Overview

Why graph theory?

Building a brain graph

Defining nodes

Defining edges

Matrices and graphs

Network analysis

EEG and fMRI connectivity Matrix

Connectivity

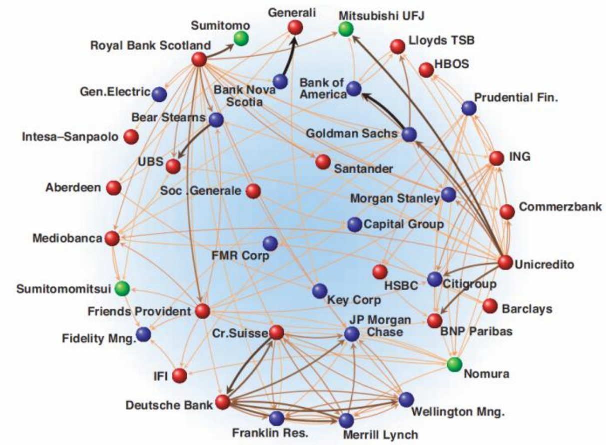
Topology

Small World Measures

Statistics

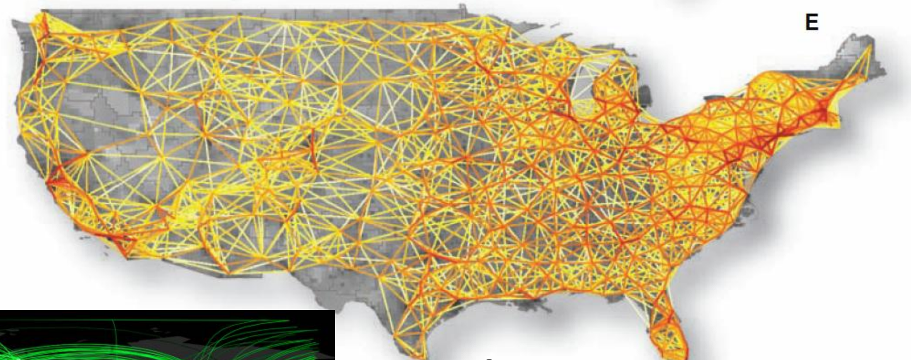
Few-Applications

Resources



Economic/Financial Networks

Schweitzer et al (2009) Science 325, 422.

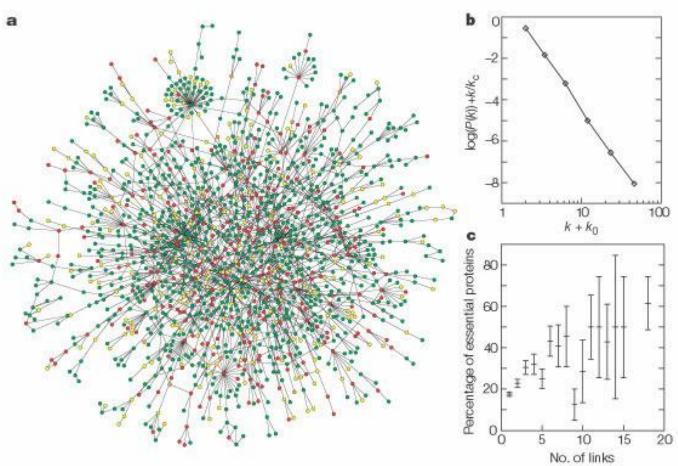


Social/Transportation Netks

Vespignani (2009) Science 325, 422

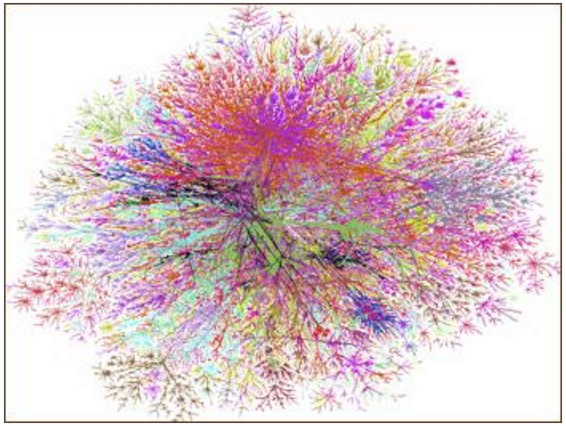
academic collaborations

Real-world networks have structure

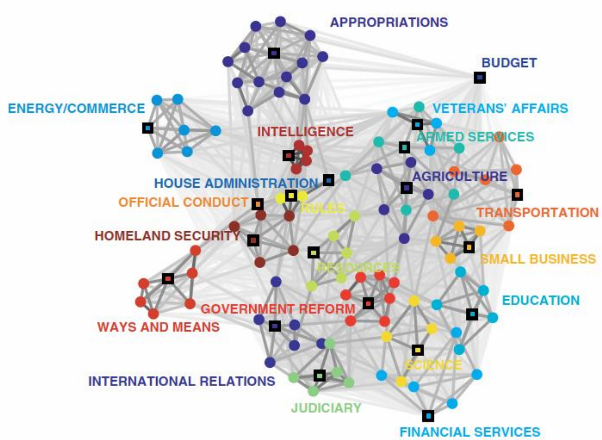


Protein Interaction Networks

Jeong et al (2001) Nature 411, 41.



world wide web

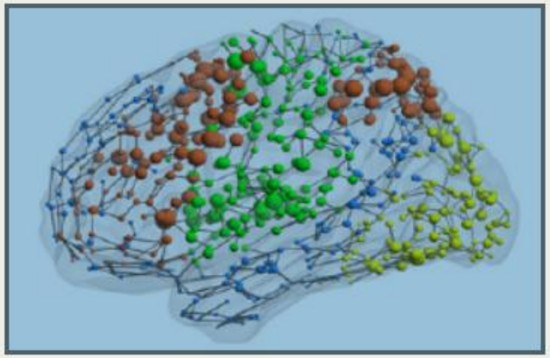


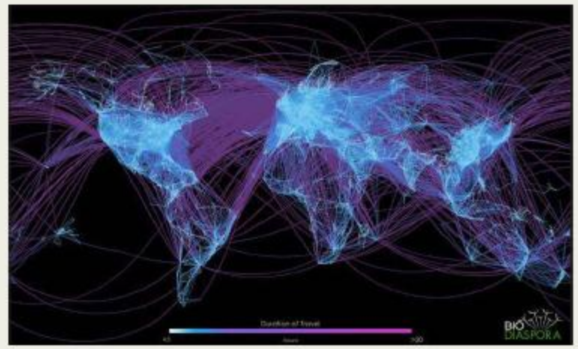
Socio-political Networks

Porter et al (2009). Notices of the AMS 56, 9.

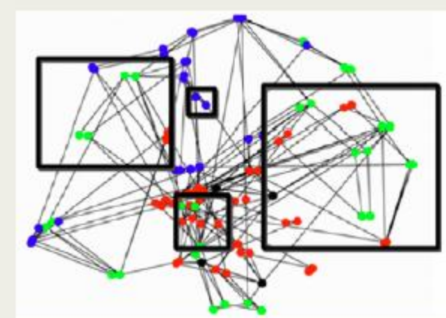
Universality and self-similarity….

What's special about brain networks?



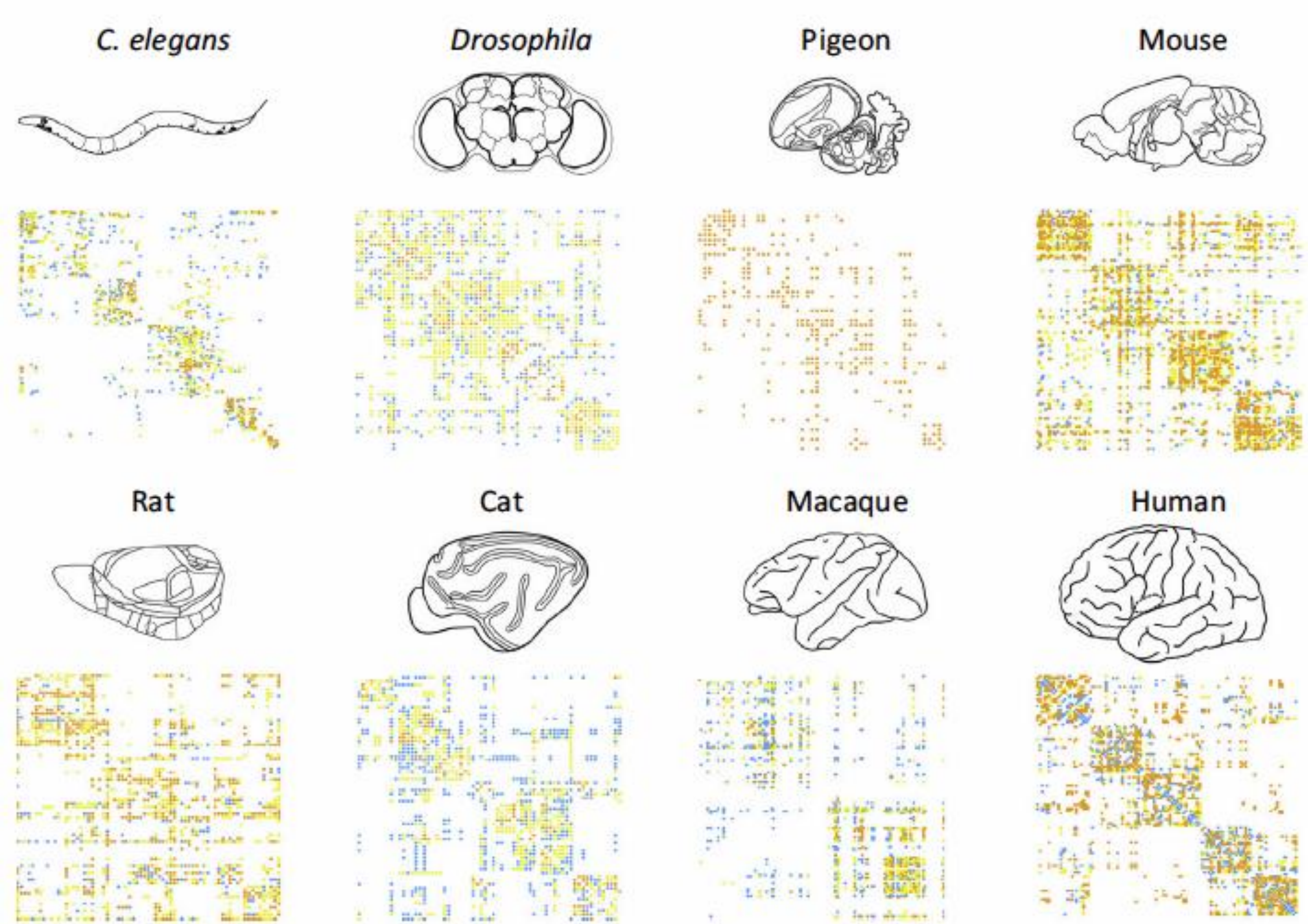


Do brain networks have fractal patterning from micro to macro scales?



Ramón y Cajal (1895); CLARITY; Bassett et al (2010) *PLoS Comp Biol*

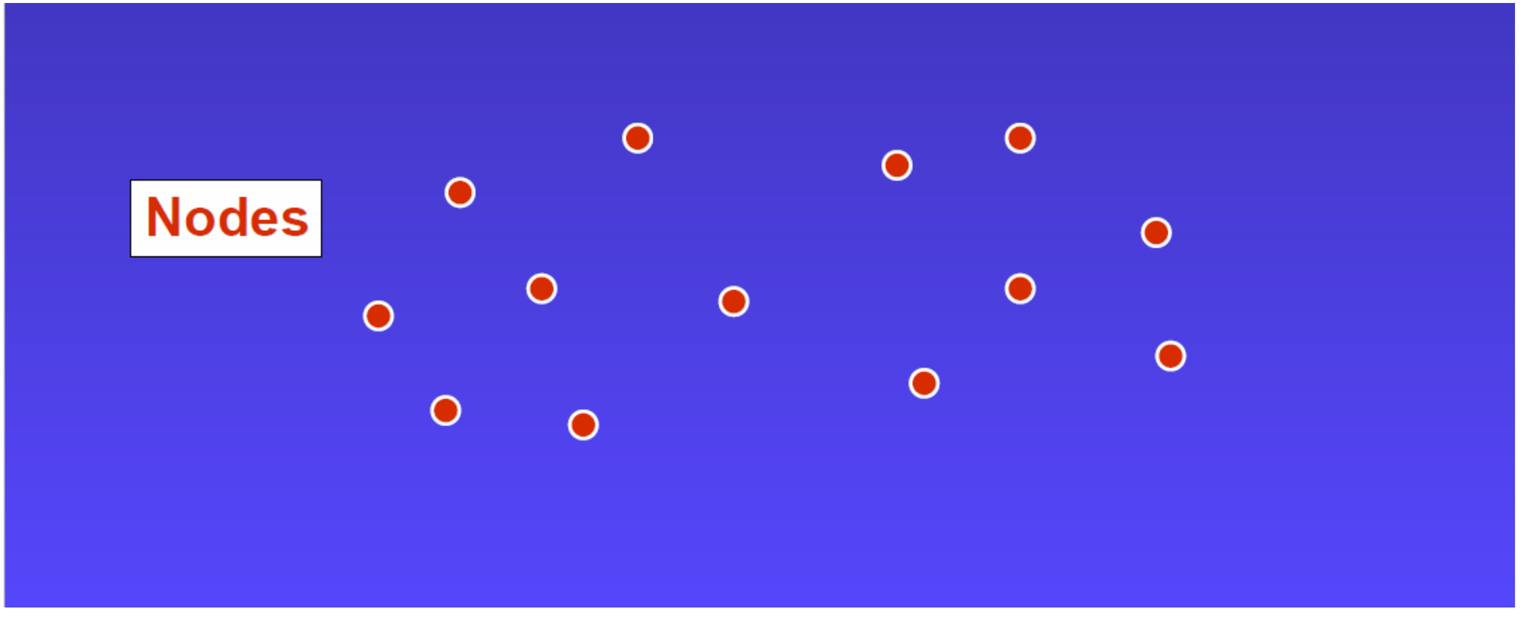
Graph theoretical analysis is generalisable to connectomes across all species…



Van den Heuvel,(2016) , Trends in Cognitive Sciences

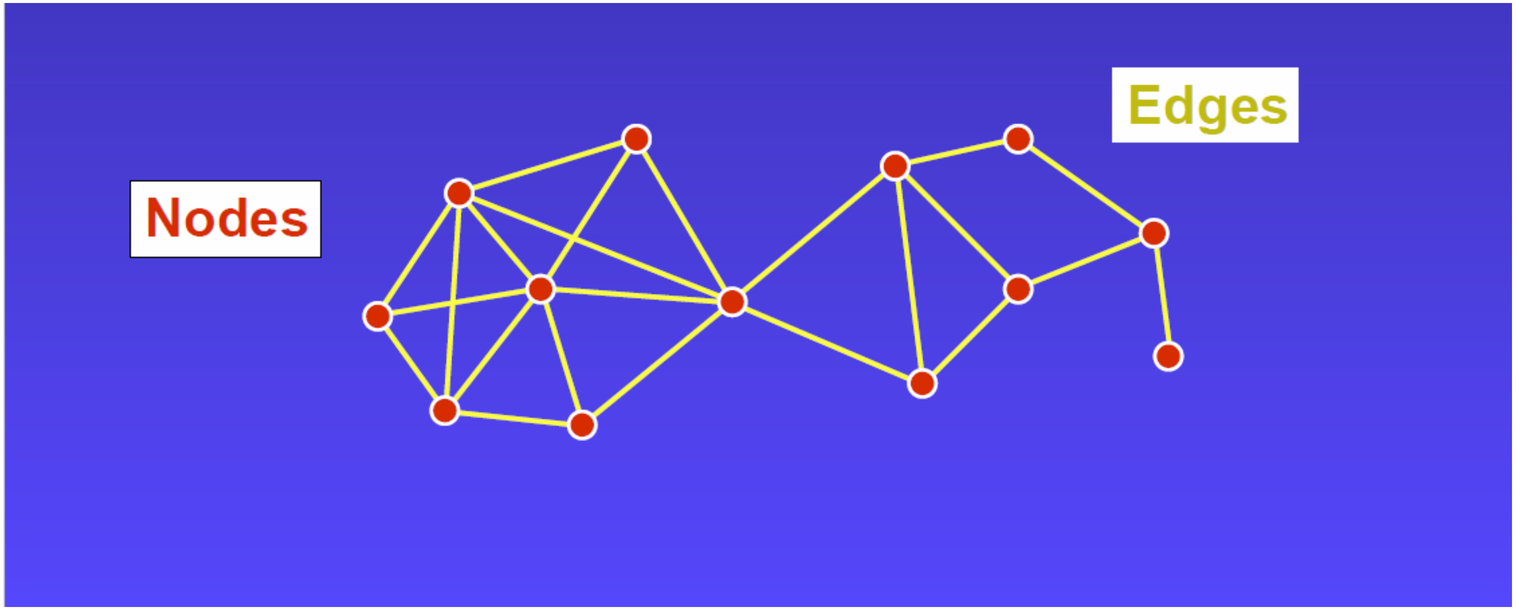
Nodes:

Nodes represent fundamental processing units
In its simplest form, a network is a collection of points (or nodes) ...



