Network Analysis I & II

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Outline

Lecture One:

1. Complexity in the Human Brain
– from processes to patterns

2. Graph Theory and Complex Network Theory
– study of patterns
– use in neuroimaging
– the brain as a complex network

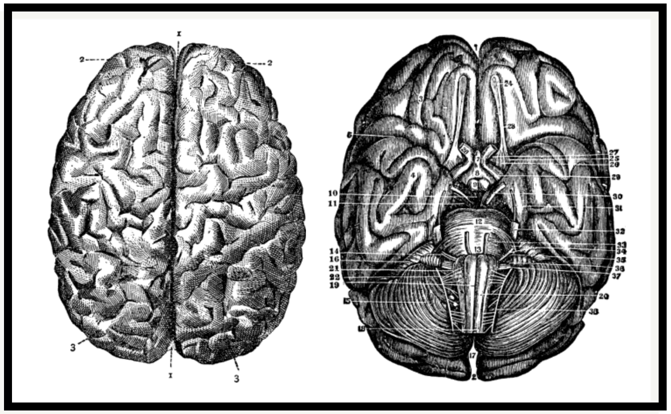
3. Connectivity and Graph Properties
– Definitions
– Example Applications

Lecture Two:

3. Methods for Comparing Networks
4. Methods for Dynamic Networks

Complexity in the Human Brain

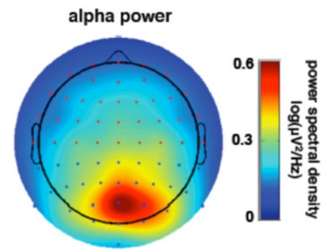
The human brain is complex over multiple scales of space and time …

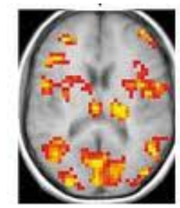


and can be examined using both low and high order statistics.

Univariate Measures – Magnitude, Power, etc.

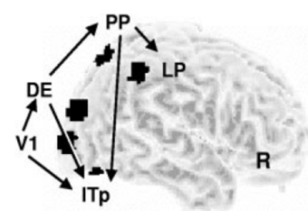
- Single regions





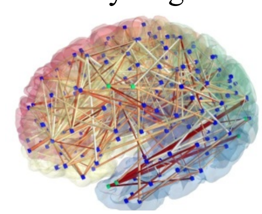
Bivariate Measures – Functional Connectivity

- Two regions

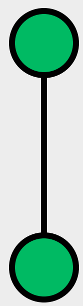
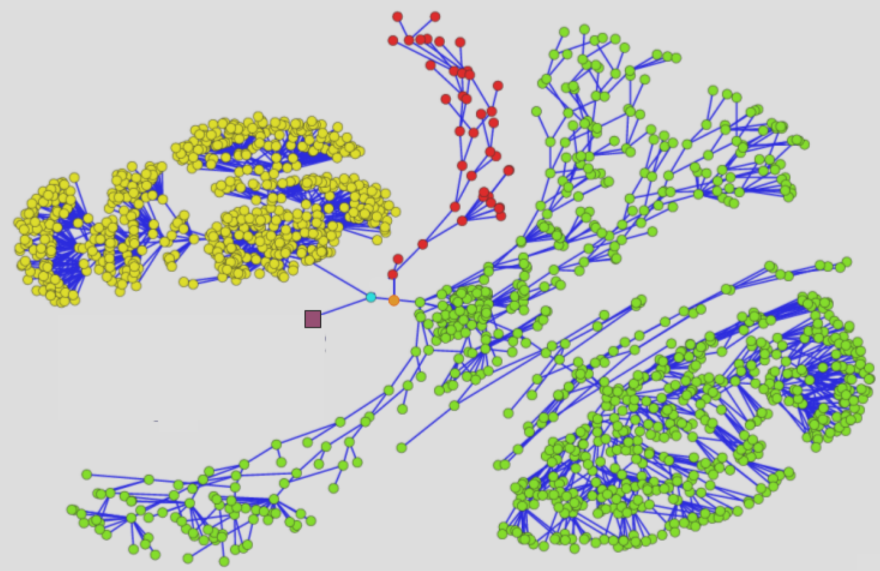


Multivariate Measures – Network Analysis

- Many Regions

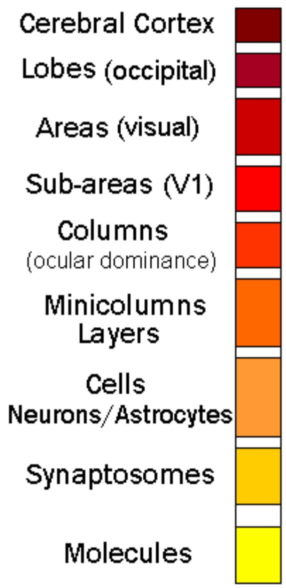


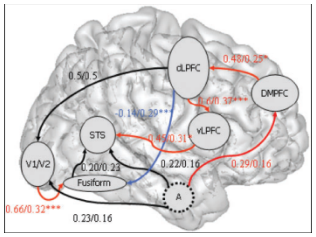
Complexity in the Human Brain

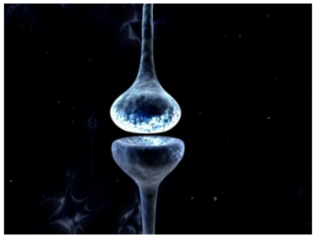
Univariate	Bivariate	Multivariate
		
Process	Interaction	Pattern

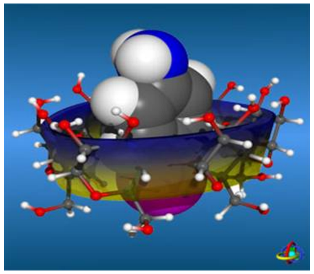
Why Higher Order Statistics?

Interactions









The function of the brain is built on multi-scale interactions.

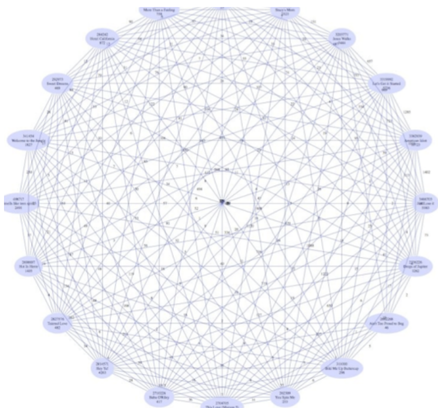
Patterns

While the function of the brain is built on multi-scale interactions, **cognition** is only possible through the combined interactions of neurons, ensembles of neurons, and larger-scale brain regions that make **oscillatory activity** and subsequent information transfer possible.

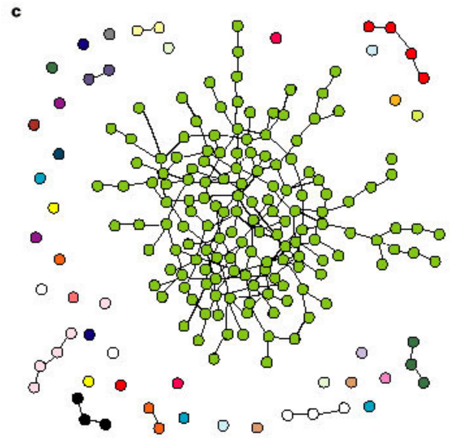
Necessitates an examination of not just **bivariate** interactions but also **multivariate** interactions over a range of spatial scales.

Patterns

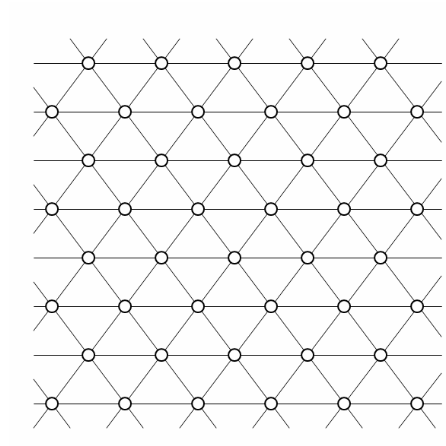
Dense

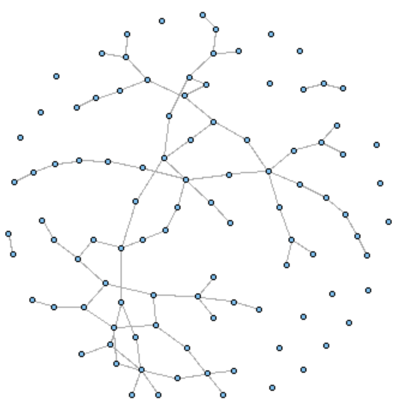


Fragmented

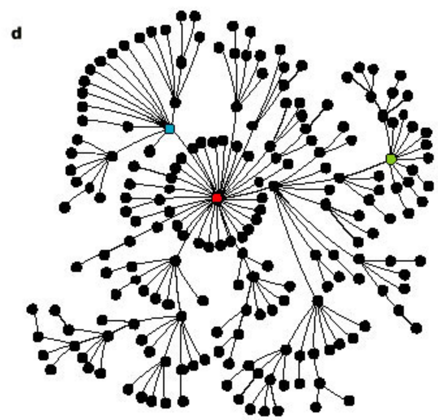


Ordered

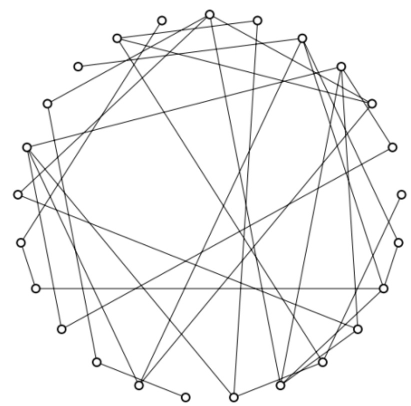




Sparse

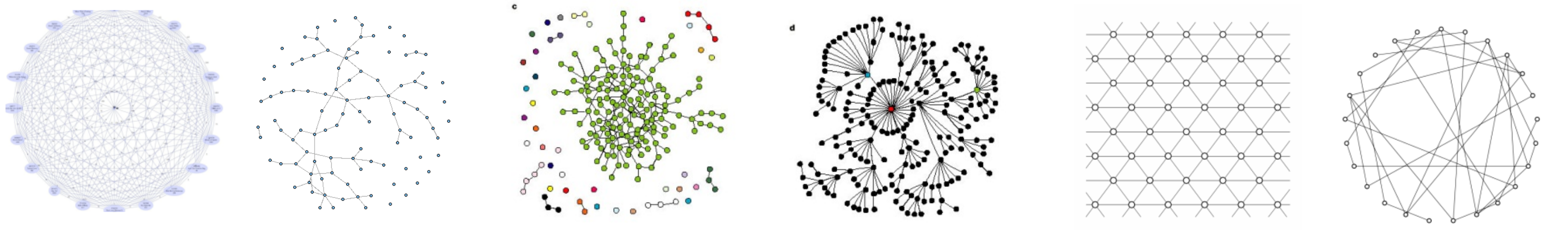


Connected



Random

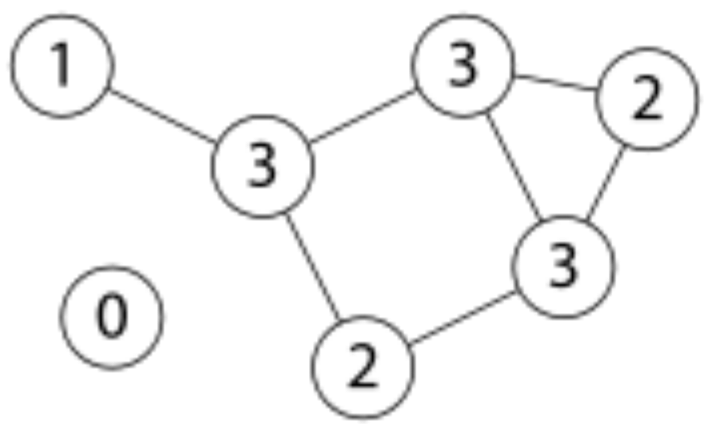
Graphs



How do we quantitatively assess these patterns?

We can use the branch of mathematics known as **Graph Theory**, and its sub-branch **Complex Network Theory**.

A graph is composed of nodes and edges.

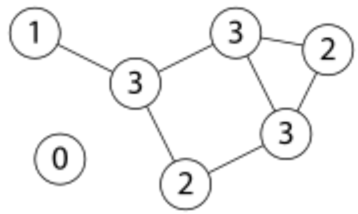


The degree of a node is equal to the number of its edges.

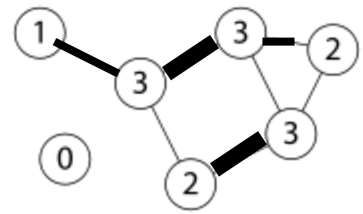
Types of Graphs

Graphs come in many flavors.

