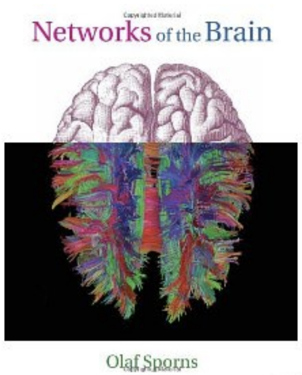
Brain networks & Functional Connectivity

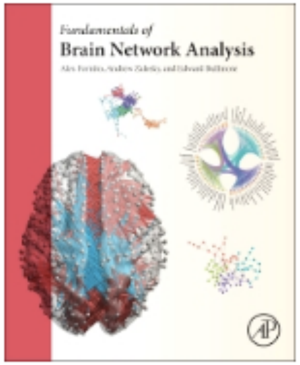
Enrico Glerean – web: www.glerean.com – twitter: @eglerean

Some fundamental references

- **Bullmore, E., & Sporns, O. (2012). The economy of brain network organization.** Nature reviews. Neuroscience, 13(5), 336–49.
- **Craddock, et al. (2013). Imaging human connectomes at the macroscale.** Nature Methods, 10(6), 524–539.

- **Networks of the Brain** Sporns, O; 2010, MIT Press.
- **Fundamentals of Brain Network Analysis.** Fornito, Zalesky, Bullmore; 2017, Elsevier





(They can be taken as book exams http://www.brain-mind.fi/courses.html)

…and something in Finnish about network science

https://www.researchgate.net/publication/242719764_Kompleksisten_verkostojen_fysiikkaa

Brain networks – Outline

- **Part 1 – Brain connectivity: ABC**
- **Part 2 – Brain network science**
- **Part 3 – Impact of this research**

Feel free to ask any question.

PART 1
Brain networks
ABC

The Brain according to wikipedia

…The brain is the most **complex** organ in a vertebrate's body…

Enrico Glerean
www.glerean.com | enrico@glerean.com

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…

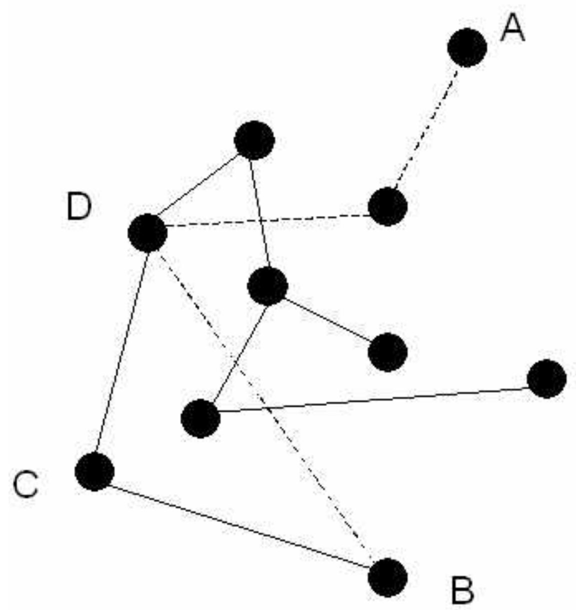
Why do we want to study brain networks?

- **The brain is a network with**
  ~10^10 neurons and ~10^4 connections per neuron
- As for **genomics** in the 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

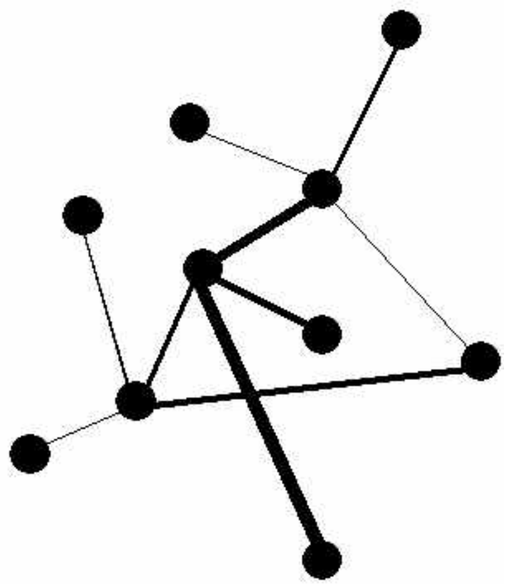
What is a network?

A (complex) network, a graph

Unweighted graph



Weighted graph



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

Directed and undirected graphs

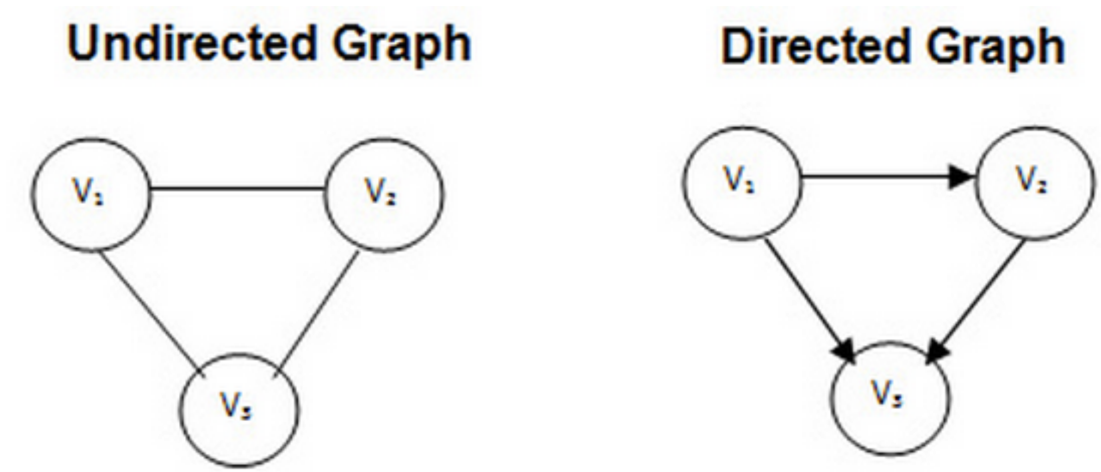


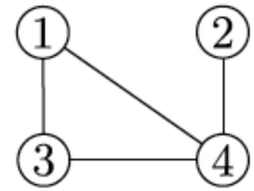
Figure 1: An Undirected Graph

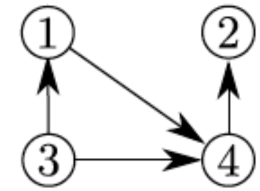
Figure 2: A Directed Graph

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

Representation of networks

Source: Jari Saramäki's course slides





Adjacency list

i : neighbors
1: 3, 4
2: 4
3: 1, 4
4: 1, 2, 3

i : neighbors
1: 4
2:
3: 1, 4
4: 2

Adjacency matrix

$$a_{ij} = \begin{cases} 1 & if(j,i) \in E, \\ 0 & if(j,i) \notin E \end{cases}$$

$$\begin{bmatrix} 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 \\ 1 & 1 & 1 & 0 \end{bmatrix}$$

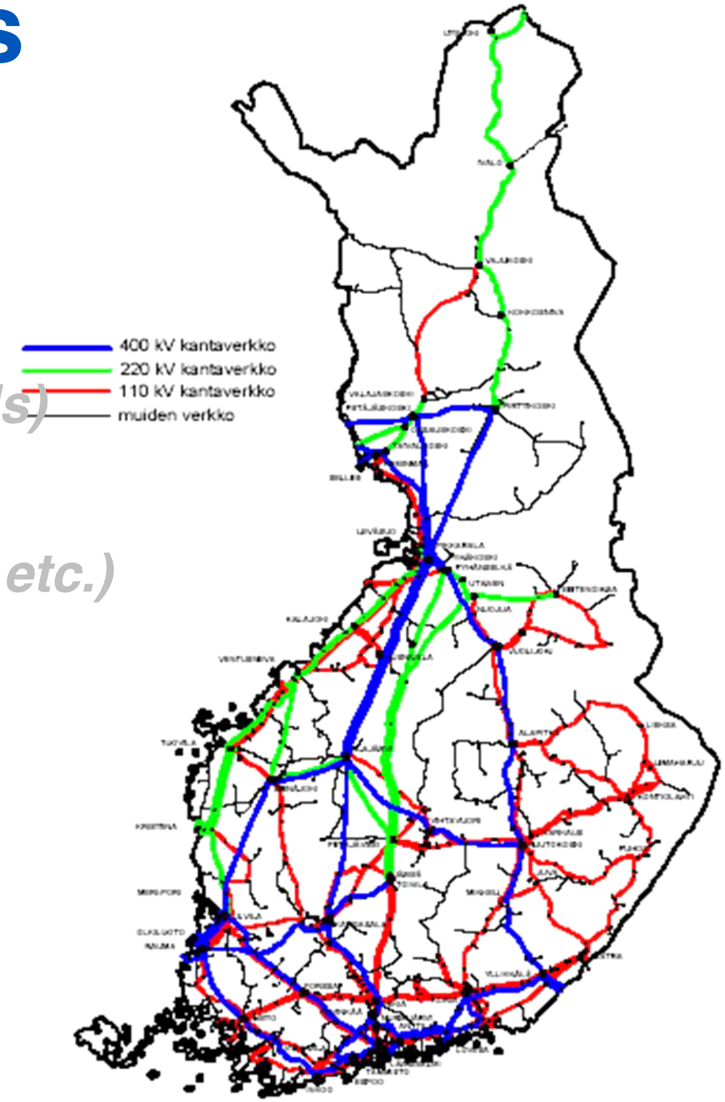
$$\begin{bmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 \end{bmatrix}$$

Many types of networks

- **Physical networks**
  - *Power grid network*
  - *Physical layer of the internet*
  - *Transportation networks (roads, rails)*
- **Non-physical networks**
  - *Social networks (Facebook, Twitter, etc.)*
  - *Stock Market*
  - *IP layer of the internet*

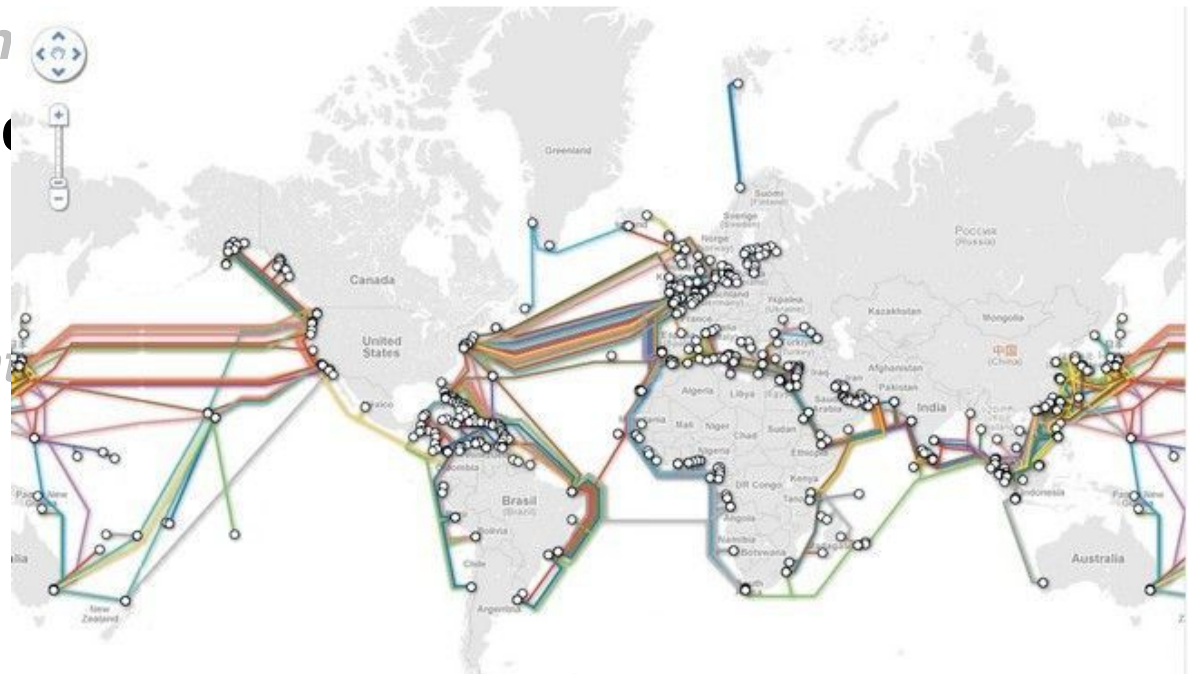
Many types of networks

- **Physical networks**
  - ***Power grid network***
  - *Physical layer of the internet*
  - *Transportation networks (roads, rails)*
- **Non-physical networks**
  - *Social networks (Facebook, Twitter, etc.)*
  - *Stock Market*
  - *IP layer of the internet*



Many types of networks

- **Physical networks**
  - *Power grid network*
  - ***Physical layer of the internet***
  - *Transportation n*
- **Non-physical n**
  - *Social networks*
  - *Stock Market*
  - *IP layer of the in*



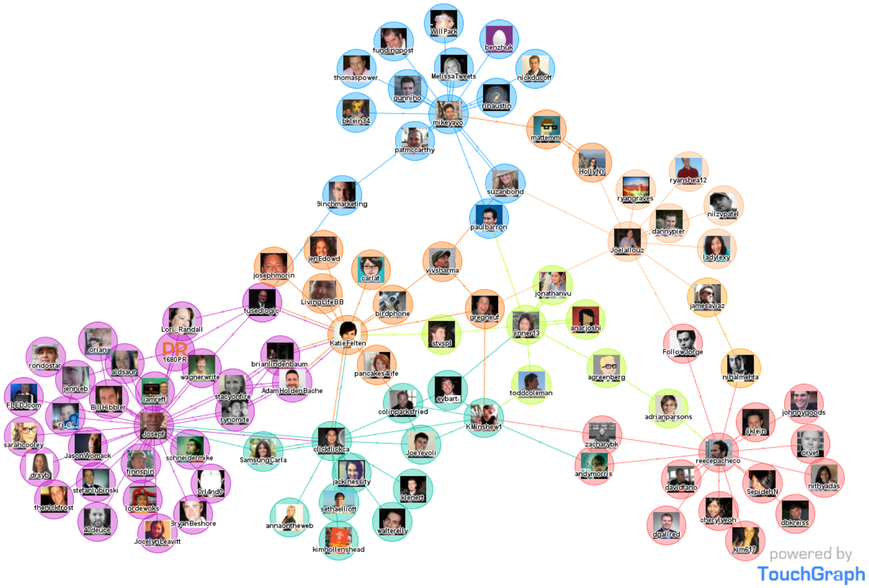
Many types of networks

- **Physical networks**
  - *Power grid network*
  - *Physical layer of the internet*
  - ***Transportation networks (roads, rails)***
- **Non-physical networks**
  - *Social networks (Faceboo*
  - *Stock Market*
  - *IP layer of the internet*

EnricoGlaesen
www.glaesen.com @eglaesen

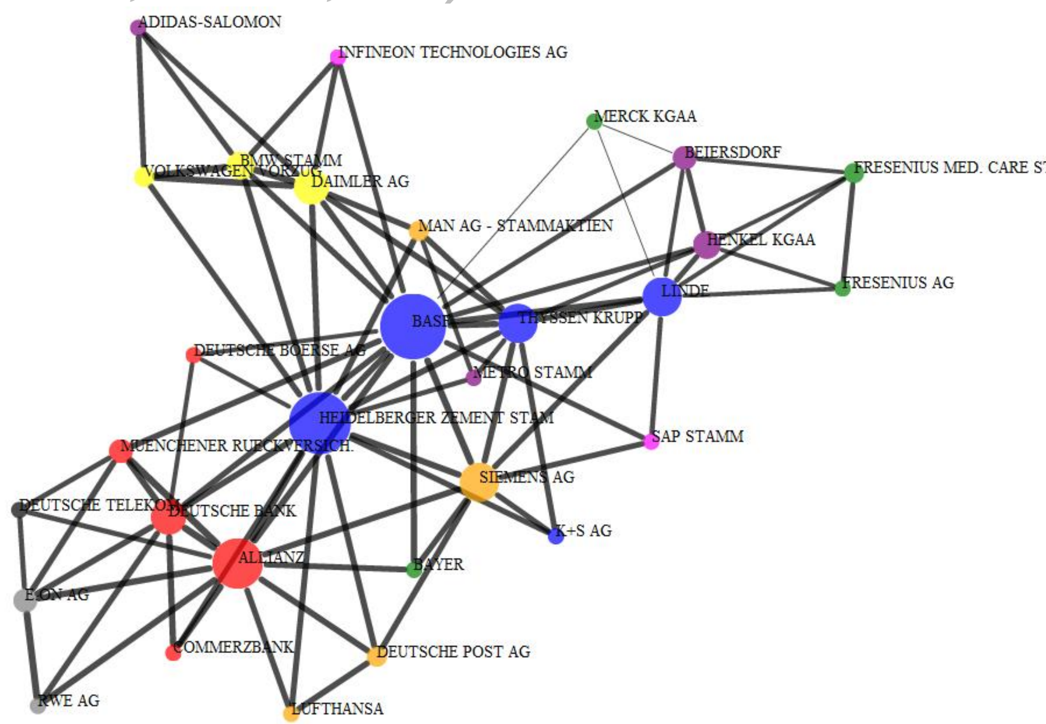
Many types of networks

- **Physical networks**
  - *Power grid network*
  - *Physical layer of the internet*
  - *Transportation networks (roads, rails)*
- **Non-physical networks**
  - ***Social networks (Facebook, Twitter, etc.)***
  - *Stock Market*
  - *IP layer of the internet*



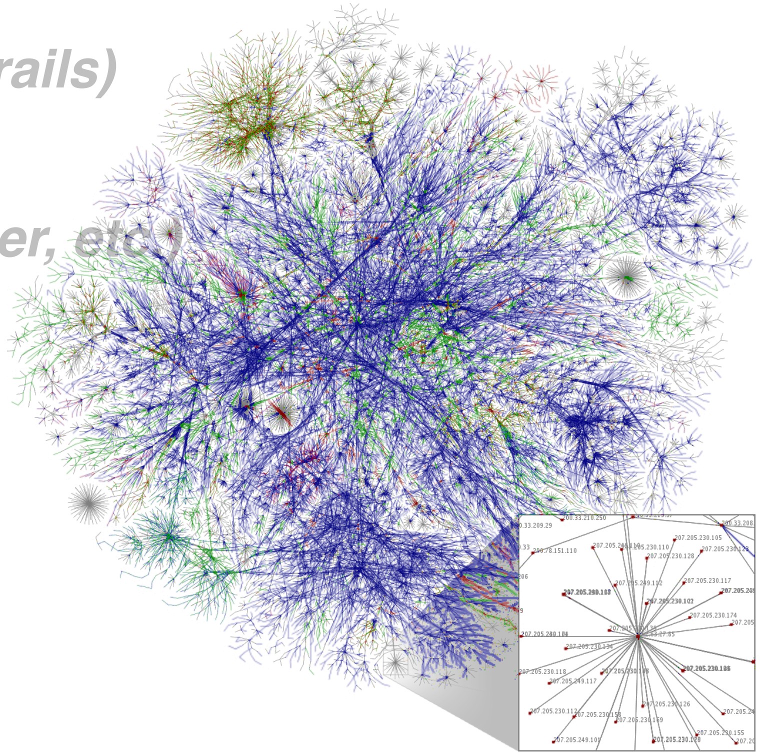
Many types of networks

- **Physical networks**
  - *Power grid network*
  - *Physical layer of the internet*
  - *Transportation networks (roads, rails)*
- **Non-physical networks**
  - *Social networks (Facebook, Twitter, etc.)*
  - ***Stock Market***
  - *IP layer of the internet*



Many types of networks

- **Physical networks**
  - *Power grid network*
  - *Physical layer of the internet*
  - *Transportation networks (roads, rails)*
- **Non-physical networks**
  - *Social networks (Facebook, Twitter, etc)*
  - *Stock Market*
  - ***IP layer of the internet***



EnricoGlaesen
www.glaesen.com @eglaesen

Visit the main page

WIKIPEDIA
The Free Encyclopedia

Create account · Log in

Article | Talk | Read | Edit source | Edit beta | View history | Search

Main page
Contents
Featured content
Current events
Random article
Donate to Wikipedia

Interaction
Help
About Wikipedia
Community portal
Recent changes
Contact page

Toolbox

Print/export

Languages
Deutsch
Español

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.

Contents [hide]

Definition [edit source | edit beta]

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

Network science

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

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.

