The background of the image is a dark, solid black. Overlaid on this black background are numerous thin, glowing lines of various colors. These lines are primarily shades of blue, purple, green, and red, creating a sense of motion and depth. They are concentrated in several distinct clusters: one large cluster in the upper left, another in the upper right, and several smaller groups in the lower half of the frame. The lines appear to be slightly curved and intersecting, suggesting a complex, three-dimensional space.

WELCOME

WELCOME + GENERAL ORGANIZATION

EVERY FRIDAY 9.30-12.30

NEURO – BELL ROOM

boris.bernhardt@mcgill.ca

bratislav.misic@mcgill.ca

OVERALL OBJECTIVES

Read and evaluate research papers

Learn about neuroimaging/connectomics – brief introduction from BB after

Learn about different analytical techniques – brief intro from BM after

Discuss the work in class with your peers

Design your study and write a mock grant proposal

REQUIREMENTS

Write 1/2 page on positive/negative impressions and suggestions for future improvements for each paper you have read

Email this page to us BEFORE the class

Come to the class

Be able to verbally summarize paper, understand the imaging methodology, and highlight good and bad aspects of the research

Discuss the paper with your peers

End of class: Write a mock grant proposal

MOCK PROPOSAL

We will send you guidelines after the class:

- 1) Start thinking about it now
- 2) Discuss your ideas with your colleagues and with us
- 3) Prepare your proposal (about 10 pages)
- 4) Submit us your full version on Monday, October 30
- 5) We will give feedback by Friday, November 3
- 6) Deadline for final version is Monday, November 20
- 7) Presentation and discussion of the work on the last day of class
(8 minutes PPT+ 4 min Q&A)

MOCK PROPOSAL

GRADING

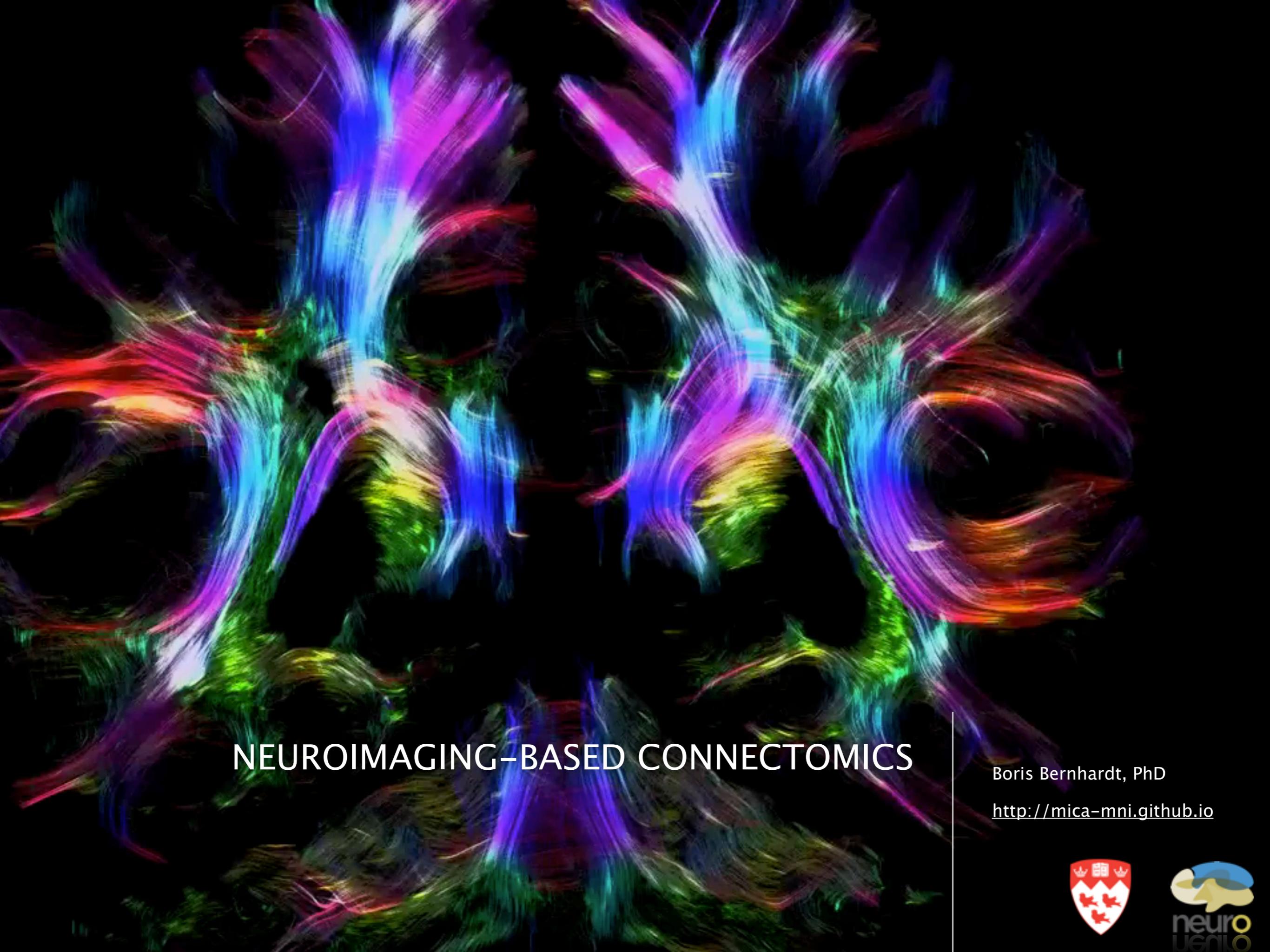
COME TO THE CLASSES (EMAIL US IF YOU CANNOT MAKE IT)

SEND SUMMARY ASSIGNMENTS ON TIME

READ PAPERS & ENGAGE IN DISCUSSIONS

WRITE STRONG MOCK PROPOSAL

GIVE ENGAGING PRESENTATION



NEUROIMAGING-BASED CONNECTOMICS

Boris Bernhardt, PhD

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



WHY STUDY CONNECTIVITY?

WHY STUDY CONNECTIVITY?

The cerebral cortex is composed of
100.000.000.000
neurons.

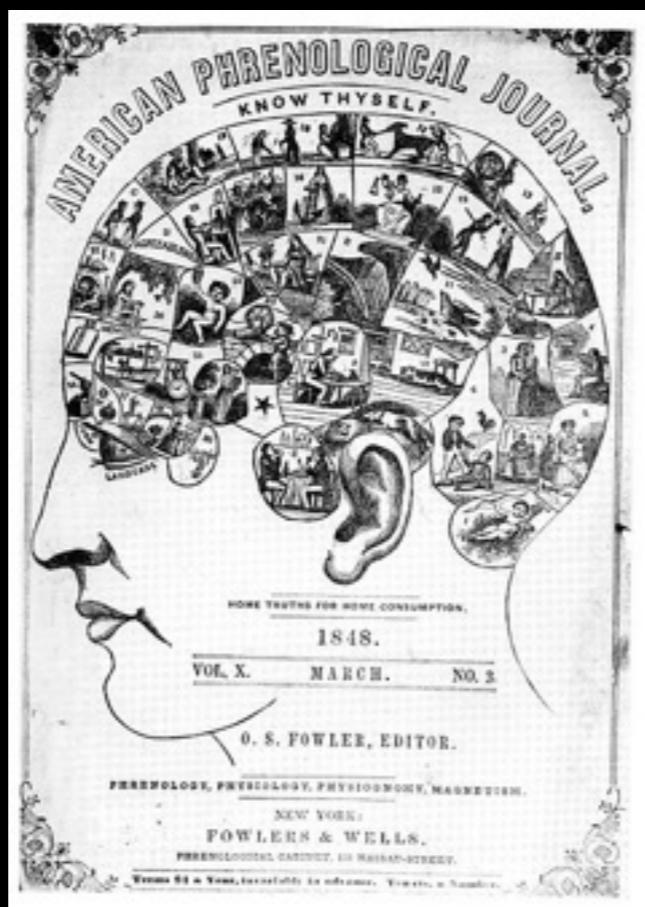
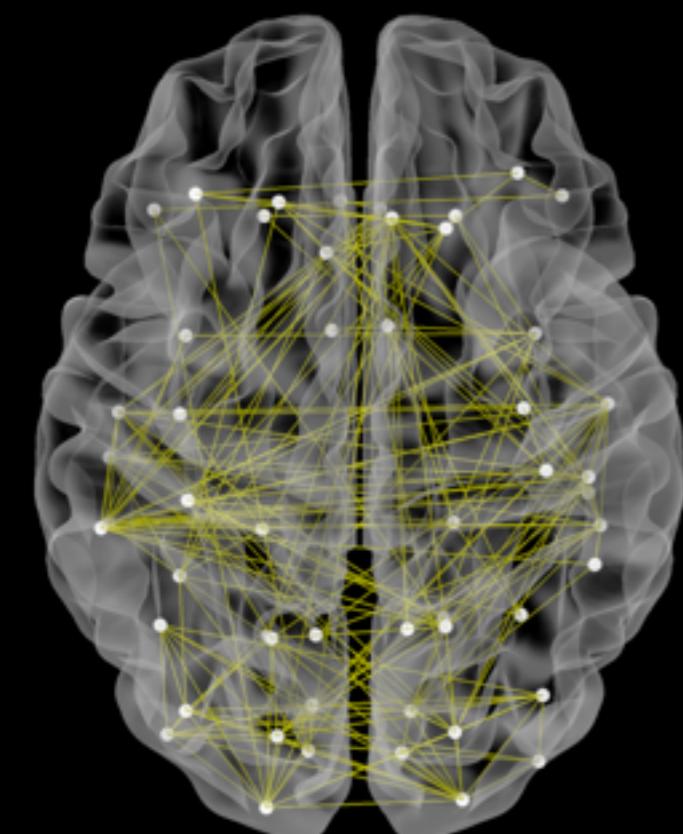
These neurons are interconnected by
100.000.000.000.000
synapses

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?

