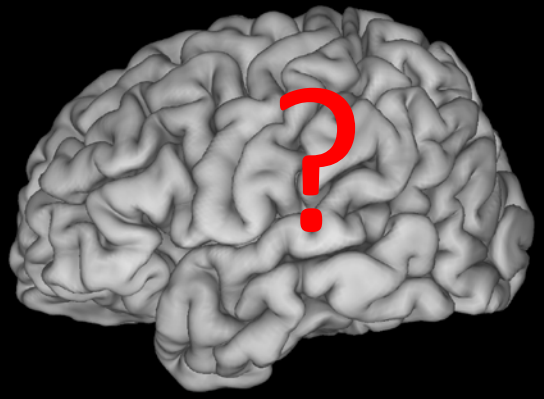
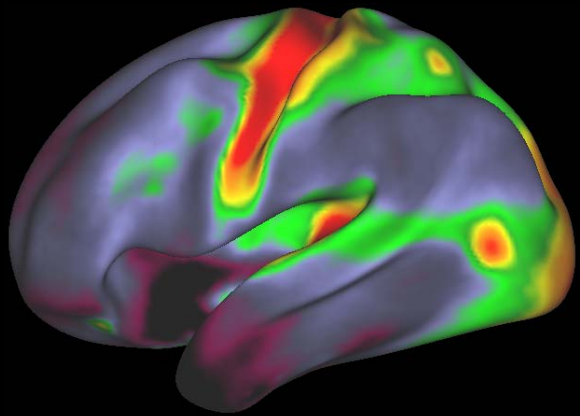
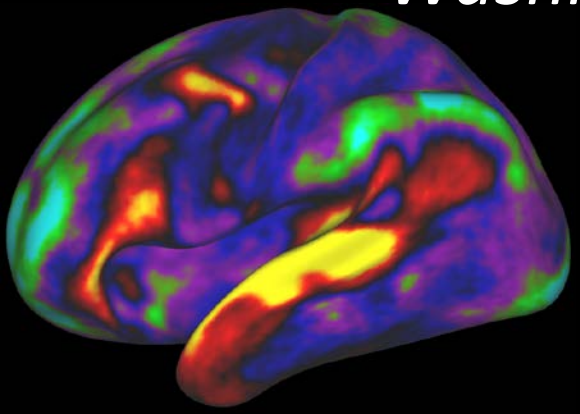


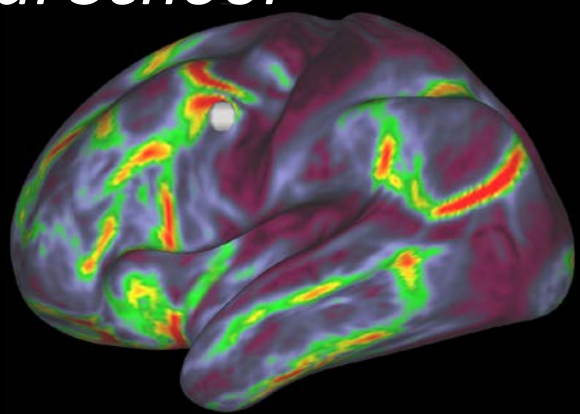


Non-invasive Cortical Parcellation with Myelin Maps and Other MRI Modalities: Methods, Results, and Tools

Matt Glasser
Department of Anatomy and Neurobiology
Washington University Medical School



HUMAN Connectome PROJECT



Learning Objectives

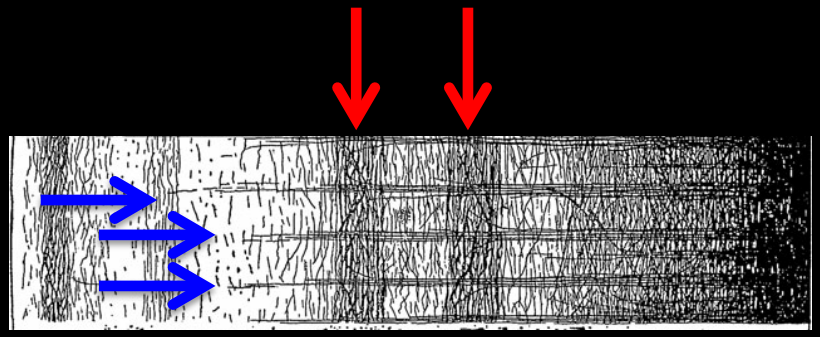
- Non-invasive MRI-based methods for mapping cortical myelin content
- HCP's multi-modal cortical parcellation with group average gradients
- Identification of cortical areas in individuals and parcellation validation

Since this course is about tools, I'll tell you about the tools that already exist and about those in development (and what data you'll want to acquire to be ready to use them)

A Brief History of Histological Myelin Mapping of the Cerebral Cortex: The Vogts

- Oskar and Cécile Vogt studied myeloarchitecture in the early 1900s (among the first brain parcellators)
- Distinct cortical areas can be recognized based on differences in several myeloarchitectonic parameters, including:
  - Overall myelin content
  - Number of tangential fibers bands (bands of Baillarger)
  - Density of radial fibers
- The Vogts thought that each cortical hemisphere contains around 200 myeloarchitecturally distinct cortical areas
  - Based on what we know from comparing monkeys and humans so far, 150-200 human cortical areas is about right

MPI for Brain Research, Frankfurt

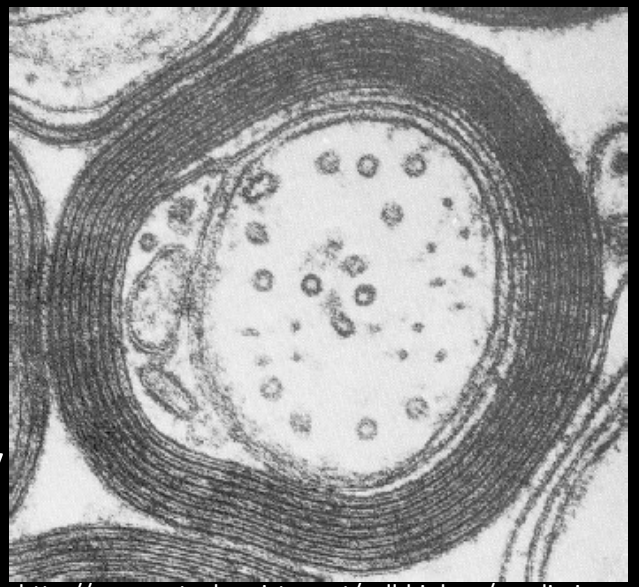


Pial Surface

White Matter

MRI Contrast Mechanisms for In Vivo Myelin Mapping

- Myelin has several properties that make it visible to MRI:
  - It is rich in lipids
  - It is colocalized with iron (particularly within the cortical grey matter)
  - It restricts the motion of some nearby water molecules

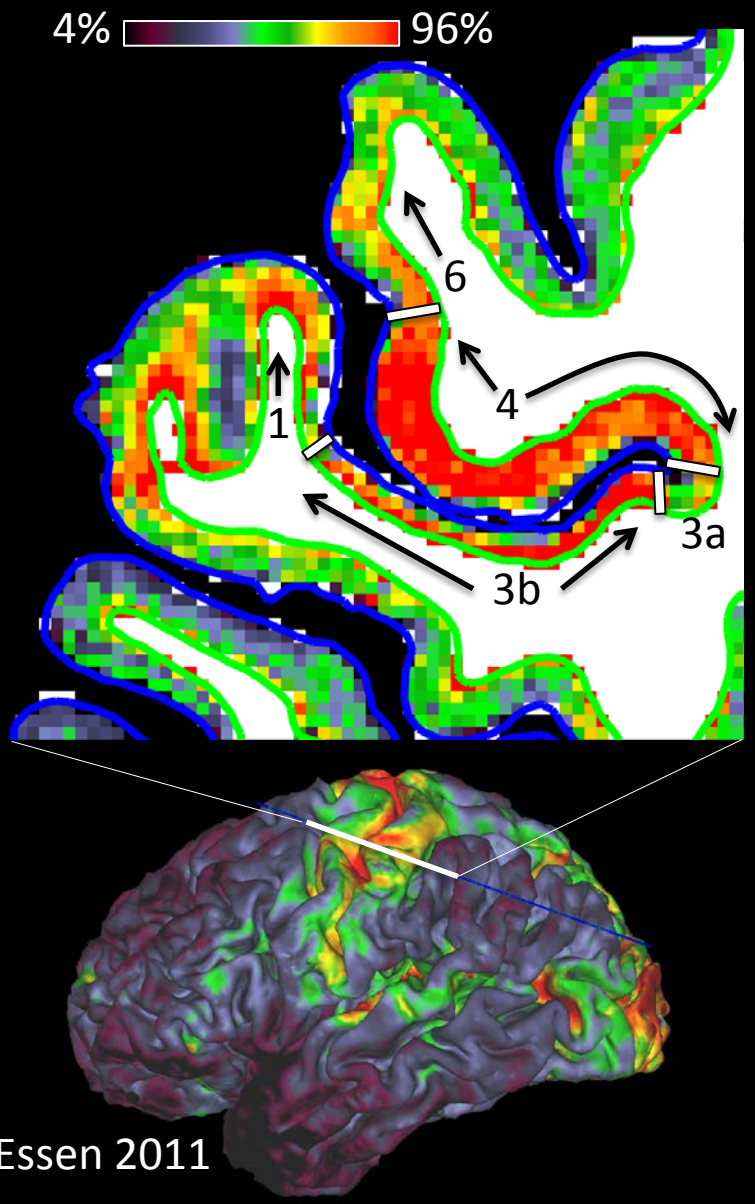


http://www.cytochemistry.net/cell-biology/myelin.jpg

- These properties lead to several forms of MR contrast
  - T1 contrast, T2* contrast, Magnetization Transfer
  - Each of these contrast mechanisms has been verified by comparing myelin stained sections to MRI-based myelin maps
    - e.g. Bock et al 2009, Fukunaga et al 2010, Schmierer et al 2004

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 all three forms of myelin contrast, T1 and T2* (in the T1w image) and T1 and MT (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

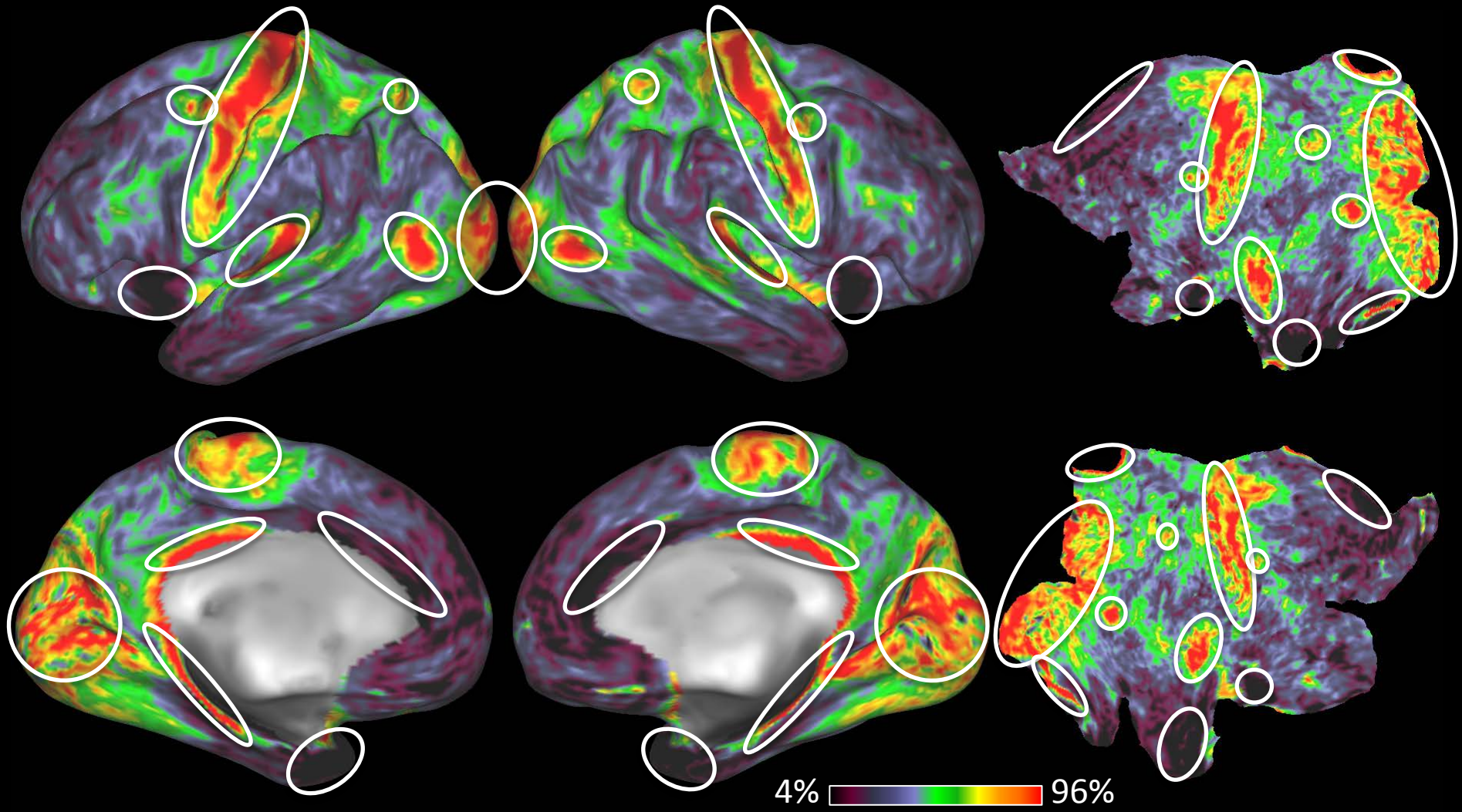


$$\frac{\text{T1w}}{\text{T2w}} \approx \frac{x * b}{(1/x) * b} = x^2$$

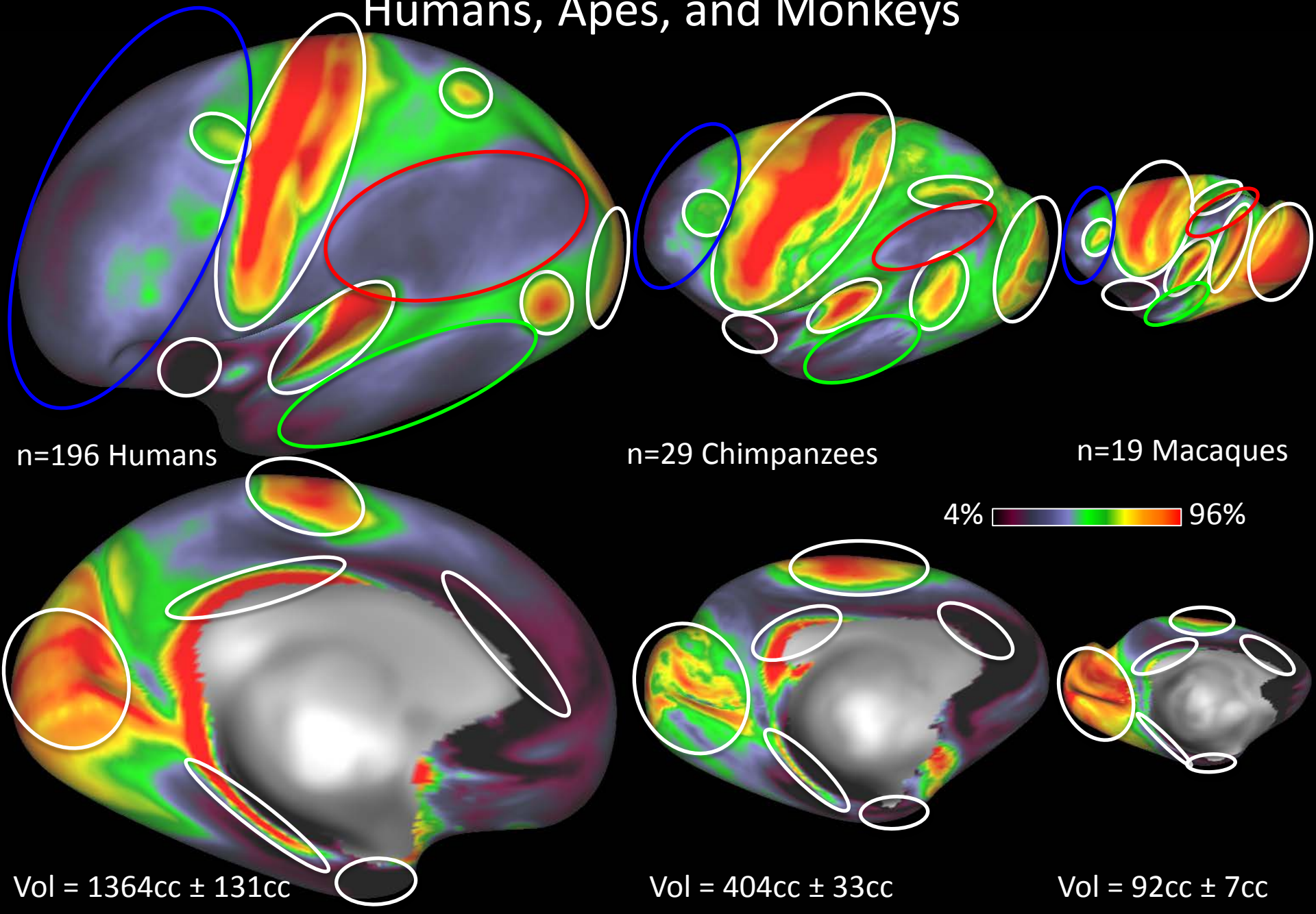
Glasser and Van Essen 2011

Myelin Maps of an Individual HCP Subject

- Many cortical areal features are visible, including:



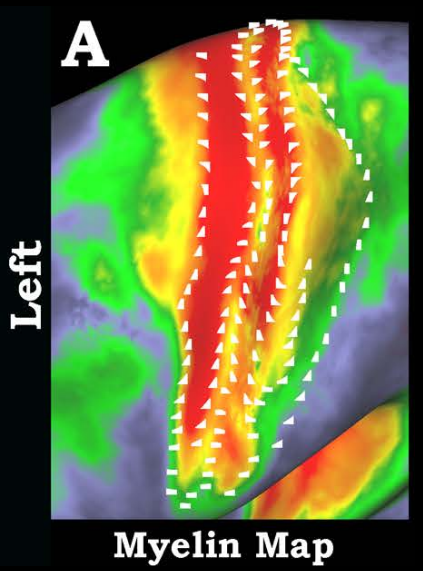
Myelin Maps Can Help Identify Homologous Areas Across Humans, Apes, and Monkeys



Neuroanatomical Validation of Myelin Maps

Glasser and Van Essen 2011
(69 In Vivo Humans)

Fischl et al 2008
(10 Post Mortem Humans)



What You Need to Know About How To Make Myelin Maps

- Images to acquire:
  - High resolution T1w and T2w (1mm or better, 0.8mm or better recommended)
  - Field map recommended (GRE or SE)
  - Example MR protocols at www.humanconnectome.org
- Analysis software:
  - HCP's structural minimal preprocessing pipelines generate myelin maps
  - Download and instructions: https://github.com/Washington-University/Pipelines
- Other approaches: Quantitative T1, T2*, MT
  - They are quantitative as opposed to relative, but will generally require more scanning time/field strength to achieve similar CNR/resolution

Learning Objectives

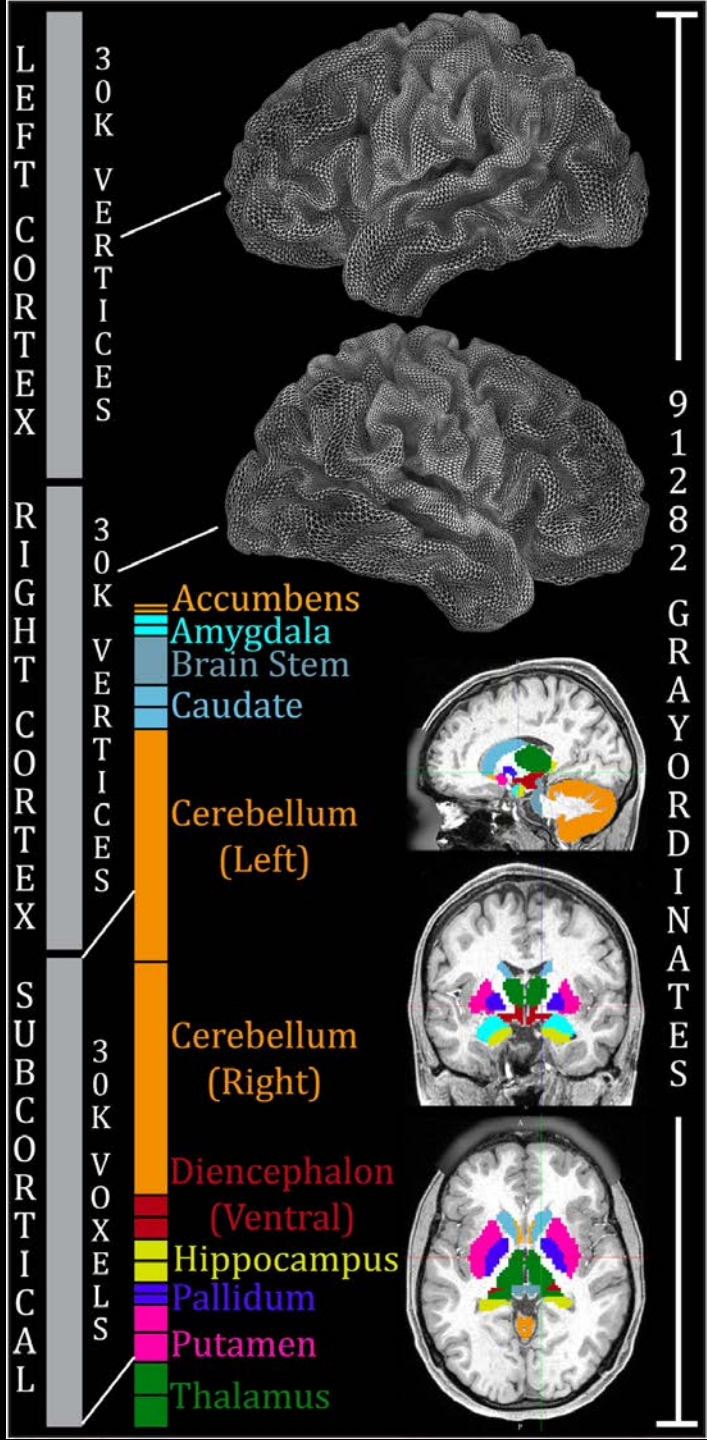
- Non-invasive MRI-based methods for mapping cortical myelin content
- HCP's multi-modal cortical parcellation with group average gradients
- Identification of cortical areas in individuals and parcellation validation

Preparing Multi-modal Data for Precise Cortical Parcellation

- The following topics will be covered in more detail at 1:30-2:00pm lecture in the Anatomy course in the interest of time
  - Were VERY important to the precision of what follows
- Important to minimize sources of blurring in data by using careful processing and analysis techniques
  - AVOID poor cortical registration, smoothing, other lossy processing
- Need to analyze and visualize cortical data on surface models instead of in 3D in the volume
  - Need to use cortical surface registration across subjects and studies
- Drive surface registration using areal features (e.g. myelin, RSNs, etc) instead of folding because of often poor areas/folds correlation
  - MSM surface registration algorithm (Robinson et al 2014)
  - Remove registration drift between studies
- The data residing in the HCP's CIFTI grayordinates standard space and file format are a good basis for parcellation

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 Grayordinates, 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
- Grayordinates-based imaging analyses can greatly reduce the analysis-induced uncertainty in spatial localization in brain imaging studies

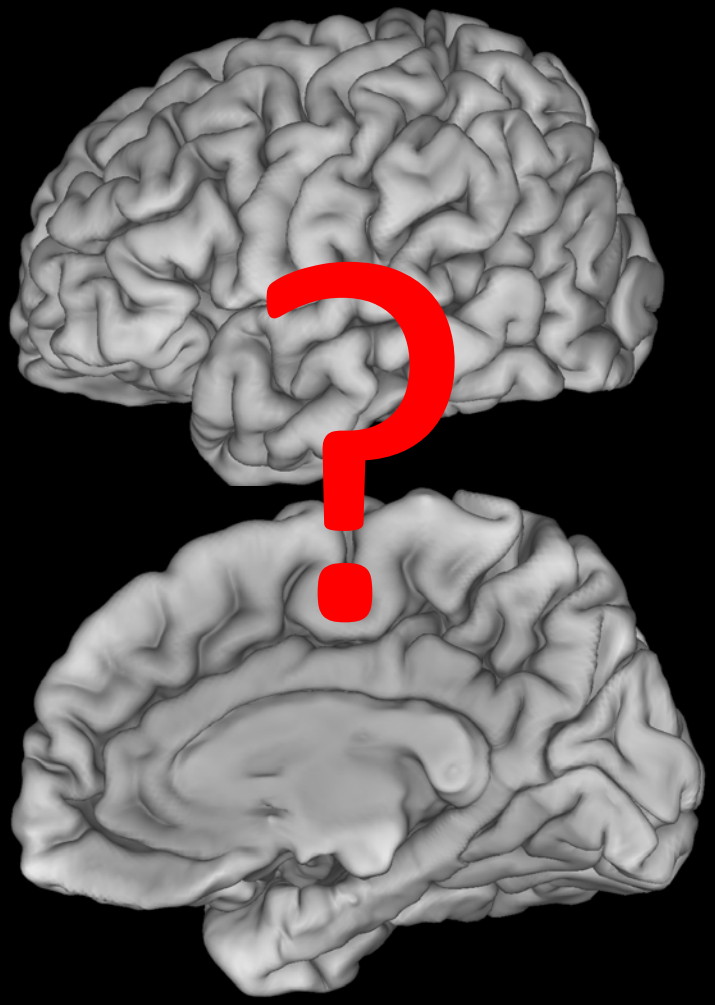


What You Need To Know About Careful Preprocessing & Registration

- Software:
  - HCP minimal preprocessing pipelines produce combined cortical surface and subcortical volume data in the CIFTI format and standard grayordinates space (https://github.com/Washington-University/Pipelines)
  - MSM software will be released in next version of FSL (soon) together with areal feature-based surface registration HCP pipeline (MSMAll)
  - CIFTI visualization + analysis: Connectome Workbench, Workbench Command, and Matlab (www.humanconnectome.org), and FSL (soon)
- Data:
  - Next HCP data release will provide MSMAll_DeDrift aligned data in addition to folding-based aligned data
- Images to acquire for using the MSMAll_DeDrift pipeline in the future:
  - T1w, T2w, field map, fMRI (with high spatial and temporal resolution over a long, e.g. 30+ mins total duration)
  - Same requirements as for the already released HCP's minimal preprocessing pipelines
- Other software: FreeSurfer, AFNI's SUMA, CBS Tools (MPI)

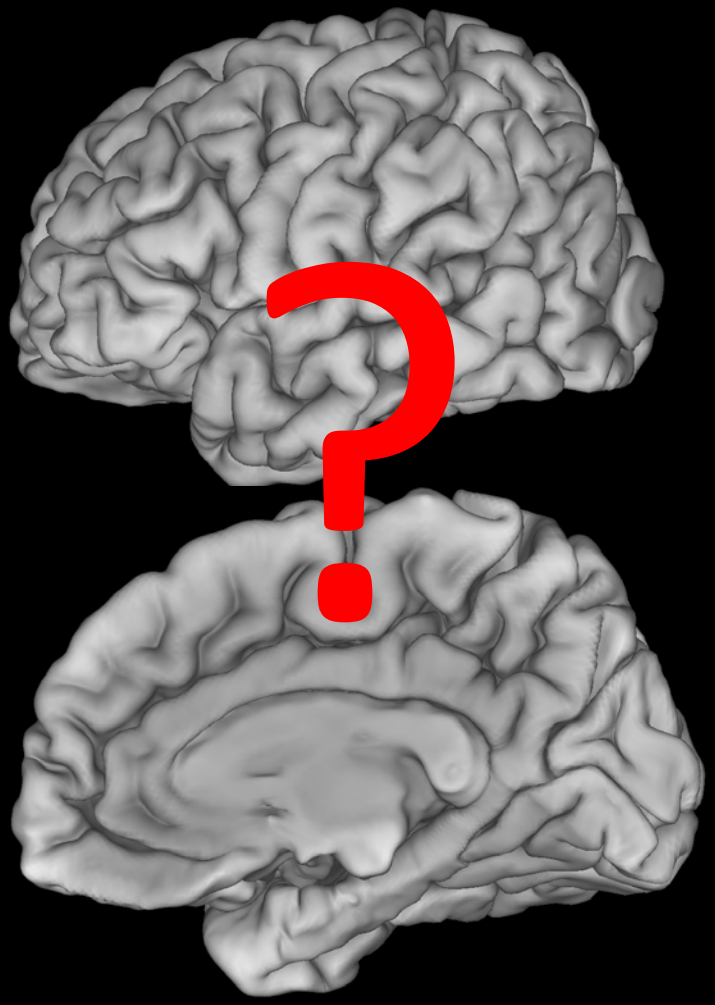
How Might One Parcellate the Brain?

- Historically, brain areas have generally been defined using invasive methods by transitions in one or more neuroanatomical properties:
  - Architecture
  - Function
  - Connectivity
  - Topography
- The HCP is measuring each of these properties non-invasively in 1200 subjects
- Today we'll focus on the cerebral cortex for multi-modal parcellation



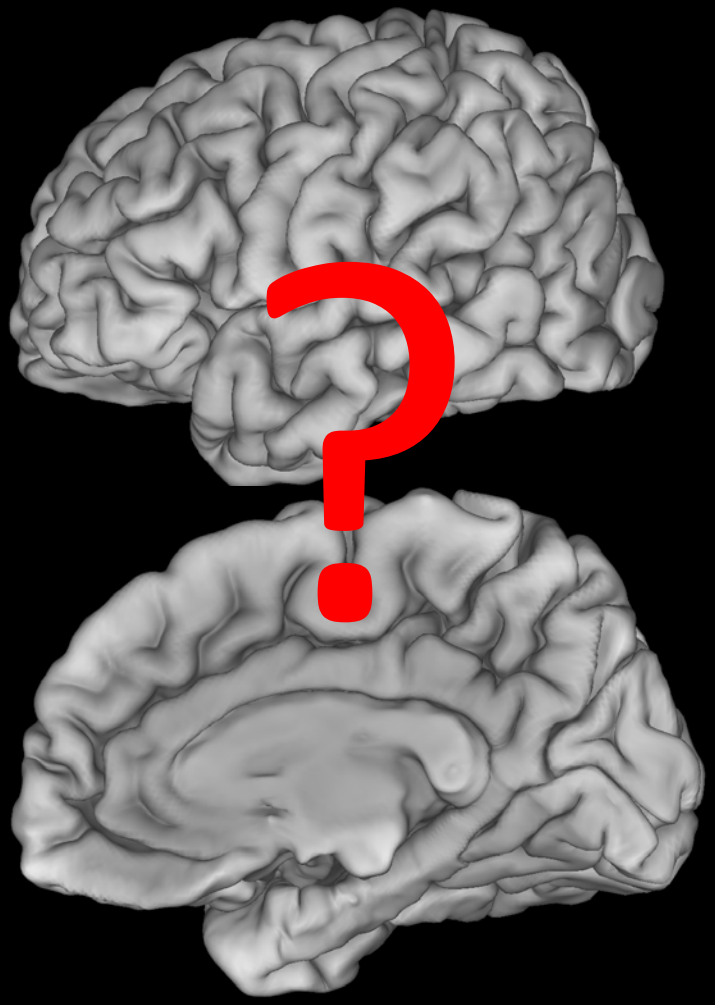
How Might One Parcellate the Cortex?