EnricoGlaean
www.glaeancom l@eglaean

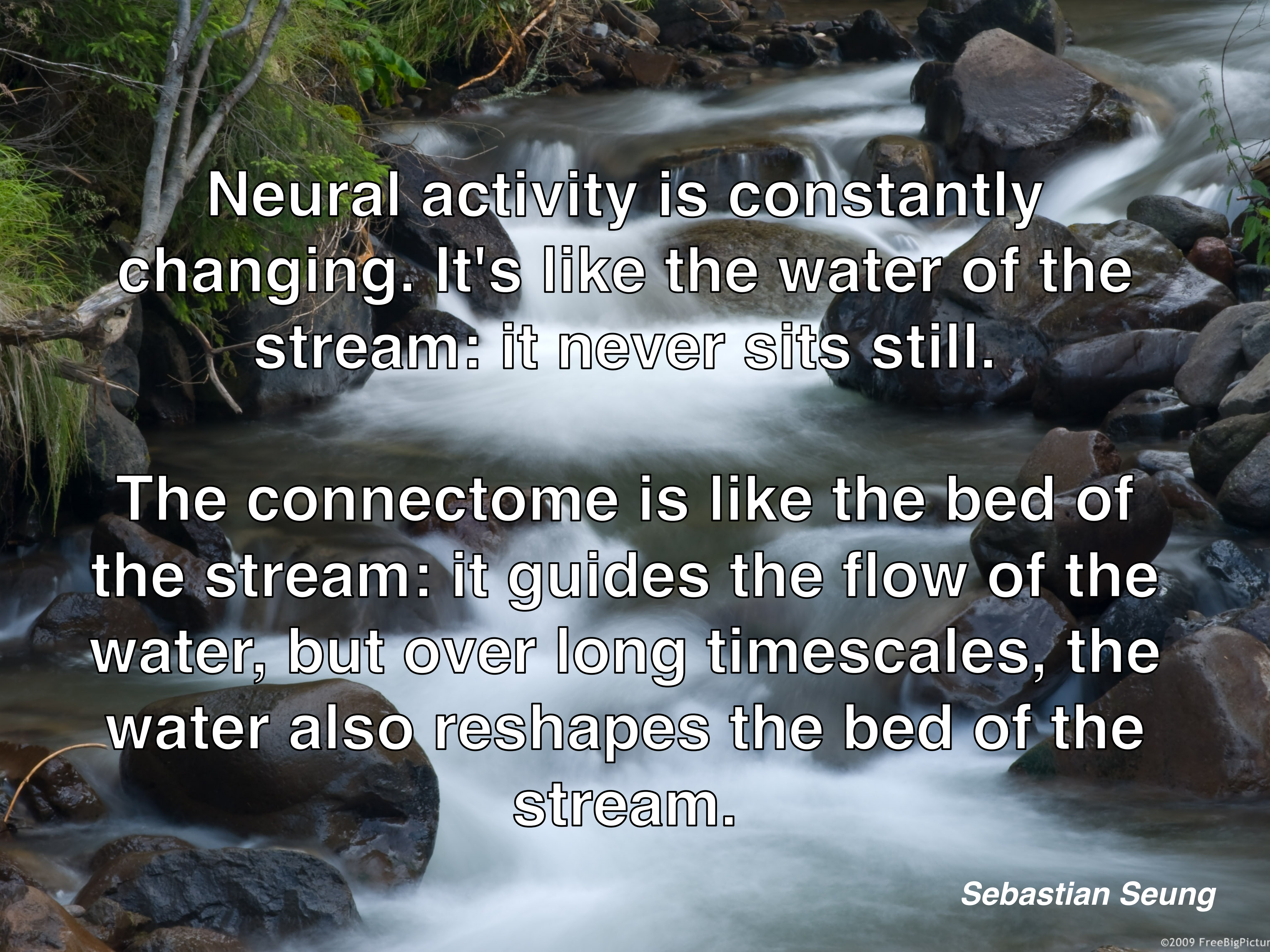
What is brain connectivity?

Brain networks

- **Structural connectivity**
  (estimating actual connections, the connectome)

- **Functional connectivity**
  (based on temporal “co-variance”)

Craddock, et al. (2013). Imaging human connectomes at the macroscale. Nature Methods, 10(6), 524–539. (*)


Neural activity is constantly changing. It's like the water of the stream: it never sits still.
The connectome is like the bed of the stream: it guides the flow of the water, but over long timescales, the water also reshapes the bed of the stream.
Sebastian Seung
©2009 FreeBigPictur

Connectivity in neuroscience

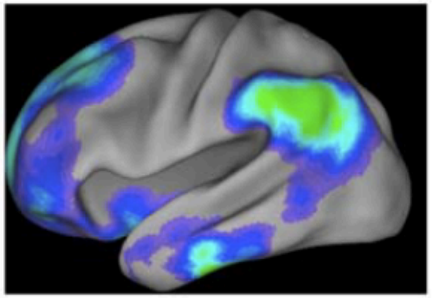
- **Structural connectivity (estimating actual connections)**
  - ***Invasive*** *(tract tracing methods, 2 photon calcium imaging)*
  - ***Non invasive*** *(Diffusion Tensor and Diffusion Spectral Imaging)*
- **Functional connectivity (based on temporal "co-variance")**
  - ***Invasive*** *(intracranial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

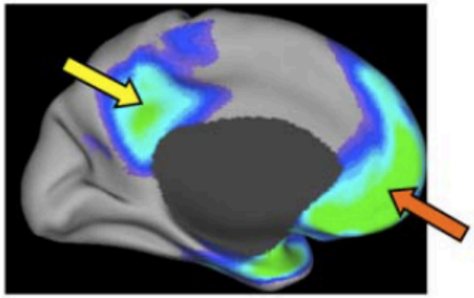
Craddock, et al. (2013). Imaging human connectomes at the macroscale. Nature Methods, 10(6), 524–539. (*)

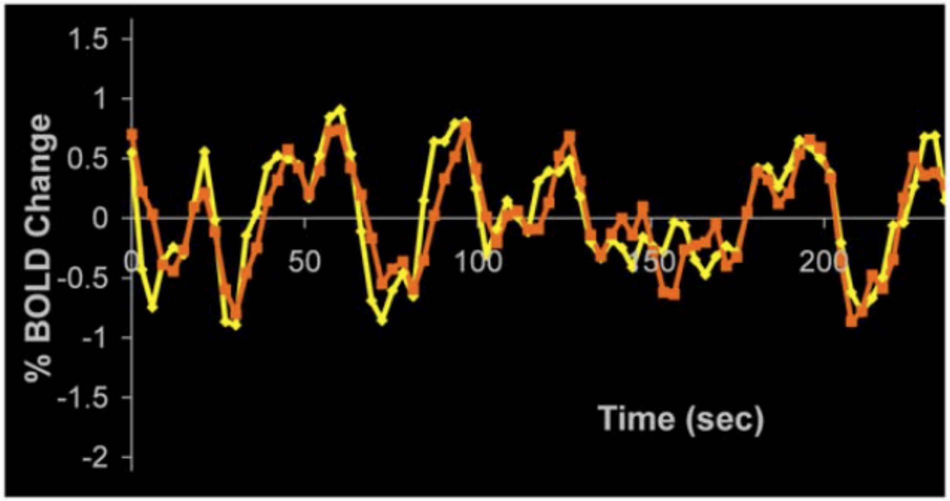
Enrico Glerean
www.glerean.com | @eglerean

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**



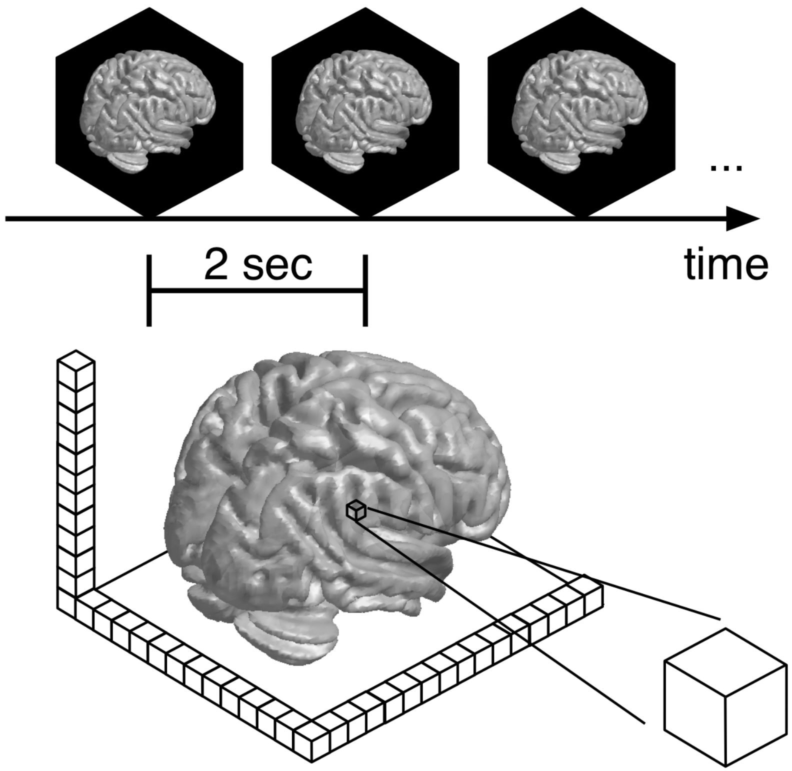




Raichle, M. E. (2010). Two views of brain function. Trends in Cognitive Sciences, 14(4)

How do we compute a functional brain network?

Functional magnetic resonance imaging (fMRI)



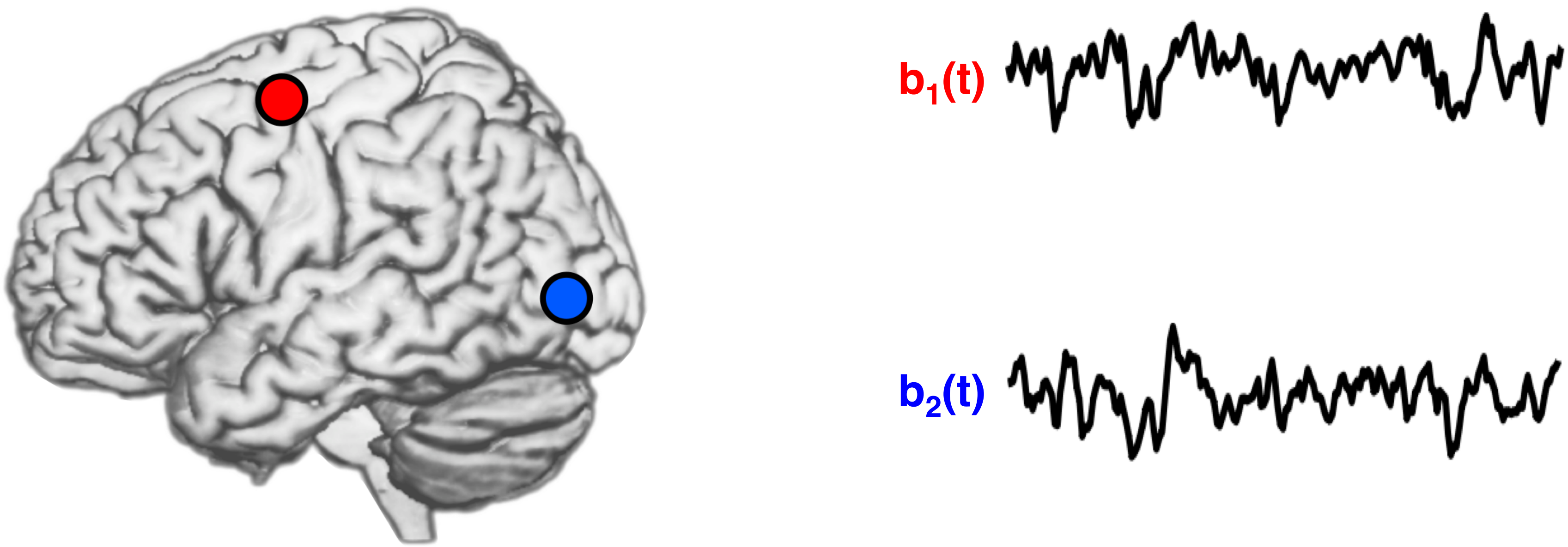
- We measure **multiple time series** at once
- We can consider them **independently** (e.g. GLM) or we can look at **mutual relationships**

Blood Oxygen Level signal

30min (900 samples)

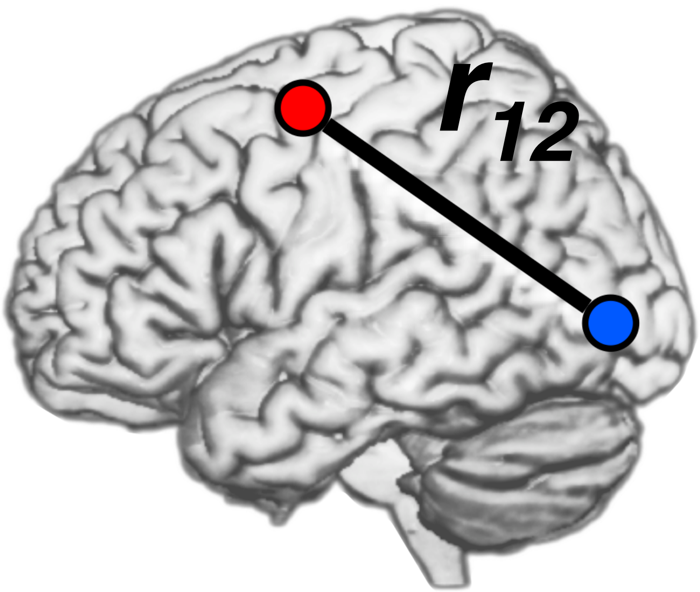
Building a functional network

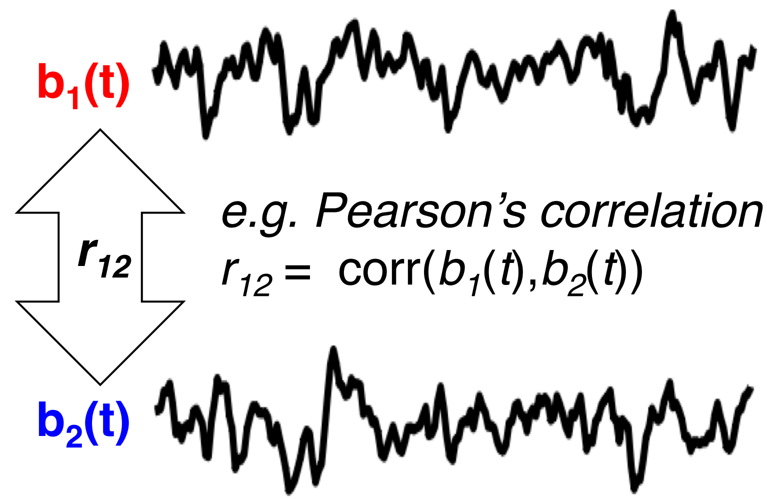
At each **node** we measure a **time series**
We compute their **similarity**



Building a functional network

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





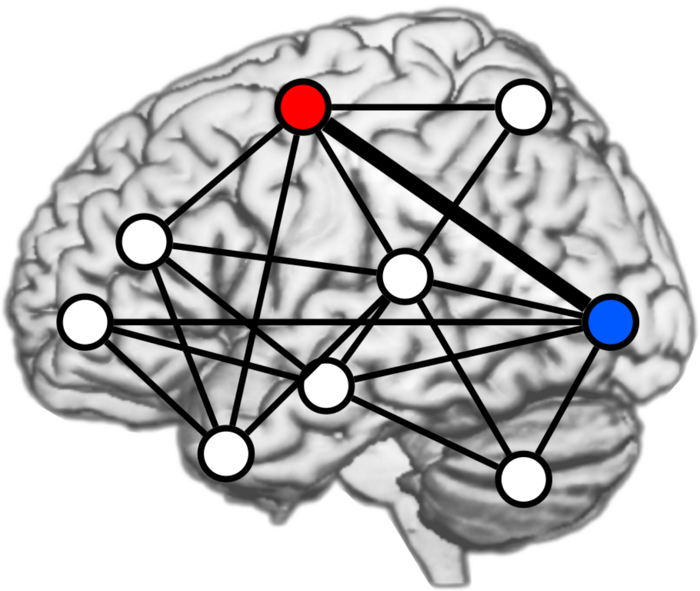
e.g. Pearson's correlation:

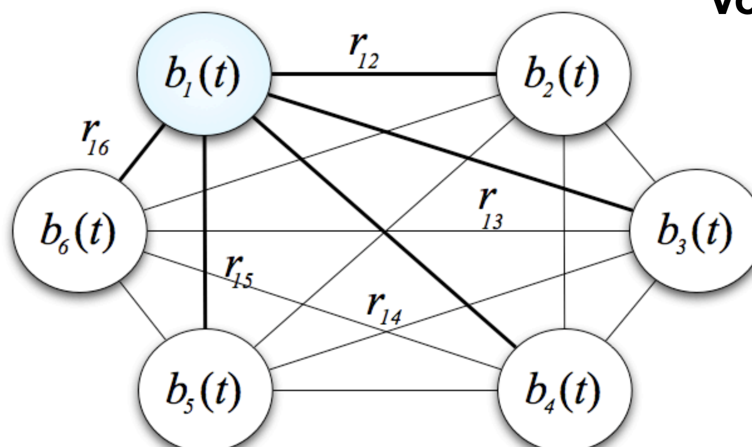
$r_{12} = \mathrm{corr}(b_1(t), b_2(t))$

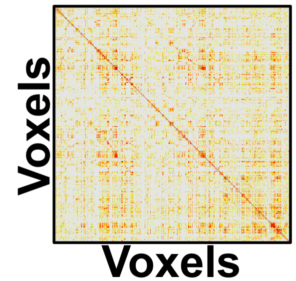
Enrico Glerean
www.glerean.com | @eglerean

Building a functional network

Repeat for all pairs of nodes and we get the full functional network







What is a node in a functional brain network?

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, Brainnettome]
  - 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 is a link in a functional brain network?

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
- Other methods related to task (**gPPI, beta series**)

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

Material not covered

Definitions
Functional and effective connectivity

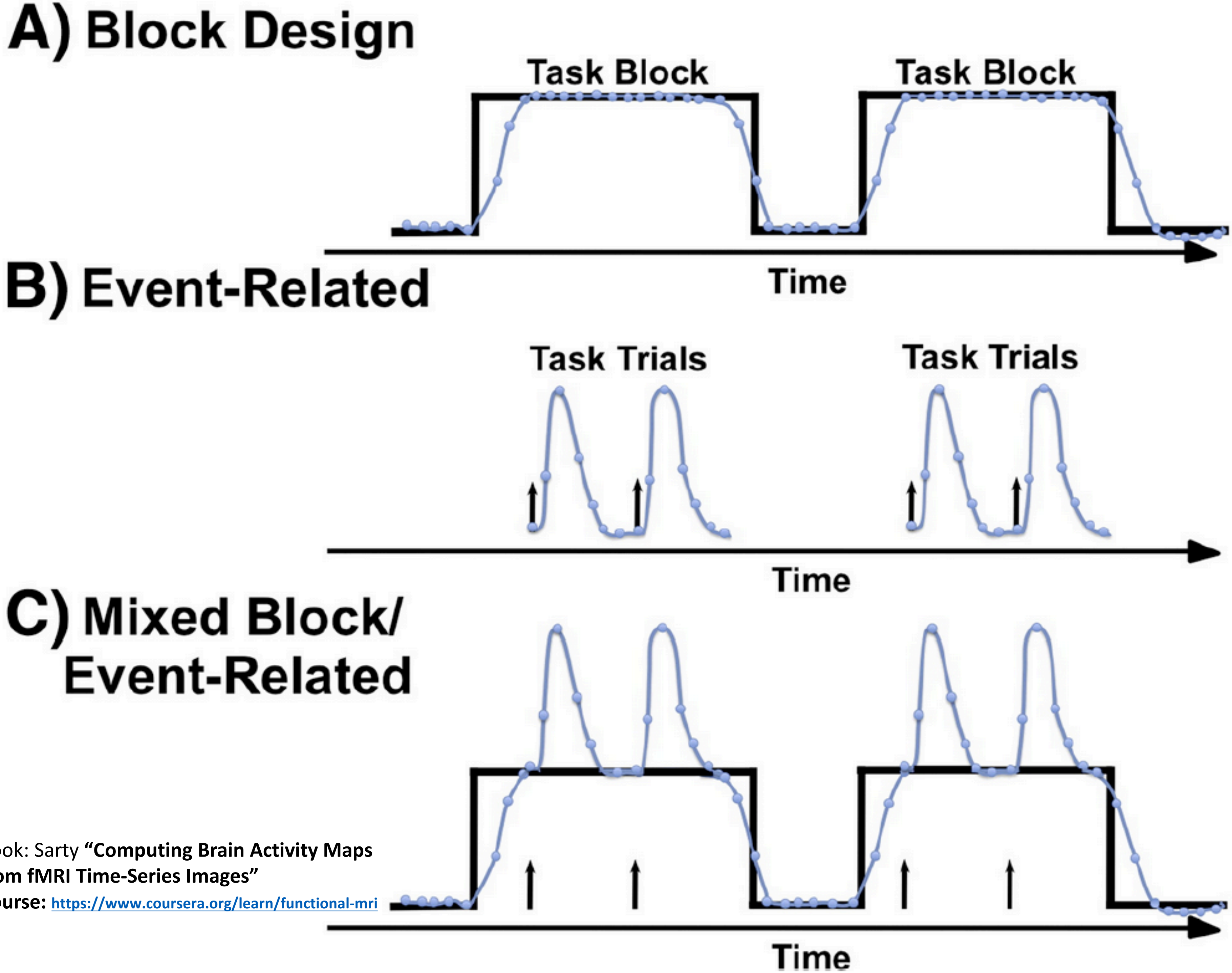
- **Functional connectivity =** statistical dependencies among remote neurophysiological events
  - *Pairwise and “data driven”*
  - *No “direction” in the estimated connections*
- **Effective connectivity =** the influence that one neural system exerts over another
  - *Estimates the direction of influence 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)

Task

1. **The subject is doing a task**
    1. Task structure
        1. *In **Blocks***
        2. *As **Events** separated in time*
        3. *As a **stream of events (naturalistic)***
    2. Passive vs Active
        1. *Pressing a **button, etc***
        2. ***Just watching and mentalizing***

