Using ICA to analyze fMRI data of multiple subjects raises some questions:

- How are components to be combined across subjects?
- How should the final results be thresholded and/or presented?

### Group ICA Approaches

#### Approach 1
- Separate ICA analysis for each subject
- Must select which components to compare between the individuals

#### Example
- Press buttons (1-4) to indicate choice
- 15 “events”
ICA revealed a large network of similar areas including:
- frontal eye fields
- supplementary motor areas
- visual association
- thalamic
- and an
- (unexpectedly) large cerebellar activation
- bilateral inferior parietal regions were deactivated (not shown)

ICA also revealed areas not identified by SPM including:
- primary motor (green)
- visual association (red)
- basal ganglia (green w/ outline)
- superior parietal regions (blue)

SPM revealed a large network of areas including:
- frontal eye fields
- supplementary motor areas
- visual association
- thalamic, and an
- (unexpectedly) large cerebellar activation
- bilateral inferior parietal regions were deactivated (not shown)

Data ICA Back-reconstruction

**ICA: Single Subject**

The ICA maps from each subject are shown for the visual and basal ganglia components are depicted along with their time courses (basal ganglia in green and visual in pink)

Note that the visual time course precedes the motor time course.

**Approach 2**

- **Group ICA (stacking images)**
  - Components and time courses can be directly compared

- **Event-Averaged Time Courses**
  - Time courses from selected voxels in the raw data (a) and time courses produced by the ICA method (b).
  - In all cases the time courses are event-averaged (according to when the figure was presented) within each participant and then averaged across all ten participants.
  - Voxels from the raw data were selected by choosing a local maximum in the activation map and averaging the two surrounding voxels in the time courses.
  - Dashed lines indicate the standard error of the mean.
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)

• A natural concern is whether the back-reconstructed maps from individual subjects will be influenced by the other subjects in the group analysis.
• This 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 to no influence between subjects.

The Stationarity Assumption

• 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.
• However, it is reasonable to assume the signal of interest (fMRI activation) will 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.

Evaluation of Group ICA Methods

Comparison of multi-subject ICA methods for analysis of fMRI data

Comparison of multi-subject ICA methods for analysis of fMRI data
Default Mode Group Maps

GICA

STR

Methods

- Scan Parameters
  - 9 slice Single-shot EPI
  - FOV = 24cm, 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)

- The same slice from nine subjects when the right (red) and left (blue) visual fields were stimulated, (a) analyzed via linear modeling (LM), (b) back-reconstructed from a group ICA analysis, or (c) calculated from an ICA analysis performed on each subject separately. A transiently task-related component is depicted in green.
- The results between the two ICA methods appear quite similar and match well with the LM results as well (note that there may be small differences due to different initial conditions for the ICA estimation)

Comparison with GLM Approach


Sorting/Calibrating

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

Prenormalization

- 1) No Normalization (NN), where data is left in its raw intensity units (Calhoun, 2003)
- 2) Intensity Normalization (IN), which involves voxel-wise division of the time series means
- 3) Variance Normalization (VN), voxel-wise z-scoring of the time series (Beckmann, 2004)

Sorting/Calibrating

<table>
<thead>
<tr>
<th>Group</th>
<th>R²</th>
<th>Subject</th>
<th>Reg1</th>
<th>Reg2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.81</td>
<td>2</td>
<td>0.73</td>
<td>0.66</td>
</tr>
<tr>
<td>1</td>
<td>0.81</td>
<td>2</td>
<td>0.89</td>
<td>0.65</td>
</tr>
<tr>
<td>4</td>
<td>0.017</td>
<td>2</td>
<td>-0.19</td>
<td>-0.40</td>
</tr>
<tr>
<td>4</td>
<td>0.017</td>
<td>2</td>
<td>-0.10</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Prenormalization

- 1) No Normalization (NN), where data is left in its raw intensity units (Calhoun, 2003)
- 2) Intensity Normalization (IN), which involves voxel-wise division of the time series means
- 3) Variance Normalization (VN), voxel-wise z-scoring of the time series (Beckmann, 2004).
Result 1: AOD and rest data produced highly similar networks:

