# The graph model of brain structure and function

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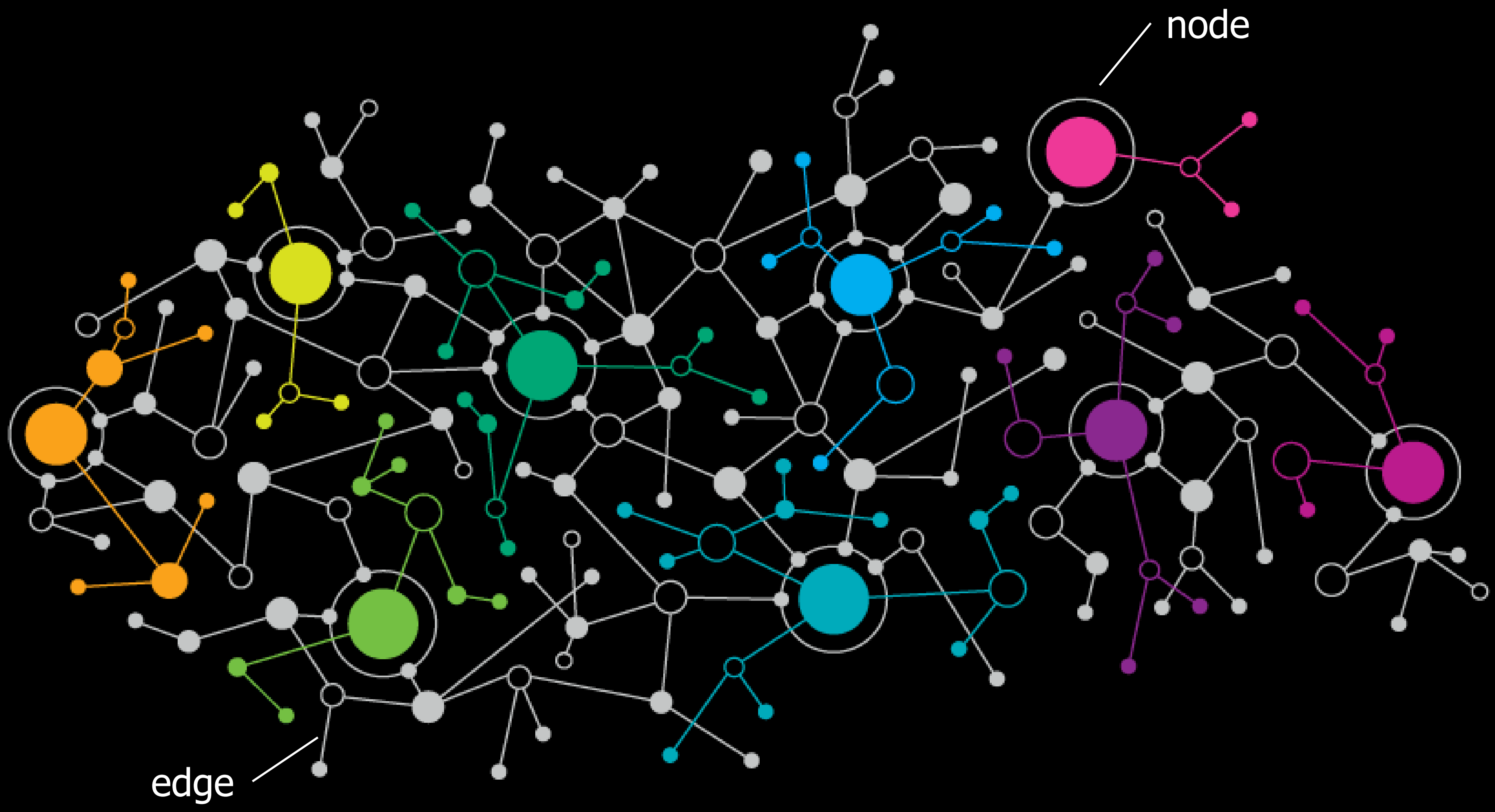
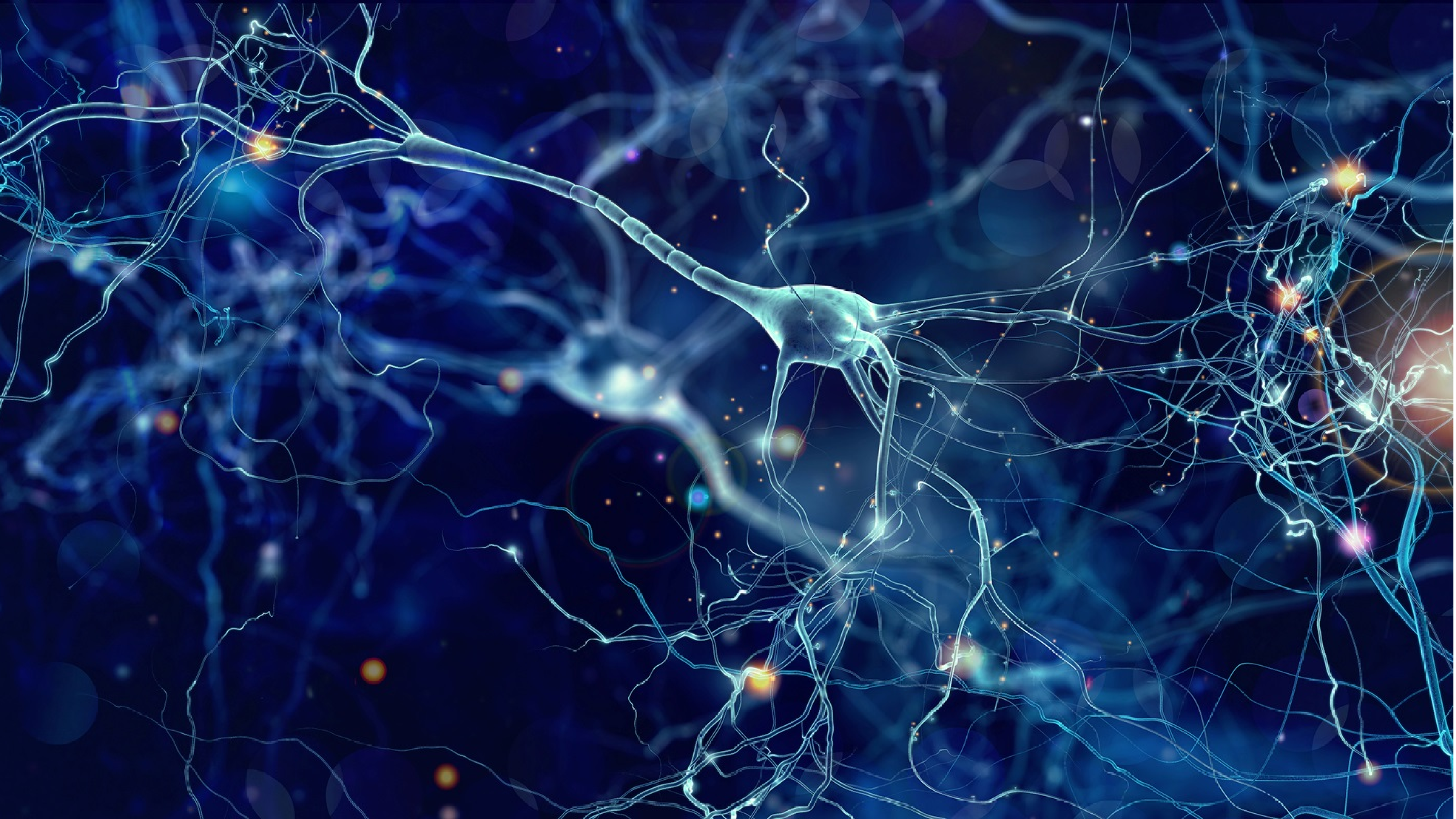
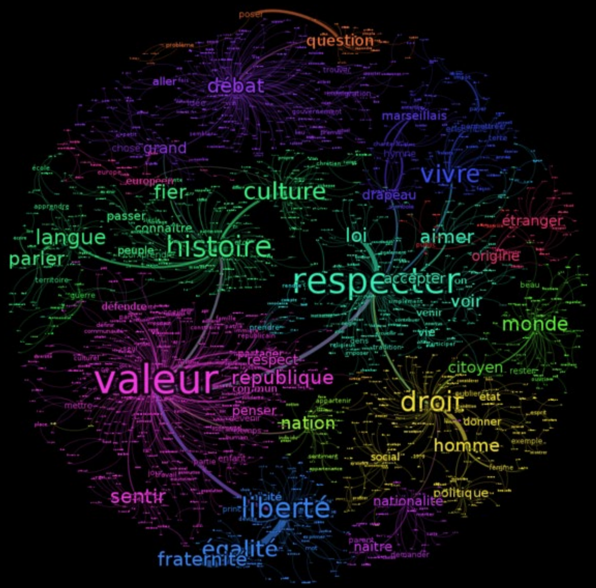
# Outline

- Why networks?
- Reconstructing brain networks
- Organizational principles of brain networks
- Interpretations and assumptions
- New frontiers
- Resources

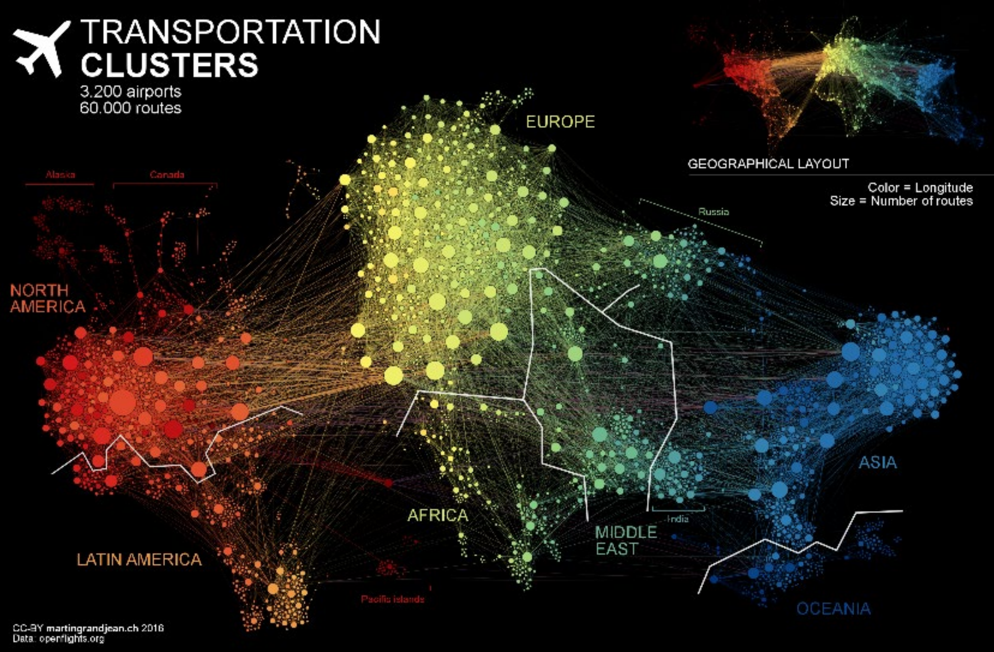

node
edge



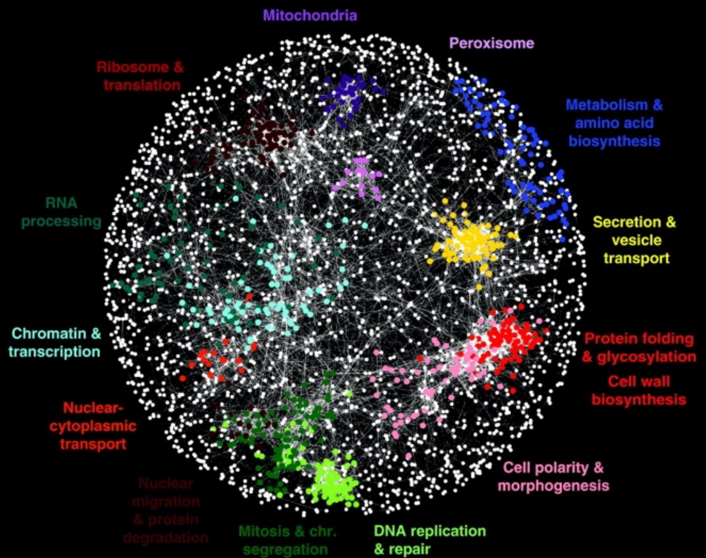



semantic landscapes

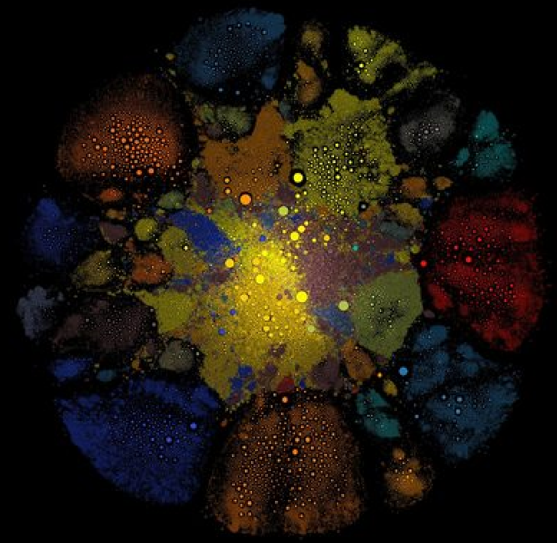
connectomes




airline routes




genetic interactions



gamer alliances

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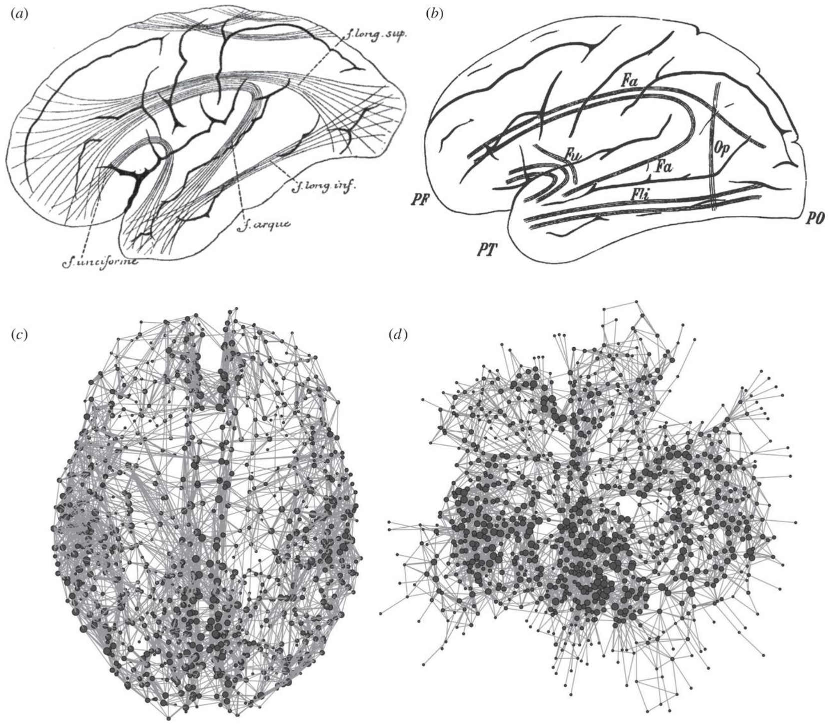
Review

