Brain Graphs

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First International Summer Institute on Network Physiology
Lake Como School of Advanced Studies

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UNIVERSITY OF CAMBRIDGE

gsk GlaxoSmithKline

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Disclosures

Employment

- **Paid Employment**
  University of Cambridge (50% FTE)
  GlaxoSmithKline (50% FTE)

- **Editorial Roles**
  Biological Psychiatry – Deputy Editor
  Network Neuroscience – Senior Editor

- **National Health Service (HCP) Role**
  Hon Consultant Psychiatrist and Director of R&D, Cambridgeshire & Peterborough NHS FT

- **Stock Equity (>$10,000)**
  GlaxoSmithKline

- **Speaker's Bureau**
  None

Sources of Research Support

- Medical Research Council

- Wellcome Trust

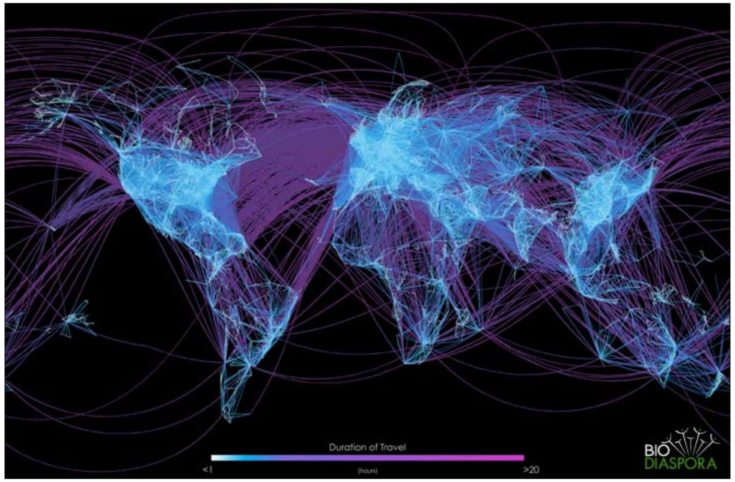
- National Institute for Health Research

- National Institutes of Health, Graduate Partnership Program

Growth of brain network science: connectomics

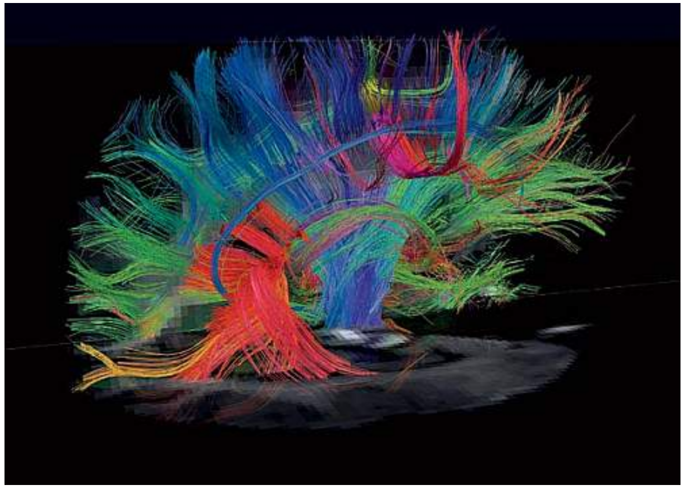
network science

graph theory of complex topology



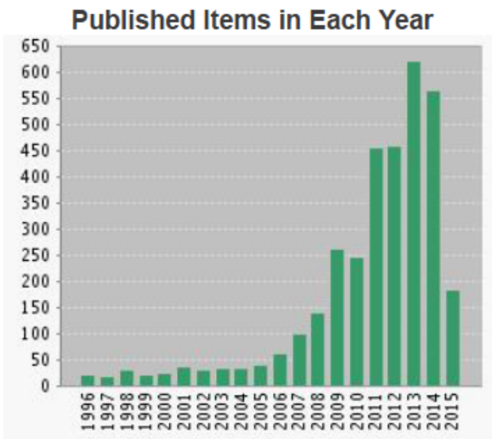
brain imaging technology

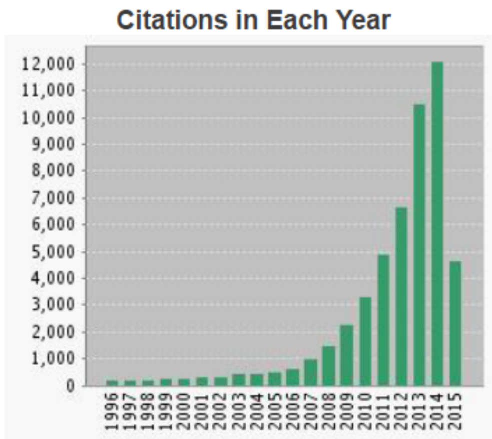
from macro to micro



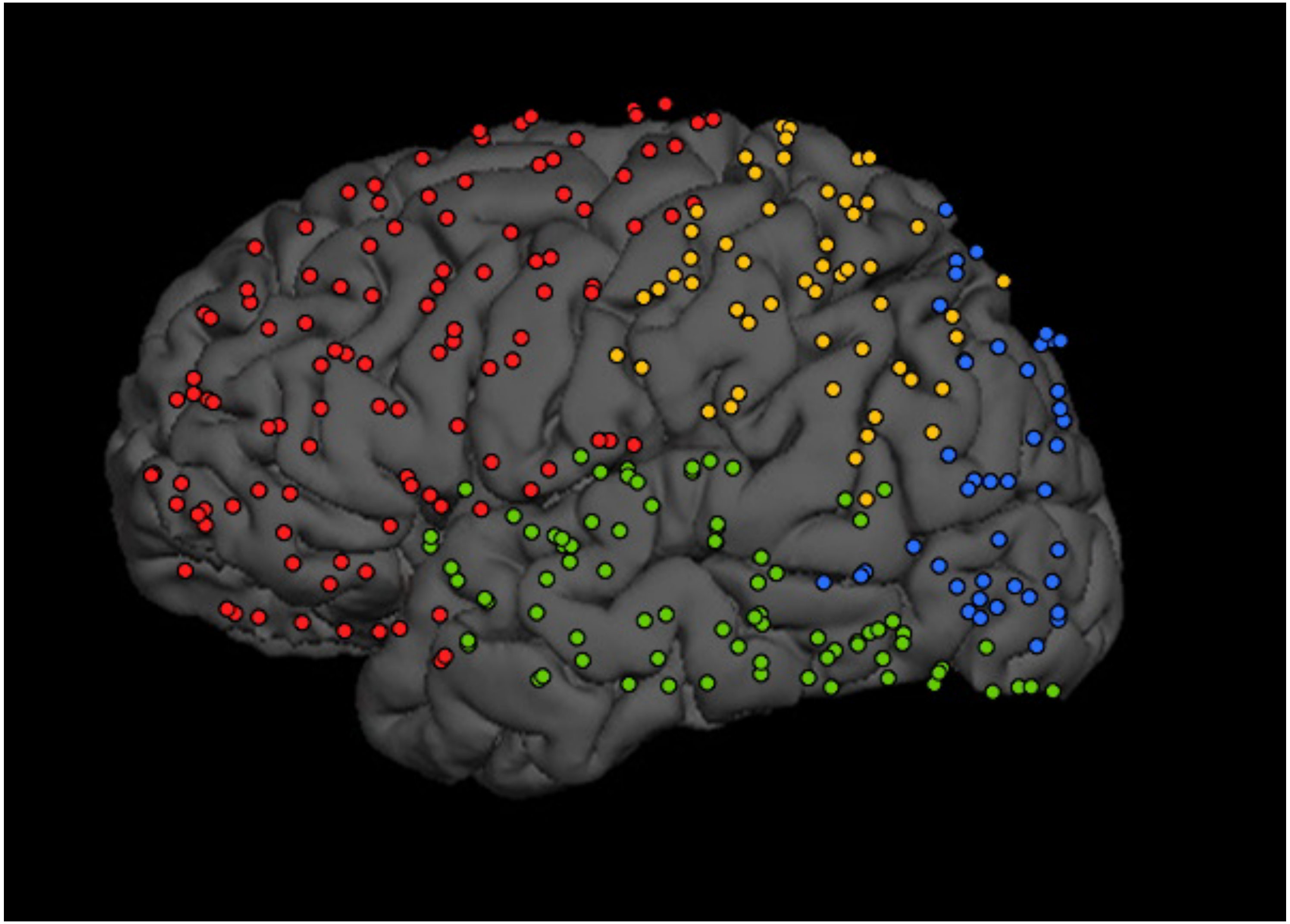
rapid growth of connectomics

WoK search on <brain> AND <graph>



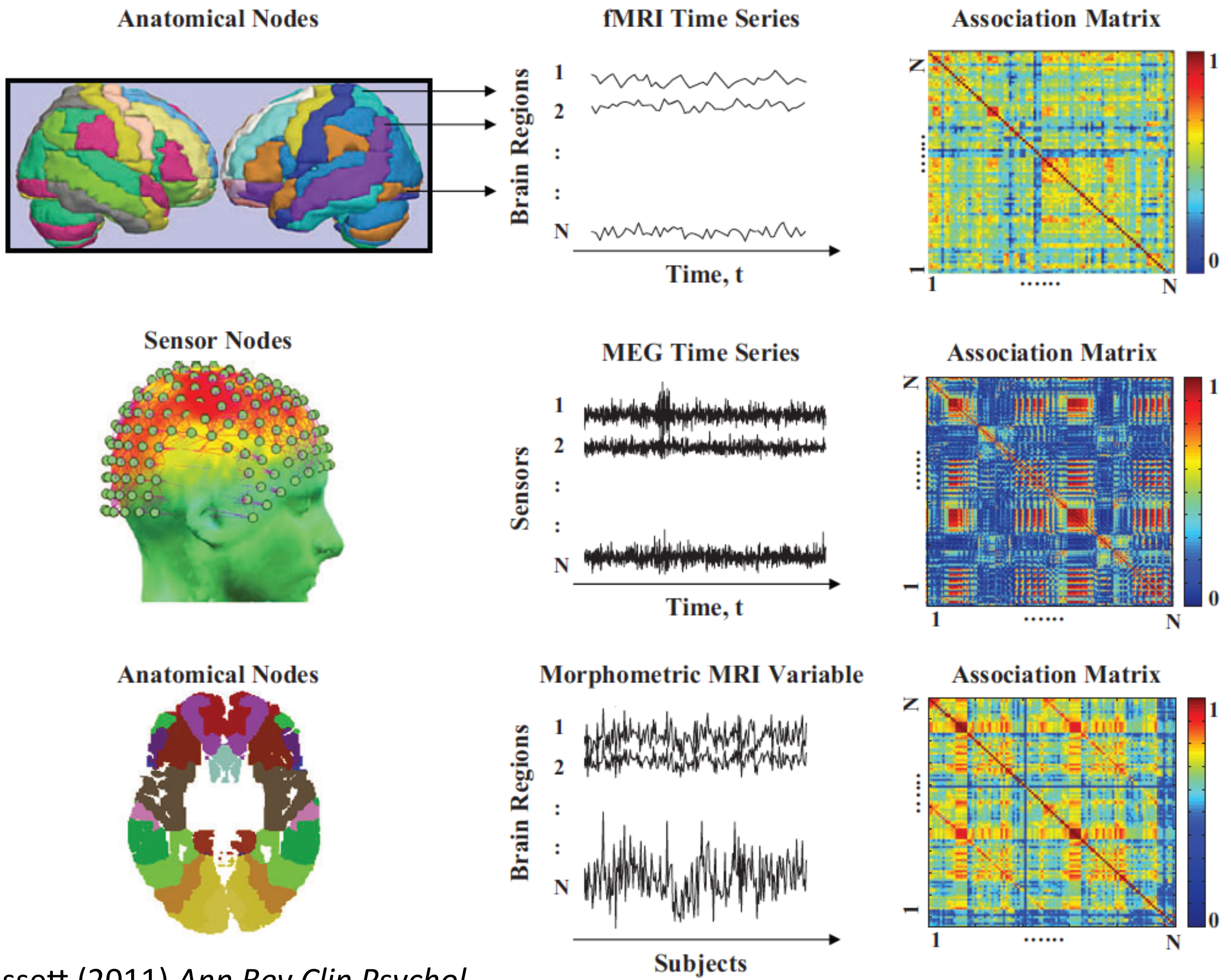


Graph theoretical analysis of magnetic resonance imaging (MRI) of the human brain



