Connectomics analysis and parcellation of the brain based on diffusion-weighted fiber tractography

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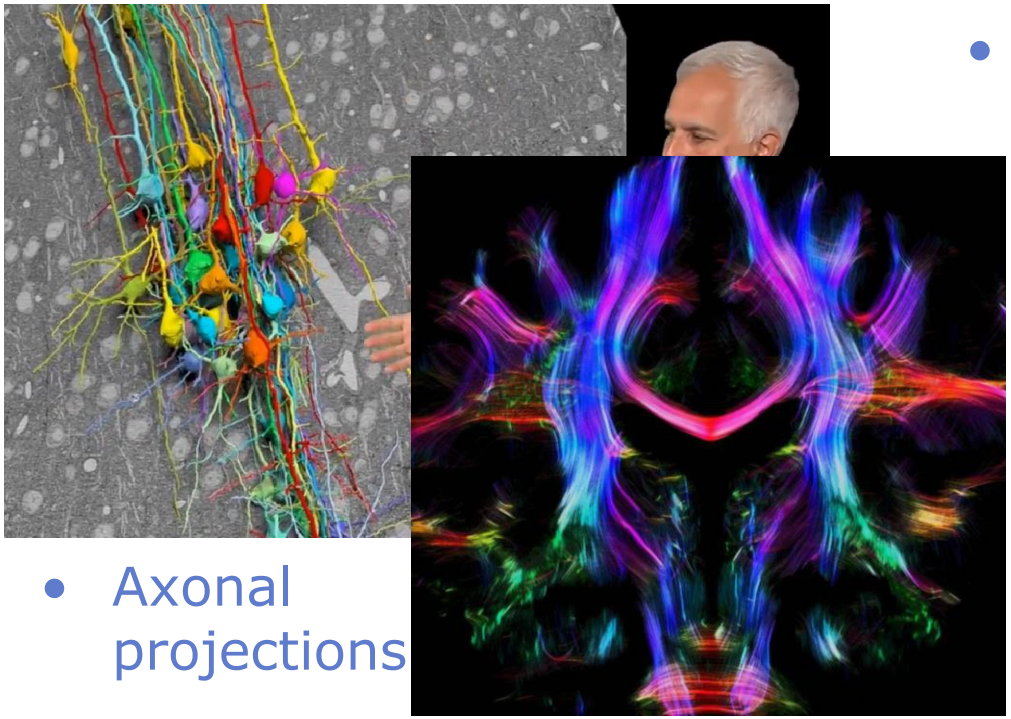
What is the Connectome?

A Network of connections between neurons in the human brain

Structural network:

- Capturing synaptic connections:

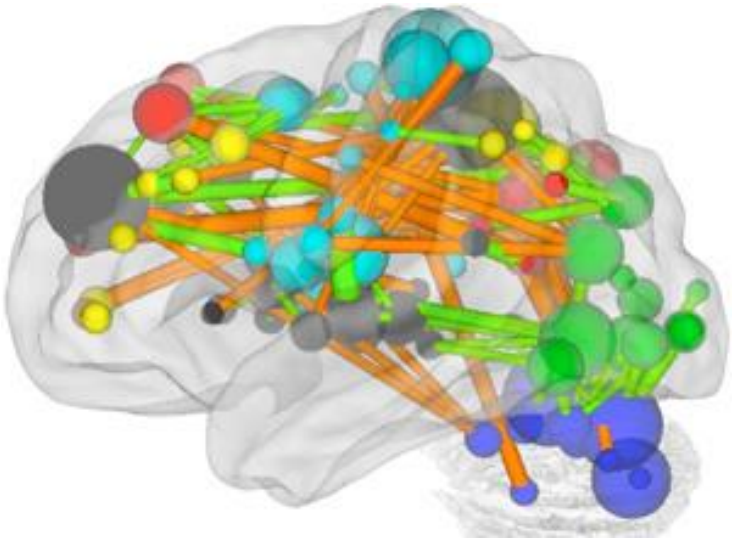


- Axonal projections

Sporns, 2012; Jeff Lichtmann. (Havard) Brain Connectomics;

Functional network:

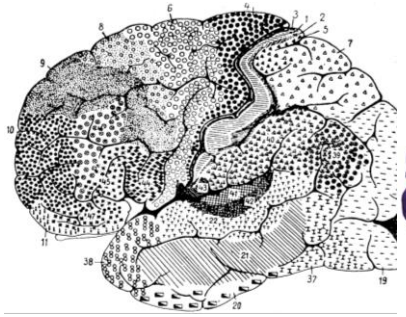
- Based on the dynamic pattern of neural activity
- Statistical dependence or coherence in activity

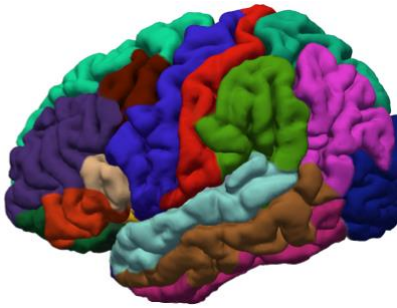


Dosenbach et al. Science 2010

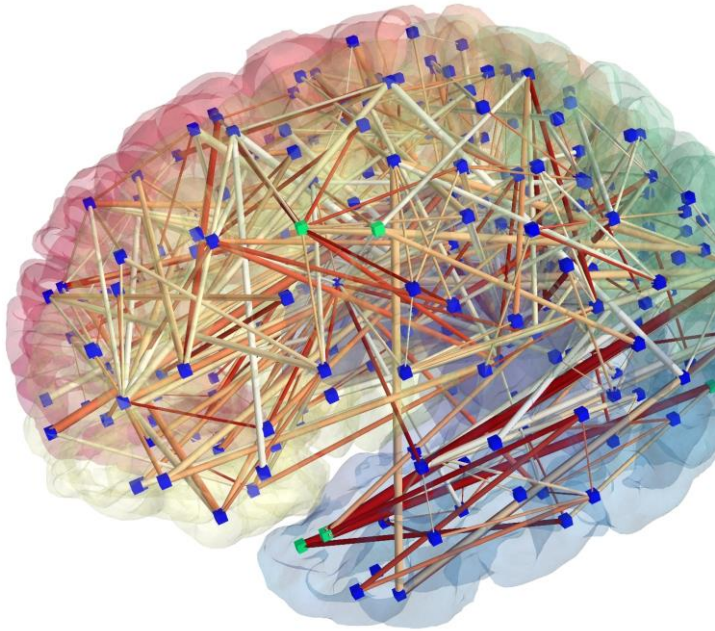
Basic components of the connectome

- The cortex parcellation as **nodes** of the network (homogeneous connectivity)





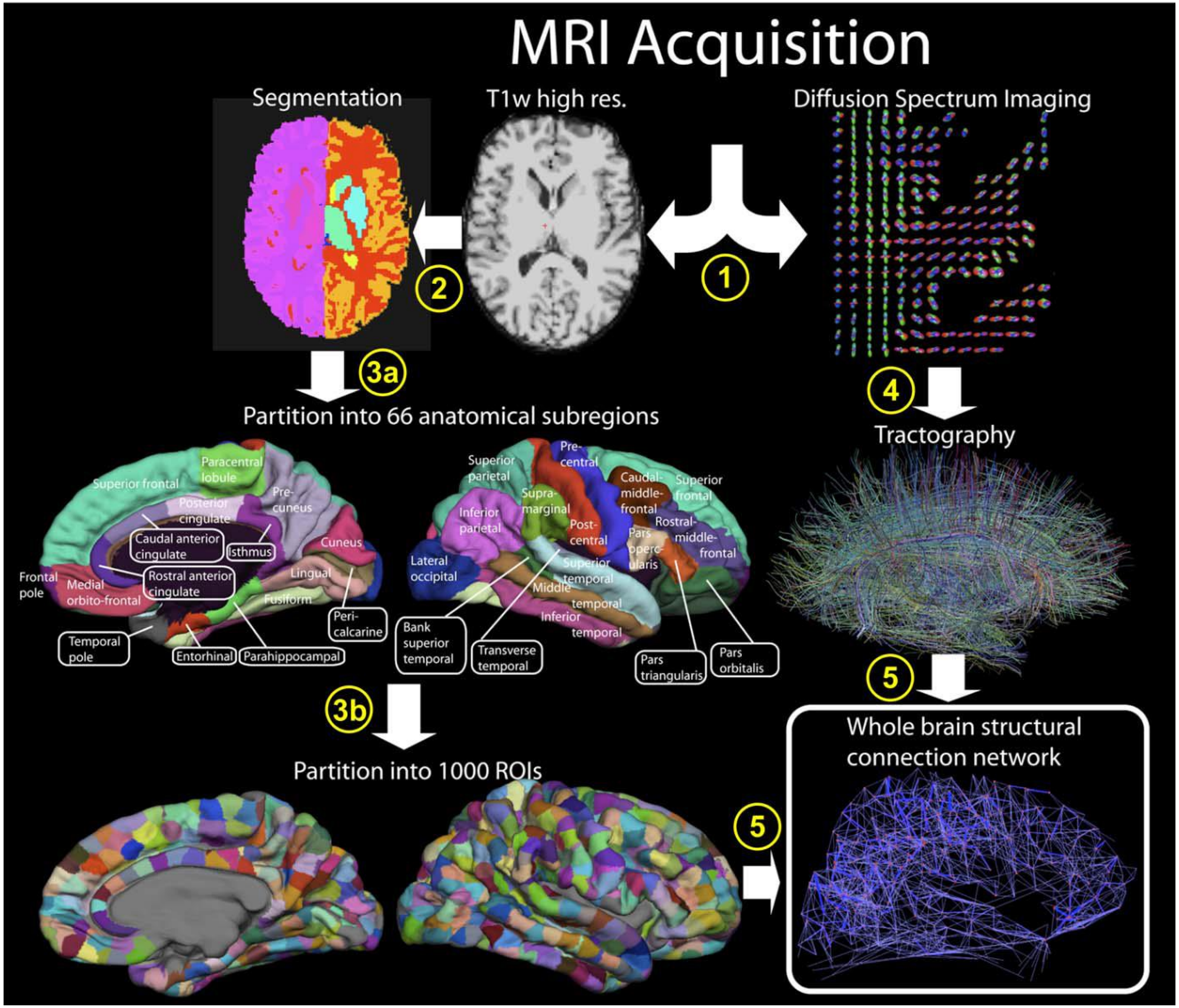
- The brain white matter connections as **edges** (extrinsic connections)



http://freesurfer.net; Brodmann, 1909; http://www.connectomics.org

Measuring the human connectome in vivo

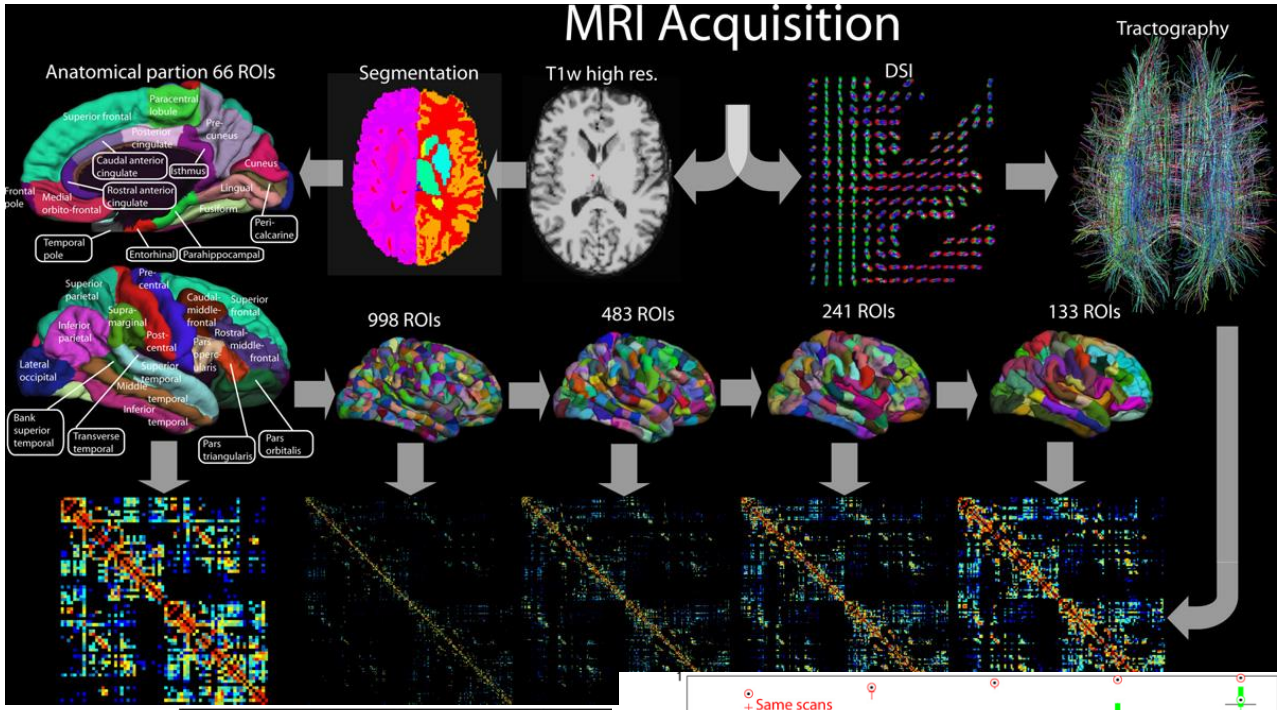
- Segmentation
- Parcellation
- **Subdivision**
- Tractography
- Represent as graph: as a connectome