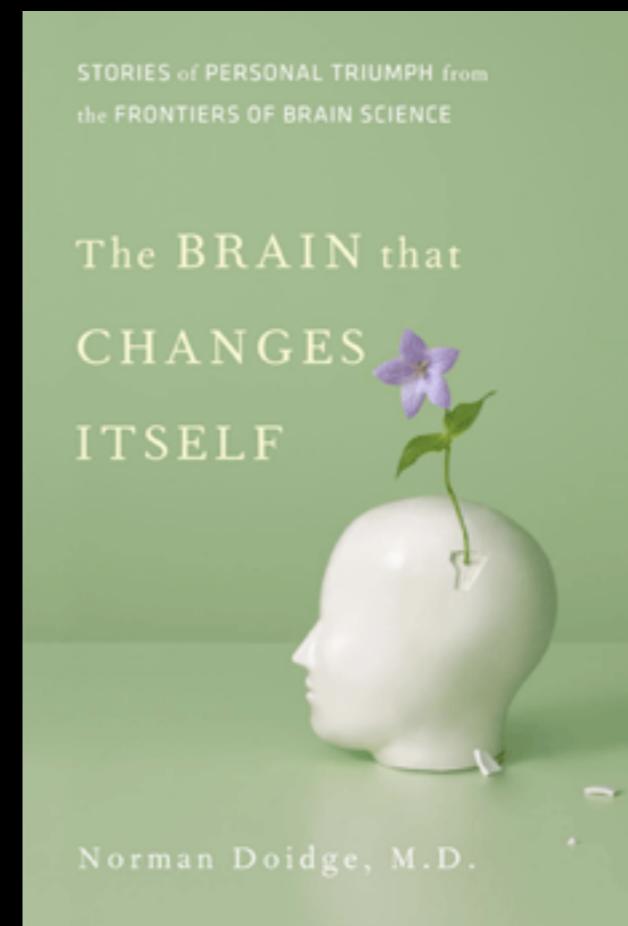


BRAIN ORGANIZATION

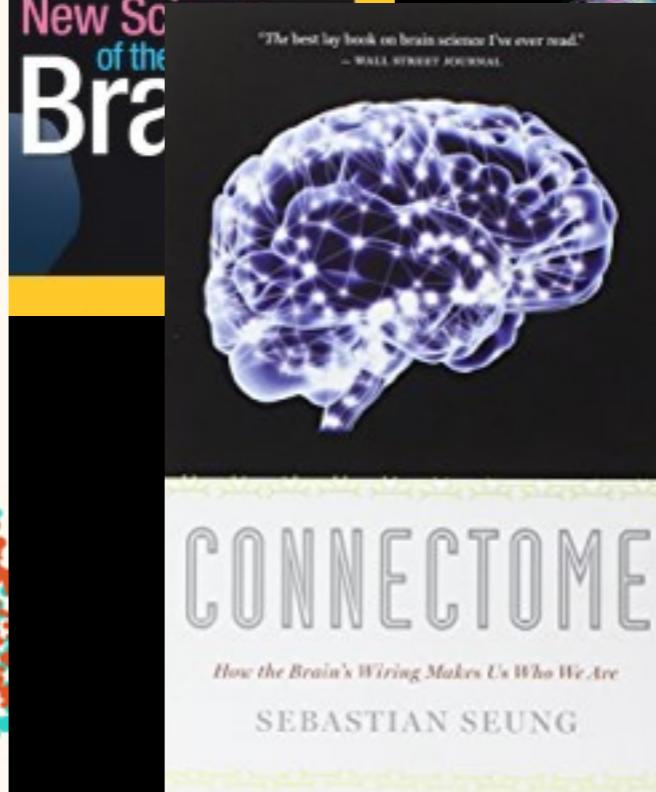
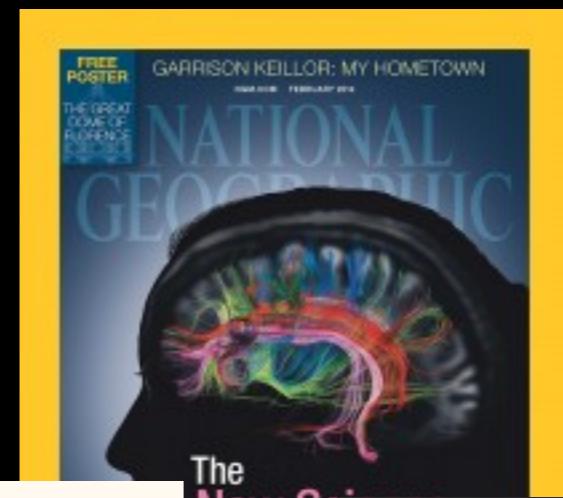
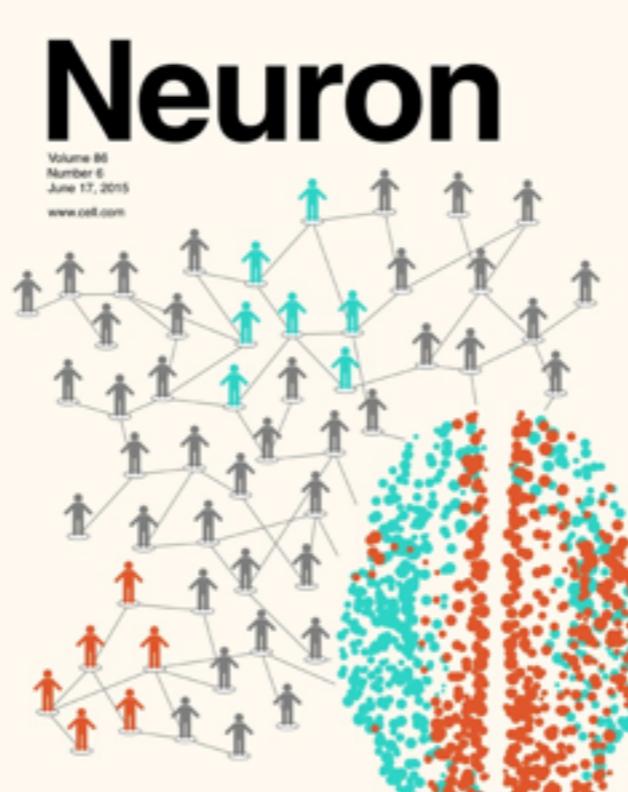
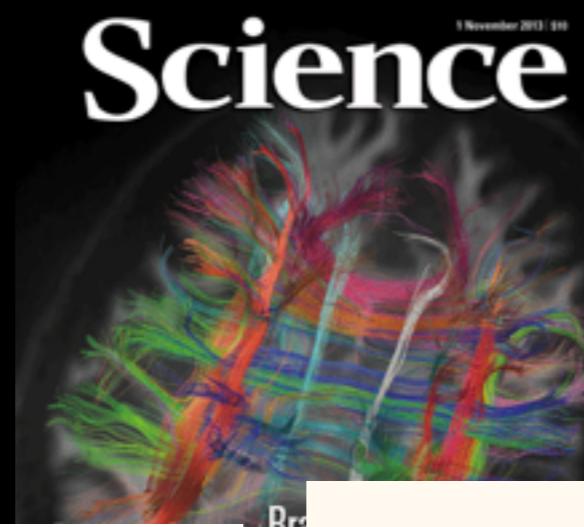
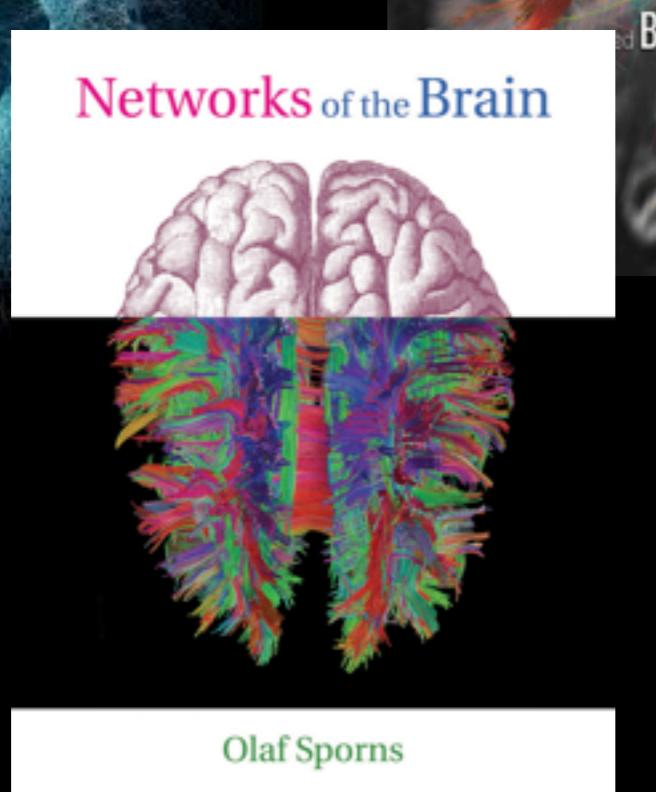
INDIVIDUAL DIFFERENCES

PLASTICITY

BRAIN DISORDERS



WHY STUDY CONNECTIVITY?



HOW TO MEASURE BRAIN CONNECTIVITY?

(ANIMAL) CONNECTIVITY

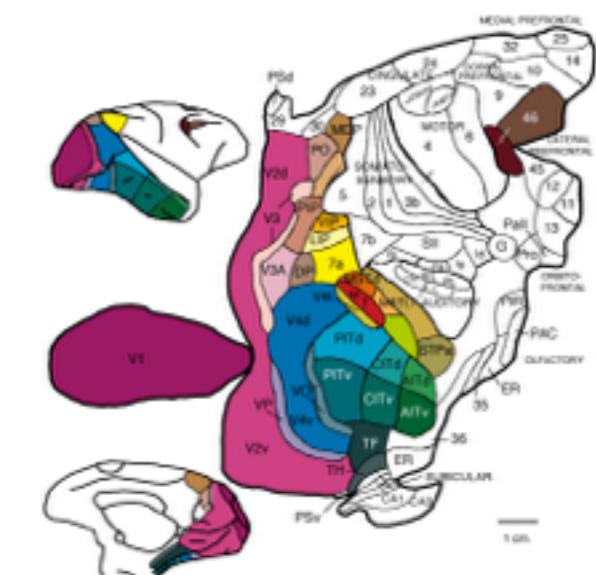
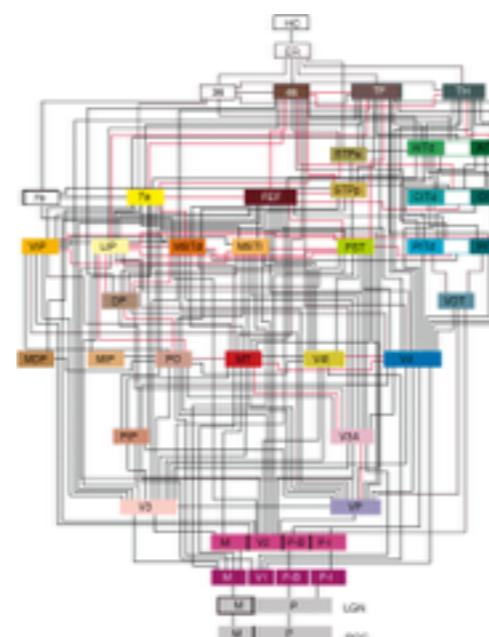
ANATOMICAL CONNECTIONS:
THE WIRING BETWEEN REGIONS

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

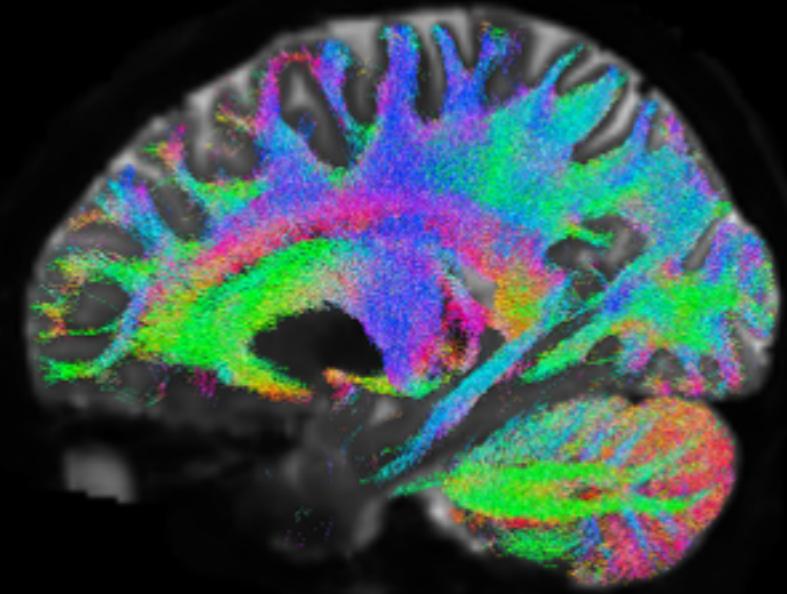
+
PROBES
WM CONNECTIVITY

DIFFUSION PARAMETER
ANALYSIS CAN BE PERFORMED AS WELL

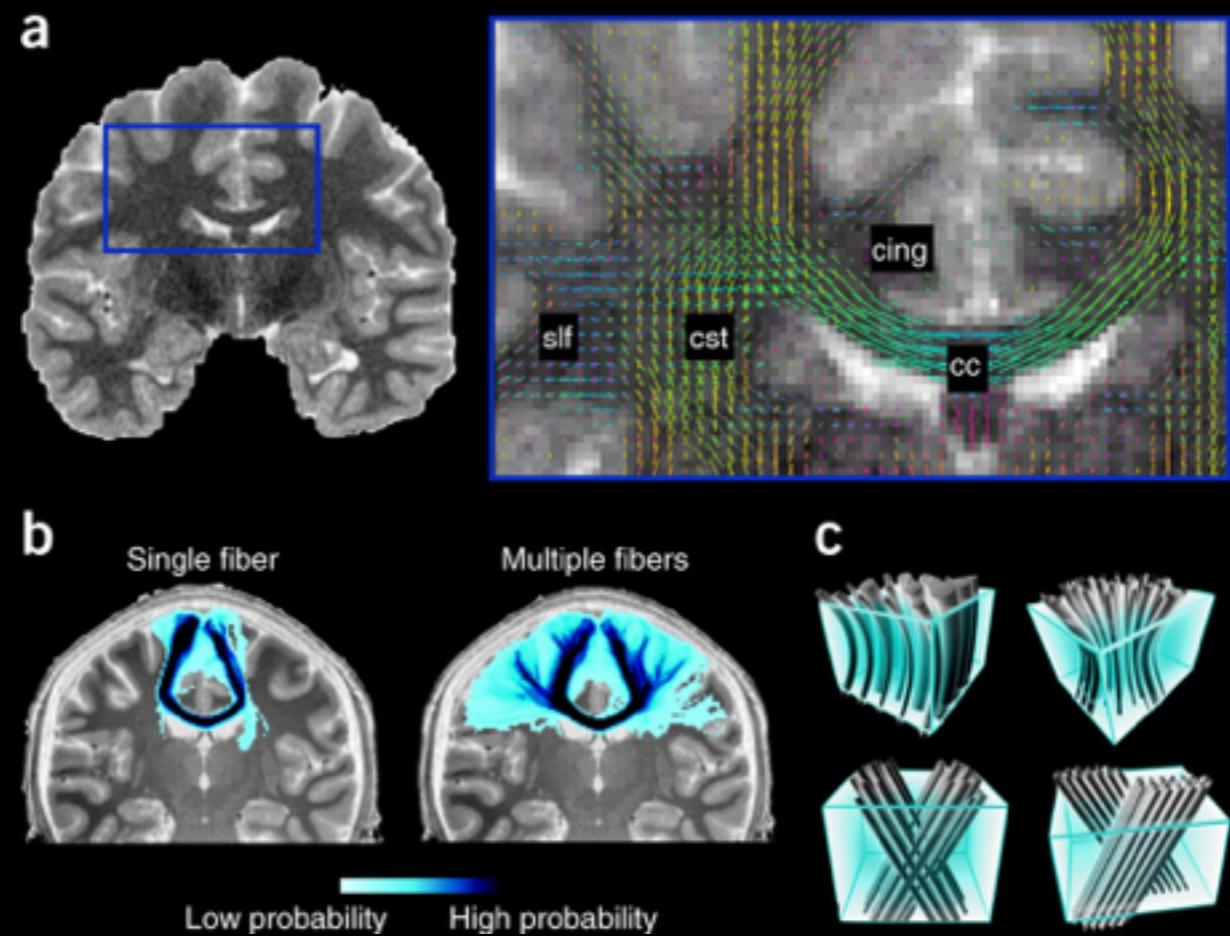
-
CHALLENGES IN REGIONS OF
FIBRE CROSSING AND UNCERTAINTY

DISTANCE BIAS

VALIDITY IN PATHOLOGICAL
REGION UNCLEAR



SINGLE SUBJECT (HCP)



