NEUROIMAGING TRAINING PROGRAM

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

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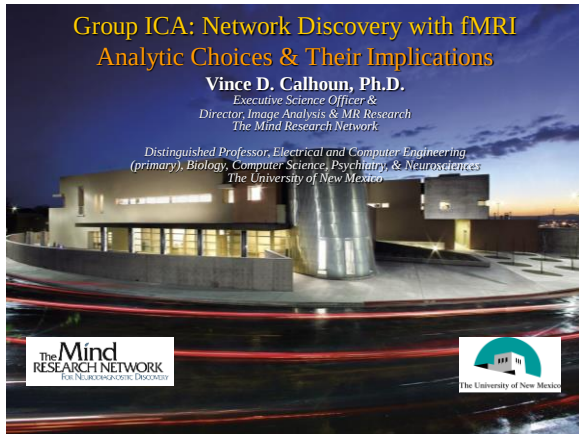
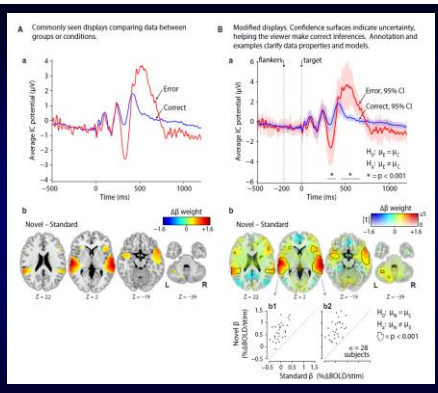
The University of New Mexico





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

http://mialab.mrn.org/datavis/

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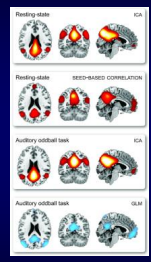
Outline of Talk

- 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



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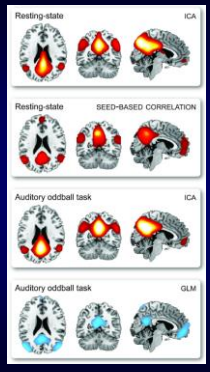
Convergence of Methods for Identifying Resting Networks



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.

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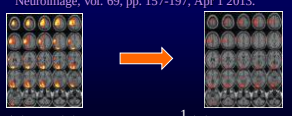
Seeds vs Components

- 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.

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

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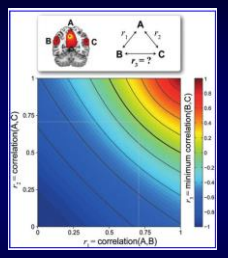
Networks and Seeds

- 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,

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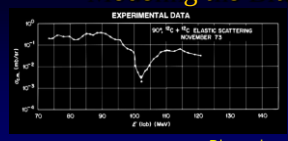
Modeling the Brain?

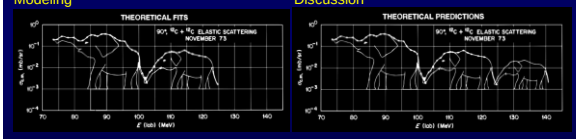
Results



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.

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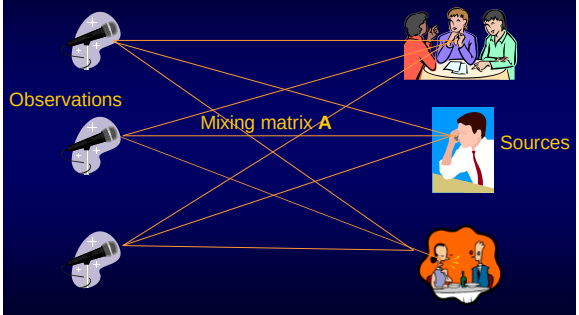
Blind Source Separation: The Cocktail Party Problem



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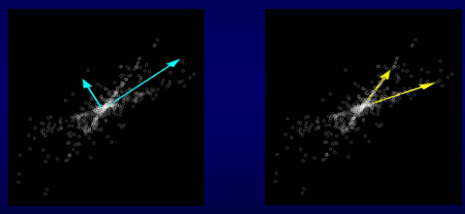
ICA vs PCA

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)

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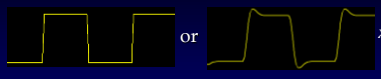
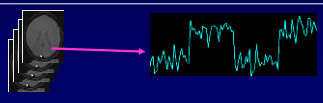
General Linear Model

1. Model (1 or more Regressors)



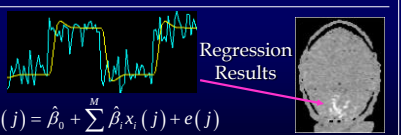
$x_i(j)$

2. Data



$y(j)$

3. Fitting the Model to the Data at each voxel



Regression Results

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

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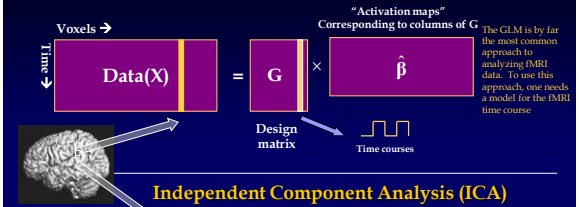
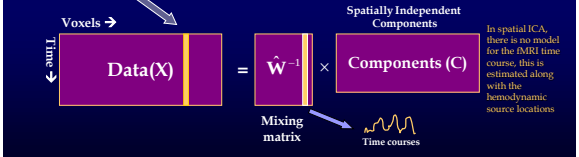
General Linear Model (GLM)



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

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ICA Halloween (Un)Mixer!

