# Resting-state fMRI and graph-based methods for analyzing functional connectivity

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Lecture SS 2014

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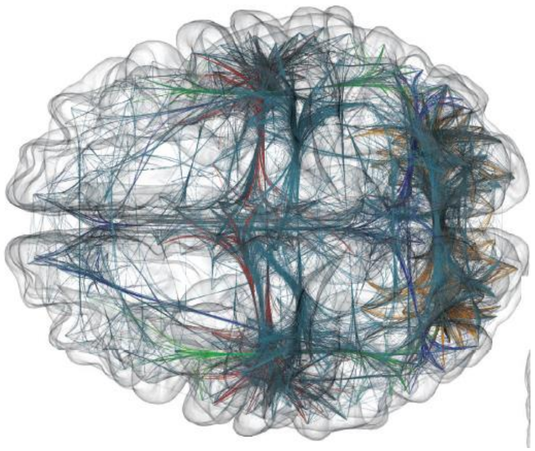
# Introduction

- Resting State fMRI
- Graphs and their Definition
- Analyze and Compare Graphs

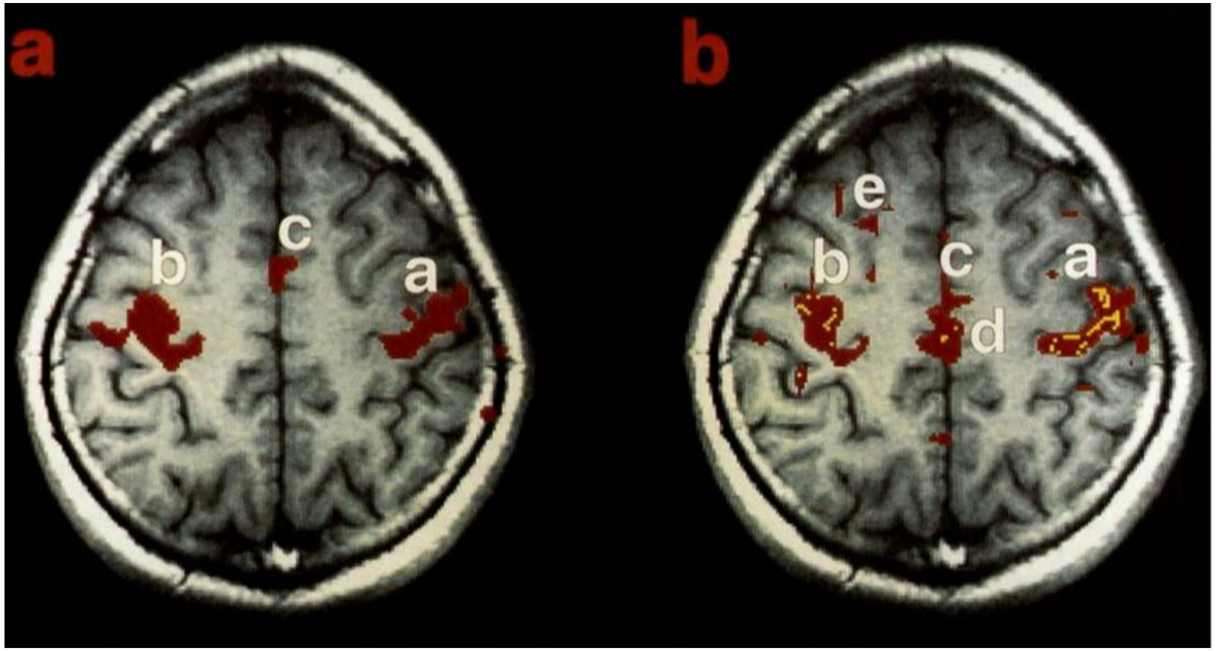
Brain Connectivity, Marie Liebert Publishing



Boettger, IEEE TVCG, 2014

# Resting State fMRI

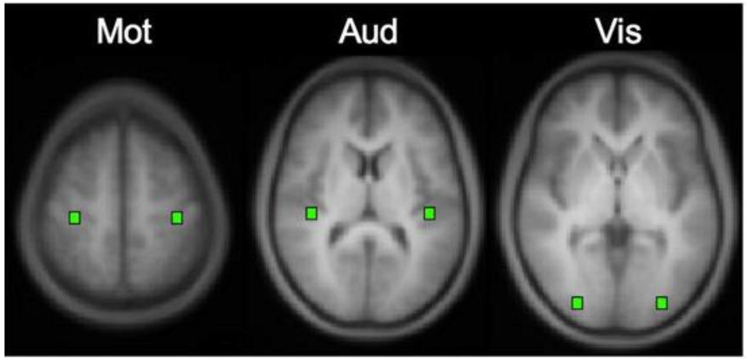
- spontaneous brain activity in the absence of task
- correlated signal in functionally coupled networks

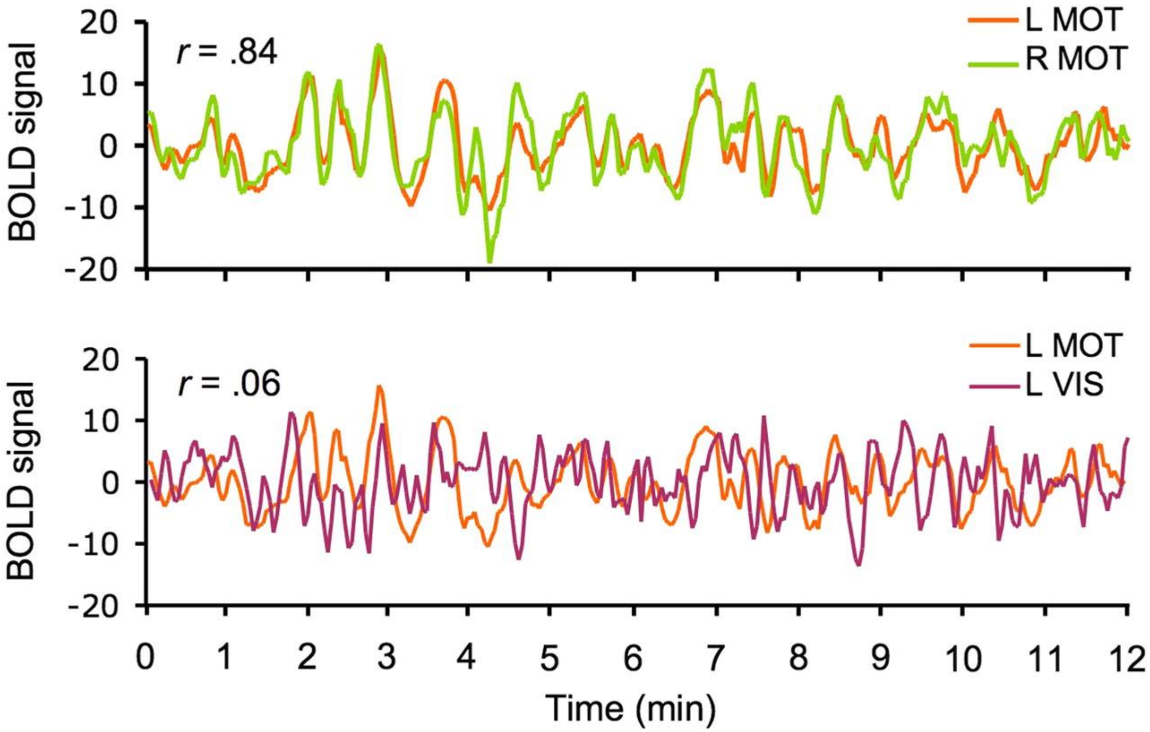



BB Biswal, MRM,1995

# Resting state fMRI

- rs-fMRI observation (Biswal95): correlated signal in functionally coupled networks



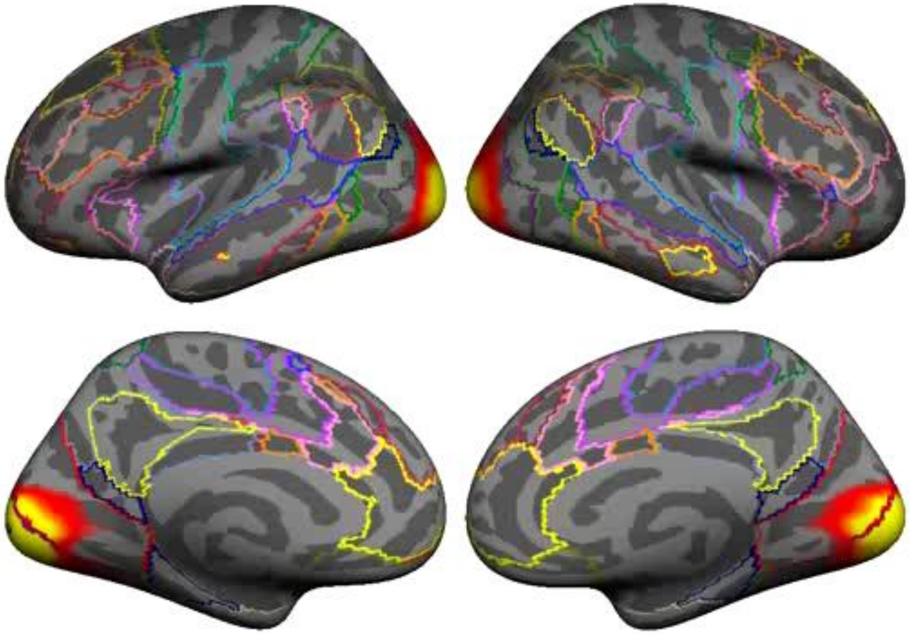

Figures adopted from Van Dijk et al., 2010, Journal of Neurophysiology

# Resting State fMRI

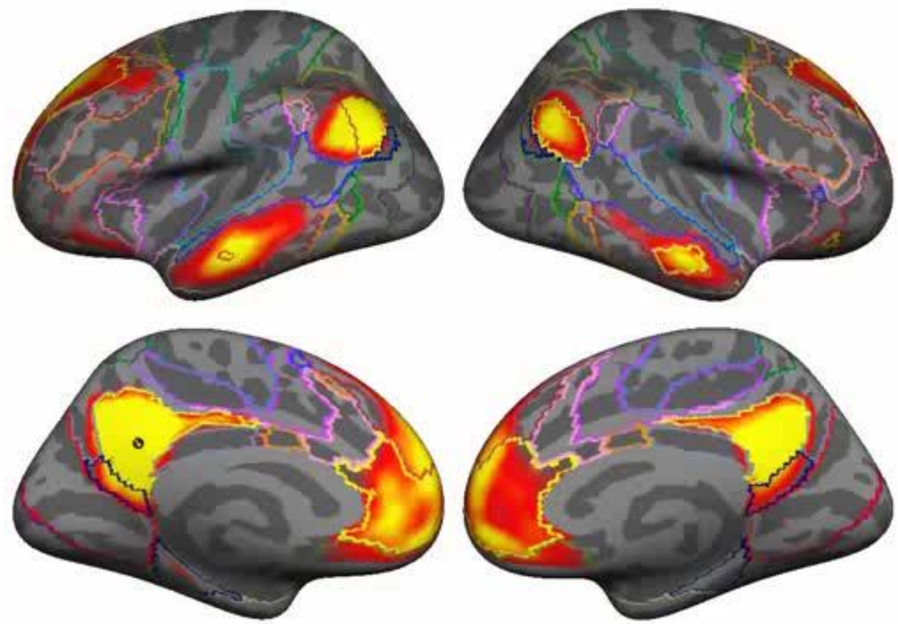
- Intrinsic connectivity
  - Present during task, in the absence of task and under anesthesia
  - Majority of the power of the signal is between is in very slow signals (0.01 – 0.05 Hz)
  - correlates with (neuronal) EEG signal (Mantini 2007)