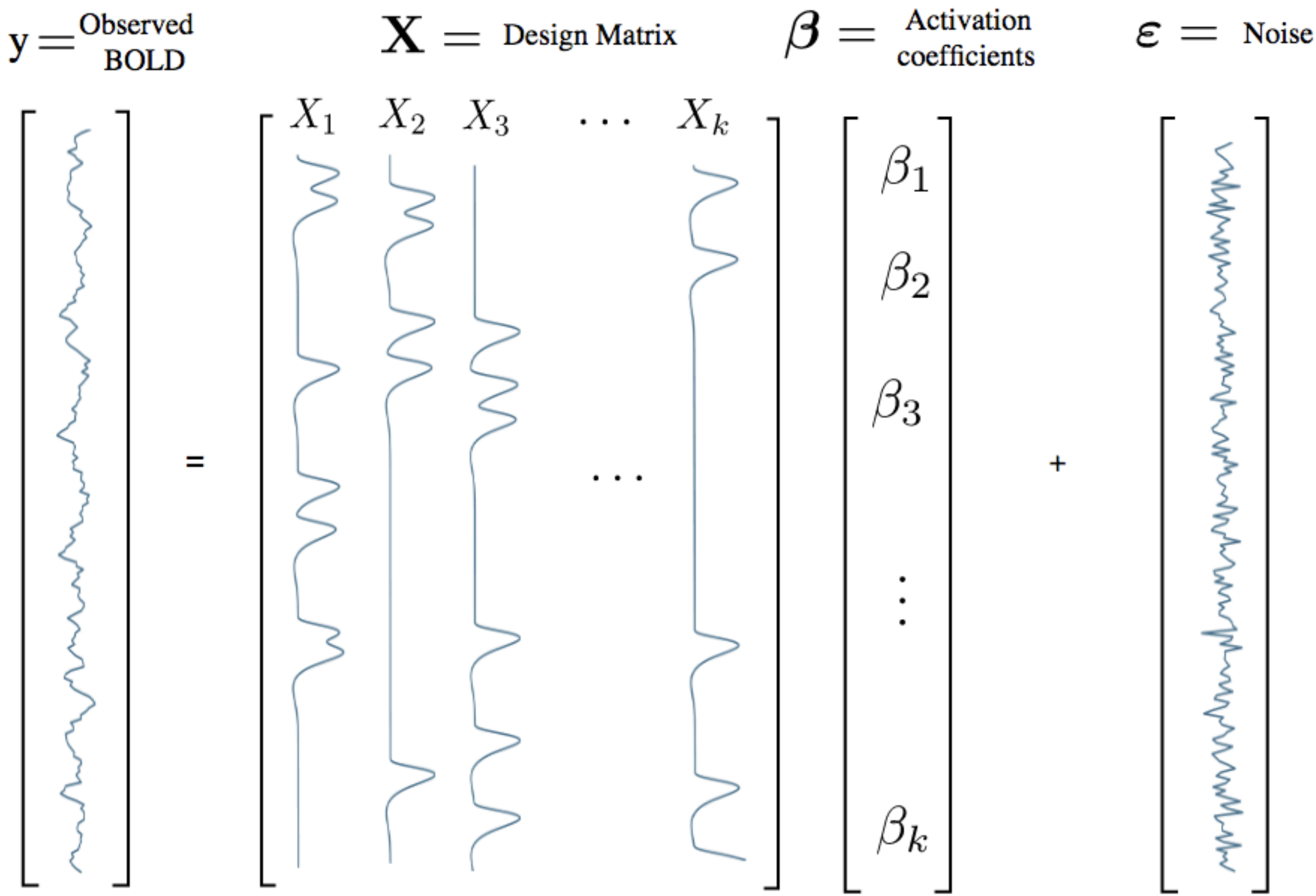


Book: Sarty **“Computing Brain Activity Maps from fMRI Time-Series Images”**
Course: https://www.coursera.org/learn/functional-mri

How to analyze task connectivity given task structure

- **The more structured the task, the less you can use the time series** (and viceversa)
- With **block** and with (not too fast) **event related** design we use the **general linear model GLM** to abstract from the time series into **"activations"**

$$
\begin{aligned}
y_1 &= b_0 + b_1 X_{11} + \cdots \cdots \cdots + b_p X_{1p} + e_1 \\
y_2 &= b_0 + b_1 X_{21} + \cdots \cdots \cdots + b_p X_{2p} + e_2 \\
y_3 &= b_0 + b_1 X_{31} + \cdots \cdots \cdots + b_p X_{3p} + e_3 \\
&\vdots \qquad\qquad\qquad \vdots \qquad\qquad \vdots \qquad \vdots \\
y_n &= b_0 + b_1 X_{n1} + \cdots \cdots \cdots + b_p X_{np} + e_n
\end{aligned}
$$



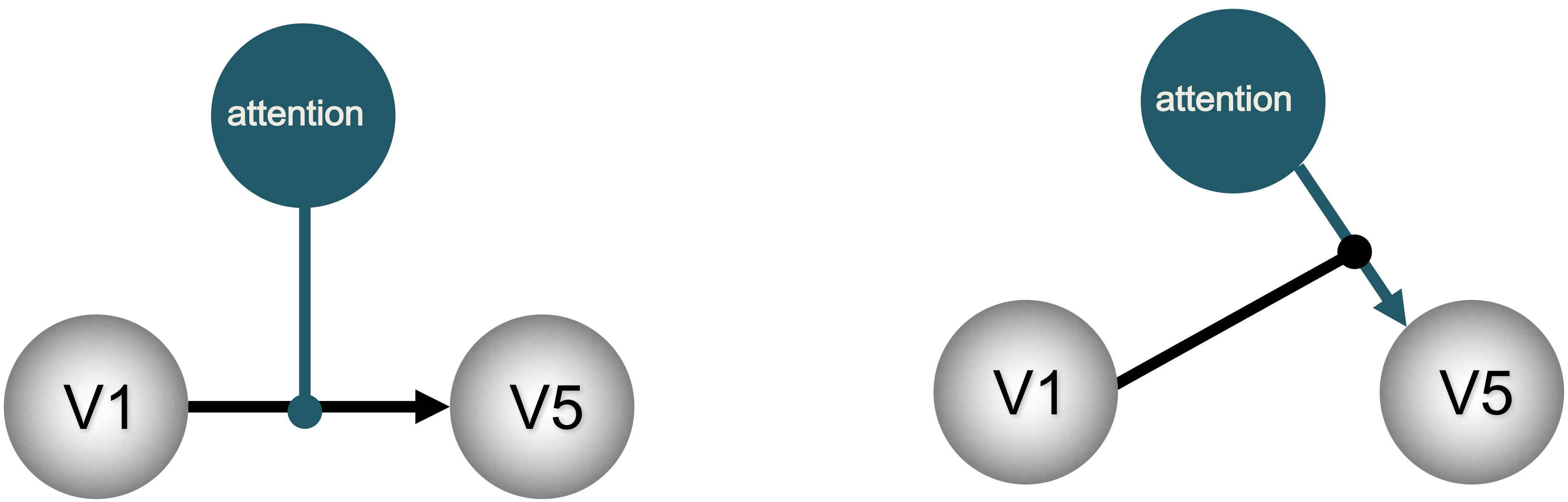
y = Observed BOLD
X = Design Matrix
β = Activation coefficients
ε = Noise
X1 X2 X3 . . . Xk
β1 β2 β3 ⋮ βk
=
+

How to analyze task connectivity given task structure

- **With 20s blocks, the best is PPI***

  $Y = (\text{Att-NoAtt})\,\beta_1 + \underline{\mathbf{V1}}\,\beta_2 + (\text{Att-NoAtt}) * \mathbf{V1}\,\beta_3 + e$

- **Modeling** signal **Y**, given **task**, given **another signal** (V1), given an **interaction between task and signal**



Source: http://www.fil.ion.ucl.ac.uk/mfd_archive/2011/page1/mfd2011_connectivity_PPI_SEM.pptx
*PPI = psychophysiological interaction

How to analyze task connectivity given task structure

- **Resources for PPI**
  - SPM (matlab)
  - FSL (stand alone)
  - gPPI (generalized PPI, https://www.nitrc.org/projects/gppi)

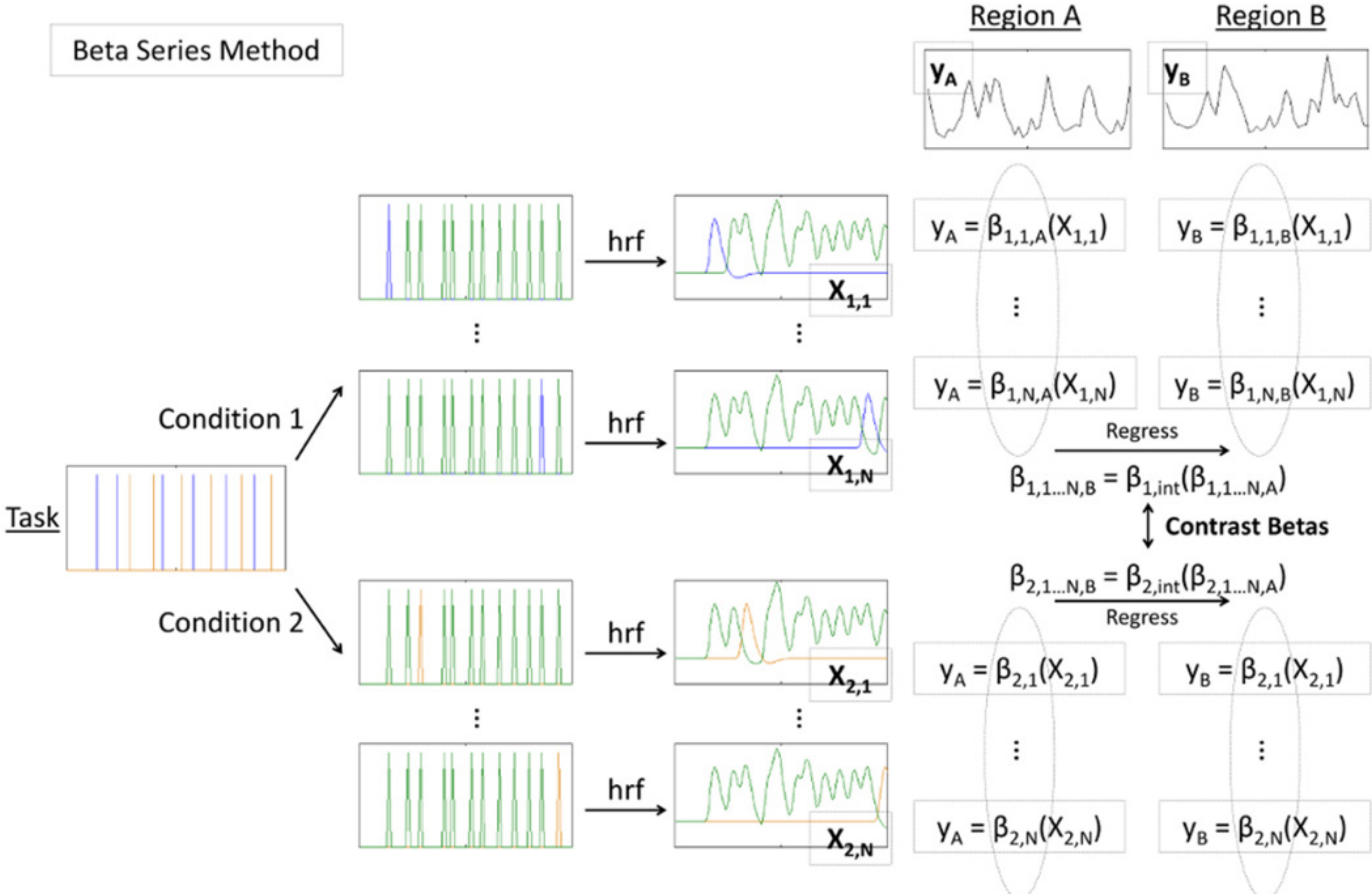
*PPI = psychophysiological interaction

Source: http://www.fil.ion.ucl.ac.uk/mfd_archive/2011/page1/mfd2011_connectivity_PPI_SEM.pptx

How to analyze task connectivity given task structure

- **Event related, the best is beta series**
- **For every event we compute a beta weight** in the GLM sense
- We replace **BOLD time series** with **beta time series**
- **We correlate beta time series between regions**

How to analyze task connectivity given task structure



How to analyze task connectivity given task structure

- **Resources for beta series**
  - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4019671/
  - **BASCO toolbox:** https://www.nitrc.org/projects/basco/
  - Mini function I made: https://version.aalto.fi/gitlab/BML/bramila/blob/master/bramila_betaseries.m

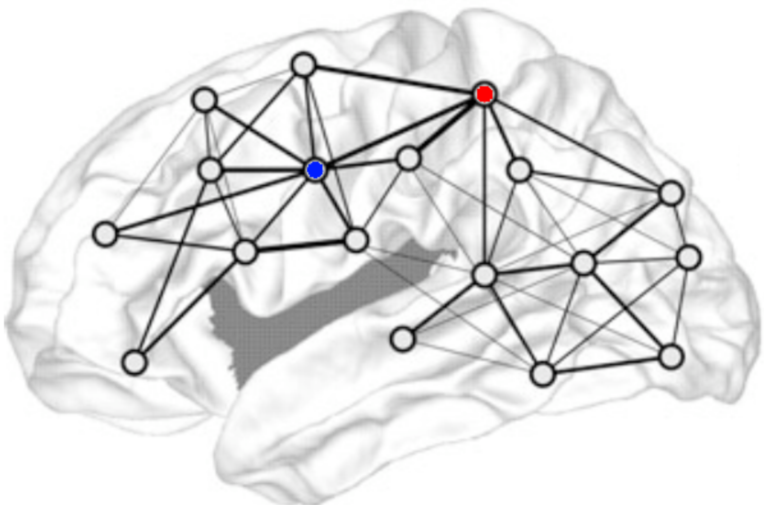
Source: http://www.fil.ion.ucl.ac.uk/mfd_archive/2011/page1/mfd2011_connectivity_PPI_SEM.pptx

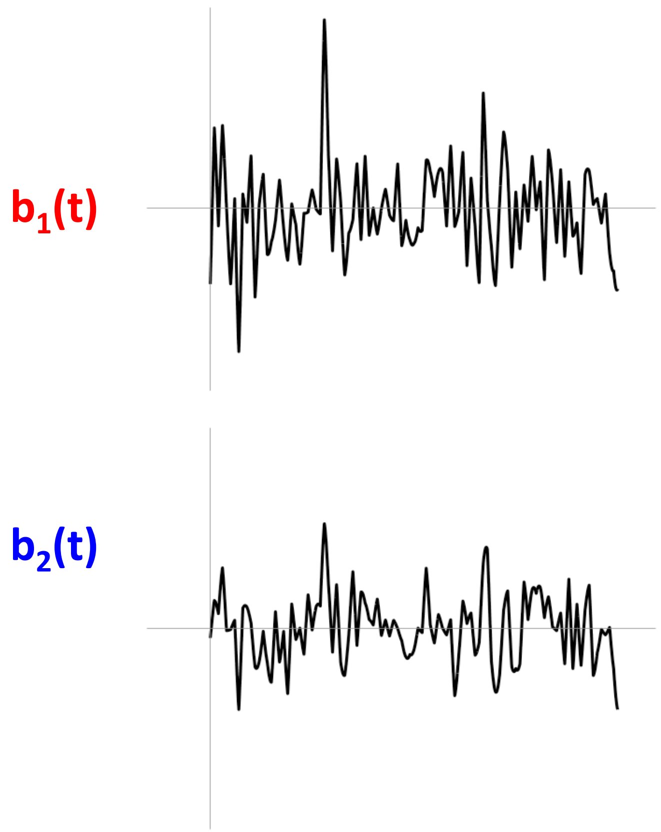
Task

1. **The subject is doing a task**
   1. Task structure
      1. *In **Blocks***
      2. *As **Events** separated in time*
      3. *As a **stream of events (naturalistic)***
   2. Passive vs Active
      1. *Pressing a **button, etc***
      2. ***Just watching and mentalizing***

Correlation approaches

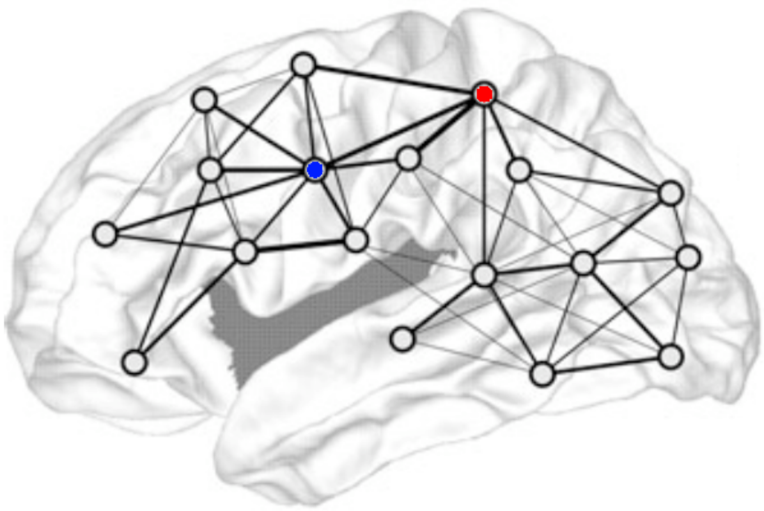
- **Let's consider two time series for two voxels**

