Network theory and brain disorders

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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

Ed Bullmore

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

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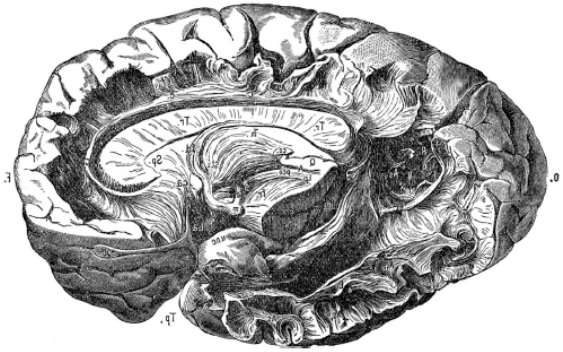
- Wellcome Trust
- National Institute for Health Research
- National Institutes of Health, Graduate Partnership Program

Brain networks and psychiatry go back a long way

Theodor Meynert

(1833-1892)

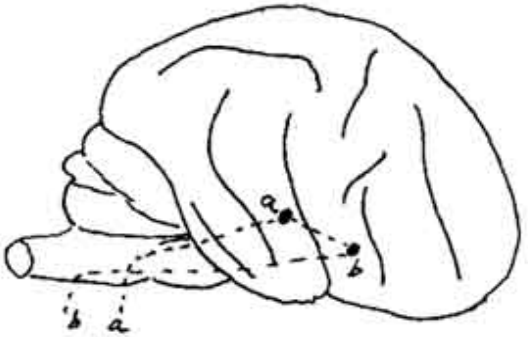
Anatomy of white matter

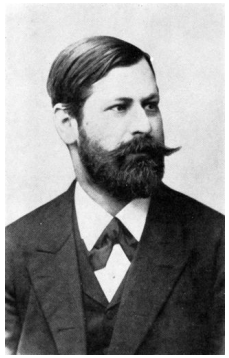


Carl Wernicke

(1848-1905)

Aphasia and psychosis as disorders of large scale brain connectivity



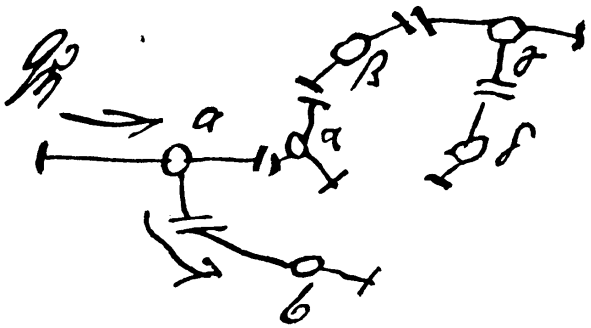


Sigmund Freud

(1856-1939)

Project for a Scientific Psychology

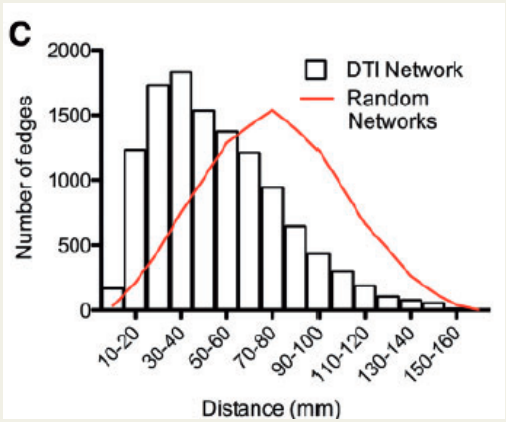
Mental states represented by flow of libido through cellular circuits

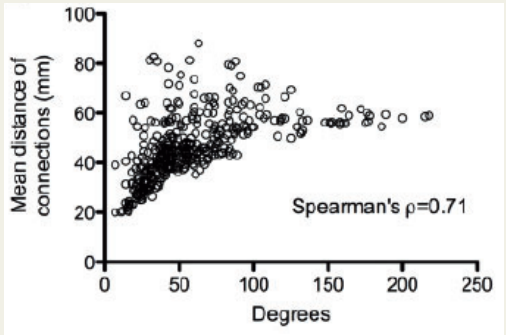


Economics of brain networks

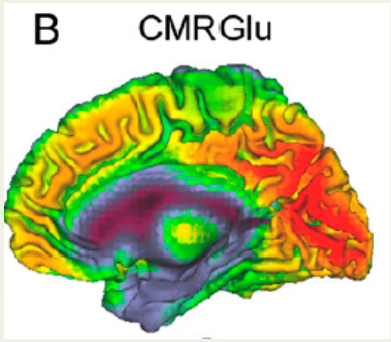
A trade-off between “biological cost” and “topological value”

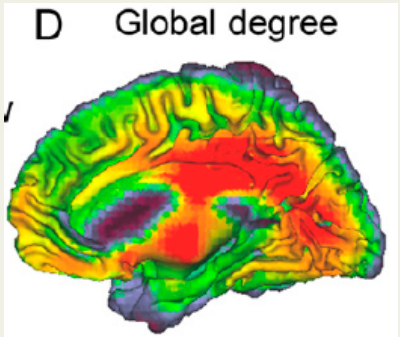
wiring cost of DTI networks

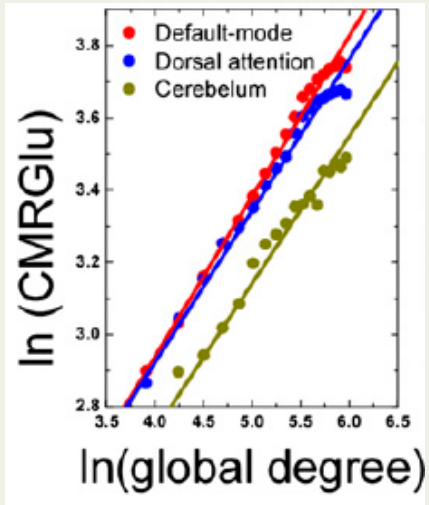




metabolic cost of fMRI networks

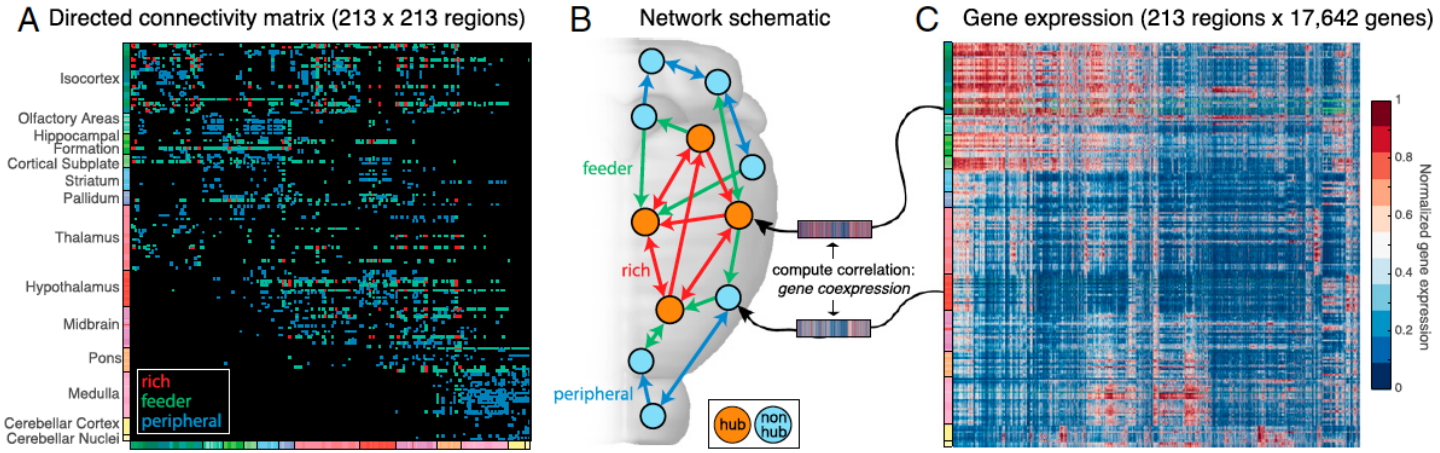


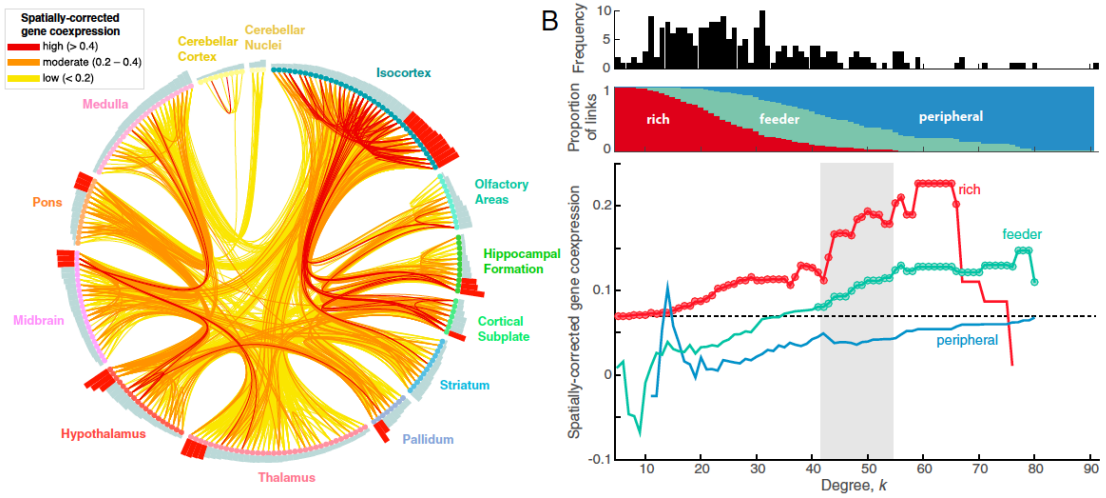




Crossley et al (2014) *Brain*
Tomasi et al (2013) *Proc Natl Acad Sci (USA)*

Mouse connectome topology and gene expression:
connected hubs co-express genes for oxidative metabolism





Anatomical connections between hub regions of the mouse tract-tracing connectome constituted a rich club.

Hub-hub connections linked brain regions that strongly co-expressed a set of genes significantly enriched for oxidative metabolism.

