The enriched connectome: *From* links between **structural** and **functional** connectivity *to* quantitative plasticity of brain connectivity

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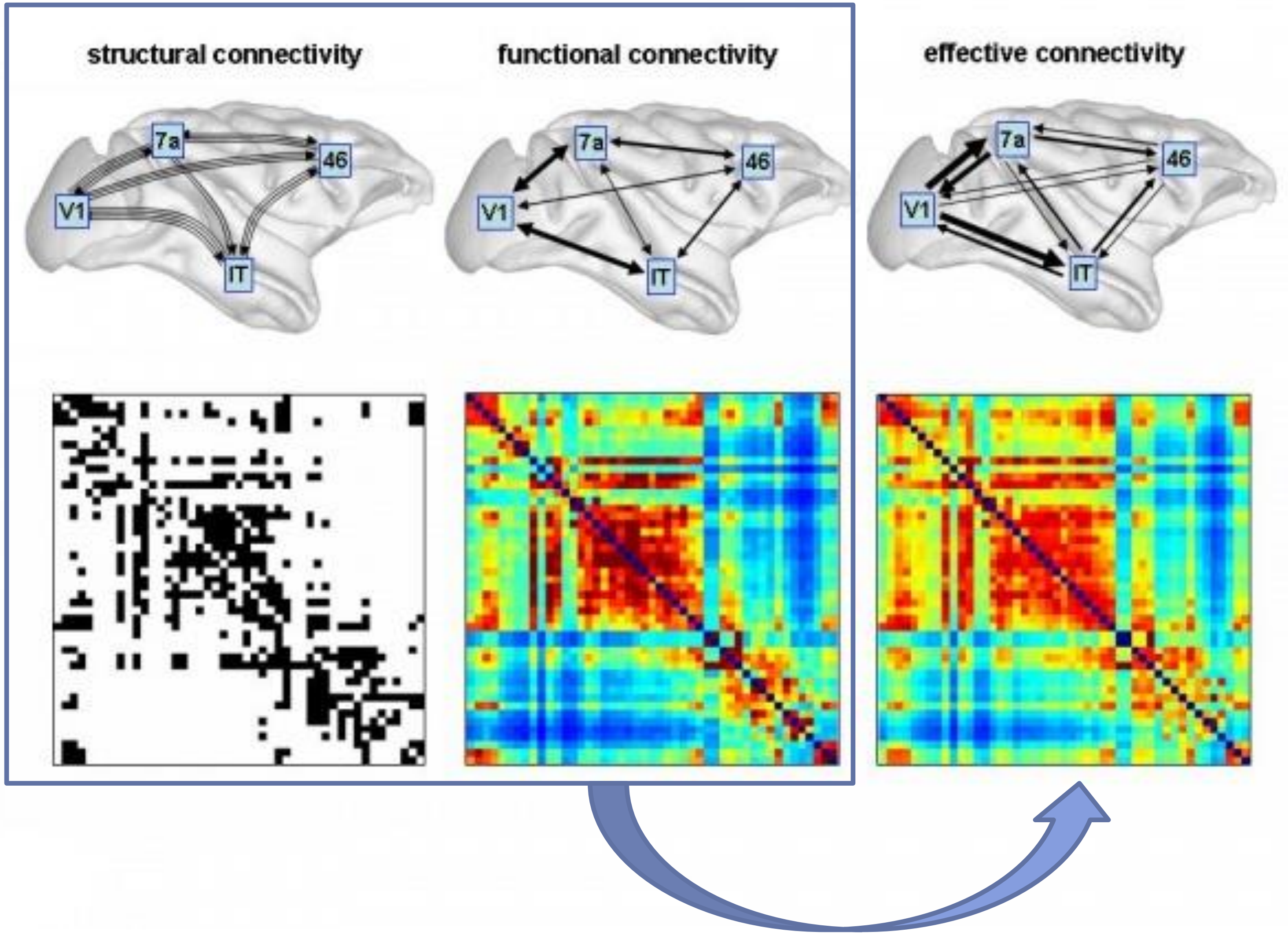
Two ways to measure the humane connectome with (MRI)

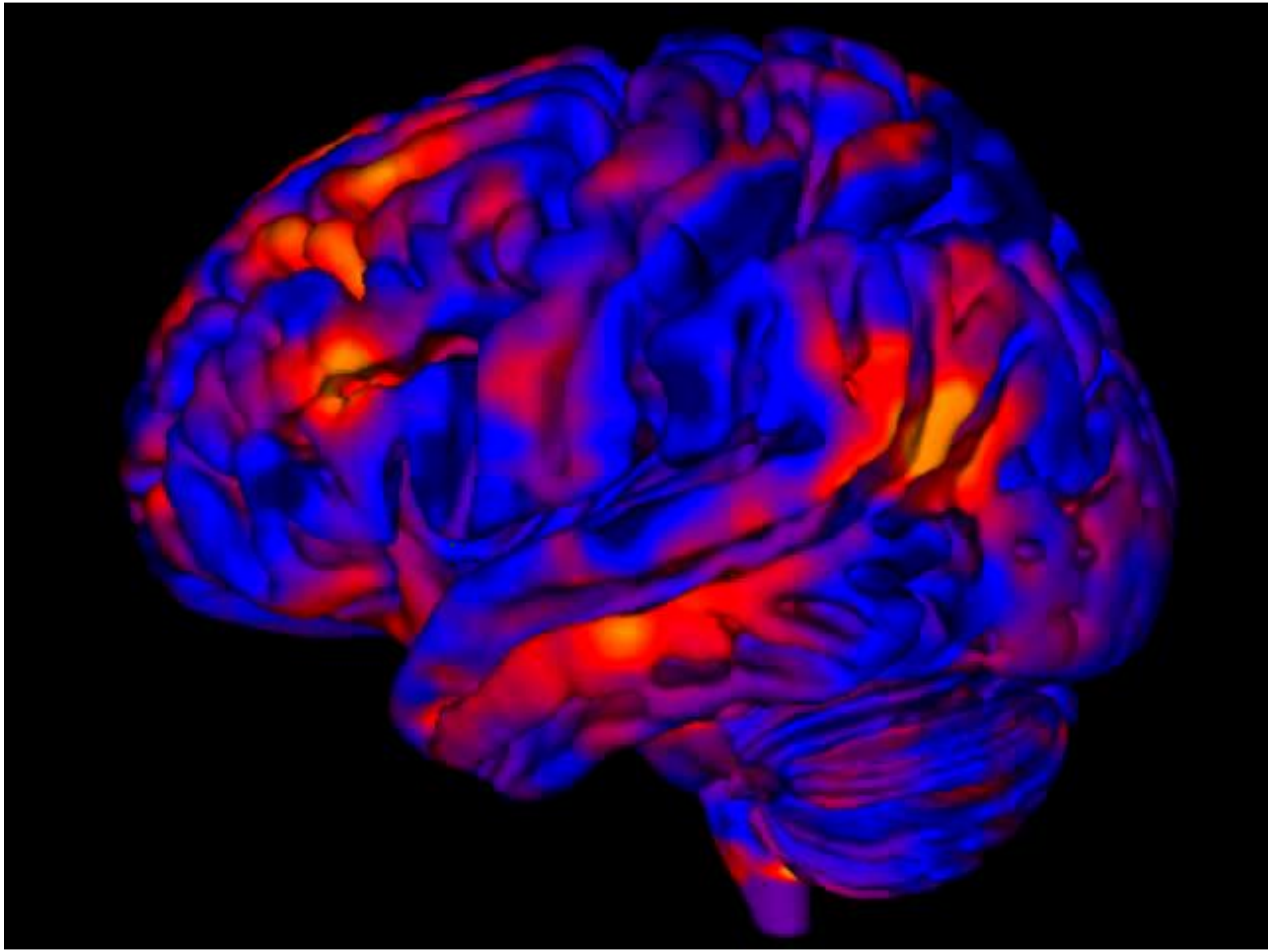
- Based on the brain structure:
  white matter fiber structure
- Based on brain activity:
  symmetric statistical relationship



Sporns Scholarpedia 2007, Sporns Discovering the Human Connectome 2012

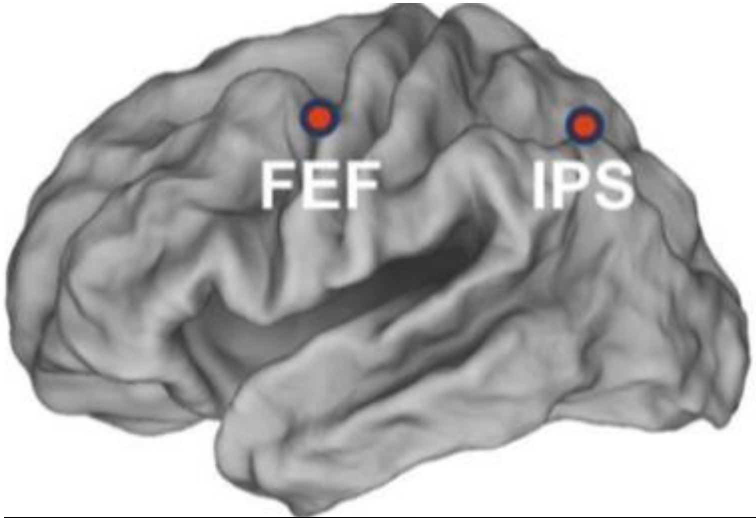
Low frequency brain activity – rs fMRI

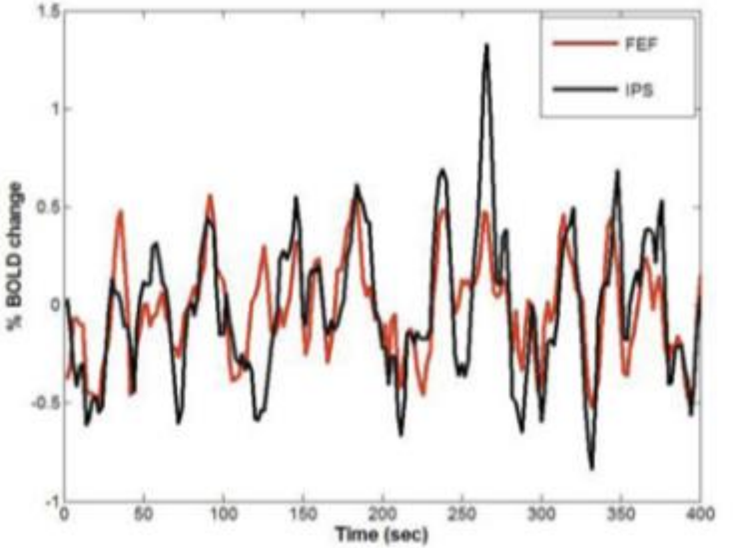
- Hemodynamic signal fluctuations
- Task-free "resting state" fMRI BOLD signal (blood oxygen level dependent)

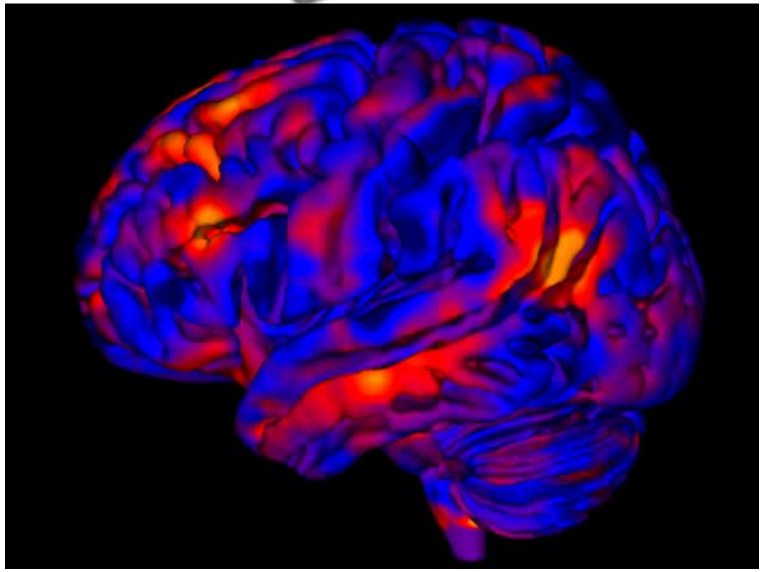


Synchronization of the functional MRI time series

- Statistical dependence:
  - Cross-correlations between nodes
- Example:
  - Seed voxel in the frontal eye field and in the intraparietal sulcus



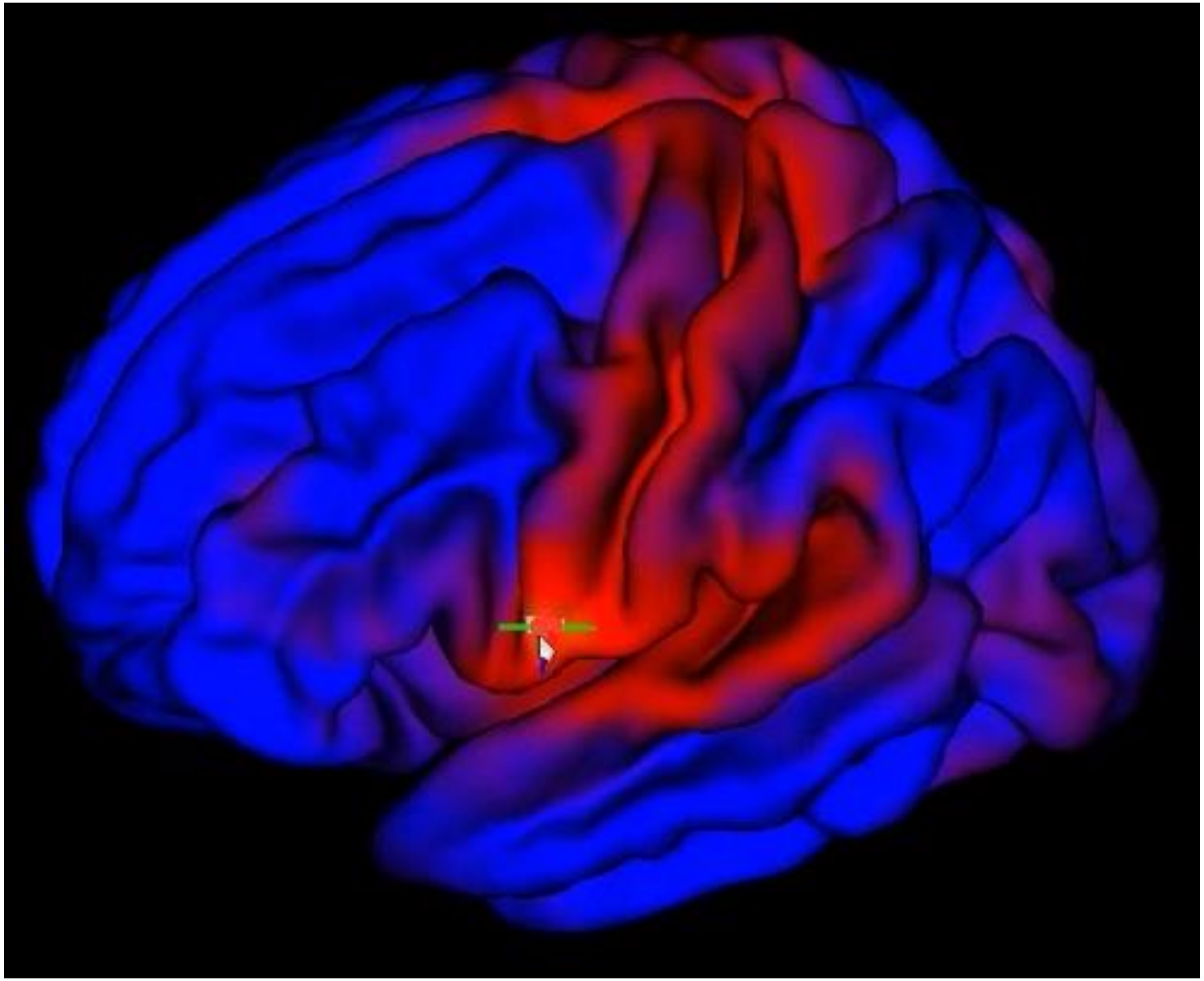




Shimony et al. 2009; Fox – Raichle 2007; van den Heuvel et al. 2010 Raichle, 2011

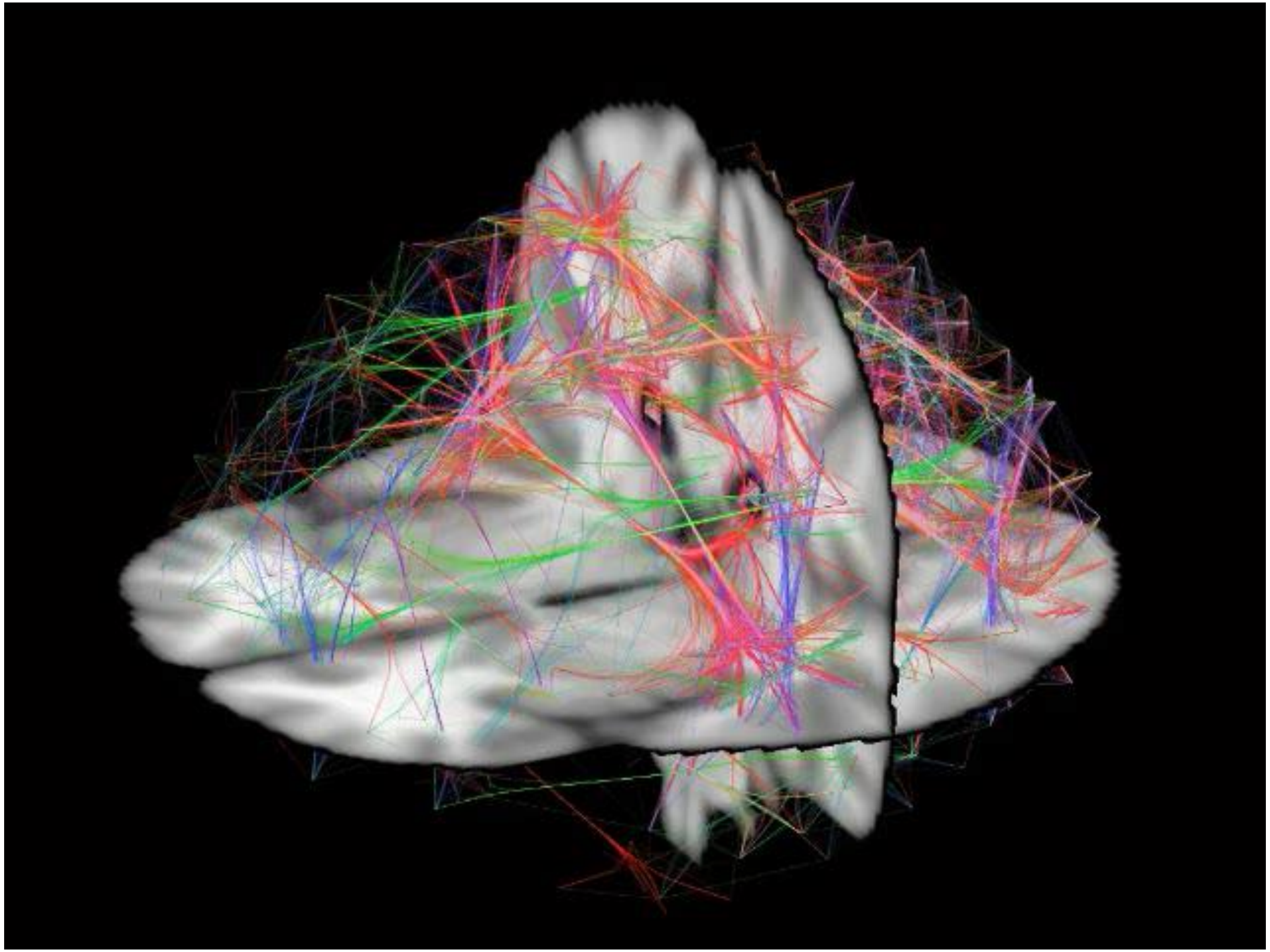
Functional connectivity: Similarity of the fMRI time series

- Correlations of individual seed voxels show synchronized areas
- Statistical dependencies over long sampling epochs (6-10 min)



Graph of connections: The functional **Connectome**

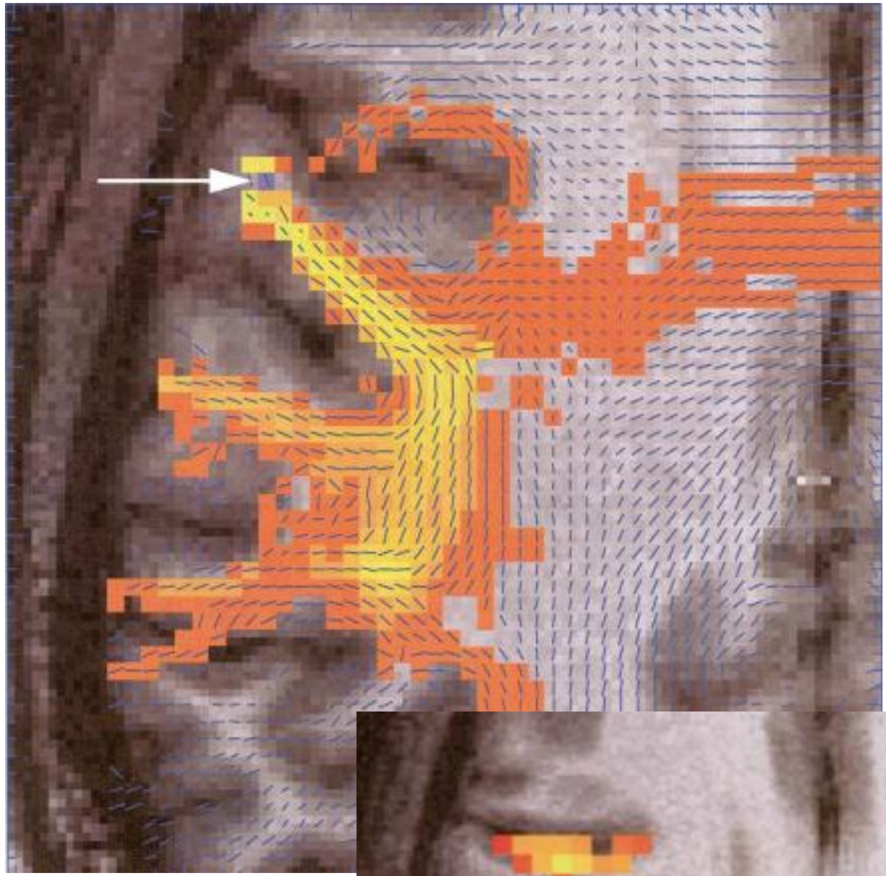
- Network of highly correlated areas
- Link between neural basis of low frequency **spontaneous fluctuations** and **oscillations in power and synchrony of neuronal activity**

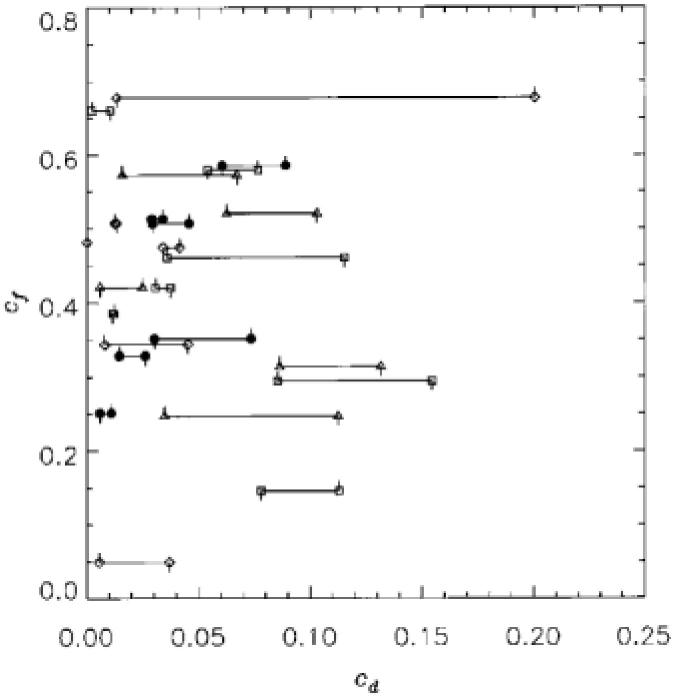


Nir Nat Neurosci 08
Böttger et al. IEEE TVCG 2013

First link between tractography and functional connectivity

- Probabilistic tractography between adjacent gyri (cd)
- Correlation coefficient (*c*f) between connected areas

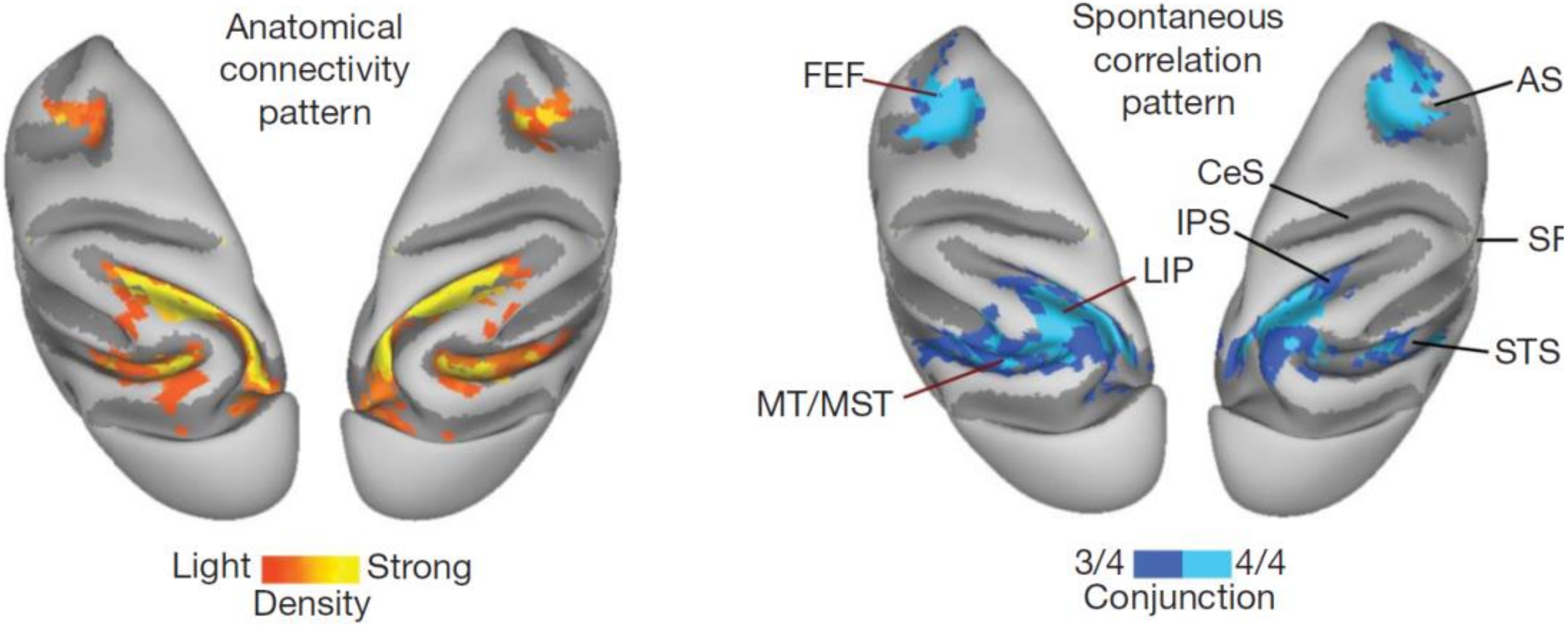




Koch et al. Neuroimage 2002

Structure-function correspondence

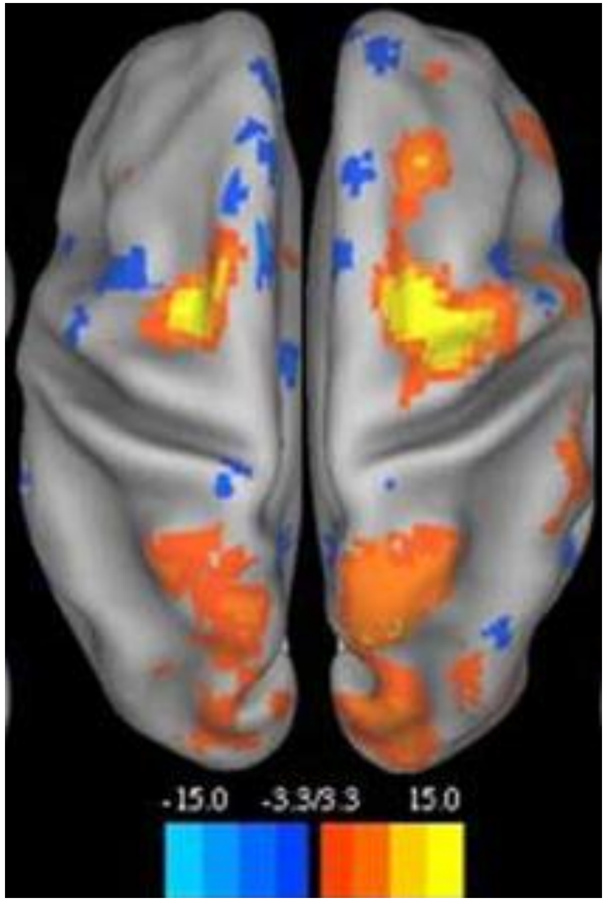
- Macaque monkey: overlap between neuroanatomical connections (tracer injections) and correlations in fMRI signal



