

# CONNECTOME ANALYSIS: PRINCIPLES AND APPLICATIONS

Boris Bernhardt, PhD

<http://mica-mni.github.io>



## WHY STUDY CONNECTIVITY?

The cerebral cortex is composed of  
100.000.000.000  
neurons.

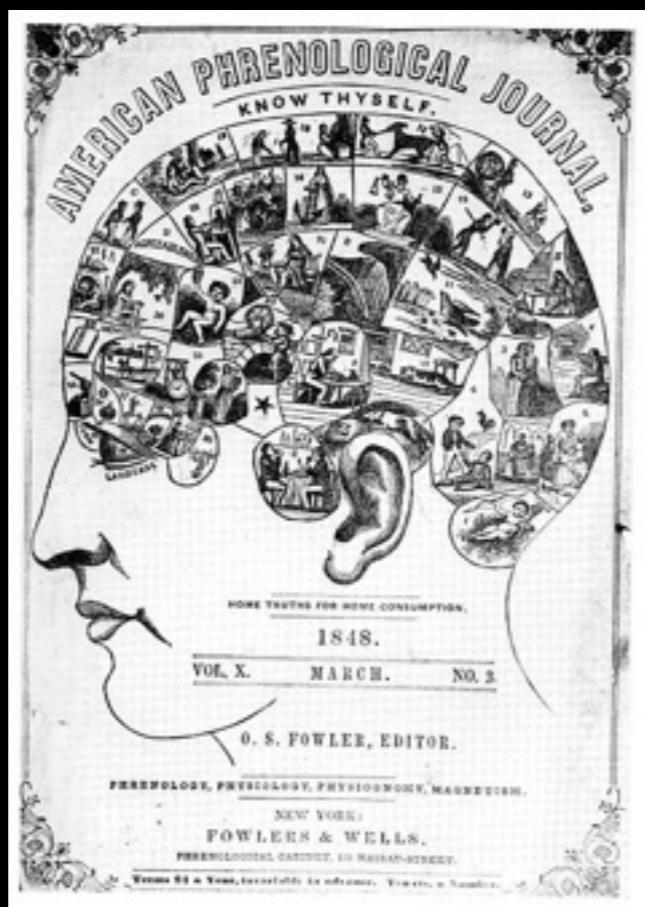
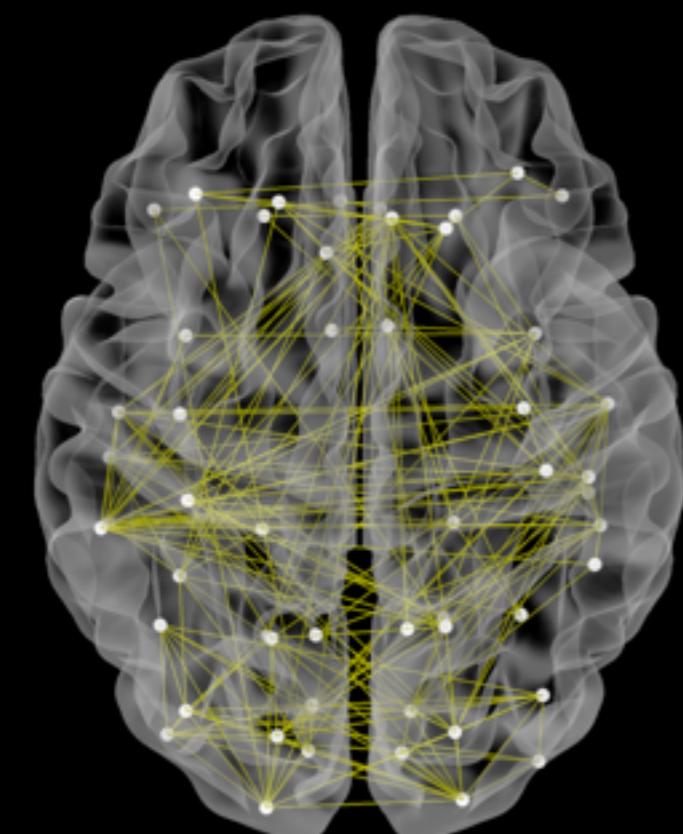
These neurons are interconnected by  
100.000.000.000.000  
synapses

## WHY STUDY CONNECTIVITY?

The cerebral cortex is composed of  
**hundreds**  
of regions.

These regions are interconnected by  
**thousands**  
of white matter tracts.

## WHY STUDY CONNECTIVITY?

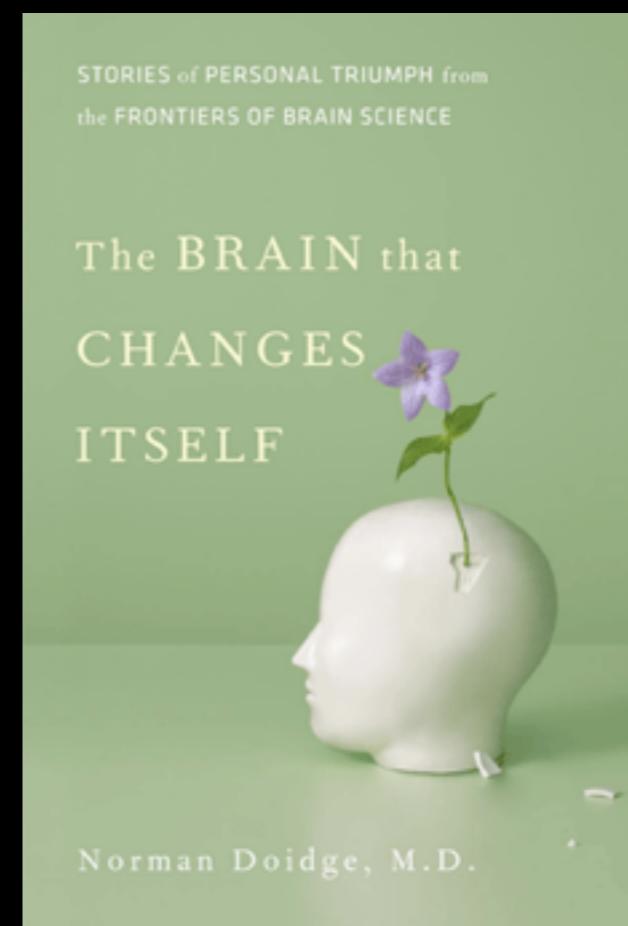


BRAIN ORGANIZATION

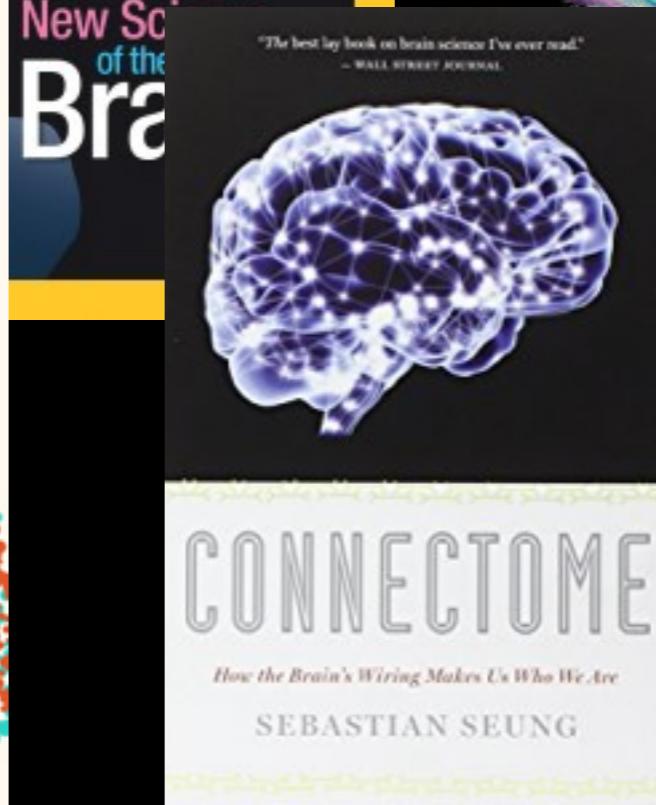
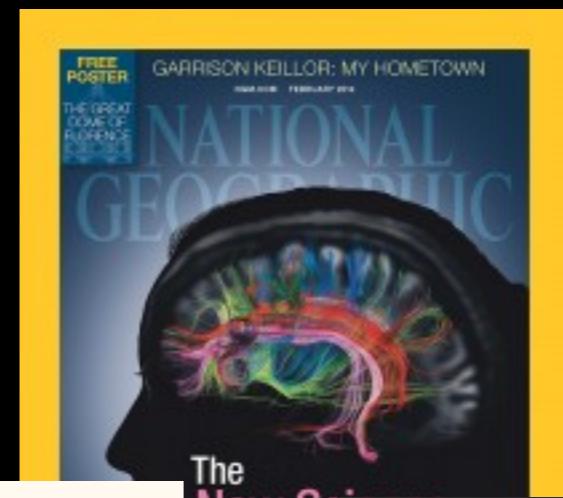
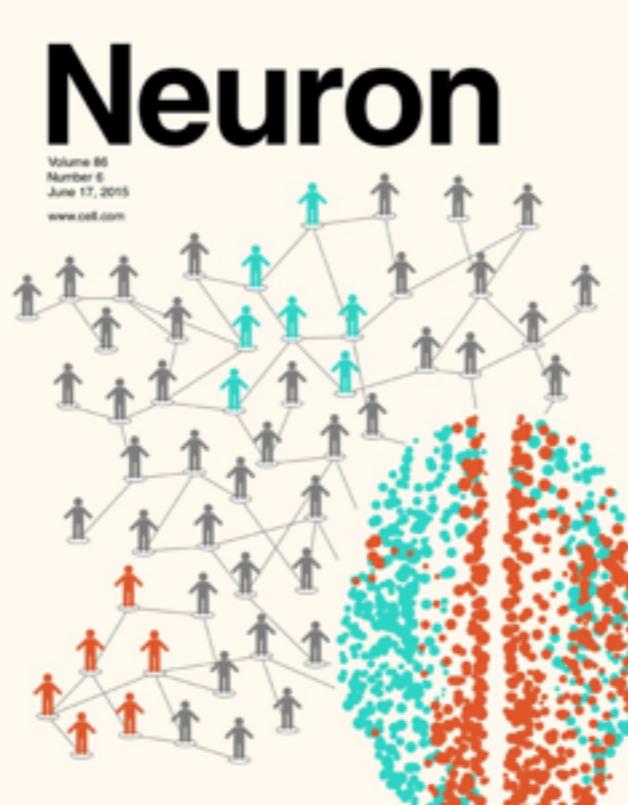
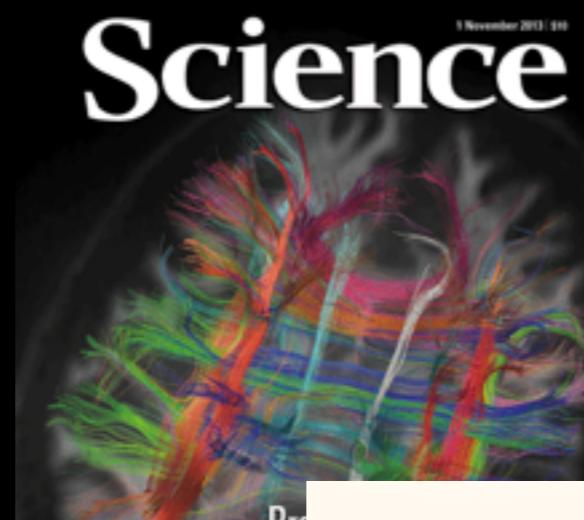
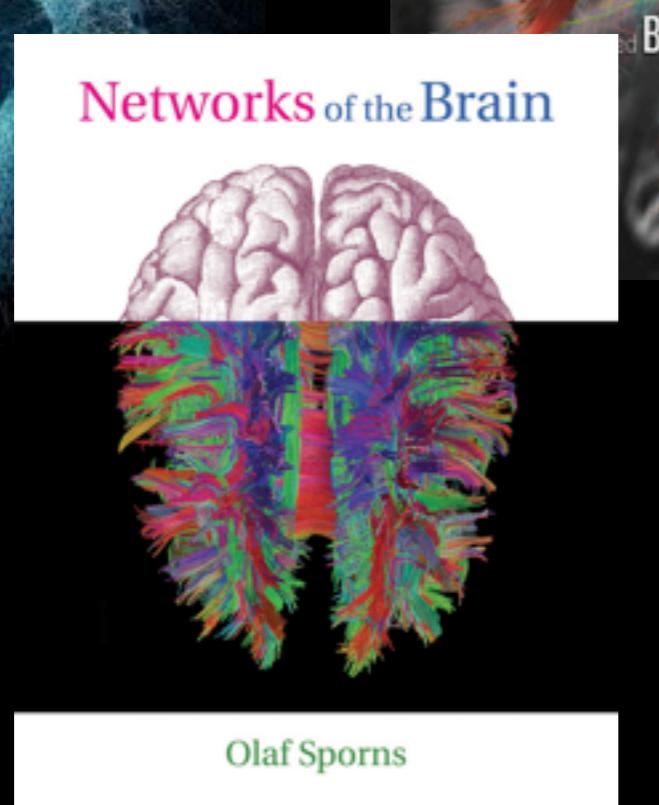
INDIVIDUAL DIFFERENCES

PLASTICITY

BRAIN DISORDERS



## WHY STUDY CONNECTIVITY?



MUSE  
THE  
2 N D  
LAW

## TALK OUTLINE

HOW TO MEASURE BRAIN CONNECTIVITY (WITH NEUROIMAGING)?

WHAT ASPECTS OF CONNECTOMES CAN BE ANALYZED AND HOW?

WHAT ARE THE NOTEWORTHY FINDINGS IN THE HEALTHY BRAIN CONNECTOME?

WHAT ARE CONNECTOME FINDINGS IN DRUG-RESISTANT EPILEPSY?

WHAT MAY IT BE GOOD FOR?

## HOW TO MEASURE BRAIN CONNECTIVITY?

## (ANIMAL) CONNECTIVITY

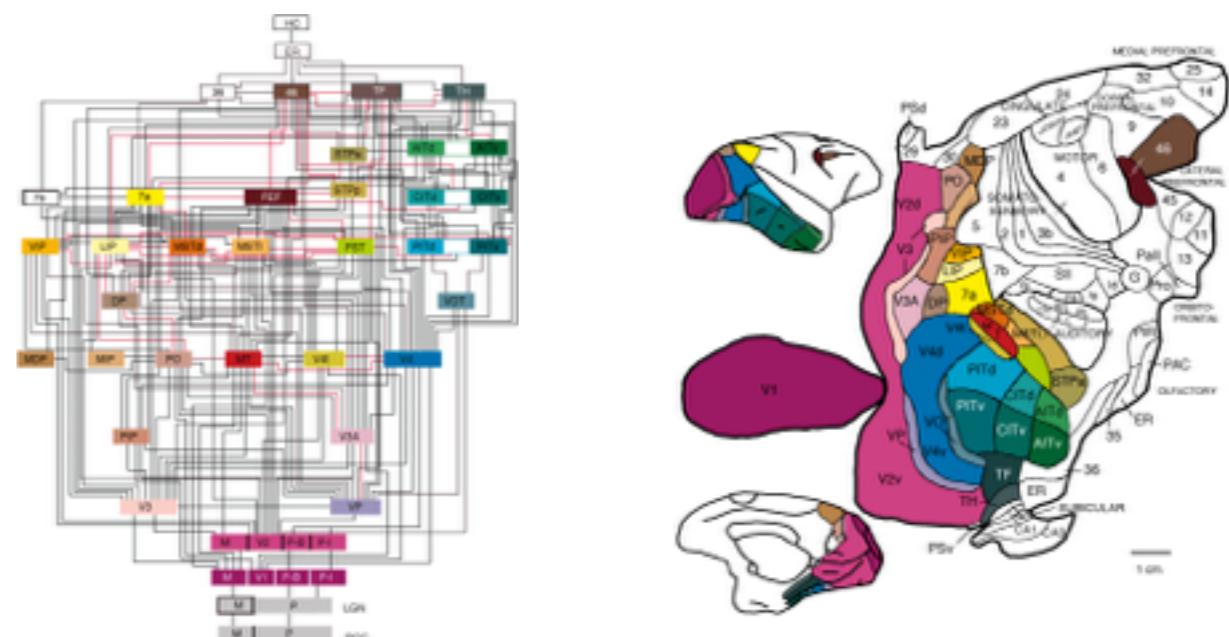
ANATOMICAL CONNECTIONS:  
THE WIRING BETWEEN REGIONS

CLASSICALLY DERIVED FROM  
TRACT-TRACER STUDIES

INVASIVE, CAN ONLY BE  
PERFORMED IN ANIMALS



Petrides & Pandya, 1999, EJN



Felleman and Van Essen, 1991, Cerebral Cortex



Stephan and Koetter, 2000, CoCoMac

## HUMAN IN-VIVO CONNECTIVITY

MRI HAS BECOME THE KEY MODALITY  
TO ASSESS BRAIN CONNECTIVITY

NON-INVASIVE

HIGH-RESOLUTION

WHOLE-BRAIN

3-DIMENSIONAL

MULTIPLE CONTRASTS:  
MEASUREMENT OF ANATOMY,  
DIFFUSIVITY, AND FUNCTION



# DIFFUSION MRI CONNECTIVITY

IDEA:  
FOLLOW PATHWAYS  
OF UNHINDERED WATER DIFFUSION

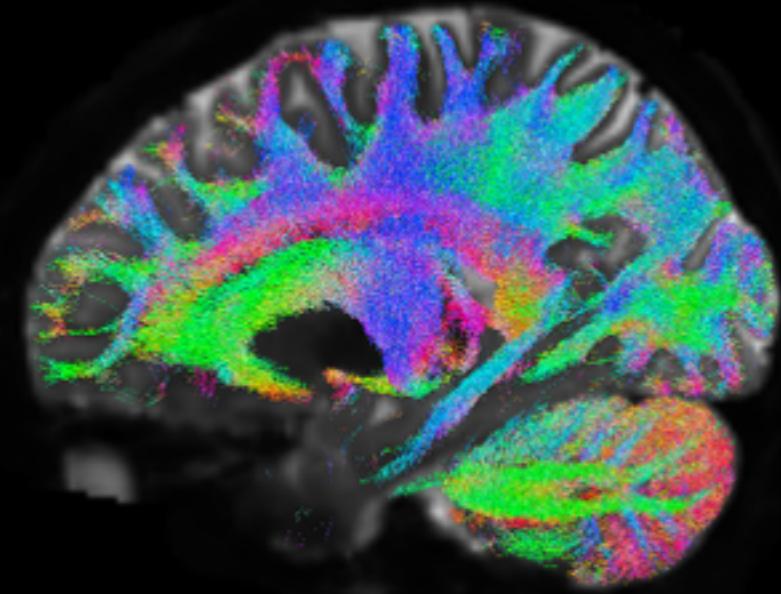
+  
PROBES  
WM CONNECTIVITY

DIFFUSION PARAMETER  
ANALYSIS CAN BE PERFORMED AS WELL

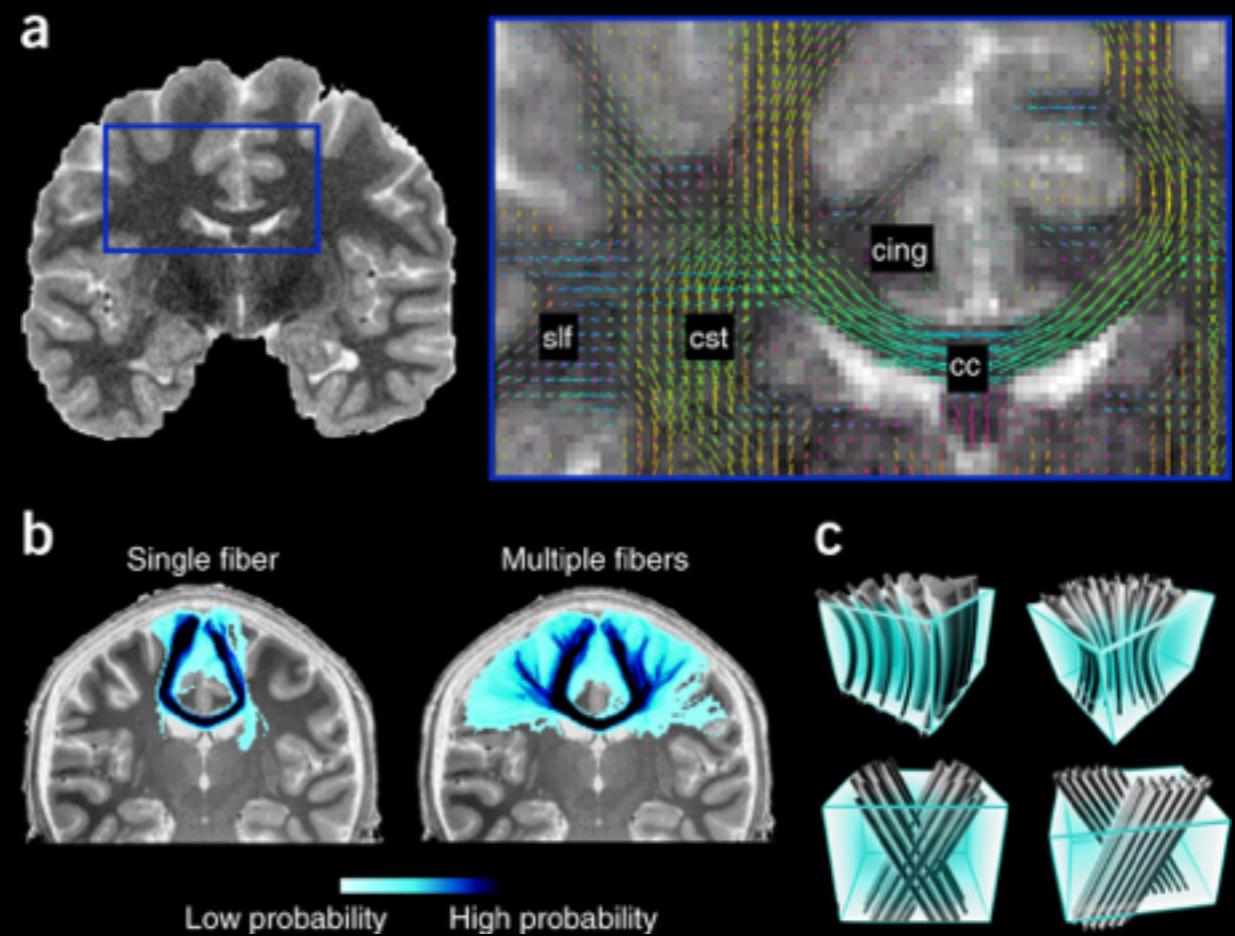
-  
CHALLENGES IN REGIONS OF  
FIBRE CROSSING AND UNCERTAINTY

DISTANCE BIAS

VALIDITY IN PATHOLOGICAL  
REGION UNCLEAR



SINGLE SUBJECT (HCP)