Edges:

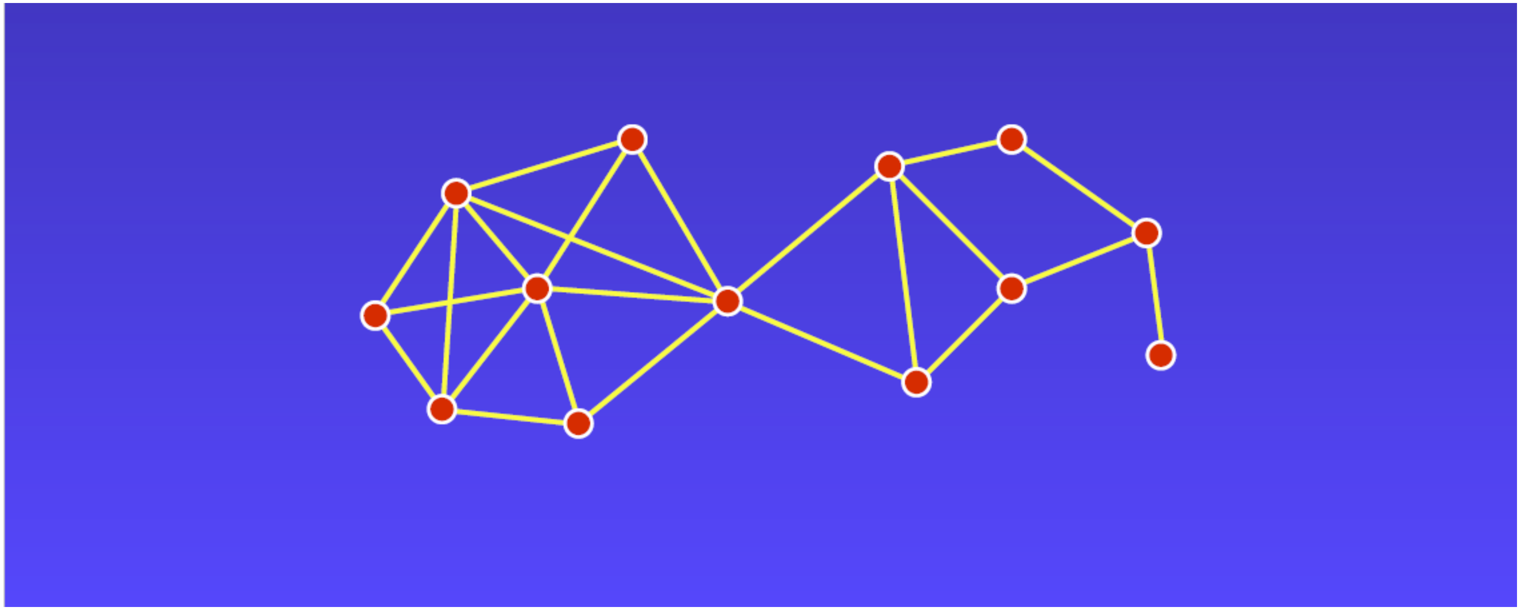
Edges represent the interactions between nodes
In its simplest form, a network is a collection of points (or nodes) ... joined by lines or edges.
The nature of nodes and links in individual brain networks is determined by combinations of brain mapping methods, anatomical parcellation schemes, and measures of connectivity. (Horwitz, 2003)
The choice of a given combination must be carefully motivated, as the nature of nodes and links largely determines the neurobiological interpretation of network topology (Butts, 2009).



What we can measure? - regarding network structure

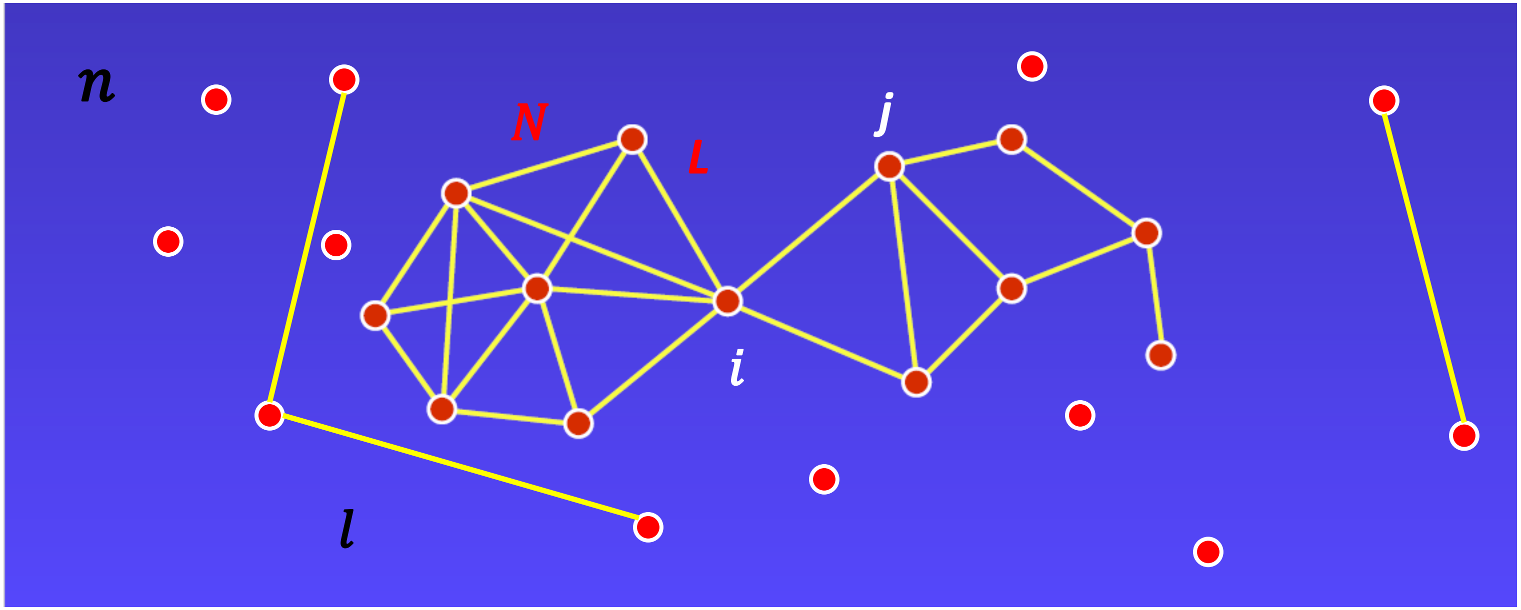
…. **Graph theoretical Analyses**

any **network can be modelled** as a graph of nodes connected by edges



Let Consider....

N is the set of all nodes in the network, and n is the number of nodes.
L is the set of all links in the network, and l is number of links.
i,j is a link between nodes i and j ($i,j \in N$) .
a_{ij} is the **connection status between *i* and *j***: a_{ij} = 1 when link i,j exists , 0-otherwise.



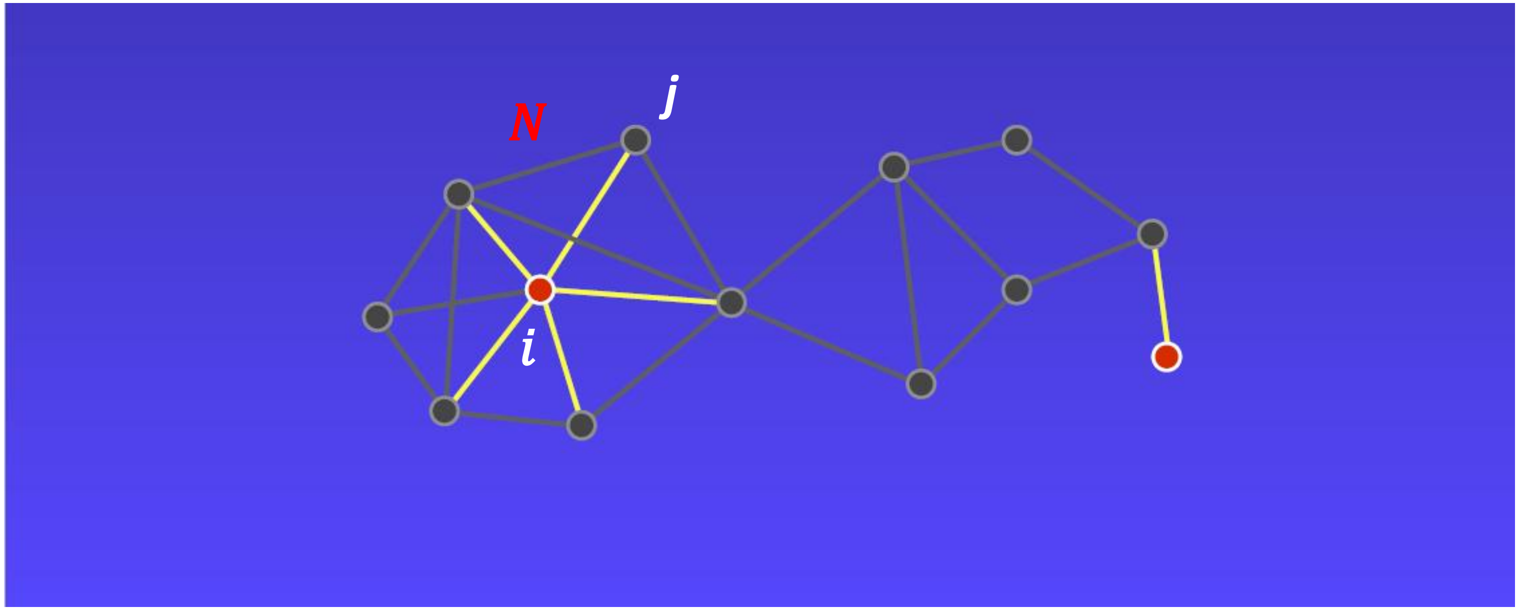
Degree

Degree - degree of an individual node = number of links connected to that node (i.e number of neighbors of the node).

- Related to **Density** - number of actual connections over total possible
- Higher degree centrality indicates regions that are more connected to the rest of the network

Degree of a node i,

$$k_i = \sum_{j \in N} a_{ij}$$



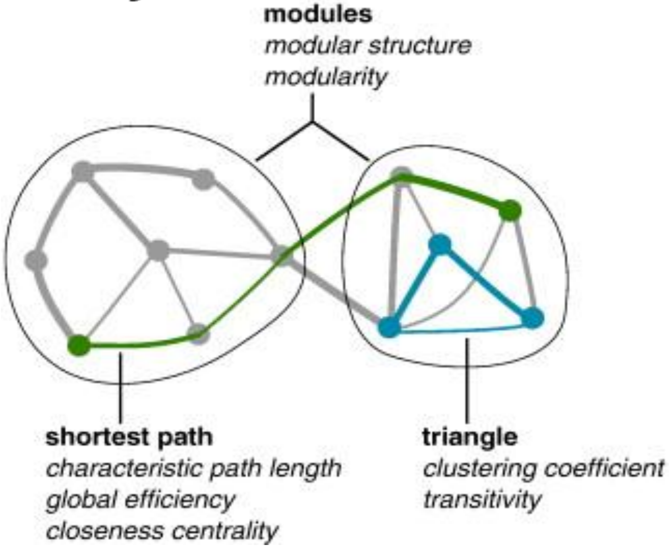
Trangle

Number of triangles: a basis for measuring segregation

- Measures of network topology.
- These measures are typically based on basic properties of network connectivity (in bold type). Thus, measures of integration are based on shortest path lengths (green), while measures of segregation are often based on triangle counts (blue) but also include more sophisticated decomposition into modules (ovals).

Number of triangles around a node i,

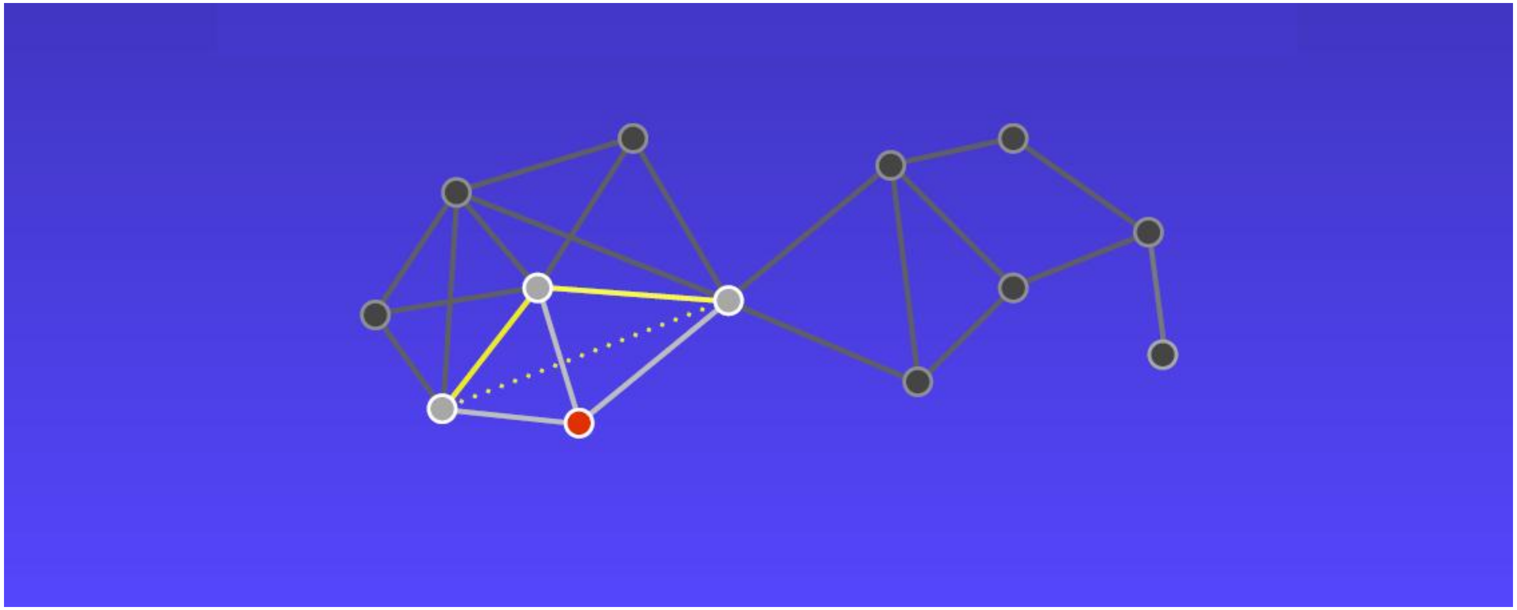
$$t_i = \frac{1}{2} \sum_{j,h \in N} a_{ij} \, a_{ih} a_{jh}$$



Clustering Coefficient

Clustering Coefficient - how many connections exist between a given node's neighbors (i.e. given N neighbors of X, what % of N-N edges exist?)

Clustering coefficient (local) - Calculated as the number of edges between the nodes within the neighborhood of a given node, divided by the total number of possible edges between the nodes in the neighborhood. Measure of how close a given node's neighbors are to forming a clique
Clustering coefficient (Global) - Calculated as the mean local clustering coefficient, averaged over all nodes in the network. Measure of the degree to which regions cluster, providing measure of local connectivity



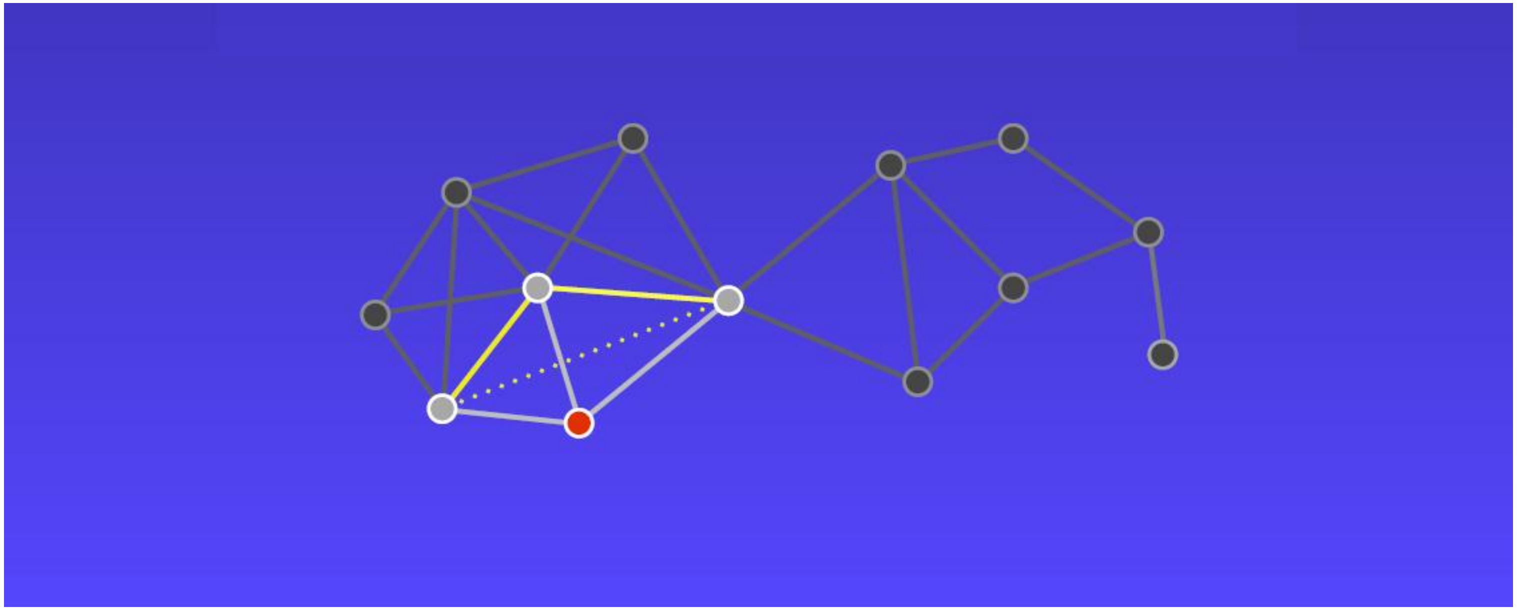
Clustering Coefficient

Clustering coefficient of the network (Watts and Strogatz, 1998),

$$C = \frac{1}{n}\sum_{i\in N} C_i = \frac{1}{n}\sum_{i\in N}\frac{2t_i}{k_i(k_i-1)},$$