# Resting State fMRI

- Correlated signal reflects functionally coupled networks (www.youtube.com/user/YeoKrienen)



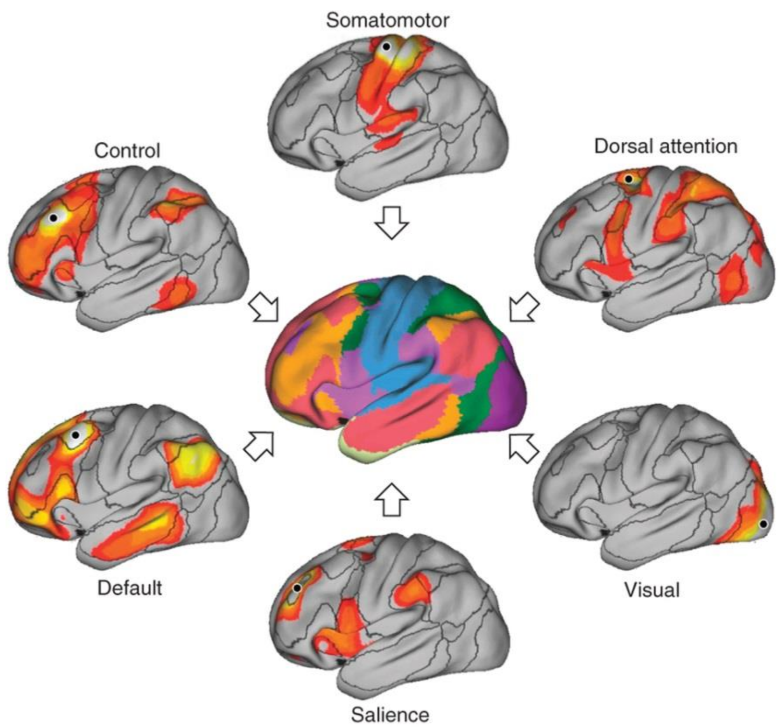
Yeo, *J. Neurophysiol.*, 2011



Yeo, *J. Neurophysiol.*, 2011

# Resting State fMRI

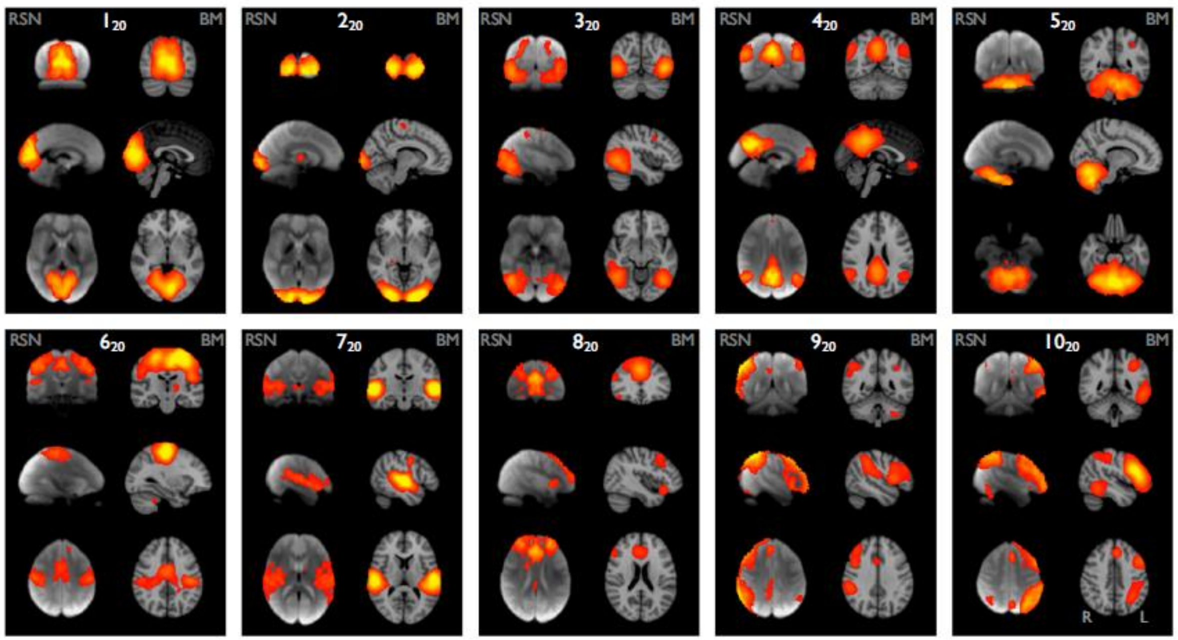
- Correlated signal reflects functionally coupled networks

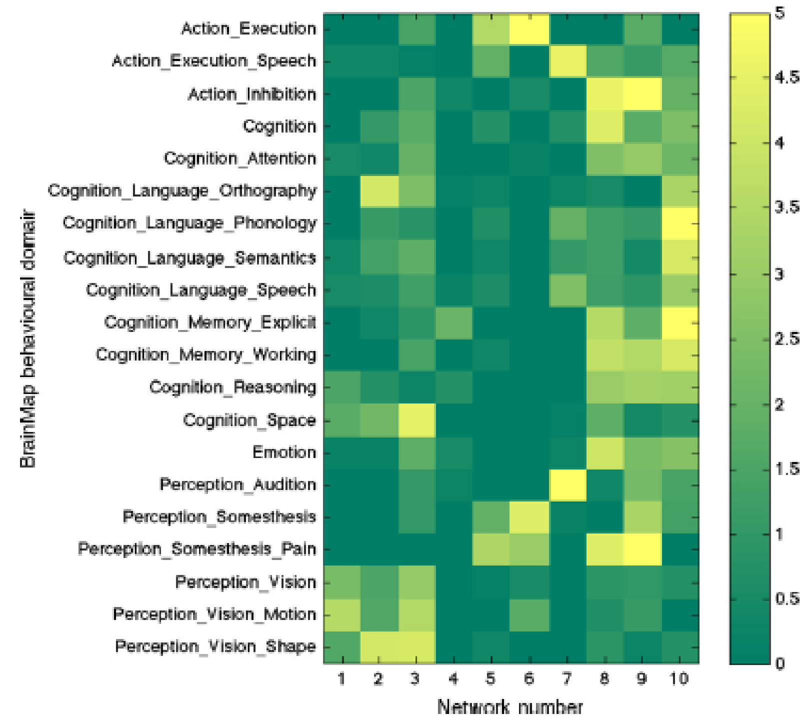



Yeo, *J. Neurophysiol.*, 2011

# Resting State fMRI

- Resembles "task-based" coactivation areas
- Database of 10,000 studies  (Smith, PNAS, 2010)



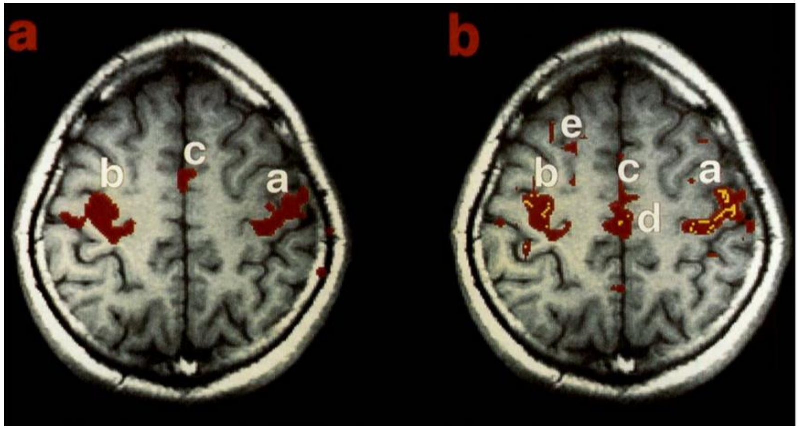



# Resting State fMRI

- Good Test-Retest Reliability (Shezad, 2009)
- Can be altered by training a task (Taubert 2010)
- Can predict the age of a subject (Dosenbach 2010)
- Can predict the disease status of a subject e.g. in Depression (Zeng, 2012), ADHD (Fair, 2013) Alzheimer (Sorg, 2007)

# Resting State fMRI

- intrinsic brain connectivity → the cross talk of brain areas
- Whole brain cross talk → functional brain network

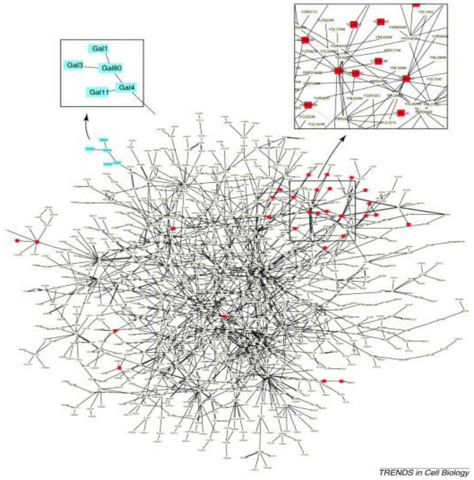



Biswal, MRM,1995

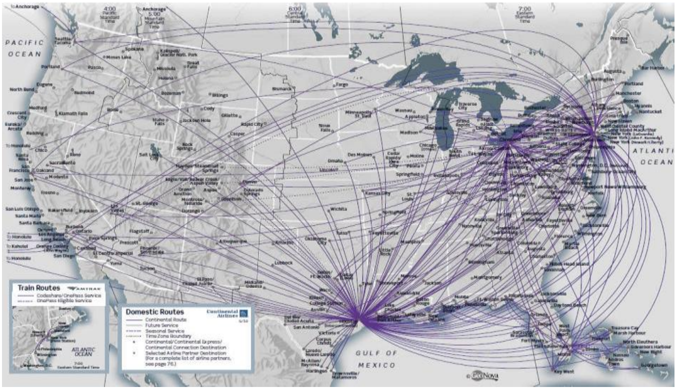
Brain Connectivity, Marie Liebert Publishing

# Graph Defintion

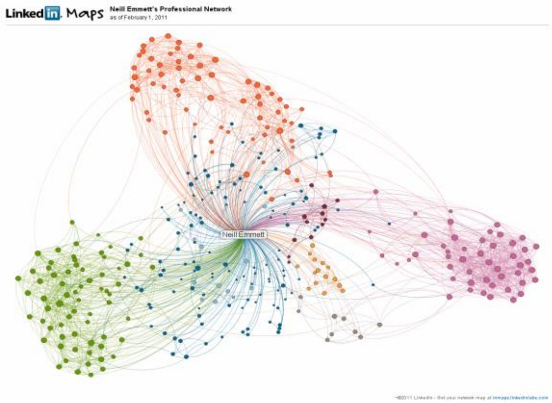
- Some examples of graphs people already work with



Protein Interaction Graph
Tucker 2001



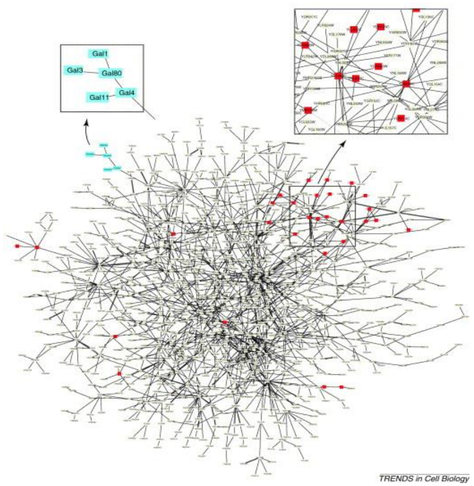
Airplane Graph
Aeorspace.org



Social Graph
Youarethem.co.uk

# Graph Defintion

- Some examples of graphs people already work with
- Advantage → we can use the same math for all of them