# The Human Connectome: A Structural Description of the Human Brain

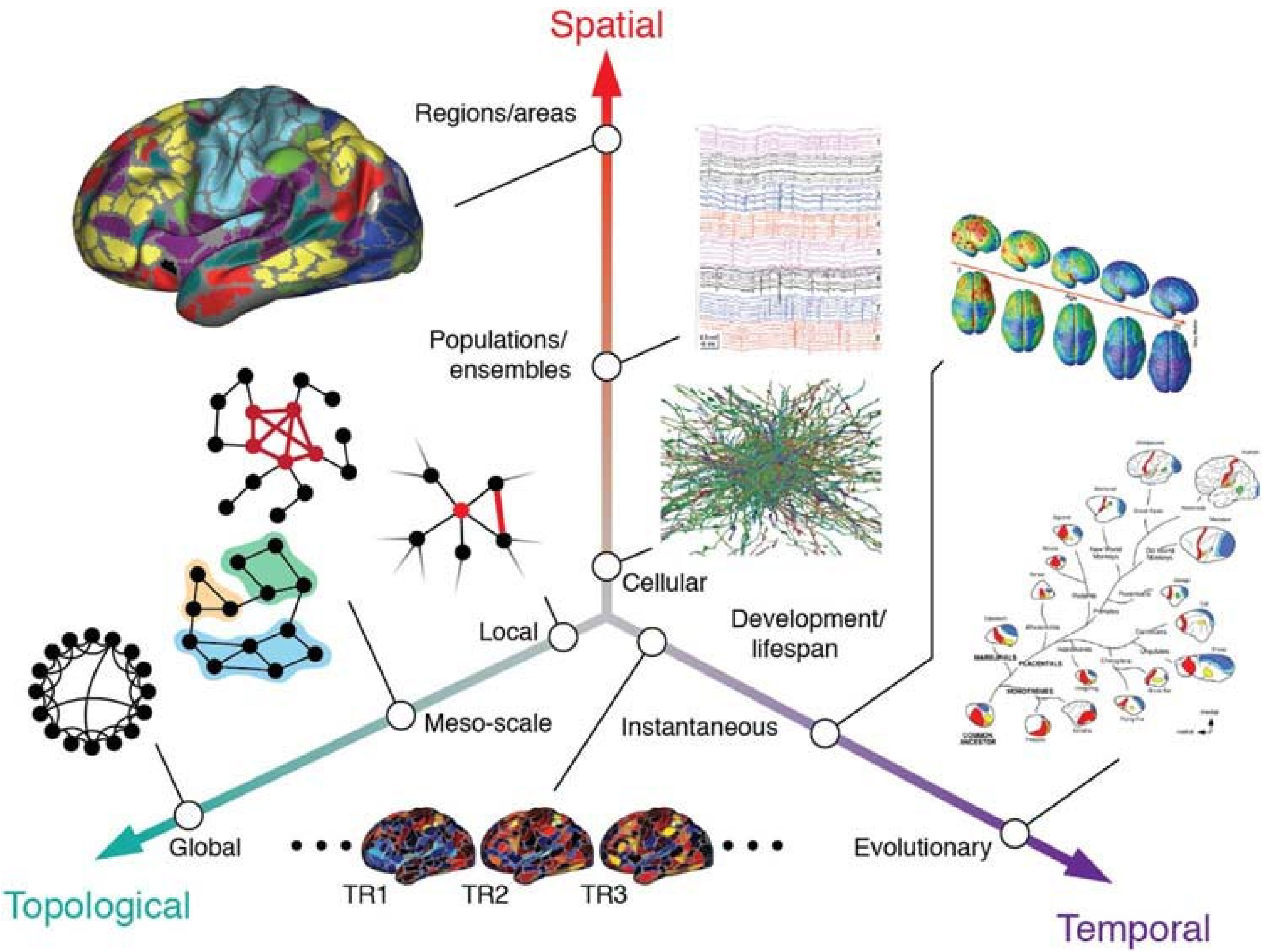
Olaf Sporns*, Giulio Tononi, Rolf Kötter

- connectome: the complete description of neural elements and their connection patterns
- network neuroscience: how to map, record, analyze and model connections and interactions in neurobiological systems
- graph: a set of nodes interconnected by a set of edges
- common framework, shared tools, universal patterns



# Networks offer a common language to study brain function

- Which network elements are important for function?
- Which connection patterns promote integration?
- How do networks reconfigure across time?
- How do individual differences in network organization relate to behaviour?



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# Reconstructing brain networks

structural connectivity (SC)

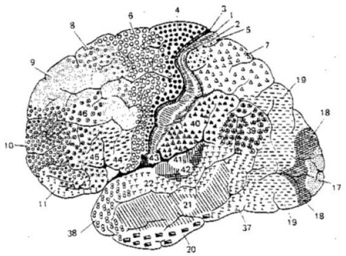
- physical infrastructure
- stable
- sparse

functional connectivity (FC)

- statistical associations
- dynamic
- multiple configurations

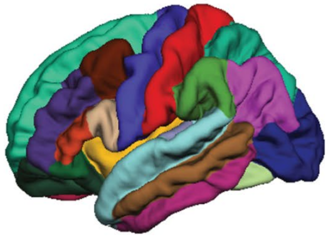
# Defining nodes

cytoarchitecture



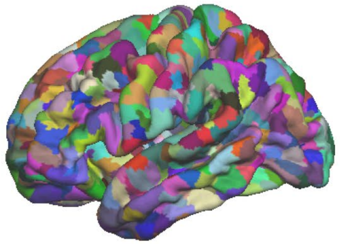
Brodmann (1909)

anatomical



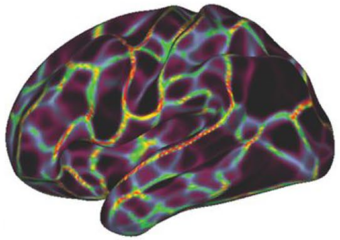
Desikan et al. (2006) NeuroImage
Tzuorio-Mazoyer et al. (2002) NeuroImage

random



Hagmann et al. (2007) PLoS ONE
Zalesky et al. (2010) NeuroImage

functional

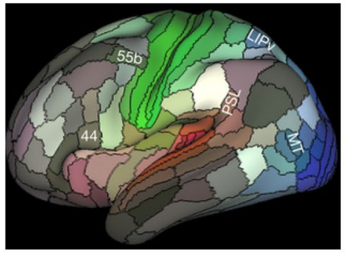


Power et al. (2011) Neuron
Yeo et al. (2011) J Neurophysiol
Gordon et al. (2015) Cereb Cortex

voxel-based

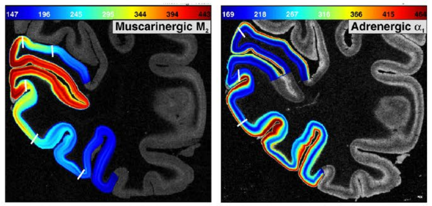
van den Heuvel et al. (2008) NeuroImage
Hayasaka & Laurienti (2010) NeuroImage

multimodal



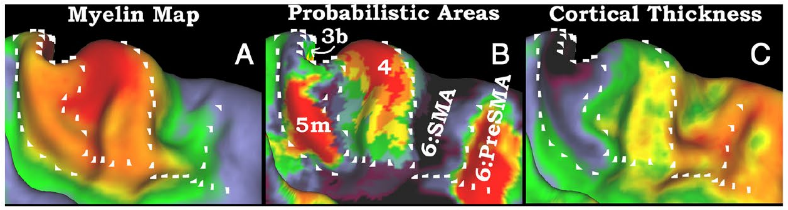

Glasser et al. (2016) Nat Neurosci

autoradiographic

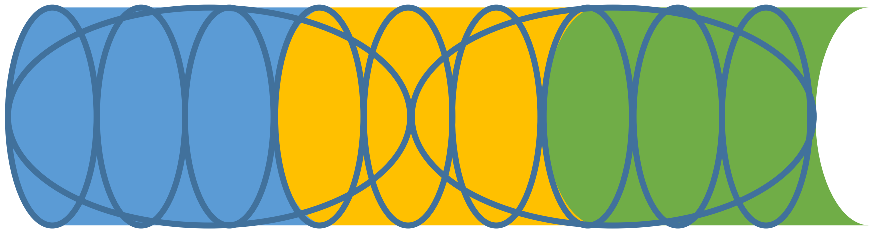



Eickhoff et al. (2007) NeuroImage

myelin




Glasser & Van Essen (2011) J Neurosci



- What is a "good" parcellation?
  - spatially constrained/contiguous
  - internal homogeneity
  - external differentiation
- Depends on scientific question and imaging modality
- Best practice: try multiple parcellations + resolutions

# Representations of brain graphs

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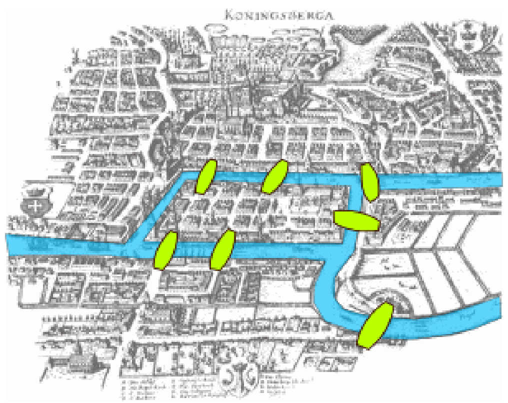
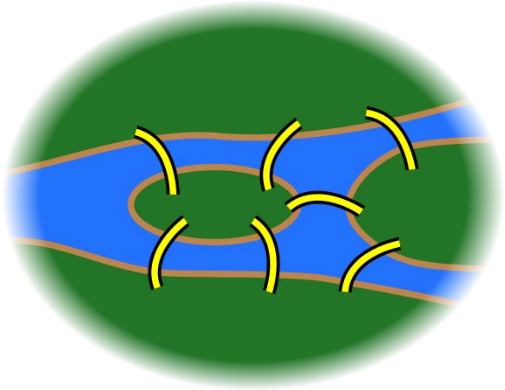
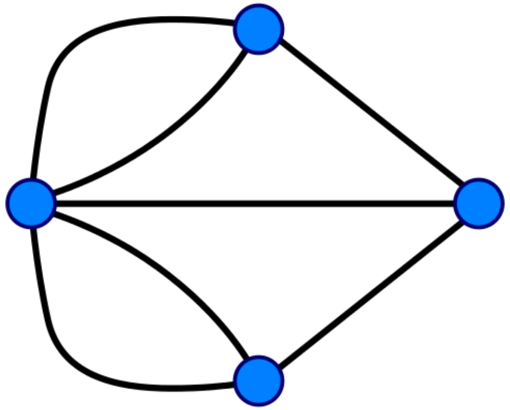
# A short history of network science

- City of Koenigsberg: 2 large islands and 7 bridges
- How to walk through the city so that you cross each bridge only once?



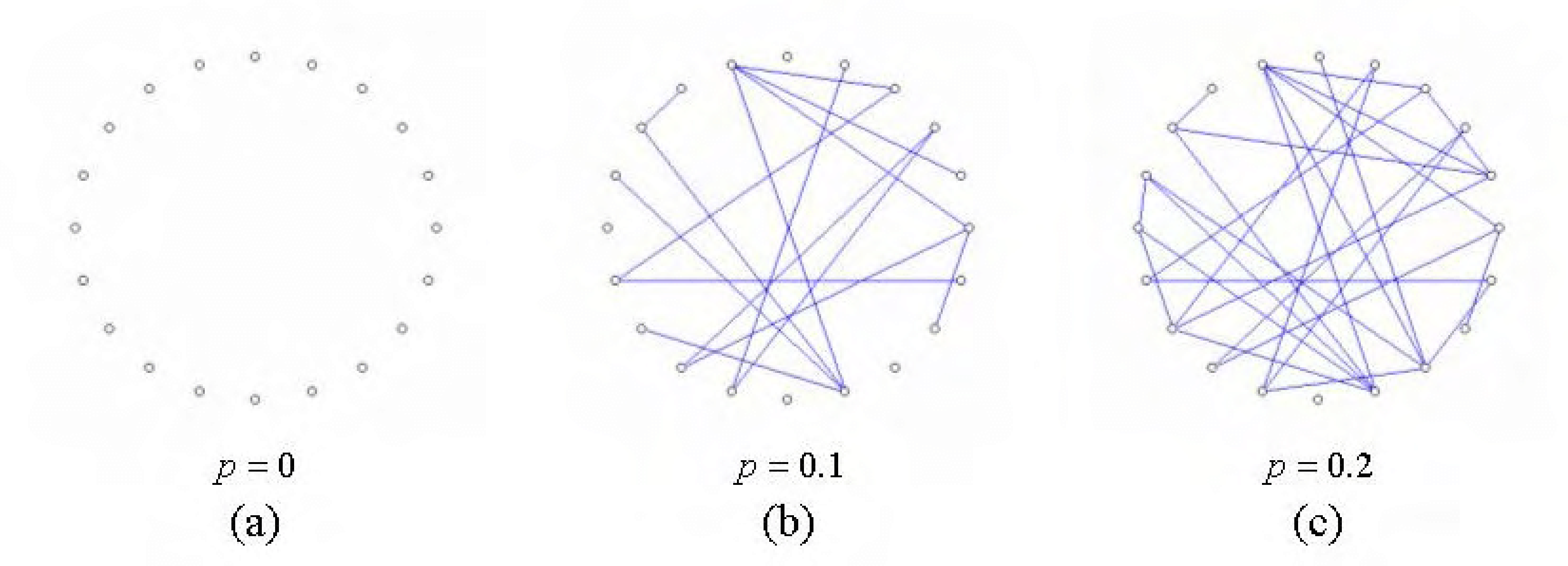




- Euler: abstract away irrelevant detail (topography, streets, etc.)
- Each landmass is a node, and the bridges are edges

