Hubs in Brain Structure and Function

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Brain Networks

Networks represent complex systems as sets of discrete nodes and edges (e.g. brain regions and interconnections).

Fundamental distinction:
- Structural networks (anatomical connections, “connectome”)
- Functional networks (statistical dependencies, dynamic interactions)

Important themes in current studies of brain networks:
- Community structure *(modules)*
- Node/edge **influence** and vulnerability
- Network **cores/clubs/cliques**

Virtually all biological networks have “network hubs”

Hubs – Definition and Detection

Functional roles of network hubs:
- High influence on network dynamics
- Focal points of communication or interaction

Measures for detecting network hubs:
- Degree, strength (local)
- Betweenness or closeness centrality (global)
- Vulnerability
- Participation in community structure

Robust detection of network hubs can be achieved by combining multiple network metrics.

Most network measures are appropriate for use in structural (connectome) networks...

... but use of some measures (degree/strength, path-based centrality) may be biased or potentially inappropriate in functional networks (e.g. resting-state fMRI)

Sporns et al. (2007) PLOS ONE 2, e1049
In some networks, highly connected/central hub nodes have a tendency to be highly connected to each other (“rich-club” organization).

Hubs, cores and rich clubs may play important roles in global communication:
- By creating short (efficient) paths
- By supporting integration of information across diverse brain systems

Outline

- Characteristic Properties of Brain Networks

  Hubs in the Human Connectome – A Very Brief Summary

  Network Hubs, Communication Processes, and Integration

- Summary and Conclusion
C. elegans

Varshney et al, 2011:
- Full network: 279 neurons, 2990 directed connections (density: 3.9%)
- High clustering, short path length
- Broad (heavy-tailed) degree distribution (neurons with high degree centrality)

Towlson et al, 2013:
- Modules
- Set of neurons with high betweenness, many inter-modular connections (“connector hubs”)  
Hubs are densely interconnected (“rich club”)
- Many hub connections are long-distance
**Networks – Drosophila Brain**

Drosophila macroscale connectome

Shi et al:
- 49 LPUs, 1193 directed weighted connections (50% density)
- High clustering, short path length
- Modules (visual L/R, auditory, olfactory L/R, pre-motor)
- Connectors and RC organization
Networks – Mouse Connectome

Wang et al. (2012) J Neurosci

Zingg et al. (2014) Cell

Oh et al. (2014) Nature
Bota et al:
- 73 areas, 1923 directed weighted connections (37% density)
- High clustering, short path length
- Modules (audiovisual, somatomotor, dorsal limbic, ventral limbic/olfactory)
- Connectors and RC organization

Bota, Sporns, Swanson (in preparation)
Networks – From Cells to Systems

Macaque macroscale connectome

Bow-tie core-periphery, rather than RC organization

Felleman and Van Essen (1991) *Cerebral Cortex*

Markov et al (2013) *Science*
Markov et al (2014) *Cerebral Cortex*
Networks – Common Properties

Common topological properties:

- Broad degree distribution – small subsets of highly connected nodes (hubs)
- Log-normal profiles of connection density (e.g. Markov et al., 2011; Wang et al., 2012; Oh et al 2014)
- Specificity of connection profiles (e.g. Passingham et al., 2002)
- High clustering, short path length
- Interconnected “modules”, or network communities
- A tendency for the formation of a “core” (a central club or clique), as distinct from a set of more peripheral nodes

Features related to spatial embedding:

- Distance-dependent connection density/probability (e.g. Young, 1992)
- Exponential distance rule (Ercsey-Ravasz et al., 2013)
- Near-minimal wiring cost – plus presence of (costly) long-distance projections (Kaiser & Hilgetag, 2006)
- Cost-efficiency trade-off (e.g. Bullmore & Sporns, 2012)
“Generative” Models for Functional Networks

Can structural connectivity (SC) “generate” functional connectivity (FC)?

- Macaque rs-fMRI (Adachi et al, 2012)
  - Empirical FC
  - Modeled FC (R = 0.55)
  - Biophysical neural model

- Human rs-fMRI (Goni et al, 2014)
  - Empirical FC
  - Predicted FC (R = 0.60)
  - Analytic network model
Generative Models for Structural Networks

Can spatially-embedded growth (Kaiser & Hilgetag) or distance-based (Ercsey-Ravasz et al., 2013) models account for empirically observed brain networks?

Betzel et al. (in preparation):

- Edges are placed between spatially embedded nodes (human brain) according to some attachment rule.
- For example:
  \[ \Pi_{ij} \propto D_{ij}^{\eta} \times K_{ij}^{\gamma} \]
  - \( D_{ij} \) is the Euclidean distance between nodes \( i \) and \( j \) and \( K_{ij} \) is the number of neighbors shared between \( i \) and \( j \)
- Networks generated by this model are scored based on how well they match empirical networks’ degree, clustering, and edge distance distributions.