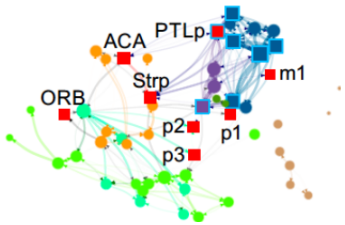
Fulcher & Fornito (2016) *Proc Natl Acad Sci USA*

Genomics meets connectomics (in the mouse brain)

Reducing the dimensionality of a high dimensional problem

O(10) nodal topology metrics

O(10^4) mRNA measurements



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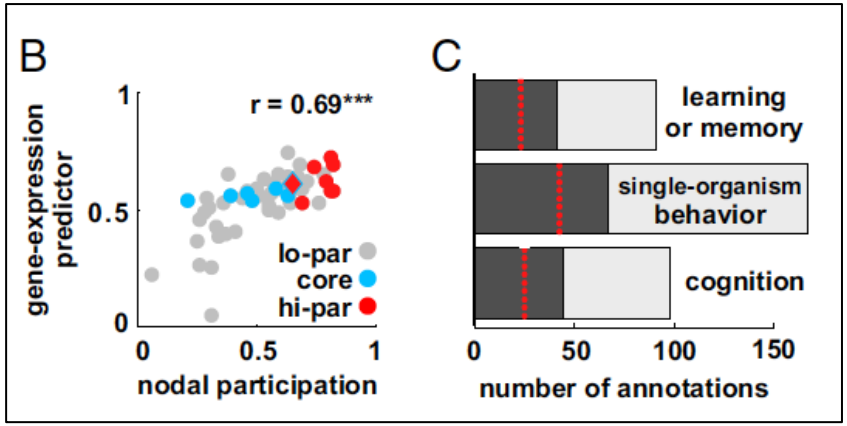
O(10^2) regions

O(10^2) regions

Partial Least Squares (PLS) is a family of multivariate methods for finding a few components that maximise the covariance between a set of response variables and a larger set of collinear predictor variables

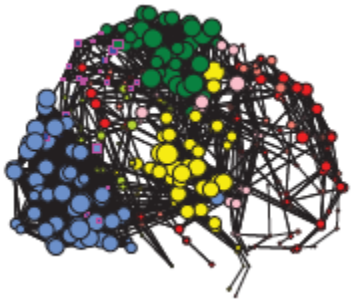
Response variables = nodal topology (participation)
Predictor variables = nodal gene expression



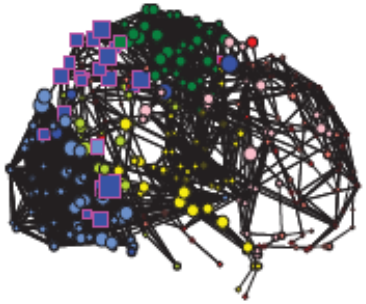
McIntosh & Bookstein (1996) *NeuroImage*
Rubinov, Ypma et al (2015*) Proc Natl Acad Sci USA*

Genomics meets connectomics (in the human brain)

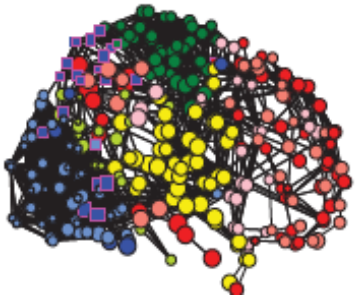
intra-modular degree



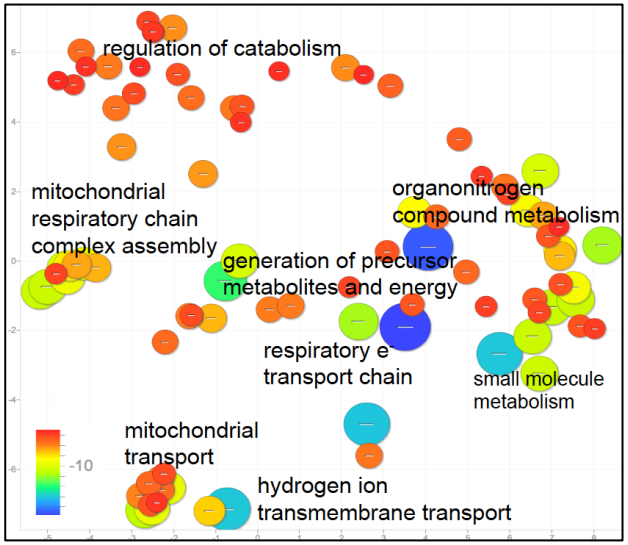
inter-modular degree



connection distance

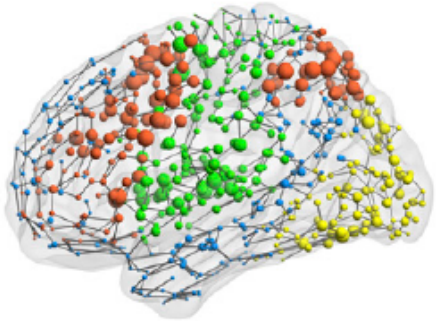


	k	PC	k_{intra}	k_{inter}	d
PLS1	*0.50*	**−0.26**	*0.59*	0.07	**−0.34**
PLS2	*0.26*	*0.45*	−0.01	*0.48*	*0.28*

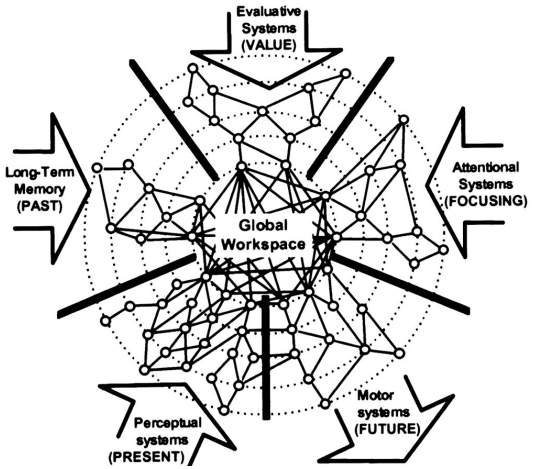


Vértes et al (2016) *Phil Trans Roy Soc*

Cartoon of the economical connectome



Efficiency
Connector hubs
Rich clubs
Higher wiring cost
Higher metabolic cost



Workspace architecture

Slow, smart thinking

Domain general functions

Clustering
Modules
Lower wiring cost

Phrenological architecture

Fast, dumb thinking

Domain specialised functions

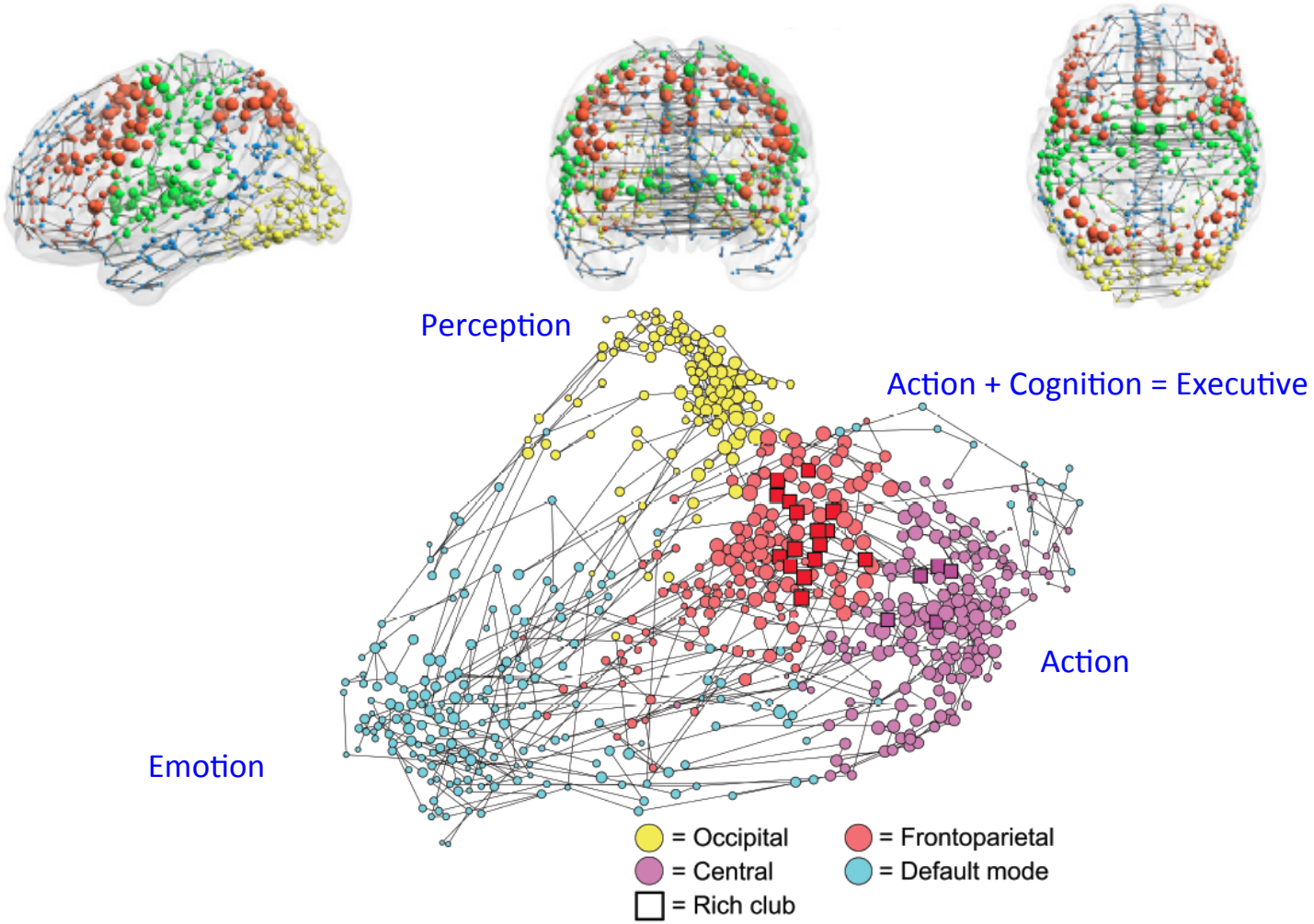
Bullmore & Sporns (2012) *Nat Rev Neurosci*

Dehaene et al (2010) *Proc Natl Acad Sci*

Fodor (1983) *Modularity of Mind*

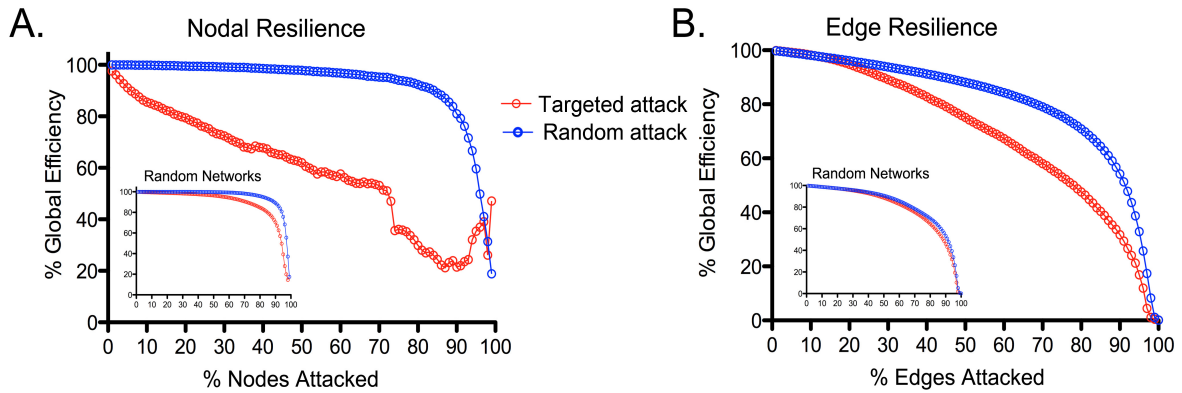
Cognitive value of topological integration in human brain

