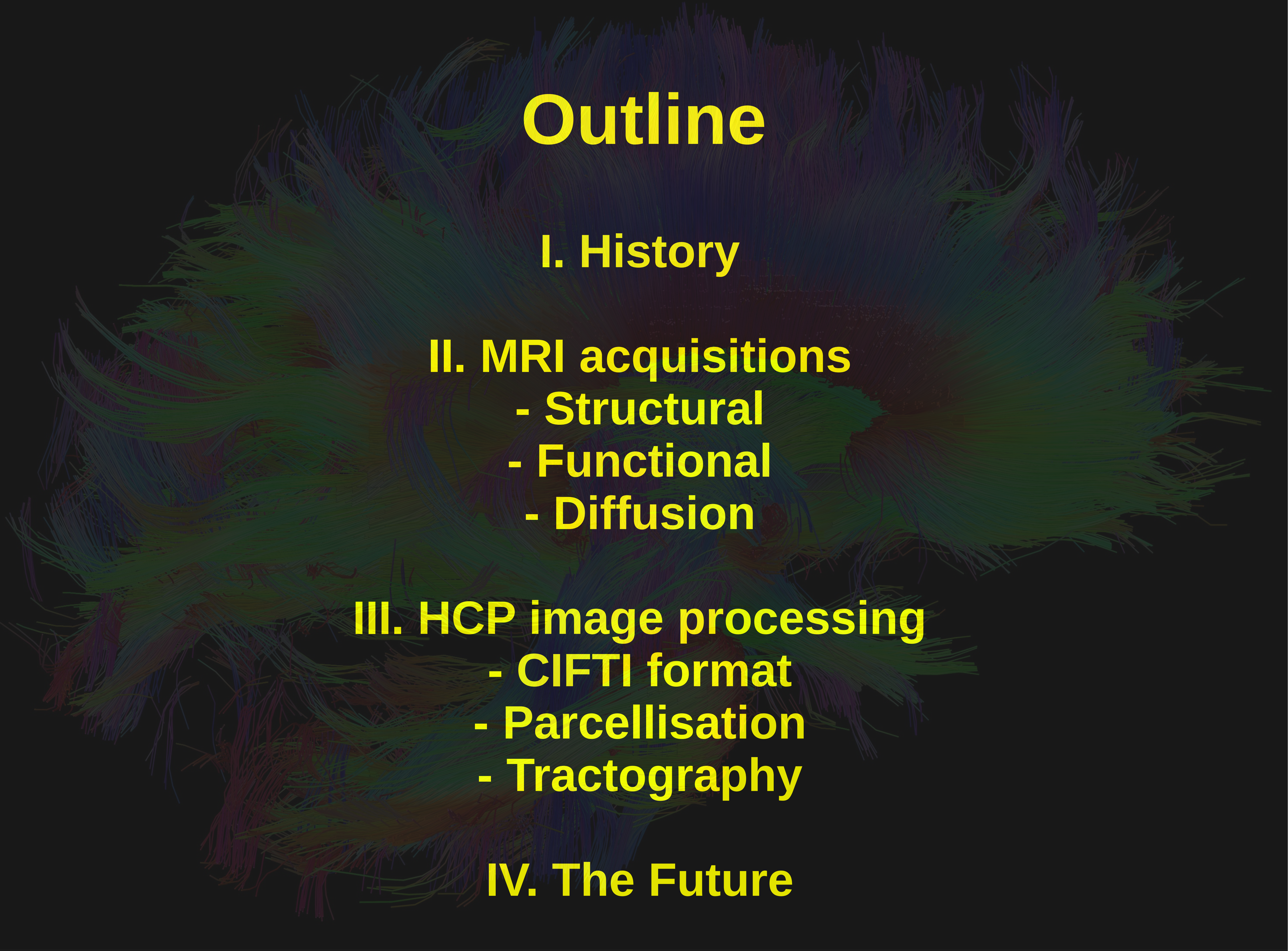
The Human Connectome Project : Past , Present , Future

Julien Sein
Centre IRM
INT - CERIMED

Background Image: Laboratory of Neuro Imaging and Martinos Center for Biomedical Imaging, Consortium of the Human Connectome Project



Outline

I. History

II. MRI acquisitions
- Structural
- Functional
- Diffusion

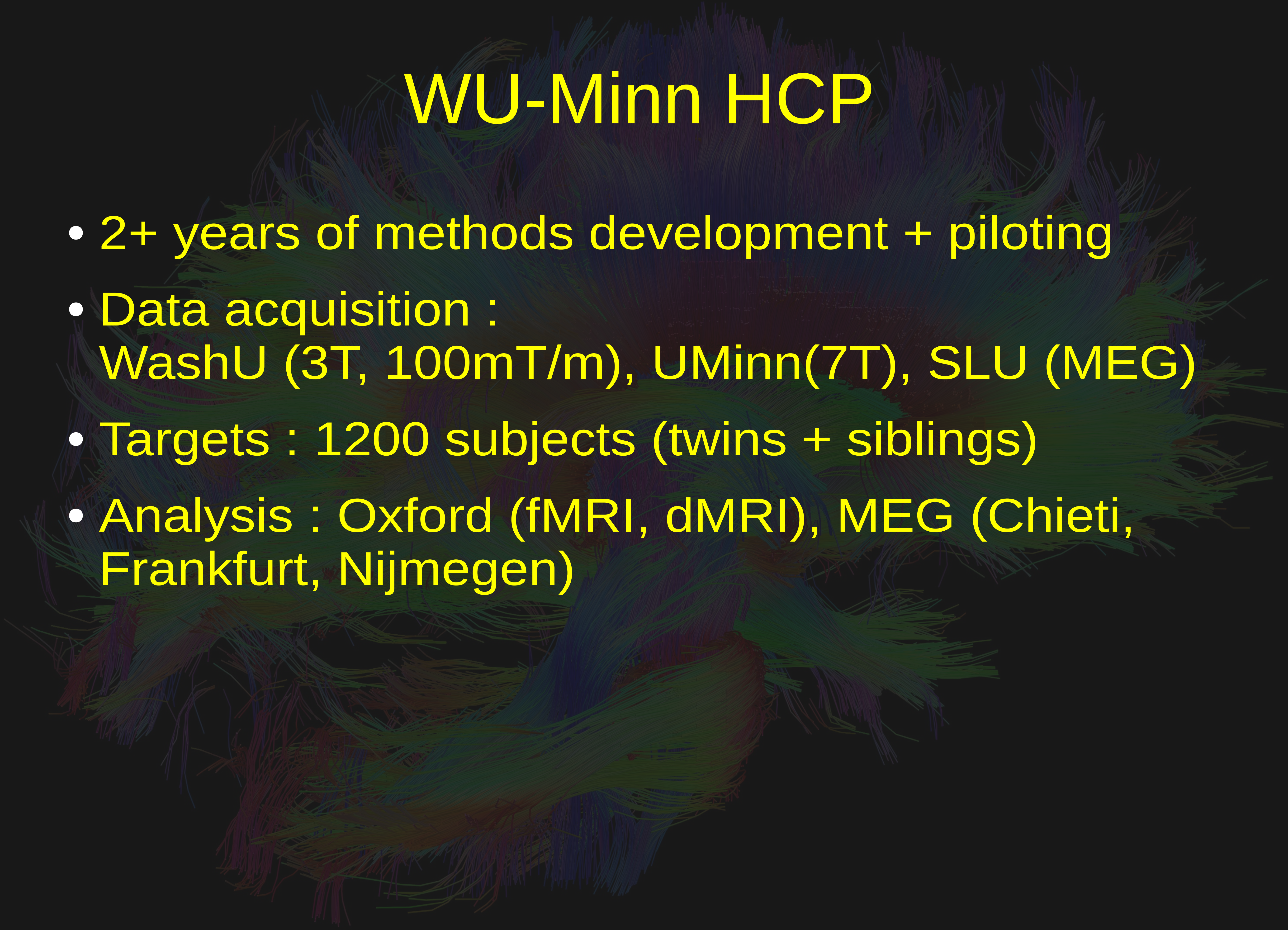
III. HCP image processing
- CIFTI format
- Parcellisation
- Tractography

IV. The Future

The BRAIN Initiative

- **B**rain **R**esearch through **A**dvancing **I**nnovative **N**eurotechnologies launched by Obama administration in 2009 supported by National Institute of Health, Defense Advanced Research Projects Agency and National Science Foundation
- Launch with $100 million of initial funding
- NIH awards to two HCP consortia
    - WU-Minn consortium
    - MGH/UCLA consortium (MGH scanner with 300mT/m gradients)
    - 2013 : « Lifespan pilot » supplements to WU-Minn, MGH consortia

WU-Minn HCP



- 2+ years of methods development + piloting
- Data acquisition :
  WashU (3T, 100mT/m), UMinn(7T), SLU (MEG)
- Targets : 1200 subjects (twins + siblings)
- Analysis : Oxford (fMRI, dMRI), MEG (Chieti, Frankfurt, Nijmegen)

1) <u>Acquire</u> data on brain structure, function, and connectivity in healthy adults (twins and non-twin siblings).

- Improved scanners, pulse sequences
- Multimodal imaging (~4 hours total scan – 4 x 1h sessions)
- Data quality: exceptionally high!
- 1200 subjects studied, ~1100 with MRI (completed September, 2015)
- 184 subjects scanned at 7T (completed November, 2015)
- Behavioral data (478 ‘subject measures’)
- Magnetoencephalography (95 subjects): Task-MEG, resting-state MEG
- Blood for genotyping (to dbGAP in fall, 2016)

2) <u>Analyze</u> the data

- Improved HCP preprocessing pipelines
- Better visualization (Connectome Workbench)
- Advanced analyses

Van Essen, HCP course 2016

3) Share the HCP data

- ConnectomeDB database – a robust infrastructure
- 900-subject data release (June, 2015)
- 7T subjects (73 subjects, Part 1 – June, 2016)
- MEG data release (95 subjects, November, 2015)
- 1100-subject release - fall, 2016
- >6,000 investigators accepted HCP Data Use Terms (~600 Restr. Access)
- >10 petabytes (10,000 TB) of HCP data shared (7 PB downloaded, 3 PB in hard drives shipped)
- Release of extensively analyzed data

  ConnectmeDB: 'Network matrices'; 'MegaTrawl; dense connectome)

  BALSA database: Glasser et al., 2016 (Nature; Nature Neuroscience)
- >140 publications using HCP data
- HCP website: www.humanconnectome.org

The HCP-style Neuroimaging Paradigm

Seven core tenets

1) Collect lots of multimodal imaging data.
2) Maximize resolution, data quality (e.g., multiband fMRI, dMRI)
3) Minimize distortion and blurring of each subject's data
4) Respect geometry of brain structure ('CIFTI grayordinates').
5) Align data precisely across individuals and across studies.
6) Analyze results using an accurate brain parcellation.
7) Freely share the extensively processed data.

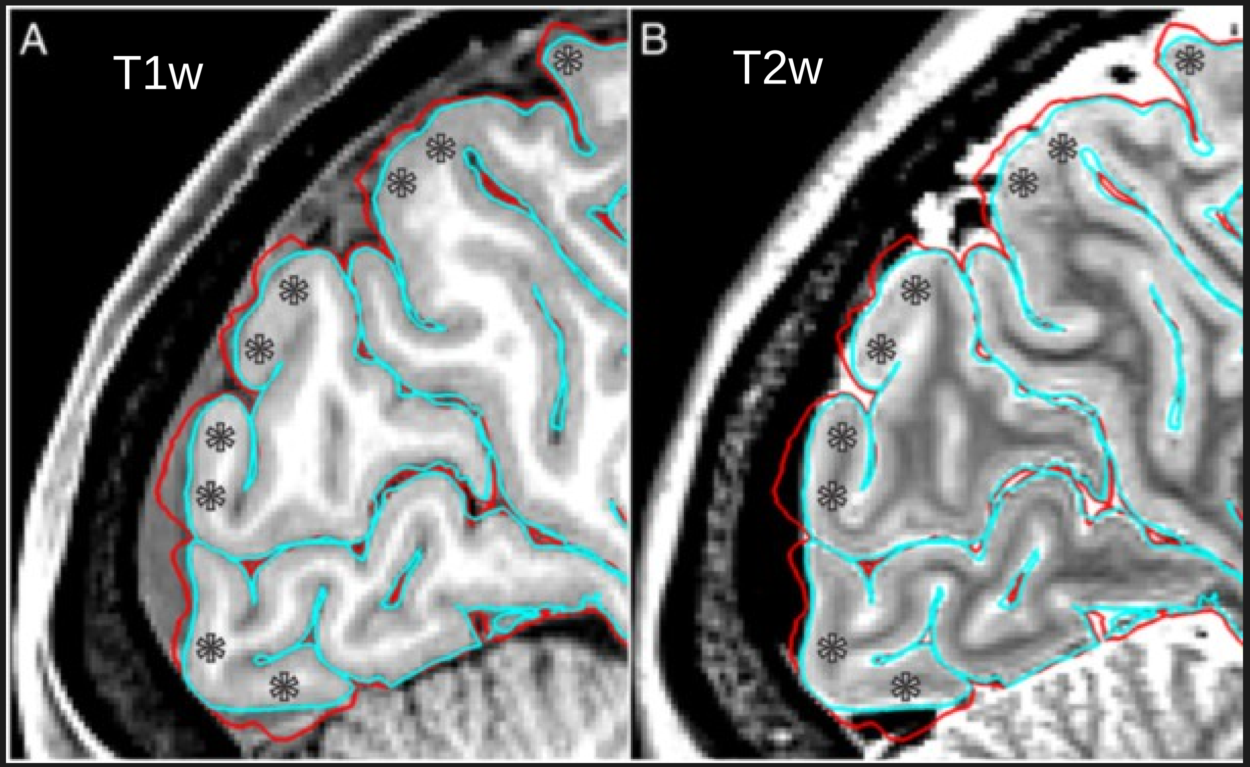
Glasser, Smith, Marcus, Andersson, Auerbach, Behrens, Coalson, Harms, Jenkinson, Moeller, Robinson, Sotiropoulos, Xu, Yacoub, Ugurbil, and Van Essen, 2016. The Human Connectome Project's neuroimaging approach. *Nature Neuroscience* doi:10.1038/nn.4361

Structural MRI

- Required : T1w and T2w MRIs (isotropic voxels)
- Highly recommended : 0.8mm resolution (or better) for improved cortical surface positioning