RESTING-STATE fMRI CONNECTIVITY

IDEA:
CORRELATE SPONTANEOUS BRAIN
ACTIVITY

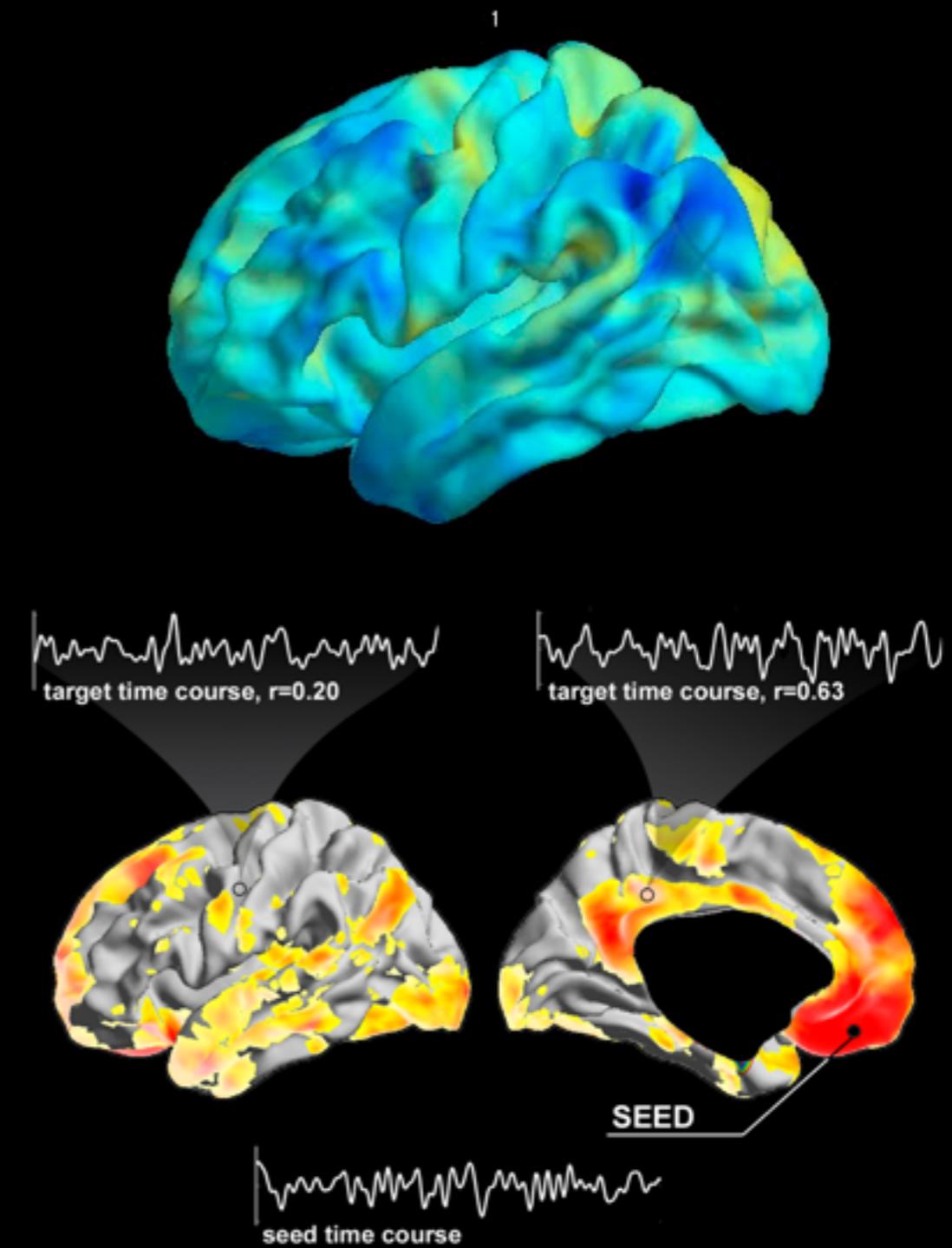
+
COST-EFFECTIVE, REPRODUCIBLE

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

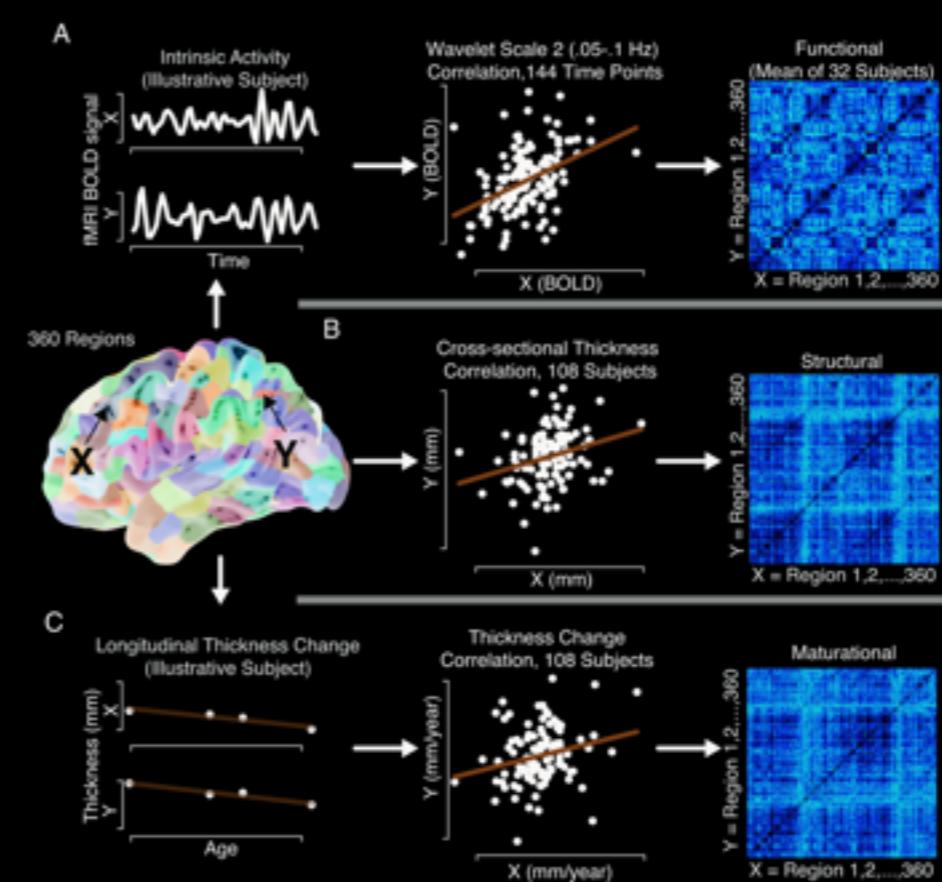
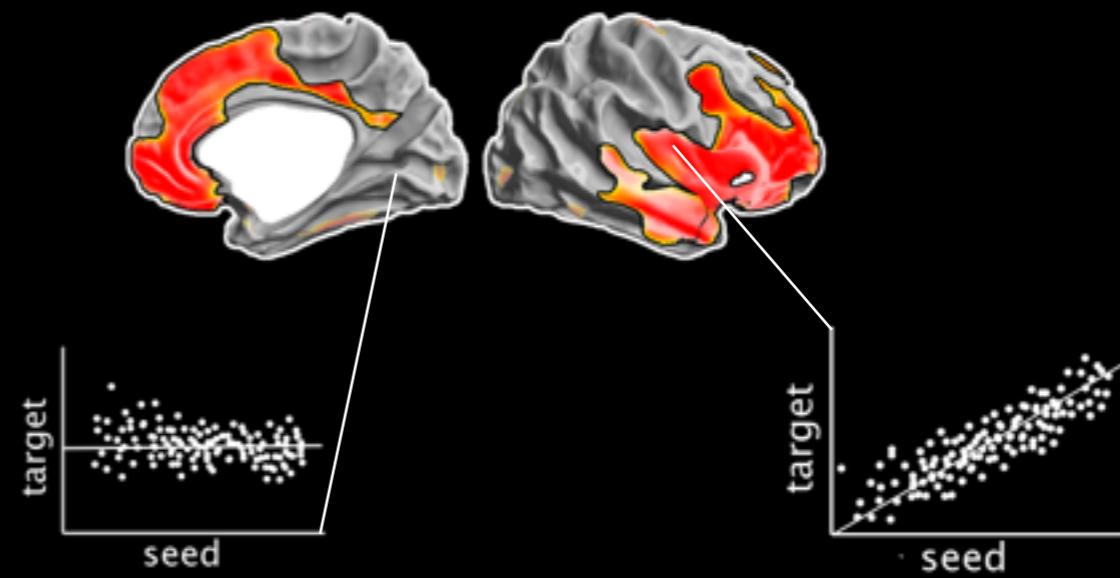
SIMPLE PREPROCESSING AND MODELLING

