky movements of FD_rms > 0.5 (N3 = 65).



A. G. Christodoulou, T. E. Bauer, K. A. Kiehl, S. Feldstein Ewing, A. D. Bryan, and V. D. Calhoun, "A Quality Control Method for Detecting and Suppressing Uncorrected Residual Motion in fMRI Studies," *Magnetic Resonance Imaging,* in press

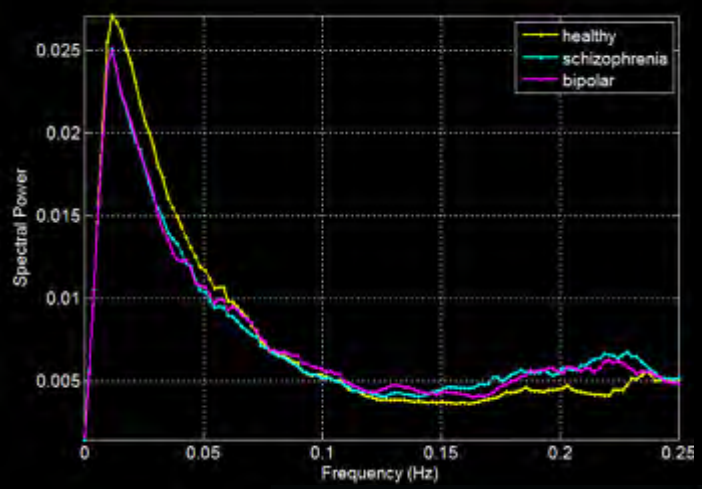
Autocorrelation

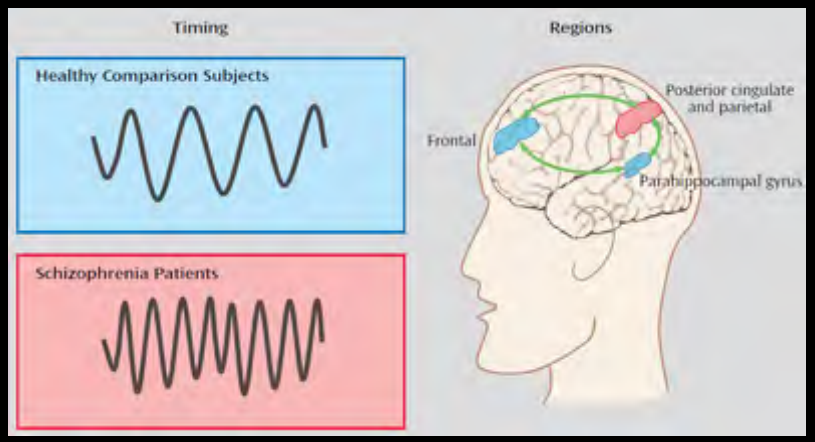


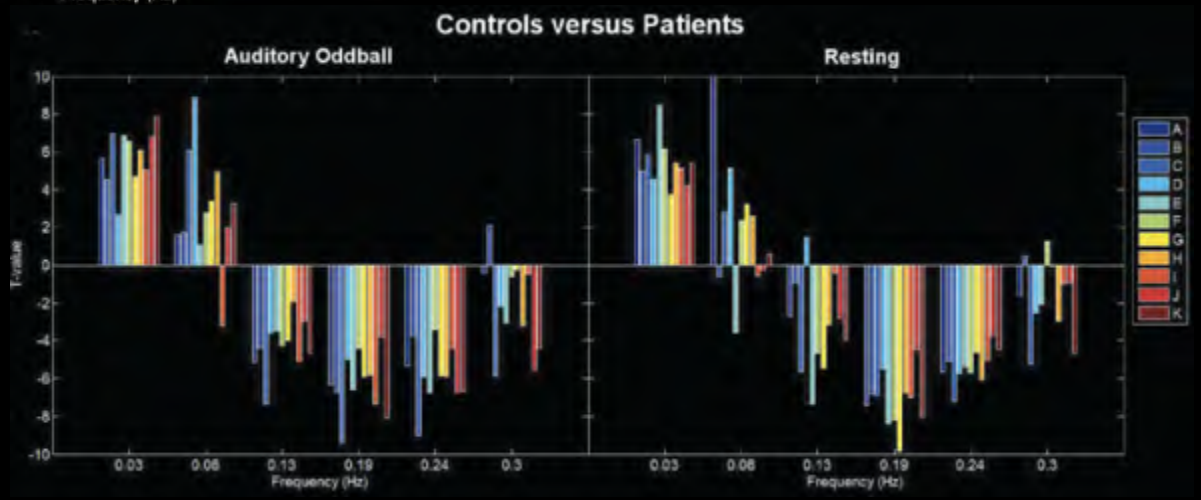


M. Arbabshirani, E. Damaraju, R. Phlypo, S. M. Plis, E. Allen, S. Ma, D. Mathalon, A. Preda, J. G. Vaidya, T. Adalı, and V. D. Calhoun, "Impact of Autocorrelation on Functional Connectivity," NeuroImage, in press.

High-Frequency: Baby vs Bathwater?





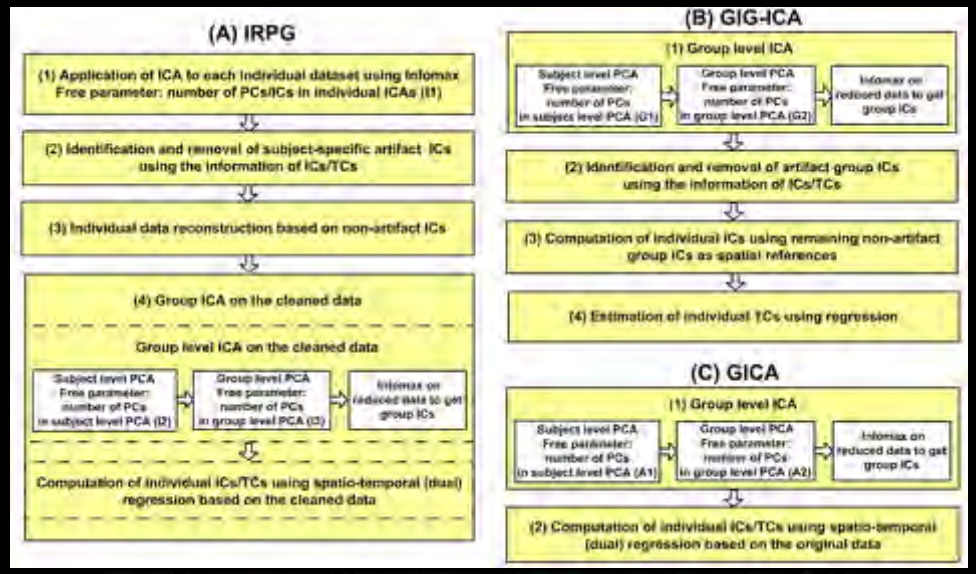


A. Garrity, G. D. Pearlson, K. McKiernan, D. Lloyd, K. A. Kiehl, and V. D. Calhoun, "Aberrant 'Default Mode' Functional Connectivity in Schizophrenia," *Am. J. Psychiatry*, 2006.

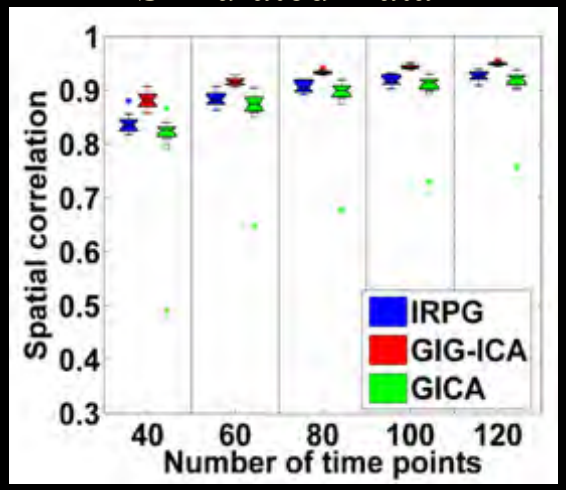
V. D. Calhoun, K. A. Kiehl, and G. D. Pearlson, "Modulation of Temporally Coherent Brain Networks Estimated using ICA at Rest and During Cognitive Tasks," Human Brain Mapping, vol. 29, pp. 828-838, 2008.

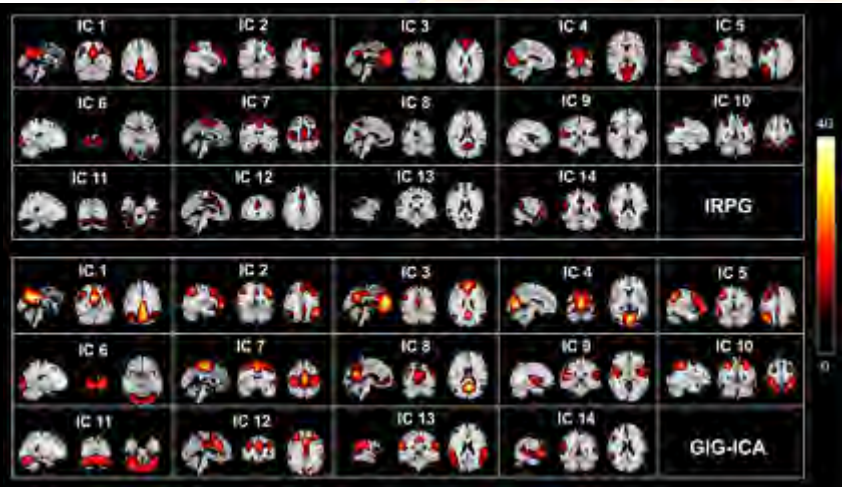
V. D. Calhoun, J. Sui, K. A. Kiehl, J. A. Turner, E. A. Allen, and G. D. Pearlson, "Exploring the Psychosis Functional Connectome: Aberrant Intrinsic Networks in Schizophrenia and Bipolar Disorder," Frontiers in Neuropsychiatric Imaging and Stimulation, vol. 2, pp. 1-13, 2012

Denoising…the easy way

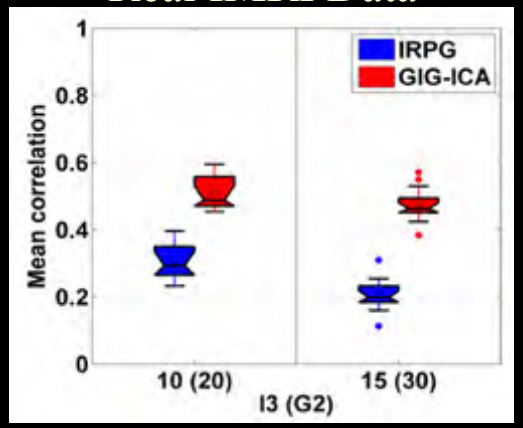


Simulated Data





Real fMRI Data



V. Sochat, K. Supekar, J. Bustillo, V. D. Calhoun, J. A. Turner, and D. Rubin, "A Robust Classifier to Distinguish Noise from fMRI Independent Components," PLoS ONE, in press.

Y. Du, E. A. Allen, H. He, J. Sui, and V. D. Calhoun, "Comparison of ICA based fMRI artifact removal: single subject and group approaches," in Proceedings of the Organization of Human Brain Mapping, Hamburg, Germany, 2014.

Y. Du, E. Allen, H. He, S. J., and V. D. Calhoun, "Brain functional networks extraction based on fMRI artifact removal: single subject and group approaches," in *EMBS*, Chicago, IL, 2014.

Outline of Talk

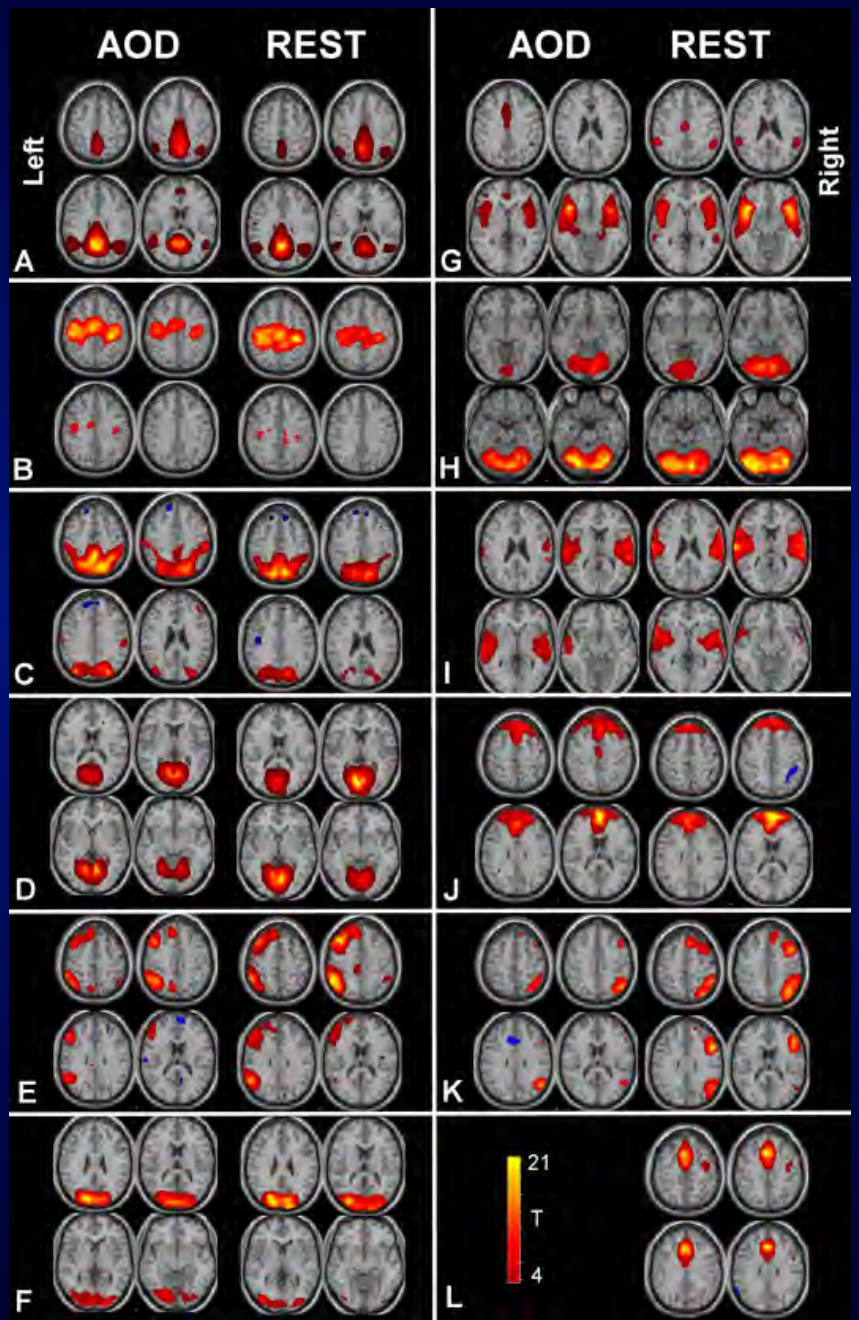
- Approaches
  - Seeds vs Components
  - Intro to ICA
  - Group ICA vs single subject
- Processing issues
  - Impact of (micro) motion
  - Autocorrelation
  - Band-pass filtering
- Other issues
  - Task vs Rest
  - Overlap of networks
- Applications
  - Diagnostic
  - Prediction
- Dynamic connectivity
- Summary

Task vs Rest

Result 1: AOD and rest data produced highly similar networks

Comp#	Comp#	Description	Corr
Oddball	***Rest***		
16	19	A: Default mode	0.9577
11	9	B: Motor	0.9156
13	12	C: Sup parietal	0.9142
10	6	D: Medial visual	0.8628
12	7	E: Left lateral frontoparietal	0.8557
14	2	F: Lateral Visual	0.8170
17	13	G: Temporal2	0.8135
8	11	H: Cerebellum	0.8059
1	15	I: Temporal1	0.8048
4	16	J: Frontal	0.7838
2	4	K: Right lateral frontoparietal	0.8170
	5	L: Anterior cingulate	0.035

