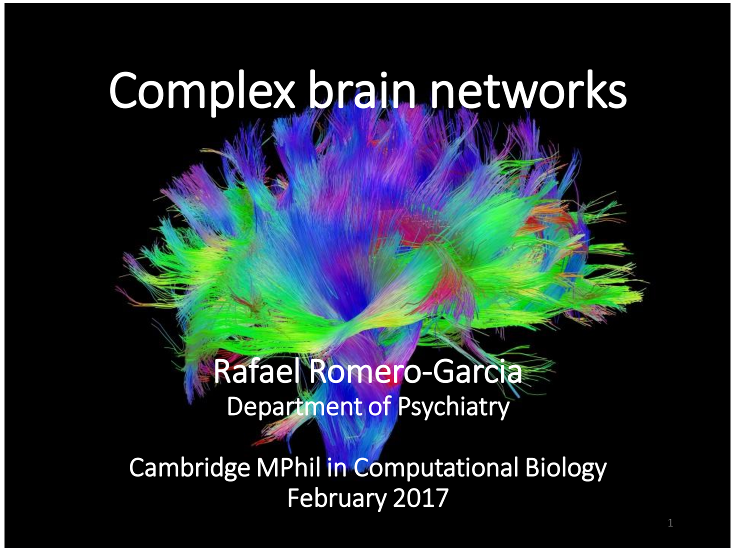

Complex brain networks
Rafael Romero-Garcia
Department of Psychiatry
Cambridge MPhil in Computational Biology
February 2017
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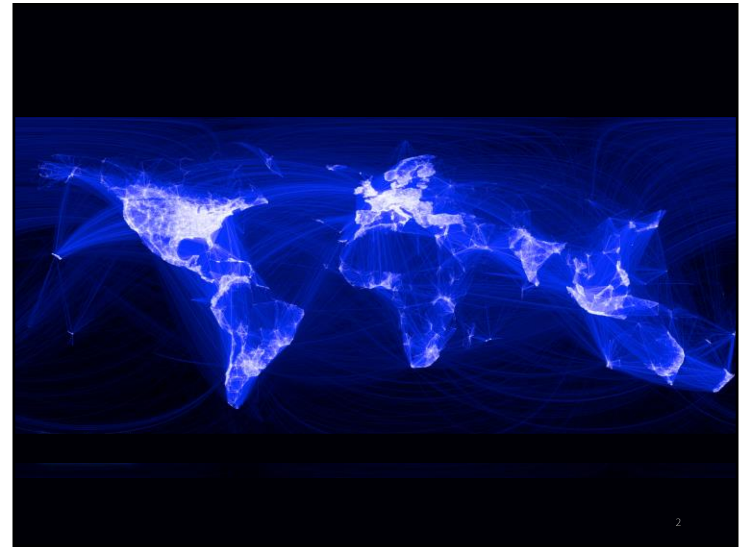

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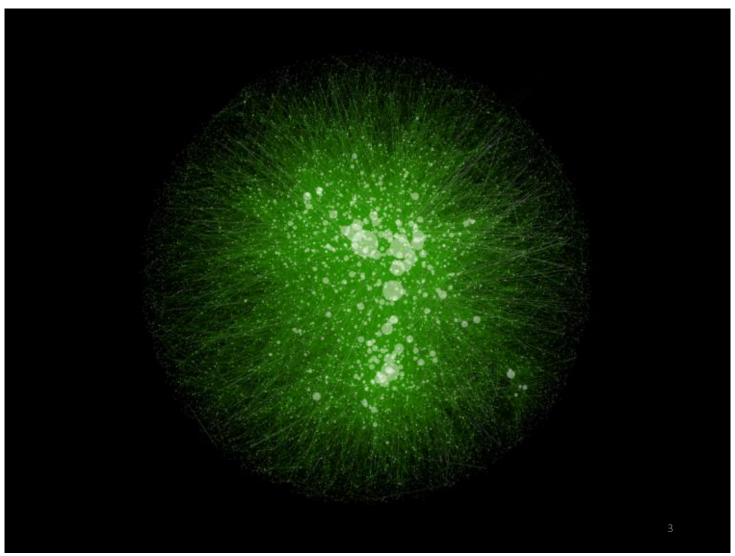

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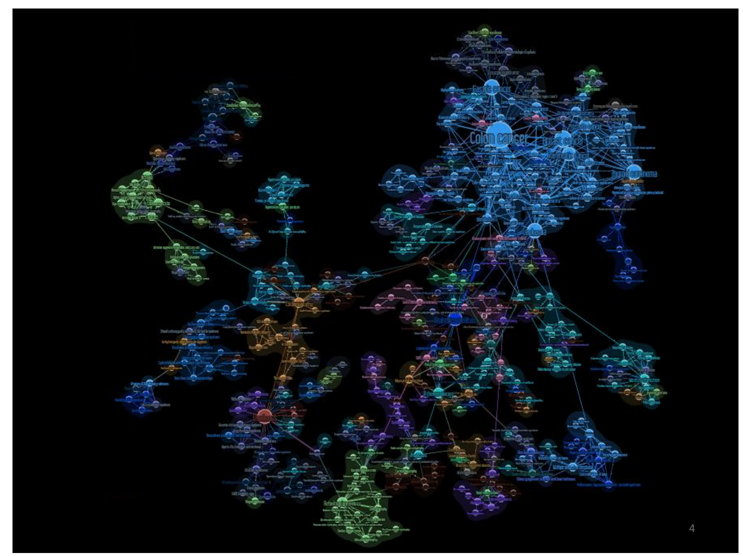


4

The brain is the most complex of networks

Human Connectome Project.

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.

Motivation for complex brain networks

Types of complex brain networks

Construction of complex brain networks

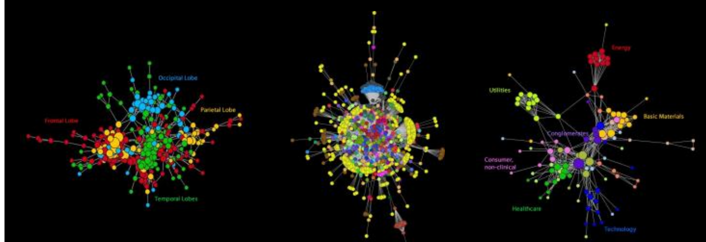
Analysis of complex brain networks

Brain network modules and hubs

MOTIVATION FOR COMPLEX BRAIN NETWORKS

Complex networks analysis draws strength from universality

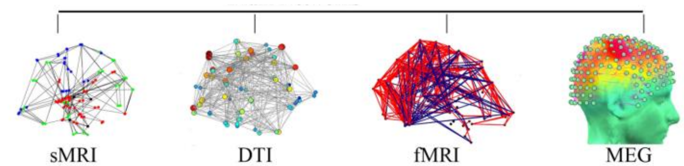
But interpretation must be dataset-type specific



functional MRI network   twitter network   NYSE network

Vertes et al., Frontiers Syst Neurosci 2011

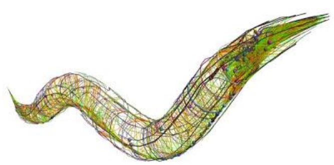
Complex networks are a universal framework for representation of multimodal brain connectivity

