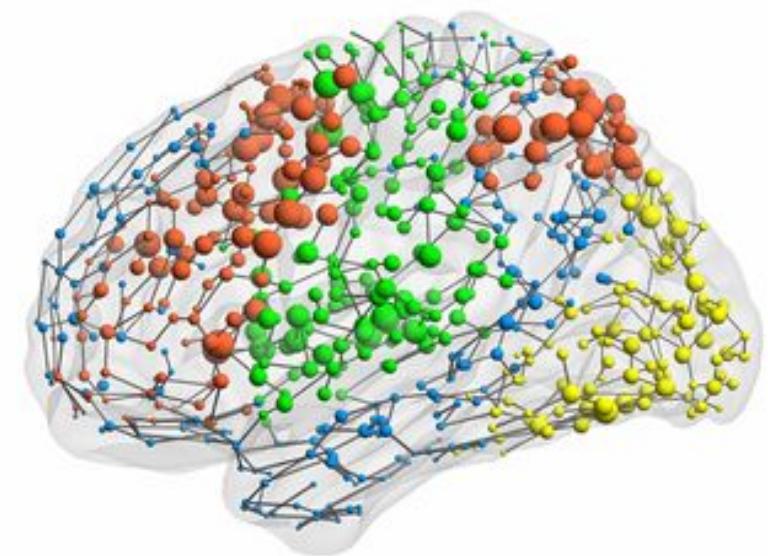




UNIVERSITY OF  
CAMBRIDGE



# Network analysis of large-scale human neuroimaging data

---

DR SARAH MORGAN, CAMBRIDGE UNIVERSITY, UK

OXBRIDGE BRAINHACK

THURSDAY 14<sup>TH</sup> NOVEMBER 2019

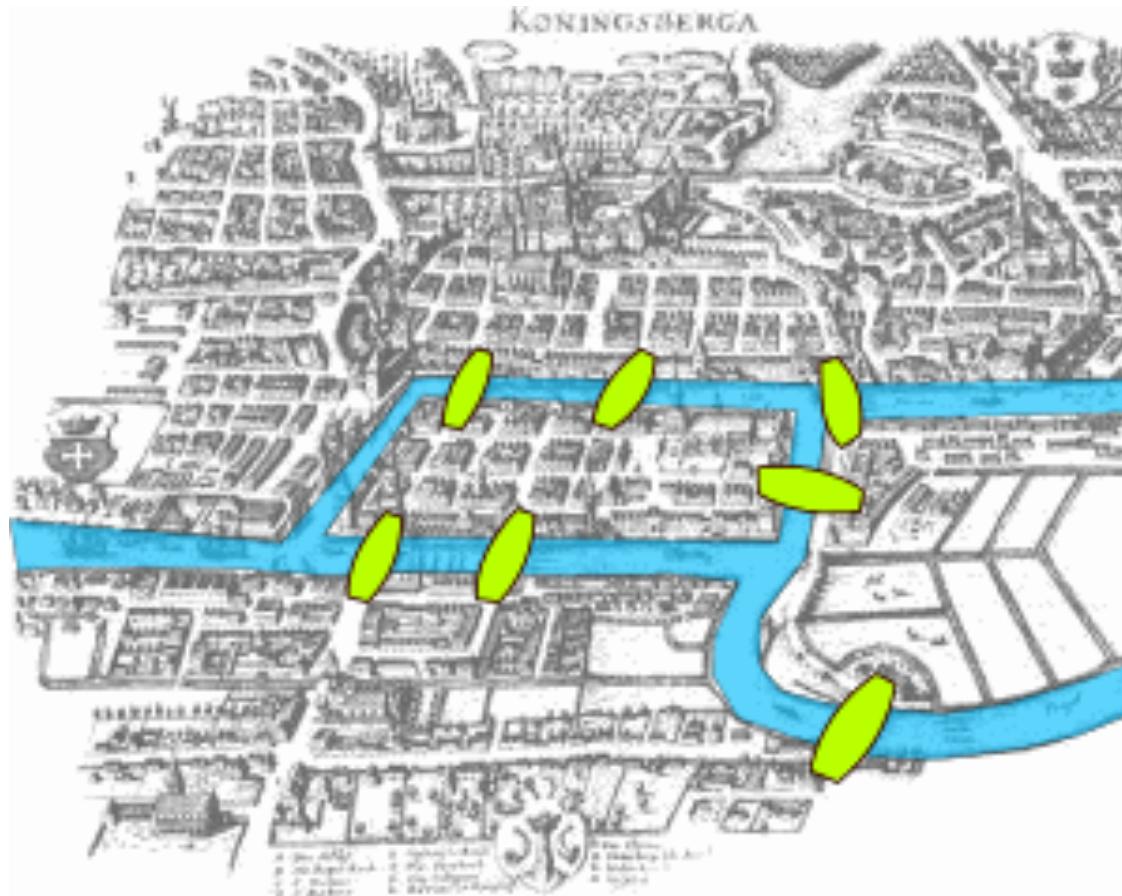


# Why networks?

---



# Seven Bridges of Königsberg

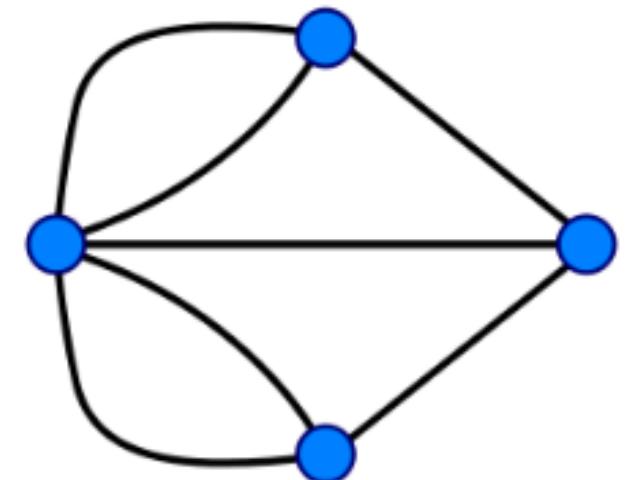
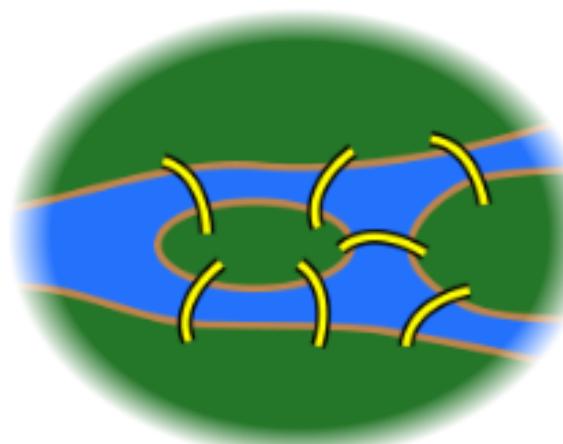
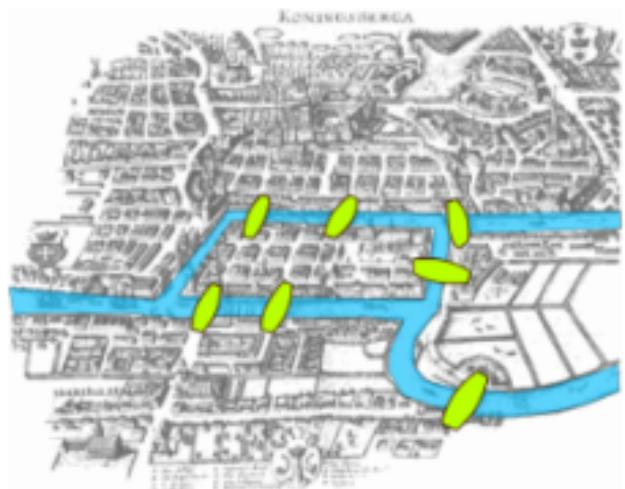


Can you walk through the city crossing all bridges only once?

In 1736, Euler used graph theory to show this is not possible.