## RESTING-STATE fMRI CONNECTIVITY

IDEA:  
CORRELATE SPONTANEOUS BRAIN  
ACTIVITY

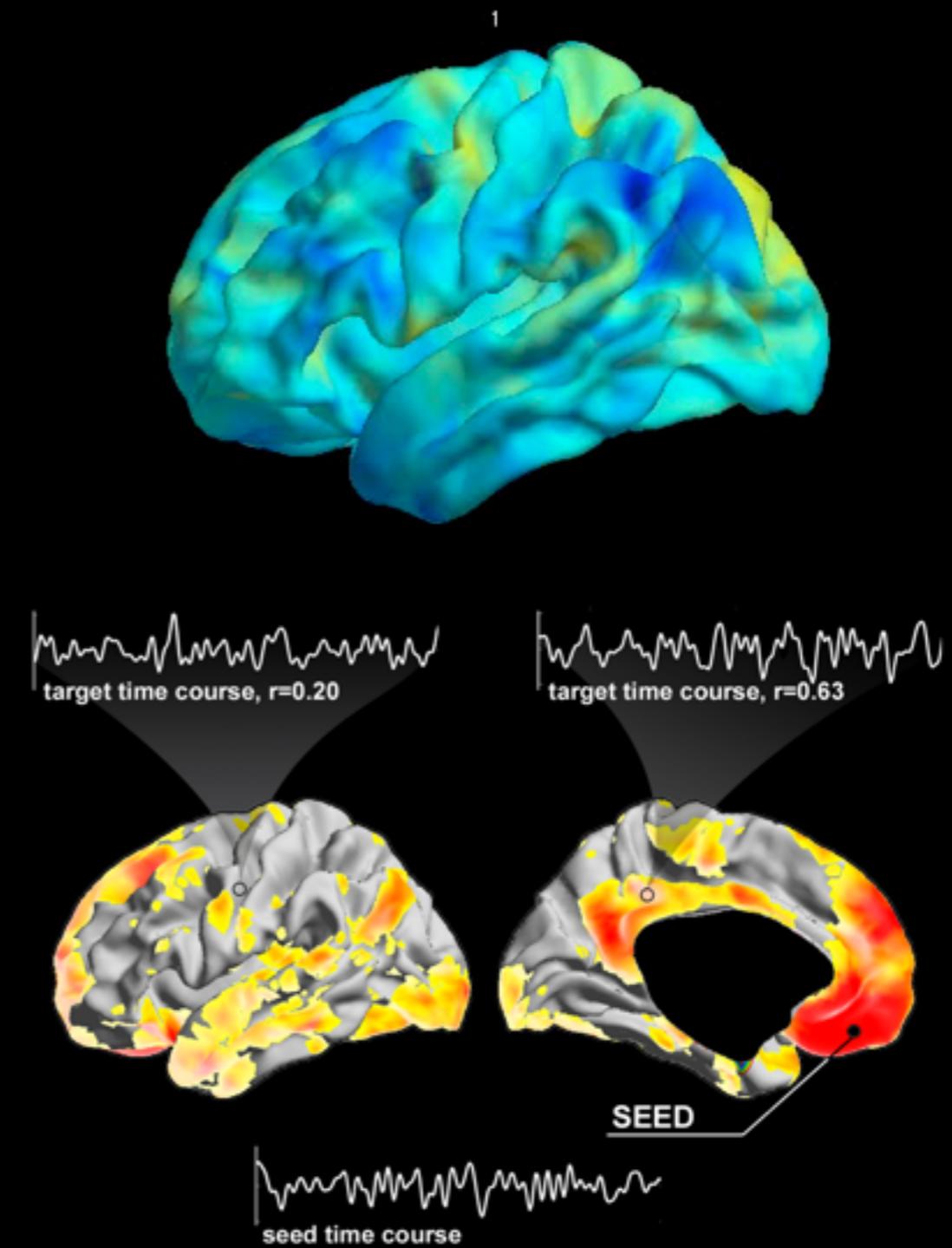
+  
COST-EFFECTIVE, REPRODUCIBLE

INDIVIDUALIZED  
REGIONAL AND INTER-REGIONAL

SEEDING FROM GM  
CORRELATION WITH MENTAL STATES  
& INDUCTION

-  
EFFECTS OF PHYSIOLOGY + MOTION  
INDIRECT CONNECTIONS

CORRELATION WITH MENTAL STATES  
& INDUCTION



# MRI COVARIANCE ANALYSIS

IDEA:  
CORRELATE MORPHOLOGICAL  
INDICES ACROSS SUBJECTS

+  
COST-EFFECTIVE, REPRODUCIBLE

DIRECT SEEDING FROM GREY  
MATTER POSSIBLE

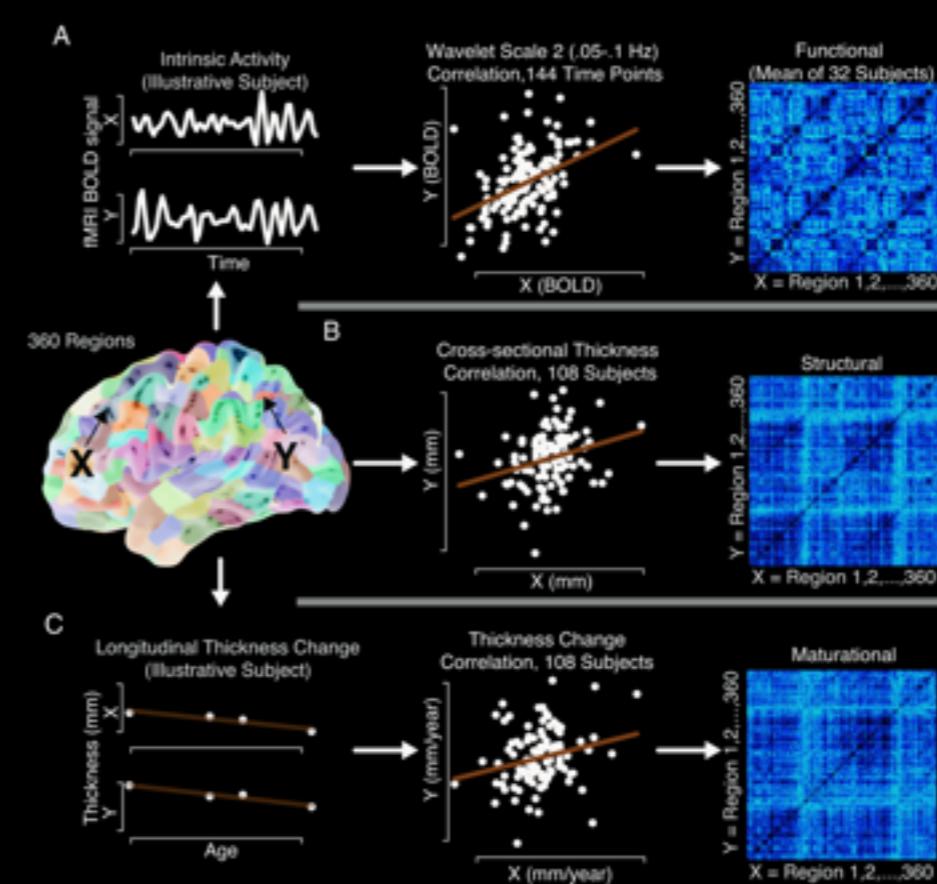
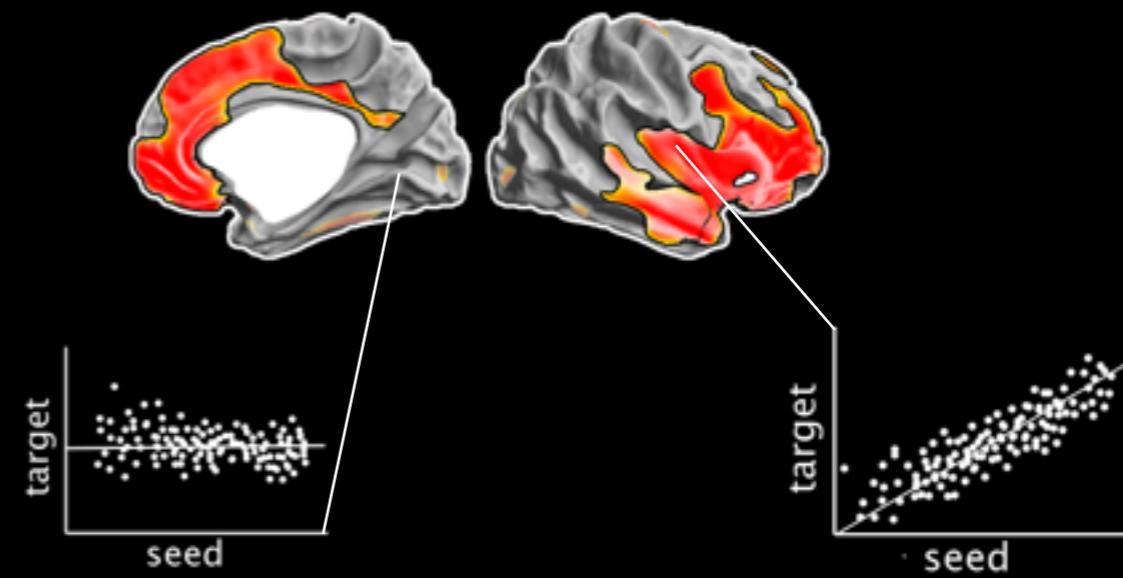
SIMPLE PREPROCESSING AND MODELLING

-

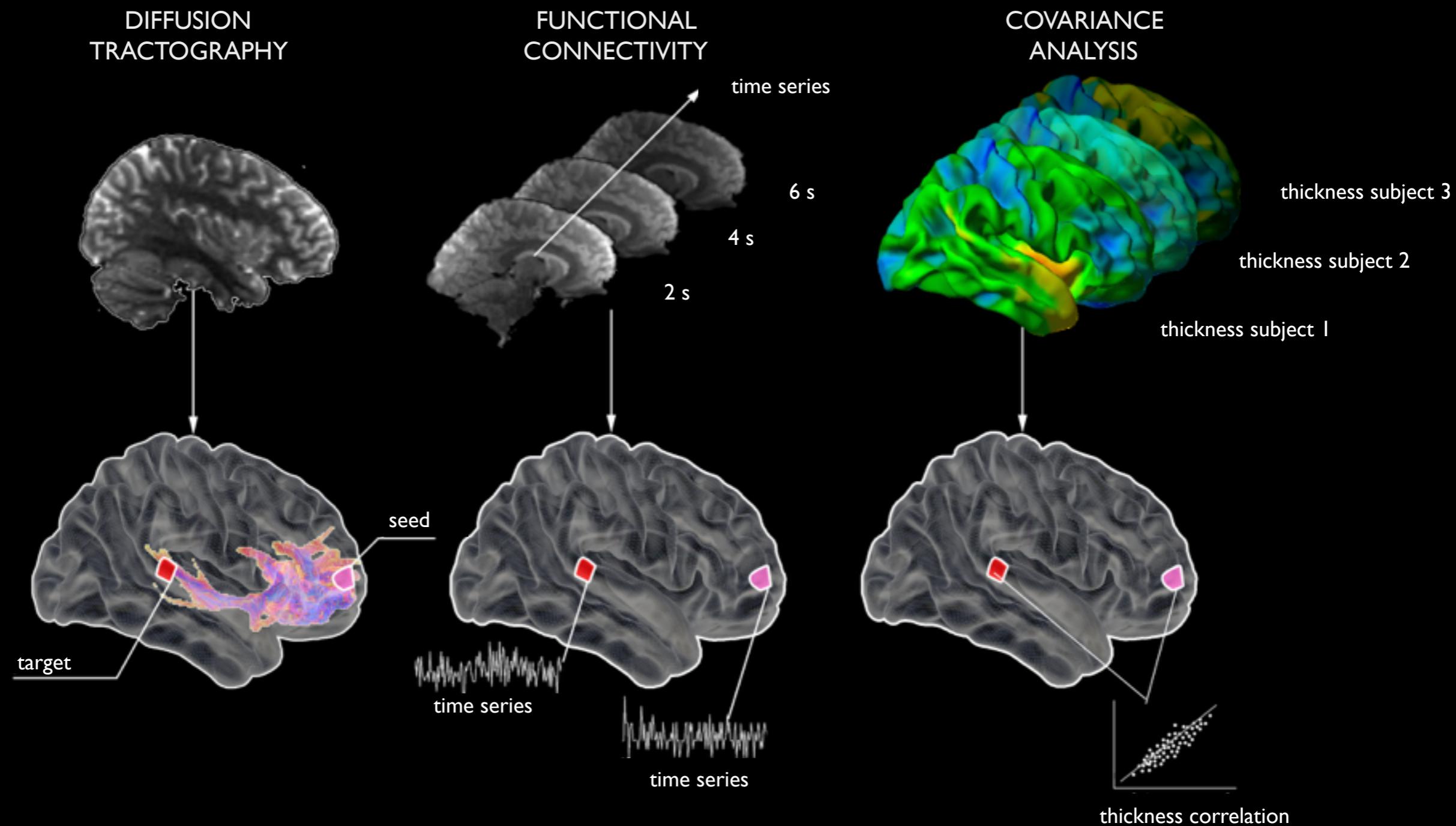
ONLY GROUP-WISE

RELATES RATHER TO PROCESSES  
THAN TO STATES

NO DIRECT WM CONNECTIVITY  
MEASUREMENT



# INTER-REGIONAL CONNECTIVITY ANALYSIS

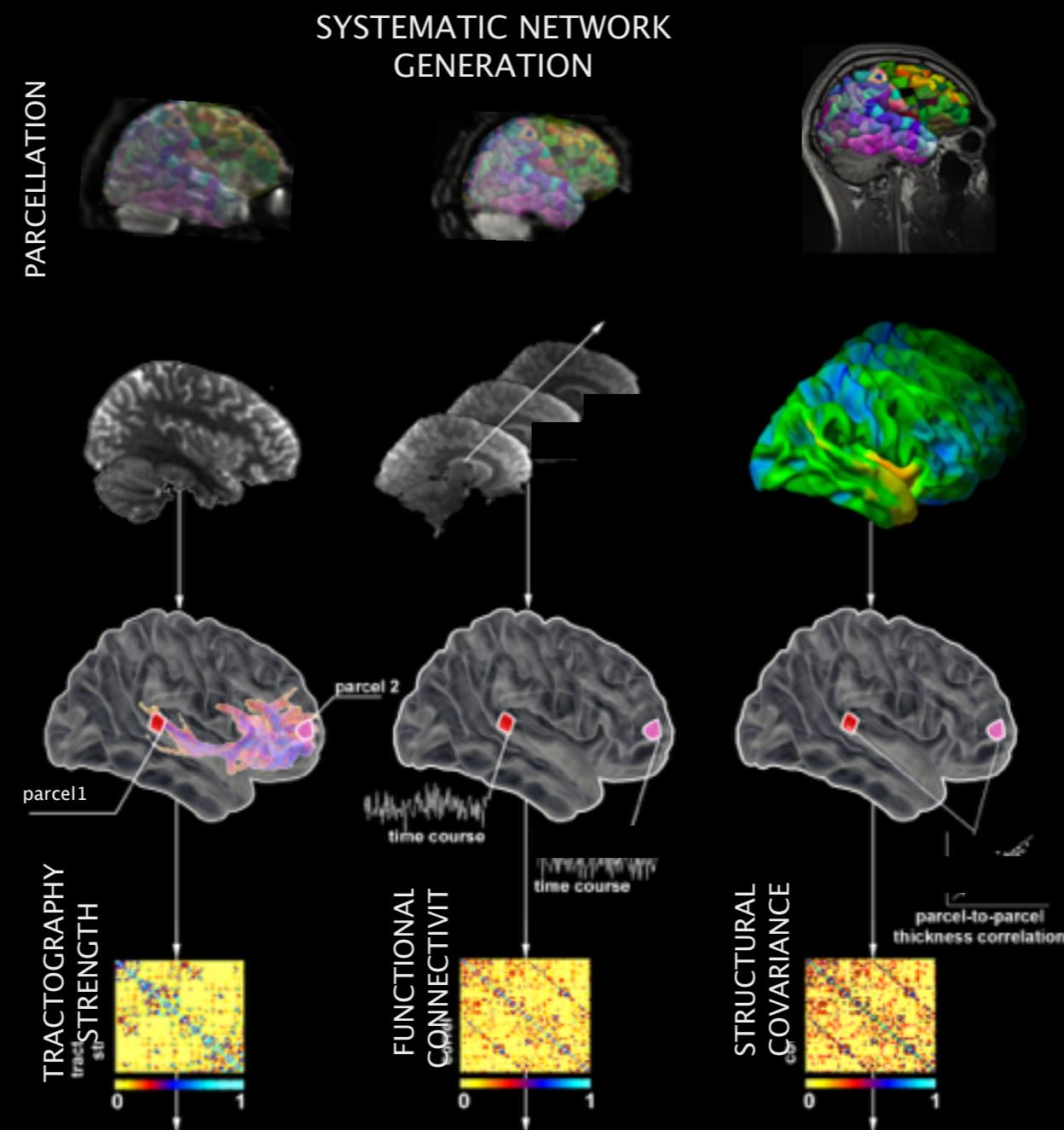


Mori et al. (1999) Ann Neu  
Behrens et al. (2007) NIMG

Friston (1994) HBM  
Smith (2012) NIMG

Lerch et al. (2006) NIMG  
Alexander-Bloch et al. (2013) NRN

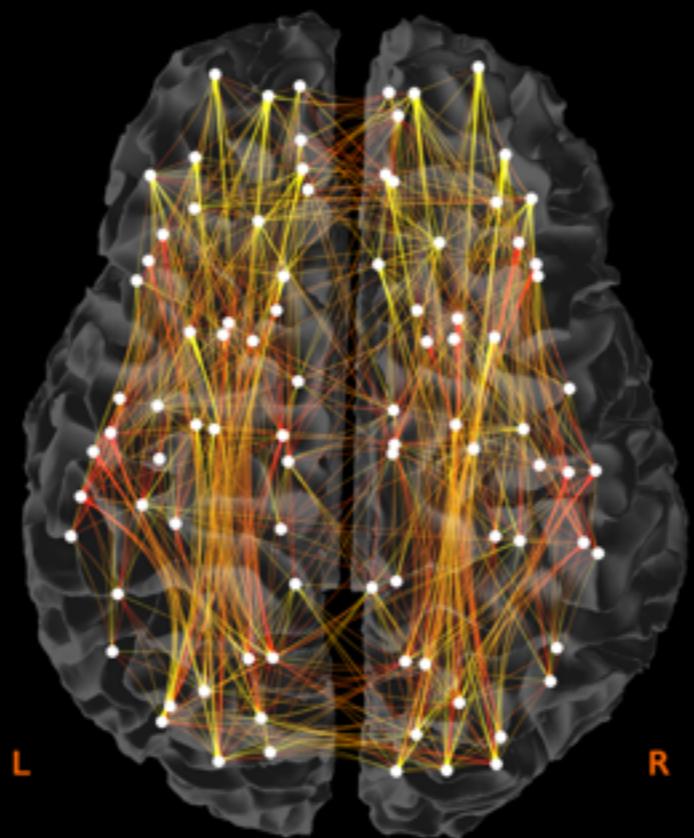
# CONNECTOME ANALYSIS



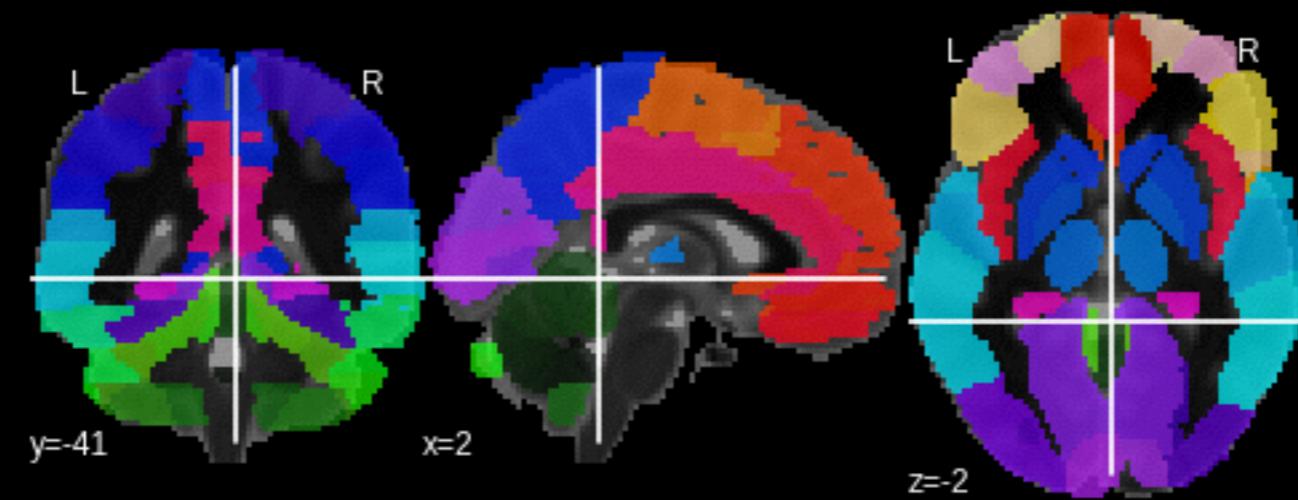
# MATRICES AND GRAPHS



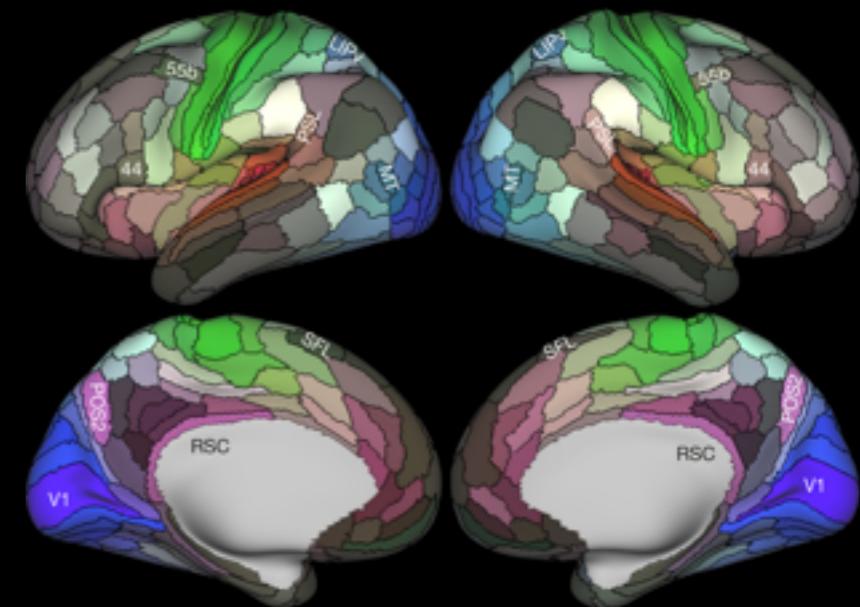
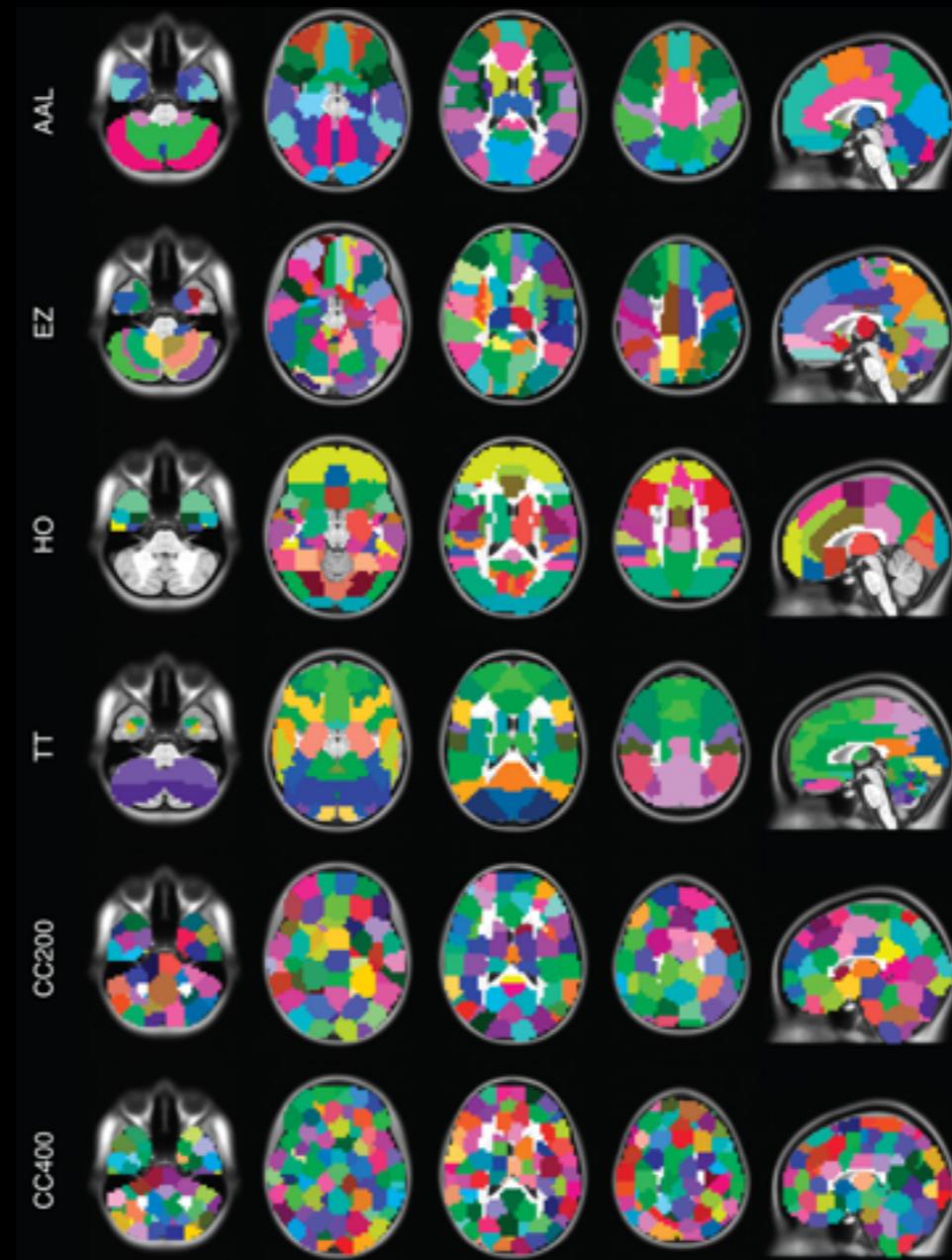
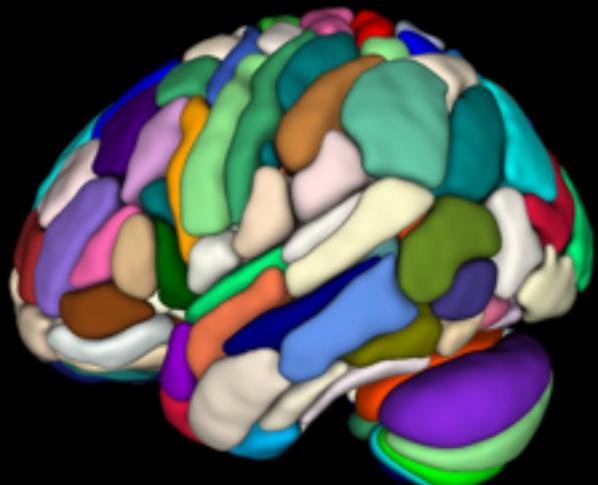
CONTROLS