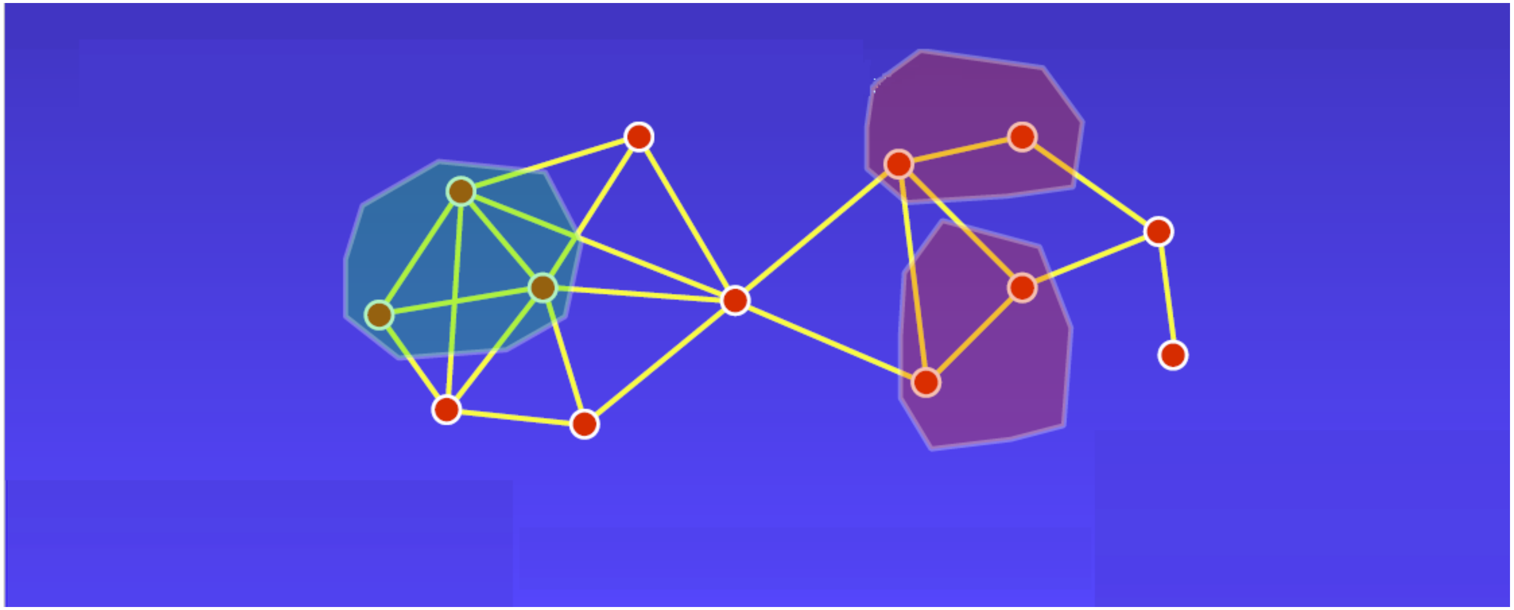
where C_i is the clustering coefficient of node i ($C_i = 0$ for $k_i < 2$).

t_i - number of triangles around a node i, k_i - Degree of a node i



Clustering Coefficient

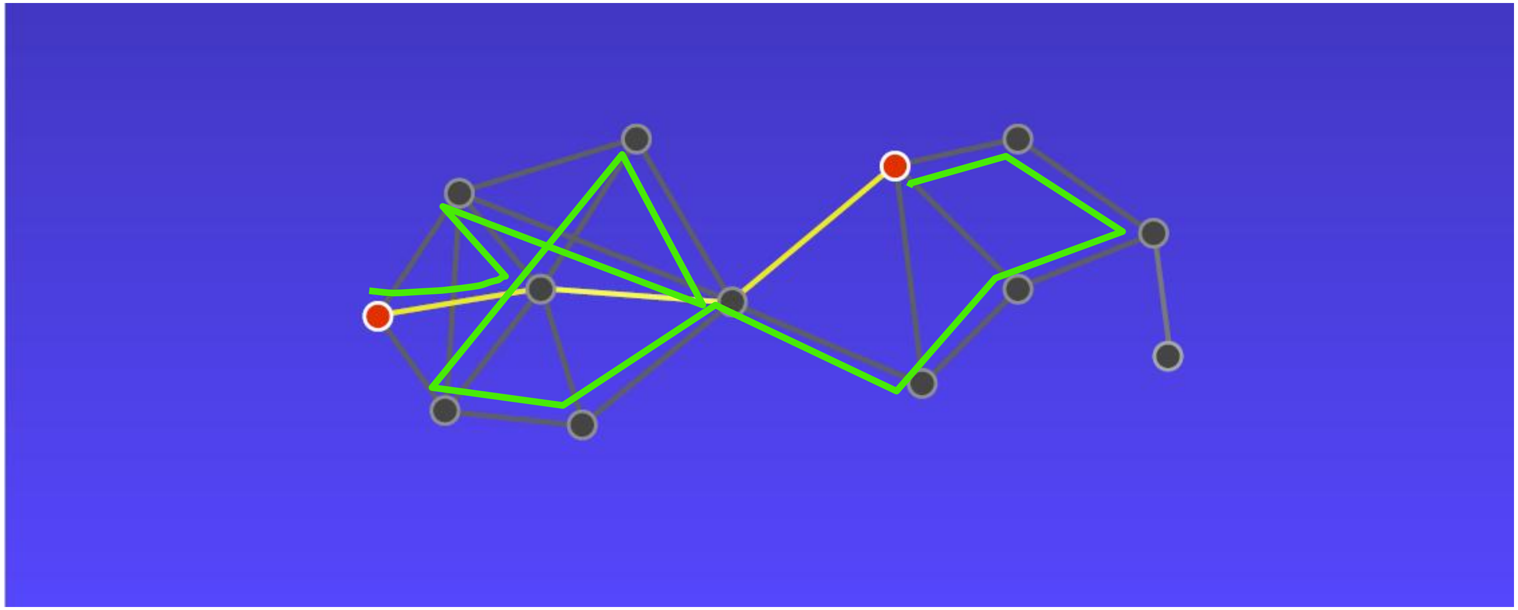
The number of triangles in the network, with a high number of triangles implying segregation . Locally, the fraction of triangles around an individual node is known as the *clustering coefficient* and is equivalent to the fraction of the node's neighbors that are also neighbors of each other (Watts and Strogatz, 1998). The mean clustering coefficient for the network hence reflects, on average, the prevalence of clustered connectivity around individual nodes.



Path length

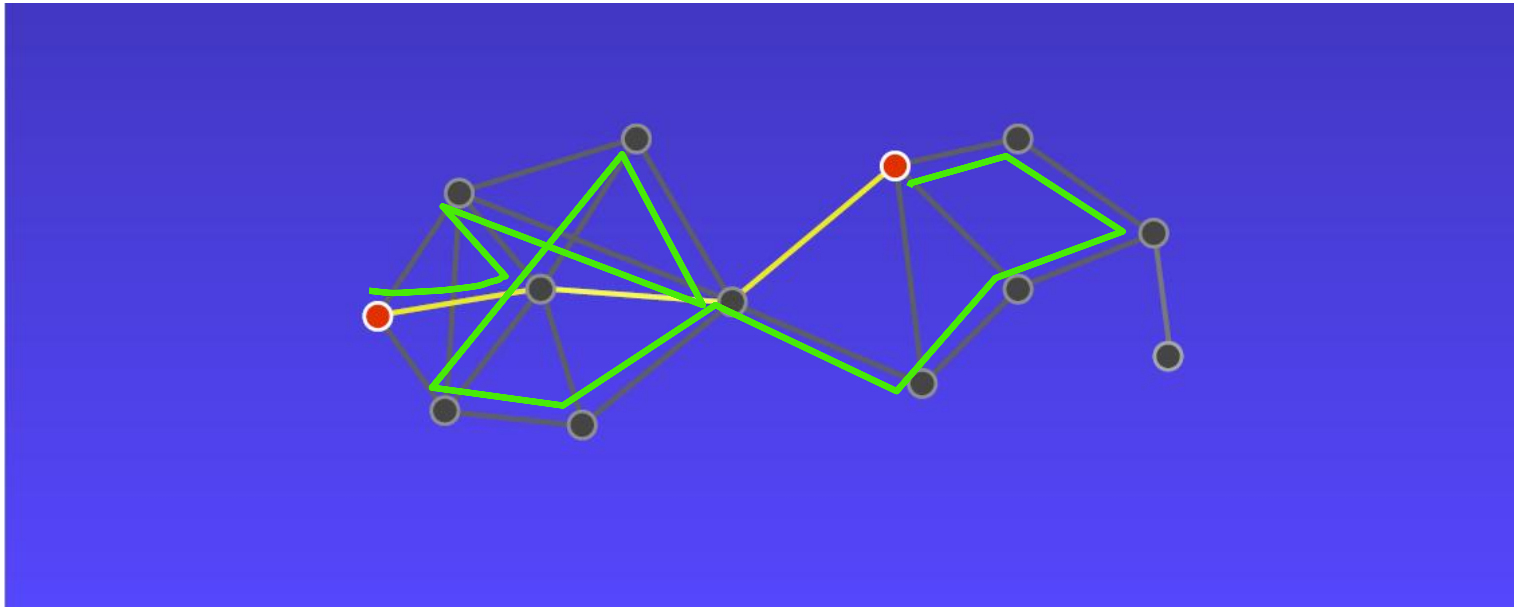
Path length - # of nodes crossed to reach another nodes .... 1/L describes the efficiency of the system

Paths are sequences of distinct nodes and links and in anatomical networks represent potential routes of information flow between pairs of brain regions.
Lengths of paths consequently estimate the potential for functional integration between brain regions, with shorter paths implying stronger potential for integration.



Path length

- The average shortest path length between all pairs of nodes in the network is known as the ***characteristic path length*** of the network (e.g., [Watts and Strogatz, 1998](#))
- The average inverse shortest path length is a related measure known as the *global efficiency* ([Latora and Marchiori, 2001](#)).
- More generally, the characteristic path length is primarily influenced by long paths (infinitely long paths are an illustrative extreme), while the global efficiency is primarily influenced by short paths.
- Paths are computed from directed and weighted networks. While a binary path length is equal to the number of links in the path, a weighted path length is equal to the total sum of individual link lengths.



Path length

Shortest path length (distance), between nodes i and j,

$$d_{ij} = \sum_{a_{uv} \in g_{i \leftrightarrow j}} a_{uv},$$

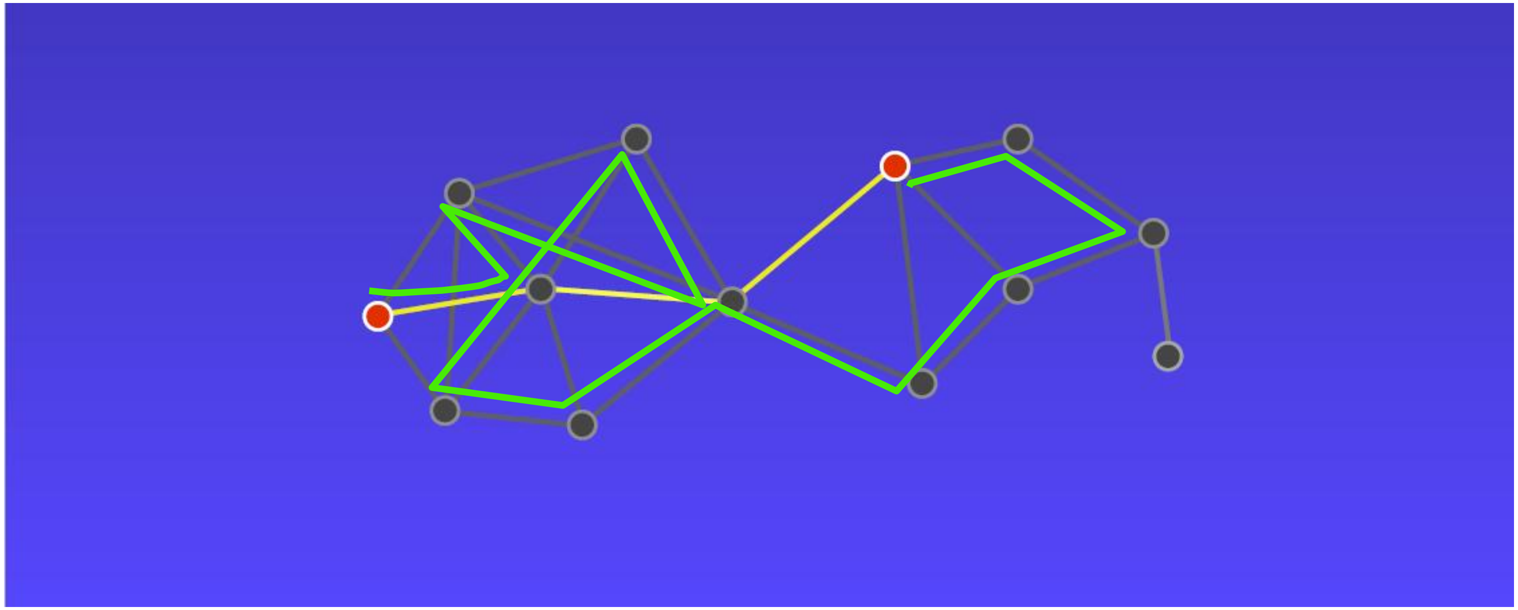
where $g_{i \leftrightarrow j}$ is the shortest path (geodesic) between i and j. Note that $d_{ij} = \infty$ for all disconnected pairs i, j.

a_{uv}- connection status of nodes in module u with nodes in module v

Characteristic path length of the network (e.g. Watts and Strogatz, 1998),

$$L = \frac{1}{n} \sum_{i \in N} L_i = \frac{1}{n} \sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}}{n-1},$$

where L_i is the average distance between node i and all other nodes.



Betweenness centrality

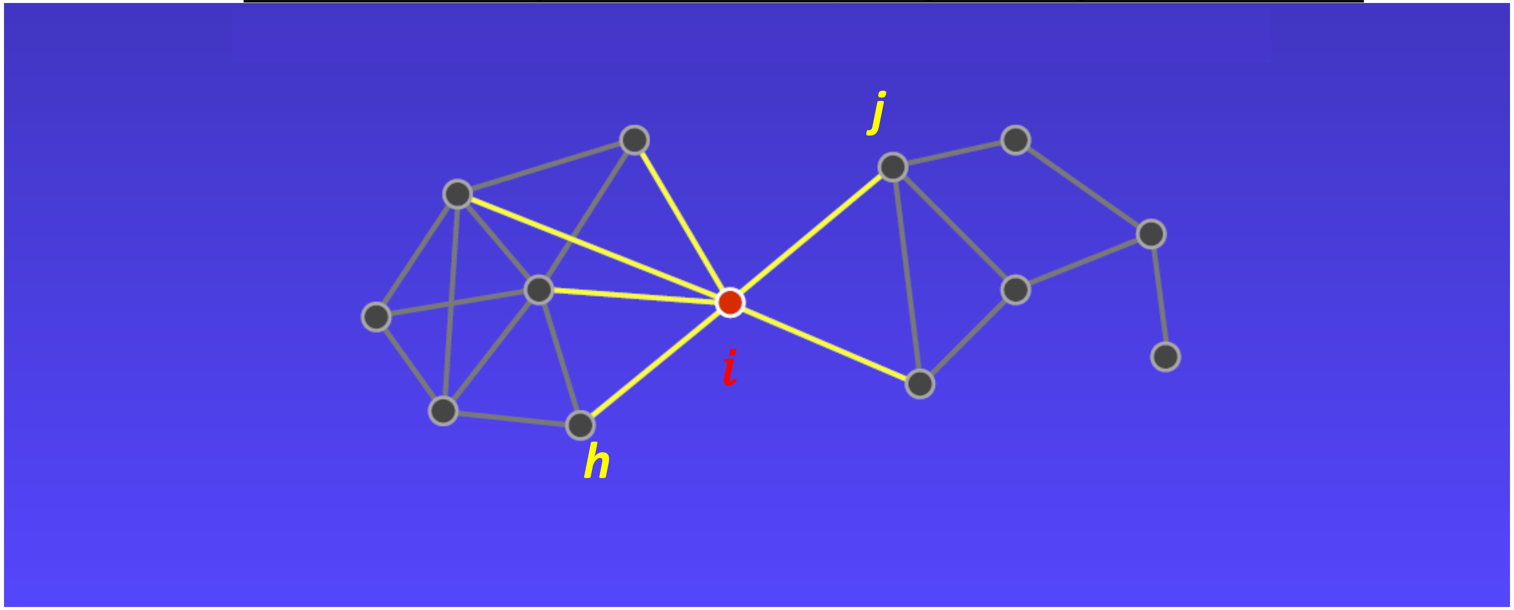
betwenness centrality- a node or edge that is central to many short paths between nodes.

Calculated as the number of all geodesics (shortest paths) in a network that pass through a given node, divided by the total number of geodesics in the network. Provides a measure of the node's importance. Nodes with high betweenness centrality are located on highly traveled paths

Betweenness centrality of node i (e.g. Freeman, 1978),

$$b_i = \frac{1}{(n-1)(n-2)} \sum_{\substack{h,j \in N \\ h \neq j, h \neq i, j \neq i}} \frac{\rho_{hj}(i)}{\rho_{hj}},$$

where ρ_{hj} is the number of shortest paths between h and j, and $\rho_{hj}(i)$ is the the number of shortest paths between h and j that pass through i.

