Measuring Connectivity with RS-FMRI

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LINEAR MODELS IN FMRI
Data as a Space-Time Matrix

Signal characteristics are important, not structure.

Spatial Dimensions: $64 \times 64 \times 48 \sim 10^5$
Temporal Dimensions: $\sim 10^2$
Linear Models

\[ Y = \beta \cdot X \]

- **Data (Y)**
- **Spatial Maps**
- **Time-Courses**

**Paired spatial and temporal “components”**

**Consistent mathematical framework**
ACQUISITION & PRE-PROCESSING
## Typical Acquisition Parameters

<table>
<thead>
<tr>
<th>Acquisition Type</th>
<th>Typically:</th>
</tr>
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<tbody>
<tr>
<td>Single-shot, gradient-echo</td>
<td></td>
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Multi-slice EPI
Typical Acquisition Parameters

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| Contrast        | T2* - BOLD                                   |

Diagram showing contrast and TE relationship.
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- **2.0 mm**
- **3.5 mm**
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0.16 ~ 0.5 Hz sampling

100 ~ 1000 time points
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<tr>
<td>Condition</td>
<td>Eyes open – “think of nothing”</td>
</tr>
</tbody>
</table>
Data Pre-Processing

<table>
<thead>
<tr>
<th>Geometry</th>
<th>Filtering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Extraction</td>
<td>Spatial Smoothing</td>
</tr>
<tr>
<td>Motion Correction</td>
<td>Temporal Filtering</td>
</tr>
<tr>
<td>Distortion Correction</td>
<td>Nuisance Regression</td>
</tr>
<tr>
<td>Registration</td>
<td>Global Signal Regression*</td>
</tr>
</tbody>
</table>

STATIC FUNCTIONAL CONNECTIVITY
Static Functional Connectivity

Functional Connectivity:
Strength of connectivity
Un-directed

Fixed connectivity pattern over time
I. SEED CONNECTIVITY
Seed-Based Correlation

Connectivity as a pattern matching problem

Biswal et al., MRM 1995
Connectivity Metric: Temporal Correlation

Seed

Voxel A
\[ r = 0.74 \]
high, positive connectivity

Voxel B
\[ r = -0.15 \]
low, negative connectivity

Chang et al., NeuroImage 2010
Connectivity Metric: Coherence

**Seeds**

- Low Frequency Seed
- Seed
- High Frequency Seed

**Voxels**

- Voxel A

**Magnitude coherence** is also insensitive to phase offsets or shifts.
Defining Seeds – ROI size

- Single Voxels
- Geometric
- Data-Driven

Regions of Interest
Defining Seeds - Sources

*a priori*

Structural

Yousry et al., Brain 1997

Functional

Smith et al., PNAS 2009

Localizer Experiment

Biswal et al., MRM 1995
Results from three task-positive seed regions: IPS, FEF, and MT. Results from three task-negative seed regions: MPF, PCC, and LP. Significantly anticorrelated.

The task-negative network consists of regions commonly activated during goal-directed tasks (3, 28). One component of the task-negative network consists of regions in the PCC, retrosplenial cortex, medial prefrontal, lateral parietal, superior frontal, insula, parahippocampal gyri, inferior temporal, and cerebellar tonsils. The task-positive network consists of regions routinely activated during task paradigms, it is clear that they show greater activity at rest than during the performance of various goal-directed tasks (3, 28). One component of the task-negative network includes a set of regions exhibiting activity decreases during task performance (4–6) and thus defines two widely distributed, anticorrelated brain networks, the default network, the cerebellar tonsils, has not been previously noted. Our currently defined task-negative network includes a set of regions often referred to as a ''default system'' to connote organized through both correlated spontaneous fluctuations and task-negative networks, it is important to comment on the dichotomy routinely observed in response to attention.

We show that widely distributed neuro-anatomical networks are organized through both correlated spontaneous fluctuations and anticorrelations between networks. We have defined this as the BOLD signal. We indicate that BOLD fluctuations are correlated within two widely distributed systems and further that these two systems are largely anticorrelated.