Meta-analysis > 1500 fMRI primary studies

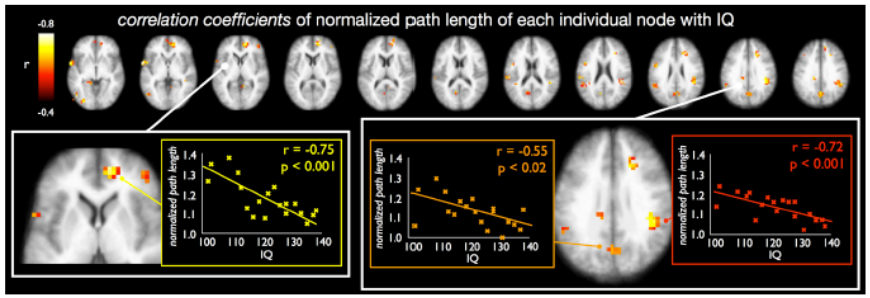


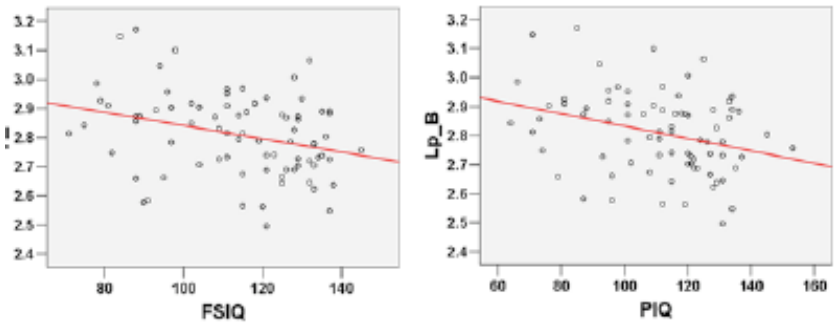
Crossley et al (2013) *Proc Natl Acad Sci (USA)*

Biologically expensive hubs may be “worth it” because they enable network integration, which is cognitively valuable



Hubs are important for integrative network configuration – targeted attack on hubs (or long distance edges) degrades global efficiency much faster than random attack



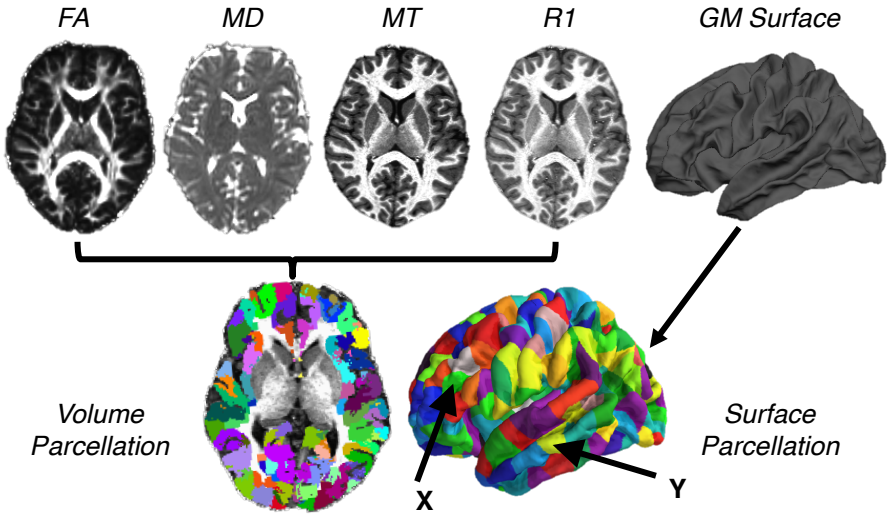


Integrative network configuration is important for adaptive behaviour and cognition – higher IQ goes with with shorter network path length (greater global efficiency)

Crossley et al (2015) *Brain*; van den Heuvel (2009) *J Neurosci*; Li et al (2009) *PLoS Comp Biol*

Morphometric similarity mapping

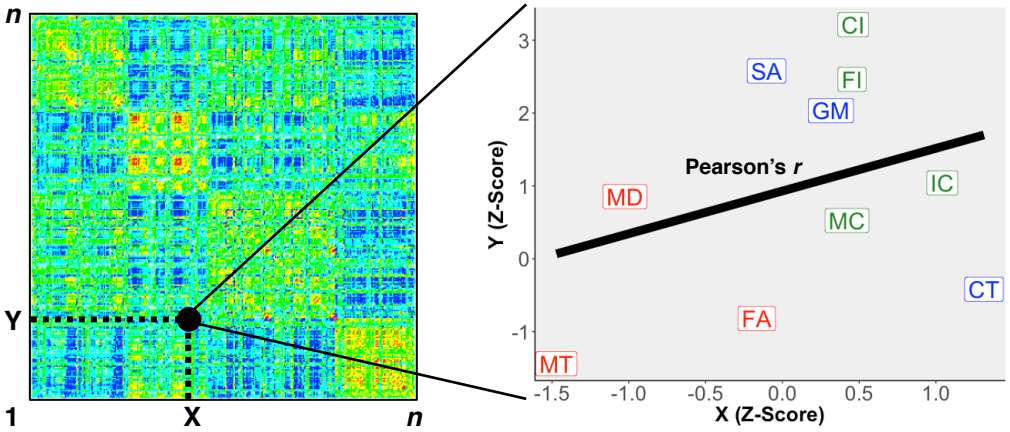
A new approach for single subject structural network analysis



Multiple morphometric features per regions

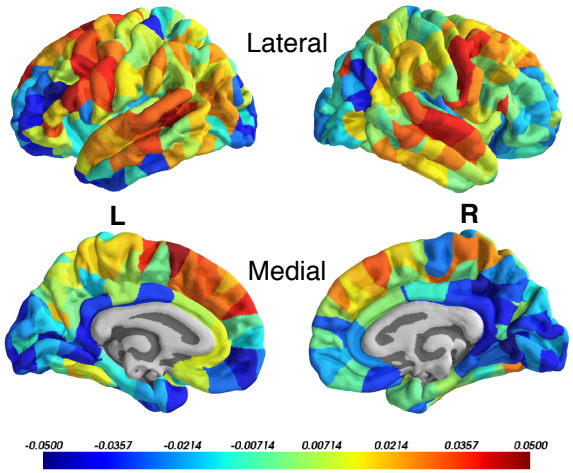
Myelination			Gray Matter			Curvature			
FA	MD	MT	GM	SA	CT	IC	MC	CI	FI

Morphometric Similarity Matrix (MSM, N=1)

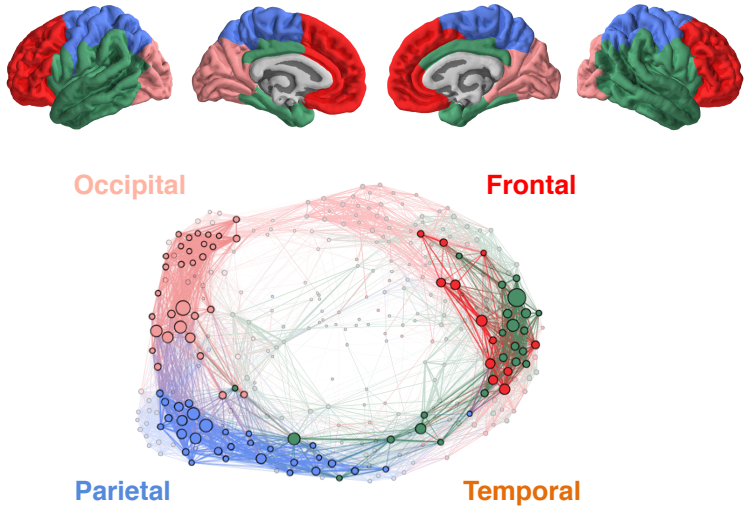


Morphometric Similarity Network (MSN, N=1)

Weighted degree

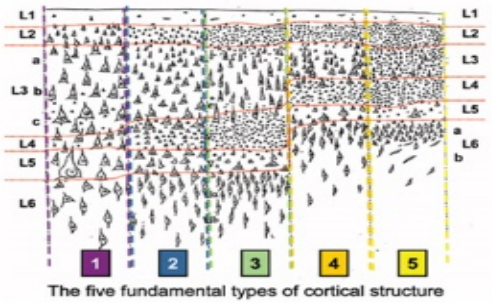


MSN Modules and Rich Club (10% Connection Density)

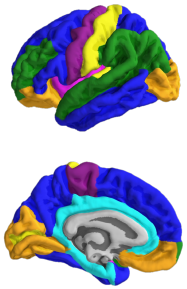


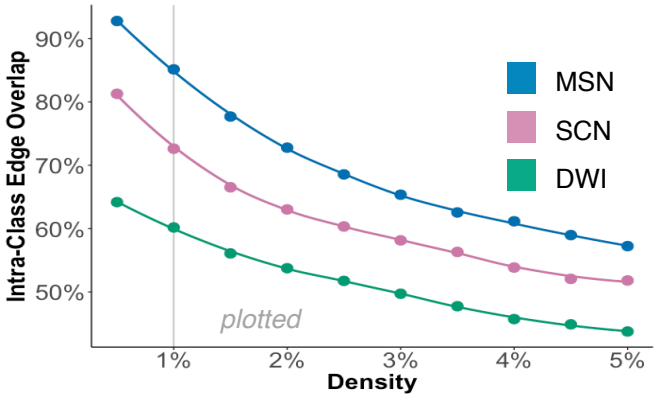
Morphometric similarity networks are more consistent with cytoarchitectonics than structural covariance networks (SCN) or diffusion weighted imaging (DWI)