-

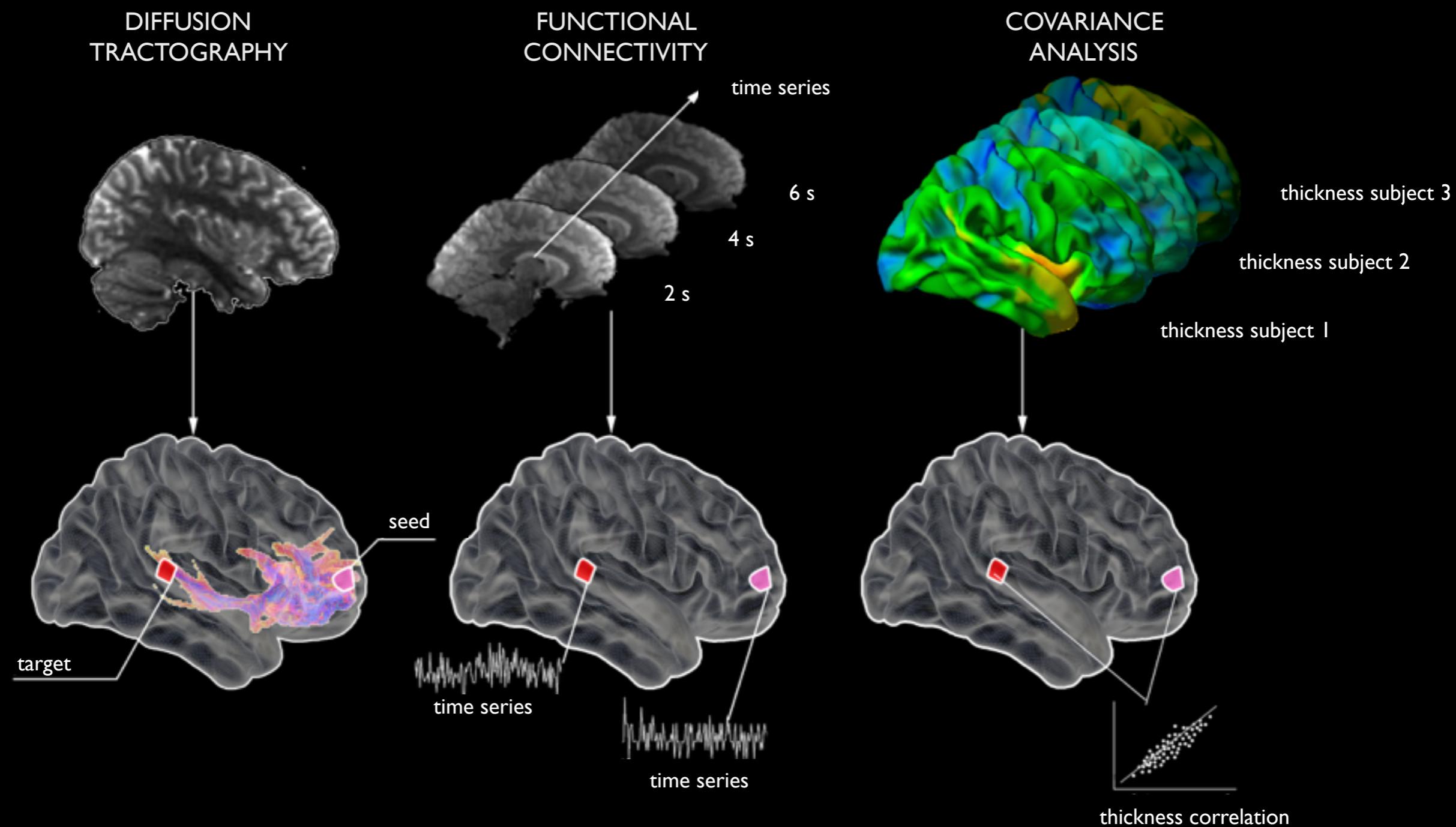
ONLY GROUP-WISE

RELATES RATHER TO PROCESSES
THAN TO STATES

NO DIRECT WM CONNECTIVITY
MEASUREMENT



INTER-REGIONAL CONNECTIVITY ANALYSIS

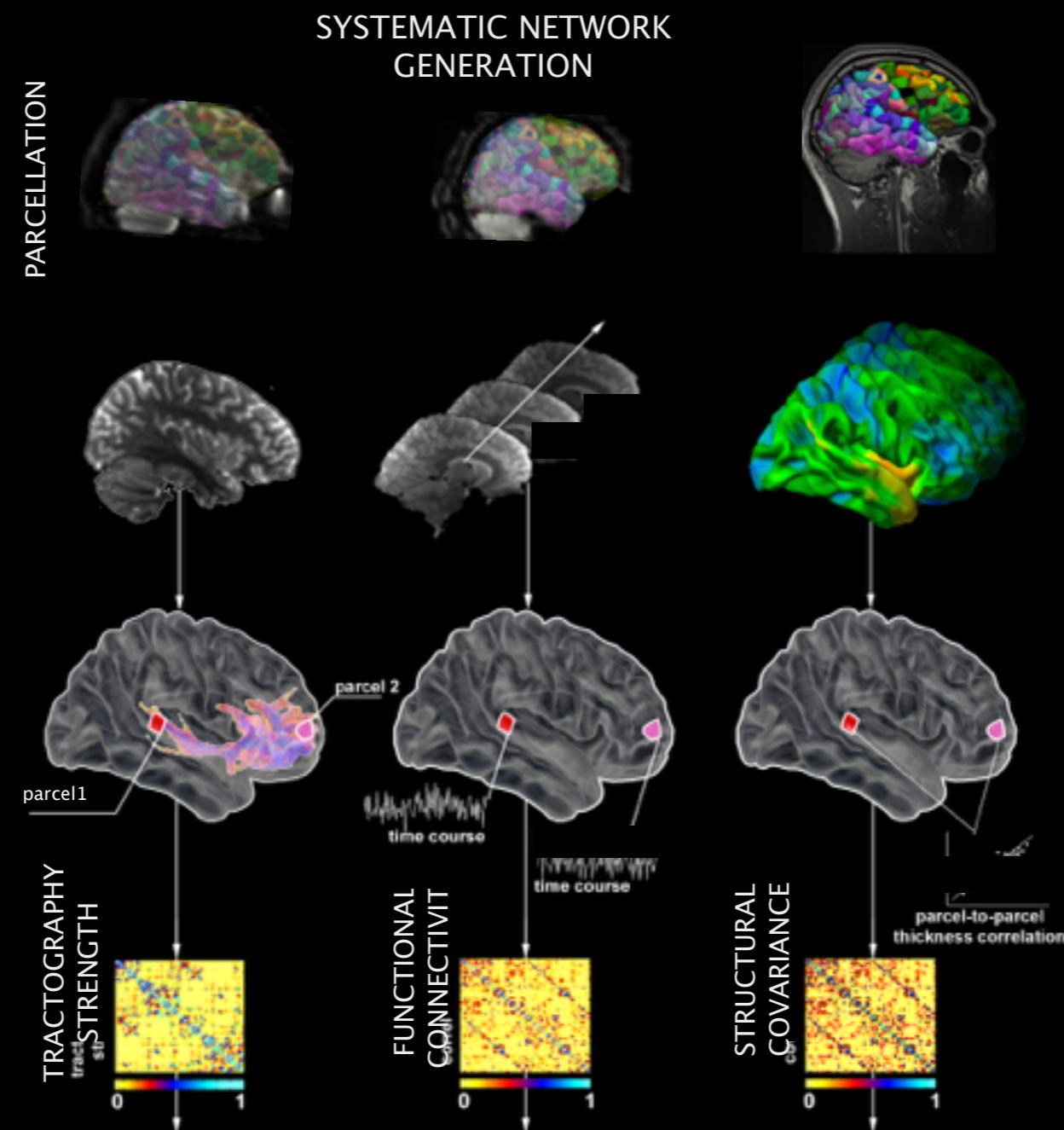


Mori et al. (1999) Ann Neu
Behrens et al. (2007) NIMG

Friston (1994) HBM
Smith (2012) NIMG

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

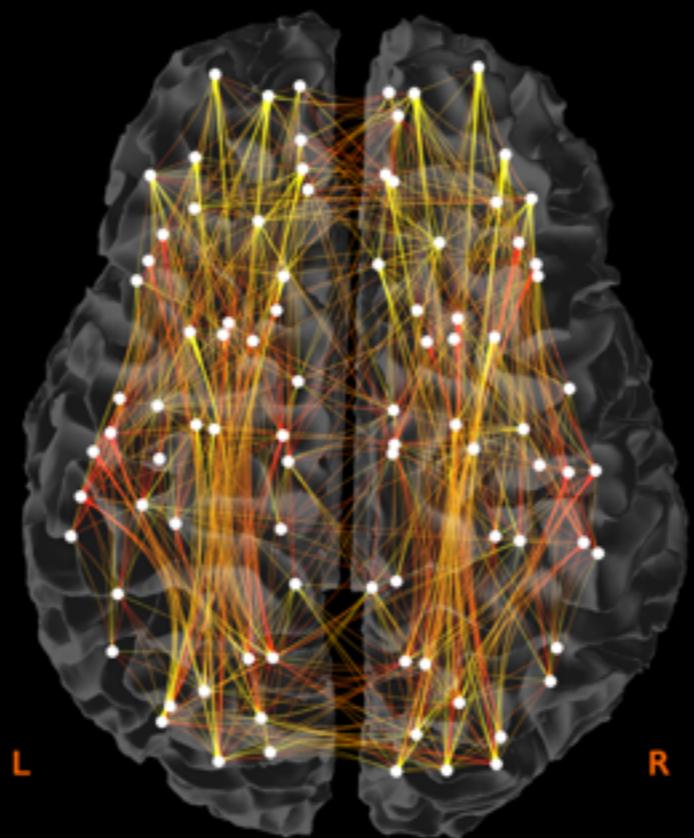
CONNECTOME ANALYSIS



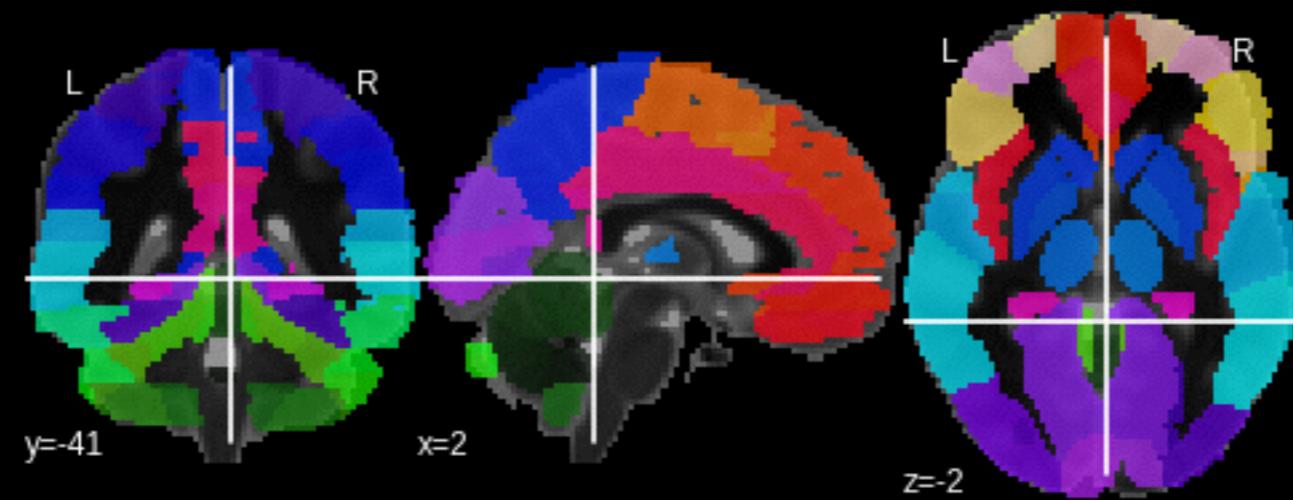
MATRICES AND GRAPHS



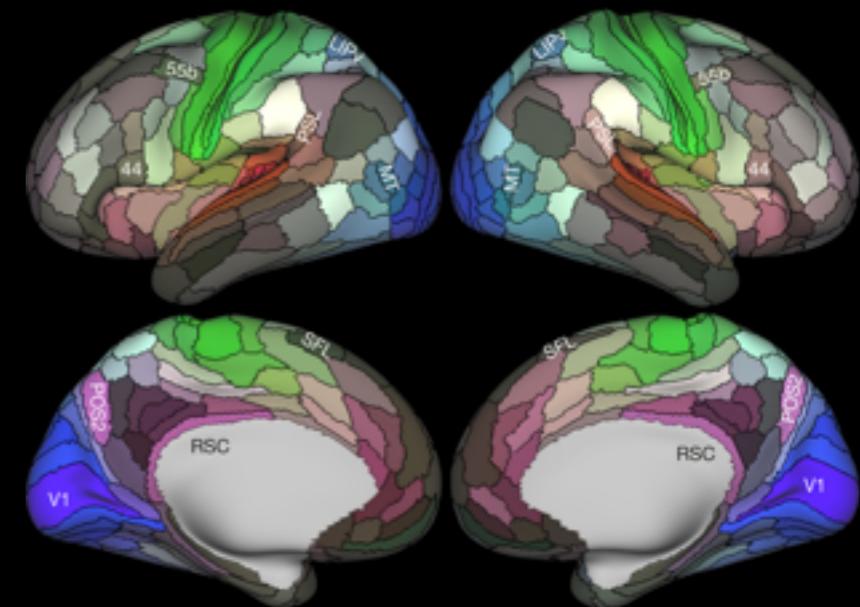
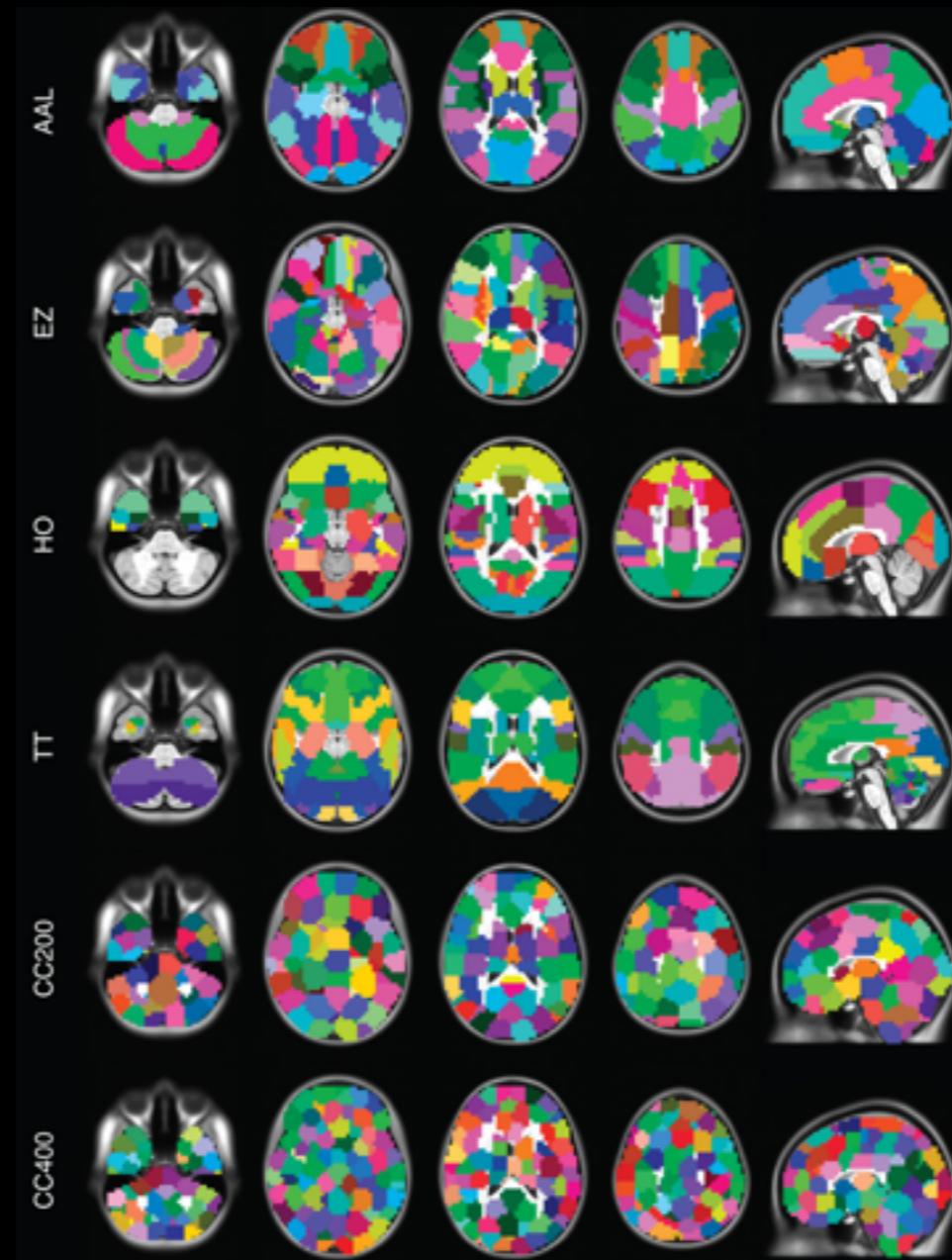
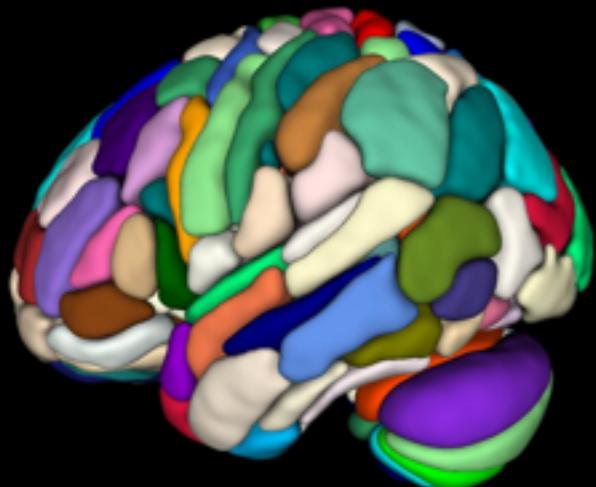
CONTROLS