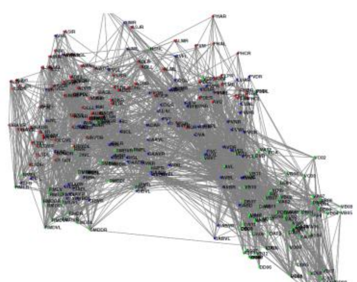


Bassett and Bullmore, Curr Opin Neurol 2009

Complex networks intuitively represents connectivity at multiple spatial scales

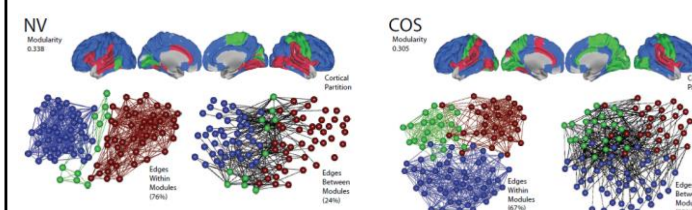
The *C. elegans* connectome





The Open Worm Project   *Chen et al., PNAS 2006*   11

Dysconnectivity in neuropsychiatric disorders is likely to be complex



Alexander-Bloch et al., Frontiers Syst Neurosci 2011

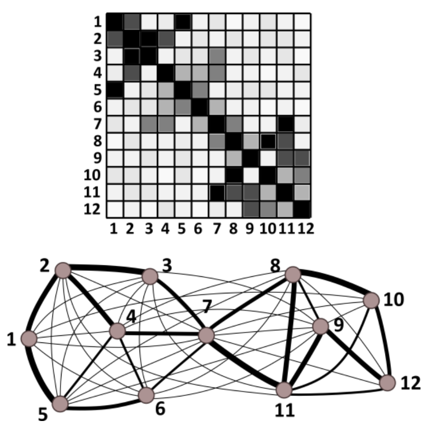
TYPES OF COMPLEX BRAIN NETWORKS

13

The connectome is a model of brain organization

14

Connectivity matrix represents a graph



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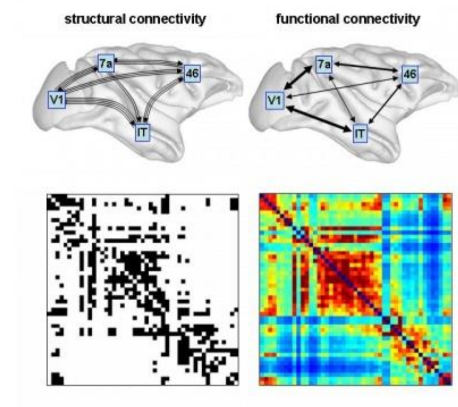
Types of brain connectivity



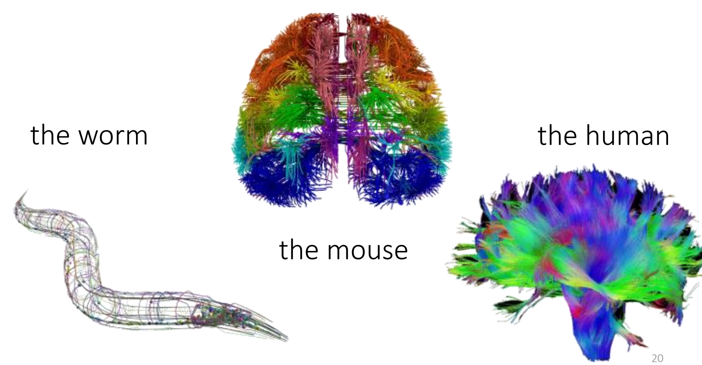
Sporns, Scholarpedia 2012

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

Structural networks	Functional networks
Physical pathways	Statistical associations (do not represent information flow)
Sparse	Dense
Positively weighted connections	Positive and negatively weighted connections

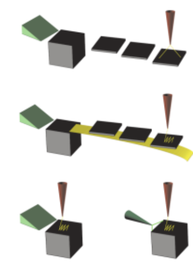
STRUCTURAL BRAIN NETWORKS

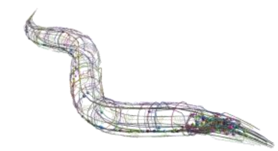
There is a data quality vs organism complexity trade-off



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*

Electron-microscopy allows dense synaptic maps of neuronal circuits

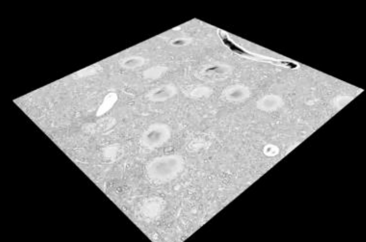


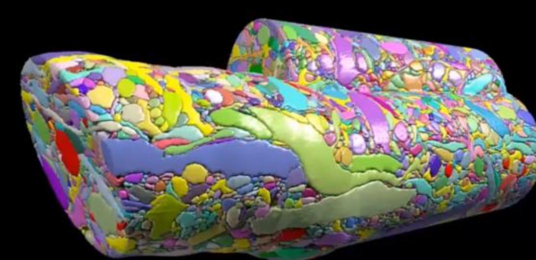


C. elegans connectome

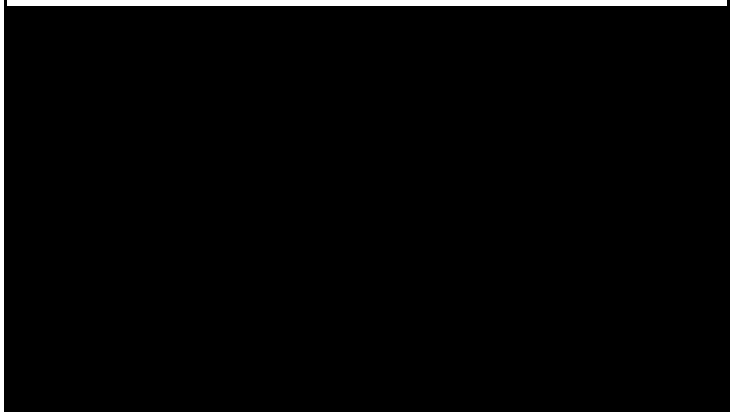
Helmstaedter, 2013; Open Worm project.

