Aalto University
School of Science

Human Brain Networks

Aivoaakkoset NBE-C3001

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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…

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TED Ideas worth spreading

http://www.ted.com/talks/sebastian_seung.html

TALKS

Sebastian Seung: I am my connectome

FILMED JUL 2010 • POSTED SEP 2010 • TEDGlobal 2010

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?

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.

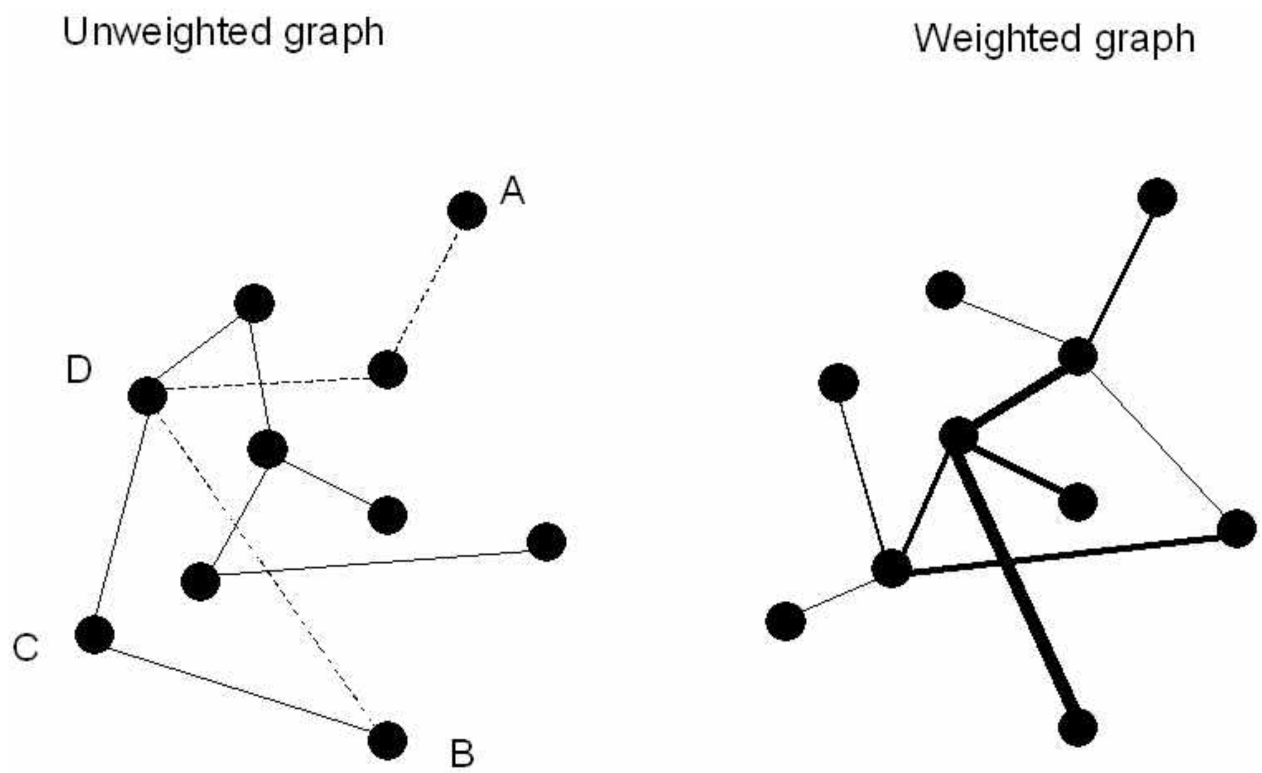
Human genome vs Human connectome

- The human genome contains over **3 billion base pairs** organized into 22 paired chromosomes
- The human connectome contains **~10^14 connections**

What?

3. What is a network?

A (complex) network, a graph



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

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*

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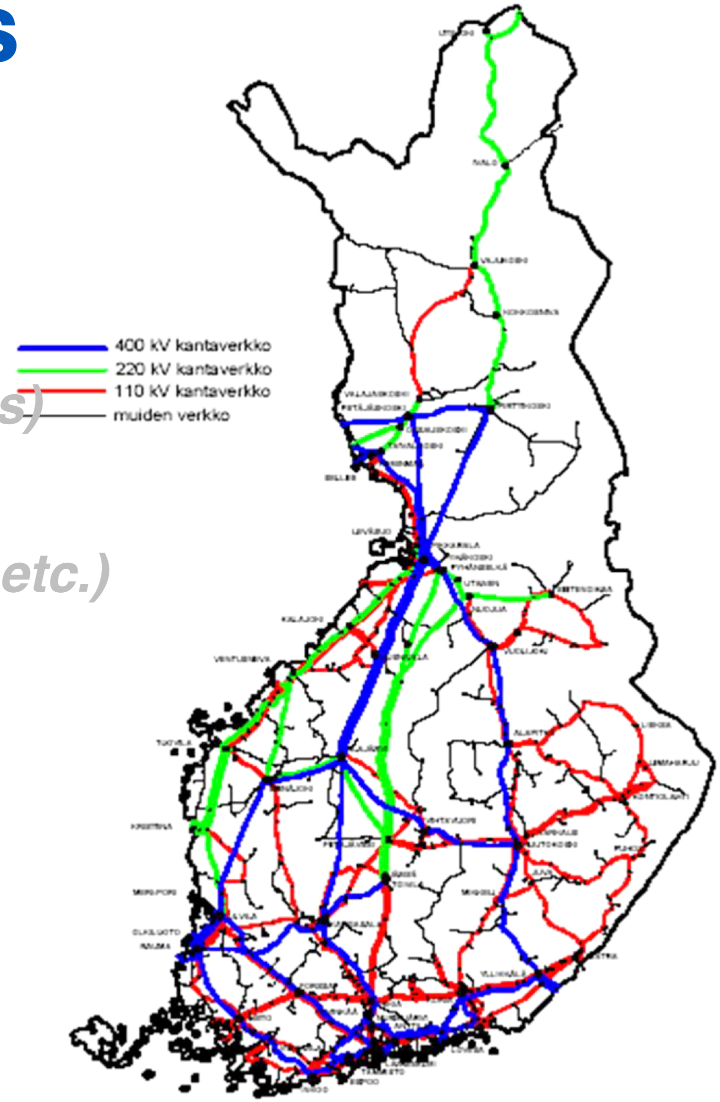

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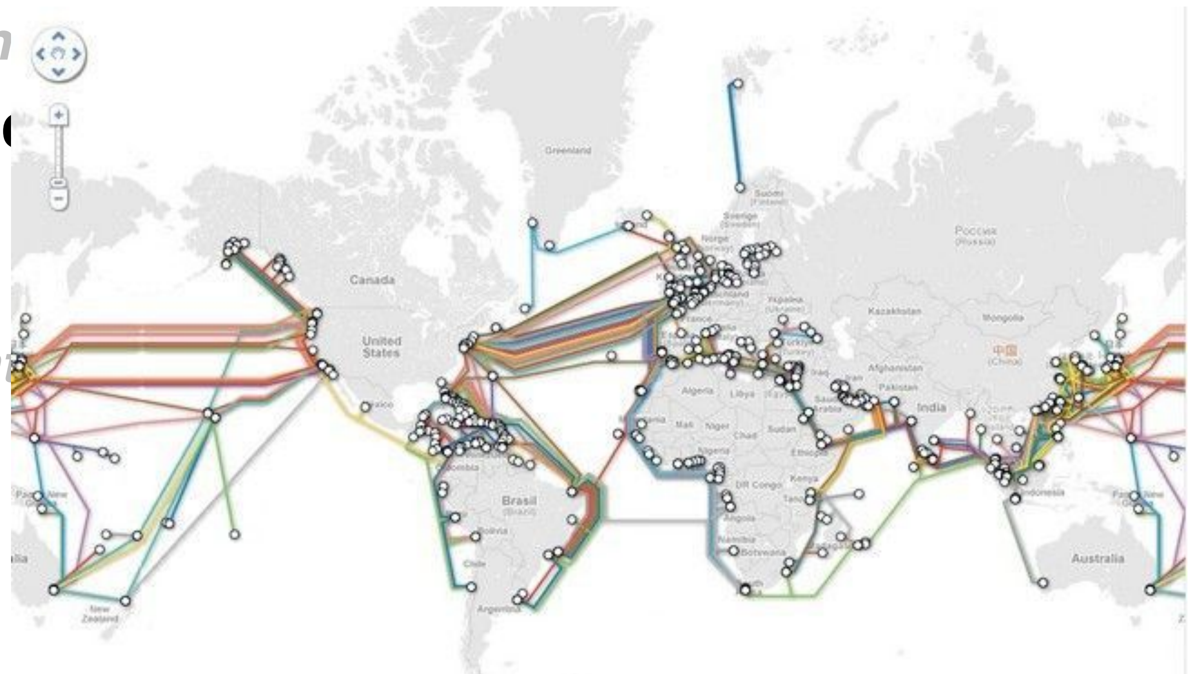

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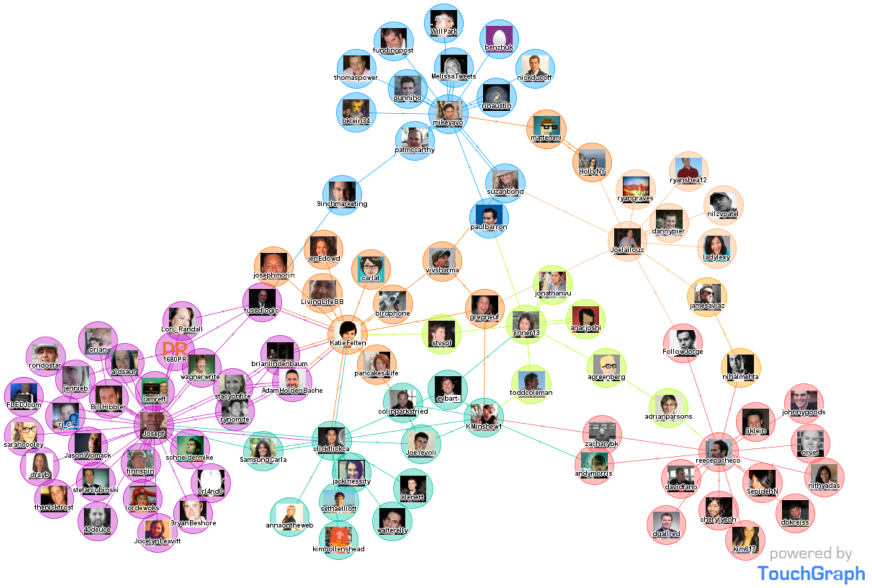

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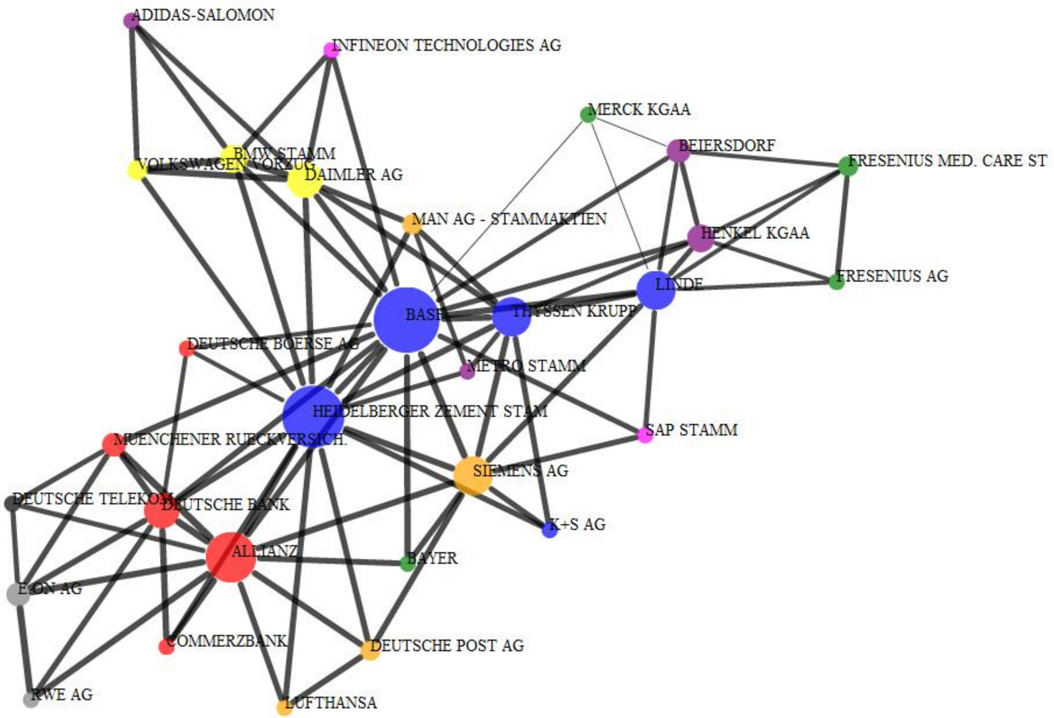

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Many types of networks

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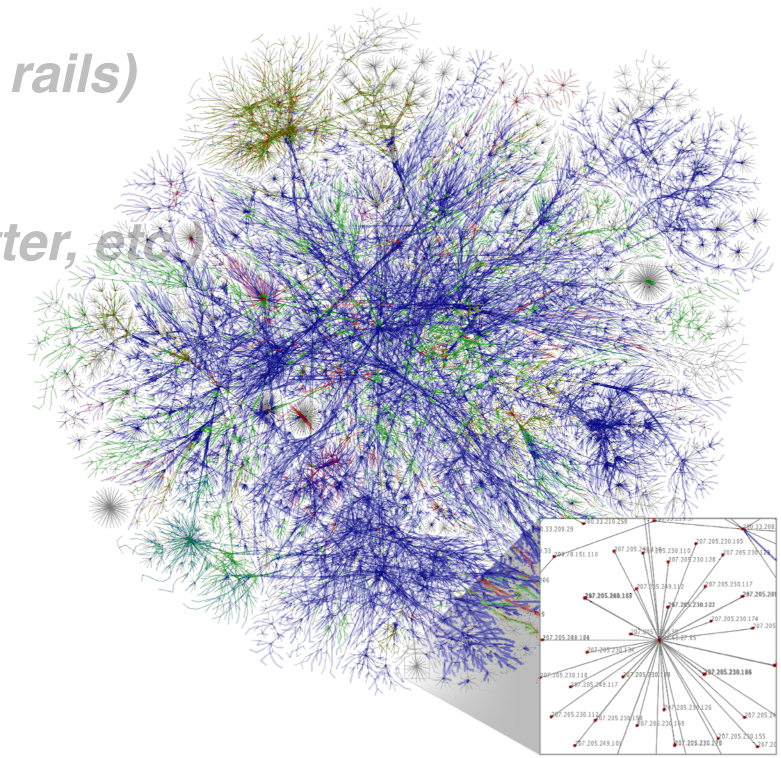

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Complex network

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.