To confirm the above impressions, the six correlation maps were corrected for multiple comparisons at a significance level of $P < 0.05$. Positive $z$-score values are significantly correlated or anticorrelated with five of the six seed regions. White contours are drawn on the conjunction map and copied onto the other maps to facilitate comparison.

The task-positive network consists of regions in the IPS and inferior parietal lobule, precentral sulcus including FEF, dorsal lateral frontal operculum, and the SMA. The task-negative network consists of regions routinely activated during directed attention, the attention system'' (IPS, FEF) active during directed attention and task-negative networks, it is important to comment on the discussion on the basis of intrinsic fluctuations in neuronal activity.
Seed-Based Correlation: Linear Model

Seed-correlation is a linear model

Data = Measured

Correlation = known input
2. SPATIAL ICA
Spatial Independent Component Analysis

Observed Mixtures

Mixtures alone: insufficient

Extra constraint: independence

Networks (sources)
Spatial ICA Statistical Model

Spatial networks are independent

Assessed with probability distributions

Space

histogram of voxel coefficients

probability density
Non-Gaussianity – Central Limit Theorem

FastICA – Non-Gaussianity
Hyvärinen et al., IEEE-NN 1999

Probabilistic ICA
Beckmann et al., IEEE-TMI 2004

InfoMax – Mutual Information
Bell et al., Neural Comp 1995

Sources
Non-Gaussian

Mixtures
More Gaussian

PCA
Even more Gaussian

ICA
Non-Gaussian

Signal Histograms

A

A+2B

not A

~A

B

3A-B

not B

~B
Spatial Independent Component Analysis

Coefficient Histograms → Mixtures

Time plays no direct role

Networks → Coefficient Histograms
These voxels are implicitly “connected” because the spatial coefficients produce a maximally non-Gaussian histogram.
Connectivity Comparison

Spatial Information
- Spatial ICA
  - Spatial coefficient distributions

Temporal Information
- Seed Correlation
  - Seed size, location
  - Temporal correlations
Space x Frequency

Time Series

Power Spectrum

Frequency (Hz)

Time (s)

Figure 1. (A) Shows the prefrontal (BA 11), dorsal anterior cingulate (BA 32), and superior parietal (BA 7) areas. The visual cortex is apparent in two large clusters at the left (BA 17-18) and right (BA 17-18) hemispheres, the middle temporal gyrus (BA 21), and the posterior cingulate (BA 23). The auditory cortex is involved mainly in the superior temporal (BA 22) area as the middle temporal (BA 21) and the posterior cingulate (BA 31) regions, which seems to be part of the default-mode network shown in Fig. 1.

Damoiseaux et al., PNAS 2006
Space x Experiment

BM (BrainMap)

Space (Activation Maps)

Experiment

Smith et al., PNAS 2009
ICA Linear Model

GLM

Measured

unknown

Known Input

Time Courses (Source Mixtures)

ICA

Measured

unknown

unknown

\[
\text{Measured} \times \text{Spatial Maps (Sources)} = \text{Time Courses (Source Mixtures)}
\]
PCA Pre-processing

Space X Time = ICA Spatial components X Mixing Matrix X Time

PCA

ICA Spatial Decomposition
ICA Time-Courses

ICA Spatial components \times \text{Mixing Matrix} \times \text{Time} = \text{ICA Component Time-courses} \times \text{ICA Spatial components}
ICA Spatial and Temporal dimensions

Temporal Dimensions: $\sim 10^2$

Spatial Dimensions: $64 \times 64 \times 48 \sim 10^5$

Gaussian or not?

300 time-points

200,000 voxels
ICA – Inputs and Dimensionality

Multiple networks simultaneously from a single decomposition

Very little user input (model free)

ICA takes a dimensionality (number of networks) input parameter

- \textit{a priori}
- maximising model evidence
- model complexity metrics: AIC/BIC/MDL

Low Dimensionality

High Dimensionality

Smith et al., Trends Cog Sci 2013
3. GRAPH METHODS
What are Graphs?

Nodes
Some spatial location
A "parcel"

node
What are Graphs?

