Brain Networks & Functional Connectivity

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Outline

1. Brain connectivity: the basics

2. Brain network science

3. Impact of this research

PART1: Brain connectivity: the basics

The Brain in the media

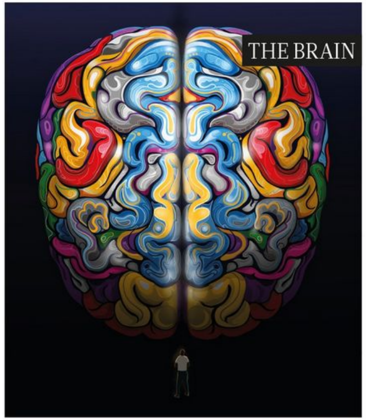
OUTLOOK | 24 July 2019

The brain

This supremely complex organ is slowly giving up its valuable secrets.

Richard Hodson

natureOUTLOOK



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The brain is the 'most complex thing in the universe'

29 May 2012

BRAIN INITIATIVE

About +

Impact +

Events +

Funding Opportunities

Resources +

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Why Study the Brain?

The brain is the most complex part in the human body. This three-pound organ is responsible for our intelligence, interpreting sensation, initiating body movement, and controlling all of our behaviors.

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The human brain, explained

Learn about the most complex organ in the human body, from its structure to its most common disorders.

Why do we want to study brain networks?

- How single elements **organize** into **dynamic patterns**?
- Understand the **integrative** functions of the brain
- Many authors are now praising the **connectomics** as the current revolution in neuroscience
- Multi-million projects like the **Human Connectome Project, the BRAIN initiative**

* Johnston, D. (1995). Foundations of Cellular Neurophysiology. MIT Press.

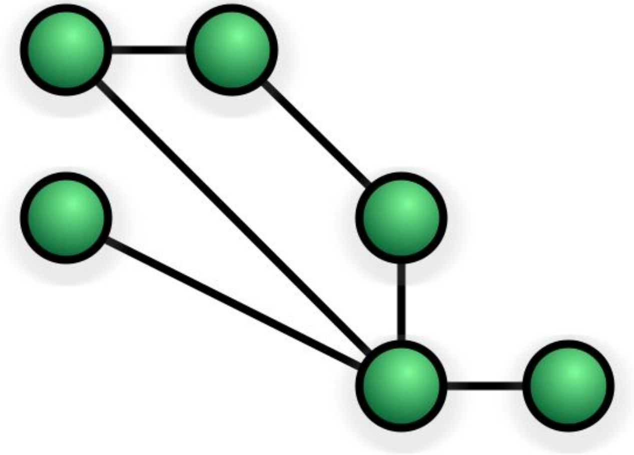
What is a network?

A (complex) network, a graph

A structure with:

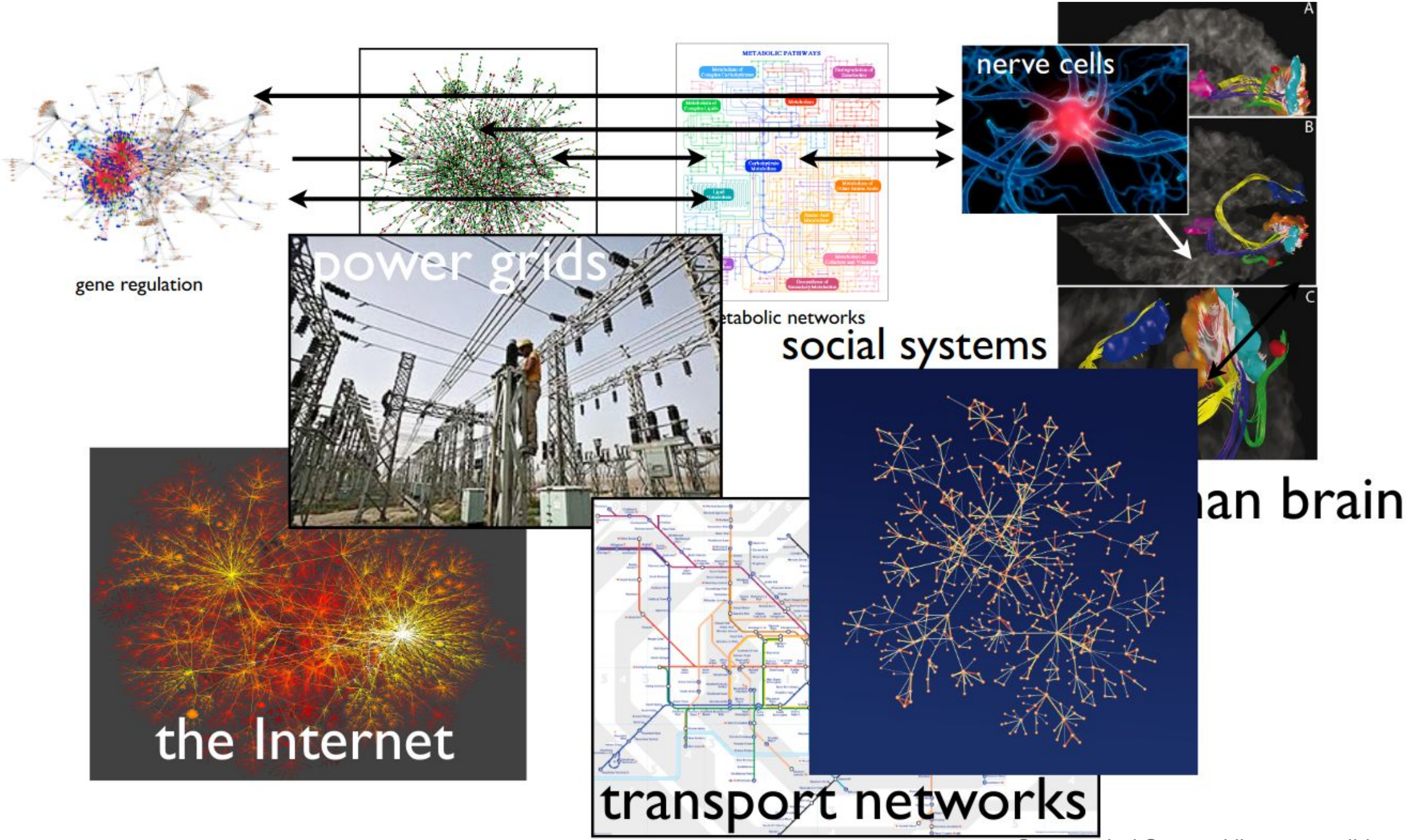
nodes → individual components

links → interaction between nodes



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

Everything can be seen as a network!



Source: Jari Saramäki's course slides. Complex Networks. 2020.

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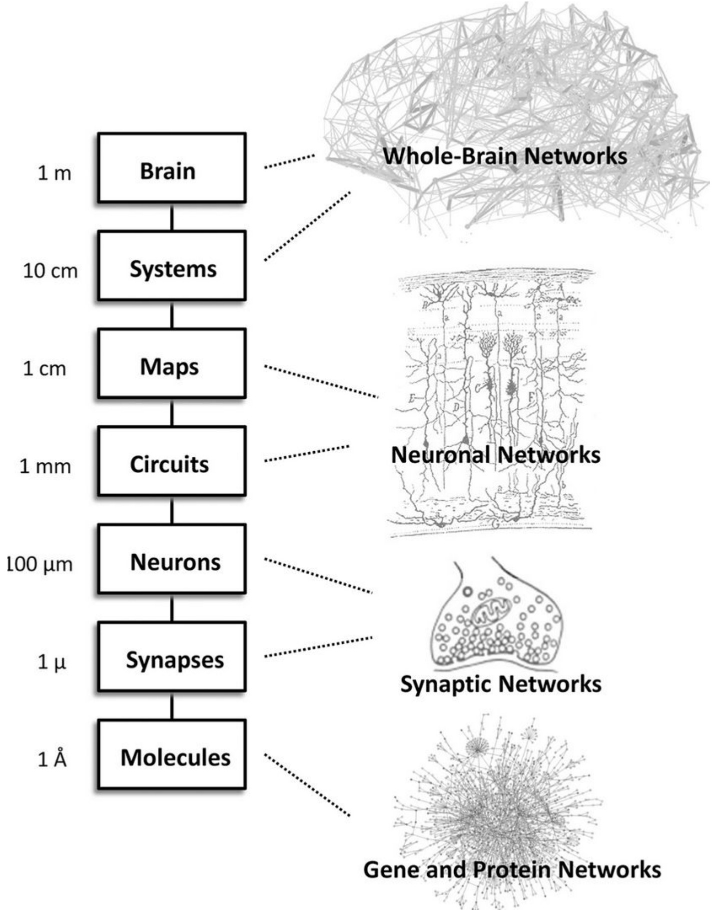
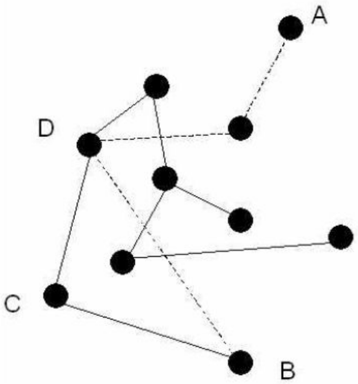


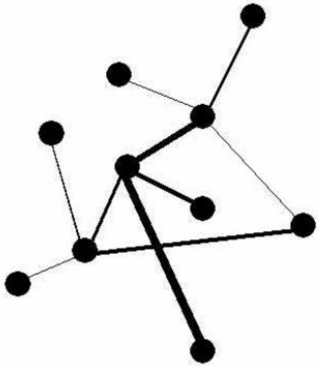
Petersen, S. E., & Sporns, O. (2015). Brain networks and cognitive architectures. *Neuron*, *88*(1), 207-219.

A (complex) network, a graph

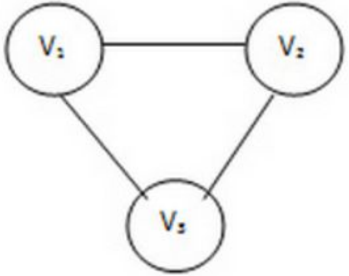
unweighted



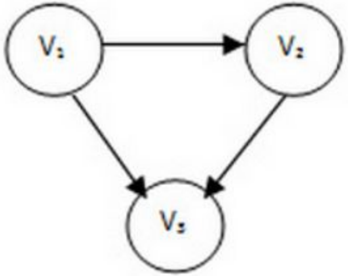
weighted



undirected

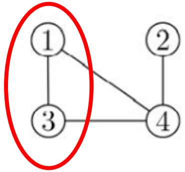


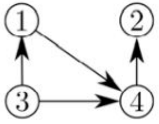
directed



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

Representation of networks





The **adjacency list** gives the neighbors of each node.

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

The $n \times n$ **adjacency matrix** A has elements a_{ij} defined by

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

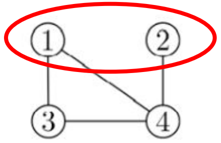
$a_{ii} = 0$ for all simple graphs

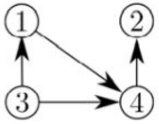
$$\begin{bmatrix} 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 \\ 1 & 1 & 1 & 0 \end{bmatrix} \qquad \begin{bmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 \end{bmatrix}$$

Source: Jari Saramäki's course slides. Complex Networks. 2020.

Representation of networks

Not neighbors





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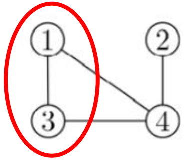

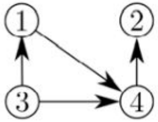

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Source: Jari Saramäki's course slides. Complex Networks. 2020.

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.

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

What is a brain connectivity?

