Discovering the Human Connectome

Olaf Sporns

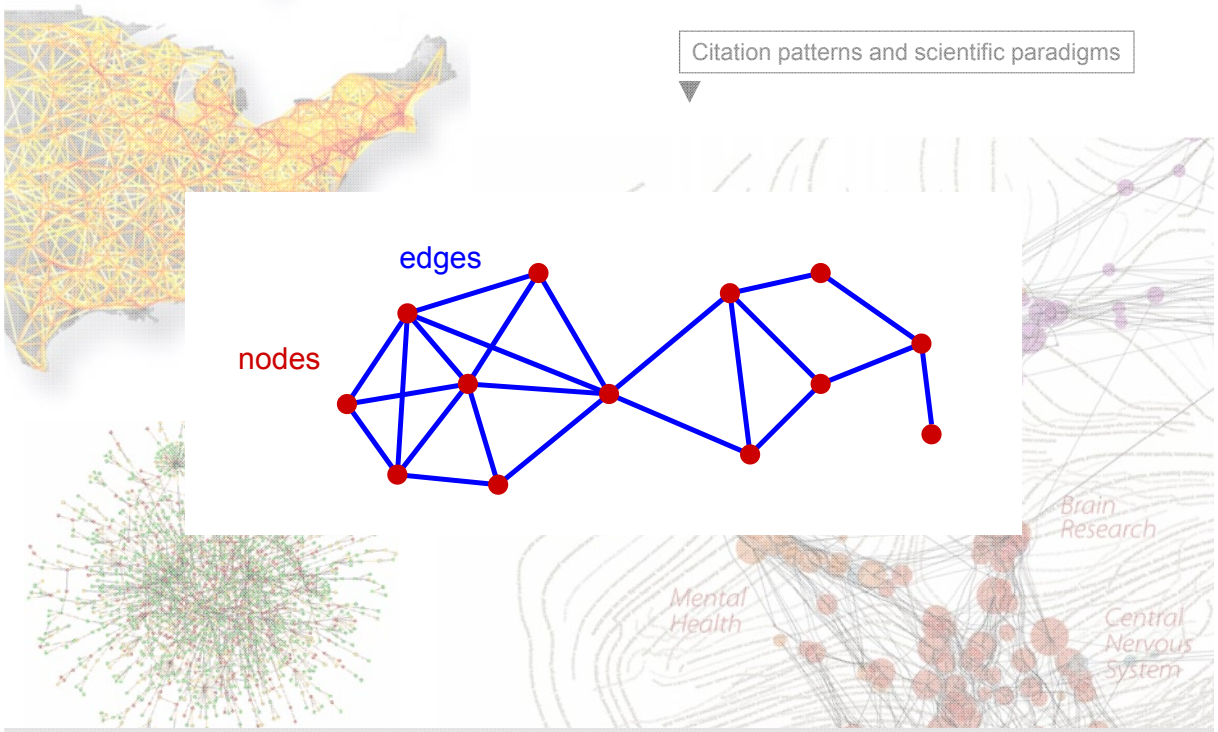
Department of Psychological and Brain Sciences
Indiana University, Bloomington, IN 47405
http://www.indiana.edu/~cortex , osporns@indiana.edu

Brain Connectivity Toolbox
www.brain-connectivity-toolbox.net

Outline

Introduction

Networks as Models of Complex Systems

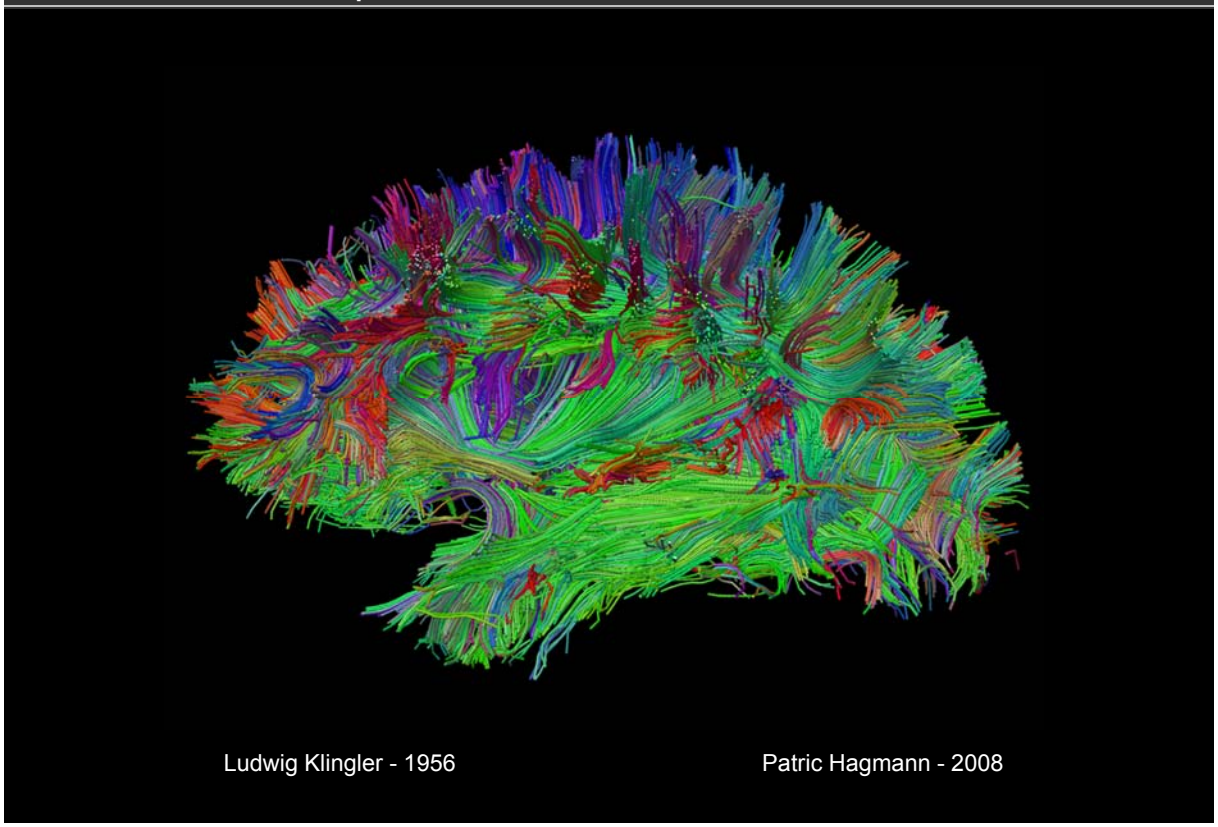


Vespignani (2009) *Science* 325, 425.
Jeong et al. (2001) *Nature* 411, 41

Kevin Boyak, Dick Klavans, Bradford Paley

Introduction

The Brain – A Complex Network



Ludwig Klingler - 1956

Patric Hagmann - 2008

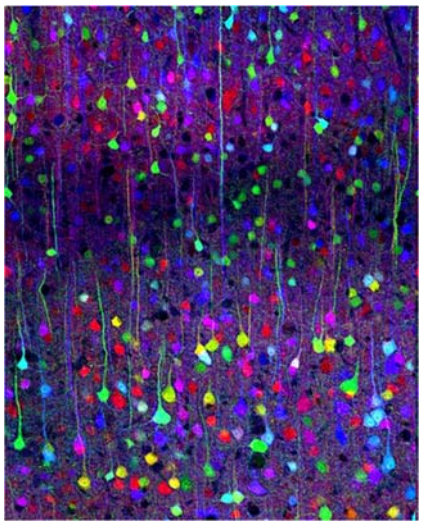
Introduction

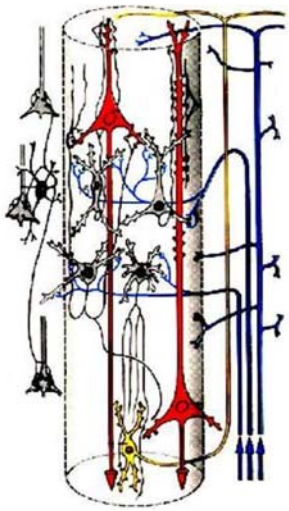
Multiple Scales – Cells, Circuits, Systems

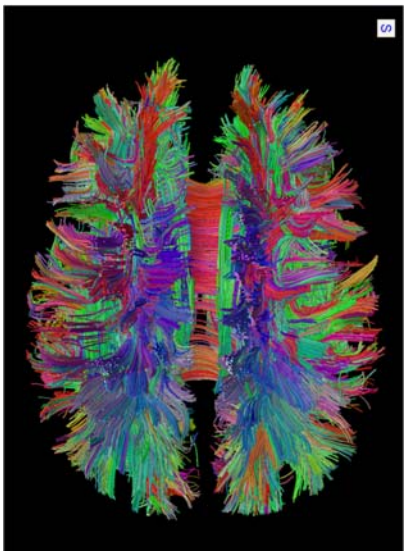
Microscopic: Single neurons and their synaptic connections.

Mesoscopic: Connections within and between microcolumns (minicolumns) or other types of local cell assemblies

Macroscopic: Anatomically segregated brain regions and inter-regional pathways.