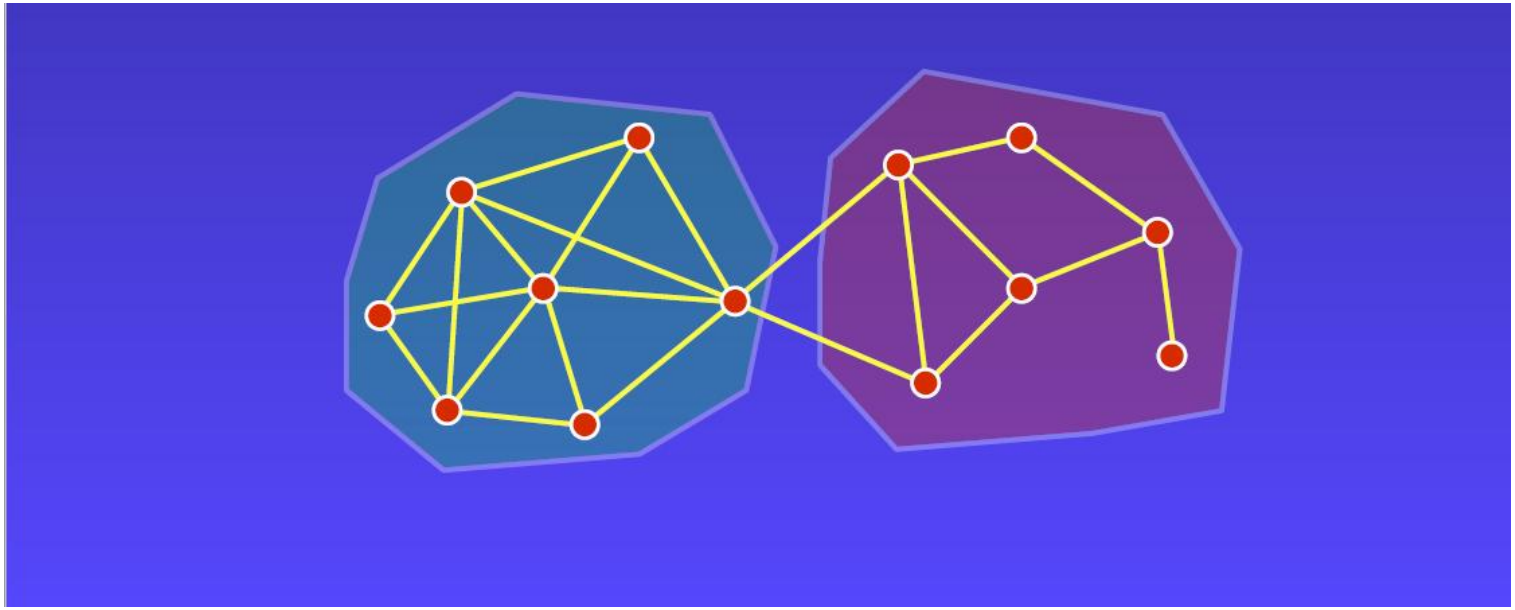


Modules

Modules - clusters of nodes that are densely connected

Moduli a subgraph of nodes which are more strongly connected to each other than the rest of the network. **Modules** often correspond to different functional aspects of the network

The degree to which the network may be subdivided into such clearly delineated and nonoverlapping groups is quantified by a single statistic, the ***modularity*** ([Newman, 2004b](#)).



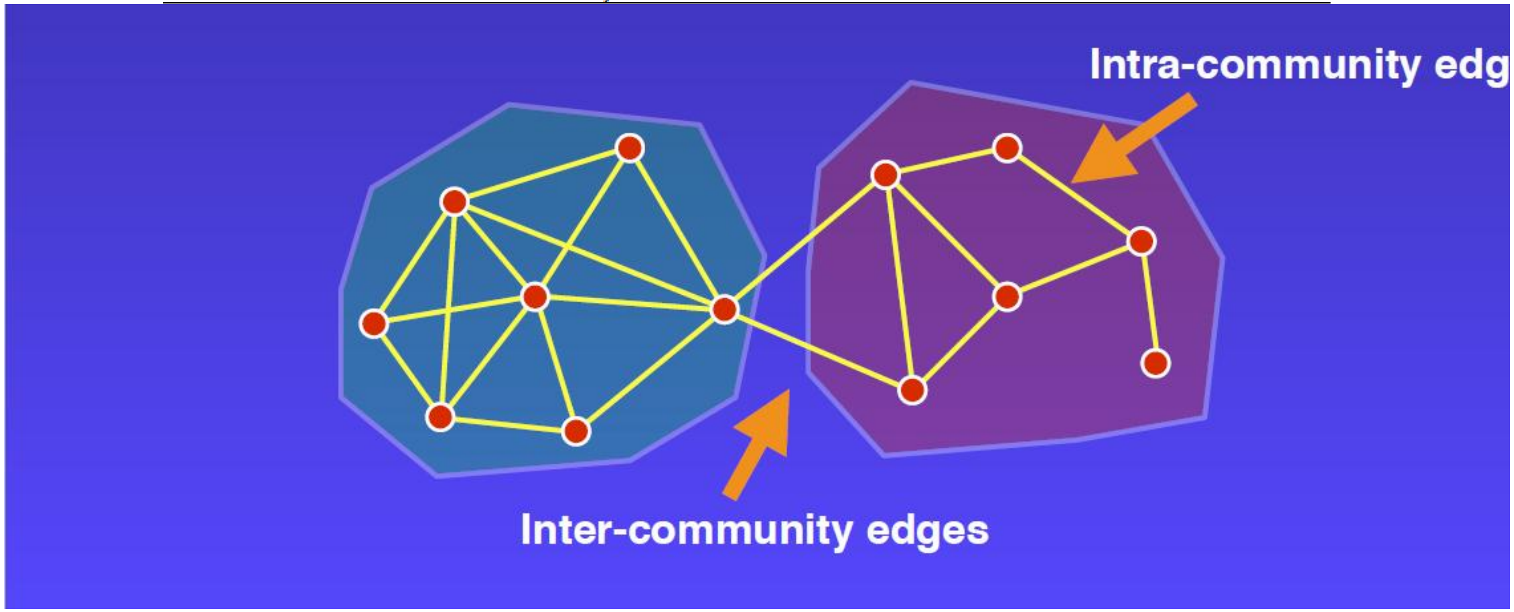
Moduarity

Modularity of the network (Newman, 2004b),

$$Q = \sum_{u \in M} \left[e_{uu} - \left(\sum_{v \in M} e_{uv} \right)^2 \right],$$

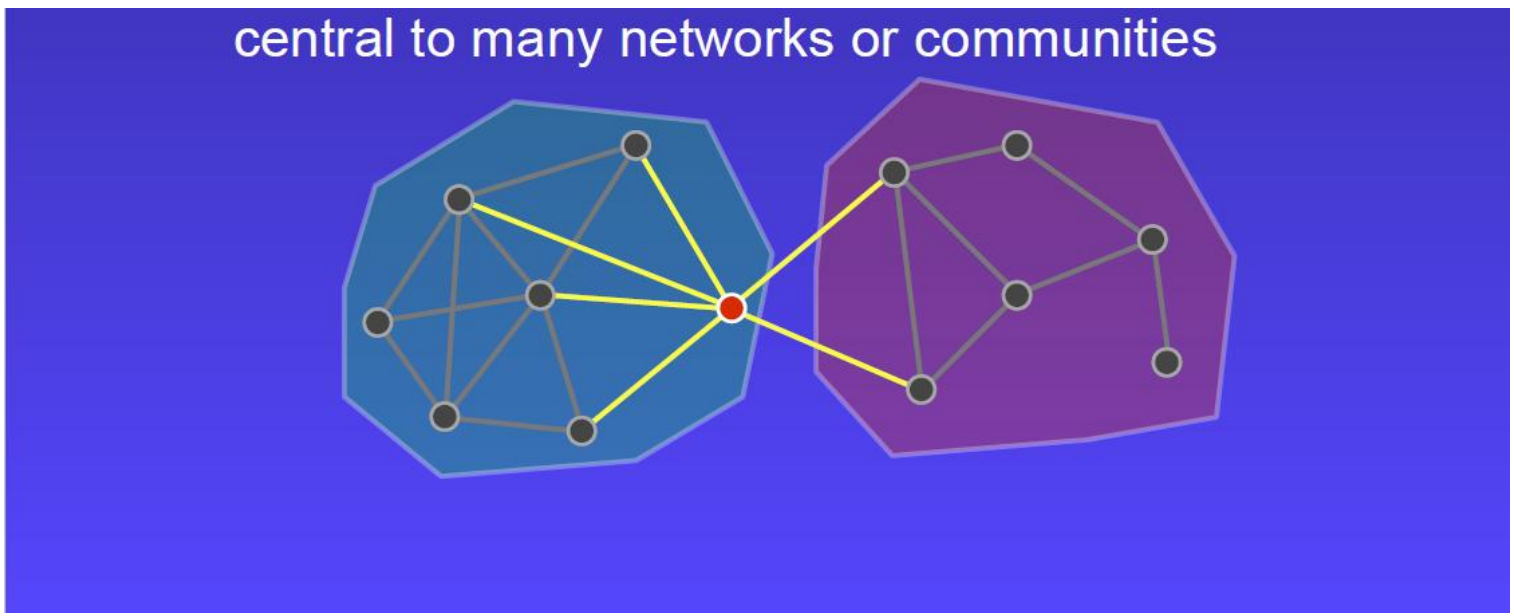
where the network is fully subdivided into a set of nonoverlapping modules M, and e_{uv} is the proportion of all links that connect nodes in module u with nodes in module v.

An equivalent alternative formulation of the modularity (Newman, 2006) is given by $Q = \frac{1}{l} \sum_{i,j \in N} \left(a_{ij} - \frac{k_i k_j}{l} \right) \delta_{m_i, m_j}$, where m_i is the module containing node i, and $\delta_{m_i, m_j} = 1$ if $m_i = m_j$, and 0 otherwise.

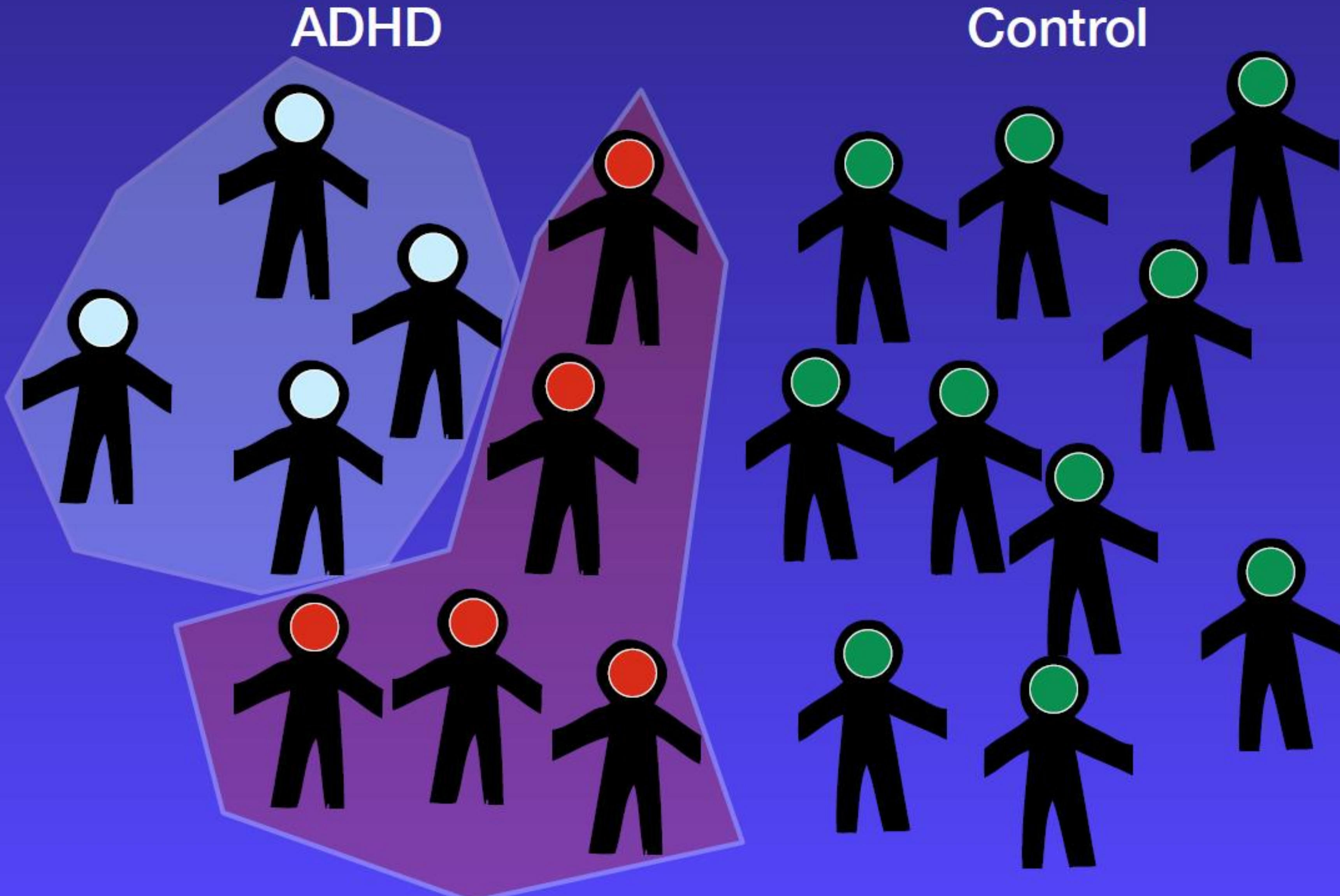


Participation Coeficient (Hubs)

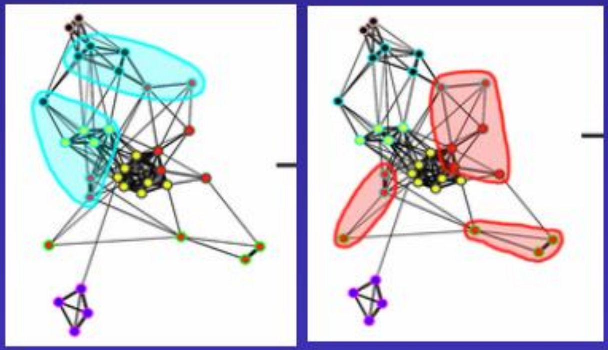
Participation Coeficient (Hubs) - a node that is central to many networks or communities



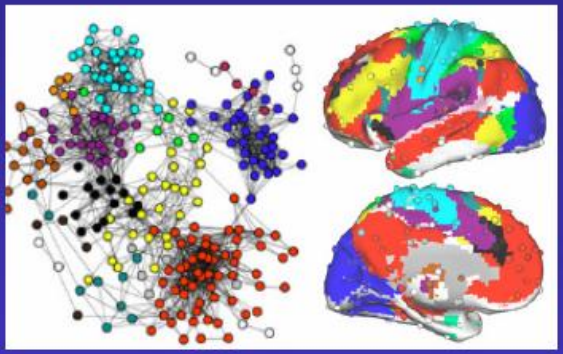
Graph theoretical Analyses



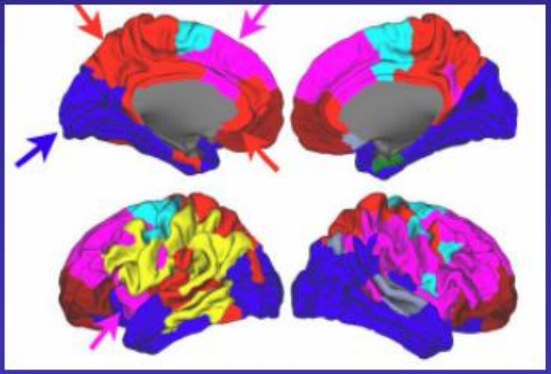
Applications community detection



Fair et al, 2009



Power et al, 2011



Grayson et al, 2014

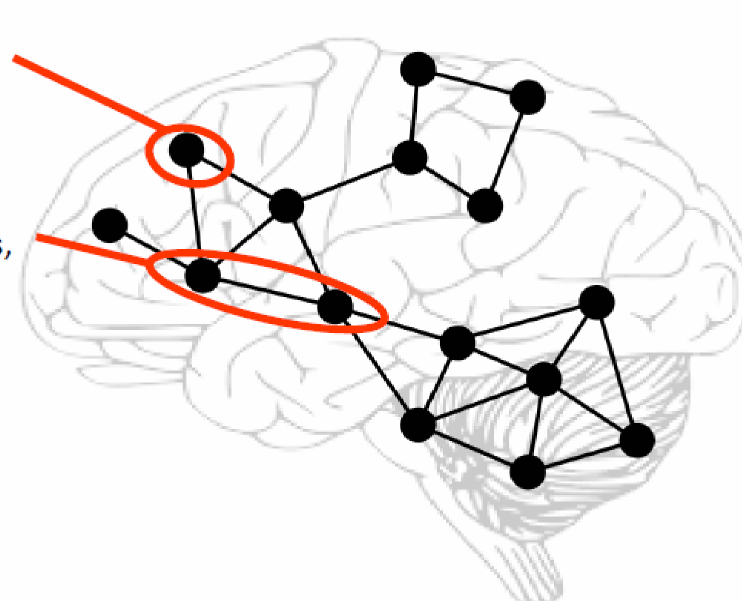
- Clustering with networks supports ***<u>segregation</u>*** and distributed information processing