Brain connectivity

“**Brain connectivity** refers to a **pattern of anatomical links** ("anatomical connectivity"), **of statistical dependencies** ("functional connectivity") **or of causal interactions** ("effective connectivity") **between distinct units within a nervous system.**”

Scholarpedia

http://www.scholarpedia.org/article/Brain_connectivity

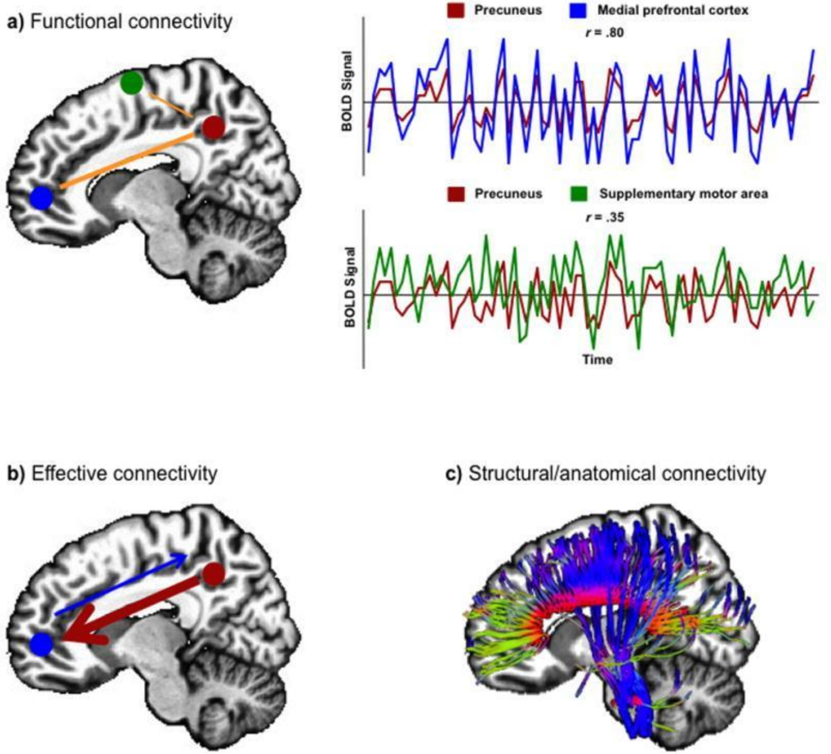
Brain networks

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. (*)

Maximo, J. O., Cadena, E. J., & Kana, R. K. (2014). *The implications of brain connectivity in the neuropsychology of autism*

Brain networks

Structural connectivity

- **Invasive** (tract tracing methods, 2 photon calcium imaging)
- **Non invasive** (Diffusion Tensor and Diffusion Spectral Imaging)

Functional connectivity

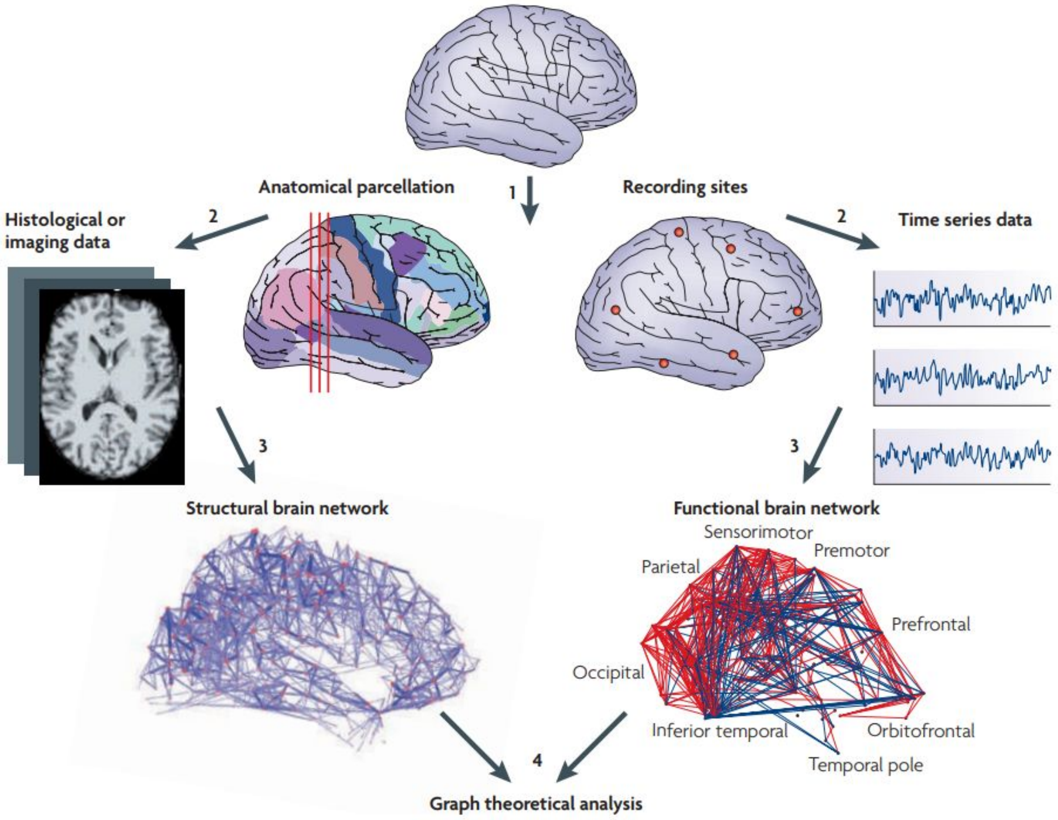
- **Invasive** (intracranial recordings)
- **Non invasive** (fMRI, M/EEG, simulated data)

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

How do we compute a brain network?

The formula

- Define nodes
- Estimate a measure of association between the nodes
- Generate the Adjacency matrix.
- Calculate the network parameters / Compare the networks

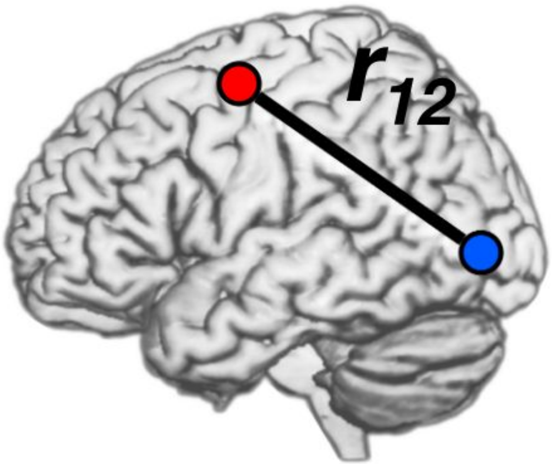


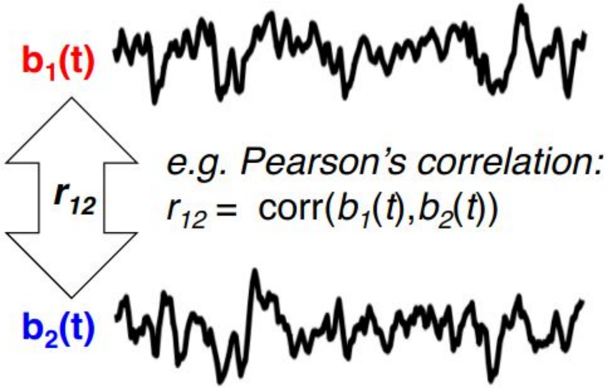
Bullmore Ed and Sporns Olaf. Complex brain networks: graph theoretical analysis of structural and functional systems. (2009)

Building a functional network

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

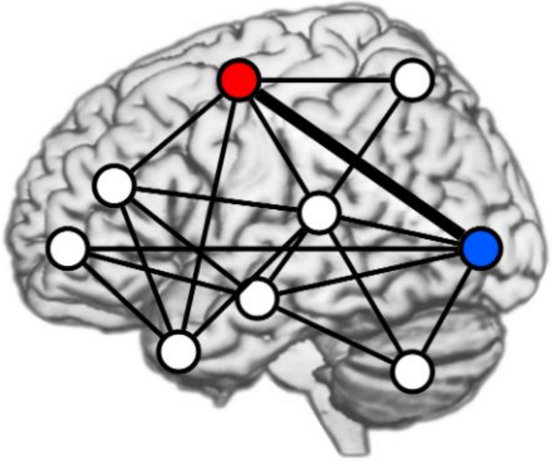
We compute their **similarity**

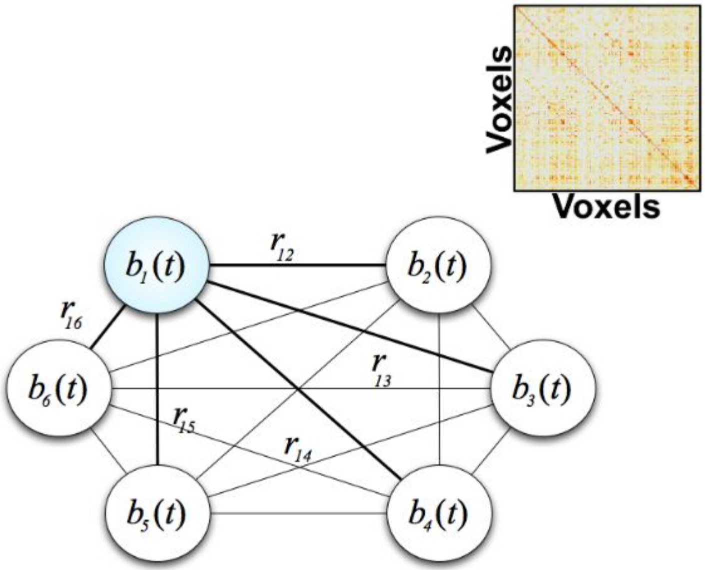




Building a functional network

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
  - The size of the voxel matters! At 2mm isotropic voxels we have ~160K nodes. At 6mm isotropic voxels we have ~6K nodes.
- 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, Brainnettome.
  - We consider a seed: a sphere centred at a specific location based on literature, or nodes templates
  - 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
- **Mutual information**: (non)linear share of information
- **Coherence**: looking at cross-spectral similarity between a frequency representation of the time series
- **Other methods** based on wavelets or related to task (gPPI, beta series)

How to choose?

The answer is: **it depends.**

For nodes, keep in mind computational and bias issues.