- Most extant parcellations were generated with only a single areal property/modality because that is all that is available
- With the HCP, we can use multiple modalities to generate a cortical parcellation
- We can use gradients (i.e. the first derivative across the surface) as an objective measure to highlight locations where a modality is rapidly changing—potential areal boundaries

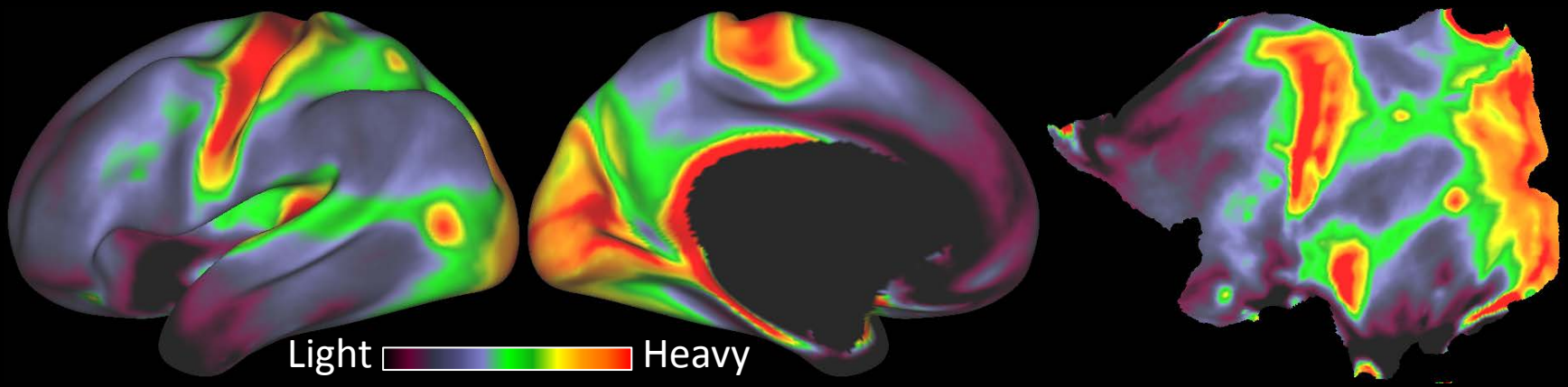


How Might One Parcellate the Cortex?

- What makes a gradient convincing as an areal boundary?
  - Agreement in spatial location of a putative boundary between two or more independent modalities
  - Presence in both hemispheres
  - Not associated with known imaging artifact
  - Prior literature evidence for the boundary
- The final step in brain parcellation is to relate the spatial relationships of areal boundaries to existing parcellations to identify areas or describe new ones

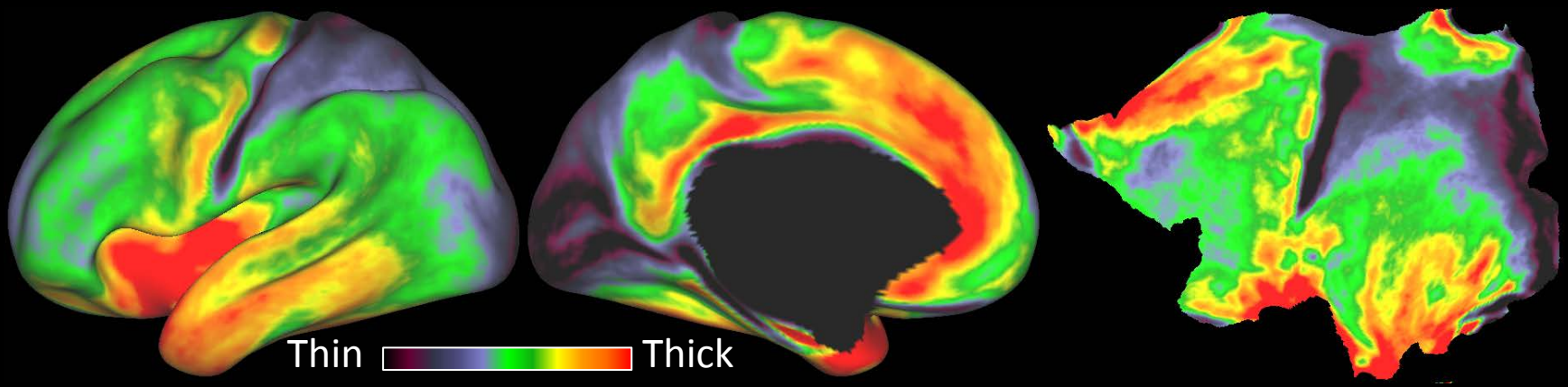


Architectonic → Myelin



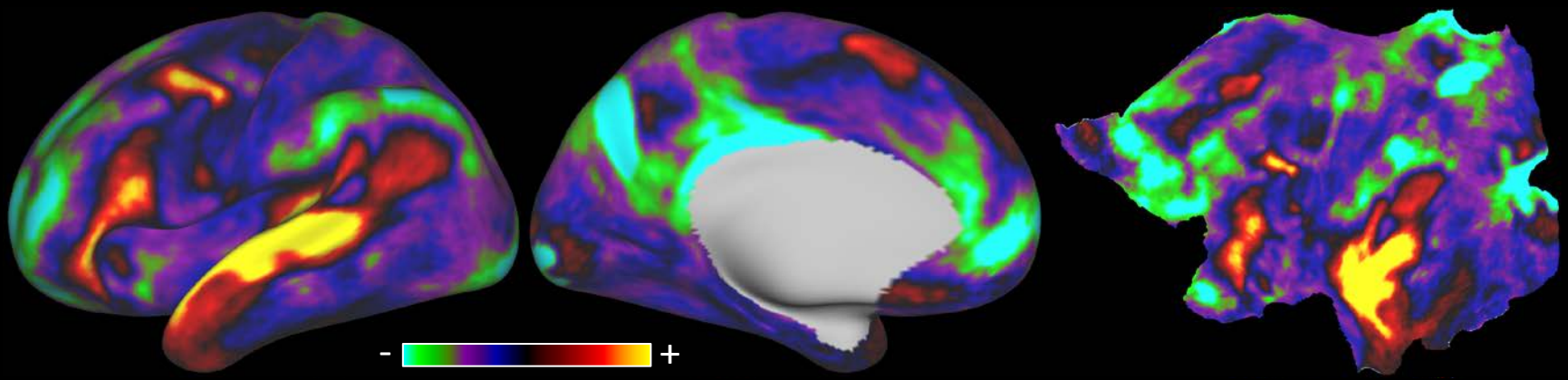
- If we want to define cortical areal borders, we're interested in where myelin content changes
- The spatial gradient tells us objectively where the transition in myelin content occurs
- The local maximum of the gradient is the most likely location of a potential areal border
- Some transitions are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

Architectonic → Thickness → Gradients



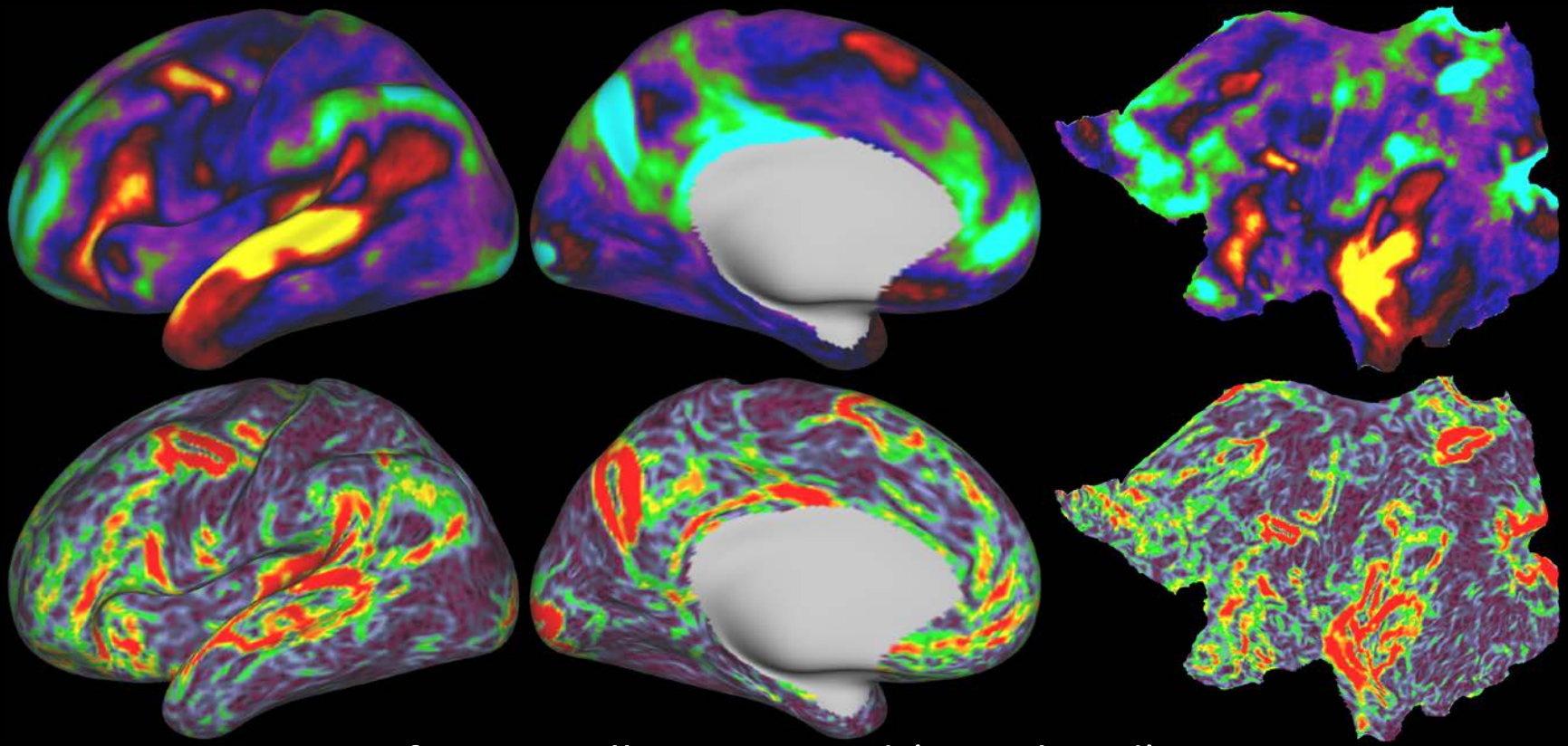
- Cortical Thickness is another modality that gives us architectural information
- Sharp transitions in cortical thickness also give us some areal boundary candidates
- Curvature is regressed out of thickness maps to reduce folding effects (thicker on gyri, thinner on sulci)

Function → task fMRI → STORY vs REST



- Positive areas have more activity during the task whereas negative areas have more activity during resting
- tfMRI contrast beta maps (i.e. effect size maps) produce gradients just like the architectonic maps

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 fnctional connectivity
- Note the similarity between the rfMRI and tfMRI maps

Topographic Connectivity

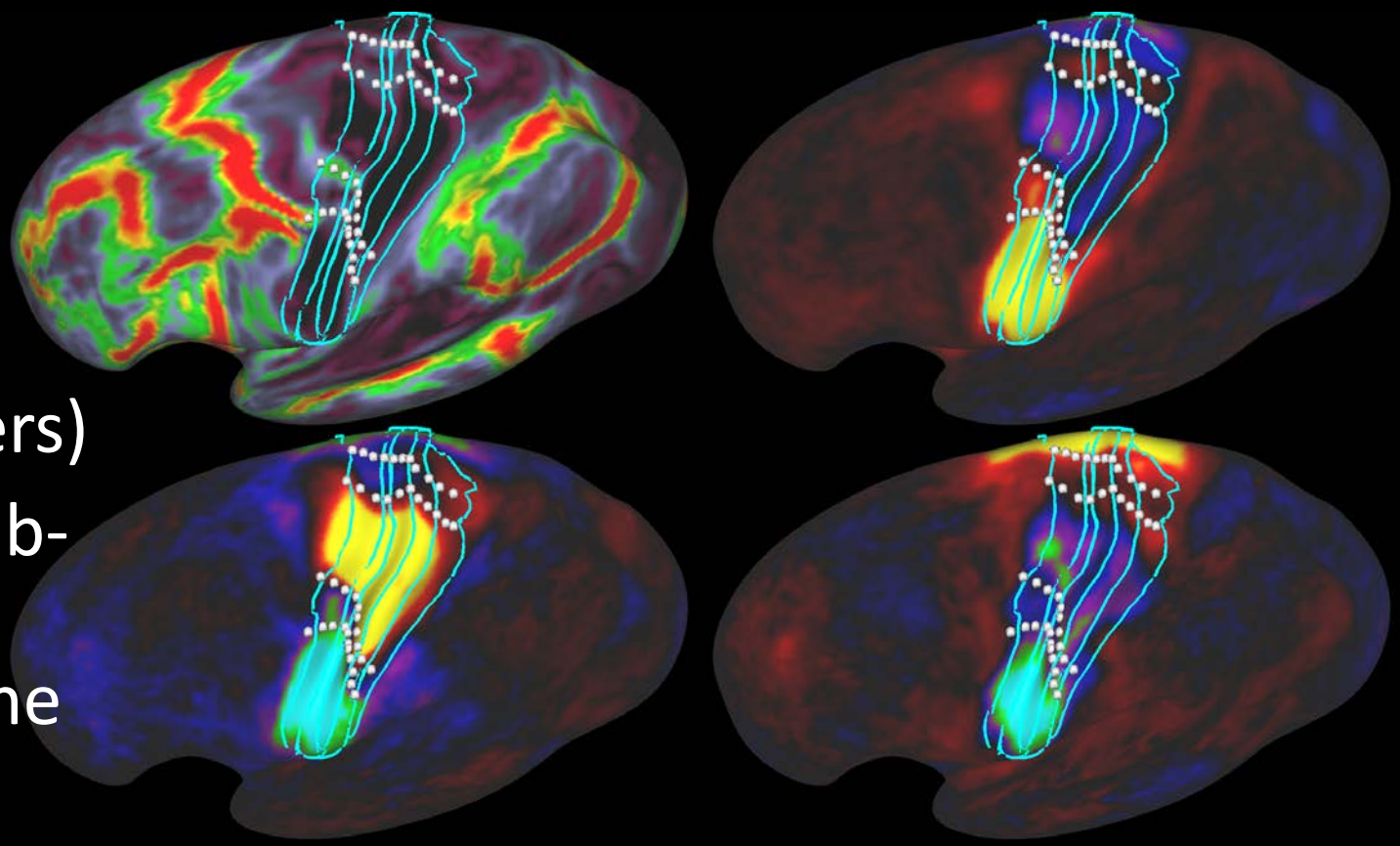
- Task fMRI and resting state connectivity can be used to define areas using topographic maps
- Retinotopic maps are a great example of this
- Visuotopic maps were used in the following parcellation
- However, this topic will be covered in more detail in the 1:30-2:00pm lecture in the Anatomy course in the interest of time