Protein Interaction Graph
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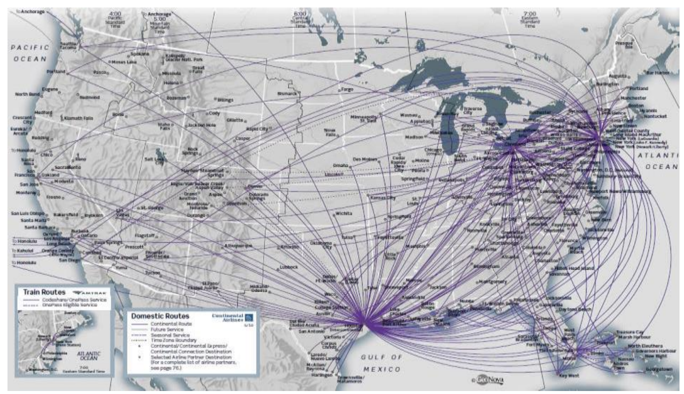


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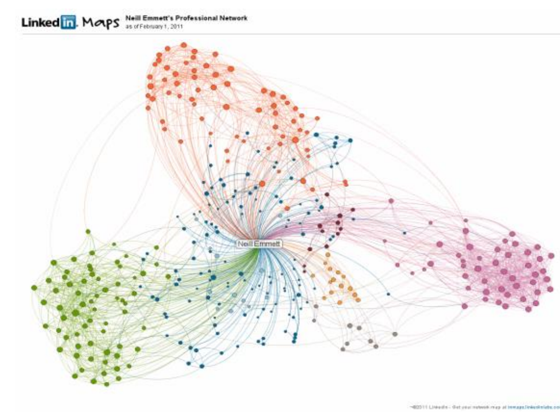


Social Graph
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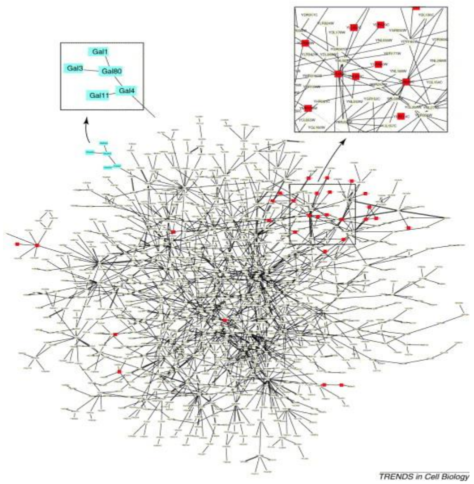
# Graph Defintion

- A Graph is a tupel (V,E)
- V is a set of vertices
- E is a set of edges, where e in E: V x V

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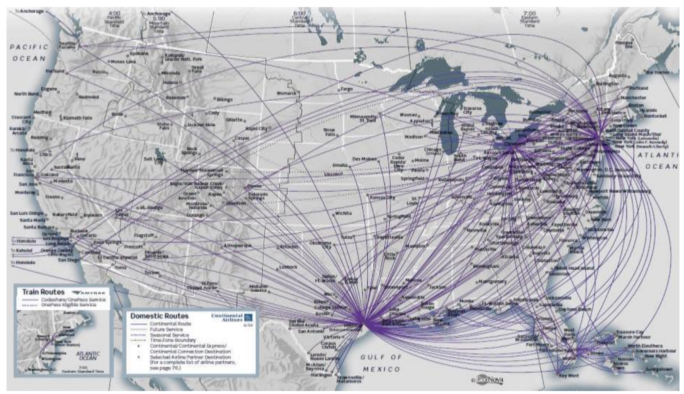
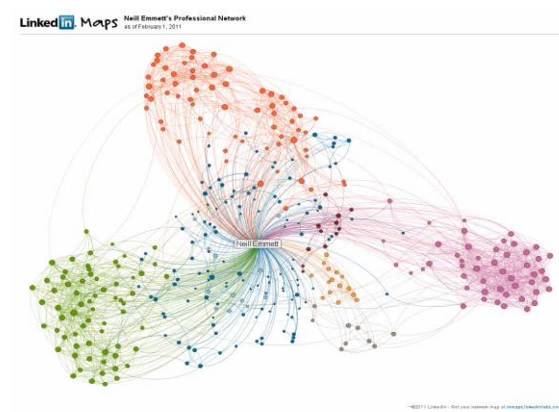



Airplane Graph
Aeorspace.org




Social Graph
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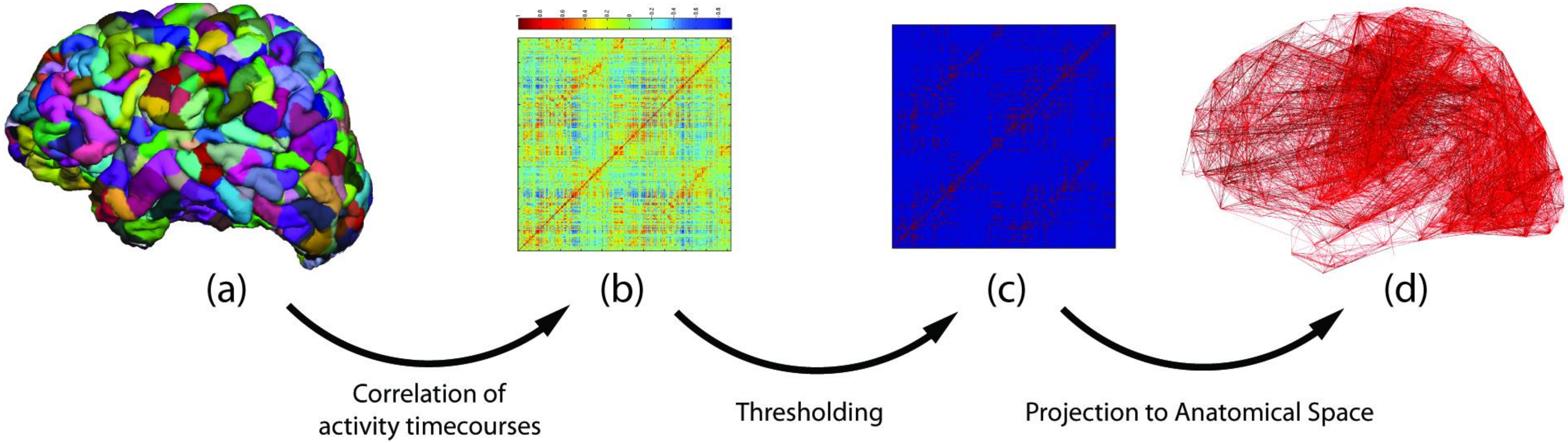


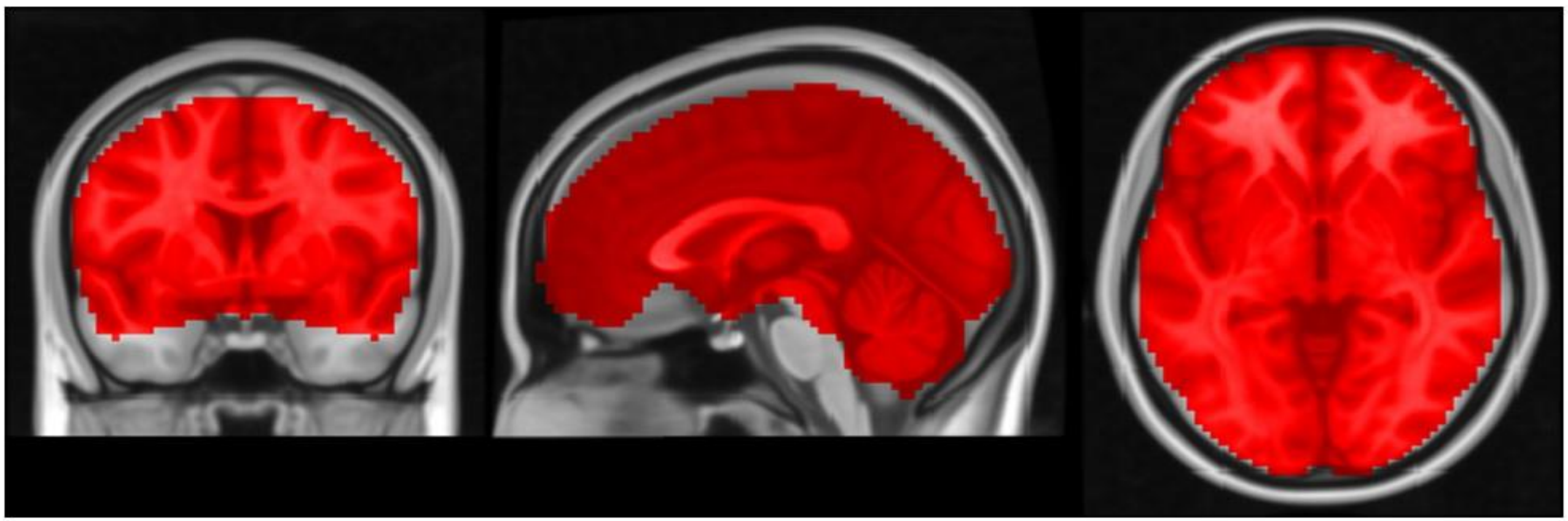

Boettger, IEEE TVCG 2014

# Set of Vertices

- "Good" definition of vertices is crucial for the following graph analysis

# Set of Vertices

- Voxel-based
  - Each voxel represents a distinct node



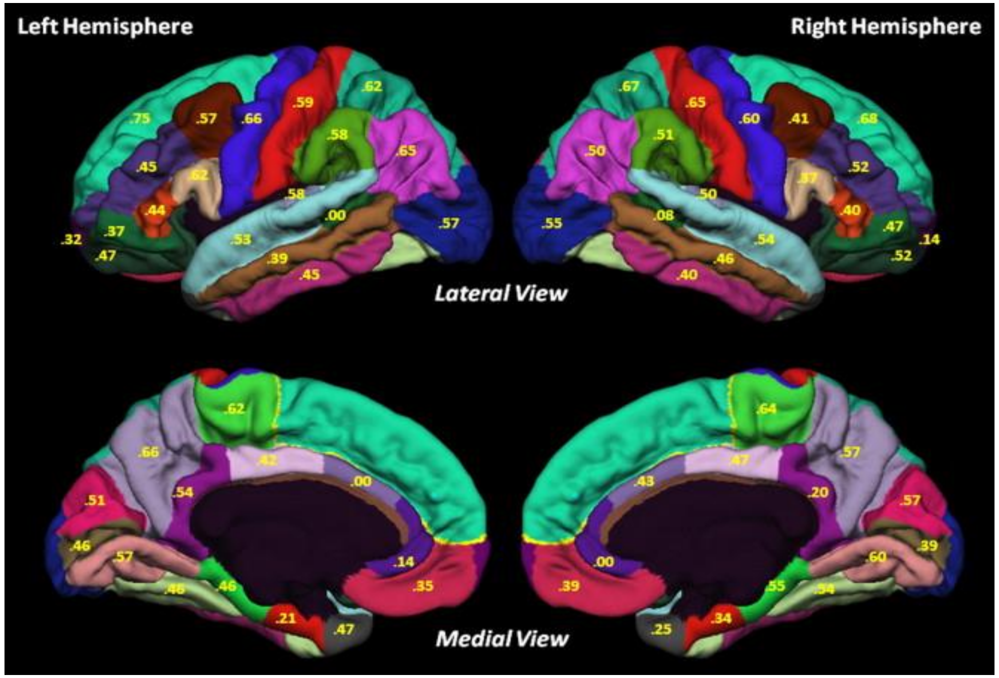
Lohmann, PloS One, 2010

# Set of Vertices

- Voxel-based
  - Pro:
    - Data Driven
    - Good reliability
    - High Resolution
  - Con:
    - Unclear Validity
    - Computational intensive
    - Higher risk of false positive short range connections

