Network statistics and thresholding

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HBM Educational Course
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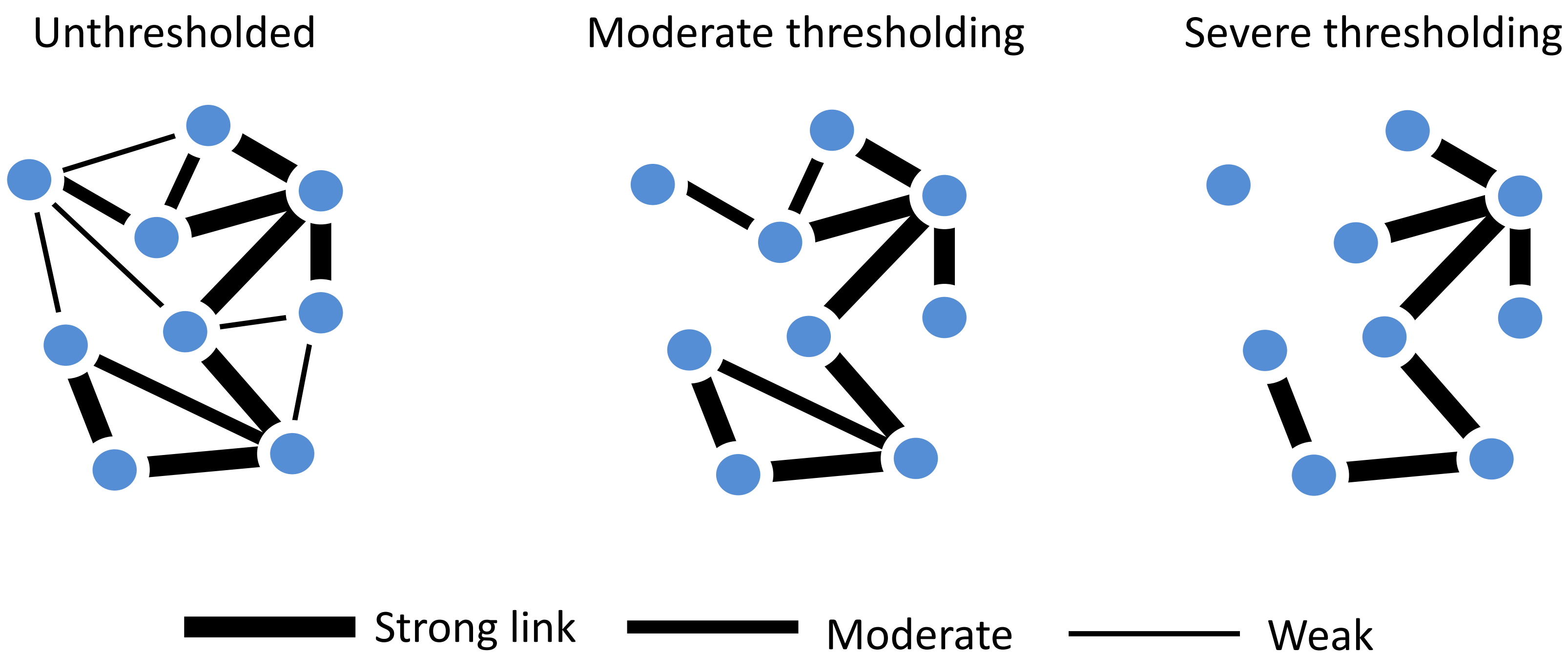
Network thresholding



Network thresholding is not essential but can assist with:

- Eliminating spurious (weak) connections
- Emphasizing topological properties
- Easing computational and storage burden of large graphs