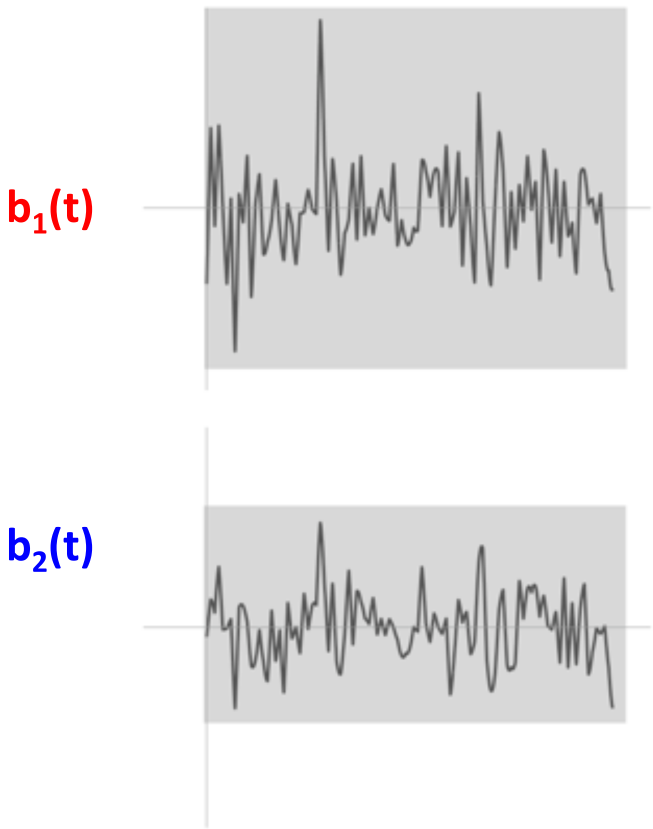




Correlation approaches

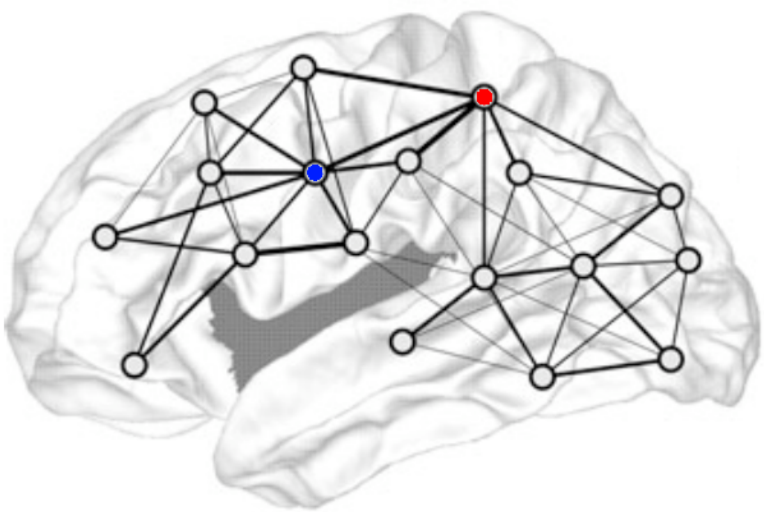
- **Let's take all time points**

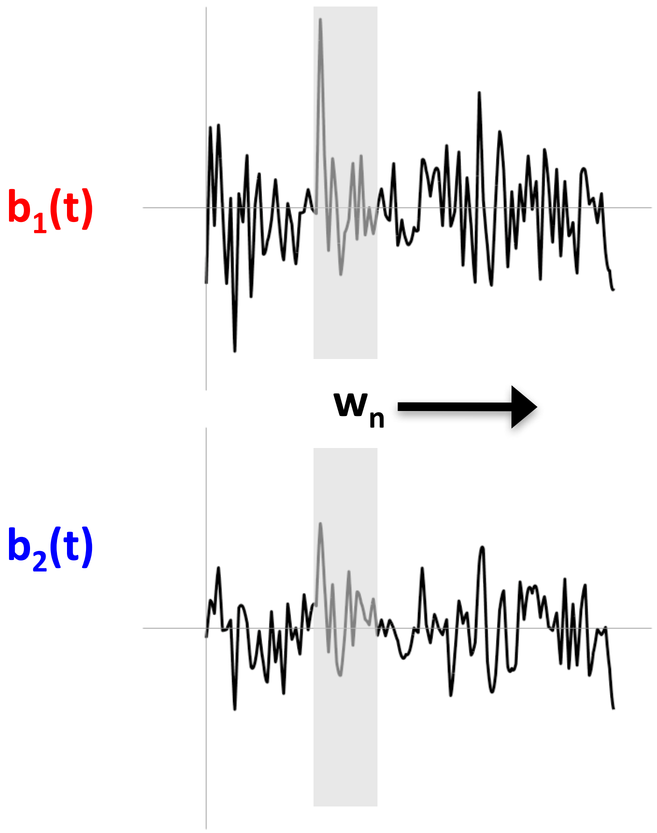




Functional connectivityin time

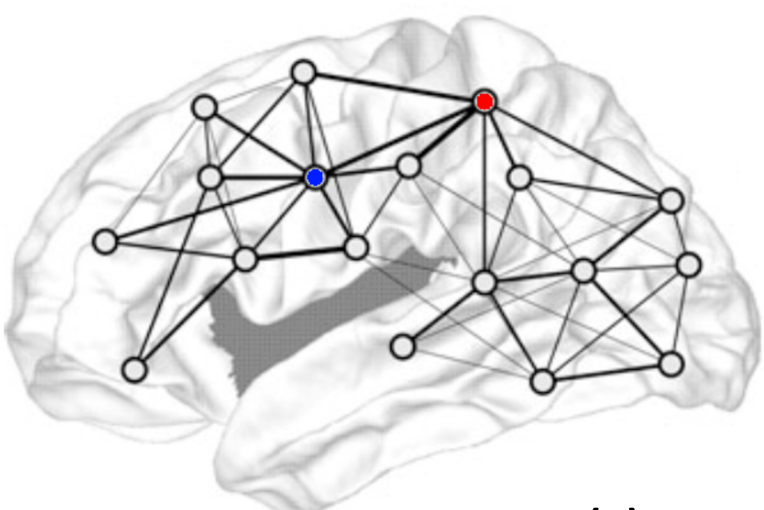
- **Sliding window correlation**

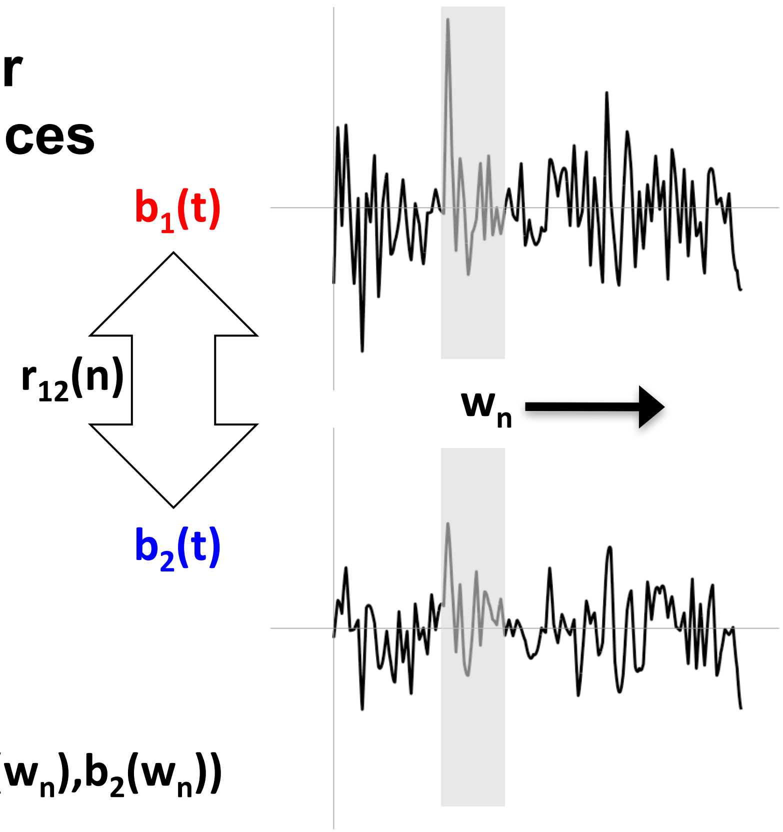




Functional connectivity in time

- **Sliding window correlation for functional connectivity produces link time-series**





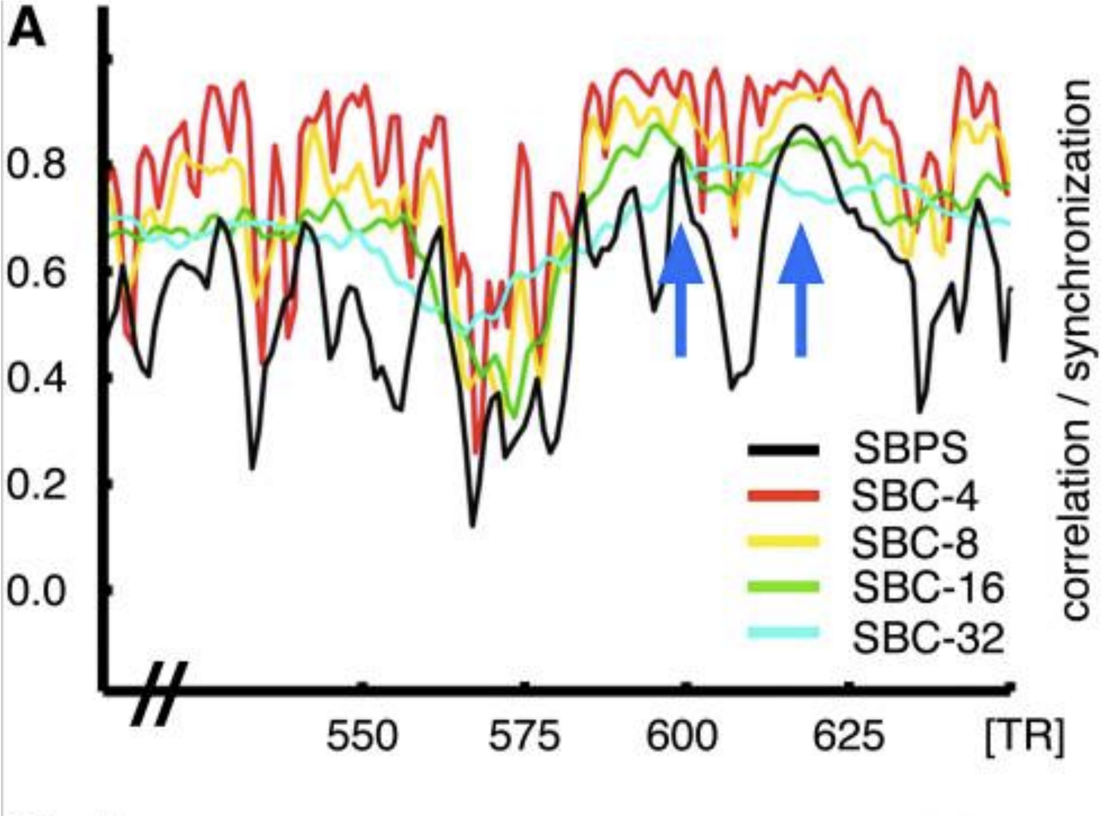
e.g. $r_{12}(n) = corr(b_1(w_n),b_2(w_n))$

Problems with sliding window connectivity

- Field is still arguing **what Dynamic Functional Connectivity means**
- **Size of window depends on the temporal frequencies of the signal**
  - http://www.sciencedirect.com/science/article/pii/S1053811914007496
  - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4758830/

Functional connectivity in time: other approaches

- **Wavelet decomposition** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2827259/
- **Multiplication of derivates** http://www.sciencedirect.com/science/article/pii/S1053811915006849
- **Phase synchronisation (Glerean et al 2012)** https://www.ncbi.nlm.nih.gov/pubmed/22559794



How do we compare networks at the link level?

Network statistics

- We have computed **links**, so you can think that links are what the voxels were in usual statistical parametric mapping and apply the same logic

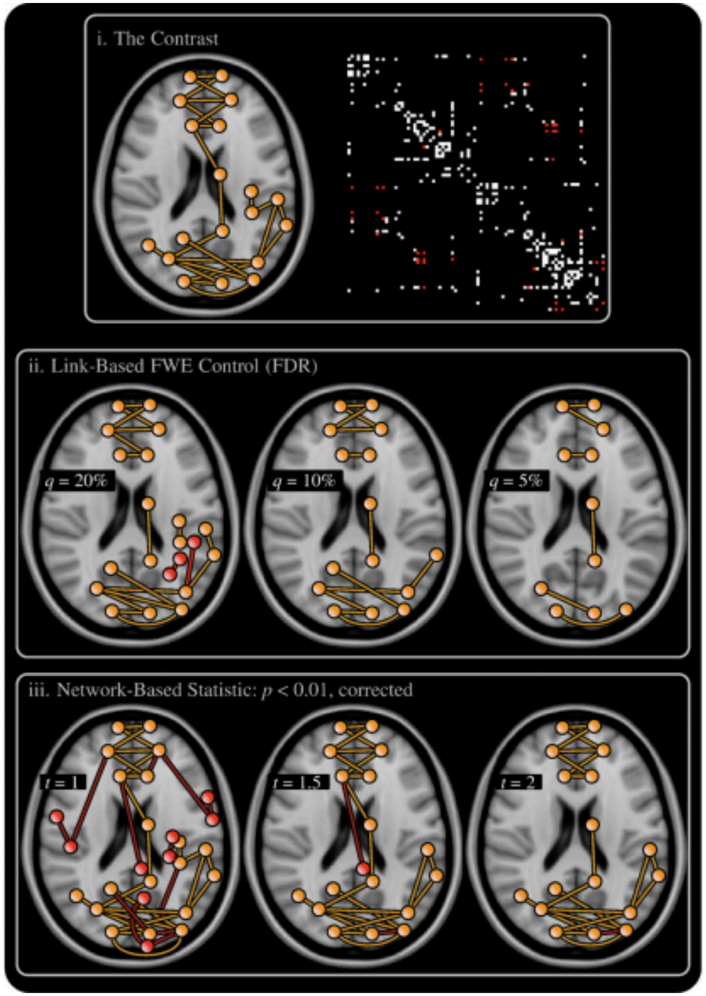
- We have a **multiple comparisons problem** as we run as many test as many links (10^3-10^6)

- If links are **correlations** (i.e. in a range -1,1) then they are usually **z-transformed** (**atanh**) so they become more gaussianly distributed

- **The best way is to use permutation based approaches**

Solving the multiple comparison problem for networks

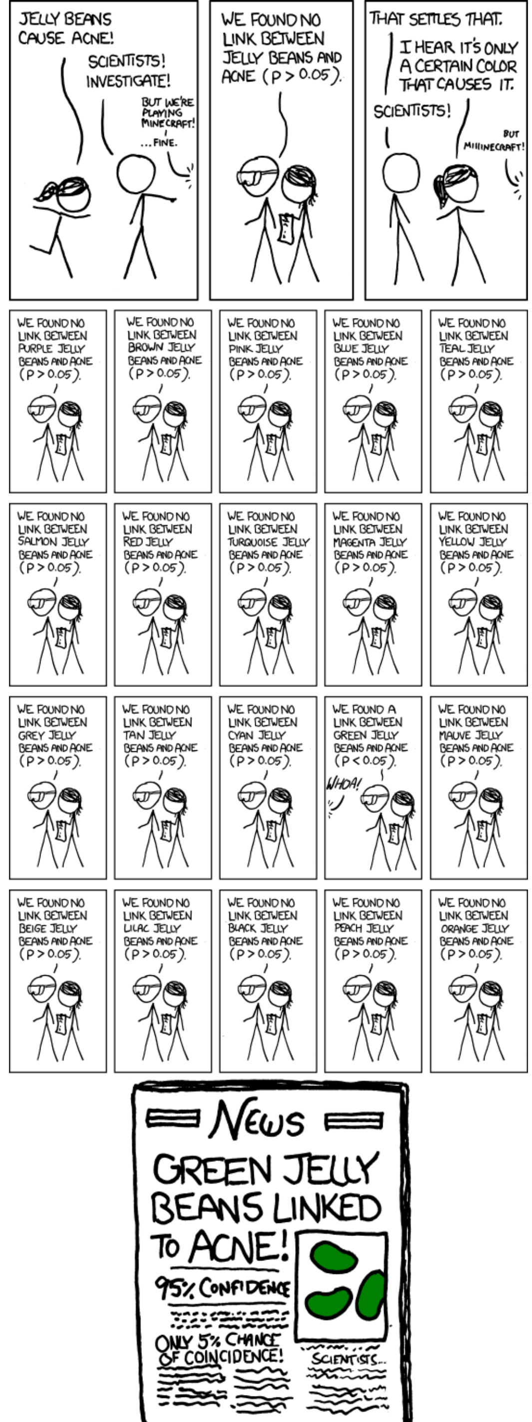
Network based statistics is the cluster correction applied to the links



Check

http://www.sciencedirect.com/science/article/pii/S1053811912000857

Understanding the multiple comparison problem



JELLY BEANS CAUSE ACNE!
SCIENTISTS! INVESTIGATE!
BUT WE'RE PLAYING MINECRAFT!
...FINE.
WE FOUND NO LINK BETWEEN JELLY BEANS AND ACNE (P > 0.05).
THAT SETTLES THAT.
I HEAR IT'S ONLY A CERTAIN COLOR THAT CAUSES IT.
SCIENTISTS!
BUT MIIIINECRAFT!
WE FOUND NO LINK BETWEEN PURPLE JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN BROWN JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN PINK JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN BLUE JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN TEAL JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN SALMON JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN RED JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN TURQUOISE JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN MAGENTA JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN YELLOW JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN GREY JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN TAN JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN CYAN JELLY BEANS AND ACNE (P > 0.05).
WE FOUND A LINK BETWEEN GREEN JELLY BEANS AND ACNE (P < 0.05).
WHOA!
WE FOUND NO LINK BETWEEN MAUVE JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN BEIGE JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN LILAC JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN BLACK JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN PEACH JELLY BEANS AND ACNE (P > 0.05).
WE FOUND NO LINK BETWEEN ORANGE JELLY BEANS AND ACNE (P > 0.05).
NEWS
GREEN JELLY BEANS LINKED TO ACNE!
95% CONFIDENCE
ONLY 5% CHANCE OF COINCIDENCE!
SCIENTISTS...

Controlling for multiple comparisons – frequentist approach

- **Family of methods also called “Family wise error rate” control**
- **Classic example: Bonferroni correction. Alpha = 0.05/NC**
- **Ok, for smallish NC, but it’s not going to work with networks (264 nodes, 34716 links -> alpha ~= 10^-6)**

Controlling for multiple comparisons – better approaches

- **False Discovery Rate (FDR)**
- **Based on distribution of p-values**
- **Procedure:**
  - Smallest p value < alpha/NC
  - Second smallest p value < alpha/(NC-1)
  - Third smallest p value < alpha/(NC-2)
  - Etc etc…

Book by Efron "Large-scale statistics"

Controlling for multiple comparisons – using permutations

- **Do permutation simultaneously for all multiple variables (e.g. all links) to generate at once many surrogate values**
- **Pick the strongest (max statistics)**
- **The null distribution will look more skewed towards the maximum**

Controlling for multiple comparisons – using permutations

- **Cluster approaches (with fMRI)**
- **Non-parametric:**
  - At each permutation set a cluster forming threshold
  - Count how many voxels in the largest connected cluster
  - Compare number of connected voxels in the un-permuted cluster

Proceedings of the National Academy of Sciences of the United States of America PNAS

> Current Issue > vol. 113 no. 28 > Anders Eklund, 7900–7905, doi: 10.1073/pnas.1602413113

Check for updates

Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates

Anders Eklund[a,b,c,1], Thomas E. Nichols[d,e], and Hans Knutsson[a,c]

Author Affiliations

Edited by Emery N. Brown, Massachusetts General Hospital, Boston, MA, and approved May 17, 2016 (received for review February 12, 2016)

This Issue

July 12, 2016
vol. 113 no. 28
Masthead (PDF)
Table of Contents

PREV ARTICLE NEXT ARTICLE

Don't Miss

http://www.pnas.org/content/113/28/7900.full

According to many of the headlines that greeted "Cluster failure", the paper is a devastating bombshell that could demolish the whole field of functional magnetic resonance imaging (fMRI):

> Bug in fMRI software calls 15 years of research into question (Wired)
>
> A bug in fMRI software could invalidate 15 years of brain research. This is huge. (ScienceAlert)
>
> New Research Suggests That Tens Of Thousands Of fMRI Brain Studies May Be Flawed (Motherboard)

http://blogs.discovermagazine.com/neuroskeptic/2016/07/07/false-positive-fmri-mainstream/#.WRq28SN97-m

Controlling for multiple comparisons – using permutations

- Cluster approach (with fMRI) recently re-tested
- Fake task using resting state data
- Comparing cluster approaches: parametric (RFT) and non parametric
- Permutations was the only one closest to the “truth”

How about networks?

How to compute differences between networks

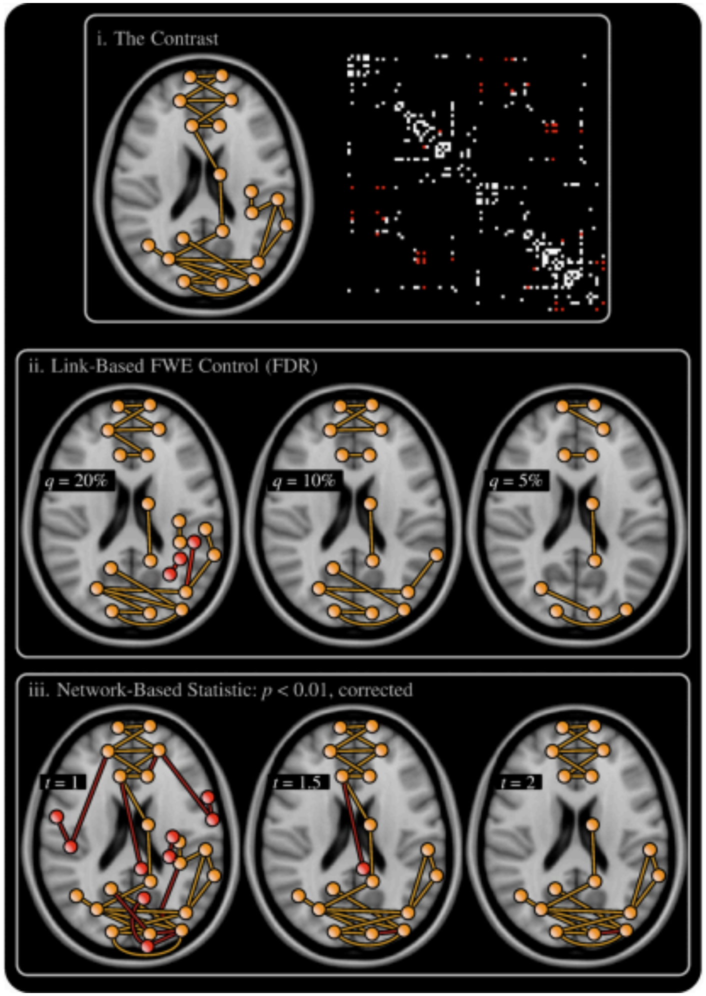
- **At each level (node/link/global) you can test for a difference between two groups or from a baseline prior knowledge**
- **Links are correlations -> they can be mapped to p-values but degrees of freedom must be estimated**

How to compute differences between networks

- **Node properties are coming from very long tailed/weirdly shaped distributions -> permutation approaches or build null models with networks**
- **Network null models have problems (suboptimal)**

Solving the multiple comparison problem for networks

Network based statistics is the cluster correction applied to the links



Check

http://www.sciencedirect.com/science/article/pii/S1053811912000857

PART 2
Brain network properties

Network topology

Network level features

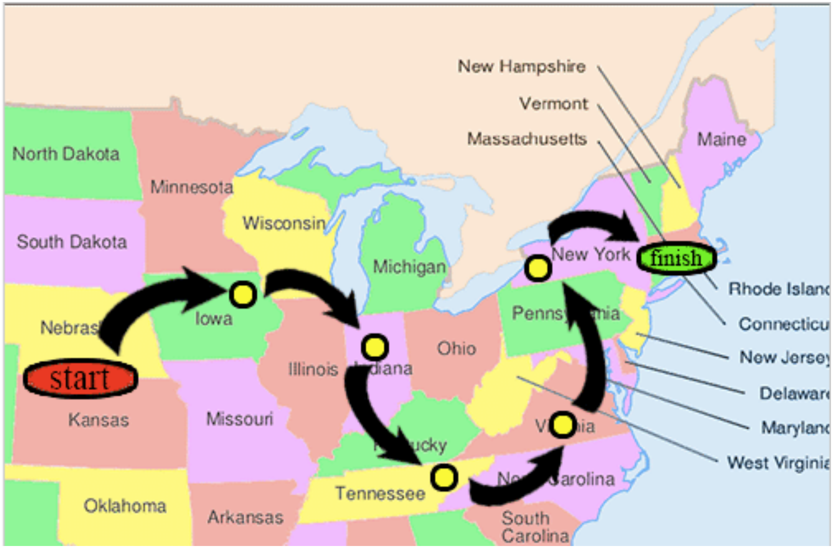
EnricoGaean
wwwgaeancom l@egaean

What?