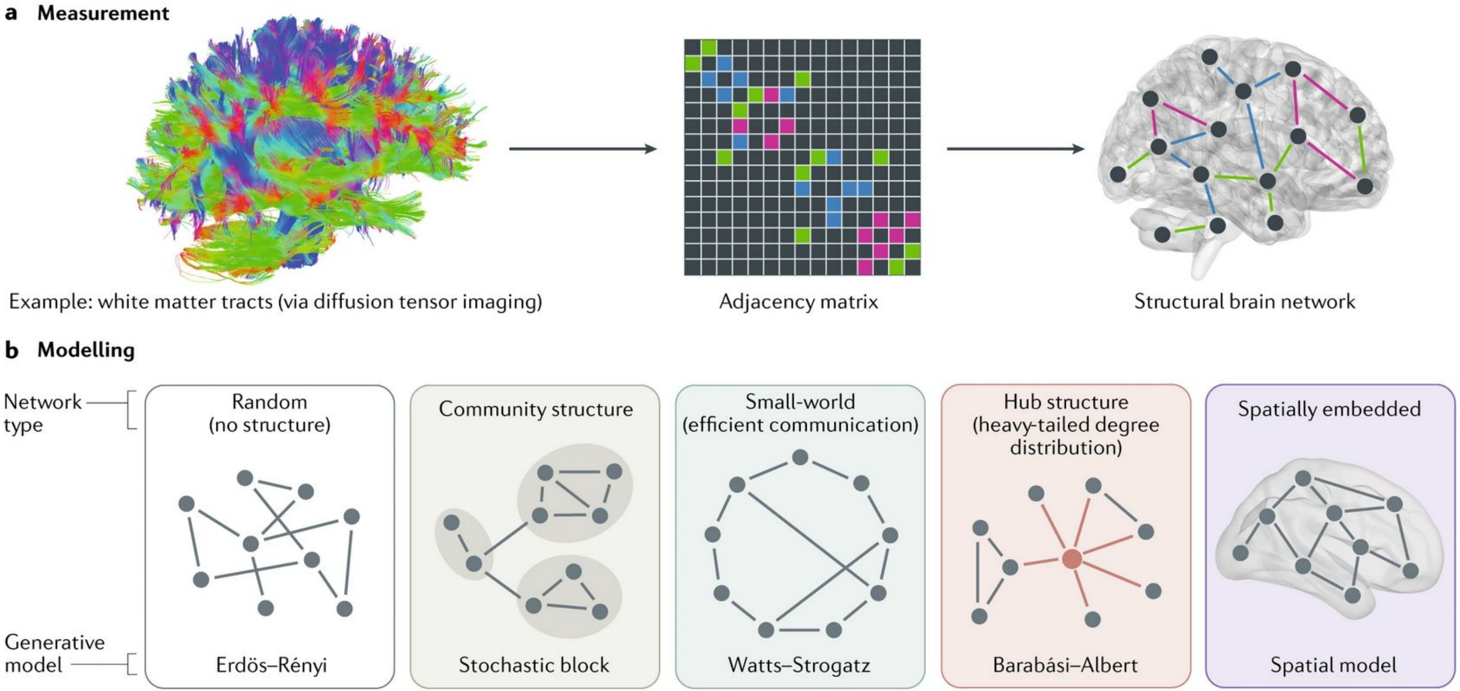
If you are looking for **subtle differences** e.g. between groups or between conditions, some more refined measures could perform better (Smith et al. showed **partial correlation**, **inverse covariance** and **Bayes-net** methods as winners)

However, in most cases simple linear correlation is enough[2]

2 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

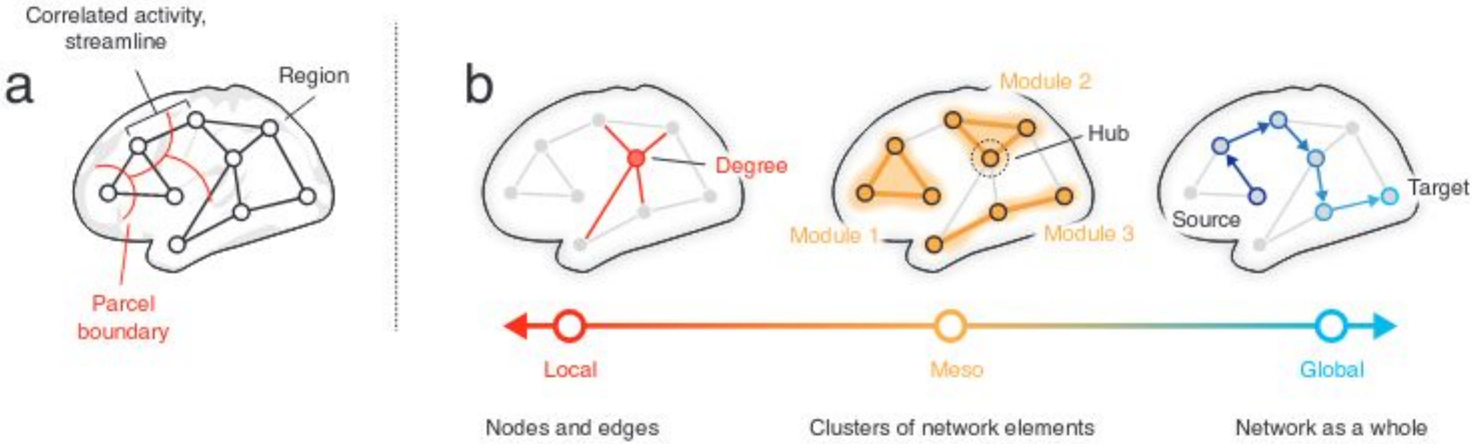
How do we analyze the brain as a network?

A 2-step process



Lynn C. and Basset D. The physics of brain network structure, function and control. Nature Reviews Physics 1, 318-322 (2019).

PART2: Brain network science

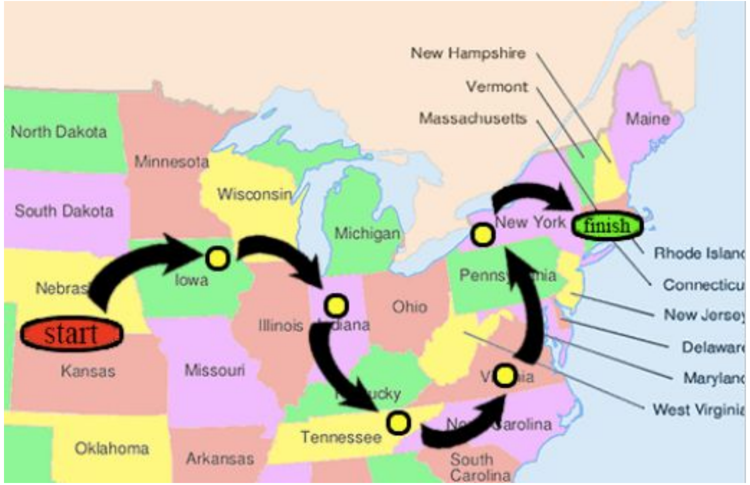


Betzel, R. F. (2020). Community detection in network neuroscience. *arXiv preprint arXiv:2011.06723*.

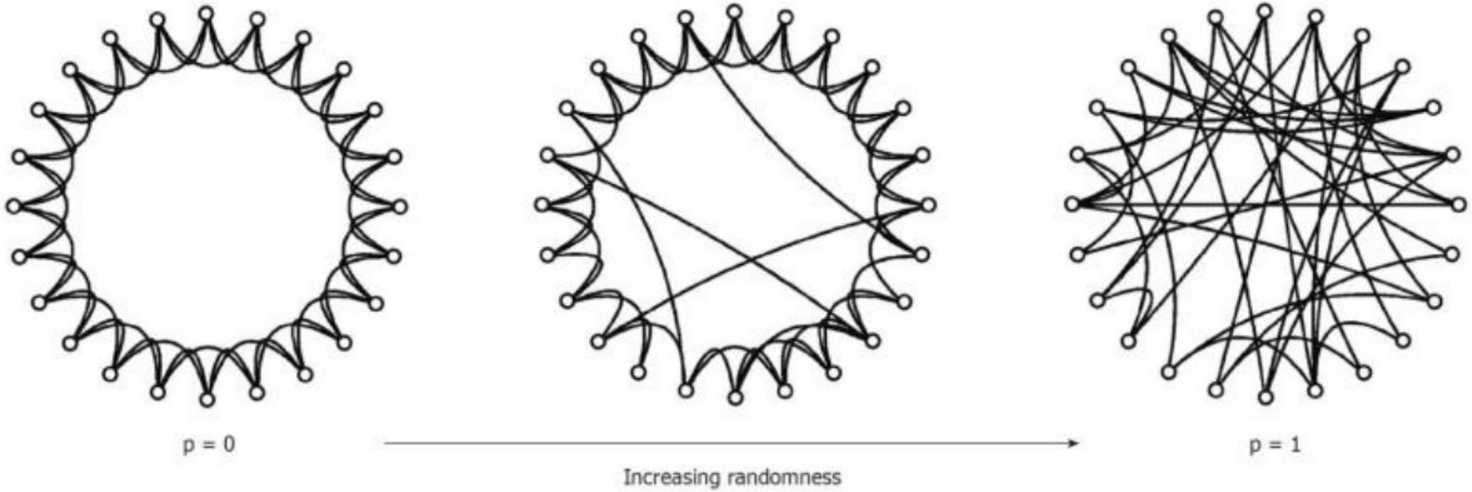
Network level-features

It's a small world!

- 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



3. 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[*], or is it?[+]

* Bassett, D. S., & Bullmore, E. T. (2017). Small-World Brain Networks Revisited. The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry, 23(5), 499–516.
+ Hilgetag, C. C., & Goulas, A. (2016). Is the brain really a small-world network?. Brain structure & function, 221(4), 2361–2366. https://doi.org/10.1007/s00429-015-1035-6

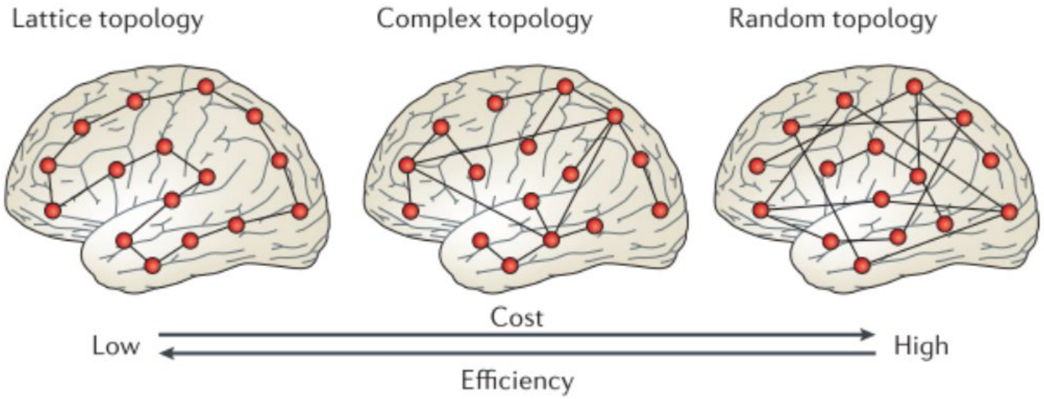
Small world networks

- **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**

It’s a small world!



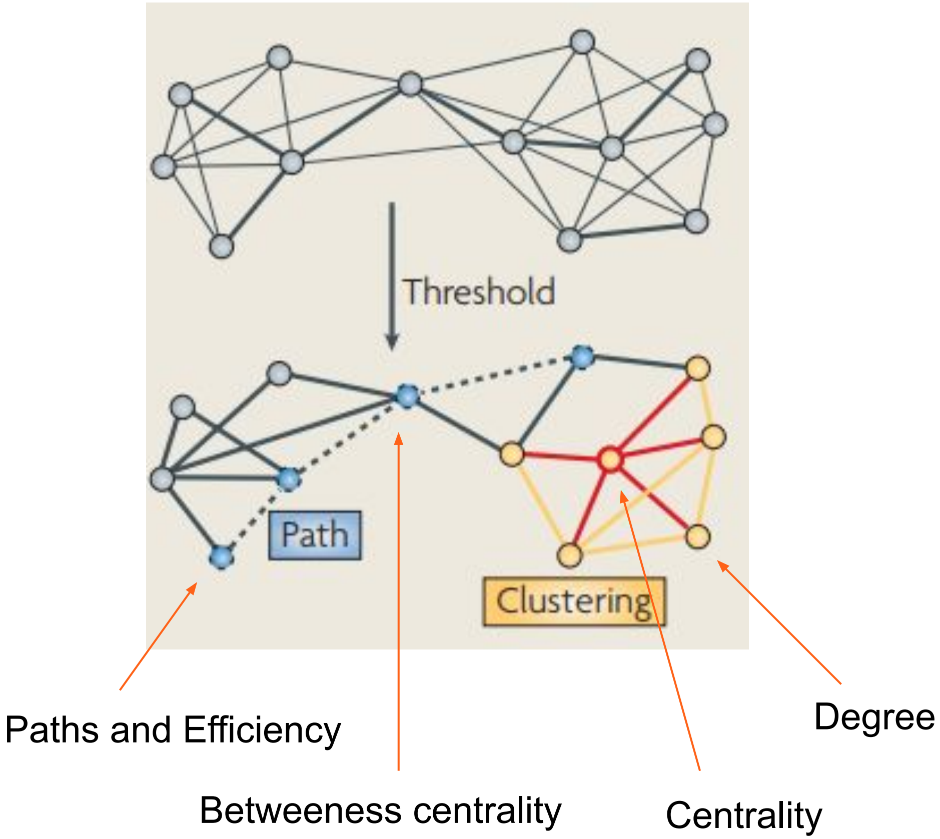
Small-world configuration optimizes communication cost and efficiency

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

Node-level features

Node-level measurements

- **Node degree/strength**
  How strong is a node?
- **Clustering**
  How close is the node with the neighbours?
- **Closeness centrality**
  How far is a node from other nodes?
- **Betweenness centrality**
  How many shortest paths through the node?

