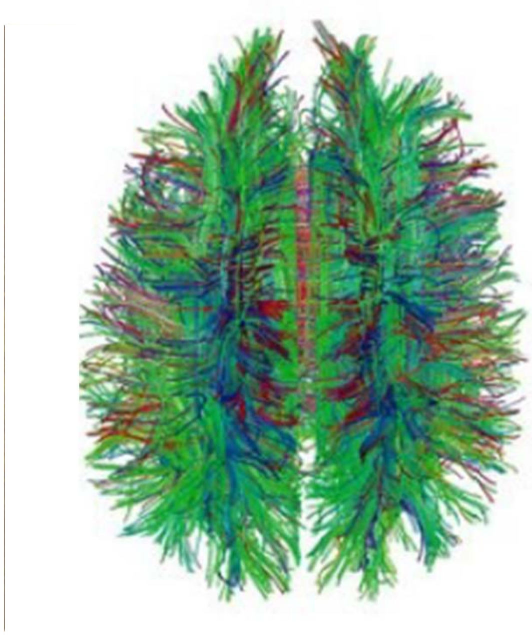
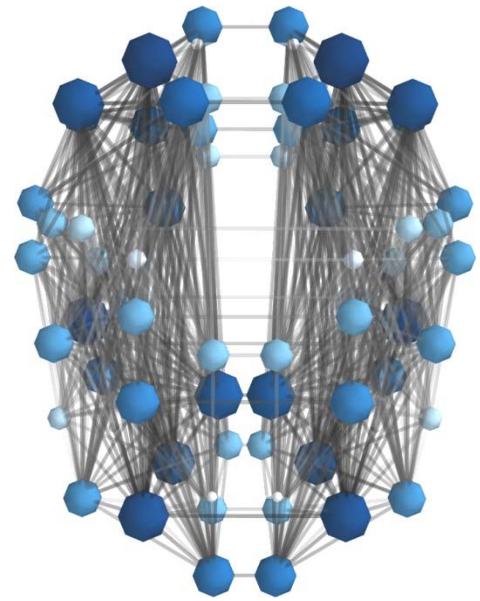
(Brain) connectivity

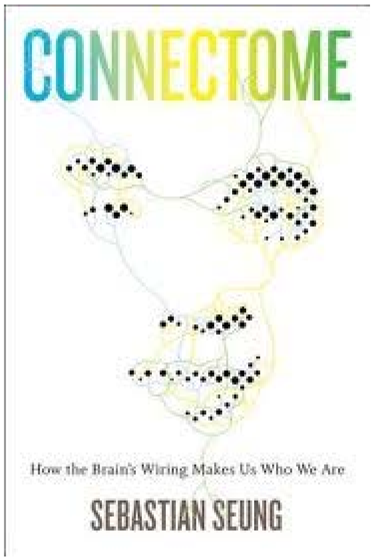
A sort of introduction

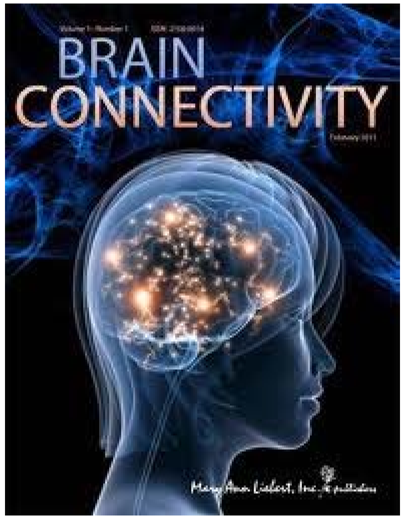
Ursus Wehrli “Kunst aufräumen”

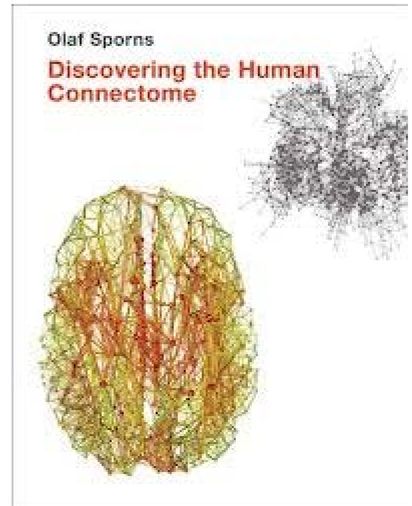


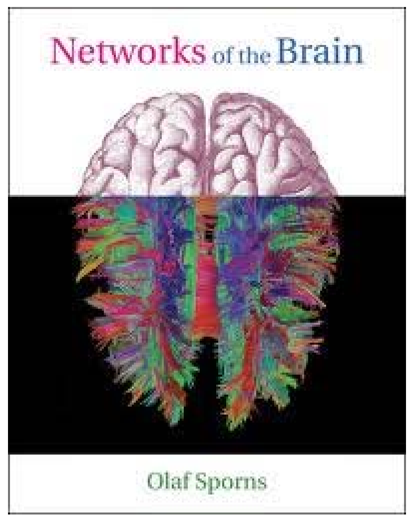


Ursus Wehrli “Kunst aufräumen”







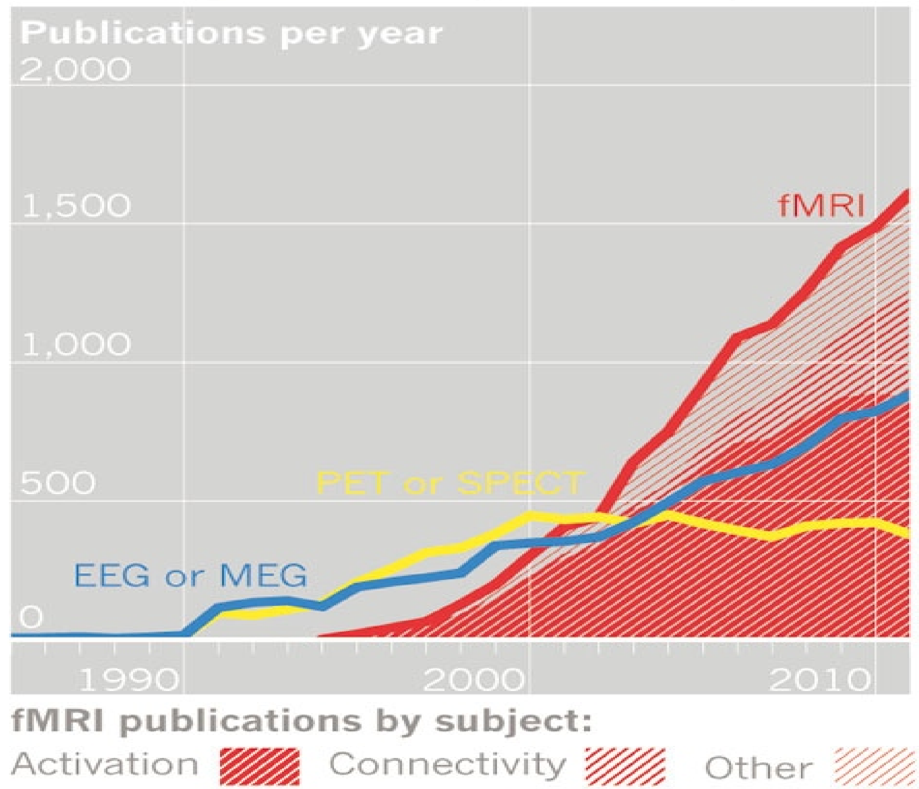


Human Connectome Project

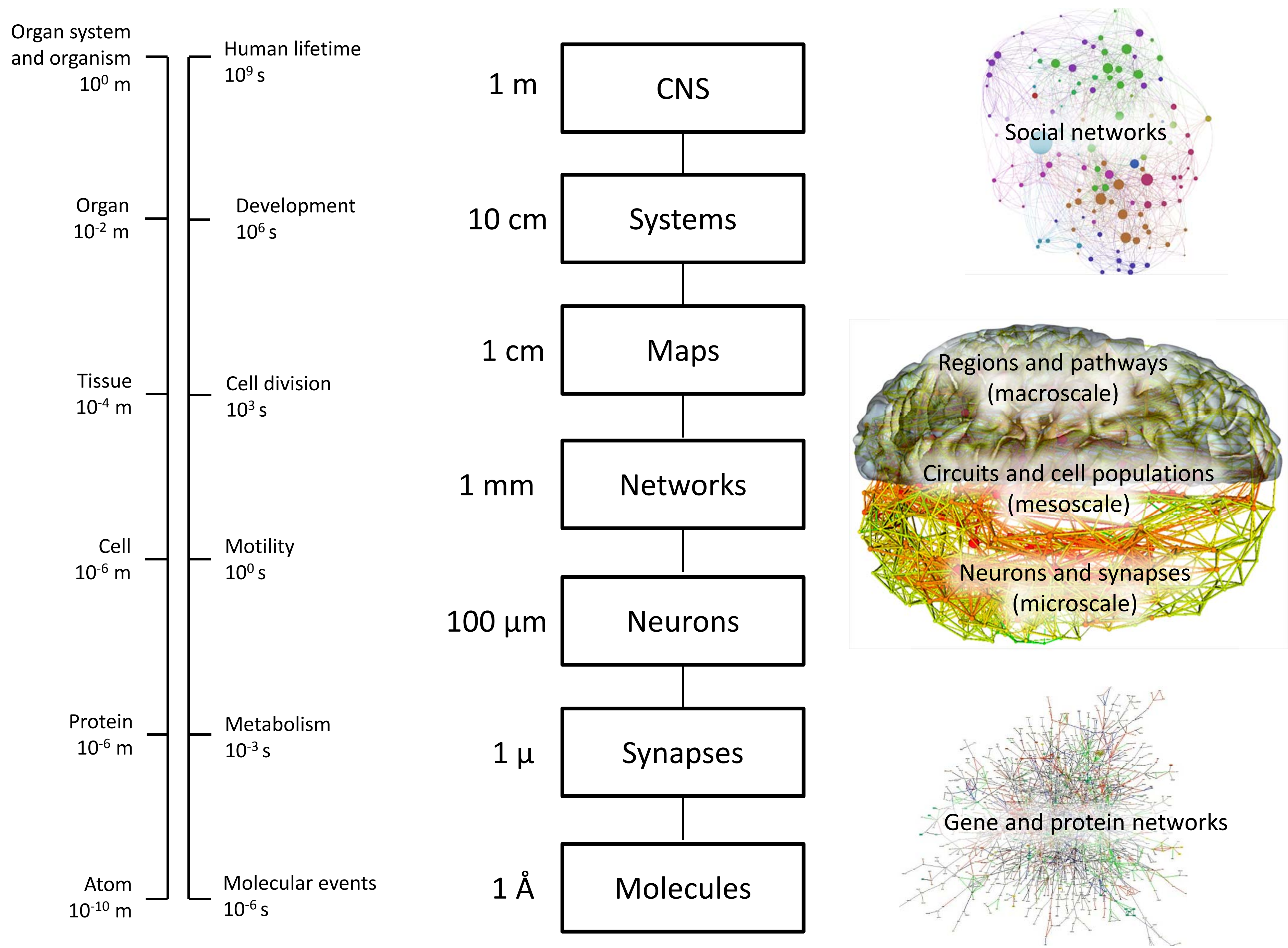
THEVIRTUALBRAIN.

THE RISE OF fMRI

Use of fMRI has rocketed, and now more studies are looking at connectivity between regions.



fMRI, functional magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography; EEG, electroencephalography; MEG; magnetoencephalography
Data from ISI Web of Knowledge.



Organ system and organism
10⁰ m
Organ
10-2 m
Tissue
10-4 m
Cell
10-6 m
Protein
10-6 m
Atom
10-10 m
Human lifetime
10⁹ s
Development
10⁶ s
Cell division
10³ s
Motility
10⁰ s
Metabolism
10-3 s
Molecular events
10-6 s
1 m
CNS
10 cm
Systems
1 cm
Maps
1 mm
Networks
100 µm
Neurons
1 µ
Synapses
1 Å
Molecules
Social networks
Regions and pathways (macroscale)
Circuits and cell populations (mesoscale)
Neurons and synapses (microscale)
Gene and protein networks

Key characteristic 1:
Networks as pathways

Key characteristic 2: Networks as an expression of collective dynamics

Adolphe Quetelet (Gent,1796-1874)

When we consider a big number of individuals, social dynamics are ruled by collective stimulations in the network to which the individual belongs, rather than the indvidual's will.

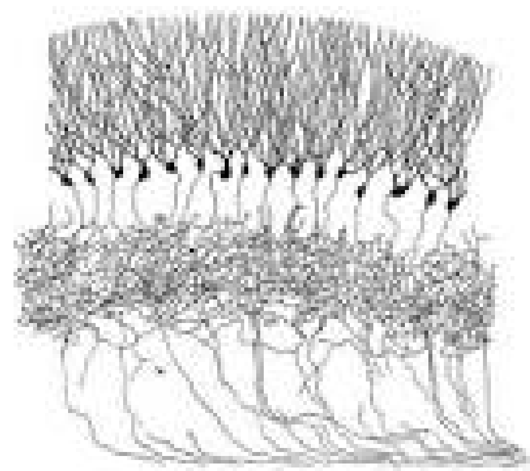
Like molecules in a gas

Like neurons

Camillo Golgi
Nobel lecture, 1906

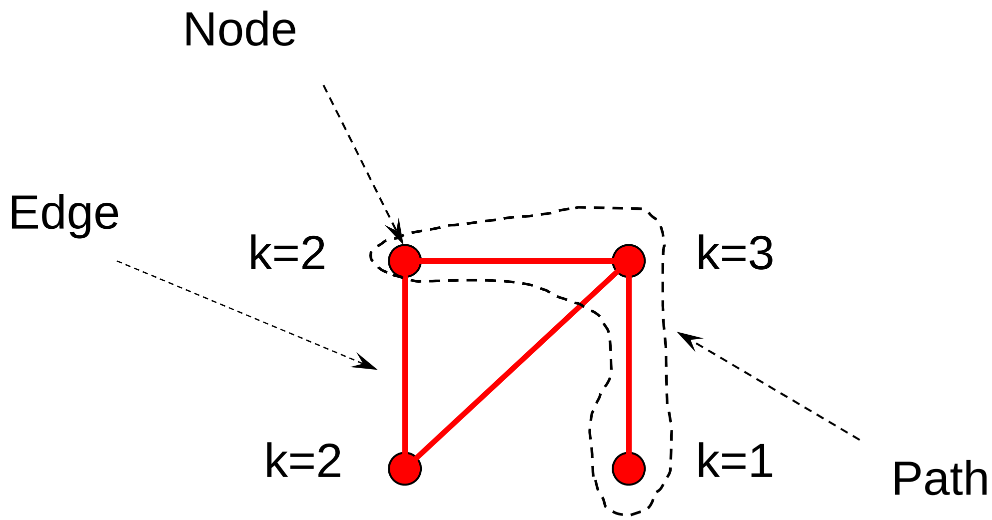
…far from being able to accept the idea of the individuality and independence of each nerve element, I have never had reason, up to now, to give up the concept which I have always stressed, that nerve cells, instead of working individually, act together [...]

However opposed it may seem to the popular tendency to individualize the elements, I cannot abandon the idea of a unitary action of the nervous system[…]



Networks: Basic definitions

1) A **Network** is a set of nodes connected by links (edges).



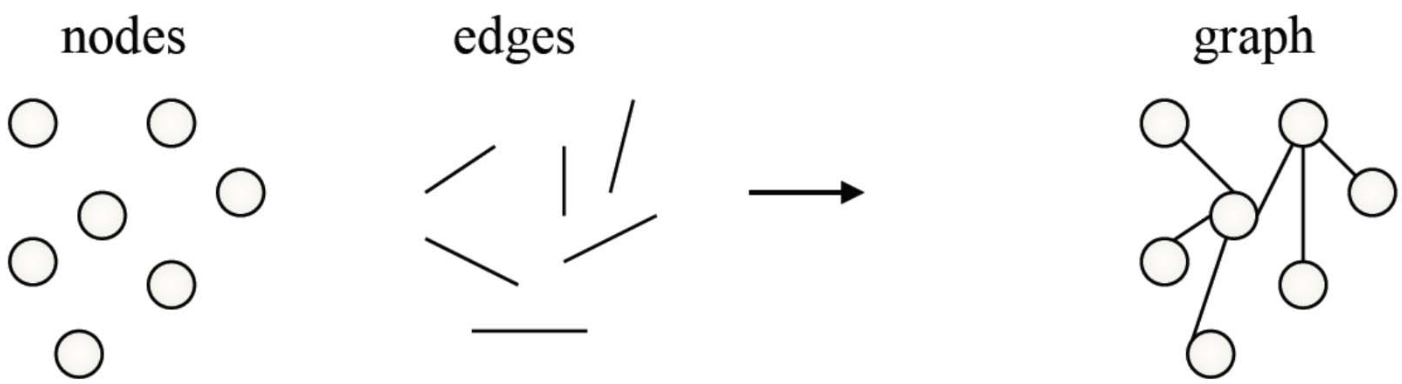
$$P(1) = 1/4$$
$$P(2) = 2/4$$
$$P(3) = 1/4$$

2) **Degree** (k) is the number of edges connected to a node

3) **Degree Distribution** *P(k)* is the fraction of nodes with degree *k*

4) Nodes can be linked directly by single edges or indirectly by sequences of intermediate nodes and edges: **paths**.

Graph theory

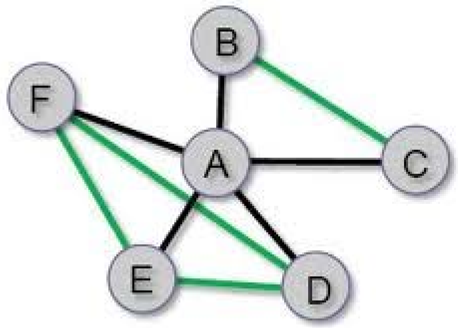


	train	internet	social	brain
node	station	server	person	brain regions
edge	rails	cables	relation	fiber/statistical dependency

The brain as a network

Interplay of (structural) segregation and (functional) integration.

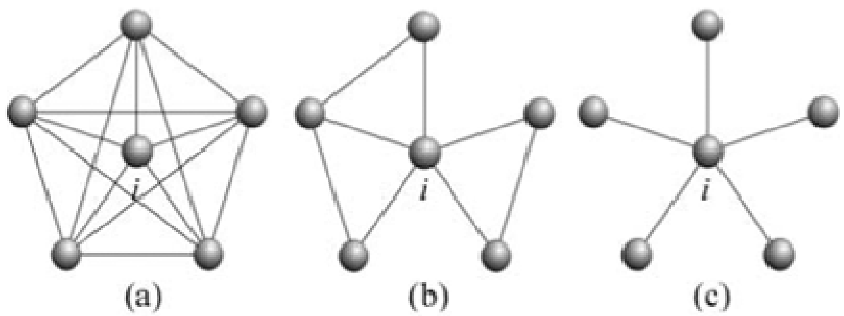
Local segregation: clustering



C_A=4/10=0.4

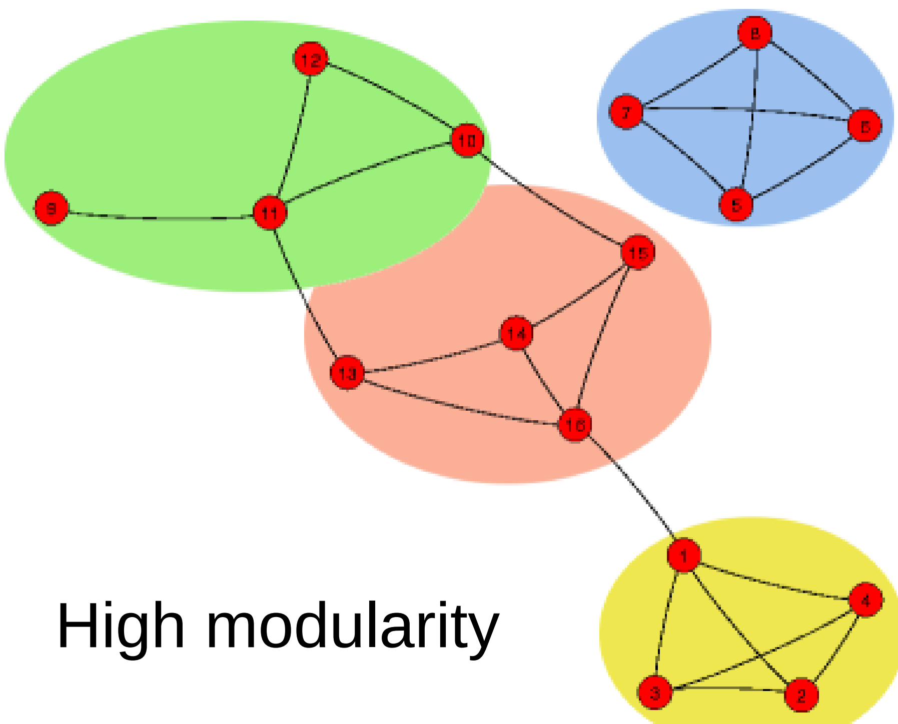
Fraction of existing links between neighbors over all possible links.

So, high clustering means connecting nodes that are well connected.