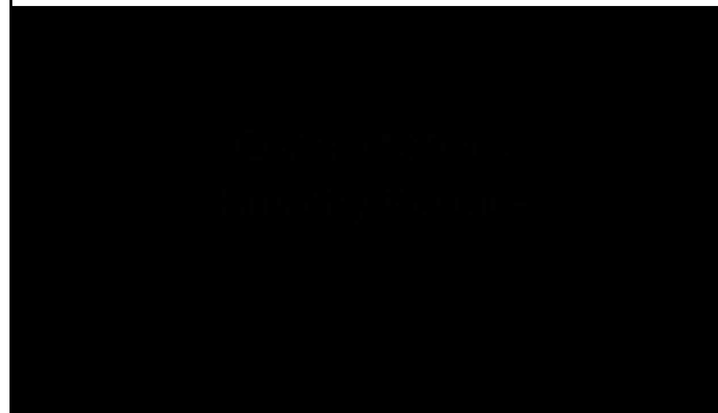
Neural circuit reconstruction





Bobby Kasthuri, Boston University

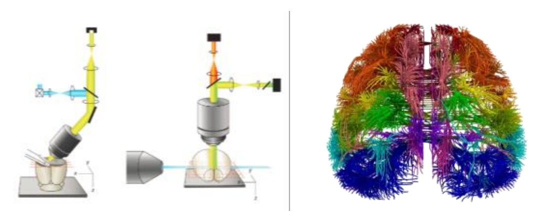




GoPiGo (Dexter Industries) Robot
running a C elegans connectome
simulation using Python 2.7 on a Raspberry Pi B+

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

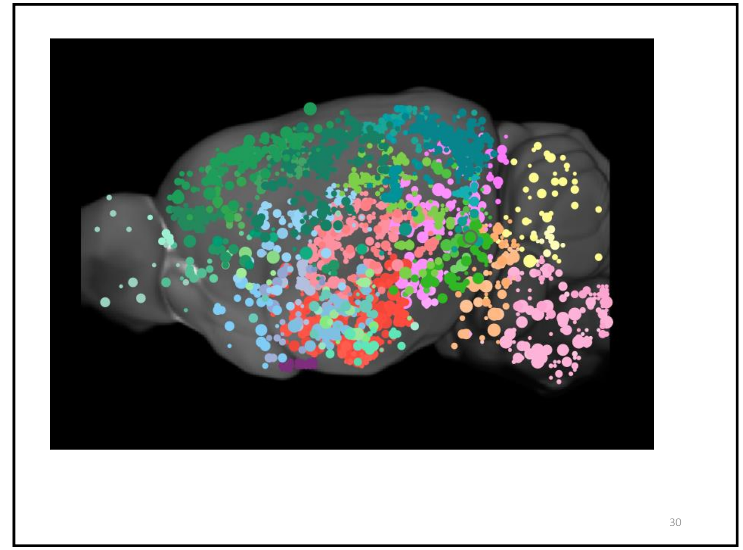
Light-microscopy allows sparse directed maps of mammalian brains



mouse connectome

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


Mouse Connectome Project, University of Southern California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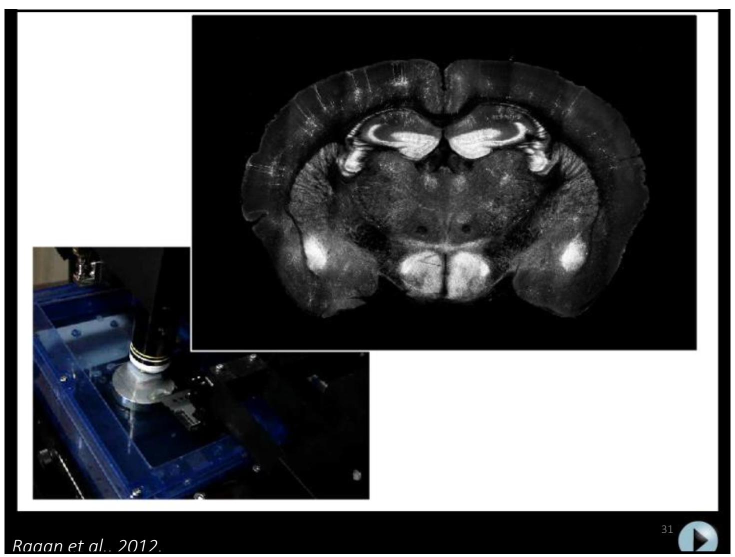
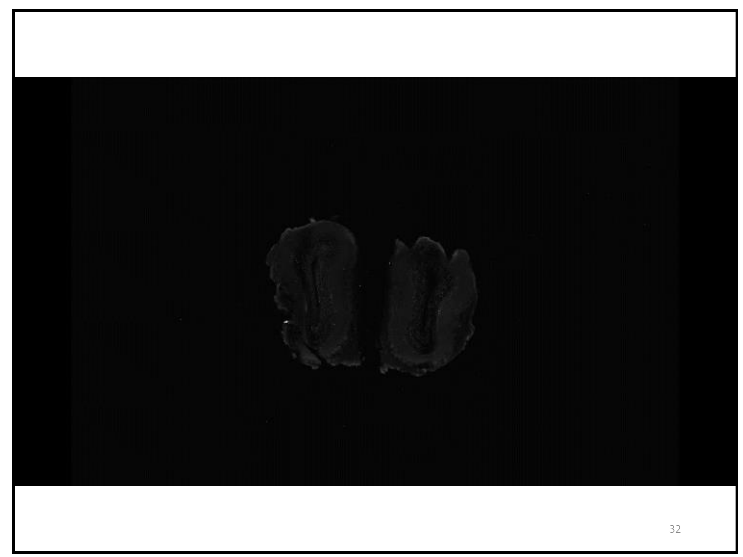

31
Ragan et al., 2012.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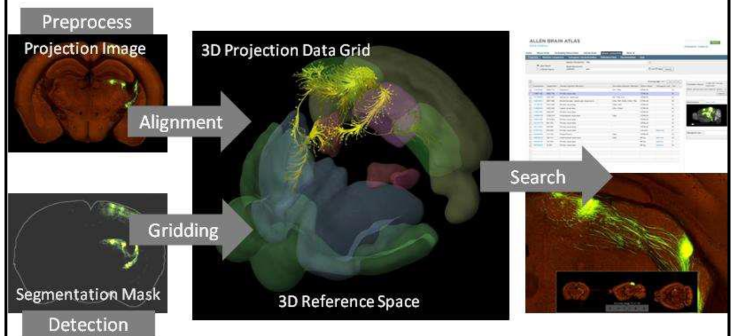

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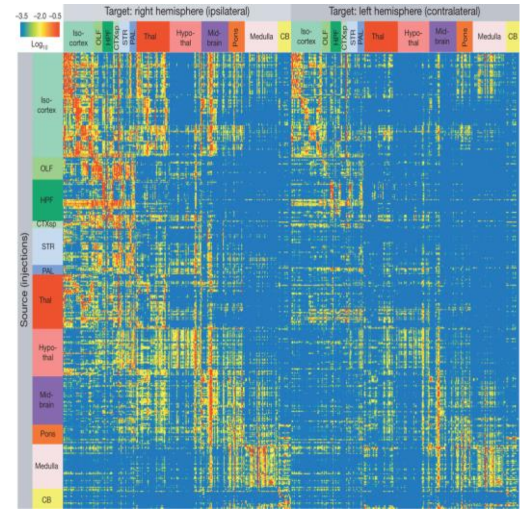

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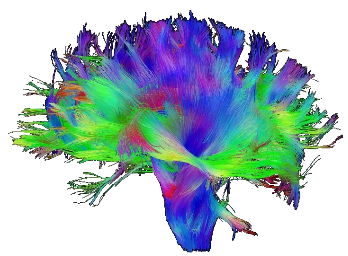
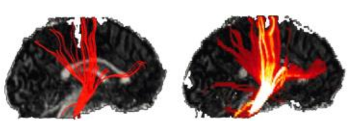
Magnetic resonance imaging allows whole-brain maps of living humans



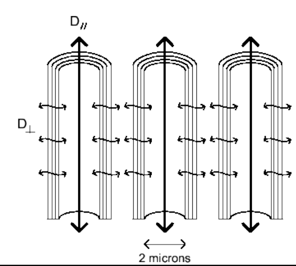


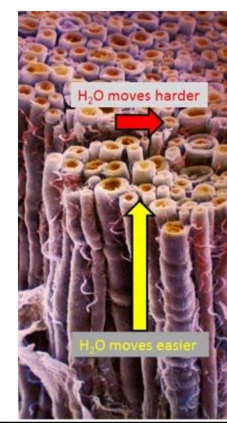
the human connectome

Craddock et al., 2013.

