Overview

- Motivation
- Joint ICA
  - ERP/fMRI
  - Multitask-fMRI
  - CC-ICA/Biomarker Identification
- mCCA
  - tMRI/fMRI/ERP
- mCCA+jICA
  - sMRI+DTI+fMRI
- Parallel ICA
  - SNPs
- Parallel Group ICA
- Conclusions

Multimodal Data Collection

Brain Function (spatiotemporal, task-related)
- Task 1-N
  - EEG
  - fMRI

Brain Structure (spatial)
- T1/T2
- DTI

Genetic Data (spatial/chronosomal)
- SNP
- Gene Expression
- Other?

Covariates (Age, etc.)

A Role For Data Fusion?:

- Voxel-based
  - Correlation (Worsley 1999)
  - Straightforward, but difficult to visualize
- Region-based
  - Interregional correlation (Herwig et al., 1998)
  - Structural equation modeling (McKeown and Gonzalez-Lima, 1994; Friston et al., 2005; Strother et al., 1995)
  - Multiple regression and extensions (e.g., Kalman filters, Buchel & Friston, 1998)
  - Bayes networks, Dynamic Causal Modeling (Friston, Penny, et al., 2003)
  - Useful for model testing, does not take into account all brain regions
- Transformation-based
  - A natural set of tools for this problem include those that transform data matrices into a smaller set of modes or components
  - Singular value decomposition (Blumenfeld et al., 1991; Friston et al., 1996)
  - Partial Least Squares (McKeown, Bucholz, et al., 1995)
  - Canonical Variates Analysis (McKeown, 1991)
  - Independent Component Analysis (McKeown et al., 1996; Calhoun et al., 2001)
Why Joint/Multimodal?

In a non-joint analysis, we maximize the likelihood functions for each modality separately:

\[ w_i = \arg \max_w \log p(x_i; w_i) \]

Resulting in two unmixing parameters, that then have to somehow be fused together.

In contrast, for a joint analysis we maximize the joint likelihood function, resulting in a single fused unmixing parameter:

\[ w = \arg \max_w \log p(x; w) \]

Why Multivariate?

<table>
<thead>
<tr>
<th>Method</th>
<th>M</th>
<th>N</th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation Method</td>
<td>250</td>
<td>5</td>
<td>89</td>
<td>7</td>
<td>80</td>
<td>4</td>
</tr>
<tr>
<td>Correlation Method</td>
<td>500</td>
<td>5</td>
<td>90</td>
<td>5</td>
<td>82</td>
<td>3</td>
</tr>
<tr>
<td>Silhouette Method</td>
<td>250</td>
<td>5</td>
<td>89</td>
<td>4</td>
<td>83</td>
<td>4</td>
</tr>
<tr>
<td>Silhouette Method</td>
<td>500</td>
<td>5</td>
<td>92</td>
<td>2</td>
<td>85</td>
<td>1</td>
</tr>
</tbody>
</table>

Cross-validation performance using the top M SNP’s selected via two different methods as the basis for an N-factor principle component model.

Why Independence?

Uncorrelated: \[ E\{x_1, x_2\} = E\{x_1\} E\{x_2\} \]

Independent: \[ p(x_1, x_2) = p(x_1) p(x_2) \]

\[ \Rightarrow E\{h(x_1) h(x_2)\} = E\{h(x_1)\} E\{h(x_2)\} \]

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

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

Why Features?

• What is a feature?
  • Lower dimensional data containing information of interest
  • Examples: An image of activation amplitudes, A gray matter segmentation image, fractional anisotropy image

Advantages

• Less-computationally complex/easier to model
• Takes advantages of existing analytic approaches
• Can be used to examine inter-relationships between multiple data types at the subject level

Feature-based ICA

Meta-level ICA


A Family of Multivariate Methods

ICA algorithms are based on cost functions which utilize the higher order statistical information

- Explicit computation of higher-order statistics
  - Cumulants — e.g., JADE (Cardoso and Souloumiac, 1993)
  - Kurtosis — e.g., FastICA (Hyvärinen 1999)
- Implicit computation of higher-order statistics
  - Mutual information
  - Maximum likelihood/information maximization — e.g., Infomax (Bell and Sejnowski, 1995)
  - Nonlinear decorrelations
  - Maximization of non-Gaussianity — e.g., FastICA

and computed using matrix diagonalizations, or iteratively using natural/relative gradient, fixed-point, and Newton variate updates.
FMRI Snapshots (movie)