Tamily A. Weissman (Harvard University)

Patric Hagmann (EPFL/CHUV Lausanne)

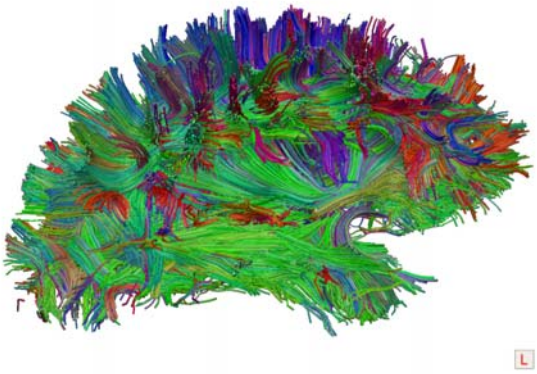
Introduction

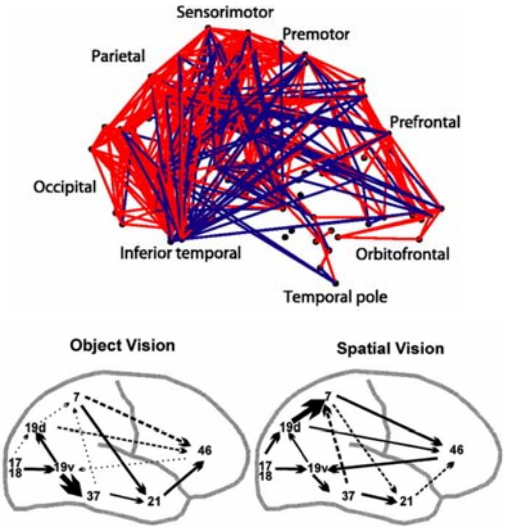
Multiple Modes – Structural, Functional, Effective

Anatomical (Structural) Connectivity: Pattern of structural connections between neurons, neuronal populations, or brain regions.

Functional Connectivity: Pattern of statistical dependencies (e.g. temporal correlations) between distinct (often remote) neuronal elements.

Effective Connectivity: Network of causal effects, combination of functional connectivity and structural model.



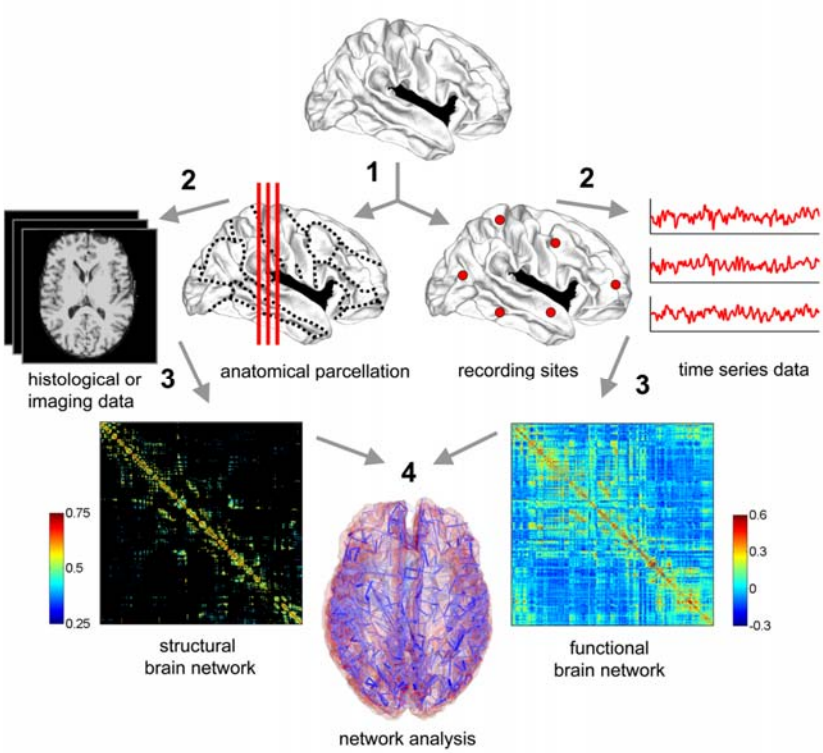


Patric Hagmann (EPFL/CHUV Lausanne)

Achard et al. (2006) *J. Neurosci.* 26, 63
McIntosh et al. (1994) *J. Neurosci.* 14, 655

Introduction

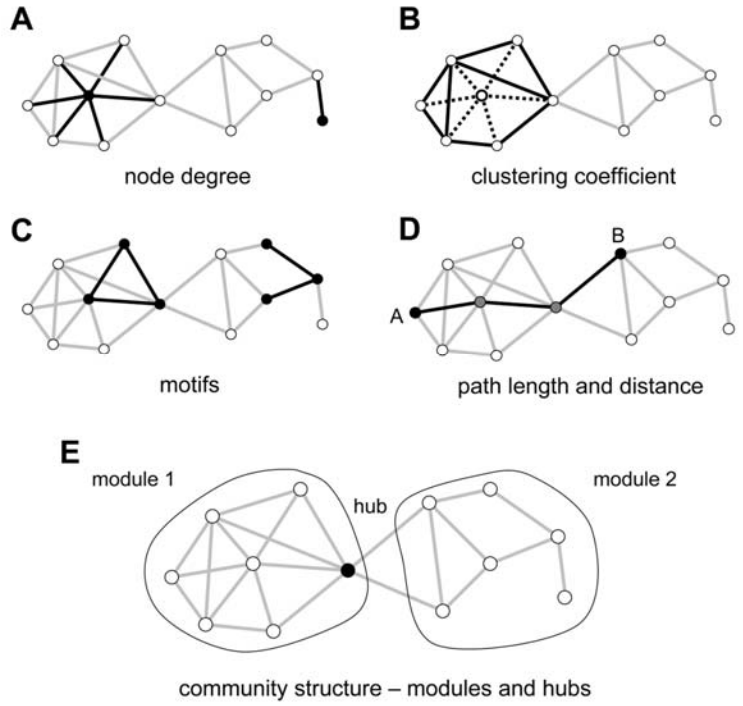
Extraction of Brain Networks from Empirical Data



Bullmore & Sporns (2009) *Nature Rev Neurosci* 10, 186.

Introduction

Graph Theory: Basic Definitions



Graph metrics capture various aspects of local and global connectivity:

Segregation
- Clustering
- Motifs
- Modularity

Integration
- Distance
- Path Length
- Efficiency

Influence
- Degree
- Centrality (Hubs)

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Outline

Introduction

Brain Networks and Graph Theory

Structural Brain Networks

Architecture of Anatomical Networks
Steps Towards the Human Connectome
A “Rich Club” in the Human Brain?

Dynamic Brain Networks

Comparison of Structural and Functional Connectivity
Computational Models of Functional Connectivity
Modeling Brain Lesions

Structural Brain Networks

Anatomical Organization of Cerebral Cortex

	OCCIPITAL									TEMPORAL													PARIETAL									FRONTAL	
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Principles of network architecture in cortex:

Specialization

Integration

Streams (modules)

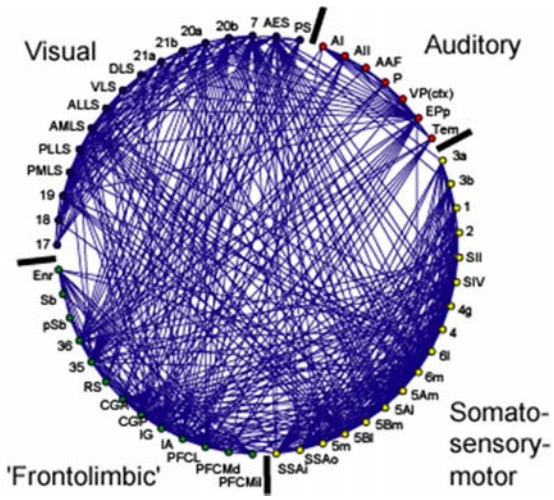
Hierarchy

Felleman and Van Essen (1991) *Cerebral Cortex* 1,1. Van Essen et al. (1992) *Science* 255, 419.

Structural Brain Networks

Modular Brain Networks

Each functionally specialized cortical region has a unique connectional fingerprint – a unique set of inputs and outputs.



Structural modules consist of nodes that have similar connections with other nodes.

Structural modules reflect functional relationships.

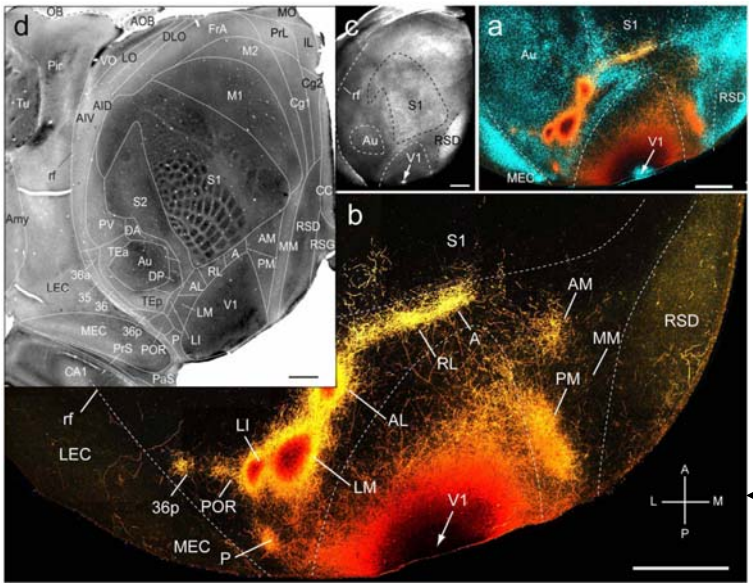
regions and interconnections of cat cerebral cortex

Passingham et al. (2002) Nature Rev Neurosci 3, 606. Hilgetag et al. (2000) *Phil. Trans. Royal Soc. B* 355, 91

Structrual Brain Networks

Modules in Mouse Cortex

Analysis of axonal projections in flat-mounted mouse cortex using the anterograde tracer Biotinylated Dextran Amide (BDA)



