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

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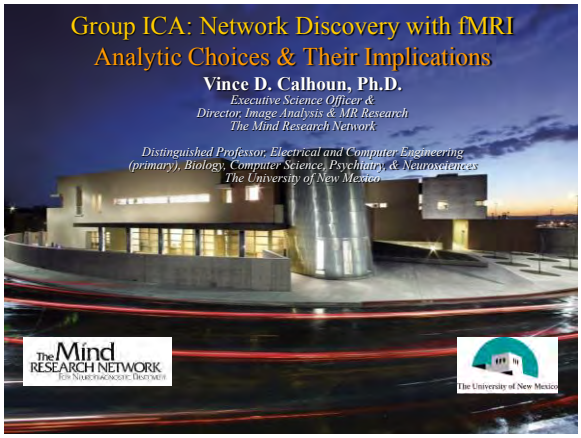
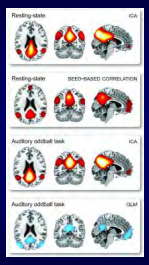
The University of New Mexico



Outline of Talk

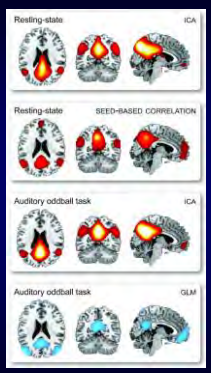
- Approaches
  - Seeds vs Components
  - Intro to ICA
  - Group ICA vs single subject
- Processing issues
  - Impact of (micro) motion
  - Autocorrelation
  - Band-pass filtering
- Other issues
  - Task vs Rest
  - Overlap of networks
- Applications
  - Diagnostic
  - Prediction
- Dynamic connectivity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



Seeds vs Components

- Seed approaches
  - Require one or more seed regions
  - Involved univariate cross-correlation
  - Require filtering
  - Require some measure of removal of physiologic noise [covary w/ physiologic noise or white/csf regions]
  - Full correlation vs partial correlation is an important decision
- Independent component analysis (ICA)
  - Fully data-driven (no seed region, though priors are possible)
  - Assumes linear covariation within components
  - Assumes linear mixing among components
  - Maximizes spatial independence
  - All components have values at all voxels (enabling spatial filtering of artifacts and overlapping components)

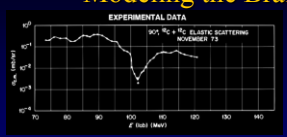
Convergence of Methods for Identifying Resting Networks



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.

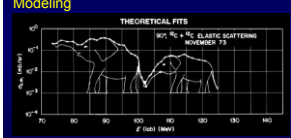
Modeling the Brain?

Results

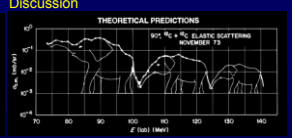


From "Science with a Smile" by Subramanian Raman

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.

ICA vs PCA

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

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

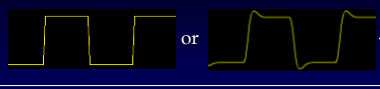
$$\Rightarrow E\{h(y_1) h(y_2)\} = E\{h(y_1)\} E\{h(y_2)\}$$

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

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

General Linear Model

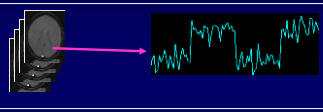
1. Model (1 or more Regressors)



or

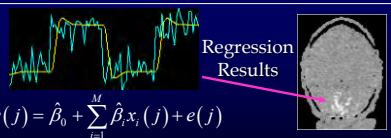
$x_i(j)$

2. Data



$y(j)$

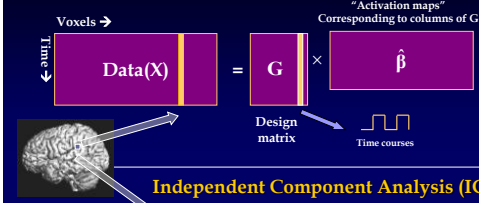
3. Fitting the Model to the Data at each voxel



Regression Results

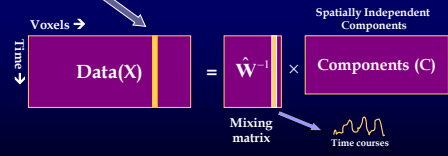
$$y(j) = \hat{\beta}_0 + \sum_{i=1}^{M} \hat{\beta}_i x_i(j) + e(j)$$

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

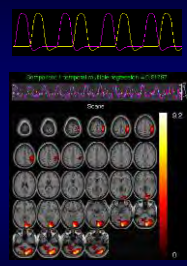
candle 2

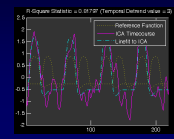
candle 3

Candle out

Assessing Task Modulation of Components

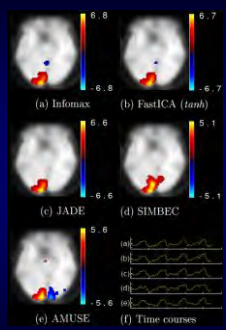
- We can evaluate the component timecourses within a standard GLM approach.





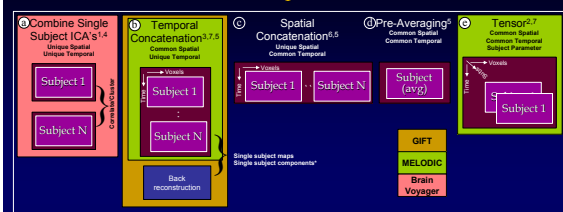
Comp#	R^2	Subject	Reg1	Reg2
3	0.81	1	1.89	0.02
		2	2.28	0.66
10	0.79	1	0.28	2.19
		2	0.65	2.03
4	0.017	1	-0.19	-0.40
		2	-0.10	0.08

Consistency of ICA Algorithms



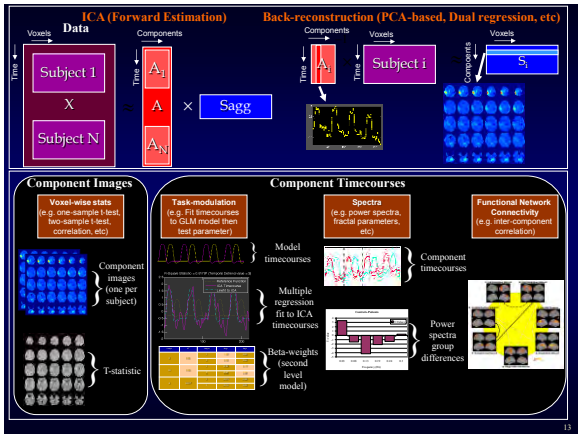
N. Correa, T. Adalı, and V. D. Calhoun, "Performance of Blind Source Separation Algorithms for fMRI Analysis," Mag.Res.Imag., vol. 25, p. 684, 2007