## DEFINITION OF REGION



# DEFINITION OF REGION



# INTERIM SUMMARY

NEUROIMAGING TECHNIQUES MAP  
FUNCTIONAL AND STRUCTURAL CONNECTIONS

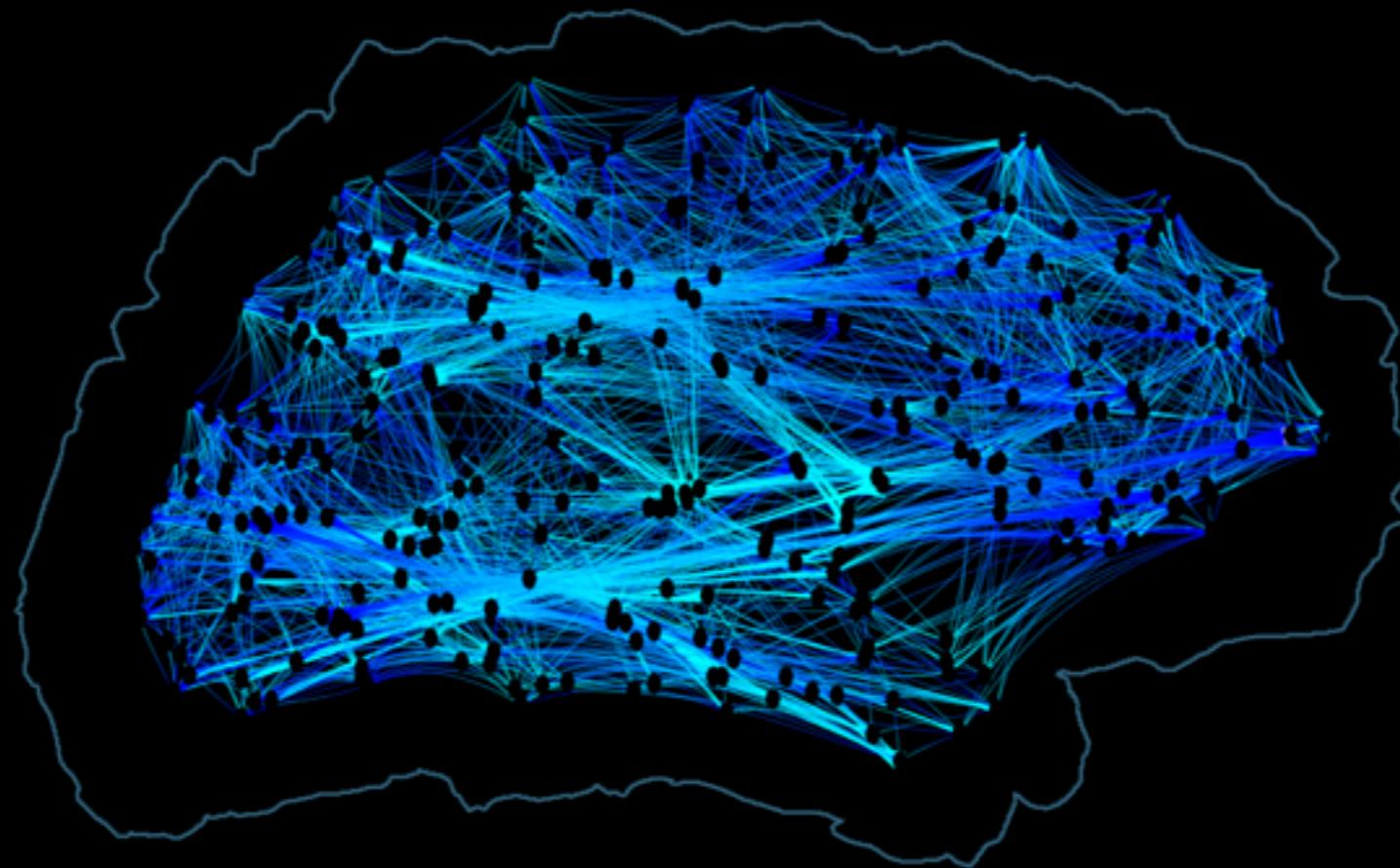
COMPLEMENTARY TECHNIQUES:  
DIFFUSION MRI TRACTOGRAPHY, RESTING-STATE FMRI CORRELATIONS, STRUCTURAL COVARIANCE

CONNECTOMES:  
MATRICES GENERATED FROM SYSTEMATIC ROI-TO-ROI CONNECTIVITY ANALYSES

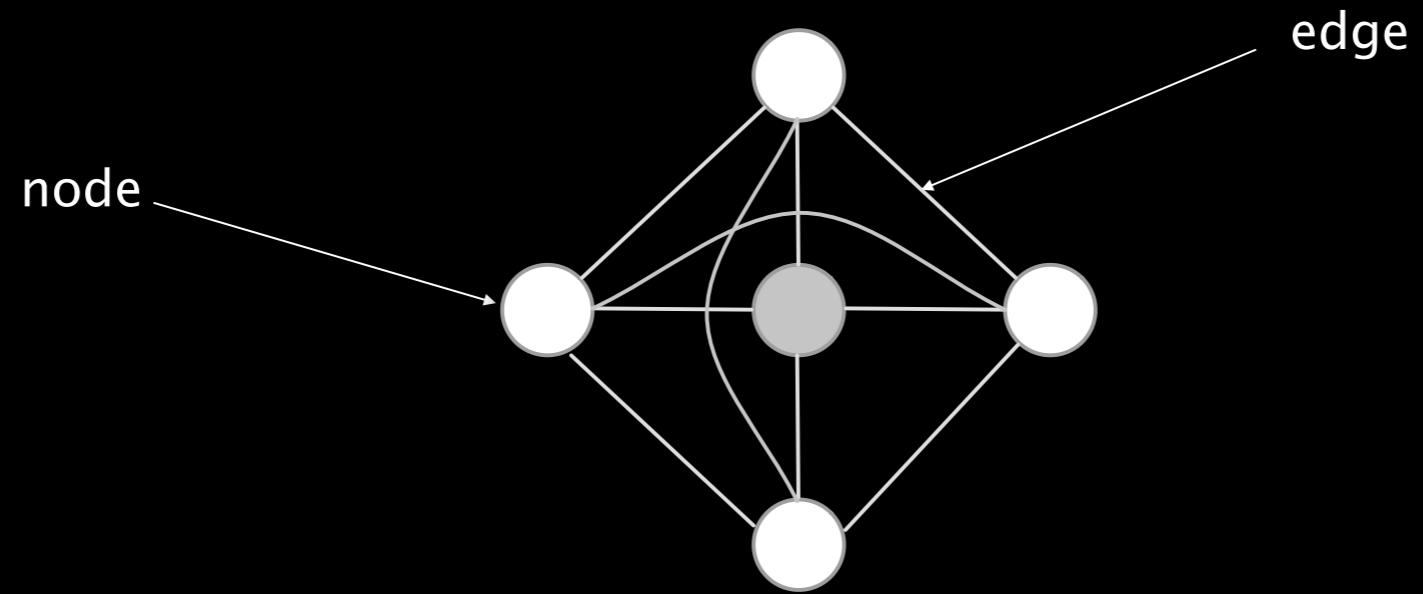
INFLUENCE OF PARCELLATION ON FINDINGS:  
AAL78, CRADDOCK200, GLASSER360, ...

WHAT ASPECTS OF NETWORKS CAN BE MEASURED?

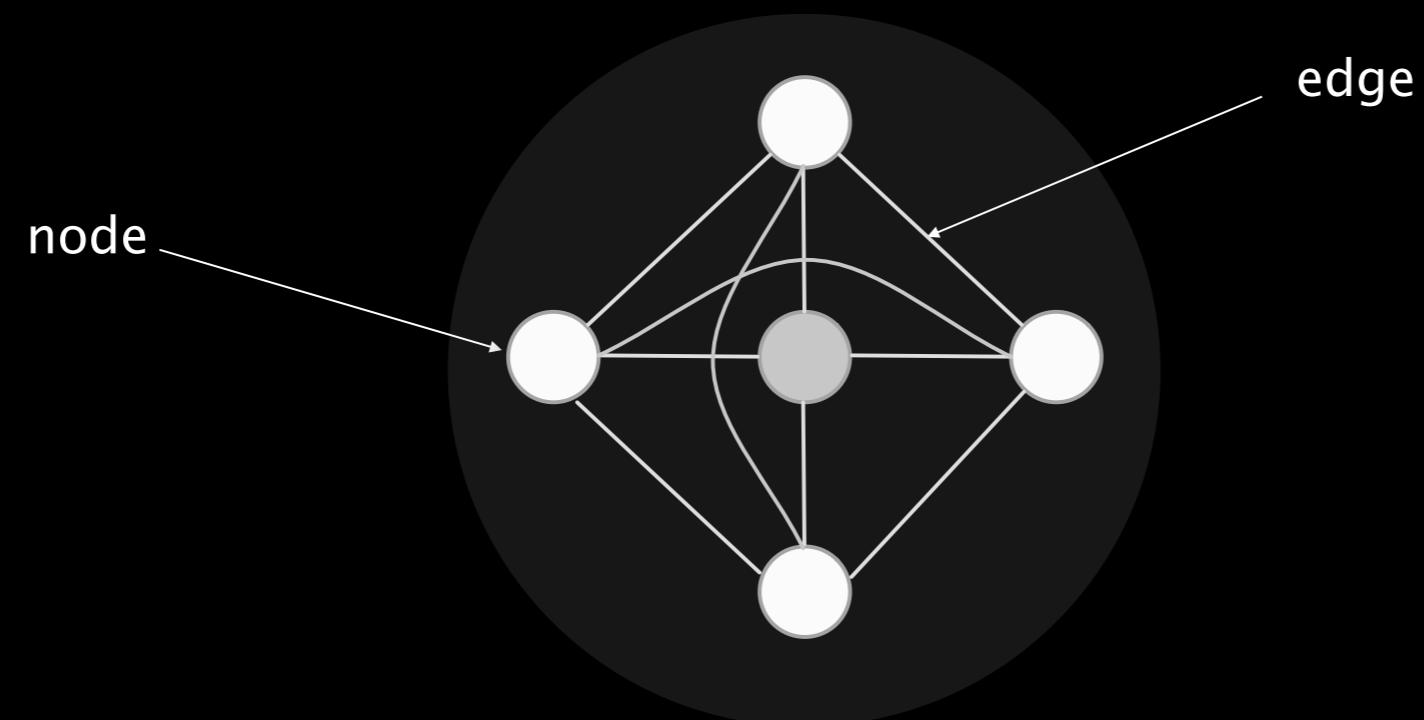
# MATRICES AND GRAPHS



# GRAPH TALK

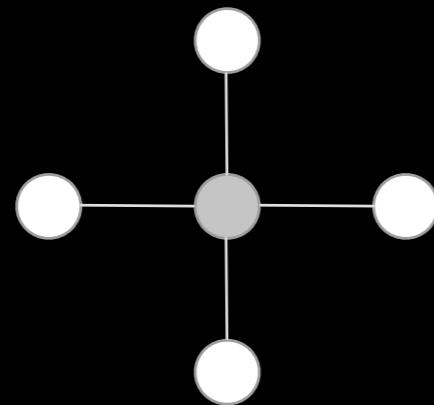


# TOPOLOGY



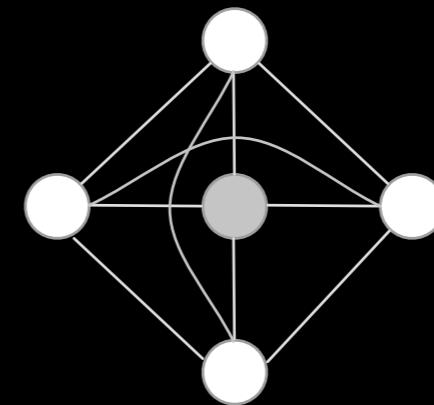
τόπος, *place*, and λόγος, *study*

## CLUSTERING COEFFICIENT C / gamma



low C

low local efficiency

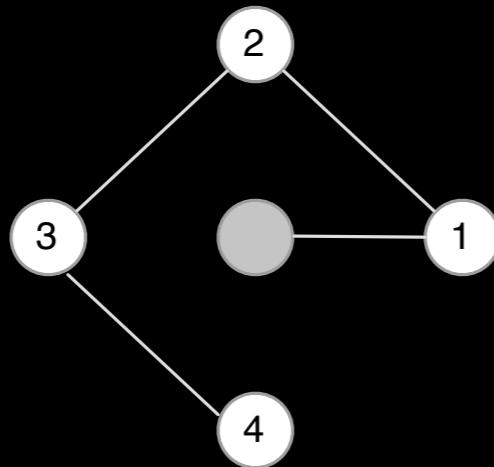


high C

high local efficiency

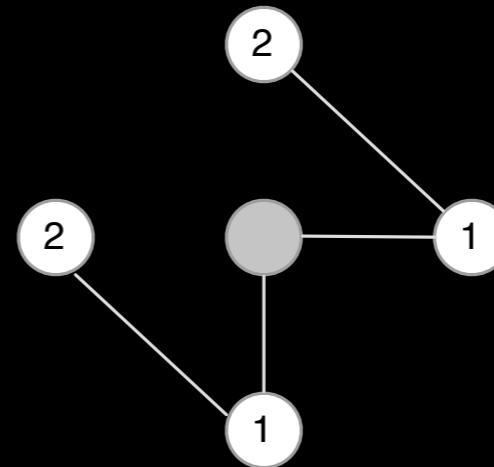
$$c_i = \frac{E_i}{\frac{k_i(k_i - 1)}{2}}.$$

## PATH LENGTH P / Lambda



HIGH P

low global efficiency



LOW P

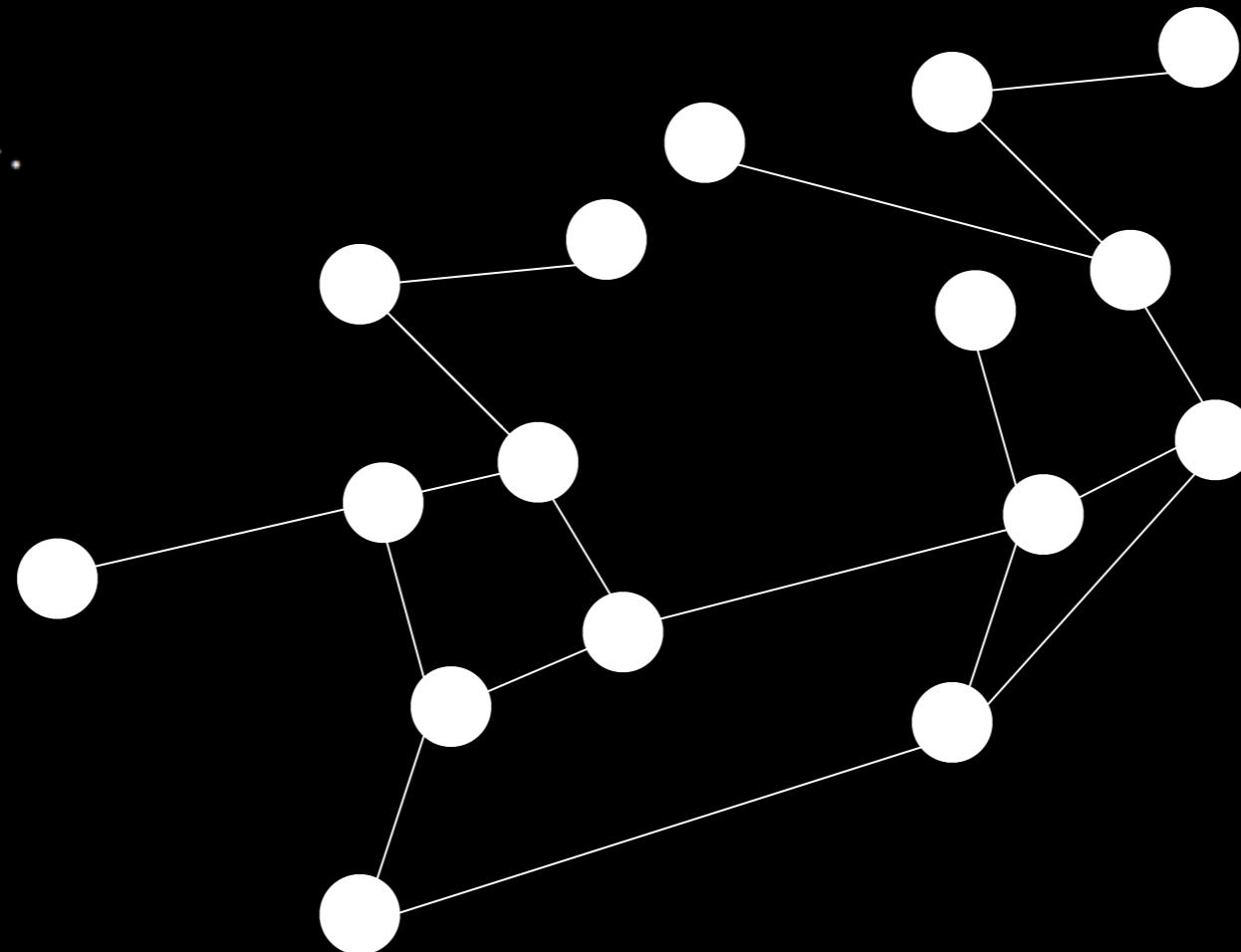
high global efficiency

$$l_i = \frac{1}{n-1} \sum_{i \neq j} \min\{l_{ij}\}.$$

## FROM NODES TO NETWORKS

$$l_i = \frac{1}{n-1} \sum_{i \neq j} \min\{l_{ij}\}.$$

$$L = \frac{n}{\sum_{i=1}^n \frac{1}{l_i}}.$$



$$c_i = \frac{E_i}{\frac{k_i(k_i-1)}{2}}.$$

$$C = \frac{1}{n} \sum_{i=1}^n c_i.$$

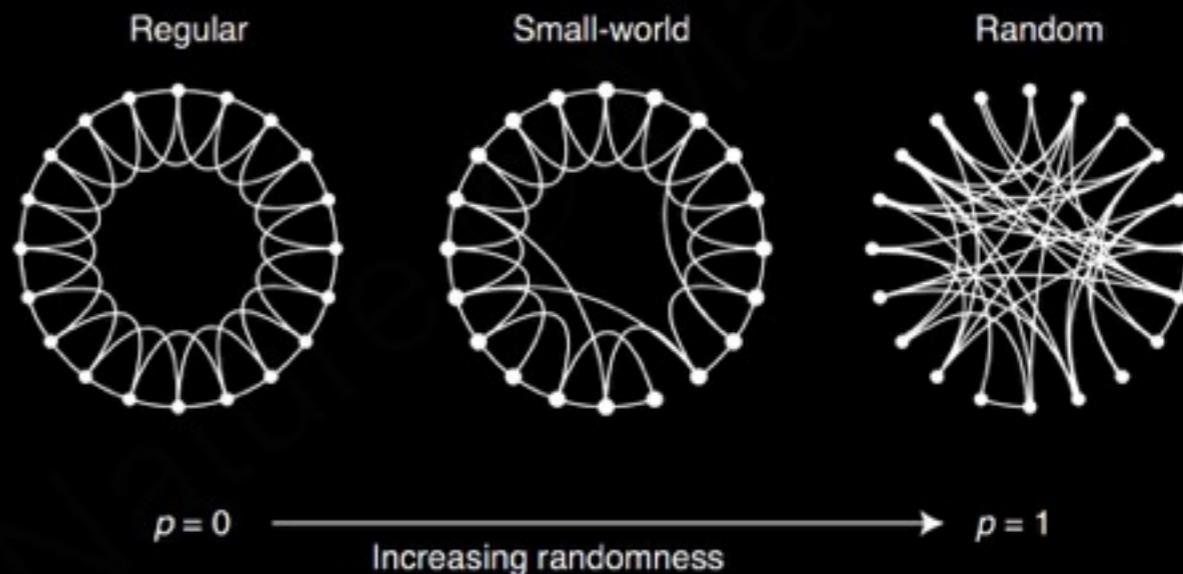
# CLUSTERING VS PATH LENGTH

## Collective dynamics of ‘small-world’ networks

Duncan J. Watts\* & Steven H. Strogatz

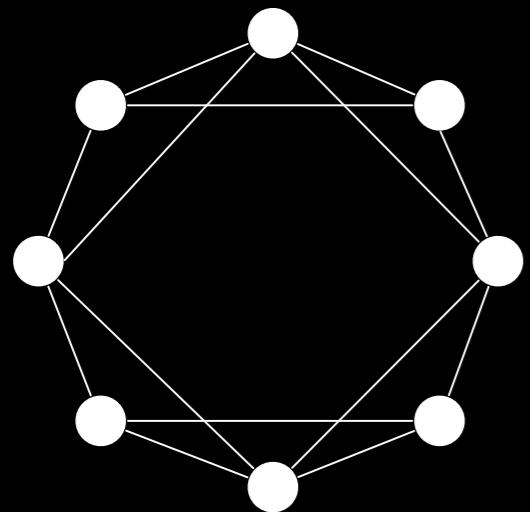
Department of Theoretical and Applied Mechanics, Kimball Hall,  
Cornell University, Ithaca, New York 14853, USA

Networks of coupled dynamical systems have been used to model biological oscillators<sup>1–4</sup>, Josephson junction arrays<sup>5,6</sup>, excitable media<sup>7</sup>, neural networks<sup>8–10</sup>, spatial games<sup>11</sup>, genetic control networks<sup>12</sup> and many other self-organizing systems. Ordinarily, the connection topology is assumed to be either completely regular or completely random. But many biological, technological and social networks lie somewhere between these two extremes. Here we explore simple models of networks that can be tuned through this middle ground: regular networks ‘rewired’ to introduce increasing amounts of disorder. We find that these systems can be highly clustered, like regular lattices, yet have small characteristic path lengths, like random graphs. We call them ‘small-world’ networks, by analogy with the small-world phenomenon<sup>13,14</sup> (popularly known as six degrees of separation<sup>15</sup>). The neural network of the worm *Caenorhabditis elegans*, the power grid of the western United States, and the collaboration graph of film actors are shown to be small-world networks. Models of dynamical systems with small-world coupling display enhanced signal-propagation speed, computational power, and synchronizability. In particular, infectious diseases spread more easily in small-world networks than in regular lattices.