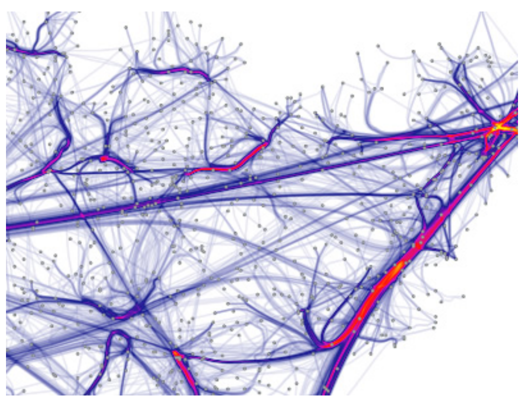
Binary Graph:



Weighted Graph:

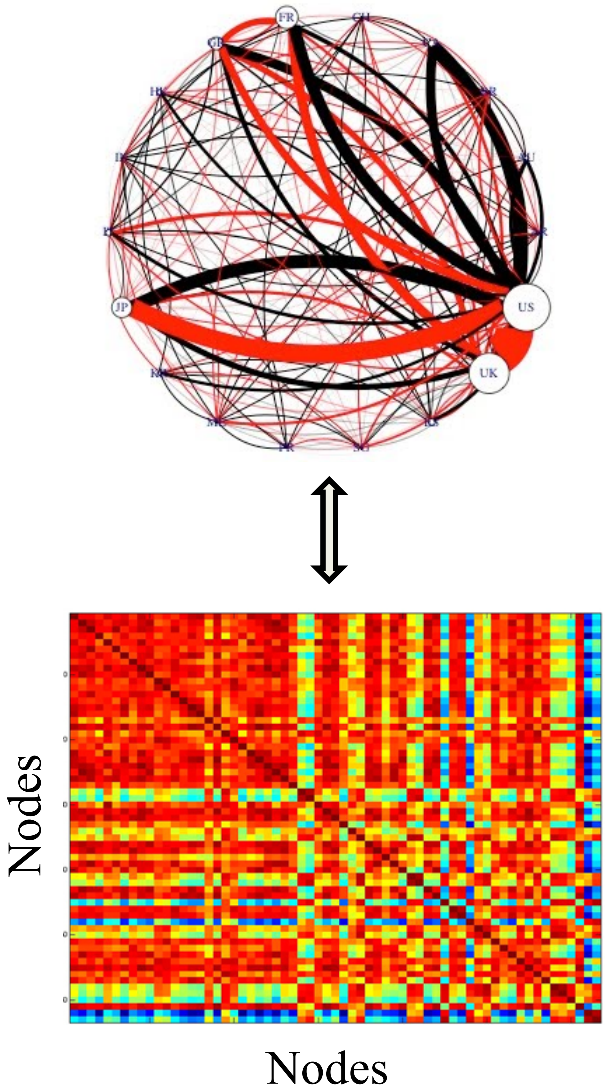


Examples of Weighted Graphs:



These visualizations have embedded the graph into some sort of space: the physical space of the US (left) or spherical space (right).

Graphs & Matrices



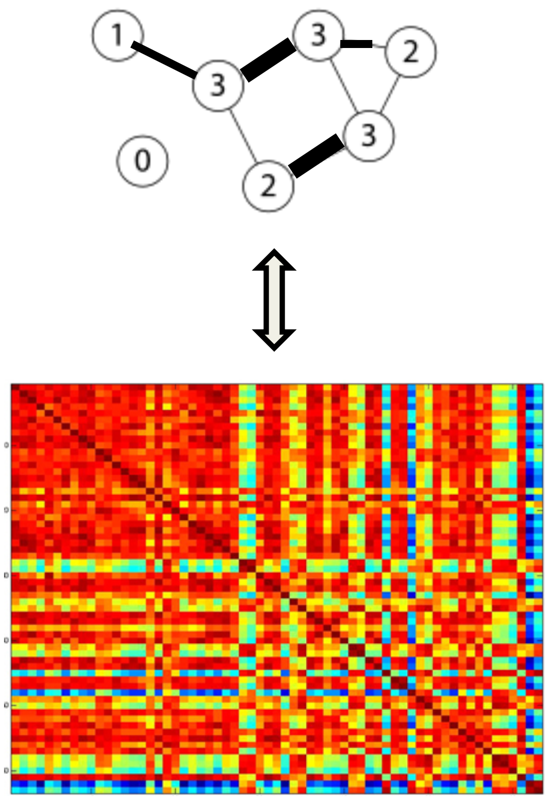
Graphs or Networks
can also be represented by Matrices

Graph/Network nodes are represented by the columns or rows of the matrix.

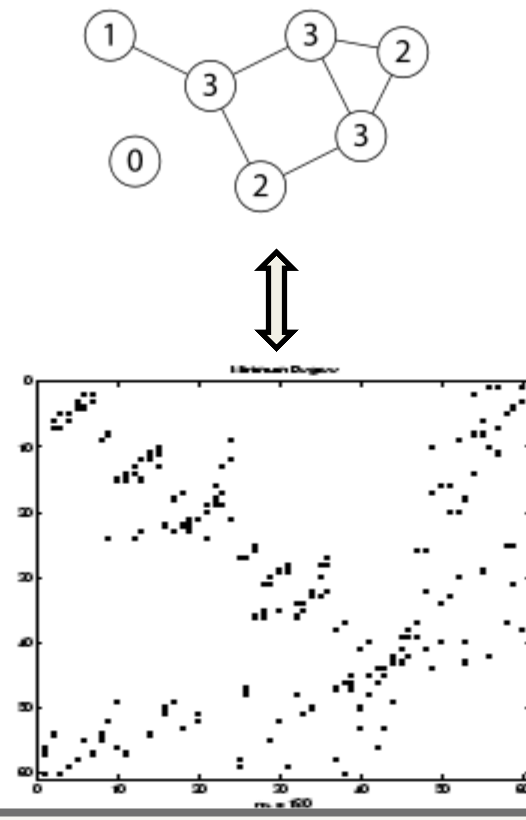
A connection between two nodes i and j is represented by matrix element (i,j).

Graphs & Matrices: Binary and Weighted

For weighted networks, matrix elements are continuous values and can range from strong (high valued number) to weak (low valued number).



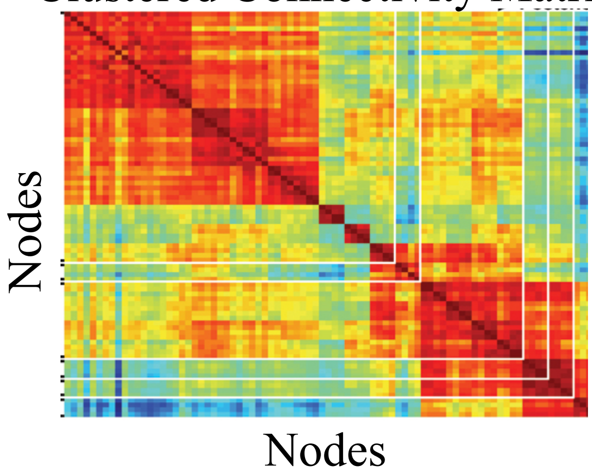
For binary networks, matrix elements are either 0 (connection does not exist) or 1 (connection exists).



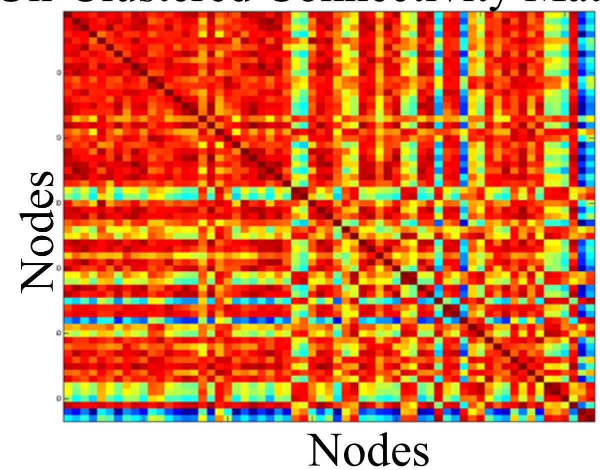
Danielle S. Bassett, Ph. D.

Patterns in Matrices

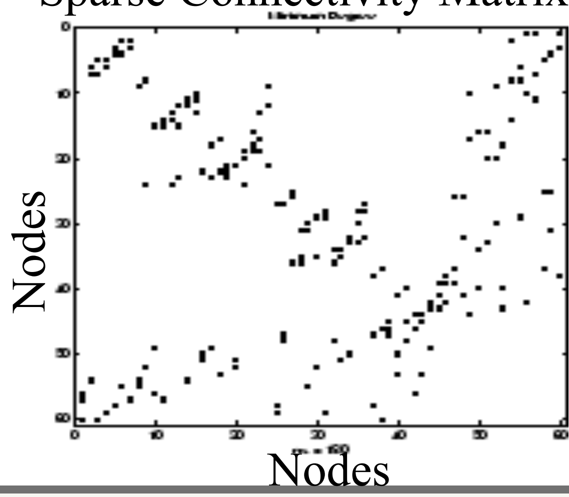
Clustered Connectivity Matrix



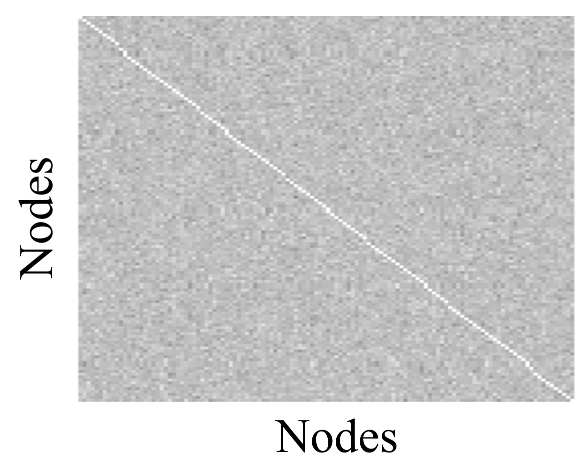
Un-Clustered Connectivity Matrix



Sparse Connectivity Matrix

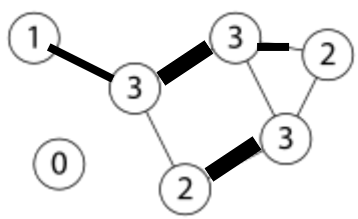


Dense Connectivity Matrix

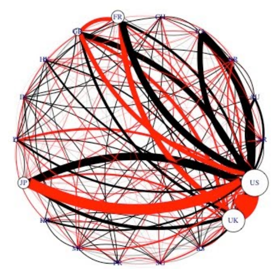


Patterns: Graphs, Networks, and Matrices

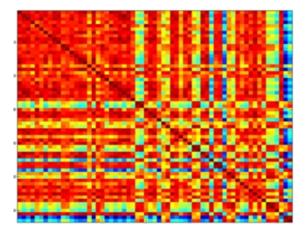
Graph



Embedded Network



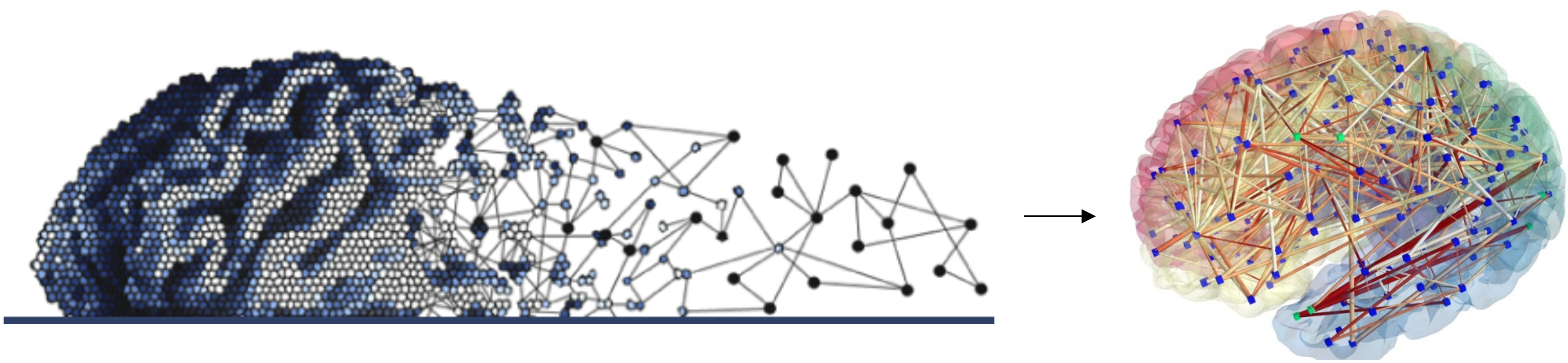
Matrix



Equivalent visualizations of the same information

Complex Network Theory in Neuroimaging

- A modeling endeavor that provides a set of representational rules that can be used to describe the brain in terms of its subcomponents (brain regions) and their relationships to one another (white matter tracts / functional connections)



Tools:
Graph Theory and
Statistical Mechanics

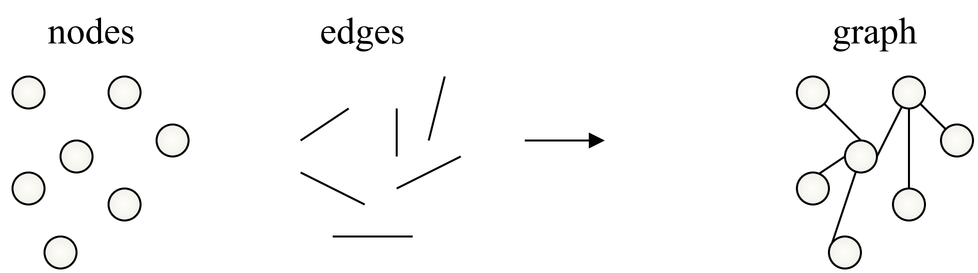


Image Credit: http://web.med.unsw.edu.au/bcw08/, http://public.kitware.com/ImageVote/

The Brain as a Complex Network

Brain networks can be constructed in two ways: one to denote structural connectivity, and one to denote functional connectivity.