Flatmap representation

↓

Optical density

↓

Matrix (network) of projection weights

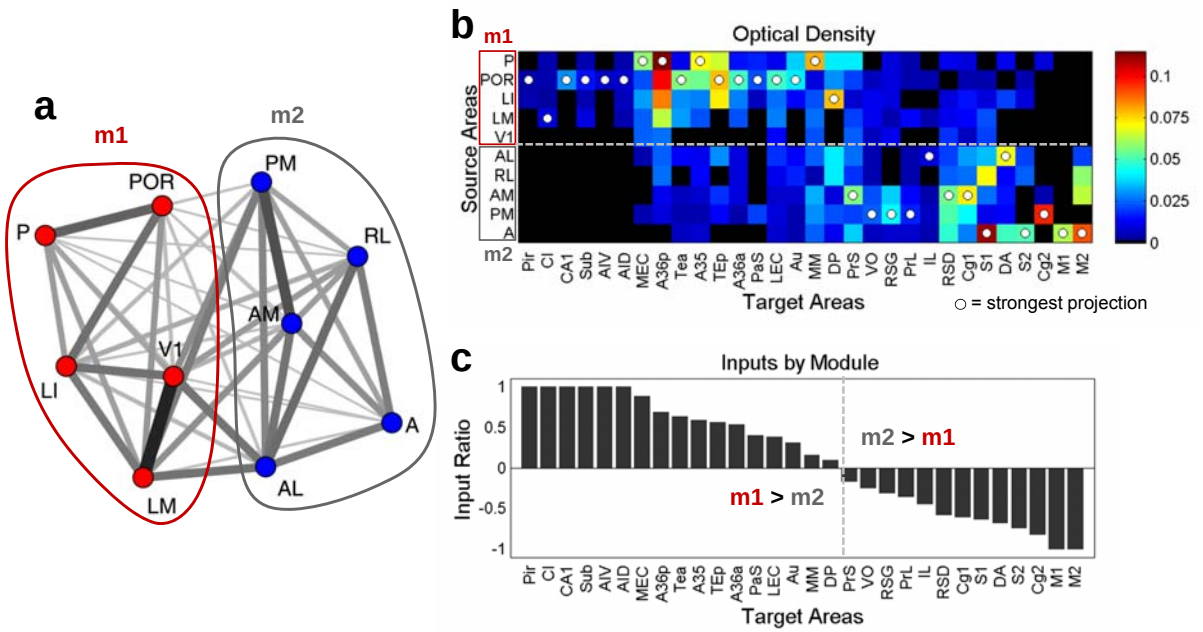
Projections revealed by BDA injection into V1

Wang, Gao & Burkhalter (2011) *J Neurosci* 31,1905 Wang, Sporns & Burkhalter (2012) *J Neurosci* 32, 4386.

Structural Brain Networks

Modules in Mouse Cortex

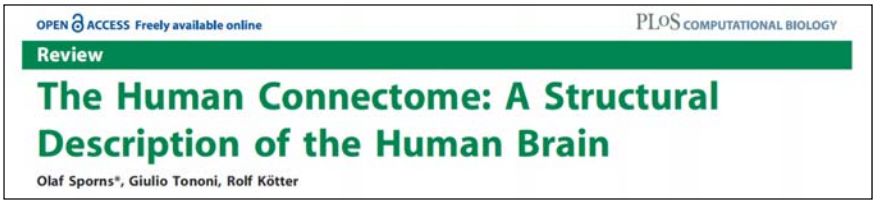
Network analysis of mouse visual cortical projections suggests the existence of analogues to primate ventral and dorsal streams.



Wang & Burkhalter (2011) J Neurosci. Wang, Sporns & Burkhalter (2012) *J Neurosci* 32, 4386.

Structural Brain Networks

The Human Connectome



The connectome can be defined on multiple scales:

- Microscale (neurons, synapses)
- Macroscale (parcellated brain regions, voxels)
- Mesoscale (columns, minicolumns)

Most feasible in humans, with present-day technology:

- macroscale, diffusion imaging
- → central aim of the NIH Human Connectome Project

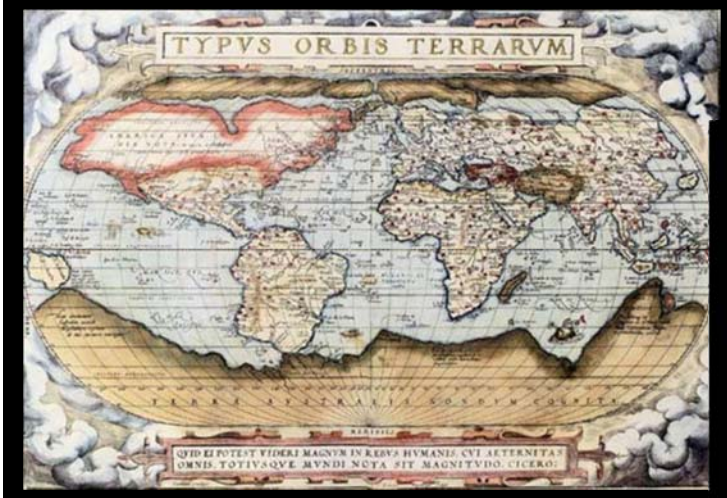
Other methodologies and systems:

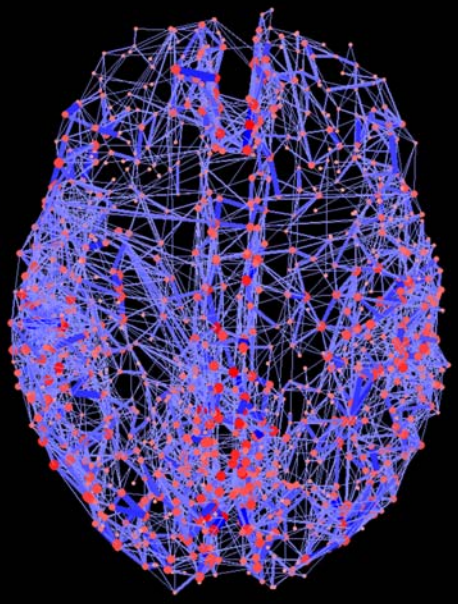
- Mesoscale mapping of mouse brain connectivity (Bohland et al.)
- Microscale mapping of neural circuitry (Lichtman et al.)
- Serial EM reconstruction (Briggman and Denk)

Sporns et al. (2005) *PLoS Comput. Biol*. 1, e42

Structural Brain Networks

Mapping Human Brain Structural Connectivity





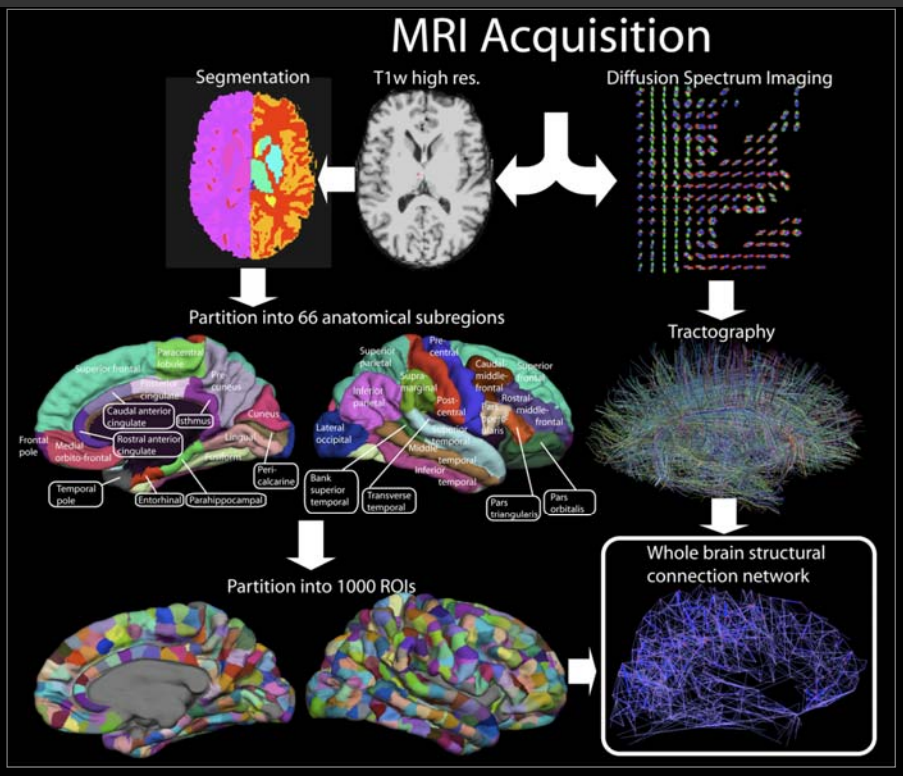
A map of the world, 1572

A map of the connectome, 2008

Hagmann et al. (2008) *PLoS Biol.* 6, e159

Structural Brain Networks

Mapping Human Brain Structural Connectivity



Patric Hagmann

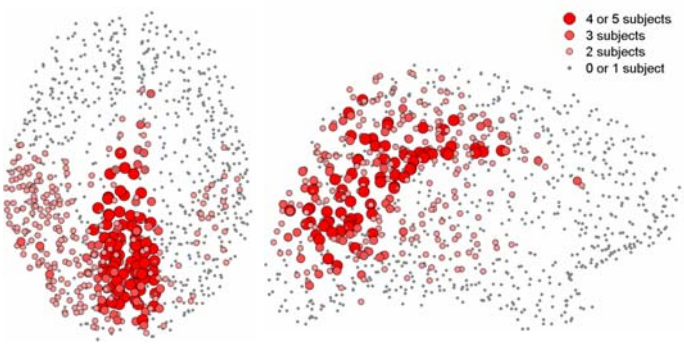
Hagmann et al. (2008) *PLoS Biol.* 6, e159