- ***<u>Integration</u>*** of such information is than accomplished via few, but likely important links

Network Measures of Brain

Neural elements (nodes)
- Neurons, areas, regions

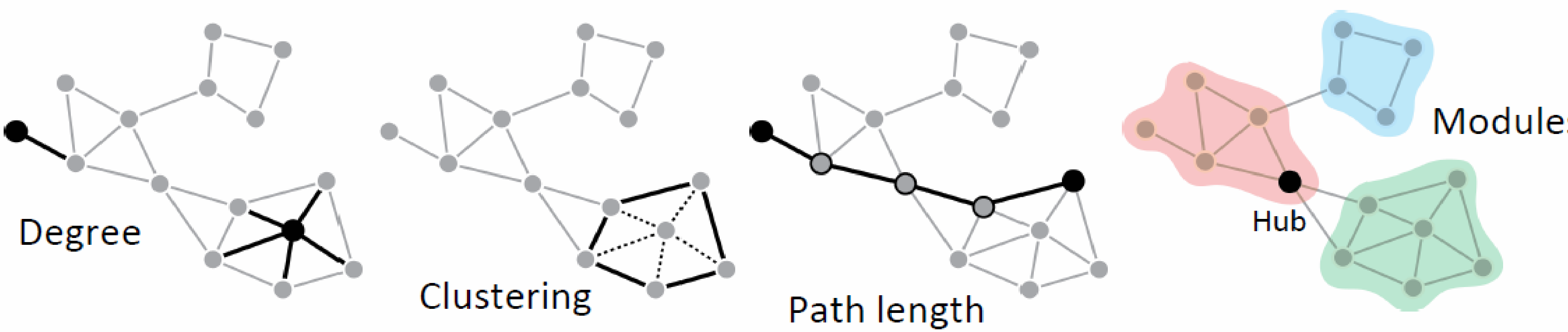
Connections (edges)
- Synapses, axonal projections, fiber pathways



Segregation
- Clustering
- Motifs
- Modularity

Integration
- Distance
- Path Length
- Efficiency

Influence
- Degree
- Participation
- Betweenness



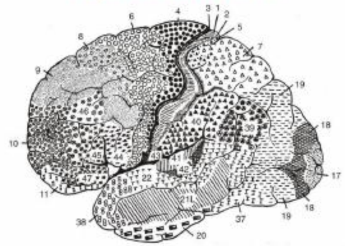
Rubinov & Sporns (2010) *Neuroimage* 52, 1059.
Sporns (2013) *Nature Methods* 10, 491

defining nodes

Brain nodes should have:
1. Intrinsic consistency
2. Extrinsic differentiation
3. Spatially constrained

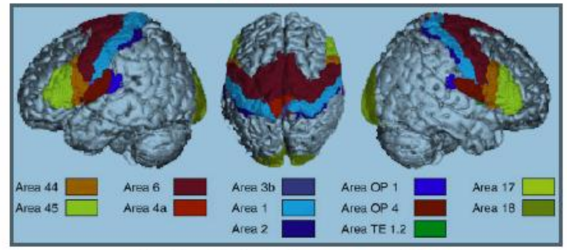
Fornito et al. NeuroImage, 2013

cytoarchitecture

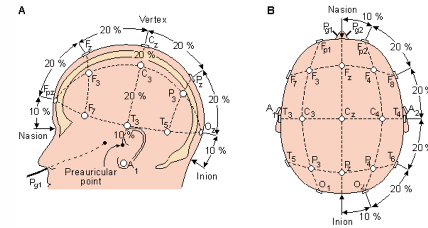


Brodmann, 1909

probabilistic

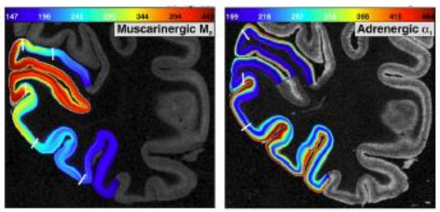


Eickhoff et al. NeuroImage, 2006



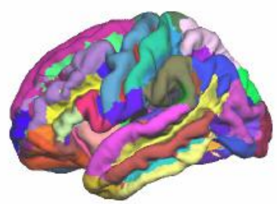
10-20 EEG System

chemoarchitecture



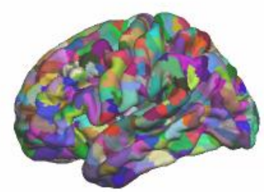
Eickhoff et al. NeuroImage, 2007

anatomical



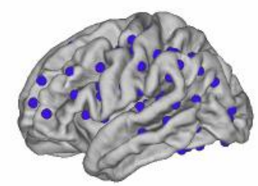
Tzuorio-Mazoyer, et al. NeuroImage, 2002
Desikan, et al. NeuroImage, 2006

random



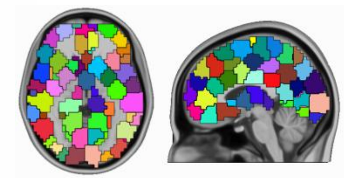
Hagmann, et al. PLoS One, 2007
Zalesky, et al. NeuroImage, 2010
Fornito et al. Font Sys Neurosci, 2010

functional



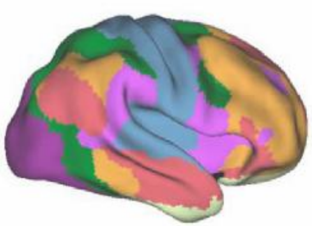
Dosenbach, et al. Science, 2010
Fornito et al. PNAS, 2012

1000 functional ROI



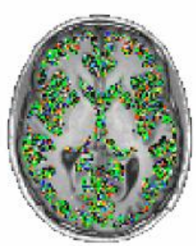
Craddock, 2012

data-driven



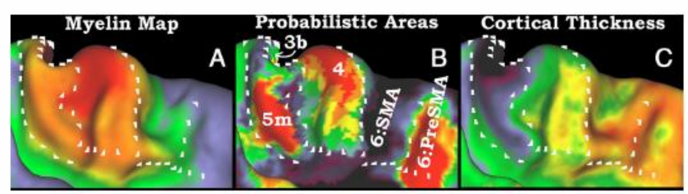
Yeo et al. J Neurophysiol, 2011
Craddock et al. Hum Brain Mapp, 2012
Power et al. Neuron, 2011

voxel-based



van den Heuvel et al. NeuroImage, 2009
Hayasaka & Laurienti, NeuroImage, 2010

myeloarchitecture



Glaser & Van Essen J Neurosci 2011

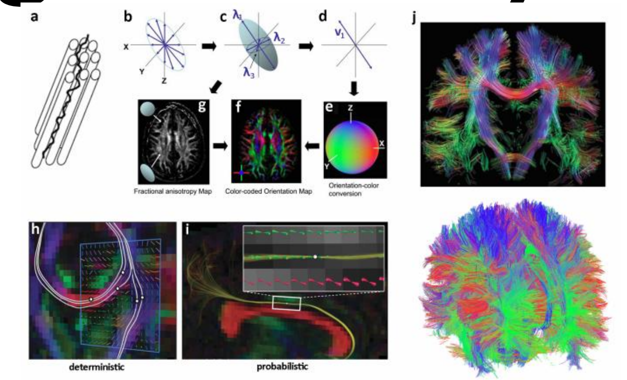
O'Donnell & Westin, 2010

Defining Edge (Building Matrices)

Structural connectivity

The physical (anatomical) connections between brain regions
Anatomical connections typically correspond to white matter tracts between pairs of brain regions (Friston, 1994).

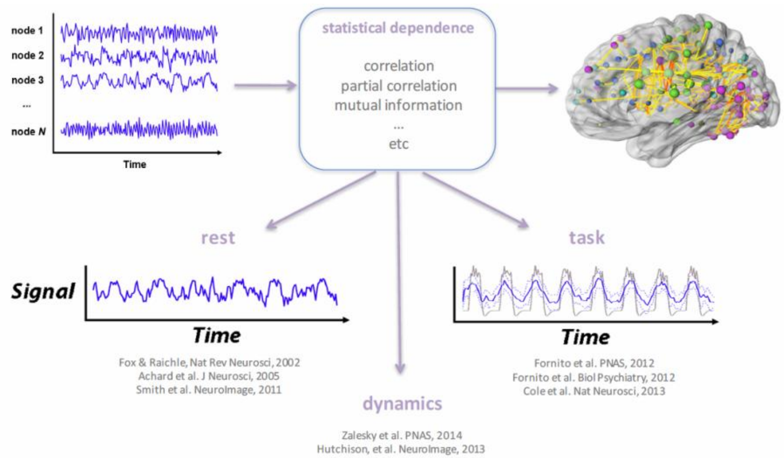
O'Donnell & Westin, 2010



Structural connectivity with DWI – track tracking
Mori & Zhang, Neuron, 2008; Thomas, et al. PNAS, 2014

Functional connectivity - fMRI

A statistical dependence between spatially distinct neurophysiological signals
Functional connections correspond to magnitudes of temporal correlations in activity and may occur between pairs of anatomically unconnected regions. Depending on the measure, functional connectivity may reflect linear or nonlinear interactions, directed or undirected, as well as interactions at different time scales (Zhou et al., 2009).

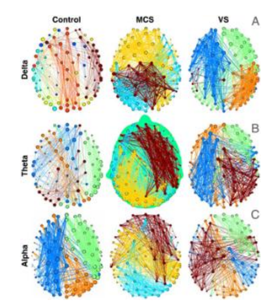


Effective connectivity

The influence that one neuronal system exerts over another
Effective connections represent direct or indirect causal influences of one Region on another and may be estimated fm observed perturbations(Friston ,2003

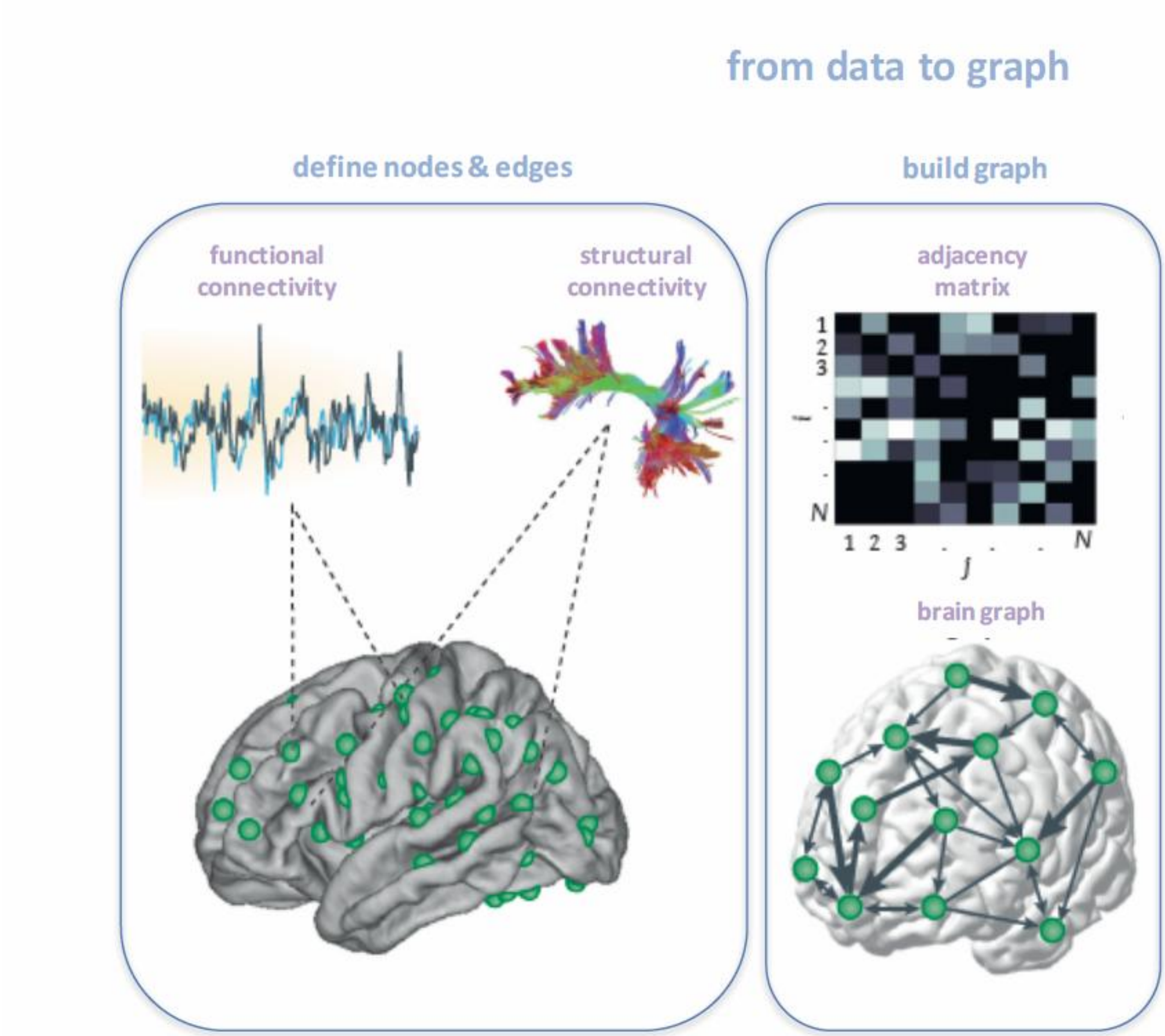
Neurophysiology (EEG/MEG) connectivity

Asymmetry of the distribution of phase differences between two signals.
It reflects the consistency with which one signal is phase loked or lagging to another signal.
Synchronization Likelihood (SL), Phase Lag Index (PLI), waited PLI (wPLI) … etc



Friston et al, 1994, Hum Brain Mapping; Fornito et al, 2015, Nat Rev Neurosci

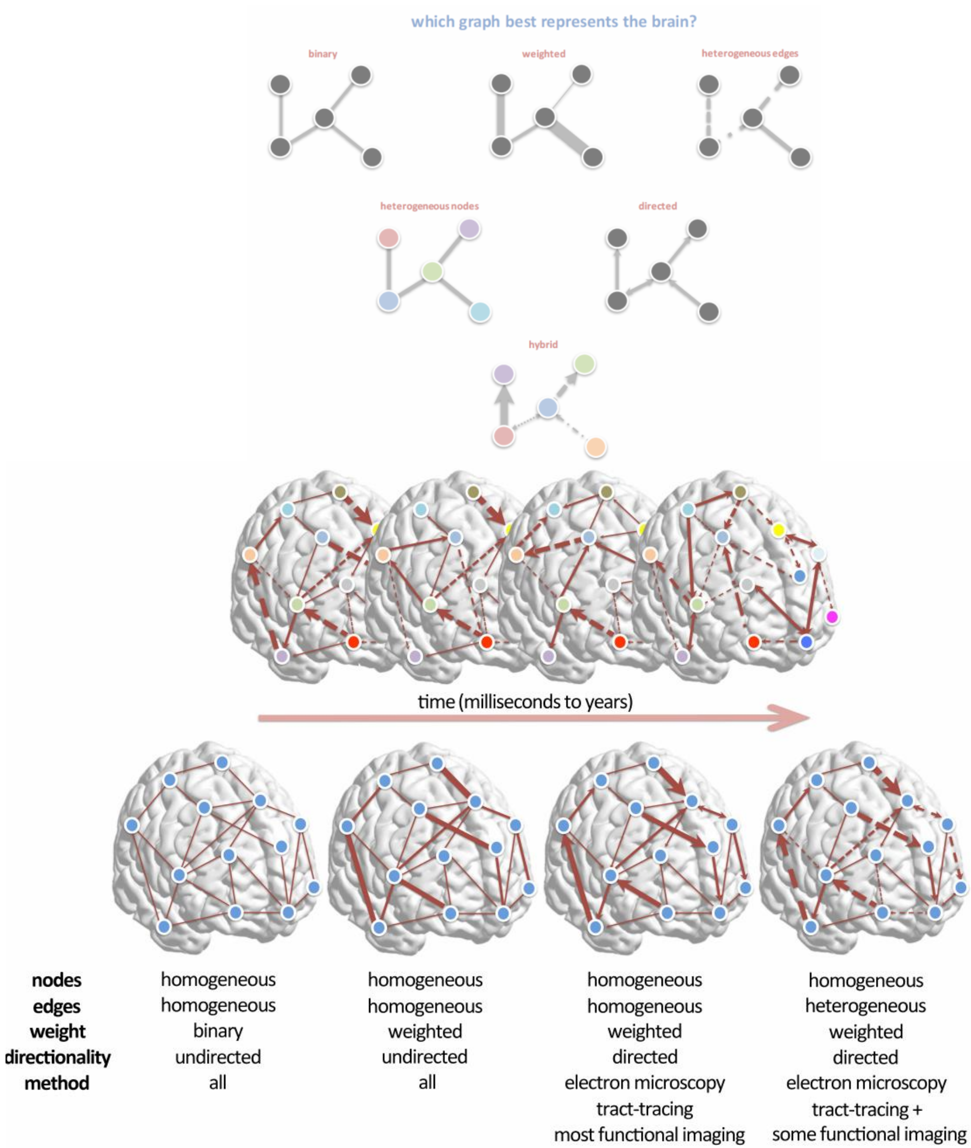
Connectivity Matrix

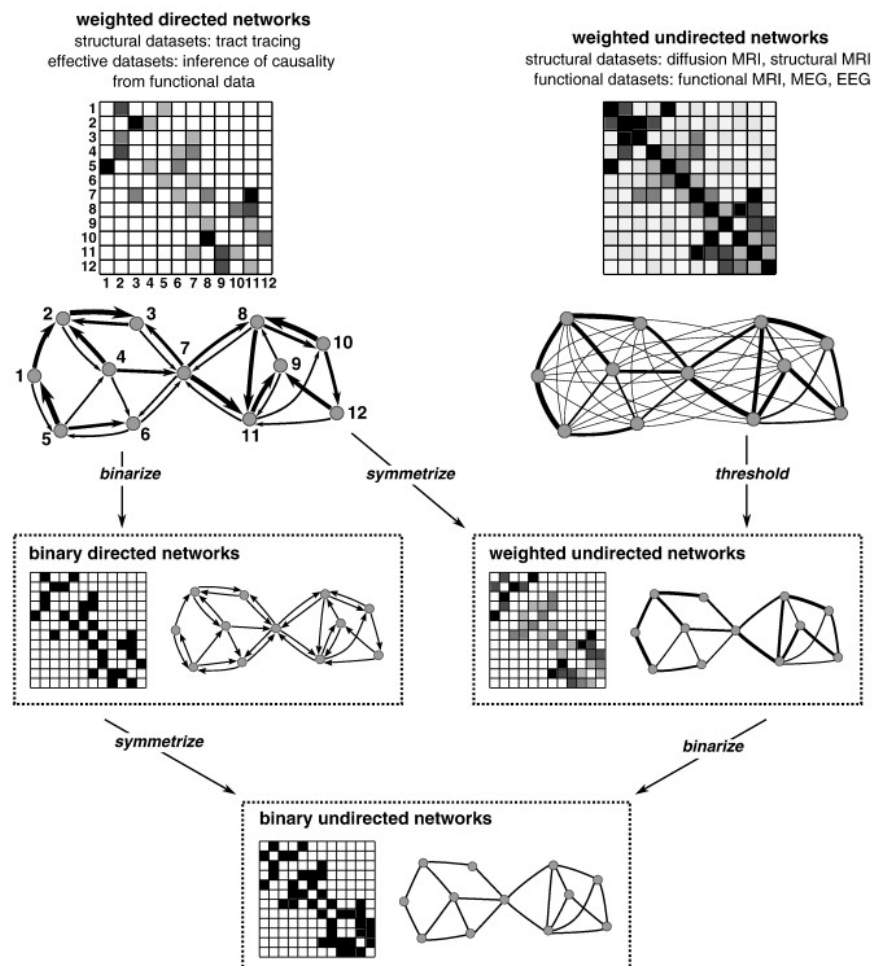


Fornito et al. , Nat Rev Neurosci 2015

Binary vs Weighted / Directed vs Undirected:

In addition to the type of connectivity (anatomical, functional or effective) and measure-specific (e.g., time scale) features of connectivity, links are also differentiated on the basis of their weight and directionality.