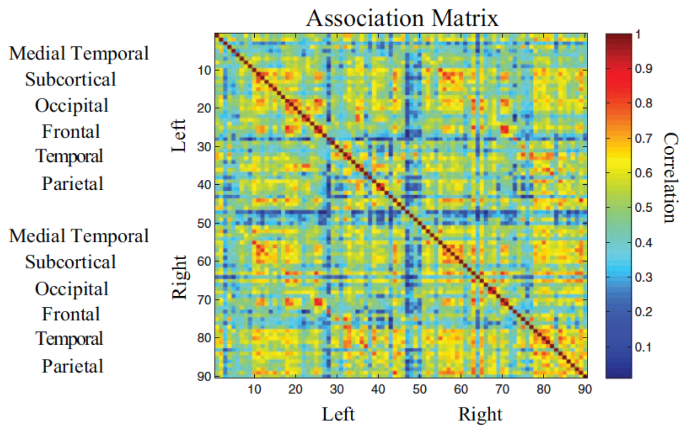
Vértes et al (2011) YouTube

From human neuroimaging to association matrices



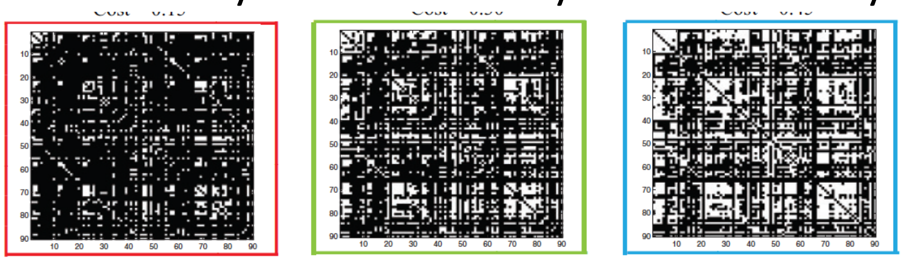
Bullmore & Bassett (2011) *Ann Rev Clin Psychol*

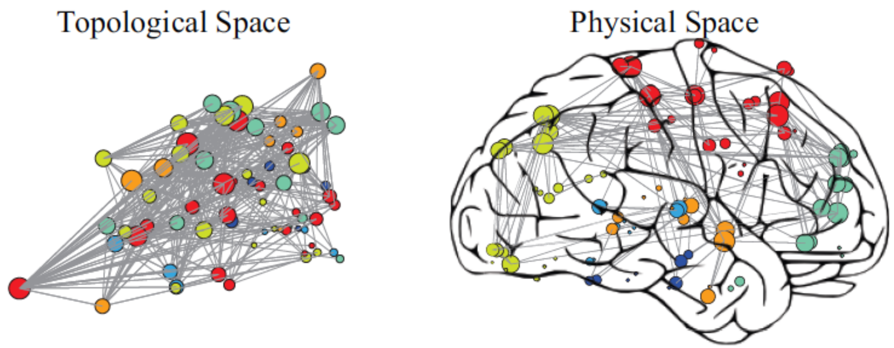
From an association matrix to a brain graph



...then draw the adjacency matrix as a graph representing the strongest X% of edges as lines or edges drawn between nodes.

15% density 30% density 45% density

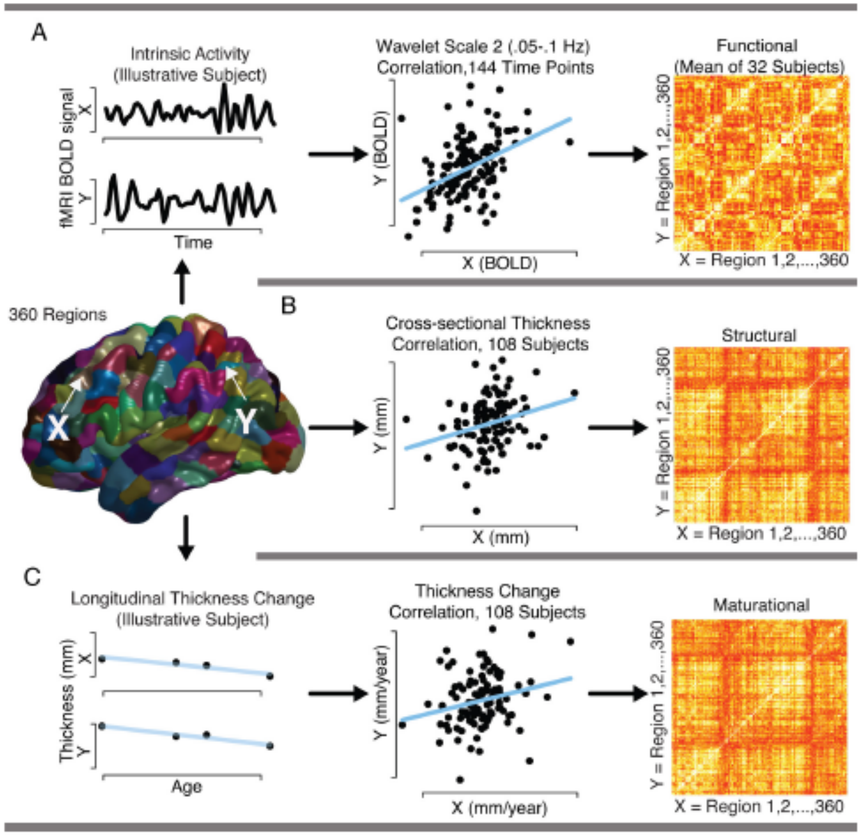


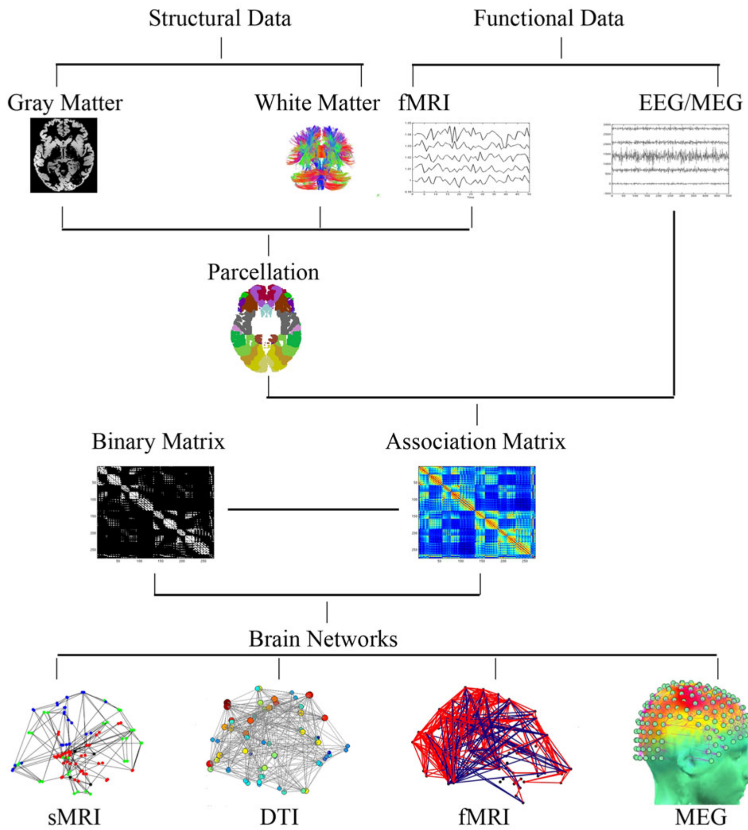


Threshold the association matrix so that the strongest X% of associations are represented as 1s in a binary (0 or 1) adjacency matrix...