Multi-modal Parcellation: Putting It All Together for One Cortical Area

- A strip of lightly myelinated cortex between the FEFs and Premotor Eye Field
  - Gradients define most likely areal boundaries
- This area also has unique task activity in the STORY vs Resting contrast
  - Task fMRI gradients line up with myelin gradients
- This area has a unique functional connectivity pattern with respect to its neighbors
  - The resting state gradients line up with the myelin and task gradients
- Multiple independent modalities (architecture, function, and connectivity) agree on area
- The last step in parcellation is to identify the area with respect to the literature, here the area largely corresponds to 55b in the Hopf (1956) myeloarchitectonic parcellation
- Lots of work to do for 150-200 cortical areas in each hemisphere, but it can be done…

Topographic Sub-areas in Somatosensory and Motor Cortex

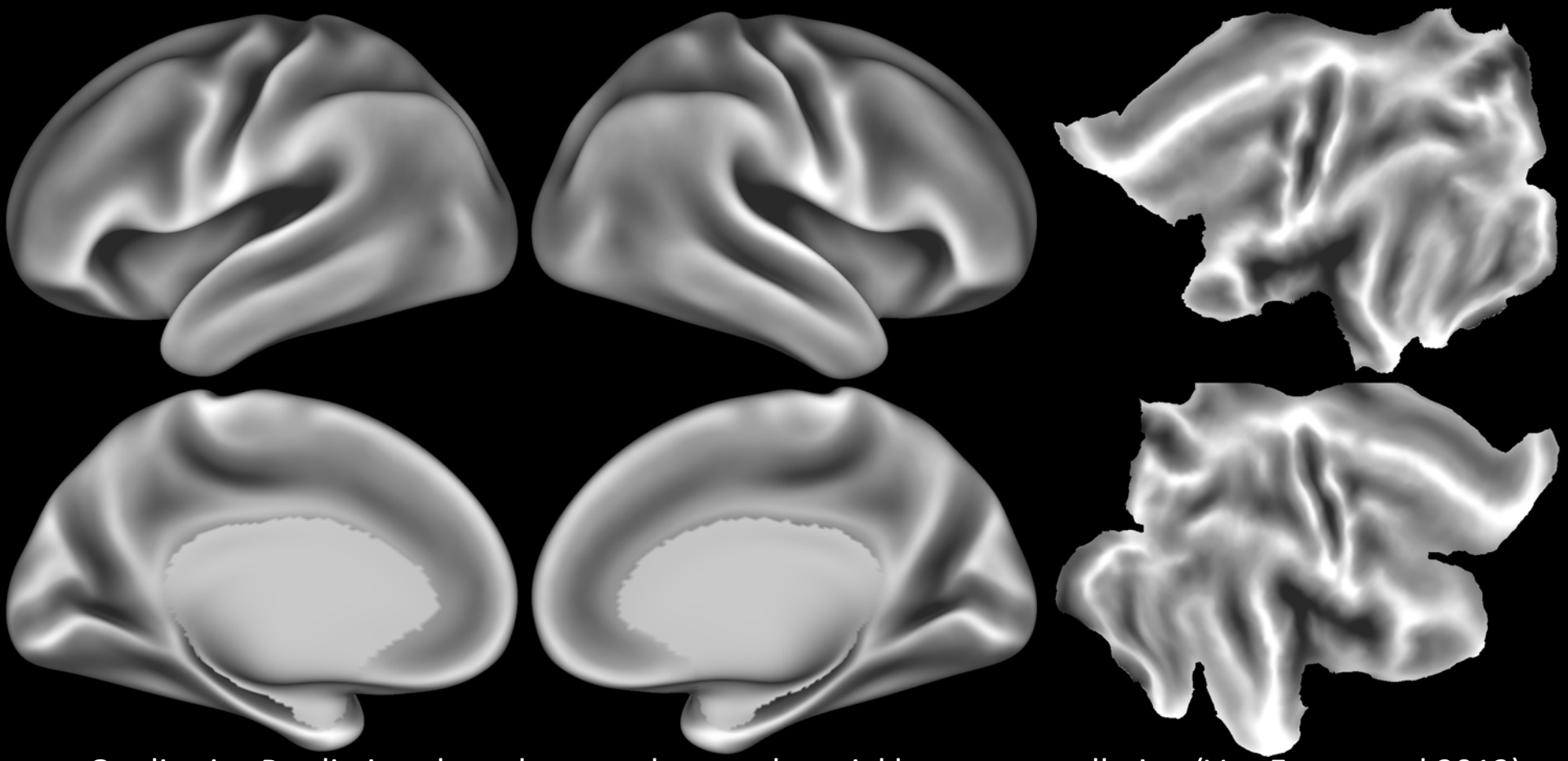
- Myelin and thickness define architectonic areas (blue borders)
- Functionally, these areas have five somatotopic subdivisions (white borders)
- 3 of these sub-areas were mapped in the motor task



Multimodal Cortical Parcellation

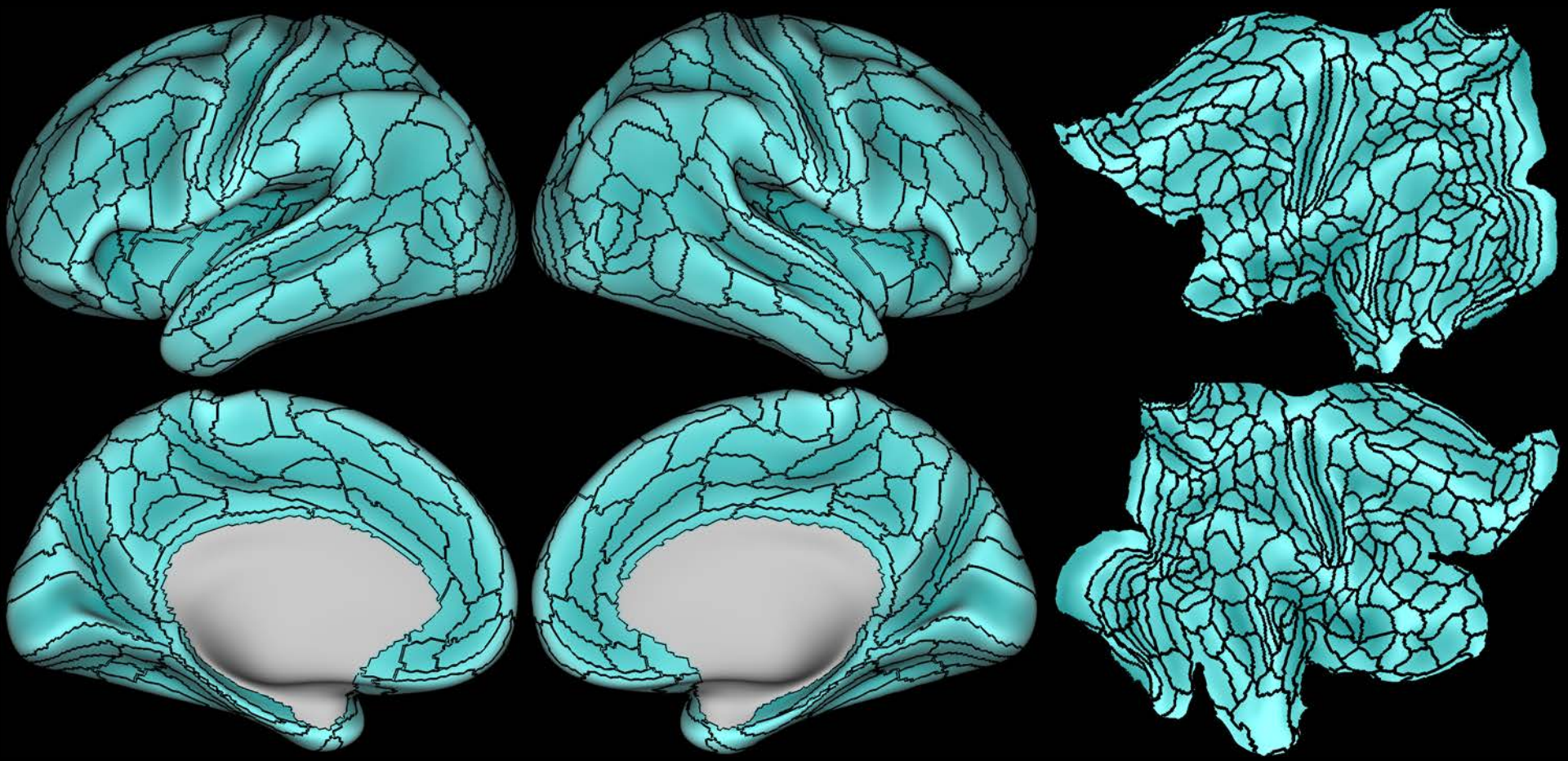
- The multi-modal parcellation was constructed from 210 HCP subjects brought into the standard grayordinates space using MSM areal-feature-based registration
- Borders were defined using gradients in
  - Architecture (myelin maps and thickness with curvature regressed out)
  - Function (86 task fMRI contrast maps from 7 tasks)
  - Connectivity (Resting state functional connectivity)
  - Topography (Visuotopic resting state functional connectivity)
- Areas were identified with reference to the prior neuroanatomical literature
  - We attempted to keep the same names when possible

Multimodal Cortical Parcellation



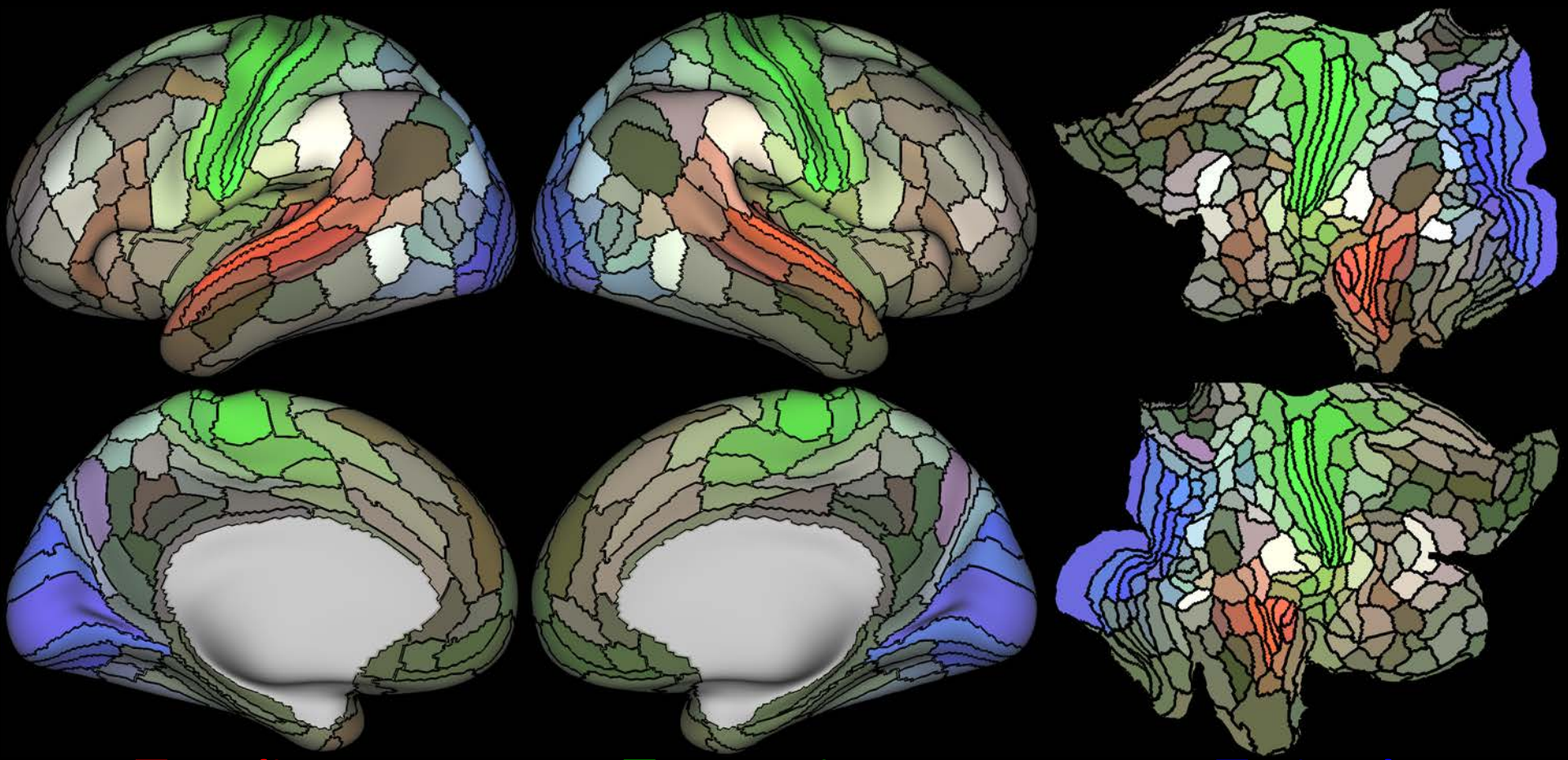
- Qualitative Predictions based on monkeys and partial human parcellation (Van Essen et al 2012):
  - 150-200 human cortical areas per hemisphere
  - Wide variability in areal size and shape
  - Will be examples of inter-areal heterogeneity (e.g. early sensory topographies)

Multimodal Cortical Parcellation



- Qualitative Results:
  - 178 Areas and Complexes (potentially containing multiple areas) per hemisphere
  - Wide variability in areal size and shape
  - Some Areas contain topographic subareas (e.g. M1 and S1)

Multimodal Cortical Parcellation

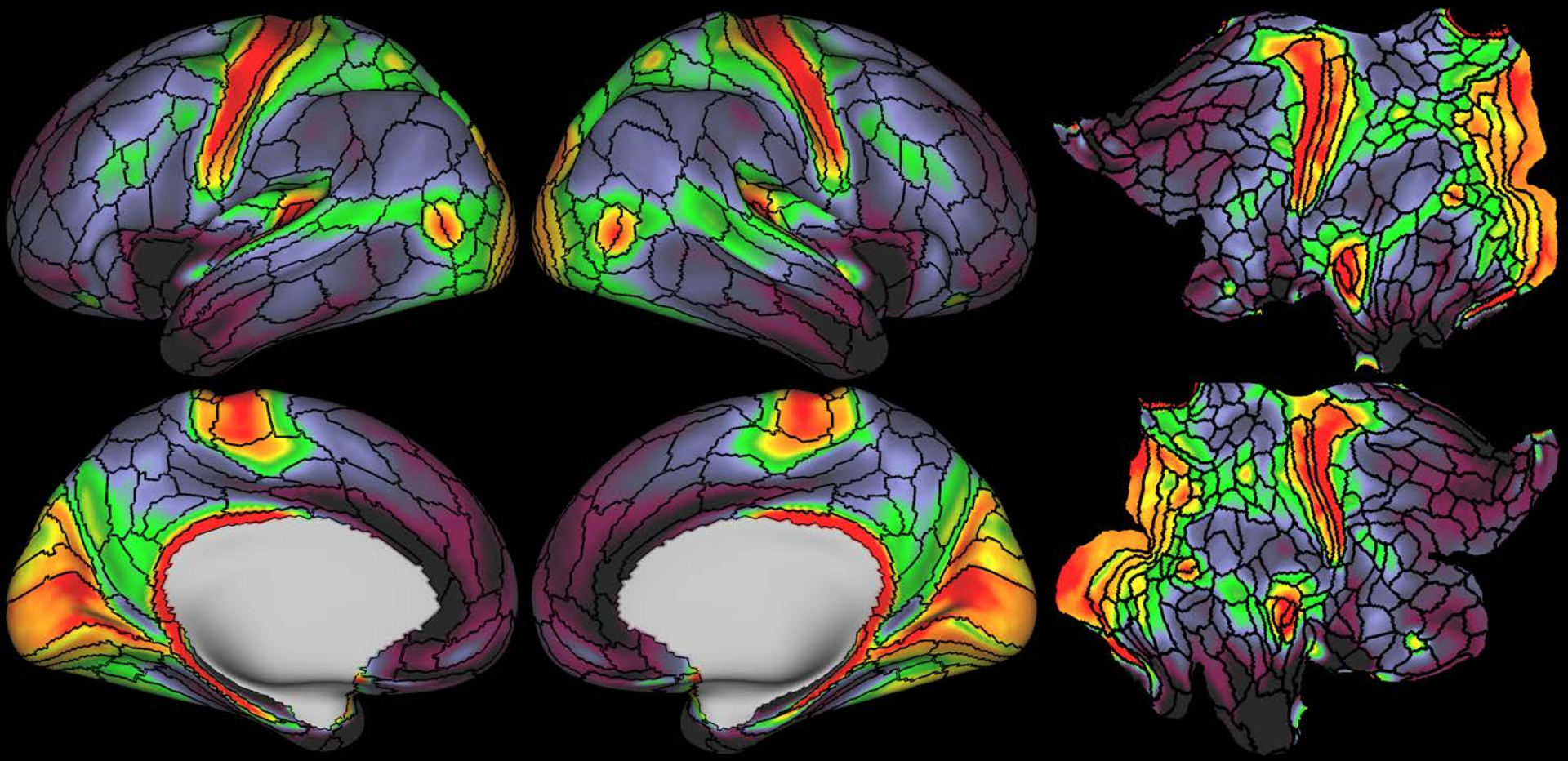


■ Auditory ■ Sensori-motor ■ Visual

□ Task-Negative (Dark) ■ Task-Positive (Bright)