X = A × S

background

→ Time

candle 1

candle 2

candle 3

Candle out

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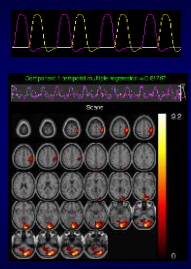
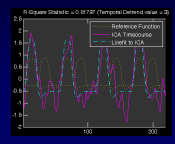
Assessing Task Modulation of Components

- 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

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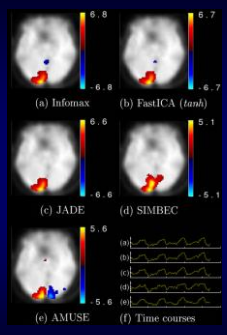
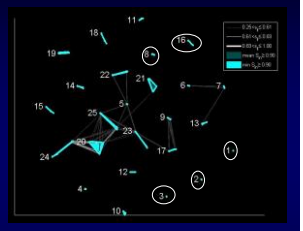
Consistency of ICA Algorithms





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

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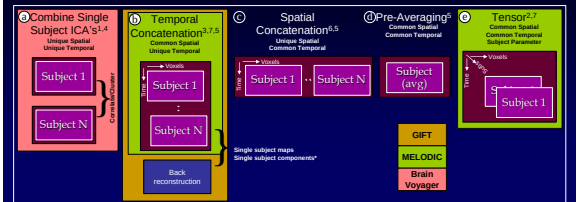
Group ICA



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. 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.

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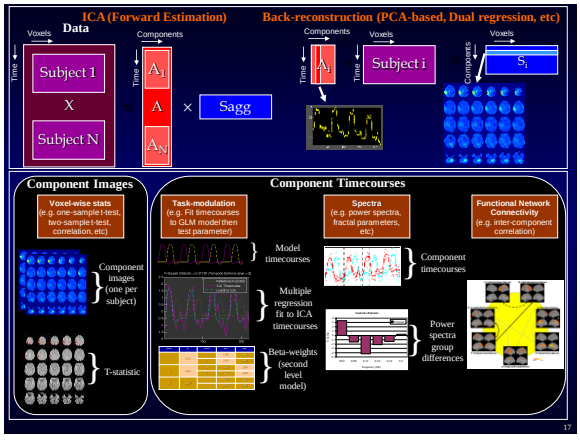

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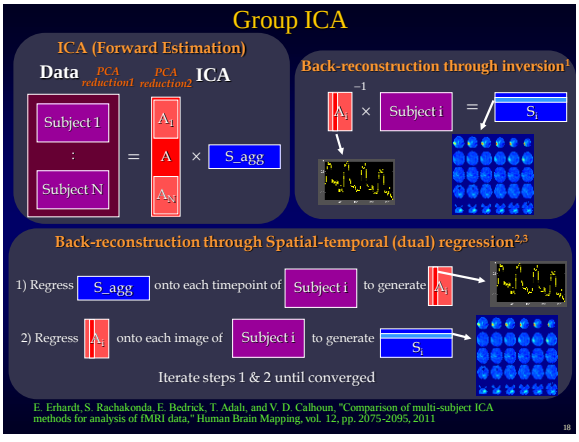
Group ICA



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

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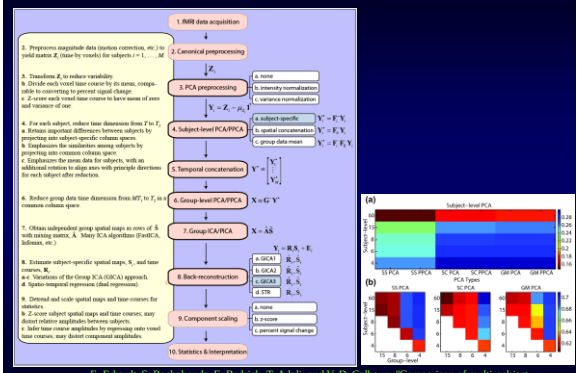
Evaluation of Group ICA Methods



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

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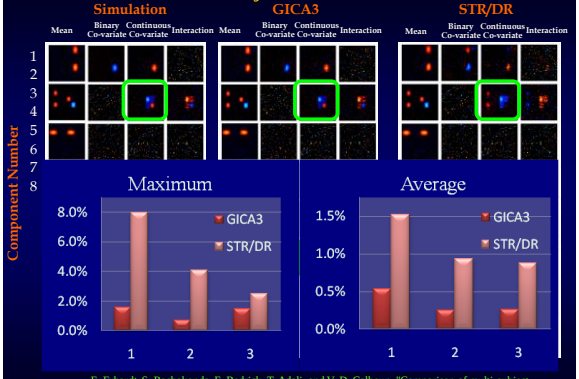
Inter-subject Covariation