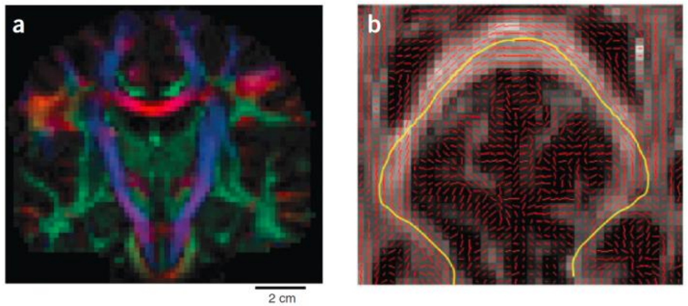
Diffusion MRI/tractography methods detect white-matter fibers from patterns of anisotropic water diffusion (I)

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



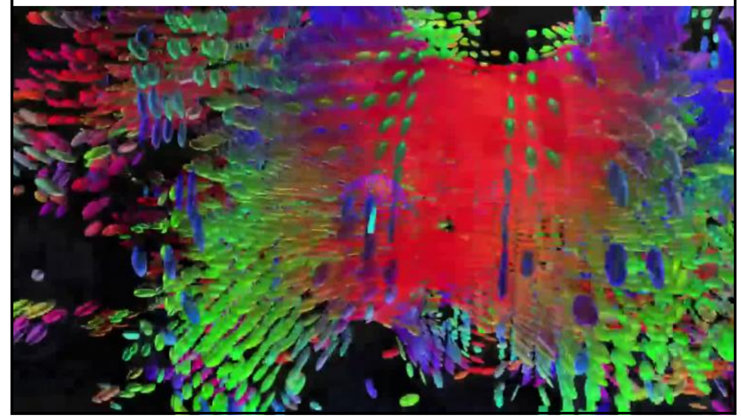


Diffusion MRI/tractography methods detect white-matter fibers from patterns of anisotropic water diffusion (II)

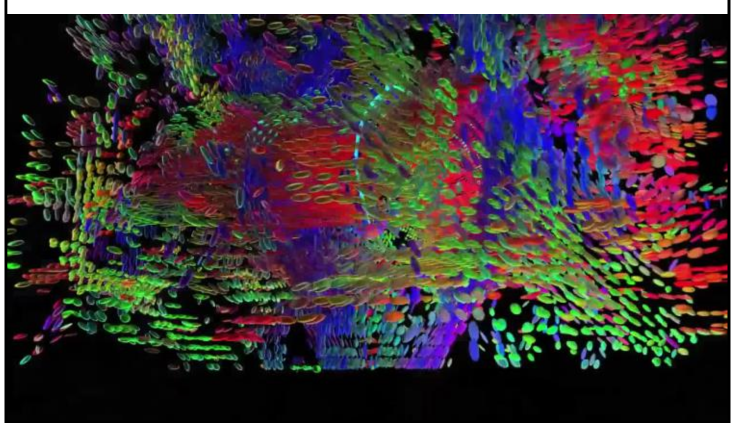


Craddock et al., 2013.

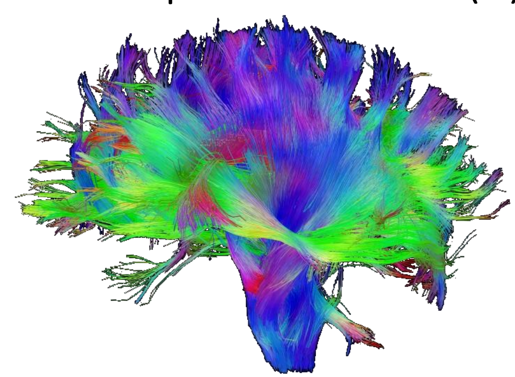
Diffusion MRI/tractography methods detect white-matter fibers from patterns of anisotropic water diffusion



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



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



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Interactive real-time
orientation-dependent opacity rendering

Functional Brain Networks

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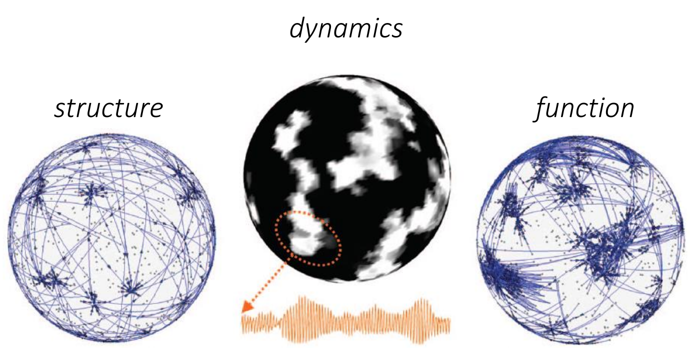
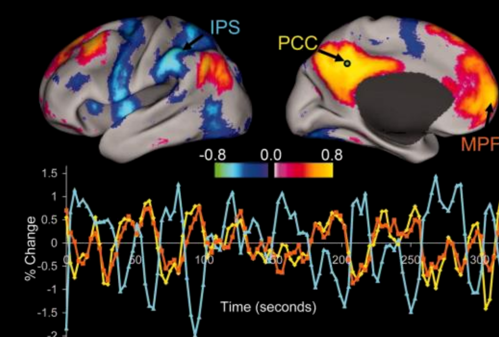
Complex brain function emerges on and is constrained by neuroanatomical network connectivity



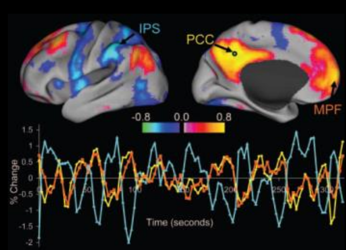
Sporns and Honey, 2006.

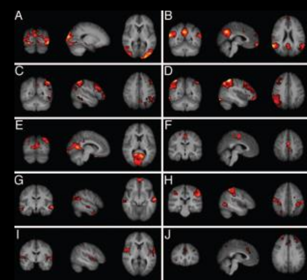
Functional MRI methods detect correlations of interregional changes in oxygenated hemoglobin



Fox et al., 2005.