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

Contents [hide]

1 Definition
2 Scale-free networks
3 Small-world networks
4 See also
5 Books
6 References

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

What?

4. What is brain connectivity?

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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)*

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

How?

5. How do we estimate structural brain networks non invasively?

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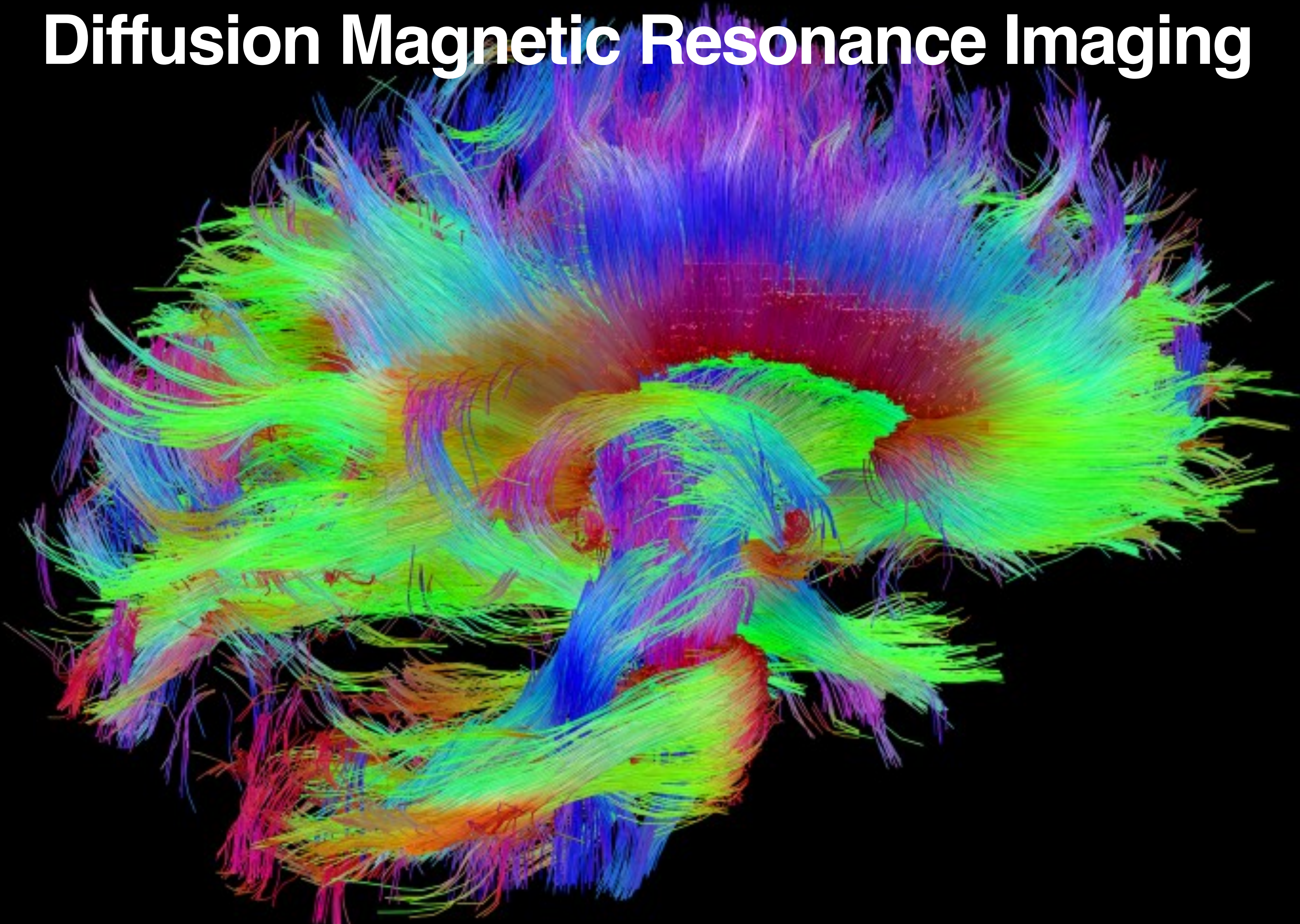
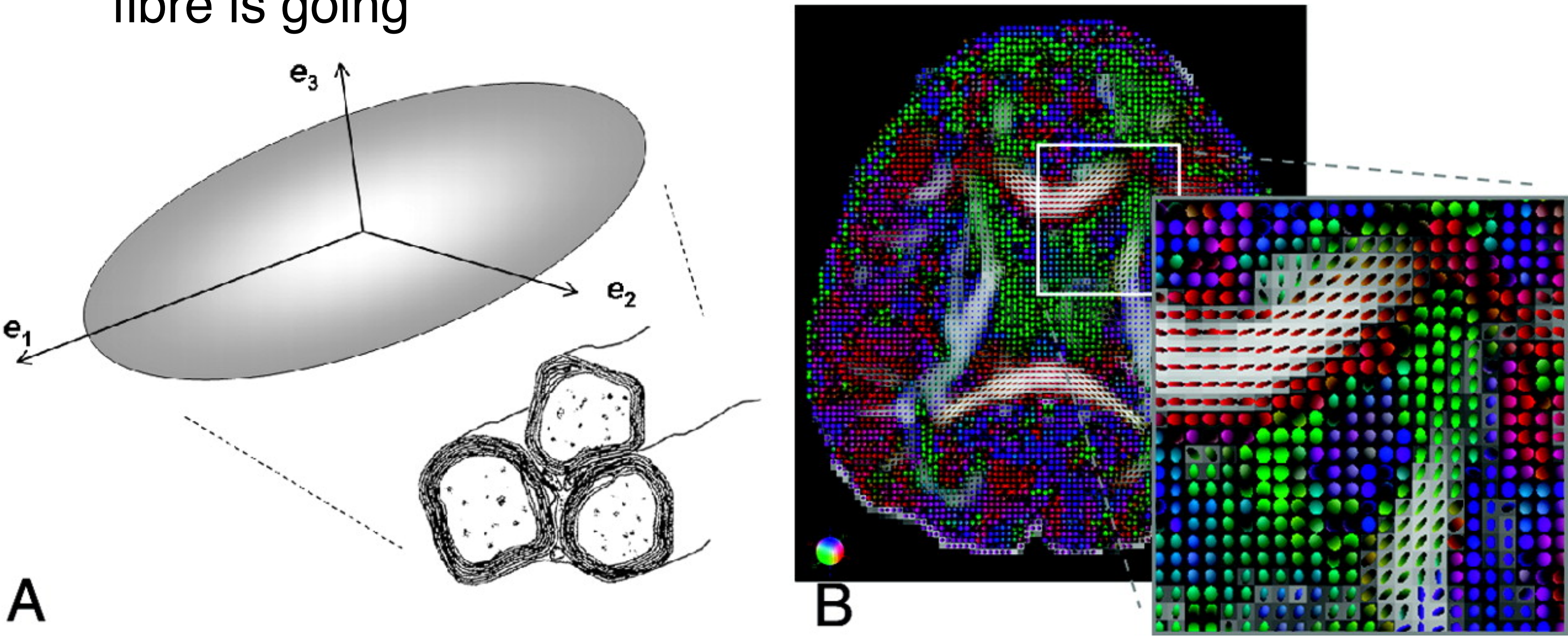
Diffusion Magnetic Resonance Imaging



http://www.humanconnectomeproject.org/gallery/

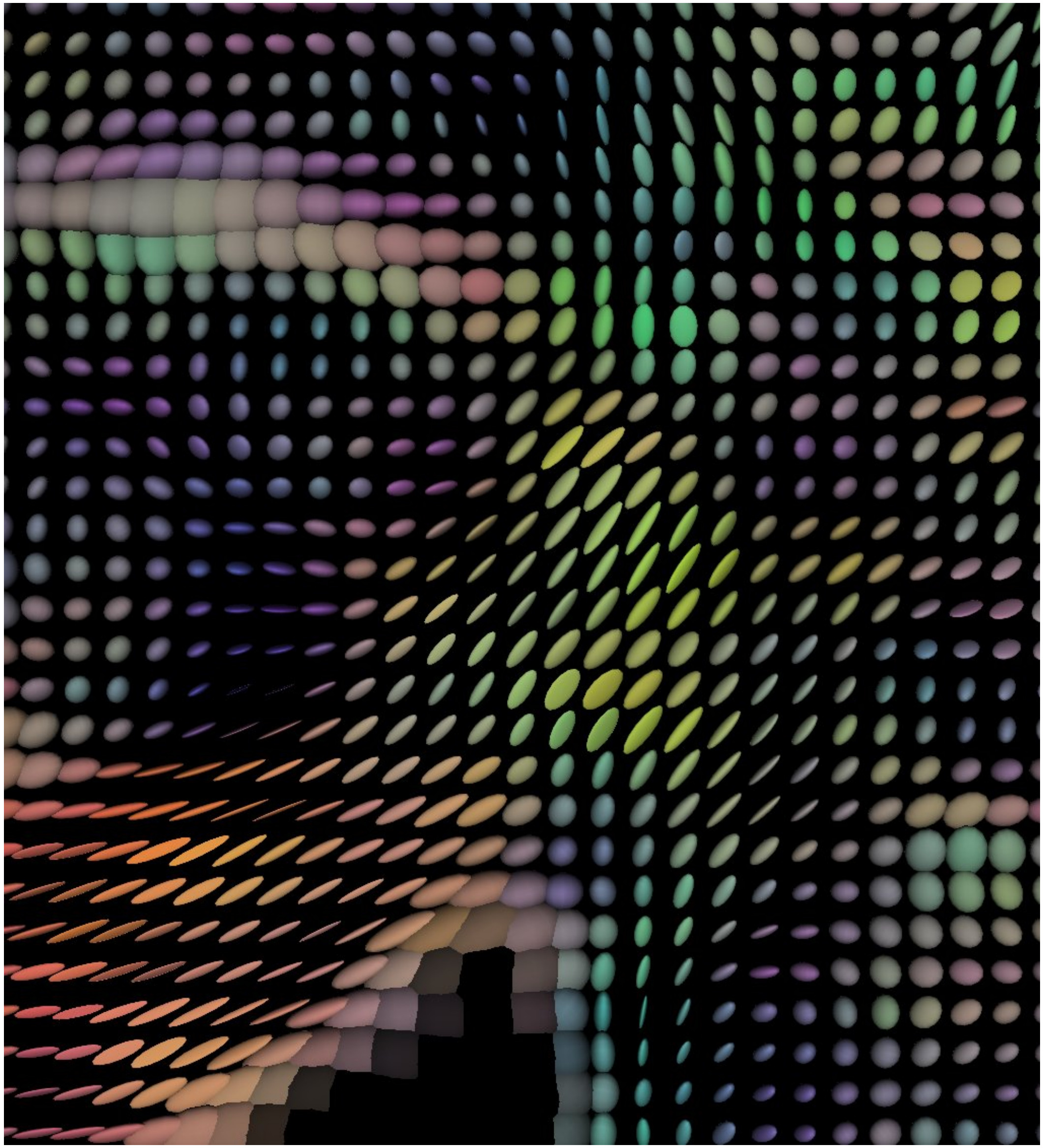
Diffusion MRI

- For every cube mm we measure the **diffusion of water**
- We can determine the main direction(s) along which the fibre is going



Diffusion MRI

- By following the directions of diffusion **we can reconstruct the tracts**



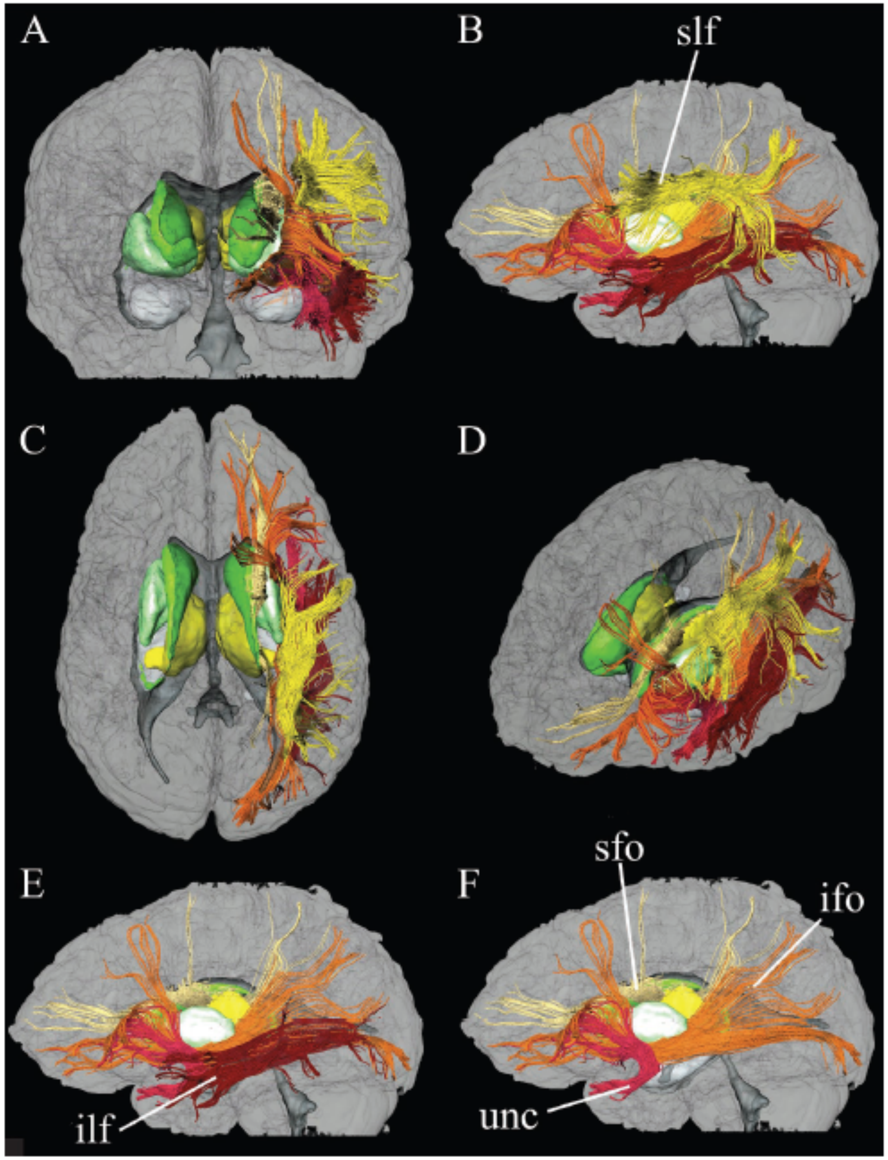


Figure 4. Four viewing angles of 3D depictions of association fibers. *A,* Anterior view; *B,* left lateral view; *C,* superior view; *D,* oblique view from right anterior angle. Reconstructed fibers are superior longitudinal fasciculus (*slf,* yellow), inferior longitudinal fasciculus (*ilf,* brown), superior fronto-occipital fasciculus (*sfo,* beige), inferior fronto-occipital fasciculus (*ifo,* orange), and uncinate fasciculus (*unc,* red). *E, F,* Left lateral views without superior longitudinal fasciculus *(E)* and inferior longitudinal fasciculus *(F).*