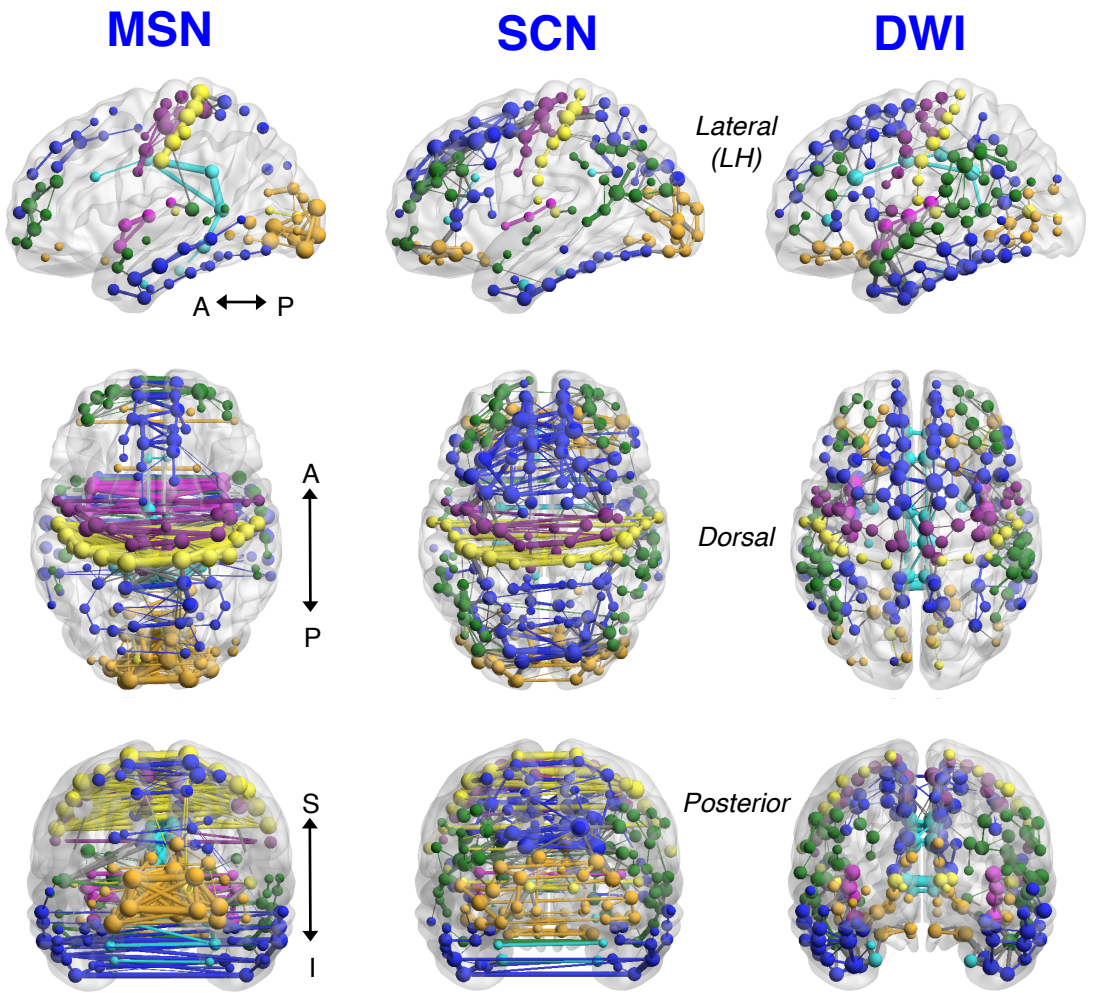
Von Economo cytoarchitectonic classification



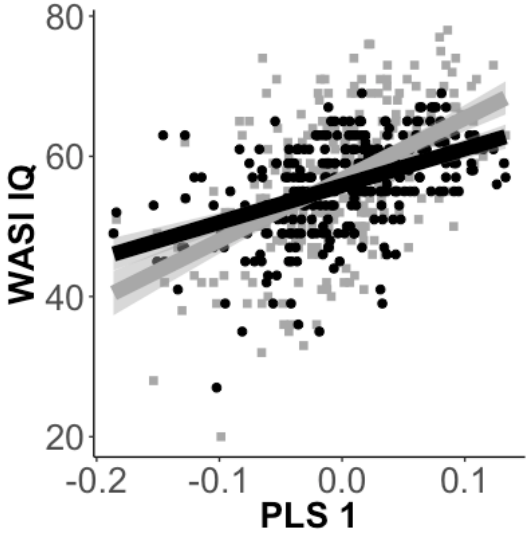
Solari & Stoner, 2011

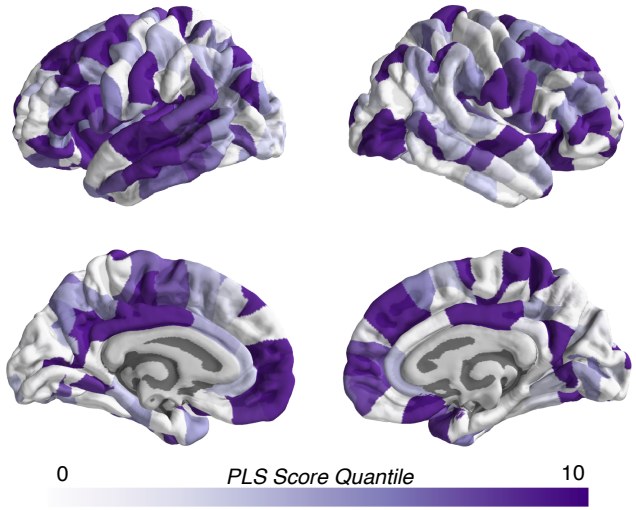


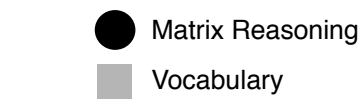


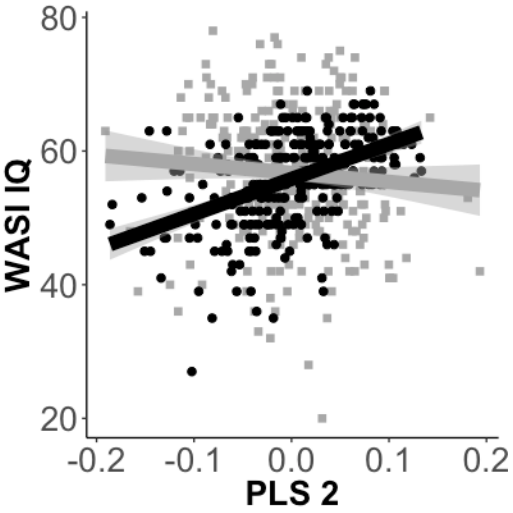


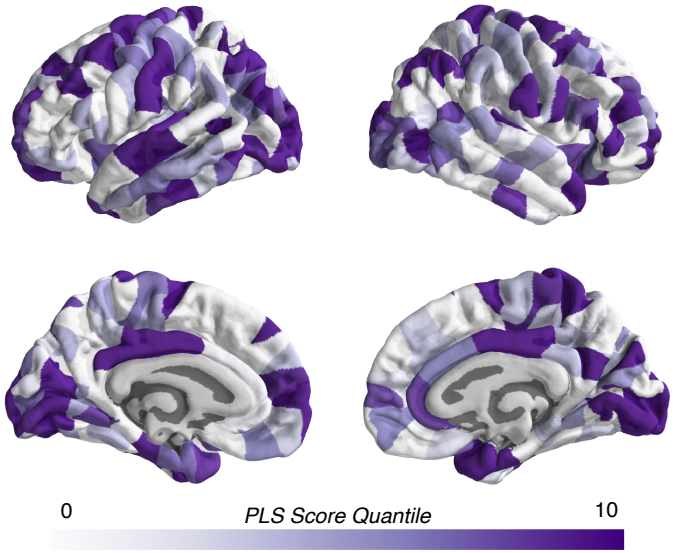
Hubs of morphometric similarity networks predict about 40% of between-subject variance in IQ