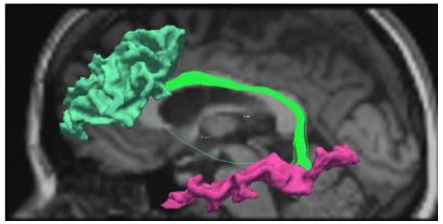


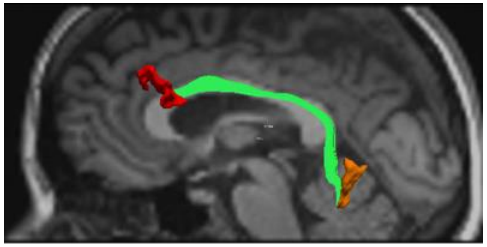
Hagmann PLoS Biol 2008

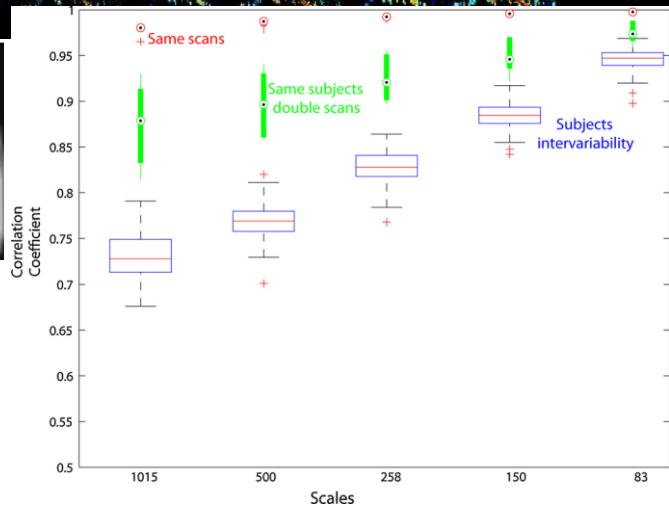
Mapping the connectome at multiple scales

- Which cortical parcellation should we use
- Cortical landmarks?
- Random ROIs
- Connectivity based parcellation
- What scale?
- Variance increases with scale



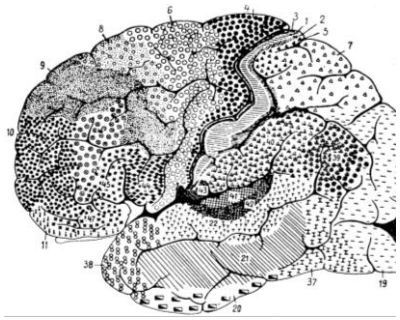


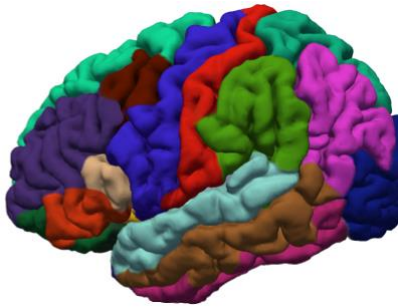




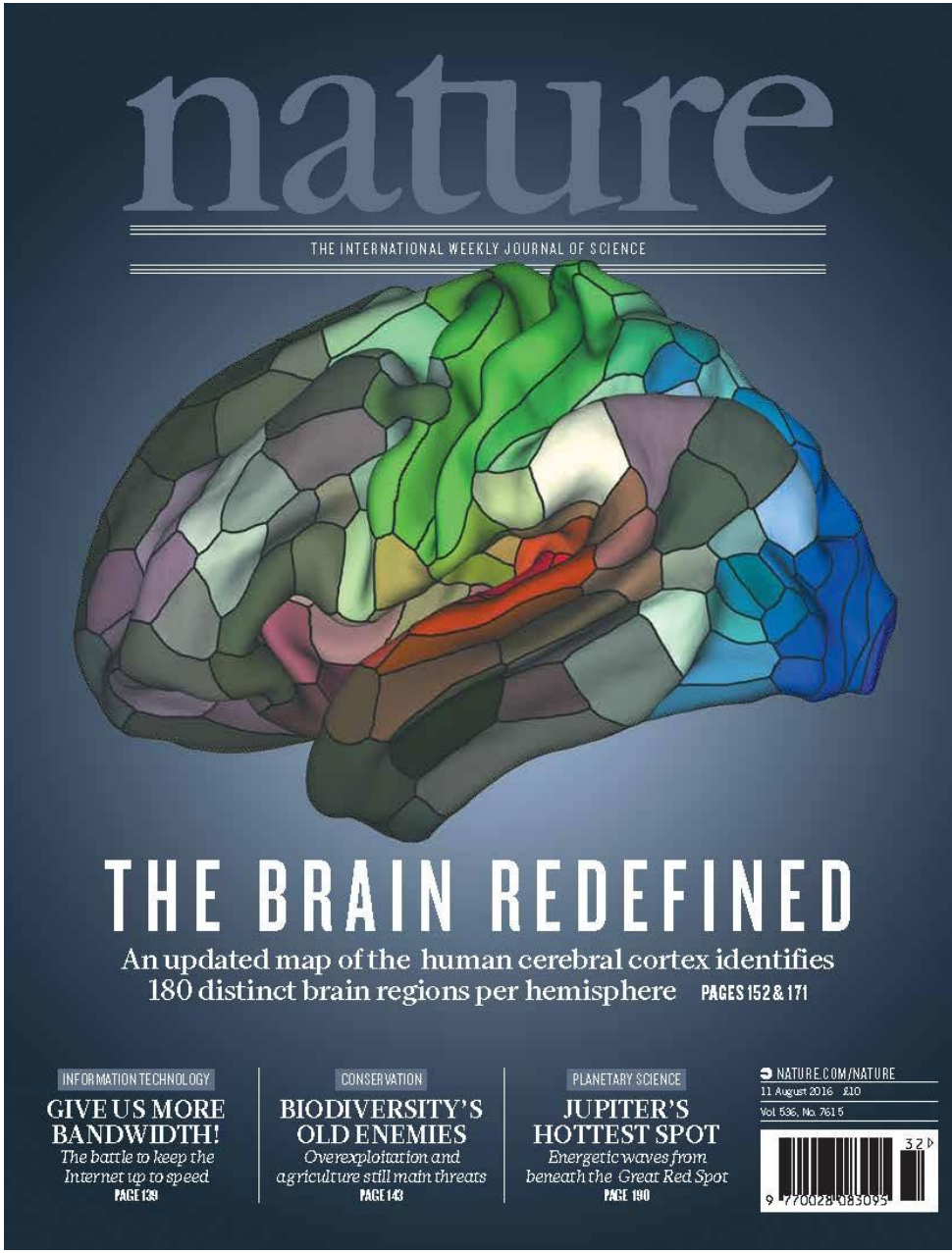
Cammoun et al. JNM 2012

Is the brain parcellation solved?





- Brodmann areas defined on the cell distribution and not connectivity
- Strongly variable connectivity within gyri
- Resting state/myelin atlas might differ from tractography connections



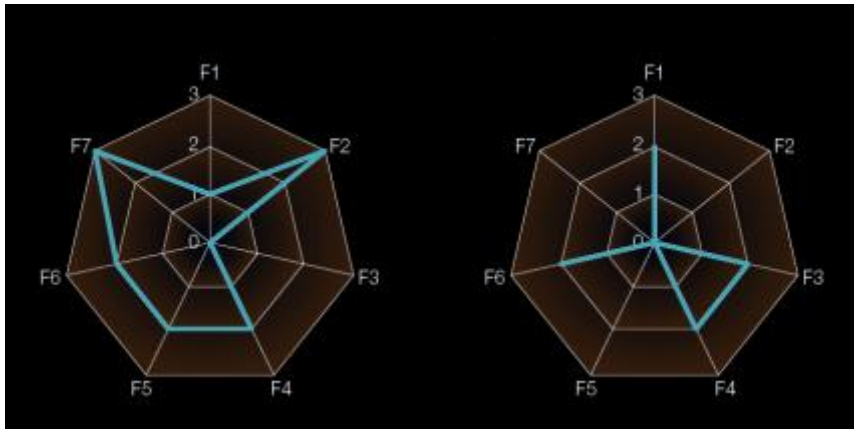
http://freesurfer.net; Brodmann, 1909 , Glasser et al. Nature 2016

Can we use long range connectivity for brain parcellation?

… and use diffusion MRI for the definition of the nodes and the edges?

Similarity of tractograms:

- Each cortical area has a unique pattern of cortico- cortical connections — a ‘connectional fingerprint’. No two areas share identical patterns.



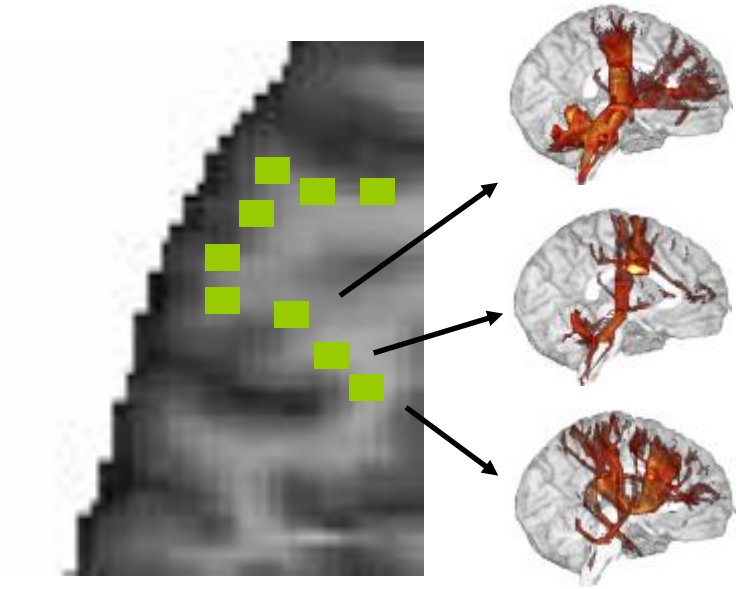
-> any tractogram within an area should be similar

-> Using individual connectivity for cortex parcellation

Passingham et al., 2002

Connectivity pattern

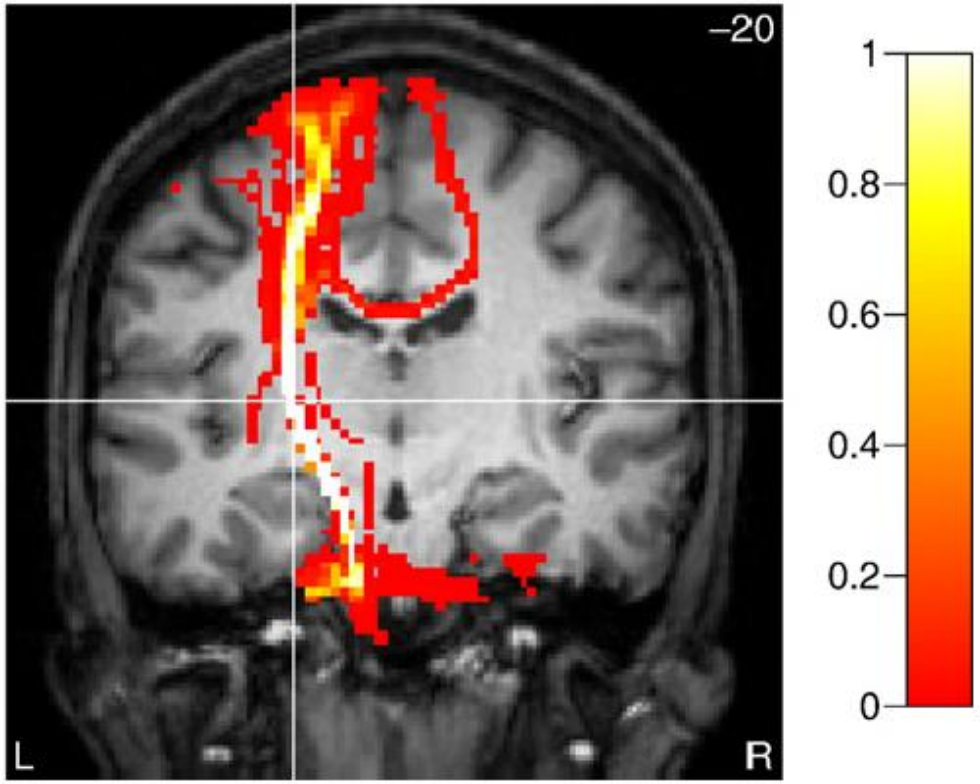
- Tractograms from different cortical areas show different connectivity patterns.



Seed points:

WM voxels at the boundary to GM

For each seed point one tractogram

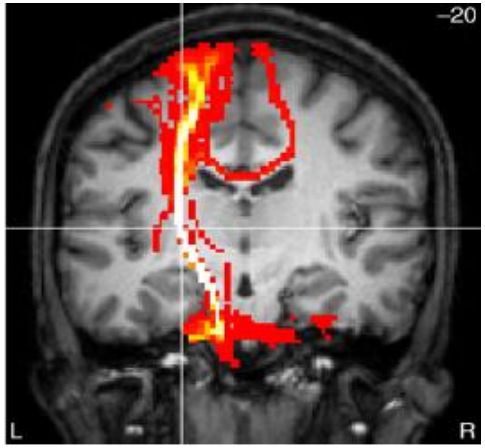


Kaden, Knösche, Anwander, Neuroimage, 2007; Descoteaux, Deriche, Knösche, Anwander IEEE TMI 2009.