# Set of Vertices

- Anatomical
  - Base on prior anatomical information



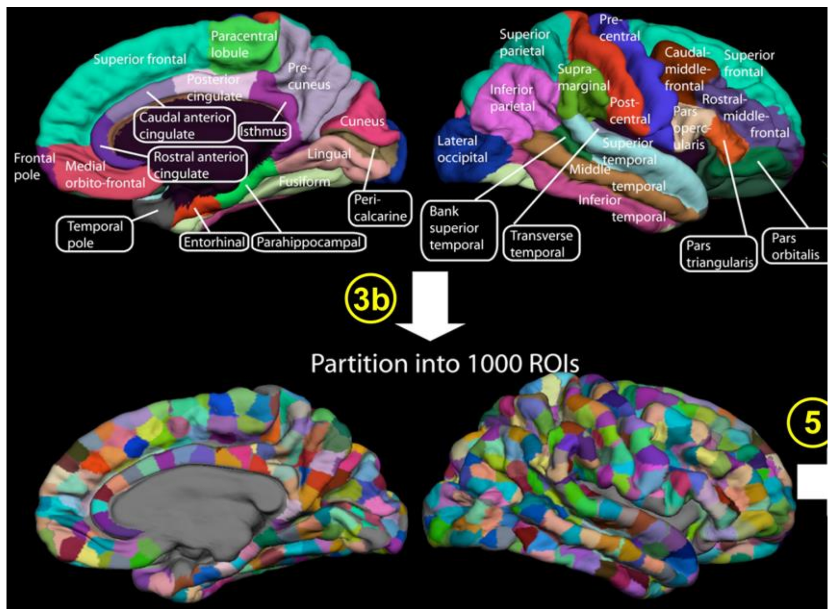

Desikan, NeuroImage 2006

# Set of Vertices

- Anatomical
  - Pro:
    - Intuitive parcellation
    - Fast to compute
    - High reliability
  - Con:
    - Low Resolution
    - Variation in node size?
    - Low validity?

# Set of Vertices

- Random Parcellation
  - Randomly into regions with similar size
  - Allows multi resolutions:



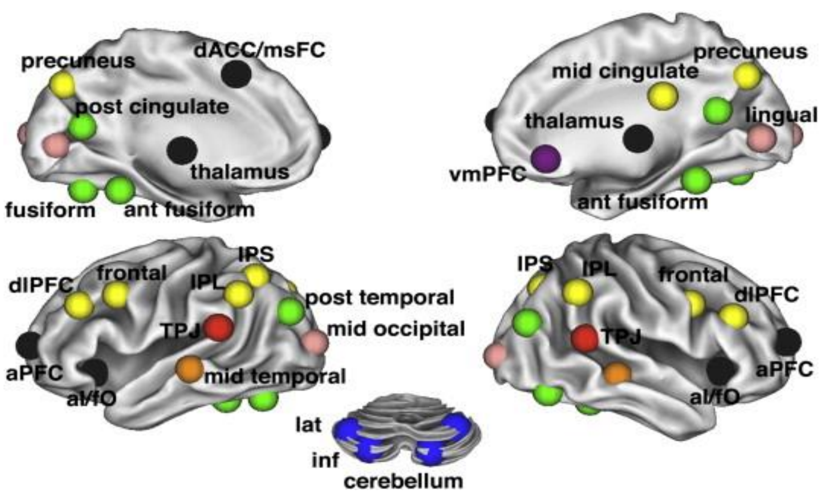

Hagmann, PloS Bio, 2007

# Set of Vertices

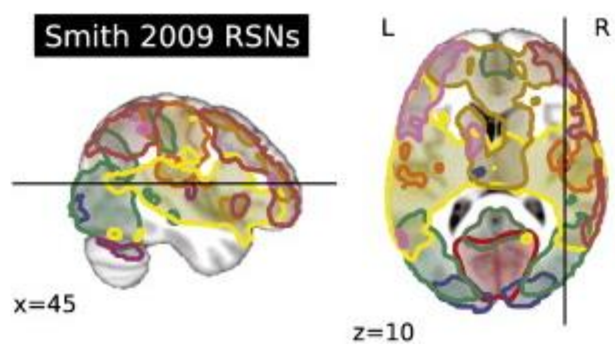
- Random
  - Pro:
    - Minimize node size variations
    - Multi resoltuion
  - Con:
    - Unclear validity / reliability

# Set of Vertices

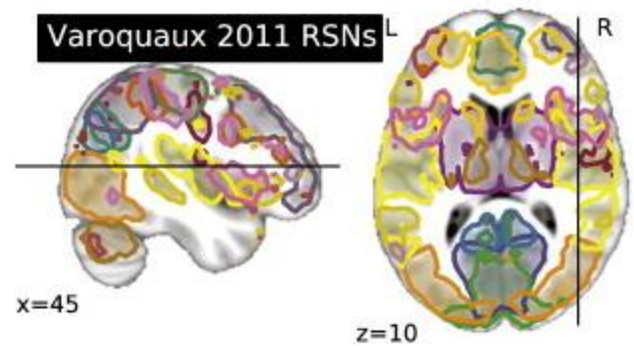
- Functional Parcellation
  - Based on prior functional information
  - Coordinates from meta analysis or functional homogeneity analysis




Dosenbach, Science, 2010




Smith, PNAS, 2009




Varoquax, Inf Proc Med, 2011

# Set of Vertices

- functional
  - Pro:
    - Good reliability
    - Good validity
  - Con:
    - May miss regions
    - Difficult to apply to DTI

# Set of Vertices

- “Good” definition of vertices is crucial for the following graph analysis
- “Good”
  - functional intra-homogeneous
  - Ideally functional inter-heterogeneous
  - reliable
  - account for spatial relationships

# Graph Defintion

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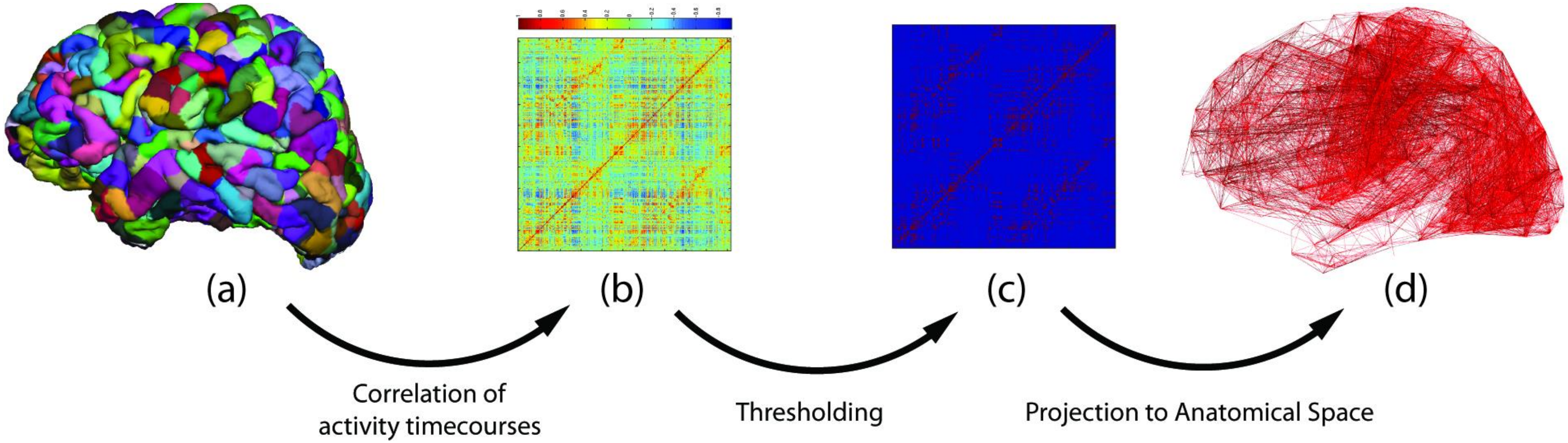
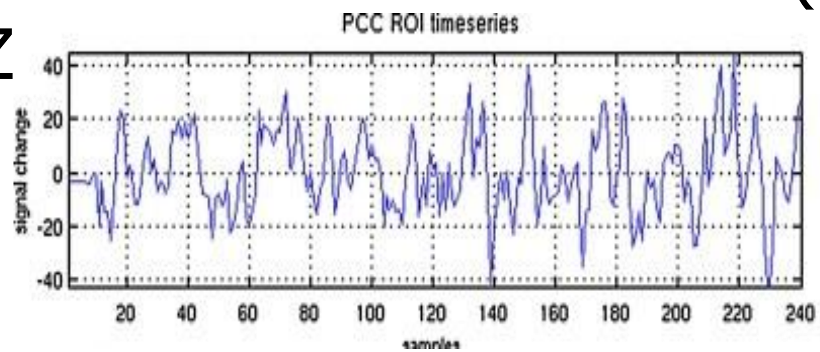



Boettger, IEEE TVCG 2014

# Set of Edges

- Estimate a “functional connection” between ROIs
- Data?
  - Average signal over Parcell
  - First eigenvector of PCA over ROI (lower reliability; Z

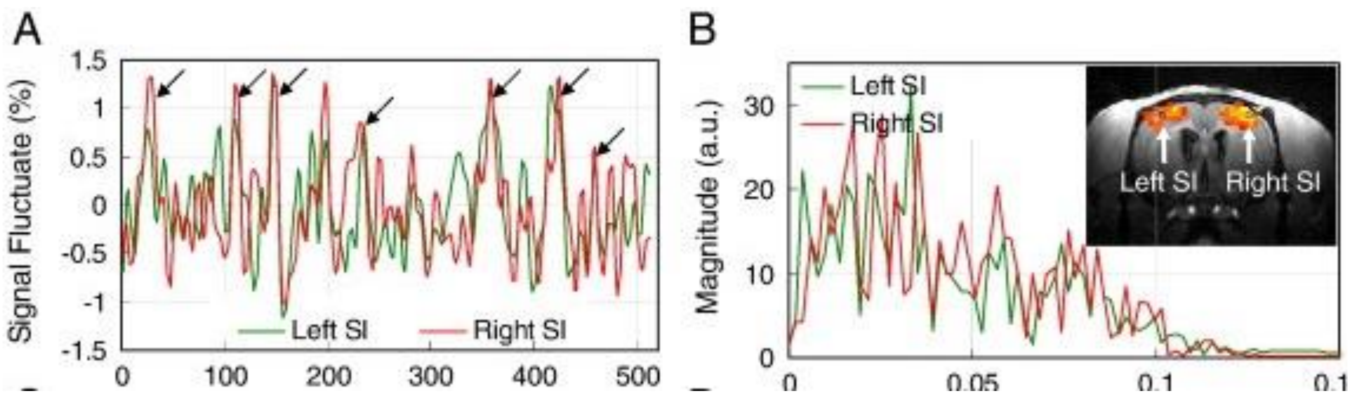



Chang, NeuroImage, 2008

- What do we do with the Data? There are many differenty ideas.