Structural Brain Networks

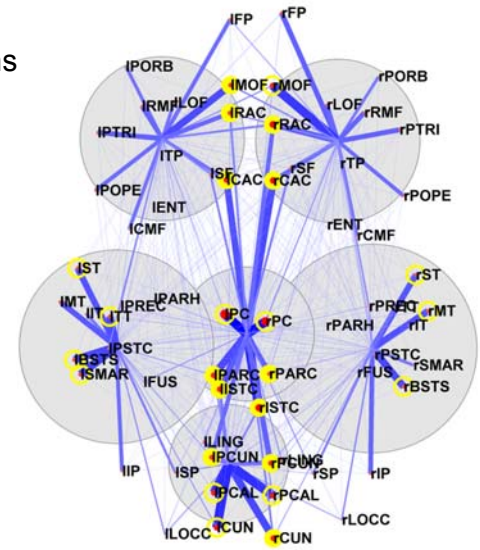
Network Analysis of the Connectome

Network analysis revealed

- Exponential (not scale-free) degree distribution
- Robust small-world attributes
- Several modules interlinked by hub regions
- Positive assortativity
- A prominent structural core



core



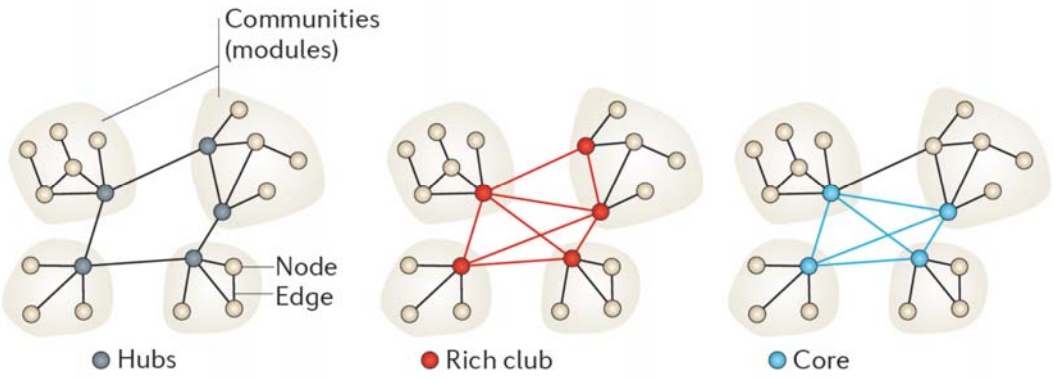
modules

Hagmann et al. (2008) *PLoS Biol.* 6, e159

Structural Brain Networks

Modules, Cores, and Rich Clubs

In some networks, highly connected/central hub nodes have a tendency to be highly connected to each other ("rich-club" organization).



Colizza et al. (2006) *Nature Physics*

Bullmore and Sporns (2012) *Nature Rev Neurosci*

Structural Brain Networks

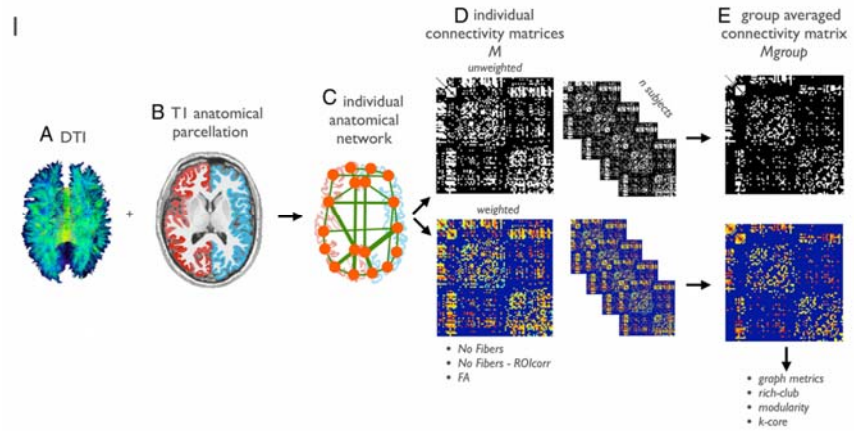
Rich-Club Organization of the Human Connectome

Human connectome data sets exhibit a prominent rich club, comprising cortical and subcortical regions.

Presence of rich-club (RC) organization suggests central role in information integration and communication.

DTI study, 21 participants, low (82 nodes) and high-resolution (1170 nodes) partition, streamline tractography

Martijn van den Heuvel

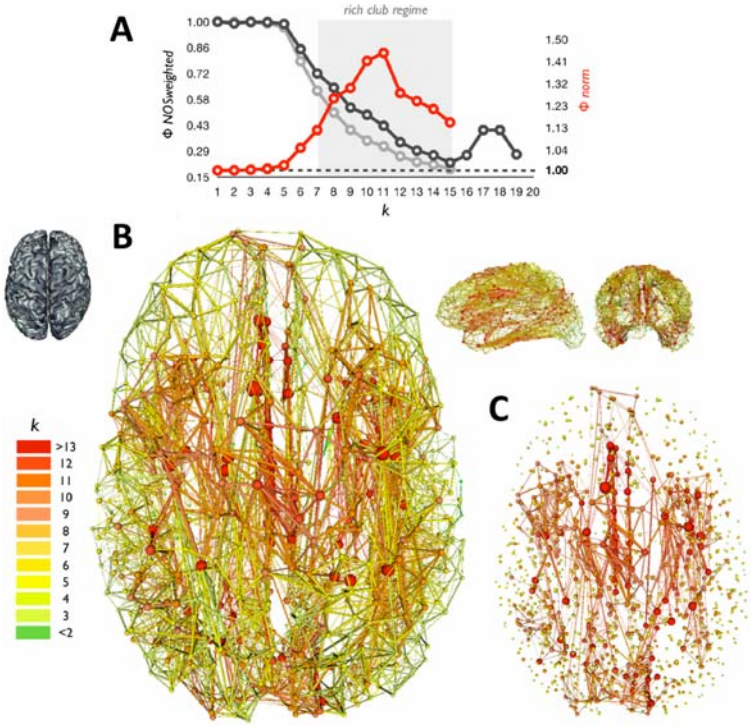


Colizza et al. (2006) Nature Physics

van den Heuvel and Sporns (2011) J. Neurosci.

Structural Brain Networks

Rich-Club Organization of the Human Connectome



RC members include: precuneus, superior parietal and frontal cortex, insula, medial temporal regions

Large proportion of short communication paths travel trough RC

RC damage has disproportionate effects on network integrity

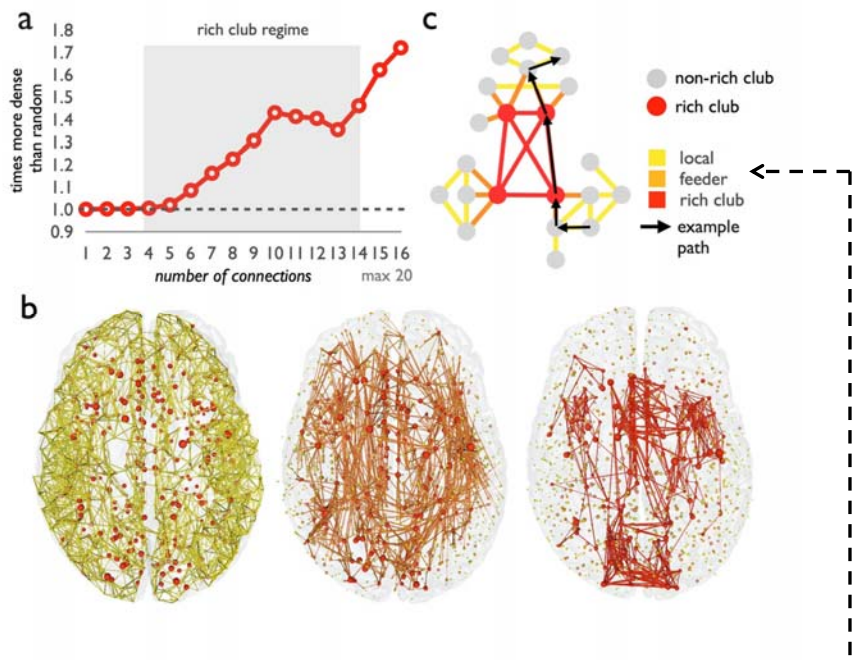
Colizza et al. (2006) *Nature Physics*

van den Heuvel and Sporns (2011) *J. Neurosci.*

Structural Brain Networks

Rich-Club Organization of the Human Connectome

Replication →

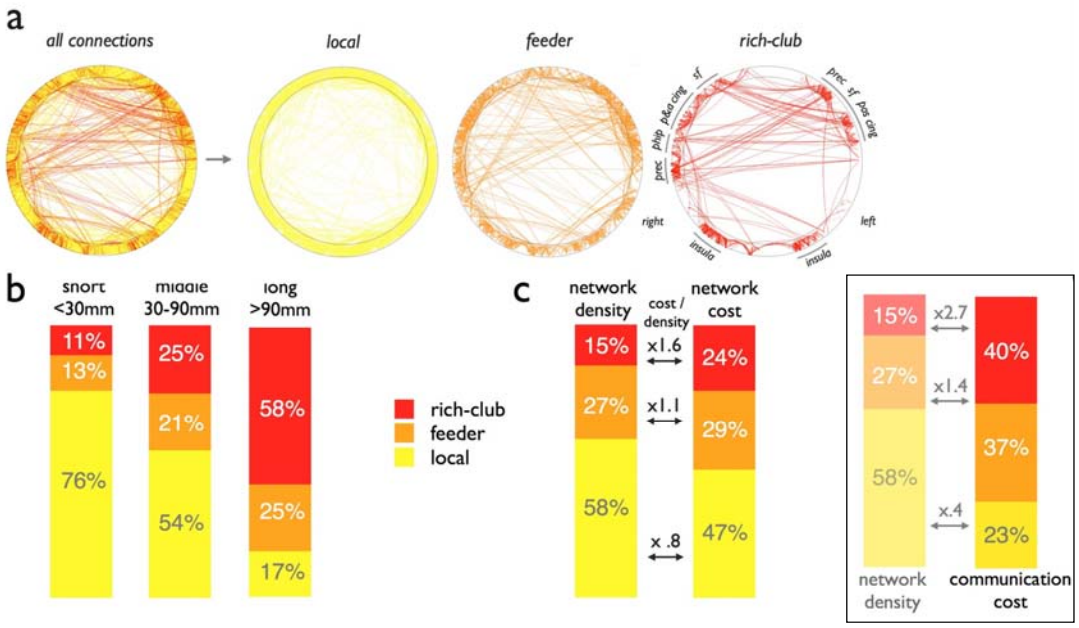


Once the RC is identified, connections can be classified as RC, feeder, local.