ERP (temporal) Components: \( T = [t_1, \ldots, t_n] \)
FMRI (spatial) Components: \( S = [s_1, \ldots, s_n] \)
ERP Timecourse Snapshot: \( M_T(v) = T \cdot S \)


Linked EEG/fMRI Results

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  • mC+ICA
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Joint Histograms: fMRI

Individual Participant Histograms

Group Average Difference Histograms (controls-patients)
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Evaluating Multiple Features

- Auditory Oddball fMRI Task
  - Target-related activity
  - Novel-related activity
- Sternberg fMRI Task
  - Recognition-related activity
- MPRAGE
  - Gray matter segmentation

Identifying the “best” combination

- Kullback-Leibler divergence: $D(s||u) = \int p_s(\xi) \ln \left( \frac{p_s(\xi)}{p_u(\xi)} \right) d\xi$
- $s, u \in \mathbb{R}^2 = \{F_{\text{SB}}, F_{\text{ADD}}, F_{\text{ADD,T}}, S_{\text{DM}}\}$

Optimal Selection of Discriminative Features

- $C = -E[\ln f(y)] + \lambda \sum \gamma_i^2$

Joint/Single GLM/ICA Imaging Biomarkers

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Prediction of cognitive scores in schizophrenia patients and controls from multimodal data

- A combination of patterns identified using functional (fMRI) and structural (sMRI) data clusters can predict cognitive scores with a cross-validated mean accuracy of 76%

MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia
HC = Healthy Control
SZ = Schizophrenia

- True MATRICS value:
  - HC: 50 ± 11
  - SZ: 31 ± 16
- Mean prediction error = 9
- Prediction accuracy is >80% for 60% of the subjects and >95% for 20% subjects

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mCCA and jICA are complementary approaches

By combining the two approaches, we can:
- Identify both feature-common and feature-distinct connections
- Make full use of the cross-information of two data sets, in order to separate sources more accurately
- Use mCCA to find features in the two datasets, then use jICA to decompose the spatial maps
- Addresses limitation of both mCCA & jICA

Comparison of jICA, mCCA, & mCCA+jICA

Group Differences HC vs SZ

<table>
<thead>
<tr>
<th>Group</th>
<th>Number (sex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC</td>
<td>116 (44 female)</td>
</tr>
<tr>
<td>SZ</td>
<td>97 (24 female)</td>
</tr>
</tbody>
</table>

Imaging: fMRI, sMRI, DTI
Site effects regressed out

Overview

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- ERP/FMRI
- Multitask-IMRI
- CC-ICA/Biomarker Identification
- mCCA
- mMR+FMRI+ERP
- mCCA+jICA
- mMR+DTI+IMRI

Parallel ICA
- SNPs
Parallel Group ICA
Conclusions

Simulation Framework for Data Fusion

- Copulas: a form of bivariate (or multivariate) distributions with uniformly distributed marginals
- Sampling from a bivariate copula leads to two sets of values (each uniformly distributed) which are associated in the way described by the specific copula
- Using the probability integral (or inverse cumulative distribution, icdf) we can assign any desired marginal distribution

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- N-wayCASH

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**Genetic Information**

- Genetic: single nucleotide polymorphism (SNP)
- Genetic copy number variation (CNV)
- Epigenetic: methylation

**Simulation**

Simulation: Designed to provide a more complete understanding of Parallel ICA while applied to generic SNP array studies. We specified the parameters for each component and input them into PLINK, an open-source whole-genome association analysis tool (http://www.burgos.uchile.cl.URLP headaches). Conditions: sample size effect, case to control ratio, SNP array size effect, case-related SNPs vs total SNPs, site size, correlation strength between phenotypes and genotypic effects.

Simulation results support the parallel ICA, in general, is able to extract more accurately the components and connections than a correlation test, in particular for brain linkages. Results also indicate that the rate of sample size to SNP size should be at least 6:1. However, when the data have a low case rate or case vs. control rates, the correlation test provides results stable enough with lower accuracy.