→ cortical surface area : 100,000 mm²/hemisphere

→ thickness : 1.5mm - 4mm

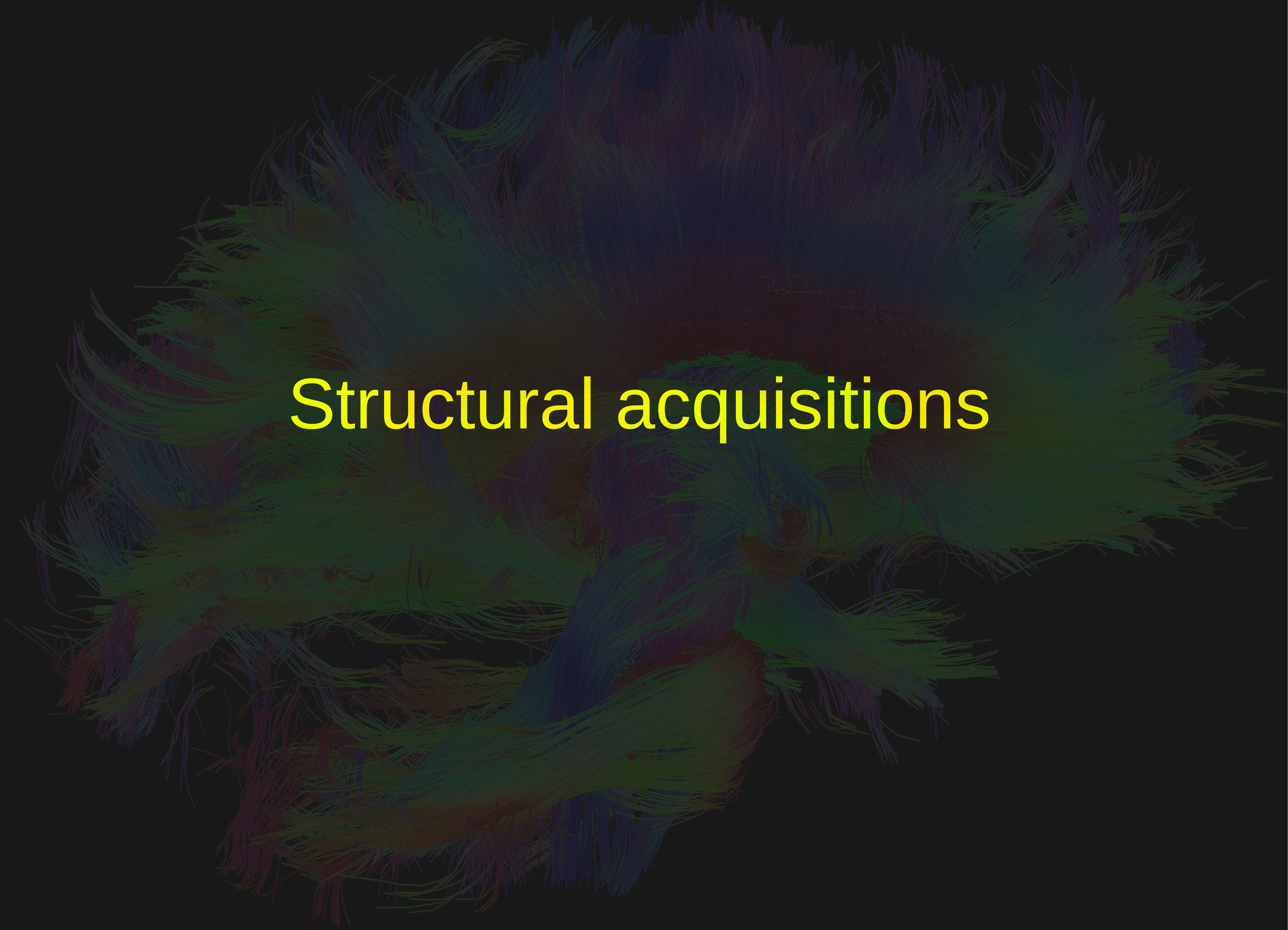


Benefits of high resolution T2w image to assist pial surface placement

- Pial surface from T1w image

- Pial surface after cleanup with T2w image

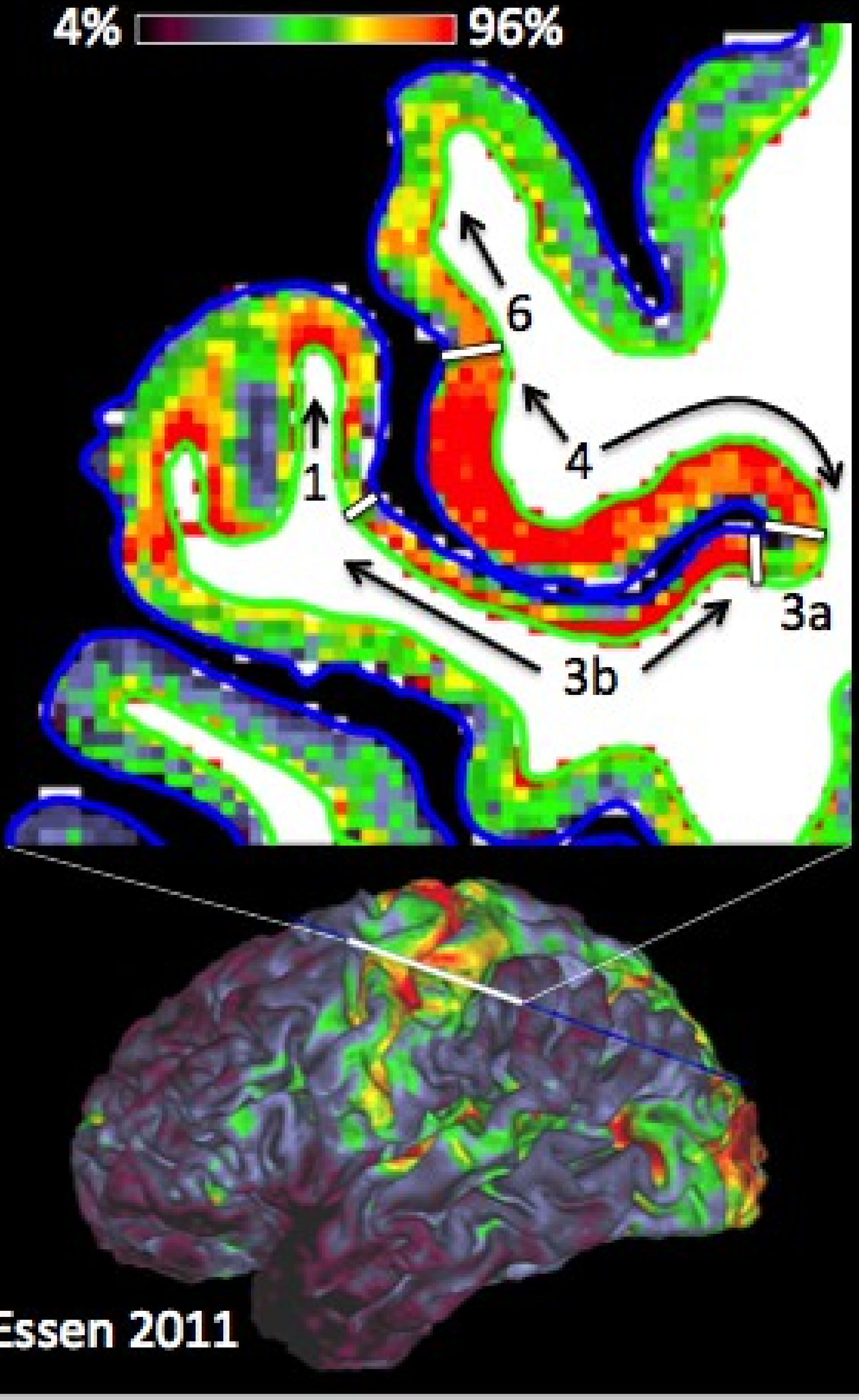
Glasser et al. 2013



Structural acquisitions

T1w/T2w Cortical Myelin Mapping

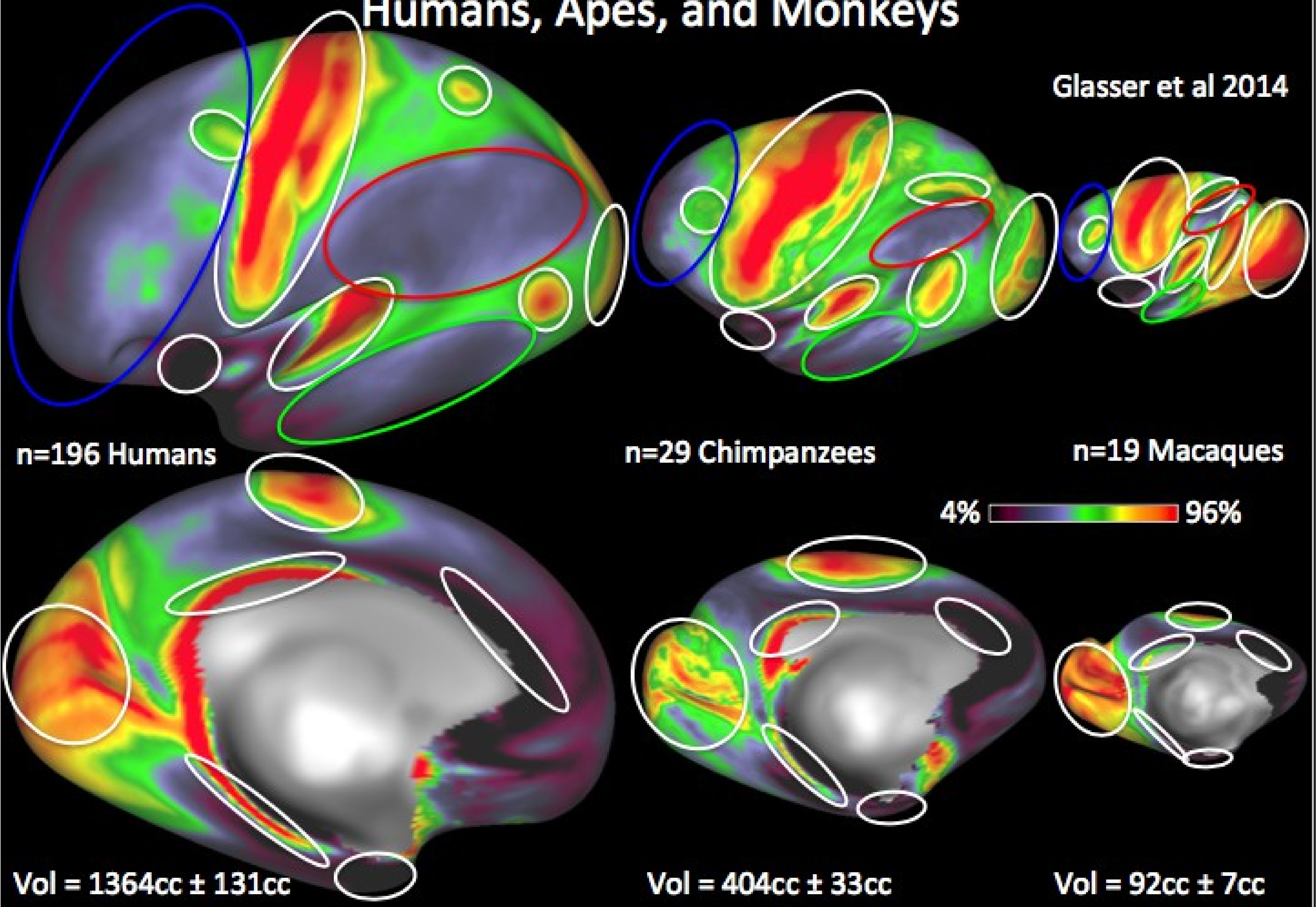
- T1w/T2w cortical myelin mapping uses T1w MPRAGE and T2w SPACE (i.e. variable flip angle TSE T2w image) images
- It uses two of the three forms of myelin contrast, T1 and T2* (in the T1w image) and T1 (in the T2w image)
- Myelin is bright in the T1w image
- Myelin is dark in the T2w image
- Because the contrast is inverted between the T1w and T2w images dividing them enhances contrast for myelin while attenuating MR intensity bias fields
- Visualization and comparison across subjects is greatly aided by mapping to the cortical surface
  - Most reliable measure is overall myelin content across the cortical layers



$$\frac{\mathrm{T1w}}{\mathrm{T2w}} \approx \frac{x * b}{(1/x) * b} = x^2$$

Glasser and Van Essen 2011

Myelin Maps Can Help Identify Homologous Areas Across Humans, Apes, and Monkeys



Glasser et al 2014

n=196 Humans

n=29 Chimpanzees

n=19 Macaques

Vol = 1364cc ± 131cc

Vol = 404cc ± 33cc

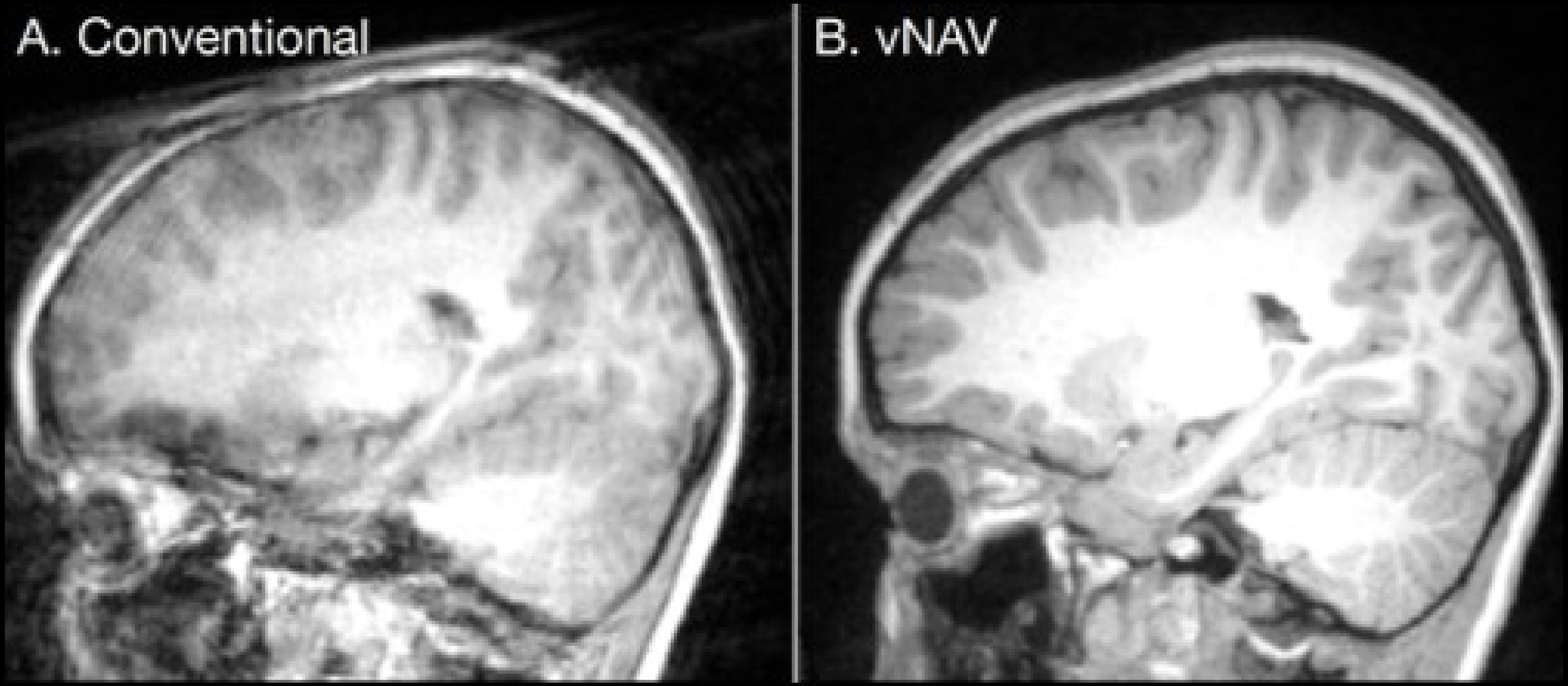
Vol = 92cc ± 7cc

Structurals

Consider use of volumetric navigator ("vNav") correction to reduce the impact of motion on T1w/T2w structurals

Tisdall et al., *NeuroImage*, 2016

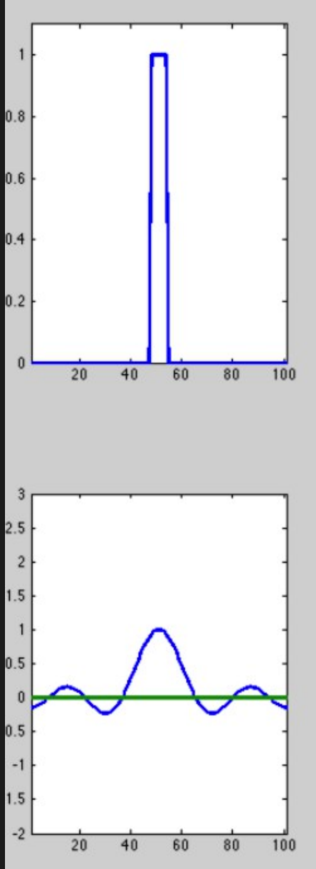
7 y.o. girl with Tourette's



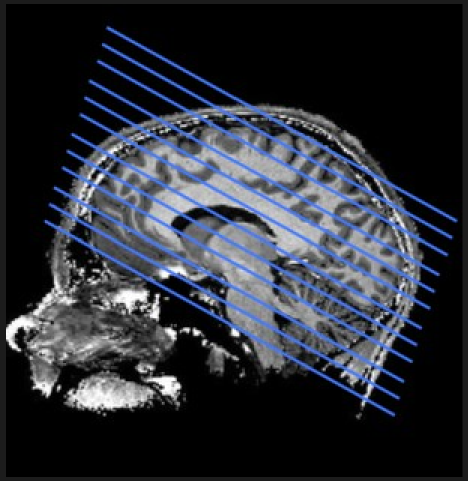
Courtesy of Nico Dosenbach

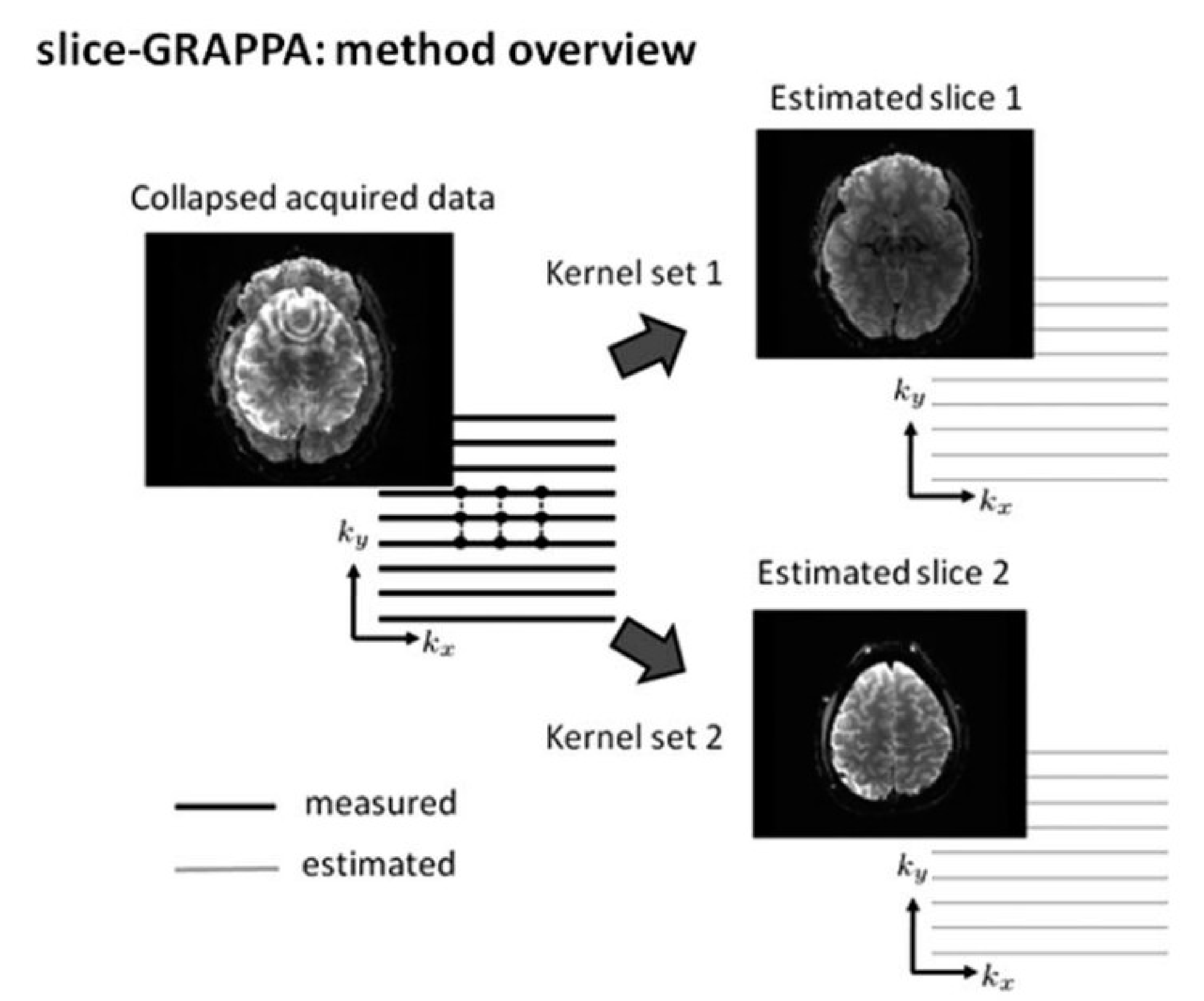
Functional and diffusion acquisitions

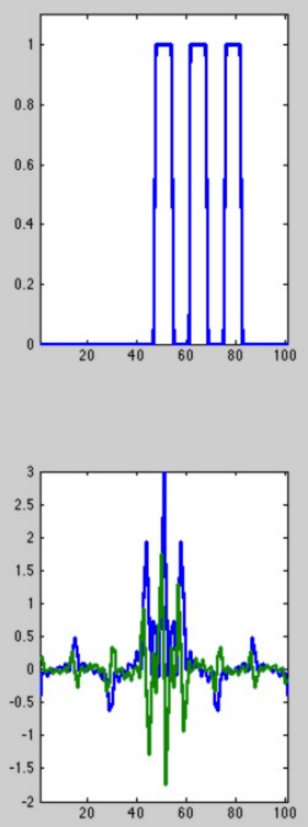
Multiband acquisition



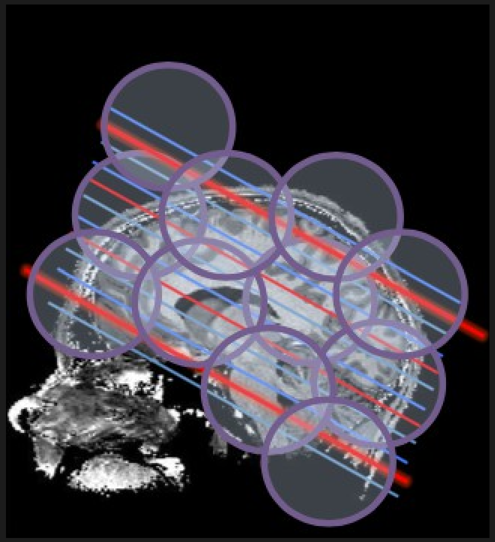
Conventional imaging :
Whole volume TR
=N_{slice} x Time per slice