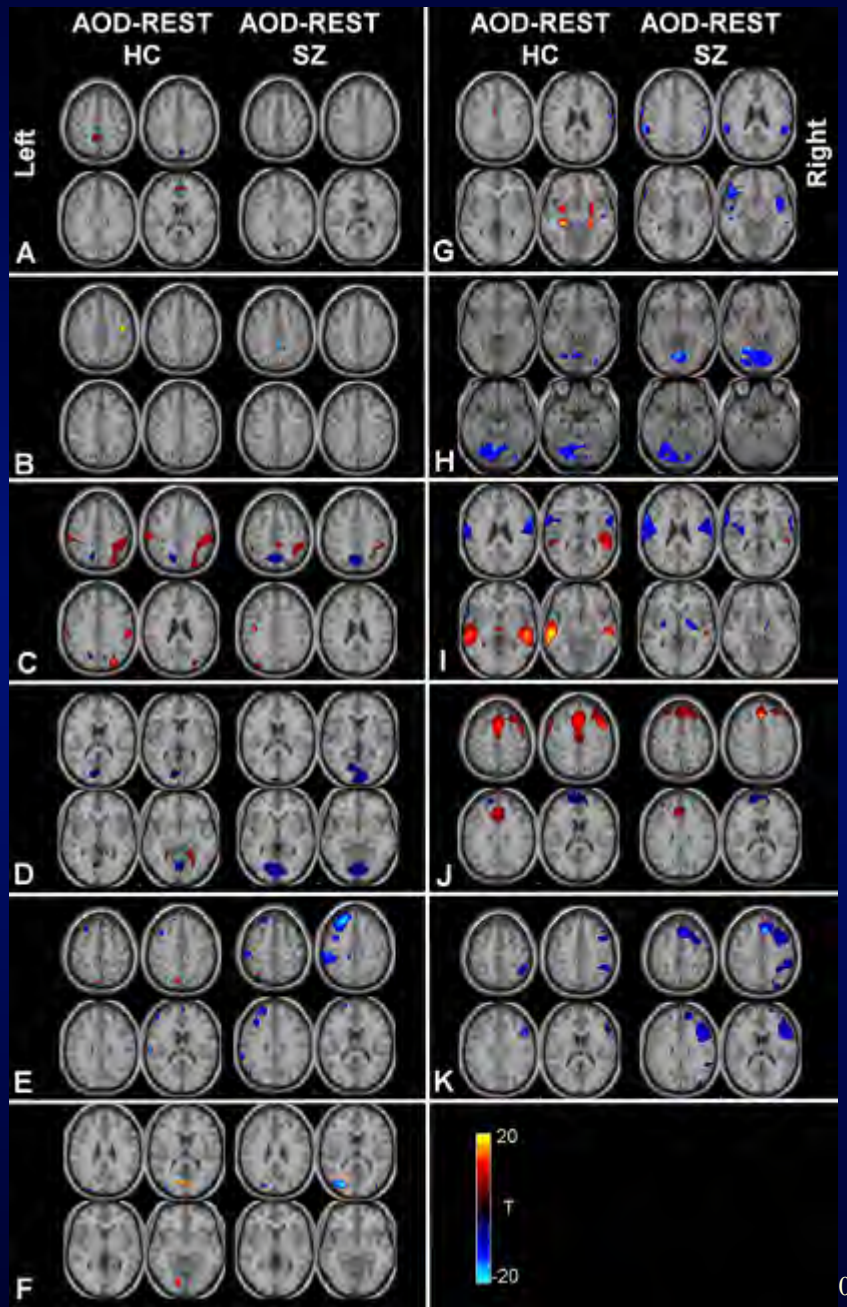
V. D. Calhoun, K. A. Kiehl, and G. D. Pearlson, "Modulation of Temporally Coherent Brain Networks Estimated using ICA at Rest and During Cognitive Tasks," *Hum Brain Mapp,* vol. 29, pp. 828-838, 2008.



Task vs Rest

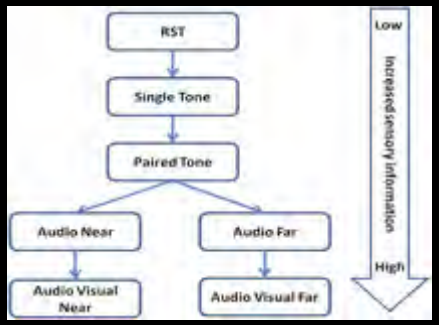
Result 2: Though similar TCNs were identified for AOD and rest, spatial and temporal task modulation was induced

Description	Tar	Nov
A: Default mode	**-8.44 (1.4e-9)**	**-5.79 (5.6e-6)**
B: Motor	**4.62 (2.3e-4)**	1.11 (1.0)
C: Sup parietal	2.51 (8.9e-2)	**-3.50 (6.5e-3)**
D: Medial visual	1.09 (1.0)	0.12 (1.0)
E: Left lateral frontoparietal	2.41 (1.1e-1)	1.21 (1.0)
F: Lateral Visual	**-4.34 (5.4e-4)**	**-3.92 (1.9e-3)**
G: Temporal2	**10.29 (6.2e-12)**	**7.76 (1.1e-8)**
H: Cerebellum	**4.09 (1.1e-3)**	-2.59 (7.4e-2)
I: Temporal1	**13.67 (1.2e-15)**	**9.30 (1.1e-10)**
J: Frontal	-2.55 (8.1e-2)	-3.28 (1.2e-2)
K: Right lateral frontoparietal	**-12.00 (6.3e-15)**	**-3.89 (2.1e-3)**



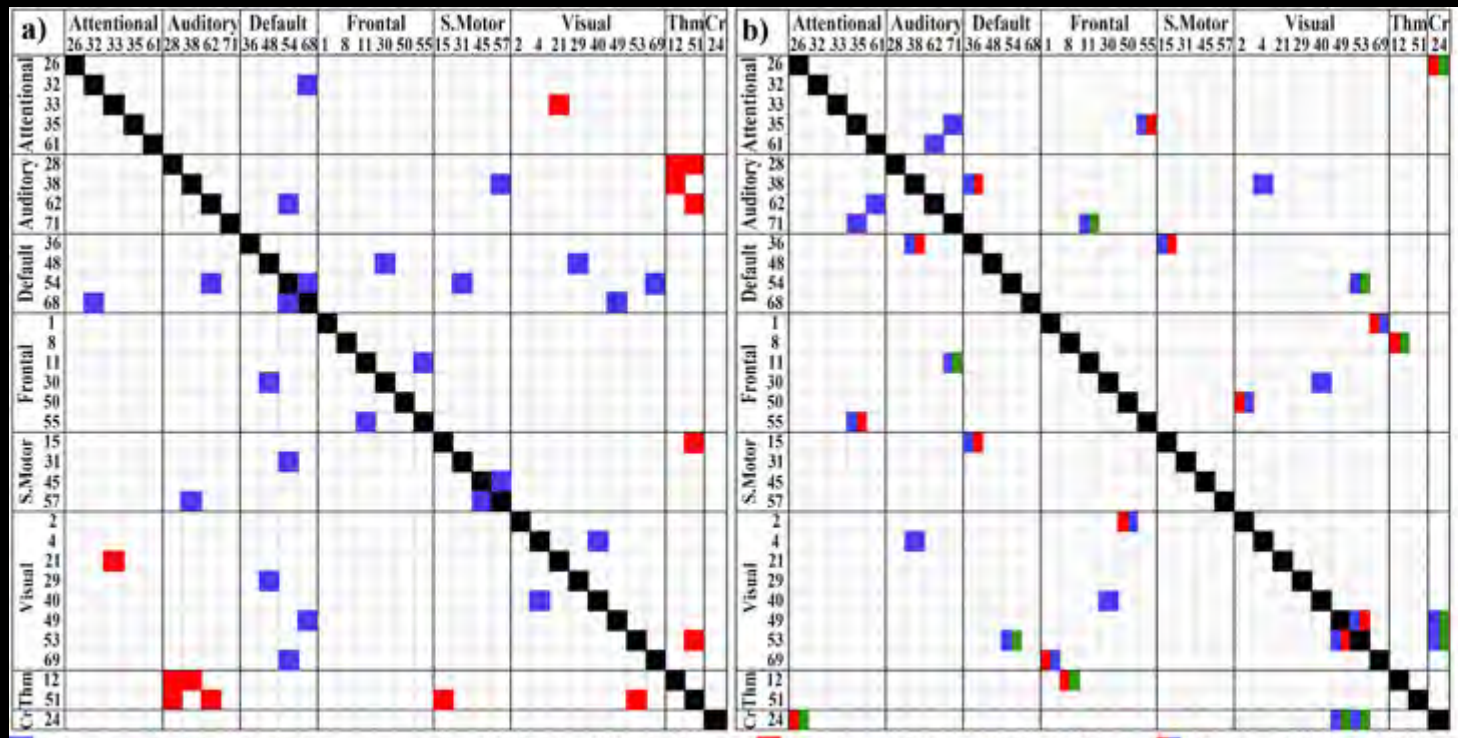
V. D. Calhoun, K. A. Kiehl, and G. D. Pearlson, "Modulation of Temporally Coherent Brain Networks Estimated using ICA at Rest and During Cognitive Tasks," *Hum Brain Mapp,* vol. 29, pp. 828-838, 2008.

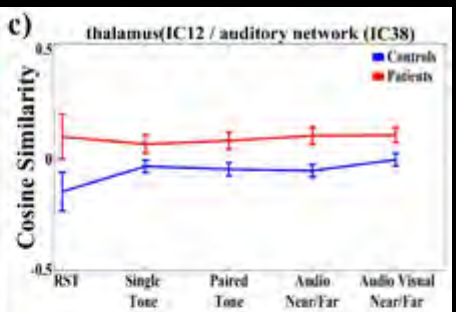
Effect of Task on Intrinsic Networks in SZ vs HC

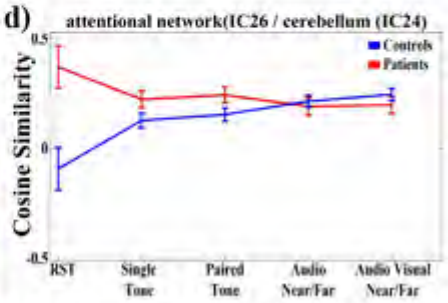


Stable Across Tasks

Variable Across Tasks



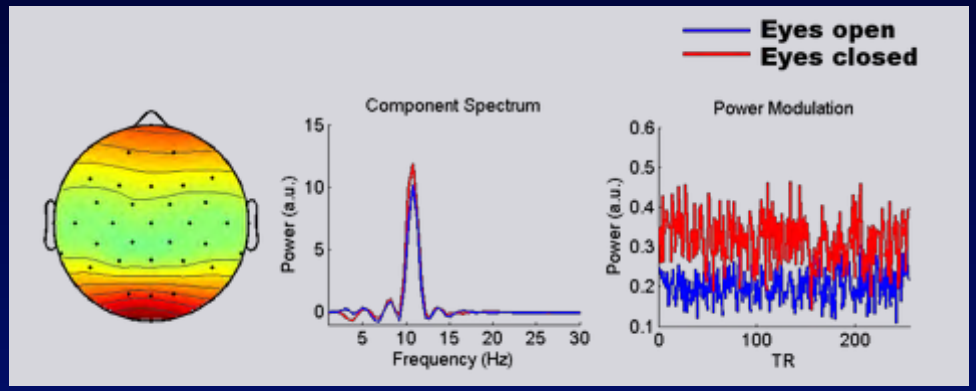


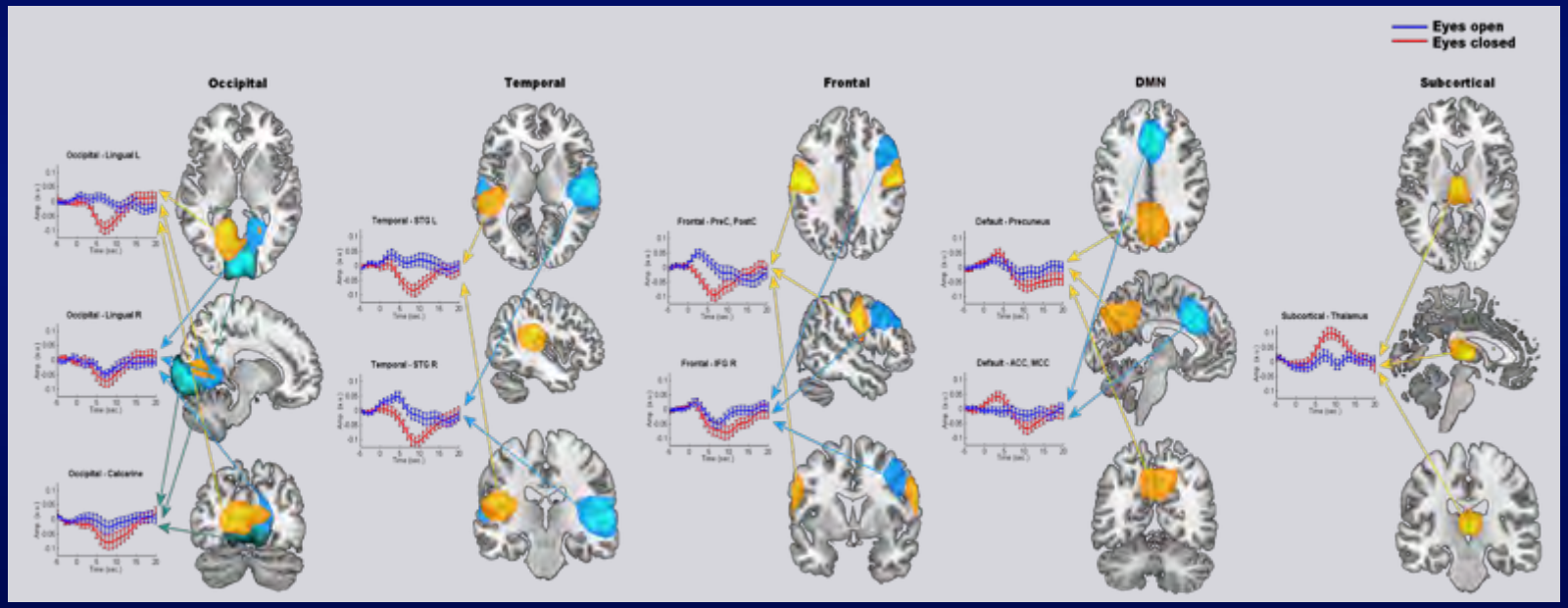


HCs show significantly higher connectivity (SHC) than SPs at all tasks. SPs show SHC than HCs at all tasks. SPs show SHC than HCs at the RST and HCs show SHC than SPs at other tasks. HCs show SHC than SPs at the RST and SPs show SHC than HCs at other tasks. HCs show SHC than SPs at the RST and neither SPs nor HCs show SHC at other tasks. SPs show SHC than HCs at the RST and neither SPs nor HCs show SHC at other tasks.

M. Cetin, F. Christiansen, J. Stephen, A. Mayer, C. Abbott, and V. D. Calhoun, "Thalamus and Wernicke's area show heightened connectivity among individuals with schizophrenia during resting state and task performance on a sensory load hierarchy," in *International Congress on Schizophrenia Research*, Orlando Great Lakes, Florida, 2013.

Concurrent EEG/fMRI: eyes open vs eyes closed



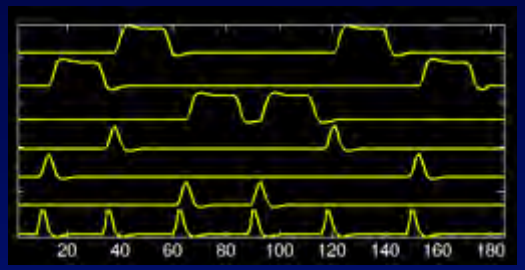


These results suggest that changes in neuronal synchronization as indicated by power fluctuations in high-frequency (>1Hz) EEG rhythms such as posterior alpha are partly mediated by widespread changes in inter-regional low-frequency (<.1Hz) functional activities detected in fMRI. They also indicate that generation of local hemodynamic responses is highly sensitive to global state changes that do not involve changes of mental effort or awareness.