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

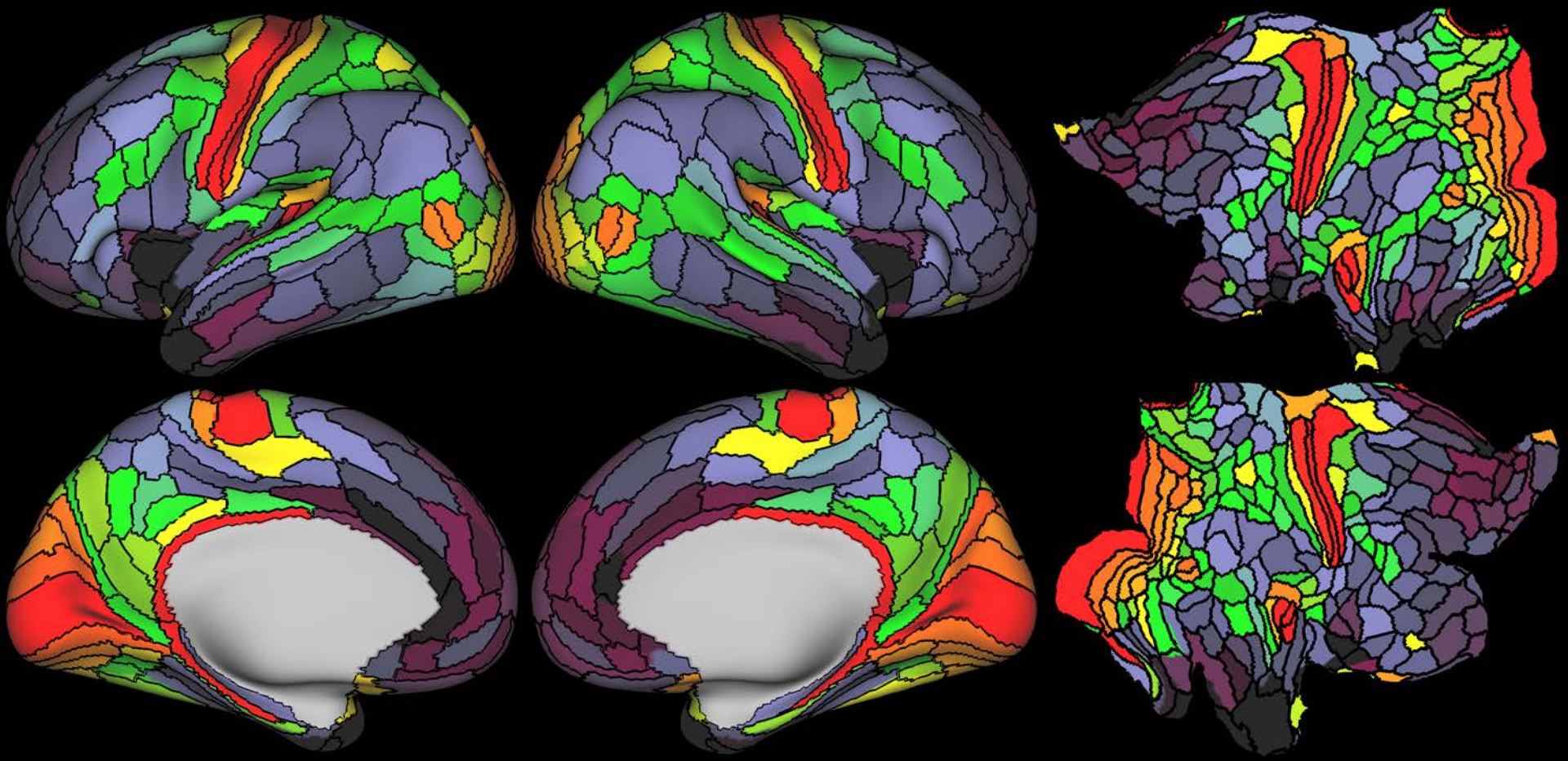
Parcellated Analyses



Dense Myelin Map

Light — Heavy

Parcellated Analyses

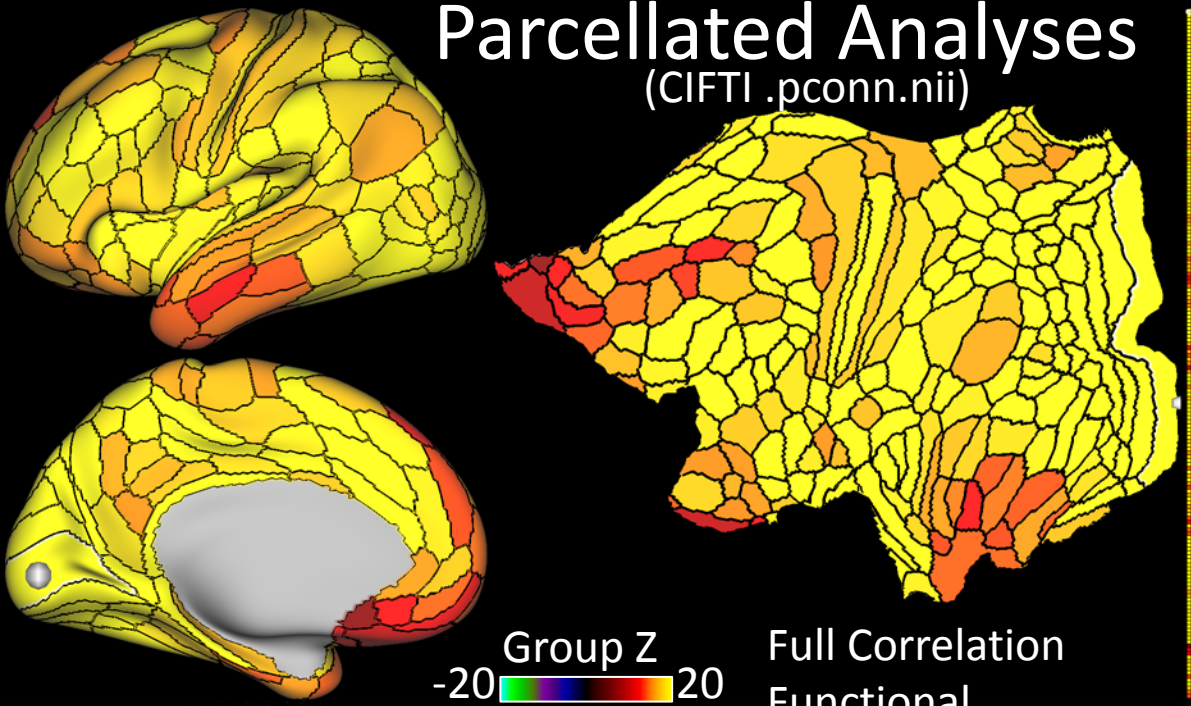


Parcellated Myelin Map

Light — Heavy

Parcellated Analyses

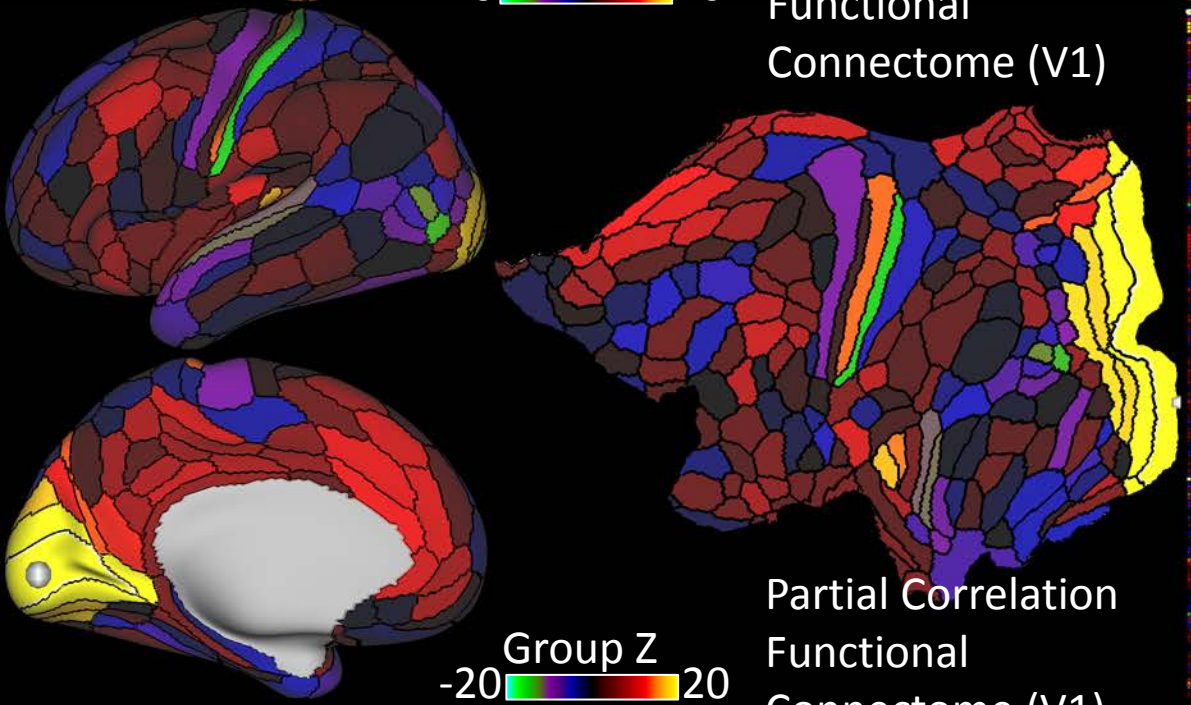
(CIFTI .pconn.nii)



Group Z

-20 20

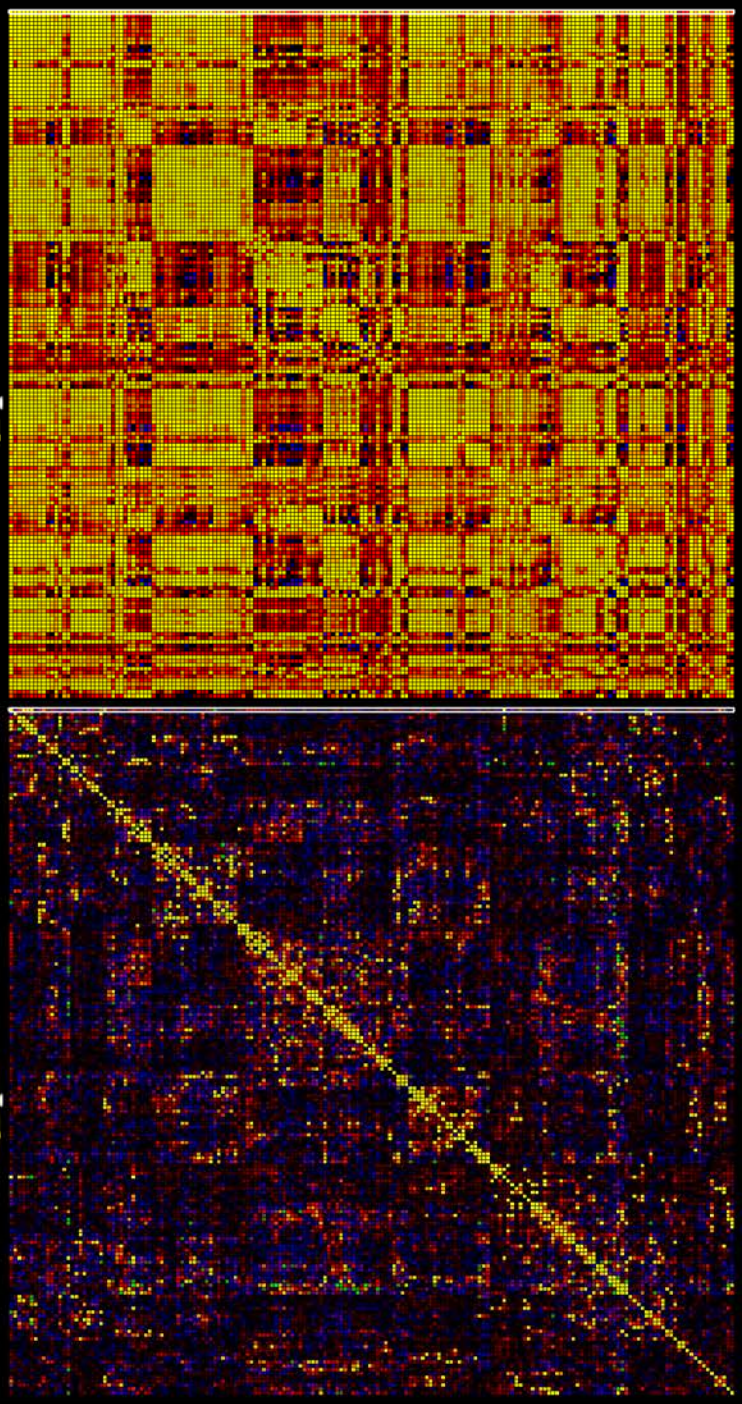
Full Correlation Functional Connectome (V1)