Bullmore & Bassett (2011) *Ann Rev Clin Psychol*

From neuroimaging to human brain graphs



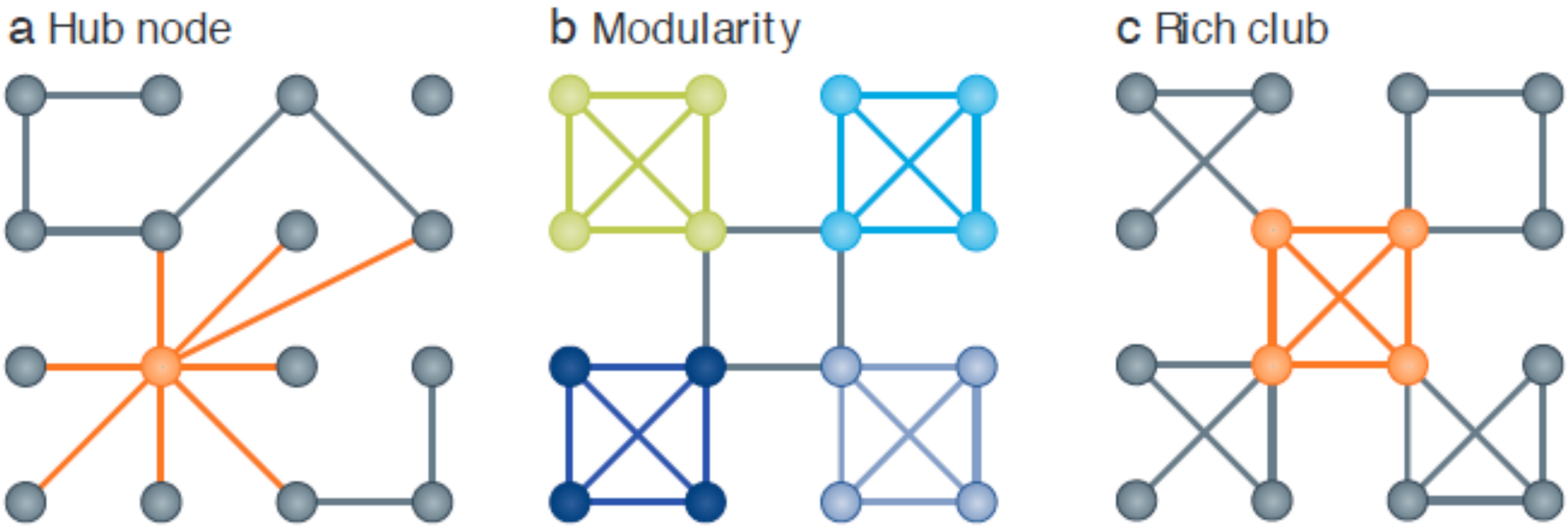


Defining nodes

Defining edges

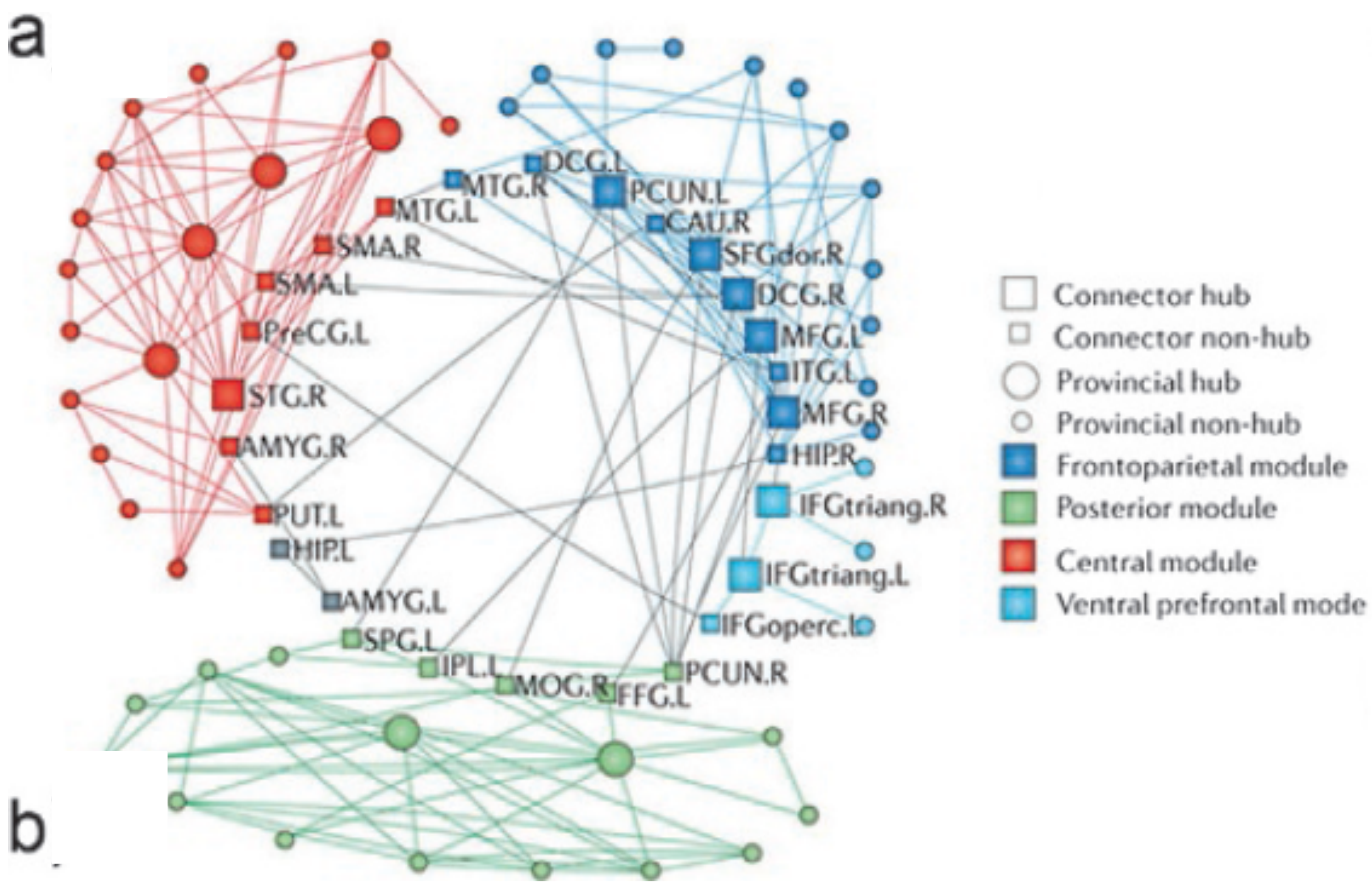
Bassett & Bullmore (2010) *Curr Op Neurol*
Bullmore & Bassett (2011) *Annu Rev Clin Psychol*
Alexander-Bloch et al (2013) *J Neurosci*

Graph theory



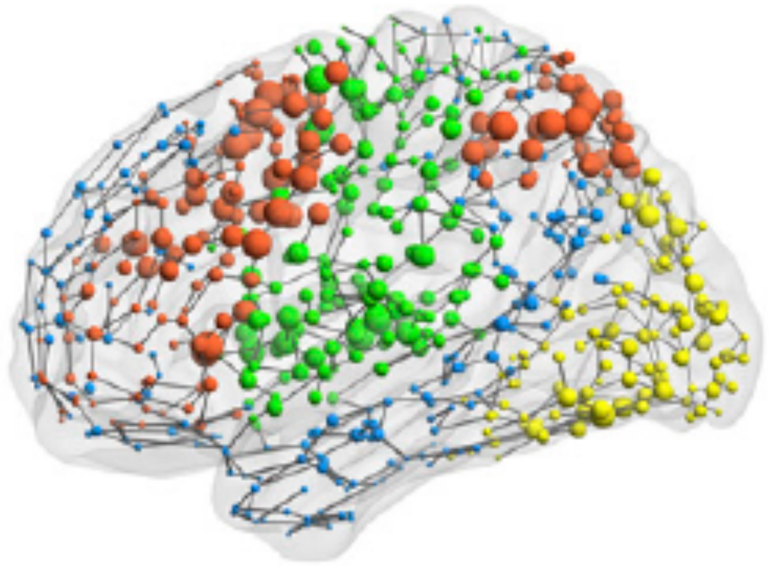
Schröter, Paulsen & Bullmore (2017) *Nat Rev Neuro*

Topological hubs and modules of a brain graph



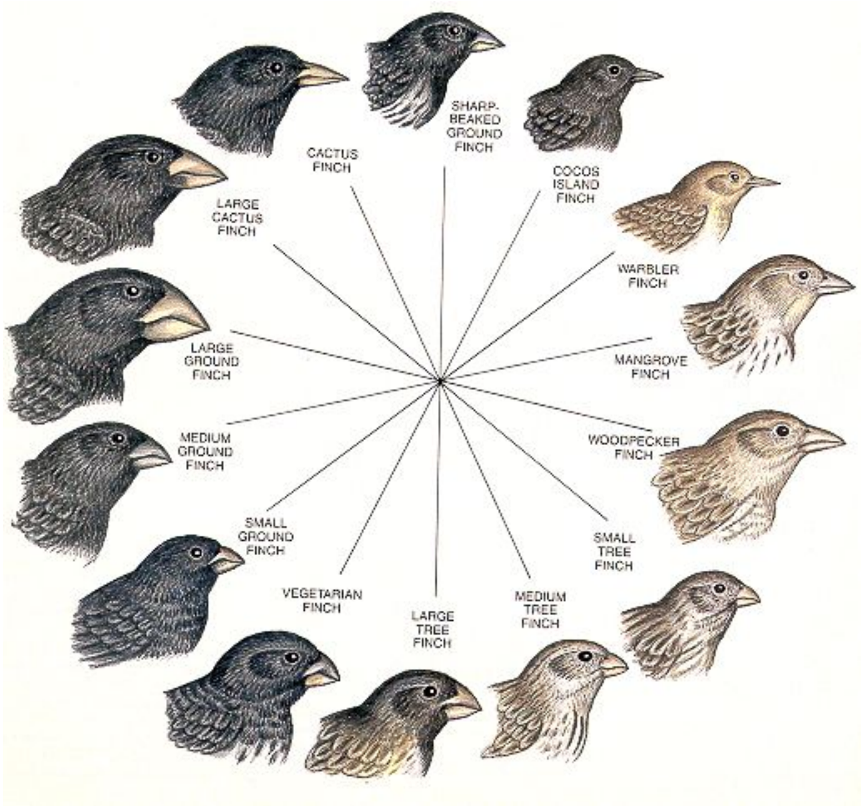
Bullmore & Sporns (2009) *Nature Reviews Neuroscience*

The central challenge is biological validation of human MRI networks



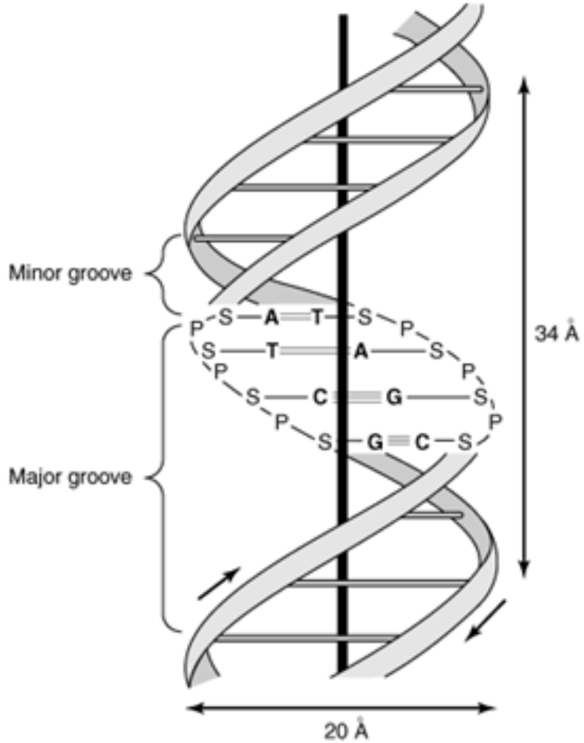
- Macro scale networks ~ 10^{-2} m, cm
- Noisy data not measured in SI units
- No gold standard for human brain networks
- No agreed biophysical explanation for functional connectivity or structural covariance
- **What do these results mean in terms that other neuroscientists can understand and respect?**

Analogy



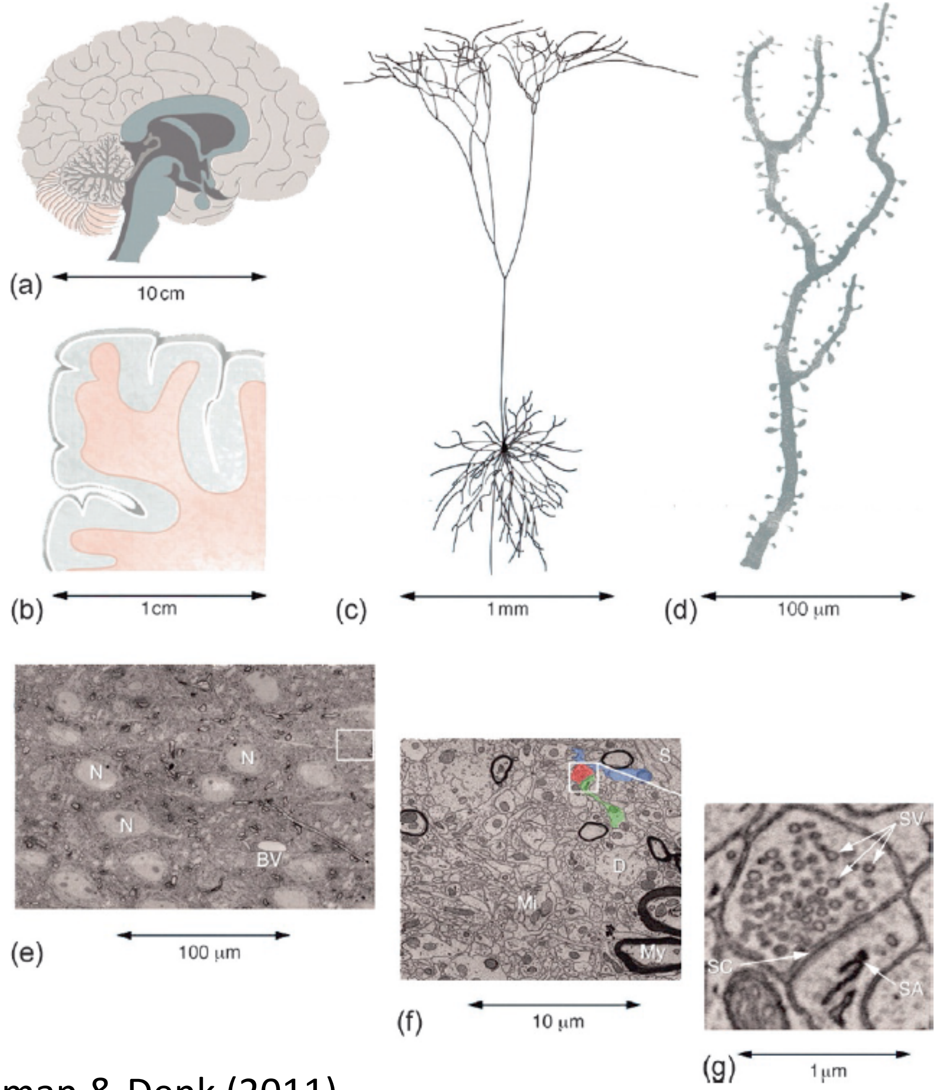
Darwin's finches

Reductionism



Double helix

The multi-scale organization of brain anatomy



Lichtman & Denk (2011)

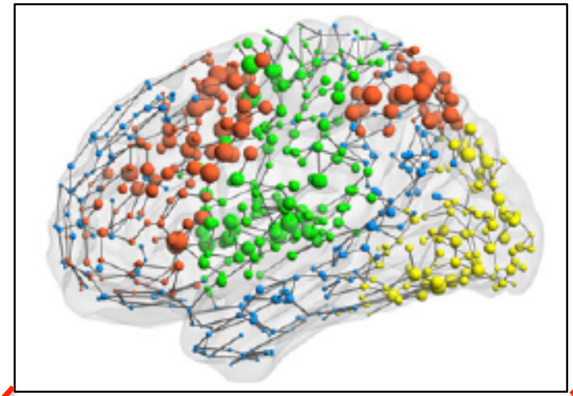
Macro 10^{-2} m
- MRI, fMRI, DWI

Meso 10^{-4} m
- Tract tracing

Micro 10^{-6} m
- Electron microscopy

Molecular
- Gene expression

Analogical or reductionist connectomics:
Two strategies for integration across scales of brain network organization