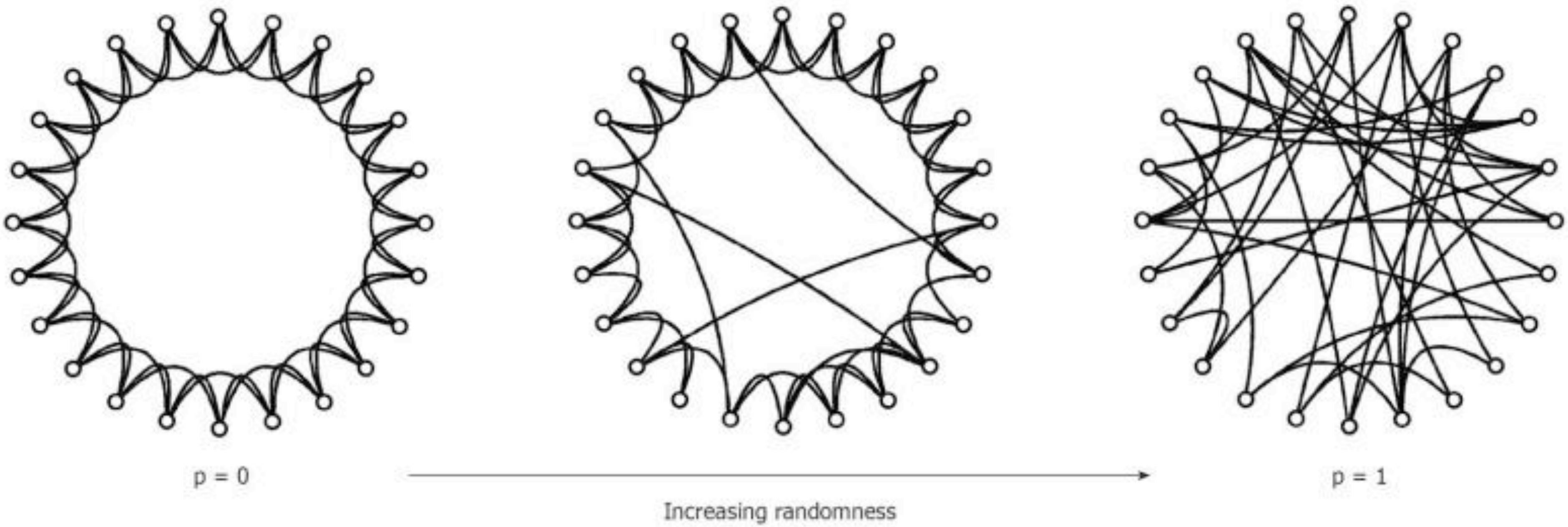
What is a small world network?

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



Watts, D. J., & Strogatz, S. H. (1998). Collective dynamics of “small-world” networks. Nature, 393(6684), 440–2. doi:10.1038/30918

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.

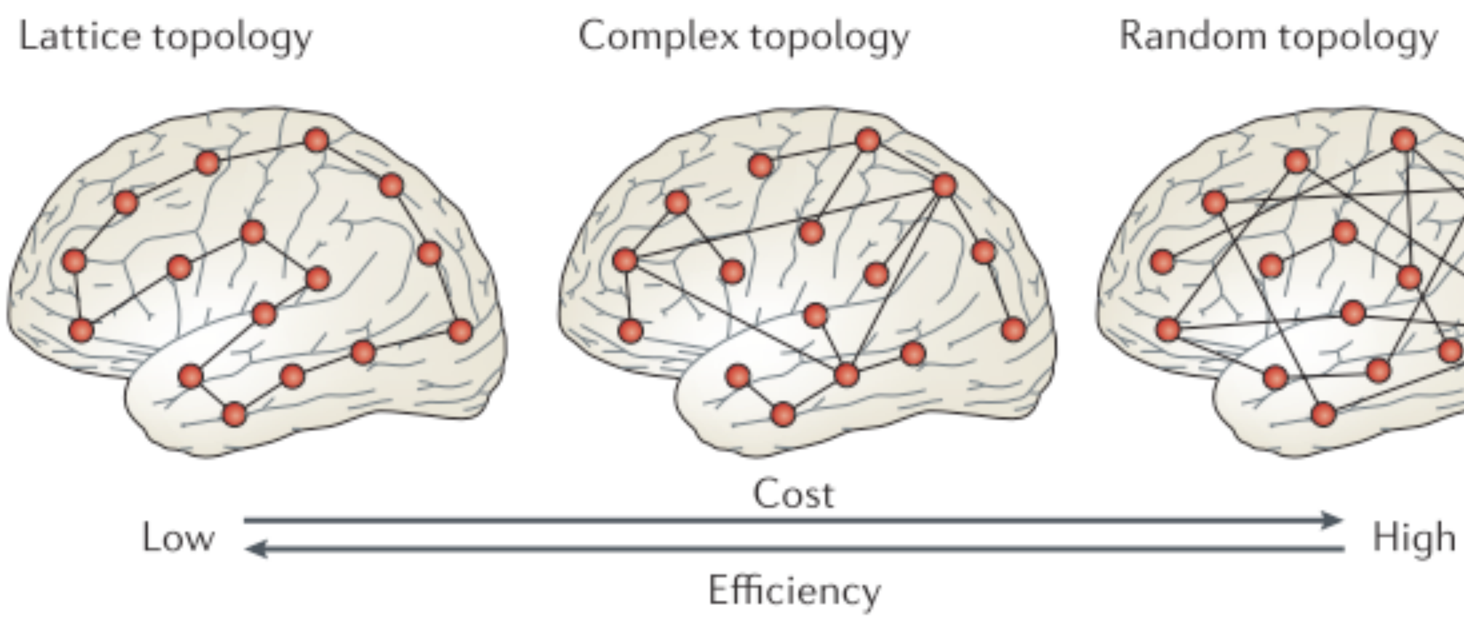
The brain is a small world network.

Why?

Why is the brain a small world network?

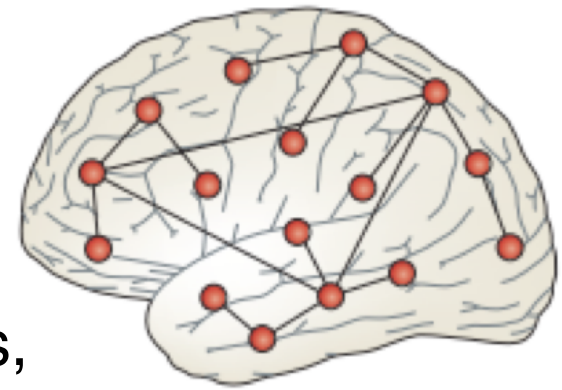
EnricoGaean
wwwgaeancom1@egaean

The small-world configuration is the optimal to optimize communication cost and efficiency



Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. Nature reviews. Neuroscience, 13(5), 336–49.(*)

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**

Network topology

NODE LEVEL FEATURES

EnicoGaean
wwwgaeancom1@egaean

What?

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**

What is a hub?

A hub is the effective center of an activity, region, or network…

i.e. **an important node in the network**

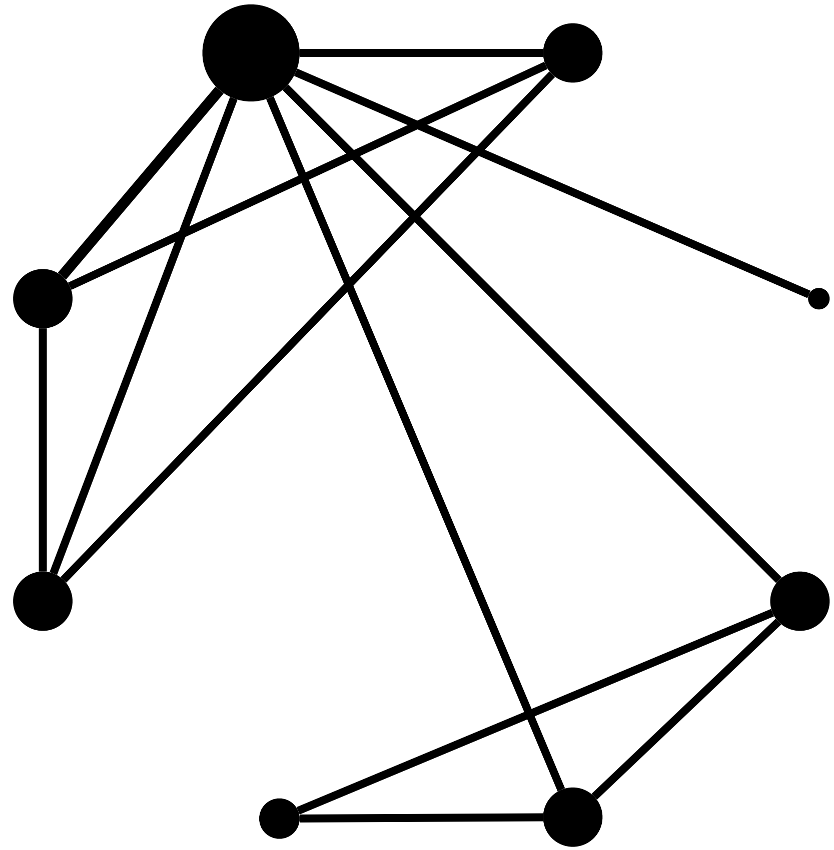
EnricoGlaean
wwwglaeancom1@eglaean

How?

HOW CAN 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?



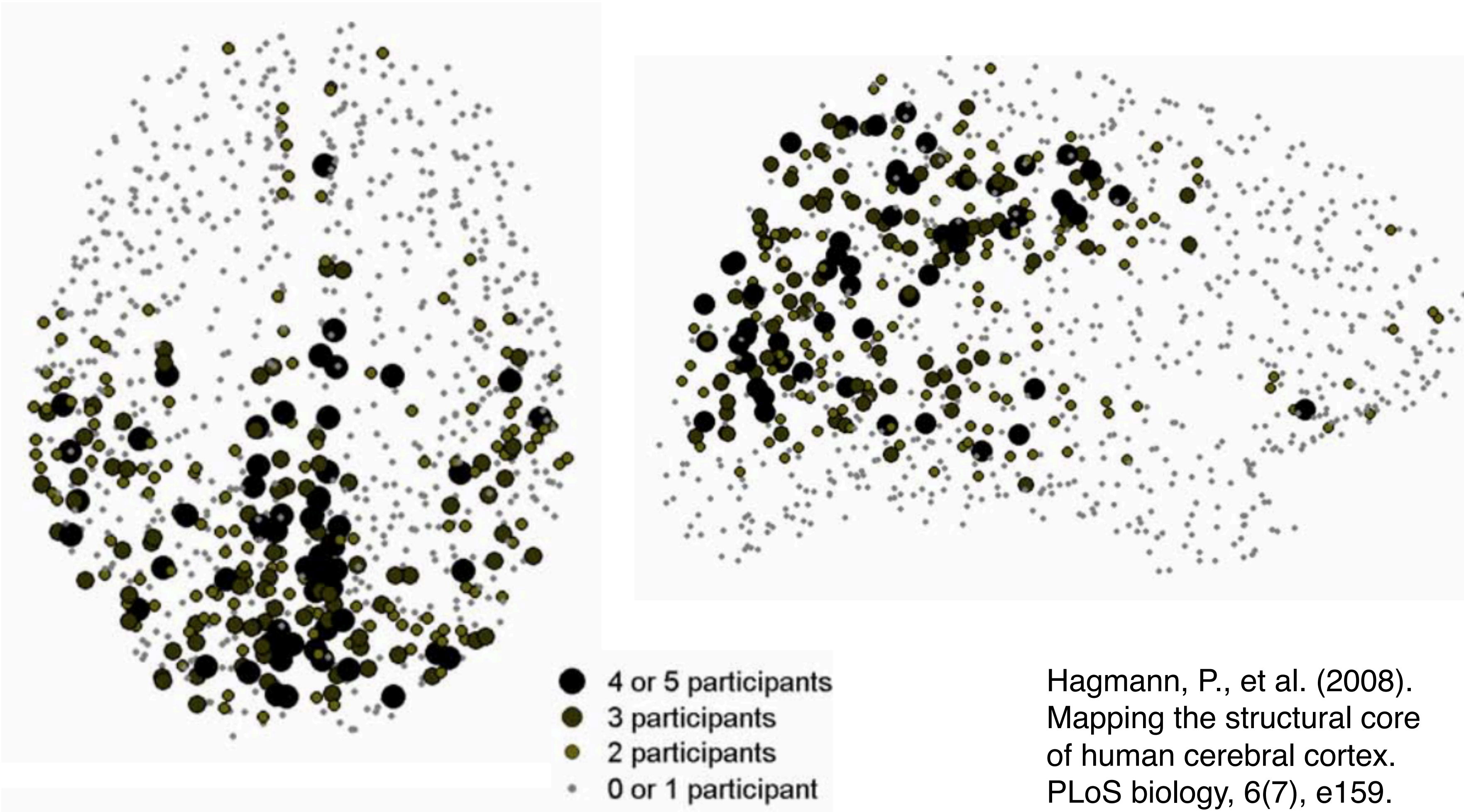
EnricoGlaean
wwwglaeancoml@eglaean

What?

What are the hubs in the brain?

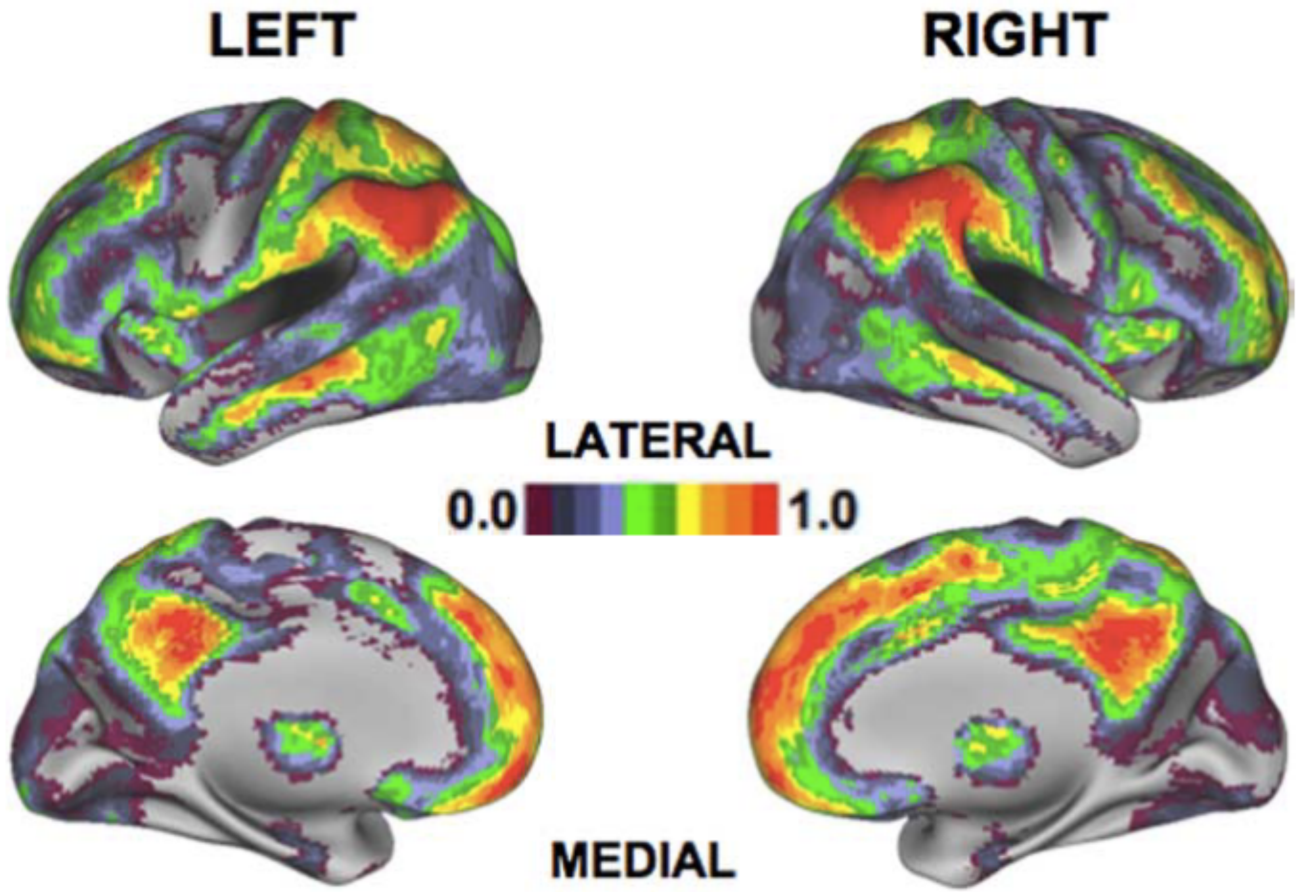
Enrico Glerean
www.glerean.com | @eglerean

Cortical hubs in the human brain



Hagmann, P., et al. (2008). Mapping the structural core of human cerebral cortex. PLoS biology, 6(7), e159.

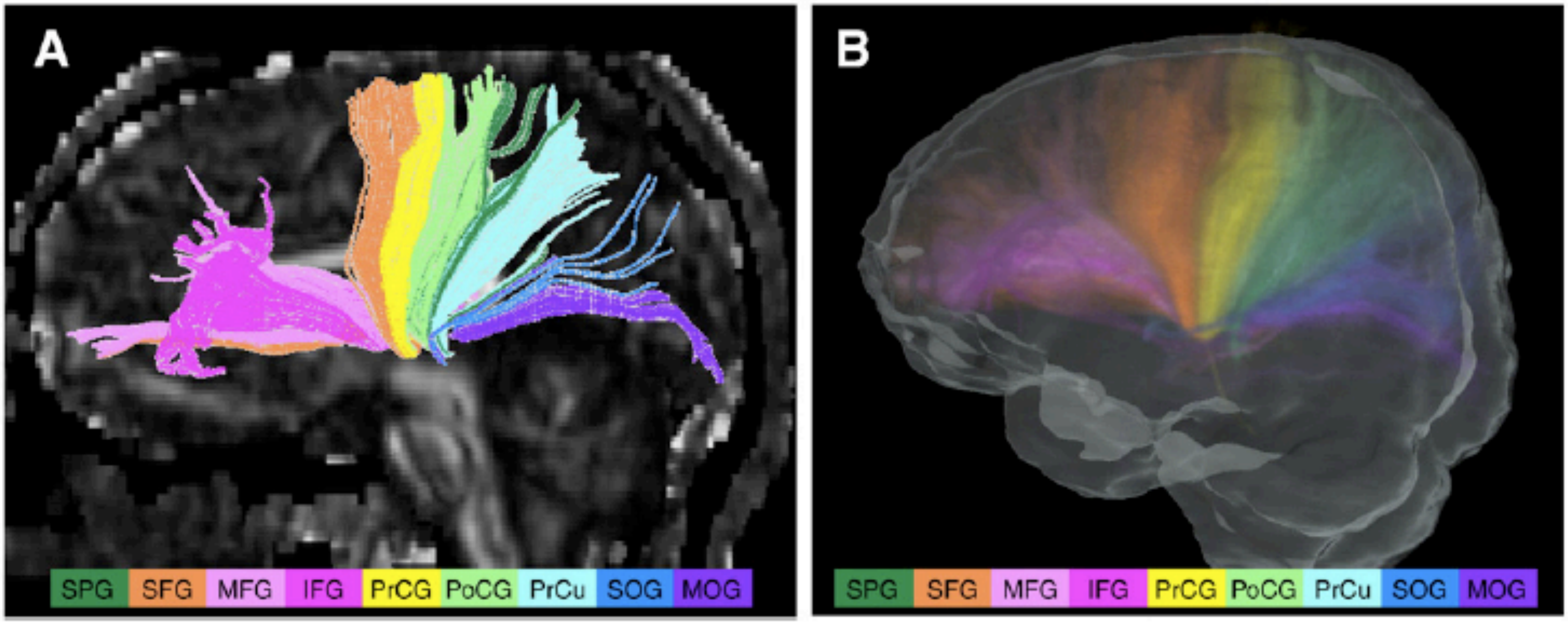
Cortical hubs in the human brain



Buckner, R. L., et al. (2009). Cortical hubs revealed by intrinsic functional connectivity. The Journal of neuroscience 29(6), 1860–73.

