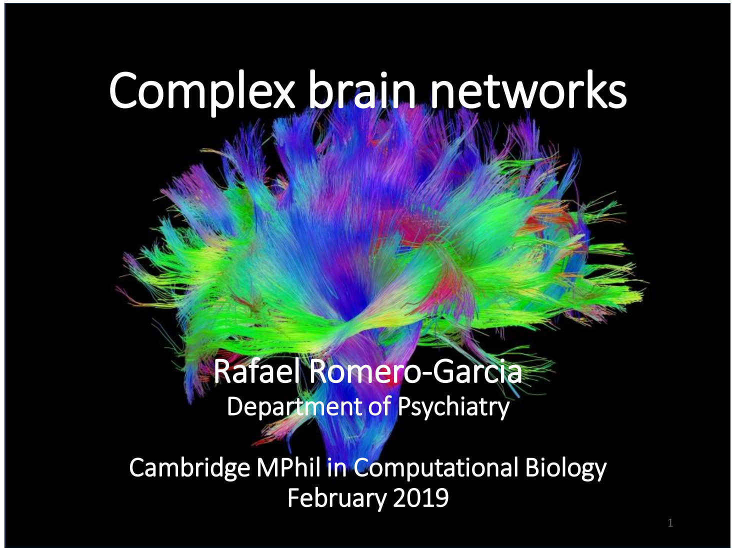
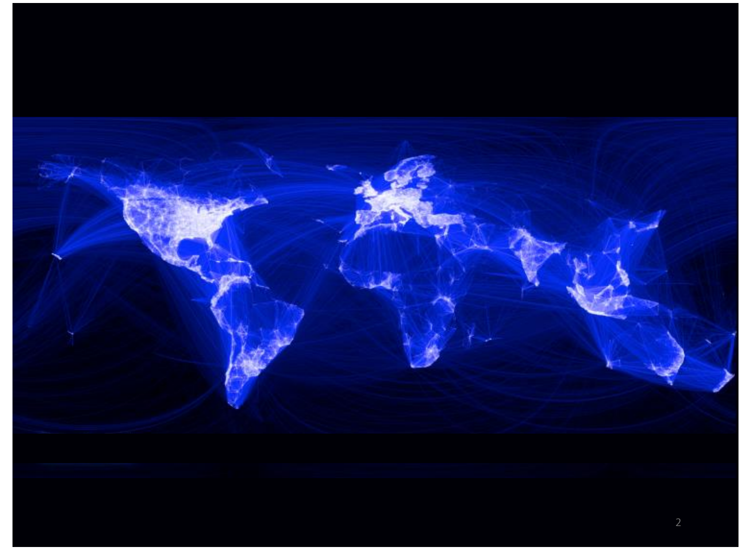

Complex brain networks
Rafael Romero-Garcia
Department of Psychiatry
Cambridge MPhil in Computational Biology
February 2019

1



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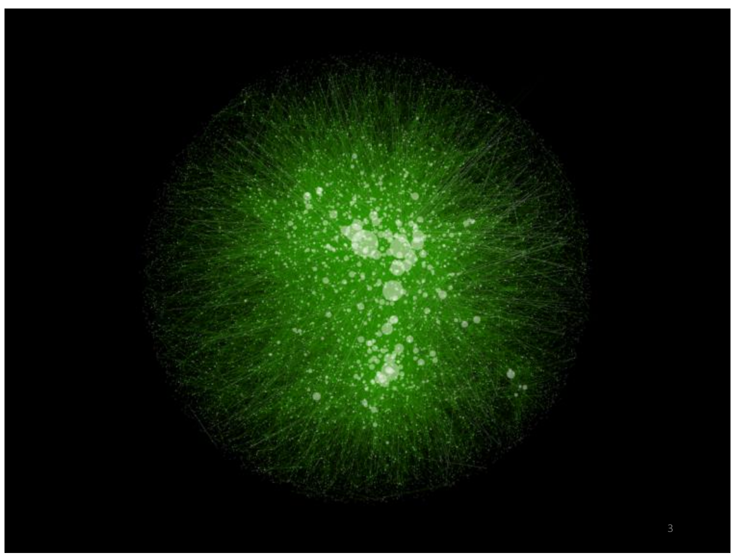

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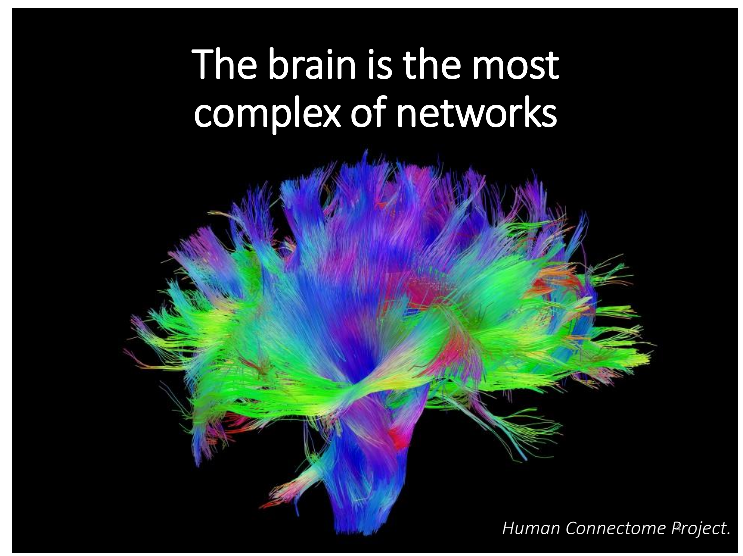
The brain is the most complex of networks
Human Connectome Project.

4

Review

The Human Connectome: A Structural Description of the Human Brain

Olaf Sporns*, Giulio Tononi, Rolf Kötter

To understand the functioning of a network, one must know its elements and their interconnections. The purpose of this article is to discuss research strategies aimed at a comprehensive structural description of the network of elements and connections forming the human brain. We propose to call this dataset the human "connectome," and we argue that it is fundamentally important in cognitive neuroscience and neuropsychology. The connectome will

Sporns et al., 2005.

5

- Motivation for complex brain networks
- Types of complex brain networks
- Construction of complex brain networks
- Analysis of complex brain networks
- Brain network modules and hubs
- Limitations

6

MOTIVATION FOR COMPLEX BRAIN NETWORKS

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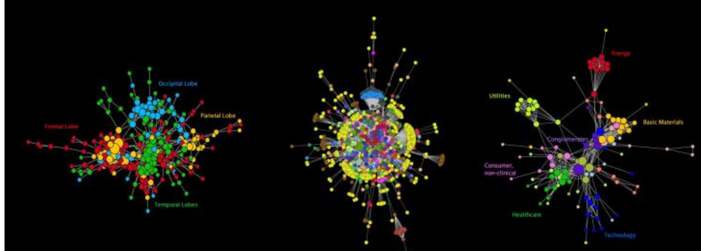
Complex networks analysis draws strength from universality

But interpretation must be dataset-type specific

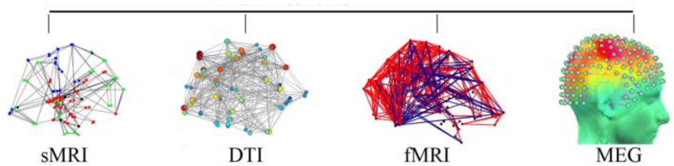


functional MRI network | twitter network | NYSE network

Vertes et al., Frontiers Syst Neurosci 2011

8

Complex networks are a universal framework for representation of multimodal brain connectivity