Analogical

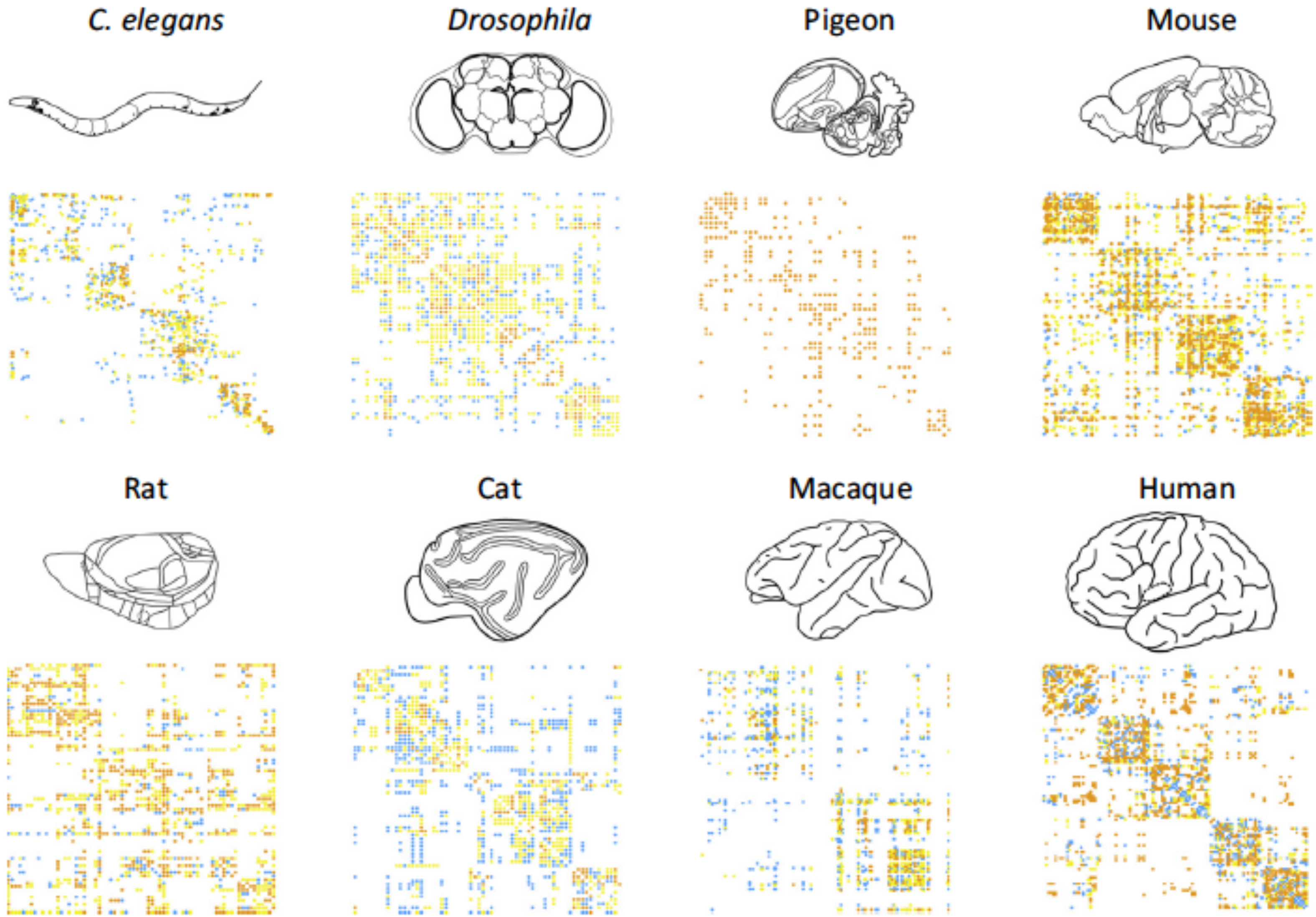
Make an informative comparison between human MRI networks and more precisely known nervous systems in other species

Reductionist

Link human MRI network organization to human cellular or genomic biology

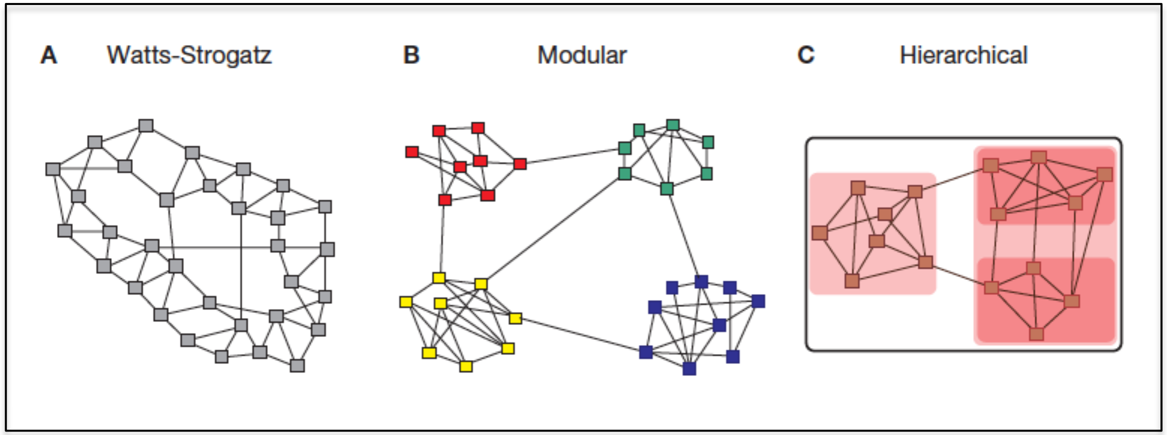
Connectomes

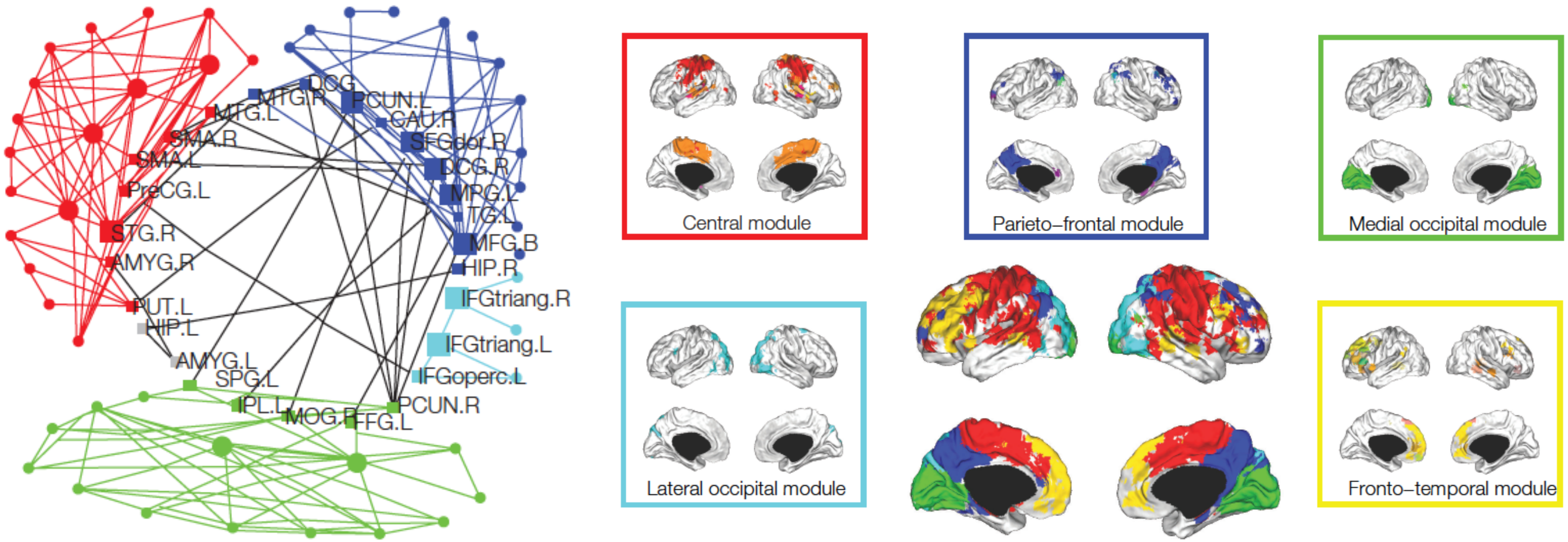
from micro to macro



Van den Heuvel et al (2016) *Trends in Cognitive Sciences*

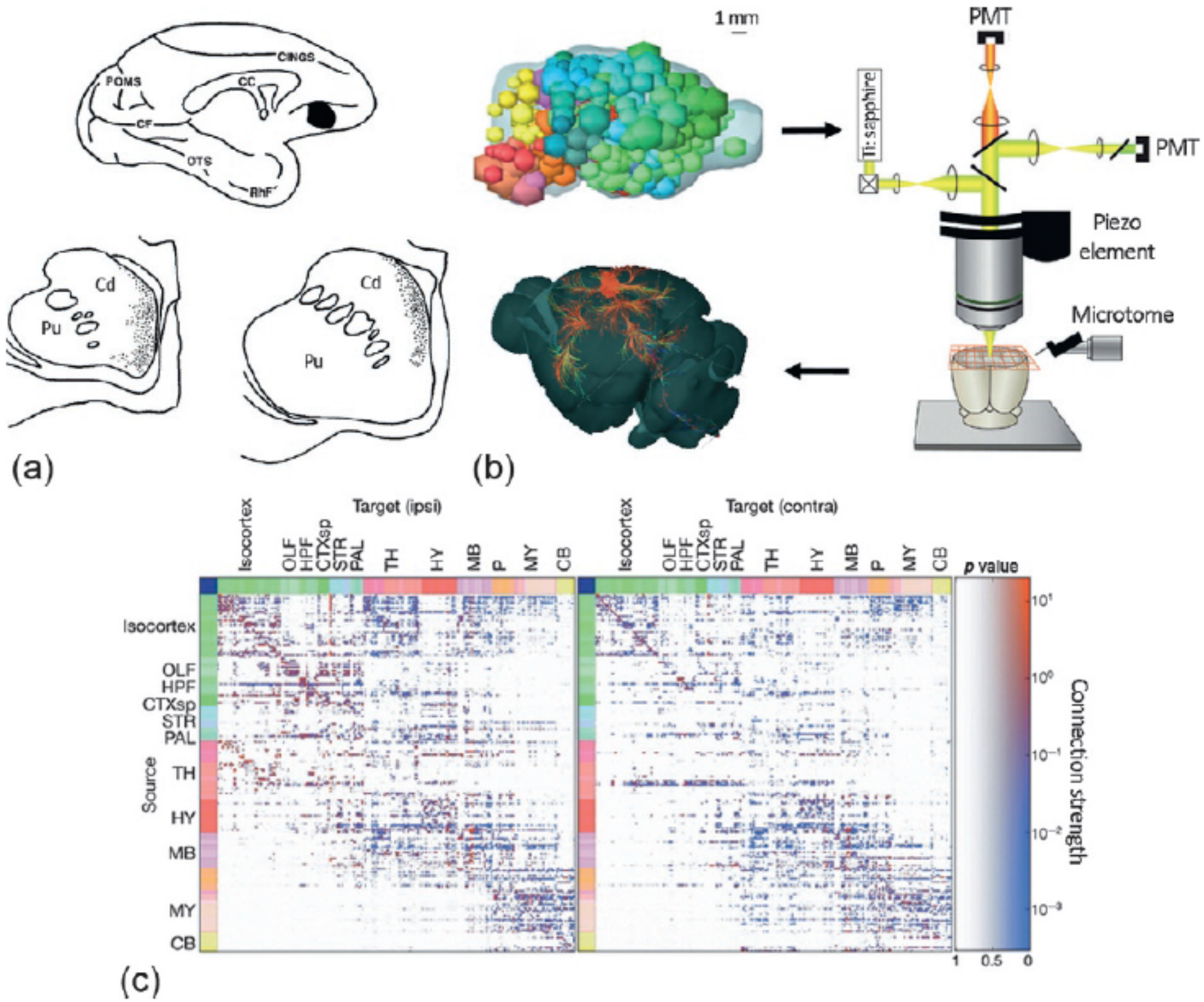
Modular community structure of human MRI networks