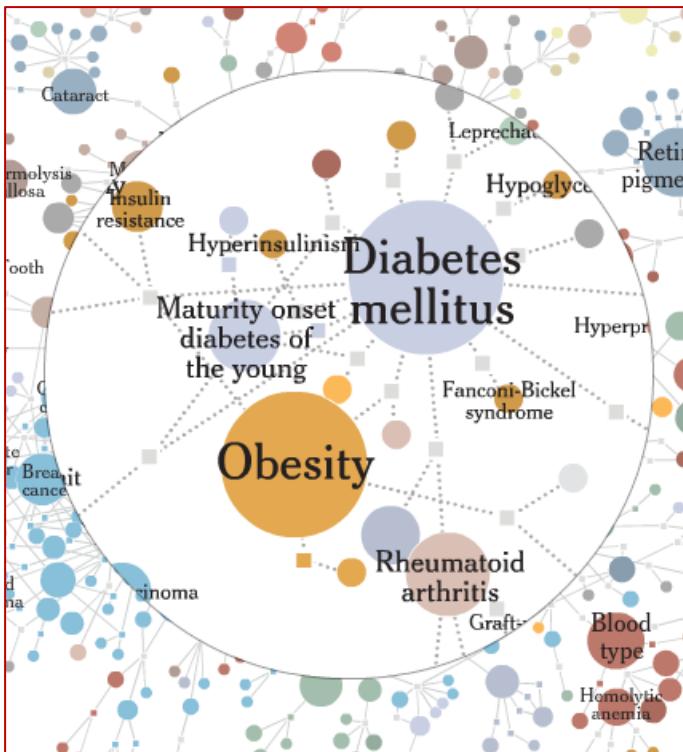


# Seven Bridges of Königsberg

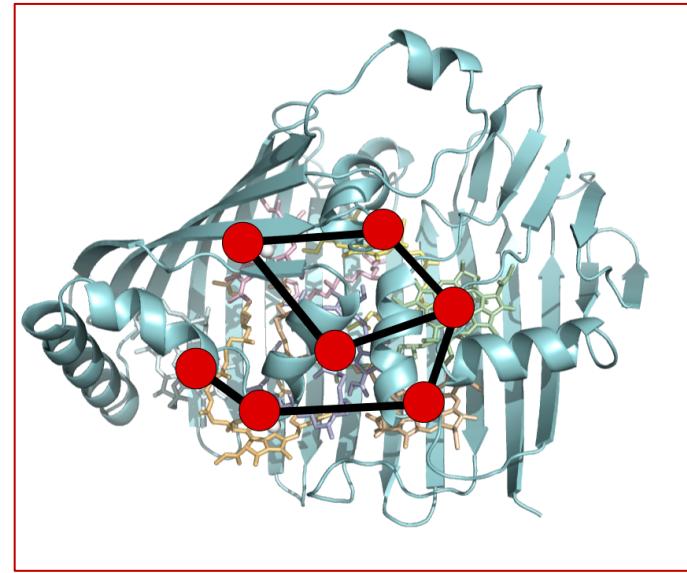


# Networks- a powerful approach to mapping complex biological systems

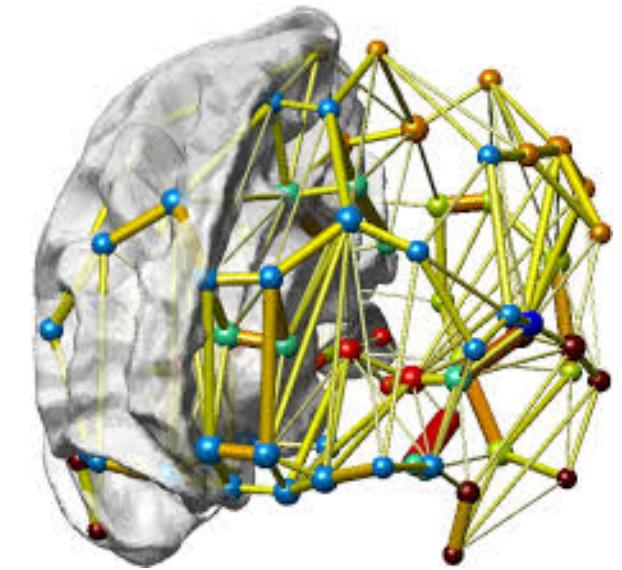
*“The 21<sup>st</sup> century will be the century of complexity”, Stephen Hawking*



Goh et al. PNAS 104, 8685 (2007)



*Adapted from Morgan et al., Sci Rep. 6, 2045-2322 (2016)*

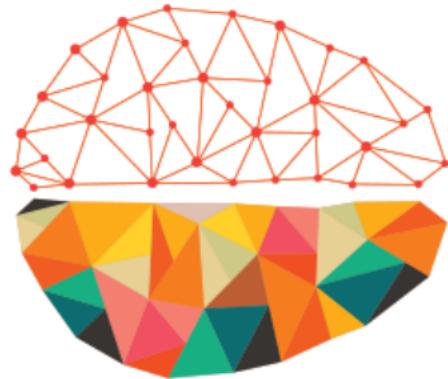


# Network Neuroscience- motivation

---

“Understanding the brain represents one of the most profound and pressing scientific challenges of the 21<sup>st</sup> century. As brain data have increased in volume and complexity, the tools and methods of network science have become indispensable for mapping and modeling brain structure and function, for bridging scales of organization, and for integrating across empirical and computational methodologies.”

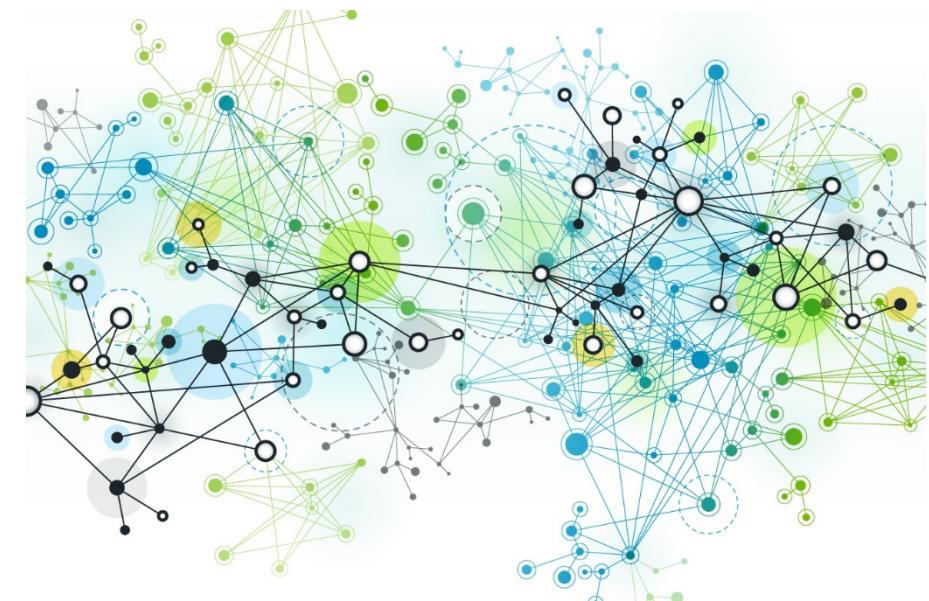
*Prof. Olaf Sporns, Network Neuroscience, 2017*



# Outline

---

1. How to model the brain as a network, using neuroimaging data?
2. Graph theory approaches to studying brain networks
3. Resources to get started!



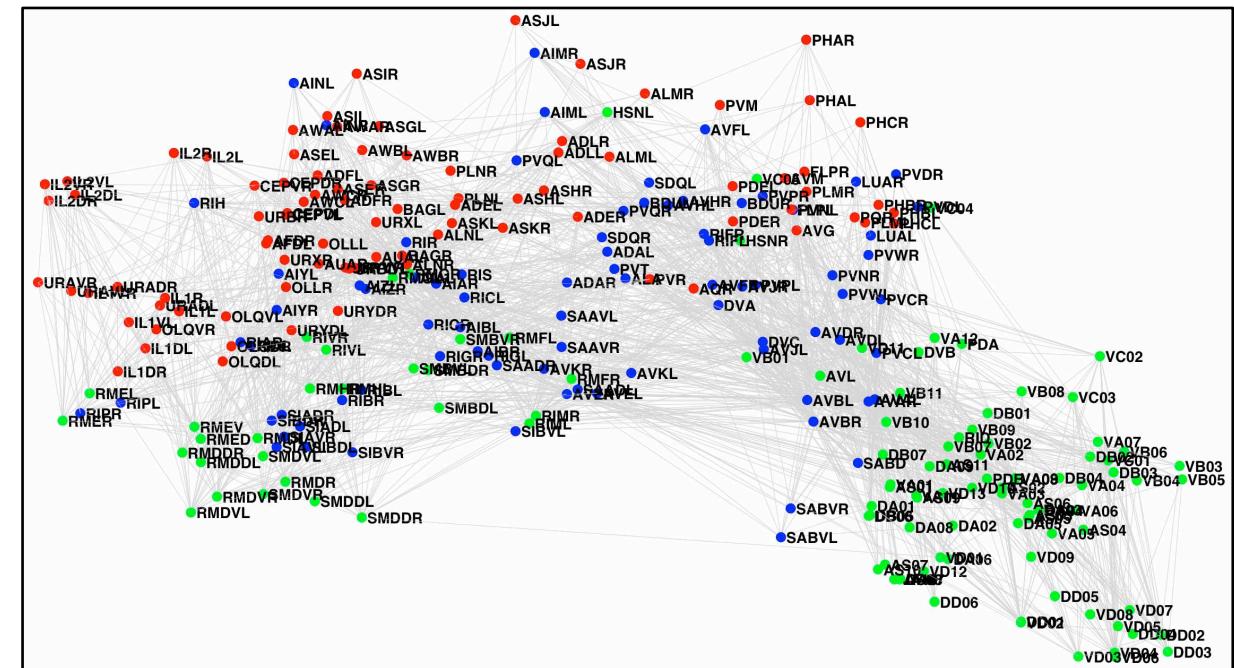
# How to model the brain as a network?