Diffusion Tractography

Structural network

fMRI, EEG, MEG

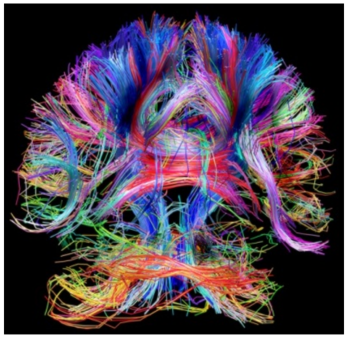
Functional network

The Brain as a Complex Network

Defining Nodes

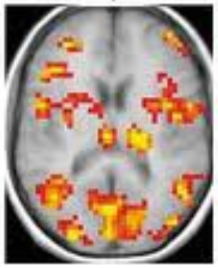
Structural network

Diffusion Tractography



Functional network

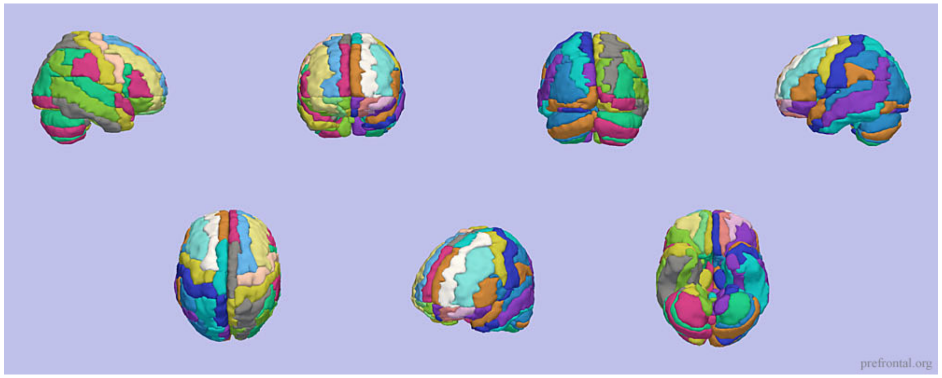
fMRI, EEG, MEG



Regional Parcellation Schemes

In Standard or Native Space

Ex: AAL, HO, LPBA40 or Freesurfer



Respecting Anatomical Boundaries or Not

Small Regions or Large Regions

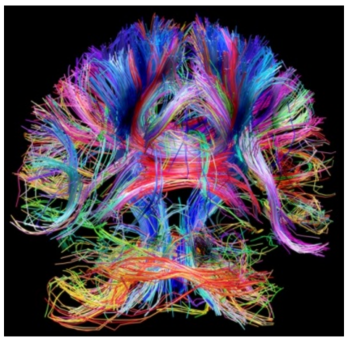
Voxel-based Parcellation Schemes

Ex: 3mm cubed, 6mm cubed, etc.

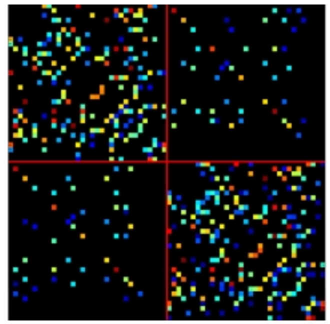
The Brain as a Complex Network

Defining Edges

Diffusion Tractography

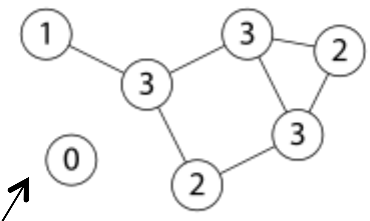


Connectivity Matrix



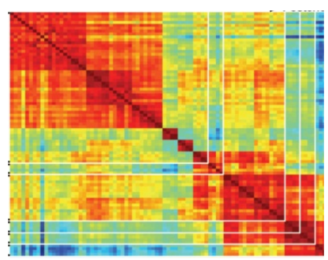
# of Tracts, FA, etc.

Binary Graph



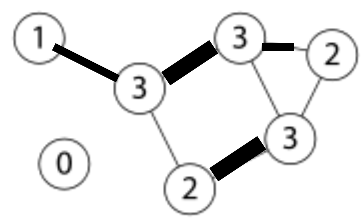
fMRI, EEG, MEG

Connectivity Matrix



Correlation, Causality, etc.

Weighted Graph



Biological Relevance of Network Architecture

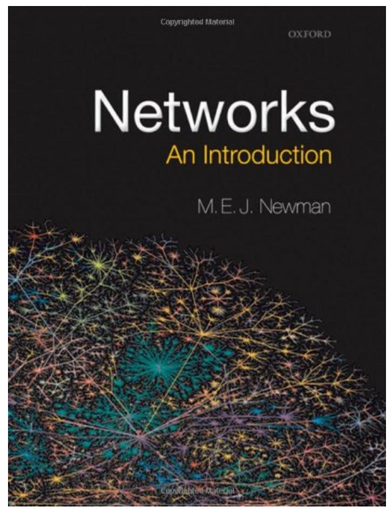
Complex brain networks have been shown to be sensitive to:

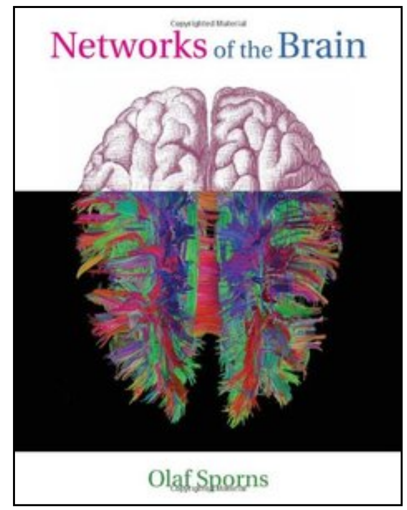
- **behavioral variability** (Bassett et al., 2009)
- **cognitive ability** (van den Heuvel et al., 2009; Li et al., 2009)
- **shared genetic factors** (Smit et al., 2008)
- **genetic information** (Schmitt et al., 2008)
- **experimental task** (Bassett et al., 2006; De Vico Fallani et al., 2008b)
- **age** (Meunier et al., 2009; Micheloyannis et al., 2009)
- **gender** (Gong et al., 2009)
- **drug** (Achard et al., 2007)
- disease such as **Alzheimer's** (He et al. 2008, Buckner et al. 2009, Supekar et al. 2008, Stam et al. 2007, Stam et al. 2009) and **schizophrenia** (Bassett et al. 2008, Lynall et al. 2010, Liu et al. 2008, Rubinov et al. 2009, Bassett et al. 2009, Micheloyannis et al., 2006) other clinical states such as **epilepsy** (Raj et al., 2010; Horstmann et al., 2010; van Dellen et al., 2009), **multiple sclerosis** (He et al., 2009b), **acute depression** (Leistedt et al., 2009), **seizures** (Ponten et al., 2009, Ponten et al., 2007), **attention deficit hyperactivity disorder** (Wang et al., 2009), **stroke** (De Vico Fallani et al., 2009; Wang et al., 2010), **spinal cord injury** (De Vico Fallani et al., 2008a), **fronto-temporal lobar degeneration** (de Haan et al., 2009), and **early blindness** (Shu et al., 2009).

Quantitative Analysis of Patterns

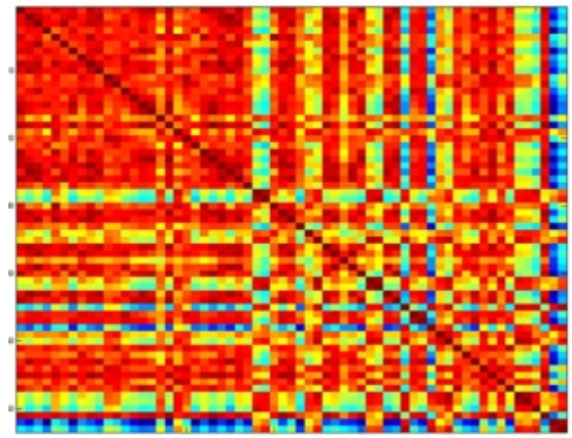
Measures and metrics

Degree centrality
Eigenvector centrality
Katz centrality
PageRank
Closeness centrality
Betweenness centrality
Edge Centrality
Random Walk Centrality
Groups of vertices
Transitivity
Reciprocity
Assortative mixing
Shortest paths
Clustering coefficients
Small-worldness
Global Efficiency
Local Efficiency
Synchronizability
Modularity
Robustness to targeted attack
Robustness to random attack
Mean Connection Distance
Rent's Exponent





Basic Connectivity Properties



Strength: average connectivity of a node

Definition: column or row mean of the connectivity matrix

Example: A node that has connections with strengths 0.25, 0.5, and 0.75, its strength is 0.5.

Diversity: variance of the connectivity of a node

Definition: column or row variance of the connectivity matrix

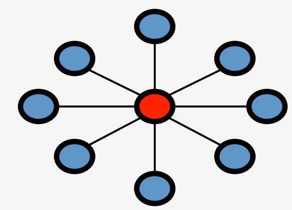
Example: A node that has connections with strengths 0.25, 0.5, and 0.75, its diversity is 0.0625.

Basic Graph Properties

Measures of local connectivity (~ local processing):

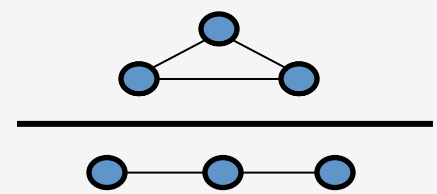
Degree, k

# of edges emanating from a node



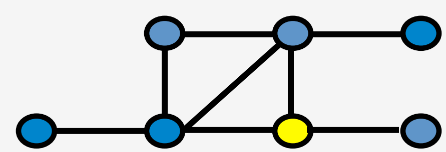
Clustering, C

$$C = \frac{\#\text{ of triangles}}{\#\text{ of connected triples}}$$



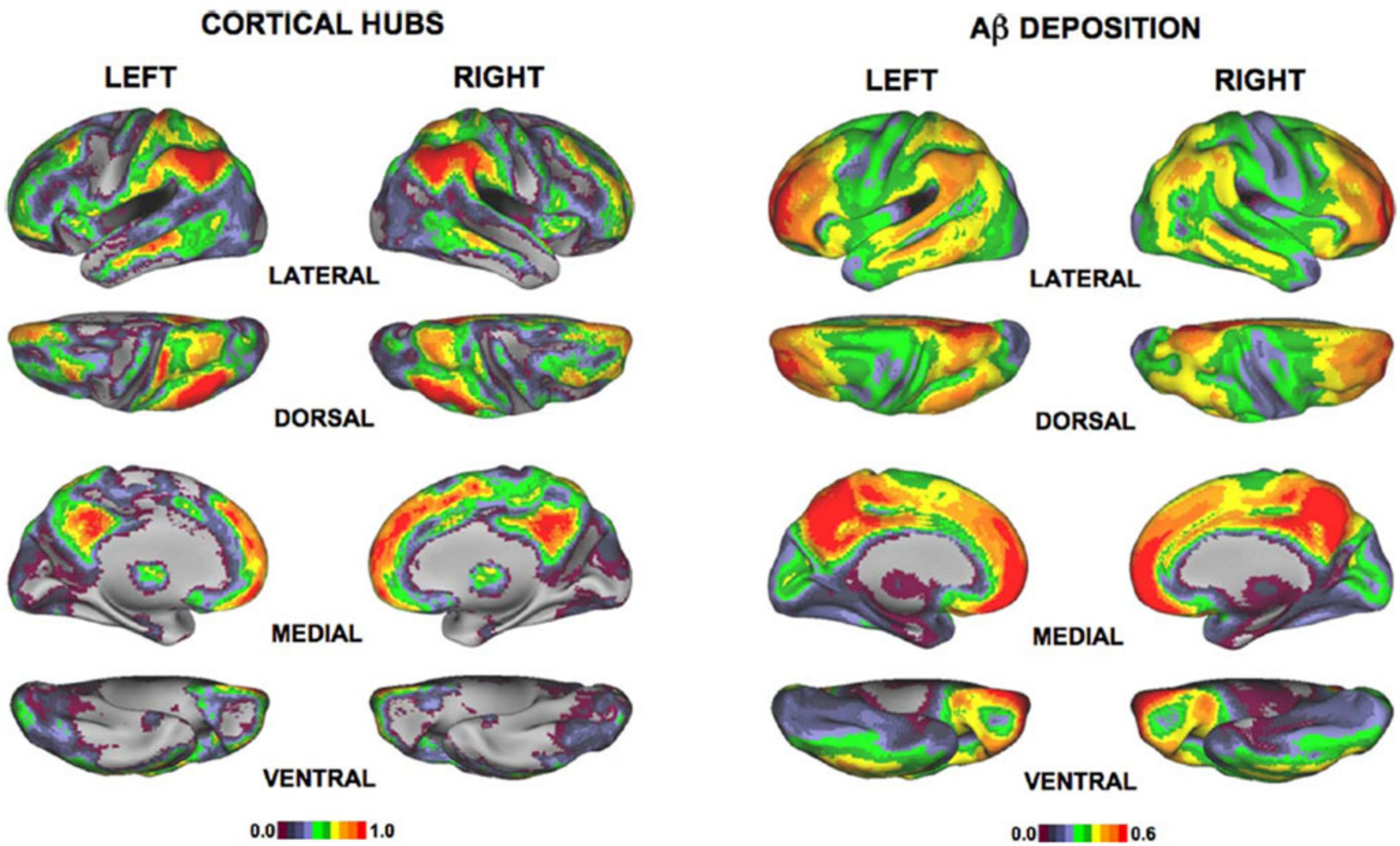
Local Efficiency, E_{loc}

Ratio of # of connections between i's neighbors to total # possible



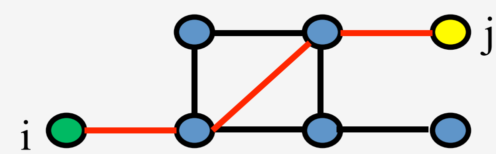
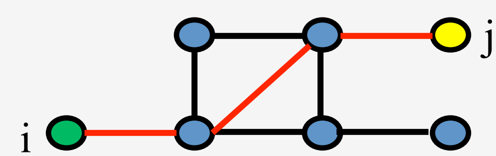
Application: Degree

Brain regions with high degree in resting state fMRI networks also show highest amyloid beta deposition in Alzheimer's disease. Buckner et al. 2009 J Neurosci.