<table>
<thead>
<tr>
<th>Comp#</th>
<th>Description</th>
<th>Corr</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>19A: Default mode</td>
<td>0.9577</td>
</tr>
<tr>
<td>11</td>
<td>9B: Motor</td>
<td>0.9156</td>
</tr>
<tr>
<td>13</td>
<td>12C: Sup parietal</td>
<td>0.9142</td>
</tr>
<tr>
<td>10</td>
<td>6D: Medial visual</td>
<td>0.8628</td>
</tr>
<tr>
<td>7</td>
<td>E: Left lateral frontoparietal</td>
<td>0.8557</td>
</tr>
<tr>
<td>14</td>
<td>2F: Lateral Visual</td>
<td>0.8170</td>
</tr>
<tr>
<td>17</td>
<td>13G: Temporal2</td>
<td>0.8135</td>
</tr>
<tr>
<td>81</td>
<td>1H: Cerebellum</td>
<td>0.8059</td>
</tr>
<tr>
<td>11</td>
<td>5I: Temporal1</td>
<td>0.8048</td>
</tr>
<tr>
<td>41</td>
<td>6J: Frontal</td>
<td>0.7838</td>
</tr>
<tr>
<td>24</td>
<td>K: Right lateral frontoparietal</td>
<td>0.8170</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Comp#</th>
<th>Description</th>
<th>Corr</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>7D: Medial visual</td>
<td>1.09 (1.0)</td>
</tr>
<tr>
<td>13</td>
<td>12E: Left lateral frontoparietal</td>
<td>2.41 (1.1e-1)</td>
</tr>
<tr>
<td>14</td>
<td>2F: Lateral Visual</td>
<td>-4.34 (5.4e-4)</td>
</tr>
<tr>
<td>17</td>
<td>13G: Temporal2</td>
<td>10.29 (6.2e-12)</td>
</tr>
<tr>
<td>8</td>
<td>5H: Cerebellum</td>
<td>4.09 (1.1e-3)</td>
</tr>
<tr>
<td>11</td>
<td>5I: Temporal1</td>
<td>13.67 (1.2e-15)</td>
</tr>
<tr>
<td>41</td>
<td>6J: Frontal</td>
<td>-2.55 (8.1e-2)</td>
</tr>
</tbody>
</table>

Example 1: ‘Default Mode’ Mask
- Using wfu pickatlas to define mask using regions reported in Rachle 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

Example 2: Spatial Sorting
- Classification of Schizophrenia
- Mapping the brain via intrinsic connectivity
Robustness of ‘modes’

The Challenge
- Accurate classification requires single-subject accuracy -> very stringent requirement!
- We cannot use knowledge of the diagnosis in the development of the classification algorithm

Target

Novel

Standard

1 kHz tone, sweep, whistle

Temporal Lobe Synchrony
- Supervised Classification
  - Step 1: Select Training Group
  - Step 2: Use ICA to extract temporal lobe maps
  - Step 3: Compute within-group mean images
  - Step 4: Subtract the mean images
  - Step 5: Set a positive and negative threshold

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

Temporal Lobe Synchrony in Schizophrenia
- Step 6: Form classification measure (average the values within each boundary and subtract)
- Step 7: Optimize group discrimination (using a sensible error metric)
- Step 8: Apply classification to new data

Temporal Sorting: fBIRN SIRP Task
Component 1: Bilateral Frontal/Parietal

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

Component 3: Temporal Lobe

Example 2: Simulated Driving Paradigm

Baseline Simulated Driving Results

Previous Work


“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 committees on traffic, as well as in traffic related political decisions, are based on what drivers are supposed to do and not do during driving and do not take into account that cognitive and attentional capacity might be affected by the stress of the situation which is not supported by our results. If driving should be rather defined as an open-ended exploration of a dynamic environment, what we should do during driving is still widely open.*
SPM Results

Interpretation of Results

Functional Network Connectivity (between groups)

FNC Software

Fusion ICA Toolbox (FIT)

FMRI Snapshots (movie)
Target Stimuli

Novel Stimuli

SNPs | Genes
--- | ---
rs1800545 | ADRB2A
rs7412 | APOE
rs1128503 | ABCB1
rs1845632 | TSH
rs7420768 | ABCC1
rs344442 | GNAO1
rs4214674 | ADRB2A
rs6578993 | APOE
rs1045642 | MDH1
rs2278718 | APOE
rs764642 | PIK3C3
rs4784642 | PIK3C3
rs521674 | ADRB2A

Demo

- 3 subject ICA
  - Sorting
  - Component Explorer (split time courses, event-related average)
  - Orthogonal Viewer
  - Composite Viewer
  - Examine Regression Parameters
  - Taking Images/Timecourses from GIFT to SPM

**Comparison of multi-subject ICA methods for analysis of fMRI data**