Tractogram dissimilarity

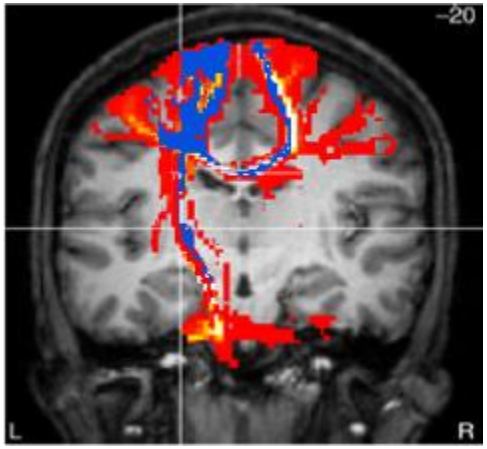
Similarity ➔ normalized scalar product. [0,1]

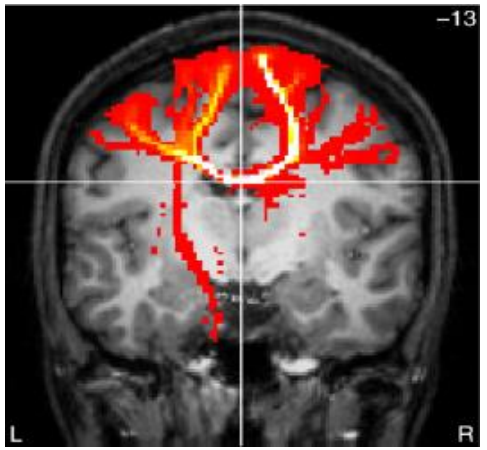
Distance = 1 - Similarity



Distance = 0 ➔ Same tractogram

Distance = 1 ➔ No overlap

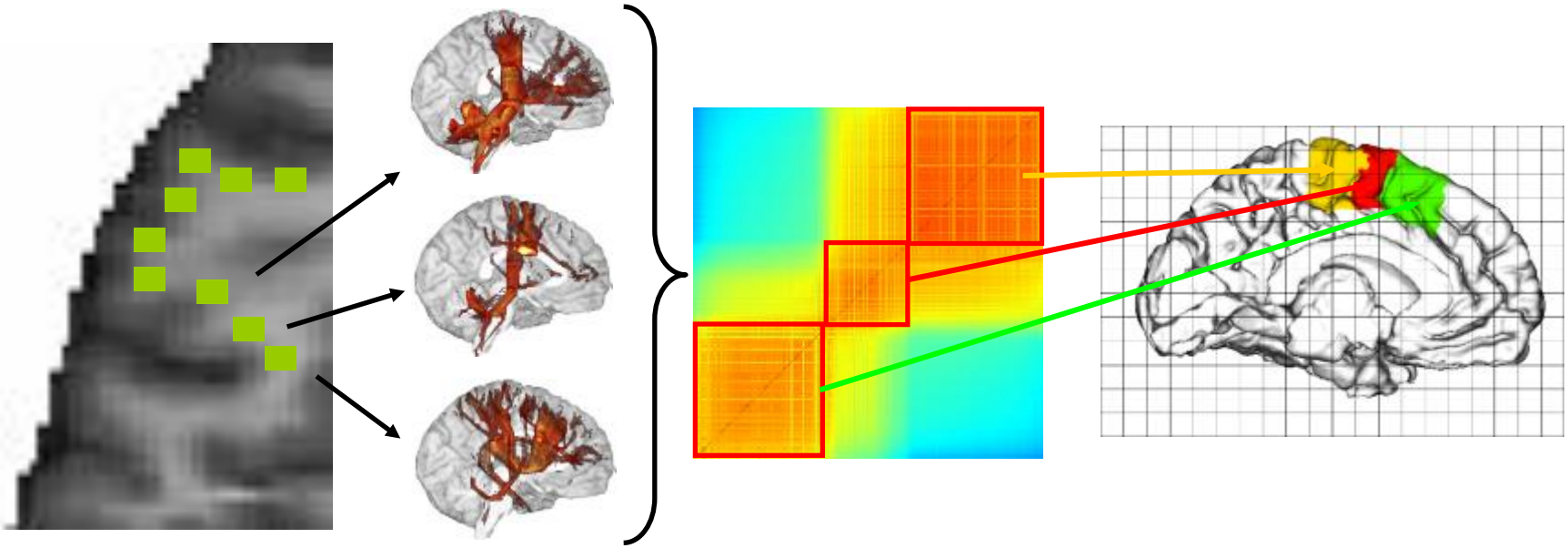




- Similarity = 0.3
- Distance = 0.7

Defining homogeneous regions: Cortex parcellation

Tractograms from different cortical areas show different connectivity patterns. The difference in such characteristic tractograms can be evaluated statistically.



Seed points:

WM voxels at the boundary to GM

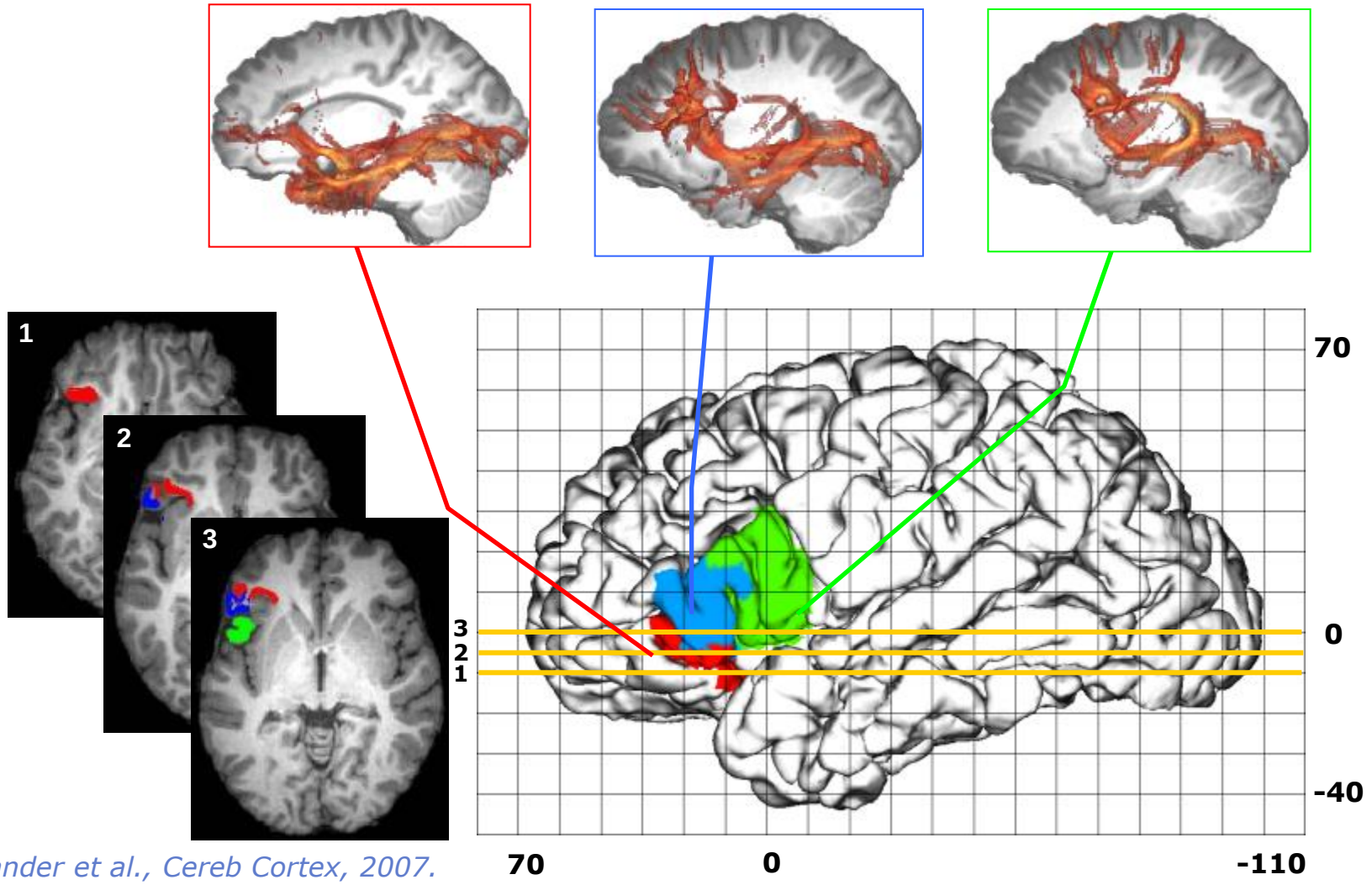
For each seed point one tractogram

Similarity between tractograms

Cortex parcellation

Anwander et al., Cereb Cortex, 2007.

Quantify connectivity differences: Connectivity based cortex parcellation. Example: Broca's area

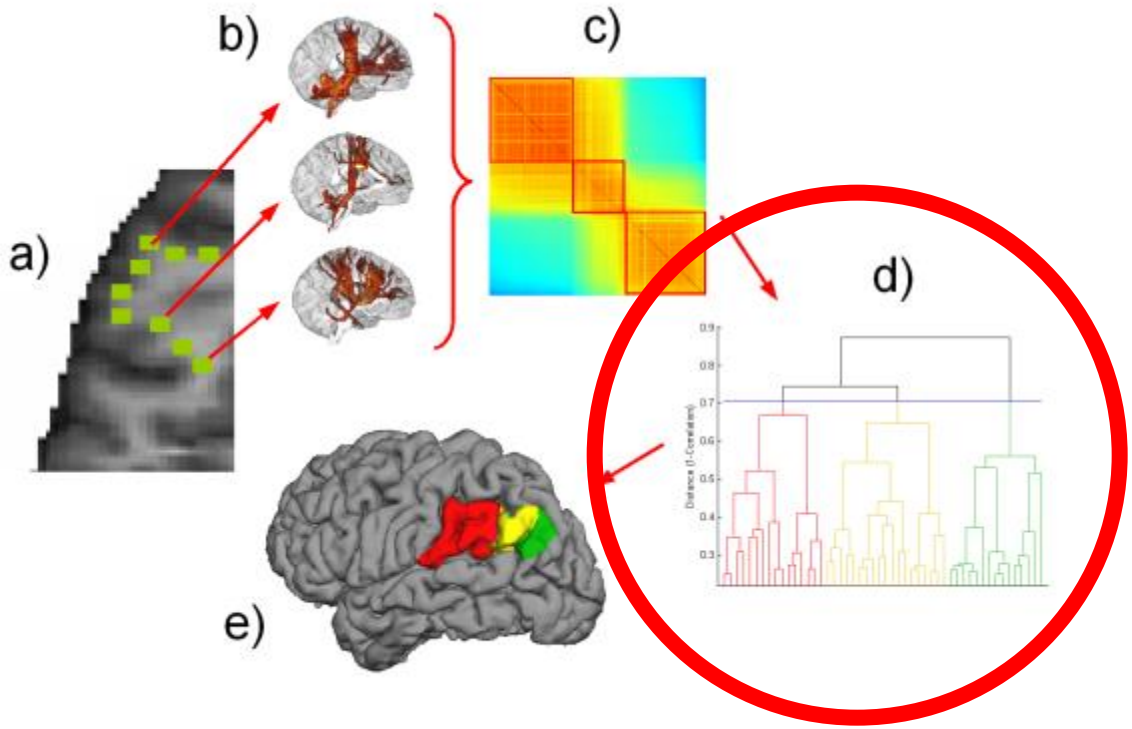


Anwander et al., Cereb Cortex, 2007.

Can we parcellate bigger regions?

Hierarchical parcellation of the human brain

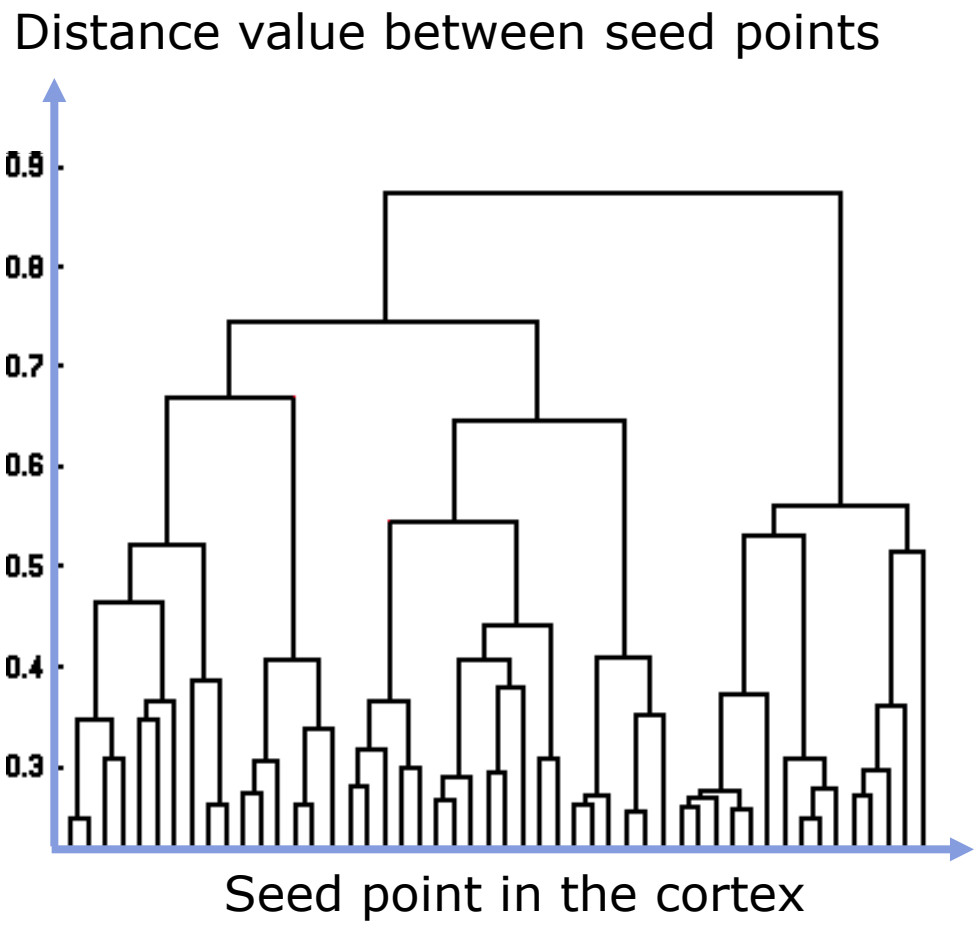
- Connectivity matrix shows hierarchical structure
- Representation as hierarchical tree