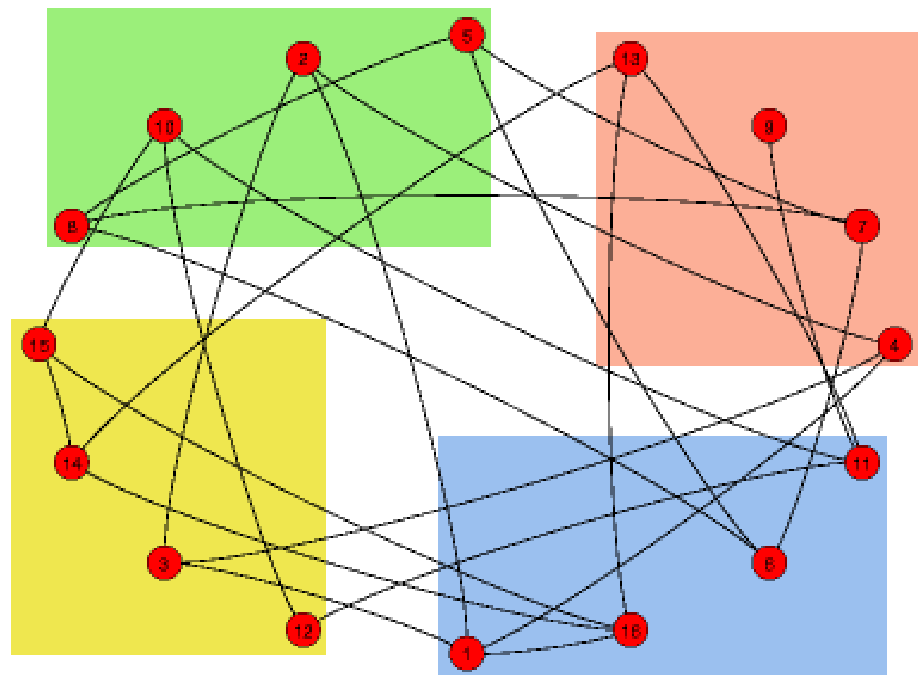


a) cc_i=10x2/5x4=1;
b) cc_i=3x2/5x4=0.3;
c) cc_i=0x2/5x4=0

Local segregation: modularity (many links within modules, few links between modules)



High modularity



Low modularity

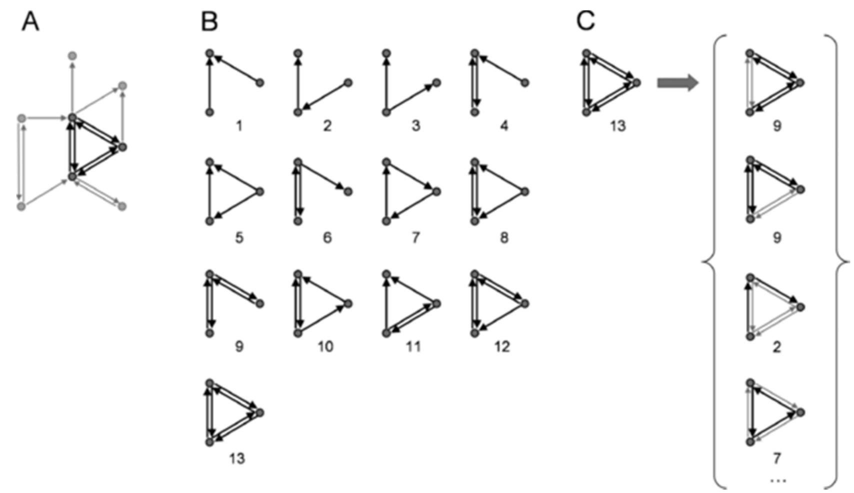
Newman & Girvan, *PRE* (2003)

Networks Motifs (Alon, 2003)

- Characteristic network building blocks
- Small connected subgraphs that occur significantly more frequently than in randomized networks
- Brain networks: small set of structural motifs, large number of functional motifs (Sporns,Bullmore)

Identifying Network motifs

- Find n-node subgraphs in real graph.
- Find all n-node subgraphs in a set of randomized graphs with the same distribution of incoming and outgoing arrows. (Newman, 2000, Sneppen, Malsov 2002)
- Assign Z-score for each subgraph.
- Subgraphs with high Z-scores are denoted as **Network Motifs**.

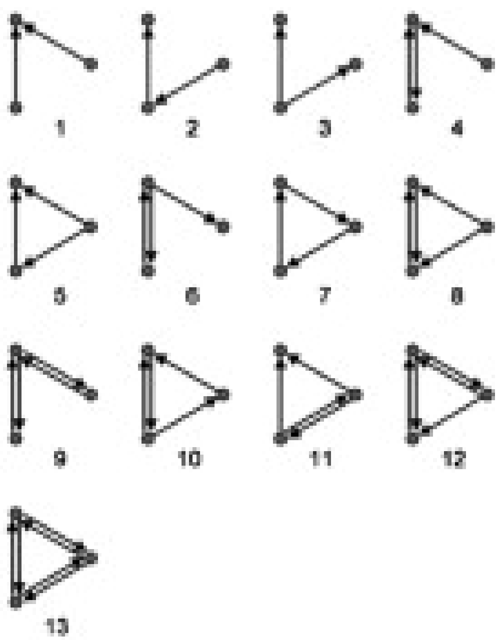


13 possible subgraphs for 3 nodes

$$Z = \frac{N_{real} - \langle N_{rand} \rangle}{\sigma_{rand}}$$

Structural motifs in the cortex across species

A



B

Brain Network	ID	Real	Random
Human Cortex	13	N/A	N/A
Macaque Visual Cortex	9	410	121.55 (21.03) z = 13.79
Macaque Cortex	9	1833	223.66 (34.99) z = 46.22
Cat Cortex	9	1217	472.33 (52.85) z = 14.16
C. elegans	4	2999	1067.03 (121.52) z = 15.98
	6	3415	1164.31 (134.71) z = 16.79

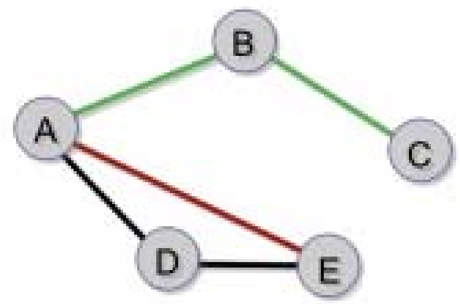
Structural and functional motifs in the cortex

Brain Network	M	Structural Motifs			Functional Motifs		
		Real	Random	Lattice	Real	Random	Lattice
Macaque Visual	2	190	243 (4)	191 (2)	432	380 (4)	431 (2)
Cortex	3	1,486	2,353 (51)	1,344 (40)	19,769	14,358 (325)	21,120 (308)
	4	10,487	18,076 (391)	8,688 (414)	1,843,308	1,013,131 (55,187)	2,259,970 (90,404)
	5	62,940	105,926 (2,059)	50,278 (2,863)	334,279,477	121,572,738 (13,874,054)	513,004,042 (50,992,845)
Macaque Cortex	2	438	654 (7)	471 (7)	1,054	838 (7)	1,021 (7)
	3	4,584	10,786 (227)	4,439 (143)	53,601	30,449 (648)	56,043 (871)
	4	51,129	173,235 (4,635)	39,345 (2,346)	5,306,188	1,850,355 (87,743)	6,617,493 (272,110)
Cat Cortex	2	519	656 (7)	510 (5)	1,054	838 (7)	1,021 (7)
	3	6,986	10,898 (160)	6,021 (122)	53,601	30,449 (648)	56,043 (871)
	4	87,673	149,791 (2,250)	65,527 (2,150)	5,306,188	1,850,355 (87,743)	6,617,493 (272,110)
C. elegans	2	1,718	1,922 (6)	1,700 (40)	2,230	2,026 (6)	2,248 (40)
	3	31,070	41,707 (279)	23,376 (1,494)	70,911	55,054 (363)	84,245 (4,200)
	4	674,125	1,081,682 (11,105)	316,228 (36,200)	3,430,885	2,160,611 (34,800)	5,326,201 (578,900)

Numbers are actual values (for real matrices) and mean and standard deviation (in parentheses, for random and lattice matrices, $n = 100$).
DOI: 10.1371/journal.pbio.0020369.t001

Functional motifs >> structural motifs

Global integration: path length and efficiency



Path length: number of connections that needs to be crossed to go from one node to another.

This measure is intuitively simple but varies greatly with size and density of graphs.

Efficiency: average of the inverse of the distances.

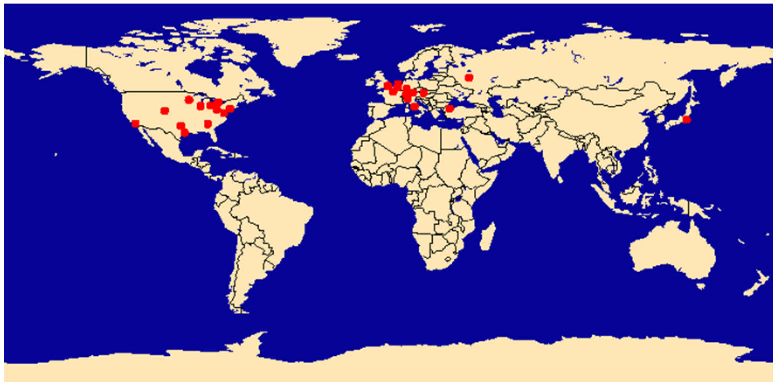
Segregation and integration place opposite demands on networks:

- Optimal clustering and modularity are inconsistent with high integration (little cross-talk among highly segregated communities)
- Optimal efficiency or integration is only achieved in a fully connected network that lacks any differentiation in its local processing

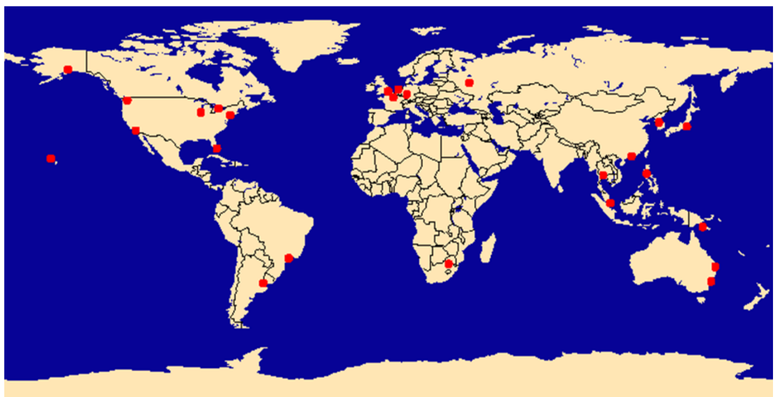
- The bridge between these two opposite requirements is made by heterogeneous contributions by individual nodes and edges.

Influence and centrality: hubs

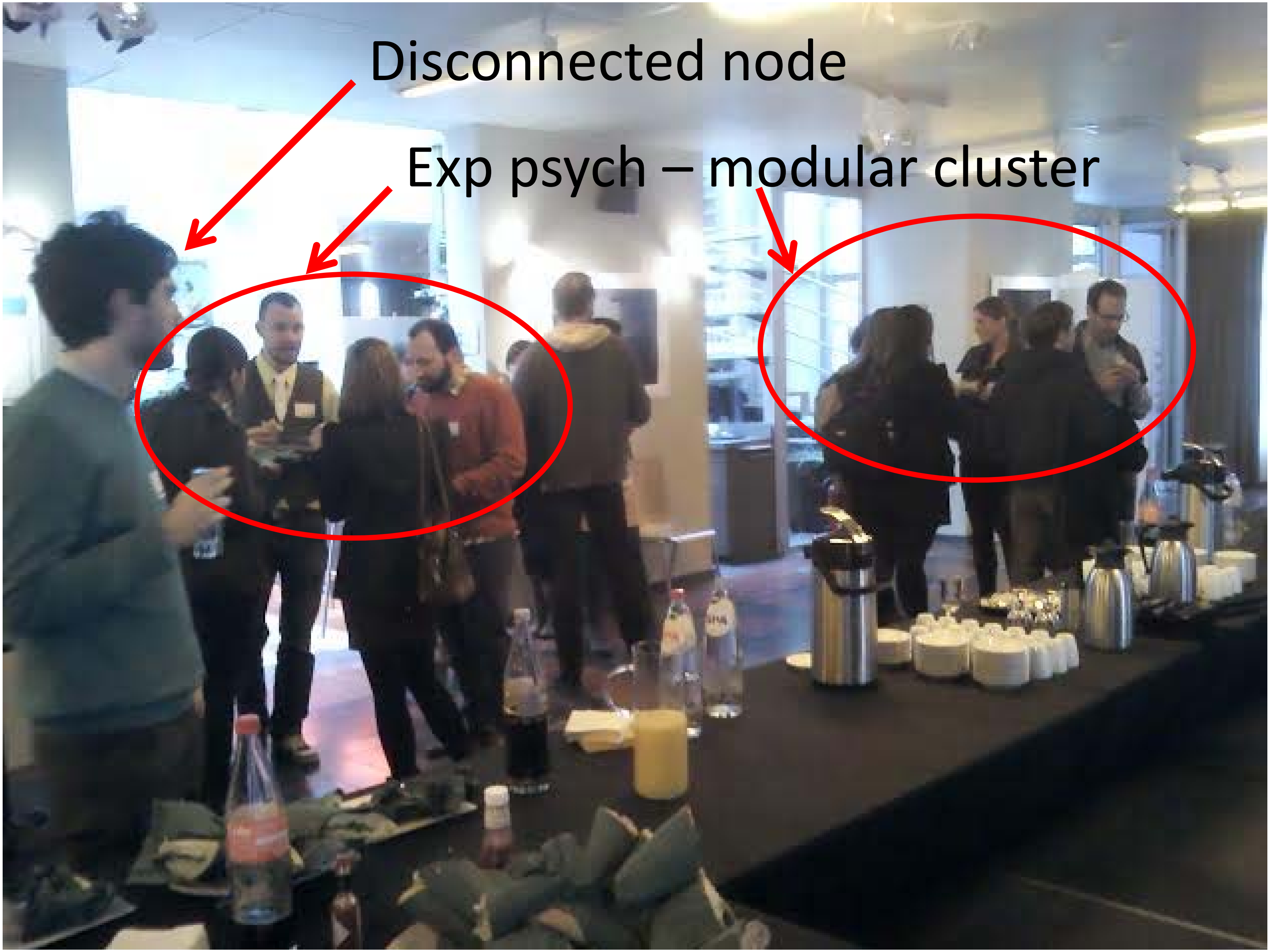
- The number of connections is not enough to quantify the importance of a node
- Centrality: fraction of short path length passing from a node.