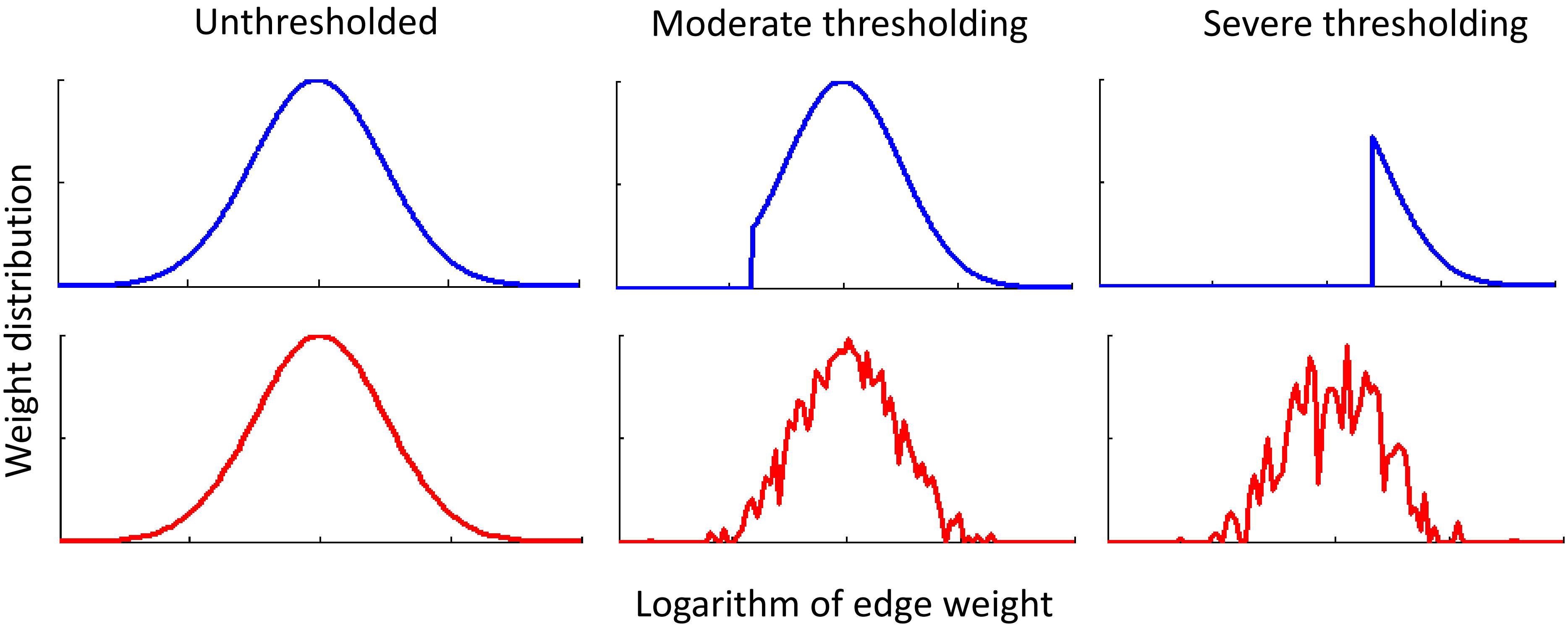
Thresholding methods

Global thresholding

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

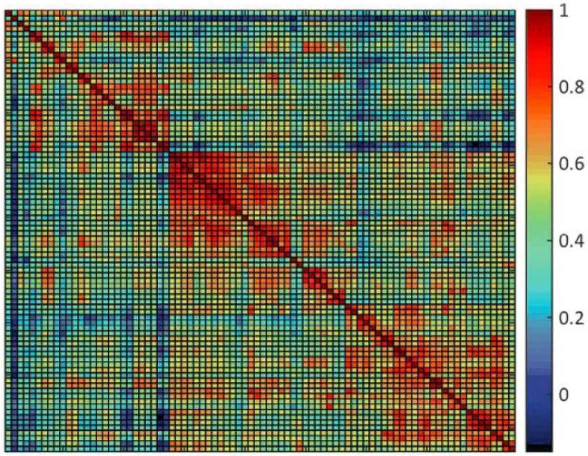
Local thresholding

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

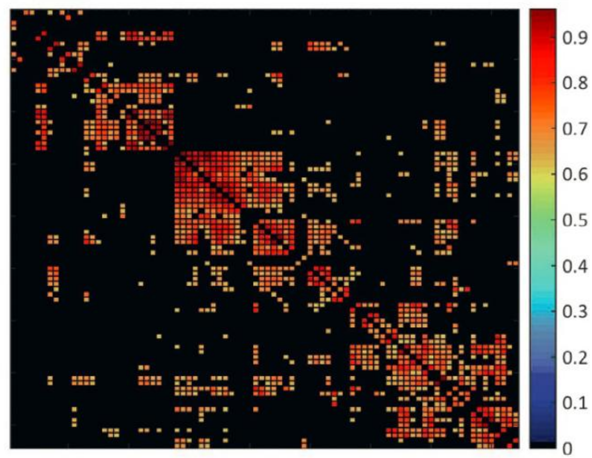


Weight-based thresholding

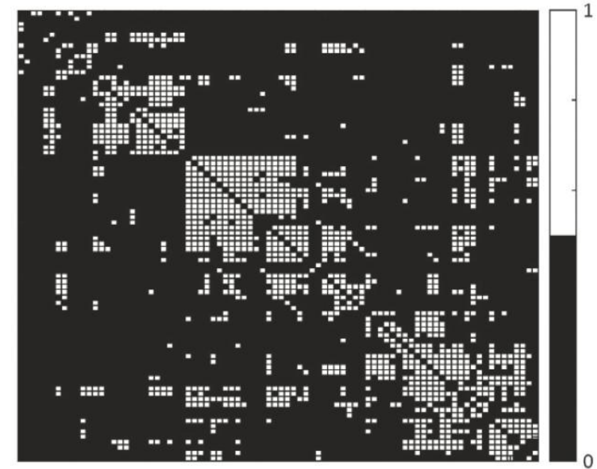
Unthresholded



Thresholded



Binarized



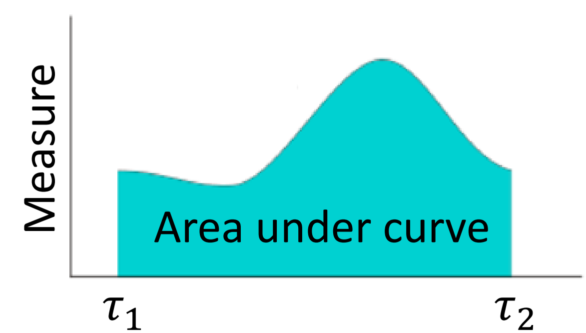
C_{ij}

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

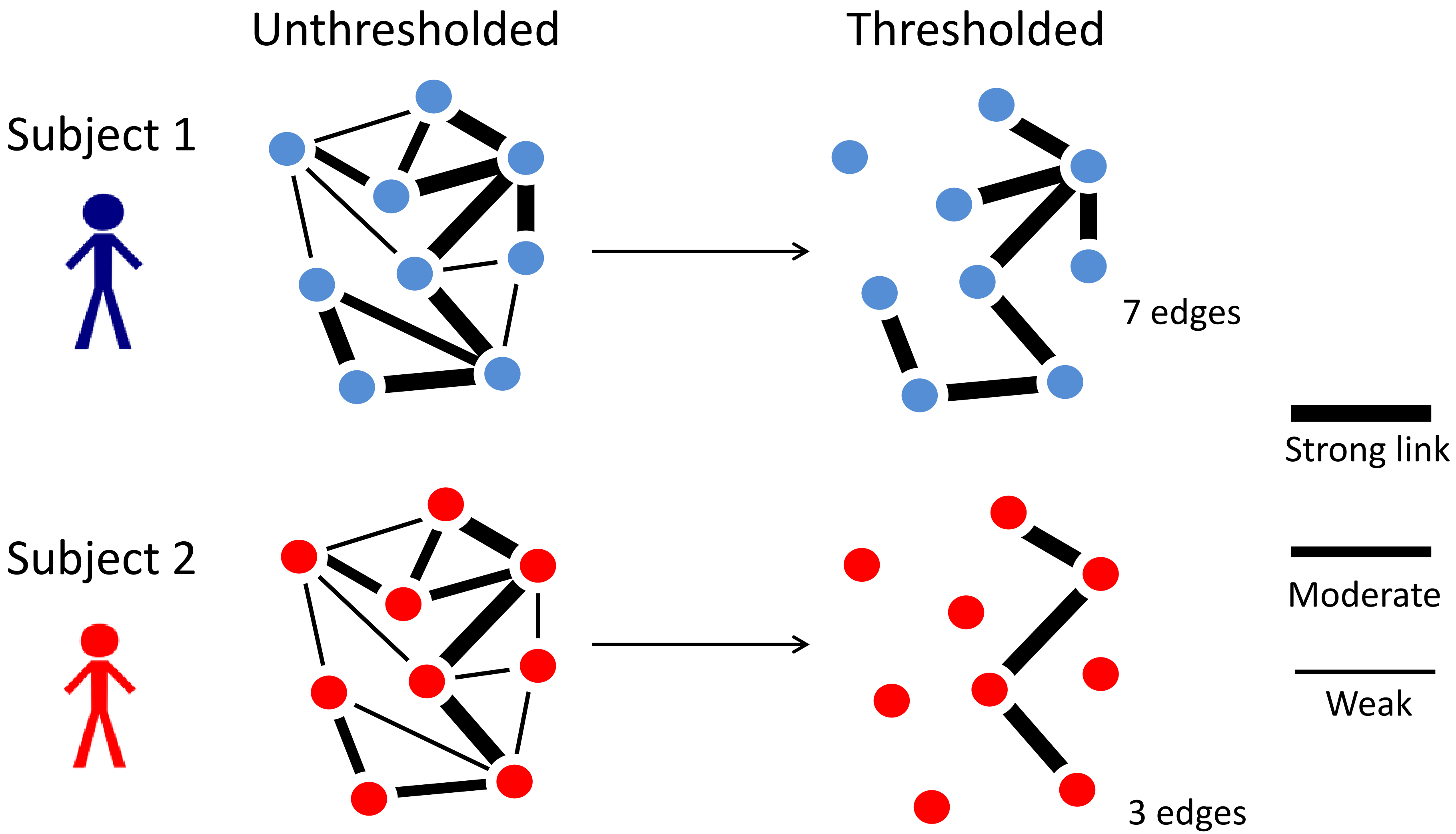
$$B_{ij} = \begin{cases} 1 & \text{if } C_{ij} > \tau \\ 0 & \text{otherwise} \end{cases}$$

How is the threshold, τ, chosen?

- Select τ to achieve a scale-free network
- Consider a range of thresholds and compute area under curve



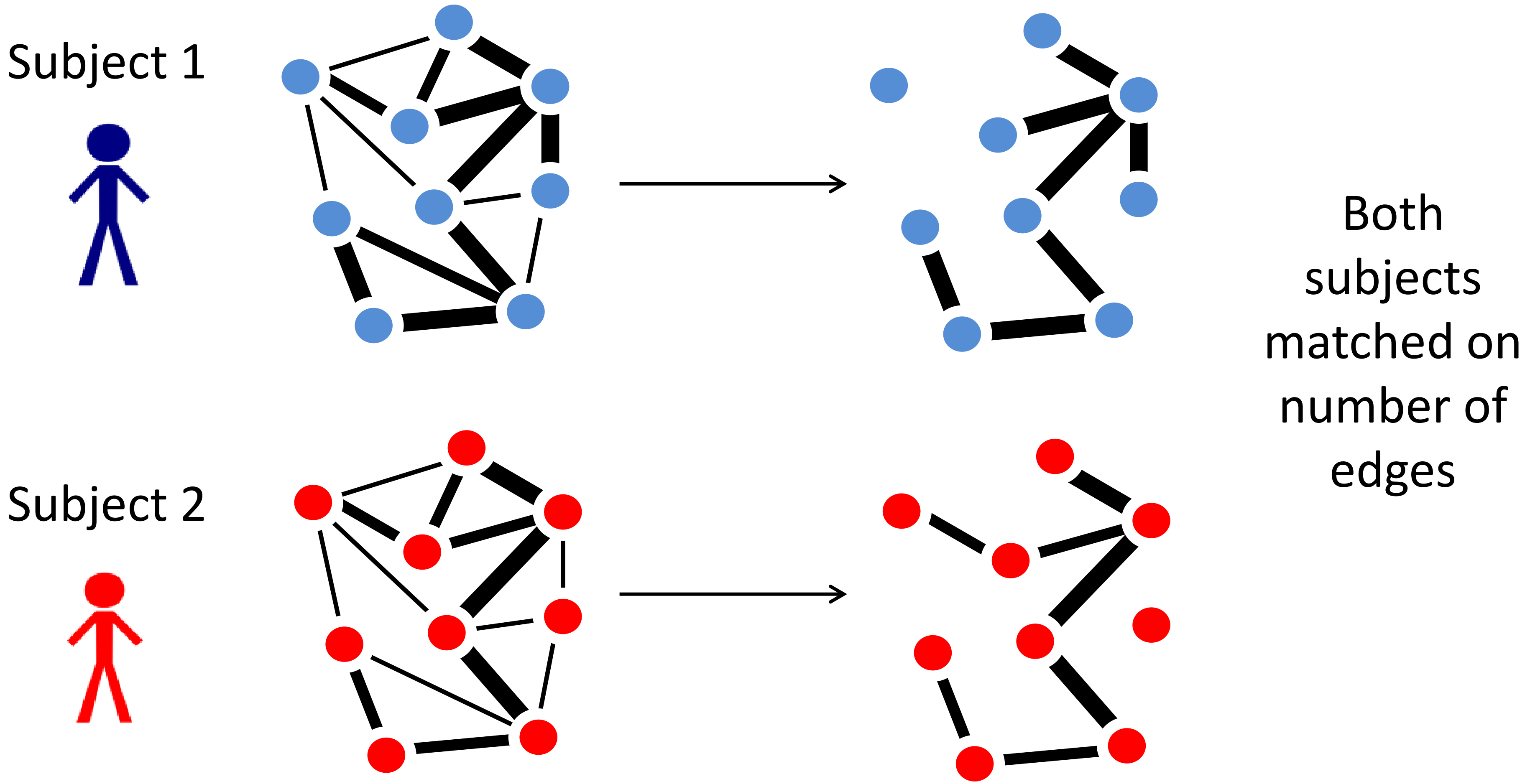
Weight-based thresholding: Disadvantages



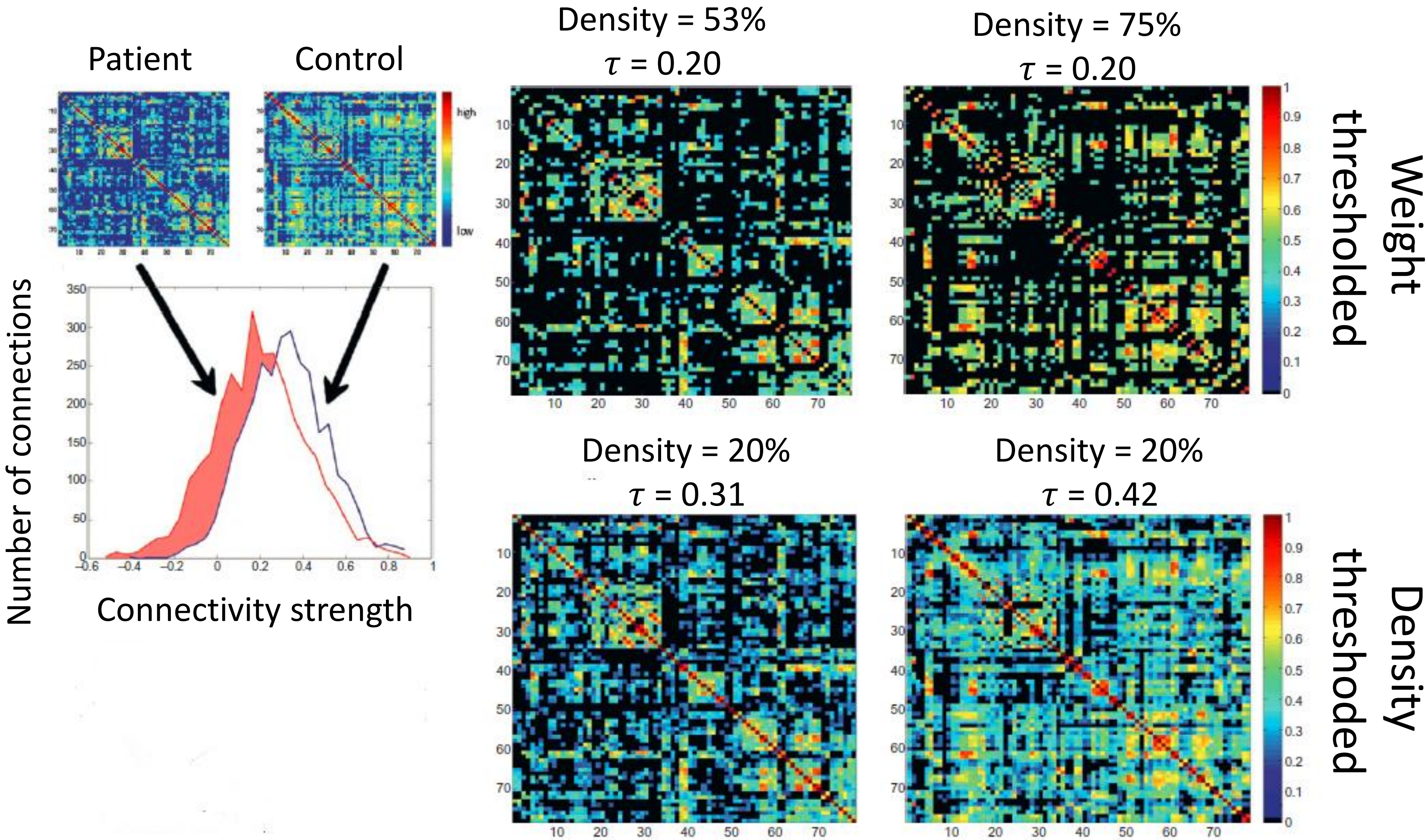
Subject differences in networks measures can be trivially due to differences in the number of edges in thresholded network