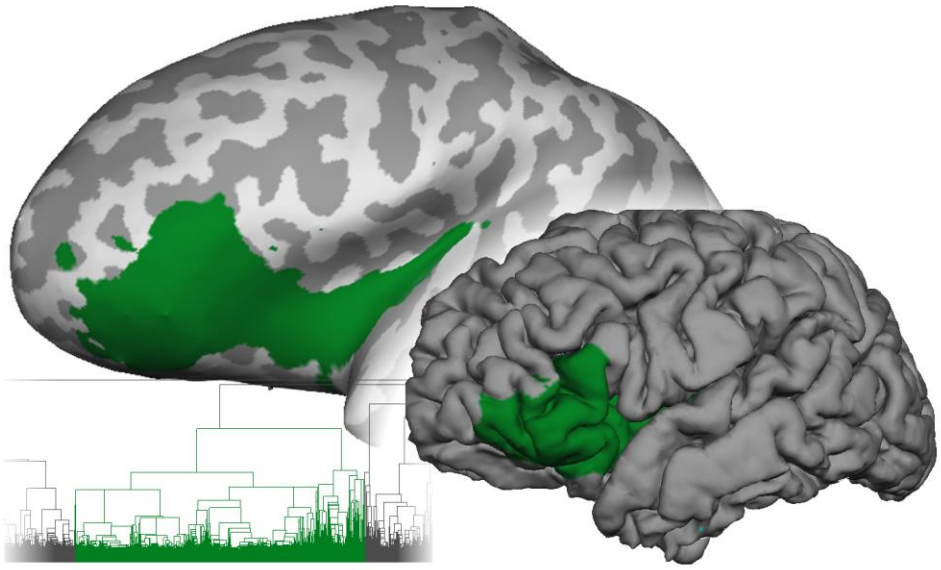
Moreno, et al. Hum Brain Mapp 2014

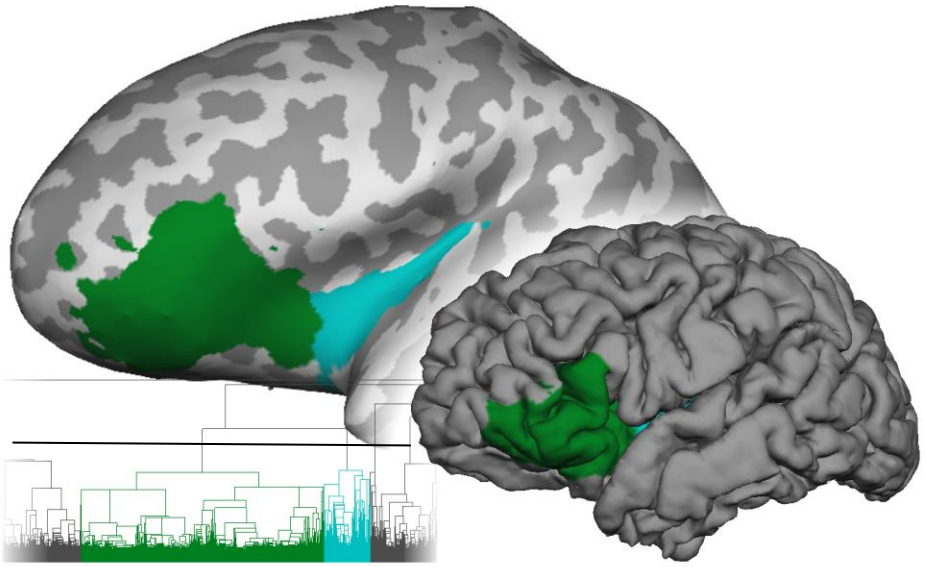
Agglomerative hierarchical clustering

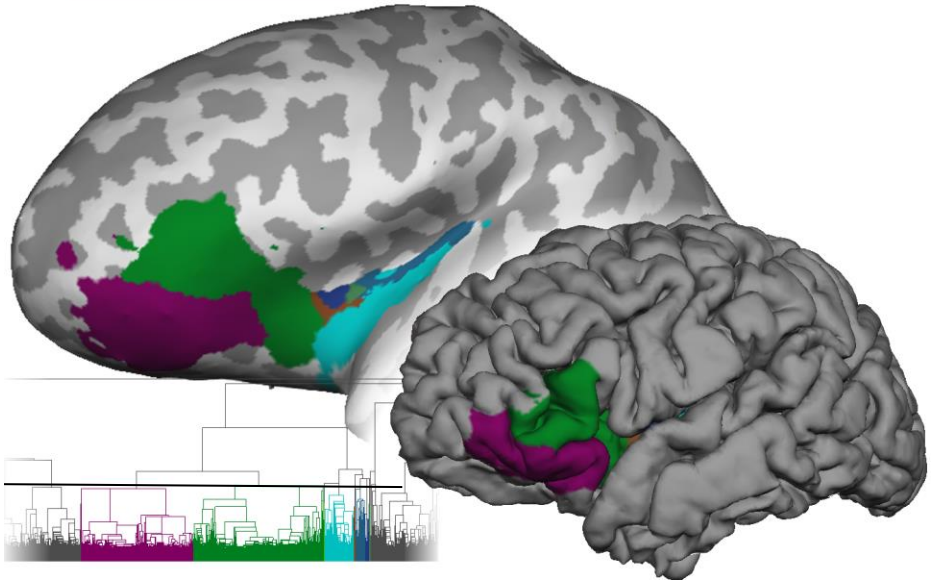
- Start with single points
- Join the two most similar elements
- Compute new distance to the other nodes
- Iterate until only one element remains (all original nodes)

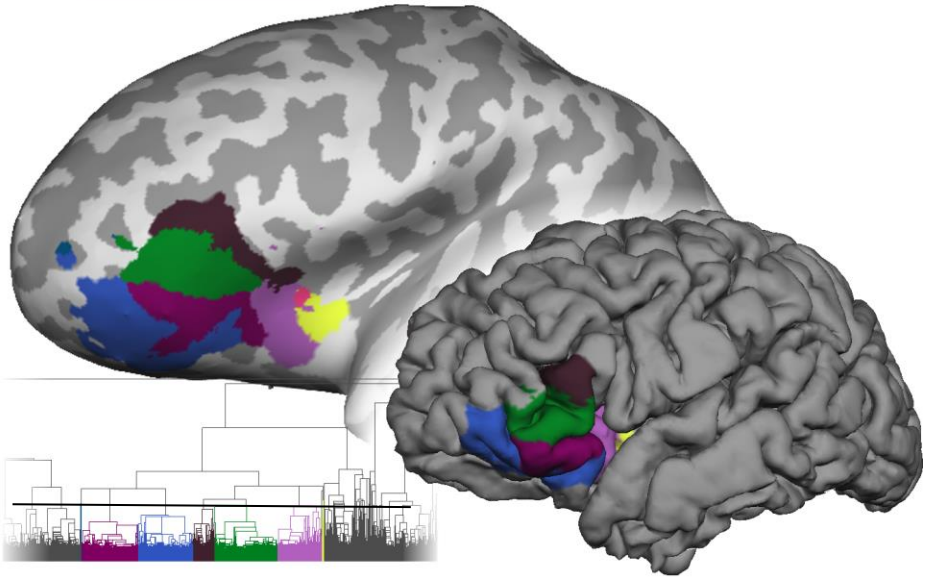


Tree navigation

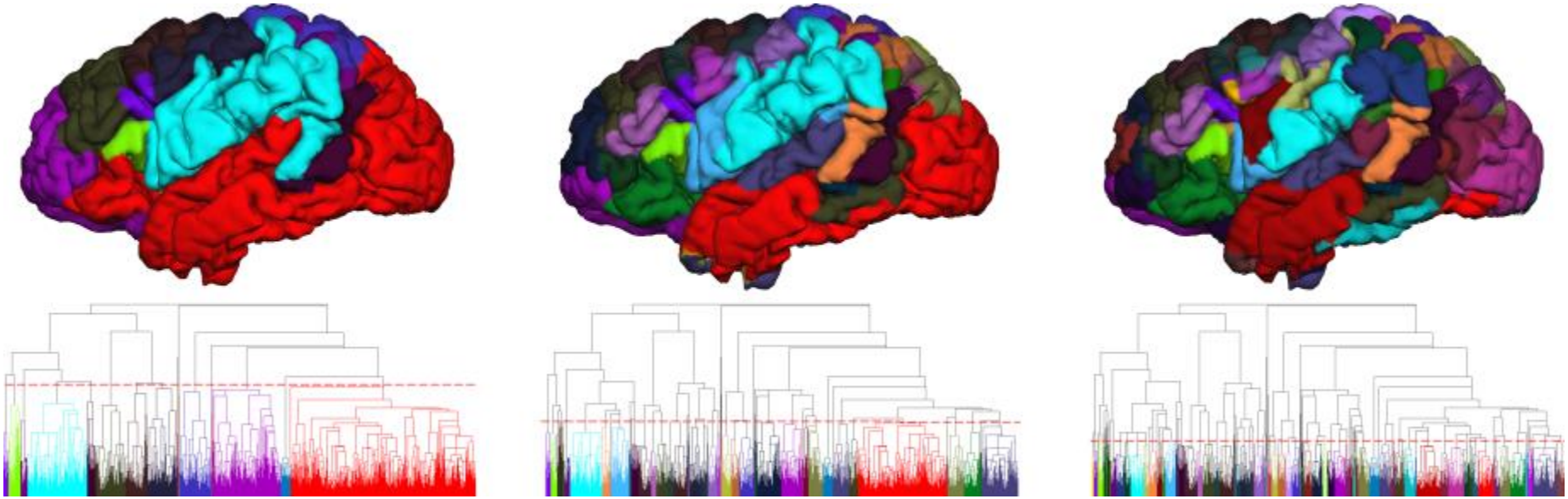








Hierarchical parcellation of the human brain

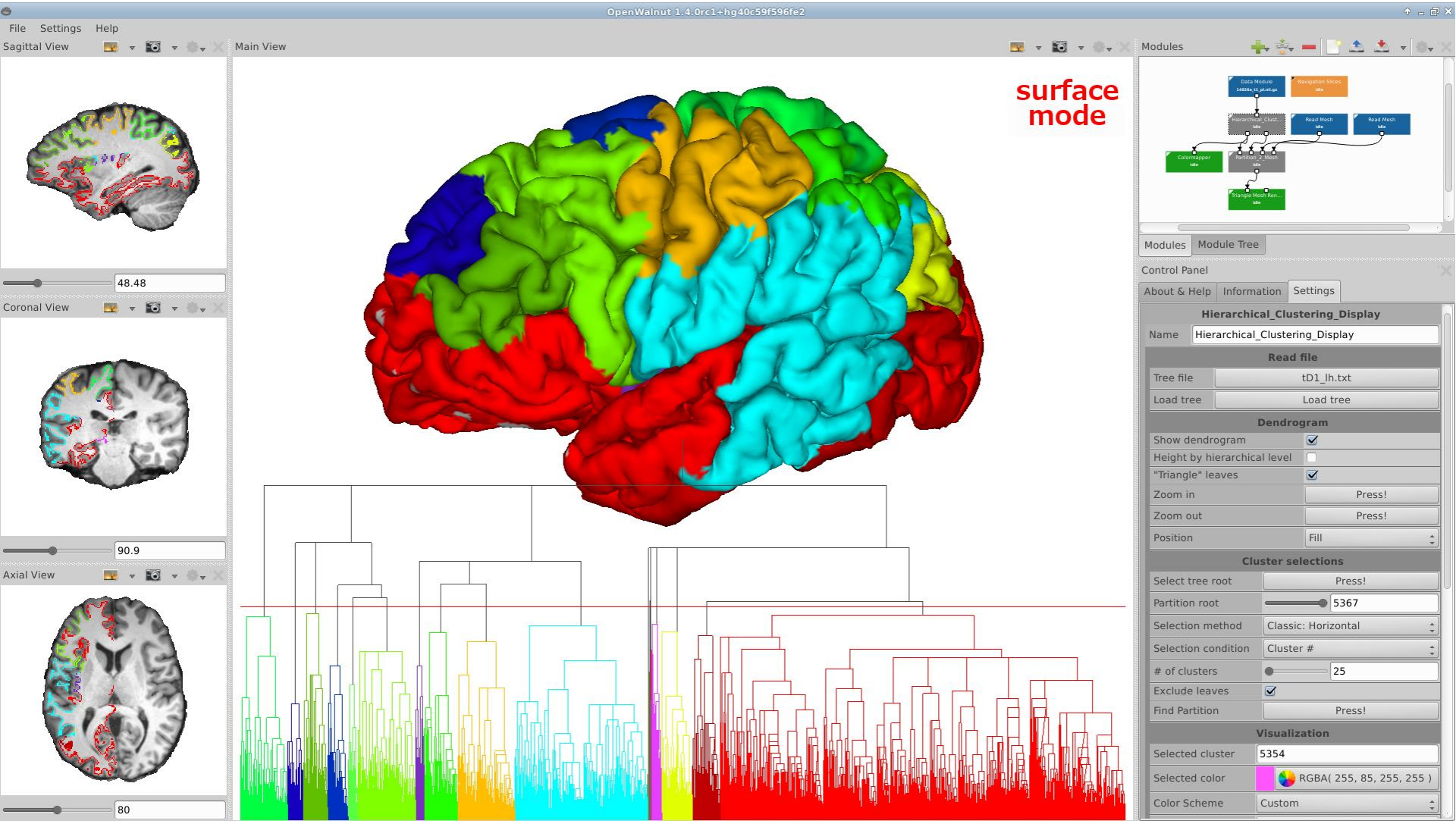


- Best representation of the tree by a series of parcellations
- Partitions yielding 15, 50 and 100 clusters for the left-hemisphere tree
- Different criteria for selecting parcellations

Moreno, et al. Hum Brain Mapp 2014 (David is now with "Mint Labs: Neuroimaging in the cloud", Booth #34)