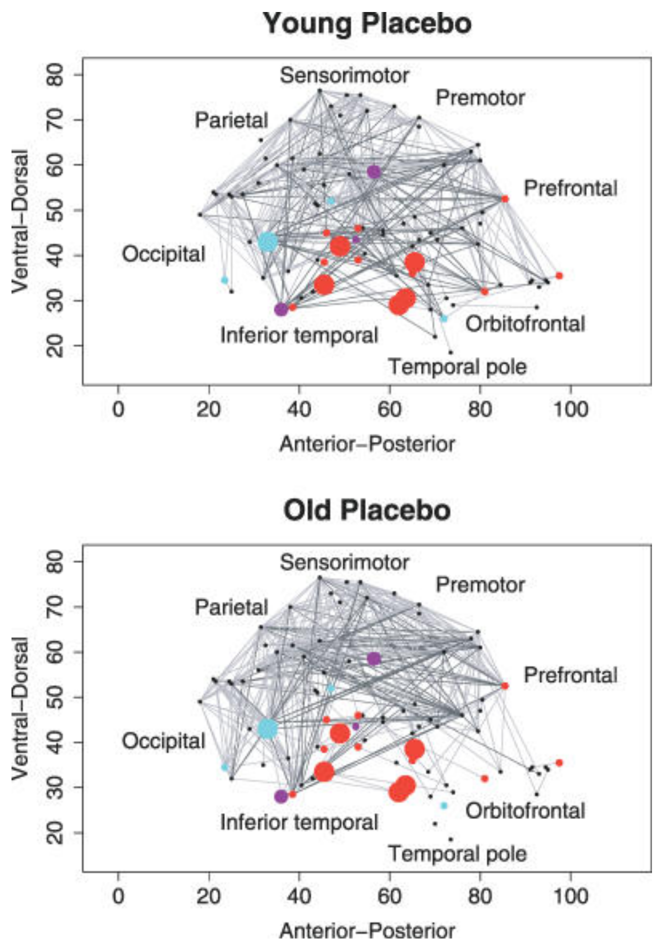
Basic Graph Properties

Measures of more global connectivity (~ global processing):

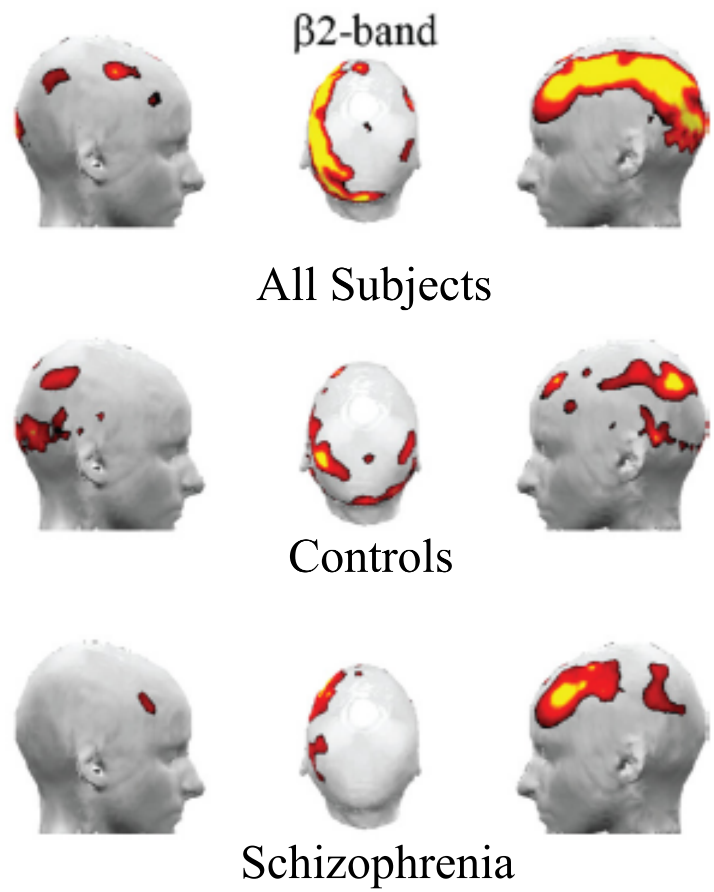
Path-length, L	fewest # of edges between nodes i and j = 3	
Global Efficiency, E_{glob}	Inverse of path-length = 1/3	

Application: Efficiency

Efficiency is decreased by age and drug.
Achard & Bullmore 2007 PloS Comp Biol.



Balance between network cost and efficiency is correlated with memory performance.
Bassett et al. 2009 PNAS.

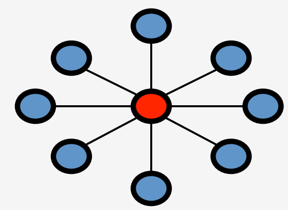


Basic Graph Properties

Measures of centrality (~ importance to processing):

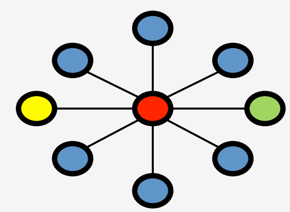
Degree Centrality, k

# of edges emanating from a node



Betweenness Centrality, B

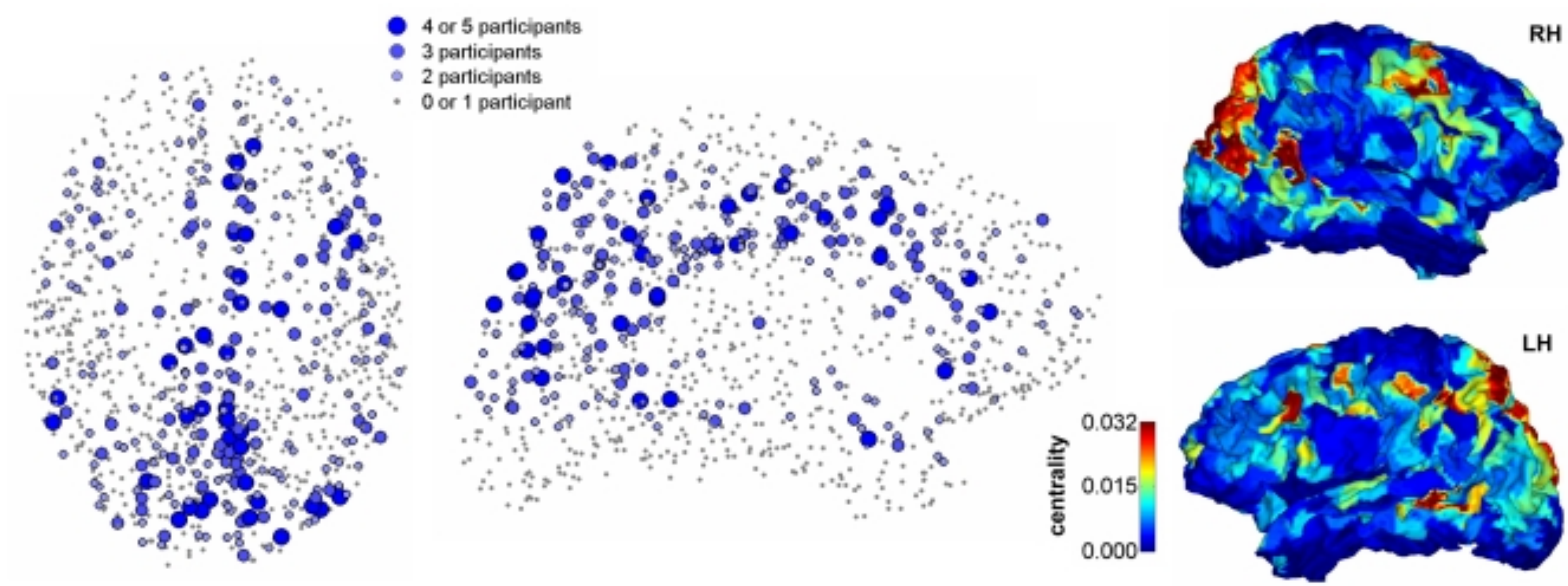
# of shortest paths from i to j that must pass through v



Other measures of centrality: eigenvector centrality, closeness centrality, edge betweenness centrality, page rank, etc.

Application: Centrality

Betweeness centrality pattern of structural networks – based on the # of tracks between regions as estimated using Diffusion Spectrum Imaging – shows striking similarity to the default mode. Hagmann et al. 2008 PLoS Biol.



Basic Graph Properties

Measures of community structure (~ functional modules):

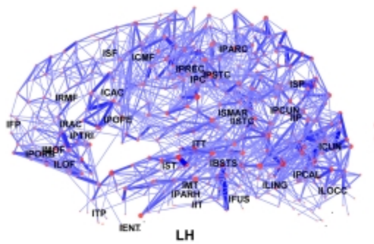
Modularity, Q

Based on an optimization that finds communities (groups of nodes) that have more connections with one another than expected in a random null model.

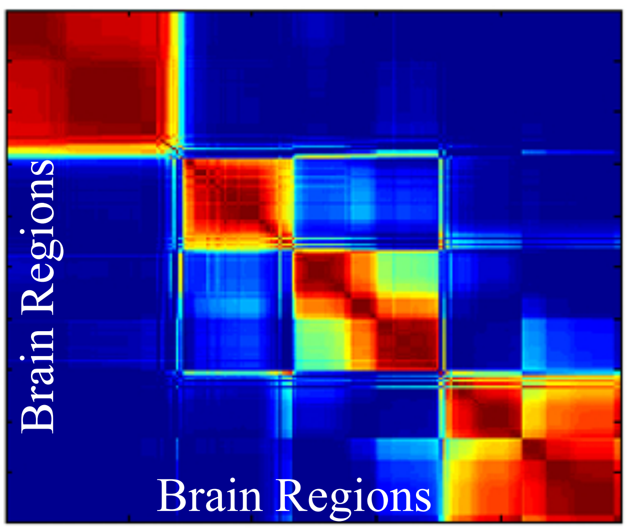
Strongly modular

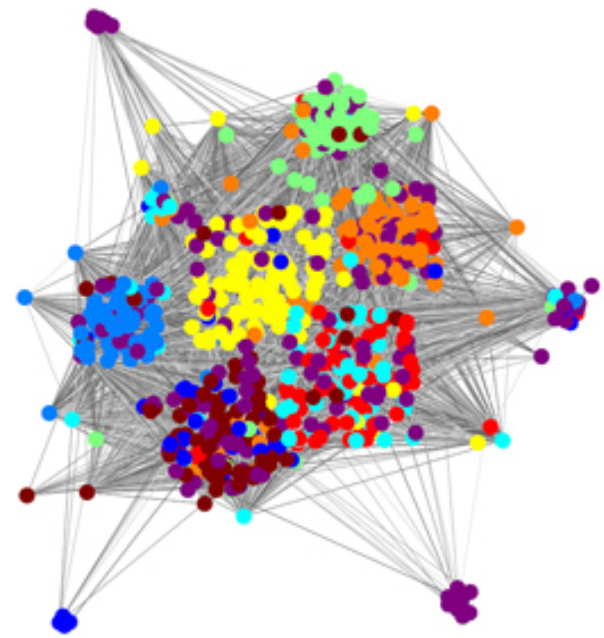
Less modular

Application: Modularity



Structural brain networks display modular organization – groups of brain regions are more highly connected to one another than to other groups. Bassett et al. 2010 PLoS Comp Biol.

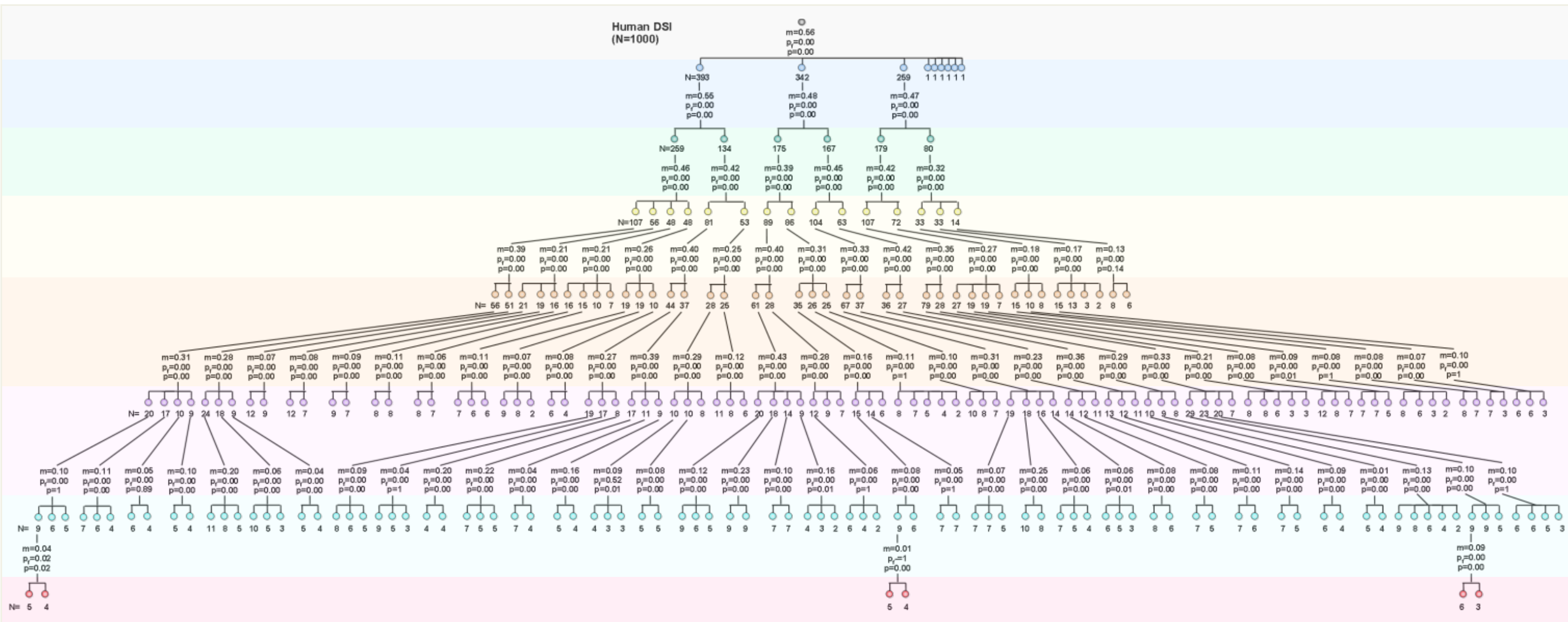




Interestingly, each large group appears to be composed of smaller groups.

Hierarchical Modularity

Equivalent tree-based visualization



Bassett et al. 2010 PLoS Comp Biol

Useful Software

There are several toolboxes available in MATLAB that can be used to perform network analysis on neuroimaging data. These include:

The Brain Connectivity Toolbox:
https://sites.google.com/a/brain-connectivity-toolbox.net/bct/Home

MATLAB Boost Graph Library:
http://www.stanford.edu/~dgleich/programs/matlab_bgl/

WMTSA – wavelet toolbox
http://www.atmos.washington.edu/~wmtsa/

Other packages are also available in R and Python.

