Temporal dynamics of resting state fMRI functional connectivity

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David Amar
2013
Functional magnetic resonance imaging (fMRI)

- Blood-oxigen levels
- High spatial resolution (2-3mm$^3$)
- Low temporal resolution (2-3 secs)
- ~160,000 voxels
- ~50,000 voxels of gray matter
- High inter-signal dependency
The resting state

• Ongoing spontaneous changes in brain activity (EEG, fMRI)
• Resting state activity - a compulsive user of brain energy
• Slow correlated activity within functional networks in the resting state (i.e. RSNs)

Characterizing RSNs

- Altered RS functional connectivity (FC) associated with
  - Self reported anxiety levels in healthy subjects [Seely et. Al. 2007, Kim et. Al 2011]
- Temporal stationary traditionally assumed (seek FC over all time points)
The study of Allen et al. Cerebral cortex 2012

• N= 400 subjects (200 females)
• C=100 components->50 ICNs/RSNs

Figure 1. Illustration of analysis steps. (A) Group ICA decomposes resting-state data from M = 405 subjects into C = 100 components, C_1 = 50 of which are identified as intrinsic connectivity networks (ICNs). GICA1 back reconstruction is used to estimate the TCs (R_i) and SMs (S_i) for each subject. (B) Stationary FC between components (left, \( \Sigma_i \)) is estimated as the covariance of \( R_i \). Dynamic FC (right, \( \Sigma_i^{L1}(w) \)) is estimated as the series of regularized covariance matrices from windowed portions of \( R_i \).
Window sub-sampling to local maxima in FC variance -> 7.5±1.5 windows per subject

K=7 (7 states)

Number and % of state occurrences in time
Our questions:

- *Given a resting state network: which parts are constant and which are transient/dynamic?*
- *Core connectome stability?*
- *Transient patterns reproducibility?*
- *What can we learn from such information?*
How to address it?

- Use a predefined parcellation
- Identify stable connections ("Core" network)
- Identify unstable connections ("Dynamic" network)
- Integrate the two into a representation of FC dynamics
Preliminary attempts – core network

• Sliding window of 15 TRs (1 TR shift)
• Node = parcel with at least 5 voxels
• an edge $e(i,j)$ exists iff
  \[
  \frac{(\sum_s \text{perc}(R_w(i,j),p))/S}{S} \geq t_R
  \]
• Evaluation:
  - Network size
  - Stability within subjects (LOOCV): precision, recall, ROC, Wilcoxon ranksum pval
Stability scores

- m = model un-weighted graph
- s = sample un-weighted graph

\[
\text{precision} = \frac{|\{e_m\} \cap \{e_s\}|}{|\{e_s\}|}
\]
\[
\text{Recall} = \frac{|\{e_m\} \cap \{e_s\}|}{|\{e_m\}|}
\]

- Given a sample weighted graph s:
  Wilcoxon ranksum pval is calculated for population of \(\{w_{es}/e_s \in m\}\) vs. \(\{w_{es}/e_s \in m\}\)

- ROC score: model edges = positive class and weights = predictions
Preliminary analysis- core

- 5min RS fMRI scan, 57 male subjects
- Craddock 500 parcellation
- 25 subjects used as train set (LOOCV)
- $t_R$ (correlation thresh) = \{0.2,0.3,0.4,0.5\}
- $P$ (cor percentile) = \{5,10,15,20\}
- Whole window was also used with $t_R$ =\{0.4,0.5,0.6,0.7\}
Core – preliminary results

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<thead>
<tr>
<th>Ct</th>
<th>Perc for thresh</th>
<th>#nodes</th>
<th>#edges</th>
<th>LOO avg(R)</th>
<th>Wilcoxon pval</th>
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<td>778</td>
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Core Models

Cor thresh= 0.3, at least 85% of wins

Cor thresh=0.6
single win

665/800 edges overlap

Cor thresh= 0.3, at least 85% of wins
Core Models

Cor thresh = 0.3, at least 95% of wins

Cor thresh = 0.7, single win

~140/250 edges overlap
STD across time windows vs. average correlation

![STD across time windows vs. average correlation graph](image)