---

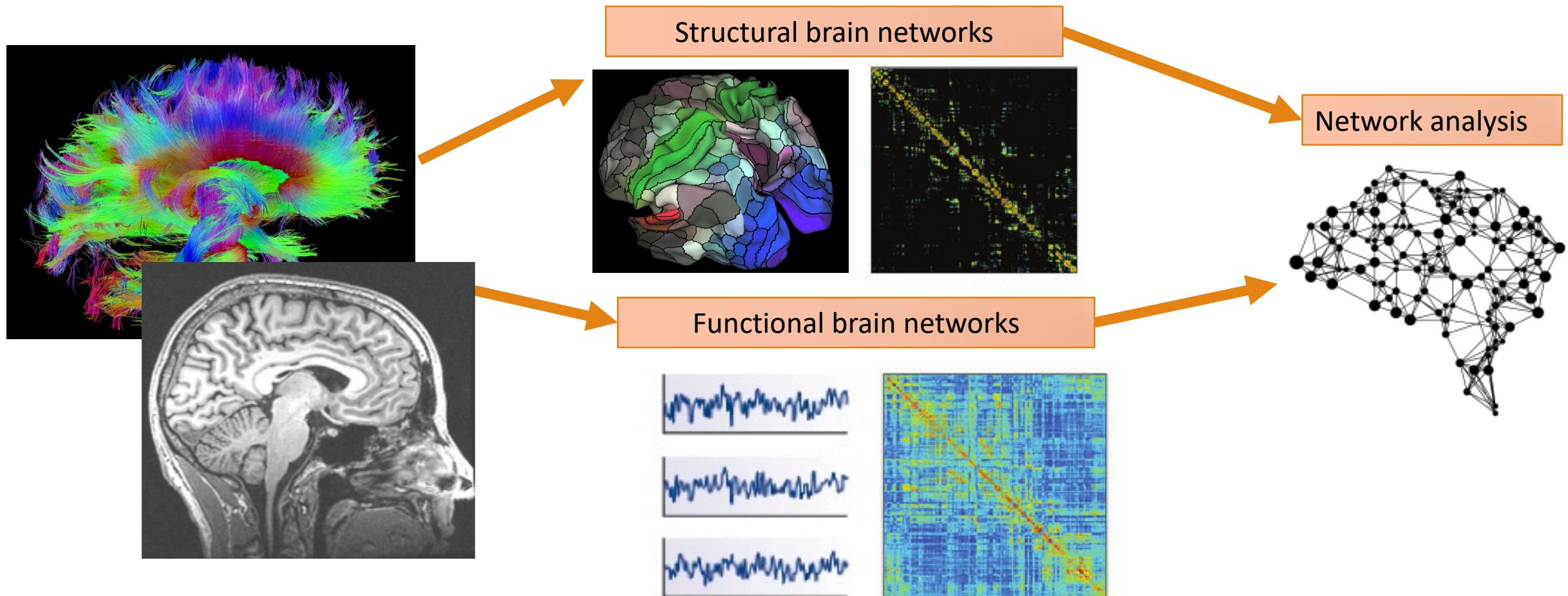
# The neuronal network

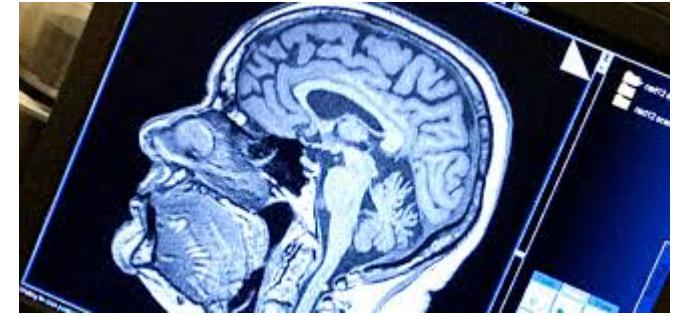
The human brain has approximately 100 billion neurons and 100 trillion connections

Impossible to map- only fully mapped neuronal network is for the C elegans worm:



# For humans, use neuroimaging instead:





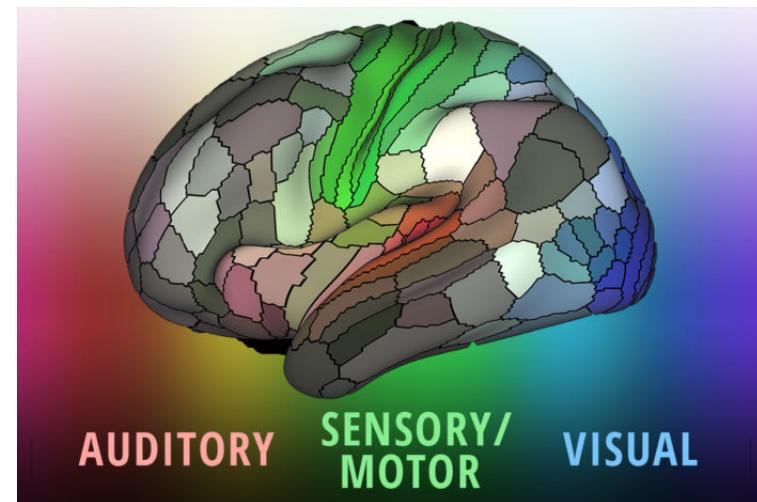
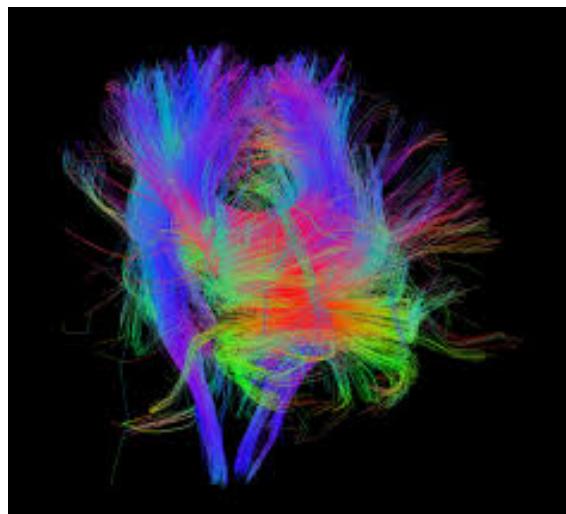
# Structural brain networks

---

# DTI

---

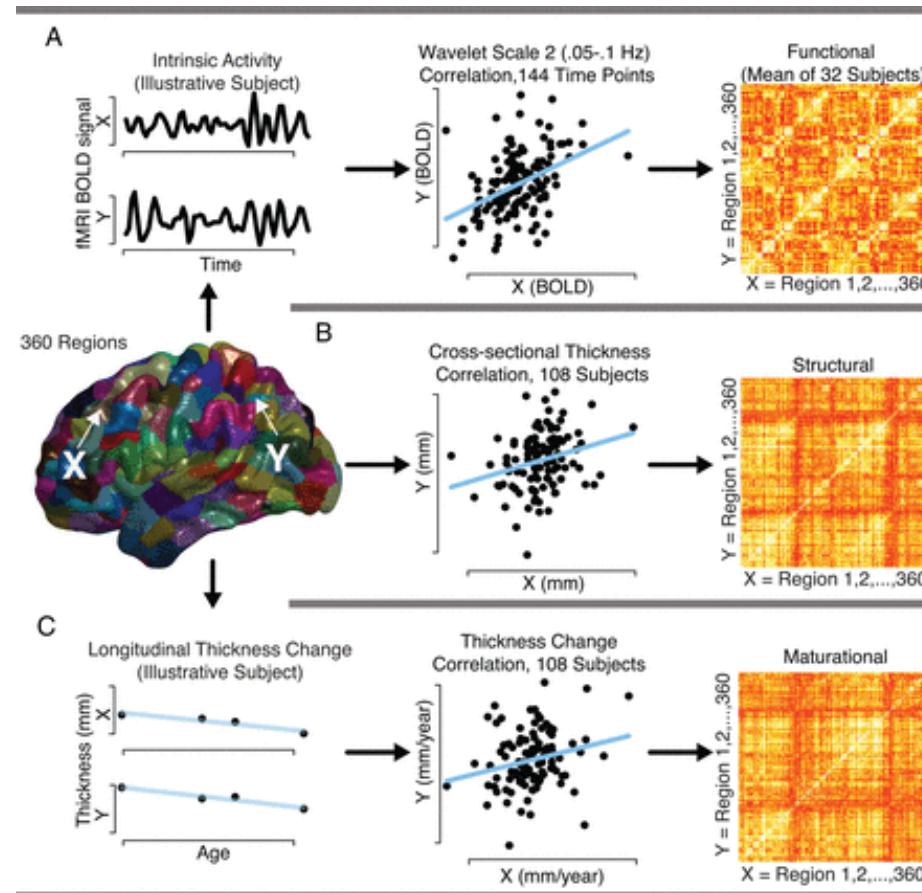
- Use the diffusion of water molecules to generate contrast in MR images
- Nodes are brain regions
- Estimate tracts between brain regions by assuming that the direction of greatest diffusivity is aligned to the local orientation of the white matter fibres
- Edges are often weighted by number of streamlines (or streamline density, or FA)