Density-based thresholding

- Keep top X% strongest edges, eliminate remaining edges
- Also known as proportional thresholding
- *Advantage:* connection density matched across a group of subjects
- *Disadvantage:* inclusion of potentially spurious connections

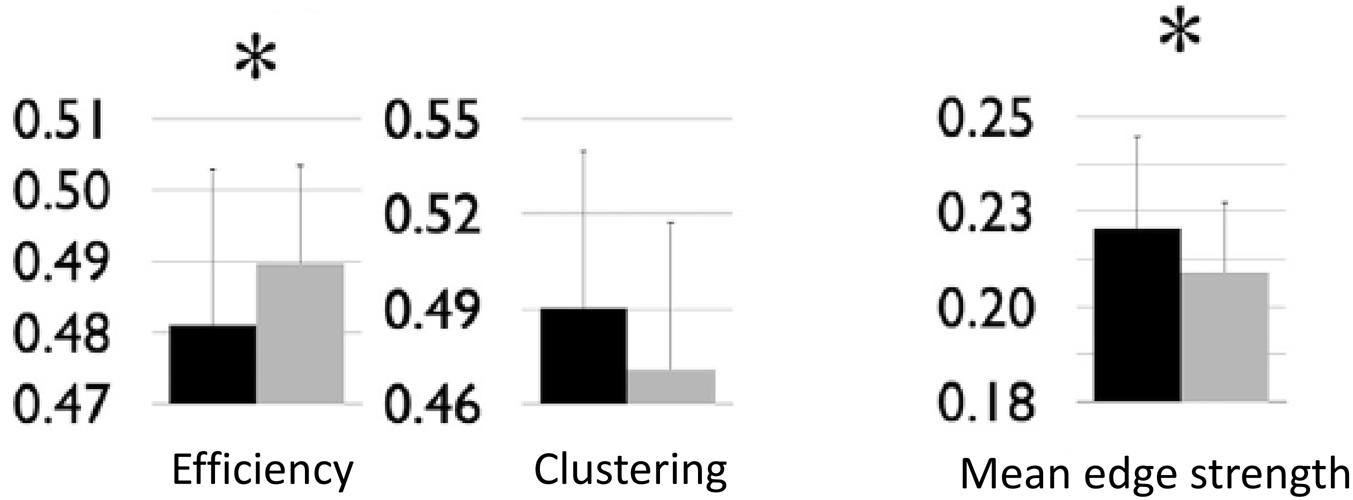


Schizophrenia example

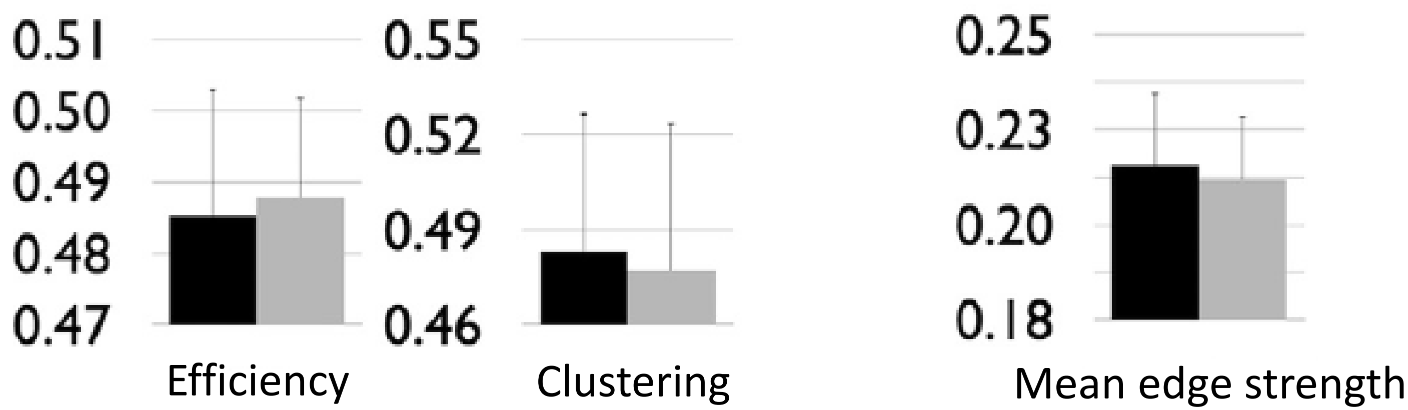


Schizophrenia example

Total sample: 48 patients, 44 controls



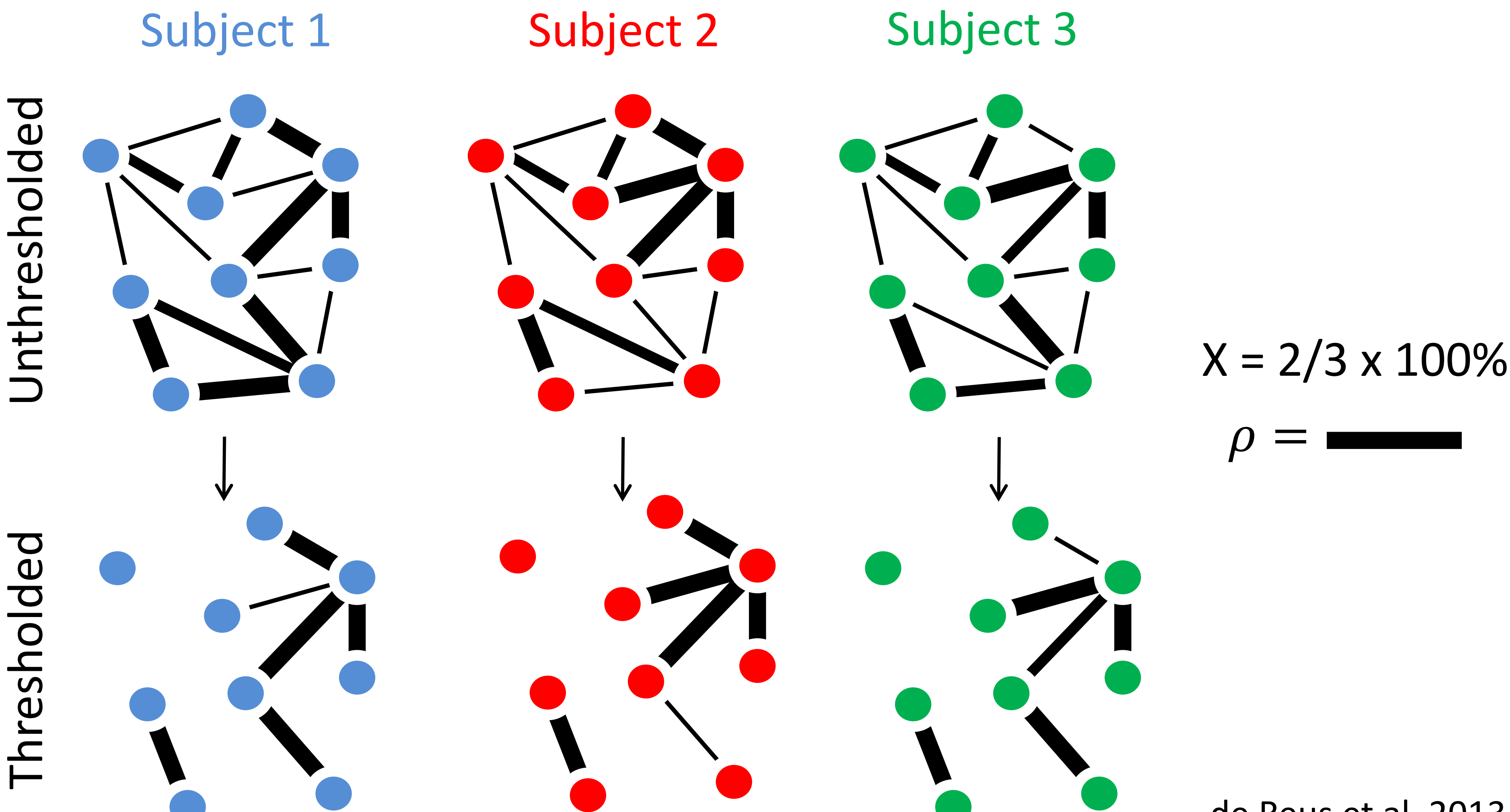
Matched sample: 44 patients, 40 controls



Van den Heuvel et al, 2017

Consensus thresholding

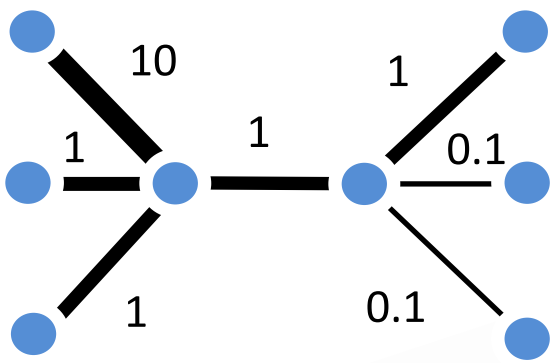
Eliminate edges that do not have **strength of at least ρ** in **at least X% of subjects**



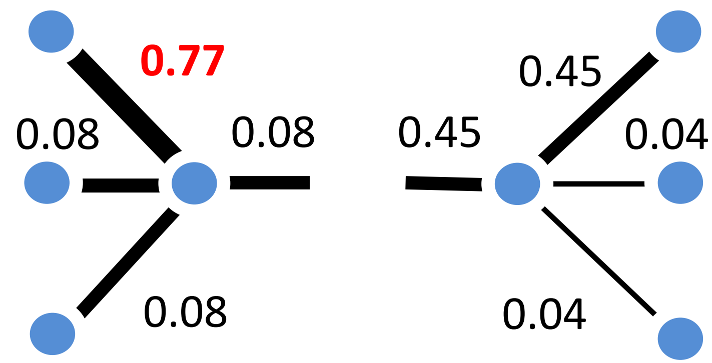
de Reus et al, 2013

Disparity filter

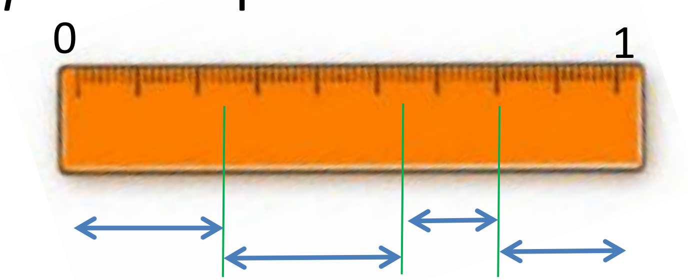
Local thresholding methods such as disparity filter account for heterogeneity in edge weights within different network locales



Step 1: Normalize per node

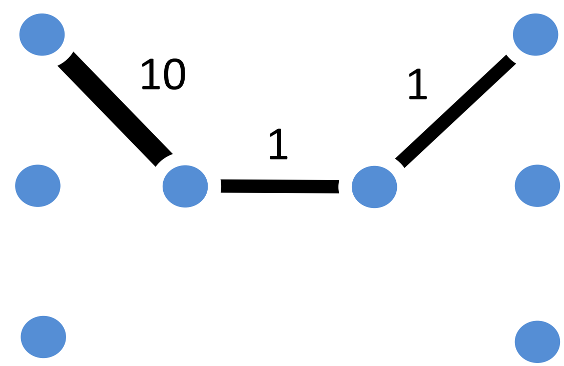


Step 2: Compute null distribution



Probability that longest segment exceeding **0.77**? Keep edge if probability below α.