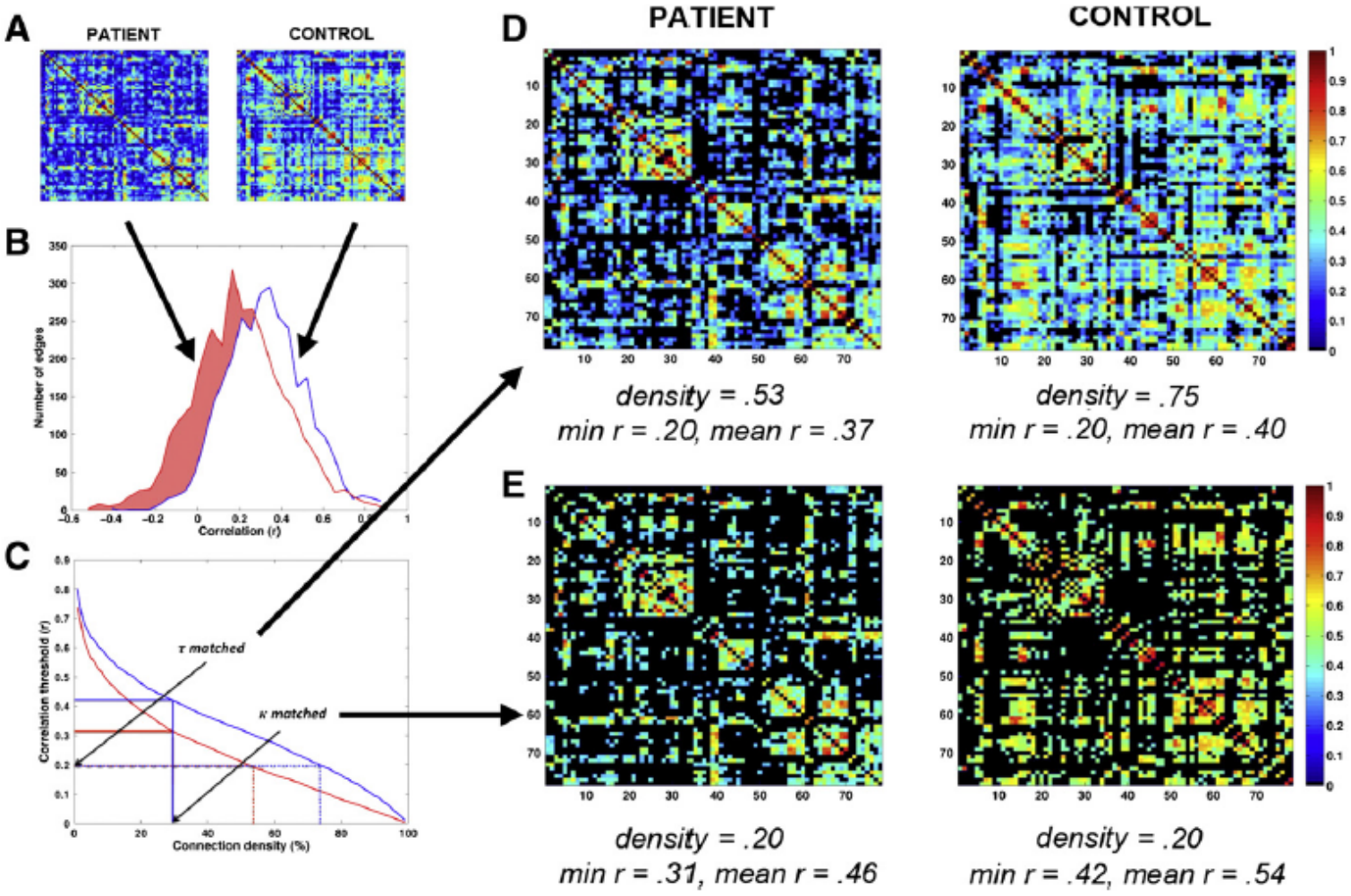






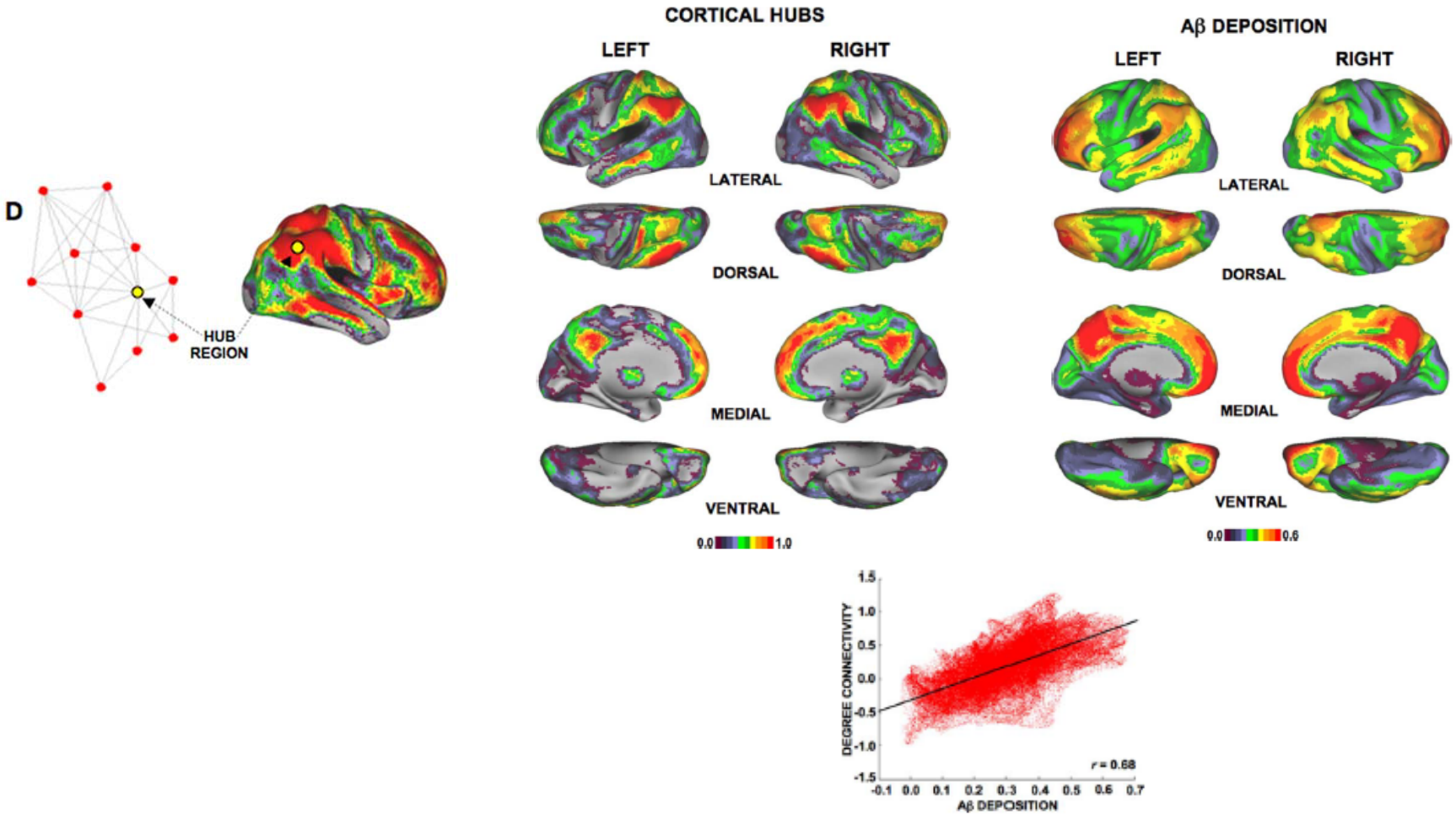


Case-control comparisons can be tricky in fMRI network studies of clinical disorders



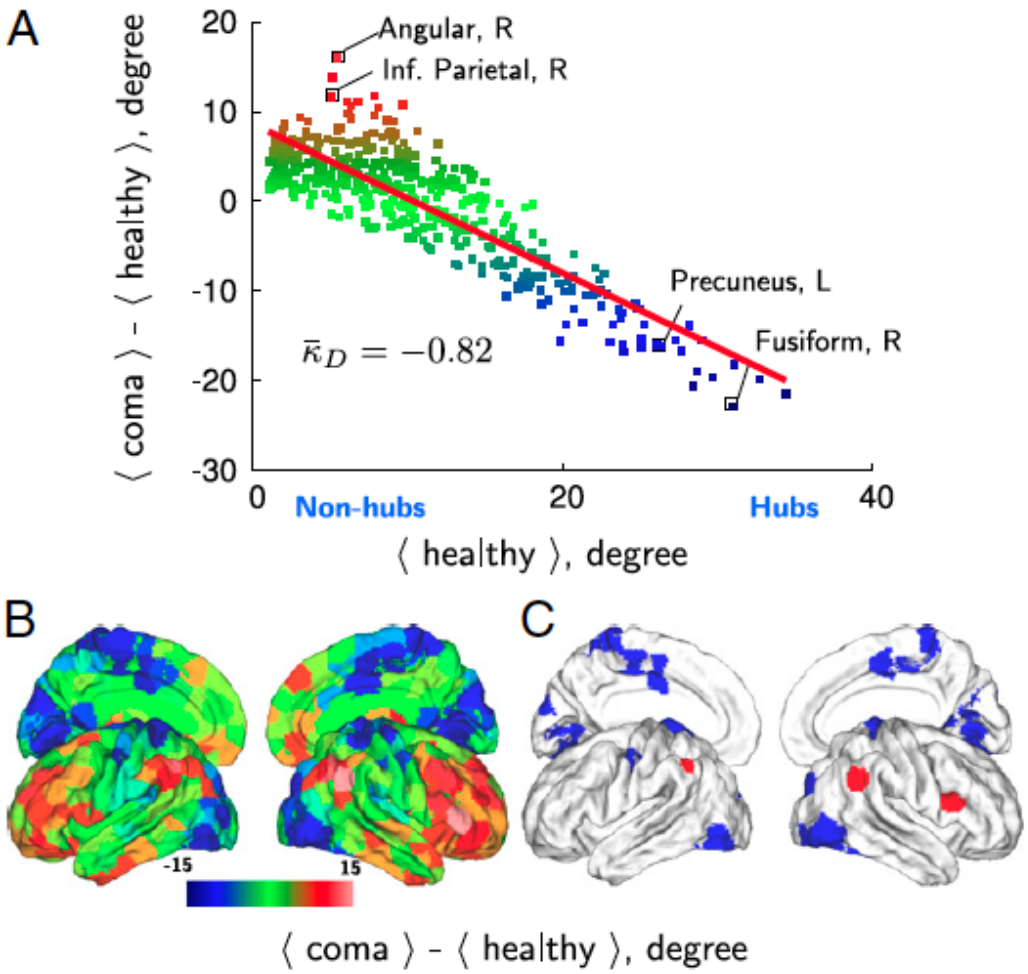
Fornito et al (2012) *NeuroImage*

The hubs of brain networks are most vulnerable to amyloid deposition in Alzheimer's disease



Buckner et al (2009) *J Neurosci*; Buckner et al (2008) *Ann NY Acad Sci* ***[review]***

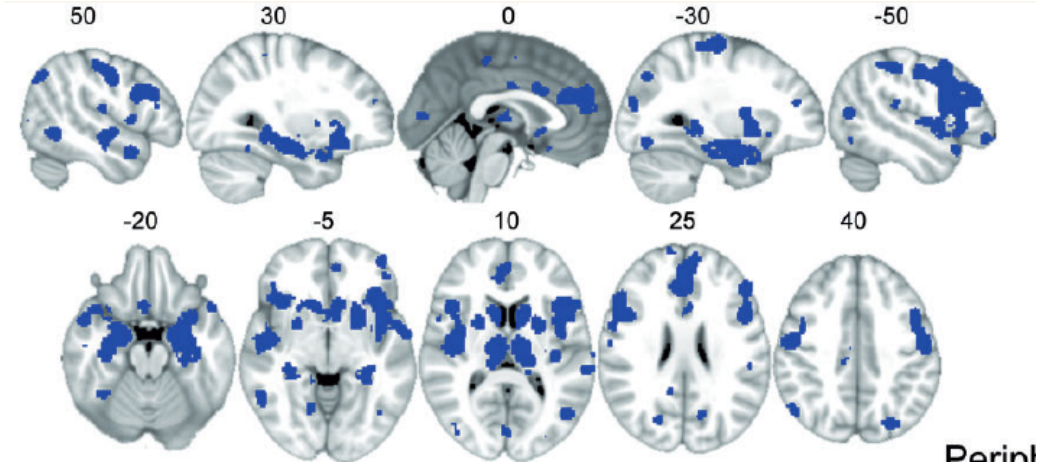
Coma due to acute brain injury is associated with radical disruption of hubs

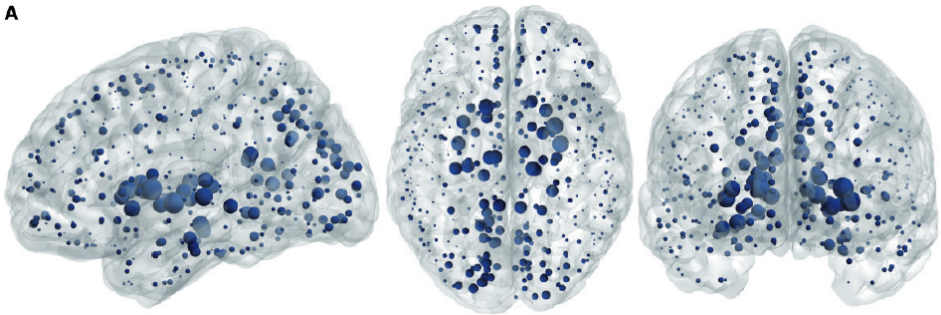


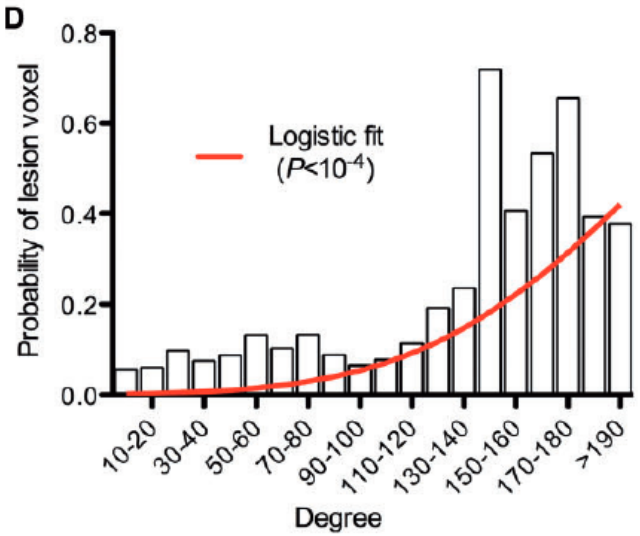
Achard et al (2012) *Proc Natl Acad Sci (USA)*

High cost / highly central hubs are brain disease “blackspots”