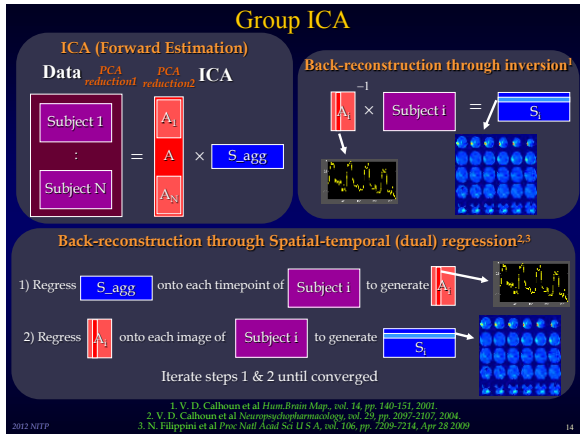
Group ICA

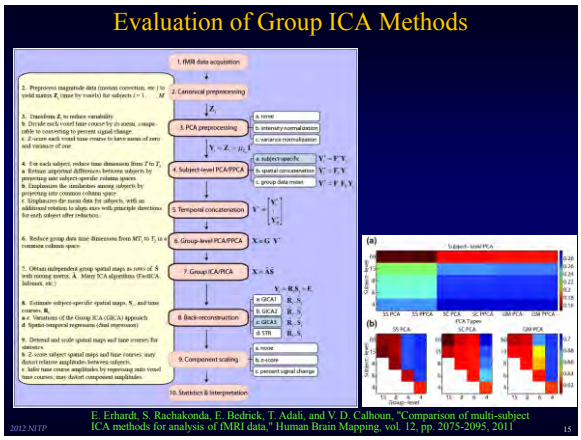


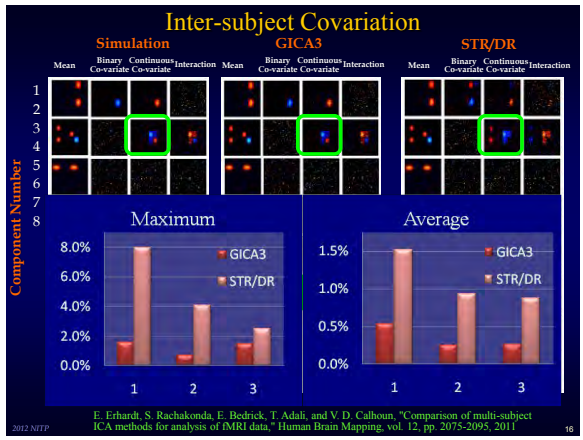
1) Calhoun VD, Adali T. McGinty V, Pekar JJ, Watson T, Pearlson GD. (2001): fMRI Activation in A Visual-Perception Task: Network Of Areas Detected Using The General Linear Model And Independent Component Analysis. NeuroImage 14(6):1080-1088.
2) Beckmann CF, Smith SM. (2005): Tensorial extensions of independent 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.

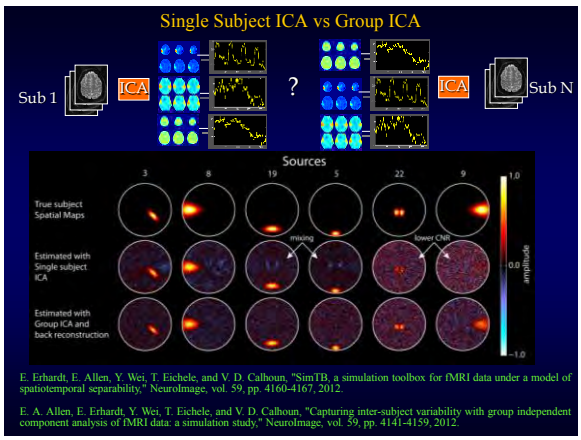
- V. D. Calhoun, J. Liu, and T. Adali, "A Review of Group ICA for fMRI Data and ICA for Joint Inference of Imaging, Genetic, and ERP data," *NeuroImage, vol. 45, pp. 163-172, 2009*.
- E. Erhardt, S. Rachakonda, E. Bedrick, T. Adali, and V. D. Calhoun, "Comparison of multi-subject ICA methods for analysis of fMRI data," *Human Brain Mapping*, vol. 12, pp. 2075-2095, 2011.
- V. D. Calhoun and T. Adali, "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.

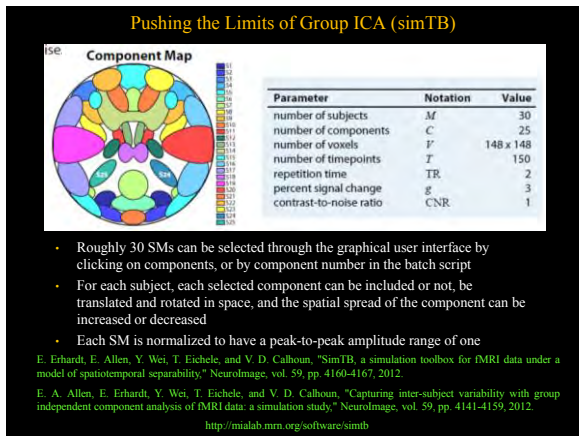

ICA (Forward Estimation)
Back-reconstruction (PCA-based, Dual regression, etc)
Data
Voxels
Components
Time
Subject 1
X
Subject N
Sagg
Subject i
Component Images
Voxel-wise stats
(e.g. one-sample t-test, two-sample t-test, correlation, etc)
Component images (one per subject)
T-statistic
Component Timecourses
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)
13


Group ICA
ICA (Forward Estimation)
Data
PCA reduction1
PCA reduction2
ICA
Subject 1
Subject N
S_agg
Back-reconstruction through inversion[1]
Subject i
Back-reconstruction through Spatial-temporal (dual) regression[2,3]
1) Regress S_agg onto each timepoint of Subject i to generate
2) Regress onto each image of Subject i to generate
Iterate steps 1 & 2 until converged
1. V. D. Calhoun et al Hum.Brain Map., vol. 14, pp. 140-151, 2001.
2. V. D. Calhoun et al Neuropsychopharmacology, vol. 29, pp. 2097-2107, 2004.
3. N. Filippini et al Proc Natl Acad Sci U S A, vol. 106, pp. 7209-7214, Apr 28 2009
2012 NITP
14

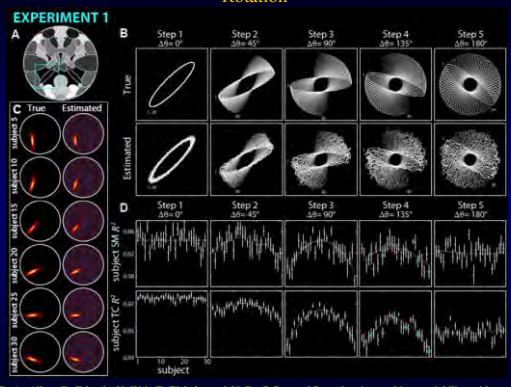

Evaluation of Group ICA Methods
E. Erhardt, S. Rachakonda, E. Bedrick, T. Adali, and V. D. Calhoun, "Comparison of multi-subject ICA methods for analysis of fMRI data," Human Brain Mapping, vol. 12, pp. 2075-2095, 2011
2012 NITP
15


Inter-subject Covariation
Simulation
GICA3
STR/DR
Mean
Binary Co-variate
Continuous Co-variate
Interaction
Component Number
Maximum
Average
GICA3
STR/DR
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
2012 NITP
16


Single Subject ICA vs Group ICA
Sub 1
ICA
?
ICA
Sub N
Sources
True subject Spatial Maps
Estimated with Single subject ICA
Estimated with Group ICA and back reconstruction
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.