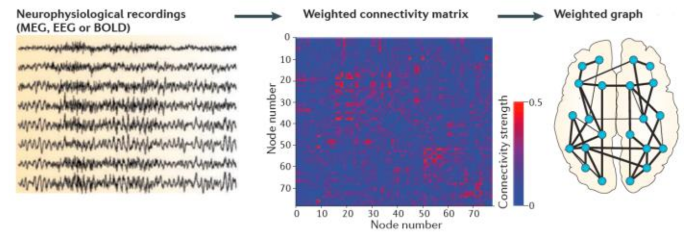
Seed correlation and independent components analyses describe specialized functional systems





Fox et al., PNAS 2005; Damoiseaux et al., PNAS 2006

EEG/MEG networks detect correlations between neurophysiological signals

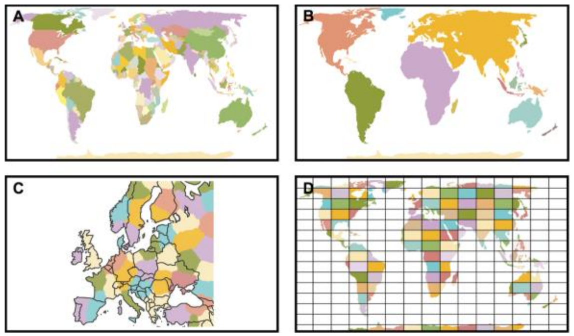


Stam, Nature Reviews Neurology 2014

Seed correlations	Independent components	Complex networks
Hypothesis-driven	Data-driven	Data-driven or hypothesis-driven
Small number of nodes		Large number of nodes
Only strong positive functional interactions		Strong and weak, positive and negative interactions
Specialized functional systems		Maps of whole-brain activity

CONSTRUCTION OF COMPLEX BRAIN NETWORKS

The definition of brain-network nodes is an important problem



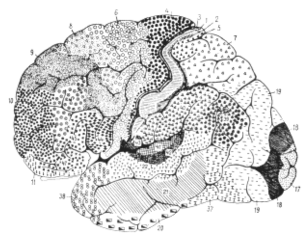
Wig et al., 2011

Features of a good parcellation scheme

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

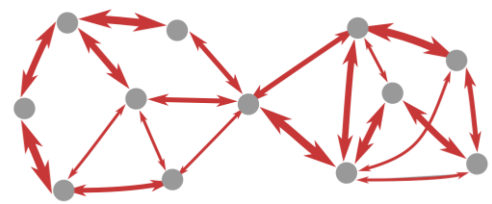
Types of parcellation approaches

- anatomical (atlases)
  - cytoarchitectonics
  - chemoarchitectonics
  - myeloarchitectonics
- functional
  - activation
  - whole-brain clustering
  - meta-analyses

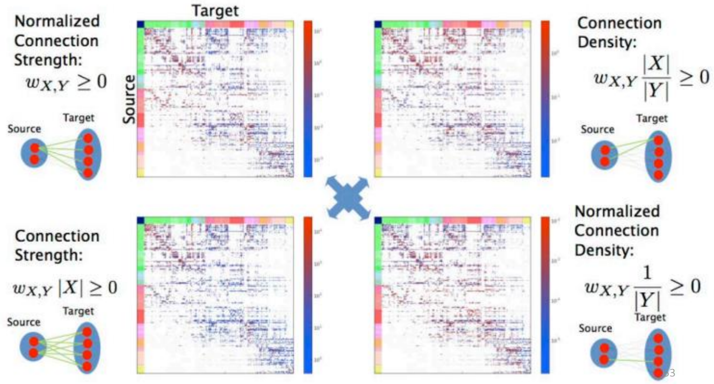


The definition of connection weights is an important problem

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



The definition of structural-connection weights is modality depedent



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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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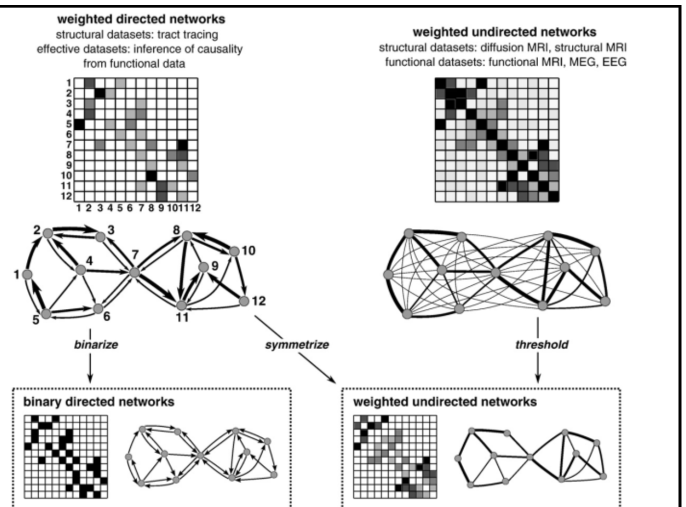

Rubinov and Sporns, Neuroimage 2010

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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

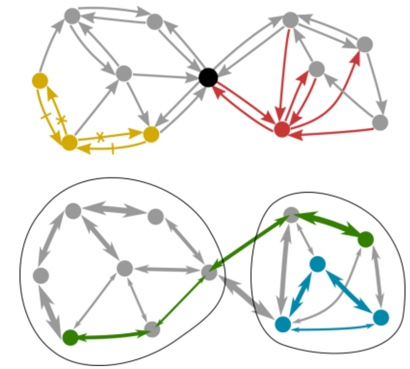
- Ramon y Cajal's principle of wiring economy:

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

- Peters' rule of wiring nonspecifity:

"The distribution of synapses on the dendritic tree of a neuron reflects simply the availability of those presynaptic elements in the tissue."

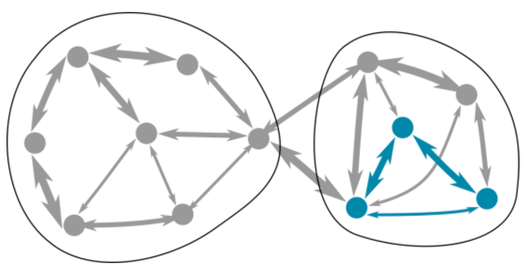
Analyses of network topology provide insights about emergent function



Rubinov and Sporns, 2010.

Measures of segregation

- clustering coefficients
- community structure



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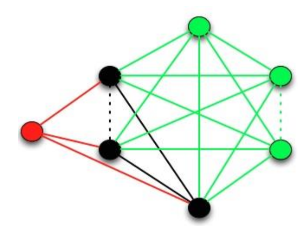
Measures of segregation: Clustering