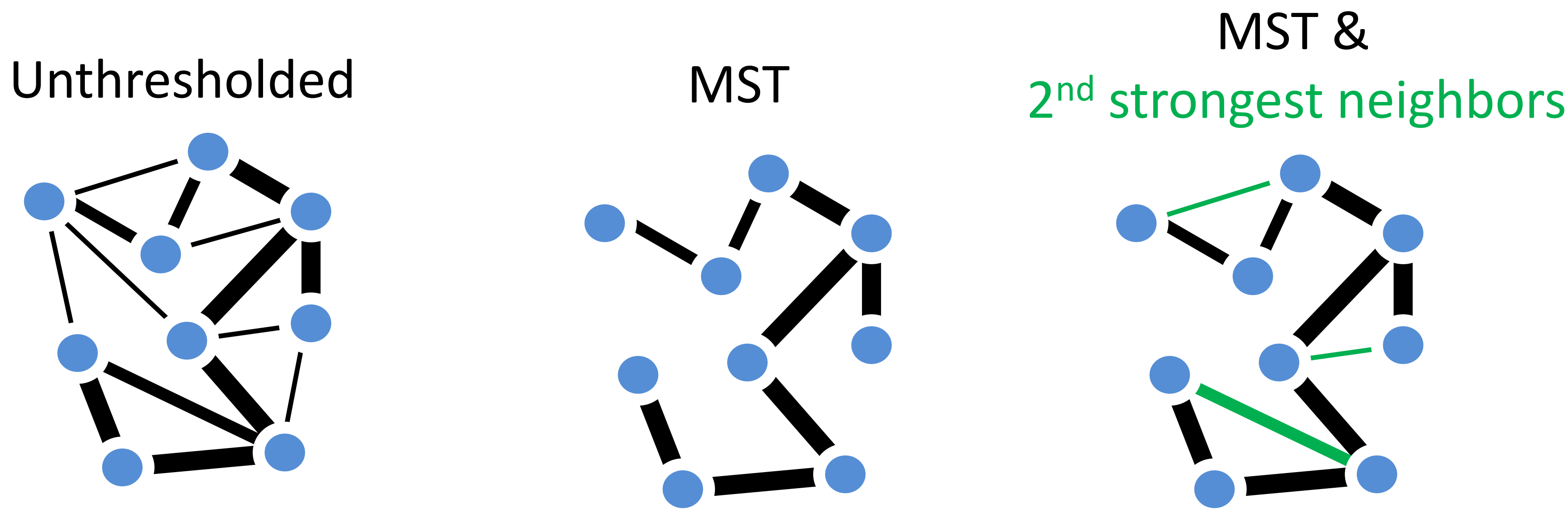
Step 3: Threshold



Serrano et al, 2009; Foti et al, 2011

Minimum spanning tree

- Minimum spanning tree (MST) protects against **network fragmentation**
- MST is the smallest subset of strongest edges that connects all nodes together
- Find the MST and then add further edges as required



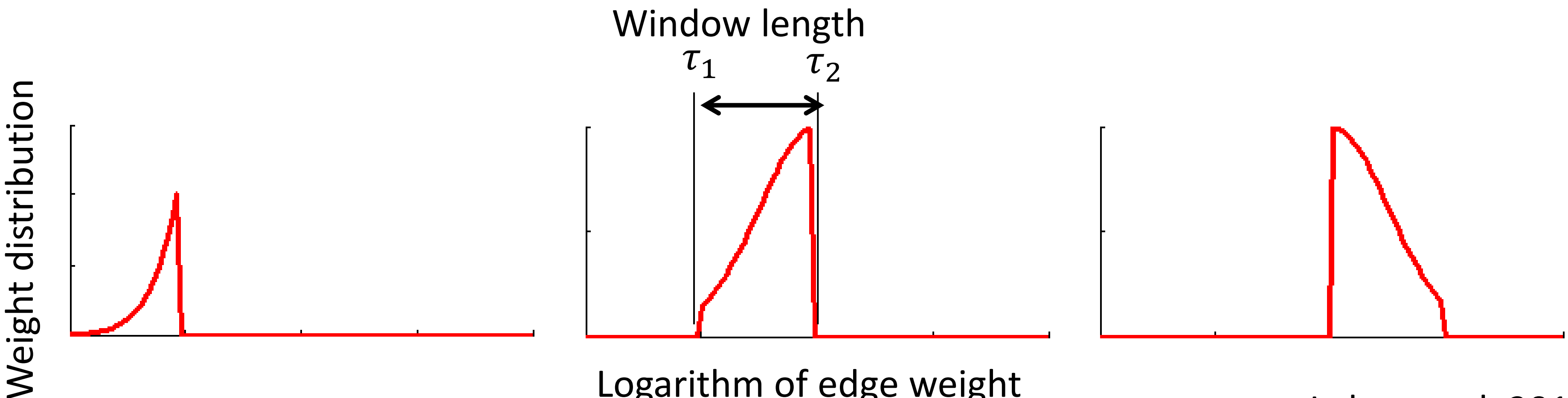
Reciprocal of edge weights used when computing MST

Alexander-Bloch et al, 2010

Multi-resolution methods

- Global thresholding creates an arbitrary distinction between edges that are useful and not useful:
  $C_{ij} > \tau \rightarrow$ useful, otherwise not
- Windowed thresholding provides insight into multi-resolution network structure

$$A_{ij} = \begin{cases} C_{ij} & \text{if } C_{ij} \in [\tau_1, \tau_2] \\ 0 & \text{otherwise} \end{cases}$$



Lohse et al, 2014

What thresholding method should I use?

Do you really need to ***threshold*** *and/or* ***binarize****?*

No - analyzing weighted brain networks can avoid arbitrary binarization cut-offs, but requires accurate estimation of edge weights

Are you comparing networks between different group of subjects?

Weight-based thresholding: Simple method, but group differences in network measures are difficult to divorce from trivial group differences in number of edges

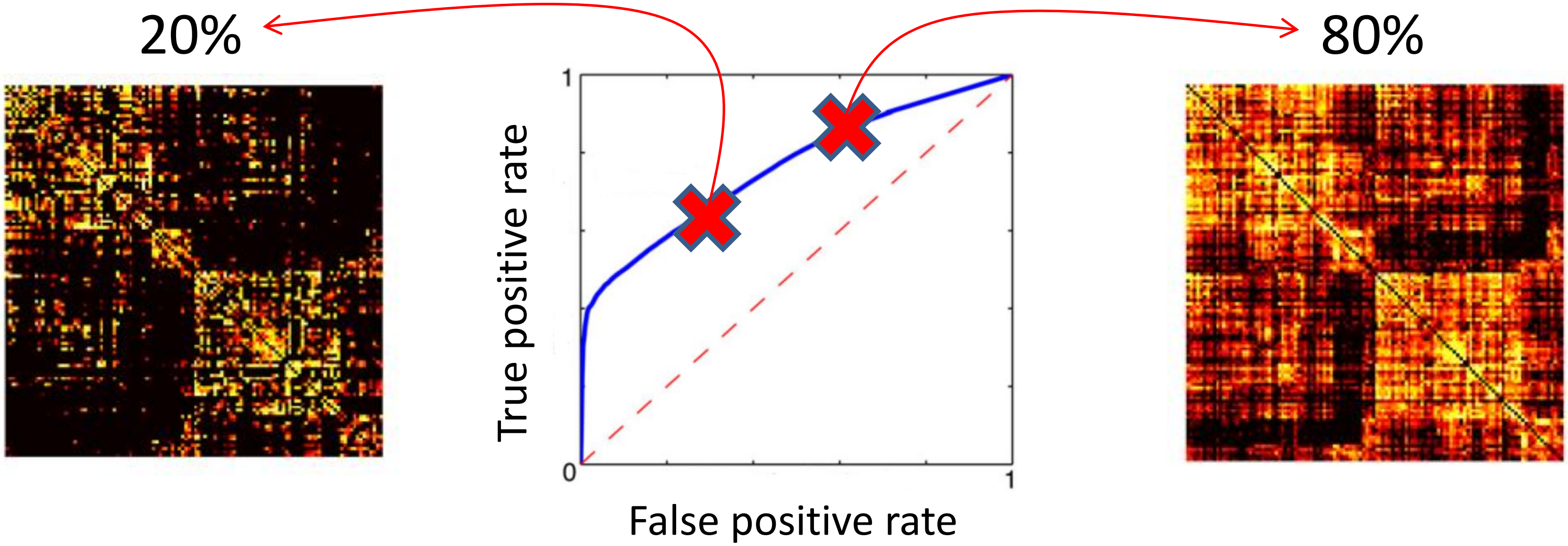
Density-based thresholding: Ok if groups matched in edge weight distribution, otherwise spurious group differences might emerge due to inclusion of spurious edges

Are you interested in network organization of specific (local) regions?

Consider local thresholding methods

How liberally should I threshold?