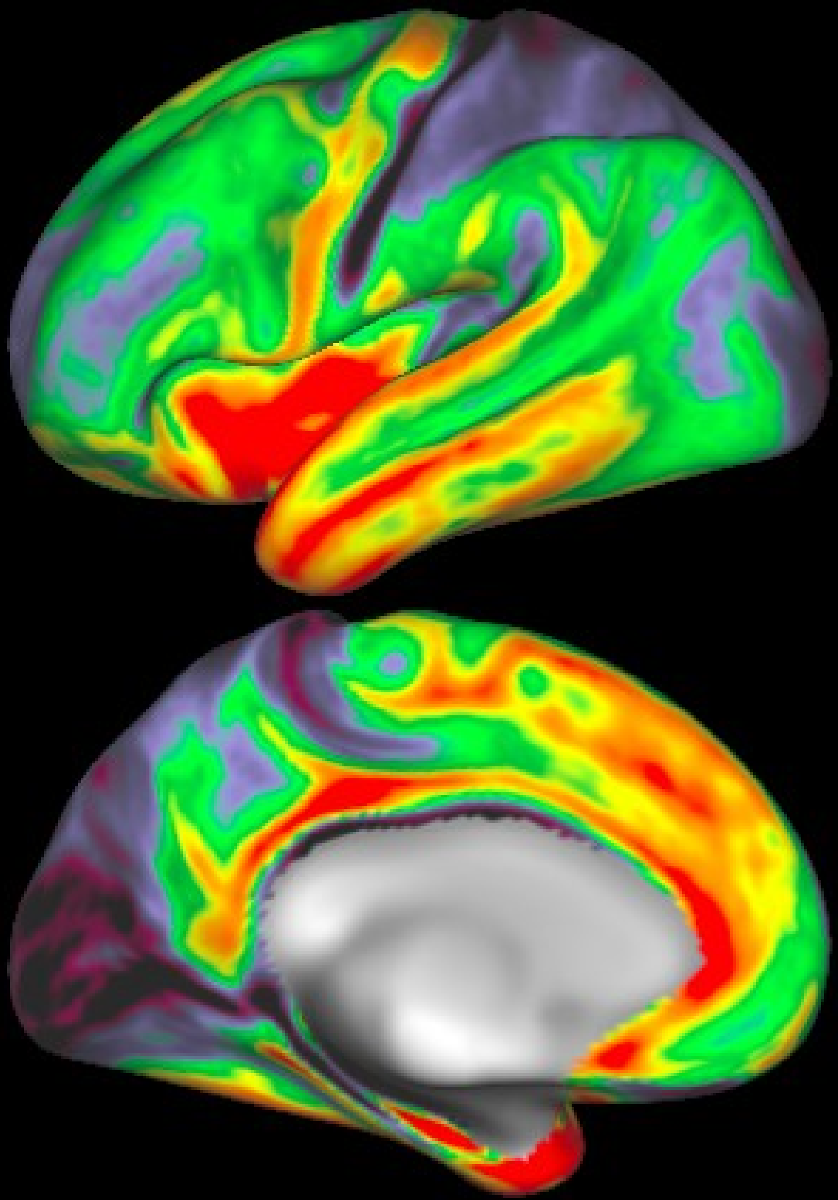


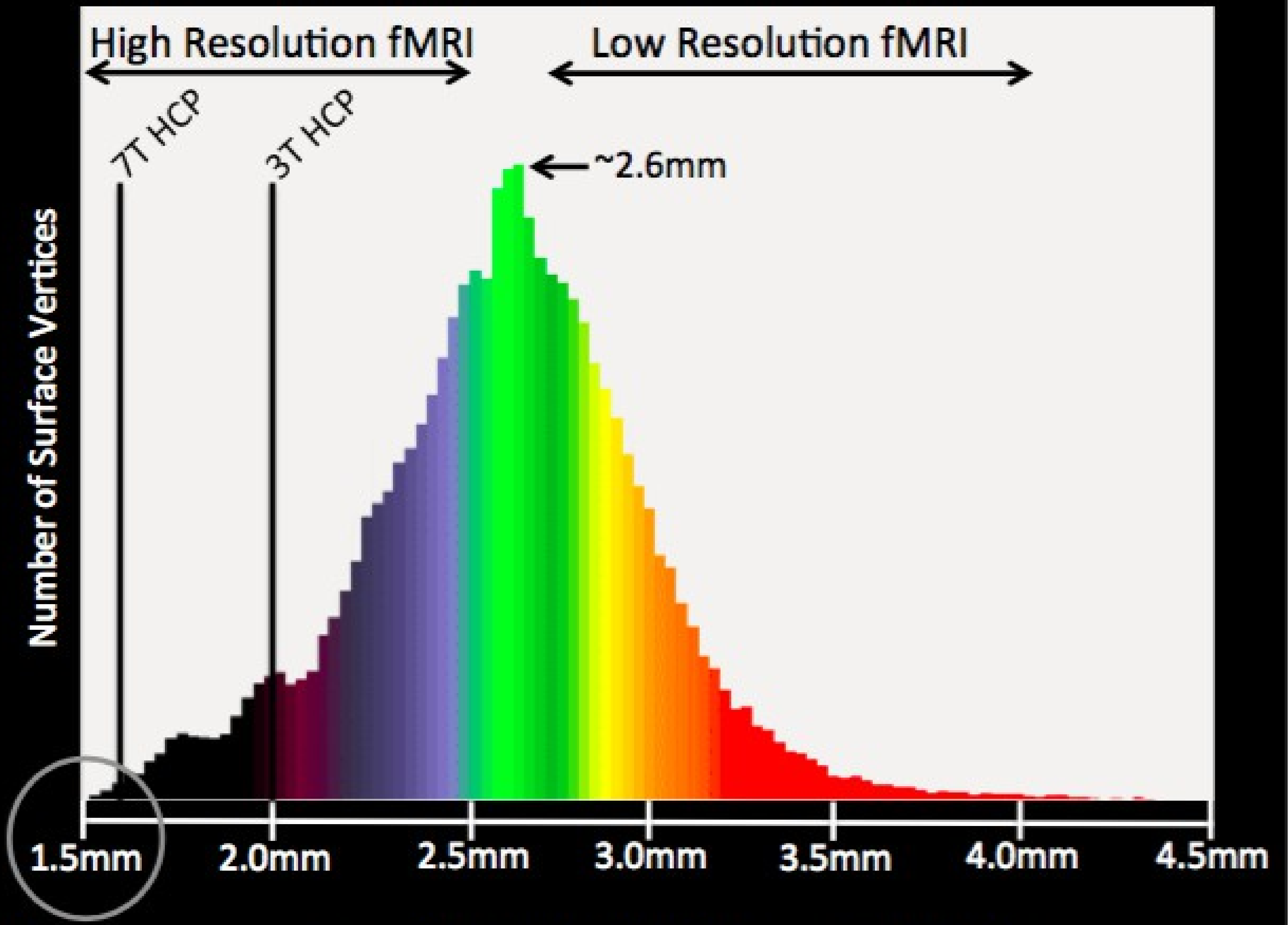
MB imaging :
Whole volume TR
=$TR_{conventional}$ / N_{bands}



Setsompop et al. 2012
Koopmans, ESMRMB course 2016

Cortical Neuroanatomy Drives Spatial Resolution Choices for Acquiring HCP-style MRI Data



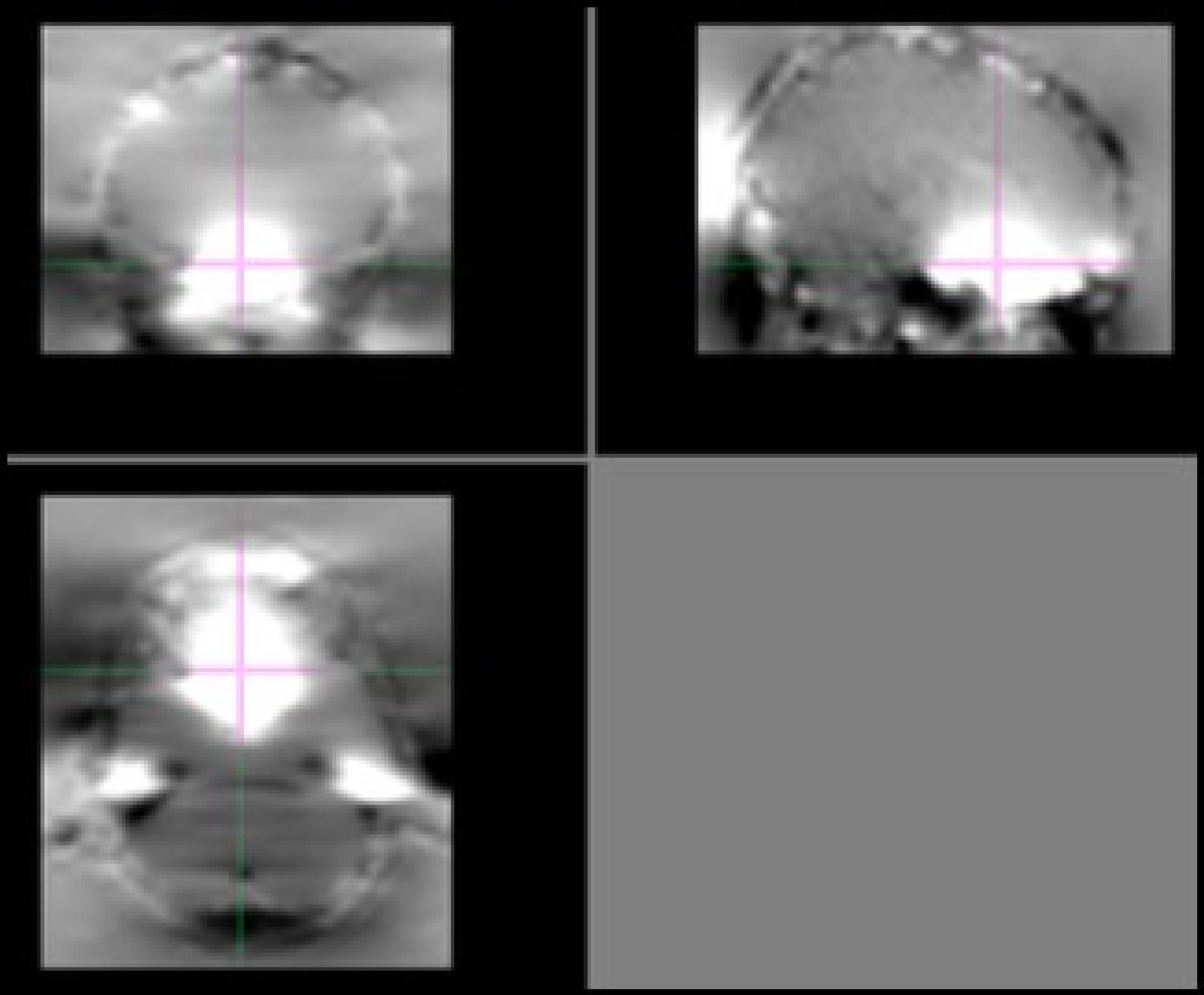


- Mean thickness of cortex: ~2.6mm
- Minimum thickness of cortex: ~1.6mm
- HCP 3T: 2.0mm resolution, 1 frame / 0.72s
- HCP 7T: 1.6mm resolution, 1 frame / 1.0s
- Other Useful Reference Points
  - 1.3mm (two lamina analysis possible)
  - 0.8mm (2 voxels for all of cortex)
- High temporal resolution is ~1.0s or less

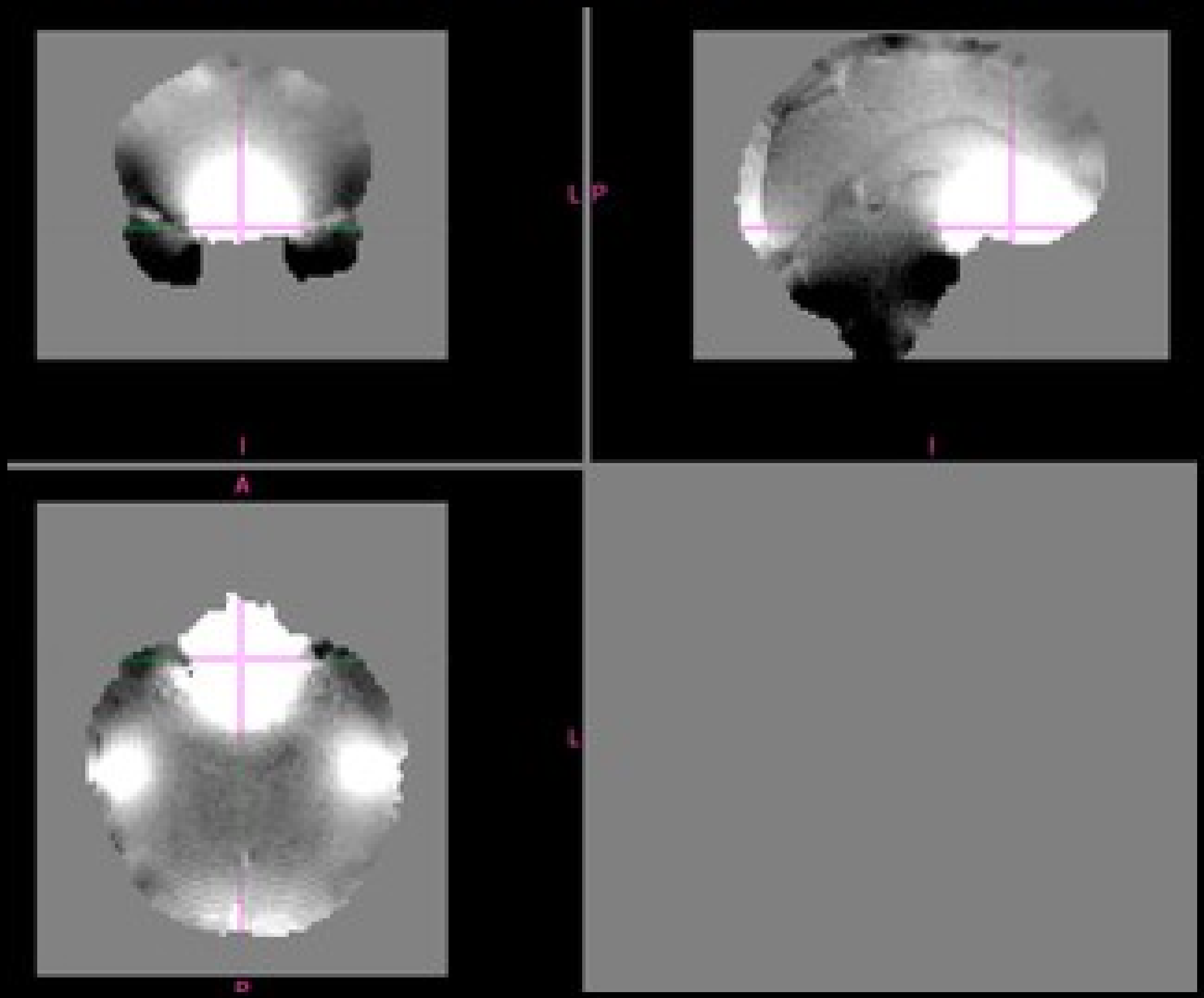
Glasser, HCP course 2016

Choice of Fieldmap

Spin Echo based FieldMap



Gradient Echo based FieldMap

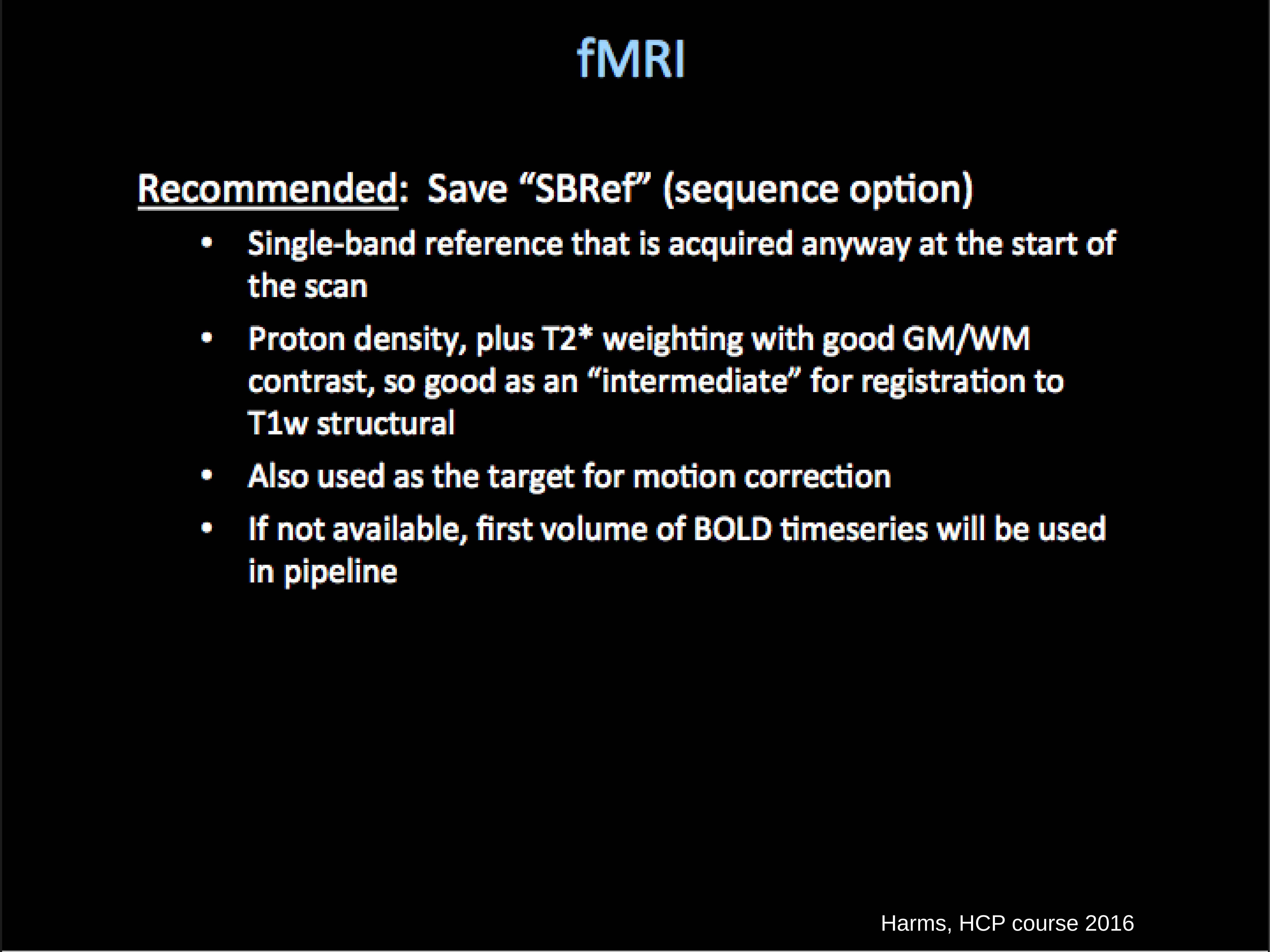


~1 min

~2.5 min

Same low frequency spatial pattern between the two approaches

Harms, HCP course 2016



fMRI

Recommended: Save “SBRef” (sequence option)

- Single-band reference that is acquired anyway at the start of the scan
- Proton density, plus T2* weighting with good GM/WM contrast, so good as an “intermediate” for registration to T1w structural
- Also used as the target for motion correction
- If not available, first volume of BOLD timeseries will be used in pipeline

Harms, HCP course 2016

fMRI

Sampling of 'HCP-Style' fMRI acquisitions:

	WU HCP-Main 3T Connectom	LifeSpan (proposed) 3T Prisma	UMN HCP 7T	ABCD (proposed) 3T (multi-vendor)
MB factor:	8	8	5 (w/ iPAT=2)	6
TR/TE (ms)	720/33	800/37	1000/22	800/30
Voxel size (mm):	2.0	2.0	1.6	2.4
Partial Fourier:	None	None	7/8	None
PE polarity	RL and LR	AP and PA	AP and PA	PA

These are also the fMRI scan parameters we've been suggesting to "Connectomics of Disease" sites in WU's advisory role as the "Connectome Coordination Facility"

Harms, HCP course 2016

dMRI

dMRI parameter choices are highly dependent on your scanner (gradient strength) and available scan time.

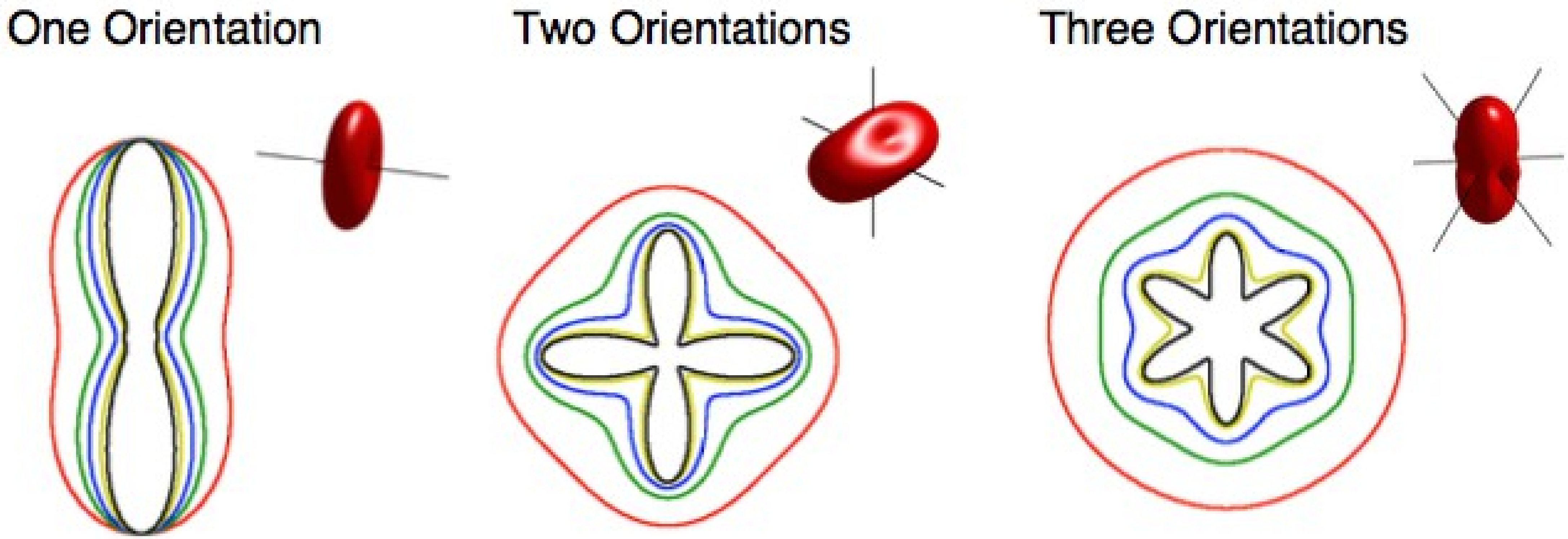
e.g., for a sampling:

	WU HCP-Main 3T Connectom	LifeSpan (proposed) 3T Prisma	UMN HCP 7T	ABCD (proposed) 3T (multi-vendor)
MB factor:	3	4	2 (w/ iPAT=3)	3
TR/TE (ms)	5520/89.5	3230/89.2	7000/71.2	4100/88.0
Voxel size (mm):	1.25	1.5	1.05	1.7
Partial Fourier:	6/8	6/8	6/8	6/8
Num shells:	3	2	2	4
b-vals:	1000, 2000, 3000	1500, 3000	1000, 2000	500, 1000, 2000, 3000
Num directions (each shell)	90	92	64	6, 15, 15, 60
Total min	60	22	40	9
PE polarity	RL and LR	AP and PA	AP and PA	PA

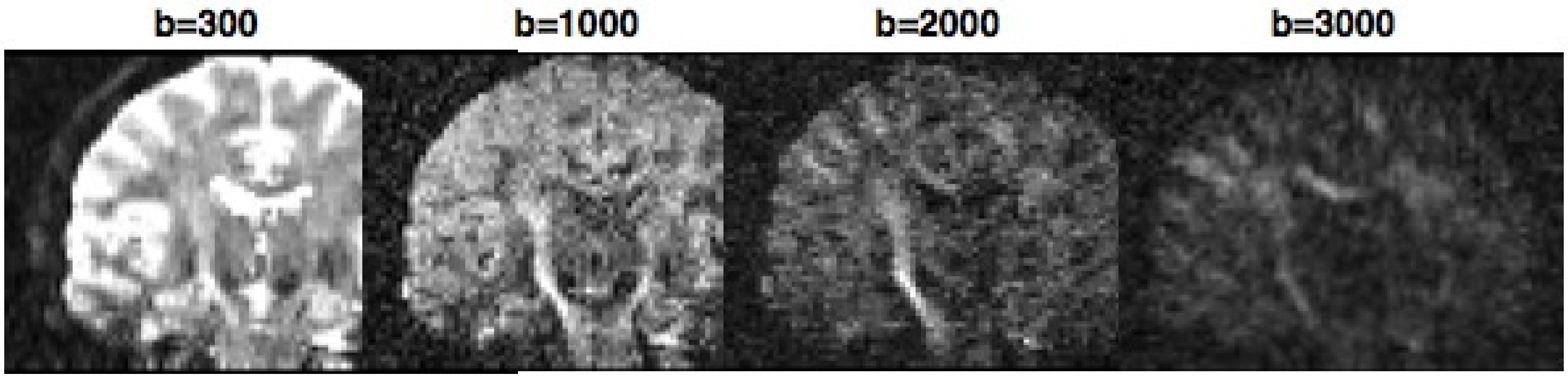
Harms, HCP course 2016

Multi-Shell Diffusion Acquisitions
Why bother?