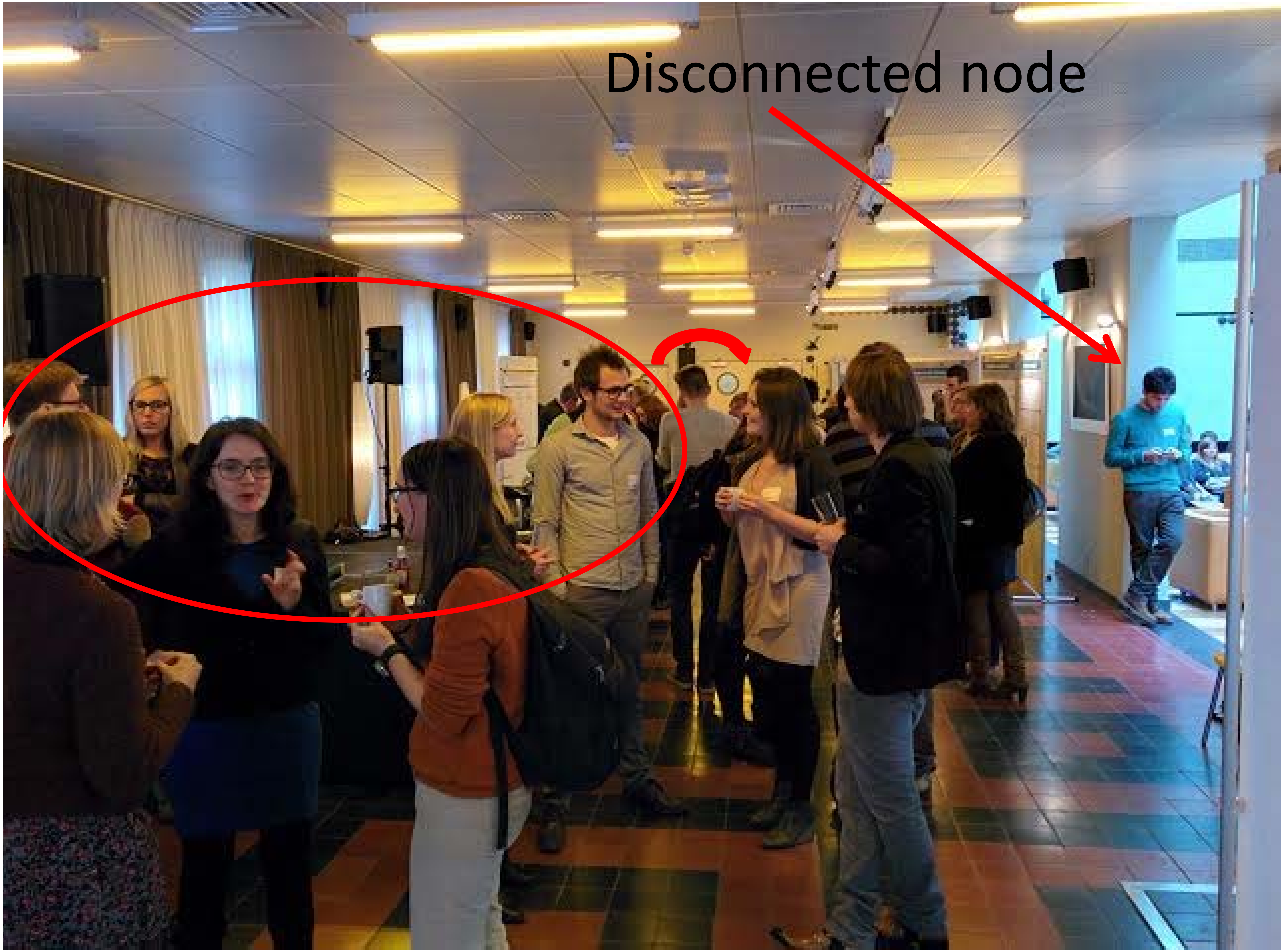
Most connected airports

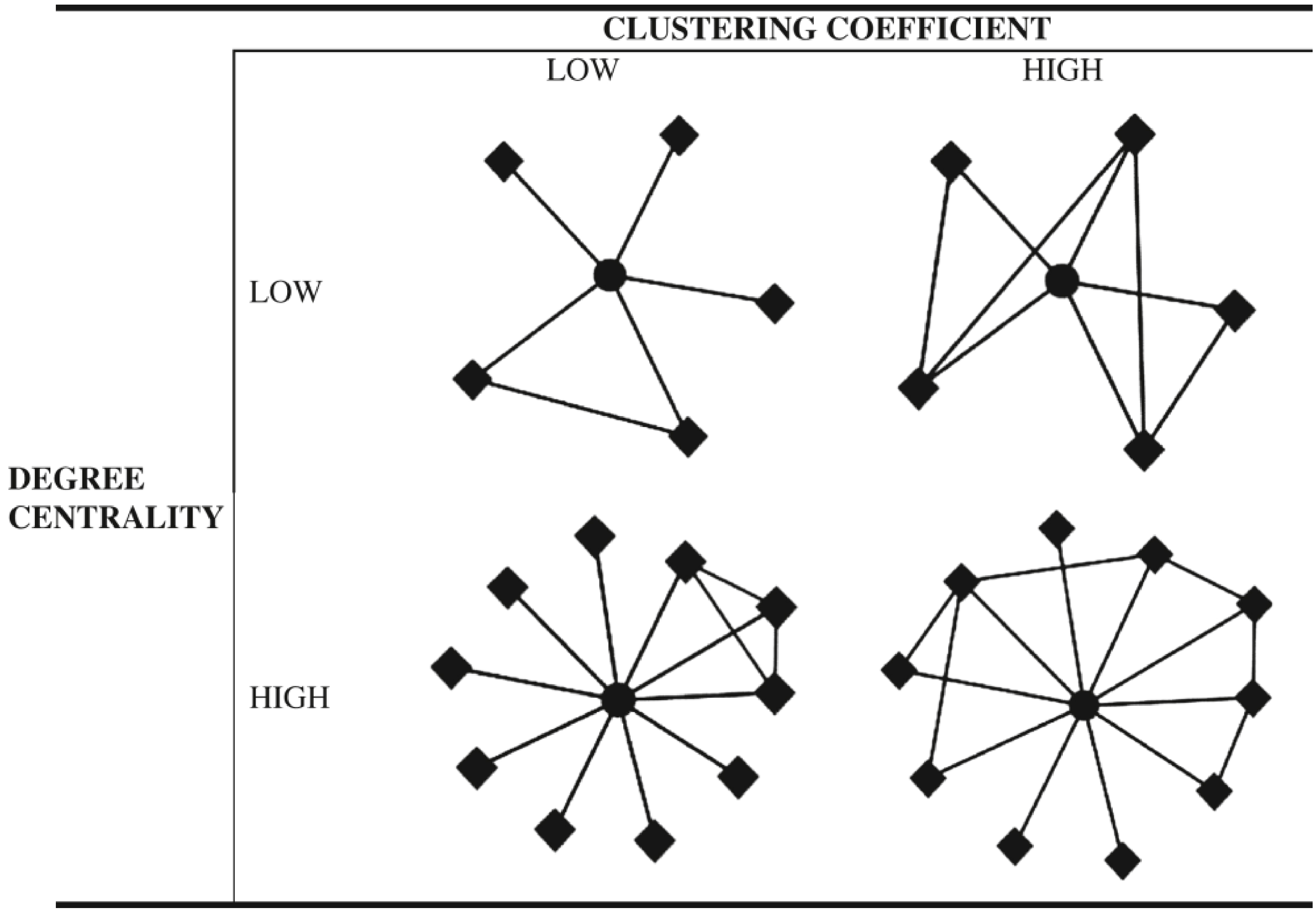


Most central airports

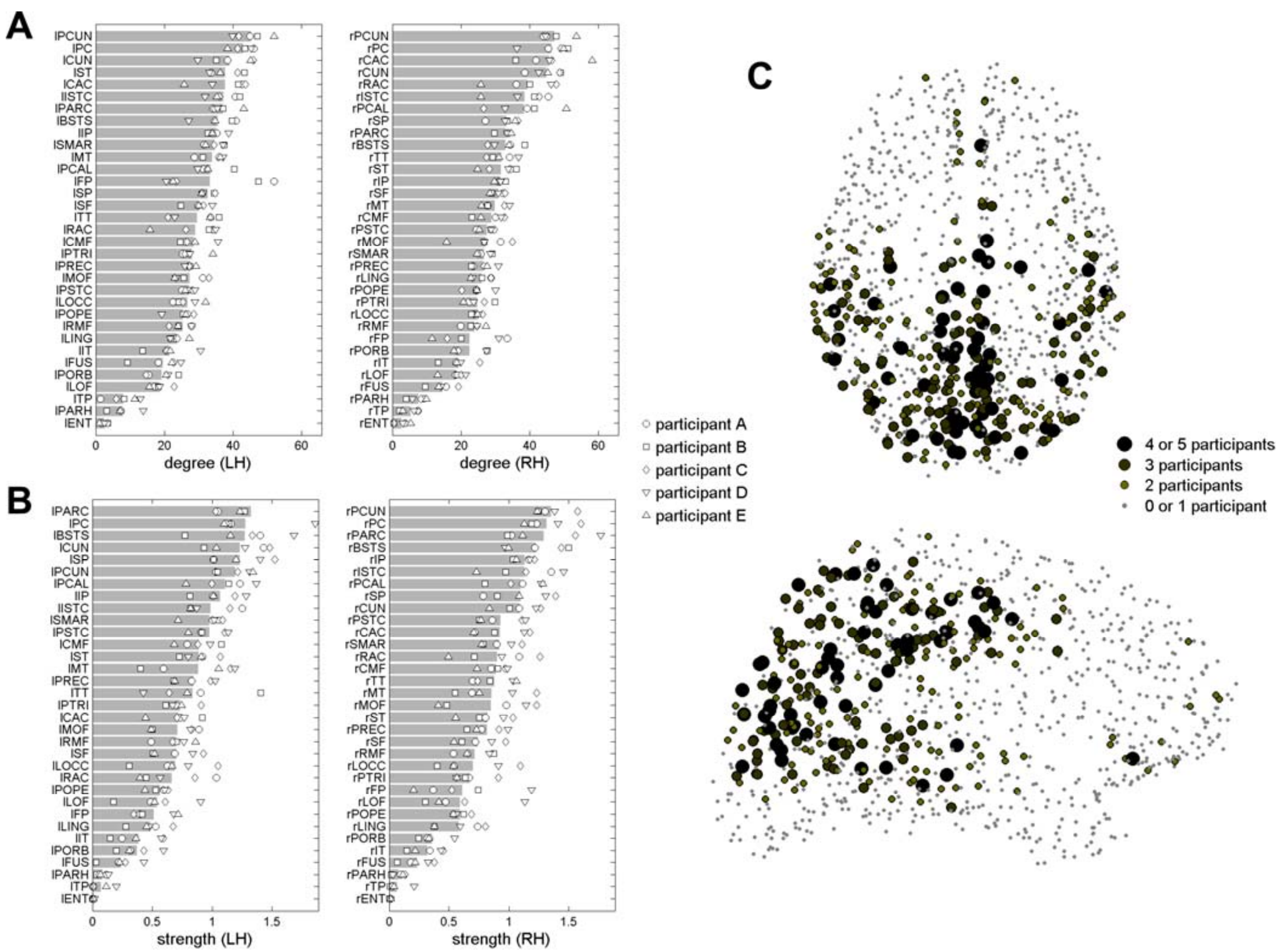

Disconnected node
Exp psych – modular cluster


Hub
uit



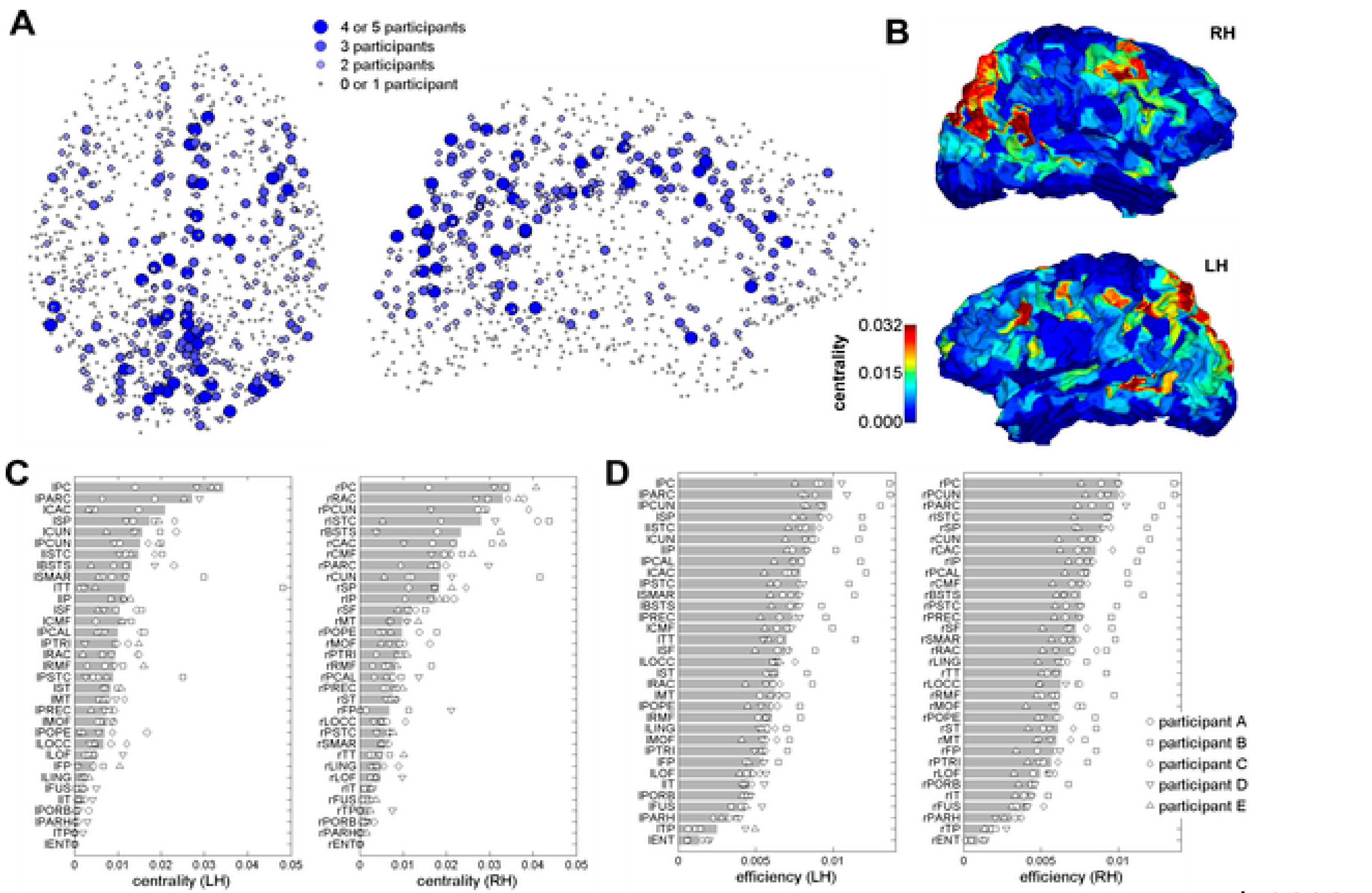

CLUSTERING COEFFICIENT
LOW
HIGH
DEGREE CENTRALITY
LOW
HIGH

Node degree and strength in the brain



Hagmann et al. 2008

Centrality and efficiency in the brain

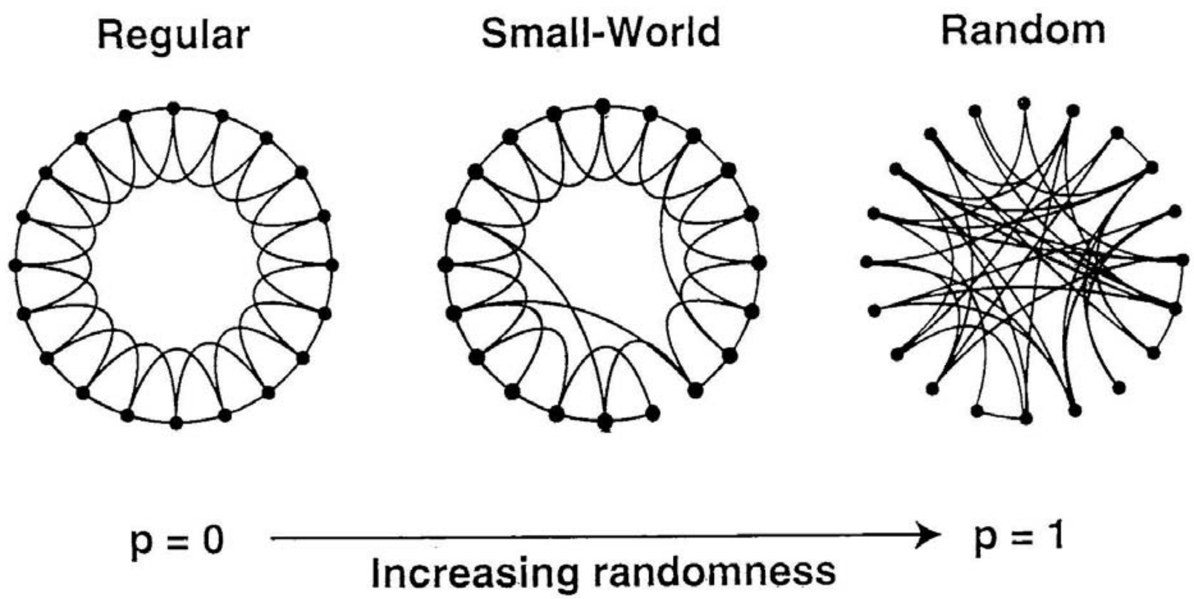


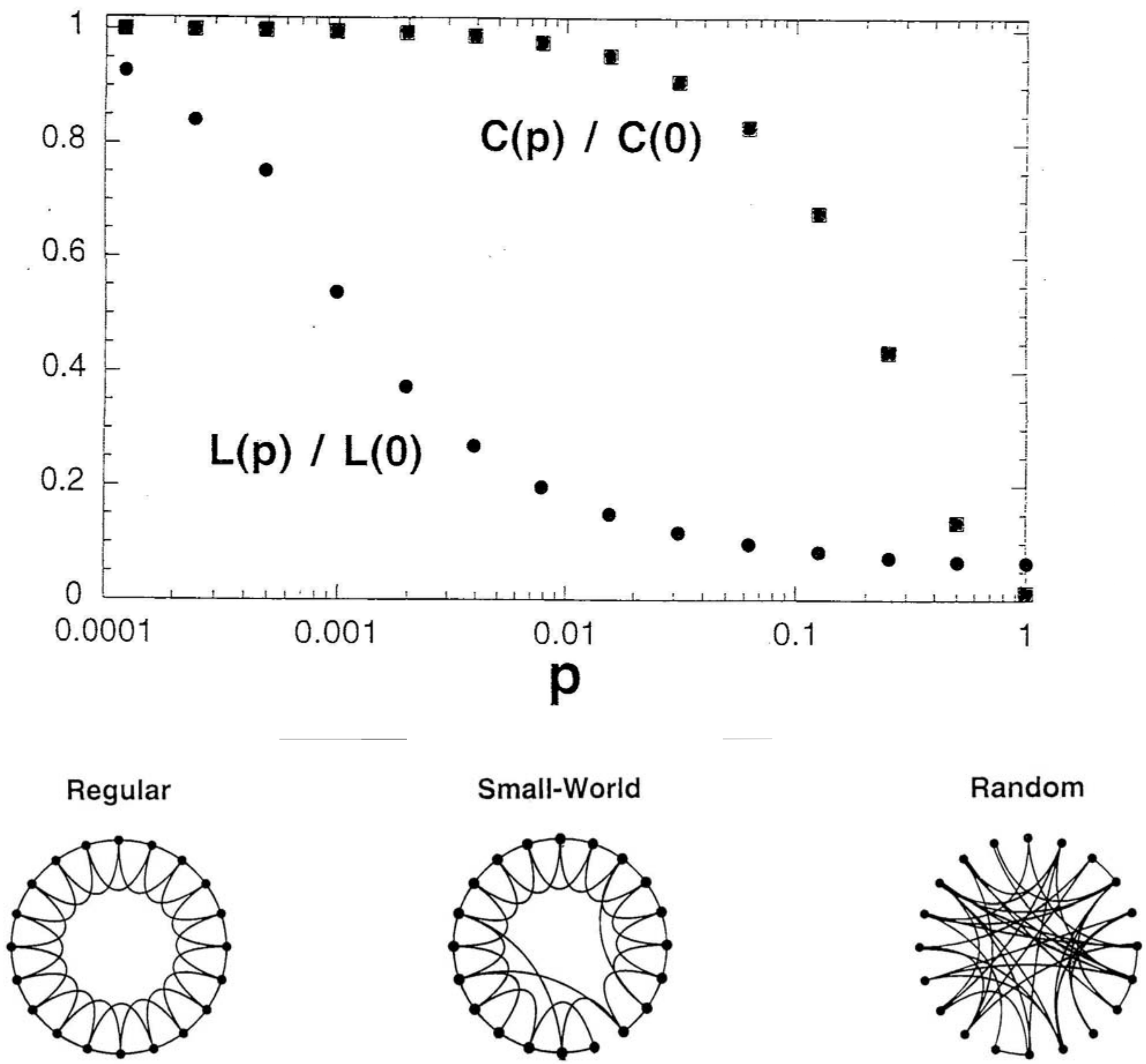
Hagmann et al. 2008

Network architectures:
order, disorder, hierarchy

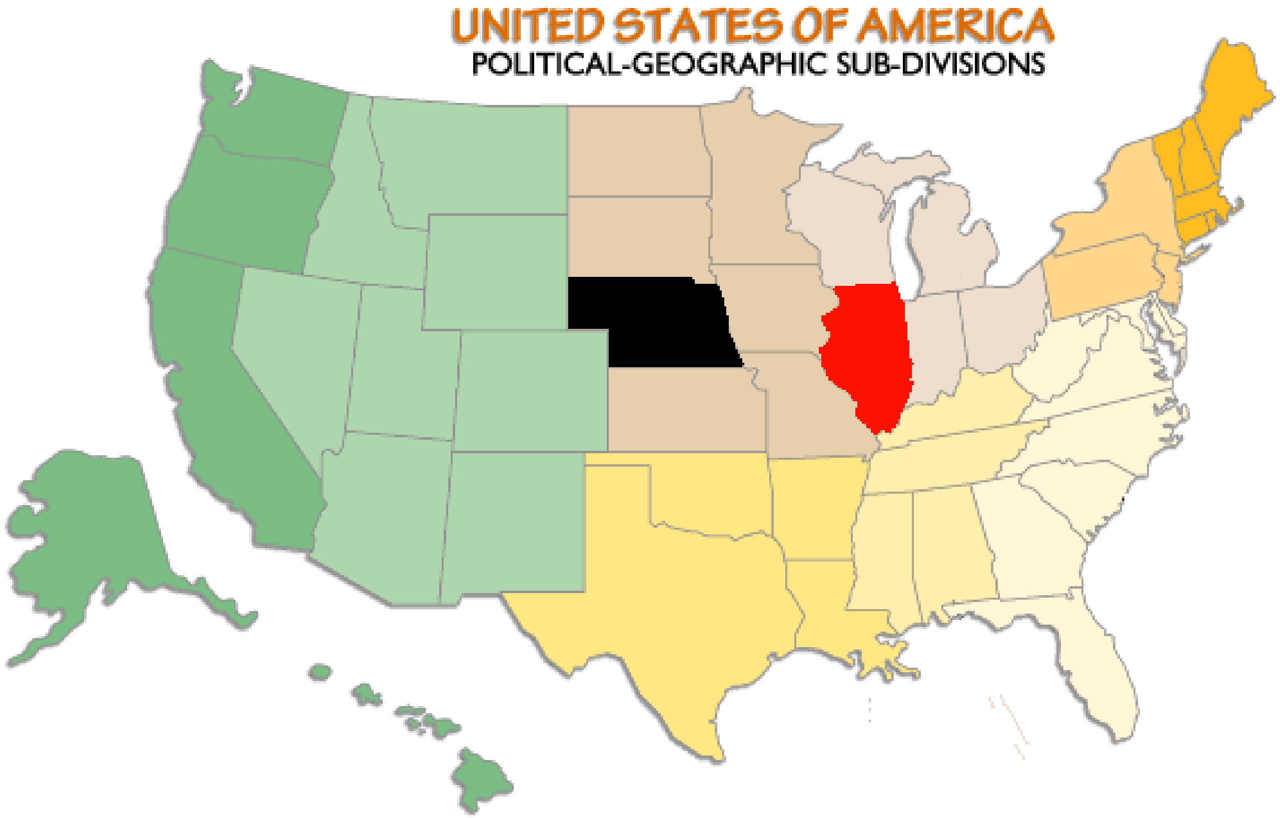
The architectural features of a graph reflect the processes by which the graph was constructed or developed.

From regular to random




1
0.8
0.6
0.4
0.2
0
C(p) / C(0)
L(p) / L(0)
0.0001
0.001
0.01
0.1
1
p
Regular
Small-World
Random

Small world effect: Milgram (1967)



Will a message arrive from a random Nebraska location to a clerk in Chicago, through hand-to hand passage?

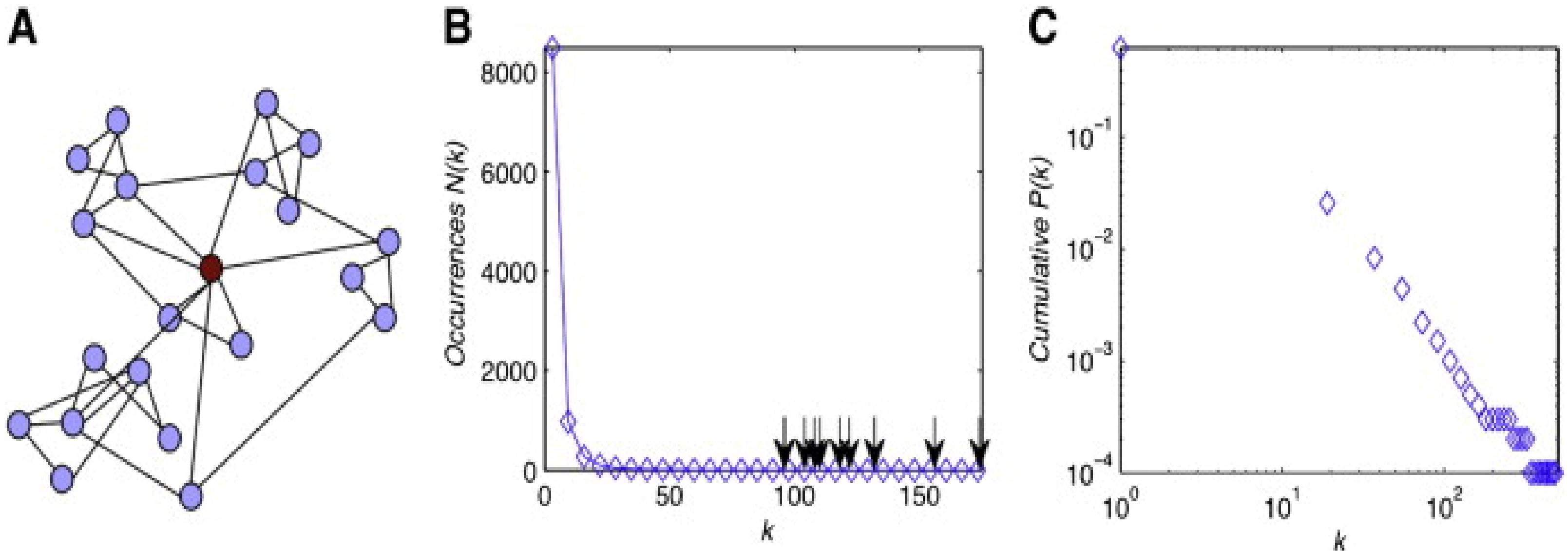
As you might have understood, a lot of networks are small world

Sometimes small-worldness can arise from non-profound mechanisms: i.e. the simple effect of using a (thresholded) correlation to obtain the links of a network, makes this network a small-world one (Zalesky et al. 2012, Hlinka et al. 2012)

What makes inter-community crossing possible?