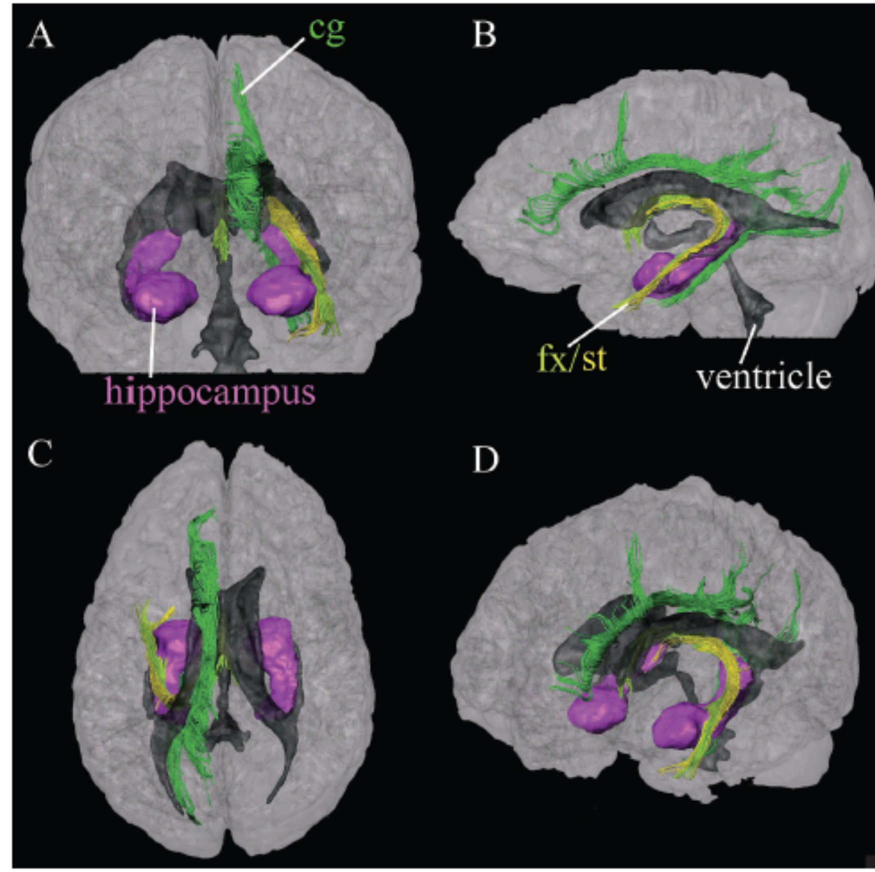


Figure 5. Four viewing angles of 3D depictions of limbic system fibers. *A,* Anterior view; *B,* left lateral view; *C,* superior view; *D,* oblique view from right anterior angle. Reconstructed fibers are cingulum (*cg,* dark green), fornix (*fx,* light green), and stria terminalis (*st,* yellow). For anatomic guidance, hippocampus and amygdala (purple) and ventricles (gray) are also shown.

Wakana, S., et al. (2004). Fiber tract-based atlas of human white matter anatomy. Radiology, 230(1), 77–87.

How?

6. How do we estimate functional brain networks non invasively?

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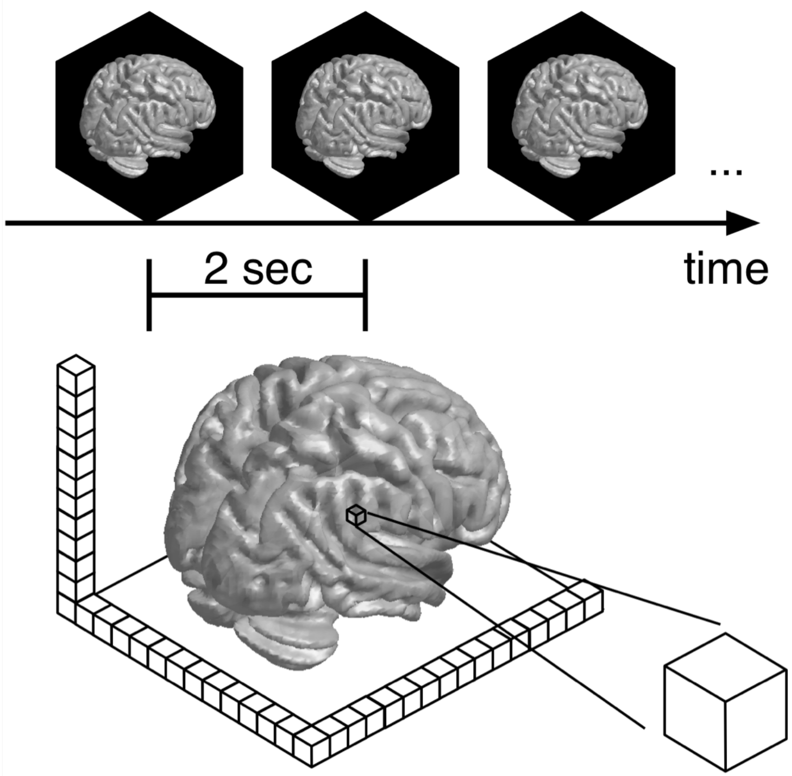
Functional magnetic resonance imaging (fMRI)



- 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

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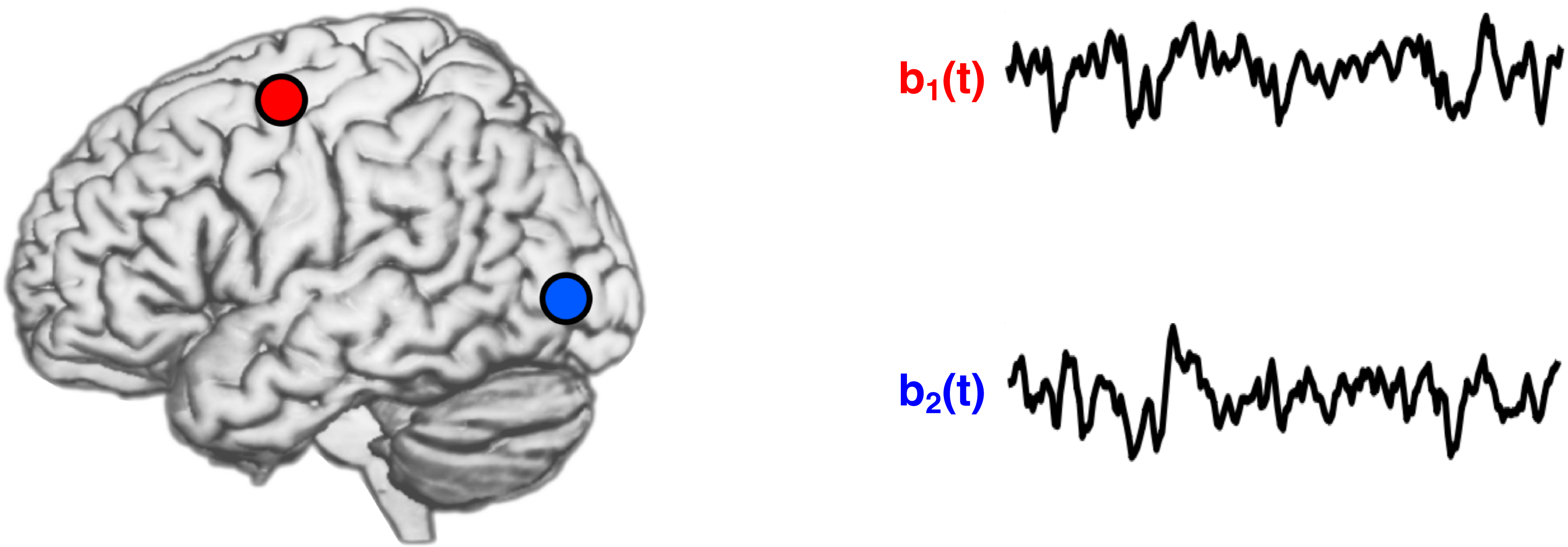
Building a functional network

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



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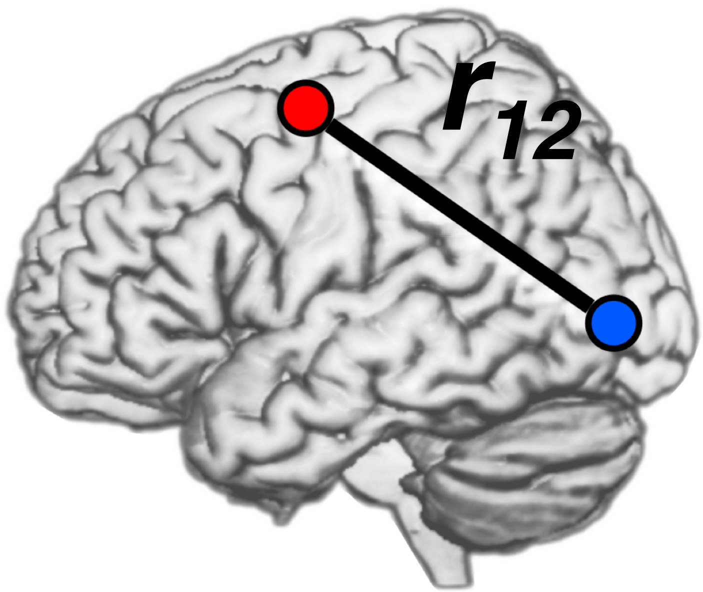
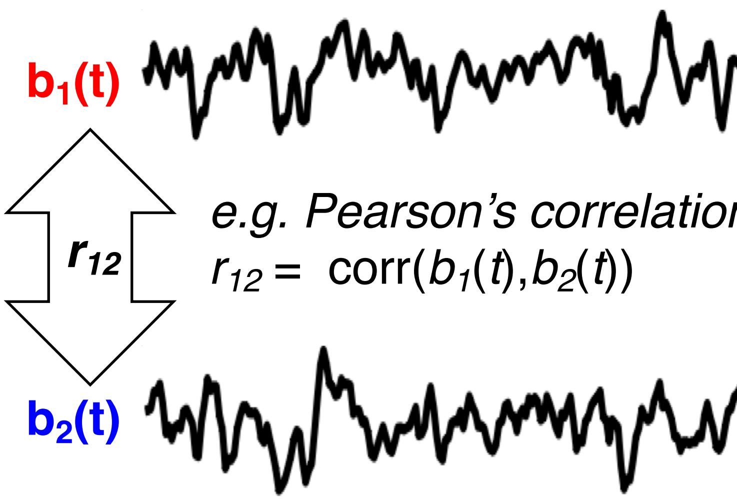
Building a functional network