Fornito et al. 2013, NeuroImage; Fornito et al. 2016, *Fundamentals of Brain Network Analysis*
Rubinov et al. 2010, Neuroimage

Thresholding and Sparsity

1. Global thresholding

- Weight-based thresholding
- Density-based thresholding
- Consensus thresholding

2. Local thresholding

- Minimum spanning tree
- Disparity filter
- Multi-scale methods

Benefits of Thresholding

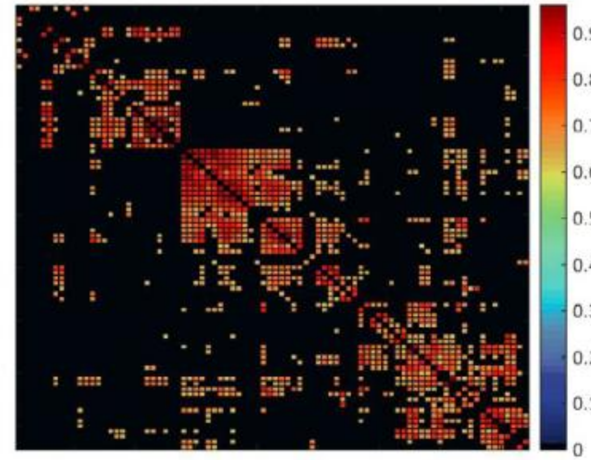
✓ Remove spurious connections, thereby improve specificity
✓ Emphasize topological properties
✓ Simplify graph analysis

Connectivity Matrix

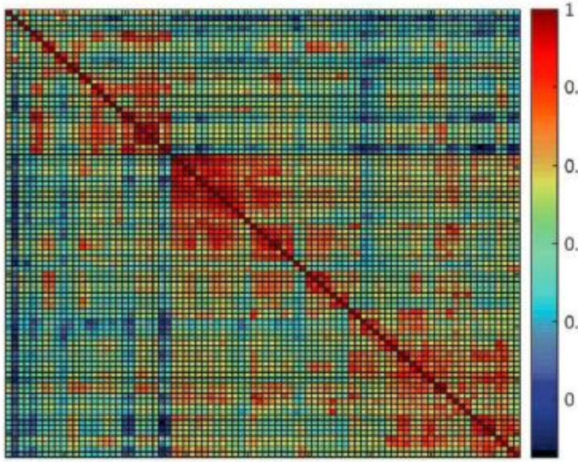
Waited Based

$$A_{ij} = \begin{cases} C_{ij} & \text{if } C_{ij} > \tau \\ 0 & \text{otherwise} \end{cases}$$

Thresholded, A_{ij}



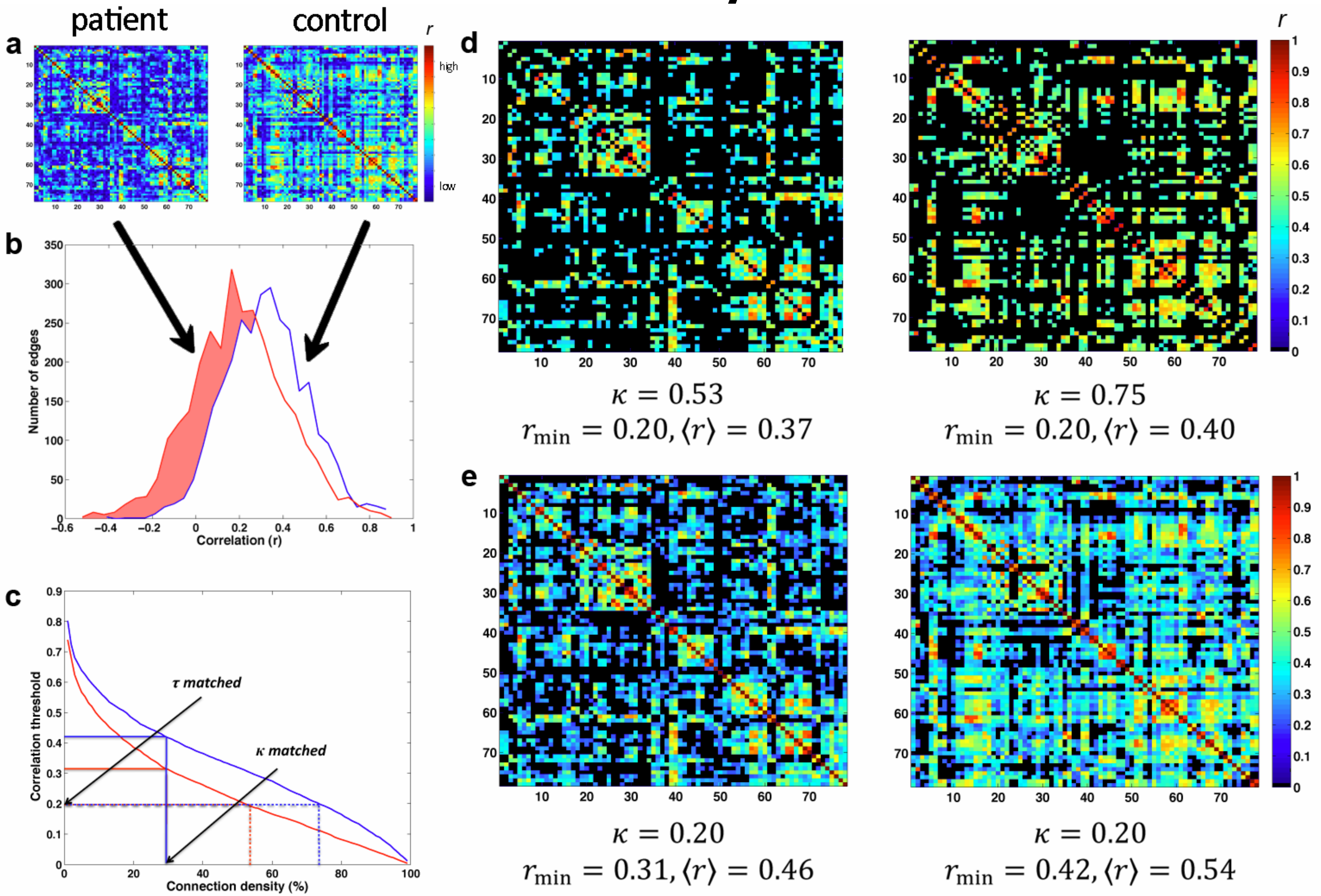
Unthresholded matrix, C_{ij}



Binarized, B_{ij}

$$B_{ij} = \begin{cases} 1 & \text{if } C_{ij} > \tau \\ 0 & \text{otherwise} \end{cases}$$

Connectivity Matrix



Connectivity Matrix

Consensus-based & group thresholding

- Eliminate connections that are not consistently identified in at least m of N individuals

Individual threshold

Group threshold

$$\frac{1}{N}\sum_{n}\left(\mathbf{1}_{C_{ij}(n)\geq\tau}\right) < m$$

$$\Rightarrow C_{ij}(n) \leftarrow 0 \quad \forall n$$

n indexes individuals

de Reus & van den Heuvel et al, 2013 ; Mišic et al, 2015

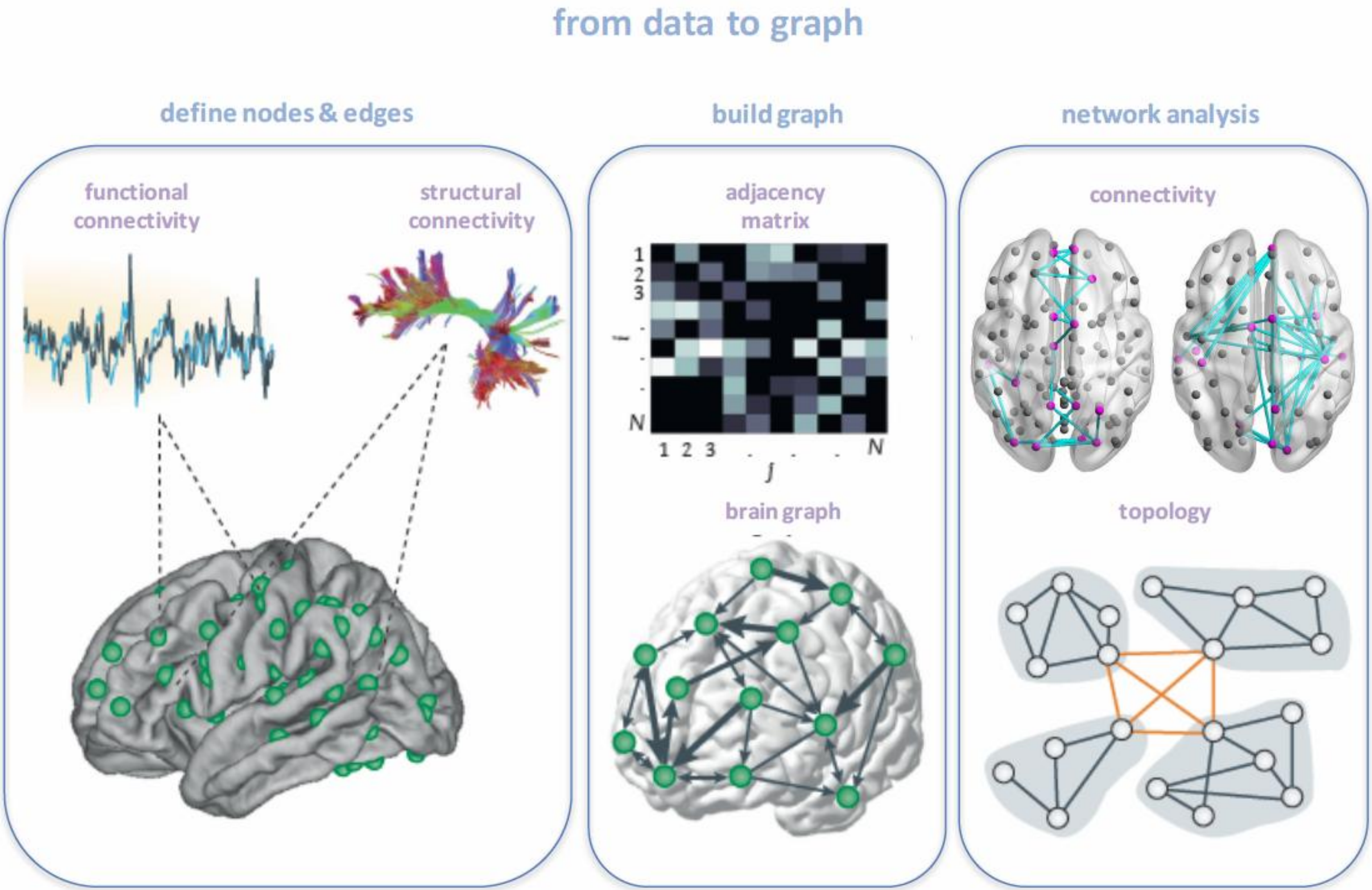
Connectivity Matrix

Assumptions made by global thresholding

1. Assumption: Thresholds and connection densities are typically chosen arbitrarily
   - *Alternatives*: Area under curve

2. Assumption: Weak connections are spurious connections
   - Is a weak connection spurious, or is a weak connection simply a weak connection?
   - Connection strength versus connection probability

Small-World measure: in Neuroscience



Small-World measure: in Neuroscience

✓ **Measures of functional segregation:**

Network measures are often represented in multiple ways. Thus, measures of individual network elements (such as nodes or links) typically quantify connectivity profiles associated with these elements and hence reflect the way in which these elements are embedded in the network.

Simply-measures of segregation are based on the number of triangles in the network, with a high number of triangles implying segregation

- *clustering coefficient / Transitivity*
- *modular structure* (community structure) / *modularity*
- *Local efficiency*

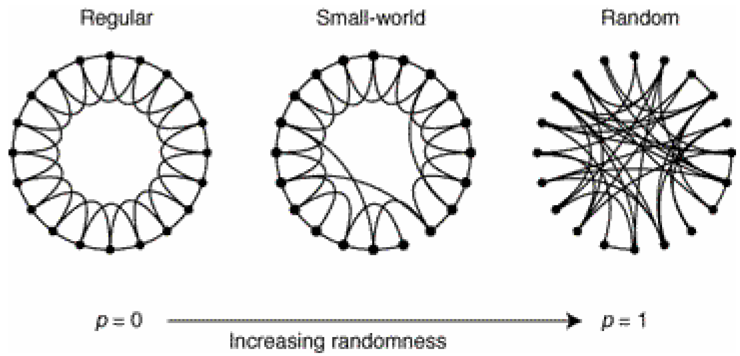
✓ **Measures of functional integration:**

Functional integration in the brain is the ability to rapidly combine specialized information from distributed brain regions. Measures of integration characterize this concept by estimating the ease with which brain regions communicate and are commonly based on the concept of a path.

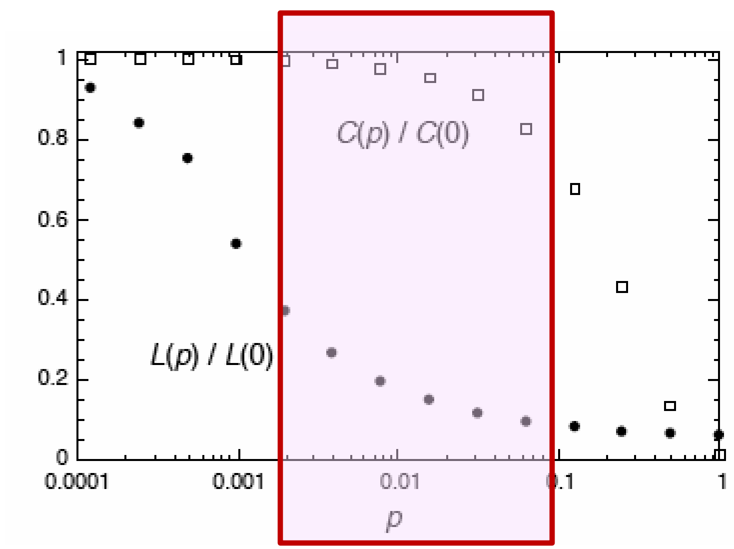
- Path Length
- Global Efficiency

major discoveries in graph theory & network science : Small-Worldnes

↑ clustering
↑ path length



↓ clustering
↓ path length



Watts and Strogatz, Nature, 1999

Small-World Connectivity: in Neuroscience

- A well-designed anatomical network could therefore combine the presence of functionally specialized (segregated) modules with a robust number of intermodular (integrating) links. Such a design is commonly termed small-world

- Small-world networks are formally defined as networks that are significantly more clustered than random networks, yet have approximately the same characteristic path length as random networks ([Watts and Strogatz, 1998]()). More generally, small-world networks should be simultaneously highly segregated and integrated.

- Calculated as the normalized ratio of the clustering coefficient to the characteristic path length. Networks with small-world architecture have small-world index >1, along with clustering coefficient >1 and characteristic path length ≈1

Network small-worldness (Humphries et al., 2008),

$$S = \frac{C/C_{\mathrm{rand}}}{L/L_{\mathrm{rand}}},$$

where C and C_{rand} are the clustering coefficients, and L and L_{rand} are the characteristic path lengths of the respective tested network and a random network. Small-world networks often have $S \gg 1$.