Signal at
different
b values
(s/mm²)
b=1000
b=2000
b=3000
b=4000
b=5000



But SNR
goes down
very quickly
with b…
☹

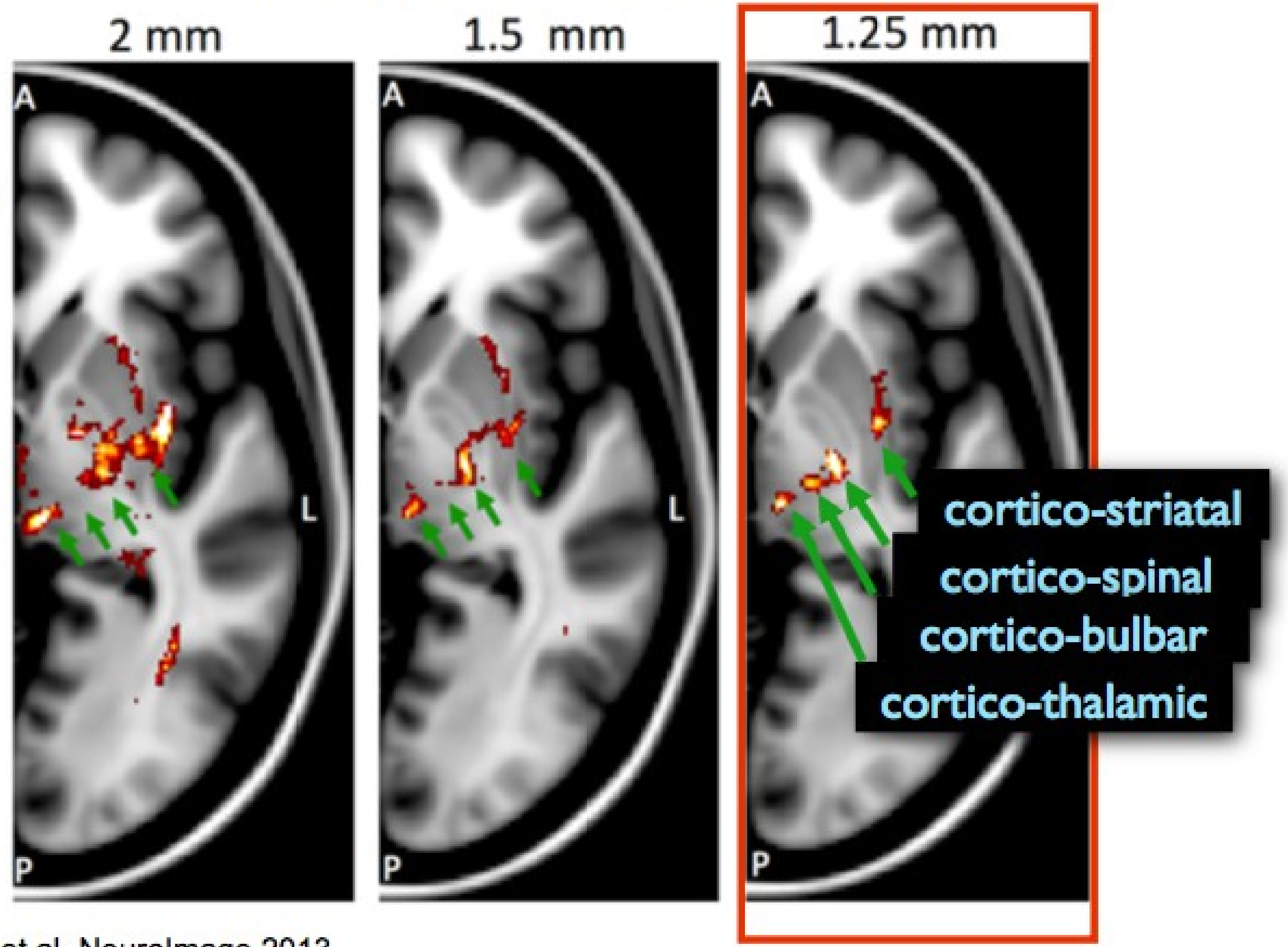


Cottaar, HCP course 2016

Examples of Probabilistic Tractography in HCP data

The Importance of spatial resolution

Seed:
Hand Area M1



2 mm

1.5 mm

1.25 mm

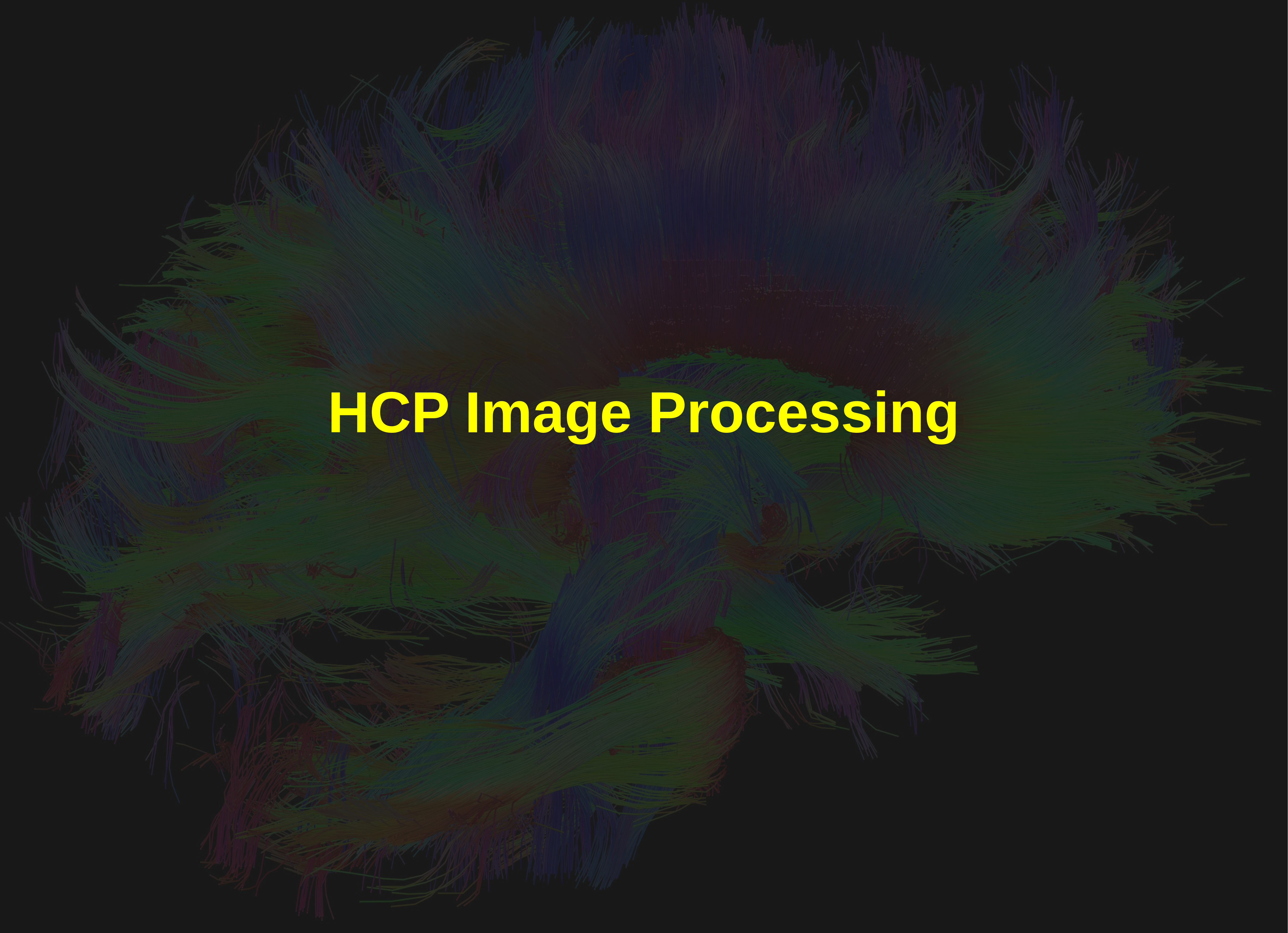
cortico-striatal

cortico-spinal

cortico-bulbar

cortico-thalamic

Sotiropoulos et al, NeuroImage 2013



HCP Image Processing

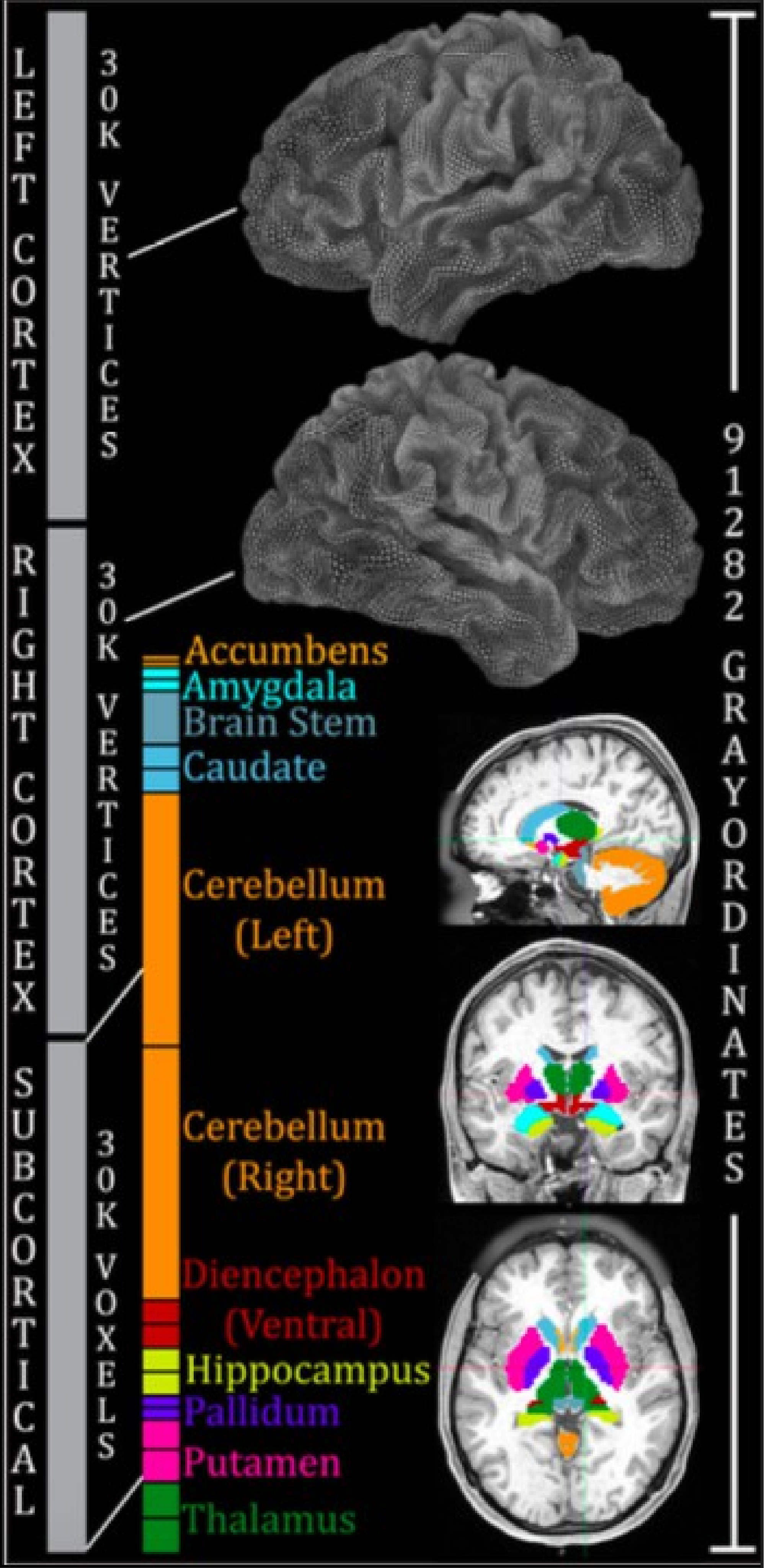
Preprocessing of data

- Generation of CIFTI format, aka « **grayordinates** » : combination of cerebral vertex and subnuclear voxels
- Improvement of cross-subjects alignment with Multi-modal Surface Matching (**MSM**) (Robinson et 2014)
- Recommended 3T data are aligned with cortical folding, myelin + resting state fMRI.
- Maintain high spatial and temporal **resolution** of the original data
- Allows for alignment of brain areas accross subjects and studies

Doing Better than Volume-based for the Whole Brain

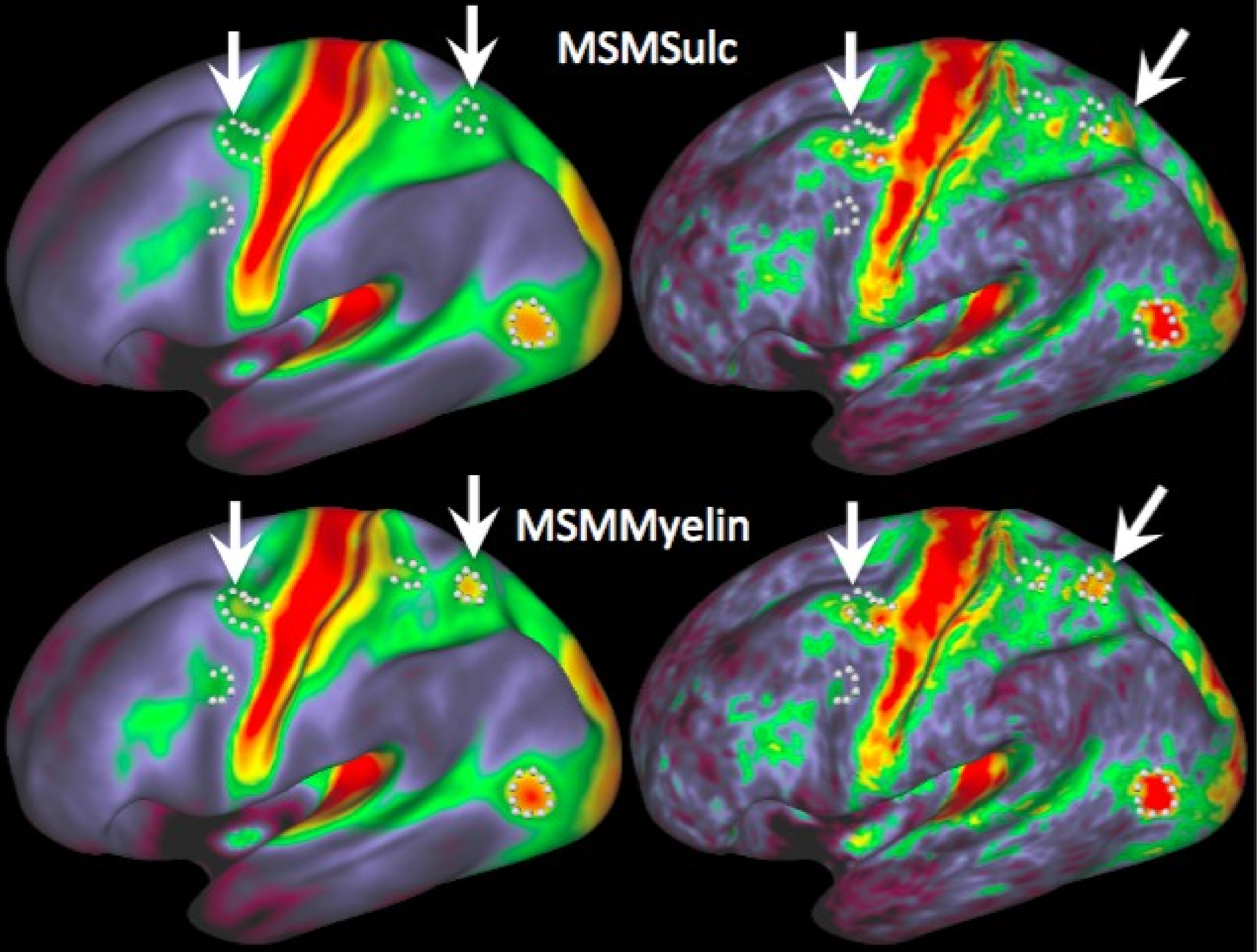
- Consider gray matter structures according to the geometric model best suited for each, surfaces for the sheet-like cerebral cortex and volumes for globular subcortical nuclei
- Use standard <u>Grayordinates</u>, which can be either surface vertices or subcortical voxels
- Register individuals' cortical data using nonlinear surface registration and subcortical data using nonlinear volume-based registration
- <u>Grayordinates-based imaging analyses</u> can greatly reduce the analysis-induced uncertainty in spatial localization in brain imaging studies

Glasser et al 2013 Neuroimage: HCP Pipelines



MSM with Myelin Maps

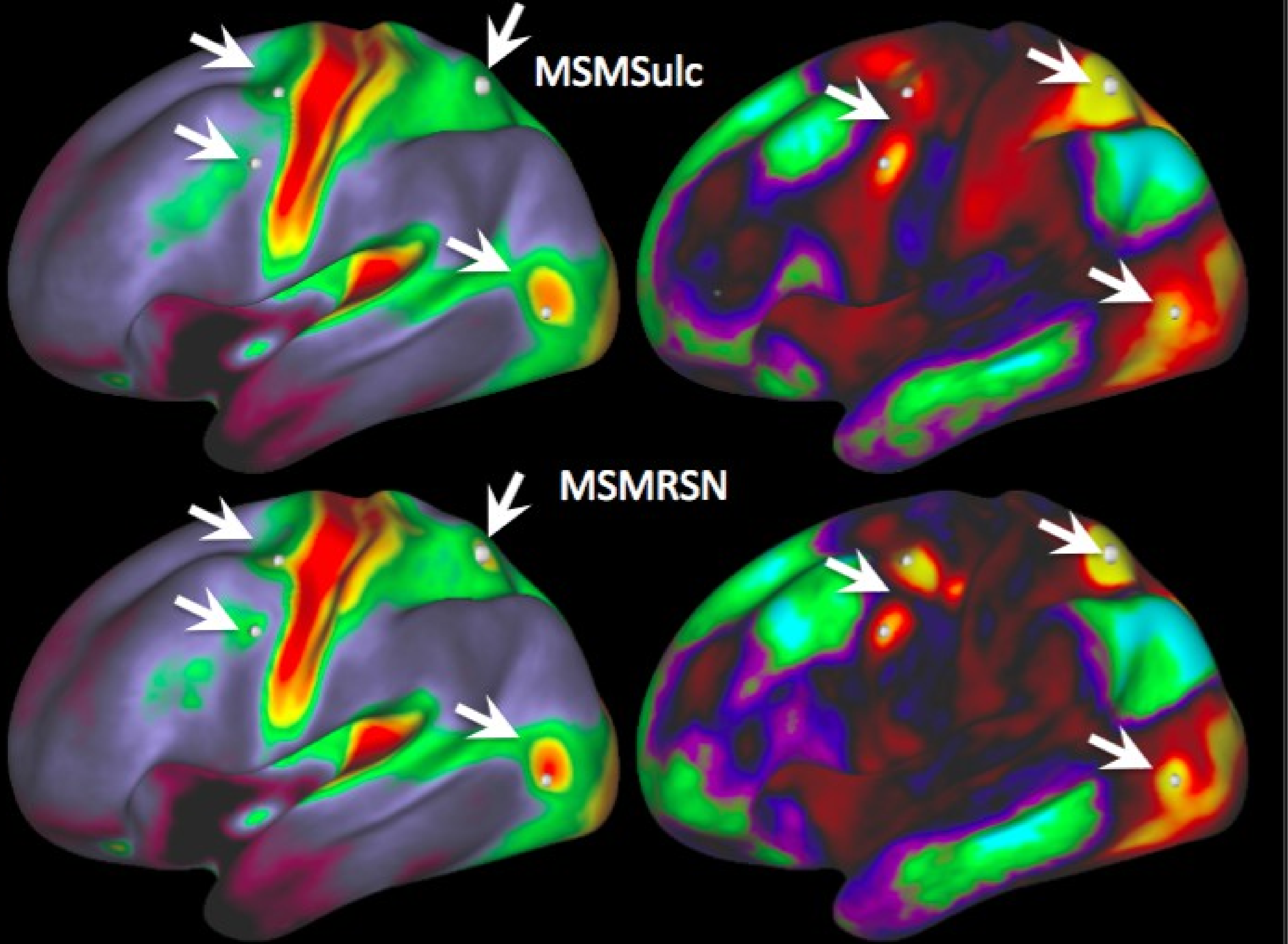
- Myelin maps are more closely tied to cortical areas than are folding patterns
- Some areas are blurry on group average myelin maps with folding-based registration (MSMSulc)
  - Because individuals are misaligned
- MSM improves the alignment of myelin maps in individuals and sharpness of group maps