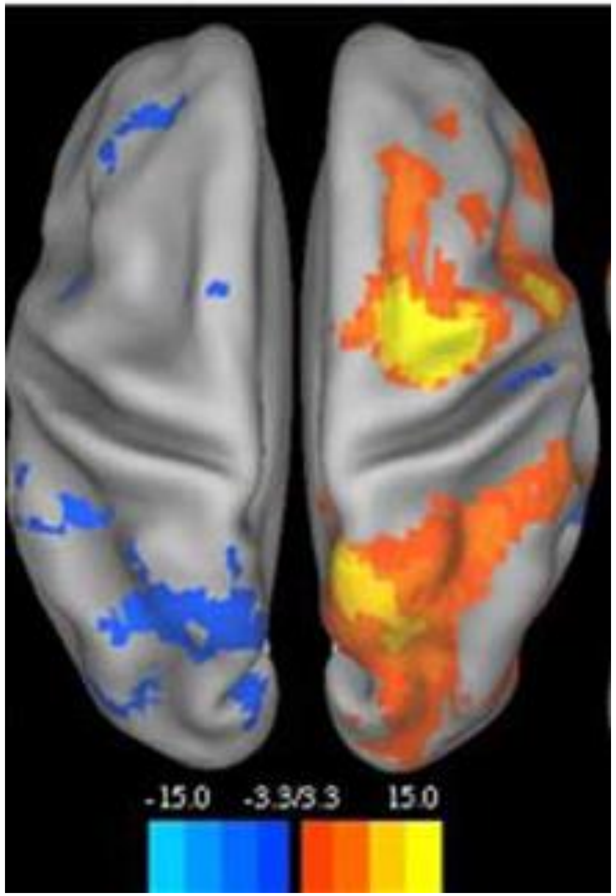
Vincent et al. Nature 2007

Role of the corpus callosum for functional connectivity across hemispheres

- Functional connectivity before and after callosotomy
- Complete sectioning of the corpus callosum of a 6y old child
- Z-score of the correlation map
- Seed in the right frontal eye field
- Lost positive functional connectivity in both hemispheres



before



after

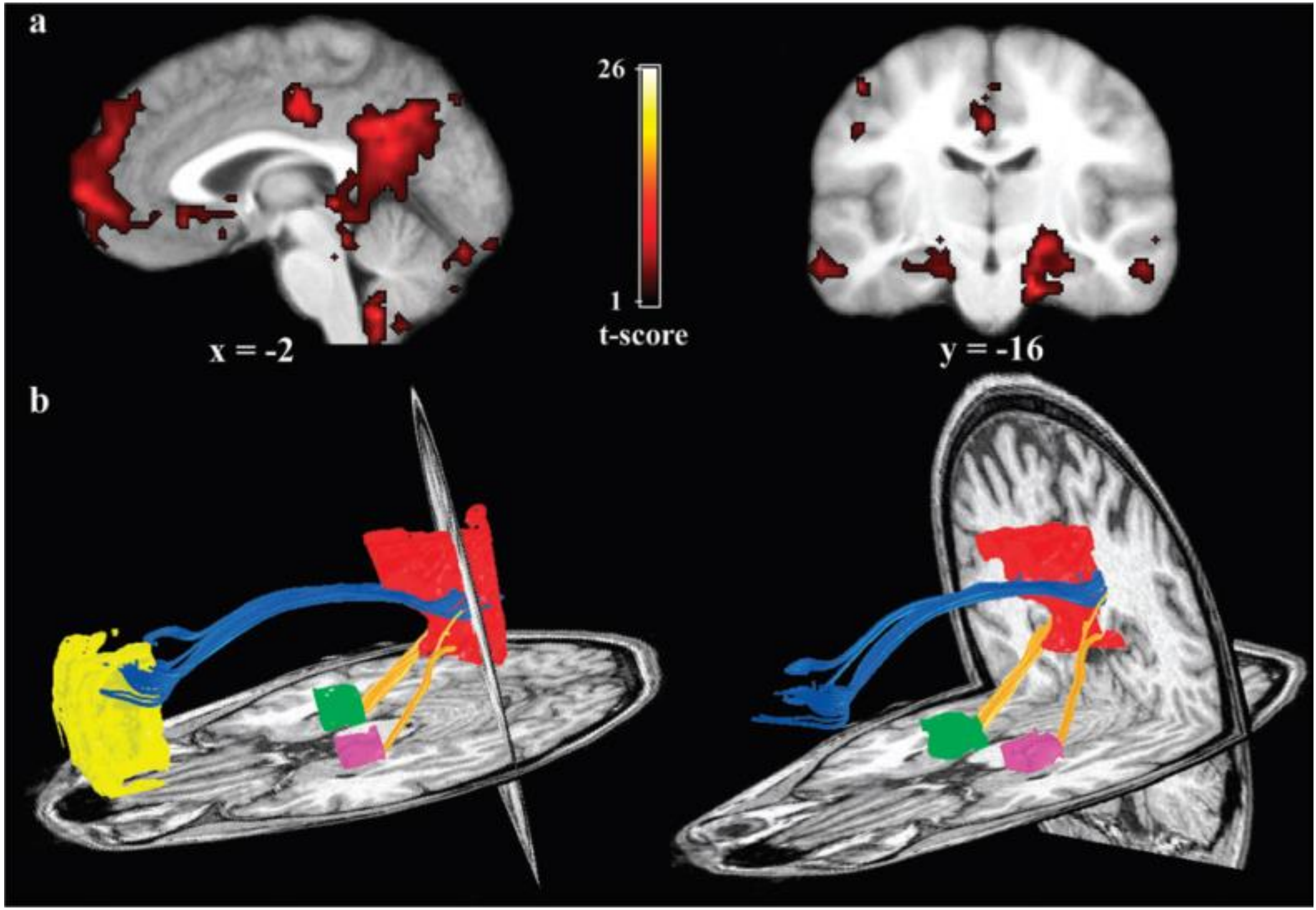
Johnston et al. J Neurosci 2008

Correspondence with tractography

Tractography of the cingulum in the default mode network

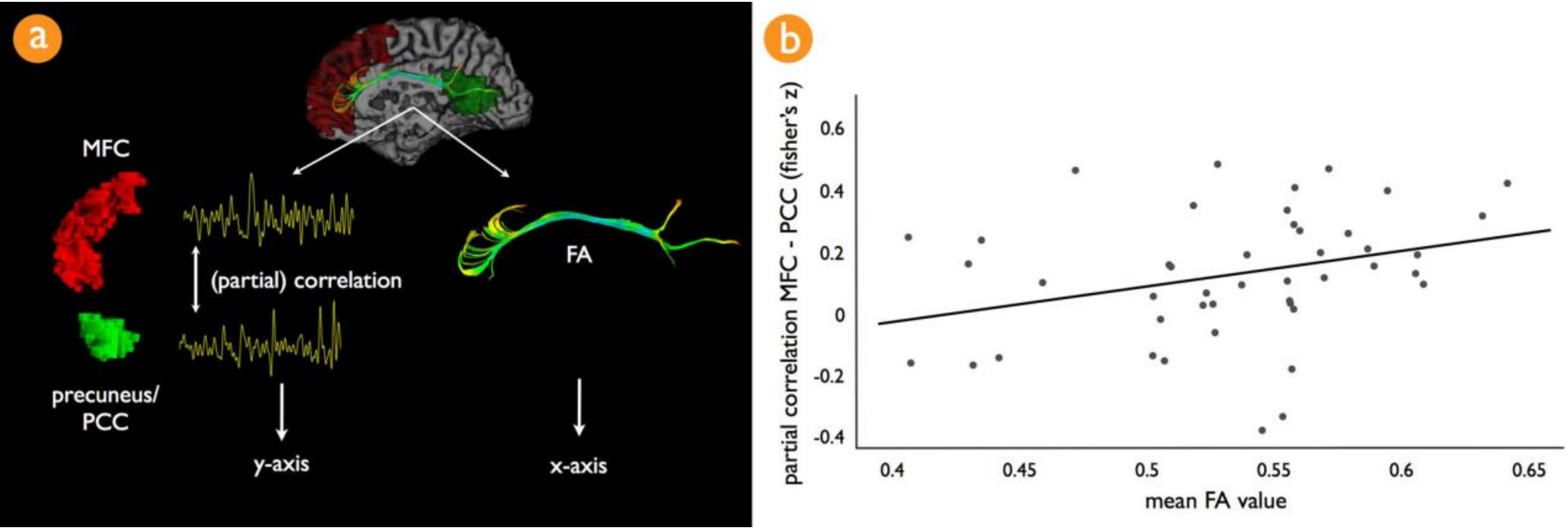
- Resting-state functional connectivity can be decomposed into networks

- Structural connectivity in the default mode network corresponds to the cingulum bundle



Greicius et al. Cereb Cortex 2009

Microstructural organization of the cingulum tract



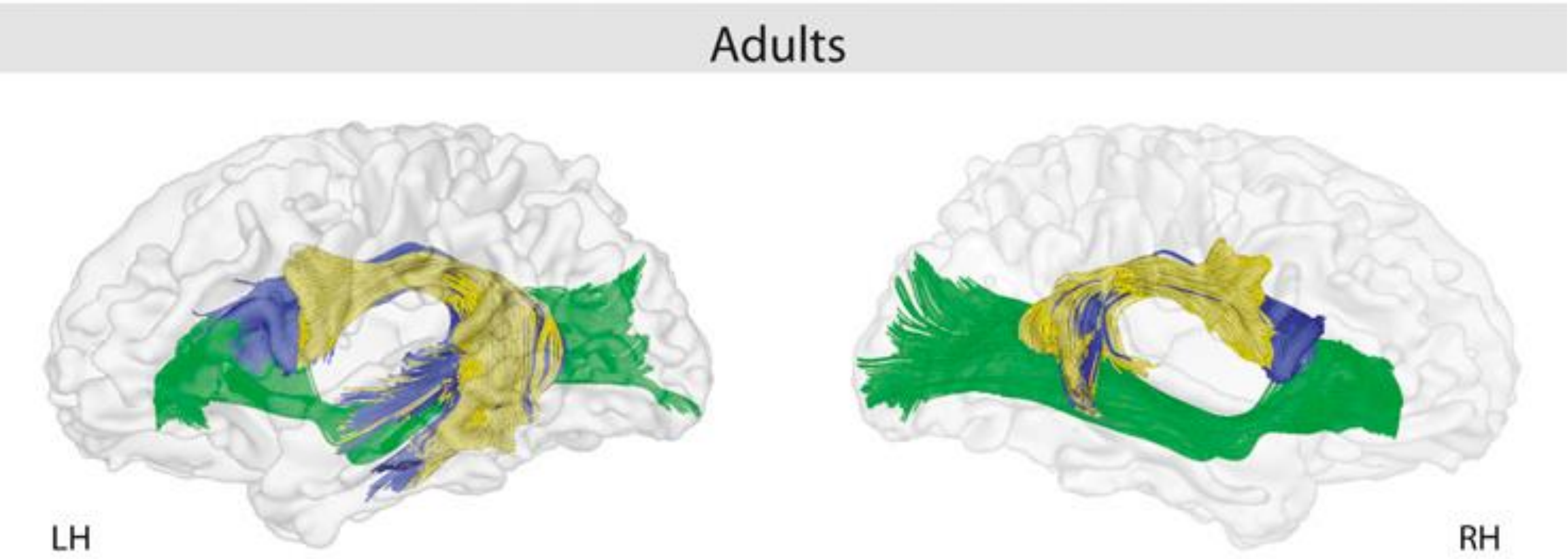
- Association between the level of default mode functional connectivity and the microstructural organization of the cingulum tract.

van den Heuvel et al J Neurosci 2008

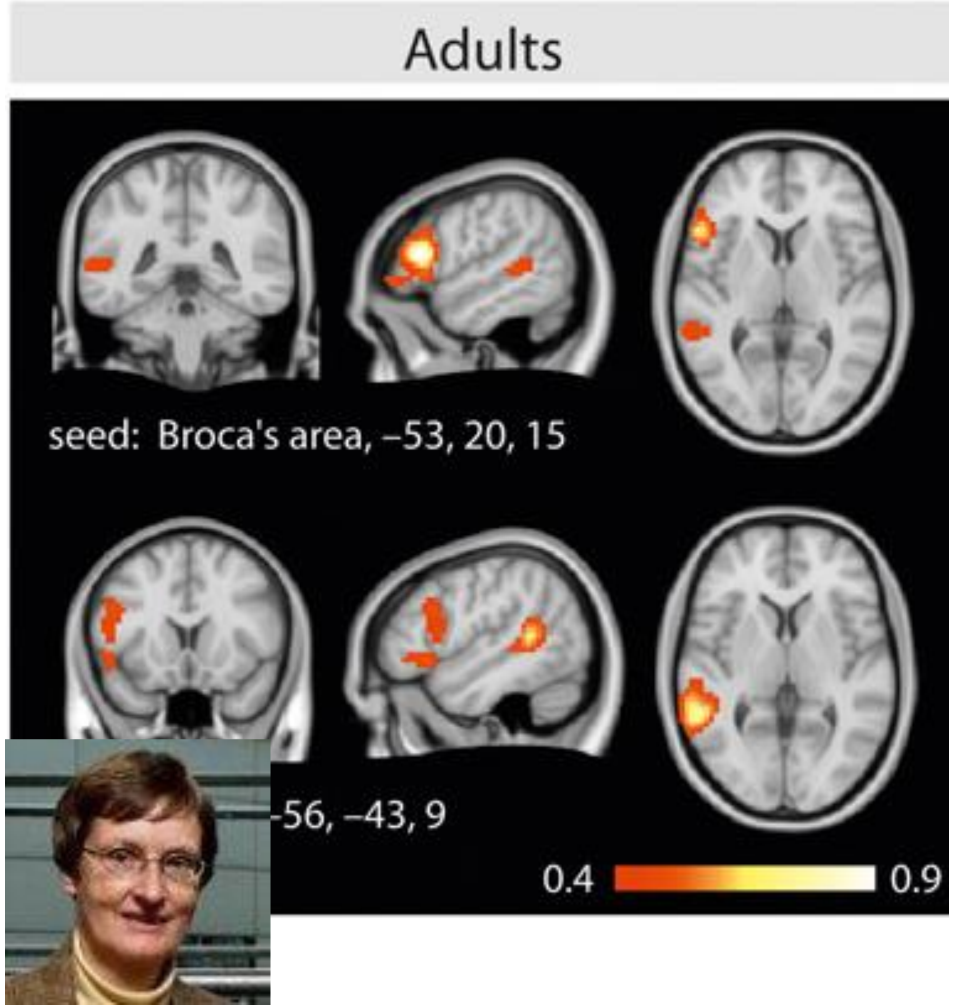
Development

of functional and structural networks

Development: from inter-hemispheric to intra-hemispheric connectivity

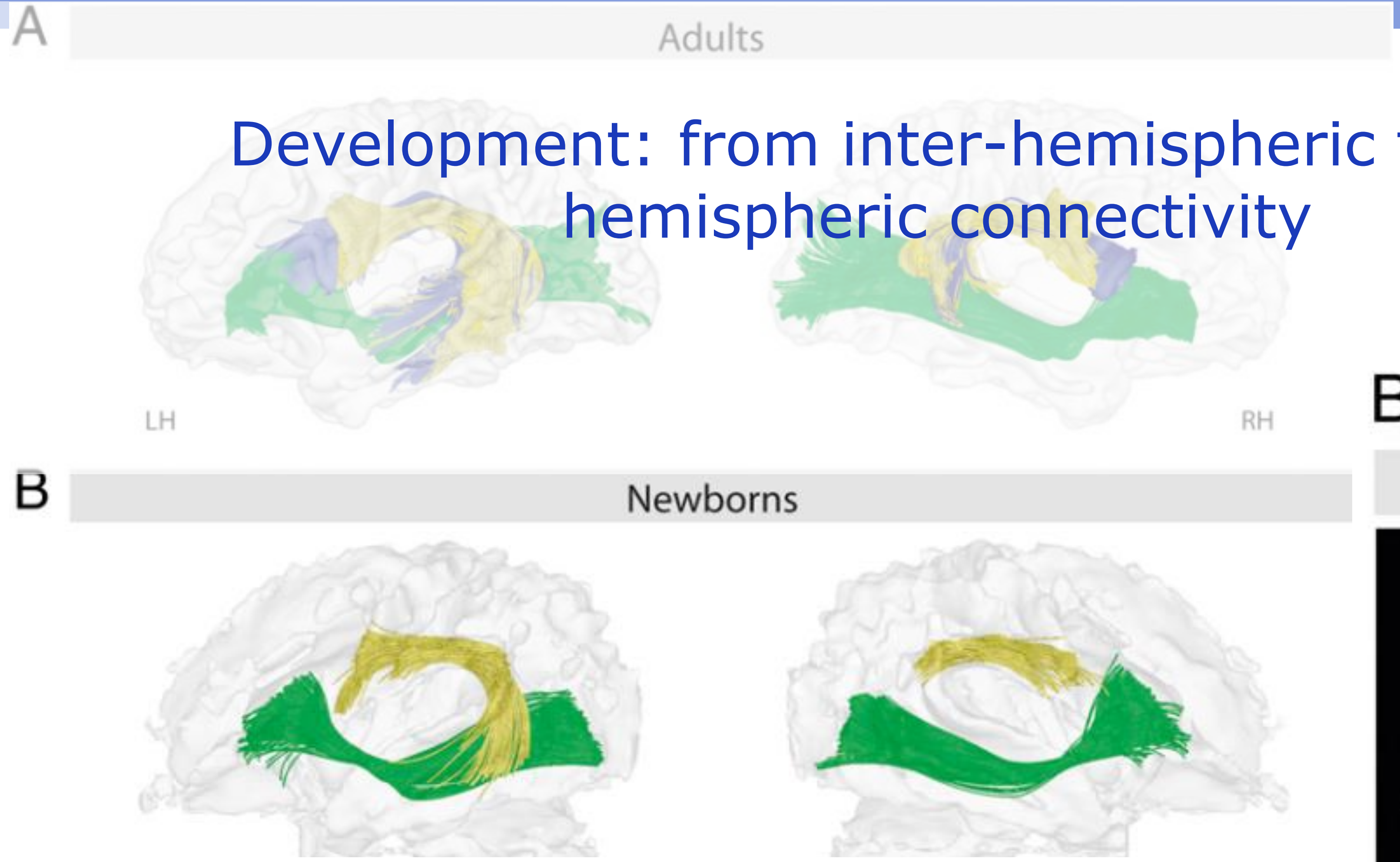


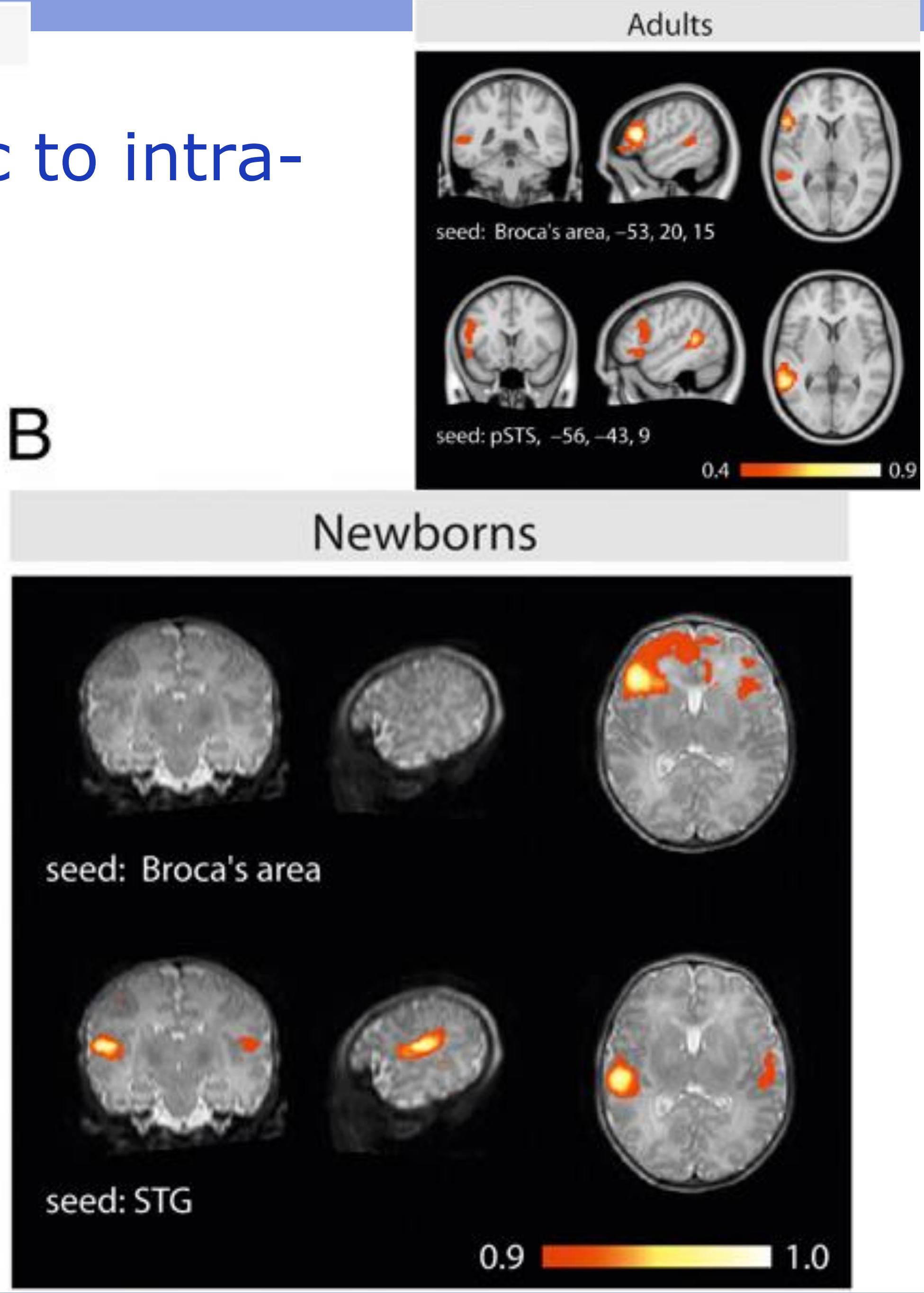
- Strong intra- and interhemispheric connections in the adult language network
- Diffusion MRI tractography and seed based resting state correlations



Perani et al. PNAS 2011, G. Lohmann

Development: from inter-hemispheric to intra-hemispheric connectivity



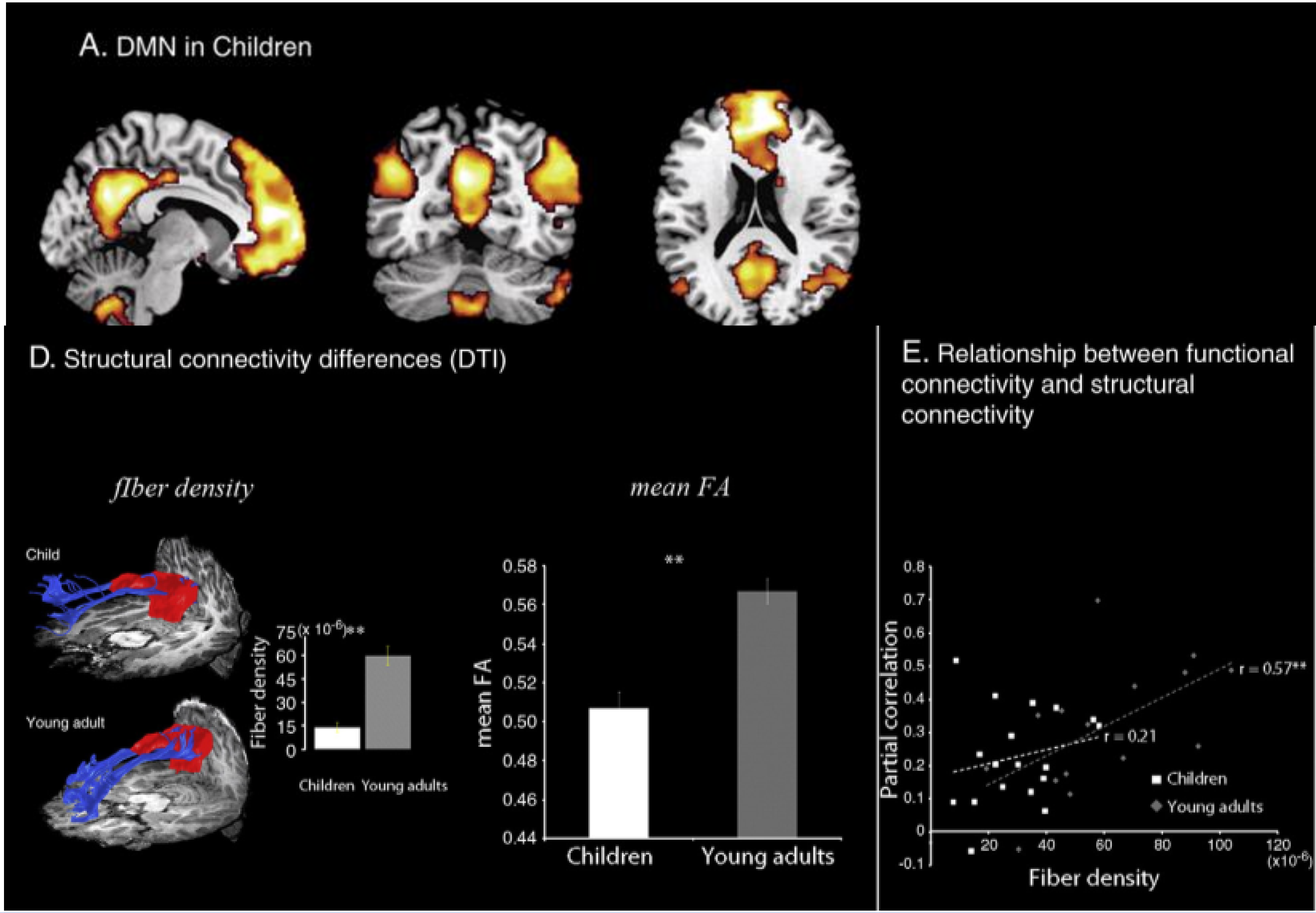


- In newborns we find only inter-hemispheric connections between the language regions
- The network of connections is molded from the external world during development

Perani et al. PNAS 2011

Development of the default mode network (DMN)

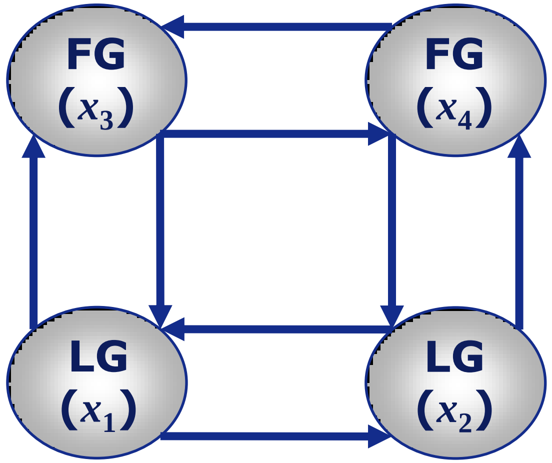
- PCC-mPFC connectivity:
  - most immature link
  - microstructural differences
- Funct. connectivity to temporal lobe mature but not the structural connectivity



Supecar et al. Neuroimage 2010

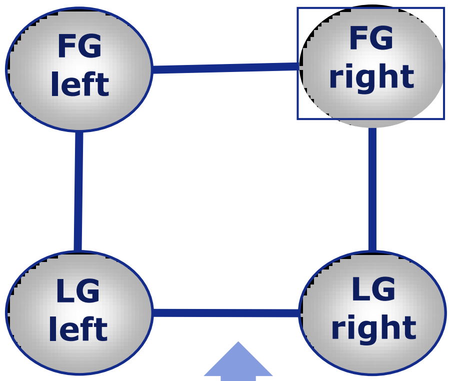
Quantification of Connectivity – Use in DCM

DCM Structure

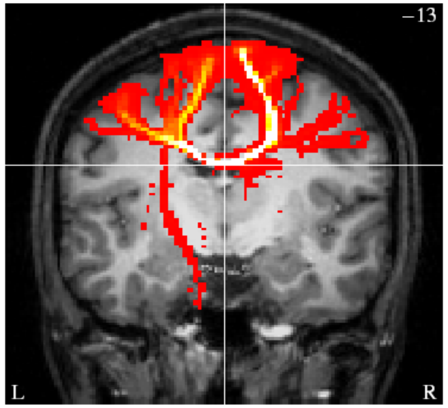


Effective connectivities are estimated using Bayesian inference.

Anat. Connectivity



Anatomical connectivity is not equivalent to effective connectivity, but quantifies the **potential for information transfer**



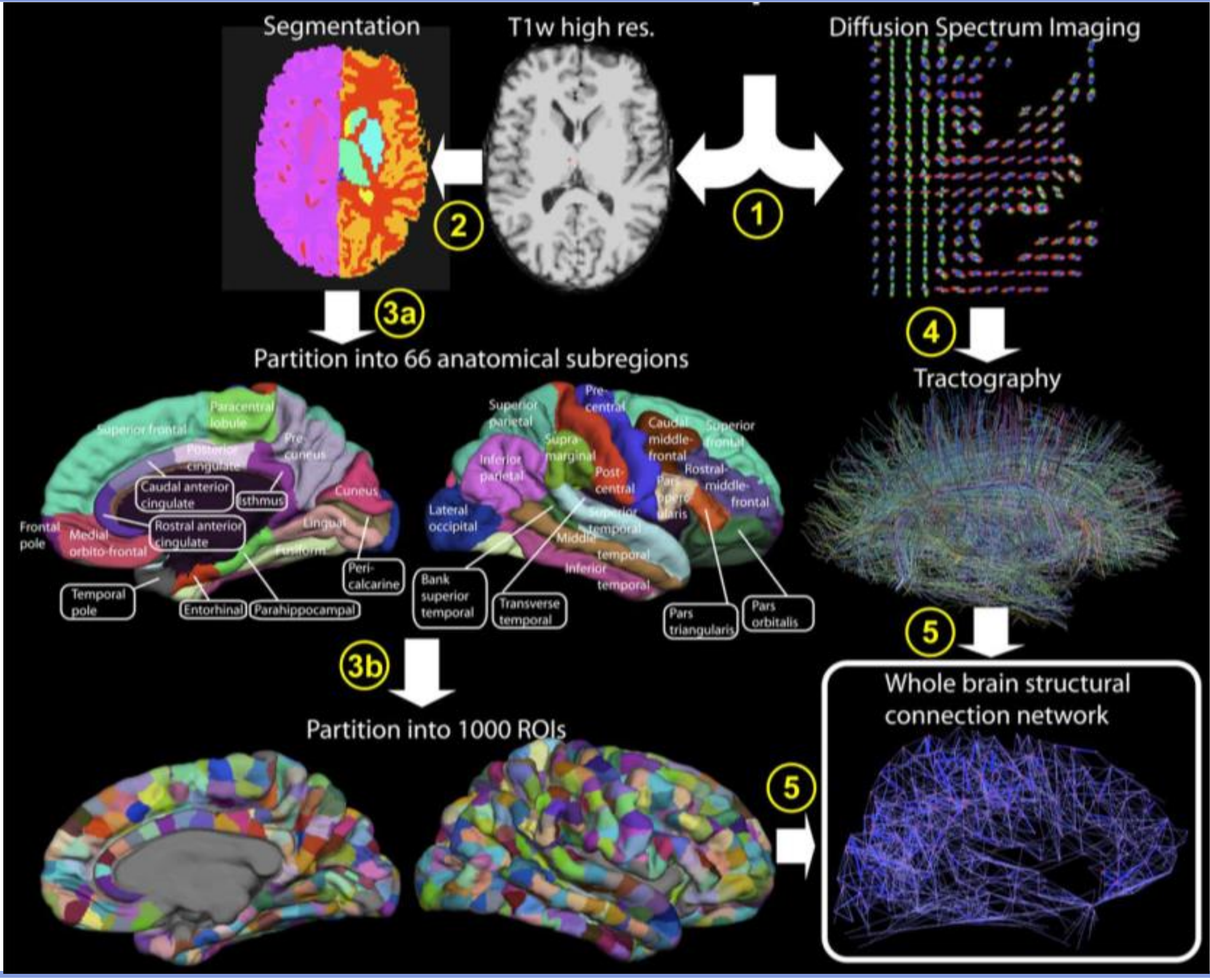
Tractography

Stephan et al. Neuroimage 2010; TR Knösche

From networks to connectomes

Measuring the human connectome in vivo

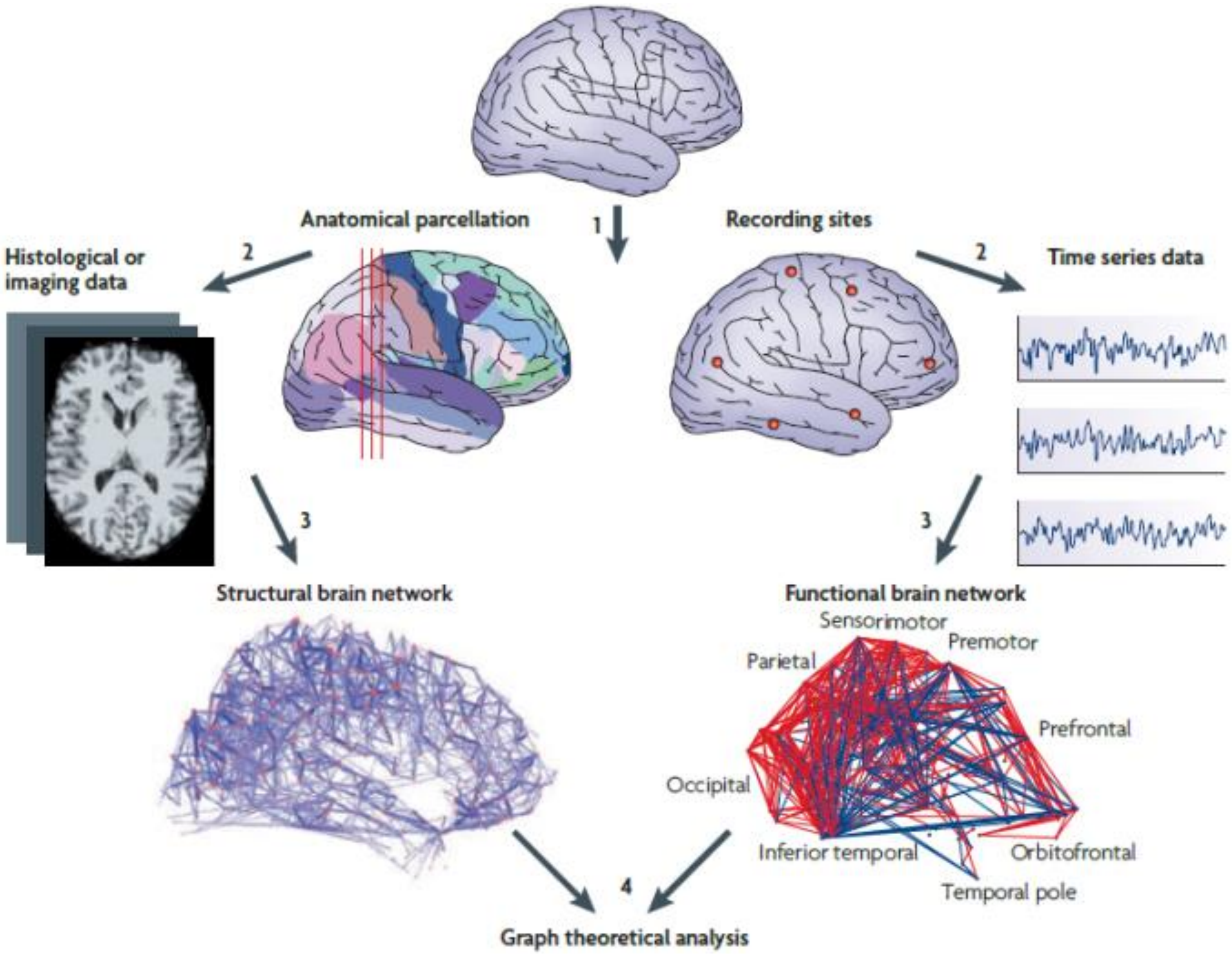
- Segmentation
- Parcellation
- Subdivision
- Tractography
- Represent as graph:
  - as a connectome