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





e.g. Pearson's correlation:
$r_{12} = \mathrm{corr}(b_1(t), b_2(t))$

The brain at rest

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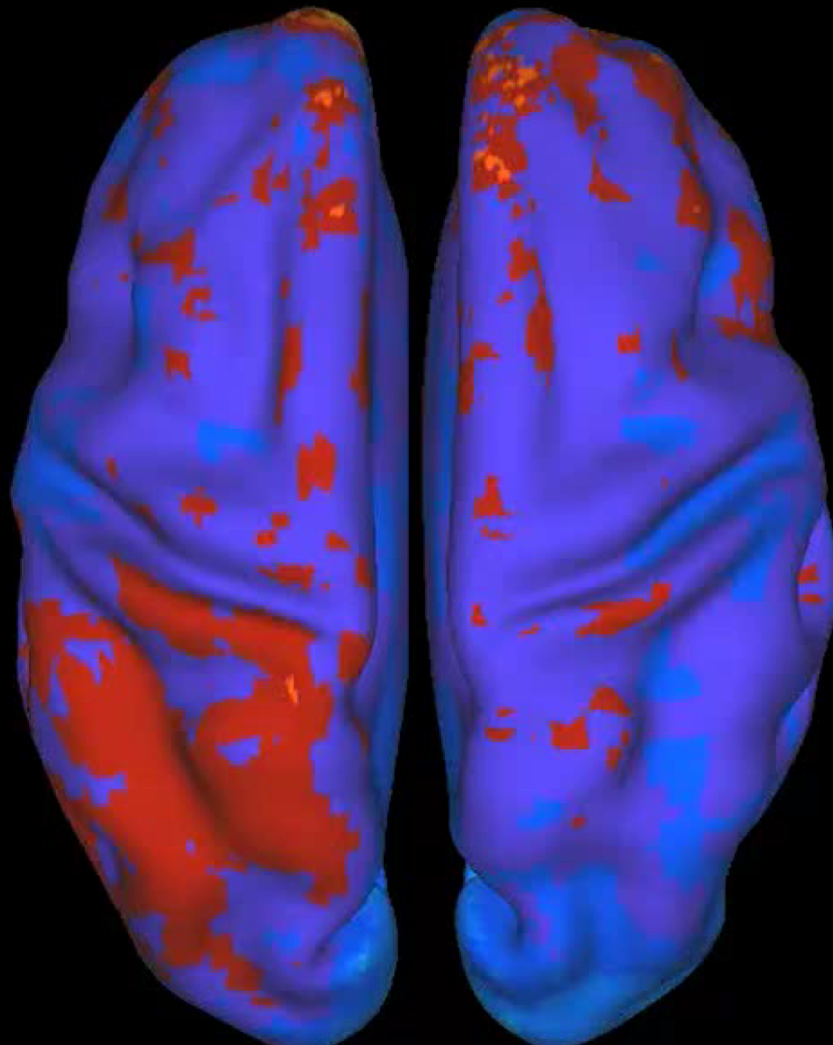
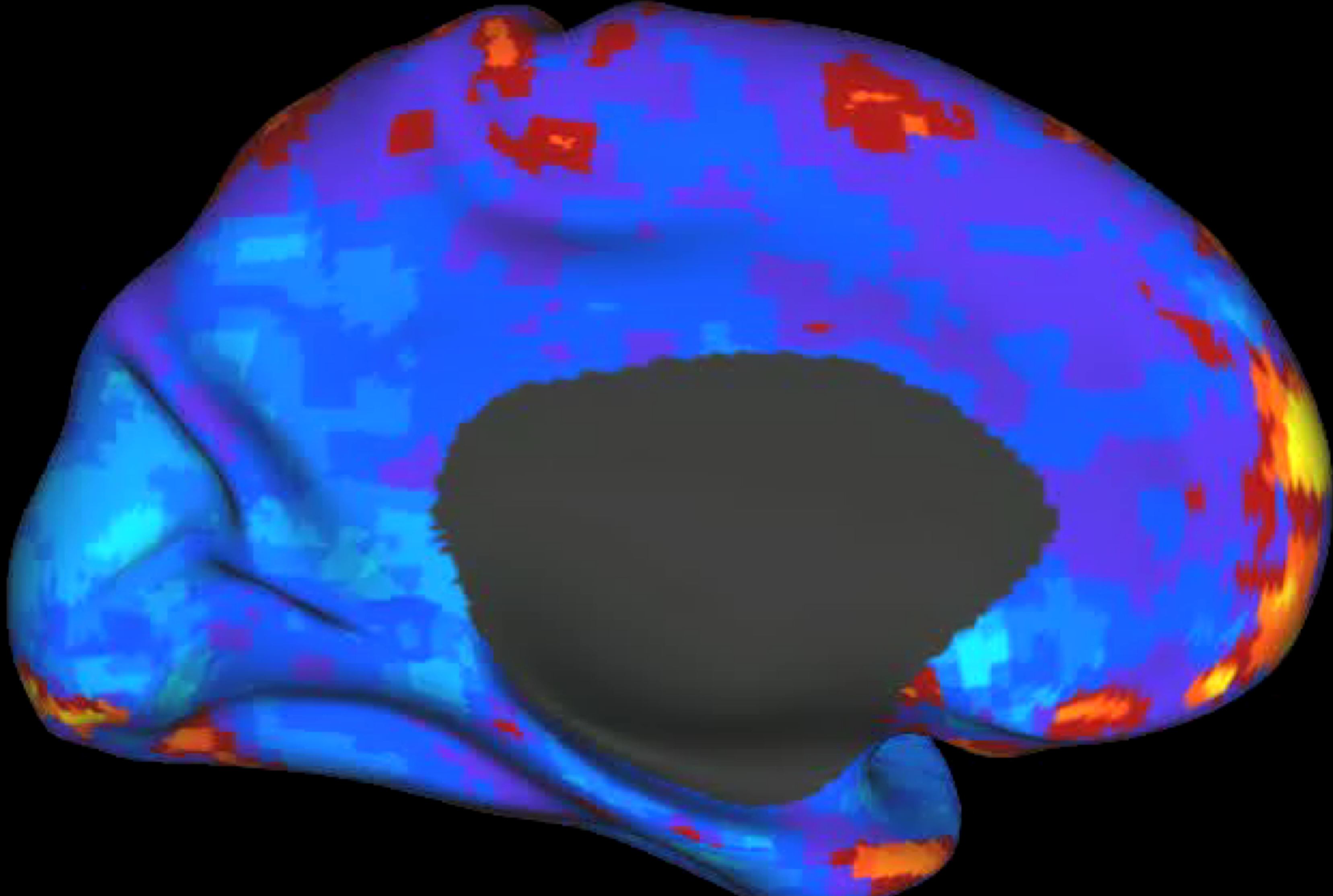


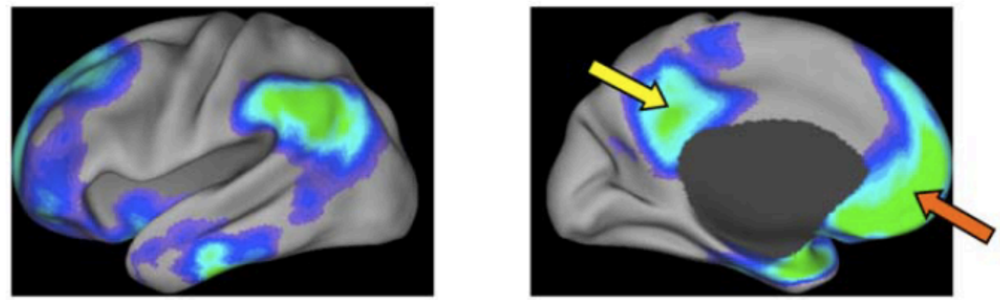
http://www.nil.wustl.edu/labs/raichle/

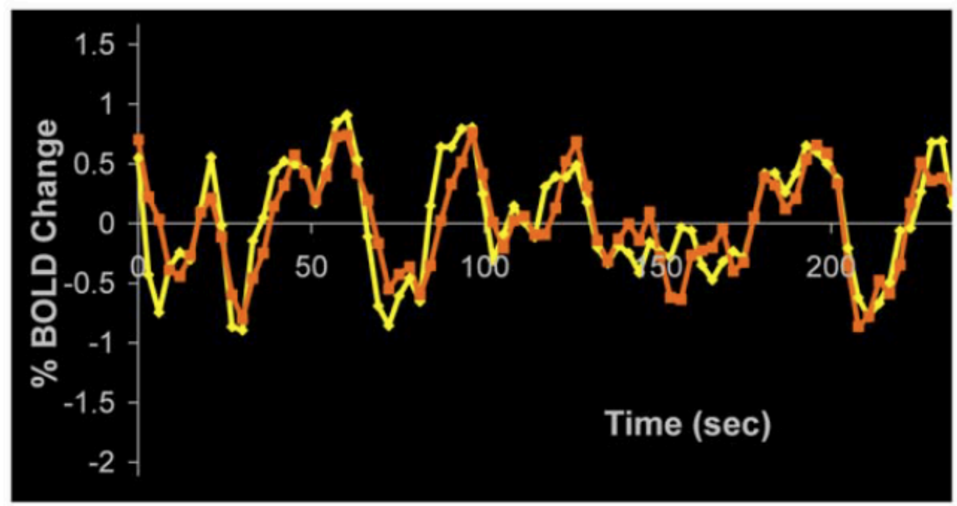


http://www.nil.wustl.edu/labs/raichle/

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**





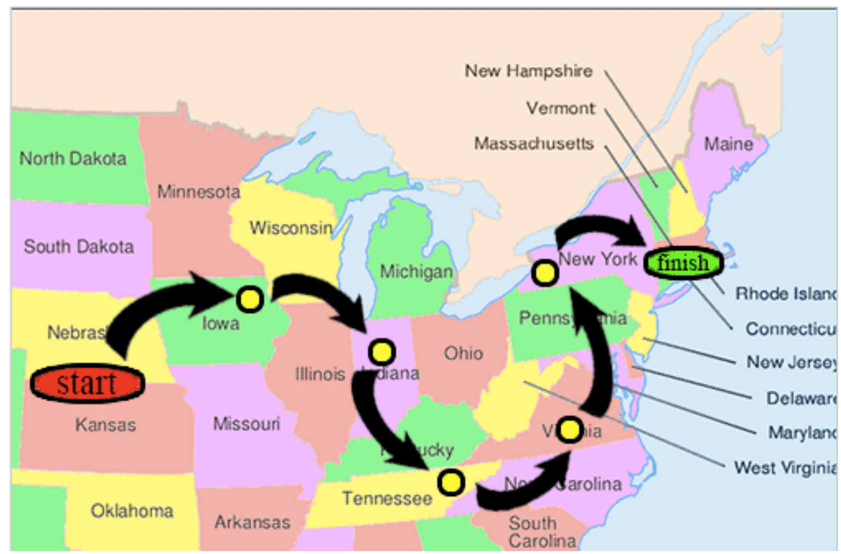
Raichle, M. E. (2010). Two views of brain function. Trends in Cognitive Sciences, 14(4)

What?

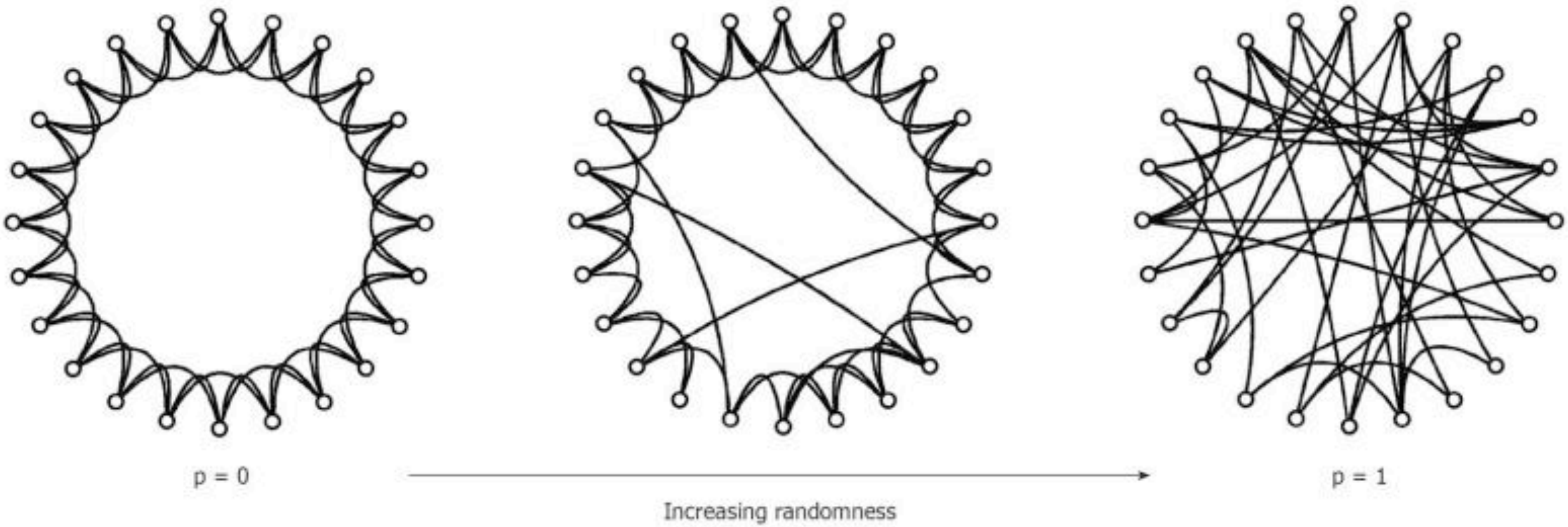
7. What is a small world network?

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?

8. Why is the brain a small world network?

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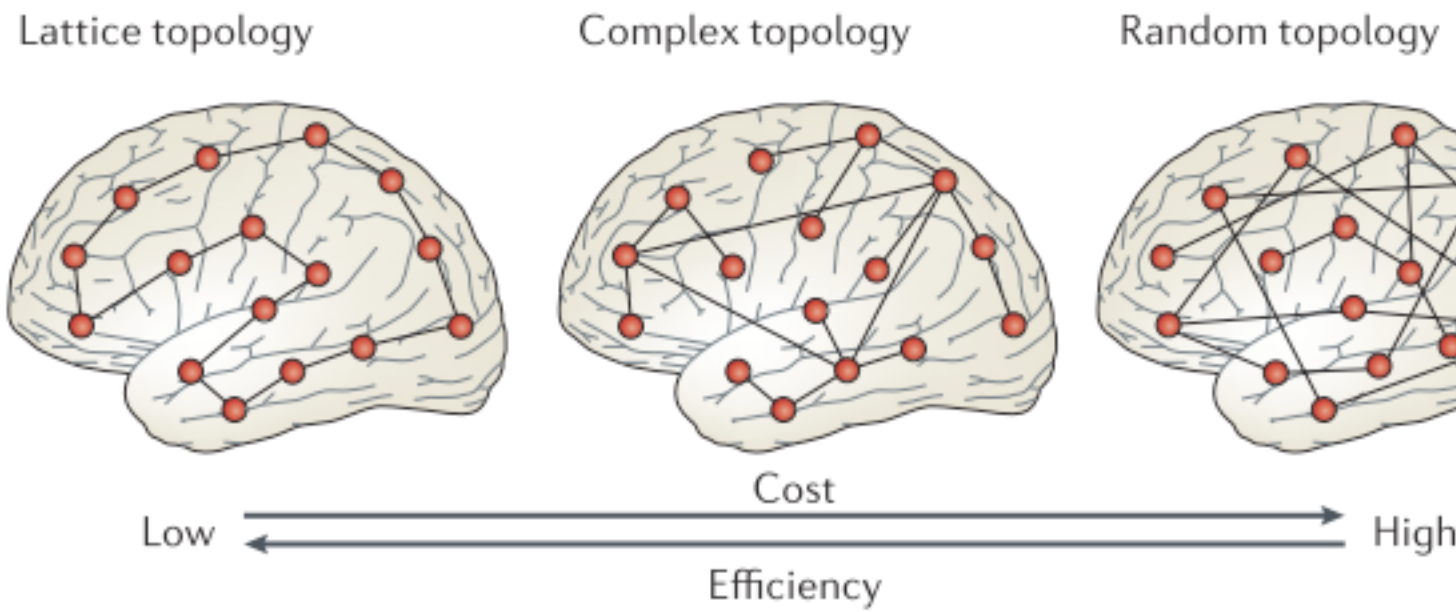
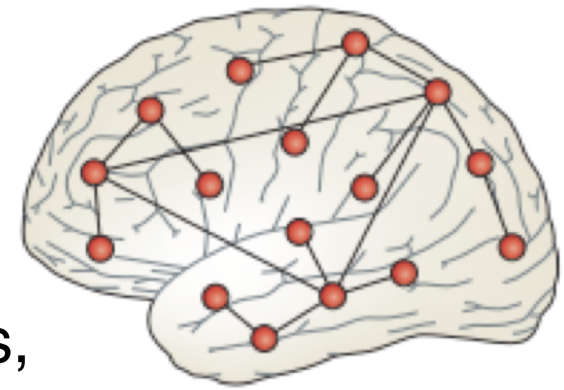
The small-world configuration is the optimal to optimize communication cost and efficiency



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**

What?