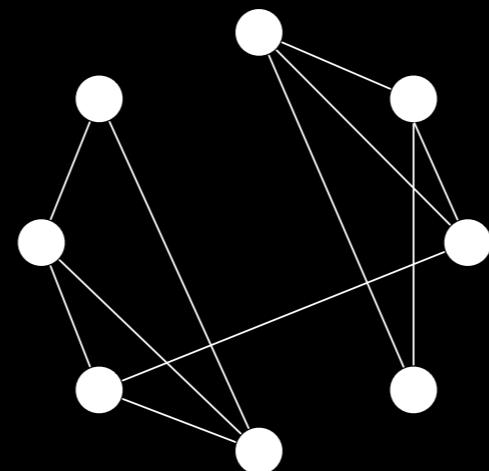
# GLOBAL TOPOLOGY

REGULAR



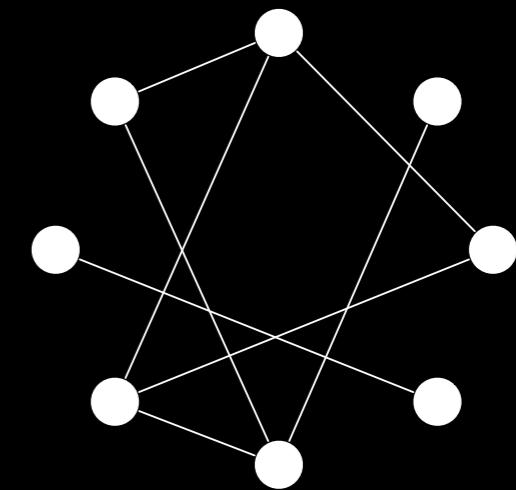
HIGH C  
HIGH P

SMALL-WORLD



HIGH C  
LOW P

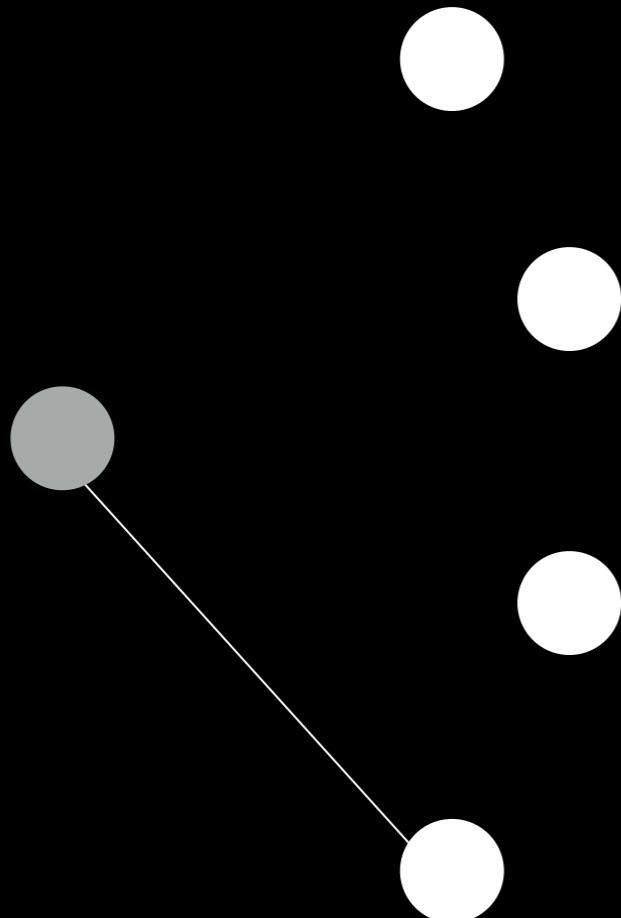
RANDOM



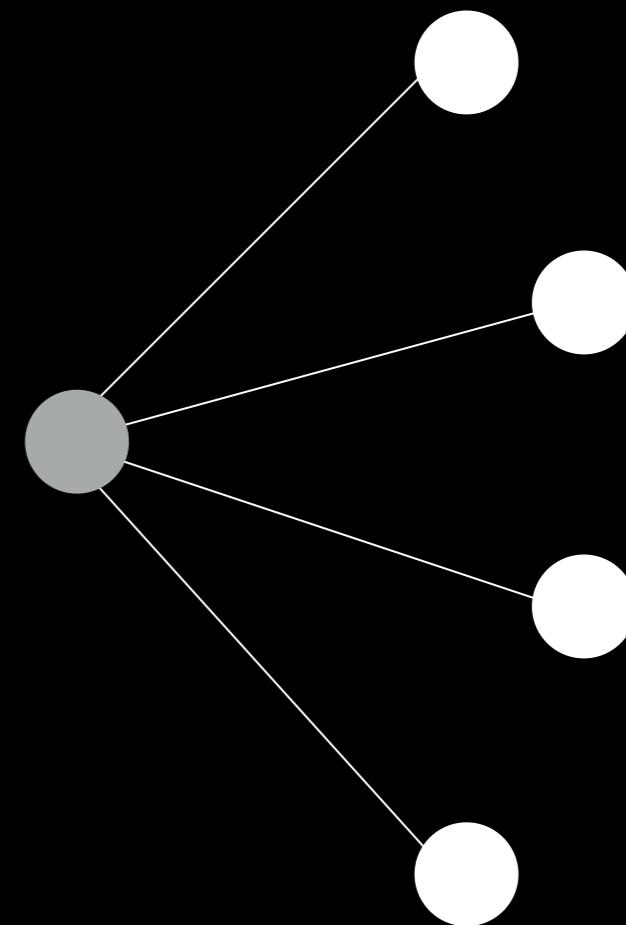
LOW C  
LOW P

## NODAL TOPOLOGY: CENTRALITY

LOW DEGREE

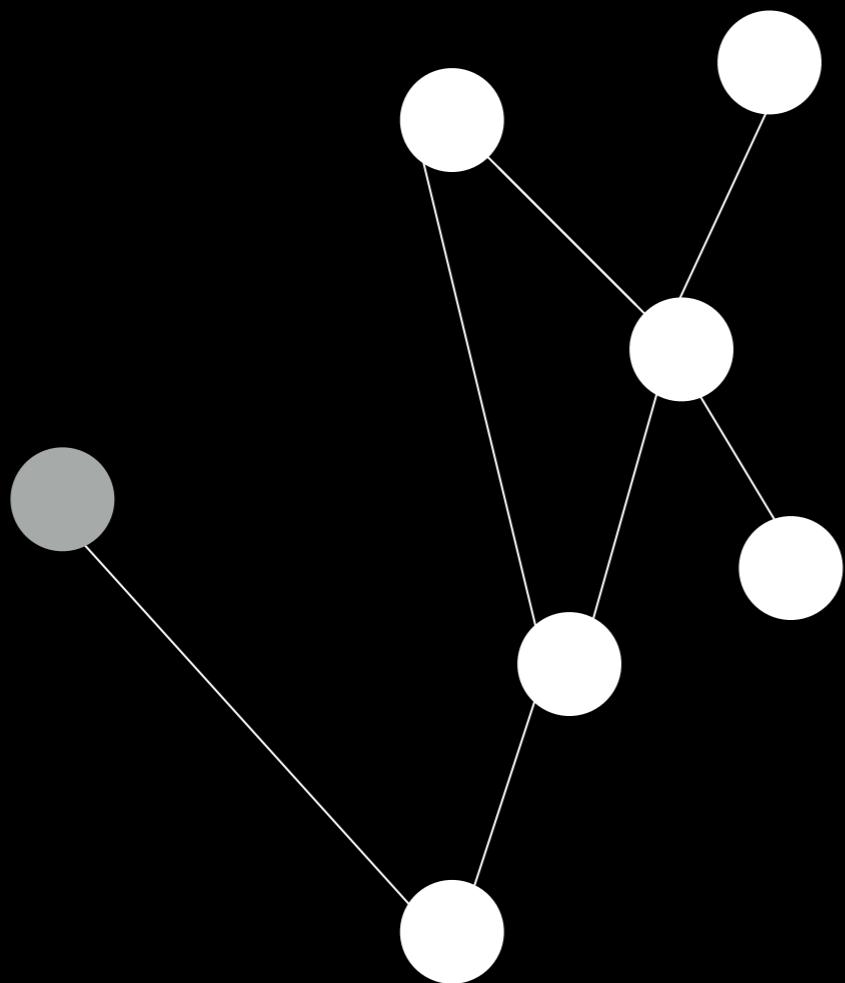


HIGH DEGREE

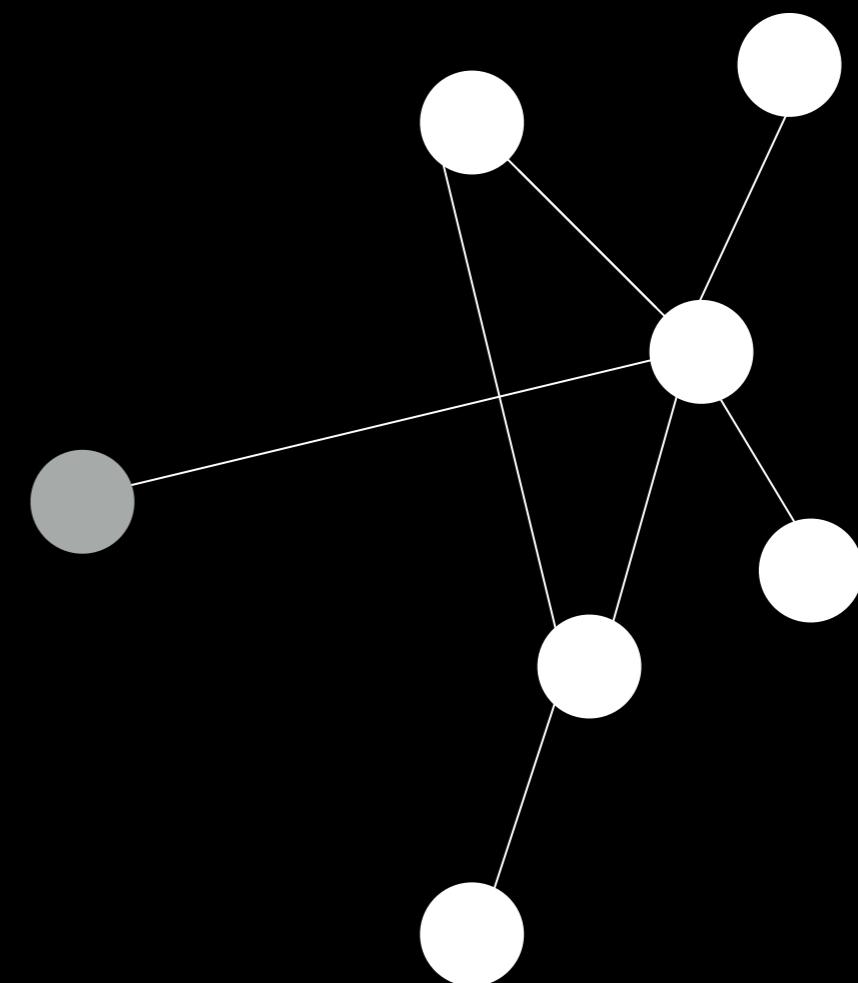


## NODAL TOPOLOGY: CENTRALITY

LOW EIGENVECTOR

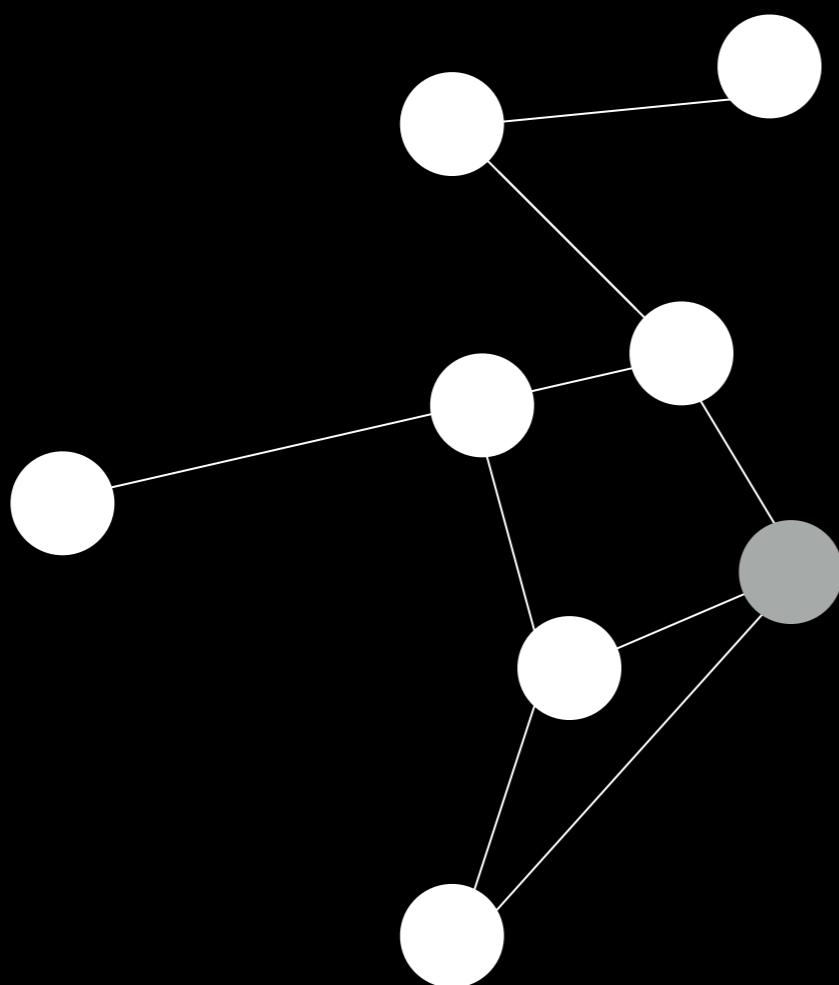


HIGH EIGENVECTOR

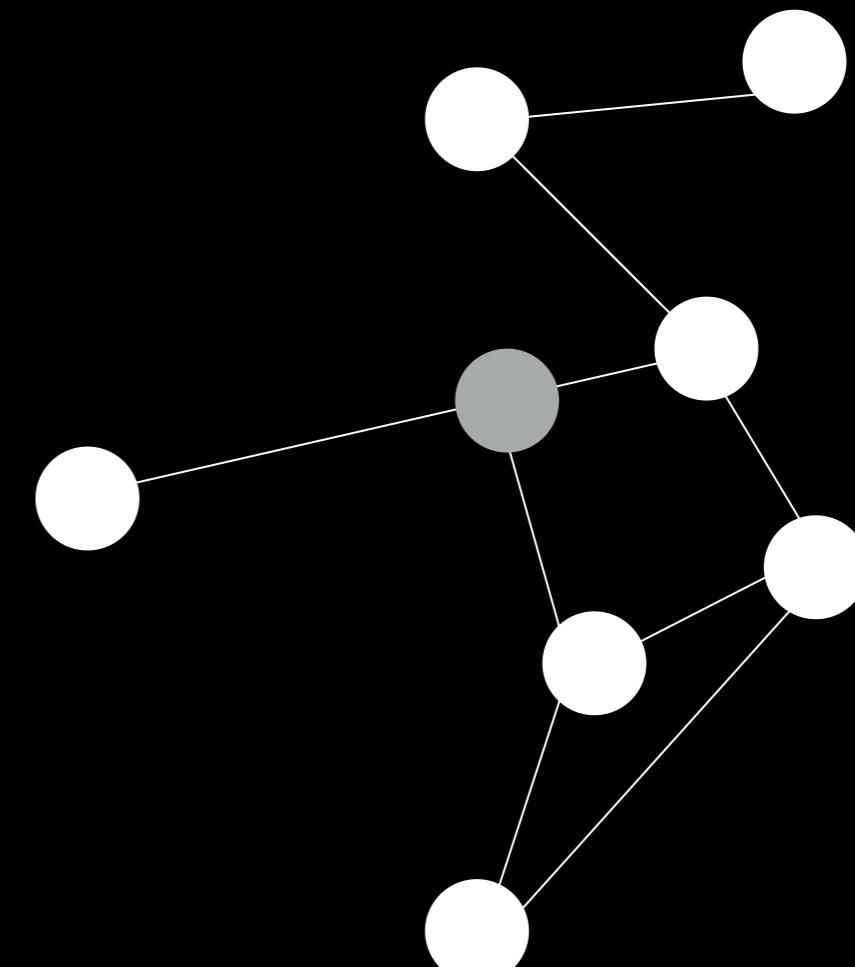


## NODAL TOPOLOGY: CENTRALITY

LOW BETWEENNESS



HIGH BETWEENNESS



# INTERMEDIATE TOPOLOGY: MODULARITY

## Modularity and community structure in networks

M. E. J. Newman\*

Department of Physics and Center for the Study of Complex Systems, University of Michigan, Ann Arbor, MI 48109

Edited by Brian Skyrms, University of California, Irvine, CA, and approved April 19, 2006 (received for review February 26, 2006)

Many networks of interest in the sciences, including social networks, computer networks, and metabolic and regulatory networks, are found to divide naturally into communities or modules. The problem of detecting and characterizing this community structure is one of the outstanding issues in the study of networked systems. One highly effective approach is the optimization of the quality function known as “modularity” over the possible divisions of a network. Here I show that the modularity can be expressed in terms of the eigenvectors of a characteristic matrix for the network, which I call the modularity matrix, and that this expression leads to a spectral algorithm for community detection that returns results of demonstrably higher quality than competing methods in shorter running times. I illustrate the method with applications to several published network data sets.

clustering | partitioning | modules | metabolic network | social network

Many systems of scientific interest can be represented as networks, sets of nodes or vertices joined in pairs by lines or edges. Examples include the internet and the worldwide web, metabolic networks, food webs, neural networks, communication and distribution networks, and social networks. The study of

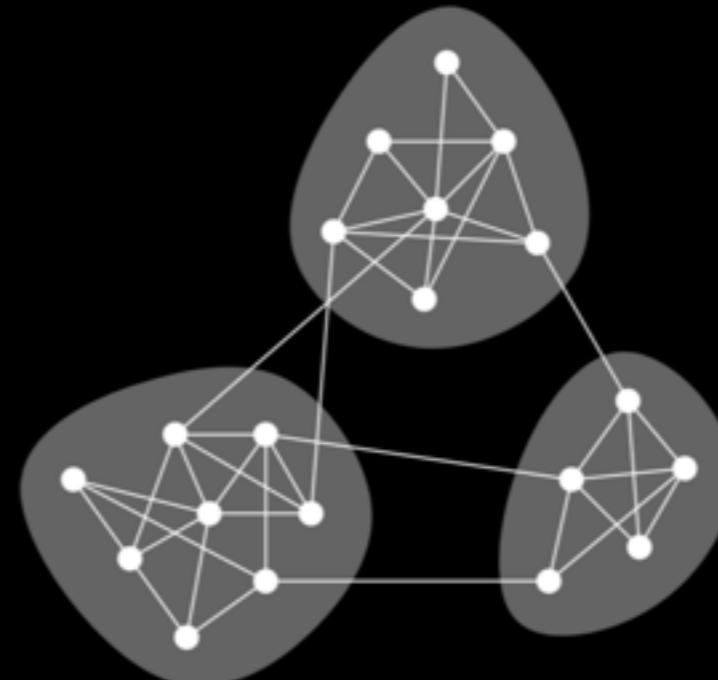
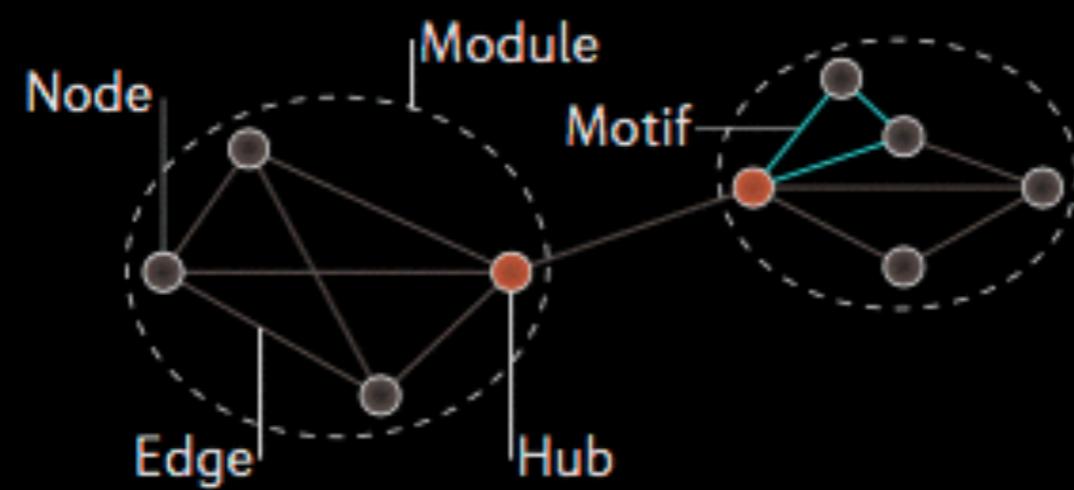


Fig. 1. The vertices in many networks fall naturally into groups or communities, sets of vertices (shaded) within which there are many edges, with only a smaller number of edges between vertices of different groups.

## TOPOLOGY OVERVIEW



# INTERIM SUMMARY

GRAPH THEORY IS A FORMALISM TO  
PARAMETERIZE NETWORKS

NETWORKS/GRAPHS = NODES + EDGES

IN ADDITION TO CHARACTERIZING NODES AND EDGES DIRECTLY,  
WE CAN EVALUATE THE TOPOLOGY OF THE GRAPH

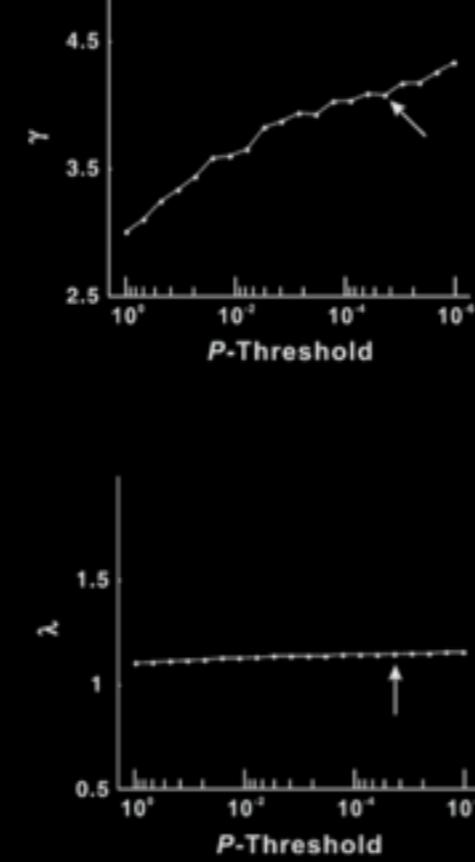
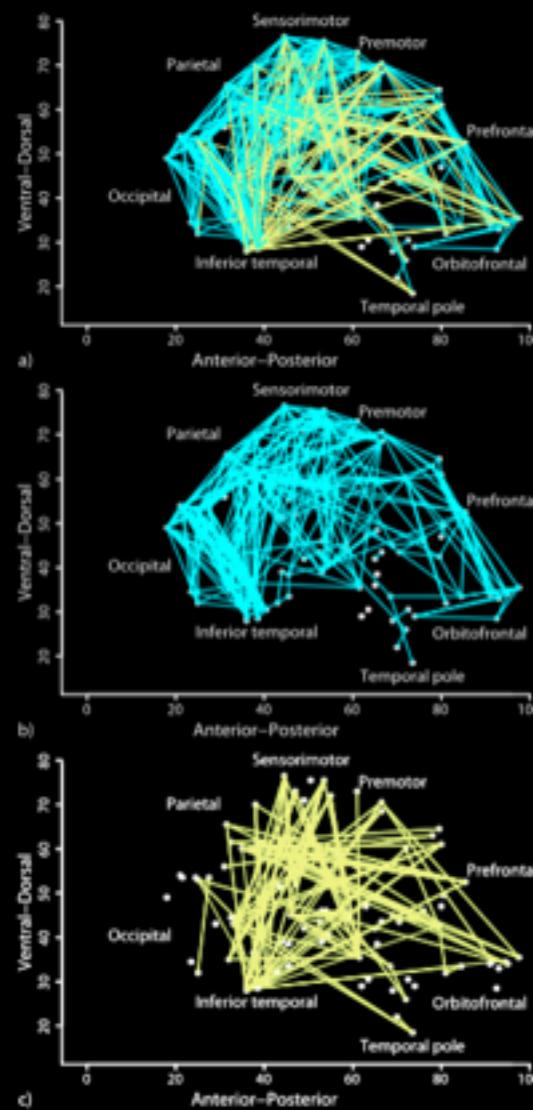
GLOBAL TOPOLOGICAL PROPERTIES:  
CLUSTERING, PATH LENGTH