Group Z

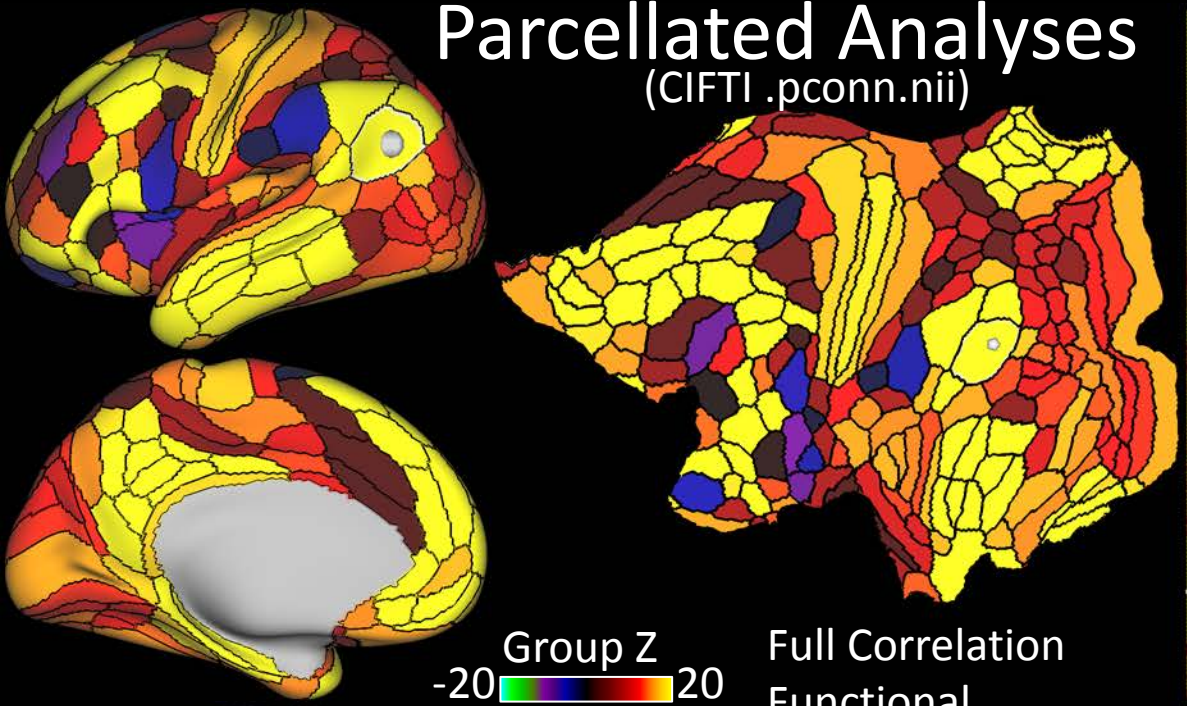
-20 20

Partial Correlation Functional Connectome (V1)



Parcellated Analyses

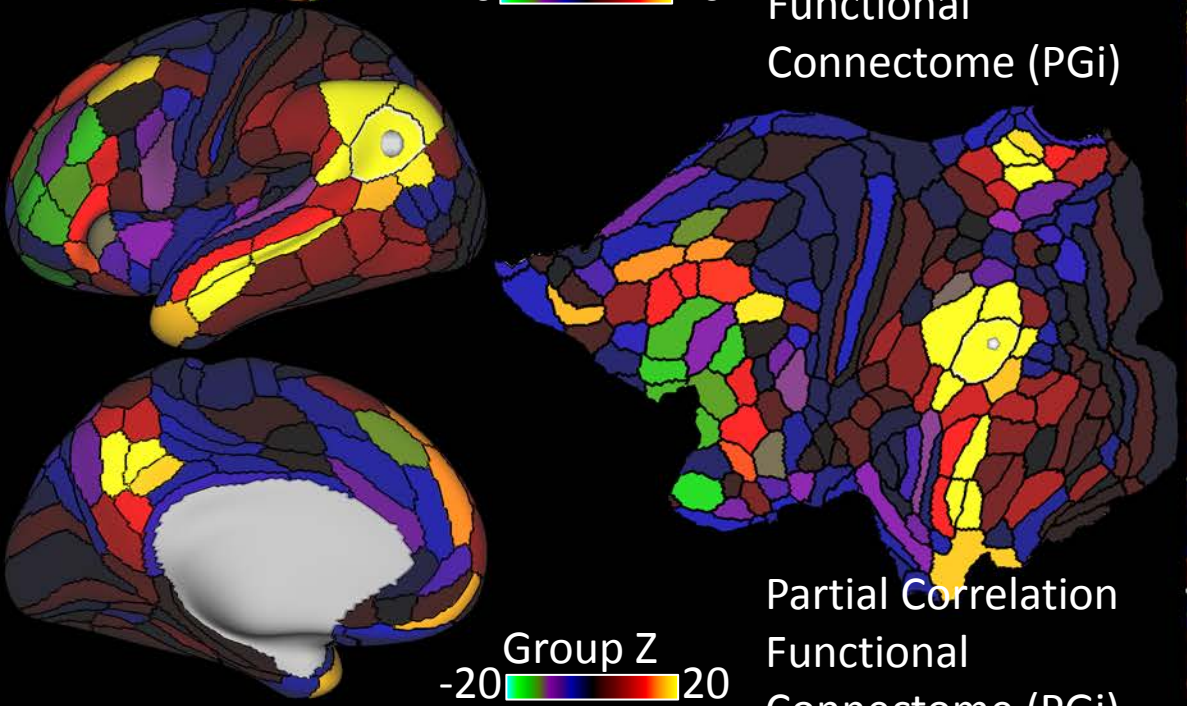
(CIFTI .pconn.nii)



Group Z

-20 20

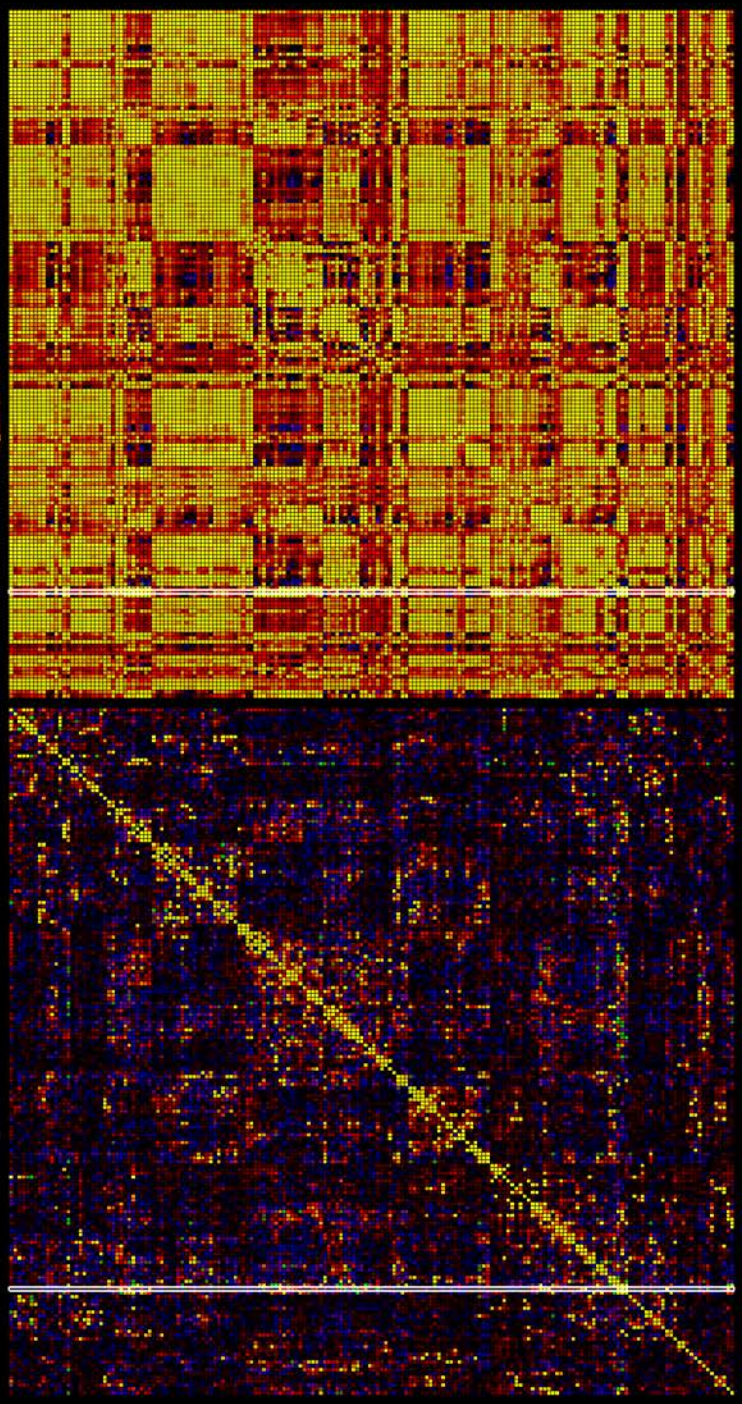
Full Correlation Functional Connectome (PGi)



Group Z

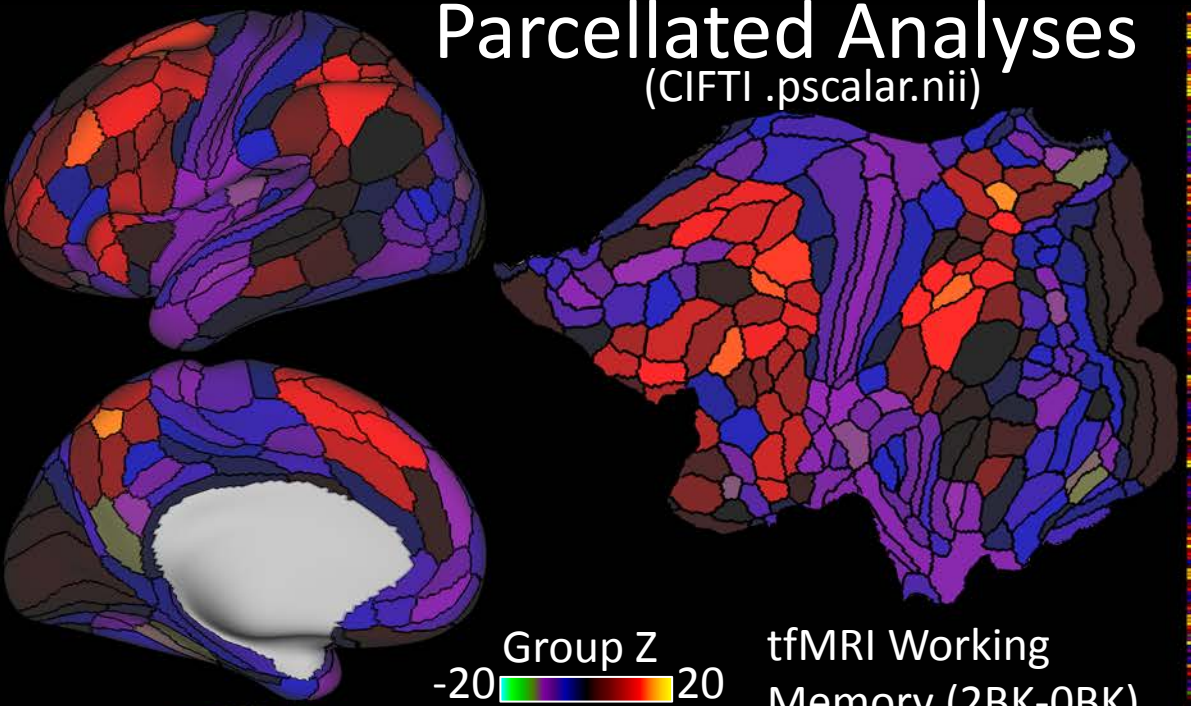
-20 20

Partial Correlation Functional Connectome (PGi)



Parcellated Analyses

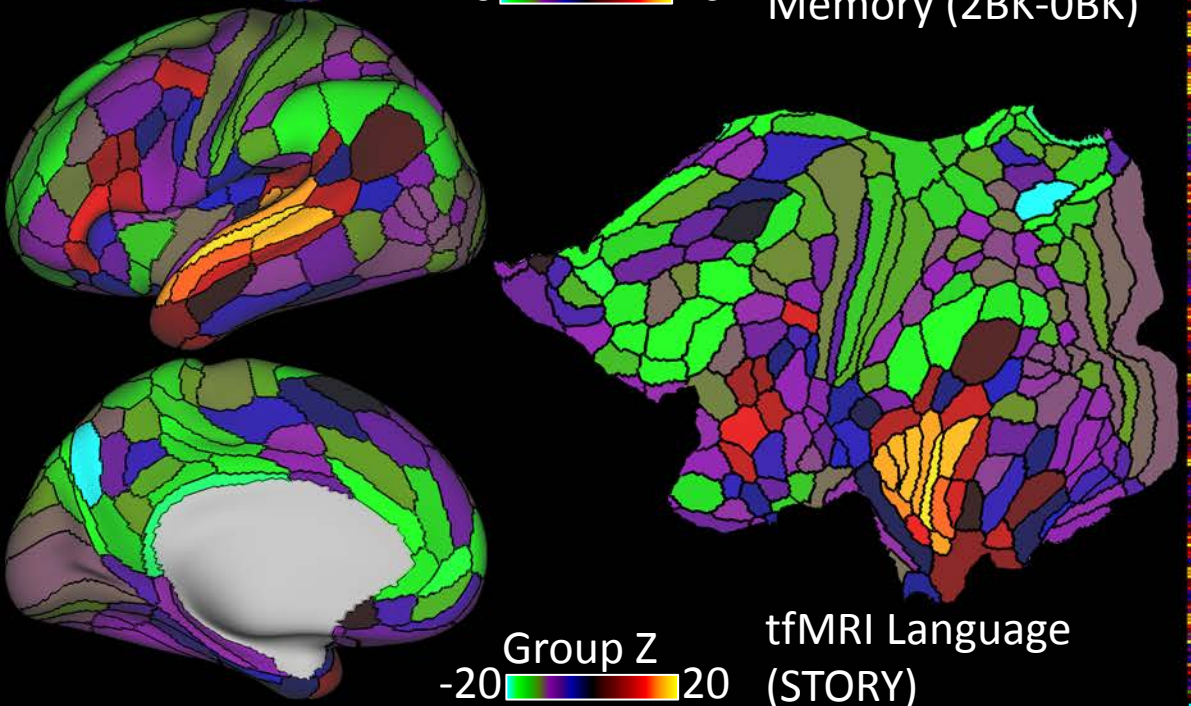
(CIFTI .pscalar.nii)



Group Z

-20 20

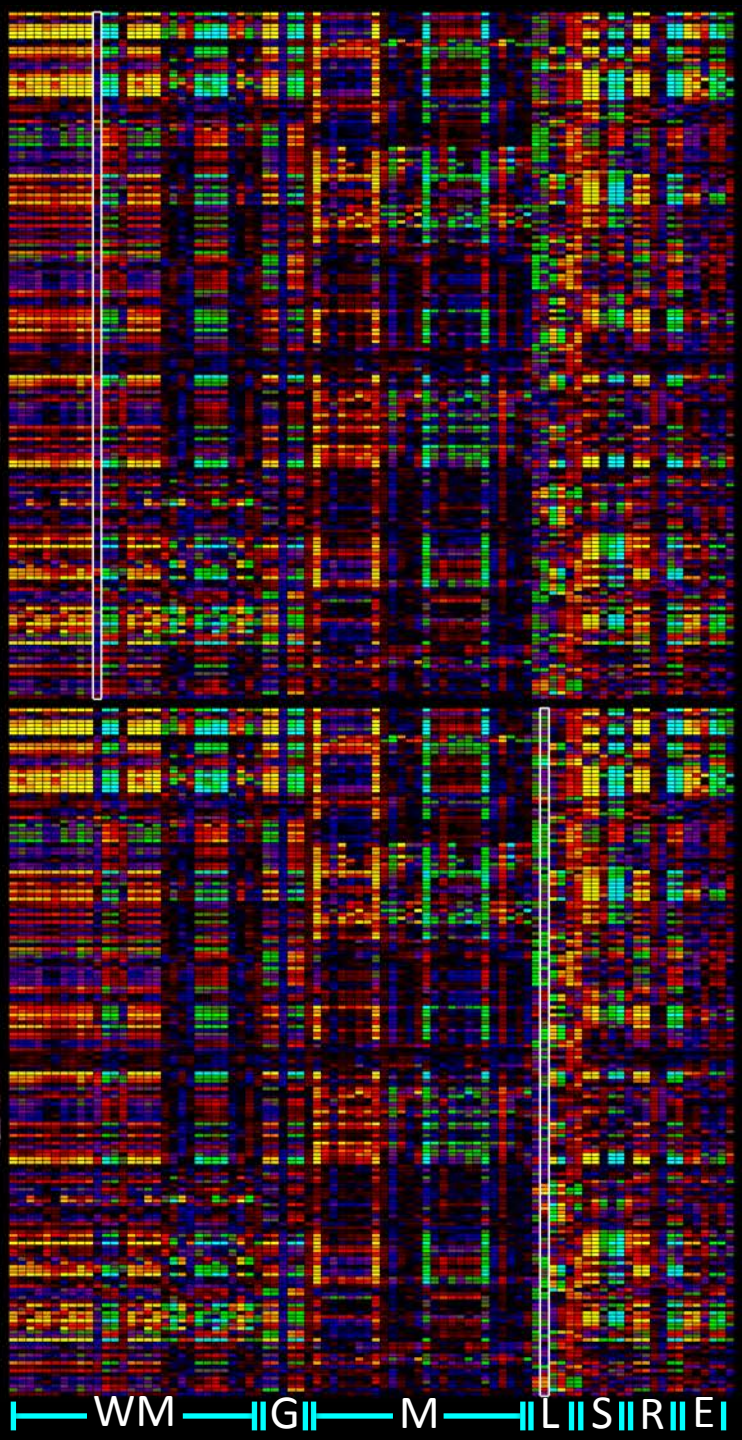
tfMRI Working Memory (2BK-0BK)