Meta-analysis of MRI data on 20,000 patients, 26 disorders





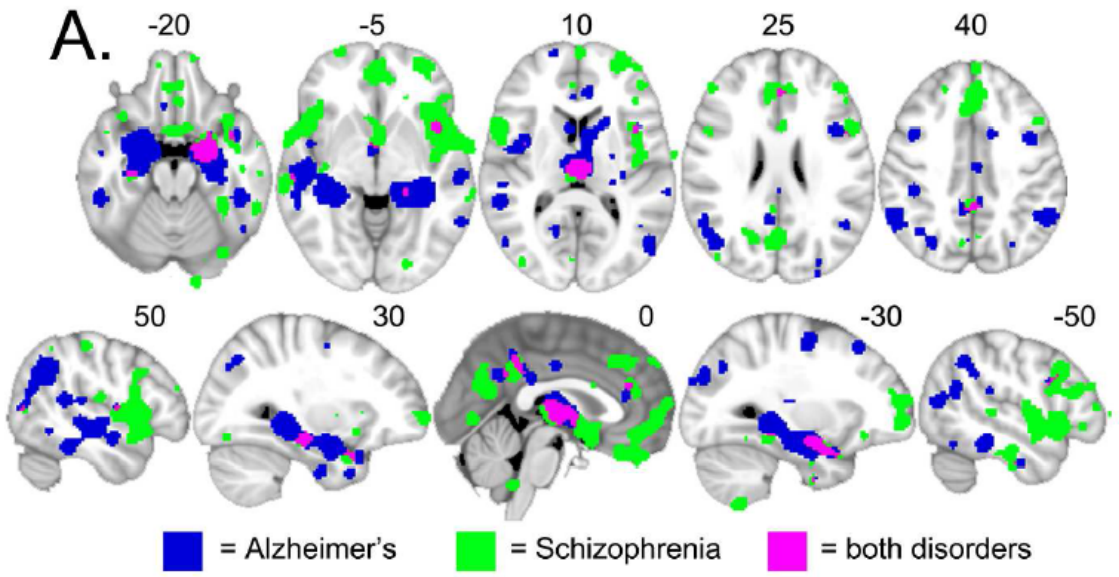


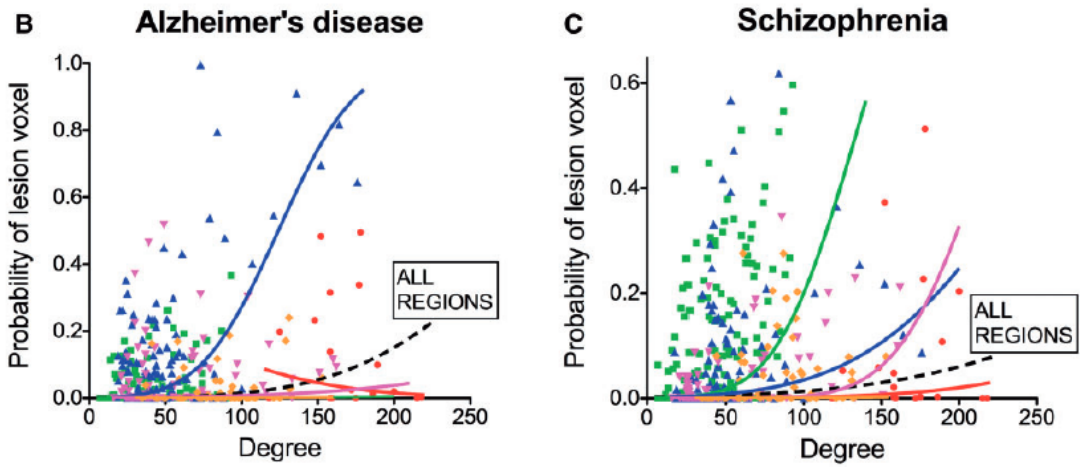
High cost could make hubs more vulnerable to disease processes

High centrality could make lesioned hubs more likely to be symptomatic

Crossley et al (2014) *Brain*

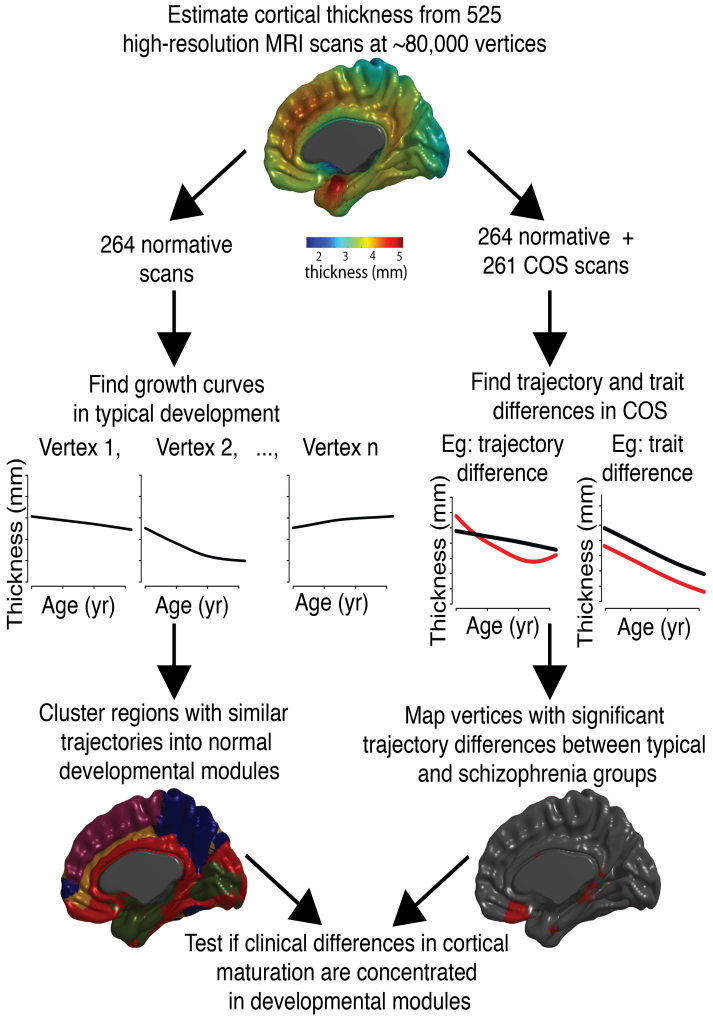
Alzheimer's disease and schizophrenia both preferentially impact hubs, but not the same hubs

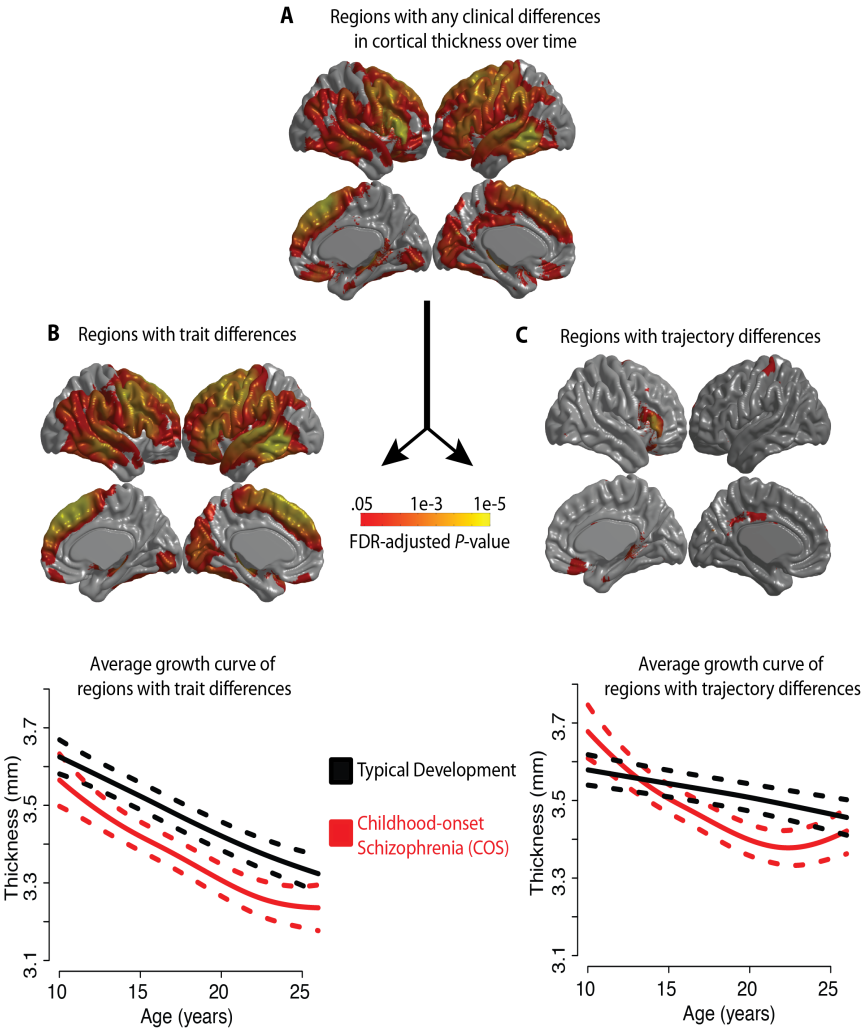




Crossley et al (2014) *Brain*

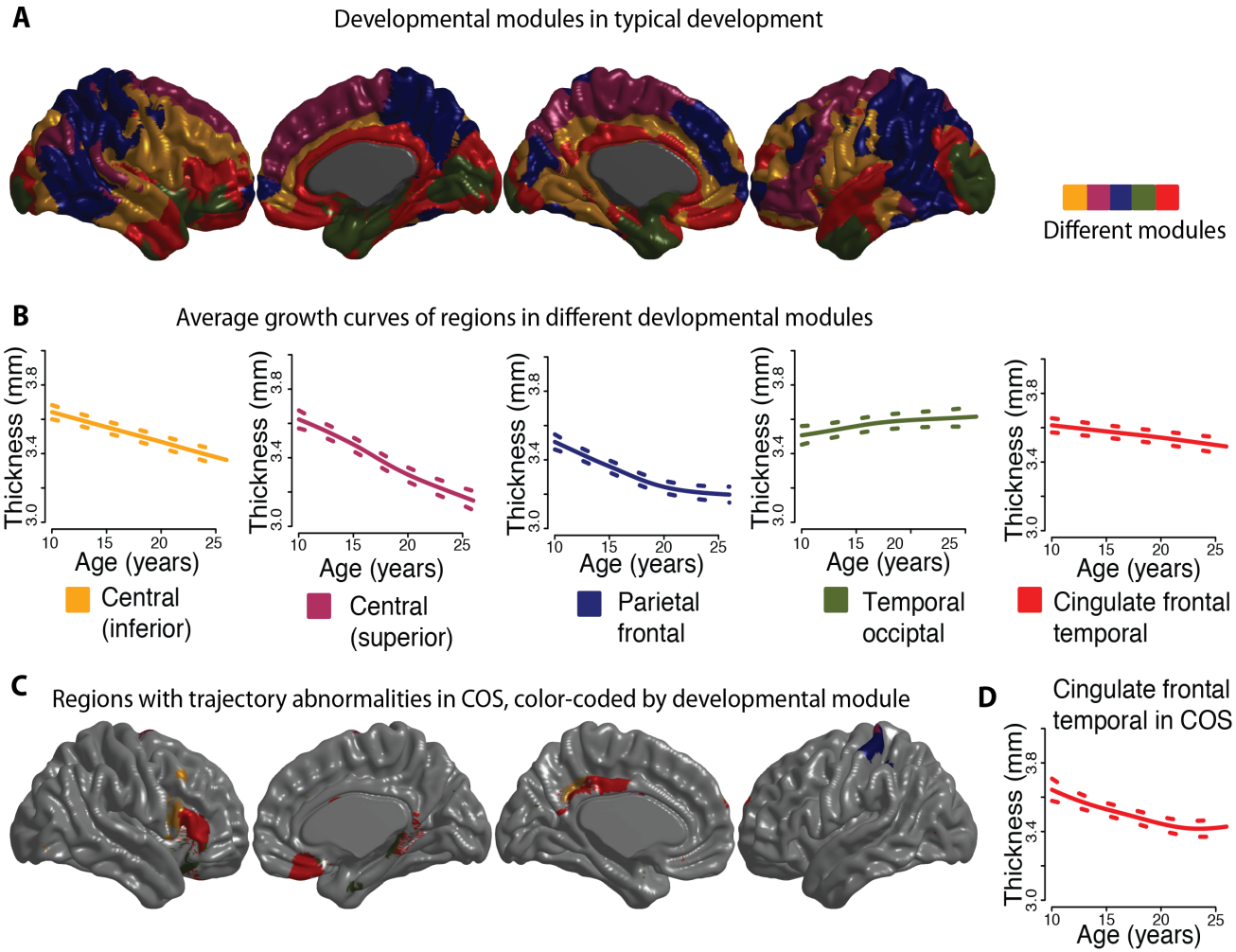
Linking abnormal cortical maturation in schizophrenia to the modular community structure of the anatomical connectome