Module in www.OpenWalnut.org

https://github.com/dmordom/hClustering.git



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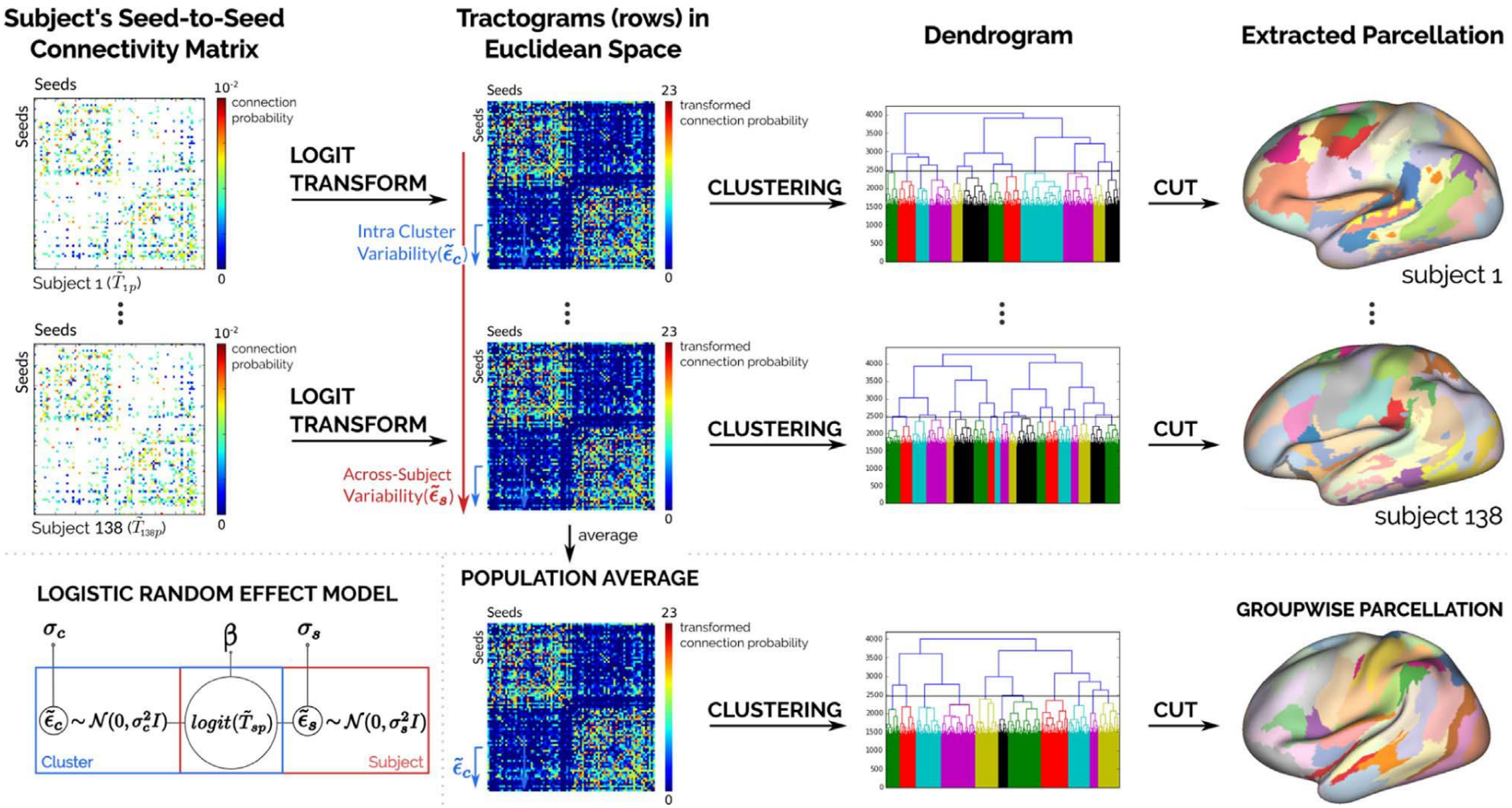
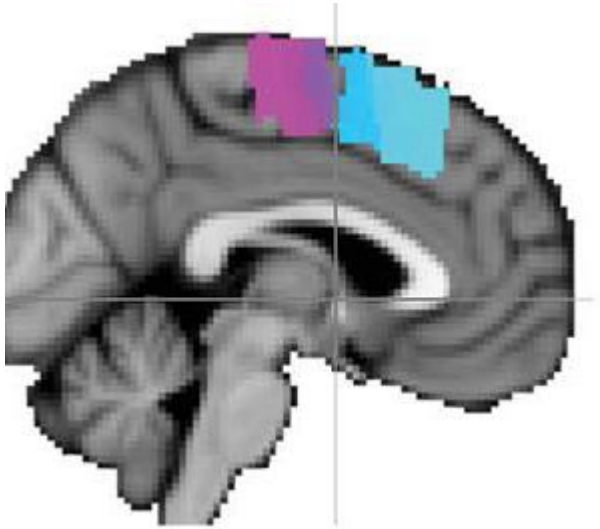
Groupwise structural parcellation of the cortex

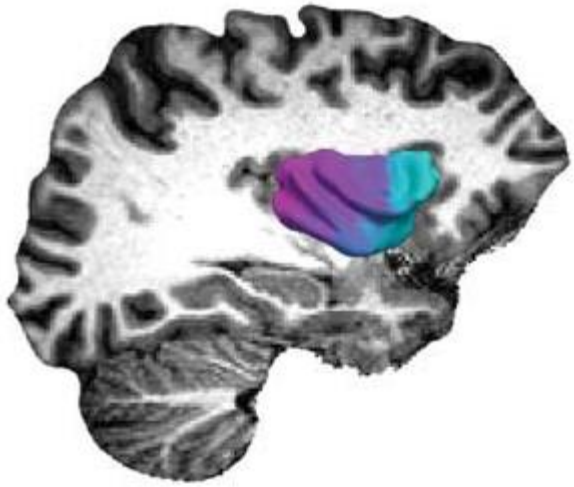


Gallardo, et al. Neuroimage 2017,
see also ***Poster 1659 Mon*** *Gallardo, Deriche, Wassermann*

How sharp are the boundaries between the areas?

Gradients of similarity





- Laplacian eigenmap of the medial prefrontal cortex
- Relative sharp boundary

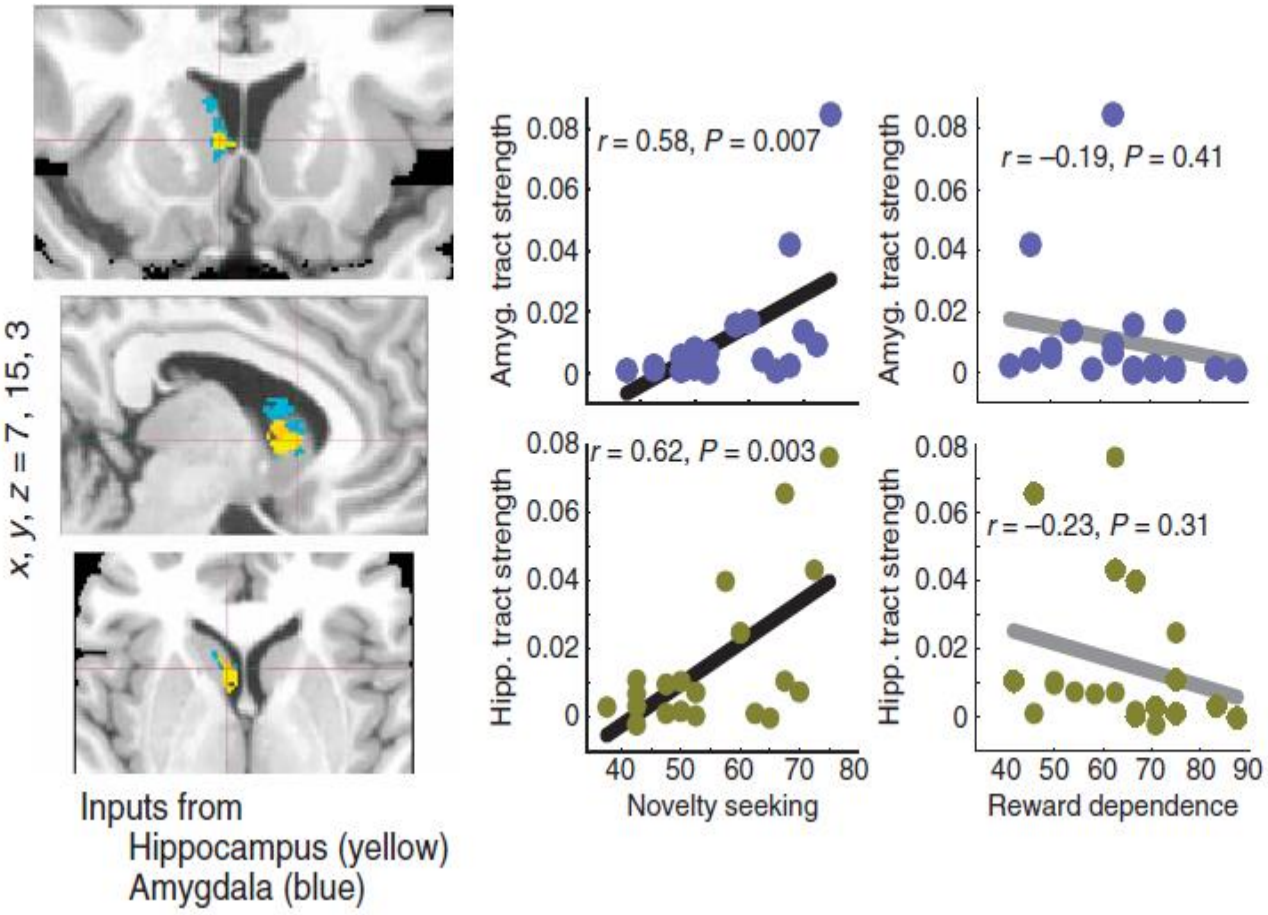
- Insula:
  Smooth gradient of the connectivity profile

- Differences in connectivity profiles,
  but no clear defined boundary

Cerliani, et al. Hum Brain Mapp 2012
Bajada et al. Neuroimage 2017

From parcellation to connectivity and connectoms

How can we quantify connectivity?
How do we get to Nature Neuroscience?

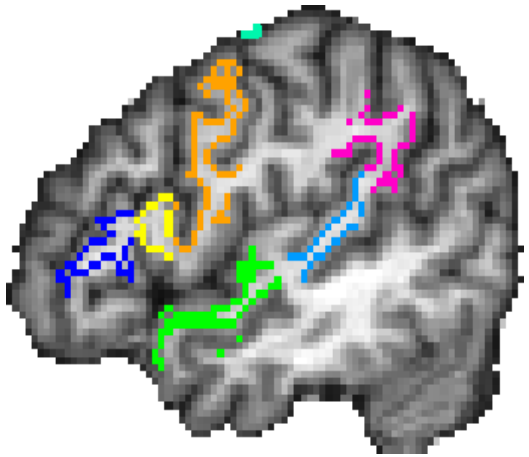


Correlate connectivity strength with behavior …

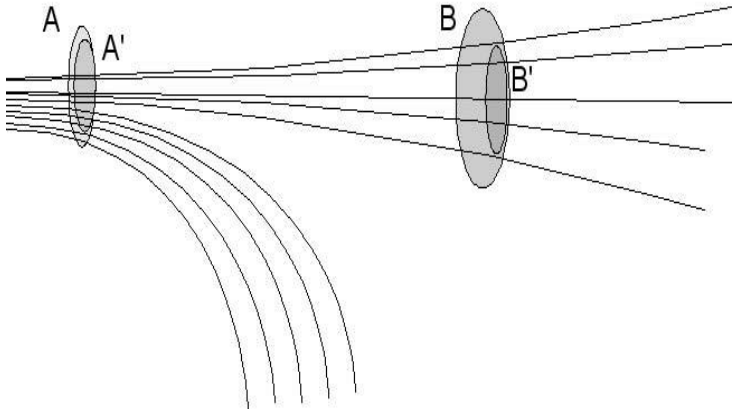
Cohen et al., Nat Neurosci , 2009

How can we compute connectivity strength?

- Who knows?
- Connectivity between regions
- Relative number of connecting fibers



$$Connectivity = \frac{N_B}{N_A} * \frac{R1}{R2}$$



N = nb. of seed fibers

n = nb. of fib. in target region

R1 = size of seed region A

R2 = size of target region B

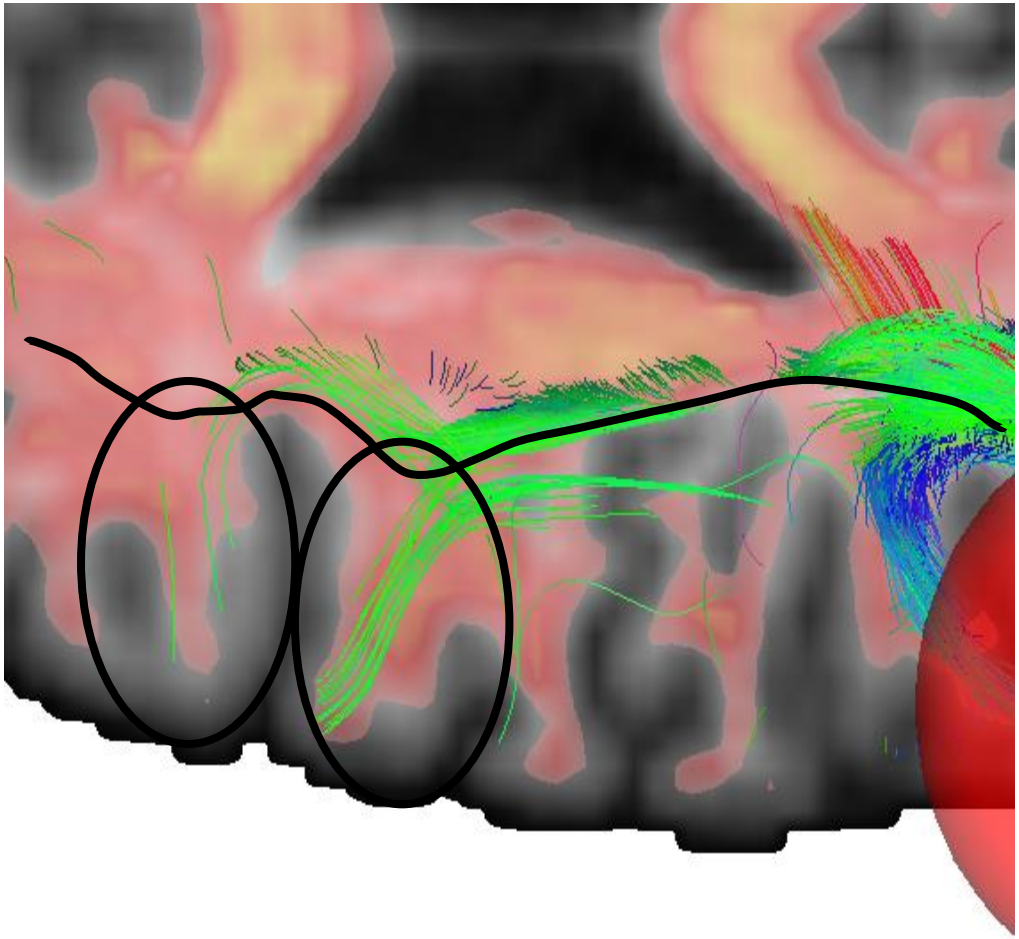
Yo, Anwander et al. MICCAI, 2009

Take care of:

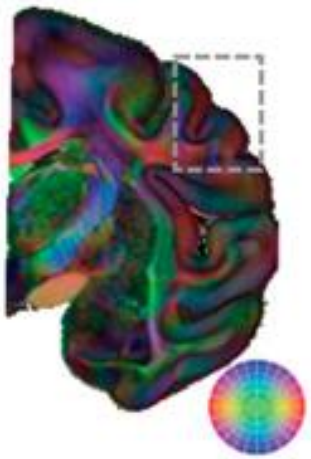
Streamlines connecting ROIs?