Euler (1736) Comment Acad Sci U Petrop

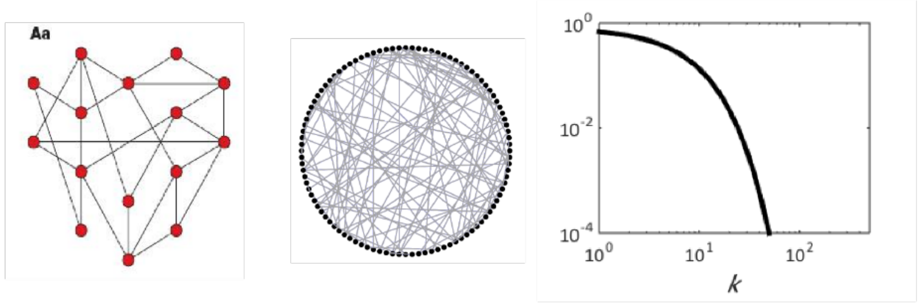
- Erdos-Renyi (ER) graphs
- Probabilistic random graphs: draw edges between nodes at random
- Allows you to derive analytical expressions for various properties of the graph



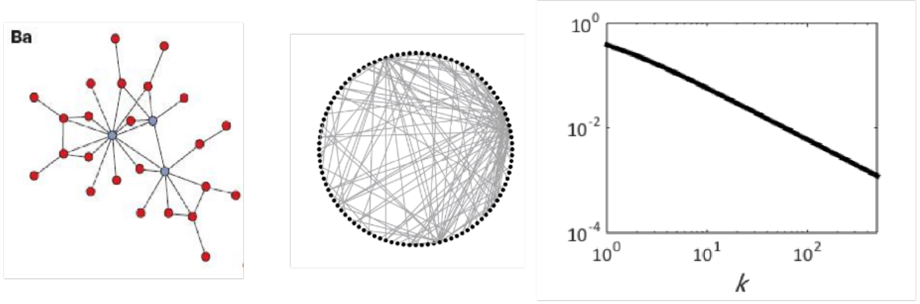

Erods & Renyi (1959) Publicationes Mathematicae

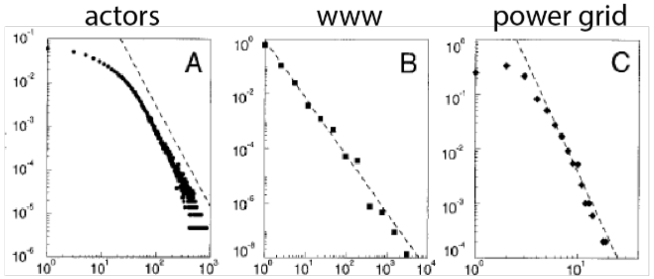
- real-world, naturally-occurring networks show some properties that are non-random
- Barabasi-Albert: degree distributions of many real networks are not Poisson, but instead have a pronounced tail
- Suggests an alternative generative mechanism, e.g. preferential attachment

ER random graph




BA preferential attachment

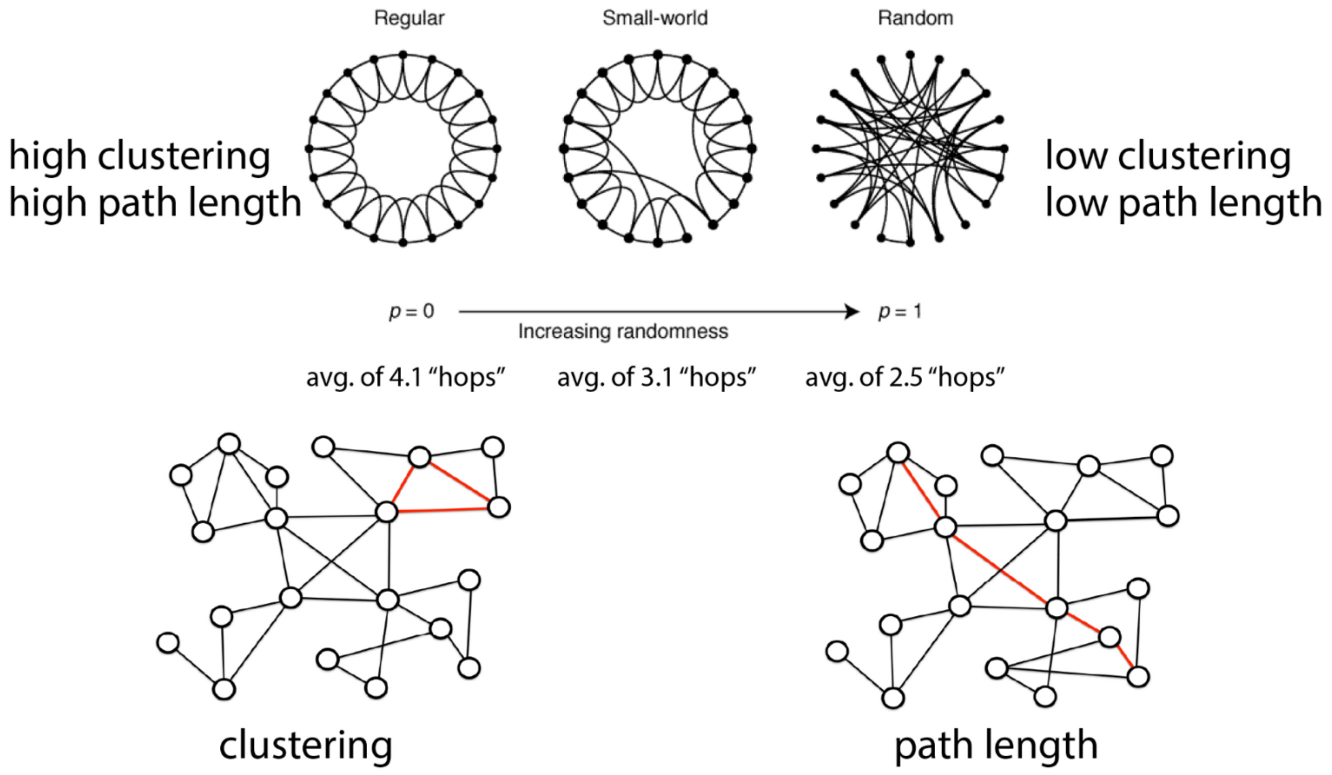


# A short history of network science

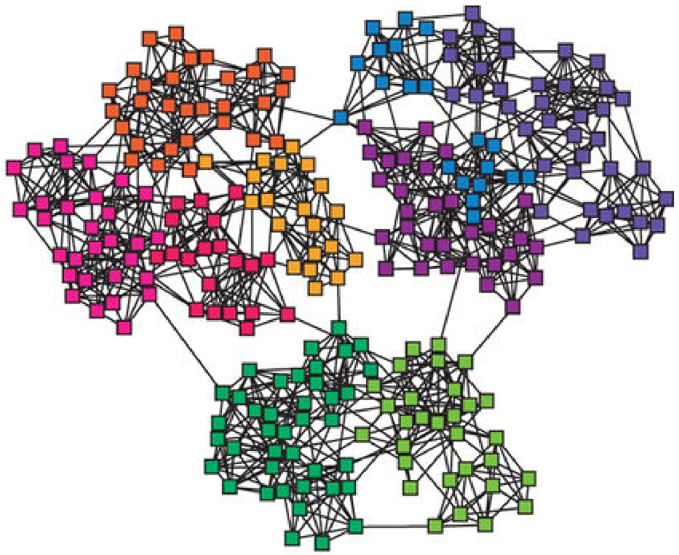
- Small-world regime: highly clustered (like social networks), but you can easily find a path between any two nodes with a short number of hops

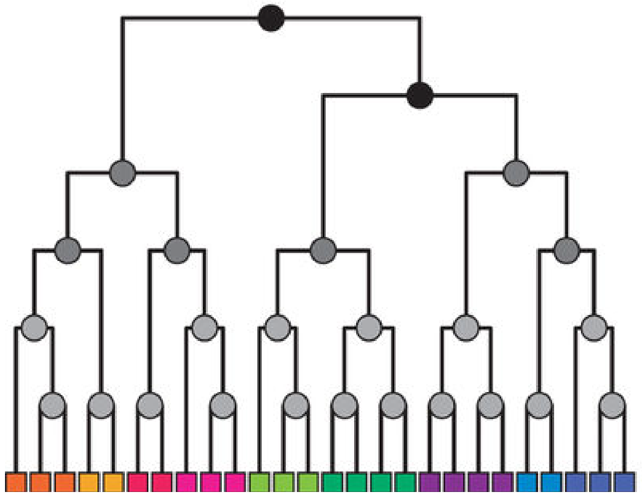
- Many real-world networks have this combination (high clustering, low path length), including C.elegans nervous system



# A short history of network science

- Girvan-Newman: many real-world networks show a modular organization
- Modular or "community" structure is often hierarchichal





Girvan & Newman (2002) Proc Natl Acad Sci USA

Clauset, Moore & Newman (2008) Nature

Brain Connectivity Toolbox

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

# Brain Connectivity Toolbox

Search this site

**Navigation**

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# Home

**Download the Toolbox**

**Getting started**

The Brain Connectivity Toolbox (brain-connectivity-toolbox.net) is a MATLAB toolbox for complex-network analysis of structural and functional brain-connectivity data sets.

**Reference and citation**

Complex network measures of brain connectivity: Uses and interpretations.
Rubinov M, Sporns O (2010) NeuroImage 52:1059-69.

**Brain Connectivity Toolbox in other projects**

The Brain Connectivity Toolbox codebase is widely used by brain-imaging researchers, and has been ported to, included in, or modified in, the following projects:

bctpy: Brain Connectivity Toolbox for Python.
bct-cpp: Brain Connectivity Toolbox in C++.
Human Connectome Project: An NIH consortium for mapping brain white-matter pathways.
Virtual Brain Project: A consortium for simulation of primate brain-network dynamics.
FieldTrip: Advanced analysis toolbox of MEG, EEG, and invasive electrophysiological data.
GraphVar: A user-friendly GUI-based toolbox for graph-analyses of brain connectivity.
Network Based Statistic Toolbox: A toolbox for testing hypotheses about the connectome.
Neuroimaging Analysis Kit: A library of modules and pipelines for fMRI processing.
Graph Theory GLM Toolbox: A GLM toolbox of brain-network graph-analysis properties.
Brainnetome Toolkit: A MATLAB GUI toolkit of complex network measures.

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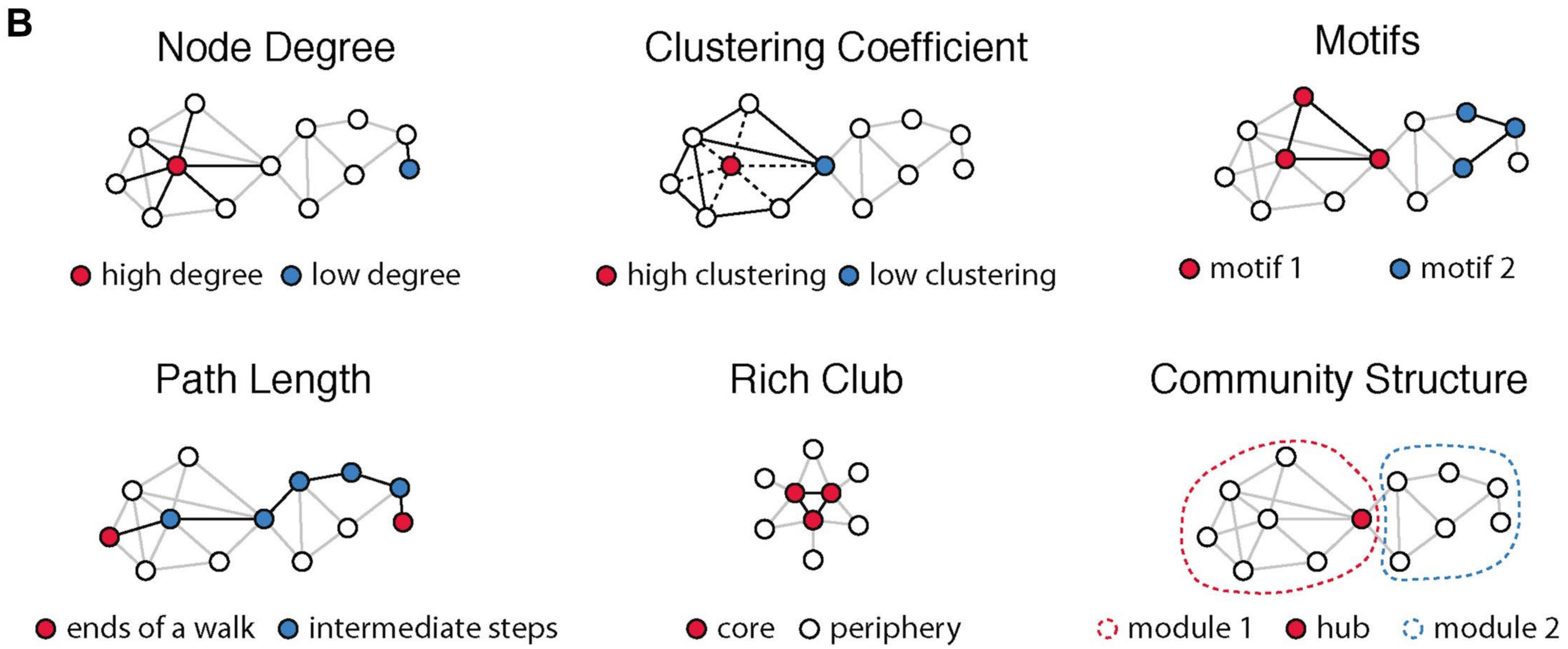
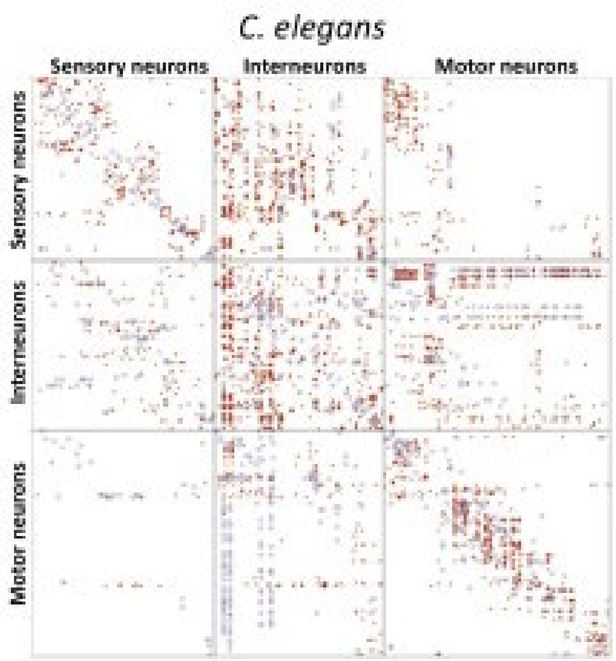
# Network measures