Group Z

-20 20

tfMRI Language (STORY)



Parcellated Analyses

- One can think of the HCP MRI data as a 3D matrix with parcels X features X subjects
  - A manageably sized, high SNR dataset!
  - Addresses multiple comparison issues with voxelwise data
  - The concept could apply to your own data
- The concept of Parcels X Features X Subjects will be important for the next section as well

Learning Objectives

- Non-invasive MRI-based methods for mapping cortical myelin content
- HCP's multi-modal cortical parcellation with group average gradients
- Identification of cortical areas in individuals and parcellation validation

Three Quick Validation Points

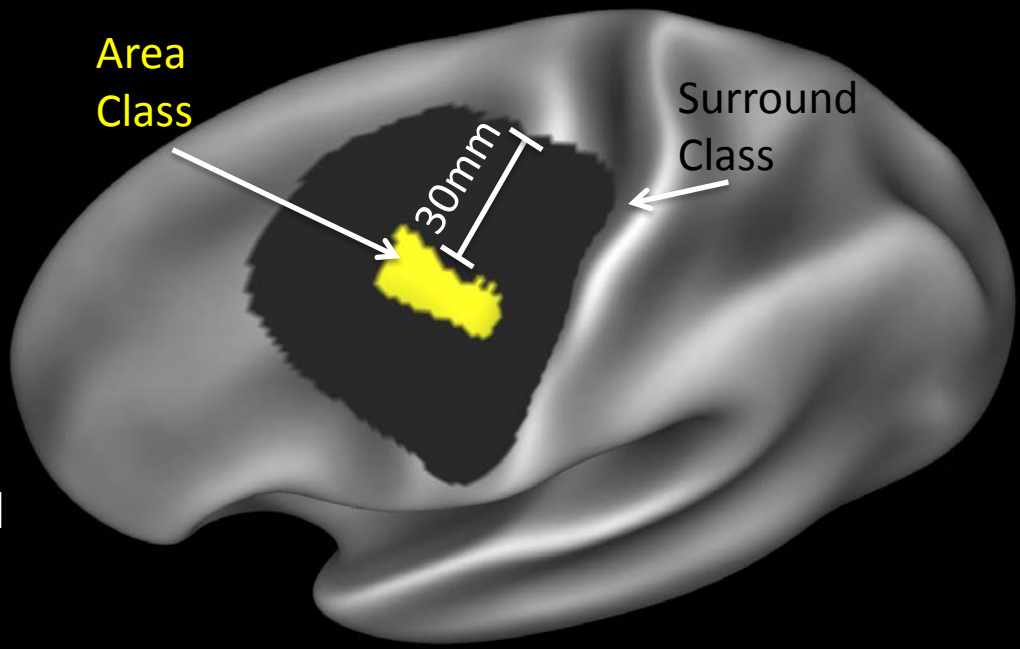
- It is possible to train a supervised classifier (actually Carl's perceptron that he'll tell you a lot more about in his lecture) to identify these cortical areas in individuals based on their multi-modal fingerprints
  - Make individual subject parcellations automatically
  - Including identification of misaligned areas (despite our best efforts at registration, some areas in some subjects have different areal topologies from the group)
  - Make probabilistic maps of areas
- Using only the trained classifier and the dense multi-modal data, one can reproduce the parcellation in an independent group of HCP data (that wasn't used to make the parcellation or train the classifier)
  - 210P used for parcellation and classifier training, 210V for validation
- The pairs of neighboring cortical areas have statistically significant and large differences across multiple modalities

Recall: What Makes a Cortical Area Distinct?

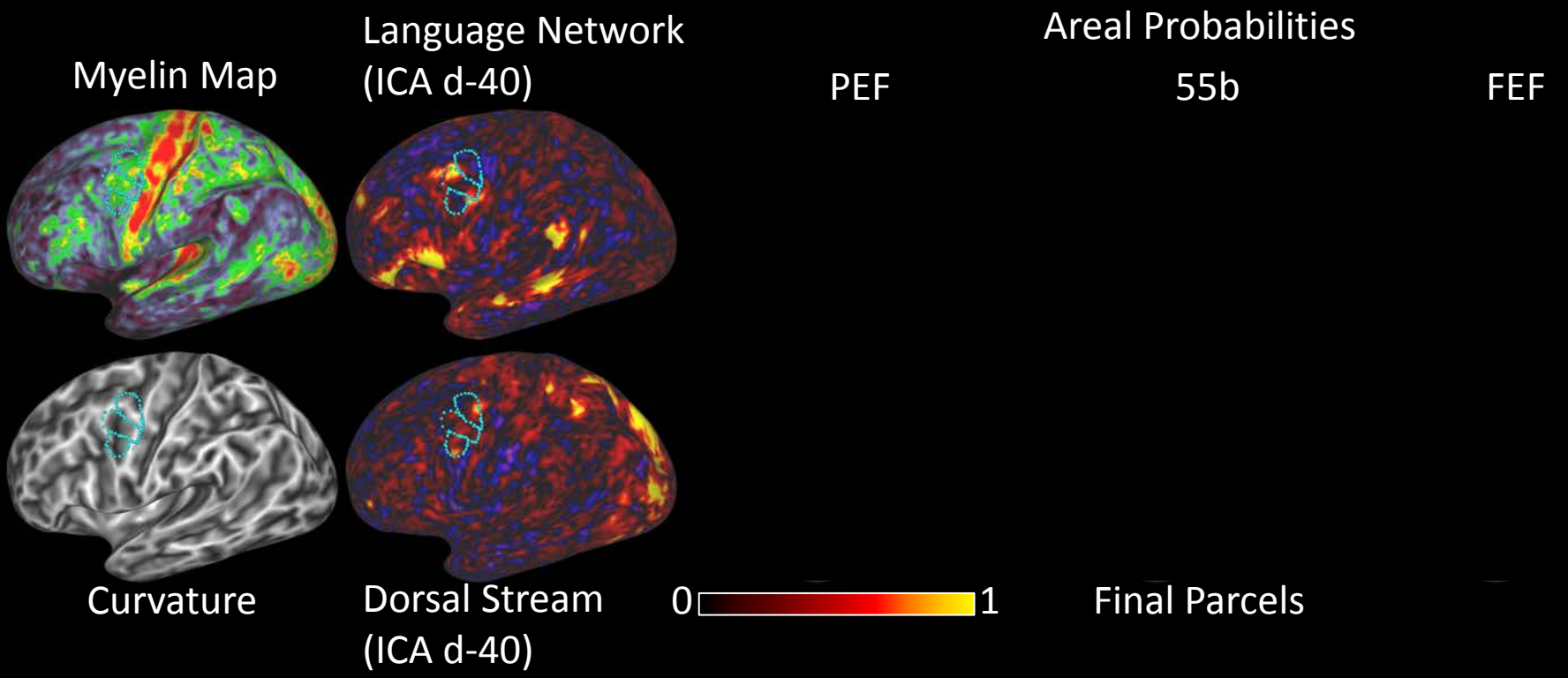
- As we've discussed above, a cortical area will have a distinct pattern of one or more of these properties from its neighbors:
  - Architecture
  - Function
  - Connectivity
  - Topography
- These can be combined into a multi-modal areal fingerprint for each cortical area
- Also, we can reasonably make some assumptions about where a cortical area is located (area V1 isn't ever located outside the occipital lobe for example)
- These neuroanatomical properties can be used to find the group defined cortical areas in individuals

Learning Areal Fingerprints to Delineate and Identify Cortical Areas in Individuals

- Carl (Hacker et al 2013) will talk about his classifier in detail in the last lecture (his application was 7 resting state networks)
- We can use the same perceptron algorithm they used with a few modifications:
  - Instead of trying to classify 178 areas at once (very hard), classify each area from its surrounding 30mm of cortex (an easier binary problem)
  - 30mm is a reasonable assumption in spite of the residual misalignments
  - We'll then combine across classifiers
  - Feed the classifier multi-modal features (myelin, thickness, tfMRI, rfMRI, topograpy) instead of just functional connectivity maps
  - Use fewer hidden nodes (a binary classifier doesn't need as many)

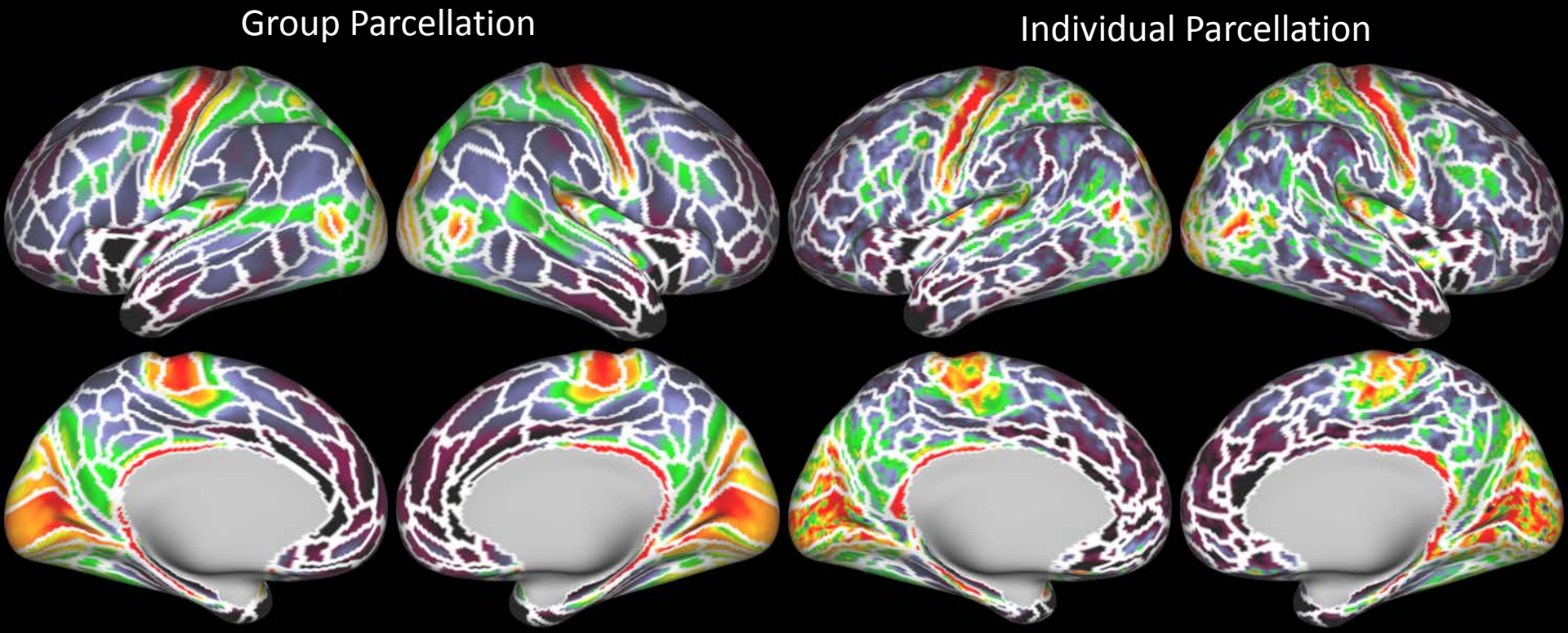


Does the Classifier Identify Misaligned Areas?



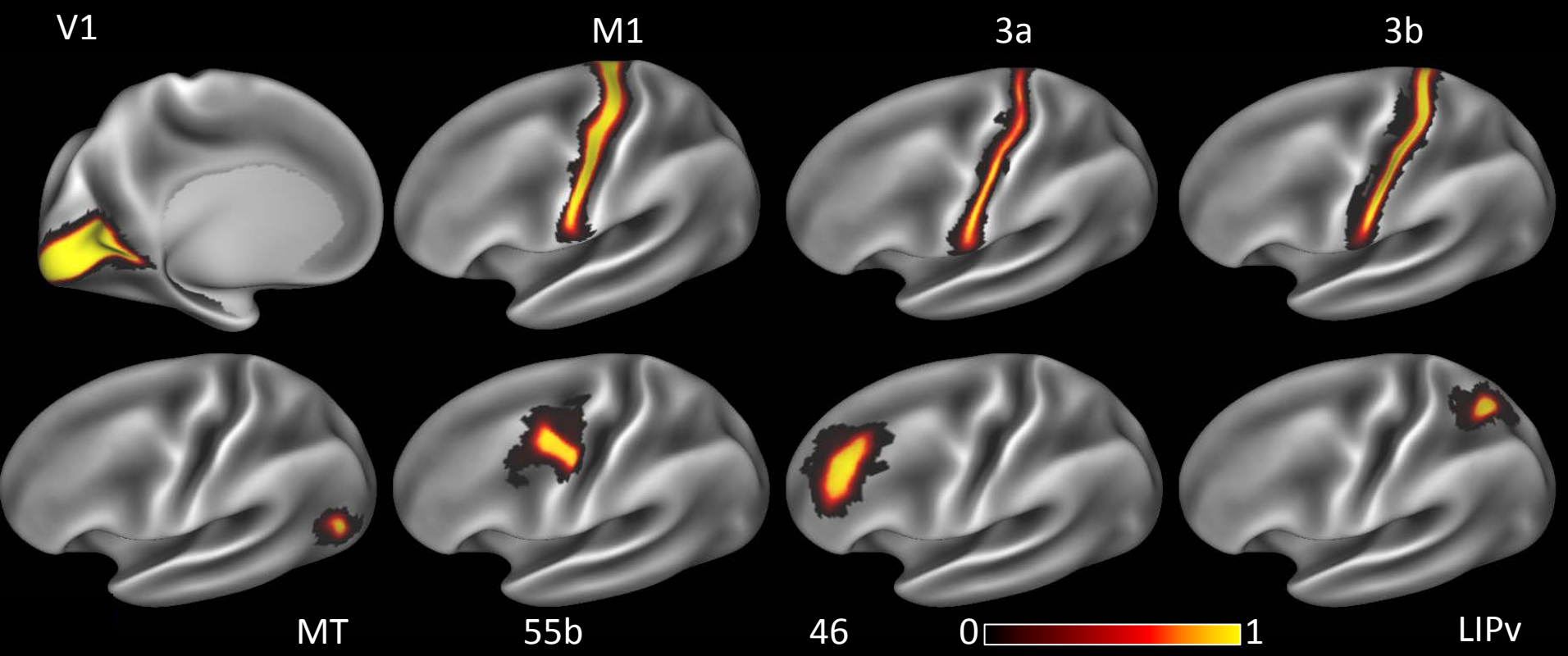
- Individual Areal Features + Folding
- Initial Classifier Probabilities
- Final Parcels (after combination across classifiers)
- Typical subject's 55b, PEF, and FEF
- Shifted subject's 55b, PEF, and FEF (55b and FEF swap)
- Split subject's 55b, PEF, and FEF (PEF and FEF are adjacent)