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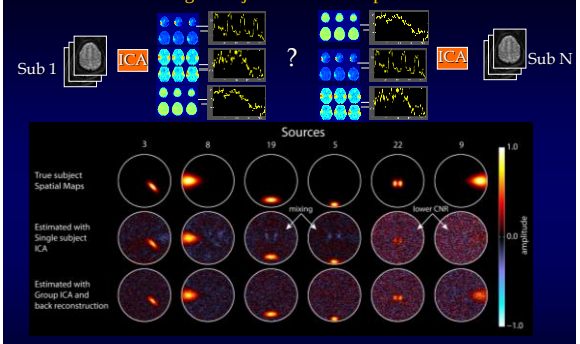
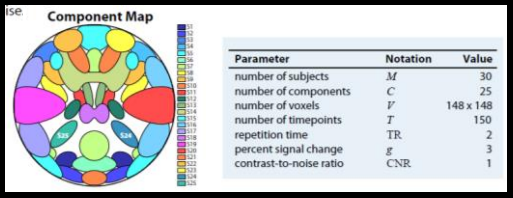
Single Subject ICA vs Group ICA



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

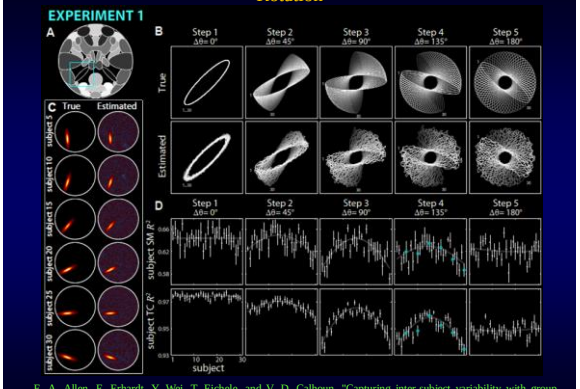
- Roughly 30 SMs can be selected through the graphical user interface by clicking on components, or by component number in the batch script
- For each subject, each selected component can be included or not, be translated and rotated in space, and the spatial spread of the component can be increased 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



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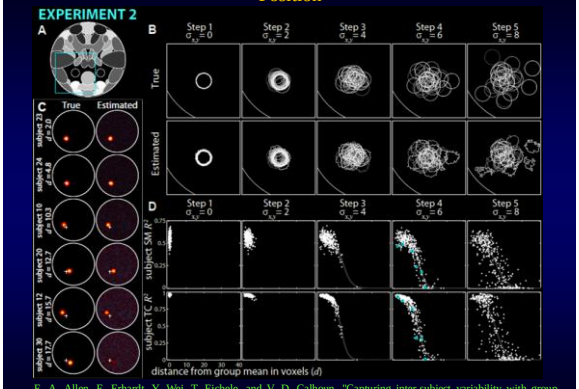
Position



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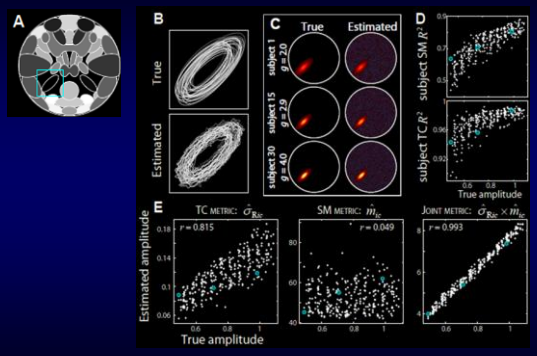
Amplitude



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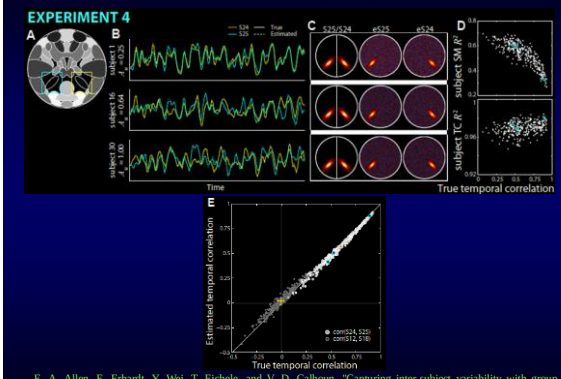
Temporal Correlation Among Components (FNC)



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)

COINS Tools

MICIS
DICOM Receiver
Assessment Manager
Self Assessment
Tablet
Query Builder
Portals
CAS
My Security
Data Exchange
oCOINS (offline)

http://coins.mrn.org
http://coins.mrn.org/dx

Fully Open Source stack (LAPP)
Current counts of important artifacts
- Studies 571
- Subjects ~ 33,160
- Scan Sessions ~ 40,234
- Clinical Assessments ~ 444,235

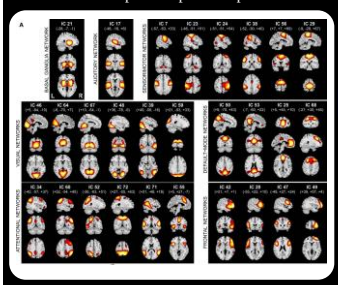
34 states
38 countries

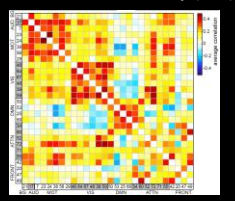
A. Scott, W. Courtney, D. Wood, R. De la Garza, S. Lane, R. Wang, J. Roberts, J. A. Turner, and V. D. Calhoun, "COINS: An innovative informatics and neuroimaging tool suite built for large heterogeneous datasets," Frontiers in Neuroinformatics, vol. 5, pp. 1-15, 2011.
M. King, D. Wood, B. Miller, R.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