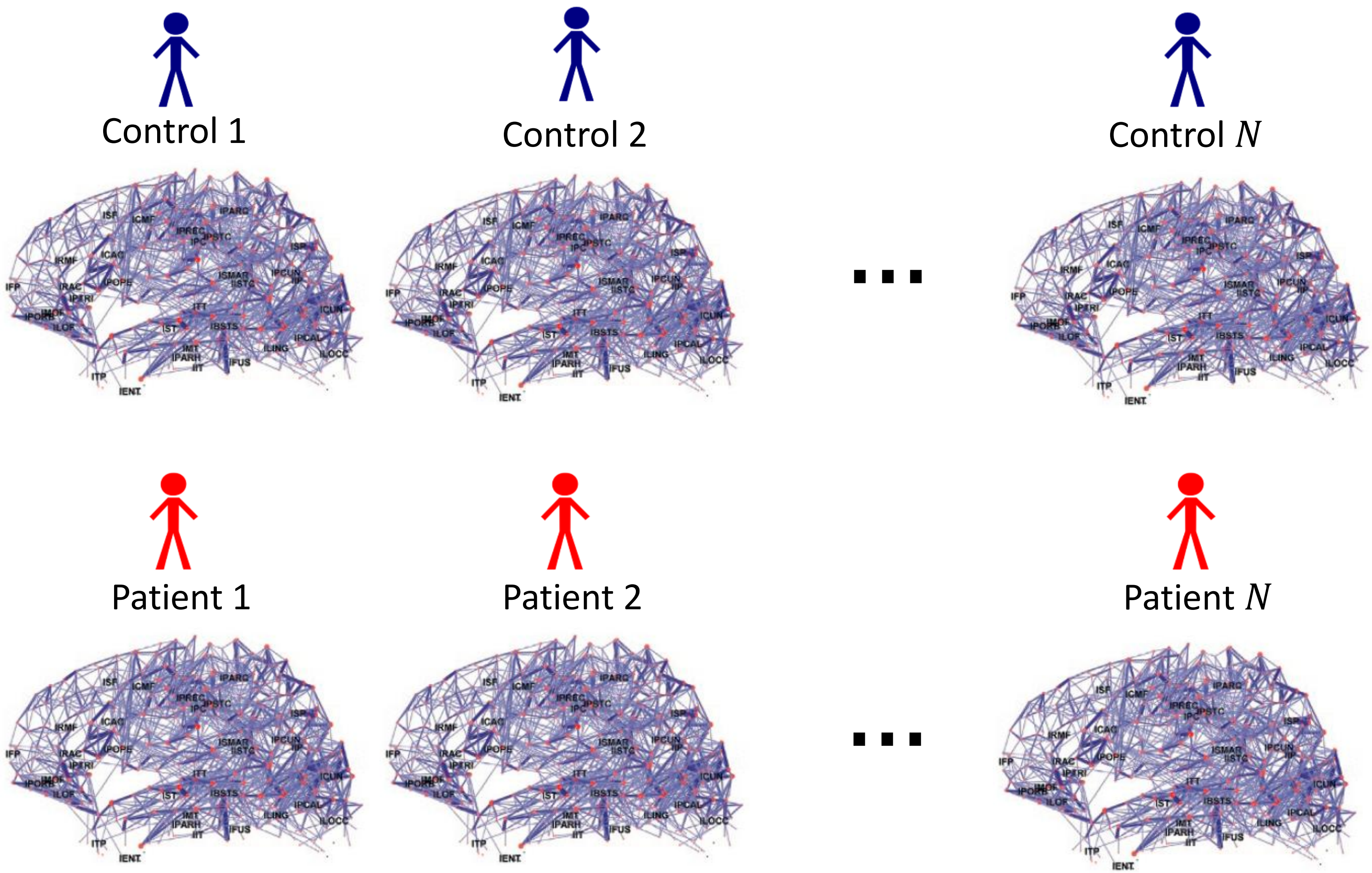
This is a question of sensitivity and specificity. Increasing severity of thresholding yields more specific but less sensitive networks.



False positives are more detrimental than false negatives to estimation of most network properties. Therefore, threshold liberally.

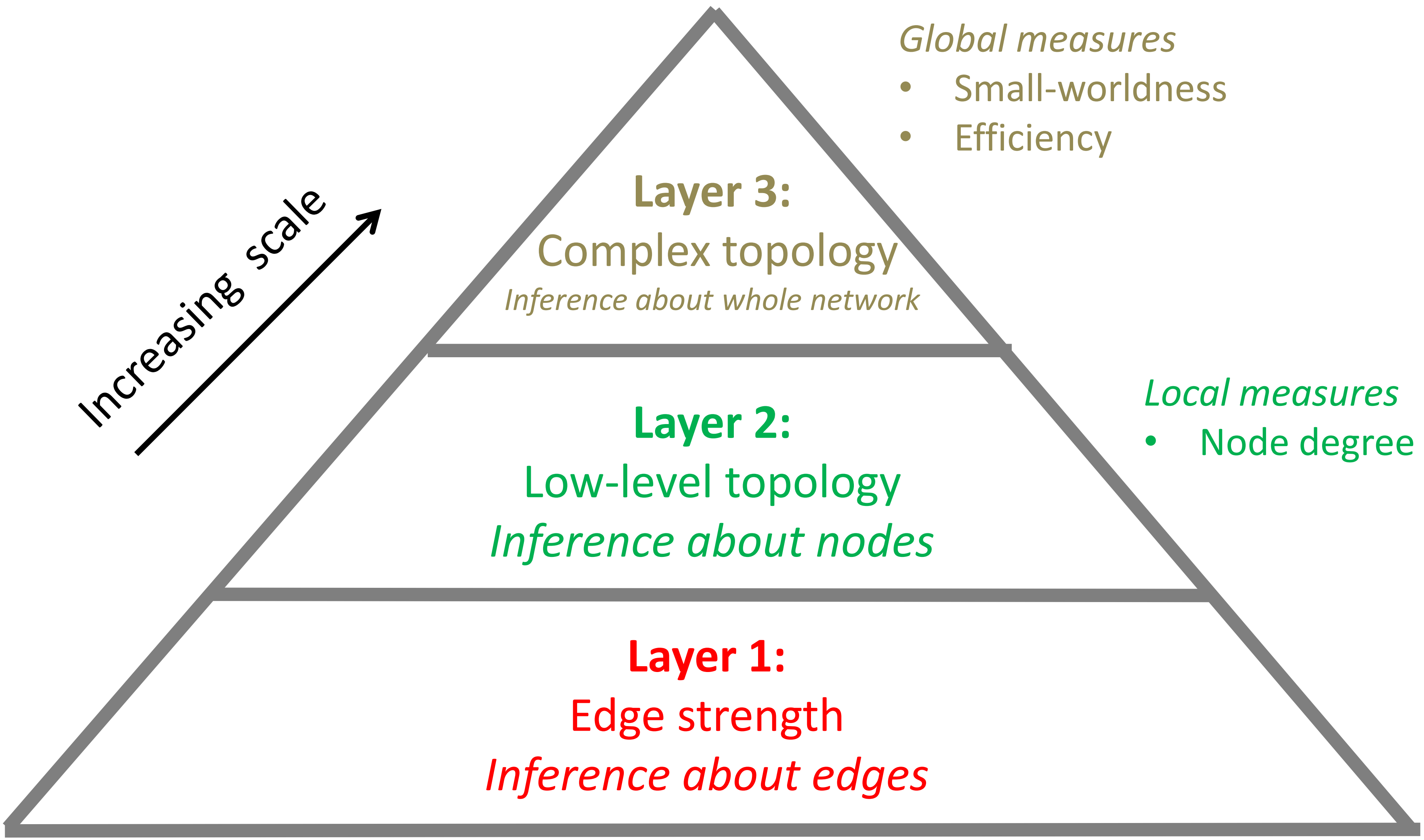
Zalesky et al, 2016

Network statistics: comparing networks

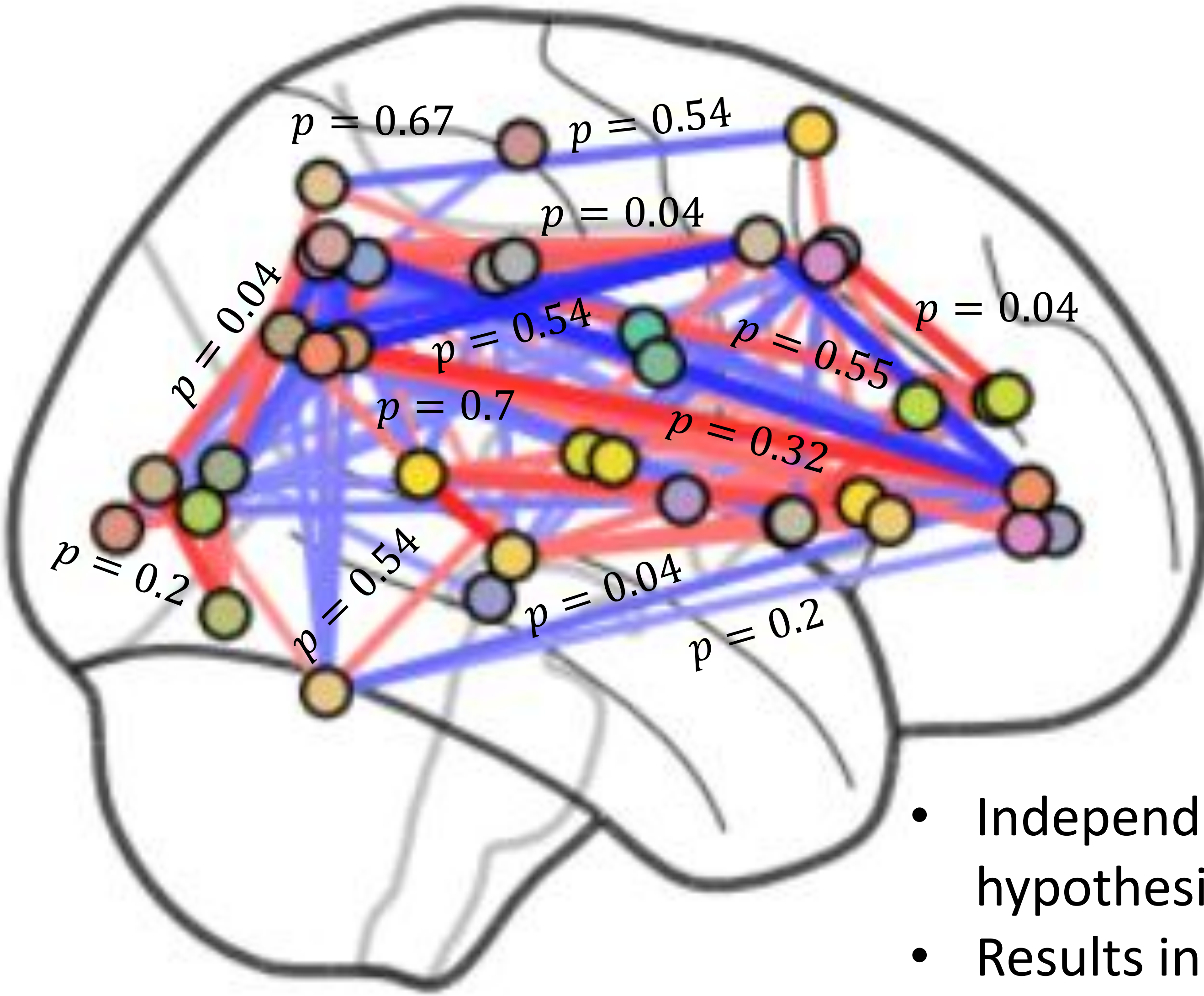


What network features differ between groups?