- clustering coefficient

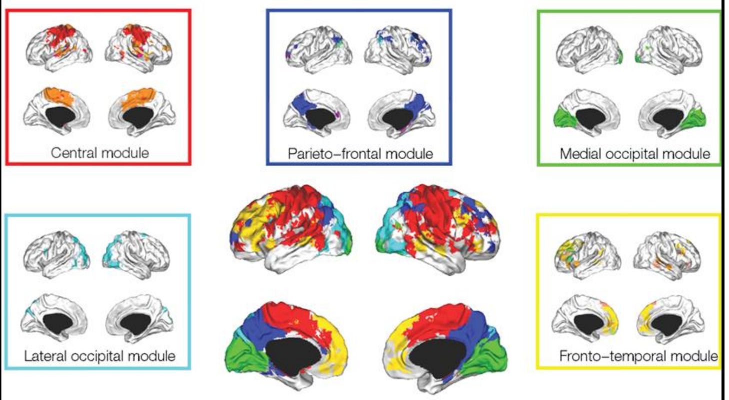
$$C_i = \frac{2\,n_i}{k_i\,(k_i - 1)}$$

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



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

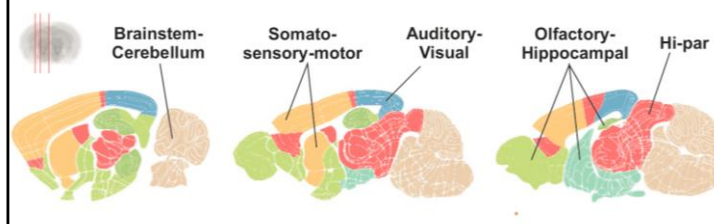
Community structure in human brain



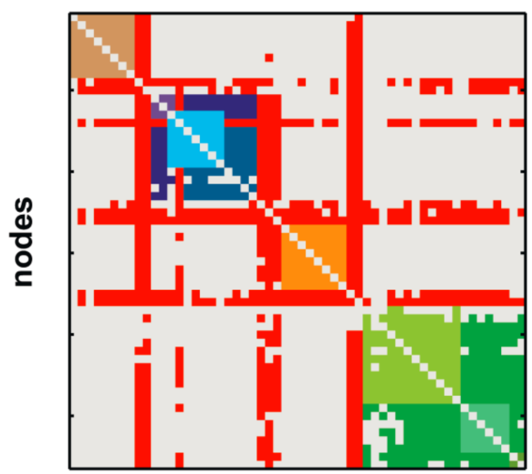
Meunier et al. , Front. Neuroinform2009

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

Examples include primary sensory and motor areas



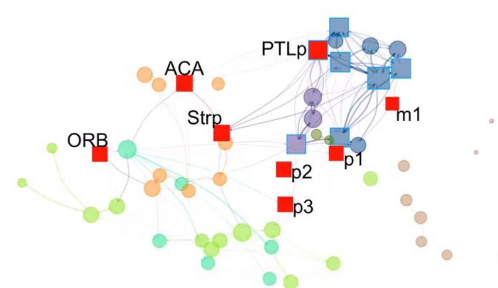
Rubinov, Ypma, Watson, Bullmore, 2015.



Rubinov, Ypma, Watson, Bullmore, 2015.

Modules of the mouse brain

Sagittal

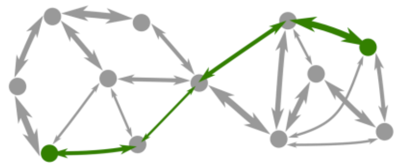


Rolf Ypma, Department of Psychiatry

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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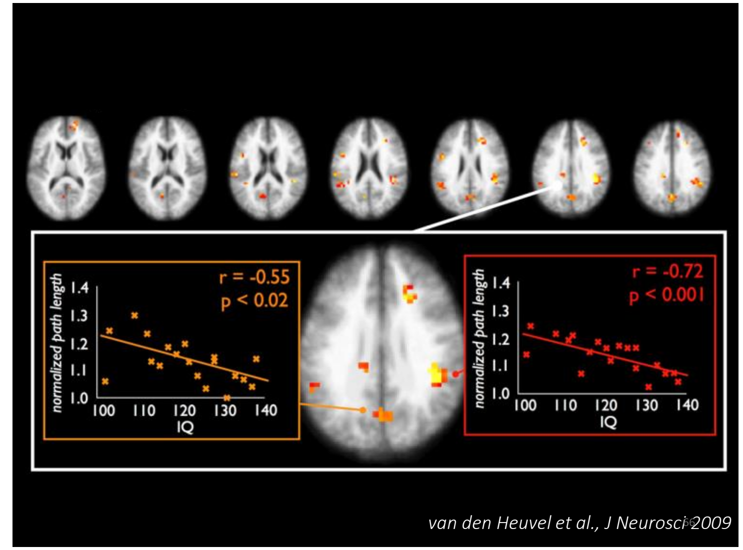
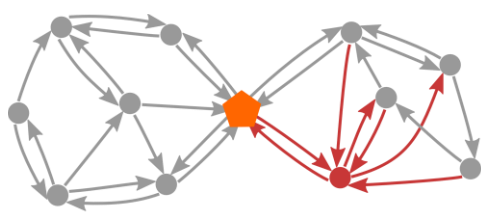


van den Heuvel et al., J Neurosci 2009

Measures of centrality

- degree centrality
- betweenness centrality



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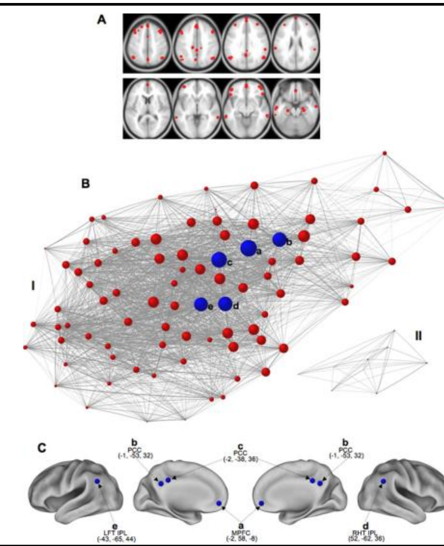
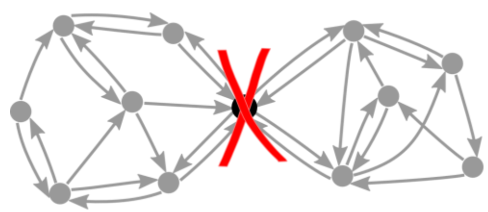


Buckner et al., J Neurosci 2009

Measures of resilience

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



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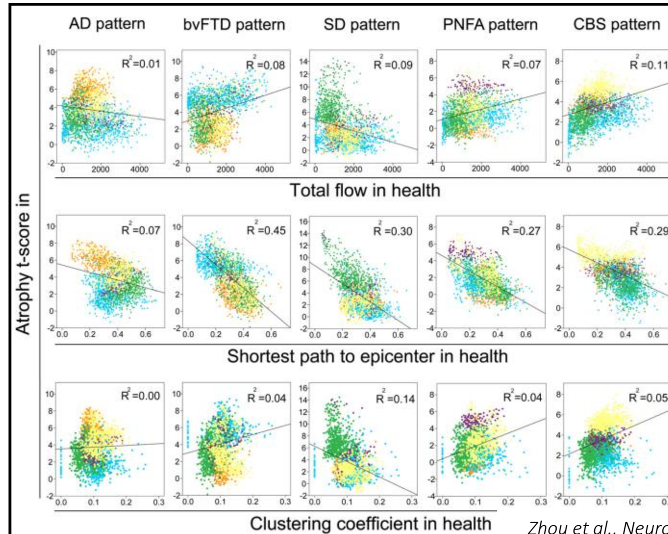
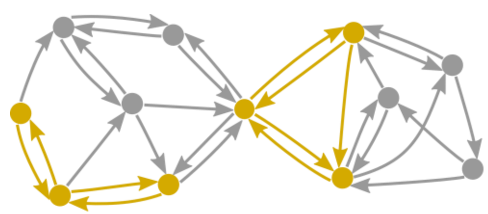