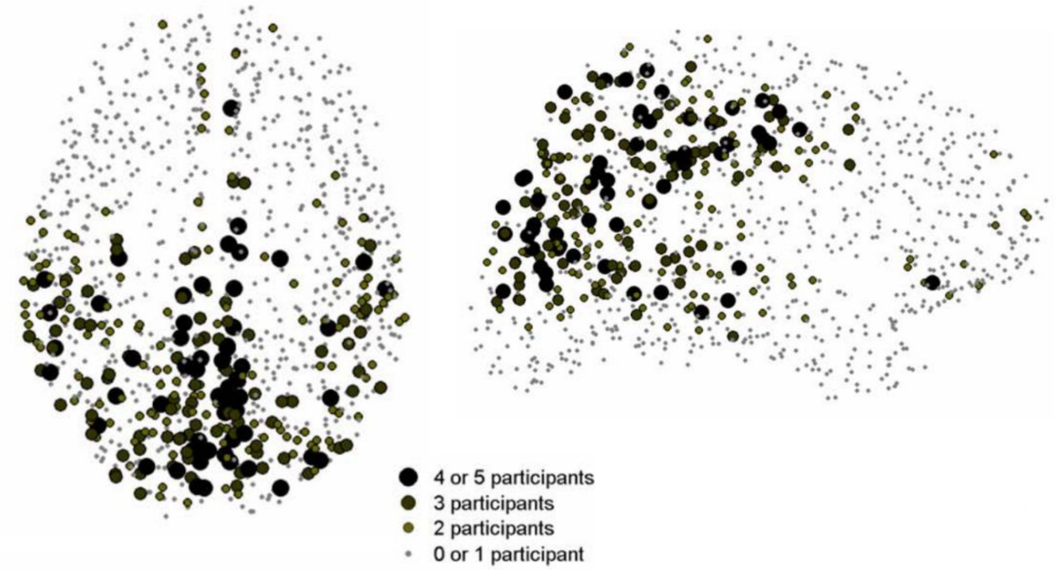


Bullmore Ed and Sporns Olaf. Complex brain networks: graph theoretical analysis of structural and functional systems. (2009)

Hubs

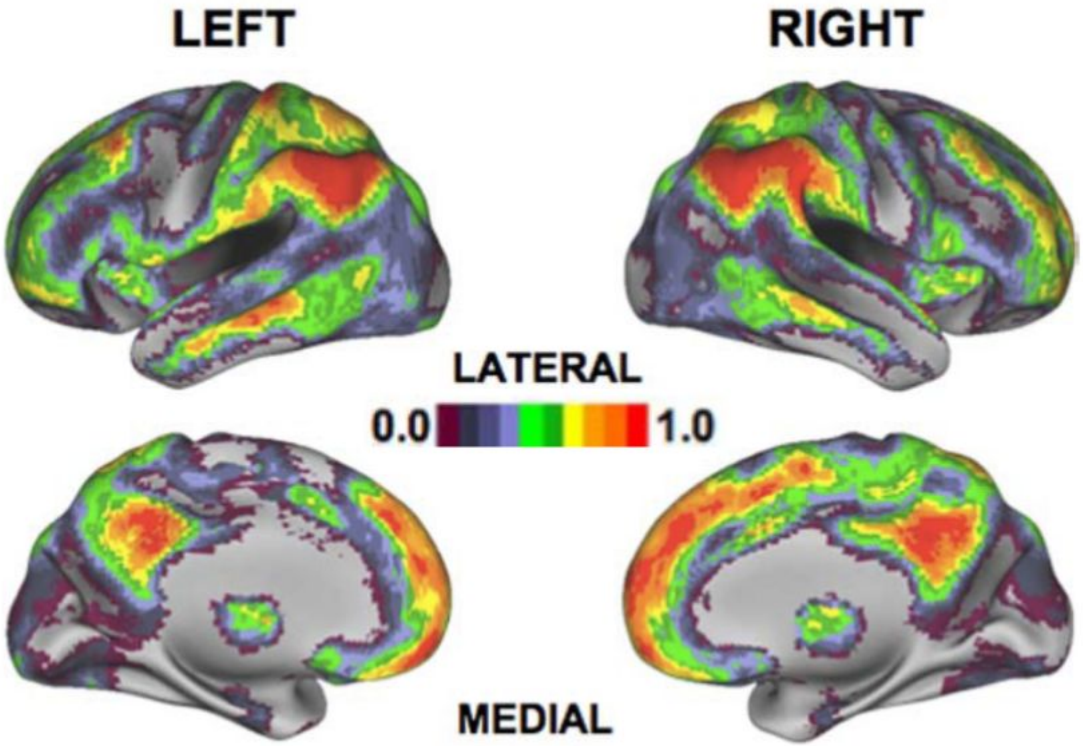
A hub is the effective center of an activity, region, or network…

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



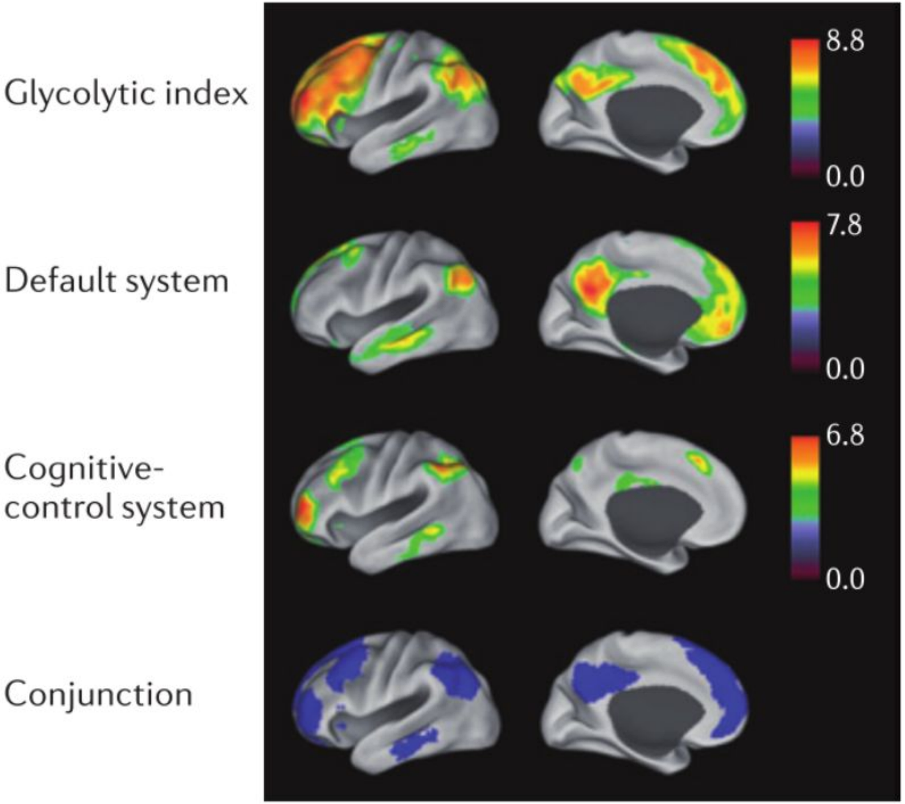
Hagmann, P., et al. (2008). Mapping the structural core of human cerebral cortex. PLoS biology, 6(7), e159.

Hubs in the brain



Buckner et. al. (2009). Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. Journal of neuroscience, 29(6), 1860-1873.

Relationship between hubs and brain activity

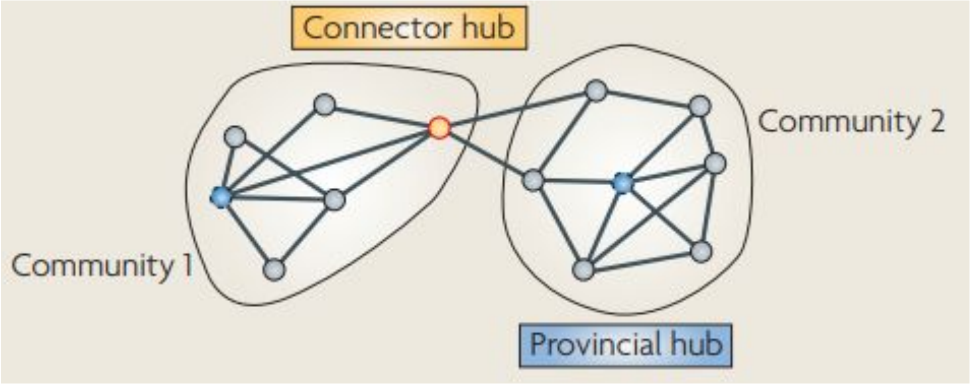


The most important (central) hubs are those with higher glycolytic index, i.e. higher metabolic cost.

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

Network modules

Modules



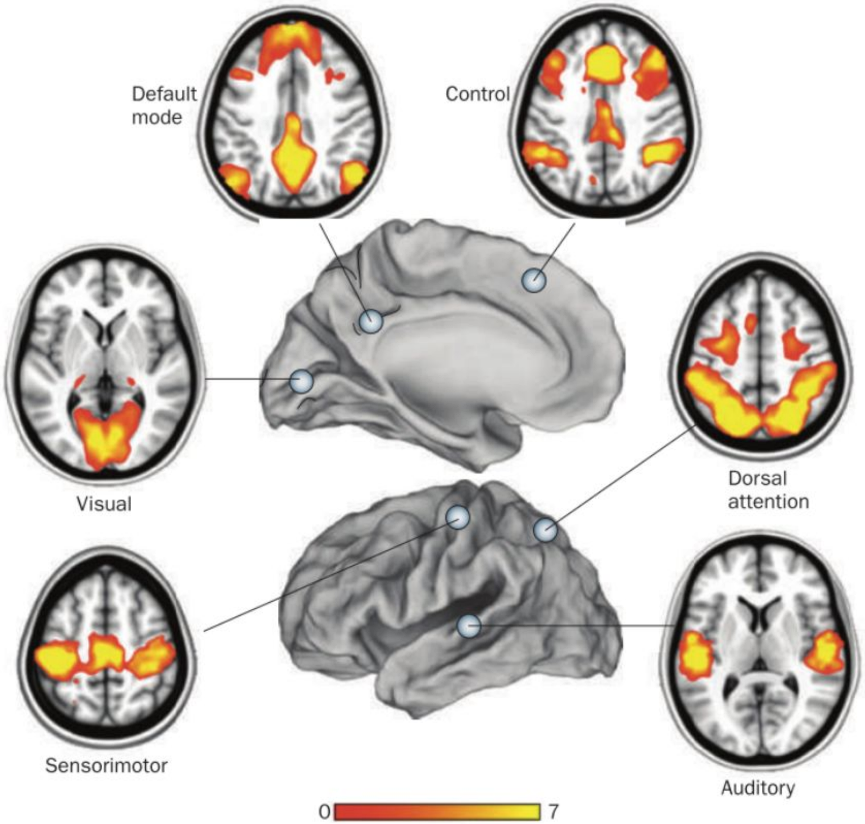
Sets of densely connected nodes, joined by sparse links. i.e. **they are more connected with each other than with other parts of the network**

