Group ICA of FMRI: Introduction and Review of Current Work

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Modeling the Brain?



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.

Outline

- ICA of fMRI
- ICA and Group Inference
 - Introduction
 - Approaches
 - Simulations
- Examples
- Conclusions









General Linear Model (GLM)



A little more detail



ICA Example



ICA Halloween (Un)Mixer! x = A ×



Candle out



ICA of fMRI

The ICA model assumes the fMRI data, **x**, is a linear mixture of statistically independent sources, **s**.

 $\mathbf{x} = \mathbf{As}$ $p(s_1, s_2) = p(s_1) p(s_2)$

The goal of ICA is to separate the sources given the mixed data and thus determine the **s** and **A** matrices



ICA of fMRI Data



Artifact Detection and Reduction

Eye movements



N/2 Nyquist Ghost



Note: Preprocessing may differ for artifact hunting approach

Source: Christian Beckmann's "Little Shop of fMRI Horrors":

Ambiguities of ICA: Sorting/Scaling

- ICA is modeling the data as a linear combination of images and time courses
- Why is sorting necessary?
 - Permutation ambiguity: X=AS=(AP⁻¹)(PS)
- Why is scaling/calibration necessary?
 - Scaling ambiguity: X=AS=(AM⁻¹)(MS)

$$data = tc_1 * im_1 + tc_2 * im_2 + E$$

$$data = (a * tc_1) * \left(\frac{1}{a} * im_1\right) + (b * tc_2) * \left(\frac{1}{b} * im_2\right) + E$$

Number of Components

- Too many -> over-splitting of the components
- Too few -> over-clumping of the components
- How to choose?
 - Between 20 and 40 appears to be a reasonable choice for typical fMRI experiment
 - Tools for estimating this number are available in GIFT and other ICA software programs (AIC/MDL/BIC)
 - Post-ICA clustering is also used to address this issue

Number of Components (Order Selection) $AIC(N) = -2M(K-N)\mathcal{L}(\hat{\theta}_N) + 2\left(1 + NK + \frac{1}{2}(N-1)\right)$ $MDL(N) = -M(K-N)\mathcal{L}(\hat{\theta}_N) + \frac{1}{2}\left(1 + NK + \frac{1}{2}(N-1)\right) \ln M$



$$\boldsymbol{\mathcal{L}}\left(\hat{\theta}_{N}\right) = \ln\left(\frac{\left(\lambda_{N+1}...\lambda_{K}\right)^{\frac{1}{K-N}}}{\frac{1}{K-N}\left(\lambda_{N+1}+...+\lambda_{K}\right)}\right)$$

M=number of voxelsK=number of time pointsN=number of sources $\lambda=eigenvalues from PCA$

[V. D. Calhoun, T. Adali, G. D. Pearlson, and J. J. Pekar, "A Method for Making Group Inferences From Functional MRI Data Using Independent Component Analysis," *Hum. Brain Map.*, vol. 14, pp. 140-151, 2001.]

Correction for correlated samples [Y. Li, T. Adali, and V. D. Calhoun, "Sample Dependence Correction For Order Selection In FMRI Analysis," in *Proc. ISBI*, Washington, D.C., 2006.]

"Hybrid" fMRI Experiment







Mixed with fMRI Data

Impact of preprocessing/algorithms/etc

Criterion: Kullback-Leibler (KL) divergence

 $D(\mathbf{s} \| \mathbf{u}) = \int p_{\mathbf{s}}(\xi) \ln\left(\frac{p_{\mathbf{s}}(\xi)}{p_{\mathbf{u}}(\xi)}\right) d\xi$

- Define sources
- Generate sources
- For all:
 - Add noise
 - Smooth
 - Reduce (PCA, cluster, etc.)
 - Unmix (Info., fastICA, jade, etc.)
 - Evaluate (KL)
- min(KL) is winner



Analysis Blocks Performed, CNR = 0.41932

2008 IPAM MBI

V.D.Calhoun, T.Adali, and G.D.Pearlson, "Independent Components Analysis Applied to FMRI Data: A Generative Model for Validating Results," Journal of VLSI Signal Proc. Systems, 2004.

Comparison of Different Algorithms



N. Correa, T. Adali, Y. Li, and V. D. Calhoun, "Comparison of Blind Source Separation Algorithms for FMRI Using a New Matlab Toolbox: GIFT," in *Proc. ICASSP*, Philadelphia, PA, 2005.

N. Correa, T. Adali, and V. D. Calhoun "Performance of Blind Source Separation Algorithms for fMRI Analysis," Mag. Res. Imag., 2006.