Scale of network comparisons



Mass univariate comparison of edge strengths



- Independently test a null hypothesis at each edge
- Results in a big multiple comparisons problem

False discovery rate (FDR)

Correction for multiple comparisons across edges can be achieved by controlling the FDR :

$$\mathrm{FDR} = \mathbf{E}\left(\frac{FP}{TP + FP}\right)$$

FP: Number of edges for which the null is falsely rejected
TP: Number of edges for which the null is correctly rejected

FDR using Benjamini-Hochberg method

Step 1. Sort p-values from smallest to largest

Let $p_{(j)}$ denote the jth smallest p-value

Step 2. Identify the **largest** j such that:

Desired FDR

$$p_{(j)} \leq \frac{j\alpha}{M}$$

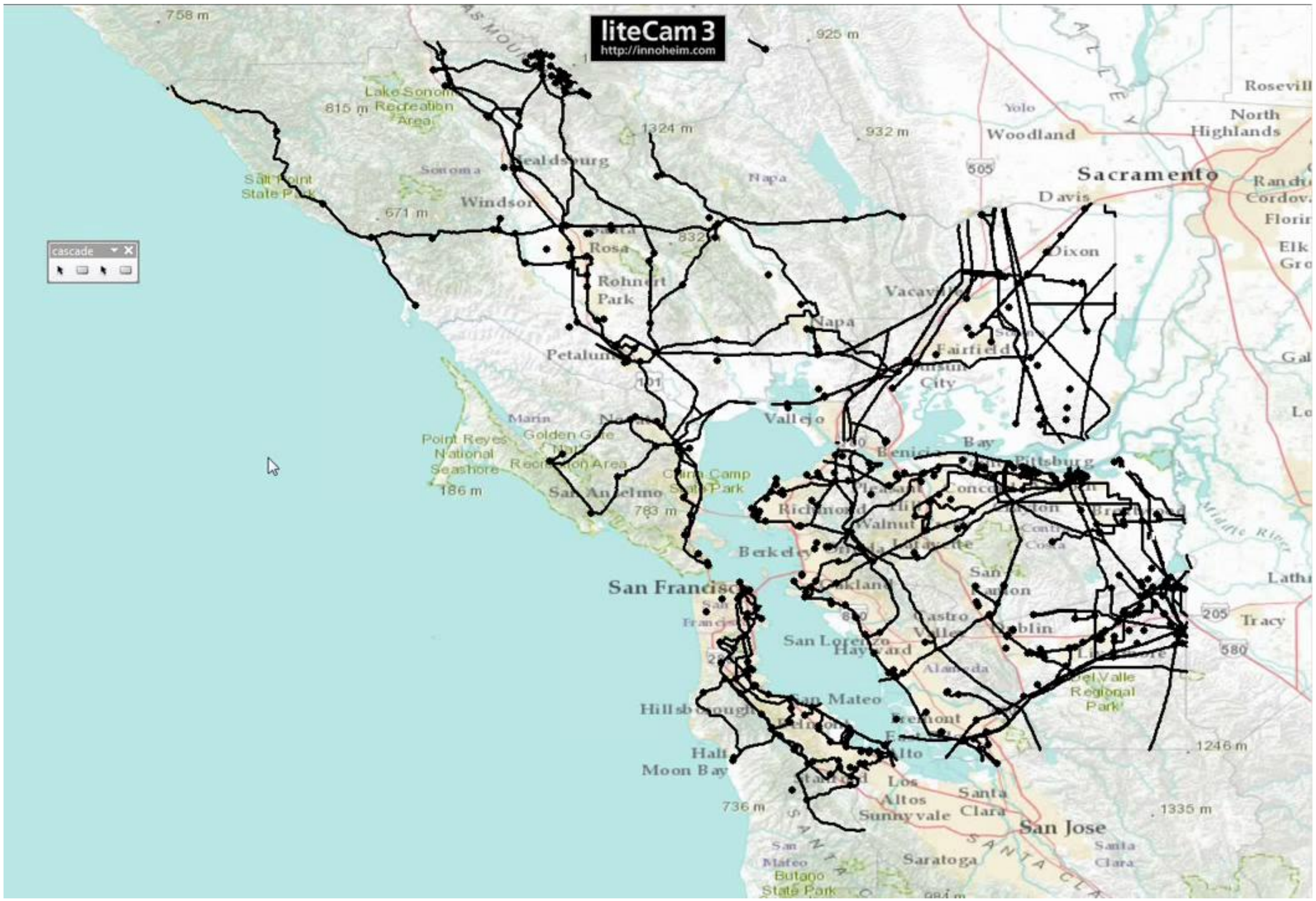
Total number of edges

Step 3. Reject the null hypothesis for $p_1, \ldots, p_{(j^*)}$

$j =$	1	2	3	4	5
$p_{(j)} =$	[0.002,	0.01,	0.3,	0.4,	0.8]
$\frac{j\alpha}{M} =$	0.01	0.02	0.03	0.04	0.05