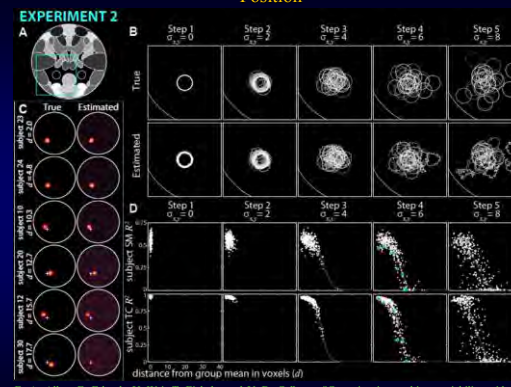

Pushing the Limits of Group ICA (simTB)
Component Map
Parameter | Notation | Value
number of subjects | M | 30
number of components | C | 25
number of voxels | V | 148 x 148
number of timepoints | T | 150
repetition time | TR | 2
percent signal change | g | 3
contrast-to-noise ratio | CNR | 1
Roughly 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



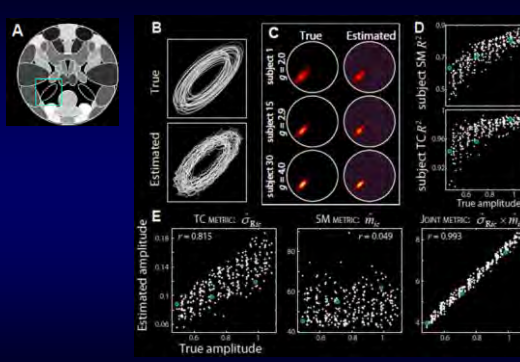
E. A. Allen, E. Erhardt, Y. Wei, T. Eichele, and V. D. Calhoun, "Capturing inter-subject variability with group independent component analysis of fMRI data: a simulation study," NeuroImage, vol. 59, pp. 4141-4159, 2012. 19

Position



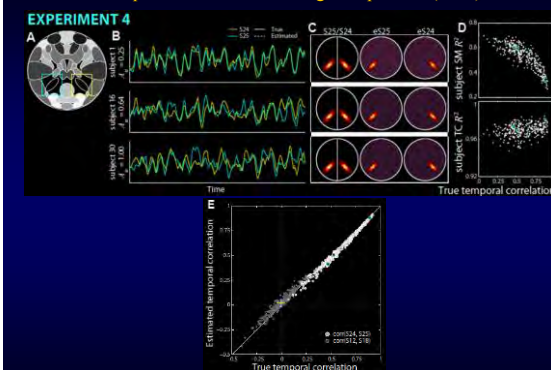
E. A. Allen, E. Erhardt, Y. Wei, T. Eichele, and V. D. Calhoun, "Capturing inter-subject variability with group independent component analysis of fMRI data: a simulation study," NeuroImage, vol. 59, pp. 4141-4159, 2012. 20

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. 21

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. 22

Collaborative Informatics & Neuroimaging Suite (COINS)

http://coins.mrn.org

COINS Tools

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

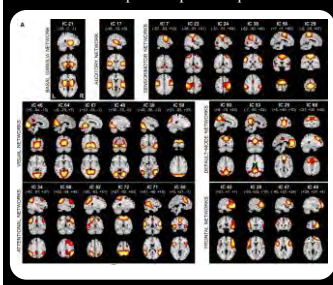
Been in use and iteratively improved for over 7 years
Fully Open Source stack (LAPP)
Current counts of important artifacts
- PIs 82
- Studies 334 (expired and on-going)
- Subjects ~ 15,000
- Scan Sessions ~ 19,000
- Clinical Assessments ~ 183,000

A. Scott, W. Courtney, D. Wood, R. De la Garza, S. Lane, R. Wang, J. Roberts, J. A. Turner, and V. D. Calhoun, "COINS: An innovative informatics and neuroimaging tool suite built for large heterogeneous datasets," Frontiers in Neuroinformatics, vol. 5, pp. 1-15, 2011.

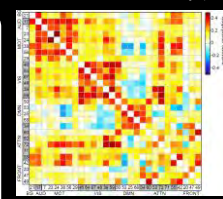
2012 UMN

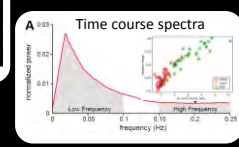
Group ICA of Rest fMRI Data: N=603

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: $\beta_1 = 0$

:

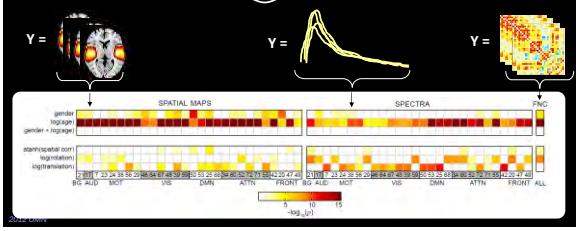
(v) H_0: $\beta_v = 0$

Is voxel i affected by age?

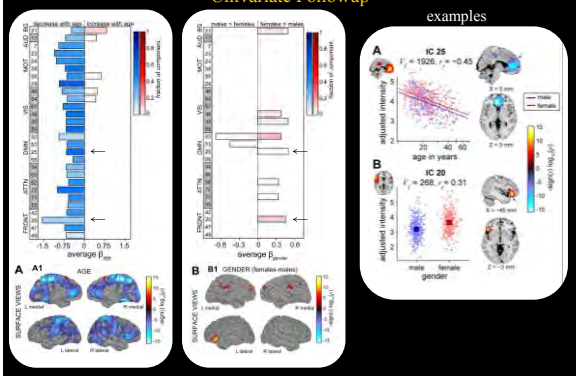
multivariate models

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

Are any of these voxels affected by age?