Glasser et al, 2016

# Structural covariance networks

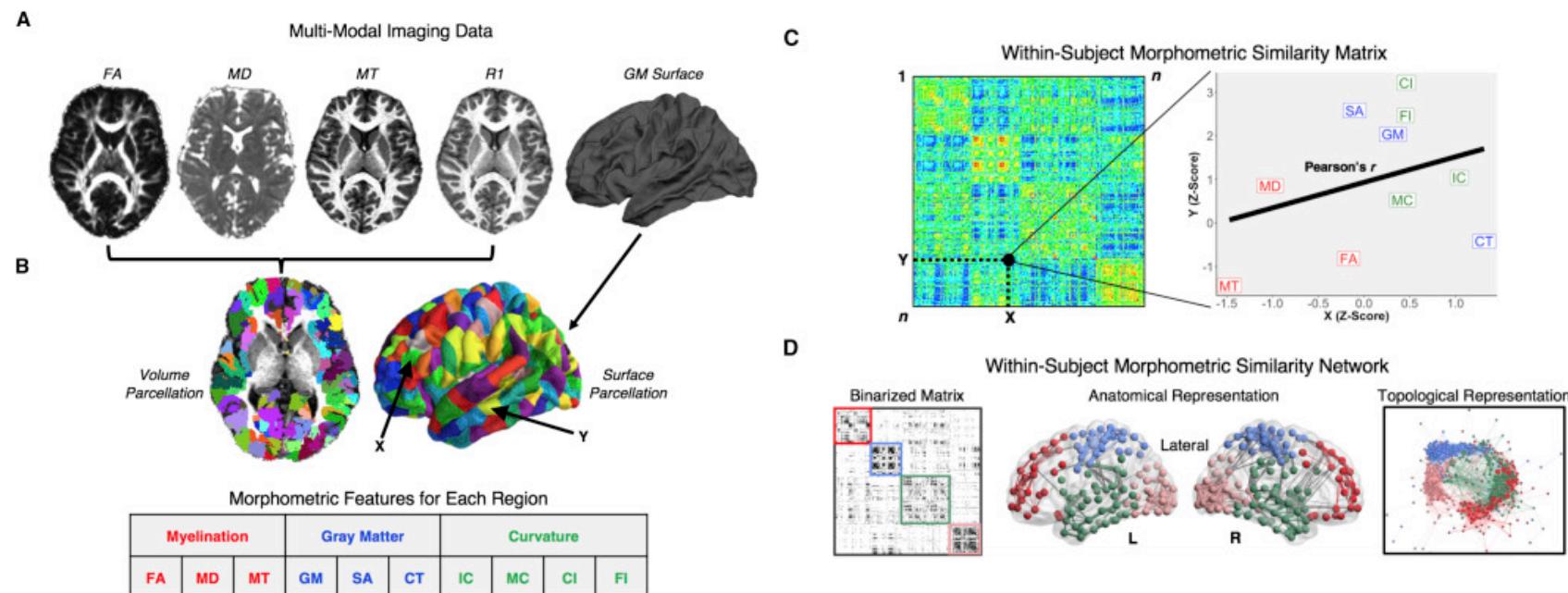
- Creates a single network per group
- Nodes correspond to brain regions
- Edges represent cross-correlations of morphological metrics between pairs of regions taken across subjects
- For a review, see Alexander-Bloch et al *Nature Reviews Neuroscience* volume 14, pages 322–336 (2013)



Alexander-Bloch et al, J. Neurosci., 2013

# Morphometric similarity networks

- A new way to construct a single structural network per subject from a T1w image
- Correlate 5-10 structural measures across regions within a single subject (Seidlitz et al, Neuron, 97, 231-247, 2018)

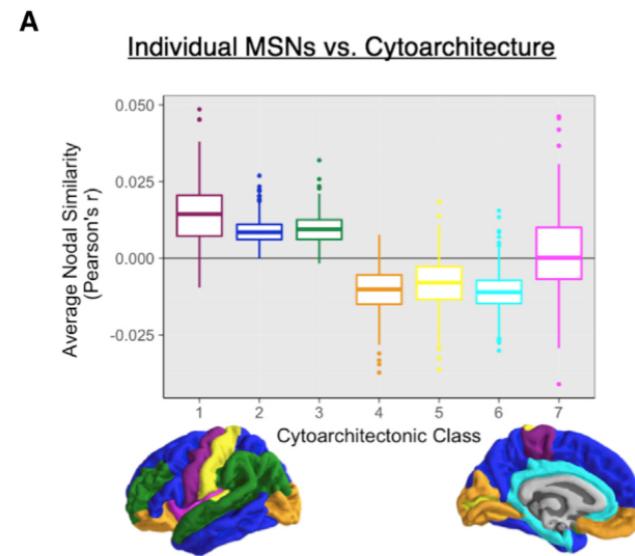
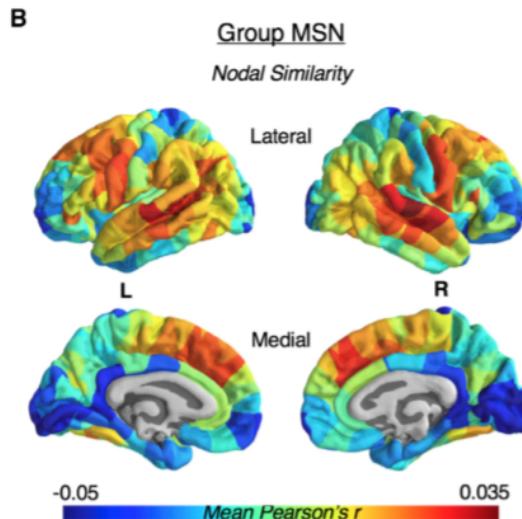


Seidlitz et al, Neuron, 2018

# What is morphometric similarity?

Seidlitz et al, Neuron 2018 key points:

1. Can generate individual structural matrices (unlike structural covariance approach)
2. Macaque MSNs map onto connectivity derived from tract tracing
3. Morphometric similarity captures known cortical cytoarchitecture and related gene expression
4. MSN degree could explain about 40% of between subject variance in IQ