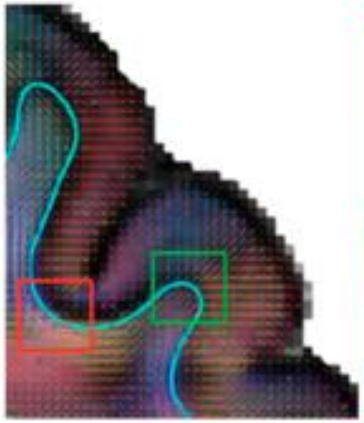
Example:

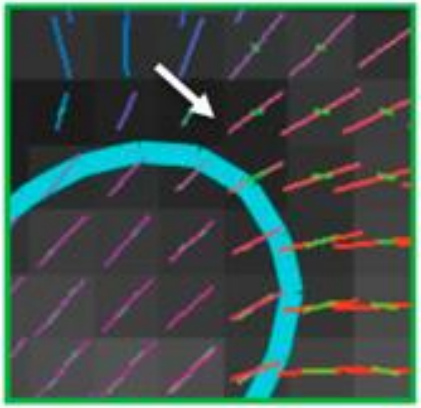
- seed in the IPCC and ROIs in the PCG and IFG
- streamlines cross several regions
- cortical endpoints are concentrated on the crown of the gyrus
- distance bias in the connectivity measure

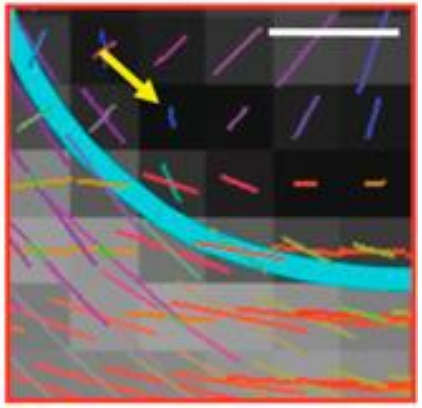


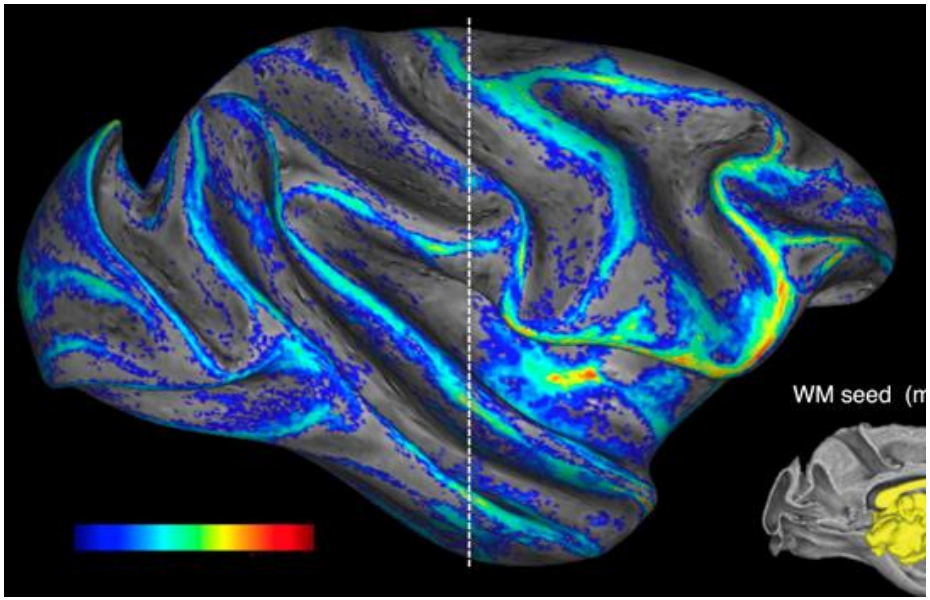
„Gyral bias“







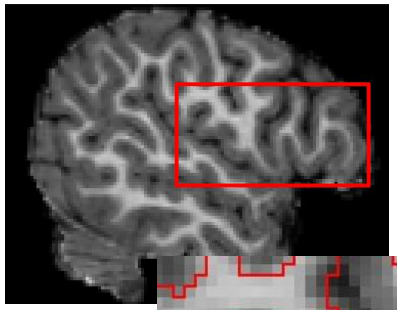




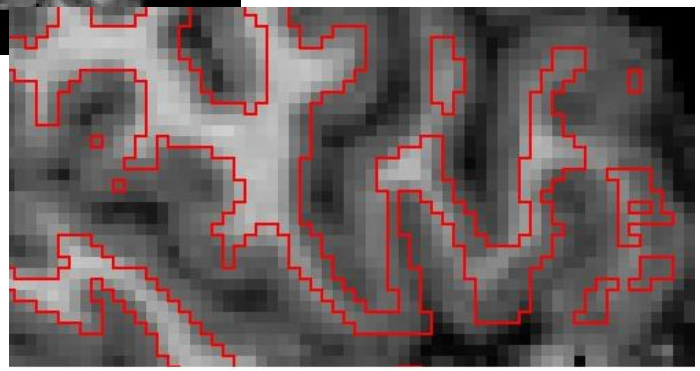
gyral crown fundus

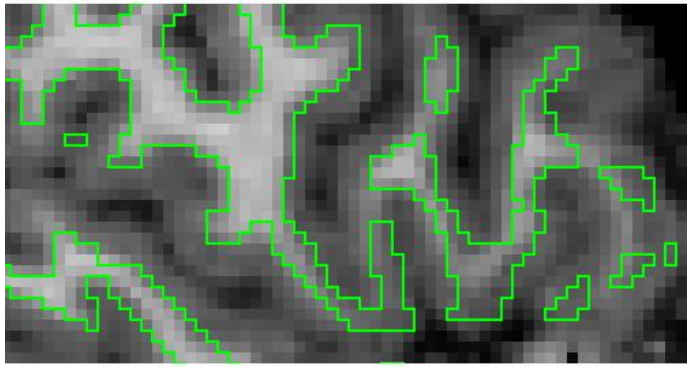
radial tangential

Reveley et al. Proc Natl Acad Sci USA 2015.

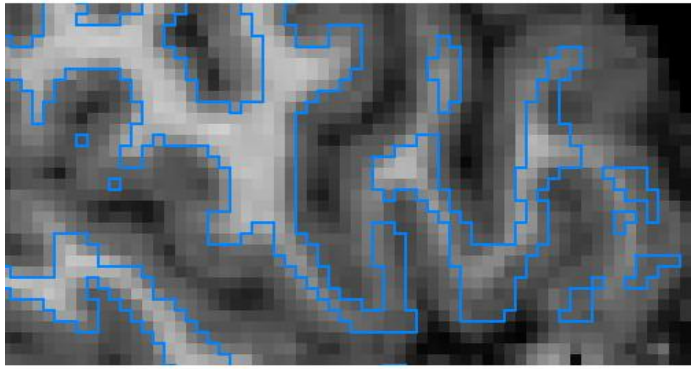


Correct EPI distortions!

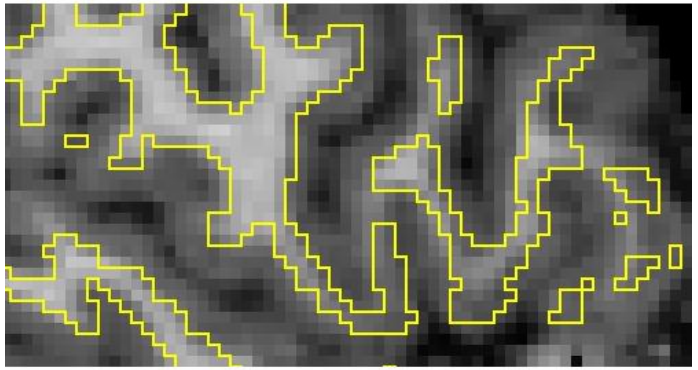




d) HySCO



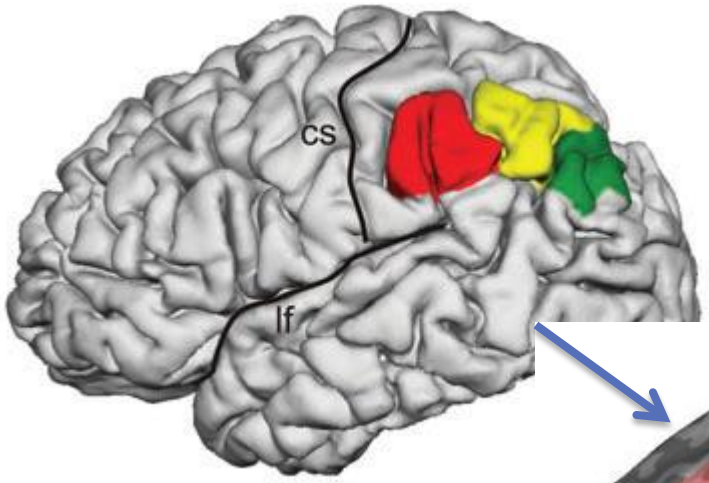
c) Field map



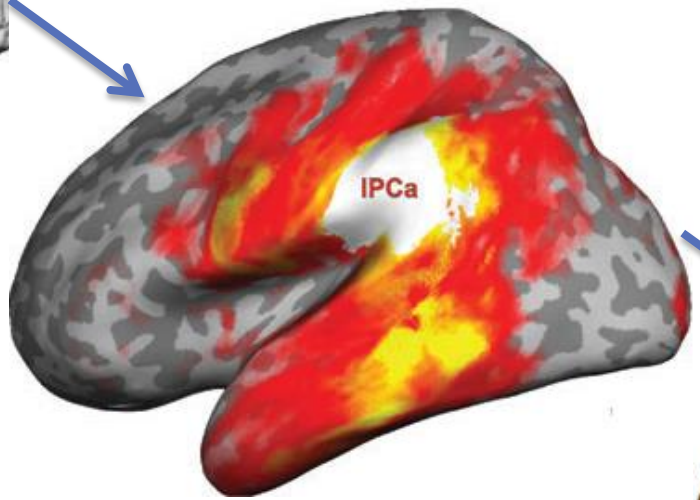
e) TopUp

Schreiber et al. OHBM 2014. d) Ruthotto et al. Phys Med Biol 2012. e) Andersson et al. Neuroimage 2002

Example: Connectivity of the inferior parietal lobe

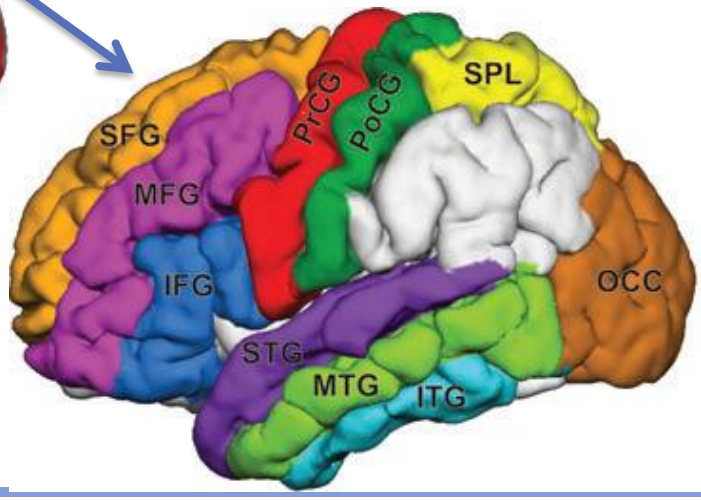


3 seed regions



Probabilistic tractography

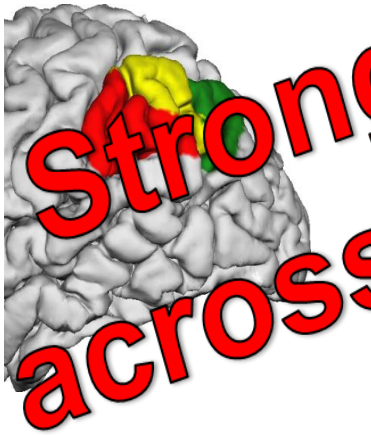
Atlas of target areas

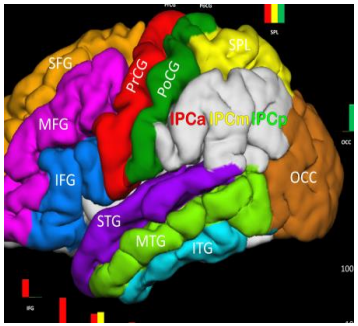


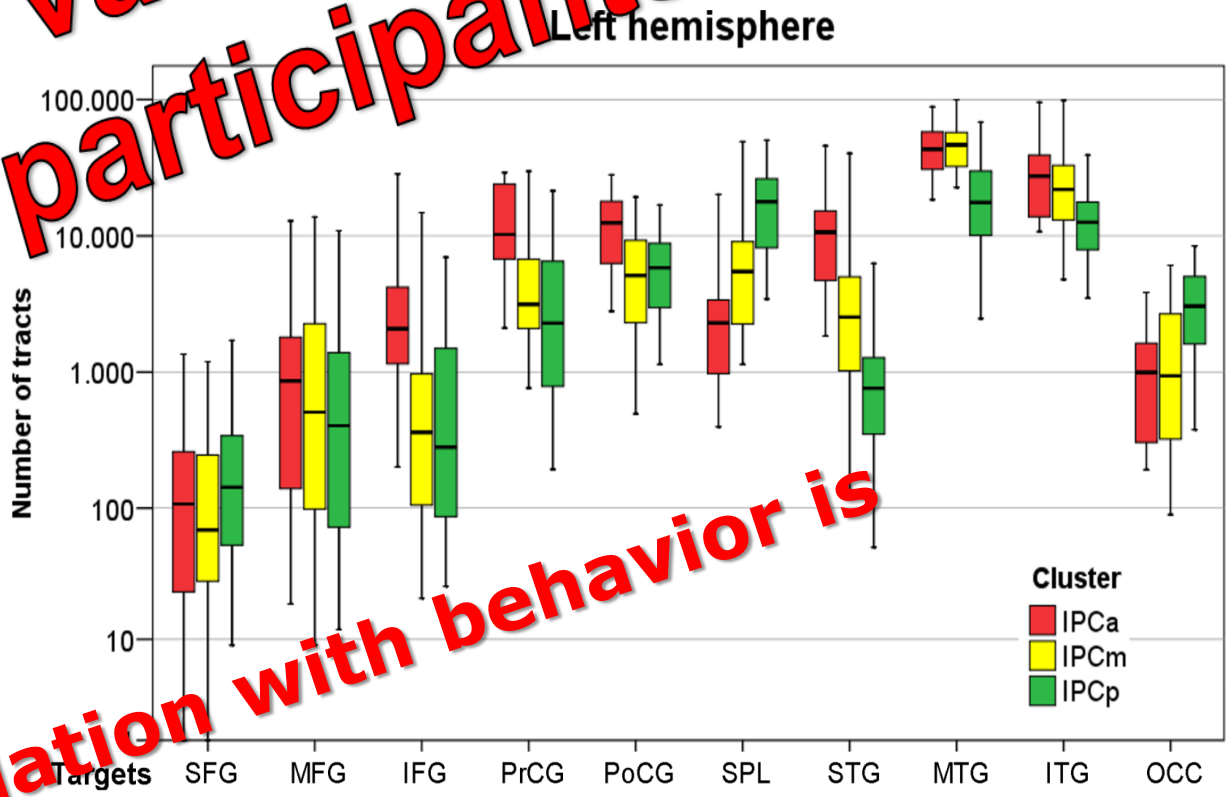
Ruschel et al. Cereb Cortex, 2014.