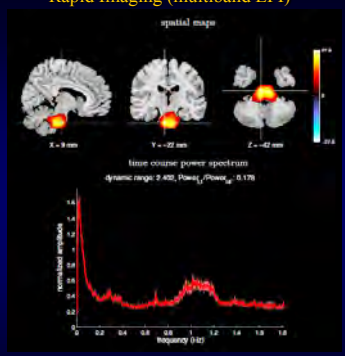


Univariate Followup



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

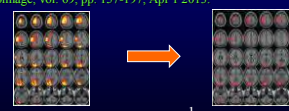
Rapid Imaging (multiband EPI)



TR=275ms, 39 subjects

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.



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

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

Outline of Talk

- Approaches
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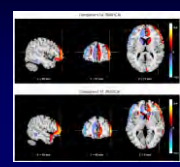
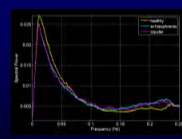
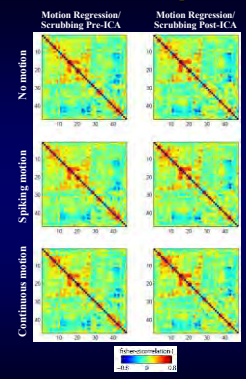
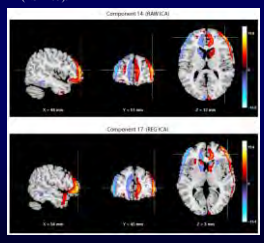




Impact of motion on FNC



- 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

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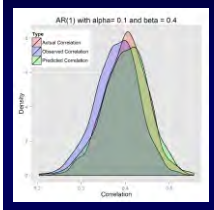
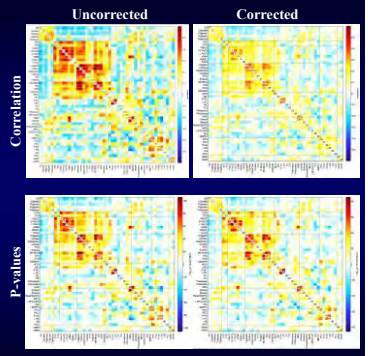
Autocorrelation

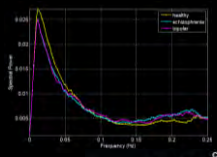


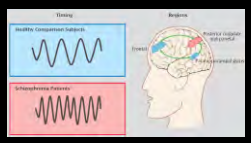


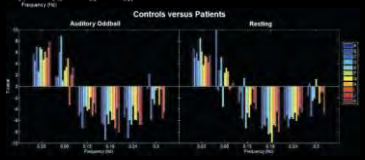
M. Arbabshirani, E. Damaraju, S. M. Plis, T. Adali, and V. D. Calhoun, "An assessment of the impact of autocorrelation on functional network connectivity," in Proc. HBM, Seattle, WA, 2013.

32

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

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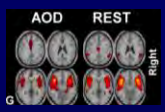

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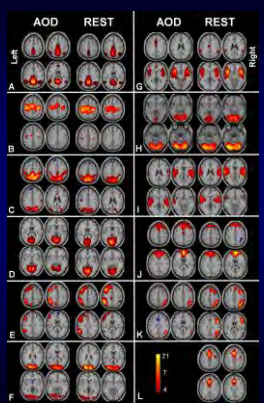
Task vs Rest

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.

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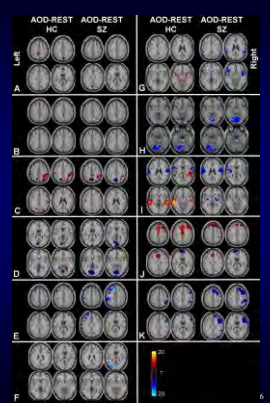
Task vs Rest

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.

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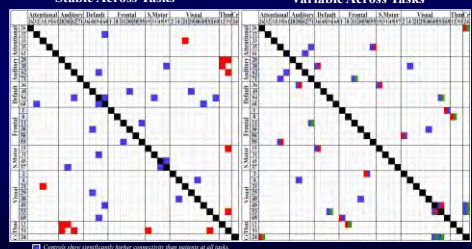
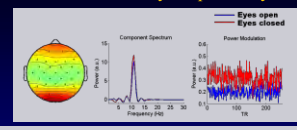
Effect of Task on Intrinsic Networks in SZ vs HC

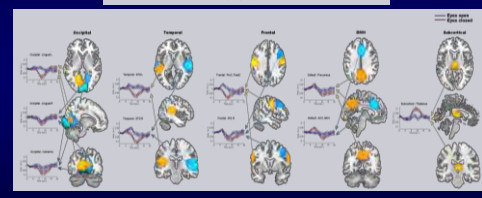
Stable Across Tasks | **Variable Across Tasks**



- Controls show significantly higher connectivity than patients at all tasks.
- Patients show significantly higher connectivity than controls at all tasks.
- Patients show significantly higher connectivity than controls in the resting state and controls show significantly higher connectivity than patients at other tasks.
- Controls show significantly higher connectivity than patients in the resting state and patients show significantly higher connectivity than controls at other tasks.
- Controls show significantly higher connectivity than patients in the resting state and neither patients nor controls show significantly higher connectivity at other tasks.
- Patients show significantly higher connectivity than controls in the resting state and neither patients nor controls show significantly higher connectivity at other tasks.

Concurrent EEG/fMRI: eyes open vs eyes closed



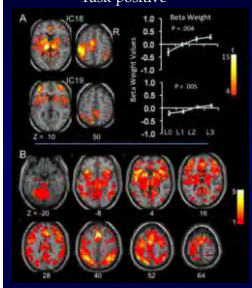


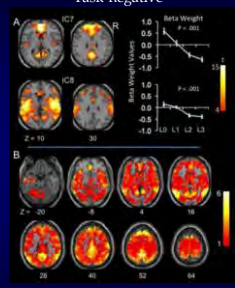
These results suggest that changes in neuronal synchronization as indicated by power fluctuations in high-frequency (>1Hz) EEG rhythms such as posterior alpha are partly mediated by widespread changes in inter-regional low-frequency (<.1Hz) functional activities detected in fMRI. They also indicate that 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

Overlap of Networks

Task-positive | Task-negative

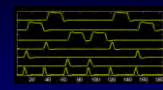




J. Xu, S. Zhang, V. D. Calhoun, J. Monterosso, C.-S. Li, P. D. Worhunsky, M. Stevens, G. D. Pearlson, and M. N. Potenza, "Task-related concurrent but opposite modulations of overlapping functional networks as revealed by spatial ICA," *NeuroImage*, in press.