Bullmore Ed and Sporns Olaf. Complex brain networks: graph theoretical analysis of structural and functional systems. (2009)

Modules in the brain: Networks

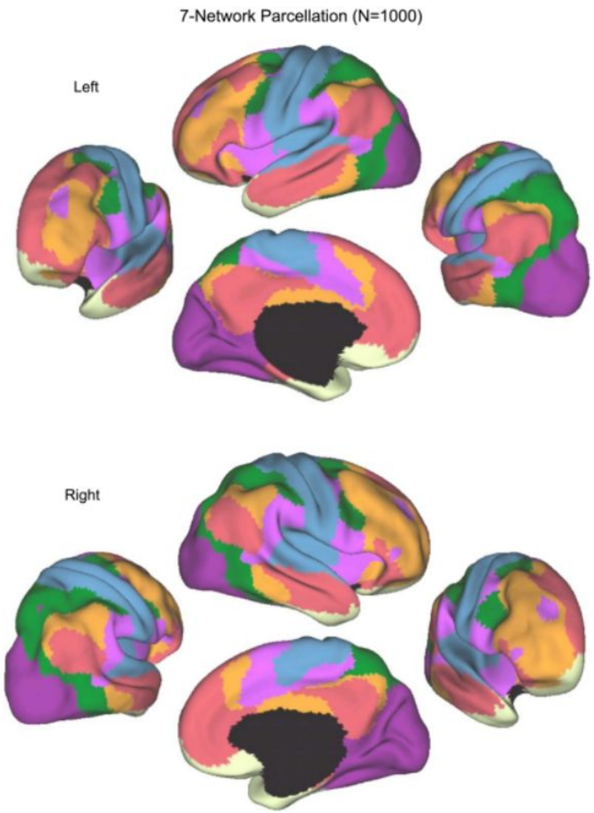
- Which regions are more connected with each other (**clustering**)
- **~6 main modules** in the human cortex that corresponds to important cognitive functions
- They are often called "**networks**" although they are technically sub-networks

Modules in the brain: Networks



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

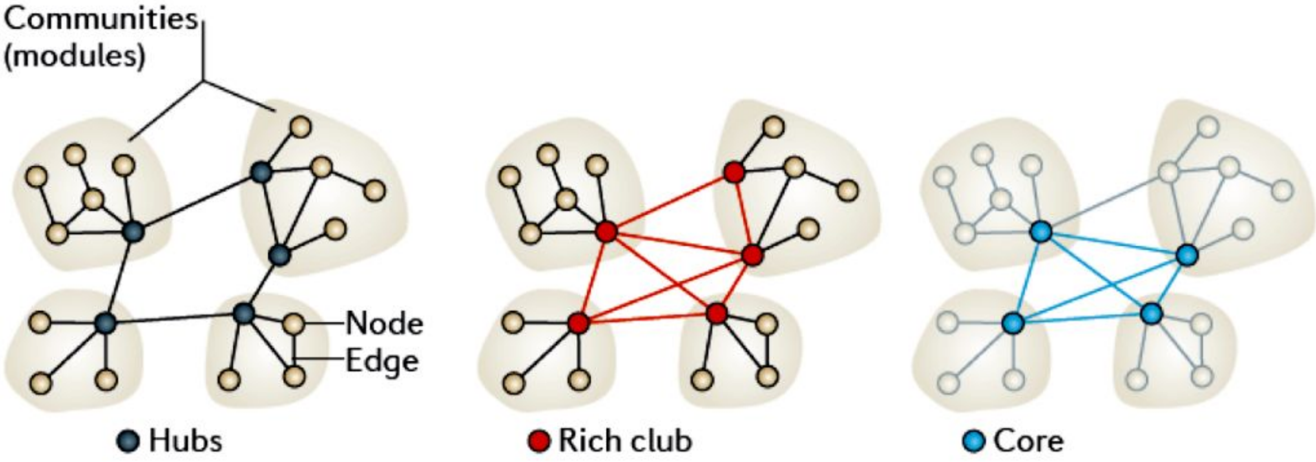
Modules in the brain: Networks



- 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.

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



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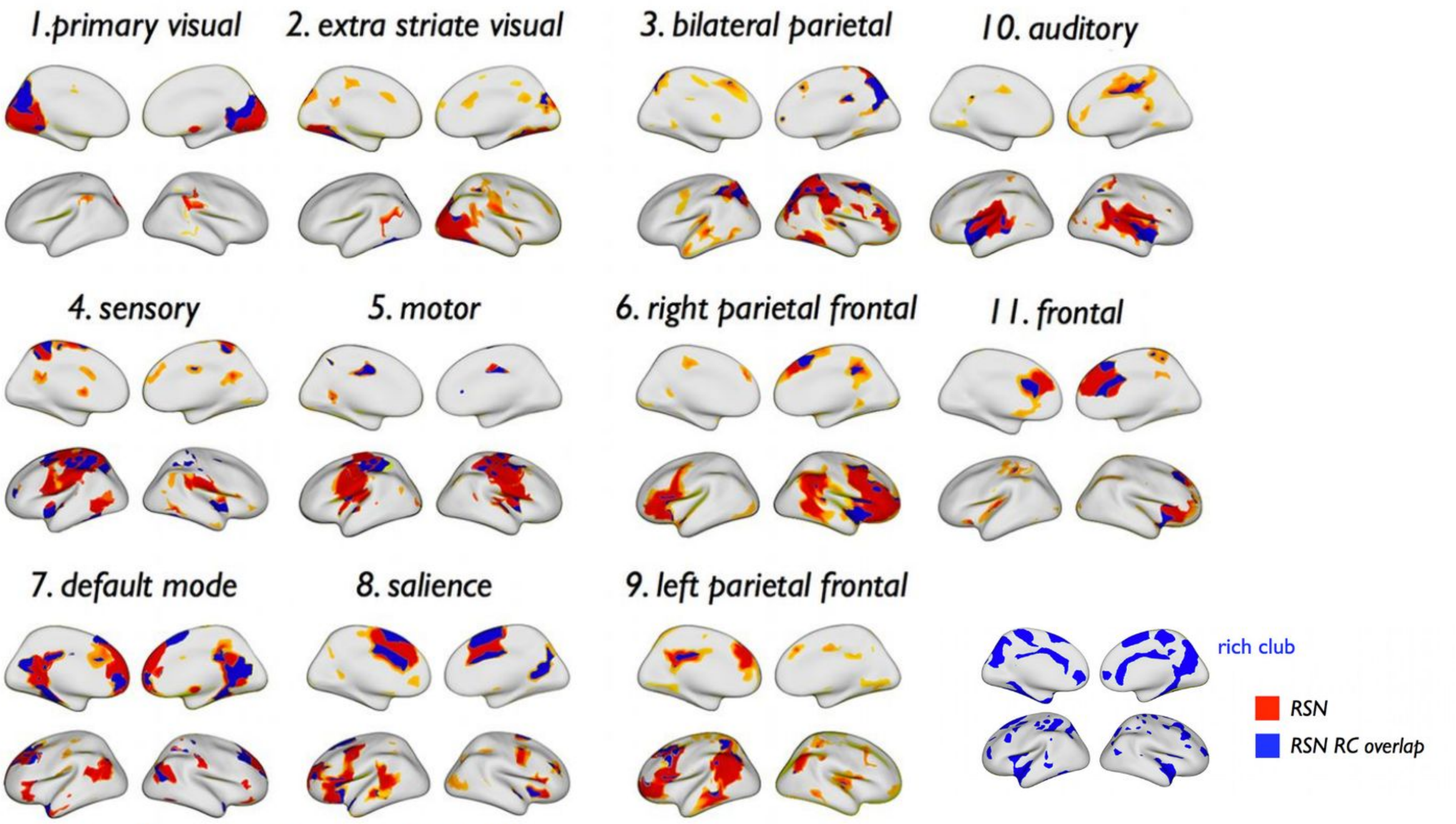
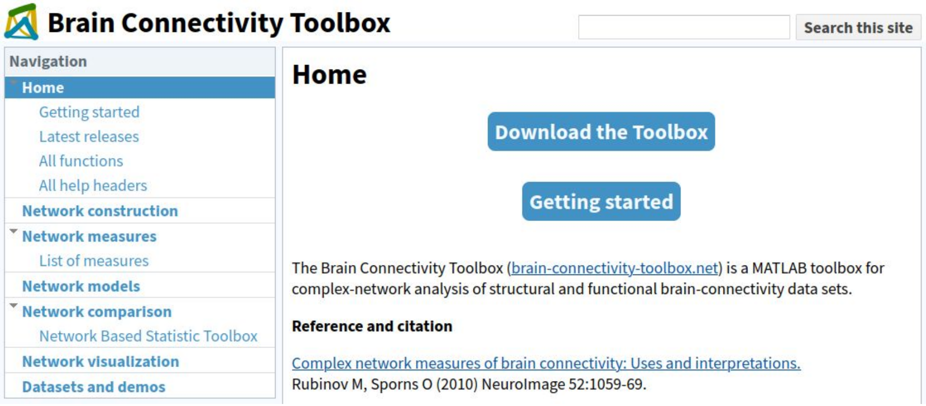


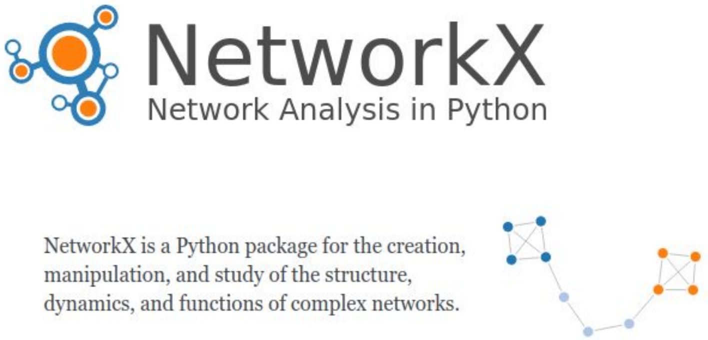
Van den Heuvel, Martijn P., and Olaf Sporns. "An anatomical substrate for integration among functional networks in human cortex." *Journal of Neuroscience* 33.36 (2013): 14489-14500.

How to estimate and compare network properties?

How to calculate network properties?

- MATLAB? **Brain Connectivity Toolbox**
- Python? **Nilearn - NetworkX**





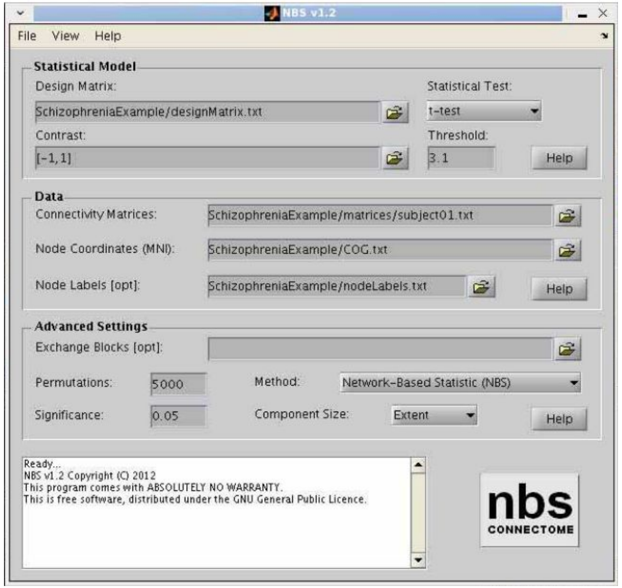
How to compare network properties?