Nodes
Some spatial location
A “parcel”

Edges
Relationship between nodes
Defined by some connectivity metric
Function connectivity \rightarrow undirected edges
What are Graphs?

**Nodes**
- Some spatial location
- A “parcel”

**Edges**
- Relationship between nodes
- Defined by some connectivity metric
- Function connectivity $\rightarrow$ undirected edges

**Degree**
- Number of connections a node has
Defining Nodes: Parcellation

Voxels

Atlas

Clustering

Multi-Modal

ICA

Craddock et al., Human Brain Mapping 2012

Glasser et al., Nature 2016

Bohland et al., PLoS One 2009

Smith et al., Trends in Cognitive Neuroscience 2013
Defining Edge Strengths

- Correlation
- Mutual Information
- Partial Correlation
- Coherence
- Patel's $\kappa$
Partial Correlation

Full Correlation
A → C strong connectivity

\[ r_{AC}^{full} = 0.58 \]

Partial Correlation
A → C weak connectivity

\[ r_{AC}^{partial} = 0.21 \]
Partial Correlation Network Matrix

Partial Correlation (Indirect)
Network Features - Hubs

Figure 1: Schematic diagram of a brain network introducing basic terminology. (a) Network consists of nodes and edges. The node degree corresponds to the number of edges that are attached to each node. (b) Network can be decomposed into communities or modules. Connections (edges) are either linking nodes within modules or between modules. Highly connected nodes are hubs, and they either connect primarily with other nodes in the same community (provincial hub) or with nodes that belong to different communities (connector hub).

Module: a subnetwork of densely interconnected nodes that is connected sparsely to the rest of the network.

Modularity: the scoring of a partition according to whether the internal densities of its modules are greater or less than the expected density structural and functional networks. Structural networks correspond to a pattern of anatomical connections, summarizing synaptic links between neurons or projections among brain regions. Most relevant for studies of the human brain are large-scale networks of interregional pathways that link cortical and subcortical gray matter regions, which taken together form the human connectome (Sporns 2013, Sporns et al. 2005). In contrast, functional networks are assembled from estimates of statistical dependencies between neuronal or regional time series data (Friston 2011). Although many different measures of functional connectivity exist (Smith et al. 2011), most human neuroimaging studies currently employ Pearson cross-correlations of hemodynamic or electrophysiological time courses. Unlike large-scale structural networks (which are thought to be stable on shorter timescales of seconds to minutes), functional networks are highly variable, exhibiting spontaneous dynamic changes during rest (Hutchison et al. 2013) as well as characteristic modulations in different task conditions (Cole et al. 2014).

Network Analysis and Modularity

Modules are encountered across a broad range of networks. They may correspond to groups of individuals in social networks, ensembles of interacting proteins, or coregulated genes in cellular networks. In this article, the term module refers exclusively to building blocks in the organization of brain networks; this usage of the term is distinct from concepts like modularity of mind in cognitive theory (Fodor 1983). Modules in networks, generally speaking, correspond to clusters of nodes that are densely connected, also called network communities (Figure 1b). Modules derive from a decomposition of the network into subcomponents that are internally strongly coupled, but externally only weakly coupled. This near-decomposability has long been regarded as a hallmark of complex systems (Simon 1962). Importantly, modules can be detected in a purely data-driven way, based only on the topology of the network, and understanding which nodes belong to which modules can yield important insights into how networks function. Although network modules seem to be easy to define, their detection presents significant obstacles and is subject to several misinterpretations and biases.
Network Features – Hubs and Centrality

Functional Connectivity Hubs

Alzheimer’s Aβ Deposition

van den Heuvel, Trends in Cog Sci 2013

google PageRank Centrality

courtesy of Wikipedia
Network Features - Communities

Community/Subgraph/Module Detection

network efficiency

Power et al., Neuron 2011

Rosvall and Bergstrom PNAS 2008

InfoMap

clustering coefficients

small-worldness

Power et al., Neuron 2011
Graph Analysis – Many Choices

Node Definition / Parcellation

Edge Metric

Feature Extraction

Table I. Comparison between anatomical atlases and clustering solutions with a similar number of clusters