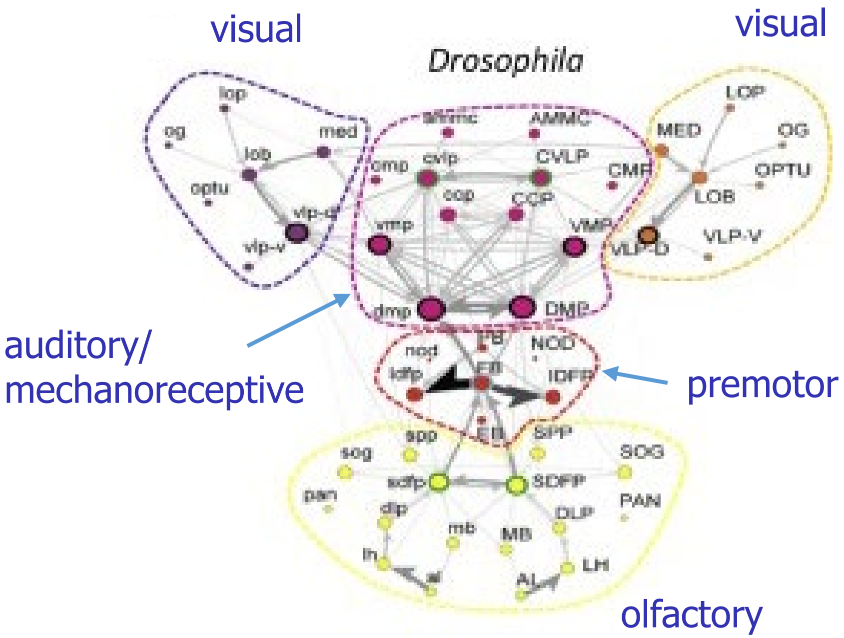


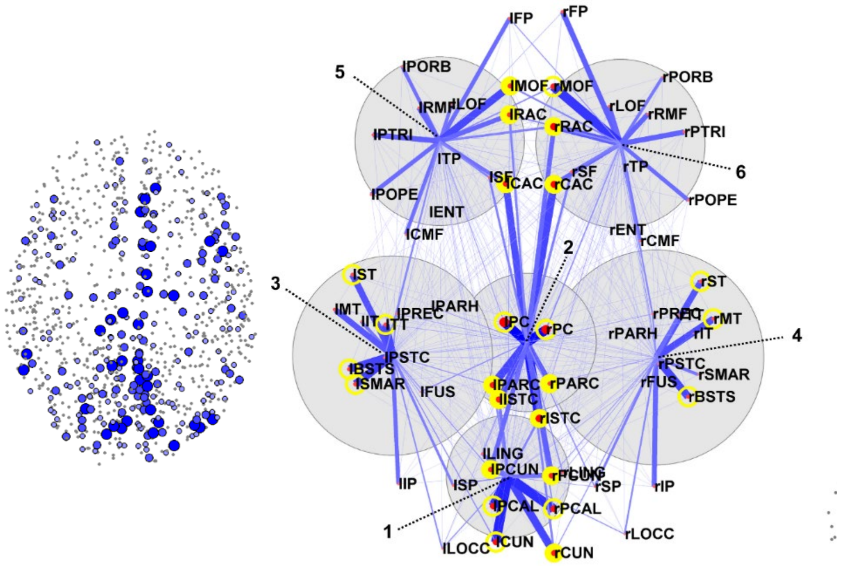

- segregation
  clustering
  motifs
  modularity
- integration
  path length
  efficiency
- influence
  degree
  betweenness
  participation

Rubinov & Sporns (2010) NeuroImage | http://www.brain-connectivity-toolbox.net/

# Network organization relates to functional domains



- Specificity of connection profiles
- High clustering, short path length
- Spatially-contiguous network communities
- Broad, heavy-tailed degree distribution with high-degree hubs
- Densely interconnected rich-club or core

- Highly conserved across species
- Replicable across scales and reconstruction techniques

Varshney et al. (2011) PLoS Comput Biol, Towlson et al. (2013) J Neurosci    Shih et al. (2015) Curr Biol    Bullmore & Sporns (2009; 2012) Nat Rev Neurosci

# Quantifying network architecture

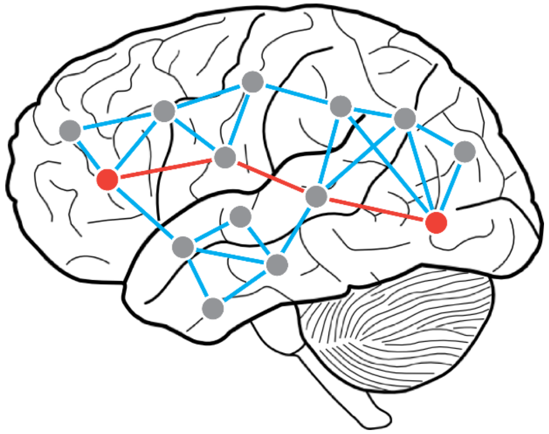
local: the influence of a node or an edge



meso: associations among groups of nodes



global: configuration of the whole network



# Global measures

- density: proportion of possible connections that are actually observed

- a fundamental property – every other property scales with density

- choosing the density:

    - keep as-is
    - match to some "ground truth"
    - set + vary statistically
    - match groups/conditions

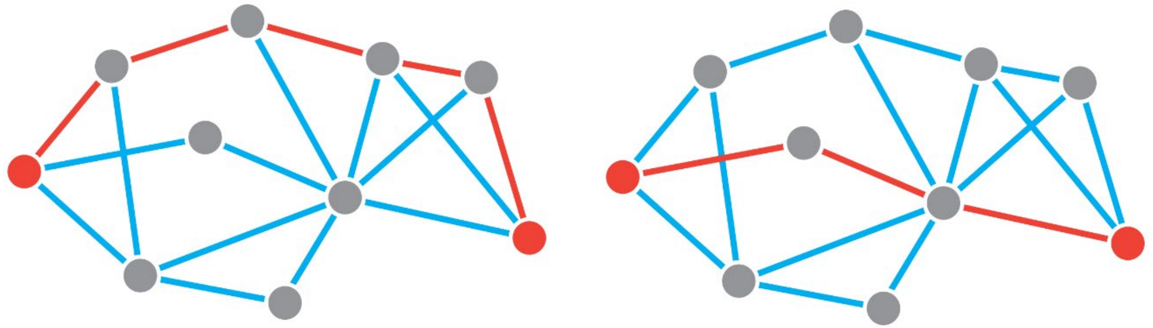
# Global measures

- path: non-repeating sequence of edges between two nodes
- characteristic path length: shortest contiguous set of edges between all pairs of nodes
- global efficiency: average reciprocal path length
- low path length / high efficiency implies greater communication capacity, lower signal attenuation
- assumptions:

(a) propagation occurs via physical connections

(b) signals possess knowledge of global topology

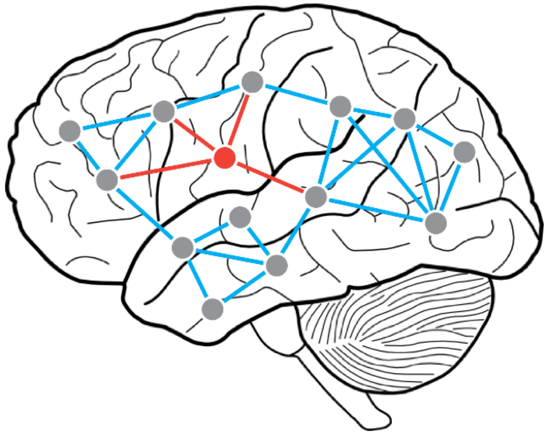
(c) communication utilizes a small proportion of total infrastructure



path length (i,j) = 5        shortest path length (i,j) = 3

# Local measures

local: the influence of a node or an edge



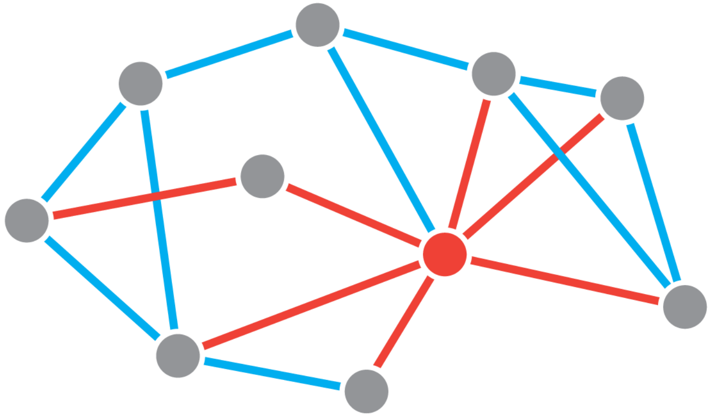
meso: associations among groups of nodes

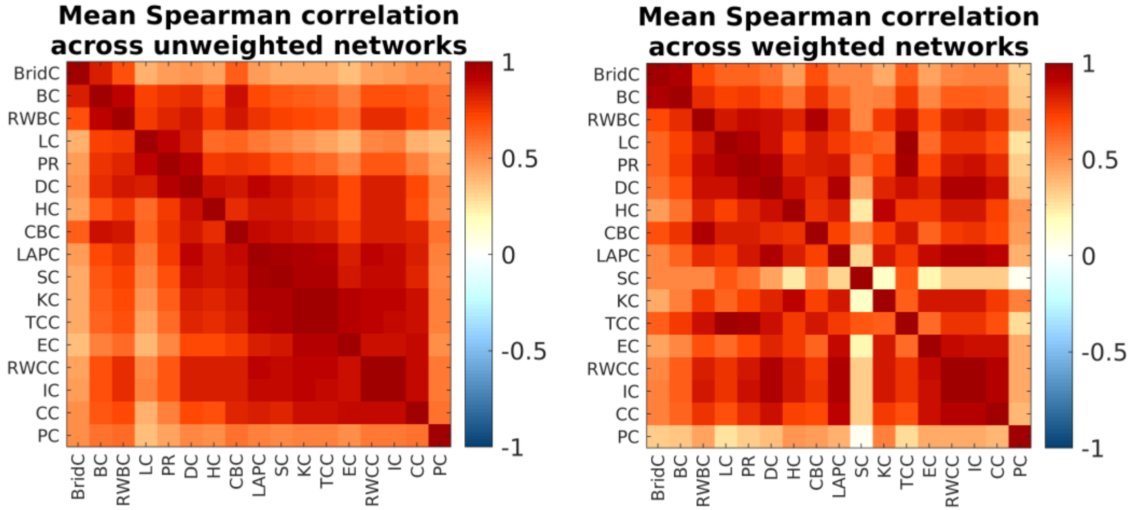


global: configuration of the whole network

# Local measures

- how important is a given network element?
- connectedness: in/out degree, in/out strength
- centrality: betweenness, closeness, eigenvector
- vulnerability: change in capacity following lesion
- most measures have signed analogues
- most measures have edge analogues
- most measures are correlated with degree and with each other
- most measures imply a specific signaling/transport mechanism

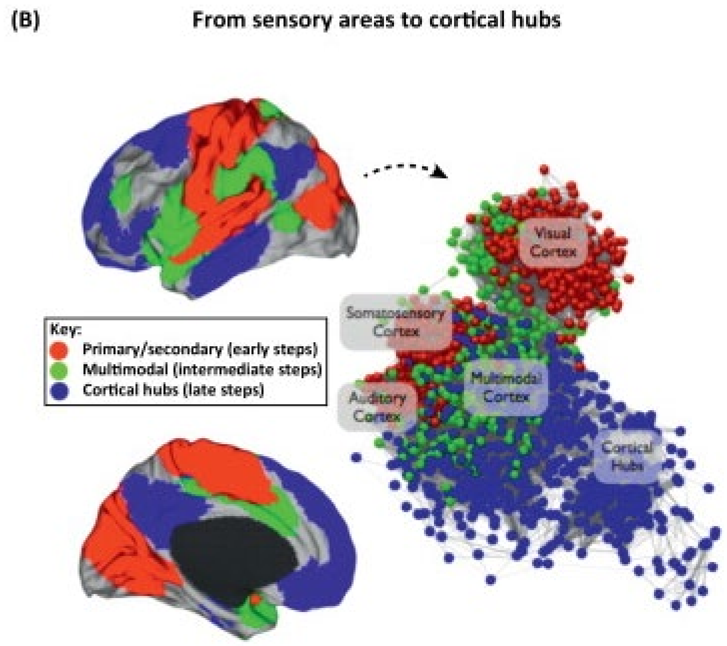





BCT: degrees_und.m | degrees_dir.m | strengths_und.m | strengths_dir.m | betweenness_bin.m | betweenness_wei.m

Oldham et al. (2018) arXiv

# Relationships among central nodes

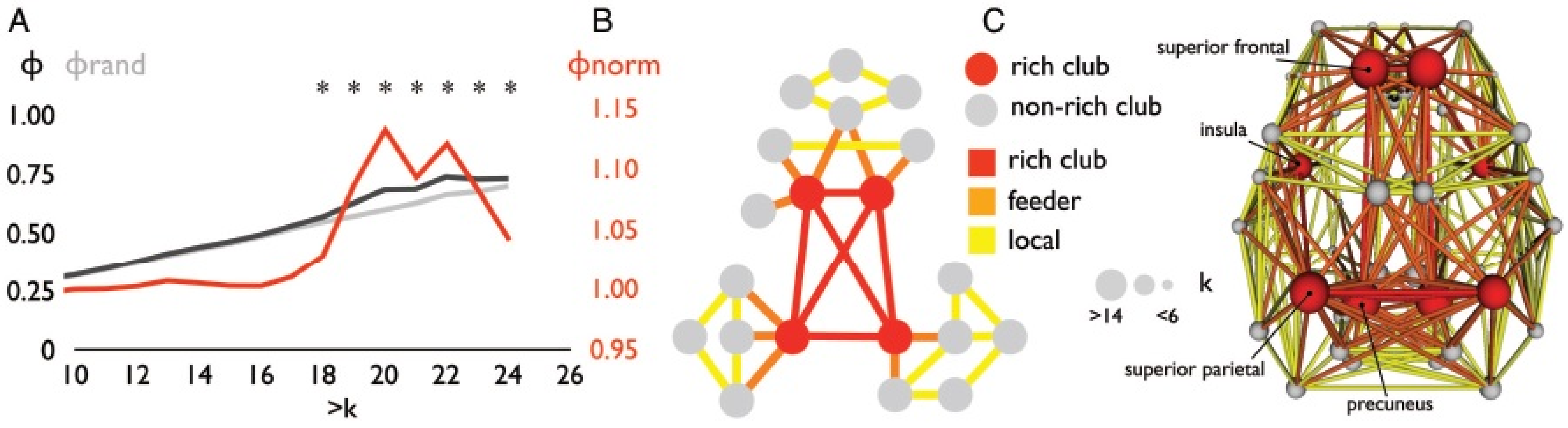



- Central nodes (highly connected, reachable, etc.) tend to be over-represented in polysensory association cortex.
- Now we go up one level: how are central nodes (hubs) related to each other?
- How do hubs sample and exchange information?