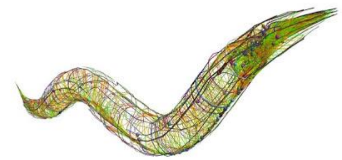


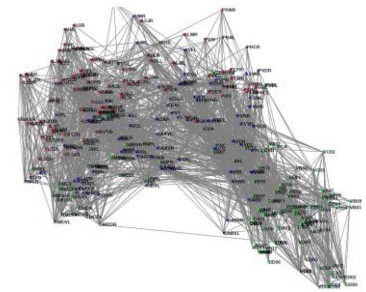
Bassett and Bullmore, Curr Opin Neurol 2009

9

Complex networks intuitively represents connectivity at multiple spatial scales

The *C. elegans* connectome



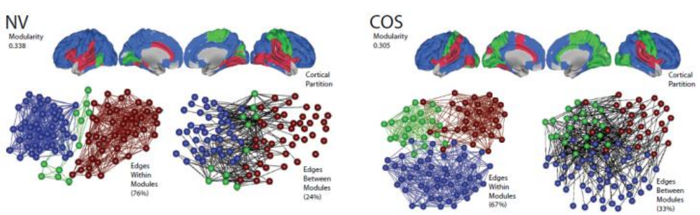


The Open Worm Project

Chen et al., PNAS 2006

10

Dysconnectivity in neuropsychiatric disorders is likely to be complex



Alexander-Bloch et al., Frontiers Syst Neurosci 2011

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TYPES OF COMPLEX BRAIN NETWORKS

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The connectome is a model of brain organization

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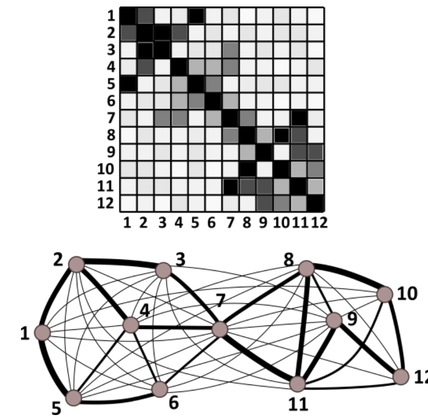
Connectivity matrix represents a graph



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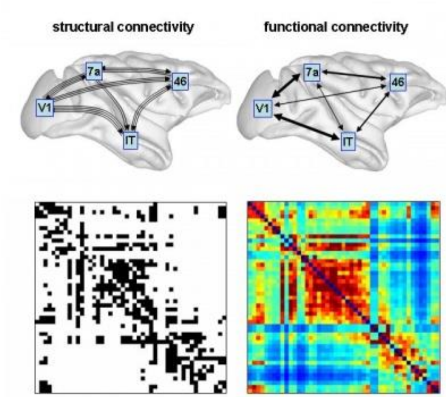
Types of brain connectivity



Sporns, Scholarpedia 2012

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Structural Connectivity	Functional connectivity
Anatomical links	Correlational links
Electron or light microscopy MRI	Multielectrode array recordings, MRI, EEG/MEG
Manual or automated reconstruction	Correlation, synchronization
Positively weighted connections	Positive and negatively weighted connections

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STRUCTURAL BRAIN NETWORKS

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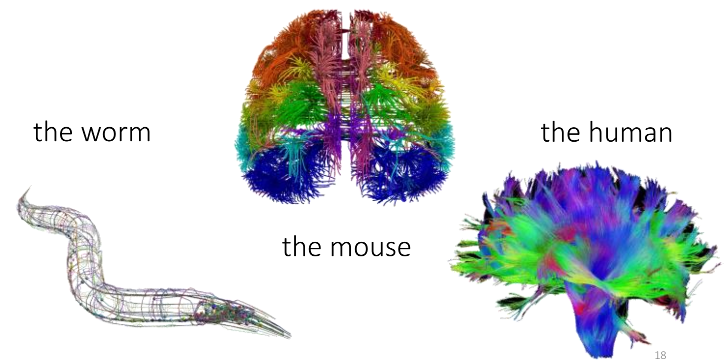
There is a data quality vs organism complexity trade-off



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Mapping Methods	Electron Microscopy	Light Microscopy	Magnetic Resonance Imaging
Resolution	nm	µm	mm
Density	dense	sparse	sparse
Connectivity	synaptic	directed	undirected
Feasibility	roundworm fruit fly *ex vivo*	small mammals *ex vivo*	large mammals *in vivo*

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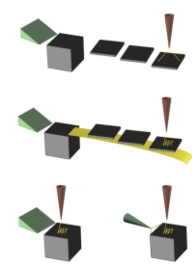
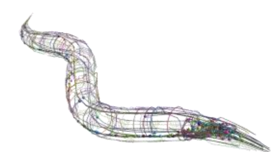
Electron-microscopy allows dense synaptic maps of neuronal circuits





C. elegans connectome

Helmstaedter, 2013; Open Worm project.

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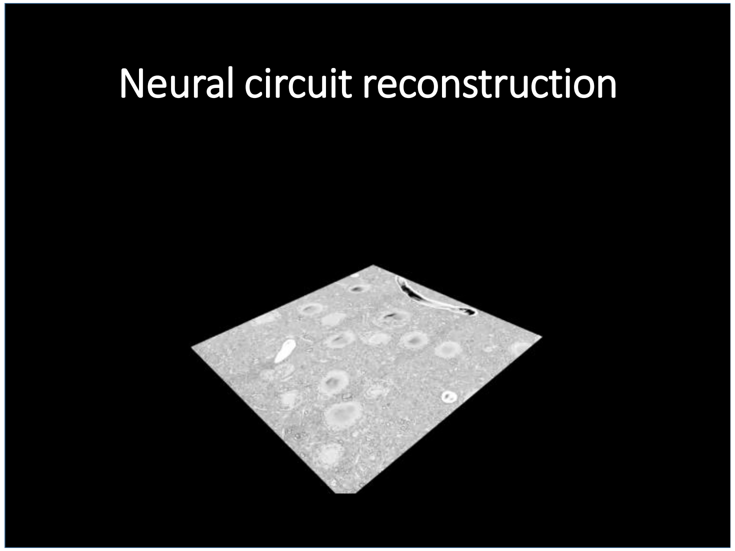

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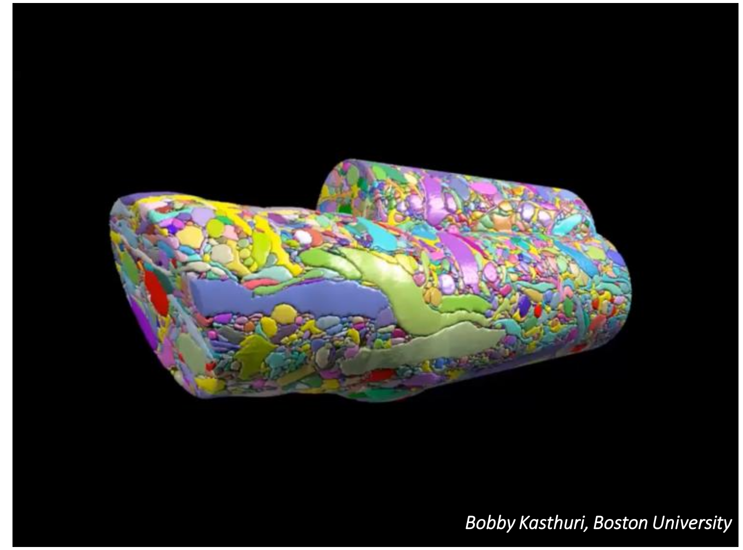