DEFINITION OF REGION



DEFINITION OF REGION



INTERIM SUMMARY

NEUROIMAGING TECHNIQUES MAP
FUNCTIONAL AND STRUCTURAL CONNECTIONS

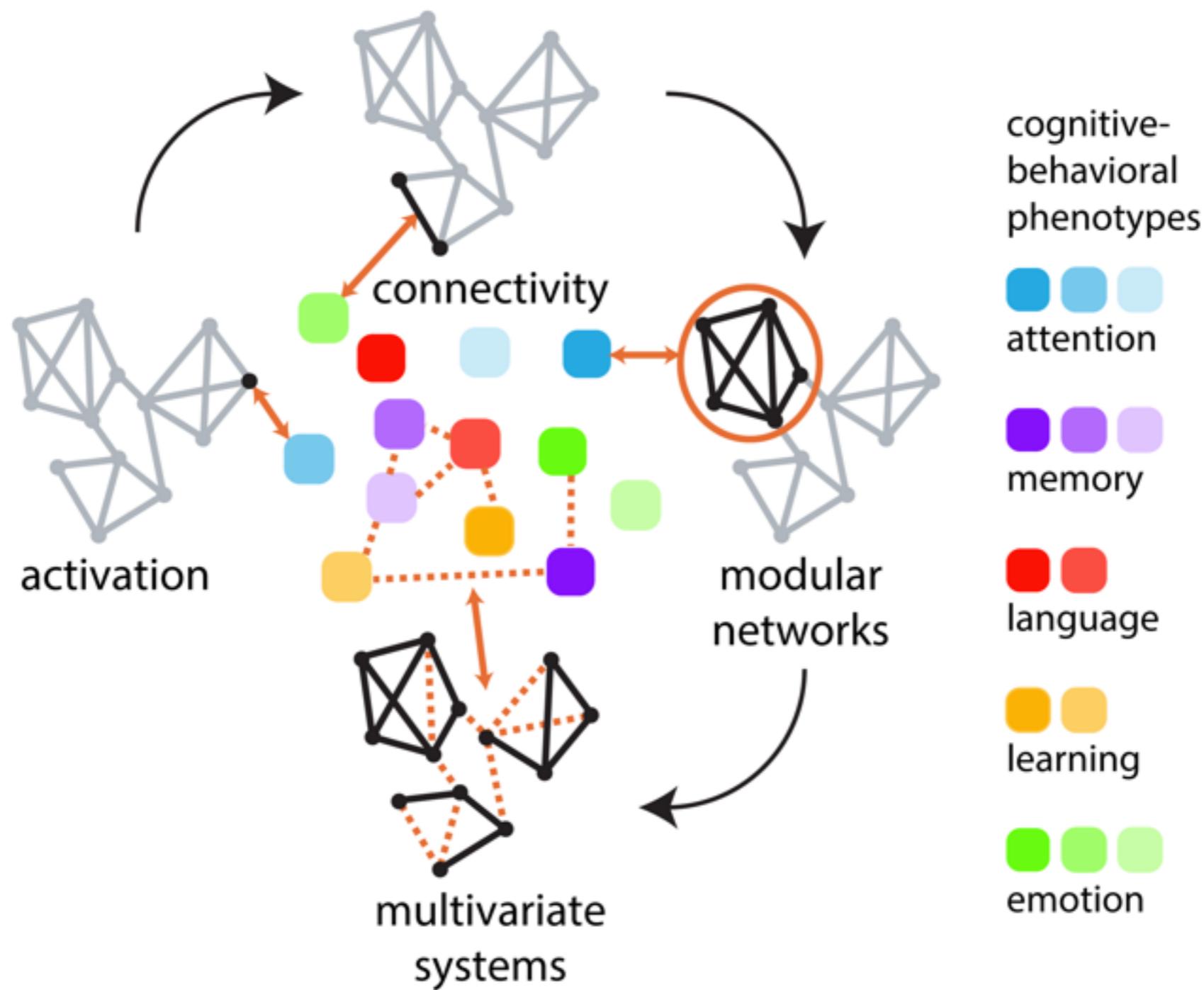
COMPLEMENTARY TECHNIQUES:
DIFFUSION MRI TRACTOGRAPHY, RESTING-STATE FMRI CORRELATIONS, STRUCTURAL COVARIANCE

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

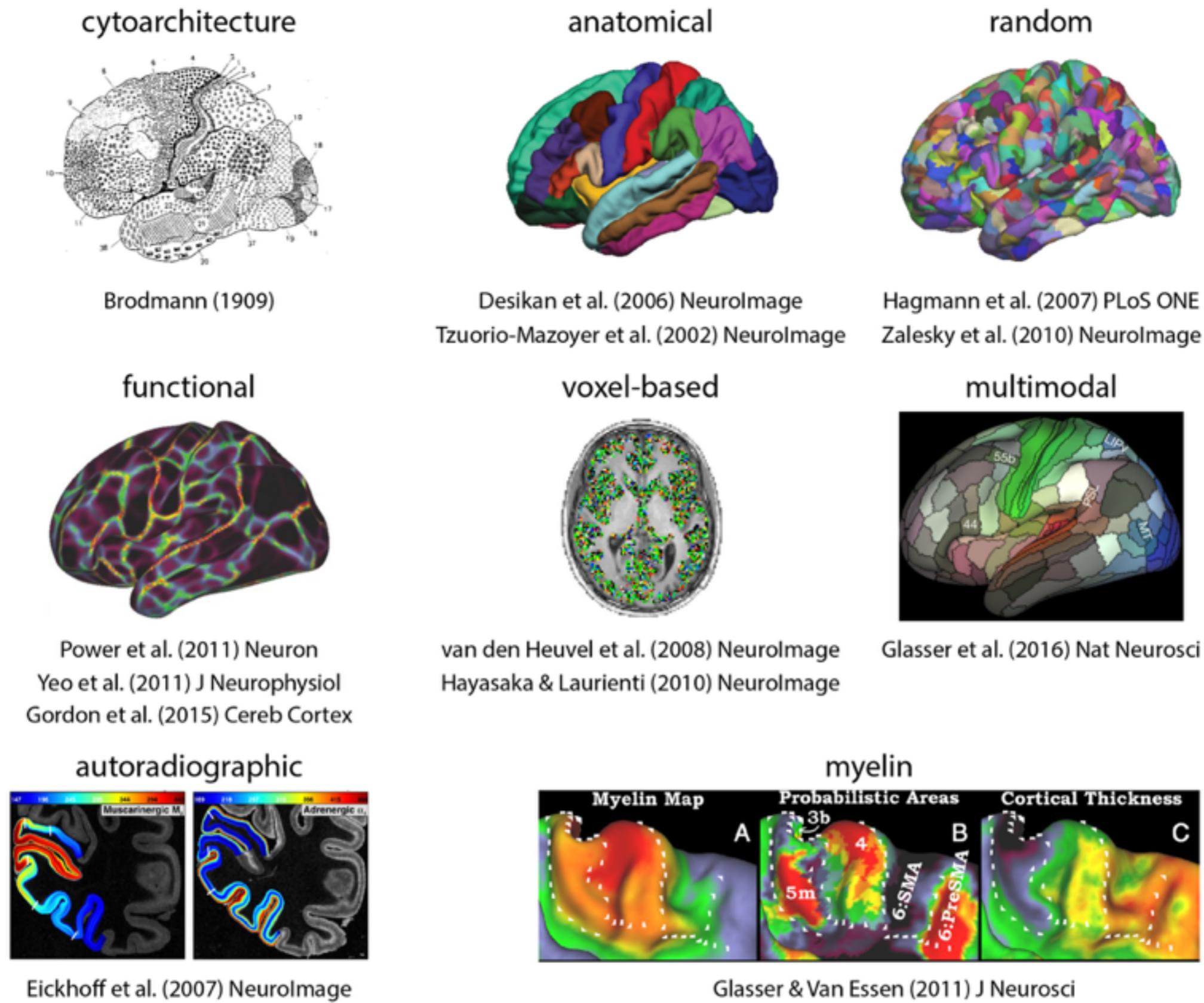
INFLUENCE OF PARCELLATION ON FINDINGS:
AAL78, CRADDOCK200, GLASSER360, ...