Hagmann et al. PLoS Biol 2008

Analysis of structural and functional systems

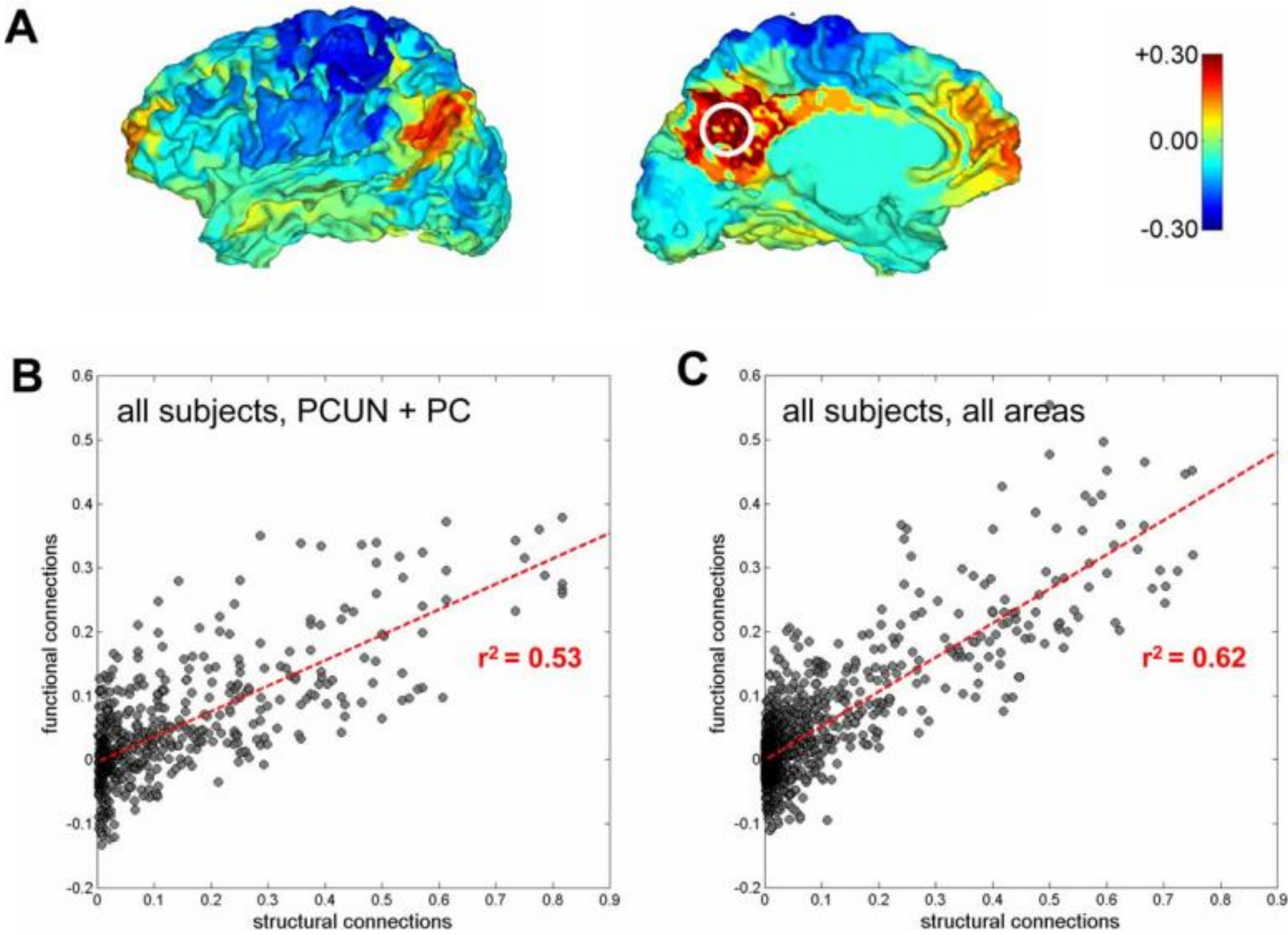
- Whole-brain structural networks derived from diffusion MRI and functional Networks
- Compute functional and structural connectivity from the same parcellation
- Comparison in the same individuals
- Individual voxels or parcellated regions



Bullmore and Sporns, Nat Rev Neurosci. 2009

Comparison of structural and functional connectivity

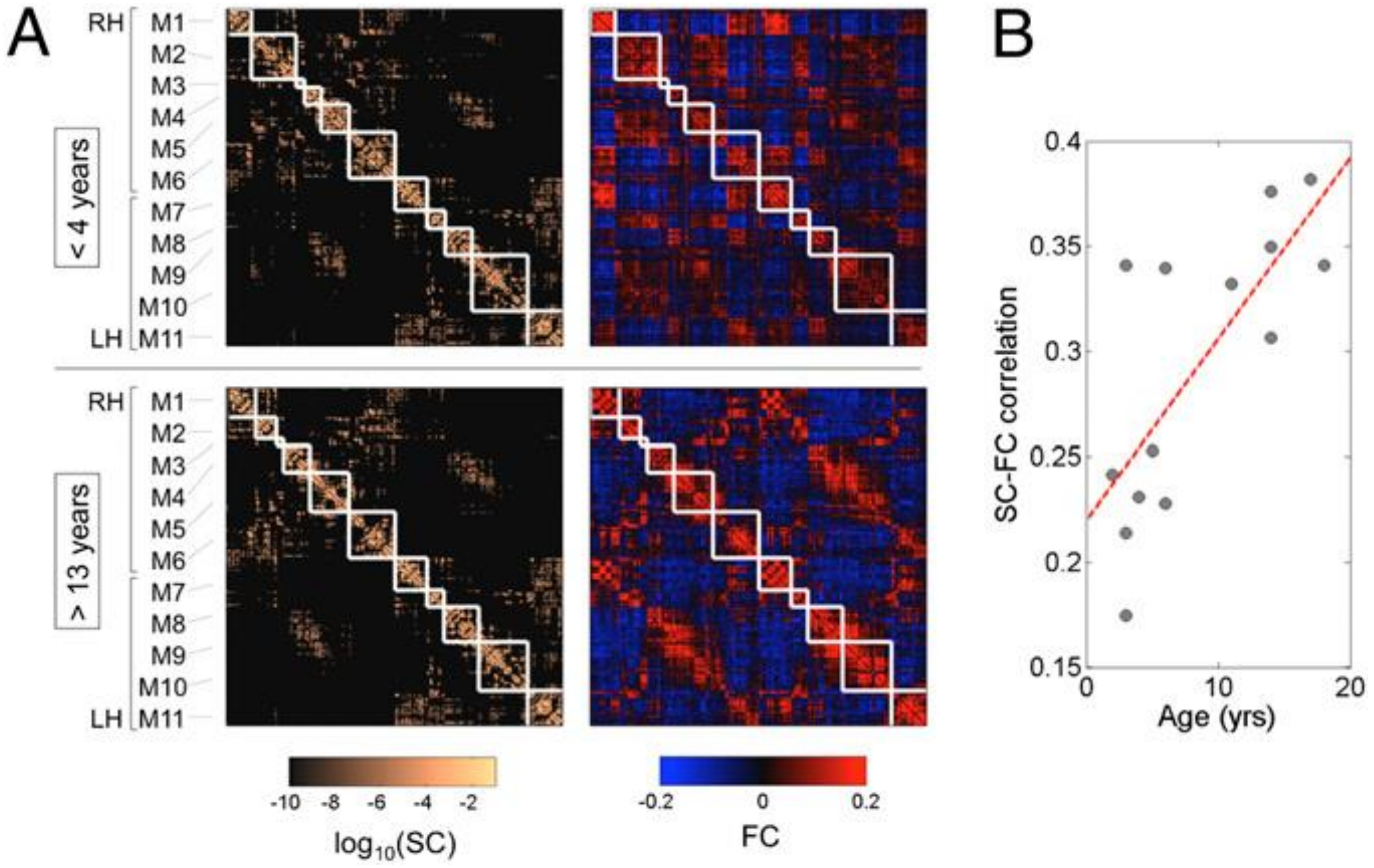
- functional correlations from resting state fMRI
- structural and functional connections of the precuneus and posterior cingulate cortex
- all anatomical subregions in both hemispheres.



Hagmann et al. PLoS Biol 2008

Structural connectivity – functional connectivity correlations in development

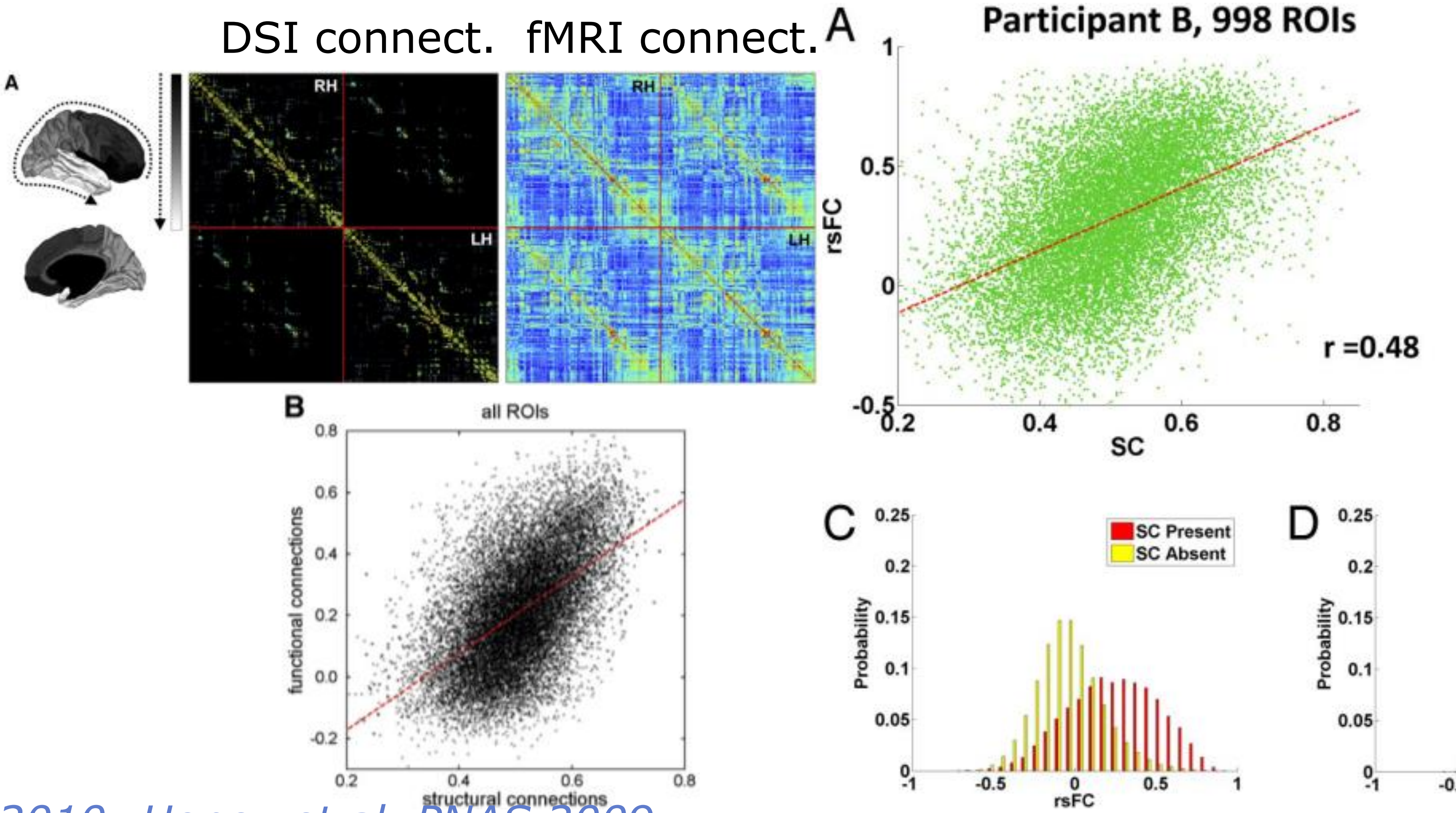
- Strengthening of structural pathway in line with changes in functional interactions.
- Positive correlation between structural and functional connectivity
- Relationship strengthened with age
- White matter connectivity play an important role in creating brain-wide coherence and synchrony



Hagmann et al. PNAS 2010

Structural and functional connectivity matrices

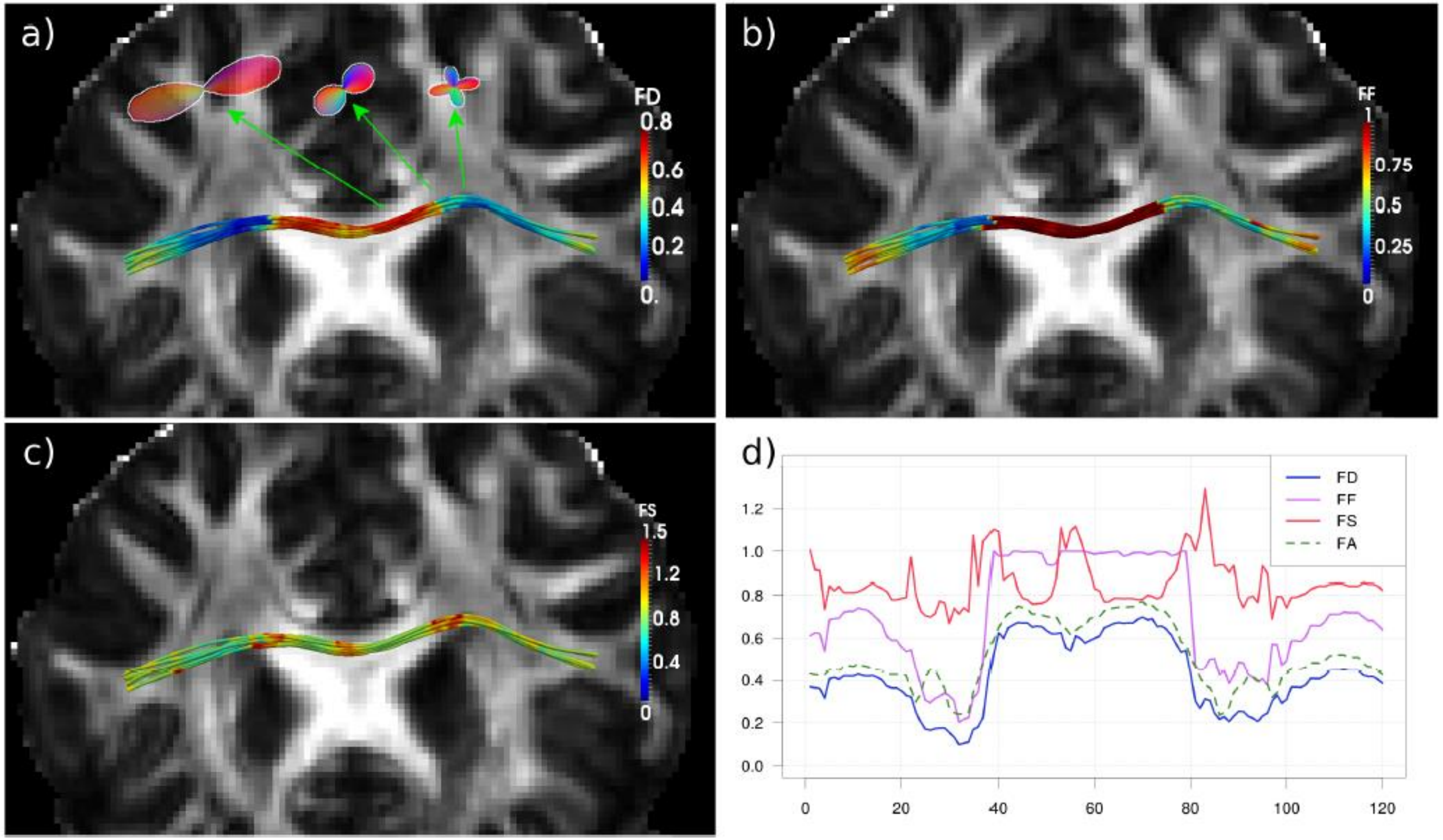
- Significant relationship between structural and functional connectivity
- Right: structurally unconnected (SC absent) regions show low and negative functional connectivity (FC)



Honey et al. Neuroimage 2010; Honey et al. PNAS 2009

Enrich the structural connectome by quantitative MRI

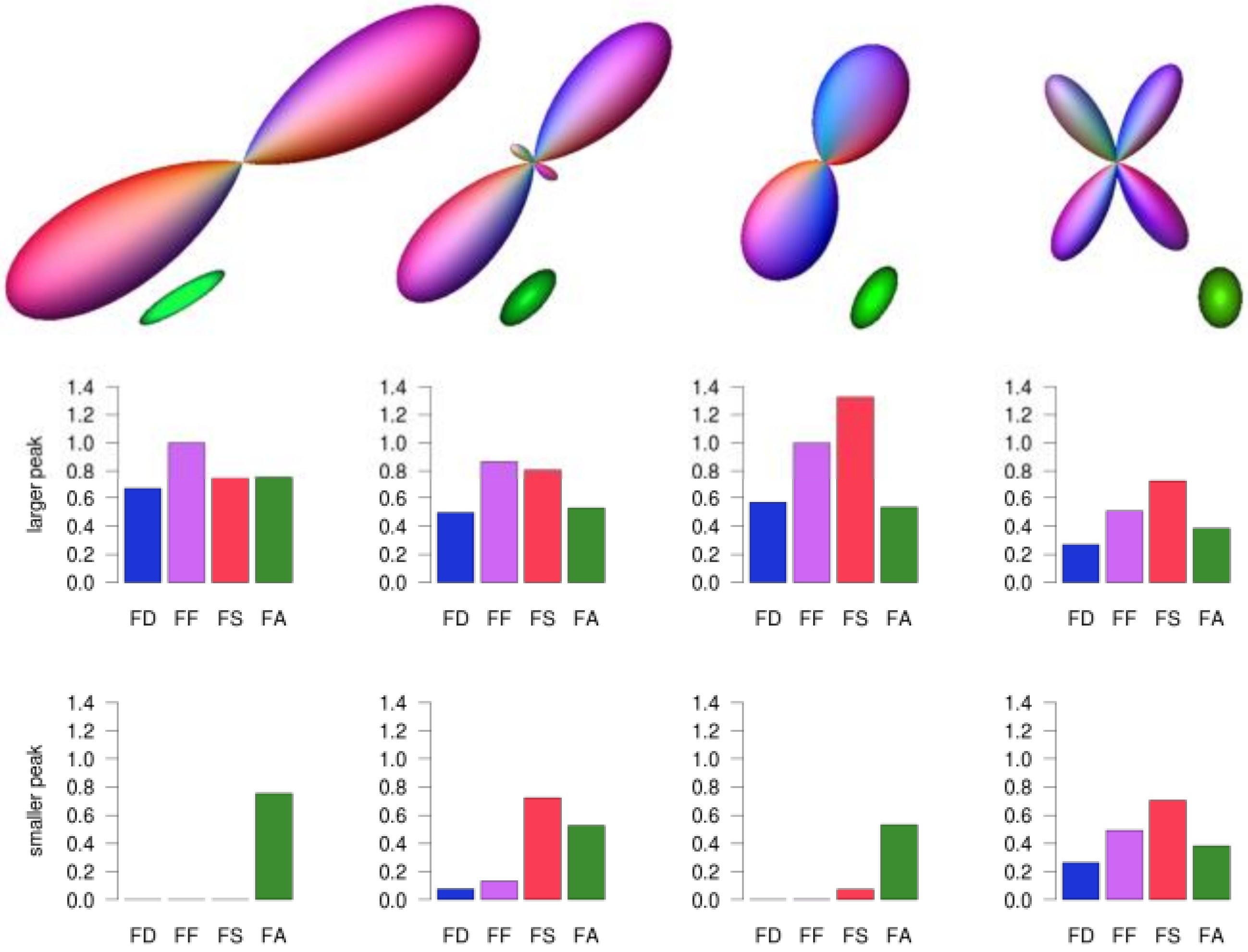
Mapping of crossing fiber parameters



FD: fiber density, FF: fiber fraction, FS: fiber spread

r et al. Neuroimage 2014

Additional microstructural parameters

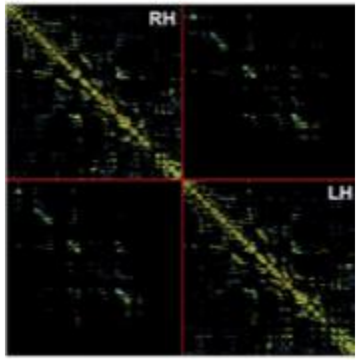


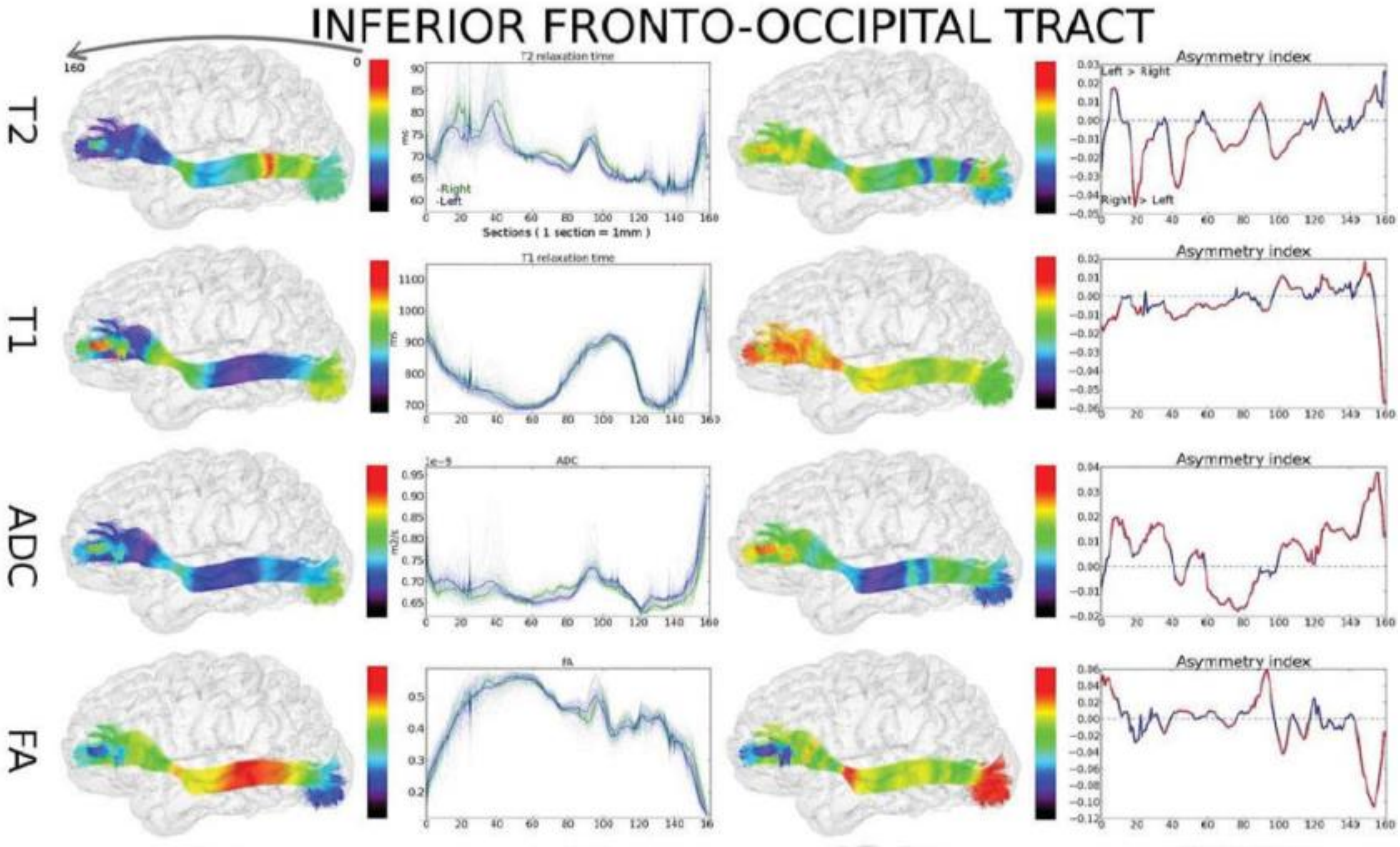
- FD: fiber density
- FF: fiber fraction
- FS: fiber spread
- FA: fractional anisotropy

Schreiber et al. Neuroimage 2014; Riffert et al. Neuroimage 2014

Edge weights for the enriched structural connectome?

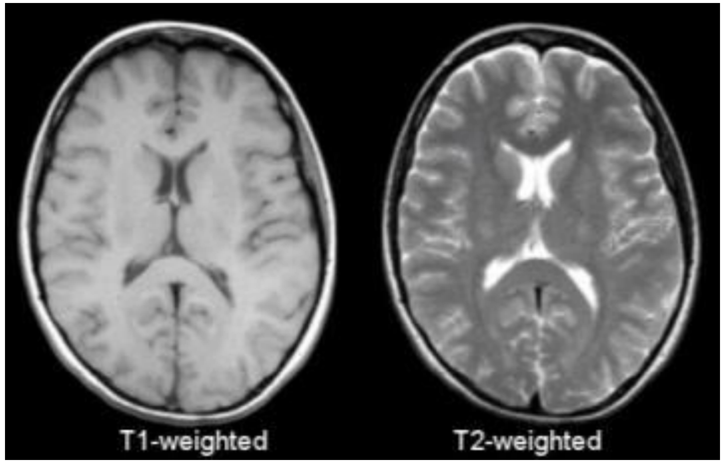
- Log-number of streamlines
- Log-connection densit
- FA or 1/ADC
- Normalize?
- Quantitative T1 and T2 relaxation time

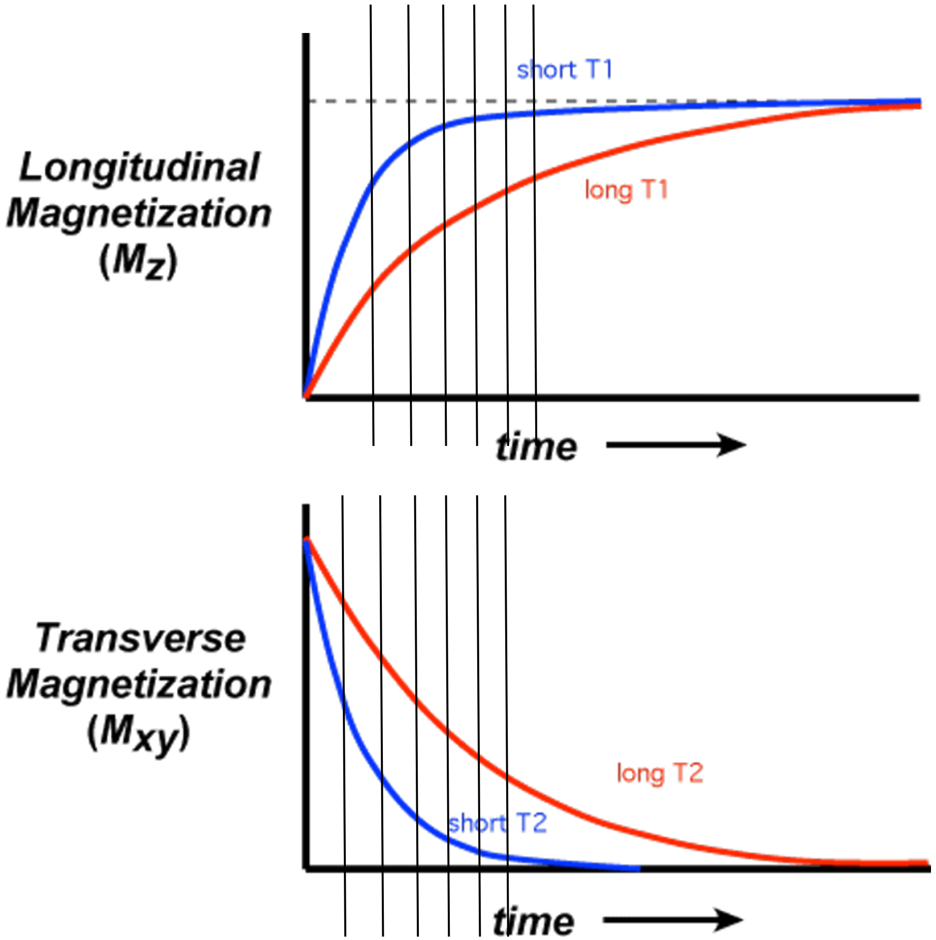


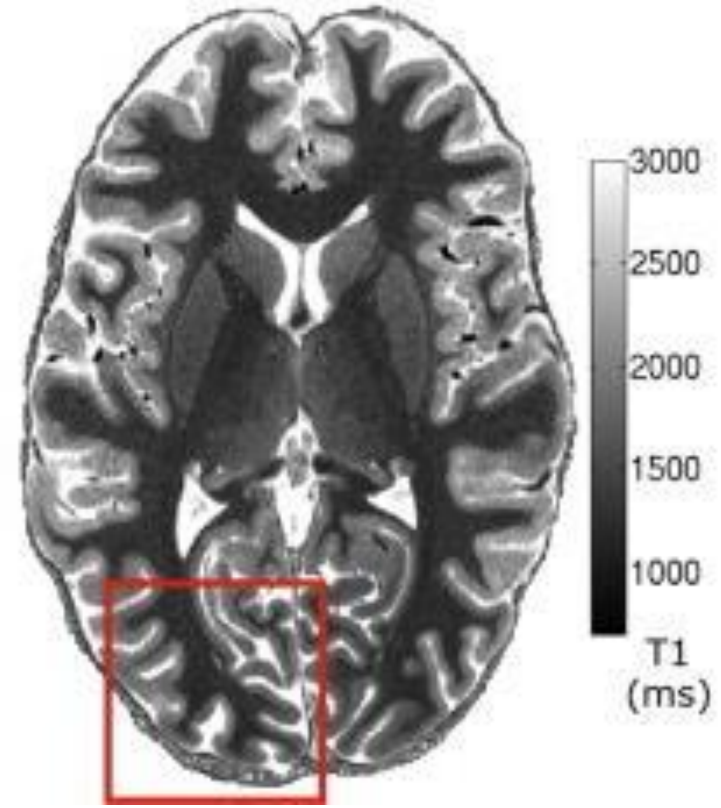


LeBois, PhD Thesis, 2014

From T_1 and T_2 weighted images to T_1 and T_2 maps





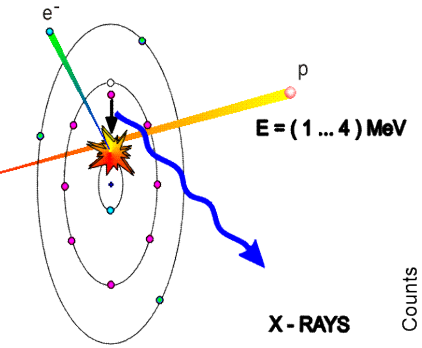


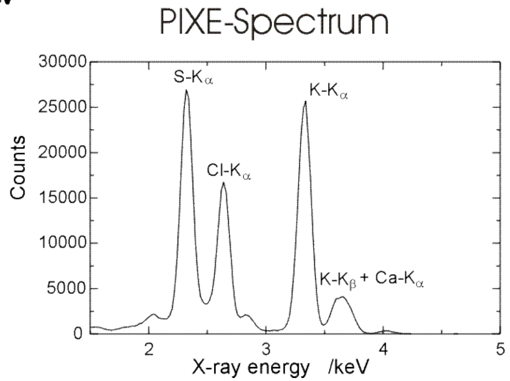
T_1 map

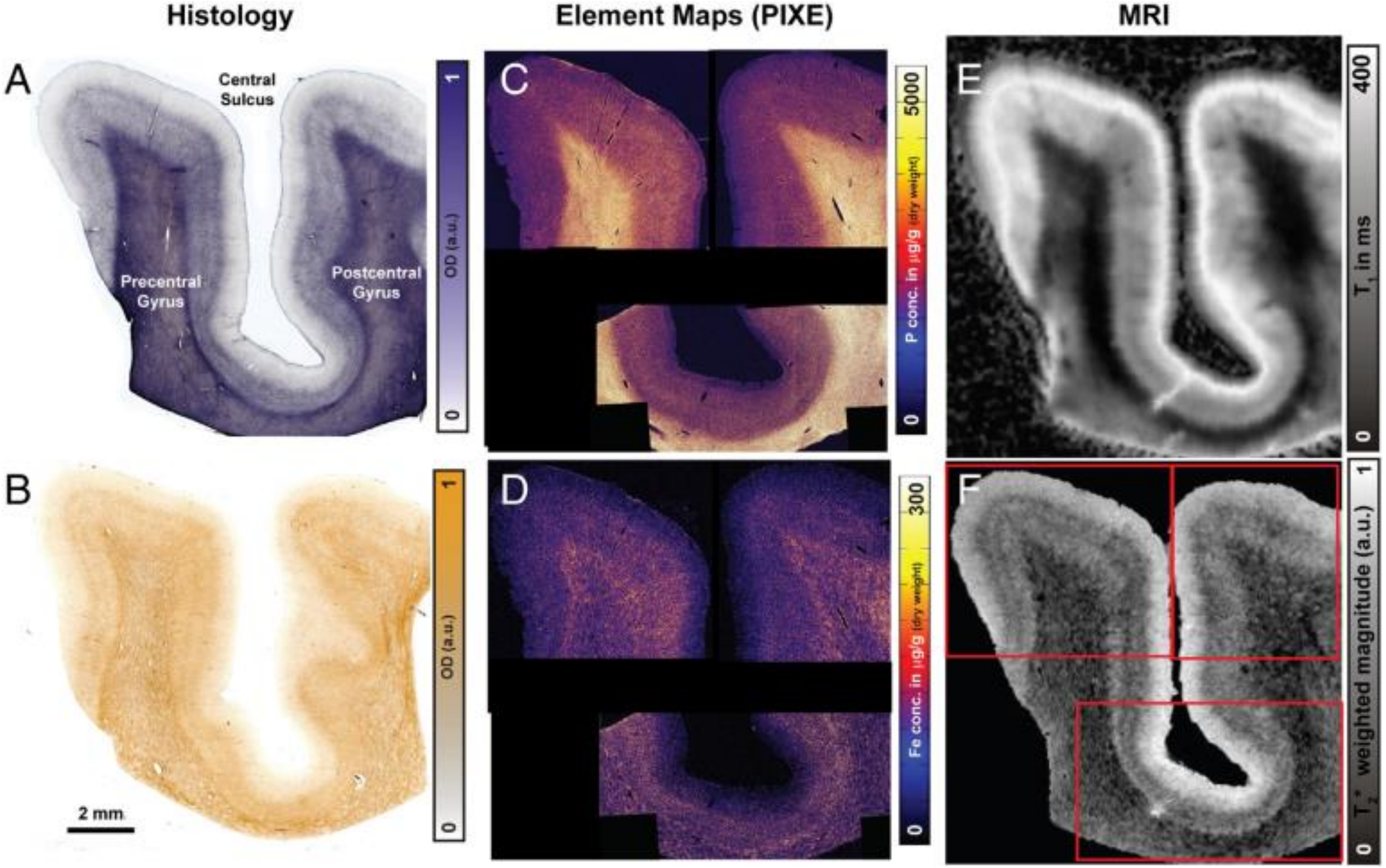
http://mriquestions.com, Tardif et al. 2015