Meunier et al (2010) *Frontiers Neuroscience*

Mesoscale connectomics of mammalian cortex has been accelerated by advances in tract-tracing technology

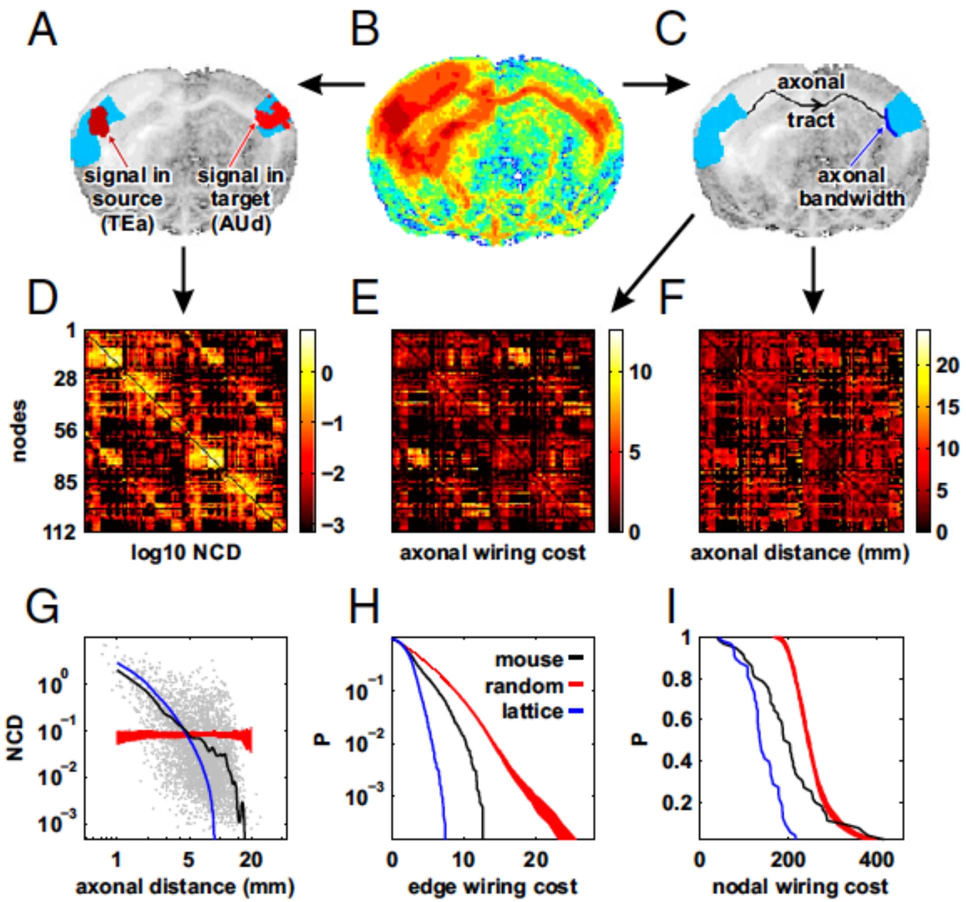


(a) Yeterian & Pandya (1991) *J Comp Neurol*; (b) Osten & Margrie (2013) *Nature Methods*; (c) Oh et al (2014) *Nature*

Multiple tract-tracing experiments for estimation of anatomical connectivity and wiring cost in the mouse connectome

Wiring cost

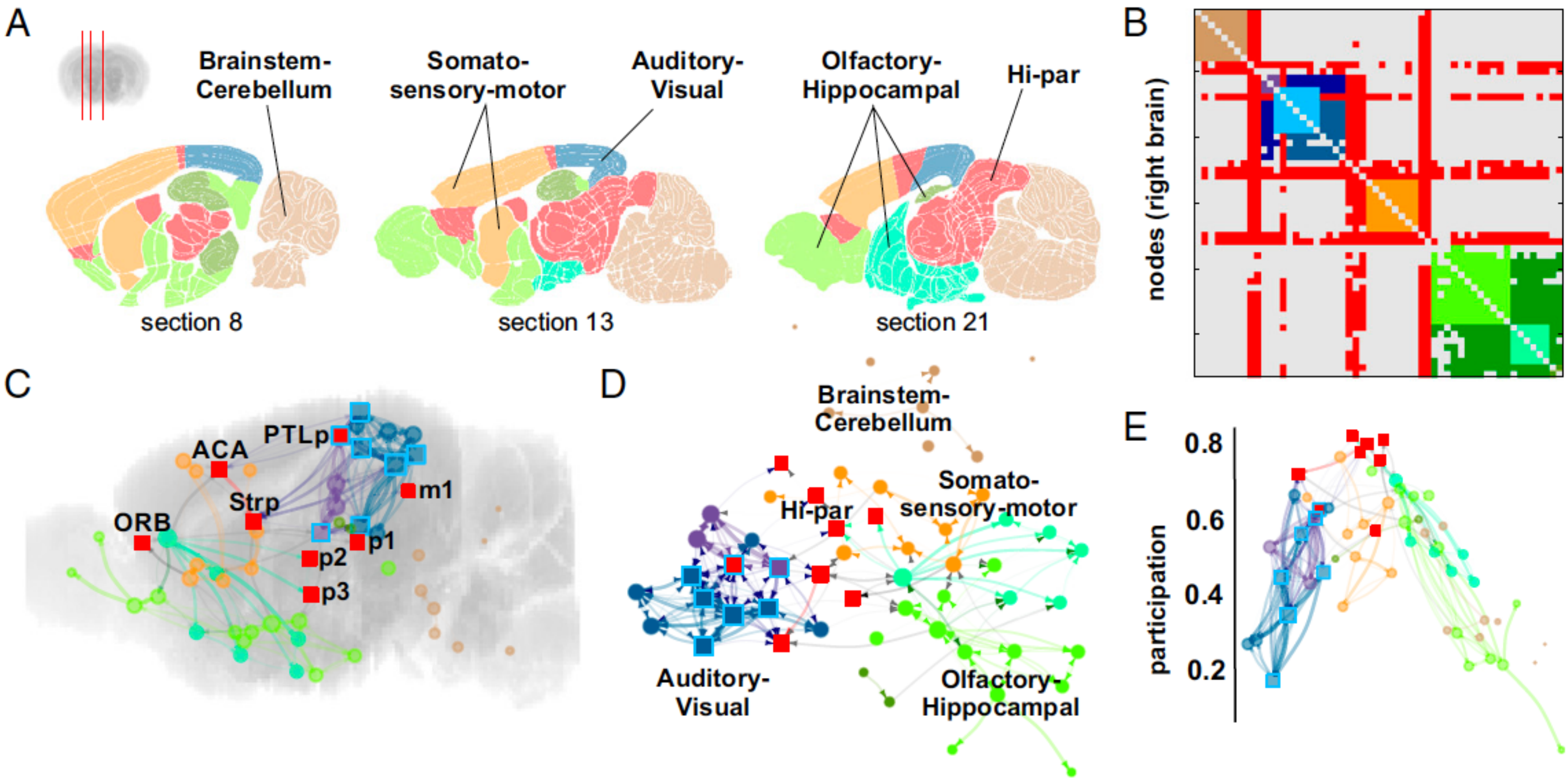
- Axonal projection is biologically expensive
- Membrane repolarisation by active ion transport is a major cost on the neuronal energy budget
- Axonal distance in 1D (often simply Euclidean distance) is a common proxy for wiring cost
- Anterograde viral tract tracing data allow more precise estimation of curvilinear axonal distance, and cross-sectional area or bandwidth of directed axonal projections, from source to target regions
- Modeling the axonal tract as a "serpentine cylinder", is a volumetric (rather than linear) estimator of wiring cost



Sterling & Laughlin (2015) *Principles of Neural Design*. MIT Press.
Rubinov, Ypma et al (2015) *Proc Natl Acad Sci USA*

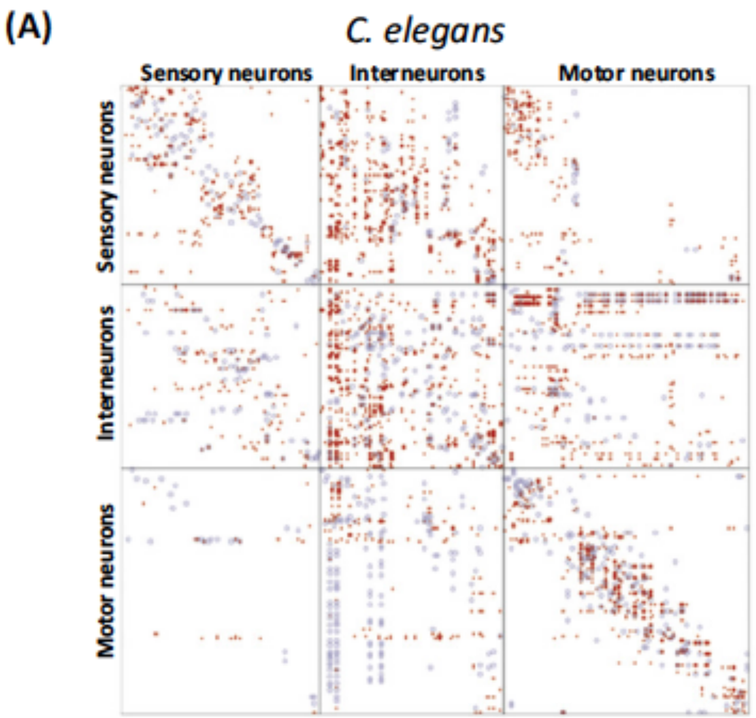
ALLEN INSTITUTE *for* BRAIN SCIENCE

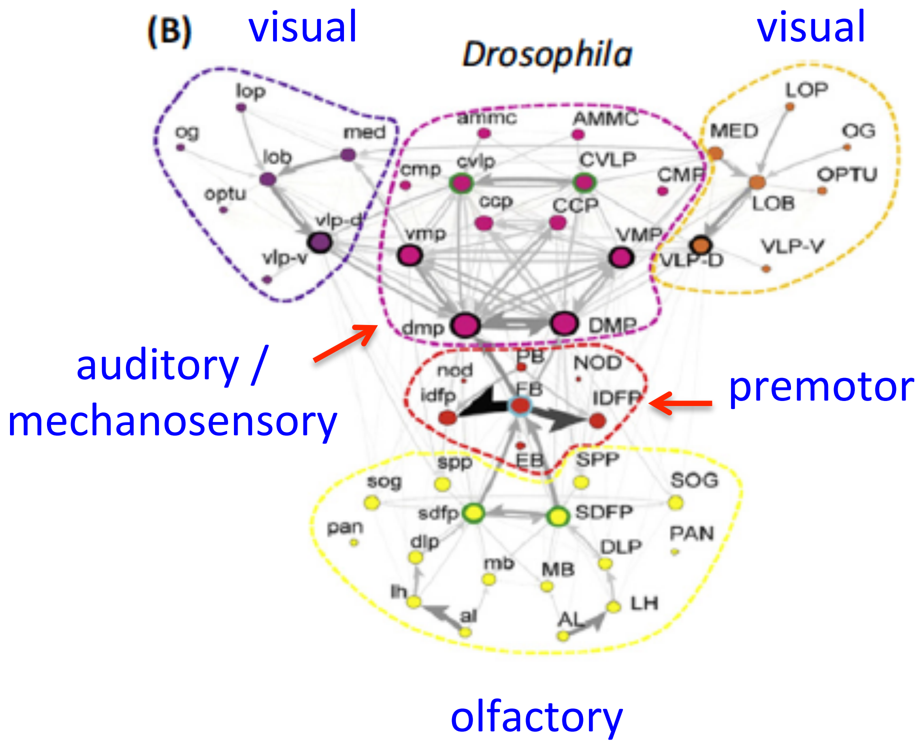
The mouse connectome has a community structure comprising functionally specialised hierarchical modules