Van den Heuvel et al. (2012) PNAS

Structural Brain Networks

Rich-Club Organization of the Human Connectome



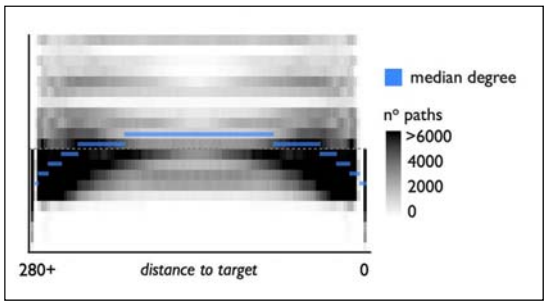
RC connections are mainly long-distance, and thus represent a high-cost feature of cortical organization – they also account for a large share of short paths.

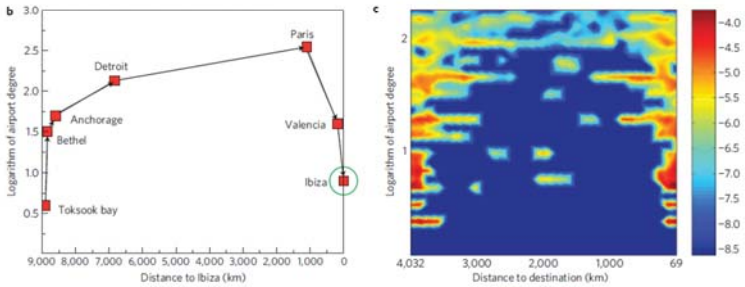
Van den Heuvel et al. (2012) PNAS

Structural Brain Networks

Rich-Club Organization of the Human Connectome

Hidden metric spaces enable "greedy routing" strategies in large communication networks (e.g. air travel)





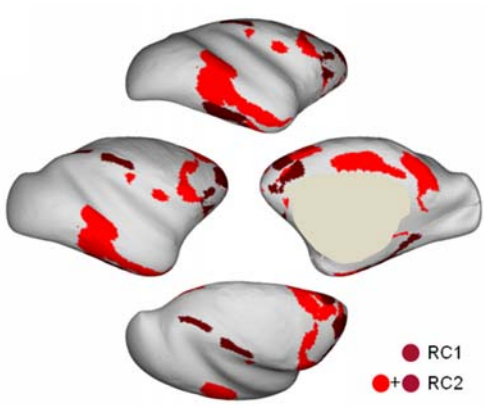
Short paths in human brain structural networks exhibit patterned degree sequences, with a central role of RC nodes and edges.

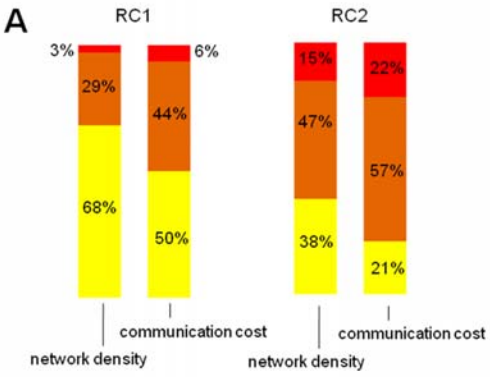
Boguna et al. (2009) *Nature Physics* 5, 74. Van den Heuvel et al. (2012) *Proc Natl Acad Sci USA*

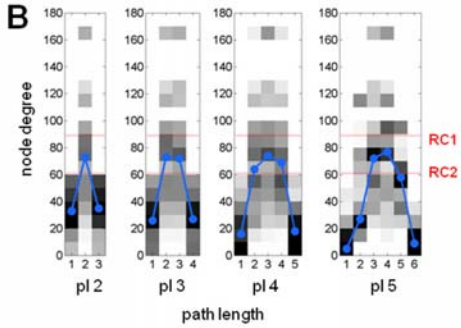
Structural Brain Networks

Rich-Club Organization of the Human Connectome

RC is detected also in macaque cerebral cortex – with similar high-cost features and central involvement of the RC in short paths, and with degree-ordering suggestive of "greedy routing".







Harriger et al. (2012) PLoS ONE

Outline

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A “Rich Club” in the Human Brain?

Dynamic Brain Networks

Comparison of Structural and Functional Connectivity
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Dynamic Brain Networks

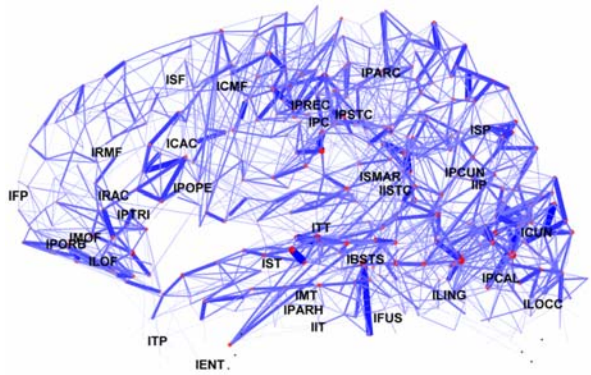
Wiring and Dynamics – Complex Interrelations

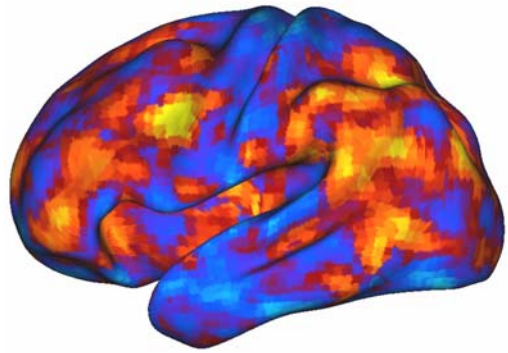
Structural connectivity is (relatively) stable across time.

Functional connectivity is dynamic (endogenous/exogenous).

How much of functional connectivity can be predicted from structural connectivity?

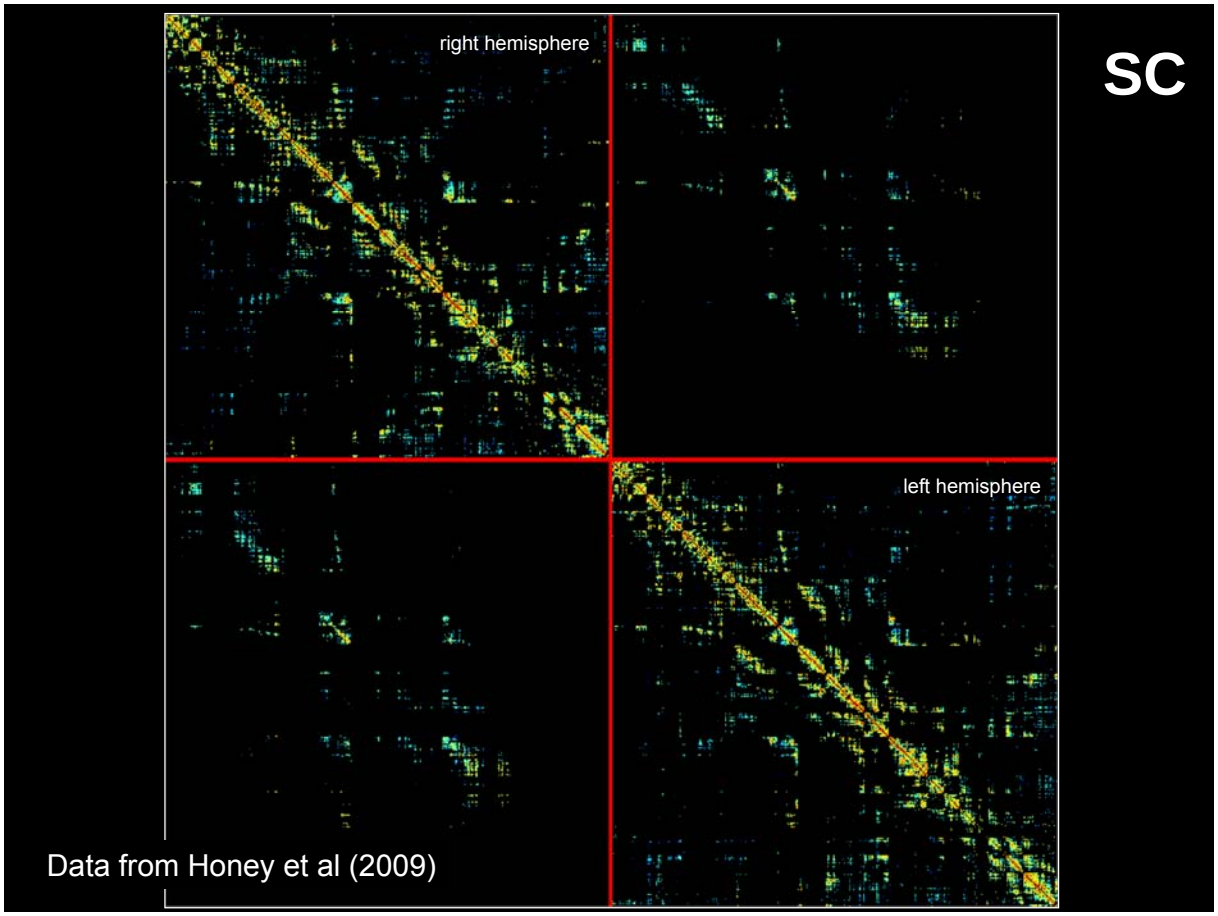
What is the contribution of network theory and modeling in understanding the nature of brain dynamics?