Zhou et al., Neuron 2012

Network motifs

- directed motifs
- undirected motifs



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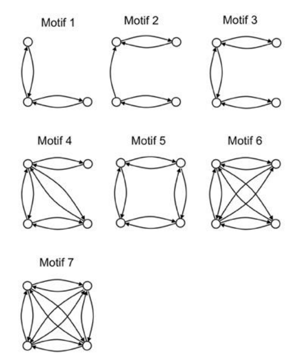
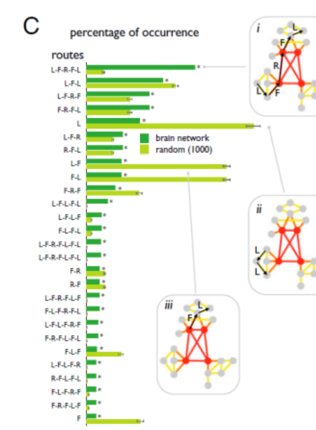
Motifs over-representation in bran network

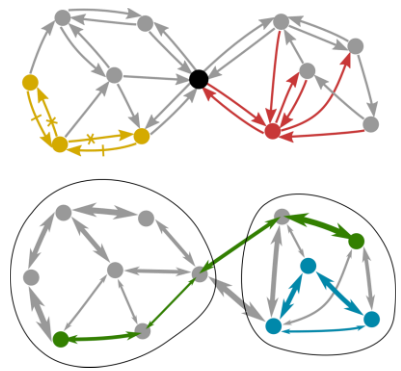


Shanahan, et al 2013



van den Heuvel and Sporns, PNAS 2012

Network measures could also be grouped by topological scale



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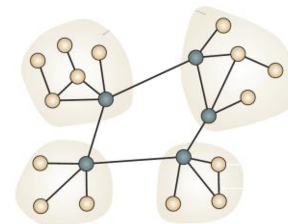
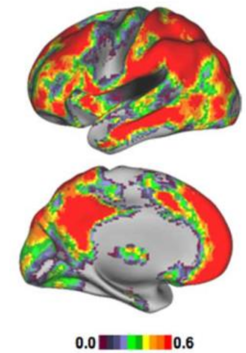
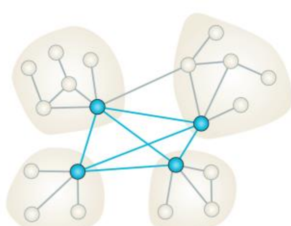
Measures of network microscale describe properties of single nodes

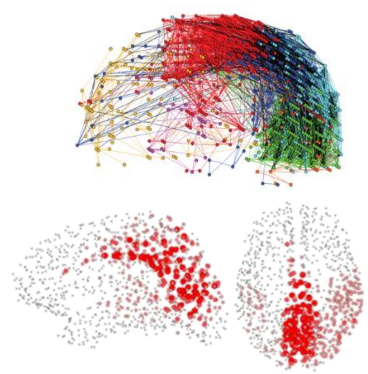




Buckner et al., 2009.

Measures of network mesoscale describe properties of groups of nodes





Hagmann et al., 2008; Meunier et al., 2011.

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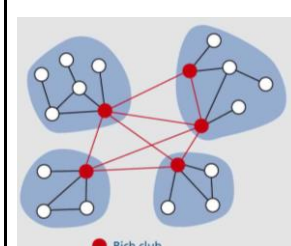
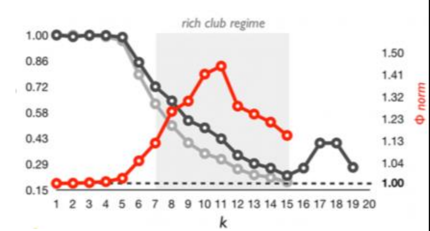
Measures of network mesoscale

- community and core-periphery structure

$$\phi(k) = \frac{2E_{>k}}{N_{>k}(N_{>k}-1)}$$

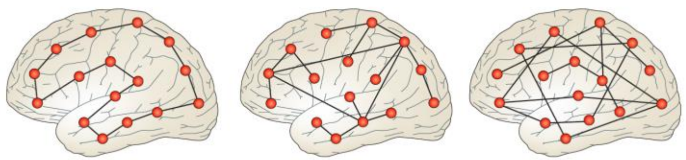
$E_{>k}$ is the number of connections between nodes with at least k connections
$N_{>k}$ is the number of nodes with at least k connections





van den Heuvel and Sporns, J Neurosci 2011

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

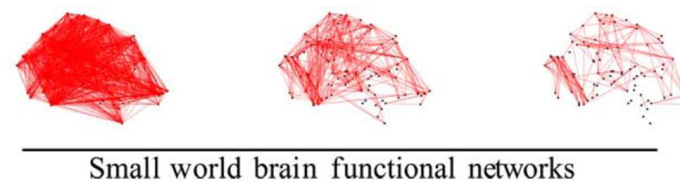


Bullmore and Sporns, 2012.

Measures of network macroscale

- small-worldness

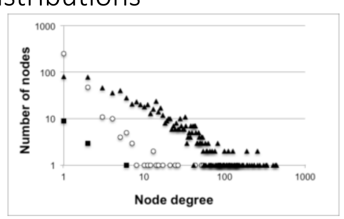
$$\sigma(G) = \frac{C(G)}{L(G)}$$

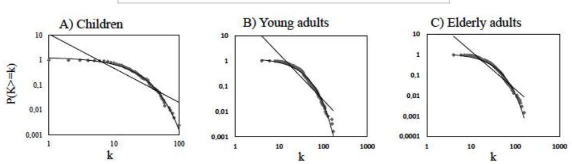


Achard et al., J Neurosci 2006

Measures of network macroscale

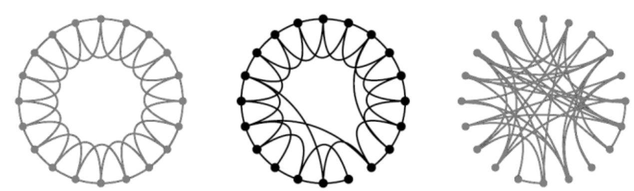
- degree distributions





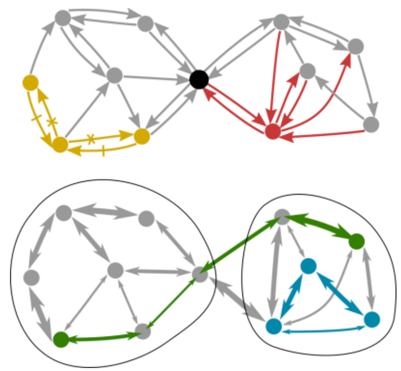
Zortea et al., 2014 79

Nontrivial properties of network topology are claimed through comparisons with reference or "null model" networks



Watts and Strogatz, Nature 1998

Current areas of interest



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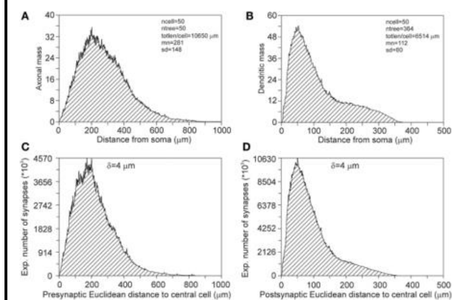
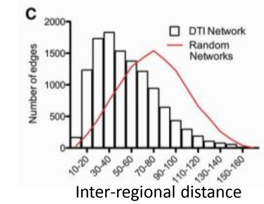
The effect of space

Brain network topology is highly determined by spatial constraints



Pelt and van Ooyenet 2013



Crossley et a. 2014

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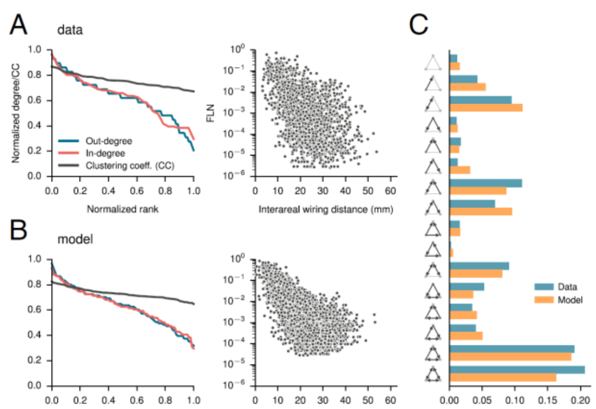
Generative models can improve our understanding of brain organization



Song et al., PNAS, 2014.