Global Efficiency & Local Efficiency

- **GE:** Calculated as the average of the inverse of the shortest path lengths in a network. Measure of network's ability for parallel information transfer

Global efficiency of the network (Latora and Marchiori, 2001),

$$E = \frac{1}{n}\sum_{i \in N} E_i = \frac{1}{n}\sum_{i \in N} \frac{\sum_{j \in N, j \neq i} d_{ij}^{-1}}{n-1},$$

where E_i is the efficiency of node i.

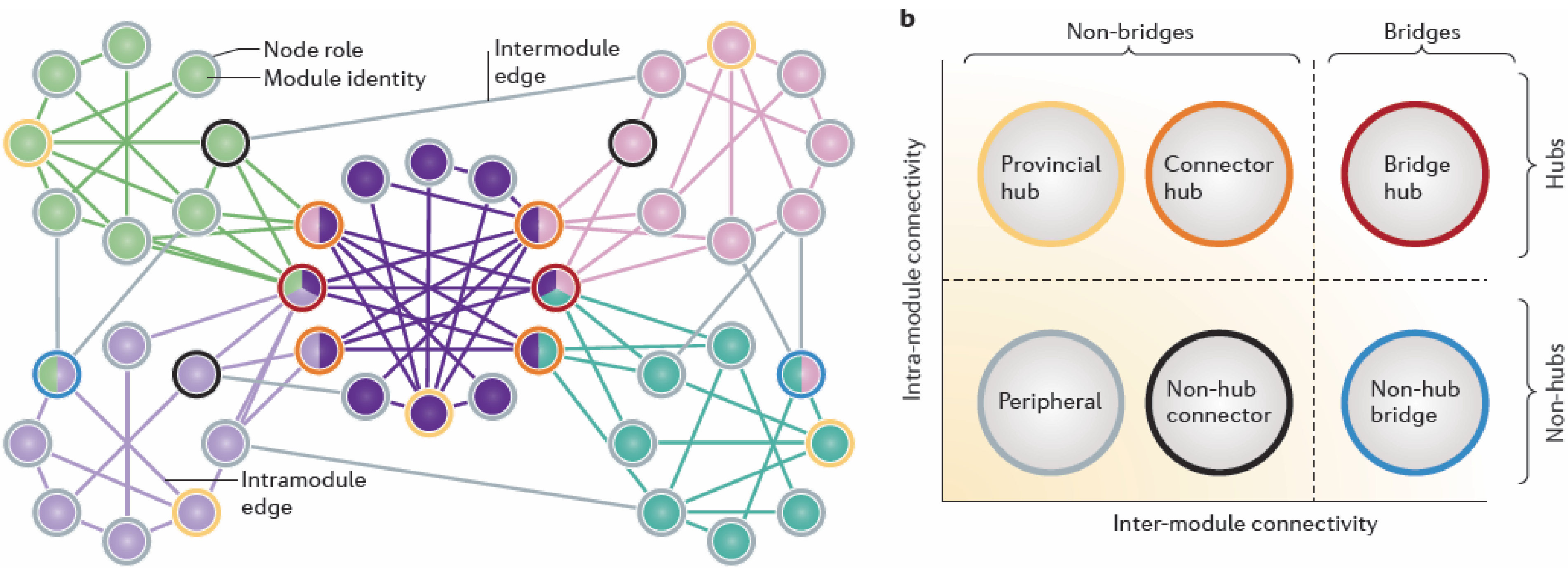
- **LE:** Calculated as the inverse of the average shortest path connecting the given node with all other nodes. Provides a measure of the efficiency of a given node in communicating with the rest of the brain

Local efficiency of the network (Latora and Marchiori, 2001),

$$E_{\text{loc}} = \frac{1}{n}\sum_{i \in N} E_{\text{loc},i} = \frac{1}{n}\sum_{i \in N} \frac{\sum_{j,h \in N, j \neq i} a_{ij} a_{ih} \left[d_{jh}(N_i)\right]^{-1}}{k_i(k_i - 1)},$$

where $E_{\text{loc},i}$ is the local efficiency of node i, and $d_{jh}(N_i)$ is the length of the shortest path between j and h, that contains only neighbors of i.

Hubs: in Neuroscience



Statistics

Student t test (Ttest 2) : for two group

$$\sum_{i}^{j} [p,h] = \text{ttest 2 (a,b,'p-value','tailing')}$$

More Than Two group (anova1):

$$\sum_{i}^{j} [p,table,stats] = \text{anova1}(X)$$

p = anova1(X) performs balanced one-way ANOVA for comparing the means of two or more columns of data in the matrix X, where each column represents an independent sample containing mutually independent observations. The function returns the p value under the null hypothesis that all samples in X are drawn from populations with the same mean.

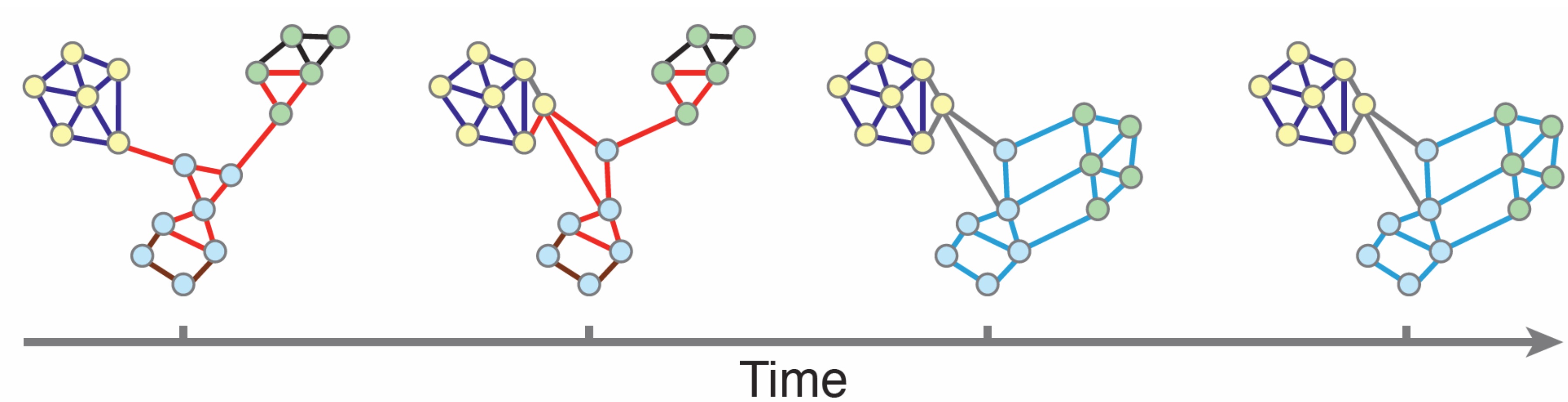
Multiple comparison test:

$$\sum_{i}^{j} [c,m,h,stats] = multcompare(s)$$

c = multcompare(stats) performs a multiple comparison test using the information in the stats structure, and returns a matrix c of pairwise comparison results. It also displays an interactive graph of the estimates with comparison intervals around them

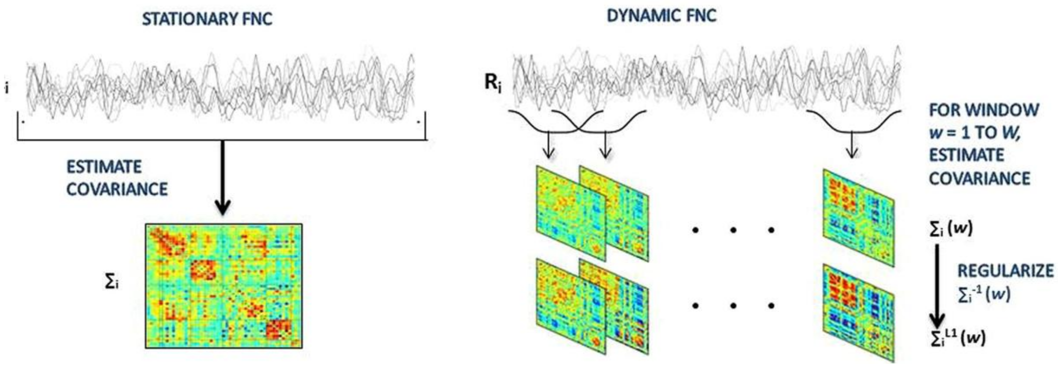
✓ Statement of the problem…

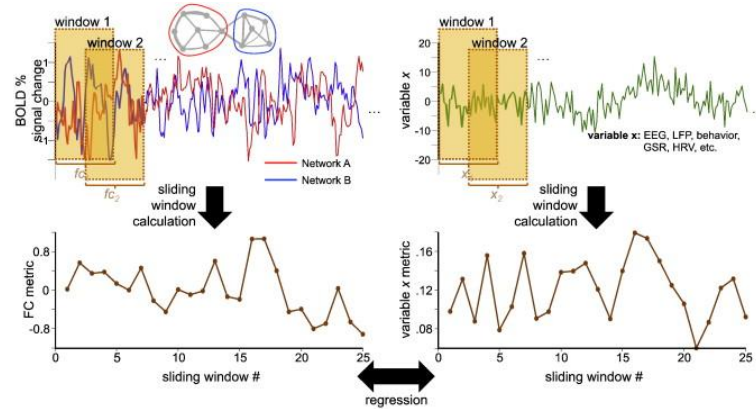
Over carton time for a particular function…Brain Networks are ***Similar not Same***



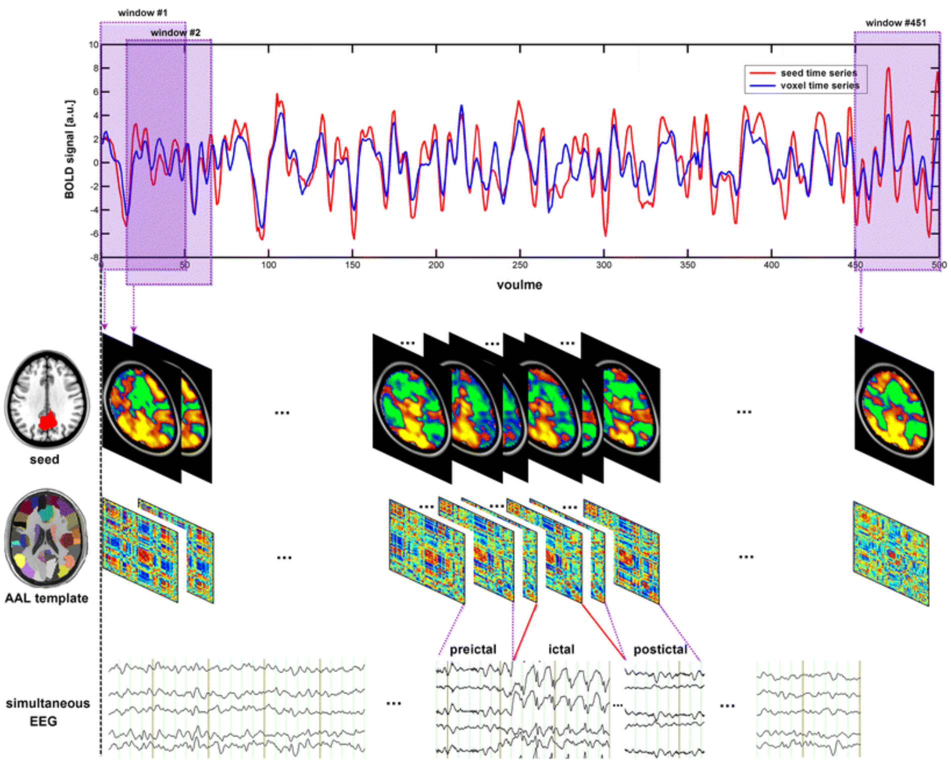
….. Solution: Dynamic characterise Graph theory measures

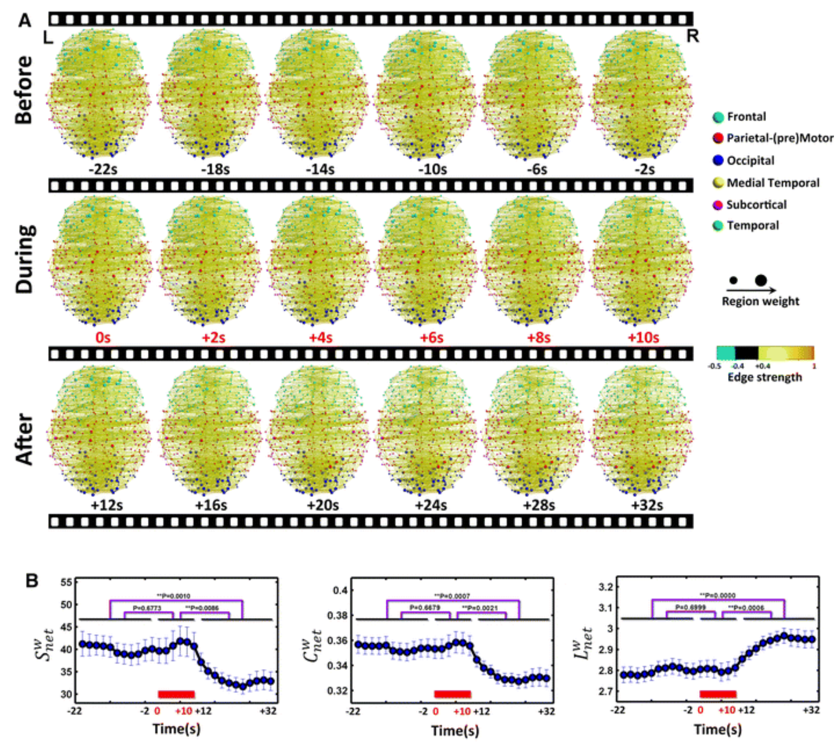
Dynamic Small World Connectivity





Hutchison et al. Neuroimage, 2014

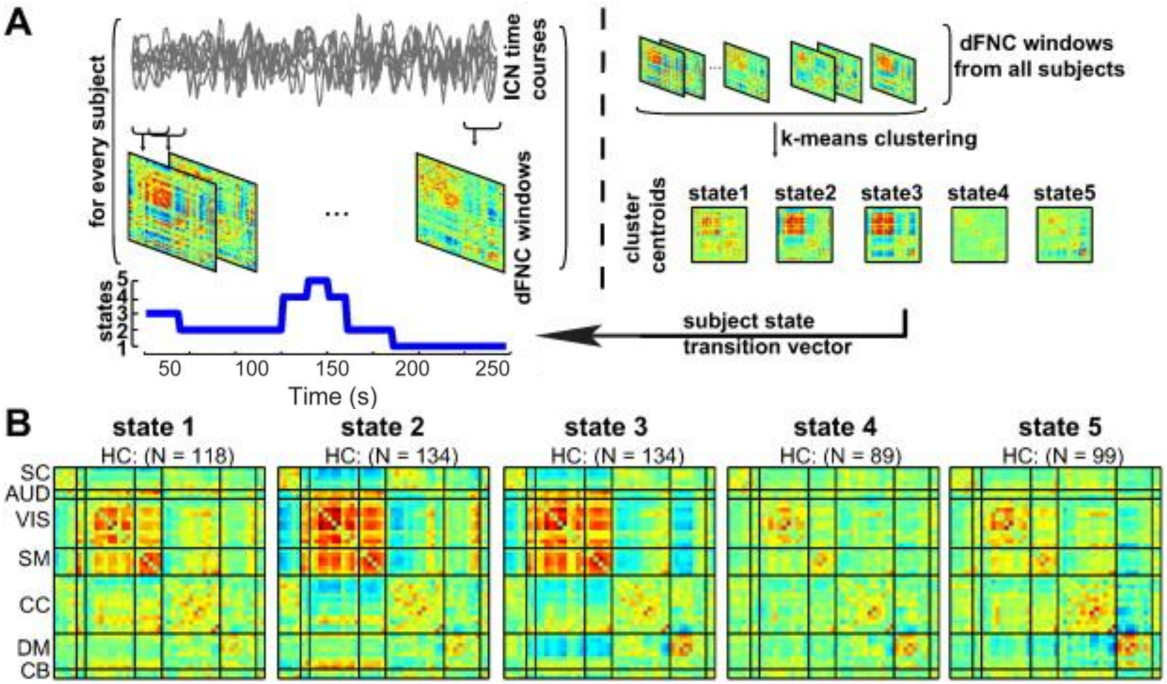


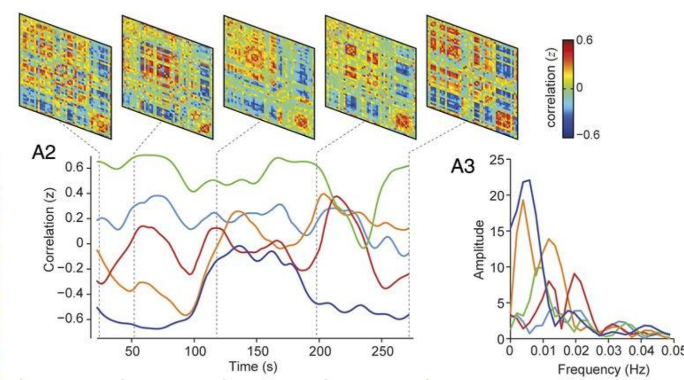


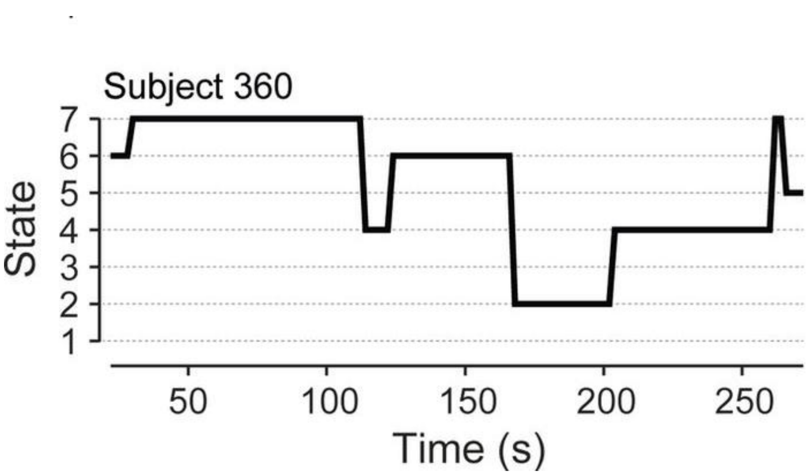
Wei Liao et al. Brain Structure and Function, 2014