Consistency of Infomax



N. Correa, T. Adali, Y. Li, and V. D. Calhoun, "Comparison of Blind Source Separation Algorithms for FMRI Using a New Matlab Toolbox: GIFT," in *Proc. ICASSP*, Philadelphia, PA, 2005.

N. Correa, T. Adali, and V. D. Calhoun "Performance of Blind Source Separation Algorithms for fMRI Analysis," Mag. Res. Imag., 2006.

Clustering of five algorithms using ICASSO



Infomax, FICA1, FICA2, FICA3, JADE

N. Correa, T. Adali, and V. D. Calhoun "Performance of Blind Source Separation Algorithms for fMRI Analysis," Mag. Res. Imag., 2006.

Stationarity



Fig. 2. Percentage of nonstationary time-courses for a 20 component decomposition of six fMRI datasets. The data was segmented into 2, 5, 10, and 20 segments and the WSS quotient was calculated for all cases. A large number of components were nonstationary, with the largest percentage jump occurring between 2 and 5 segments.



Fig. 5. Percentage of spatial components who matched with a cc greater than 0.5, 0.8, and 0.9. The data were divided into three segments and decomposed using a reduction to 20 components. The components from the first and third segment were matched by their correlation.

G. H. Turner and D. B. Twieg, "Study of temporal stationarity and spatial consistency of fMRI noise using independent component analysis," IEEE Trans Med Imaging, vol. 24, pp. 712-718, Jun 2005.

Robustness of 'modes'







A Few Software Packages

- 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

(<u>http://www.fmrib.ox.ac.uk/analysis/research/mel</u> <u>odic/</u>):

- C
- FastICA+
- Complete Package
- AnalyzeFMRI

(<u>http://www.stats.ox.ac.uk/~marchini/software.ht</u><u>ml</u>)

- R
- FastICA
- BrainVoyager(<u>http://www.brainvoyager.com/</u>)
 - Commercial
 - FastICA
 - Complete Package

- FMRLAB (<u>http://www.sccn.ucsd.edu/fmrlab/</u>)
 - matlab
 - infomax algorithm
 - fMRI specific with additional tools
- ICALAB
 - matlab
 - multiple ICA algorithms
 - not fMRI specific although one fMRI example included
- GIFT (<u>http://icatb.sourceforge.net</u>)
 - matlab
 - >9 ICA algorithms (more coming) including infomax and fastICA
 - Constrained ICA algorithms
 - Visualization tools and sorting options.
 - Sample data and a step-by-step walk through

Outline

• ICA of fMRI

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Group ICA

?













Group ICA Approaches



- 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.

Comparison of Several Approaches

• Group ICA (Calhoun et al., 2001) $X_i = A_i S_i$

- \mathbf{X}_i ($T \times V$) observation from the *ith* subject
- A_i (T × q) mixing matrix for the *i*th subject
- **S** $(q \times V)$ statistically independent group spatial source

• Tensor group ICA model (Beckmann and Smith, 2005)

$$\mathbf{X}_{i} = \sum_{\ell=1}^{q} \mathbf{a}_{\ell} \otimes \mathbf{s}_{\ell} \otimes \mathbf{c}_{\ell} + \mathbf{E}_{i} \qquad \Leftrightarrow \quad x_{itv} = \sum_{\ell=1}^{q} a_{t\ell} s_{v\ell} c_{i\ell} + \varepsilon_{itv}$$

- \mathbf{a}_{ℓ} (T ×1) latent time series associated with the ℓth IC
- \mathbf{s}_{ℓ} (V ×1) spatial signal map of the ℓth IC
- \mathbf{c}_{ℓ} (N ×1) subject loading vector of the ℓth IC

• Unified Tensor ICA (Guo, In Press)

where

$$\mathbf{X} = \mathbf{M}\mathbf{S} + \mathbf{E},$$

$$\mathbf{X} = \begin{bmatrix} \mathbf{A}_{1} \\ \vdots \\ \mathbf{X}_{N} \end{bmatrix} (TN \times V \text{ voxels}) \quad :\mathbf{X}_{i} \ (T \times V) \text{ is the observation from the ith subject}$$

$$\mathbf{S} \ (q \ \mathrm{ICs} \times V \text{ voxels}) \quad :\text{statistically independent group spatial sources}$$

$$\mathbf{M} = \begin{bmatrix} \mathbf{A}_{1} \\ \vdots \\ \mathbf{A}_{N} \end{bmatrix} (TN \times q \ \mathrm{ICs}) \quad :\text{group mixing matrix, where } \mathbf{A}_{i} \ (T \times q) \text{ is the mixing matrix}$$

$$\mathbf{E} = \begin{bmatrix} \mathbf{E}_{1} \\ \vdots \\ \mathbf{E}_{N} \end{bmatrix} (TN \times V \text{ voxels}) \quad : \quad \mathbf{E}_{i} \ (T \times V) \text{ is noise from the ith subject}$$