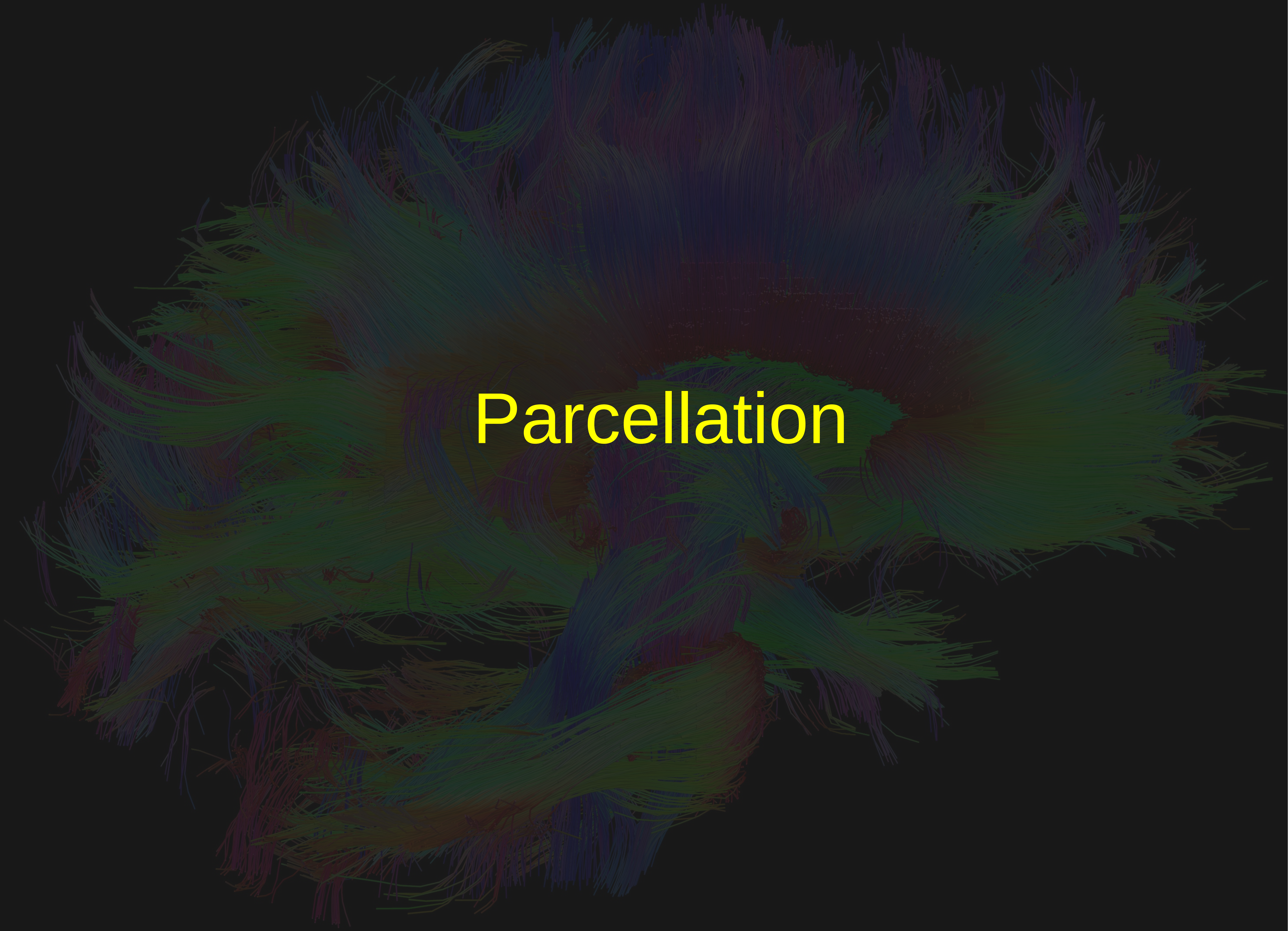
Glasser, HCP course 2016

Resting State Networks Can Also Be Used with MSM for Cross-subject Registration

- RSNs have useful contrast over more of the brain than myelin maps
- They improve the alignment of functional connectivity maps
- They still do a good job aligning myelin maps

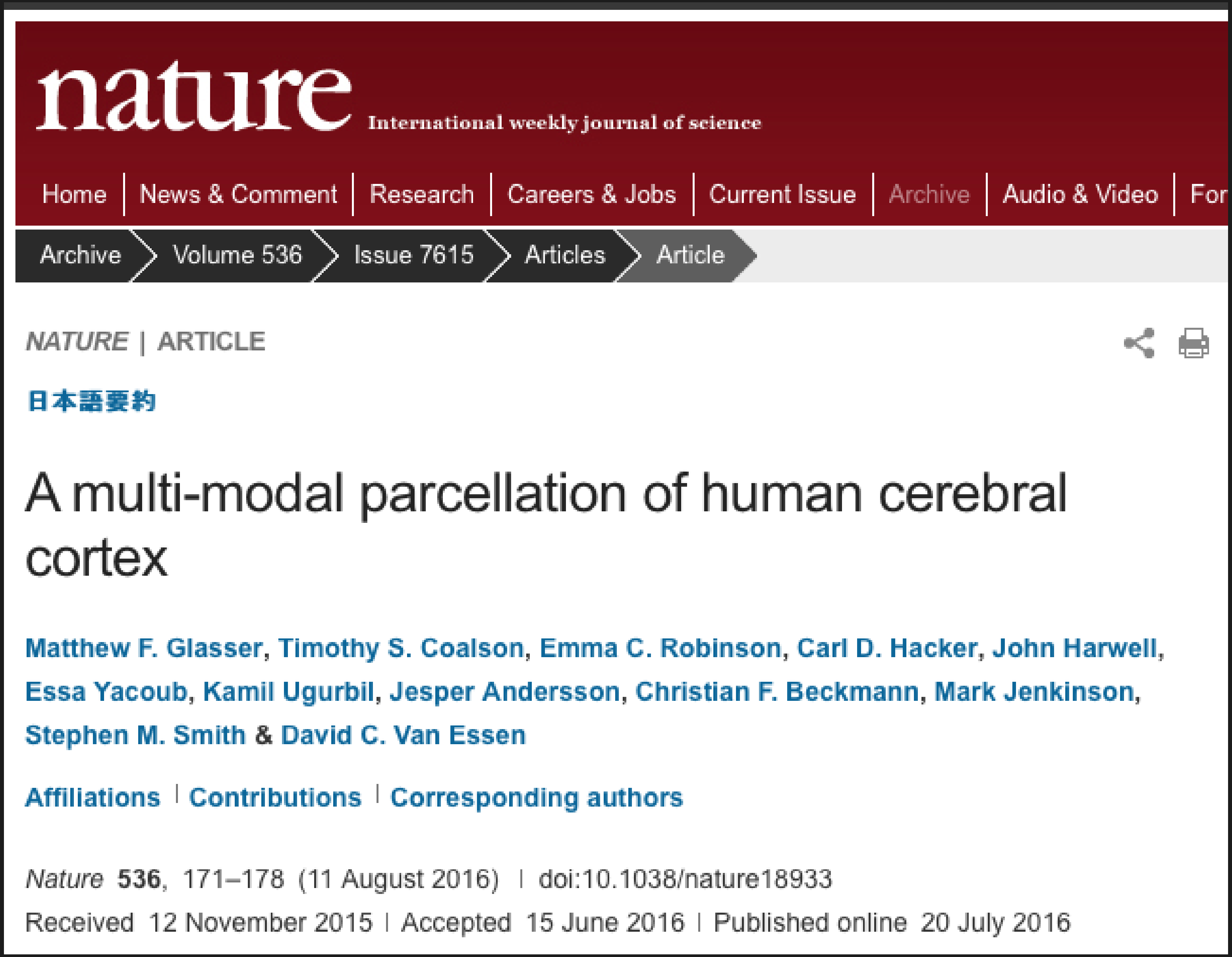


Glasser, HCP course 2016



Parcellation

Brain parcellation



NATURE | ARTICLE

日本語要約

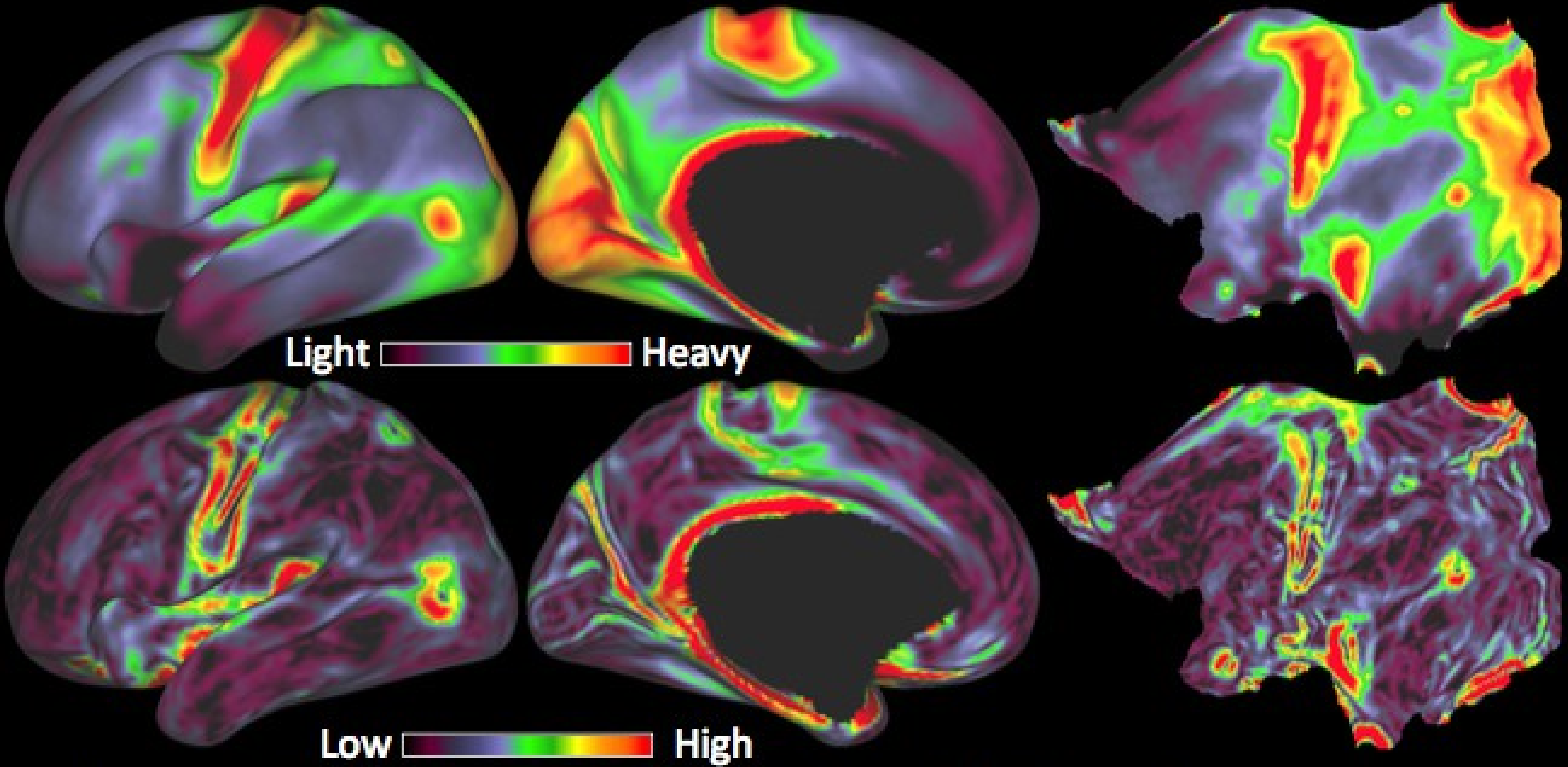
A multi-modal parcellation of human cerebral cortex

Matthew F. Glasser, Timothy S. Coalson, Emma C. Robinson, Carl D. Hacker, John Harwell, Essa Yacoub, Kamil Ugurbil, Jesper Andersson, Christian F. Beckmann, Mark Jenkinson, Stephen M. Smith & David C. Van Essen

Affiliations | Contributions | Corresponding authors

Nature **536**, 171–178 (11 August 2016) | doi:10.1038/nature18933
Received 12 November 2015 | Accepted 15 June 2016 | Published online 20 July 2016

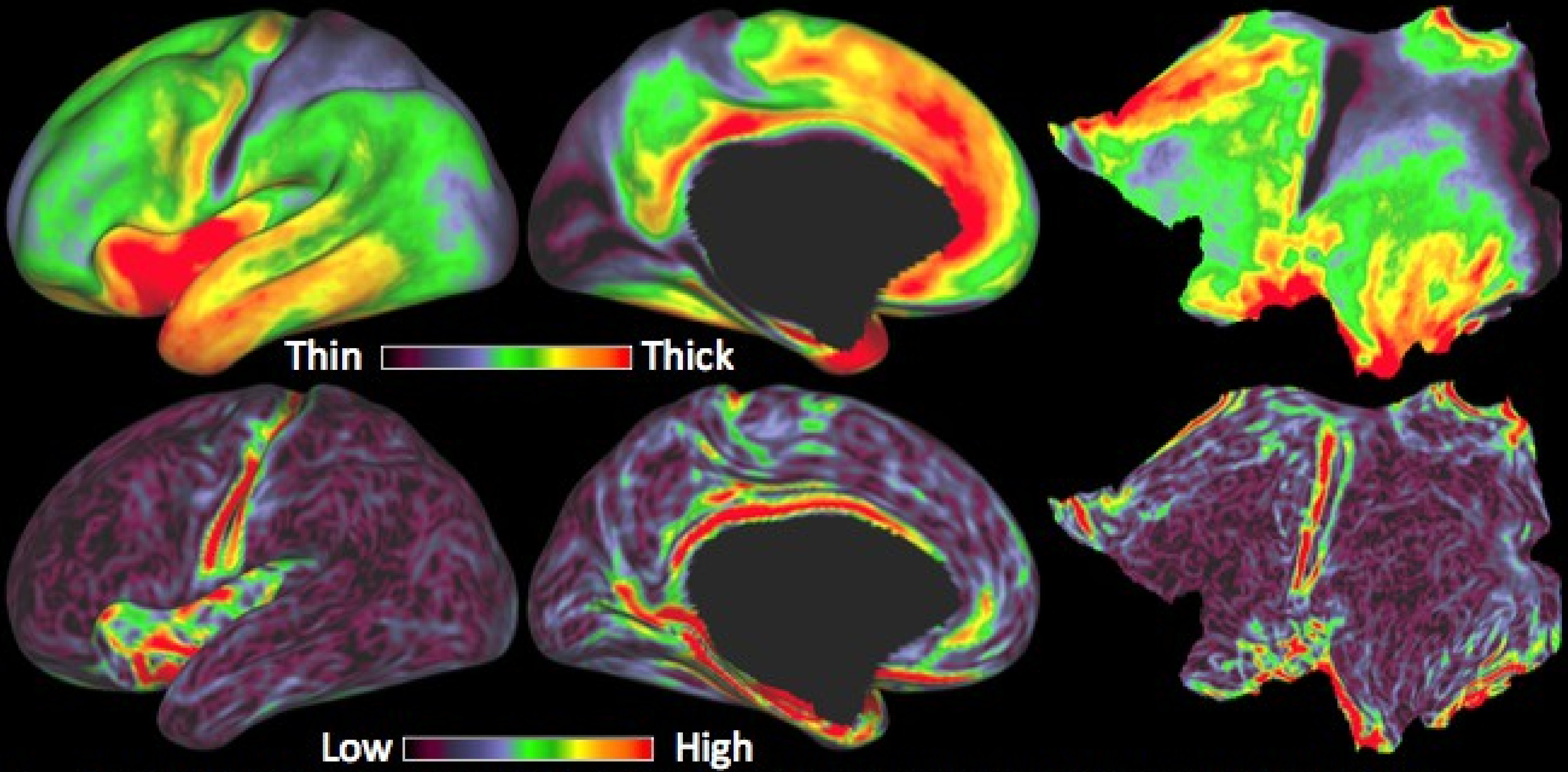
Architectonic → Myelin



- If we want to define cortical areal borders, we're interested in where myelin content changes
- The spatial gradient tells us objectively where the transition in myelin content occurs
- The local maximum of the gradient is the most likely location of a potential areal border
- Some transitions are larger than others, but transitions that occur in multiple modalities are especially interesting as areal border candidates

Glasser, HCP course 2016

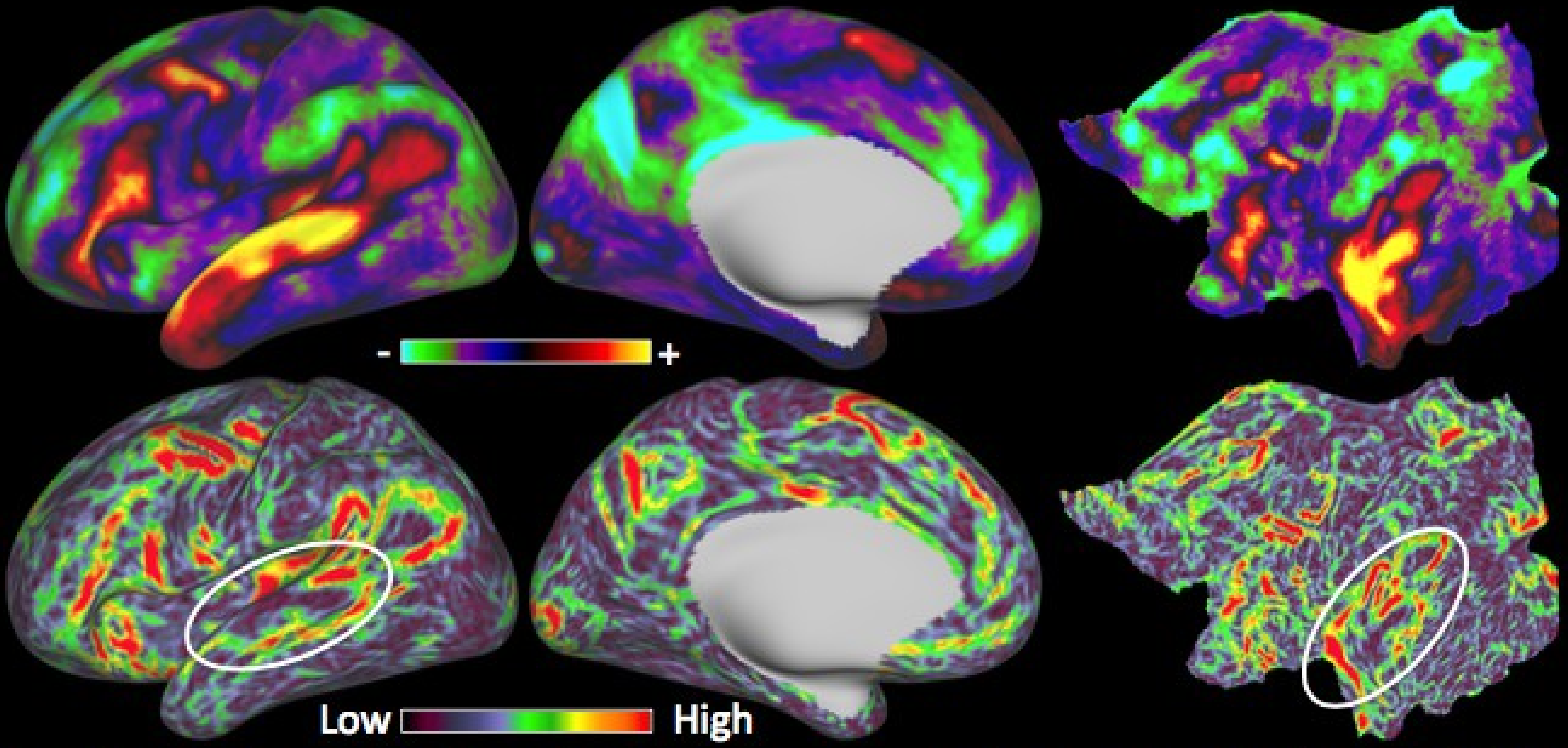
Architectonic → Thickness → Gradients



- Cortical Thickness is another modality that gives us architectural information
- Sharp transitions in cortical thickness also give us some areal boundary candidates
- Curvature is regressed out of thickness maps to reduce folding effects (thicker on gyri, thinner on sulci)