Enrico Glerean
www.glerean.com | @eglerean

Sub-cortical hubs in the human brain: the thalamus

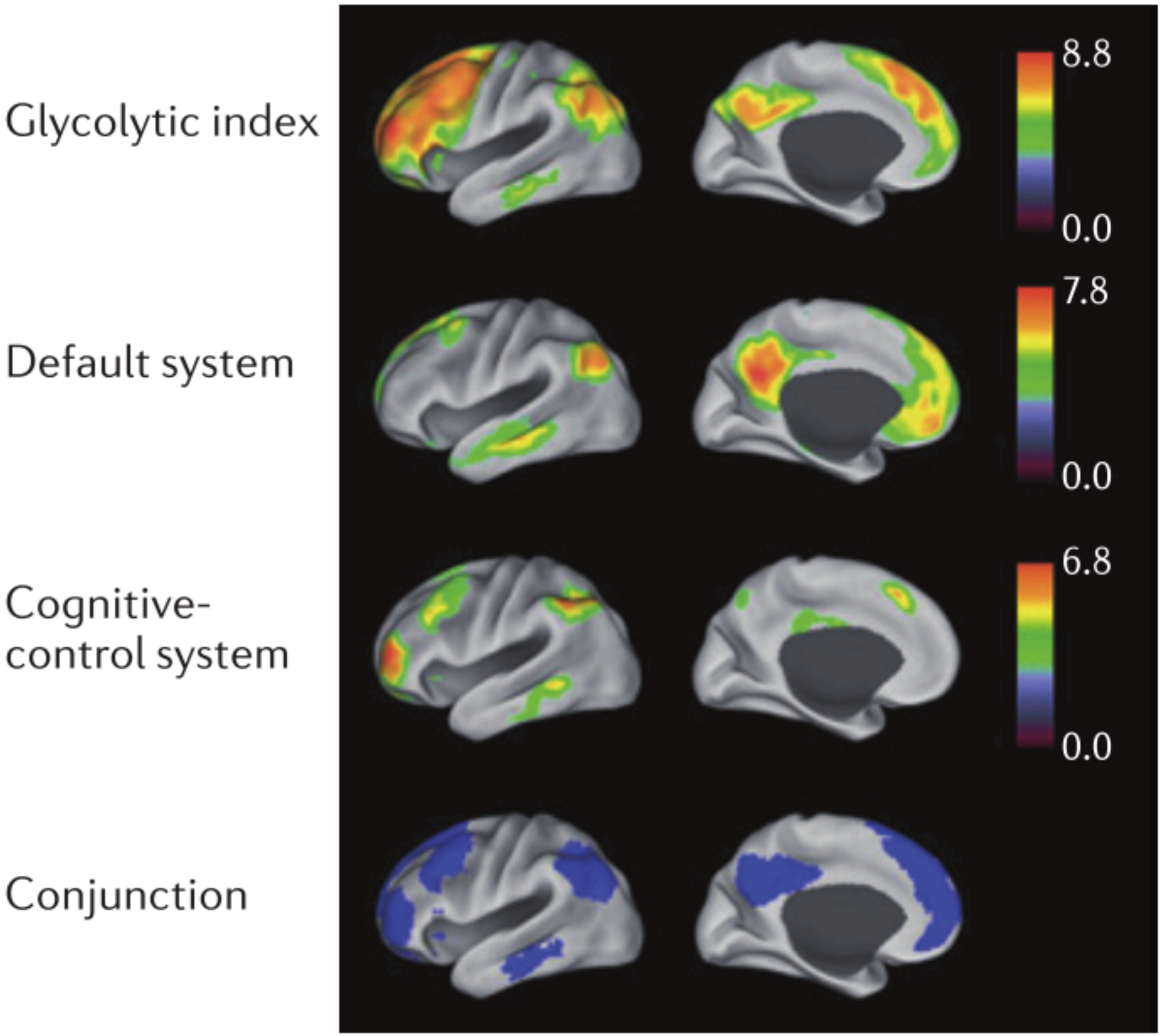


Zhang et al. (2010) Atlas-guided tract reconstruction for automated and comprehensive examination of the white matter anatomy. Neuroimage. 2010 Oct 1;52(4):1289-301.

What?

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.

Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. Nature reviews. Neuroscience, 13(5), 336–49.

What?

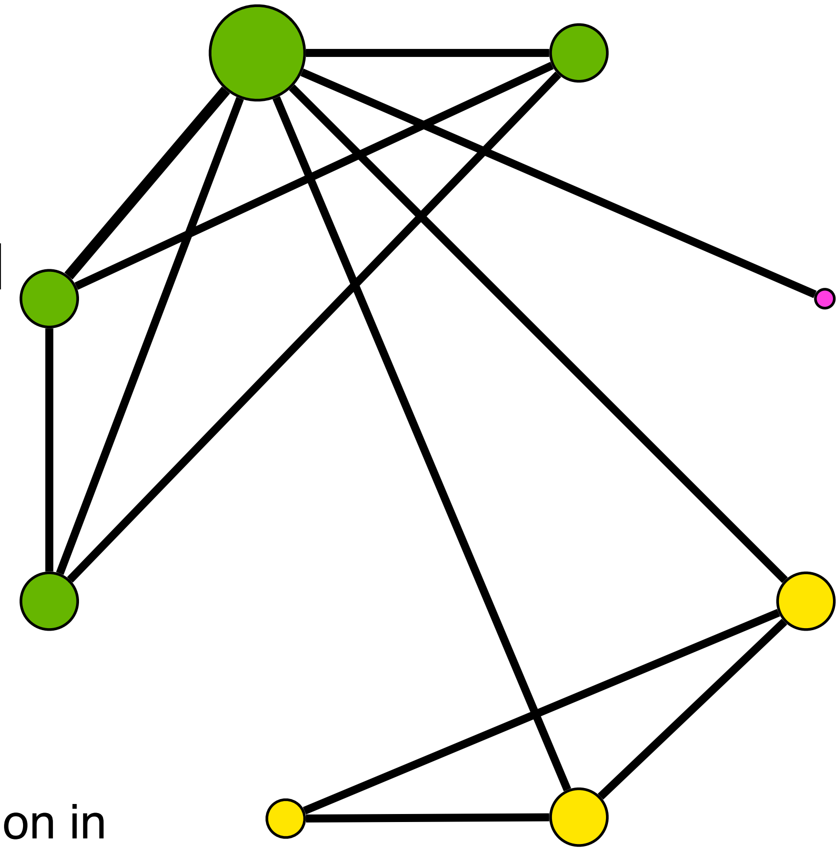
What is a network module?

Enrico Glerean
www.glerean.com | @eglerean

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



Fortunato, S. (2010). Community detection in graphs. Physics Reports, 486(3-5), 75–174

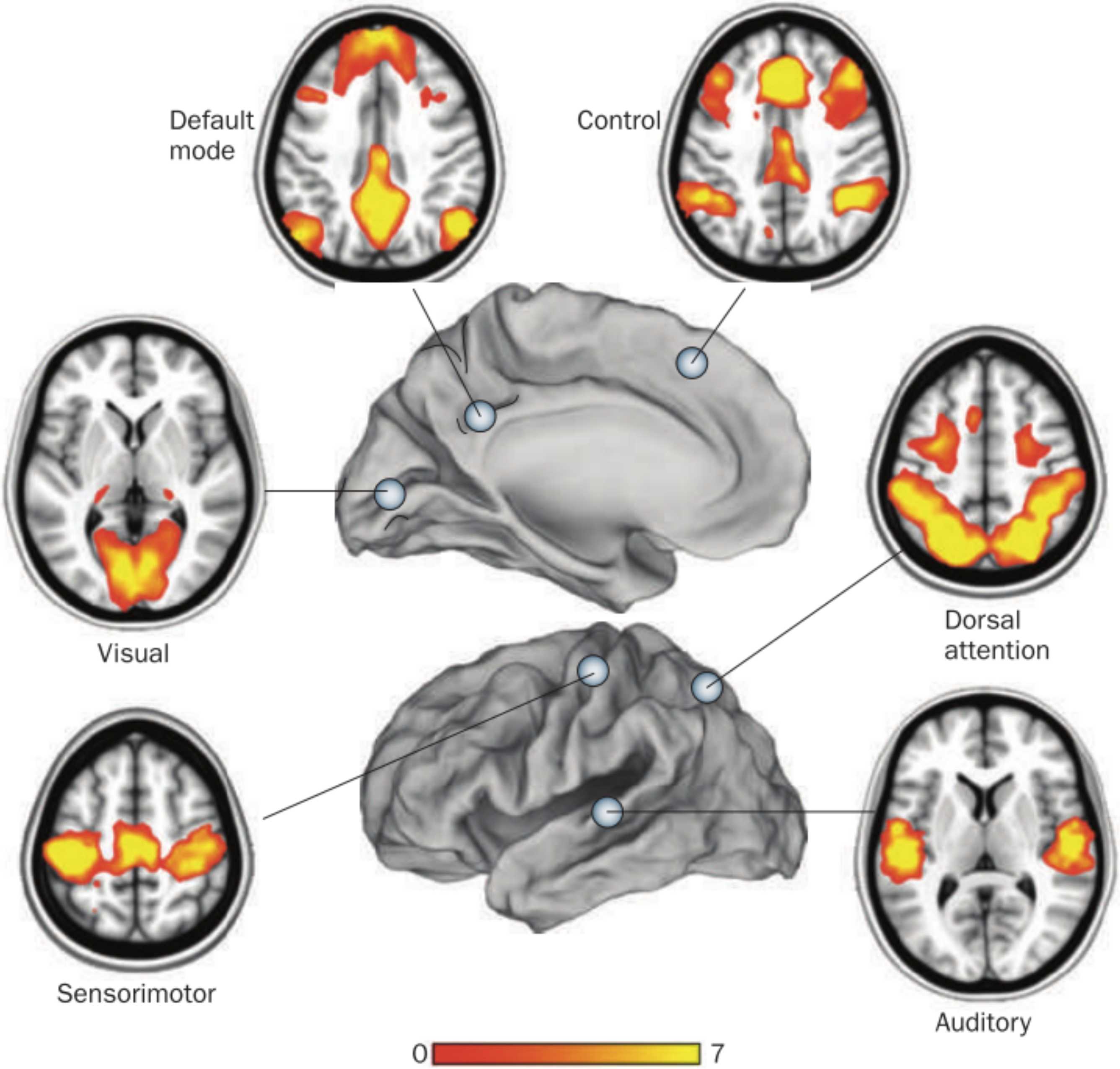
What?

What are the modules in the brain?

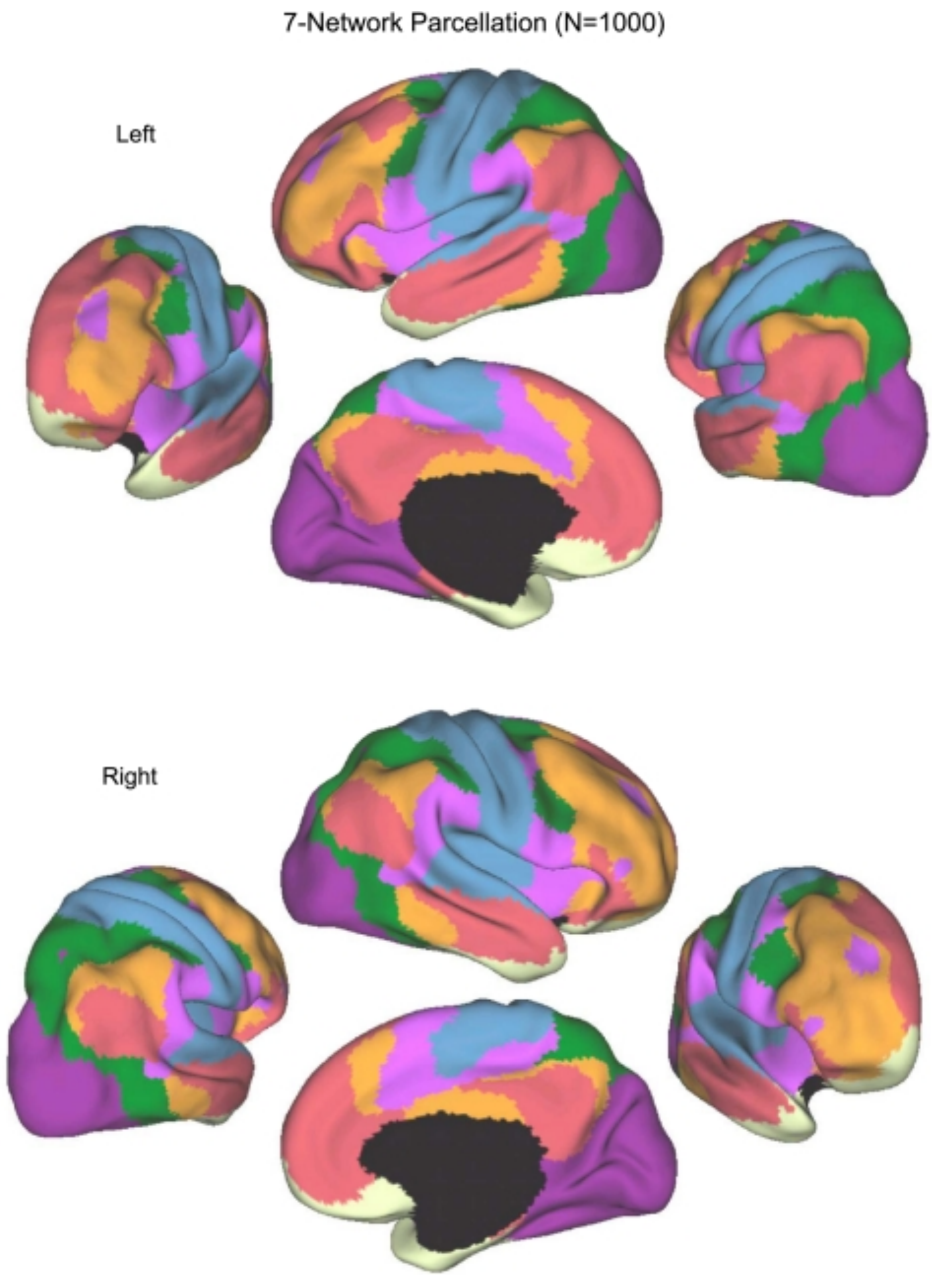
Enrico Glerean
www.glerean.com | @eglerean

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



Zhang, D., & Raichle, M. E. (2010). Disease and the brain's dark energy. Nature reviews. Neurology, 6(1), 15–28.



Purple (Visual)

Blue (Somatomotor)

Green (Dorsal Attention)

Violet (Ventral Attention)

Cream (Limbic)

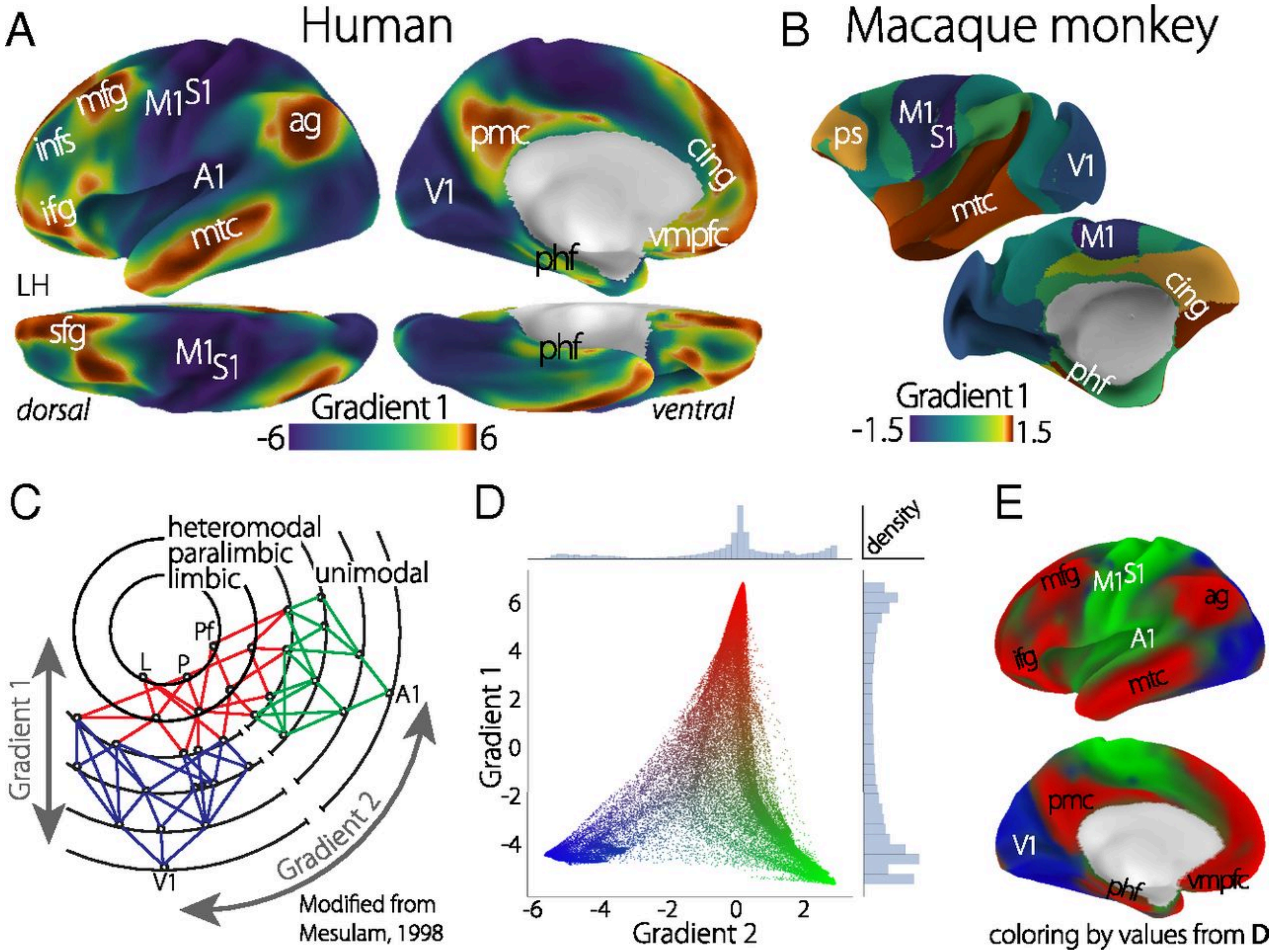
Orange (Frontoparietal)

Red (Default)

Yeo et al. (2011)

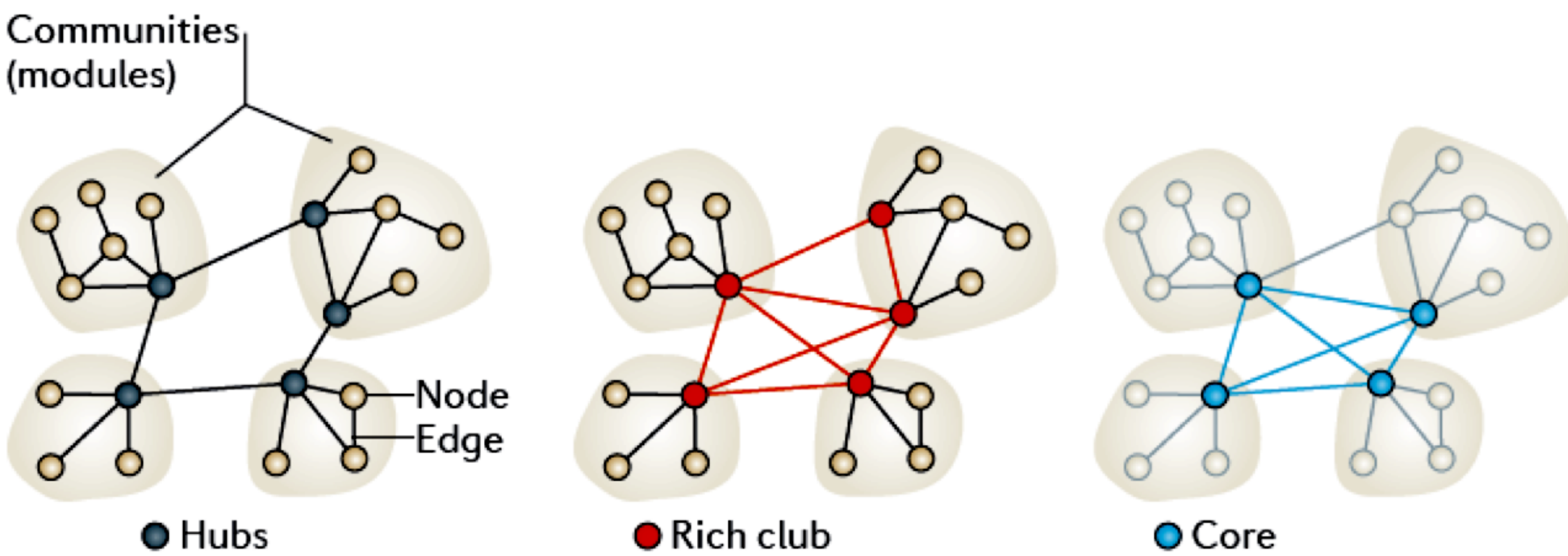
The organization of the human cerebral cortex estimated by intrinsic functional connectivity

J Neurophysiol. 106(3):1125-65.