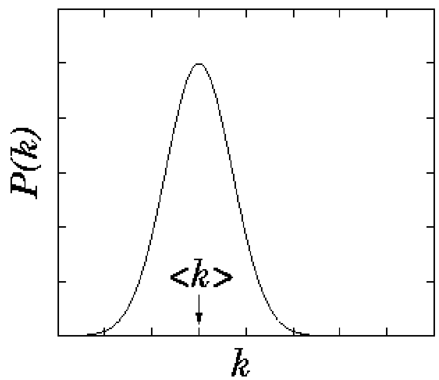
1. Weak, random ties
2. Hubs

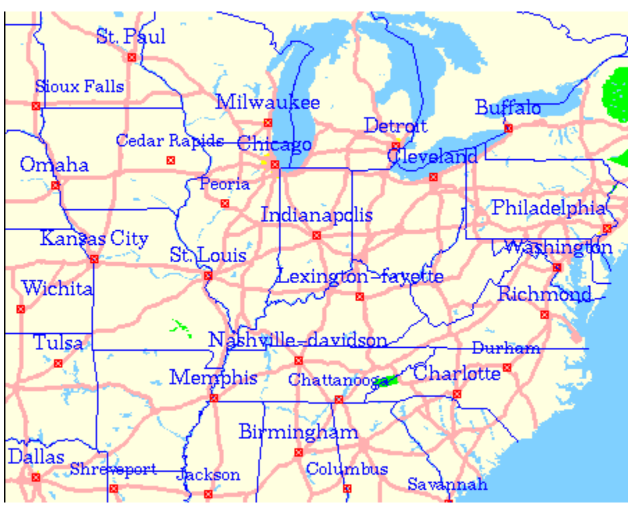
Signature of hubs in degree distribution



Hierarchical vs symmetric networks

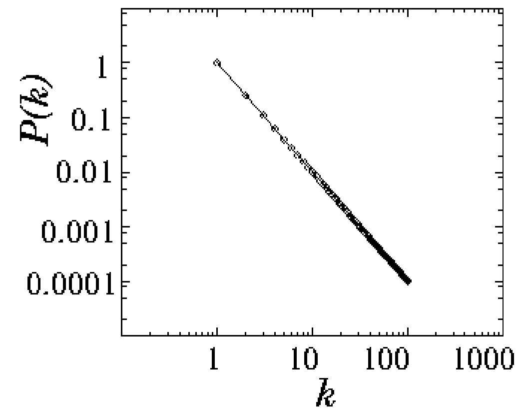
Homogeneous network



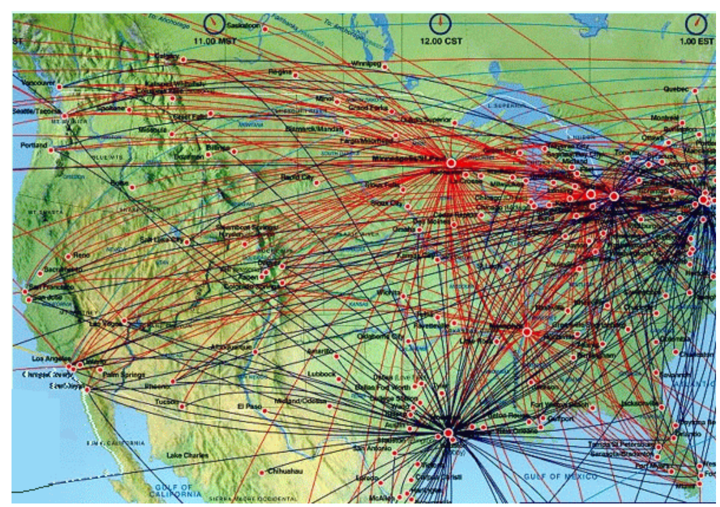


Hierarchical network: hubs

-

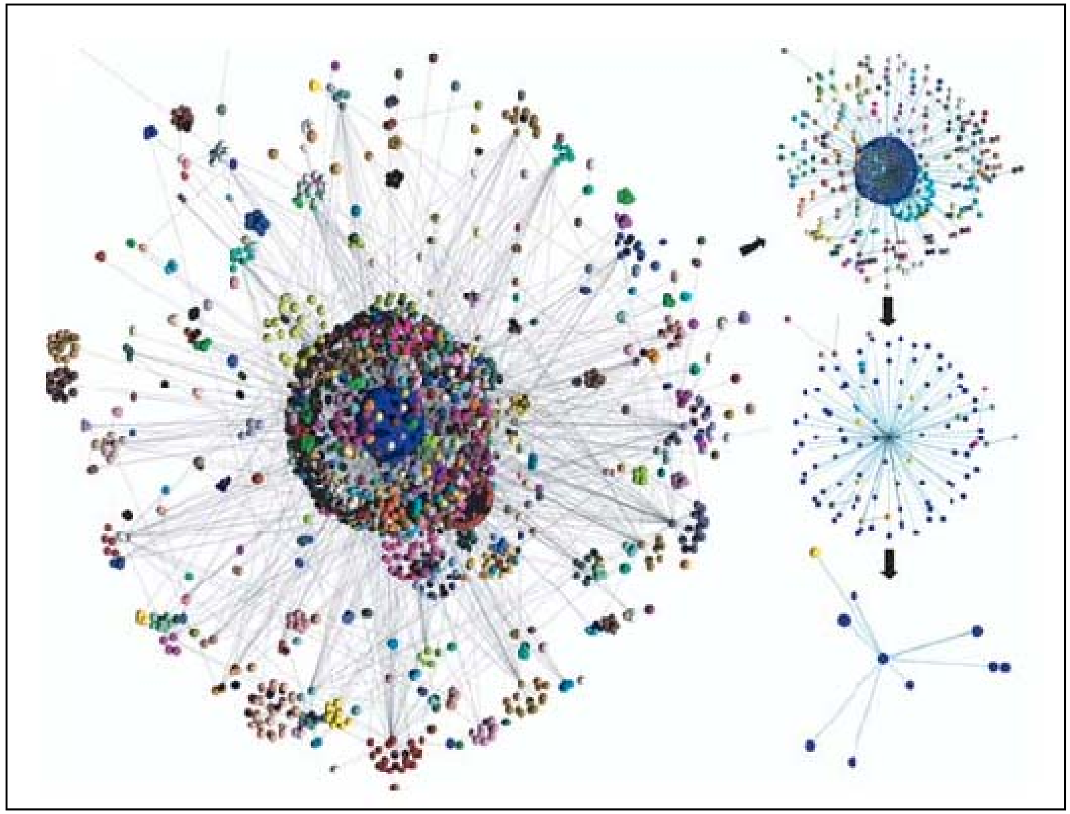


Scale-free



Self-similarity of scale free networks

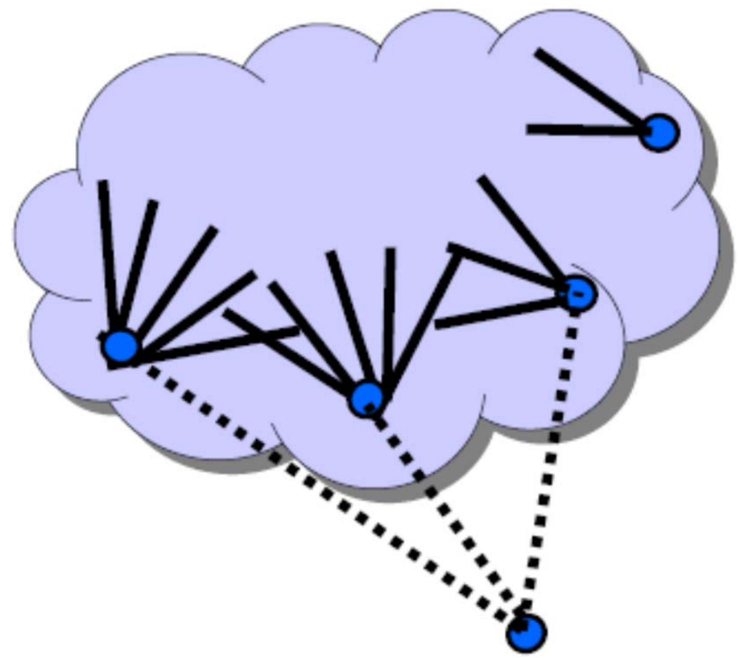
$$P(k) \sim k^{-\gamma}$$



WWW (in)	Internet	Actor	Citation index	Sex Web	Cellular network	Phone call network	linguistics
$\gamma = 2.1$	$\gamma = 2.5$	$\gamma = 2.3$	$\gamma = 3$	$\gamma = 3.5$	$\gamma = 2.1$	$\gamma = 2.1$	$\gamma = 2.8$

What is the mechanism originating scale-free networks?
PREFERENTIAL ATTACHMENT
(Albert & Barabasi, 1999)

Matthew effect



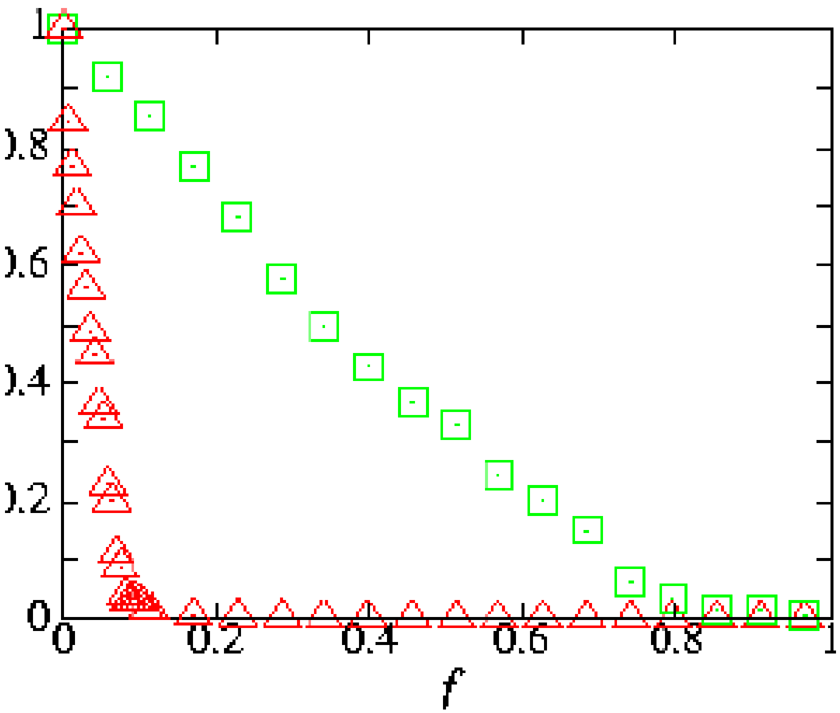
For unto every one that hath shall be given, and he shall have abundance: but from him that hath not shall be taken even that which he hath.
Matthew 25:29

Robustness wrt casual or targeted attacks

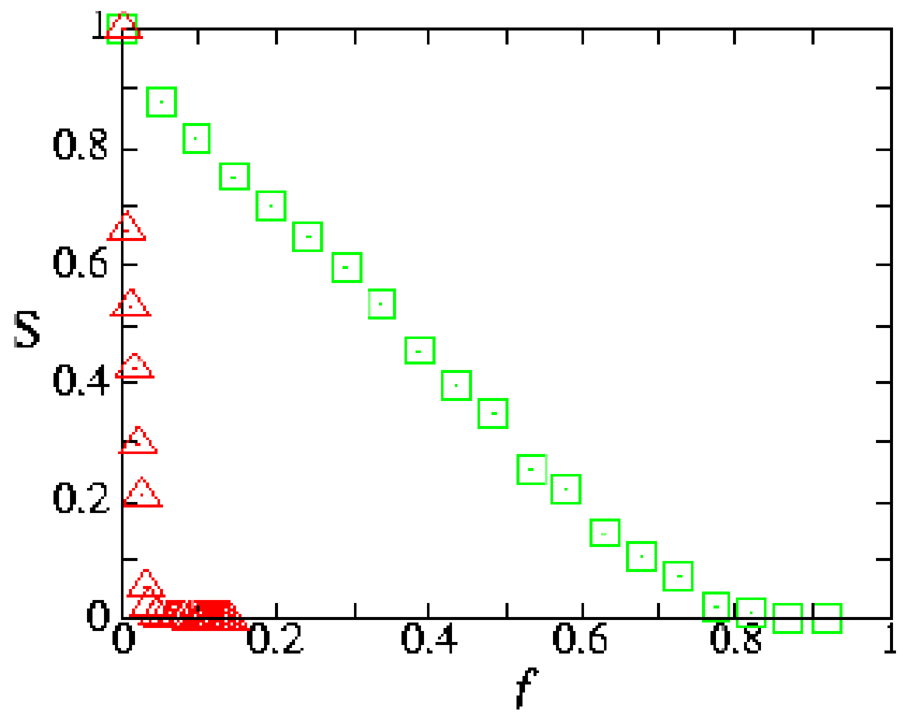
Random

Targeted

Internet



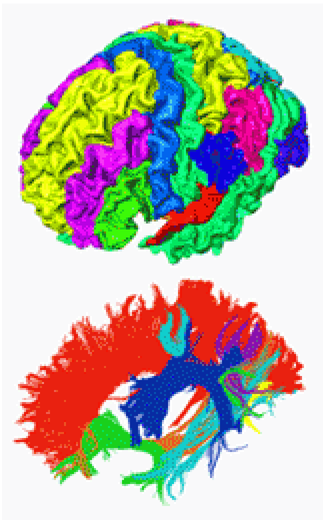
Protein

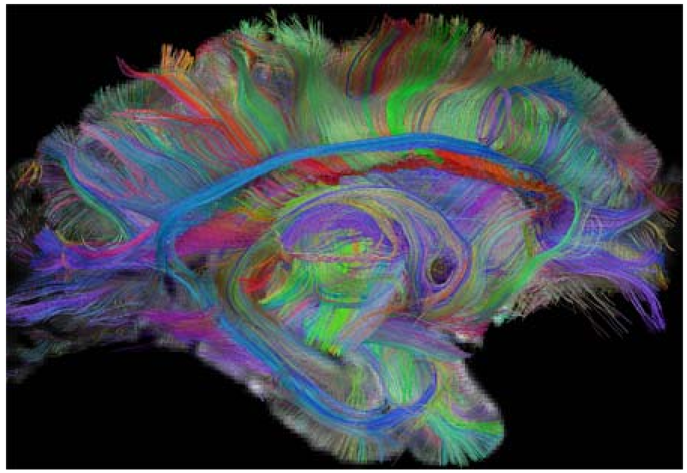


Networks in the brain

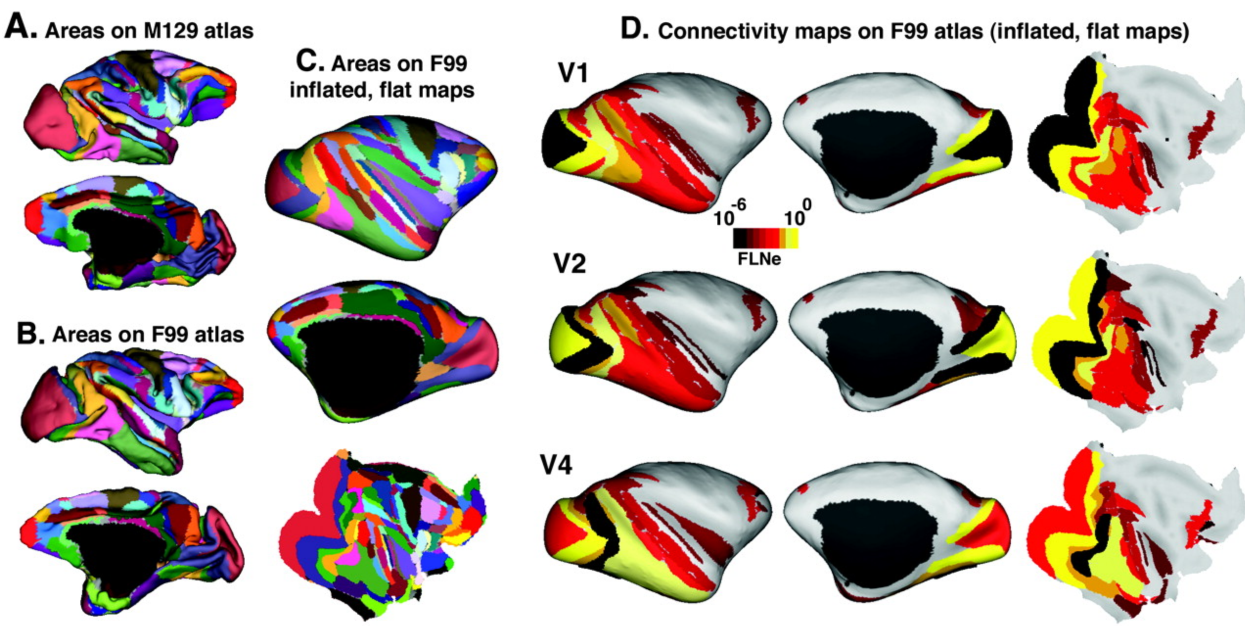
- Which connections exist in the brain?
- Is it possible that regions that are not connected by neural fibers still communicate?
- Is it possible to detect the flow of information in the brain?
- Which properties has this network of communications?
- How does this network change during task performing vs rest, or disease vs health?

Anatomic or structural connectivity (at large scale)





DTI (humans)



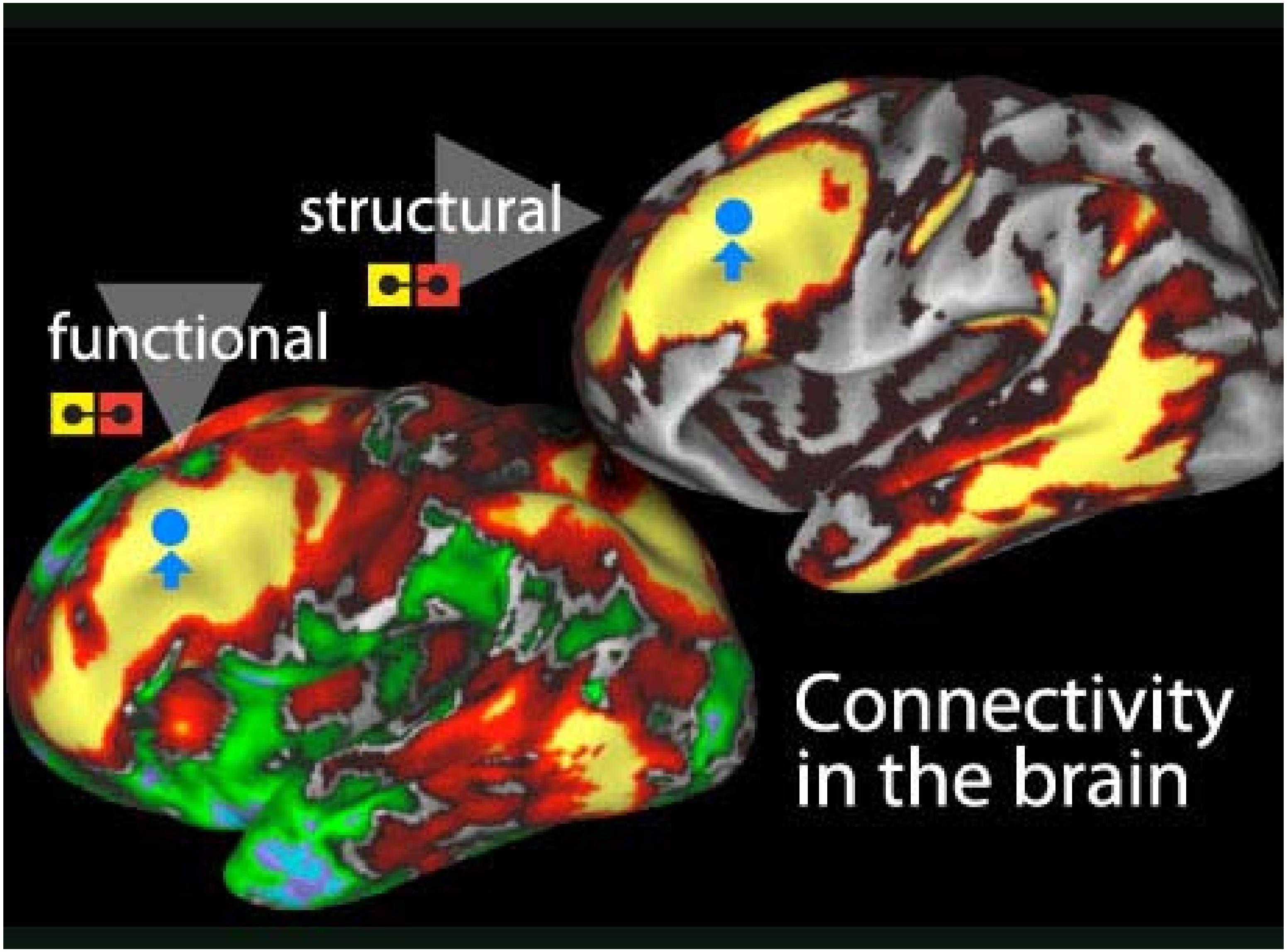
Dye tracing (animals)