Petersen & Sporns (2016) Neuron

Bullmore & Sporns (2009) Nat Rev Neurosci

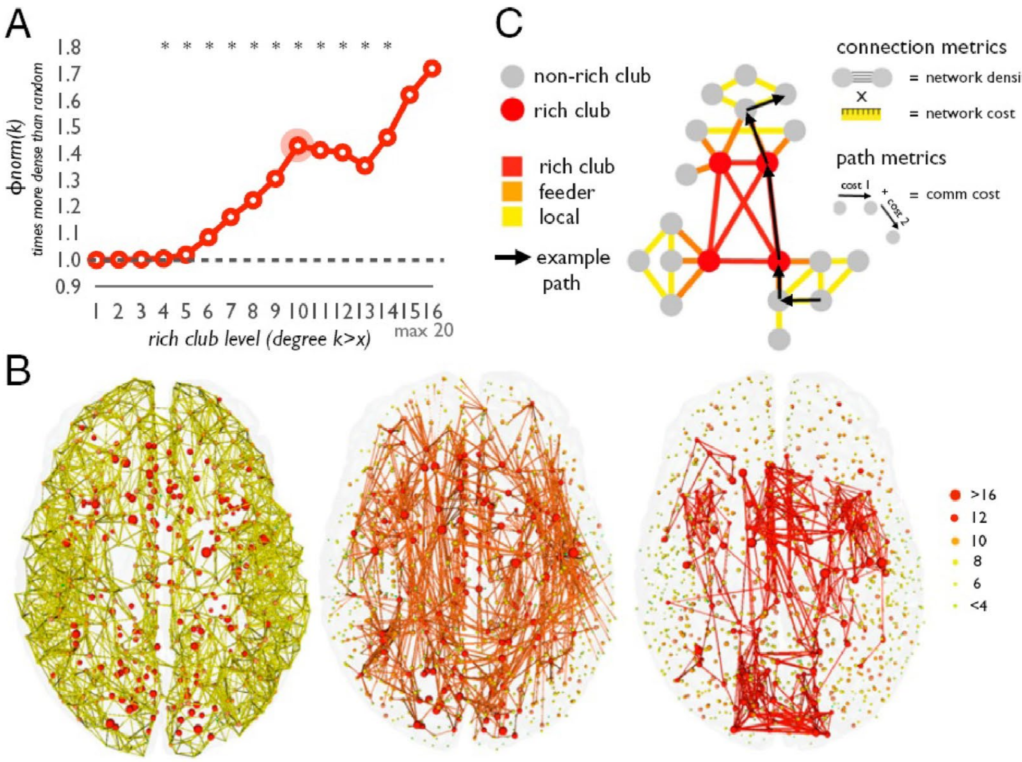
# Relationships among central nodes

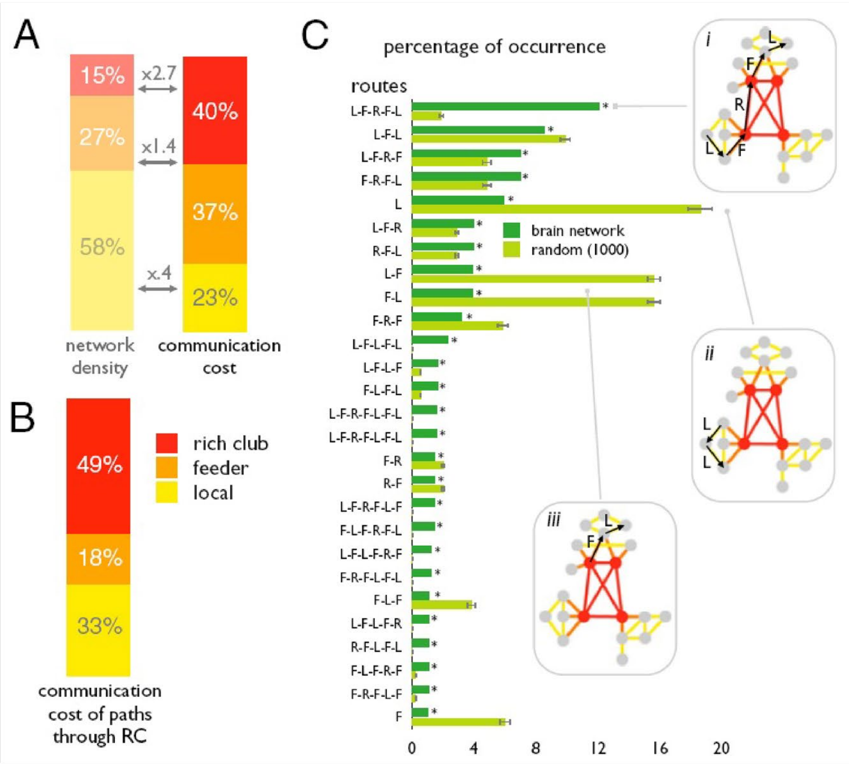



degrees

- Rich club: a collective of high-degree nodes that are more densely interconnected with each other than expected by chance

1. Prune nodes with progressively higher degrees (k) to create subgraphs
2. Compare density of remaining subgraph with a null model



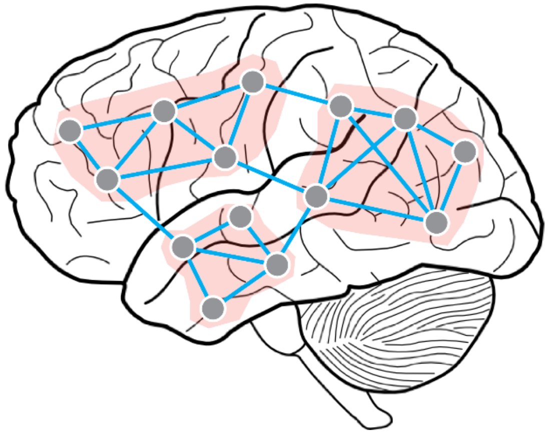

- Rich-rich and rich-peripheral (feeder) connections are more expensive (long distance) than connections between spatially neighbouring, topologically peripheral nodes, but:
- High proportion (89%) of communication paths pass through at least one RC node (66% through an RC edge)
- L-F-R-F-L is most commonly occurring path motif → rich club acts as a 'backbone' for communication

# Local measures

local: the influence of a node or an edge



meso: associations among groups of nodes



global: configuration of the whole network

# Meso-scale structure

- meso-scale structure is rarely visually apparent

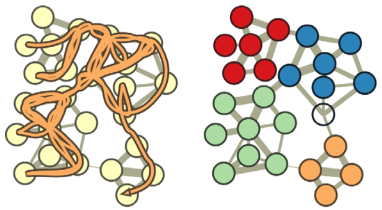
- modules or communities must be detected algorithmically
  - user must specify criteria (i.e. what is a community?)
  - user must specify detection algorithm
  - user must specify parameters and validate

- communities: groups of nodes whose observed density of connections is maximally greater than expected by chance

- high-quality partitions concentrate the strongest elements of B within communities

# Community detection

- many potential algorithms and heuristics:
  - agglomerative clustering
  - spectral clustering
  - simulated annealing
- in brain imaging, modularity-maximization algorithms (e.g. the 'Louvain' algorithm) are particularly popular

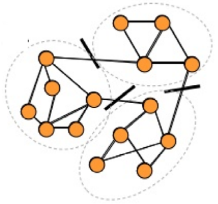


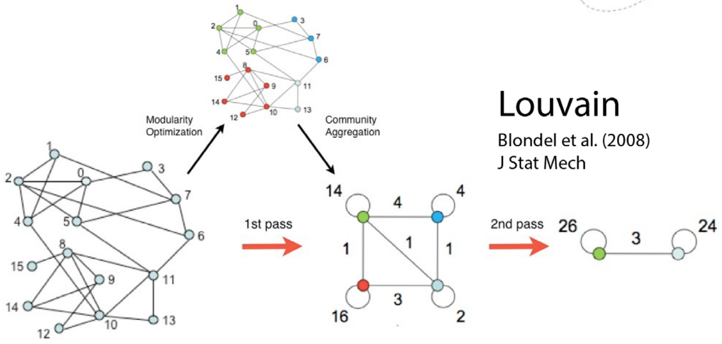
walktrap

Rosvall & Bergstrom (2008)
Proc Natl Acad Sci USA

Girvan-Newman

Girvan & Newman (2002)
Proc Natl Acad Sci USA






Louvain

Blondel et al. (2008)
J Stat Mech

modularity function: the quality of a given partition $c$

Kronecker delta function is 1 when $c_i = c_j$, and 0 otherwise

$$Q = \sum_{ij} [A_{ij} - P_{ij}] \delta(c_i, c_j)$$

community assignment of node i

observed connection weight between nodes $i$ and $j$

expected connection weight between nodes $i$ and $j$

- keep a running sum for all node pairs
- if two nodes are in the same community, compute the difference between observed and expected, and add to sum
- the final value of $Q$ is a measure of how prominent or statistically unexpected the within-community connections are

BCT: community_louvain.m

Newman & Girvan (2004) Phys Rev E

Fortunato (2010) Phys Rep

# Multi-scale modularity

$$Q = \sum_{ij} [A_{ij} - P_{ij}]\delta(c_i, c_j) \longrightarrow Q(\gamma) = \sum_{ij} [A_{ij} - \boxed{\gamma} P_{ij}]\delta(c_i, c_j)$$

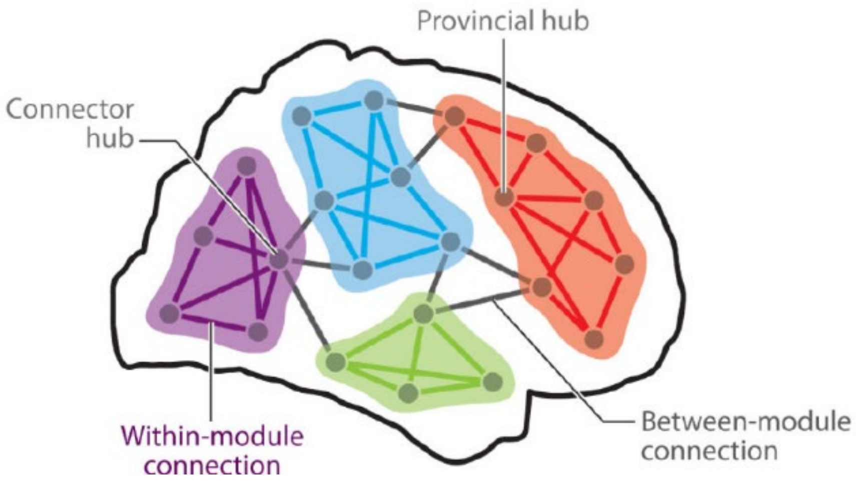
- Introduce a “resolution” parameter ($\gamma$) that weighs the importance of the null model
- Low values make it more likely to identify large communities
- High values make it more likely to identify small communities

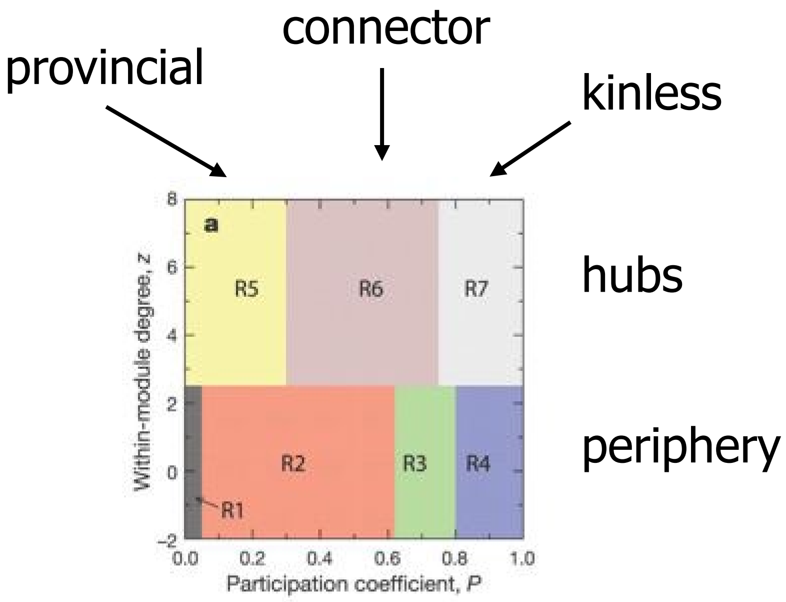
Fortunato & Barthelemy (2007) Proc Natl Acad Sci USA

Sporns & Betzel (2015) Annu Rev Psychol

Reichardt & Bornholdt (2010) Phys Rev E

# Identifying influential nodes




- Is a node more/less connected than other nodes in the same community?

$$z_i = \frac{\kappa_i - \bar{\kappa}_{g_i}}{\sigma_{g_i}}$$

- Are a node's links distributed across communities or concentrated within?

$$P_i = 1 - \sum_{g=1}^{M} \left( \frac{\kappa_{ig}}{k_i} \right)^2$$

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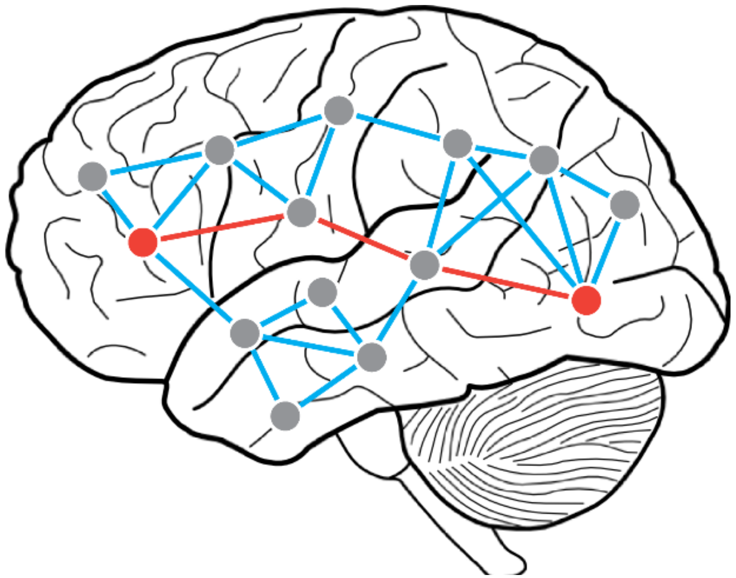
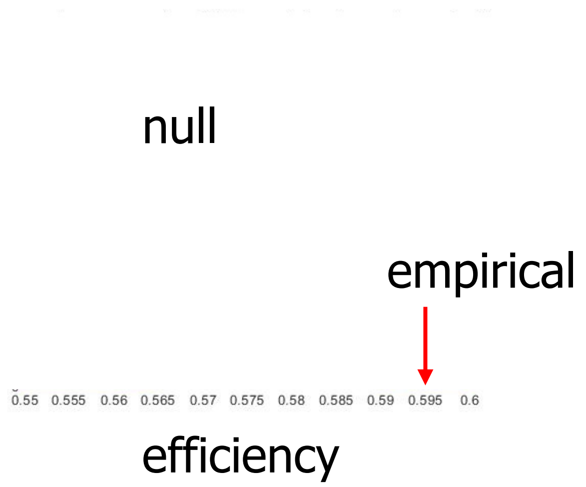
# Interpretations and assumptions