Group ICA of fMRI Toolbox (GIFT)

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Group ICA of fMRI Toolbox GIFT					
Analysis Functions Group ICA	Single Subject ICA	Analysis Info			
Visualization Options	Display GUI				
Component Explorer	Composite Viewer	Orthogonal Viewer			
Help		Exit			

950+ unique downloads http://icatb.sourceforge.net

Funded by NIH 1 R01 EB 000840 (to V. Calhoun)

Major Contributors: Tülay Adalı – University of Maryland Andrzej Cichocki, RIKEN, Japan



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Group ICA



In equations

• Single subject maps can be calculated by backreconstructing from the ICA analysis of all the subjects

$$\begin{bmatrix} \mathbf{G}_{1} \hat{\mathbf{A}}_{1} \\ \vdots \\ \mathbf{G}_{M} \hat{\mathbf{A}}_{M} \end{bmatrix} \hat{\mathbf{S}} = \begin{bmatrix} \mathbf{F}_{1}^{-1} \mathbf{Y}_{1} \\ \vdots \\ \mathbf{F}_{M}^{-1} \mathbf{Y}_{M} \end{bmatrix}$$

$$\hat{\mathbf{S}}_i = \left(\mathbf{G}_i^{-1}\hat{\mathbf{A}}_i\right)^{-1}\mathbf{B}_i\mathbf{X}$$

single-subject map

full decomposition

$$\mathbf{F}_{i}\mathbf{G}_{i}\hat{\mathbf{A}}_{i}$$

single-subject time course

$$\hat{\mathbf{s}}_{1i} \geq \tau$$

hypothesis test for component 1 (first row of \hat{S}_i)

• These maps can then be tested for a significant amplitude by using a voxel-by-voxel t-test on the single subject maps (thus providing a random effects inference of the amplitude)

Simulation



Nine simulated source maps and time courses were generated, followed by an ICA estimation. The red lines indicate the t<4.5 boundaries

Are the data separable? (Simulation)

Individual ICA Maps Back-Reconstructed ICA Maps Source #2 Source #1

• A natural concern is whether the backreconstructed maps from individual subjects will be influenced by the other subjects in the group analysis

• A simulation was performed in which one of the nine "subjects" had a structured, source #2 map (whereas all of the nine "subjects" had a similar, source #1 map).

• As one can see, in this example, the back-reconstructed ICA maps are very close to the individual maps and there appears to be little influence between subjects

The Stationarity Assumption

Stationary source S common to all five "subjects"



ICA results source #1 source #2

Sources S1-S5 differing across the five "subjects"

• The ICA estimation requires the data to be stationary across subjects

•Some signals in the data (e.g. physiologic noise) will most likely *not* be stationary

• A simulation was performed to examine how non-stationary sources would affect the results

•One stationary signal (fMRI activation) and one non-stationary signal were simulated for a five-subject analysis

• The ICA results reveal that the fMRI activation is preserved

Visual Stimulation Task

• Scan Parameters

- 9 slice Single-shot EPI
- FOV = 24 cm, 64x64
- TR=1s, TE=40ms
- Thickness = 5/.5 mm
- 360 volumes acquired
- Preprocessing
 - Timing correction
 - Motion correction
 - Normalization
 - Smoothing
- ICA
 - An ICA estimation was performed on each of the nine subjects
 - Data were first reduced from 360 to 25 using PCA, the data were concatenated and reduced a second time from 225 to 20 using PCA
 - An ICA estimation was performed after which single subject maps and time courses were calculated
 - Group averaged maps were thresholded at t<4.5, colorized, and overlaid onto an EPI scan for visualization



Are the data separable? (fMRI experiment)



V.D. Calhoun, T. Adali, G.D. Pearlson, and J.J. Pekar, "A Method for Making Group Inferences From Functional MRI Data Using Independent Component Analysis," *Hum. Brain Map.*, vol. 14, pp. 140-151, 2001.

Comparison with GLM Approach



V.D. Calhoun, T. Adali, G.D. Pearlson, and J.J. Pekar, "A Method for Making Group Inferences From Functional MRI Data Using Independent Component Analysis," *Hum. Brain Map.*, vol. 14, pp. 140-151, 2001.