NEUR 602: OVERVIEW

Towards multivariate analysis

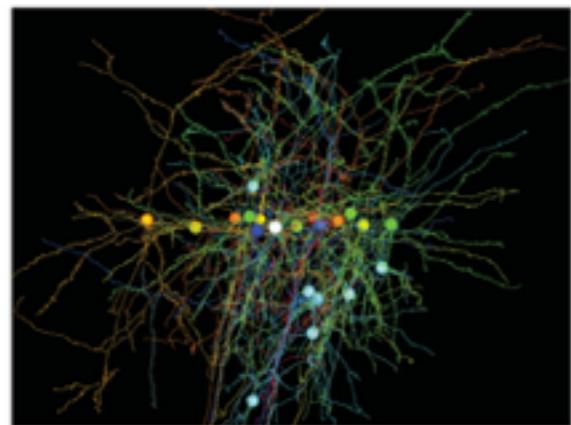


Defining brain areas



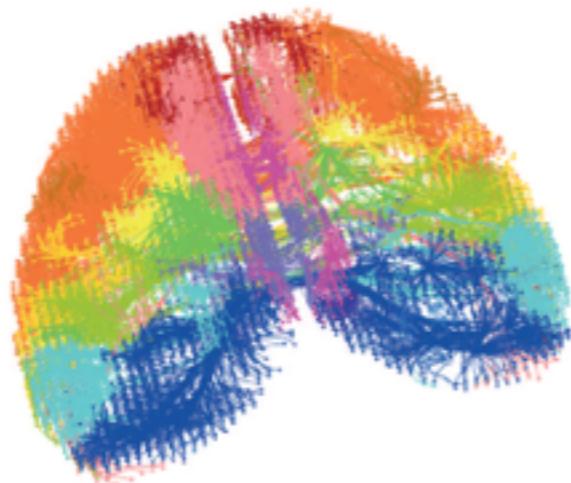
Defining activity and interactions

electron microscopy



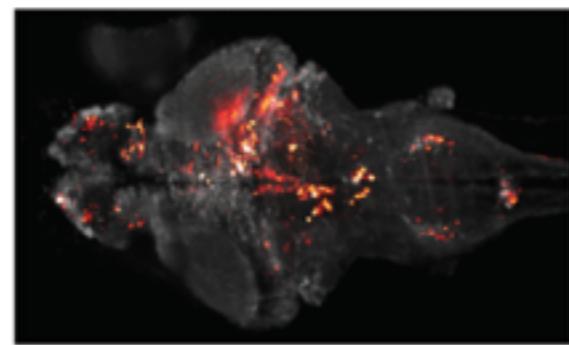
Bock et al. (2011) Nature

tract tracing



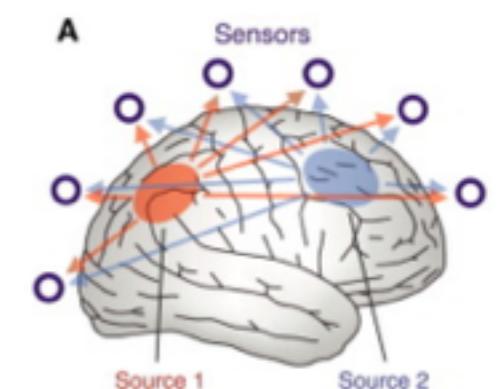
Oh et al. (2014) Nature

calcium imaging



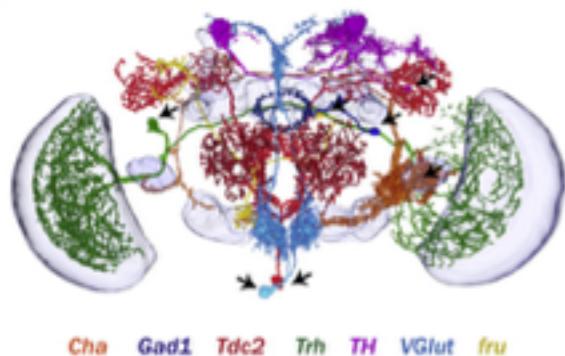
Ahrens et al. (2013) Nat Meth

M/EEG



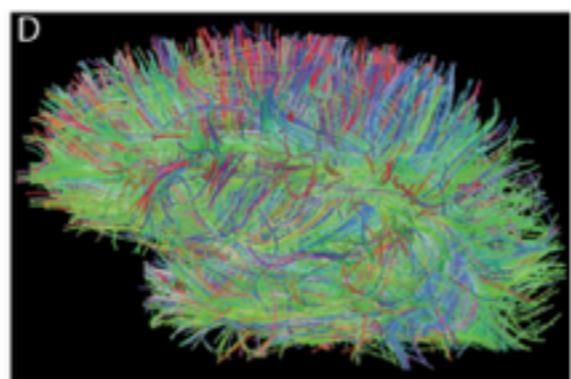
Engel et al. (2013) Neuron

genetic labeling



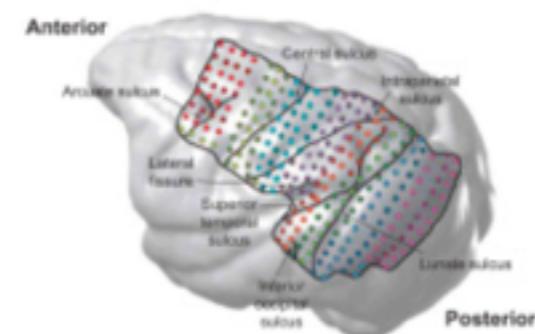
Chiang et al. (2011) Curr Biol

diffusion imaging



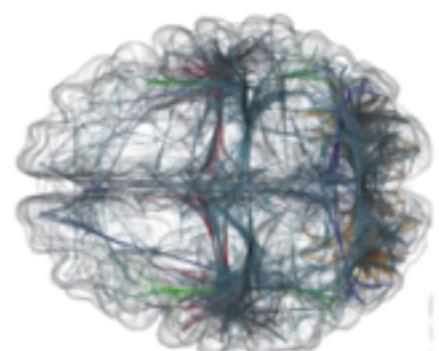
Hagmann et al. (2007) PLoS ONE

electrophysiology



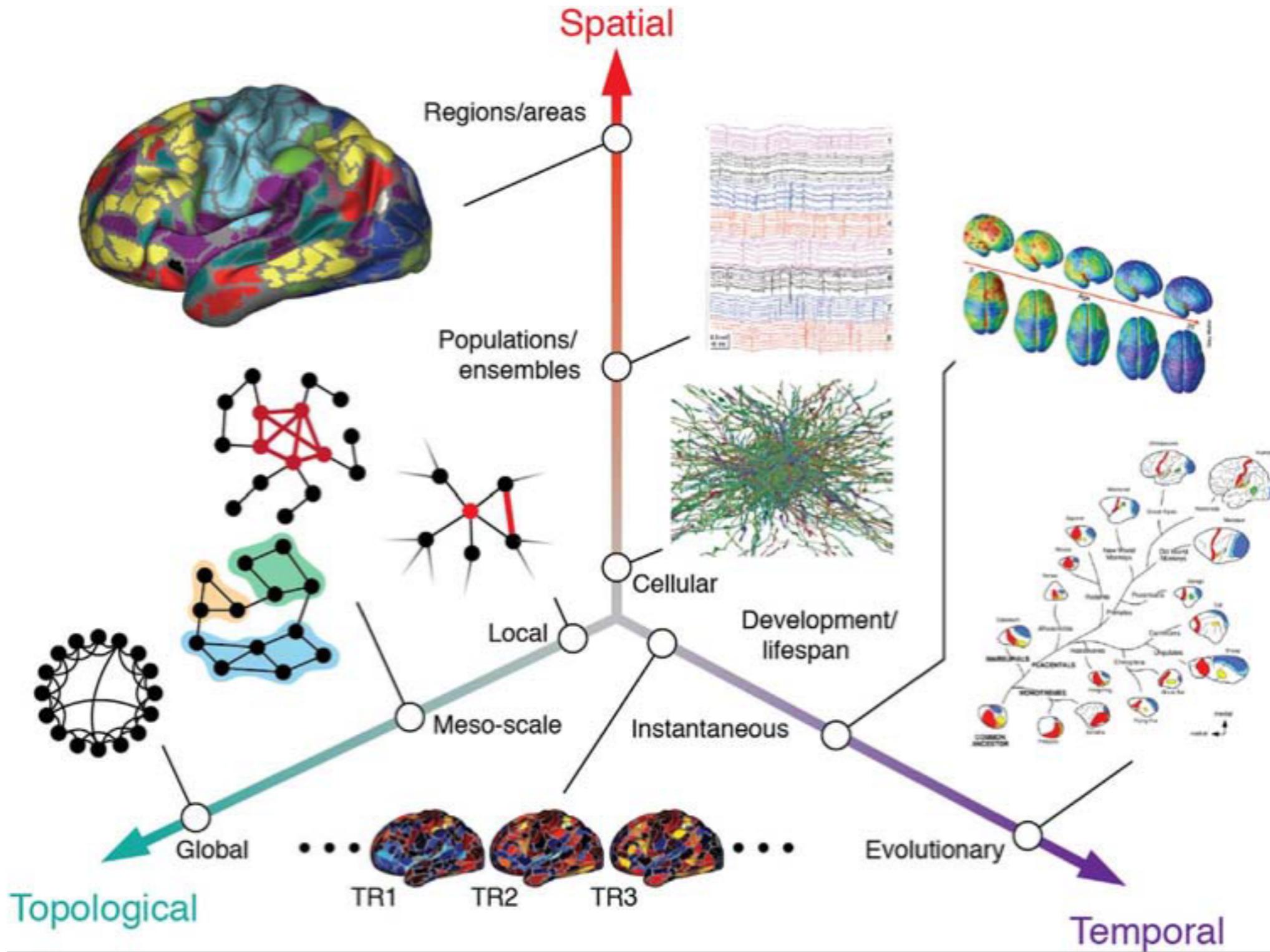
Bastos et al. (2015) Neuron

haemodynamics

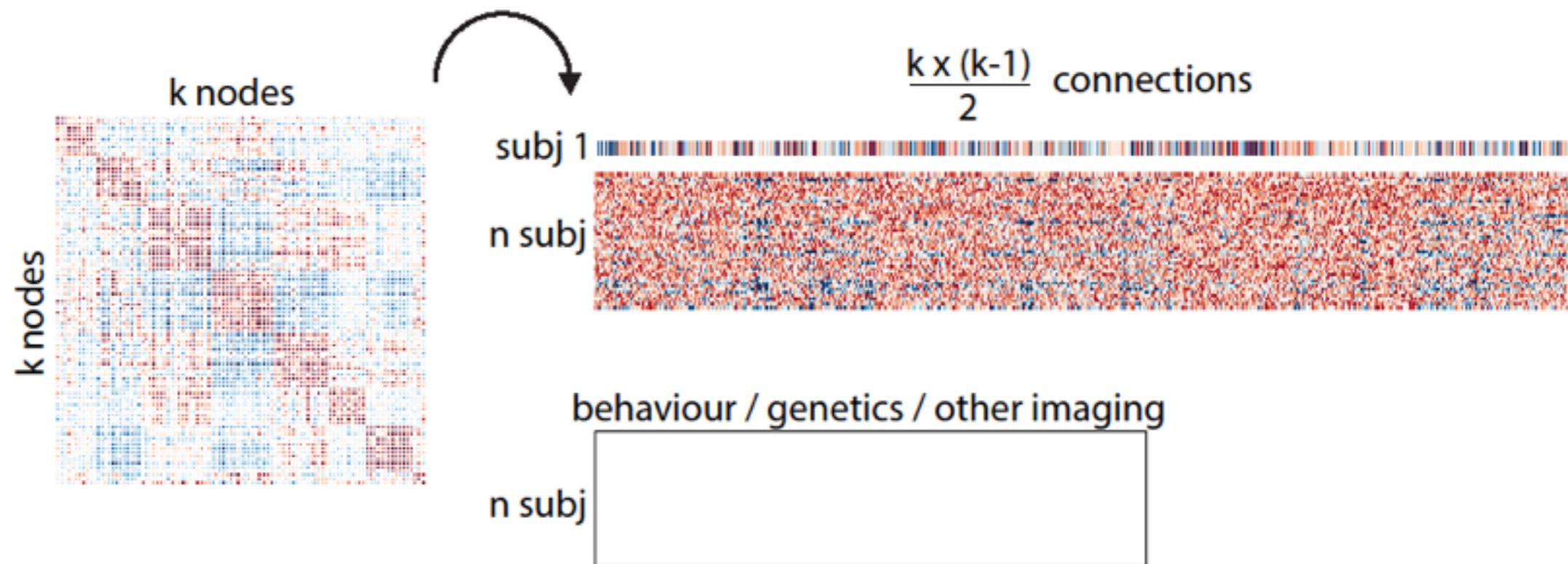


Boettger et al. (2014)
IEEE Trans Vis Comput

Multi-scale brain networks



Emerging questions

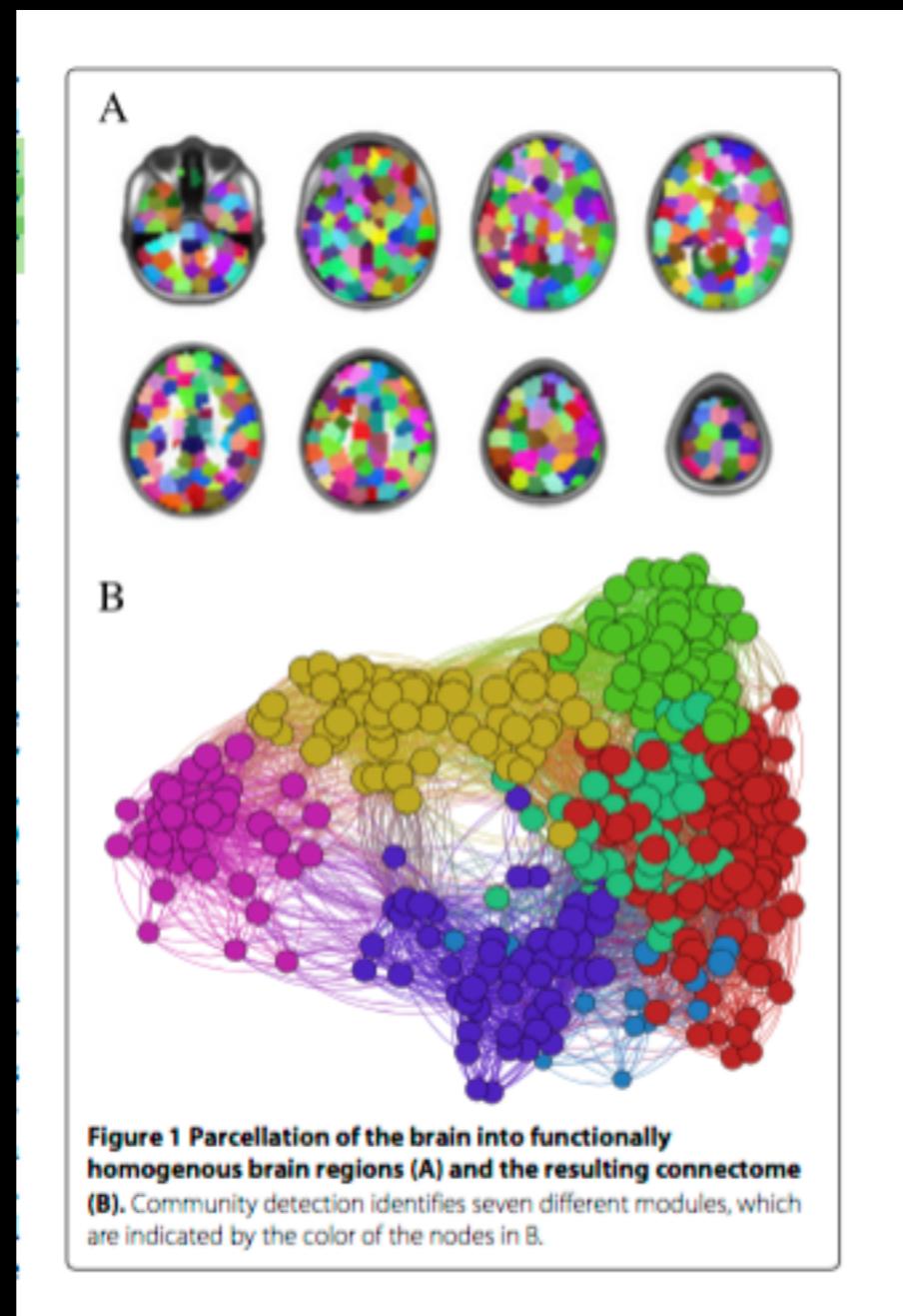


- How to deal with more variables than observations?
- How to relate multiple data sets / modalities with one another?
- How to operationalize the network property?
- How to infer large-scale mechanisms?