9. WHAT IS A HUB?

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What is a hub?

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

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

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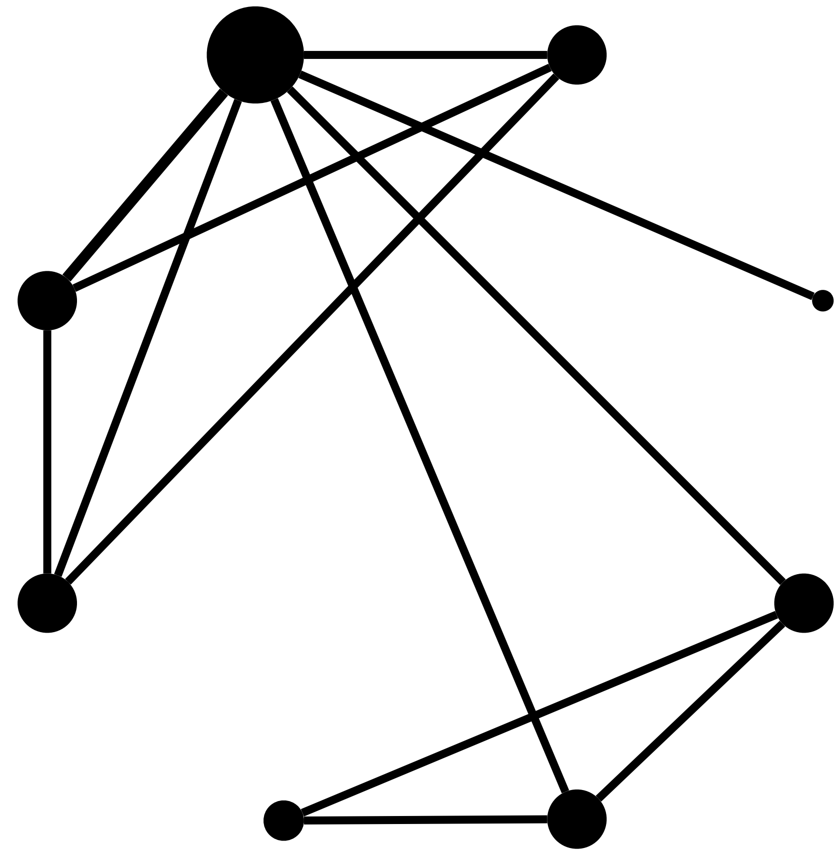
How?

10. 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?



What?

11. What are the hubs in the brain?

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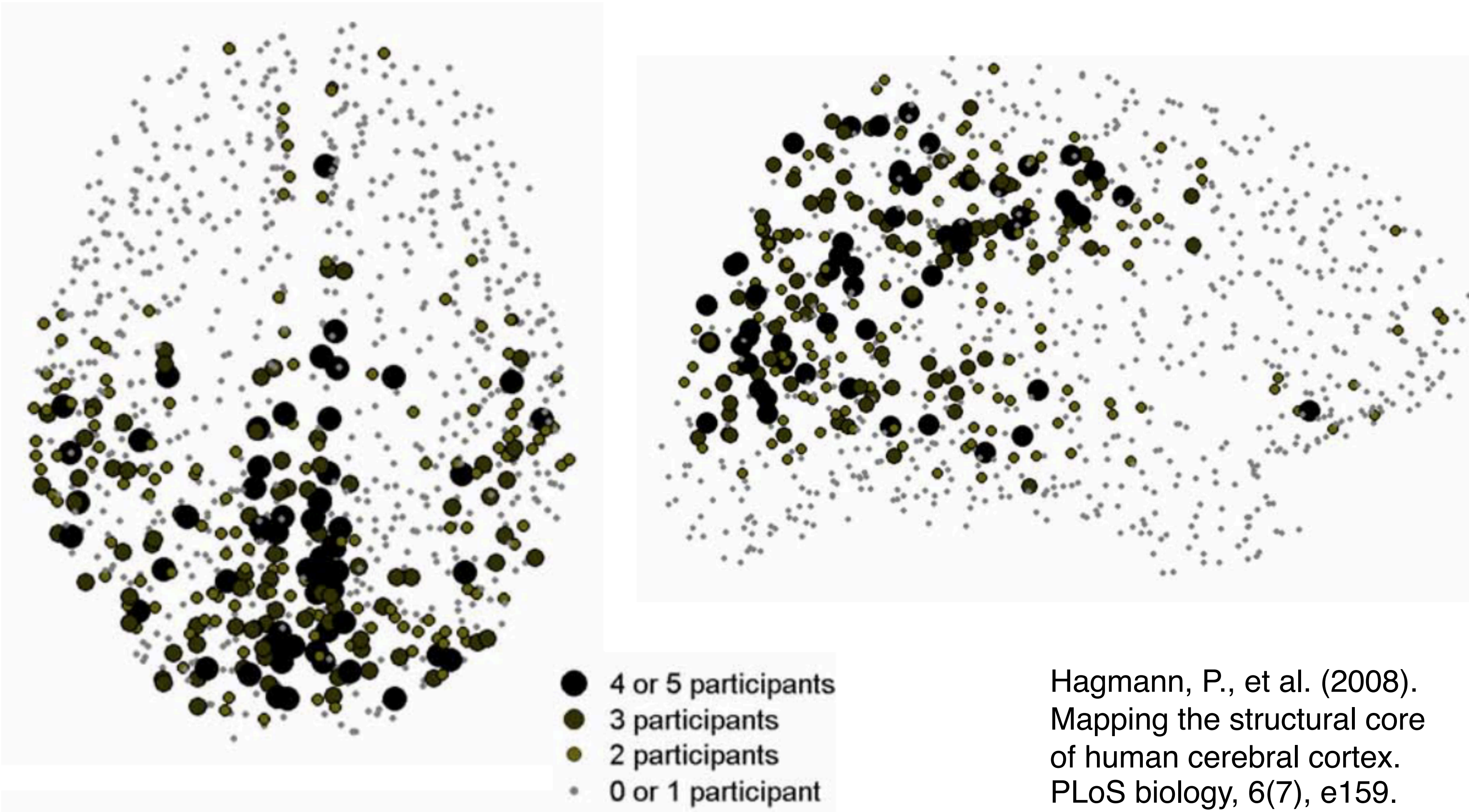
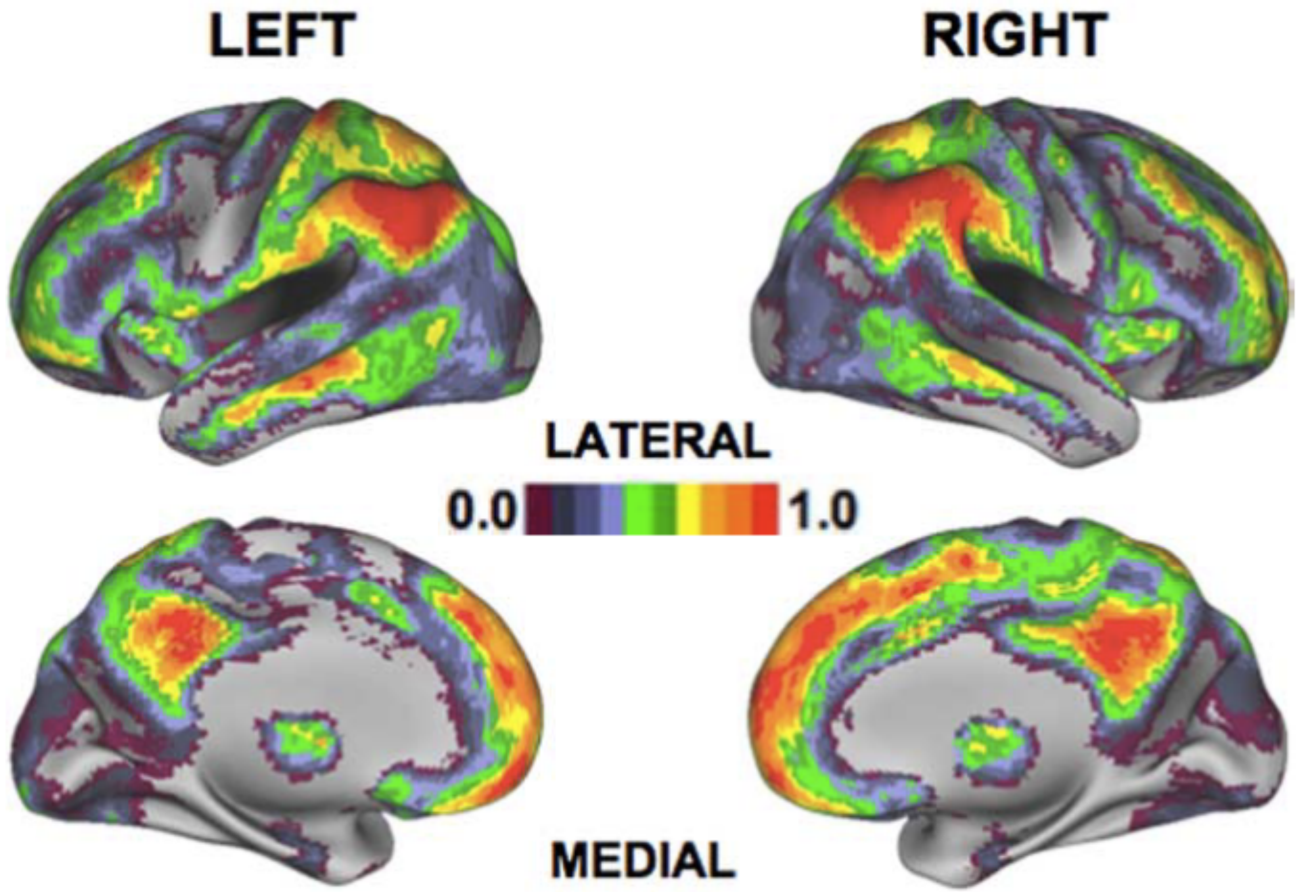
Cortical hubs in the human brain



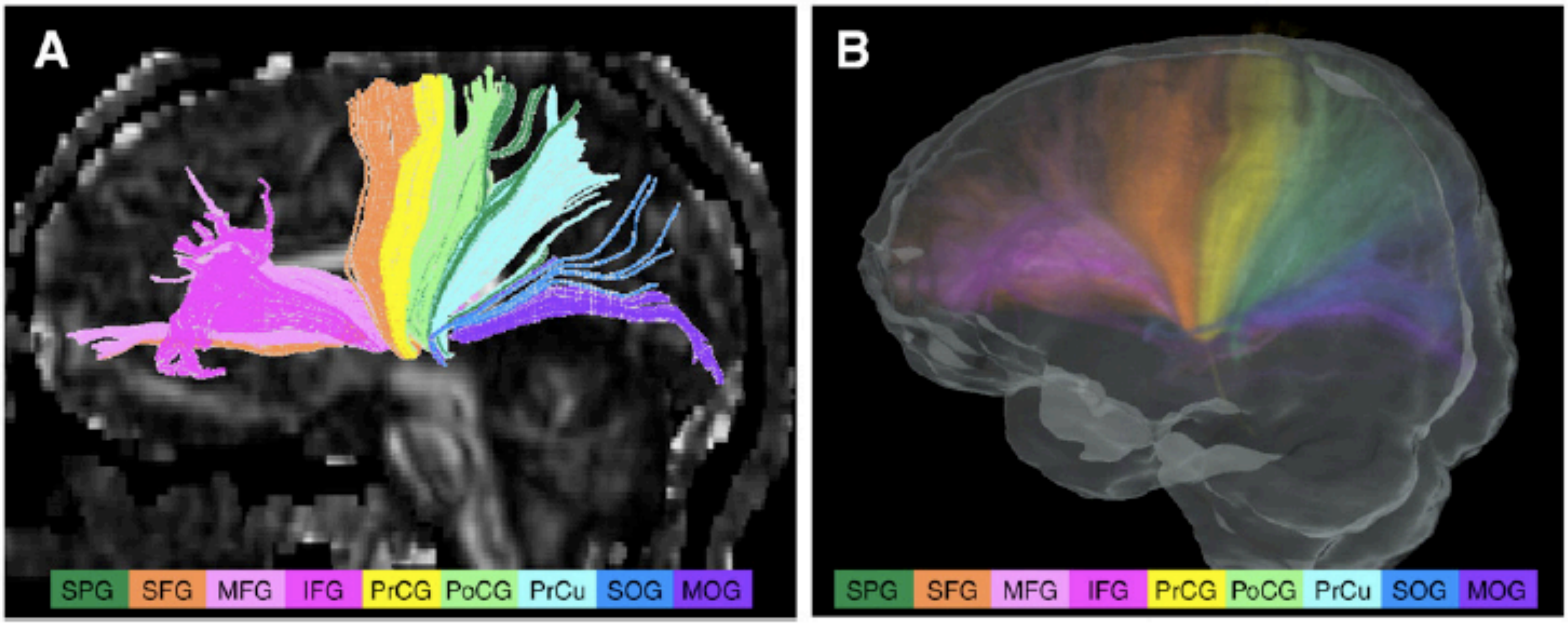
Hagmann, P., et al. (2008). Mapping the structural core of human cerebral cortex. PLoS biology, 6(7), e159.