Functional (dynamical) connectivity

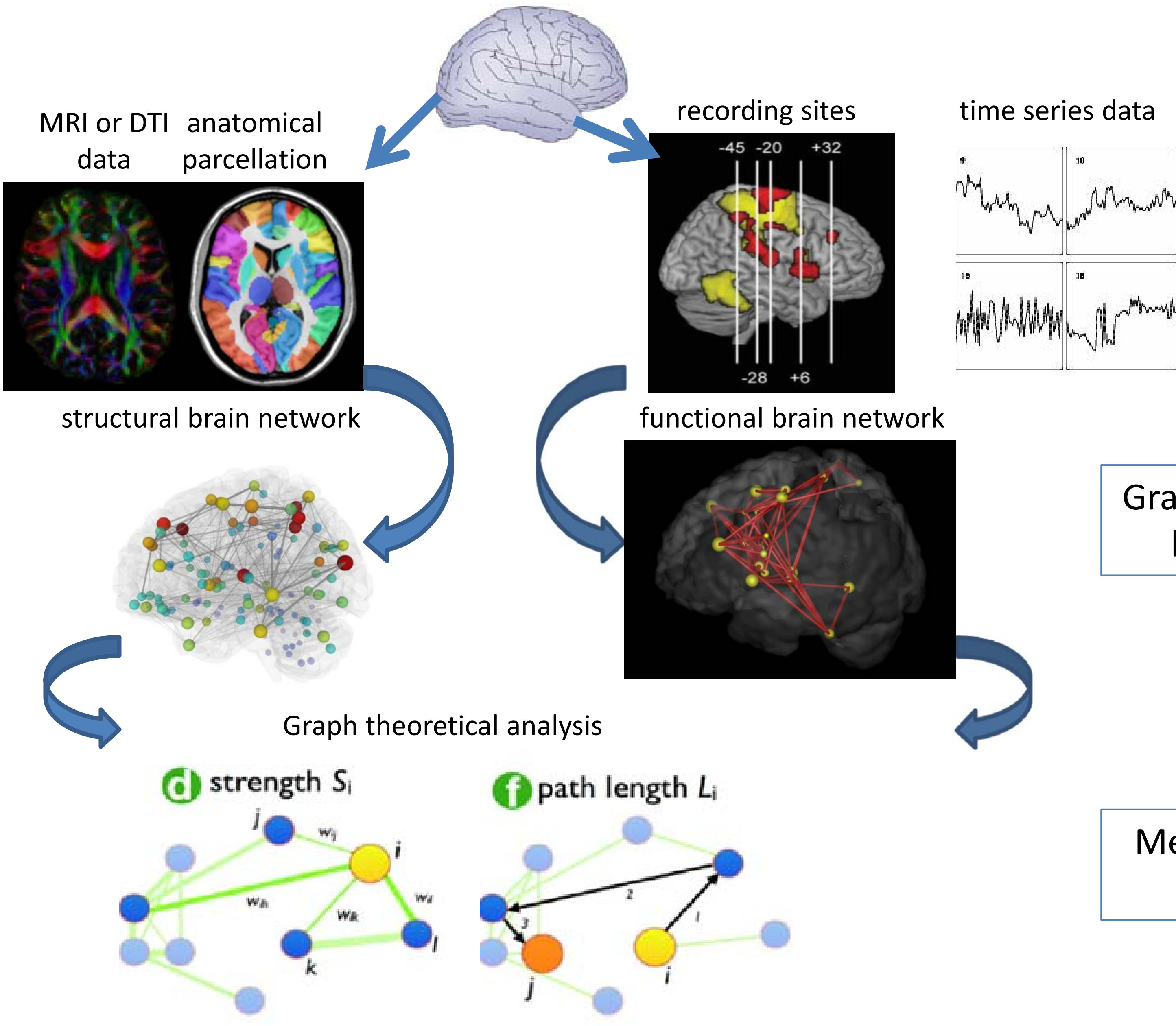
Find statistical dependencies between even remote regions:

- Correlation
- Coherence
- Phase synchronization
- Mutual information
- …

Functional vs structural



Networks in the brain: structural and functional

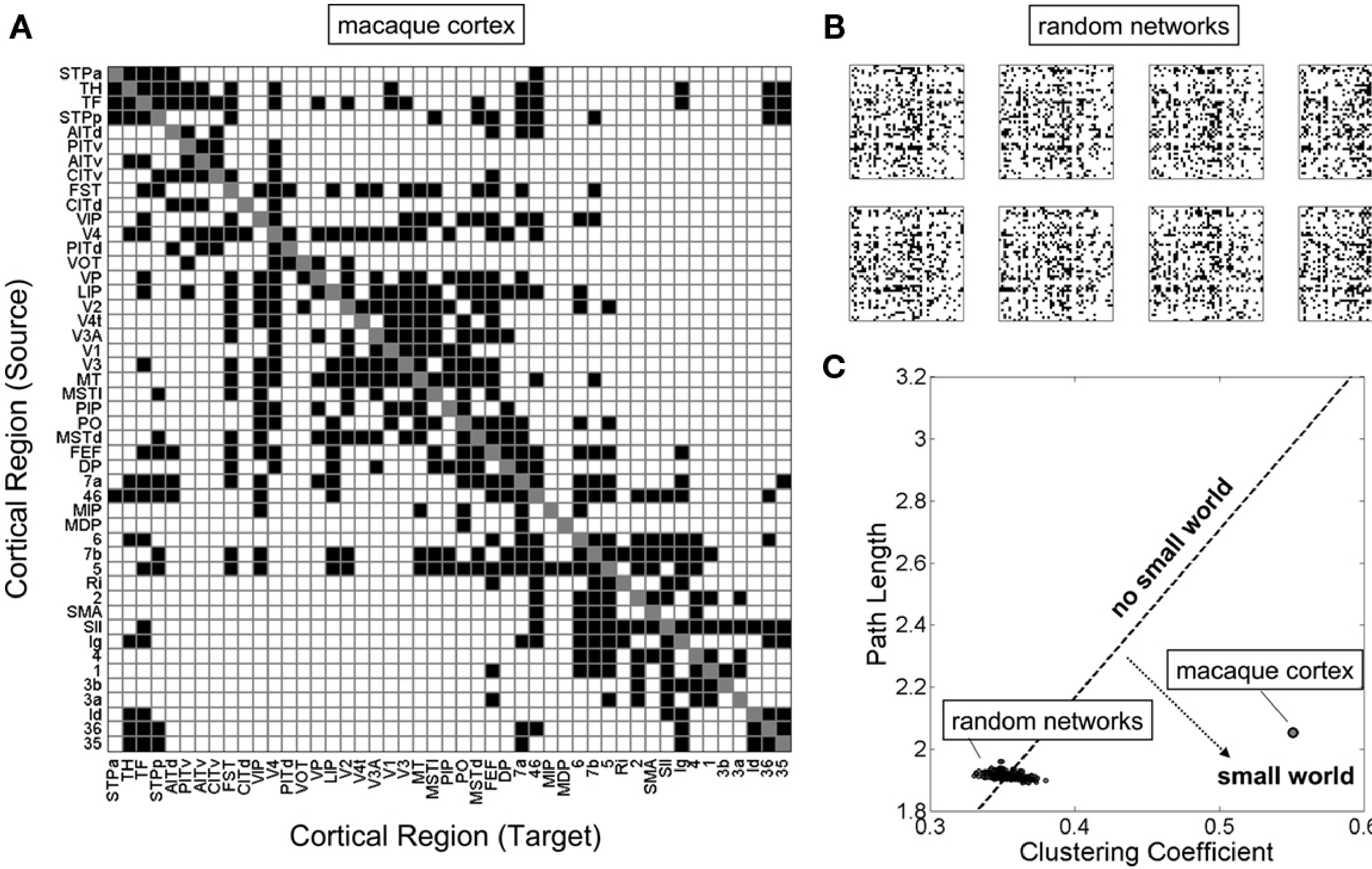


Structural/Functional Data

Graph depicts connections between brain areas

Measurements extracted from graph

Where are cortical maps?



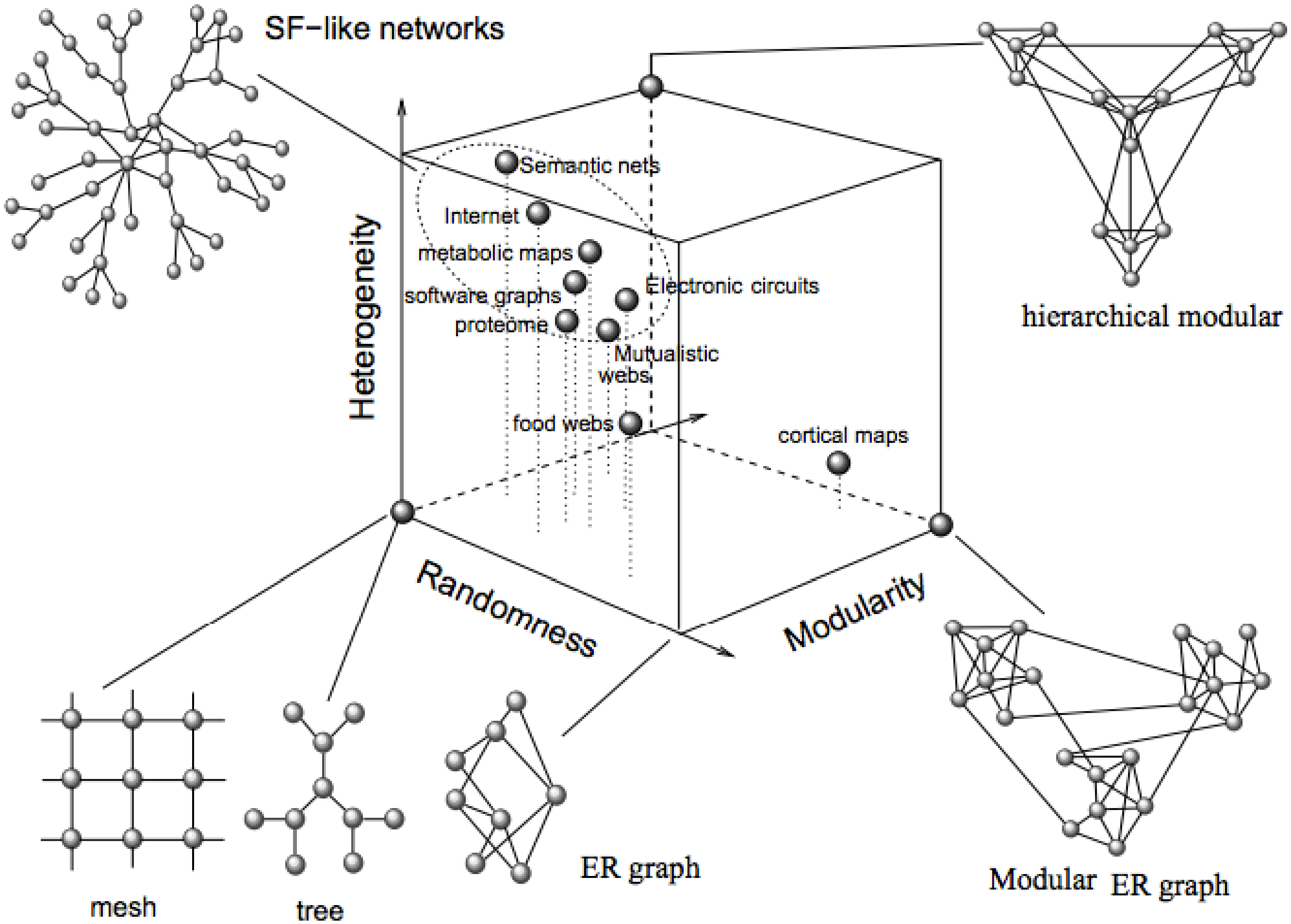
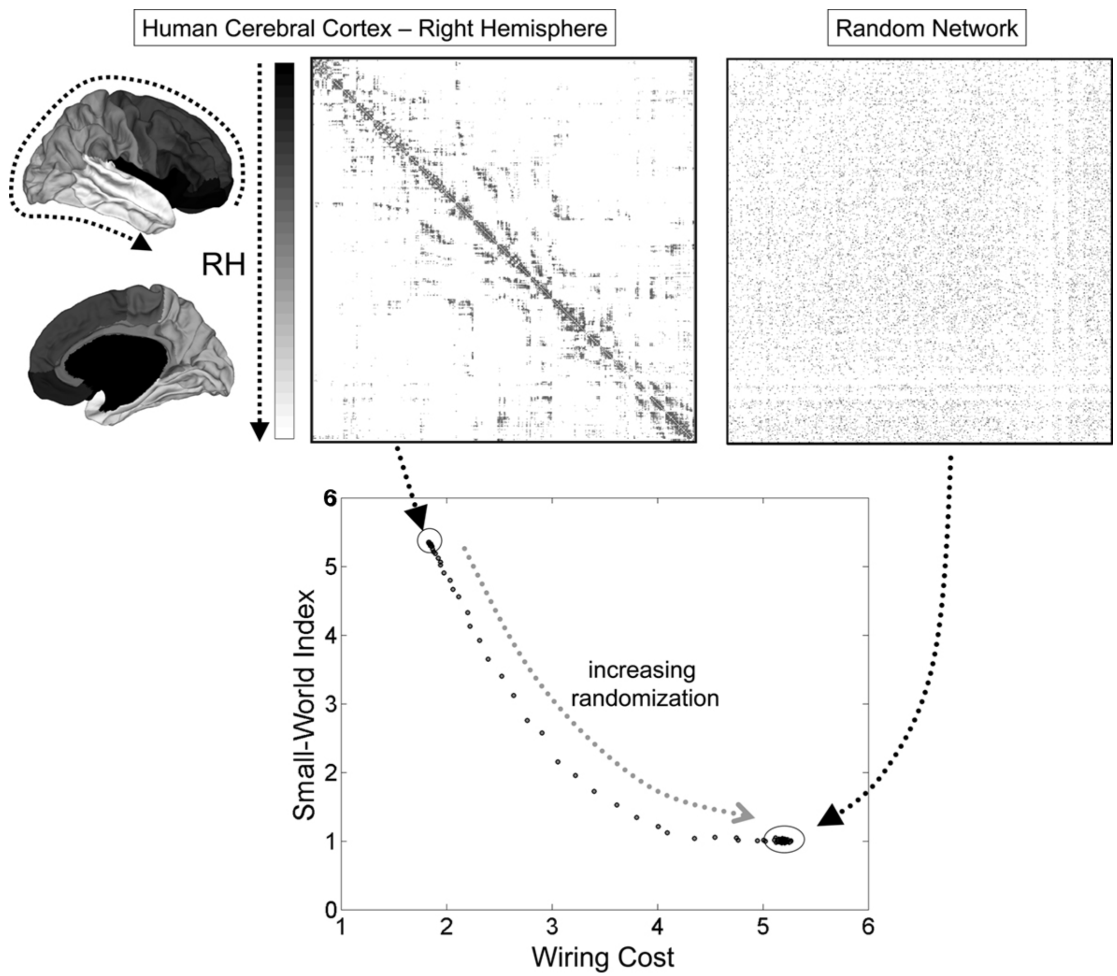


FIG. 3 A zoo of complex networks. In this qualitative space, three relevant characteristics are included: randomness, heterogeneity and modularity. The first introduces the amount of randomness involved in the process of network's building. The second measures how diverse is the link distribution and the third would measure how modular is the architecture. The position of different examples are only a visual guide. The domain of highly heterogeneous, random hierarchical networks appears much more occupied than others. Scale-free like networks belong to this domain.

Solé and Valverde 2004

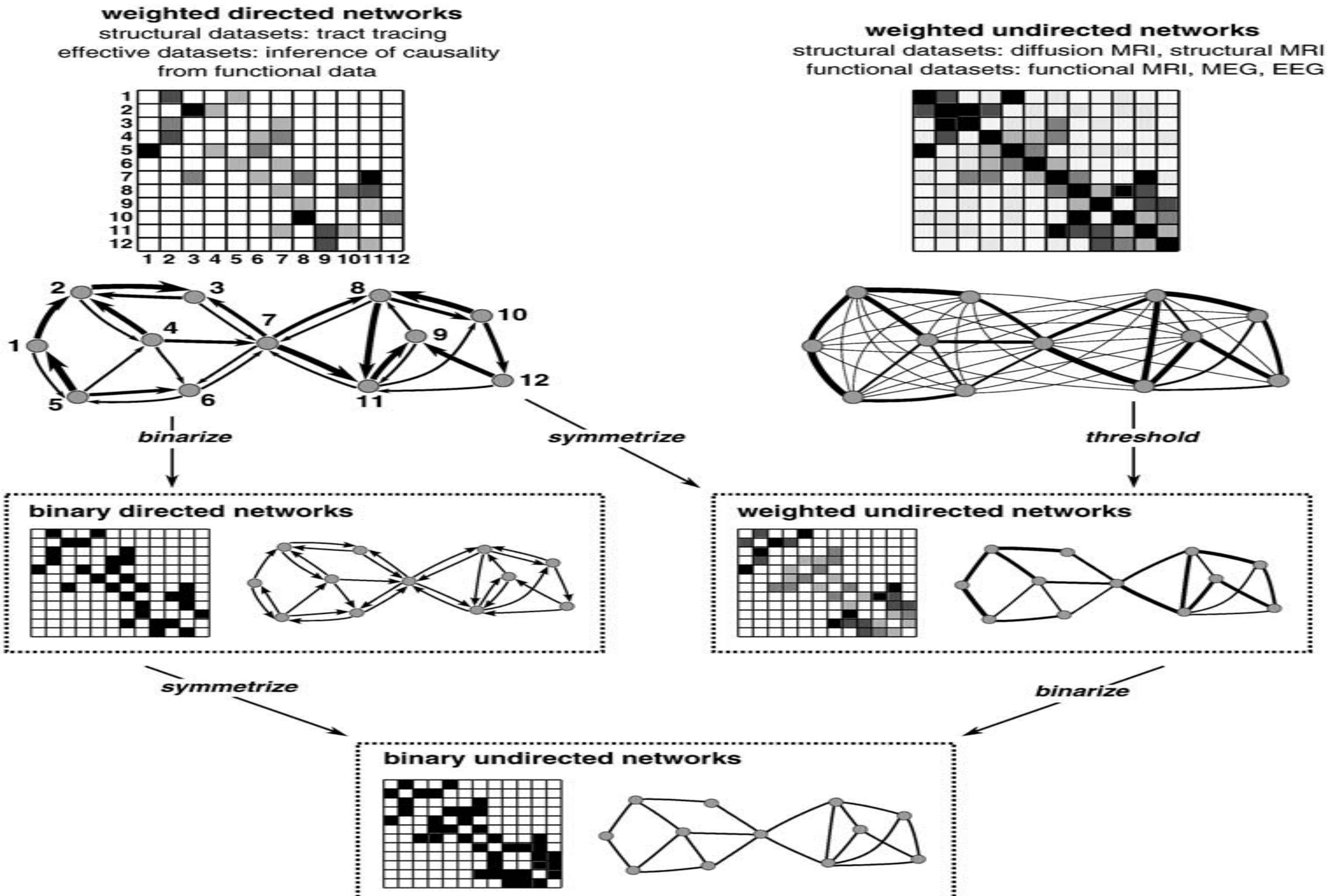
Small-world topology allows for lower resource consumption



Sporns 2011

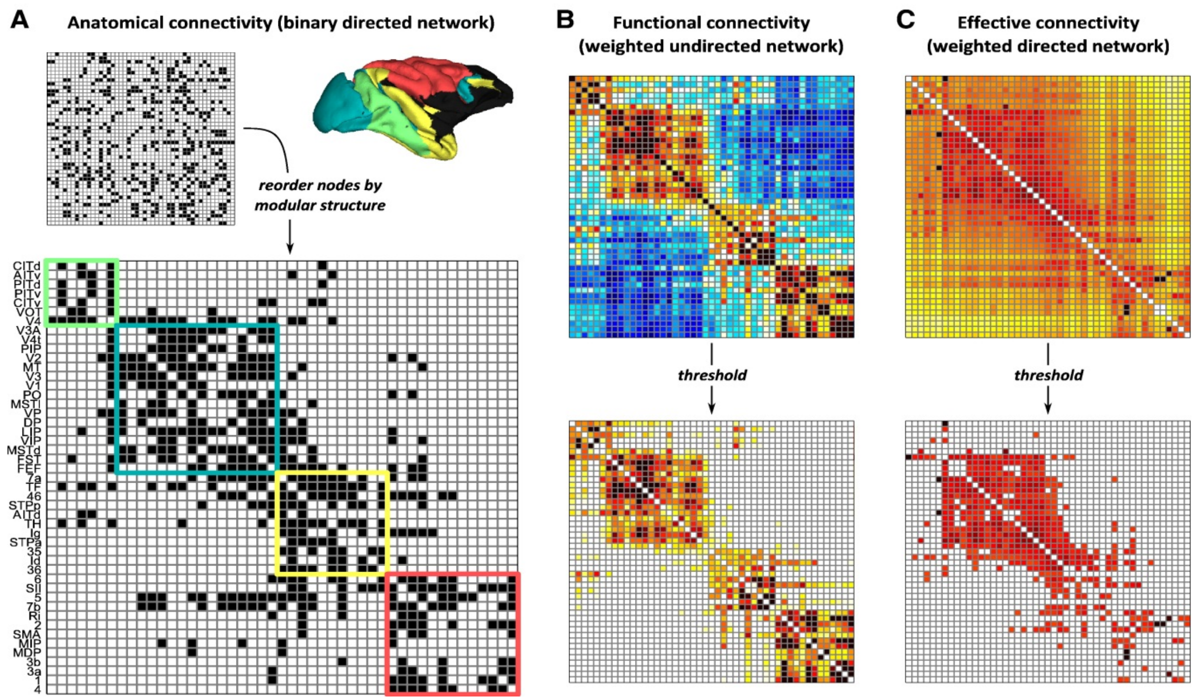
Network modality	Edge representation	Empirical techniques	Network characteristics
Structural connectivity	Physical links (synapses, pathways), biophysical efficacy, time delay	Microscopy: tissue volume reconstruction Neuroanatomy: tract tracing Neuroimaging: diffusion imaging/tractography	Weighted or unweighted, sparse and directed (synapses, projections), sparse and undirected (diffusion MRI)
Functional connectivity	Statistical relationships between neural time courses (e.g. spikes, EEG, BOLD)	Neurophysiology: spike or LFP correlations EEG/MEG: correlation, sync, coherence, phase locking fMRI: BOLD cross-correlations, partial correlations	Full and weighted, or sparse and weighted (or unweighted) after thresholding; undirected
Effective connectivity	Causality inference based on temporal precedence or on generative model	Spikes, EEG/MEG, fMRI: time series analysis (Granger causality, Transfer entropy) or model inference (dynamic causal modeling)	Full or sparse; weighted or unweighted; directed