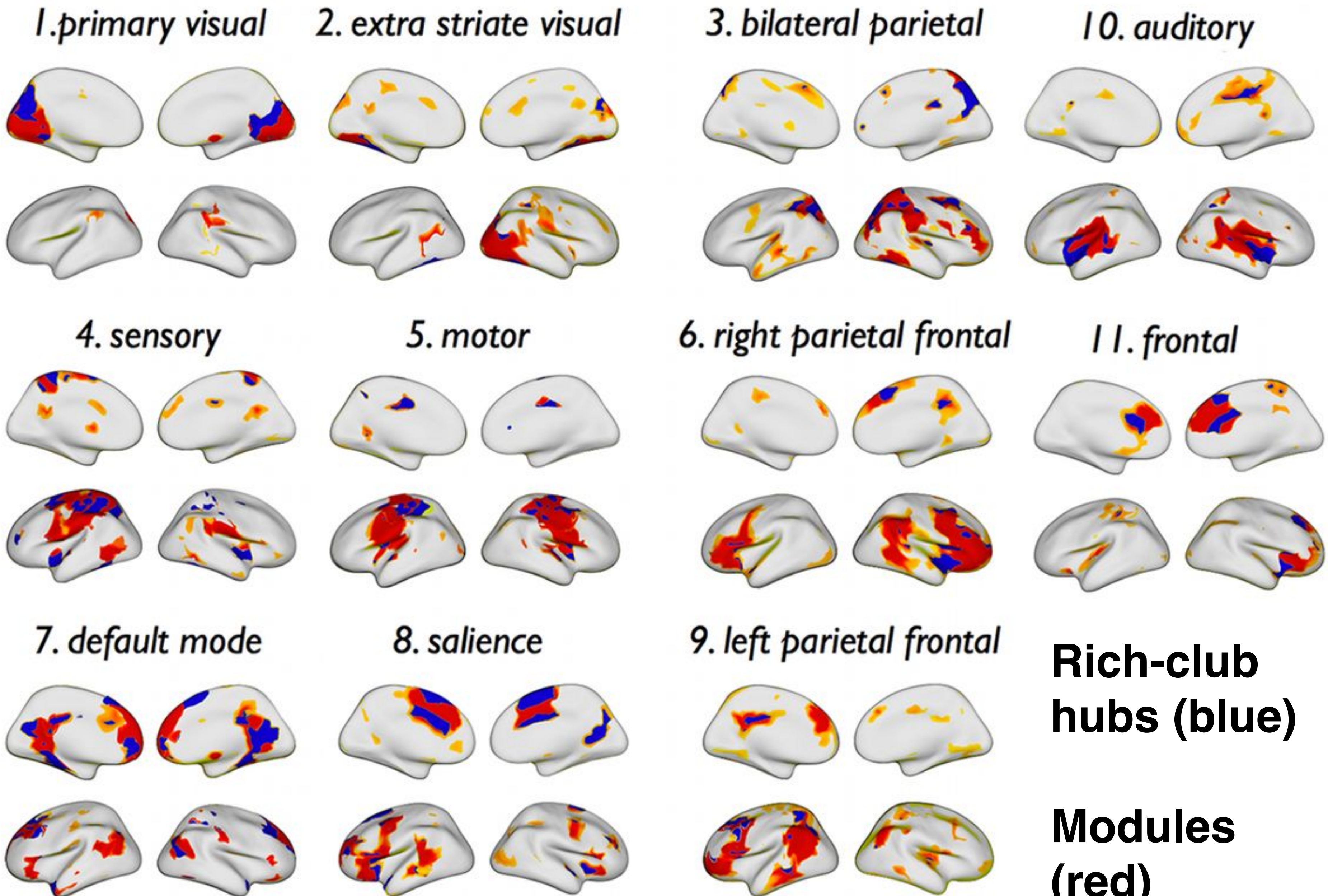


Margulies et al (2016) **Situating the default-mode network along a principal gradient of macroscale cortical organization.** PNAS

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



Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. Nature reviews. Neuroscience, 13(5), 336–49



Rich-club hubs (blue)

Modules (red)

Van den Heuvel & Sporns (2013). JNeurosci.

How?

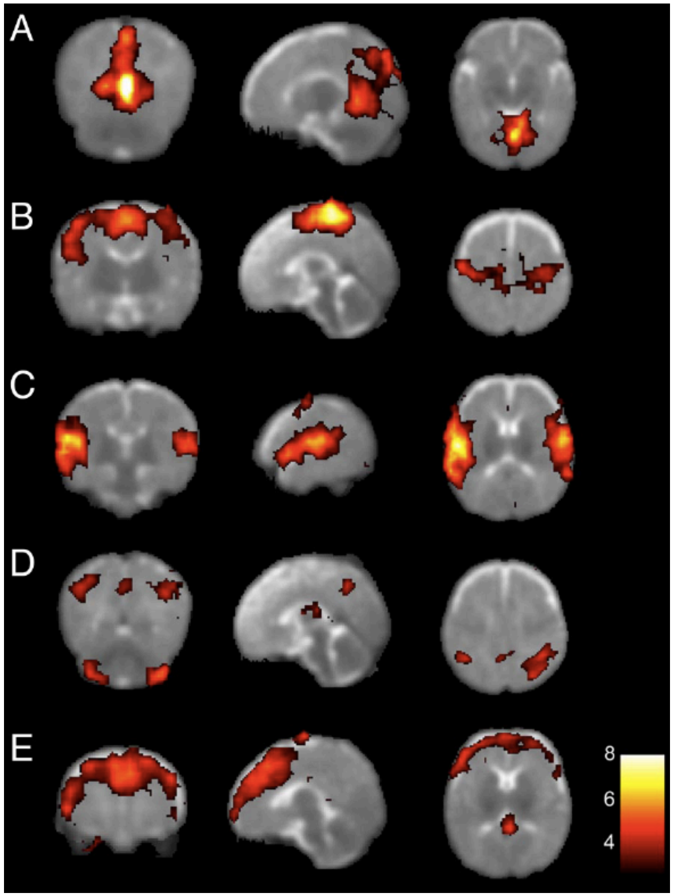
HOW DOES CONNECTIVITY CHANGE IN TIME?

EnricoGlaean
wwwglaeancomrl@eglaean

Temporal scales of connectivity

- Changes across **(milli)seconds**
  - **Fast** functional changes due to **extrinsic** or **intrinsic** processes
- Changes across **years**
  - **Slow** structural changes due to **genetics**, **environment** and **noise**

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

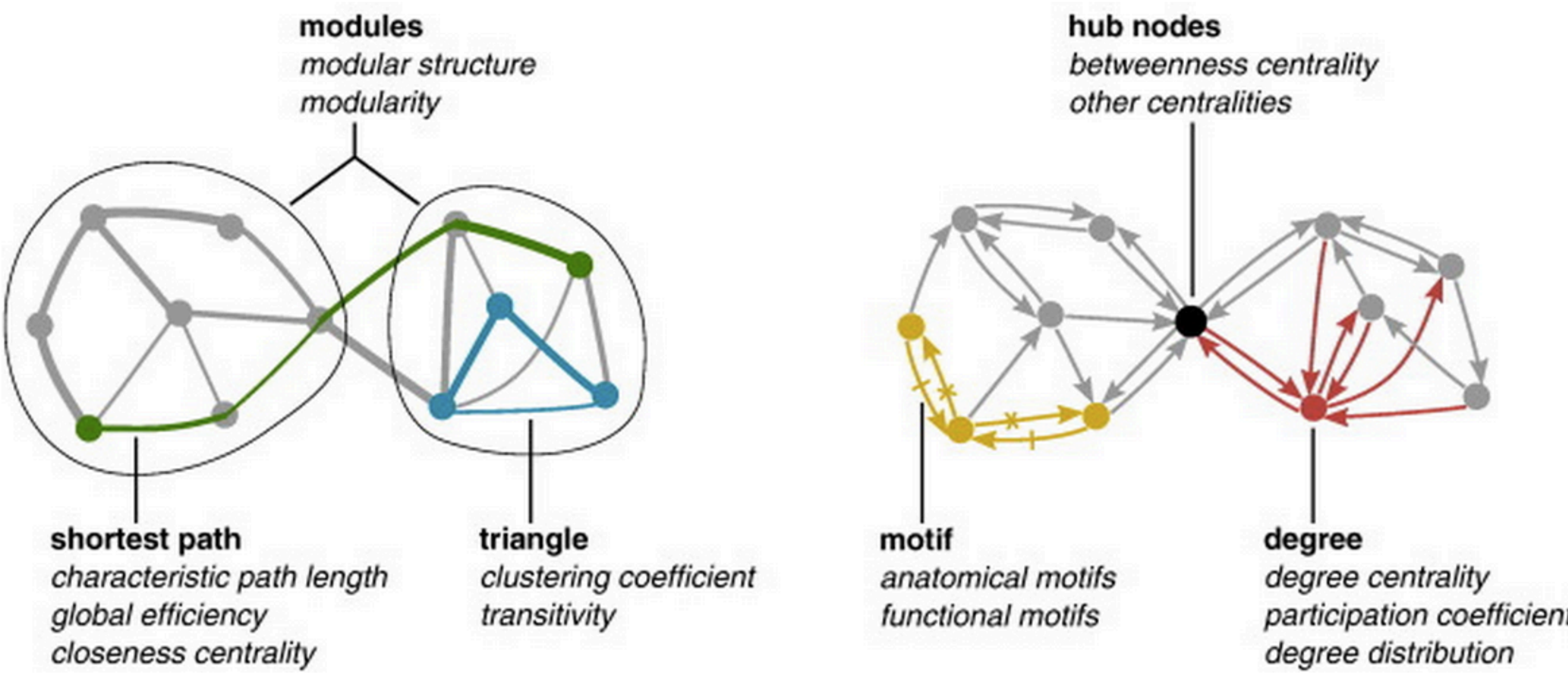
Fransson et al (2007) PNAS

Enrico Glerean
www.glerean.com @eglerean

How to estimate and compare network properties

How to calculate these network features?

- **See Brain Connectivity Toolbox and its related papers**



Rubinov & Sporns 2010, Neuroimage http://www.neuroscience.cam.ac.uk/publications/download.php?id=17703

Bullmore & Sporns 2009 Nature Review Neuroscience http://www.nature.com/nrn/journal/v10/n3/full/nrn2575.html

How to compare network properties?

- It's tricky because **network properties do not follow a gaussian distribution**
- Best is to NOT assume anything and use **permutation testing:** e.g. for a node, shuffle labels and compute surrogate group difference. Repeat x 5000 and get null distribution.
- **Remember to correct for multiple comparisons**

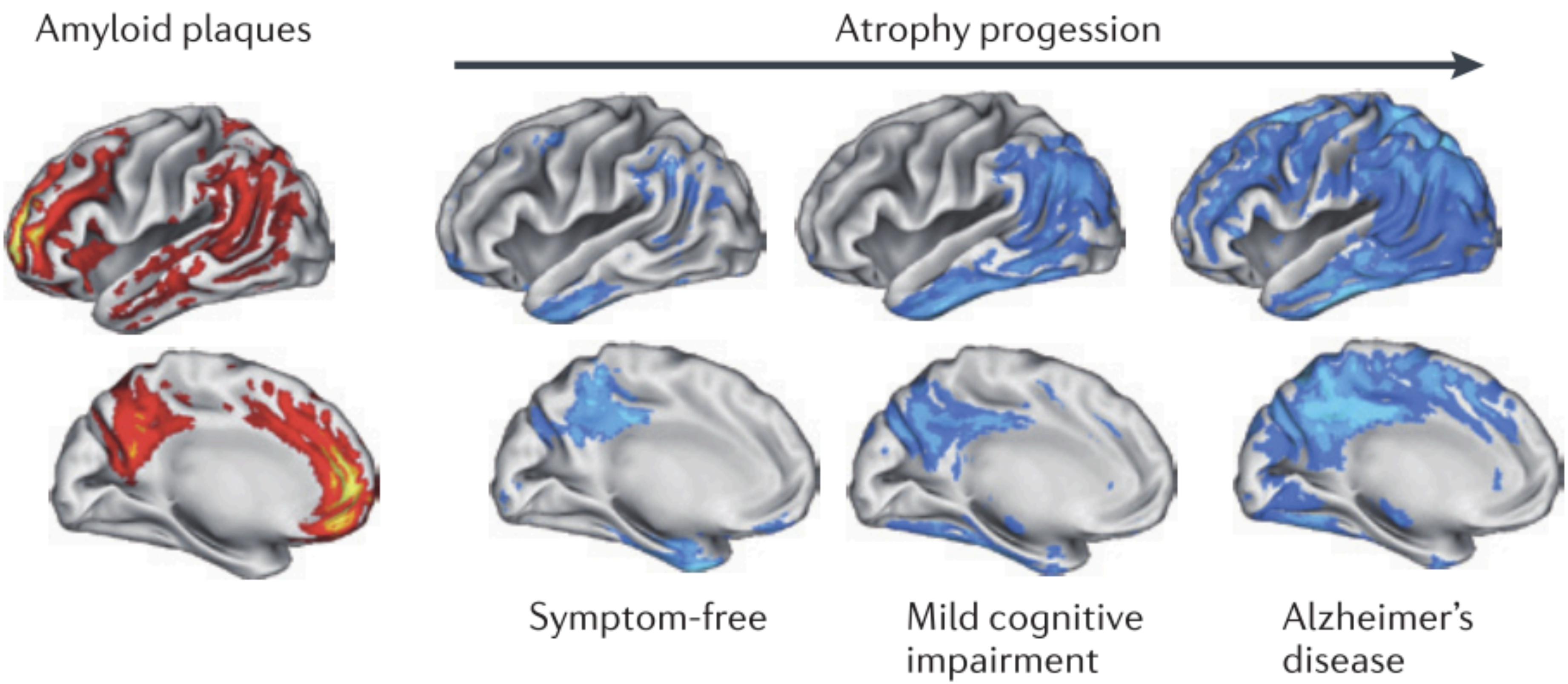
Part 3
Connectivity and its impact

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**

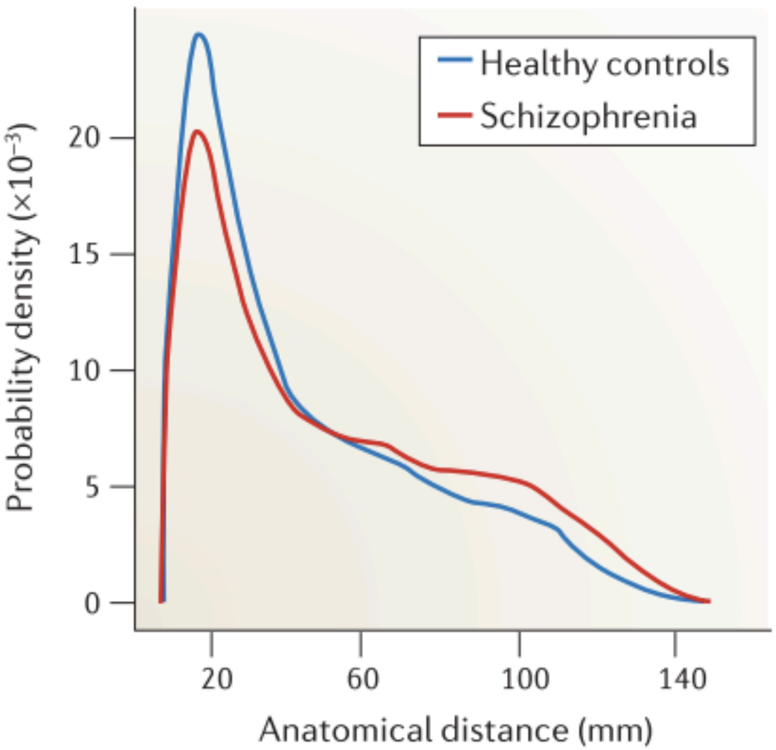


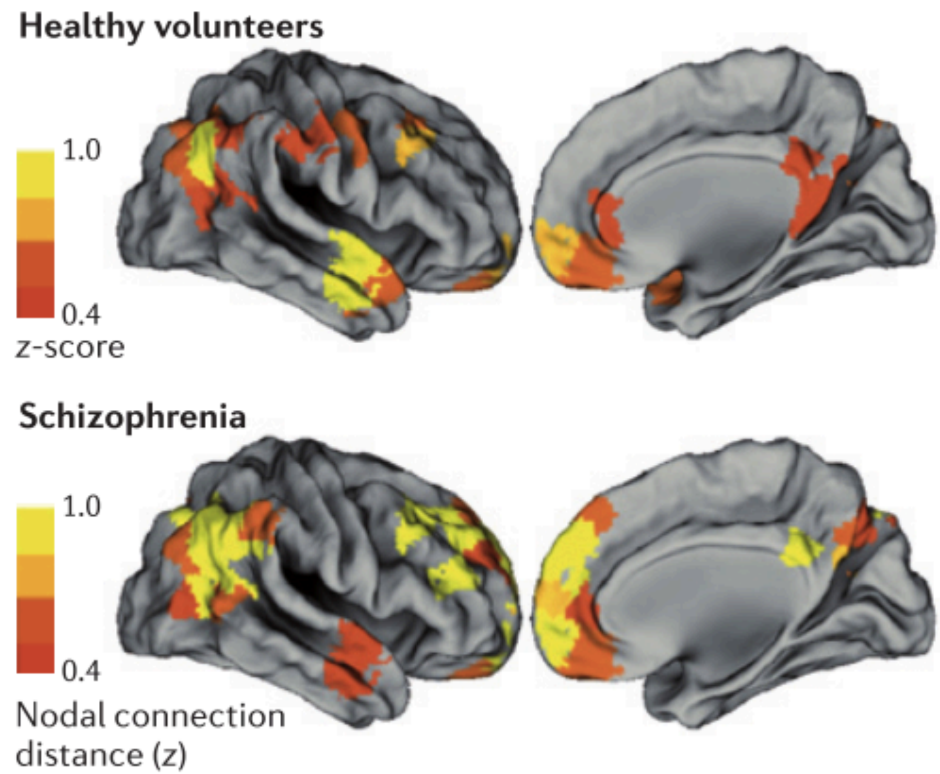
Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. Nature reviews. Neuroscience, 13(5), 336–49

Schizophrenia

Bullmore, E., & Sporns, O. (2012). The economy of brain network organization.

- **Unbalanced small-worldness**





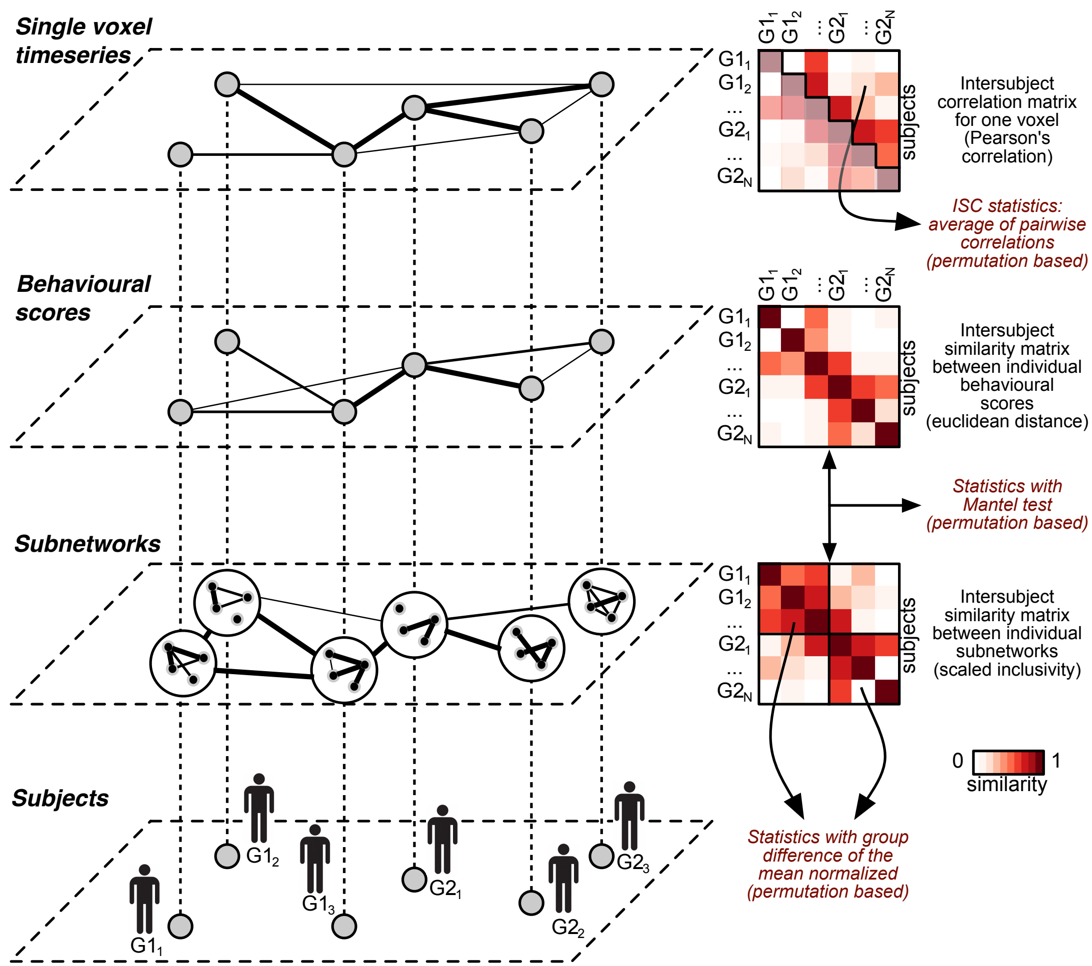
Reorganization of functionally connected brain subnetworks in high-functioning autism (Glerean et al 2016)

- Neuroimaging literature of ASD reports a **mixture of decreased and increased functional connectivity**.
  AIM1) intersubject analysis framework to take into account the **heterogeneity of the disorder**.
  AIM2) analyze connectivity at the **subnetwork level** to possibly resolve the mixture of findings at single node/link level.