L. Wu, T. Eichele, and V. D. Calhoun, "Reactivity of hemodynamic responses and functional connectivity to different states of alpha synchrony: a concurrent EEG-fMRI study," *NeuroImage,* vol. 52, pp. 1252-1260, 2010

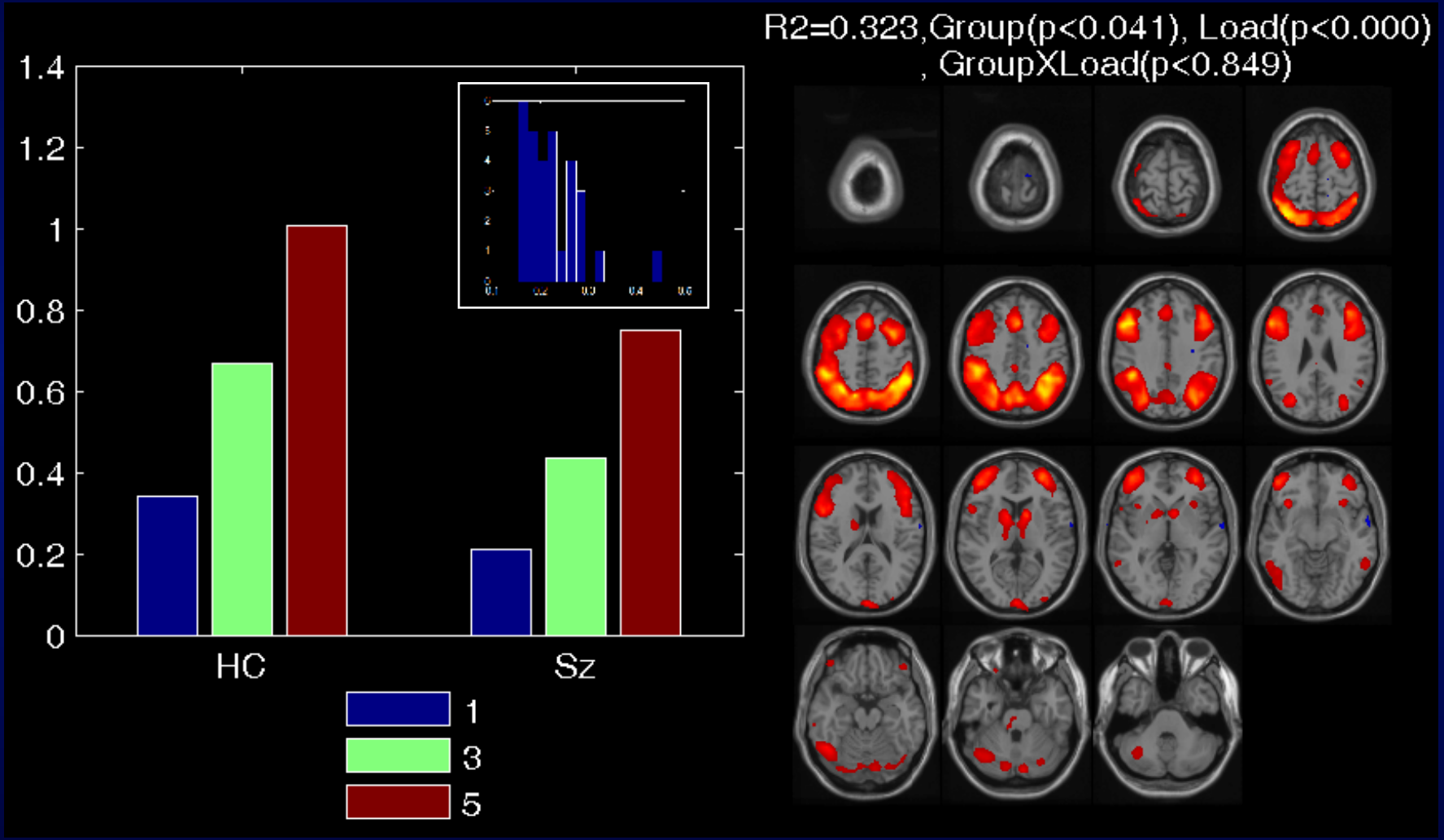
fBIRN SIRP Task

- Methods
  - Subjects & Task
    - 28 subjects (14 HC/14 SZ) across two sites
    - Three runs of SIRP task preprocessed with SPM2
  - ICA Analysis
    - All data entered into group ICA analysis in GIFT
    - ICA time course and image reconstructed for each subject, session, and component
    - Images: sessions averaged together creating single image for each subject and component
    - Time courses: SPM SIRP model regressed against ICA time course
  - Statistical Analysis:
    - Images: all subjects entered into voxelwise 1-sample t-test in SPM2 and thresholded at t=4.5
    - Time courses: Goodness of fit to SPM SIRP model computed, beta weights for load 1, 3, 5 entered into Group x Load ANOVA



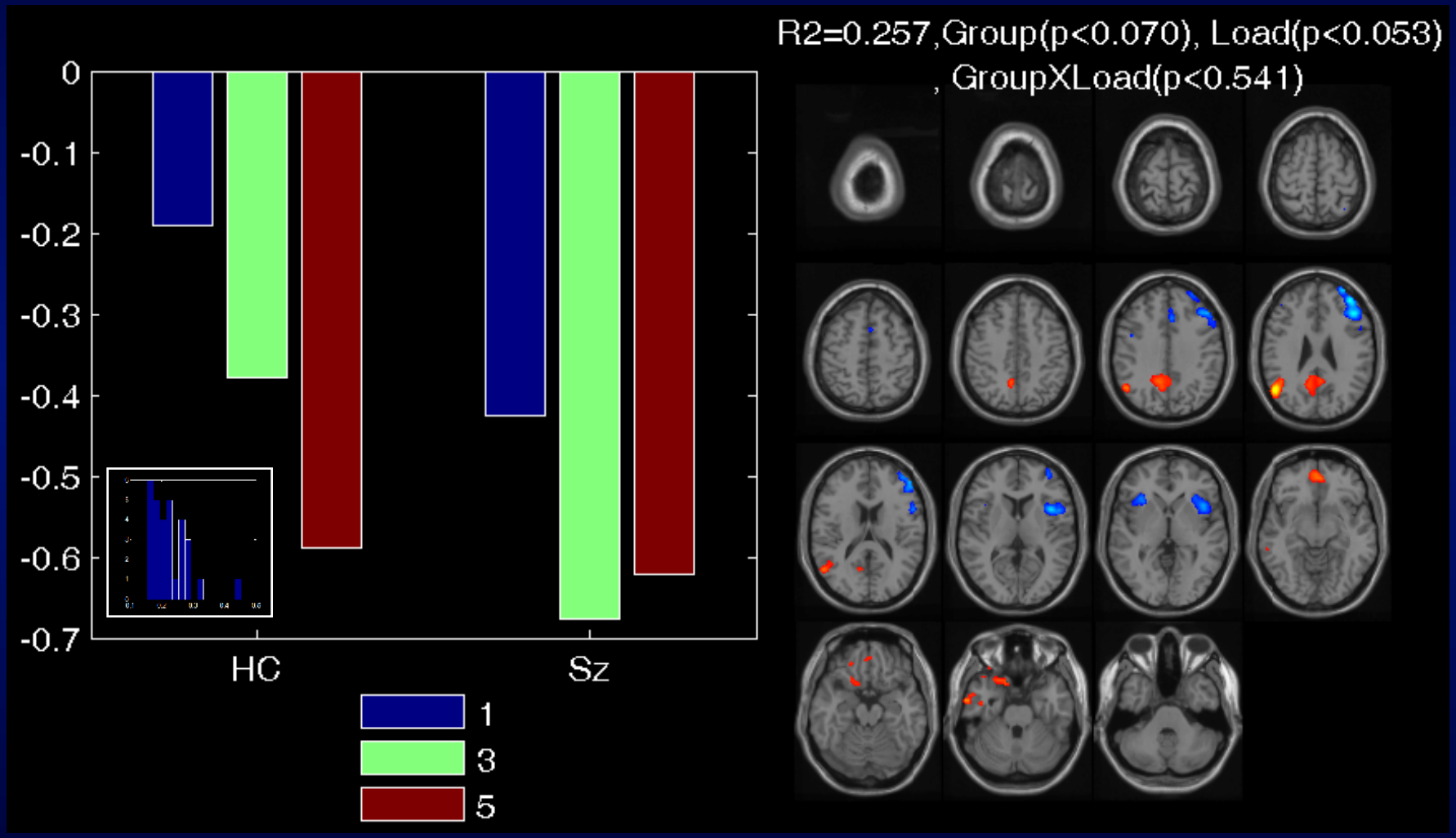
fBIRN Phase II Data: www.nbirn.net;
NCRR (NIH), 5 MOI RR 000827 (2002-2006) and 1 U24 RR0219921 (2006 onwards)

Component 1: Bilateral Frontal/Parietal



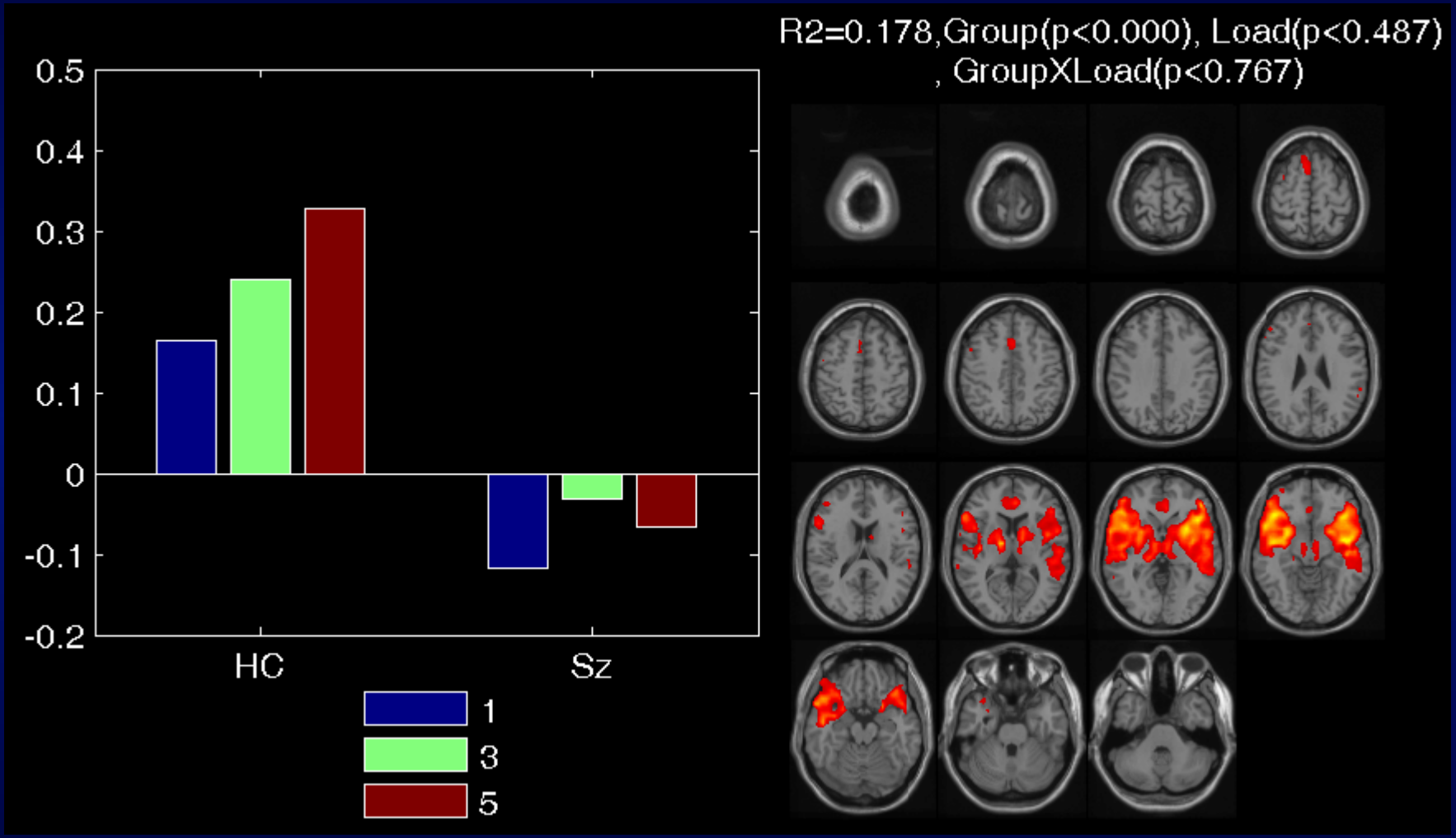
fBIRN Phase II Data: www.nbirn.net;
NCRR (NIH), 5 MOI RR 000827 (2002-2006) and 1 U24 RR0219921 (2006 onwards)

Component 2: Right Frontal, Left Parietal, Post. Cing.



fBIRN Phase II Data: www.nbirn.net;
NCRR (NIH), 5 MOI RR 000827 (2002-2006) and 1 U24 RR0219921 (2006 onwards)

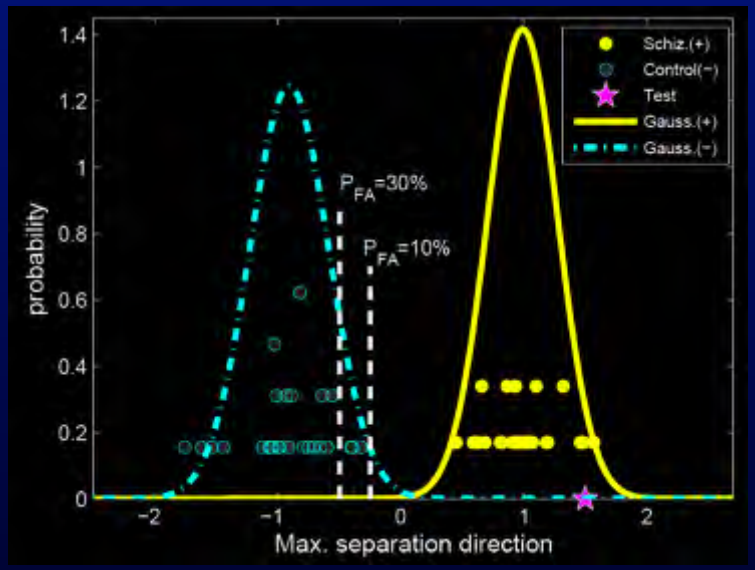
Component 3: Temporal Lobe



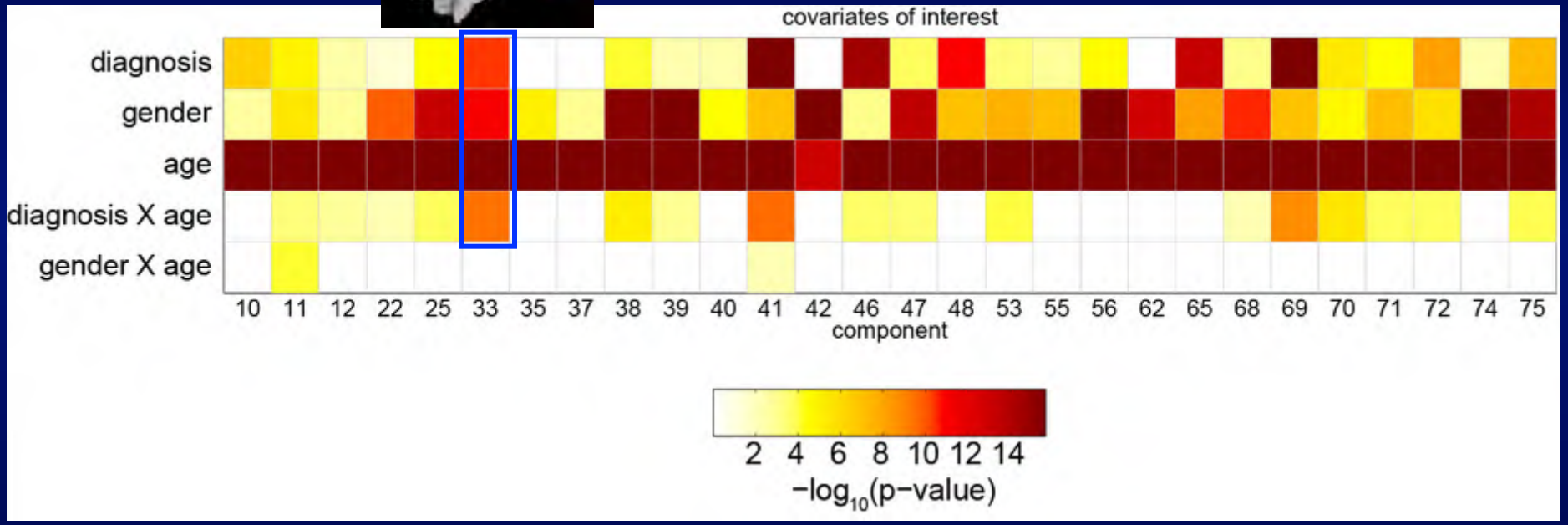
fBIRN Phase II Data: www.nbirn.net;
NCRR (NIH), 5 MOI RR 000827 (2002-2006) and 1 U24 RR0219921 (2006 onwards)

Outline of Talk

- Approaches
  - Seeds vs Components
  - Intro to ICA
  - Group ICA vs single subject
- Processing issues
  - Impact of (micro) motion
  - Autocorrelation
  - Band-pass filtering
- Other issues
  - Task vs Rest
  - Overlap of networks
- Applications
  - Diagnostic
  - Prediction
- Dynamic connectivity
- Summary