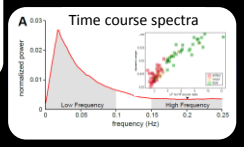
Group ICA of Rest fMRI Data: N=603

Component spatial maps

Functional network connectivity (FNC)



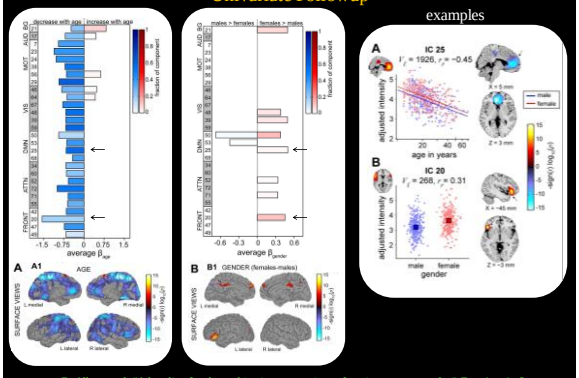




28 labeled components
& superset of 75 components
N=603 subjects
http://mialab.mrn.org/data

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

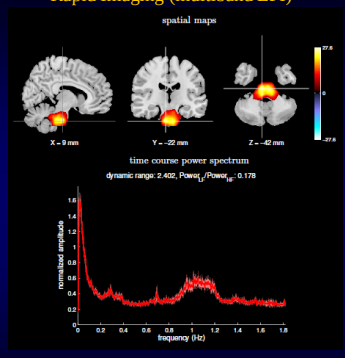
Univariate Followup



examples

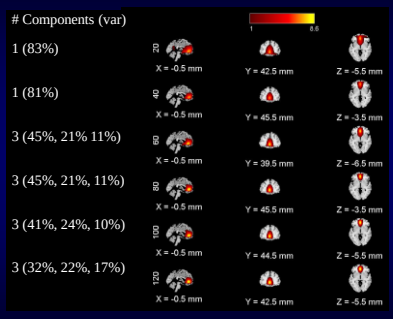
E. Allen, et al, "A baseline for the multivariate comparison of resting state networks," *Frontiers in Systems Neuroscience*, vol. 5:2, 2011.

Rapid Imaging (multiband EPI)



TR=275ms, 39 subjects

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



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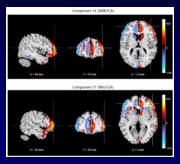
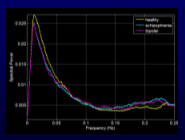
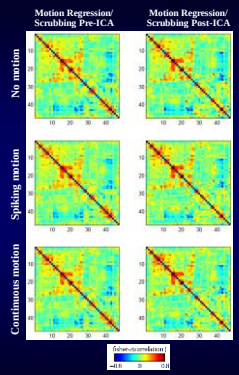


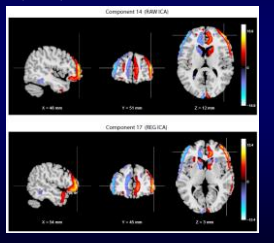


32

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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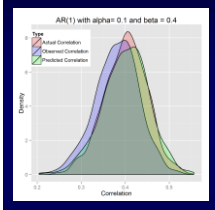
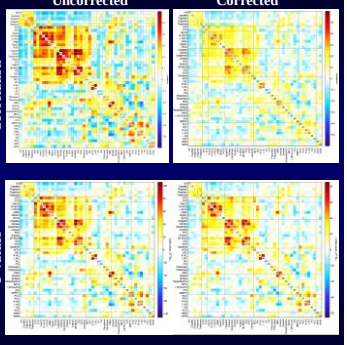
Autocorrelation

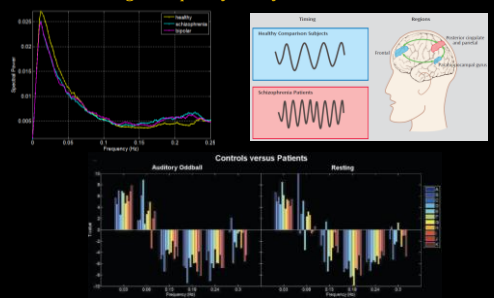




M. Arbabshirani, E. Damaraju, R. Phlypo, S. M. Plis, E. Allen, S. Ma, D. Mathalon, A. Preda, J. G. Vaidya, T. Adali, and V. D. Calhoun, "Impact of Autocorrelation on Functional Connectivity," NeuroImage, in press.

34

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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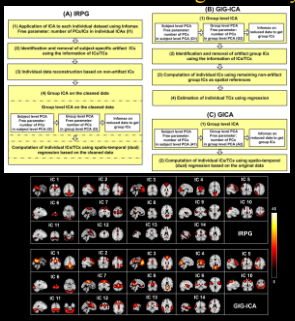
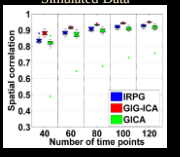
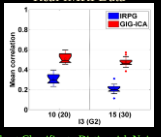
Denoising…the easy way







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.