# Set of Edges

- What do we do with the Data? There are many differenty ideas.
- Simplest idea (maybe best): measure the pairwise similarity between regions




Zhao, NeuroImage, 2008

# Set of Edges

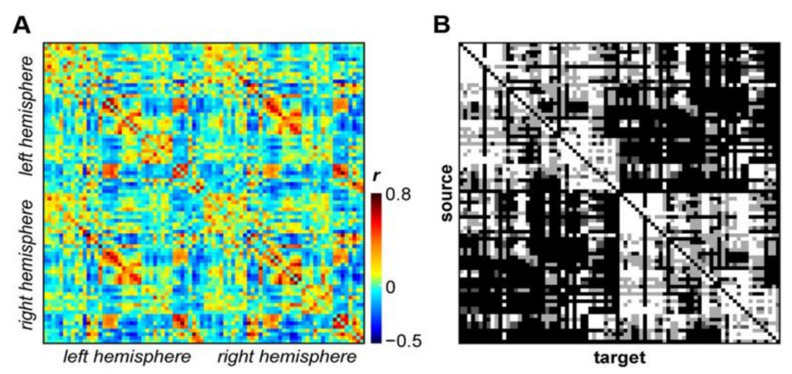
- Pearson Correlation: $$r = \frac{\sum_{i=1}^{n}(X_i - \bar{X})(Y_i - \bar{Y})}{\sqrt{\sum_{i=1}^{n}(X_i - \bar{X})^2}\sqrt{\sum_{i=1}^{n}(Y_i - \bar{Y})^2}}$$
- Notice: → Correlation Matrix: normalized Covariance Matrix
- Positive correlations indicate

a functional connection

- Matrix has dimension

Vertices x Vertices

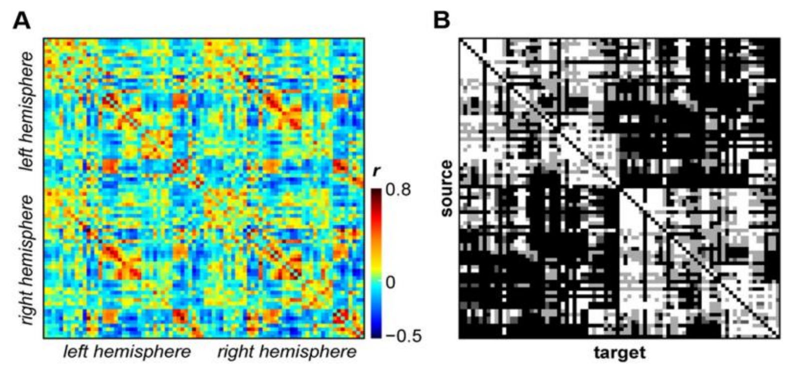
- Matrix can describe the complete Graph




Shen, J Neuro, 2012

# Set of Edges

- Pearson Correlation: $r = \frac{\sum_{i=1}^{n}(X_i - \bar{X})(Y_i - \bar{Y})}{\sqrt{\sum_{i=1}^{n}(X_i - \bar{X})^2}\sqrt{\sum_{i=1}^{n}(Y_i - \bar{Y})^2}}$
- Notice: → Correlation Matrix: normalized Covariance Matrix
- Performs quite well
- But induces indirect connections
- A → B → C
- False positive A – C




Shen, J Neuro, 2012

# Set of Edges

- Solution → Partial Correlation:
  - Regress out all other timeseries from the data and then perform correlation
  - Gets rid of indirect connections!
  - Problem in (rs-) fMRI: low number of timepoints

# Set of Edges

- Solution → Partial Correlation:
  - Regress out all other timeseries from the data and then perform correlation (or compute the inverse Covariance Matrix)
  - Gets rid of indirect connections!
  - Problem in (rs-) fMRI: low number of timepoints
  - Voxel-level: 60 000 voxels * 200 timepoints
  - Rank of Correlation Matrix?

# Set of Edges

- Solution → Sparse Inverse Covariance:
  - Idea: regress less by eliminating some connections from the regression process (sparse matrix)
  - some connections are not essential to explain data
  - Problem: Finding this sparse matrix is computationally hard
  - Solution: approximation algorithm (graphical lasso)

# Set of Edges

- Conclusion
  - Pearson Correlation has problems with false positives
  - Partial Correlation performs better but has problems with low d.o.f. in fMRI
  - Sparse methods might help

NeuroImage xxx (2010) xxx–xxx

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

ELSEVIER

Network modelling methods for FMRI

Stephen M. Smith [a,*], Karla L. Miller [a], Gholamreza Salimi-Khorshidi [a], Matthew Webster [a], Christian F. Beckmann [a,b], Thomas E. Nichols [a,c], Joseph D. Ramsey [d], Mark W. Woolrich [a,e]

[a] FMRIB (Oxford University Centre for Functional MRI of the Brain), Dept. Clinical Neurology, University of Oxford, UK
[b] Department of Clinical Neuroscience, Imperial College London, UK
[c] Departments of Statistics and Manufacturing, Warwick University, UK
[d] Department of Philosophy, Carnegie Mellon University, Pittsburgh, PA, USA
[e] OHBA (Oxford University Centre for Human Brain Activity), Dept. Psychiatry, University of Oxford, UK

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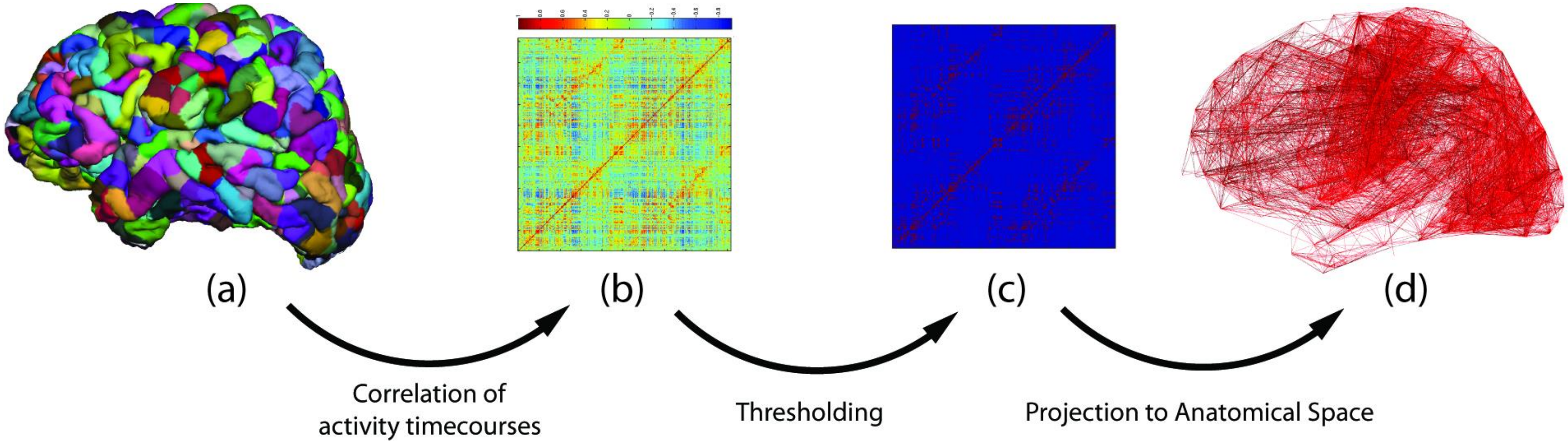



Boettger, IEEE TVCG 2014

# Thresholding

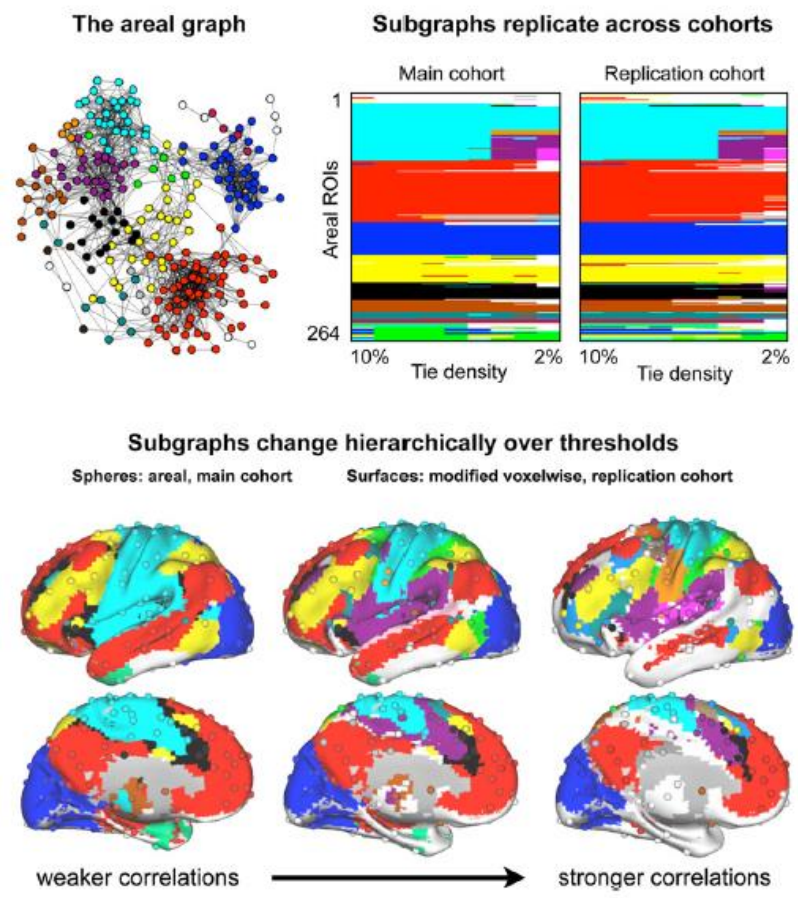
- Validity: mix of correlations and anti-correlations
- Reliability: higher for stronger correlations
- Strategies:
  - Sparsity Thresholding: use only the strongest x% of edges
  - Soft Thresholding: use only edges above value x
  - Hard Thresholding: use only edges above value x and set them to 1 (binarization)

# Graph Analysis / Graph Comparison

- Analysis of Brain Organization
- Comparing Graphs / Brains
  - Centrality Mapping
  - Graph-topological metrics
  - Predictive Modeling

# Graph Analysis / Graph Comparison

- Investigate Brain Organization
- Unsupervised machine learning
- Power, Neuron, 2011
  - info map algorithm (Rosvall, Bergstrom, 2008)
  - random walk
  - optimal code to describe this random walk
  - code word -> subgraph