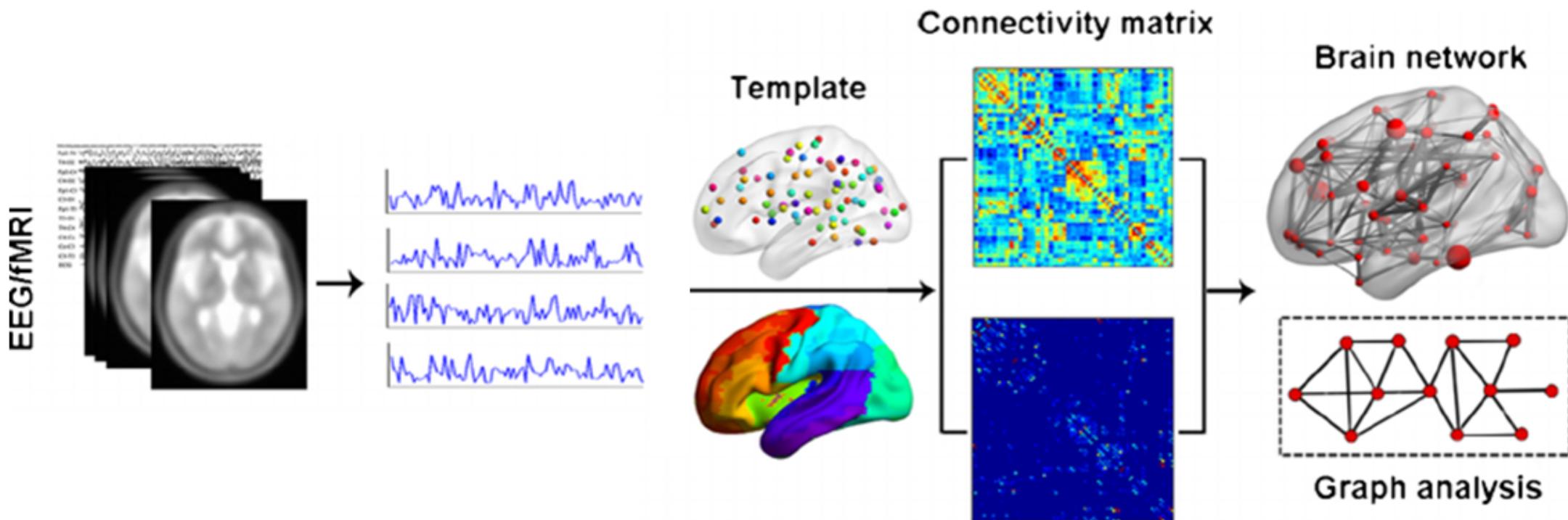


Seidlitz et al, Neuron, 2018

# Functional brain networks

---

# Functional brain networks:

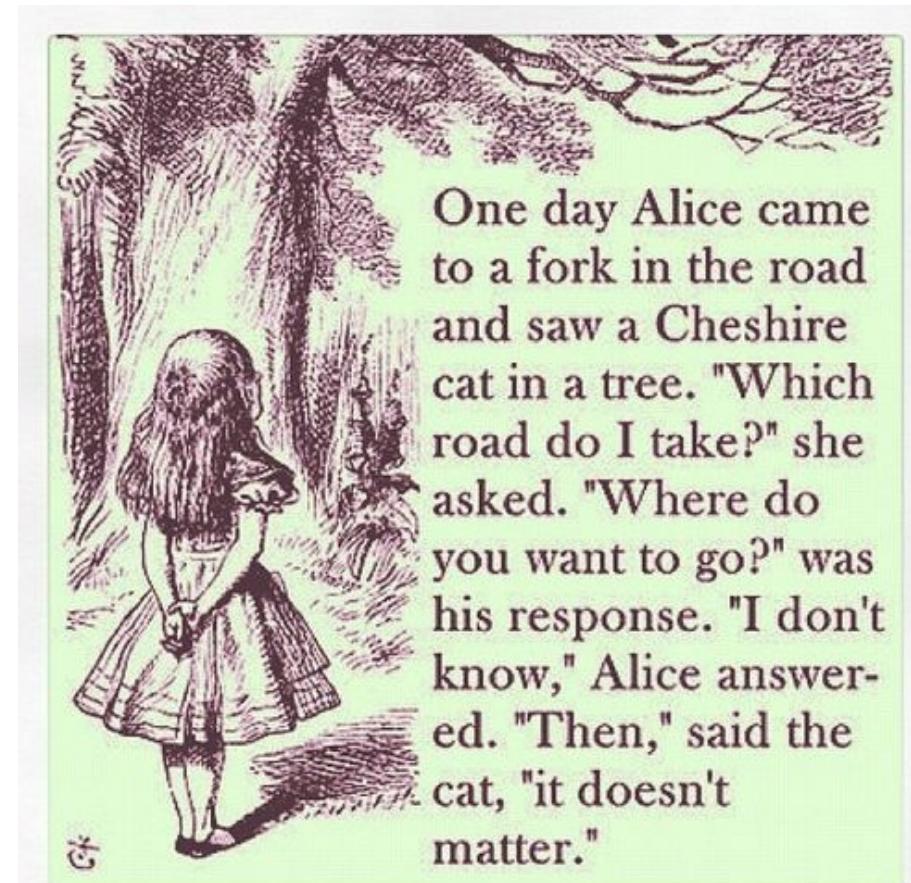


Adapted from Cao et al, Molecular Neurobiology, 2014

# fMRI- notes about pre-processing:



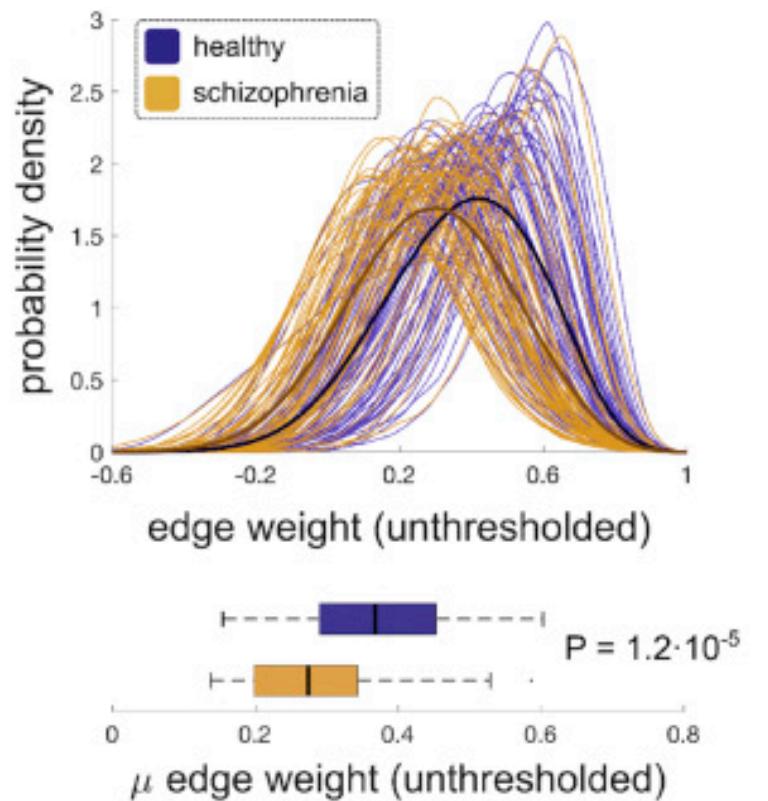
- Different pre-processing steps will often affect higher order graph theory results
- Whether to perform global signal regression (GSR) is controversial- (Murphy and Fox, NeuroImage, 154, 169-173, 2017)
- There are no 'right' or easy answers ("Different processing approaches reveal complimentary insights about brain function"), but you need to bear these issues in mind when interpreting your results



# Mean fMRI also often varies between subject group:



- Mean fMRI correlation often varies between subject group and can play a strong role in determining graph theory metrics (van den Heuvel et al, NeuroImage, 152, 437-449, 2017)
- Best to start by plotting the correlation distributions, and getting to know your data as well as possible!

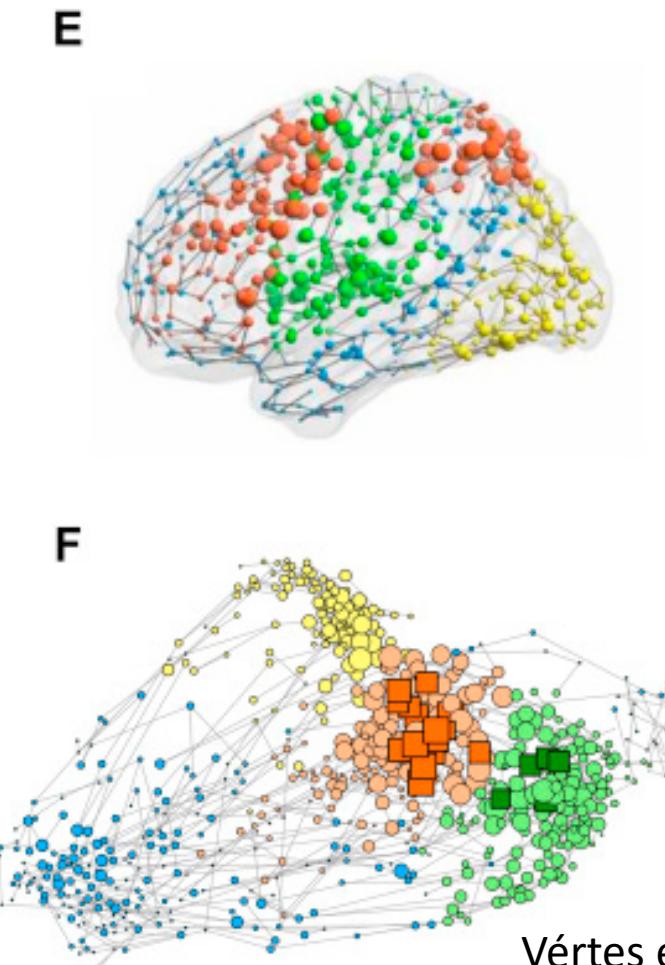
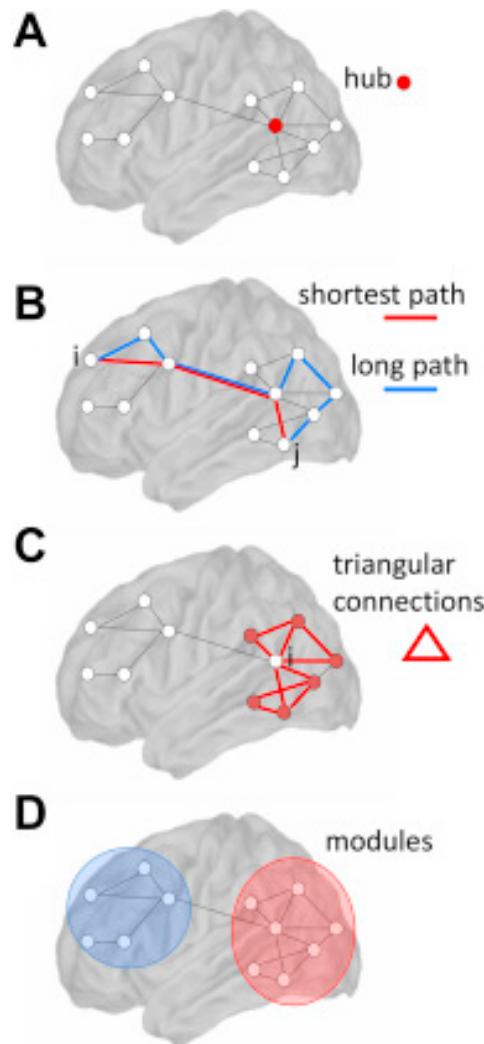