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C. elegans

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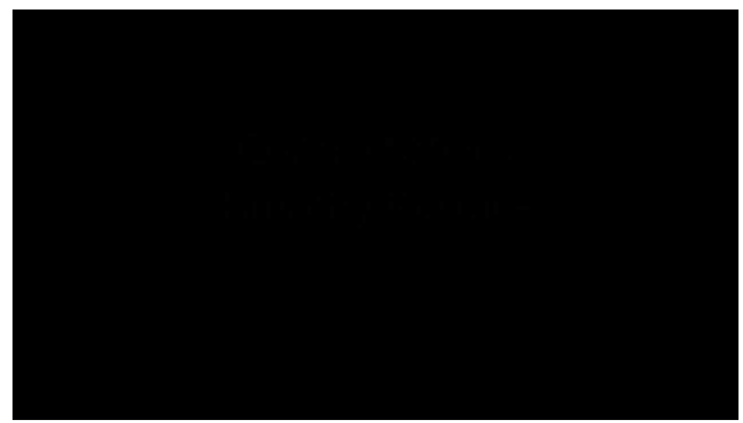

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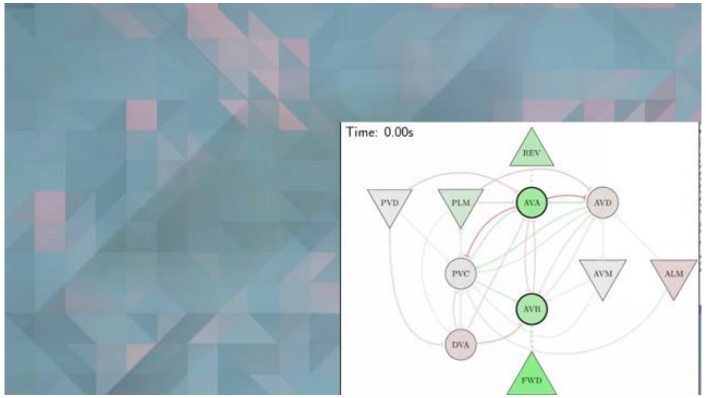
2018-02-06 [Florian Aigner | Press Release 10/2018]

Worm Uploaded to a Computer and Trained to Balance a Pole

Is it a computer program or a living being? At TU Wien (Vienna), the boundaries become blurred. The neural system of a nematode was translated into computer code – and then the virtual worm was taught amazing tricks.



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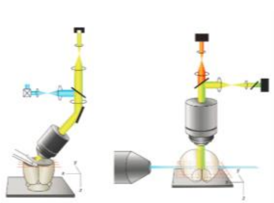
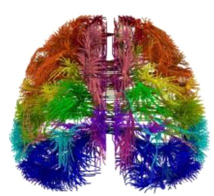
GoPiGo (Dexter Industries) Robot
running a C elegans connectome
simulation using Python 2.7 on a Raspberry Pi B+

Timothy Busbice
http://www.connectomeengine.com
@interintel
(c) 2015

26

Light-microscopy allows sparse directed maps of mammalian brains





mouse connectome

Osten and Margrie, 2013; Oh et al., 2014.

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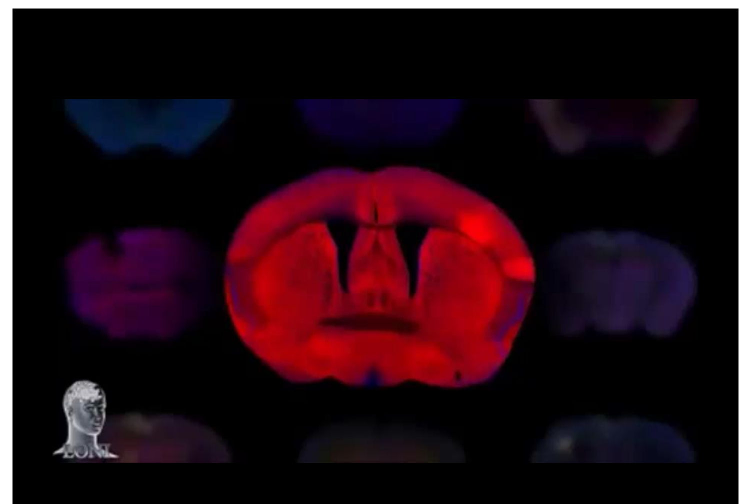

Mouse Connectome Project, University of Southern California

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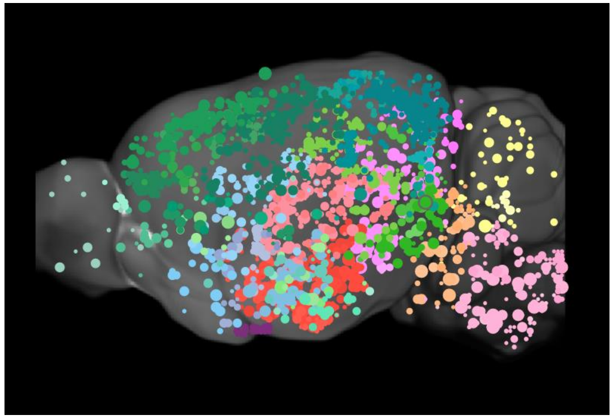

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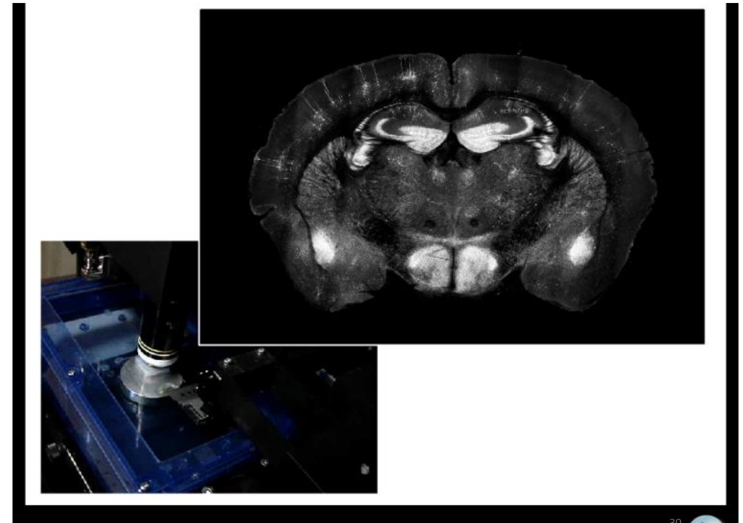

Ragan et al., 2012.