NODAL FEATURES:  
CENTRALITY INDICES

INTERMEDIARY TOPOLOGY:  
MODULES AND COMMUNITIES

## FINDINGS IN THE HEALTHY BRAIN CONNECTOME

# GLOBAL TOPOLOGY: SMALL WORLD



$$\theta = \gamma/\lambda > 1$$

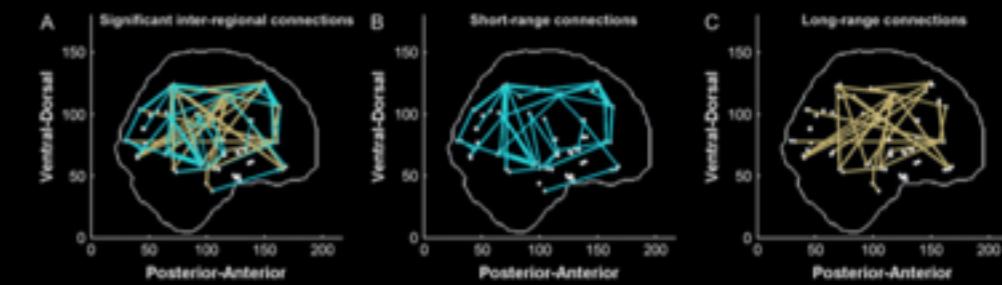
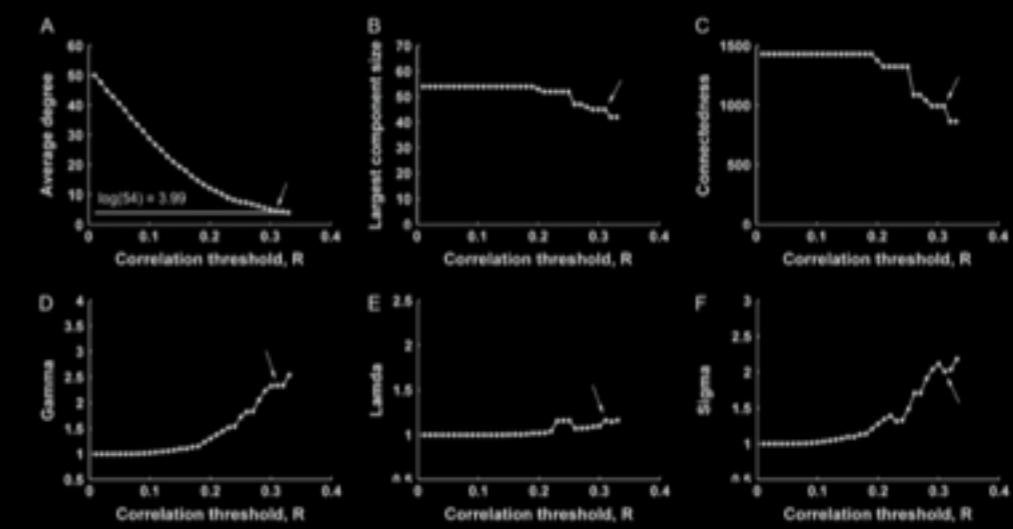
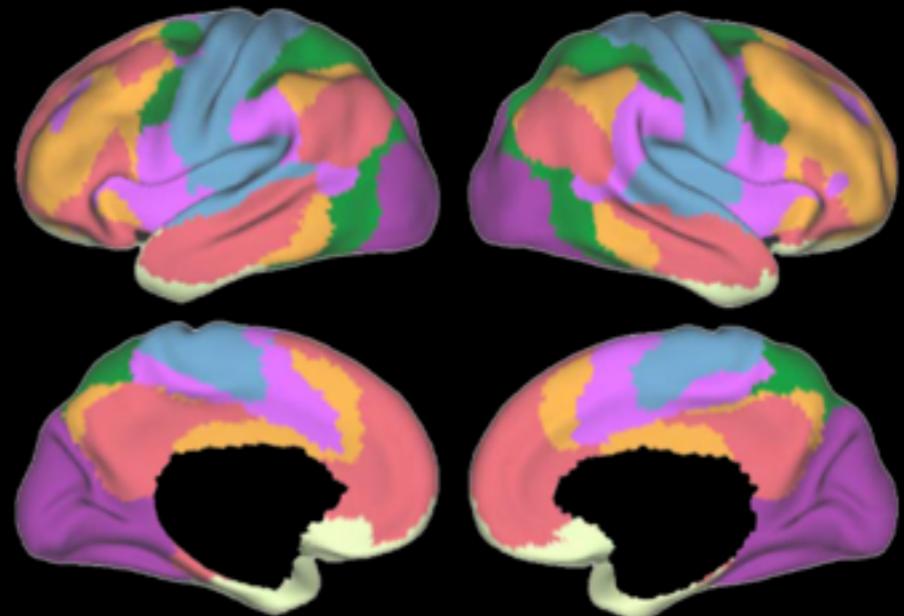
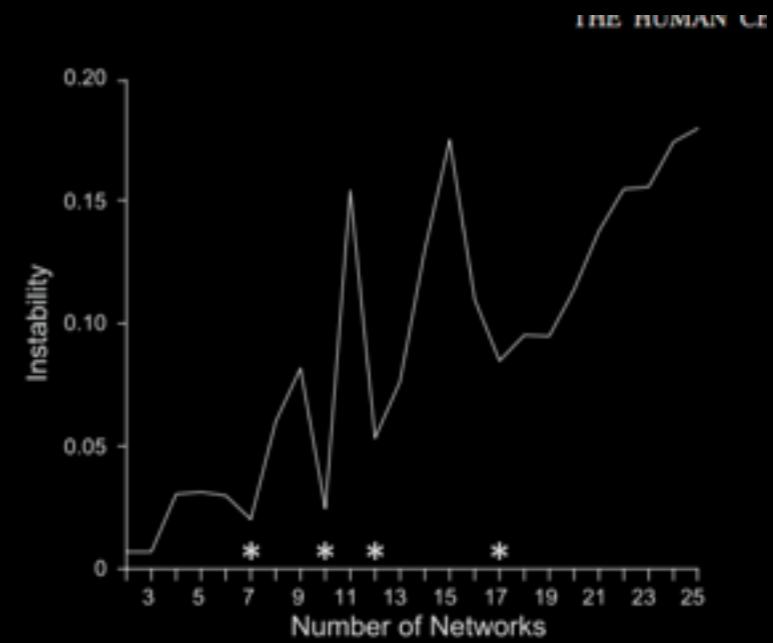
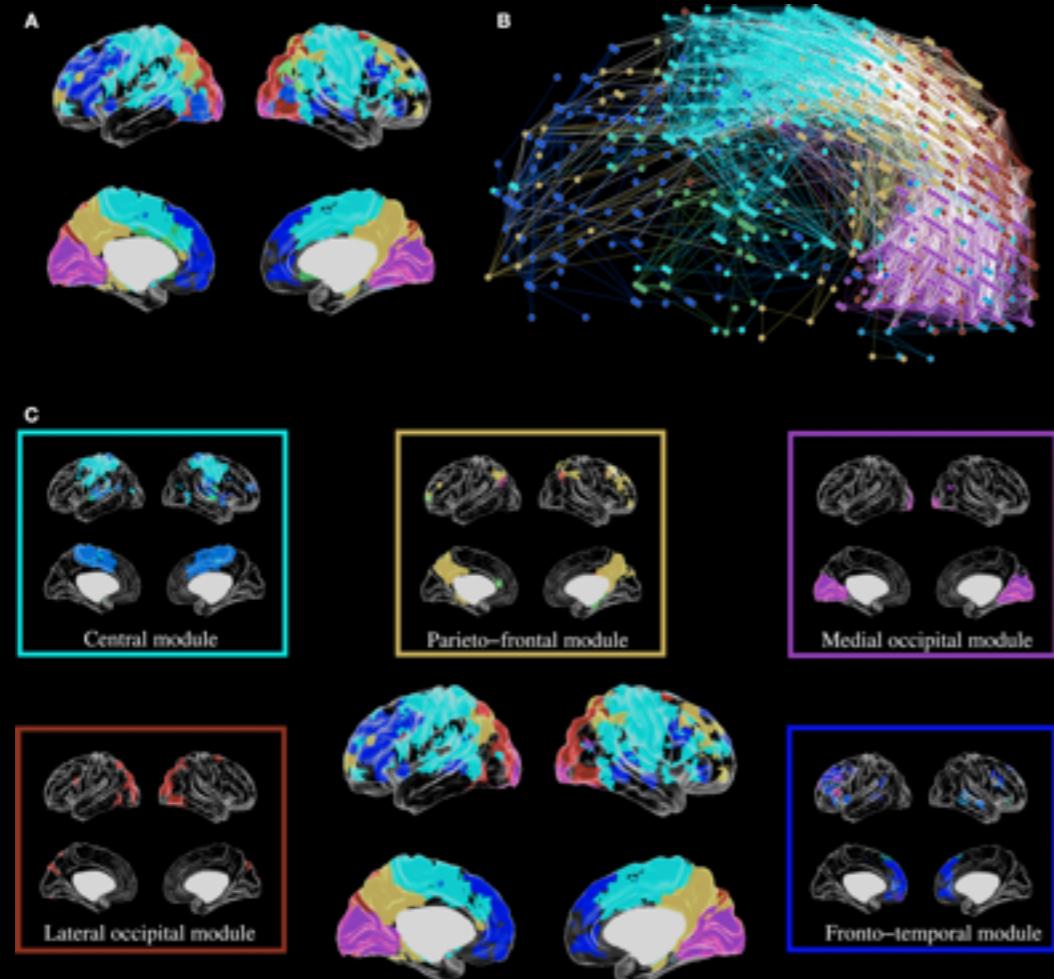


Figure 3. Short- and long-range anatomical connections in the anatomical space. (A) One hundred and four undirected edges ( $\sim 7.2\%$  of the 1401 possible connections among regions) representing the significant connections were shown in a sagittal view of the brain. Edges were classified into (B) short-range connections ( $D < 75$  mm, red) and (C) long-range connections ( $D > 75$  mm, blue). The locations of the nodes indicated the  $y$  and  $z$  coordinates of the regional centroids in Talairach space.

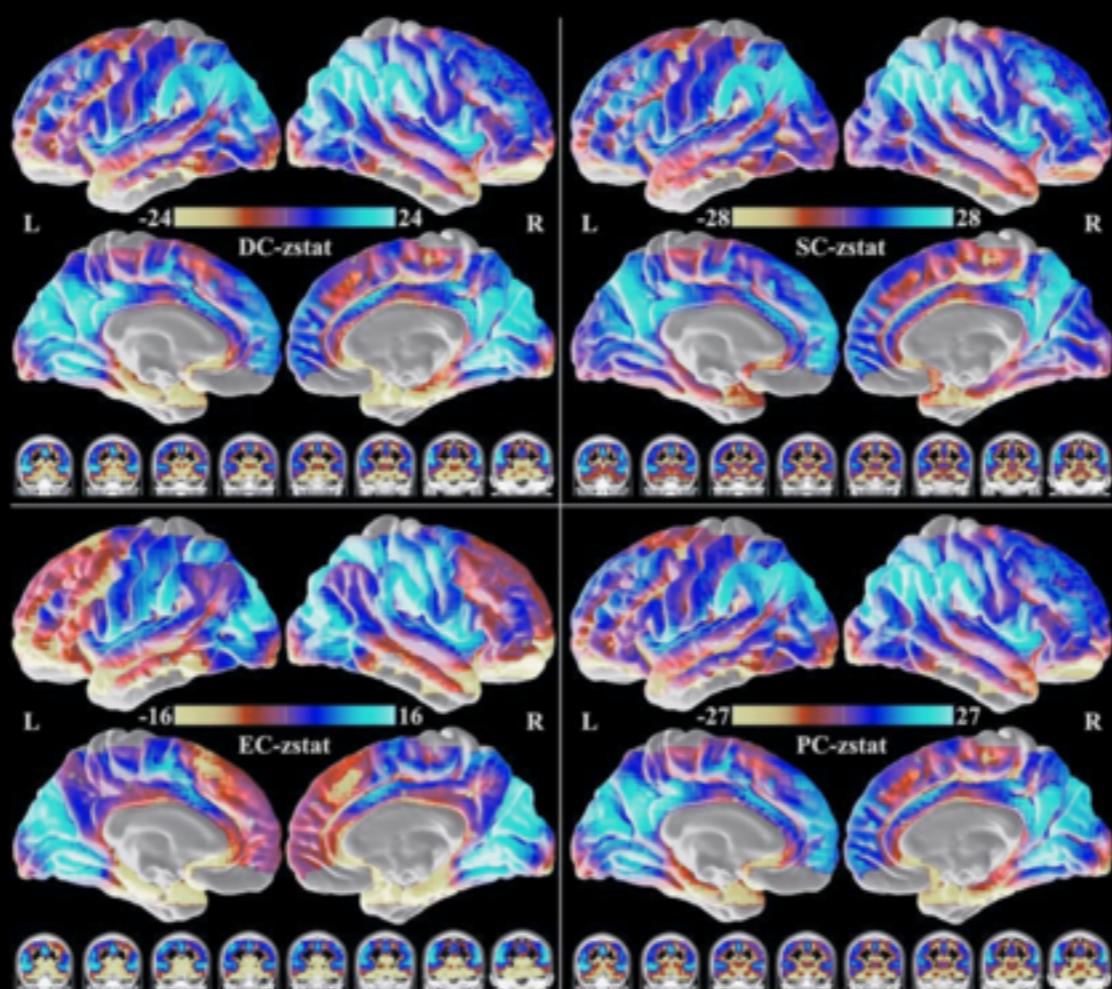


$$\theta = \gamma/\lambda > 1$$

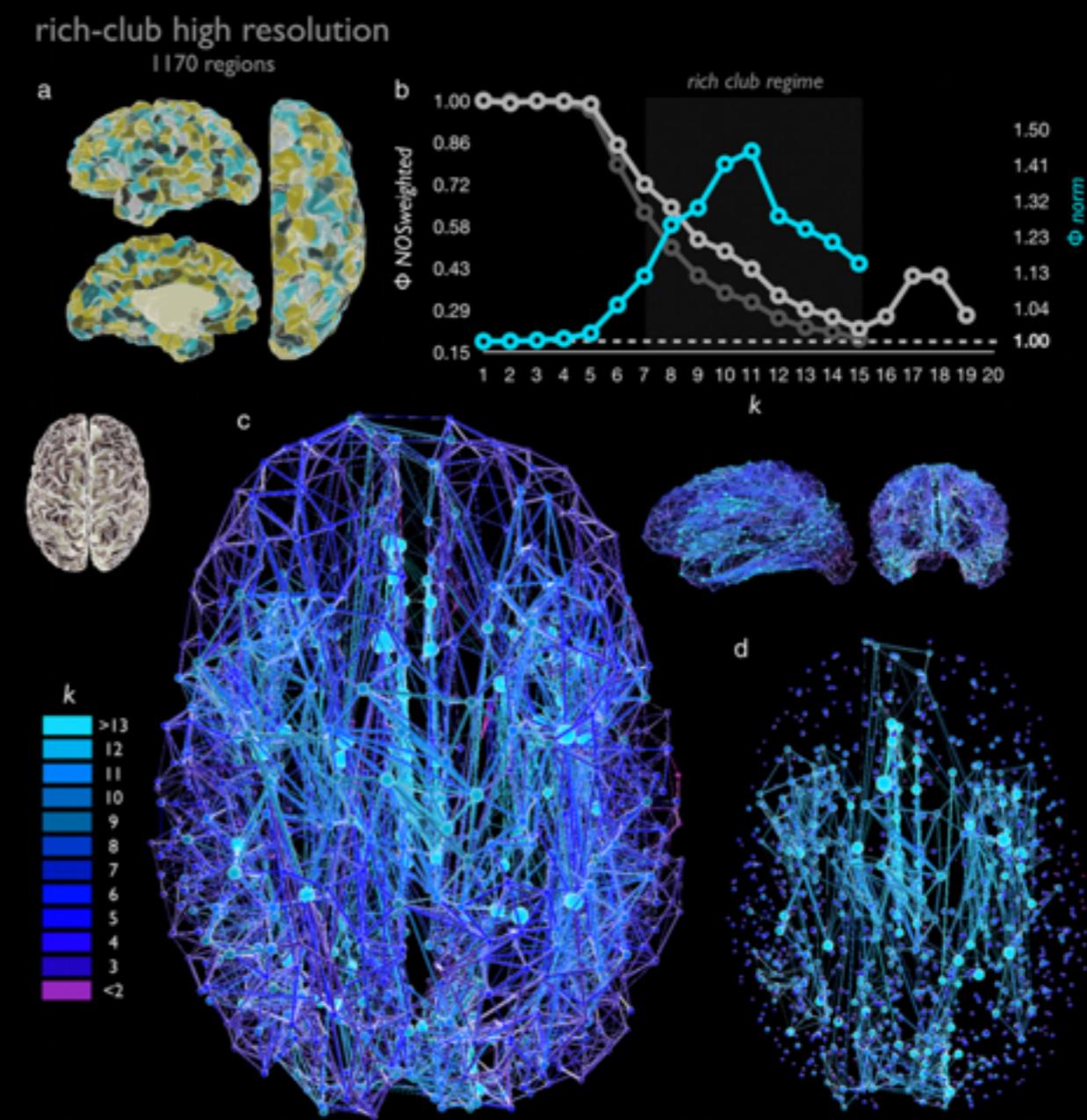
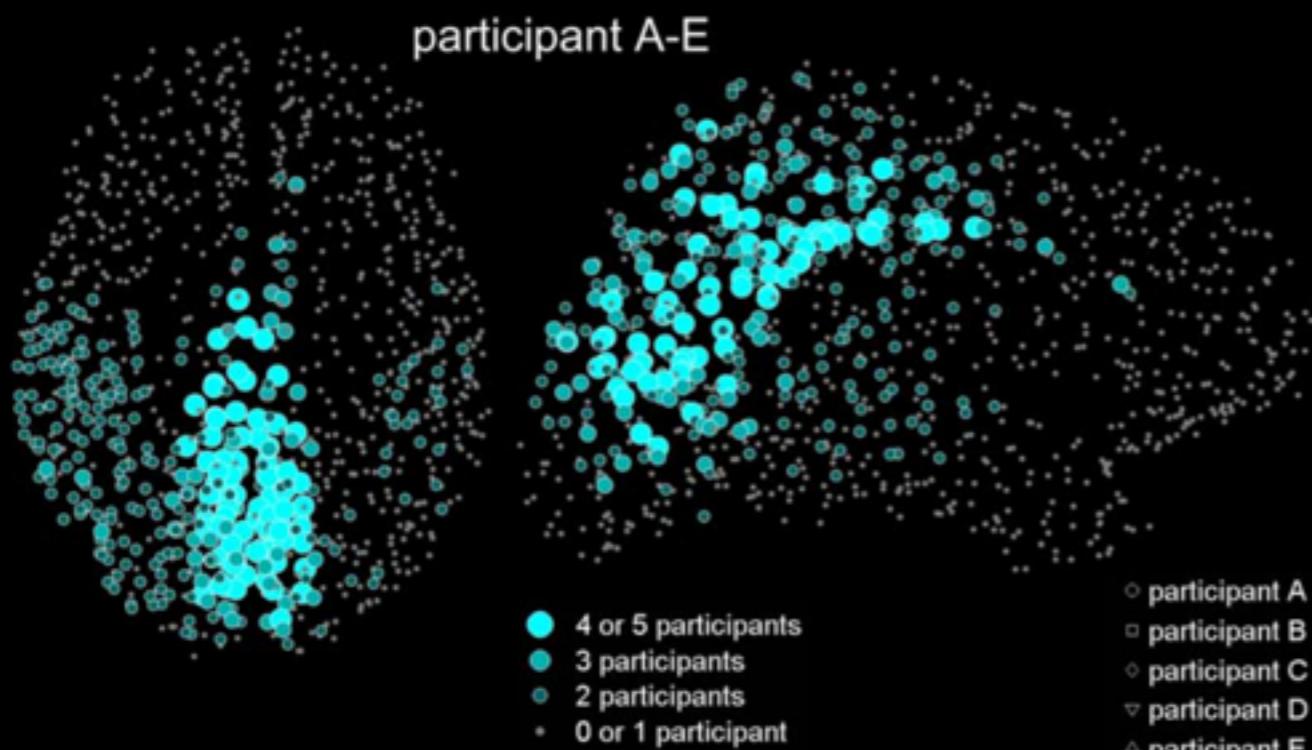
# INTERMEDIATE TOPOLOGY: MODULARITY



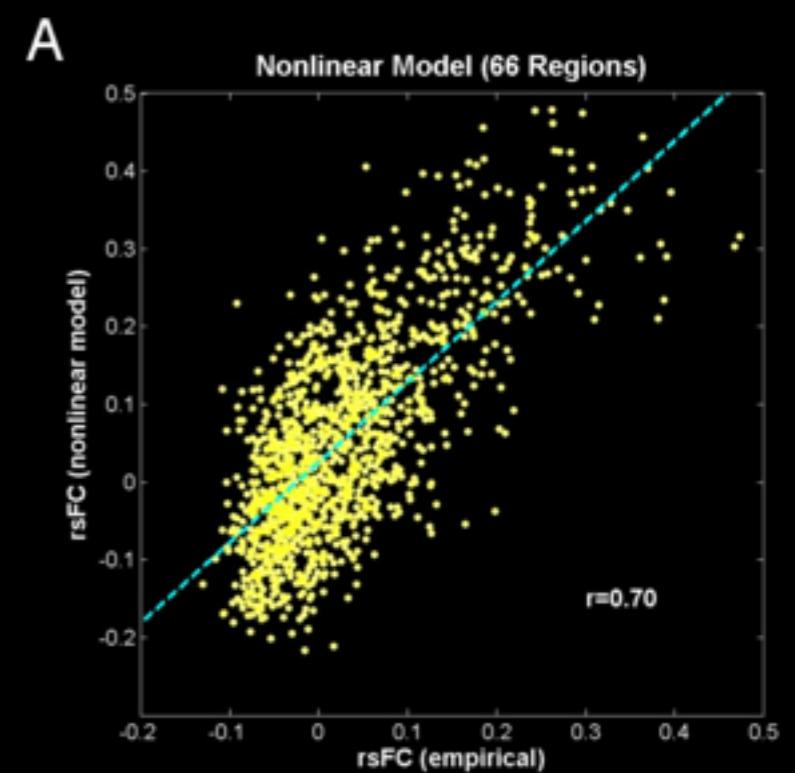
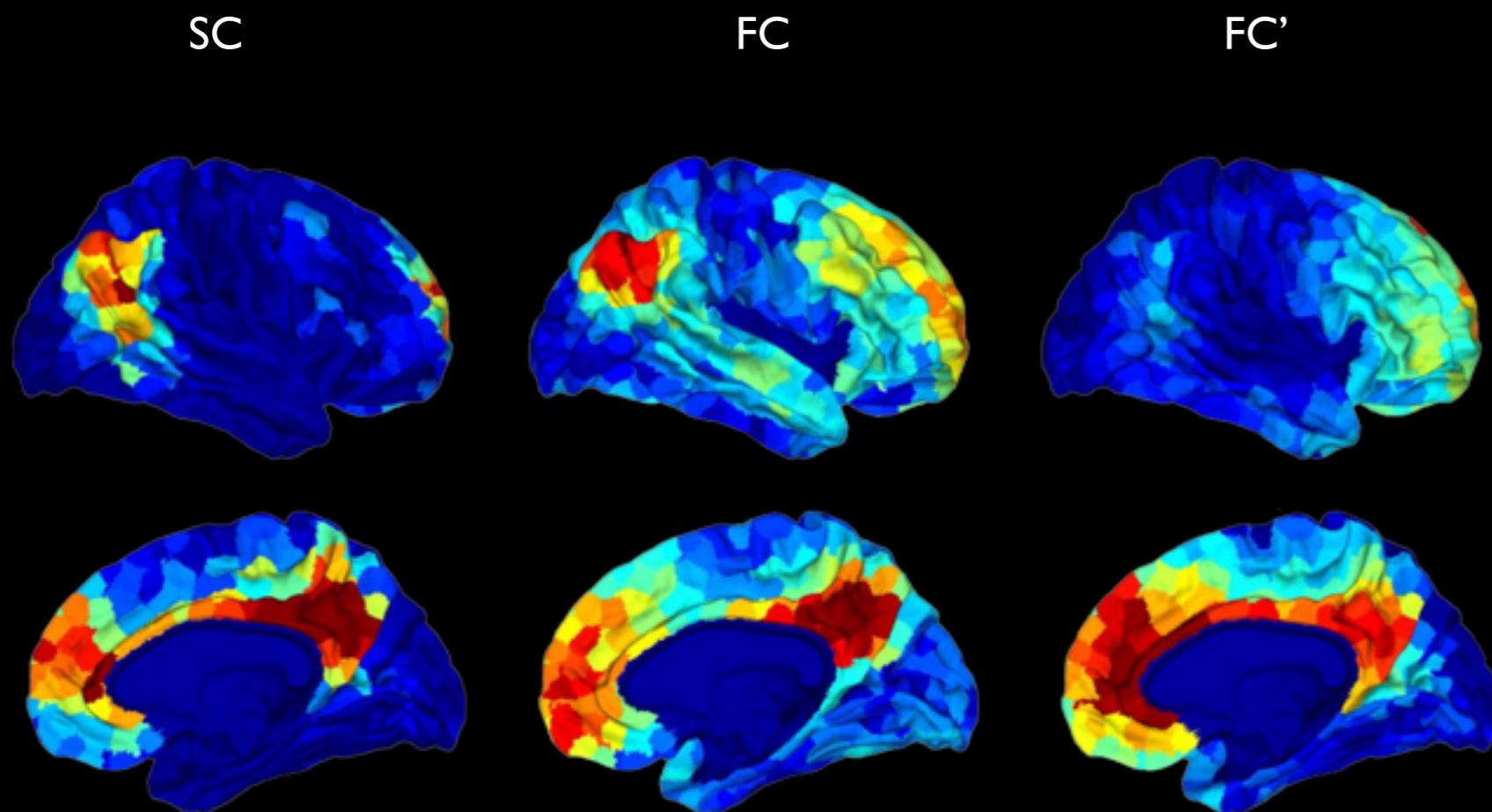
## NODAL TOPOLOGY: CENTRALITY