Rubinov, Ypma et al (2015) *Proc Natl Acad Sci USA*

C elegans and *Drosophila* connectomes also have a community structure of functionally specialised modules



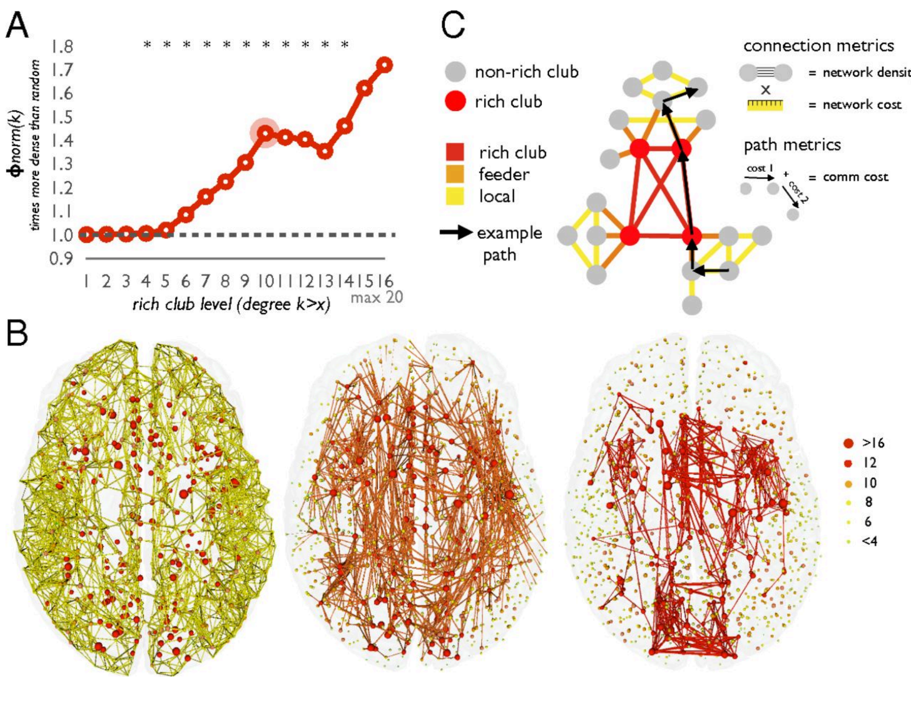


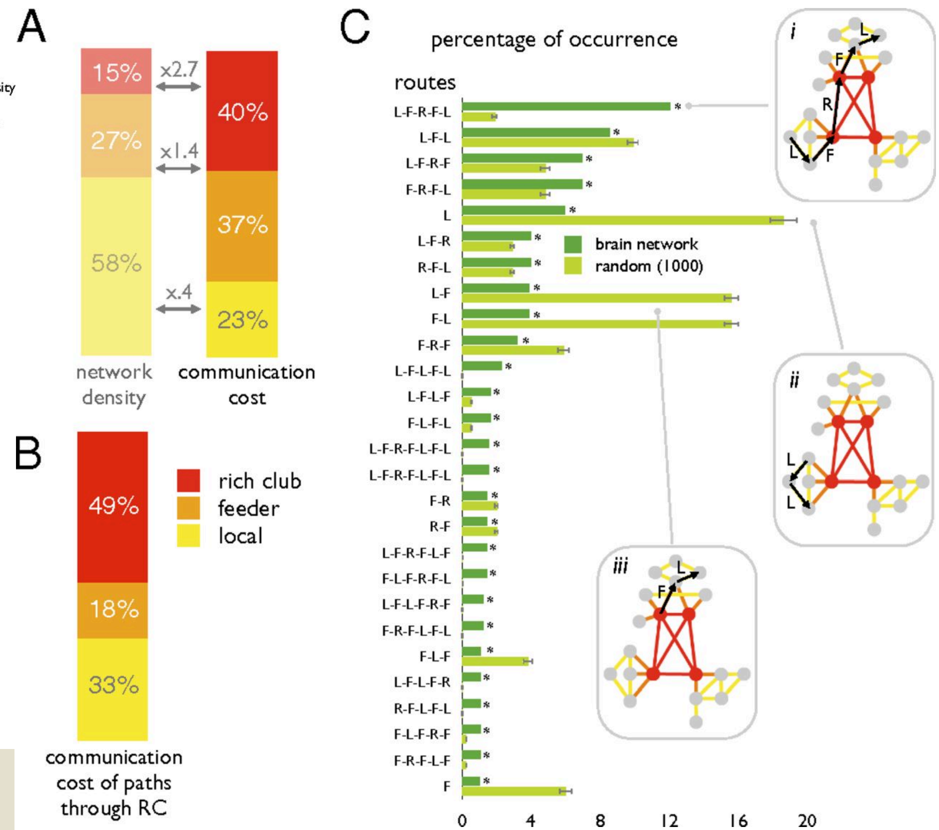
(a) Varshney et al (2010) *PLoS Comput Biol*
(b) (b) Shih et al (2015) *Curr Biol*
Simon (1965) *Architecture of Complexity*

Motor and sensory neuronal modules are “nearly-decomposed” or almost completely segregated from each other

In the worm, the interneuronal module has a more integrative role, linking sensory and motor modules

Human DTI macro scale networks have a high cost, highly integrative rich club





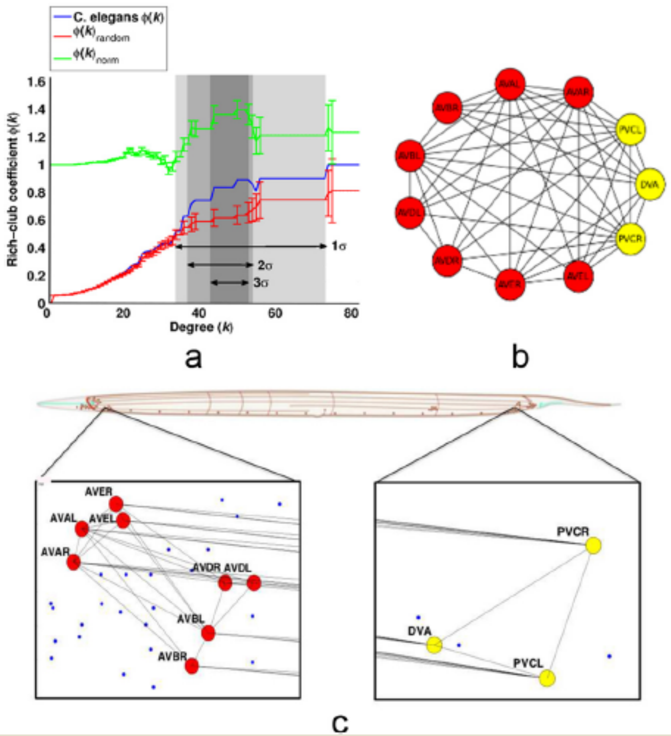
High degree hub nodes of the DTI connectome are more densely inter-connected than chance – a rich club

Rich-rich and rich-peripheral (feeder) connections are more expensive (long distance) than connections between spatially neighbouring, topologically peripheral nodes

Feeder connections to rich-club nodes mediate many of the shortest paths between spatially distributed peripheral nodes

van den Heuvel et al (2012) *Proc Natl Acad Sci USA*

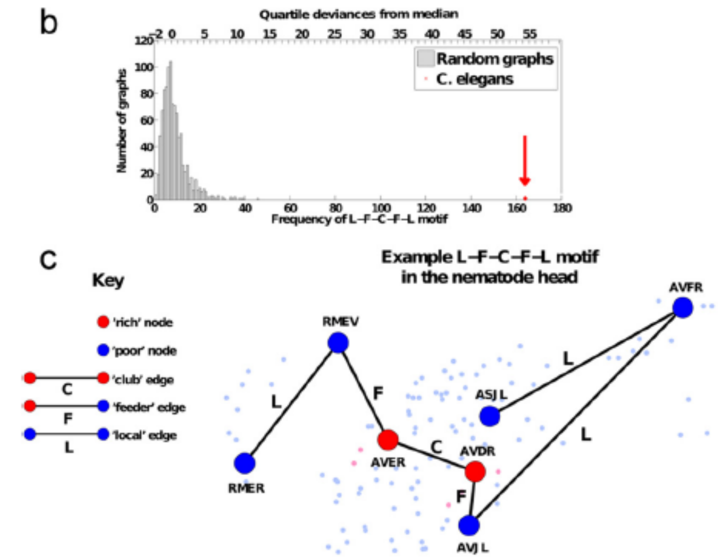
The *C elegans* micro scale connectome has a high cost, highly integrative rich club

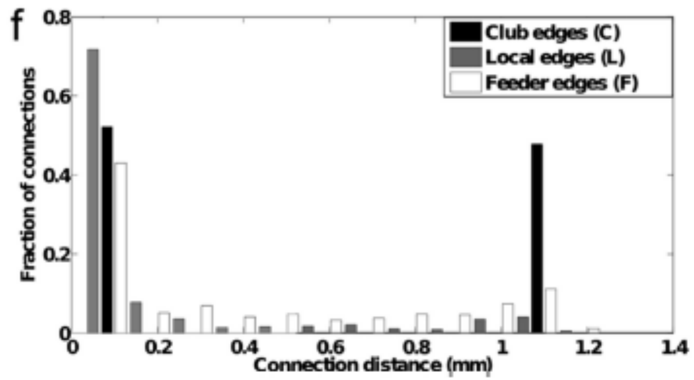


High degree hub neurons of the worm EM connectome are more densely inter-connected than chance – a rich club

Rich-rich and rich-peripheral (feeder) connections are more expensive (long distance) than connections between spatially neighbouring, topologically peripheral nodes

Feeder connections to rich-club nodes mediate many of the shortest paths between spatially distributed peripheral nodes





Towlson et al (2013) *J Neurosci*

A generative model that optimises wiring cost is not sufficient to recapitulate the human DTI macro network

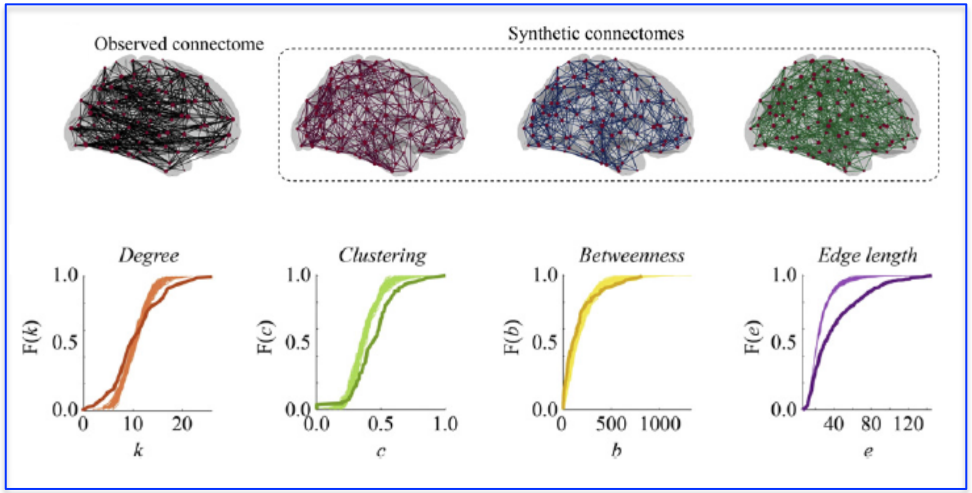
$$P(u,v) = E(u,v)^{\eta} \times K(u,v)^{\gamma}$$