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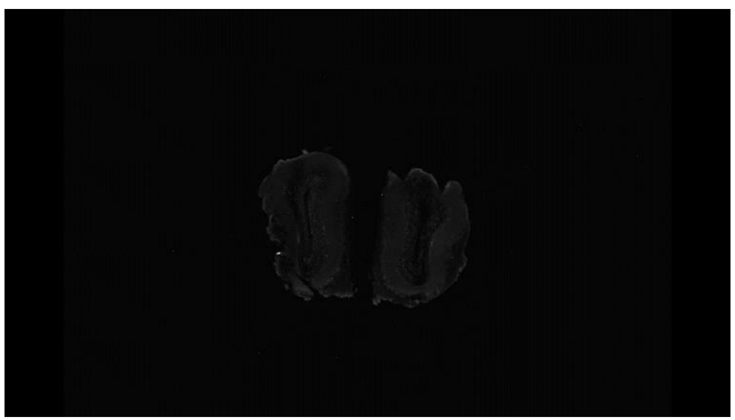

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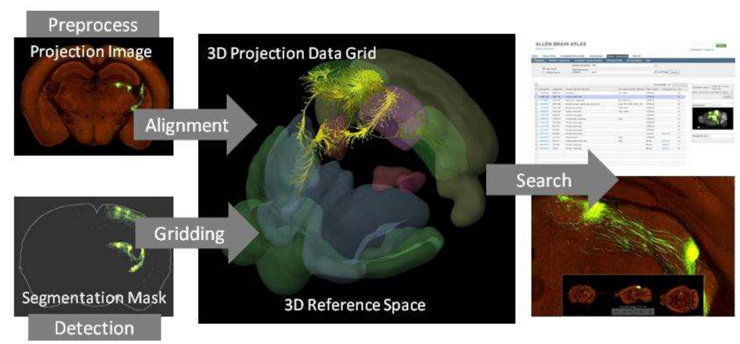

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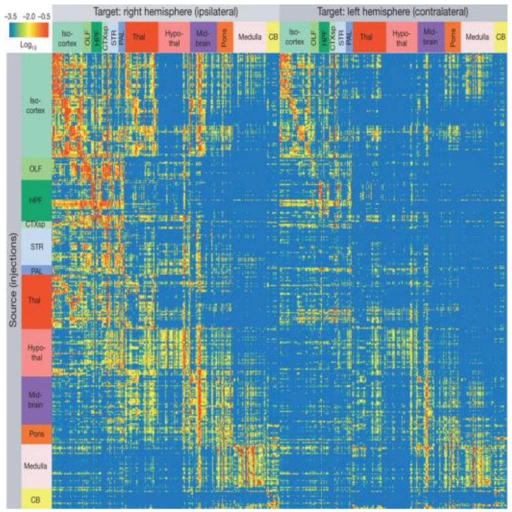

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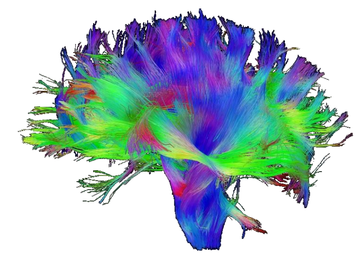
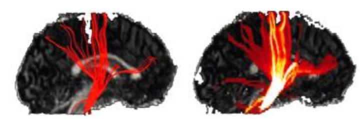
Magnetic resonance imaging allows whole-brain maps of living humans





the human connectome

Craddock et al., 2013.

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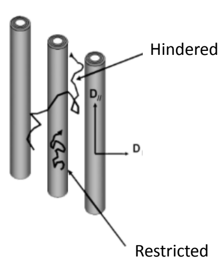
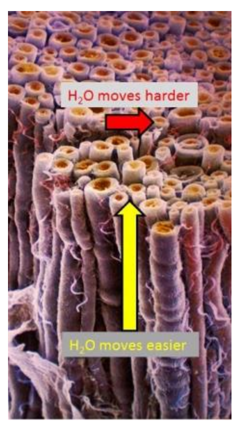
Diffusion MRI/tractography methods detect white-matter fibers from patterns of anisotropic water diffusion (I)

- Gradients are applied in different directions and attenuation is measured
  - Mobility is higher in white-matter fiber direction





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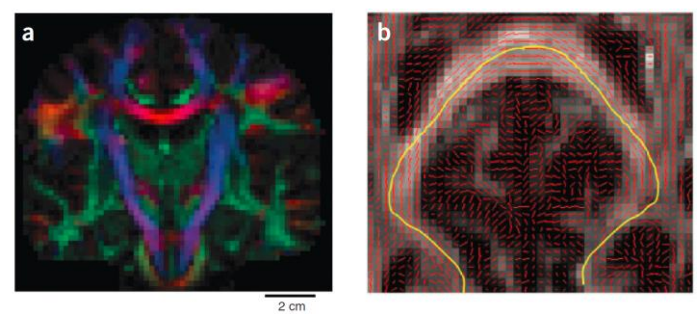
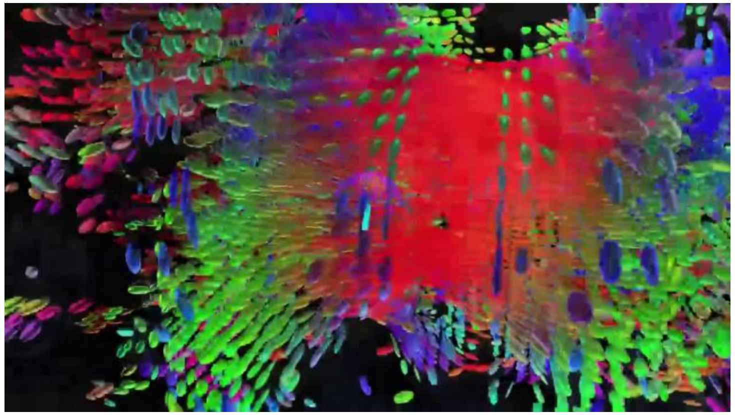
Diffusion MRI/tractography methods detect white-matter fibers from patterns of anisotropic water diffusion (II)



Craddock et al., 2013.

36

Diffusion MRI/tractography methods detect white-matter fibers from patterns of anisotropic water diffusion



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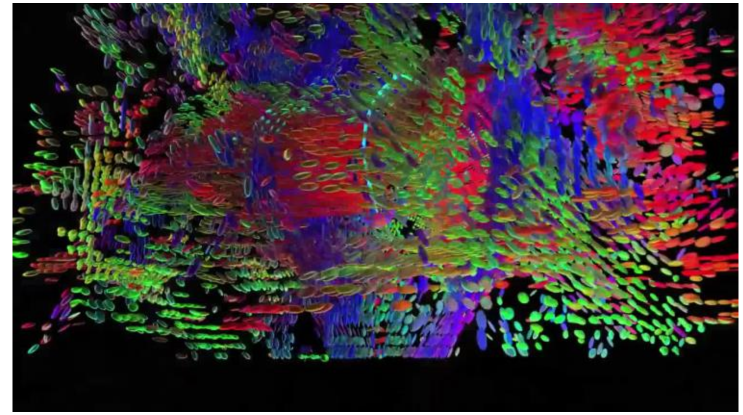
Diffusion MRI/tractography methods detect white-matter fibers from patterns of anisotropic water diffusion



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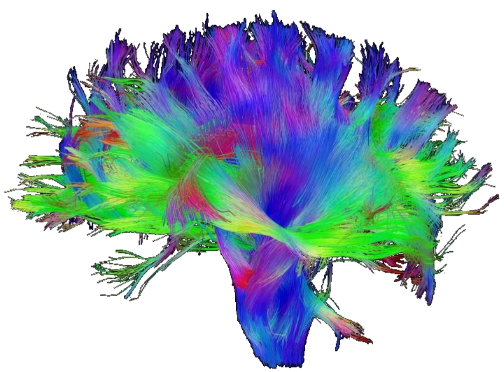
Diffusion MRI/tractography methods detect white-matter fibers from patterns of anisotropic water diffusion (III)



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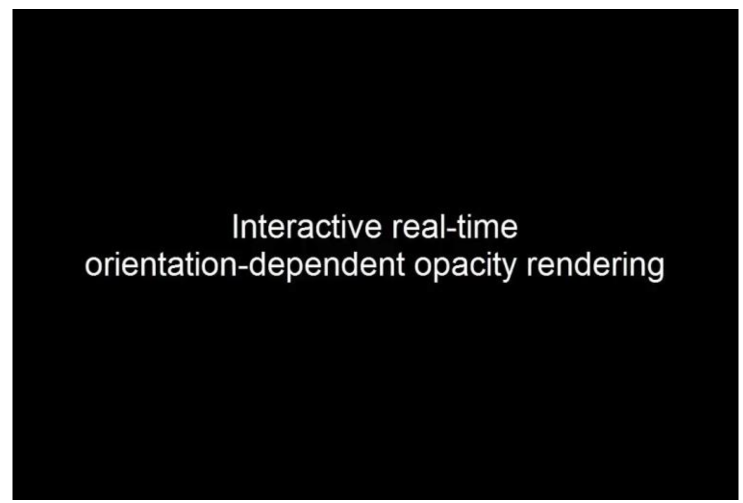