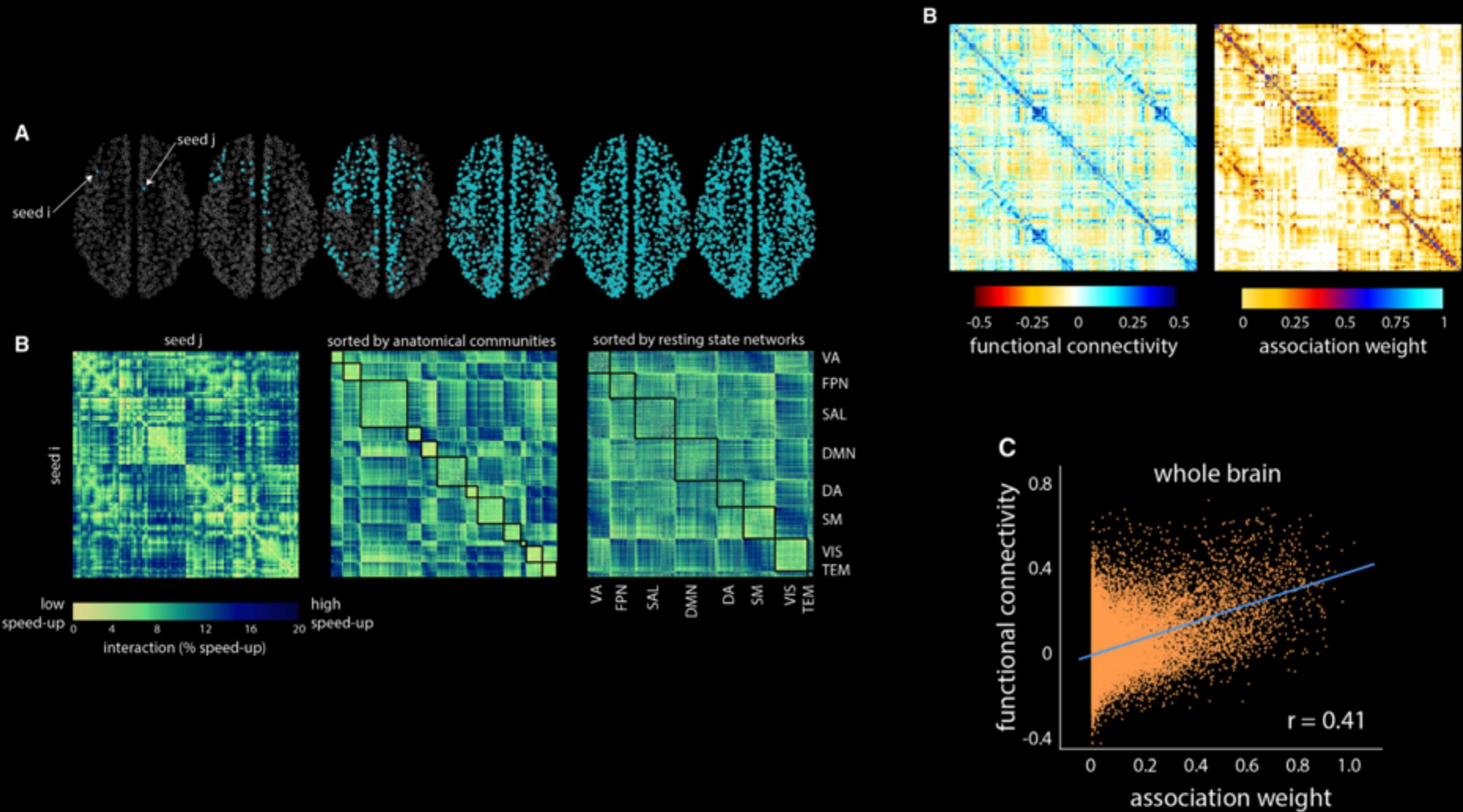
# NODAL TOPOLOGY: RICH-CLUB AND CORES



# FROM DESCRIPTION TO DYNAMICS



# FROM DESCRIPTION TO DYNAMICS



## INTERIM SUMMARY

HEALTHY BRAIN CONNECTOME IS FOUND TO BE  
CHARACTERIZED BY SMALL-WORLD TOPOLOGY

HIGH LOCAL AND GLOBAL EFFICIENCY

HIGHLY REPLICABLE FUNCTIONAL COMMUNITIES:  
DMN,TPN,SN,VN,...

BACKBONE/CORE/RICH-CLUB STRUCTURE  
PROVIDES STABILITY OF NETWORK AND MEDIATES  
CROSS-MODULE COMMUNICATION

STRUCTURAL SCAFFOLD OF THE NETWORK  
CAN BE USED TO SIMULATE FUNCTIONAL DYNAMICS  
WITH REASONABLE GOF

# FINDINGS IN THE EPILEPTIC CONNECTOME



AMERICAN  
EPILEPSY  
SOCIETY

# PRE-CONNECTOME AGE

		No. of cases	Percentage of 55 cases
Hippocampus	...	36	65
Cerebellum	...	25	45
Amygdaloid nucleus	...	15	27
Thalamus	...	14	25
Cortex	...	12	22

TABLE II.—Ammon's Horn Sclerosis Group with Diffuse and Disseminated Lesions Arranged in Order of Severity. The Various Possible Aetiological Agencies are Given.

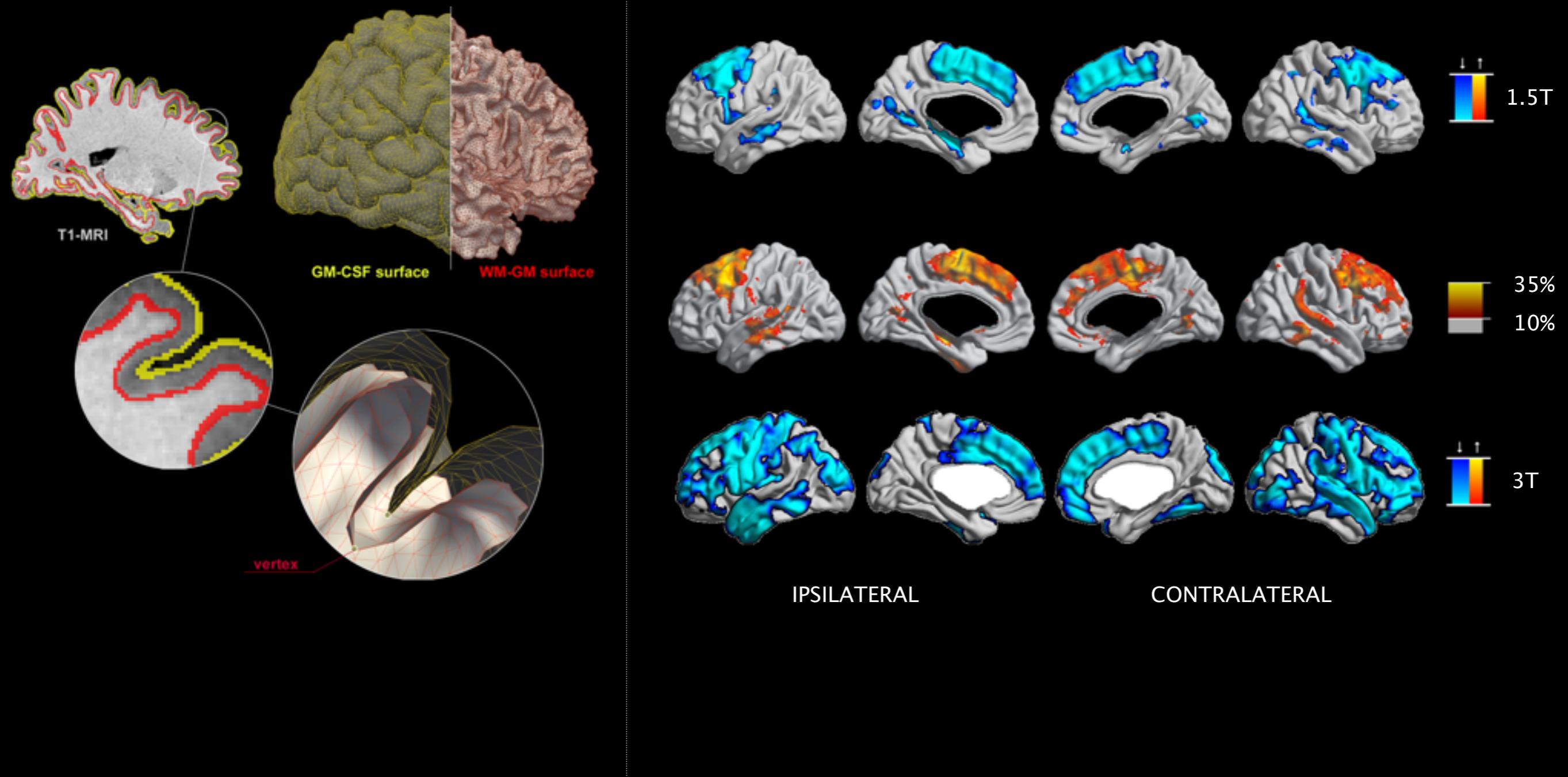
Case and Sex	Age at Onset and Operation	Status at Onset	Grand Mal	Difficult Birth	Other Causes	Side of Lobotomy	Meningo- Fibrosis	Marginal Glosso-	Gyr								Ammon's horn	Uncus	Amygdaloid			
									Middle		Inferior		Fusiform		Hippoc.							
									C	W	C	W	C	W	C	W						
Esh. F	4 13	—	+	—	Hemiplegia following measles	L.	O	■	▲	■	■	■	■	■	■	■	■	■	■	■		
Max. F	11 25	+	+	+	—	P.L.	O	■	■	■	■	■	■	■	■	■	■	■	■	■		
Ren. F	2 13	+	+	+	Meningitis at 11/12	L.	O	■	■	■	■	■	■	■	■	■	■	■	N.A.	N.A.		
Nob. F	45 18	+	+	—	—	L.	O	■	■	■	■	■	■	■	■	■	■	■	■	■		
Pat. M	2 13	—	+	+	Teething convulsions 2 years	P.L.	▲	■	■	■	■	■	■	■	■	■	■	■	■	■		
Low. M	3 11	+	+	—	Head trauma 8 years	L.	▲	■	■	■	■	■	■	■	■	■	■	■	■	■		
Garr. F	8 18	—	—	—	—	L.	▲	■	■	■	■	■	■	■	■	■	■	■	■	■		
Nev. M	9 16	—	—	—	Status at 23/12	R.	▲	■	■	■	■	■	■	■	■	■	■	■	N.A.	N.A.		
Job. F	2 21	+	+	—	—	R.	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
Wal. M	22 22	—	—	—	—	R.	■	■	■	■	■	■	■	■	■	■	■	■	N.A.	N.A.		
Har. M	22 26	—	—	—	—	R.	■	■	■	■	■	■	■	■	■	■	■	■	■	■		
And. F	22 23	+	+	+	—	L.	▲	■	■	■	■	■	■	■	■	■	■	■	■	■		
Tur. E. F	22 22	+	+	—	Whooping cough 1/12 before status	L.	▲	■	■	■	■	■	■	■	■	■	■	■	■	■		
Pri. M	2 23	+	+	—	Teething convulsions	R.	▲	■	■	■	■	■	■	■	■	■	■	■	N.A.	N.A.		
Tur. J. F	14 20	+	+	+	—	L.	▲	■	■	■	■	■	■	■	■	■	■	■	■	■		
Chu. M	40 49	+	+	+	—	L.	▲	■	■	■	■	■	■	■	■	■	■	N.A.	N.A.	N.A.		
Ric. M	2 32	—	—	—	—	L.	■	■	■	■	■	■	■	■	■	■	■	N.A.	N.A.	N.A.		
Mac. M	2 45	+	+	+	Status compl. Ch. pox	R.	O	■	■	■	■	■	■	■	■	■	■	N.A.	N.A.	N.A.		
Kev. F	4/12 43	+	+	—	—	L.	O	▲	○	○	○	○	○	○	○	○	○	N.A.	N.A.	N.A.		

■ = ++ Severity, ▲ = + Severity, □ = Doubtful lesion, ○ = No abnormality, N.A. = Not available, C = Cortex, W = White matter.

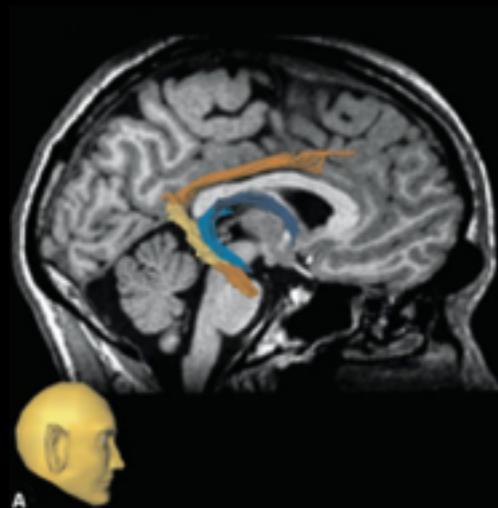
TABLE III.—Group with Minimal Lesions and no Ammon's Horn Sclerosis Arranged in Order of Severity and Showing Possible Aetiological Factors

Case and Sex	Age at Onset and Operation	Status at Onset	Grand Mal	Difficult Birth	Other Causes	Side of Lobotomy	Meningo- Fibrosis	Marginal Glosso-	Gyr								Ammon's horn	Uncus	Amygdaloid			
									Middle		Inferior		Fusiform		Hippoc.							
									C	W	C	W	C	W	C	W						
Lee. M	8 38	—	—	—	Bacillary	L.	O	■	□	▲	□	▲	□	□	▲	□	□	N.A.	N.A.	N.A.		
Str. P	2 21	—	—	—	—	L.	O	▲	○	○	○	○	○	○	○	○	○	○	○	○		
Par. M	18 25	—	—	—	—	R.	O	▲	○	○	○	○	○	○	○	○	○	○	○	○		
You. F	13 45	—	—	—	Head injury at 19 years	L.	O	▲	○	○	○	○	○	○	○	○	○	○	○	○		
Cha. F	16 27	—	—	—	Wh. cough at 25 years	R.	▲	▲	○	○	○	○	○	○	○	○	○	N.A.	N.A.	○		
Tay. M	14 27	—	—	—	Sinusitis at 16 years	L.	O	▲	○	○	○	○	○	○	○	○	○	○	○	○		
Par. M	18 25	—	—	—	T.B. hip with meningitis at 12 years	L.	O	▲	○	○	○	○	○	○	○	○	○	○	○	○		
Fox. M	18 45	—	—	—	Otitis media	L.	O	□	○	○	○	○	○	○	○	○	○	○	○	○		
					Head injury at 18 years	R.	O	○	○	○	○	○	○	○	○	○	○	○	○	○		

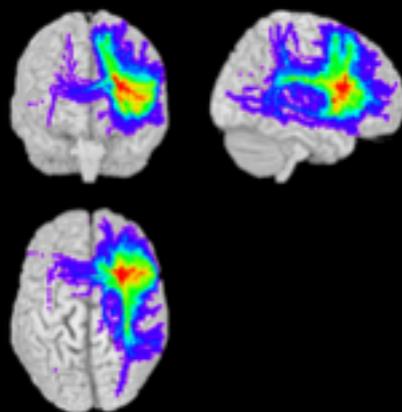
■ = ++ Severity, ▲ = + Severity, □ = Doubtful lesion, ○ = No abnormality, N.A. = Not available, C = Cortex, W = White matter.



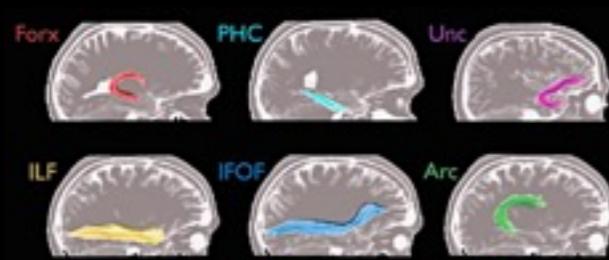
# LITERATURE ON REGIONAL CONNECTIVITY CHANGES IN EPILEPSY



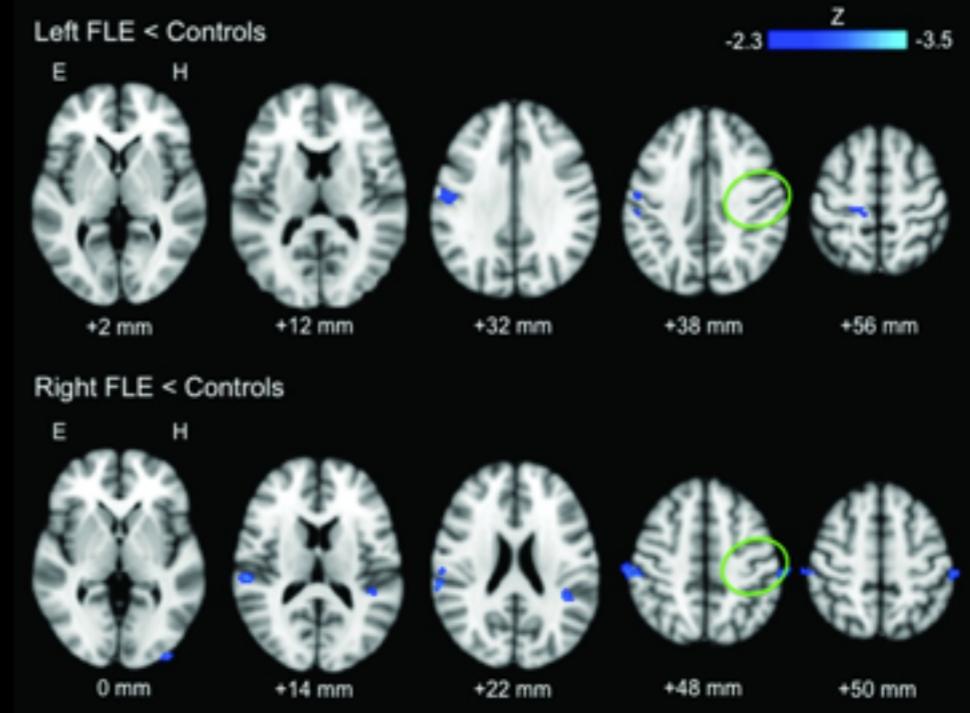
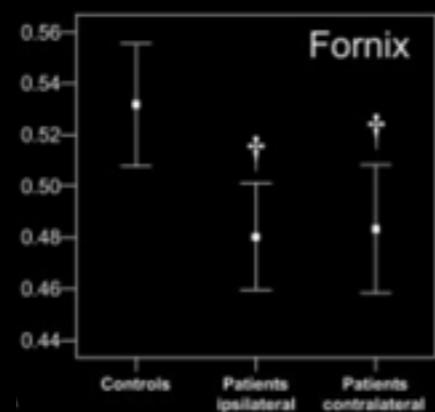
Concha et al (2005) Ann Neu



Powell et al (2006) NIMH

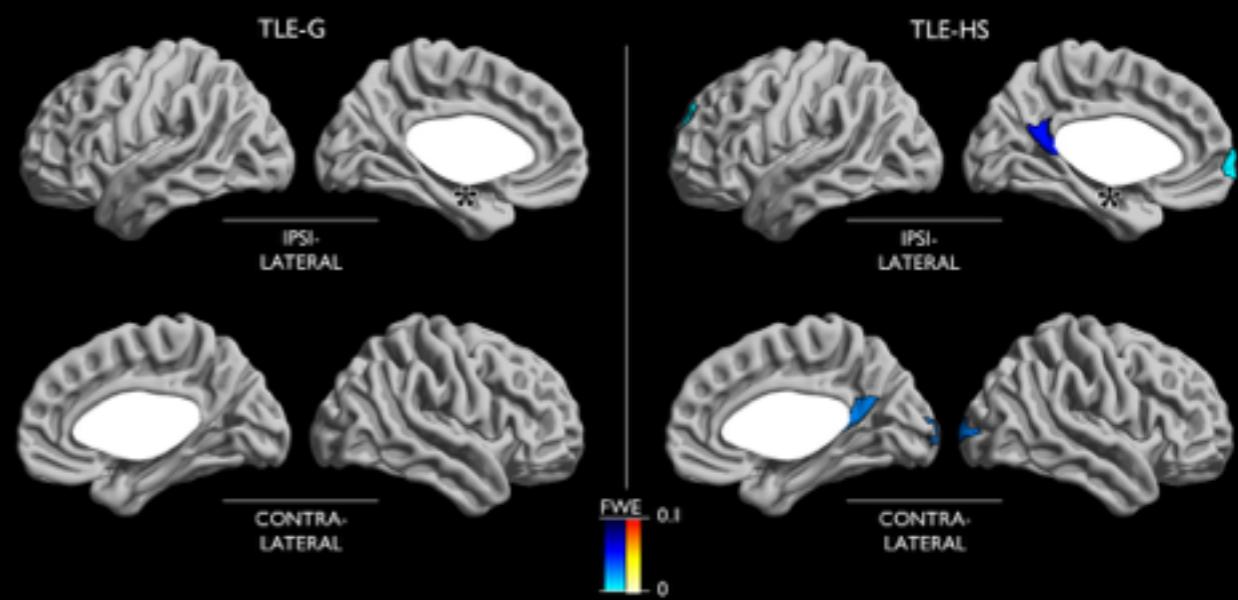


Kemmotsu et al (2011) Epilepsia



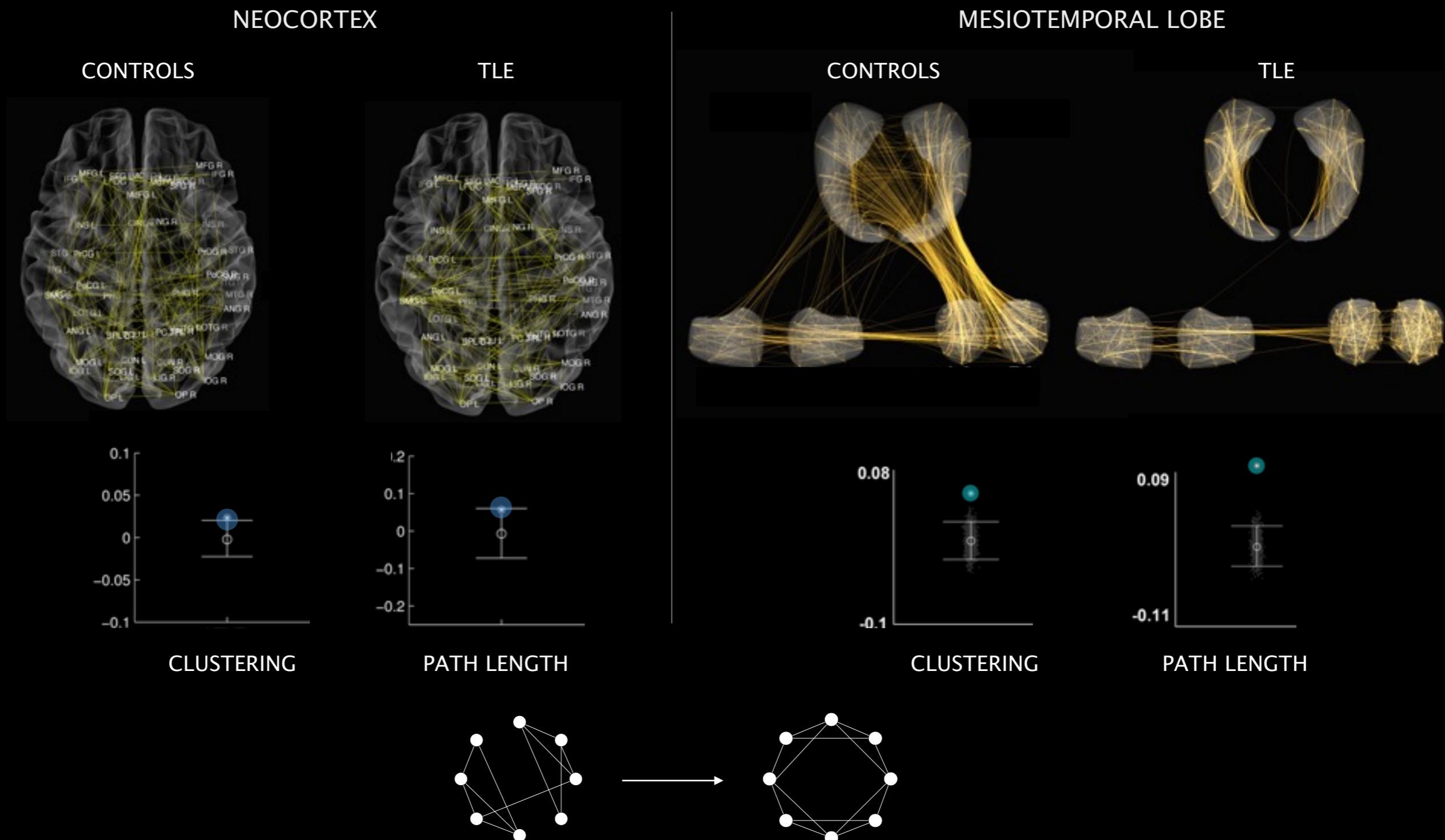
Woodward et al (2014) Brain connectivity