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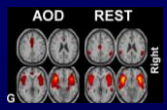
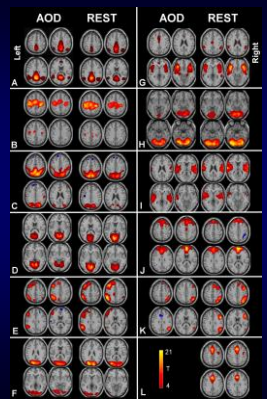


Task vs Rest

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

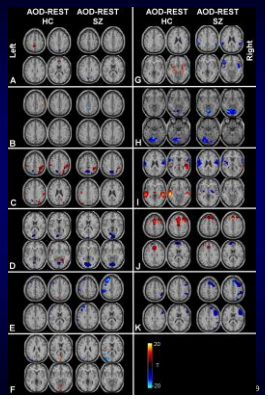


V. D. Calhoun, K. A. Kiehl, and G. D. Pearlson, "Modulation of Temporally Coherent Brain Networks Estimated using ICA at Rest and During Cognitive Tasks," *Hum Brain Mapp*, vol. 29, pp. 828-838, 2008.

Task vs Rest

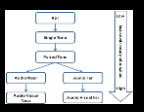
Result 2: Though similar TCNs were identified for AOD and rest, spatial and temporal task modulation was induced

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)**



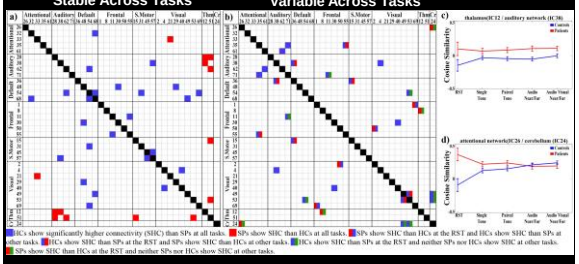
V. D. Calhoun, K. A. Kiehl, and G. D. Pearlson, "Modulation of Temporally Coherent Brain Networks Estimated using ICA at Rest and During Cognitive Tasks," *Hum Brain Mapp*, vol. 29, pp. 828-838, 2008.

Effect of Task on Intrinsic Networks in SZ vs HC



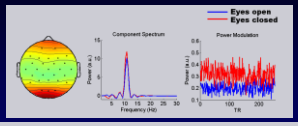
Stable Across Tasks

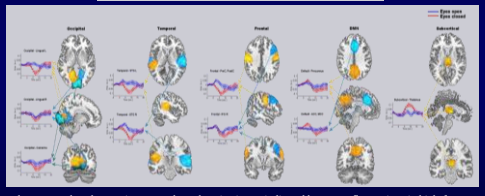
Variable Across Tasks



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



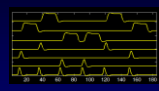


These results suggest that changes in neuronal synchronization as indicated by power fluctuations in high-frequency (>1Hz) EEG rhythms such as posterior alpha are partly mediated by widespread changes in inter-regional low-frequency (<.1Hz) functional activities detected in fMRI. They also indicate that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

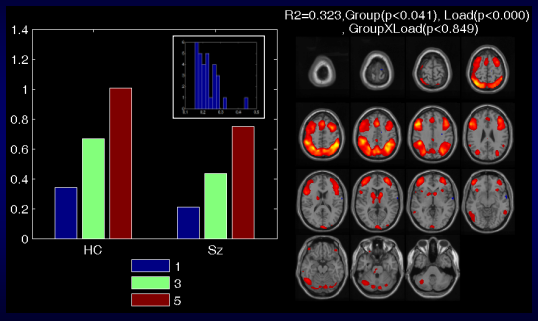
fBIRN SIRP Task

- 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 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)

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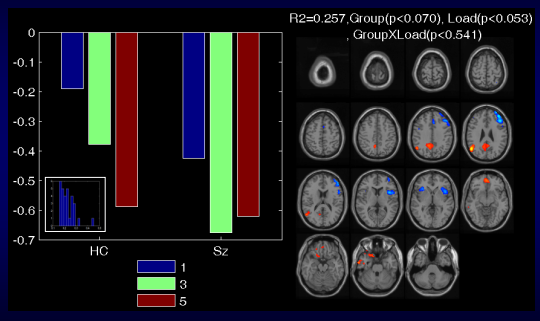
Component 2: Right Frontal, Left Parietal, Post. Cing.



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

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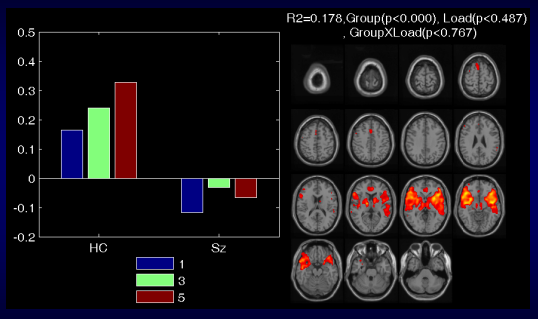
Component 3: Temporal Lobe



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

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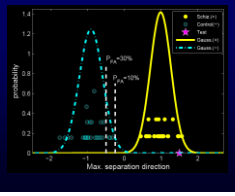