Probability of connection between nodes u and v

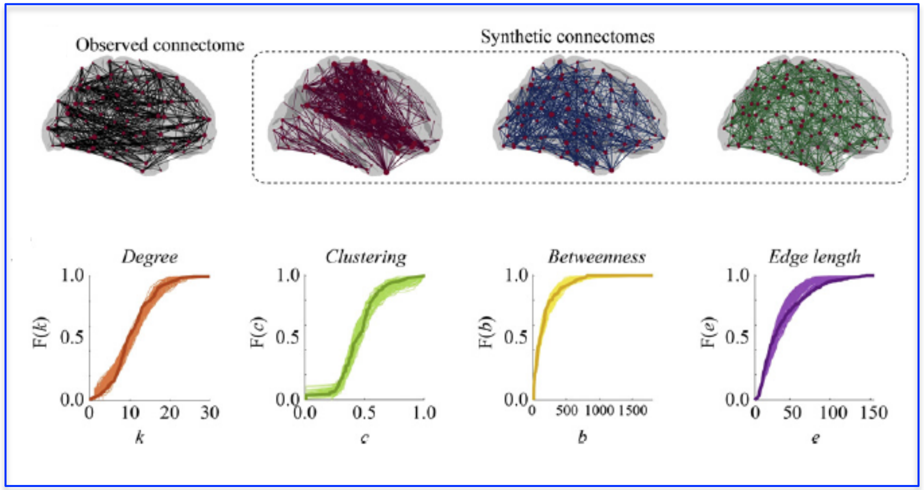
Euclidean distance between nodes

Topological relationship between nodes

Optimising distance parameter only: η



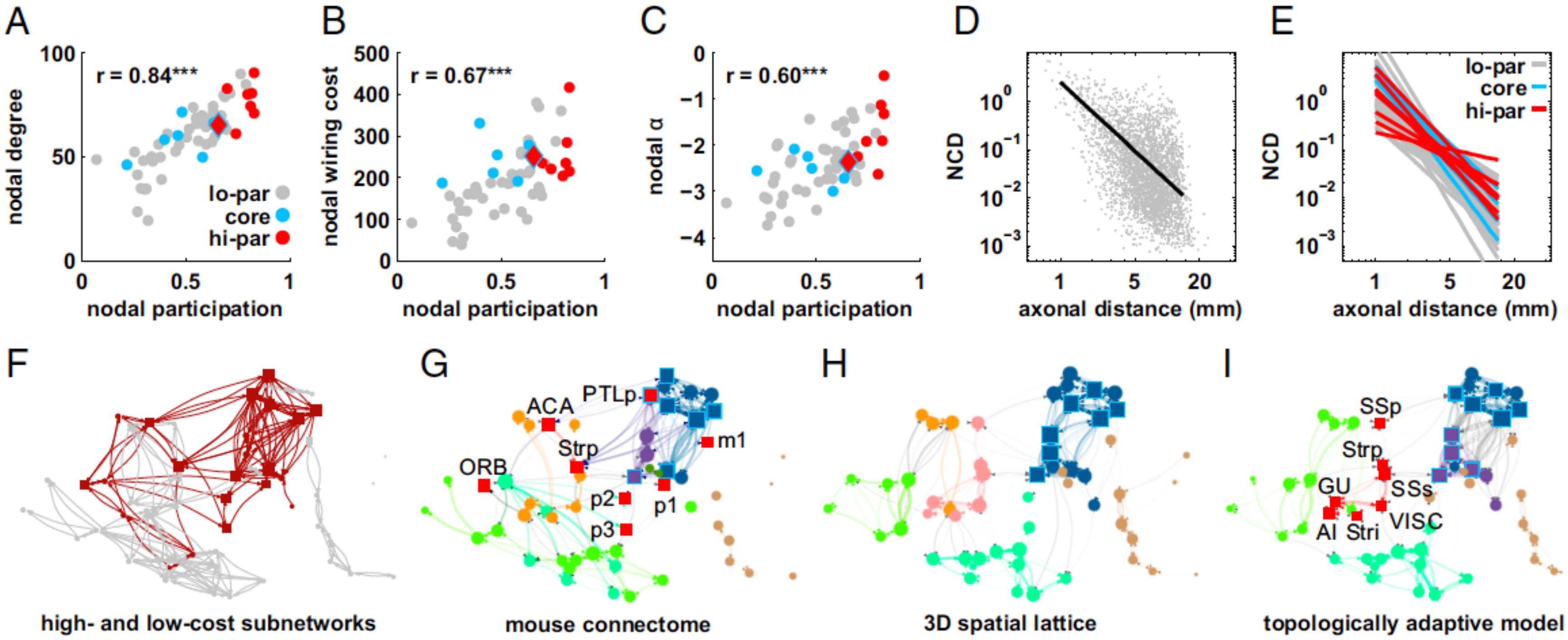
Optimising distance & topology parameters: η, γ



Results favouring cost-topology trade-off models, compared to cost-minimization models were internally replicated across 4 independently designed and conducted DTI studies

Betzel et al (2016) *NeuroImage*

A generative model that minimizes wiring cost is not sufficient to recapitulate the mouse tract-tracing meso network



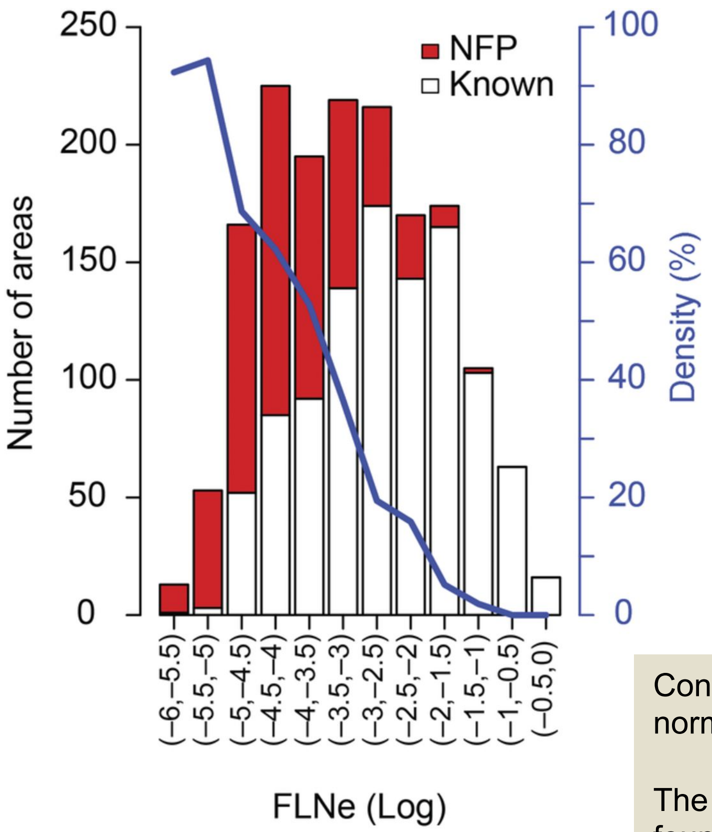
High degree hub regions have high participation – indicating a high ratio of inter-modular to intra-modular efferent axonal projections from hi-par regions

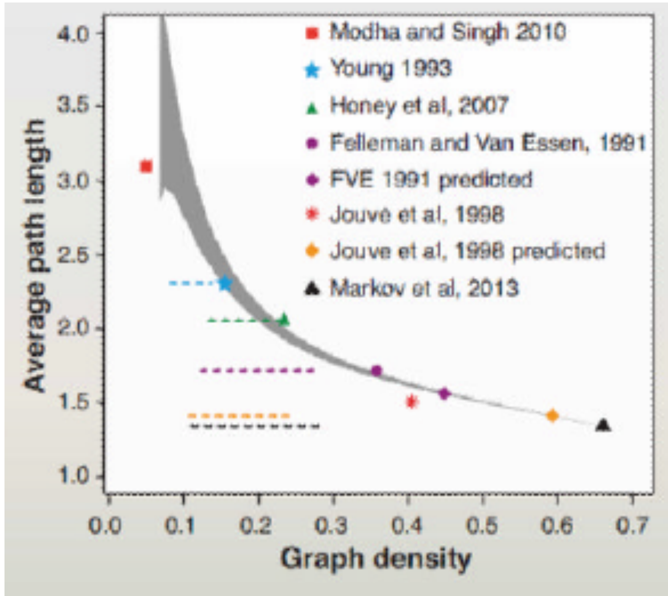
Hi-par regions have higher wiring cost and the power law relationship between anatomical connectivity strength (NCD) and axonal distance has a less negative exponent α, indicating that connectivity strength falls off less sharply as a function of increasing distance between hi-par nodes

A generative model that minimizes wiring cost (tract distance) approximately reproduces the topologically and spatially clustered specialist modules but not the more integrative hi-par nodes

Rubinov, Ypma et al (2015) *Proc Natl Acad Sci USA*

Analogical or comparative analysis across scales and species will often be conditioned by methodological differences





Markov et al (2012) *Cereb Cortex*
Markov et al (2013) *Science*

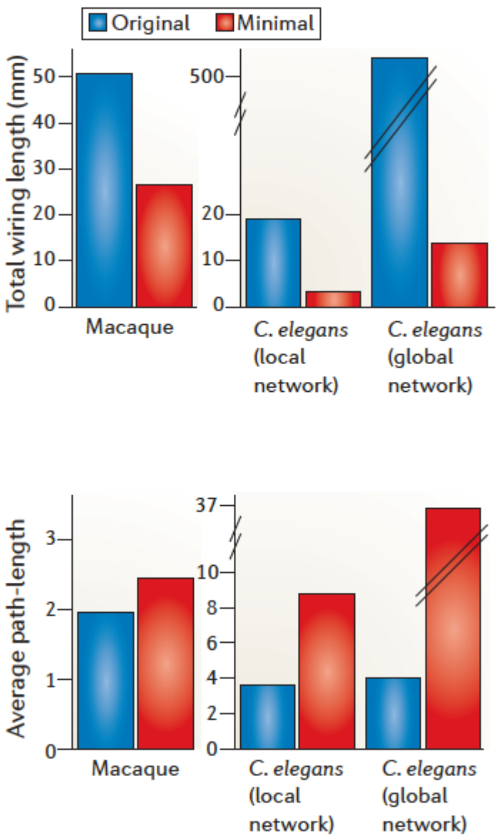
Contemporary tract tracing indicates that weight of anatomical connectivity is log-normally distributed over 5 orders of magnitude

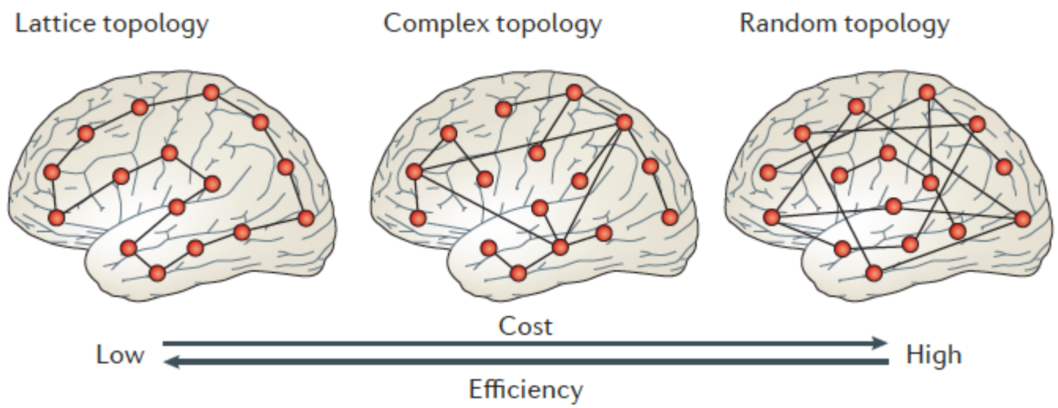
The weaker connections – low fraction of labelled neurons (FLNe) are often new found projections (NFPs), not known to classical tract-tracing techniques

The connection density of macaque (and mouse) cortex is >60% -much less sparse than previously estimated

In contrast, human MRI networks will often have connectivity estimated by correlations in the range (-1,1) and thresholded graph density in the range 5-30%

Comparative connectomics supports general economical principles of brain network organization