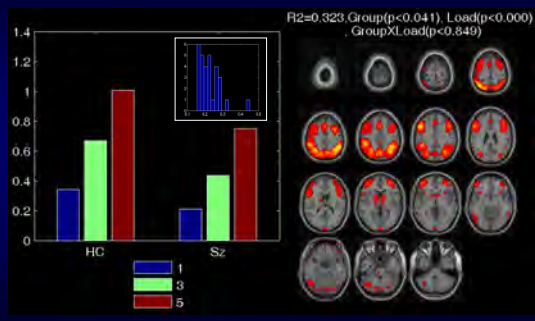
fBIRN SIRP Task

- 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



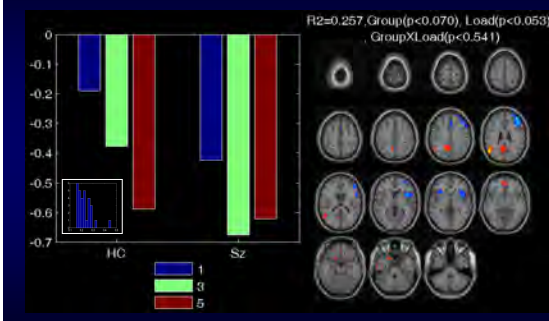
fBIRN Phase II Data: www.nbirn.net;
NCRR (NIH), 5 MO1 RR 000827 (2002-2006) and 1 U24 RR0219921 (2006 onwards)

Component 1: Bilateral Frontal/Parietal



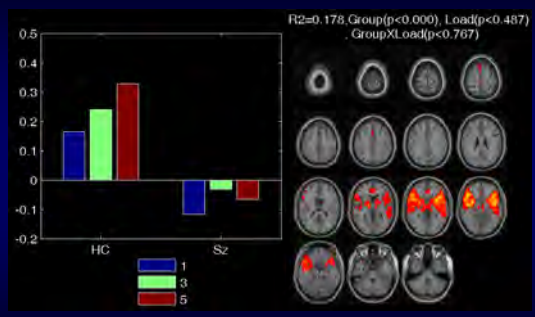
fBIRN Phase II Data: www.nbirn.net;
NCRR (NIH), 5 MO1 RR 000827 (2002-2006) and 1 U24 RR0219921 (2006 onwards)

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



fBIRN Phase II Data: www.nbirn.net;
NCRR (NIH), 5 MO1 RR 000827 (2002-2006) and 1 U24 RR0219921 (2006 onwards)

Component 3: Temporal Lobe



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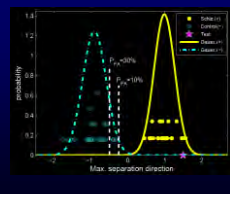

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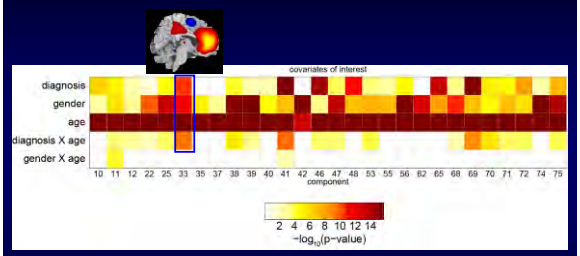
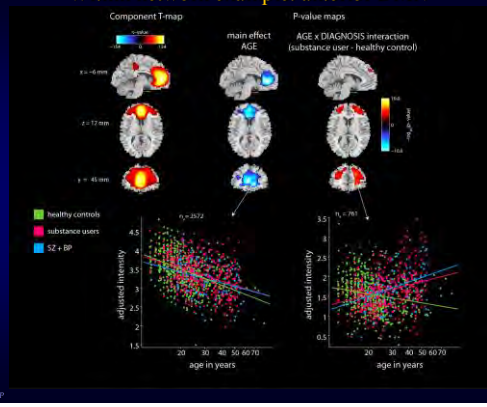
Relationship to Disease (N=1140)



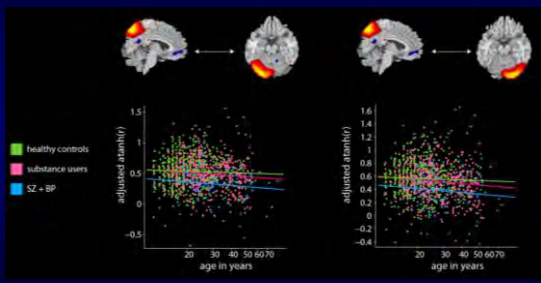
Healthy (N=590)
Substance Use (N=469)
Schizo/BP (N=81)

Within network example: anterior DMN

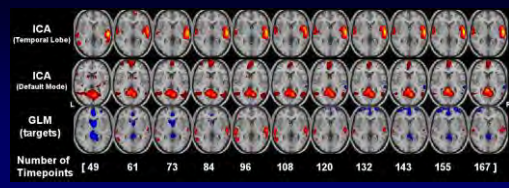


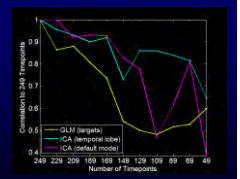
2012 NITP

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

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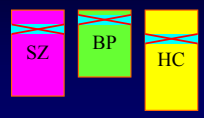
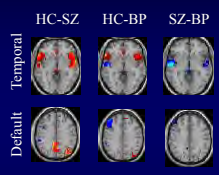
3-way Classification of Schizophrenia, Bipolar, Control

1) Remove subjects from each group



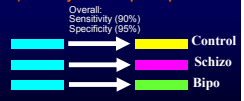
2) Identify regions which maximally separate remainder



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



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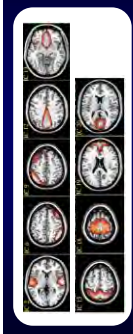
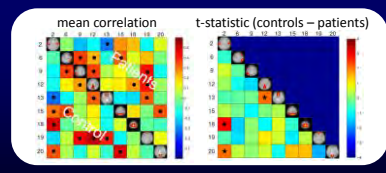
Diagnostic Classification: FNC

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



Mohammad R. Arbabshirani and Vince D. Calhoun, In submission

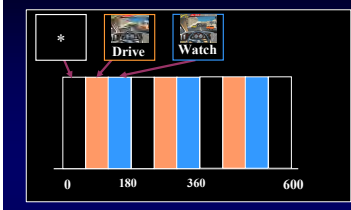
Diagnostic Classification: FNC

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

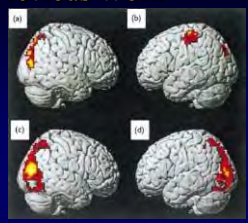
Mohammad R. Arbabshirani and Vince D. Calhoun, In submission

Simulated Driving Paradigm



Previous Work

- Walter, 2001.



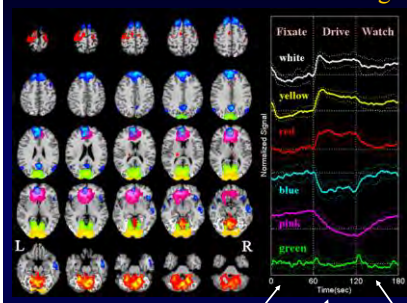
Driving

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.