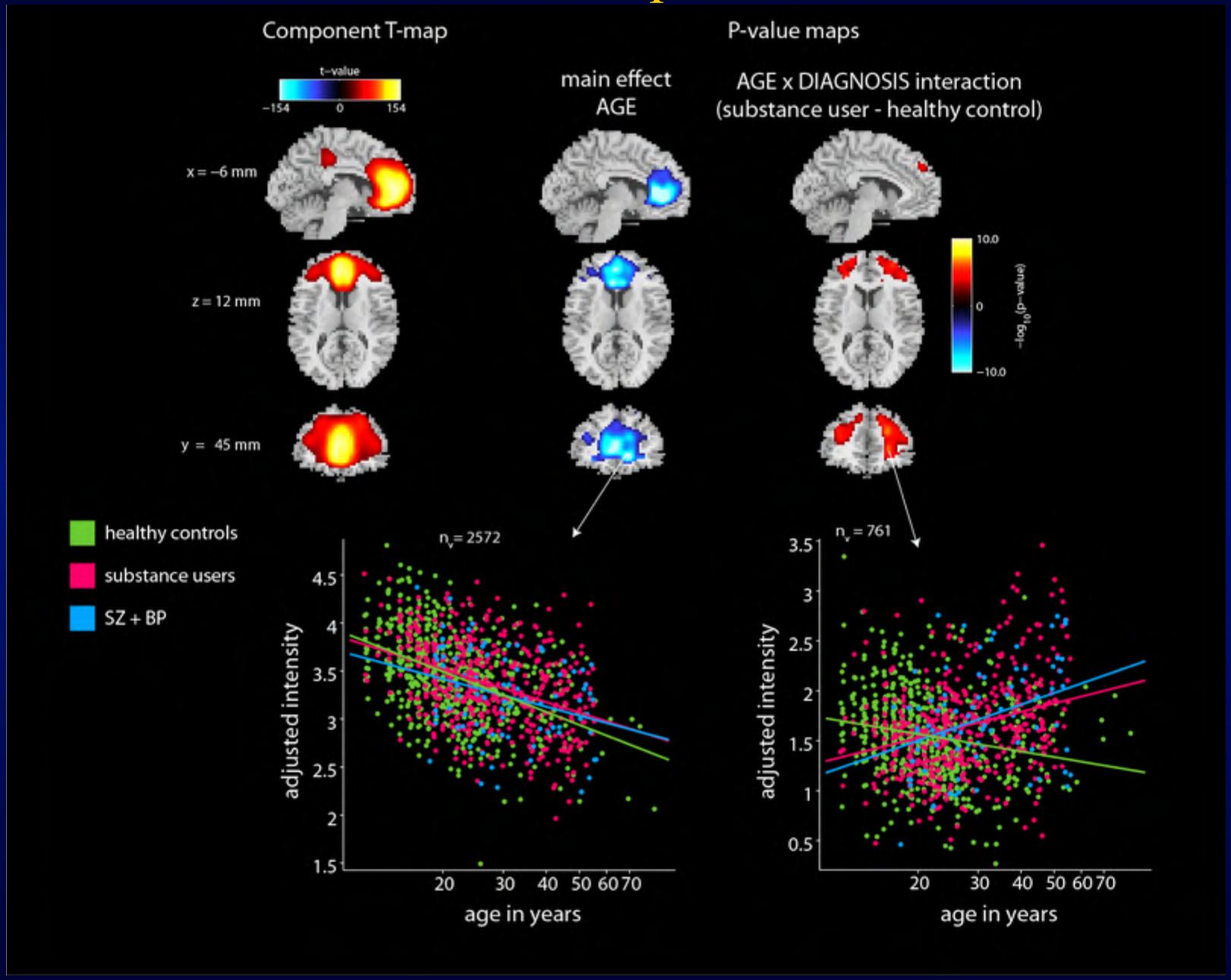


Relationship to Disease (N=1140)

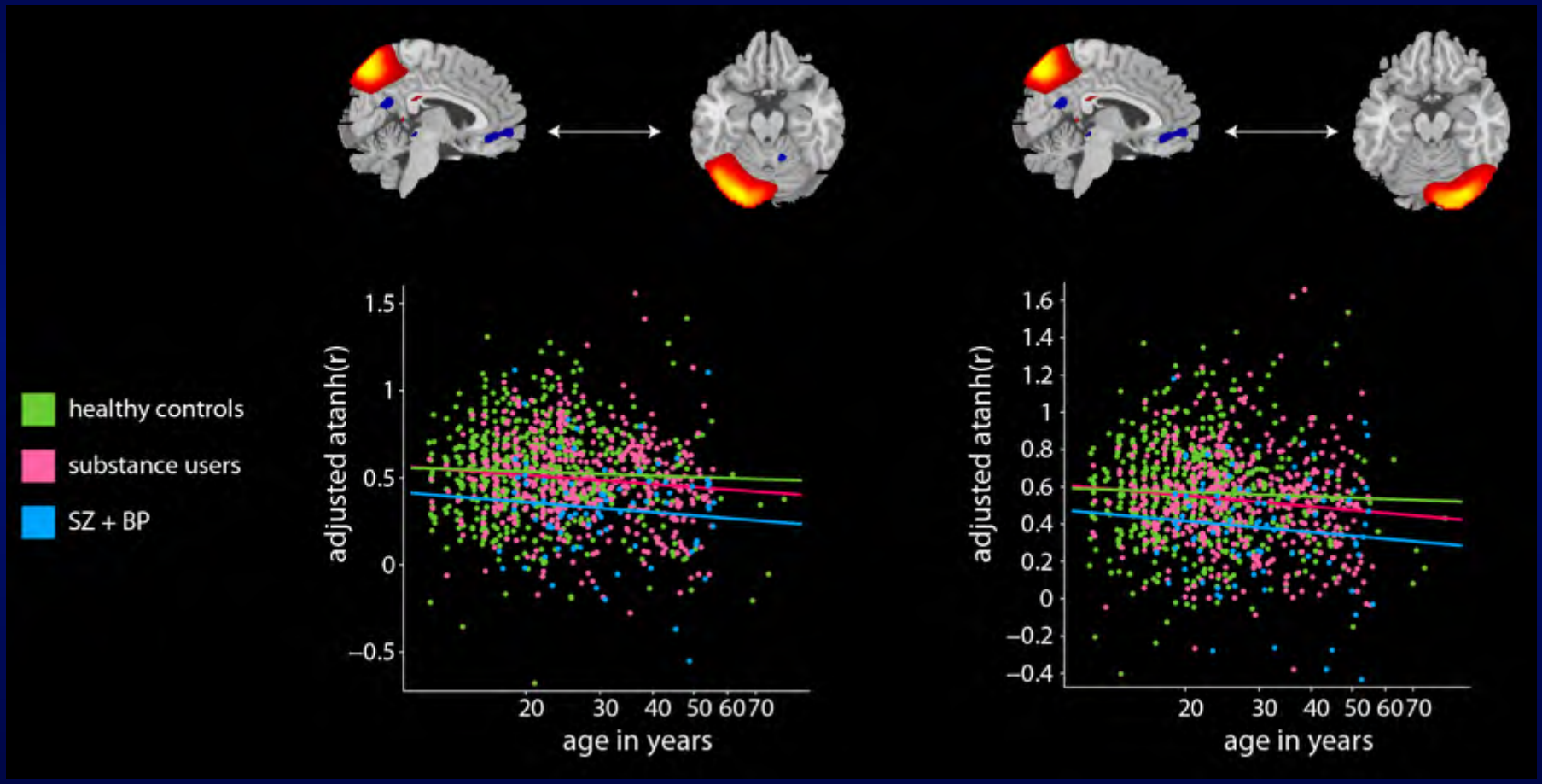


Healthy (N=590)
Substance Use (N=469)
Schizo/BP (N=81)

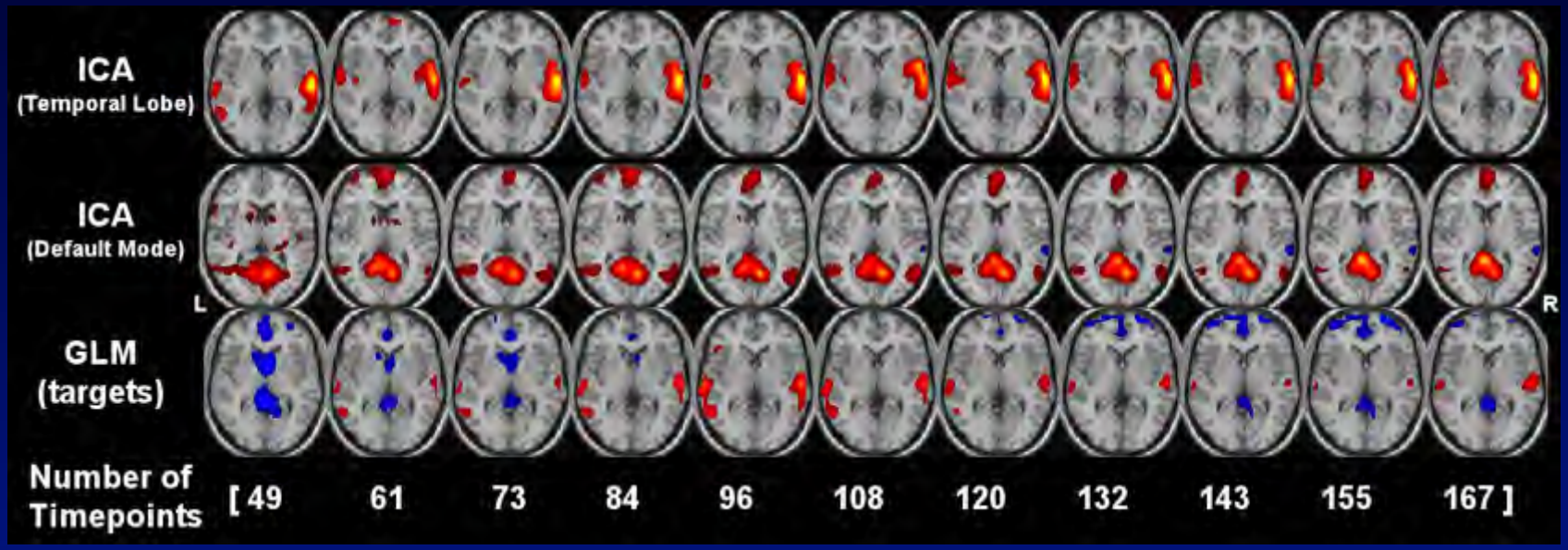
Within network example: anterior DMN

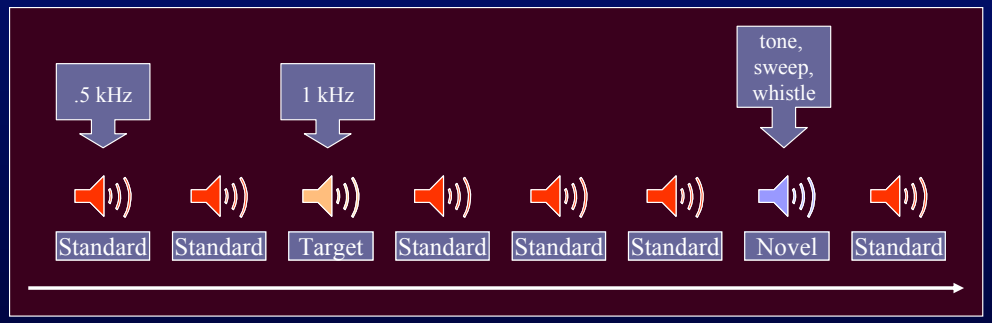


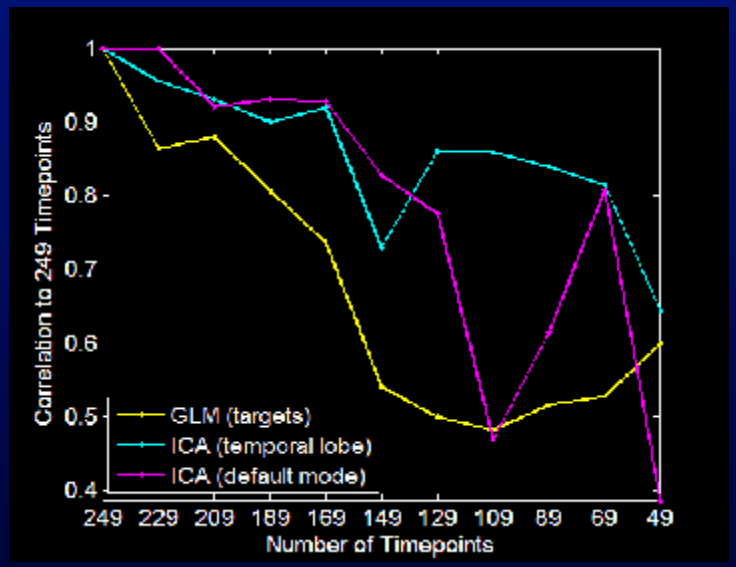
Between network example: precuneus-cerebellar connectivity



Robustness of 'modes'



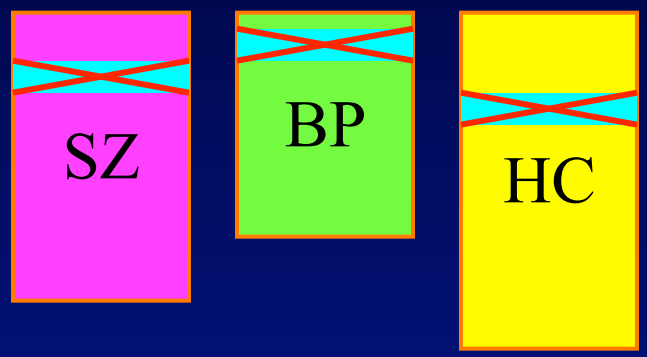




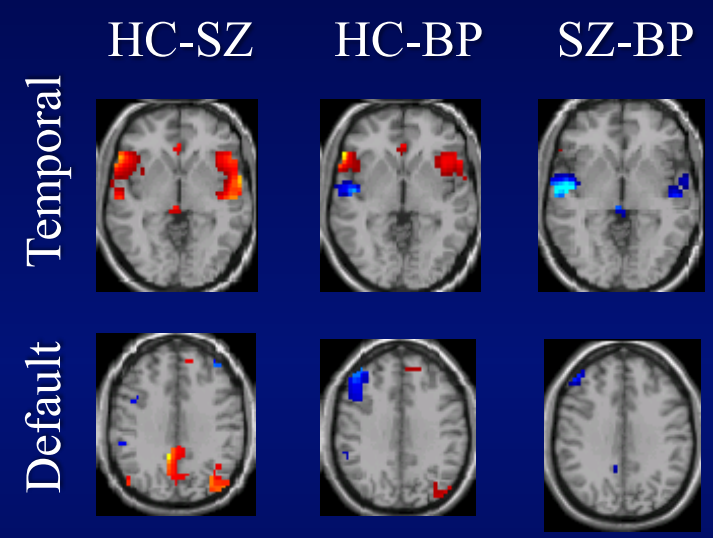
V. D. Calhoun, G. D. Pearlson, P. Maciejewski, and K. A. Kiehl, "Temporal Lobe and 'Default' Hemodynamic Brain Modes Discriminate Between Schizophrenia and Bipolar Disorder," *Hum. Brain Map.*, vol. 29, pp. 1265-1275, 2008

3-way Classification of Schizophrenia, Bipolar, Control

1) Remove subjects from each group



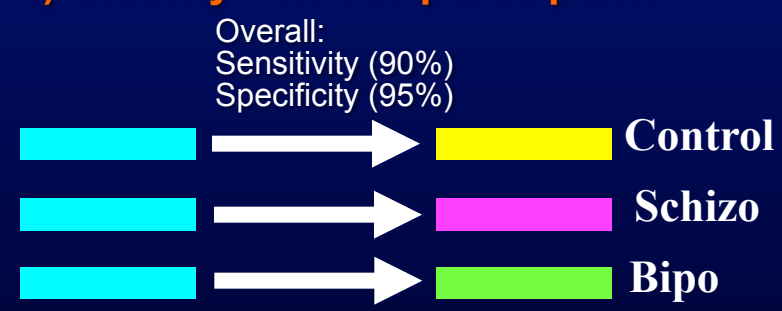
2) Identify regions which maximally separate remainder



3: Develop simple classifier based upon 'distance' between each group:

Classify as cont if $D_{cont,i} > D_{schizo,i}$ and $D_{cont,i} > D_{bipo,i}$,
schizo if $D_{schizo,i} > D_{cont,i}$ and $D_{schizo,i} > D_{bipo,i}$,
bipo if $D_{bipo,i} > D_{cont,i}$ and $D_{bipo,i} > D_{schizo,i}$

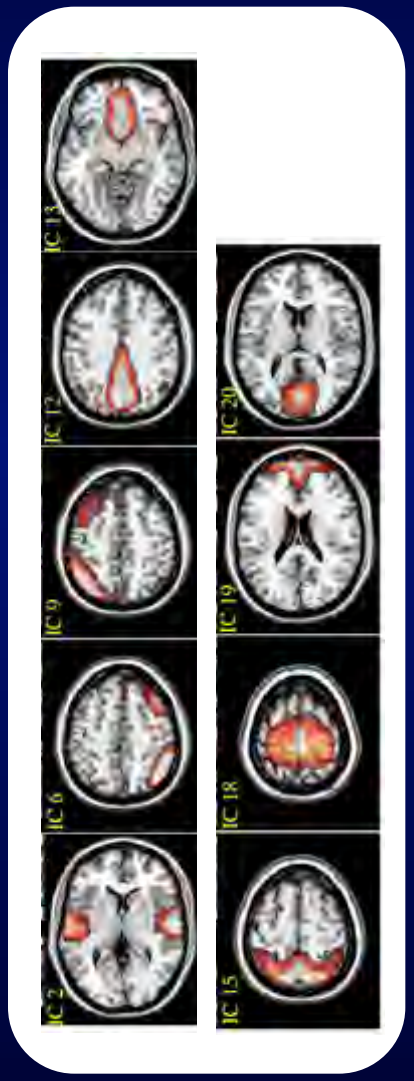
4) Classify 'left out' participants



V. D. Calhoun, G. D. Pearlson, P. Maciejewski, and K. A. Kiehl, "Temporal Lobe and 'Default' Hemodynamic Brain Modes Discriminate Between Schizophrenia and Bipolar Disorder," Hum. Brain Map., vol. 29, pp. 1265-1275, 2008.