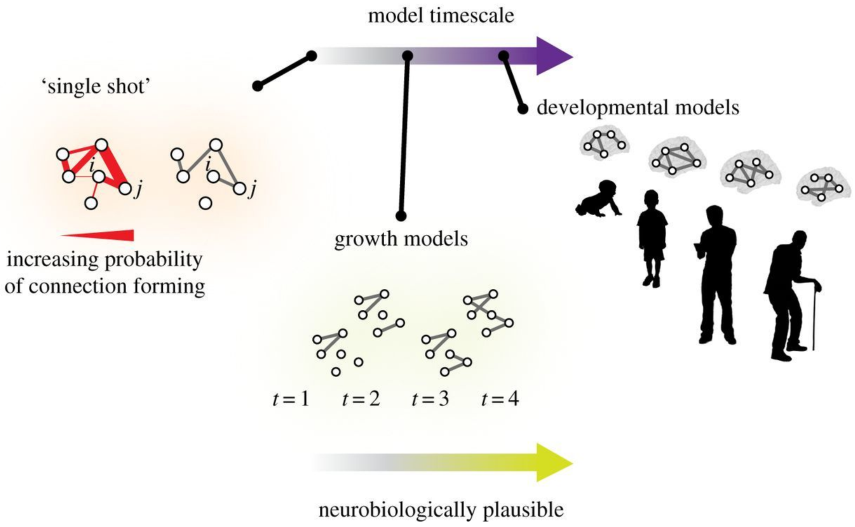
- Network measures are relative – how do you know that property X is special? Is X specific to your network?
  - Example: *efficiency* = 0.5
- Many properties depend on simple features such as the number of nodes, the mean node degree or the density of the network
- Topological differences between organisms, groups or conditions may be masked or over-emphasized by trivial differences in these basic features
- Key questions:
  - Is this property statistically unexpected?
  - Is this property biologically meaningful?



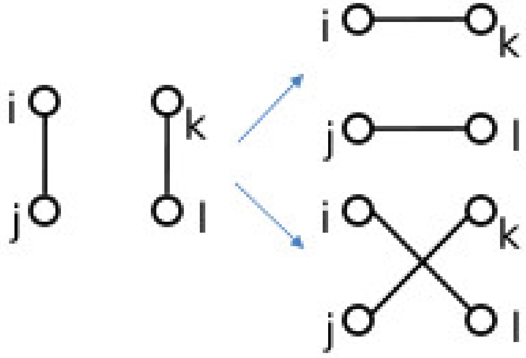
# Null models

- Null model: systematically disrupt topology, but retain other properties (e.g. density, degree, etc.)
- Use this process to build up a null distribution for property X. Benchmark/reference your empirical network against this null




generative model: generate a network using a small set of wiring rules




rewiring model: rewire the empirical network under some constraints

# Rewiring models

- Start with empirical network, fix some properties and randomize other by rewiring connections with constraints

- Maslov-Sneppen degree-preserving rewiring:
  - randomly swap pairs of connections
  - systematically disrupts topology, but retains density and degree sequence

- Null models may additionally control for geometry, wiring cost, directionality, etc. → allow you test a range of hypotheses



Maslov & Sneppen (2001) Science

# Rewiring models

- Null models (esp. degree-preserving rewiring) have been subsumed into many fundamental network measures and definitions
  - small-world property: ratio of 'normalized' clustering and path length

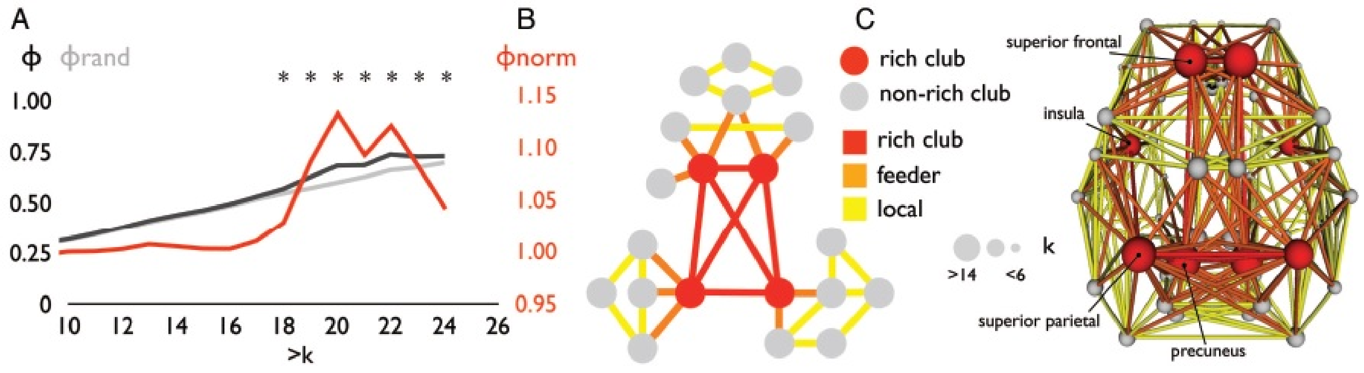
$$\sigma = \frac{C/C_r}{L/L_r}$$

  - rich club property: high degree hubs that more likely to be connected with each other than 'expected'

$$\phi_{norm} = \frac{\phi}{\phi_{rand}}$$

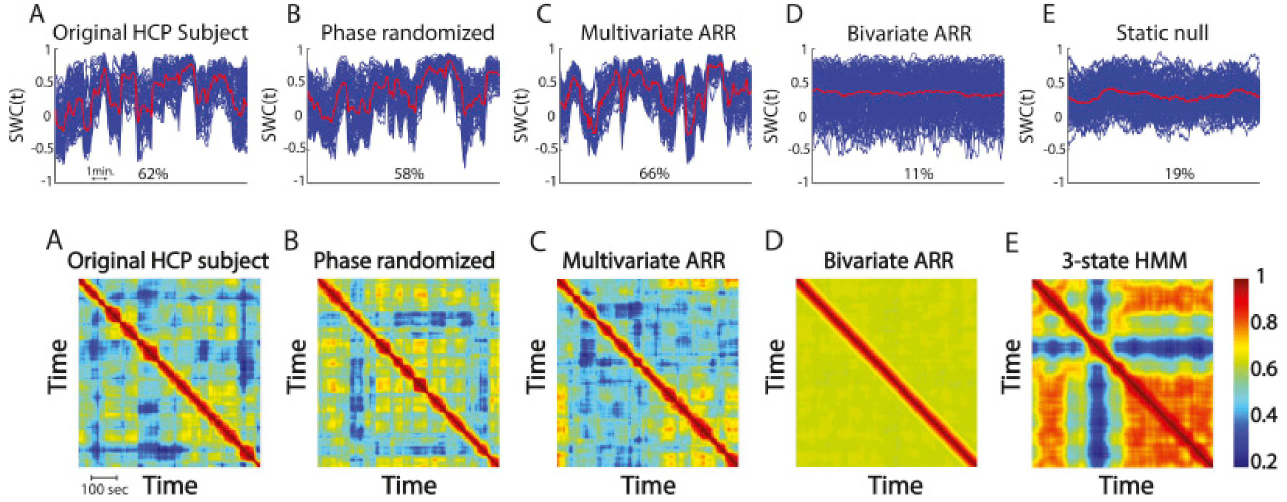
  - modularity: communities of nodes with greater than 'expected' connectivity

$$Q = \sum_{ij} [A_{ij} - P_{ij}]\delta(c_i, c_j)$$



# Null models for correlation-based networks

- Functional networks describe correlations/covariances arising from an underlying dynamical system
- Correlations are transitive: values of A-B and A-C are not independent of B-C
- Edge-swapping null models of FC networks may generate topologies that could never naturally arise from correlations
- Phase-randomized surrogates: preserve power spectra but randomize phases
- Autoregressive surrogates: preserve lagged correlation structure

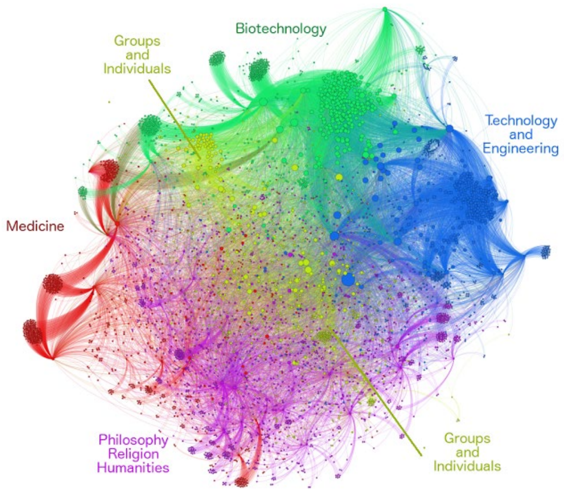



Zalesky et al. (2012) NeuroImage

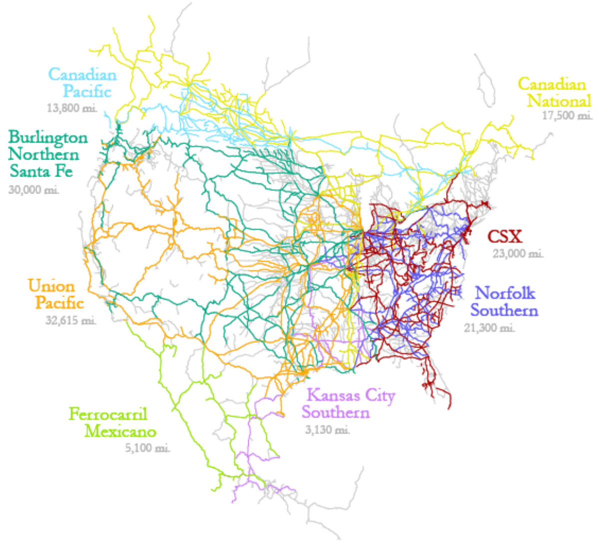
Ligeois et al. (2017) NeuroImage

# Spatial models

- A lot of methods in graph theory come from purely topological networks, where there is no cost to placing connections
- The brain is a spatially-embedded, energy-consuming system with finite resources
- Placing connections in spatially-embedded systems requires space, material and energy



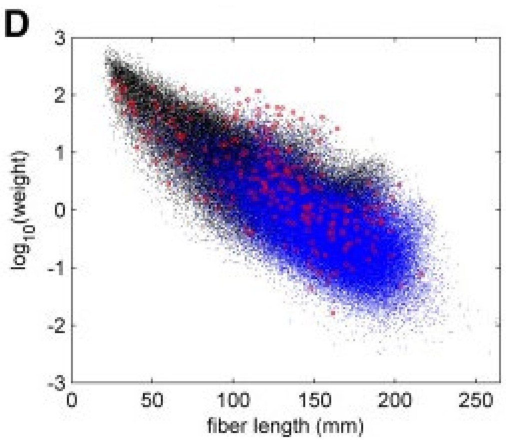

wikipedia



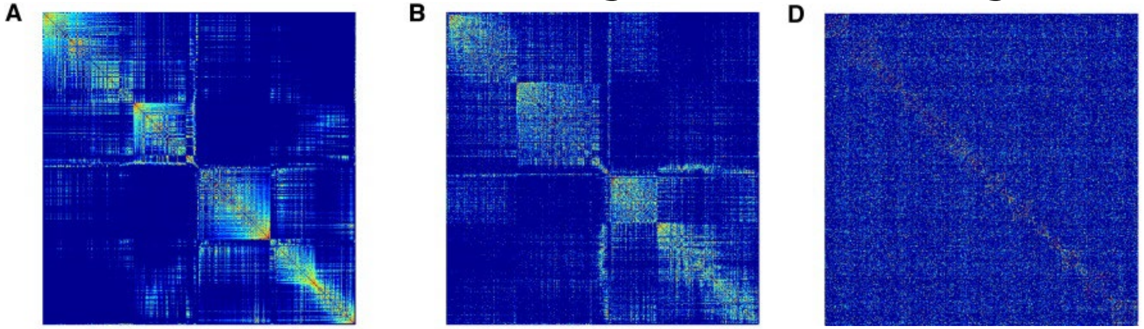

railway

# Spatial models

- Probability of connection and weight of connection between neural elements decrease monotonically with spatial separation
- Decrease is roughly exponential
- Wiring rule: set node positions, add connections with probability that decreases with distance $\mathrm{P}(i,j) \propto \mathrm{d}(\mathrm{i},\mathrm{j})$ (e.g. $\mathrm{P}(i,j) \propto e^{-d(i,j)}$ )
- Simple distance penalties can reproduce many basic properties




real network | geometric surrogate | random surrogate

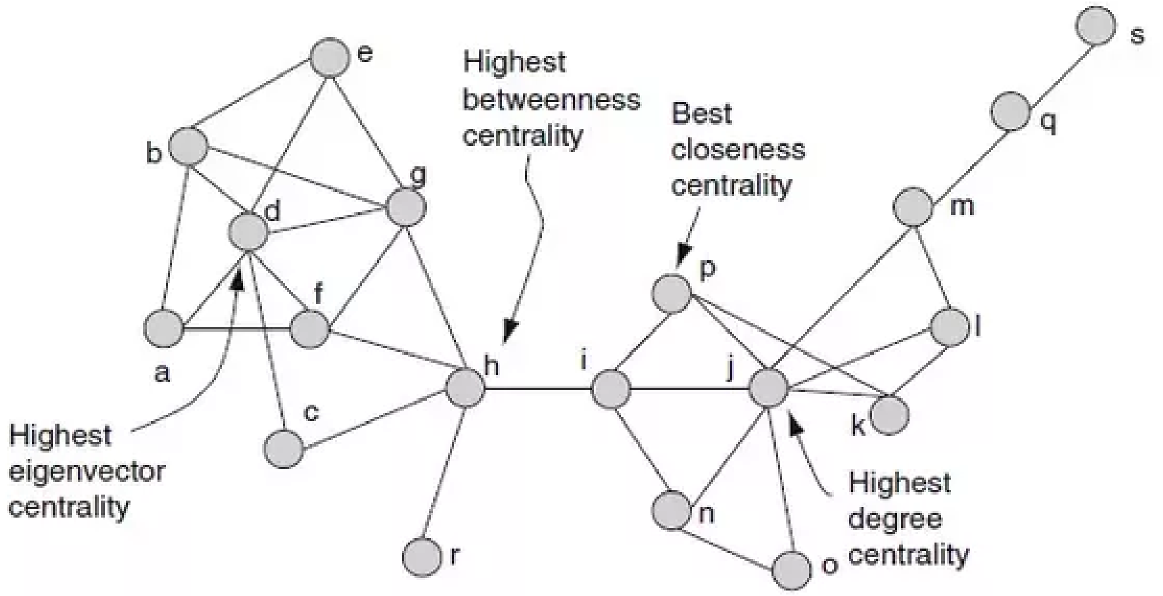



Horvat et al. (2016) PLoS Comput Biol

Roberts et al. (2016) NeuroImage

# Checking assumptions

- Most measures entail assumptions about how the network functions
- Example #1: the importance of a node depends on the dynamic processes unfolding on the network