From T_1 and T_2 maps to myelin

- Quantify myelin
- Proton induced X-ray emission



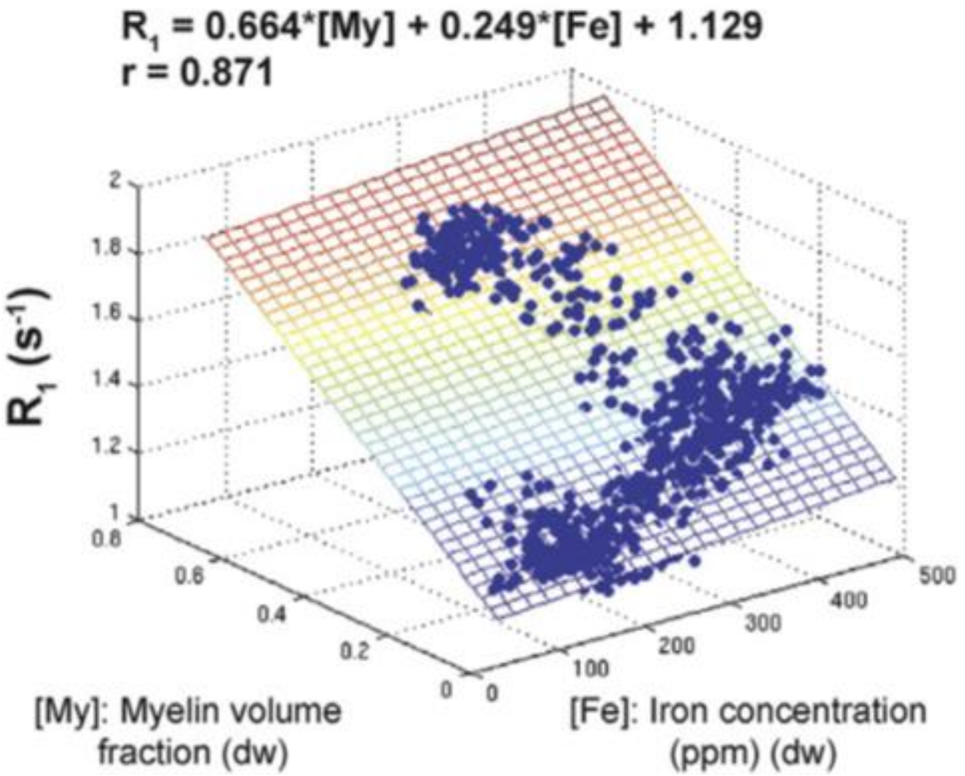


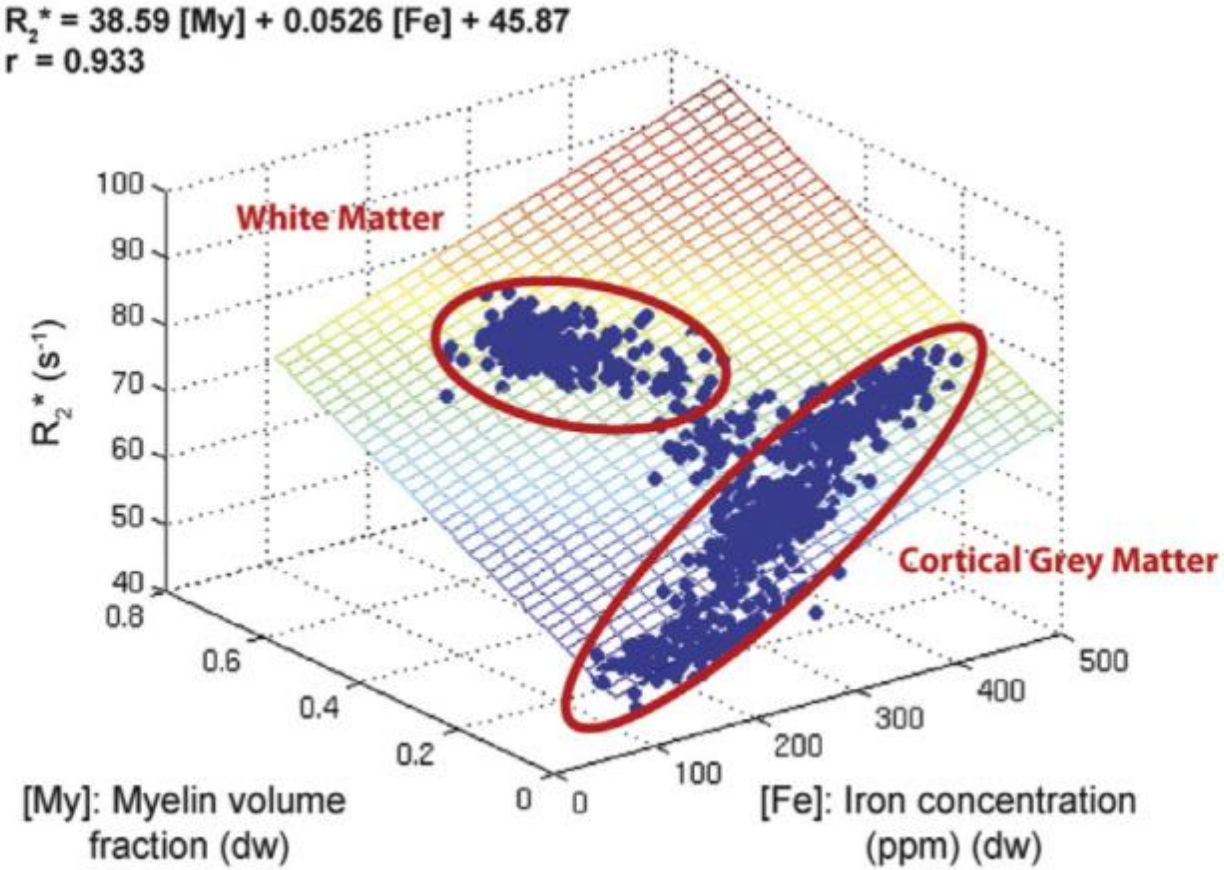


C. Stüber et al. Neuroimage 2014, https://bloch.physgeo.uni-leipzig.de

From T_1 and T_2 maps to myelin ($R_1=1/T_1$)

- $\mathbf{R_1} = a_{Fe}c_{Fe} + a_{My}\mathbf{c_{My}} + a_{Off}$
- $\mathbf{R_2{*}} = b_{Fe}c_{Fe} + b_{My}\mathbf{c_{My}} + b_{Off}$



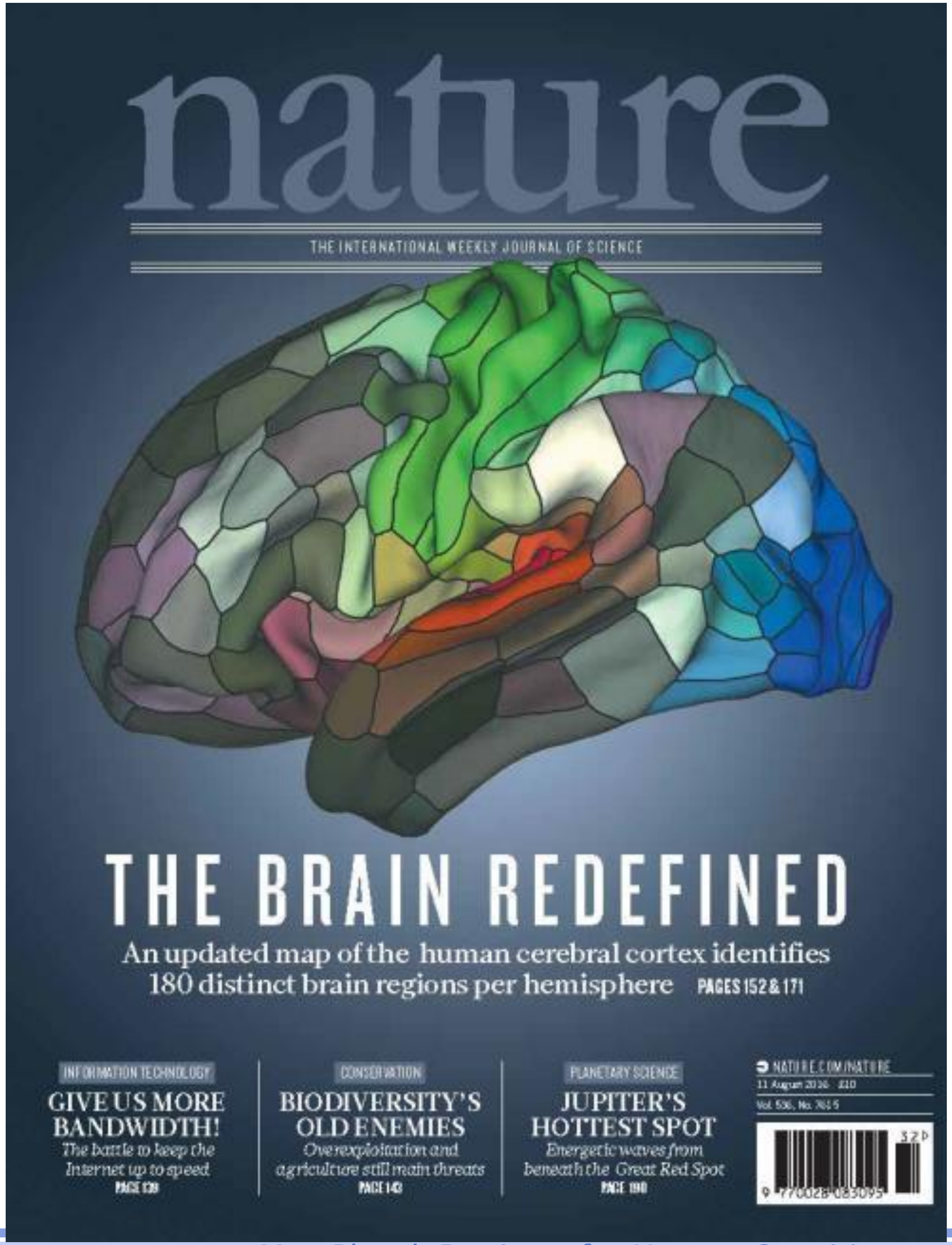


Multivariate Linear Regression

C. Stüber et al. Neuroimage 2014

Individual parcellation for structural and functional data?

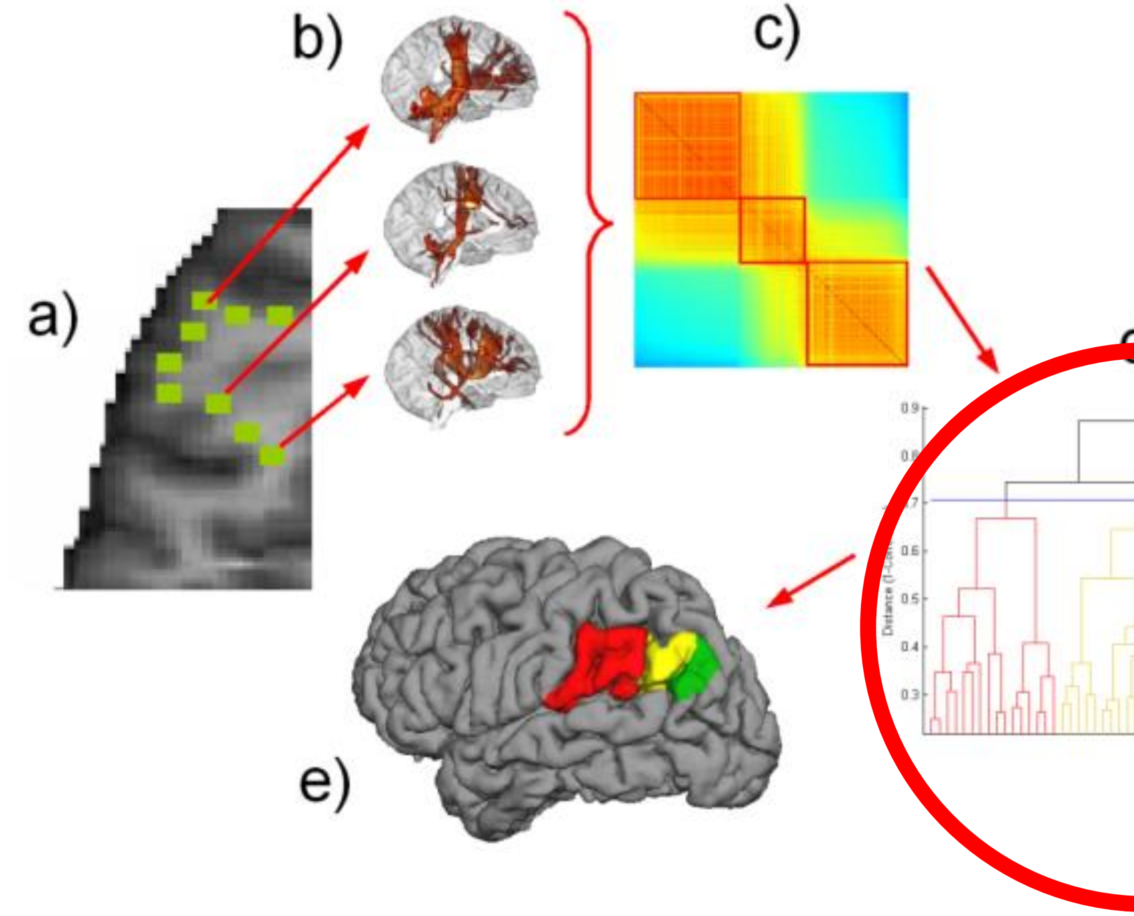
Is it solved?

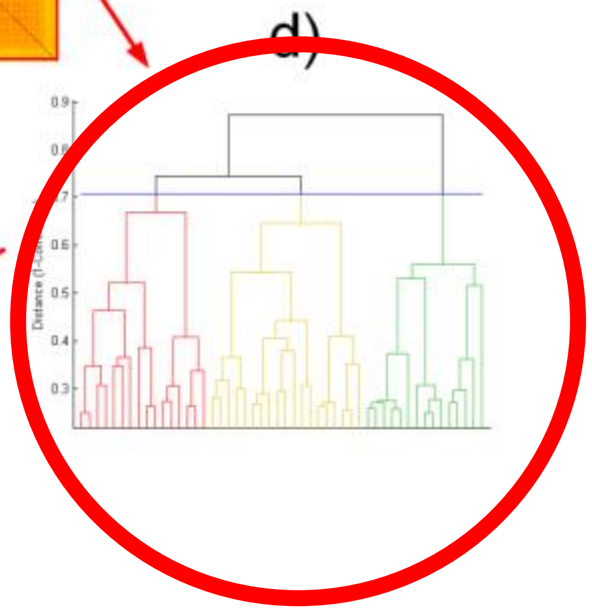


Glasser et al. Nature 2016

Tractography based hierarchical parcellation of the human brain

- Structural connectivity differs between cortical areas
- The difference in such characteristic tractograms can be evaluated statistically
- Similarity matrix of probabilistic tractography
- Connectivity matrix shows hierarchical structure
- Representation as hierarchical tree



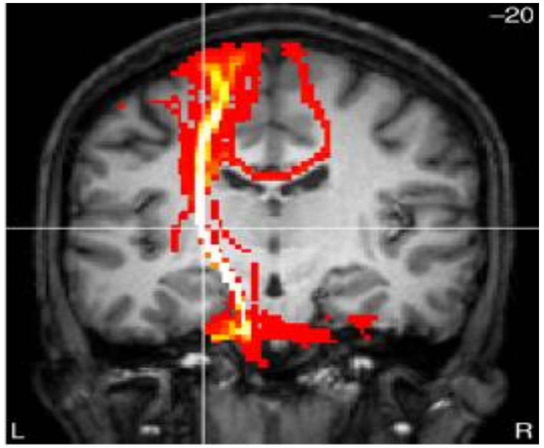


Anwander et al. Cereb Cortex 2007, Moreno-Dominguez et al. Hum Brain Mapp 2015

Tractogram dissimilarity

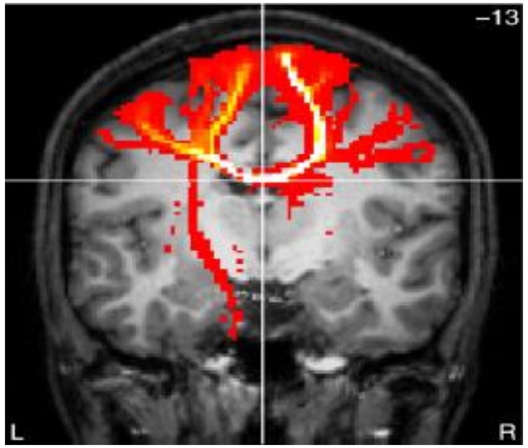
Similarity ➔ normalized scalar product. [0,1]

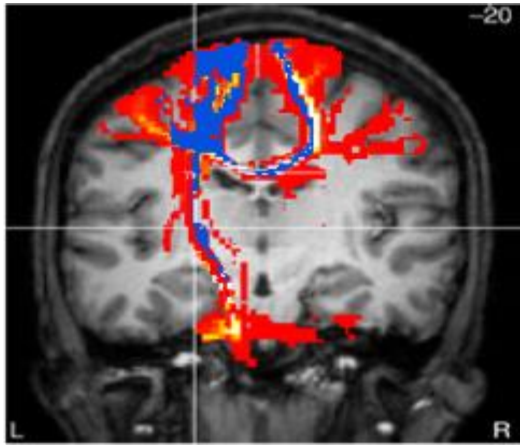
Distance = 1 - Similarity



Distance = 0 ➔ Same tractogram

Distance = 1 ➔ No overlap



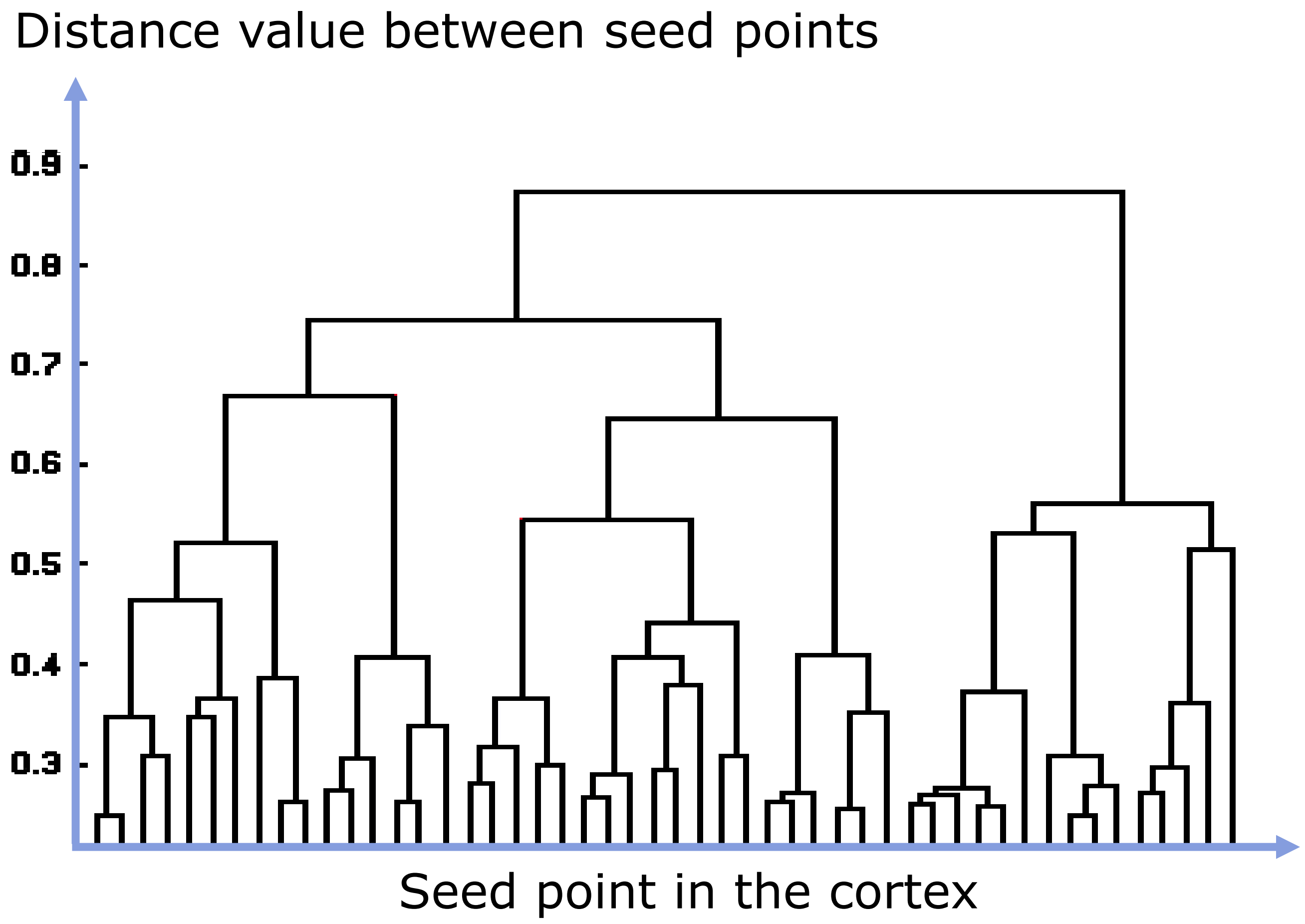


Similarity = 0.3

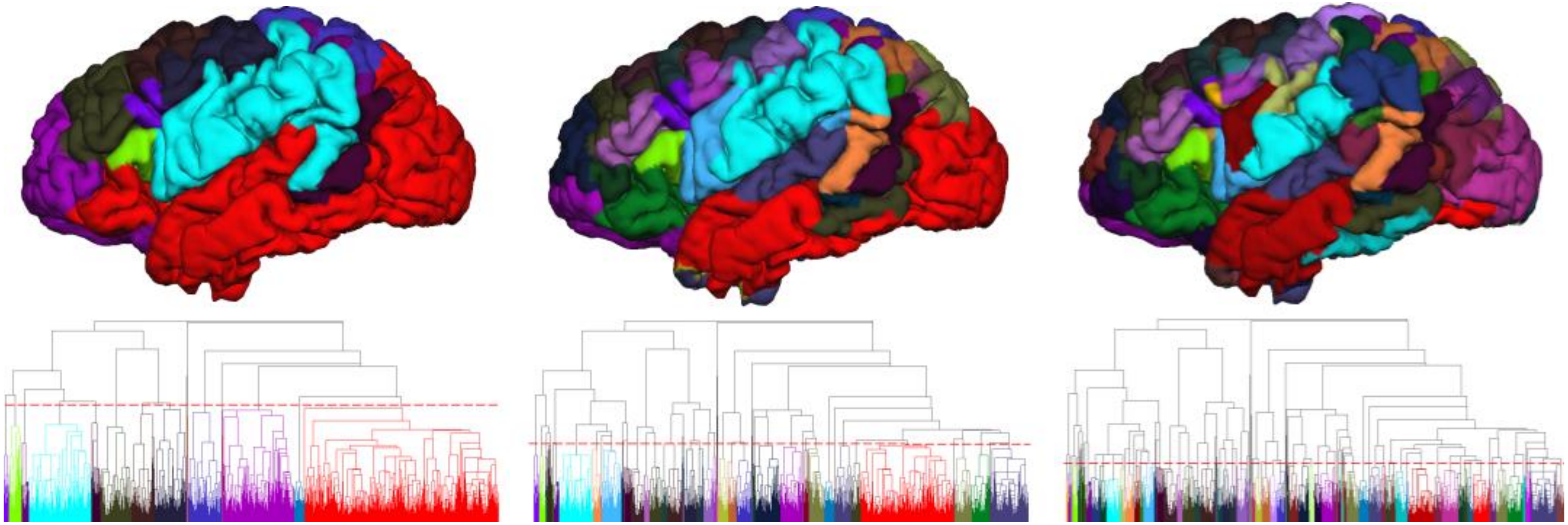
Distance = 0.7

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)
- Initial elements are called leaves, all other elements nodes.