Alexander-Bloch et al (2014) *Biol Psychiatry*

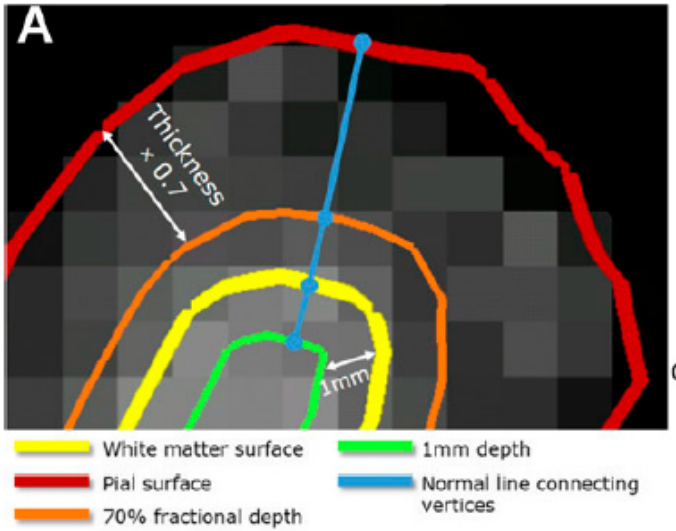
Abnormal trajectories of cortical shrinkage in adolescent schizophrenia are concentrated within a single module of the normal connectome

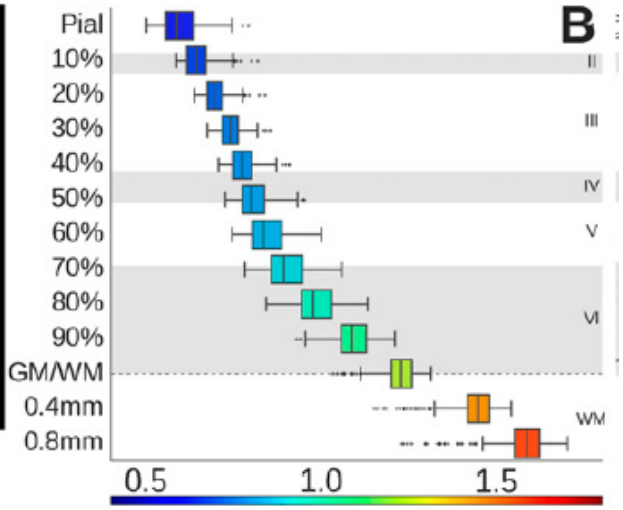


Alexander-Bloch et al (2014) *Biol Psychiatry*

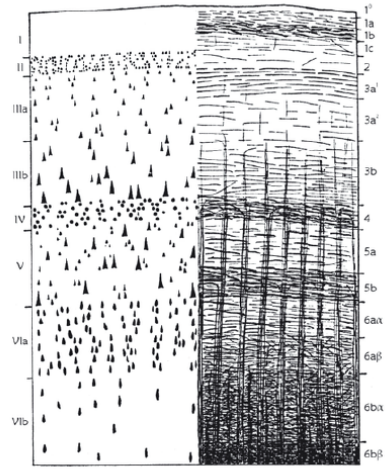
MRI is great for measuring the difference between fat and water

(in the brain that's the difference between myelin and everything else)





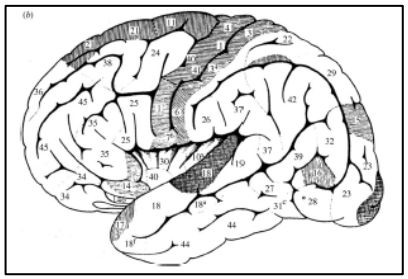
Myelination (MT)



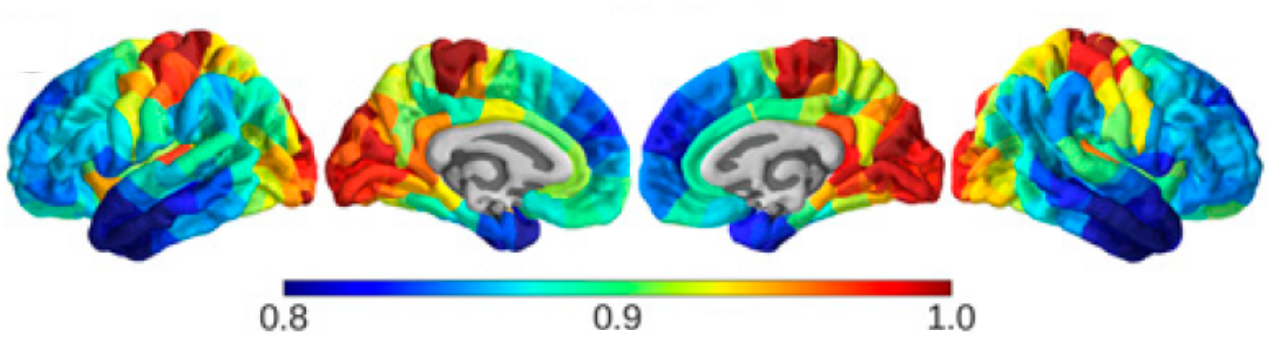
Myelination (Vogt,1903)

Whitaker, Vértes et al (2016) *Proc Natl Acad Sci*

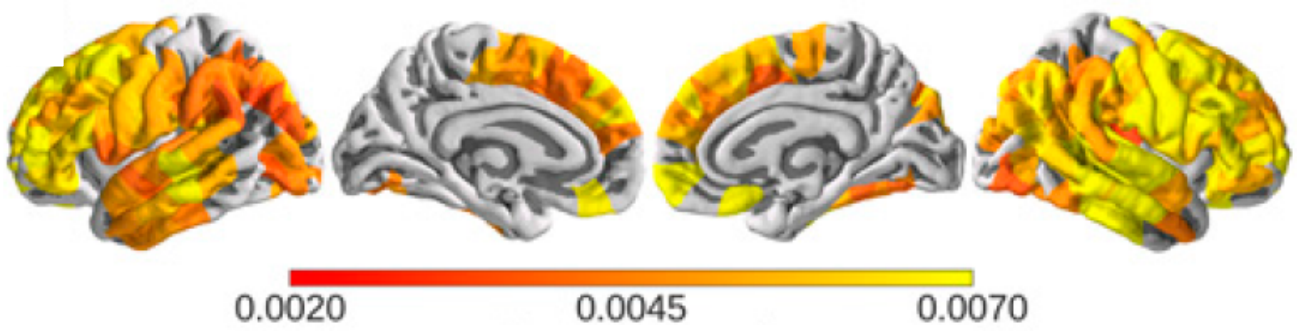
Adolescent shrinkage of association cortex is highly correlated with intracortical myelination



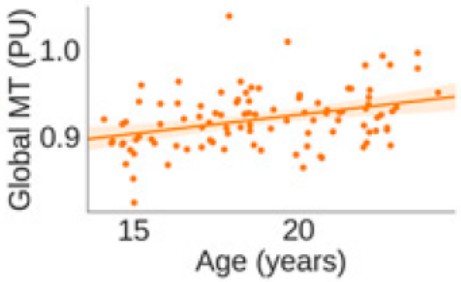
Paul Flechsig (1847-1929)



Myelination map at 14 years old



Map of increasing myelination during adolescence, 14-25 years



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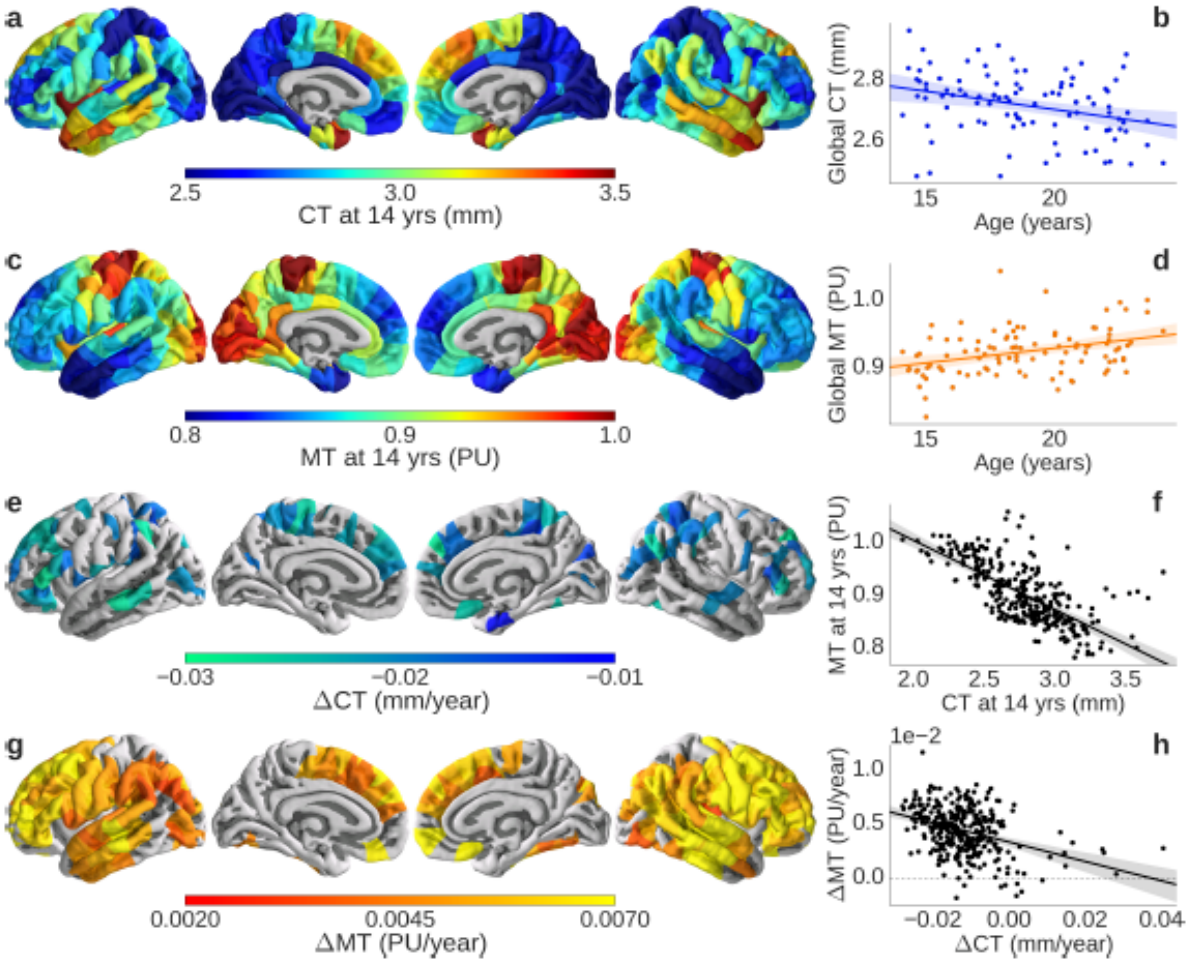
Adolescent shrinkage of association cortex is highly correlated with intracortical myelination