Vasa et al, 2018

# Graph theory approaches to studying brain networks

---

# Traditional graph theory metrics

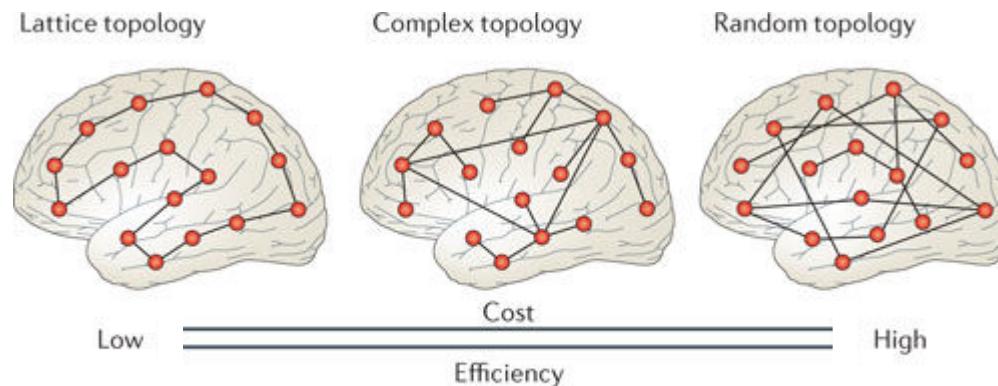


Vértes et al, J Child Psychol Psychiatry, 2015  
Morgan et al, BP CNNI, 2018

# Economic trade-off

Brain networks have been shown to make an economic trade-off:

- Long distance edges are expensive to create and maintain
- But they have useful topological benefits



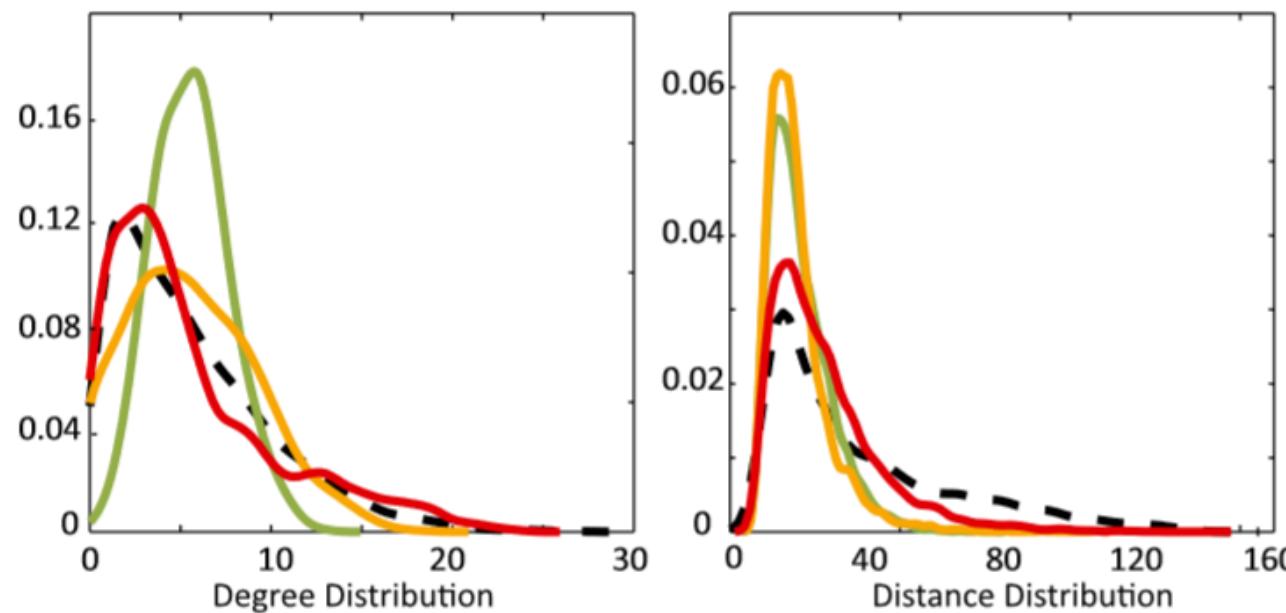
# Degree and distance distributions:

---

Degree = the number of connections a node makes.

Degree distribution = the probability distribution of these degrees over the network.

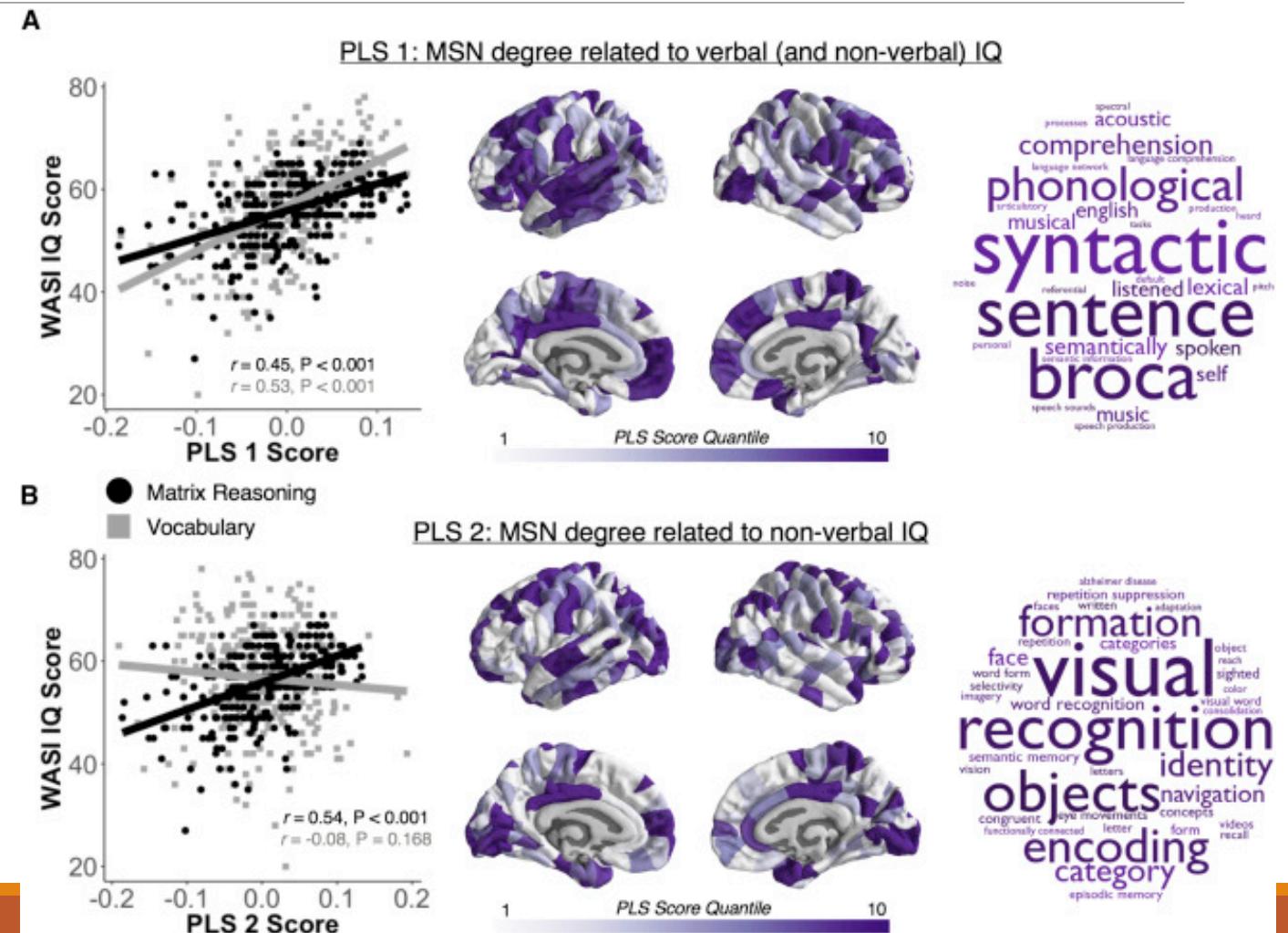
Distance distribution = the probability distribution of the distance of edges over the network.



Degree can already tell you a lot...