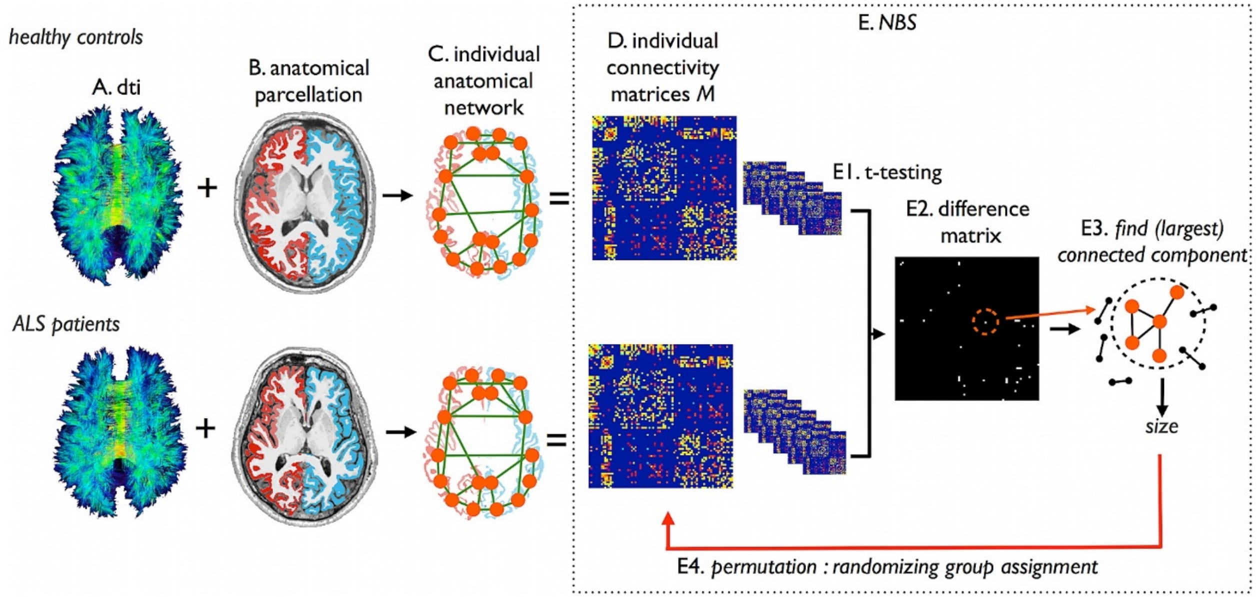

- Example #2: the types of communities (i.e. subnetworks) you find depend on the type of architecture you assume is present

# A case for simpler measures

- Systematic changes in a simple local properties (e.g. a single connection) can manifest in more complex global measures and properties

- It is important to verify why network properties change, and to justify why a complex measure (e.g. efficiency) is required over a simpler measure (e.g. degree)

- Ideally, a topological analysis should be accompanied by a statistical analysis to pinpoint origin (e.g. Network Based Statistics; NBS)




Zalesky et al. (2010) NeuroImage

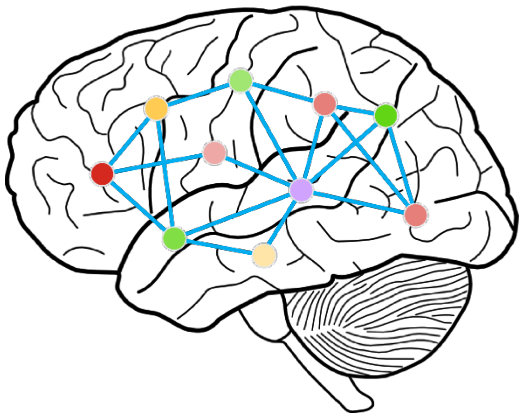
Verstraete et al. (2011) PLoS ONE

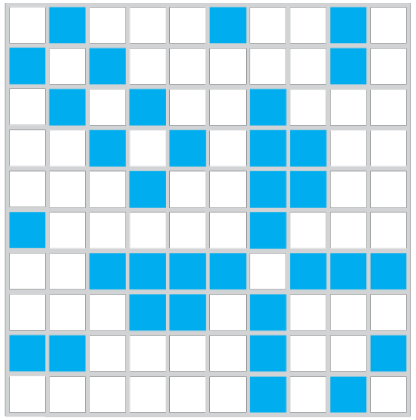
# Outline

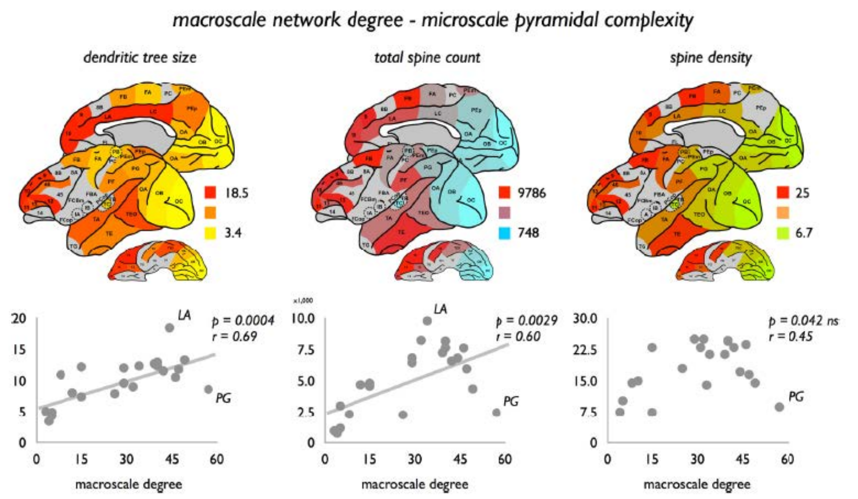
- Why networks?
- Reconstructing brain networks
- Organizational principles of brain networks
- Interpretations and assumptions
- New frontiers
- Resources

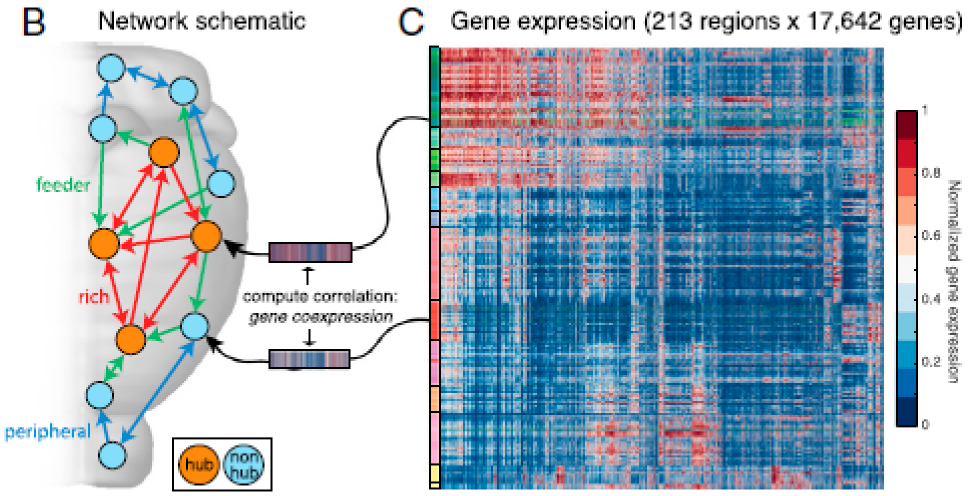
# Relating local and global properties

- in a graph representation, all nodes are the same
- BUT: brain areas differ in cytoarchitectonics, morphology, receptor profile, gene expression, temporal dynamics, etc.
- increasing focus on annotated graphs







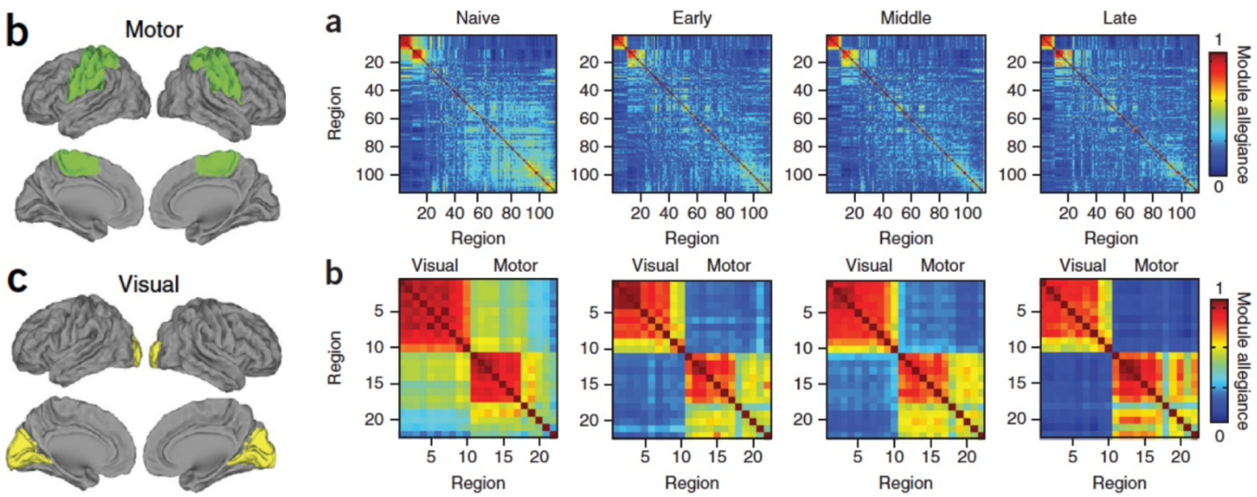

Khambati et al. (2017) NeuroImage

Scholtens et al. (2014) J Neurosci

Fulcher & Fornito (2015) Proc Natl Acad Sci USA

# Dynamic networks

- Network interactions evolve across multiple time scales
- Many network properties can be extended to multi-layer networks
- Example: increasing autonomy of sensory and motor systems during motor learning

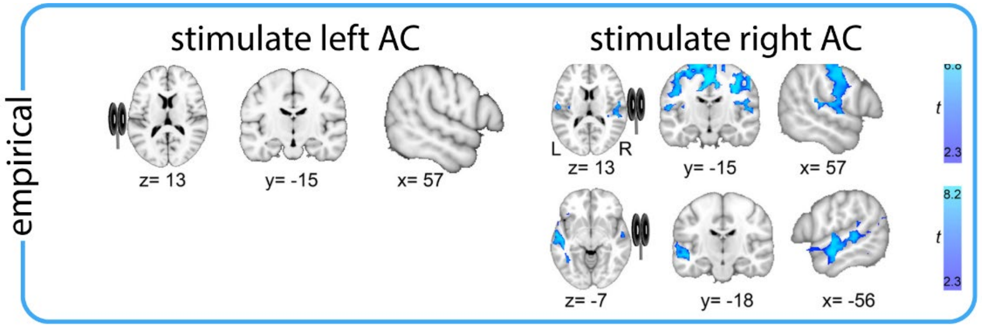


## Structure, function and communication

- How does structure shape function?
- A set of elementary signaling events (communication) on the structural network manifests as a pattern of inter-regional temporal covariance.
- Many possible ways to conceptualize dynamics, from biophysically detailed models (see talk by Kelly and Amanda), to simple stylized models.
- Communication models vary along a broad centralized-decentralized axis.