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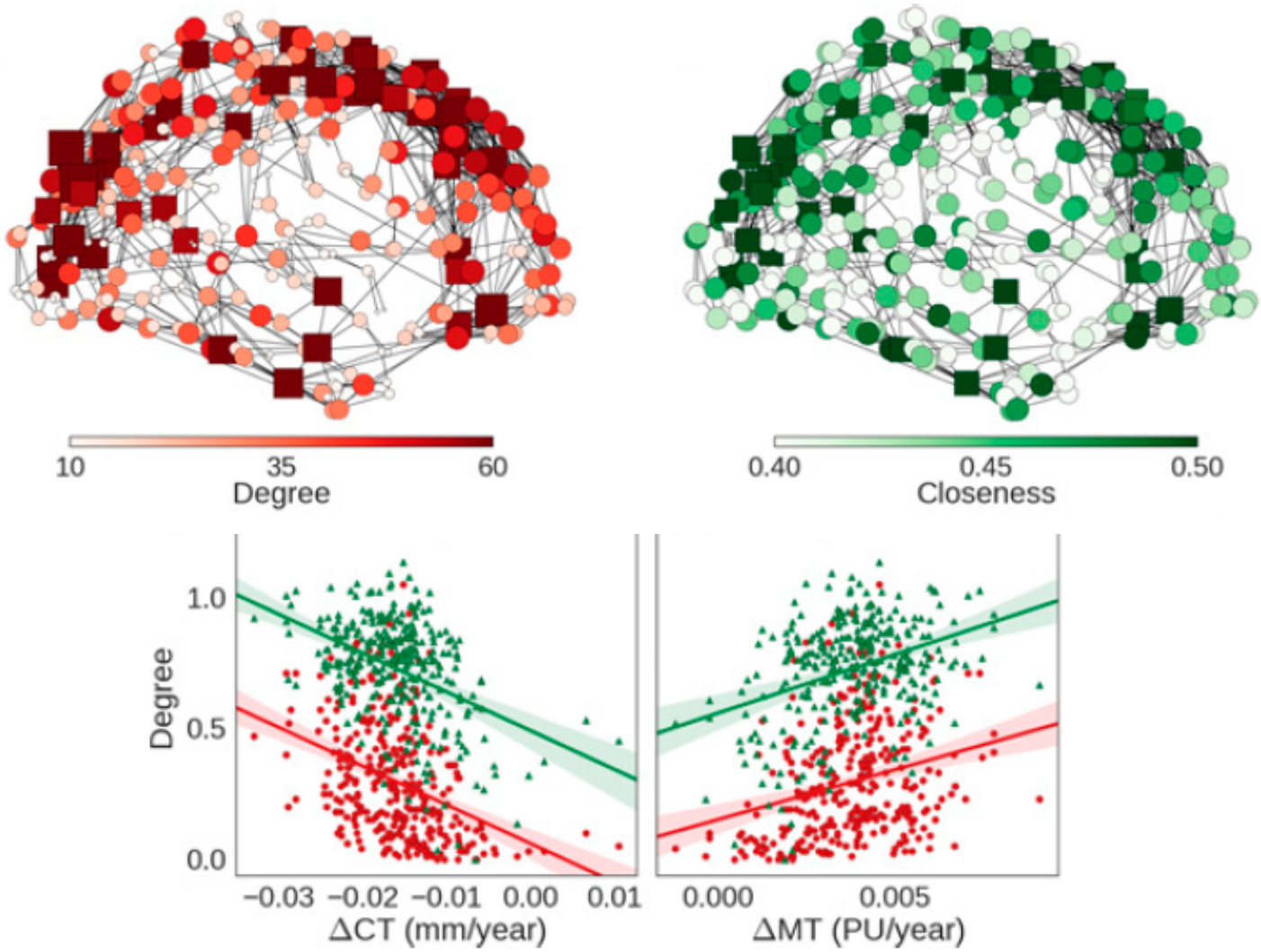
Connectome hubs have fastest rates of cortical myelination (and shrinkage) during adolescence



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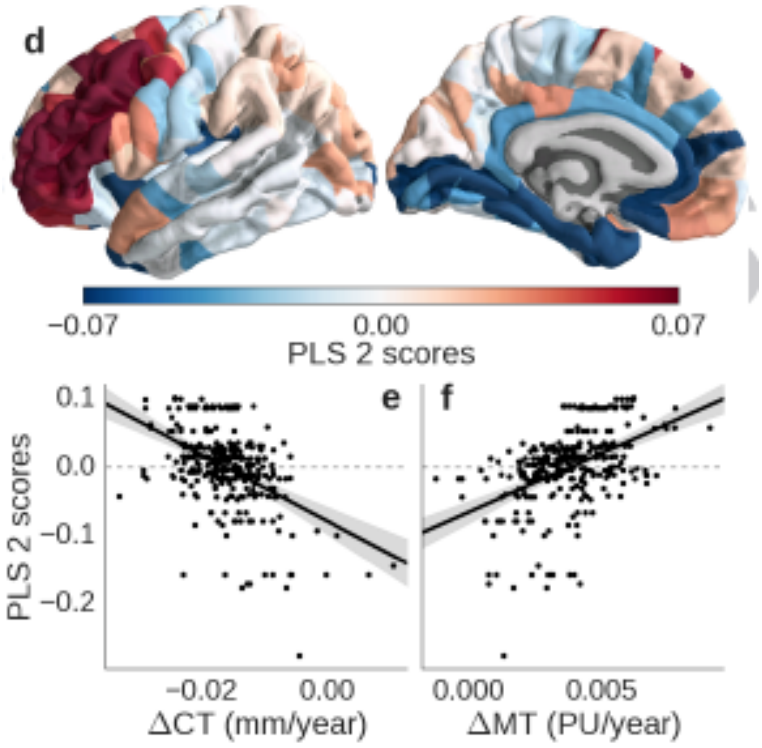
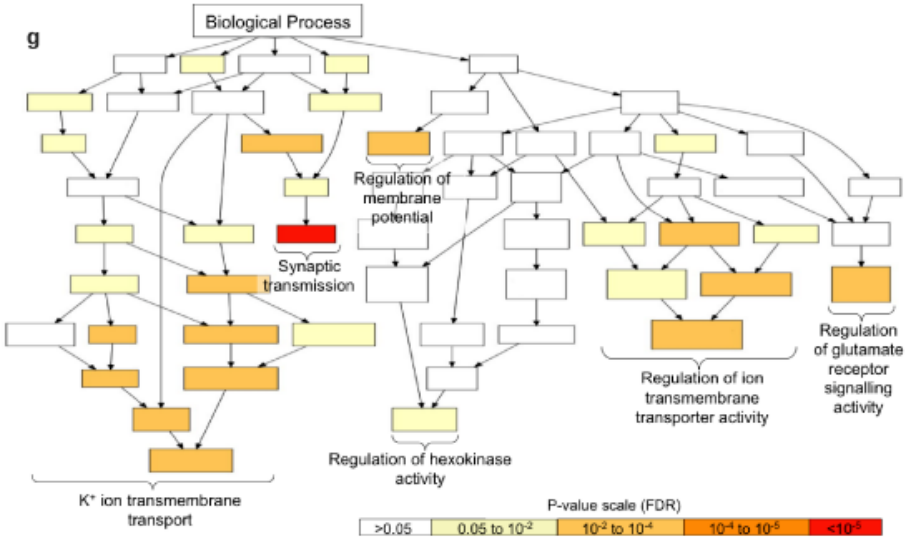
Adolescent myelination of connectome hubs is associated with expression of risk genes for schizophrenia





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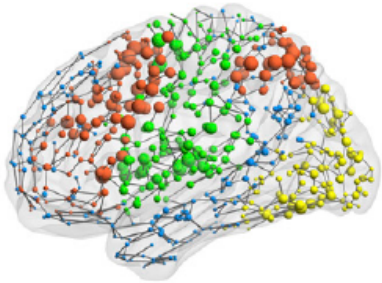
Review



- Psychiatry wanted to understand the connectome long before it was possible
  - Our history is rooted in ideas of brain network disorganization and development
- Connectomes represent a trade-off between biological cost and topological integration
  - Hubs and clubs are biologically expensive but “worth it” for cognitive value added
- High cost / high value network hubs are blackspots for brain disorders
  - Brain network hubs are likely more vulnerable to disease and more symptomatic if lesioned
- Schizophrenia is a disorder of adolescent consolidation of connectome hubs
  - Linking connectomics to genetics can lead to a more mechanistic understanding of abnormal brain network development in mental health disorders

Many Thanks!

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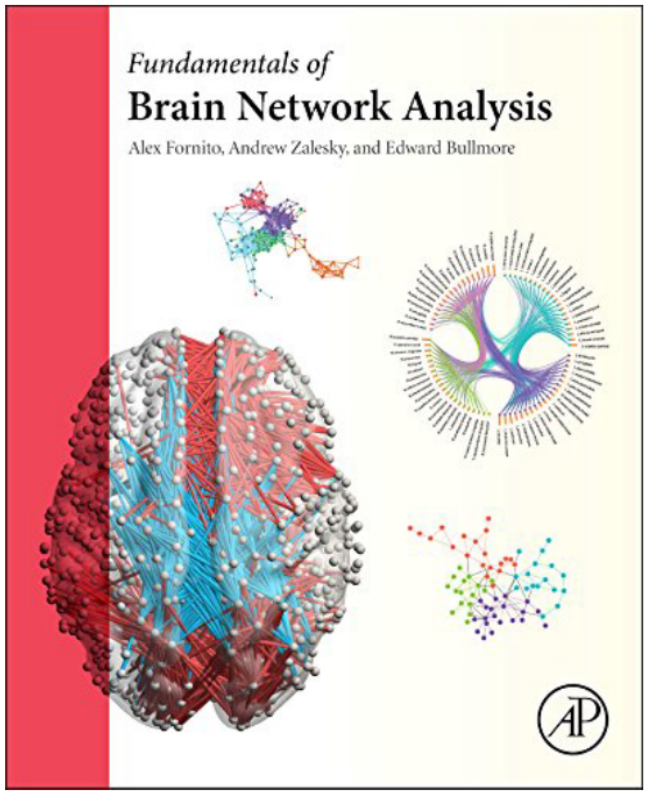
- Rolf Ypma
- Andrew Zalesky



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