From data to network



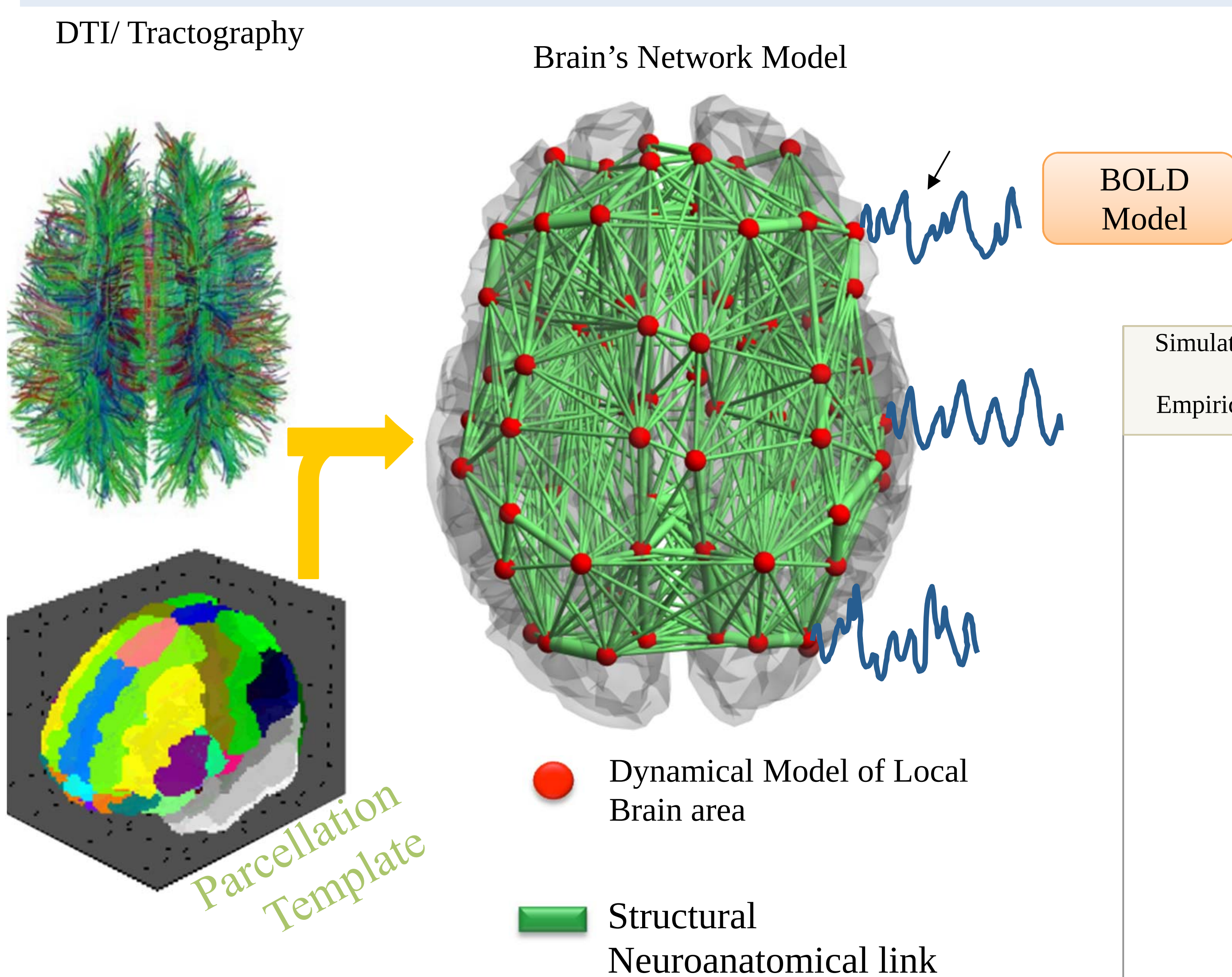
Sporns 2011

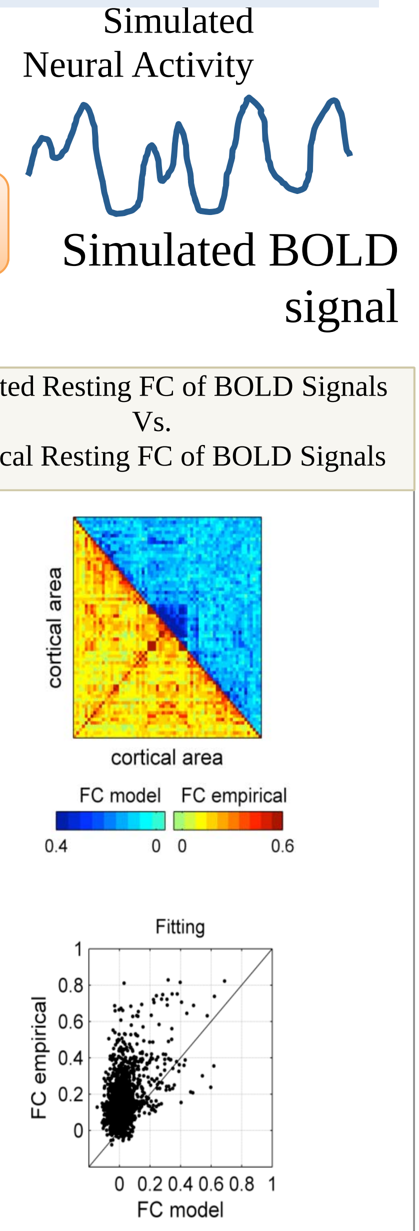
From data to network



Rubinov and Sporns, 2010

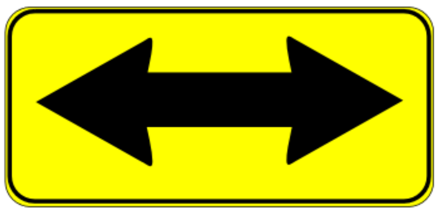
Model dynamics on brain structure





Deco, Jirsa, McIntosh, Nat Rev Neurosci 2011
Deco, Jirsa J. Neurosci. 2012
Deco, Jirsa, McIntosh, Trends in Neuroscience 2013

Network inference from temporally correlated data



Correlations

Coherence

Phase synchronization

Generalized synchronization

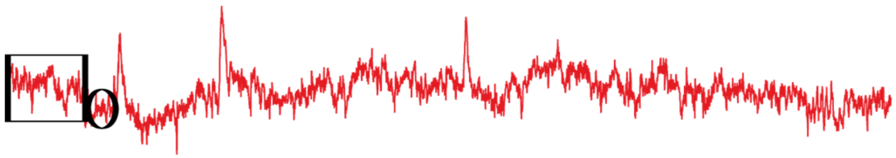
Mutual information

Transfer entropy

Granger causality

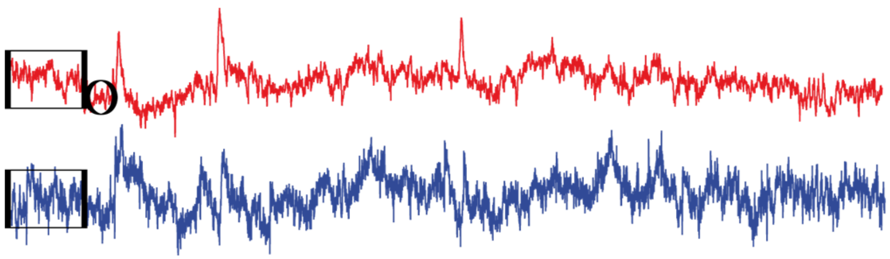
Predicting the future of a time series

Using only its past…



$$x = AX + \varepsilon_X$$

… or including the past of another time series



$$x = B[X\ Y] + \varepsilon_{X,Y}$$

$\varepsilon_{X,Y} < \varepsilon_X \quad \rightarrow$ Y Granger-causes X

Granger causality and Transfer Entropy

GC and TE are equivalent for Gaussianly distributed variables and other quasi-Gaussian distribution (Barnett et al. 2009, Hlavackova 2011, Barnett and Bossomaier 2012)

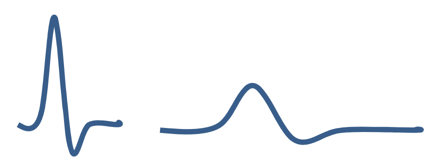
In this case they both measure information transfer

- Unified approach
- Mathematically more treatable
- You make heavy assumptions and you could lose important features

Establishment of a general framework for GC and TE, which computations that can be both exact and approximate

Advances for (fMRI) connectivity

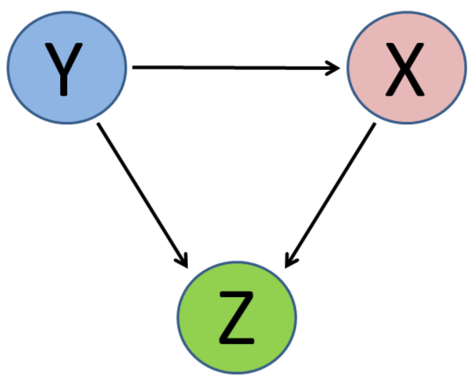
- Many variables, few samples
- Confounding HRF effect

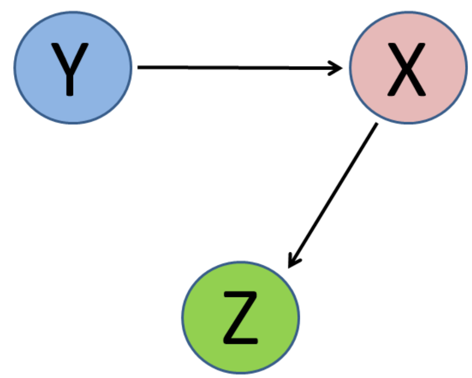


- Bad temporal resolution

GC in multivariate datasets

We must condition GC to the presence of other variables

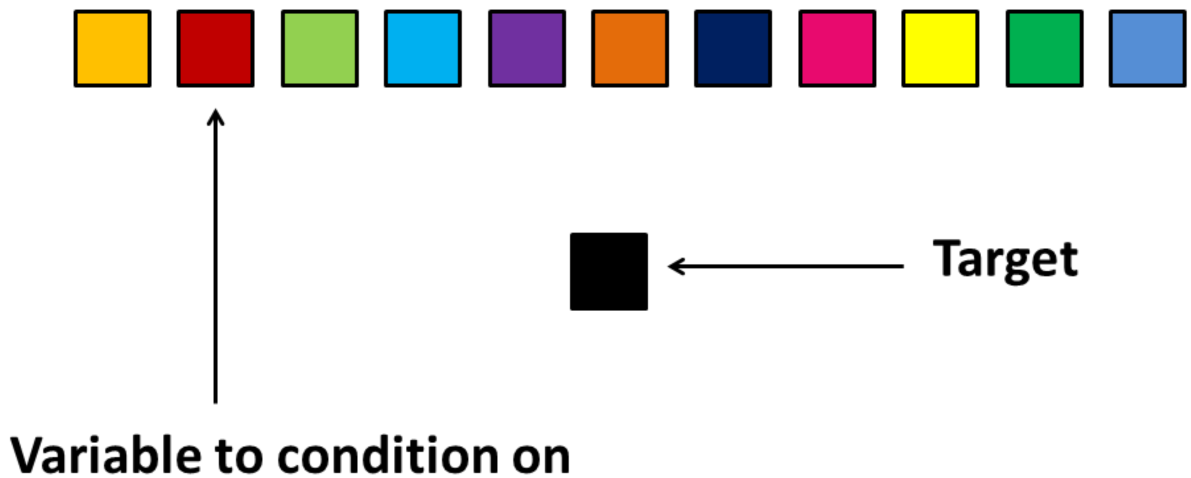




This problem has been known from the start, and the solution is usually the conditioned approach (Geweke 1982)

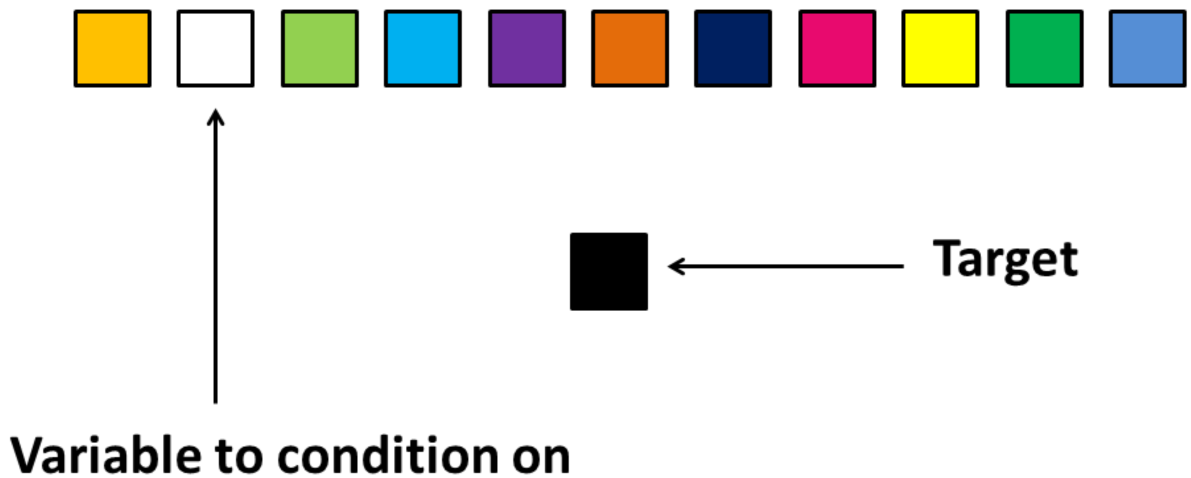
Full conditioning in multivariate dataset

We compare the model including …



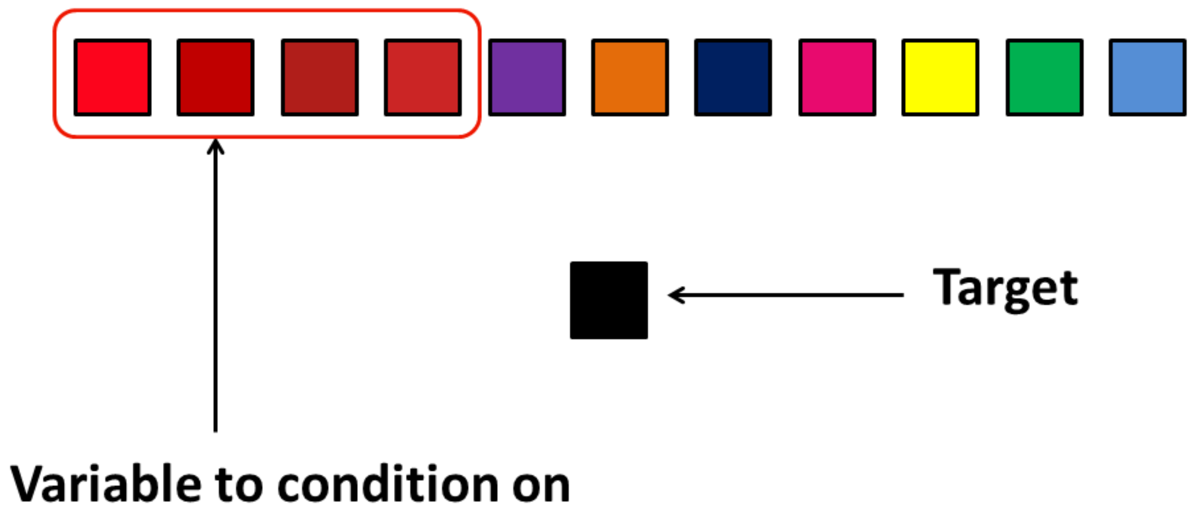
Full conditioning in multivariate dataset

… and excluding the conditioning variable



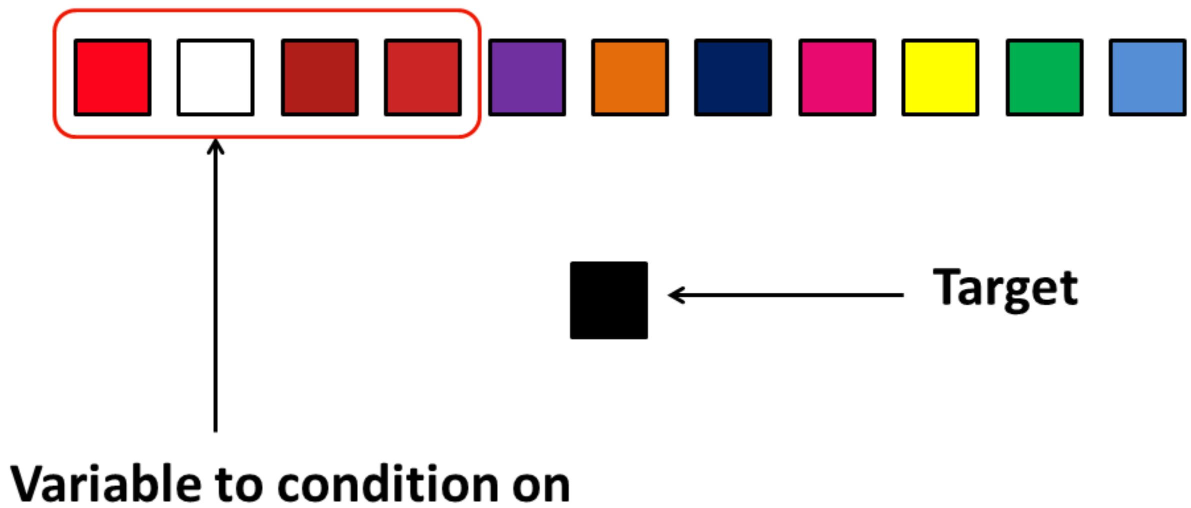
Presence of redundancy

When a number of variables share the same info on the target …



Presence of redundancy

… in the model we still have info on the target

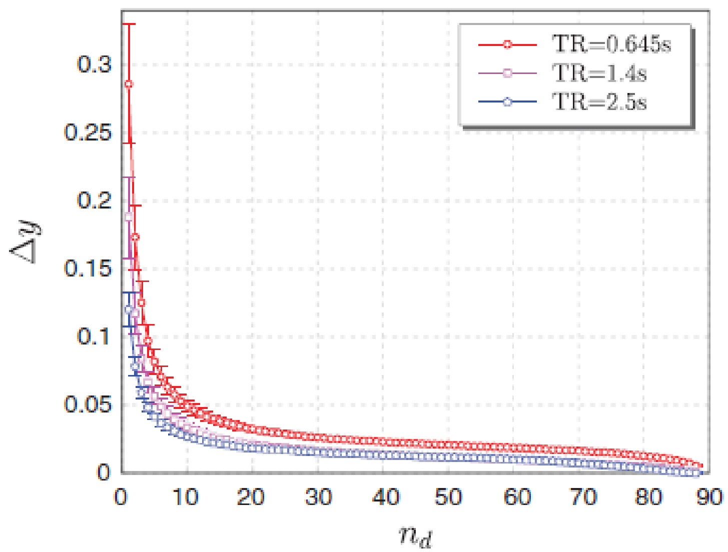


and the conditioning variable and all those correlated with it will be regarded as not relevant

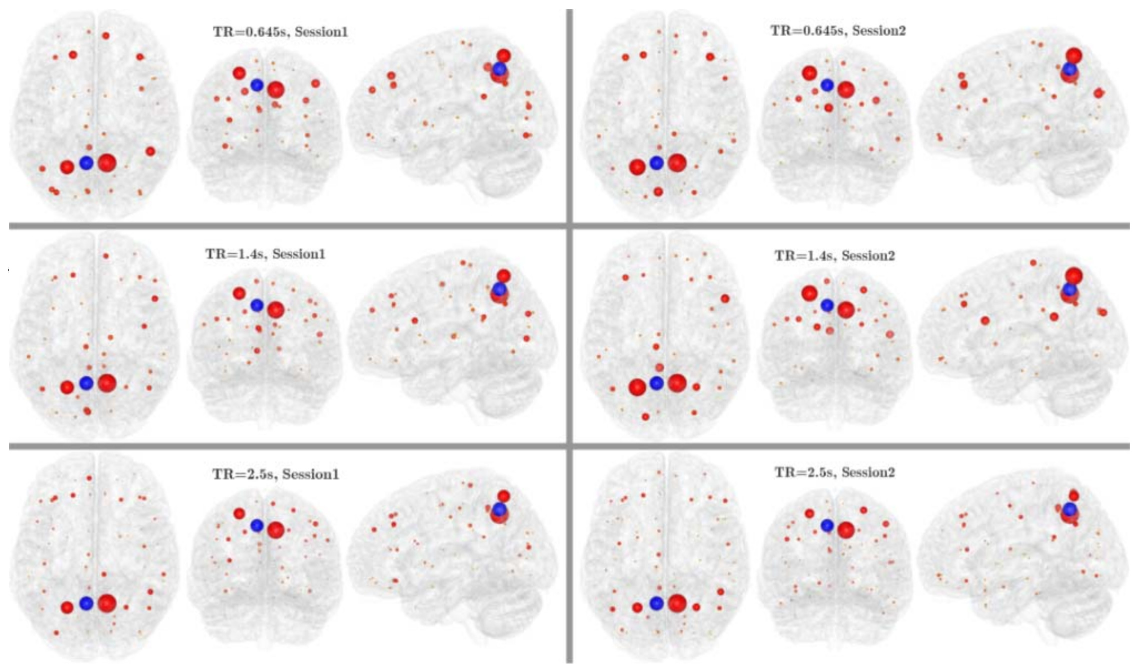
Partially conditioned Granger causality

- Redundancy in multivariate datasets leads to false GC estimations
- Conditioning on the most informative variables for each candidate driver