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FUNCTIONAL BRAIN NETWORKS

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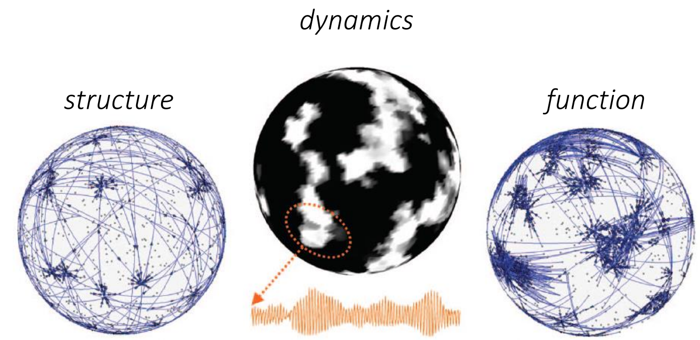
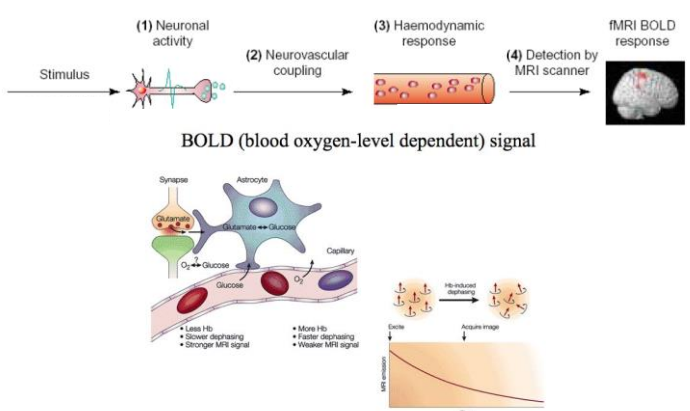
Complex brain function emerges on and is constrained by neuroanatomical network connectivity



Sporns and Honey, 2006.

42

FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI)



Arthurs & Boniface, 2002

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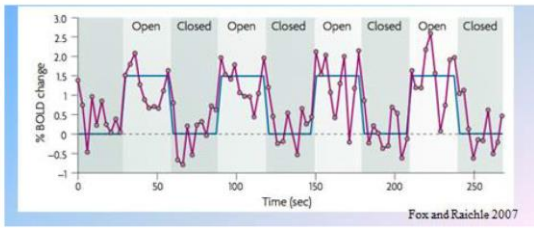
fMRI: Functional Magnetic Resonance Imaging

- There is blood in the brain at all times so a good *experimental paradigm* will contrast two brain states to see which areas are *more active* in one than the other



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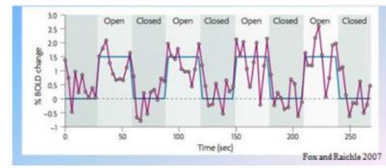
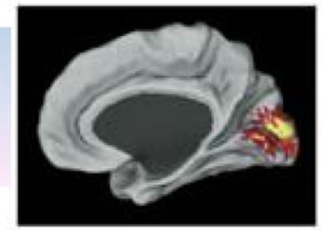
fMRI: Functional Magnetic Resonance Imaging

- For example occipital cortex is more active when eyes are open than when eyes are closed





- OPEN – CLOSED

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Natural speech reveals the semantic maps that tile human cerebral cortex

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Movie reconstruction from human brain activity

Presented clip

Clip reconstructed from brain activity

Nishimoto et al., 2011, Current Biology

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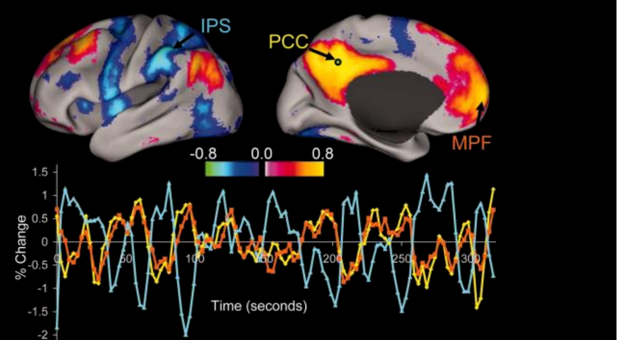
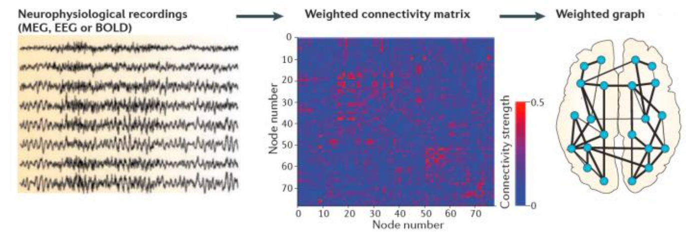
Functional MRI methods detect correlations of interregional changes in oxygenated hemoglobin



Fox et al., 2005.

49

EEG/MEG networks detect correlations between neurophysiological signals



Stam, Nature Reviews Neurology 2014

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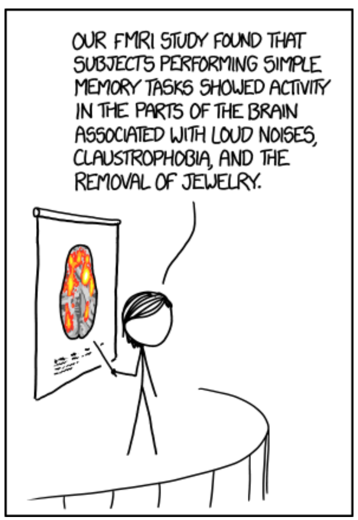

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CONSTRUCTION OF COMPLEX BRAIN NETWORKS

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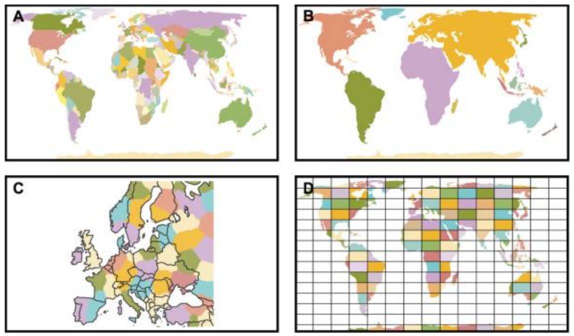
The definition of brain-network nodes is an important problem



Wig et al., 2011

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Features of a good parcellation scheme

- Structural/functional homogeneity
- spatial contiguity
- whole-brain coverage
- high signal-to-noise ratio
  - clear choice for number of regions
- between-subject reproducibility

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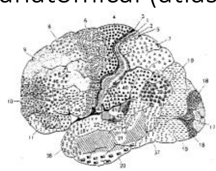
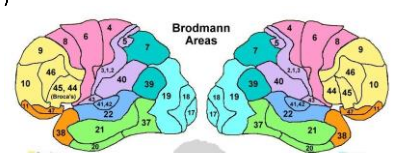
Types of parcellation approaches