Glasser, HCP course 2016

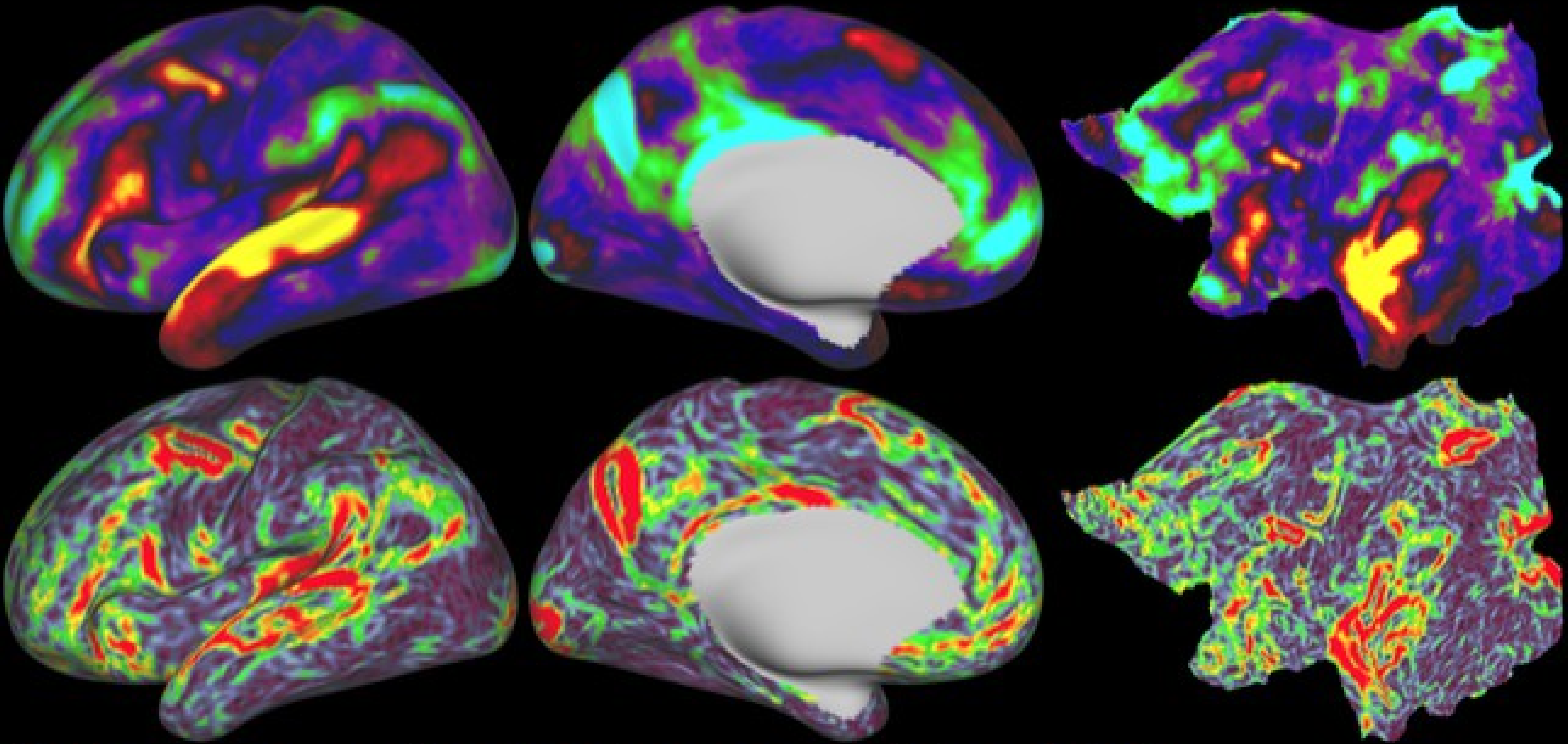
Function → task fMRI → STORY vs REST → Gradients



- Gradients of statistical significance maps are not the same as gradients of effect size maps
    - zstat maps have had a number of nonlinear transformations applied to them to scale them according to sample size and measurement precision
- In parcellation, we are interested in the location where the effect size (i.e. in % of mean fMRI image) changes sharply across the surface

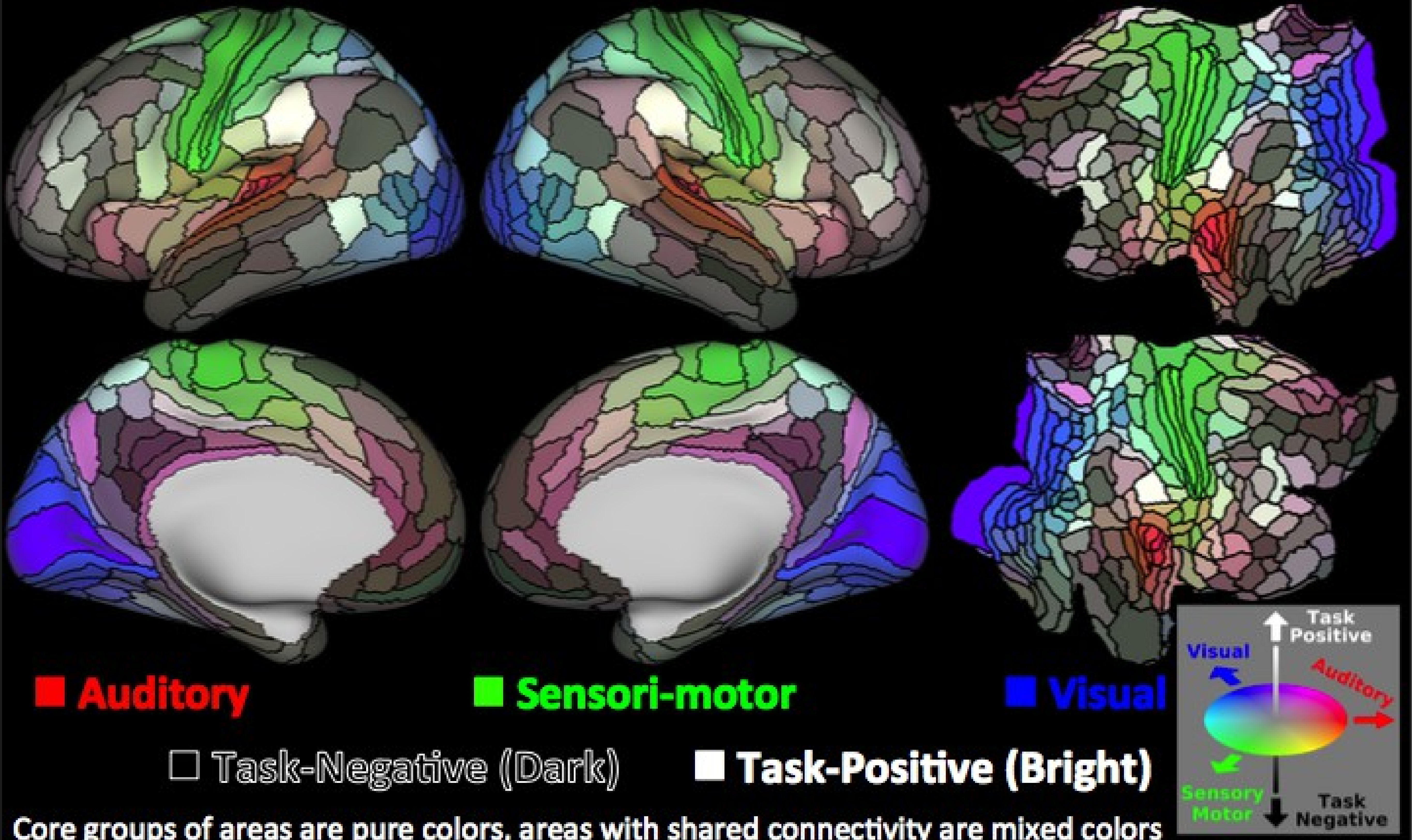
Glasser, HCP course 2016

Connectivity → Resting State fMRI



- Positive areas are functionally connected (correlated)
- Gradient tells us where functional connectivity changes across the cortex and by how much
  - Stepping across a strong gradient leads to a dramatic change in functional connectivity
- Note that areas that activate together are often functionally connected

Multimodal Cortical Parcellation: Colors



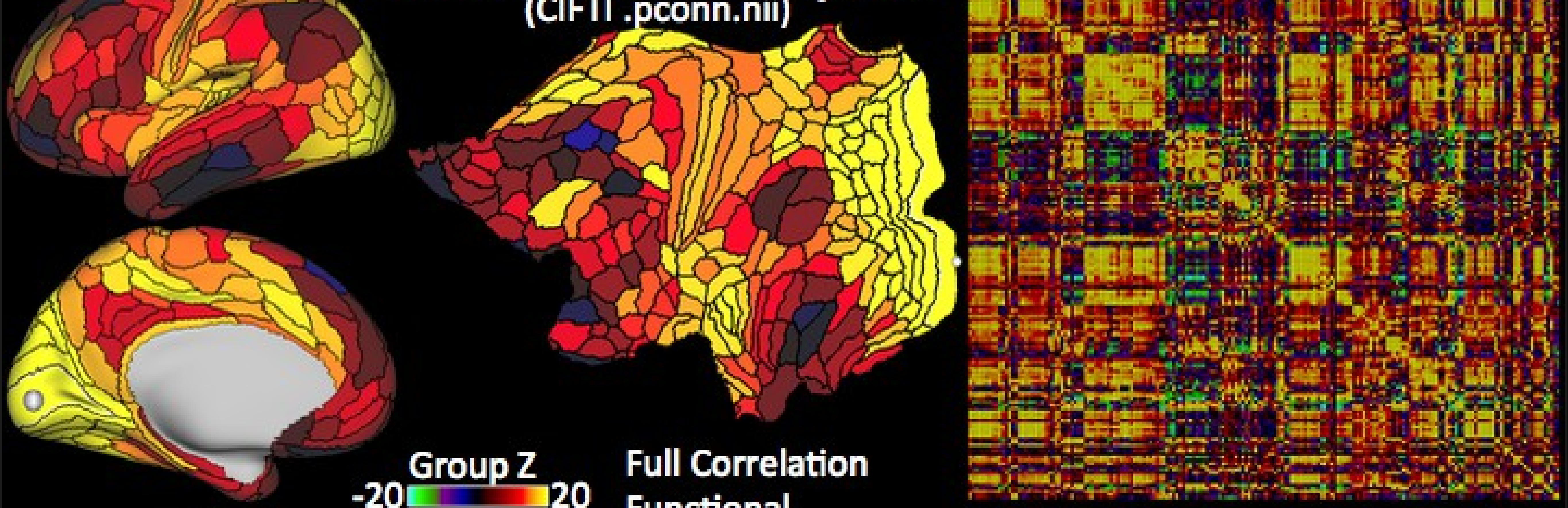
🟥 Auditory 🟩 Sensori-motor 🟦 Visual

☐ Task-Negative (Dark) ⬜ Task-Positive (Bright)

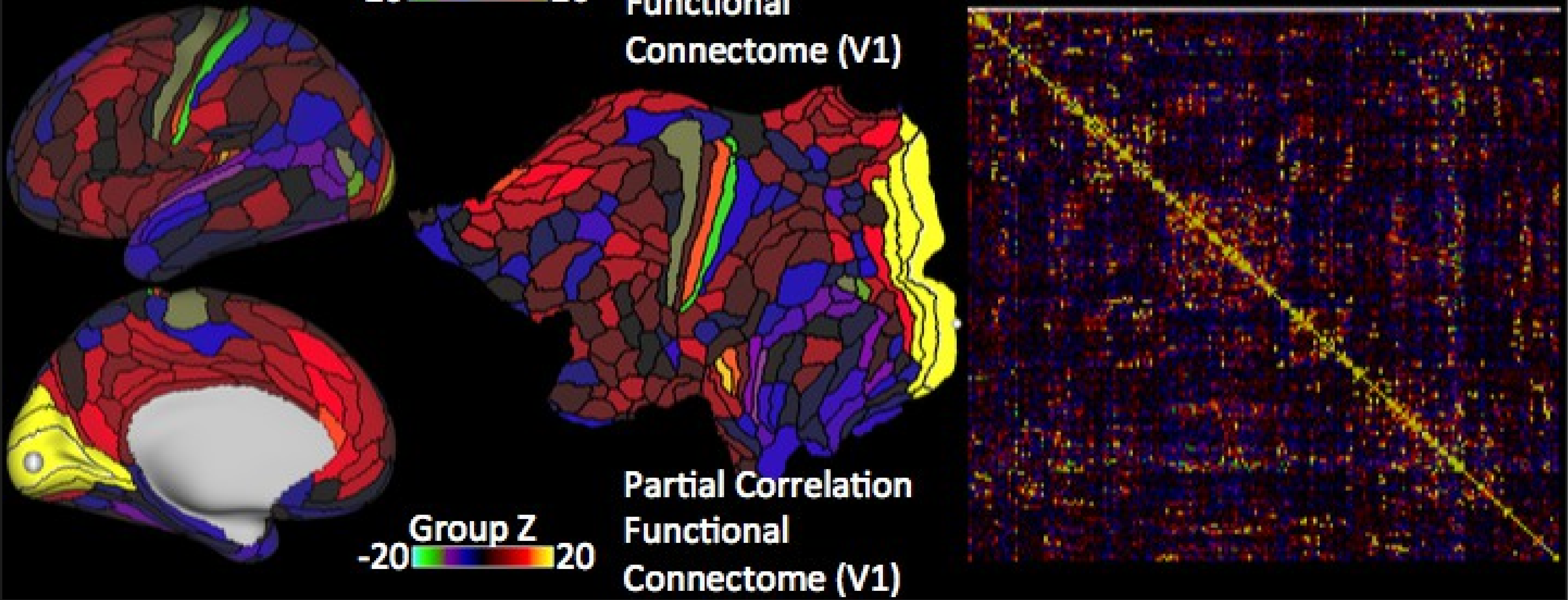
Core groups of areas are pure colors, areas with shared connectivity are mixed colors

Parcellated Analyses

(CIFTI .pconn.nii)



Full Correlation Functional Connectome (V1)



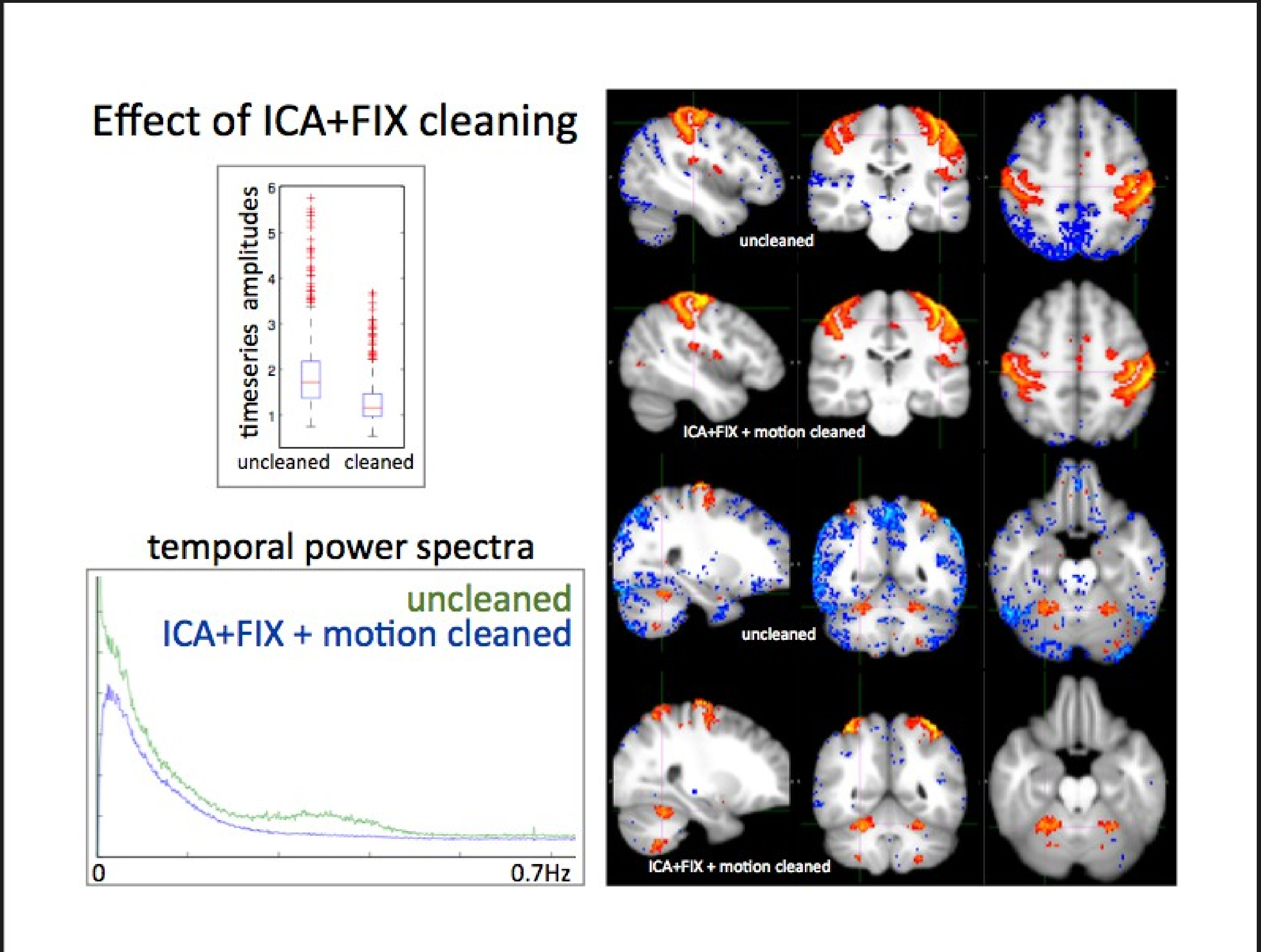
Partial Correlation Functional Connectome (V1)

Parcellation : summary

- 180 cortical area were found in each hemisphere, within the expected range of 150-200
- These areas vary widely in shape and size
- Parcellated analyses can be performed with most modalities, architecture, function, or connectivity
- Minimal loss of details at the area level with a good parcellation

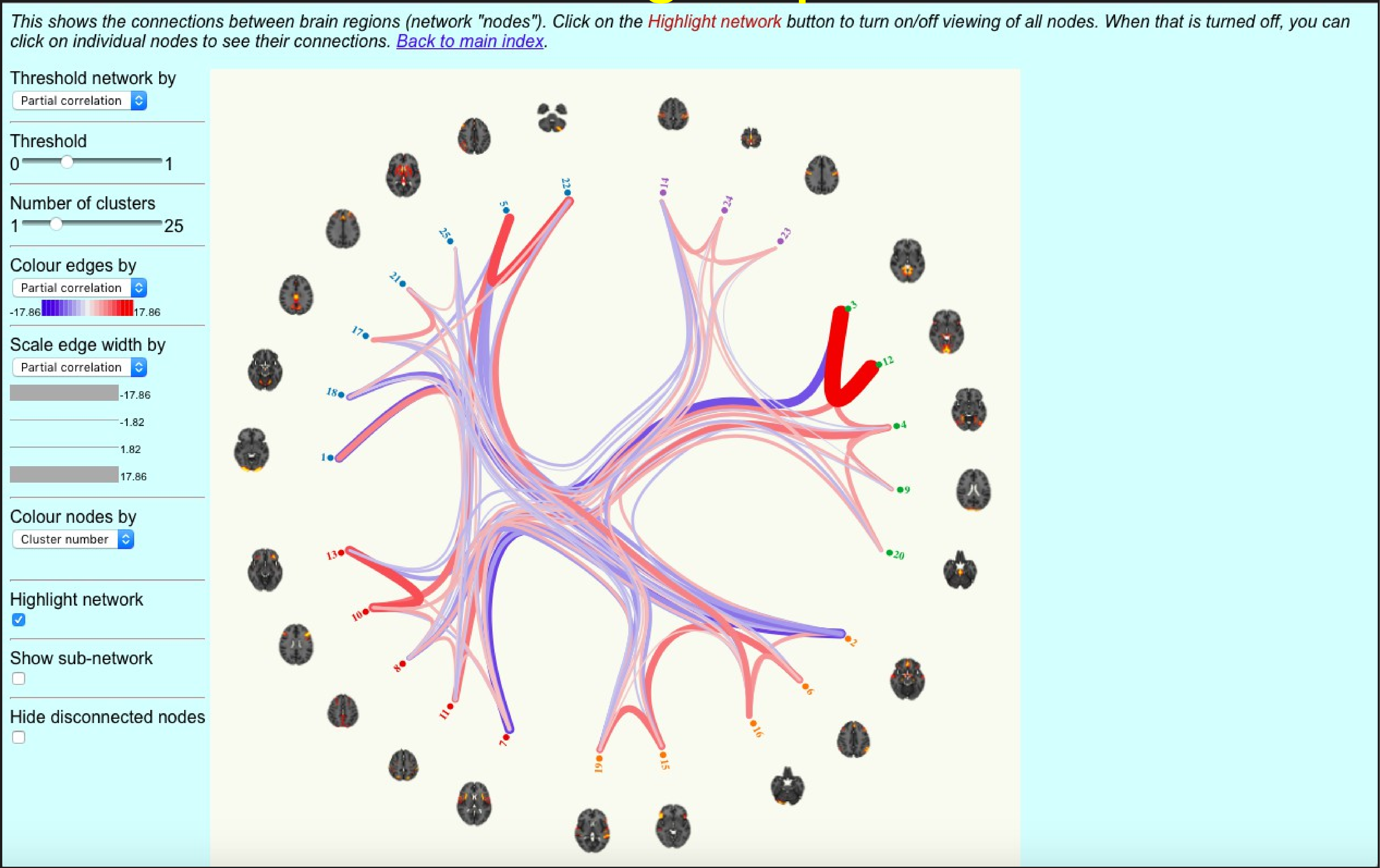
Cleaning rfMRI

- rfMRI artefacts and cleanup : FIX (FMRIB's ICA-based X-noiseifier (Salimi-Korshidi 2014, Griffanti, 2014)



Smith, HCP course 2016

rfMRI : group-ICA



This shows the connections between brain regions (network "nodes"). Click on the Highlight network button to turn on/off viewing of all nodes. When that is turned off, you can click on individual nodes to see their connections. Back to main index.