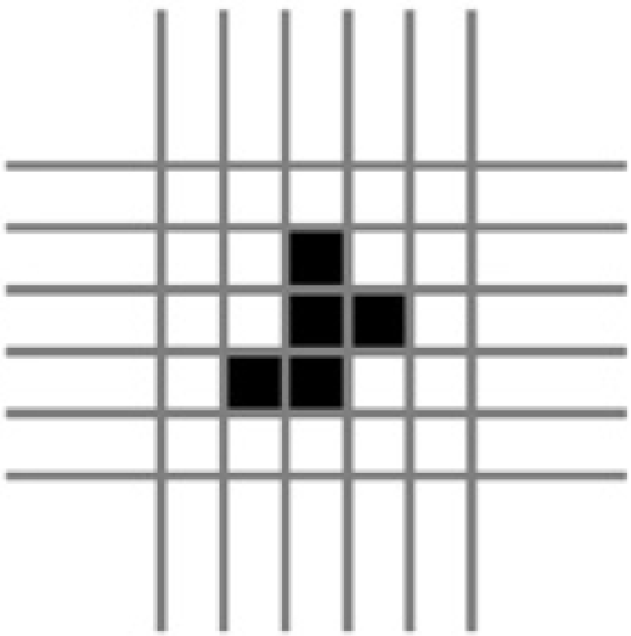
Network cascades

Failures cascading through power transmission network

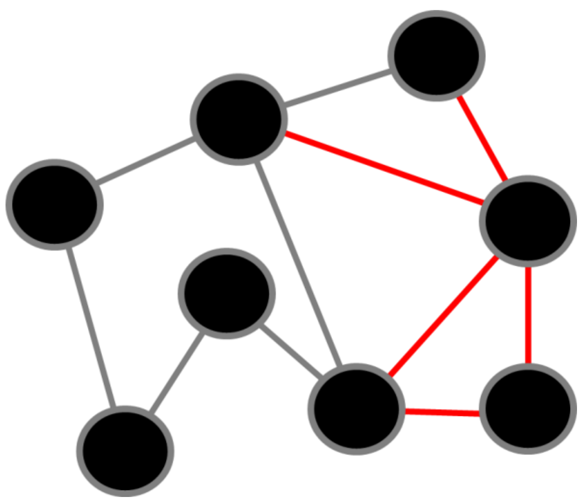


Clusters and components

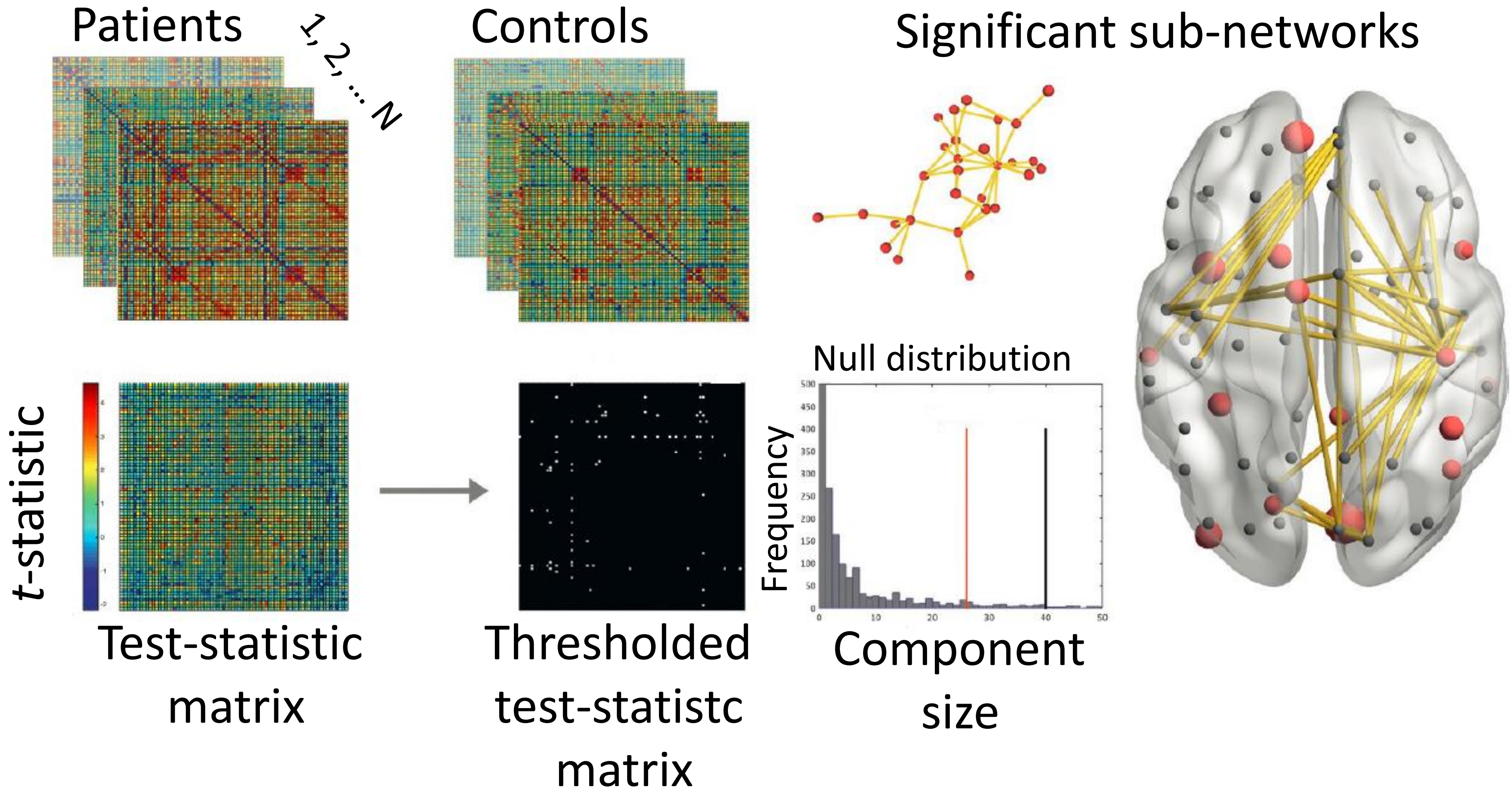
Cluster of voxels in an image



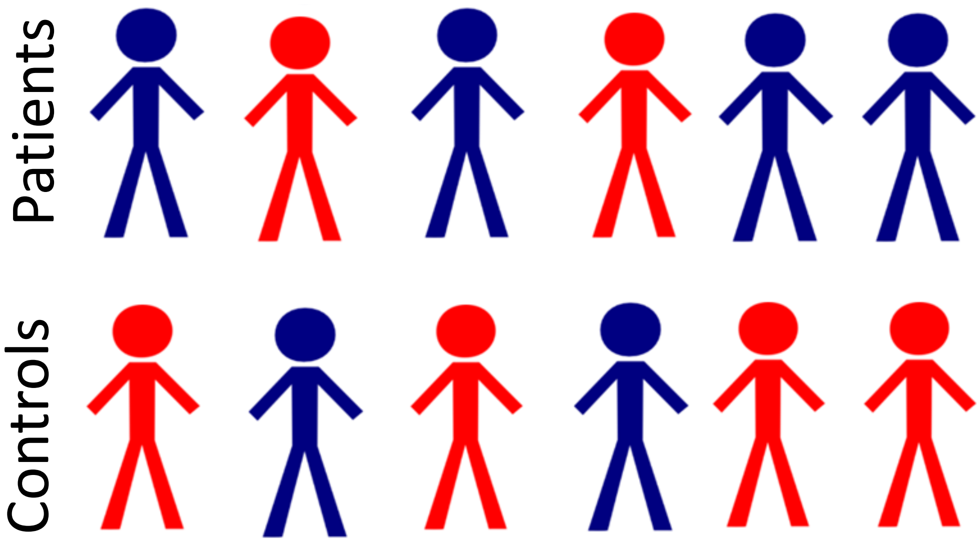
Connected component in a network



Network-based statistic (NBS)

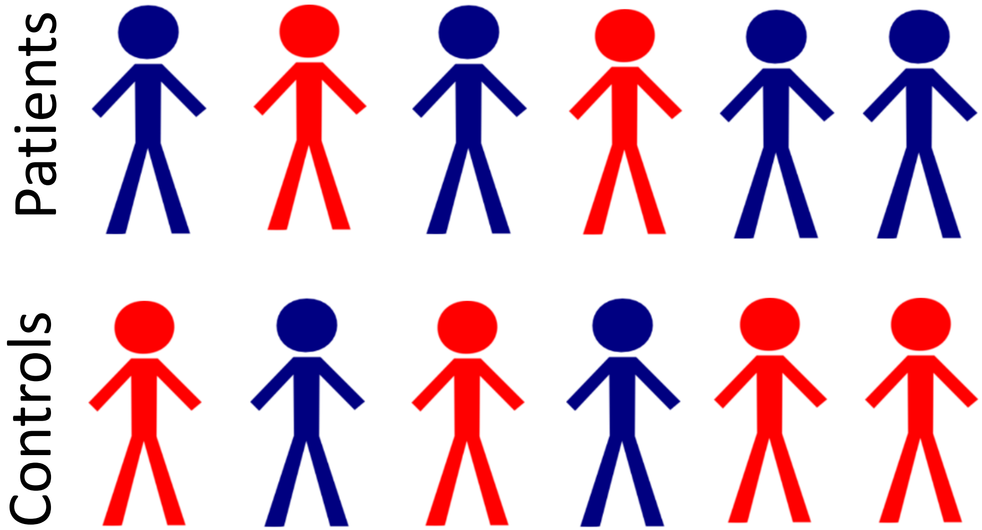


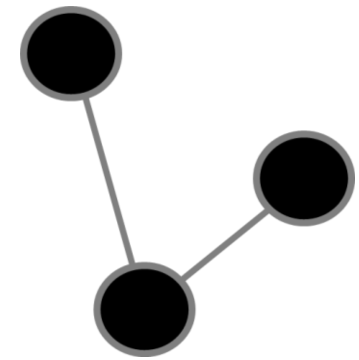
Permutation testing



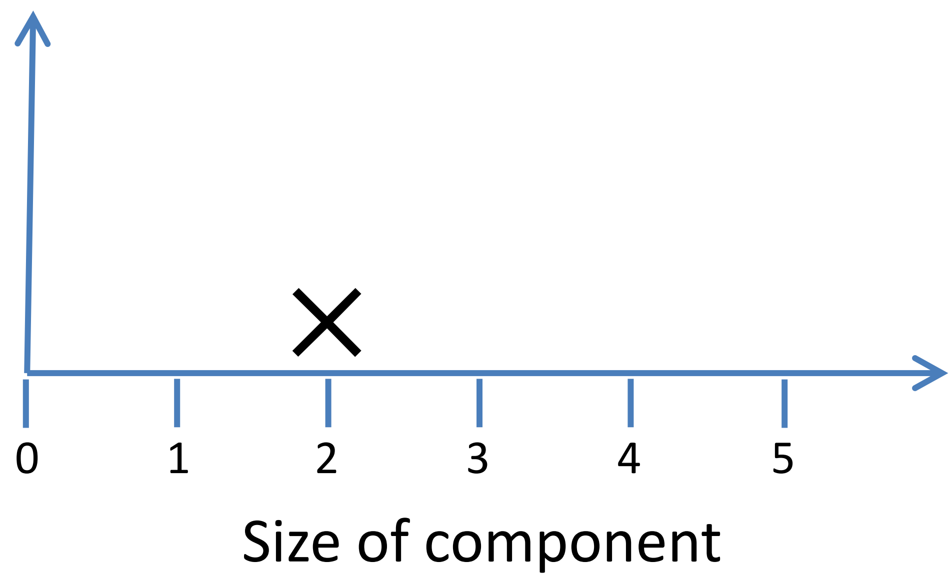
If null hypothesis is true, distribution of test statistic is insensitive to permutation of patients and controls