Original Group Parcellation and Individual Combined Areal MPMs



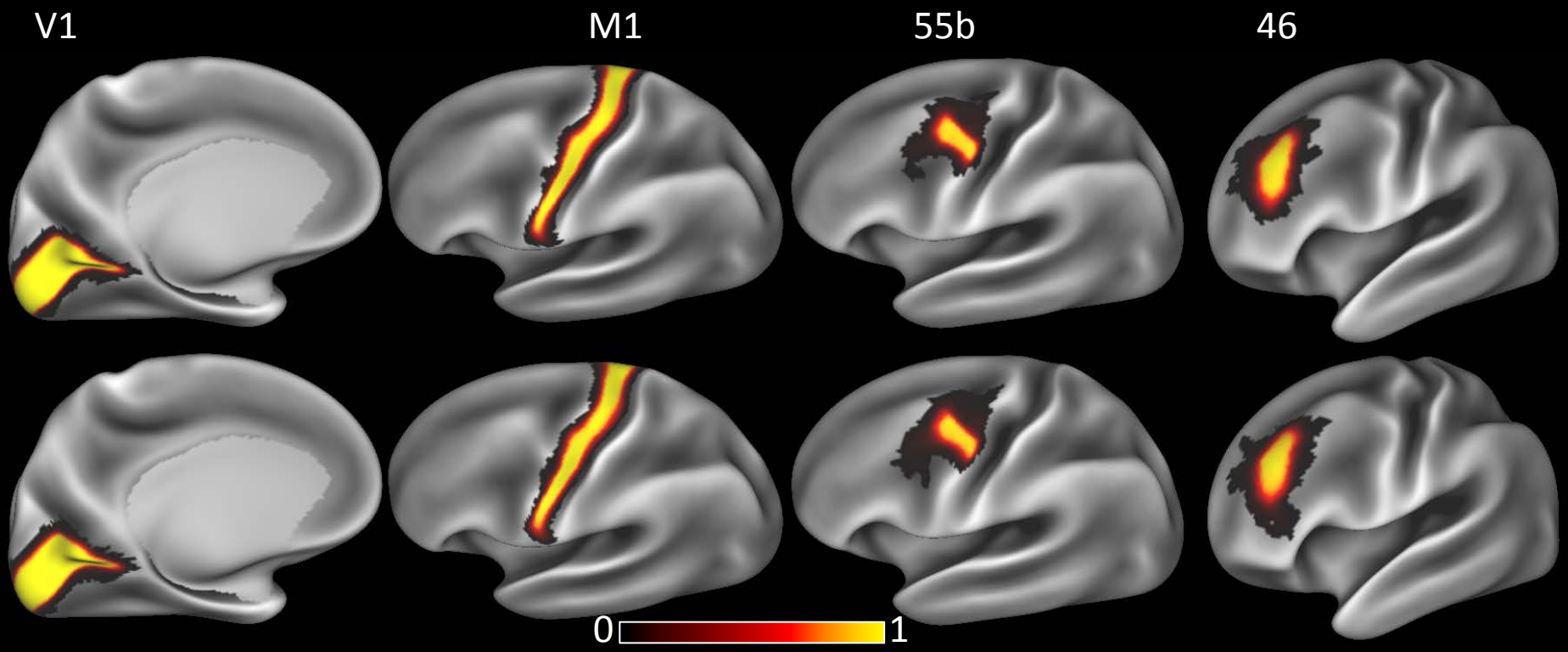
- Subject 1
- Subject 2
- Subject 3

Areal Probabilistic Maps



- Some areas have little variability in spatial location
- Others have more

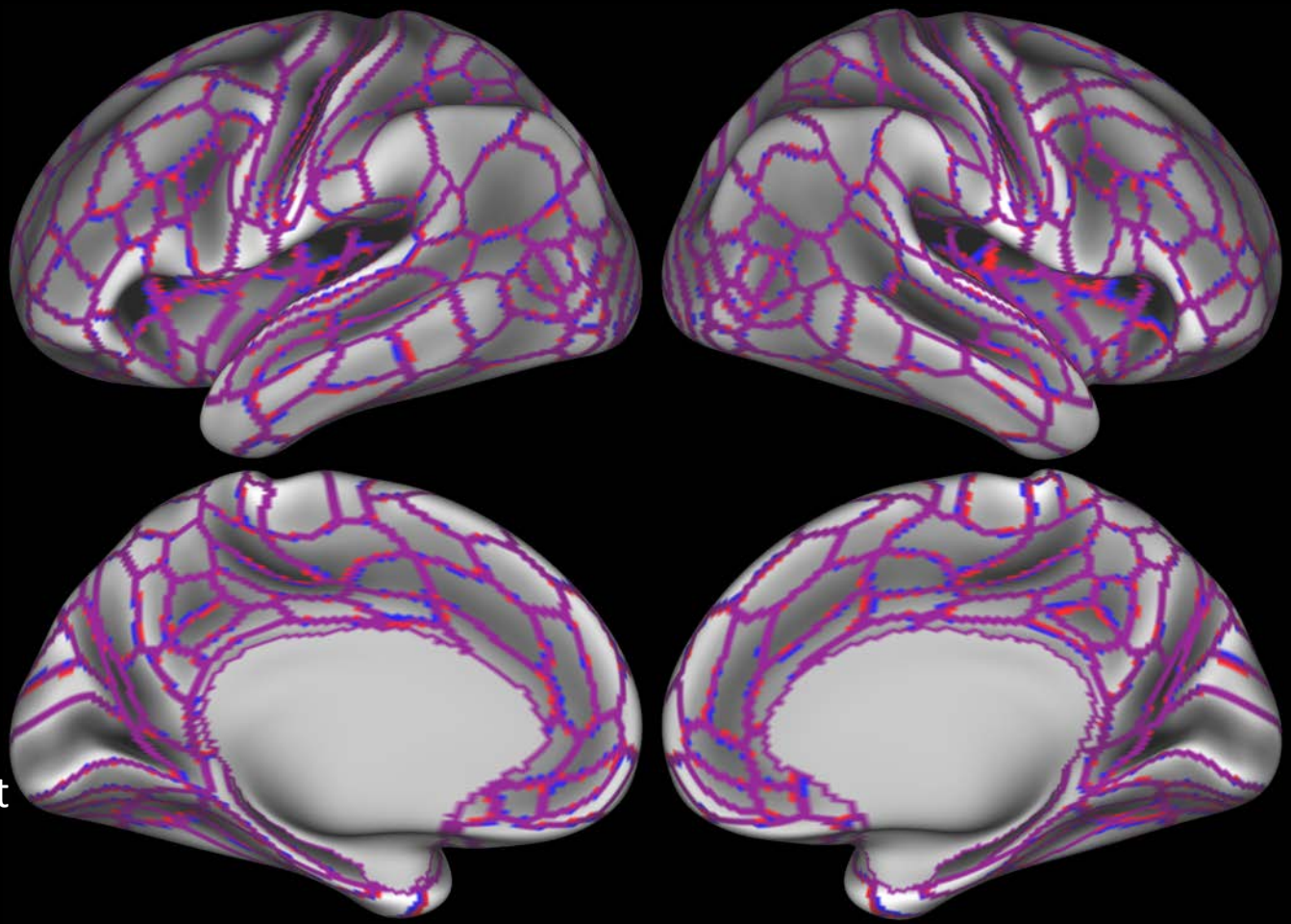
Reproducing the Multi-modal Parcellation Using Only Areal Fingerprints: Probabilistic Maps



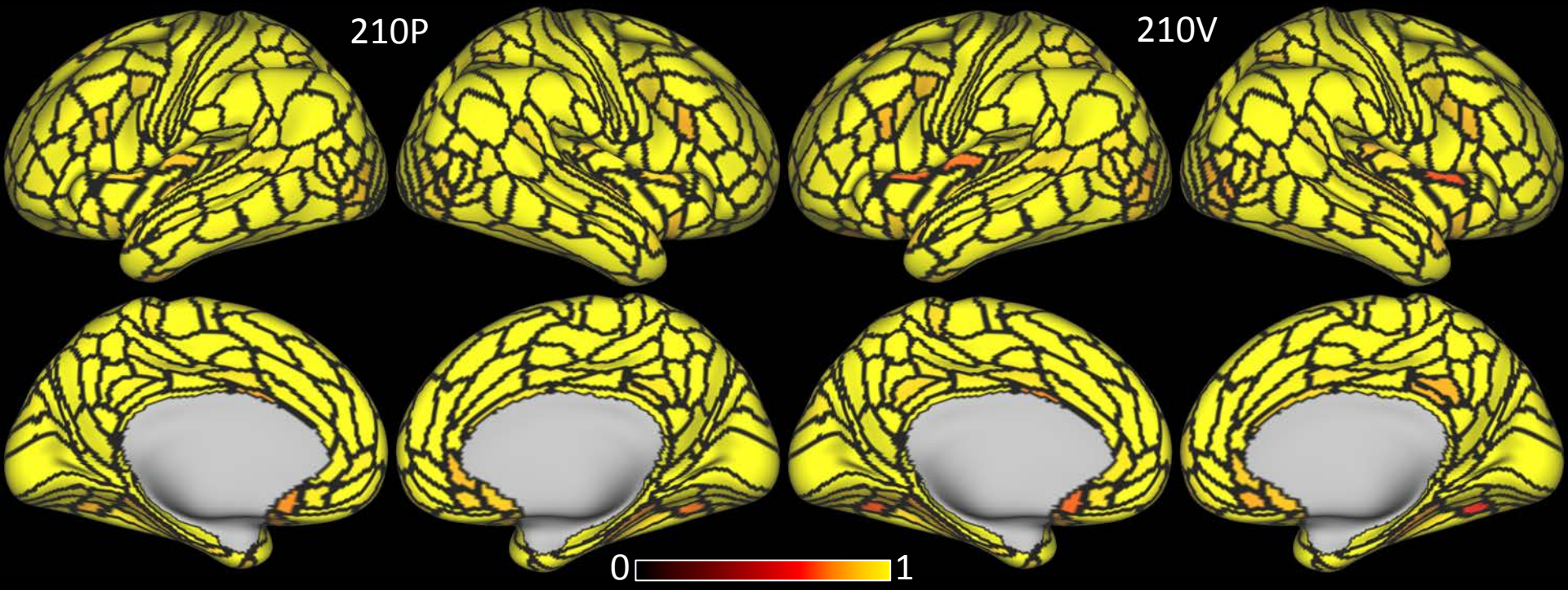
- The trained classifier was applied to the 210P and 210V datasets to generate individual subject parcellations
- These parcellations were averaged across subjects to produce probabilistic areas
- The probabilistic maps are very similar across the two groups

Reproducing the Multi-modal Parcellation Using Only Areal Fingerprints: MPMs

- The group maximum probability map was computed for both groups
- The areal boundary grayordinates displayed
  - Blue for 210P
  - Red for 210V
  - Purple for both
- The boundaries are in very high agreement
- Correlation of these parcellations is 0.97
  - This is in line with the dense map reproducibilities that we've measured in 210P and 210V



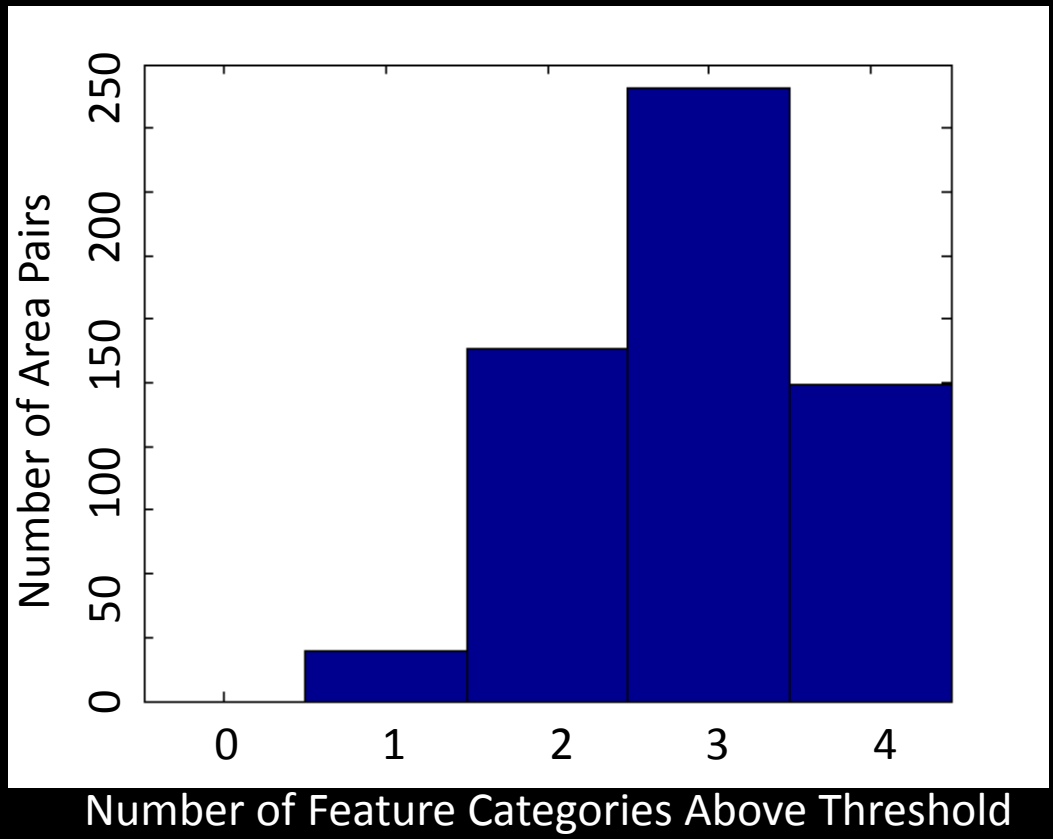
Comparison of Areal Detection Rates in 210P and 210V



- Detection is area within 0.33x and 3x of group area size
- 210V has very similar areal detection rates as 210P
  - Still most areas in most subjects despite not having been used in the parcellation or classifier training

Spatially Adjacent Areal Differences According to Four Independent Feature Categories

- Paired two tailed t-test between area pairs for each feature across subjects
- Threshold of Cohen's d>1 and $p<1.8 * 10^{-7}$ (Bonferroni corrected for 523 pairs * 266 features = 139,118 comparisons)
- Combined across feature categories
  - Myelin
  - Thickness
  - rfMRI
  - tfMRI



- Most neighboring area pairs have very large & significant differences across more than one category/modality

What You Need To Know About The HCP's Multi-modal Parcellation and Individual Subject Areal Classification

- Atlas: HCP's multi-modal cortical parcellation atlas will be released in the future (after publication)
  - Additionally, parcellated analysis (e.g. connectomes, task activity matrices) will also be released for each subject
- Software:
  - Computing gradients: Connectome Workbench Commandline Tools
  - Visualizing multiple modalities and parcellated datasets: Connectome Workbench
  - Code to apply the areal classifier to new subjects + the training data will be released in the future
- Images to acquire to make use of this code:
  - T1w, T2w, fMRI, field map (same as before)
- Other approaches already released by the HCP: rfMRI ICA-based parcellated connectomes (www.humanconnectome.org)
- Questions?