- 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. https://version.aalto.fi/gitlab/BML/bramila/-/blob/master/bramila_ttest2_np_v2.m
- Remember to **correct for multiple comparisons**

How to compare network links?

- **Network-based statistic**

- Use **permutation testing.** Remember to **correct for multiple comparisons**



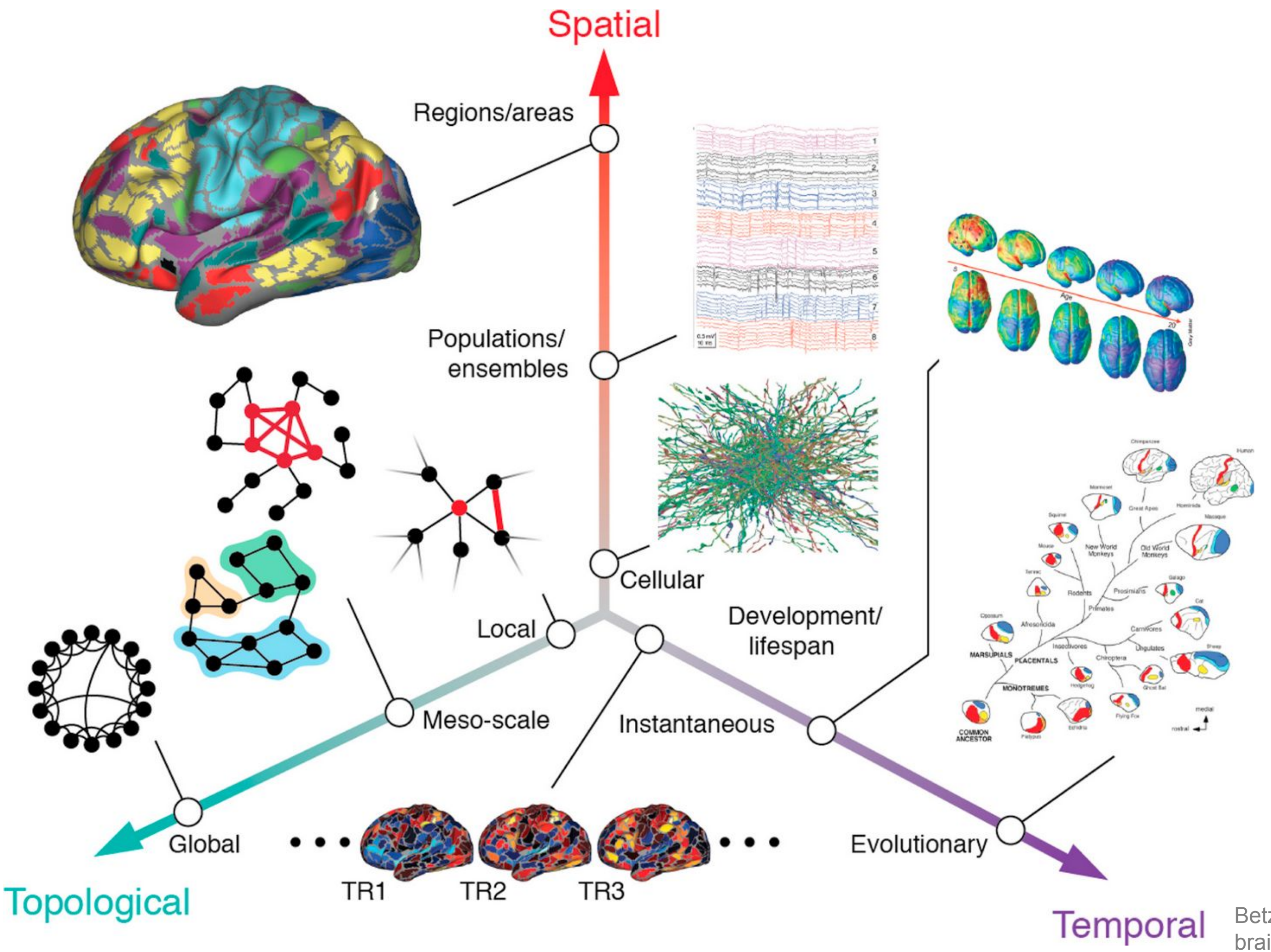
https://sites.google.com/site/bctnet/comparison/nbs

Network-based statistic

- Identifies significantly different links that form a connected structure instead of individual links, i.e. **the network structure is taken into account**
- For each link, **compute a test statistic**
- Threshold the test statistic (**suprathresholded links**)
- **Identify any possible connected components** and **store the number of links in the components**.
- **Permute** the membership of the groups M times.
- Determine the **maximal component size**.
- **Compare** the “true” maximal component size with the null-distribution obtained and check the p-value.

https://sites.google.com/site/bctnet/comparison/nbs

Advanced methods



Betzel, R. F., & Bassett, D. S. (2017). Multi-scale brain networks. *Neuroimage*, *160*, 73-83.

Temporal scales of connectivity

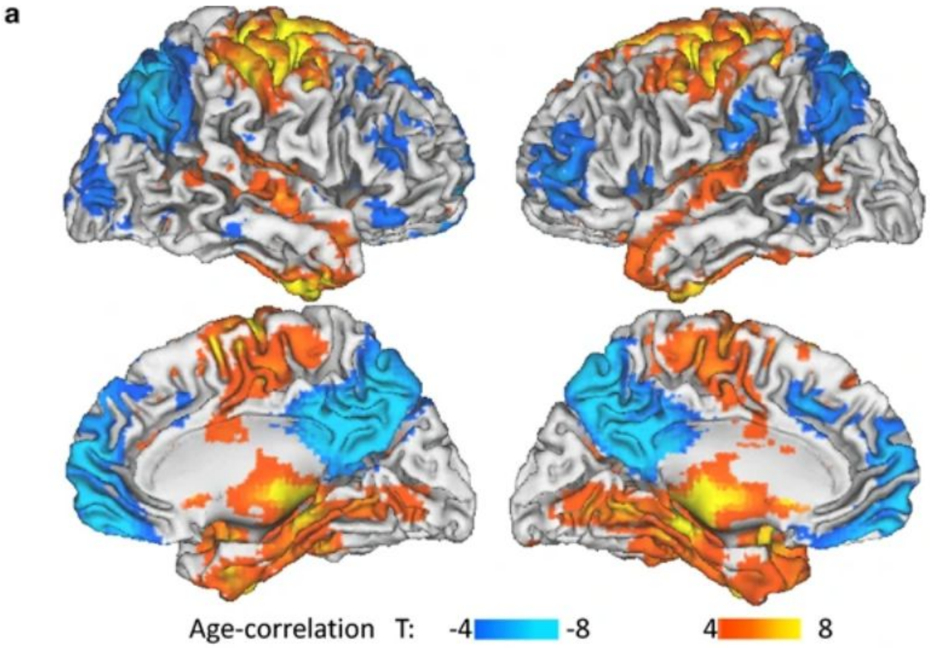
Changes across (milli)seconds

- Fast functional changes due to extrinsic or intrinsic processes

Changes across years

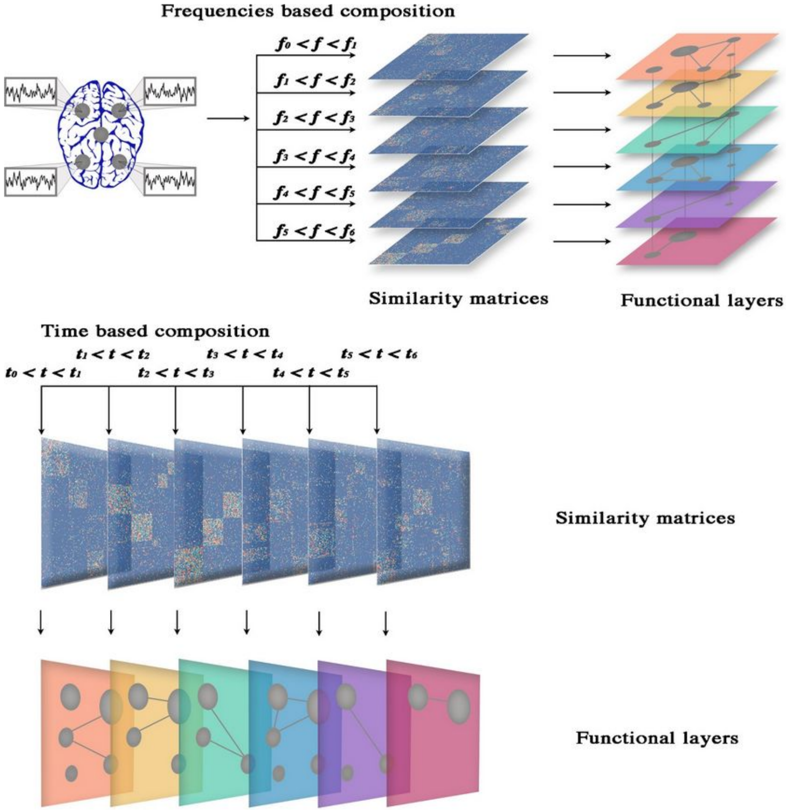
- Slow structural changes due to genetics, environment and noise

Temporal scales of connectivity



Tomasi, D., Volkow, N. Aging and functional brain networks. *Mol Psychiatry* **17,** 549–558 (2012).

Multilayer brain networks



Manlio De Domenico, Multilayer modeling and analysis of human brain networks, GigaScience, Volume 6, Issue 5, May 2017, gix004

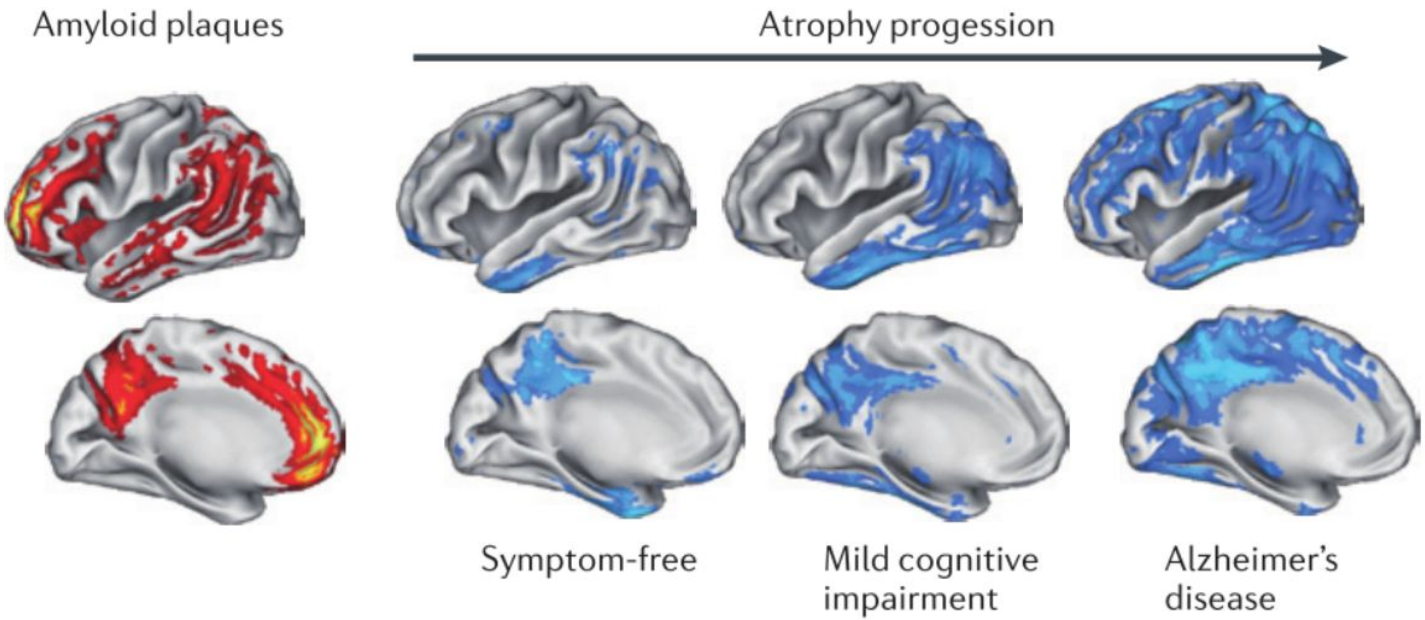
PART3: Impact of this research

Mapping the connectome and clinical applications

- The **connectome** (has) 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
  - Depression