Residual information gain



Most informative regions consistently distributed across the brain

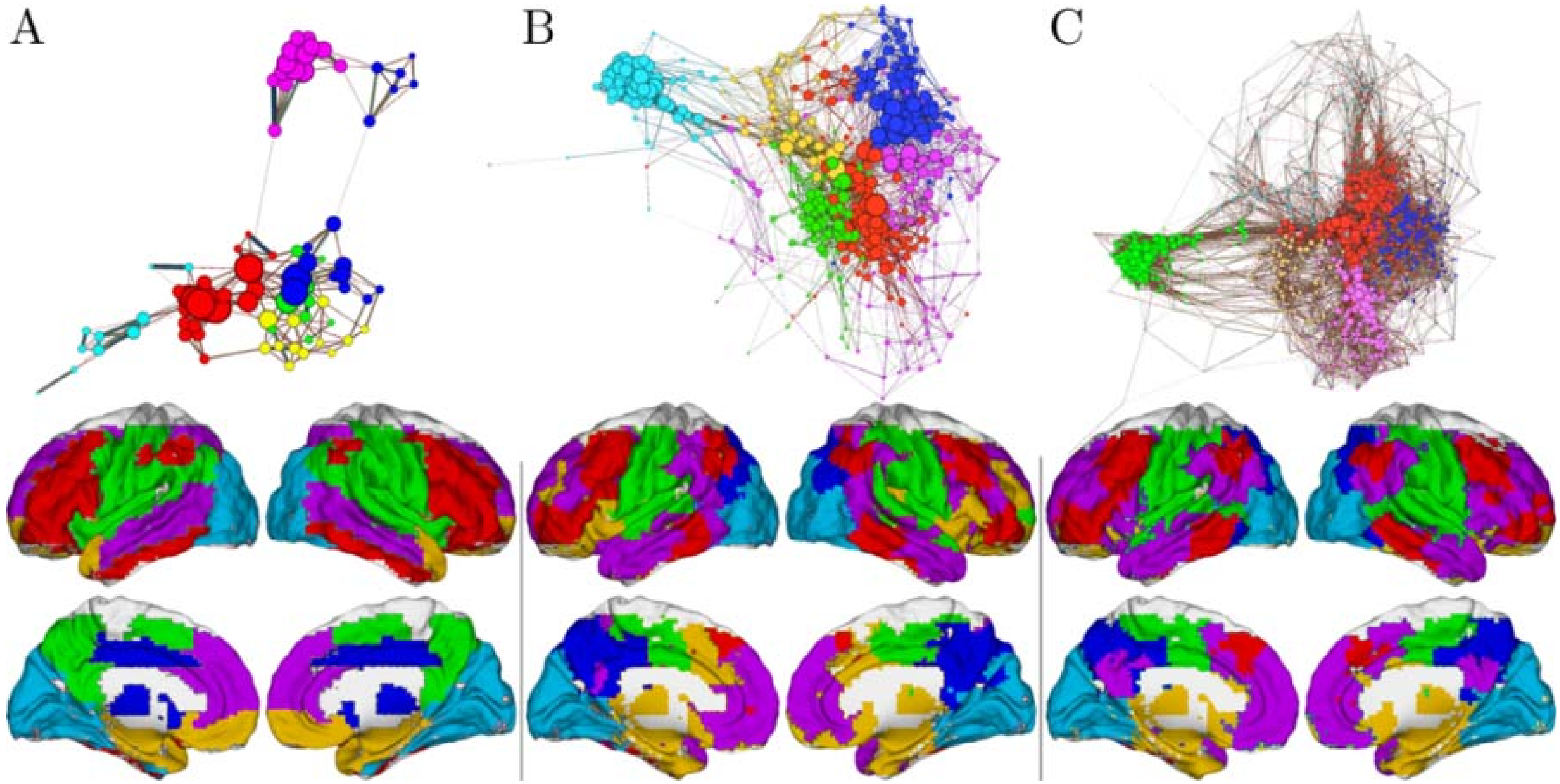


Marinazzo et al, Computational and mathematical methods in medicine, 2012
Wu et al. Brain Connectivity 2013

From regional to voxel level

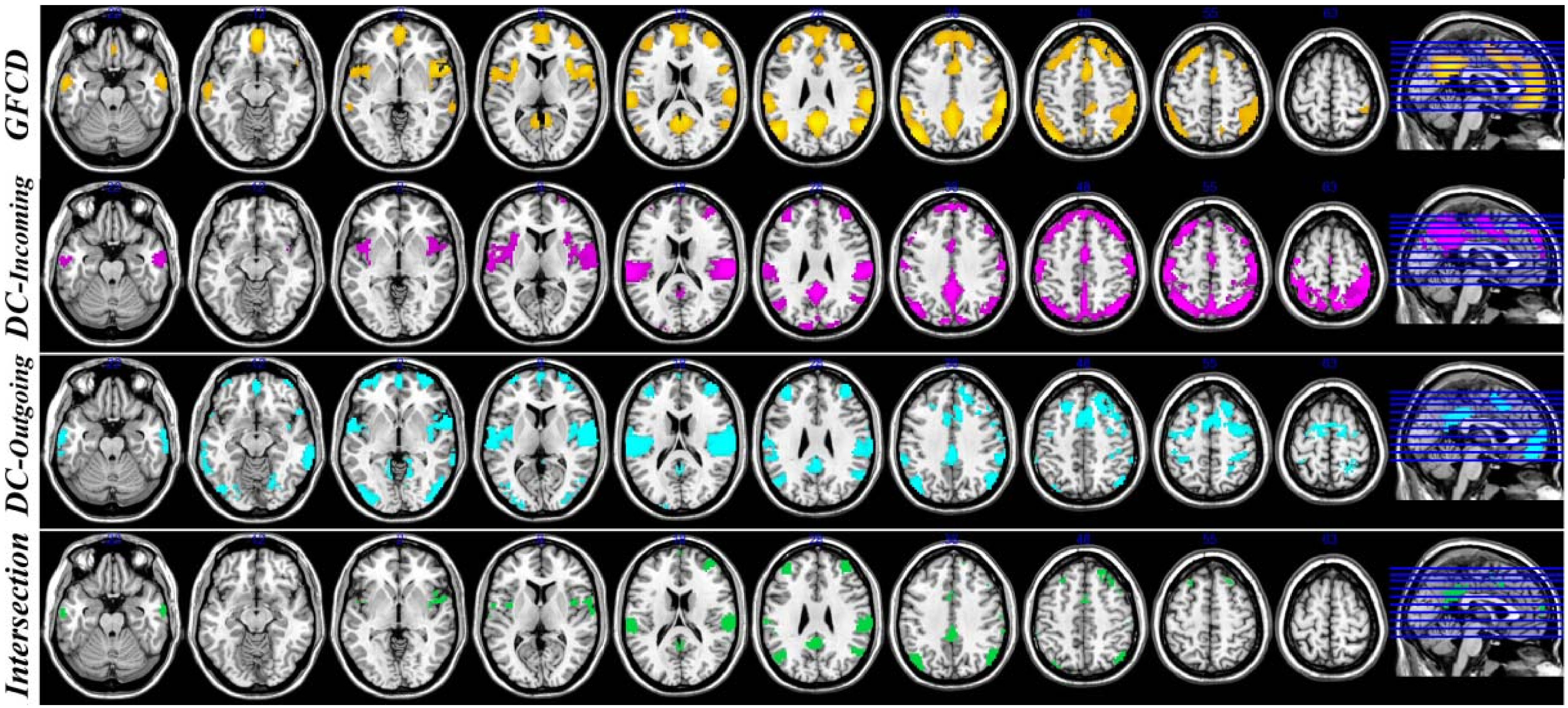
The modular structure of brain networks can as a prior for further dimensionality reduction

Reconstruction of voxel-wise directed networks: hubs for outgoing and incoming information



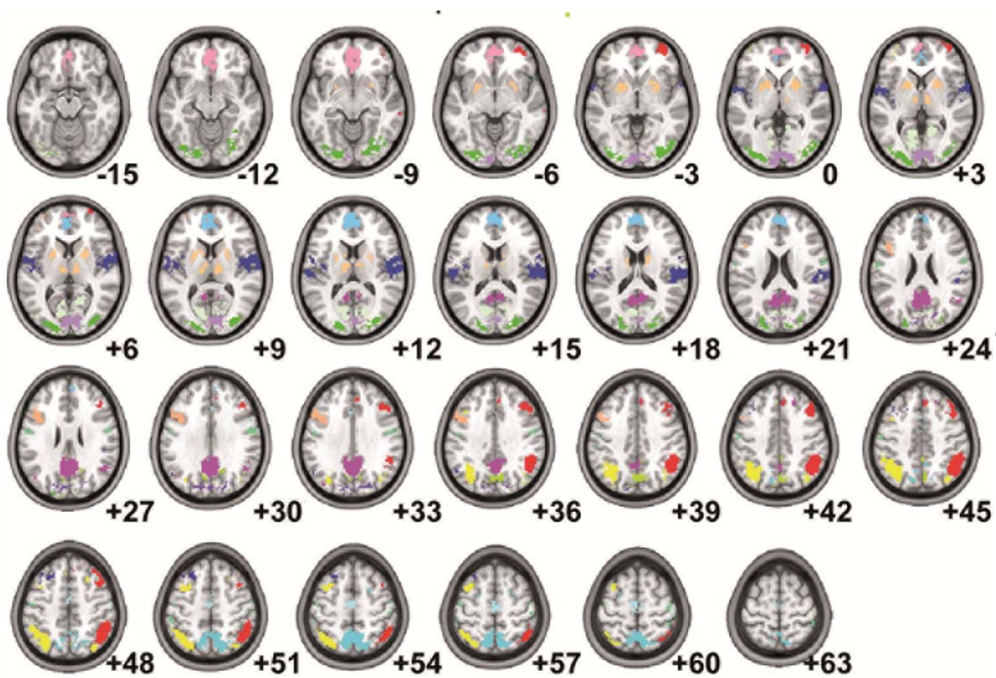
Wu et al. PLOS One 2013

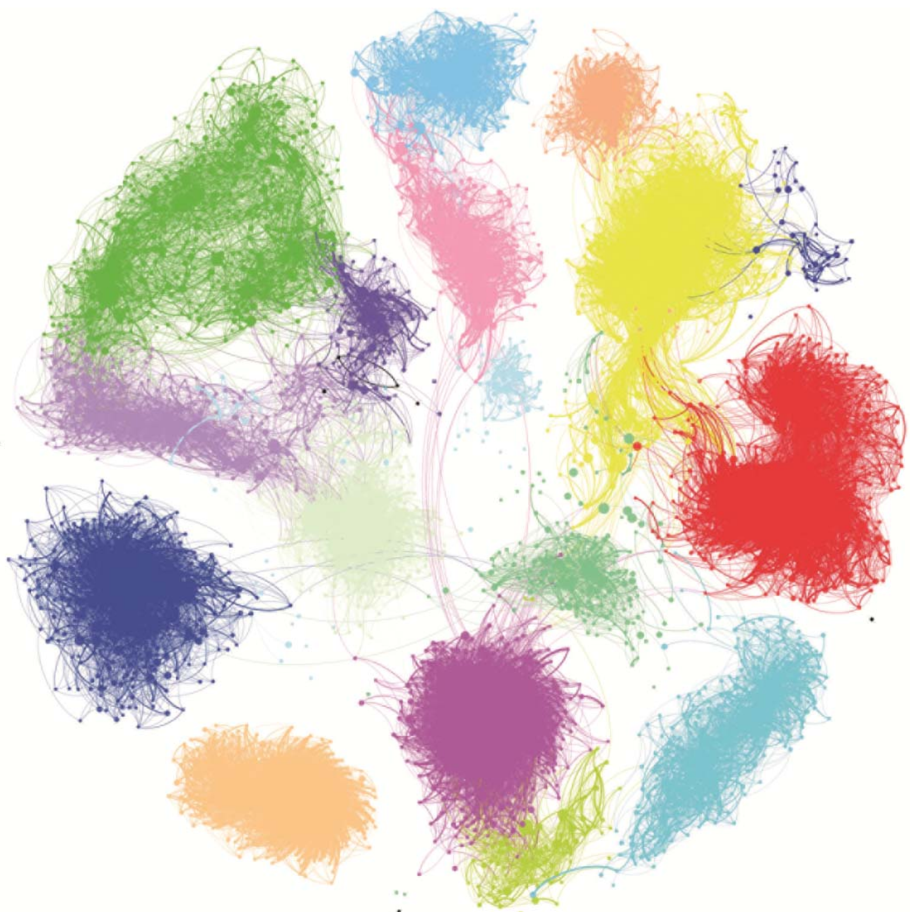
Connectivity density



Wu et al. PLOS One 2013

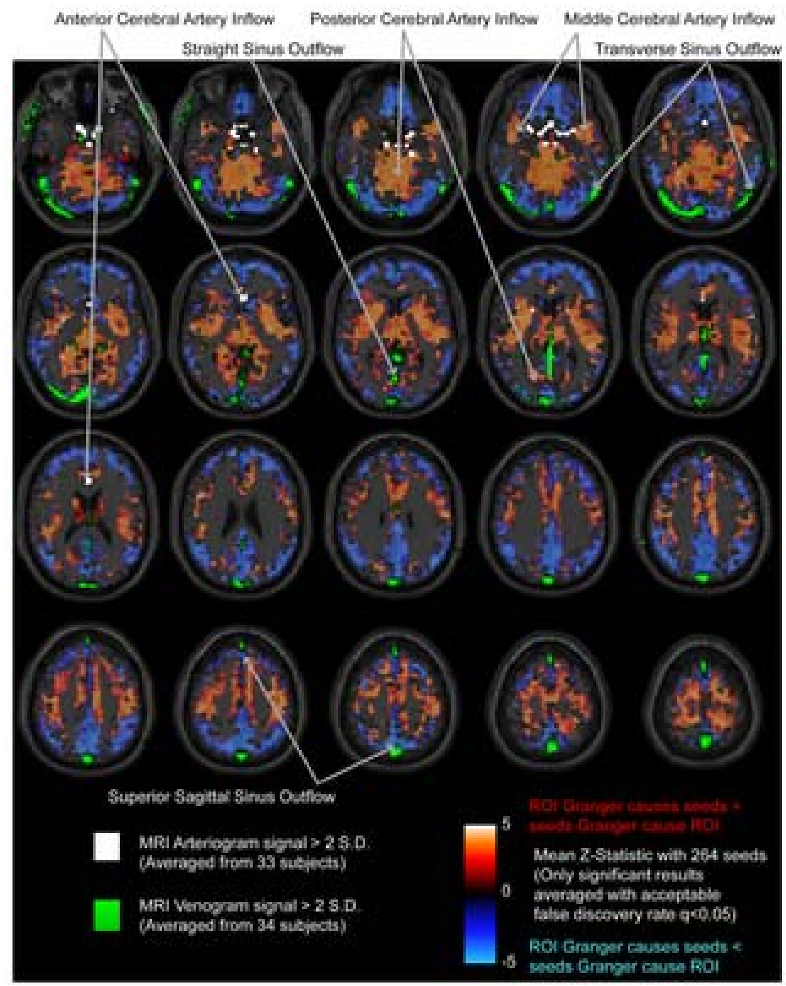
Connectome at voxel level





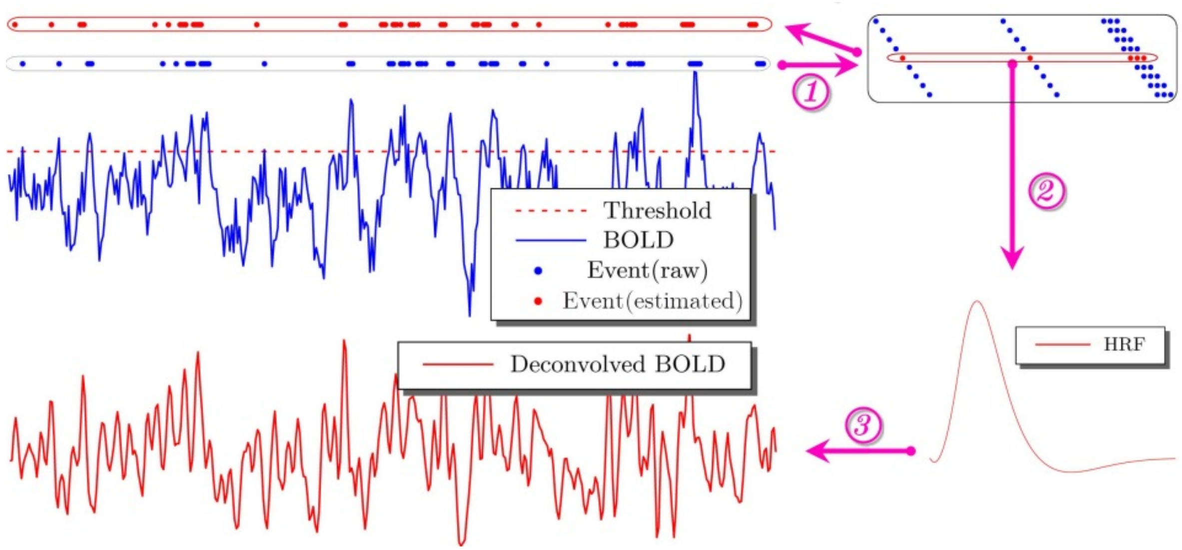
The importance of deconvolution

Alard Roebroeck's talk today, discussion on David et al. 2008



Anderson et al. PLOS One, 2013

Point processes in BOLD signal

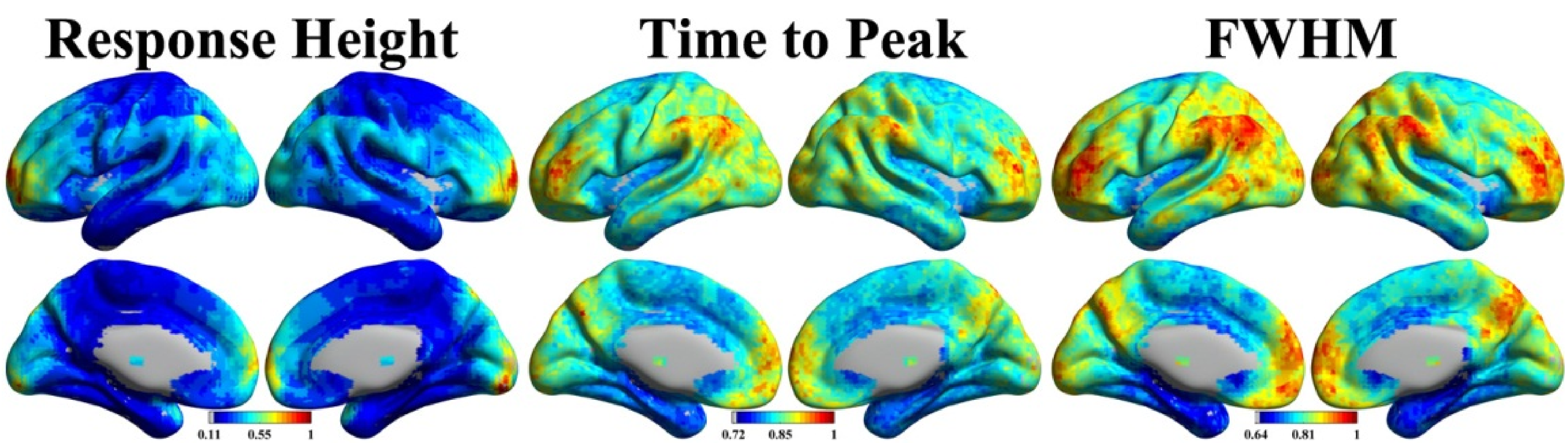


Peak events in BOLD time series can be considered as neural pseudoevents.

