Discovering the Human Connectome

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

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
Introduction

Networks as Models of Complex Systems

Jeong et al. (2001) Nature 411, 41

Kevin Boyak, Dick Klavans, Bradford Paley

Citation patterns and scientific paradigms

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.

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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.
Introduction

Extraction of Brain Networks from Empirical Data


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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Structural Brain Networks

Anatomical Organization of Cerebral Cortex

Principles of network architecture in cortex:
Specialization
Integration
Streams (modules)
Hierarchy

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**.

Structural Brain Networks

Modular Brain Networks


Modular Brain Networks

Structural Brain Networks


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

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)
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

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Structural Brain Networks
Mapping Human Brain Structural Connectivity

MRI Acquisition

Segmentation
T1w high res.
Diffusion Spectrum Imaging

Partition into 66 anatomical subregions

Tractography

Partition into 1000 ROIs

Whole brain structural connection network

Patric Hagmann

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

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

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

Colizza et al. (2006) Nature Physics
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.

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

Large proportion of short communication paths travel through the RC.

RC damage has disproportionate effects on network integrity.
Once the RC is identified, connections can be classified as RC, feeder, local.

Van den Heuvel et al. (2012) PNAS

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
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.

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".
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?

Movie: Vincent, Raichle et al. (Washington University)
Data from Honey et al (2009)

**Dynamic Brain Networks**
**Wiring and Dynamics – Human Brain**

SC

DSI structural connections

prediction → inference

DSI structural connections

seeds placed in PCC, MPFC

functional connectivity (rsFC) – nonlinear model

modeling

comparison

functional connectivity (rsFC) - empirical

rs-fMRI functional connections


**Dynamic Brain Networks**
**Direct Comparison of Structural and Functional Connections**

Thresholding rsFC does not allow the reliable inference of SC.

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 $R \approx 0.50$ (998 nodes; $R \approx 0.4-0.45$ in single participants) to $R \approx 0.72$ (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.

The strength of the SC/rsFC relationship increases during development (ages 2-18 years)
**Connectivity + Dynamics = Endogenous Brain Activity**

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

\[
\frac{dV(x)}{dt} = -(\theta_c + (1-c)\theta_{\text{activation}} \phi(x) + \theta_{\text{deactivation}} \phi(x) < Q_k(x) >) E_{\text{c}}(P(x) - V_c) - E_{\text{k}} f'(P(x) - V_k) \\
- g_{\text{e}} (P(x) - V_f) - g_{\text{m}} m + (1-c) a_{\text{e}} \phi(x) + c a_{\text{m}} \phi(x) > Q_k(x) > P(x) - V_m \\
+ a_x ZQ(x) + a_y I_j.
\]

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


**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.

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.”

Empirical and simulated FC are significantly correlated.
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).

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

**Static Brain Networks**
Model Comparison with Human MRI

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)

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


Lab: www.indiana.edu/~cortex

NIH Human Connectome Project: www.humanconnectome.org

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


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