Permutation #1

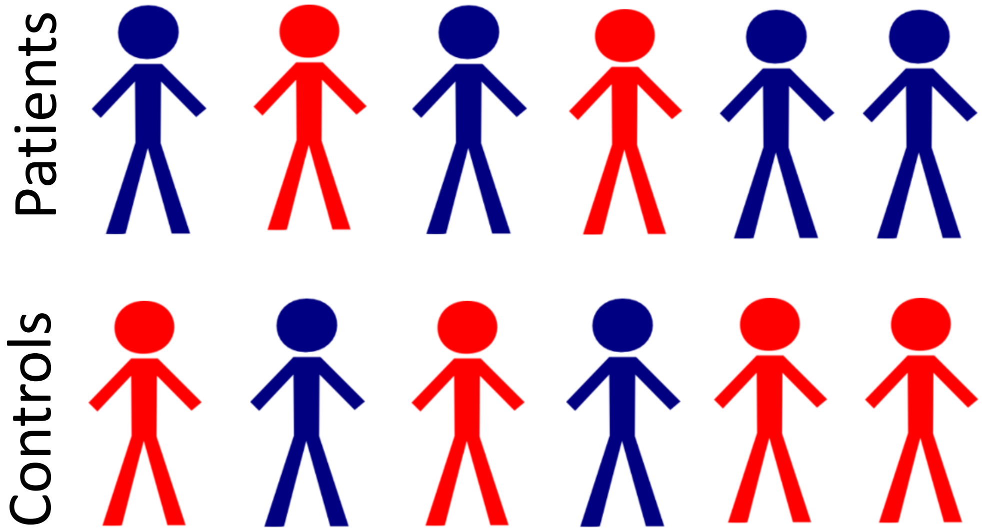


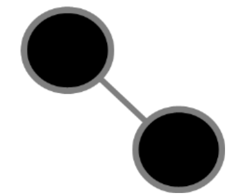


Largest component found in Permutation 1 has $Size = 2$

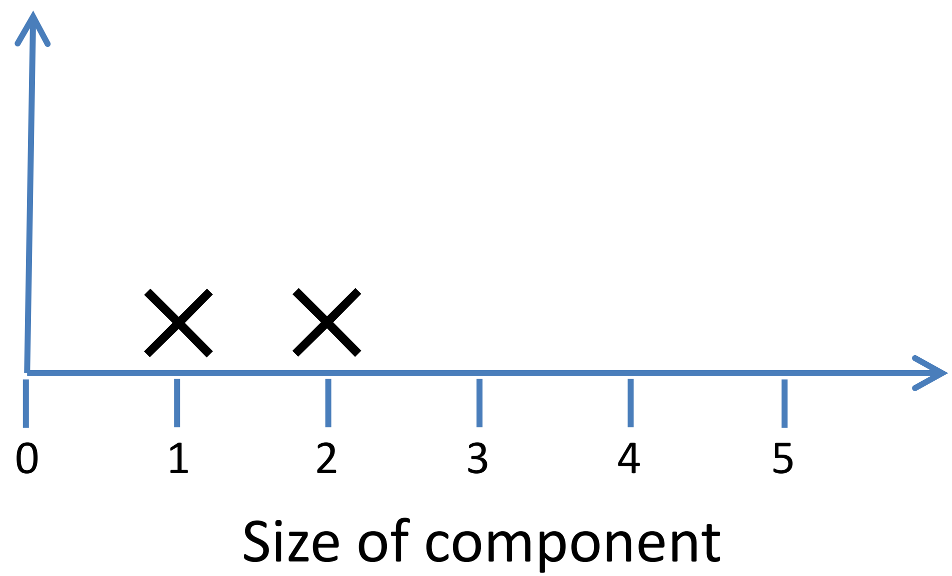


Permutation #2



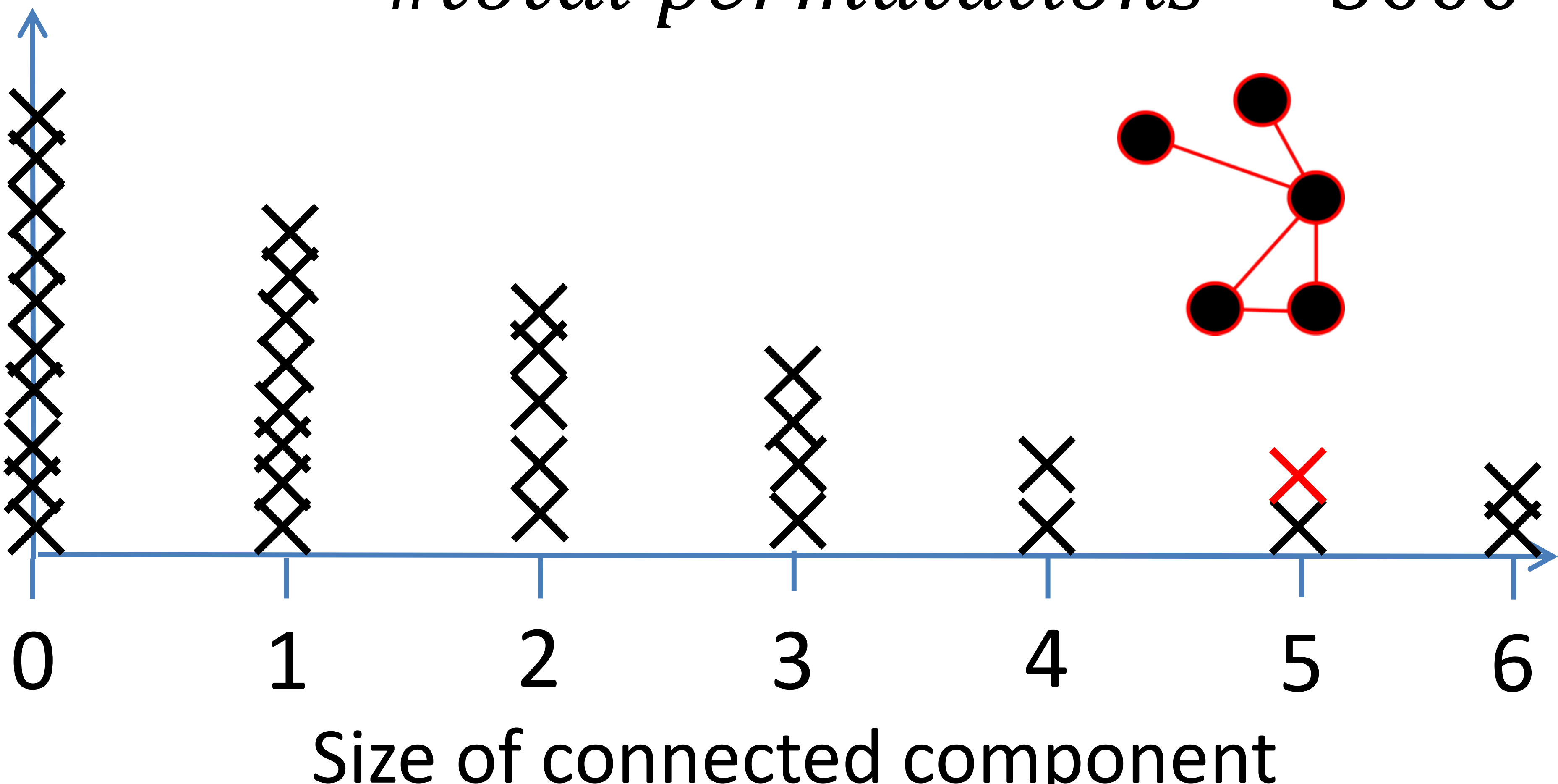


Largest component found in Permutation 1 has
$Size = 1$



Permutation #5000

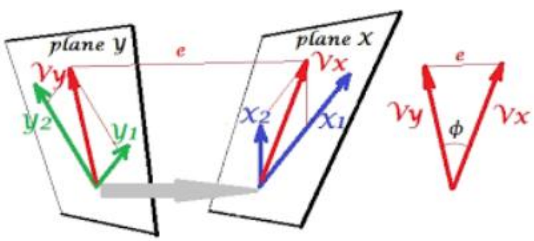
$$p = \frac{\#permutations \geq 5}{\#total\ permutations} = \frac{3}{5000}$$



Multivariate network inference

Mass univariate testing reduces complex network interactions to isolated elements (edges and nodes)

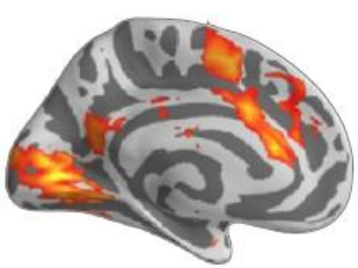
Multivariate inference attempts to recognize and learn complex patterns spanning multiple network elements



Canonical correlation analysis (CCA) and partial least squares (PLS)

$$\min_{\beta}\left\{\frac{1}{N}\sum_{i=1}^{N}\left(y_i - x_i^t\beta\right)^2\right\}$$

Network-based sparse regression and fused lasso



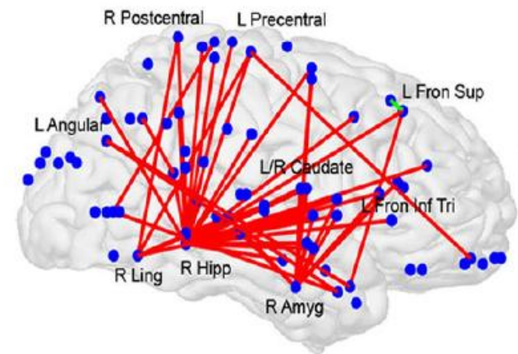
Multivariate distance matrix regression

Software for connectome inference

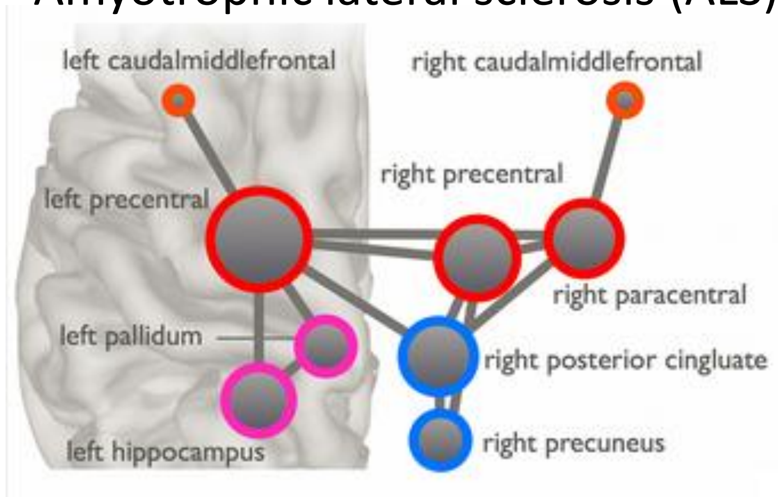
- CONN: functional connectivity toolbox
  https://www.nitrc.org/projects/conn/
- NBS: network-based statistic
  https://www.nitrc.org/projects/nbs/
- Graphvar
  https://www.nitrc.org/projects/graphvar/
- BCT: brain connectivity toolbox
  https://sites.google.com/site/bctnet/
- Connectome Viewer
  http://cmtk.org/viewer/
- GLG: graph theory GLM (MEGA LAB)
  https://www.nitrc.org/projects/metalab_gtg/

Disease connectomics

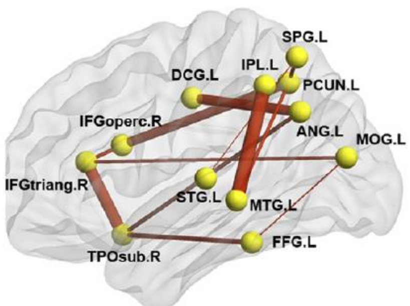
Task-based functional connectivity



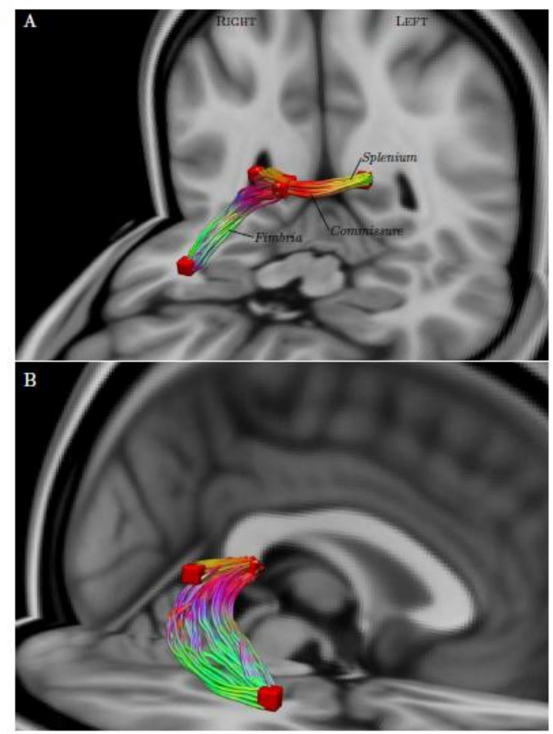
Amyotrophic lateral sclerosis (ALS)



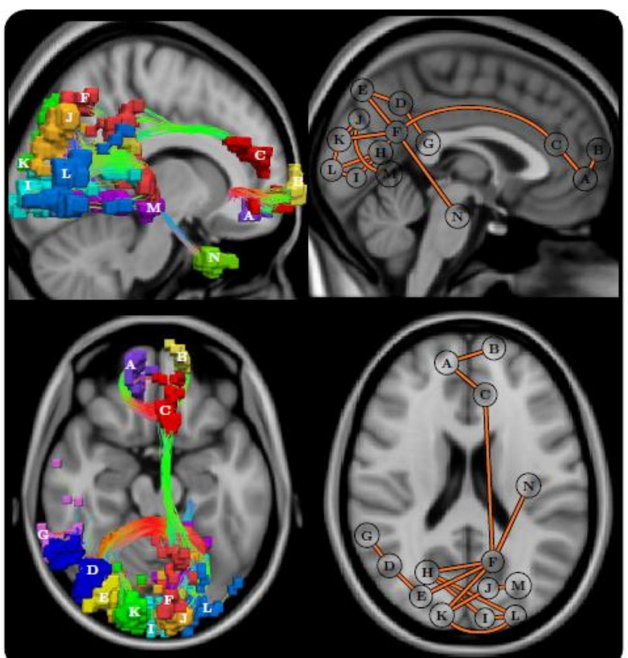
Depression

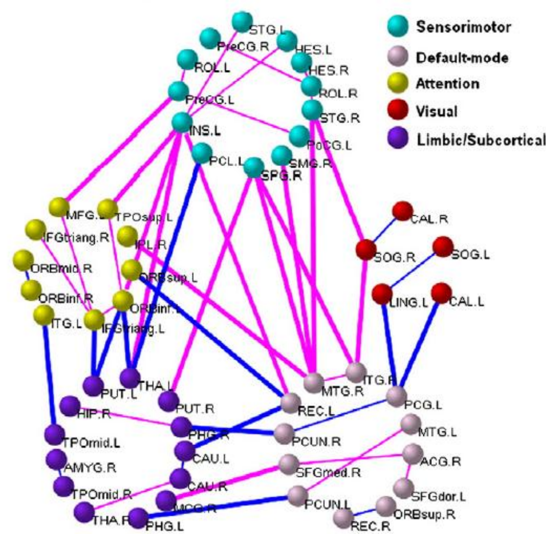


Cannabis use



Schizophrenia





Further reading

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