- anatomical (atlases)





- functional

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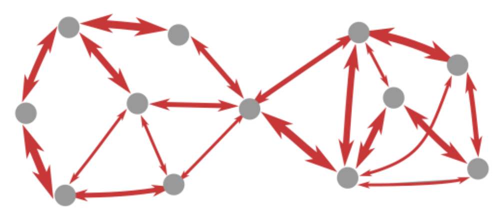
The definition of connection weights is an important problem

- structural or functional
- choice of acquisition
- choice of connection measure
- link magnitude, weight and sign



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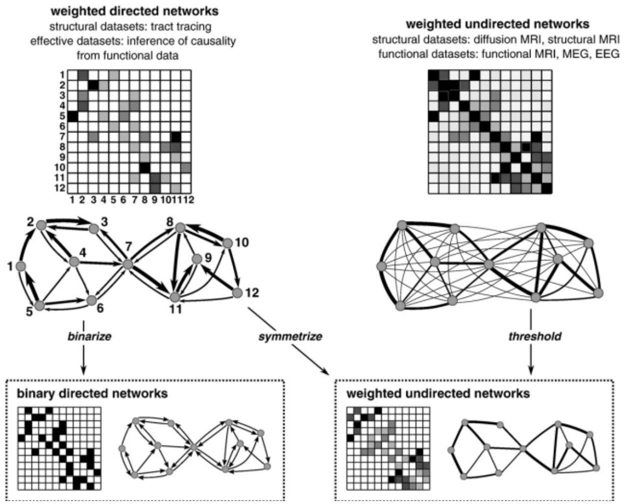

Rubinov and Sporns, Neuroimage 2010

57

There are many measures of functional association

- Most common measures include:
  - Pearson correlation coefficient
  - Partial correlation coefficient
  - Mutual information
  - Lag-based measures:
    E.g. Granger causality and transfer entropy
  - Inference is less common (networks are too big)

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ANALYSIS OF COMPLEX BRAIN NETWORKS

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Pre-connectome-era descriptions of neuroanatomical circuits emphasize spatial constraints and nonspecific wiring

- Ramon y Cajal's principle of wiring economy:

"All of the conformations of the neuron and its components are simply morphological adaptations governed by laws of conservation for time, space, and material"

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Hierarchical organisation of the monkey visual cortex

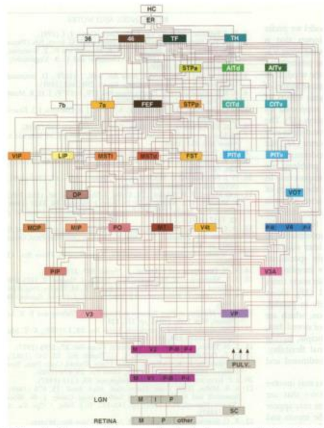
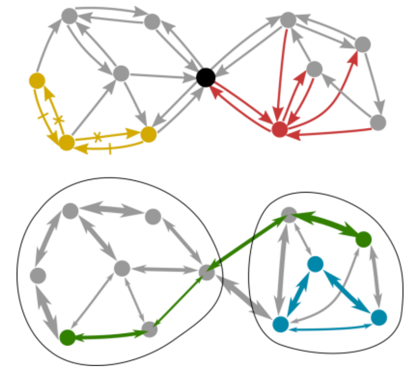


Fig. 2. A hierarchy of visual areas in the macaque, based on laminar patterns of anatomical connections. About 90% of the known pathways are consistent with this hierarchical scheme; the exceptions may reflect either inaccuracies in the reported anatomical data or genuine deviations from a rigid hierarchical scheme. [Modified, with permission, from (1), with subcortical connections based on (37)]

Van Essen et al. 1992

61

Analyses of network topology provide insights about emergent function



Rubinov and Sporns, 2010.

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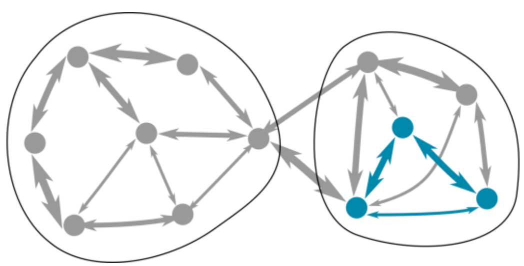
Measures of segregation

- clustering coefficients
- community structure



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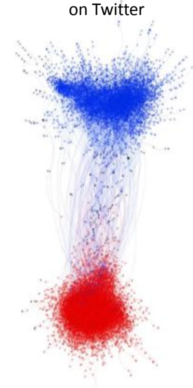
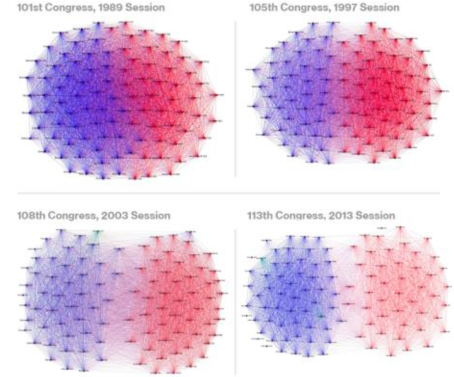
Network segregation in social networks





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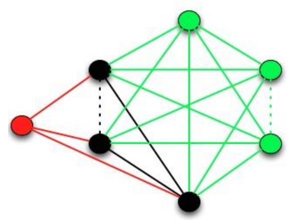
Measures of segregation: Clustering

- clustering coefficient

$$C_i = \frac{2\, n_i}{k_i\,(k_i - 1)}$$

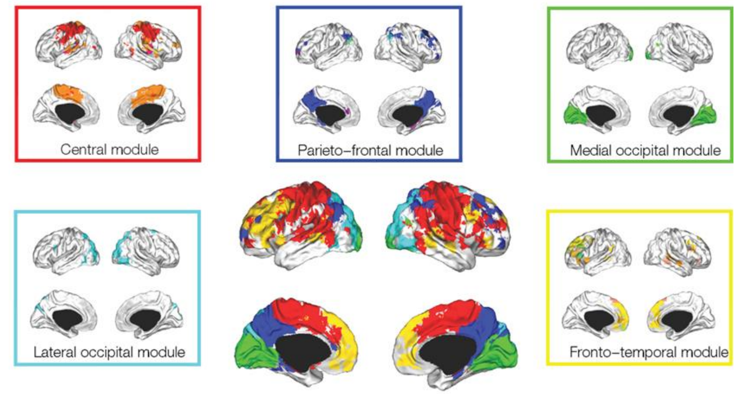
where n_i denotes the number of links connecting the k_i neighbors of node *i*.



$$C_{red} = \frac{2*2}{3*(3-1)} = 0.66$$

65

Community structure in human brain



Meunier et al. , Front. Neuroinform2009

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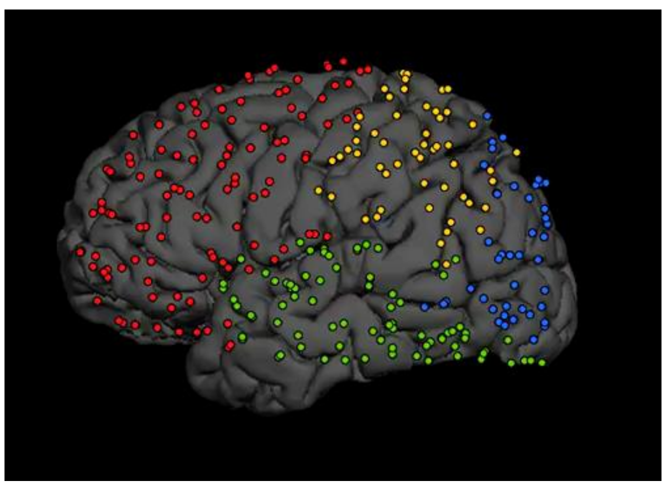