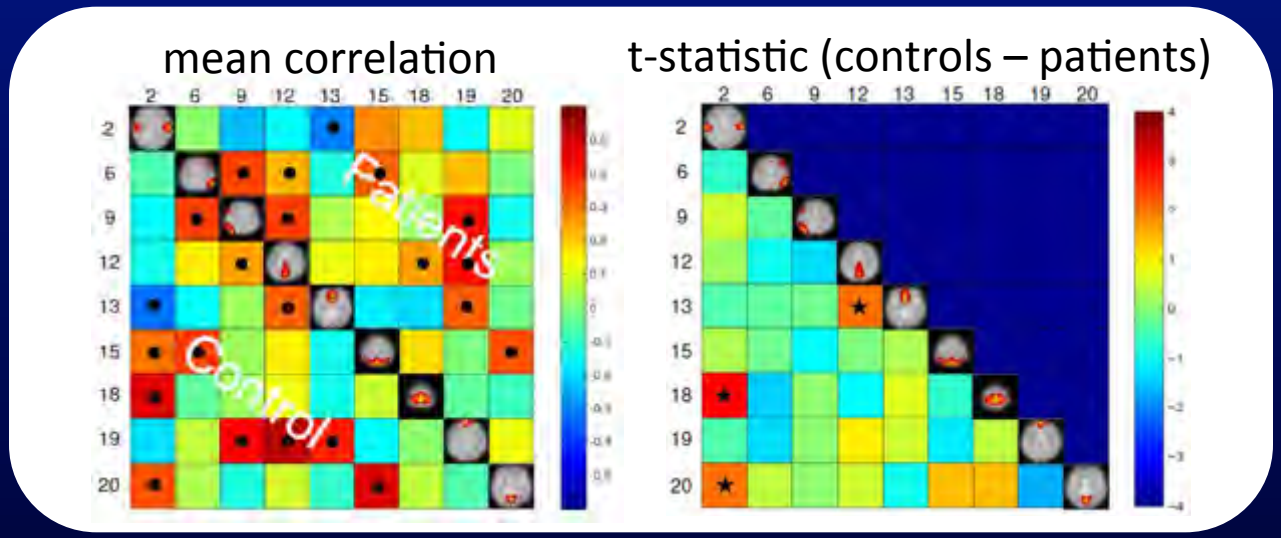
Diagnostic Classification: FNC

How informative is 5 minutes of resting-state fMRI data?



Separate ICAs performed on training/testing sets, 9 RSNs selected

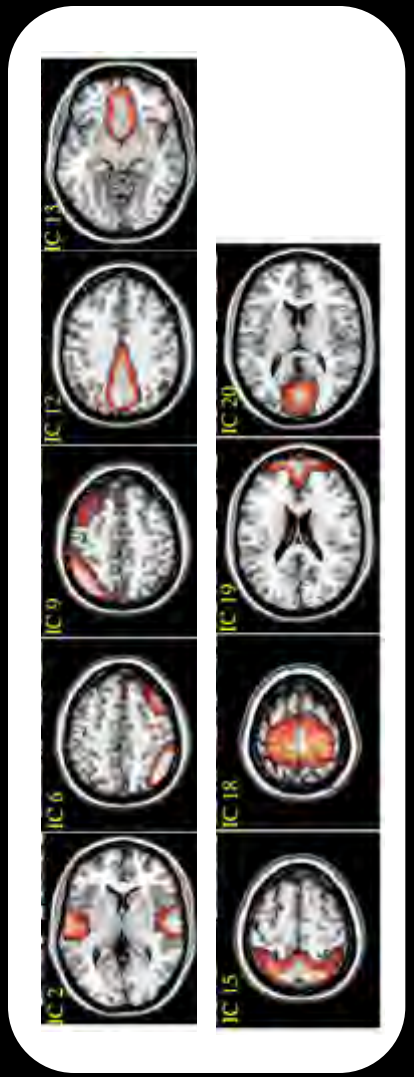
Features are the temporal correlations between components



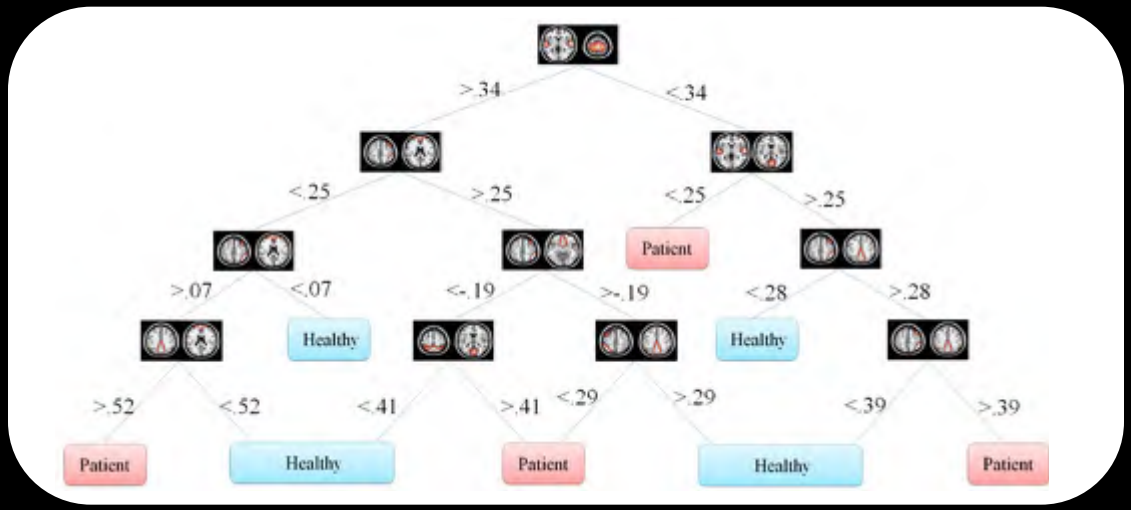
M. Arbabshirani, K. A. Kiehl, G. Pearlson, and V. D. Calhoun, "Classification of schizophrenia patients based on resting-state functional network connectivity " Frontiers in Brain Imaging Methods, in press.

Diagnostic Classification: FNC

How informative is 5 minutes of resting-state fMRI data?

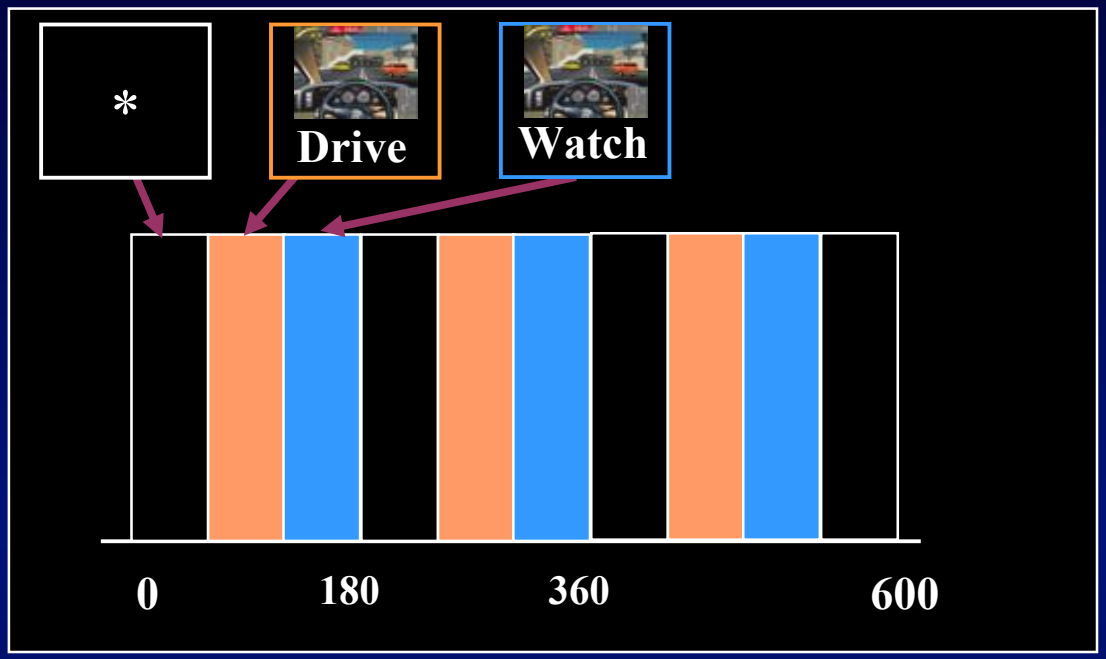


Method	Overall Error (%)	Sensitivity (%)	Specificity (%)
Linear Discriminant	29.17	41.67	100
SVM (linear)	16.67	75	91.67
SVM (RBF)	4.17	100	91.67
K nearest neighbors	0	100	100
Naïve Bayes	20.83	75	83.33
Neural Net (bp)	0	100	100



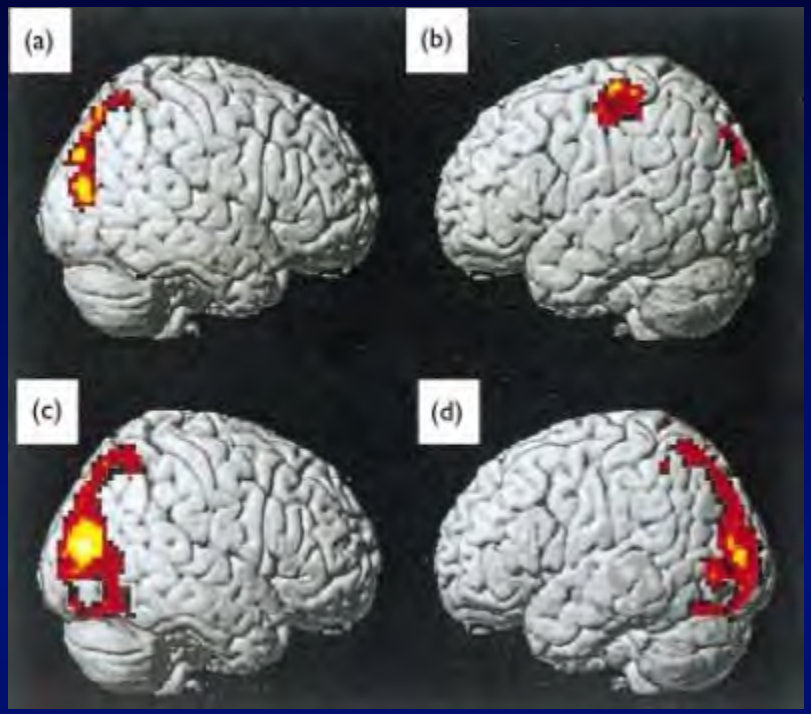
M. Arbabshirani, K. A. Kiehl, G. Pearlson, and V. D. Calhoun, "Classification of schizophrenia patients based on resting-state functional network connectivity " Frontiers in Brain Imaging Methods, in press.

Simulated Driving Paradigm



Previous Work

- Walter, 2001.



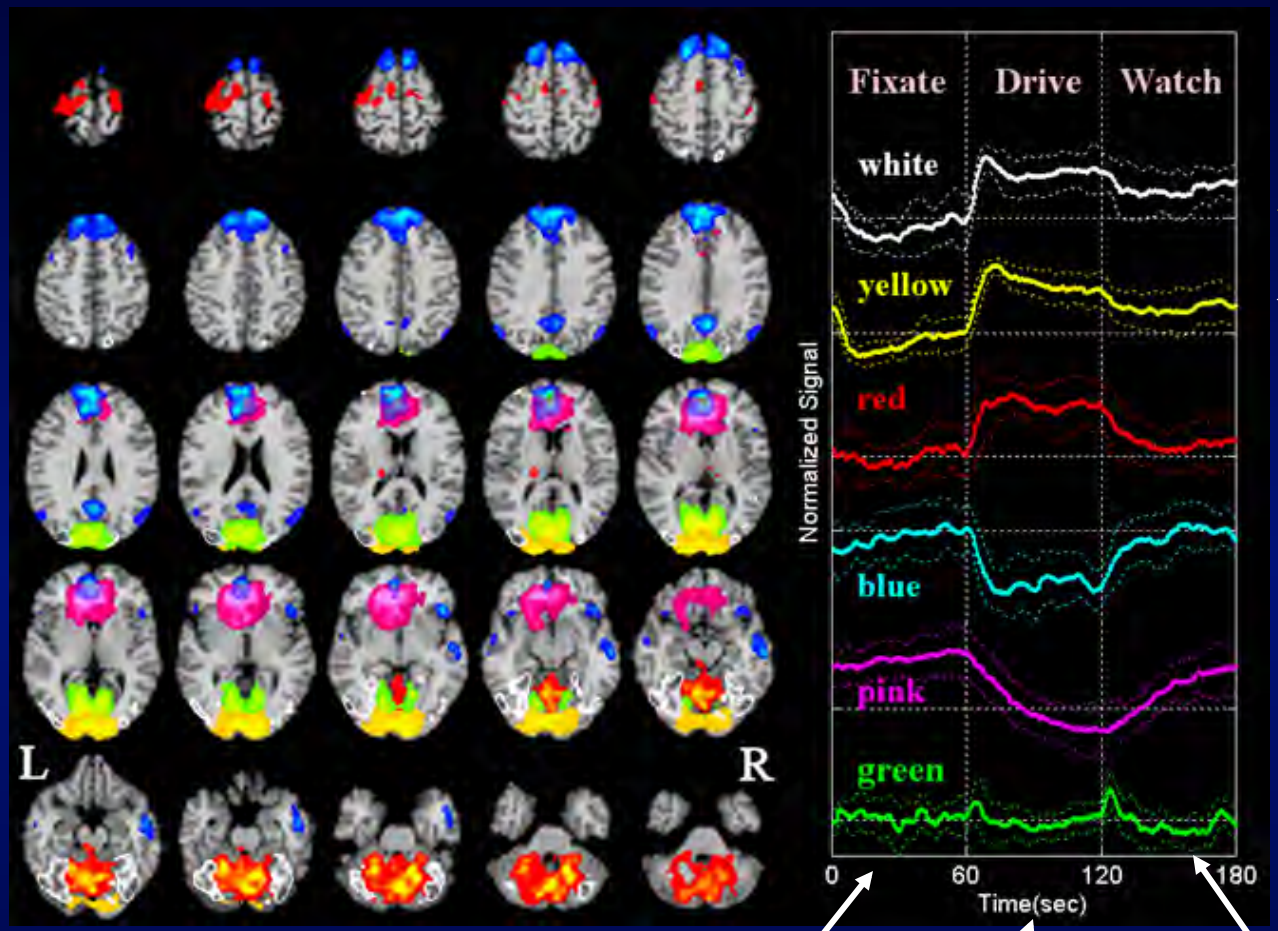
Driving

Watching

"Our results suggest that simulated driving engages mainly areas concerned with perceptual-motor integration and does not engage areas associated with higher cognitive functions."

"our study suggests that the main ideas of cognitive psychology used in the design of cars, in the planning of respective behavioral experiments on driving, as well as in traffic related political decision making (i.e. laws on what drivers are supposed to do and not to do during driving) may be inadequate, as it suggests a general limited capacity model of the psyche of the driver which is not supported by our results. If driving deactivates rather than activates a number of brain regions the quests for the adequate design of the man-machine interface as well as for what the driver should and should not do during driving is still widely open."

Baseline Simulated Driving Results



Higher Order Visual/Motor: Increases during driving; less during watching.

Low Order Visual: Increases during driving; less during watching.

Motor control: Increases only during driving.

Vigilance: Decreases only during driving; amount proportional to speed.

Error Monitoring & Inhibition: Decreases only during driving; rate proportional to speed.

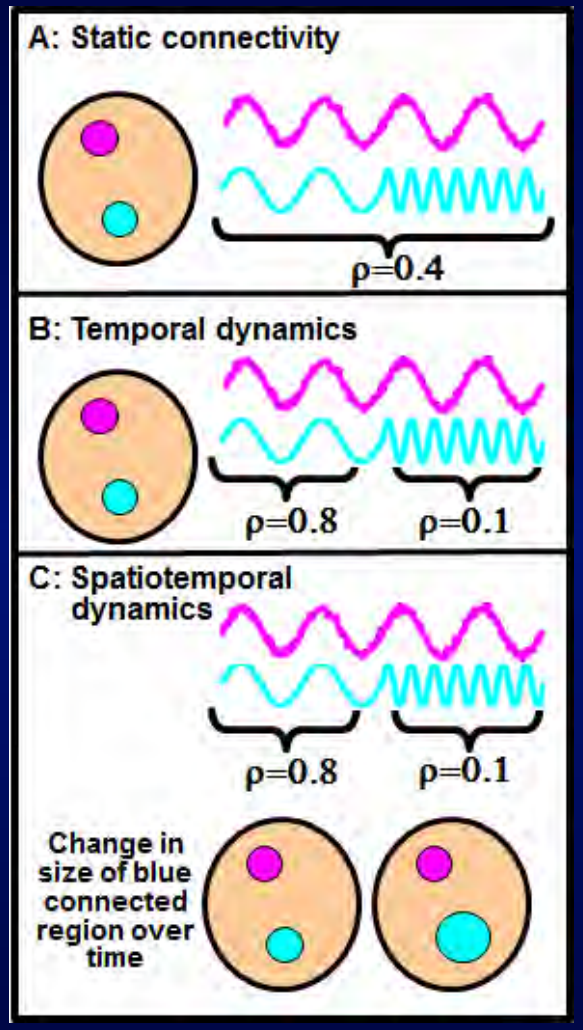
Visual Monitoring: Increases during epoch transitions.