Alzheimer's disease

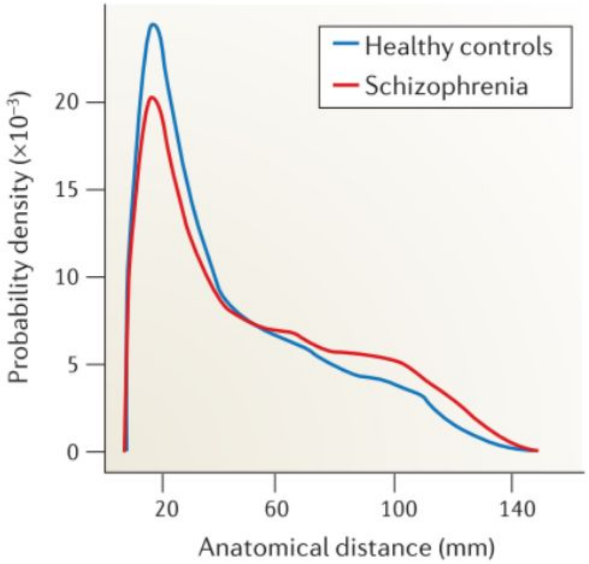
The most **expensive hubs are attacked by the disease**

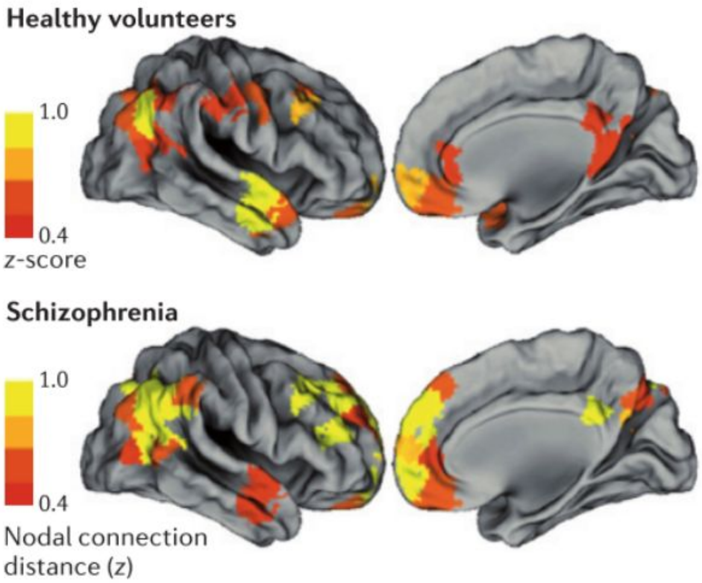


Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. Nature reviews. Neuroscience, 13(5), 336–49

Schizophrenia

Unbalanced small-worldness





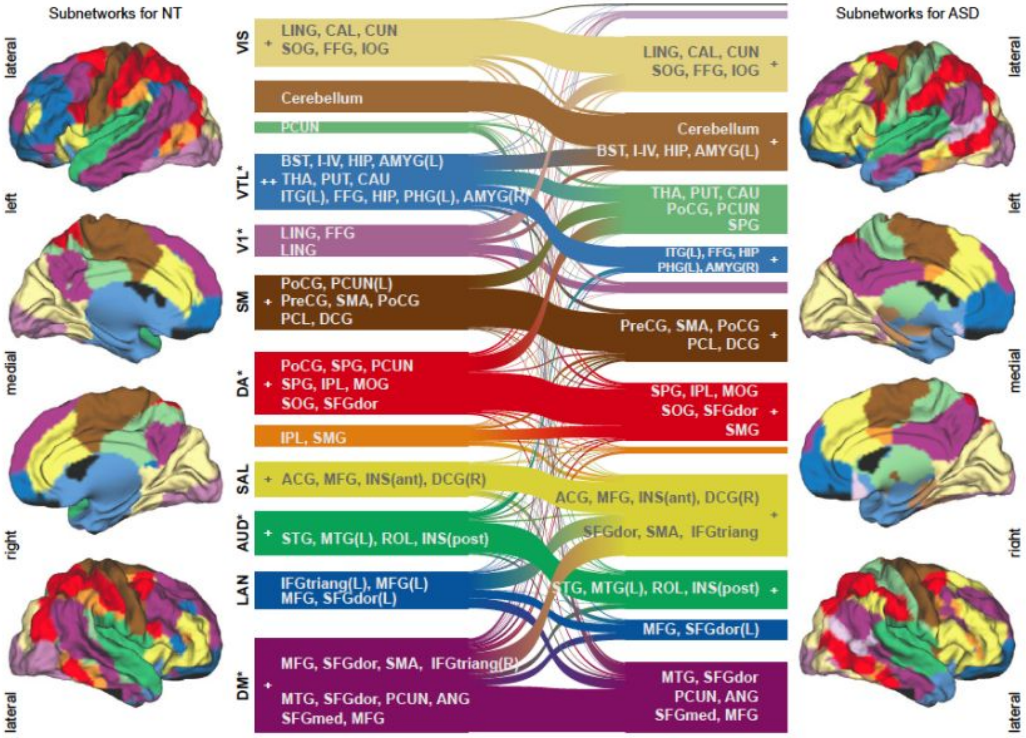
Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. Nature reviews. Neuroscience, 13(5), 336–49

Autism

Disruptive connectivity theory:

- **Weak connections between distant areas** (underconnected)
- **Strong connections within local areas** (overconnected)

Autism



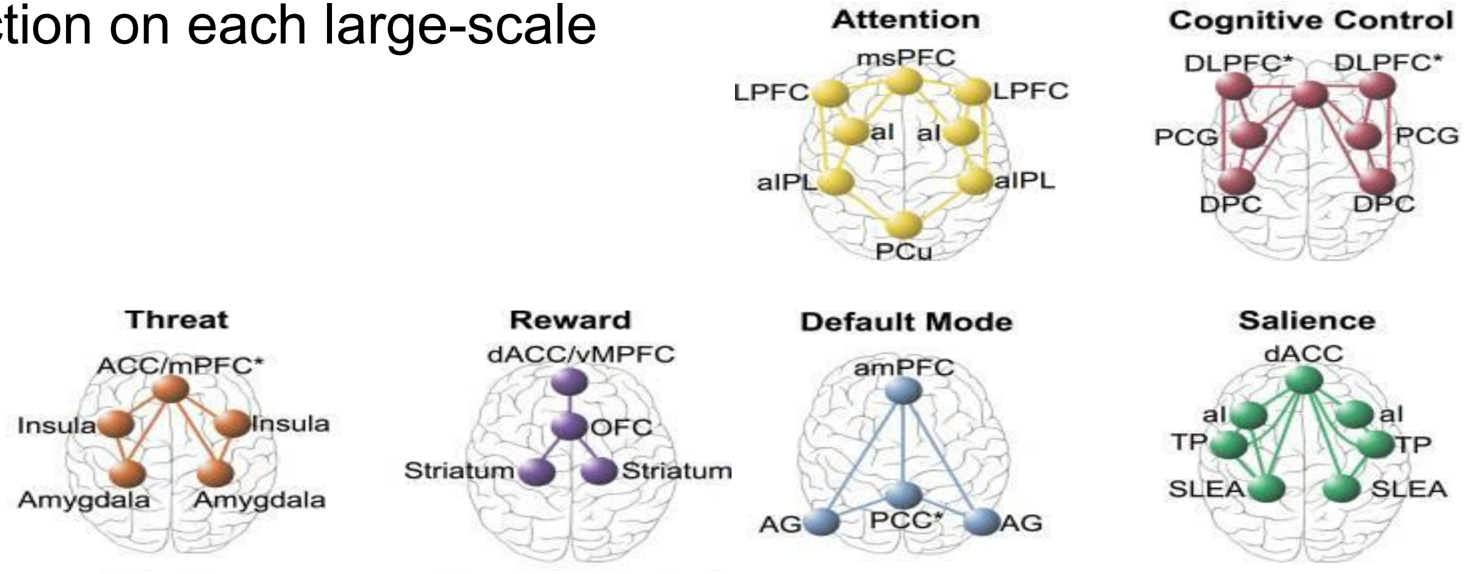
Significant differences in:

- Default Mode
- Auditory
- Dorsal attention
- Visual primary
- Ventro-temporal-limbic (VTL)

Glerean et. al(2016). Reorganization of functionally connected brain subnetworks in high-functioning autism. *Human brain mapping*, *37*(3), 1066-1079.

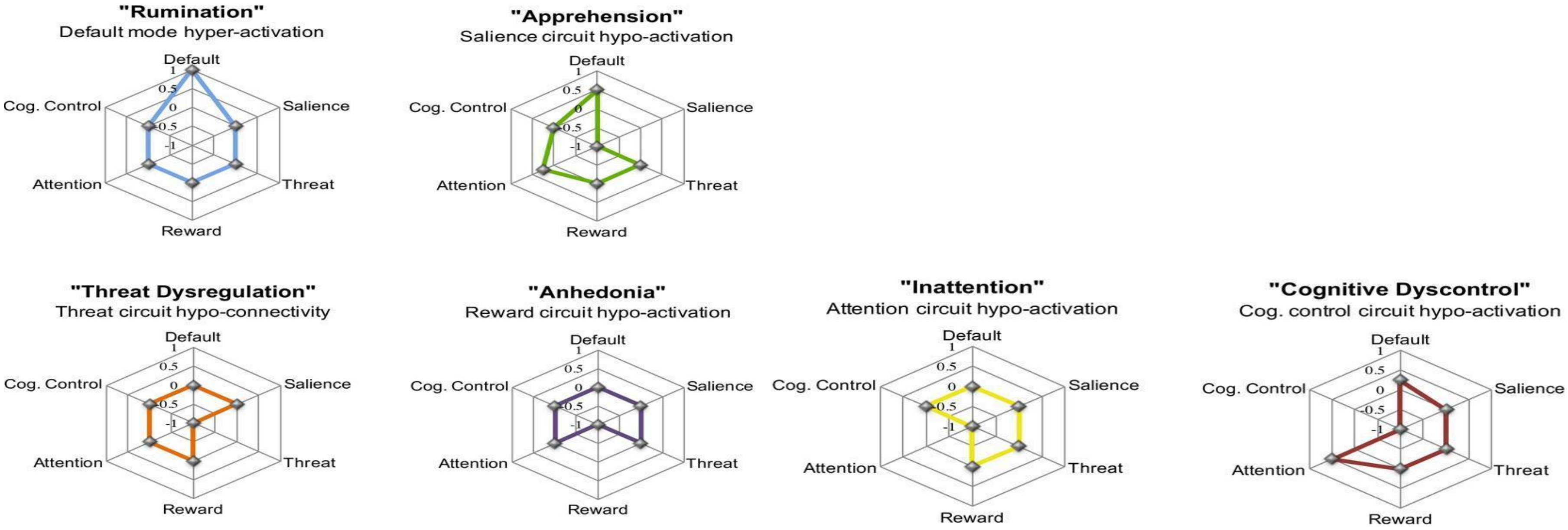
Depression

Biotypes: profiles of extent of dysfunction on each large-scale circuit



Williams L. M. (2016). Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation.