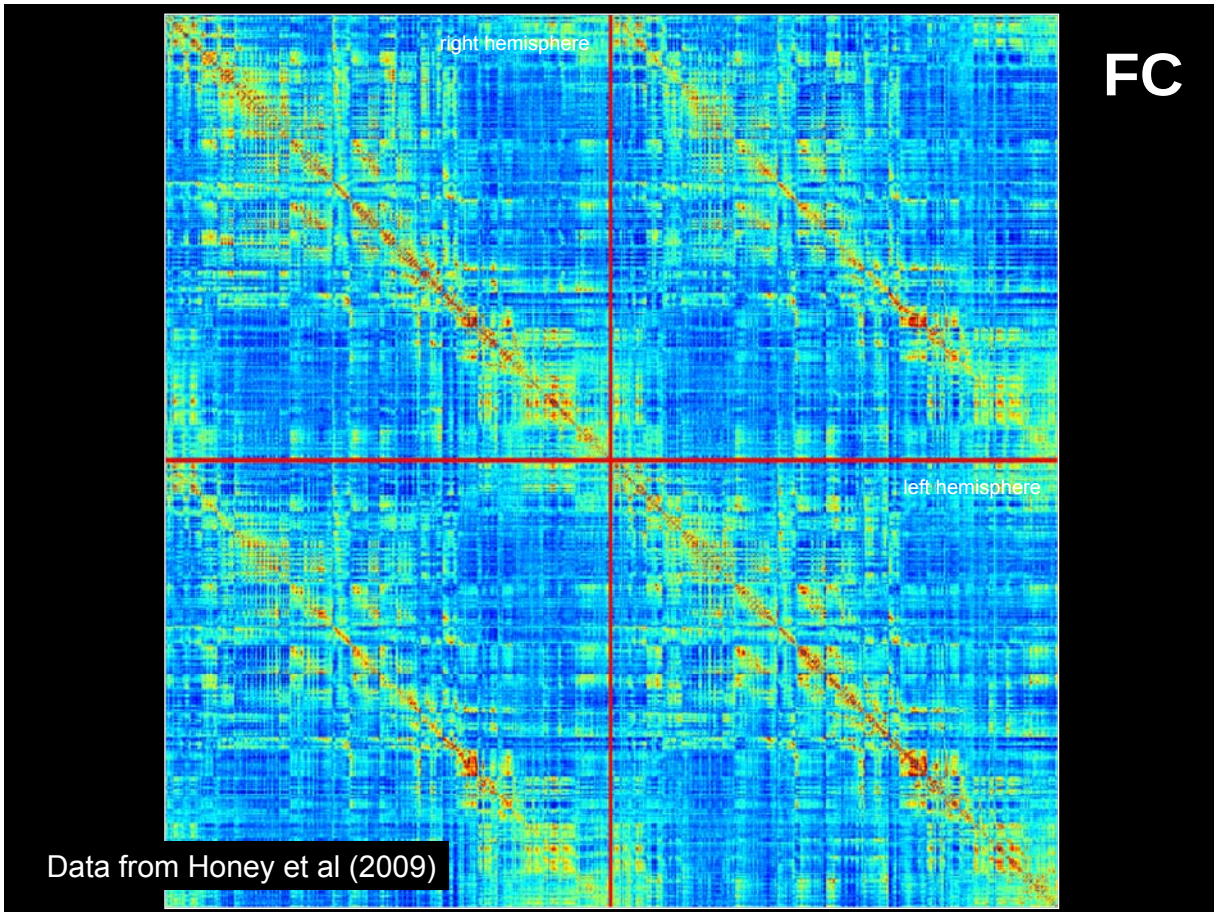




Hagmann et al. (2008) *PLoS Biol.* 6, e159

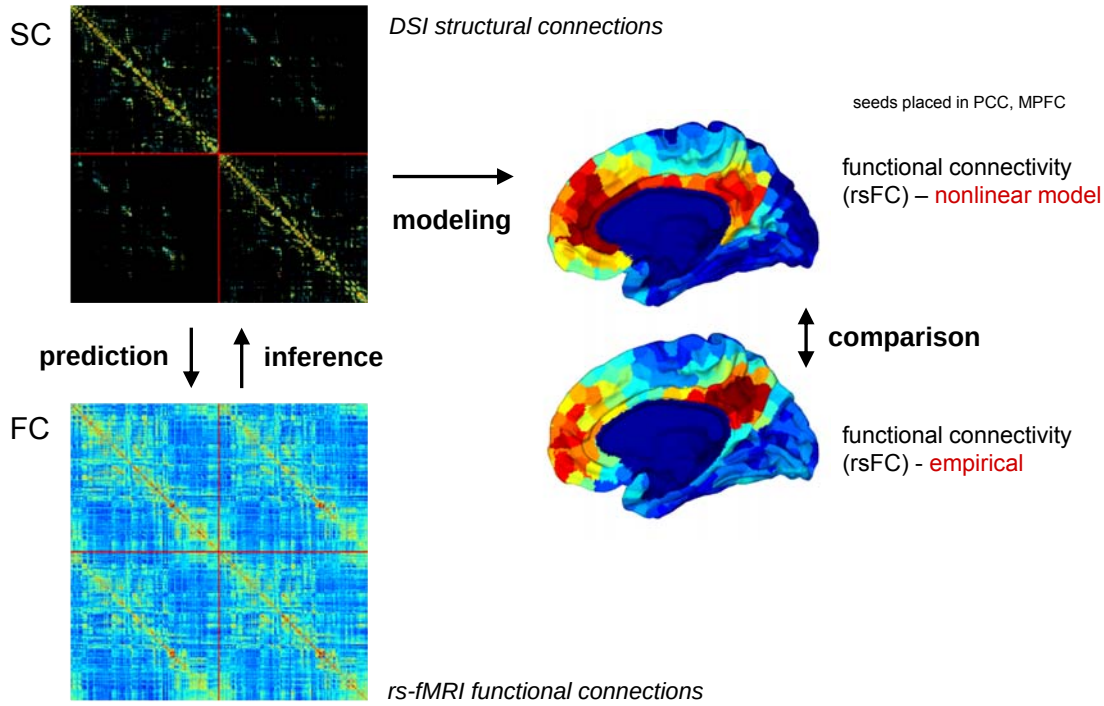
Movie: Vincent, Raichle et al. (Washington University)


right hemisphere
left hemisphere
SC
Data from Honey et al (2009)


right hemisphere
left hemisphere
FC
Data from Honey et al (2009)

Dynamic Brain Networks

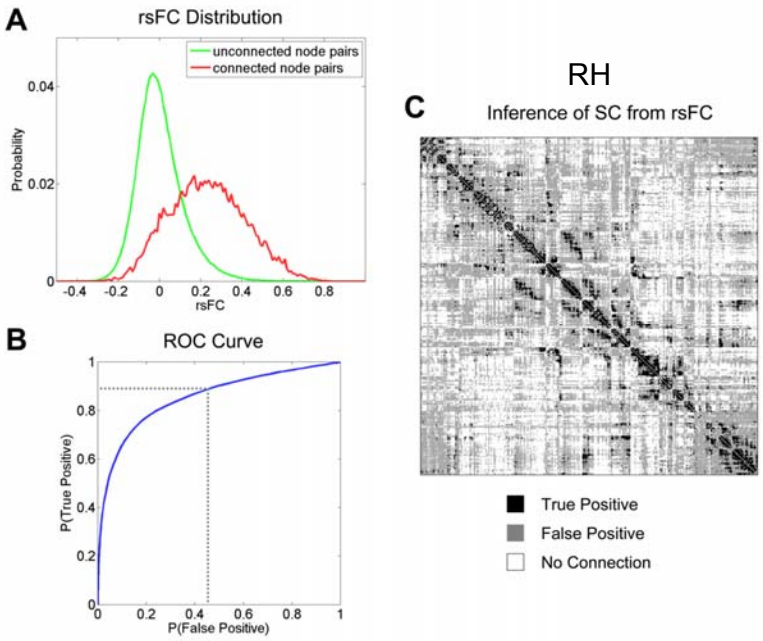
Wiring and Dynamics – Human Brain



Honey et al. (2009) *PNAS* 106, 2035.

Dynamic Brain Networks

Direct Comparison of Structural and Functional Connections



Thresholding rsFC does not allow the reliable inference of SC.

Honey et al. (2009) *PNAS* 106, 2035. Sporns (2011) *Ann NY Acad Sci* 1224, 109.

Dynamic Brain Networks

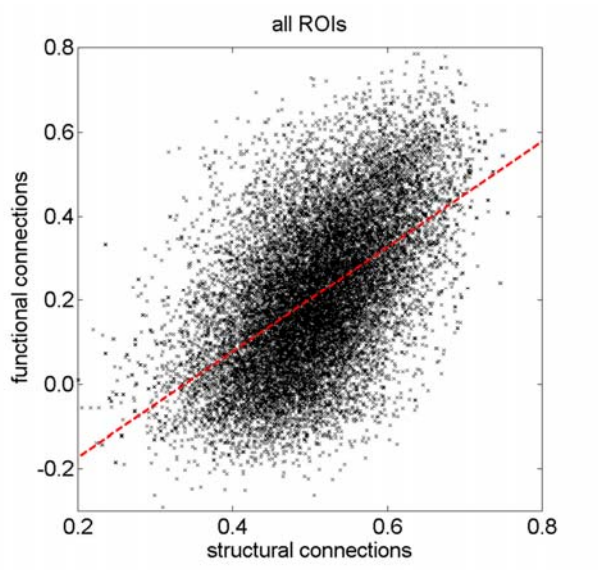
Direct Comparison of Structural and Functional Connections

Where SC is present, its strength is partially predictive of the strength of rsFC on the same node pair.

