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Functional Connectivity and Network Methods with functional magnetic resonance imaging

Enrico Glerean (MSc), Brain & Mind Lab, BECS, Aalto University www.glerean.com | @eglerean | becs.aalto.fi/bml | enrico.glerean@aalto.fi

2 Questions

WHY DO WE STUDY BRAIN NETWORKS? HOW DO WE STUDY BN WITH FMRI?



Why do we want to study brain connectivity?

• The brain is a network

~10^10 neurons and ~10^4 connections per neuron

- As for genomics in the 20th century, many authors are now praising the connectomics as the current revolution in neuroscience
- Multi-million projects like the Human Connectome
 Project, the BRAIN initiative
- Charting the connectome presents challenges



How do we study brain connectivity? Outline of this lecture

- Concepts of functional connectivity (FC)
- Overview of methods to compute FC
- Artefacts and confounds in FC
- Preprocessing for FC
- Quantifying results and graph theoretical measures
 (mini-course on network science)
- Tools and resources

Three important References Network modelling methods for FMRI Smith S.M. et al.; Neuroimage 2011, doi:10.1016/j.neuroimage.2010.08.063

Complex brain networks: graph theoretical analysis of structural and functional systems

Bullmore, E, Sporns, O; Nature Rev. Neuroscience 2009 doi:10.1038/nrn2575 Networks of the Brain

Networks of the Brain Sporns, O; 2010, MIT Press.





Connectivity in neuroscience Concepts

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Connectivity in neuroscience

Structural connectivity (estimating actual connections)

- Invasive (tract tracing methods, 2 photon calcium imaging)
- Non invasive (Diffusion Tensor and Diffusion Spectral Imaging)
- Functional connectivity (based on temporal "co-variance")
 - Invasive (intracranial recordings)
 - Non invasive (fMRI, M/EEG, simulated data)



From univariate to multivariate (via *bivariate*)



- We measure **multiple time series** at once
- We can consider them independently (e.g. GLM) or we can look at mutual relationships

Blood Oxygen Level signal

30min (900 samples)



Functional connectivity is multivariate

- Functionally connected = there is a relationship between two or more voxel time series
- Pairwise (bivariate / multivariate) = we consider two time series and compute their relationship to build a network. Repeat for all pairs and then use multivariate approaches e.g. network science.
- Multivariate = consider multiple voxels at once (PCA, ICA, MVPA)



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Complex network

From Wikipedia, the free encyclopedia

In the context of network theory, a **complex network** is a graph (network) with non-trivial topological features -- features that do not occur in simple networks such as lattices or random graphs but often occur in real graphs. The study of complex networks is a young and active area of scientific research inspired largely by the empirical study of real-world networks such as computer networks and social networks.

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Definition [edit source | edit beta]

Most social, biological, and technological networks display substantial nontrivial topological features, with patterns of connection between their elements that are neither purely regular nor purely random. Such features



Theory · History

Graph · Complex network · Contagion Small-world · Scale-free · Community structure · Percolation · Evolution · Controllability · Topology · Graph drawing · Social capital · Link analysis · Optimization Reciprocity · Closure · Homophily Transitivity · Preferential attachment Balance · Network effect · Influence

Types of Networks

Information · Telecommunication Social · Biological · Neural Interdependent · Semantic Random · Dependency · Flow

A (complex) network, a graph

Unweighted graph

Weighted graph



Newman, M. E. J., **Networks: An introduction**. Oxford University Press, Oxford, March 2010.

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Directed and undirected graphs



Figure 1: An Undirected Graph

Figure 2: A Directed Graph

Newman, M. E. J., **Networks: An introduction**. Oxford University Press, Oxford, March 2010.