## B CONNECTIVITY ALTERATIONS IN TLE

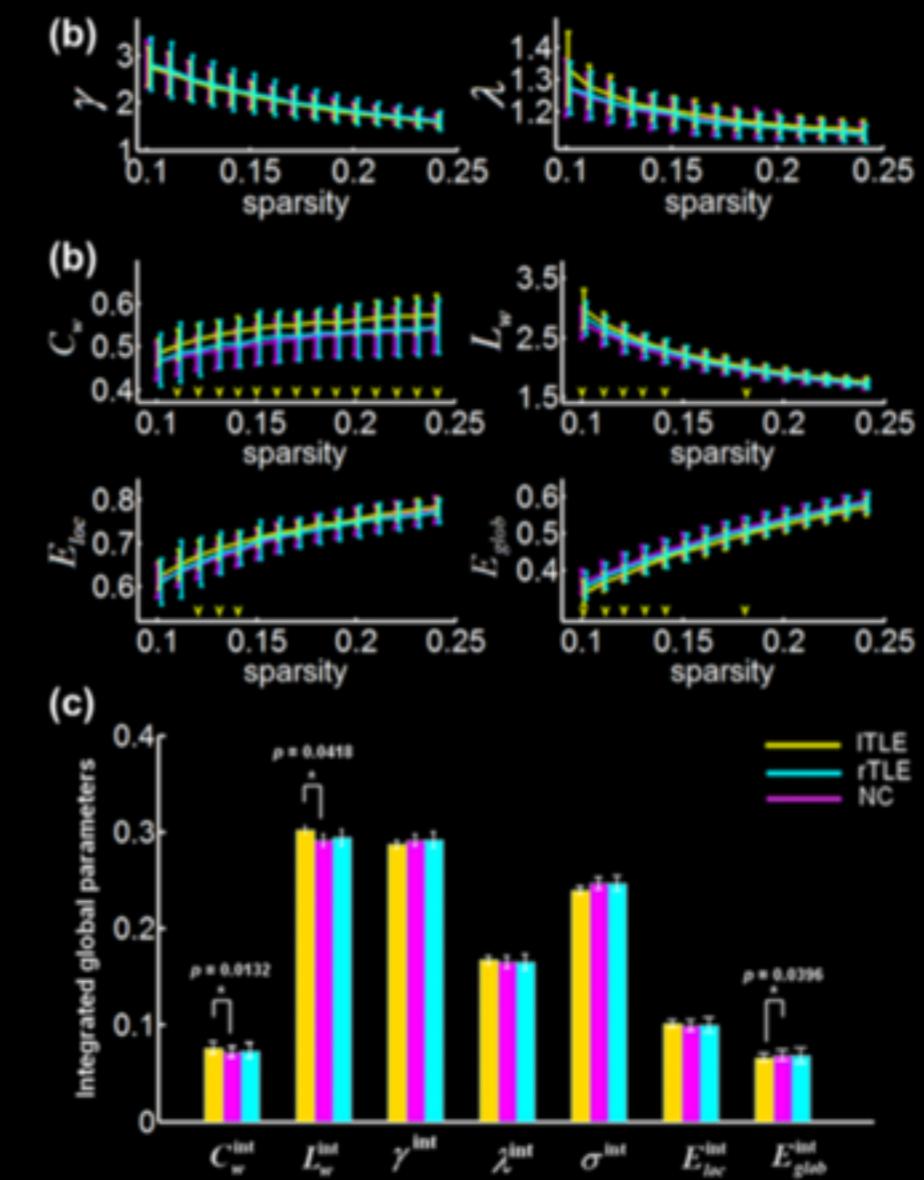
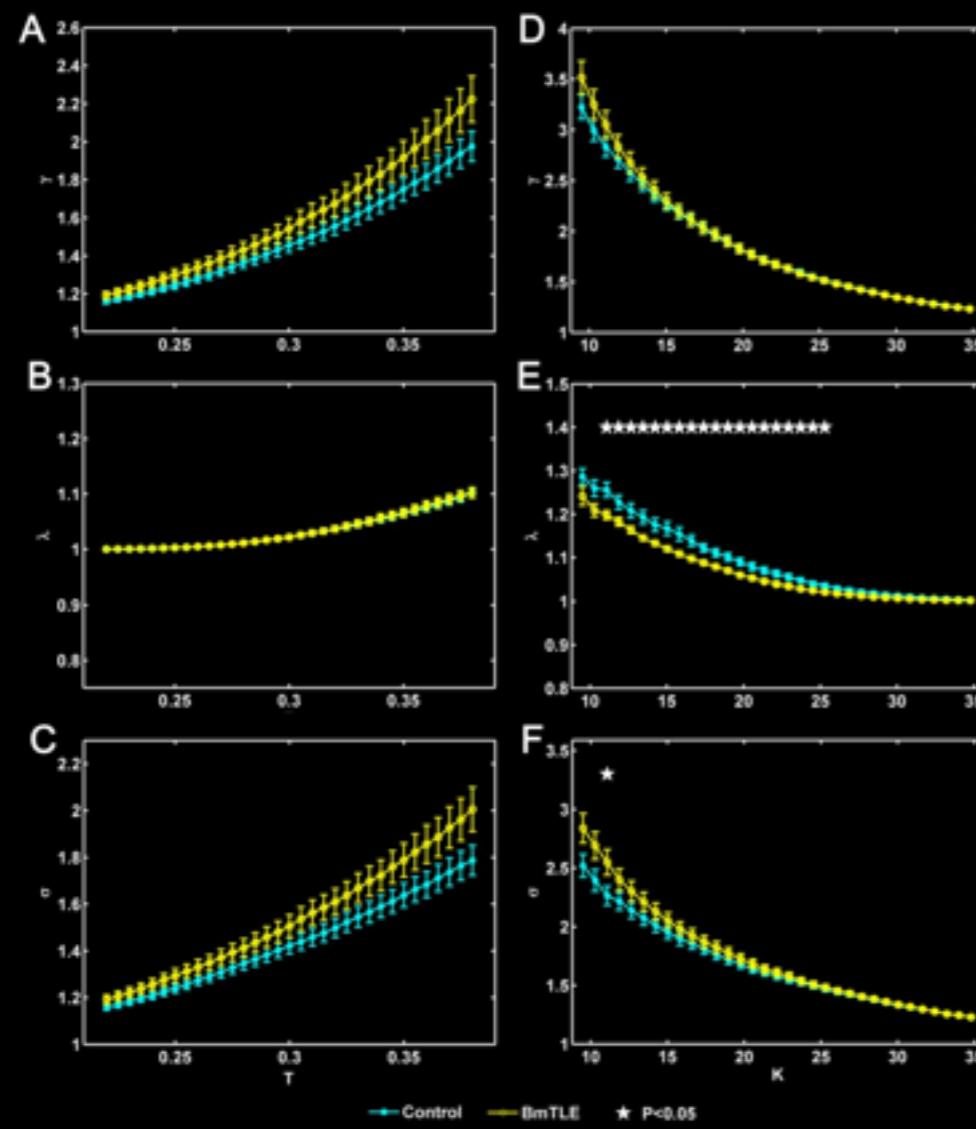


Bernhardt et al (2016) Ann Neu

# LARGE-SCALE CHANGES: STRUCTURAL COVARIANCE NETWORKS

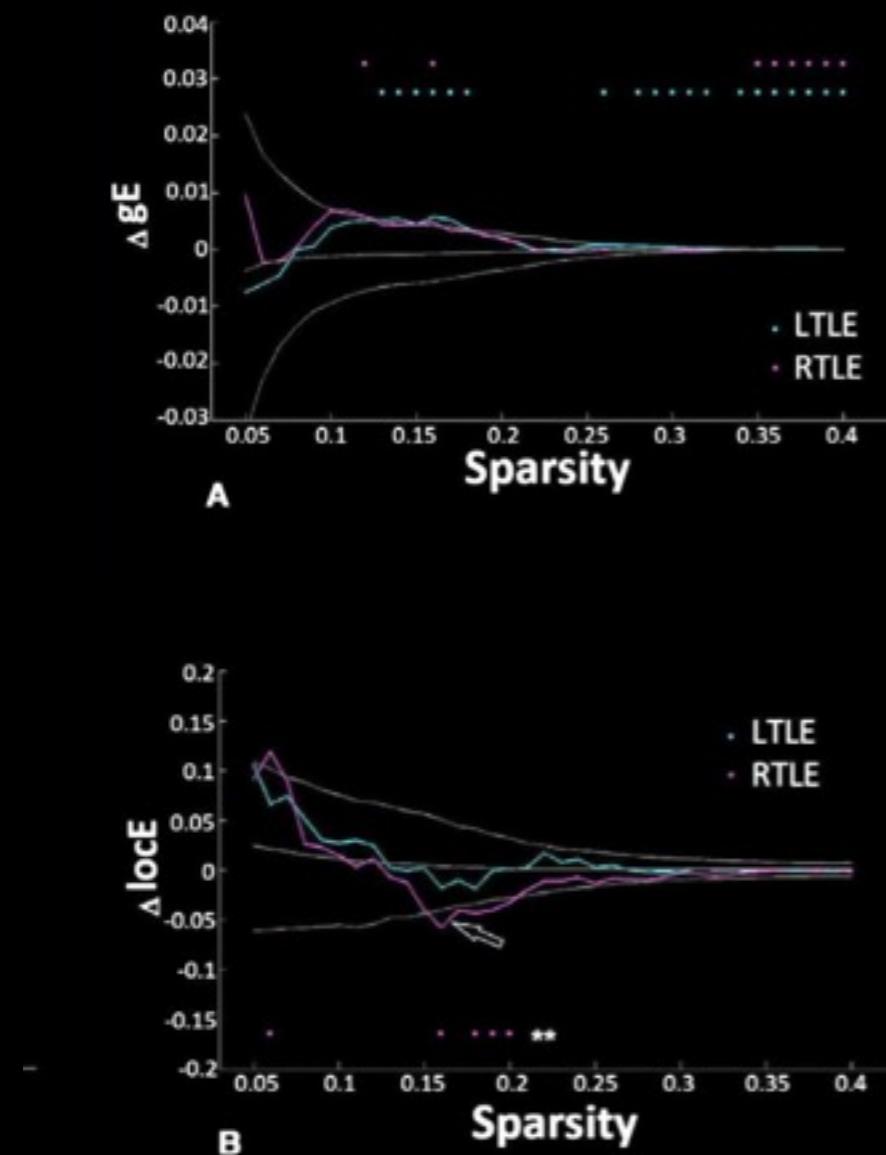


# LARGE-SCALE ALTERATIONS: FUNCTIONAL CONNECTOME

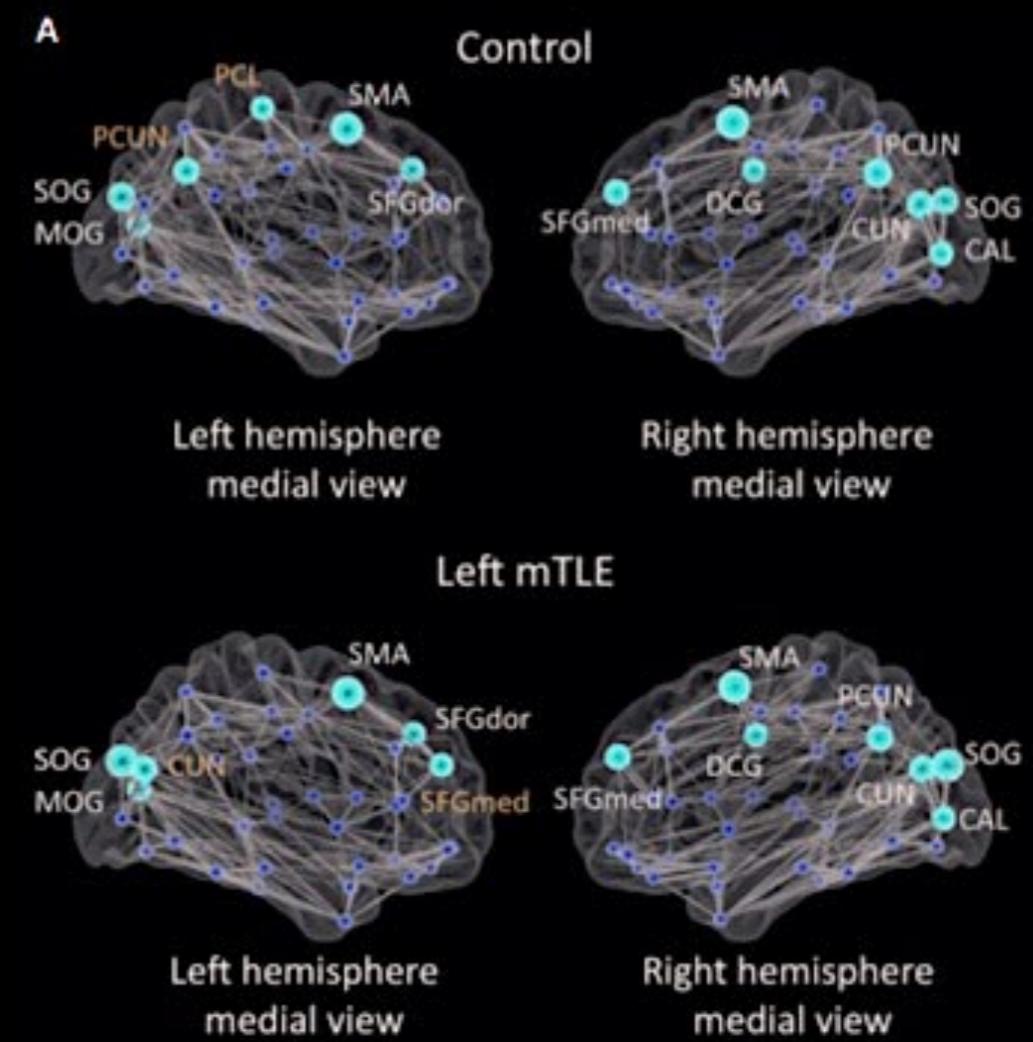


# LARGE-SCALE STRUCTURAL CHANGES

## CORTICAL AND SUBCORTICAL VOLUME COVARIANCE

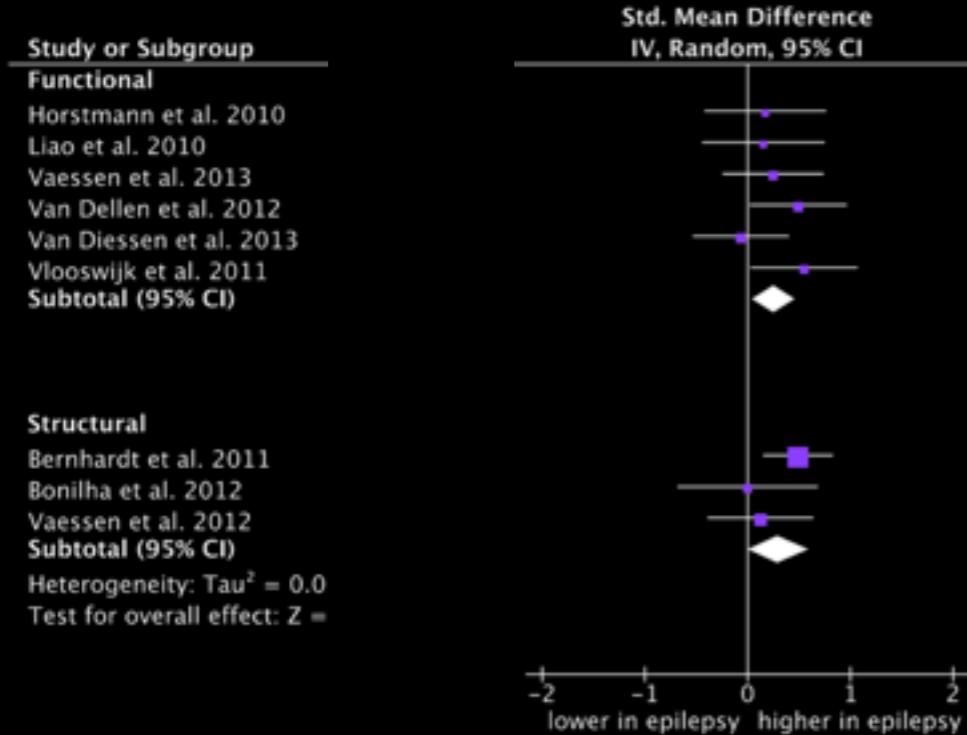


## DETERMINISTIC DIFFUSION TRACTOGRAPHY

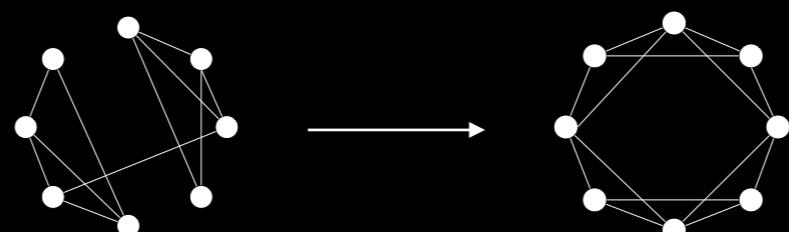
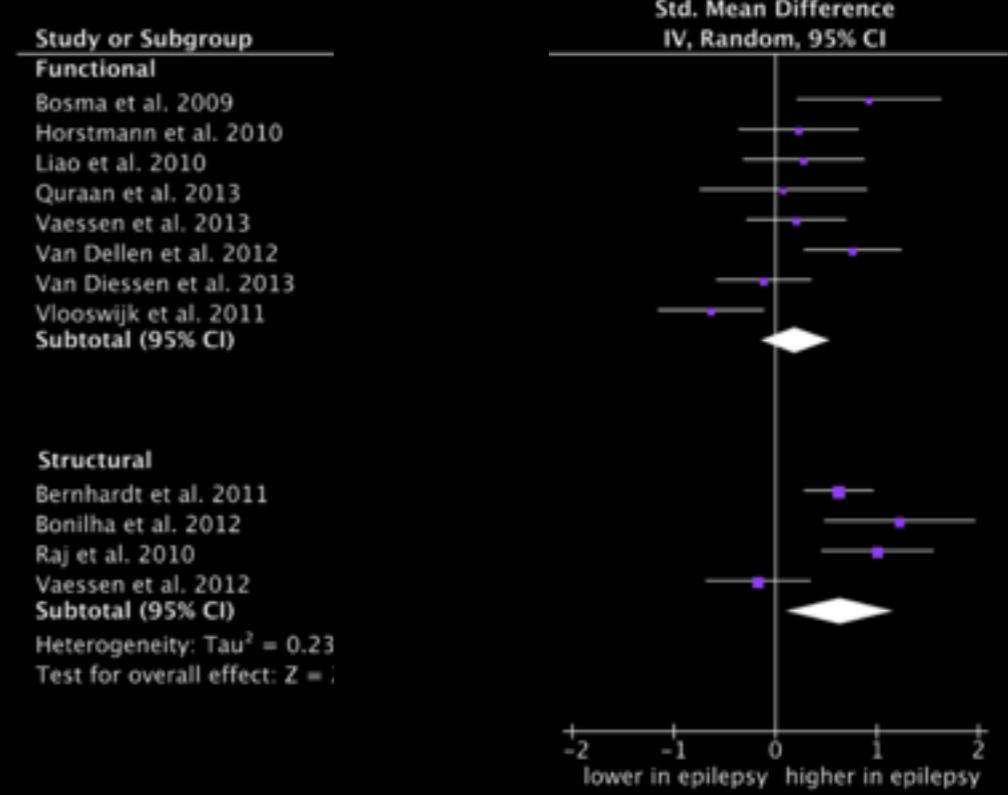