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.

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?

12. What is a network module?

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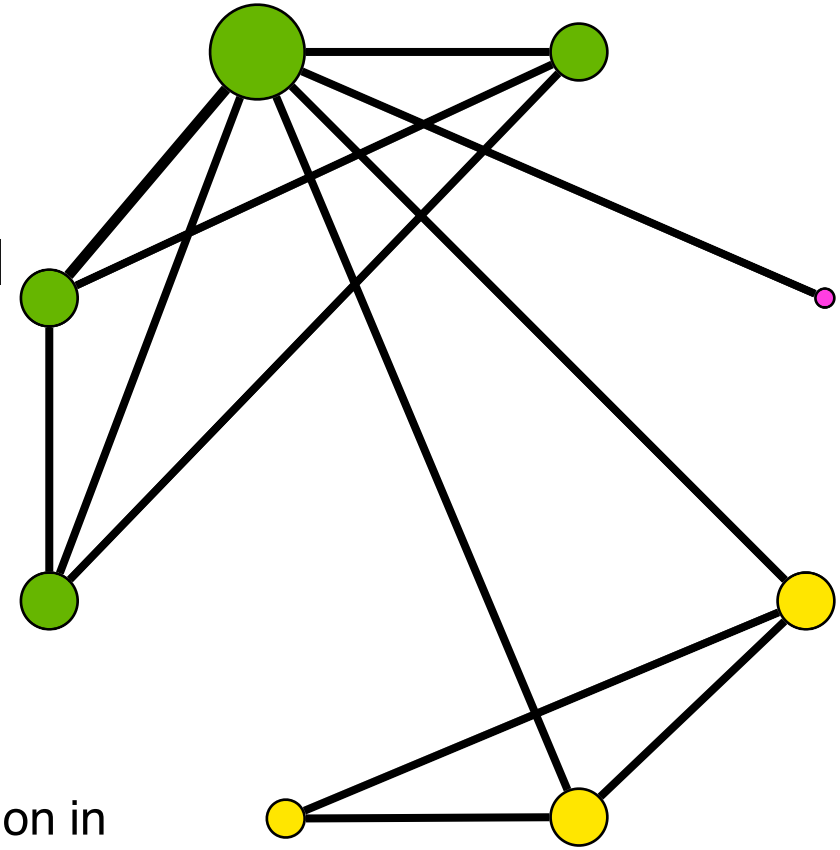
Quantifying modules in networks

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?

13. 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

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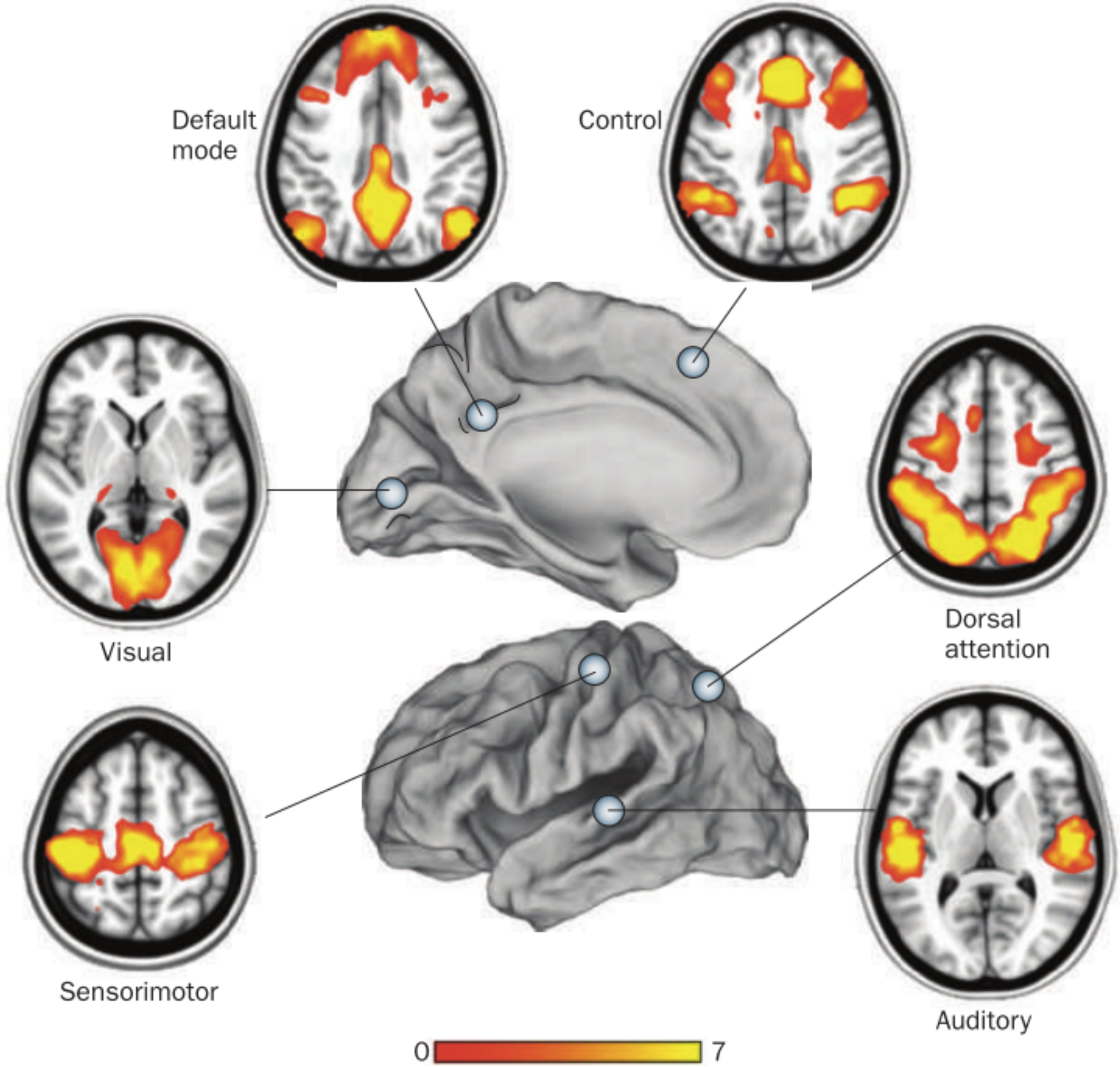
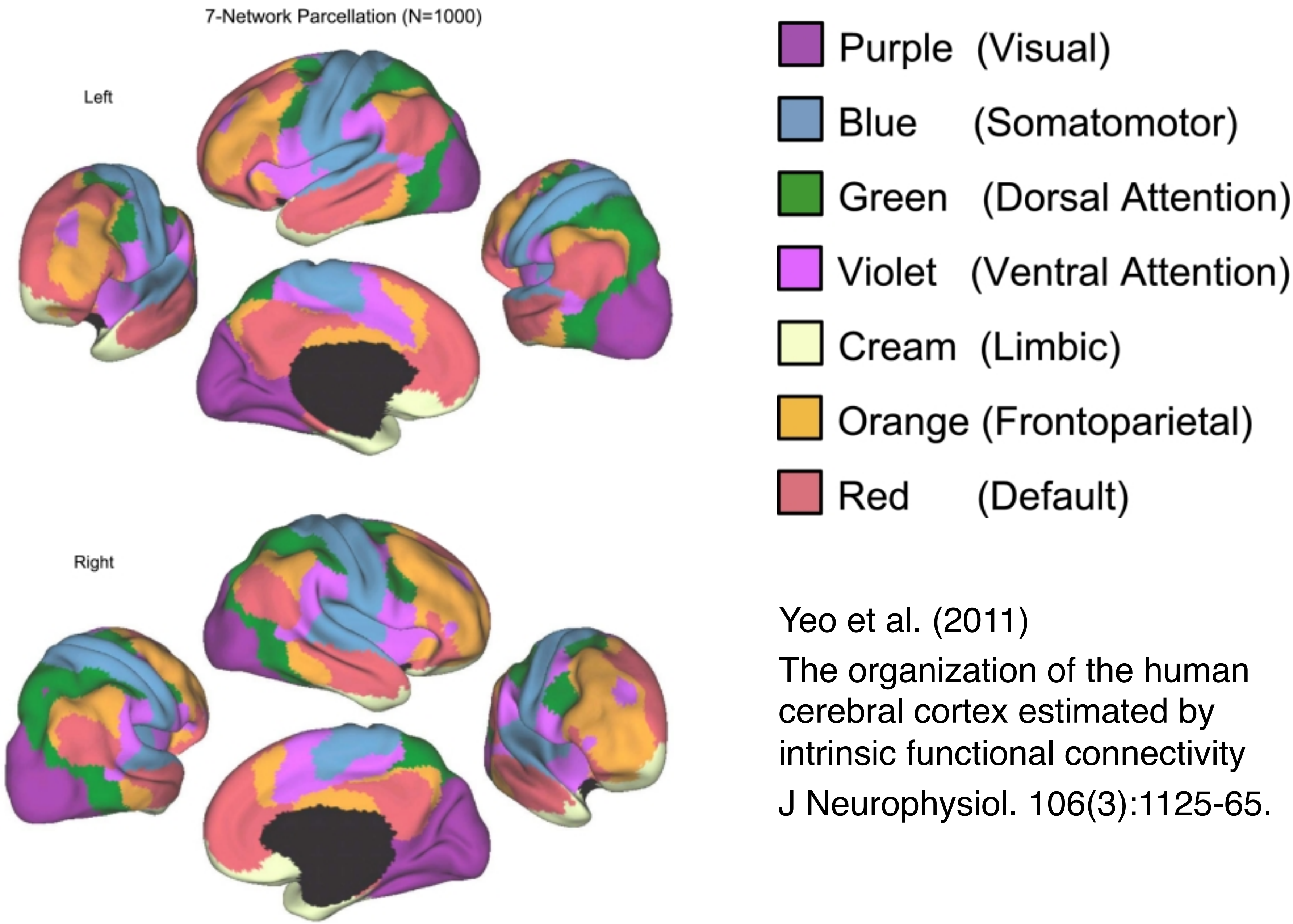


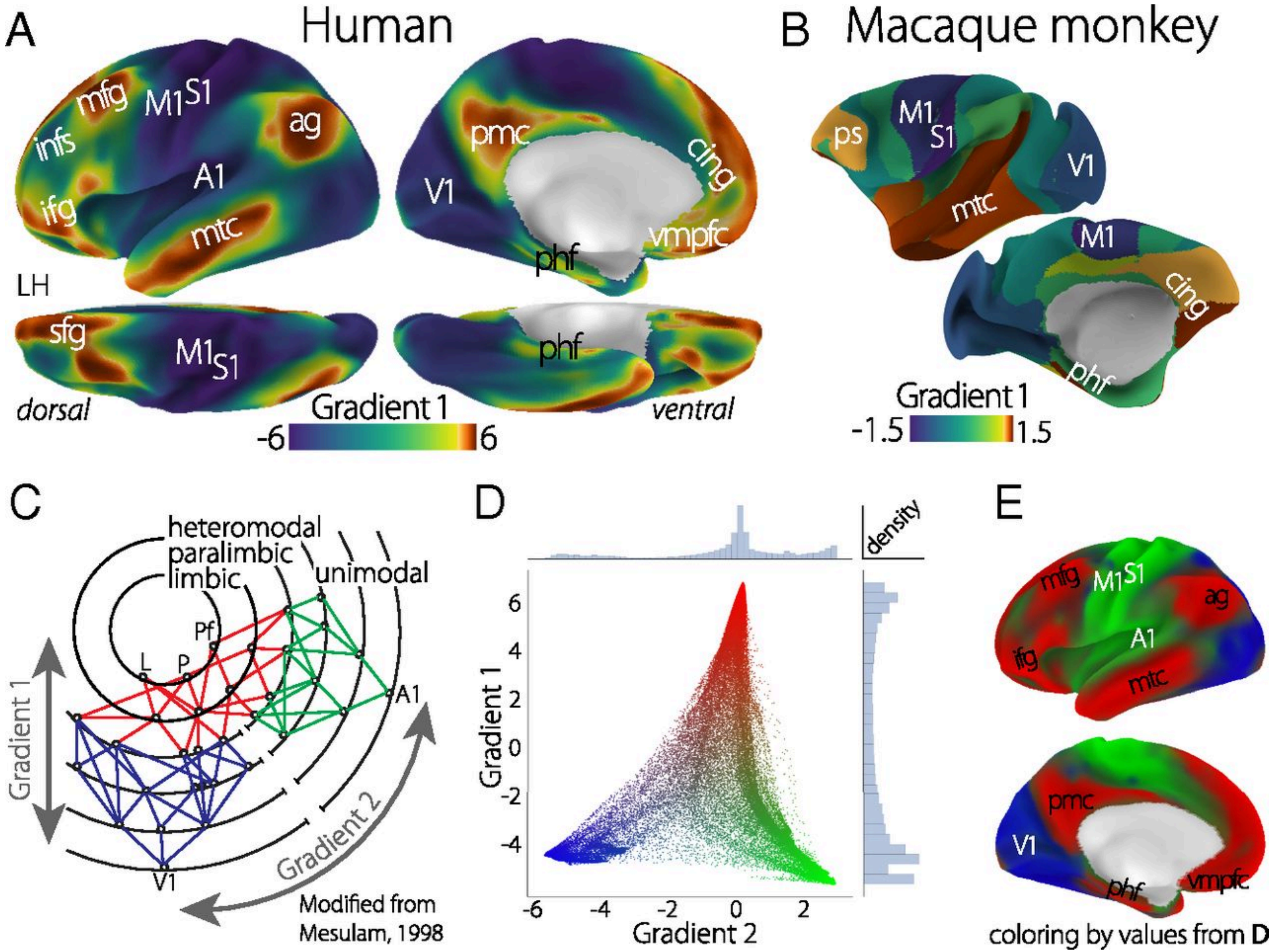
Zhang, D., & Raichle, M. E. (2010). Disease and the brain's dark energy. Nature reviews. Neurology, 6(1), 15–28.