Methodological and philosophical questions

- Univariate vs Multivariate
- Multivariate methods: single-table (PCA, FA, ICA) vs multi-table (CCA, PLS)
- Exploratory (PCA, PLS) vs Confirmatory (SEM, DCM)
- Explanation (CCA) vs Prediction (LDA)
- Learning: Supervised vs Unsupervised
- Networks: Static (e.g. communities) vs Dynamic (e.g. multilayer, neural masses)
- Inference: Parametric vs Nonparametric

CRADDOCK



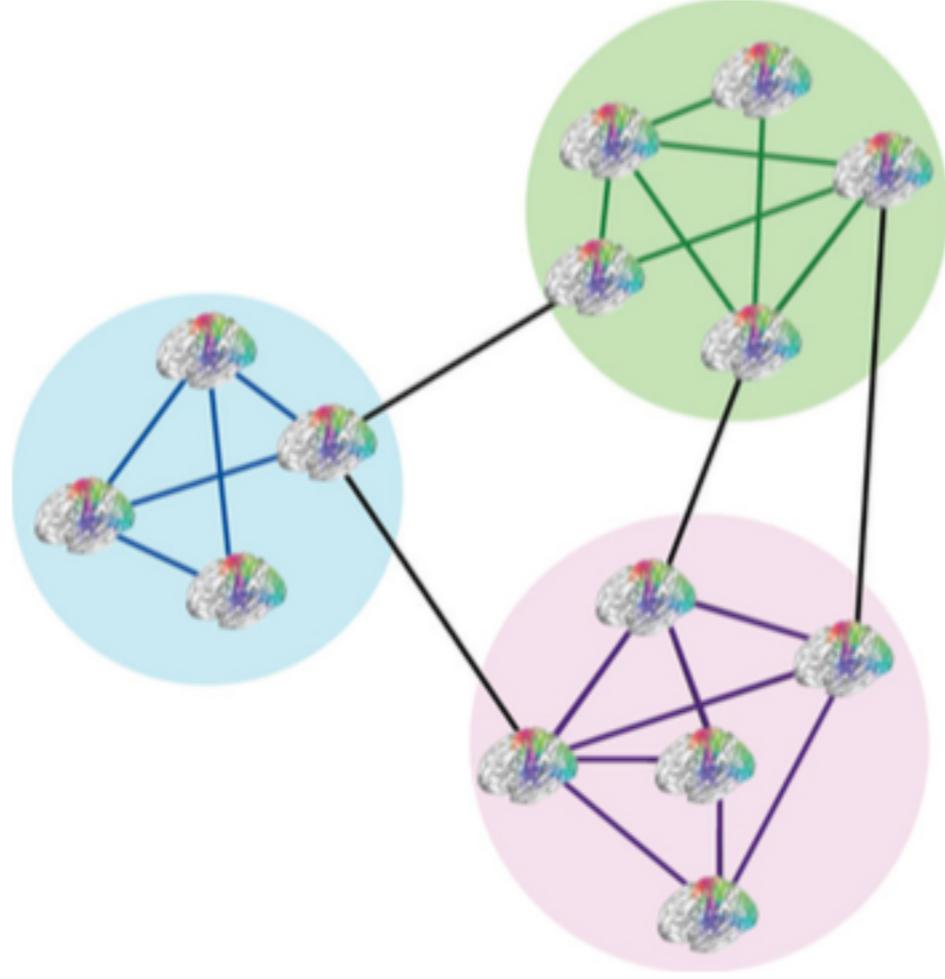


Figure 2 Identifying communities based on neurophenotypes. Brain glyphs provide succinct representations of whole brain functional connectivity [85].

JBABDI

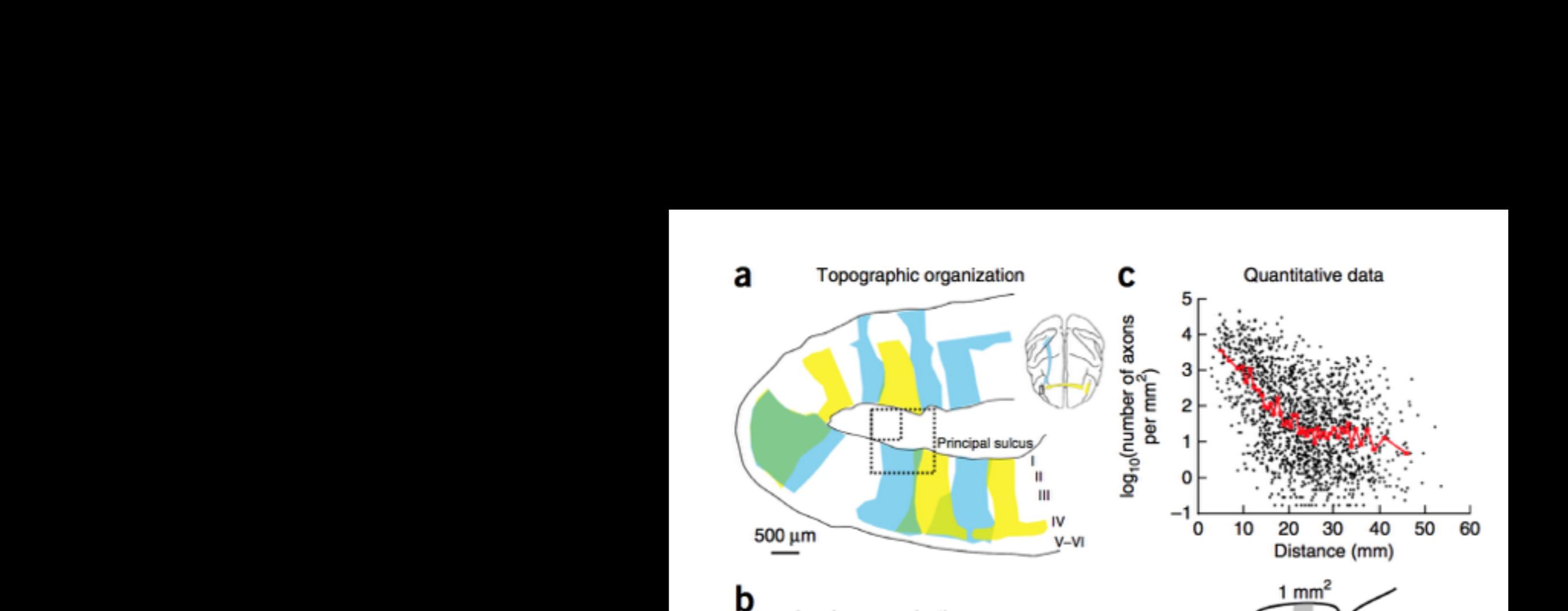


Figure 1 Examples of complex white-matter organization in monkey brains. **(a)** Topographic organization of afferent ipsilateral and contralateral connections to the principal sulcus in the macaque brain showing columnar interdigitation. Typical 1-mm and 0.5-mm isotropic voxels are shown as dashed boxes, indicating the resolution needed to reveal such macro-scale organization (modified with permission from ref. 9). **(b)** Laminar pattern of efferent connections from visual area V2. Cells connecting to V1 sit primarily in superficial and deep layers, whereas those connecting to V4 originate from layer 2/3. No labeled cells are found in layer 4 (modified with permission from ref. 115). **(c)** Top, estimate of the number of efferent ipsilateral association axons from 1 mm² of cortex as a function of the distance between source and target regions. Bottom, estimate of the number of axons from 1 mm² of cortex forming different categories of fiber tracts. Estimates are based on ref. 1 and data from <http://core-nets.org>.

Figure 2 Diffusion MRI and tractography. (a) A coronal section through a human brain (left) and estimated fiber orientations from diffusion MRI data (right). Voxel-wise fibers are color-coded according to their orientation (red = left-right, green = anterior-posterior, blue = ventral-dorsal). Major fiber bundles can be visualized on the orientation maps (cing = cingulum bundle, cc = corpus callosum, cst = cortico-spinal tract, slf = superior longitudinal fasciculus). Note the many voxels with multiple orientation estimates (crossing fibers) allowing the major bundles to cross each other. Tractography algorithms use this type of local orientation estimates to infer long trajectories of white matter bundles. Data are from the Human Connectome Project^{65,116}. (b) Probabilistic tractography of the corpus callosum pathways consists of constructing a spatial histogram that represents the likelihood that streamlines, through the diffusion field, pass through any voxel of the brain. The scenario of a single fiber orientation in a voxel is not always representative of the underlying anatomy. Crossings of fiber bundles are very common in white matter. The figure shows probability maps arising from the body of the corpus callosum when modeling multiple versus single fiber orientations. Ignoring fiber crossings gives rise to many false negatives (the lateral callosal projections are missing), but also false positives (paths merging with the internal capsule). (c) Ambiguities in modeling voxel-wise fiber orientations. Four different putative voxel-wise patterns of axonal organization can give rise to the same diffusion scatter pattern when averaged over a voxel. Top left, bending fibers; top right, 'kissing' fibers; bottom left, inter-digitated fibers; bottom right, 'touching' fibers. Simple crossing fiber modeling cannot distinguish these cases, which may lead to false positive and false negative connections. Figure reproduced with permission from ref. 117.

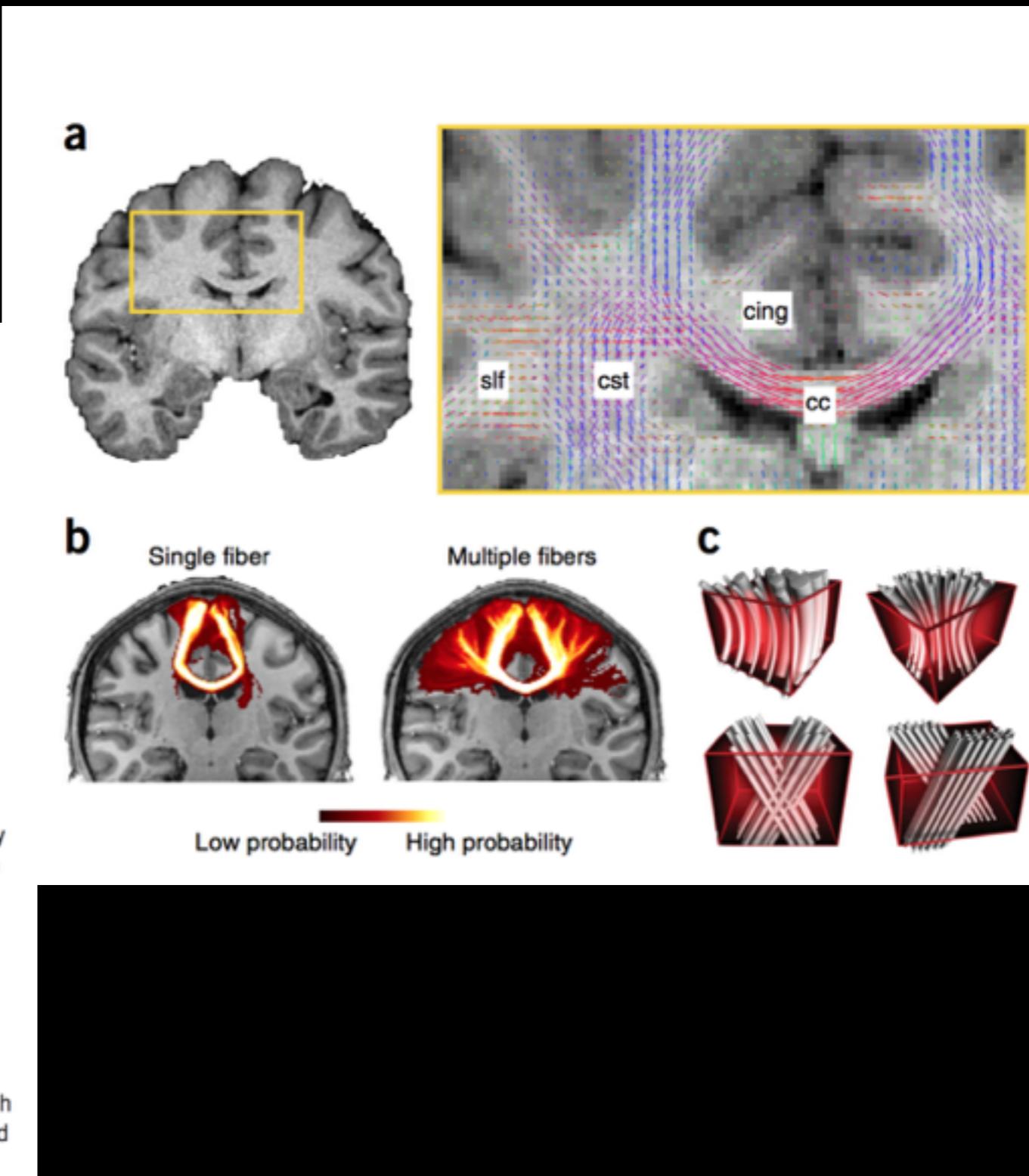


Figure 3 Textbook and estimated cortico-cerebellar connections using functional and diffusion MRI.