Example: Quantifying connectivity from IPCC

Insights







Strong variability across participants.

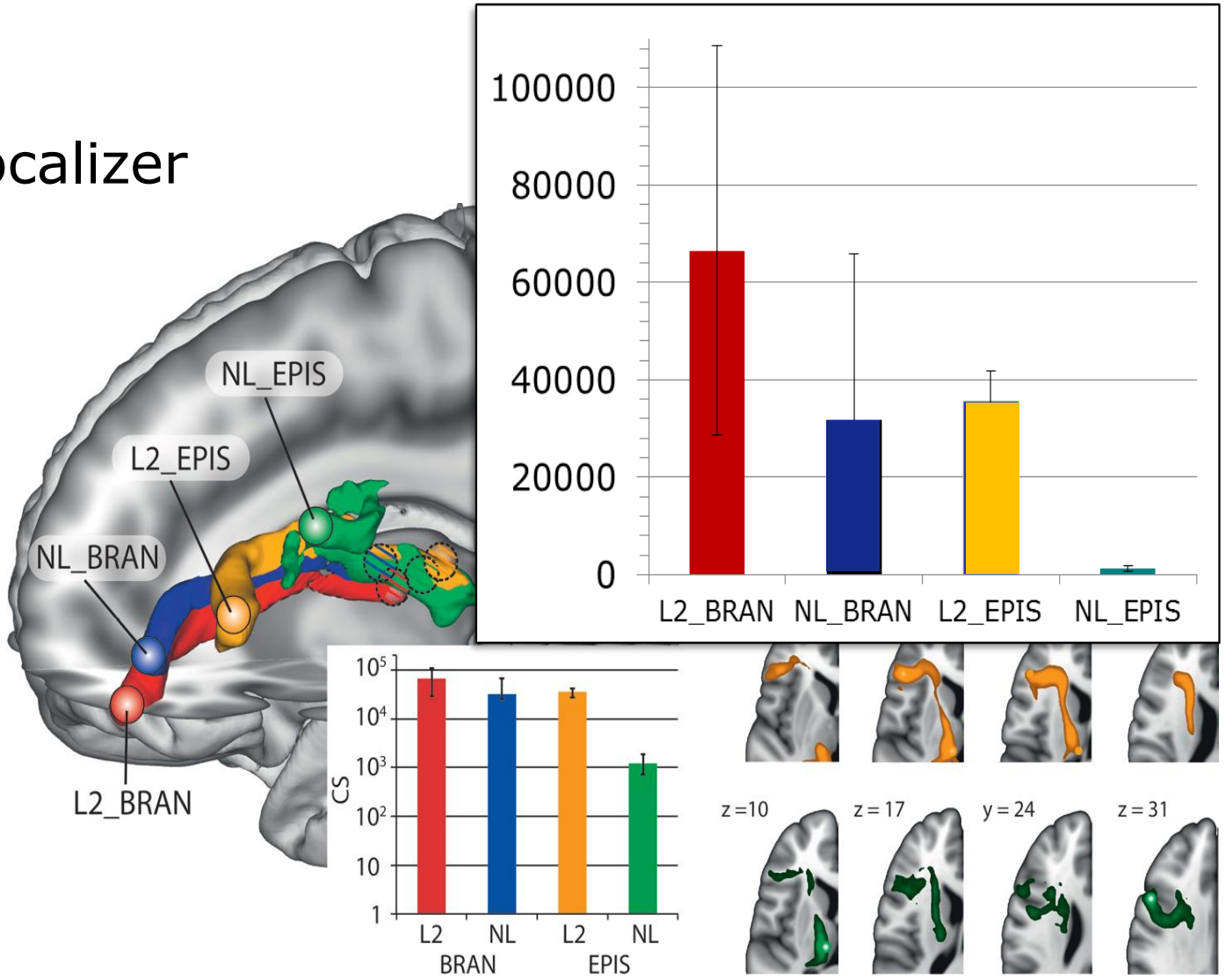
Correlation with behavior is difficult!

Ruschel et al. Cereb Cortex, 2014.

Example: Prefrontal-thalamic connectivity

- Functional localizer
- 7T dMRI
- 1mm iso
- FSL probtrackX

- variation across participants up to a factor 10



Jeon et al. J Neurosci, 2014

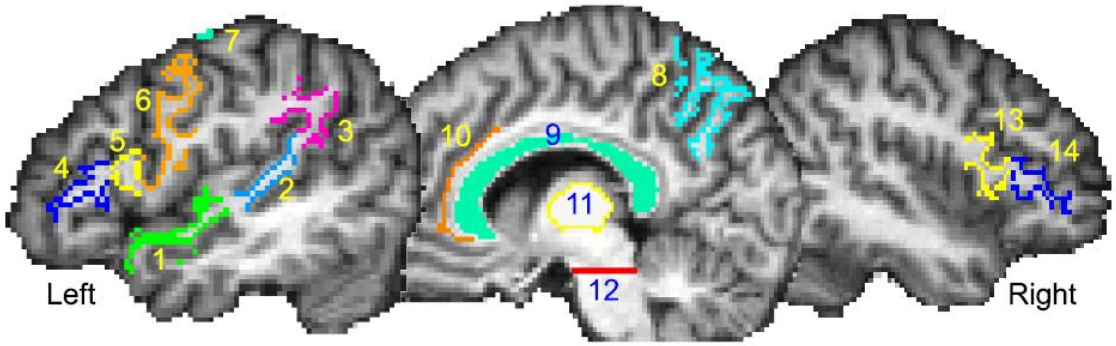
Comparison between Tractography Methods

Local Model	Probabilistic Tractography	Deterministic Tractography
Diffusion tensor (DT, Basser et al. 1994)	Anwander et al. 2007	MedINRIA[1] (Toussaint et al. 2007)
Multi-tensor (MDT, Parker & Alexander 2003)	Camino[2] (Parker & Alexander 2003)	Camino[2] (Parker et al. 2003)
Multiple ball-and-stick (Behrens et al. 2007)	FSL[3] (Behrens et al. 2007)	N/A
Spherical deconvolution (SD, Tournier et al. 2007)	MRtrix[4] (Tournier et al. 2007)	MRtrix[4] (Tournier et al. 2007)
Persistent angular structure (PAS, Jansons & Alexander 2003)	Camino[2] (Jansons & Alexander 2003)	Camino[2] (Cook et al. 2006)

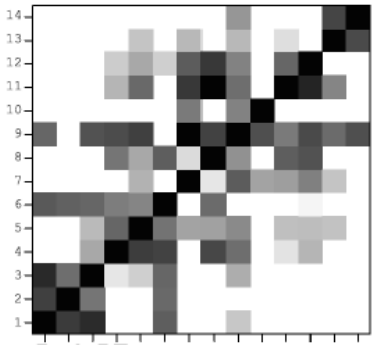
Yo, Anwander et al. MICCAI, 2009.

Representation in a graph structure

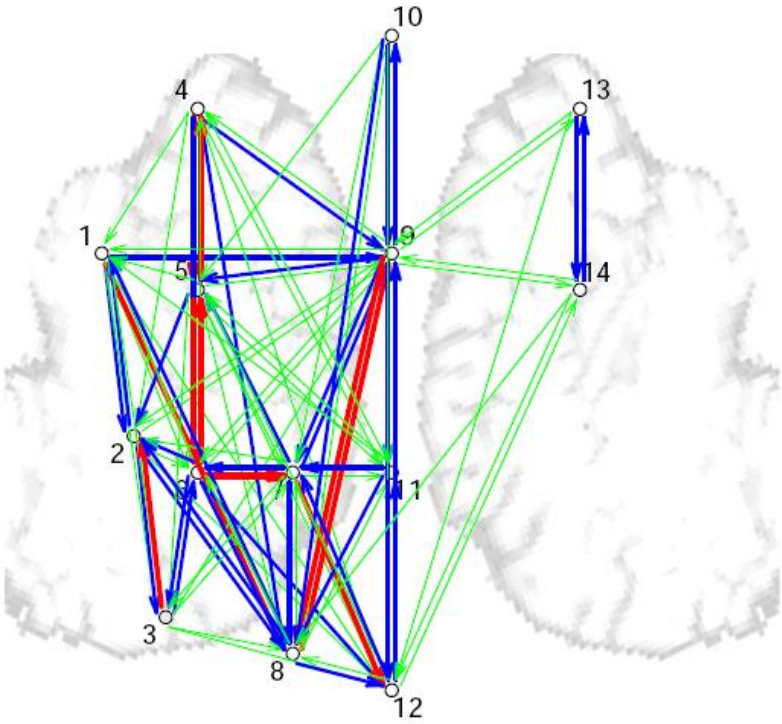
- Selected nb. of seed/target regions



- Connectivity matrix

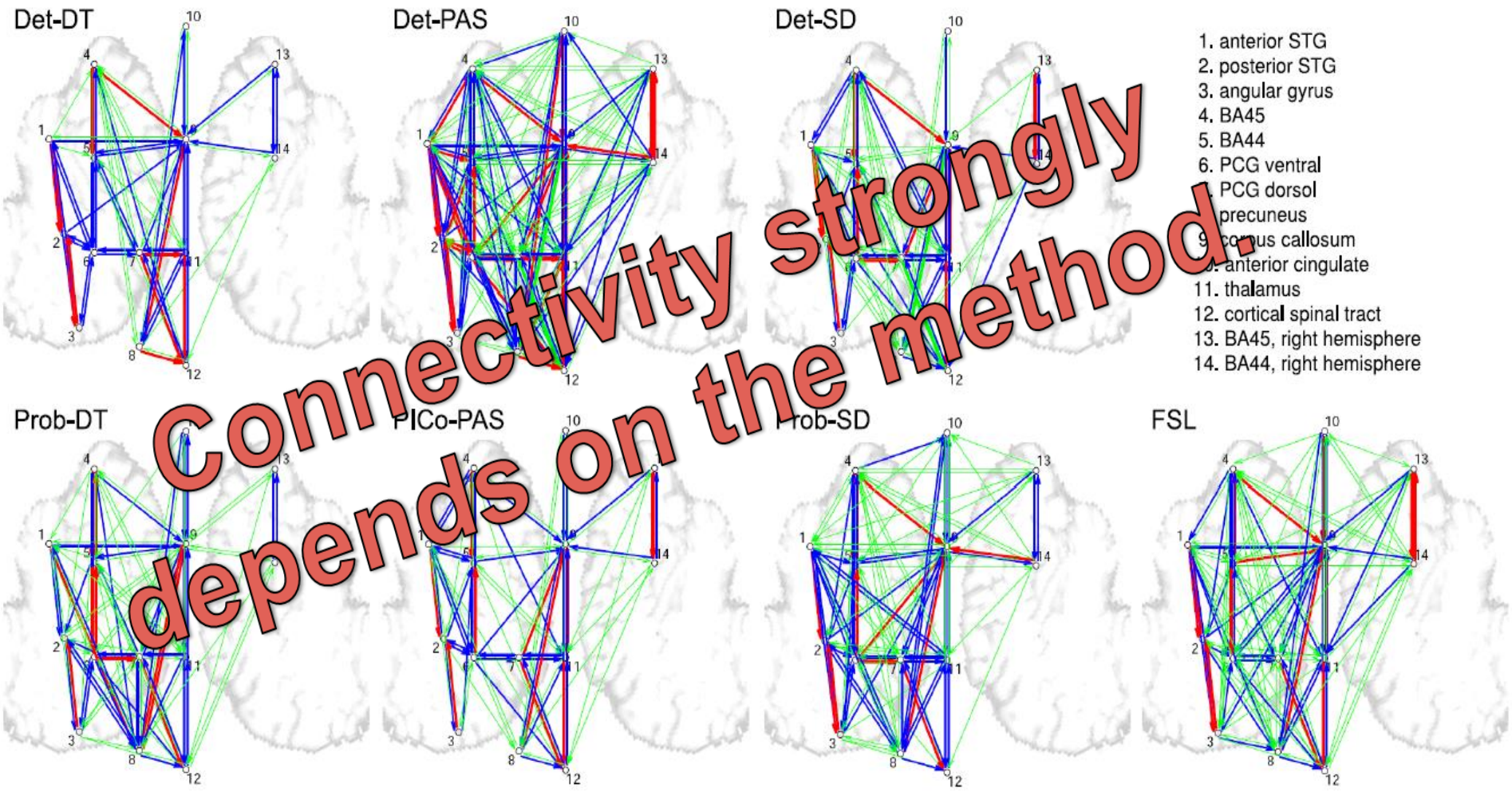


- Representation as connectogram
- Graph based analysis of network properties



Yo, Anwander et al. MICCAI, 2009.