# Graph Analysis / Graph Comparison

- Edge clustering
- Similarity between connections
- Hierarchical clustering

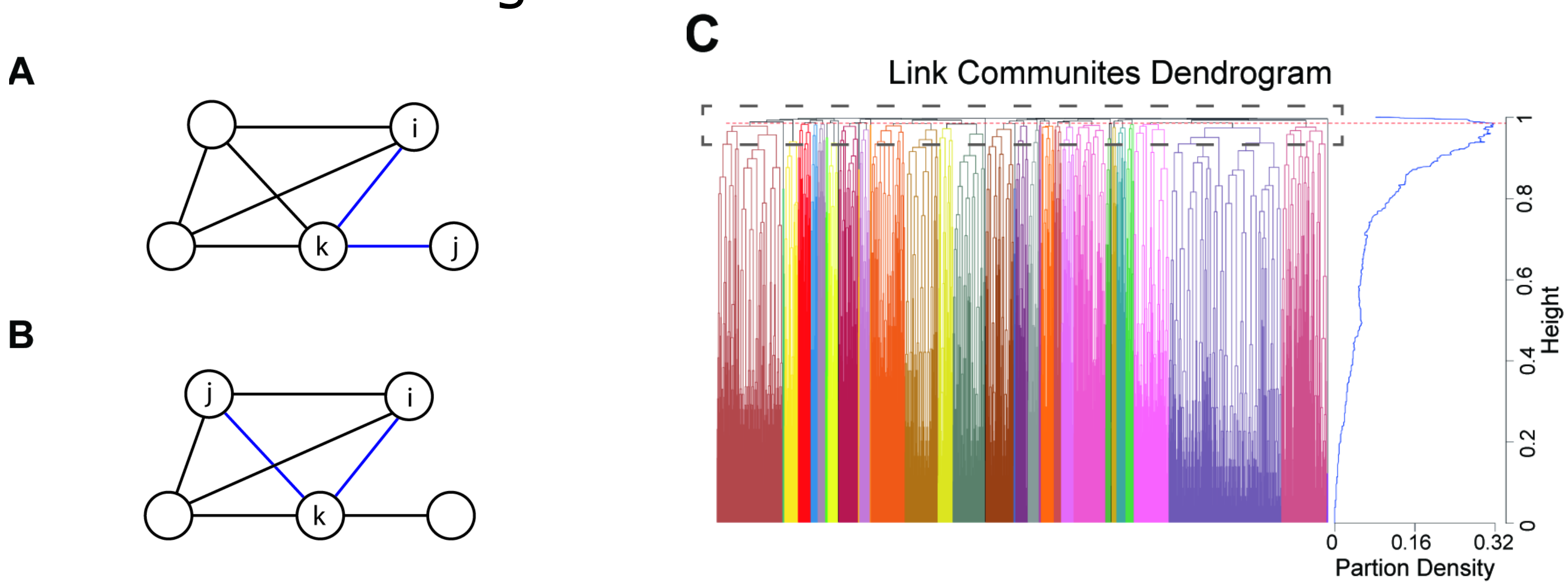
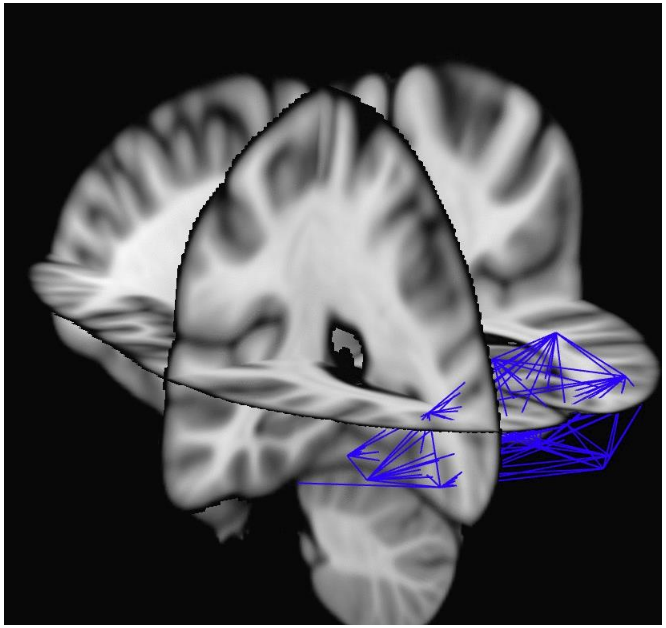



Figure adopted from Schaefer et al., 2014, Frontiers in Human Neuroscience

# Graph Analysis / Graph Comparison

- Edge clustering
- http://openscience.cbs.mpg.de/schaefer/



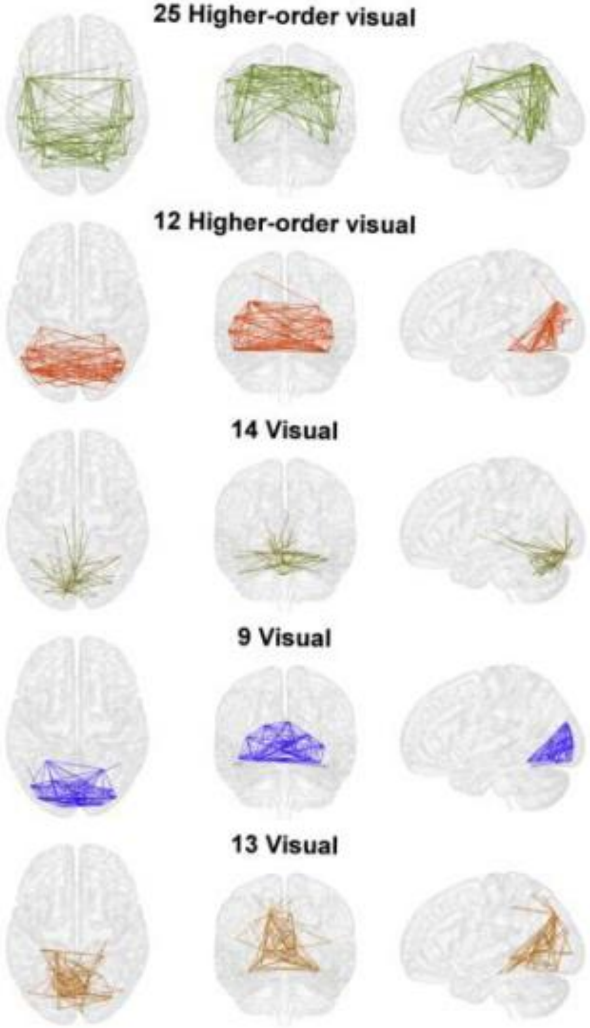
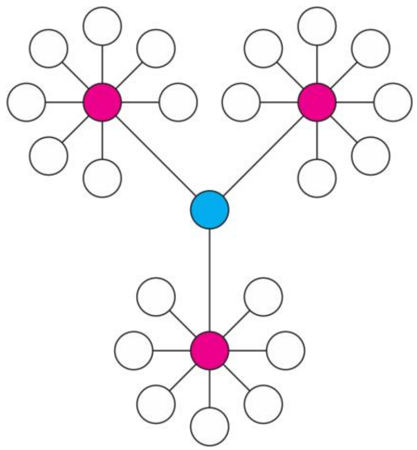



Figure adopted from Schaefer et al., 2014, Frontiers in Human Neuroscience

# Graph Analysis / Graph Comparison

- Comparing Graphs
- Centrality Analysis
  - Degree Centrality
    - Assign each Vertex the Sum over its weighted edges:

$$\mathrm{DC}(i) = \sum_{j=1}^{N} a_{ij} \,.$$

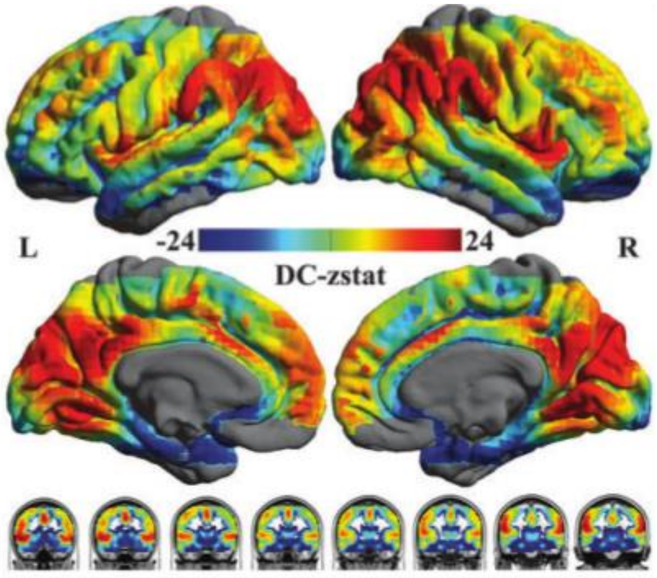


Junker, BioInf, 2006

# Graph Analysis / Graph Comparison

- Centrality Mapping
  - Degree Centrality
    - Assign each Vertex the Sum over its weighted connections:

$$\mathrm{DC}(i) = \sum_{j=1}^{N} a_{ij}.$$



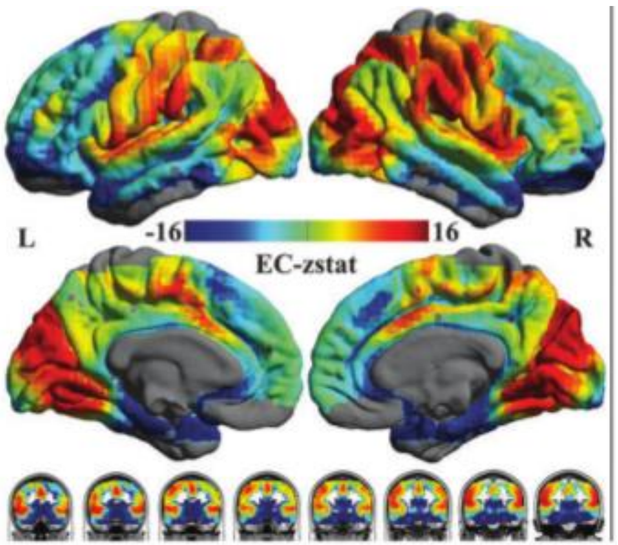

Zuo, Cerb. Cortex, 2010

# Graph Analysis / Graph Comparison

- Centrality Mapping
  - Eigenvector Centrality
    - Assign each Vertex the load of its first eigenvector:

$$EC(i) = \mu_1(i) = \frac{1}{\lambda_1} A\mu_1 = \frac{1}{\lambda_1}\sum_{j=1}^{N} a_{ij}\mu_1(j).$$

    - Cares also about indirect connections




Zuo, Cerb. Cortex, 2010

# Graph Analysis / Graph Comparison

- Centrality Mapping
  - Further information in Zuo, Cererbral Cortex, 2012

Cerebral Cortex
doi:10.1093/cercor/bhr269

**Network Centrality in the Human Functional Connectome**

Xi-Nian Zuo[1,2], Ross Ehmke[3], Maarten Mennes[2], Davide Imperati[2], F. Xavier Castellanos[2,4], Olaf Sporns[3] and Michael P. Milham[5]