Example empirical network
(human cortex, NKI lifespan sample, Xi-Nian Zuo, Beijing)

Generative Models for Functional Networks

\[ P_{i,j} \propto D_{i,j}^\eta \times K_{i,j}^\gamma \]

Varying parameters of the generative model allows scoring model networks against empirical networks.
Outline

Characteristic Properties of Brain Networks

- Hubs in the Human Connectome – A Very Brief Summary

Network Hubs, Communication Processes, and Integration

Summary and Conclusion
Mapping Human Brain Structural Connectivity

MRI Acquisition

Segmentation → T1w high res. → Diffusion Spectrum Imaging

Partition into 66 anatomical subregions

Partition into 1000 ROIs

Tractography

Whole brain structural connection network

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

Patric Hagmann
Network Analysis of the Connectome

Network analysis revealed

- Unique regional connectivity fingerprints
- Broad (exponential) degree distribution
- High clustering, short path length
- Existence of modules interlinked by hub regions
- A prominent structural core

Hubs in the Human Connectome

Nijhuis et al. (2013) *PLOS ONE* 8, e65511.
Hubs in the Human Connectome

Hub regions:
- Relation to brain metabolism and energy demand
- Points of vulnerability in brain damage and disorders (see recent review/meta-analysis by Crossley et al. 2014)

Brain Disorders

- Amyotrophic lateral sclerosis
- Dystonia
- Developmental dyslexia
- Anorexia nervosa
- Obsessive-compulsive disorder
- Parkinson's disease
- Hereditary ataxia
- Dementia in Parkinson's
- Chronic pain
- Panic disorder
- Attention deficit hyperactivity disorder
- Bipolar affective disorder
- Multiple sclerosis
- Frontotemporal dementia
- Obstructive sleep apnea
- Autism
- Schizophrenia
- Alzheimer's disease
- Asperger syndrome
- Huntington's disease
- Depressive disorder
- Right temporal lobe epilepsy
- Post traumatic stress disorder
- Progressive supranuclear palsy
- Left temporal lobe epilepsy
- Juvenile myoclonic epilepsy
- Meta-analysis of all disorders

Vaishnavi et al. (2010) PNAS
Crossley et al. (2014) Brain
Alstott et al. (2009) PLOS Comput Biol
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.

Rich-Club Organization of the Human Connectome

RC members include: precuneus, posterior cingulate cortex, superior frontal cortex, medial orbitofrontal cortex, caudal anterior cingulate cortex, insula, portions of medial temporal cortex.

Overlap of RC and structural core.

High proportion (89%) of short communication paths travel trough at least one RC node (66% through an RC edge).

RC damage (node/edge deletion) has large effects on network integrity and efficiency.

Once the RC is identified, connections can be classified as RC, feeder, local.
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 109, 11372
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.

Rich-Club Organization of the Macaque Connectome

RC is detected also in macaque cerebral cortex (242 areas, 4090 directed projections, collated from Cocomac by Modha & Singh, 2010):

- Mostly composed of multimodal/association areas (RC1: areas 9, 46, 4b, LIP, 13a, 32, 12o, 12l, 11, 24, TF, TH)
- RC areas overlap and interconnect all structural network communities (modules)


A Model of Communication in the Macaque Cortex

Use of a communication model to estimate metrics of information flow (Misic et al, 2014)

Units of information are modeled as packets that traverse the macaque cortical network. Allows, for example, to track mean throughput (mean number of signals carried by each connection) and transit time.

Model suggests that signal traffic concentrates on RC connections, and that RC nodes with high mean throughput receive and transmit signals faster than lower throughput (non-RC) nodes.
Rich-Club and Resting-State Networks (RC-RSN)

Resting-state neural activity can be decomposed into independent components or network modules ("resting-state networks" - RSNs).

Functional connectivity and RSNs have an anatomical/structural basis:
- Robust (but complex) relationship between SC and FC
- RSNs are internally linked via structural projections (e.g. Greicius et al., 2009; van den Heuvel et al., 2009)

Non-stationary fluctuations in resting brain dynamics (reviewed in Hutchison et al., 2013 – see Zalesky et al., 2014):
- Possible changes in internal coherence within RSNs
- Possible changes in coupling between RSNs

How does RC organization (in structural connectivity) relate to functional RSNs?

Hypothesis:
- Structural RC cross-links functional RSNs
- Structural RC is topologically positioned to act as a "central switch" or integrator for time-varying cross-RSN communication.

Greicius et al. (2009) *Cerebr Cortex* 19, 72
Hutchison et al. (2013) *Neuroimage* 80, 360
van den Heuvel et al. (2009) *Hum Brain Mapp* 30, 3127
Zalesky et al. (2014) *PNAS* 111, 10341.
RC-RSN: Acquisition and Analysis Workflow

RC-RSN: RC Node Distribution

RC nodes overlap with all 11 RSNs – with varying levels of participation.

Many RC nodes (determined from SC) are connector hubs (linking RSN modules determined from FC).

9 out of 11 RSNs contain RC connector hubs – highest proportion in DMN.

RC nodes were found at or near regions of the cortical surface where multiple RSNs overlap.

RC and feeder connections are over-represented in short communication paths that cross RSN boundaries.

Proposal: Hierarchical model for structural relations among RSNs
Outline

Introduction – Brain Networks

The Human Connectome – A Very Brief Summary

Rich-Club Organization – Network Hubs and Integrative Processes

▸ Summary and Conclusion
**Summary and Conclusion**

**Connectomics** is beginning to reveal the network architecture of the human brain.

Highly connected and highly central **hub nodes** are a prominent feature in human and non-human connectome networks.

Network science approaches are increasingly important for analysis and modeling of connectome data.

Hubs are densely interconnected to form a “rich club” – a high-cost and high-efficiency attribute of the connectome.

Network hubs and their interconnections may provide an important structural substrate for **functional integration** across segregated brain regions and resting-state networks.
Further Reading:


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McDonnell Foundation, NIH, NSF