Delay from event to BOLD peak by error minimization

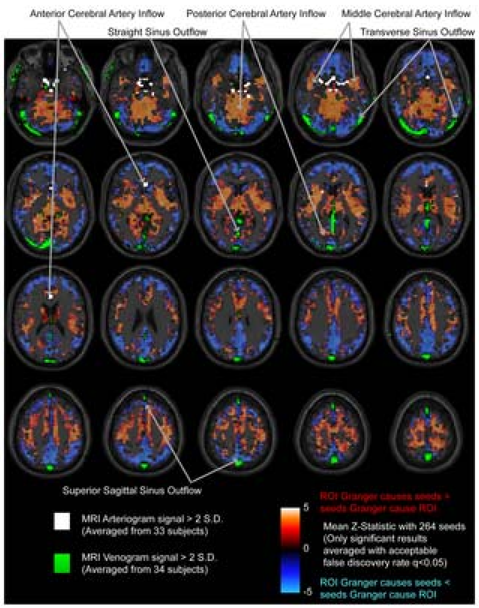
HRF reconstructed as canonical, FIR, or rbeta

Map HRF parameters across the brain

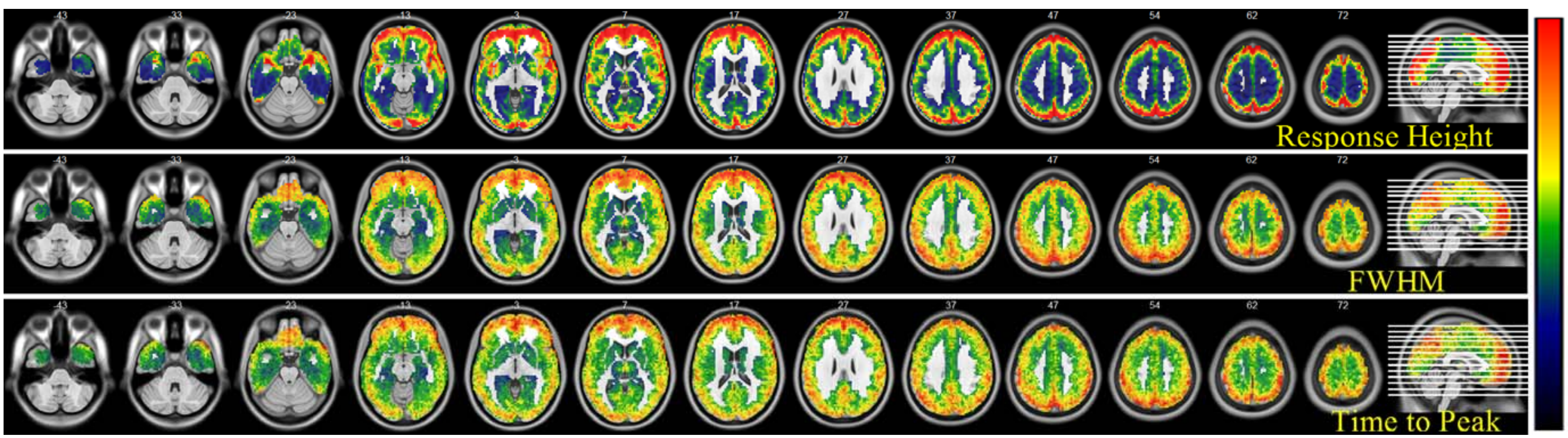


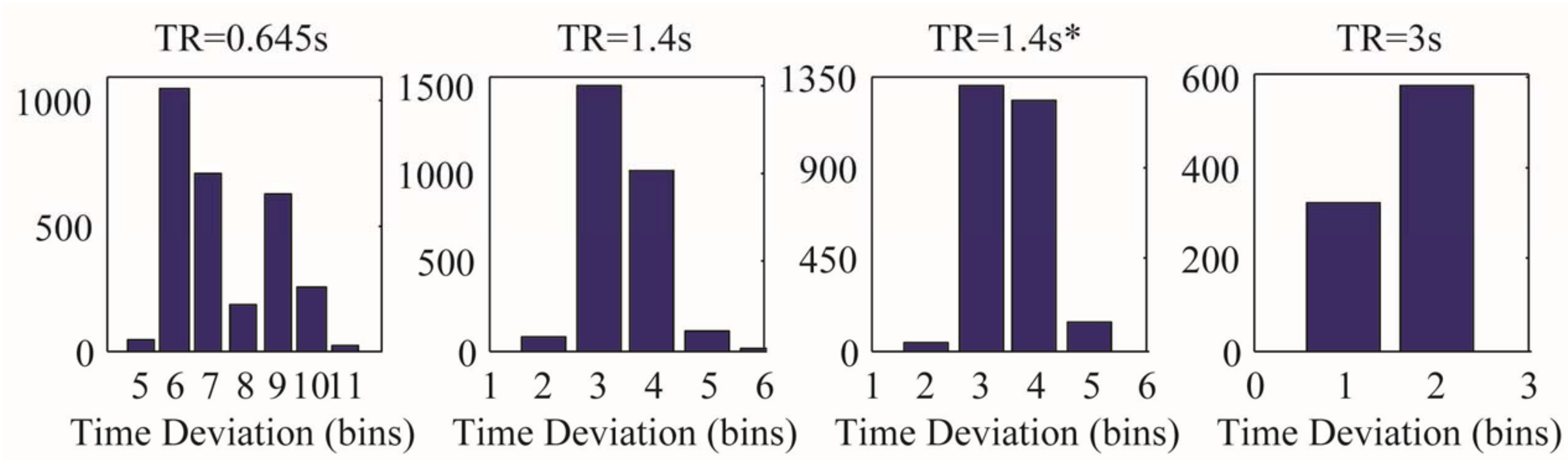
Wu et al. Medical Image Analysis 2013

The importance of deconvolution

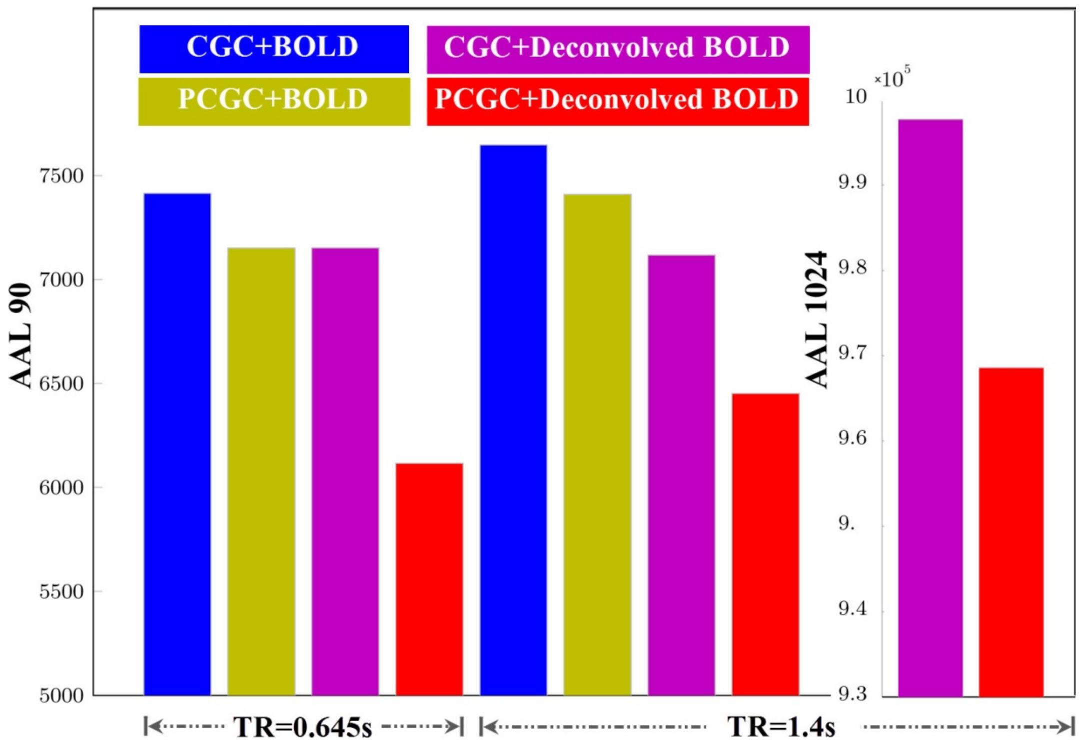


http://figshare.com/articles/HRF_parameter/886139





Distribution of delays between neural onset and bold peak

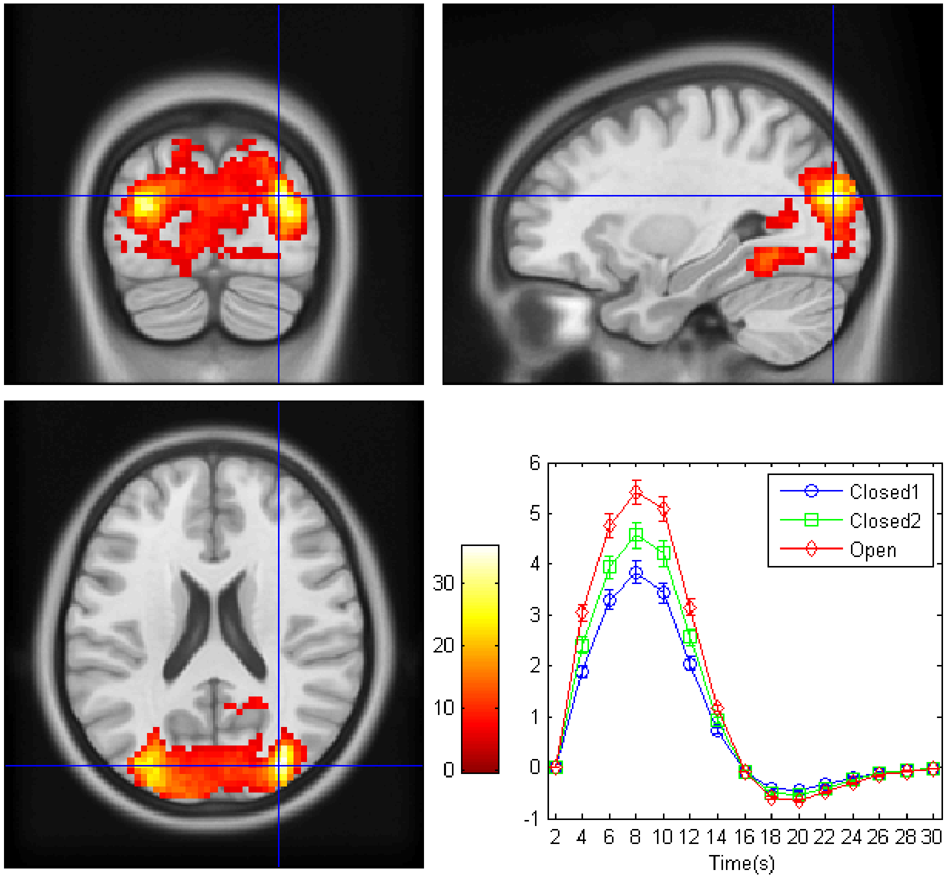


Decreased variance of results with PCGC + deconvolution

Wu et al. Medical Image Analysis 2013

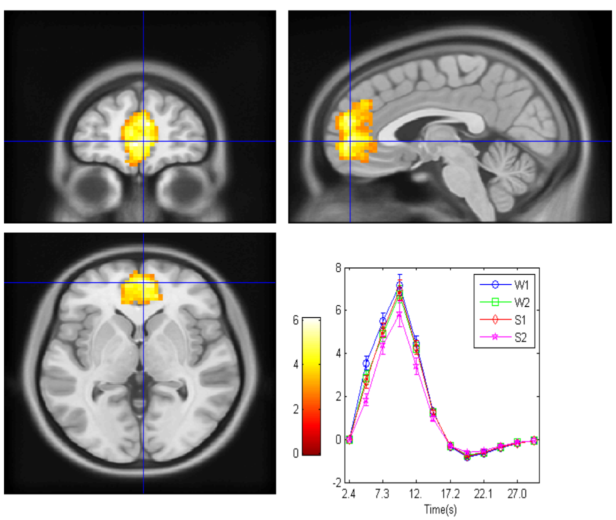
HRF shape as a marker of brain function

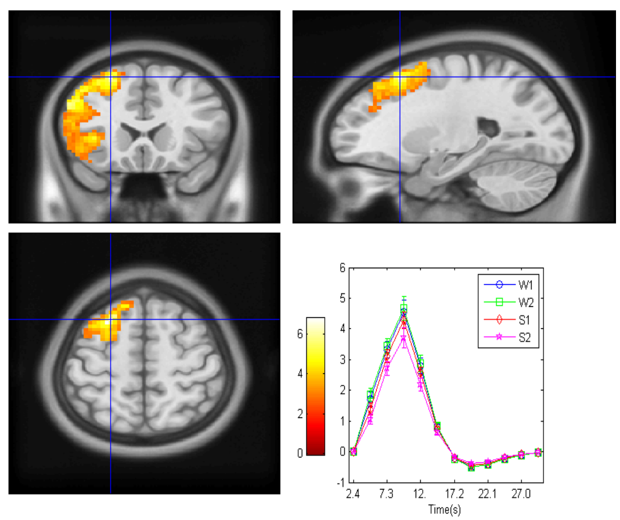
Eyes closed, then open, then closed again

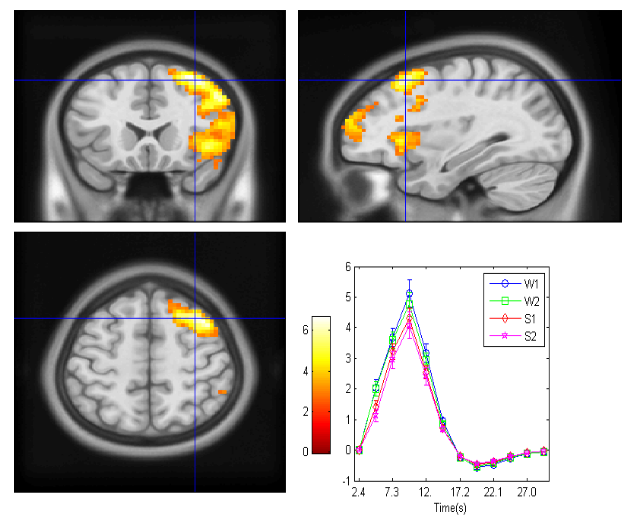


HRF shape as a marker of brain function

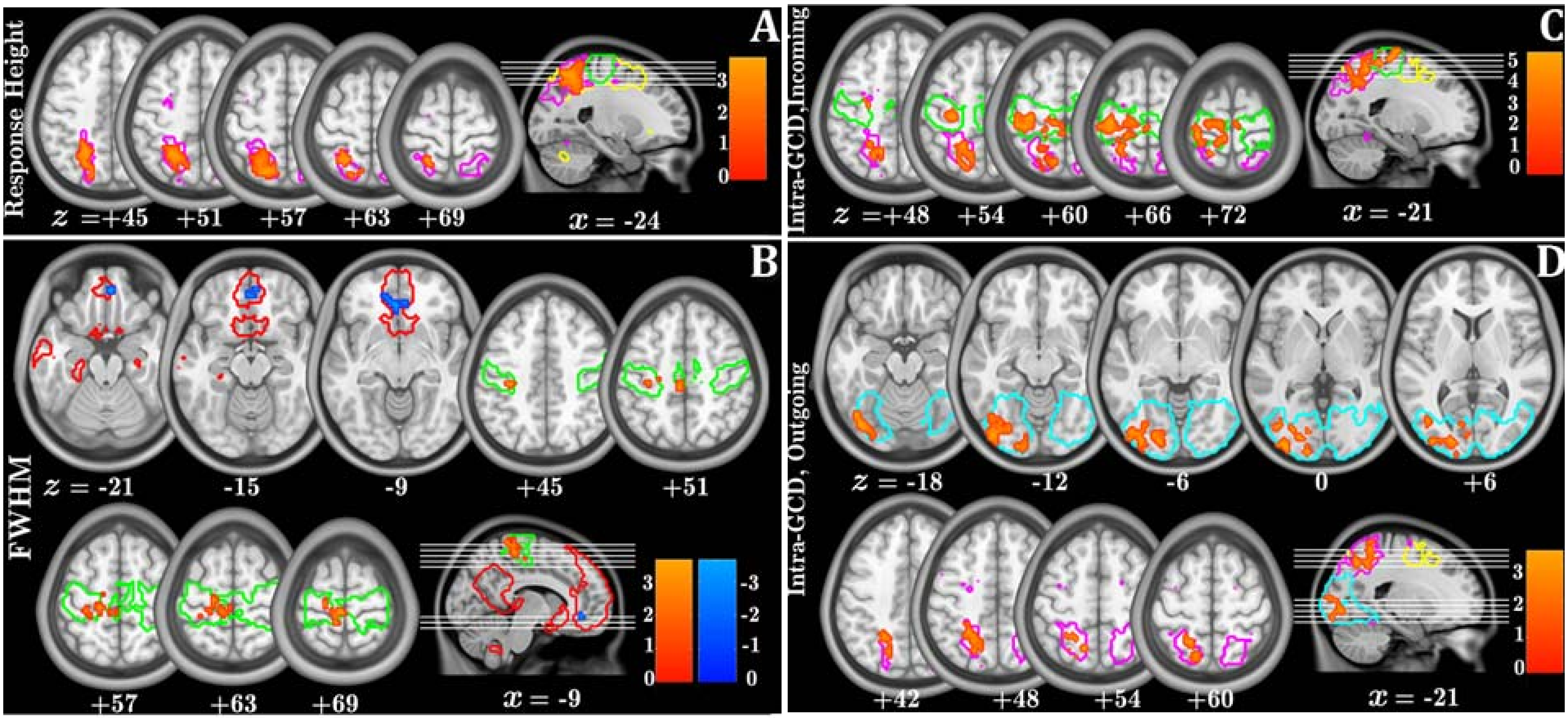
Propofol anesthesia
Wake -> Mild sedation -> Deep sedation -> Recovery of consciousness





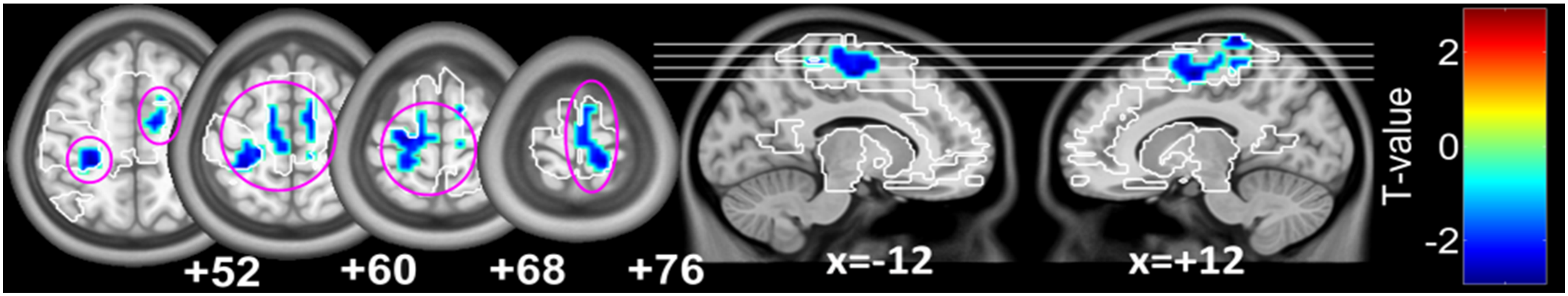


HRF shape and GCD in left handers vs right handers

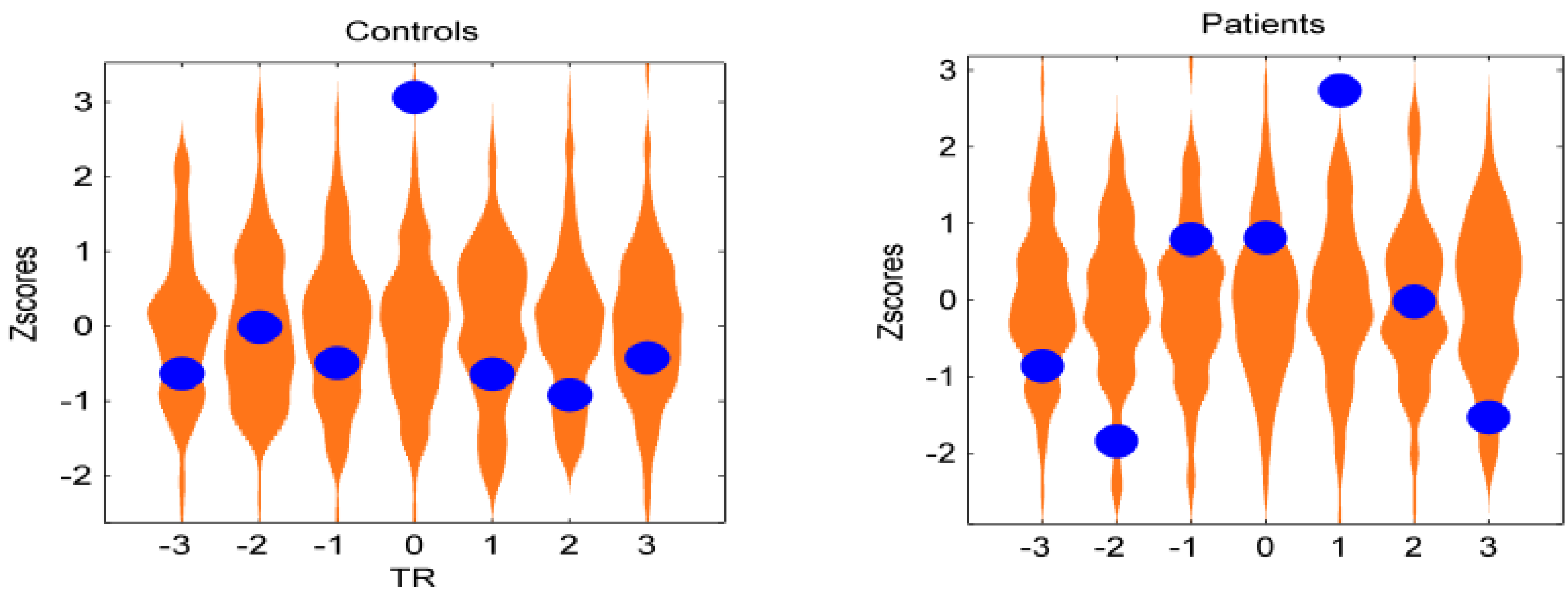


Connectivity from point processes

Probability of an event in the target region after an event in the driver region



Nucleus accumbens-pain matrix: correlation in controls, lagged influence in chronic back pain



Tools

- GCCNT Toolbox (Wu)
- BCT Toolbox (Rubinov and Sporns)
- GAT Toolbox (Hosseini)
- Brainnetviewer (Xia)

The C-word curse

"Every decade or so, a grandiose theory comes along, bearing similar aspirations and often brandishing an ominous-sounding C-name. In the 1960 it was cybernetics. In the '70s it was catastrophe theory. Then came chaos theory in the '80s and complexity theory in the '90s."

Steven Strogatz, *Sync*

- **C**orrelation
- **C**ausality
- **C**onnectivity