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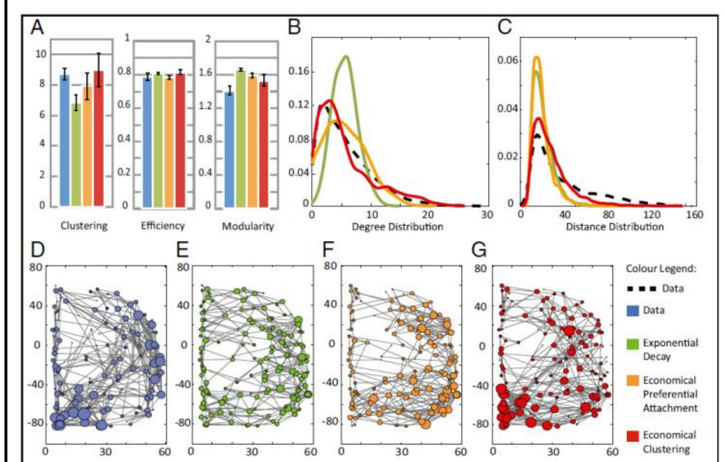

Vertes et al., PNAS 2012

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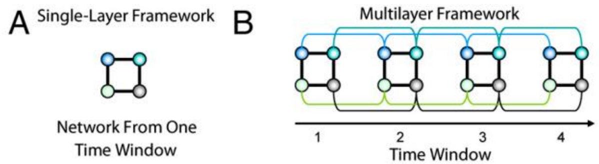
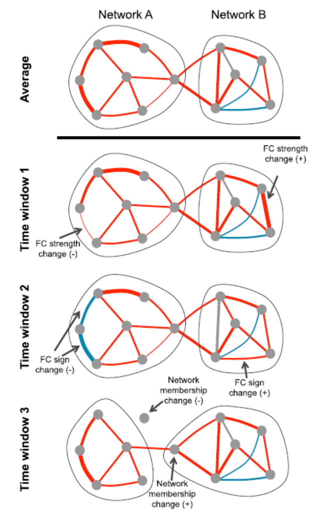
The effect of time

Studies are beginning to capture network states with temporally local measures

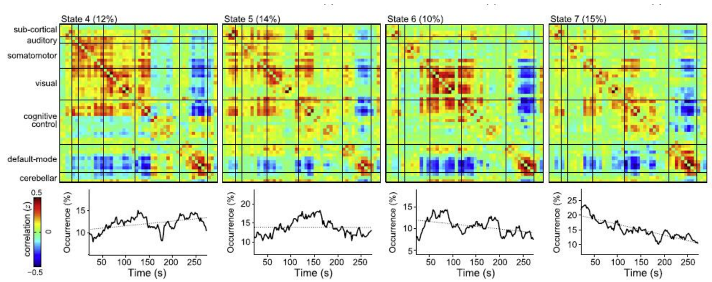


Bassett et al., PNAS 2011



Hutchison et al., 2013

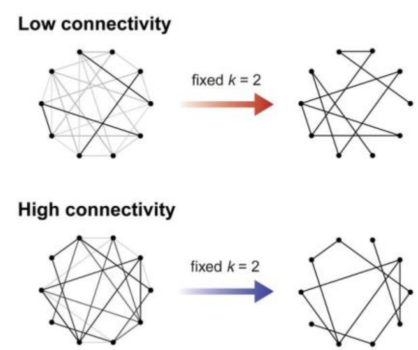
Temporally local measures can capture distinct network states



Hutchison et al., 2013

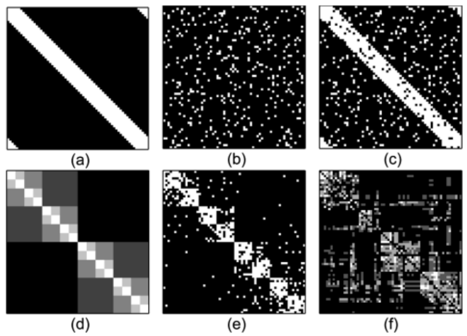
Network comparison is hard

Size and connectivity influence topology



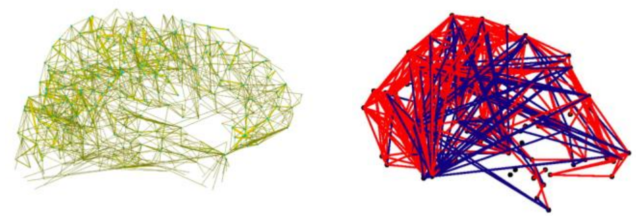
van Wijk et al., PLoS ONE 2010

We need more realistic reference models



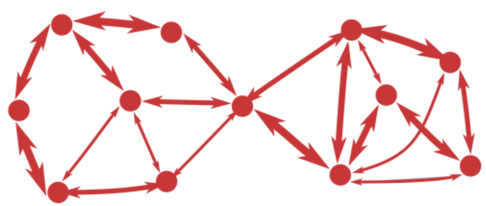
Interpretability can be hard

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



Measures of network macroscale are often too general to be useful

- small-worldness



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").

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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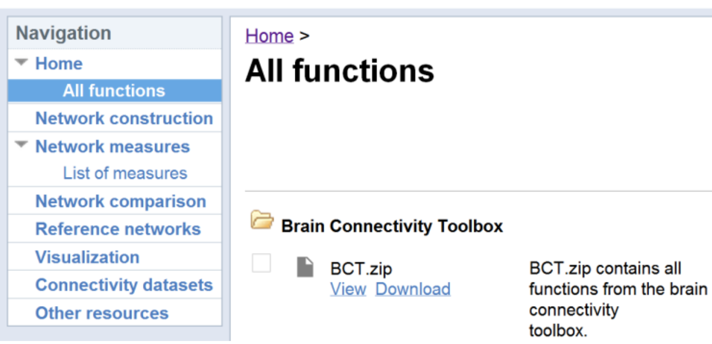
Brain Connectivity Toolbox



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

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Toolbox overview

- MATLAB-based toolbox
- complex-network measures
- network comparison
- control and reference networks
- example datasets

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Literature: see recent (2013-2016) special issues on connectomics and mapping the brain in Nature Methods, Science, Neuron, Trends in Cognitive Science, etc.

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