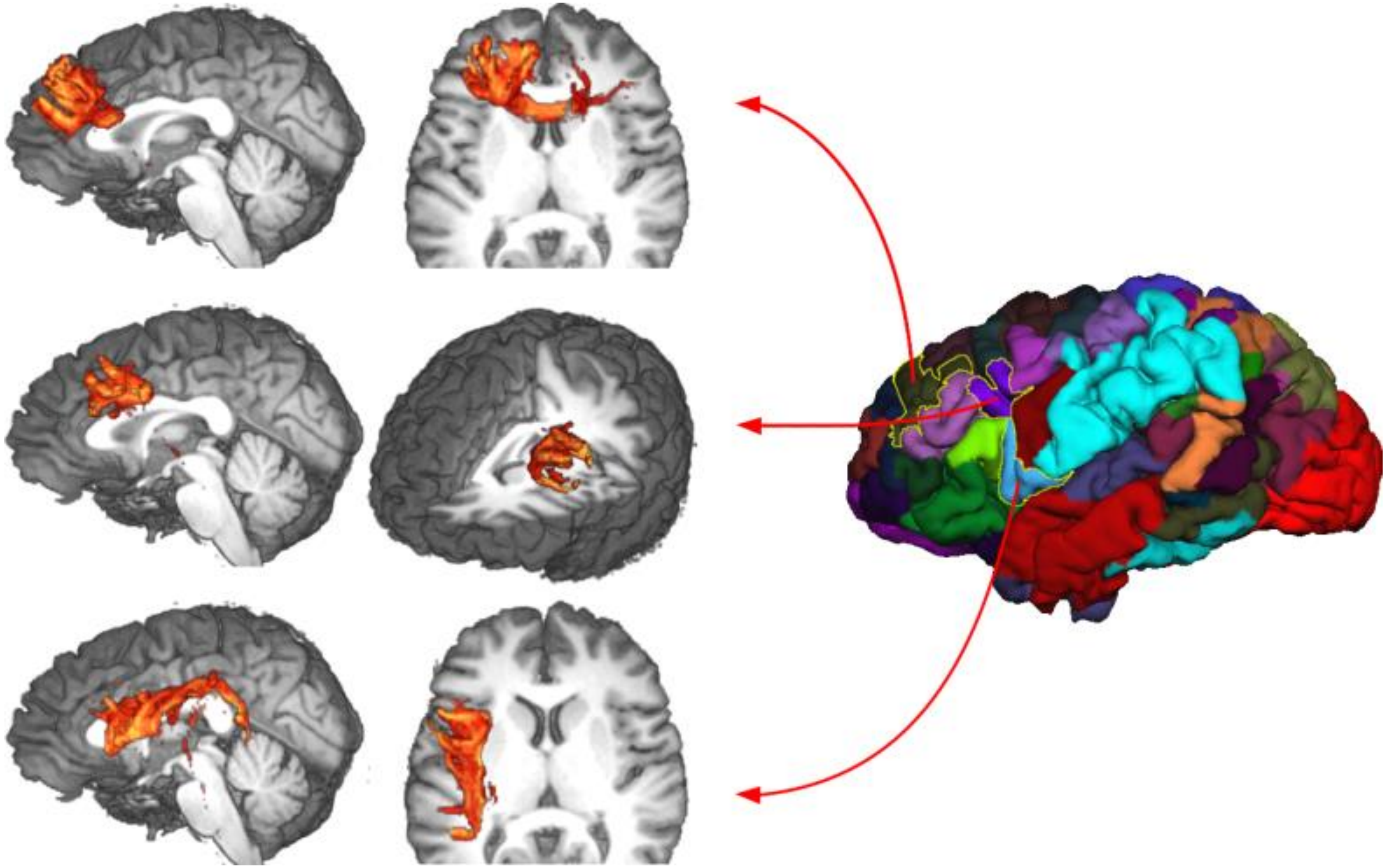
Hierarchical parcellation of the human brain



- 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 proposed

Moreno-Dominguez, Anwander et al. Hum Brain Mapp 2015

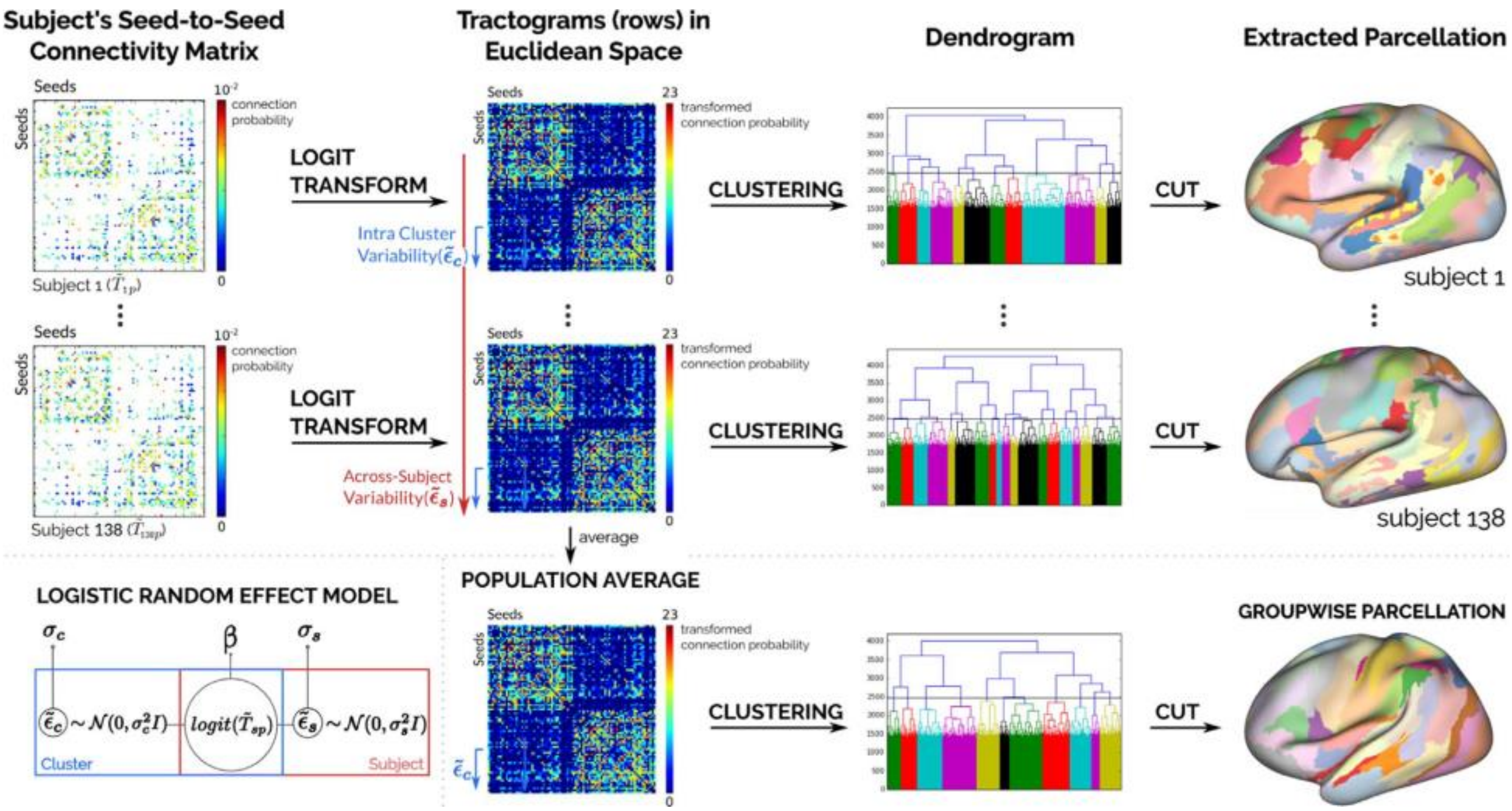
Hierarchical connectom:
Connectivity between regions



Mean tractograms of clusters on the superior and lateral frontal lobe.

Moreno, et al. ESMRMB 2011

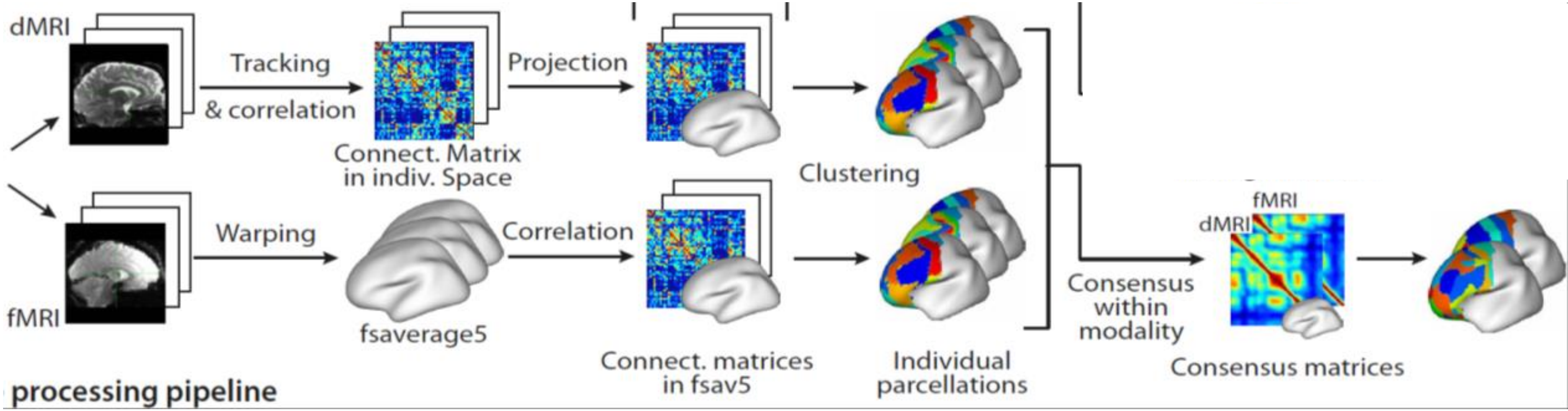
Groupwise structural parcellation



G. Gallardo et al., Neuroimage 2017

Functional and structural parcellation of the individual brain

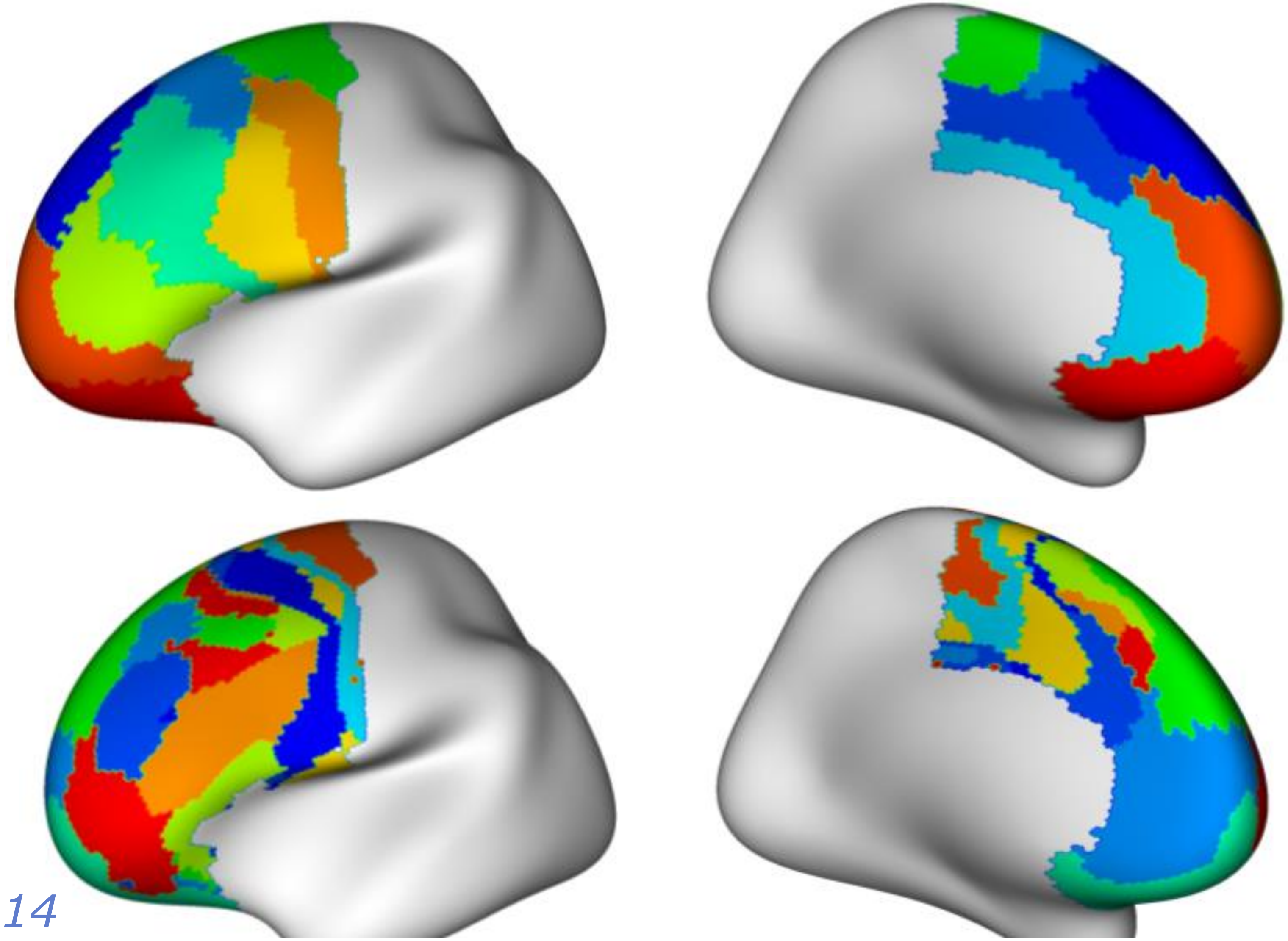
- Separate individual parcellation based on the structural and functional connectivity matrix
- Consensus clustering over groups



Moreno-Dominguez et al. OHBM 2014

Functional and structural parcellation of the individual brain

- Diffusion MRI tractography based consensus parcellation
- fMRI connectivity based consensus parcellation
- See also poster 90: Guillermo Gallardo



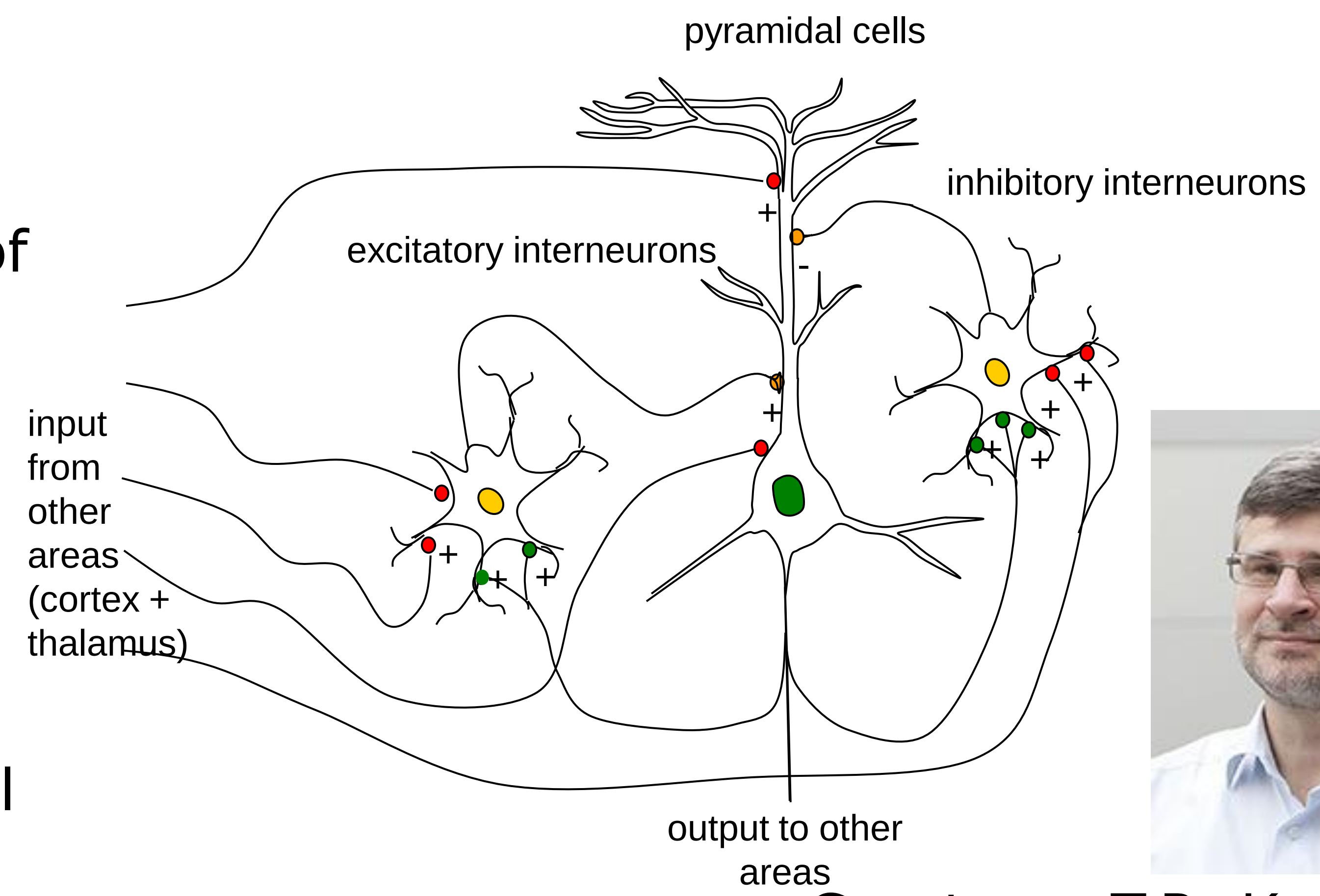
Moreno-Dominguez et al. OHBM 2014

Can we do better?

Can we predict functional data?

Computation of functional connectivity from the connectome

- Non-linear neural mass model
  - Neural mass: region of homogeneous activity
  - pyramidal cells
  - interneurons
- Balloon-Windkessel hemodynamic model to compute the BOLD signal

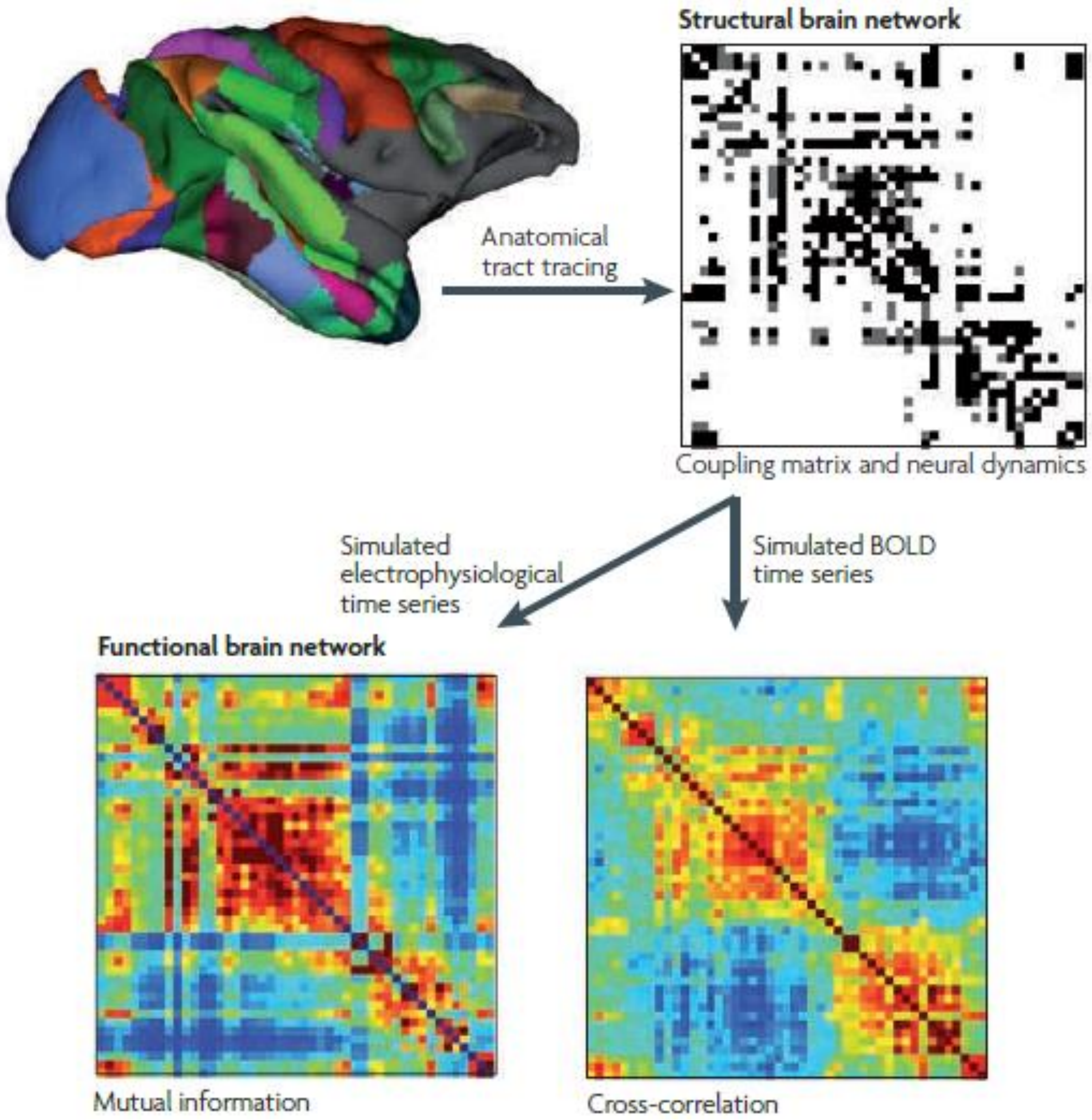


Courtesy: T.R. Knösche

Siegler et al Neuroimage 2010; Breakspear et al. 2003; Buxton, MRM 1998

Computational models to simulate dynamic patterns of activity

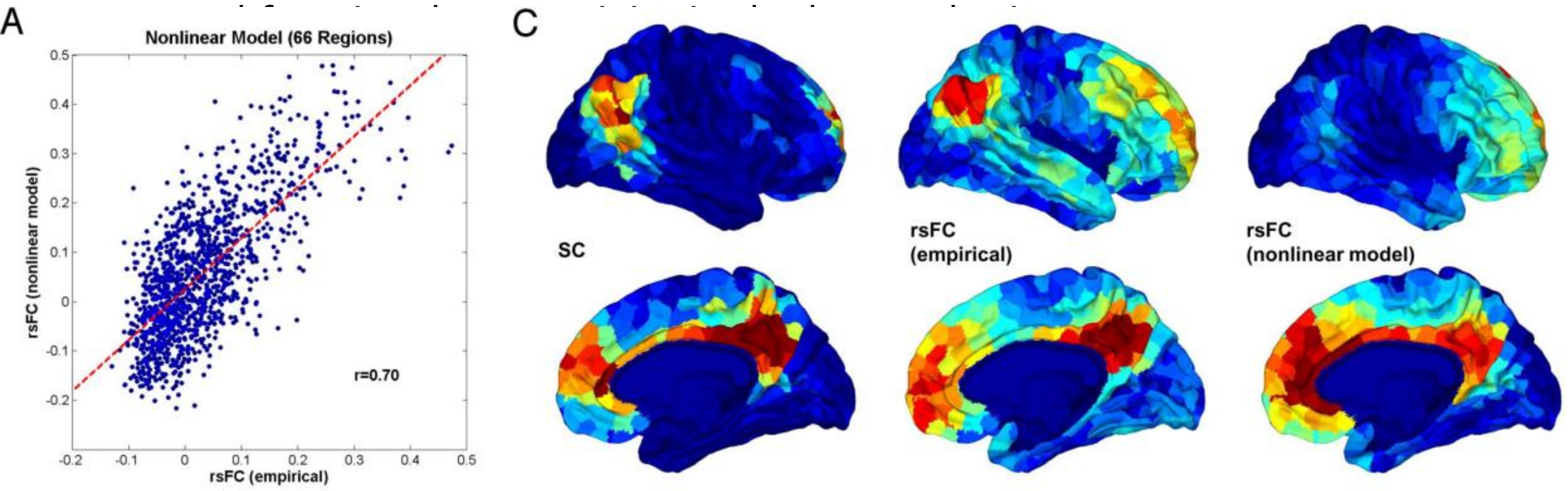
- Neural mass model – conductance based model of neural dynamics
- Emulate neuronal dynamics in macaque neocortex
- Simulated electrophysiological data
- Simulated BOLD data
- Compute connectivity matrices from the data



Bullmore & Sporns Nat Rev Neurosci 2009, Honey et al. PNAS 2007

Predicting human resting-state functional connectivity from structural connectivity

- Systematic analyses of the relationship between structural

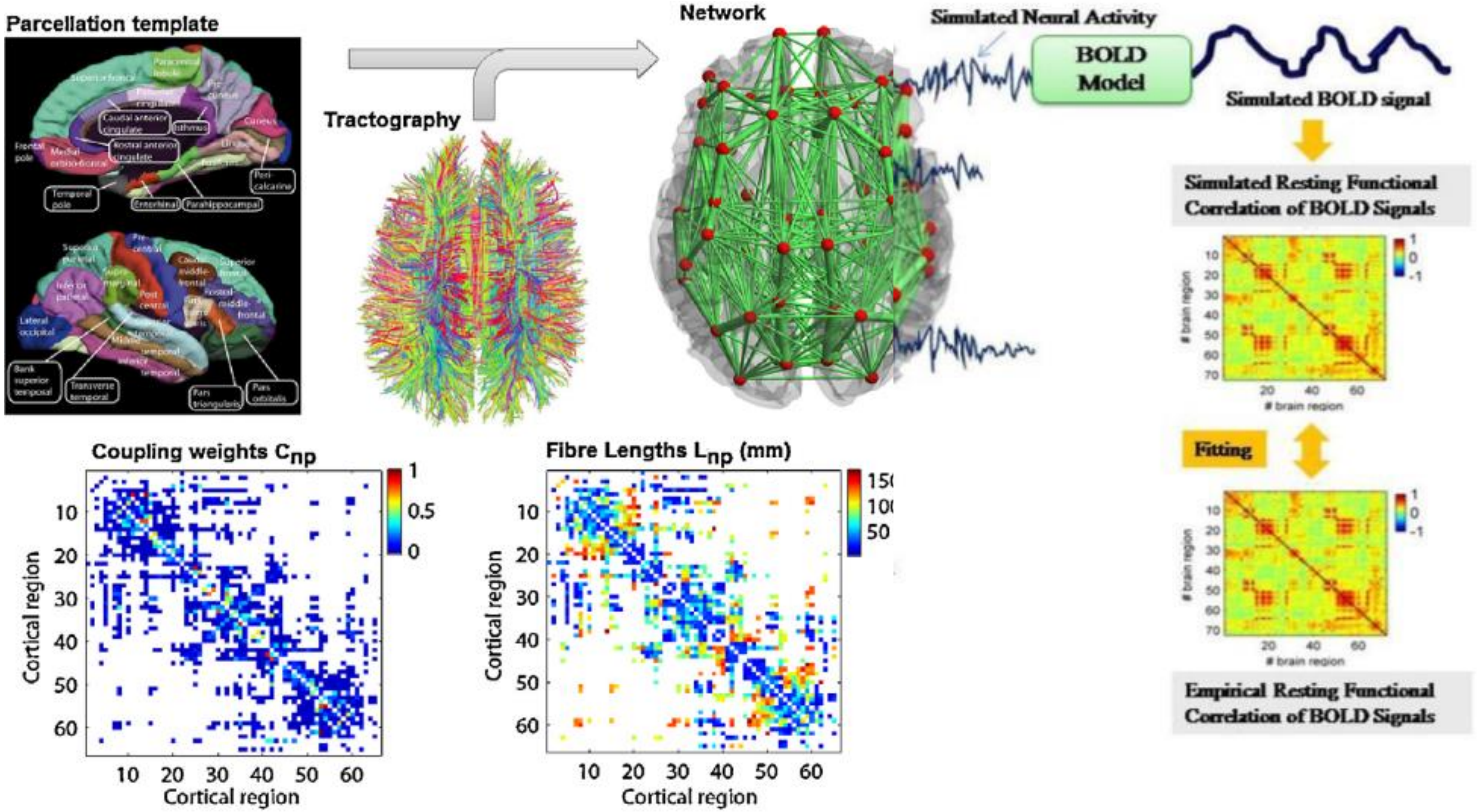


Honey et al. PNAS 2009

Can we do better?

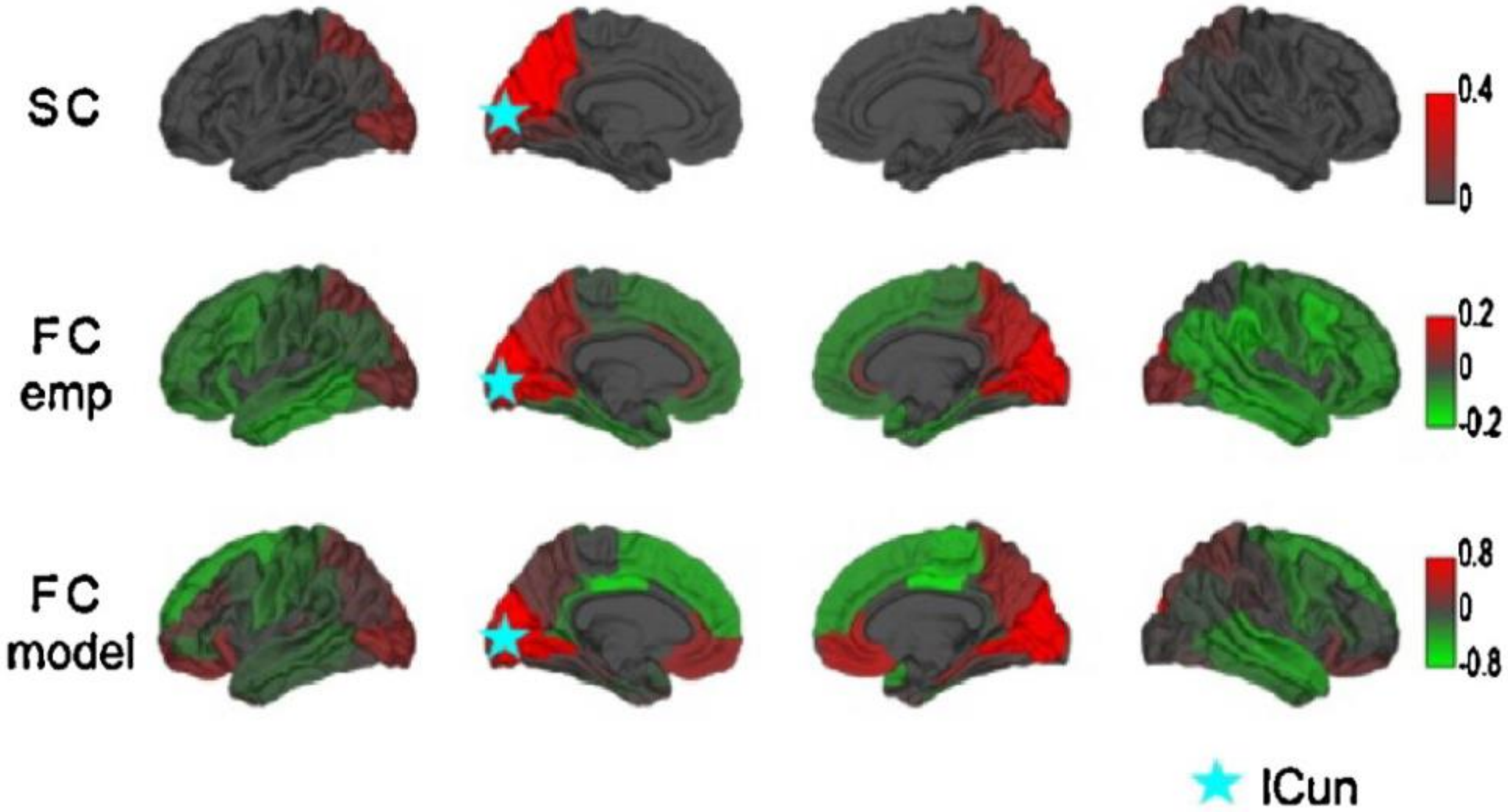
Include the enhanced connectome

Exploring the network dynamics



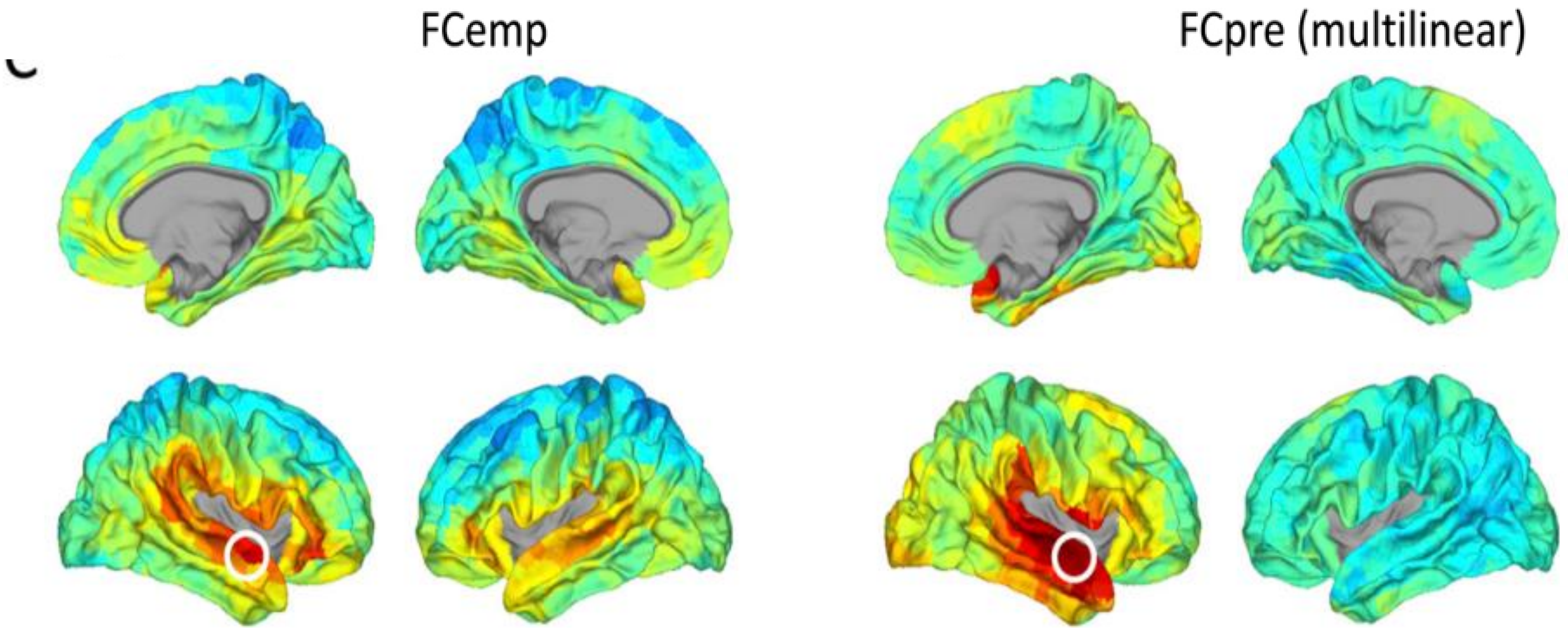
Cabral et al. Prog Neurobiol 2014, http://www.thevirtualbrain.org