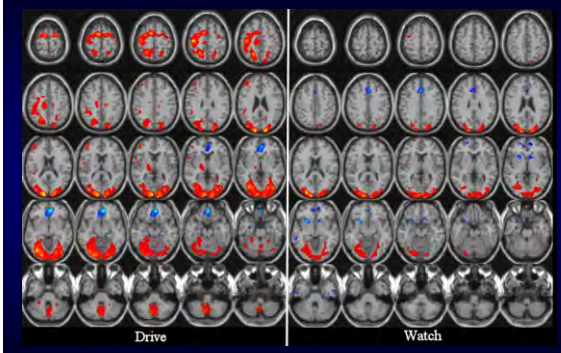
Vigilance: Decreases only during driving; amount proportional to speed.

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

Visual Monitoring: Increases during epoch transitions.

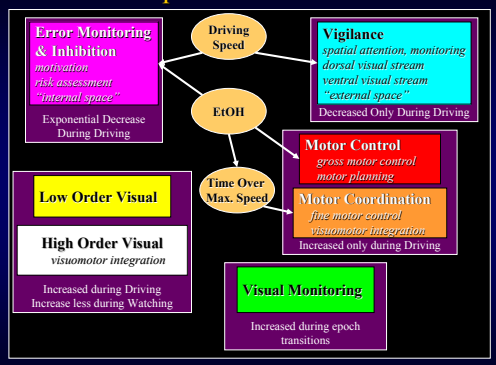
V. D. Calhoun, J. J. Pekar, V. B. McGinty, T. Adali, T. D. Watson, and G. D. Pearlson, "Different Activation Dynamics in Multiple Neural Systems During Simulated Driving," *Hum. Brain Map.*, vol. 16, pp. 158-167, 2002.

SPM Results



Calhoun, V. D., Pekar, J. J., and Pearlson, G. D. "Alcohol Intoxication Effects on Simulated Driving: Exploring Alcohol-Dose Effects on Brain Activation Using Functional MRI". *Neuropsychopharmacology* 2004.

Interpretation of Results



Calhoun, V. D., Pekar, J. J., and Pearlson, G. D. "Alcohol Intoxication Effects on Simulated Driving: Exploring Alcohol-Dose Effects on Brain Activation Using Functional MRI". *Neuropsychopharmacology* 2004.

Outline of Talk

- Approaches
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  - Intro to ICA
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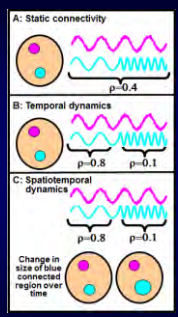
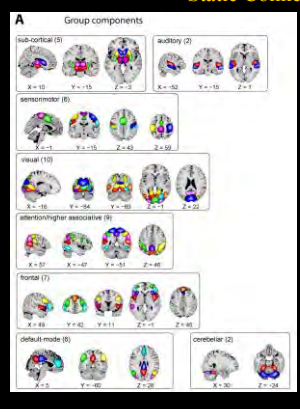
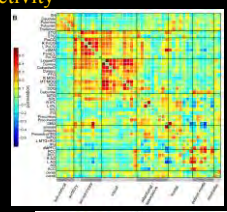
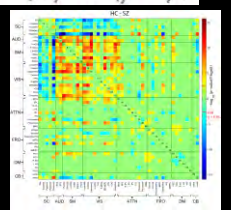


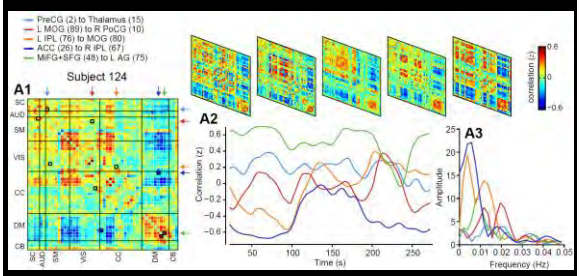
Static Connectivity





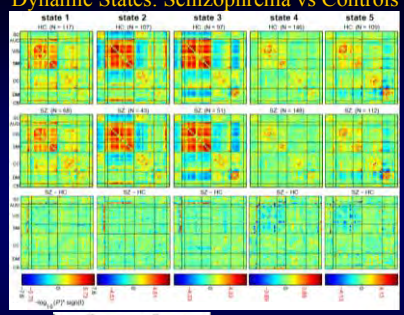


Dynamic FNC



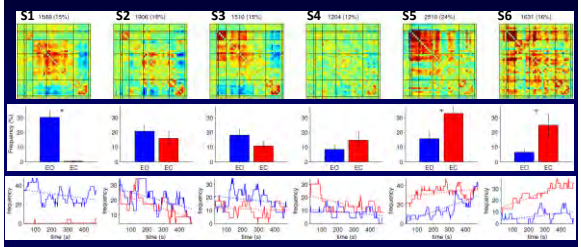
E. Allen, E. Damaraju, S. M. Plis, E. Erhardt, T. Eichele, and V. D. Calhoun, "Tracking whole-brain connectivity dynamics in the resting state," *Cereb Cortex*, in press.

Dynamic States: Schizophrenia vs Controls



E. Damaraju, J. Turner, A. Preda, T. Van Erp, D. Mathalon, J. M. Ford, S. Potkin, and V. D. Calhoun, "Static and dynamic functional network connectivity during resting state in schizophrenia," in American College of Neuropsychopharmacology, Hollywood, CA, 2012.

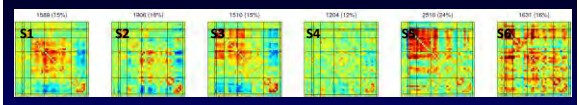
EEG Signature of FNC States

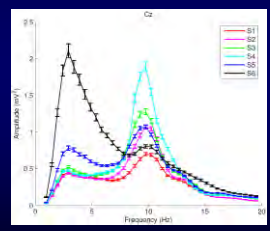


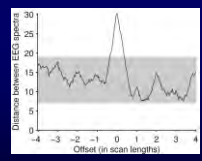
- Some FC states show excellent segregration with regard to EO/EC condition.
- Most states also show temporal trends, highly consistent with those seen in our previous study.
- Perhaps the most notable feature of States 5 and 6, which increase in frequency over time and are much more likely to appear in EC, is the **lack of antagonism** between the DMN and sensorimotor and/or cognitive control networks.

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

EEG Signature of FNC States

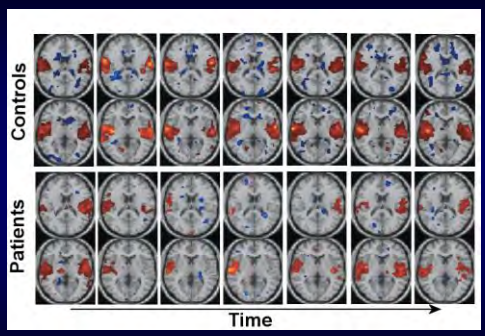






E. Allen, T. Eichele, L. Wu, and V. D. Calhoun, "EEG Signatures of Functional Connectivity States," in *Human Brain Mapping*, Seattle, WA, 2013.