V. D. Calhoun, J. J. Pekar, V. B. McGinty, T. Adali, T. D. Watson, and G. D. Pearlson, "Different Activation Dynamics in Multiple Neural Systems During Simulated Driving," *Hum. Brain Map.*, vol. 16, pp. 158-167, 2002.

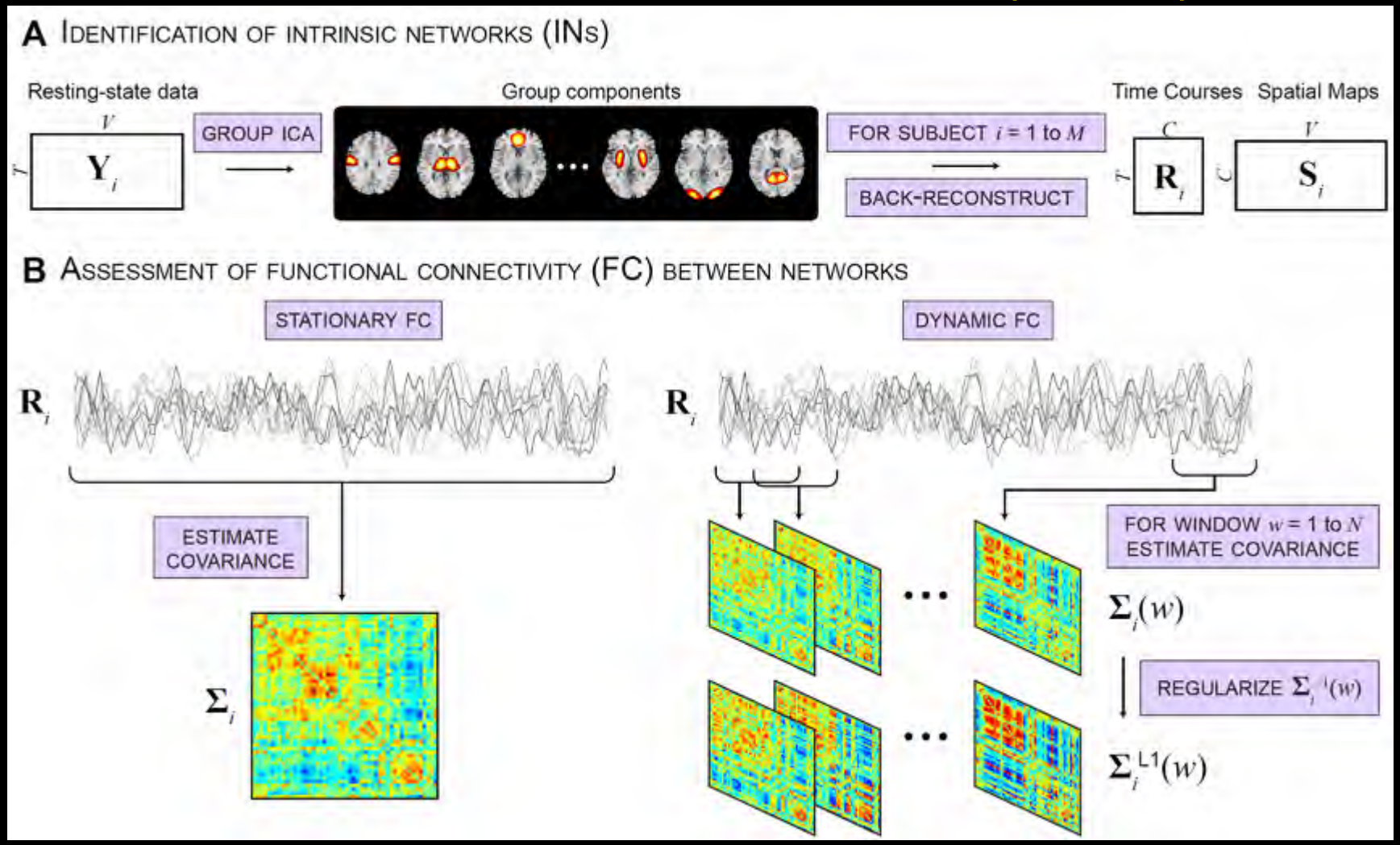
V. D. Calhoun and G. D. Pearlson, "A Selective Review of Simulated Driving Studies: Combining Naturalistic and Hybrid Paradigms, Analysis Approaches, and Future Directions," NeuroImage, vol. 59, pp. 25-35, 2012.

Outline of Talk

- Approaches
  - Seeds vs Components
  - Intro to ICA
  - Group ICA vs single subject
- Processing issues
  - Impact of (micro) motion
  - Autocorrelation
  - Band-pass filtering
- Other issues
  - Task vs Rest
  - Overlap of networks
- Applications
  - Diagnostic
  - Prediction
- Dynamic connectivity
- Summary



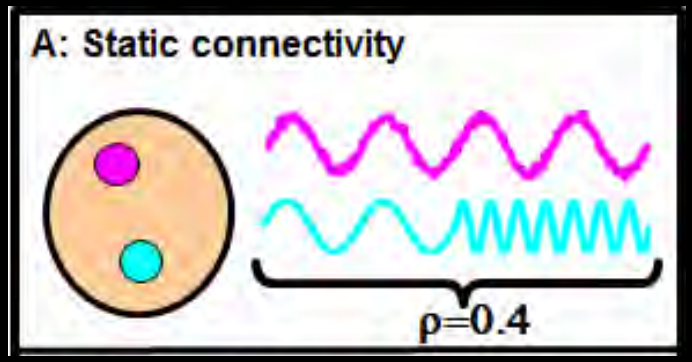
The windowed FNC approach (dFNC)

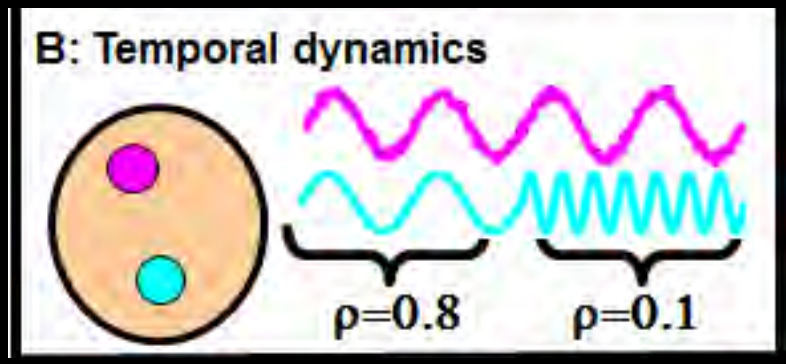


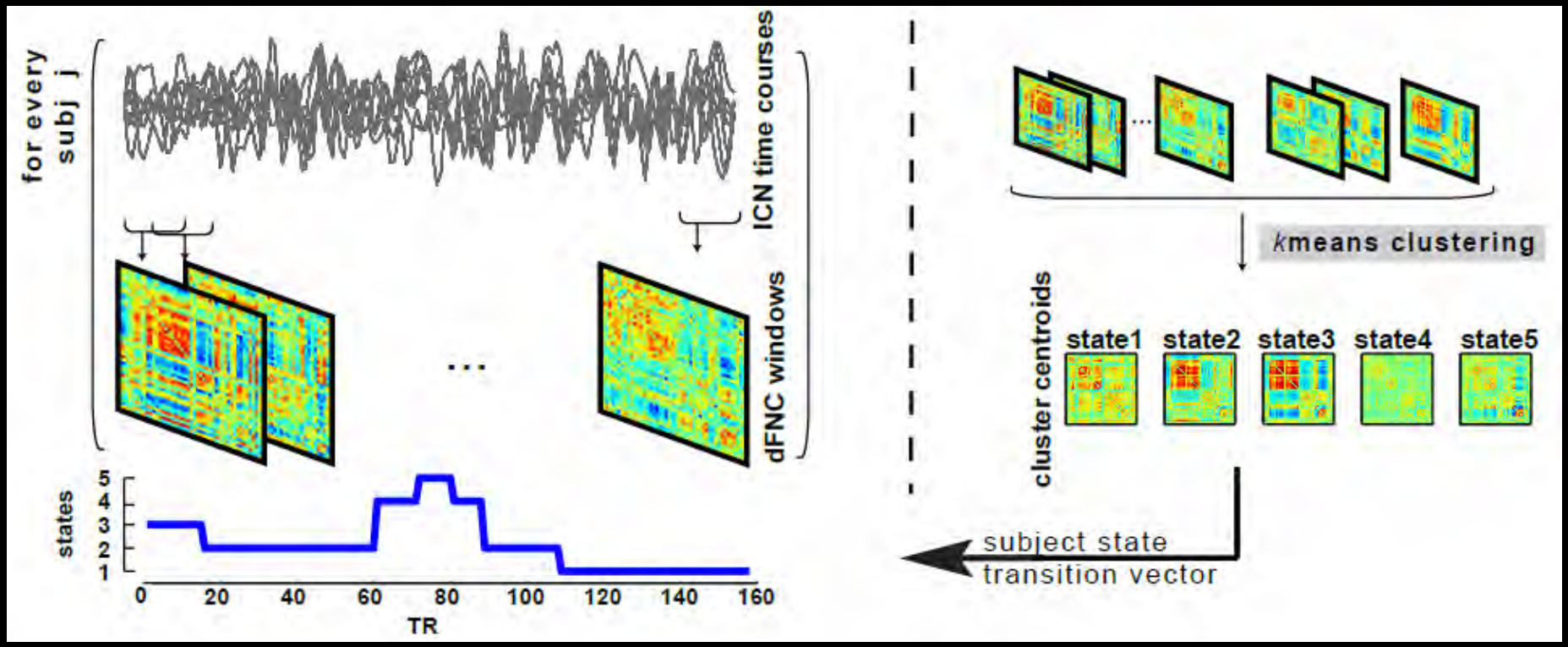
U. Sakoglu, G. D. Pearlson, K. A. Kiehl, Y. Wang, A. Michael, and V. D. Calhoun, "A Method for Evaluating Dynamic Functional Network Connectivity and Task-Modulation: Application to Schizophrenia," MAGMA, vol. 23, pp. 351-366, 2010

E. Allen, E. Damaraju, S. M. Plis, E. Erhardt, T. Eichele, and V. D. Calhoun, "Tracking whole-brain connectivity dynamics in the resting state," *Cereb Cortex*, 2014.

Dynamic Connectivity





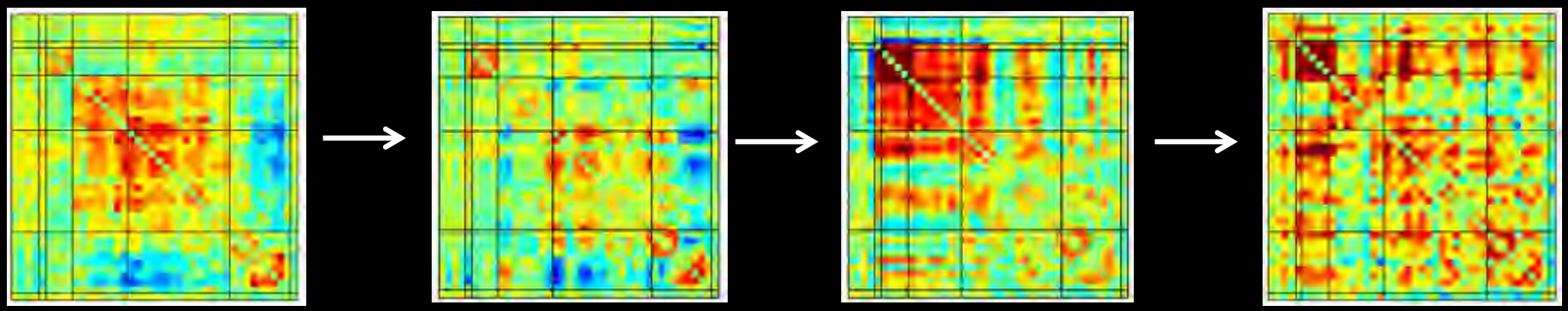


E. Allen, E. Damaraju, S. M. Plis, E. Erhardt, T. Eichele, and V. D. Calhoun, "Tracking whole-brain connectivity dynamics in the resting state," *Cereb Cortex,* 2014.

Concurrent EEG/fMRI, Observations/Conclusions...

- Qualitative replication of previous FC states and temporal trends in a much smaller sample.
- Classification of EEG by FC confirms that different FC states indeed exhibit different electrophysiological signatures.
- Overview of dynamics (greatly simplified):

time and increased drowsiness



Strong antagonism between DMN and attentional networks corresponds to less low frequency power (delta, theta, and alpha).

Partial antagonism corresponds to increased alpha power.

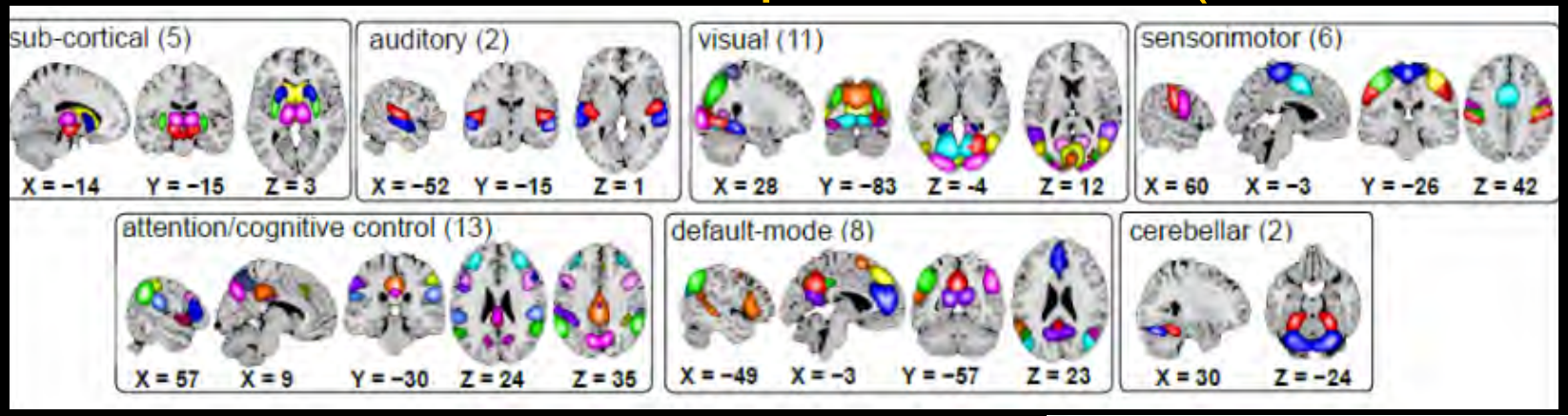
Cortical-subcortical antagonism and decreased intra-DMN connectivity corresponds to increased delta/theta power.

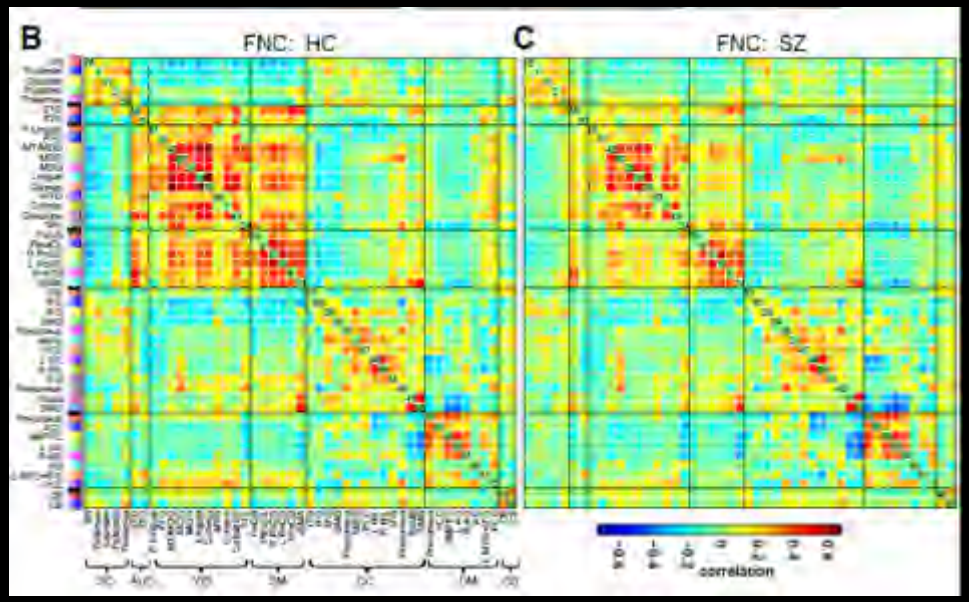
Hyper-synchronization corresponds to larger increases in delta/theta power and decreases in alpha.