Temporal Sorting

• A 'second-level' or group analysis involves taking certain parameters (estimated by ICA) such as the amplitude fit for fMRI regression models, or voxel weights, and testing these within a standard GLM hypothesis-testing framework





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

Temporal Sorting: 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: <u>www.nbirn.net;</u> NCRR (NIH), 5 MOI RR 000827 (2002-2006) and 1 U24 RR0219921 (2006 onwards)

Component 1: Bilateral Frontal/Parietal



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

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



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

Component 3: Temporal Lobe



Spatial Sorting: Example 1

- Using wfu pickatlas to define mask using regions reported in Raichle 2001 paper
 - Posterior parietal cortex BA7
 - Occipitoparietal junction BA 39
 - Precuneus
 - Posterior cingulate
 - Frontal Pole BA 10
- Smooth in SPM with same kernel used on fMRI data
- Sort in GIFT using spatial sorting



Garrity, A., Pearlson, G.D., McKiernan, K., Lloyd, D., Kiehl, K.A., and Calhoun, V.D. (2007). Aberrant 'default mode' functional connectivity in schizophrenia. AmJPsychiatry.

ICA to identify 'Default Mode' Network



Garrity, A., Pearlson, G.D., McKiernan, K., Lloyd, D., Kiehl, K.A., and Calhoun, V.D. (2007). Aberrant 'default mode' functional connectivity in schizophrenia. AmJPsychiatry.



Spatial Sorting: Example 2

- Classification of Schizophrenia
 - Mapping the brain via intrinsic connectivity





TL & DM Components for BP, SZ, and HC



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.*, In Press.

Task-relatedness of spatial 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.*, In Press. 2008 IPAM MBI

Algorithm: Leave-1-out

1) Remove 1 from each group



2) Identify regions which maximally separate remainder



3: Develop 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



Classification Results



Results show a high average sensitivity (90%) and specificity (95%). Controls were correctly classified 95% of the time, schizophrenia patients 92%, and bipolar patients 81%.

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.*, In Press. 2008 IPAM MBI



Three Review Articles



Current Opinion in Neurobiology 2003, 13:620-629

Independent component analysis of functional MRI: what is signal and what is noise?

Martin J McKeown*[†], Lars Kai Hansen[‡] and Terrence J Sejnowski^{§#}

4th International Symposium on Independent Component Analysis and Blind Signal Separation (ICA2003), April 2003, Nara, Japan

ICA OF FUNCTIONAL MRI DATA: AN OVERVIEW

V. D. Calhoun^{§ ∇o}, T. Adali^{*}, L. K. Hansen¹, J. Larsen¹, J. J. Pekar^{$\dagger \ddagger$}



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Unmixing fMRI with Independent Component Analysis

Using ICA to Characterize High-Dimensional fMRI Data in a Concise Manner.

BY VINCE D. CALHOUN AND TÜLAY ADALI

IEEE ENGINEERING IN MEDICINE AND BIOLOGY MAGAZINE

MARCH/APRIL 2006

UNCTIONAL MAGNETIC RESONANCE IMAGING

Incorporation of Prior Information

- Semi-blind ICA [V. D. Calhoun, T. Adali, M. Stevens, K. A. Kiehl, and J. J. Pekar, "Semi-Blind ICA of FMRI: A Method for Utilizing Hypothesis-Derived Time Courses in a Spatial ICA Analysis," *NeuroImage*, vol. 25, pp. 527-538, 2005.]
- Adaptive ICA [B. Hong, G. D. Pearlson, and V. D. Calhoun, "Source-Density Driven Independent Component Analysis Approach for FMRI Data," *Hum. Brain Map.*, vol. 25, pp. 297-307, 2005.]
- Regularized Spectral Matching [H. Snoussi and V. D. Calhoun, "Regularized Spectral Matching for Blind Source Separation. Application to FMRI Imaging," *IEEE Trans. Signal Proc.*, vol. 53, pp. 3373-3383, 2005.]
- Feature selective ICA [Y. Li, T. Adali, and V. D. Calhoun, "Feature-Selective ICA and Its Convergence Properties," in *Proc. IEEE Int. Conf. Acoustics, Speech, Signal Processing (ICASSP)*, Philadelphia, PA, 2005.]
- Latency Insensitive ICA [V. D. Calhoun, T. Adali, J. J. Pekar, and G. D. Pearlson, "Latency (in)Sensitive ICA: Group Independent Component Analysis of FMRI Data in the Temporal Frequency Domain," *NeuroImage*, vol. 20, pp. 1661-1669, 2003.]



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Thank You!



Anaiah Christine Calhoun June 7 2008 6lb 14 oz