Which of the published algorithms is the best to compute connectivity from diffusion MRI?



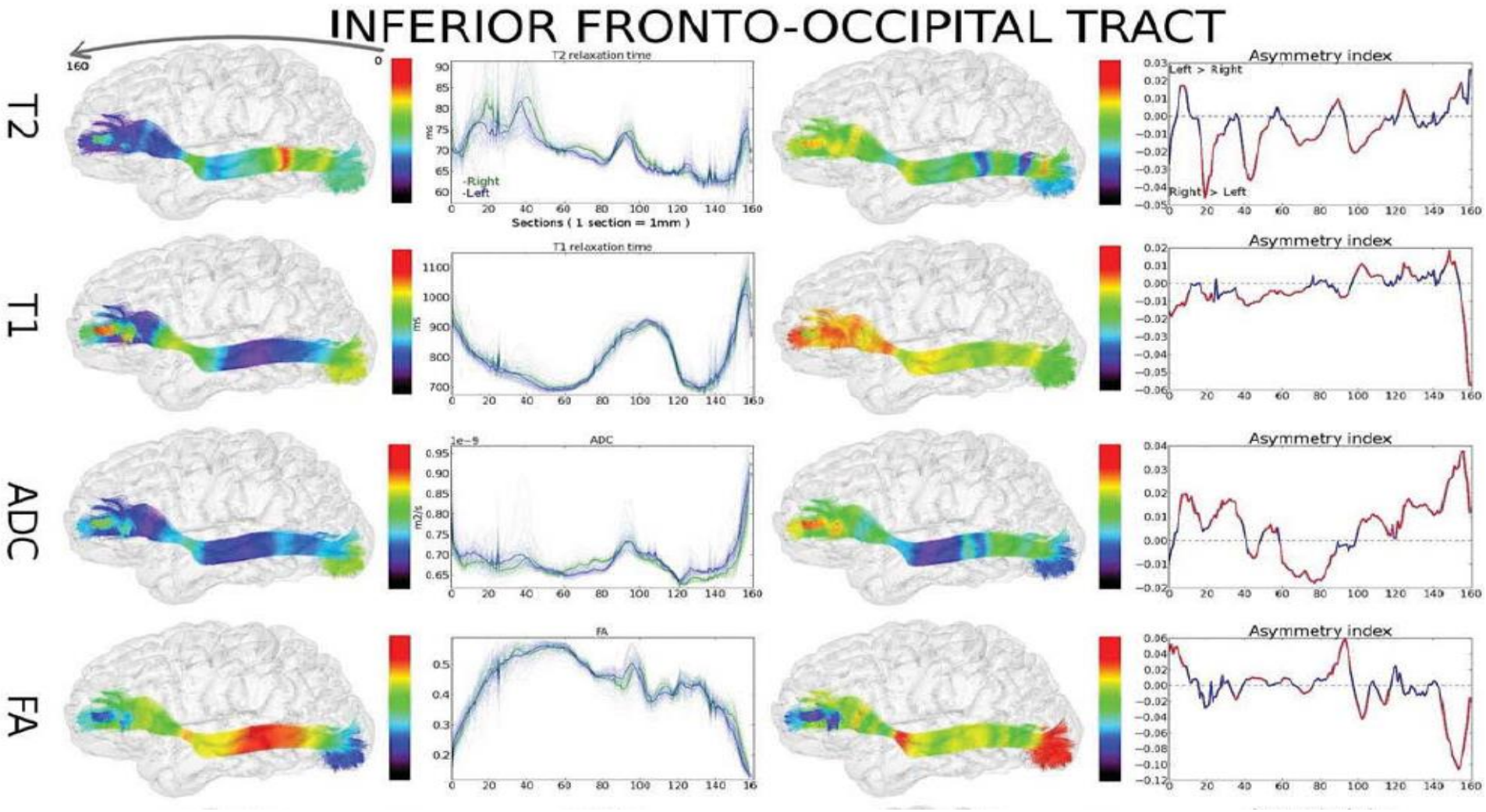
Yo, Anwander et al. MICCAI, 2009.

Robust quantification of connectivity

Information transfer rate and delay is related to quantitative microstructural measures:

- Myelination - T1 relaxation time
- Axonal diameter
- Fiber density
- Length of the connection of the connection

Quantitative T1 & T2 relaxation time (relaxometry)



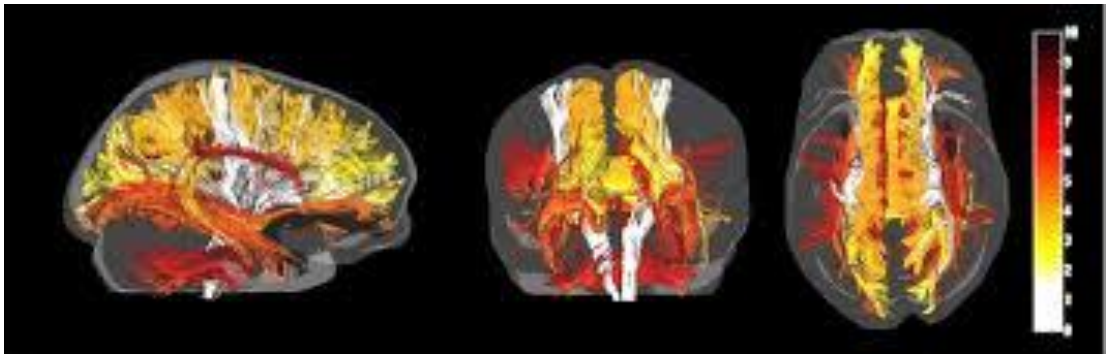
Edge weights for the enriched structural connectome

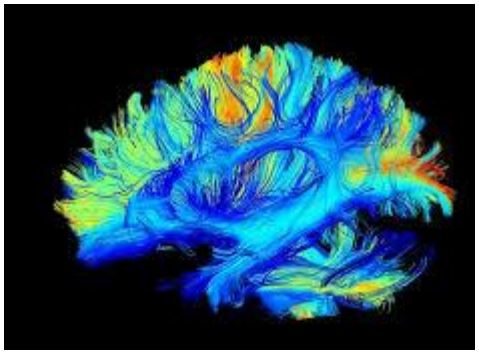
Alice LeBois, PhD 2014

3-Dimensional axon diameter estimation

- 96 directions
- 3 different diffusion times
- 7 b-values for each Δ

Bval	directions
500	8
1000	17
2000	12
3000	13
4000	14
5000	15
6000	17

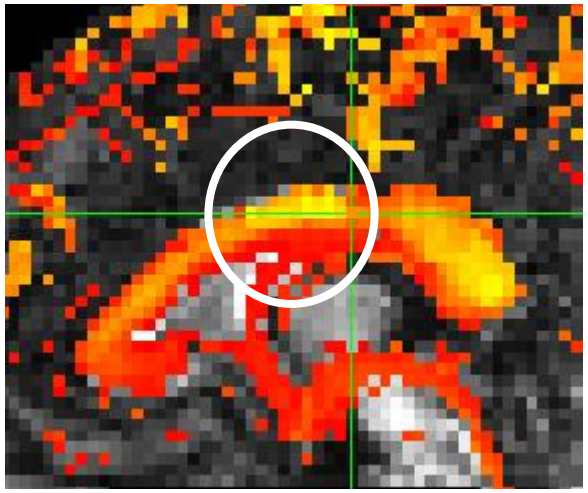


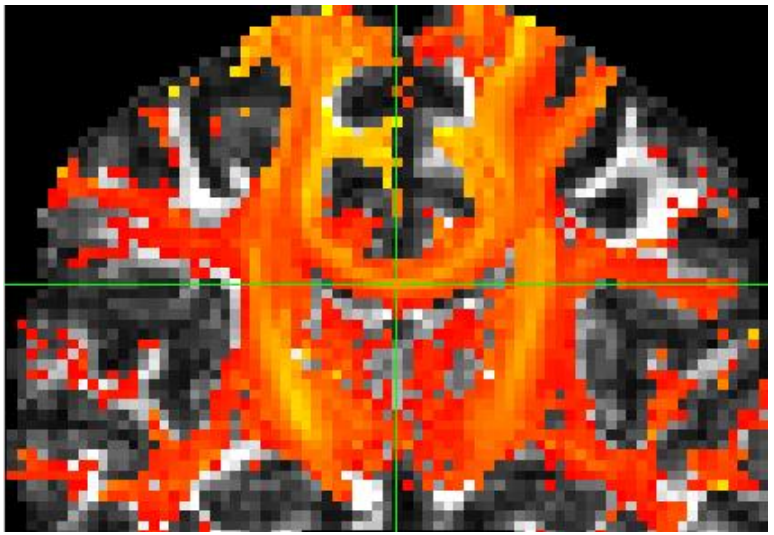


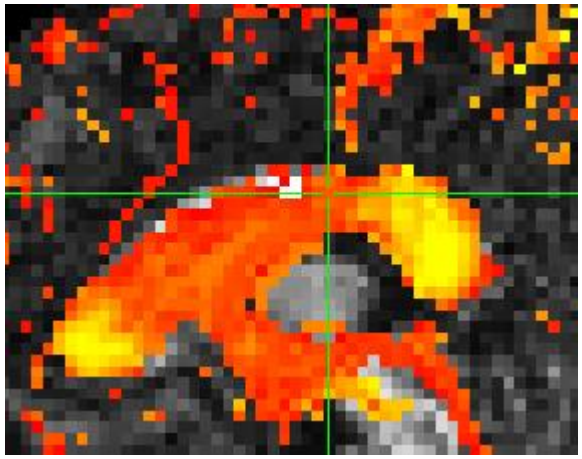
- Fitting of **two distributions**:
- Small axons
- Large axons
- small/large axons ratio variable for different tracts

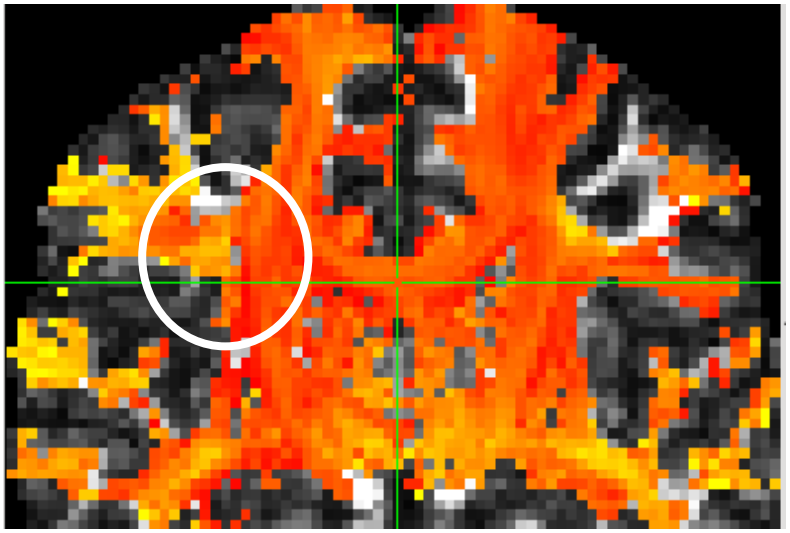
Ben Amitay et al OHBM, 2016

Axon diameter on the "Connectom MRI" with 300 mT/m gradients









- Large axons
- Small axons

Shorter diffusion times!

In collaboration with Yaniv Assaf and Shani Ben Amitay

Take home message

- Diffusion MRI allows us to study the structural connectivity of the brain
- Tractography based parcellation useful for connectome analysis
- Network based analysis captures the complexity of the brain network
- Integration with cognition still challenging

Thank you!

Angela D. Friederici
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Jan Schreiber
Till Riffert
Ralph Schurade
Enrico Kaden
Yaniv Assaf

and you for your attention and questions!

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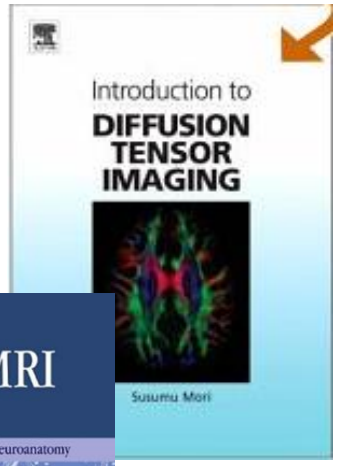
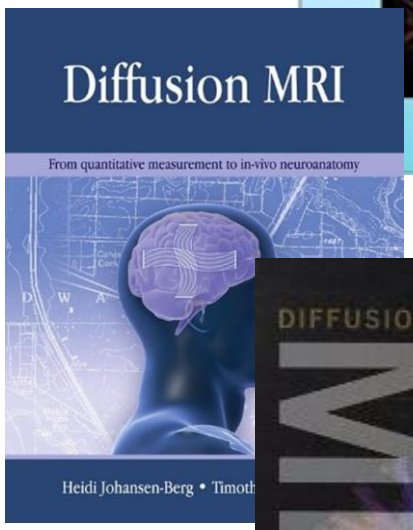
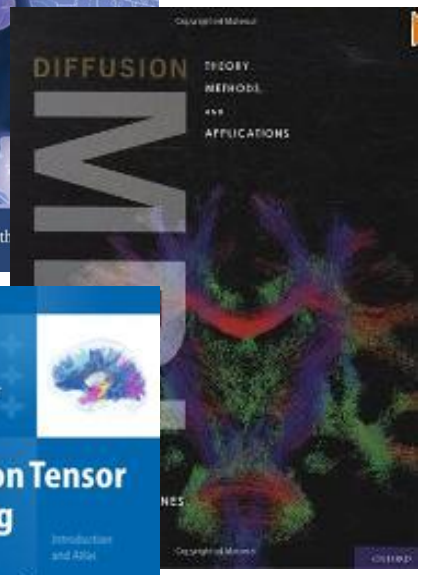
Literature







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- **H. Johansen-Berg and T. E.J. Behrens: "Diffusion MRI"**
- **D. Jones: Diffusion MRI: Theory, Methods, and Applications**
- B. Stieltjes et al. Diffusion Tensor Imaging. Introduction and Atlas
- O. Sporns