# META-ANALYTICAL FINDINGS ON NETWORK TOPOLOGY

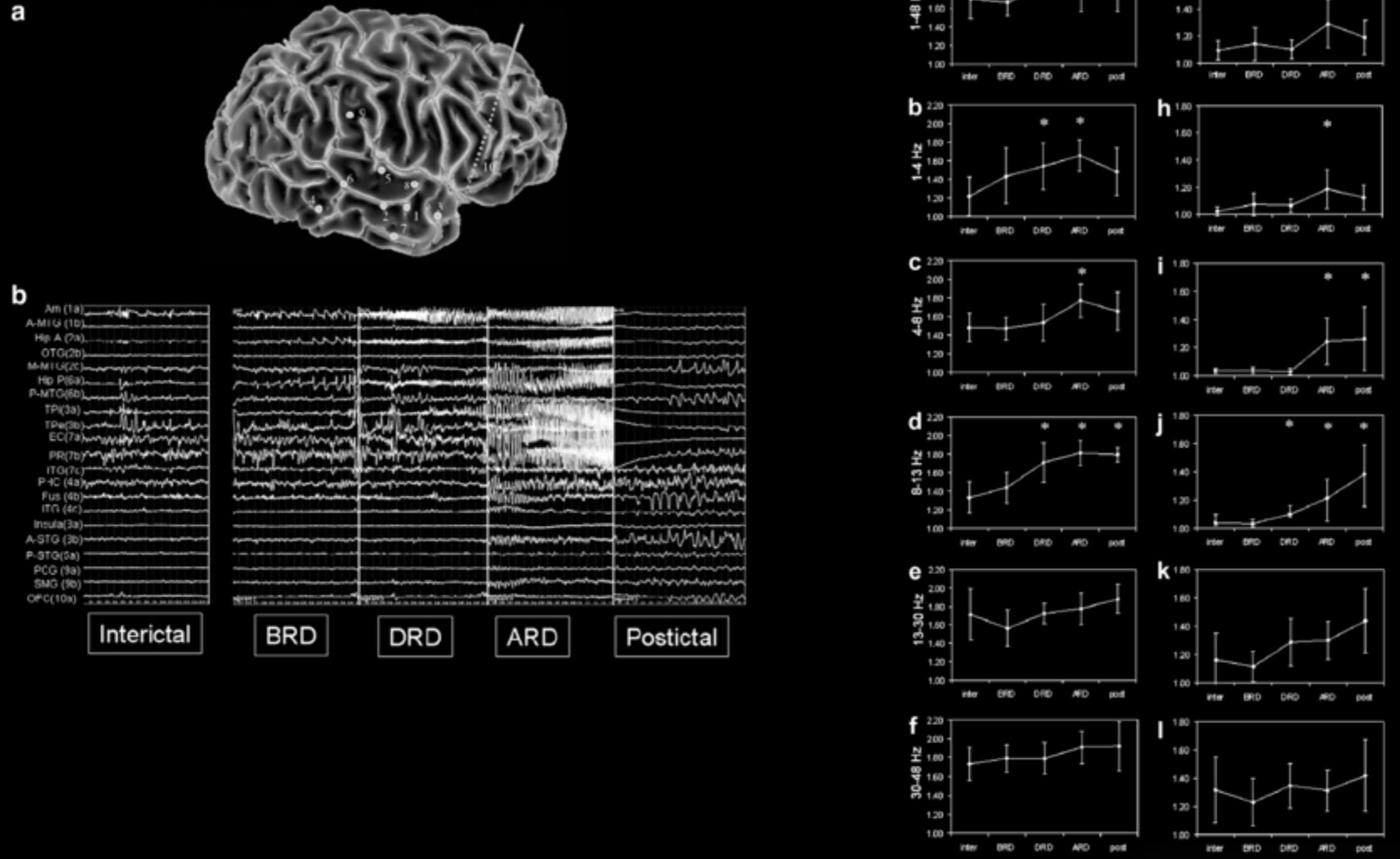
## CLUSTERING COEFFICIENT



## PATH LENGTH

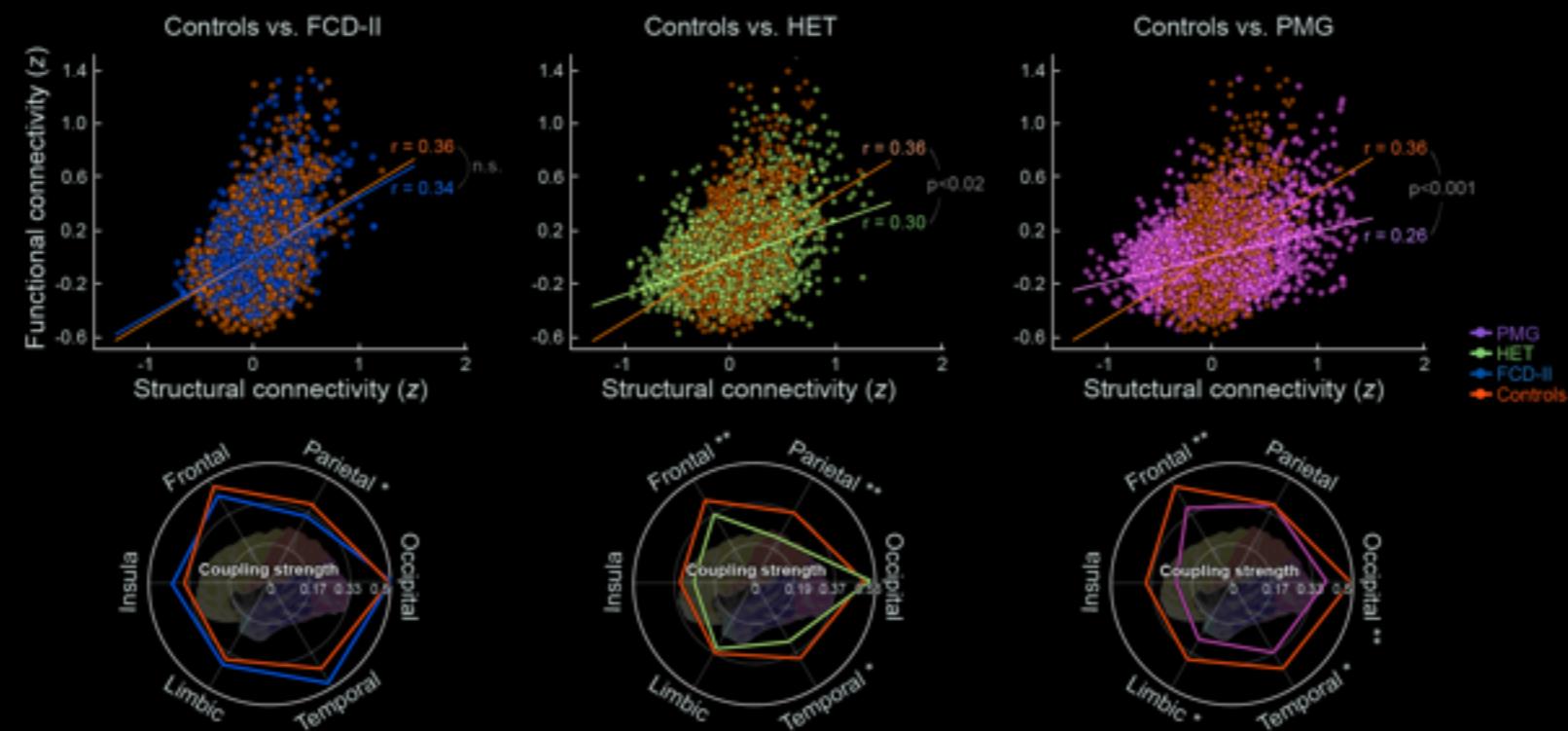
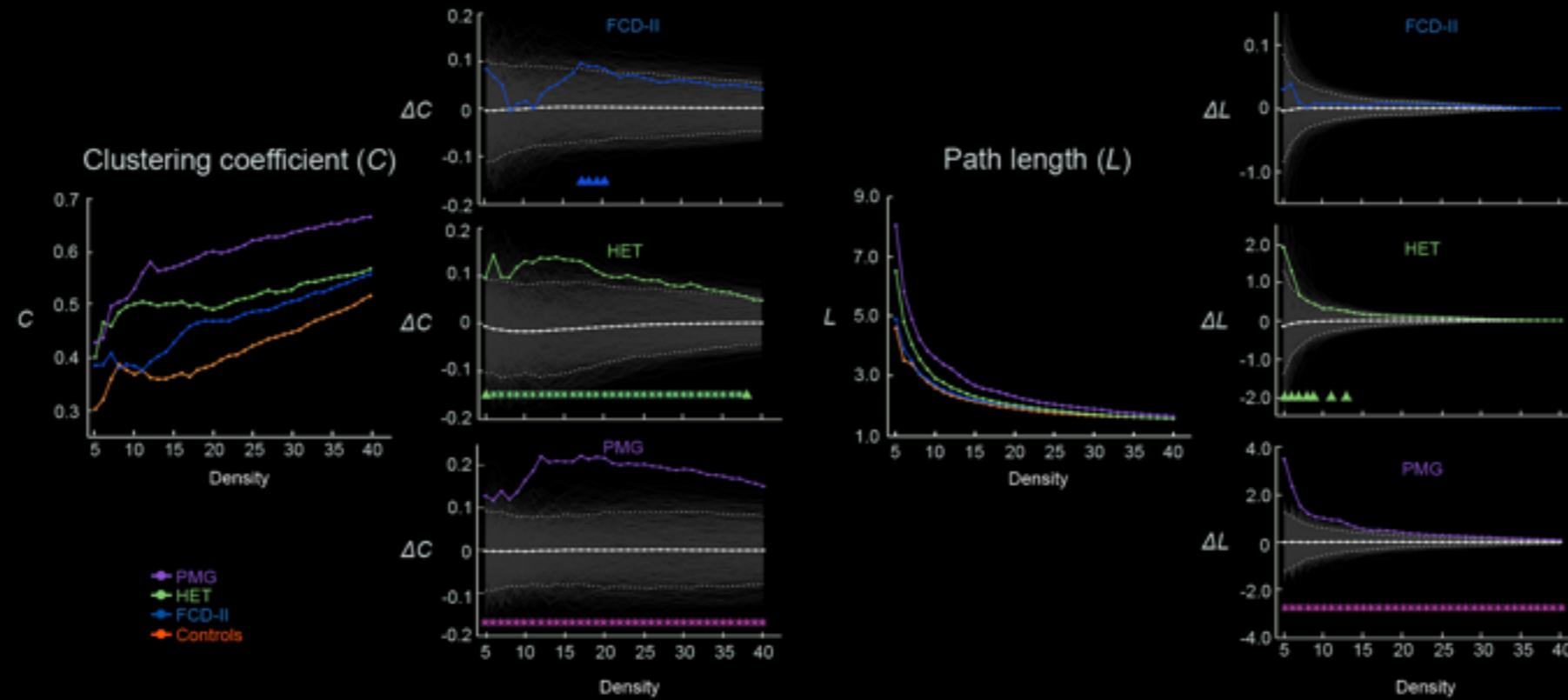


# REGULARIZATION ALSO SEEN DURING SEIZURES

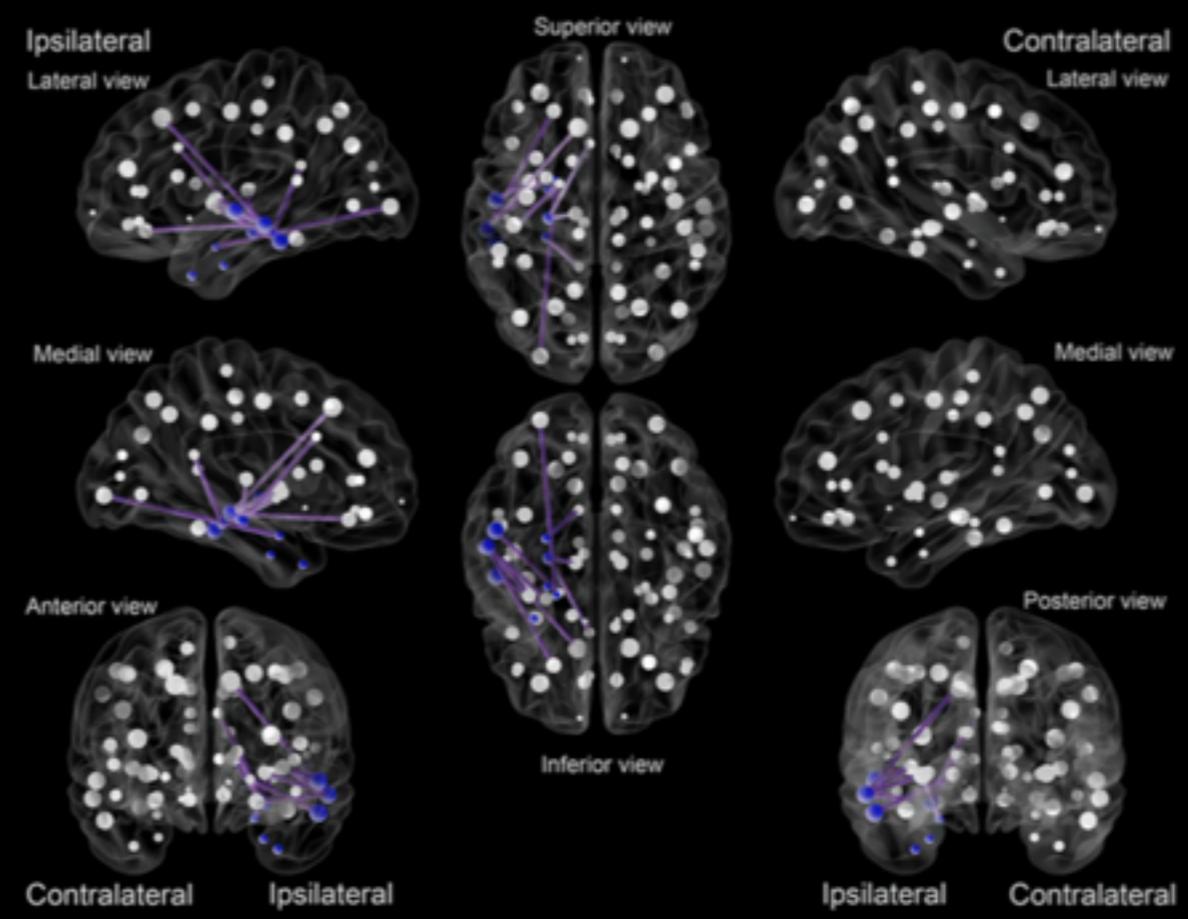
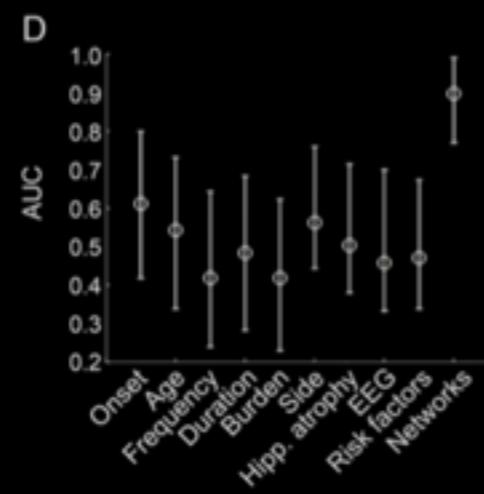
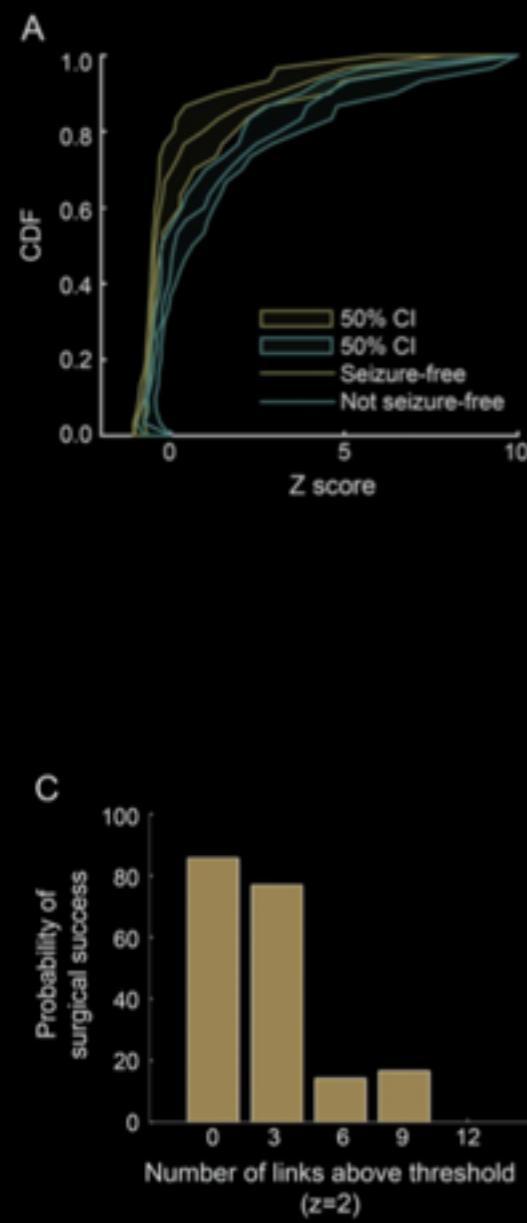


WHAT IS THIS GOOD FOR?

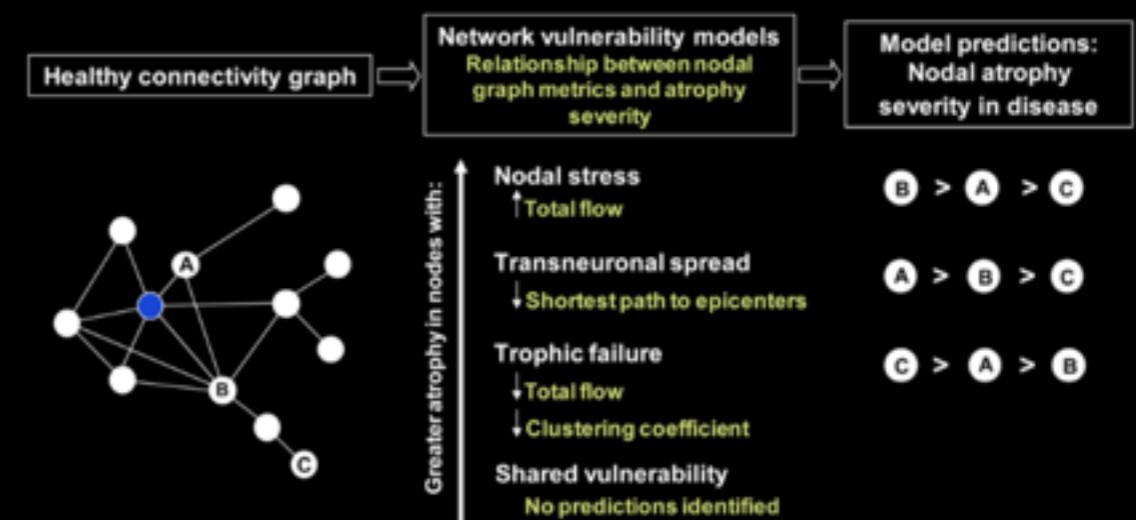
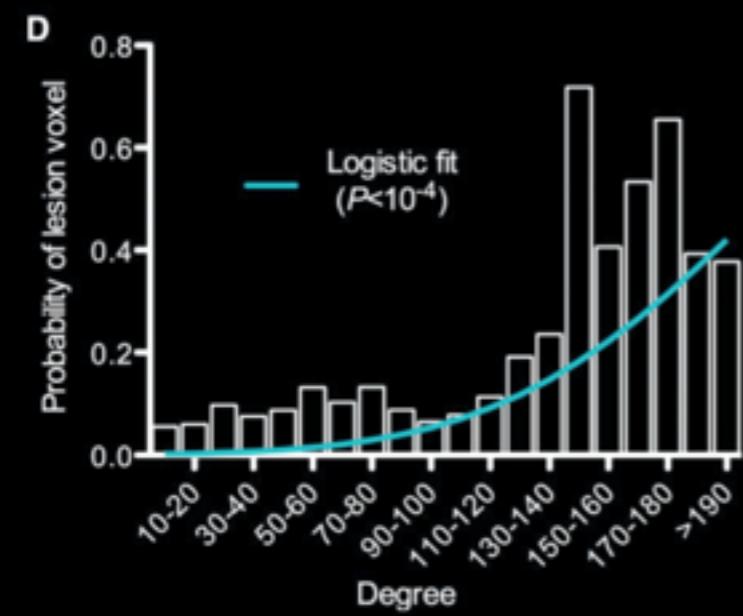
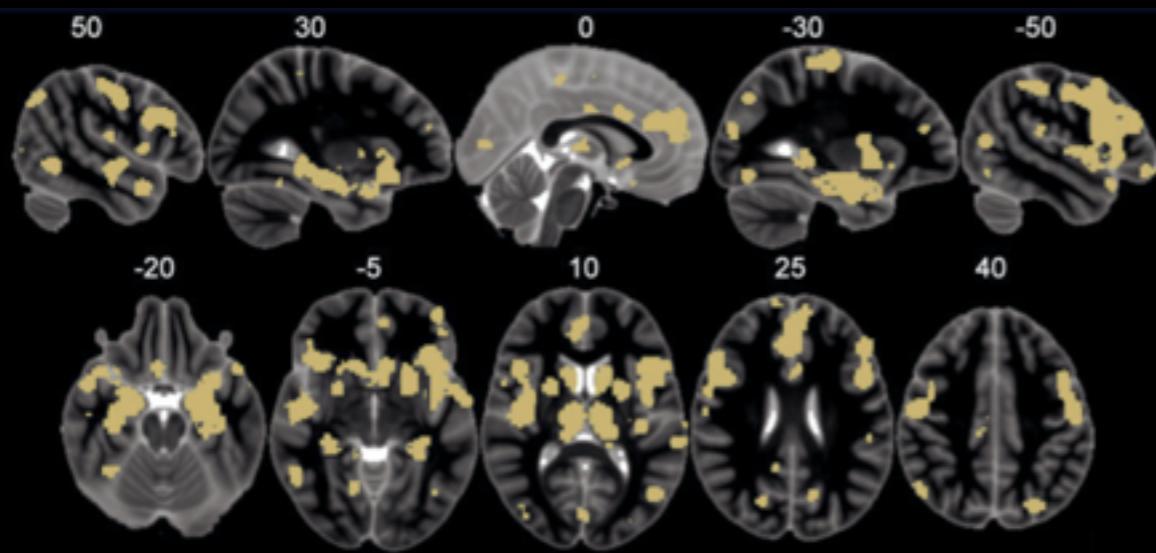
# BEYOND DESCRIPTION 1: STRUCTURE FUNCTION STUDIES

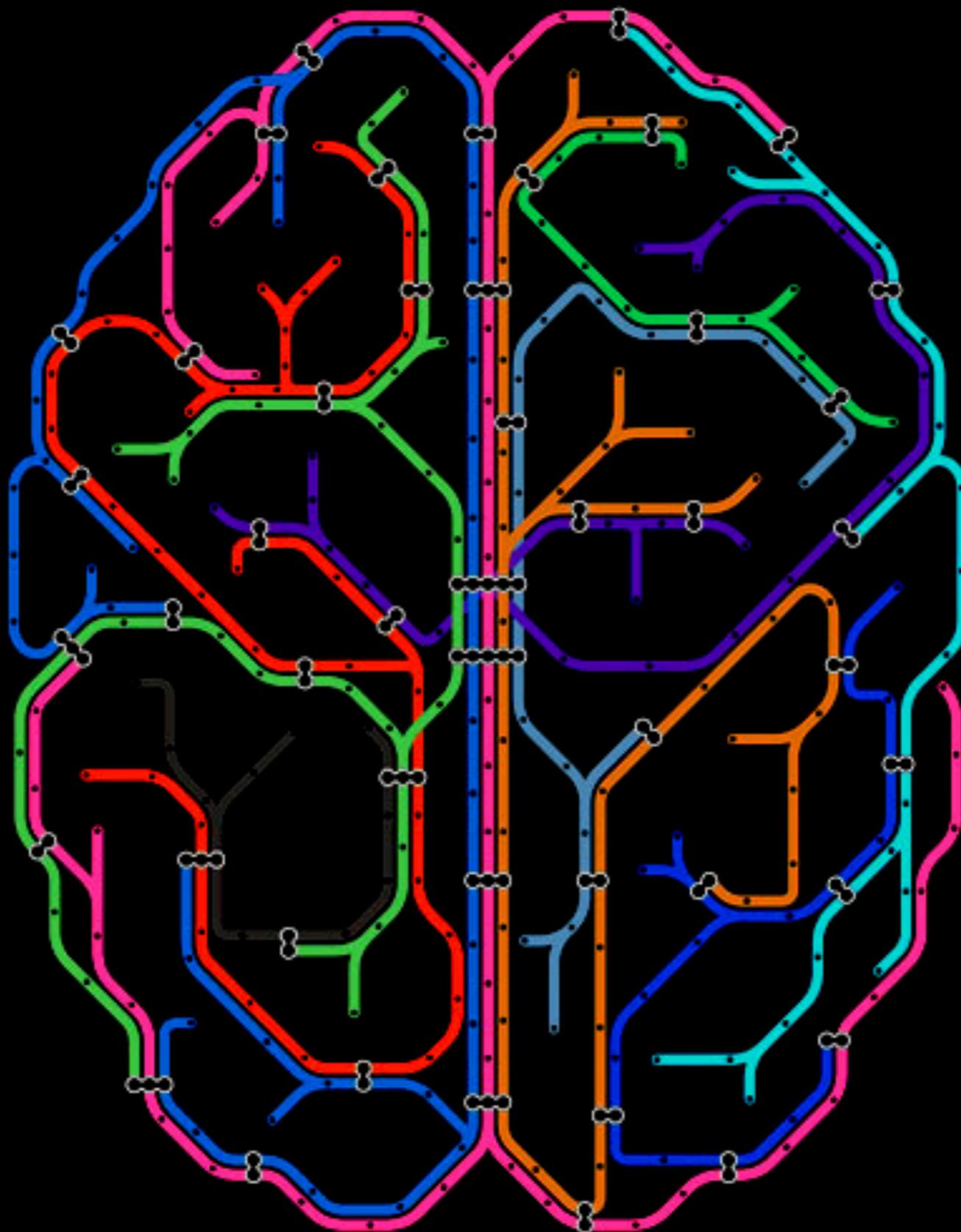


## BEYOND DESCRIPTION 2: PREDICTION OF OUTCOMES



## BEYOND DESCRIPTION 3: PREDICTION OF SUSCEPTIBILITY





## SUMMARY

RISE OF CONNECTOMIC STUDIES OF  
HEALTHY AND DISEASED BRAINS

ASSESSMENT OF SPECIFIC CONNECTIONS  
VS  
LARGE-SCALE NETWORK TOPOLOGY

NEW INSIGHTS INTO SYSTEM LEVEL ORGANIZATION  
OF THE BRAIN

NETWORK NEUROSCIENCE PROMISES TO BRIDGE  
STRUCTURE AND FUNCTION

POTENTIAL BENEFITS FOR 'INDIVIDUALIZED FINGERPRINTING'.  
OUTCOME PREDICTION, DEFINITION OF DISEASE PATHWAYS

## MICA

Reinder Vos De Wael

Sara Lariviere

Brian Hyung

Tabea Haas Heger

Seok-Jun Hong

## NOEL

Neda Bernasconi

Andrea Bernasconi

Seok-Jun Hong

Fatemeh Fadaie

Ravnoor Gill

Benoit Caldairou

Sophie Adler

Mauricio Giradi-Schappo

## ALFRED ANWANDER