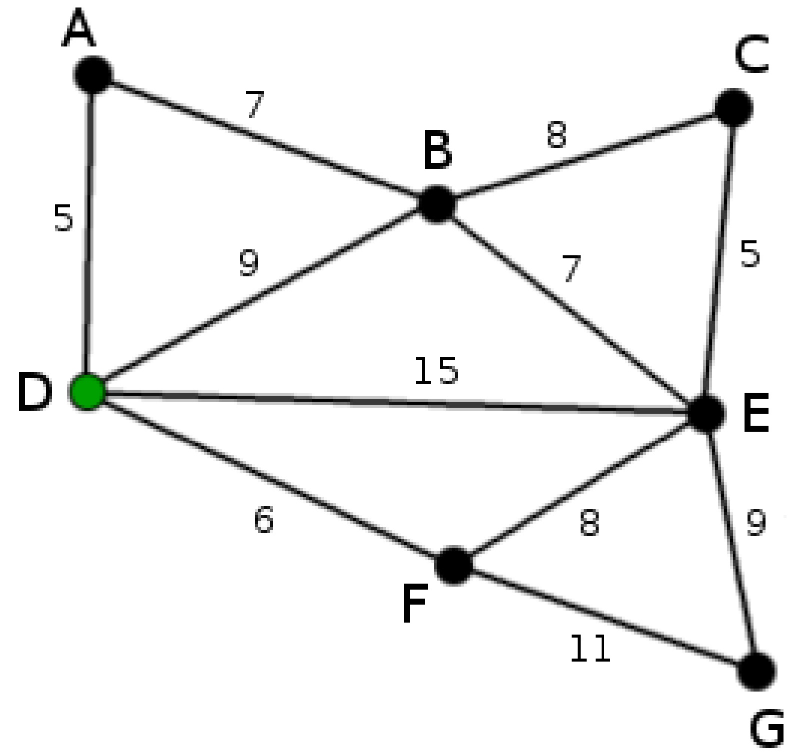
# Graph Analysis / Graph Comparison

- Graph-topological metrics
  - Path Length

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

  - Average Path Length

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




Wikipedia

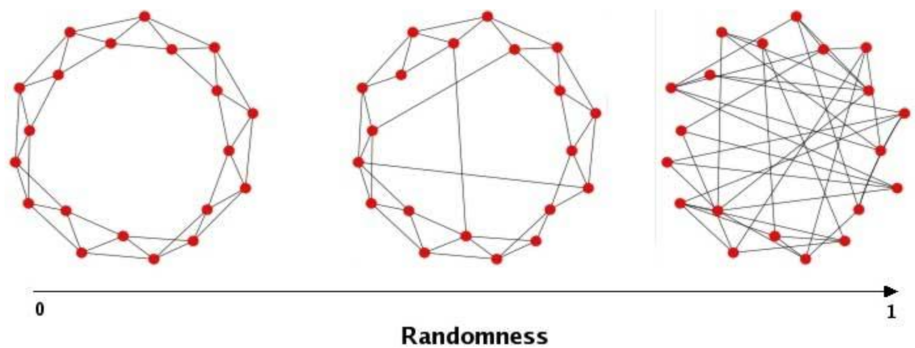
# Graph Analysis / Graph Comparison

- Graph-topological metrics
  - Clustering Coefficient

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

  - Small Worldness

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




Watts, Nature, 1998

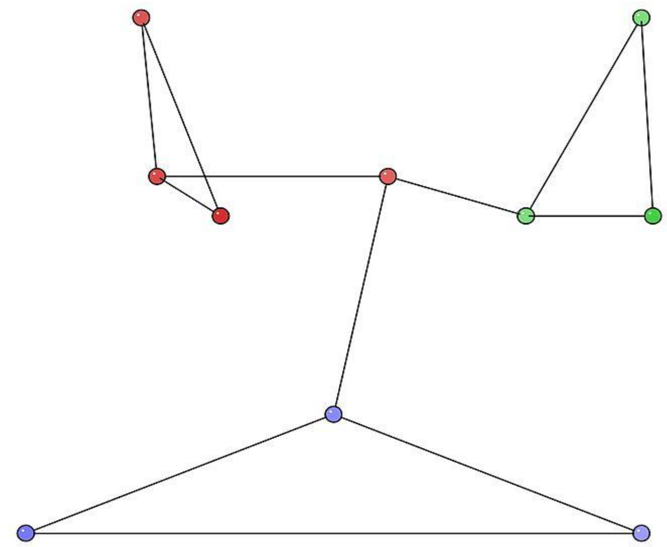
  - Problem: What is random, what is artificial?

# Graph Analysis / Graph Comparison

- Graph-topological metrics
  - Modularity:

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

  - within module connections
    - (inter module connections)^2



Wikipedia

# Graph Analysis / Graph Comparison

- Graph-topological metrics
  - Pro:
    - Many of these Measures are quite intuitive
  - Con:
    - The topology itself is reduced to a single number. To simplistic?
    - Results are not very reliable

# Graph Analysis / Graph Comparison

- Graph-topological metrics
  - Further Reading

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Complex network measures of brain connectivity: Uses and interpretations

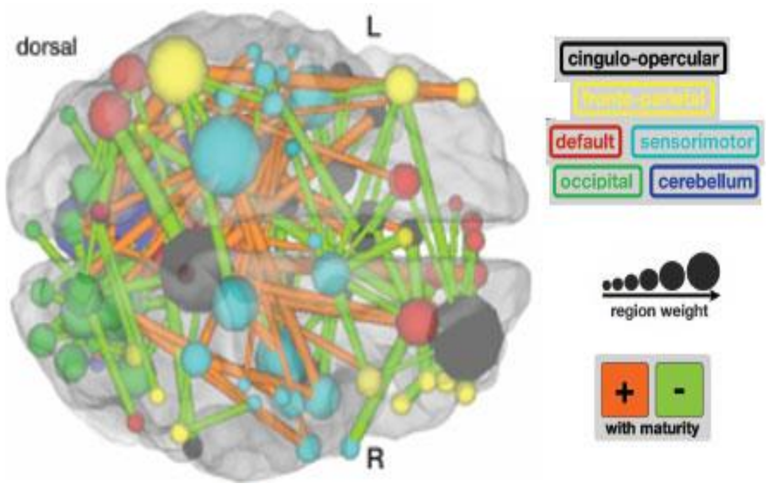
Mikail Rubinov [a,b,c], Olaf Sporns [d,*]

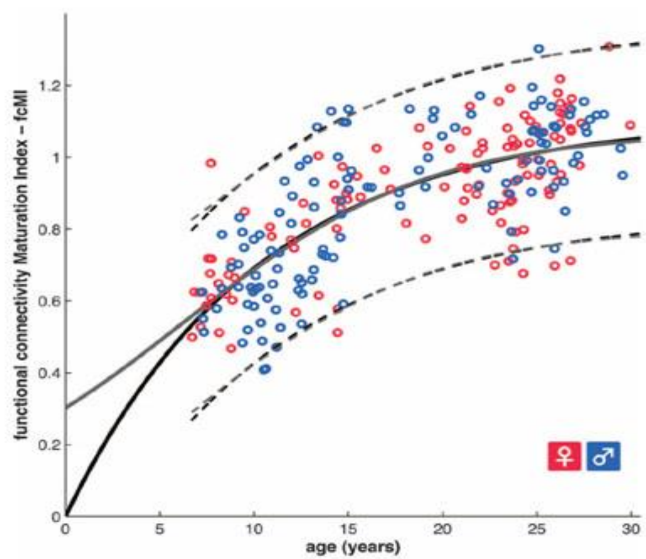
# Graph Analysis / Graph Comparison

- Predictive Modeling
  - Supervised machine learning problem
  - Targets of prediction: age, disease or cognitive state
  - Features are connectivity, centrality or topology metrics
  - To prevent over - fitting of the model one uses cross validation

# Graph Analysis / Graph Comparison

- Predictive Modeling: Predicting Age

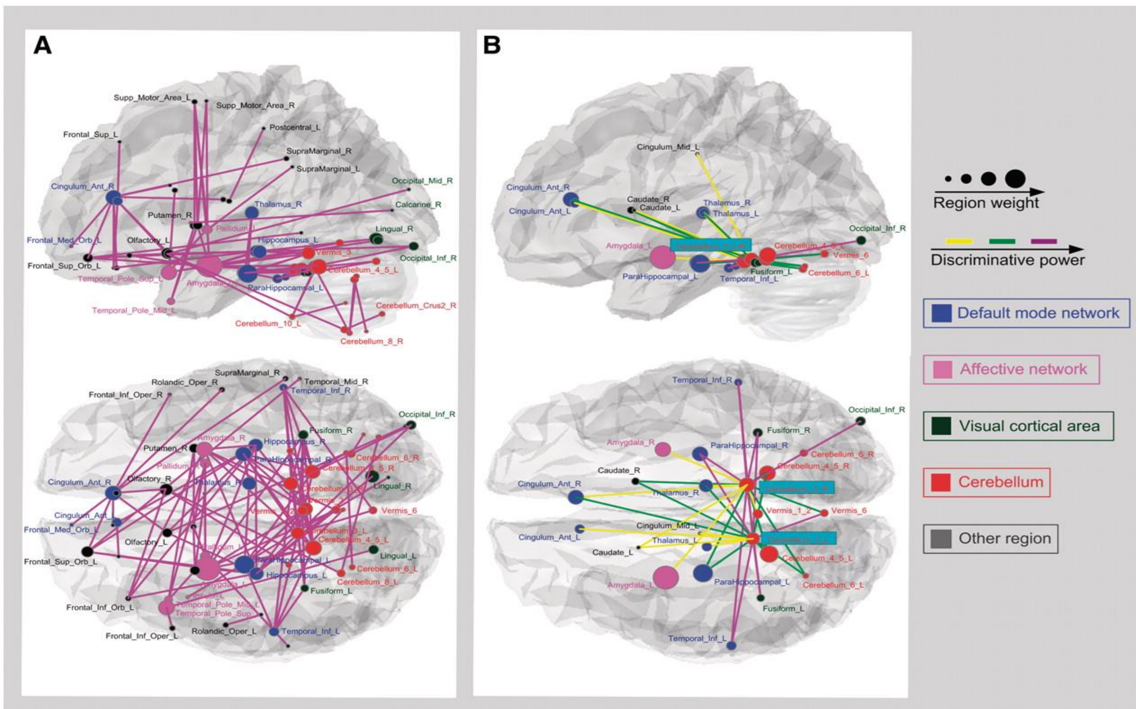



Dosenbach, Science, 2010

# Graph Analysis / Graph Comparison

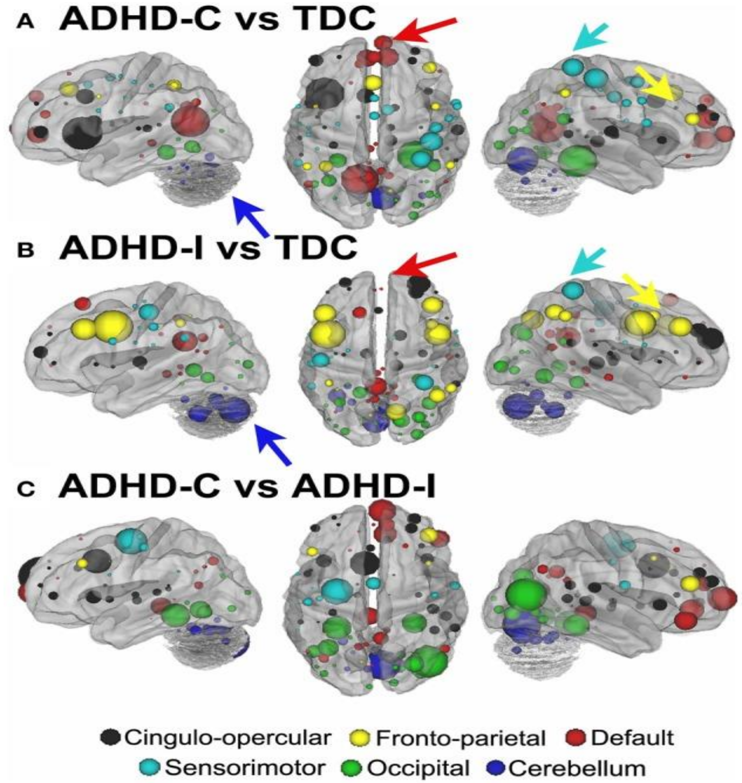
- Predictive Modeling: Predicting Depression




Zeng, Brain, 2012

# Graph Analysis / Graph Comparison

- Predictive Modeling: Predicting ADHD




Fair, Fron Hum, 2013

# Graph Analysis / Graph Comparison

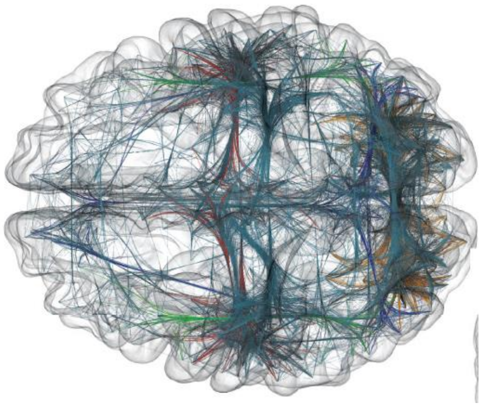
- Predictive Modelling
  - Pro:
    - Allows more complex interactions
      - “multivariate like the brain”
    - Closer to the single subject level
  - Con:
    - Complex models on high dimensional data with very few samples (over fitting!)