Avena-Koenigsberger, Misic & Sporns (2017) Nat Rev Neurosci

# Network manipulation and network transport




- modeling the effects of brain stimulation
- modeling the spread of misfolded proteins in neurodegenerative disease

Misic et al. (2018) Cereb Cortex

Zheng et al. (under review) | preprint: https://doi.org/10.1101/449199 code: https://github.com/yingqiuz/SIR_simulator

# Outline

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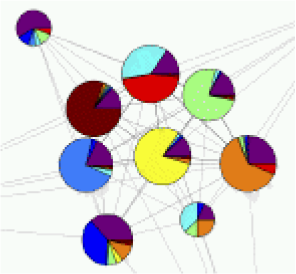
# Resources: code



GenLouvain

Gephi

Cytoscape

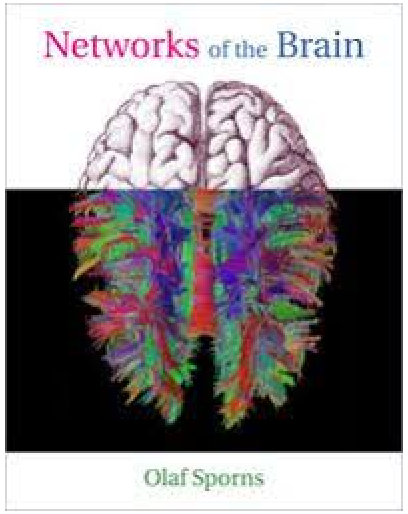
Brain Connectivity Toolbox

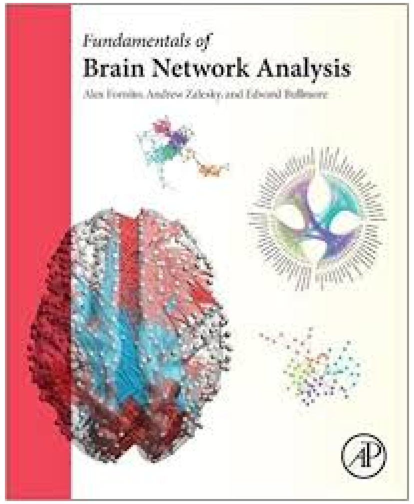
Graph Var

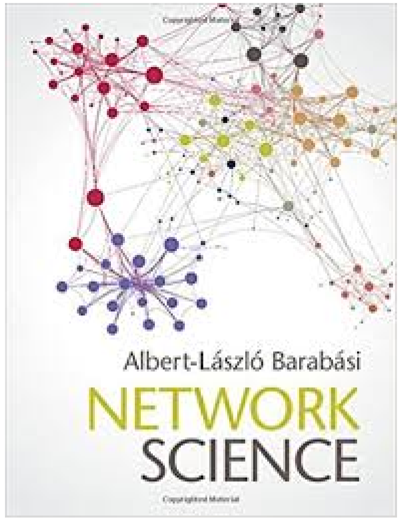
NetworkX

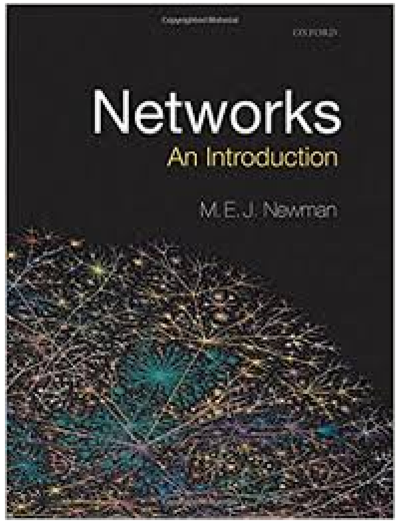
Matlab BGL

# Resources: text



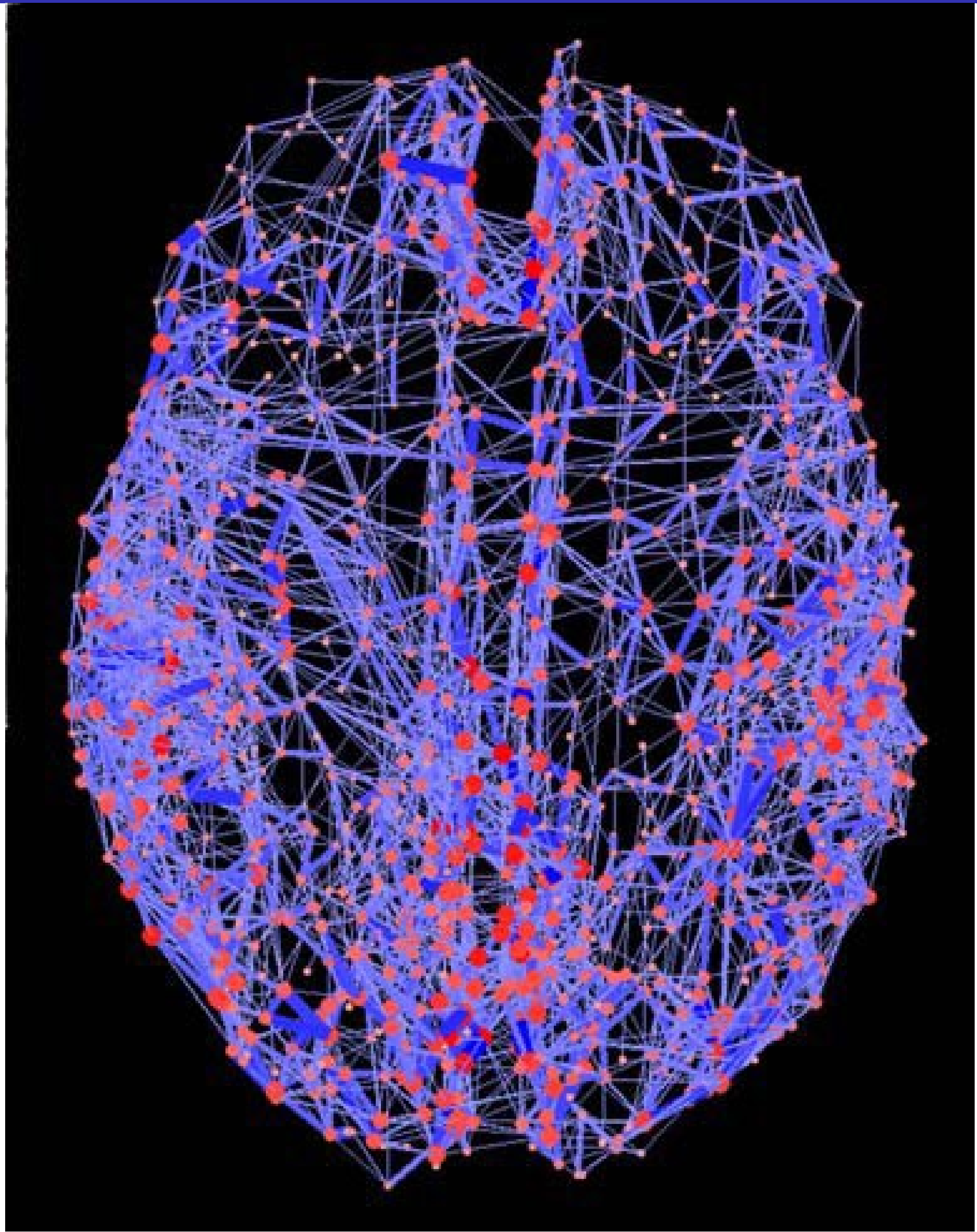



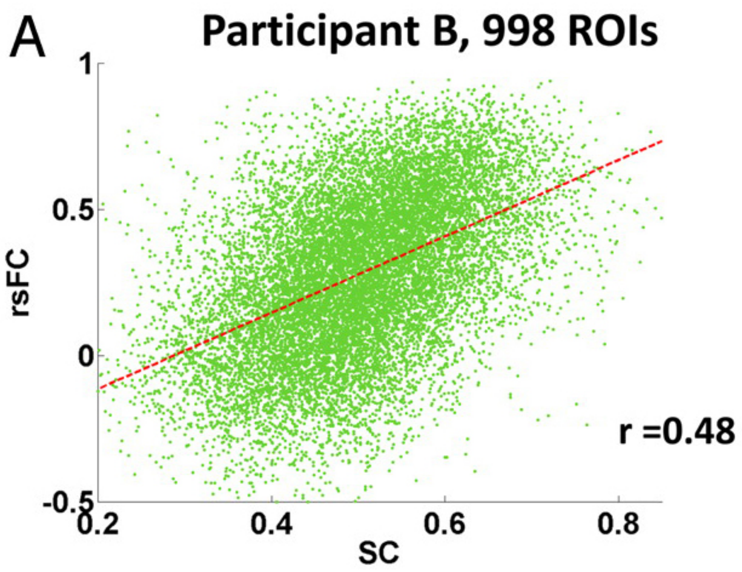

NETWORK
NEURO
SCIENCE

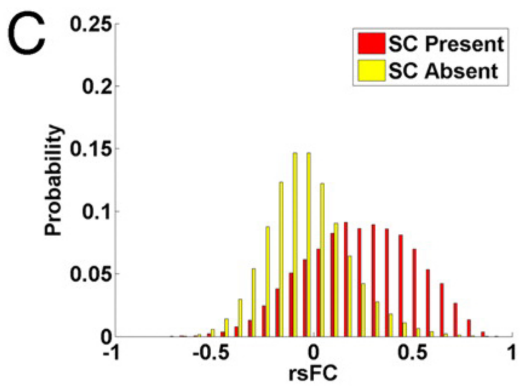
# Summary

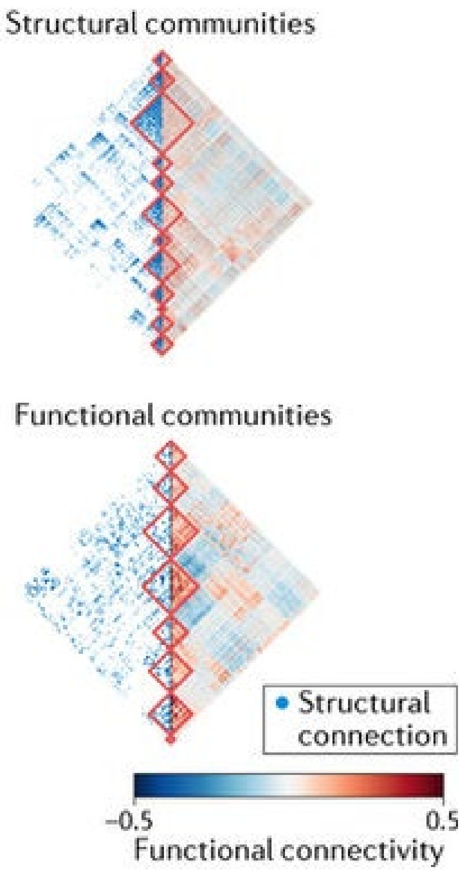
- Neural organization can be fruitfully represented as a graph
- Graphs are models/abstractions
- Questions to keep in mind:
    - can you justify assumptions?
    - can you verify that property is non-trivial?
    - can you do it with a simpler measure?
    - where does the observed effect come from?
- Exciting extensions and applications: node annotation, multiple layers, etc.



# Linking structural and functional connectivity



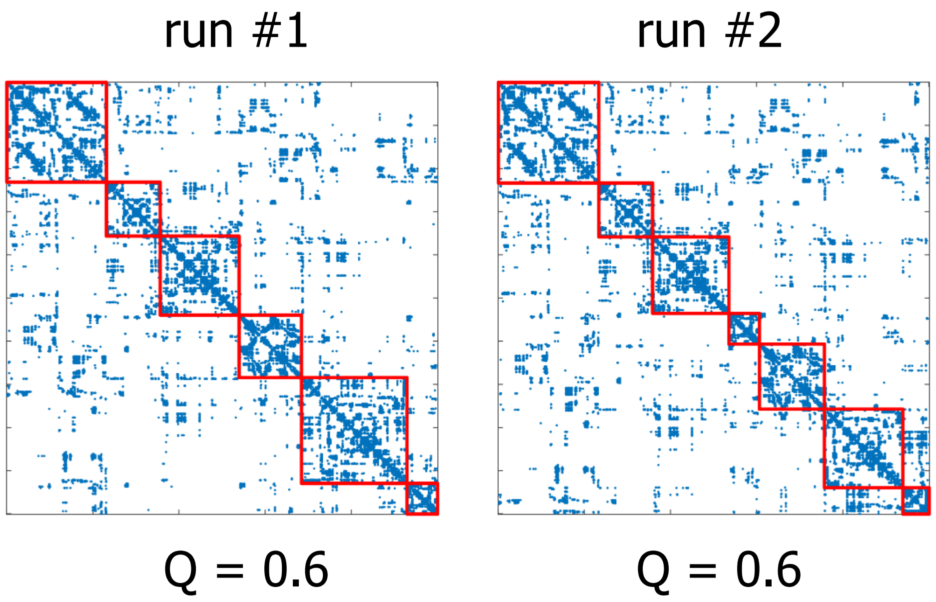

- Moderate correlations between SC and FC
- Better correspondence for directly-connected nodes than indirectly-connected nodes
- SC and FC communities do not match

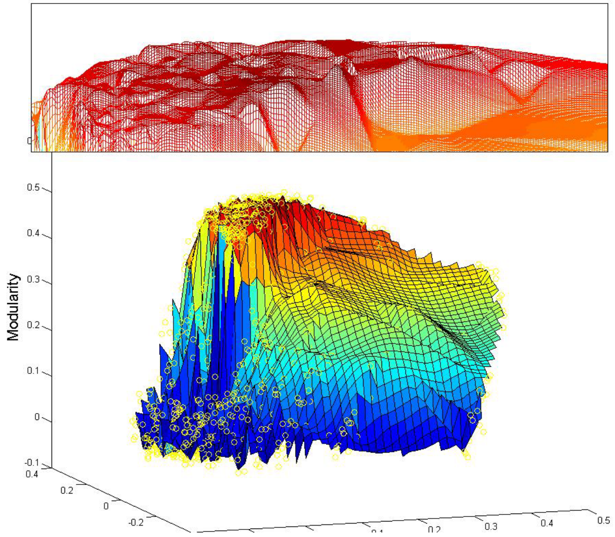
Honey et al. (2009) Proc Natl Acad Sci USA

Misic et al. (2016) Cereb Cortex

# The near-degeneracy of modularity

- Run the Louvain algorithm twice, and you will likely get two different partitions of similar quality



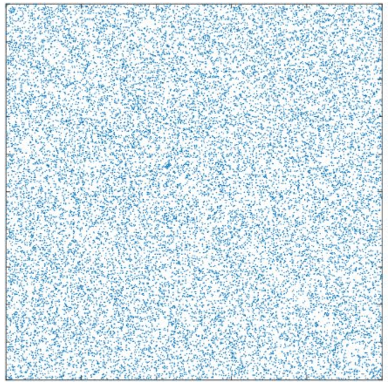

- In many applications, there exist multiple nearly-optimal partitions

# Choosing the null model

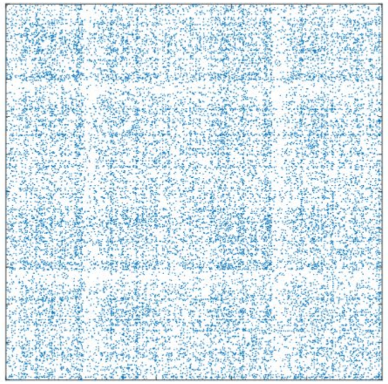
$$Q = \sum_{ij} [A_{ij} - \boxed{P_{ij}}]\delta(c_i, c_j)$$

- Null model determines which connections we consider 'expected' and 'unexpected'
- The 'correct' null model depends on context (type of network) and research question

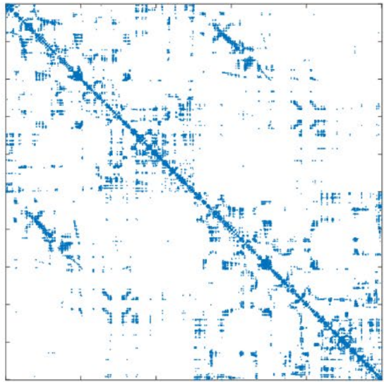
connections generated randomly and uniformly



random connections but same degree sequence



random connections but same spatial relationships



# Network structure tells us a lot about its function


- How fast is transport on this network compared to the TTC or STM?
- How well does this network utilize resources, such as fuel, electricity, geography?
- What is the fastest way to travel from station A to station B?
- Which lines get the most traffic?
- Which stations are critical for the overall system? Which stations are peripheral?