Human Brain Networks
estimated with functional connectivity

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Why?

1. Why brain networks?
The Brain according to wikipedia

…The brain is the most complex organ in a vertebrate's body…
The Brain according to wikipedia

...In a typical human the cerebral cortex (the largest part) is estimated to contain 15–33 billion ($10^{9!!}$) neurons each connected by synapses to several thousand other neurons...
Why do we want to study brain networks?

• The brain is a network with ~10^{10} neurons and ~10^4 connections per neuron

• As for genomics in the 20^{th} 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
What?

2. WHAT IS A CONNECTOME?
The connectome

The connectome is the complete description of the structural connectivity (the physical wiring) of an organism’s nervous system.

*Olaf Sporns (2010), Scholarpedia, 5(2):5584.*
Human genome vs Human connectome

• The human genome contains over 3 billion base pairs organized into 22 paired chromosomes
• The human connectome contains $\sim 10^{14}$ connections
What?

3. WHAT IS A NETWORK?
A (complex) network, a graph

Many types of networks

• Physical networks
  – *Power grid network*
  – *Physical layer of the internet*
  – *Water distribution network*
  – *Transportation networks (roads, rails)*

• Non-physical networks
  – *Social networks (Facebook, Twitter, etc.)*
  – *Stock Market*
  – *IP layer of the internet*
  – *Citations in science*
What?

4. WHAT IS BRAIN CONNECTIVITY?
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*)

5. WHAT IS FUNCTIONAL AND EFFECTIVE CONNECTIVITY?
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)

Smith SM et al. (2011) Network modelling methods for FMRI. Neuroimage
How?

6. How do we estimate functional brain networks non invasively?
Functional magnetic resonance imaging (fMRI)

- 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)
Building a functional network

At each node we measure a time series
We compute their similarity

\( b_1(t) \)

\( b_2(t) \)
Building a functional network

Similarity value used as **weight of the edge** between the two nodes. Repeat for each pair of nodes.

\[ r_{12} = \text{corr}(b_1(t), b_2(t)) \]
What?

7. What is a functional node?
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
What?

8. **WHAT METHODS CAN WE USE TO COMPUTE SIMILARITY BETWEEN TIME SERIES?**
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 series

Smith SM et al. (2011) Network modelling methods for FMRI. Neuroimage
9. Which one is the best method?
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
The brain at rest
The activity of the brain at rest is ideal for estimating the connectome

By looking at regions that change together in time we can estimate their connectivity

Network topology

NETWORK LEVEL FEATURES
What?

10. **What is a small world network?**
The small world experiment
Stanley Milgram (1969)

• Try to send a letter to Boston through a chain of people by only forward it to a friend who might know the final recipient

• Six degrees of separation
  i.e. an average path of 6 links in the network
Small world networks

Small world networks

Small world networks are present in biological system as an efficient way to keep the average path low and limit connection cost.

The brain is a small world network.
Why?

11. WHY IS THE BRAIN A SMALL WORLD NETWORK?
The small-world configuration is the optimal to optimize communication cost and efficiency.

Small world topology implies segregation and integration

• Small world topology implies high clustering:
  within a region we have more connections, regions are specialized (e.g. visual cortex, auditory cortex)

• Small world topology implies short path:
  densely connected regions are joined together by long-range links

• Clustering -> Segregation
• Short path -> Integration
12. What is a Hub?
What is a hub?

A hub is the effective center of an activity, region, or network… i.e. an important node in the network
13. How do we quantify a hub?
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?

14. WHAT ARE THE HUBS IN THE BRAIN?
Cortical hubs in the human brain

Cortical hubs in the human brain

15. What is the relationship between hubs and brain activity?
Energy consumption in the brain

The most important (central) hubs are those with higher glycolytic index, i.e. higher metabolic cost.

16. What is a network module?
Quantifying modules in networks

Communities/clusters
Finding subsets of nodes that are forming a module, i.e. they are more connected with each other than with other parts of the network

Mesoscopic:
between microscopic and macroscopic

What?

17. WHAT ARE THE MODULES IN THE BRAIN?
The networks of the human brain

• We look at **which regions are more connected with each other (clustering)**
• We identify ~**6 main modules** in the human cortex that corresponds to important cognitive functions
• They are often called “**networks**” although they are technically sub-networks
Yeo et al. (2011)

The organization of the human cerebral cortex estimated by intrinsic functional connectivity

A *rich club* of strong hubs in multiple modules is at the core of the human brain

Rich-club hubs (blue)

Modules (red)

How?

18. HOW DOES CONNECTIVITY CHANGE IN TIME?
Temporal scales of connectivity

• Changes across (milli)seconds

• Changes across years
Sub-network modules in the infant brain at rest with fMRI

- Five consistent modules
  - A) primary visual
  - B) somatosensory/motor
  - C) primary auditory
  - D) Posterior lateral and midline of parietal cortex
  - E) medial and lateral anterior frontal cortex

Fransson et al (2007) PNAS
Evolution of brain networks in time

A) Focus on frontal areas

B) Focus on default mode

19. **What is the impact of this research on society?**
Mapping the connectome and clinical applications

• The connectome will provide novel insights on the functioning of the brain.

• There are multiple mental diseases that are caused by dysfunctions of brain networks, for example:
  • Alzheimer’s disease
  • Schizophrenia
  • Autism
Alzheimer’s disease

• The most expensive hubs are attacked by the disease

Schizophrenia

• Unbalanced small-worldness

Clinical uses?

20. CAN WE USE THESE TOOLS FOR DIAGNOSTIC/NEUROSURGICAL PURPOSES?
Clinical applications of resting state fMRI and network analysis

• Idea of putting a patient in the MRI scanner resting for ~5 minutes and get a diagnosis is intriguing, but **does it work?**

• Open discussion in the field:
  • Lee et al. 2013, *Resting-State fMRI: A Review of Methods and Clinical Applications*, AJNR doi: 10.3174/ajnr.A3263
Clinical applications of resting state fMRI and network analysis

• Examples:
  • **Presurgical planning** in patients with **brain tumor** or **intractable epilepsy** (less demanding than an active task in the scanner) [e.g. tumor in sensorimotor cortex, medial temporal lobe epilepsy]
  • Diagnosis of **Alzheimer’s disease** (classification based on network clustering coefficient of hippocampus), children with **ADHD** (although another paper has shown that classification based on behavioural score had the same or better performance than resting state)
  • Resting state fMRI and **deep brain stimulation** (please refer to previous references for more detailed examples and discussions)
Clinical applications of resting state fMRI and network analysis

• My two cents
  • there are still methodological issues to consider (what is a node? Best way of computing a network? Global signal and other BOLD related artifacts: head motion, breathing rate, heart rate)
  • Shifting from a “biomarker from a distribution” approach to combination of biomarkers and comparison between large pools of subjects using machine learning
Two important references and a book


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

…and something in Finnish about network science
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/