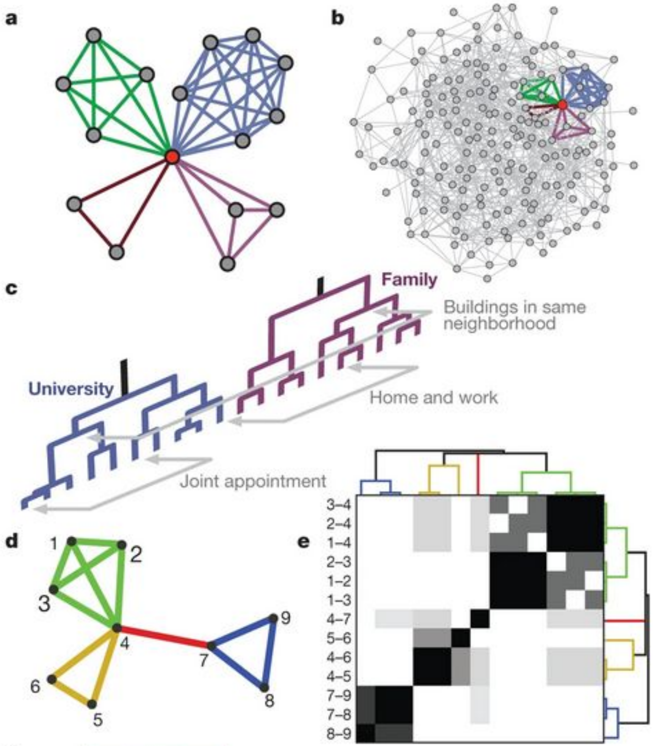
Depression

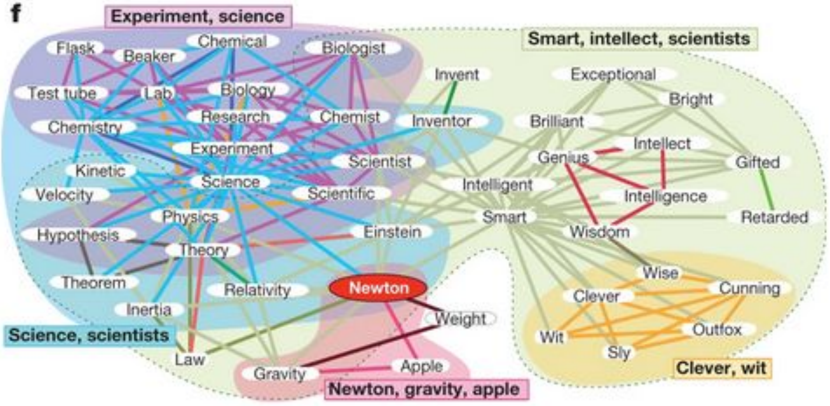


Williams L. M. (2016). Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation

Future directions

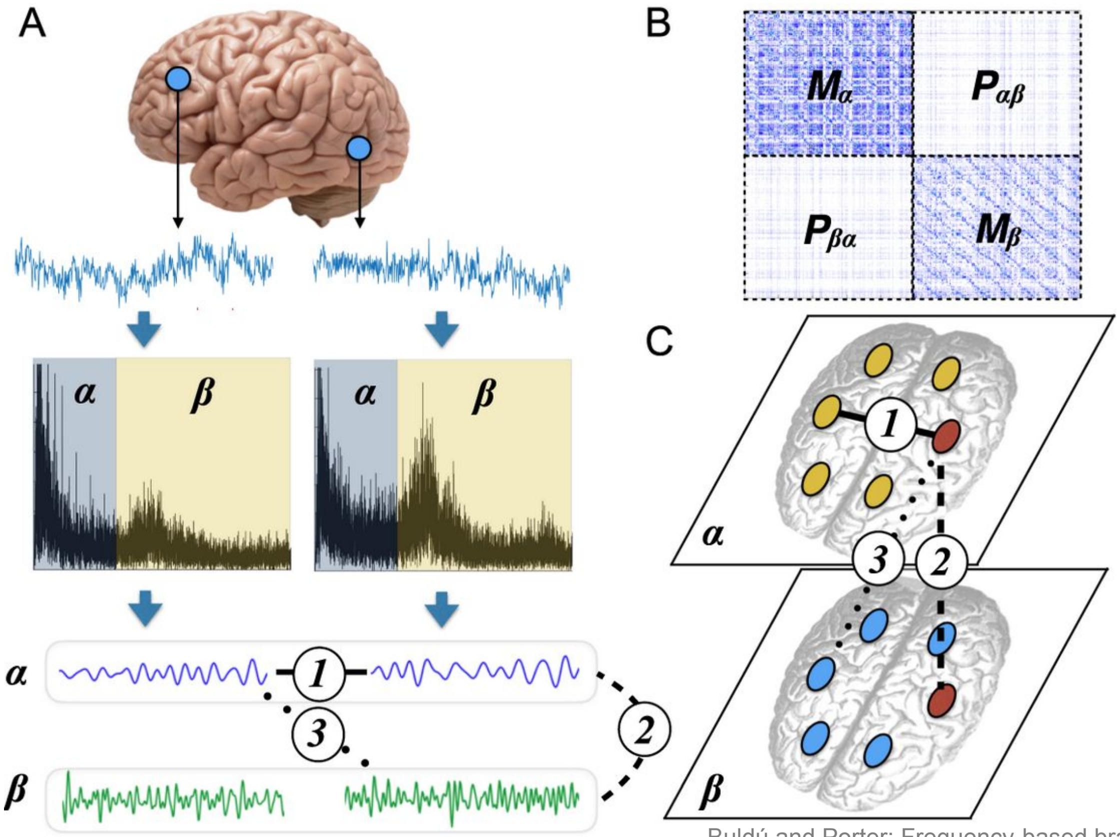
Link networks





Ahn, YY., Bagrow, J. & Lehmann, S. Link communities reveal multiscale complexity in networks. *Nature* **466,** 761–764 (2010)

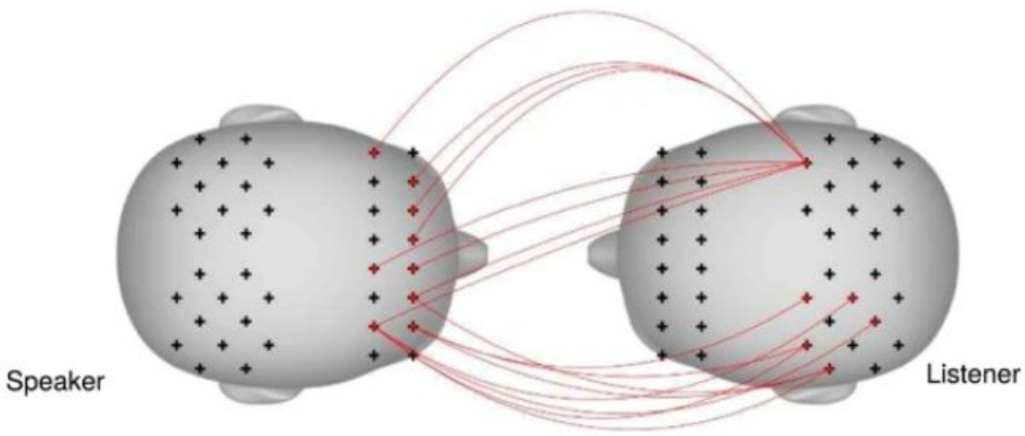
Multilayer networks



Buldú and Porter; Frequency-based brain networks: From a multiplex framework to a full multilayer description. *Network Neuroscience* 2018; 2 (4): 418–441.

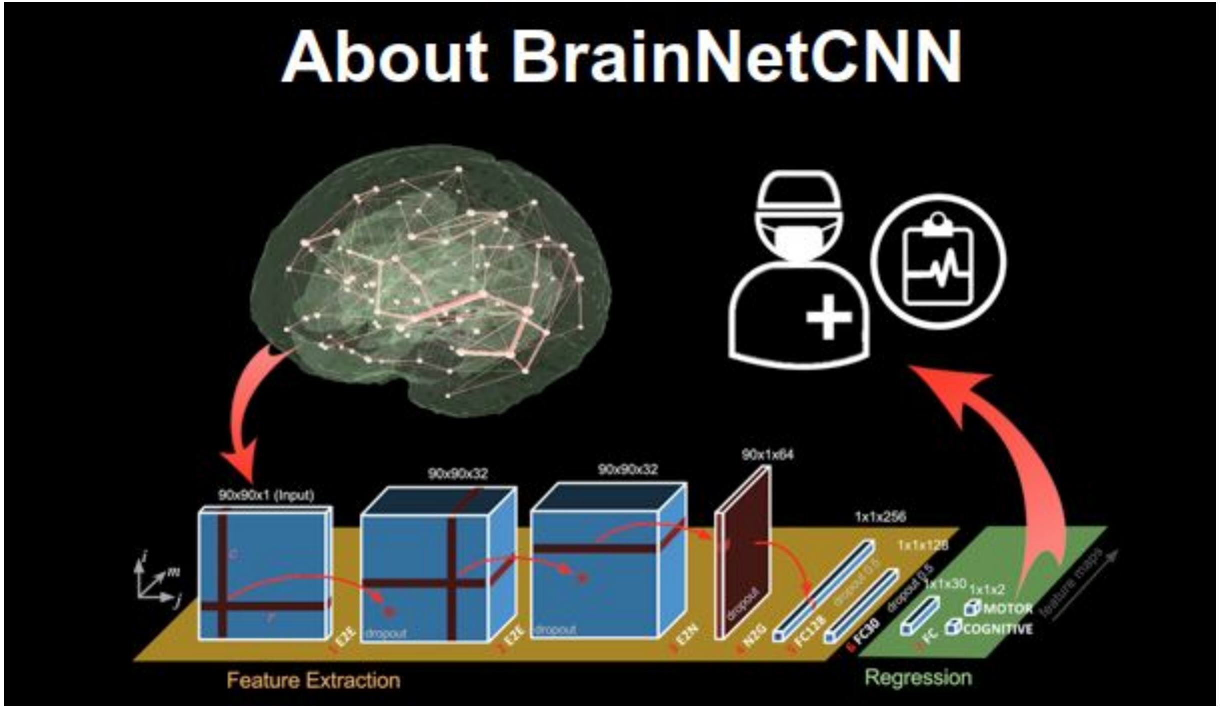
Network of networks

- Functional networks between subjects



Liu, Y., Piazza, E., Simony, E. *et al.* Measuring speaker–listener neural coupling with functional near infrared spectroscopy. *Sci Rep* **7,** 43293 (2017).

Network prediction



https://brainnetcnn.cs.sfu.ca/About.html
Kawahara et. al. BrainNetCNN: Convolutional Neural Networks for Brain Networks; Towards Predicting Neurodevelopment. NeuroImage, 146(1):1038-1049, 2017.

Thank you!