Yeo et al. (2011)

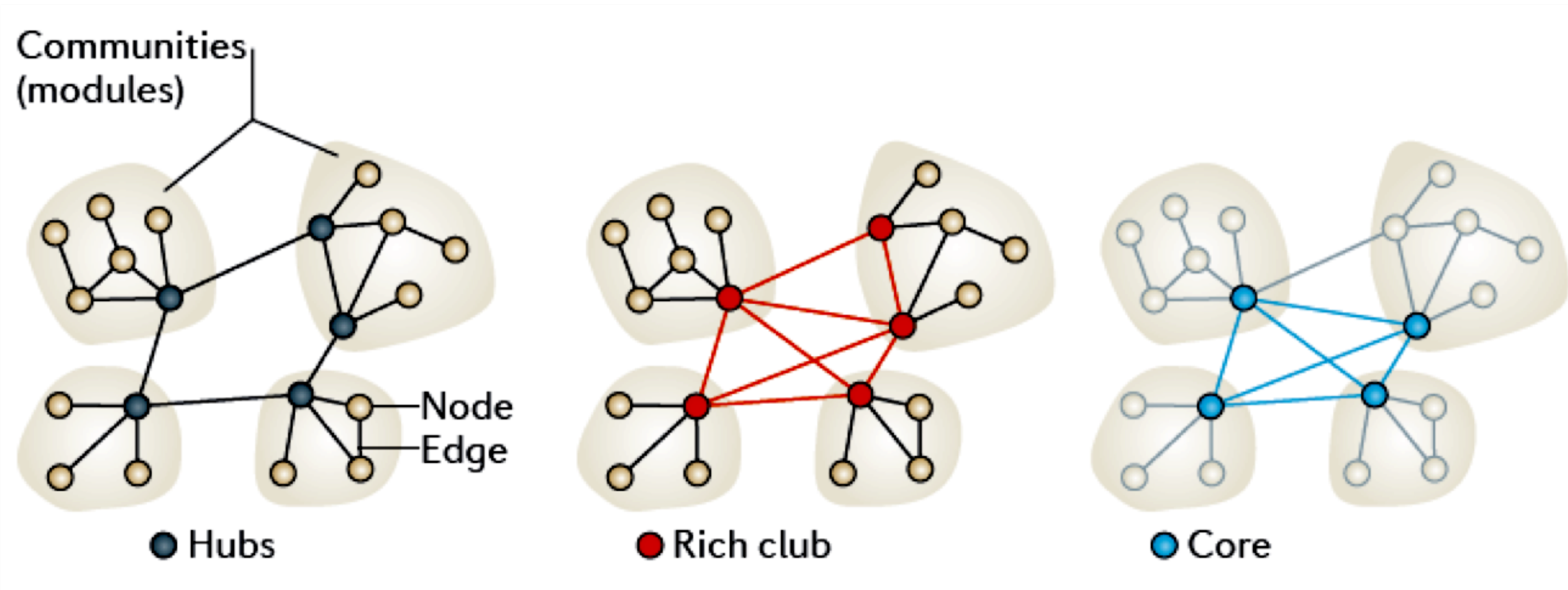
The organization of the human cerebral cortex estimated by intrinsic functional connectivity

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

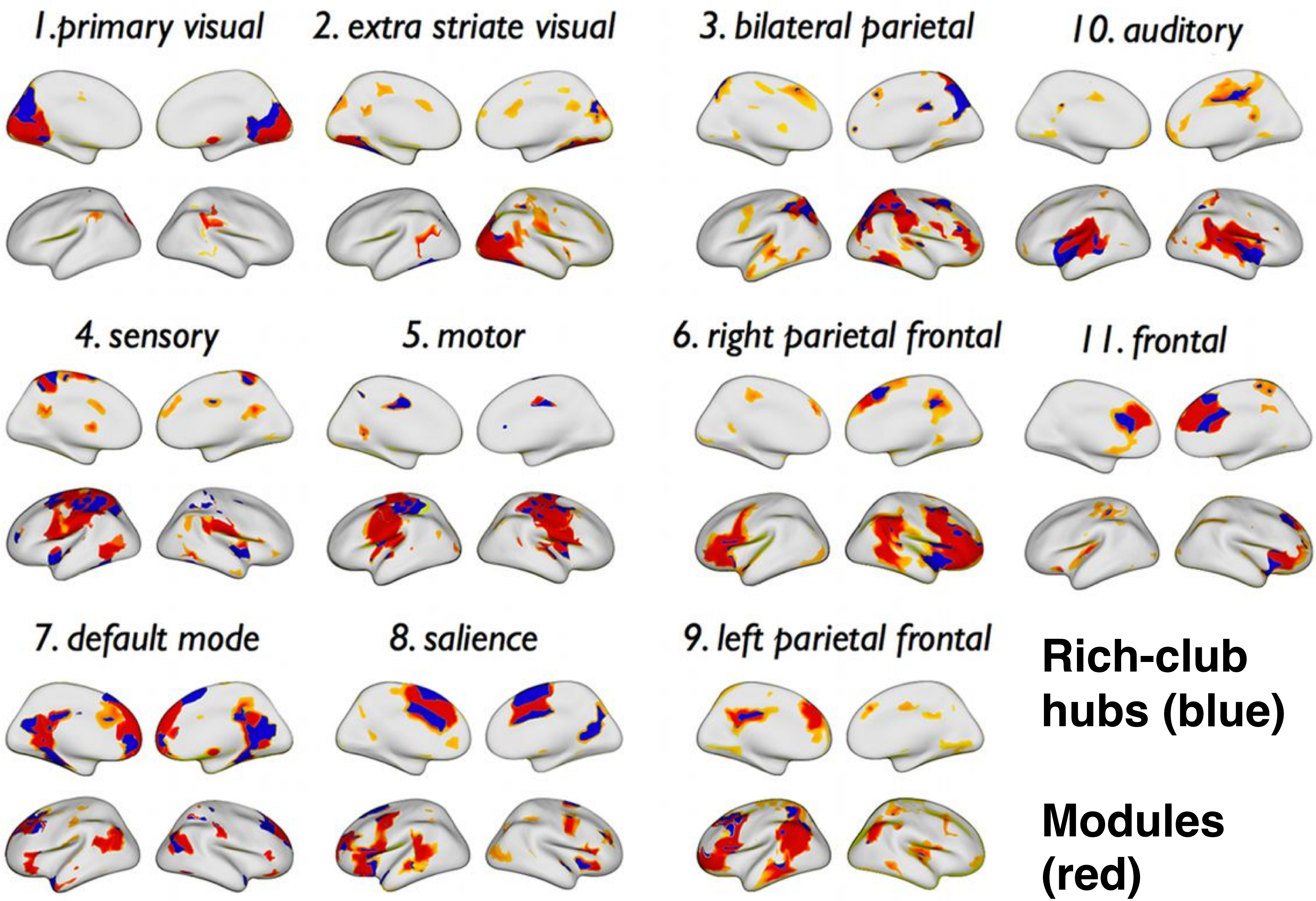


Margulies et al (2016) **Situating the default-mode network along a principal gradient of macroscale cortical organization.** PNAS

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?

14. How does connectivity change in time?

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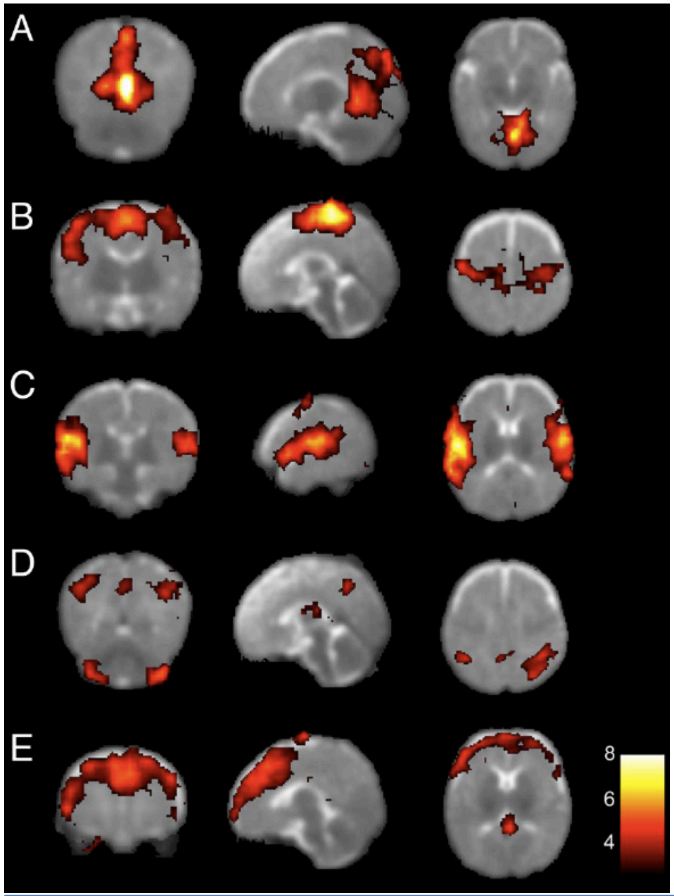
Temporal scales of connectivity

- 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

What?

15. What is the impact of this research on society?

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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

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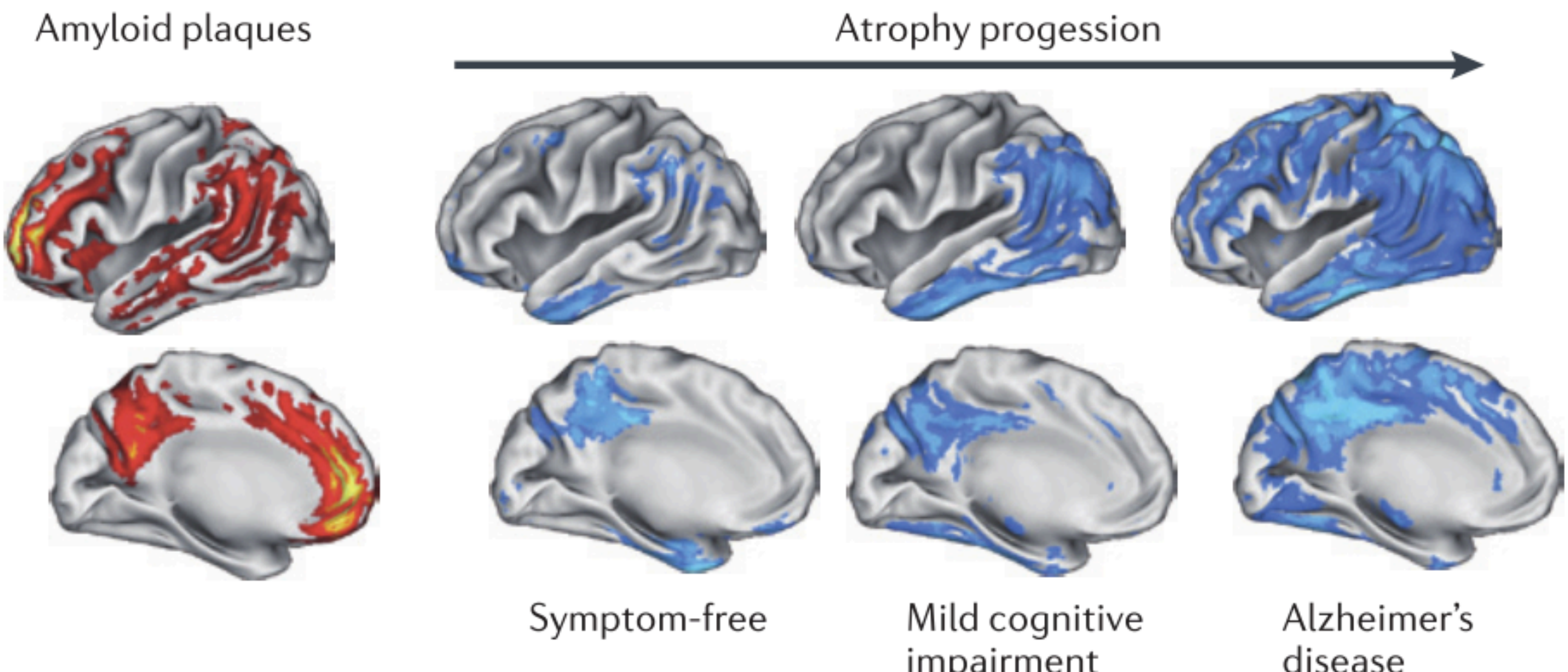
Alzheimer's disease