Threshold network by
Partial correlation

Threshold
0 1

Number of clusters
1 25

Colour edges by
Partial correlation
-17.86 17.86

Scale edge width by
Partial correlation
-17.86
-1.82
1.82
17.86

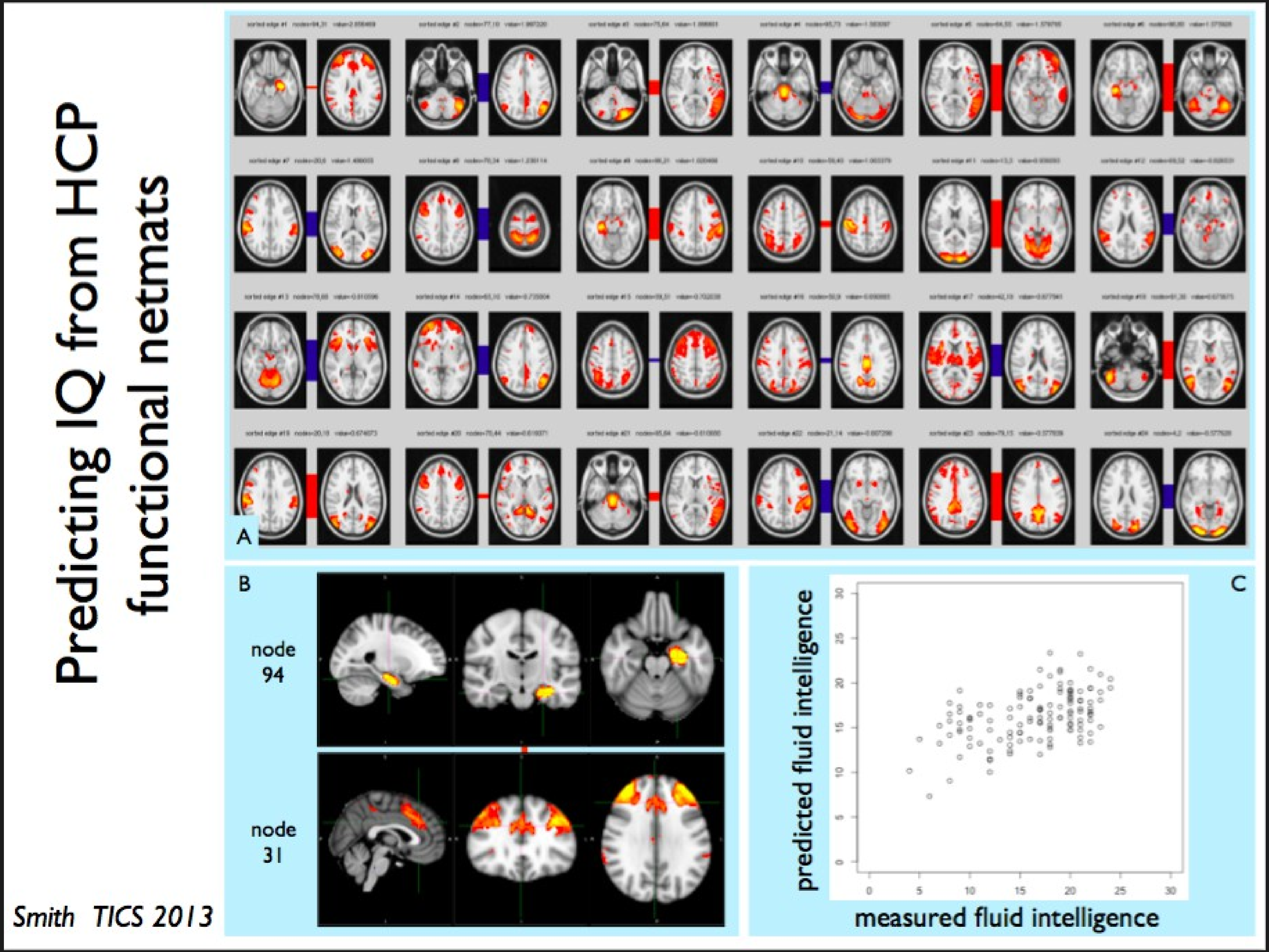
Colour nodes by
Cluster number

Highlight network
☑

Show sub-network
☐

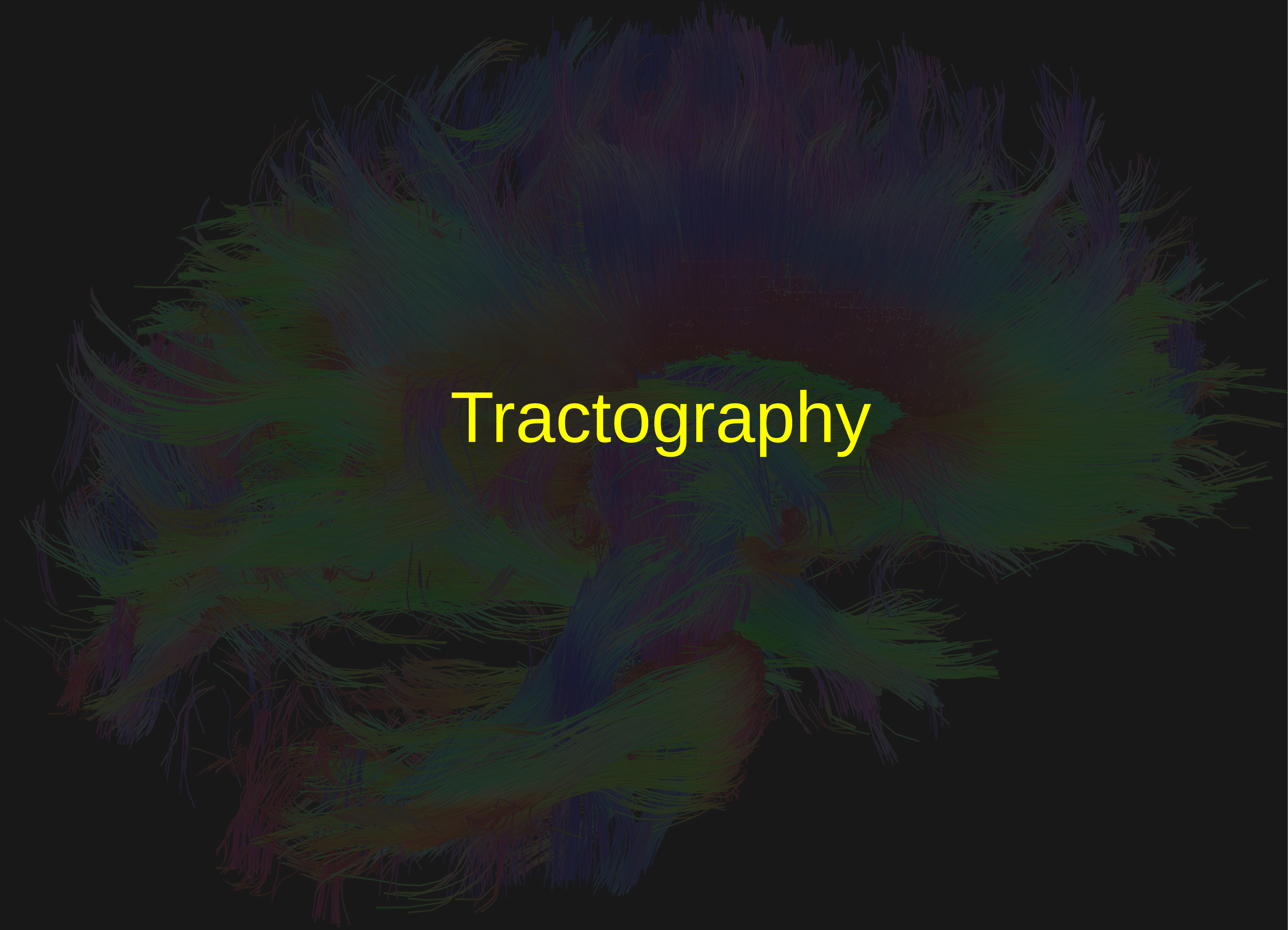
Hide disconnected nodes
☐

MegaTrawl: MRI + non MRI data



Predicting IQ from HCP functional netmats

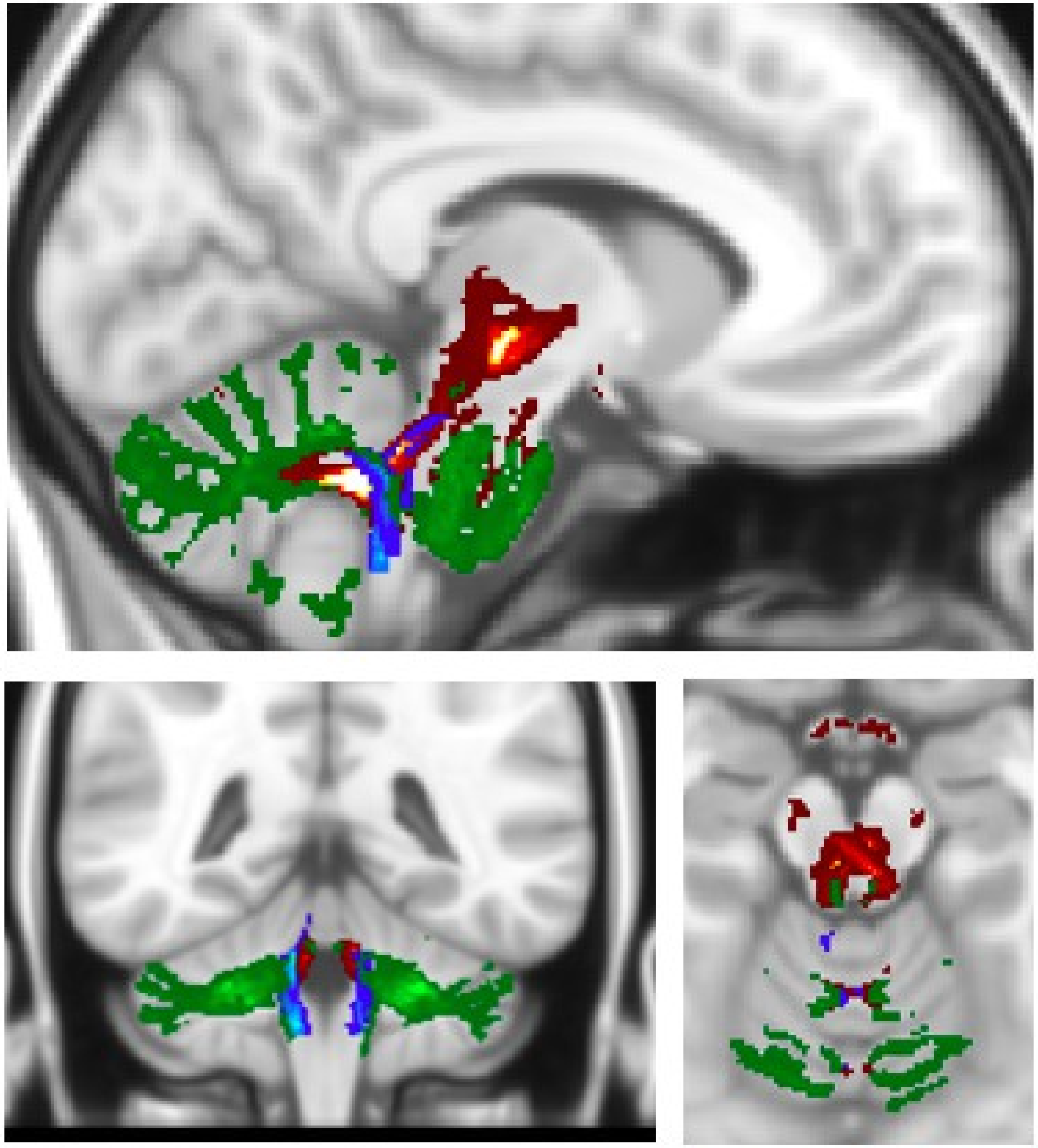
Smith TICS 2013

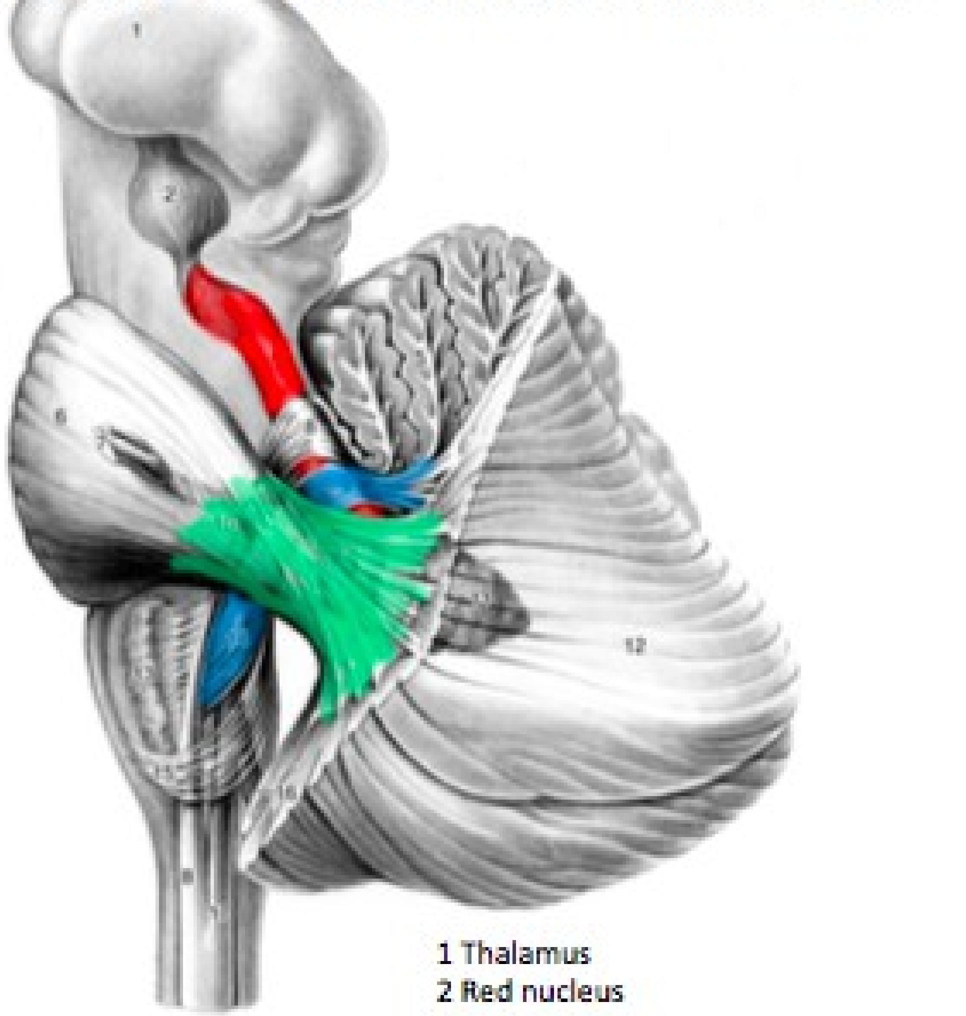


Tractography

Examples of Probabilistic Tractography in HCP data

Resolving the cerebellar peduncles and the decussation of the SCP





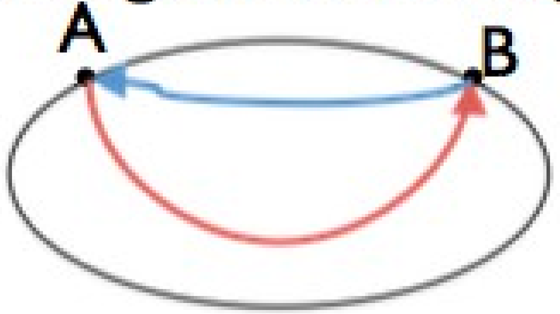
1 Thalamus
2 Red nucleus
3 Decussation
4 Superior cerebellar peduncle
5 Vermis
6 Pons
7 Trigeminal nerve
8 Ventral spinocerebellar tract
9 Inferior cerebellar peduncle
10 Middle cerebellar peduncle
11 Dentate
12 Inferior olive
14 Olivocerebellar fibres
15 External arcuate fibres

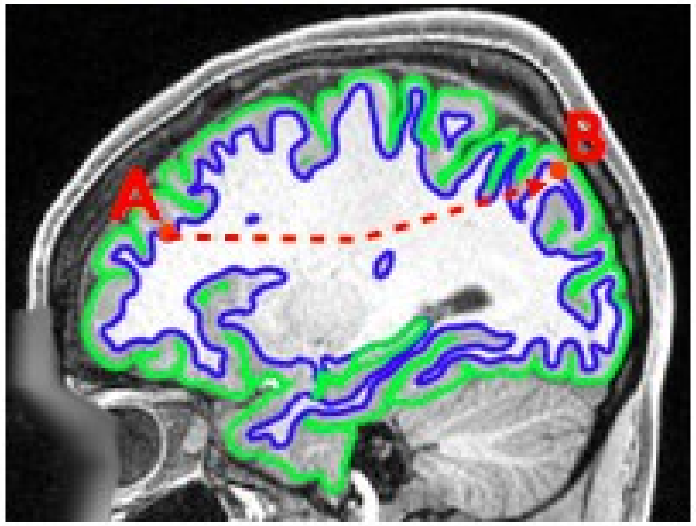
van Baarsen et al., Neuroimage, 2015

Options for Connectome Matrices

$Con1=M1+M1^T$

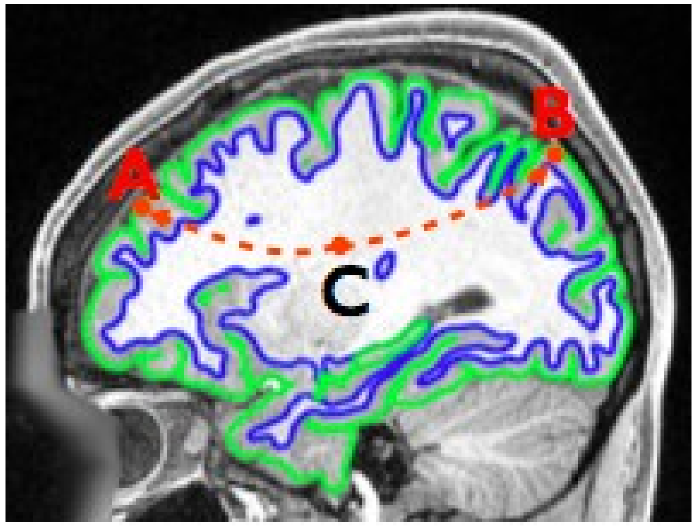
All paths starting from A ending at B
and starting from B ending at A