The strength of the prediction ranges from R ≈ 0.50 (998 nodes; R ≈ 0.4-0.45 in single participants) to R ≈ 0.72 (66 nodes), and persists when physical distance between nodes is regressed out.

Significant variance is unaccounted for by the strength of direct SC. Indirect SC improves prediction.

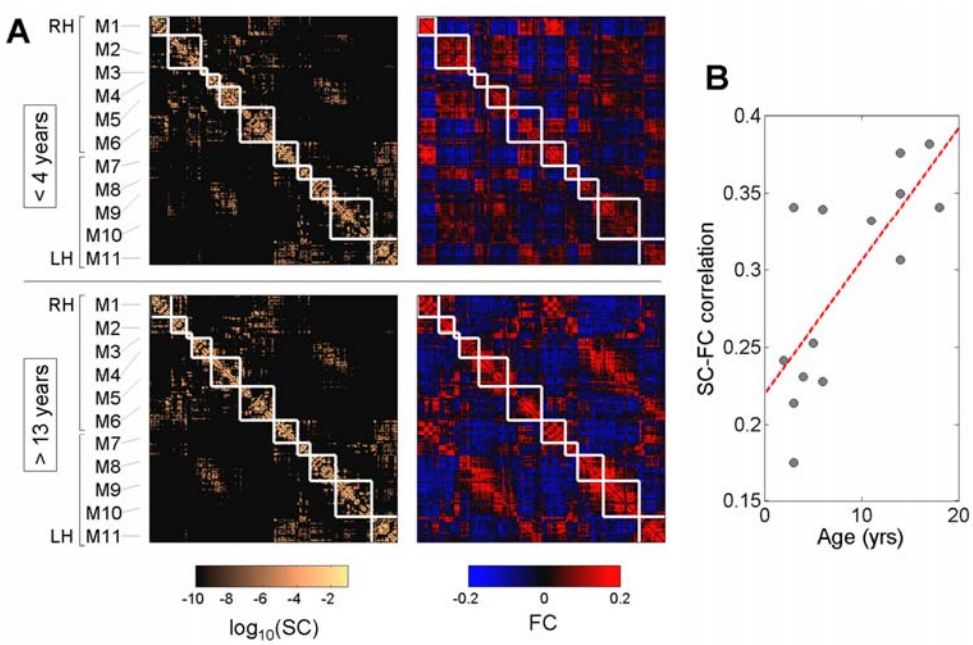
All Participants, All Areas



Hagmann et al. (2008) *PLoS Biol.* 6, e159. Honey et al. (2009) *PNAS* 106, 2035.

Dynamic Brain Networks

Direct Comparison of Structural and Functional Connections



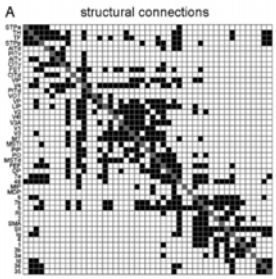
The strength of the SC/rsFC relationship increases during development (ages 2-18 years)

Hagmann et al. (2010) *Proc. Natl. Acad. Sci USA 107, 19067.*

Dynamic Brain Networks

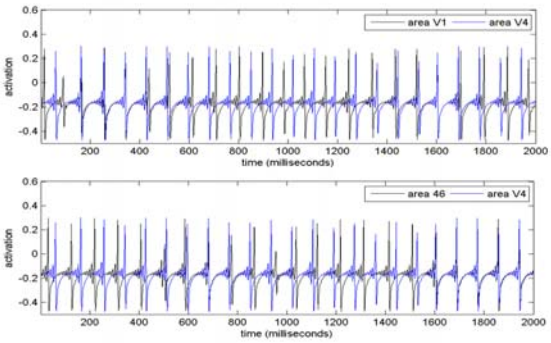
Modeling Endogenous Brain Activity

Connectivity + Dynamics = Endogenous Brain Activity



Connection matrix of visual/sensorimotor macaque cortex
+
Dynamic equations describing the physiology of a neural population (neural mass)

$$\frac{dV(\mathbf{x}_i)}{dt} = -\left(g_{Ca} + (1-c)r_{NMDA}a_{ee}Q_V(\mathbf{x}_i) + cr_{NMDA}a_{ee} < Q_V(\mathbf{x}) >\right)m_{Ca}\left(V(\mathbf{x}_i) - V_{Ca}\right) - g_K W\left(V(\mathbf{x}_i) - V_K\right)$$
$$- g_L\left(V(\mathbf{x}_i) - V_L\right) - \left(g_{na}m_{na} + (1-c)a_{ee}Q_V(\mathbf{x}_i) + ca_{ee} < Q_V(\mathbf{x}) >\right)\left(V(\mathbf{x}_i) - V_{na}\right) \qquad \text{(A6)}$$
$$+ a_{ie}ZQ_Z(\mathbf{x}_i) + a_{ne}I_\delta,$$



=
Spontaneous (endogenous) neural dynamics (chaoticity, metastability)

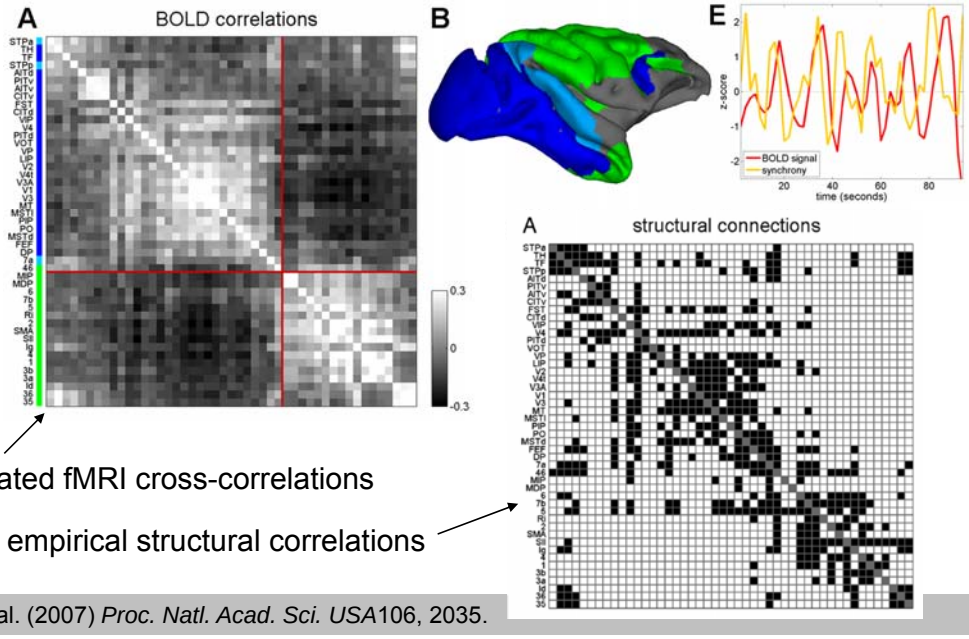
Honey et al. (2007) *Proc. Natl. Acad. Sci. USA*106, 2035.

Dynamic Brain Networks

Modeling Endogenous Brain Activity

Functional brain networks (simulated BOLD fluctuations) reflect the network architecture of their underlying structural substrate (structural/functional modularity).

Fast fluctuations in neural synchrony → slow fluctuations in neural population activity.



simulated fMRI cross-correlations

empirical structural correlations

Honey et al. (2007) *Proc. Natl. Acad. Sci. USA*106, 2035.

Dynamic Brain Networks

Model Comparison with Macaque fMRI

Cerebral Cortex
doi:10.1093/cercor/bhr234

Functional Connectivity between Anatomically Unconnected Areas Is Shaped by Collective Network-Level Effects in the Macaque Cortex

Yusuke Adachi[1], Takahiro Osada[1], Olaf Sporns[2], Takamitsu Watanabe[1], Teppei Matsui[1,3], Kentaro Miyamoto[1] and Yasushi Miyashita[1,3]

[1]Department of Physiology, The University of Tokyo School of Medicine, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, [2]Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN 47405, USA and [3]Department of Physics, The University of Tokyo School of Science, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Central question: What determines the strength of FC, particularly across unconnected regions?

Data: Recordings of BOLD-fMRI (anesthesia, 15 min runs, 26 runs, 3 sessions, 1 mm voxels) in 2 macaque monkeys, processed into standard cortical parcellation covering 39 areas.