# Graph Analysis / Graph Comparison

- Few samples
  - Problem: Scanning is expensive
  - Solution: Data Sharing Initiatives:
    - » ADNI (***adni****.loni.usc.edu/*)
    - » ADHD200 (fcon_1000.projects.nitrc.org/indi/adhd200)
    - » ABIDE (*fcon_1000.projects.nitrc.org/indi/****abide***)
    - » Human Connectome Project (*www.****human****connectome.org/*)

# Software

- Preprocessing rs-fMRI:
  - Nipype (*nipy.sourceforge.net/nipype/*)
  - FCON1000 (nitrc.org/projects/fcon_1000/)
- Building graphs (learned here)
  - Nipy and Numpy
  - Matlab
- Visualizing Graphs
  - brainGL (http://code.google.com/p/braingl/)
  - Gephi (https://gephi.org/)



Boettger, IEEE TVCG, 2014

# Further Reading


- Varoquaux, Gaël, and R. Cameron Craddock. "Learning and comparing functional connectomes across subjects." *NeuroImage* 80 (2013): 405-415.
- Fornito, Alex, Andrew Zalesky, and Michael Breakspear. "Graph analysis of the human connectome: promise, progress, and pitfalls." *Neuroimage* 80 (2013): 426-444.

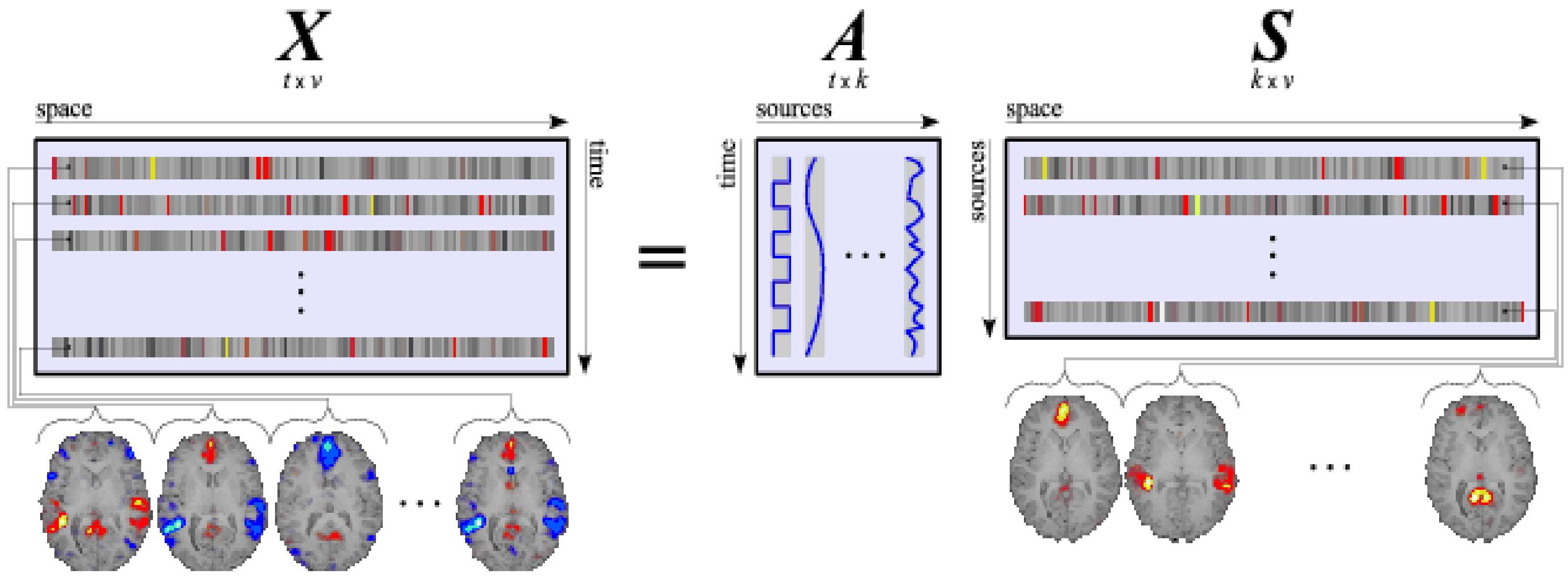
# Thank you

- Dept. of Neurology
- Resting State Group

Zuo, Cereb Cortex, 2012

# Appendix

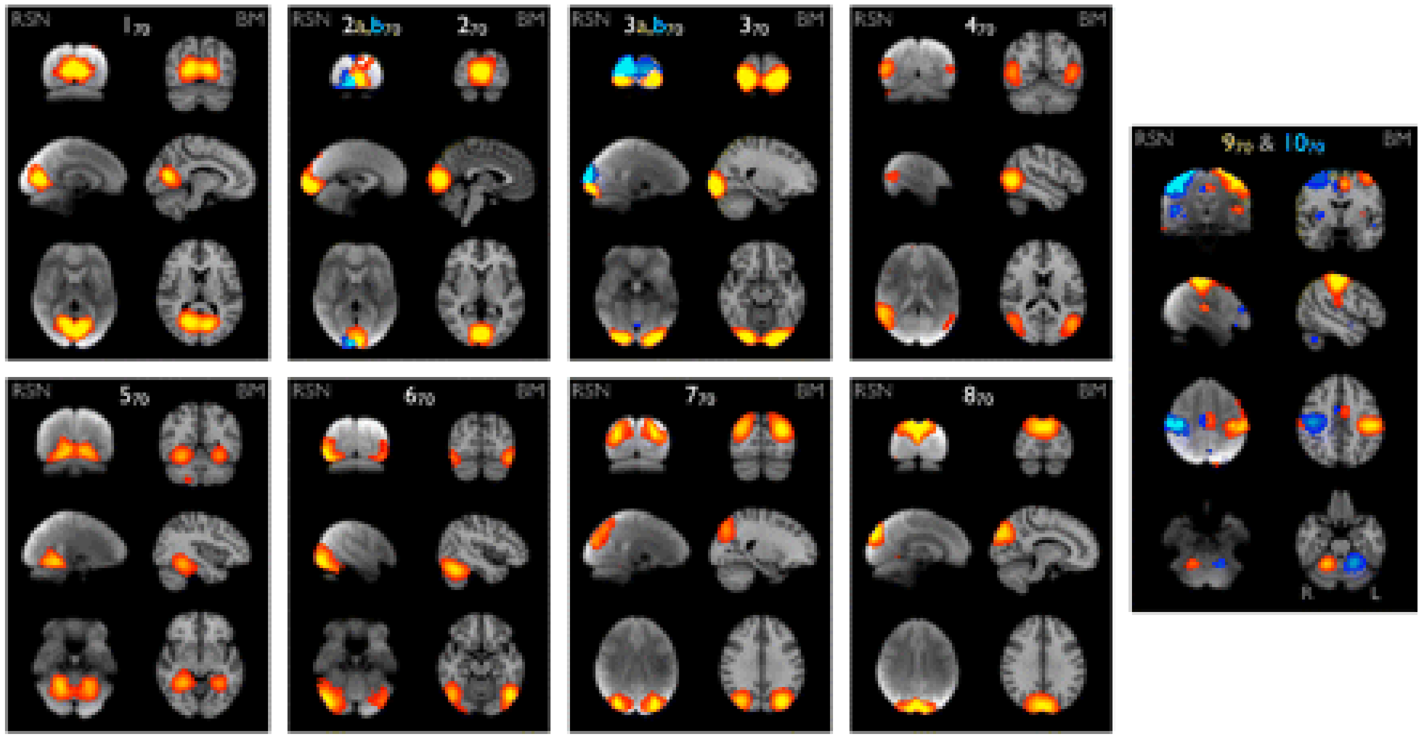
- Ylipaavalniemi, 2005




Ylipaavalniemi, 2005

# Appendix

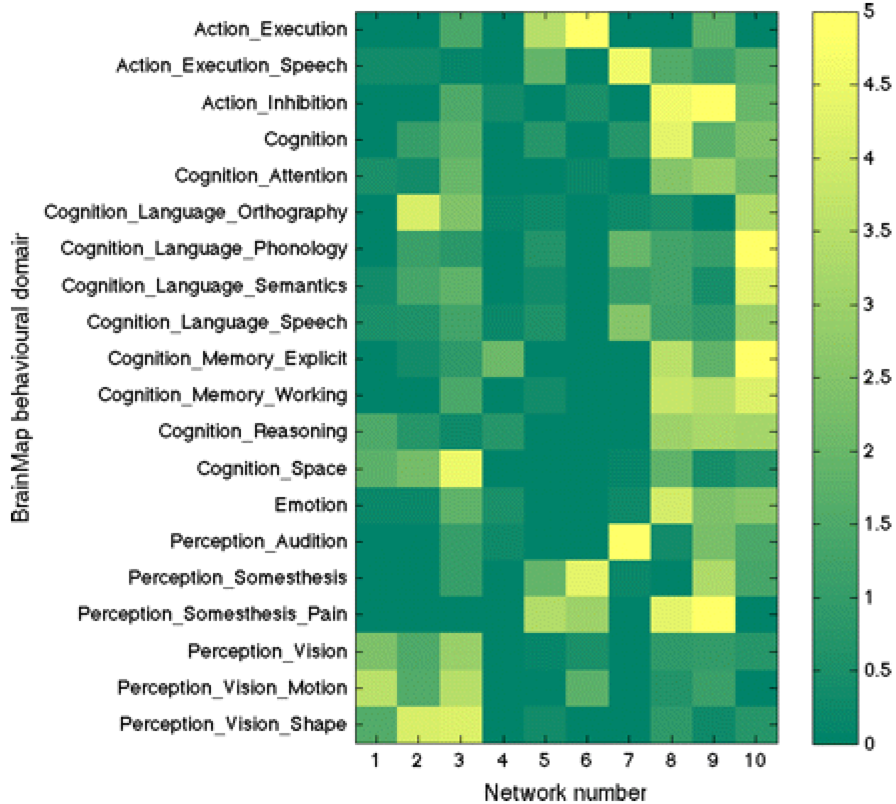
- Smith PNAS 2009




Smith, PNAS, 2009

# Appendix

- Smith PNAS 2009




Smith, PNAS, 2009

# Appendix

- Preprocessing

1) discarding the first four EPI volumes to allow for signal equilibration,
2) 3D motion correction
3) time series despiking,
4) 4D mean-based intensity normalization,
5) band-pass temporal filtering (0.01-0.1 Hz),
6) removing linear and quadratic trends and
7) regressing out eight nuisance signals (white matter, cerebro-spinal fluid and six motion parameters).