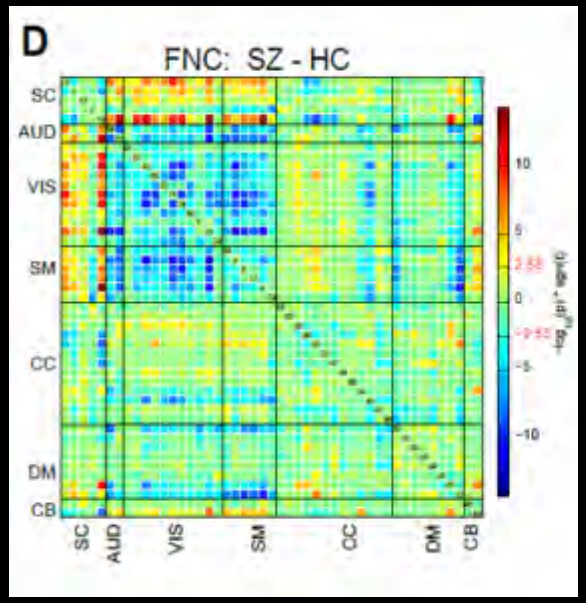
E. Allen, T. Eichele, L. Wu, and V. D. Calhoun, "EEG Signatures of Functional Connectivity States," in *Human Brain Mapping*, Seattle, WA, 2013.

L. Wu, T. Eichele, and V. D. Calhoun, "Reactivity of hemodynamic responses and functional connectivity to different states of alpha synchrony: a concurrent EEG-fMRI study," NeuroImage, vol. 52, pp. 1252-1260, 2010

Static FNC in fBIRN Schizophrenia Data (n~315 HC/SZ)





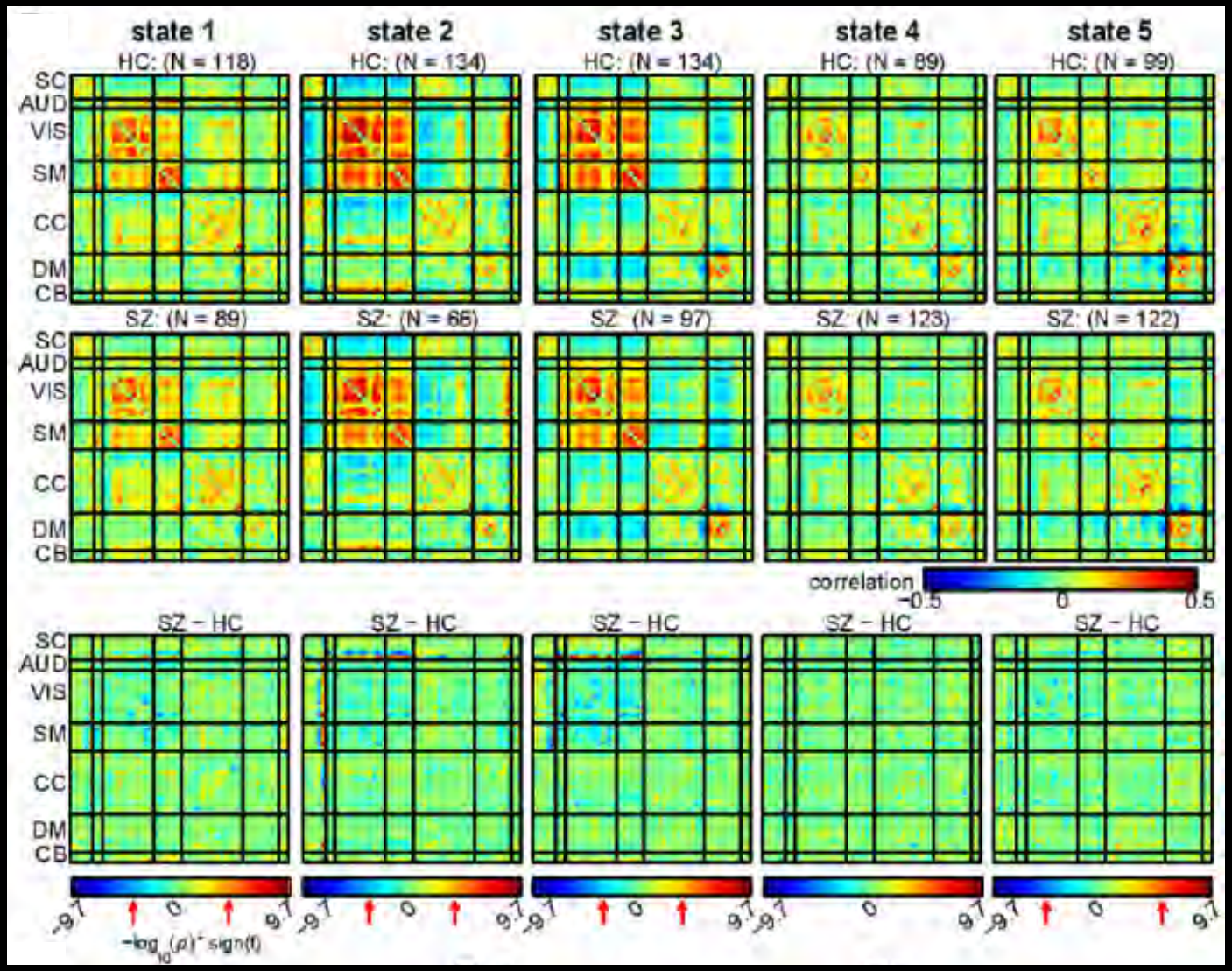


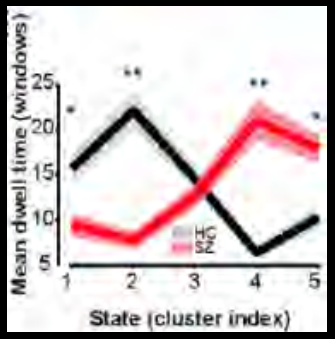
* Hyper: thalamus-sensorimotor
* Hypo: thalamus-(prefrontal-striatal-cerebellar)

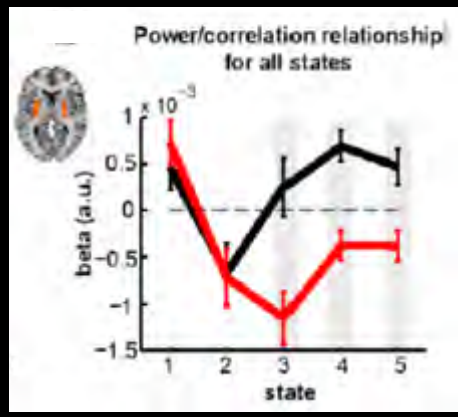
} Inversely related (less so in patients)
Sensorimotor region & cortical-subcortical antagonism co-occur with thalamic hyperconnectivity

E. Damaraju, E. A. Allen, A. Belger, J. Ford, S. C. McEwen, D. Mathalon, B. Mueller, G. D. Pearlson, S. G. Potkin, A. Preda, J. Turner, J. G. Vaidya, T. Van Erp, and V. D. Calhoun, "Dynamic functional connectivity analysis reveals transient states of dysconnectivity in schizophrenia," *Neuroimage Clinical,* in press

Dynamic States: Schizophrenia vs Controls



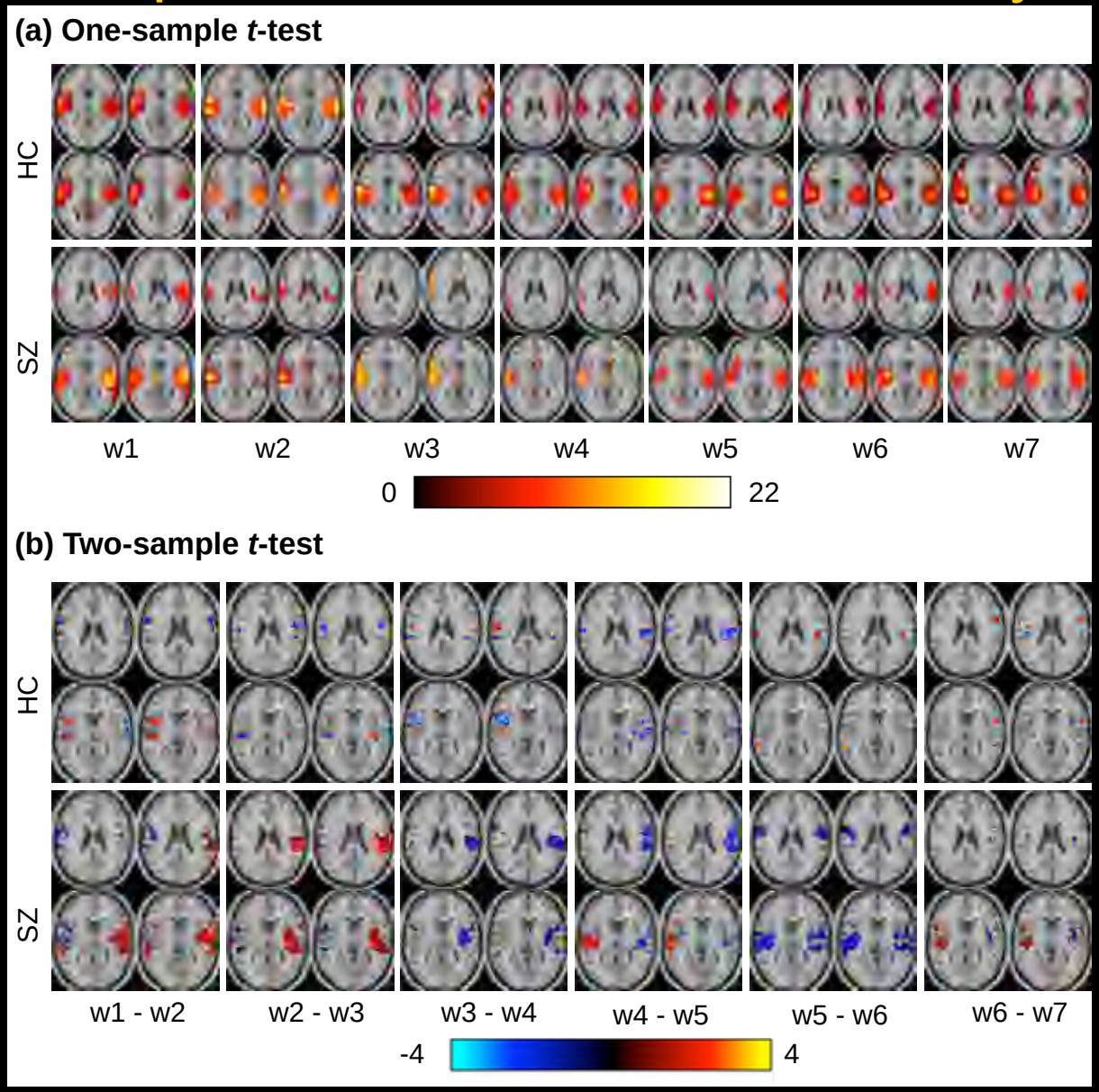


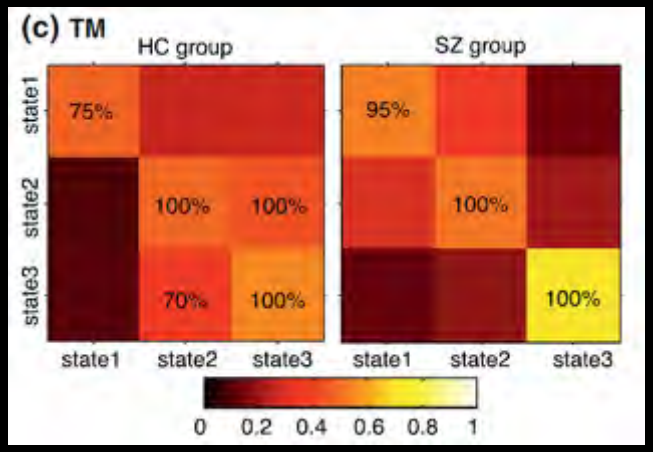


Putamen - Sensorimotor hypo-connectivity

E. Damaraju, E. A. Allen, A. Belger, J. Ford, S. C. McEwen, D. Mathalon, B. Mueller, G. D. Pearlson, S. G. Potkin, A. Preda, J. Turner, J. G. Vaidya, T. Van Erp, and V. D. Calhoun, "Dynamic functional connectivity analysis reveals transient states of dysconnectivity in schizophrenia," *Neuroimage Clinical,* in press

Spatial Patterns of Connectivity are also Dynamic





- The DMN spatial patterns in patients are more likely to stay linked to the other network spatial patterns.
- The DMN spatial patterns in controls are more dynamic in their links to the other network spatial patterns.

S. Ma, V. D. Calhoun, R. Phlypo, and T. Adalı, "Dynamic changes of spatial functional network connectivity in healthy individuals and schizophrenia patients using independent vector analysis.," *NeuroImage,* in press

Outline of Talk

- Approaches
  - Seeds vs Components
  - Intro to ICA
  - Group ICA vs single subject
- Processing issues
  - Impact of (micro) motion
  - Autocorrelation
  - Band-pass filtering
- Other issues
  - Task vs Rest
  - Overlap of networks
- Applications
  - Diagnostic
  - Prediction
- Dynamic connectivity
- Summary

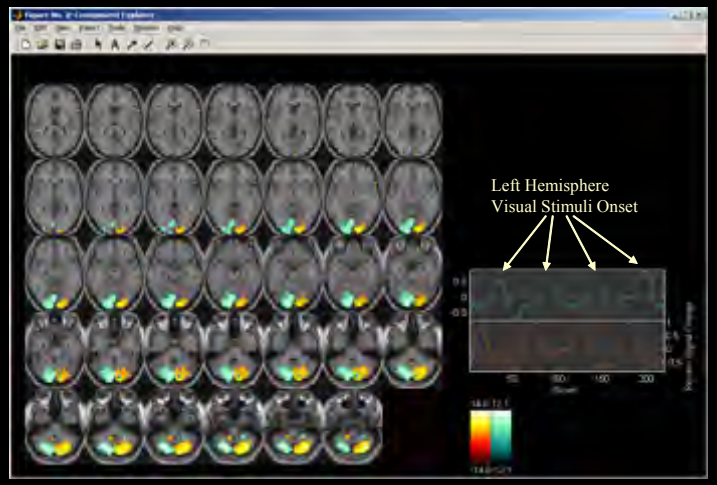
A Few ICA Software Packages (RAM?)

- The ICA:DTU toolbox (http://mole.imm.dtu.dk/toolbox/ica/index.html)
  - matlab
  - three different ICA algorithms
  - fMRI specific with demo data
- FMRIB Software Library, which includes the ICA tool MELODIC (http://www.fmrib.ox.ac.uk/analysis/research/melodic/):
  - C
  - FastICA+
  - Complete Package
- AnalyzeFMRI (http://www.stats.ox.ac.uk/~marchini/software.html)
  - R
  - FastICA
- BrainVoyager(http://www.brainvoyager.com/)
  - Commercial
  - FastICA
  - Complete Package
- FMRLAB (http://www.sccn.ucsd.edu/fmrlab/)
  - matlab
  - infomax algorithm
  - fMRI specific with additional tools
- ICALAB
  - matlab
  - multiple ICA algorithms
  - not fMRI specific although one fMRI example included
- GIFT (http://icatb.sourceforge.net)
  - matlab
  - >14 ICA algorithms (more coming) including infomax and fastICA
  - Constrained ICA algorithms
  - Dynamic FNC algorithms
  - Visualization tools and sorting options.
  - Sample data and a step-by-step walk through

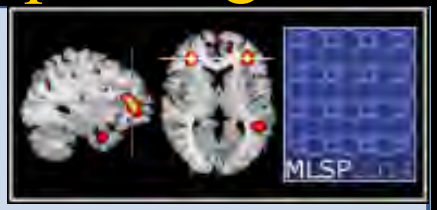
S. Rachakonda and V. D. Calhoun, "Efficient Data Reduction in Group ICA Of fMRI Data," in *Proc. HBM*, Seattle, WA, 2013.

Mialab Software

- http://mialab.mrn.org/software
- freeware, written in MATLAB (also offering compiled versions): over 11,000 unique downloads
- Group ICA of fMRI Toolbox (GIFT)
  - Single subject/Group ICA
  - MANCOVA testing framework
  - Source Based Morphometry
  - Model order estimation
  - ICASSO (clustering/stability)
- Fusion ICA Toolbox (FIT)
  - Parallel ICA, jICA
  - mCCA+jICA & much more!
- Simulation Toolbox (SimTB)
  - Flexible generation of fMRI-like data
- COINS
  - http://coins.mrn.org/dx



Speaking of Prediction…..