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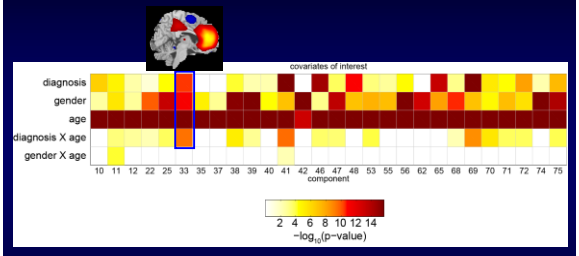
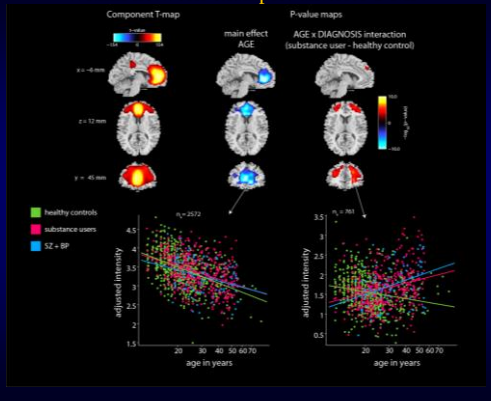
Relationship to Disease (N=1140)

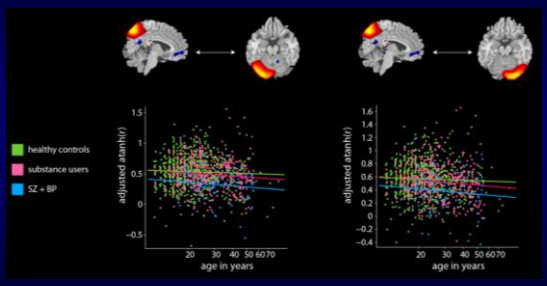


Healthy (N=590)
Substance Use (N=469)
Schizo/BP (N=81)

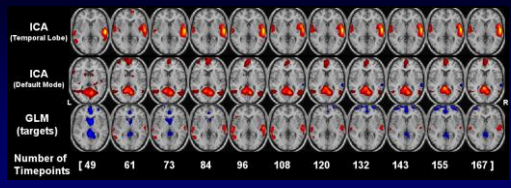
Within network example: anterior DMN

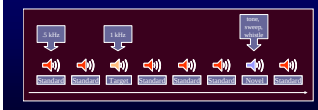


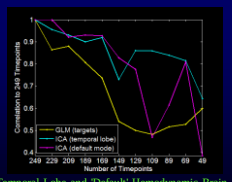
Between network example: precuneus-cerebellar connectivity



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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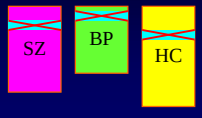
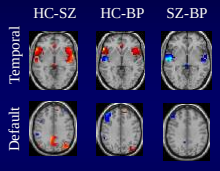
3-way Classification of Schizophrenia, Bipolar, Control

1) Remove subjects from each group



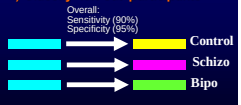
2) Identify regions which maximally separate remainder



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 $D_{bipo,i} > D_{schizo,i}$

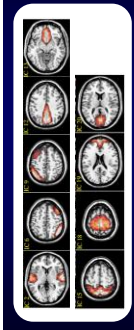
4) Classify 'left out' participants



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.

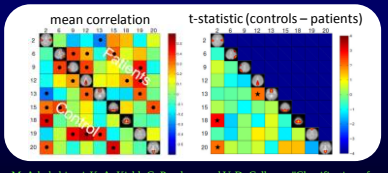
Diagnostic Classification: FNC

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.

Schizophrenia Classification w/ FNC/SBM

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:

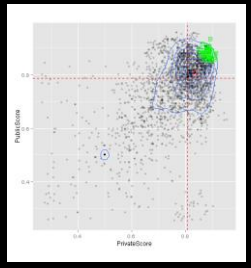
Multi-modal brain imaging data (functional and structural MRI)

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 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).

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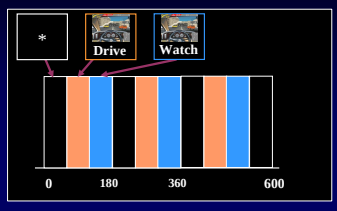
Simulated Driving Paradigm



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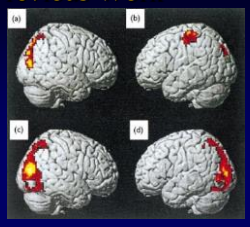
Previous Work

- 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."

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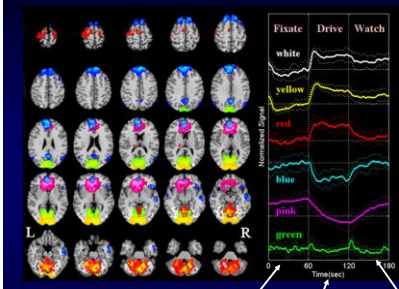
Baseline Simulated Driving Results



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.

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Outline of Talk

- Approaches
  - Seeds vs Components
  - Intro to ICA
  - Group ICA vs single subject
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  - Impact of (micro) motion
  - Autocorrelation
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- Other issues
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  - Overlap of networks
- Applications
  - Diagnostic
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- Dynamic connectivity
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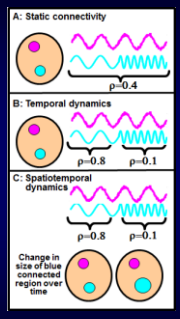