A Note on Interpretation

Measures of local connectivity (~ local processing)
Measures of global connectivity (~ global processing)
Measures of centrality (~ importance to processing)
Measures of community structure (~ functional modules)

The appropriate interpretations of graph properties depend on the appropriateness of the model we have constructed: our definition of nodes and edges.

Does increased clustering in the DLPFC really mean increased local processing in this region? We have yet to truly test these hypotheses.

Summary

Lecture One:

1. Complexity in the Human Brain
- from processes to patterns

2. Graph Theory and Complex Network Theory
- study of patterns
- use in neuroimaging
- the brain as a complex network

3. Connectivity and Graph Properties
- Definitions
- Example Applications

Lecture Two:

3. Methods for Comparing Networks
4. Methods for Dynamic Networks

Questions?

Network Analysis II

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Outline

Lecture Two:

3. Methods for Comparing Networks

- Comparisons to benchmarks or between groups
- Challenges to viable comparisons
- Statistical methods for comparison

4. Methods for Dynamic Networks

- Types of dynamic networks
- Statistical methods for dynamic networks

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Comparing Networks

Once we compute graph properties (such as degree, clustering, path-length, local efficiency, global efficiency, centralities, modularity, etc.), we will want to know what these numbers mean.

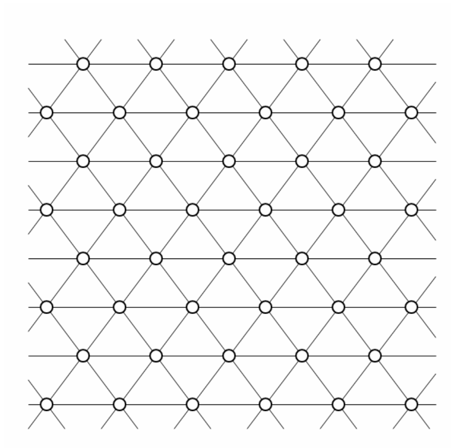
Two common means of determining graph structure are:

1. Comparison to benchmark networks
   -> Test statistically whether the graph properties values are higher or lower than a benchmark (e.g., random) network

2. Comparison other real brain networks (e.g., other groups of subjects, experimental conditions, etc.)
   -> Test statistically whether the graph properties are different between the two networks

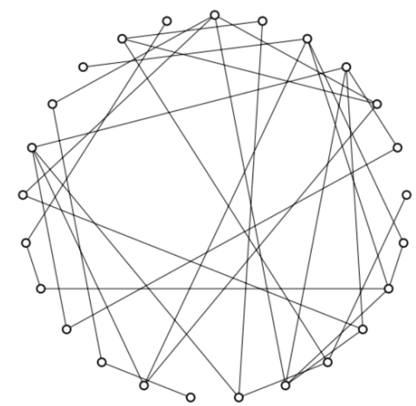
Comparing to Benchmark Networks

For example, to determine if a graph is "small-world", we must compare to purely random graphs.



Regular (Lattice) Graph

Small-world Regime



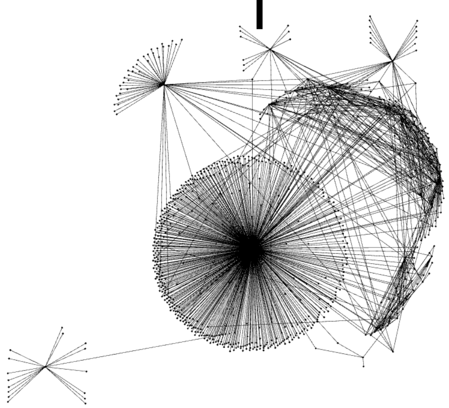
Random Graph

A small-world graph is one that has a clustering coefficient higher than a random graph, and a path-length similar to a random graph. Small-world graphs are thought to be optimally organized for efficient information transfer.

Comparing to Benchmark Networks

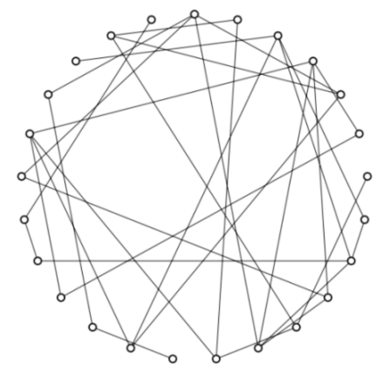
Similarly, to determine how modular a graph is, we compare to a random network null model both within the optimization to determine Q, and then after optimization in order to determine the statistical significance of Q.

1. Compare brain network to random network during optimization to determine Q.



Modular Graph

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



Random Graph

2. Compare Q value obtained from the brain network to Q values obtained from a null model (e.g., a random graph). For statistical validation, test for differences between Q and Q_{rand} using, for example, a t-test.

Comparing to Real Networks

In addition to comparing to benchmark networks, our scientific investigations may also require that we compare two or more (sets) of real networks. For example, we may want to compare two groups by

Age
Gender
Disease
Drug
Cognitive Ability
Experimental Task
Etc….

Challenges to Viable Comparisons

Graph properties are dependent on:

1. Number of nodes in the graph

2. Number of edges in the graph

3. Degree distribution

For weighted networks

4. Average weight of the network

5. …

But often we want to say that a network architecture is different from a benchmark or different between two groups. Therefore, we need to first account for these potentially spurious sources of apparent architectural differences.

Statistical Comparisons

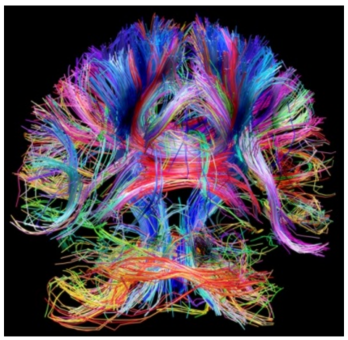
1. When comparing to random graphs:
    1. Random graphs are constructed with the same number of nodes as the brain graph
    2. Random graphs are constructed with the same number of edges as the brain graph
    3. Often, two types of random graphs are used:
        1. Pure random graph
        2. Random graph with the same degree distribution as the brain network

2. When comparing two groups:
    1. Both sets of networks use the same parcellation scheme (number of nodes)
    2. If binary, both sets of networks are thresholded such that all networks have the same number of edges
    3. If weighted, the average weight of the networks are normalized prior to comparisons

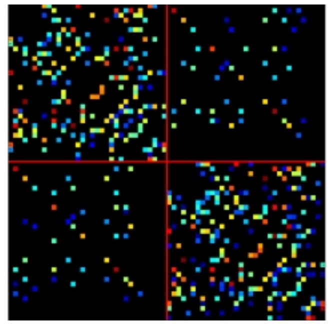
Constructing Binary Graphs: Thresholds

Defining Edges

Diffusion Tractography

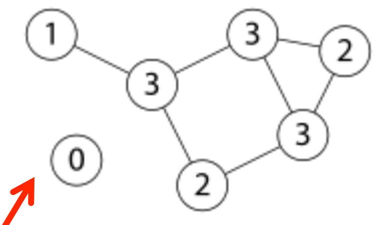


Connectivity Matrix



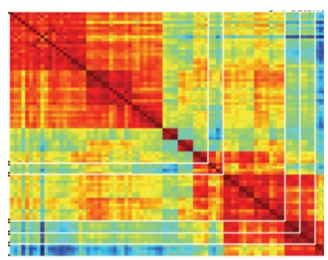
# of Tracts, FA, etc.

Binary Graph



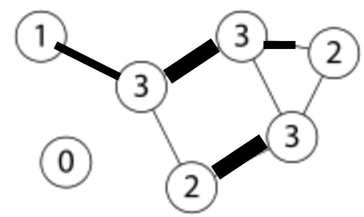
fMRI, EEG, MEG

Connectivity Matrix



Correlation, Causality, etc.

Weighted Graph

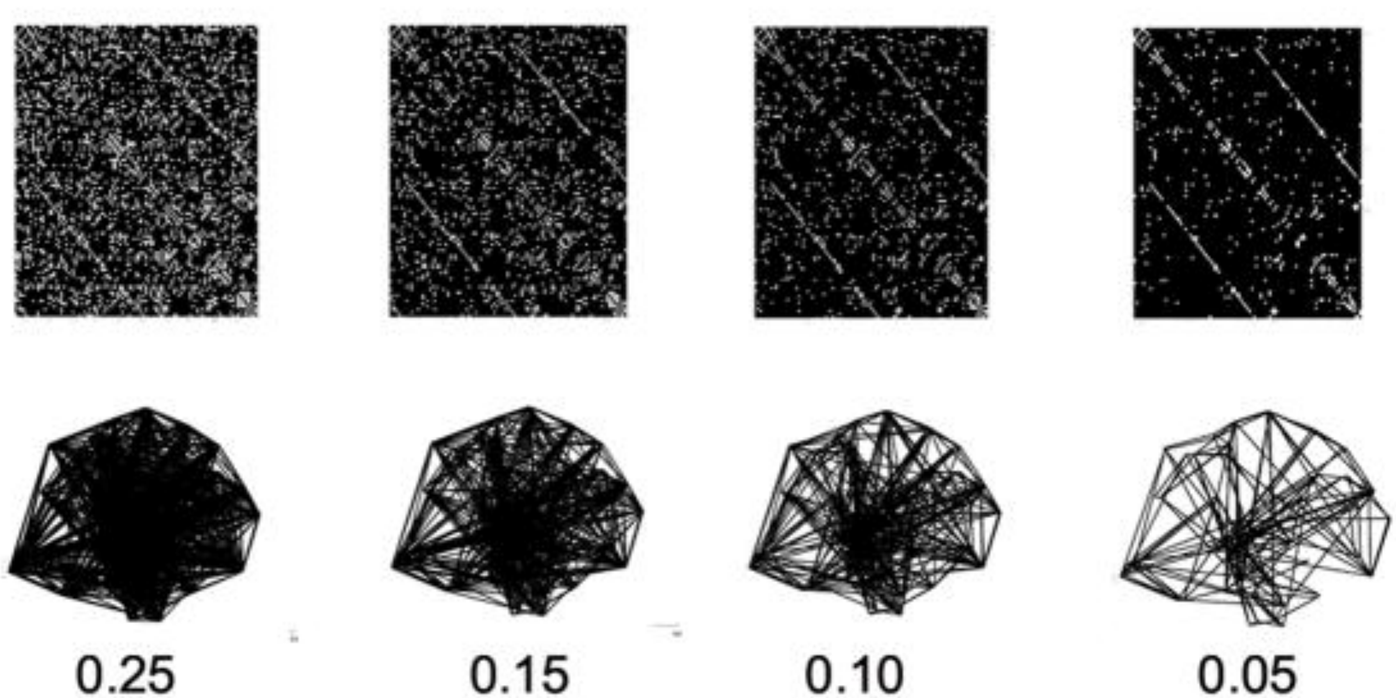


Thresholds Determine Network Sparsity

Threshold

minimum → maximum

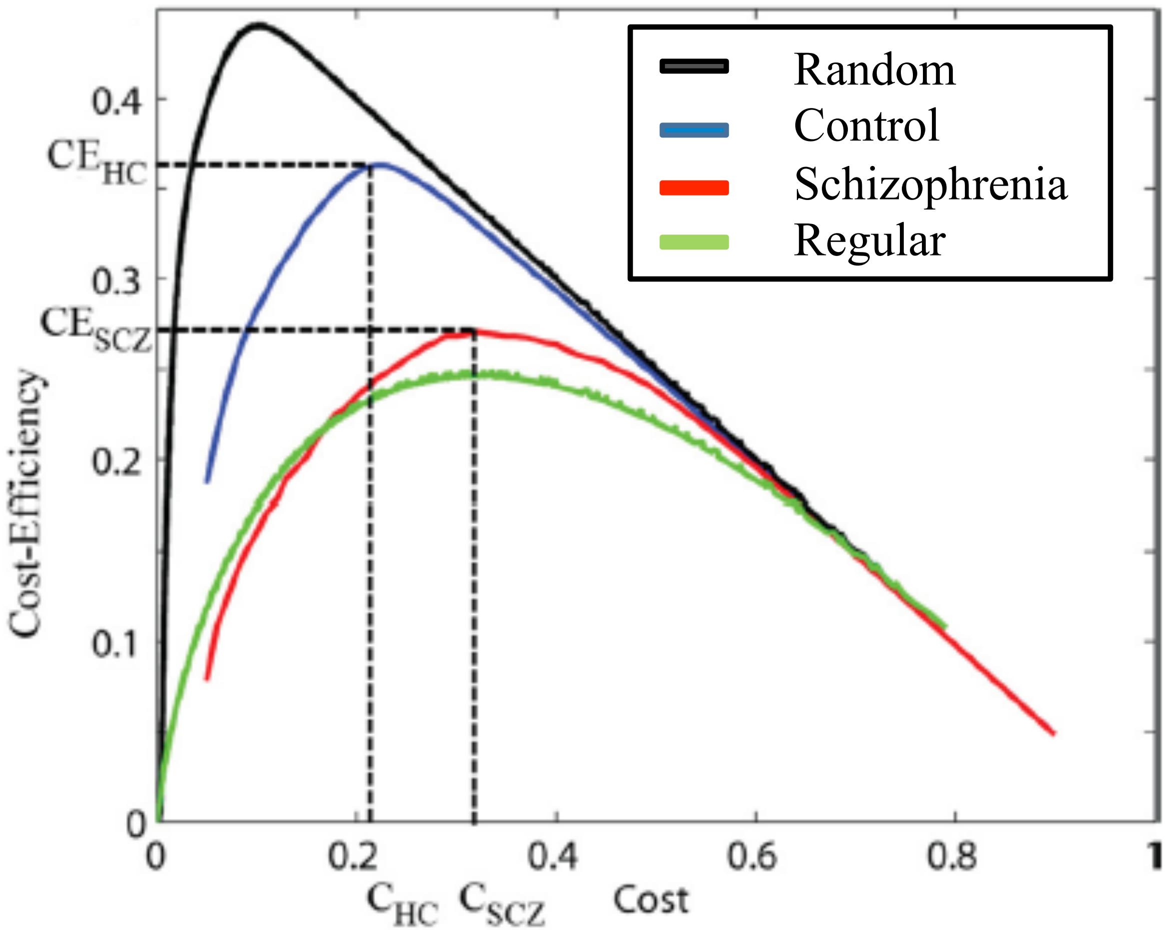
Dense Graph | Sparse Graph



High Cost | Low Cost

The Entire Range of Costs

All graph properties can be computed over the entire range of costs.