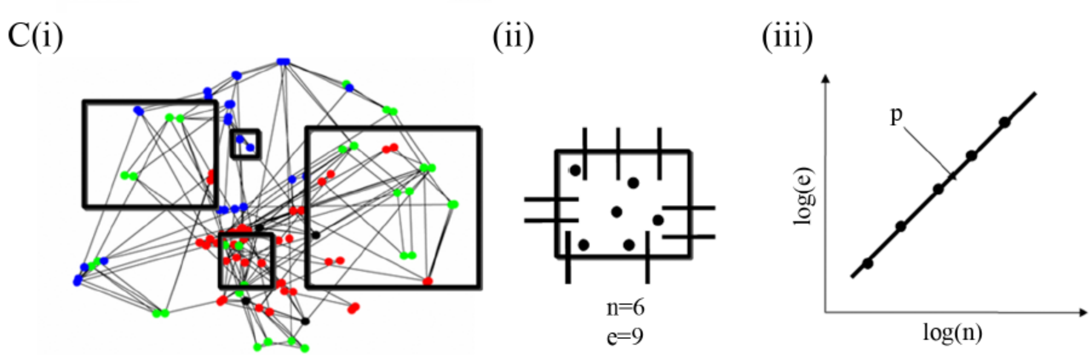


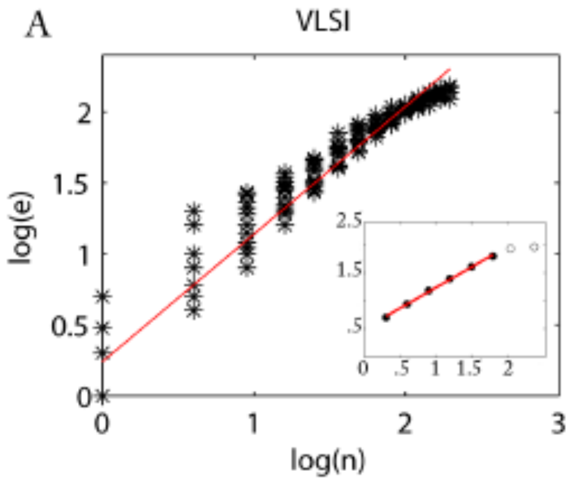
Economical principle of a trade-off between minimization of biological costs versus maximisation of the integrative capacity of the network

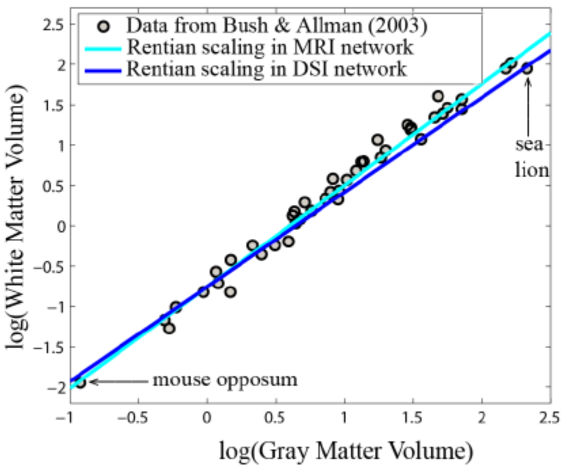
Kaiser & Hilgetag (2006) *PLoS Comp Biol;* Bullmore & Sporns (2012) *Nat Rev Neurosci*

What's special about the human brain network?

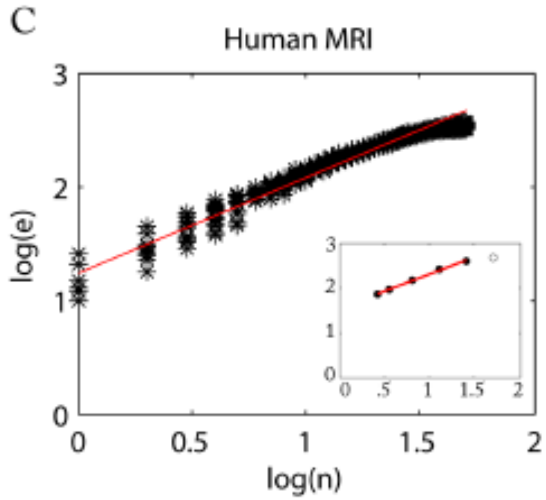
Rentian scaling as a measure of topological dimension, economical embedding and allometric scaling in chips and brains







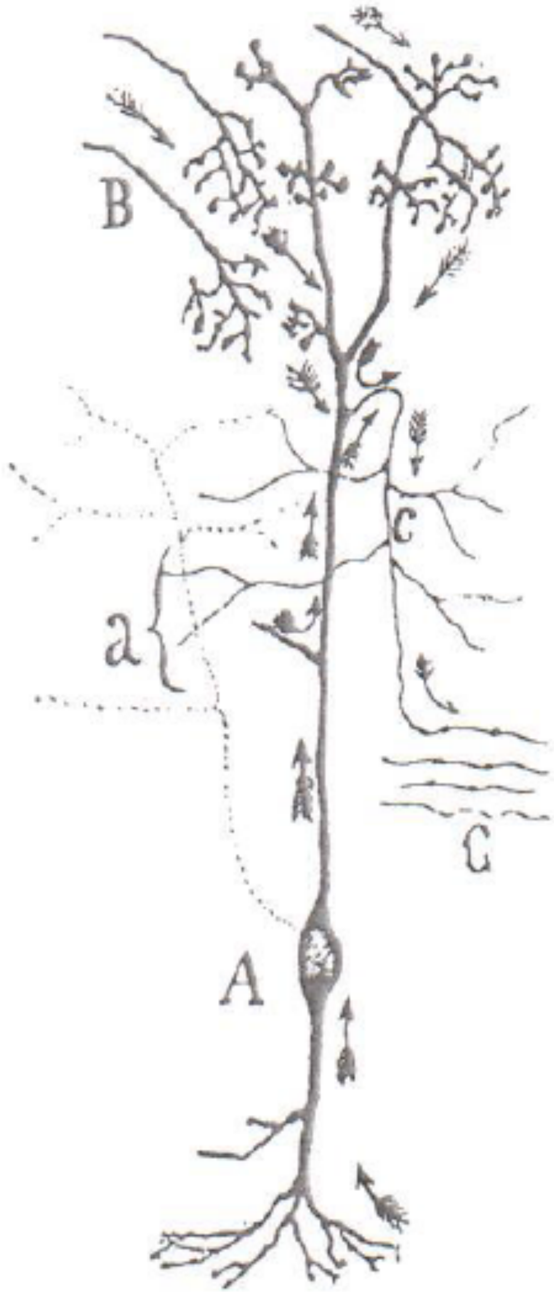
High dimensional (>4) brains and VLSI circuits are both economically embedded in lower dimensional physical space (3) with hierarchical modularity and near-minimal Rent exponents



Bassett et al (2010) *PLoS Comp Biol*

Conservation laws of nervous systems

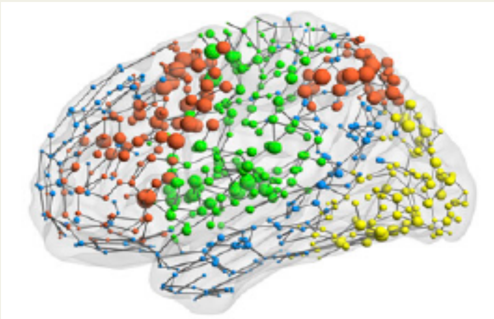
"Finally we realized that all of the various conformations of the neuron are simply morphological adaptations governed by laws of conservation for time, space and material which must be considered the final cause of all variations in the shape of neurons"

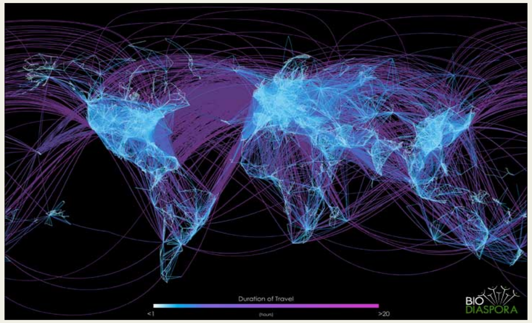


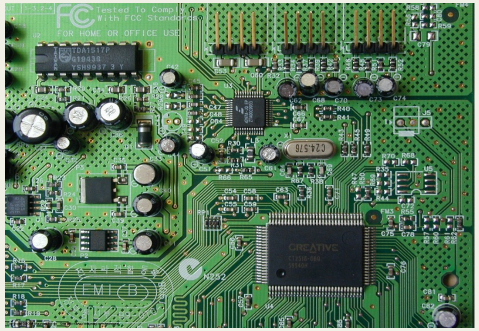
Ramón y Cajal (1899-1904) *Histology of the Vertebrate Nervous System*
(Translated: Swanson & Swanson (1995))

Universality and self-similarity

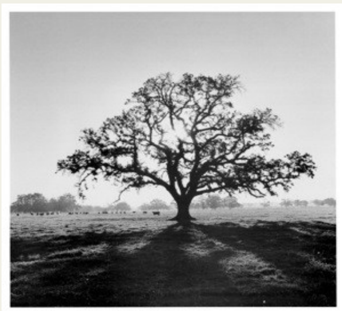
What's special about brain networks?

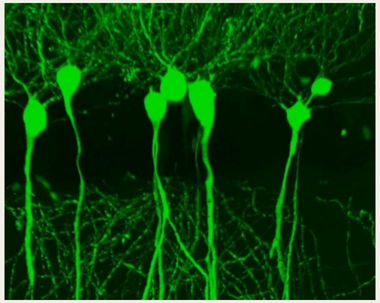


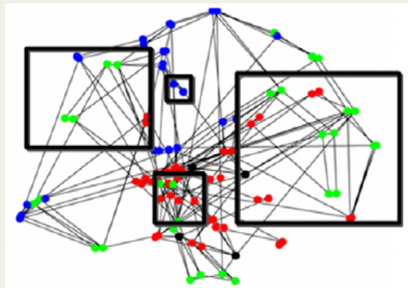




Do brain networks have fractal patterning from micro to macro scales?

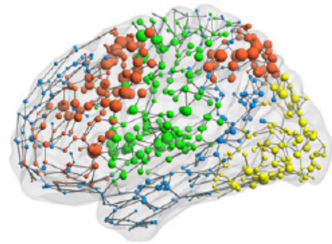






Ramón y Cajal (1895); CLARITY; Bassett et al (2010) *PLoS Comp Biol*

Conclusions



- Biological validation of human MRI networks can be addressed by analogical (comparative) or reductionist strategies

- Analogously or comparatively, many aspects of MRI network topology have been recapitulated in more certainly known brain networks

- Reductionistically, we are entering an exciting phase of being increasingly able to link MRI network topology to cellular organization, neuronal network dynamics, myelination, and gene expression

- A common theme emerging from both analogical and reductionist analyses is the economical principle that more integrative elements of network topology are more biologically expensive

Many Thanks!

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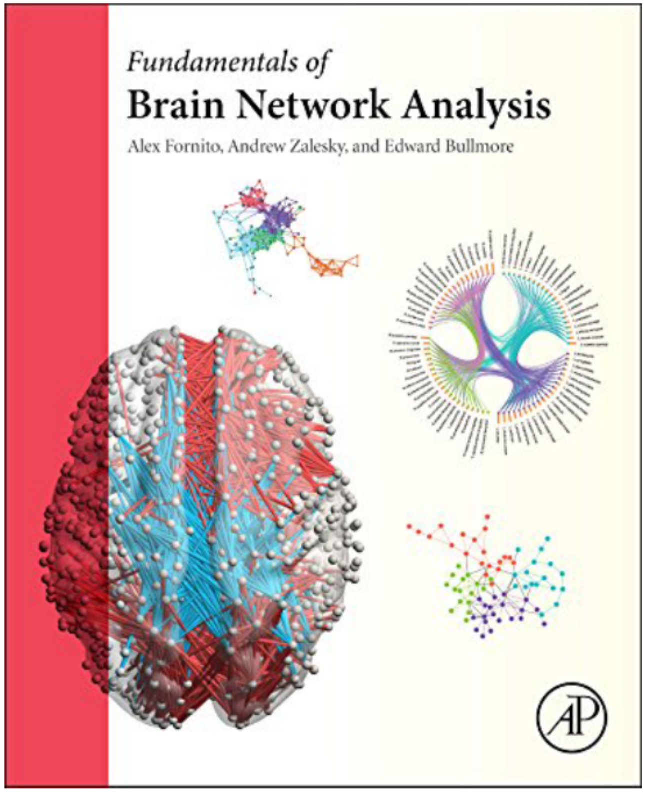
- Emma Towlson
- Martijn van den Heuvel
- Frantisek Vasa
- Petra Vértes
- Kirstie Whitaker
- Rolf Ypma
- Andrew Zalesky



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