<table>
<thead>
<tr>
<th>Method</th>
<th>ROIs</th>
<th>Volume</th>
<th>vPCC</th>
<th>Sim M1</th>
<th>Sim V1</th>
<th>Sim</th>
<th>V2</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAL</td>
<td>167 (34)</td>
<td>0.14 (0.04)</td>
<td>0.22 (0.05)</td>
<td>0.51 (0.06)</td>
<td>0.48 (0.10)</td>
<td>0.51 (0.10)</td>
<td></td>
</tr>
<tr>
<td>2-Level</td>
<td>115 (119)</td>
<td>0.16 (0.04)</td>
<td>0.27 (0.05)</td>
<td>0.55 (0.06)</td>
<td>0.50 (0.10)</td>
<td>0.51 (0.10)</td>
<td></td>
</tr>
<tr>
<td>Random</td>
<td>109 (36)</td>
<td>0.19 (0.04)</td>
<td>0.31 (0.05)</td>
<td>0.58 (0.07)</td>
<td>0.54 (0.11)</td>
<td>0.55 (0.09)</td>
<td></td>
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**RESULTS**

Graph Analysis

**Node Definition / Parcellation**

- Whole brain clustering of resting state data was performed using every combination of similarity metric, instead of a group level clustering method. The principal components analysis (PCA) was used to summarize voxel timecourses.

**Feature Extraction**

- Using this code, we can describe the walk in the lower right corner. The Huffman code illustrated here is an efficient way to do so. The 314 bits shown under the network describe the sample trajectory.

**Figure 3.**

(A) A basic approach is to give a unique name to each module, such that important structures have unique names. The orange line shows one sample trajectory.

- Reporting only the module names, and not the locations within the modules, provides an efficient coarse graining of the network.

**Figure 1.**

- The first three bits indicate that the walk begins in the red module, the code specifies the first node on the walk, etc.
Connectivity Comparison

Spatial Information

Spatial ICA
Spatial coefficient distributions

Graph Methods
Parcellations
Edge metrics

Seed Correlation
Seed size, location
Temporal correlations

Temporal Information
Connectivity Comparison

- Default Mode Network
  - Seed Correlation (PCC) by Uddin et al., HBM 2009
  - Spatial ICA by De Luca et al., NeuroImage 2006
  - Subgraph Detection (red) by Power et al., Neuron 2011
Dynamic Connectivity

Changing connectivity profiles over time
Dynamic Connectivity

Changing connectivity profiles over time

Typically refers to changes during a scan or experiment
Dynamic Connectivity

Changing connectivity profiles over time

Typically refers to changes during a scan or experiment

Changes in:
- internal “state”
- top-down modulation
- attention
- learning
- etc
Dynamic Connectivity

Changing connectivity profiles over time

Typically refers to changes during a scan or experiment

Changes in:
- internal “state”
- top-down modulation
- attention
- learning
- etc

Sliding Window Correlation

Chang et al., NeuroImage 2010
Temporal Independent Component Analysis

Time-courses are independent

Functional Integration:

Spatial ICA – spatially non-overlapping

Temporal ICA – spatially overlapping

Accounts for temporal non-stationarity in correlation models
Spatial vs Temporal Decompositions

**RSN: Spatial ICA**
- Spatially non-overlapping
- Visual Field: A
- Visual Field: B

**TFM: Temporal ICA**
- Spatially overlapping
- LGN
- Visual Field: A+B
- Visual Field: B-A

Smith et al., PNAS 2012
Temporal Dimensionality

Temporal Dimensions: \( \sim 10^2 \)

Temporal Dimensions: \( \sim 10^4 \)

36 \times 10\text{ minute scans}
(SMS-EPI, multiple subjects)

Smith et al., PNAS 2012

300 time-points

24,000 time-points
SUMMARY
Summary

• Not an exhaustive list of connectivity methods!

• Many different methods and metrics for quantifying connectivity
  — Using information across space, time, or some combination

• Connectivity in RS-FMRI shows remarkably robust structures

• But outputs reflect constraints, assumptions and models used