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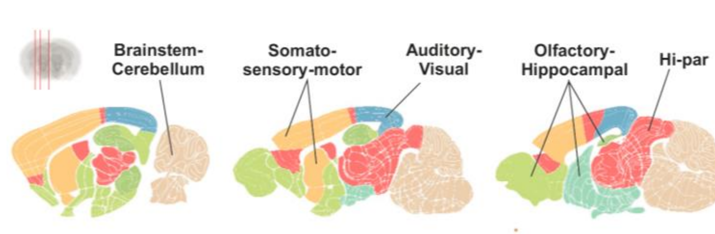
Network modules reflect functionally specialized brain areas and are often spatially contiguous

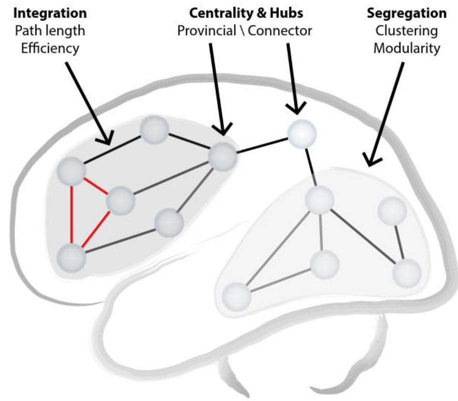
Examples include primary sensory and motor areas



Rubinov, Ypma, Watson, Bullmore, 2015.

68

Some nodes cannot be assigned to any module



Hart, 2017

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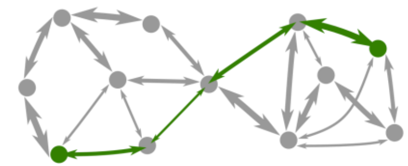
Measures of integration

- path lengths $L(G) = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \min(d_{ij})$
- global efficiency $E_{glob}(G) = \frac{1}{N(N-1)} \sum_{i \neq j \in G} \frac{1}{\min(d_{ij})}$

where N is the number of nodes and d_{ij} denotes the distance between node *i* and node *j*.



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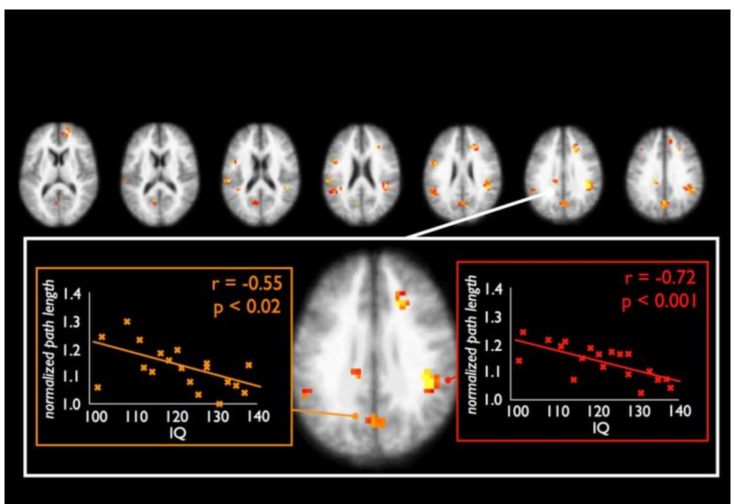

van den Heuvel et al., J Neurosci 2009

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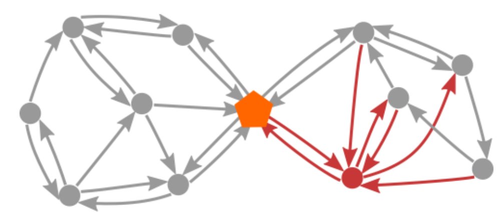
Measures of centrality

- degree centrality
- betweenness centrality
- participation coefficient



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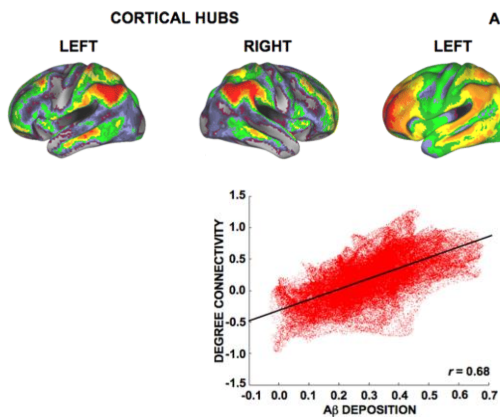
Central nodes (hubs) are more vulnerable to disease



Buckner et al., J Neurosci 2009

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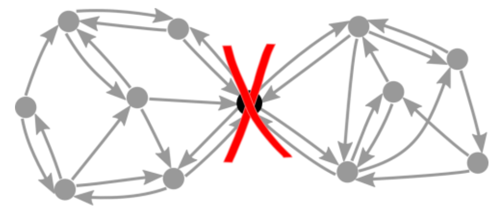
Measures of resilience

- indirect, e.g. presence of core structure
- direct, e.g. response to lesions



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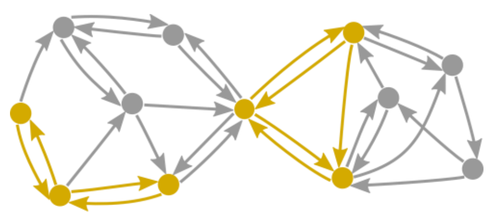
Network motifs

- directed motifs
- undirected motifs



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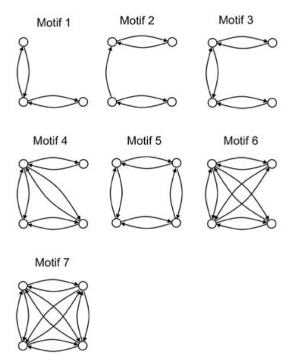
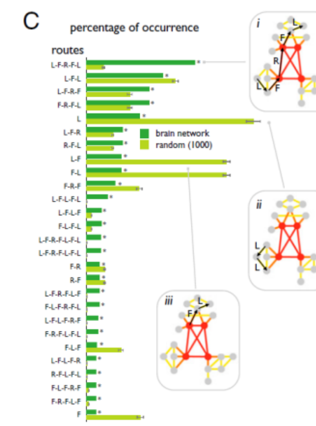
Motifs over-representation in bran network



Shanahan, et al 2013



van den Heuvel and Sporns, PNAS 2012

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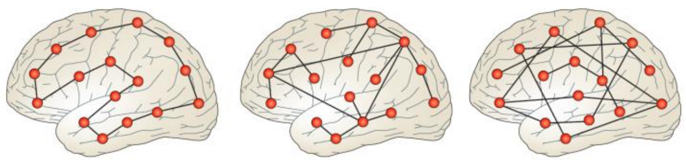
Measures of network macroscale summarize properties of the whole network in a single statistic



Bullmore and Sporns, 2012.