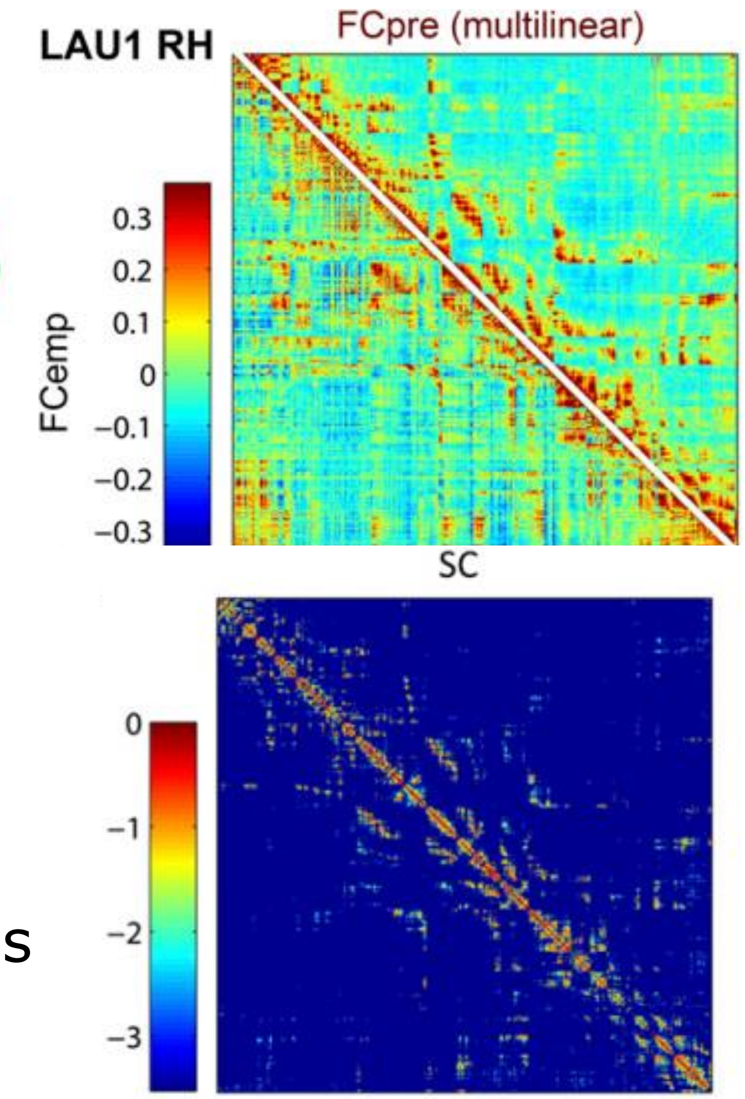
Exploring the network dynamics



Cabral et al. Prog Neurobiol 2014

Prediction of functional connectivity





- pattern of empirical FC (FCemp) and
- predicted FC (FCpre)
- multilinear model comb. 4 communication measures

Goñi et al PNAS 2014

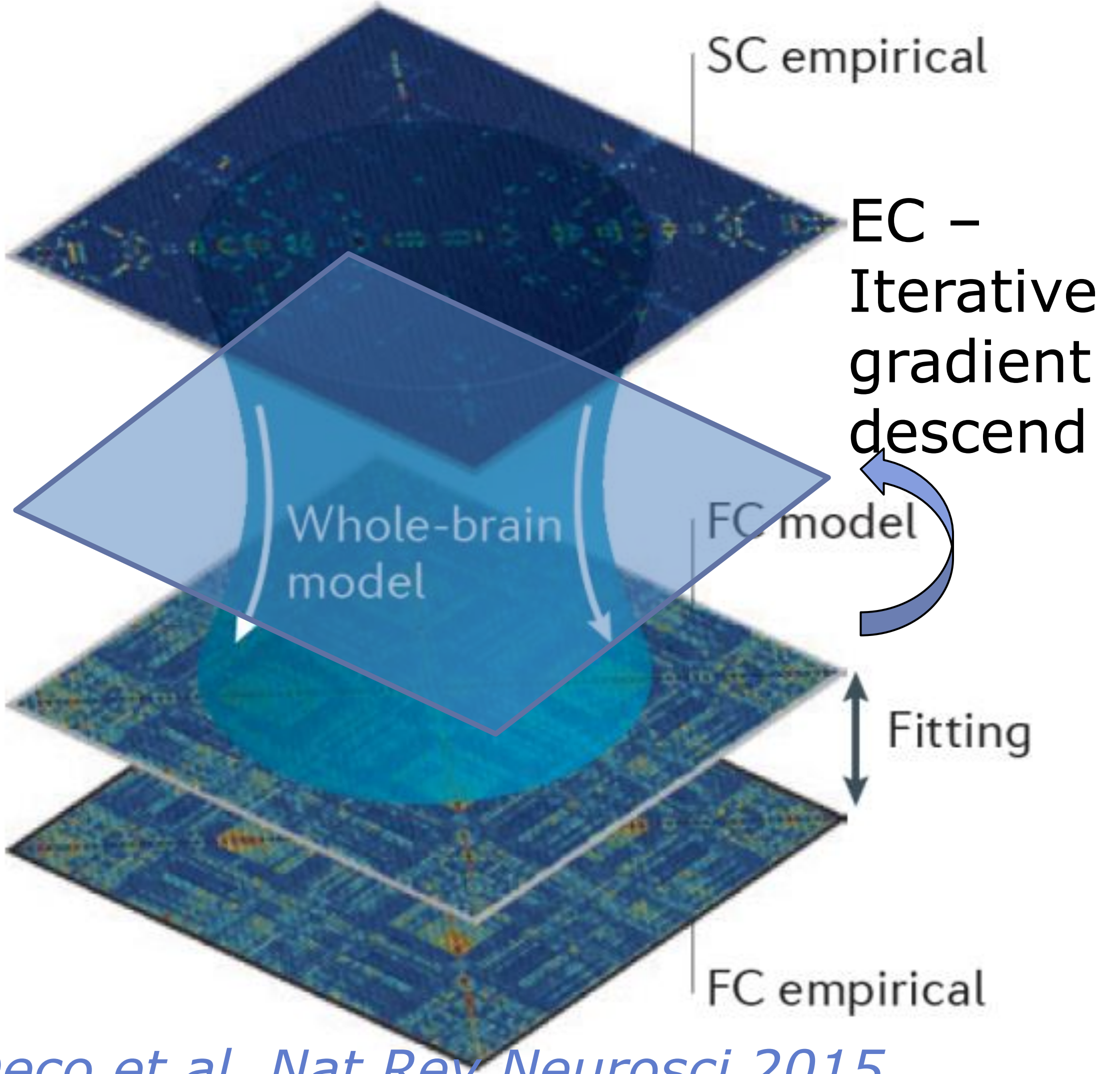
Can we do better?

Compute directed connectivity

Directed effective connectivity from fMRI and dMRI

- Structural connectome provides empirical data
- Interaction depends also on the dynamical properties: excitation / inhibition
- Directedness of regional interaction can be incorporated

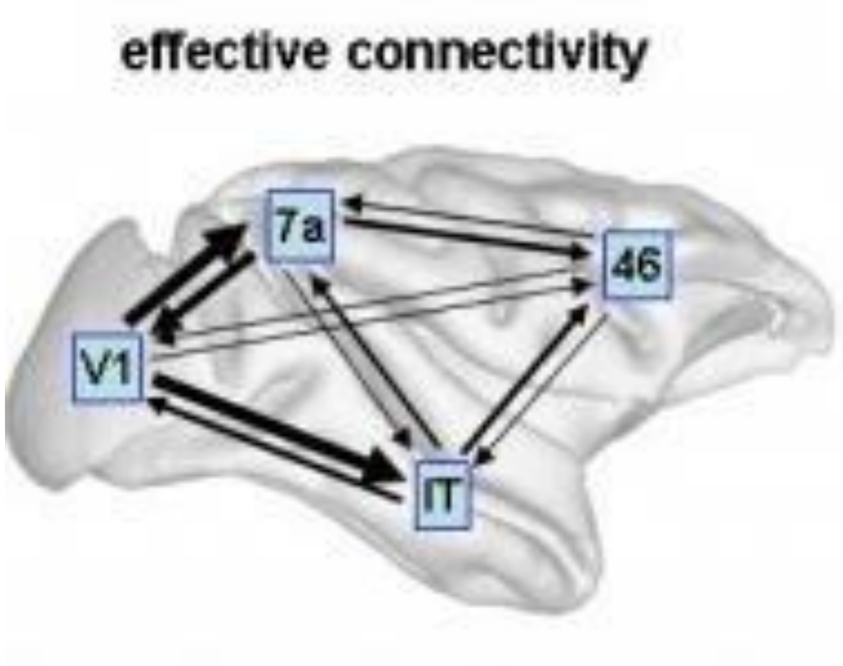
Optimize effective connectivity parameters in a gradient descent iterative algorithm



Gilson PLoS Comput Biol. 2016, Deco et al. Nat Rev Neurosci 2015

Structure and function must be linked to compute effective connectivity

- Functional connectivity **correlates** with structural connectivity
- Causal relation to structural connectivity
- Functional connectivity can be **computed from structural** connectivity
- **Enriched connectomes** improves the prediction
- Advanced computational neuroscience models provides Effective connectivity: directed (causal) interregional interaction



Information transfer in the brain

- Axonal conduction speed ~ axonal myelination
  - R1/MT in MPM

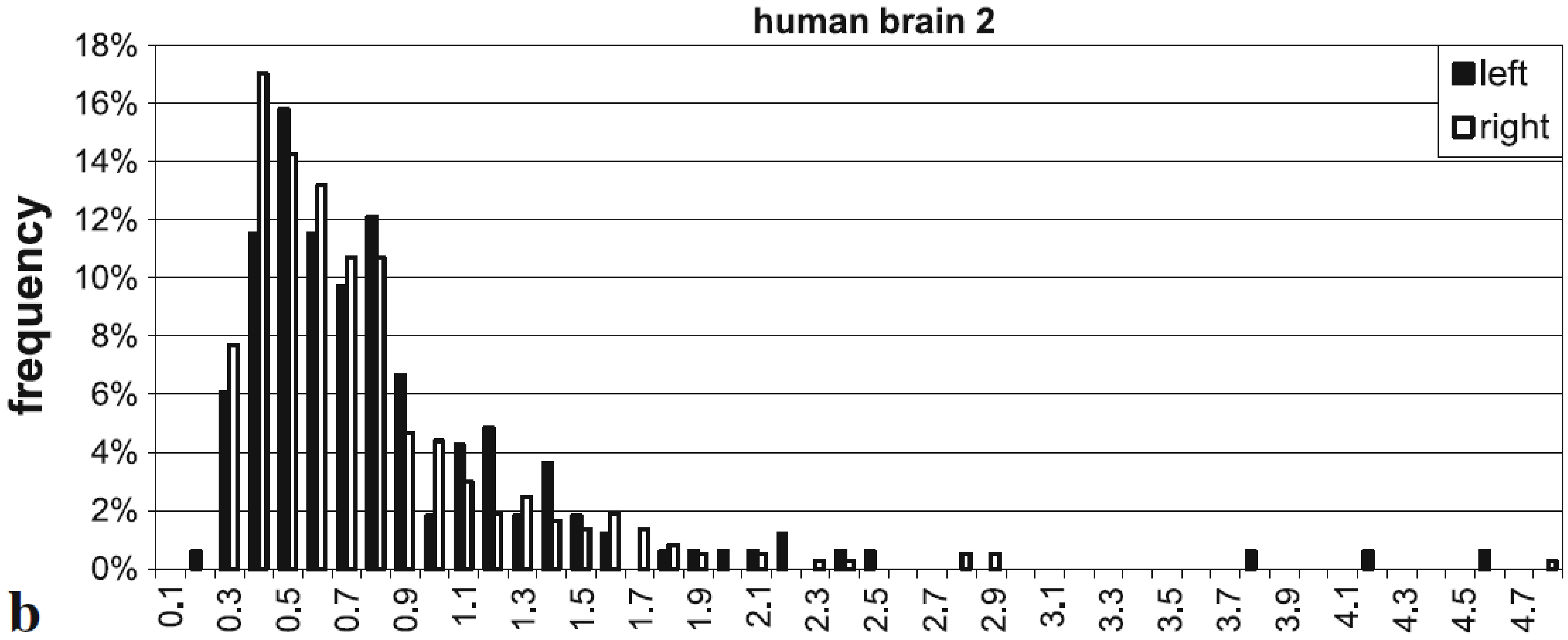
- Axonal conduction speed ~ axonal diameter
  - AxCaliber

- Connection strength ~ axonal density
  - NODDI / CHARMED

- Combined models needed

Information transfer speed in the connectome

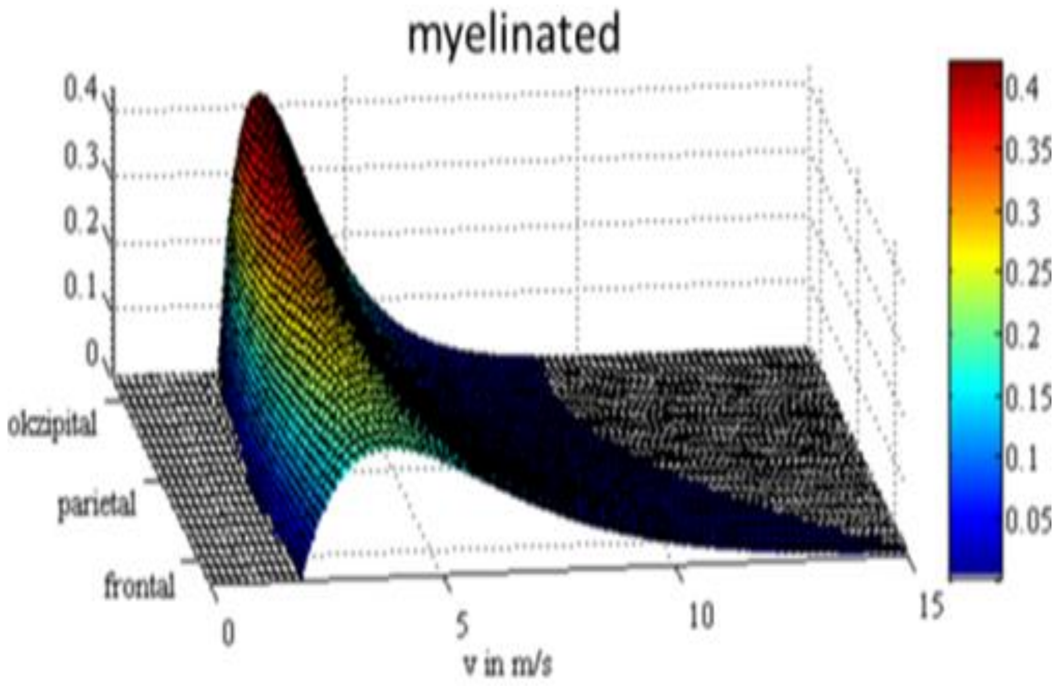
- axonal delay time
- tract length
- axonal density
- myelination
- g-ratio
- axonal diameter

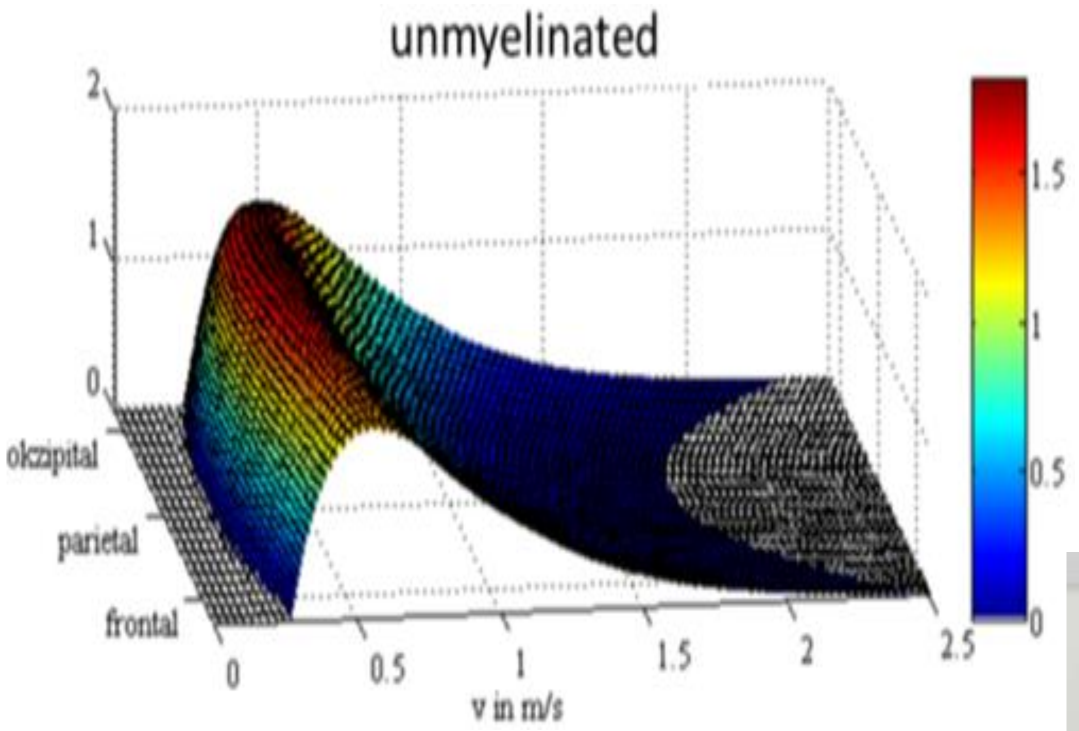


- Axonal diameter distribution of myelinated axons in the superior longitudinal fascicle of the three human brains in the *left* and *right hemisphere*

Liewald et al. 2014

Estimated velocity profiles for myelinated and unmyelinated fibers in the corpus callosum

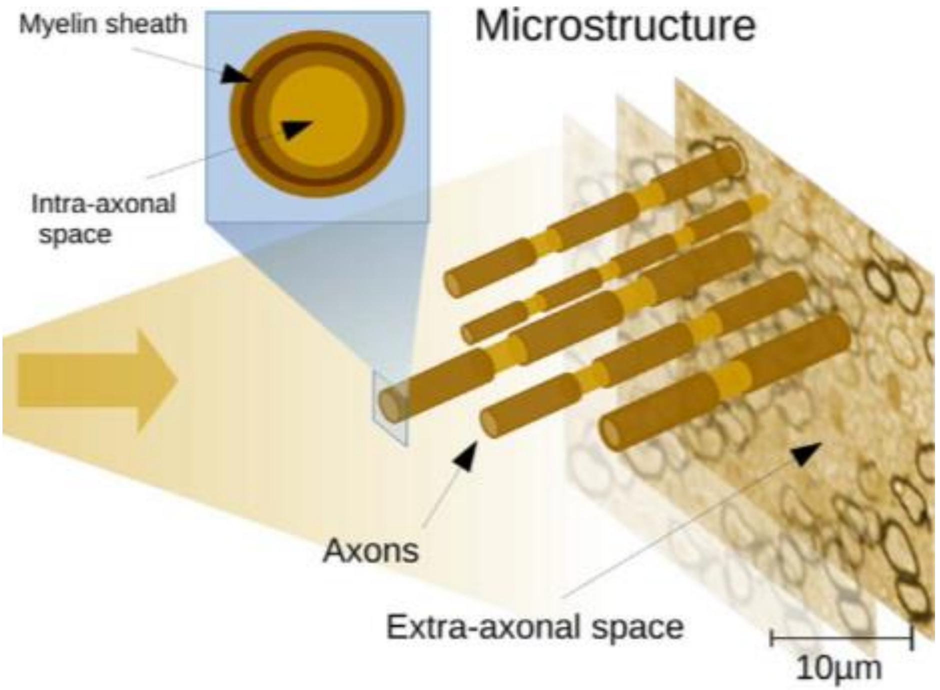


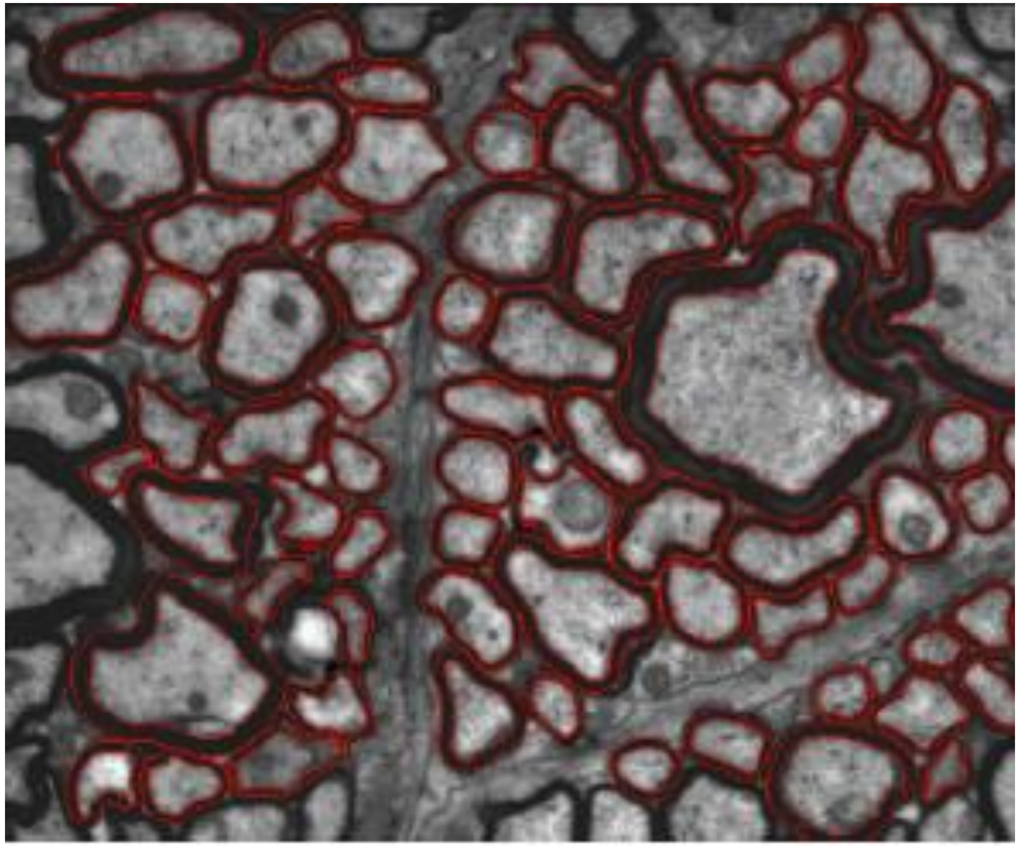


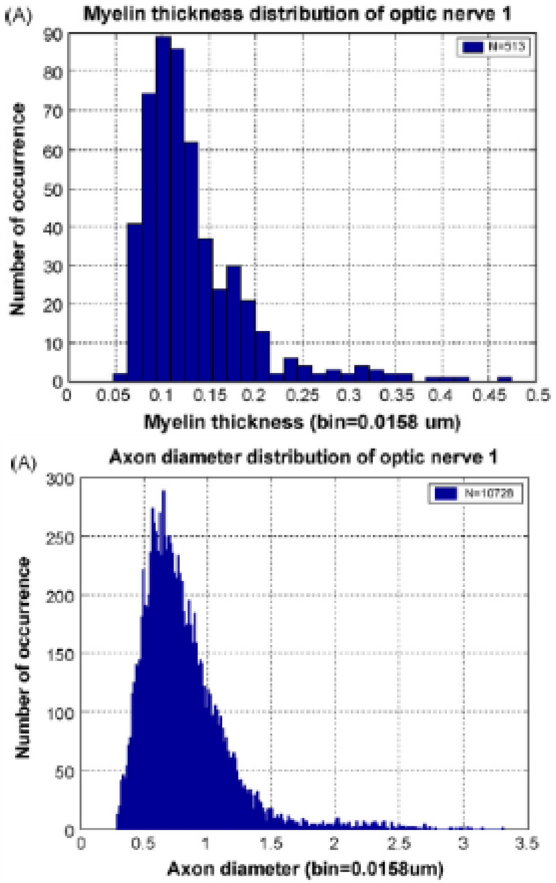
- Estimated velocity profiles in the rat's corpus callosum, based on axonal caliber measurementsof Partadiredja et al.

Koch Master 2011, Partadiredja et al. J Neurocytology, 2003

But how can we measure the axonal diameter?
Electron microscopy





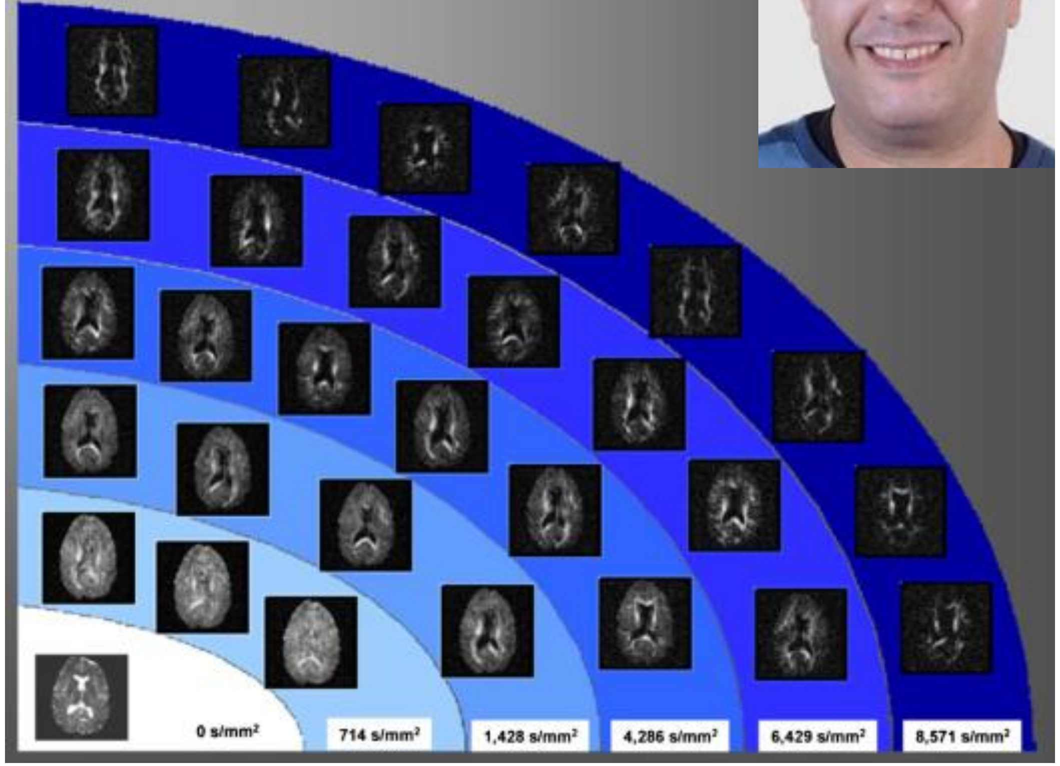


M. Reisert et al. Neuroimage 2017; Zhao et al., Comput Med Imaging Graph 2010

MRI models for micro-structural properties

CHARMED (Composite hindered and restricted model of diffusion: Assaf 2004)

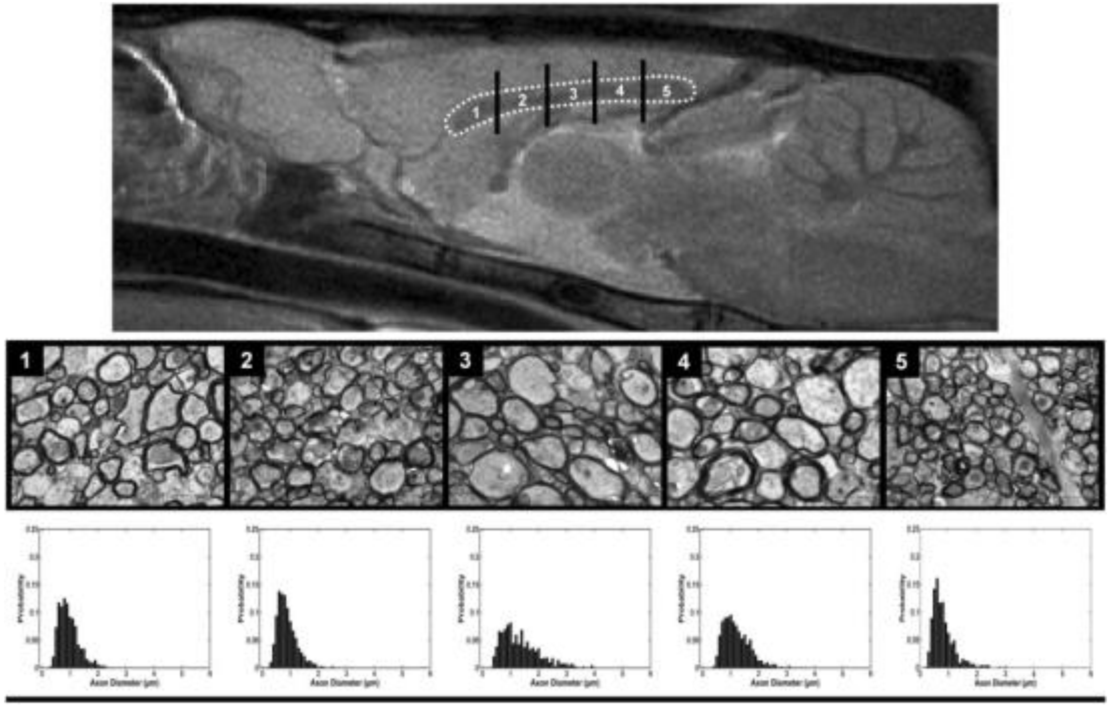
- **axonal density**
- two diffusion comp.: hindered and restricted
- Multi-shell acq. -> high b-values

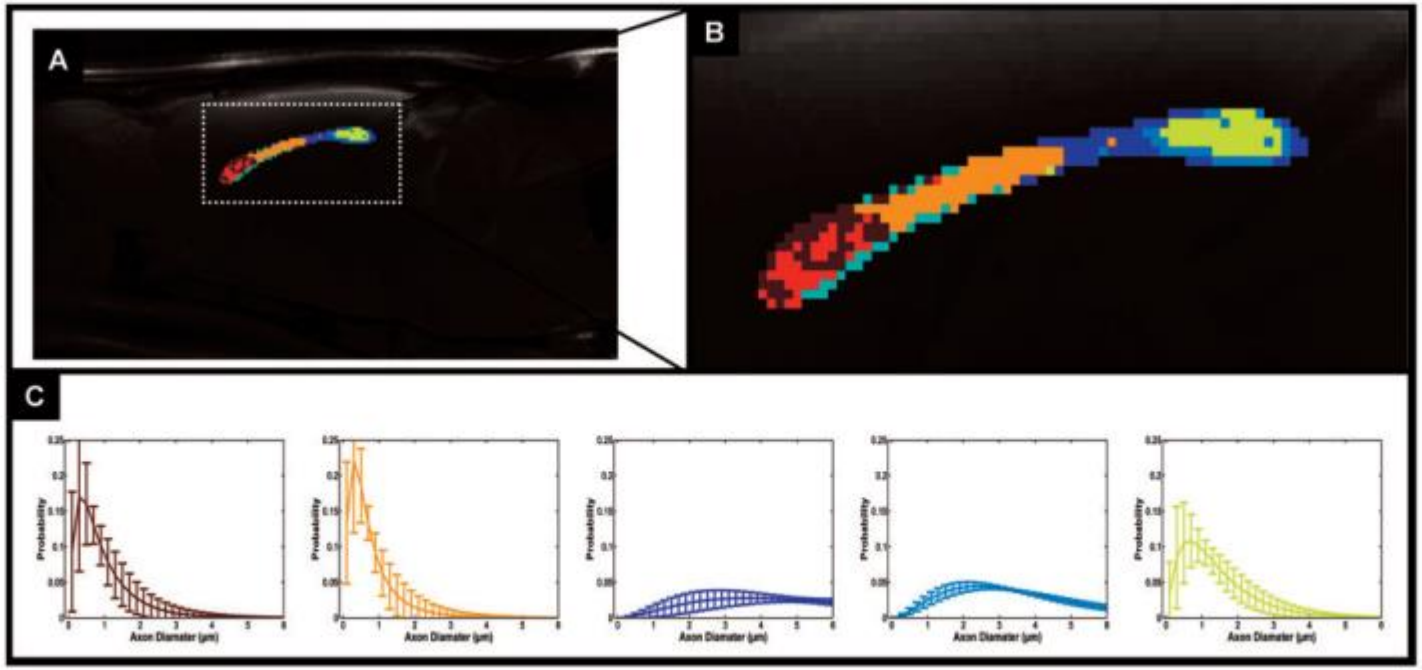


AxCaliber (Assaf et al. 2008)