Spatial Patterns of Connectivity are also Dynamic



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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.

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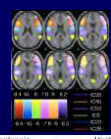
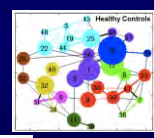
Current Directions

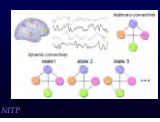
- Individual variability

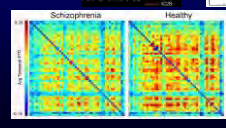
- Dependencies in space, time, space/time

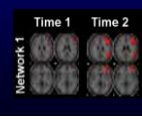




- Dynamics



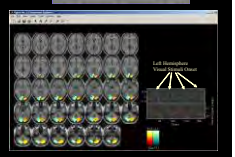




2012 NITP

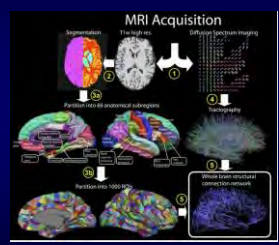
Mialab Software

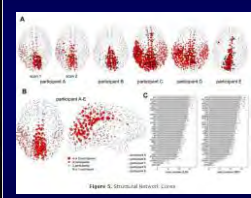
- http://mialab.mrn.org/software
- freeware, written in MATLAB
- Group ICA of fMRI Toolbox (GIFT)
  - Single subject/Group ICA
  - MANCOVA testing framework
  - Source Based Morphometry
  - Model order estimation
  - ICASSO (clustering/stability)
- Fusion ICA Toolbox (FIT)
  - Parallel ICA, jICA
  -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



Structure/Function

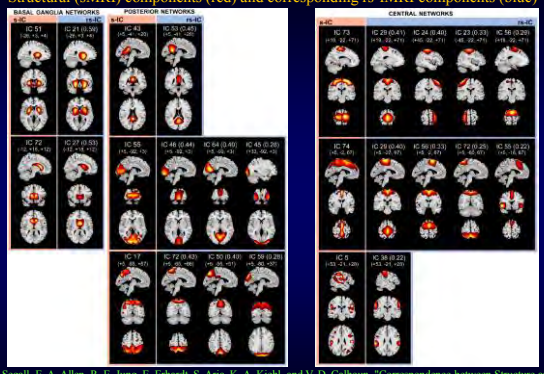
- Mapping the Structural Core of Human Cerebral Cortex. Hagman, et al. 2008 PLOS Biology





- **Structural Core:** (For both hemipheres) Posterior cingulate cortex, precuneus,cuneus, paracentral lobule, isthmus of the cingulate, banks of the superior temporal sulcus, & inferior/superior parietal cortex

Structural (sMRI) components (red) and corresponding rs-fMRI components (blue)



J. Segall, E. A. Allen, R. E. Jung, E. Erhardt, S. Arja, K. A. Kiehl, and V. D. Calhoun, "Correspondence between Structure and Function in the Human Brain at Rest," *Frontiers in Neuroinformatics (special issue on human connectome),* Under Review.

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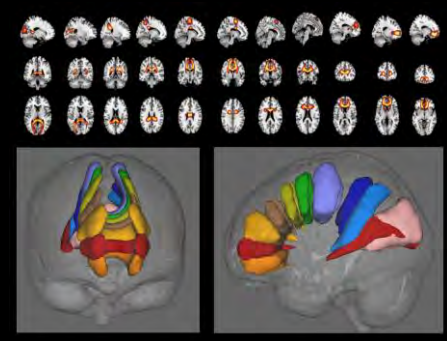
Group ICA of DTI identifies separate microstructures of corpus callosum



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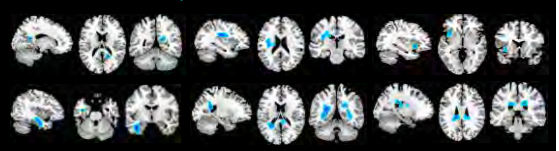
Patient/Control Differences

P' < 0.05 FDR corrected
Age effect removal*
Cluster size > 5 voxels

Decreased connectivity



Increased connectivity

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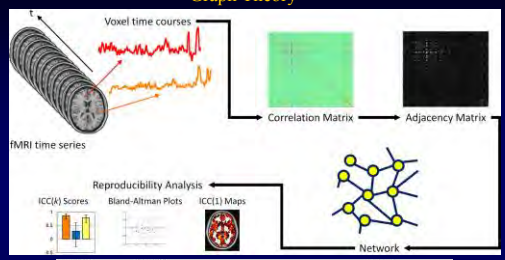
Graph Theory



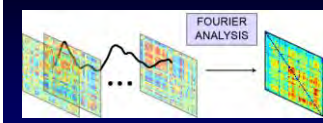
Graph metric	Description	Equation
Degree	Measures the connectivity of each node	$K_i = \sum_{j \in N} A_{ij}$
Clustering coefficient	Measures local neighborhood connectivity, calculated as the likelihood that neighbors of a node are also neighbors	$C_i = 2e_i / (K_i(K_i - 1))$
Path length	Measures the distance between nodes in the network and is calculated as the shortest geodesic distance between each node and every other node	$L = 1/N(N-1) \sum_{i \neq j \in N} d_{ij}$
Global efficiency	Measures the closeness of an individual node to all other nodes in the network	$E_{glob} = EIG = 1/N(N-1) \sum_{i \neq j \in N} 1/d_{ij}$
Local efficiency	Describes how interconnected the neighbors are in a particular area of the network	$E_{loc} = 1/N \sum_{i \in N} EIG(i)$

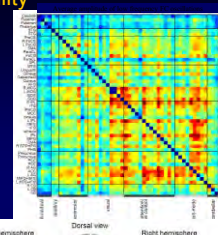
Q. K. Telesford, A. R. Morgan, S. Hayasaka, S. L. Simpson, W. Barret, R. A. Kraft, J. L. Mozolic, and P. J. Laurienti, "Reproducibility of graph metrics in FMRI networks," *Front Neuroinform*, vol. 4, p. 117, 2010.

Qingbao's stuff???

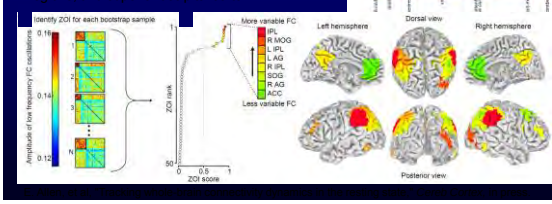
77

FNC variability

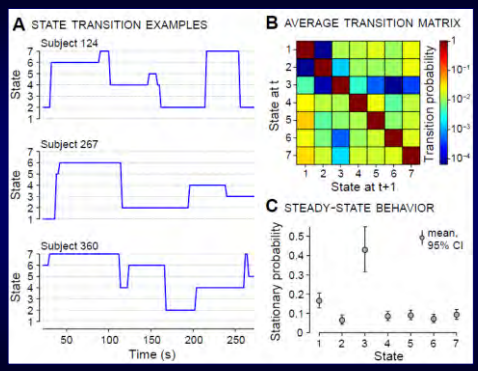




A "zone-of-instability" (ZOI) is apparent between dorsal attention areas, particular default-mode regions, and superior occipital cortex.