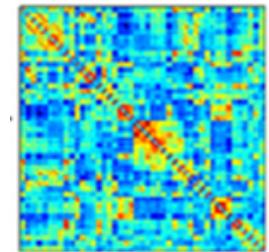
E.g. Seidlitz et al showed that the degree of morphometric similarity networks can explain about 40% of between-subject variance in IQ



*Seidlitz et al, Neuron 2018*

# Network based statistics

- One approach to go beyond regional degree is Network Based Statistics (NBS)
- NBS is a method to control the family wise error rate when performing mass-univariate testing at every edge in a graph (e.g. to test for case-control differences)
- It exploits the interconnections between regions (the fact that edges are not independent of each other) to give a large increase in power
- A NBS toolbox is available online-  
<https://sites.google.com/site/bctnet/comparison/nbs>



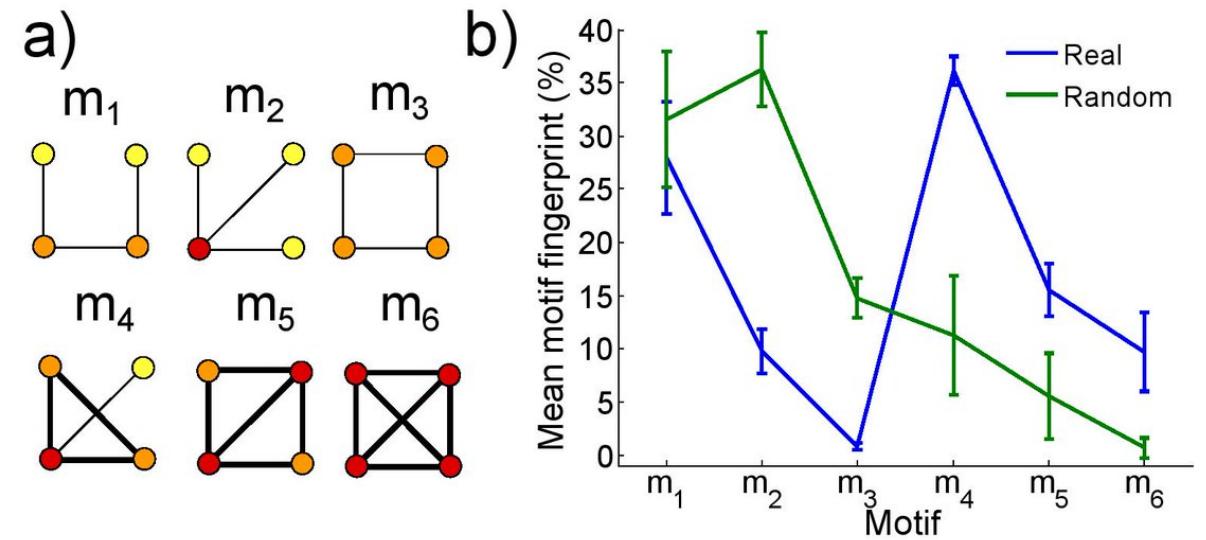
(a) FDR ( $q = 10\%$ )



(b) NBS ( $p = 0.037$ )

# Motif analysis:

- Network motifs have been described as the 'building blocks' of complex networks (Alon et al, Science 2002)
- By counting the occurrence of each possible motif, you can create a motif fingerprint for your network
- Flexible approach to studying local connectivity patterns
- E.g. Sporns and Kotter, PLoS Biol, 2004 suggested that brain networks maximize both the number and the diversity of functional motifs, while the repertoire of structural motifs remains small
- The FANMOD tool allows for fast motif detection- <http://theinf1.informatik.uni-jena.de/motifs/>



Morgan et al, Network Neuroscience, 2018

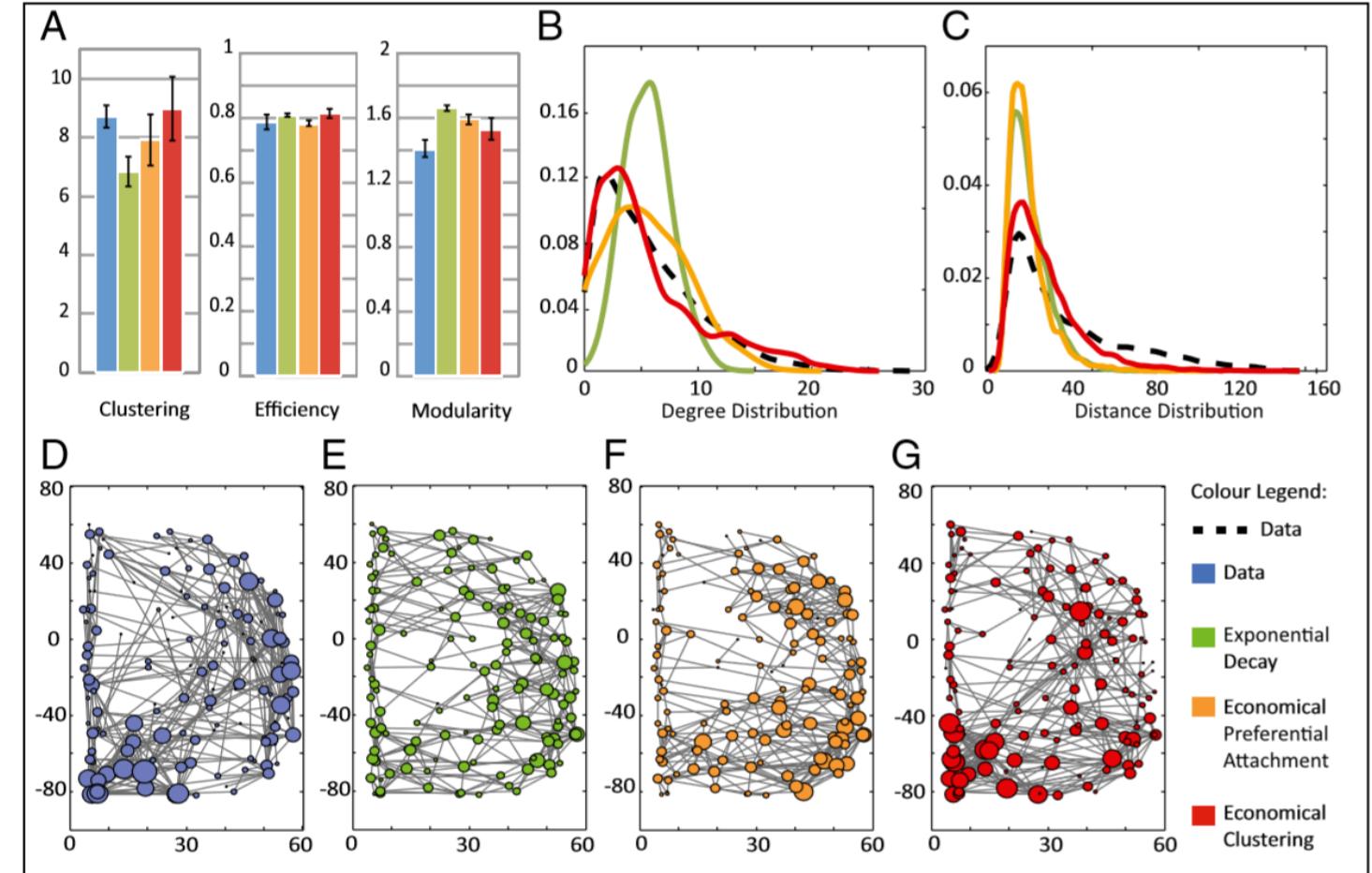
# Generative models

Vértes et al, PNAS 2012

What are the organisational principles underlying brain networks?

Vértes et al, PNAS 2012 showed you can use a simple function to generate networks with brain-like topologies:

$$P_{i,j} \propto (k_{i,j})^\gamma (d_{i,j})^{-\eta}$$



# Probabilistic thresholding

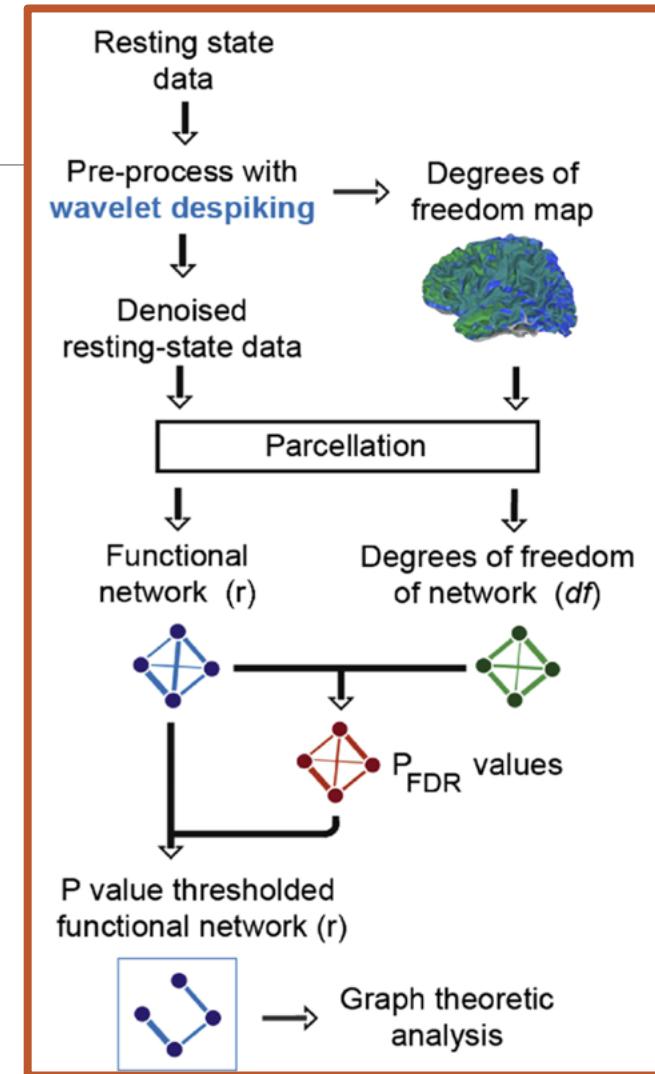
For fMRI data, another approach is probabilistic thresholding (**Patel et al, NeuroImage 2016**).