- **Correlation STD**
- **Inter parcel signal correlation**
Clustering core with Markov Clustering (MCL) - Background

- MCL = a graph clustering algorithm based on random walks
- Random walk: at each step randomly select an outgoing edge
- Upon visiting a dense cluster, high probability of covering a large fraction of it before leaving
- Markov Chain: a sequence of variables $X_1, X_2, X_3$ (e.g., transition matrix) where, given the present state, the past and future states are independent
MCL

- In MCL, two processes are alternated between repeatedly:
  - Expansion (taking the Markov Chain transition matrix powers)
  - Inflation

  \[
  \begin{pmatrix}
  0 & 1/2 \\
  1/6 & 0 \\
  1/3 & 0
  \end{pmatrix}
  \begin{pmatrix}
  1/4 & \\
  1/4 & 1/4 \\
  1/4 & 0
  \end{pmatrix}
\]

  Square, and then normalize

- Expansion allows flow to connect different regions of the graph
- Inflation strengthens intra-cluster connections and weakens inter-cluster connections
MCL Algorithm

• Input: an un-directed graph, power parameter $e$, and inflation parameter $r$
• Create associated matrix
• Add self loops (optional)
• Normalize matrix (divide vecs by norm)
• Expand by taking the $e^{th}$ power of the matrix
• Inflate by taking inflation of the resulting matrix with parameter $r$
• Repeat steps 5 and 6 until a steady state is reached (convergence)
• Interpret resulting matrix to discover clusters
MCL on core 0.6 whole window - results

- # Clusters: 88
- Average size: 4.193
- Maximum size: 23
- Minimum size: 2
- Modularity: 0.697

$|E_w(g_o)|/|E(g_o)| - |E_w(g_r)|/|E(g_r)|$

$g_o =$ observed graph

$g_r =$ random edge distrib graph

$E_w =$ group of edges within modules

Modularity range = $[-1/2, 1)$
## Core – preliminary results – test set

<table>
<thead>
<tr>
<th>Ct</th>
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Preliminary attempts – dymanic network

- Sliding window of 15 TRs (1 TR shift)
- Node = parcel with at least 5 voxels
- an edge e(i,j) exists iff
  \[
  \text{STD}(R_w(i,j)) \geq \text{STD}_p
  \]
  in at least f fraction of the subjects
  p= percentile of STDs (within subject)
  \( R_w(i,j) \)=the correlation between signals i and j in the \( w^{th} \) window
- Evaluation: network size, stability within subjects (LOOCV) (?)
Preliminary analysis- dynamic

- 5min RS fMRI scan, 57 male subjects
- Craddock 500 parcellation
- 25 subjects used
  $P(\text{min std perc}) = \{70, 80, 90\}$
Dynamic edge distributions

Frac subjects

70%

80%

90%

frac subjects

# edges
Analysis of network pairs – ModuleMap algorithm

• Interaction types can differ: **within** ("positive") vs. **between** ("negative") functional units

• Input: networks P, N with same vertex set

• Goal: summarize both networks in a **module map**
  – **Node** – module: gene/voxel set highly connected in P
  – **Link** – two modules highly interconnected in N

• **ModuleMap algorithm:**
  - Initiator (initial modules)
  - Improver (merging/excluding)
    * Different definitions for the links and the optimization objective function
    * Problems are NP hard

*DICER algorithm, Amar et al. PLoS CB 2013*
Preliminary results – ModuleMap

• Results effected mainly by dynamic graph
• Best results obtained with the 80% std dynamic graph

Bonferoni corrected p<=0.05
Module 21 to module 29 connections

Correlation across wins

Significance?

# subjects
Where are 21 and 29 in the Brain
Future plans – dynamic FC

• Healthy-Schizophrenic core comparisons
• Task-rest core comparisons
• Evaluate dynamic networks (reproducibility)
• Compare results with previous works (e.g. Allen et. Al)
• Compare subject groups in terms of dynamic patterns
• Can this add information in relation to stationary analysis?