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Representation of networks

Source: Jari Saramäki's course slides





Adjacency list	i: neighbors	<i>i</i> : neighbors
	1: 3, 4	1: 4
	2: 4	2:
	3: 1, 4	3: 1, 4
Adjacency matrix	4: 1, 2, 3	4: 2
$a_{ij} = \begin{cases} 1 & if(j,i) \in E, \\ 0 & if(j,i) \notin E \end{cases}$	$\begin{bmatrix} 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 \\ 1 & 1 & 1 & 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 \end{bmatrix}$



Connectivity with fMRI DEFINITIONS AND METHODS



Definitions Functional and effective connectivity

- Functional connectivity = statistical dependencies among remote neurophysiological events
 - Pairwise and "data driven"
 - No "direction" in the estimated connections
- Effective connectivity = the influence that one neural system exerts over another
 - Estimates the direction of influence between nodes in the network
 - Lag based methods (Granger causality)
 - Model based (Bayesian methods such as Dynamic Causal Modelling
 - Higher order statistics via ICA (e.g. LiNGAM)



Paradigms for functional connectivity

Resting state FC

Looking at spontaneous BOLD activity while the subject is in the scanner Correlated with anatomy

Task related FC

The subject is performing a task with multiple conditions (usually block design or *naturalistic design*, i.e. a block design with longer blocks)



Building a functional network

At each **node** we measure a **time series**





Nodes in fMRI FC

A node is a voxel

- At 2mm isotropic voxels we have ~160K nodes, i.e. 12.8e9 links!
- At 6mm isotropic voxels we have ~6K nodes, i.e. 18e6 links

• A node is a region of interest (ROI)

- We consider multiple voxels that are anatomically defined and derive one time series (using average or first PC) [e.g. atlas based: AAL atlas, Harvard Oxford atlas, UCLA atlas]
- We consider a *seed:* a sphere centred at a specific location (usual size of diameter is 1cm) [based on literature, or nodes templates e.g. "Functional network organization of the human brain" Power JD, et al. Neuron. 2011 Nov 17; 72(4):665-78.
- WARNING: selection of ROIs can introduce bias



Building a functional network

At each **node** we measure a **time series** Let's compute their **similarity**



 $b_2(t)$



Building a functional network

Similarity value used as weight of the edge between the two nodes



e.g. Pearson's correlation: $r_{12} = \operatorname{corr}(b_1(t), b_2(t))$ **b**₁(t) ₩ **r**₁₂



b₂(t)



Methods for similarity between time series

- Pearson's correlation: simple correlation
- **Partial correlation**: choose a pair of nodes, regress out all other nodes (more towards a multivariate than bivariate)
- Regularised inverse covariance: useful for short sess.
- Mutual information: (non)linear share of information
- **Coherence:** looking at cross-spectral similarity between a frequency representation of the time serience



Which one is the best method?

- The answer is: it depends.
- If you are looking for subtle differences e.g. between groups or between conditions, some more refined measures could perform better (Smith et al. showed partial correlation, inverse covariance and Bayes-net methods as winners)
- However, in most cases simple linear correlation is enough, see Hlinka, J., et al (2011). Functional connectivity in resting-state fMRI: is linear correlation sufficient? NeuroImage, 54(3), 2218–25. doi:10.1016/ j.neuroimage.2010.08.042



Artefacts and confounds EFFECTS OF HEAD MOTION AND NOISE



How does motion affect FC?

- Carefully assessed by a recent paper Power, J. D et al. (2011) Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. NeuroImage. doi:10.1016/ j.neuroimage.2011.10.018
- They show that motion affects FC
- Propose a method to quantify motion (and quality of motion corrected data)
- Propose a method to **mitigate effects of motion** with FC



Quantify amount of motion



Quantify amount of motion

- Given the rigid body parameters $\begin{bmatrix} d_{ix} d_{iy} d_{iz} \alpha_i \beta_i \gamma_i \end{bmatrix}$
- Estimate the Framewise Displacement at each time point *i*

 $FD_i = \mid arDelta d_{ix} \mid + \mid arDelta d_{iy} \mid + \mid arDelta d_{iz} \mid + \mid arDelta lpha_i \mid + \mid arDelta eta_i \mid + \mid arDelta eta_i \mid + \mid arDelta eta_i \mid + \mid arDelta arDelta_{\gamma i} \mid + arDelta arDel$