**Genomic Information**

- SCHizophrenia patients and healthy controls
- MCIC data: Boston, Iowa, Minnesota and New Mexico
- Genome-wide 1M SNP data - Tagall coding (AA, AB, or BB)
- fMRI sensorimotor task: Block design motor response to auditory stimulation
- SNP data
  - Subject control: heterozygosity, nearest neighbor, 2nd degree or closer relatives, duplication
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  - Other subject excluded
- Data2: 208 subjects with SNPs (773735 SNPs) and fMRI data (52322 voxels)


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**Parallel ICA: Two Goals**

- Identify Hidden Features
- Identify Linked Features

**Identified fMRI component**

- Brain region: Superior Temporal Gyrus
- Brain region: Inferior Parietal Lobule
- Brain region: Medial Frontal Gyrus
- Brain region: Postcentral Gyrus

**Resulting Linked Component**

- fMRI component number = 8, SNP component number = 5
- One pair of linked components is identified, with p-value passing Bonferroni correction

<table>
<thead>
<tr>
<th>fMRI component index</th>
<th>SNP component index</th>
<th>t-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>-0.065</td>
<td>3.49E-01</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0.042</td>
<td>5.48E-01</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0.099</td>
<td>5.15E-01</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>-0.138</td>
<td>4.54E-02</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0.141</td>
<td>4.16E-02</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>-0.128</td>
<td>6.44E-02</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>0.178</td>
<td>9.95E-03</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>0.282</td>
<td>3.39E-05</td>
</tr>
</tbody>
</table>


**Epigenetic Information**

- Methylation

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Conduct pathway analysis and functional annotation clustering based on identified 94 genes.

IPA (Ingenuity Pathway Analysis) identifies “Schizophrenia of humans” as one of the top biomolecules, involving 11 genes.

IPA also identifies a number of significant canonical pathways, four of which are related to neurotransmitter signaling.

David’s Bioinformatics Resource reports the most significant cluster to be associated with schizophrenia.

Summary of SNP Results

- Conduct pathway analysis and functional annotation clustering based on identified 94 genes.
- IPA (Ingenuity Pathway Analysis) identifies “Schizophrenia of humans” as one of the top biomolecules, involving 11 genes.
- IPA also identifies a number of significant canonical pathways, four of which are related to neurotransmitter signaling.
- David’s Bioinformatics Resource reports the most significant cluster to be associated with schizophrenia.

Genetics and P3 ERP generation

- Subjects: 41 healthy subjects (24 female, 17 male).
- EEG collected during AOD task, target/novel ERPs extracted.
- Blood sample collected, genotyped 384 SNPs from 222 genes 6 physiological systems.

ERP Topography & SNP Associations

- Subjects: 41 healthy subjects (24 female, 17 male).
- EEG collected during AOD task, target/novel ERPs extracted.
- Blood sample collected, genotyped 384 SNPs from 222 genes 6 physiological systems.

Pathway Analysis

Parallel ICA w/ Reference

sMRI/SNP

Structural deficits in brain regions consistently implicated in previous schizophrenia reports, including frontal and temporal lobes and thalamus, were related to SNPs in 50 genes, functionally associated with schizophrenia risk and/or involved in normal CNS development, including ACT, PIS, SLCAAI, DRD2, CHRM2, and ADORA2A.

- A. sMRI component – A (group difference)
- B. sMRI component – B (linked, but no group difference)
pICA-R: Schizophrenia & ANK pathway

3-way parallel ICA

Results (N=112, fMRI, sMRI, 65K SNPs in coding genes)

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Parallel Group ICA: Concurrent EEG/fMRI

Parallel Group ICA: Concurrent EEG/fMRI

The SNC results for component pairs that are $r < 0.4$. The edges in red refer to components pairs that survived age adjustment. The correlation coefficient values are adjacent to the edges.

L. Wu, V. D. Calhoun, R. Jung, and A. Caprihan, “Connectivity-based Whole Brain Dual Parcellation by Group ICA reveals Tactile Interactions and Decreased Connectivity in Schizophrenia,” Brain Imaging, in press.


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
• You do not need separate MCCA/CCA and IVA figures. IVA includes MCCA and CCA both. IVA takes all-order statistics into account and when it is used with the Gaussian model (hence taking one 2nd order stats) it reduces to MCCA—which includes CCA of course.

• Then, you need two models for IVA as well, one for associations among components and one for associations among mixing matrix columns. For the latter, you will need to consider the transposed form of the data matrices—which you have for MCCA.

• This will simplify the figures you have and also eliminate the unnecessary correlated-dependent distinction. Just consider IVA as a generalization of MCCA to higher-order (all-order) statistics and only consider dependence, which reduces to linear dependence (correlation) with Gaussian model—and equivalently to MCCA.

Abbreviations:
F: frontal lobe
P: parietal lobe
T: temporal lobe
O: occipital lobe
SLF: Superior longitudinal fasciculus
CGC: Cingulum
CST: Corticospinal tract
UF: Uncinate fasciculus
IPD: Inferior fronto-parietal fasciculus
ILF: Inferior longitudinal fasciculus
ATR: Anterior thalamic radiation