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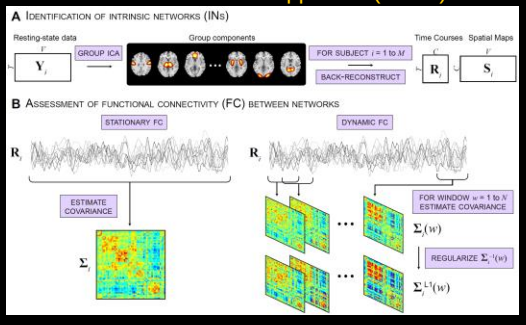
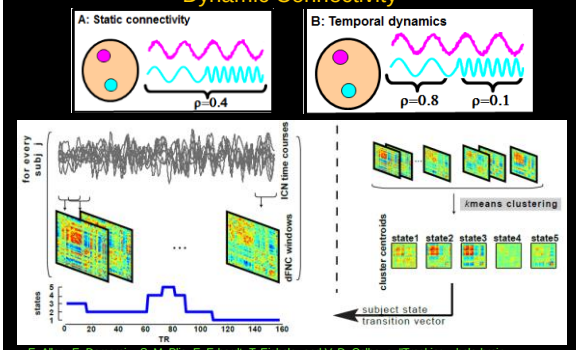
The windowed FNC approach (dFNC)



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.

V. D. Calhoun, R. Miller, G. D. Pearlson, and T. Adali, "The chronnectome: Time-varying connectivity networks as the next frontier in fMRI data discovery," Neuron, vol. 84, pp. 262-274, 2014.

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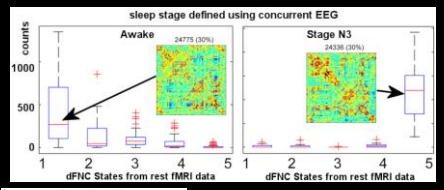
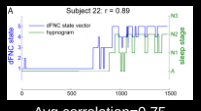
Dynamic States & Sleep Staging





Avg correlation=0.75

Resting state functional MRI data was collected from 55 subjects for 50 minutes each (1500 volumes, TR=2.08 s) with a Siemens 3T Trio scanner while the subjects transitioned from wakefulness to at most sleep stage N3.

E. Damaraju, E. Tagliazucchi, H. Laufs, and V. D. Calhoun, "Dynamic functional network connectivity from rest to sleep," in OHBM, Honolulu, HI, 2015.

E. Tagliazucchi and H. Laufs, "Decoding wakefulness levels from typical fMRI resting-state data reveals reliable drifts between wakefulness and sleep," Neuron, vol. 82, pp. 695-708

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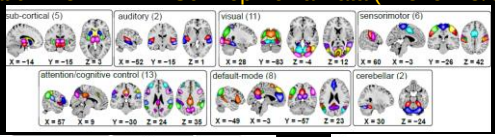
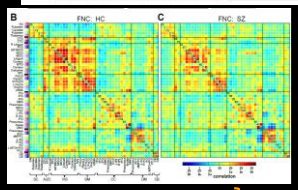
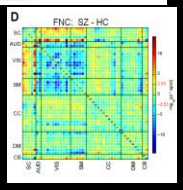
Static FNC in fBIRN Schizophrenia Data (n~315 HC/SZ)





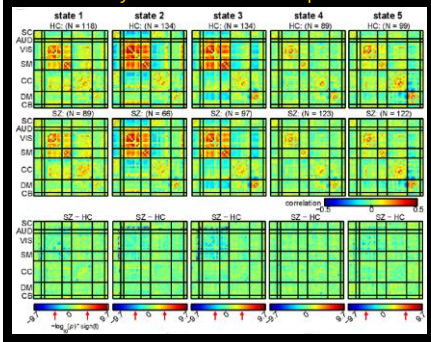


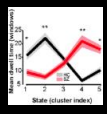
* Hyper: thalamus-sensorimotor
* Hypo: thalamus-(prefrontal-striatal-cerebellar)

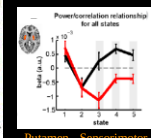
} Inversely related (less so in patients)
Sensoriomotor region & cortical-subcortical antagonism co-occur with thalamic hyperconnectivity

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





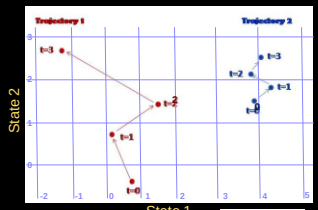


Putamen - Sensorimotor hypo-connectivity

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

Meta-state approach: add flexibility by allowing occupancy of multiple states at the same time

Imagine the two trajectories from the previous slide moving In an integer lattice. They now have a 2D a parameterization involving the lattice point they are closest two at each moment in time.

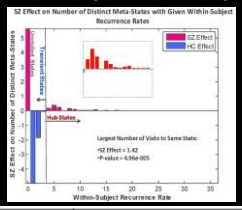


Trajectory in 2D integer-lattice *not* constant: changes at every timepoint, moves L1 distance 6

Trajectory in 2D integer-lattice almost constant moves L1 distance 1

V. D. Calhoun, R. Miller, G. D. Pearlson, and T. Adalı, "The chronnectome: Time-varying connectivity networks as the next frontier in fMRI data discovery," Neuron, vol. 84, pp. 262-274, 2014

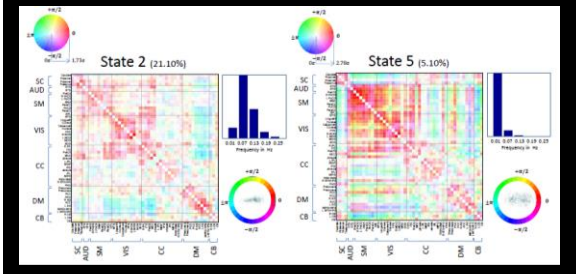
Schizophrenia reduced dynamic fluidity & dynamic range