- axonal diameter distribution
- acquisition **perpendicular** to the fiber direction (e.g. CC)
- **Multi-shell + multi-diffusion time measurement**

MRI of axon diameter distribution in the corpus callosum

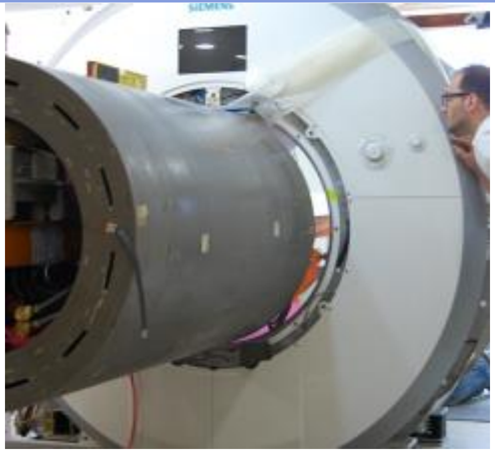




- AxCaliber: intra- and extra-axonal water diffusion
- Axon diameter distribution (ADD)
- Restricted diffusion in the axon, restricted outside

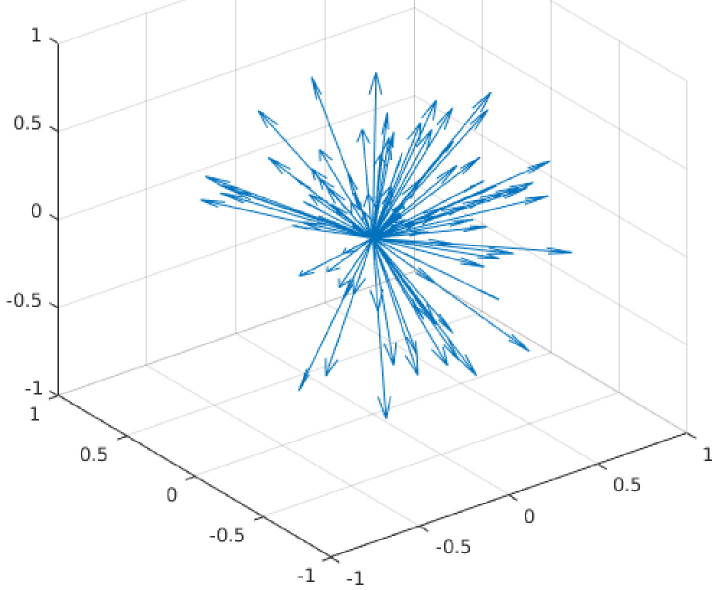
Assaf et al. Magn Reson Med 2008; Barazany et al. Brain 2009

Axon diameter modelling AxCaliber 3D
300 mT/m gradients
(with Assaf group and Prof. Weiskopf)



- Diameter of crossing fibers
- Full sphere acq. - compute data orthogonal to fibers

- 79 directions
- 6 b-values (multi-shell)
- b-value=500 - 5000 s/mm²
- 3 CHARMED scans with different diffusion times 16 - 40 ms
  - (Prisma: 40 - 95ms)
- Fast pulses: delta=9ms

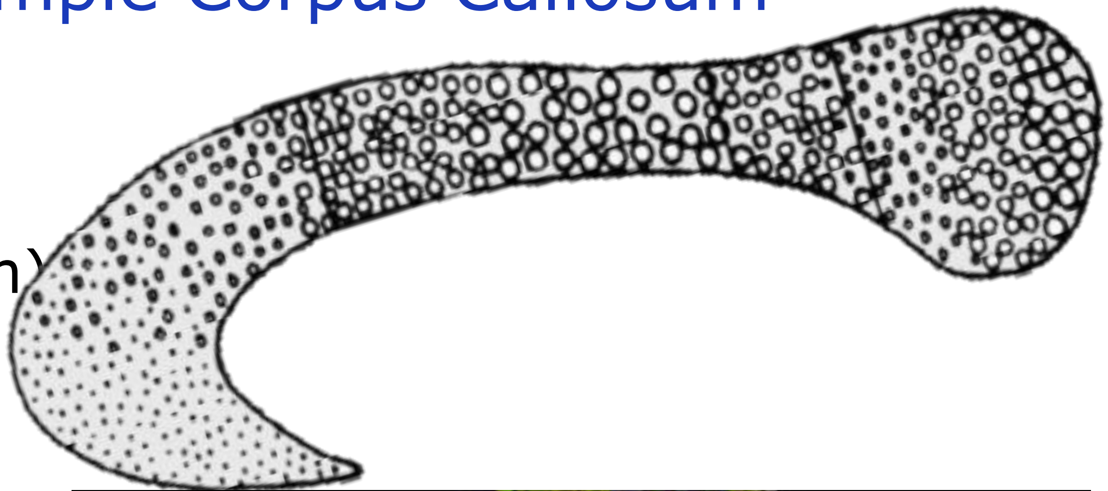


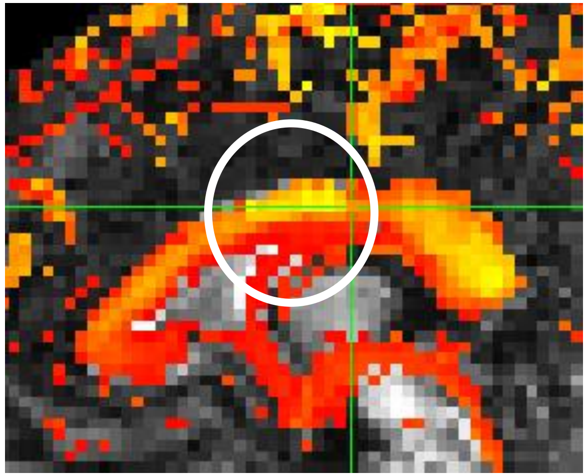
Bval (s/mm²)	Number of directions
500	8
1000	17
2000	12
3000	13
4000	14
5000	15

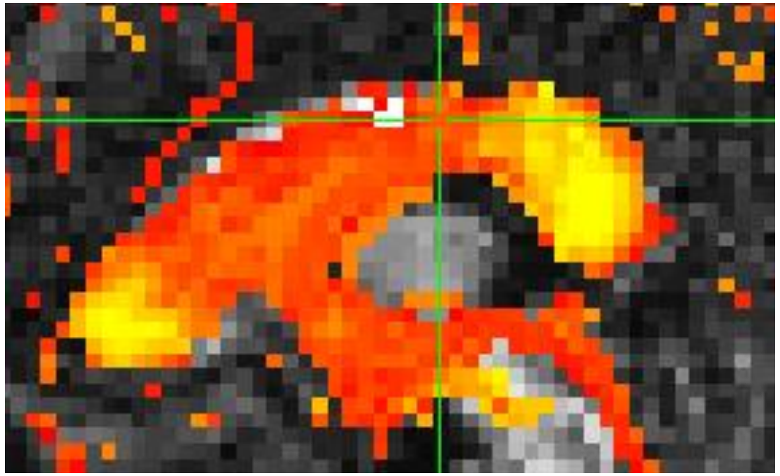
Ben Amitay et al OHBM, 2016 ; Assaf, NI 2005

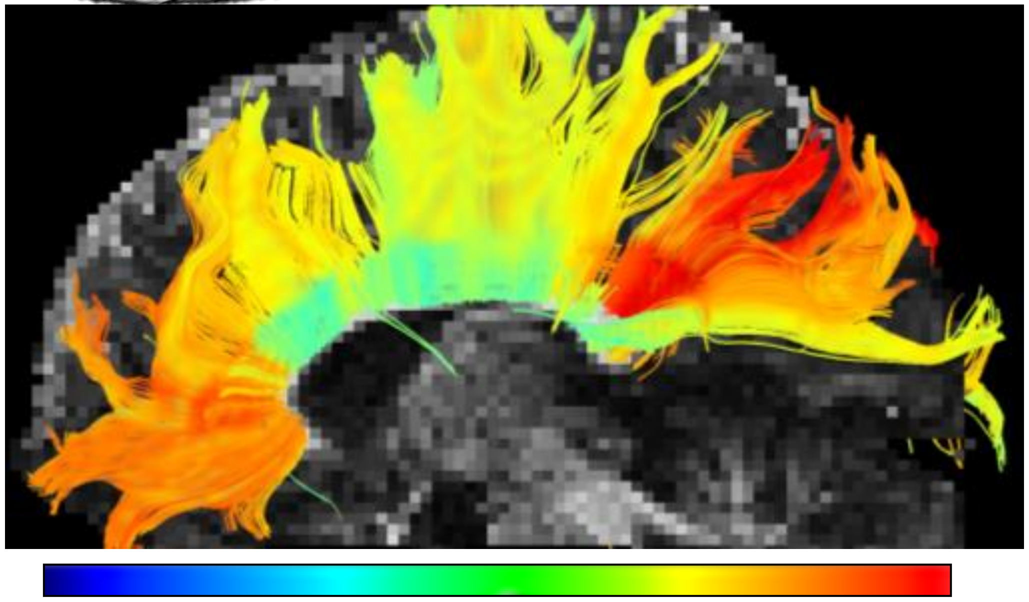
Axon diameter modelling – example Corpus Callosum

- A CSF component, a hindered diffusion
- Two axonal populations
  - small axons: narrow distr.: center 1.5µm)
  - large axons: broad distr.: center 4µm).









large axons

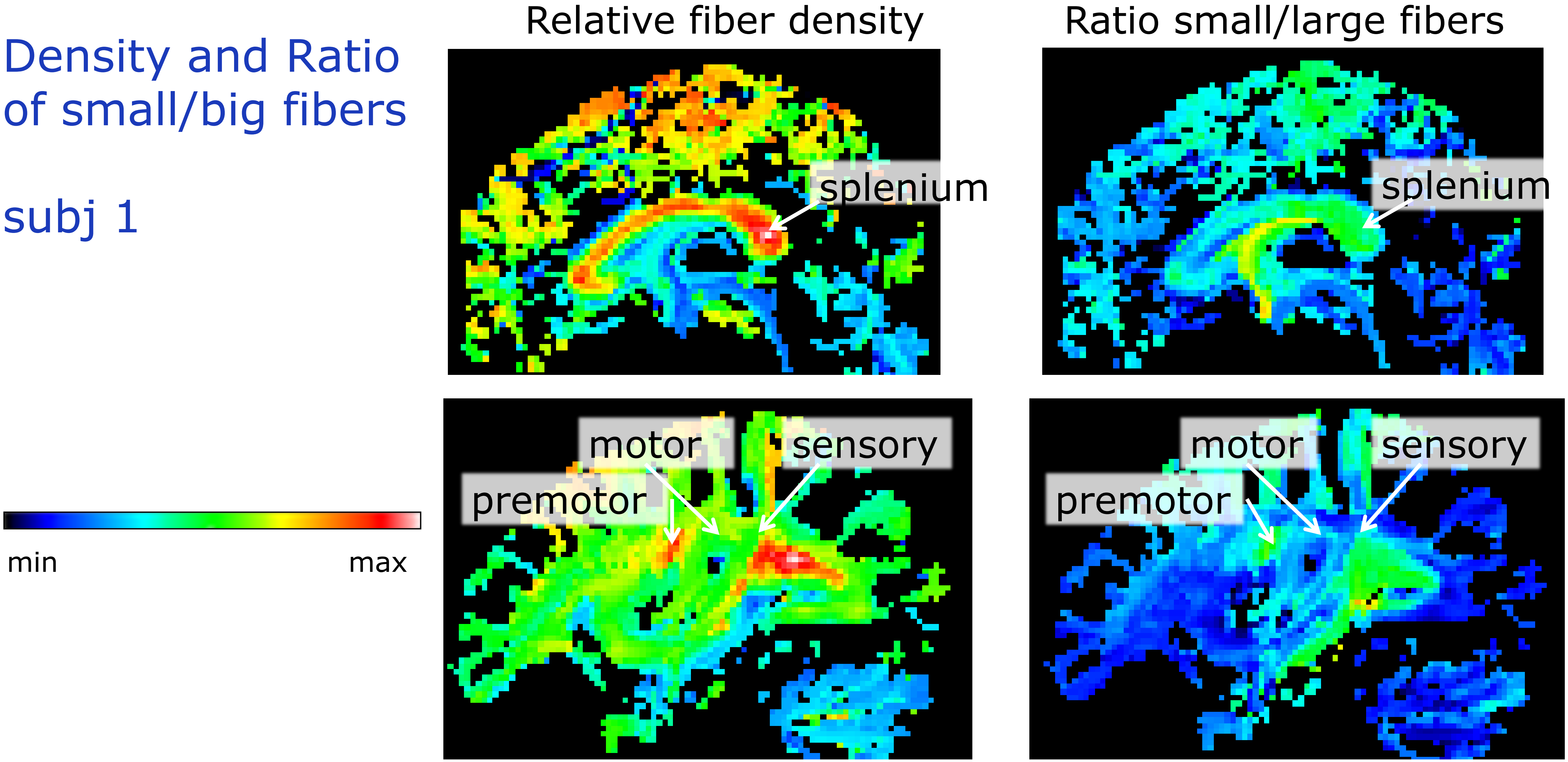
small axons

small axons

In collaboration with Yaniv Assaf and Assaf Horowitz, Aboititz et al. 1992

Density and Ratio of small/big fibers

subj 1



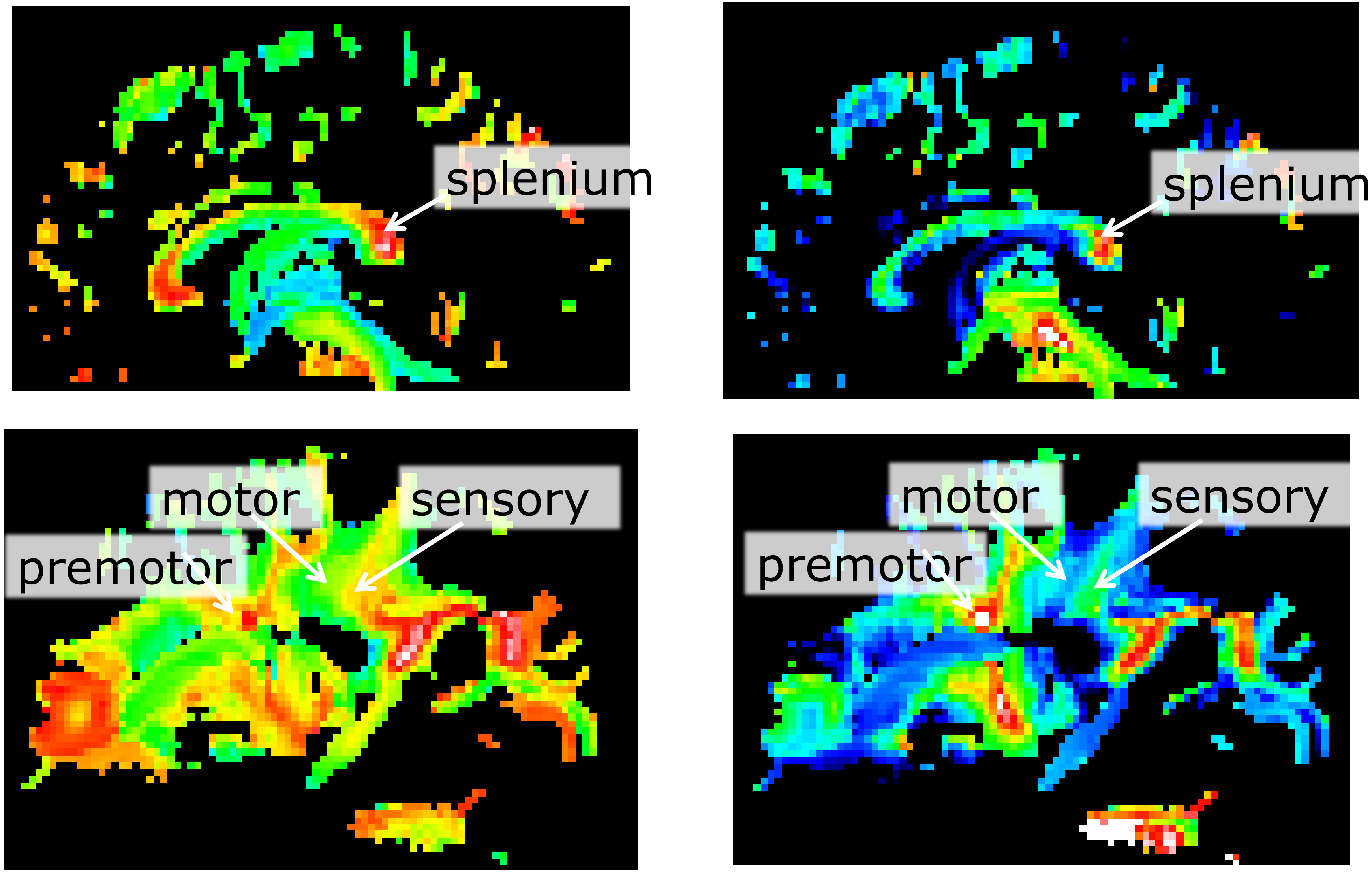
In collaboration with Yaniv Assaf and Assaf Horowitz, Aboititz et al. 1992

Density and Ratio of small/big fibers

subj 2

Relative fiber density

Ratio small/large fibers



In collaboration with Yaniv Assaf and Assaf Horowitz, Aboititz et al. 1992

Axonal diameter - Perspectives

PhD and Post-doc positions available

- Stronger gradients allowed to
  - reduce δ (from 22 to 9 ms compar
  - reduce Δ (from 100 to 40 ms)
  - increasing the sensitivity to shorter displacements
- Optimize 3D AxCaliber model / acquisition
  - crossing fibers + myelin
- Combination with MEG measurements
  - with T. Knösche and G. Deco
  - transfer speed, synchronization, information flow
- **Can we detect plastic changes in axonal diameter?**

Quantitative Brain Plasticity: Application to in second language learning

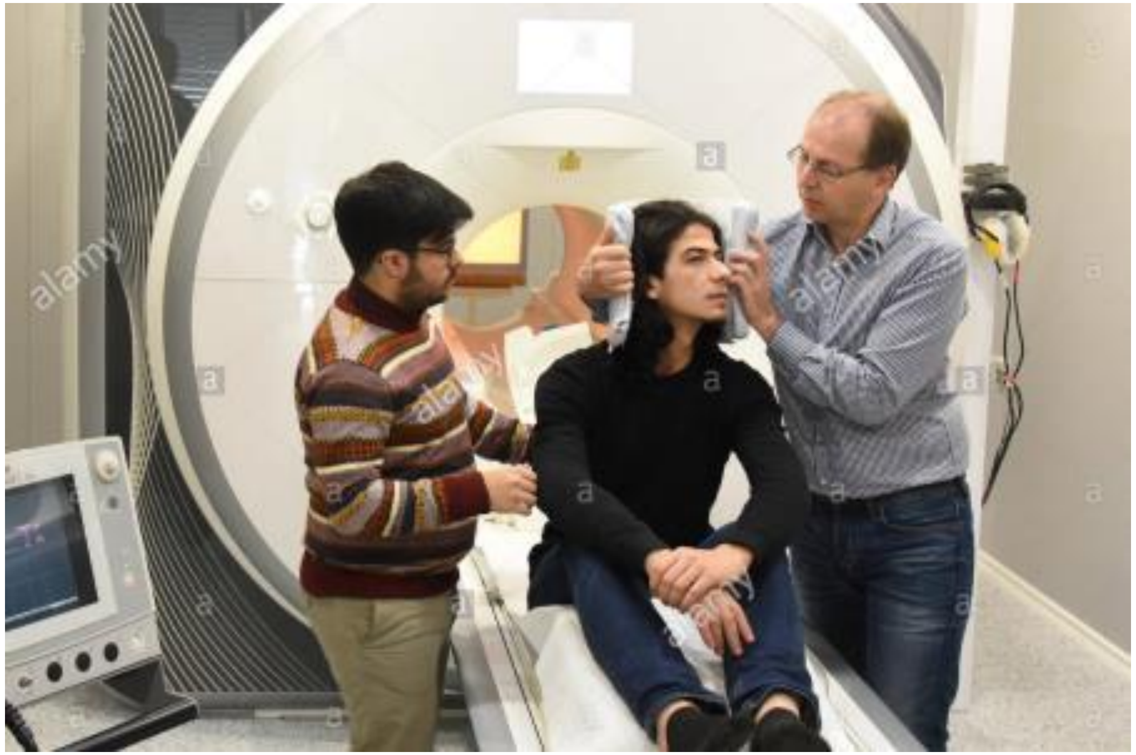
Prof. A.D. Friederici

Tomás Goucha

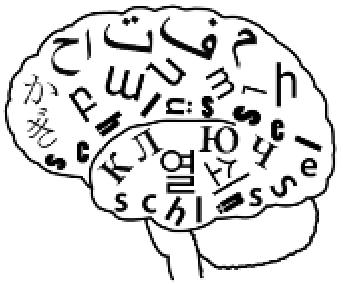
How does adult brain **change** when **learning** a second language?

What are the dynamic mechanisms of long term brain plasticity?

In 2015, we had a crazy idea!



Second language acquisition



90 Arabic mother tongue speakers

- Intensive course — 6 Months — 5 h x 5 days a week
- ~300h of language learning : level B1 (CEFR)

T_0 – before course
only **Structural MRI**

T_1 – after 3 months
Structural and **functional MRI**

T_2 – after 6 months
Structural and **functional MRI**

56 complete datasets
50 German control datasets without training
Follow up: 6 months (35 people & Connectom)

MRI protocol

- High resolution **diffusion** MRI (PRISMA)
  - 1.3 mm isotropic
  - 60 directions, b=1000, SMS 2, GRAPPA 2, 21 min
- **NODDI** (neurite orientation dispersion and density imaging), 7 min
- Quantitative **Multiparametric Mapping** (qMPM) sequence
  - Multi-echo 3D FLASH (25 min) including:
  - predominant T1-, PD-, and MT-weighting
  - RF transmit field map, static magnetic (B0) field map
- Task **fMRI**. 2.5 mm isotropic, TR 1.5 sec

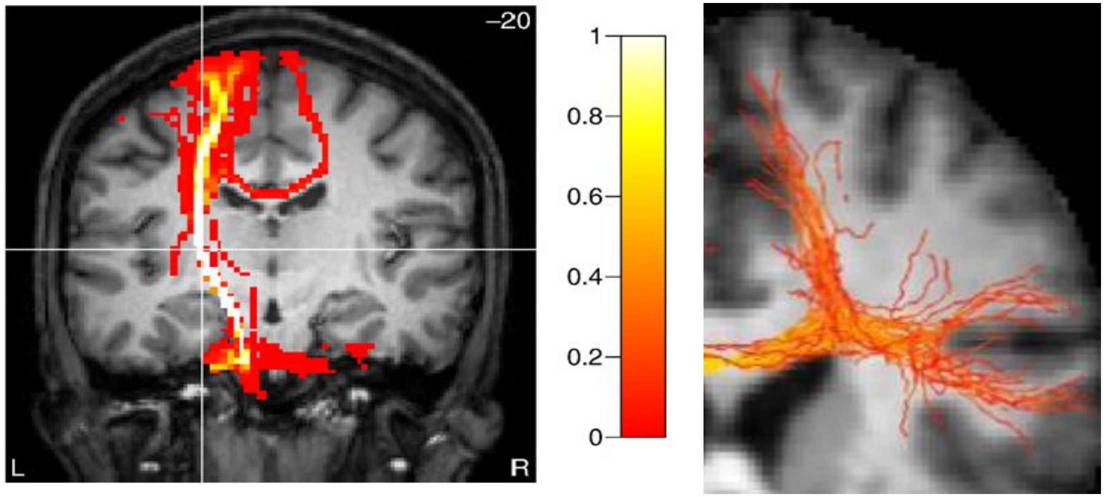
Zhang et al., Neuroimage, 2012; Weiskopf et al., Curr Opin Neuro, 2012

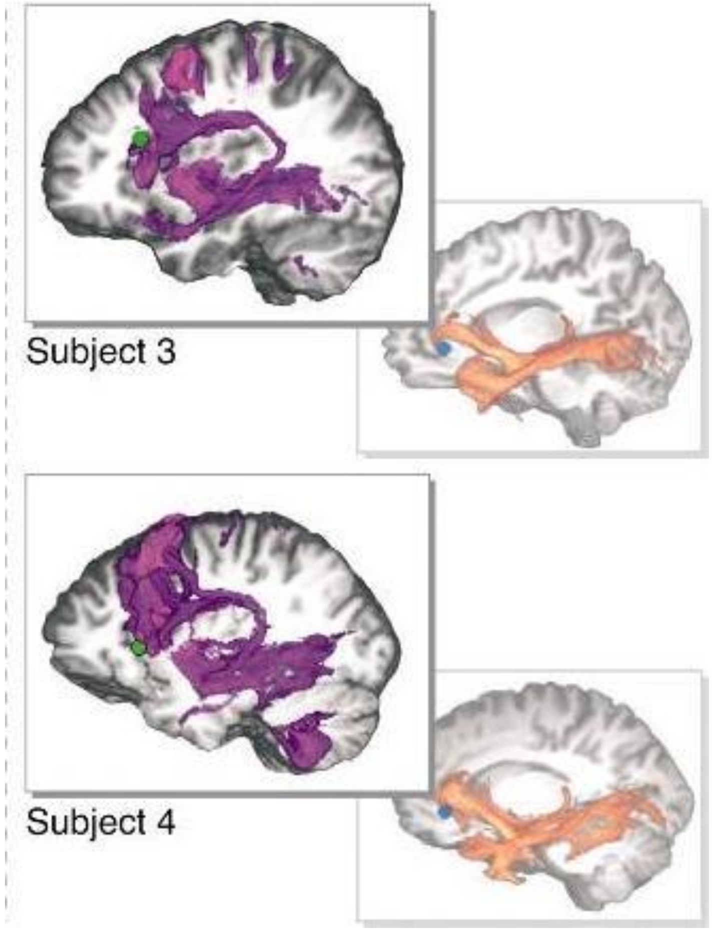
- Initial research questions:
- Do we find differences in the mother tongue language networks?
- Does the network of L2 learners adapt to the shape of the new language?

New method: Directly compare probabilistic connectivity maps

- "Free" probabilistic tracking from seed ROI:
  Example: Broca's area and FOP

- Value in every voxel correspond to the rel. number of streamlines

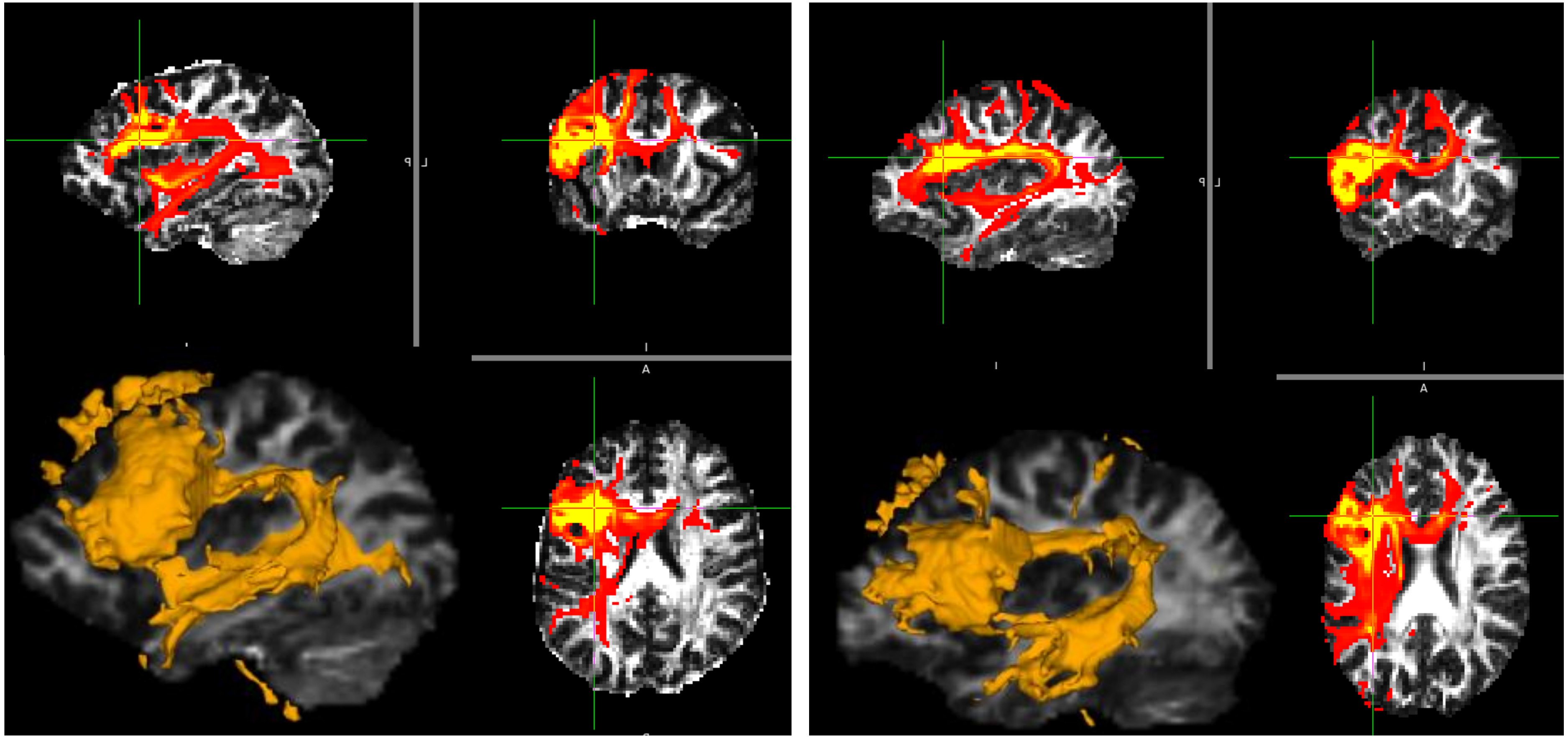




Friederici, Bahlmann, Heim, Schubotz, Anwander. PNAS 2006; Kaden, Knösche, Anwander, Neuroimage, 2007.

How can we compare two connectivity maps?