Here, instead of thresholding networks at a fixed threshold (e.g. taking the strongest 10% of edges), you threshold at a fixed, edge-specific p-value.

Requires knowing the degrees of freedom for each timeseries, which can be output by wavelet despiking motion correction (Patel et al, NeuroImage 2014)

With this method, each subject's network has a different number of edges, can then calculate e.g. size of largest connected component.

See Vasa et al, NeuroImage 2018 for an example **application** to schizophrenia.



Vasa et al, NeuroImage 2018

# Connectivity gradients

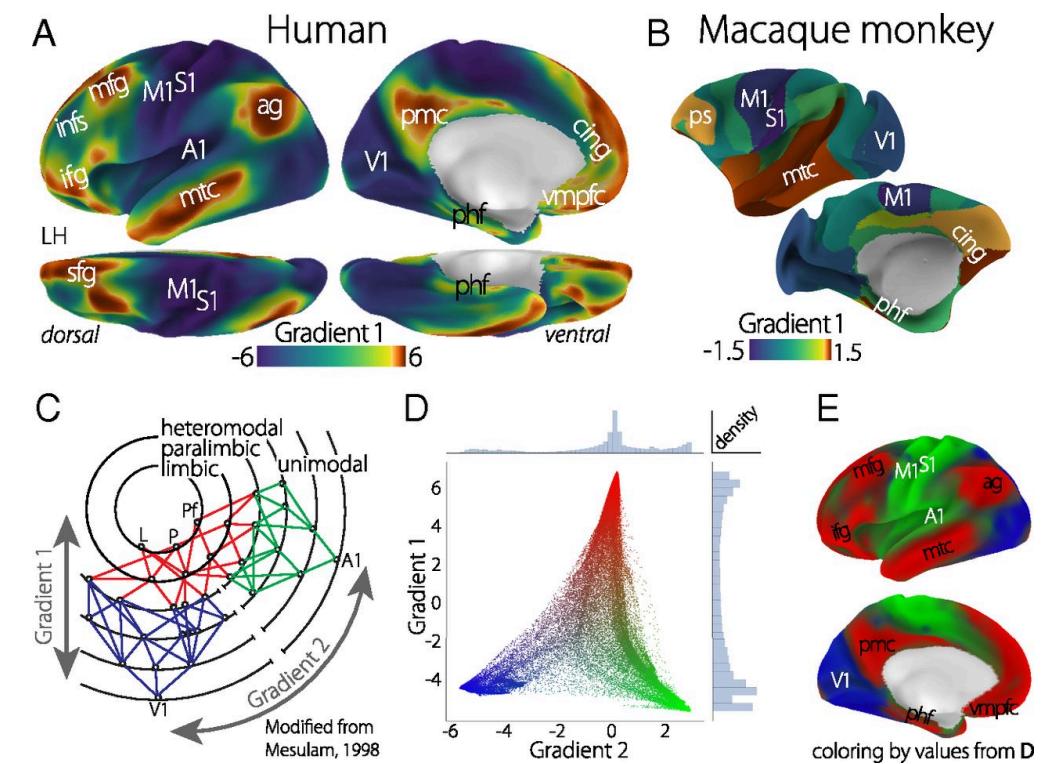
**Margulies et al, PNAS 2016** took an alternative approach to studying resting state fMRI connectivity using diffusion embedding.

Here they calculate a dense functional connectivity matrix by correlating activity between grayordinates, then use diffusion embedding to represent the global connectivity structure as a distribution of cortical points in space.

The resulting gradient places the DMN at the opposite end of a spectrum from primary sensory and motor regions.

For a **review**, see- Huntenburg et al, Trends in Cognitive Sciences 2016.

For an example **application** (to autism), see- Hong et al, Nat. Comm.s 2019.





And many more!

---

# Resources

---

# Toolboxes for graph theoretical analysis:

---

For Matlab, the Brain Connectivity Toolbox (BCT) can be downloaded online at:

<https://sites.google.com/site/bctnet/>

Another helpful Matlab toolbox is the BGL:

<http://www.mathworks.com/matlabcentral/fileexchange/10922>

There are other options available, e.g. NetworkX in Python:

<https://networkx.github.io/>

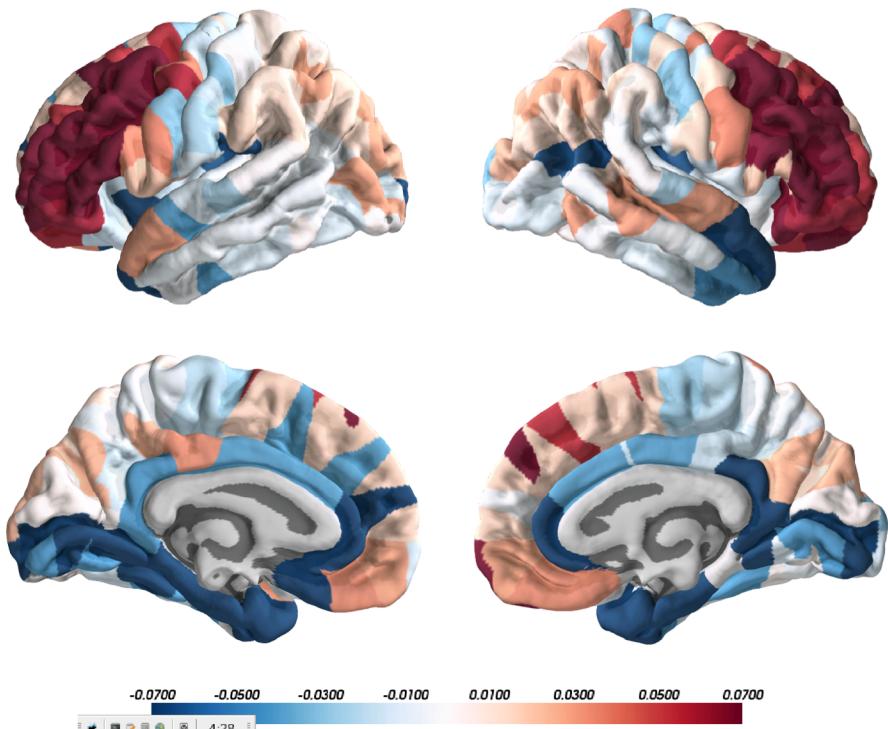


# Tools for visualisation:

To plot regional values:

<https://github.com/WhitakerLab/BrainsForPublication>

(open project, feel free to contribute!)



To plot the whole network:

<https://www.nitrc.org/projects/bnv/>

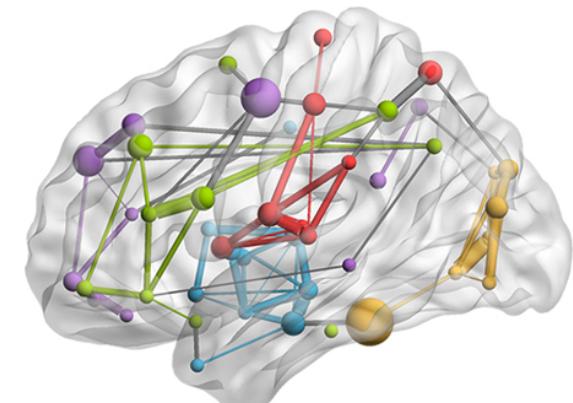
## BrainNet Viewer

Please cite:

Xia M, Wang J, He Y (2013) BrainNet Viewer: A Network Visualization Tool for Human Brain Connectomics. *PLoS ONE* 8: e68910.

Version 1.53 Released 20150807  
National Key Laboratory of Cognitive Neuroscience and Learning,  
Beijing Normal University.

Contact Information:  
Mingrui Xia: mingruixia@gmail.com  
Yong He: yong.h.he@gmail.com



# Openly available datasets



For a list of open sMRI datasets, see: <https://github.com/cMadan/openMorph>

Biobank: approx. 15,000 scans (including fMRI, DWI, sMRI). Application process.  
<http://www.ukbiobank.ac.uk/>

HCP data: Includes relatively long fMRI timeseries-  
<https://www.humanconnectome.org/study/hcp-young-adult/data-releases>

schizconnect.org : datasets related to schizophrenia/psychosis (sMRI, DTI, fMRI)

ABIDE- autism, sMRI, fMRI and DWI [http://fcon\\_1000.projects.nitrc.org/indi/abide/](http://fcon_1000.projects.nitrc.org/indi/abide/)

For a table of openly available datasets related to healthy and atypical development, see Table 5 of Morgan et al, BP CNNI, 2018 (<https://doi.org/10.1016/j.bpsc.2018.03.003>)



# Good luck!

---

([sem91@cam.ac.uk](mailto:sem91@cam.ac.uk), @Sarah\_Morgan\_UK)