The IEEE International Workshop on Machine Learning for Signal Processing is proud to announce:

The 2014 Schizophrenia Classification Challenge

This year's learning task features:

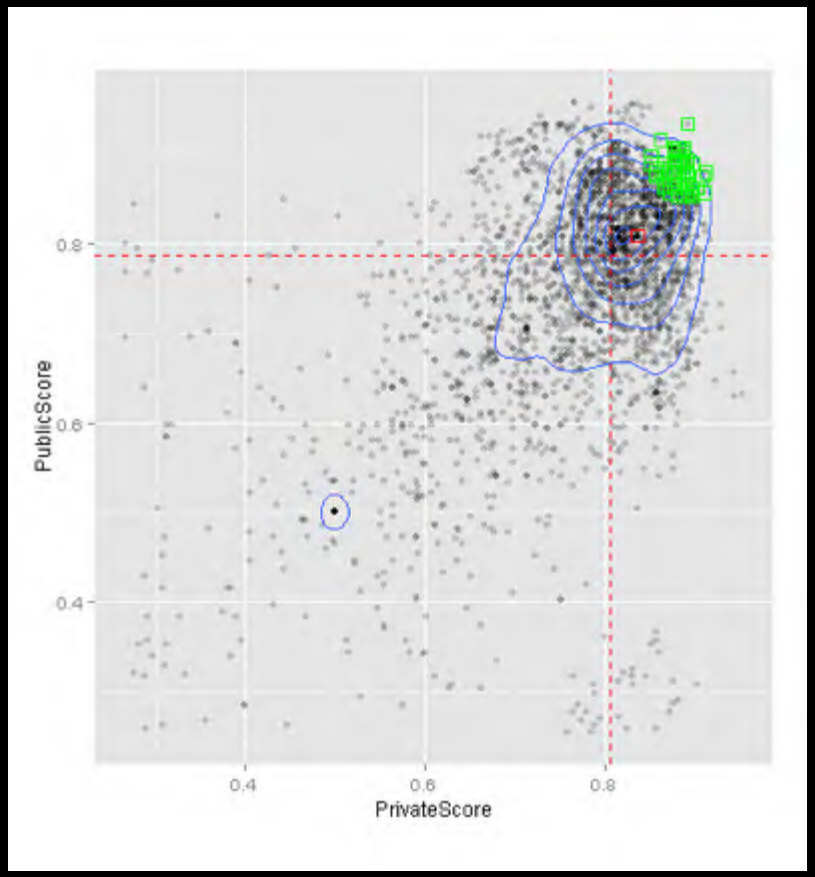
Multi-modal brain imaging data (functional and structural MRI)

We encourage all the participants to identify abnormal functional and structural brain patterns as well as interactions between them to improve diagnosis prediction.

Please visit the website for full details about the competition and submission instructions.

https://www.kaggle.com/c/mlsp-2014-mri

IEEE Signal Processing Society kaggle



371 teams
Over 400 individuals
Over 2200 submissions

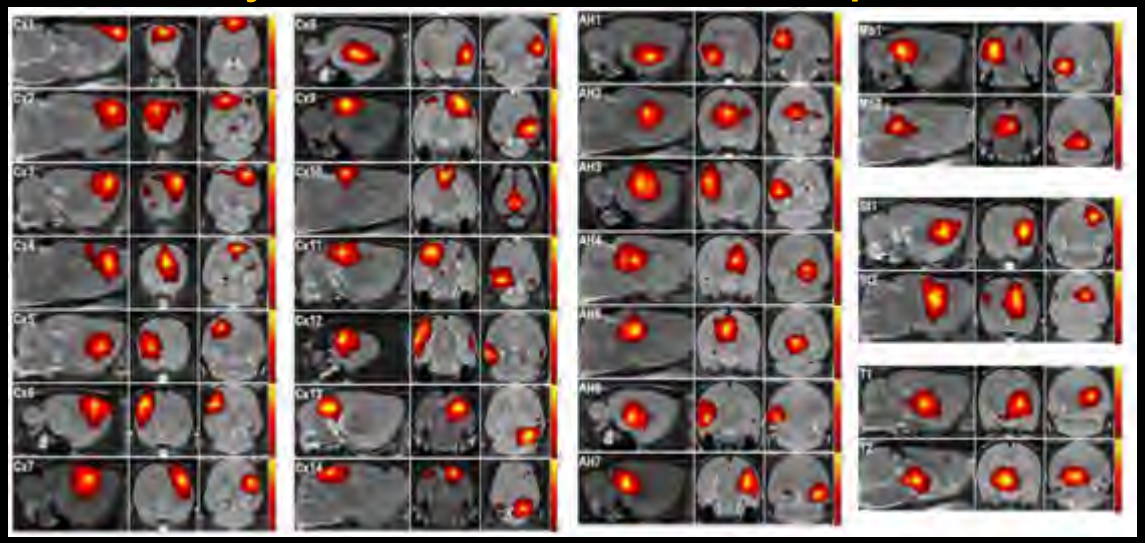
Collection of this dataset was made under an NIH NIGMS Centers of Biomedical Research Excellence (COBRE) grant P20GM103472 to Vince Calhoun (PI).

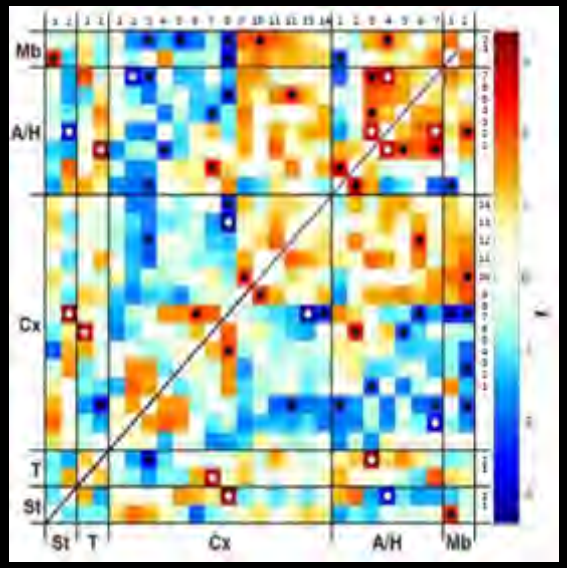
MIALAB

Medical Image Analysis Lab

http://mialab.mrn.org

Application to Animal Work: Resting Connectivity, Behavioral, and Exposure to Phencyclidine



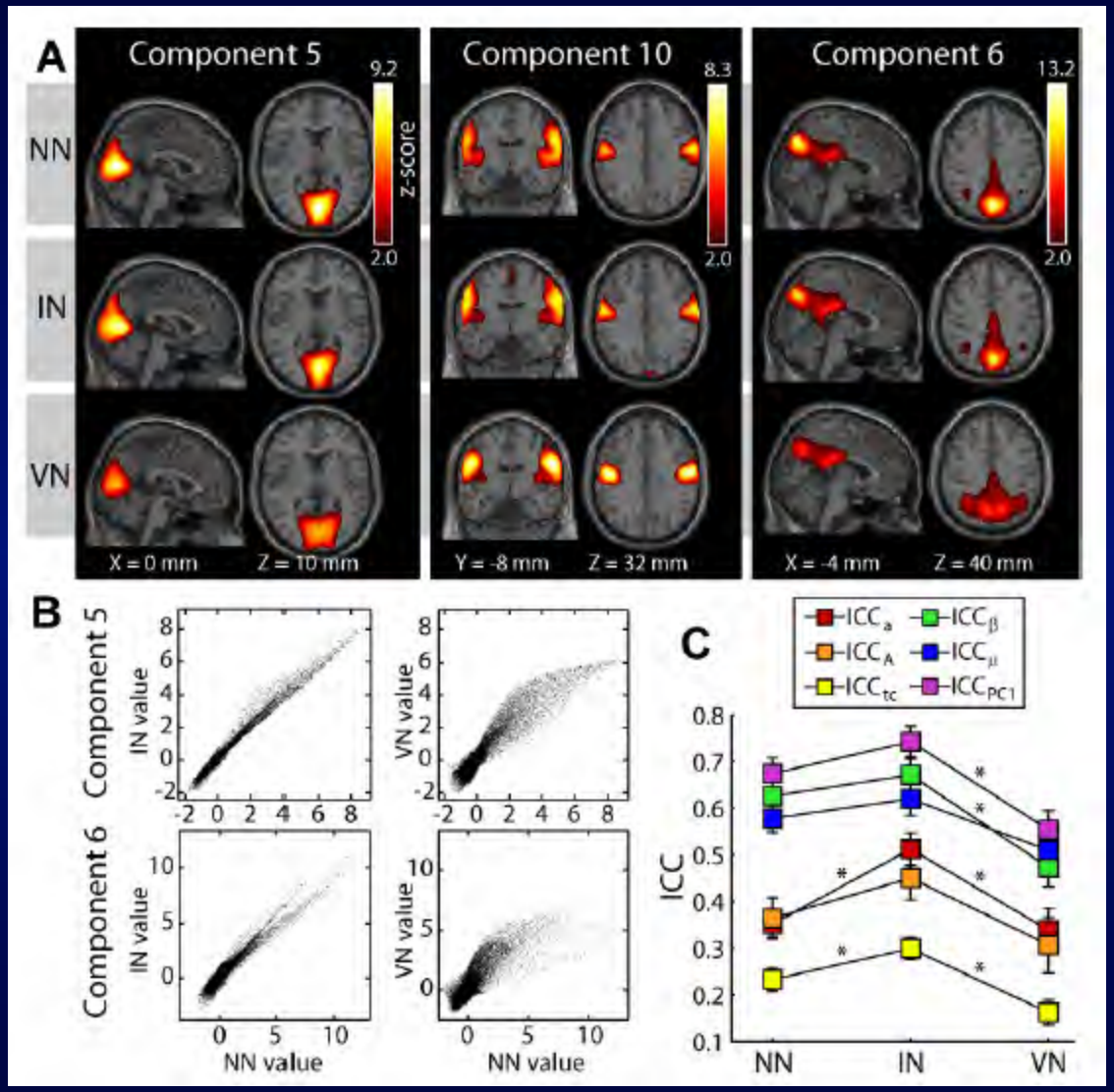


PCP exposure induced a long-term spatial memory deficit, but did not impair subsequent spatial learning.

- PCP exposed animals displayed stronger negative relationships between cortical-hippocampal and cortical-midbrain components and stronger positive relationships within the amygdala/hippocampi components.
- Sub-chronic exposure to PCP caused widespread alterations in FNC.

C. M. Magcalas, N. Perrone-Bizzozero, V. D. Calhoun, J. Bustillo, and D. A. Hamilton, "Examining Resting State Functional Network Connectivity and Behavioral Performance in a Rat Chronically Exposed to Phencyclidine," in *Society for Neuroscience*, 2013.

Prenormalization & Reliability



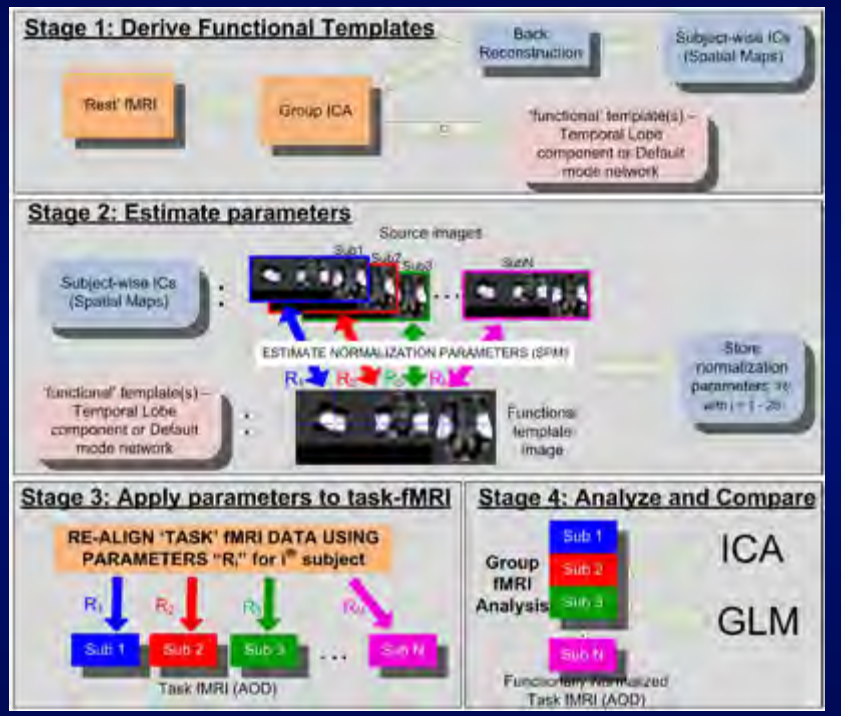
1) No Normalization (NN), where data is left in its raw intensity units

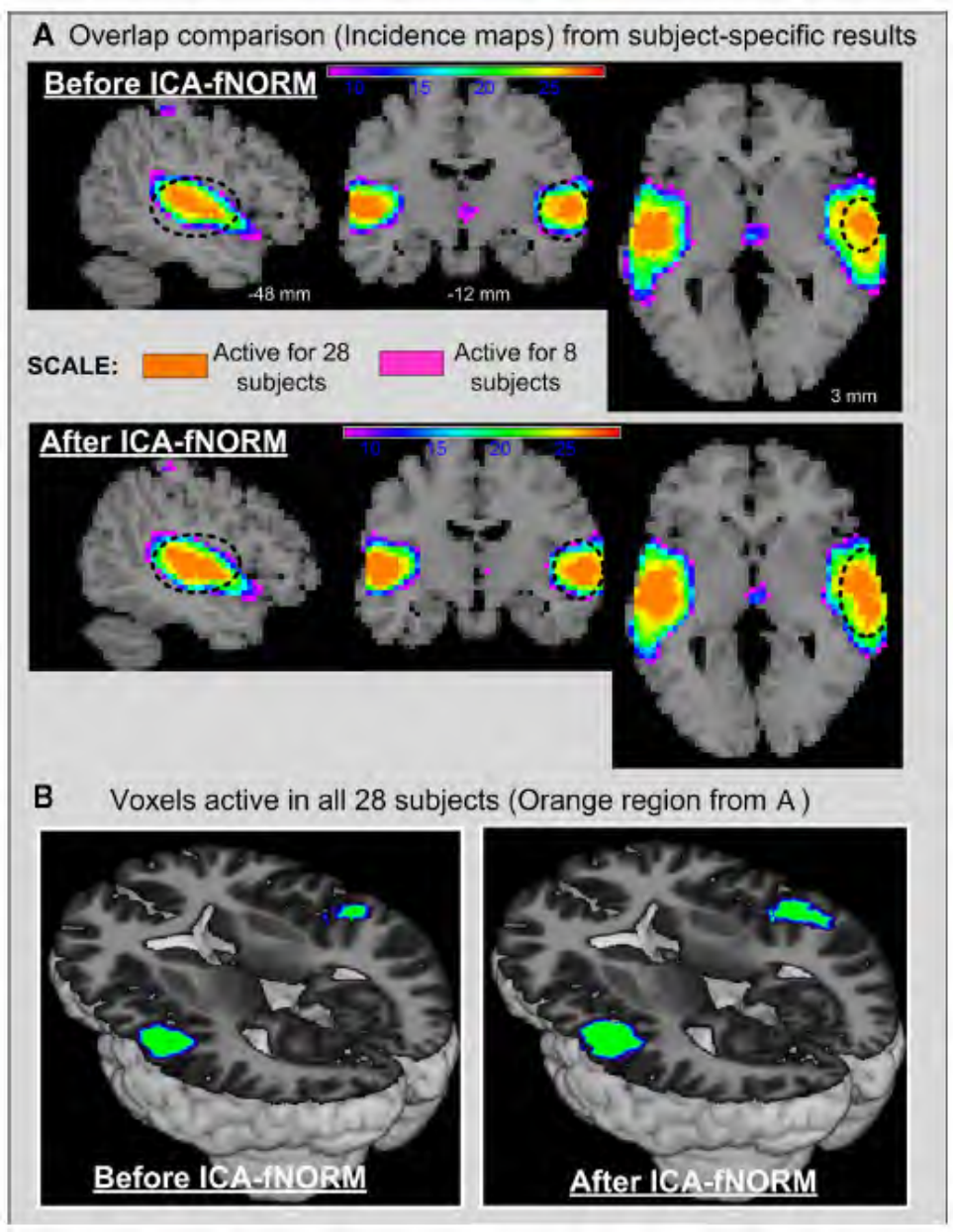
2) Intensity Normalization (IN), which involves voxel-wise division of the time series mean

3) Variance Normalization (VN), voxel-wise z-scoring of the time series

E. Allen, E. Erhardt, T. Eichele, A. R. Mayer, and V. D. Calhoun, "Comparison of pre-normalization methods on the accuracy of group ICA results," in *Proc. HBM, Barcelona, Spain, 2010.*

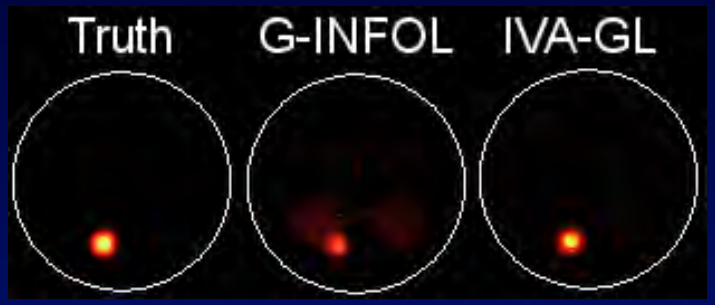
Functional Normalization (fNORM)



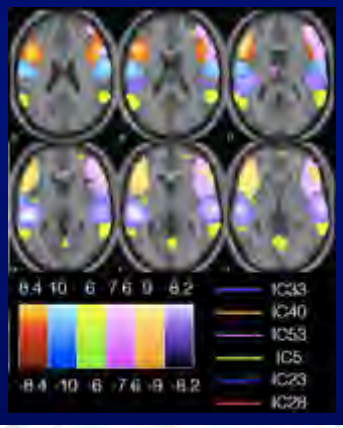


Current Directions

- Individual variability



- Dependencies in space, time, space/time



- Dynamics