So at what threshold do we compare graphs?

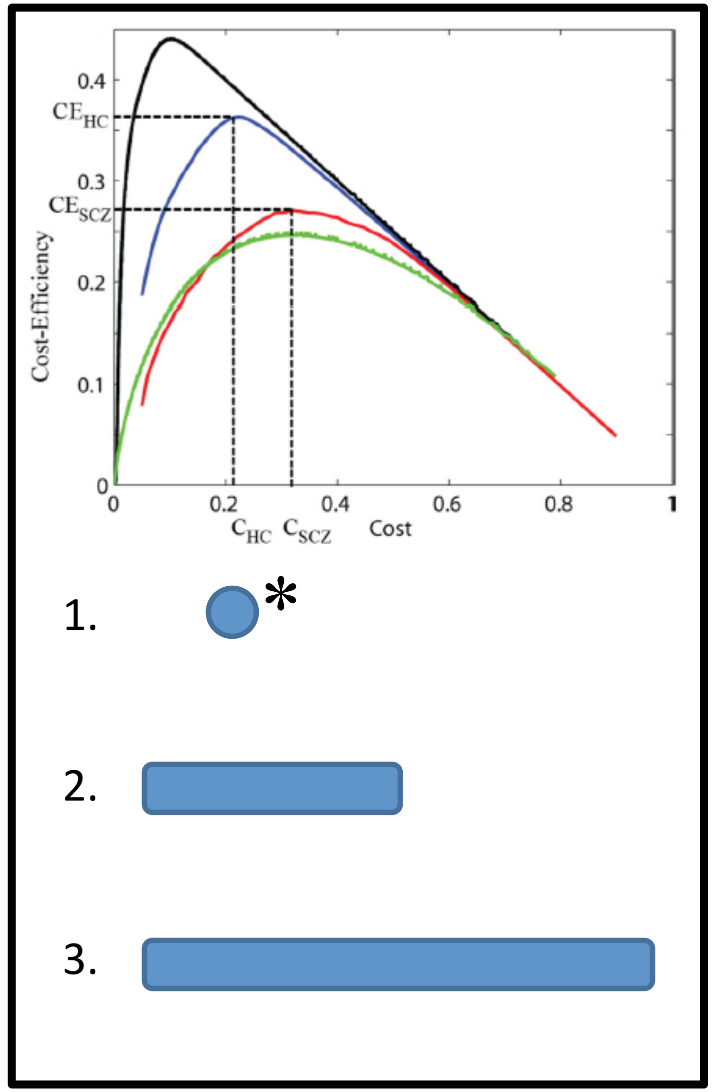
Solutions

Multiple solutions have been proposed to choose thresholds for graph comparison.

1. Choose a single threshold
    1. Pros: The threshold can be based on a statistical test, for example of which edges are significant
    2. Cons: The graph derived from a single threshold may not be representative of the network structure as a whole

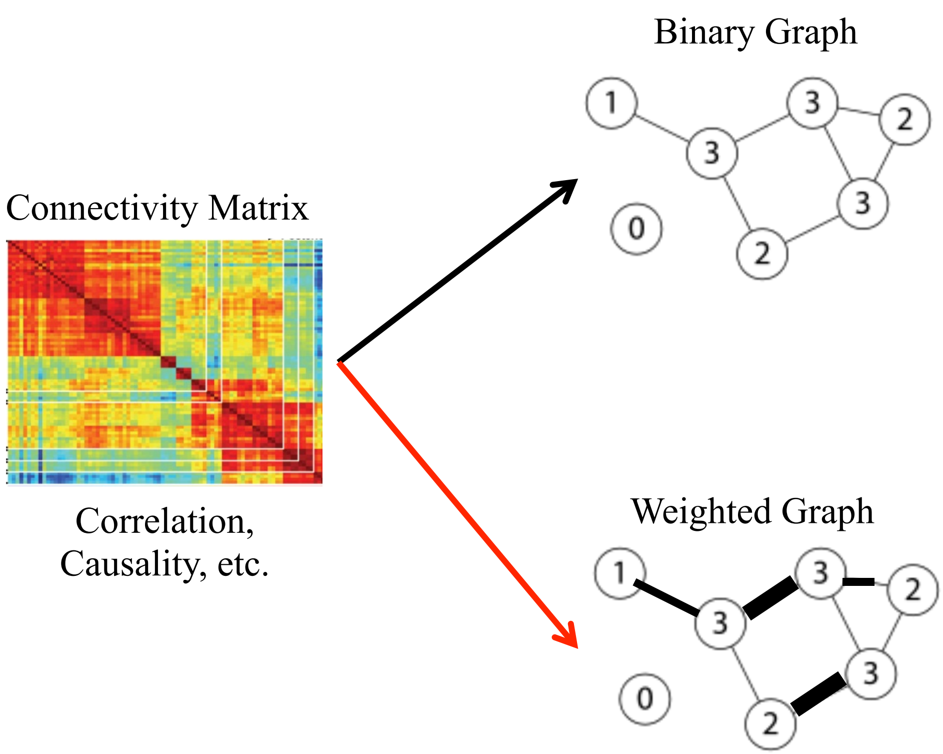
2. Choose a range of thresholds and average graph property values over that range

3. Take the entire range of thresholds, and integrate the graph property values over that range



Alternative Solution: Weighted Networks

Alternatively, we can construct weighted rather than binary graphs and therefore circumvent thresholding altogether.



Caution when comparing weighted networks:

Graph properties are highly dependent on the average weight of a network (which is a variable independent of network architecture).

Solutions: divide each matrix by its mean, median, or max (less robust).

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Types of Dynamic Networks

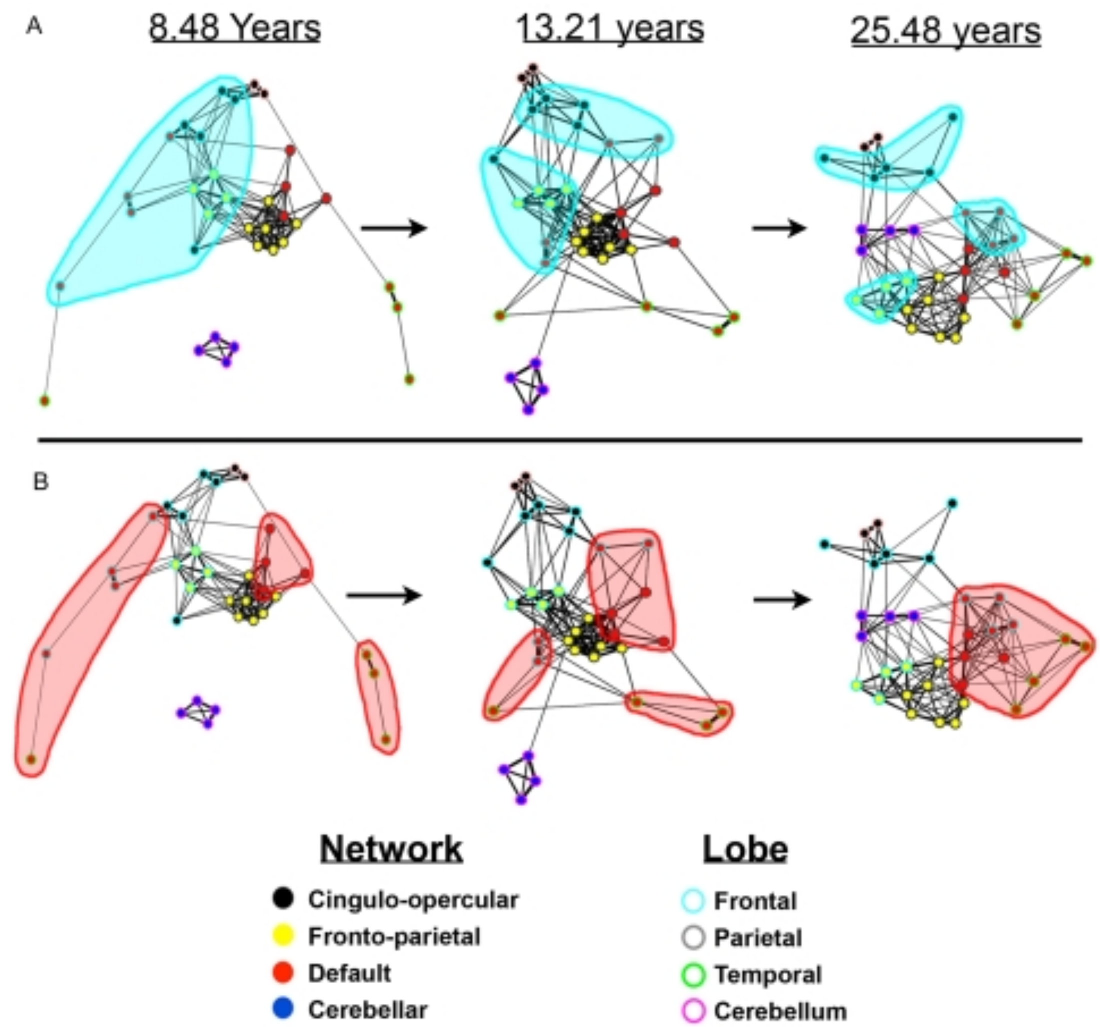
Brain function (and structure to a lesser extent) changes. Much of the work to date has focused on static network structure, but recently the focus has broadened to include an analysis of dynamic network structure – how the brain changes.

Dynamics can be studied in many contexts:

- Over long periods of time – e.g., Age, development
- Over short periods of time – e.g., over a single experimental session
- With varying cognitive load
- During rehabilitation
- Over disease progression
- Etc.

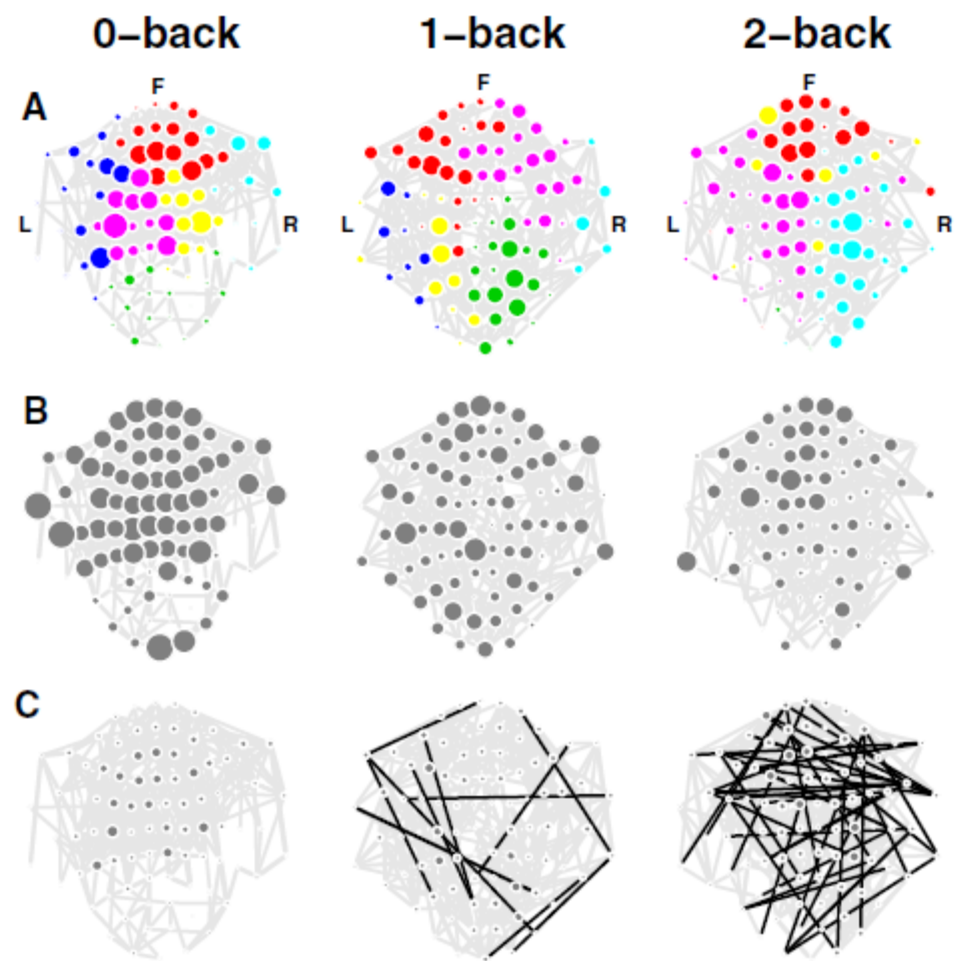
Types of Dynamic Networks: Age

Over age, graph architecture in resting state fMRI networks matures from a “local” organization to a more “distributed” organization. Fair et al. 2009 PLoS Comp Biol.