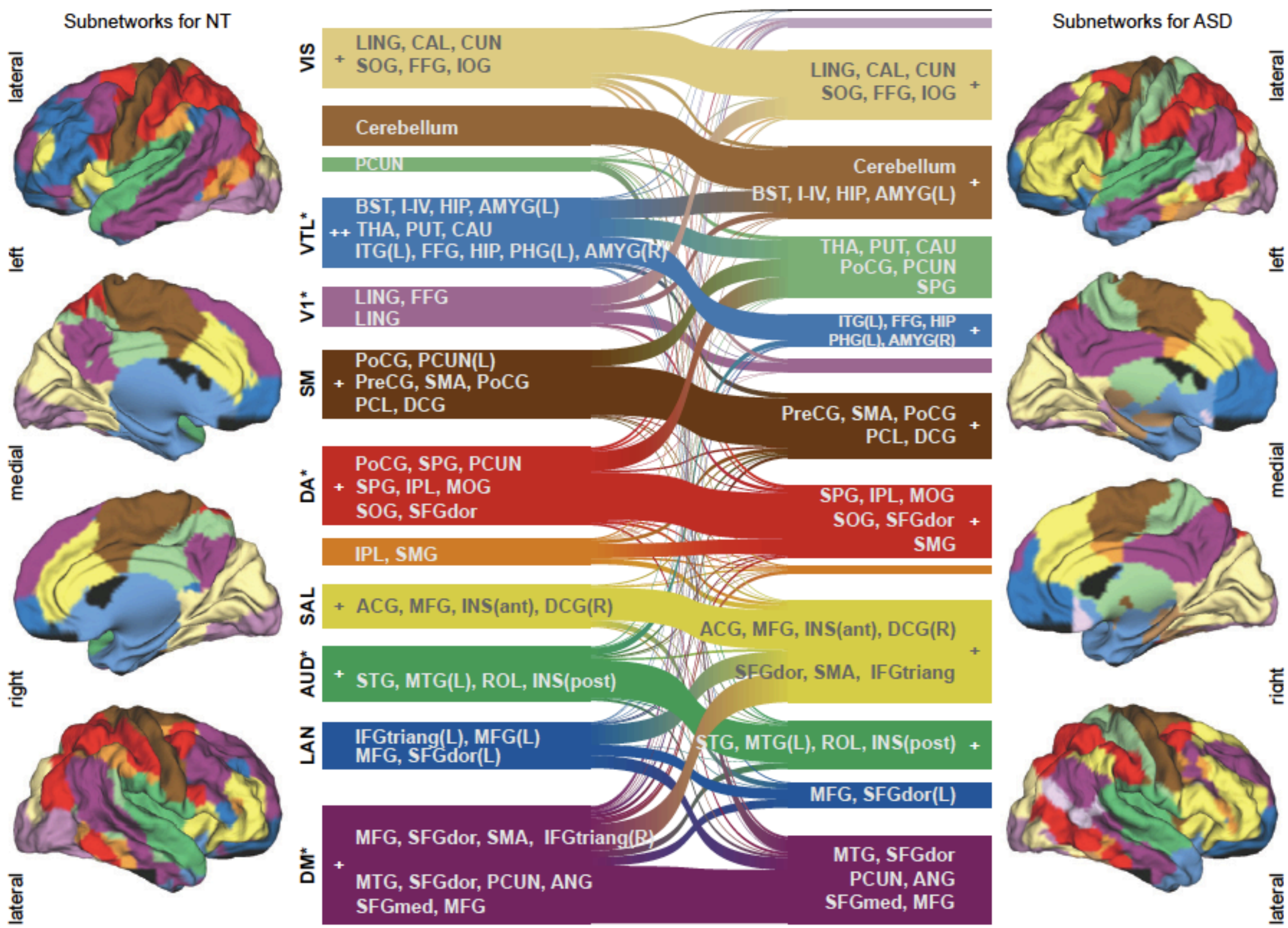
- **Data:** 26 participants (13 with ASD), watching the movie *Tulitikkutehtaan tyttö* while undergoing fMRI. A replication resting-state dataset was included (data from the ABIDE initiative).

Intersubject analysis framework

- Assessing **significance of ISC matrix**
- **Mantel test** (comparison between similarity matrices)
- **Comparing within groups/conditions similarities**



Autism subnetworks (Glerean et al 2016)



Significant differences in:

Default Mode

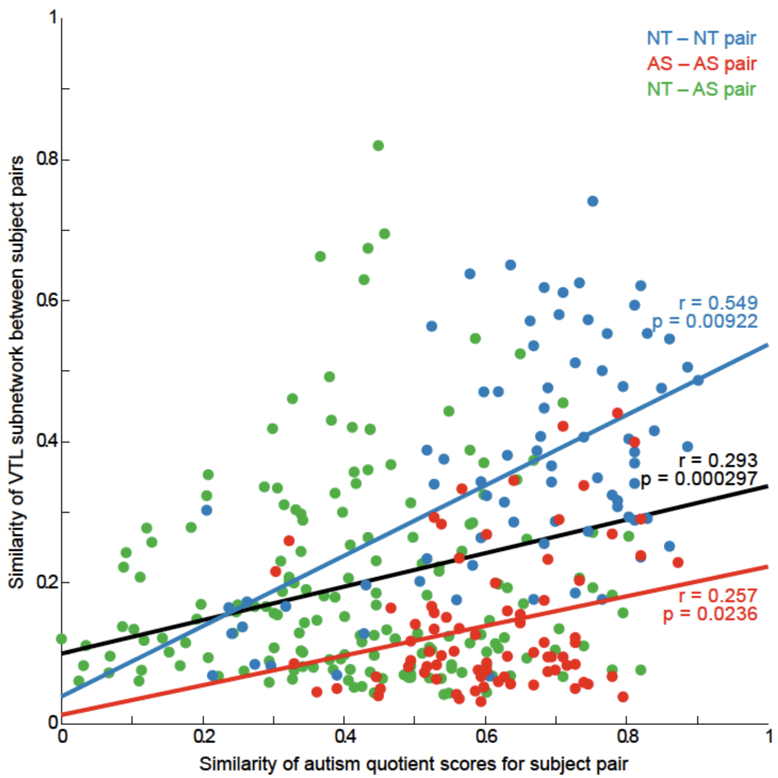
Auditory

Dorsal attention

Visual primary

Ventro-temporo-limbic (VTL)

Results: correlation between AQ similarity and VTL similarity



The more two subjects have a similar VTL subnetwork, the more they have similar symptoms (amygdala, nucleus accumbens, putamen, caudate, thalamus, ventral visual pathway, ventro-medial prefrontal cortex)

The relationship is **also significant for controls**

Clinical uses?

- 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
  - Lang et al. 2014, **Resting-State Functional Magnetic Resonance Imaging: Review of Neurosurgical Applications**, Neurosurgery doi: 10.1227/NEU.0000000000000307
  - Castellanos et al, 2013, **Clinical applications of the functional connectome**, Neuroimage, doi: 10.1016/j.neuroimage.2013.04.083

EnricoGlerean
www.glerean.com | @eglerean

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 (**UK Biobank project**)

Future?

Future directions in the fields of network science and brain connectivity

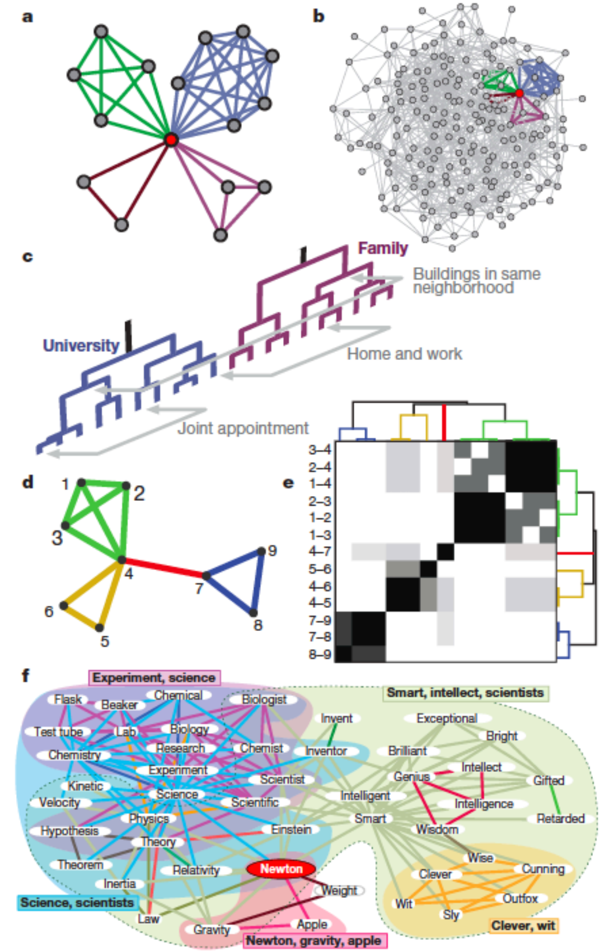
Future directions in the field

- **Line networks (link networks) and overlapping communities**
- **Multilayer and multiplex networks**
- **Networks of networks**

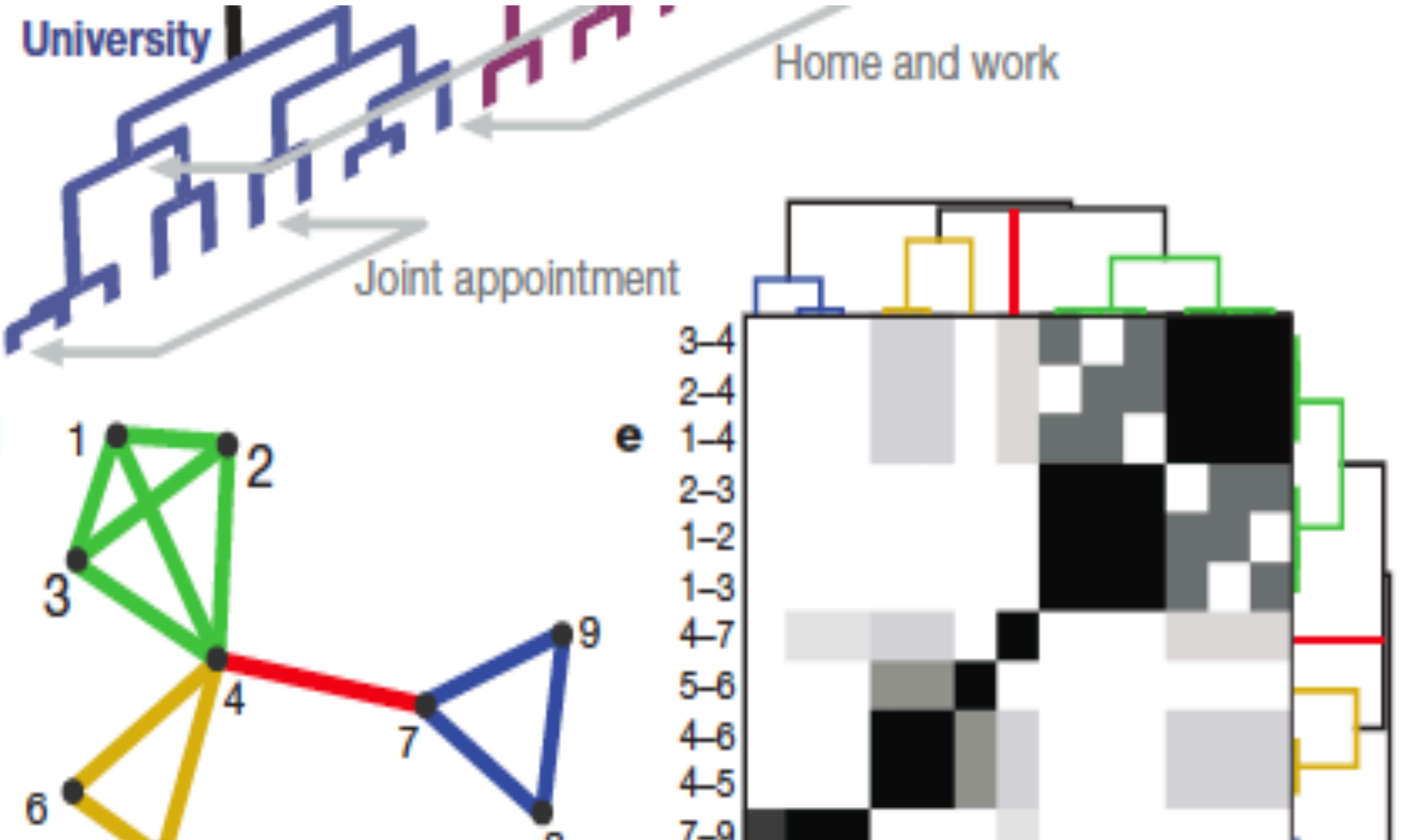
EnrioGlaean
wwwglaeancoml@eglaean

Overlapping communities

- **Line networks (link networks) and overlapping communities**
- **See paper: http://www.nature.com/nature/journal/v466/n7307/abs/nature09182.html**

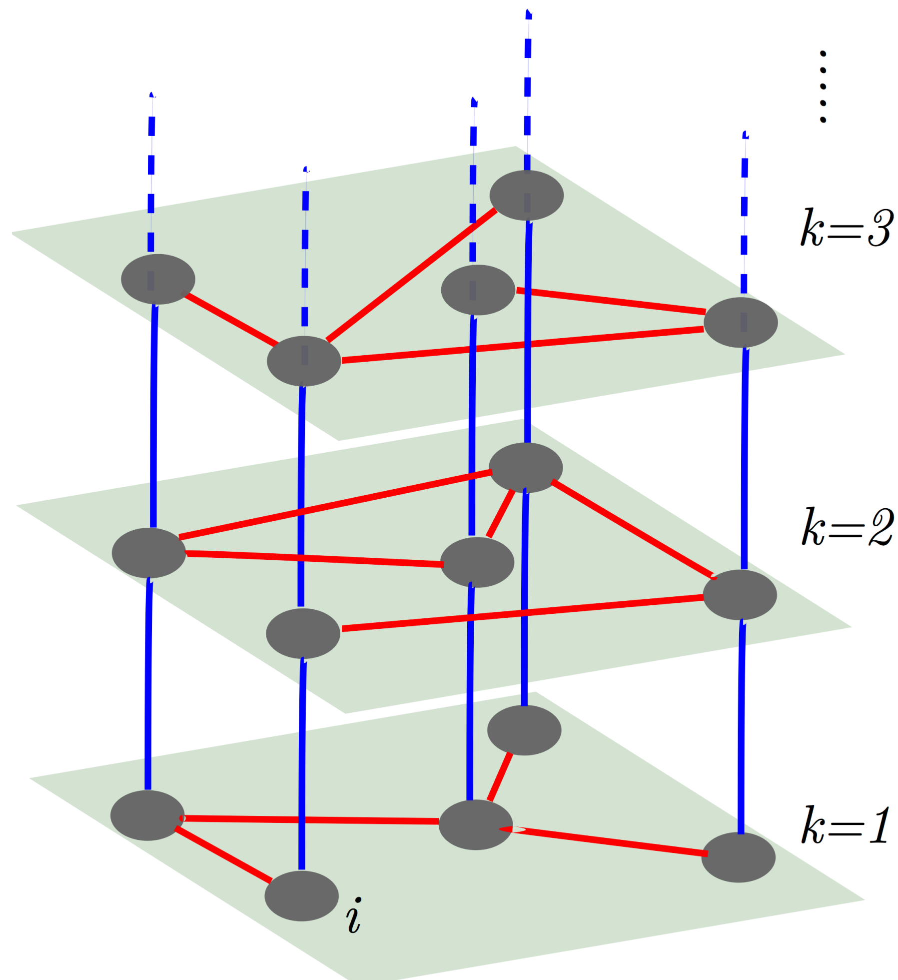


Overlapping communities



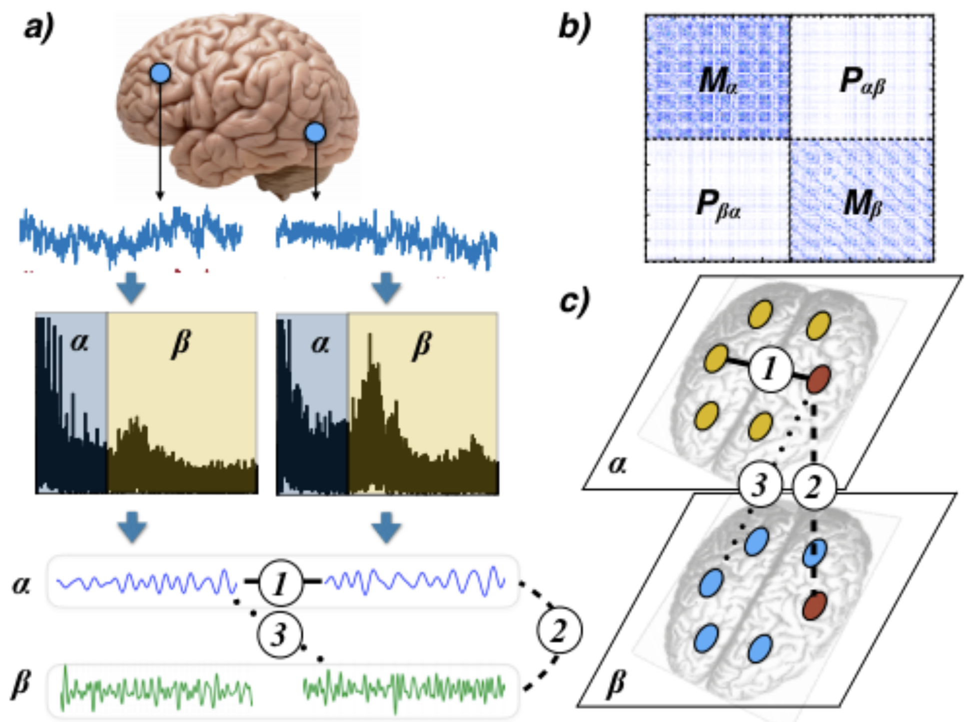
Multiplex networks

- **Multiple networks where nodes are the same and connected with themselves through a 3rd dimension** (e.g. subjects, time points, frequency bands)



Multilayer networks

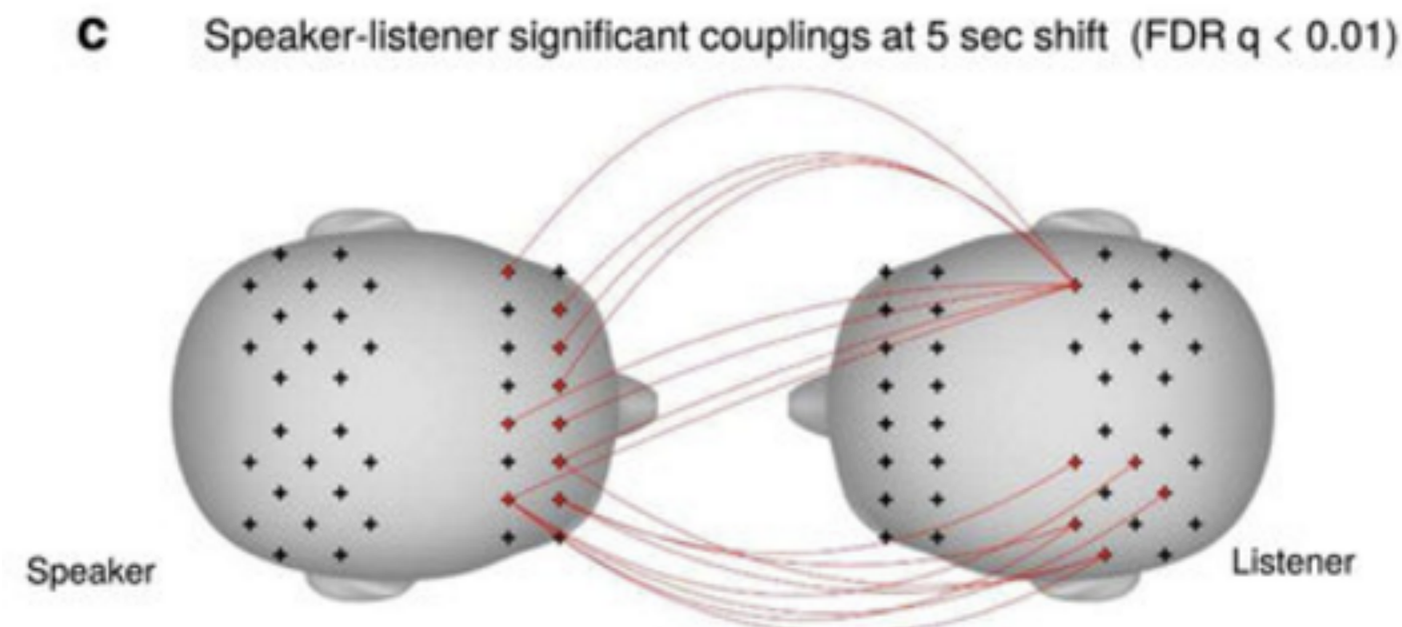
- **Multiple networks where nodes are connected with all other nodes in other layers**



https://arxiv.org/pdf/1703.06091.pdf

Networks of networks

- **Functional networks between subjects**



https://www.nature.com/articles/srep43293

Take home messages

Human brain networks
Take home messages

- **Brain network science** is a relatively recent field that is still evolving as new graph-theory methods are coming out. I personally think it is the way to go, and recent top papers in the field have been using brain connectivity methods.

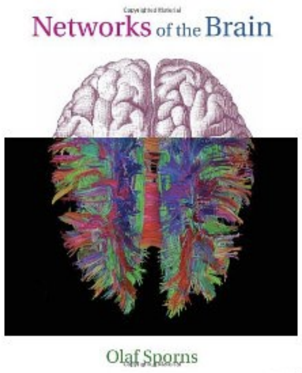
- There are **multiple ways of modelling the brain as a network** and you just saw a glimpse. Do not be scared by the vast amount of options, start by replicating a paper you like.

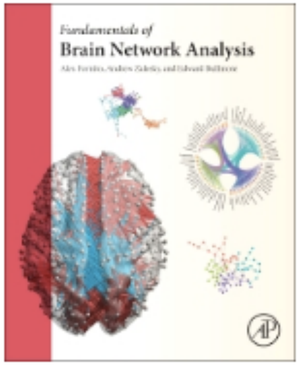
- **Tools are still a bit scattered and choice of many parameters are left to the end user.** More rigorous automatic approaches should be devised

Some fundamental references

- **Bullmore, E., & Sporns, O. (2012). The economy of brain network organization.**
  Nature reviews. Neuroscience, 13(5), 336–49.
- **Craddock, et al. (2013). Imaging human connectomes at the macroscale.** Nature Methods, 10(6), 524–539.

- **Networks of the Brain**
  Sporns, O; 2010, MIT Press.
- **Fundamentals of Brain Network Analysis.** Fornito, Zalesky, Bullmore; 2017, Elsevier





(They can be taken as book exams http://www.brain-mind.fi/courses.html)

…and something in Finnish about network science

https://www.researchgate.net/publication/242719764_Kompleksisten_verkostojen_fysiikkaa