		Method of Decomposing wFNCs into BCPs			
		tICA	sICA	PCA	K-means
Dynamism Measure	Number of Distinct Meta-States	-5.65 (p=4.11e-006)	-2.63 (p=0.007)	-5.78 (p=6.03e-008)	-6.52 (p=1.52e-007)
	Number of Meta-State Changes	-2.20 (p=6.62e-008)	-1.29 (p=2.71e-006)	-2.22 (p=2.09e-010)	-5.57 (p=8.23e-007)
	L2 Span of Realized Meta-States	-5.37 (p=1.41e-006)	-2.59 (p=0.003)	-4.80 (p=5.88e-007)	-2.71 (p=1.52e-009)
	Total Distance Traveled in State Space	-9.19 (p=1.89e-006)	-4.29 (p=0.0008)	-6.78 (p=1.76e-006)	-10.04 (p=5.31e-007)

V. D. Calhoun, R. Miller, G. D. Pearlson, and T. Adalı, "The chronnectome: Time-varying connectivity networks as the next frontier in fMRI data discovery," Neuron, vol. 84, pp. 262-274, 2014.

Capturing additional information via time-frequency analysis



M. Yaesoubi, E. A. Allen, R. Miller, and V. D. Calhoun, "Dynamic coherence analysis of resting fMRI data to jointly capture state-based phase, frequency, and time-domain information," NeuroImage, in press.

V. D. Calhoun, R. Miller, G. D. Pearlson, and T. Adalı, "The chronnectome: Time-varying connectivity networks as the next frontier in fMRI data discovery," Neuron, vol. 84, pp. 262-274, 2014

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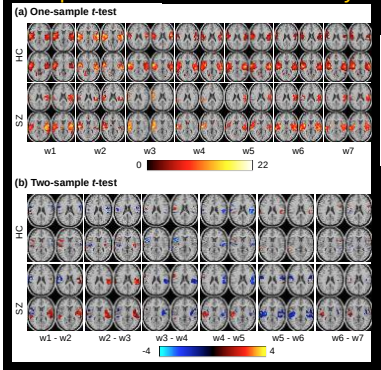
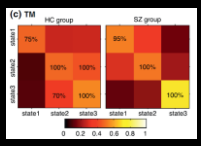
Spatial Patterns of Connectivity are also Dynamic





- 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

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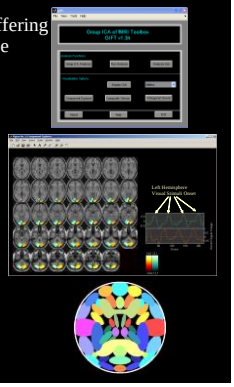
A Few ICA Software Packages (RAM)

- 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.
V. D. Calhoun, R. Silva, T. Adalı, and S. Rachakonda, "Comparison of PCA approaches for large N group ICA," NeuroImage, in press,

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

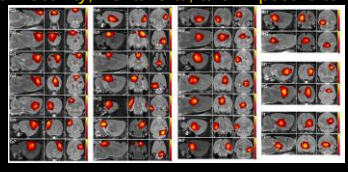


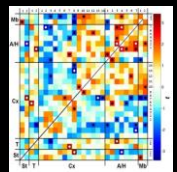
MIALAB
MEDICAL IMAGE ANALYSIS LAB

http://mialab.mrn.org

R01EB005846 , R01EB006841, P20GM103472, 1U01NS082074, 5R41MH100070, R01MH094524, 1R01MH104680

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





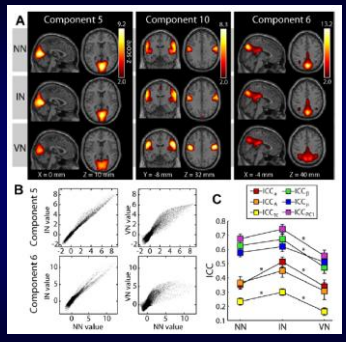
PCP exposure induced a long-term spatial memory deficit, but did not impair subsequent spatial learning.

• 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.*

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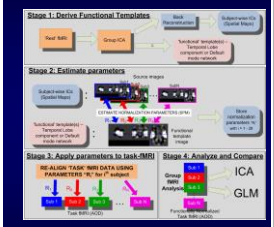
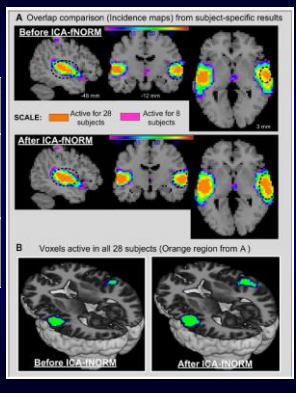
Functional Normalization (fNORM)





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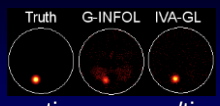
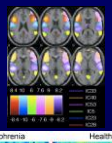
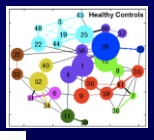
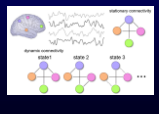
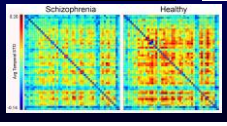
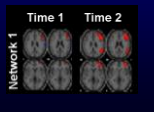
Current Directions

- Individual variability



- Dependencies in space, time, space/time

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