- Given a subset of voxels or ROIs
- Estimate the **DVARS** (Derivative of VARS = variance over voxels) [Warn: handle with care with non rest data]

$$DVARS({\Delta I})_i = \sqrt{\left\langle \left[{\Delta I_i (ec{x})}
ight]^2
ight
angle} = \sqrt{\left\langle \left[{I_i (ec{x}) - I_{i-1} (ec{x})}
ight]^2
ight
angle}$$

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Scrubbing

 Once you identified the bad time points, you do scrubbing: i.e. you avoid considering them in your pairwise correlations (discard subjects that had less than 5 minutes left)



Effects of motion on FC

- In most cases scrubbing recovered long distance connections
- In few cases it mitigated false positives
- Short distance connections are basically untouched



Sources of noise in the BOLD signal

- Physiological noise but also scanner drift
- Having the same noise in two time series will cause them to be similar because of the noise
- Ideally you should de-noise the data, often this is not possible and data is band-pass filtered (0.01 – 0.08 Hz)



Source: Glerean et al 2012, Brain Connectivity doi:10.1089/brain.2011.0068

Preprocessing Pipeline For Functional Connectivity



Preprocessing pipeline for FC

- **Standard pipeline**: motion correction, coregistration to standard brain, slice time correction (optional see next)
- Spatial smoothing (conseq. of spatial downsampling)
- Scrubbing and/or de-noising and/or band-pass filtering ("Careful with that axe, Eugene")
- Regressing out the six rigid body parameters
- Regressing out signal at **ventricles** (!)
- Regressing out average white matter signal (!!)
- Regressing out **global mean of all voxels (!!!)**

Koene R. A. Van Dijk et al. Intrinsic Functional Connectivity As a Tool For Human Connectomics: Theory, Properties, and Optimization, 2010, Journal of Neurophysiology doi:10. 1152/ jn. 00783. 2009



Quantifying results Seed based analysis Network analysis

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Seed based analysis

- Connectivity from **one seed** to rest of the brain
- Usually a **sphere** in a selected region based on literature
- You will end up with one correlation map per subject per task, and then you look at group or task differences (t-test, permutation tests, etc)



Network analysis

- First build the network by looking at functional similarity for each pair of nodes
- Obtain one **network** per subject or per task
- Extract meaningful information from the networks with tools from Network science and graph theory



Building the network

- First step is to threshold the network to obtain a sparse graph
- Thresholding based on statistics or percentage of links





Microscopic (node level) measures

- Node degree/strength How strong is a node?
- Clustering

How close is the node with the neighbours?

- Closeness centrality How distant is the node?
- Betweenness centrality How many shortest paths through the node?





Microscopic (node level) measures

- Node degree/strength How strong is a node?
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How close is the node with the neighbours?

- Closeness centrality How distant is the node?
- Betweenness centrality How many shortest paths through the node?





Mesoscopic (module level) measures

Communities/clusters

Finding subset of nodes that are forming a module

 Comparisons of modularity

How different brains have different (sub)networks

Fortunato, S. (2010). Community detection in graphs. Physics Reports, 486(3-5), 75–174
Alexander-Bloch, et al. (2012). The discovery of population differences in network community structure NeuroImage, 59(4), 3889–900.





Global measures

Clustering

How densely connected are the nodes?

Path length

Average distance between nodes

 "Small world-ness" Many short distance links (high clustering) and few important long distance ones (short path)





Quantifying network results: statistics

- Micro/meso/macro scopic measures can be compared across groups or conditions with standard tests
- Correlation between measures
- Non independency of values
- Permutation based tests



Tools and resources



Interesting toolboxes

CONN toolbox

http://www.nitrc.org/projects/conn/

- Functional Connectivity toolbox https://sites.google.com/site/functionalconnectivitytoolbox/
- Brain connectivity toolbox https://sites.google.com/site/bctnet/
- All Matlab® based but check NiTime for Python stuff



Interesting resources

- 1000 resting state subjects http://fcon_1000.projects.nitrc.org/
- Human Connectome Project
 http://www.humanconnectomeproject.org/
- ADHD 200

http://fcon_1000.projects.nitrc.org/indi/adhd200/

• Alzheimer's Disease Neuroimaging Initiative http://adni.loni.usc.edu/