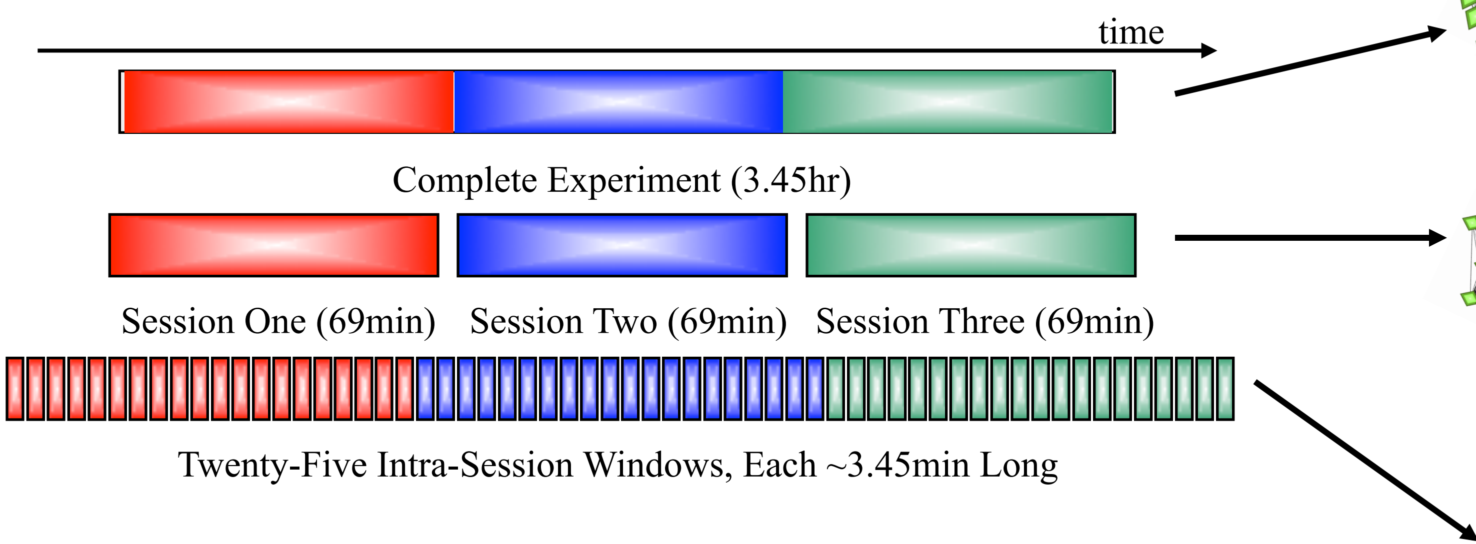
Types of Dynamic Networks: Cognitive Effort

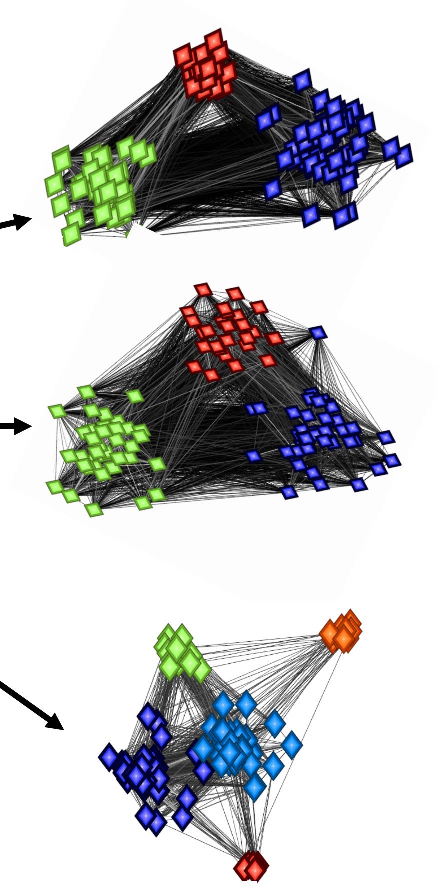
With increasing cognitive effort in a working memory (Nback) task, MEG brain networks become more efficient, less clustered, and less modular particularly in the beta and gamma frequency bands. Kitzbichler et al. 2011 J Neurosci.



Types of Dynamic Networks: Time

In task conditions, we may want to know how network organization changes as a function of temporal scale.





Dynamic Networks & Modularity

<u>Modularity:</u>

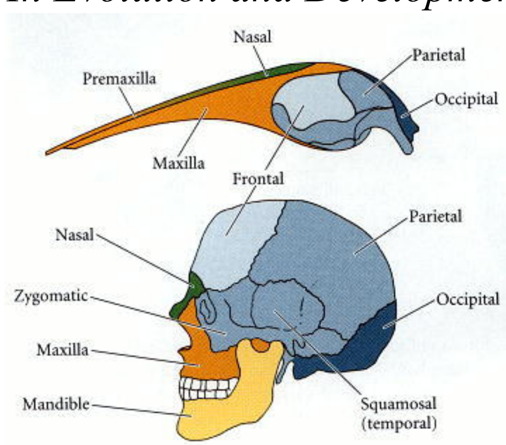
Static advantages

– physical constraints on energy, metabolic expenditure for wiring

Dynamic advantages

– facilitates system adaptability

In Evolution and Development

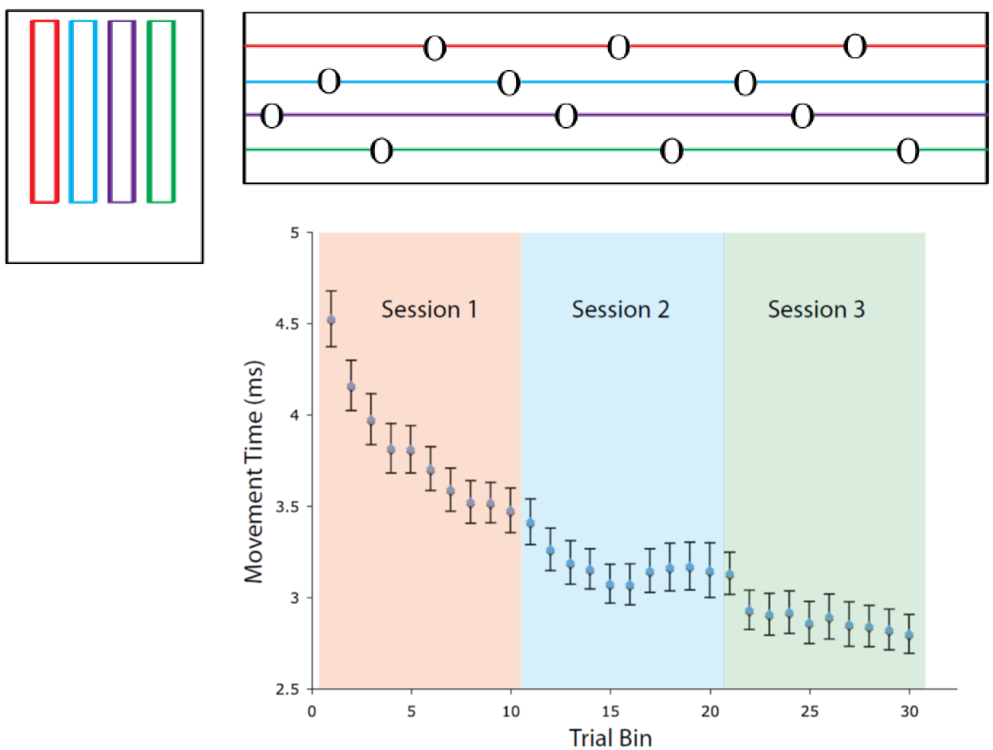


In Function

Modularity and Learning

<u>Learning requires a system to be adaptable.</u>

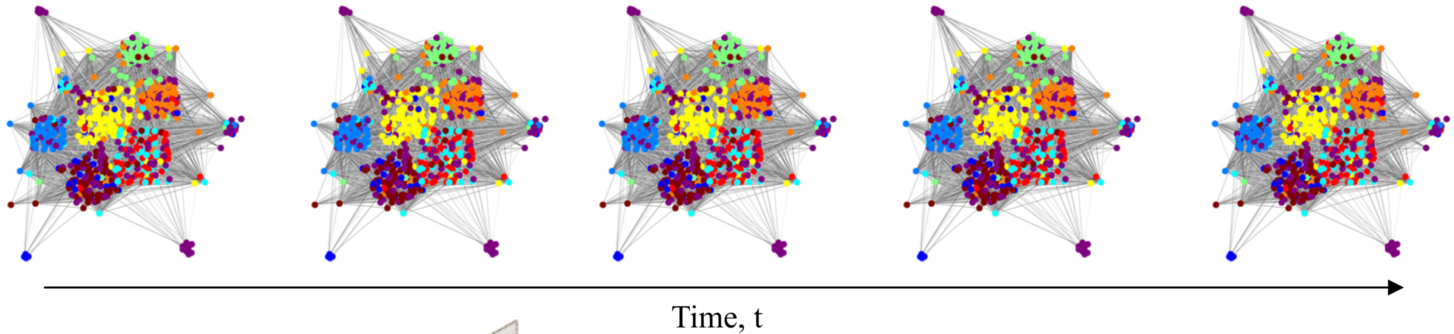
Human learning requires flexibility to adapt existing brain function and precision in selecting new neurophysiological activities to drive desired behavior. This selective adaptability is naturally provided by *modular structure*.

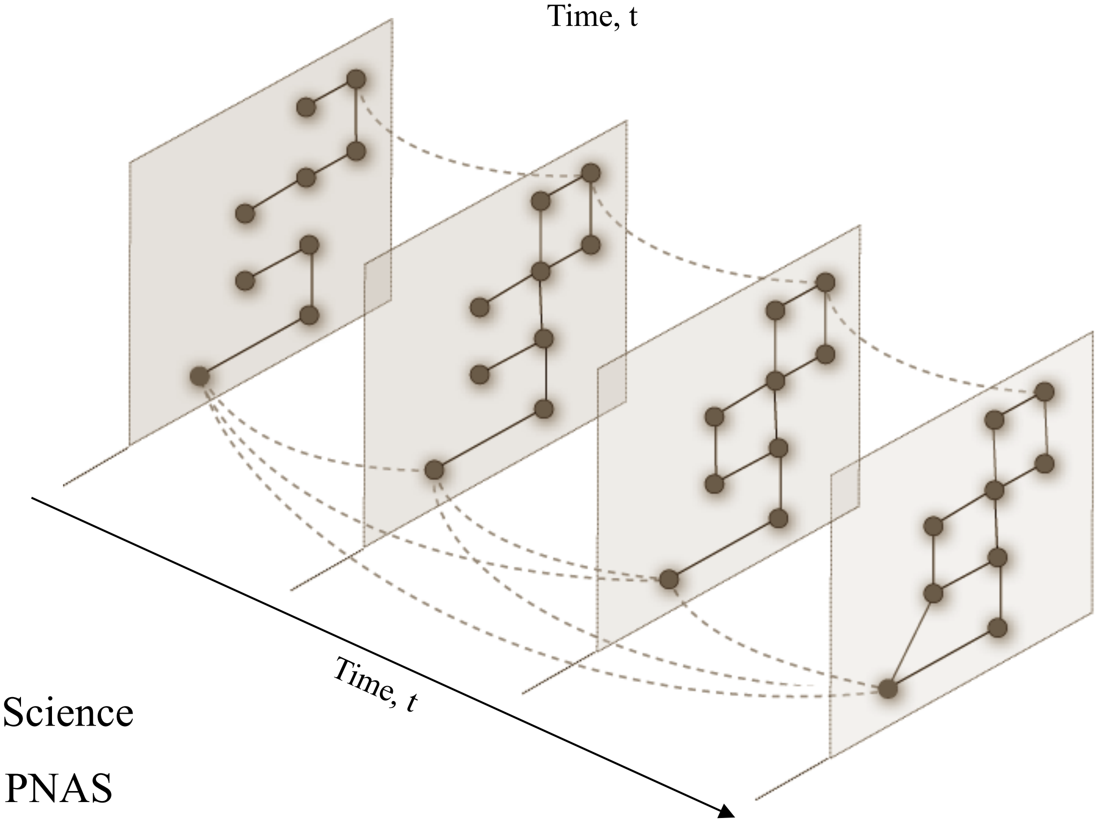


Model System: Simple Motor Learning Paradigm

Hypothesis: Modularity of human brain function changes dynamically during learning, and that characteristics of these dynamics are associated with learning success.