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

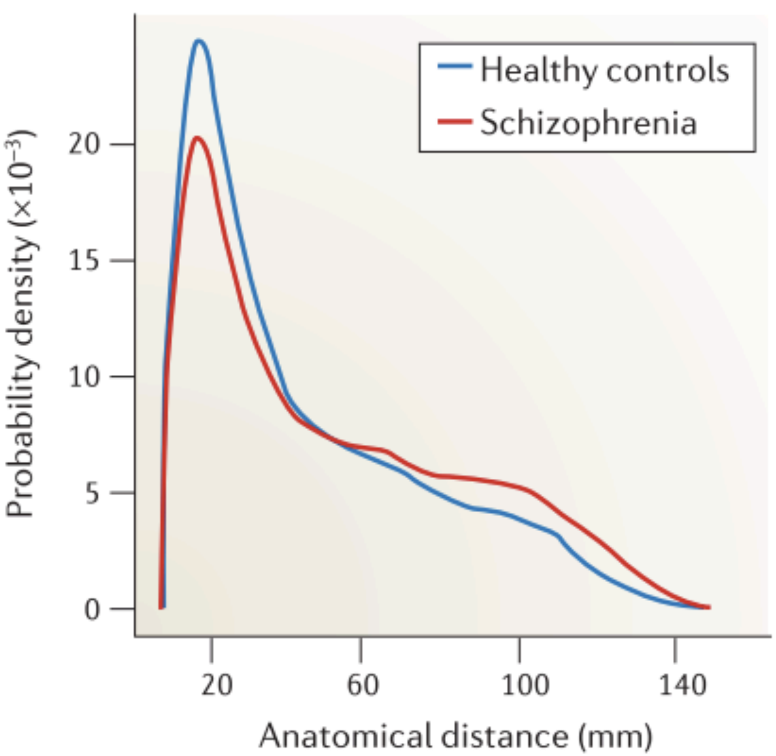


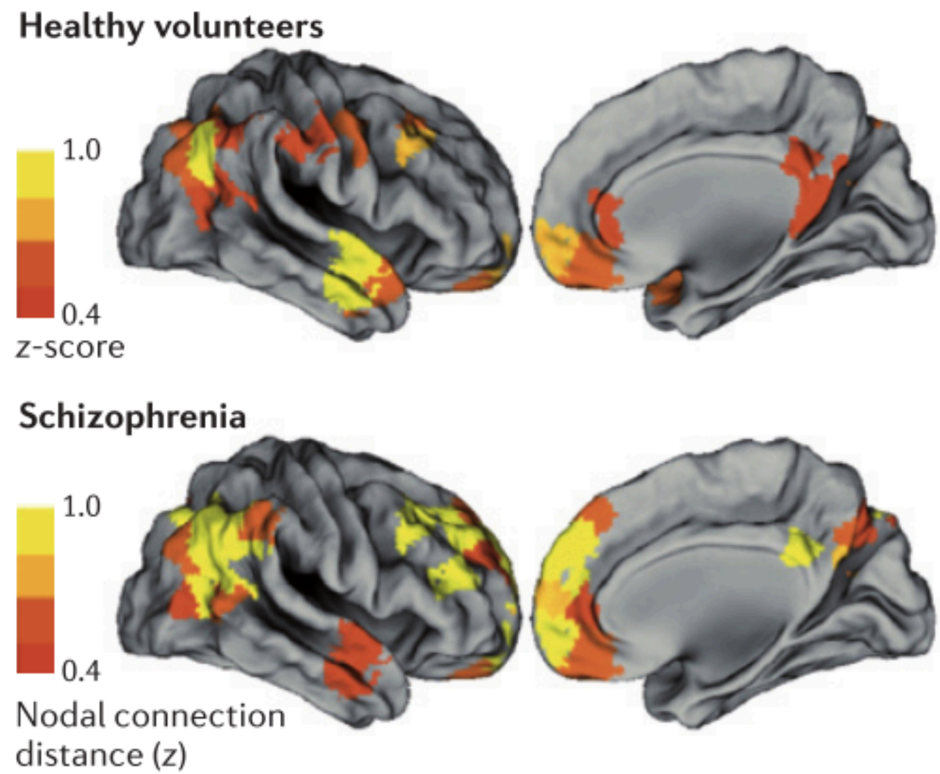
Bullmore, E., & Sporns, O. (2012). The economy of brain network organization. Nature reviews. Neuroscience, 13(5), 336–49

Schizophrenia

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

- **Unbalanced small-worldness**





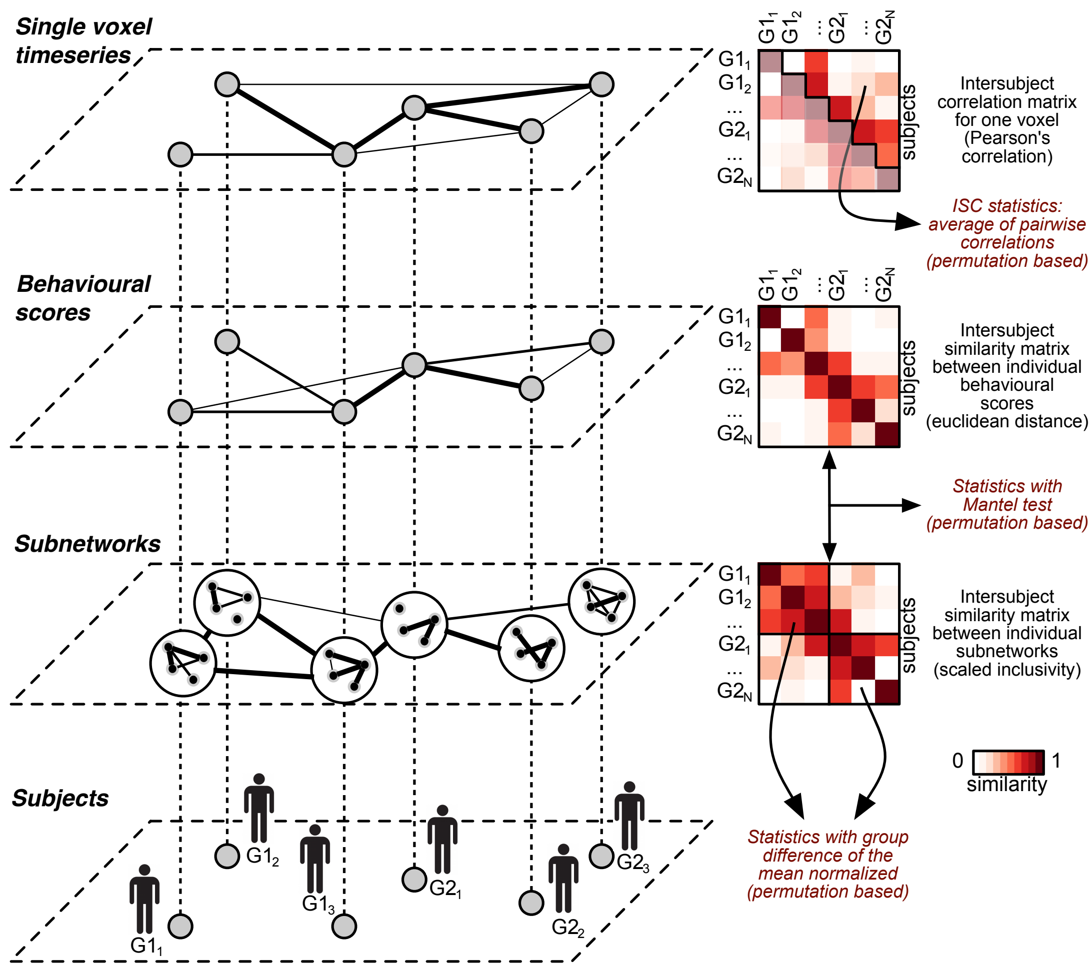
Reorganization of functionally connected brain subnetworks in high-functioning autism (Glerean et al 2016)

- 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.

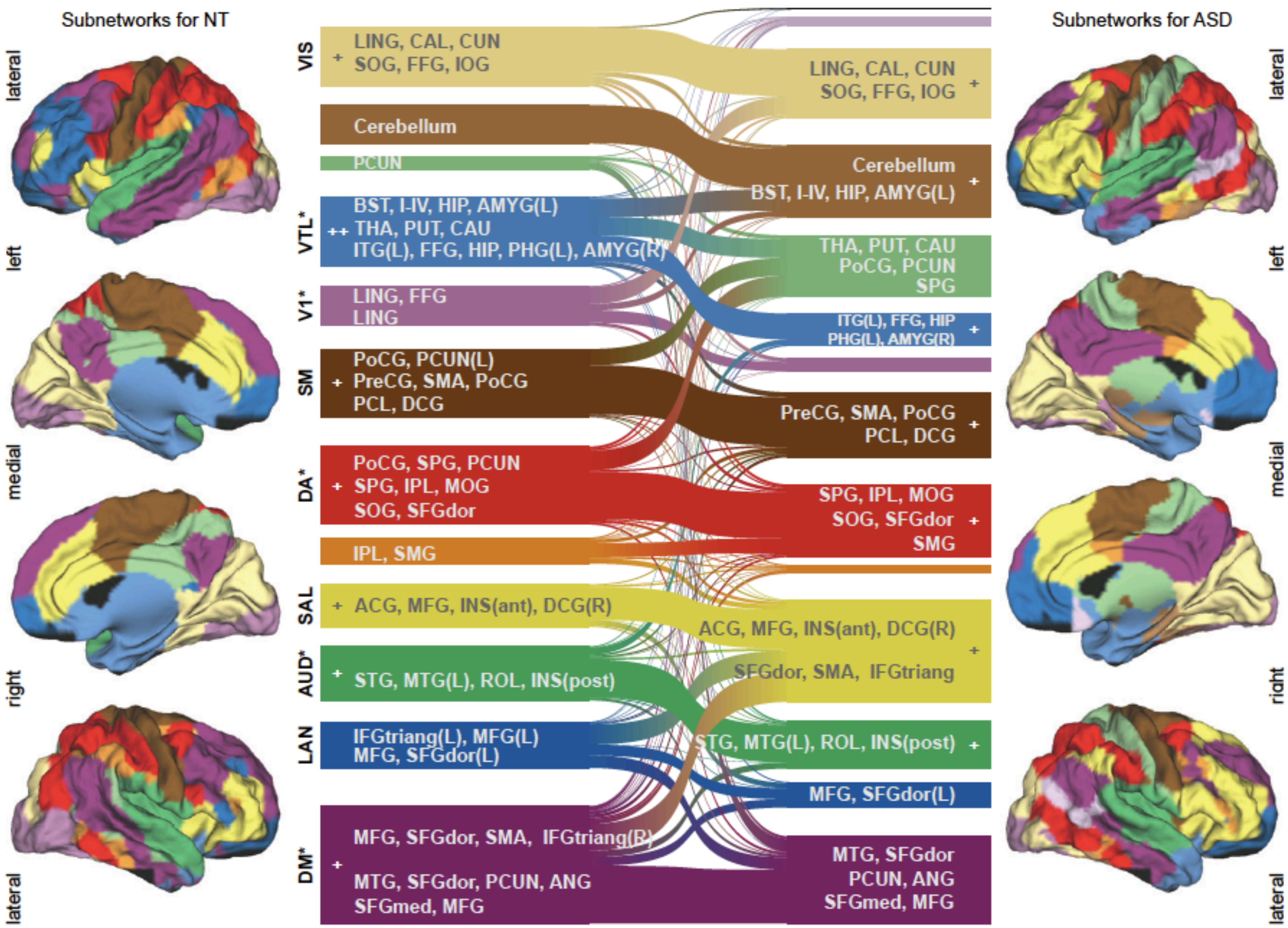
- **Data:** 26 participants (13 with ASD), watching the movie *Tulitikkutehtaan tyttö* while undergoing fMRI. A replication resting-state dataset was included (data from the ABIDE initiative).

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

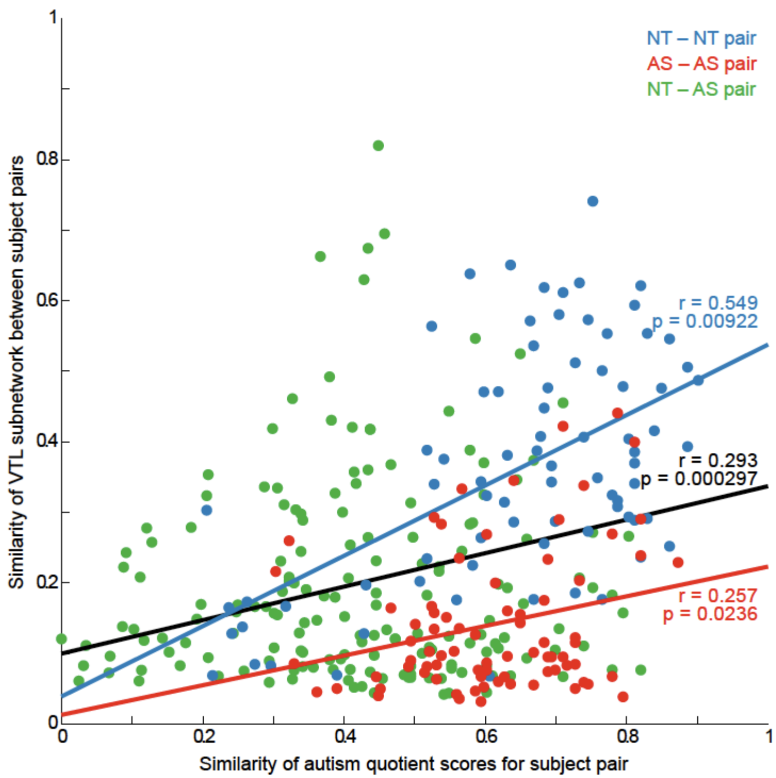
Auditory

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?

16. 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

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)

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Clinical applications of resting state fMRI and network analysis

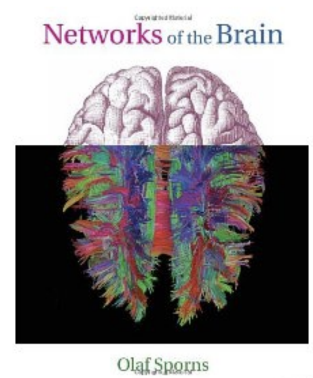
- **My two cents**
  - there are still **methodological issues** to consider (what is a node? Best way of computing a network? Global signal and other BOLD related artifacts: **head motion**, breathing rate, heart rate)
  - Shifting from a “biomarker from a distribution” approach to **combination of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

Two important references and a book

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.



…and something in Finnish about network science
https://www.researchgate.net/publication/242719764_Kompleksisten_verkostojen_fysiikkaa

Bonus materials / food for thoughts

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Could a Neuroscientist Understand a Microprocessor?

Eric Jonas, Konrad Paul Kording

Published: January 12, 2017 • https://doi.org/10.1371/journal.pcbi.1005268 • >> See the preprint

https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1005268

Biochemistry (Moscow), Vol. 69, No. 12, 2004, pp. 1403-1406.

DISCUSSIONS

Can a Biologist Fix a Radio? — or, What I Learned while Studying Apoptosis

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https://bml.bioe.uic.edu/BML/Stuff/Stuff_files/biologist%20fix%20radio.pdf