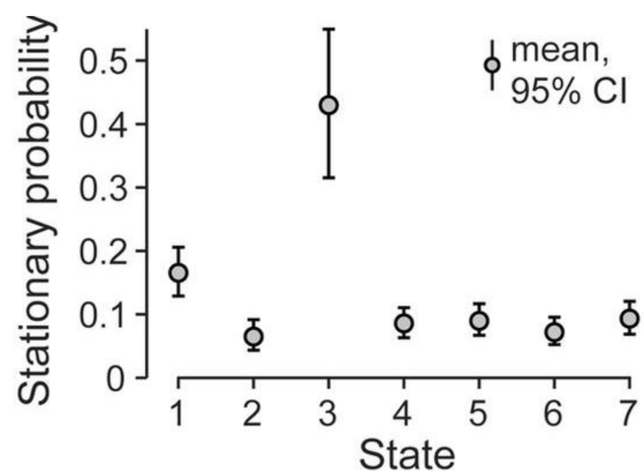
Dynamic Connectivity :

...State to Microstate



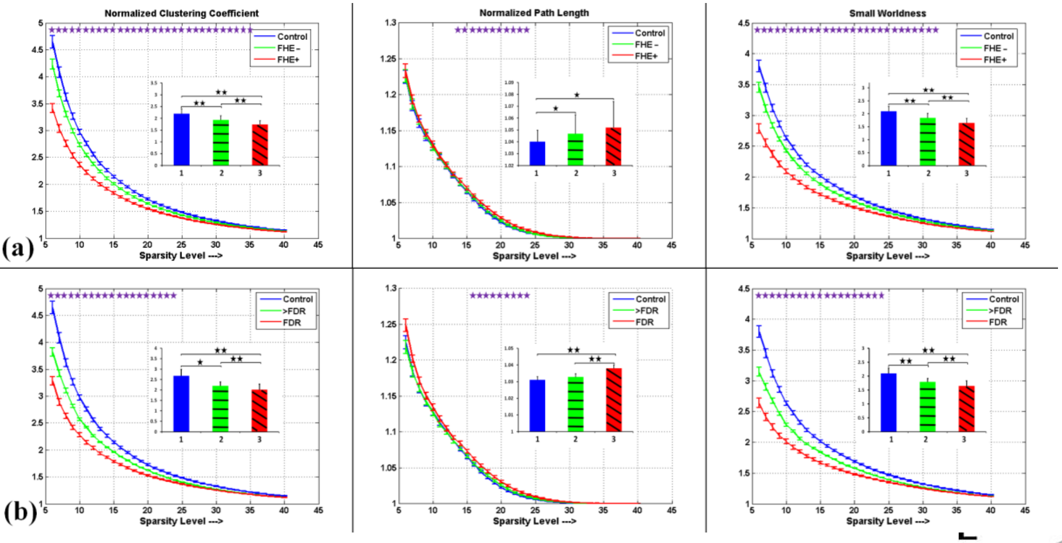






Elena A. Allen et al. Cereb. Cortex, 2014
Damaraju et al, Neuroimage, 2014
Barttfelda, PNAS, 2014
Fukushima, Neurons and Cognition, 2015

Application: Reduced small world brain connectivity in probands with a family history of epilepsy



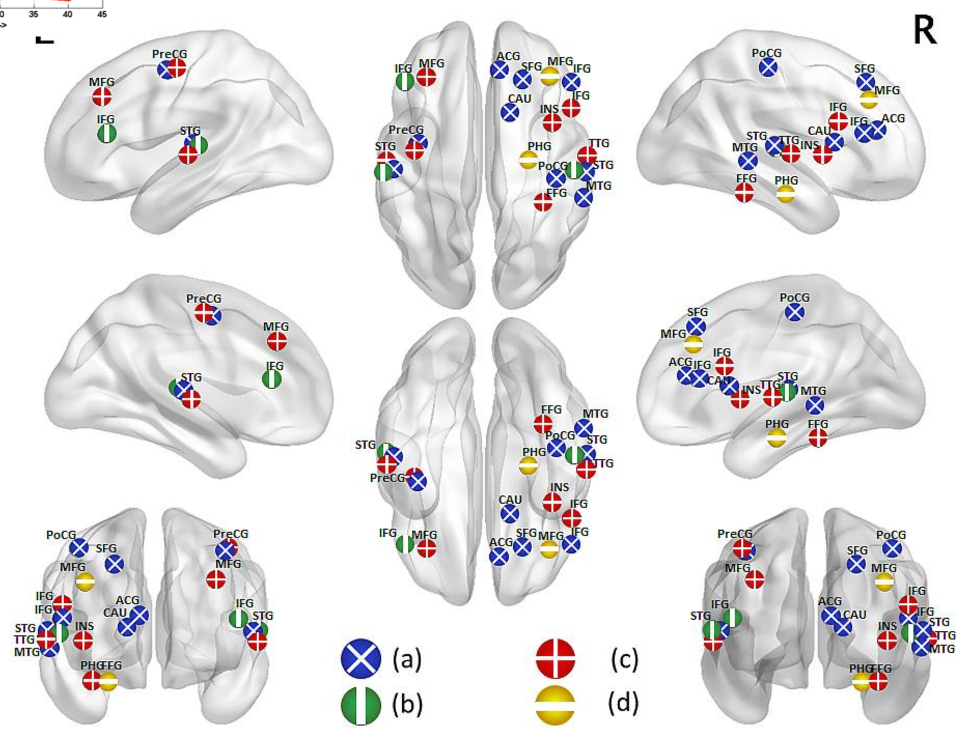
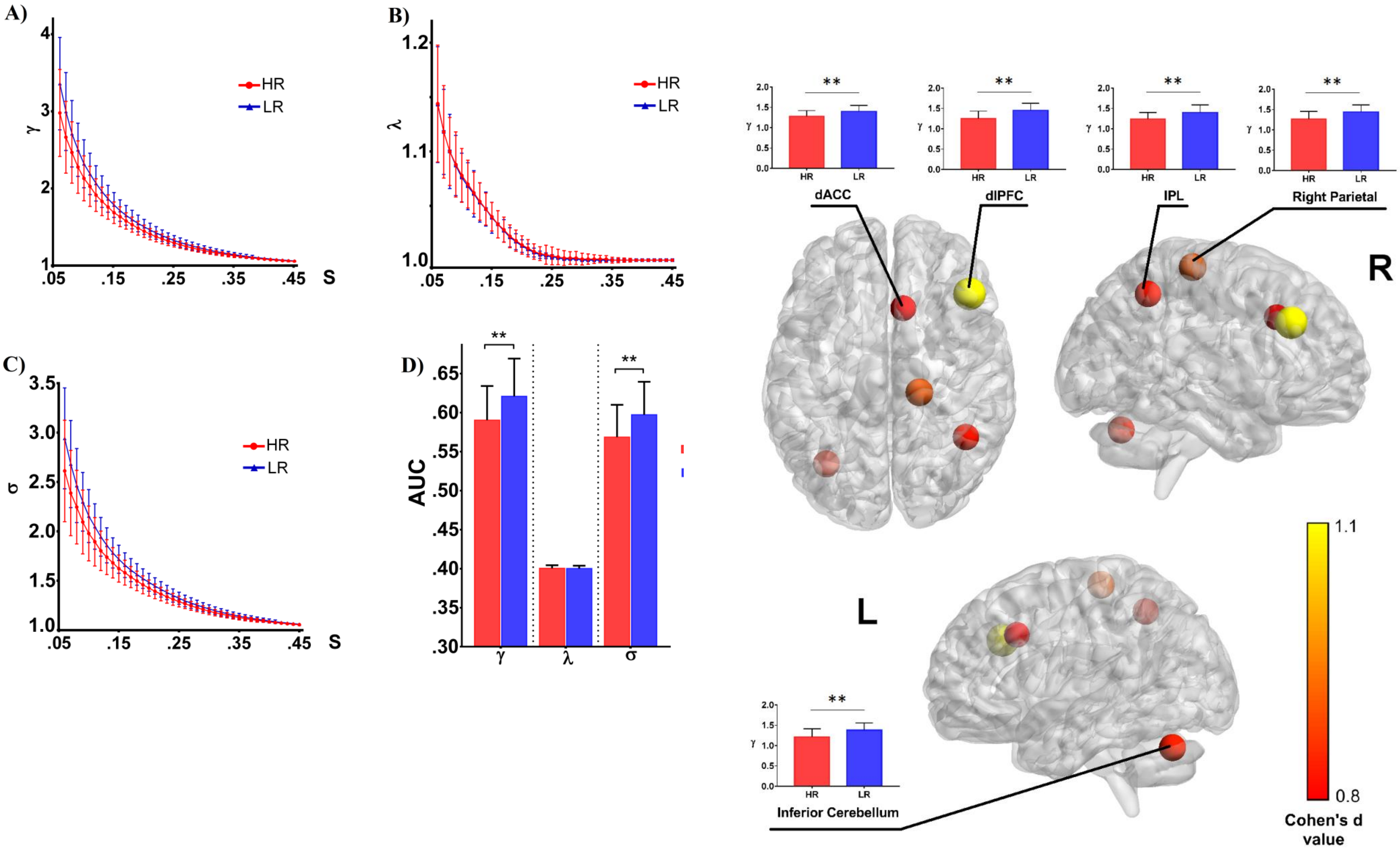
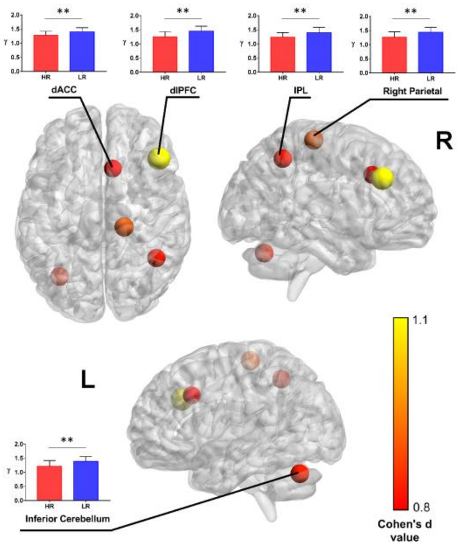


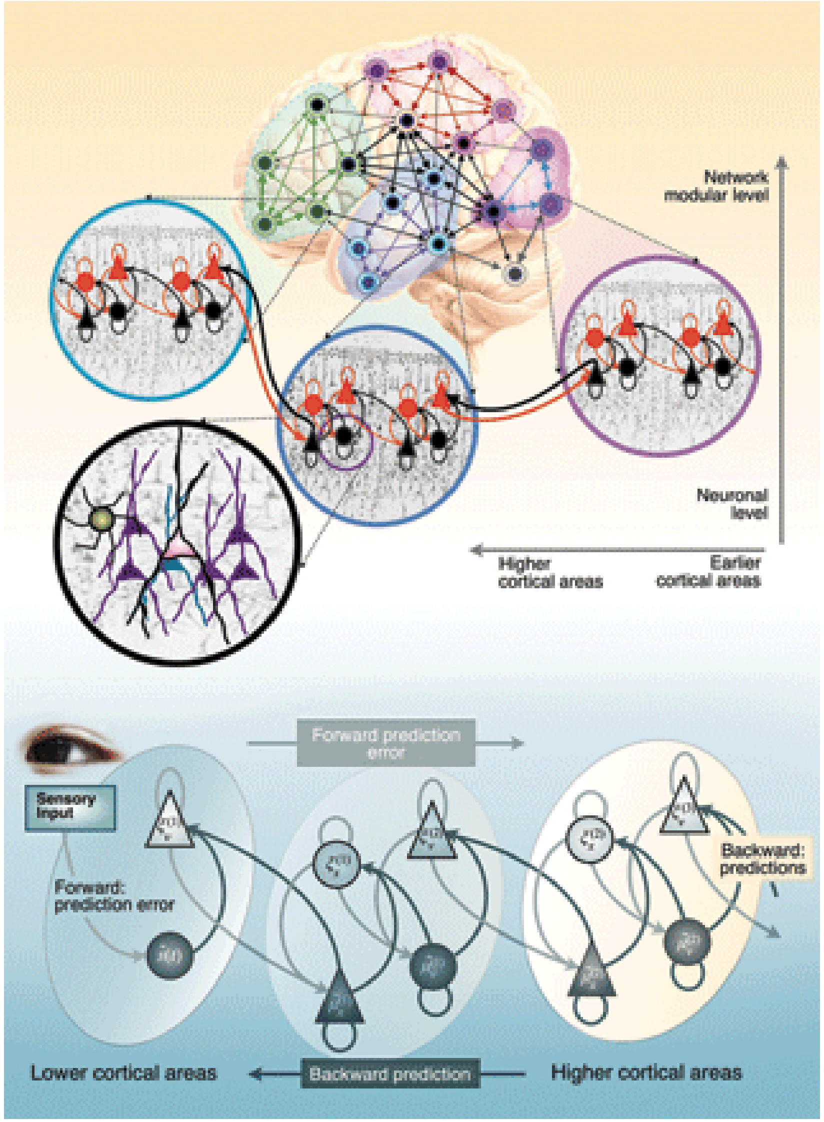
Figure 2 The brain regions derived from the normalized clustering coefficient. The brain regions that showed significant differences (P < 0.0062 FDR) between the patient groups (sparsity 6%–40%) were rendered onto a surface model of the brain: (a) represents the difference between FHE+ and FHE, (b) between FDRs and >FDR, (c) between Sibs with Mat and Pat groups and (d) between FHE of HWE and FHE other than HWE.

Application: Disrupted Resting Brain Small -Worldness Predicts Greater Externalizing Symptoms in Children of Alcoholics



Application: Small world brain dynamics at cognitive task performance state





Summury

Graphs provide useful models of brain networks

A unified framework for representing multiscale organization

There are different methods for defining brain nodes and edges

Each has pros and cons, and constrains interpretation of findings

Brain networks can be analysed at the level of connectivity or topology

Effects can be mapped at individual edges, nodes, or globally

Null models should be chosen carefully

Different methods/measures/questions require specific null models

Dynamic brain connectivity may explain in depth of network properties

Resources

graph theory/network science

Newman (2010) Networks: An introduction.
Newman (2003) SIAM Rev.
Albert & Barabasi (2002) Rev Modern Physics

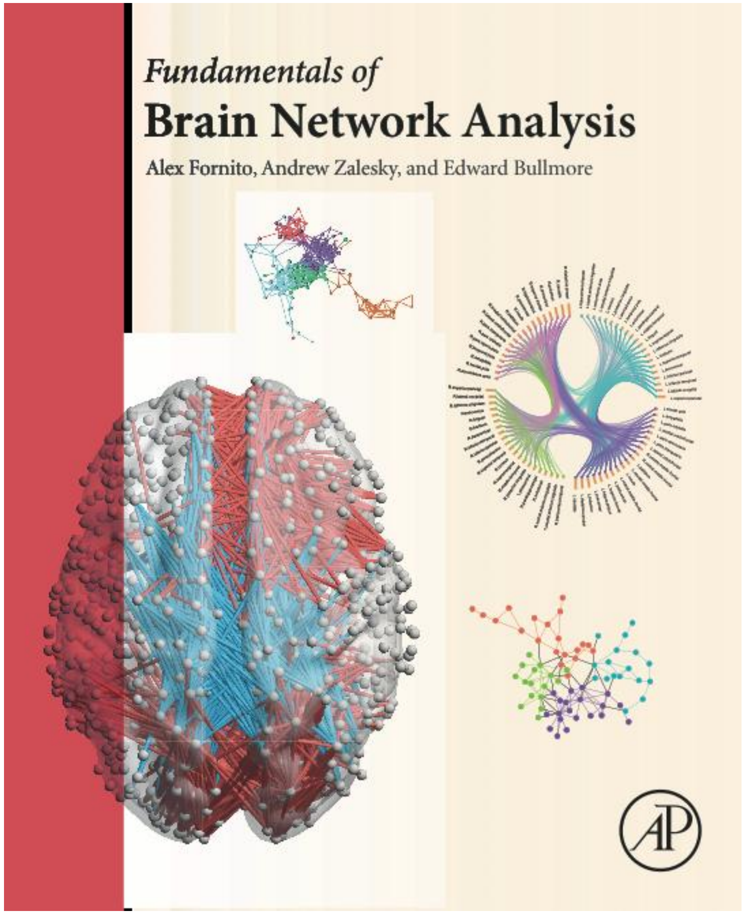
graph theory and the brain

Sporns (2011) Networks of the brain.
Sporns (2012) Discovering the human connectome.
Bullmore & Sporns (2009) Nat Rev Neurosci.
Bullmore & Bassett (2011) Annu Rev Clin Psychol.
Fornito, Zalesky & Breakspear (2013) NeuroImage.

Software's

BCT: brain connectivity toolbox

NBS: network-based statistic



Thank You