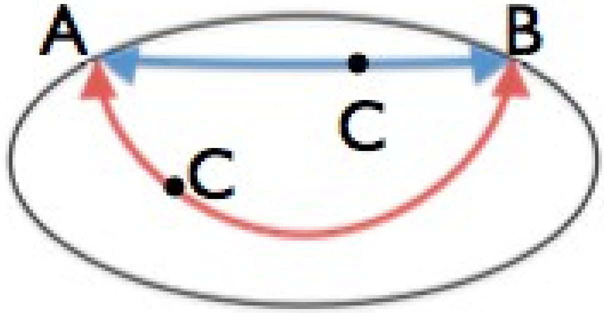




$Con3=M3$

All paths starting from any point C and
connect A and B

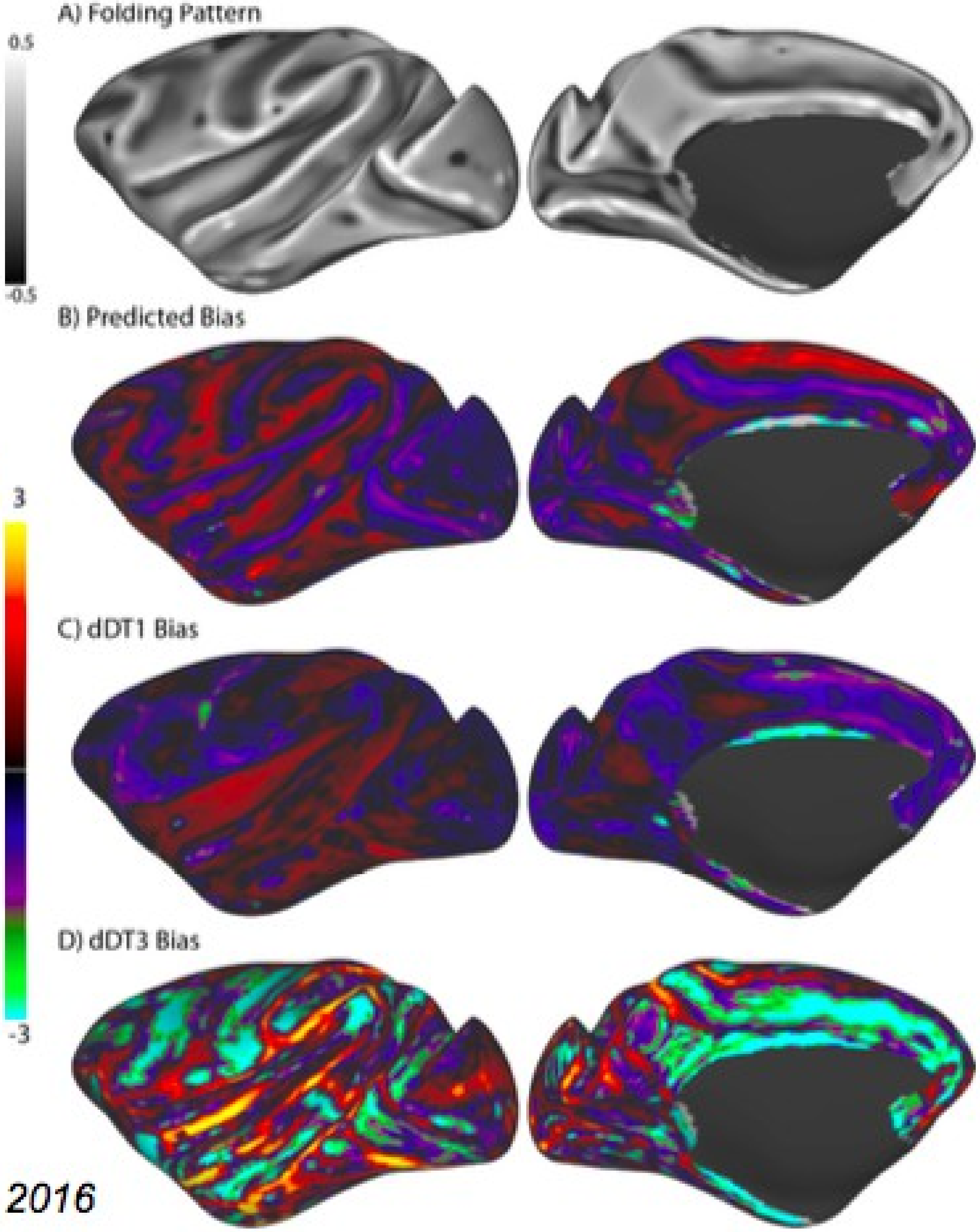




Pros & Cons of each Option

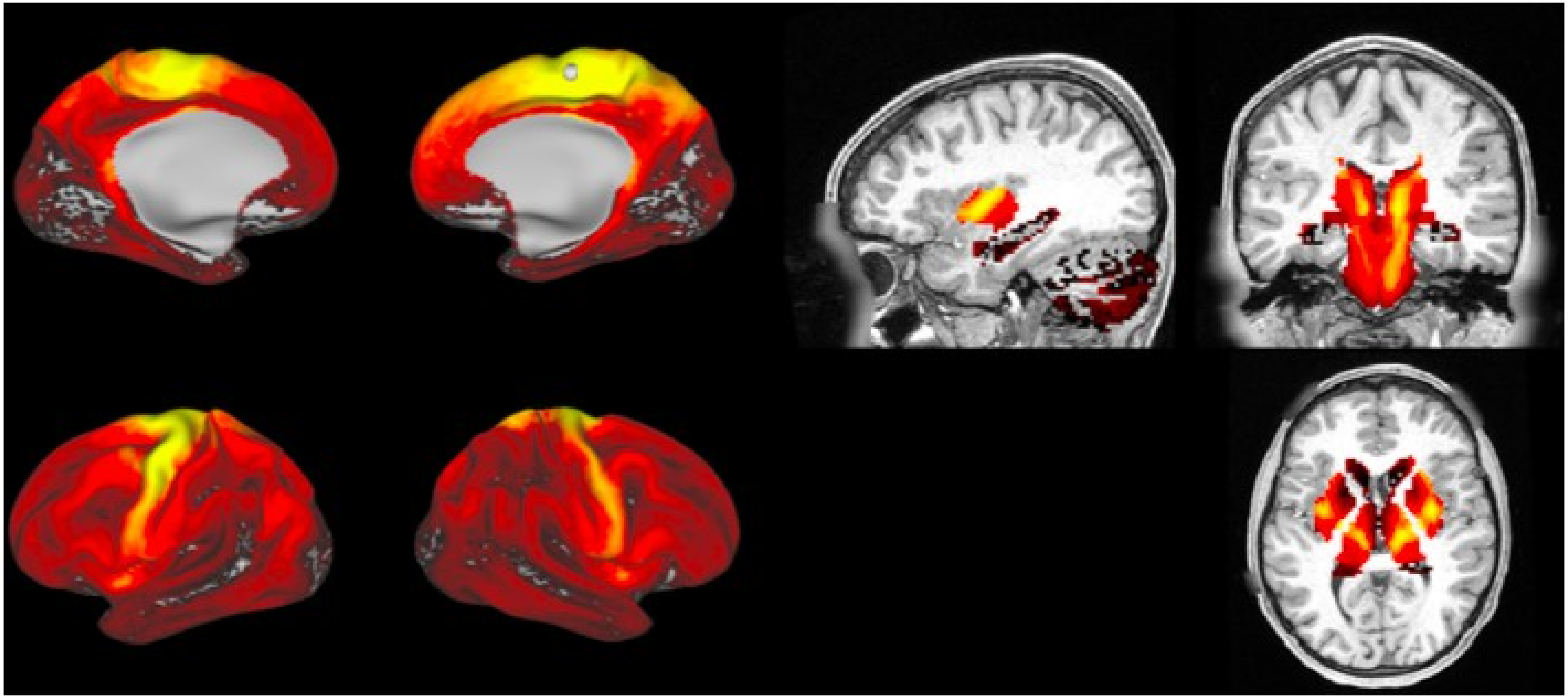
Con1: Less Gyral bias
More path-length dependent

Con3: Less path-length dependence
More Gyral bias

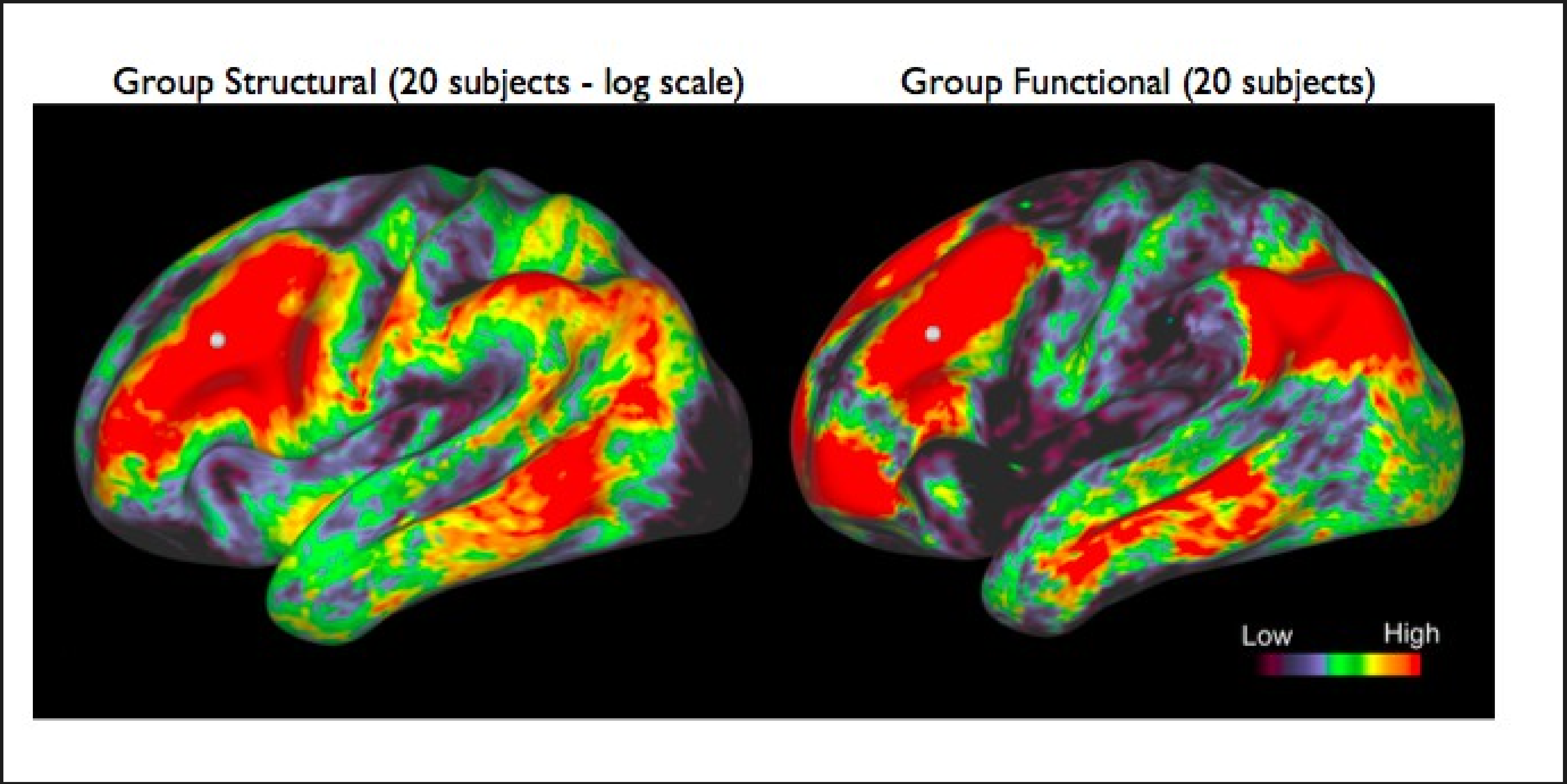


Donahue et al., J Neurosci, 2016

SMA to motor cortex

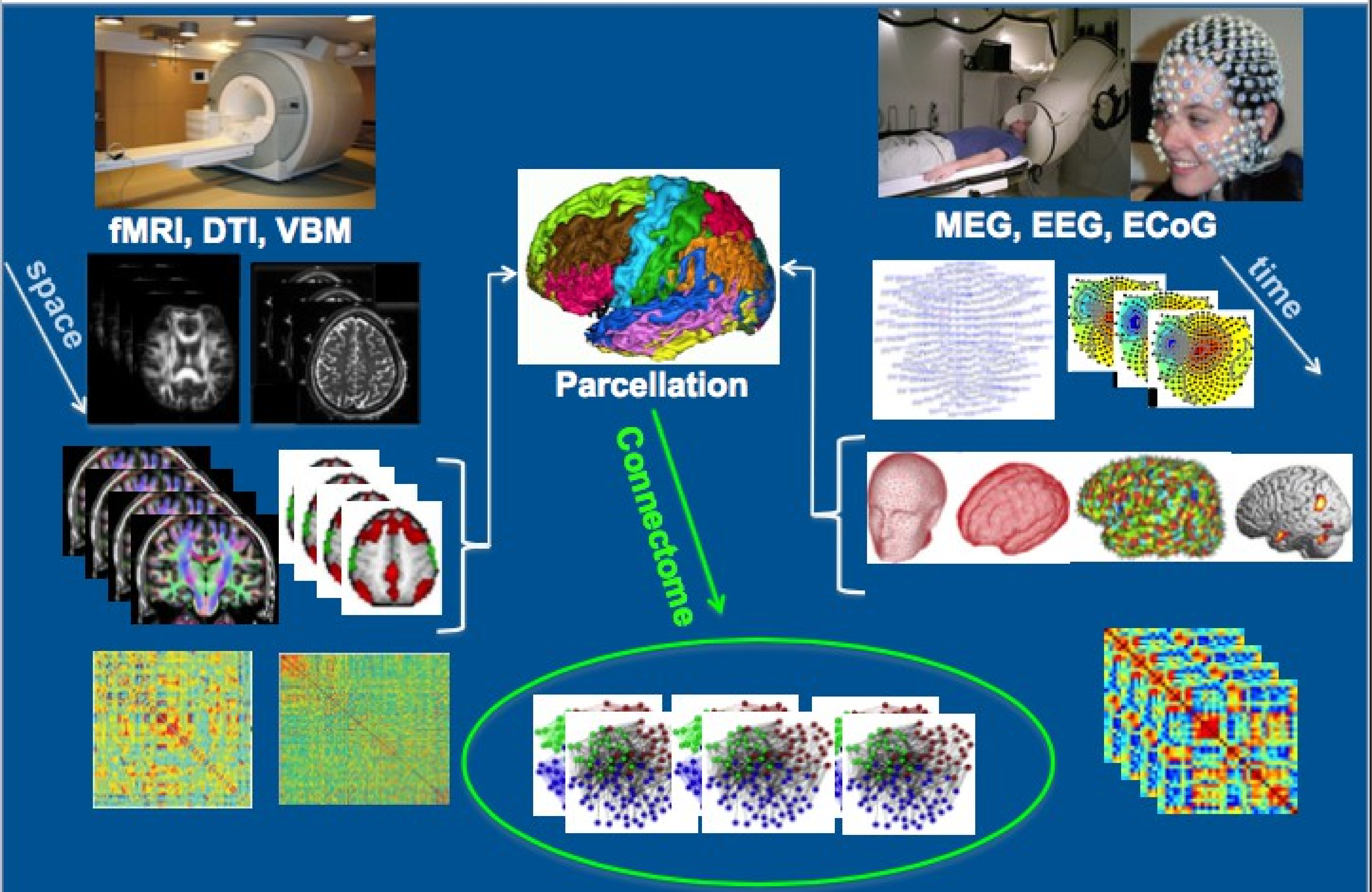


Structural vs Functional connectivity



Smith, HCP course 2016

III. Data Sharing: Multi-modal Integration



fMRI, DTI, VBM

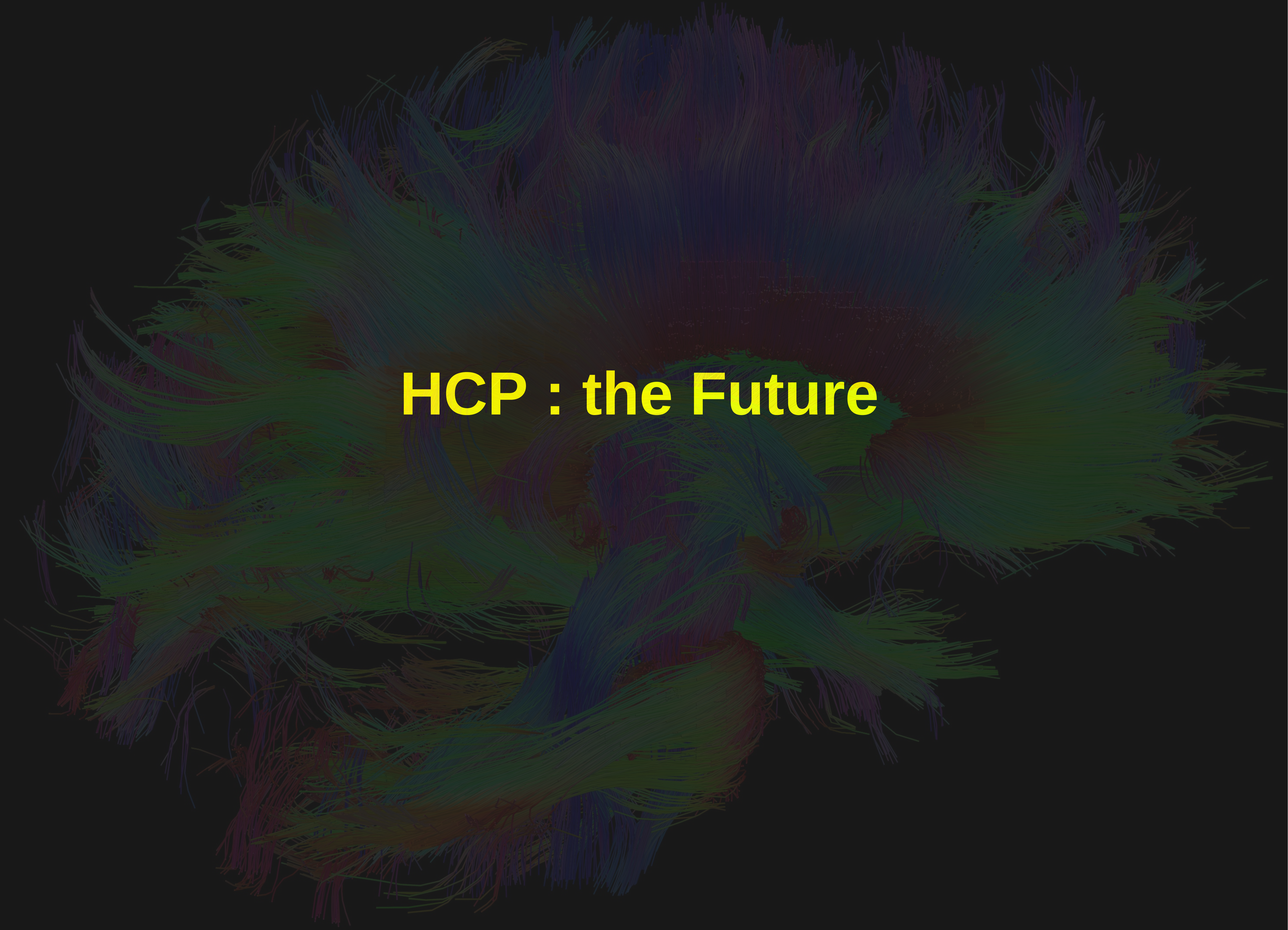
MEG, EEG, ECoG

space

time

Parcellation

Connectome



HCP : the Future

HCP: The next generation

Large-scale projects using 'HCP-style' acquistion and anaysis:

- Lifespan Human Connectome Project (L-HCP)
  - ✓ Development (5 - 21 yr) & Aging (36 - 75 yr)
    (WashU, UMinn, UCLA, MGH/Harvard, Oxford)
  - ✓ Baby Connectome (0 – 5 yr): UNC/UMinn
  - ✓ Developing Human Connectome (prenatal, newborn (UK)

- Connectomes Related to Human Disease
  13 funded, more to come
- Data sharing via the Connectome Coordination Facility (WashU)

Issues:

- Scan protocols similar but not identical
  - Prisma vs customized Skyra
  - Potential refinements (e.g. vNav prospective motion correction?)
  - Different scan durations (e.g. 30 vs 60 min rfMRI)
- Potential analysis confounds
  - Head motion differs across age and clinical diagnosis
  - Opportunity to refine cross-project comparison approaches

Tools for the community

- New acquisitions techniques and sequences : MB, vNav
- HCP-style processing pipelines, FSL and Freesurfer developments
- To be released : Modified FS Pipeline that automatically generates macaque and chimpanzee surfaces and subcortical segmentations
- HCP DataBase ConnectomeDB
- Workbench : visualization and creation of figures for papers
- Balsa : data sharing for papers

Workbench-balsa Demo ...

Thank you for your attention !

Workbench Demo ...