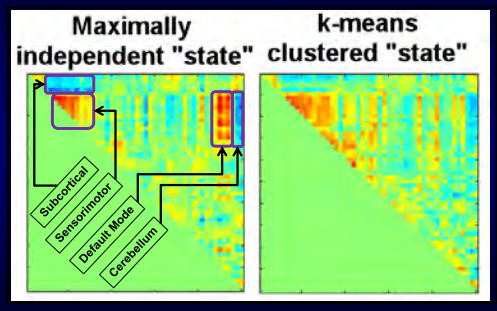
Markov modeling



Overview

- Motivation
- Simulations
- Studying with large N healthy dataset
- Converging evidence with concurrent EEG/fMRI
- Application to Schizophrenia
- Ongoing work
- Conclusions

Independence appears to be a useful way to identify states



A couple definitions

- Connectome
  - Scale (Macro/Meso/Micro)
  - Function vs Structure

O. Sporns, G. Tononi, and R. Kotter, "The human connectome: A structural description of the human brain," PLoS Comput Biol, vol. 1, p. e42, Sep 2005, 1239902.

- Network
  - Context determines the meaning and interpretation of the word "network" in brain imaging analysis.
  - GLM and seed-based method define a network as a subset of voxels whose timeseries are significantly correlated with a reference signal.
  - Using graph theory, a network may be defined as a connectivity matrix between nodes, which represent voxels, areas, or components.
  - ICA provide a description of the relationships among all voxels.
  - FNC is a network of networks (e.g. graph theory or correlations among network timecourses)
  - Each author should explicitly state the interpretation implicit in the method.

E. Erhardt, E. Allen, E. Damaraju, and V. D. Calhoun, "On network derivation, classification, and visualization: a response to Habeck and Moeller," *Brain Connectivity*, In Press

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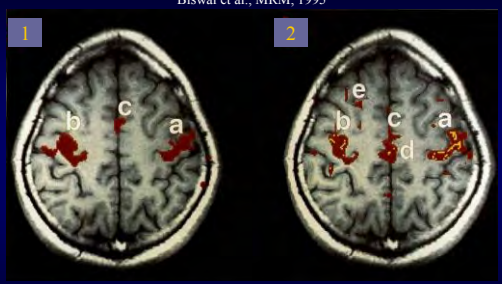
Functional connectivity: the first study

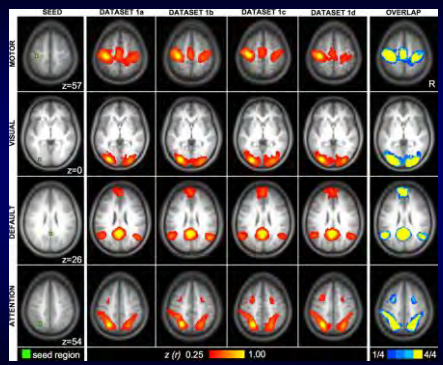
Biswal et al., MRM, 1995



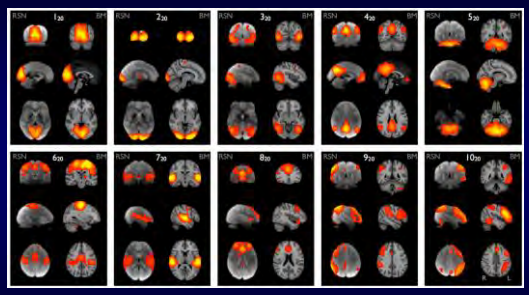
Correlation with model time course during simple motor task

Correlation with time course from **b**, during **rest**

seed-based correlation maps



Van Dijk et al., J Neurophys, 2010



S. M. Smith, P. T. Fox, K. L. Miller, D. C. Glahn, P. M. Fox, C. E. Mackay, N. Filippini, K. E. Watkins, R. Toro, A. R. Laird, and C. F. Beckmann, "Correspondence of the brain's functional architecture during activation and rest," *Proc Natl Acad Sci U S A*, vol. 106, pp. 13040-13045, Aug 4 2009, 2722273.

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Heritability and the Default Mode

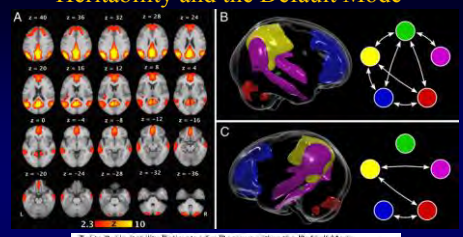

Table 2. Heritability Estimates for Regions within the Default Mode

Region	Functional Connectivity Heritability	Functional Connectivity p-value*	Gray Matter Density Heritability	Gray Matter Density p-value*
Posterior Cingulate/Precuneus	**0.423 (0.17)**	4.4×10^{-3}	**0.623 (0.16)**	6.5×10^{-6}
Medial Prefrontal Cortex	**0.376 (0.15)**	3.8×10^{-3}	**0.631 (0.15)**	5.3×10^{-6}
Left Temporal-Parietal Region	0.331 (0.18)	3.1×10^{-2}	0.387 (0.21)	3.1×10^{-2}
Right Temporal-Parietal Region	**0.420 (0.16)**	3.5×10^{-3}	0.355 (0.21)	3.4×10^{-2}
Left Cerebellum	0.104 (0.13)	2.0×10^{-1}	**0.493 (0.15)**	4.9×10^{-4}
Right Cerebellum	**0.304 (0.16)**	1.6×10^{-2}	**0.596 (0.14)**	1.6×10^{-5}
Cerebellar Tonsil	0.219 (0.18)	1.1×10^{-1}	0.271 (0.16)	3.2×10^{-2}
Left Parahippocampal Gyrus	**0.273 (0.14)**	1.7×10^{-2}	**0.420 (0.18)**	7.5×10^{-3}

* Bolded figures are significant at 5% FDR. * Estimated heritability, ±2 standard errors. # P-value

D. C. Glahn, A. M. Winkler, P. Kochunov, L. Almasy, R. Duggirala, M. A. Carless, J. C. Curran, R. L. Olvera, A. R. Laird, S. M. Smith, C. F. Beckmann, P. T. Fox, and J. Blangero, "Genetic control over the resting brain," *Proc Natl Acad Sci U S A, vol. 107, pp. 1223-1228, Jan 19 2010, 2824276.*

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