Investigating Dynamic Modularity



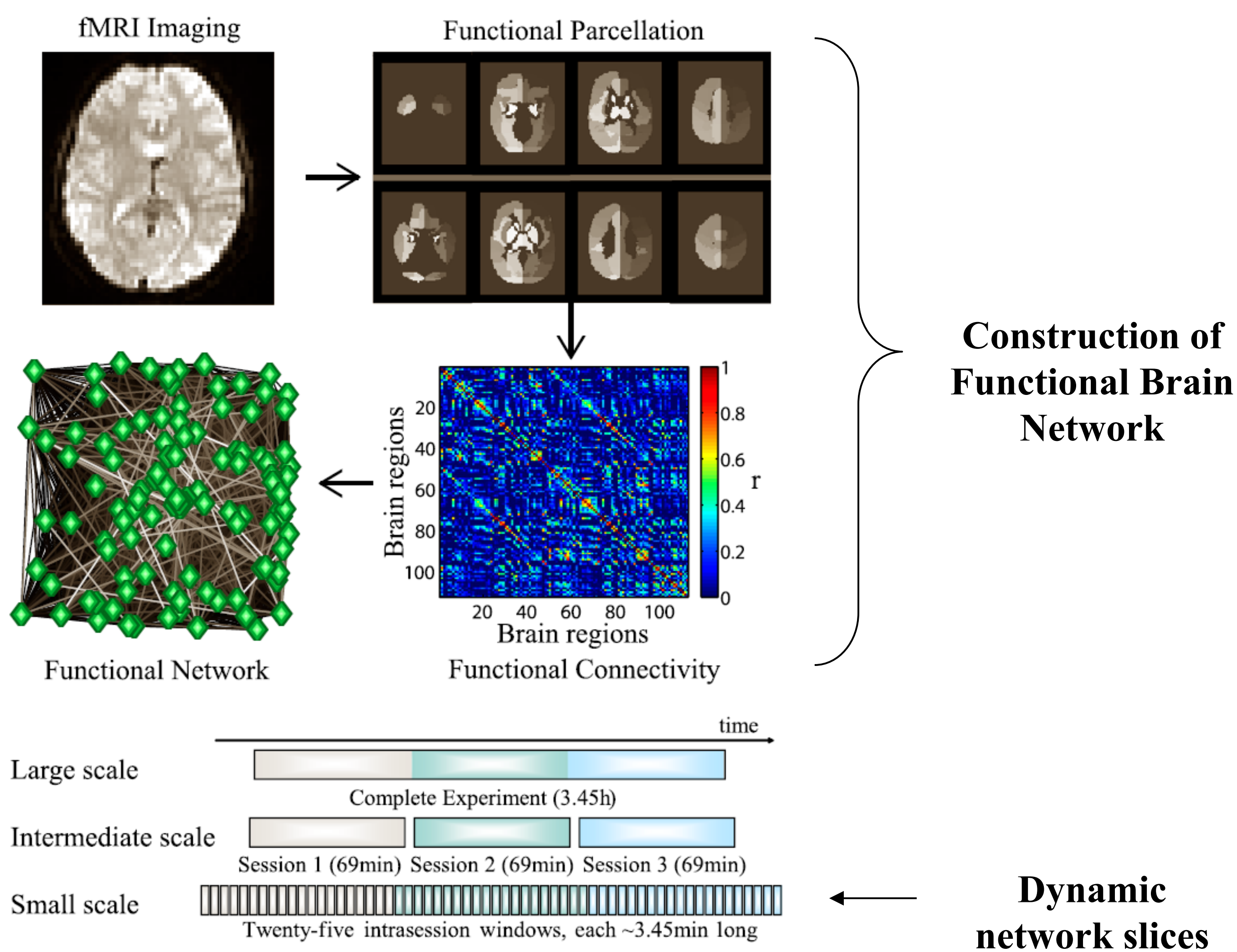


Dynamic extension of previous static modularity optimization

Mucha et al. 2010 Science

Bassett et al. 2011 PNAS

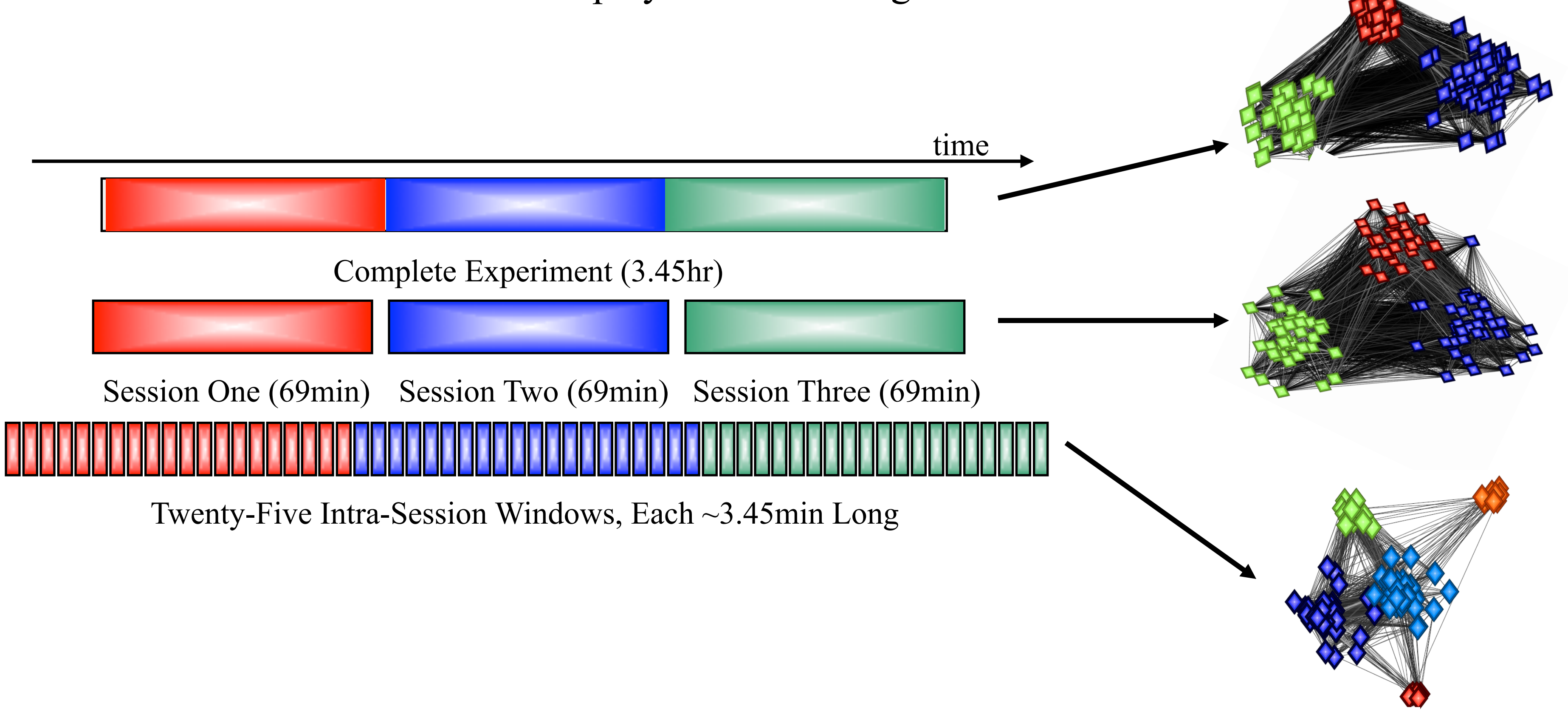
Constructing Dynamic Brain Networks



Bassett et al. 2011 PNAS

Modularity over Temporal Scales

Over multiple temporal scales from days to hours to minutes, functional brain networks displayed modular organization.



Robust Statistical Testing

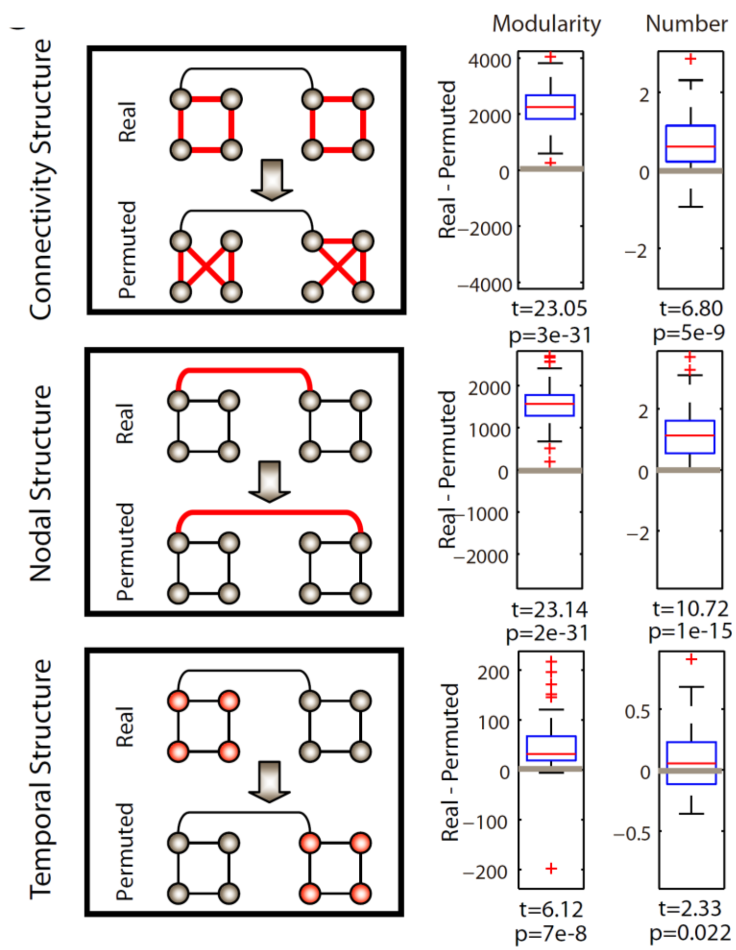
How do we determine whether this modularity is significantly different from that expected in a random null model? We construct 3 separate null models, and test for differences between the brain and these models.

Results:

1) The topological organization of cortical connectivity is highly structured

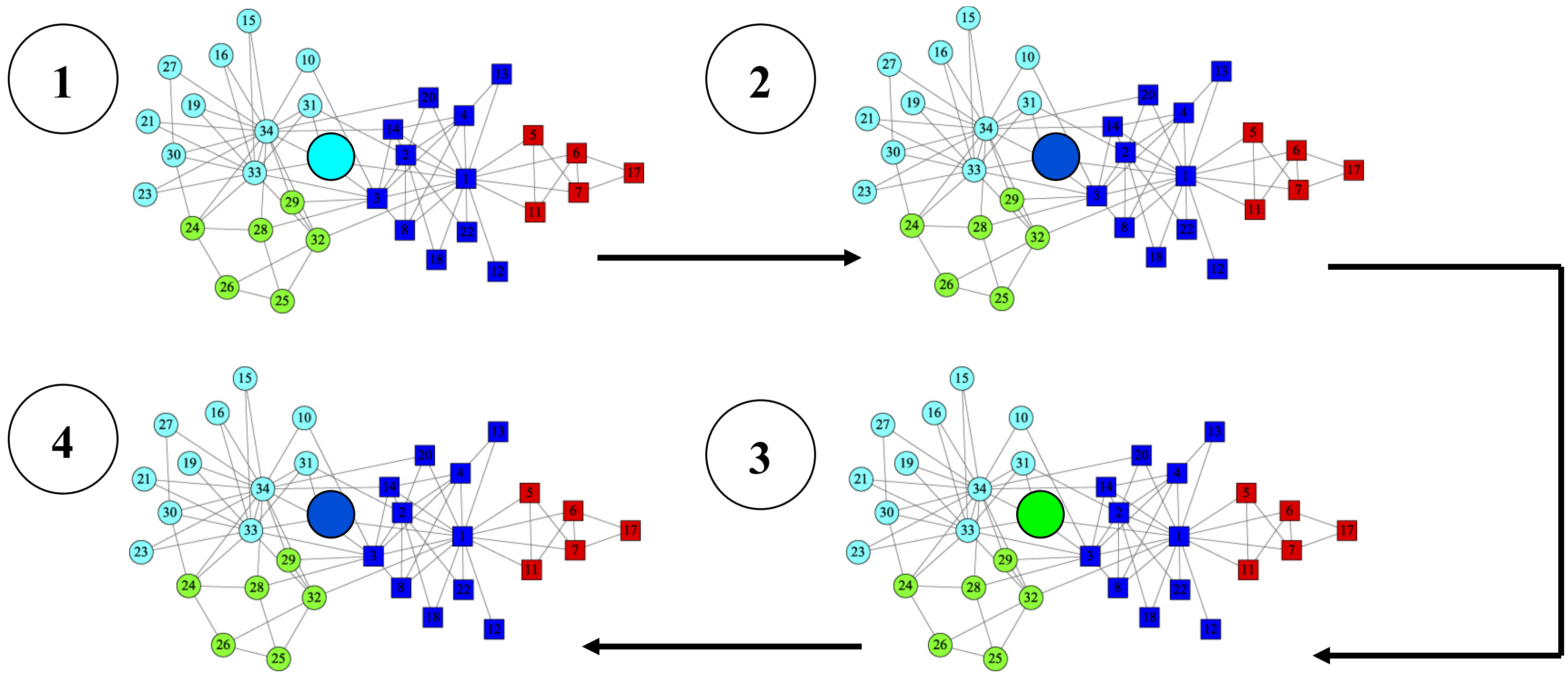
2) Diverse brain regions perform distinct non-interchangeable tasks throughout the experiment

3) The evolution of modular architecture in human brain function is cohesive in time.



Bassett et al. 2011, PNAS

Network Flexibility

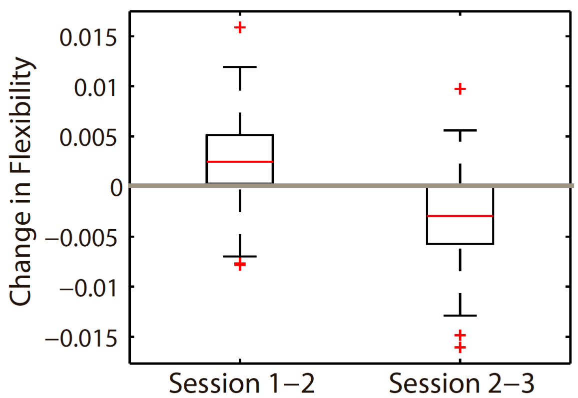


Flexibility might be driven by physiological processes that facilitate the participation of cortical regions in multiple functional communities or by task-dependent processes that require the capacity to balance learning across subtasks.

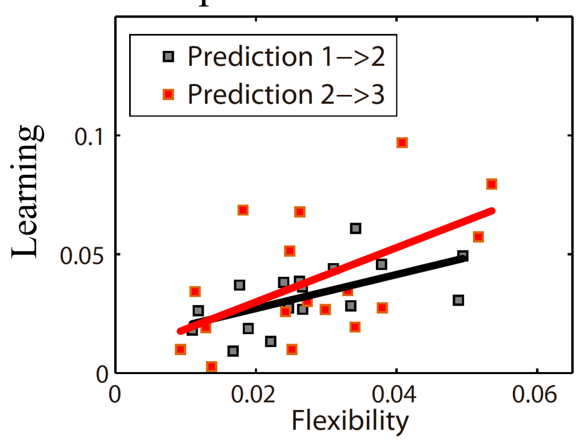
Bassett et al. 2011, PNAS

Flexibility and Learning

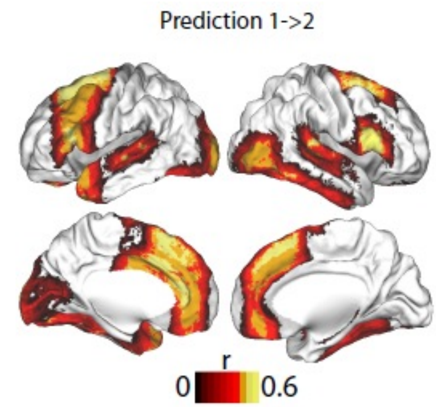
Flexibility changes with learning.

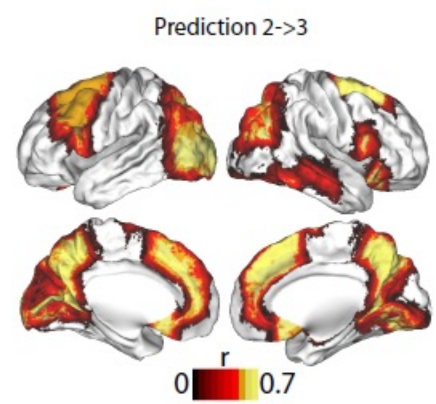


Flexibility predicts learning in future experimental sessions.



Brain regions responsible included association processing areas.





Bassett et al. 2011, PNAS

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