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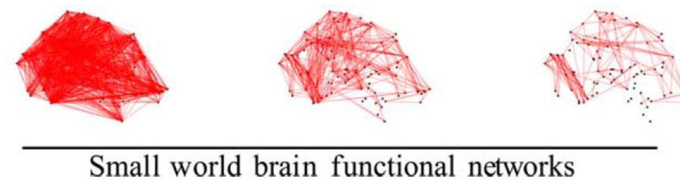
Measures of network macroscale

- small-worldness $\sigma(G) = \frac{C(G)}{L(G)}$



Achard et al., J Neurosci 2006

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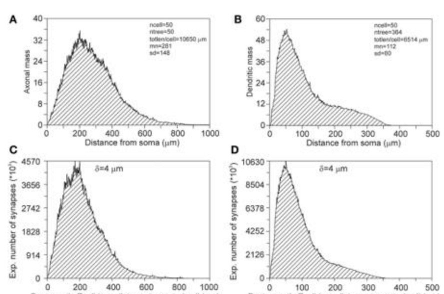
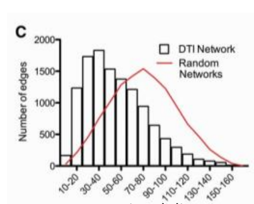
The effect of space

Brain network topology is highly determined by spatial constraints



Pelt and van Ooyenet 2013



Inter-regional distance

Crossley et a. 2014

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Limitations

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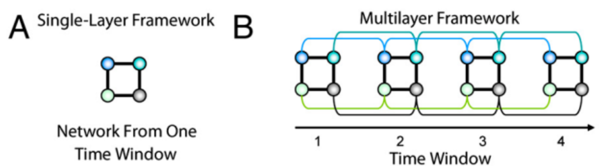
The effect of time

Studies are beginning to capture network states with temporally local measures



Bassett et al., PNAS 2011

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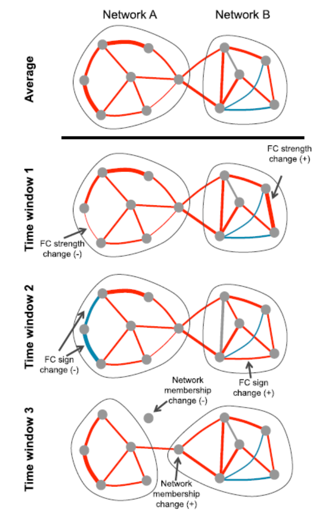

Hutchison et al., 2013

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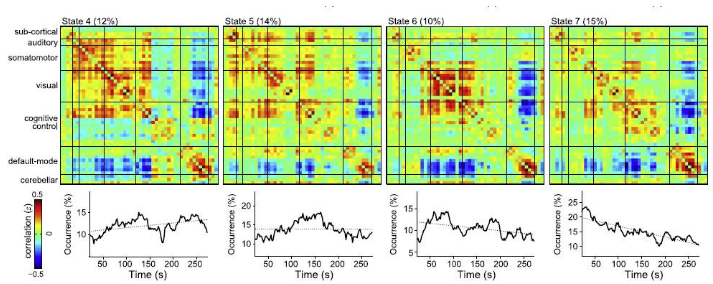
Temporally local measures can capture distinct network states



Hutchison et al., 2013

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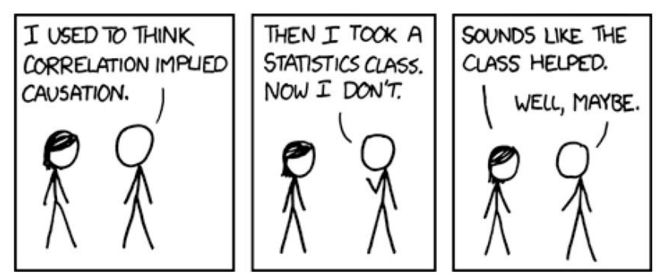
Interpretability can be hard

Functional connectivity is a statistical measure that does not necessarily describe causal interactions or information flow.



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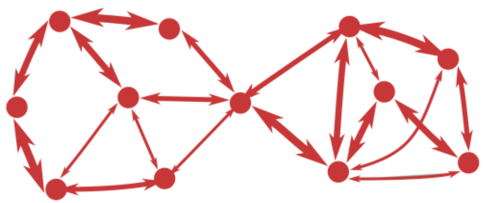
Measures of network macroscale are often too general to be useful

- small-worldness



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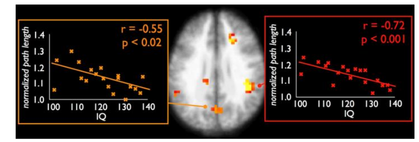
Replicability crisis

Efficiency of Functional Brain Networks and Intellectual Performance



van den Heuvel et al., J Neurosci 2009

General, crystallized and fluid intelligence are not associated with functional global network efficiency: a replication study with the human connectome project 1200 data set.

J.D. Kruschwitz *[1,2], L. Waller *[1], L.S. Daedelow[1], H. Walter +[1], I.M. Veer +[1]

Krushwitz et al., Neuroimage 2018

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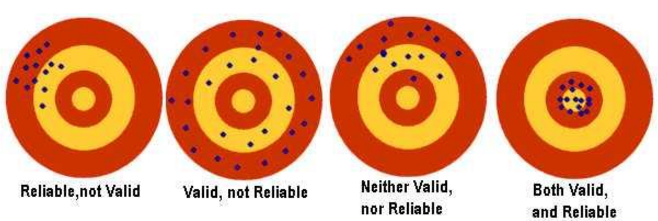
Methodological considerations

- Common problems:
  - Results change depending on the processing pipeline
  - Findings are specific of each modality
  - Healthy brains are as different as pathological brains
  - Low Replicability
  - Small sample size



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UK Biobank

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Some take home thoughts

- Complex brain networks are an intuitive and powerful representation of brain systems.
- There is a data quality vs organism complexity trade-off in connectomes. Model organisms should be chosen carefully if possible (humans aren't necessarily "optimal").

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Some take home thoughts

- The definition of nodes and edges is fundamental to network analysis.
- Analysis may be generic but interpretation needs to be organism and modality specific.
- Network specificity is important for translation and mechanistic relevance.

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Complex-networks software

- igraph (C-based, multiple wrappers)
  http://igraph.sourceforge.net/
- networkX (python library)
  https://networkx.github.io
- Visualization
  - Pajek: http://pajek.imfm.si/doku.php
  - Brainnet: https://www.nitrc.org/projects/bnv/

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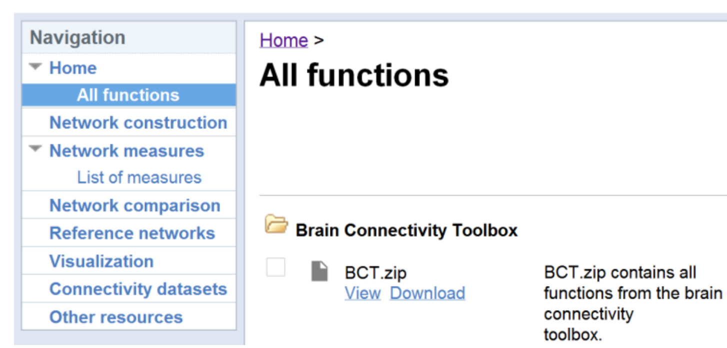
Brain Connectivity Toolbox



http://www.brain-connectivity-toolbox.net

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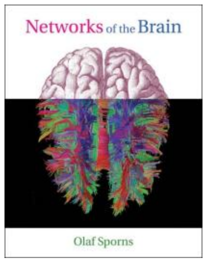
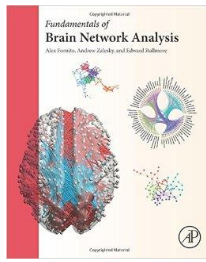
Any questions: rr480@cam.ac.uk
Further reading

Literature: see recent (2013-2019) special issues on connectomics and mapping the brain in Nature Methods, Science, Neuron, Trends in Cognitive Science, etc.





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