(a) Multi-synaptic efferent (blue) and afferent (red) cerebellar connections decussate at the level of the pons.
(b) Resting-state functional connectivity of motor cortical regions to cerebellum (foot, hand and face area as green, red and blue, respectively).
The somatotopic organization is evident, but notice that, except for the hand area, homolog seed areas in the right and left hemisphere may yield almost identical connectivity results. (c) Diffusion MRI tractography streamlines when seeding from the hand area of the primary motor cortex. Tractography reconstructs the correct paths, but fails to decussate at the pons as a result of the smoothness constraints used in tracking algorithms.

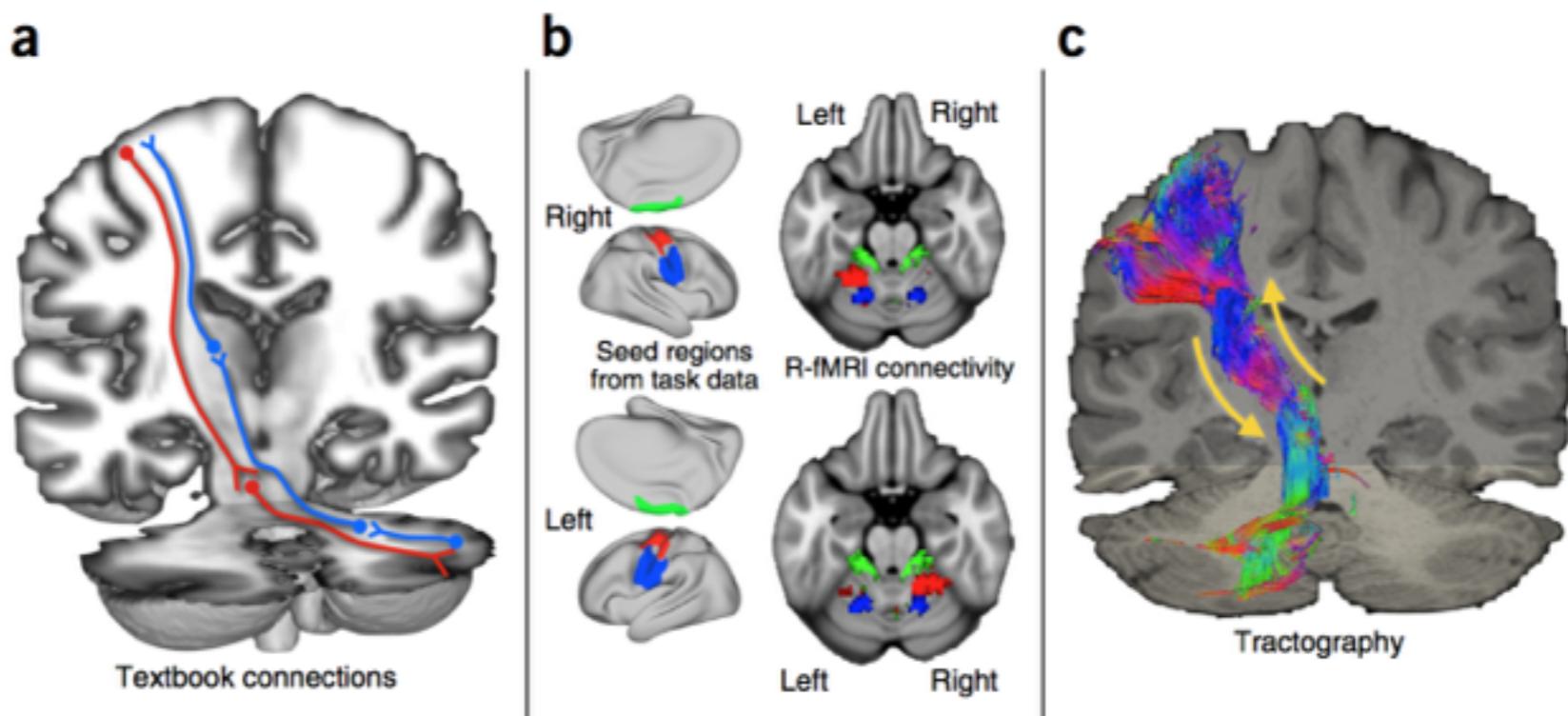
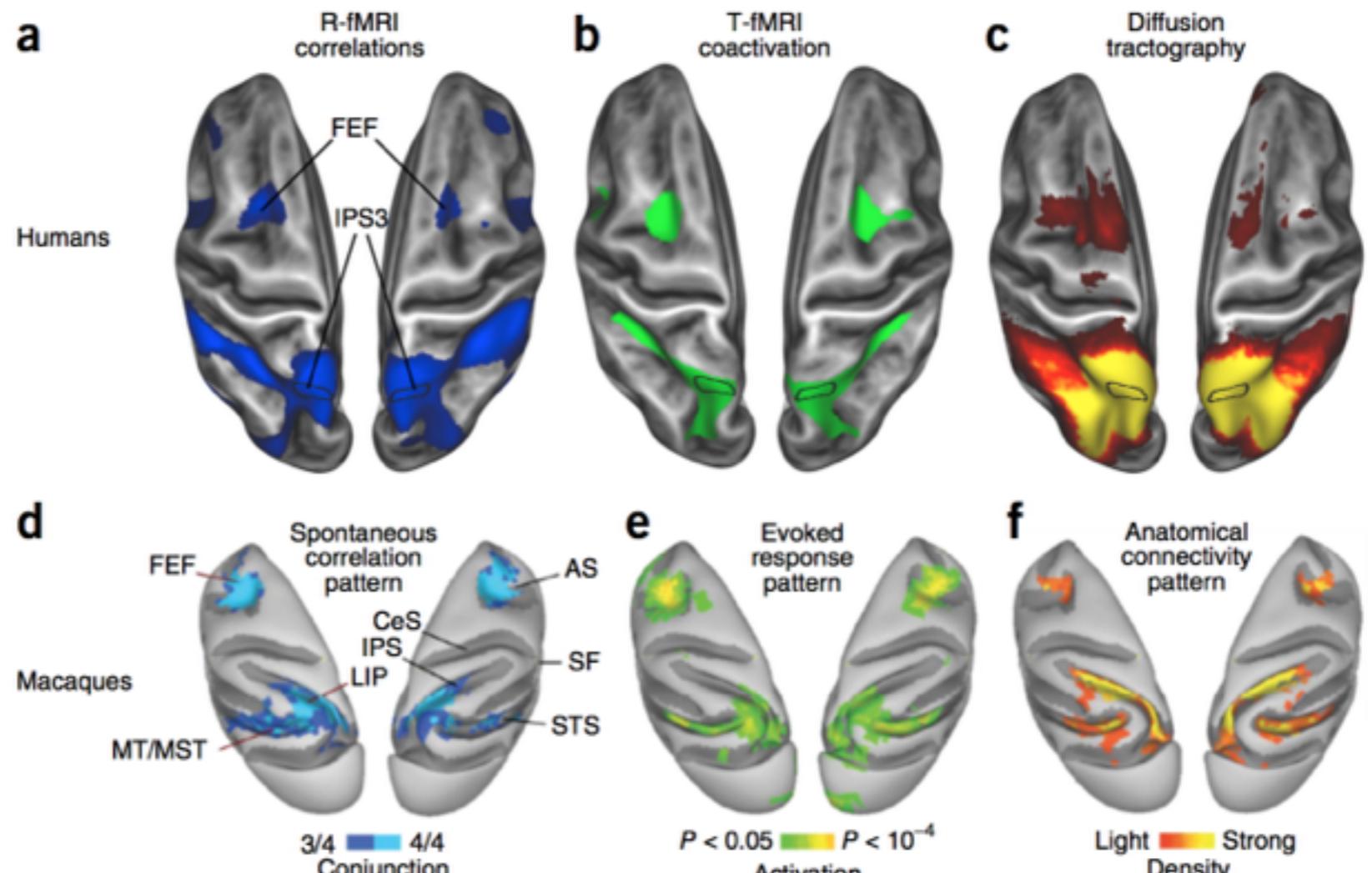


Figure 4 Agreement between functional and structural connectivity in measuring connections in human and macaques. (a–c) Connectivity maps for area IPS3 obtained from data acquired for the Human Connectome Project⁶⁵ (average connectivity of 40 unrelated subjects). (a) Functional connectivity using correlations of R-fMRI time series. (b) Functional connectivity using correlations of activations across multiple tasks (7 tasks and 42 contrasts). (c) Structural connectivity using diffusion MRI and probabilistic tractography.

(d) Map of voxels exhibiting BOLD correlations in spontaneous activity amongst at least three of four regions of the oculomotor system in the anesthetized macaque (dorsal views, AS: arcuate sulcus, CeS: central sulcus, FEF: frontal eye fields, IPS: intraparietal sulcus, LIP: lateral intraparietal area, MT: middle temporal area, SF: sylvian fissure, STS: superior temporal sulcus). (e) Activation pattern evoked by performance of a saccadic eye movement task (average of two monkeys). (f) Density of cells labeled by retrograde tracer injections into LIP (average of three monkeys). Images in d–f are adapted with permission from ref. 63.



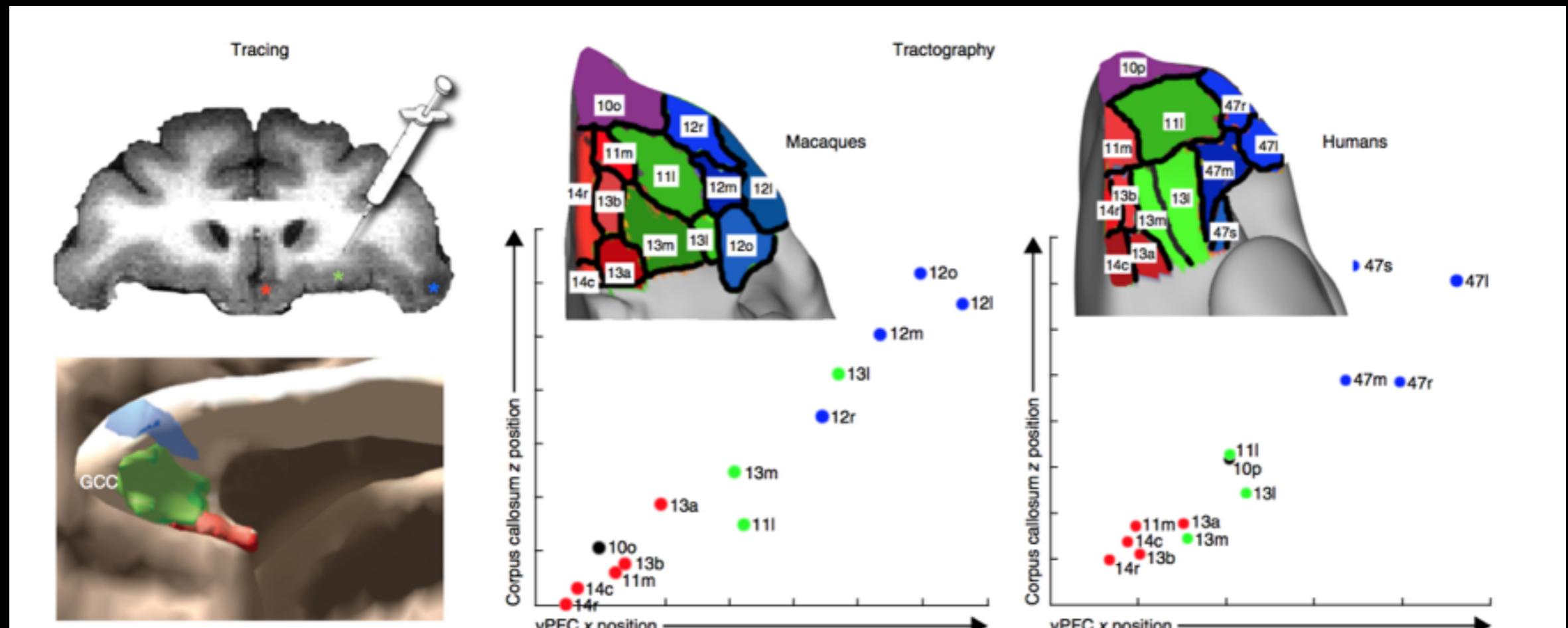


Figure 5 Testing generic organization principles using tractography. Injection of tracers into three locations of the macaque vPFC reveals that the medial-lateral position of the injection sites in the vPFC dictates the relative position of the corresponding pathways in the genu of the corpus callosum (GCC). Tractography is then utilized to test and confirm that this pattern is generalizable to the entire vPFC, both in macaques and humans. The scatter plots show the positions of the centers of gravity of the vPFC seed regions plotted against the centers of gravity of the pathways. It is clear that the *x* position (medial-lateral) of the seed regions correlates significantly with the *z* position (ventral-dorsal) of the corpus callosum projections. The insets show subdivisions of the vPFC into 13 regions according to ref. 105 for macaques and ref. 104 for humans. The regions are colored in red, green and blue according to their approximate medial-dorsal positions for ease of visualization. Figure adapted with permission from refs. 26,69.