- Example: BA44 connectivity of two participants



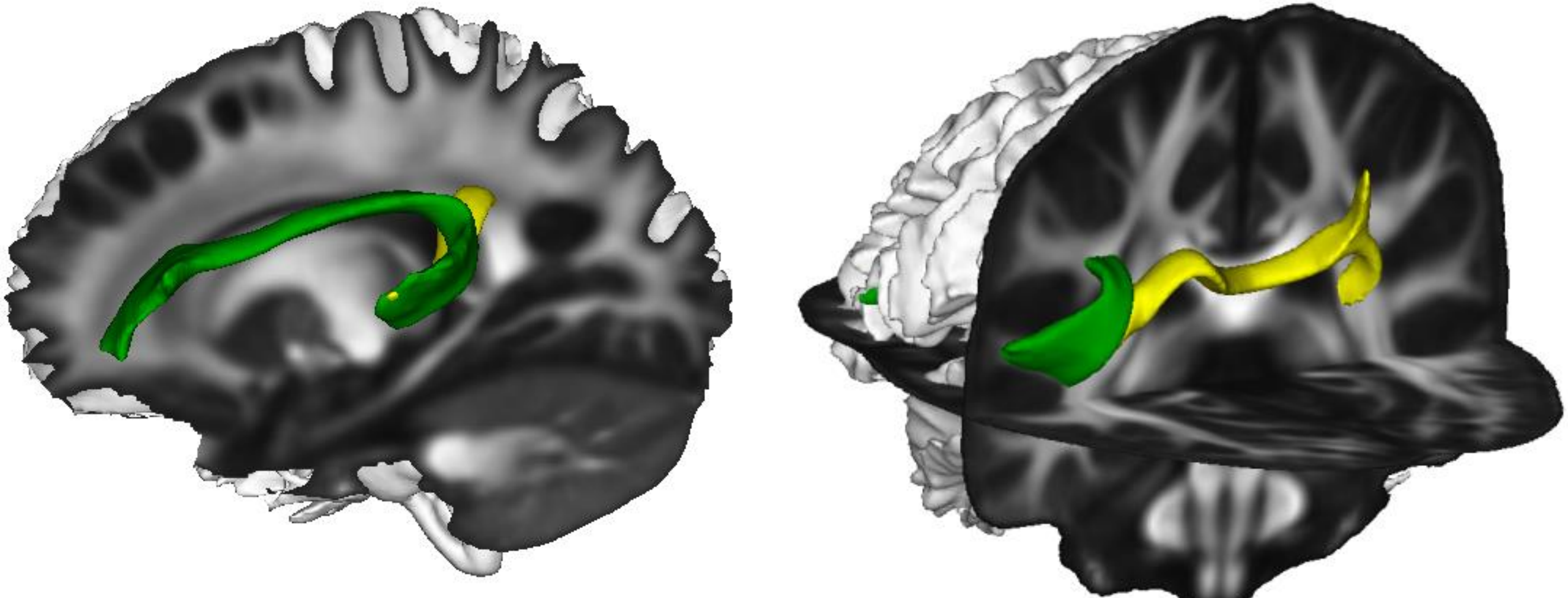
Statistical comparison: 3 Steps

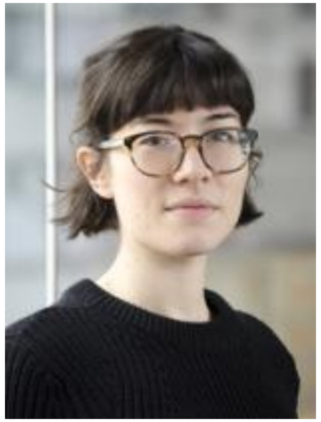
1. **Normalize connectivity maps** to common template (using the TBSS no-FA procedure on connectivity maps; without skeletonization).

2. **Mask noisy voxels** with low connectivity values: Probabilistic tractography is only reliable in region of high connectivity (sufficient sampling).

3. **Voxel based statistics** using SPM with cluster level correction

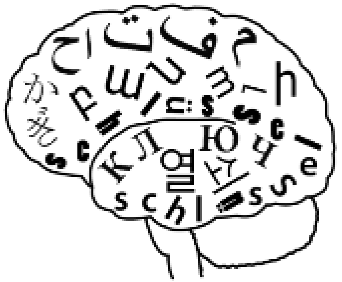
Mother tongue comparison (T_0) – German vs Arabic





Helyne Adamson

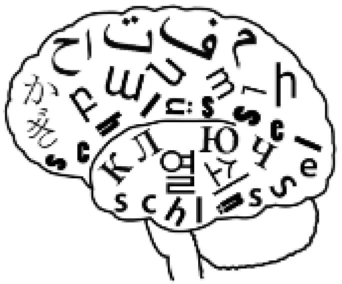
- German speakers show stronger intrahemispheric connectivity (green) (prob. Tract. From post. STP
- Arabic speakers: stronger interhemispheric conect. (yellow)



The **language network**, through **lifelong** exposure, bears **traces** of a subject’s mother tongue

How does this **mature** network **change** when **learning** a second language?

Language fMRI experiment L1/L2



- **Lexical task (word level semantic) :**
  - Word list with matching / non-matching target word; ex.:

    *“house – apartment – room   target word: **door**”*

- **Sematic task (sentence level):**
  - Sentence with matching / non-matching target word; ex.:

    *“The hardworking student reads in the library **a tree**”*

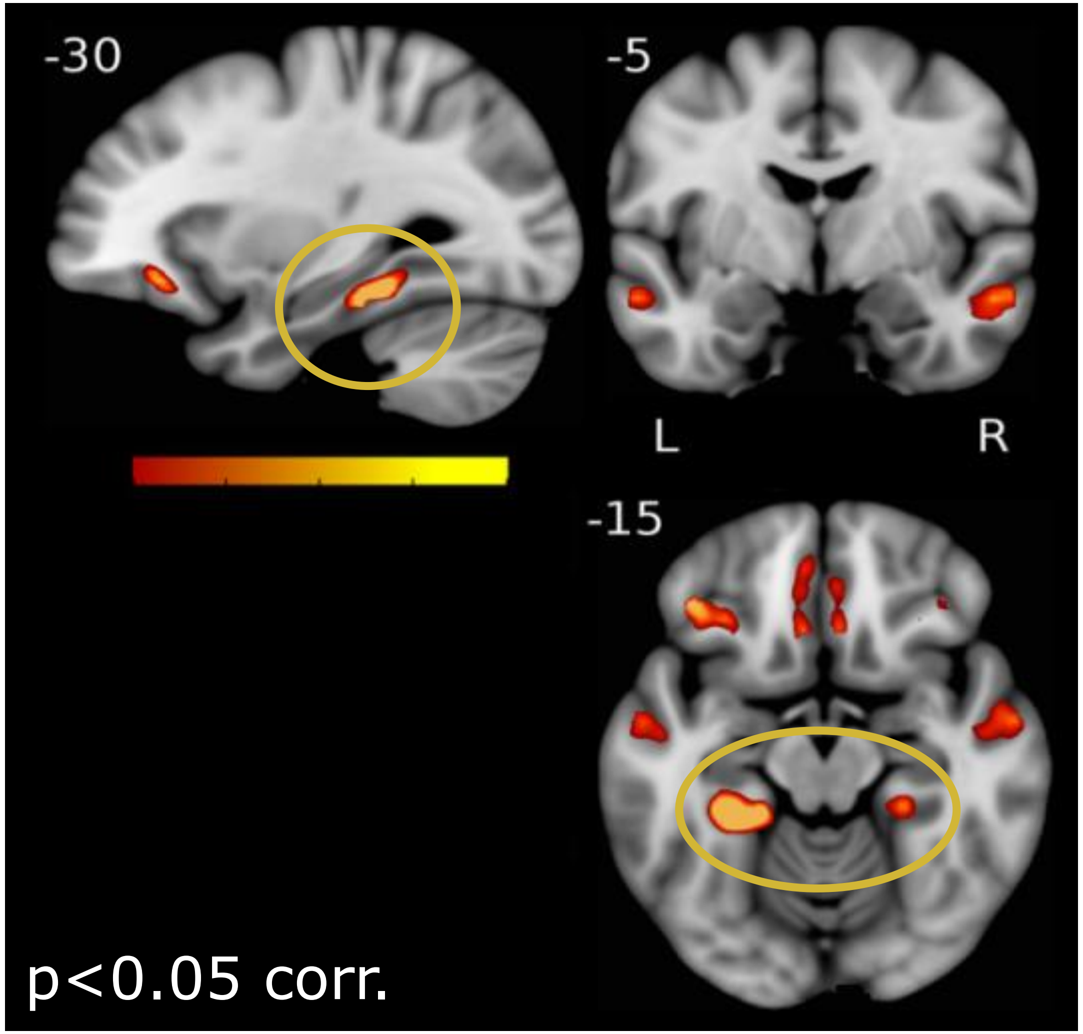
- **Grammar task:**
  - Grammaticality judgment of a sentence

    “The book, that read me, is long.”

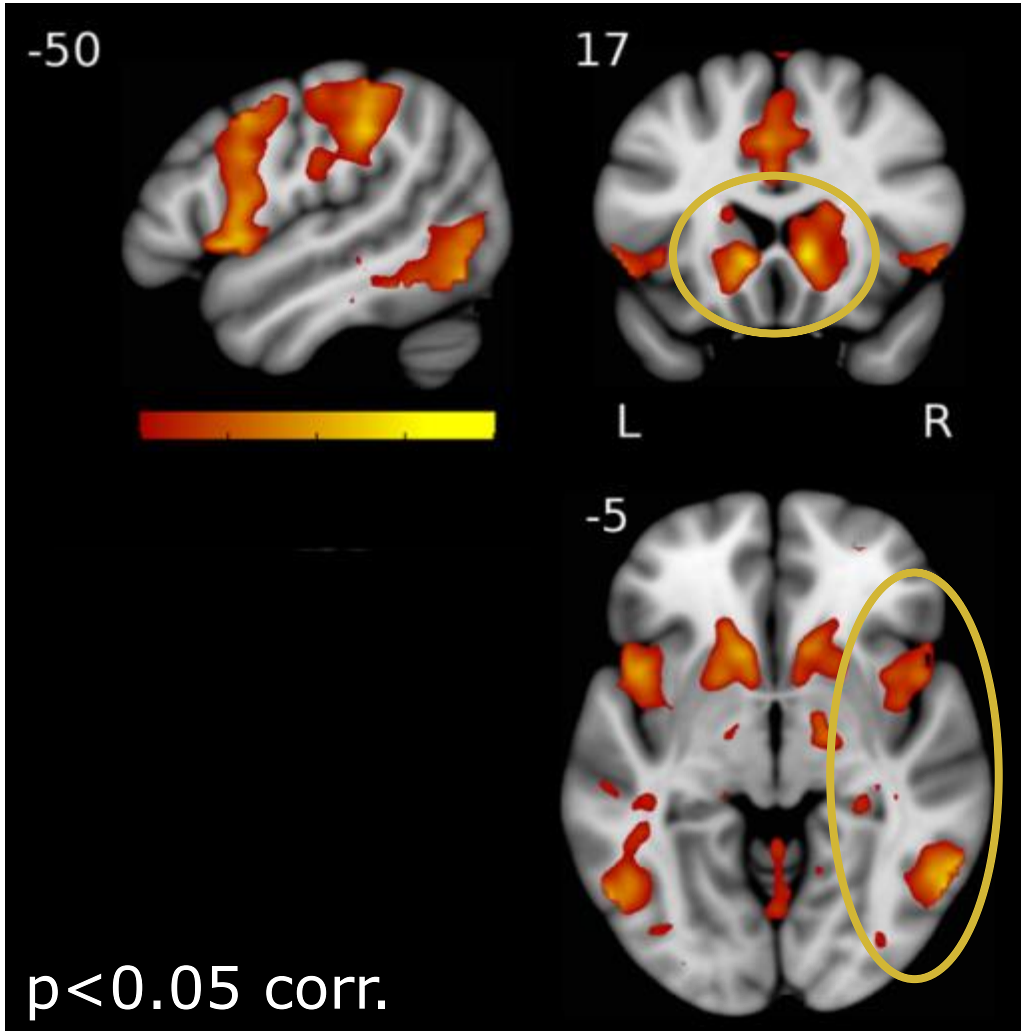
Martin Lisanik

L2 fMRI after 3 months learning

fMRI semantic > lexical task



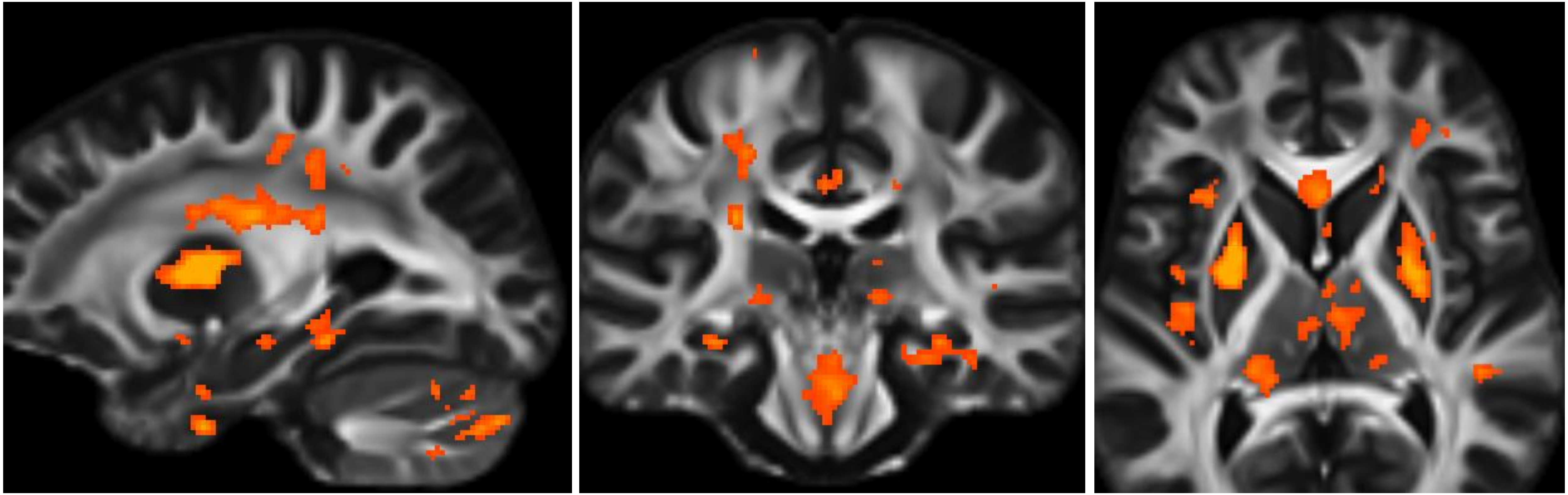
fMRI syntactic > lexical task



Longitudinal diffusion MRI analysis

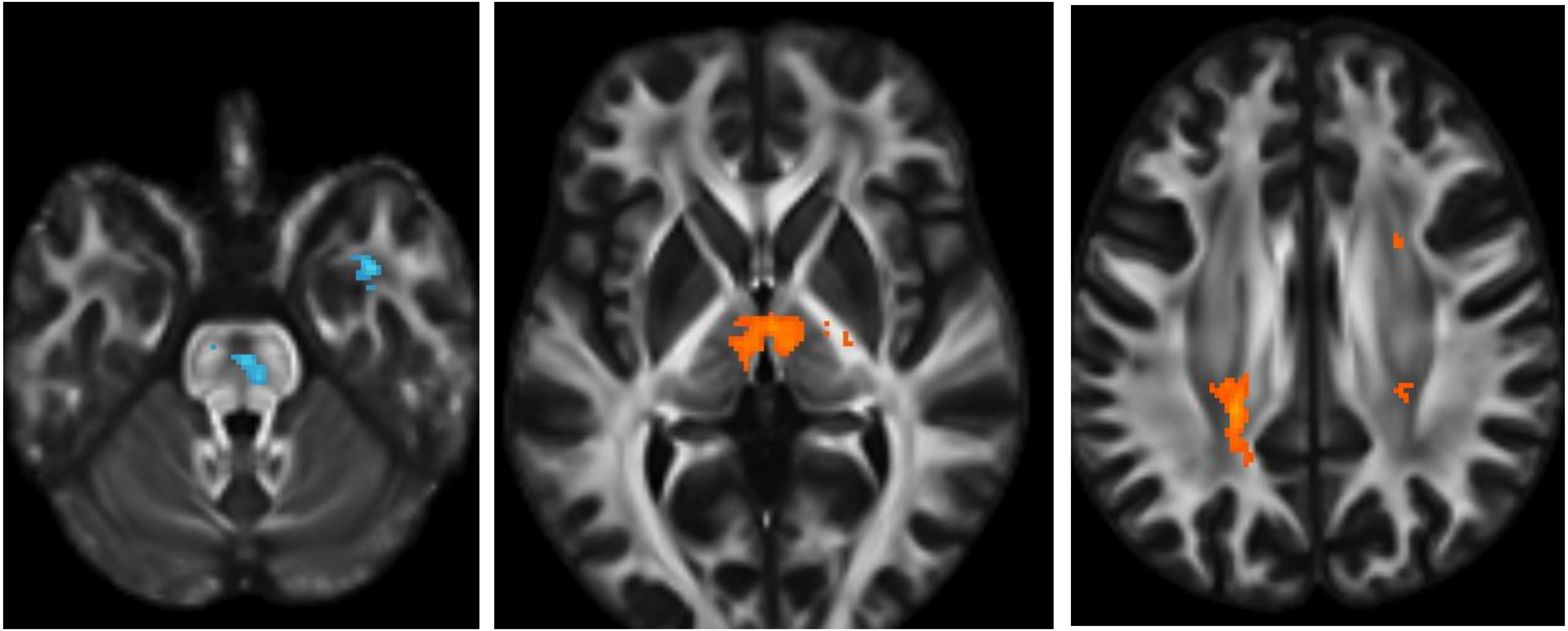
- 3* 60 diffusion directions, **1.3 mm isotrop**
- **dwidenoise** (MrTrix)
- **TopUp/eddy** artefact correction (FSL)
- DTI fit and FA computation
- ANTS **within subject** and **group FA template** generation
- Normalization on single subject and group template
- 3mm FWHM smoothing
- SPM – VBS statistics:
  - **f-test** on all timepoints and
  - **t-test** between timepoints

FA changes within 6 months learning



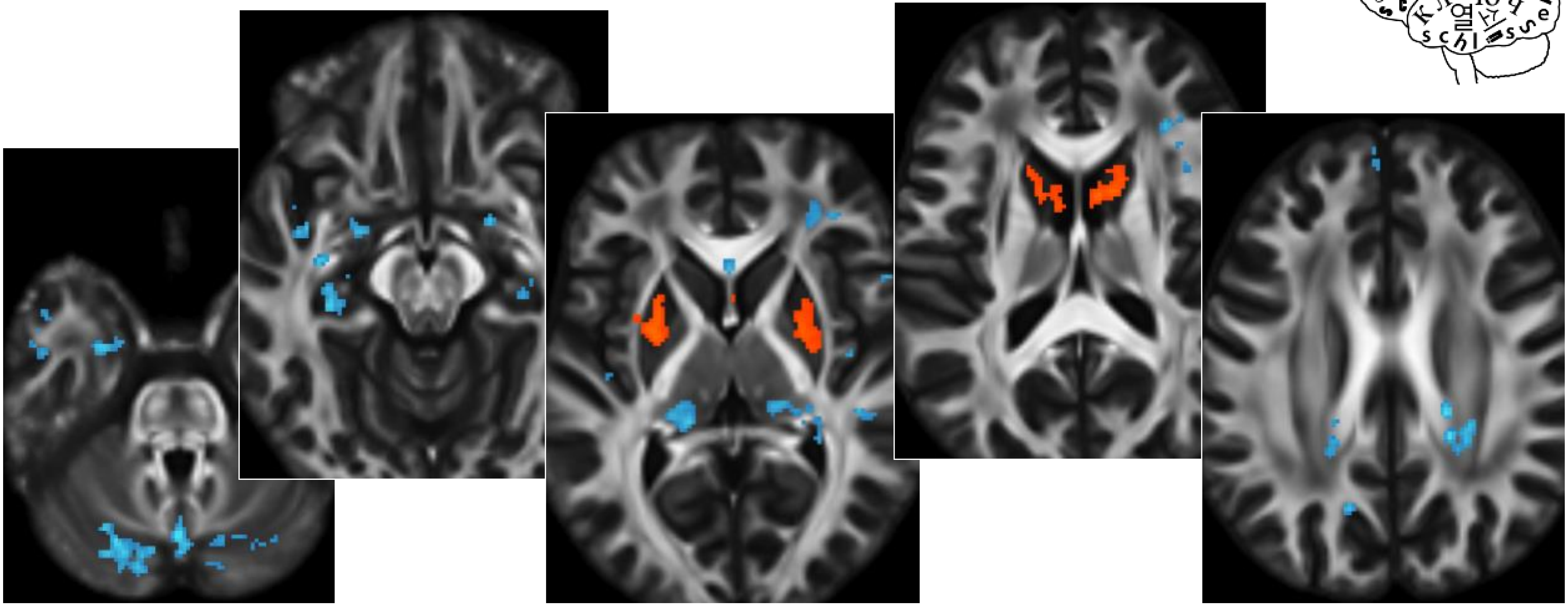
- Clusters ($p<0.05$ corr.) of significant FA changes (N=56) after learning German as second language (f-test)

FA increase/decrease: month 0-3



- Clusters (p<0.05 corr.) of significant FA changes (N=56)
  blue: decrease; orange: increase

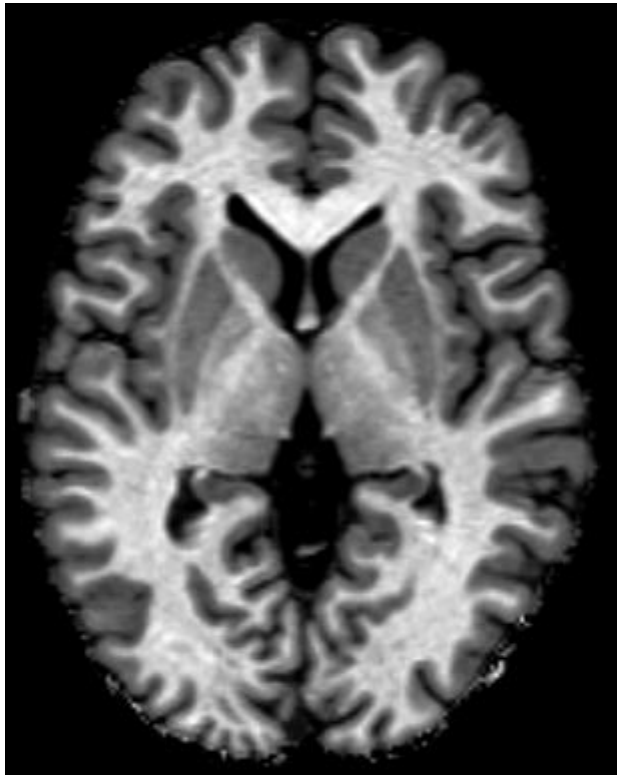
FA increase/decrease: month 4-6

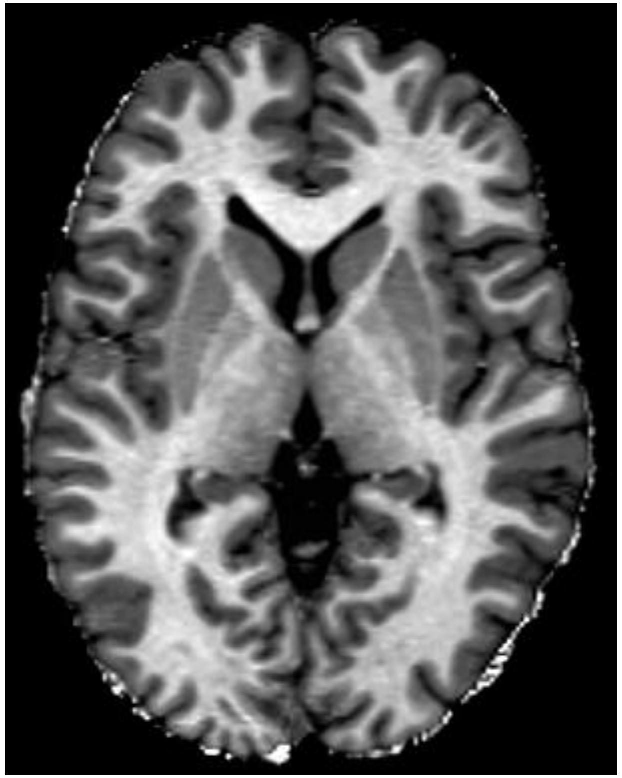


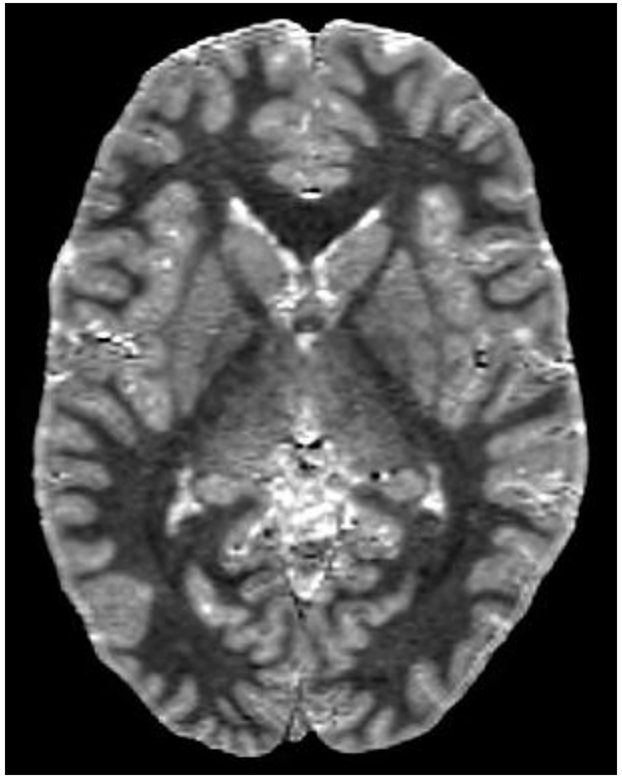
- Clusters ($p<0.05$ corr.) of significant FA changes (N=56)
  blue: decrease; orange: increase

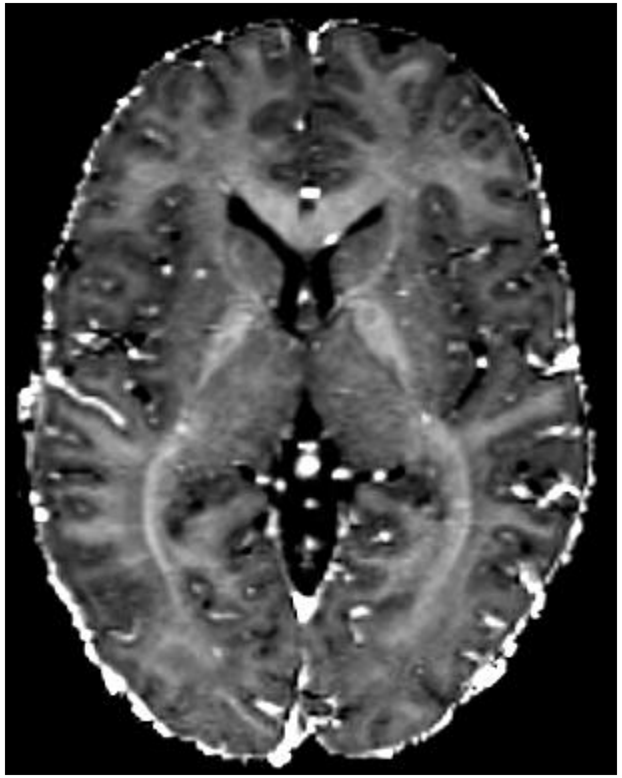
Longitudinal analysis of quantitative MPMs

MT maps (magnetization transfer)	R1 maps (T1 relaxation rate)	PD maps (proton density)	R2* maps (T2 relaxation rate)









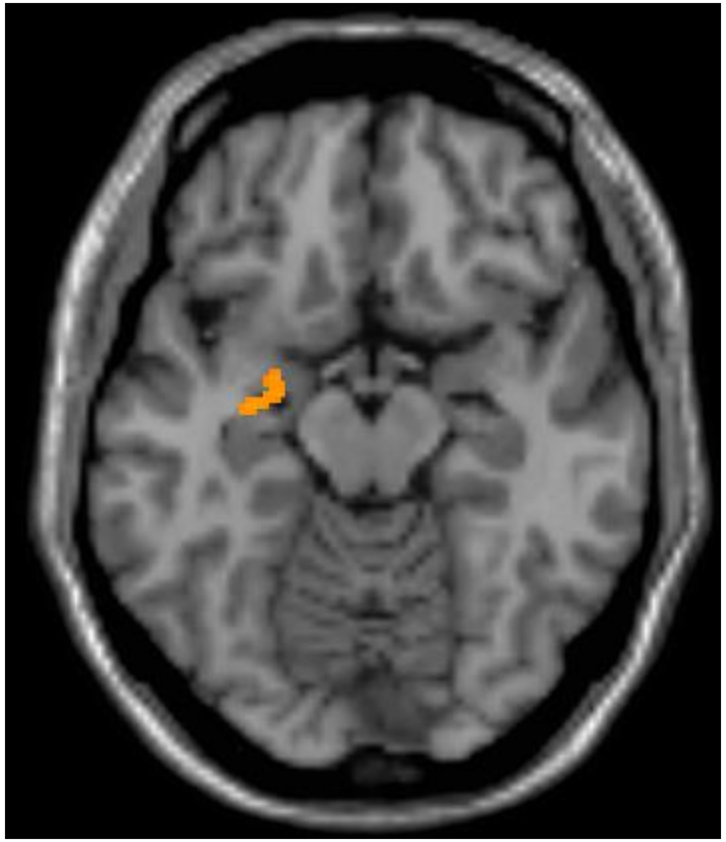
Weiskopf et al., CurrOpinNeurol 2015

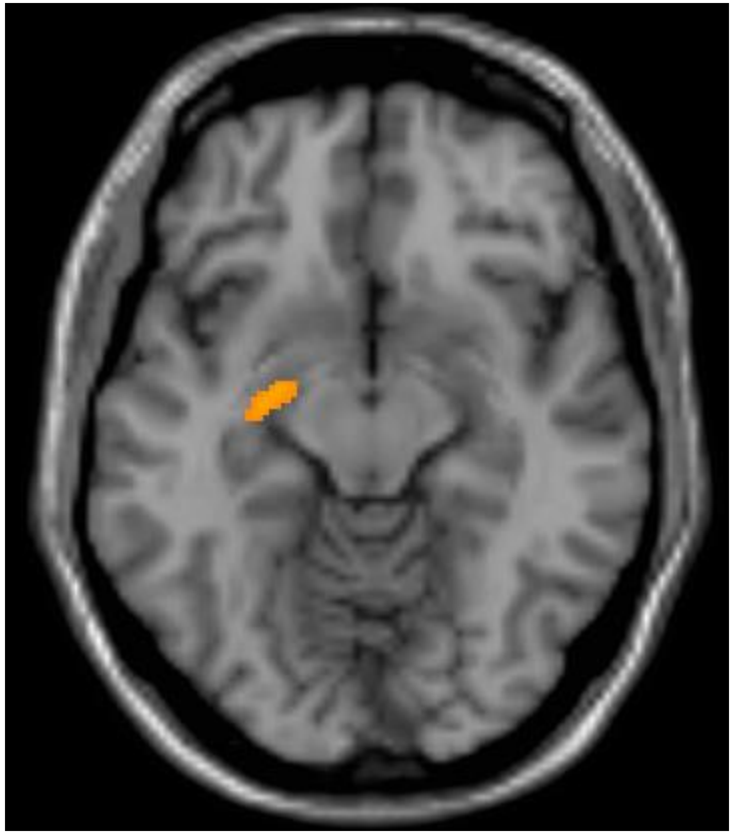
Longitudinal analysis of quantitative multiparametric maps (MPM)

- 1mm isotropic
- Processing with the **SPM-VBQ** toolbox
- Segmentation, normalization
- Tissue specific smoothing (5mm FWHM)
- T-Test between timepoints (SPM)

Weiskopf et al.,CurrOpinNeurol 2015

Preliminary results: MT changes month 0-3





- **orange: increase** in 3 months within **gray matter**
  Clusters ($p<0.05$ corr.) of significant MT changes ($N=56$)

Preliminary results: R1 changes in 3/6 months

- **orange: increase** in 6 months within **white matter**
  blue: decrease in the first 3 months within the **gray matter**
  Clusters ($p<0.05$ corr.) of significant R1 changes (N=56)

Relate changes to language performance

- Cognitive assessment
- Language proficiency
  - comprehension, production
  - semantics
  - phonetic
  - grammaticality judgement

- Executive functions
  - e.g. working memory

Conclusion and perspectives

- Understand the biological mechanisms of brain plasticity
- Use of additional quantitative modalities to characterize the dynamic changes (**NODDI**, tract based analysis
- Build combined models of the multiparametric maps and the diffusion parameters including **axonal diameter**
- Use of machine learning and multivariate analysis to predict performance from the brain data

Thank you!

شكراً جزيلاً!

Nik Weiskopf

Angela D. Friederici

T. Goucha

A. Lutti, T. Leutritz

T.Witzel

M. Schwendemann

M. Lisanik, H. Adamson

Departments of NPHY and NPSY @ MPI CBS and all collaborators and you for your questions!

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