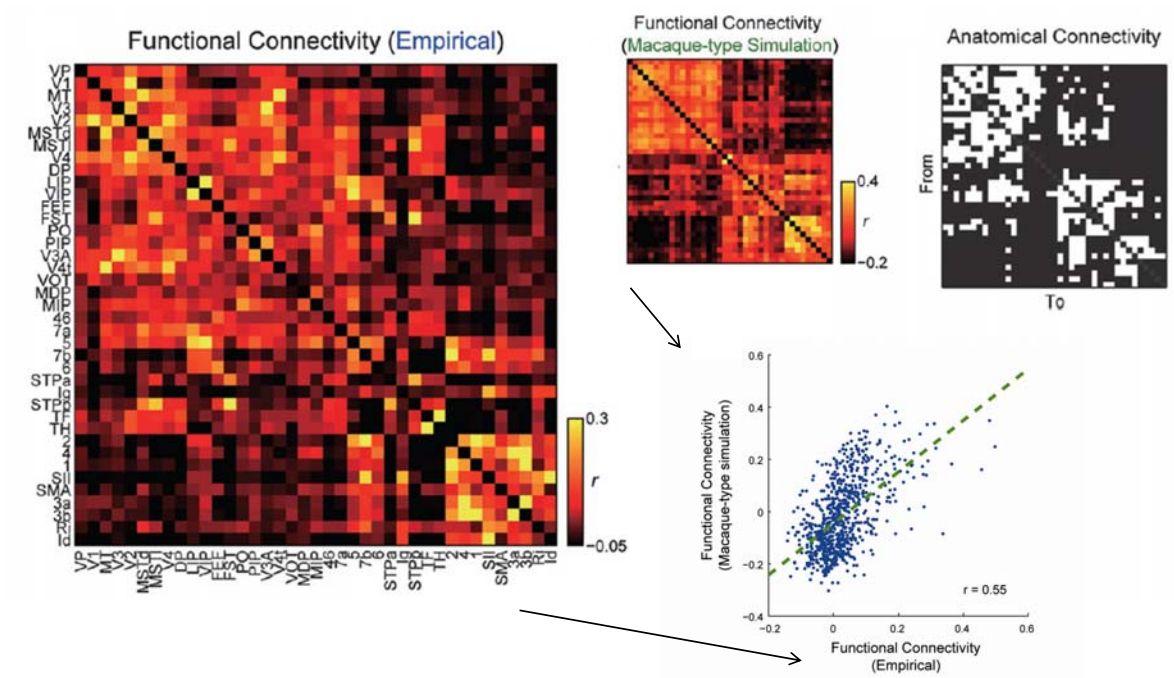
SC (AC): cocomac database of macaque cortical connections.

Imaging reveals many instances of "indirect FC"

Adachi et al. (2011) *Cerebral Cortex*

Dynamic Brain Networks

Model Comparison with Macaque fMRI



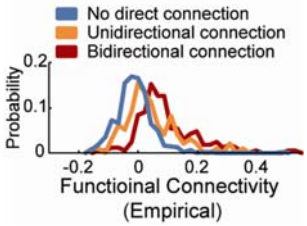
Empirical and simulated FC are significantly correlated.

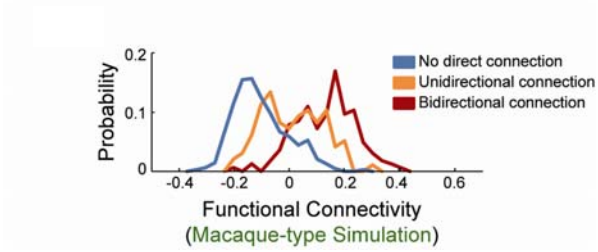
Adachi et al. (2011) *Cerebral Cortex*

Dynamic Brain Networks

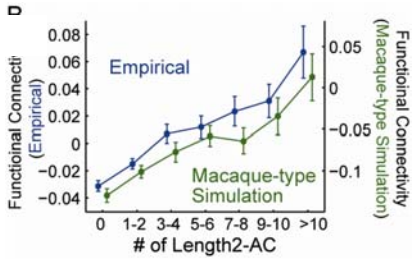
Model Comparison with Macaque fMRI

On average FC on connected region pairs is higher (both empirically and modeled).





On unconnected region pairs, the strength of FC is partially predicted by the number of paths of length 2 (indirect paths - both empirically and modeled).



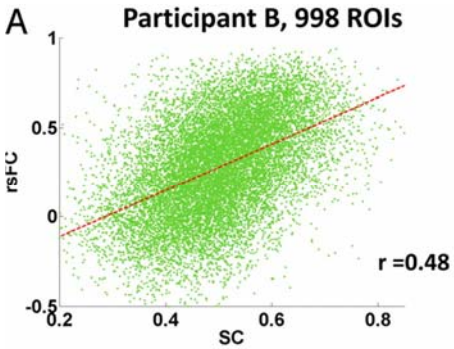
Adachi et al. (2011) *Cerebral Cortex*

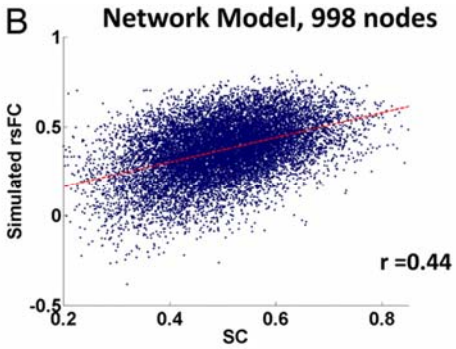
Dynamic Brain Networks

Model Comparison with Human MRI

The relation between SC and rsFC is similar in strength for empirical data (left) and computational model (right).

Note that the fully deterministic (nonlinear and chaotic) model does not yield a “simple” linear SC-rsFC relationship.





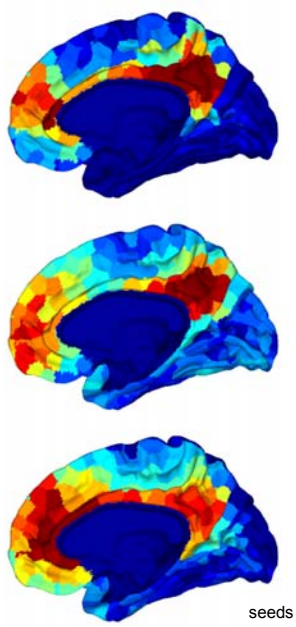
Hagmann et al. (2008) *PLoS Biol.* 6, e159.

Honey et al. (2009) *PNAS* 106, 2035.

Dynamic Brain Networks

Model Comparison with Human MRI

Structural connections of the human brain predict much of the pattern seen in resting state functional connectivity.

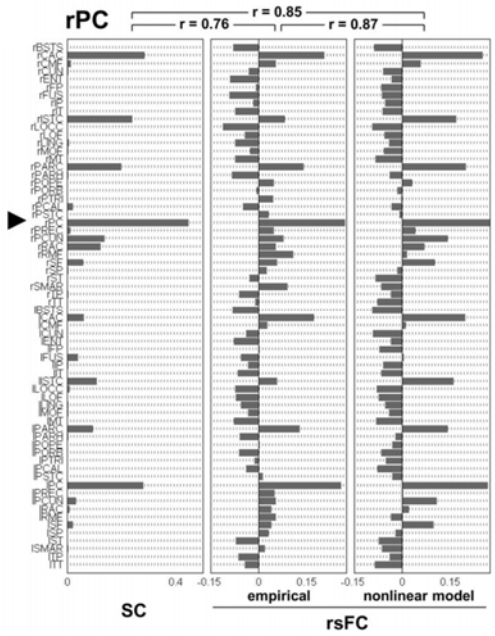


structural connectivity (SC)

functional connectivity (rsFC) - empirical

functional connectivity (rsFC) – nonlinear model

seeds placed in PCC, MPFC



Honey et al. (2009) *PNAS* 106, 2035.

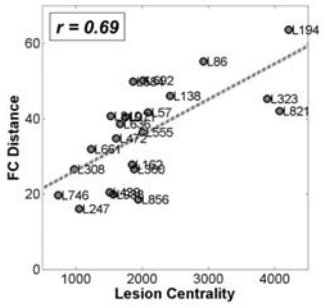
Dynamic Brain Networks

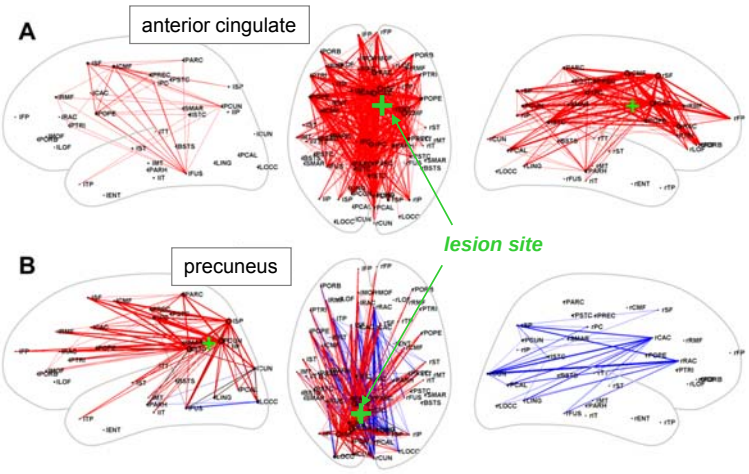
Modeling the Functional Impact of Lesions

Lesions of structural brain networks result in system-wide functional disturbances.

Models of endogenous fluctuations in neural activity can be used to estimate the functional impact of structural lesions.

Centrality of lesion site partially predicts lesion effects.





Effects of lesions in anterior cingulate or precuneus (decreased FC = red, increased FC = blue)

Alstott et al. (2009) *PLoS Comput Biol* 5, e1000408

Summary

The brain is a complex network.

Brain networks are organized on multiple scales, and shape patterns of neural dynamics.

Network science offers a theoretical framework for the study of the nervous system.

The connectome is a comprehensive description of brain connectivity – a foundational data set

The connectome will inform the design of global computational models of the human brain.

Further Reading and Acknowledgements

Sporns O (2011) *Networks of the Brain.* MIT Press.

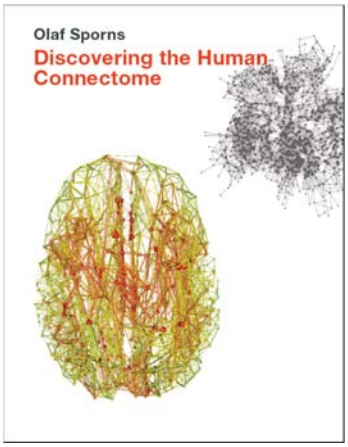
Sporns O (2012)
Discovering the Human Connectome. MIT Press.

Lab: www.indiana.edu/~cortex

NIH Human Connectome Project:
www.humanconnectome.org

The Virtual Brain Project:
http://thevirtualbrain.org

Network Analysis Toolbox (Matlab):
www.brain-connectivity-toolbox.net



HUMAN Connectome PROJECT

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